Cognitive and motor dysfunction in the early phase of Parkinson’s disease

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To Erik, Edith and Karin
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Abstract

**Background:** Parkinson’s disease (PD) is a chronic and progressive neurodegenerative disease. The diagnosis is based on a combination of the motor signs: tremor, bradykinesia, rigidity and postural abnormalities. Mild Cognitive Impairment (MCI) is common early in the disease and a large proportion of patients with PD develop dementia (PDD). Associations between motor symptoms and cognitive decline have been suggested but the results are inconclusive due to differences in the selection of participants and variables tested. Large population based studies with comprehensive neuropsychological investigation in newly diagnosed cases with PD followed prospectively are rare. The aim of this thesis was to improve characterization and understanding of cognition in PD, and to explore the relationship to motor impairment in the early phase of PD.

**Methods:** All new patients with suspected idiopathic parkinsonism in the catchment area (142 000 inhabitants) were examined during a period of five years and four months. Among other investigations, a comprehensive neuropsychological evaluation was carried out in 119 of 148 patients with PD together with 30 age matched healthy controls. Assessments were repeated after one three and five years.

**Results:** Patients performed worse than healthy controls in a majority of neuropsychological tests. MCI at the time of diagnosis were found in 36% according to recently published MCI criteria. Thirty% were cognitively impaired using another definition. One fourth of the patients developed PDD within five years after diagnosis and 25 % of those with MCI at baseline reversed back to normal cognition. Age and MCI were significant predictors of dementia. Education was an independent predictor for severe cognitive dysfunction at diagnosis but did not predict PDD. Patients with MCI converting to PDD had worse performance on visuospatial function, semantic fluency, episodic memory, mental flexibility and conceptual thinking. There were no differences in cognitive performance between patients with predominant Postural and Gait Disturbances (PIGD) and the tremor dominant subtype at the baseline investigation and belonging to the PIGD subgroup at baseline did not predict PDD. Dementia converters declined more rapidly than non-converters in posture/gait function. Associations between bradykinesia and measures of executive functions and working memory were found, and between posture and gait disturbances and visuospatial function. Some of these associations were persistent after one year. Patients receiving the dopamine agonist pramipexole performed significantly worse on a measure of verbal fluency at the one year follow up.

**Conclusions:** The differences in proportions of cognitively impaired in the different studies emphasize the value of joint criteria for PD-MCI. Even when using such criteria, a substantial proportion of patients revert back to
normal function. The increase in motor disability in patients with PDD could have several different causes that need to be further investigated. Associated motor and cognitive dysfunctions could reflect common pathophysiological processes in partly shared networks. Both dopaminergic and non-dopaminergic motor and cognitive functions seem to be involved in PDD which suggests that pharmacological treatment in PD needs to go beyond the scope of dopaminergic deficiency in search for new therapies that would also be effective for non-motor symptoms.
Abbreviations

α-synuclein  Alpha-synuclein
β-amyloid  Beta-amyloid
BBB  Blood Brain Barrier
BVMT  Brief Visuospatial Memory Test
BNT  Boston Naming Test
COWAT  Controlled Oral Word Assessment Tool
CBD  Corticobasal Degeneration
DA  Dopamine agonists
DBL  Dementia with Levy Bodies
FCSRT  Free and Cued Selective Reminding Test
fMRI  Functional Magnetic Resonance Imaging
FP-CIT  $^{123}$I-N (omega)-flouropropyl-2-β-carbomethoxy-3-β-(4-iodophenyl) nortropane
H&Y  Hoehn & Yahr
ID  Indeterminate
MADRS  Montgomery-Åsberg Depression Rating Scale
MCI  Mild Cognitive Impairment
MDS  Movement Disorder Society
MMSE  Mini-Mental State Examination
MSA  Multiple System Atrophy
NYPUM  Ny (New)-Parkinson Umeå
NPV  Negative Predictive Value
PD  Parkinson’s Disease
PDD  Parkinson’s Disease Dementia
PIGD  Postural Instability and Gait Disturbances
PPV  Positive Predictive Value
PSP  Progressive Supranuclear Palsy
UPDRS  Unified Parkinson’s Disease Rating Scale
SD  Standard Deviation
SE  Standard Error
Parkinsons sjukdom (PS) är en kronisk och progressiv neurodegenerativ sjukdom. Den kliniska diagnosen bygger på en kombination av motoriska symptom: skakningar (tremor), rörelsehämning (bradykinesi), muskelstelhet (rigiditet) samt balans och gångsvårigheter. Förekomsten av PS ökar med ålder. Hos individer över 60 år är PS den vanligaste neurodegenerativa sjukdomen efter Alzheimers sjukdom.


De flesta tidigare studier som har undersökt kognitiv funktion vid PS har varit tvärsnittsstudier och/eller inkluderat patienter i olika skeden av sjukdomen. Associationer mellan motorproblem och kognitiva nedsättningar har föreslagits men resultaten är även där ofullständiga på grund av olikheter i de studerade patientgrupperna och vilka variabler som studerats. Stora populationsbaserade studier av kognitiva problem vid PS med omfattande neuropsykologisk utredning följa över tid är få. Därför var målet med den aktuella avhandlingen att förbättra förståelsen av kognitiva nedsättningar vid PS samt utforska relationen mellan kognition och motorik i sjukdomens tidiga skede.


I enlighet med tidigare studier presterade patienter med PS sämre än friska kontroller på mängder av neuropsykologiska test. Andelen som
klassificerades som kognitivt nedsatta varierade mellan studierna mycket på grund av att olika kriterier användes: 36 % när nyligen publicerade kriterier anpassade till PS användes samt 30 % när en annan definition användes. En fjärde del av ursprungsgruppen utvecklade demens under uppföljningstiden medan en fjärde del av de med kognitiv nedsättning vid första mättillfället återgick till normal kognition under uppföljningstiden. Ålder och MCI var starka prediktörer för demens. Utbildningsnivå var starkt kopplat till kognitiv nedsättning vid första mättillfället men predicerade inte senare utveckling av demens. Patienter med kognitiv nedsättning som senare utvecklade demens presterade sämre än de med kognitiv nedsättning som inte utvecklade demens på flera olika kognitiva tester.


Sammanfattningsvis så har denna studie visat olikheter i andelen kognitivt nedsatta beroende på vilka kriterier som användes vilket betonar värdet av en gemensamt kriterier för vad som utgör kognitiva nedsättningar vid PS. Församlingen av motoriska problem i patienter med parkinson demens kan bero på flera olika anledningar och behöver utredas ytterligare. Kopplingarna mellan motoriska och kognitiva funktioner kan spegla gemensamma patofysiologiska processer i delvist delade nätverk. Slutligen så har vi visat att både traditionellt dopaminerga funktioner samt icke dopaminerga funktioner på olika sätt är i kopplade till Parkinson demens vilket ger en indikation till att interventioner vid PS behöver se bortom det dopaminerga nätverken.
Original papers


II. Domellöf ME, Elgh E, Forsgren L. The relation between cognition and motor dysfunction in drug naïve newly diagnosed patients with Parkinson’s disease. Movement Disorders. 2011:26:2183-2189


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Introduction

Parkinson’s disease (PD) is a chronic and progressive neurodegenerative disease whose diagnosis is based on a combination of the motor signs: tremor, bradykinesia, rigidity and postural abnormalities. The incidence of PD increases with age and it is the most common neurodegenerative disease next to Alzheimer’s disease (AD) in people over the age of 60 years. As life expectancy increases and people over 60 years of age is the fastest growing age group [1], the number of patients with PD will most likely increase.

PD was initially described by Dr James Parkinson in “An essay of the shaking palsy” [2]. The description of the disorder was similar to how we describe it today, as a progressive disease due to probable degenerative pathology in the central nervous system. The main symptoms were characterized by resting tremor, flexed posture and shuffling gait. The intellect and senses were described as being intact. It was not until the beginning of the 20th century that the first reports of mental deterioration in PD came (see Pollock and Horanbrook for review) [3], and not until the 1970’s that dementia was considered an important part of the clinical picture [4]. Today it is well established that a substantial proportion of patients with PD develop Parkinson’s Disease Dementia (PDD) [5] and that mild cognitive impairment (MCI) is common at the time of diagnosis [6–8]. Despite this PD is still primarily described as a movement disorder with treatment mostly focusing on the reduction of motor symptoms.

Attempts have been made to find predictors for cognitive decline and dementia in PD. Associations between motor symptoms and cognitive decline have been suggested but the results are inconclusive due to differences in the selection of participants and variables tested. Prospective studies in large cohorts of well-defined newly diagnosed patients with PD assessed with extensive neuropsychological protocols are rare [6–8]. This thesis presents data from the NYPUM study where cognitive function in early stages of PD and its association to motor function has been explored both cross-sectionally and longitudinally.

Parkinson’s disease

Definition and diagnosis

PD is one of several disorders with parkinsonism. The most commonly used diagnostic criteria for parkinsonism is the United Kingdom Parkinson’s Disease Society Brain Bank (UK PDSBB) definition which is also used in this
thesis. It requires bradykinesia plus at least one of the following symptoms: tremor, muscular rigidity or postural abnormalities for diagnosis [9].

Parkinsonism can be idiopathic, i.e. of unknown cause, and includes PD and the atypical forms referred to as Parkinson plus syndromes or atypical parkinsonism: Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), Cortico Basal Degeneration (CBD) and Dementia with Levy Bodies (DLB). Parkinsonism that is secondary to known cause is classified as secondary parkinsonism, e.g. treatment with neuroleptic drugs.

Diagnostic accuracy of PD is a big problem. Clinical-pathological studies report incorrect diagnosis of PD in 10-24% of patients with advanced PD [10]. This is due to the existence of several similar conditions with parkinsonism but also due to the heterogeneity of PD both in presentation and in response to medication. Clinical signs that may differentiate PD from other parkinsonian disorders are: more often an asymmetrical onset of motor symptoms, the presence of rest tremor and a positive clinical response to dopaminergic medication [9].

No radiological methods can readily distinguish between the different parkinsonian disorders. Nuclear imaging methods such as single photon computed tomography (SPECT) or positron emission tomography (PET) can reveal decreased dopaminergic nerve terminals in both PD and Parkinson plus syndromes but do not distinguish between them [11]. A definite diagnosis can only be confirmed with autopsy.

**Symptoms**

**Cardinal signs**

Bradykinesia is the main feature of parkinsonism and is characterized by slowness or weakened and reduced amplitude of movements. Bradykinesia is a collective term for hypokinesia and akinesia. Hypokinesia refers to reduced spontaneous movement such as arm swing and reduced facial expression. Akinesia refers to difficulty in initiating movement, which is more common in the later stages of PD.

Tremor seen in PD is a slow (4-6 hertz) rest tremor, often initially unilateral. It is common that the tremor increases with anxiety and affect. Other types of tremor such as postural and action tremor can also be present.

Rigidity (stiffness) refers to an increased resistance to passive bending and stretching of the patients arm. If the muscle tone varies it can give rise to
what is called the “cogwheel” phenomena with jerky movements during bending of the limb.

Postural instability and gait disturbances are often present in PD. They are characterized by slow pace while walking, small shuffling steps, balance problems and gives an increased risk of falling. Postural instability is more common in the later stages of PD and is believed to be due to impaired postural reflexes.

Other motor symptoms
Apart from the motor symptoms that are used in the diagnostic procedure there are several other common motor features such as impaired articulatory ability (dysarthria), soft speech resulting from lack of coordination in the vocal musculature (hypophonia), swallowing difficulties (dysphagia) and drooling (sialorrhoea). All combined these are referred to as bulbar functions.

In later stages of the disease motor complications and freezing of gate are common phenomena. Motor complications are usually a result of long term treatment and consist of motor fluctuations and dyskinesias. Motor fluctuations refer to decline in motor performance usually in the wearing off phase of the medication cycle. Sometimes with disease progression there can also be off-periods that seem to appear more or less at random [12]. Dyskinesias are involuntary movements that are presented as stereotypic, choreatic or dystonic movements. They usually appear at peak dose (when the L-dopa has reach the plateau) and more rarely when the drug levels rise or fall [12].

