General introduction
Paragraphs on cognitive dysfunction and dementia in this chapter have been updated from:

HISTORICAL PERSPECTIVE ON PARKINSON’S DISEASE

Parkinson’s disease (PD) has traditionally been regarded as a pure movement disorder, of which motor symptoms have most likely been known and treated since ancient times. The first account is probably found as far back as 5000 years BC in the Indian medical system of Ayurveda under the name Kampavata [1]. This system describes patients suffering from this condition as having tremors of hand and feet in combination with difficulty in body movements. Behavioural descriptions matching PD motor symptoms can further be found in ancient Chinese texts [2], the classical Greek epic poem Iliad [3] and both the old (Ecclesiastes 12:3) and new (Luke 13:11) testament of the Bible. There is even some evidence to suggest that herbal preparations containing anticholinergics, levodopa and monoamine oxidase inhibitors had already been used in the treatment of PD-like motor symptoms in ancient times in India, China and the Amazon basin [4].

In Western medical literature, the Greek physician Galen was the first to describe a patient most likely suffering from PD around 175 AD. In one of his accounts of a disease he named katalepsis (catalepsy), this personal physician to the Roman Emperor Marcus Aurelius described the typical parkinsonian motor triad of tremor, rigidity and bradykinesia, as well as an inexpressive face with overconfident expression of the eyes (masked face), which were open and showed markedly reduced blinking (loss of spontaneous movement) [5]. A famous account of what was probably PD is that by Italian homo universalis Leonardo da Vinci, who described a patient having difficulty with voluntary movement in combination with tremor [6]. It was not until the 19th century, however, that the disease was formally recognized as a clinical entity and some of its cardinal motor symptoms were documented by the British physician James Parkinson in ‘An Essay on the Shaking Palsy’ published in 1817 [7]. This essay was based on merely six cases he had observed in his own practice as well as on walks around his London neighbourhood. Parkinson coined the term paralysis agitans (shaking palsy) and described the affected individuals as ‘having involuntary tremulous motion with lessened muscular power, in parts not in action and, even when supported, with a propensity to bend the trunk forward and to pass from a walking to a running pace (loss of postural reflexes and gait disturbances), ‘the senses and intellect being uninjured’. The German statesman Wilhelm von Humboldt, himself a sufferer from PD, supplemented the symptoms bradykinesia (and the closely related symptom of hypokinesia) and micrographia to the clinical description [8]. The eminent French
neurologist Jean-Martin Charcot truly recognized the importance of Parkinson’s work four decades later. He emphasized that tremor need not be present in the disorder and thus argued against the term *paralysis agitans*. He suggested, instead, that the disease be named ‘Parkinson’s disease’, added a fourth symptom, muscular rigidity, to the clinical picture and noted that *intellectual impairments might very well also be associated with the condition* [9]. In current clinical practice, tremor, rigidity, brady/hypokinesia and loss of postural reflexes are still regarded as the four cardinal motor symptoms of PD. This symptom complex is commonly known under the name of parkinsonism.

