Lower $^{123}$I-FP-CIT binding to the striatal dopamine transporter, but not to the extrastral serotonin transporter, in Parkinson’s disease compared with dementia with Lewy bodies

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ABSTRACT

In this retrospective cross-sectional study we compared $^{123}$I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropine ($^{123}$I-FP-CIT) binding to the striatal dopamine and the extrastral serotonin transporter (DAT and SERT, respectively) between Parkinson’s disease (PD) and dementia with Lewy bodies (DLB) to gain more insight in the pathophysiology of the two diseases.

We compared $^{123}$I-FP-CIT single photon emission computed tomography scans of, age-, gender matched patients with cognitive decline in same range of severity with PD (n = 53) or DLB (n = 53) using a regions of interest (ROIs) approach. We derived ROIs anatomically from individual magnetic resonance imaging brain scans. To corroborate the ROI findings, we performed additional whole-brain voxel-based analyses.

In both ROI and voxel-based analyses, $^{123}$I-FP-CIT binding in PD patients was significantly lower in the bilateral posterior putamen than in DLB patients (left: $F_{(1,103)} = 18.363, \omega^2 = 0.14$; right: $F_{(1,103)} = 20.434, P < 0.001, \omega^2 = 0.15$) ($P_{corr} < 0.033$). Caudate/putamen ratios were also significantly lower in DLB than in PD ($U_{(105)} = 724.0, P < 0.001$). Extrastral SERT binding showed no difference between PD and DLB.

These results suggest similar involvement of serotonergic structures in the degenerative process in PD and DLB.

1. Introduction

Parkinson’s disease (PD) and dementia with Lewy bodies (DLB) are both characterised by dopaminergic neurodegeneration and Lewy body pathology in the brain, mainly in the substantia nigra (Bethlem and Den Hartog Jager, 1960; Braak et al., 2003; Hansen et al., 1990). The dopaminergic neurodegeneration is associated with the classical motor symptoms of parkinsonism, which includes bradykinesia, rigidity, resting tremor and postural instability. Both PD and DLB encompass non-motor symptoms such as depression, anxiety, hallucinations and cognitive decline. The clinical distinction between PD and DLB is currently based on the timing of the onset of cognitive decline relative to the onset of motor symptoms: DLB is diagnosed when cognitive decline appears before, or no longer than one year after the development of parkinsonism (one year rule) (McKeith et al., 2005), while PD is diagnosed when parkinsonism predates cognitive decline for more than a year. PD and DLB are thought to be manifestations of a single Lewy body-disease spectrum. However, we still do not know the extent of this spectrum, and why some patients have a PD phenotype rather than a DLB phenotype, and vice versa. It is therefore interesting to explore differences and similarities of both diseases.

Considering the clinical differences between PD and DLB in phenotype and disease course, one might expect a differential involvement of neurotransmitters systems. The results of neuropathological and molecular imaging suggest that the pattern of neurodegeneration in dopaminergic (Piggott et al., 1999), serotonergic (Roselli et al., 2010) and cholinergic (Hepp et al., 2013) systems differs between DLB and PD. In vivo it is possible to visualise both dopaminergic...
and serotonergic systems with a single tracer, $^{123}$I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ($^{123}$I-FP-CIT). This well-validated single photon emission computed tomography (SPECT) radiotracer has high affinity for the presynaptic serotonin transporter (SERT) (Abi-Dargham et al., 1996). Previous studies have shown that $^{123}$I-FP-CIT SPECT imaging is sensitive enough to study the integrity of the dopaminergic system in the striatum (Bootj et al., 1999), and the serotoninergic system in extrastriatal brain areas (Koopman et al., 2012; Ziebell et al., 2010). Striatal DAT loss in both PD and DLB has been well documented using $^{123}$I-FP-CIT SPECT. The reported differences between PD and DLB include a more extensive loss of DAT binding in the putamen than in the caudate nucleus in PD, which is also reflected in a flatter rostrocaudal (caudate-putamen) gradient in DLB than in PD (O’Brien et al., 2004; Walker et al., 2004). In addition to the differences in striatal $^{123}$I-FP-CIT binding, in a preliminary study, Roselli and co-workers reported lower extrastriatal $^{123}$I-FP-CIT binding to SERT in the midbrain in DLB (n = 16) than in PD patients (n = 15) (Roselli et al., 2010). In clinical studies the prevalence of neuropsychiatric symptoms associated with a serotonergic deficit, such as anxiety, appears to be different in DLB than in PD, although the results vary (Chiu et al., 2016; Kao et al., 2009). This observation is relevant, from both a scientific and a clinical point of view, because if we would be able to confirm the differences in the constellation of serotonergic degeneration in PD and DLB, this would stimulate research on the relationship between serotonergic degeneration and clinical symptoms in DLB.

