Chapter 1

GENERAL INTRODUCTION
**Parkinson’s disease**

Over two hundred years ago, in 1817, the English physician James Parkinson described a combination of symptoms that he attributed to a single, distinct nervous disorder in his monograph ‘*An essay on the shaking palsy*’. He described the symptoms as follows:

“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.” (1)

Armand Trousseau later showed that movements in a patient with this *shaking palsy* progressively slowed down when asking the patient to repetitively open and close a hand (2, 3), thereby demonstrating what we now call bradykinesia (4). Jean-Martin Charcot noticed that bradykinesia, rather than palsy, characterised this disorder. He furthermore added rigidity to the symptoms and suggested to rename the disease to Parkinson’s disease (PD), because in his opinion the term *shaking palsy* did not encompass all of the symptoms that he observed in these patients (2, 5). The symptoms bradykinesia, rigidity, postural instability and resting tremor, are nowadays referred to as the classical motor symptoms of PD; the presence of bradykinesia and at least one of the other classical motor symptoms is defined as *parkinsonism* (6).

James Parkinson also noticed the presence of *non-motor symptoms* in the disease that was later to bear his name (1). Over the years it has become clear that the spectrum of non-motor symptoms in PD is quite wide, and encompasses not only psychiatric symptoms like depression, anxiety, psychosis and impulse control disorders, but also rapid eye movement (REM) sleep behaviour disorder and other sleep disturbances. Moreover, although James Parkinson reported “*the senses and intellects being uninjured*” (1), subtle cognitive problems are frequently present, even in the early stages of PD (7). In up to 75% of PD patients cognitive decline progresses and eventually develops into PD dementia (PDD) (8). Other important non-motor symptoms are autonomic symptoms such as constipation and orthostatic hypotension (9, 10). In many cases non-motor symptoms are already present at the time of the clinical diagnosis, and sometimes even precede the clinical diagnosis for years (11-14).

Currently, approximately 1% of persons older than 60 years have a diagnosis of PD (15). With the relative ageing of populations in Western societies, the number of individuals with PD is likely to increase, thereby intensifying the disease burden that falls on these societies. Treatment of PD remains purely symptomatic since the cause of the disease process has yet to be fully elucidated.

**Pathology of PD**

The symptoms of PD are caused by a neurodegenerative process that affects the brain following a specific pattern, as described in detail by Braak and Braak (16). In PD, neurons in many brain areas contain proteinaceous aggregates, first described as *Lewy bodies* by Konstantin Tretiakoff in 1919, the main constituent of which is α-synuclein (17-21). Lewy bodies are considered to be the neuropathological hallmark of PD (18, 21-24). Nigrostriatal dopaminergic neurons are...
notoriously affected (25-27). These neurons have cell bodies that reside in the substantia nigra pars compacta and project most pronouncedly onto the putamen and the caudate nucleus (28). Together with the nucleus accumbens these nuclei constitute the striatum. Among others, the striatum regulates learned and subconscious movement patterns, and degeneration of dopaminergic neurons inhibits the performance of these patterns, producing many of the motor symptoms that characterise parkinsonism.

The loss of dopaminergic neurons not only plays a role in the motor symptoms of PD, but also contributes to at least some of the non-motor symptoms (29). Not surprisingly, much of the research into PD is directed at the dopaminergic deficits. Yet, dopaminergic neurons are not exclusively affected: degeneration of other neurotransmitter systems, such as the serotonergic (30, 31), noradrenergic (30, 32) and cholinergic systems (33) appears to contribute to the non-motor symptoms of PD. Degeneration of the serotonergic system, for example, has been linked to depression and anxiety (34), and in PD patients anxiety occurs more often than in the general elderly population (35).

Parkinsonisms

The symptom complex of parkinsonism is not exclusive for PD. It is also observed in several other brain disorders and conditions, often making the clinical diagnosis challenging. They comprise for example drug-induced parkinsonism associated with the use of antipsychotics or antidepressants (36), or exposure to toxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (37). Prominent representatives of other neurodegenerative brain disorders associated with parkinsonism, the so-called atypical parkinsonisms, are: progressive supranuclear palsy (PSP) and multiple system atrophy (MSA).

PSP is a neurodegenerative disease, initially described by Steele, Richardson and Olszewski (38), in which aggregates of a protein called tau are found (39). This disorder is therefore classified as a tauopathy. Like in PD, the substantia nigra is also affected in PSP (38). PSP is clinically characterised by a supranuclear impairment of vertical eye movements, cognitive impairment, symmetrical parkinsonism, retrocollis and a poor or transient response to dopaminergic replacement therapy (DRT) (40). Although PSP has a notably different disease course from PD, the similarities in symptoms sometimes make it difficult to confer a clinical diagnosis on these patients in the early disease stages.

MSA is an α-synucleinopathy, like PD, but in contrast to PD the α-synuclein is not aggregated in Lewy bodies. Instead, α-synuclein-rich cytoplasmic inclusions mainly involve glial cells, as observed in post-mortem studies of brains of MSA patients. These glial cytoplasmic inclusions are considered to be the neuropathological hallmark of MSA (41, 42). Two clinical subtypes of MSA can be distinguished: the first is characterised by more pronounced parkinsonian features and is called MSA-P, whereas the other subtype comprises symptoms that can be linked to cerebellar neurodegeneration, and is therefore called the cerebellar subtype or MSA-C (43). Especially in MSA-P, the early stages can be suggestive of a diagnosis of PD. As in PD, the substantia
nigra is also affected (42). Indeed, a former name for MSA-P is striatonigral degeneration (43). Therefore, the differential diagnosis between PD and MSA-P can be difficult at the initiation of symptoms. Distinguishing features from PD are that patients with either of the two MSA subtypes have, generally speaking, a more rapid, aggressive disease course (44), pronounced autonomic symptoms (44) and respond poorly to DRT (45).

