PET AND MR IMAGING IN PARKINSON'S DISEASE PATIENTS WITH COGNITIVE IMPAIRMENT

A study of dopaminergic dysfunction, amyloid deposition, cortical hypometabolism and brain atrophy

by

Pekka Jokinen

Unit of Clinical Physiology, Nuclear Medicine and PET activities
Turku PET Centre
Department of Neurology

Supervised by

Professor Juha Rinne
Turku PET Centre
University of Turku
Turku, Finland

Reviewed by

Professor Aapo Ahonen
Department of Clinical Physiology and Nuclear Medicine
Helsinki University Central Hospital
Helsinki, Finland

Professor Tapani Keränen
Deparment of Clinical Pharmacology
University of Eastern Finland
Kuopio, Finland

Dissertation opponent

Docent Jaana Suhonen
Jokilaakson Terveys Oy
Jämsä, Finland

To Pauliina

ABSTRACT

Pekka Jokinen

PET AND MR IMAGING IN PARKINSON'S DISEASE PATIENTS WITH COGNITIVE IMPAIRMENT

A study of dopaminergic dysfunction, amyloid deposition, cortical hypometabolism and brain atrophy.

Parkinson's disease (PD) is the second most common neurodegenerative disorder. It is characterized by a severe loss of substantia nigra dopaminergic neurons leading to dopamine depletion in the striatum. PD affects movement, producing motor symptoms such as rigidity, tremor and bradykinesia. Non-motor symptoms include autonomic dysfunction, neurobehavioral problems and cognitive impairment, which may lead to dementia. The pathophysiological basis of cognitive impairment and dementia in PD is unclear.

The aim of this thesis was to study the pathophysiological basis of cognitive impairment and dementia in PD. We evaluated the relation between frontostriatal dopaminergic dysfunction and the cognitive symptoms in PD patients with [^{18}F]Fdopa PET. We also combined [^{11}C]PIB and [^{18}F]FDG PET and magnetic resonance imaging in PD patients with and without dementia. In addition, we analysed subregional striatal [^{18}F]Fdopa PET data to find out whether a simple ratio approach would reliably separate PD patients from healthy controls. The impaired dopaminergic function of the frontostriatal regions was related to the impairment in cognitive functions, such as memory and cognitive processing in PD patients. PD patients with dementia showed an impaired glucose metabolism but not amyloid deposition in the cortical brain regions, and the hypometabolism was associated with the degree of cognitive impairment. PD patients had atrophy, both in the prefrontal cortex and in the hippocampus, and the hippocampal atrophy was related to impaired memory. A single 15-min scan 75 min after a tracer injection seemed to be sufficient for separating patients with PD from healthy controls in a clinical research environment. In conclusion, the occurrence of cognitive impairment and dementia in PD seems to be multifactorial and relates to changes, such as reduced dopaminergic activity, hypometabolism, brain atrophy and rarely to amyloid accumulation.

Key words: Parkinson disease, PET, MRI, [18F]Fdopa, [^{11}C]PIB, [^{18}F]FDG, cognition, dementia, quantification.

TIIVISTELMÄ

Pekka Jokinen

PET- JA MAGNEETTIKUVANTAMINEN PARKINSONIN TAUDIN MUISTISAIRAUDESSA

Tutkimus dopaminergisestä vajaatoiminnasta, amyloidikertymästä, aivojen aineenvaihdunnasta ja surkastumisesta.

Kliinisen fysiologian, isotooppilääketieteen ja PET-toiminnan yksikkö ja neurologian klinikka, Turun yliopisto.
Annales Universitatis Turkuensis
Painotalo, Turku 2011

Parkinsonin tauti (PT) on toiseksi yleisin hermoston rappeutumissairaus. Sille on ominaista mustatumakkeen dopaminergisten hermosolujen kato, mikä johtaa dopamiinin puutokseen striatumissa. PT:lle tyypillisiä liikeoireita ovat lihasjäykkyys, vapina ja liikkeiden hitaus. Muita oireita ja löydöksiä ovat autonomisen hermoston toimintahäiriöt, neurobahavioraaliset ongelmat ja kognitiivinen heikentyminen, joka voi johtaa dementoitumiseen. Kognitiivisen heikentymisen ja dementian patofysiologia on epäselvä.

Tämän väitöskirjan tavoitteena oli selvittää patofysiologisia syitä kognitiiviseen heikentymiseen ja dementoitumiseen PT:ssa. Arvioimme kognitiivisen heikentymisen ja frontostriataalisen dopaminergisen vajaatoiminnan välistä yhteyttä. PT:n dementiaa sairastavilla selvitimme aivojen amyloidiplakkien ja alentuneen aineenvaihdunnan merkitystä dementoitumiseen. Lisäksi arvoimme PT:a sairastavien potilaiden aivojen surkastumamuutoksia. Metodologisena osatyönä arvioimme dopamiinijärjestelmän kuvantamiseen liittyvän suhdeanalyysin käyttöä PT-potilaiden ja terveiden kontrollien erottamisessa toisistaan. Kuvantamismenetelminä käytimme magneettikuvantamista ja positroniemissiotomografiaa, jonka merkkiaineina olivat [^{18}F]Fdopa, [^{11}C]PIB ja [^{18}F]FDG. Frontostriataalisten aivoalueiden alentunut dopaminerginen toiminta oli yhteydessä heikentyneisiin kognitiivisiin toimintoihin, kuten muistiin ja kognitiiviseen prosessointiin. PT:n dementiaa sairastavilla potilailla oli monella aivoalueella alentunut aineenvaihdunta, mikä korreloi kognitiivisen heikentymisen kanssa. Aivojen amyloidikertymän määrässä ei ollut eroa dementoituneiden ja ei-dementoituneiden välillä. Potilailla oli terveisiin verrattuna enemmän otsalohkon ja aivoturson surkastumaa, mikä korreloi heikentyneeseen muistiin. Yksinkertainen, aikaa ja resursseja säästävä suhdeanalyysi näytti olevan tehokas menetelmä potilaiden ja kontrollien erottamiseen toisistaan. Tutkimuksen tulokset viittaavat siihen, että kognitiivinen heikentyminen ja dementia PT:ssa ovat seurausta monesta eri osatekijästä. Näitä osatekijöitä ovat dopamiinijärjestelmän vajaatoiminta, aivojen surkastuminen ja alentunut aineenvaihdunta.

Avainsanat: Parkinsonin tauti, PET, MRI, [^{18}F]Fdopa, [^{11}C]PIB, [^{18}F]FDG, kognitio, dementia, kvantifikaatio.

