

REVIEW

Dopamine Receptors in Parkinson's Disease: A Meta-Analysis of Imaging Studies

Valtteri Kaasinen, MD,^{1,2*} Tero Vahlberg, MSc,³ A. Jon Stoessl, MD,⁴ Antonio P. Strafella, MD,^{5,6,7} and Angelo Antonini, MD⁸

¹*Clinical Neurosciences, Department of Clinical Medicine, Faculty of Medicine, University of Turku, Turku, Finland*

²*Neurocenter, Turku University Hospital, Turku, Finland*

³*Biostatistics, Department of Clinical Medicine, Faculty of Medicine, University of Turku, Turku, Finland*

⁴*Pacific Parkinson's Research Centre, Division of Neurology and Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Vancouver, British Columbia, Canada*

⁵*Division of Brain, Imaging and Behaviour-Systems Neuroscience, Krembil Research Institute, UHN, University of Toronto, Toronto, Ontario, Canada*

⁶*Research Imaging Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada*

⁷*Morton and Gloria Shulman Movement Disorder Unit and E.J. Safra Parkinson Disease Program, Neurology Division, Department of Medicine, Toronto Western Hospital, UHN, University of Toronto, Toronto, Ontario, Canada*

⁸*Parkinson and Movement Disorders Unit, Department of Neuroscience, University of Padua, Padua, Italy*

ABSTRACT: Dopamine receptors are abundant along the central nigrostriatal tract and are expressed as 5 subtypes in two receptor families. In PD, compensatory changes in dopamine receptors emerge as a consequence of the loss of dopamine nerve terminals or dopaminergic pharmacotherapy. We performed a systematic review and meta-analysis of the available PET and single-photon emission computed tomography studies that have investigated dopamine receptors in PD, PSP and MSA. The inclusion criteria were studies including human PET or single-photon emission computed tomography imaging; dopamine receptor tracers (D1-like or D2-like) and idiopathic PD, PSP, or MSA patients compared with healthy controls. The 67 included D2-like studies had 1925 patients. Data were insufficient for an analysis of D1-like studies. PD patients had higher striatal binding early in the disease, but after a disease duration of 4.36 years, PD patients had lower binding values than healthy controls. Striatal D2R binding was highest in unmedicated early PD patients and in

the striatum contralateral to the predominant motor symptoms. PSP and MSA-P patients had lower striatal D2R binding than PD patients (14.2% and 21.8%, respectively). There is initial upregulation of striatal D2Rs in PD, which downregulate on average 4 years after motor symptom onset, possibly because of agonist-induced effects. The consistent upregulation of D2Rs in the PD striatum contralateral to the predominant motor symptoms indicates that receptor changes are driven by neurodegeneration and loss of striatal neuropil. Both PSP and MSA patients have clearly lower striatal D2R binding values than PD patients, which offers an opportunity for differential diagnostics. © 2021 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; neuroimaging; dopamine receptors; PSP; MSA

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

***Correspondence to:** Dr. Valtteri Kaasinen, Neurocenter, Turku University Hospital, POB 52, 20521 Turku, Finland; E-mail: valtteri.kaasinen@tyks.fi

Relevant conflicts of interest/financial disclosures: Nothing to report.

Funding agency: None

Received: 29 December 2020; **Revised:** 15 March 2021; **Accepted:** 15 April 2021

Published online 6 May 2021 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.28632

Endogenous dopamine and most antiparkinsonian drugs exert their actions via postsynaptic dopamine receptors. The two dopamine receptor families (D1- and D2-like) and 5 dopamine receptor subtypes (D1R–D5R) are encoded in humans by 5 genes (*DRD1–DRD5*).¹ In Parkinson's disease (PD), the therapeutic use of dopamine receptor agonists bypasses degenerated mesencephalic dopamine production, but the clinical benefits of agonists are generally less than those with levodopa, and their use can be complicated by various

side effects ranging from fibrotic heart disease with ergoline derivatives to impulsive/compulsive disorders.^{2,3} There are also results to suggest that long-term and intermittent administration of dopaminergic drugs may cause dopamine receptor downregulation in advanced PD, when response to levodopa is suboptimal and characterized by fluctuations and dyskinesias.⁴

Dopamine receptor upregulation in PD was first demonstrated in the striatum of postmortem brains of PD patients.⁵ The effect was assumed to be a consequence of dopaminergic denervation. Later postmortem studies and in vivo imaging have provided mixed results of this upregulation in relation to temporal associations during PD progression. Although many studies have suggested that there is detectable upregulation in striatal dopamine receptors in early PD, advanced PD patients appear to show downregulation (eg, references 6–9). A critical question is whether the dynamic changes in dopamine receptor availability represent disease or treatment effects and whether receptor downregulation is a factor that reduces the efficacy of dopaminergic drug treatment.

From a diagnostic point of view, it is possible that patients with progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) lack the initial upregulation phase of dopamine receptor binding, which would support the use of combined pre- and postsynaptic dopaminergic imaging in patients with clinically uncertain parkinsonian syndromes.^{10,11} However, small sample size is a major limitation of most functional neuroimaging studies, which complicates the interpretation of individual studies. Meta-analysis increases the power to detect differences while making it possible to study potential moderating variables and biases associated with single studies.

The present meta-analysis aimed to investigate dopamine receptor changes in PD patients using pooled published PET and single-photon emission computed tomography data. We specifically aimed to answer: (1) whether there is dopamine receptor upregulation in early PD or downregulation in advanced PD, (2) when the possible upregulation turns to downregulation and how this is associated with drug treatments, (3) if there are clinically relevant interhemispheric differences in dopamine receptor binding, and (4) if dopamine receptor binding characteristics could be used to help in the differential diagnosis of PD versus atypical parkinsonian syndromes.

Methods

The study was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹²

Search Strategy

PubMed was searched with specific headings alone and in combination with key words for longitudinal progression studies from database inception until March 6, 2020 (Fig. 1). The references of retrieved articles and review articles were also manually searched for missed studies.

Specific Aims for the Meta-Analysis

This meta-analysis aimed to systematically investigate changes in striatal dopamine receptor binding in PD patients compared with healthy controls and patients with PSP and MSA. The primary outcome was the mean difference in striatal subregions in relation to potential effect size moderators such as age, disease duration, and motor symptom severity measures.

Selection Criteria

All titles and abstracts from searches were reviewed, and studies were excluded if the title and/or abstract were not appropriate for the aim of the review. Full texts were obtained for eligible studies or when the relevance of an article was uncertain. The inclusion criteria for the selected studies were: (1) study involved human PET or single-photon emission computed tomography (SPECT) imaging; (2) binding of a dopamine receptor tracer (D1-like or D2-like) was assessed; (3) idiopathic PD, PSP, or MSA patients were compared with healthy controls (unmedicated or medicated, patients with deep brain stimulation [DBS] or thalamotomy excluded in group comparisons); and (4) binding was reported as the mean \pm SD in at least one striatal region. If more than one population was reported in a study (eg, early and advanced PD patients), those populations were included as separate samples with the same control sample.

