General discussion and Conclusions
The main findings of this thesis are summarized and discussed in this section. 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). In the first part, we assessed complex upper limb motor tasks in early-stage, untreated PD patients and controls, and considered their merits as potential diagnostic screening tools for PD. In the second part, the predictive value of olfactory disturbances and executive cognitive dysfunction for the development of clinical PD was explored in a cohort of first-degree relatives of PD patients. In this cohort of first-degree relatives, we explored a two-step approach of olfactory testing followed by SPECT scanning of the nigrostriatal dopaminergic system in hyposmic individuals as a potential prodromal diagnostic tool for PD.

1. COMPLEX UPPER LIMB MOTOR DEFICITS IN EARLY STAGE PARKINSON’S DISEASE

In chapter 2 we showed 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.

2. THE PREDICTIVE VALUE OF OLFACTORY DYSFUNCTION FOR INCIPIENT PARKINSON’S DISEASE

In considering that olfactory deficits are present at the earliest stage of the disease and have been found in asymptomatic relatives of patients with either familial or sporadic forms of PD\(^1,2\), the question arises whether olfactory dysfunction might be a prodromal sign of PD. From the two-year follow-up results of a longitudinal study in a cohort of first-degree relatives of PD patients, described in chapter 4 of this thesis, 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, showed that the risk of developing PD associated with idiopathic hyposmia had increased to 12.5%. The association between hyposmia and the risk of future PD has now been confirmed in other selected and non-selected populations\textsuperscript{3,4}. Although the predictive value of 12.5% in our cohort is relatively high compared to the results presented in other studies\textsuperscript{3,4}, the absolute risk to develop PD conferred by hyposmia is not very high. Because, olfactory impairments may occur as a result of many conditions and disorders, it is unlikely that olfactory testing alone is a useful screening method to detect individuals at risk for PD.

Although the association between hyposmia and the risk of future PD\textsuperscript{3-6}, is now well-established, the length of the prodromal phase of PD remains to be determined. The results described in chapter 4 and 6 indicate that the risk of developing clinical PD in hyposmic relatives of PD patients is higher in the first two years from baseline than in the subsequent three years. This observation is in line with the population-based study by Ross et al. demonstrating that hyposmia is associated with an increased risk of developing PD during the first four years and not the second period of four years of follow-up\textsuperscript{3}. Another small study in World War II veteran twins showed that olfaction was not a sensitive indicator of incident PD when measured seven or more years before onset of motor signs\textsuperscript{7}. Based upon their neuropathological studies, Braak and colleagues have suggested that the disease process of PD affects the olfactory structures long before the substantia nigra\textsuperscript{8}. Considering that there is a delay between the onset of dopaminergic neuronal loss and the appearance of the classical clinical motor symptoms, which is estimated at four to six years\textsuperscript{9,10}, the Braak staging system would predict olfactory disturbances to arise even longer before the onset of motor symptoms. So far, the available data on hyposmia and the future risk of PD do not seem to support a very long prodromal phase. However, there may be a delay of several years between the pathological involvement of the olfactory system and the actual onset of clinical olfactory deficits. Future studies are necessary to clarify these uncertainties.

Olfactory deficits in PD are not restricted to a single functional modality but include impairments of odour detection, discrimination and identification\textsuperscript{11-18}. Odour recognition memory, on the other hand, is not independently impaired in PD patients\textsuperscript{18}. Each of these various aspects of olfactory function can be assessed by means of so-called psychophysical olfactory processing tasks\textsuperscript{13,19-22}. The association between olfactory dysfunction (as defined in this thesis by using a combined Z-score derived from the test scores on odour detection, identification and discrimination tasks) and the risk of future PD raises the question which individual test or combination of tests would have the highest predictive value for the later development of PD. In chapter 5 we showed that, over a five-year follow-up period in first degree relatives
of PD patients, decreasing performance on each of the three olfactory tests used (odor discrimination, odor detection and odor identification) was associated with an increased risk of future PD. Impaired odor discrimination appeared to be the best predictor for future PD. The latter finding is somewhat unexpected since studies evaluating olfactory function in the clinical motor stage of PD have revealed a higher prevalence of impaired odor identification performance than of a deficit in odor discrimination performance. In other studies reporting on the predictive value of olfactory testing in the prodromal phase of PD, only a single olfactory function test was used or the predictive value for future PD was not analyzed separately for each single olfactory function test used. Future studies are necessary to determine the exact value of testing individual aspects of olfactory function when aiming to predict future PD.