Non motor symptoms
Apart from the motor features in PD there are a range of non-motor features and some of them are common. Non-motor symptoms in PD include neuropsychiatric symptoms with depression, apathy, hallucinations, cognitive impairment and dementia, sleep disorders with restless legs, REM-sleep behavior disorder, excessive daytime somnolence, vivid dreaming and insomnia, autonomic symptoms with bladder disturbances, orthostatic hypotension and sweating, sensory symptoms with olfactory disturbance, pain and visual dysfunction and gastrointestinal symptoms with constipation. Most of the non-motor features develop after motor onset but there are a few that can be present years before diagnosis: olfactory dysfunction, mild dysautonomia as well as mood and sleep disturbances [13].
**Epidemiology**

The prevalence of PD in people over 65 years of age is around 1-2% and increases from 0.6% in the ages 65-69 to 2.8% in the ages 85-89 [14]. The cumulative incidence (which can be regarded as the lifetime risk) of PD up to 89 years of age is close to three% [15]. Early onset PD, i.e. clinical signs developing before the age of 50 constitutes only three-four% of the PD population [15, 16].

The incidence of PD in high quality studies ranges from 8.4 to 20.0 per 100 000 with a mean of 14.5 per 100 000 (95 % CI, 12.2-17.3) [17]. The mean age at symptom onset is in the late 60’s and population based studies report age at diagnosis to around 70 years of age [8, 15]. Most studies have reported slightly higher prevalence for PD in men, but there are also studies reporting no differences between men and women (see de Lau et al for review) [18].

**Histopathology and etiology**

Most cases with PD have an unknown etiology. Both genetic and environmental factors have been implicated and PD is most likely caused by an interaction of genetic, aging and environmental factors. Environmental factors that have been linked to PD are lifestyle, dietary and occupational exposures, such as increased risk with pesticide exposure or protective effect of substances such as caffeine and smoking [18].

There are subsets of patients of about 10% that report a positive family history [18]. Some families show an autosomal dominant inheritance pattern, others a recessive inheritance pattern. Through the genetic forms of PD, the hope is to unravel biological processes that are also of importance for the vast majority with sporadic PD.
Pathology, biochemistry and physiology

A histopathological diagnosis of PD requires loss of dopaminergic cells in substantia nigra pars compacta and Lewy-bodies and Lewy-neurites in some of the surviving dopaminergic neurons. Lewy-bodies and Lewy-neuritis are mainly composed of the protein alpha synuclein (α-synuclein) which is encoded by the SNCA gene [19]. Lewy bodies are not exclusively found in the nigrostriatal network, and they are believed to spread throughout the brain in a sequential manner during different stages of the disease with onset in the olfactory structures and the dorsal motor nucleus of the vagus nerve [20, 21].

**FIGURE 1.** Sixty times magnification of Lewy-bodies and Lewy-neuritis in substantia nigra in a patient with Parkinson’s disease. (photo: Suraj Rajan)

The deterioration of dopaminergic neurons in the substantia nigra projecting to the basal ganglia is believed to cause two of the cardinal signs seen in PD, rigidity and bradykinesia. Bradykinesia has been described as the best clinical correlate of the nigrostriatal lesion [22]. Tremor has been suggested to be both a result of the disruption in the striatopallidal circuit and a result of a disruption in the cerebello-thalamo-cortical circuit [23], as well as involving serotonergic dysfunction [24].

Postural abnormalities that often appear at later disease stages are believed to have origins other than dopaminergic failure. They have been connected to cholinergic denervation of the pedunculopontine nucleus (PPN) [25, 26]. Increased neocortical β-amyloid deposition which is common in AD has also been associated with more severe postural and gait disturbances in PD [27].
Treatment of motor symptoms

Available treatments are mainly focused on reducing motor symptoms. They have no effect on underlying pathophysiological processes and consequently do not have curative or disease modifying effects. The most commonly used treatments are pharmacological interventions with drugs that affect the dopamine system, so called dopaminergic drugs.

Levodopa
The first drug available for treatment of PD was levodopa; it was developed in the early 1960s based on the findings of the Swedish Nobel prize winner, professor Arvid Carlson and early clinical trials by Ehringer and Hornykiewicz [28, 29]. Dopamine cannot pass through the blood brain barrier (BBB) but levodopa (L-dopa), a precursor of dopamine, can. L-dopa is taken up by dopaminergic neurons and decarboxylates into dopamine presynaptically. When released it binds to both D1 class receptors (including D1 and D5) and D2 class receptors (including D2, D3 and D4) postsynaptically. Dopamine that does not bind to postsynaptic receptors is taken up into the presynaptic cell by the dopamine transporter.

Decarboxylase and COMT inhibitors
To prevent levodopa from being metabolized to dopamine in the periphery before passing the BBB and entering the brain, levodopa is combined with decarboxylase inhibitors (carbidopa or benserazide) and sometimes also with catechol-O-methyl transferase (COMT) inhibitors (entacapone or tolcapone). The result is that more of the drug enters the brain, and peripheral side effects are reduced (e.g. nausea, hypotension).

Dopamine agonist and MAO-B inhibitors
Other dopaminergic drugs are dopamine agonists and monoamine oxidase (MAO) B inhibitors. MAO-B metabolizes dopamine in the dopaminergic neuron and inhibition of the enzyme increases the availability of dopamine.

Dopamine agonists (DA) act directly on the postsynaptic system. The various DA used have different receptor profiles. The commonly used non ergot dopamine agonists, such as pramipexole and ropinirole have a high affinity for D2 class receptors [30]. DA is today often used as monotherapy in early phase of PD, mostly in younger patients, in order to reduce/delay motor complications. Although use of DA early in the disease gives the benefits of delaying the start of motor fluctuations accompanied with the use of L-dopa there are other side-effects of DA such as higher risk of hallucinations, orthostatic hypotension, excess daytime sleepiness, sleep attacks and impulse control disorder [31].
Treatment in later disease stages
In later stages of the disease a portable pump delivering apomorphine subcutaneously or levodopa delivered intestinally can be used for continuous dopaminergic stimulation to reduce variation in motor performance (motor fluctuations and dyskinesias). An antagonist on the glutamate N-methyl-D-aspartate (NMDA) receptor (amantadine) can also be tried for treatment of dyskinesias and fluctuations. Neurosurgical interventions with targeted lesions in the brain in advanced cases with PD have largely been replaced by Deep Brain Stimulation (DBS). Most DBS operations for PD target the subthalamic nucleus which has a central role in the motor circuits that are disturbed in PD.

Cognitive impairment
Cognition can be defined as higher order brain functions that help the individual to interact with the environment in a successful way. Sometimes the cognitive functions do not work as intended, due to functional or structural impairment. This can lead to dysfunction for the individual. These disturbances can be reversible if caused by stress, medication, depression, or sleep deprivation. They can also be due to degenerative processes which can only be treated symptomatically. There are different ways to describe and measure human cognition. No cognitive tests measures only one cognitive domain and tests usually tap into different cognitive functions. A poor result in a single test can be due to damage in various parts of the brain.

Cognitive impairment in PD
The profile of cognitive impairment in PD varies between individuals and is as heterogenic as the rest of the clinical picture, probably because of the diverse nature of the underlying pathology. Already in the early stages of the disease a wide range of cognitive impairments have been demonstrated [6–8], e.g. in memory, visuospatial function and executive functions. Some suggest that executive problems are related to the early phase of the disease due to an altered dopaminergic tone in the frontal cortex. On the other hand impairment in visuospatial dysfunction and semantic verbal production display an involvement of temporal and posterior structures. The visuospatial dysfunction has been suggested to be related to later disease stages and subsequent development of dementia [32].

Executive functions
Executive functions include a set of abilities that control and regulate other cognitive functions. It can be described as our ability to plan, perform abstract reasoning, solve problems, focus despite disturbances and shift
focus when appropriate. Executive functions have been linked to distributed networks with an interaction between prefrontal and subcortical regions. Cognitive decline in PD has sometimes been described as resembling the pattern seen in frontal lobe patients with mainly frontally mediated attention and executive problems [33]. Executive functions are affected both in PD and PDD and have been suggested to be more affected in PDD than in AD (the most common dementia disorder)[34].

**Memory**

Human memory consists of multiple systems. A basic distinction can be made between short-term or working memory and long-term memory (LTM). Working memory temporarily hold information while LTM refers to the ability to store information [35]. Working memory has been shown to be distinctly different from LTM. Connections between dopamine, aging and cognition [36], especially working memory processes have been suggested [37].

![Figure 2. Overview of memory processes](image)

LTM can be subdivided into declarative and non-declarative memory. In turn declarative LTM can be separated into semantic and episodic memory. Semantic memory refers to a network of associations and concepts of basic knowledge about the world. Episodic memory refers to information about personally experience of past events. Different memory processes involved are encoding, consolidation and retrieval of information (Figure 2.). Disturbances of any of the three memory components, i.e. encoding, consolidation or retrieval, can result in memory failure.

The medial temporal lobes are involved in acquisition and retrieval of new episodic memories [38]. Consolidation of new memories has been linked to hippocampus and surrounding structures [39].
Frontally mediated cognitive processes that are engaged in working memory and executive function are believed to be collaborating in long term memory as well, especially in free recall [40]. In a test situation episodic memory is often assessed by asking a person to recall or recognize information learned at the time. Episodic memory impairment is present in PDD although some studies claim that it is less severe than in AD [41]. Some suggest that memory impairment in PD is more related to a frontally mediated retrieval deficit than to an encoding problem. In PDD there is evidence of recognition deficiencies as well (see Emre et al for review) [34].

**Attention**

Attention is a multidimensional function that involves processes that focus, select, divide, sustain and inhibit behavior. Attention is important for all cognitive skills and, in tests, especially difficult to separate from working memory and executive functions. The term attention has been used interchangeably with executive functions in some prior PD studies [34].

**Visuospatial skills**

Visuospatial function includes mental imagery and navigation, distance and depth perception and visuospatial construction. It is the ability to understand visual representations and their spatial relationships and is governed by several different pathways originating from parietal cortex (Occipito-parietal, parieto prefrontal, parieto pre-motor and parieto-medial temporal) (see Kravitz et al for review) [42]. Both constructional abilities and visuospatial function without the demands of fine motor control have been shown more affected in PDD than in AD [34].

**Language function**

Language can be described as the capacity for acquiring and using complex systems of communication. Language functions include abilities such as reading, arithmetic, oral and written word production and comprehension. Common test for language function are verbal fluency and word comprehension test. Some studies use tests of verbal fluency as a measure of language function whereas other includes it to measure executive functions. Patients with PDD are considered to have less language impairment than patients with AD [34].

**PD-MCI**

The concept of Mild Cognitive Impairment (MCI) was developed by Petersen et al. [43] to detect individuals with an increased risk of developing AD. It is defined as a transition stage between normal aging and dementia. The original criterion was focused on memory impairment but it was later suggested that also patients with impairment in other cognitive domains
could be at risk for developing dementia [44]. Studies have applied Petersen’s MCI criteria on patients with PD with various results. To create conformity between studies and clinicians within the field of PD a task force commissioned by the Movement Disorder Society adapted the MCI criteria to fit the specific cognitive profile seen in PD [45] and constructed guidelines to assist in the MCI classification. The PD-MCI criteria are based on a combination of literature review and expert consensus.

**PDD**

Dementia is defined as a progressive, irreversible deterioration of cognitive function. The pathologies behind dementia disorders can be different types of neurodegeneration and vascular lesions. The definition of dementia in the Diagnostic and Statistical Manual of Mental Disorders IV is an overall decline in intellectual function including difficulties with language, simple calculations, planning and judgment, and motor skills. Furthermore a loss of memory that is severe enough to interfere with activities of daily living that is not due to physical decline. PDD require onset of motor symptoms at least one year before the onset of dementia [34]. The one year rule is to differentiate between PDD and DLB.

**Epidemiology of cognitive impairment in PD**

Five to seven percent of adults over the age of 60 are demented [46]. Of the dementia population three-four% have PDD [47]. The proportion of patients with PDD in PD populations varies between 28% and 90% [48] depending on selection of participants and criteria used.

In community based studies of PDD the annual incidence rate has been around 100 per 1000 person years [49–51] which corresponds to around 10% of the PD population developing dementia each year. The annual incidence rate of dementia in population based studies with newly diagnosed patients with PD has been 38.7 per 1000 person-years (95% CI, 23.9-59.3)] [32]. See table 1 for longitudinal studies of newly diagnosed patients with PD.