Risk of Bias in Included Studies

The presence of publication bias was explored by funnel plots and Egger's tests for asymmetry, together with the trim-and-fill method with imputed data points. The quality of studies was evaluated with a modified Newcastle-Ottawa scale.¹

Data Extraction

The variables extracted were study year, first author's family name, study site (city, state, country), method for binding uptake calculation, number of subjects in each group, mean \pm SD age (years), sex of participants, mean \pm SD disease duration (years), mean \pm SD Unified Parkinson's Disease Rating Scale (UPDRS) motor score, mean \pm SD Hoehn and Yahr stage score, scanner type, mean injected dose (MBq), scan duration

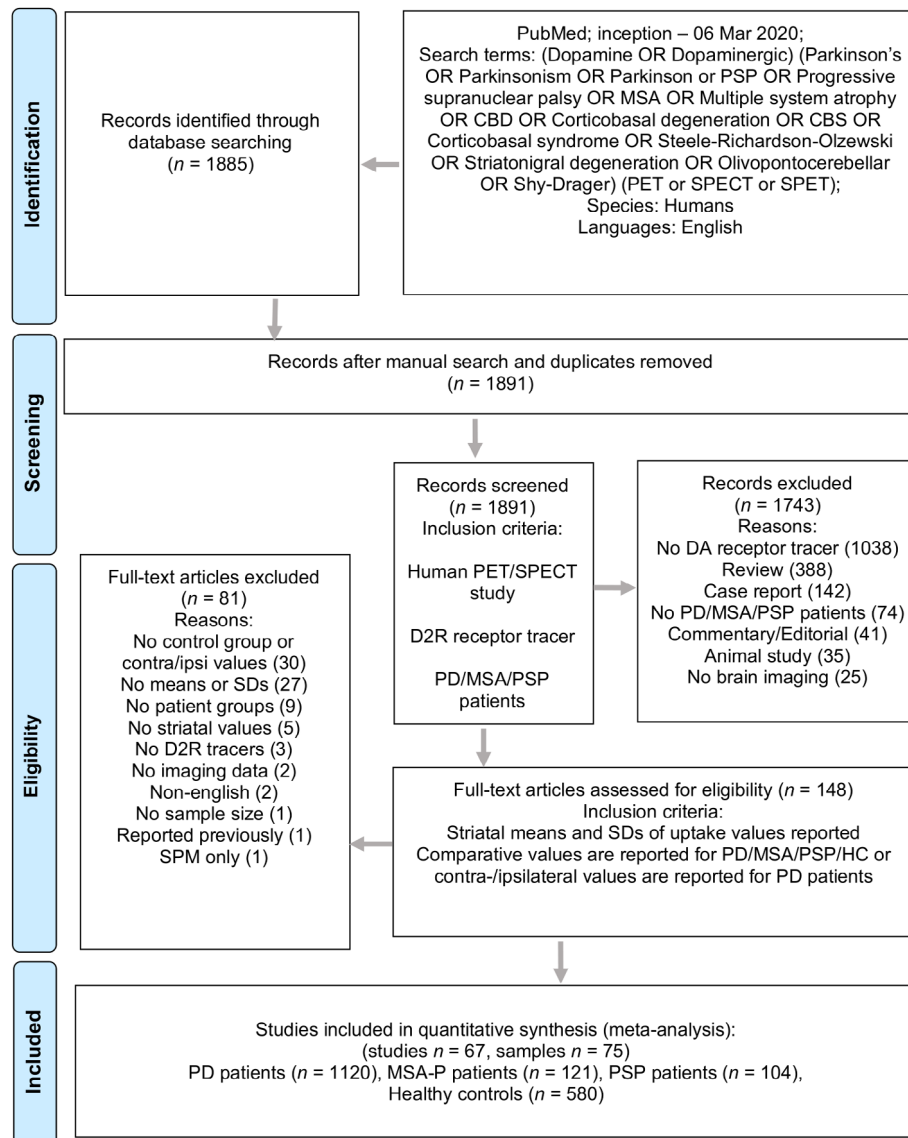


FIG. 1. Flowchart of study inclusion and exclusion.

(minutes), and mean \pm SD uptake data (for each group and brain region; if the study did not report mean striatal values, they were generated using means of caudate and putamen values).

Statistical Analysis

Brain regional group comparisons were conducted using Meta-Essentials (version 1.0; Erasmus University, Rotterdam, The Netherlands).¹³ The effect sizes were measured with Hedges' g values as standardized mean differences using a random-effects model. Heterogeneity of the effect sizes was examined using I^2 statistics. If substantial heterogeneity with $I^2 > 50\%$ was observed, the influence of effect moderators, including age, disease duration, UPDRS motor score, and HY scale, on tracer uptake was analyzed using meta-regression analyses with

SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC). The normality assumptions of the residuals were examined with histograms. The homoscedasticity was checked with scatterplots between predicted values and residuals. Both the normality and homoscedasticity assumptions were met.

Subgroup analyses between medicated and unmedicated PD patients and between PET and SPECT studies were performed using random effects for between-subgroup weighting and random effects (tau separate for subgroups) for within-subject weighting. Differences in the combined effect sizes of the subgroups were tested with an analysis of variance based on sums of squares.¹⁴ Interhemispheric correlation coefficients were calculated from 4 studies that reported individual hemispheric values.^{15–18} The weighted mean r of 0.913 was used for the remaining studies in the meta-analysis of

dependent effect sizes. Percent differences were expressed as weighted relative differences (weighting according to sample size). Statistical significance was set at two-tailed $P < 0.05$.

Results

Study Characteristics

The demographic and clinical characteristics of the patient samples included in the 67 D2R studies are presented in Table 1 and in Tables S1–S3. Data were insufficient for analyses of D1R studies, as only 5 D1R studies reported PET or SPECT results in PD, MSA, or PSP patients. The 67 included D2R studies had 75 individual patient samples involving 1925 patients (Fig. 1, Table S1). Because MSA-C samples were reported only in two studies, they were excluded from the analysis, and the included MSA samples had patients with MSA-P or unspecified MSA.

Parkinson's Disease

D2R binding in the caudate nucleus was 9.8% lower in PD patients (medicated and unmedicated combined) than in healthy controls ($g = 0.67$; CI, 0.34–1.01; n [samples/patients], 29/680; $I^2 = 71.6\%$, $P < 0.0001$), but there were no differences in the putamen ($g = -0.32$; CI, -0.73 to 0.10 ; $n = 29/680$, $I^2 = 79.6\%$, $P = 0.12$) or the striatum ($g = 0.16$; CI, -0.06 to 0.39 ; $n = 50/1292$, $I^2 = 65.3\%$, $P = 0.13$; Fig. 2).

In subgroup analyses of unmedicated de novo PD patients compared with healthy controls, there were no differences in the mean striatal binding ($g = -0.18$; CI, -0.43 to 0.07 ; $I^2 = 19.8\%$; Fig. 2), caudate nucleus binding ($g = 0.43$; CI, -0.06 to 0.92 ; $I^2 = 67.0\%$) or putamen binding ($g = -0.46$; CI, -1.45 to 0.52 , $I^2 = 88.9\%$). The mean striatal binding was 2.7% lower in medicated PD patients than in healthy controls ($g = 0.30$; CI, 0.03–0.58; $I^2 = 68.6\%$; Fig. 2), and the caudate nucleus binding was 10.0% lower ($g = 0.80$; CI, 0.38–1.23; $I^2 = 73.8\%$), whereas there was no difference in the putamen ($g = -0.23$; CI, -0.58 to 0.13 ; $I^2 = 65.8\%$). The effect sizes for D2R binding differed between unmedicated and medicated patients in mean striatal binding ($P = 0.007$).

Binding in the striatum contralateral to the predominant motor symptoms of PD was 2.8% higher than that in the ipsilateral side ($g = -0.19$; CI, -0.26 to -0.11 ; $n = 27/475$, $I^2 = 69.7\%$, $P < 0.0001$; Fig. 3). Twenty-three of 27 samples showed higher binding values on the contralateral side.

PD disease duration was an effect moderator for striatal D2R binding. PD patients had higher binding early in the disease, but the regression line crossed zero at a disease duration of 4.36 years, after which PD patients had lower binding values than healthy controls

($\beta = 0.13$; CI, 0.06–0.21; $P < 0.001$; Fig. 4). A similar moderator effect was observed for Hoehn and Yahr stage, as striatal D2R binding was elevated in patients with a Hoehn and Yahr stage score below 2.1 and reduced in motorically more severely affected patients ($\beta = 0.52$; CI, 0.17–0.86; $P = 0.002$) and for motor UPDRS score ($\beta = 0.04$; CI, 0.00–0.08; $P = 0.031$) but not for age of PD patients ($\beta = 0.02$; CI, -0.02 to 0.06 ; $P = 0.28$).

