

# **Cognitive impairment in patients with Parkinson's disease: profiles and implications for prognosis**

**By**

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## **EMPIRICAL REPORTS**

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### **Report 2:**

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### **Report 3:**

Janvin, C., Larsen, J.P., Hugdahl, K., Aarsland, D. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Movement Disorders 2006;21:1343-1349.

### **Report 4:**

Janvin, C., Larsen, J.P., Salmon, D., Galasko, D., Hugdahl, K., Aarsland, D. Cognitive profiles of individual patients with Parkinson's disease and dementia: comparison with patients with dementia with Lewy bodies and Alzheimer's disease. Movement Disorders 2006;21:337-342.

## **ABSTRACT**

### **Objectives:**

The main objective of the present thesis was to explore cognitive impairment in patients with Parkinson's disease (PD), focussing on non-demented patients and elucidating cognitive profile, the course and predictive power of cognitive impairment for the development of dementia.

### **Methods:**

The sample of 139 patients with PD was drawn from an epidemiological study of PD performed in Rogaland County, Norway in 1993. In 1997, the survivors performed a baseline evaluation consisting of neurological, psychiatric and neuropsychological assessments. They were re-assessed 4 years later with the same test-battery. A group of 38 healthy elderly controls performed the same neuropsychological test battery at baseline, in order to obtain normative data.

PD was diagnosed according to explicit and generally accepted criteria based on clinical examination. The cognitive assessment consisted of a battery of neuropsychological tests assessing visual memory (Benton Visual Retention Test, multiple choice version), visuospatial abilities (Judgement of Line Orientation), and executive functions (Stroop Word Test), as well as of two screening instruments: the Mini Mental Status Examination (MMSE) and Dementia Rating Scale (DRS). Dementia in PD was diagnosed according to Diagnostic and Statistical Manual of Mental Disorders, 3<sup>rd</sup> edition, revised (DSM- III-R) criteria based on a semi-structured clinical caregiver-based interview and the results of the neuropsychological tests. The diagnosis of mild cognitive impairment (MCI) was made according to a modified version of the criteria proposed by Petersen et al 2001.

### **Results:**

Fifty-five percent of the PD patients without dementia were cognitively impaired. Impairment on the Stroop Word Test was associated with an increased risk for incident dementia. Thirty-eight PD patients (52.7%) who fulfilled the criteria for MCI were identified. The progression rate to dementia after 4 years was 60% in subjects with MCI, compared to only 20% among the cognitively intact PD patients. Finally, cognitive heterogeneity was found both in patients with MCI and with dementia: In both groups, the majority exhibited a predominantly executive impairment (i.e. "subcortical" cognitive profile), although a considerable proportion had a predominantly memory impairment (i.e. "cortical" cognitive profile).

## Conclusions:

These findings show that cognitive impairment is common even in non-demented patients with PD, and that MCI is an early manifestation of the dementia in PD. The cognitive profiles indicate that in most patients with PD, fronto-subcortical changes are the main contributing factor to dementia, whereas in other patients, cortical and hippocampal changes predominate.

## INTRODUCTION

### Parkinson's disease

Parkinson's disease (PD) is a common neurodegenerative disorder. The prevalence of PD is 100-150 patients per 100000 inhabitants (Mutch, Dingwall-Fordyce, Downie, Paterson, & Roy, 1986; Tandberg, Larsen, Nessler, Riise, & Aarli, 1995). It increases with age, reaching a maximum around 75-80 years, affecting about 1.5% of people aged 65 or older (de Rijk et al., 1997; Tandberg et al., 1995). PD is present in all countries where prevalence studies have been conducted, in all ethnic groups, and is approximately equally prevalent in men and women (Zhang & Roman, 1993). The specific aetiology of PD remains unknown in most cases. However, genetic factors, infections and sub-clinical intoxications, as well as head trauma and vascular disease, have all been suggested as possible risk factors (Duvoisin, 1993; Rybicki, Johnson, Uman, & Gorell, 1993; Tipton, McCrodden, & Sullivan, 1993).

The cardinal clinical features are resting tremor, bradykinesia, rigidity and postural instability. Pathologically, PD is defined as a loss of dopaminergic neurones in the substantia nigra, with the formation of  $\alpha$ -synuclein positive Lewy bodies (LB) within the remaining neurones (Braak et al., 2002). In addition to degeneration of the dopaminergic system, other ascending subcortical neurotransmitter systems are affected as well: the cholinergic system (nucleus basalis of Meynert), the noradrenergic system (locus coeruleus), and the serotonergic system (dorsal raphe nuclei) (Jellinger, 1999a). Cortical changes, LB and amyloid plaques, and neurofibrillary tangles (NFT) are also found in most patients at autopsy (Jellinger, Seppi, Wenning, & Poewe, 2002).

### Diagnosis of Parkinson's disease

PD is found in approximately 70% of patients with parkinsonism. The diagnosis of PD is mainly based on medical history and clinical examination. Criteria for the clinical diagnosis of PD have been proposed in the literature (Hughes, Daniel, Kilford, & Lees, 1992; Larsen, Dupont, & Tandberg, 1994). Functional imaging, in particular the visualisation of the dopamine transporter by means of recently developed tracers with single photon emission computed tomography (SPECT), may be useful for effecting a differential diagnosis (Chou et al., 2004; Walker et al., 2004).



## Differential diagnosis of Parkinson's disease

The clinical differentiation of PD from other types of parkinsonism is critically important for effective management, evaluation of prognosis, and research. Thus, PD must be differentiated from the secondary parkinsonism induced by neuroleptics or other causes (i.e. intoxication, infections, traumatic, and vascular) as well as from parkinsonism which arises in the course of other neurodegenerative diseases (i.e. Alzheimer's disease (AD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP)). The following findings are suggestive of PD: 1) resting tremor; 2) no atypical motor signs; 3) lack of dementia and obvious autonomic deficiency at the onset of the disease; 4) asymmetrical disease, particularly among the elderly; 5) no demonstrable precipitating factors; 6) good response to levodopa /apomorphine test.

