# Four

## Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease

Chris Vriend
Anna H. Nordbeck
Jan Booij
Ysbrand D. van der Werf
Tommy Pattij
Pieter Voorn
Pieter Raijmakers
Elisabeth M.J. Foncke
Elsmarieke van de Giessen
Henk W. Berendse
Odile A. van den Heuvel

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## Abstract

Impulse control disorders (ICD) are relatively common in Parkinson's disease (PD) and generally are regarded as adverse effects of dopamine replacement therapy, although certain demographic and clinical risk factors are also involved. Previous single photon emission computed tomography (SPECT) studies showed reduced ventral striatal dopamine transporter binding in Parkinson patients with ICD compared with patients without. Nevertheless, these studies were performed in patients with preexisting impulse control impairments, which impedes clear-cut interpretation of these findings. We retrospectively procured follow-up data from 31 medication-naïve PD patients who underwent dopamine transporter SPECT imaging at baseline and were subsequently treated with dopamine replacement therapy. We used questionnaires and a telephone interview to assess medication status and ICD symptom development during the follow-up period (31.5±12.0 months). Eleven patients developed ICD symptoms during the follow-up period, eight of which were taking dopamine agonists. The PD patients with ICD symptoms at follow-up had higher baseline depressive scores and lower baseline dopamine transporter availability in the right ventral striatum, anterior-dorsal striatum, and posterior putamen compared with PD patients without ICD symptoms. No baseline between-group differences in age and disease stage or duration were found. The ICD symptom severity correlated negatively with baseline dopamine transporter availability in the right ventral and anterior-dorsal striatum. The results of this preliminary study show that reduced striatal dopamine transporter availability predates the development of ICD symptoms after dopamine replacement therapy and may constitute a neurobiological risk factor related to a lower premorbid dopamine transporter availability or a more pronounced dopamine denervation in PD patients susceptible to ICD.

## Introduction

Impulse control disorders (ICD) affect at least 14% of all patients with Parkinson's disease (PD) and are generally regarded as adverse effects of dopamine replacement therapy (Weintraub *et al.* 2010a). ICDs are described as behavioral addictions in which patients no longer have the ability to suppress an impulse, drive, or urge that is potentially dangerous to the patients themselves or their surroundings (American Psychiatric Association 1994). Other than dopamine replacement therapy, early disease onset, male sex, depression, and a positive (family) history of substance abuse are also associated with ICD development (Voon *et al.* 2009; Joutsa *et al.* 2012d). The pathophysiology of ICD in PD is poorly understood, although studies suggest that ICDs are associated with increased ventral striatal dopamine release (Steeves *et al.* 2009; O'Sullivan *et al.* 2011), reduced (ventral) striatal dopamine transporter availability (Cilia *et al.* 2010; Voon *et al.* 2014), and dysfunction of brain areas involved in motivation and reward (van Eimeren *et al.* 2010; Cilia *et al.* 2011). Because the aforementioned studies were performed in PD patients with preexisting impulse control impairments, it is unclear whether these results are the consequence of prolonged dopamine replacement therapy, neuronal adaptations associated with the impulsive behaviors, or a premorbid trait predisposing to ICD.

This study aimed to identify a neurobiological risk factor for the development of ICD. Dopamine transporter availability may be a suitable marker, because previous studies have shown reduced availability in patients with ICD (Cilia *et al.* 2010; Hou *et al.* 2012) and a negative correlation with reward-related impulsivity (Aarts *et al.* 2012). To this end we procured follow-up data on medication-naïve PD patients who underwent dopamine transporter single-photon emission computed tomography (SPECT) imaging and clinical evaluation at the time of diagnosis and were subsequently treated with dopamine replacement therapy. We predicted that PD patients that developed ICD after commencing dopamine replacement therapy would show reduced ventral striatal dopamine transporter availability at baseline.

## Methods

*Patients*

Patients were consecutive cases diagnosed clinically with idiopathic PD (Daniel and Lees 1993) by an experienced movement disorders specialist (H.B., E.F.) between May 2008 and December 2011. Patients were naïve for dopamine replacement therapy (de novo PD patients) and had undergone dopamine transporter SPECT imaging. Only patients that had commenced dopamine replacement therapy during the interval between imaging and follow-up interview were eligible. Patients on selective serotonin reuptake inhibitors during

SPECT imaging were excluded from analyses, because of their potential influence on dopamine transporter binding (Booij and Kemp 2008). Patients with signs of dementia (Mini Mental State Examination [MMSE] score ≤ 24) or ICD (Scales for Outcomes in Parkinson's disease-Psychiatric complications [SCOPA-PC]) were also excluded (figure 4.1). All but one patient had a PD onset of greater than 40 years. To assess the development of ICD, we gathered follow-up data after a mean follow-up period of 31.5 ± 12.0 months from the initial diagnosis and SPECT acquisition. This study was approved by the medical ethical committee of the VU University medical center, and all patients provided written informed consent.

*Clinical Measurements*

At baseline, we assessed disease severity with the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) and disease stage with the modified Hoehn & Yahr scale. The MMSE was used to evaluate the presence of dementia. Baseline symptoms of ICD were assessed with the SCOPA-PC and the severity of depressive symptoms with the Beck Depression Inventory (BDI). All baseline evaluations were performed on the day of the dopamine transporter SPECT acquisition.

