General discussion
PD is a common, slowly progressive neurodegenerative multisystem disorder clinically characterized not only by motor deficits, but also by a wide range of non-motor disturbances such as affective disorders, autonomic dysfunction, sleep disturbances, pain, fatigue, sensory deficits and cognitive impairments [22]. Mild cognitive impairment is a frequent symptom of PD [24], which can already be observed in the earliest clinical stages of disease [26]. In a high percentage of patients, cognitive dysfunction may eventually progress to or be succeeded by full-blown dementia [58-61, 65]. Dementia in PD constitutes not only an important risk factor for the occurrence of psychosis, patient and caregiver distress and nursing home placement [55, 56], but is also associated with increased mortality [57]. In spite of the impact of cognitive deficits and dementia, the pathophysiological basis of cognitive deterioration and the determinants of progression to dementia, clinical or otherwise, remain largely unknown.

Cognitive deficits and dementia (and possibly also psychosis) in PD are potentially treatable by means of drugs such as cholinesterase inhibitors [125, 285, 286]. As these drugs probably have a limited time window in which they are clinically effective, early identification could be of major clinical significance. The ongoing development of neuroprotective drugs aimed at slowing down or preventing the development of cortical pathology leading to dementia [287] further add to this importance. Early treatment of cognitive disturbances may very well postpone the development of overt dementia, which will enable the PD patient to remain independent for a longer period of time. Postponement of nursing home placement will also lead to substantial reductions in healthcare costs.

To gain a better understanding of the pathophysiology of cognitive deficits in PD, it is important to know whether these deficits can be found in the earliest clinical stages of PD and to gain more insight into the neurophysiological mechanisms that might play a role in these deficits. Moreover, selected cognitive deficits as well as specific neurophysiological changes may very well mark or even predict future cognitive deterioration and dementia.

**COGNITIVE DEFICITS IN EARLY-STAGE PD**

In chapter 2 of this thesis, a number of cognitive deficits were demonstrated in early-stage PD using selected neuropsychological tasks. The first section showed that, in comparison with control subjects, both recently diagnosed untreated as well
as early-stage treated PD patients were relatively unable to generate random motor sequences [170]. These deficits in randomization are thought to be the result of a decreased ability to switch cortical behavioural programs in PD [160], an impairment more commonly known under the term cognitive perseveration. In section two of this chapter, abnormalities in visuo-motor control were demonstrated in early-stage PD patients relative to controls [201]. In the third section, a decrease in sequential visuo-spatial span was shown in early-stage treated PD patients relative to controls, something which was not observed in early-stage untreated PD patients [288]. From the latter data, it would appear that a decrease in memory span is a relatively early-stage feature of PD. However, mnemonic deficits are typically not found in early-stage PD [183]. In view of recent studies pointing to executive involvement in spatial memory span tasks [188, 189], the observed deficits most likely reflect executive rather than mnemonic dysfunction.

To summarize, the first part of this thesis demonstrated deficits relating to tasks of motor randomization, visuo-motor coordination and spatial memory span in early-stage PD patients. Impairments in the random generation of motor sequences, adaptive visuo-motor control as well as the efficient and flexible use of mnemonic strategies may well be the result of attentional deficits, especially those that involve the switching of internally driven behavioural programs or response generation strategies. As the resulting cognitive perseveration can already be observed in the earliest, untreated clinical stages of PD, it may very well be one of the earliest cognitive deficits noticeable in PD. It is tempting to speculate that cognitive deficits may even precede the first motor deficits. This notion is supported by a study in an animal model of PD; in MPTP-treated monkeys cognitive deficits were indeed present before any clear motor disturbances [156]. Furthermore, in first degree relatives of familial PD patients, the incidence of PD-like cognitive dysfunction is increased, possibly as a manifestation of preclinical PD [181]. However, the relatively modest sensitivity and specificity of these impairments would not support a purely neuropsychological approach to the early diagnosis of PD. An integrated approach, however, which besides a neuropsychological assessment incorporates testing of other potential markers of pre-motor PD (e.g. genetic vulnerability, hyperechogenicity of the substantia nigra, olfactory dysfunction, autonomic disturbances, depression, REM sleep behaviour disorder) might result in a test battery with receiver operating characteristics far superior to any single test. Interestingly, as evidenced in chapters 3 and 4 of this thesis, changes in neural synchrony measured using neurophysiological techniques might
also be useful in this regard. Some of the changes in neural synchrony occur early in the disease process and may even represent the earliest changes in brain function in PD.