The proportion of patients with MCI in studies of newly diagnosed patients with PD has ranged between 19 and 36% [6–8, 52, 53] with a higher proportion in community-based samples. In adults older than 65 years in the general population the proportion of MCI has ranged between three and 19% [54].
<table>
<thead>
<tr>
<th>Study, inclusion</th>
<th>Follow up years</th>
<th>Cases/controls</th>
<th>Mean age</th>
<th>Started treatment for PD</th>
<th>Cognitive domains: tests included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sidney multicenter [55, 56][a] 1985-1988</td>
<td>20</td>
<td>91/50*</td>
<td>63</td>
<td>13.6%</td>
<td>Vocabulary, Block Design, Ravens Colored Progressive Matrices, RAVLT, Benton visual retention test, simple and choice reaction time test, COWAT, Austin Maze, Western aphasia battery</td>
</tr>
<tr>
<td>CamPaIGN [8, 32][b] 2000-2002</td>
<td>10</td>
<td>159/na</td>
<td>69.9</td>
<td>47.2%</td>
<td>Phonemic fluency (FAS), Category fluency (animals), Pattern and Spatial Recognition Memory, ToL</td>
</tr>
<tr>
<td>CARPA [6, 57][b] 2002-2005</td>
<td>5</td>
<td>115/70</td>
<td>66.2</td>
<td>67.8%</td>
<td>Psychomotor speed: Digit symbol test, TMT A, Stroop A and B, Attention: Digit span, TMT B, Stroop C, Language: BNT, Memory: RAVLT, RBMT, Logical Memory Test, face recognition, Visual Association Test</td>
</tr>
<tr>
<td>ParkWest [7, 58][c] 2004-2006</td>
<td>3</td>
<td>196/201</td>
<td>67.3</td>
<td>0%</td>
<td>Memory: California verbal learning test, Visuospatial ability: Silhouettes and Cube test, Attention/Executive function: category fluency, serial seven from MMSE, Stroop test</td>
</tr>
</tbody>
</table>

*a references for three and five year follow up, b references for baseline and five year follow up, c references for baseline and three year follow up. *Also included cases with dementia before the onset of motor signs. ToL= Tower of London, TMT=Trail Making Test, BNT=Boston Naming Test, RAVLT= Ray Auditory Verbal Learning Test, RBMT=Rivermead Behavioural Memory Test, MWCST= Modified Wisconsin Card Sorting Test, JOLOT=Judgement of Line Orientation, GIT=Groeningen Intelligence Test, COWAT=Controlled Word Association Test.
**Risk factors for cognitive impairment in PD**

Identification of clinical factors that predict development of dementia are important for clinical practice and disease management [59]. Age [55], depressive symptoms, specific neuropsychological impairments [60], specific motor impairment, male sex, fewer years of education, visual hallucination, REM sleep disorder and orthostatic hypotension have all been associated with an increased risk of PDD. For MCI older age, motor disease severity, non-tremor dominant motor phenotype and fewer years of education have been reported as associated factors.

Older age is one of the primary clinical features predicting PDD [61, 62]. Early presence of frontal executive problems has been pointed out to be a predictor for development of PDD [63]. Recent research has started to evaluate this and connects the development of PDD also to posterior cognitive problems such as visuospatial, verbal function and episodic memory (see Kehagia, et al. for review) [64]. Preliminary results suggest that PD-MCI with posterior cognitive deficits predicts a shorter time to PDD [45].

Patients with predominantly postural instability and gait difficulties (PIGD) have been suggested to have a faster rate of cognitive decline [65]. However, following patients with early PD for up to 10 years have not rendered in the same results [66]. Some mean that it is change from tremor dominant subtype to PIGD dominant subtype that is a predictor for developing PDD [67].

**Neuropathology of cognitive impairment in PDD**

The neuropathology underlying cognitive decline and PDD is heterogeneous and studies exploring pathological correlates of cognitive impairment in PD have rendered conflicting results [68].

Cortical Lewy bodies and Lewy neuritis have been shown to be the most significant correlate of dementia in PD [69]. α-synuclein pathology in the parahippocampal gyrus and anterior cingulate gyrus is more pronounced in PDD than in PD [70, 71]. Some individuals have pronounced α-synuclein burden without being demented, which suggests that α-synuclein burden by itself is not sufficient for dementia. Other factors such as cognitive reserve or brain plasticity might determine the cognitive performance in relation to the α-synuclein burden (See Irvin et al for review) [59]. Furthermore, some patients with PDD express only small amounts of α-synuclein. Cholinergic deficits have been seen in patients with PDD that have less pronounced cortical and limbic Lewy bodies and Lewy neuritis.
Some studies claim that less than 10% of PDD cases have coexisting AD [72, 73], whereas others have reported proportions as high as 30-40% [69, 74, 75]. For example, low CSF β amyloid levels, have been linked to development of PDD [76]. Differences between demented and non-demented patients have also been found in the distribution of neurofibrillary tau pathology (also common in Alzheimer disease). The spread for non-demented patients was restricted to the entorhinal areas whereas neurofibrillary tangles had spread to the rest of the limbic system, lateral temporal areas and beyond in patients with PDD [21].

The contribution of vascular lesions to PDD is not well studied but some indications of higher degrees of vascular lesions in PDD than PD without dementia have been found [77]. A cross-sectional study combining the cortical Lewy, β-amyloid and tau stages have shown that this combination perfectly discriminates between demented and non-demented PD [76].

**Genes and cognition in PD**

Familial associations to the development of PDD have been reported [78]. However, not much is known about how genes contribute to cognitive impairment and PDD and only a few of the findings have been linked to biological processes likely to be involved in cognitive impairment and/or PDD.

The genetic polymorphism Catechol-O-methyl-transferase (COMT) gene (Val<sup>158</sup>Met) has been suggested to have an impact on executive functions through its link to the dopamine system but has not been connected to PDD [32]. Monoamine oxidase (MAO) has also been suggested to be a candidate gene linked to executive heterogeneity in PD.

Some of the familial forms of PD are linked to PDD. The gene SNCA coding for α-synuclein on chromosome four can be multiplied and cause increases in the concentration of α-synuclein. Triplicated cases are more often than duplicated cases associated with cognitive decline and dementia with a more rapid progression. A polymorphism of the DYRK1A gene has been connected to the PDD and LBD [79] through effects on a kinase that phosphorylates α-synuclein and amyloid precursor protein. Mutations in the ATP13A2 gene results in a rare genetic variant that can cause young onset parkinsonism (Kutor-Rakeb syndrome: PARK 9). These patients become demented and the predominant pathology is atrophy with iron accumulation in basal ganglia [80]. The MAPT H1/H1 genotype seems to have a strong influence on cognitive functions, especially posterior cortical cognitive impairments and give a higher risk of developing PDD [81].
Treatment of cognitive impairment and other non-motor features in PD

Treatment for non-motor and non-dopaminergic symptoms in PD has started to be evaluated because of the recent focus on the disabling effect of the non-dopaminergic and non-motor features of the disease.

Cholinesterase inhibitors have been shown to have positive effect for cognitive dysfunction and PDD, but also for behavioural disturbances and activities of daily living in patients with PDD [82]. Rivastigmine is the cholinesterase inhibitor with strongest evidence as an effective treatment of PDD [83]. Special characteristics of responders are hard to find but those with visual hallucinations [84] and those with elevated levels of homocysteine [85] seem to respond especially well.

For psychotic symptoms in PD a gradual reduction of antiparkinson medication is recommended [86]. If neuroleptic treatment is needed, atypical forms (e.g. clozapine) shows the best effect/side effect profile for PD patients [87].

Treating depression in patients with PD is complicated. A recent meta-analysis concluded that there is insufficient evidence to suggest selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), pramipexole or pergolide for treatment of depression in patients with PD [88]. According to the same meta-analysis the treatment with the best effect on reducing depressive symptoms in PD was tricyclic antidepressants (TCAs).

Dopaminergic medication has been suggested to have both detrimental and positive effects on cognitive functions. One explanation for this is that the relationship between dopamine levels and cognitive performance is believed to follow an inverted U-shaped curve, where both low and high levels of dopamine cause impaired cognitive performance [89]. Individuals with initially low levels of dopamine are believed to improve performance with intake of dopaminergic drugs while patients with higher levels decline in performance due to excessive levels of dopamine. Different functions are mediated by different brain networks and affected differently by dopaminergic depletion. In early PD for example, the loss of dopaminergic neurons in striatum is most prominent in putamen and dorsal caudate, both involved in the motor and dorsolateral circuit. The ventral striatum, involved in limbic and orbitofrontal circuits is mostly intact.
High levels of dopamine agonists and levodopa are believed to have a negative effect on reversal learning, decision-making and impulse control [64]. The dopamine agonist pramipexole, has been suggested to have a more harmful effect than pergolide [64]. Some studies have suggested that short term use of the dopamine agonist pramipexole might cause decline in short term verbal memory, attentional-executive functions and verbal fluency [90]. A slight cognitive decline in semantic verbal fluency, executive functions, verbal learning and memory has been shown shortly after subthalamic deep brain stimulation [91].

**Cognitive motor relationship**

The association of motor control and cognitive function has been studied in children [92], patients with brain injury [93] and patients with neurodegenerative disorders [94]. One goal in linking motor and cognitive function is to find which aspects of cognitive and motor functions are processed by a given area or brain network [95]. Associations between cognitive and motor function have been found in the elderly and in patients with neurological disease. These associations can be unspecific reflecting co-existence of common age-related syndromes or reflecting a more widespread pathology affecting both motor and cognitive structures. They can also be specific as in the association of specific cognitive and motor functions being governed by the same neural networks.

Apart from the relation between PIGD subtype and PDD [67, 96], other cognitive motor relationships have been suggested in PD. Early findings reported bradykinesia and rigidity [4] to be associated with PDD and the severity of bradykinesia has been connected with visuospatial reasoning and psychomotor speed [97]. Others found no motor cognitive relationships [98, 99]. The results are inconclusive due to differences in the selection of participants and variables tested.

**Rationale of the thesis**

Cognitive impairment in PD has severe consequences with increased mortality, nursing home placement and caregiver stress [100]. A better characterization and understanding of cognition in the early phase of the disease is particularly important as this is the phase when early intervention with potential neuroprotective drugs or other therapies is likely to be most effective. Studying motor and cognitive relationships in early stages of the disease is important to be able to estimate the risk of early development of dementia or other type of cognitive problems with regard to motor function. Also finding relationships between specific motor and cognitive functions
may provide new ideas about the underlying pathophysiological processes for the motor and non-motor functions in PD.

Most studies on cognitive function in PD have been retrospective, cross sectional, including a mixture of incident and prevalent cases or been biased towards younger cases. Good descriptions of cognition in the early phase of PD in unselected study populations followed prospectively were almost completely lacking [8] when this study was initiated [15]. Prospective studies in large cohorts of well-defined newly diagnosed patients with PD assessed with extensive neuropsychological protocols can help connect cognitive motor associations to specific functions rather than global cognitive and motor decline and perhaps dissociate predictive clinical factors from associated factors.
**Aims**

The aim of this thesis was to improve characterization and understanding of cognition in early phases of PD, to investigate clinical determinants of cognitive decline and dementia and to explore what aspects of cognitive function are connected to different motor functions. Further aims were to investigate the variability of cognitive performance in PD in patients followed prospectively from time of diagnosis and during the following five years.

1. To describe the character and predictors of cognitive dysfunction in a population based cohort with drug naive newly diagnosed PD. (Paper I)

2. To explore the relationship between cognition and motor dysfunction in a population based cohort with drug naive newly diagnosed PD. (Paper II)

3. To explore if motor and cognitive variables associated at baseline change in parallel after one year. (Paper III)

4. To report the magnitude of cognitive change one year after diagnosis and investigate if different types of dopaminergic medication have an impact on the results. (Paper III)

5. To explore the five-year course of cognitive functions in a prospectively followed cohort of patients with PD and search for predictors for PDD (Paper IV).

5. To explore the difference in the evolution of motor function in patients that develop PDD compared to those who do not develop PDD (Paper IV).
Materials and methods

This thesis is based on data from the NYPUM-project (new parkinsonism in Umeå), a population-based study of idiopathic parkinsonism addressing etiological, diagnostic and prognostic factors. The patients were recruited from southern part of Västerbotten County in northern Sweden with a catchment area of 142 000 inhabitants.

