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ORIGINAL ARTICLE

Nigrostriatal dopamine transporter availability, and its metabolic and clinical correlates in Parkinson's disease patients with impulse control disorders

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Abstract

Purpose Previous studies in patients with Parkinson's disease (PD) and impulse control disorders (ICDs) have produced heterogeneous results regarding striatal dopamine transporter (DaT) binding and activity in the mesocorticolimbic network. Our aim here was to study the relationship between striatal DaT availability and cortical metabolism, as well as motor, behavioural and cognitive features of PD patients with ICD.

Methods In a group of PD patients with ICD (PD-ICD, $n = 16$) and 16 matched PD patients without ICD (PD-noICD, $n = 16$), DaT single-photon emission computed tomography (SPECT) imaging (DaTSCAN) was used to study DaT availability in predefined striatal volumes of interest (VOIs): putamen, caudate nucleus and ventral striatum (VS). In addition, the specific association of striatal DaT binding with cortical limbic and associative metabolic activity was evaluated by ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in PD-ICD patients and investigated using statistical parametric mapping (SPM8). Finally, associations between DaT availability and motor, behavioural and cognitive features were assessed.

Results PD-ICD patients had a significantly lower DaT density in the VS than PD-noICD patients, which was inversely associated with ICD severity. Lower DaT availability in the VS was associated with lower FDG uptake in several cortical areas belonging to the limbic and associative circuits, and in other regions involved in reward and inhibition processes ($p < 0.0001$ uncorrected; $k > 50$ voxels). No significant results were observed using a higher conservative threshold ($p < 0.05$; FDR corrected). PD-ICD patients also displayed impairment in interference and attentional Stroop Task execution, and more anxiety, all associated with reduced DaT availability in the VS and caudate nucleus.

Conclusions ICDs in PD patients are related to reduced DaT binding in the VS, which accounts for dysfunction in a complex cortico-subcortical network that involves areas of the mesolimbic and mesocortical systems, being associated with reward evaluation, salience attribution and inhibitory control processes.

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Keywords Parkinson's disease · Impulse control disorders · Dopamine transporter · Cerebral metabolism · Cognition

Introduction

Dopamine transporter (DaT) imaging with single-photon emission computed tomography (SPECT) has been used extensively to visualize striatal dopaminergic depletion in Parkinson's disease (PD) patients. The striatum is functionally subdivided into limbic [ventral striatum (VS)], associative [caudate nucleus (CN) and ventral putamen] and motor [dorsal CN and dorsal putamen] regarding their relationship with cortical areas and midbrain dopaminergic nuclei [ventral tegmental area (VTA) and substantia nigra pars compacta (SNc)] [1, 2]. Afferences of the limbic striatum are mostly from the ventromedial prefrontal cortex, orbitofrontal cortex and anterior cingulate cortex (ACC), whilst afferences of the associative and motor striatum come from associative cortices including the dorsolateral prefrontal cortex (PFC), supplementary motor cortex and motor cortex, respectively. Furthermore, these three striatal systems are functionally and spatially overlapped thus showing an ascending spiral between regions originating from the shell of the VS via mesencephalic dopamine cells [1].

The most severe dopaminergic cell loss in PD patients is found in the ventrolateral SNc, which mainly innervates the dorsolateral putamen, a structure involved in controlling movement through the motor circuit of the basal ganglia. Accordingly, reduced [^{123}I]FP-CIT binding to the DaT in the posterior putamen contributes directly to motor signs in PD patients, correlating inversely with bradykinesia and rigidity [3].

A milder reduction in DaT density is also observed early in PD patients in the CN and VS, structures that receive innervation mainly from the ventromedial and dorsal parts of the SNc, or from the VTA, respectively. Dopaminergic denervation plays a major role in the expression of behavioural and cognitive disturbances in PD patients, although other non-dopaminergic neurotransmitter systems are also involved, such as the serotonergic or cholinergic systems [4]. Thus, apathy, depression and anxiety have been related to dopaminergic dysfunction within the mesolimbic circuit (specifically in the VS for apathy, and in the CN for anxiety and depression [5]), while executive dysfunction has been related to CN-PFC dopaminergic disturbances in the mesocortical circuit [6].

Impulse control disorders (ICDs) such as pathological gambling (PG), hypersexuality (HS), binge eating (BE) and compulsive shopping (CS), as well as other impulsive-compulsive behaviours (ICBs) that include punding or hobbyism, are commonly observed in PD patients treated with dopaminergic drugs, with a prevalence around 14% [7]. Studies in these patients have reported abnormalities in dopaminergic pathways [8]. In fact, neuroimaging studies that focus on the dopaminergic system in PD patients with ICDs (PD-ICD) showed that these patients have a decreased synaptic DaT availability in the VS [9], yet not all cases show this result [10]. Moreover, reduced DaT availability predates the incidence of ICD [11]. Taken together, these findings could suggest an effect of reduced DaT availability in the VS on the development of ICD symptoms.

In addition, perfusion SPECT and functional magnetic resonance imaging (fMRI) studies have shown reduced or enhanced activation in regions known to support cognitive control and the inhibition of inappropriate behaviours, such as the PFC, inferior frontal cortex (IFC) and ACC [12, 13]. Additionally, studies that have investigated cognitive characteristics associated with ICDs in PD have also yielded mixed results, linking this condition to an impairment in reward evaluation, decision making and inhibitory control processes in some [14] but not all cases [15]. Previous inconsistencies among studies could be due to methodological factors such as inclusion of heterogeneous cohorts of patients, pharmacological states of the patients (*on* and *off* medication state) or different imaging techniques, thus not reaching robust conclusions.