TABLE OF CONTENTS

Contents

ABBREVIATIONS

AADC   amino acid decarboxylase

AC   anterior cingulate

AD   Alzheimer's disease

CERAD   Consortium to Establish a Registry for Alzheimer's Disease

COMT   catechol 0-methyltransferase

[^{11}C]PIB   N-methyl-^{11}C-2-(4'-methylaminophenyl)-6-hydroxybenzothiazole

DA   dopamine

DLPFC   dorsolateral prefrontal cortex

DLB   dementia with Lewy body

ERC   entorhinal cortex

[^{18}F]FDG   2-[^{18}F]-fluoro-2-deoxy-D-glucose

FDOPA   L-6-^{18}F-fluoro-3,4-dihydroxyphenylalanine

GMR   glucose metabolic rate

LN   Lewy neurite

LB   Lewy body

MAO   monoamine oxidase

MMSE   Mini-Mental State Examination

MRI   magnetic resonance imaging

PET   positron emission tomography

PD   Parkinson's disease

ROI   region of interest

SN   substantia nigra

SPM   statistical parametric mapping

UPDRS   Unified Parkinson's Disease Rating Scale

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numbers I-IV.

I   Jokinen P, Brück A, Aalto S, Forsback S, Parkkola R, Rinne JO. Impaired cognitive performance in Parkinson's disease is related to caudate dopaminergic hypofunction and hippocampal atrophy, Parkinsonism Relat Disord. 2009 Feb;15(2):88-93. Epub 2008 Apr 22.

II   Jokinen P, Helenius H, Rauhala E, Brück A, Eskola O, Rinne JO. Simple ratio analysis of 18F-fluorodopa uptake in striatal subregions separates patients with early Parkinson disease from healthy controls, J Nucl Med. 2009 Jun;50(6):893-9. Epub 2009 May 14.

III   Jokinen P, Scheinin N, Aalto S, Någren K, Savisto N, Parkkola R, Rokka J, Haaparanta M, Röyttä M, Rinne JO. [^{11}C]PIB-, [^{18}F]FDG-PET and MRI imaging in patients with Parkinson's disease with and without dementia, Parkinsonism Relat Disord. 2010 Dec;16(10):666-70. Epub 2010 Sep 25.

IV   Jokinen P, Karrasch M, Brück A, Johansson J, Jörgen Bergman, Rinne JO. Cognitive slowing in Parkinson's disease is related to frontostriatal dopaminergic dysfunction. Submitted.

1. INTRODUCTION

Parkinson's disease (PD), is one of the most common neurodegenerative diseases of unknown etiology. PD is currently an incurable condition, but symptoms can be treated with a range of medications. The incidence of the disease rises steeply with age, from 17.4 in 100 000 person years between 50 and 59 years of age to 93.1 in 100 000 person years between 70-79 years, with a lifetime risk of developing the disease of 1.5 % (Bower, et al. 1999, de Rijk, et al. 1995, Kempster, et al. 2007). The age-adjusted prevalence of idiopathic parkinsonism in the Finnish population is about 166 per 100 000 population, and the total age-adjusted incidence is 14.9 per 100 000 population (Kuopio, et al. 1999). PD affects over one million people in North America, and in Finland there are about 10 000 PD patients. Neurodegenerative diseases (PD, motor neuron disease, and dementia) are projected to surpass cancer among the elderly by the year 2040 (Lilienfeld and Perl. 1993).

The diagnosis of PD is made on the basis of clinical criteria. PD presents with four cardinal motor manifestations: tremor at rest, rigidity, bradykinesia (or slowing of movement), and postural instability. However, there are a wide variety of dysfunctions extending well beyond these classic motor disabilities associated with the disease. PD patients appear to be at an increased risk for a variety of cognitive and psychiatric dysfunctions. The most common are dementia and depression. Hallucinations, delusions, irritability, apathy, and anxiety have also been reported (Aarsland, et al. 1999). In addition to neurologic signs and symptoms, PD patients often have disturbing sensory problems and pain in affected limbs. Many PD patients also have signs of autonomic failure, including orthostatic hypertension, constipation, urinary hesitancy, and impotence in men (Koike and Takahashi. 1997, Mathias. 1998, Quigley. 1996).

Cognitive decline in the course of PD is of particular importance for the progression of overall disability in PD. Most of the patients with PD suffer from selective cognitive impairments, including difficulties with attention, concentration, problem solving, set-shifting, and memory, which are thought to reflect the dysfunction of cortical circuits subserving the frontal brain regions. The prevalence of cognitive imapirment in PD has been suggested to be around 55% (Janvin, et al. 2003). Aarsland and co-workers (Aarsland, et al. 1996) identified dementia in 28% of PD patients. In another study, 65% of the surviving members of a cohort of patients over the age of 85 had dementia (Mayeux, et al. 1990). Dementia has been correlated with a faster progression of disability and is a major risk factor for home placement in PD. Therefore, there is a highly important potential and target for disease modification strategies in PD.

PD is characterized by a severe loss of substantia nigra (SN) dopaminergic neurons. The nigral cell loss results in the regional loss of dopamine, most prominently in the dorsal and intermediate subdivisions of the putamen (Kish, et al. 1988b), a process that

is believed to account for motor symptoms such as akinesia and rigidity. According to post mortem studies, the clinical symptoms in PD seem to appear only after 50% of the nigral neurons and 80% of the striatal dopamine is lost (Bernheimer, et al. 1973, Fearnley and Lees. 1991). The aetiology of cognitive impairment and dementia in PD is not yet established in detail. It has been suggested that a greater degree of medial nigral cell loss, with enhanced involvement of projections to the caudate nucleus, could result in more cognitive dysfunction (Gibb and Lees. 1991). Some theories suggest that the diverse disturbances present in PD likely involve disruption in functionally segregated neuronal circuits in different components of the basal ganglia, thalamus, and cerebral cortex (Alexander, et al. 1986, Wichmann and DeLong. 1996). The neurochemical basis of frontostriatal and cognitive dysfunction in PD (particularly in the early stages) is hypothesized to be linked predominately to a dopaminergic dysfunction within the neural networks linking the dorsal striatum (i.e. dorsolateral putamen and dorsal caudate nucleus) to the dorsolateral prefrontal cortex (Cools. 2006, Owen. 2004). Lewy bodies, plaques, and vascular changes are present in both PD with dementia and dementia with Lewy bodies. On the other hand, many elderly individuals, or PD patients without dementia, or with only mild cognitive impairment, have neuritic Alzheimer-type changes (neurofibrillary tangles and/or neuropil threads) in the entorhinal cortex (ERC) (Jellinger, et al. 1991). It has also been suggested that widespread glucose hypometabolism in the cerebral cortex may be associated with dementia in PD (Ma, et al. 2008b, Sasaki, et al. 1992b). In addition, structural imaging with MRI has shown that, when compared to age-matched healthy controls, non-demented patients with PD have a significant rate of median or global brain volume loss, and these changes correlated with global measures of cognitive decline (Hu, et al. 2001). Thus, the pathophysiological basis of cognitive impairment and dementia in PD may be heterogenous involving brain atrophy, cortical hypometabolism, cortical Lewy bodies, concomitant AD pathology or degeneration of subcortical projection nuclei of neurotransmitter systems (such as dopamine, noradrenaline, serotonin), or a combination of these brain changes.

