SUMMARY

The studies described in this thesis were performed with the aim of gaining more insight into the pathophysiological processes underlying Parkinson's disease (PD) related cognitive decline and dementia by longitudinally studying local synchrony, functional connectivity and topology of the functional brain network in PD patients and controls. In addition, we aimed to identify surrogate markers of clinical disease progression in PD, in particular related to cognitive decline, and to find predictors for conversion to Parkinson's disease dementia (PDD).

In chapter 1, cognitive impairment and dementia in PD are introduced as increasingly recognized problems with a profound socio-economic impact. Considering the current incomplete knowledge of the underlying pathophysiological mechanisms, we emphasize that an increase in our understanding of these mechanisms is essential for the future development of targeted therapeutic strategies, which are very limited at this point in time.

Next, a number of important neurophysiological principles of brain function are outlined and we discuss the potential value of magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) as functional brain imaging techniques that provide the opportunity to study the pathophysiological processes involved in PD-related cognitive decline in great detail in a completely non-invasive way.

Subsequently, we present the concept of studying the brain as an integrative network of functionally (and structurally) linked regions. Within this functional brain network, distinct aspects of the dynamics of brain activity can be studied using specific signal analysis approaches. We expand on the three aspects that are assessed in this thesis: local synchrony, functional connectivity and the overall topological organization of the brain network. Thereafter, we review previous functional brain network studies performed using electroencephalography, MEG and fMRI in PD. The results of these (cross-sectional) studies suggest that changes in the different aspects of the functional brain network (i.e. local synchrony, functional connectivity and the topological organization) may reflect important pathophysiological mechanisms underlying cognitive decline and dementia in PD.

In the last part of chapter 1, we identify the most important issues that have not been resolved in previous functional imaging studies in PD and describe the specific research questions addressed in this thesis, which include the identification of changes in local synchrony (chapter 2), functional connectivity (chapters 3 and 4) and the topological organization of the functional brain network (chapter 5) in PD patients in relation to clinical measures of disease progression and the identification of changes in functional brain activity in non-demented PD patients as predictors for the development of dementia (chapter 6).

All studies described in this thesis were performed in a cohort of PD patients and healthy controls who were longitudinally followed for seven years. At baseline, a total of 70 non-demented patients (disease duration 0-13 years) with idiopathic PD and 21 healthy controls were prospectively included and underwent longitudinal motor and cognitive assessments, as well as repeated MEG and structural MRI recordings, at baseline and at two follow-up
visits scheduled 4 and 7 years after the baseline visit. fMRI was acquired twice, at the first and second follow-up visits.

In chapter 2 we describe the results of a longitudinal study in which we used MEG to longitudinally study changes in local synchrony in initially non-demented PD patients that may be associated with cognitive decline. In this study, we assessed changes in peak frequency and relative spectral power in 49 PD patients and 14 healthy controls over a 4-year time interval and demonstrated widespread progressive slowing of oscillatory brain activity and a slowing of the dominant peak frequency in initially non-demented PD patients, independent of ageing effects. The slowing of oscillatory brain activity strongly correlated with cognitive decline and was therefore considered as a potential early marker for the development of dementia in PD.

In chapter 3 we present a longitudinal MEG study that evaluated functional connectivity changes in relation to clinical measures of disease progression in PD. In this study, we used a source-space based approach with detailed anatomical mapping to assess functional connectivity of individual cortical brain regions known to be affected neuropathologically in early clinical disease stages. We demonstrated altered resting-state functional connectivity for temporal cortical brain regions in early stage, untreated PD patients (n = 12) compared to healthy controls (n = 14). Longitudinal analyses over a 4-year period in a larger patient group (n = 43) revealed a reversal of the initial changes in alpha1 and additional decreases in alpha2 band connectivity evolving in a more widespread cortical pattern. These longitudinal changes in functional connectivity were associated with motor and cognitive deterioration and thus appear to reflect clinically relevant phenomena. We therefore concluded that these functional connectivity alterations hold promise as a marker of disease progression, with potential predictive value for clinical outcome.