Therefore, despite the studies undertaken to date, the pathophysiology of ICDs in PD remains poorly understood. In this context, there is a need to study the DaT availability, and the association between striatal DaT expression and functional brain abnormalities in these patients. In addition, the relationship between such DaT density, the clinical severity of ICDs and the motor, behavioural and cognitive manifestations is also of interest. Therefore, the main goal of this study was (i) to investigate the regional striatal differences in dopaminergic DaT binding ratio (BR) between PD-ICD patients and PD patients without ICD (PD-noICD) using ^{123}I-FP-CIT SPECT; (ii) to examine the relationship between DaT availability in each striatal region and the cortical metabolism of limbic and associative areas assessed by ^{18}F-fluorodeoxyglucose (FDG) PET in PD-ICD patients; and (iii) to study the association of striatal DaT BR with motor, behavioural and cognitive manifestations.

Methods

Subjects

This study was carried out on 32 patients with PD, diagnosed according to the UK Parkinson's Disease Society Brain Bank criteria (16 PD-ICD patients and 16 PD-noICD patients), matched by age, gender, education, premorbid intelligence quotient (IQ) and disease severity, and who were recruited at the Movement Disorders Unit at the Hospital Donostia (HUD). The inclusion criteria for the ICD group were at least one current ICD that had emerged after PD diagnosis and the

initiation of dopaminergic treatment. Each patient was routinely asked about any abnormal behaviour, and both a neurologist and a psychiatrist detected and confirmed ICD presence based on the Diagnostic and Statistical Manual of Mental Disorders research criteria and on the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease [16]. Afterwards, ICD severity was scored using the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) [17]. We also confirmed that in every ICD subtype detected in each patient, the score in the QUIP-RS was above the established cutoff value. We excluded patients with dementia [18], mild cognitive impairment [19] or dyskinesias, those who had undergone brain surgery, patients with a history of ICD prior to PD onset, and those ICD patients who were no longer symptomatic when examined. The protocol for this study was approved by Gipuzkoa's Clinical Research Ethics Committee. Patients gave their written informed consent prior to their enrolment.

Demographic and clinical assessment

All assessments were carried out under the effect of the first morning dose of usual dopaminergic medication. Motor assessment was performed using the Unified Parkinson's Disease Rating Scale (UPDRS-III) and the Hoehn and Yahr scale. The total levodopa equivalent daily dose ($LEDD_{TOTAL}$), the daily levodopa dose ($LEDD_{L\text{-}DOPA}$) and the levodopa equivalent daily dose of dopamine agonist ($LEDD_{DA}$) [20] were also calculated. Behavioural scales included the Hospital Anxiety and Depression Scale (HADS), the Novelty Seeking subscale of the revised Temperament and Character Inventory (TCI-R), the Barratt Impulsiveness scale (BIS), the Starkstein Apathy Scale and the Parkinson's Disease Questionnaire (PDQ-8). In addition, a cognitive evaluation was performed using the Montreal Cognitive Assessment (MoCA) to assess global cognition and an extensive neuropsychological battery for the cognitive domains. Moreover, the computerized version of the Iowa Gambling Task (IGT) was used, a task that simulates real-life decision making [21] in which patients have to choose between four decks of cards in trying to win as much money as possible in five blocks of trials. The subject must take into account that some decks will tend to reward the player (advantageous) more often than other decks (disadvantageous: see Supplementary data for further details).

Image data acquisition

^{123}I-FP-CIT SPECT (DaTSCAN)

To measure presynaptic striatal DaT availability, all patients underwent a ^{123}I-2β-carbometoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl) nortropane (^{123}I-FP-CIT) SPECT scan (DaTSCAN®, GE Healthcare) at the Nuclear Medicine Unit of the Instituto Onkologikoa (San Sebastian, Spain). In compliance with the EANM 2010 Imaging Guidelines, patients were required to stop any medication that would bind to the DaT 7 days prior to the scan. All patients received 1% Lugol's solution (Hi-Tech Pharmaceuticals, Norcross, GA, USA) to block thyroid uptake of free radioactive iodide. The ^{123}I-FP-CIT radiotracer was administered intravenously 3 h before image acquisition at an approximate dose of 5 mCi (185 MBq: specific activity >185 MBq/nmol; radiochemical purity >99%). The acquisition of SPECT images was undertaken with a multislice spiral SPECT/TC (Infinia Hawkeye 4, GE Healthcare). Two hundred and forty projections were acquired over a 2 × 360° orbit using low-energy high-resolution (LEHR) collimators, a 128 × 128 pixel matrix with a 1.23 zoom, continuous rotation and angular sampling of 3°. Each projection was acquired for 16 s, and the overall scanning time for each patient was 38 min. The raw projection data sets were later processed to obtain the reconstructed images using a back-filtered projection with post-reconstruction filtering (Butterworth 10th order, cutoff 0.64 cycles/cm).

MRI imaging

All patients were scanned in a 3T Siemens Magnetom TIM TRIO MRI scanner (Siemens Medical Solutions, Erlangen, Germany) using a 32-channel head coil. Structural T1-weighted images were acquired using an MPRAGE sequence, with TR = 2530 ms, TE = 2.97 ms, inversion time = 1100 ms, flip angle = 7°, FOV = 256 × 256 mm and voxel size = 1 mm^3 (isotropic).