PSP and MSA

PSP patients had 26.5% lower striatal D2R binding ($g = 1.59$; CI, 1.19–1.99; $n = 6/89$, $I^2 = 0\%$, $P < 0.0001$), and MSA-P patients had 32.6% lower striatal D2R binding than healthy controls ($g = 2.08$; CI, 0.03–4.13; $n = 4/75$, $I^2 = 75.6\%$, $P = 0.001$). PSP patients had 14.2% lower striatal D2R binding ($g = -0.99$; CI, -1.65 to -0.34 ; $n = 11/204$, $I^2 = 62.5\%$, $P = 0.001$), and MSA-P patients had 21.8% lower striatal D2R binding ($g = -1.32$; CI, -0.71 to -2.95 ; $n = 12/221$, $I^2 = 63.1\%$, $P < 0.001$) than PD patients. There were no differences in striatal ($g = -0.10$; CI, -0.52 to 0.33 ; $n = 8/122$, $I^2 = 0\%$, $P = 0.59$), caudate ($g = -0.07$; CI, -1.67 to 1.53 ; $n = 4/55$, $I^2 = 67.7\%$, $P = 0.89$), or putamen ($g = -0.16$; CI, -0.88 to 0.56 ; $n = 4/55$, $I^2 = 0\%$, $P = 0.49$) D2R binding between PSP and MSA-P patients (Fig. S1).

Data Quality

Twelve studies scored 1–2 of 6 stars on the Newcastle-Ottawa scale (Table S4). When these studies were excluded from the analysis, the results remained essentially the same except for the striatal D2R difference between unmedicated PD patients and healthy controls, which became significant (higher binding in PD; $g = -0.34$; CI, -0.59 to -0.09). There were no differences in mean striatal effect sizes between PET (25 studies, 27 samples) and SPECT (19 studies, 23 samples) studies ($P = 0.27$). Funnel plots with imputed data points for the striatum in PD and PSP samples suggested no significant publication bias with 0–1 negative studies missing (PD: Egger intercept $P = 0.55$). One negative study was missing in MSA versus HC and MSA versus PD analyses (Egger intercept $P < 0.05$), but trim-and-fill-adjusted effect sizes remained essentially the same, suggesting minimal impact of publication bias.

Discussion

There are three primary results in this meta-analysis. First, the pooled results demonstrate that there was initial upregulation of striatal D2Rs in PD patients, which was reversed to downregulation on average 4.4 years after motor symptom onset. Second, there was

TABLE 1 Summary of included studies

Study	Site ^a	Method	Tracer	Patients	Scanner ^b
Baron 1986 ¹⁹	PAR	PET	[⁷⁶ Br]bromospiperone	PSP	LETI prototype
Hägglund, 1987 ²⁰	UPP	PET	[¹¹ C]NMSP	PD	Scanditronix PC 382-3B
Rutgers, 1987 ¹⁵	GRO	PET	[¹¹ C]NMSP	PD	—
Brücke, 1991 ²¹	VIE	SPECT	[¹²³ I]IBZM	PD	Siemens Dual Rota ZLC37
Tatsch, 1991 ²²	MUN	SPECT	[¹²³ I]IBZM	PD	Siemens Rota II
Brooks, 1992 ⁶	LON	PET	[¹¹ C]raclopride	PDP, PSP, MSA	CTI 931/08/12
Sawle, 1993 ²³	LON	PET	[¹¹ C]raclopride	PD	CTI 931/12/8
Shinotoh, 1993 ²⁴	CHI	PET	[¹¹ C]NMSP	PD, MSA	Three-ring PET system
Brücke, 1993 ²⁵	VIE	SPECT	[¹²³ I]IBZM	PD	Siemens Dual Rota ZLC37
Cordes, 1993 ²⁶	BER	SPECT	[¹²³ I]IBZM	PD	APEX 409, Elscint
Pizzolato, 1993 ²⁷	PAD	SPECT	[¹²³ I]IBZM	PD	—
Laulumaa, 1993 ²⁸	KUO	SPECT	[¹²³ I]IBZM	PD	Siemens Orbiter
van Royen, 1993 ²⁹	AMS	SPECT	[¹²³ I]IBZM	PSP, MSA	Strichman 810
Giobbe, 1993 ³⁰	TUR	SPECT	[¹²³ I]IBZM	PD	GE 400 T
Schwarz, 1994 ³¹	MUN	PET	[¹¹ C]raclopride	PD	CTI 933/04-16
Hublin, 1994 ³²	HEL	SPECT	[¹²³ I]IBZM	PD	Picker DDC4096
Antonini, 1994 ⁷	VIL	PET	[¹¹ C]raclopride	PD	CTI 933/04-16
Schulz 1994 ³³	TÜB	SPECT	[¹²³ I]IBZM	PD, MSA	Picker Digital Dyna
Antonini, 1995 ³⁴	VIL	PET	[¹¹ C]raclopride	PD	CTI 933/04-16
Buck, 1995 ³⁵	ZÜR	SPECT	[¹²³ I]IBZM	PD, PSP	Picker Prism 3000
Knable, 1995 ¹⁶	BET	SPECT	[¹²³ I]IBZM	PD	Ceraspect
Nadeau, 1995 ³⁶	GAI	SPECT	[¹²³ I]IBZM	PD	Triad 88
Rinne, 1995 ³⁷	TKU	PET	[¹¹ C]raclopride	PD	ECAT 931/08-12
Pizzolato, 1995 ³⁸	PAD	SPECT	[¹²³ I]IBZM	PD	GE Starcam 400 AC
Cordes, 1996 ³⁹	BER	SPECT	[¹²³ I]lisuride	PD	—
Antonini, 1997 ⁴⁰	VIL	PET	[¹¹ C]raclopride	PD	CTI 933/04-16
Staffen, 1997 ⁸	SAL	SPECT	[¹²³ I]IBZM	PD	Picker Prism 3000
Turjanski, 1997 ⁴¹	LON	PET	[¹¹ C]raclopride	PD	CTI 931/-08/12
Pirker, 1997 ⁴²	VIE	SPECT	[¹²³ I]epidepride	PD, MSA	—
Schwarz, 1997 ⁴³	MUN	SPECT	[¹²³ I]IBZM	PD	Rota II Siemens
Antonini, 1997 ⁴⁴	VIL	PET	[¹¹ C]raclopride	PD, MSA	CTI 933/04-16
Wenning, 1998 ¹⁷	INN	SPECT	[¹²³ I]IBZM	PD	Siemens Orbiter Digitrac ZLC
Hierholzer, 1998 ⁴⁵	BER	SPECT	[¹²³ I]IBZM	PD, PSP, MSA	Apex 409
Ichise, 1998 ⁴⁶	TOR	SPECT	[¹²³ I]IBF	PD	Prism 3000XP, Picker
Dentresangle, 1999 ⁴⁷	LYO	PET	[¹¹ C]raclopride	PD	TTV03 LETI
Samii, 1999 ⁹	VAN	PET	[¹¹ C]raclopride	PD	ECAT 953B
Nagabepu, 1999	KAG	SPECT	[¹²³ I]IBF	PD, PSP, MSA	—
Kaasinen, 2000 ¹⁸	TKU	PET	[¹¹ C]raclopride	PD	ECAT 931/08-12

(Continues)