Many years after Parkinson’s formal description, in 1871 the basal ganglia were first recognized by Meynert as being involved in disorders of abnormal movement [10]. In 1913, the German-born American neurologist Lewey was the first to document specific abnormalities in the brains of individuals who in life suffered from PD [11]. At autopsy, he found cytoplasmic inclusions in the brains of PD patients, now widely recognized as the pathological hallmark of the disorder and referred to as Lewy bodies. Soon after, the Russian neuropathologist Tretiakoff was the first to emphasize the importance of the substantia nigra when he reported a loss of pigmented cells in this midbrain nucleus in PD patients in 1919 [12]. Although involvement of other brain stem nuclei such as the locus coeruleus has been reported in studies in the ensuing decades [13, 14], pathology in the substantia nigra was still regarded to be most constant and severe [15]. Arvid Carlsson, who later won a Nobel Prize for his work on signal transduction in the brain, was the first to suggest that dopamine might well play a role in neurotransmission in 1955. A few years later, his Swedish team observed high dopamine concentrations throughout the brain [16]. Subsequent work showed the newly discovered neurotransmitter to be particularly abundant in the striatum, which led Carlsson to suggest that PD may well be associated with dopamine deficiency in this area [17]. This speculation was confirmed by the studies of Hornykiewicz [18] and Sourkes [19] in PD patients and in the mid-1960’s considerable evidence was gathering in favour of the existence of a nigrostriatal dopaminergic pathway, involved in the regulation of motor behaviour. Up to then, pharmacological treatment was largely limited to administration of anticholinergic agents, but now introduction of the first exceptionally successful pharmaceutical treatment of PD followed closely; Birkmayer and Hornykiewicz [20] and almost concurrently Sourkes and Barbeau [19], conceived the idea of administering levodopa, a precursor to dopamine, in patients with PD, with spectacular results.
The treatment of PD evolved in the following years, with optimization of administration regimens by Cotzias et al. [21], as well as with the introduction of decarboxylase inhibitors. In the mid-1960's the concept of dopamine as a neurotransmitter had reached mainstream status and the nigrostriatal pathway had even become a model for the study of central synapses. The prevailing view of PD over the rest of the 20th century was that of a disorder of unknown aetiology, which was principally associated with the degeneration of dopaminergic neurons in the substantia nigra, resulting in low levels of dopamine in its projection areas in the basal ganglia.

CURRENT CONCEPT OF PARKINSON'S DISEASE

PD is now regarded as a true multisystem disorder, which is 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 impairments, cognitive deficits and dementia [22]. Perhaps surprisingly, cognitive impairments have actually long been documented in patients that probably suffered from PD. In the previously mentioned Indian medical system of Ayurveda, symptoms of the condition Kampavata included sleep disturbances and dementia [1]. In one of his descriptions of patients suffering from catalepsy, the Greek physician Galen described bradyphrenia and occasional mental deterioration in combination with the classical parkinsonian motor triad of tremor, rigidity and bradykinesia around 175 AD [5]. As mentioned previously, the famous neurologist Charcot noted that intellectual impairments could be associated with PD [9]. It is only since the last two decades, however, that cognitive symptoms have been recognized as an important and disabling feature of the disease.

From a neuropathological perspective, PD is now no longer viewed as a disorder that is mainly characterized by the loss of dopaminergic neurons in the substantia nigra, leading to striatal dopamine deficiency. Although degeneration of non-dopaminergic nuclei has already been known since 1938 [14], the concept of PD as a neurodegenerative disorder that involves progressive degeneration of a multitude of corticopetal ascending neurotransmitter systems, leading to a wide range of biochemical deficits, has only recently reached mainstream status. According to a recently published neuropathological PD staging system [23], brain pathology evolves following a predictable topographical sequence over the course
of the disease. In the preclinical (I and II) and the earliest clinical stage (III) of this system, neuropathological changes are most prevalent in the brainstem (and the olfactory bulb and tract). This includes not only dopaminergic neurons in the substantia nigra and ventral tegmental area, but also the noradrenergic system (locus coeruleus) and serotonergic system (dorsal raphe nuclei) as well as several other neurotransmitter systems. Interestingly, damage to non-dopaminergic ascending neurotransmitter systems appears to precede damage to dopaminergic systems. To a lesser extent, also the forebrain cholinergic system (nucleus basalis of Meynert) is affected. In more advanced stages pathology exacerbates and ascends to include more forebrain structures (IV), eventually spreading into the neocortex in disease stages associated with dementia (V and VI). Consequently, cognitive deficits in early-stage PD are thought to mainly be the result of brainstem pathology, while PD-related dementia probably additionally involves damage to the forebrain cholinergic system as well as more severe cortical pathology.

**COGNITIVE DYSFUNCTION IN PARKINSON’S DISEASE**

Mild cognitive impairment is a very common finding in PD [24], although deficits are usually relatively subtle and not clinically apparent or may not overtly affect daily functioning. Nevertheless, cognitive deficits have been shown to be associated with a lower quality of life also in PD patients not (yet) fulfilling DSM criteria for dementia [25]. Moreover, when comparing to controls, subtle cognitive impairment can even be demonstrated in PD patients in the earliest clinical stages of disease [26]. A wide variety of cognitive deficits has now been described in non-demented PD patients, the most prominent of which is a deficit in executive function.