^{18}F-FDG PET

PD-ICD patients also underwent an integrated PET-computed tomography (CT) study with a Siemens Biograph 6 scanner (Siemens, Erlangen, Germany). All subjects fasted overnight before PET scanning, and their blood glucose was checked prior to radiopharmaceutical injection to ensure it was <120 mg/dL. After a few minutes with the subject awake, in a resting state and under low lighting, ^{18}F-FDG (bolus injection of 5.3 MBq/kg) was injected intravenously, and the subjects were required to rest for 40 min in the supine position on the PET scanner bed with their eyes closed. Subsequently, 74 planes (a 128 × 128 matrix) were acquired with a voxel size of 2.06 × 2.06 × 2.06 mm during a 20-min scan. At the end of the acquisition period, attenuation correction was derived from the CT data [22]. PET images were reconstructed with an ordered-subset expectation maximization (OSEM) method using Siemens software (version 7.2). All DaTSCAN, MRI and FDG PET studies were performed on the same patient over 72 h.

Image handling and processing

^{123}I-FP-CIT SPECT (DaTSCAN)

SPECT image data were preprocessed using the Statistical Parametric Mapping (SPM) software (SPM8, Wellcome Department of Neurology, London, UK) in Matlab (version R2014a, MathWorks, Natick, MA, USA). First, we co-registered each subject's DaT image with their corresponding MRI images. DaT images were corrected for a partial volume effect using the voxel-by-voxel method [23]. We then normalized the structural MRI scan to the Montreal Neurological Institute (MNI) space and applied the resulting normalization parameters to the DaT image, while correcting for volume changes induced by normalization. Spatially normalized ^{123}I-FP-CIT SPECT scans showed the DaT with detectable specific tracer uptake confined to the striatum. Second, a volume of interest (VOI) analysis was performed using PMOD software (version 3.2; PMOD Technologies Ltd., Adliswil, Switzerland) to quantify the ^{123}I-FP-CIT SPECT images. A brain atlas generated with the PMOD software contains a predefined delineation of the CN and putamen to guide the manually established VS outline from −6 to −12 mm in the z axis [MNI coordinates], thus including the nucleus accumbens, medial CN and rostroventral putamen [9, 24] based in functional anatomy and previous structural connectivity works [1, 25]. Moreover, the right and left CN and putamen VOIs were redefined as the extension of the whole atlas, except in the z axis < −6 mm. Thus, six custom-defined VOIs from the striatum were finally used, three in each hemisphere (Supplementary Fig. 1). Tracer binding in the occipital lobe was used as a reference, as the occipital cortex is assumed to not express DaT [26]. The outcome measure was the specific-to-non-displaceable BR: (striatal BR – occipital BR) / occipital BR. These values were calculated for the right and left CN, putamen and VS [27], and the average BR values for both sides and VOIs (CN, putamen and VS) were used for analysis.

^{18}F- FDG PET

All ^{18}F-FDG PET images were realigned and spatially normalized into a standard stereotaxic MNI space using an ^{18}F-FDG PET template previously customized by our group [28]. All images were corrected for a partial volume effect using the voxel-by-voxel method [29]. For every spatially normalized PET image, voxel values were normalized to the pons activity using the pons VOI as a reference region (Nifti format) from WFU PickAtlas v3.0 as described previously [28, 30]. Finally, the resulting PET images were smoothed using an isotropic 8-mm full-width at half-maximum (FWHM) Gaussian filter to blur the individual variations in gyral anatomy and to increase the signal-to-noise ratio. An application with components of the Yale BioImage Suite Package (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html) was used to transform the MNI coordinates into a Talairach space, and anatomical locations were found using the Talairach Client [31].

Statistical analysis

The normality of the distribution of the variables was assessed using the Shapiro–Wilk test. Differences in the demographic and clinical features between the PD groups were analysed using two-sample *t* tests for continuous and normally distributed variables, or a Mann–Whitney *U* test for continuous and non-parametric variables. A Chi-squared test was used to examine the differences between categorical measures. Performance in the IGT was analysed following the standard procedure of dividing the task into five blocks of 20 consecutive card selections (see Supplementary text) [21], and a mixed-model analysis of variance (ANOVA) was applied, with group as a between-subject factor, block as a within-subject factor and the net score (advantageous decks – disadvantageous decks) as the dependent measure.

Regarding VOI-based analyses of the ^{123}I-FP-CIT SPECT data, differences in DaT availability were examined using an analysis of covariance (ANCOVA) according to the factors of group (PD-ICD or PD-noICD), side (right or left) and area (CN, putamen, VS). This analysis was adjusted by age and UPDRS-III as covariates, as these factors were the main contributors to general dopamine loss in PD patients [32, 33], applying post hoc Bonferroni multiple comparisons. A multiple linear regression analysis was then performed to study the associations between these factors (group, side and area).

In PD-ICD patients, the correlation between the binding of [^{123}I]FP-CIT to the DaT of the different striatal regions and ^{18}F-FDG uptake of limbic and associative areas was assessed using a SPM regression analysis, considering an uncorrected significance at the voxel level of $p < 0.0001$, as the present statistical approach is driven by an a priori hypothesis of specific striatal-cortical associations. Further family-wise error (FWE) correction for cluster volume of >50 voxels was also performed.

Finally, a two-step approach was used to explore the association of DaT density with clinical variables. First, a bivariate Spearman's correlation analyses was performed and a Benjamini-Hochberg false discovery rate (FDR) correction for multiple comparisons was applied to minimize the chance of false-positive findings. Then, significant correlations were included in a multiple linear regression analysis in which age and motor disability (UPDRS-III) were entered as covariates. When the dependent variable was not normally distributed, a logarithmic transformation was performed. A two-tailed probability value of <0.05 was regarded as significant (SPSS Statistics v16.0, SPSS Inc., Chicago, IL, USA).