Neuroimaging with positron emission tomography (PET) and magnetic resonance imaging (MRI) *in vivo* can provide unprecedented insights into human brain function in both health and disease. PET is based on the utilization of artificially produced positron-emitting radionuclides (tracers). The most widely used tracer for demonstrating and quantifying the dopaminergic system is L-6-^{18}F-fluoro-3,4-dihydroxyphenylalanine (FDOPA) (Garnett, et al. 1983). PET studies of the resting state cerebral glucose metabolism using 2-[^{18}F]-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) as a tracer, has become a major functional imaging tool for investigating the age-related brain pathology, such as PD or AD (Eidelberg, et al. 1995, Thobois, et al. 2001). Since most dementia researchers regard amyloid deposition as the most important and specific pathophysiological events in Alzheimer's disease (AD), newly developed tracers that label amyloid plaques and neurofibrillary tangles have been developed. The Pittsburg compound B ([^{11}C]PIB, N-methyl-^{11}C-2-(4'-methylaminophenyl)-6-hydroxybenzothiazole) is the most widely

studied amyloid tracer in AD and PD patients. MRI is a unique medical imaging technique used in radiology to visualize detailed internal structures. MRI is more widely available than PET and most commonly used in clinical practice to differentiate idiopathic PD from the secondary causes of parkinsonism, such as vascular disease and other structural lesions. In addition, several studies have analysed atrophic patterns using various MR methods to better understand the anatomical substrate for cognitive impairment in PD.

This doctoral thesis was initiated to study the pathophysiological basis of cognitive impairment and dementia in PD. We evaluated the relation between frontostriatal dopaminergic dysfunction and the cognitive symptoms in PD patients with [^{18}F]Fdopa PET. It is unknown whether dopaminergic frontostriatal loops are involved in relatively automatic processing, such as two-choice reaction time, and more controlled cognitive processing, such as mental calculation. In addition, we combined different functional ([^{11}C]PIB, [^{18}F]FDG) and structural imaging (MRI) methods in PD patients with and without dementia. Since normally [^{18}F]Fdopa PET scans yield a total duration of 60 to 90 minutes and a variety of analytical methods have been developed to quantify Fdopa PET images, we wanted to evaluate whether a single 15-min scan, 75 min after a tracer injection, and a simple ratio analysis of [^{18}F]FDOPA in striatal subregions, is feasible for distinguishing patients with early PD from healthy controls. FDOPA PET scanning, which takes normally 60 to 90 minutes, poses a compliance issue, may increase potential bias because of subject movement, and may diminish the cost-effectiveness of the cameras and tracers used.

2.   REVIEW OF THE LITERATURE

2.1.   Dopaminergic circuits linking the basal ganglia and cortex

The entire dopamine projection system arises from neurons located in the midbrain. Dopamine neuron cell bodies located in the midbrain project to the basal ganglia and cerebral cortex. The basal ganglia are subcortical structures, including the striatum (caudate nucleus and putamen) and the globus pallidus (internal and external parts). Functionally, substantia nigra (pars compacta and pars reticularis) is also considered as a part of basal ganglia. Dopamine (DA) functions as a catecholamine neurotransmitter, activating dopamine receptors. Dopamine has many functions in the brain, including important roles, for example, in behavior, cognition and voluntary movement. Dopaminergic pathways are non-diffuse, topographically organized, anatomical tracts, which transmit the neurotransmitter dopamine from one region of the brain to another, and there are three main dopaminergic pathways in the brain. These are the nigrostriatal, the mesolimbic-mesocortical, and the tuberoinfundibular pathways (Figure 1). Nigrostriatal DA neurons have cell bodies in pars compacta of substantia nigra and their axons terminate in the striatum. Mesolimbic-mesocortical DA neurons originate from cell bodies in substantia nigra and the ventromedial tegmentum; they project into the limbic forebrain regions and to the cerebral cortex. The tuberoinfundibular pathway courses from the arcuate nucleus of the hypothalamus to the pituitary stalk.

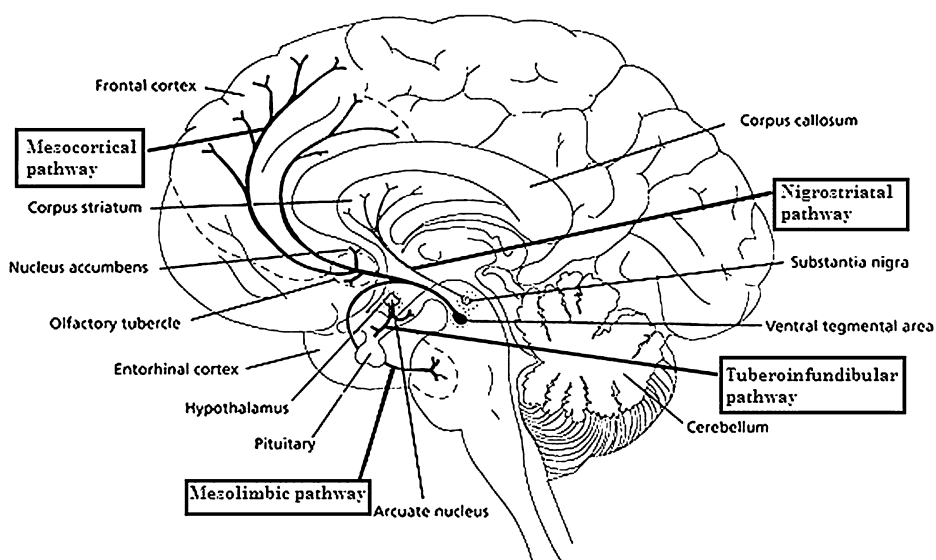**Figure 1.** Sagittal section of human brain showing anatomical sturctures of the brain and the three major dopaminergic pathways in the human brain: the nigrostriatal, mesocorticolimbic and tuberoinfundibular pathway (Modified from Crocker. 1994).

The nigrostriatal system is a component of a larger, mesotelencephalic system with perikarya in the ventral midbrain and projections into the striatum, pallidum, basal forebrain, limbic structures, and the cerebral cortex. Projections of the mesotelencephalic system have three major components: a nigrostriatal pathway, a mesolimbic pathway, and a mesocortical pathway. The nigrostriatal system connects the substantia nigra with the striatum. It originates from the subtantia nigra and innervates to the putamen and caudate nucleus. Neurons in the lateral part of the substantia nigra project into the putamen, whereas the caudate receives its nigral input from the medial nigral and ventral tegmental area (for a review, see (Fuxe and Agnati. 1985). The nigrostriatal projections are far more extensive than simply an innervation of the neostriatum and adjacent areas, and all components of the projections are highly topographically organized (for a review, see (Björklund and Lindvall. 1984, Joel and Weiner. 2000, Lewis and Seasack. 1997). Thenigrostriatal pathway is particularly involved in the production of movement. Mesolimbic-mesocortical DA neurons originate from cell bodies in substantia nigra and the ventromedial tegmentum. The mesocortical tract projects into several cortical regions (particularly the frontal lobes), the septum and the anterior olfactory nucleus, whereas the mesolimbic pathway is connected to the nucleus accumbens, the olfactory tubercle, the amygdale and the piriform cortex. This system plays a role in affect, emotion, reward processes, cognitive functions and motivational behaviours. (Fuxe and Agnati. 1985). Tuberoinfundibular dopaminergic neurons originate from the periventricular and arcuate hypothalamic nuclei and projects into the median eminence. The main functional role of tubero-infundibular dopaminergic neurons is the inhibition of prolactin secretion from the pituitary. In addition to these pathways, there are small projections into the locus coeruleus and to the spinal cord and a number of local pathways within the hypothalamus, the olfactory system, the brain stem and the retina. (Fuxe and Agnati. 1985).