Questionnaires used for follow-up measurements included the self-reported BDI and the Questionnaire for Impulsive-Compulsive disorders in Parkinson's disease Rating Scale (QUIP-RS) (Weintraub *et al.* 2012). QUIP-RS is designed to rate the severity of ICD symptoms related to pathological gambling, hypersexuality, compulsive buying, and compulsive eating, as well as symptoms of the related disorders: punding and dopamine dysregulation syndrome. Because we expected the number of patients with clinically significant ICD to be limited and to improve statistical power, we used the sum of the subscores on gambling, sexual, buying, and eating behavior, rather than the individual subscores, as a measure of ICD symptom severity (demoted as QUIPRS-ICD). Symptoms of punding and dopamine dysregulation syndrome were disregarded because they are thought to lie outside the ICD spectrum (Antonini and Cilia 2009; Evans *et al.* 2009). Patients were also asked for their current and past medication status, which was verified by their pharmacist. Dopamine replacement therapy dosages were converted to levodopa equivalent daily dose (LEDD) as described previously (Olde Dubbelink *et al.* 2013). We also carefully examined patients' medical records for signs of ICD symptoms after dopamine replacement therapy onset. Finally, patients were contacted by telephone by a trained interviewer (A.N.) to discuss possible discrepancies between the questionnaire data provided by the patient and the notes in their medical records. During this interview we used the Questionnaire for Impulsive-Compulsive disorders in Parkinson's disease (QUIP) (Weintraub *et al.* 2009), to assess both current and past symptoms of ICD. All clinical measurements were scored independently and separately (i.e., blinded) from the dopamine transporter SPECT scans.

*Dopamine Transporter SPECT Imaging and Regions of Interest*

We used the established [123I]FP-CIT ([123I]N-ω-Fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane) SPECT tracer to measure presynaptic striatal dopamine transporter availability in six predefined regions of interest (ROIs): left and right ventral striatum, anterior-dorsal striatum, and posterior putamen. Tracer binding in the bilateral superior, medial, and inferior occipital gyri was used as a reference. Because dopamine transporter availability declines with natural aging (Varrone *et al.* 2013), [123I]FP-CIT binding ratios from PD patients were normalized for age by expressing the binding ratios of specific to nonspecific dopamine transporter binding as a percentage of age-expected binding (Pirker 2003). The advantage of this approach is that it also controls for possible effects of between-group age differences on dopamine transporter binding ratios. More details on the procedure of SPECT imaging, delineation of the ROIs, and calculation of age-normalized binding ratios are provided in the supplementary Methods.



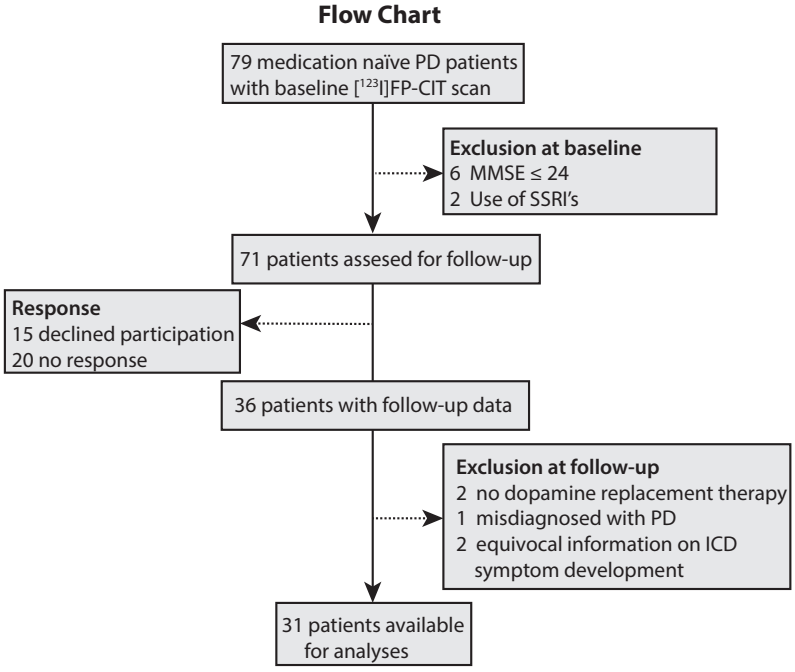


**Figure 4.1** – Flowchart of patients included in this study.

*Data Analyses*

Analyses were performed using SPSS 20. Associations between ICD symptoms and other clinical measures or dopamine transporter availability were analyzed with Pearson's correlations (r) or Spearman's rank-correlation-coefficients (rs), depending on the distribution of the variable. Semipartial correlations were performed to control for the influence of possible confounders. Differences on continuous clinical measures or dopamine transporter availability between PD patients with or without ICD symptoms were analyzed with two-sample T-tests (t) or Mann-Whitney U-tests (U). Categorical variables were analyzed with the $\chi 2$-test. We corrected the between-group analyses on dopamine transporter availability for multiple comparisons using interactive statistical analysis (http://www.quantitativeskills.com/sisa/calculations/bonhlp.htm; SISA), which resulted in a critical value of $P < 0.033$ (mutual correlation coefficient: 0.77, 6 ROIs). Alpha was set to $P < 0.05$ for all other analyses.

