General introduction
James Parkinson (1755-1824) first officially described in 1817 the clinical entity of Parkinson’s disease (PD) in his celebrated Essay on the Shaking Palsy. He established the signs and symptoms of tremor, bradykinesia and gait and postural disturbances into a recognizable clinical entity. Parkinson’s description, however, was based on only six cases he had observed in his own practice as well as on walks around his London neighborhood. Four decades later the French neurologist Jean-Martin Charcot emphasized that tremor need not be present in the disorder and added a fourth symptom, muscular rigidity, to the clinical picture. In addition, he suggested that the disease should be named Parkinson’s disease. In current clinical practice, tremor, rigidity, brady/hypokinesia and loss of postural reflexes are still regarded as the four cardinal motor symptoms of PD. This symptom complex is commonly known under the name of parkinsonism.

Many years after Parkinson’s formal description, in 1871, the basal ganglia were first recognized by Meynert as being involved in disorders of abnormal movement. In 1913, the German neurologist Lewy found at autopsy cytoplasmic inclusions, now widely recognized as the pathological hallmark of PD and referred to as Lewy bodies. In the ensuing decades, a loss of pigmented cells in the substantia nigra of PD patients was reported as well as cell loss in other brain stem nuclei such as the locus coeruleus. In the mid-1960s, the existence of the nigrostriatal dopaminergic pathway, involved in the regulation of motor behaviour, was demonstrated. Up to then, pharmacological treatment was largely limited to the administration of anticholinergic agents. The discovery that the nigrostriatal dopaminergic system was involved in PD led to the introduction of levodopa. The treatment of PD evolved in the ensuing years, with optimization of administration regimens, as well as the introduction of decarboxylase inhibitors.

In recent years, the spectrum of PD-related signs and symptoms has been expanded to include many non-motor features. PD is now regarded as a multisystem disorder, which is clinically characterized by a combination of motor deficits and a wide range of non-motor disturbances such as olfactory deficits, cognitive deficits, dementia, autonomic disorders, sleep disturbances, affective disorders, pain, fatigue and sensory impairments.

**Prodromal phase of PD**

Traditionally, the appearance of parkinsonism is considered the onset of clinical PD. However, several lines of evidence suggest that PD has an extensive prodromal (also referred to as preclinical or premotor) phase that precedes the development of the classical motor signs.
Firstly, a pathological study based on postmortem cell counts of pigmented neurons in the substantia nigra has shown that the onset of dopaminergic cell loss probably antedates the clinical diagnosis by about four to five years. Confirmation of this pathological finding came from neuroimaging studies using positron emission tomography (PET) or single-photon emission computed tomography (SPECT) to visualize the degeneration of dopaminergic neurons located in the substantia nigra, pars compacta, and their projections to striatal regions. A substantial loss of striatal dopamine transporters in PD was demonstrated using SPECT ligands such as \(^{123}\text{I}\)-labeled 2β-carbomethoxy-3β-(4-iodophenyl)-tropane (\([^{123}\text{I}]\beta\text{-CIT}\)) or its \([^{123}\text{I}]\)fluoropropyl derivate (\([^{123}\text{I}]\text{FP-CIT}\)) \(^{17-19}\). Studies in newly diagnosed PD patients showed a substantial (58-64%) loss of dopaminergic neurons already at the time of the clinical diagnosis \(^{20-22}\). Based upon the extent of degeneration at clinical diagnosis, and a subsequent seven to nine percent annual rate of decline of in vivo dopaminergic markers, the onset of dopaminergic neuronal loss was estimated to antedate the clinical diagnosis by about four to six years \(^{23,24}\).

