Summary
Parkinson’s disease is a common neurodegenerative disorder, which mainly affects the elderly. To date only symptomatic therapies are available and no treatment exists yet to stop or even delay the underlying process. Neuroprotective therapies are interventions interfering with the basic pathogenetic mechanism of cell death, resulting in a slowing or even stopping of the progression of neuronal degeneration. Apoptosis seems to play a role in the pathogenetic mechanism of Parkinson’s disease. Inhibition of apoptosis may therefore have a neuroprotective effect in this disorder. A possible apoptosis-inhibitor with neuroprotective effects is TCH346.

If neuroprotection would be available, this should be given in the beginning of the disease, as progression is fastest in this phase. However, diagnosing Parkinson’s disease correctly in the beginning can be difficult. Conventional imaging techniques of the brain, like CT or MRI scans, are not useful in this respect. However, functional imaging by means of PET and SPECT is able to visualize and measure the functioning of the presynaptic striatal dopaminergic system. This implies that SPECT and PET might be useful to diagnose Parkinson’s disease correctly, also at early stages of the disease. But diagnosing Parkinson’s disease correctly is not only important in a research setting. Also in daily clinical practice it can be difficult for the neurologist to make the right diagnosis in an early phase of the disease, as other (non-) neurodegenerative disorders may mimic Parkinson’s disease. The aim of this thesis is to evaluate if FP-CIT SPECT and F-DOPA PET can be useful in diagnosing Parkinson’s disease both in clinical practice and in research settings.

In chapter 2 an extensive overview of Parkinson’s disease is presented, in which epidemiology, symptoms (motor and non-motor), pathology findings, comparison with other movement disorders, subclassifications of Parkinson’s disease and brain metabolism in aging and Parkinson’s disease, are described.

From this description, it becomes clear, that Parkinson’s disease is a common neurodegenerative disorder, mainly affecting the elderly. Motor symptoms according to the UK Parkinson’s Disease Society Brain Bank criteria, consist of the classic triad of resting tremor, rigidity and bradykinesia. Postural impairment has often been called the fourth major motor symptom of PD. Next to the motor symptoms, patients with Parkinson’s disease may also suffer from cognitive problems, depressive disorder, and hallucinations. Pathology is characterized by degeneration of neuromelanin-containing neurons in the pars compacta of the substantia nigra, mainly in the ventrolateral part. This pattern of cell loss is unique for Parkinson’s disease.

Thereafter, other movement disorders are described. In some of these, the presynaptic dopaminergic system is not involved, like essential tremor, vascular parkinsonism, normal pressure hydrocephalus, drug-induced parkinsonism, and metabolic or endocrine disorders. But also movement disorders which may mimic idiopathic Parkinson’s disease and in which
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the presynaptic dopaminergic system is involved as well, like multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and cortico-basal ganglionic degeneration (CBD), are described.

Finally, the metabolic topography of Parkinson’s disease seems to be characterized by relatively increased activity in striatum, thalamus, pons and cerebellum, whereas activity was decreased in several association areas. In normal aging, the metabolic pattern of the brain changes also.

In chapter 3 the correlation between F-DOPA uptake and motor behavior in monkeys is described. F-DOPA PET provides a means to assess the integrity of the nigrostriatal dopaminergic system, in humans and in animal models. The MPTP-lesioned monkey is a validated animal model of Parkinson’s disease. Although it has been reported that striatal F-DOPA uptake is decreased in MPTP-lesioned monkeys, the correlation between F-DOPA uptake and motor behavior has not been evaluated in a systematic manner yet. A total of eight monkeys received MPTP bilaterally in two phases. They underwent an F-DOPA PET scan and their behavior was being analyzed in the non-lesioned phase, after unilateral administration of MPTP and after a second administration of MPTP resulting in lesions bilaterally. After administration of MPTP, striatal F-DOPA uptake decreased ipsilaterally and parkinsonian symptoms score increased, while the amount of limb movements contralaterally decreased. A significant relationship was found between mean striatal F-DOPA uptake and mean parkinsonian scores. Also, F-DOPA uptake was correlated with the amount of limb movements contralaterally.