## Clinical heterogeneity within patients with Parkinson's disease

The clinical heterogeneity within the patient population with PD is well recognised with different neuropathological mechanisms underlying PD, and genetic factors as well as different aetiologies thought to contribute to this heterogeneity (Foltynie, Brayne, & Barker, 2002; Lewis, Foltynie et al., 2005). Different cohorts of patients have been robustly identified: younger onset, tremor dominant, non-tremor dominant, and rapid disease progression. The subgroup of PD patients with young onset of disease (Dubois, Pillon, Sternic, Lhermitte, & Agid, 1990; Giovannini et al., 1991) is characterized by a slower rate of disease progression (Goetz, Tanner, Stebbins, & Buchman, 1988; Jankovic et al., 1990; Zetusky, Jankovic, & Pirozzolo, 1985) and a greater potential to develop motor fluctuations, possibly as a consequence of prolonged levodopa exposure (Gibb & Lees, 1988; Hughes, Daniel, Blankson, & Lees, 1993), compared with subgroups of later disease onset. Many studies have pointed out the distinction between a benign "tremulous" form of the disease compared with the more aggressive "bradykinetic-rigid" form. The tremor dominant subgroup have a slower rate of disease progression (Jankovic et al., 1990; Zetusky et al., 1985) and less cognitive impairment (Mortimer, Pirozzolo, Hansch, & Webster, 1982; Portin & Rinne, 1987; Zetusky et al., 1985). By contrast, PD patients in the non-tremor dominant subgroup are afflicted with mild depression and executive impairment. A final subgroup of PD patients includes patients with a rapid rate of motoric disease progression, but no marked cognitive impairment. These patients may comprise a parkinsonian syndrome other than idiopathic PD in light of their more rapid natural history (Colosimo, Albanese, Hughes, de Bruin, & Lees, 1995; Wenning, Ben Shlomo, Magalhaes, Daniel, & Quinn, 1994).

Previous studies have suggested differing neural pathologies for distinct motor symptoms, such as akinesia (Morrish, Sawle, & Brooks, 1995; Nandi, Aziz, Giladi, Winter, & Stein, 2002) and tremor (Doder, Rabiner, Turjanski, Lees, & Brooks, 2003; Parker, Tzourio, Blond, Petit, & Mazoyer, 1992) as well as the cognitive features of the disease (Dubois, Pilon, Lhermitte, & Agid, 1990; Ito et al., 2002; Lewis, Dove, Robbins, Barker, & Owen, 2003; Mattay et al., 2002). It is likely that different clinical subgroups have different pathological processes and foci (Brooks, 1999; Jellinger, 1999b), which in turn may have different aetiologies.

Defining subgroups of patients with PD is helpful in delineating the natural history, prognosis and therapeutic options. Thus, identification of different patient subgroups may be a helpful predictor for current management strategies and also relevant to neurosurgical interventions and pharmacological treatment of cognitive impairment in PD.

### **Cognitive functioning in Parkinson's disease**

Contrary to the claim of James Parkinson who first described the disease that the intellect is preserved (Parkinson, 1817), the clear evidence is that cognitive impairment is common even in early PD and affects a variety of cognitive functions (Foltnie, Brayne, Robbins, & Barker, 2004; Janvin, Aarsland, Larsen, & Hugdahl, 2003; Levy, Jacobs et al., 2002; Muslimovic, Post, Speelman, & Schmand, 2005; Weintraub, Moberg, Culbertson, Duda, & Stern, 2004). In many instances these impairments may not be clinically apparent, but are detectable with specific neuropsychological tests. As the disease progresses, a substantial proportion of patients with PD develop dementia (Emre, 2003; Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003). In addition, other neuropsychiatric symptoms, such as visual hallucinations, depression and apathy, are also common (Aarsland & Karlsen, 1999). Thus, it is increasingly recognised that PD is also a neuropsychiatric disorder and not merely a movement disorder. In addition to being common, there is convincing evidence demonstrating the clinical importance of such symptoms for the quality of life of patients and their caregivers, as well as the health-economic impact due to increased risk for nursing home admission (Schrag, Jahanshahi, & Quinn, 2000; Aarsland, Larsen, Tandberg, & Laake, 2000).

## Executive functions

Impairment of executive functions (defined as the ability to plan, organise, and regulate goal-directed behaviour) constitutes the core feature of neuropsychological dysfunction in PD patients (Litvan, Mohr, Williams, Gomez, & Chase, 1991; Pillon, Deweer, Agid, & Dubois, 1993; Pillon, Dubois, Lhermitte, & Agid, 1986). The term refers to impairment in concept formation and rule finding, problem solving, set elaboration and planning, set shifting, and set maintenance (Pillon, 2001). These impairments are similar, but not identical (Owen, 1993) to those seen in patients with frontal lesions and are thought to represent a dysfunction of the fronto-striatal neuronal circuitry (Rogers, 1998; Rowe, 2002).

## Visuospatial abilities

Visuospatial impairment has been described in patients with PD (Montse, 2001; Pillon, Dubois, Ploska, & Agid, 1991), even when tests reveal few motor component involvement (Hovestadt, 1987). In non-demented patients with mild to moderate PD visual impairment has been found to correlate with impairments in cognition (i.e. executive functions and verbal memory), postural control and gait, and functional disability (Uc et al., 2005). Furthermore, visuospatial impairment was found to be more severe in patients with PD and dementia (PDD) than in AD patients with an equivalent severity of dementia (Huber, Shuttleworth, & Freidenberg, 1989; Mosimann et al., 2004; Mosimann et al., 2005; Stern, Richards, Sano, & Mayeux, 1993). It has been suggested that such visuospatial impairment may be at least partly attributable to frontal-executive dysfunction in addition to deficit in temporal and parietal cortices.

## Memory

Memory impairment has frequently been reported in PD and is characterised by poor free recall, but relatively better recognition than free recall. Impaired immediate and delayed recall can largely be remedied by semantic cueing or probing (Pillon et al., 1993; Scheltens, 1999), suggesting that the memory deficits in PD may be due to retrieval problems (Jacobs et al., 1995; Stern, Marder, Tang, & Mayeux, 1993; Aarsland, Andersen et al., 2003), as opposed to the deficient encoding seen in AD (Helkala, 1988; Kramer, 1989; Massman, Delis, Butters, Levin, & Salmon, 1990). This may reflect a deficiency in internally-cued search strategies due to the dysexecutive syndrome (Pillon, 2001). However, a recent study demonstrated that although a frontal-type memory impairment was the most common memory profile in PD, a considerable subgroup showed impairment of both recall and recognition, a

pattern similar to that found in patients with AD (Weintraub et al., 2004). This finding suggests that hippocampal pathology, which in fact is common in PD (Junque et al., 2005; Tam, Burton, McKeith, Burn, & O'Brien, 2005) may also contribute to memory impairment in a subgroup of patients with PD.

### Attention

Attentional dysfunction is prominent among the cognitive impairments described in PD and is probably closely related to the executive function impairment reported in these patients. This hypothesis is supported by several studies showing that attentional dysfunction appears most usually in connection to complex tasks requiring shifting and/or sustained attention (Downes et al., 1989; Lewis, Slabosz, Robbins, Barker, & Owen, 2005; Wright, Burns, Geffen, & Geffen, 1990), as well as mental calculations that require sustained mental tracking (Huber, 1990). Attentional dysfunction is a characteristic feature of dementia in PD (PDD) and DLB, and consists both of reduced and fluctuating performance (Ballard et al., 2002). The underlying pathological substrate of this dysfunction is not yet clear, but metabolic activity (O'Brien, Firbank, Mosimann, Burn, & McKeith, 2005) and cholinergic deficits in the thalamus (Ziabreva et al., 2005) have been put forward as being responsible.

