Functional brain imaging of cognitive status in Parkinson's disease

Table of Contents

Abstract

Parkinson's disease (PD) is next to Alzheimer's disease (AD) the second most common neurodegenerative disease. PD has traditionally been characterised as a motor disorder, but more recent research has revealed that cognitive impairments are frequent. Cognitive impairments in executive functions, attention, and working memory with reliance on dopaminergic transmission, are often described as dominating the cognitive profile in early-phase PD. However, although knowledge about the neuropathology that underlies the cognitive impairments in PD has increased, its features are complex and knowledge remains insufficient. Therefore, the aim of the current thesis was to improve the understanding of how task-evoked brain responses relate to cognitive status in patients with PD, with and without mild cognitive impairment (MCI), and to evaluate the predictive value of PD-MCI in respect of prodromal Parkinson's disease dementia (PDD). This was conducted within the "new Parkinsonism in Umeå" (NYPUM) project, which is a prospective cohort study. Patients with idiopathic PD were included in this thesis, and the patients were examined with a comprehensive neuropsychological battery and with a functional MRI (fMRI) working memory protocol. During scanning, patients conducted a verbal two-back task in which they needed to maintain and actively update relevant information, and the primary outcome measure was blood-oxygen-level-dependent (BOLD) signal. This thesis shows that patients with PD-MCI had significantly lower BOLD signal responses than patients without MCI in frontal (anterior cingulate cortex) and striatal (right caudate) regions (Study I). The altered BOLD response in the right caudate was associated with altered presynaptic dopamine binding. The fronto-striatal alterations persisted across time but without any additional change. However, decreased posterior cortical (right fusiform gyrus) BOLD signal responses were observed in patients with PD-MCI relative to patients without MCI across time (Study II). Finally, PD-MCI at baseline examination is highly predictive for prodromal PDD with a six-fold increased risk. Cognitive tests with a posterior cortical basis, to a greater extent, are predictive for prodromal PDD than tests with a fronto-striatal basis. The observed working memory related alterations in patients with PD-MCI suggest that early cognitive impairments in PD are linked to fronto-striatal dopaminergic dysfunction. The longitudinal development of cognitive impairment in PD reflects additional posterior cortical dysfunction. This might reflect a dual syndrome, with dopamine-depleted fronto-striatal alterations that characterise PD-MCI in general, whereas additional posterior cortical

cognitive alterations with a non-dopaminergic basis to a greater extent characterise prodromal PDD. If, and how, the two potential syndromes interact, is still unclear. Thus, this thesis provides information on cognitive neuropathological changes in PD that might contribute to more relevant choices of pharmacotherapy and diagnostic accuracy in respect of PDD. However, additional large-scale longitudinal imaging studies are needed to further clarify the neuropatholgogical features of PD-MCI in respect of prodromal PDD.

Keywords: Parkinson's disease, functional MRI, Mild cognitive impairment, Working memory, Parkinson's disease dementia, BOLD.

Abbreviations

ACC	Anterior cingulate cortex
AD	Alzheimer's disease
BOLD	Blood oxygen level dependent
CBD	Cortico-Basal Degeneration
DLB	Dementia with Lewy bodies
DLPFC	Dorsolateral prefrontal cortex
EEG	Electroencephalographic
fMRI	Functional magnetic resonance imaging
FWHM	Full width at half maximum
HY	Hoehn and Yahr scale
LB	Lewy Body
L-dopa	Levodopa
MCI	Mild cognitive impairment
MDS	Movement Disorders Society
MNI	Montreal Neurological Institute
MPS	Mild Parkinsonian signs
MRI	Magnetic resonance imaging
MSA	Multiple System Atrophy
NYPUM	New Parkinsonism in Umeå
PD	Parkinson's disease
PDD	Parkinson's disease dementia

PD-MCI	Parkinson's disease – Mild cognitive impairment
PET	Positron emission tomography
PFC	Prefrontal cortex
PSP	Progressive Supranuclear Palsy
ROI	Region of interest
SN	Substantia nigra
SNc	Substantia nigra pars compacta
SPECT	Single photon emission computed tomography
SPM	Statistical parametric mapping
TMT	Trail making test
SWEDDs	Scans without evidence of dopaminergic deficits
UK PDSBB	United Kingdom Parkinson's disease Society Brain Bank criteria
UPDRS	Unified Parkinson's disease rating scale

Sammanfattning på svenska (summary in Swedish)

Parkinsons sjukdom (PD) är efter Alzheimers sjukdom (AD) den näst vanligaste neurodegenerativa sjukdomen. Trots att PD historiskt sett har karaktäriserats som en motorisk problematik så har även många patienter med PD kognitiv problematik, och mellan 20 och 40% av patienter med PD har lindrig kognitiv svikt (mild cognitive impairment: MCI) redan i tidiga skeden av sjukdomsutvecklingen. Även om inte alla patienter med PD-MCI utvecklar PD demens (PDD), så är risken att utveckla PDD kraftigt förhöjd för patienter med PD-MCI jämfört med patienter utan MCI. Kognitiva nedsättningar har regelbundet noterats för exekutiva funktioner, episodiskt minne, uppmärksamhet, visuospatiala funktioner, och arbetsminne. Även om kunskapen har ökat om de kognitiva problemens underliggande neurala korrelat, så är den fortfarande bristfällig. Avhandlingens övergripande syfte är att öka kunskapsläget om hur kognitivt processande relaterar till neurala responser för patienter med PD i olika faser av deras kognitiva problematik. Deltagarna rekryterades inom ramen för NY Parkinsonism i UMeå projektet (NYPUM), vilket är en longitudinell prospektiv kohortstudie som påbörjades 2004. De inkluderade deltagarna med PD fick utföra en arbetsminnesuppgift i en magnetkamera (fMRI) där förändringar i hjärnans syresättning observerades. Detta kompletterades i studie I med att mäta striatala presynaptiska dopaminnivåer som registrerades med en SPECT-kamera. Avhandlingen visar att patienter med PD-MCI hade lägre arbetsminnes-relaterad hjärnaktivitet i frontala (anteriora cingulum) och striatala (caudatus) områden jämfört med patienter utan MCI, redan i samband med deras initiala PD diagnoser. Lägre nivåer av presynaptiskt dopaminupptag noterades i högra caudatus för patienter med PD-MCI jämfört med patienter utan MCI, och dopaminnivåerna korrelerade med fMRI-aktiviteten. Den longitudinella utvecklingen för patienter med PD-MCI relaterade till nedsatt aktivitet i temporala cortex (fusiform gyrus) men inte i någon ytterligare omfattning till fronto-striatala nedsättningar. Patienter som har PD-MCI i samband med sin initiala diagnos hade drygt sex gånger ökad risk att utveckla PDD, och de kognitiva test som är mest prediktiva för PDD regleras av posteriora kortikala regioner är i högre grad än test som regleras av fronto-striatala regioner. Avhandlingen har visat att aktivitetsnedsättningar i fronto-striatala hjärnsystem som regleras av dopamin är karaktäristiskt för patienter med PD inom ramen för tidig kognitiv problematik. Dock tyder avhandlingen på att posteriora kortikala aktivitetsnedsättningar i högre grad än fronto-striatala aktivitetsersättningar är en riskfaktor för påföljande PDD. Avhandlingen ökar därmed kunskapsläget om kognitiv neuropatologi i PD, vilket

potentiellt har implikationer på medicinska och icke-medicinska interventioner i relation till kognitiv problematik, samt till PDD diagnostik.

List of studies

The present thesis is based on the following studies:

I. Ekman U, Eriksson J, Forsgren L, Susanna Jakobson Mo, Katrine Riklund, Lars Nyberg. Functional brain activity and presynaptic dopamine uptake in patients with Parkinson's disease and mild cognitive impairment. The Lancet Neurology 2012; 11: 679-687.

II. Ekman U, Eriksson J, Forsgren L, Domellöf ME, Elgh E, Lundquist A, Nyberg L. Longitudinal changes in task-evoked brain responses in Parkinson's disease patients with and without mild cognitive impairment. Frontiers in Neuroscience 2014; 8: article 207.

III. Domellöf ME, Forsgren L, Ekman U, Elgh E. Cognitive function in the early phase of Parkinson's disease, a five year follow up. Manuscript submitted for publication.

Introduction

Parkinson's disease (PD) is the most common form of Parkinsonism (1), and next to Alzheimer's disease (AD), PD is the second most common neurodegenerative disease (2). In the early 19th century Dr James Parkinson shed light on the characteristic motor symptoms when "An essay of the shaking palsy" was published (3). However, it was not until the early 20th century that mental disabilities in PD were reported for the first time, and in the 1970s dementia was part of the clinical considerations (4). The clinical knowledge of mental disabilities has thus increased, and cognitive impairment and depression are more commonly considered in the diagnostic procedure of PD. The development of cognitive dysfunction due to a neurodegenerative illness typically proceeds insidiously over several years, and the neuropathological changes precede the clinical symptoms (5). The therapeutic approaches in treatment of motor symptoms in PD are relatively successful in the early stages of the disease, but knowledge of the neuropathology underlying cognitive impairment remains insufficient with implications for the therapeutic approaches (6). Brain imaging techniques have proven useful to increase the knowledge of the specific neurochemical and neuropathological bases of cognitive impairment in PD. However, prospective cohort studies that aim to identify patients with PD at risk of severe cognitive impairment are lacking (7, 8). To distinguish between normal age-related cognitive decline and early signs of prodromal dementia is a great clinical challenge. The current thesis intends to present results from a prospective cohort study that explores how working memory-related neural correlates associate with cognitive decline in early PD, both cross-sectionally and longitudinally. The thesis studies were deliberated and conducted within the settings of a prospective population-based study.

Parkinson's disease

Epidemiology, aetiology, and neuropathology

Parkinsonism is an umbrella term for disorders with motor symptoms mimicking those occurring in PD. PD is the most common diagnosis within the Parkinsonism family. The prevalence of PD is approximately 160/100,000 in Western Europe (9); the crude annual incidence rate is up to 21/100,000 and the incidence increases with increasing age (10). The mean age at onset is around 70 years, and most studies find a higher frequency of PD in males than in females. With an ageing population, the neurodegenerative disorders are a challenging feature for the medical community (11). This is also true for PD because age is the dominant risk factor for development and progression of

the disease (12). However, the pathogenic mechanism in PD is not well understood, and older people without known neurological disease might also have mild Parkinsonian signs (MPS) (13). The causes of PD are divergent: mitochondrial dysfunction, oxidative stress, and misfolded (impaired functionality) proteins are proposed as central players (14). PD is a multisystem disorder marked by alpha-synuclein pathology that aggregates into Lewy bodies (LBs) in the somata of involved neurons (1). The pathological hallmark of PD is neurodegeneration within the substantia nigra pars compacta (SNc) in the midbrain, affecting the dopaminergic projections to the basal ganglia structures, especially the striatum (caudate nucleus and putamen). Dopamine concentrations in the striatum are markedly decreased, which leads to motor symptoms, and potentially to non-motor symptoms, as cognitive impairments. In cases of established PD, the cell loss in the SNc is approximately ten times greater than in normal ageing (15). The characteristic symptoms in PD have a long pre-symptomatic phase estimated to at least five years with an expected dopaminergic cell loss of at least 50% in the SNc (5). However, Braak and colleagues have suggested that the earliest documented changes in PD are observed in the lower brainstem in the dorsal motor nucleus, the pontine tegmentum/medulla oblongata, and in the olfactory bulb, and these changes occur in advance of changes in the nigra pathways and later in the neocortex (i.e., Braak stage 1-2; Figure 1) (16). First in stage 3-4 when the pathology evolves upward towards the basal, mid- and forebrain structures as SNc, Meynert's nucleus (cholinergic producing nuclei), and amygdala, the symptomatic phase begins. In the final stages (5-6), the LB lesions appear in the neocortex. There are currently no treatments that cure the underlying pathology that causes PD. However, pharmacological treatments in an attempt to decrease the motor symptoms are used. Most frequent are the dopaminergic agents, where levodopa (L-dopa) was the first available treatment of PD. L-dopa, the precursor of dopamine, passes through the blood brain barrier and bindes to dopaminergic neurons. Arvid Carlsson and colleagues were the first to show the role of dopamine (17), and that achievement rewarded Arvid Carlsson with the Nobel Prize in 2000. Other common drugs are dopamine agonists that act directly on dopamine receptors.
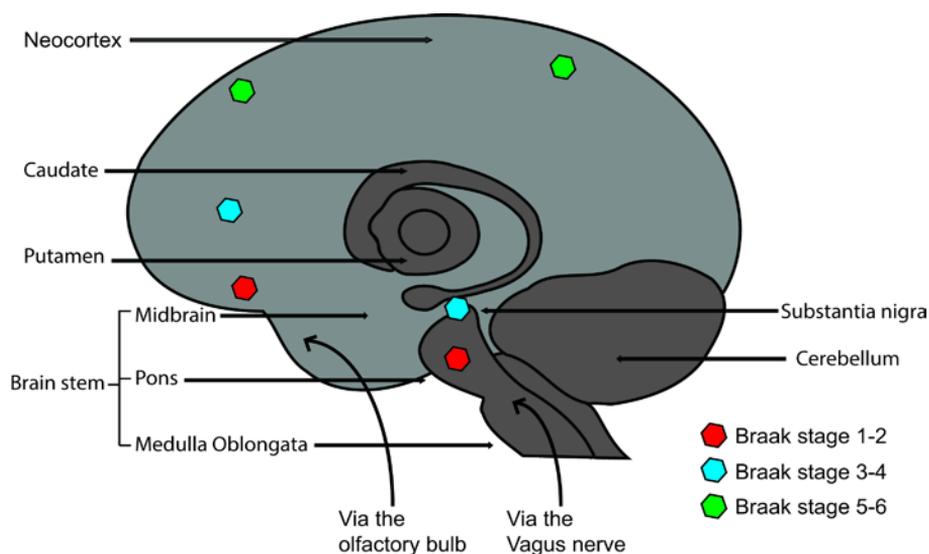
Figure 1. Neuropathological features of PD

According to Braak and colleagues the presymptomatic phase occurs when Lewy bodies appear in the brain stem (stages 1-2), the degeneration is severe in the substantia nigra (stages 3-4), and then the symptomatic phase begins. In the later stages of the disease, the neocortex is affected (stages 5-6).

PD diagnosis

James Parkinson identified six cases of whom he examined three, and the other three he observed on the streets of London (18). Essentially, the diagnosis of PD still remains a clinical one that relies on symptom observations, i.e., there are no biological markers, and the symptoms are followed during several years to increase certainty. Thus, there are limitations in the diagnostic procedure, and it has been suggested that a diagnostic accuracy of 90% might be the highest that can be expected using current diagnostic criteria (19). A clinical challenge is to differentiate the various forms of idiopathic (unknown causes) Parkinsonism, e.g. PD and the more atypical and less common forms: Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), Cortico-Basal Degeneration (CBD), and dementia with Lewy Bodies (DLB) (20). Because of the diverse profiles and variable expression of those affected with PD, the symptoms should be evaluated in the context of each patient's needs and goals (21). The clinical diagnoses in this thesis are based on the United Kingdom Parkinson's Disease Society Brain Bank (UK PDSBB) criteria, which are the most commonly used criteria for Parkinsonism (22). The criteria are divided into three steps. The first step is to diagnose the occurrence of the Parkinsonian syndrome where bradykinesia is required plus at least one of the following: rest tremor,

muscular rigidity, or postural instability. The additional steps assess exclusion criteria and supportive prospective positive criteria. Neuroimaging techniques might serve as supplementary tools. For example, a normal striatal uptake ^{123}I-N-(omega)-fluoropropyl-2-beta-carbomethoxy-3-beta-(4-iodophenyl) nortropane (^{123}I-FP-CIT) single photon emission computed tomography (SPECT) examination implies another underlying cause, without dopaminergic degeneration (i.e., SWEDDs = scans without evidence of dopaminergic deficits). MRI examinations are currently not a part of the clinical diagnostic procedures. However, some promise has been shown for detecting pathological changes in PD with diffusion imaging, T2* relaxometry of iron accumulate in SN, structural MRI, and resting-state fMRI to access the anatomical and functional connectivity changes in PD (23).

Motor symptoms

There are four cardinal motor symptoms in the early phases of PD. First, bradykinesia, which implies a slowness of initiation of voluntary movement with progressive reduction in speed (manifest bradykinesia is necessary for PD diagnosis (22). This is followed by muscular rigidity (causing stiffness of the limbs, neck or trunk), rest tremor (shaking or oscillating movement), and finally postural instability and gait disturbances (impaired balance and coordination when standing upright). Secondary motor symptoms in PD that might appear are: micrographia (shrinkage in handwriting), unwanted accelerations (movements that are too quick), dysarthria (impaired articulatory ability), flexed posture, etc. (see Table 1 for an overview of common symptoms).

Several rating scales are used to evaluate motor impairments and disabilities in patients with PD. The Unified Parkinson's Disease Rating scale (UPDRS) and the modified Hoehn and Yahr scale (HY) are two of the most well established rating scales (24, 25). The HY scale is used to describe and stage patients in their current level of motor function. The HY scale consists of five stages in the original form, and seven stages in the modified scale. The first stage is restricted to unilateral PD symptoms whereas the last stage represents severe motor dysfunction, e.g., wheelchair- or bed-bound. The UPDRS has a moderate-to-good reliability and validity (26), and consists of four subscales aimed at assessing: I: non-motor experiences, II: motor experiences of daily living, III: motor examination, and IV: motor complications. The UPDRS-III subscale is used as a covariate in the fMRI analyses to control for inter-individual motor variability.