![Figure 3. Map of the investigation area (Pantzare Information AB, Luleå, Sweden)](image)

Patients were included from January 1\textsuperscript{st} 2004 to April 30\textsuperscript{th} 2009 and classified into different forms of parkinsonism (PSP, MSA, CBG and LBD) according to established clinical criteria. Cases were investigated extensively at the time of presentation and repeatedly during follow up which was between 4.5-9 years except for those who died. To avoid selection bias cases were identified prospectively during the inclusion period and through many sources to make case identification as complete as possible. A total of 185 patients with idiopathic parkinsonism were identified.
Study population

The study populations participating in the studies of this thesis are presented below. The differences in participants between the studies are due to sample selection and change in diagnosis during follow up. Paper I is based on the first four years of inclusion whereas paper II, III and IV include the whole sample. Figure 4 (a, b, c, d) describes the flow chart of participants in each paper.

Thirty age and sex matched controls based on the 50 first patients included in the study were recruited. The controls were recruited by advertisements in the local newspaper or among friends and family of the PD participants. Requirements for controls were that they needed to be healthy with no neurological disorders and normal neurological examination, and have a normal FP-CIT scan.

Non-participation

About 20% (Paper I 21%, Paper II-IV 19%) of the patients declined to participate in the neuropsychological assessment at baseline. They were significantly older (79 vs. 69 years, \( p<0.001 \)), had various medical conditions, such as blindness, deafness, severe cardiac disease and had higher scores on the UPDRS part III (35 vs. 26, \( p<0.001 \)) and scored worse on the MMSE (27.5 vs. 28.7; \( p=0.04 \)).

There were also a substantial amount of patients that did not participate at follow up. This loss was bigger for the neuropsychological evaluation than for the study as a whole. Patients that did not participate in neuropsychological testing at follow-up were older, had fewer years of education and higher scores on the UPDRS. Furthermore, they performed worse on all neuropsychological tests at baseline except a test of language.
**FIGURE 4A.** Flow chart showing the participants in Paper I

**FIGURE 4B.** Flow chart showing the participants in Paper II
FIGURE 4C. Flow chart showing the participants in Paper III
Total PD sample N=148
- Declined neuropsychology N=29
- Lacking test N=2
  - Normal FP-CIT scan N=4
  - Severe depression N=2

Baseline PD sample N=111
- MCI N=40
  - Withdrew from study N=2
  - Died without PDD N=1

One year follow-up
- Clinical observation N=108
  - Neuropsychology N=86
  - Died without PDD N=2
  - Died with PDD N=1

Three year follow-up
- Clinical observation N=105
  - Neuropsychology N=76
  - Withdrew from study N=1
  - Died without PDD N=3
  - Died with PDD N=2

Five year follow-up
- Clinical observation N=77
  - Neuropsychology N=54

**Figure 4D.** Flow chart showing the participants in paper IV
Assessment tools

Global cognitive ability was measured with the Mini-mental State Examination (MMSE) [101]. Depression was assessed with the Montgomery and Åsberg Depression Rating Scale (MADRS); participants with scores over eight were considered to have a mild depression and severe depression if scores were 18 or over [102]. Dopamine transporter (DAT) Single-photon emission computed tomography (SPECT) imaging using $^{123}$I-Ioflupane ($^{123}$I-FP-CIT) was performed within 1-2 months following inclusion. Levodopa Equivalent Dose (LED) was calculated based on the conversion factors suggested by Tomlinson et al [103].

Assessment of motor function

The severity of parkinsonism was measured by the Unified Parkinson’s Disease Rating Scale (UPDRS) [9] and the Hoehn and Yahr staging. Variables of the different motor-scores were calculated from the UPDRS III [104]: the sum of UPDRS III items 20 and 21 for tremor, item 22 for rigidity, the sum of items 24, 25, 26, and 31 for bradykinesia, the sum of items 27, 28, 29, and 30 for the posture and gait score (arising from chair, posture, gait and postural stability), and the sum of items 18 and 19 for the bulbar score (speech and facial expression) [105].

Previously published divisions of motor subtype were used to divide patients into groups based on predominant motor feature: postural instability and gait disturbances (PIGD), tremor or indeterminate phenotypes [106]. A patient was classified as having tremor dominant PD if mean tremor score divided by mean PIGD score was $\geq$1.5, PIGD subtype if mean tremor score divided by mean PIGD score was $\leq$1.0 and indeterminate subtype if mean tremor score divided by mean PIGD score was between $>$1.0 and $<$1.5.

Assessment of cognitive function

Cognitive functions were thoroughly investigated at the time of inclusion (baseline) and after one, three, and five years. The patients were tested at their optimal motor stage. The tools used were neuropsychological tests of verbal and non-verbal episodic memory, working memory, attention, psychomotor function, visuospatial function and executive function. Table 2 shows the total battery of neuropsychological tests with an explanation of what cognitive domain each test was intended to measure and how the test was executed. The tests are listed in the order of presentation.
The tests were chosen to assess important cognitive functions within a reasonable amount of time. Since motor function is affected in PD, tests that are not affected by motor function were chosen when possible. All tests included in the battery are frequently used both in research and in clinical practice and have good validity and reliability. Most of the tests have age and education adjusted norms.

Instruments were chosen to minimise the effect of repeated testing, e.g. parallel versions. Tests that did not have alternate forms or could be affected by close repeated measurements were excluded from the 12-month follow-up [107].

The assessments were performed by trained research assistants with backgrounds in psychology and neuroscience supervised by a consultant in clinical neuropsychology. To assure that the assessments would be coherent within and between testers they were instructed to perform the assessment in accordance with the standardized protocol of the different tests. They practiced before they performed the first testing accompanied by a senior tester during one or more testing and performed an assessment on a patient during supervision with feedback. The test protocols were checked for errors.

Patients were encouraged to participate in all neuropsychological tests. For some participants this was impossible due to tiredness or technical issues. The tests with most missing cases were the WCST (n=15), logical memory (n=9) and logical memory delayed (n=11). Missing data varied between one and six for the other neuropsychological variables at baseline. Cases were omitted if they had missing values on most tests. Otherwise we conducted pairwise deletion of the data.
**TABLE 2.** Total battery of neuropsychological tests in order of presentation.

<table>
<thead>
<tr>
<th>Neuropsychological test</th>
<th>Cognitive domain</th>
<th>Execution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Finger tapping test</td>
<td>Psychomotor speed</td>
<td>Tap left and right index finger during 10 s</td>
</tr>
<tr>
<td>2. Free and Cued Selective Reminding test</td>
<td>Episodic memory</td>
<td>Cued and free recall after encoding 16 words x3</td>
</tr>
<tr>
<td>(FCSRT)[108]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Mental Control from WMS[109]</td>
<td>Conceptual tracking</td>
<td>Counting back and forth and reciting alphabet</td>
</tr>
<tr>
<td>4. Trail Making Test A (TMT A)[110]</td>
<td>Attention/psychomotor speed</td>
<td>Drawing lines between numbers</td>
</tr>
<tr>
<td>5. Trail Making Test B (TMT B)[110]</td>
<td>Attention/psychomotor speed</td>
<td>Drawing lines alternating between numbers &amp; letters</td>
</tr>
<tr>
<td>6. Benton Judgement of Line Orientation (JOLOT)[111]</td>
<td>Visuospatial function</td>
<td>Judging the slope of two lines</td>
</tr>
<tr>
<td>8. FCSRT delayed recall</td>
<td>Episodic memory</td>
<td>Cued and free recall after a delay</td>
</tr>
<tr>
<td>9. Boston Naming Test (BNT)</td>
<td>Verbal naming</td>
<td>Picture naming</td>
</tr>
<tr>
<td>10. Brief Visuospatial Memory Test [112]</td>
<td>Visuospatial memory</td>
<td>Drawing 6 figures after 10 min encoding x3</td>
</tr>
<tr>
<td>11. Associative Learning Test (WMS)</td>
<td>Episodic memory</td>
<td>Remembering word pairs x3</td>
</tr>
<tr>
<td>12. Logical memory, immediate recall (WMS)</td>
<td>Episodic memory</td>
<td>Repeating short story directly after encoding</td>
</tr>
<tr>
<td>13. Controlled Oral Word Association Test</td>
<td>Verbal function/executive function</td>
<td>Naming as many words beginning with the letter F,A or S, during one minute</td>
</tr>
<tr>
<td>(COWAT)[113], phonemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. COWAT, categories</td>
<td>Verbal function/executive function</td>
<td>Naming as many words from a given category: animals, colours or fruits</td>
</tr>
<tr>
<td>15. BVMT delayed recall</td>
<td>Visuospatial memory</td>
<td>Drawing encoded figures after a 25 minute delay</td>
</tr>
<tr>
<td>16. Logical memory, delayed recall</td>
<td>Episodic memory</td>
<td>Reciting short story after delay</td>
</tr>
<tr>
<td>17. Wisconsin Card Sorting Test-computer version</td>
<td>Executive function</td>
<td>Matching cards based on unknown rules</td>
</tr>
</tbody>
</table>
Diagnosis

**PD**

PD was diagnosed according to the United Kingdom Parkinson’s Disease Society Brain Bank (UK PDSBB) criteria for definite PD, requiring at least three supportive criteria. Cases with 1-2 supportive criteria were classified as probable PD. All cases were checked against diagnostic criteria for MSA [114], PSP [115], CBD [116] and DLB [117]. In cases that fulfilled the diagnostic criteria for multiple syndromes we classified the patient with the atypical diagnosis. Definite PD and probable PD are included in all studies. Since the diagnosis changed at follow up for a small number of patients, the latest diagnosis available at the time of statistical analysis for each paper was used.

**Box 1. UK PDSBB clinical diagnostic criteria for PD**

**Step 1. Diagnosis of parkinsonism**
Bradykinesia and at least one of the following:
- a. Muscular rigidity
- b. 4-6 hz tremor
- c. Postural instability

**Step 2. Exclusion criteria for PD**
History of repeated strokes and head injuries
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at onset of symptoms
More than one affected relative
Sustained remission
Strictly unilateral features after three years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement**

**Step 3. Supportive prospective criteria for PDD. Three or more required for PD definite**
Unilateral onset
Rest tremor
Progressive disorder
Persistent asymmetry affecting the side of onset most
Excellent response to levodopa
Severe levodopa induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

*We excluded the criterion “more than one affected relative” since it is now known that PD can have a genetic background

**Defined as symptomatic orthostatic blood pressure fall or presence of urinary incontinence within 12 months of baseline visit.
Cognitive impairment

In Paper I a cognitive domain was considered to be impaired if more than half of single test results within that domain were below cutoff level. Lezak et al have presented a classification system for ability levels based on a statistically defined range of scores [118]. Average performance is according to this classification: mean +/-0.6 SD low averages, -0.6 to -1.3 SD borderline, -1.3 to – 2.0 SD impaired. We chose -1.5 SD as a cut-off level score for lowered test performance, which is commonly accepted in clinical practice.

### Table 3. Neuropsychological measures used for classification of cognitive impairment (Paper I) and MCI according to MDS Task force criteria (Paper IV).

<table>
<thead>
<tr>
<th>Cognitive domain</th>
<th>Neuropsychological test</th>
<th>Paper IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic memory</td>
<td>FCSRT free and cued recall</td>
<td>Paper I</td>
</tr>
<tr>
<td></td>
<td>Logical Memory and Paired Associative Learning from WMS (healthy controls)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BVMT</td>
<td>Paper IV</td>
</tr>
<tr>
<td>Working memory</td>
<td>Digit span from WAIS III</td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>TMT A and B</td>
<td></td>
</tr>
<tr>
<td>Executive functioning</td>
<td>WCST</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mental control from WMS</td>
<td></td>
</tr>
<tr>
<td>Visuospatial functioning</td>
<td>The Benton Judgment of Line orientation</td>
<td></td>
</tr>
<tr>
<td>Verbal function</td>
<td>Boston naming test</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controlled Oral Word Association (FAS and categories)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Boston naming test</td>
<td></td>
</tr>
</tbody>
</table>

FCST=Free and cued selective reminding test, WMS=Weschler memory scale, BVMT=Brief Visuospatial Memory Test, TMT=Trail Making Test, WCST=Wisconsin Card Sorting Test, BNT=Boston Naming Test
**MCI**

To classify patients as MCI in Paper IV the MDS Task Force criteria were used [45]. The task force guidelines require a diagnosis of PD based on the UK PD Brain Bank criteria [119], gradual decline in cognitive ability reported by either patient, informant or observed by clinician, cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities, and cognitive deficits that is not sufficient to interfere significantly with functional independence, no dementia and a minimum of two neuropsychological tests with 1-2 SD below the mean value of established norms or a control group, and subjective cognitive complaints. As in Paper I, 1.5 SD below established norms were used to detect impaired domains in Paper IV.