TABLE 1 Continued

Study	Site ^a	Method	Tracer	Patients	Scanner ^b
Hilker, 2001 ⁴⁸	COL	PET	[¹¹ C]raclopride	PD	ECAT EXACT HR
Prunier, 2001 ⁴⁹	TOU	SPECT	[¹²³ I]lisuride	PD, PSP, MSA	Helix Elscint
Kim, 2002 ¹¹	TOR	SPECT	[¹²³ I]IBF	PD, PSP, MSA	Prism 3000XP, Picker
Arnold, 2002 ⁵⁰	MUN	SPECT	[¹²³ I]IBZM	PSP	Siemens Rota II
Ghaemi, 2002 ⁵¹	COL	PET	[¹¹ C]raclopride	PD	ECAT EXACT/ECAT EXACT HR
Oyanagi, 2002 ⁵²	KYO	SPECT	[¹²³ I]IBF	PD, PSP	Prism 3000 Picker
Hilker, 2003 ⁵³	COL	PET	[¹¹ C]raclopride	PD	ECAT EXACT HR
Schreckenberger, 2004 ⁵⁴	MAI	PET	[¹⁸ F]fallypride	PD	ECAT EXACT
Scherfler, 2004 ⁵⁵	LON	PET	[¹¹ C]raclopride	PD	ECAT EXACT HR++
Seppi, 2004 ⁵⁶	INN	SPECT	[¹²³ I]IBZM	PD, MSA	ADAC VertexPlus
Plotkin, 2005 ¹⁰	BER	SPECT	[¹²³ I]IBZM	PD, PSP	Multispect 3
Mishina, 2005 ⁵⁷	CHI	PET	[¹¹ C]raclopride	PD	HEADTOME V
Nakagawa, 2005 ⁵⁸	FUK	PET	[¹¹ C]raclopride	PD, PSP, MSA	ECAT EXACT HR+
Strafella, 2005 ⁵⁹	MON	PET	[¹¹ C]raclopride	PD	CTI-Siemens HR+
Hesse, 2006 ⁶⁰	LEI	SPECT	[¹²³ I]IBZM	PD	Ceraspect
Strafella, 2006 ⁶¹	MON	PET	[¹¹ C]raclopride	PD	CTI/Siemens HR+
Verstappen, 2007 ⁶²	NIJ	SPECT	[¹²³ I]IBZM	PD	Multispect 2
Ribeiro, 2009 ⁶³	ORS	PET	[¹¹ C]raclopride	PD	ECAT EXACT HR+
Ishibashi, 2010 ⁶⁴	TOK	PET	[¹¹ C]raclopride	PD	SET-2400 W
Pifarre, 2010 ⁶⁵	BAR	SPECT	[¹²³ I]IBZM	PD, PSP, MSA	Siemens E-CAM
Lin, 2010 ⁶⁶	TAO	SPECT	[¹²³ I]IBZM	PD, PSP	Siemens E.CAM
Südmeyer, 2011 ⁶⁷	DÜS	SPECT	[¹²³ I]IBZM	PD	Prism 2000
Hellwig, 2012 ⁶⁸	FRE	SPECT	[¹²³ I]IBZM	PD, PSP, MSA	Siemens E.CAM
Hammesfahr, 2016 ⁶⁹	DÜS	SPECT	[¹²³ I]IBZM	PD	Prism 2000
Akamatsu, 2017 ⁷⁰	KOB	PET	[¹¹ C]raclopride	PD	Discovery 690 PET/CT
Mishina, 2017 ⁷¹	KAN	PET	[¹¹ C]raclopride	PD	SET-2400 W
Politis, 2017 ⁷²	LON	PET	[¹¹ C]raclopride	PD	ECAT HR+
Stark, 2018 ⁷³	NAS	PET	[¹⁸ F]fallypride	PD	GE Discovery STE PET/CT
Sacheli, 2018 ⁷⁴	VAN	PET	[¹¹ C]raclopride	PD	HRRT

[¹¹C]NMSP, 3-N-[¹¹C]methylpiperone; [¹²³I]IBZM, [¹²³I]-(S)-2-hydroxy-3-iodo-6-methoxy-N([l-ethyl-2-pyrrolidyl]methyl)-benzamide.

^aAMS, Amsterdam, The Netherlands; BAR, Barcelona, Spain; BER, Berlin, Germany; BET, Bethesda, MD USA; CHI, Chiba, Japan; COL, Cologne, Germany; DÜS, Düsseldorf, Germany; FRE, Freiburg, Germany; FUK, Fukuoka, Japan; GAI, Gainesville, FL, USA; GRO, Groningen, The Netherlands; HEL, Helsinki, Finland; INN, Innsbruck, Austria; LON, London, UK; LYO, Lyon, France; KAG, Kagoshima, Japan; KAN, Kanawaga, Japan; KOB, Kobe, Japan; KUO, Kuopio, Finland; KYO, Kyoto, Japan; LEI, Leipzig, Germany; MAI, Mainz, Germany; MON, Montreal, QC, Canada; MUN, Munich, Germany; NAS, Nashville, TN, USA; NIJ, Nijmegen, The Netherlands; ORS, Orsay, France; PAD, Padova, Italy; PAR, Paris, France; SAL, Salzburg, Austria; TAO, Taoyuan, Taiwan; TKU, Turku, Finland; TOK, Tokyo, Japan; TOR, Toronto, ON, Canada; TOU, Tours, France; TUR, Turin, Italy; TÜB, Tübingen, Germany; UPP, Uppsala, Sweden; VAN, Vancouver, BC, Canada; VIE, Vienna, Austria; VIL, Villigen, Switzerland; ZÜR, Zürich, Switzerland.

^bScanner models written as they were reported in the original articles.

consistent upregulation of D2Rs in the striatum contralateral to the predominant motor symptoms in PD patients. Third, both PSP and MSA patients clearly had lower striatal D2R binding than PD patients despite similar or even more profound loss of dopamine nerve

terminals, which is potentially important for neuroimaging-based differential diagnostics.

A critical question is whether the downregulation of striatal D2Rs seen in advanced PD patients was because of disease progression or dopaminergic medication.