### Speed of mental processing

Several studies have shown mental slowing (i.e. bradyphrenia) in PD (Cooper, Sagar, Tidswell, & Jordan, 1994; Mayeux, Stern, Sano, Cote, & Williams, 1987), although this is still a matter of considerable controversy in the literature. 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 (Smith, Goldman, Janer, Baty, & Morris, 1998). However, recent studies support the early literature, and suggest that mental slowing, possibly secondary to attentional dysfunction, is in fact a symptomatic characteristic of patients with LB associated dementia.

### Summary and unresolved issues

In summary, there is convincing evidence that cognitive functioning is affected in patients with PD, even early in the course of the disease. However, divergent findings concerning the frequency and severity of impairment of the various cognitive domains have been reported. These are probably due to the small and selected patient samples which characterize most studies, as well as the idiosyncratic features of the disease itself. Overall,

the cognitive pattern is typically characterised by impaired executive functions, including attention and visuospatial abilities, in addition to memory impairment, which is usually less pronounced.

There are, however, a number of unresolved issues requiring further investigation. The clinical profile and course in PD differ markedly, and clinical subgroups of PD have been proposed. However, since nearly all studies have presented findings on overall group means rather than how individuals are clustered into subgroups, little is known as to whether subgroups of PD patients with different cognitive profiles in fact exist. This is perhaps to be expected, given the findings of subgroups with different motor profiles in PD (Lewis, Foltynie et al., 2005). Preliminary evidence indicates that there is also cognitive heterogeneity in PD, but very few studies have explored this to any meaningful depth, and the possibility of cognitive subgroups in PDD has not been explored at all. Another largely unresolved issue is cognitive functioning over time, and whether the early and mild cognitive impairments in PD are stable or progress to dementia. Comparison between studies is hampered by methodological differences, such as the different diagnostic criteria for PD, the selection of patients, with most studies being based on convenience samples from highly specialised centers and thus not necessarily representative of the population of PD, the criteria to define dementia, and the methods used to assess cognition.

#### Clinical correlates of cognitive dysfunction in Parkinson's disease

##### *Age and age of onset*

Several studies have explored the demographic and clinical factors associated with cognitive impairment. Later onset of the disease has been associated with increased risk for cognitive dysfunction and subsequent dementia in several studies (Hobson & Meara, 2004; Mahieux et al., 1998; Muslimovic et al., 2005). In contrast, other studies found that age at entry in the study (Hughes et al., 2000; Levy, Jacobs et al., 2002; Stern, Marder et al., 1993; Aarsland et al., 2001), but not age at onset was associated with later onset of dementia. Overall, it would seem that PD patients with early disease onset have less severe cognitive problems than patients with later disease onset, and have a disease that progresses more slowly, although it is not yet clear whether the effect of age at onset is independent of the effect of age itself (Marder, 2005).

### *Medication effects*

Levodopa is widely used for the treatment of motor symptoms, but there is a lack of consensus regarding its effect on cognition in PD. Treatment with levodopa has been reported to either improve (Cooper et al., 1992; Downes et al., 1989), impair (Gotham, Brown, & Marsden, 1988; Kulisevsky et al., 1996) or not affect (Pillon, Dubois, Bonnet et al., 1989) frontal cognitive performance in patients with PD (i.e. working memory, set switching), and to improve (Cooper et al., 1992; Rogers, Lees, Smith, Trimble, & Stern, 1987), impair (Huber, Shulman, Paulson, & Shuttlesworth, 1989; Poewe, Berger, Benke, & Schelosky, 1991) or not affect (Kulisevsky et al., 1996; Rafal, Posner, Walker, & Friedrich, 1984) memory functions. One possible explanation for these discrepant findings is that the effect of levodopa depends on whether the brain area responsible for the cognitive domain is depleted of dopamine or not. Thus, if cognitive dysfunction is associated with dopaminergic deficit in a specific brain area, levodopa treatment may improve functioning. In contrast, if the cognitive dysfunction is caused by problems with brain circuits not depleted of dopamine, levodopa may in fact lead to dopaminergic overstimulation and worsening of the function (Kulisevsky, 2000). Although limited research exists, there is some evidence that dopamine agonists may also influence cognition in PD, and that the effect may differ according to the pharmacological characteristics. Specifically, preliminary evidence suggested that the D2/D3 agonist pramipexole, but not the D1/D2 agonist pergolide may worsen cognitive functions such as verbal fluency, verbal memory and attentional-executive functions (Brusa et al., 2003; Brusa et al., 2005).

Several studies have found that anticholinergic treatment impairs memory and other cognitive functions in PD (Dubois et al., 1987; Sadeh, Braham, & Modan, 1982), and has even been associated with inducing morphological changes such as accumulation of amyloid plaques and NFT (Perry, Kilford, Lees, Burn, & Perry, 2003). However, other studies report no evidence of memory deterioration (Levin, Llabre, Reisman, Weiner, & Brown, 1991). Glutamatergic overstimulation exists in PD and may contribute to cognitive impairment. Accordingly, glutamatergic antagonists, such as amantadine, may therefore protect against cognitive decline. Convincing evidence supporting this hypothesis is lacking, however. Further studies including studies with drug naïve patients are needed to resolve the impact of pharmacological drugs on cognitive functioning in PD, particularly from a longitudinal perspective.

### *Motor symptoms and cognitive impairment*

Studies of the association between cognitive and motor symptoms in patients with PD have revealed several consistent trends. First, patients with predominant postural instability (Zetuský et al., 1985), gait disorder (Alves, Larsen, Emre, Wentzel-Larsen, & Aarsland, 2006; Pillon, Dubois, Cusimano et al., 1989), rigidity (Huber, Paulson, & Shuttleworth, 1988; Marttila & Rinne, 1976), and bradykinesia (Ebmeier et al., 1990; Huber et al., 1988; Marttila & Rinne, 1976) exhibit greater cognitive impairment than patients with tremor dominant disease. Second, more severe motor symptoms have consistently been associated with a more rapid cognitive decline and increased risk of dementia (Marder, Tang, Cote, Stern, & Mayeux, 1995; Stern, Marder et al., 1993; Aarsland et al., 2001; Aarsland et al., 2004). Finally, there is some evidence suggesting that the side of the motor onset may influence cognitive outcome, with the left-sided onset group performing poorer than the right on several cognitive measures, including immediate and delayed recall, word retrieval, semantic verbal fluency, attention, and mental tracking (Tomer, Levin, & Weiner, 1993), although such a relationship has not been consistently observed (Finali, Piccirilli, & Rizzuto, 1995; St Clair, Borod, Sliwinski, Cote, & Stern, 1998).

In summary, patients with tremor dominant disease seem to have less severe cognitive impairment than those with predominant postural instability and gait disturbance.