In this cross-sectional molecular imaging study we aimed to obtain more information on possible DAT and SERT differences between PD and DLB. In line with the literature, we expected to find a difference in the rostrocaudal pattern of $^{123}$I-FP-CIT DAT binding between PD and DLB patients. In addition, we hypothesised that DLB patients would show a different pattern of $^{123}$I-FP-CIT binding in SERT-rich extrastriatal regions than PD patients.

2. Patients and methods

2.1. Participants

In this retrospective cross-sectional study we selected clinically diagnosed PD and DLB patients from consecutive cases that presented between December 2006 and March 2017 from both the outpatient clinic for movement disorders and the memory clinic (Amsterdam Dementia Cohort, Alzheimer Center (van der Flier et al., 2014)), both at the department of Neurology of the VU University Medical Center (VUmc) in Amsterdam, The Netherlands. We included probable DLB and PD patients in whom $^{123}$I-FP-CIT SPECT imaging had been performed, and a T₁-weighted magnetic resonance imaging (MRI) brain scan and a mini mental state examination (MMSE) were available. PD and DLB patients on serotonin reuptake inhibitors (SRIs) were excluded, because these drugs may influence $^{123}$I-FP-CIT SERT binding (Booj et al., 2007). Apart from this, the use of common anti-parkinsonian drugs like levodopa, as well as dopamine agonists was not used as an exclusion criterion. From this selection, fewer DLB than PD patients were available for analysis, therefore we matched the DLB patients subject by subject with eligible PD patients based on age and gender, and MMSE scores in the same range of severity, since previous studies showed effects of ageing, gender and cognitive deficits on striatal $^{123}$I-FP-CIT binding (Siepel et al., 2014; Varrone et al., 2013). In- and exclusion criteria are listed in the flowchart in Fig. 1.

PD patients were diagnosed by a movement disorder specialist using the clinical diagnostic criteria of the United Kingdom PD Society Brain Bank criteria (Hughes et al., 1992). Severity of the motor symptoms was rated with the Unified Parkinson’s Disease Rating Scale–motor section.
The clinical characteristics of both patient groups are summarized in Table 1. There was no significant difference in median disease duration ($P = 0.831$). For PD patients, the mean UPDRS-III was 29.44 (SD 13.32). Fifty DLB patients (94.3%) had one or more of the classical motor signs of Parkinsonism registered in their patient records. Sixteen PD (30.2%) and 23 DLB (50.9%) patients had an MMSE-score below 25. $123^I$-FP-CIT SPECT scans were also rated in routine practice: forty-three (84.9%) DLB patients and 53 (100%) PD patients had an abnormal rated scan based on a combination of visual assessment and semi-quantitative analysis. Of the remaining eight DLB patients, two (3.7%) had a normal $1^23$I-FP-CIT-SPECT scan, and in six (11.3%) the baseline scan was normal. All six subjects had had second scans at a later time-point, that were classified as abnormal.