Great potential lies in the use of neuropsychological testing in early-stage PD to select individuals at high risk for the development of full-blown dementia in later stages of disease. Several longitudinal studies have shown that prodromal frontal/executive dysfunction in PD patients predicts incident dementia [66, 72-74, 289, 290], and may be a marker of an early tendency of the pathologic process to involve cerebral structures in a more widespread way [291]. As such, cognitive perseveration may well be one of the earliest indicators of an increased risk of developing dementia. Longitudinal studies are now underway to validate the predictive value of cognitive perseveration for the subsequent development of PD-related dementia.

ABNORMAL NEURAL SYNCHRONY IN EARLY-STAGE PD

The results of an MEG study on resting-state oscillatory brain activity within distributed regions in PD patients described in chapter 3 have made it clear that PD is characterised by a widespread, diffuse slowing of cortical oscillatory activity from the earliest clinical stages of PD onwards that is (largely) independent of disease duration, stage and severity and hardly influenced by dopaminomimetic treatment [268]. This suggests that these changes in synchronization within distributed brain regions may not be related to dopamine neuron loss in the substantia nigra, but rather to the degeneration of extranigral, non-dopaminergic systems, quite possibly including the noradrenergic and/or serotonergic systems. Why these early-stage changes in synchronization remain relatively stable with further disease progression remains to be determined, but may involve some sort of release phenomenon. In any case, changes in synchronization within distributed brain regions may well prove to be a marker for extranigral pathology.

The first section of chapter 4 presents data showing that increased resting-state functional connectivity across distributed brain regions in the 8-10 Hz alpha1 range is another feature of early-stage PD. Contrary to the changes in spectral power distribution described in chapter 3, the increases in functional connectivity progressively involve neighbouring frequency bands with disease progression [278]. This development of changes in functional connectivity over the course of the
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Disease may be linked to the topographical progression of PD pathology over the brain.

The data presented in the second section demonstrated 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. Yet, at the individual level, a particularly strong motor response to DRT appears to be associated with decreases in local beta band coupling [292]. We hypothesized that this phenomenon might be associated with the development of motor response fluctuations and/or dyskinesias. When this hypothesis is confirmed in future studies, changes in resting-state functional connectivity might serve to detect individuals at an increased risk of developing the aforementioned motor complications.

Taken together, the results described in chapters 3 and 4 of this thesis make it clear that PD is associated with a range of abnormalities in the temporal patterning of neural activity. Changes in the frequency distribution of neural activity as well as increases in synchronization across distributed neural populations can already be found in the earliest clinical stages of disease. Some of these changes, those in the alpha1 band, are associated with cognitive impairments, specifically those reflecting cognitive perseveration, further illustrating the importance of appropriate adjustment and coordination of temporally structured neuronal activity for cognition.

COGNITIVE PERSEVERATION IN EARLY-STAGE PD IS ASSOCIATED WITH CHANGES IN NEURAL SYNCHRONY

A wide range of cognitive functions requires the coordination of distributed neural activity. Current theories highlight neural synchrony as a putative mechanism for this coordination. Studies in MCI and AD have already provided support for this hypothesis by demonstrating correlations between abnormal synchronization and specific cognitive deficits [145, 150, 259]. These data have also suggested that deficits of mainly large-scale integration correlate with cognitive impairments. Cognitive perseveration, which was shown to be one of the earliest cognitive deficits in PD in chapter 2 [170], was associated with both increased alpha1 synchronization within centroparietal brain regions (chapter 3) [268], as well as increased alpha1 synchronization between homologous regions on the left and right side of the brain (chapter 4) [278] in early-stage untreated PD patients.
Obviously, the correlation of neurophysiological measures during a resting state with performance on separately applied cognitive tasks may seem rather counterintuitive. However, there is accumulating evidence to suggest that effective cognition requires the constant changing of synchronous neural cell assemblies [137]. This dynamic process probably calls for a moderate average degree of functional connectivity between brain regions, which further allows for rapid formation and decay of functional networks. This would enable the integration of information on the one hand, while retaining flexibility on the other. From this perspective, the increases in resting-state functional connectivity as described in this thesis may be interpreted as a sign that the aforementioned balance has been compromised, resulting in the normally dynamic process of synchronization and desynchronization becoming overly static. The cognitive deficits found during subsequent neuropsychological testing in the same PD patients, especially those observed using tests that require rapid changes between cognitive concepts, might be the clinical manifestation of the loss of adequate cortical network dynamics.