**Table 4.1** – Sample characteristics

| | All | Non-ICD | ICD | Test statistic (P-value) |
|---|---|---|---|---|
| N patients (% male) | 31 (71.9) | 20 (55.0) | 11 (100) | 7.0 (.01)a |
| Age | 61.6 ± 11.8 | 63.2 ± 13.4 | 58.7 ± 7.8 | 1.01 (.32)b |
| Disease duration (y) | 2.0 ± 2.3 | 2.1 ± 2.6 | 1.8 ± 2.0 | 100.5 (.68)c |
| UPDRS III | 21.7 ± 10.1 | 19.2 ± 9.2 | 26.3 ± 11.5 | -1.88 (.07)b |
| H&Y stage | 2.0 ± 0.5 | 2.0 ± 0.6 | 1.9 ± 0.4 | 2.61 (.63)a |
| MMSE | 28.7 ± 1.4 | 28.4 ± 1.5 | 29.2 ± 1.0 | 73.0 (.11)c |
| BDI baseline | 7.9 ± 6.7 | 5.0 ± 5.4 | 13.3 ± 5.7 | 28.5 (.001)c |
| BDI follow-up | 6.3 ± 4.6 | 5.5 ± 5.3 | 8.0 ± 2.9 | 46.5 (.03)c |
| QUIP-RS | 11.9 ± 10.3 | 7.7 ± 5.8 | 19.9 ± 12.5 | 33.0 (.004)c |
| - ICD symptoms | 6.69 ± 6.0 | 3.8 ± 3.6 | 12.1 ± 6.1 | 24.5 (.001)c |
| LEDD highest | 470.6 ± 387.9 | 315.8 ± 142.7 | 762.5 ± 552.7 | 46.5 (.01)c |
| LEDD current | 452.2 ± 382.6 | 303.3 ± 156.5 | 747.5 ± 546.3 | 47.5 (.01)c |
| - LEDD DA | 109.4 ± 130.3 | 78.3 ± 105.1 | 165.9 ± 156.0 | 75.0 (.12)c |
| - LEDD levodopa | 331.5 ± 342.0 | 236.3 ± 204.0 | 504.5 ± 469.8 | 74.5 (.13)c |
| Follow-up period (months) | 31.5 ± 12.0 | 27.9 ± 10.4 | 38.4 ± 10.4 | 46.0 (.03)c |

(left page) All variables are listed as mean ± standard deviation. Abbreviations: UPDRS-III = Unified Parkinson's Disease Rating Scale part 3, H&Y = Hoehn and Yahr, MMSE = Mini Mental State Examination, BDI = Beck Depression Inventory, QUIP-RS = Questionnaire for Impulsive-Compulsive in Parkinson's disease – Rating Scale, ICD symptoms = total score of gambling, sex, buying and eating behavior on the QUIP-RS, LEDD = Levodopa Equivalent Daily Dose, DA = dopamine agonists. a = Chi-square, b = two sample T-test, c = Mann-Whitney U test.

## Results



*Clinical Data*

None of the patients exhibited symptoms of ICD at baseline as assessed by the SCOPA-PC. QUIPRS-ICD at follow-up correlated positively with BDI at baseline ($r = 0.58$, $P = 0.001$) and follow-up ($r = 0.44$, $P = 0.02$) but not baseline UPDRS-III score. Neither current nor highest medication dosage (LEDD) correlated with the QUIPRS-ICD, although LEDD did correlate positively with the length of the follow-up period (current LEDD: $rs = 0.37$, $P = 0.05$, highest LEDD: $rs = 0.45$, $P = 0.02$). None of the clinical measures correlated with age.

*SPECT Data*

The QUIPRS-ICD score showed a negative correlation with age-normalized binding ratios in the right ventral striatum ($rs = -0.39$, $P = 0.04$) and right anterior-dorsal striatum ($rs = -0.40$, $P = 0.03$), see figure 4.2A and 4.2B. These correlations remained even after correcting for BDI at baseline and follow-up, LEDD, UPDRS-III, and follow-up interval (see Supplementary Results and Table S4.1).

*Between-Group Analyses*

Based on the combined information obtained from the medical records, cutoff scores of the QUIP (Weintraub *et al.* 2009) and QUIP-RS (Weintraub *et al.* 2012) and the telephone interview, we divided our patients into groups of patients that developed ICD symptoms during the follow-up period and a group that did not. Eleven PD patients (35.5%) were classified as having developed ICD symptoms. Medication statuses are listed in supplemental Table S4.2.

Using SISA to correct for multiple comparisons, the ICD group, compared with the non-ICD group, showed significantly lower dopamine transporter binding ratios in the right ventral striatum ($t(27,01) = 2.72$, $P = 0.01$), right anterior-dorsal striatum ($t(29) = 2.63$, $P = 0.01$), and right posterior putamen ($t(29) = 2.48$, $P = 0.02$; also figure 4.3). Groups did not differ in age, disease stage or duration, and MMSE score, although patients with ICD symptoms had a longer interval between baseline [123I]FP-CIT scan and follow-up interview ($U = 46$, $P = 0.03$; Table 4.1). We also observed a trend toward higher UPDRS-III scores in PD patients with ICD symptoms ($t(29) = -1.88$, $P = 0.07$), a difference in sex ($\chi 2 = 7.0$, $P = 0.01$), BDI scores (baseline: $U = 28.5$, $P = 0.001$, follow-up: $U = 46.5$, $P = 0.03$), and total LEDD (LEDD current: $U = 47.5$, $P = 0.01$), although the dosages of dopamine agonists

(U = 75.0, P = 0.12) and levodopa (U = 74.5, P = 0.13) were comparable. Because these differences could have confounded our findings, we performed additional post-hoc analyses to control for these variables and observed similar results as those reported (see Table S4.3).