In chapter 4, the possible neuroprotective effect of the compound TCH346 in MPTP-lesioned primates is evaluated. Until so far, only symptomatic treatment is available for patients with Parkinson’s disease. There is no therapy available yet to delay or even stop the underlying processes. Apoptosis seems to play a role in the pathogenetic mechanism of Parkinson’s disease. By inhibiting apoptosis, the underlying process may be blocked and neuroprotection may thus be achieved. Eight monkeys received MPTP in a two-phase model and became parkinsonian. Four of them received TCH346 and four of them received saline. Behavior was analyzed and F-DOPA PET scans were performed in the naïve state, after administration of 2.5 mg MPTP into the left carotid artery and after a second administration of 1.25 mg MPTP into the right carotid artery. The first MPTP infusion, into the left carotid artery, caused mild parkinsonian symptoms, reduced amount of right limb movements and reduced F-DOPA uptake in the left striatum. In the saline-treated monkeys, the second MPTP treatment (into the right carotid artery), resulted in a worsening of the parkinsonian symptoms with a reduced amount of left limb movements and a decrease of the F-DOPA uptake in the right striatum. However, in the TCH346 treated monkeys, the second MPTP
treatment did not further worsen parkinsonian symptoms, did not affect the amount of right limb movements and did not decrease the F-DOPA uptake in the right striatum. Thus, it can be concluded from this study, that TCH346 is able to prevent nigrostriatal damage and motor symptoms induced by MPTP in monkeys.

The aim of the study in chapter 5 is to compare FP-CIT SPECT and F-DOPA PET in patients with different stages of Parkinson’s disease and to assess their power in demonstrating striatal dopaminergic damage. Diagnosing Parkinson’s disease can be difficult in the early phases of the disease and PET and SPECT enable visualization and evaluation of the striatal dopaminergic functioning. F-DOPA PET is already being used since the eighties of the last century for quantification of striatal dopaminergic capacity. However, its use is restricted by the limited availability of F-DOPA. SPECT scans using FP-CIT are more widely available and could therefore form an attractive alternative. A total of 30 patients with Parkinson’s disease, consisting of 13 de novo patients and 17 patients with advanced stage of disease underwent both an FP-CIT SPECT scan and an F-DOPA PET scan. The patients were clinically examined in the ‘off-state’. Striatal uptake of F-DOPA and FP-CIT correlated well with each other and also putaminal uptake of both tracers correlated well with each other. Both imaging techniques correlated moderately with several clinical scores in a similar way. By means of both scanning methods the two patient groups could be well distinguished from each other. From this study it could be concluded that both techniques can be used to measure the presynaptic dopaminergic system in patients with different stages of Parkinson’s disease.

The study described in chapter 5 has been extended in chapter 6 in which FP-CIT SPECT scans and F-DOPA PET scans have been compared with each other in patients with Parkinson’s disease and in healthy volunteers. Ten healthy volunteers underwent an FP-CIT SPECT scan and ten healthy volunteers underwent an F-DOPA PET scan. These uptake values were compared with the uptake values derived from the study described in chapter 5. Uptake values of caudate, putamen and striatum of both FP-CIT and F-DOPA were significantly reduced in parkinsonian patients compared to the uptake values in healthy volunteers. By means of contralateral putaminal and striatal uptake values of FP-CIT SPECT as of F-DOPA PET, the group of healthy volunteers could be completely separated from the group with patients with Parkinson’s disease. It can therefore be concluded that FP-CIT SPECT and F-DOPA PET scans are both able to diagnose presynaptic dopaminergic damage, also in an early phase of the disease, with an excellent sensitivity and specificity.