CHAPTER 6

Summary
Parkinson’s disease is a severe and progressive neurodegenerative disorder pathologically characterized by preferential loss of neurons in the substantia nigra. The etiological mechanism responsible for this neuronal degeneration remains largely unknown. The cardinal clinical features are rigidity, bradykinesia, resting tremor and postural instability. The most of patients eventually face significant functional deterioration that cannot adequately be controlled with available medications. Better long term management of PD includes development of therapies which would be able to prevent or slow down the progressive neuronal degeneration and clinical disability. In seeking for such a therapy several issues are of crucial importance. Besides the need for understanding of the underlying pathological mechanism responsible for cell death, in order to be able to develop promising neuroprotective agents, it is imperative to be able to detect patients at early stages of the disease and to identify the subjects at risk. Only administered as early as possible in the disease course the neuroprotective therapies can be effective. In addition, it is necessary to define reliable endpoints for clinical trials that reflect disease progression, in order to determine whether the therapeutic intervention indeed influenced the disease course.

The aim of this thesis was first to address the early clinical (motor) features of PD. Using the tools from dynamical theory of movement coordination we tried to obtain more insight in the nature of the clinical signs of PD early in its course, which might be valuable in the early detection of the disease. Next, we highlighted the etiopathogenetic mechanisms of PD within the frame of oxidative stress theory and discussed leads for the development of putative neuroprotective strategies. In search for a tool which could be used to measure the effects of putative neuroprotective interventions we investigated the utility of $^{123}$I$\beta$-CIT and $^{123}$IFP-CIT SPECT in the assessment of the rate of progression of dopaminergic degeneration in early PD patients.

In chapter 1 general background information on Parkinson's disease (pathology, pathogenesis, clinical features, diagnosis, natural course, prognosis and therapy) is provided. The need for development of therapies which could prevent further dopaminergic degeneration and thereby slow down or halt the disease progression is underlined. The possibilities to identify patients in early or even preclinical disease stage are discussed.

In chapter 2 the clinical features of early PD such as tremor, rigidity and bradykinesia, are analyzed, partly from the perspective of dynamical systems theory. In chapter 2.1 we attempted to disclose the nature of the resting tremor in PD and its relationship with the disruption of the dopaminergic pathway, assessed with $^{123}$I$\beta$-CIT SPECT, in early, de novo PD patients. We found that rigidity significantly influenced the expression of tremor in the same arm. However, when confounding influence of rigidity was taken into account, no significant correlation was found between striatal radioligand binding and the degree of tremor. This suggests that other pathophysiological mechanisms
might be involved in the development of resting tremor in PD. The appearance of dominant tremor and rigidity in the same extremity makes it important to correct for the influence of rigidity in settings where the resting tremor in PD patients is investigated.

In chapter 2.2 the coordination patterns in early, de novo PD patients during walking were investigated using dynamical systems approach. The walking speed was systematically manipulated. We hypothesized that classical PD symptoms such as bradykinesia and rigidity reduce the flexibility of coordination patterns of arm and leg movements during walking with systematically manipulated speed even in the early stage of the disease. Our findings indicated that early-stage PD patients were generally, to a certain degree, able to adapt their arm and leg coordination during walking with externally manipulated speed. However, this adaptation was markedly limited by rigidity as well as bradykinesia and its extent was related to the degeneration of the presynaptic dopaminergic pathway as expressed by $^{123}$I$\beta$-CIT SPECT.

In chapter 3 etiopathogenic mechanisms of PD are discussed along the line of the oxidative stress hypothesis and within this frame the possible targets for neuroprotective treatment in PD are proposed. Especially the role of glutathione (loss) in PD, phase II bio-transformation enzymes, dopamine auto-oxidation and detoxication are highlighted.

Dopamine transporter (DAT) imaging with PET and SPECT are valuable tools for the assessment of the integrity of presynaptic dopaminergic nerve terminals in PD. In search for a reliable method to detect the rate of disease progression in PD, that can be used to measure the effects of putative protective therapies we focused on DAT SPECT.

In chapter 4.1 we describe the results of longitudinal assessment of disease progression in early stage, de novo PD patients with SPECT and two DAT radioligands, $^{123}$I$\beta$-CIT and $^{123}$IFP-CIT. SPECT imaging with both radioligands shows comparable imaging quality, however the faster kinetics of $^{123}$IFP-CIT allows for image acquisition as early as 3 h post-injection (versus 24 h post-injection in case of $^{123}$I$\beta$-CIT). Our results indicated the mean annual rate of dopaminergic degeneration in early stage PD to be about 8%, which is much faster than in normal aging. We concluded that SPECT imaging with both radioligands, $^{123}$I$\beta$-CIT and $^{123}$IFP-CIT, is an adequate tool to measure the rate of disease progression in PD.

Then we investigated the influence of dopaminergic medication (dopamine agonists) on SPECT DAT binding measures. In a subgroup of PD patients sequentially imaged while on treatment with $D_2$ receptor agonists and drug-naive or withdrawn from $D_2$ agonist treatment no significant changes in the binding of $^{123}$I$\beta$-CIT to striatal dopamine transporters was found, suggesting the stability of DAT imaging upon this dopaminergic medication.

Additionally, we performed sample size calculations for future studies on the evaluation of neuroprotective treatments.
In chapter 4.2 we reviewed the evidence on the utility of DAT imaging in early PD detection, as a biological marker of PD progression as well as a tool to monitor the effects of putative neuroprotective drugs. Since it is clear that, in neuroprotective trial design, the biomarker should reflect a biological process that changes with progression of PD and that its measurement should be reproducible and not affected by the study drug or by symptomatic treatments for PD, we critically addressed the issues of sensitivity, reproducibility as well as potential regulatory effects of drugs on DAT imaging results.

Chapter 5 contains concluding remarks and discusses the directions for future research.