Within the striatum and elsewhere, DA receptors are found in both presynaptic and postsynaptic locations, with D1 and D2 receptors being the predominant subtypes. The cellular effects of DA are related to these different receptors. It can be emphasized that its action through D2 receptors generally depresses the activity of the target neurons, whereas via the D1 receptors DA could contribute to the interaction with other receptors and particularly those relying on the action of fast-signaling neurotransmitters, such as the excitatory amino acids, thus contributing to the modulation of the input to target neurons (Nicola, et al. 2000). The striatum transmits the flow of information received from the cortex to the basal ganglia output nuclei, substantia nigra pars reticulate and medial or lateral globus pallidus, via a direct and indirect pathway. In the direct pathway, striatal neurons expressing D1 dopamine receptors, project monosynaptically to the substantia nigra pars reticulate and medial (internal) globus pallidus. In the indirect pathway, the striatal output reaches the target nuclei via a more complicated route. Neurons expressing D2 receptors projects into the lateral (external) globus pallidus, which sends projections into the subthalamic nucleus. The subthalamic nucleus, in turn, sends its efferents to the output nuclei and to the lateral globus pallidus. From the output

nuclei, inhibitory projections reach the ventral lateral and ventral anterior nuclei of the motor thalamus. Thalamic nuclei then send projections to the motor cortex, thus closing the loop (Alexander and Crutcher. 1990) (Figure 2). The direct pathway facilitates movement, and the indirect pathway inhibits movement, thus the nigrostriatal pathway is of fundamental importance in movement disorders (for a review, see Blandini, et al. 2000, Fuxe and Agnati. 1985).
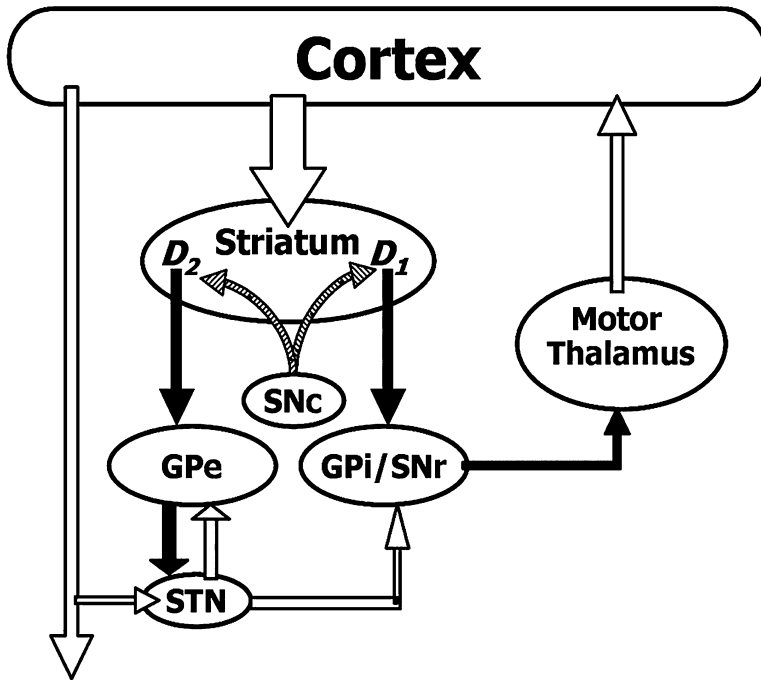
Figure 2. The striatum transmits the flow of information received from the cortex to the basal ganglia output nuclei via a direct and indirect pathway. Cortical activation of the direct pathway (striatum–GPi–thalamus) facilitates movement by releasing the motor thalamus from inhibition from GPi and allowing excitation of corresponding cortical motor areas. Activation of the indirect pathway (striatum–GPe–STN–GPi–thalamus) has the opposite effects. Filled arrows correspond to inhibitory connections, open arrows correspond to excitatory connections, and hatched arrows represent the dopaminergic innervation of the striatum. SNc = substantia nigra, GPe = external/lateral globus pallidus, GPi = internal/medial globus pallidus, SNr = subtantia nigra pars reticulate, STN = subthalamic nucleus. (Adapted from Rubchinsky, et al. 2003)

The basal ganglia are organized in a series of parallel cortico-striatal loops and play important roles, not only in motor control, but also in higher cognitive functions. Anatomical studies on the neuronal connections between the basal ganglia, cerebral cortex, and thalamus have demonstrated that these nuclei and cortical areas are interconnected via independent parallel loop circuits (Alexander and Crutcher. 1990). The function of each loop is determined by the cortical area it includes.

The association, motor, and limbic cortices project into specific domains in the striatum, which, in turn, project back into the corresponding cortical areas via the substantia nigra/ globus pallidus and the thalamus. These parallel cortico-basal ganglia-thalamo-cortical loops have been thought to be the basic anatomical structures involved in the basal ganglia functions. In addition, neuronal projections communicating between different loops (or functional domains) have also been discovered. In the striatum sensorimotor, cognitive, and limbic regions can be distinguished, based on their connections with the cerebral cortex (Haber, et al. 2000, Parent. 1990). Roughly speaking, these are the posterior putamen (sensorimotor), caudate and anterior putamen (cognitive), and ventral striatum or nucleus accumbens (limbic/affective). The dorsal striatum (caudate and putamen) receives input from the motor, association, and prefrontal cortex, while the ventral striatum receives input from the limbic areas, such as the hippocampus, amygdala, and orbitofrontal cortex (Figure 3). In humans, dopaminergic terminals innervate the entire cortical areas according to a rostro-caudal gradient, the density being highest in the frontal areas. This development of cortical dopaminergic innervation during evolution would correlate with the progressive involvement of the cortex in the processing of sensory information through basal ganglia. (Nieoullon. 2002)
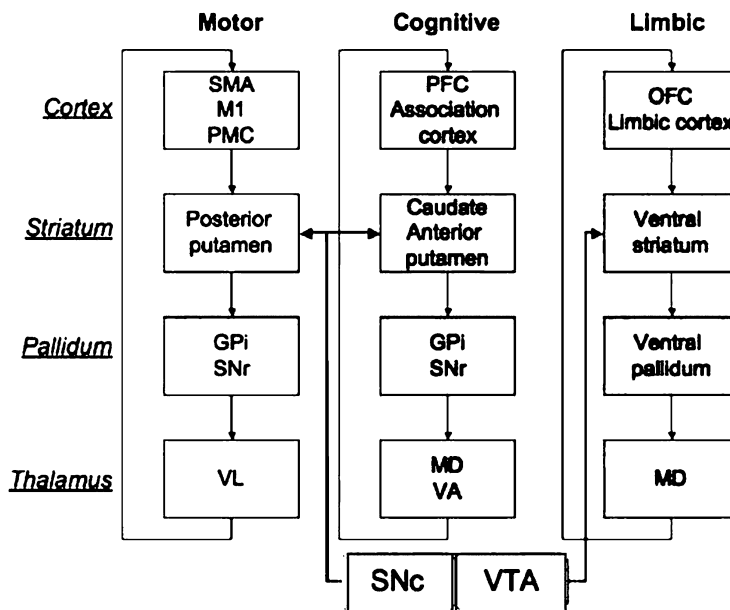
Figure 3. Schematic diagram of the cortico-basal ganglia-thalamo-cortical loops. The cognitive and motor loops receive dopaminergic innervation from a different group of midbrain neurons than the limbic loop. SMA, Supplementary motor area; M1, primary motor cortex; PMC, premotor cortex; PFC, prefrontal cortex; OFC, orbitofrontal cortex; GPi, globus pallidus internal segment; SNr, substantia nigra pars reticulate; VL, ventrolateral; MD, mediodorsal; VA, ventral anterior; SNc, substantia nigra pars compacta; VTA, ventral tegmental area. (Adapted from Dagher and Nagano-Saito. 2007)