### *Cognition and depression in Parkinson's disease*

There is a close and enigmatic relationship between depression and PD. Prevalence estimates of depression in PD range from 7% to 90%, depending on the diagnostic criteria and selection of the study population (Nilsson, Kessing, Sorensen, Andersen, & Bolwig, 2002; Tandberg, Larsen, Aarsland, Laake, & Cummings, 1997; Troster, 2000; Aarsland & Cummings, 2002). Depression seems to be more common in PD with dementia (Tandberg, Larsen, Aarsland, & Cummings, 1996; Veazey, Aki, Cook, Lai, & Kunik, 2005). On the other hand, depression is considered to be a risk factor for PD (Leentjens, Van den Akker, Metsemakers, Lousberg, & Verhey, 2003; Schuurman et al., 2002). As is also the case in depressed patients without PD, depression is associated with cognitive impairment, particularly in executive and memory tasks (Kuzis, Sabe, Tiberti, Leiguarda, & Starkstein, 1997; Norman, Troster, Fields, & Brooks, 2002; Starkstein et al., 1989; Troster, Paolo et al., 1995; Troster, Stalp, Paolo, Fields, & Koller, 1995). These findings are consistent with neuroimaging studies showing greater frontal and temporal lobe metabolic abnormalities in patients with depression with or without PD (Mayberg, 1994; Mayberg et al., 1990). Recent

research suggests that mild depression probably has little if any impact on cognition in PD, and that depression must be of at least moderate severity before it has a significant impact on cognition (Boller, Marcie, Starkstein, & Traykov, 1998; Starkstein, 1993). Whether depression is associated with a later development of dementia in PD is still a controversial issue. One older study (Stern, Marder et al., 1993) indicated that depression was a risk factor for dementia in PD, while other studies did not (Hobson & Meara, 2004; Hughes et al., 2000; Mahieux et al., 1998; Aarsland et al., 2001). Since depression has consequences for PD patients and their caregivers in terms of quality of life (Karlsen, Tandberg, Arslan, & Larsen, 2000; Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999), it is important to properly diagnose and treat depression in PD. Furthermore, studies of the effects of depression on cognition need to control for the possible effect of antidepressants on cognition, since these may ameliorate aspects of cognitive dysfunction in these patients (Norman et al., 2002).

In summary, certain demographic and clinical characteristics are associated with cognitive performance in PD. Age, and possibly age at onset, more severe parkinsonism, in particular non-tremor symptoms such as rigidity and postural symptoms, to some extent antiparkinsonian agents, and depression, have all been found to be negatively associated with cognition in PD.

#### Mild cognitive impairment in Parkinson's disease

Mild cognitive impairment (MCI) is common in the general population (Graham et al., 1997; Waite, Broe, Grayson, & Creasey, 2001) and it refers to a transitional state between the cognition of normal ageing and mild dementia (*Diagnostic and statistical manual of mental disorders*, 1994). Subjects with MCI have been found to have an increased risk of dementia, with an annual progression to dementia between 6% and 15% (Petersen et al., 1999). Recently, different MCI subtypes were described, and a classification into amnesic, single domain non-memory, and multiple domains slightly impaired MCI was suggested (Petersen et al., 2001). A recent study (Lopez et al., 2006) described the neuropsychological characteristics of MCI subgroups, providing further support for the classification of MCI in different subtypes. In addition, there is some evidence that the different MCI subtypes progress to different types of dementia disorders. Patients with amnesic MCI usually progress to Alzheimer's disease at a high rate (Petersen et al., 1999), while patients with a single non-memory MCI (i.e. executive or visuospatial impairment) are more likely to progress to a non-AD dementia such as dementia with Lewy bodies (Boeve, 2004), fronto-temporal dementia,



vascular dementia or primary progressive aphasia (Petersen, 2004). Although the concept of MCI is largely accepted in the context of AD, it has not been validated for PD populations.

Different cognitive profiles may exist within PD. In a study of recently diagnosed patients with PD, (Foltnie et al., 2004) 11% had a specific fronto-striatal type impairment, 8% a specific temporal lobe type impairment, and 18% impairments in both domains (global impairment). However, few prospective studies of cognition in PD have been reported, and thus the rate of progression to dementia from the different cognitive MCI types in PD is as yet unknown. Overall, the annual rate of cognitive decline in PD is stable over time, but with wide inter-individual variations (Aarsland et al., 2004). Executive and memory impairments have been found to be associated with a subsequent development of dementia in PD (Levy, Jacobs et al., 2002; Woods & Troster, 2003), but how this finding relates to the progression from MCI to dementia in individual patients is unclear.

#### Cognitive impairment in Parkinson's disease with dementia

There is abundant evidence showing that dementia is more common in PD than in the general population. The point prevalence of dementia in PD is approximately 31% (Aarsland, Zaccai, & Brayne, 2005). Since dementia is associated with increased mortality (de Lau, Schipper, Hofman, Koudstaal, & Breteler, 2005; Levy, Tang et al., 2002), prospective studies are needed to accurately describe the frequency of dementia in PD. Patients with PD have an almost six-fold risk for becoming demented compared to healthy controls (Aarsland et al., 2001), and the cumulative prevalence rises steadily. In one study following a PD sample for 8 years, the cumulative prevalence of dementia approached 80% (Aarsland, Andersen et al., 2003).

The dementia associated with PD resembles that observed in subcortical dementia (Cummings, 1990). Qualitatively, the neuropsychological profile of patients with PDD encompasses the same type of deficits found in non-demented PD patients (Girotti et al., 1988): marked deficits in executive function, attention, and visuospatial and constructional abilities (Dubois & Pillon, 1997). Memory is also impaired, although recall can be improved by cueing when compared with AD (Pillon, Dubois, & Agid, 1991; Stern, Richards et al., 1993). A similar pattern of cognitive impairment is found in DLB (Aarsland, Litvan et al., 2003), suggesting that similar neuropathological mechanisms might be involved. The cognitive pattern in DLB and PDD has been described as reflecting the superimposition of fronto-subcortical cognitive deficits on the cortical deficits typically associated with AD (Galasko, 2000).

Previous studies of the cognitive profiles in PD patients have been based on mean group data that may mask differences in cognitive patterns in subgroups of patients. To our knowledge, no study has yet investigated differences in the cognitive impairment profiles within the group of patients with PDD, and thus whether a similar cognitive heterogeneity as described in mildly impaired PD patients exists also in PD patients with dementia.

Knowledge of the pattern of cognitive impairment profiles within the group of patients with PDD would be helpful in the clinical diagnosis of patients with dementia and parkinsonism, and also provide information about the relative contribution of the different neuropathological and neurochemical factors underlying the cognitive dysfunction (for example, the contribution of dopaminergic and/or non-dopaminergic mechanisms, and cortical or subcortical lesions), with potential importance to effective pharmacotherapy of dementia in PD.