More recently, novel neuropathological findings using alpha-synuclein antibodies to visualize Lewy bodies and neurites have emphasized that PD specific brain pathology extends far beyond the nigrostriatal dopaminergic system \(^{25}\). In addition, PD pathology appeared to evolve following a predictable topographical sequence over the course of the disease. In the preclinical (I and II) and the earliest clinical stages (III), neuropathological changes are most prevalent in the brainstem (and the olfactory bulb and tract). Degeneration of brainstem nuclei includes not only the dopaminergic neurons in the substantia nigra and the ventral tegmental area, but also noradrenergic (locus ceruleus) and serotonergic neurons (dorsal raphe nuclei). In addition, several other neurotransmitter systems such as the cholinergic system (nucleus basalis of Meynert) are involved as well. In the more advanced stages pathology exacerbates and ascends to include forebrain structures and limbic cortical areas (IV), eventually spreading into the neocortex in disease stages associated with dementia (V and VI). Interestingly, damage to extranigral areas, such as the olfactory system, appears to precede damage to the dopaminergic neurons in the substantia nigra.

The progressive degeneration of different neuronal populations in PD, including that of the mesencephalic dopaminergic neurons, is an ongoing and irreversible process. Although the etiology of PD is still unknown, several mechanisms have been proposed such as abnormal protein accumulation, in particular of alpha-synuclein, mitochondrial dysfunction, oxidative stress and neuroinflammation \(^{26-28}\). Based on this knowledge, a considerable array of promising neuroprotective agents has been developed and tested in animal models and clinical settings \(^{29}\). The evidence for a prodromal phase in PD provides a unique opportunity for early diagnosis and neu-
roprotective intervention, provided that we are able to accurately detect the pathological process early in its course.

Potential biomarkers of early stage, prodromal PD include subtle motor abnormalities (including changes in handwriting, clumsiness, decreased arm swing when walking, subtle asymmetric hypokinesia, fatigue and abnormalities of visuomotor control), nonmotor symptoms related to extranigral pathology (such as olfactory disturbances and subtle cognitive dysfunction), and imaging of the presynaptic element of the nigrostriatal dopaminergic system.

**Early motor signs in Parkinson’s disease**

Several observational studies have shown that motor abnormalities can be identified years before the diagnosis of PD is made. One example is the case of a soccer player who, when videotapes of his games were reviewed, showed evidence of motor problems 10 years before the diagnosis of PD\(^30\). Similarly, in a retrospective analysis of handwriting, Tetrud\(^31\) showed changes in a patient’s signature on checks years before the diagnosis. In line with these observations, a number of studies have proposed methods to identify and quantify early motor abnormalities in incipient PD\(^32-36\). These motor tests mainly focused on velocity, reaction time and precision of movements. Most of these investigations revealed significant group differences between patients with idiopathic PD and controls. However, there was also a considerable overlap between individual patients and controls with a significant number of PD patients scoring in the same range as controls. Although it is therefore unlikely that these previously described tests of motor function can stand alone as an early diagnostic tool for PD, it may be possible to develop novel motor function tests with higher sensitivity and specificity.

**Olfactory dysfunction in Parkinson’s disease**

Olfactory deficits in PD were first empirically documented in 1975 by Ansari and Johnson\(^37\), who reported decreased olfactory acuity in a heterogeneous group of PD patients. Over the ensuing years it has become clear that most PD patients have olfactory disturbances that are not restricted to a single functional modality but include impairments of odour detection, discrimination and identification\(^38-44\). Olfactory deficits are quite common even in untreated, newly diagnosed PD patients\(^38,40,44,45\). The latter observations as well as reports of olfactory dysfunction in first-degree relatives
of PD patients\textsuperscript{33,46}, suggest that olfactory dysfunction may already be present in the prodromal phase of the disease.

**Cognitive Dysfunction in Parkinson’s Disease**

Mild cognitive impairment is a very common finding in PD\textsuperscript{47}. Although deficits are usually relatively subtle and may not affect daily functioning, cognitive deficits can, nevertheless, be associated with a lower quality of life in PD even in patients not fulfilling DSM criteria for dementia\textsuperscript{48}. A wide variety of cognitive deficits have been reported in non-demented PD patients, the most prominent of which are deficits in executive function\textsuperscript{49,50}. Executive function is a broad term used to describe a range of cognitive functions involved in the realization of goal-directed, adaptive behaviour in response to new, challenging environmental situations, including attention, inhibition, task management, planning, monitoring and coding\textsuperscript{51}. Besides executive dysfunction, there is compelling evidence of visuospatial deficits in non-demented PD, even when tests contain only few motor components\textsuperscript{52-54}.