2.2. Parkinson's disease

2.2.1. General

Parkinson's disease (PD) is named after James Parkinson, who provided a detailed description of what he termed "shaking palsy" in an essay published in1817. In his essay, he detailed six patients with "involuntary tremulous motion with lessened muscular power, in parts not in action even when supported, with a propensity to bend the trunk forward and to pass from a walking to a running pace". Nowadays PD is one of the most common neurodegenerative disorders, and its cause is unknown. Age is the single most consistent risk factor, and with the increasing age of the general population, the prevalence of PD will rise steadily in the future. The incidence of the disease rises steeply with age, from 17.4 in 100 000 person years between 50 and 59 years of age, to 93.1 in 100 000 person years between 70-79 years, with a lifetime risk of developing the disease of 1.5 % (Bower, et al. 1999, de Rijk, et al. 1995, Kempster, et al. 2007). The age-adjusted prevalence of idiopathic parkinsonism in the Finnish population is about 166 per 100 000 population and the total age-adjusted incidence 14.9 per 100 000 population (Kuopio, et al. 1999). PD affects over one million people in North America, and in Finland there are about 10 000 PD patients. Neurodegenerative diseases (PD, motor neuron disease, and dementia) are projected to surpass cancer among the elderly by the year 2040 (Lilienfeld and Perl. 1993). There is a good evidence that men are about 1.5 times more likely than women to develop PD, but this difference is not the same across different studies, and is more pronounced in, and might be restricted to, people over 70 years of age in western populations (Twelves, et al. 2003). PD is not related to race, but the lowest incidence is among Asians and African blacks and the highest among whites (Lang and Lozano. 1998a). Remarkably few environmental causes or triggers of PD have so far been identified (Dick, et al. 2007, Tanner. 2003, Taylor, et al. 2005). Similar to other neurodegerative diseases, ageing is the major risk factor, although 10% of people with PD are younger than 45 years of age. Non-smokers are twice as likely to develop PD (Allam, et al. 2004, Hernan, et al. 2001), and men and postmenopausal women who are not taking hormone replacements, who take no or very low quantities of daily caffeine, seem to be at increased risk (about 25% more) (Ascherio, et al. 2003, Ascherio, et al. 2004). A weak association between PD and head injury, rural living, middle-age obesity, lack of exercise, well-water ingestion, and herbicide and insecticide exposure have also been reported (Elbaz and Tranchant. 2007, Thacker, et al. 2008). Enviromental toxins (eg. 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP], cyanide, carbon disulphide, and toluene) can produce a similar, but not identical, clinical picture (Tanner and Aston. 2000).

Although the cause of PD remains still elusive, important genetic and pathological clues have recently been found. According to genetic studies, several mutations in seven genes are linked with L-dopa-responsive parkinsonism. Six pathogenic mutations in gene LRRK2 (leucine rich repeat kinase 2) have been reported. The most common of these, the Gly2019Ser mutation, has a worldwide frequency of 1% in sporadic cases and 4% in patients with hereditary parkinsonism, making it as common as multiple system atrophy

and progressive supranuclear palsy (Healy, et al. 2008, Paisan-Ruiz, et al. 2004). Both point mutations and gene triplications of α-synuclein also cause a parkinsonian syndrome indistinguishable from PD, but these are much rarer (Polymeropoulos, et al. 1997, Singleton, et al. 2003). Duplications of α-synuclein have rarely been found in sporadic PD (Theuns and Van Broeckhoven. 2008). Loss-of-function mutations in four genes (Parkin, DJ-1, PINK1 and ATP13A2) cause recessive early onset parkinsonism (age onset <40 years). Parkin mutations are the second most common genetic cause of L-dopa-responsive parkinsonism, whereas mutations in the other three genes are rare. PINK1 shares the same mitochondrial pathway as parkin, and a dysfunction of the mitochondria could be the key reason for at least some of the autosomal recessive forms of parkinsonism (Clark, et al. 2006, Park, et al. 2006, Schapira. 1994). The heterozygous loss of the function of GBA (glucocerebrosidase) increases the risk of developing PD more than five fold (Goker-Alpan, et al. 2004). In the UK, about 4% of PD patients have a GBA mutation. It is speculated that α-synuclein, LRRK-2, and GBA are implicated in a common biochemical pathway that is important in the pathogenic process, like pathological aggregates of Lewy bodies.

2.2.2. Pathology

A region-specific selective loss of dopaminergic, neuromelanin-containing neurons from the pars compacta of the substantia nigra is the pathological hallmark of PD. In addition, there exists also cell loss in the locus coeruleus, dorsal nuclei of the vagus, raphe nuclei, nucleus basalis of Meynert, and some other catecholaminergic brain stem structures, including the ventrotegmental area (Damier, et al. 1999b). This nerve cell loss is accompanied by three distinctive intraneuronal inclusions: the Lewy body, the pale body, and the Lewy neurite. PD is suggested to progress in six neuropathological stages, each of which is marked by the continual development of distinctive inclusion bodies that present in the form of spindle-like or thread-like and, in part, branching Lewy neurites (LNs) within cellular processes, and as granular aggregations and spherical pale bodies and/or Lewy bodies (LBs) in the somata of the involved nerve cells (Apaydin, et al. 2002, Braak, et al. 1998, Takahashi and Wakabayashi. 2001). All of the affected neurons eventually develop LNs and LBs, and, despite the presence of these inclusion bodies, some neurons survive for a long period of time, although LB/LN-bearing cells probably cease functioning long before they die. The intracerebral formation of abnormal proteinaceous LBs and LNs begins at defined induction sites and advances in a topographically predictable sequence. As the disease progresses, components of the autonomic, limbic, and somatomotor systems become particularly badly damaged. During presymptomatic stages 1-2, inclusion body pathology is confined to the medulla oblongata/pontine tegmentum and olfactory bulb/anterior olfactory nucleus. The anatomic pattern of the earlier Braak stages fits remarkably well with proposed premotor disease manifestations, including hyposmia (olfactory bulb), constipation (enteric nervous system), and sleep disorder (brainstem reticular formation) (Braak and Del Tredici. 2008). In stages 3-4, the substantia nigra and other nuclear grays of the midbrain

and forebrain become the focus of initially slight and then severe pathological changes. At this point, most individuals probably cross the threshold to the symptomatic phase of the illness. In the end-stages 5-6, the process enters the mature neocortex, and the disease manifests itself in all of its clinical dimensions (Braak, et al. 2004) (Figure 4).