Executive function is a broad term used to describe a range of cognitive functions involved in the realisation of goal-directed, adaptive behaviour in response to new, challenging environmental situations, including attention, inhibition, task management, planning, monitoring and coding [27]. A dysexecutive syndrome, resembling cognitive deficits as established in frontal lobe patients [28], is often thought to be at the heart of cognitive dysfunction and dementia in PD and is usually one of the earliest cognitive symptoms found [26].

Besides executive dysfunction, there is compelling evidence of visuospatial deficits in non-demented PD, even when tests contain only few motor components [29-31]. Most authors, however, believe visuospatial dysfunction to be the result of
the high cognitive demand that is usually required by such tasks. Indeed, with the possible exception of judgment of line orientation, it would appear that visuospatial dysfunction in PD can be readily explained by the demand of visuospatial tasks on executive functions such as planning and (shifting of) attention [32-36].

Mnemonic dysfunction has also frequently been reported in PD. The most consistent findings in patients with PD are deficits of working memory [37-41] and explicit memory [42-44]. Working memory can be defined as the ability to hold internal representations in short-term memory and to manipulate this mnemonic information on line to enable adaptive behaviour to be based on these representations rather than on immediate stimuli [45]. Most studies find preserved short-term memory in non-demented PD [46]. The executive processes that operate on the contents of this memory, however, are often impaired [47]. Therefore, most deficits in working memory can probably also be explained in terms of executive dysfunction. Defective explicit memory in PD can largely be remedied by semantic cueing or probing [48, 49]. This suggests that although new information is stored, it is not readily accessed, pointing to defective usage of stored information. Thus, the memory deficit in PD is different from the amnesia of Alzheimer's disease, which is mainly characterized by impaired storage of new information. In conclusion, quite analogous to visuospatial function, mnemonic function would for the most part be secondarily impaired, due to the reliance of its manifestation on executive functionality.

Several studies have also reported bradyphrenia in PD [50, 51], although this is still a matter of some controversy. It has been suggested that the finding of reduced cognitive speed may very well have been caused by the inclusion of patients with mild dementia or depression [52]. Also, bradykinesia could interfere with the assessment of bradyphrenia in cognitive tests that require a motor response, although bradyphrenia has been reported independent of motor slowing [53]. For an excellent and comprehensive review of the literature on cognitive deficits in PD, the reader is referred to the excellent chapter on these matters by Pillon and colleagues in volume 6 of “Aging and Dementia” [54].

DEMENTIA IN PARKINSON’S DISEASE

In a number of patients, the aforementioned cognitive deficits may eventually progress to or be succeeded by overt dementia. Dementia in PD constitutes not
only an important risk factor for the occurrence of psychosis, caregiver distress and nursing home placement [55, 56], but is also associated with increased mortality (independent of severity of motor symptoms) [57]. Prevalence and incidence vary considerably among studies, possibly due to differences in patient population, study design and criteria for diagnosing PD and dementia. In cross-sectional studies, the prevalence of dementia in PD ranges from 10 to over 40% [58-61]. Features positively associated with the prevalence of dementia include most notably aging [58, 59, 61], but also age at onset of PD [58-60], disease severity [59, 61], disease duration [58], depression [58] and presence of atypical parkinsonian symptoms [58].

Prospective studies have reported a cumulative incidence of 19 to 53% (the follow up period varied in these studies) [57, 62-64]. Recently, in a prospective study with 8 years follow-up, 78.2% of patients eventually developed dementia [65]. Incidence rates vary from 31.4 to 122.5 cases per 1000 person years [58, 62, 64-67] and the risk for developing dementia in PD-patients is up to six times higher than in age-matched control subjects [68]. Again, older age [57, 62, 68, 69], older age at onset of PD [66] and greater severity of disease [63, 64, 68, 70] as well as a confusional state [69, 70], early hallucinations and both the akinetic dominant and mixed tremor/akinetic form of PD [65] were found to be associated with a higher risk.