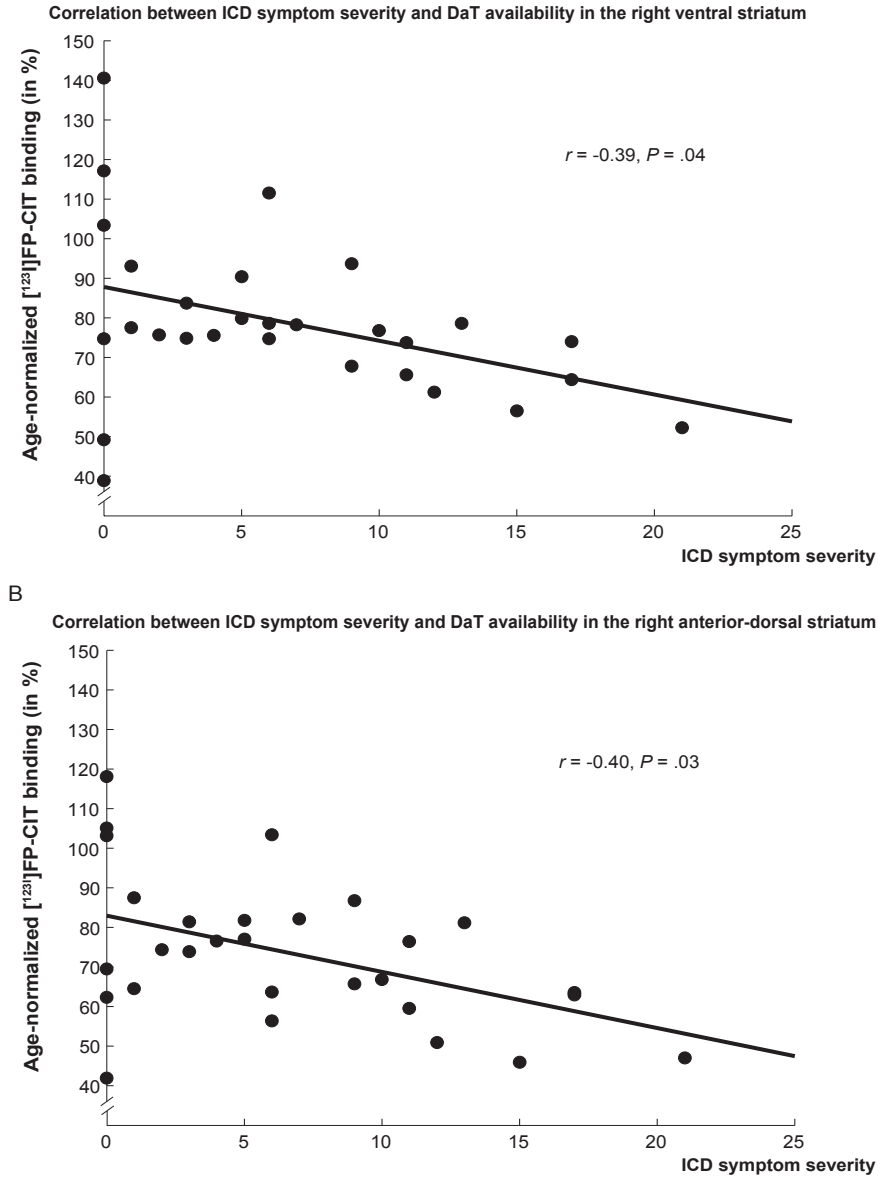


**Figure 4.2** – Correlation plots between the severity of ICD symptoms and dopamine transporter (DaT) availability. Negative correlations between the ICD symptom severity and [123I]FP-CIT binding in the right ventral striatum (A) and right anterior-dorsal striatum (B). Binding of the DaT tracer [123I]FP-CIT are normalized for age. Severity of ICD symptoms is defined as the sum of the gambling, sex, buying and eating subscores of the Questionnaire for Impulsive-Compulsive disorders in Parkinson's disease Rating Scale (QUIP-RS).