One could also explain the correlation between increased synchronous neural activity and cognitive deficits in PD in terms of attentional deficits. Increased alpha power has previously been associated with increased levels of attention [251-253]. In addition, alpha1 synchronization (in the range of about 6–10 Hz) is thought to reflect general task demands and attentional processes, and is topographically widespread over the entire scalp (Klimesch, 1999). The role of the alpha band in attention is further underlined by a study combining functional MRI and EEG, which showed the alpha rhythm to be negatively correlated with activity in the dorsal attention resting-state network [141]. This suggests that a pathologically high level of attention may be involved in some of the cognitive deficits observed in early-stage PD patients. This notion is in agreement with the emerging view that complex cognitive processes, such as attention, memory, dynamic grouping, and awareness require large-scale integration of activity [135, 256, 293], and may very well be related to the aforementioned issue of inadequate cortical network dynamics in PD.

Whether increased spectral power and functional coupling are primary mechanisms that induce cognitive deficits or, instead, reflect a compensatory mechanism for another as yet unidentified pathophysiological mechanism remains to be established. More insight may be gained by future methodological improvements that facilitate the study of rapidly changing sequential network configurations and by studying task-related changes in functional connectivity. In
any case, these findings further illustrate the importance of appropriate adjustment and coordination of temporally structured neuronal activity for normal cognitive function.

CONCLUSIONS

The wide range of motor and non-motor symptoms in PD develops over time, presumably in parallel with a topographical progression of Lewy body pathology. There is now some evidence to suggest that this notion also holds true for the progression of cognitive deficits to full-blown dementia. In preclinical and early clinical stages Lewy bodies first appear in the lower brainstem (and also the olfactory bulb), subsequently encroaching upon the upper parts of the brainstem and the basal forebrain in more advanced stages of disease, and ultimately spreading into the entire neocortex in stages associated with full-blown dementia. The early-stage neuropathological changes in PD affect anatomical structures and neurotransmitter systems known to influence cognitive processes as well as mechanisms involved in synchronization of neuronal activity. The divergent patterns of altered neural synchrony within and between brain areas that appear to occur in various stages of PD suggest a link between the topographical progression of Lewy body pathology over the brain and evolving changes in neuronal synchronization over the course of the disease. From this perspective, it is likely that there will be several patterns of disturbed neural synchrony that are each most typical for a specific neuropathological stage. As such, it may very well be that changes in synchronization may not only mark or predict the onset of clinical PD, but can also be used to detect individuals at an increased risk for progression of subtle cognitive deficits to overt PD-related dementia. Future longitudinal analyses will have to determine how the different patterns observed in cross-sectional studies are linked in time and related to cognitive deterioration.

Cognitive dysfunction in PD is also associated with structural brain changes. Cross-sectional studies utilizing voxel-based morphometry have shown atrophy in (pre)frontal [294, 295] and limbic/paralimbic areas [295] in non-demented PD patients relative to controls, which extended into temporal, occipital and subcortical regions in demented PD patients [294, 295]. Interestingly, in non-demented PD patients, gray matter density in the dorsolateral prefrontal area and parahippocampal gyrus correlated with executive function [295]. Atrophic changes
in these areas might therefore also be related to the development of dementia in PD.

In conclusion, prospectively designed, longitudinal studies which combine clinical assessments, structural imaging as well as functional imaging are required to determine whether early-stage cognitive (executive) dysfunction, changes in brain morphology and/or altered neural synchrony may serve as an early diagnostic marker for subsequent cognitive deterioration and the development of PD-dementia.