#### Pathophysiology of cognitive dysfunction in Parkinson's disease

The variety of cognitive impairments in PD suggests that a number of different neurochemical and neuropathological factors contribute to these cognitive changes. Executive impairment is related to the dopaminergic deficits, caused by either disruption of the nigro-striatal circuitry with altered outflow from the caudate nuclei to the frontal cortex via the thalamus (Lewis et al., 2003; Rinne et al., 2000) or diminished dopamine activity in the frontal projections consequent to degeneration of mesocortical projections (Mattay et al., 2002). This hypothesis is supported by the worsening of executive functioning, but not memory, after withdrawal of levodopa (Lange, Paul, Naumann, & Gsell, 1995). Although the exact contribution of non-dopaminergic transmitter changes to the cognitive impairments in PD is not known, there is some evidence linking the cortical noradrenergic system to extradimensional shift performance (Robbins, 2003), whereas visual memory may be dependent on acetylcholine rather than being dopamine dependent (Lange et al., 1992). However, cholinergic deficits may also contribute to the executive and attentional deficits (Bohnen et al., 2006).

The more extensive global cognitive impairment in the later disease stages suggests that cortical regions become involved. Brain imaging with SPECT revealed a differential relationship between cortical perfusion and cognitive functions, with temporal and parietal perfusion exhibiting a relationship to global cognitive impairment, while dorsolateral frontal perfusion relates to executive impairment (Firbank, Colloby, Burn, McKeith, & O'Brien, 2003; Jagust, Reed, Martin, Eberling, & Nelson-Abbott, 1992; Mito et al., 2005).

Furthermore, with increasing cognitive impairment, cerebral atrophy probably adds to the neurochemical changes, and recent studies using MRI have demonstrated widespread areas of cortical atrophy in frontal, temporal and parietal cortices (Burton, McKeith, Burn, Williams, & JT, 2004; Tam et al., 2005).

The aetiology of dementia in PD is not yet established in detail. Previous studies have reported that Alzheimer-type changes, i.e. neuritic plaques and NFT are the main correlates of dementia in PD (Braak et al., 1996; Cordato, Halliday, Harding, Hely, & Morris, 2000; de Vos, Jansen, Stam, Ravid, & Swaab, 1995; Jellinger et al., 2002). On the other hand, it has recently been suggested that the LB degeneration in PD is not confined to the brain stem, but rather develops in stages which subsequently involve the basal forebrain, limbic structures and finally neocortical association areas (Braak, Ghebremedhin, Rub, Bratzke, & Del Tredici, 2004). Recent studies, using more sophisticated staining methods, have indeed suggested that the limbic and cortical LB lesions are the main pathological correlate of dementia in PD (Apaydin, Ahlskog, Parisi, Boeve, & Dickson, 2002; Braak, Rub, Jansen Steur, Del Tredici, & de Vos, 2005; Hurtig et al., 2000; Kovari et al., 2003; Samuel, Galasko, Masliah, & Hansen, 1996; Aarsland, Perry, Brown, Larsen, & Ballard, 2005). In addition, hippocampal atrophy has commonly been reported in PDD (Junque et al., 2005; Tam et al., 2005). Thus, a wide range of neurochemical and morphological changes develop in PD, potentially inducing or at least contributing to cognitive impairment and dementia. It is likely that the relative importance of these changes varies among the different patients, but this is not yet understood in detail. The direct relationship of these diverse pathological changes to the different cognitive deficits in patients with PD and PDD is not established. Detailed clinico-pathologic and related studies are needed to provide answers to these questions.

#### Pharmacological treatment of dementia in Parkinson's disease

There are currently no treatments available to limit the LB neurodegenerative process in PD. However, pharmacological agents can influence several of the neurochemical changes. As stated above, clinical experience and clinical trials indicate that treatment with levodopa does not have a major functional impact on the dementia of PD. As discussed above, there is convincing evidence to suggest that cholinergic deficits (i.e. related to cellular loss in the nucleus basalis of Meynert) play a role in the aetiology of cognitive deficits in PD (Dubois, Ruberg, Javoy-Agid, Ploska, & Agid, 1983; Perry et al., 1985). These findings have led to pharmacological studies of cholinergic agents in PD. Several open-label and small, placebo-controlled studies with cholinesterase inhibitors have indicated that these agents may be

effective (Leroi et al., 2004; Aarsland, Hutchinson, & Larsen, 2003; Aarsland, Laake, Larsen, & Janvin, 2002). These preliminary findings were recently confirmed in a large-scale placebo controlled trial with rivastigmine, showing that rivastigmine had a positive effect not only on cognition, but also on neuropsychiatric symptoms and the activities of daily living. (Emre et al., 2004), as well as several aspects of attention (Wesnes, McKeith, Edgar, Emre, & Lane, 2005).

## **OBJECTIVES OF THE STUDY**

- 1) To examine the frequency and characteristic profile of cognitive impairment in non-demented patients with PD, and the association with demographic and clinical variables
- 2) To examine whether cognitive impairments in PD can predict the development of dementia.
- 3) To explore the frequency of mild cognitive impairment in patients with PD, whether different subtypes of mild cognitive impairment exist, and whether mild cognitive impairment is associated with the development of dementia.
- 4) To identify the pattern of cognitive profile within sub-groups of patients with PDD.

## **HYPOTHESES OF THE STUDY**

- 1) Non-demented patients with PD will exhibit impairment in several cognitive domains, and it is predicted that this impairment is associated with older age, depression, and more severe parkinsonism, in particular severity of non-tremor symptoms.
- 2) Impairment on selected cognitive tests predicts incidence of dementia in patients with PD.
- 3) Subgroups of PD patients with different types of mild cognitive impairment have an increased risk of developing dementia compared to patients with intact cognition.
- 4) Different impairment profiles are predicted within the group of PDD patients. One sub-group will exhibit a subcortical-type profile, whereas another sub-group a more cortical dementia type. The distribution of cognitive profiles is characteristic for patients with LB type dementia and distinct from that in patients with AD.

## **SUBJECTS AND METHODS**

### **Subjects**

The patients were recruited from an epidemiological study of PD in the county of Rogaland, Norway conducted between 1992 and 1993. A total of 245 PD patients were identified after a comprehensive selection procedure, yielding a prevalence of PD of 110.9 per 100.000 inhabitants (Tandberg et al., 1995). During 1996/1997 the survivors were invited to participate in the baseline evaluation of the present study and were given a comprehensive assessment consisting of neurological, psychiatric and neuropsychological evaluation. Of the 245 patients evaluated in 1993, 7 had subsequently been diagnosed as not having PD, 88 had died, and 11 choose not to participate in the study. Accordingly, 139 patients participated at the baseline evaluation and represented the study population. Seventy-six patients were free of dementia, 58 were demented, and 5 received a diagnosis of questionable dementia. The sample of PD without dementia represented the at-risk population studied in papers 1 to 3. These patients were re-assessed 4 years later (2000/2001) with the same evaluations (neurological, psychiatric and neuropsychological) performed at baseline. Sixty patients with PD performed the follow-up evaluation (13 patients had died, and 3 refused to participate).