Subtle cognitive impairment has been demonstrated in the earliest clinical stages of PD\textsuperscript{49,55,56}. Moreover, PD-like executive dysfunction has also been observed in first-degree relatives of PD patients\textsuperscript{57}. Another argument in favor of cognitive deficits as a manifestation of prodromal PD comes from a study in the MPTP-treated primate, an animal model of PD. In this study, executive deficits were found before the appearance of clinical motor disturbances\textsuperscript{58}, suggesting that these impairments may occur as a pre-motor feature of a dopaminergic deficit.

**Nuclear Imaging of the Presynaptic Nigrostriatal Dopaminergic System**

As has already been mentioned above, the nigrostriatal dopaminergic cell loss in PD can be visualized by means of PET or SPECT scanning. In most patients with PD, the early course of the disorder is characterized by unilateral onset of motor symptoms with subsequent bilateralization of symptoms. Nuclear imaging studies in hemiparkinsonian patients have shown a significant bilateral degeneration of the dopaminergic system i.e. also on the side corresponding to the clinically unaffected body half\textsuperscript{59-61}. In addition, \textsuperscript{18}F\textit{dopa} PET studies have shown subclinical nigrostriatal dysfunction in the unaffected sibling of monozygotic twin pairs one of whom suffered from PD, and in unaffected relatives of patients with a familial form of PD, some of whom subsequently developed clinical parkinsonism\textsuperscript{62-65}. Moreover, a SPECT study demonstrated subclinical reductions of dopamine transporter bind-
ing in asymptomatic relatives of sporadic PD patients. These findings suggest that prodromal decreases in nigrostriatal dopaminergic function are detectable by means of both SPECT and PET imaging.

**RESEARCH QUESTIONS AND OUTLINE OF THESIS**

The general objective of this thesis was to explore potential diagnostic strategies to detect prodromal PD. The following main research questions were addressed:

- Can complex upper limb motor tasks be used to distinguish between early stage, untreated PD patients and controls, and are these tasks suitable as diagnostic screening tools for PD?
- Is olfactory dysfunction associated with an increased risk of developing PD?
- Is executive cognitive dysfunction associated with an increased risk of developing PD?
- Is a two-step approach of olfactory testing followed by SPECT scanning of the nigrostriatal dopaminergic system a potential diagnostic strategy for prodromal PD?

The first part of this thesis includes the results of two studies in which complex upper limb motor tasks were administered to early-stage, untreated PD patients. Chapter two describes the results of four unimanual upper limb motor tasks. Using a handwriting task, a pointing task, an aiming task and a Fitt’s task, subtle motor deficits were explored in early-stage, untreated PD patients. In the study described in chapter three, bimanual coordination function was explored in early-stage, untreated PD patients to determine whether bimanual coordination dysfunction is an early motor sign of PD.

The second part of this thesis is based upon the results of the two- and five-year follow-up of a prospective study in first-degree relatives of PD patients aimed at determining the predictive value of olfactory disturbances and executive cognitive dysfunction for the development of clinical PD. Baseline data of this prospective study were published in advance of this thesis, showing subclinical degeneration of the nigrostriatal system in hyposmic, asymptomatic, first degree relatives of PD patients. The two year follow-up results, including clinical data and SPECT imaging of the nigrostriatal dopaminergic system, of this study are described in chapter 4. In chapter 5, the focus is on the predictive value of olfactory dysfunction and cognitive dysfunction for developing PD based on a Cox regression analysis. Finally, in the sixth chapter, the combination of olfactory testing and dopamine transporter SPECT scanning in predicting future PD over a five-year period is described.
REFERENCES