A progressive dysexecutive syndrome characterizes the neuropsychological profile of PD-related dementia. In essence, the same types of deficits are found in non-demented patients [71], but are more severe in demented patients. From this perspective, it is not surprising that several recent studies have pointed to the predictive value of prodromal impairment of executive function (along with deficits of immediate and delayed recall) [72-74]. Although memory deficits are present in PD-related dementia, they are usually less severe when compared to AD [65]. Moreover, the quality of memory impairment differs from that seen in AD. In both conditions it is characterized by a deficit in free recall, but in PD with dementia (PDD), as mentioned before, this can often be corrected by semantic cueing [48]. Therefore, in PDD the problem seems to be one of retrieval, and not of encoding. Indeed, recognition memory is often well preserved in demented PD-patients. In contrast to AD, instrumental disorders such as aphasia, apraxia or agnosia are not very common in PDD [75, 76].

Psychotic symptoms are especially common in PDD. Hallucinations (sensory perceptions in the absence of an external stimulus [77]), mainly visual, are the...
most frequent symptom. These are mostly non-threatening and often consist of vivid, colourful and sometimes fragmented figures of beloved (deceased) familiar persons and/or animals, which are described in detail [78]. Insight is retained in the majority of occasions, but with reality testing deteriorating, the hallucinations may change and become more frightening, possibly inducing anxiety and panic attacks [79]. Loss of insight is particularly seen in demented patients [80]. Delusions (false beliefs based on incorrect inference about external reality [77]) are less common than hallucinations and mainly of the paranoid type, dealing with persecution, spousal infidelity or jealousy [81].

Attentional deficits and fluctuating cognition are also very common in PDD. These features, together with parkinsonism and the above mentioned visual hallucinations, are also the main characteristics of dementia with Lewy bodies (DLB), possibly accounting for 15-20% of the dementias [82]. Indeed, PDD and DLB share many clinical [75, 83, 84] and pathological [85] features and are often difficult to differentiate other than by the time of onset of dementia in relation to parkinsonism [86]. Therefore, Parkinson’s disease and dementia with Lewy bodies are often considered to be part of the same disease spectrum [87-89], although this matter is still under considerable debate [90]. It has been suggested that similar pathological mechanisms may underlie the clinical symptoms, including dementia and psychotic symptoms.

**PATHOPHYSIOLOGY OF COGNITIVE DYSFUNCTION AND DEMENTIA IN PARKINSON’S DISEASE**

Despite the profound negative impact of cognitive deficits and dementia, the exact pathophysiology of cognitive dysfunction in both non-demented and demented PD patients remains largely unknown. A number of neuropathological and neurochemical changes in PD are thought to be involved, not surprisingly including the central dopaminergic denervation. As early as 1986, Alexander described five parallel, segregated circuits interconnecting well-defined sub-regions of the basal ganglia to particular cortical fields via the thalamus [91]. Disruptions at either the basal ganglia or cortical points in such a circuit have been shown to produce similar behavioural effects [92]. One of these circuits, the so-called dorsolateral prefrontal loop, is thought to be involved in executive behaviour. This loop connects the dorsolateral part of the prefrontal cortex to the caudate nucleus.
General introduction

Hence, projections lead through pallidum and thalamus back to the prefrontal cortex. Based on imaging studies [93, 94], it may be inferred that degeneration of the dopaminergic nigrostriatal pathway affects executive function by causing a disruption at the level of the caudate nucleus. On the other hand, this dysfunction might also be considered the result of dopamine depletion in the frontal cortex itself, caused by degeneration of the mesocortical dopaminergic system mainly projecting from the ventral tegmental area. In any case, the exact contribution of dopaminergic deficiency to cognitive defects in PD remains controversial, largely because the cognitive effects of dopaminomimetics appear heterogeneous. While some studies point to a positive effect on executive function [95, 96], (working)memory and attention [97], others actually find deleterious effects, especially in the executive domain [98] or show no effects at all. A longitudinal study has shown the beneficial effect of dopaminergic medication to be particularly prominent in the very early stages of disease [99]. To complicate matters further, some cognitive deficits in PD have been shown to correlate with motor symptoms that show little or no response to dopaminergic treatment (axial symptoms and gait disturbances), but not with levodopa-responsive symptoms (akinesia and rigidity) [57, 100, 101]. Recent studies suggest that dopaminomimetics probably improve or impair cognitive performance depending on both the nature of the task and the integrity of the underlying nigrostriatal and mesocortical dopaminergic circuitry [102].