In chapter 4 we describe a study in which we longitudinally evaluated fMRI whole-brain resting-state functional connectivity in relation to cognitive decline in PD. First, we performed overall (i.e. one whole-brain mean) as well as regional (i.e. for individual regions of interest) cross-sectional functional connectivity analyses on resting-state fMRI data acquired in 55 PD patients and 15 matched controls. After a follow-up period of 3 years, 36 PD patients and 12 controls were re-scanned to study functional connectivity changes over time, and to correlate the changes in functional connectivity with measures of cognitive and motor function in the PD group. We found widespread decreases in resting-state functional connectivity in PD patients in comparison to controls that were independent of aging effects in the subsequent longitudinal analysis. The functional connectivity changes were most prominent for posterior parts of the brain and correlated longitudinally with clinical measures of disease progression, especially cognitive decline. We concluded that our results support the pathophysiological role of reduced functional connectivity in cognitive decline and the development of dementia in PD.

The topological organization of the functional brain network in PD is described in a study in chapter 5. In this study, we characterized whole-brain functional networks in 43 PD patients
and 14 controls by means of a standard graph analysis approach as well as the construction of a minimum spanning tree (MST), a novel approach that allows a unique and unbiased characterization the brain network. We observed in a cross-sectional analysis that the brain network in early stage, untreated PD (n = 12) displayed lower local clustering with preserved path length in the delta frequency band in comparison to controls. Longitudinal analysis over a 4-year period in the entire group of patients showed a progressive decrease in local clustering in multiple frequency bands together with a decrease in path length in the alpha2 frequency band. In addition, MST analysis revealed a decentralized and less integrated network configuration in early stage, untreated PD that also progressed over time. Moreover, the longitudinal changes in network topology identified with both techniques were associated with deteriorating motor function and cognitive performance. We concluded from these data that impaired local integration and network decentralization are very early features of PD that continue to progress over time, together with reductions in global efficiency. Based upon the correlation with clinical measures of disease progression, we considered changes in network topology as promising markers of disease progression in PD.

The study described in chapter 6 evaluated the predictive value of slowing of oscillatory brain activity for future cognitive decline and the development of dementia. In a group of 63 initially non-demented PD patients, we assessed the risk of converting to dementia over a 7-year period conveyed by cognitive and MEG-derived neurophysiological markers in individual as well as combined risk factor analyses. Nineteen PD patients (30.2%) developed dementia during the follow-up period. We showed that baseline cognitive performance and neurophysiological markers reflecting slowing of oscillatory brain activity each individually predict conversion to PDD. In combination, baseline cognitive performance and neurophysiological measures had even stronger predictive value. The highest dementia risk was conferred by a combination of low beta band power and impaired fronto-executive task performance. We concluded that combining neurophysiological markers with cognitive assessment can substantially improve dementia risk profiling in PD, providing potential benefits for clinical care as well as for the future development of therapeutic strategies.

In the final chapter (chapter 7), the main findings of this thesis are discussed and placed in a broader perspective. We consider a number of methodological issues and provide directions for future research. In the final paragraphs, we conclude that alterations in local synchrony, functional connectivity and the topology of the functional brain network are present in early-stage, drug-naïve PD patients and, with increasing disease duration, evolve in close association with clinical deterioration, in particular cognitive decline. The close association with the progression of clinical impairments indicates that changes in functional brain network characteristics hold great promise as surrogate markers of disease progression in PD. Such markers may serve to monitor disease progression and assess the effects of drug treatment.

Another important conclusion that can be drawn from this thesis is that slowing of oscillatory brain activity in PD patients carries a strong predictive value for the conversion to PDD, and that neurophysiological markers that reflect this slowing can effectively
complement cognitive assessment in the early identification of PD patients at a high risk for conversion to dementia. The identification of high- and low-risk subgroups of PD patients is an essential step in the future development and evaluation of therapies to effectively treat cognitive decline and dementia in PD. In the short term, establishing a high risk for conversion to PDD at an early disease stage will provide patients and caregivers with better prognostic information that would help them to anticipate and recognize PDD-related problems such as depression and psychosis, and improve personal future planning.