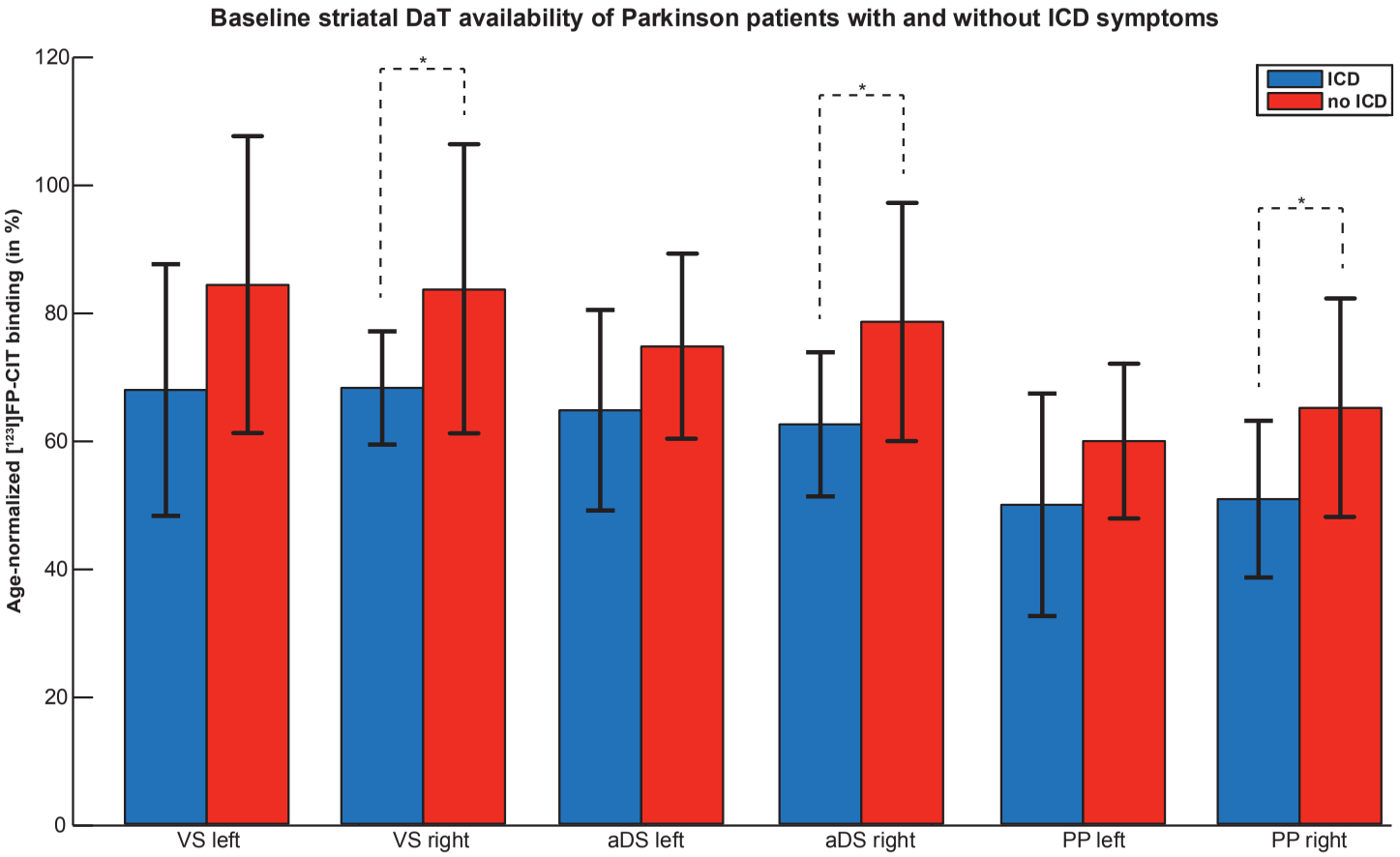


**Figure 4.3** – Baseline differences in dopamine transporter availability between PD patients with and without ICD symptoms. Abbreviatons: VS = ventral striatum, aDS = anterior-dorsal striatum, PP= posterior putamen.

## Discussion

Supporting our hypothesis, we observed reduced baseline dopamine transporter availability in the ventral striatum in PD patients who developed ICD symptoms compared with PD patients without these symptoms. Moreover, the severity of ICD symptoms correlated negatively with baseline dopamine transporter availability in the right ventral striatum. The ICD symptoms in PD were also related to reduced baseline dopamine transporter availability in the right anterior-dorsal striatum and right posterior putamen. These results are consistent with earlier observations in PD patients with and without ICD (Cilia *et al.* 2010; Voon *et al.* 2014). Nevertheless, in contrast to our design, these studies were performed in patients that had already developed ICD, and so the reduced dopamine transporter availability could also have been the consequence of prolonged dopamine replacement therapy or brain alterations associated with ICD. A recent study showed that PD patients without medication or ICD already show aberrations in reward processing during a rewarded task-switching paradigm, a neurocognitive characteristic commonly observed in PD patients with ICD (Housden *et al.* 2010). This shows that reward processing may already be altered in PD before chronic dopamine replacement therapy or ICD development.

Because our study design excludes the possible effects of dopamine replacement therapy or neuronal adaptations associated with ICD on dopamine transporter availability, our main finding of reduced ventral striatal dopamine transporter availability in de novo PD patients susceptible to ICD may have two non–mutually exclusive interpretations: (1) a premorbid, possibly genetically, determined lower availability of the dopamine transporter (Dreher *et al.* 2009); or (2) a more pronounced dopaminergic denervation (Scherfler *et al.* 2007). Patients with lower dopamine transporter availability could have increased striatal dopamine levels because of reduced presynaptic reuptake by the transporter (Cilia *et al.* 2010). Increased ventral striatal dopamine signaling impairs the processing of negative feedback during reward-based learning (Frank *et al.* 2004) and is commonly associated with disruption of impulse control in PD (Steeves *et al.* 2009; O'Sullivan *et al.* 2011) and animal models (Pattij *et al.* 2007; Baarendse and Vanderschuren 2012). Because dopamine transporter is localized in the presynaptic terminal, reductions in dopamine transporter availability also might point toward dopaminergic denervation. Dopaminergic denervation has been suggested to reduce the availability of D2/D3-autoreceptors in the remaining intact dopaminergic neurons (Aarts *et al.* 2012), which has previously been associated with impulsivity in PD (Ray *et al.* 2012) and non-PD samples (Buckholtz *et al.* 2010). Dopamine degeneration also may lead to denervation-induced postsynaptic receptor hypersensitivity (Gerfen *et al.* 2002), which develops in striatal neurons after dopamine depletion (Prieto *et al.* 2009) and seems primarily dependent on enhanced sensitivity of D3-receptors (Prieto *et al.* 2011). Either of these mechanisms may potentially underlie the development of

ICD (Voon *et al.* 2009). Furthermore, our findings included not only the ventral striatum but also the anterior-dorsal striatum and posterior putamen, which suggest that a globally reduced dopamine transporter availability is associated with the development of ICD symptoms and is consistent with previous research (Voon *et al.* 2014). Future investigations on the contribution of the segregated striatal areas to ICD development in PD are needed.

Patients with and without ICD symptoms differed in the severity of depressive symptoms. Post-hoc analyses showed that patients who scored high versus low on depressive symptoms did not differ in dopamine transporter availability, nor was there a correlation between depressive symptoms and striatal binding ratios. In contrast, our previous study on 100 PD patients showed a negative correlation between dopamine transporter availability in the caudate nucleus and severity of depressive symptoms ($r = -0.25$) (Vriend *et al.* 2014d). This incongruity is likely explained by the smaller sample size and restricted range in BDI scores in the present study and the smaller effect size of dopamine transporter availability on depressive symptoms compared with ICD symptoms (ventral striatum: $r = -0.39$; anterior-dorsal striatum: $r = -0.40$).



Unlike previous studies (Booij *et al.* 2001; Vriend *et al.* 2014d), UPDRS-III did not correlate with dopamine transporter binding in the posterior putamen. This analysis may have been biased by the homogeneity of our sample (i.e., all early, drug-naïve PD patients with a limited range of motor-UPDRS scores) and our relatively small sample size (Tissingh *et al.* 1998). Indeed, when considering the entire sample of 79 drug-naïve PD patients (figure 4.1), the baseline UPDRS-III score correlated negatively with dopamine transporter binding in the bilateral posterior putamen (data not shown).