Non-motor symptoms

Patients with PD have a pre-clinical phase (i.e., before severe SNc impairment, Braak stage 3) during which non-motor symptoms such as depression, olfactory impairments, and autonomic dysfunction might precede the motor symptoms (27) (see Table 1 for an overview of common non-motor symptoms). Depression and other non-motor symptoms are common in PD, and a systematic review shows that minor depression frequently occurs in 22% and major depression in 17% of patients with PD (28). The equivalent level of depression in a normal healthy population, without differentiating between minor and major depression, is approximately 10-12% (29). It is important to consider mood states (e.g., depression) in studies of cognitive status (30), and groups should be well matched in that respect. Cognitive impairments are one of the most common non-motor aspects of PD, and cognitive impairments are frequently present already in the early phases of PD (31). The focus of the current thesis is on the clinical manifestations of early cognitive impairments in PD, and their relation to brain responses. In clinical settings the classifications of cognitive impairments usually ranges from mild cognitive impairment (MCI) to Parkinson's disease dementia (PDD).

Table 1. Overview of common PD symptoms

Motor symptoms	Non-motor symptoms
Bradykinesia, tremor, rigidity, postural instability	Cognitive impairments
Micrographia, dysarthria	Depression, fatigue, behavioural problems
Difficulty rising from chair, turning in bed	Sensory symptoms (as pain) and olfactory impairment
Cutting food, hygiene, feeding	Abnormal sweating, weight loss, constipation, urinary and sexual dysfunction
Abnormal postures, scoliosis, striatal deformity	Sleep disorders

Clinical considerations of cognitive impairments in PD

Mild cognitive impairment in Parkinson's disease

The concept of MCI was initially developed as a prodrome for persons at risk of Alzheimer's disease (AD) (32), and the concept has shown to be useful both clinically, and as a research entity. The MCI concept is generally considered as a transitional zone between those with normal cognitive function and those with probable dementia (normal distribution; Figure 2). Importantly, when persons with MCI are followed across time, some progress to dementia, but some are stable or even recover to their former cognitive status (33), which implies a heterogeneous aetiology. The prevalence rate for MCI in an elderly (60 to 76-year old) population (n = 1,150) was 5.3% (34). The equivalent prevalence rate of MCI in patients diagnosed with early PD ranged from 20 to 40% (mean: 67.5 years) (35), and the risk of developing PDD is greatly increased for patients with PD-MCI relative to patients without MCI (36). Thus, many patients with PD exhibit cognitive impairment during the major part of their disease. Historically, there has been a large heterogeneity in the definition of MCI in PD (37), and due to the broad spectrum of cognitive impairments in PD, the Movement Disorder Society commissioned a Task Force that recently proposed a uniform definition of PD-MCI (37). The aim was to enable the identification of the earliest stage of cognitive impairments in PD. These criteria were published just in time for Study I in this thesis, and they are also assessed in Studies II and III (see Materials and Methods for the classification procedure). A recent study examined the prevalence and longitudinal development of newly diagnosed patients with PD-MCI (assessed with the new consensus criteria). That study revealed that the initial PD-MCI prevalence of 35% had increased to 50% after five years (38). In addition, another study revealed that more than 25% of newly diagnosed patients with PD-MCI developed PDD within three years (39). Importantly, the predicitive value of PD-MCI in respect of PDD development was fairly good already at the basline examinaion (27.8%), with a sensitivity of 90.9% and a specificity of 84.2%. In Study III, the aim was partly to evaluate the predictive value of PD-MCI (assessed with the new criteria) in respect to prodromal PDD, and to identiy clinical variables that predict evolving PDD.
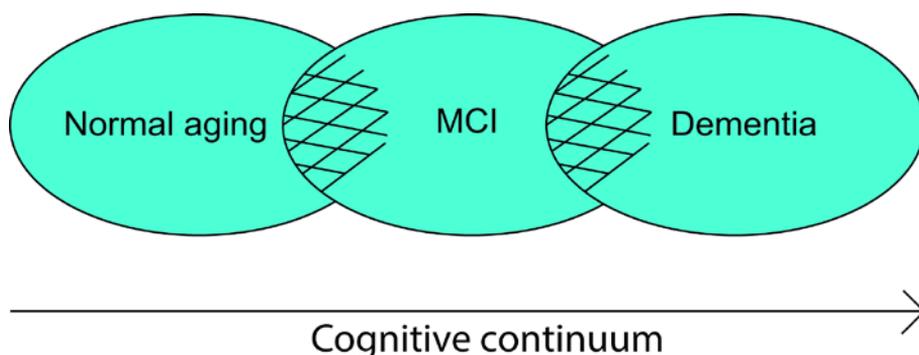
Figure 2. Overview of the translational stage between the cognitive changes of aging and dementia. MCI = mild cognitive impairment.

Parkinson's disease dementia

PDD has marked negative effects on patients' welfare and increases the burden on care-givers (40). Patients with PD have approximately a six-fold increased risk of developing dementia compared with healthy age-matched individuals (36), and as described above, PD-MCI is a strong predictor of PDD (39). In the mid 80s it was reported that 15 to 20% of patients with PD developed PDD. Lately, it has been proposed that in the long term, PDD can occur in up to 80% of the patients with PD (41). Thus, clinicians have to consider the aetiology and the profile of the cognitive impairments and then approach several questions. Clinicians have to consider if the cognitive impairments are age-related decline, PD-MCI, PDD, or other possible factors, e.g., mood disturbances, which might affect cognition. It is also important to assess if medication and/or deep brain stimulation (DBS) might have a negative effect on cognition (42). Furthermore, a clinician must consider the premorbid level of cognitive functioning, and assess if any change from that baseline level occurs across time. In addition, it is important to consider if subjective cognitive complaints are related to objective cognitive measures or not. A thorough case history is important and contributes significantly in that respect. Alzheimer's disease (AD) is the most common dementia characterised by severe (43) memory loss, and the incidence rate of PDD is approximately one-tenth that of AD (44). However, neuropathological similarities between PDD and AD have been reported (45), and global cognitive decline in PDD has been related to early-phase atrophy in the temporal cortex (especially in the hippocampus) (43), and β-amyloid (a hallmark neuropathology of AD) reductions in CSF (46, 47). In addition, PDD and dementia with Lewy Bodies (DLB) share significant cognitive symptomatology and alpha-synuclein pathophysiology to a greater extent than AD. One of the major clinical challenges is to differentiate between the two

dementias, and to set reliable diagnoses. The time course of the symptoms is critical, and PDD should be diagnosed when PD is established (i.e., at least one year before PDD onset). In contrast, DLB should be diagnosed when dementia symptoms occur prior to or during the first year following the onset of motor symptoms (48). It is also important to determine if cerebrovascular pathology contributes to the observed symptoms. MRI scanning has the potential to provide additional information in that respect. See Materials and Methods for the classification procedure for PDD in the current thesis.

Cognitive impairments in PD

Contrary to James Parkinson's narrative "the senses and intellects being uninjured", J-M Charcot emphasised about 50 years later that "the mind becomes clouded and the memory is lost" in PD (49). Cognitive impairment is indeed common in PD, and the cognitive problems usually affect quality of life to a great extent (50). In addition, cognitive impairments in PD also increase health-related costs (51), caregiver burden, and hospital stays (52). Despite Charcot's considerations, PD is still primarily described as a movement disorder and only approximately 25% of patients with dementia are recognised by clinicians in routine care (53). In addition, extensive research on cognitive impairments in PD has only been ongoing for about two decades (54). PD is a perfect example of an age-related disease, as ageing is probably the main risk-factor for development and progression of PD (12). Cognitive decline is a common effect of ageing. Age-related cognitive decline affects perceptual speed and visuospatial ability (55, 56), although the greatest degree of age-related decline might be related to episodic memory and working memory (57, 58). Importantly, there is a substantial heterogeneity in the aging population, in which some individuals remain stable in their cognitive status whereas others decline substantially (59). The prevalence of cognitive impairment (without dementia) in large-scale cohort studies (n > 1,800) is between 10.7 and 16.8% (age > 65 years) (60, 61). The equivalent number for dementia (including all types of dementia) in a systematic review is between 5 and 7% for individuals older than 60 years (62). Thus, age-related cognitive decline is common, but additional development of PD might add to age-related decline with more severe cognitive decline as a consequence (see also MCI and PDD sections on this matter). For example, patients just diagnosed with PD have a twofold increased risk for development of MCI relative to healthy age-matched individuals (63). The cognitive impairments in PD are heterogeneous and are commonly reported early in the course of PD in relation to episodic memory, visuospatial functions, executive functions, attention, and working memory (48, 64, 65). Patients with early-phase PD generally have similar cognitive symptoms to those with frontal lobe lesions

(66). These alterations probably relate to dopamine depletions that severely affect the cortico-striatal connectivity (67). The early cognitive impairments are broadly related to fronto-striatal catecholaminergic dysmodulation (primarily dopaminergic dysmodulation), and include deficits on tests of planning (68), response inhibition (69), attentional set-shifting (70), and working memory (71). Bradyphrenia is also common and refers to impaired attention and vigilance that results in slowness of thought (72). However, although cognitive impairments with a fronto-striatal basis have been proposed as a prodrome to PDD (73), posterior cortical (parietal, temporal and/or occipital circuitry) AD-like alterations might evolve across time in parallel and/or in addition (74). The posterior cortical alterations are to a larger degree associated with tests of visuospatial/visuo-constructive abilities, semantic word fluency (75), and episodic memory, and are pathologically associated with the number of cortical LBs (76), cholinergic degeneration (77), and cortical amyloid-β (45). However, cognitive impairments in executive functions, attention, and working memory are often described as dominating the cognitive profile in early-phase PD (78). Thus, working memory processing provides a perfect model for investigating PD-related cognitive impairments due to its reliance on dopamine transmission. Consequently, because the overall aim of the Newly Parkinsonism in Umeå (NYPUM) project is to assess newly diagnosed patients with PD and increase knowledge of prognostic information, the main focus of this thesis is to examine brain responses during a demanding working-memory updating task (fMRI) in relation to cognitive impairment in PD.

The Working memory concept

Potentially, a memory can be retained for a couple of seconds or throughout a life-time. In 1890, William James postulated the theory of fractionating cognitive abilities into separate distinct systems (79). In line with that postulation, the theoretical distinction between different memory systems has been a hot topic (see Figure 3). The concept of working memory essentially refers to brain systems that temporarily store and manipulate information that is necessary for a complex cognitive task (80). Working memory supports or aids fulfillment of goal-directed behaviour, in relation to motor systems, sensory systems, and other cognitive systems. Baddeley proposed a domain-general control mechanism in his working-memory model called the central executive that comprises an attentional controller (81). The enduring and influential multicomponent working memory model comprises three temporary holding stores that are regulated by the supervisory central executive system (i.e., referred to as executive functions; see Figure 3). Lately, large-scale network models with high levels of interactions between

perceptual (posterior mediated) and executive (frontal mediated) cortical hierarchies have been proposed to regulate working memory (82). In addition, state-based conceptual models have been developed, which suggest that working memory relates to different states of activation via attentional systems for representations of information to be held in the working memory. Oberauer proposes three states of representations in working memory (83): (I) An activated part of long-term memory, which includes representations that are easy to retrieve, but not currently in the central part of working memory, (II) A region of direct access, which represents a set of items and their relations, and which has a restricted capacity, and (III) Focus of attention, which represents one or more items that are held in the direct-access region. The working memory models and landmarks in cognitive neuroscience have shown that long-term memory processes also engage similar regions that previously were thought to be specific for working memory and executive control (84).
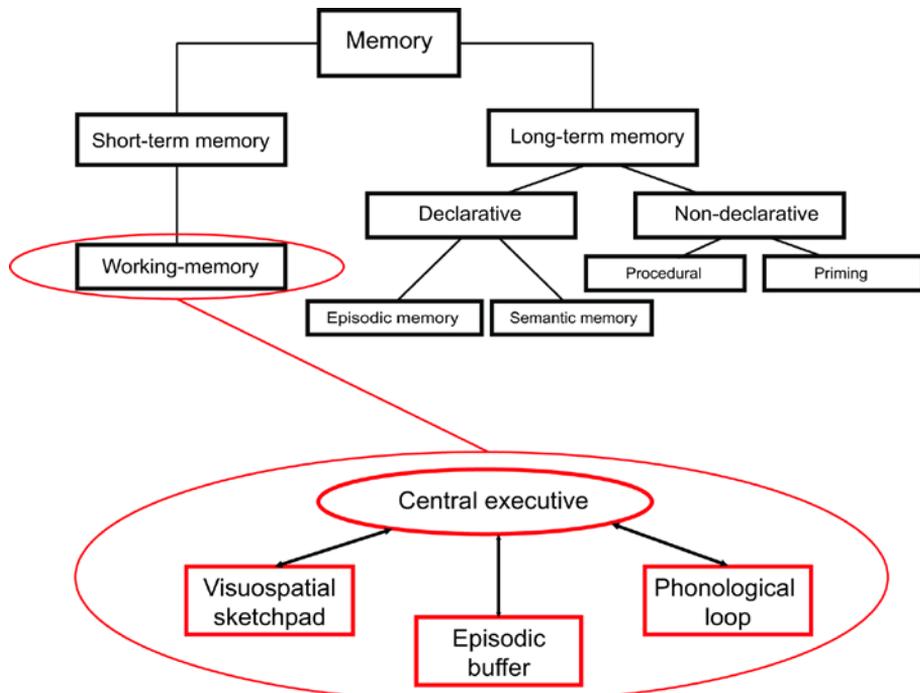
Figure 3. Overview of commonly proposed memory systems
Declarative memory = explicit memories ("knowing what") such as facts and events. Non-declarative memories = implicit memories such as skill knowledge (procedural) and increased sensitivity to certain stimuli due to prior experience (priming). Episodic memories = memories that relate to personal experiences in time. Semantic memory = memories that relate to general facts and knowledge. Central executive = a supervisory system that regulates and allocates information to subsystems.

Visuospatial sketchpad = a system that processes visual information. Episodic buffer = a system that temporarily links information from long-term memory and subsystems. Phonological loop = a system that processes auditory information. The figure is inspired by Tulving (85), and Baddeley (80).

Executive mechanisms, such as focusing attention, task management, encoding, monitoring/updating, inhibition, and planning, rely on efficient working memory processing, and these mechanisms are primarily mediated by the prefrontal cortex (PFC) (86). However, there have been reflections if executive functions can be considered as unitary or not (i.e., if they have the same underlying mechanism or ability) (87). Miyake and colleagues found evidence that three commonly proposed executive functions (information updating, mental set shifting, and inhibition of prepotent responses) are moderately correlated with one another, but are also clearly separable (88). The authors speculate that the reported commonality between the executive control functions is related to control processes that keep important task-relevant material active in the working memory. Thus, cognitive control seems to be important in regulating information flow and attention in working memory. Both active maintenance and manipulation of working memory require cognitive control that regulates a dynamic balance between stability and flexibility. The physiological basis for working memory is complex and is a challenge for cognitive neuroscience. High levels of dopamine in the PFC are important for attention stability (tonic dopamine release) (89), whereas high levels of dopamine in the striatum seem to be more important for attention flexibility (phasic dopamine release), as during working-memory updating (90), and planning of self-generated novel responses (91). Generally, the PFC interacts with the rest of the brain, and working memory capacity and active maintenance are related to fronto-parietal neural networks (89, 92–94) rather than striatal networks. In contrast, more executively demanding (cognitive control) working-memory updating involves fronto-striatal neural networks to a larger extent (95, 96). In accordance, computational models have demonstrated that the basal ganglia regions can perform dynamic adaptive gating and allow task-relevant information to be maintained in the PFC. The basal ganglia can also inhibit task-irrelevant information, such as during updating (96). Potentially, this might happen when Go neurons in the dorsal striatum fire and inhibit SN pars reticulata and consequently disinhibit the PFC. This may be the reason for the gating modulation that prompts representations in PFC and results in onset of working-memory updating (97). The fronto-striatal dopaminergic depletions are strongly associated with impairments in working memory function in early phase PD (98), and thus motivate the chosen in-scanner working-memory updating task. See Figure 4 for an overview on proposed executive control on working-memory updating.
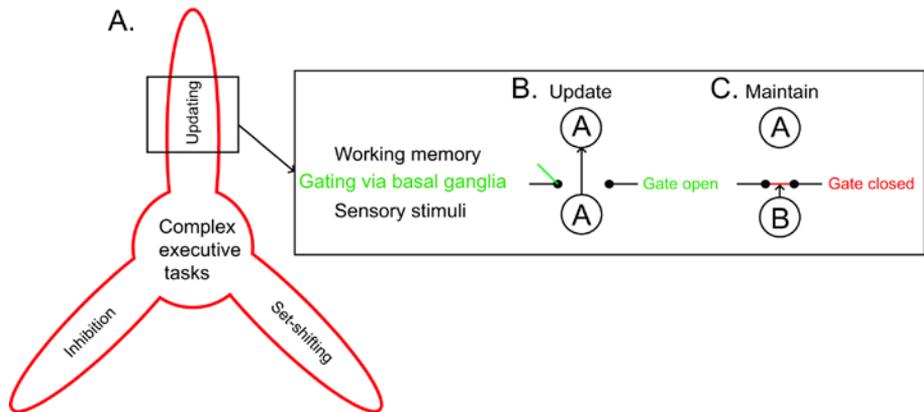
Figure 4. Overview of executive control on working-memory maintenance and updating

(A) Three executive control functions that are moderately correlated. However, they are also clearly separable. (B) During working-memory updating, there is a possibility for sensory and memory information to rapidly update when the gate is open. (C) However, when the gate is closed, no interfering sensory information can potentially interfere with the working-memory maintenance of previously stored information. The figure is inspired by Miyake et al. (88), and Hazy et al. (97).