Results

Clinical data

The general demographic, motor and behavioural features of the PD-ICD and PD-noICD patients are summarized in Table 1. No differences were evident in the patient's demographics, dopaminergic medication, motor severity or disease duration. The impulsiveness and anxiety scores were significantly higher in PD-ICD patients than in PD-noICD patients. Among the former, there were seven patients that reported a single 'isolated' ICD and nine patients with 'combined' ICD/ICB (Supplementary Table 1).

The cognitive data obtained are summarized in Table 2. PD-ICD patients showed stronger impairment than PD-noICD patients in the three different conditions of the Stroop Color-Word Interference Test (SCWT, Stroop Word, Stroop Color and Stroop Color-Word Interference). By contrast, ANOVA of the net IGT scores revealed no significant main effect of group [F (1, 30) = 0.60, $p = 0.44$, η_p^2 0.02], or any interaction. No other differences were observed.

Regional differences in DaT availability

DaT density analysis

An ANCOVA analysis with age and UPDRS-III as covariates revealed that the binding of [^{123}I]FP-CIT to the DaT was significantly different between the group (F (2, 191) = 8.32: $p = 0.004$, η_p^2 0.12) and area (F (2, 191) = 4.83: $p = 0.03$, η_p^2 0.08)

Table 1 Demographic, motor and behavioural characteristics of PD patients

	PD-ICD $n = 16$	PD-noICD $n = 16$	p value
Age	61.5 ± 8.8	61.8 ± 7.9	0.917[a]
Sex, male (%)	14 (87.5)	13 (81.3)	0.626[c]
Education (years)	12.5 [9–19]	11.5 [9.2–17.5]	0.790[b]
Premorbid-IQ (WAIS-III vocabulary sub-test)	44.4 (9.1)	45.1 (10.6)	0.832[a]
Disease duration (years)	8 [6–10]	6 [4–10]	0.471[b]
$LEDD_{TOTAL}$ (mg)	917 (183.2)	816 (199.8)	0.102[a]
$LEDD_{DA}$ (mg)	324.4 (135.6)	302 (151.2)	0.814[a]
$LEDD_{L\text{-}DOPA}$ (mg)	775.5 (154.3)	643.9 (166.3)	0.178[a]
UPDRS-III	20.2 (6.8)	24.2 (8.6)	0.152[a]
H & Y stage	2 [1–2.5]	2 [1.5–2]	0.485[b]
HADS total	8 [5–18.8]	4.5 [2–5.8]	0.003[b]
HADS anxiety	5.6 (4.2)	3.2 (2.1)	0.039[a]
HADS depression	3.5 [1.2–7.5]	2.5 [0.8–3.7]	0.108[b]
TCI-R Novelty Seeking total	97 [89–103.7]	85 [74.2–92]	0.006[b]
NS1: Exploratory excitability	28 (5.9)	26.2 (4.4)	0.335[a]
NS2: Impulsiveness	26.2 (6.7)	19.25 (3.7)	0.001[a]
NS3: Extravagance	27.1 (4.2)	24.9 (3.2)	0.359[a]
NS4: Disorderliness	18.5 (6.1)	14.8 (3.9)	0.023[a]
BIS total	44 [30.2–61.2]	30 [26.2–38]	0.019[a]
I: Cognition	13.4 (6.1)	10.2 (3.8)	0.090[a]
II: Motor	14.9 (6.7)	10.3 (4.9)	0.035[a]
III: Lack of planning	14.5 [10–25.5]	9.5 [8–13.8]	0.079[a]
Starkstein Apathy Scale	5 [1.5–7]	3.5 [2–15.2]	0.820[b]
PDQ-8	7 (4.2)	5 (3.6)	0.382[a]
QUIP-RS	14.5 [11–22.2]	–	–

The data are given as absolute numbers, mean (SD), median (IQR) or n (%): [a] Two-sample t test. [b] Mann–Whitney U test. [c] Chi-square

Abbreviations: IQ, intelligence quotient; WAIS-III, Wechsler Adult Intelligence Scale-III; $LEDD_{TOTAL}$, total daily levodopa equivalent dose, calculated according to Parkin et al., 2002: $LEDD_{DA}$, daily levodopa equivalent dose of dopamine agonist according to the same formula; $LED_{L\text{-}DOPA}$, daily levodopa dose is calculated according to the same formula; UPDRS, Unified Parkinson's Disease Rating Scale; H & Y, Hoehn and Yahr scale; HADS, Hospital Anxiety and Depression Scale; TCI-R, Revised Temperament and Character Inventory; NS, Novelty Seeking Subscales; BIS, Barratt Impulsiveness Scale; PDQ-8, Parkinson's Disease Questionnaire; QUIP-RS, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale

Table 2 Cognitive evaluation of PD patients

	PD-ICD $n = 16$	PD-noICD $n = 16$	*P* value
Global cognition assessment			
MoCA	27.7 (2.1)	27 (3.2)	0.099[a]
Attention domain			
Digit span			
• Forward	6 [5–6]	5.5 [5–6.75]	0.695[b]
TMTA	48.5 [35.7–108.2]	51 [37.2–125]	0.624[b]
Stroop			
• Words	85.4 (14.3)	94.5 (13.9)	0.009[a]
• Colors	55.6 (14.6)	62.9 (10.1)	0.004[a]
Executive domain			
TMTB	89 [72.2–144.2]	82 [65.7–112.2]	0.451[b]
Phonemic fluency (initial letter)	14 (2.3)	15 (3.3)	0.300[a]
Stroop words-colors	28.5 (9.4)	39.9 (10.6)	0.0004[a]
LNS	11 [8.2–12]	10 [8–11]	0.294[b]
Digit span			
• Backwards	4 [3–4]	4 [3–4]	0.290[b]
Memory function			
RAVLT			
• Total recall	46.9 (7.2)	43.4 (13.9)	0.371[a]
• Delayed recall	11 [8.2–12.8]	8.5 [4.2–13]	0.414[b]
• Recognition	14 [12–15]	12 [11–14.5]	0.170[b]
Language domain			
Semantic fluency (animals)	16.5 (5.7)	16 (6.5)	0.819[a]
Boston	13 [11.2–13.8]	13 [9.2–14]	0.788[b]
Visuospatial function			
VOSP			
• Object decision	16.9 (2.2)	16.6 (2.6)	0.716[a]
• Number location	10 [10–10]	9.5 [8–10]	0.075[b]
IGT net score from advantageous decks (C–D) minus disadvantageous decks (A–B) over the course of the five blocks			0.444[c]