The control group consisted of 38 healthy elderly subjects who were either relatives of the patients or relatives of inpatients in the psychogeriatric ward at the Stavanger University Hospital. They performed the same cognitive test battery at baseline as PD patients to obtain normative data. The age and gender distribution as well as education were similar to the patients with PD. None had a history of alcoholism, drug abuse, psychiatric illness, Central Nervous System (CNS) disease, or head injury, and none were currently taking centrally active drugs. Individuals with evidence of intellectual deterioration (Mini Mental Status Examination score  $\leq 24$ ) (MMSE) (Folstein, Folstein, & McHugh, 1975) were not included.

Fifty of the 58 patients diagnosed with PD and dementia completed the Dementia Rating Scale (DRS) (Mattis, 1976) and represented the population studied in the fourth paper. The remaining 8 patients had severe dementia and were not able to perform the DRS. The performance on the DRS was compared with the performance of 62 patients with DLB, and 39 patients with AD. The patients with DLB were recruited from the Alzheimer Research Center at the University of California San Diego, US in whom the DRS had been

administered during life and who had undergone autopsy post mortem. The patients with AD were consecutive patients attending the outpatient clinic of the Section of Geriatric Psychiatry, Stavanger University Hospital.

#### Diagnosis and clinical evaluation of Parkinson's disease

Information on disease history, drug therapy, response to levodopa and demographic variables was obtained in a semi-structured interview conducted by a neurologist. A diagnosis of PD required the presence of at least two of the four cardinal symptoms of PD and at least a moderate response to levodopa. Patients with clinically significant cognitive impairment at disease onset, other neurological diagnoses or drugs which could cause parkinsonism, or the presence of radiological structural brain abnormalities compatible with diagnoses other than PD were excluded (Larsen et al., 1994). The clinical examination of the motor symptoms consisted of a complete Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn, 1987) assessment, including the Hoehn & Yahr scale (Hoehn & Yahr, 1967). The diagnostic evaluation was performed at each evaluation, and only those patients who fulfilled the diagnostic criteria for PD at each examination were included. Autopsy has been performed in a subgroup of 22 patients of this cohort, and in all cases, the neuropathological diagnosis was consistent with PD. Patients with motor fluctuations were assessed in the "ON" phase.

#### Assessment of cognition

Patients with PD and a MMSE score >16 and control subjects were given a neuropsychological battery assessing cognitive domains known to be affected in PD, including visual memory, visuospatial abilities, and executive functions. The selected neuropsychological tests were to the fullest extent possible independent of motor abilities. The tests were administered by a neuropsychologist, and scored according to conventional procedures outlined in the test manuals. The following neuropsychological tests were included:

- (i) The multiple choice version of the Benton Visual Retention Test (Benton, 1974) designed to assess short-time visual memory: subjects recognise one or more designs that they have seen before. The test consists of 15 items, each item being presented for 10 seconds.
- (ii) (ii) The Judgement of Line Orientation Test (Benton, Varney, & Hamsher, 1978) designed to assess visual/spatial abilities: subjects estimate the angular relationship between line segments by visually matching angled line pairs to 11 numbered radii

forming a semicircle. The test consists of 30 items, each showing a different pair of angled lines to be matched to the display cards. Its two forms, H and V, present the same items but in different order. Score corrections are provided for both age and sex (Benton, 1994).

- (iii) (iii) The Stroop Word Test (Golden, 1978) designed to assess selective attention/executive functions. Several versions of the Stroop Word Test are available on the market and they differ from each other with regard to the number of trials required to fulfil the test and the number of items on each card. The version used in the present study consists of three cards, each card containing 6x8 items: subjects name the colours of coloured patches (1<sup>st</sup> card), read printed words (2<sup>nd</sup> card), and read printed colour names in which the ink used for printing is a colour different from the colour designed by the printed name (3<sup>rd</sup> card). Both the time needed to complete each card and the number of errors was recorded.

In addition, two brief screening instruments were administered: the DRS (Mattis, 1976) and the MMSE (Folstein et al., 1975). The DRS is divided into five subtests (attention, conceptualisation, initiation and perseveration, construction, and memory) and provides a total score and five subscale scores. The scale has been shown to robustly and accurately distinguish the dementia profile of cortical and subcortical dementias (Paulsen et al., 1995; Salmon, Kwo-on-Yuen, Heindel, Butters, & Thal, 1989). For individuals with PD, the scale has been shown to be a valid mental screening test of cognitive functioning and the subtests show strong convergent and discriminant validity (Brown et al., 1999). MMSE assesses orientation, learning, short- term memory, concentration, and higher cortical functions and it is widely used in order to differentiate between cognitively intact and cognitively impaired elderly subjects. Population-based, age- and education- corrected normative data are available for both DRS and MMSE (Crum, Anthony, Bassett, & Folstein, 1993; Lucas et al., 1998).

## Diagnosis of dementia

### *Diagnosis of dementia in Parkinson's disease*

A semi-structured interview based on the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) (*Diagnostic and statistical manual of mental disorders*, 1987) criteria for dementia was administered to the caregiver by a psychiatrist with experience in geriatric psychiatry and neuropsychiatry. Two experienced clinical researchers, a psychiatrist and a neurologist, made the diagnosis of dementia according to the DSM-III-R

criteria for dementia as based on the clinical interview, the cognitive screening and the neuropsychological tests. To qualify for a diagnosis of dementia, the interview, the rating scales and the neuropsychological tests had to be compatible with a diagnosis of dementia. Population-based, age- and education-corrected normative data for the MMSE (Crum et al., 1993) and DRS (Lucas et al., 1998) were used, and scores below the lowest quartile (MMSE) or below the 19<sup>th</sup> percentile (DRS) were considered as cognitive impairment. Impairment on the neuropsychological tests was considered to be present if the score was at least 1.5 standard deviations below the mean for the control subjects. In cases of inconsistencies among these measures, all available material was reviewed, and both raters made a diagnosis of dementia or no dementia independently, according to the DSM-III R criteria for dementia. A final diagnosis was made by consensus.

#### *Diagnosis of dementia with Lewy bodies*

The diagnosis of DLB was necropsy confirmed in all patients. All patients with DLB were diagnosed clinically as having dementia at the time of their initial evaluation. The procedures used to prepare and study the brains of the patients with DLB have been described in detail before (Hansen & Samuel, 1997). The neuropathological diagnosis of DLB required the presence of subcortical and cortical LB.

#### *Diagnosis of Alzheimer's disease*

The patients with AD were diagnosed according to ICD-10 (*International classification of diseases*, 1992) criteria for AD. The diagnosis of AD was based on interviews with patients and caregivers, cognitive testing, physical examination, routine blood tests, and cranial computed tomography or MRI. None of the patients had either parkinsonism or clinically significant psychiatric symptoms.