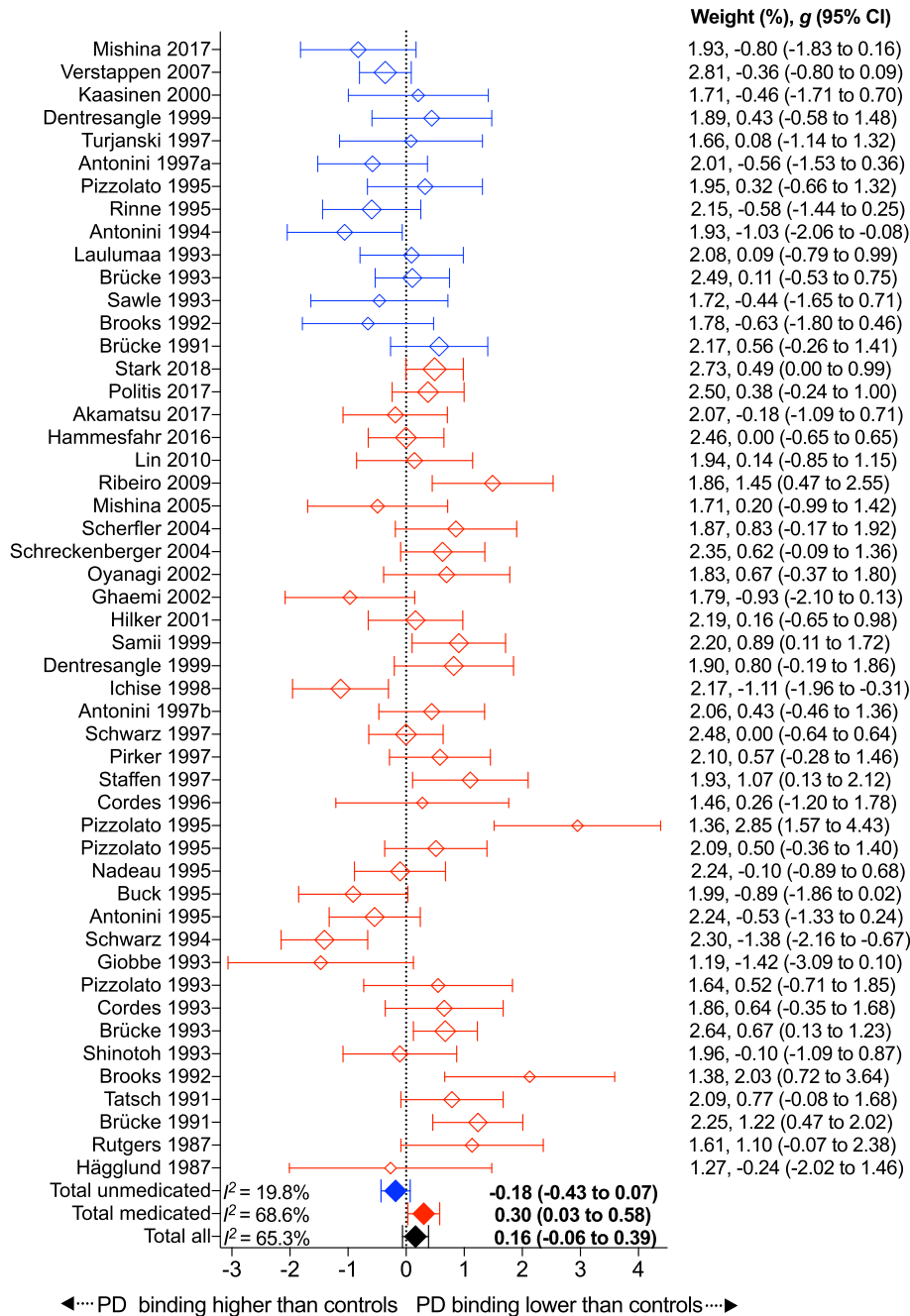


FIG. 2. Forest plot of differences in striatal dopamine D2 receptor binding between PD patients and healthy controls. Red, samples with PD patients treated with antiparkinsonian medications, mixed samples (medicated and unmedicated), or medication not reported; blue, samples with unmedicated PD patients.

There are neuroimaging results in DBS-treated patients that support the hypothesis that receptor downregulation is a consequence of drug treatment, as the downregulation seems to disappear in patients whose medications are withdrawn after DBS implantation.⁴ There is also evidence indicating that changes in D1 versus D2 dopamine receptor density contribute to the development of dyskinesia.⁷⁵ Indeed, in the present meta-analysis, both longer disease duration and pharmacotherapy were associated with lower D2 receptor

binding in PD patients. Because there are practically no unmedicated PD patients with disease duration longer than 4 years, it is not possible to determine if the downregulation in advanced patients was from disease progression. Given that agonist-induced downregulation of receptors has been described in a number of other central neurotransmitter systems, such as 5-HT receptors,⁷⁶ muscarinic acetylcholine receptors,⁷⁷ AMPA receptors,⁷⁸ and opioid receptors,⁷⁹ the agonist-induced mechanism seems likely in PD, a view that is supported by studies

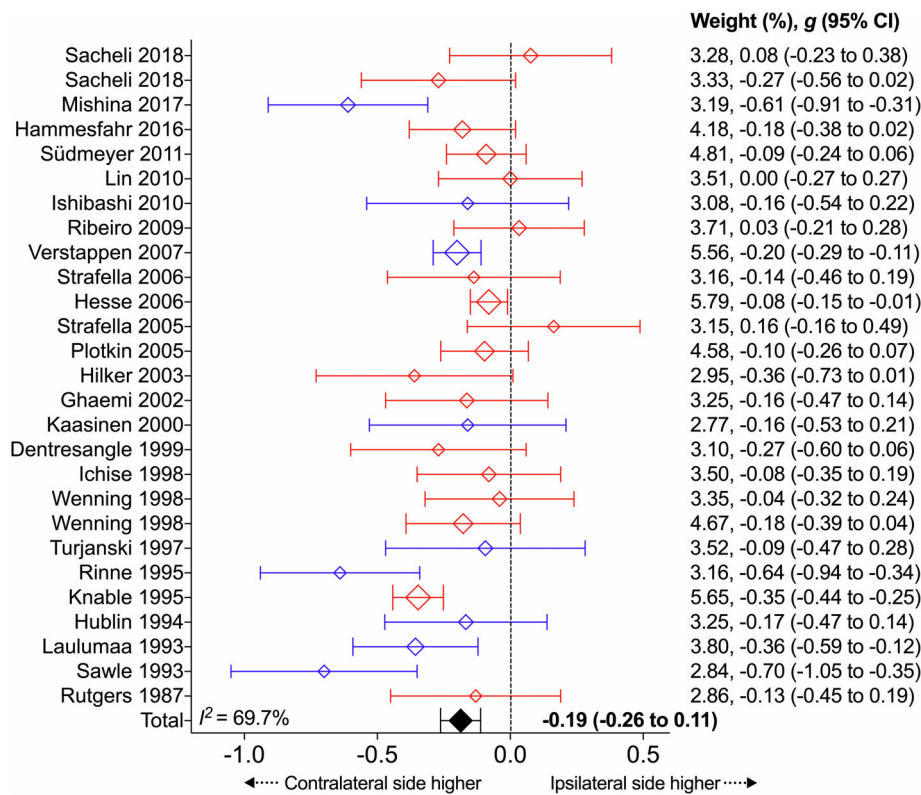


FIG. 3. Forest plot of D2R interhemispheric differences in PD patients. The analysis was carried out with studies that reported separate values for striatal D2R binding in hemispheres contra- and ipsilateral to the predominant motor symptoms of PD. Note the higher contralateral binding in all but 4 samples. Red, samples with PD patients treated with antiparkinsonian medications, mixed samples (medicated and unmedicated), or medication not reported; blue, samples with unmedicated PD patients.

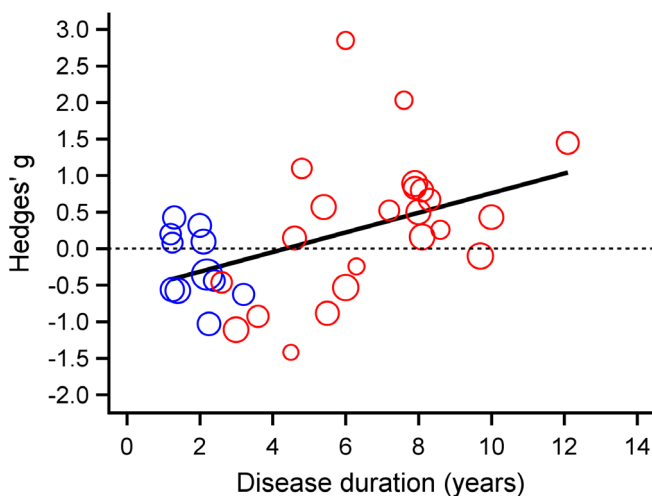


FIG. 4. Association between effect size (Hedges' *g*) and disease duration in PD patients. Negative effect sizes indicate receptor upregulation in relation to healthy controls. The initial upregulation becomes downregulation 4.36 years after disease onset. Blue, unmedicated patient samples; red, medicated patient samples. Circle size denotes sample size.

with rodents demonstrating a reduction in D2Rs after continuous treatment with dopamine receptor agonists,⁸⁰ as well as findings in advanced PD patients withdrawn from all medication following STN DBS.⁴ Although the

downregulation may be secondary to therapy, the consistently higher D2R binding in the hemisphere contralateral to the predominant symptoms of PD points to a regionally specific mechanism and indicates that the increase in D2R binding is associated with a decrease in presynaptic dopamine function. This is a strong indicator of pathology-driven changes in dopamine receptor density. As the increase in contralateral binding does not seem to be directly related to synaptic dopamine levels,¹⁸ it is possible that the upregulation is a consequence of the loss of striatal neuropil in PD.