The data are given as absolute values, mean (SD), median (IQR) or n (%): [a] Two-sample *t* test; [b] Mann–Whitney *U* test; [c] ANOVA with repeated measures

Abbreviations: *MoCA* Montreal Cognitive Assessment, *TMTA* part A of Trail Making Test, *TMTB* part B of Trail Making Test, *LNS* Letter–Number Sequencing, *RAVLT* Rey Auditory Verbal Learning Test, *VOSP* Visual Object and Space Perception Battery, *IGT* Iowa Gambling Task

factors. Subsequently, a multiple linear regression analysis revealed that the existence of lower DaT density in the VS was the only factor significantly associated with ICDs in PD patients (ß = −0.25, t (86) = −3.18: $p = 0.002$, $R^2 = 0.20$).

Correlation between DaT density and FDG regional uptake in PD-ICD patients

DaT availability in the VS positively correlated with the FDG uptake ($p < 0.0001$ uncorrected; $k > 50$ voxels) in the bilateral primary motor cortex, bilateral supplementary motor area (SMA), right anterior PFC, ventral and dorsal ACC, bilateral entorhinal cortex and subgenual area (Fig. 1, Supplementary Table 2). There was also a positive correlation between the DaT density in the CN and the FDG uptake in the left motor cortex ($p < 0.0001$; $k < 50$ voxels: Fig. 2). DaT availability in the putamen was not correlated with FDG in any cortical area. Correlation analysis using a relatively higher conservative threshold did not show any significant result ($p < 0.05$; FDR-corrected).

The association of regional DaT density with clinical variables

In PD-ICD patients, a multiple linear regression analysis showed that the QUIP-RS score was negatively associated with DaT availability in the VS (ß = −0.82, t (14) = −7.1: $p < 0.001$, $R^2 = 0.74$), yet not in the CN or the putamen (Fig. 3, Table 3). The anxiety sub-score of the HADS scale

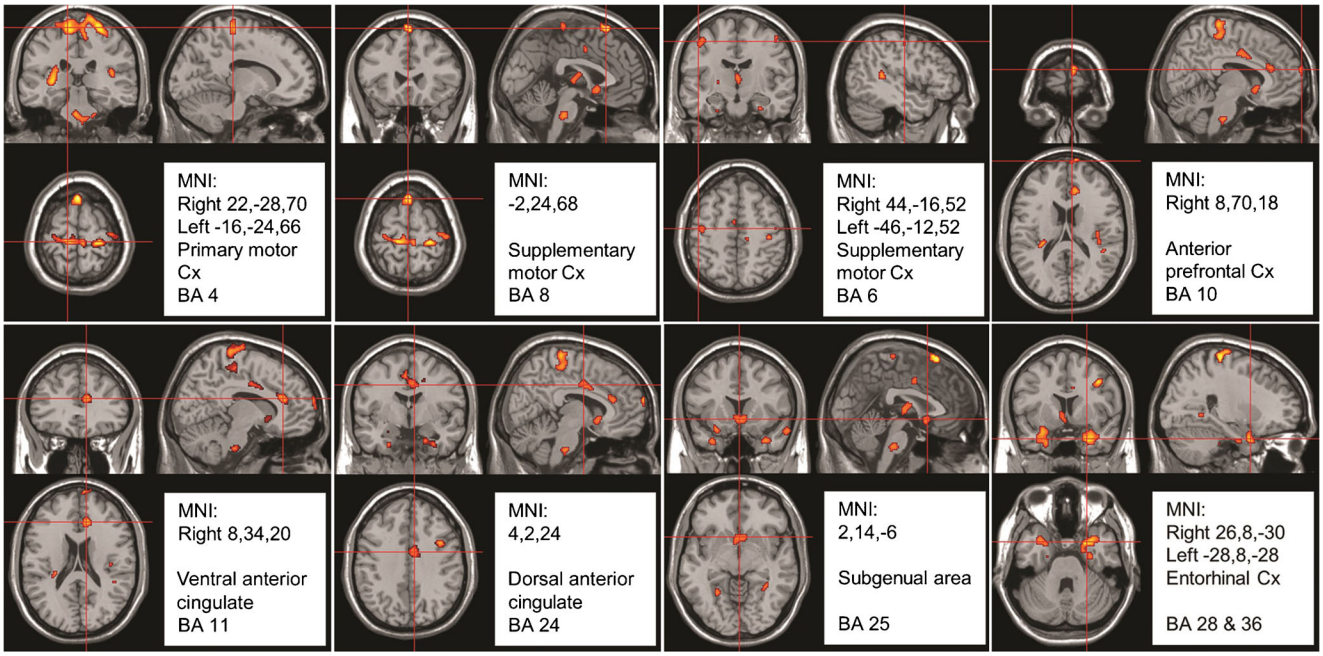

Fig. 1 DaT availability in the VS of PD-ICD patients was positively correlated ($p < 0.0001$ uncorrected) with FDG uptake in the bilateral primary motor cortex, bilateral supplementary motor area, right anterior prefrontal cortex, ventral and dorsal anterior cingulate cortex, bilateral entorhinal cortex and subgenual area. BA = Brodmann area