Brain imaging of cognitive impairments in PD

Modern imaging techniques that examine anatomical changes or monitor brain responses during cognitive operations have significantly contributed to the emergence of the discipline of cognitive neuroscience (see methods for further information on brain imaging methodology). In PD, neuroimaging has provided advances in the understanding of cognitive impairment and its neural correlates. The traditional model of nigro-striatal dopamine depletion has been extended to also involve other dopaminergic pathways, and also non-dopaminergic systems. Broadly, a dual syndrome hypothesis has recently been proposed that associates cognitive impairments in PD to two main syndromes (99, 100). First, a dopamine-modulated fronto-striatal syndrome, and second, a syndrome with a more posterior cortical basis that might relate to increased LB formation and AD-like pathology. Here, a review of cognitive impairments in PD and its neural correlates is surveyed. Structural (anatomical) changes in PD have been related to cognitive impairment to a large extent. Gray matter atrophy has been reported in early diagnosed patients with PD-MCI relative to patients without MCI in both anterior and posterior cortical regions (101). Significant cortical thinning has been observed in patients with PD-MCI relative to patients without MCI, in regions within

temporo-occipito-parietal circuits (102, 103), but also in subcortical regions (103,104), and the PFC (105). Thus, even though gray matter atrophy has been reported in patients with PD-MCI, it is commonly exhibited to a far lesser extent than in patients with PDD (106). Atrophy in fronto-temporal cortices might be greater in patients with PDD than patients with PD, with and without MCI (105, 107). The aetiology of PDD is related to complex neurochemical and cognitive dysfunction (108). Indeed, there are similarities in neuropathology between PDD and AD, and global cognitive decline has been related to atrophy in the temporo-parietal cortex and the hippocampus (43), and related to β-amyloid reductions in CSF (46, 47). In addition, cholinesterase inhibitors are often prescribed to patients with PDD, which might enhance cognitive functions in PDD (109). However, patients with PDD might exhibit greater levels of behavioural disturbances, sleep disturbances, and cognitive fluctuation disturbances than patients with AD (110). In addition, patients with PDD and DLB commonly have a similar distribution within subcortical executive and attentional-dominant cognitive profiles (111). Thus, in that respect, the PDD symptomatology is more in keeping with LBD pathology. In accordance, no volumetric differences were observed when patients with PDD were compared with patients with DLB (112). However, although similarities are evident, another study has shown that the underlying neuropathology between DLB and PDD might differ with more severe posterior cortical atrophy in patients with DLB (113). All in all, a combination of DLB and AD pathologies seems to be a pathological correlate of PDD (45).

Functional (i.e., physiological changes) brain imaging techniques give an opportunity to increase the understanding of how the brain produces and organizes cognition. The core pathology in PD is degeneration of dopaminergic cells in the midbrain, which severely affects the striatal depletion due to the high density of D_2 receptors (phasic-mediated) in the striatum (114). Traditionally, the basal ganglia have been viewed as a nucleus that is primarily involved in control of movements. However, many lines of evidence have shown that the basal ganglia contribute to non-motor functions, such as cognition (115). The cognitive dopamine-related impairments in PD are commonly related to the striatum, and to a larger degree to the caudate rather than to the putamen (116, 117). The head of the dorsal caudate nucleus is one of the main output targets of the dopaminergic nigro-striatal transmission (118), and the dorsal caudate is strongly connected to the dorsal parts of the PFC. In addition, the ventral tegmental area (VTA) projects its dopamine directly to several cortical regions (mainly to pre-frontal cortex with predominantly tonic-mediated D_1 receptors) directly via the meso-cortical pathways, or indirectly via the meso-limbic pathways that project their dopamine to the ventral striatum (119, 120). However, the ventral striatum is

proposed to be relatively intact in early-phase PD in respect to dopaminergic function relative to the dorsal counterpart (121). Cognitive impairment have been related to striato-thalamo-prefrontal alterations as the basis for executive dysfunction and working memory failure (73, 122, 123), and hypo-metabolism in the right DLPFC has been related to altered attentional set-shifting in patients with PD (124). Recently, a resting state fMRI study reported that executive impairments in PD are associated with an imbalance between cortical (mainly fronto-parietal) and subcortical processing at rest (125). However, although the nigro-striatal dopaminergic substrate is important for cognitive performance in PD, the degree of striatal involvement seems to be critical for corresponding PFC activation (i.e., significant involvement of the caudate nucleus is associated with reduced responses in the PFC) (126). In vivo studies of patients with PD support the computational models described above (Figure 3), by suggesting a profound role of the striatal dopamine-dependent basal ganglia in working-memory updating (127). In contrast, functional changes have also been related to increased frontal cortical working-memory activation during hypo-dopaminergic states (128). The author's interpretation was that working memory is primarily mediated via the meso-cortical pathways, rather than via the nigro-striatal-thalamo-cortical pathways. Thus, a complex deficient interplay between the nigro-striatal and meso-cortical dopaminergic pathways might be related to executive impairments in PD (126). Previous research have reported that patients with PD commonly exhibit altered brain responses relative to age-matched healthy individuals during working memory processes. Patients with PD are generally more impaired at manipulation of information that requires larger executive demands than during maintenance of information relative to healthy individuals (98). The working-memory related brain alterations in PD during manipulation of information have been related to updating (71, 128), inhibition (69), planning and executing set shift (70, 126). However, the observed differences between patients with PD and healthy individuals could potentially have been driven by patients with cognitive impairments, because it is common to exclude MCI individuals in control groups (30). Functional changes have also been related to evolving glucose metabolism decline within cognitive networks of prefrontal- and parietal cortices in patients with PD (129, 130). Those findings are partly in keeping with suggestions that tests probing posterior cortical function rather than tests probing fronto-striatal cortical function have been demonstrated to enhance predictions of PDD (131). In keeping with that postulation, activity in the cholinergic system with projections from the substantia innominate (SI) correlates with cognitive status, and the SI is more atrophied in patients with PD with cognitive impairments than un-impaired patients (132). In addition, decreased fractional anisotropy in posterior cortical white-matter tracts is associated with cognitive impairment in PD (133), as well as abnormalities in frontal and inter-

hemispheric white-matter connections (134). Importantly, the number of studies that examine specific task-evoked brain responses (with fMRI) in relation to cognitive impairments in PD are limited. Lewis and colleagues observed fronto-striatal phasic hypo-activity in patients with executive impairments during working-memory manipulation relative to non-impaired patients (135). That was the first time that fMRI was used to identify how executive impairments in PD are related to task-evoked neural correlates. In addition, Nagano-Saito and colleagues recently showed that PD patients with MCI during planning of set shift (a computerised Wisconsin Card Sorting Task) had lower BOLD signal responses than patients without MCI in cognitive loops of PFC and caudate, but also in motor-related regions during the execution phase of the task (136). Thus, although studies have considered how PD-related cognitive status is related to its neural correlates, those studies mainly assess the brain's structure or conditions in which direct sensory input is not considered. Thus, there is a shortage of studies that relate cognitive impairments in PD (assessed with the Movement Disorder Societies consensus criteria) with task-evoked brain responses (e.g., working-memory updating), and the current thesis aims to increase knowledge in that respect.

Aims

Cognitive impairments in executive functions, attention, and working memory are often described as dominating the cognitive profile in early-phase PD. However, the reviewed material (described above) revealed a lack of population-based studies that assess task-evoked brain responses in cognitively impaired patients with PD, especially with a longitudinal perspective. Importantly, working memory processing provides a perfect model for investigating PD-related cognitive impairments due to its reliance on dopamine transmission. Therefore, the overall aim of this thesis was to increase knowledge of the neuropathology underlying cognitive impairment in patients with PD during working memory processing. The thesis studies were deliberated and conducted within the settings of a prospective population-based study – The NYPUM project. The specific aims of the thesis where:

I.   To examine if working memory related brain responses in patients with PD, compared with age-matched healthy individuals, showed the same patterns as previously suggested. In addition, to cross-sectionally examine if working-memory related brain responses (fMRI), and dopamine striatal integrity (SPECT) differs between newly diagnosed drug-naïve patients with PD, with and without MCI (Study I).

II. To longitudinally (at baseline and at a 12-month follow-up) examine working memory related brain responses (fMRI) in an attempt to detect brain changes across time between patients with PD, with and without MCI (Study II).

III. To prospectively evaluate the frequency of PD-MCI at baseline examination, and determine the predictive value of PD-MCI in respect to prodromal PDD. An additional aim was to evaluate if certain cognitive measures were more sensitive in predicting prodromal PDD (Study III).

Materials and methods

Study population

All patients in the current thesis were recruited within the frame of the NYPUM (New Parkinsonism in Umeå) project, which is a prospective population-based cohort study of incident patients with idiopathic (unknown pathogenesis) Parkinsonism (10). The overall aim of the NYPUM project was to study new cases with idiopathic parkinsonism to increase knowledge about prognostic information, physiological and cognitive disease mechanisms, and diagnostic accuracy. Between January 1, 2004, and April 2009, all physicians in the Umeå catchment area (approximately 142,000 inhabitants) were asked to refer all patients with suspected parkinsonism to the Department of Neurology at Umeå University. All referred patients underwent a standardised clinical examination by a neurologist specialised in movement disorders, and repeatedly followed-up (up to 96 months). Presynaptic dopamine integrity was examined (see SPECT section below in the Material and Methods).

Healthy age- and sex-matched control individuals were included (Study I). Thirty control individuals were recruited via advertisements in the local newspaper and matched with the first 50 patients included in the NYPUM study. The included control individuals had no history of neurological disorders, a normal neurological examination, and a normal dopamine uptake (^{123}I-FP-CIT; see SPECT section). Flow charts of the study profiles for the respective studies are presented in the articles. The thesis studies were approved by the Ethics Committee of the Faculty of Medicine at Umeå University. Written informed consent was obtained from all participants before inclusion in the studies.

PD-diagnosis, inclusion, and exclusion

Only patients who fulfilled the UK PDSBB criteria for PD (definite or probable PD) were included in the current thesis. Patients were classified as definite PD when they had at least three supportive criteria, and as probable PD when they had only 1 or 2 supportive criteria. The diagnoses were reassessed and confirmed at the latest available follow-up in relation to the specific study. Patients with atypical Parkinsonism (i.e., MSA, PSP, CBD, and DLB) were not included.

General inclusion criteria in the NYPUM project

- Idiopathic parkinsonism
- Resident within the Umeå catchment area
- Informed consent for participation in the NYPUM project

General exclusion criteria in the NYPUM project

- A Mini Mental state examination (MMSE) score below 24 at the baseline examination that might indicate dementia
- Secondary parkinsonism
- Reluctance to participate

Neuropsychological examination and diagnostic criteria

Cognitive status was examined at the time of inclusion (baseline = approximately 1-2 months after PD-diagnosis), and after 12, 36, and 60 months. The neuropsychological test procedures were conducted by a clinical psychologist or by a trained research assistant who had a background in neurosciences and/or psychology, and the research assistant was supervised by the clinical psychologist. All test leaders were thoroughly trained in advance of their first testing. The order in which the tests were administered was similar for all patients and all occasions, and the tests were conducted according to the test manuals' standardised protocols. The included cognitive tests were chosen to minimise the effect of repeated testing, e.g. by using parallel versions. The complete test procedure took approximately two hours.

Neuropsychological test battery

The neuropsychological tests were chosen to assess aspects of episodic memory, working memory/attention, executive functions, visuospatial functions, and language (64). Only test measures with good psychometric properties and large-scale age-matched norms were included in the assessment of MCI (see Table 2).

Table 2. Neuropsychological tests used for classifying MCI.

Cognitive domain	Neuropsychological assessments
Episodic memory	BVMT free recall BVMT delayed recall FCSRT free recall
Working memory/attention	TMT B Digit Span backwards
Executive functions	Animal fluency WCST total errors WCST perseverative responses
Language	Boston naming test
Visuospatial functions	The Benton Judgment of Line orientation. (Pentagon copying from MMSE in Study III)

BVMT = brief visuospatial memory test. FCSRT = free and cued selective reminding test. TMT B = trail making test version B. WCST = Wisconsin card sorting test. MMSE = Mini mental state examination.

Criteria for PD-MCI

The Movement Disorders Society (MDS) Task Force criteria for PD-MCI were used, and these define the syndrome by clinical, cognitive, and functional criteria (37). The criteria utilize a two-level operational schema depending on the comprehensiveness of the neuropsychological testing. In brief, the diagnosis of PD must be established, and the cognitive impairment should not interfere significantly with functional independence (for example: management of finances, and household tasks). Cognitive impairments should be observed on neuropsychological testing, and cognitive decline may be reported either by the patient, the informant (for example: partner or colleague), and/or clinician. Level I and level II criteria differ in respect to methods of assessment, and level I criteria provide less certainty than level II. For the classification of PD-MCI by level II criteria the Task Force recommends at least two cognitive tests within a single cognitive domain, and at least two test measures should be impaired, either within a single domain or across different cognitive domains. The cut-off should be 1 to 2 standard deviations below the age, education, and gender norms, or a significant decline from estimated premorbid abilities. In the current thesis, patients that scored ≥ 1.5 SDs (commonly accepted in clinical practice) below the normative age-matched mean value in at least two cognitive test measures were classified as having MCI. Because only one cognitive measure was assessed in the language and visuospatial domains, and no subjective cognitive measures were used, the level I criteria were applied in Studies I and

II. This was motivated because there was a great discrepancy between the objective cognitive measures and the patients' subjective reports, and the relatively small sample sizes prevented a more conservative approach (35). The discrepancy between objective and subjective measures might reflect different mood states within each diagnosis group or different rates of disease progression (28). Thus, subjective measures were only used for assessing PDD in Studies I and II (where the subjective and objective measure converged to a larger extent). However, subjective complaints were considered in Study III. Study III had a significantly larger sample size than those of Studies I and II and allowed for the use of more conservative criteria, which might have provided a better estimate in respect of prodromal PDD. In a recent study, the authors eliminated the necessity to have subjective cognitive impairment which led to a small increase in the frequency of PD-MCI (from 33% to 41%) (137). Subjective cognitive complaints were gathered via a short questionnaire given to the patient and/or relative at study enrolment, questions on cognitive status at the neuropsychological test occasions, and the Parkinson's disease Questionnaire 39 (PDQ 39). In addition, in time for Study III, the Pentagon coping from Mini Mental State Examination (MMSE) test was included in the visuospatial domain, and two cognitive measures were thus included in that domain. Participants were excluded if they had a major depression that might have affected their cognitive ability. If the participants had a rating score > 17 on the Montgomery and Åsberg Depression Rating Scale they were excluded (138).

Criteria for PDD

The MDS-commissioned task force criteria for dementia in PD were used in the current thesis for exclusions (Studies 1-2) and inclusions (Study 3) (48). The core features are a manifest PD diagnosis (according to UK PDSBB), impairments in more than one cognitive domain, a decline from premorbid level, and deficits severe enough to impair activities of daily life. Furthermore, a substantial decline on objective measures was required with impairments in at least two cognitive domains with performances ≥ 2 SDs below normative age-matched t-values. See criteria for PD-MCI section on how assessment of subjective cognitive measures were performed. The one-year rule was applied to exclude dementia of Lewy Body (DLB) type (i.e., the diagnosis of DLB precedes and coincides within one year of the development of motor symptoms).

Brain imaging

Brain imaging has become an increasingly important tool both in neuroscience research and in clinical settings. Brain imaging techniques have provided

increased understanding of physiological and biochemical processes, but also of the neural basis involved in cognitive processes. The imaging concept includes several techniques with different potentials: nuclear medicine imaging methods such as positron emission tomography (PET), and single photon emission computed tomography (SPECT) provide information on molecular functioning (metabolism) that are traced by emitted radiation. Both techniques have good spatial resolution, however PET has a higher resolution than SPECT. Two non-invasive techniques that measure voltage changes or magnetic fields are Electroencephalography (EEG), and magnetoencephalography (MEG), respectively. However, although MEG has better spatial resolution than EEG, the spatial resolution is generally relatively poor. In contrast, the temporal resolution is great in both techniques (milliseconds). Examinations with a magnetic resonance imaging (MRI) scanner enable examinations of brain structures, but also functional brain activations (i.e., functional MRI: fMRI). The MRI-technique provides excellent spatial resolution (down to 1 millimeter), but poorer temporal resolution (a few seconds). The current thesis relies on functional brain data collected with fMRI, and in Study 1, there were additional striatal presynaptic dopamine SPECT data (see below).