To capture subjective cognitive complaints from decline from premorbid level, information on self-perceived cognitive decline or information from family or friends were gathered through a semi structured short questionnaire given to the patient when enrolling in the study. The questionnaire addressed the patient and/or family members experience of cognitive decline, a question of how the patient function cognitively was asked before the neuropsychological assessment and information regarding self-perceived memory and concentration from the Parkinson’s Disease Questionnaire 39 (PDQ-39) [120].

**Dementia**

A diagnosis of PDD was made according to published criteria through a consensus between three of the authors in paper IV (MED, LF and UE) [34]. The PDD diagnosis requires a diagnosis of PD a minimum of one year prior to the onset of dementia and cognitive deficiency severe enough to affect Activities of Daily Living (ADL). All available information were used including medical files, neuropsychological testing, temporal cognitive decline measured by repeated neuropsychological testing or MMSE, and interview by the study nurse and information from family members.

**Ethics**

Written, informed consent was obtained from all participants and healthy controls. The study was approved by the Regional Ethics Committee at Umeå University.
Statistics

All statistical analyzes were two tailed and p-values under 0.05 were considered significant for most analyzes. The Statistical Package for the Social Sciences (SPSS) versions 15, 19 and 21 and the Predictive Analytics Software (PASW) Statistics 17.0 were used for statistical analysis. Depending on the distribution of scores parametric and non-parametric tests was used where appropriate. The residuals of the regression models were explored to see if they fulfilled the assumptions of normality, linearity and homoscedasticity.

Empirical studies

Paper I

Patients with newly diagnosed PD were compared to healthy controls on the total battery of cognitive tests. Patients and controls were also classified as being impaired in different cognitive domains. Neuropsychological investigations were performed in 88 of 111 classified as PD. Only two had received pharmacological treatment for PD before the neuropsychological testing (low doses for a few weeks). Two individuals did not complete enough tests to make it possible to judge impairment in different domains. Table 2 shows the tests that were used for each domain. Those impaired in one or more domains were compared to those with normal function. Furthermore, those with two or more impaired domains were compared to the rest. Characteristics of this sample are presented in table 4.

Table 4. Characteristic of the population in Paper I

<table>
<thead>
<tr>
<th></th>
<th>Patients n=88</th>
<th>Healthy controls n=30</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female/male)</td>
<td>39/49</td>
<td>14/16</td>
<td>0.825</td>
</tr>
<tr>
<td>Age, years</td>
<td>68.1 (9.3)</td>
<td>68.2 (6.6)</td>
<td>0.979</td>
</tr>
<tr>
<td>Education, years</td>
<td>9.9 (4.1)</td>
<td>11.5 (3.5)</td>
<td>0.055</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.7 (1.4,24-30)</td>
<td>29.1 (0.8,28-30)</td>
<td>0.074</td>
</tr>
<tr>
<td>Mild depression a n (%)</td>
<td>14 (16%)</td>
<td>0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>23.8 (9.7,5-48)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dopaminergic medication</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>FP-CIT scan normal</td>
<td>5</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

MMSE= Mini Mental State Examination, MADRS= Montgomery and Åsbergs Rating Scale; UPDRS= Unified Parkinson’s Disease Rating Scale, DAT= dopamine transporter. aMADSR 9-17. Reprinted from Paper I with kind permission from the copyright holders.
Independent two-tailed t-tests were used to analyze differences in demographics, clinical characteristics and cognitive tests raw scores between patients and controls. For adjusted p-value linear regressions were performed with age, gender, years of education and psychomotor function as covariates for each cognitive variable. Patients being impaired in one or more cognitive domain were compared to those with intact cognition on demographic and clinical variables analyzed with Student’s t-test or Mann-Whitney U-test. Binary logistic regression was performed between patients with two or more cognitive domains impaired for the purpose of exploring predictors for cognitive impairments. Demographic and clinical variables that significantly differed between the groups in independent analyses were included as covariates in the model: years of education, disease duration, bradykinesia, facial expression, rigidity and total UPDRS III subscore.

**Paper II**

The associations between cognitive and motor functions were assessed. Furthermore, a comparison between PIGD/Tremor/Indeterminate phenotypes was made for baseline cognitive variables. Neuropsychological assessments were performed in 122 of 150 patients that fulfilled the diagnostic criteria for PD. Seventeen patients that started their dopaminergic treatment before performing the neuropsychological investigation and two with a normal FP-CIT scan were not included in the study. Thus 103 patients were included (Table 5).

**TABLE 5.** Characteristic of the sample in Paper II.

<table>
<thead>
<tr>
<th></th>
<th>Total n=103 (SD)</th>
<th>PIGD n=55 (SD)</th>
<th>Tremor n=35 (SD)</th>
<th>Indeterminate n=13 (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (f/m)</strong></td>
<td>41/62</td>
<td>20/35</td>
<td>15/20</td>
<td>6/7</td>
<td>0.731</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>68.4 (9.2)</td>
<td>69.5 (8.7)</td>
<td>63.0 (9.9)</td>
<td>69.3 (9.4)</td>
<td>0.492</td>
</tr>
<tr>
<td><strong>Years of education</strong></td>
<td>9.9 (4.1)</td>
<td>10.4 (4.9)</td>
<td>9.4 (2.9)</td>
<td>9.3 (3.2)</td>
<td>0.894</td>
</tr>
<tr>
<td><strong>Disease duration (months)</strong></td>
<td>22 (23)</td>
<td>20 (16)</td>
<td>27 (33)</td>
<td>19 (11)</td>
<td>0.866</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>28.8 (1.3)</td>
<td>28.6 (1.4)</td>
<td>29.0 (1.1)</td>
<td>25.5 (1.1)</td>
<td>0.496</td>
</tr>
<tr>
<td><strong>UPDRS III</strong></td>
<td>24.8 (10.6)</td>
<td>27.5 (10.5)</td>
<td>21.1 (9.9)</td>
<td>23.5 (10.3)</td>
<td>0.020</td>
</tr>
</tbody>
</table>

PIGD=Postural impairment and gait disturbances, MMSE= Mini Mental State Examination, MADRS=Montgomery and Åsberg Rating Scale; UPDRS= Unified Parkinson’s Disease Rating Scale. Reprinted from Paper II with kind permission from the copyright holders.
Differences in demographic, clinical and cognitive characteristics between the PIGD, tremor and indeterminate group were analyzed with two-tailed ANOVA, Kruskal-Wallis, chi-square or Fisher’s exact test when appropriate. The nonparametric Spearman’s rho was used to explore correlations between demographic, motor and neuropsychological variables. Multiple linear regression analysis was performed to explore if the relationships found in the correlation analysis between motor and cognitive variables were unique or affected by other variables. To meet the assumptions of normality and reduce skewing and outlier influence, some variables were transformed with square root transformation or logarithm transformation. Most variables were approximately normally distributed after transformation.

**Paper III**

The persistence of associations between motor score and cognitive functions were investigated together with the magnitude of cognitive change between baseline and follow-up for the total group and for patients receiving different dopaminergic medication (pramipexole ± levodopa and without dopamine agonists). Data from baseline and 12 month assessment were used. Neuropsychological assessments were performed in 122 of 150 patients that fulfilled the diagnostic criteria for PD. Six patients were excluded due to: not enough tests performed (n=1), having dementia at baseline (n=1), normal SPECT FP CIT scan (n=3) or severe depression according to MADRS (n=1). Of the remaining 115 patients 88 (76%) participated in the 12 month neuropsychological follow up. Twelve patients had started their medication for parkinsonism before the baseline evaluation and were therefore excluded from the analysis of the different effects of dopaminergic medication. Five patients did not receive either levodopa or dopamine agonist at follow-up. Two patients that received ropinirole instead of pramipexole were excluded from the medication analysis (Table 6).
Spearman’s rho’s was used to assess correlation in change between baseline and 12 month follow-up in cognitive and motor variables for the total group. The analysis was based on the 12-month follow-up score subtracted from the baseline score. For all cognitive variables, except for TMT A and TMT B, a negative score meant improvement. For all motor variables a negative score meant decline in function. Thus, a negative correlation between motor and cognitive scores meant that an improvement in motor function corresponded to an improvement in cognitive function, except for TMT A and B. The cognitive variables that showed a cognitive-motor relationship in study II and the cognitive and motor variables that correlated in their differences between baseline and the 12 month follow-up were used as dependent variables in separate linear regressions. The motor variable that correlated with the cognitive variable of interest was used as the independent variable. Age at baseline, years of education, LED and baseline score of the dependent variable were used as covariates.

To assess the differences between baseline and the 12 month assessment paired sample t-tests, Mann-Whitney U-tests, chi-square or Fisher’s exact test were applied when appropriate. Change in cognitive performance depending on the dopaminergic medication (dopamine agonist ±levodopa vs. no agonist) was explored. Cognitive variables that had shown to be affected by the intake of pramipexole in a previous study (FCSRT recognition, verbal fluency, category fluency, TMT A and TMT B) [90] was analyzed with univariate analysis of covariance (ANCOVA). The follow up score of the variable of interest was the dominant variable; medication was
entered as between subject factors and the baseline score of the variable of investigation, age, years of education and LED were entered as covariates. Interaction effects between medication and the covariates were checked before the full factorial models were executed. Further, the proportion that declined in variables with significant differences in the different medication groups were calculated and a Chi square test was performed to evaluate if the groups differed (two or more words less at follow-up vs. those with improvement or smaller change). U-shaped associations between motor and cognitive variables were checked separately for each medication group in a regression model with cognitive variables as dependent variable, squared change in motor score (motor²) as independent variable and change in motor score as covariate.

**Paper IV**

Neuropsychological investigations were performed in 119 of 150 patients that fulfilled the diagnostic criteria for PD. Eight were excluded, four had normal presynaptic dopamine uptake, two could not perform tests and two had severe depression. Thus 111 patients with PD were included. There were 17 (15 %) participants that had started their dopaminergic treatment before the baseline assessment and these had been on dopaminergic medication for an average of three months. Baseline, one year, three and five year follow up data for the patients were included. (Table 7)

**TABLE 7.** Baseline characteristics for the total group and for MCI+ and MCI- in Paper IV.

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>MCI- (n=71)</th>
<th>MCI+ (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68.7 (9.4)</td>
<td>67.4 (9.4)</td>
<td>71.0 (9.1)</td>
<td>0.048</td>
</tr>
<tr>
<td>Years of education</td>
<td>10.1 (4.1)</td>
<td>10.6 (4.4)</td>
<td>9.3 (3.5)</td>
<td>0.088</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>68/43</td>
<td>38/33</td>
<td>30/10</td>
<td>0.026</td>
</tr>
<tr>
<td>Duration (months)</td>
<td>22.2 (22)</td>
<td>22 (22)</td>
<td>21 (15)</td>
<td>0.673</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.7 (1.3)</td>
<td>29.1 (0.9)</td>
<td>28.0 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MADRS</td>
<td>4.3 (3.4)</td>
<td>3.8 (3.5)</td>
<td>5.2 (3.1)</td>
<td>0.053</td>
</tr>
<tr>
<td>Started dopaminergic treatment</td>
<td>15%</td>
<td>13%</td>
<td>20%</td>
<td>0.304</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>25.4 (10.9)</td>
<td>23.4 (10.3)</td>
<td>28.9 (11.0)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

UPDRS=Unified Parkinson’s Disease Rating Scale, MADRS=Montgomery and Asberg Depression Rating Scale (MADRS), MMSE=Mini Mental State Examination
Proportions and the annual incidence of dementia with a 95% confidence interval (CI) were calculated. The time of dementia were estimated as the midpoint between assessments that dementia was diagnosed. Person-years at risk were calculated as the total follow-up time until dementia or study end for those not developing dementia. Incidence was calculated as the number of cases with dementia divided by the total number of person years at risk during follow-up. To study the association of age, education, PIGD sub-type and MCI to the development of dementia a Cox-proportional hazard model was performed.

Patients with MCI (MCI+) that converted to dementia were compared to patients with MCI who did not convert on baseline-demographics or cognitive and motor measurements. Student’s t-test, Mann-Whitney U-tests and chi-square tests were used when appropriate.