was inversely associated only with the DaT density in the CN (ß = −0.54, t (14) = −2.24: $p = 0.03$, $R^2 = 0.43$: Fig. 3, Table 3). The Stroop test score was positively associated with DaT availability in the CN (Stroop Word sub-score: ß = 0.75, t (14) = 3.21, $p = 0.001$, $R^2 = 0.52$) and VS (Stroop Color-Word Interference sub-score: ß = 0.69, t (14) = 3.22: $p = 0.004$, $R^2 = 0.58$; Fig. 3). A negative association was observed between the UPDRS-III score and the putamen DaT density in PD-ICD patients (ρ (14) = −0.4: $p = 0.04$; Table 3), although it did not persist when corrected for multiple comparisons. In PD-noICD patients, DaT availability in the putamen was negatively correlated with motor impairment (UPDRS-III: ρ (14) = −0.5: $p = 0.001$; Table 3), while no other association was found between the striatal DaT density and the clinical variables.

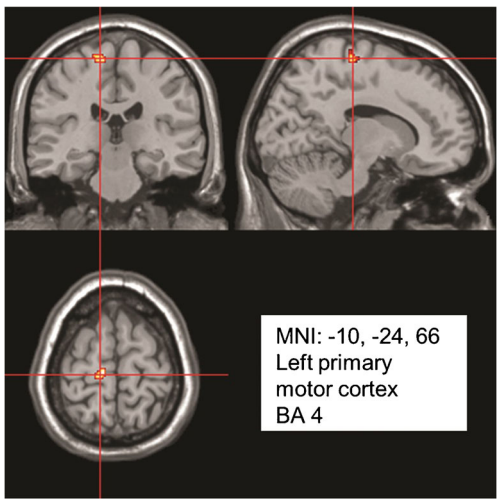

Fig. 2 DaT density in the caudate nucleus of PD-ICD patients was positively correlated with FDG uptake in the left motor cortex. BA = Brodmann area

Discussion

In the present study, reduced DAT availability in the VS in PD-ICD patients was showed when compared to PD-noICD, which in turn was associated with decreased cortical metabolism of mesolimbic and mesocortical areas as well as functionally related regions involved in salience attribution, reward processing and inhibitory control. Moreover, reduction of DaT binding in the VS showed a negative association with clinical severity of ICD. In addition, PD-ICD patients displayed more anxiety, thus performing worse in attentional and interference Stroop task execution that in turn was associated with reduced DaT density in the CN and VS, respectively. To the best of our knowledge, this is the first study showing an association between regional striatal DaT availability, brain metabolism and motor, behavioural and cognitive features of PD-ICD patients.

Reduced dopaminergic innervation in the VS of PD-ICD patients is consistent with previous cross-sectional studies [9, 34], as well as with a longitudinal study on newly diagnosed PD patients, in which the reduction in VS DaT density at baseline and over time was associated with the emergence of ICDs after the initiation of dopaminergic treatment [11].

