Parkinson’s disease (PD) is characterized pathologically by a progressive loss of dopamine producing neurons in the mesencephalon. By the time a clinical diagnosis of PD is made, a significant loss (>50%) of dopaminergic neurons has already occurred. The onset of dopaminergic neuronal loss probably antedates the onset of clinical signs and symptoms by about 4 to 6 years. Recent studies in PD have provided compelling evidence for pathological involvement of extranigral brain areas, including the olfactory bulb and tract. The four cardinal motor symptoms of PD are tremor, rigidity, bradykinesia and loss of postural reflexes. However, PD is now regarded as a multisystem disorder, which is clinically characterized by these cardinal 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. In PD, functional impairment and disability increase with disease duration and reduce social, psychological and economic well-being of both patient and care-giver. The current symptomatic treatment of PD can only delay functional impairment for some years. Furthermore, long term treatment with levodopa is accompanied by dyskinesias and motor response fluctuations, resulting in additional disease burden. Accordingly, there has been an intensive search for neuroprotective therapies that are able to slow down the degenerative process. Considering the substantial loss of dopaminergic and other neurons by the time a clinical diagnosis of PD is made, any type of neuroprotective treatment should be started as early as possible, preferably in the prodromal phase of the disease. This would not only delay the onset of clinical signs and symptoms of PD, but also the stage of disease in which patients become dependent on their care-givers.

The general objective of this thesis was to explore potential diagnostic strategies for the detection of prodromal (i.e. the phase preceding the classical motor signs) Parkinson’s disease (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?

Complex upper limb motor deficits in early stage PD.

In chapter 2 we show that, compared to their healthy controls, newly diagnosed, untreated PD patients are impaired in performing complex unimanual upper limb movements including handwriting, an aiming and a pointing task. The results of the study described in chapter 3 demonstrate that bimanual coordination dysfunction is also a very early motor impairment in PD.

Taken together; the studies described in the first part of this thesis have shown that both unimanual and bimanual motor deficits are present in newly diagnosed, untreated PD patients. Since these tests are easy to administer, they might be considered as elements of an early diagnostic test battery for PD. However, our results also made clear that both uni- and bimanual motor impairments have only modest sensitivity and specificity in distinguishing newly diagnosed, untreated PD patients from controls. Therefore, based upon the results described in this thesis, it is unlikely that a purely motor approach to the detection of PD in its prodromal phase would be successful.

The predictive value of olfactory dysfunction for incipient PD.
The results described in chapters 4 and 6 of this thesis are based on a prospective study, involving a cohort of 361 first-degree relatives of PD patients. Baseline evaluation included a combination of olfactory detection, identification and discrimination tasks. Based on olfactory performance, groups of hyposmic (n=40) and normosmic (n=38) individuals were selected for SPECT scanning, using $^{123}$Iβ-CIT as a dopamine transporter ligand, to assess nigrostriatal dopaminergic function. From the two year follow-up results of this study, described in chapter 4, we learned that idiopathic olfactory dysfunction is associated with an increased risk of developing PD of at least 10%. Five year follow-up data from the same cohort, presented in chapter 6, show that the risk of developing PD associated with idiopathic hyposmia had increased to 12.5%. In chapter 5 we show that, over a five-year follow-up period in these first degree relatives of PD patients, decreasing performance on each of the three olfactory tests used (odor discrimination, odor detection and odor identification) is associated with an increased risk of future PD. Impaired odor discrimination appears to be the best predictor for future PD.

**The predictive value of cognitive dysfunction for incipient PD.**

As described in chapter 5 we also assessed baseline executive cognitive function in the same cohort of asymptomatic first-degree relatives of PD patients and demonstrated that executive dysfunction is not associated with the risk of developing PD within five years.

**A two-step approach in detecting incipient PD: olfactory testing followed by SPECT imaging.**

In line with previous observations, showing prodromal decreases in nigrostriatal dopaminergic function, the results described in chapter 4 demonstrate that baseline
SPECT imaging served to detect incipient PD in hyposmic first degree relatives of PD. In addition, at two year follow-up, an increased rate of loss of striatal dopamine transporter binding was present in hyposmic relatives that remained non-parkinsonian, possibly indicative of incipient degeneration of the nigrostriatal dopaminergic system in these individuals. However, the five year follow-up results (chapter 6) could not confirm the presence of a subclinical degeneration of the nigrostriatal dopaminergic system in non-parkinsonian hyposmic relatives. The discrepancy between the two-year and five-year SPECT data may be explained by a decreased susceptibility to biological variation as the interval between SPECT scans increases. It is important to note that all hyposmic individuals who developed PD within five years from baseline had abnormal striatal dopamine transporter binding at baseline (chapter 6).

To summarize, the studies described in the second part of this thesis, show that only those individuals with both an impaired sense of smell and an abnormal baseline SPECT scan developed clinical PD within a five year follow-up period. This suggests that a two-step approach using olfactory testing followed by SPECT scanning in hyposmic individuals may have very high sensitivity and specificity in detecting cases of incipient PD. However, this proof-of-principle needs confirmation in larger and community-based populations.

The general discussion, described in chapter 7, combines the data presented in the various chapters of this thesis and provides a consideration of the potential implications as well as future research perspectives. The main conclusion of this thesis is that olfactory dysfunction in first degree relatives of PD patients is associated with an increased risk of developing PD within five years. Furthermore, a two-step approach of olfactory testing and subsequent nuclear imaging of the nigrostriatal system in hyposmic subjects seems to be a potential early diagnostic strategy to detect individuals with
incipient PD. By contrast, executive cognitive impairment is not associated with an increased risk of developing PD over a period of five years. Lastly, subtle motor deficits can be quantified in early-stage, untreated PD patients using easy-to-administer motor tasks. However, considering the modest sensitivity and specificity of these tasks in distinguishing early stage PD patients from controls, it is unlikely that subtle motor deficits will contribute substantially to an early diagnostic screening strategy aimed at the prodromal phase of PD. Future research should be aimed at further improving the two-step approach toward the early detection of PD by combining olfactory testing with additional clinical, genetic or imaging markers to make this approach feasible for large scale screening purposes in clinical practice and ultimately as part of neuroprotective treatment strategies.