Population average regression models for correlated data i.e. Generalized Estimation Equations (GEE) were applied to investigate the association of dementia to the evolvement of motor scores. GEE was chosen because it can model non-normal distributed data and take non-independent measurements such as repeated measurements or clustered data into consideration. It is also flexible with unbalanced and missing data [121]. An autoregressive model with Tweedie log link function was used. The dependent variable was the motor score (posture/gait, bradykinesia, tremor, rigidity or bulbar) in five separate models. The factors were set to dementia status (dementia converters and non-converters) and follow-up (baseline, one year, three years and five years). No dementia and baseline testing were set to be the redundant parameters to which the other parameters were compared. Covariates were age at baseline and LED. The significance level was set to p<0.01 because of five dependent measures being tested.
Results

Paper I

Patients with PD performed significantly worse than healthy controls in tests measuring episodic memory (free recall), attention, psychomotor function and category fluency. Thirty% of the patients were impaired in one or more cognitive domain and 16% were impaired in two or more cognitive domains. Impairment was evenly distributed between episodic, executive and verbal functions. Speech, facial expression, rigidity and bradykinesia were significantly more affected amongst the cognitively impaired patients. Compared to patients with intact cognition, patients with impaired cognition had lower scores on the MMSE, shorter disease duration and more motor problems (facial expression, speech, bradykinesia and rigidity) (Table 8). The strongest predictor for impairment in two or more cognitive domains was years of education (10.3 years for <2 vs. 7.8 years for >2 cognitive domains impaired, p=0.01).

<table>
<thead>
<tr>
<th></th>
<th>≥ Impaired domains</th>
<th>Intact cognition</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=26</td>
<td>n=60</td>
<td></td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>8/18</td>
<td>29/31</td>
<td>0.131</td>
</tr>
<tr>
<td>Age, years</td>
<td>65.9 (8.4)</td>
<td>68.9 (9.7)</td>
<td>0.084</td>
</tr>
<tr>
<td>Years of education</td>
<td>9.8 (3.4)</td>
<td>9.9 (4.5)</td>
<td>0.659</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.0 (1.8)</td>
<td>29.0 (1.1)</td>
<td>0.018*</td>
</tr>
<tr>
<td>MADRS</td>
<td>5.4 (4.0)</td>
<td>3.8 (3.7)</td>
<td>0.078</td>
</tr>
<tr>
<td>UPDRS III</td>
<td>28.3 (10.4)</td>
<td>21.8 (8.9)</td>
<td>0.004**</td>
</tr>
<tr>
<td>Speech</td>
<td>0.8 (0.7)</td>
<td>0.3 (0.5)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Facial expression</td>
<td>1.5 (0.8)</td>
<td>0.8 (0.8)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Tremor</td>
<td>2.8 (2.7)</td>
<td>2.8 (2.4)</td>
<td>0.775</td>
</tr>
<tr>
<td>Rigidity</td>
<td>7.4 (4.2)</td>
<td>4.8 (3.6)</td>
<td>0.004**</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>9.8 (4.4)</td>
<td>7.8 (3.8)</td>
<td>0.029*</td>
</tr>
<tr>
<td>Axial impairment</td>
<td>2.6 (2.1)</td>
<td>2.3 (1.5)</td>
<td>0.507</td>
</tr>
</tbody>
</table>

MMSE= Mini Mental State Examination, MADRS=Montgomery and Åsberg’s Rating Scale; UPDRS= Unified Parkinson’s Disease Rating Scale. Reprinted from Paper I with kind permission from the copyright holders.
Paper II

No significant differences were found between PIGD, tremor or indeterminate subtypes in their cognitive test performance at baseline. Instead there was an association between different cognitive test scores and different motor functions measured by the UPDRS III. Correlation analysis showed that bradykinesia, posture/gait score and bulbar function were correlated to a range of cognitive functions. Tremor did not correlate to any cognitive measures. After controlling for age, sex, education and the other motor signs bradykinesia was associated with WCST, digit span and TMT B. Postural instability and gait function were associated with visuospatial function and visuospatial episodic memory while bulbar dysfunction were associated with episodic verbal memory (Table 9).

TABLE 9. Results for linear regression analysis to assess the association between motor and cognitive performance with age, sex education and other motor signs controlled for. (Paper II)

<table>
<thead>
<tr>
<th></th>
<th>$R^2$</th>
<th>Standardized $\beta$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bradykinesia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WCST category completed</td>
<td>0.232</td>
<td>-0.246</td>
<td>0.022*</td>
</tr>
<tr>
<td>Digit span</td>
<td>0.214</td>
<td>-0.288</td>
<td>0.002**</td>
</tr>
<tr>
<td>TMTB²</td>
<td>0.444</td>
<td>0.197</td>
<td>0.038*</td>
</tr>
<tr>
<td><strong>PIGD²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Line orientation</td>
<td>0.187</td>
<td>-0.251</td>
<td>0.016*</td>
</tr>
<tr>
<td>BVMT total</td>
<td>0.364</td>
<td>-0.210</td>
<td>0.022*</td>
</tr>
<tr>
<td><strong>Bulbar dysfunction²</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FSCRT recognition</td>
<td>0.330</td>
<td>-0.329</td>
<td>0.001**</td>
</tr>
<tr>
<td>FSCRT total¹</td>
<td>0.248</td>
<td>-0.373</td>
<td>0.001**</td>
</tr>
<tr>
<td>Mental control</td>
<td>0.162</td>
<td>-0.299</td>
<td>0.003**</td>
</tr>
</tbody>
</table>

¹Log transformation, ²square root transformation, $\beta$=beta, $R^2$=how much of the variance in the dependent variable is explained by the independent variables. WCST Wisconsin Card Sorting Task, TMT Trail Making Test, BVMT Brief Visuospatial Memory Test, FCSRT Free and Cued Selective Reminding Test, BNT Boston Naming Test. Reprinted from Paper II with kind permission from the copyright holders.
Paper III

The associations found in Paper II partly remained when looking at change between baseline and 12 months. Change in postural instability and gait problems correlated with change in visuospatial memory and change in bradykinesia correlated with change in working memory after controlling for age at baseline, years of education, and LED at the 12-month follow-up (Table 10).

<p>| TABLE 10. Results for linear regression analysis to assess the association between change in motor and cognitive performance in 88 patients with PD. after controlling for baseline age, years of education and LED. |
|---------------------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Standardized $\beta$</th>
<th>95% CI for $\beta$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIGD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BVMT total</td>
<td>-0.272</td>
<td>-1.601-0.190</td>
</tr>
<tr>
<td>Line orientation</td>
<td>-0.099</td>
<td>-0.658-0.254</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit span</td>
<td>-0.300</td>
<td>-0.311-0.050</td>
</tr>
<tr>
<td>TMT B</td>
<td>0.243</td>
<td>0.212-7.315</td>
</tr>
<tr>
<td>BVMT total</td>
<td>-0.160</td>
<td>-0.496-0.082</td>
</tr>
<tr>
<td>Digit span forward (n=34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>-0.473</td>
<td>-0.047-0.006</td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>-0.042</td>
<td>-0.159-0.126</td>
</tr>
</tbody>
</table>

PIGD=postural imbalance and gait disturbance. BVMT=Brief visuospatial memory test. FCSRT=Free and Cued Selective Reminding Test. TMT B=Trail Making Test part B. *p-value<0.05, **p-value<0.01, Bradykinesia statistics based on only patients receiving pramipexole. Reprinted from Paper III with kind permission from the copyright holders.

No differences in the total group were found between baseline and follow-up in any of the cognitive variables, except for a small improvement in MMSE (baseline mean 28.8, follow-up mean 29.2, $p=0.025$) and MADRS (baseline mean 4.37, follow-up mean 3.34, $p=0.017$). Significant changes in the motor variables were seen in UPDRS III total (baseline mean 24.4, follow-up mean 22.0, $p=0.014$) as well as for tremor (baseline mean 2.5, follow-up mean 1.49, $p<0.001$) and posture/gait sub-score (baseline mean 2.36, follow up 1.88, $p=0.008$). The only cognitive test that significantly differed between medication groups was phonemic fluency $[F (1.67)=5.244 p=0.025$, partial eta square$=0.073$, ANCOVA$]$. Patients receiving pramipexole± levodopa performed significantly worse at the one-year follow-up (baseline mean: 43.7 words, follow-up mean: 38.5). The patients that did not receive pramipexole showed a non-significant improvement between assessments (baseline mean: 36.2 words, follow-up mean: 37.5). In the pramipexole± levodopa group 74% produced two or more words less at follow-up compared to only 31% of those not receiving pramipexole. For patients receiving pramipexole the correlation between bradykinesia and digit span forward was U-shaped.
That is, patients with less bradykinesia at follow-up either improved or deteriorated in their working memory performance.

Paper IV

Twenty-seven patients with PD (24%) developed dementia within five years, corresponding to an annual incidence of 56.0 per 1000 person-years (95% CI, 37.2-80.3). Forty patients (36%) had MCI at baseline of which 22 (55%) transitioned to dementia, corresponding to an annual incidence of 148 per 1000 person-years (95% CI, 94.9-215.0) in patients with MCI. Five (7%) patients with normal cognition at diagnosis transitioned to dementia corresponding to an annual incidence of 15 per 1000 person-years (95% CI, 4.9-34.6). Seven patients with MCI at baseline reversed back to normal cognition and three patients shifted between MCI and normal cognition between assessments. The sensitivity for MCI to predict dementia in early stages of PD was 81%, the specificity 79%, the PPV 55% and the NPV 92%.

MCI converters performed significantly poorer than non-converters on several cognitive measures at baseline: MMSE, FCSRT free recall, BVMT, mental control, line orientation, animal fluency, and TMT B.

MCI (B=-2.486, Exp(B)=0.083, CI for Exp(B) 0.031-0.225, p<0.001) and baseline age (B=1.077, Exp(B)=2.936, CI for Exp(B) 1.23-6.99, p=0.003) were both significant predictors for dementia. Education and motor subtype at baseline were not significant predictors of dementia. None of the patients with the tremor subtype at the latest visit had developed dementia.

There were significant negative changes for posture and gait impairment (Wald Chi-Square 23.862 p<0.001), bulbar dysfunction (Wald Chi-Square 20.627, p<0.001), and bradykinesia (Wald Chi-Square 54.963, p<0.001) during the follow-up period. Dementia converters had more bradykinesia (Wald Chi-Square 25.035, p<0.001), rigidity (Wald Chi-Square 20.376, p<0.001), bulbar dysfunction (Wald Chi-Square 12.557, p<0.001) as well as posture and gait impairment (Wald Chi-Square 16.231, p<0.001). There was an interaction effect between follow-up and dementia for posture and gait (Wald Chi-Square 14.523, p=0.002); i.e. patients developing PDD differed from PD patients that did not develop dementia in their evolvement of posture and gait impairment (Figure 6a). The interaction effect for follow up and dementia were close to significant for bradykinesia (figure 6b) between baseline and three years (p=0.02), and for rigidity (figure 6c) between baseline and five years (p=0.01) but not significant for the total follow up period (rigidity: Wald Chi-Square 8.214, p=0.042, bradykinesia: Wald Chi-
Square 6.449, p=0.092). The evolvement of tremor and bulbar dysfunction did not significantly differ between patients.

**FIGURE 6.** The evolvement of a) postural instability/gait disturbances, b) bradykinesia and c) rigidity in patients converting to PDD compared to those who did not. Significant p-values indicate interaction between time and dementia status compared to baseline.
Discussion

Main findings

The main focus of this thesis is cognitive function in early PD and its association to motor disturbances. In line with previous studies [6–8, 98] we found, in comparison with healthy controls, that cognitive impairment is common in newly diagnosed patients with PD and that a range of functions are affected already at diagnosis. Patients with cognitive impairment at baseline had significantly more motor problems according to the UPDRS III, than those with intact cognition, and education was an independent predictor for impairment in two or more cognitive domains at baseline but did not predict dementia within five years.

Associations were found between bradykinesia and worse performance on tasks measuring working memory and executive functions as well as between posture/gait dysfunction and lower scores on tests measuring visuospatial function and visuospatial memory. Some of these associations persisted also after one year.

MCI at the time of diagnosis was found in 36% when diagnosed by recently published MDS Task Force criteria (Paper IV). Thirty% were classified as having cognitive impairment when using slightly different criteria (Paper I). One fourth of the patients developed PDD within five years after diagnosis. Age at diagnosis and MCI according to MDS Task Force criteria were significant predictors of dementia. There were 25 % of those classified as having MCI at baseline that converted to normal cognition or reversed back and forth over the 1.5 SD limit between assessments.