#### *Diagnosis of mild cognitive impairment*

A diagnosis of MCI was made according to a modified version of the criteria proposed by Petersen et al (Petersen et al., 2001). MCI was defined as impaired performance (i.e. 1 1/2 standard deviation or more below the mean of the control group) on one, two or all three neuropsychological tests. In addition, information regarding memory complaint or other subjective cognitive complaints was gathered by means of the caregiver-based interview and the mentation item from the Mental Subscale of UPDRS (Fahn, 1987). To qualify for a diagnosis of MCI in this thesis, cognitive impairment should not be severe enough to affect



activities of daily living, and thus the criteria for dementia were not met. Based on the performance on the cognitive tests, three subtypes of cognitive impairment were described:

- 1) Amnesic MCI: individuals with impaired performance on the Benton Visual Retention Test, but who are performing reasonably well on the other neuropsychological tests.
- 2) Multiple domains slightly impaired: impairment on two or more cognitive tests.
- 3) Single non-memory domain: impairment in a single cognitive domain other than memory, i.e. on Judgement of Line Orientation or Stroop Word Test.

#### Psychiatric assessment

The patients with PD completed the Beck Depression Inventory (BDI)(Beck, 1978), a frequently used depression questionnaire with proven psychometric properties in PD (Leentjens, Verhey, Luijckx, & Troost, 2000; Visser, Leentjens, Marinus, Stiggelbout, & van Hilten, 2006). A cut-off score of 10 was used in order to differentiate between depressed and non-depressed PD patients (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). They also completed the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) which is an instrument specifically designed to assess psychopathology in patients with brain disorders. The NPI has proved validity and reliability in patients with dementia and assesses both the frequency and severity of 10 syndromes: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability, and abnormal motor output.

## SUMMARY OF REPORTS

**Report 1:** Neuropsychological profile of patients with Parkinson's disease without dementia.

In order to describe the frequency of neuropsychological impairment and its profile in PD patients without dementia, a sample of 103 PD patients was compared with a control group consisting of 38 healthy elderly subjects. Dementia was diagnosed in 27 patients. Among the 76 non-demented patients, 34 (45%) had no cognitive impairment and 42 (55%) had a mild cognitive impairment. Within the cognitively impaired PD group, three different types of cognitive profile were identified: 11 patients (26.1%) exhibited only executive dysfunction, 7 patients (16.6%) impaired visual memory and /or visuospatial abilities without executive dysfunction, and 19 patients (45.2%) a global cognitive impairment.

**Report 2:** Cognitive predictors of dementia in Parkinson's disease. A community- based, 4 year longitudinal study.

In order to identify whether cognitive impairment is associated with later development of dementia, the 76 non-demented PD patients were re-examined 4 years later. Twenty-five (42%) PD patients were demented at follow-up, whereas 35 PD remained without dementia. Compared to patients who did not become demented during the study period, those who became demented had lower baseline scores on the MMSE, Benton Visual Retention Test, and Judgement of Line Orientation; performed more slowly and had more errors on the Stroop Word Test third card; had more advanced PD, and had a trend toward higher depression score and older age. Factors significantly associated with incident dementia in the bivariate analysis were entered together with covariates (age, gender, education, age at disease onset, disease duration) in a logistic regression analysis to identify possible risk factors for dementia in PD. Time to complete the 3rd card of the Stroop Word Test was the only variable that was found to be independently associated with dementia.

**Report 3:** Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia.

In order to identify potential subtypes of MCI in PD and establish whether MCI tends to progress to dementia, 72 of the non-demented PD patients were assessed at baseline and 4 years later. Thirty-eight patients were diagnosed with MCI (amnesic n=6, single non-memory domain n=17, multiple domains slightly impaired n=15). At follow-up, 18 (62%) of the patients with MCI and 6 (20%) of the cognitively intact PD patients were demented. The difference was statistically significant ( $p=.001$ ). Single domain non-memory MCI and multiple domain slightly impaired MCI were associated with subsequent development of dementia ( $p=0.003$ ,  $p=0.04$ ), while amnesic MCI was not ( $p=0.76$ ).

**Report 4:** Cognitive profiles of individual patients with Parkinson' disease and dementia: a comparison with dementia with Lewy bodies and Alzheimer's disease.

In order to describe the pattern of cognitive profiles within a community-based sample of PD patients with dementia we used cluster analysis on the raw subscores on the DRS. The results were compared with data from patients with DLB and AD. Fifty patients with PDD and 39 with AD from Stavanger, Norway, and 60 patients with DLB from San Diego, USA were included in the analysis. Four subgroups were identified: two subgroups with a subcortical cognitive profile (one with mild and one with moderate dementia severity), one

subgroup with global impairment and severe dementia, and one subgroup with a cortical cognitive profile and moderate dementia. Twenty-eight (56%) of the patients with PDD and 34 (55%) of the patients with DLB were included in one of the two groups with a subcortical cognitive profile, compared to only 33% of the patients with AD (chi square=12.52, df=2, p=0.002). Conversely, 30% of the patients with PDD and 26% of those with DLB were included in the group with a cortical cognitive profile, compared to 67% of the patients with AD.

## **DISCUSSION**

### Heterogeneity of cognitive impairment in Parkinson's disease

The results confirm that cognitive impairment is common in non-demented PD patients and that the cognitive impairment is heterogeneous in its presentation. Over 50% of the non-demented patients with PD had some form of cognitive impairment: 19% exhibited predominantly memory impairment and /or visuospatial impairment, 30% a dominant executive impairment, and 51% had a global cognitive impairment.

Similarly, cognitive heterogeneity was also present within the group of patients with PDD. The majority of PDD patients with mild to moderate dementia exhibited a subcortical cognitive profile, while a small proportion exhibited a cortical cognitive profile. The patients with DLB showed a similar pattern of cognitive impairment supporting and extending previous research showing both a clinical and neurobiological similarity between DLB and PDD (Ballard et al., 2002; Harding, Broe, & Halliday, 2002; Tiraboschi et al., 2000). These findings suggest that these syndromes represent aspects of a continuum of LB disease rather than distinct disease entities. Previous findings from MRI and neurochemical studies suggest that distinct brain changes are related to the different cognitive impairments in PD. For example, memory impairment is related to hippocampal atrophy, whereas attention and executive impairment is related to atrophy of prefrontal cortex (Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004). Neurochemically, executive and attention deficits appear to be associated with dopaminergic disturbances within fronto-subcortical circuits (Owen, 2004), whereas cholinergic deficits, which are also marked in patients with PD and dementia (Jellinger, 1999a), may be causally linked to the impairment of memory and attention seen in PD. The different cognitive profiles observed in this thesis strongly suggest marked inter-

individual differences in the relative severity of the different brain changes, leading to different cognitive subtypes. However, clinico-pathologic studies are needed to explore how the different neuropsychological profiles specifically relate to distinct brain changes. Another unexplored issue is whether the cognitive subgroups are stable across the full spectrum of cognitive impairment in PD, i.e. whether the PD patients with MCI of the executive type will progress to a dysexecutive PDD syndrome, or whether the cognitive profile changes over time in the individual patient. The present findings underline that a considerable proportion of patients with PDD, as well as DLB, have a cortical cognitive profile which is similar to the profile in patients with AD. This finding has implications for the diagnostic clinical practice, although it is possible that somewhat different results might emerge with the use of a more extensive and detailed neuropsychological battery.