**123I-FP-CIT: SPECT imaging in parkinsonisms**

Because of the challenge the clinical diagnosis of PD, as well as the differential diagnosis between the different types of parkinsonism, often poses (46, 47), clinicians need additional tools to aid in the diagnostic process. An example of such a tool is 123I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (123I-FP-CIT), a cocaine analogue that is used as a single-photon emission computed tomography (SPECT) radiotracer (48). It has a high affinity for the presynaptic dopamine transporter (DAT) (49, 50), and can consequently be used to visualise and quantify degeneration of nigrostriatal dopaminergic projections *in vivo* (49). Using this method it is therefore possible to distinguish degenerative from non-degenerative forms of parkinsonism (51).

In addition, 123I-FP-CIT also has a modest affinity for the presynaptic serotonin transporter (SERT) (50), and it has been shown that, like the DAT binding for the dopaminergic system, SERT binding can be used as an *in vivo* proxy for the integrity of the serotonergic system (52, 53) (see *Figure 1*). DAT is more prominent in the striatum (54), and striatal 123I-FP-CIT binding is therefore assumed to preferentially represent DAT binding (49) (*Figure 2A*). SERT is also present in the striatum, but much less abundantly (55). By contrast, DAT is much less abundantly present in areas outside of the striatum (54), the extrastriatal areas. Increased binding in extrastriatal brain areas on 123I-FP-CIT SPECT scans is therefore assumed to preferentially represent SERT binding (52, 53, 55, 56) (*Figure 2B*).

The capacity of 123I-FP-CIT to bind to the SERT has scarcely been utilised to study parkinsonisms to date, even though it is of potential interest to use this additional information, which can be derived from the same 123I-FP-CIT SPECT scan that is often made to establish degeneration of the nigrostriatal dopaminergic system as part of the differential diagnostic process in parkinsonism. Moreover, many 123I-FP-CIT SPECT studies have focused on the role of the striatal DAT in motor symptoms of parkinsonisms, yet the same imaging tool may be used to examine the role of extrastriatal SERT, particularly in the non-motor symptoms in which serotonin plays a role, such as anxiety (34).
Figure 1. Schematic depiction of a dopaminergic and a serotonergic synaptic cleft with $^{123}I$-FP-CIT present.
A Lewy body disease spectrum

Dementia with Lewy bodies (DLB) and PD are considered to be part of a spectrum of α-synucleinopathies. Currently, for DLB, the one year rule, where cognitive decline appears before or no longer than one year after the development of parkinsonism, is the primary basis for a clinical distinction from PD (57, 58). However, PD and DLB also vary in other clinical aspects. Additional distinguishing features of DLB include: fluctuations in cognitive function, hallucinations and a rapid disease progression (57, 58). For patients and caregivers it is important to be able to predict what treatment options will be most successful and what prognosis can be expected. From that perspective, a distinction between PD and DLB is still clinically useful.

Neuropathological studies have revealed differences in the severity of the degeneration of the dopaminergic system (59), and differential presence of pathological lesions in the striatum (60) between PD and DLB. In addition, a difference in the extent of the rostro-caudal gradient of striatal $^{123}$I-FP-CIT binding has also been reported between PD and DLB (61, 62). These dissimilarities in the degeneration of the dopaminergic system make it tempting to suggest that there may be differences in other neurotransmitter systems as well. The serotonergic system, for example, is also affected in DLB: in neuropathological studies a loss of serotonergic neurons has been observed (63). It is therefore interesting to study the serotonergic system in both PD and DLB by means of $^{123}$I-FP-CIT (64), and to add information to determine their position in the spectrum of α-synucleinopathies.

Figure 2. Transverse images of $^{123}$I-FP-CIT SPECT scans of healthy controls with binding intensity ranging from black (no binding), through red (low to modest binding) and yellow (pronounced binding) to white (highest binding). A. $^{123}$I-FP-CIT binding in the striatum, mainly representing binding to the DAT (green arrows). B. $^{123}$I-FP-CIT binding in extrastriatal areas, such as the midbrain, mainly representing binding to the SERT (blue arrow).
Aims and outline of this thesis

The abovementioned background information and the relative paucity of extrastriatal SERT-directed studies into parkinsonisms led to the following questions:

1. Do various forms of parkinsonism (PD vs PSP vs MSA-P vs MSA-C) differ in extrastriatal 123I-FP-CIT binding, on top of the well-documented loss of striatal 123I-FP-CIT binding?
2. Is there a difference in striatal and/or extrastriatal 123I-FP-CIT binding between PD and DLB?
3. Do PD and DLB have reduced extrastriatal 123I-FP-CIT binding relative to healthy controls?
4. Is extrastriatal 123I-FP-CIT binding associated with neuropsychiatric symptoms in PD patients, specifically anxiety?

In Chapter 2 we describe the results of a study aimed to answer question 1 by analysing striatal and extrastriatal 123I-FP-CIT SPECT binding in scans obtained in a population of PD, PSP, MSA-P and MSA-C patients. Chapter 3 provides a description of an 123I-FP-CIT SPECT study in which we compared scans of PD patients with scans of DLB patients to find an answer to question 2. In Chapter 4 we extend the search from Chapter 3 with question 3 to gain more insight in the differences in 123I-FP-CIT binding between PD and DLB and healthy controls. In Chapter 5 we report on a study into the link between extrastriatal 123I-FP-CIT SPECT binding and anxiety symptoms in PD patients, thereby trying to answer question 4. In Chapter 6 we summarise the results described in this thesis and provide some suggestions for future research.