Another aspect is the subregional differences in dopamine receptor-binding characteristics in PD patients. When the caudate nucleus and putamen were studied separately in the present meta-analysis, PD patients (early and advanced combined) showed lower binding in the caudate than healthy subjects with no difference observed in the putamen. This suggests relatively more pronounced receptor loss in the caudate over the disease course of PD. It is of high importance to note that executive cognitive deficits in early patients with PD appear to be particularly associated with deficits in dorsal caudate dopaminergic function.⁸¹ Although associations between dopamine and cognitive measures should be considered in the context of frontostriatothalamic circuitry, caudate D2R activity seems to be especially

important for response inhibition and temporal organization of material together with motor performance.⁸² Unfortunately, only a few studies reported cognitive measures in the present meta-analysis. Cognitive function in association with regional dopamine receptor status should be a focus of a future meta-analysis.

Compared with PD, the loss of D2R function in PSP and MSA was far more severe in the early stages. This suggests that D2R imaging in PSP and MSA could have some diagnostic value. However, in individual cases, the relative changes in PD D2R binding characteristics can be small, and the sensitivity/specificity of D2R imaging in PD versus PSP/MSA differential diagnostics is probably suboptimal. Furthermore, it cannot be excluded that there is a similar albeit shorter D2R upregulation phase in atypical parkinsonisms. If the mechanism of receptor upregulation is compensation for the loss of dopaminergic function, it could be expected that the mechanism could extend to other hypodopaminergic conditions, such as PSP and MSA, but is less apparent, owing to the associated loss of striatal projection neurons. In light of these uncertainties, the use of fluorodeoxyglucose (FDG) PET, MRI, or protein-specific tracers in the future are probably superior to D2R imaging in the differential diagnosis of atypical parkinsonisms.

A limitation of the present study is the lack of a sufficient number of D1R studies. The conclusions are therefore only valid for D2Rs. However, from the viewpoint of PD, the D2R family may be more relevant because D2R-knockout mice are known to exhibit reduced spontaneous movements resembling the movement disorder in PD and atypical parkinsonisms.⁸³ This is in stark contrast to D1R-knockout mice, which either appear to demonstrate behavioral hyperactivity or no behavioral alterations in movement.^{84,85} Therefore, the present results should be interpreted to show dynamic changes in D2Rs, and the effects could be very different for D1Rs.

To conclude, pooled functional neuroimaging data show temporal and regional changes in dopamine D2-like receptors in PD. The initial upregulation of receptors reverses to steep downregulation, possibly because of an agonist-induced effect. The contralateral upregulation indicates that receptor binding increases are mainly driven by neurodegeneration. Finally, the dopamine receptor differences in PD compared with atypical parkinsonisms may assist in the differential diagnosis of patients with clinically uncertain parkinsonian syndromes, although other imaging modalities (FDG or misfolded protein-specific PET, MRI) may be preferable. ■

References

1. Beaulieu JM, Espinoza S, Gainetdinov RR. Dopamine receptors - IUPHAR review 13. *Br J Pharmacol* 2015;172(1):1–23.
2. Horvath J, Fross RD, Kleiner-Fisman G, et al. Severe multivalvular heart disease: a new complication of the ergot derivative dopamine agonists. *Mov Disord* 2004;19(6):656–662.
3. Lopez AM, Weintraub D, Claassen DO. Impulse control disorders and related complications of Parkinson's disease therapy. *Semin Neurol* 2017;37(2):186–192.
4. Thobois S, Vingerhoets F, Fraix V, et al. Role of dopaminergic treatment in dopamine receptor down-regulation in advanced Parkinson disease: a positron emission tomographic study. *Arch Neurol* 2004; 61(11):1705–1709.
5. Lee T, Seeman P, Rajput A, Farley IJ, Hornykiewicz O. Receptor basis for dopaminergic supersensitivity in Parkinson's disease. *Nature* 1978;273(5657):59–61.
6. Brooks DJ, Ibanez V, Sawle GV, et al. Striatal D2 receptor status in patients with Parkinson's disease, striatonigral degeneration, and progressive supranuclear palsy, measured with 11C-raclopride and positron emission tomography. *Ann Neurol* 1992;31(2):184–192.
7. Antonini A, Schwarz J, Oertel WH, Beer HF, Madeja UD, Leenders KL. [11C]raclopride and positron emission tomography in previously untreated patients with Parkinson's disease: influence of L-dopa and lisuride therapy on striatal dopamine D2-receptors. *Neurology* 1994;44(7):1325–1329.
8. Staffen W, Honold N, Trinka E, Zenzmaier R, Ladurner G. SPET investigations in extrapyramidal diseases using specific ligands. *Nucl Med Commun* 1997;18(2):159–163.
9. Samii A, Markopoulou K, Wszolek ZK, et al. PET studies of parkinsonism associated with mutation in the alpha-synuclein gene. *Neurology* 1999;53(9):2097–2102.
10. Plotkin M, Amthauer H, Klaffke S, et al. Combined 123I-FP-CIT and 123I-IBZM SPECT for the diagnosis of parkinsonian syndromes: study on 72 patients. *J Neural Transm (Vienna)* 2005;112(5):677–692.
11. Kim YJ, Ichise M, Ballinger JR, et al. Combination of dopamine transporter and D2 receptor SPECT in the diagnostic evaluation of PD, MSA, and PSP. *Mov Disord* 2002;17(2):303–312.
12. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097.
13. Van Rhee HJ, Suurmond R, Hak T. User Manual for Meta-Essentials: Workbooks for Meta-Analysis (Version 1.0). Erasmus Research Institute of Management: Rotterdam, The Netherlands; 2015.
14. Borenstein M. Effect sizes for continuous data. In: Cooper H, Hedges LV, Valentine JC, eds. *The Handbook of Research Synthesis and Meta-Analysis*. New York, NY: Russell Sage Foundation; 2009:221–235.
15. Rutgers AW, Lakke JP, Paans AM, Vaalburg W, Korf J. Tracing of dopamine receptors in hemiparkinsonism with positron emission tomography (PET). *J Neurol Sci* 1987;80(2–3):237–248.
16. Knable MB, Jones DW, Coppola R, et al. Lateralized differences in iodine-123-IBZM uptake in the basal ganglia in asymmetric Parkinson's disease. *J Nucl Med* 1995;36(7):1216–1225.
17. Wenning GK, Donnemiller E, Granata R, Riccabona G, Poewe W. 123I-beta-CIT and 123I-IBZM-SPECT scanning in levodopa-naive Parkinson's disease. *Mov Disord* 1998;13(3):438–445.
18. Kaasinen V, Ruottinen HM, Nägren K, Lehtikainen P, Oikonen V, Rinne JO. Upregulation of putaminal dopamine D2 receptors in early Parkinson's disease: a comparative PET study with [11C]raclopride and [11C]N-methylspiperone. *J Nucl Med* 2000;41(1): 65–70.
19. Baron JC, Mazière B, Loc'h C, et al. Loss of striatal [76Br] bromospiperone binding sites demonstrated by positron tomography in progressive supranuclear palsy. *J Cereb Blood Flow Metab* 1986; 6(2):131–136.
20. Hägglund J, Aquilonius SM, Eckernäs SA, et al. Dopamine receptor properties in Parkinson's disease and Huntington's chorea evaluated by positron emission tomography using 11C-N-methyl-spiperone. *Acta Neurol Scand* 1987;75(2):87–94.
21. Brücke T, Podreka I, Angelberger P, et al. Dopamine D2 receptor imaging with SPECT: studies in different neuropsychiatric disorders. *J Cereb Blood Flow Metab* 1991;11(2):220–228.