3.2. ROI-based $123^I$-FP-CIT SPECT analyses

3.2.1. Striatal DAT binding

Analysis of covariance with age as covariate showed significantly lower striatal $1^23$I-FP-CIT binding in PD patients than in DLB patients in both left and right posterior putamen (left: $F(1,103) = 18.363$, $P < 0.001$, $\omega^2 = 0.14$; right: $F(1,103) = 20.434$, $P < 0.001$,
Table 1

| PD       | DLB       | Statistic/df/P |
|----------|-----------|----------------|
| N        | 53        | 53             |
| Gender   | 10/43     | 10/43          |
| Age at 123I-FP-CIT SPECT scan, mean (SD) | 69.50 (6.39) | 67.83 (5.94) |
| Disease duration, median (IQR) | 3.00 (4.00) | 3.00 (2.00) |
| MMSE, median (IQR) | 26 (5) | 24 (6) |
| UPDRS-III, mean (SD) | 29.44 (13.32) | N/A* |
| H&Y, median (IQR) | 2 (0.5) | N/A |

SD, standard deviation.

PD, Parkinson’s disease; DLB, Dementia with Lewy bodies; SPECT, single photon emission computed tomography; MMSE, mini mental state examination; UPDRS-III, Unified Parkinson’s Disease Rating Scale—motor symptoms; H&Y, Hoehn & Yahr stage; IQR, inter quartile range; U, Mann-Whitney U test statistic; \( \chi^2 \), Chi squared test statistic.

* The presence of motor signs (bradykinesia, rigidity and tremor) was registered dichotomously.

\( \omega^2 = 0.15 \) \((P_{cor} < 0.033)\). Caudate/putamen ratios were also significantly different, with a lower ratio in DLB than in PD \((U (105) = 724.0, P < 0.001)\). There were no significant differences in 123I-FP-CIT binding between PD and DLB in the other striatal ROIs \((Fig. 2)\). UPDRS-III scores in PD patients correlated negatively with 123I-FP-CIT binding between PD and DLB in the other striatal ROIs. Adding the ROI volumes as nuisance covariate in the ROI analysis of covariance did not alter the outcome substantially (data not shown).

3.4. Post-hoc analysis

We did not find a significant difference between PD and DLB patients \((F(1,103) = 0.397, P = 0.530)\) in the midbrain. In addition, we did not find a significant difference between PD and DLB in the volumes of the ROIs. Adding the ROI volumes as nuisance covariate in the ROI analysis of covariance did not alter the outcome substantially (data not shown).

4. Discussion

In this molecular imaging study we compared striatal and extrastriatal 123I-FP-CIT binding between DLB and PD patients matched for age and gender, with MMSE values in the same range of severity. As expected from the literature, we observed significantly lower 123I-FP-CIT binding in the bilateral posterior putamen in PD patients compared to DLB patients with a large effect size \((left: \omega^2 = 0.14; right: \omega^2 = 0.15)\). This difference was observed in both ROI-based and voxel-based analyses. Contrary to our hypothesis, we did not find any significant group differences in 123I-FP-CIT binding in extrastriatal areas, including the thalamus, hippocampus, and amygdala.

The difference in striatal 123I-FP-CIT binding between PD and DLB corroborates the results of previous studies. O’Brien and co-workers, for example, reported a greater loss of 123I-FP-CIT binding in the posterior putamen in PD patients than in DLB patients, reflected by a flatter rostrocaudal gradient in DLB \((O’Brien et al., 2004)\). The same group...
demonstrated that, in comparison to the DLB patients, the rate of decline in $^{123}$I-FP-CIT binding in the posterior putamen in PD patients was higher, measured over an interval of approximately one year (Colloby et al., 2005). Furthermore, other studies have also demonstrated that the posterior putamen in DLB patients is less affected than in PD patients (Piggott et al., 1999; Walker et al., 2004).

In our current sample, we observed no statistically significant differences in $^{123}$I-FP-CIT binding between PD and DLB in extrastriatal SERT-rich ROIs, including bilateral thalamus, amygdala and hippocampus. Since we did not include healthy age-matched controls, we cannot state with certainty that loss of SERT occurred in any of our patient groups, but loss of SERT in PD has been shown before with $^{11}$C-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile.