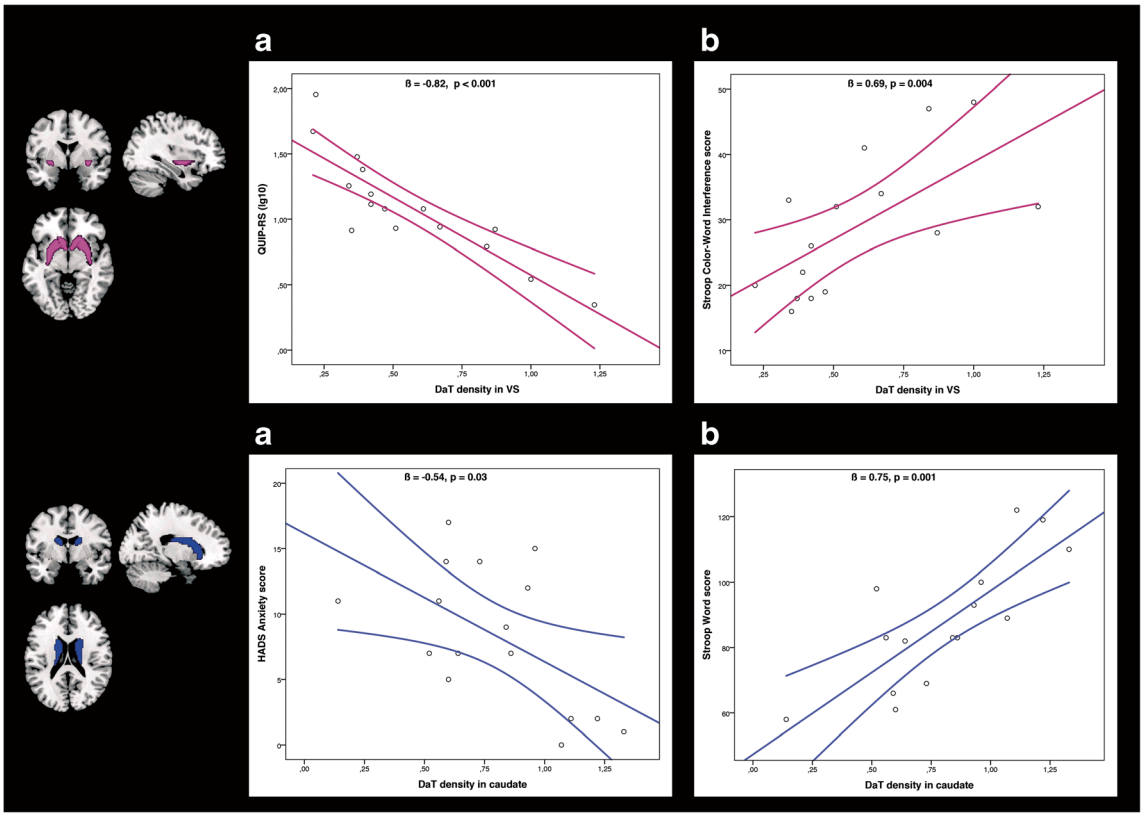

Fig. 3 DaT availability correlates with the clinical variables of PD-ICD patients. Upper panels: (A) DaT density in the VS was negatively correlated with ICD severity (measured by the QUIP-RS score) and (B) it was positively associated with the Stroop Color-Word score (measured as the total number of ink colours named in an interference task). Lower panels: (A) DaT availability in the caudate nucleus was inversely correlated with anxiety (measured with the HADS anxiety score), and (B) it is positively

Table 3 Correlation between striatal [^{123}I]-FP-CIT uptake ratios on SPECT and clinical scores in both groups of PD patients

	PD-ICD			PD-noICD		
	CN Coefficient/p	PN Coefficient/p	VS Coefficient/p	CN Coefficient/p	PN Coefficient/p	VS Coefficient/p
UPDRS-III	−0.1/0.562	−0.4/0.043	0.0/0.991	−0.3/0.802	−0.5/0.001*	−0.2/0.764
HADS total	−0.1/0.602	−0.0/0.887	0.2/0.442	0.1/0.769	0.0/0.852	0.0/0.943
- HADS anxiety	−0.5/0.013*	−0.2/0.322	0.1/0.636	0.1/0.677	0.1/0.520	0.1/0.507
- HADS depression	0.1/0.608	0.1/0.615	0.1/0.654	−0.0/0.898	−0.1/0.647	−0.2/0.367
TCI-R Novelty Seeking total	−0.1/0.686	−0.2/0.351	−0.4/0.099	−0.2/0.424	−0.1/0.502	−0.3/0.186
BIS total	0.2/0.554	−0.0/0.955	−0.1/0.554	−0.3/0.257	−0.3/0.274	−0.0/0.828
QuIP-RS	−0.5/0.080	−0.2/0.448	−0.8/0.000*	–	–	–
MoCA	−0.1/0.744	−0.1/0.795	−0.3/0.280	0.0/0.967	0.2/0.484	0.1/0.767
- Stroop words	0.6/0.012*	−0.5/0.055	0.5/0.085	−0.1/0.634	0.0/0.941	−0.0/0.939
- Stroop colors	−0.0/0.973	0.0/0.936	0.4/0.111	0.0/0.941	0.0/0.789	0.0/0.946
- Stroop words-colors	−0.0/0.973	0.0/0.936	0.5/0.011*	−0.2/0.265	−0.5/0.061	−0.4/0.141

Abbreviations: *UPDRS* Unified Parkinson's Disease Rating Scale, *HADS* Hospital Anxiety and Depression Scale, *TCI-R* Revised Temperament and Character Inventory, *BIS* Barratt Impulsiveness Scale, *QUIP-RS* Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale, *MoCA* Montreal Cognitive Assessment, *CN* caudate nucleus, *PN* putamen nucleus, *VS* ventral striatum, *Coefficient/p* correlation coefficient ρ (rho) / *p* value

* Significant correlation after Bonferroni correction

However, other studies with F-Dopa PET and DaTSCAN did not replicate these results, indicating that the dorsal striatum may also play a role [10, 35, 36]. These discrepancies may be due to methodological issues, such as the use of different dopaminergic radiotracers, imaging techniques, heterogeneous PD-ICD cohorts or different regional striatal subdivisions. In this sense, the strong negative correlation between the DaT BR in the VS and the severity of the ICD showed in the present study reinforces the hypothesis that a reduced availability of DaT in VS is directly involved in the development of ICDs in PD patients.

Another compelling finding is the association between lower DaT availability in the VS and reduced metabolism in several cortical areas pertaining to the limbic and associative circuits, or functionally related regions that are involved in reward processing and inhibitory control. In this sense, the pathophysiological mechanisms underlying ICDs were related to the so-called mesolimbic and mesocortical systems embedded within the mesocorticolimbic network. These involve the VTA, VS, ventral pallidum (VP), amygdala and hippocampus, the mediodorsal thalamus, PFC/orbitofrontal cortex (OFC) and the ACC [37]. The VS receives its main cortical input from the OFC and the ACC, and it is modulated by dopaminergic input from the VTA, projecting to the VP, VTA and the SNc, which in turn projects back to the PFC [25]. Thus, the PFC inhibits emotional responses to salient stimuli involved in aversion-related cognition, which enables actions that result in negative outcomes to be inhibited [38]. Moreover, the ACC and the subgenual area are implicated in discriminative learning, the monitoring of activity and cognitive control [2]. Furthermore, the entorhinal cortex provides contextual memories relevant to motivational stimuli, responses relevant to encoding and retrieval [39]. In addition, the SMA has consistently been recruited in the resolution of conflict, most commonly characterized as intrusion between competing motor plans, although it is also involved in decision conflict [40]. Our results indicate that in PD patients receiving dopaminergic treatment, stronger lack of DaT availability in the VS contributes to the development of impulsive behaviours through hypofunction in some regions of the mesolimbic and mesocortical pathways, which impairs reward-related behaviour and response inhibition [39].