Patients with MCI converting to PDD within five years had worse performance on several cognitive tests at baseline: visuospatial function, semantic fluency, episodic memory, conceptual tracking and mental flexibility; but not in tests measuring executive function, working memory, verbal phonemic fluency and language function.

There were no differences in baseline measures of cognitive function between PIGD, tremor and indeterminate phenotype. PIGD phenotype at baseline did not predict dementia within five years. None developed dementia among those having a tremor dominant phenotype. Worsening of posture/gait was more pronounced in patients developing dementia than in patients that did not. A similar pattern was seen in bradykinesia and rigidity but not for tremor and bulbar dysfunction.
Patients treated with the dopamine agonist pramipexole performed significantly worse on a measure of verbal fluency at the one year follow up compared with patients not treated with the drug.

**Impaired cognitive functions**

Compared with healthy controls, patients with PD performed significantly worse already at the time of diagnosis on tests measuring attention, semantic fluency and episodic memory (free recall). Attention/working memory and episodic memory were the domains mostly affected followed by executive, visuospatial and verbal function. This shows a diversity of cognitive decline within patients with PD, in line with previous studies [6]. This could be expected considering the heterogeneity of the disease.

A diverse pattern of differences in baseline test performance between patients with MCI converting to dementia compared with those not converting to dementia was shown in Paper IV. WCST, a measure of executive function, together with working memory, phonemic fluency and verbal naming did not significantly differ between MCI converters compared with non-converters at baseline. Interestingly many of the same tests did not differ between patients and controls in Paper I.

Previous research has connected executive impairment [122, 123], and memory [123] as predictors of PDD. Neuropsychological measures with a more posterior cortical basis such as pentagon copying and semantic fluency have been suggested to be predictors of dementia [124]. A recent study comparing MCI converting to dementia within two years with those that did not convert proposed that frontal lobe associated performance together with atrophy in both frontostriatal areas and cholinergic structures, and not visuospatial function, were predictors of dementia in PD-MCI [125].

Tests that significantly differed between MCI converters and non-converters in Paper IV were tests measuring visuospatial function and semantic fluency in line with Williams-Gray et al. [66], but also tests measuring episodic memory free and delayed recall, conceptual tracking, and mental flexibility where the latter tests are believed to be more frontally mediated.

Together this shows a diverse picture of cognitive function associated with PDD with a range of different cognitive functions that are different between MCI converters and non-converters. We need to look at both the striatal network in combination with a more widespread cortical network in the search for predictors for PDD.
Proportions of MCI and Dementia

MCI

The proportion of patients that were classified as being cognitively impaired differed somewhat between Paper I (30%) and Paper IV (36%). Different classification procedures with stricter criteria and removal of TMT A and TMT B from the classification battery in Paper I and the use of MDS Task Force criteria in paper IV were the reasons for this. The MDS Task Force criteria had not yet been published when paper I was assembled. The differences of results within the same study population depending on which classification is used show that MCI classification relies on the tests included and the cut-off values used and emphasizes the value of joint criteria for PD-MCI, in research and in clinical practice.

Proportions of MCI in newly diagnosed cases with PD published prior to the MDS Task Force criteria have ranged between 19 to 36% [6–8, 52, 53, 126]. The proportions of patients classified as MCI according to the MDS Task Force criteria in newly diagnosed PD have been 25 to 35% [57, 58, 127]. This makes the proportion of 36% in Paper IV at the higher range.

Dementia

In cross-sectional studies the prevalence of dementia has been around 30% and increases over 20 years to 76% [128]. The majority of studies have been based on prevalent PD cases with different disease duration. Following patients from disease onset gives a more accurate estimate of dementia rates and give a better base for determining the dementia risk. Studies on prospectively studied newly diagnosed cases with PD are rare, and the proportion of patients developing PDD in such studies within five years has been 17% [32, 129] [incidence 38.7 per 1000 person-years (95% CI, 23.9-59.3)] [32]. This makes the proportion of patients developing dementia (24.3%) and the incidence rate (56 per 1000 person-years) slightly higher than reported in previous studies on newly diagnosed cases, but longer follow up times have rendered incidence rates similar to our study [54.7 per 1000 person-years (95% CI, 35.4-74.1)] [66].

Higher dementia and MCI rates

There could be several reasons for the high dementia and MCI rates in this cohort. Cognition was mapped extensively and was more thoroughly investigated than in most other longitudinal studies [58, 60]. Our patients were older [57] and they had less education [57, 58]. Furthermore, the
annual incidence of PD reported from the NYPUM cohort is among the highest reported in the literature [15]. This could be due to meticulous case finding strategies that might also influence the proportion of patients with cognitive impairment.

**Predictive value of MDS-Task Force MCI criteria for PDD**

The MDS Task Force MCI criteria were found to have a relatively good sensitivity and specificity where 22 of 40 (55%) patients with MCI developed dementia within 5 years. There are two longitudinal studies on newly diagnosed patients with PD using MDS Task Force guidelines for MCI [57, 58]. A three year follow up where ten out of 37 (27%) patients with MCI converted to dementia [58] and a five-year follow-up where 11 out of 43 (26%) converted [57]. The three-year study had an annual incidence rate of dementia of 98.9 per 1000 person-years in patients with MCI at diagnosis. After three years there were 11 out 40 patients with MCI at baseline that had converted to dementia in our study and only one of 71 of those with normal cognition.

Half of the patients that were classified as having MCI at baseline did not develop dementia within five years. With prolonged follow-up the PPV might increase as more patients with MCI may develop dementia, the NPV will most likely decrease as more patients classified as having normal cognition at baseline will probably also convert to dementia.

During follow-up 25% that were initially classified as MCI at baseline reversed to normal cognitive function or shifted between normal cognition and MCI between follow-up. In those cases the MCI at baseline might be due to reversible causes, such as nervousness, depression or sleep deprivation, rather than neurodegenerative. In some cases the cognitive improvement could also be due to the intake of dopaminergic medication [130].

Previous studies in the general population have shown a reversion rate from MCI to normal cognition between 13-41% [131–133]. A recently published study using MDS Task Force criteria reported a reversion rate from MCI to normal cognition to around 20% [58]. A study from Norway suggests that patients with PD classified as MCI both at baseline and after 12 months have a higher proportion of MCI converting to dementia as well as a lower proportion of MCI reversing back to normal cognition than for those having MCI at baseline or at the 12-month follow-up [58].


**Education, age, disease duration and gender aspects**

In Paper I shorter length of education was a predictor for having more than two cognitive domains impaired. Less education did not predict the development of dementia. Previous longitudinal studies on non PD participants have found that short education does not increase the risk of developing dementia [134, 135] but Kryscio et al. [134] found that education significantly predicted transition from normal cognition to MCI.

Our finding of shorter disease duration among those with impaired cognitive function in Paper I suggests an aggressive PD phenotype with cognitive decline early in the disease. However in Paper IV we found no significant differences in disease duration between those with MCI at baseline compared to the rest. Disease duration did not differ between those developing dementia compared with those who did not. This is in line with a prospective population-based study that through separating general age from age at motor onset showed that patients with PD have a similar dementia age regardless of when they first are presented with motor symptoms [136].

The only significant gender difference found were the difference between how many were classified as MCI according to the MDS Task Force criteria where 75% of those with MCI were male. The reason for this is hard to grasp since this has not been shown in previous studies. There could be gender differences in whether to agree to participate in the neuropsychological testing if one experiences cognitive decline. One explanation could be that female patients with PD have been suggested to more often be presented with the tremor dominant phenotype [137]. However, there were no significant differences in motor subtypes between male and female participants in the present study.

**Cognitive motor relationship**

A pattern of motor cognitive associations already in early stages of PD could be depicted from the connection found between motor and cognitive measures, and the different motor and cognitive variables associated with MCI and dementia. Bradykinesia was associated with worse working memory performance and executive functions whereas postural instability and gait disturbances were associated with visuospatial memory and visuospatial function. Tremor showed no association with any cognitive measures either at baseline or in the change over time. Bradykinesia, rigidity and postural and gait disturbances were all more severe in those with MCI.
and those developing PDD. Furthermore, there was a more pronounced worsening of motor functioning over time in those developing dementia.

Some cross-sectional studies have investigated the cognitive motor relationship in PD [4, 97, 98, 138]. Most of the earlier studies have been rather small and included prevalent cases with various disease duration that have received dopaminergic treatment of various duration. It can be problematic to demonstrate motor cognitive relationships in medicated patients since dopaminergic medication has shown to affect motor and cognitive abilities differently. Correlation between the UPDRS motor score and a range of neuropsychological measures, but not visuospatial function has been reported [139], although a recent study using objective measures of motor dysfunction connected visuospatial function to postural instability in PD [94].

**The association of bradykinesia with impaired working memory and executive function**

Both bradykinesia and decline in executive functions and attention/working memory are common in PD. Bradykinesia [22], working memory [37] and executive functions have been linked to the frontostriatal brain network and further linked to nigrostriatal dysfunction. The association of bradykinesia with executive dysfunction and attention/working memory dysfunction found in Paper II supports the possibility of joint underlying networks.

Patients classified as having cognitive impairment (Paper I and Paper IV) had more severe bradykinesia at baseline which suggests dopaminergic involvement in MCI in early stages of PD. A recent cross-sectional functional magnetic resonance imaging (fMRI) study of early PD linked cognitive impairment in PD to frontostriatal dysfunction by showing under recruitment in dorsal caudate nucleus and bilateral anterior cingulate while performing an updating task in patients with PD-MCI [140].

Patients that developed PDD had more bradykinesia and rigidity than those not developing dementia. This also indicates early frontostriatal dopaminergic involvement in PDD.

**The association of posture and gait disturbances with impaired visuospatial function and visuospatial memory**

Significant associations between postural and gait scores and visuospatial memory and visuospatial function were found and further confirmed in the
association between change in posture and gait score and visuospatial memory in Paper III.

PIGD/tremor and indeterminate subtype did not significantly differ in any cognitive tests at diagnosis. The evolvement of postural instability and gait scores differed between those developing dementia compared with those who did not, with a significantly more pronounced decline in those developing dementia. We showed in line with previous results that PIGD subtype at the time of diagnosis did not predict the development of dementia [66]. Together this shows that PIGD phenotype does not seem to be a predictor of cognitive impairment in early stages of PD or a predictor of developing dementia. It rather seems to be a parallel process with decline in visuospatial function and memory and the development of PDD. In the general population poor gait and cognition have been connected [141]. Dementia and falls often coexist and gait impairments have been related to the severity of cognitive impairments [142].

Previous studies have shown that PIGD phenotype at diagnosis predicts worse outcome in PD [66, 143]. PIGD has also been shown more common among patients with worse cognitive performance [144] and has been identified as a risk factor for dementia [96]. Both previous studies [96, 144] included cases in various disease stages that had started their dopaminergic medication before the first assessment. In line with our results is a study by Alves et al (2006), which suggested that changing from tremor to PIGD subtype is a risk factor of dementia and that having a persistent tremor phenotype was protective of dementia [67].

A recent study found a connection between increased neocortical β-amyloid deposit and higher PIGD features in PDD which could possibly be one underlying factor explaining the association of postural instability and gait disturbances with impairment in visuospatial function and memory and later development of dementia [27]. A specific association of gait dysfunction, cognitive impairment and reduced cholinergic activity has been described with several lines of evidence (see Ambioni et al. for review) [145].

Other explanations could be the association of degeneration of the pedunculopontine nucleus (PPN) and the lateral pontine tegmentum area (rich in acetylcholine) in gait disturbances [146]. Impaired cholinergic integrity of the PPN has been associated with frequent falls in PD [147]
The effect of dopaminergic medication

Study III showed that there were some differences in change in cognitive functions over one year (phonemic fluency) and the association of the change between motor and cognitive functions (digit span forward and bradykinesia) in patients receiving the dopamine agonist pramipexole compared to patients who did not. Since we did not compare different agonist we cannot tell whether our finding is a specific effect for pramipexole or an effect that could also be found in other DA. Pramipexole is believed to have a high affinity for D3 receptors [148] which could be connected to both findings. A possible explanation for the decline in verbal fluency for patients receiving DA could be that D3 auto receptors have been shown to contribute to the presynaptic regulation of tonically released dopamine which leads to a moderate inhibitory action on locomotion [148]. If this is also the case for cognitive function, this could result in an inhibitory effect on word production.