MRI

MRI relies on the concept that hydrogen atoms behave like small magnets. When the participant lies in the strong electromagnetic field many of the hydrogen nuclei (mostly in water molecules) align with the electromagnetic field. However, a radio frequency magnetic pulse redirects the alignment. When the hydrogen atoms return to their former positions (relaxation), they emit a weak magnetic radiation that the MR scanner can detect. Different relaxation times are applied, and those times depend on the characteristics of the tissue; the transverse relaxation (T2) is faster than the longitudinal relaxation (T1) (139). Both sequences are used in clinical settings where images are evaluated and contribute to diagnostic considerations (140). Whereas structural MRI (especially with T1 relaxation) distinguishes between different types of tissues, fMRI distinguishes between different levels of metabolic activity, blood perfusion, blood volume, and changes in blood oxygenation (see below regarding BOLD). fMRI is a neuroimaging method that is used to relate functional activation in regions/networks to different cognitive functions (task conditions). In an fMRI experiment, the in-scanner task shifts between two or more conditions (for example: task condition vs. baseline rest condition) that the participant solve while images is rapidly acquired. The observed brain changes are then correlated with the known time course of the task, which enables interpretations of task-evoked brain responses (141). The T2* pulse sequence (fast relaxation) is most commonly

used, and provides a good signal-to-noise ratio (SNR), and covers the whole brain in about 2 seconds (142).

BOLD signal

Much of the work in the fMRI field uses the blood-oxygen-level-dependent (BOLD) signal as a dependent measure (143). Whereas structural MRI distinguishes between different types of tissues, fMRI BOLD distinguishes between different levels of metabolic activity, changes in blood oxygenation, and changes in perfusion. When neural tissue becomes active, such as during cognitive operations, changes in the local blood flow occur to accommodate the metabolic demands. As a result, an increase of oxygenated blood indicates that the tissue is active. By using a gradient echo (GE) imaging sequence, it is possible to detect the paramagnetic state of deoxygenated hemoglobin (144). Oxygenated hemoglobin and deoxygenated hemoglobin have different magnetic exposure. Deoxygenated hemoglobin has a higher magnetic decay rate than oxygenated hemoglobin, and those differences can be detected by the fMRI scanner. The temporal shape of a BOLD signal response depends on factors such as blood volume, blood flow, and oxygenation state. The BOLD signal peaks approximately 4-5 seconds after task-stimulation, and returns to baseline level after approximately 10 additional seconds, followed by a 10 second undershoot (145). Importantly, because the causal relationship between BOLD signal and neural activity is unclear, it is not possible to make conclusions on the neural activity per se, and this is the main critique against fMRI. However, it is relatively established that the BOLD signal change is strongly related to neural activity. The BOLD signal might reflect synaptic activity to a higher degree than neural spiking (142).

Imaging examination and data management

Scanners and data acquisition

The fMRI acquisition was conducted on two different scanners: A 1.5T Philips Intera scanner and a 3T Philips Achieva scanner (both scanners from Philips Medical Systems, the Netherlands). T refers to Tesla, which is the measure for magnetic induction. Information on scanner acquisition parameters, preprocessing, and first-level analyses are detailed in the articles.

At the initiation of the NYPUM project (2004), the aim was to address several hypotheses regarding brain function in patients with PD. Specifically, the long and irregular inter-stimulus interval for the 1.5T scanner was to enable a separation between transient and sustained brain activity (71), whereas other issues are addressed with the 3T protocol. In the current thesis the aim was to maximize the number of patients with MCI, and therefore data was used from both scanners.

Because data acquisition was conducted on two different scanners, it was important to determine if confounding effects from scanners would overlap the effects of interest. Therefore, in all studies, the model estimations from each individual were input into a second-level group-by-scanner factorial analysis (146). Motor scores (UPDRS III) from each individual were also included as a covariate in each model due to group differences. The study design made it possible to conduct post-hoc *F*-tests on confounding effects of scanner and motor scores (146).

Task protocol

During scanning the participants performed a verbal working-memory 2-back updating task (Figure 5). The task requires the participants to actively maintain and update information (nouns) that are regularly presented on the screen. The task was chosen because of its usefulness regarding dopaminergic fronto-striatal involvement, and because working memory often is described as the dominating cognitive impairment profile in early-phase PD (78, 147).

The participants received instructions and practiced on the 2-back task prior to scanning. They were asked to respond "yes" (right index finger) when the word matched the word presented two items earlier (i.e., 2-back), and "no" when it was different (left index finger), using MR-compatible keypads (Lumitouch reply-system, Lightwave Medical Industries, Canada). During the baseline rest condition participants were instructed to do nothing except keeping their gaze fixed on a small circle that was displayed at the center of the screen.
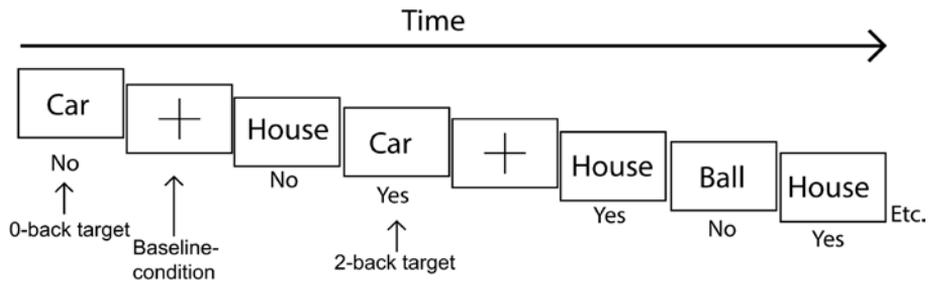
Figure 5. The fMRI working-memory 2-back task protocol.
The participants received instructions to respond "yes" when the word matched the word presented two items earlier (i.e., 2-back), and "no" when it was different. The participants were instructed to keep their gaze fixed on the cross during the baseline rest condition.

In the 1.5T scanner, the nouns were presented for 2.5 seconds each, and the inter-stimulus intervals were between 2 and 20 seconds. Four task blocks (eight trials in each block) were interleaved with baseline blocks. In the 3T scanner, the nouns were presented for 1.5 seconds each, and the inter-stimulus intervals were three seconds. Four task blocks (15 trials in each block) were interleaved with baseline blocks.

fMRI-related exclusions

Participants were excluded if they performed < 55% correct answers on the in-scanner working memory task. This threshold was used to exclude answers by chance (i.e., 50%), and to insure that participants actually performed working-memory updating processing. Some participants were excluded due to fMRI-related technical issues that affected the image quality. This was assessed by manual observations of the images. Finally, participants were excluded if their movements within the scanner induced image artifacts. This was assessed by manual observations, and correlation analyses between movements and task performances in doubtful cases.

SPECT

SPECT is an invasive neuroimaging method where gamma camera detectors register the emitted radiation. The collected projection data are then reconstructed in a computer to create a three-dimensional image of the examined activity distribution. The presynaptic dopamine uptake was the dependent SPECT measure in Study I in the current thesis.

Participants were examined on a dual-head hybrid gamma camera system (Infinia Hawkeye, General Electric, Milwaukee, WI, USA). Semi-quantitative analysis of the SPECT image date was performed using regions of interest (ROIs) in bilateral caudate and putamen, and a background ROI was applied to the occipital cortex. Uptake was calculated by dividing the uptake in the striatal sub-regions by the reference region. A detailed description is provided in Study I.

Results

Study I

Findings from functional brain imaging studies have previously shown that altered fronto-striatal activity often characterises patients with PD as compared with healthy individuals. However, the neuropathological features that underlie cognitive impairments in patients with PD-MCI have been insufficient to form a clear hypothesis.

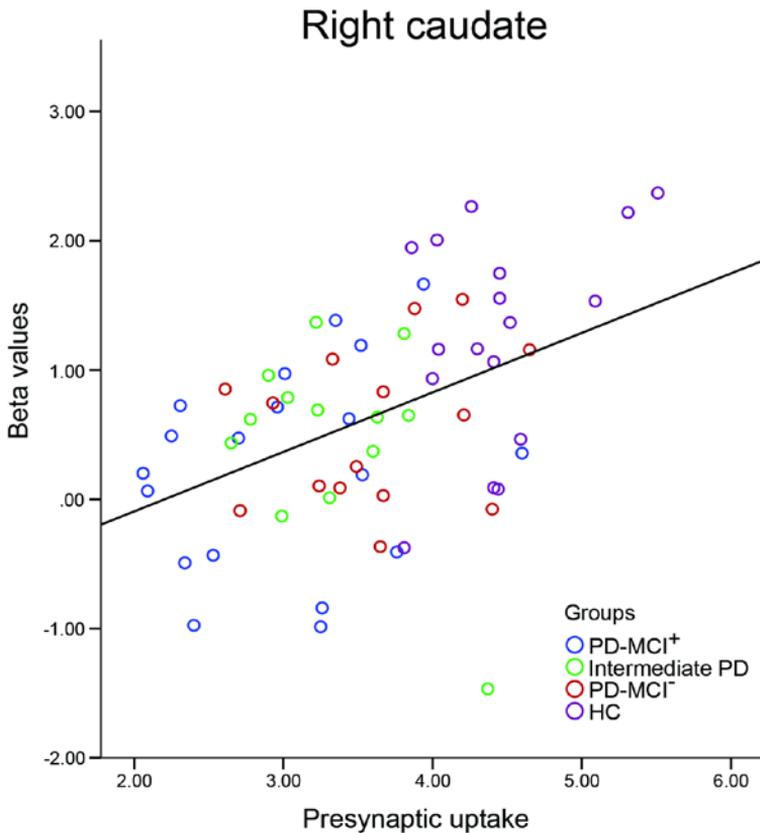**Figure 6. Correlation between BOLD signal intensity and SPECT dopamine presynaptic uptake**
Correlation ($r = 0.44$, $p < 0.001$) pattern in the right caudate nucleus between BOLD-signal (fMRI) and presynaptic dopamine uptake (SPECT). PD-MCI[+] = patients with PD and MCI. Intermediate PD = patients with PD and intermediate cognitive impairment. PD-MCI[-] = patients with PD without MCI. HC = healthy controls.

The key finding was that patients with PD-MCI had lower BOLD-signal intensity in the right dorsal caudate nucleus and bilateral anterior cingulate cortex (ACC, within the prefrontal cortex) than patients without MCI during performance of the in-scanner working memory task. In addition, patients with PD-MCI had lower levels of presynaptic dopamine uptake in the right caudate nucleus (sub-cortical) than patients without MCI. There was also a significant correlation between the fMRI beta values and the SPECT presynaptic uptake in the right caudate nucleus (Figure 6). In addition, within the large-scale sample, patients with PD under-recruited an extensive brain network including bilateral striatal and frontal regions as compared with healthy age-matched individuals.

Study I provided novel information on the association between striatal dopamine transporter binding and fMRI signal change, and those data support the notion that fronto-striatal alterations characterise patients with early-diagnosed PD-MCI. Thus, although nigro-striatal dopaminergic transmission was associated with cognitive impairments in PD, additional meso-cortical dopaminergic depletion and/or other neurochemical dysfunction might to some extent have contributed to the current findings.

Study II

The cross-sectional approach in Study I provided important information on how task-evoked brain responses are related to PD-MCI. However, longitudinal approaches might provide more sensitive information on brain changes, and longitudinal approaches would be much less susceptible to cohort differences than cross-sectional approaches.

The key findings were that patients with PD-MCI showed persistent under-recruitment (lower BOLD-signal intensity) across time in the fronto-striatal circuitry compared with patients without MCI. Most importantly, the longitudinal evolution of PD-MCI translated to task-evoked posterior cortical decreased BOLD-signal intensity across time within the left fusiform gyrus (temporal cortex), whereas patients without MCI were stable across time (Figure 7).
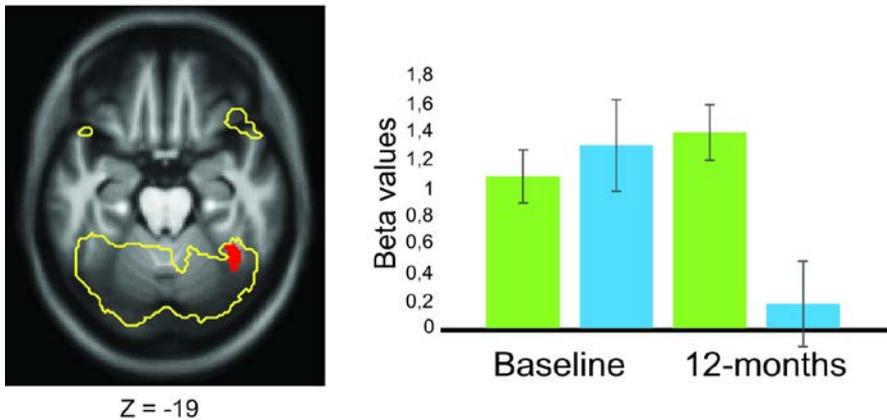
Left fusiform gyrus

Z = -19

Figure 7. Group-by-time interaction effect in the right fusiform gyrus
A group-by-time interaction effect (red) was observed in the right fusiform gyrus, which showed a stable level of BOLD signal responses across time for patients with PD without MCI, whereas patients with MCI showed decreased BOLD signal responses at follow-up. The yellow outline illustrates the working memory task activation area (i.e., contrast between 2-back and resting baseline condition). Mean beta values are presented as plots for patients with PD with MCI (blue) and without MCI (green) at baseline examination and at the 12-month follow-up. Z = anatomical location in the Montreal Neurological Institute transversal space. Error bars are standard error.

Taken together, the results are in keeping with hypotheses that relate development of severe cognitive dysfunction in PD to posterior cortical change (75,131). These evolving posterior cortical changes might characterise prodromal PDD. It has been proposed that PDD pathology and AD pathology are closely related, and that the fusiform change might be related to cholinergic AD-like pathology.

Study III

The PD-MCI-concept was applied in Studies I and II and related to brain responses. However, the predictive value of PD-MCI in respect of PDD has been sparsely investigated.

The key findings were that 42.6% of the study's PD-population had PD-MCI at the baseline examination, and of those PD-MCI patients, 51% developed PDD within five years (i.e., a 6.5-fold increased risk; Figure 8). Only 9% of

the patients with normal age-matched cognitive status progressed to PDD within five years. PD-MCI at baseline examination predicted PDD with a sensitivity of 80.6%, and a specificity of 71.7%. Patients with PD-MCI that later developed PDD performed significantly worse than patients that did not later develop PDD on tests of episodic memory, visuospatial functions, cognitive flexibility, and semantic fluency.
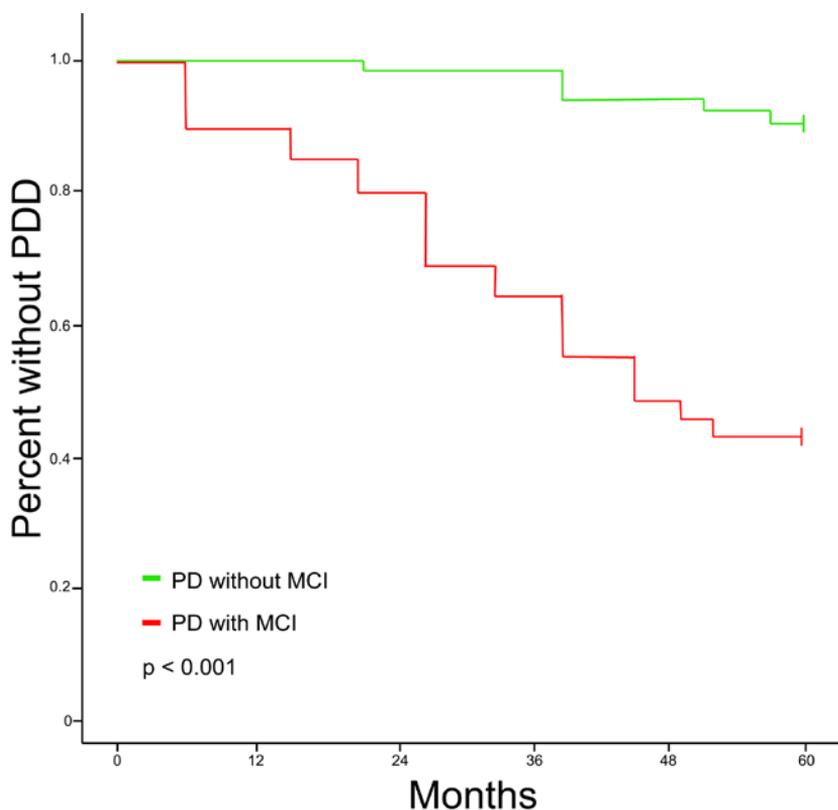
Figure 8. Proportion of patients with PD that develop PDD
A Kaplan Meier survival curve (Mantel-Cox) that describe the time until PD-patients with and without MCI develop PDD. Patients with PD-MCI developed PDD to a greater extent that patients without MCI. X-axis shows number of months. Y-axis shows the proportion of patients without PDD. p = p-value.

Importantly, PD-MCI is a fairly good predictor of prodromal PDD, and only a low proportion of patients with PD-MCI reverted to normal cognitive status. Primarily, cognitive tests with a posterior cortical basis might be predictive for PDD to a greater extent than tests with a fronto-striatal basis. These findings might in part reflect a dual-syndrome hypothesis.

Discussion

The current thesis investigated working-memory related brain responses in patients with PD, with and without MCI. The overall aim was to increase knowledge about the neuropathology underlying cognitive impairment in patients with PD, both cross-sectionaly and longitudinaly, and to evaluate the predictive value of PD-MCI in respect to PDD. The aims are summarised as follows:

I.   The first objective was to examine working-memory related brain responses (fMRI), and dopamine striatal integrity (SPECT) in newly diagnosed drug-naïve patients with PD, with and without MCI.