Because of the retrospective nature of our study, we were unable to sufficiently match PD patients with and without ICD symptoms on UPDRS-III scores, which was significantly higher in PD patients with ICD symptoms. Nevertheless, we deem it unlikely that our findings are confounded by differences in disease severity, because (1) no correlation appeared between ICD symptom severity and UPDRS-III score; (2) ICD symptom severity and dopamine transporter availability correlated negatively over all PD patients; and (3) post-hoc analysis in an adequate UPDRS-III score matched subsample of PD patients showed similar reductions in dopamine transporter availability in PD patients with ICD symptoms. Previous studies also showed no difference in UPDRS-III scores between PD patients with and without ICD (Voon *et al.* 2011d; Kim *et al.* 2013). The slightly younger age of PD patients with ICD symptoms is also unlikely to have biased our findings, because of the age normalization of the dopamine transporter binding ratios and the lack of a correlation between age and severity of ICD symptoms.

The longer interval between baseline [123I]FP-CIT imaging and follow-up interview in PD patients that developed ICD symptoms compared with those without may possibly be considered a source of confound. Some patients in the "non-ICD" group may have developed ICD symptoms, given a longer follow-up

period. Nevertheless, of the PD patients able to report on the onset of their ICD symptoms, more than half reported these symptoms after on average 11.4 ± 3.9 months, which is shorter than the average follow-up period of PD patients without ICD symptoms (27.9 ± 10.4 months). This follow-up period is also longer than the median follow-up period recently reported for the development of clinically significant ICD (Bastiaens *et al.* 2013). We therefore believe that differences in follow-up period between our patient groups do not explain the development of ICD. We also observed no correlation between follow-up period and ICD symptom severity, nor did adding the duration of the follow-up period as a control variable to the correlation between ICD symptom severity and dopamine transporter availability in the right ventral striatum and anterior-dorsal striatum affect the results.

At follow-up, the ICD group had a higher total LEDD. We observed no correlation between LEDD and severity of ICD symptoms, and previous studies indicated that the dosage of dopamine replacement therapy alone is insufficient to explain the development of ICD symptoms (Weintraub *et al.* 2010a; Voon *et al.* 2011d; Joutsa *et al.* 2012d). Furthermore, the correlation between ICD symptom severity and dopamine transporter availability in the right ventral striatum and anterior-dorsal striatum remained even after controlling for LEDD, UPDRS-III, and length of the follow-up period, and LEDD did not directly correlate with dopamine transporter availability in the right ventral striatum or anterior-dorsal striatum, the striatal areas related to severity of ICD symptoms. We therefore believe that the between-group LEDD difference did not contribute to the development of ICD symptoms but is explained by the higher UPDRS-III score and longer follow-up period in PD patients with ICD compared with those without. Both UPDRS-III and follow-up duration were positively correlated with LEDD but unrelated to the severity of ICD symptoms.

Some important limitations of this study need to be addressed. First, with a response rate of 51%, this study possibly suffers from a certain selection bias. We do not know whether the nonresponders and patients that declined participation are more or less likely to experience ICD symptoms. Nevertheless, most patients stated that they declined because of cognitive problems. Second, we used the QUIP and QUIP-RS, validated screening questionnaires for ICD in PD, instead of clinical psychiatric assessments to distinguish PD patients with and without symptoms of ICD. In contrast to a full Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis, the QUIP and QUIP-RS also recognize mild or subsyndromal ICD not severely interfering with daily life and not always warranting interventions. Given the negative correlation between dopamine transporter availability and ICD symptom severity, possibly a comparison between PD patients with and without clinically significant ICD would result in an even greater between-group difference in dopamine transporter availability. We therefore think our approach led to a conservative estimate of the relation between baseline dopamine transporter availability and follow-up development

of ICD symptoms. Other limitations of this study relate to the possible influence of confounding variables, which is intrinsic to retrospective study designs. For example, although according to the SCOPA-PC none of our patients had clinically significant symptoms of hypersexuality, compulsive buying, and pathological gambling at baseline, we were unable to obtain a baseline QUIP(-RS) measure. This is in part because the QUIP and QUIP-RS were introduced later than the first measurements. Because of the discordance in impulsivity measures, possibly the symptoms of compulsive eating, which are not assessed by the SCOPA-PC, may have been overlooked at baseline. Furthermore, although we performed additional post-hoc analyses to control for the between-group differences on clinical measures, we cannot completely rule out the confounding influence of these variables. Therefore, the findings of this preliminary study require replication by means of a prospective longitudinal design to allow adequate matching of patients.



To conclude, this study shows that lower striatal dopamine transporter availability predates the development of ICD symptoms in PD patients after commencing dopamine replacement therapy and may possibly constitute a neurobiological risk factor that may be related to a premorbid lower dopamine transporter availability or a more pronounced dopamine denervation in PD patients susceptible to ICD.

## Supplementary Methods

*DaT SPECT imaging - procedure*

All patients received oral potassium perchlorate to block thyroid uptake of free radioactive iodide. [123I]FP-CIT was injected intravenously three hours before image acquisition at an approximate dose of 185 MBq (specific activity >185 MBq/nmol; radiochemical purity >99%). Subjects were imaged using a dual-head gamma camera (E.Cam; Siemens, Munich, Germany) with a fan-beam collimator. We acquired 60 x 30 second views per head over a 180° orbit on a 128×128 pixel matrix resulting in a total imaging time of 30 minutes. Image reconstruction was performed using a filtered back projection with a Butterworth filter (order 8, cut-off 0.6 cycles/cm; voxel size: 3.9 mm3 after reconstruction). Scans were reoriented manually to ensure that left and right striatum were aligned.