22. Tatsch K, Schwarz J, Oertel WH, Kirsch CM. SPECT imaging of dopamine D2 receptors with 123I-IBZM: initial experience in controls and patients with Parkinson's syndrome and Wilson's disease. *Nucl Med Commun* 1991;12(8):699-707.
23. Sawle GV, Playford ED, Brooks DJ, Quinn N, Frackowiak RS. Asymmetrical pre-synaptic and post-synaptic changes in the striatal dopamine projection in dopa naive parkinsonism. Diagnostic implications of the D2 receptor status. *Brain* 1993;116(Pt 4):853-867.
24. Shinotoh H, Hirayama K, Tateno Y. Dopamine D1 and D2 receptors in Parkinson's disease and striatonigral degeneration determined by PET. *Adv Neurol* 1993;60:488-493.
25. Brücke T, Wenger S, Asenbaum S, et al. Dopamine D2 receptor imaging and measurement with SPECT. *Adv Neurol* 1993;60:494-500.
26. Cordes M, Hierholzer J, Schelosky L, et al. IBZM-SPECT imaging in Parkinson's disease. Quantification of binding ratios from sequential SPECT measurements in patients and controls. *Adv Neurol* 1993;60:525-528.
27. Pizzolato G, Chierichetti F, Rossato A, et al. Dopamine receptor SPET imaging in Parkinson's disease: a [123I]-IBZM and [99mTc]-HM-PAO study. *Eur Neurol* 1993;33(2):143-148.
28. Laulumaa V, Kuikka JT, Soininen H, Bergström K, Lämsimies E, Riekkinen P. Imaging of D2 dopamine receptors of patients with Parkinson's disease using single photon emission computed tomography and iodobenzamide I 123. *Arch Neurol* 1993;50(5):509-512.
29. van Royen E, Verhoeff NF, Speelman JD, Wolters EC, Kuiper MA, Janssen AG. Multiple system atrophy and progressive supranuclear palsy. Diminished striatal D2 dopamine receptor activity demonstrated by 123I-IBZM single photon emission computed tomography. *Arch Neurol* 1993;50(5):513-516.
30. Giobbe D, Castellano GC, Podio V. Dopamine D2 receptor imaging with SPECT using IBZM in 16 patients with Parkinson disease. *Ital J Neurol Sci* 1993;14(2):165-169.
31. Schwarz J, Antonini A, Tatsch K, Kirsch CM, Oertel WH, Leenders KL. Comparison of 123I-IBZM SPECT and 11C-raclopride PET findings in patients with parkinsonism. *Nucl Med Commun* 1994;15(10):806-813.
32. Hublin C, Launes J, Nikkinen P, Partinen M. Dopamine D2-receptors in human narcolepsy: a SPECT study with 123I-IBZM. *Acta Neurol Scand* 1994;90(3):186-189.
33. Schulz JB, Klockgether T, Petersen D, et al. Multiple system atrophy: natural history, MRI morphology, and dopamine receptor imaging with 123I-IBZM-SPECT. *J Neurol Neurosurg Psychiatry* 1994;57(9):1047-1056.
34. Antonini A, Vontobel P, Psylla M, et al. Complementary positron emission tomographic studies of the striatal dopaminergic system in Parkinson's disease. *Arch Neurol* 1995;52(12):1183-1190.
35. Buck A, Westera G, Sutter M, Albani C, Kung HF, von Schulthess GK. Iodine-123-IBF SPECT evaluation of extrapyramidal diseases. *J Nucl Med* 1995;36(7):1196-1200.
36. Nadeau SE, Couch MW, Devane CL, Shukla SS. Regional analysis of D2 dopamine receptors in Parkinson's disease using SPECT and iodine-123-iodobenzamide. *J Nucl Med* 1995;36(3):384-393.
37. Rinne JO, Laihinne A, Ruottinen H, et al. Increased density of dopamine D2 receptors in the putamen, but not in the caudate nucleus in early Parkinson's disease: a PET study with [11C]raclopride. *J Neurol Sci* 1995;132(2):156-161.
38. Pizzolato G, Chierichetti F, Rossato A, et al. Alterations of striatal dopamine D2 receptors contribute to deteriorated response to L-dopa in Parkinson's disease: a [123I]-IBZM SPET study. *J Neural Transm Suppl* 1995;45:113-122.
39. Cordes M, Hierholzer J, Schelosky L, et al. Iodine-123-iodo-lisuride SPECT in Parkinson's disease. *J Nucl Med* 1996;37(1):22-25.
40. Antonini A, Schwarz J, Oertel WH, Pogarell O, Leenders KL. Long-term changes of striatal dopamine D2 receptors in patients with Parkinson's disease: a study with positron emission tomography and [11C]raclopride. *Mov Disord* 1997;12(1):33-38.
41. Turjanski N, Lees AJ, Brooks DJ. In vivo studies on striatal dopamine D1 and D2 site binding in L-dopa-treated Parkinson's disease patients with and without dyskinesias. *Neurology* 1997;49(3):717-723.
42. Pirker W, Asenbaum S, Wenger S, et al. Iodine-123-epidepride-SPECT: studies in Parkinson's disease, multiple system atrophy and Huntington's disease. *J Nucl Med* 1997;38(11):1711-1717.
43. Schwarz J, Tatsch K, Gasser T, Arnold G, Oertel WH. [123I]IBZM binding predicts dopaminergic responsiveness in patients with parkinsonism and previous dopaminomimetic therapy. *Mov Disord* 1997;12(6):898-902.
44. Antonini A, Leenders KL, Vontobel P, et al. Complementary PET studies of striatal neuronal function in the differential diagnosis between multiple system atrophy and Parkinson's disease. *Brain* 1997;120(Pt 12):2187-2195.
45. Hierholzer J, Cordes M, Venz S, et al. Loss of dopamine-D2 receptor binding sites in parkinsonian plus syndromes. *J Nucl Med* 1998;39(6):954-960.
46. Ichise M, Kim YJ, Ballinger JR, et al. SPECT imaging of pre- and postsynaptic dopaminergic alterations in L-dopa-untreated PD. *Neurology* 1999;52(6):1206-1214.
47. Dentresangle C, Veyre L, Le Bars D, et al. Striatal D2 dopamine receptor status in Parkinson's disease: an [18F]dopa and [11C]raclopride PET study. *Mov Disord* 1999;14(6):1025-1030.
48. Hilker R, Klein C, Ghaemi M, et al. Positron emission tomographic analysis of the nigrostriatal dopaminergic system in familial parkinsonism associated with mutations in the parkin gene. *Ann Neurol* 2001;49(3):367-376.
49. Prunier C, Tranquart F, Cottier JP, et al. Quantitative analysis of striatal dopamine D2 receptors with 123 I-iodolisuride SPECT in degenerative extrapyramidal diseases. *Nucl Med Commun* 2001;22(11):1207-1214.
50. Arnold G, Tatsch K, Kraft E, Oertel WH, Schwarz J. Steele-Richardson-Olszewski-syndrome: reduction of dopamine D2 receptor binding relates to the severity of midbrain atrophy in vivo: (123I)IBZM SPECT and MRI study. *Mov Disord* 2002;17(3):557-562.
51. Ghaemi M, Raethjen J, Hilker R, et al. Monosymptomatic resting tremor and Parkinson's disease: a multitracer positron emission tomographic study. *Mov Disord* 2002;17(4):782-788.
52. Oyanagi C, Katsumi Y, Hanakawa T, et al. Comparison of striatal dopamine D2 receptors in Parkinson's disease and progressive supranuclear palsy patients using [123I] iodobenzofuran single-photon emission computed tomography. *J Neuroimaging* 2002;12(4):316-324.
53. Hilker R, Voges J, Ghaemi M, et al. Deep brain stimulation of the subthalamic nucleus does not increase the striatal dopamine concentration in parkinsonian humans. *Mov Disord* 2003;18(1):41-48.
54. Schreckenberger M, Hägele S, Siessmeier T, et al. The dopamine D2 receptor ligand 18F-desmethoxyfallypride: an appropriate fluorinated PET tracer for the differential diagnosis of parkinsonism. *Eur J Nucl Med Mol Imaging* 2004;31(8):1128-1135.
55. Scherfler C, Khan NL, Pavese N, et al. Striatal and cortical pre- and postsynaptic dopaminergic dysfunction in sporadic parkin-linked parkinsonism. *Brain* 2004;127(Pt 6):1332-1342.
56. Seppi K, Schocke MF, Donnemiller E, et al. Comparison of diffusion-weighted imaging and [123I]IBZM-SPECT for the differentiation of patients with the Parkinson variant of multiple system atrophy from those with Parkinson's disease. *Mov Disord* 2004;19(12):1438-1445.
57. Mishina M, Ishiwata K, Ishii K, et al. Function of sigma1 receptors in Parkinson's disease. *Acta Neurol Scand* 2005;112(2):103-107.
58. Nakagawa M, Kuwabara Y, Taniwaki T, et al. PET evaluation of the relationship between D2 receptor binding and glucose metabolism in patients with parkinsonism. *Ann Nucl Med* 2005;19(4):267-275.
59. Strafella AP, Ko JH, Grant J, Fraraccio M, Monchi O. Corticostriatal functional interactions in Parkinson's disease: a rTMS/[11C]raclopride PET study. *Eur J Neurosci* 2005;22(11):2946-2952.
60. Hesse S, Oehlwein C, Barthel H, et al. Possible impact of dopamine SPECT on decision-making for drug treatment in Parkinsonian syndrome. *J Neural Transm (Vienna)* 2006;113(9):1177-1190.
61. Strafella AP, Ko JH, Monchi O. Therapeutic application of transcranial magnetic stimulation in Parkinson's disease: the contribution of expectation. *Neuroimage* 2006;31(4):1666-1672.
62. Verstappen CC, Bloem BR, Haaxma CA, Oyen WJ, Horstink MW. Diagnostic value of asymmetric striatal D2 receptor upregulation in