Stages 5-6
Cinculate cortex (C)
Temporal cortex (T)
Frontal cortex (F)
Parietal cortex
Occipital cortex

Stage 4
Amygdala (A)
Nucleus of Meynert
Hippocampus

Stage 3
Substantia nigra
pars compacta (SN)

Stage 1-2
Dorsal motor nucleus of vagus (DM)
Raphe nucleus (RN)
Locus coeruleus
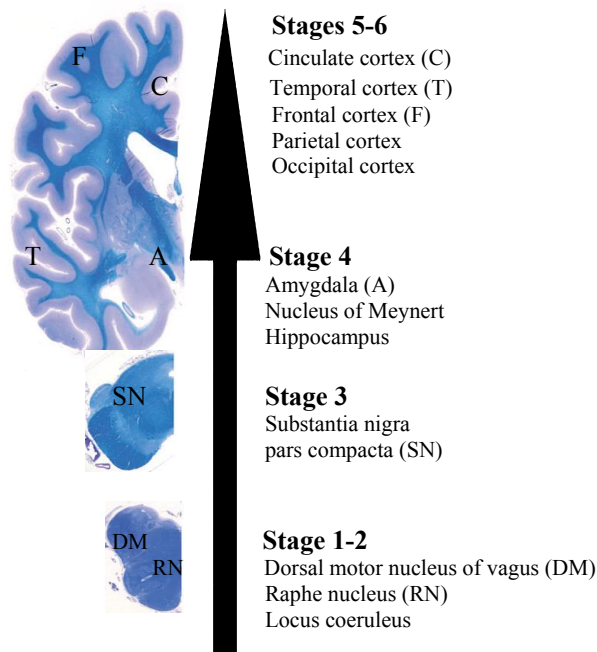
Figure 4. Progression of Parkinson's disease (PD) pathology. Schematic outlining the major stages of PD pathology, as proposed by Braak et al. (Braak, et al. 2003). In stages 1–2, Lewy neurites and Lewy bodies are found within the medulla and pons. Only in stage 3 does aggregated α-synuclein affect the substantia nigra. Later stages (4–6) involve the supratentorial compartment in a graded fashion, which ultimately leads to substantial neocortical pathology in stage 6 (Modified from Shulman, et al. 2011)

Lewy bodies are subdivided into classical (brainstem) and cortical types on the basis of their morphology. The brain-stem shape is a spherical structure measuring 8-30 um with a hyaline core surrounded by a peripheral pale-staining halo, and is composed ultrastructurally of 7-20 nm wide filaments with dense granular material and vesicular structures. Cortical Lewy bodies lack the inner core and halo, and are especially common in small-to-medium-sized pyramidal neurons of layers V and VI of the temporal, frontal, parietal, insular cortices, cingulum, and entorhinal cortex. Pale bodies are large rounded eosinophilic structures that often displace neuromelanin and are the predecessors of the Lewy body. In contrast to neurofibrillary tangles, Lewy bodies are continuously forming and disappearing in the diseased substantia nigra (Greffard, et al. 2010). The main

component of Lewy bodies is an abnormal, post-translationally modified, and aggregated form of the presynaptic protein α-synuclein. α-synuclein antibodies stain Lewy bodies and Lewy neuritis, and have become the standard and most sensitive immunohistochemical method for routine diagnostic purposes (Wakabayashi, et al. 2007).

Cortical Lewy bodies are present in small numbers in almost all cases of PD (Halliday, et al. 2008). Extensive neocortical Lewy body pathology is common in patients with severe memory loss when additional Alzheimer-type changes are frequently seen (Apaydin, et al. 2002, Braak, et al. 2005, Hurtig, et al. 2000, Jellinger and Attems. 2008, Kosaka, et al. 1984, Tsuboi and Dickson. 2005). A substantial proportion of non-demented patients with PD also have widespread cortical Lewy body pathology. The implication of this is that neocortical Lewy bodies are not necessarily the pathological correlate of dementia in PD (Colosimo, et al. 2003, Parkkinen, et al. 2005a, Parkkinen, et al. 2005b). Lewy bodies are present in the brain in about 10% of people older than 60 years of age who have died without evidence of neurological disease. This occurrence has been named incidental Lewy body pathology and might be a presymptomatic phase of PD (DelleDonne, et al. 2008, Dickson, et al. 2008). According to this, there would be ten times more people at risk of developing PD than ever manifest bradykinesia. The cell loss in incidental Lewy body disease seems to be in between normal and PD, and the earlier damage is seen in the middle and lateral part of the substantia nigra, the same area where the most severe cell loss occurs in PD (Gibb and Lees. 1988).

Cell loss occurs not only in the dopaminergic cells in the subtantia nigra, but also in many other non-dopaminergic areas of the brain, including the noradrenergic locus coeruleus, the cholinergic nucleus basalis of Meynert, the serontonergic raphe nucleus and the autonomic nervous system. In the very early stages of PD where Lewy bodies are found in the brain stem, there is already cell loss without Lewy bodies in the substantia nigra. The substantia nigra has two divisions, the pars reticulata and the pars compacta, with the pars compacta subdivided into ventral and dorsal tiers. Within the substantia nigra pars compacta, neuronal loss tends to be greatest in the ventrolateral tier, followed by the medial ventral tier and dorsal ties (Fearnley and Lees. 1991). The nigral cell loss results in a regional loss of dopamine, most prominently in the dorsal and intermediate subdivisions of the putamen (Kish, et al. 1988b), a process that is believed to account for akinesia and rigidity. It has been suggested that a greater degree of medial nigral cell loss, with enhanced involvement of projections into the caudate nucleus, could result in more cognitive dysfunction (Gibb and Lees. 1991, Rinne, et al. 1989b). This pattern of cell loss is relatively specific to PD. It is the opposite of that seen in normal aging and differs from patterns found in striatonigral degeration and progressive supranuclear palsy. At post mortem, only a quarter of the cells in the substantia nigra pars compacta remain in PD, compared with normal people, with surviving cells being in the dorsal tier (Fearnley and Lees. 1991). In normal aging, the dorsal tier is preferentially affected by a ratio of 3:1 (Rudow, et al. 2008) with 5% loss per decade after the age of 40 years. According to post mortem studies, the clinical symptoms in PD seem to appear only after

50% of the nigral neurons and 80% of the striatal dopamine is lost (Bernheimer, et al. 1973, Fearnley and Lees. 1991).