3. The Predictive Value of Cognitive Dysfunction for Incipient Parkinson’s Disease

In chapter 5 we also assessed baseline executive function in asymptomatic first-degree relatives of PD patients and demonstrated that executive dysfunction is not associated with the risk of developing PD within five years. Therefore, this finding does not support the results of a previous study, which suggested that cognitive deficits, in particular executive dysfunction, may precede motor symptoms in PD. However, this could be due to the type of tasks we have used. Other tests assessing (executive) cognitive function, such as the Wisconsin Card Sorting test or the Tower of London-Drexel test may be more sensitive in predicting future PD.

4. A Two-Step Approach in Detecting Incipient Parkinson’s Disease: Olfactory Testing Followed by SPECT Imaging

Imaging biomarkers have been widely used to assess early stage PD. Results of multiple studies have shown that prodromal decreases in nigrostriatal dopaminergic function are detectable by means of both SPECT and PET imaging of the presynaptic element of the nigrostriatal dopaminergic system. In line with these observations, 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, 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. An ongoing observational study (the PARS study) will evaluate the combination of olfactory testing and nuclear imaging in a more extensive cohort of first degree relatives of PD patients.

5. Diagnostic strategies in the early detection of Parkinson’s disease

An early diagnosis of PD is desirable to provide appropriate management and an adequate prognosis. 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. To date, many promising candidate neuroprotective agents, based on pathological and laboratory research are being studied. 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.

Although the two-step approach using olfactory testing followed by SPECT scanning in hyposmic individuals, as described in this thesis, holds promise as a means to identify patients with prodromal PD, a wider application for screening purposes would require too many SPECT scans in healthy individuals. As demonstrated in this thesis, hyposmia is a sensitive marker for incipient PD, but unfortunately insuf-
ficiently specific for PD. To resolve this problem, the prodromal period of PD needs to be characterized further to identify additional markers that can be used together with hyposmia to increase specificity of the first screening step for PD. Potential markers include other non-motor symptoms associated with extranigral pathology, such as REM sleep behavior disorder (RSBD) and autonomic disturbances as well as genetic risk factors and novel imaging techniques.

Much like hyposmia, RSBD can precede PD and is diagnosed by means of non-invasive polysomnography. Other studies have shown compelling evidence for constipation preceding the onset of motor symptoms. Changes in gastrointestinal function can be assessed using a brief questionnaire. Over the past decade, five gene mutations have been identified that cause either autosomal dominant or autosomal recessive PD. Furthermore, numerous efforts have been made to detect susceptibility genes associated with an increased risk of PD. Recently, the international LRRK2 Consortium has been established to evaluate the combination of genetic and other potential markers to clarify the prodromal period in LRRK2-associated PD patients.

In addition to clinical and genetic markers, a number of imaging techniques hold promise as tools to identify individuals with incipient PD. Transcranial ultrasound of the substantia nigra, for example, is an emerging and easy-to-administer, noninvasive diagnostic test. This technology must still be validated beyond the small number of research centers that perform the procedure regularly before it can be established as a screening tool. Recently, high resolution diffusion tensor imaging (DTI) has been used to differentiate between early stage PD patients and healthy individuals. Considering the degree of separation between the groups that could be achieved, DTI clearly holds promise as a noninvasive biomarker for prodromal PD. Future studies are necessary to provide independent confirmation of these findings.

Conclusions

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 clinical 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 neuro-protective treatment strategies.
REFERENCES


Chapter 7


54. Becker G, Seufert J, Bogdahn U, Reichmann H,