*DaT SPECT imaging – image processing*

Since [123I]FP-CIT scans contain insufficient anatomical details to sustain correct spatial normalization, an indirect approach described by Kas *et al.* (2007) was employed. Sixteen [123I]FP-CIT reoriented scans from healthy controls were normalized onto an in-house PET 11C-Raclopride template in Montreal Neurological Institute (MNI) space. The creation of this [123I]FP-CIT template was performed in SPM2 software (Wellcome Trust Center for Neuroimaging, London,

UK) due to several misregistrations in SPM8. We used SPM2 default settings to normalize the scans and resliced the individual scans to voxels of 2 mm3. The 16 individual scans were mirrored in the mid-saggital plane, averaged and smoothed using a full width at half maximum (FWHM) smoothing of 5 mm to create the [123I]FP-CIT template. The preprocessing steps and analyses of the PD patient scans were performed in SPM8. Scans were normalized using the [123I]FP-CIT template. All scans were visually inspected for possible misregistrations. We used trilinear interpolation to reslice the scans to a voxel size of 2 mm3 and spatially smoothed the scans with a 6 mm FWHM Gaussian kernel to correct for inter-individual anatomical differences.

*Binding ratios and regions of interest*

Individual binding ratios (BR) of specific to non-specific DaT binding were calculated for the left and right ventral striatum (VS), anterior-dorsal striatum (aDS) and posterior putamen (PP). Tracer binding in the bilateral superior, medial and inferior occipital gyri was used as a reference. The VS was defined according to the method described by Tziortzi *et al.* (2011) and traced on the coronal slices of a standard single subject T1-weighted MRI scan available in SPM8 (see figure S4.1). The aDS was delineated on the same coronal slices as the VS. To minimize spillover effects, a gap of approximately 5 mm was left between the borders of the VS and aDS. These voxels were excluded from BR calculation. We based the PP ROI on the putamen ROI from the AAL (Automated Anatomical Labeling) atlas such that it comprised only voxels posterior to the anterior commissure (Helmich *et al.* 2010; Aarts *et al.* 2012). Since DaT availability declines with natural aging (Varrone *et al.* 2013), [123I]FP-CIT BR from PD patients were normalized for age by expressing the BR as a percentage of age-expected binding, conform (Pirker 2003). The advantage of this approach is that it controls for possible effects of between-group age differences on DaT BR. Age-expected BR were derived from 19 healthy controls (age range 42–72 years). Linear regression lines for age and DaT BR in all six ROIs were calculated and used to normalize BR for age in PD patients according to the formula:

$$\frac{[(\text{Striatal BR} - \text{Occipital BR}) / \text{Occipital BR}]_{PD}}{[(\text{Striatal BR} - \text{Occipital BR}) / \text{Occipital BR}]_{control}} * 100$$

## Supplementary Results

Because between-group (trend) differences in gender, BDI and UPDRS-III score could have confounded the results we performed additional post-hoc analyses (supplementary Table S4.3). We dichotomized BDI scores into low or high scores (median-split) and observed no differences in striatal DaT BR, nor did we observe differences between sexes (supplementary Table S4.3). By excluding the quartile (N=5) with the lowest UPDRS-III scores in the non-ICD group we matched patient

groups with and without ICD symptoms on UPDRS-III scores (non-ICD: 23.5±5.6, ICD: 26.3±11.5, U=69.0, P=.48). Significant between-group differences in DaT BR were still observed in the right VS (t(24)=2.45, P=.02) , aDS (t(24)=3.08, P=.005) and PP (t(24)=2.98, P=.007), which indicates that our findings are not explained by differences in disease severity.

Consistent with previous studies, patients with ICD symptoms were predominantly male ($\chi$2=7.0, P=.01) and had higher BDI scores at baseline (U=28.5, P=.001) and follow-up (U=46.5, P=.03). Patients with ICD symptoms also had higher LEDD (LEDD current: U=47.5, P=.01; LEDD highest: U=46.5, P=.01), although the dosages of dopamine agonists (U=75.0, P=.12) and levodopa (U=74.5, P=.13) were comparable. In-depth examination showed that the difference in total LEDD was caused by the use of COMT (catechol-O-methyl transferase) inhibitors by two patients in the ICD group that increase levodopa LEDD by 20% (Olde Dubbelink *et al.* 2013) . By excluding these two patients on COMT-inhibitors the between-group difference in total LEDD was no longer significant whereas the differences in striatal BR remained (Table S4.3).



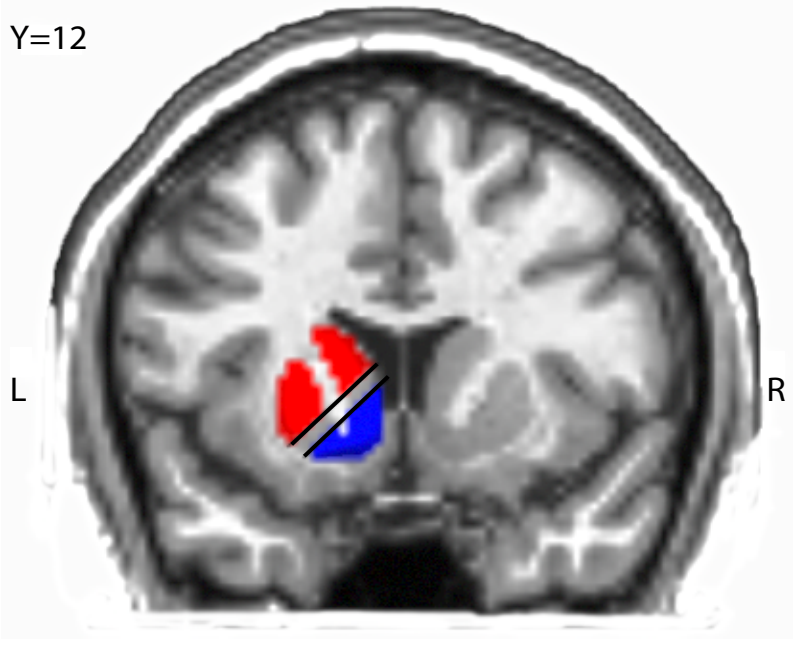


**Figure S4.1** – Manually delineated region's of interest (ROI's) of the ventral (blue) and anterior-dorsal (red) striatum. Note the 5 mm gap between the ROI's to minimize spillover effects.