The aforementioned deterioration of the dopaminergic system may contribute to the progression of cognitive deficits into overt dementia. Although of a correlative nature, some support for this notion is found in two studies showing an association between dementia and the loss of dopaminergic neurons in the medial part of the substantia nigra [103, 104], projecting to the nucleus caudatus, and in the ventral tegmental area, with ascending dopaminergic projections to cortical and limbic areas [105, 106]. In any case, dopaminergic deficiency by itself is not considered sufficient for the development of dementia. Non-dopaminergic systems are likely to be involved as well. As already mentioned, several neuromodulatory systems are affected to varying degree in PD, mainly the serotonergic, noradrenergic and cholinergic systems [107]. Although one study has reported higher neuronal loss in the locus coerules in demented relative to non-demented PD patients [108], others have been unable to show any relation of PD-related dementia with neuronal loss in the locus coerules [109] or with cortical noradrenalin levels [103]. Loss of serotonergic neurons in the dorsal raphe nucleus (DRN) has mainly been
associated with depression, while demented and non-demented patients did not
differ on neuronal counts in this area [103, 110]. Perry et al. [111] could not
establish any correlation at all between dementia in PD and monoaminergic
activity, but did report an association between cholinergic deficiency and dementia.
Indeed, not only in AD [112, 113], but especially in PDD and DLB, a cholinergic
deficit has been implicated in the pathophysiology of cognitive impairment. In these
patients, a definite and more pronounced depletion of cholinergic neurons is found
in the nucleus basalis of Meynert compared with AD patients and non-demented
PD patients [114, 115], together with diminished cholinergic activity in the cortex
[111, 116-118]. This nucleus in the basal forebrain, consisting for 90% of
cholinergic neurons, provides major cholinergic projections to the amygdala and
neocortex [114, 115, 119, 120]. The cholinergic deficit, possibly superposed upon a
normal age-related deterioration of the cholinergic system [121], is strongly
 correlated with cognitive impairment in both conditions [114, 117, 122] and
therefore is likely to constitute an important mechanism in the development of
dementia. This is further supported by the propensity of anticholinergic agents to
elicit cognitive dysfunction in non-demented PD patients [123, 124] and the clinical
beneficial results of cholinesterase inhibitors in demented PD patients [125]. Along
with these subcortical neuropathological changes in PDD, important cortical
changes have been implicated in the aetiology of PD dementia. AD pathology has
been shown to be more abundant in demented PD patients when compared to
non-demented patients, especially with regard to AD neurites, and correlates with
the severity of PDD in a number of studies [126, 127]. On the other hand, several
authors have pointed to the importance of cortical Lewy bodies as a
neuropathological substrate for dementia in PD [85, 128-130], independent of AD-
pathology [128, 129, 131]. This, on the other hand, was opposed by studies
reporting comparable cortical Lewy body distribution in demented and non-
demented PD-patients [86, 127].

A prospective, community-based study, however, showed the extent of cortical
Lewy body pathology in a group of demented PD patients to be associated with the
rate of cognitive decline, while only modest levels of concurrent AD pathology
could be identified [132]. A recent clinicopathologic correlation study supports the
notion of Lewy bodies as the main substrate driving the progression of cognitive
impairment in PD [133]. In this study in a large cohort, which included demented as
well as non-demented PD patients, cognitive status in the year preceding autopsy
was highly correlated to the neuropathological stage as assessed using the Braak
PD staging system [23], while a much lower correlation with AD pathology was observed. Interestingly, the authors of this study note that, in some individuals, cognitive decline can develop in the presence of mild PD–related cortical pathology and, conversely, widespread cortical lesions do not necessarily lead to cognitive decline.