II. A longitudinal objective was to evaluate brain changes across time (at baseline and after a 12-month follow-up) in patients with PD, with and without MCI.

III. Finally, the aim was to prospectively determine the predictive value of PD-MCI in respect of prodromal PDD, and to examine which cognitive measures were most clinically relevant.

In the following paragraphs, the results will be discussed in relation to the aims of the thesis and previous research. Methodological considerations will be addressed as well as future prospects.

Main findings

This thesis provided novel information on how task-evoked brain responses relate to PD-MCI (assessed with the recently proposed Movement Disorders Society's Task Force Criteria). The findings highlight that fronto-striatal working-memory related dysfunction characterises early-diagnosed patients with PD that were classified with MCI. Patients with drug-naïve PD-MCI had lower presynaptic dopaminergic binding in the right caudate than patients without MCI, and binding correlated significantly with the caudate BOLD signal responses (Study I). In addition, the findings confirm (71, 126) that patients with PD have functional fronto-striatal alterations when compared with age-matched healthy individuals. Importantly, the evolution of cognitive impairment in patients with PD-MCI is related to changes in the right fusiform gyrus (Study II), but not to any additional fronto-striatal changes. In addition, although a test measuring cognitive flexibility (dopamine sensitive) was predictive for prodromal PDD, especially tests with a more posterior cortical

neural basis were predictive in respect to prodromal PDD (Study III). Thus, this thesis gives some support for a dual syndrome hypothesis (99, 100) with both fronto-striatal- as well as posterior cortical cognitive dysfunctions in patients with early phase PD-MCI. The fronto-striatal alterations in PD-MCI, to a larger extent, seem to be related to PD pathology per se, rather than evolving PDD. In addition, evolving PDD, to a larger extent, seems to be related to posterior cortical alterations already at the time for the initial PD diagnosis. The degree of pathological interactions between the two potential syndromes is not possible to answer within the framework of this thesis. However, interactions to some degree, seem to be likely (Study III), especially when more profound cognitive decline evolves. Potential beneficial effects of dopaminergic medication (Study II) might also have prevented additional fronto-striatal changes that were seen in the current thesis.

Striatum

In the current thesis, the striatal alterations show a step-wise pattern with superior activation for healthy controls, intermediate activation for patients with PD but without MCI, and poorer activation for patients with PD-MCI (Study I). Taken together, the findings are in keeping with previous observations showing that the caudate nucleus is critical to successfully update information in the working memory (71, 95), and that dopamine D_2 receptor binding is elevated during working-memory updating (148). Functional alterations, such as reduced dopamine integrity in the caudate nucleus, commonly lead to impaired working-memory related performance (90, 117, 149), and individuals with low working-memory capacity generally have low dopamine synthesis capacity in the striatum (150). The right caudate ROI in this thesis is located in the dorsal head of the structure (see Study I on how the ROI was defined), and that region is one of the main output targets of the nigro-striatal tract (118). Therefore, deficits in the nigro-striatal dopaminergic transmission, at least in part, are associated with the cognitive impairments that are reported for patients with PD with cognitive impairments (6, 117, 151). In addition, fronto-striatal alterations have previously been observed in patients with PD with executive impairments, and also recently observed in patients with MCI (135, 136). In the longitudinal follow-up (Study II), patients with MCI showed a (small but non-significantly) increased BOLD signal response at follow-up, which might have reflected a beneficial medication effect due to the onset of anti-parkinsonian treatment. Dopamine depletion has negative effects on the cortico-striatal connectivity, and might in part explain the frequently observed cognitive impairments in PD with frontal lobe characteristics (67). The caudate nucleus is involved in numerous cognitive processes. The ventral striatum mediates functions such as encoding of stimulus associations, and that area is commonly less dopamine-depleted

in early-phase PD. The dorsal striatum mediates functions such as incorporation of various influences on selections, and working-memory updating, and is commonly more dopamine-depleted in early phase PD (152). Dopaminergic medication can potentially have contrasting effects due to cognitive processes and due to basal levels of striatal dopamine (153). Medicated patients with PD might exhibit deficits when having to ignore distracting stimuli, whereas non-medicated patients with PD might show deficits in updating a new set shift (127). Thus, the effects of dopaminergic medication on brain activation and cognition have previously shown both positive and negative outcomes (121), and the relation between cognitive performances and dopamine level is dose-dependent (i.e., inverted-U-shaped function), where too much or too little dopamine seems to impair different cognitive performances (90). Generally, high levels of dopamine within the striatum (but not too high) and low levels in the PFC might optimise phasic updating (121). However, studies that assess if patients with PD-MCI have more beneficial effects of dopaminergic medication on cognition than patients without PD are few. One study showed that Rasagiline (monoamine oxidase type-B (MAO-B)) inhibitor, by enhancing dopaminergic transmission, had beneficial effects on aspects of attention and executive functions (154). Another study showed that dopaminergic agonist supplementation improved working-memory updating in patients with low performance (below the median of the sample) (155). The effects of dopaminergic medication in patients with PDD have been mixed, with beneficial effects on some measures and negative effects on others (42). Thus, although indications of beneficial effects of dopaminergic medication on BOLD signal intensity in patients with PD-MCI was shown (Study II), the relatively small sample in relation to the in-group differences in dopaminergic agents (7 patients with levodopa, 3 with a combination of levodopa and dopamine agonists, and 1 with only dopamine agonists), makes conclusions uncertain. In addition, dopaminergic medication may have different effects on different patients, and this difference is related to each patient's baseline dopaminergic level (90). It is indeed important to examine the effect of different dopaminergic agents in future studies. Dysfunction of adrenergic receptors is evident in PD, and this dysfunction might have contributed to the observed PD-related cognitive alterations in this thesis. However, the understanding of adrenergic receptor dysfunction on cognitive impairments in PD needs to be further investigated (156).

Frontal cortex

Patients with PD and MCI showed lower BOLD signal responses than patients without MCI in the bilateral ACC (Studies I, II). However, the longitudinal change in PD-MCI was not associated with any additional ACC

alterations. The ACC is involved in high-level cognitive control processing (157) such as during competing representations and conflict monitoring (158). In addition, during high working-memory load and distractor competition, the functional connections between the ACC and the primary visual cortex tend to increase (159). Importantly, it has also been shown that the ACC is frequently involved in working-memory updating (160). The caudate nucleus has strong cortico-striatal connections, and co-activations between the caudate and the DLPFC, as well as the ACC, have previously been reported (161). Thus, the down-regulated activity in the right caudate might have secondary implications resulting in lower BOLD signal responses in the ACC and the DLPFC (approaching significance in Study I) for patients with PD-MCI. In that respect the thesis results are in keeping with the traditional model of the disease pathology. The traditional model suggests that nigro-striatal dopaminergic dysmodulation leads to increased inhibitory basal ganglia output and decreased thalamo-cortical activity (162). This is also in keeping with the notion that decreased cortical task-evoked activity in PD is related to substantial involvement of the caudate nucleus in the cognitive task (126). However, the meso-cortical dopaminergic system is involved in working memory processes by projecting dopamine directly to the PFC, and indirectly via the meso-limbic system (119, 120). Depletions in all three - the nigro-striatal, the meso-cortical, and the meso-limbic areas, are evident at later stages of cognitive decline in PD. Thus, several dopaminergic pathway might have contributed to the observed PFC alterations in patients with PD-MCI.

Posterior cortical circuitry

For quite some time, there has been a notion that cognitive impairments in PD are not only related to fronto-striatal dopaminergic circuitry, but also to posterior cortical circuitry (163), and cognitive tests with a posterior cortical basis might be more predictive of PDD than tests with a fronto-striatal basis (75). The current thesis shows that the longitudinal evolution of cognitive impairment is related to posterior cortical dysfunction (right fusiform gyrus) rather than further fronto-striatal dysfunction (Study II), and that cognitive tests with a posterior cortical basis are predictive for PDD. This is in keeping with the notion that longitudinal evolution of PD-MCI relates to increased posterior cortical atrophy (103, 164), and that the atrophy is more pronounced in patients with PDD than in PD-MCI (164). In addition, lower metabolism levels in the frontal cortex have been observed in patients with MCI than in patients without MCI, but primarily, the posterior regions such as the temporal cortices are affected (165, 166).

There was a lack of further behavioural changes across time in Study II that did not correspond to the fusiform change. It is possible that the observed brain changes preceded the behavioural changes, as commonly occur in neurodegenerative diseases such as AD (167) and PD (15). In agreement, increased cortical thinning in posterior cortical regions, as in the temporal lobe, have recently been related to PD-MCI, rather than further fronto-striatal decline (103). At first view, the fusiform gyrus is primarily interpreted as a region involved in higher-order visual processing, but the fusiform is also associated with visual working memory (168). The right fusiform gyrus change was located within the task-specific network (i.e., working memory task condition > baseline rest condition), and might process the visual representations to be maintained in the working memory (94). In Study II, there were also functional connections between the left fusiform gyrus and bilateral caudate areas during performance of the in-scanner working memory task that imply a similar time-related task-activation pattern. In addition, decreased fractional anisotropy in posterior cortical white-matter tracts is associated with cognitive impairment in PD (133).

Patients with PDD and DLB commonly have similar cognitive symptoms with deficits in executive functions, attention, working memory, visuospatial function, and episodic memory (110). However, the episodic memory impairments are commonly more profound in AD than PDD and DLB (6). It has been proposed that preclinical biomarkers of PDD might be AD patterns with temporal atrophy (43). However, these patterns might be present already in a PD-MCI stage (102, 103). So, does AD pathology and PDD pathology have parallel evolvements or do they interact? Patients with PD-MCI have an increased risk of developing PDD (39), which implies a greater proneness than for patients without MCI. However, the PD-MCI group is indeed heterogeneous, and some patients seem to be more sensitive to the additional PDD degenerative process. In line with that, the longitudinal evolution of cerebral glucose metabolism features in PDD has been reported as mixed with both striatal and posterior cortical changes (169), implying a heterogeneous pattern. Proposed baseline predictors of PDD are high age and non-tremor motor phenotype (In Study III, this was only observed later in the disease progression), and cognitive impairments with posterior-cortical basis (131). In Study III, when controlling for age, sex, and education, patients with PD-MCI that later converted to PDD performed worse on several cognitive tests than non-converters. This was primarily related to tests, which are suggested to be regulated by posterior cortical circuitries (visuospatial functions, episodic memory, semantic fluency), rather than fronto-striatal circuitries. Importantly, although this thesis primarily suggests that posterior cortical dysfunction is a prodrome of PDD, additional fronto-striatal dopaminergic dysmodulations might also contribute. In Study III, patients with PD-MCI that

later developed PDD, performed inferior on the trail making test (TMT) (version A and B) than patients with non-evolving PD. TMT A and B are cognitive tests that require attentional and executive demands (170), which partly rely on dopaminergic neurotransmission (67). However, although the frontal cortex is involved in task execution (for example the ACC), task activation is also related to the visual processing streams, which extent from the fusiform gyrus (171, 172). Thus, impaired performance in the TMT might be related to fronto-striatal alterations and/or posterior cortical alterations, and it is reasonable to suggest that fronto-striatal dopaminergic depletion at least in part could be related to prodromal PDD. In addition, although episodic memory is usually described as a cognitive ability with a posterior cortical basis (medial temporal cortex), the neurocognitive networks underlying episodic memory are indeed complex. For example, different parts of the PFC are involved in both encoding and retrieval of episodic memory processing (173), and dopamine is influential in respect to hippocampal memory formation (174). All in all, tests with a posterior cortical basis commonly interact with dopaminergic neurotransmission and have fronto-striatal connectivity in different degrees.

Posterior cortical neurotransmission

As described above, Studies II and III provided evidence that evolving PD-MCI and prodromal PDD are related to changes in the temporal cortex and cognitive tests with primarily posterior cortical basis. Besides the characteristic dopaminergic deficits, cholinergic deficits in PD are also common due to significant degeneration of cholinergic neurons such as in the nucleus basalis of Meynert (nbM) (175, 176). It has long been acknowledged that decreases in nbM neurons might relate to declining cognitive functions in PD (77). Alterations in cortical cholinergic depletion might relate to attention and/or executive deficits (177) and altered episodic memory (6). However, besides the cholinergic hypothesis, there might be additional dopaminergic and/or noradrenergic dysmodulations that relate to the thesis findings. A link between BOLD activity in extra-striatal regions and striatal dopamine mediation has previously been reported during cognitive processing (178). In addition, deficits in noradrenaline (NA) transmission might affect executive processes (179). Locus coeruleus mainly projects NA to several cortical regions in the frontal and temporal circuits (180), and treatment with a noradrenaline inhibitor has shown beneficial results for patients with PD with executive dysfunction (181). However, these treatments need to be further examined (179). Thus, a complex neurochemical depletion pattern might characterise prodromal PDD, and underlie the thesis findings (Figure 9). Increased knowledge about the deficiencies underlying cognitive impairment might increase the possibilities for relevant medical interventions. The thesis

studies have thus provided information on possible underlying neuro-pathological features that relate to evolving cognitive impairments. As shown above, dopaminergic medication has the potential to both improve and impair cognitive functions dependent on the underlying neurotransmission. A balance between optimal motor levels in relation to cognitive function is critical to consider, and this important information needs to be applied in clinical practice to a greater degree (6). However, although research has contributed significantly on the effects of dopamine medication, additional research on medication effects on other neurotransmission, such as noradrenaline and acetylcholine, is critical. fMRI techniques, with its cognitive protocols, have indeed an important role in evaluating potential medication effects.
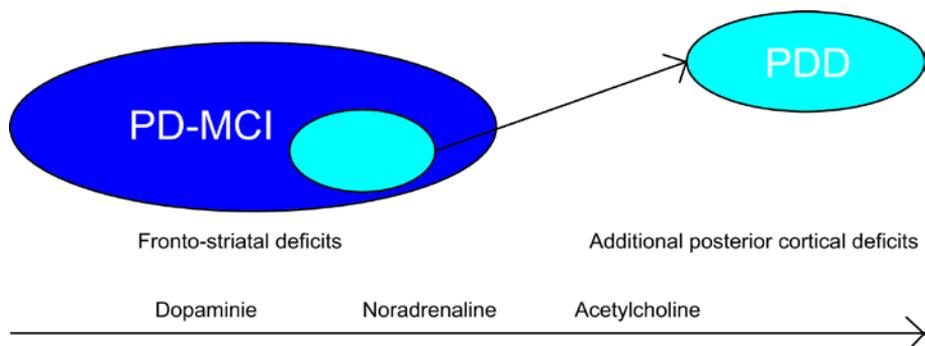

Figure 9. **Overview of working-memory related neuropathology in PD.** Fronto-striatal alterations with dopamine (and potential noradrenaline) depletions characterise the PD-MCI population in general. PDD might relate to additional posterior cortical alterations with proposed cholinergic depletions. The figure is inspired by Kehagia et al. (99).

Compensatory activation?

As seen in Studies I and II, patients with PD-MCI had a higher BOLD-signal activation in parts of the parietal cortex and the parahippocampus than patients without MCI. The increased BOLD activity in patients with PD-MCI might relate to larger attentional demands and increased reliance on declarative (see Figure 2) memory systems due the fronto-striatal related dopaminergic depletions. This has previously been proposed as a shift to declarative memory systems in PD during executive tasking due to impaired working memory capacity (182). In agreement, cortical thinning in the parahippocampus has recently been observed in PD patients with subjective cognitive impairments as compared with patients without subjective cognitive impairments (183), and increased hippocampus activity in PD has been proposed to serve as compensatory activation for striatal dysfunction (136). However, it is unclear

if high fMRI-related activity should be interpreted as possible forms of compensatory brain activations. Several theories have been proposed. The brain reserve hypothesis suggests that successful cognitive performance in old age is determined by high premorbid abilities that prevent or minimise cognitive decline (i.e., better handling to prevent cognitive pathology as dementia) (184). Thus, increased cortical activation in elderly individuals might relate to compensation and counteract age-related cognitive impairments through plastic reorganisation (185). In contrast, according to the dedifferentiation hypothesis, additional activation is dysfunctional (i.e., non-selective activation), and reflects difficulties to recruit specialised neural circuitry. In contrast, the concept of brain maintenance proposes that preserved cognitive functionality in aging is associated with preserved brain functions (i.e., lack of gradual deterioration of brain pathology) (186). However, longitudinal studies with longer follow-ups than in the current thesis might increase the possibilities to assess potential compensatory activations.

Clinical implications

A great clinical challenge is to differentiate between PD-MCI with prodromal PDD and PD-MCI with other bases. Cognitive tests probing functions with posterior cortical bases might increase the likelihood to detect early signs of prodromal PDD. In agreement, in Study III there was evidence that cognitive tests with a posterior cortical basis differentiated between patients with prodromal PDD and patients with PD-MCI in the early phases to a greater extent than tests with a frontal cortical basis. High age seems to characterise patients with PD-MCI with prodromal PDD (75), and this was also the pattern in Study III. Thus, this thesis has provided useful information that increases knowledge on the predictive value of cognitive tests that might be useful in clinical settings. Even though knowledge has increased, a majority of the cognitive symptoms are still going unrecognised and untreated in clinical settings (53). As shown in this thesis, functional MRI can provide information on how cognitive status relates to brain responses in PD and provides knowledge about the underlying neuropathology that is important for clinical practice. In addition, fMRI has indeed great potential and can especially play an important role in evaluating medical and non-medical interventions on cognition (see below on future prospects), and might be useful in PD-diagnostic procedures (23).