**Table 2**

Voxel-based analysis.

| Region of interest     | $K_c$ | $P_{FW}$ peak-voxel | $T$ | $x/y/z$ (mm) |
|------------------------|-------|----------------------|-----|---------------|
| Left posterior putamen | 35    | < 0.001              | 5.22| −24/−8/10     |
|                        | 3     | 0.006                | 4.44| −30/−12/2     |
| Right posterior putamen| 70    | < 0.001              | 5.99| 30/−8/2       |
|                        | 2     | 0.022                | 4.02| 24/−2/12      |

Analysis on the ROIs with significant difference between patients with Parkinson’s disease and dementia with Lewy bodies. $K_c$, size of significant cluster of voxels; $P_{FW}$, Family-wise corrected $P$-value; $T$, $T$-statistic value; $x/y/z$, millimetres from the anterior commissure in Montreal Neurological Institute-space.

**Fig. 3.** Mean extrastriatal $^{123}$I-FP-CIT binding ratios in Parkinson’s disease (PD) and dementia with Lewy bodies (DLB); error bars represent the standard deviation (SD).

**Fig. 4.** Voxel based analysis: striatal voxels in which Parkinson’s disease (PD) patients has lower binding than dementia with Lewy bodies (DLB) patients, corrected for age, masked for posterior putamen.
of this study and the use of clinical scans this was not possible. Furthermore, we know from our previous study on SERT binding that ratios of specific to non-specific \(^{123}\)I-FP-CIT binding to SERT remain stable up to 3 h post-injection. Therefore, relative differences in \(^{123}\)I-FP-CIT binding to SERT are still detectable at 3 h post-injection.

In this study, patients on SRIs were excluded, since these drugs block the SERT, and consequently may influence \(^{123}\)I-FP-CIT binding to the SERT. However, inevitably in this retrospective study performed in routine care patients, many were using common dopaminergic agents (e.g., levodopa or dopamine agonists). Although these classes of drugs are usually allowed when performing \(^{123}\)I-FP-CIT SPECT in routine patient care (Booij and Kemp, 2008), we cannot exclude that the use of these drugs may have had an impact on the results of the present study. However, if such an effect indeed occurred, one would expect this to impact DAT binding in all subregions of the striatum. Consequently, we believe it is unlikely that such an effect would explain the difference in \(^{123}\)I-FP-CIT binding between PD and DLB patients.

Another discussion point in our study is that we included patients from two different outpatient clinics, which introduced the risk of a diagnostically different view on equivocal cases. Moreover, there was no consistency in the assessment of motor- and neuropsychiatric variables, both representing important symptom groups in PD and DLB. Since UPDRS-III scores were not determined for the DLB patients we could not compare neural correlates of motor function, which are usually linked to the loss of striatal dopaminergic synapses, also in DLB (Del Sole et al., 2015). Therefore, we cannot exclude the possibility that we failed to find lower caudate \(^{123}\)I-FP-CIT binding in DLB than in PD, and conversely found lower \(^{123}\)I-FP-CIT binding in the posterior putamen in PD just because PD patients had a more severe parkinsonism. A possible mitigating factor for this limitation could be a similar disease duration.

This is another potential limitation of our study: We did not use disease duration as an inclusion criterion. Disease duration was, however, fortunately not different in both diseases. Although we defined disease duration for DLB and PD differently, which by definition makes it less suitable as inclusion criterion: for DLB patients we chose the first appearance of cognitive symptoms as an approximation of disease onset, whereas for the PD patients we used the patient-reported onset of the cardinal motor symptoms.

In conclusion, this study is the first to extensively compare \(^{123}\)I-FP-CIT binding in both striatal and extrastriatal brain areas between PD patients and DLB patients in a relatively large cohort. The results confirm earlier observations of a more severe loss of \(^{123}\)I-FP-CIT binding in the posterior putamen in PD patients than in DLB patients. Furthermore, we found no differences in extrastriatal \(^{123}\)I-FP-CIT binding between the two disease groups, which suggest similar degree of degeneration of serotonergic structures in both diseases.

Disclosure statement

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