Overall, dementia in PD would appear to be the result of a combination of subcortical and cortical pathological changes. Subcortical mechanisms include both dopaminergic deficiency in nigrostriatal and mesocortical projections as well as cortical cholinergic deficiency, mainly due to degeneration of the nucleus basalis of Meynert. The latter may further deteriorate the patient's executive functions by inducing attentional deficits (possibly together with noradrenergic deficiency). Superimposed AD-like changes and especially cortical Lewy bodies are likely to further compromise cognitive functions, with development of dementia as soon as a certain threshold is reached [134].

SYNCHRONIZATION OF NEURONAL ACTIVITY

Complex brain functions, including cognitive as well as behavioural processes, involve the coordinated activity of neurons distributed within and across different specialized brain areas [135]. The mechanism of transient synchronization of neuronal activity has been forwarded as a means of binding distributed sets of neurons into functionally coherent ensembles that represent the neural correlates of cognitive contents or behavioural programmes [136]. Depending on the nature of the task that is ongoing, patterns of synchronization and desynchronisation of neuronal activity will continuously change in space and time. These rapidly changing spatiotemporal patterns appear to reflect networks of interacting brain areas that can involve linear as well as non-linear mechanisms [137]. Although it is self-evident that the brain is far from being at rest during no-task conditions, one would expect undirected cognitive activity that results in more or less random brain activity. Quite to the contrary, recent studies have demonstrated that the resting-state is a far more stable and active condition than previously assumed [138, 139] that is characterized by activation within a series of functional–anatomic networks implicated in motor, sensory and cognitive functions [140]. Each of these resting-state networks appears to have a specific electrophysiological signature, that combines the involvement of different brain rhythms [141].
Local synchrony of neuronal activity is a prerequisite for recording brain activity non-invasively in living human subjects using neurophysiological techniques such as electroencephalography (EEG) and magnetoencephalography (MEG). Whole-head MEG is particularly useful in capturing the spatiotemporal dynamics of human brain activity since this technique does not require a reference electrode and is much less influenced by the skull than EEG [135]. The oscillatory activity of neuronal populations recorded using EEG and MEG can be analysed in several ways. First, local neuronal synchrony can be quantified by calculating relative or absolute power (square of the EEG/MEG amplitude) in distinct frequency bands at each sensor or electrode position using spectral decomposition. Secondly, task- or stimulus-associated changes in local oscillatory neuronal synchrony can be measured in two different ways. Evoked oscillations are related to early, stimulus-driven encoding processes and can thus be revealed by stimulus-locked averaging. Induced oscillations, however, are not phase-locked to the stimulus and will not manifest after stimulus-driven averaging. Induced oscillations are mostly of high frequency and occur in association with a variety of stimulus-triggered cognitive processes such as focused attention and movement preparation. Thirdly, the coupling or synchronization of brain activity between distributed neuronal populations can be analyzed by measuring statistical interdependencies over different brain regions, a concept aptly known as functional connectivity [142].

Traditional measures of functional connectivity include correlation and coherence [143]. A potentially more sensitive measure of functional coupling is synchronization likelihood (SL). This recently introduced measure is sensitive to both linear and nonlinear interdependencies between signals derived from distributed brain regions [144]. Using SL, a loss of resting-state functional network architecture has been demonstrated in a variety of brain diseases, involving both focal as well as more diffuse brain pathology [145-150].

PATHOLOGICAL SYNCHRONIZATION IN PARKINSON’S DISEASE

Under normal conditions, increased synchrony in the beta frequency range accompanies movement preparation and disappears during the actual execution of movements [135, 151]. Recent studies in tissue slice preparations, animal models of PD and PD patients have demonstrated widespread abnormal synchronization in a broad ‘basal ganglia beta frequency band’ (ranging from 8 to 30 Hz) at multiple
levels of the basal ganglia thalamocortical circuits [151]. Moreover, correlations have been reported between the excessive beta synchronization and PD motor deficits, in particular akinesia. Pathological beta synchronization appears to also influence cortico-cortical functional connectivity.