The U-shaped association for change in bradykinesia and working memory could possibly be explained by the U-shaped association between dopamine levels and cognitive functions. Bradykinesia has been described as the best measure of the nigrostriatal lesion [22] and is related to the dorsal striatum that is severely dopamine depleted in the early stages of the disease. There is a high density of D3 auto receptors in the ventral striatum that is less dopamine depleted early on in the disease. Therefore the U-shaped association for patients receiving DA perhaps indicates that pramipexole is more likely to impair working memory by overdosing than other types of medication.

These findings have to be interpreted with caution. A lot of comparisons were made and the findings could because of this be spurious. Still the finding could be indicative of a possible influence of DA on certain aspects of cognition that needs to be further investigated. In line with our result Brusa et al. showed in 20 right handed patients with PD that pramipexole produced significant impairment of short term verbal memory, attentional executive functions and verbal fluency [90]. None of the previous studies that have investigated the more prolonged effect of DA (6-24 months) has included patients that received pramipexole as monotherapy. Patients receiving pramipexole differed from the other patients in age and baseline performance which could have influenced the results. This was because the decision on the type of dopaminergic medication used was made by the treating physician based on personal experience and the common practice of using dopamine agonist in younger onset patients (before 65-70 years of age).
Ethics

Studying elderly clinical populations in which a large proportion of the patients eventually will develop dementia renders certain demands of ethical considerations. Both cognitively impaired and borderline cognitively impaired patients with PD have impairments in their decisional capacity measured by the MacArthur Competence Assessment Tool for Clinical Research [149]. This might be especially problematic when enrolling patients with MCI whose reduced decisional capacity might be less obvious. It is also important to note that many of the patients will change in their decisional capacity during the course of the study. When enrolling patients in a prospective study with repeated investigations it can be hard for the patient to grasp how the extensive assessments will interfere with their daily life at present, but even more so in the future, especially for a patient that is not functioning at an optimal cognitive level.

Since the NYPUM study is implemented at a hospital there is close contact between clinic and science. A clinical study where many health care persons are involved can make the participants feel pressure to give consent and continue in the research project. It is important to make clear that the decision whether to remain in the study or not should under no circumstances influence the future care of the patient.

Studies have shown that incidental findings of significant clinical importance in fMRI research are around one-two % [150]. There is probably an even higher proportion in elderly populations. This highlights the importance of having a plan for taking care of possible findings and for bringing back the results to the patient. One example of an ethical challenge could be whether the participant should be told that they are a part of a risk group.

Methodological considerations

Study design

The main strength of the study is the population-based approach with a close to complete identification of cases (making generalization of results possible) and an extensive assessment of neuropsychological functions within a few weeks of diagnosis. This allows testing of almost all patients prior to the introduction of pharmacological treatment with dopaminergic agents. The neuropsychological evaluation is repeated after one, three and five years and can provide knowledge of the prognosis of cognitive function in PD. It also makes it possible to identify factors at diagnosis that are predictive of different outcomes and thereby can imply causality. This is in contrast to
cross-sectional investigations that only can confirm associations. One limitation is the lack of histopathologically confirmed diagnosis.

**Loss to follow up and missing values**

A methodological problem seen in longitudinal studies of the elderly is a cohort bias, i.e. selective loss to follow-up. There are many drop-outs, people are old and die, they have a chronic progressive disease that affects them to such a degree that they are unable to participate at follow-up. In the present study already at the baseline testing, the dropouts differed from those participating in the neuropsychological investigation. This is a problem when describing the true progression for the entire population with PD. The picture provided here is probably a little bit too optimistic. In the group that developed dementia there were only five patients performing the five year neuropsychological follow up. Therefore describing the longitudinal change in the cognitive measures would be misleading. Fortunately there were more evaluations of these participants and most of them remained in the study allowing evaluation of cognitive function/dementia even when they did not perform the extensive neuropsychological test battery. This particular loss to follow-up is hard to avoid but one way of minimizing the skewed loss to follow-up is to perform home visits for the patients who are too tired to come to the hospital.

There is also loss of individual measures due to tiredness and technical issues. WCST was the test with most missing values which could be one explanation why the result of WCST did not differ between the groups. We did not omit patients who had not performed isolated tests. Since the missing values were rather few for most variables, and distributed in different cases, we used pairwise deletion of the data (except for a few cases). The drawback with this method is that the parameters of the model will be based on different set of data. The positive side is that we do not lose as much power as we would have if all cases would have been omitted.

**Statistics**

A lot of variables and comparisons were used in the studies which increases the risk for type I errors. We did not want to exclude possible true relationships by adjusting for alpha error inflation by applying the strict Bonferroni adjustment [151]. The risk for Dementia in PD seems to be exponential, i.e. there is an exponential increase of new dementia cases with age. This is problematic when using the Cox proportional Hazard model.
**Diagnosis of PD**

The number of patients with PD at baseline is different in all the four papers. This is due to differences in the number of patients that had been included at the time of the particular paper and to changes in diagnosis in some patients as the disease progressed. Since the diagnosis of PD is more accurate as time progresses and diagnostic criteria that are based on what happens prospectively, e.g. the response to dopaminergic treatment, the diagnosis is destined to change in some individuals.

**UPDRS**

The total score of UPDRS III is a validated and reliable tool for measuring the progression of motor dysfunction in PD. The division into the different motor components (e.g. bradykinesia, rigidity etc.), even though used in several studies [106], is not validated as used in the thesis. UPDRS is a clinical scale that relies solely on the investigators judgment. An alternative to the clinical measures could be to use quantitative measures of the different motor functions which could also enable description of other aspects of motor functions. This could give a more precise picture into what part of movement that is correlated with different cognitive functions.

**SWEDDs**

In patients clinically diagnosed with PD four-15% have normal imaging of dopaminergic function (Scans Without Evidence of Dopaminergic Deficit [SWEDDs]) [152]. SWEDDs patients are not likely to progress in severity or develop motor and non-motor complications and it is highly likely that they do not have PD at all [153]. We have treated the SWEDDs differently in the different papers. In Paper I SWEDDs were included in the analysis. In Paper II-IV the SWEDDs were excluded. The reason for this is that we did not have as many prospective scans in Paper I and therefore we could not tell if the normal datscan was an expression of early disease or if they were actually true SWEDDs. Patients in Papers II –IV had been repeatedly scanned for three to five years when the studies were assembled and therefore the SWEDD classification was considered more stable.

**MCI and Dementia**

We tried to find variables that differed between MCI that developed dementia and those who did not as a way of dissociating patients developing early dementia from the rest of the group at diagnosis. The question that we hoped to answer was how patients with MCI that converted to dementia in
the early phase differed from those who did not. It is likely that additional patients from the MCI group will develop dementia therefore the specificity and sensitivity for MCI is only for the early phase of PD, i.e. up to five years after diagnosis.

**Motor fluctuations**

The occurrence of dyskinesias and motor fluctuations is common, and in the long term management most patients will be affected by those treatment-related side effects [154]. There is some evidence that cognitive performance together with arousal state might be affected during motor fluctuations in PD [155]. This is important when studying patients with PD for a longer period of time. In the present study the ambition was to avoid testing if substantial dyskinesias or other wearing-of symptoms were present. In the cases where this was impossible or if the testing for some reason was performed anyway, this was noted in the test protocol. Since the study population was in the early phase of PD, dyskinesias and motor fluctuations were minor problems.

**Neuropsychological testing**

Different neuropsychological tests aim to capture certain aspects of cognition and manage to do so to a certain degree. However, it is complicated to apply a reductionist view when looking at cognition since different cognitive functions does not operate separately from each other. This is important to have in mind when using standardized neuropsychological tests. It is obvious in the PD literature that researchers are using different cognitive tests to measure the same function. There are also examples were different studies claim that a certain task measures different abilities. This is one contributing factor to the various results between studies.

Some of the tests used in the studies require motor function such as both TMT A and B. TMT B but not TMT A is correlated with bradykinesia which indicates that it is likely that it is mental flexibility that contributes to the association. BVMT is a test that requires drawing which can indeed be influenced by especially tremor. According to the instructions for the test, for example shaky handwriting should be overlooked in the judgment of correctness of the figures.

The aim for the present study was to assemble a test battery that captured different functional levels and could be performed even when functions start to deteriorate. This is important to be able to measure change and at the same time avoid ceiling as well as floor effects. It is also important for
minimizing the loss of study patients over time. If tests get too complicated when functions deteriorate it can be hard to assess patients with severe cognitive decline.

**Control group**

The small control group is a weakness of the study. The control group was assessed with the UPDRS III, but associations between motor and cognitive scores could not be calculated in the control group, as the controls had scores of zero, at baseline and later. Thus it was not possible to see if the pattern of association differed between the control group and the PD group. It has been discussed whether to use norm values based on a control group or normative values from other cohorts. Well-developed normative values taken from big cohorts strictly following the standardization of the tests in similar age groups that are being studied provide adequate data for comparison with the study group of interest. It may be difficult to find such norm values, especially with the tests in an assessment battery taken from different sources. The optimal solution would be a large sample of controls tested under the same conditions as the clinical subjects under investigation.

**Future implications**

The papers in the thesis discuss cognitive dysfunction in early stages of PD and its relation to motor function for baseline and follow-up data up to five years after diagnosis. We have so far completed the eight-year follow-up for patients recruited during the first two years. This will allow investigations of baseline measures that predict early onset and late onset dementia. Later we will also receive autopsy results that will confirm the clinical diagnosis of PD and enable identification of cellular signatures associated with the development of dementia.

With longer follow-up we can study patients maintaining cognitive function. This will make it possible to investigate what distinguishes patients with preserved cognitive function from the large proportion of patients that decline.

Combining different motor and cognitive measures as predictors for dementia might display subtypes that go beyond the scope of studying cognition and motor functions separately. Studying patients with postural and gait impairment together with impairment in visuospatial memory and function might give a better prediction for future outcome. Furthermore, investigating objective measures of movement might provide a more specific pattern of deficit connected to specific cognitive functions.
Blood samples and cerebrospinal fluid (CSF) from patients and controls will enable genotyping and metabolomic profiling which could assist in the interpretation of the motor and cognitive associations discussed in the present thesis as well as finding predictors for cognitive decline and dementia.
Conclusions

The findings in this thesis confirm results from previous studies, namely that a large proportion of patients are cognitively impaired already at the time of diagnosis with a range of cognitive functions being affected. The present study is unique in that it combines being truly community-based with employing an extensive neuropsychological test battery with repeated investigation. All patients within the study are referred to the same neurological department. This resulted in almost a complete recruitment of affected cases all in early disease stages.

The findings show a diverse picture of cognitive and motor functions with both dopaminergic and non-dopaminergic motor and cognitive functions associated with cognitive impairment and PDD. This indicates that we need to look at both the striatal network in combination with a more widespread cortical network in the search for mechanisms behind cognitive impairment in PD. The associations found between motor and cognitive dysfunction could reflect shared underlying pathology in motor and cognitive disturbances.

The differences in proportions of cognitively impaired in Paper I and Paper IV were mostly due to the use of different criteria. This shows that MCI classification is largely determined by the tests included in diagnosis and the cut-off values used. This emphasizes the value of joint criteria for PD-MCI, both in research and in clinic. Even when using joint criteria there is a substantial amount of patients that reverts back to normal cognitive function at follow-up.

There could be several explanations for increased motor severity in patients with PDD. Patients with more posture and gait difficulties could be more advanced in their disease progression, i.e. dementia and postural and gait difficulties may represent a more advanced disease stage. Alternative explanations could be that patients with dementia for unknown reasons respond less well to medication compared with patients without dementia and therefore have worse and declining motor performance. The parallel decline in motor and cognitive functions might also affect each other (e.g. less physical activity due to motor dysfunction resulting in a more inactive life which leads to accelerating cognitive decline which in turn results in worsening of motor performance). To answer these questions further studies that are specifically designed to answer these questions are needed.
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References


87. Pollak P. Clozapine in drug induced psychosis in Parkinson’s disease: a randomised, placebo controlled study with open follow up. *J Neurol Neurosurg Psychiatry* 2004, **75**:689–695.


102. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Brit J Psychiatry* 1979, **134**:382–389.


151. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990, **1**:43–46.