Methodological considerations and limitations

Scanner factor

The fMRI data were collected with two different scanners (see Materials and Methods). This is indeed a limitation that induced additional variability. Furthermore, the detection ability is more restricted in subcortical regions when using the 1.5T scanner than the 3T scanner (187). Effort was dedicated to control for potential scanner effects. The scanner factor was assessed by performing F-tests (146) to evaluate if scanner effects overlapped with the reported effects of interest (no such overlap was observed in Study I). Brain regions showing confounding effects from scanner differences were reported and interpreted with caution. Importantly, effect sizes (Cohen's d for t-test and eta^2 for ANOVAs) were reported on each scanner separately.

Note that the observed scanner patterns generally revealed comparable magnitudes of BOLD signal change between the 1.5T and 3T scanners (medium to large effect sizes). Importantly, the observed scanner effects (in Study II) were rather related to changes in detection abilities/scanner protocols and not related to group differences that were manifested irrespective of the scanner. Sometimes, a main effect of scanner analysis overlapped with the effects of interest. Retrospectively, those effects were maybe too cautiously interpreted in Study II. In that study a significant main effect of group was evident in the right putamen when comparing patients with PD-MCI and patients without MCI, and those effects were only reported in the supplementary material (see Figure 10). Therefore, group differences, which show scanner effects (i.e., main effect of scanner) should not necessarily be interpreted with caution as long as there are large effect sizes with similar patterns between scanners.
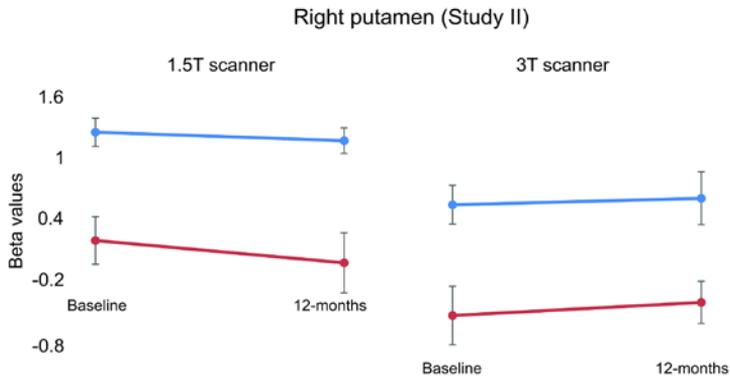
Figure 10. Showing scanner effects separately in the right putamen (Study II)

A main effect of scanner was reported to overlap with the main effect of group in the right putamen (p < 0.001). However, consistent BOLD signal changes were observed between scanners (the 1.5T scanner to the left, and the 3T scanner to the right) with large effect sizes (Cohen's d > 0.8). Blue = patients with PD but without MCI. Red = patients with PD and with MCI. Error bars are standard error.

Scanner upgrades and/or changes are frequent in clinical settings and with longitudinal approaches. Pooled MRI analyses of data acquired from different scanners/centers have become increasingly frequent (146, 188, 189), but need to be critically considered.

Neuropsychological battery for assessing PD-MCI

The neuropsychological test battery was not initially selected to assess MCI, and some of the included tests did not have proper age-matched norms (providing a basis for comparing patients with healthy individuals in the same age-group). In addition, the healthy control group in this thesis contained too few individuals to define a normal distribution (i.e., a new norm evaluation). Therefore, the assessed neuropsychological battery did not completely fulfil the requirements for level-II criteria (i.e., at least two tests in each cognitive domain). However, lately studies that almost fulfil the requirements for PD-MCI level II criteria have used the term "modified level-II criteria" because the test battery was more extensive than the level-I criteria (190). In retrospect, the term "modified level-II criteria" could potentially have been applied in Studies I and II, besides Study III in the current thesis. Importantly, use of cognitive test batteries with better sensitivity for categorising MCI and prodromal PDD is critical. Population-based studies are therefore required to examine the validity of current neuropsychological tests, and could potentially

provide stronger norms that would increase knowledge on their potential to detect cognitive changes across time.

No subjective measures were part of the MCI classification in Studies I and II. It is very common that there is a great discrepancy between the objective cognitive measures and the patients' subjective reports in the early phases of cognitive decline (35). These heterogeneous patterns were also observed in newly diagnosed patients with PD within the NYPUM project (Study I). This might reflect different mood states within each diagnosis group or different rates of disease progression (28). The longitudinal approach generally provides a better sensitivity and reflects a better estimate of PD-MCI in respect of PDD. In Study II, which had a longitudinal approach, the correspondence between objective and subjective measures of cognitive decline were enhanced (i.e., 10 out of 11 patients with PD-MCI reported subjective cognitive impairments, although subjective cognitive impairments were not required for PD-MCI). Subjective measures were thus only used in Studies I and II for assessing PDD (where the subjective and objective measures converged) and not MCI. In a recent study, the authors removed the criterion of subjective cognitive impairment in the PD-MCI classification, which led to an increase in the frequency of PD-MCI (from 33% to 41%) (137). Thus, using the complete level-II criteria potentially provides a stronger estimate for prodromal PDD (as in Study III), but on the other hand, that might prevent early phase detection of cognitive decline in PD. A stricter cut-off (i.e., > 1.5 SDs) has a higher predictive value for PDD (191), but might affect the ability to detect individuals in early phases of cognitive decline. The balance between sensitivity and specificity is a challenge, but > 1.5 SDs on at least two cognitive measures seems like a good compromise (192), and it is regularly applied (35), also in the current thesis.

MCI concept

As shown in Study III, PD-MCI is predictive for prodromal PDD. However, 11% with PD-MCI reverted to normal cognitive status, and 8.7% fluctuated in their cognitive status across time. Thus, although PD-MCI has a clinical relevance, longitudinal follow-up is necessary, especially in uncertain cases. Is it possible to use normal distributions as diagnostic criteria? It is an open issue since many previous studies have demonstrated cognitive deficits for PD patients without reference specifically to the MCI classification scheme (193), in combination with the variability of implementing MCI criteria (ranging between 1 and 2 SD below normal). It is not inconceivable that the relation between (aspects of) PD severity and cognitive decline is graded - a pattern that is apparent in the added fMRI-SPECT correlation analysis in Study I. In fact, it seems likely.

The majority of the included patients did not have any records of previous cognitive functioning (i.e., premorbid cognitive ability). Even though the premorbid abilities are commonly estimated in clinical settings, this was not done in any systematic fashion in the current thesis. This is a limitation, especially in the cross-sectional study (Study I), where patients with cognitive performances within the age-matched normal-zone might exhibit cognitive decline as compared with their former and higher level of premorbid ability. The longitudinal estimates increase the prognostic value of severe cognitive decline (39).

Finally, subtype classification of PD-MCI into single cognitive domains is recommended (54). However, in the current thesis patients with MCI frequently showed a simultaneous decline in several cognitive domains. Therefore, subtyping of specific cognitive domains would have been difficult to perform even if the cognitive battery would have permitted it (i.e., at least two measures in each cognitive domain). Thus, larger sample sizes would probably have been required, and that might be better assessed in multi-center studies.

Variables not considered in this thesis

This thesis did not consider several important points. Differences in striatal lateralization (in respect to which side was most affected), were not considered and might have induced variability. Integrity between the right and left striatum is important for adequate performance on verbal executive tasks, and deficits in respect to lateralization might reflect differential dopamine loss (194). In addition, gender differences were not considered in this thesis, and more males than females had cognitive impairments. This pattern, with more cognitively impaired males than females, is common. Gender differences with respect to cognition in PD have been reported previously, and females generally have higher levels of striatal uptake binding than males, which might imply a more benign preclinical phase of PD in females than in males (195). In addition, this thesis only considered PD subgroups with different motor features in Study III. Non-tremor dominant subtypes (i.e., postural instability, and gait disturbances), are usually associated with shorter time to cognitive impairment than tremor-dominant subtypes (54). Finally, this thesis did not consider genotyping although genetic factors might affect and contribute to the development of PDD (54). A proposed baseline predictor of PDD is microtubule-associated protein tau (MAPT, H1/H1) genotype (131).

Methodology and statistics

The applied population-based study design is a major strength and probably increased the possibilities to generalise the findings to the general PD population. In addition, the study design likely increased the possibilities to identify new cases with Parkinsonism within the catchment area. Longitudinal approaches are also more sensitive and are better able to detect brain changes than cross-sectional approaches, and longitudinal approaches are not as susceptible to cohort differences (196, 197). Unfortunately, although the initial aim was to investigate brain responses also at the 36-month follow-up in Study II, a substantial dropout and other methodological issues (e.g., changes in cognitive status) made that aim impossible to meet. Importantly, although the thesis relied on data from a population-based study, Study II had a relatively small sample size with low statistical power. This is indeed a limitation that affects the reliability of the results (198). Thus, the results, especially in Study II, should not be overestimated, and studies that reaffirm these findings are important.

To verify that group differences were driven by cognitive differences rather than motor differences, the UPDRS-III motor scores were used as covariate of no interest in the fMRI analyses. Control analyses and group matching (Study I) were conducted to assess the influence of the motor factor. In addition, during the in-scanner task execution, patients answered "no" with the left index finger and "yes" with the right index finger that might have induced variability. However, comparisons between patients with PD-MCI and patients without MCI showed no significant difference in the proportion of "yes" and "no" answers between the groups (p = 0.79 in Study I). Thus, the motor aspect in respect to lateralisation between groups does not seem to have interfered with activations on the in-scanner working memory task.

Finally, it would also have been interesting to analyse correct and incorrect responses separately in relation to brain responses. However, the high level of accuracy prevented meaningful analysis of incorrect execution owing to the limited number of incorrect responses (in Study I, patients with PD without MCI had 88.8% correct answers, and patients with MCI had 83.1% correct answers).

Future prospects

fMRI protocols for the future

In the current thesis, the results in Study II are in keeping with the notion that cognitive impairments with posterior cortical basis (right fusiform gyrus), rather than further fronto-striatal (right caudate, and bilateral ACC) alterations across time, associate to prodromal PDD. However, although this thesis showed that a working-memory updating task can assess vital information on posterior cortical functions, fMRI protocols that assess cognitive tasks with pronounced posterior cortical bases could provide additional information. A longitudinal fMRI protocol with both fronto-striatal- (for example, working-memory updating or task-set shifting) as well as posterior cortical (for example, visuospatial judgement or episodic memory encoding) basis, assessed on patients with PD, with and without MCI, would be of interest. That would potentially provide vital information on the evolution of cognitive impairments in PD in relation to functional brain circuitry.

In addition, in the current thesis, some participants had to be excluded because of impaired performances on the in-scanner working memory task (see flow-charts in respective Study articles), or due to movement artefacts. Therefore, it is critical to create a relaxed setting so that participants with the most severe cognitive impairments do not have to be excluded. Resting state fMRI is a rather new approach and has the potential to enhance information on interactions between brain areas. A resting-state protocol is commonly run for 6-8 minutes with no complicated task-demands (usually the participants are instructed to keep their gaze fixed at a stable stimulus across time). Such a resting-state protocol does not require any motor actions. Thus, its simplicity might prevent exclusions due to task-difficulties, and it might inspire doubtful participants to participate (125).

Interventions to prevent cognitive decline

There is no medical cure, which prevents the degeneration in PD or PDD. However, medical interventions such as dopamine replacement therapy might have beneficial effects on cognition. Dopamine supplementation in PD patients commonly improves cognitive functions mediated by the dorsal striatum such as selective attention (152). In contrast, ventral striatum-mediated functions such as reversal learning and inhibition might be impaired by dopamine supplementation. In Studies I and II, the PD-MCI related alterations were in part associated to the dorsal striatum (caudate nucleus), and in Study I with presynaptic dopamine depletions. As described above, onset

of dopaminergic medication, to some degree, might have normalised activity in the dorsal caudate in patients with PD and MCI (Study II), and prevented further cognitive decline. It is important to note that although beneficial effects might occur, there is a risk for dopamine overdose in less depleted striatal regions (and potentially in prefrontal regions as well), and that might cause severe symptoms (100). Thus, dopaminergic medical intervention in respect to cognitive impairments in PD has to be conducted with caution. PD leads to degeneration and neurotransmitter deficiencies that extend to other systems than the dopaminergic ones (199). Patients with PDD might have beneficial cognitive effects of cholinesterase inhibitors that are commonly prescribed (109). Future medical interventions affecting other neurotransmitter systems, such as adrenergic neurotransmission, may also be investigated for their effect on cognition. However, a majority of cognitive symptoms is going unrecognised and untreated in the clinical setting (53). Thus, it is critical that cognitive function should be assessed properly and regularly in patients with PD to make it feasible to study interventions that try to improve cognition.

Even though pharmacological treatment might enhance cognitive functions in patients with cognitive impairments, non-pharmacological treatments should also be considered. Cognitive training of working-memory updating has shown transfer effects (beneficial effects on non-trained cognitive tasks) in healthy individuals that were mediated by the striatum (95), and enhanced striatal dopamine release is associated with training of updating (148). This is indeed in keeping with the observed striatal cognitive impairments in this thesis. Cognitive memory training in patients with PD has shown some promise (200), and a randomised controlled study recently showed that the experimental PD group improved on measures of working memory as an effect of cognitive training (201). In addition, physical training might be beneficial on executive functioning in patients with PD (202). Importantly, although these results are promising and intriguing, there is a great need for randomised controlled studies of non-pharmacological interventions for cognitive impairments in PD (203).

Main conclusions

This thesis provides novel information on task-evoked brain responses in patients with PD and cognitive impairments. Patients with PD-MCI had significantly lower BOLD signal responses than patients without MCI in frontal (anterior cingulate cortex) and striatal (right caudate) regions, and striatal BOLD signals correlated with the presynaptic dopamine levels. The fronto-striatal alterations persisted across time but without any additional change. However, decreased posterior cortical (right fusiform gyrus) BOLD signal responses across time were observed in patients with PD-MCI relative to patients without MCI. Patients with PD-MCI at baseline examination exhibited a six-fold increased risk of later PDD, and cognitive tests with a posterior cortical basis were more predictive than tests with a fronto-striatal basis. The findings suggest that early cognitive impairments in PD are linked to fronto-striatal dopaminergic dysfunction, whereas the longitudinal development of cognitive impairment in PD reflects additional posterior cortical dysfunction that might predict PDD. However, some degree of overlap between fronto-striatal and posterior-cortical is likely, but essentially it is a question for the future. It is important to note that this thesis provides information on cognitive neuropathological changes in PD that might contribute to more relevant choices of pharmacotherapy, cognitive enhancement interventions, and diagnostic accuracy in respect of PDD. Given the complex neuropathological aetiology in PD and the variable expression of cognitive impairments, large-scale longitudinal imaging studies are needed to further clarify early predictors for patients at risk for PDD.

Acknowledgements

References

1.   Eriksen JL, Wszolek Z, Petrucelli L. Molecular pathogenesis of Parkinson disease. Archives of Neurology 2005; 62: 353–357.

2.   de Lau LML, Breteler MMB. Epidemiology of Parkinson's disease. The Lancet Neurology 2006; 5: 525-535.

3.   Parkinson J. An essay on the shaking palsy. London: Sherwood, Neely, and Jones; 1817: 66.

4.   Marttila RJ, Rinne UK. Dementia in Parkinson's disease. Acta Neurologica Scandinavica 1976; 54: 431-441.

5.   Farnley M, Lees AJ. Ageing and Parkinson's disease: substantia nigra regional selectivity. Brain 1991; 114: 2283–2301.

6.   Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. The Lancet Neurology 2010; 9:1200–1213.

7.   Barone P, Aarsland D, Burn D, Emre M, Kulisevsky J, Weintraub D. Cognitive impairment in nondemented Parkinson's disease. Movement Disorders 2011 ;26: 2483–2495.

8.   Monchi O, Stoessl AJ. Imaging neural correlates of mild cognitive impairment in Parkinson's disease. The Lancet Neurology 2012; 11: 653–655.

9.   Mutch WJ, Dingwall-fordyce I, Downie AW, Paterson JG, Roy SK. Parkinson's disease in a Scottish city. British Medical Journal 1986; 292: 534–536.

10.   Linder J, Stenlund H, Forsgren L. Incidence of Parkinson's disease and parkinsonism in northern Sweden: a population-based study. Movement Disorders 2010; 25: 341–348.

11.   Kirkwood TBL. The most pressing problem of our age. BMJ 2003; 326: 1297–1299.

12.   Hindle J V. Ageing, neurodegeneration and Parkinson's disease. Age and Ageing 2010; 39: 156–161.

13.   Louis ED, Bennett D a. Mild Parkinsonian signs: An overview of an emerging concept. Movement Disorders 2007; 22: 1681–1688.

14.   Greenamyre JT, Hastings TG. Parkinson's-Divergent causes, convergent mechanisms. Science 2004; 1120.

15.   McGeer PL, Itagaki S, Akiyama H, McGeer EG. Rate of cell death in parkinsonism indicates active neuropathological process. Annals of Neurology 1988; 24: 574-576.