#### Cognitive risk factors for dementia in Parkinson's disease

The results show that impaired performance on an executive test (Stroop Word Test), but not on tests sensitive to memory or visuospatial dysfunction, was the only independent risk factor associated with dementia. This finding is consistent with previous longitudinal studies reporting that impairments on selected neuropsychological tests, such as memory and executive functioning, are associated with later dementia (Levy, Jacobs et al., 2002; Mahieux et al., 1998). Impaired performance on a verbal fluency test (shopping list from DRS) was not associated with later development of dementia either, although previous studies (Jacobs et al., 1995; Levy, Jacobs et al., 2002) reported the opposite. Discrepant findings regarding whether or not verbal fluency is an independent predictor of dementia in PD may be due to differences in task demands and instructions (Jacobs et al., 1995). Better preserved recognition memory in non-demented PD patients compared to recall memory might explain why impaired performance on Benton Visual Retention Test was not found to be an independent predictor of later dementia in our study.

The present findings indicate that executive dysfunction is the initial manifestation of dementia in PD, and that the changes may spread from fronto-striatal circuits to subsequently involve hippocampus and temporal-parietal cortex.

## Mild cognitive impairment and progression to dementia in Parkinson's disease

52.7% of the non-demented patients fulfilled our criteria for MCI. Three subtypes of MCI were identified based on explicit criteria: amnesic MCI (15.8%) single domain non-memory MCI (44.7%) and multiple domains slightly impaired MCI (39.5%). The majority of the non-demented PD patients with MCI (62%) developed dementia during the four-year follow-up, compared to only a small proportion (20%) of the cognitively intact PD patients. This is a novel finding, to our knowledge not previously reported in the literature, showing a conversion rate of MCI to dementia as high as in individuals with MCI in the general population. These findings suggest that MCI is not a stable condition of PD, but rather represents the initial stage of a progressive cognitive decline leading to dementia. PD patients with non-memory MCI subtypes (i.e. single non-memory domain and multiple domains slightly impaired) were more likely to become demented than patients with amnesic MCI. However, the low number of patients limits the generalizability of the results. Longitudinal studies including a larger number of patients with PD-MCI are needed to evaluate whether the rate of progression to dementia differs for the different cognitive subtype of MCI in PD.

It should be pointed out that the findings that MCI in PD progresses to dementia must be interpreted with some caution. Although there is largely agreement about the existence of MCI in the general population and several subtypes MCI have been described (Petersen, 2004), the concept of MCI having a role in PD patients is new and has not been validated yet. However, although slightly modified, the MCI criteria used in the present thesis are in agreement with the current consensus view about MCI. Finally, the growing evidence of cognitive and neuropathological heterogeneity in PD patients (Foltnie et al., 2002; Lewis, Foltnie et al., 2005) supports the hypothesis that MCI is a useful prognostic sign for patients with PD.

## Cognitive functioning and motor symptoms

Patients with left-sided parkinsonism performed poorer than right-sided patients only on the Benton Visual Retention Test. Previous studies suggested that patients with onset of PD on the left side performed poorer than patients with right-sided onset on several cognitive measures (Tomer et al., 1993), although such a relationship has not been consistently observed (Finali et al., 1995; St Clair et al., 1998). Furthermore, no significant differences in neuropsychological test performance were seen between the akinetic versus tremor groups. These were surprising findings as previous research had shown better cognitive performance

in the tremor group, compared to the akinetic group (Ebmeier et al., 1990; Huber et al., 1988; Marttila & Rinne, 1976). Again, the low number of patients and the resulting low statistical power might have influenced the conclusion.

#### Cognitive functioning and depression

In the present thesis, depression did not differ between the cognitive intact and cognitive impaired PD patients, suggesting that the observed cognitive impairments in the current thesis can not be explained exclusively by the presence of depression. Furthermore, depression did not seem to be an independent risk factor for the development of dementia, as has been reported by other studies (Hobson & Meara, 2004; Hughes et al., 2000; Mahieux et al., 1998; Aarsland et al., 2001). Thus, our findings suggest that depression coexists with rather than contributes to the development of dementia, i.e. “the depression of dementia as opposed to the dementia of depression” (Andersen, Vestergaard, Riis, & Ingeman-Nielsen, 1996).

#### Medication effects on cognition in Parkinson’s disease

As previously described, medication with levodopa may affect cognitive functioning, but we did not find any association between the levodopa dose and the pattern of cognitive deficits. Furthermore, none of the patients included in the study were on anticholinergic drugs. Thus, a pharmacological explanation for our findings does not seem likely. Further studies including drug naïve patients will be needed to definitively resolve the impact of pharmacological drugs on cognitive functioning in PD, particularly from a longitudinal perspective.

#### Clinical implications of the findings

Early identification of PD patients at high risk of developing dementia has important clinical consequences for the management of these patients. It is established that dementia in PD contributes to caregiver distress, placement in nursing homes, and reduced quality of life in these patients. Cognitive assessment should therefore be regularly performed in patients with PD to carefully monitor their cognitive abilities. We have shown that even brief test batteries may identify patients at high risk for dementia.

In addition, the finding that different cognitive profiles exist in PDD (and DLB), strongly argues against that these disorders should be diagnosed only in the presence of an executive-visuospatial type of cognitive impairment.

Finally, although, treatment is now available for PD with dementia, future studies are urgently needed to explore whether the progression from MCI to dementia in PD can be reduced or even prevented. With the high risk of progression to dementia, PD patients with MCI constitute a potential target group for testing new preventive treatment strategies such as proteasome inhibitors. The findings of distinct cognitive sub-groups with apparently different underlying brain substrates suggest the possibility that sub-groups of patients who may respond differently to different anti-dementia drugs will be identifiable by means of neuropsychological testing.

## **Conclusions**

Cognitive impairment is common in patients with PD. Different subtypes of MCI have been described, and MCI is a marker of subsequent development of dementia. MCI can be understood as the initial stage of a progressive cognitive decline leading to dementia in PD. The cognitive profiles obtained in both demented and non-demented patients with PD confirm the heterogeneity of cognitive impairment in PD. They also indicate that in most patients with PD, fronto-subcortical changes are the main contributing factor to dementia, whereas in other patients, cortical and hippocampal changes are more important. From a clinical standpoint, neuropsychological assessment is crucial for detecting mild cognitive impairment and early dementia in PD. It should hence be included in the routine evaluation of patients with PD in order to allow effective management of the patients. In addition, the neuropsychological assessment can provide the patients and their families with adequate information enabling them to conduct a proper planning of their own future needs.

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