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

Merijn Joling[a,b,c,e,*], Chris Vriend[c,d,e], Jessica J. van der Zande[a,c,f], Afina W. Lemstra[a,c,f], Odile A. van den Heuvel[c,d,e], Jan Booij[b,c], Henk W. Berendse[a,c]

[a] Department of Neurology, VU University Medical Center, Amsterdam, The Netherlands
[b] Department of Radiology and Nuclear Medicine, Academic Medical Center, Amsterdam, The Netherlands
[c] Amsterdam Neuroscience, Amsterdam, The Netherlands
[d] Department of Psychiatry, VU University Medical Center, Amsterdam, The Netherlands
[e] Department of Anatomy and Neurosciences, VU University Medical Center, Amsterdam, The Netherlands
[f] Alzheimer Center, VU University Medical Center, Amsterdam, The Netherlands

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ABSTRACT

In this retrospective cross-sectional study we compared ^{123}I-*N*-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (^{123}I-FP-CIT) binding to the striatal dopamine and the extrastriatal 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: $F(1,103) = 18.363$, $P < 0.001$, $\omega^2 = 0.14$; 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 ($U(105) = 724.0$, $P < 0.001$). Extrastriatal 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 also 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

* Corresponding author at: VU University Medical Center, Department of Neurology, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail address: me.joling@vumc.nl (M. Joling).

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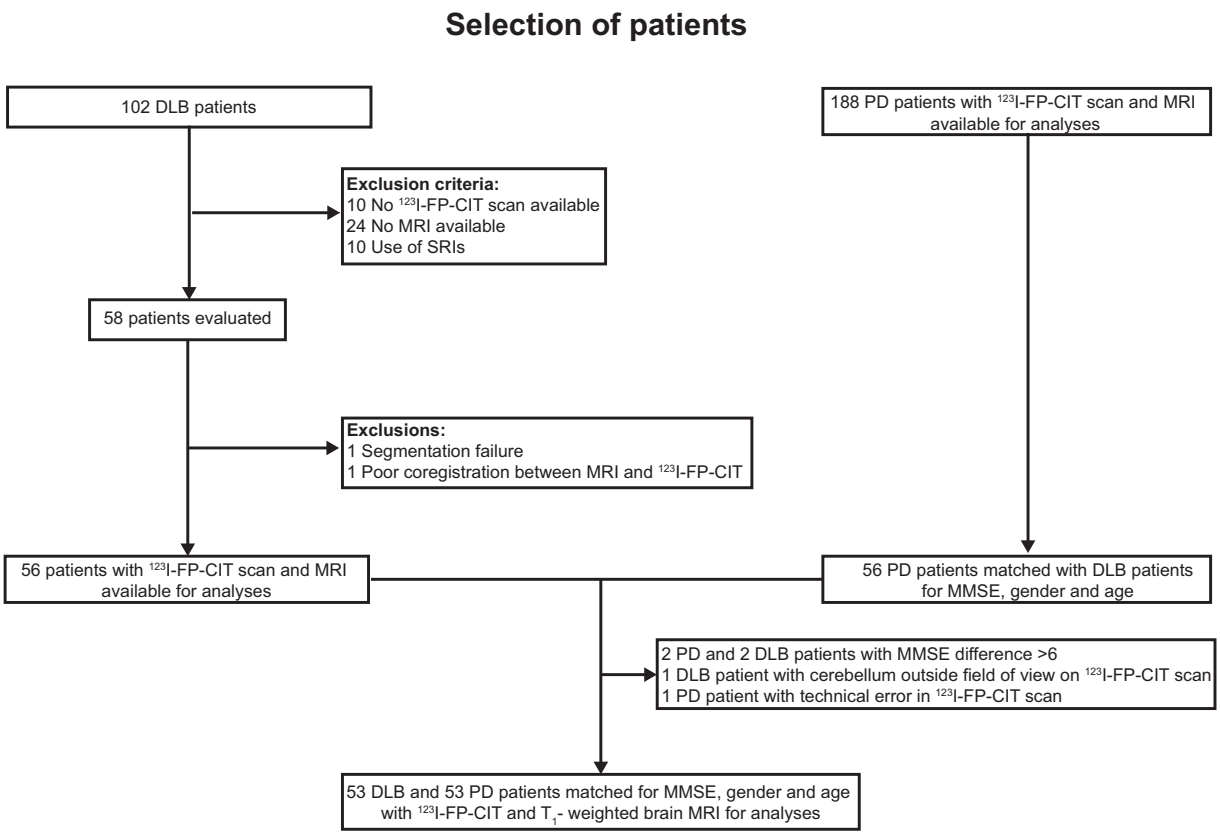

Fig. 1. Patients included in the study - PD, Parkinson's disease; DLB, Dementia with Lewy bodies; MRI, magnetic resonance imaging; SRI, serotonin reuptake inhibitor; MMSE, mini mental state examination.

and serotoninergic 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 dopamine transporter (DAT) (Booij et al., 1997), and, additionally a modest 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 (Booij 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 T_1-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 (Booij 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