16.   Braak H, Bohl JR, Müller CM, Rüb U, de Vos RAI, Del Tredici K. Stanley Fahn Lecture 2005: The staging procedure for the inclusion body pathology associated with sporadic Parkinson's disease reconsidered. Movement Disorders 2006; 21: 2042–2051.

17.   Carlsson A. The occurrence, distribution and physiological role of catecholamines in the nervous system. Pharmacological Review 1959; 11: 490-493.

18.   Jankovic J. Parkinson's disease: clinical features and diagnosis. Journal of Neurology, Neurosurgery & Psychiatry 2008; 79: 368–376.

19.   Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of Lewy body Parkinson's disease 2001; 57:1497-1499.

20.   Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002; 125: 861–870.

21.   Jankovic J. Pathophysiology and clinical assessment of Parkinsonian symptoms and signs. In: Pahwa R, Lyons K, Koller WC, eds. Handbook of Parikinson's disease. New York: Taylor and Francis Group; LLC, 2007: 79-104.

22.   Gibb WRG, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. Movement Disorders 1988; 51: 745–752.

23. Pyatigorskaya N, Gallea C, Garcia-Lorenzo D, Vidailhet M, Lehericy S. A review of the use of magnetic resonance imaging in Parkinson's disease. Therapeutic Advances in Neurological Disorders 2014; 7: 206–220.

24. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord. 2008 Nov 15;23:2129–70.

25. Goetz CG, Poewe W, Rascol O, Sampaio C, Stebbins GT, Counsell C, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. Movement Disorders 2004; 19: 1020–1028.

26. Ramaker C, Marinus J, Stiggelbout AM, Van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Movement Disorders 2002; 17: 867–876.

27. Siderowf A, Lang AE. Premotor Parkinson's disease: concepts and definitions. Movement Disorders 2012; 27: 608–616.

28. Reijnders JSAM, Ehrt U, Weber WEJ, Aarsland D, Leentjens AFG. A systematic review of prevalence studies of depression in Parkinson's disease. Movement Disorders 2008; 23: 183–189.

29. Steffens DC, Fisher GG, Langa KM, Potter GG, Plassman L. Prevalence of depression among older Americans: the aging, demographics amd memory study. International Psychogeriatrics 2010; 21: 879–888.

30. Monchi O, Degroot C, Mejia-Constain B, Bruneau M-A. Neuroimaging studies of different cognitive profiles in Parkinson's disease. Parkinsonism and Related Disorders 2012; 18: 77–79.

31. Lees AJ, Smith E. Cognitive deficits in the early stages of Parkinson's disease. Brain 1983; 106: 257-270.

32. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Kokmen E, Tangelos EG. Aging, memory, and mild cognitive impairment. International Psychogeriatrics 1997; 9: 65–69.

33. Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L-O, et al. Mild cognitive impairment--beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. Journal of Internal Medicine 2004; 256: 240–246.

34. Hänninen T, Hallikainen M, Tuomainen S, Vanhanen M, Soininen H. Prevalence of mild cognitive impairment: a population-based study in elderly subjects. Acta Neurologica Scandinavica 2002; 106: 148–154.

35. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, et al. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. Neurology 2010; 75: 1062–1069.

36. Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, kragh-Sörensen P. Risk of dementia in Parkinson's disease: a community-based, prospective study. Neurology 2001; 56: 730-736.

37. Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Movement Disorders 2012; 27: 349–356.

38. Broeders M, de Bie RMA, Velseboer DC, Speelman JD, Muslimovic D, Schmand B. Evolution of mild cognitive impairment in Parkinson disease. Neurology 2013; 81: 346–352.

39. Pedersen KF, Larsen JP, Tysnes O-B, Alves G. Prognosis of mild cognitive impairment in early Parkinson disease: the Norwegian ParkWest study. JAMA Neurology 2013; 70: 580–586.

40. Emre M. Review Dementia associated with Parkinson's disease. The Lancet Neurology 2003; 2: 229–237.

41. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sörensen P. Prevalence and characteristics of dementia in Parkinson's disease: an 8-year prospective study. Archives of Neurology 2003; 60: 387-392.

42. Emre M, Ford PJ, Bilgiç B, Uç EY. Cognitive impairment and dementia in Parkinson's disease: practical issues and management. Movement Disorders 2014; 29: 663–672.

43. Weintraub D, Dietz N, Duda JE, Wolk D a, Doshi J, Xie SX, et al. Alzheimer's disease pattern of brain atrophy predicts cognitive decline in Parkinson's disease. Brain 2012; 135: 170–180.

44. Alzheimer's Association Report. 2012 Alzheimer's disease facts and figures. Alzheimers and Dementia 2012; 8: 131–168.

45. Compta Y, Parkkinen L, O'Sullivan SS, Vandrovcova J, Holton JL, Collins C, et al. Lewy- and Alzheimer-type pathologies in Parkinson's disease dementia: which is more important? Brain 2011; 134: 1493–1505.

46. Alves G, Lange J, Blennow K, Zetterberg H, Andreasson U, Førland MG, et al. CSF A b 42 predicts early-onset dementia in Parkinson disease. Neurology. 2014;82:1784–90.

47. Montine TJ, Shi M, Quinn JF, Peskind ER, Craft S, Ginghina C, et al. CSF Aβ42 and tau in Parkinson's disease with cognitive impairment. Movement Disorders 2011; 25: 2682–2685.

48. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Movement Disorders 2007; 22: 1689–1707.

49. Charcot JM. On paralysis agitans (lecture V). In: lectures on the diseases of the nervous system. England, London: New Sydenham Society, 1977.

50. Winter Y, von Campenhausen S, Arend M, Longo K, Boetzel K, Eggert K, et al. Health-related quality of life and its determinants in Parkinson's disease: results of an Italian cohort study. Parkinsonism and Related Disorders 2011; 17: 265–269.

51. Vossius C, Larsen JP, Janvin C, Aarsland D. The economic impact of cognitive impairment in Parkinson's disease. Movement Disorders 2011; 26: 1541-1544.

52. Fletcher P, Leake A, Marion M-H. Patients with Parkinsons's disease dementia stay in the hospital twice as long as those without dementia. Movement Disorders 2011; 26: 919.

53.   Hu M, Cooper J, Beamish R, Jones E, Butterworth R, Catterall L, et al. How well do we recognise non-motor symptoms in a British Parkinson's disease population? Journal of Neurology 2011; 258: 1513–1517.

54.   Svenningsson P, Westman E, Ballard C, Aarsland D. Cognitive impairment in patients with Parkinson's disease: diagnosis, biomarkers, and treatment. The Lancet Neurology 2012; 11: 697–707.

55.   Wilson RS, Beckett LA, Barnes LL, Schneider JA, Bach J, Evans DA, et al. Individual differences in rates of change in cognitive abilities of older persons. Psychology and Aging 2002; 17: 179–193.

56.   Hedden T, Gabrieli JDE. Insights into the ageing mind: a view from cognitive neuroscience. Nature Reviews Neuroscience 2004; 5: 87–96.

57.   Rönnlund M, Nyberg L, Bäckman L, Nilsson L-G. Stability, growth, and decline in adult life span development of declarative memory: cross-sectional and longitudinal data from a population-based study. Psychology and Aging 2005; 20: 3–18.

58.   Park DC, Lautenschlager G, Hedden T, Davidson NS, Smith AD, Smith PK. Models of visuospatial and verbal memory across the adult life span. Psychology and Aging 2002; 17: 299–320.

59.   Pudas S, Persson J, Josefsson M, de Luna X, Nilsson L-G, Nyberg L. Brain characteristics of individuals resisting age-related cognitive decline over two decades. Journal of Neuroscience 2013; 33: 8668–8677.

60.   Graham JE, Rockwood K, Beattie BL, Eastwood R, Gauthier S, Tuokko H, et al. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. The Lancet 1997; 349: 1793–1796.

61.   Di Carlo A, Baldereschi M, Amaducci L, et al. Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact of disability. The Italian Longitudinal Study on Aging. Journal of The American Geriatrics Society 2000; 48: 775-782.

62. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers and Dementia 2013; 9: 63–75.

63. Aarsland D, Brønnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology 2009; 72: 1121–1126.

64. Elgh E, Domellöf M, Linder J, Edström M, Stenlund H, Forsgren L. Cognitive function in early Parkinson's disease: a population-based study. European Journal of Neurology 2009; 16: 1278-1284.

65. Levin BE, Llabre MM, Weiner WJ. Cognitive impairments associated with early Parkinson's disease. Neurology 1989; 39: 557-561.

66. Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease. Brain 1986; 109: 845-883.

67. Nagano-Saito A, Leyton M, Monchi O, Goldberg YK, He Y, Dagher A. Dopamine depletion impairs frontostriatal functional connectivity during a set-shifting task. Journal of Neuroscience 2008; 28: 3697–3706.

68. Owen A, James M, Leigh PN, Summers BA, Marsden CD, Quinn NP, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. Brain 1992; 115: 1727–1751.

69. Gauggel S, Rieger M, Feghoff TA. Inhibition of ongoing responses in patients with Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 2004; 75: 539-544.

70. Monchi O, Petrides M, Doyon J, Postuma RB, Worsley K, Dagher A. Neural bases of set-shifting deficits in Parkinson's disease. Journal of Neuroscience 2004; 24: 702–710.

71. Marklund P, Larsson A, Elgh E, Linder J, Riklund KA, Forsgren L, et al. Temporal dynamics of basal ganglia under-recruitment in Parkinson's disease: transient caudate abnormalities during updating of working memory. Brain 2009; 132: 336–346.

72.   Mayeux R, Stern Y, Sano M, Cote L, Williams JBW. Clinical and biochemical correlates of bradyphrenia in Parskinson's disease. Neurology 1987; 37: 1130-1134.

73.   Woods SP, Tröster AI. Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. Journal of International Neuropsychological Society 2003; 9: 17–24.

74.   Firbank MJ, Colloby SJ, Burn DJ, McKeith IG, O'Brien JT. Regional cerebral blood flow in Parkinson's disease with and without dementia. Neuroimage 2003; 20: 1309–1319.

75.   Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007; 130: 1787–1798.

76.   Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: a prospective, community-based study. Annals of Neurology 2005; 58: 773–776.

77.   Perry EK, Curtis M, Dick DJ, Candy JM, Atack JR, Bloxham CA, et al. Cholinergic correlates of cognitive impairment in Parkinson's disease: comparisons with Alzheimer's disease. Journal of Neurology, Neurosurgery & psychiatry 1985; 48: 413–421.

78.   Lewis SJG, Foltynie T, Blackwell AD, Robbins TW, Owen AM, Barker RA. Heterogeneity of Parkinson's disease in the early clinical stages using a data driven approach. Journal of Neurology, Neurosurgery & Psychiatry 2005; 76: 343–348.

79.   James W. The principles of psychology (vol. 1 & 2). USA, New York: Dover Publications, Inc, 1980.

80.   Baddeley A. Working Memory. Science 1992; 255: 556-559.

81.   Baddeley AD. Working memory. England, Oxford: Oxford University Press, 1986.

82.   Fuster JM, Bressler SL. Cognit activation: a mechanism enabling temporal integration in working memory. Trends in Cognitive Sciences 2012; 16: 207–218.

83.   Oberauer K. The focus of attention in working memory-from metaphors to mechanisms. Frontiers in Human Neuroscience 2013; 7: 673.

84.   Nyberg L, Marklund P, Persson J, Cabeza R, Forkstam C, Petersson KM, et al. Common prefrontal activations during working memory, episodic memory, and semantic memory. Neuropsychologia 2003; 41: 371–377.

85.   Tulving E. Episodic and semantic memory. In Tulving e. & Donaldson W. (Eds), Organisation of memory. New York: Academic Press, 1972.

86.   Smith EE. Storage and executive processes in the frontal lobes. Science 1999; 283: 1657–1661.

87.   Teuber H-L. Unity and diversity of frontal lobe functions. Acta Neruobiologiae Experimentalis 1972; 32: 615–656.

88.   Miyake a, Friedman NP, Emerson MJ, Witzki a H, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cognitive Psychology 2000; 41: 49–100.

89.   Landau SM, Lal R, O'Neil JP, Baker S, Jagust WJ. Striatal dopamine and working memory. Cerebral Cortex 2009; 19: 445–454.

90.   Cools R, D'Esposito M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biological Psychiatry 2011; 69: 113–125.

91.   Provost J-S, Petrides M, Monchi O. Dissociating the role of the caudate nucleus and dorsolateral prefrontal cortex in the monitoring of events within human working memory. European Journal of Neuroscience 2010; 32: 873–880.

92.   Darki F, Klingberg T. The role of fronto-parietal and fronto-striatal networks in the development of working wemory: a longitudinal study. Cerebral Cortex 2014; 9: 1–9.

93. Durstewitz D, Seamans JK, Sejnowski TJ, Cano-colino M, Almeida R, Gomez-cabrero D, et al. Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. Journal of Neurophysiology 2014; 83: 1733–1750.

94. D'Esposito M. From cognitive to neural models of working memory. Philosophical Transactions of the Royal Society of London, Series B, Biological sciences 2007; 362: 761–772.

95. Dahlin E, Neely AS, Larsson A, Bäckman L, Nyberg L. Transfer of learning after updating training mediated by the striatum. Science 2008; 320: 1510–1512.

96. O'Reilly RC, Frank MJ. Making working memory work: a computational model of learning in the prefrontal cortex and basal ganglia. Neural Computation 2006; 18: 283–328.

97. Hazy TE, Frank MJ, O'reilly RC. Towards an executive without a homunculus: computational models of the prefrontal cortex/basal ganglia system. Philosophical Transactions of the Royal Society of London, Series B, Biological sciences 2007; 362: 1601–1613.

98. Lewis SJG, Slabosz A, Robbins TW, Barker RA, Owen AM. Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. Neuropsychologia 2005; 43: 823–832.

99. Kehagia AA, Barker RA, Robbins TW. Cognitive impairment in Parkinson's disease: the dual syndrome hypothesis. Neurodegenerative Diseases 2013; 11: 79–92.

100. Robbins TW, Cools R. Cognitive deficits in Parkinson's disease: a cognitive neuroscience perspective. Movement Disorders 2014; 29: 597–607.

101. Pereira JB, Svenningsson P, Weintraub D, Brønnick K, Lebedev A, Westman E, et al. Initial cognitive decline is associated with cortical thinning in early Parkinson disease. Neurology 2014; 82: 2017–2025.

102. Segura B, Baggio HC, Marti MJ, Valldeoriola F, Compta Y, Garcia-Diaz AI, et al. Cortical thinning associated with mild cognitive impairment in Parkinson's disease. Movement Disorders 2014; 29: 1495-1503.

103. Hanganu A, Bedetti C, Degroot C, Mejia-Constain B, Lafontaine A-L, Soland V, et al. Mild cognitive impairment is linked with faster rate of cortical thinning in patients with Parkinson's disease longitudinally. Brain 2014; 137: 1120–1129.

104. Mak E, Bergsland N, Dwyer MG, Zivadinov R, Kandiah N. Subcortical atrophy is associated with cognitive impairment in mild Parkinson's disease: a combined investigation of volumetric changes, cortical thickness, and vertex-based shape analysis. American Journal of Neuroradiology; In press.

105. Song SK, Lee JE, Park H-J, Sohn YH, Lee JD, Lee PH. The pattern of cortical atrophy in patients with Parkinson's disease according to cognitive status. Movement Disorders 2011; 26: 289–296.

106. Melzer TR, Watts R, MacAskill MR, Pitcher TL, Livingston L, Keenan RJ, et al. Grey matter atrophy in cognitively impaired Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 2012; 83: 188–194.

107. Beyer MK, Janvin CC, Larsen JP, Aarsland D. A magnetic resonance imaging study of patients with Parkinson's disease with mild cognitive impairment and dementia using voxel-based morphometry. Journal of Neurology, Neurosurgery & Psychiatry 2007; 78: 254–259.

108. Tröster AI. Neuropsychological characteristics of dementia with Lewy bodies and Parkinson's disease with dementia: differentiation, early detection, and implications for "mild cognitive impairment" and biomarkers. Neuropsychology Review 2008; 18: 103–119.

109. Wang H-F, Yu J-T, Tang S-W, Jiang T, Tan C-C, Meng X-F, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. Journal of Neurology, Neurosurgery & Psychiatry 2014; In press.

110. Lippa CF, Duda JE, Grossman M, Hurtig HI, Aarsland D, Boeve BF, et al. DLB and PDD boundary issues: diagnosis, treatment, molecular pathology, and biomarkers. Neurology 2007; 68: 812–819.

111. Janvin CC, Larsen JP, Salmon DP, Galasko D, Hugdahl K, Aarsland D. Cognitive profiles of individual patients with Parkinson's disease and dementia: comparison with dementia with lewy bodies and Alzheimer's disease. Movement Disorders 2006; 21: 337–342.

112. Burton EJ, McKeith IG, Burn DJ, Williams ED, O'Brien JT. Cerebral atrophy in Parkinson's disease with and without dementia: a comparison with Alzheimer's disease, dementia with Lewy bodies and controls. Brain 2004; 127: 791–800.

113. Lee JE, Park B, Song SK, Sohn YH, Park H-J, Lee PH. A comparison of gray and white matter density in patients with Parkinson's disease dementia and dementia with Lewy bodies using voxel-based morphometry. Movement Disorders 2010; 25: 28–34.