**Table S4.1** – Semi-partial correlations between DaT availability and ICD symptom severity* while controlling for possible confounders

| Striatal region | Confounders | r | P |
|---|---|---|---|
| DaT VS right | BDI baseline | -0.42 | .02 |
| | BDI follow-up | -0.37 | .05 |
| | UPDRS-III | -0.43 | .02 |
| | Current LEDD total | -0.38 | .04 |
| | LEDD dopamine agonists | -0.38 | .04 |
| | LEDD levodopa | -0.39 | .04 |
| | Follow-up time | -0.41 | .03 |
| DaT aDS right | BDI baseline | -0.45 | .01 |
| | BDI follow-up | -0.40 | .03 |
| | UPDRS-III | -0.50 | .006 |
| | Current LEDD total | -0.44 | .02 |
| | LEDD dopamine agonists | -0.45 | .02 |
| | LEDD levodopa | -0.46 | .01 |
| | Follow-up time | -0.45 | .02 |

*Severity of ICD symptoms is defined as the sum of the gambling, sex, buying and eating subscores of the Questionnaire for Impulsive-Compulsive disorders in Parkinson's disease Rating Scale (QUIP-RS).

**Table S4.2** – Medication status of PD patients that did or did not develop ICD symptoms

| Medication | Non-ICD group | ICD | Total |
|---|---|---|---|
| monotherapy dopamine agonists | 6 (60%) | 4 (40%) | 10 |
| monotherapy levodopa | 13 (81.2%) | 3 (18.8%) | 16 |
| dopamine agonist and levodopa | 1 (20%) | 4 (80%) | 5 |

**Table S4.3** – post-hoc between-group analyses to control for confounders

| Post-hoc analyses | Variable | Group 1 | Group 2 | Test statistic (P-value) |
|---|---|---|---|---|
| **UPDRS-III match** | Groups | Non-ICD | ICD | |
| | N | 15 | 11 | |
| | UPDRS-III | 23.5 ± 5.6 | 26.3 ± 11.5 | 69.0 (.48)a |
| | Age | 63.5 ± 14.5 | 58.7 ± 7.8 | 0.98 (.34)b |
| | DaT VS right* | 84.9 ± 21.4 | 68.1 ± 8.8 | 2.45 (.02)b |
| | DaT aDS right* | 80.5 ± 16.9 | 62.4 ± 11.3 | 3.08 (.005)b |
| | DaT PP right* | 66.5 ± 14.1 | 50.7 ± 12.4 | 2.98 (.007)b |
| | DaT VS left* | 87.5 ± 22.0 | 67.7 ± 19.7 | 2.37 (.03)b |
| | DaT aDS left* | 75.9 ± 13.4 | 64.6 ± 15.7 | 1.98 (.06)b |
| | DaT PP left* | 61.8 ± 11.6 | 49.8 ± 17.4 | 2.12 (.04)b |
| **BDI median split** | Groups | Low BDI | High BDI | |
| | N | 16 | 15 | |
| | DaT VS right* | 76.5 ± 19.1 | 79.9 ± 22.0 | -0.47 (.64)b |
| | DaT aDS right* | 72.7 ± 17.3 | 73.1 ± 19.3 | -0.058 (.95)b |
| | DaT PP right* | 60.4 ± 15.2 | 59.7 ± 19.0 | 0.12 (.91)b |
| | DaT VS left* | 74.7 ± 21.2 | 82.4 ± 25.1 | -0.93 (.36)b |
| | DaT aDS left* | 69.4 ± 15.3 | 73.1 ± 15.8 | -0.66 (.51)b |
| | DaT PP left* | 55.7 ± 11.2 | 57.1 ± 18.2 | -0.27 (.79)b |
| **Sexes** | Groups | Female | Male | |
| | N | 9 | 22 | |
| | DaT VS right* | 81.9 ± 22.8 | 76.6 ± 19.5 | 0.66 (.51)b |
| | DaT aDS right* | 77.8 ± 20.0 | 70.9 ± 17.2 | 0.96 (.34)b |
| | DaT PP right* | 63.4 ± 17.8 | 58.7 ± 16.7 | 0.92 (.49)b |
| | DaT VS left* | 79.6 ± 22.5 | 78.0 ± 23.9 | 0.17 (.87)b |
| | DaT aDS left* | 73.9 ± 16.8 | 70.0 ± 15.1 | 0.64 (.53)b |

| | | | | |
|---|---|---|---|---|
| | DaT PP left* | 56.6 ± 11.8 | 56.3 ± 16.1 | 0.05 (.96)b |
| Post-hoc analyses | Variable | Group 1 | Group 2 | Test statistic (P-value) |
| **COMT exclusion** | Groups | No-ICD | ICD | |
| | N | 20 | 9 | |
| | DaT VS right* | 83.7 ± 22.7 | 66.2 ± 8.6 | 2.22 (.04)b |
| | DaT aDS right* | 78.6 ± 18.6 | 61.4 ± 12.3 | 2.5 (.02)b |
| | DaT PP right* | 65.2 ± 17.0 | 49.9 ± 13.6 | 2.36 (.03)b |
| | DaT VS left* | 84.3 ± 23.2 | 67.6 ± 21.7 | 1.84 (.08)b |
| | DaT aDS left* | 74.8 ± 14.4 | 64.1 ± 17.4 | 1.73 (.10)b |
| | DaT PP left* | 60.0 ± 12.1 | 50.0 ± 19.1 | 1.71 (.10)b |

a = Mann-Whitney U-Test, b = two-sample T-test. ***** Dopamine transporter availability (DaT) is expressed as a percentage of age appropriate DaT availability. Also see Supplementary Methods.