Recently, Silberstein and co-workers described a correlation between increased beta band EEG coherence over central brain areas and the severity of parkinsonism as expressed by the motor section of the Unified Parkinson’s disease Rating Scale (UPDRS, [152]). In this and other studies, dopaminergic treatment, ablative surgery or deep-brain stimulation suppressed beta band coherence in parallel with an improvement in bradykinesia and rigidity [151]. It should, however, be noted that all studies in human subjects involved patients at an advanced stage of disease who were treated with deep brain stimulation. Consequently, results do not necessarily apply to patients at earlier disease stages. Furthermore, comparative studies in humans that have included a reference control group are still non-existent. Nevertheless, these studies do highlight the importance of pathologically altered synchronization within and between brain regions in the pathophysiology of PD related motor impairments.

Treatment-induced suppression of beta synchrony, however, does not correlate with an improvement of parkinsonian resting tremor. Apparently, the pathophysiological mechanism involved in resting tremor is different from that involved in bradykinesia [151]. This notion is further supported by the relative resistance of tremor to treatment with dopaminergic agents as well as deep-brain stimulation of the STN. There is some evidence for a direct relationship between low-frequency oscillatory neuronal activity and tremor. Using non-invasive MEG recordings, Timmerman and colleagues demonstrated an extended tremor-related network featuring oscillatory activity that was harmonically related to the frequency of tremor [153]. Others have emphasized the importance of theta synchronization in the pathophysiology of PD [154].

RESEARCH QUESTIONS AND OUTLINE OF THE THESIS

In the previous sections, it was emphasized that cognitive dysfunction is a common symptom of PD and that mild cognitive deficits progress to full-blown dementia in a large percentage of patients. Dementia in PD constitutes not only an important risk factor for the occurrence of psychosis, caregiver distress and nursing home
placement, but is also associated with increased mortality. Furthermore, preceding sections demonstrated that synchronization of neuronal activity within and between distributed brain regions is a fundamental property of cortical and subcortical networks and serves a variety of functions including motor and cognitive processes. Consequently, clinical deficits in neurological diseases are expected to be associated with changes in oscillatory brain activity. Indeed, pathologically exaggerated synchronization appears to play an important pathophysiological role in PD-related motor deficits, at least in the relatively advanced stages of disease.

Despite the profound negative impact of cognitive dysfunction in PD, still little is known about the presence of these impairments in the earliest, untreated stages of disease, their pathophysiological basis or about predictors for the conversion of these relatively mild cognitive deficits to overt dementia during the course of the disease. Specifically, the relation between abnormal synchronization and cognitive dysfunction in PD remains to be clarified.

In this thesis the following research questions are addressed:

• Can cognitive deficits be observed in the earliest clinical stages of PD and what is the nature of these deficits?

• Is early-stage PD associated with changes in synchronization of resting-state neuronal activity within and across distributed brain regions, are these changes related to (progression of) cognitive and/or motor deficits and can they be modulated by dopaminomimetics?

The first question is addressed in chapter 2, which includes the results of three separate neuropsychological studies in PD. Using a motor randomization task, a visuo-motor coordination task and a task of spatial memory span, cognitive deficits were explored in early-stage treated and untreated PD patients.

Resting-state synchronization within distributed brain regions was explored in PD using MEG, as described chapter 3. The emphasis was on changes in resting-state oscillatory brain activity in the earliest clinical stages of PD, before the start of dopaminergic treatment. In addition, we studied the effects of disease duration, disease stage, disease severity and dopaminergic medication on the observed changes, as well as the relationship of any alterations in spectral power with changes in cognitive function.

In chapter 4 the focus is on changes in resting-state synchronization across distributed brain regions. The first section provides the results of an MEG study of resting-state functional connectivity in the earliest clinical stages of PD and its development over the disease course. In addition, analyses of the relationship
between resting-state functional connectivity and clinical measures of motor and cognitive function are described. The second section is a description of the effects of an acute dopaminomimetic challenge on cortico-cortical resting-state functional connectivity in PD patients in the relatively early stages of dopamine replacement therapy. The relation of this modulation with motor improvement is described as well.

Finally, chapter 5 provides a synthesis of the various hypotheses and conclusions stated in the preceding chapters and discusses potential implications as well as future perspectives.