The rate of cell loss in the pars compacta of patients with PD is estimated at a 45% fall in the first decade. Loss of pigmented neurons in PD seems to be exponential, with losses being greatest in the early disease stages and decereasing as it progresses (Fearnley and Lees. 1991). Pathological and imaging studies estimate a 3-6 year or even longer period between the onset of neuronal loss in SN and the onset of motor symptoms in PD. However, emerging evidence suggest that the neuropathological process in PD likely involves other nervous structures before the SN, such as the lower brainstem and the olfactory bulb, or even more distant structures from SN, such as the myenteric, abdomino-pelvic, and cardiac autonomic plexuses. Studies on "premotor" hyposmia or depression, suggest that these symptoms may be present or develop 7 years or longer before the motor symptoms of PD, while REM sleep behavior disorder may antedate motor signs by an average interval of 11-12 years, and constipation may present 12-18 years or for even a longer time before Parkinsonism develops. (for a review, see Gaig and Tolosa. 2009).

Many elderly individuals, or PD patients without dementia or with only mild cognitive impairment, have neuritic Alzheimer-type changes (neurofibrillary tangles and/or neuropil threads) in the entorhinal cortex (ERC) (Jellinger, et al. 1991). On the other hand, there are PD patients with severe dementia who have no significant Alzheimer's disease (AD) pathology, suggesting other underlying pathology for intellectual deterioration (Jellinger. 1987). The estimates of AD pathology in PD have varied from 42 % to 91 % (Boller, et al. 1980, Gaspar and Gray. 1984, Hakim and Mathieson. 1979). Differences in study designs, patient populations and criteria for AD are factors, which may have contributed to the variation in estimates of concomitant AD pathology in PD. Patients with idiopathic PD have more frequently AD pathology in the ERC and hippocampus than controls (Alvord, et al. 1974, Ince, et al. 1991, Perry, et al. 1985, Perry, et al. 1990). The presence and severity of dementia in PD have been reported to correlate with the intensity of cortical AD-type lesions, particularly neurofibrillary tangles in both the frontal cortex (Jellinger. 1987, Vermersch, et al. 1993) and the hippocampus (Braak and Braak. 1990, Duyckaerts, et al. 1993, Jellinger. 1987, Quinn, et al. 1986), and thus dementia in PD could be attributable to co-existent AD pathology (Gaspar and Gray. 1984, Jellinger, et al. 2002). On the other hand, clinicopathological studies have shown that cognitive impairment and dementia in PD are related to the number of limbic and cortical Lewy bodies (Bertrand, et al. 2004, Gibb, et al. 1989), even when the possible co-existing AD-pathology has been taken into account (Mattila, et al. 1998). Thus, the pathophysiological basis of cognitive impairment and dementia in PD may be heterogenous, involving cortical Lewy bodies, concomitant AD pathology or the degeneration of subcortical projection nuclei of neurotransmitter systems (such as dopamine, noradrenaline, serotonin), or a combination of these brain changes.

2.2.3. Pathophysiology

The striatum is the main input structure of the basal ganglia circuit, and the major neural input to the striatum is excitatory in nature. Glutamatergic projections from nearly all cortical areas (McGeorge and Faull. 1989) converge onto striatal neurons. Other important excitatory inputs to the striatum arise from the midline and intralaminar nuclei of the thalamus (Berendse and Groenewegen. 1990), and from limbic structures, especially amygdale (Kelley, et al. 1982). Another important input to the striatum originates from dopaminergic neurons located in the pars compacta of the substantia nigra and in the ventral tegmental area (Nieuwenhuys. 1985). The striatum also receives serotonergic afferent projections from the dorsal nucleus of the raphe and caudal linear nucleus (Halliday, et al. 1995) and a sparse noradrenergic innervation from the locus coeruleus (Aston-Jones. 1995). Because of its input nucleus nature, the striatum exhibits a variety of neurotransmitter receptors, which show a considerably higher density at the striatal level, compared to other basal ganglia nuclei. The major neuronal population in the striatum is represented by spiny projection neurons, accounting for almost 95% of total striatal cells (Kemp and Powell. 1971) and using y-amino-butyric acid (GABA) as a neurotransmitter (Kita and Kitai. 1987). Within the projection neurons, GABA can be co-localized, alternatively, with enkephalin or substance P/dynorphin (Beckstead. 1985).