Alternatively, cognitive assessment revealed that PD-ICD patients perform worse in all the conditions of the SCWT, with no significant differences in other tests, including the IGT. Previous neuropsychological assessments of PD-ICD patients revealed controversial results, indicating dysfunction in cognitive control and executive processes in some [41, 42] but not all studies [43, 44]. Impaired conflict resolution and inhibitory control may be a cognitive process underlying poorer SCWT performance [45, 46]. Interestingly, in our PD-ICD patients, there was a positive association between DaT availability in the CN and performance in the Stroop Word test, denoting a loss of speed in `automatic´ processing when CN DaT BR is reduced [46]. Similarly, there was a relationship between DaT availability in the VS and the Stroop Interference sub-test, indicating the involvement of reduced DaT BR in the VS in conflict adaptation [47]. Along similar lines, impaired SCWT performance was associated with lower regional blood flow in the ACC and VS of PD patients treated with deep brain stimulation (DBS) of the subthalamic nucleus (STN) [48]. Thus, in PD-ICD patients, the interaction between dopaminergic treatment and reduced DaT BR in the CN and VS would lead to poor executive function involving automatic processing and conflict resolution, reflecting a dysfunction of attentional, inhibitory efficiency and interference control processes. Moreover, the lack of differences in the IGT task between patients with and without ICD reflects similar risk-taking behaviour, as shown previously in most [49, 50] but not all studies [51].

We also found increased anxiety in PD-ICD patients, in line with a recent meta-analysis [52]. Importantly, we showed that the anxiety scores from PD-ICD patients were negatively associated with DaT availability only in the CN, but not in VS. This finding is in keeping with some [53, 54] but not all [55, 56] previous DaTSCAN studies. Although the aetiology of anxiety in PD is likely to be multifactorial, and the role of other neurotransmitters cannot be overlooked, dysfunction of the dopaminergic system, especially in the CN, seems to be a main contributor, as supported by the fact that anxiety is among the most frequent non-motor fluctuations [57].

We have to acknowledge certain limitations in this study, such as the small sample size and the relatively poor spatial resolution of SPECT. Nevertheless, both groups of patients have been matched by demographic and clinical characteristics in order to reduce variability (age, sex, education, premorbid IQ, disease duration and dopaminergic treatment), and their motor, behavioural and cognitive features were well characterized. In addition, SPECT images were co-registered with the MRIs from the same patient in order to improve anatomical accuracy. Another limitation of the study is that cerebral metabolism was only assessed in the PD-ICD group. The main objective in this work was to investigate the regional striatal differences in DaT BR between the two groups of patients, and afterwards, to ascertain the relationship between DaT BR in different striatal areas and metabolism in limbic and associative areas, which was found to be abnormal in PD-ICD in previous reports. Therefore, focussing on the PD-ICD group, correlations were obtained using a less conservative threshold (uncorrected $p < 0.0001$), as the present statistical approach is driven by an a priori hypothesis of specific striato-cortical associations. Although we also limited the cluster threshold to 50 voxels, we were not able to find any significant correlation with FDR-corrected threshold, which may be due to our sample size, even though we recruited a homogenous cohort of patients, with the presence of ICD being almost the only difference [28]. Moreover, to date this is the first study to comprehensively

assess striatal DaT BR, cortical metabolism and clinical parameters in the same cohort of PD patients with ICD, thus giving light to the present findings. Finally, we want to highlight the fact that, as motor severity (UPDRS-III) and age are strongly linked to reduced DaT BR in PD, we have used them as covariates to overcome this issue, since it may have impeded finding other differences between the two groups [58].

In summary, the results presented in this study emphasize the critical role played by the reduced availability of DaT in the VS in PD-ICD patients. Thus, dopaminergic reduction in VS may predispose PD patients to functional abnormalities in the mesocorticolimbic circuit when treated chronically with dopaminergic drugs, which in turn could lead to the development of ICD. Moreover, reduced DaT density in the VS and CN is associated with an impairment in conflict resolution and inhibitory control in PD-ICD patients, which may reflect dysfunction of the ventral fronto-striatal loops. In these patients, reduced DaT binding in the CN also seems to be related to a higher predisposition to develop affective symptoms, such as anxiety. In conclusion, the present results indicate that reduced DaT availability in the VS is a potentially predictive marker of ICD development in PD patients.

Author contributions M.C.R.-O. and I.N.-G. designed and organized the study; I.N.-G, R.D.-A. and M.C.R.-O. collected the data; M.C.R.-O. supervised the study; A.B.-P., F.M.-D. and I.N.-G. performed the statistical analysis; I.N.-G and M.C.R.-O. interpreted the results of the analysis with substantial contribution from all the authors; I.N.-G. and F.M.-D. drafted the manuscript, to which all the authors contributed with revisions.

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Compliance with ethical standards

Conflict of interest I.N.-G. received honoraria for travel and accommodation to attend scientific meetings from Zambon. R.D.-A., F.M.-D., H.J.-U, B.G. and A.Q.-V. have no disclosures to declare. A.M.-B received honoraria for travel and accommodation from Zambon and Bial. M.C.R.-O. received honoraria for lectures, travel and accommodation to attend scientific meetings from Abbvie, Zambon, Bial and Boston Scientific, and she received financial support for her research from national and local government funding agencies in Spain (Institute of Health Carlos III, Basque Country Local Government, and CIBERNED). M.D.-A. received honoraria for travel and accommodation to attend scientific meetings from UCB and Zambon. None of these bodies influenced the content of the manuscript or the decision to publish in any way.

Ethical approval All the procedures carried out involving human participants were in accordance with the ethical standards of the Gipuzkoa Clinical Research Ethics Committee, and with the principles of the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards.

Informed consent Informed consent was obtained from all the participants prior to their inclusion in the study.

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