114. Dauer W, Przedborski S. Parkinson's disease: mechanisms and models. Neuron 2003; 39: 889–909.

115. Middleton FA, Strick PL. Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies. Brain and Cognition 2000; 42: 183–200.

116. Kish SJ, Shannak K, Hornykiewitz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. The New England Journal of Medicine 1988; 318: 876-880.

117. Rinne JO, Portin R, Ruottinen H, Nurmi E, Bergman J, Haaparanta M, et al. Cognitive impairment and the brain dopaminergic system in Parkinson disease: [18F]fluorodopa positron emission tomographic study. Arch Neurol 2000; 57: 470–475.

118. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington clinical, morphological and neurochemical correlations. Journal of the Neruological Sciences 1973; 20: 415-455.

119. Lavin A, Nogueira L, Lapish CC, Wightman RM, Phillips PEM, Seamans JK. Mesocortical dopamine neurons operate in distinct temporal domains using multimodal signaling. Journal of Neuroscience 2005; 25: 5013–5023.

120. Floresco SB, Magyar O. Mesocortical dopamine modulation of executive functions: beyond working memory. Psychopharmacology 2006; 188: 567–585.

121. Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neuroscience and Biobehavioral Reviews 2006; 30: 1–23.

122. Marié RM, Rioux P, Eustache F, Travère JM, Lechevailer B, Baron JC. Clues about the functional neuroanatomy of verbal working memory: a study of resting brain glucose metabolism in Parkinson's disease. European Journal of Neurology 1995; 2: 83-94.

123. Christopher L, Marras C, Duff-Canning S, Koshimori Y, Chen R, Boileau I, et al. Combined insular and striatal dopamine dysfunction are associated with executive deficits in Parkinson's disease with mild cognitive impairment. Brain 2014; 137: 565–575.

124. Sawada Y, Nishio Y, Suzuki K, Hirayama K, Takeda A, Hosokai Y, et al. Attentional set-shifting deficit in Parkinson's disease is associated with prefrontal dysfunction: an FDG-PET study. PLoS One 2012; 7: e38498.

125. Lebedev A V, Westman E, Simmons A, Lebedeva A, Siepel FJ, Pereira JB, et al. Large-scale resting state network correlates of cognitive impairment in Parkinson's disease and related dopaminergic deficits. Frontiers in Systems Neuroscience 2014; 8: 45.

126. Monchi O, Petrides M, Mejia-Constain B, Strafella AP. Cortical activity in Parkinson's disease during executive processing depends on striatal involvement. Brain 2007; 130: 233–244.

127. Moustafa AA, Sherman SJ, Frank MJ. A dopaminergic basis for working memory, learning and attentional shifting in Parkinsonism. Neuropsychologia 2008; 46: 3144–3156.

128. Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN, et al. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Annals of Neurology 2002; 5: 156–164.

129. Huang C, Tang C, Feigin A, Lesser M, Ma Y, Pourfar M, et al. Changes in network activity with the progression of Parkinson's disease. Brain 2007; 130: 1834–1846.

130. Huang C, Mattis P, Perrine K, Brown N, Dhawan V, Eidelberg D. Metabolic abnormalities associated with mild cognitive impairment in Parkinson disease. Neurology 2008; 70: 1470–1477.

131. Williams-Gray CH, Mason SL, Evans JR, Foltynie T, Brayne C, Robbins TW, et al. The CamPaIGN study of Parkinson's disease: 10-year outlook in an incident population-based cohort. Journal of Neurology, Neurosurgery & Psychiatry 2013; 84: 1258–1264.

132. Choi SH, Jung TM, Lee JE, Lee S-K, Sohn YH, Lee PH. Volumetric analysis of the substantia innominata in patients with Parkinson's disease according to cognitive status. Neurobiology of Aging 2012; 33: 1265–1272.

133. Hattori T, Orimo S, Aoki S, Ito K, Abe O, Amano A, et al. Cognitive status correlates with white matter alteration in Parkinson's disease. Human Brain Mapping 2012; 33: 727–739.

134. Agosta F, Canu E, Stefanova E, Sarro L, Tomić A, Špica V, et al. Mild cognitive impairment in Parkinson's disease is associated with a distributed pattern of brain white matter damage. Human Brain Mapping 2014; 35: 1921–1229.

135. Lewis SJG, Dove A, Robbins TW, Barker RA, Owen AM. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. Journal of Neuroscience 2003; 23: 6351–6356.

136. Nagano-Saito A, Habak C, Mejía-Constaín B, Degroot C, Monetta L, Jubault T, et al. Effect of mild cognitive impairment on the patterns of neural activity in early Parkinson's disease. Neurobiology of Aging 2014; 35: 223–231.

137. Geurtsen GJ, Hoogland J, Goldman JG, Schmand B a, Tröster AI, Burn DJ, et al. Parkinson's disease mild cognitive impairment: application and validation of the criteria. Journal of Parkinsons's Disease 2014; 4: 131–137.

138. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. British Journal of Psychiatry 1979; 134: 382–389.

139. Bottomley PA, Hardy CJ, Argersinger RE, AllenMoore G. A review of 1H nuclear magnetic resonance relaxation in pathology: Are T1 and T2 diagnostic? Medical Physics 1987; 14: 1–37.

140. Edelman RR, Warach S. Magnetic resonance imaging. New England Journal of Medicine 1993; 328: 708–716.

141. Matthews PM, Jezzard P. Functional magnetic resonance imaging. Journal of Neurology, Neurosurgery & Psychiatry 2004; 75: 6–12.

142. Bandettini P. Functional MRI today. International Journal of Psychophysiology 2007; 63: 138–145.

143. Ogawa S, Lee TM, Kay AR, Tank DW. Brain magnetic resonance imaging with contrast dependent on blood oxygenation. PNAS 1990; 87: 9868–9872.

144. Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, et al. Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. PNAS 1992; 89: 5675–5679.

145. Boynton GM, Engel S a, Glover GH, Heeger DJ. Linear systems analysis of functional magnetic resonance imaging in human V1. Journal of Neuroscience 1996; 16: 4207–4221.

146. Stonnington CM, Tan G, Klöppel S, Chu C, Draganski B, Jack CR, et al. Interpreting scan data acquired from multiple scanners: a study with Alzheimer's disease. Neuroimage 2008; 39: 1180–1185.

147. Miller KM, Price CC, Okun MS, Montijo H, Bowers D. Is the n-back task a valid neuropsychological measure for assessing working memory? Archives of Clinical Neuropsychology 2009; 24: 711–717.

148. Bäckman L, Nyberg L, Soveri A, Johansson J, Andersson M, Dahlin E, et al. Effects of working-memory training on striatal dopamine release. Science 2011; 333: 718.

149. Marie RM, Barre L, Dupuy B, Viader F, Defer G, Baron JC. Relationships between striatal dopamine denervation and frontal executive tests in Parkinson's disease. Neuroscience Letters 1999; 260: 77–80.

150. Cools R, Gibbs SE, Miyakawa A, Jagust W, D'Esposito M. Working memory capacity predicts dopamine synthesis capacity in the human striatum. Journal of Neuroscience 2008; 28: 1208–1212.

151. Sawamoto N, Piccini P, Hotton G, Pavese N, Thielemans K, Brooks DJ. Cognitive deficits and striato-frontal dopamine release in Parkinson's disease. Brain 2008; 131: 1294–1302.

152. Macdonald PA, Monchi O. Differential effects of dopaminergic therapies on dorsal and ventral striatum in Parkinson's disease: implications for cognitive function. Parkinsons Disease 2011; 2011: 572743.

153. Cools R, Barker R a, Sahakian BJ, Robbins TW. l-Dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia 2003; 41:1431–1441.

154. Hanagasi HA, Gurvit H, Unsalan P, Horozoglu H, Tuncer N, Feyzioglu A, et al. The effects of rasagiline on cognitive deficits in Parkinson's disease patients without dementia: a randomized, double-blind, placebo-controlled, multicenter study. Movement Disorders 2011; 26: 1851–1858.

155. Costa A, Peppe A, Dell'Agnello G, Caltagirone C, Carlesimo GA. Dopamine and cognitive functioning in de novo subjects with Parkinson's disease: effects of pramipexole and pergolide on working memory. Neuropsychologia 2009; 47: 1374–1381.

156. Xu Y, Yan J, Zhou P, Li J, Gao H, Xia Y, et al. Neurotransmitter receptors and cognitive dysfunction in Alzheimer's disease and Parkinson's disease. Progress in Neurobiology 2012; 97: 1–13.

157. Duncan J, Owen a M. Common regions of the human frontal lobe recruited by diverse cognitive demands. Trends in Neurosciences 2000; 23: 475–483.

158. Carter CS, van Veen V. Anterior cingulate cortex and conflict detection : An update of theory and data. Cognitive, Affective, & Behavioural Neuroscience 2007; 7:367–379.

159. Kelley TA, Lavie N. Working memory load modulates distractor competition in primary visual cortex. Cerebral Cortex 2011; 21 :659–665.

160. Borst JP, Anderson JR. Using model-based functional MRI to locate working memory updates and declarative memory retrievals in the fronto-parietal network. PNAS 2013; 110: 1628–1633.

161. Postuma RB, Dagher A. Basal ganglia functional connectivity based on a meta-analysis of 126 positron emission tomography and functional magnetic resonance imaging publications. Cerebral Cortex 2006; 16: 1508–1521.

162. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. Trends in Neurosciences 1989; 12: 366-375.

163. Pillon B, Dubois B, Cusimano G, Bonnet A, Lhermitte OIS, Agid Y. Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? Journal of Neurology, Nerosurgery & Psychiatry 1989; 52: 201–206.

164. Weintraub D, Doshi J, Koka D, Davatzikos C, Siderowf AD, Duda JE, et al. Neurodegeneration across stages of cognitive decline in Parkinson's disease. Archives of Neurology 2011; 68: 1562–1568.

165. Lyoo CH, Jeong Y, Ryu YH, Rinne JO, Lee MS. Cerebral glucose metabolism of Parkinson's disease patients with mild cognitive impairment. European Neurology 2010; 64: 65–73.

166. Hosokai Y, Nishio Y, Hirayama K, Takeda A, Ishioka T, Sawada Y, et al. Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. Movement Disorders 2009; 24: 854–862.

167. Bateman RJ, Xiong C, Benzinger TLS, Fagan AM, Goate A, Fox NC, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. New England Journal of Medicine 2012; 367: 795–804.

168. Courtney SM, Ungerleider LG, Keil K, Haxby JV. Transient and sustained activity in a distributed neural system for human working memory. Nature 1997; 386: 608–611.

169. Bohnen NI, Koeppe R a, Minoshima S, Giordani B, Albin RL, Frey K a, et al. Cerebral glucose metabolic features of Parkinson disease and incident dementia: longitudinal study. The Journal of Nuclear Medicine 2011; 52: 848–855.

170. Sánchez-Cubillo I, Periáñez J a, Adrover-Roig D, Rodríguez-Sánchez JM, Ríos-Lago M, Tirapu J, et al. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. Journal of the International Neuropsychological Society 2009; 15: 438–450.

171. Müller LD, Guhn A, Zeller JBM, Biehl SC, Dresler T, Hahn T, et al. Neural correlates of a standardized version of the trail making test in young and elderly adults: a functional near-infrared spectroscopy study. Neuropsychologia 2014; 56: 271–279.

172. Allen MD, Owens TE, Fong AK, Richards DR. A functional neuroimaging analysis of the Trail Making Test-B: implications for clinical application. Behavioural Neurology 2011; 24: 159–171.

173. Nyberg L, Persson J, Habib R, Tulving E, McIntosh AR, Cabeza R, et al. Large scale neurocognitive networks underlying episodic memory. Journal of Cognitive Neuroscience 2000; 12: 163–173.

174. Shohamy D, Adcock RA. Dopamine and adaptive memory. Trends in Cognitive Sciences 2010; 14: 464–472.

175. Braak H, Ghebremedhin E, Rüb U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell and Tissue Research 2004; 318: 121–134.

176. Hall H, Reyes S, Landeck N, Bye C, Leanza G, Double K, et al. Hippocampal Lewy pathology and cholinergic dysfunction are associated with dementia in Parkinson's disease. Brain 2014; 137: 2493–2508.

177. Bohnen NI, Kaufer DI, Hendrickson R, Ivanco LS, Lopresti BJ, Constantine GM, et al. Cognitive correlates of cortical cholinergic denervation in Parkinson's disease and parkinsonian dementia. Journal of Neurology 2006; 253: 242–247.

178. Bäckman L, Karlsson S, Fischer H, Karlsson P, Brehmer Y, Rieckmann A, et al. Dopamine D(1) receptors and age differences in brain activation during working memory. Neurobiology of Aging 2011; 32: 1849–1856.

179. Vazey EM, Aston-Jones G. The emerging role of norepinephrine in cognitive dysfunctions of Parkinson's disease. Frontiers in Behavioral Neuroscience 2012; 6: 48.

180. Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. Annual Review of Neuroscience 2005; 28: 403–450.

181. Marsh L, Biglan K, Gerstenhaber M, Williams JR. Atomoxetine for he treatment of executive dysfunction in Parkinson's disease: A pilot open-label study. Movement Disorders 2010; 24: 277–282.

182. Dagher A, Owen AM, Boecker H, Brooks DJ. The role of the striatum and hippocampus in planning: A PET activation study in Parkinson's disease. Brain 2001; 124: 1020-1032.

183. Hong JY, Yun HJ, Sunwoo MK, Ham JH, Lee J-M, Sohn YH, et al. Cognitive and cortical thinning patterns of subjective cognitive decline in patients with and without Parkinson's disease. Parkinsonism and Related Disorders 2014; 20: 999–1003.

184. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. Journal of the International Neuropsychological Society 2002; 8: 448–460.

185. Cabeza R, Anderson ND, Locantore JK, McIntosh AR. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage 2002; 17: 1394–1402.

186. Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L. Memory aging and brain maintenance. Trends in Cognitive Sciences 2012; 16: 292–305.

187. Nyberg L, Larsson A, Eriksson J, Birgander R, Sundström T, Riklund K. Comparing 1.5T and 3T bold fMRI imaging of finger tapping with familiar and novel sequences. In: Schaller B. Neuroscience imaging research trends, New York, NY: Nova Science Publishers.

188. Abdulkadir A, Mortamet B, Vemuri P, Jack CR, Krueger G, Klöppel S. Effects of hardware heterogeneity on the performance of SVM Alzheimer's disease classifier. Neuroimage 2011; 58: 785–792.

189. Marchewka A, Kherif F, Krueger G, Grabowska A, Frackowiak R, Draganski B. Influence of magnetic field strength and image registration strategy on voxel-based morphometry in a study of Alzheimer's disease. Human Brain Mapping 2014; 35: 1865–1874.

190. Yarnall AJ, Breen DP, Duncan GW, Khoo TK, Coleman SY, Firbank MJ, et al. Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study. Neurology 2014; 82: 308–316.

191. Liepelt-Scarfone I, Graeber S, Feseker A, Baysal G, Godau J, Gaenslen A, et al. Influence of different cut-off values on the diagnosis of mild cognitive impairment in Parkinson's disease. Parkinson's Disease 2011; 2011: 540843.

192. Dalrymple-Alford JC, Livingston L, MacAskill MR, Graham C, Melzer TR, Porter RJ, et al. Characterizing mild cognitive impairment in Parkinson's disease. Movement Disorders 2011; 26: 629–636.

193. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology 2005; 65: 1239–1245.

194. Cheesman a L, Barker RA, Lewis SJG, Robbins TW, Owen AM, Brooks DJ. Lateralisation of striatal function: evidence from 18F-dopa PET in Parkinson's disease. Journal of Neurology, Neurosurgery & Psychiatry 2005; 76: 1204–1210.

195. Miller IN, Cronin-Golomb A. Gender differences in Parkinson's disease: clinical characteristics and cognition. Movement Disorders 2011; 25: 2695–2703.

196. Nyberg L, Salami A, Andersson M, Eriksson J, Kalpouzos G, Kauppi K, et al. Longitudinal evidence for diminished frontal cortex function in aging. PNAS 2010; 107: 22682–22686.

197. Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cerebral Cortex 2005; 15: 1676–1689.

198. Button KS, Ioannidis JPA, Mokrysz C, Nosek BA, Flint J, Robinson ESJ, et al. Power failure: why small sample size undermines the reliability of neuroscience. Nature Reviews Neuroscience 2013; 14: 365–376.

199. Bohnen NI, Albin RL. The cholinergic system and Parkinson disease. Behavioural Brain Research 2011; 221: 564–573.

200. Naismith SL, Mowszowski L, Diamond K, Lewis SJG. Improving memory in Parkinson's disease: a healthy brain ageing cognitive training program. Movement Disorders 2013; 28: 1097–1103.

201. Petrelli A, Kaesberg S, Barbe MT, Timmermann L, Fink GR, Kessler J, et al. Effects of cognitive training in Parkinson's disease: a randomized controlled trial. Parkinsonism and Related Disorders 2014; In press.

202. Cruise KE, Bucks RS, Loftus a M, Newton RU, Pegoraro R, Thomas MG. Exercise and Parkinson's: benefits for cognition and quality of life. Acta Neurologica Scandinavia 2011; 123: 13–19.

203. Hindle JV, Petrelli A, Clare L, Kalbe E. Nonpharmacological enhancement of cognitive function in Parkinson's disease: a systematic review. Movement Disorders 2013; 28: 1034–1049.