Parkinson’s disease (PD) is a chronic, slowly progressive neurodegenerative disorder, of which the initial pre-motor stages are neuropathologically characterized by a loss of non-dopaminergic ascending corticopetal projections from the brainstem. With the onset of classical motor symptoms, there is involvement of the midbrain dopaminergic system, followed by degeneration of cholinergic basal forebrain neurons known to have widespread cortical projections. Finally, in the most advanced stages, pathology spreads further upwards to include the entire neocortex. Apart from the clinical motor hallmarks of bradykinesia, rigidity, tremor and postural instability, PD is associated with affective disorders, cognitive deficits, autonomic dysfunction, sleep disturbances and sensory deficits.

Cognitive dysfunction in PD mainly comprises executive dysfunction, with secondary visuospatial and mnemonic disturbances. In over a quarter of patients these cognitive deficits eventually proceed to full-blown dementia, which constitutes an important risk factor for the occurrence of psychosis, caregiver distress, decreased quality of life and nursing home placement. Despite the profound negative impact of cognitive deficits and dementia in PD, still little is known about their pathophysiological basis. The first part of this thesis describes studies that explore the presence of cognitive deficits in the early clinical stages of PD. In the second part, neurophysiological mechanisms involved in the pathophysiology of PD as well as their relation with motor and cognitive disturbances were explored.

Chapter 1 provides information on the historical development of the concept of PD as a pure movement disorder, mainly characterized by degeneration of the nigrostriatal dopaminergic pathway, into the concept of PD as a multi-system disorder, which involves all major ascending neurotransmitter systems and presents with a multitude of motor as well as non-motor disturbances. Subsequent paragraphs underline the disabling nature of cognitive dysfunction and dementia in PD and the potential involvement of non-dopaminergic systems in these clinical deficits. Finally, the concept of pathological synchronisation of oscillatory brain activity in PD and its investigation by means of neurophysiological brain imaging techniques is introduced. It is increasingly clear that synchronized oscillatory brain activity, even during a no-task resting-state condition, reflects information processing in the brain. As such, motor and cognitive dysfunction in PD may very
well be associated with changes in resting-state oscillatory brain activity, both within as well as between distributed brain regions.

In chapter 2, three cross-sectional studies on cognitive dysfunction in PD patients in the earliest treated and untreated stages of disease are described. Section 2.1 describes a study using a motor randomization task. Results include deficits in the generation of random motor behaviours even in recently diagnosed, untreated PD patients, indicating that perseveration is one of the earliest cognitive deficits in PD. Section 2.2 covers a study using a visuomotor coordination task. Although this task does discriminate between early-stage PD patients and controls, its strong dependence on the subjects’ level of computer experience makes it less ideal for the use in screening test batteries, especially in subjects with high computer aptitude. Finally, in section 2.3 a study using a visuo-spatial memory span task that has traditionally been regarded as a pure memory paradigm shows deficits also in the early-stages of PD. As mnemonic deficits are not thought to be characteristic of early-stage PD, these results are explained in light of recently published studies, which suggest more executive involvement in this task than has previously been assumed. The most important conclusion that can be drawn from these neuropsychological investigations is that even in the earliest, untreated clinical stages of PD subtle cognitive, mainly executive deficits can already be observed relative to healthy controls.

Chapter 3 presents data on resting-state synchronization of oscillatory brain activity within distributed regions. This phenomenon was studied in a large cohort of PD patients with varying disease duration and severity (including a group of recently diagnosed, untreated PD patients) as well as in healthy controls. Relative spectral power was computed using frequency analysis of whole-head magnetoencephalography (MEG) data acquired in a resting-state condition. Levodopa treated PD patients were examined both in a practically defined “OFF” as well as in the “ON” state. Relative power, which is a measure of the strength of oscillatory brain signals within a certain frequency band relative to the amount of activity over the full frequency range, reflects synchronous neural activity within the neural population recorded by the sensor. Results reveal a widespread, diffuse slowing of cortical oscillatory activity from the earliest untreated clinical stages of PD onwards that was (largely) independent of disease duration, stage and severity of motor symptoms and hardly influenced by dopaminomimetic treatment. In
contrast to motor deficits, synchronous neural activity within distributed brain regions does appear to play a role in some early cognitive deficits in PD; increased alpha1 spectral power within centroparietal regions was found to be associated with cognitive perseveration.

In **chapter 4**, two studies on resting-state synchronization of oscillatory brain activity *across* distributed brain regions are described. In both studies, cortico-cortical functional connectivity was explored using synchronisation likelihood (SL) analysis of whole-head MEG data acquired in a resting-state condition. SL is a general measure of statistical interdependencies between the time series of two oscillatory signals and hence reflects functional interactions between two distributed populations of neurons. In the study described in **section 4.1**, we set out to determine whether changes in cortico-cortical functional connectivity are a feature of early-stage Parkinson’s disease (PD), explore how functional coupling might evolve over the course of the disease and establish its relationship with clinical deficits. To this end, whole-head MEG was performed in an eyes-closed resting-state condition in a substantial cohort of PD patients with varying disease duration and severity (including a group of recently diagnosed, untreated PD patients) and in healthy controls. Results included increased low alpha band functional connectivity, which expanded to neighbouring frequency bands with disease progression. Levels of theta and beta band coupling were positively correlated with severity of parkinsonism. Synchronous neural activity across distributed brain regions also appears to play a role in early cognitive deficits in PD; increased alpha1 band coupling between homologous brain regions on the left and right side of the brain was found to be associated with cognitive perseveration. **Section 4.2** describes a study in which we set out to determine whether functional connectivity is modulated by dopamine replacement therapy (DRT) and explore the relationship of therapy-induced changes in coupling with motor improvement in the relatively early stages of DRT in PD. To this end, functional connectivity was explored in a group of levodopa treated PD patients which were examined both in a practically defined “OFF” as well as in the “ON” state. The main finding of this study was that the already elevated levels of resting-state cortico-cortical functional connectivity in the 4-30 Hz range in mild to moderately advanced PD are on average increased even further by DRT. A particularly interesting observation was that a strong motor response appeared to be associated with *decreases* rather than increases in local beta band coupling in response to a dopaminergic challenge. The
transition from increases in beta band coupling in response to dopamine administration to decreases may mark a disease phase characterized by an increased risk of motor response fluctuations or dyskinesias.

In chapter 5 an overview is given of the results of the various studies described in this thesis and future perspectives are discussed. The most intriguing idea in this chapter finds its basis in the notion that effective cognition probably requires the constant changing of synchronous neural cell assemblies, enabling the rapid formation and decay of functional networks. Increased functional connectivity in the resting-state may be a sign of this dynamic process becoming overly static, something that is clinically manifested by a decreased cognitive flexibility during subsequent neuropsychological testing.