- Parkinson's disease: an [123I]IBZM and [123I]FP-CIT SPECT study. *Eur J Nucl Med Mol Imaging* 2007;34(4):502–507.
63. Ribeiro MJ, Thobois S, Lohmann E, et al. A multitracers dopaminergic PET study of young-onset parkinsonian patients with and without parkin gene mutations. *J Nucl Med* 2009;50(8):1244–1250.
 64. Ishibashi K, Ishii K, Oda K, Kawasaki K, Mizusawa H, Ishiwata K. Regional analysis of age-related decline in dopamine transporters and dopamine D2-like receptors in human striatum. *Synapse* 2009;63(4):282–290.
 65. Pifarré P, Cuberas G, Hernández J, Lorenzo C, Miquel F, Castell-Conesa J. Cortical and subcortical patterns of I-123 iodobenzamide SPECT in striatal D(2) receptor parkinsonisms. *Clin Nucl Med* 2010;35(4):228–233.
 66. Lin WY, Lin KJ, Weng YH, et al. Preliminary studies of differential impairments of the dopaminergic system in subtypes of progressive supranuclear palsy. *Nucl Med Commun* 2010;31(11):974–980.
 67. Südmeyer M, Antke C, Zizek T, et al. Diagnostic accuracy of combined FP-CIT, IBZM, and MIBG scintigraphy in the differential diagnosis of degenerative parkinsonism: a multidimensional statistical approach. *J Nucl Med* 2011;52(5):733–740.
 68. Hellwig S, Amtage F, Kreft A, et al. [¹⁸F]FDG-PET is superior to [¹²³I]IBZM-SPECT for the differential diagnosis of parkinsonism. *Neurology* 2012;79(13):1314–1322.
 69. Hammesfahr S, Antke C, Mamlins E, et al. FP-CIT- and IBZM-SPECT in Corticobasal syndrome: results from a clinical follow-up study. *Neurodegener Dis* 2016;16(5–6):342–347.
 70. Akamatsu G, Ohnishi A, Aita K, et al. A revisit to quantitative PET with. *Ann Nucl Med* 2017;31(2):163–171.
 71. Mishina M, Ishii K, Kimura Y, et al. Adenosine A1 receptors measured with 11C-MPDX PET in early Parkinson's disease. *Synapse* 2017;71(8). <https://doi.org/10.1002/syn.21979>.
 72. Politis M, Wilson H, Wu K, Brooks DJ, Piccini P. Chronic exposure to dopamine agonists affects the integrity of striatal D. *Neuroimage Clin* 2017;16:455–460.
 73. Stark AJ, Smith CT, Petersen KJ, et al. [18F]fallypride characterization of Striatal and extrastriatal D2/3 receptors in Parkinson's disease. *Neuroimage Clin* 2018;18:433–442.
 74. Sacheli MA, Murray DK, Vafai N, et al. Habitual exercisers versus sedentary subjects with Parkinson's disease: multimodal PET and fMRI study. *Mov Disord* 2018;33(12):1945–1950.
 75. Mela F, Marti M, Bido S, Cenci MA, Morari M. In vivo evidence for a differential contribution of striatal and nigral D1 and D2 receptors to L-DOPA induced dyskinesia and the accompanying surge of nigral amino acid levels. *Neurobiol Dis* 2012;45(1):573–582.
 76. Saucier C, Albert PR. Identification of an endogenous 5-hydroxytryptamine2A receptor in NIH-3T3 cells: agonist-induced down-regulation involves decreases in receptor RNA and number. *J Neurochem* 1997;68(5):1998–2011.
 77. El-Fakahany EE, Lee JH. Agonist-induced muscarinic acetylcholine receptor down-regulation in intact rat brain cells. *Eur J Pharmacol* 1986;132(1):21–30.
 78. Hossain S, Liu HN, Fragoso G, Almazan G. Agonist-induced down-regulation of AMPA receptors in oligodendrocyte progenitors. *Neuropharmacology* 2014;79:506–514.
 79. Afify EA, Law PY, Riedl M, Elde R, Loh HH. Role of carboxyl terminus of mu-and delta-opioid receptor in agonist-induced down-regulation. *Brain Res Mol Brain Res* 1998;54(1):24–34.
 80. Chen JF, Aloyo VJ, Weiss B. Continuous treatment with the D2 dopamine receptor agonist quinpirole decreases D2 dopamine receptors, D2 dopamine receptor messenger RNA and proenkephalin messenger RNA, and increases mu opioid receptors in mouse striatum. *Neuroscience* 1993;54(3):669–680.
 81. Sawamoto N, Piccini P, Hotton G, Pavese N, Thielemans K, Brooks DJ. Cognitive deficits and striato-frontal dopamine release in Parkinson's disease. *Brain* 2008;131(Pt 5):1294–1302.
 82. Cropley VL, Fujita M, Innis RB, Nathan PJ. Molecular imaging of the dopaminergic system and its association with human cognitive function. *Biol Psychiatry* 2006;59(10):898–907.
 83. Baik JH, Picetti R, Saiardi A, et al. Parkinsonian-like locomotor impairment in mice lacking dopamine D2 receptors. *Nature* 1995;377(6548):424–428.
 84. Xu M, Moratalla R, Gold LH, et al. Dopamine D1 receptor mutant mice are deficient in striatal expression of dynorphin and in dopamine-mediated behavioral responses. *Cell* 1994;79(4):729–742.
 85. Drago J, Gerfen CR, Lachowicz JE, et al. Altered striatal function in a mutant mouse lacking D1A dopamine receptors. *Proc Natl Acad Sci U S A* 1994;91(26):12564–12568.
 86. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25(9):603–605.

Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.