In the striatum, the GABAergic output neurons projecting directly into the internal segment of the globus pallidus and pars reticulata of the substantia nigra, contain a predominance of D1 dopamine receptors, whereas D2 receptors predominate on neurons projecting into the external segment of the globus pallidus. Dopamine has different effects on these receptors and, therefore, on the subpopulations of striatal output neurons. Dopamine excites neurons expressing D1 receptors (the origin of the direct striatopallidal pathway) and inhibits those with D2 reseptors (the origin of the indirect striatopallidal pathway). Figure 5a illustrates and simplifies the balance of activity between the direct and indirect pathways acting on the internal segment of the globus pallidus and pars reticulata of the substantia nigra in the normal, non-dopamine-deficient state. As a result of the nigral cell loss and dopamine deficiency in PD, the excitatory dopamine projections into the striatal D1 receptors and the inhibitory projections into the striatal D2 receptors are weakened. This causes the overactivity of the indirect pathway, resulting in an excessive glutamatergic drive to the internal segment of the globus pallidus and pars reticulata of the substantia nigra, and the reduced activity of the inhibitory GABAergic direct pathway, further disinhibating the activity of the internal segment of the globus pallidus and pars reticulate of the substantia nigra. Because these structures use the inhibitory neurotransmitter GABA, the increased output of the basal ganglia leads to excessive inhibition and, effectively, to a shutdown of the thalamic and brainstem nuclei that receive their outflow (Figure 5b). The excessive thalamic inhibition leads to the suppression of the cortical motor system, possibly resulting in akinesia, rigidity and tremor. The inhibition of descending projection into the brainstem may contribute to the abnormality of gait and posture. (Lang and Lozano. 1998b).
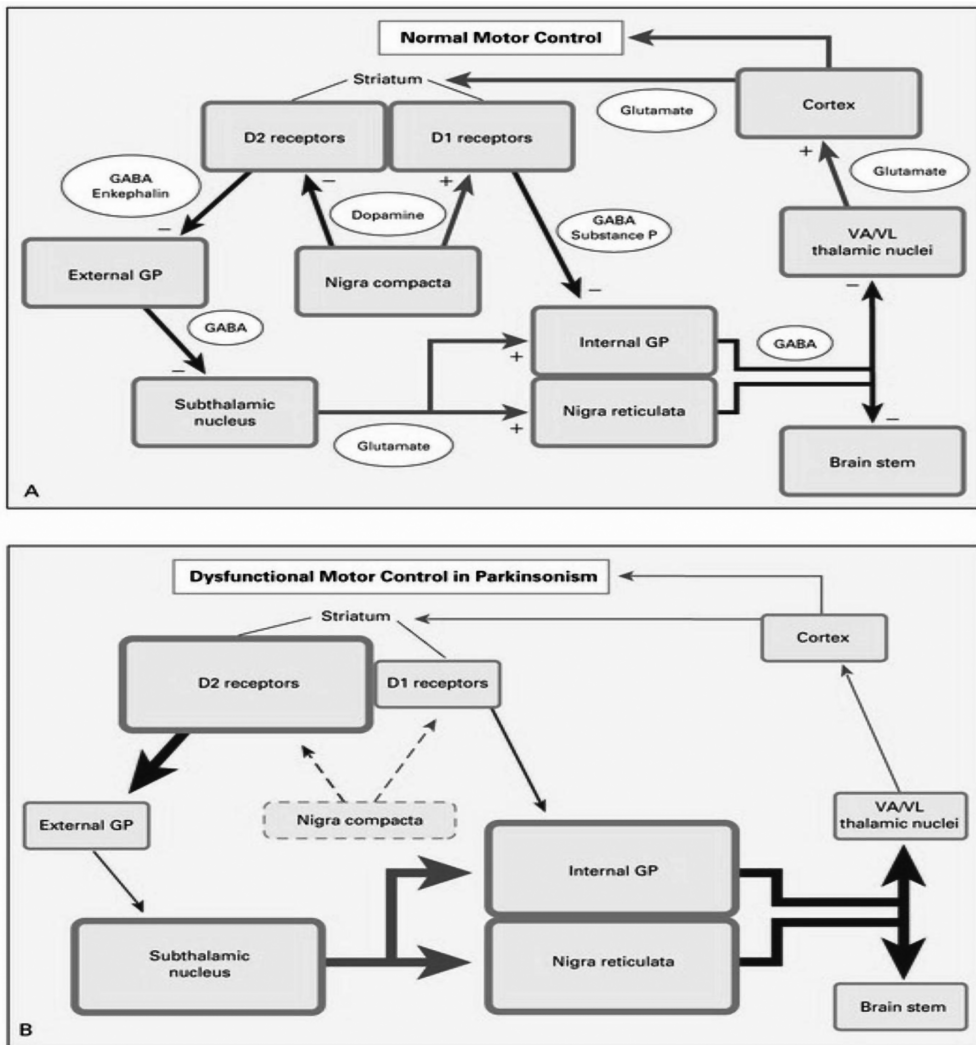
Figure 5. Proposed functional model of the basal ganflia in persons with normal motor control (A) and patients with parkinsonism (B). The neuroanatomy and the interconnections are simplified here for reasons of clarity. Arrows with a plus indicate excitatory pathways, and arrows with a minus inhibitory pathways. The width of the arrows indicates the degree of overall functional change in the activity of each pathway (changes in neuronal firing rates) as compared with the normal state (A), and the size and outlining of each box indicate the activity of the brain region as compared with the normal level of activity (A). Dashed lines and arrows indicate the dysfunctional nigrostriatal dopamine system in PD. The circled substances are neurotransmitters used by the neighboring pathway. The brain stem, as depicted, includes the pedunculopontine nucleus, and the cortex includes supplementary motor areas and premotor cortex. D1 receptors denotes neurons containing predominantly D1 dopamine receptors, D2 receptors neurons containing predominantly D2 dopamine receptors. Nigra compacta, the pars compacta of the substantia nigra; external GP, the external portion of the globus pallidus; internal GP, the internal portion of the globus pallidus; nigra reticulate, the pars reticulata of the substantia nigra; VA/VL, ventral anterior and ventrolateral; GABA, γ-aminobutyric acid. Parkinsonism (B) is associated with increased inhibition of the motor thalamus (and, as a result, premotor cortexes) and brain-stem locomotor areas resulting from overactivity of the internal segment of the globus pallidus and pars reticulata of the substantia nigra. The excessive activity of these two areas is due to reduced direct inhibition from the striatum and especially to excessive stimulation from the overactive subthalamic nucleus. An increase in dopaminergic action at the level of the striatum due to drug therapy (e.g., levodopa or dopamine agonists) would partially reverse this state (not shown). (Adapted from Lang and Lozano. 1998b)

2.2.4. Diagnosis and clinical assesment

PD commonly presents with the impairment of dexterity or, less commonly, with a slight dragging of one foot. The onset is gradual and the earliest symptoms might be unnoticed or misinterpreted for a long time. Fatigue and stiffness are common but non-specific complaints. Work colleagues or family members might notice a lugubrious stiff face, a hangdog appearance, a flexion of one arm with lack of swing, a monotonous quality to the speech, and an extreme slowing down. These changes are rarely noticed by the patient. The early physical signs are often erroneously ascribed to old age, misery, introspection, or rheumatism, and a lag of 2-3 years from the first symptoms to diagnosis is not unusual. Once the diagnosis has been confirmed, patients and their families often start to remember potentially relevant symptoms and signs going back more than a decade.

The diagnosis of PD is made on the basis of clinical criteria. PD presents with four cardinal motor manifestations: tremor at rest, rigidity, bradykinesia (or slowing of movement), and postural instability. Not all patients initially present with all of the classic signs of the disorder; there may be only one or two. There is currently no laboratory test that can definitely establish a diagnosis. Even neuroimaging, which can be used to obtain an estimate of DA loss, is imperfect and too expensive to be used as a routine diagnostic tool. However, structural and functional neuroimaging techniques are evolving rapidly, and imaging characteristics that distinguish patients with PD from normal controls and from patients with other parkinsonian conditions have been described. Neuroimaging techniques such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT) have increasingly been employed to detect PD, to elucidate the neuropathological mechanism and compensatory responses underlying symptoms and treatment associated complications, and to monitor disease progression in vivo. In the EU SPECT, using the dopamine transporter ligand (DAT), FP-CIT has received regulatory approval as a diagnostic test to detect loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain parkinsonian syndromes. In a previous study with two-year follow-up in 150 consecutive cases with normal dopamine transporter imaging it was found that nearly all patients with normal baseline FP-CIT SPECT scan have a benign movement disorder rather than degenerative parkinsonism (Marshall, et al. 2006). Besides clinical evaluation, with brain MRI it is possible to exclude secondary causes of extrapyramidal symptoms, such as tumour, infarct or hydrocephalus. With laboratory tests it is possible to exclude metabolic disorders.

Bradykinesia is the centrepiece of the clinical diagnosis of parkinsonism and it refers to the slowness of the initiation of voluntary movement with a progressive reduction in the speed and amplitude of repetitive actions. In the hand this is best seen when the patient is asked to repetitively open and close the thumb and index finger. What then happens is that successive movements become slower and smaller and movement may even grind

to a halt. The increased tone of PD is commonly referred to as either "lead pipe" rigidity or "cog-wheel" rigidity. When rigidity is not obvious, it may be brought out by the motor activation of the contralateral limb. Rest tremor is the first clinical symptom in about three-quarters of patients. It usually begins in a single extremity, and it may remain localized to one hand or even a single finger for months and sometimes for years. Resting tremor in a limb classically stops when the limb is moved. The rest tremor is said to be in the 4-6 Hz frequency range. Of the cardinal motor signs, postural instability is the most potentially dangerous, because it can lead to falls with resulting features. Especially advanced patients with PD suffer from postural instability, which can be tested by pulling the patient backwards to check for balance recovery. If the patient's postural reflexes are severely impaired they will fall over unless you catch them. An additional motor feature of PD is the freezing phenomenon. In its most typical form, freezing occurs as a sudden inability to step forward while walking. It is transient, lasting seconds or minutes, and suddenly abates. Combined with postural instability, it can be devastating.

In PD there is a wide variety of dysfunctions extending well beyond the classic motor disabilities associated with the disease. PD patients appear to be at increased risk for a variety of cognitive and psychiatric dysfunctions. Most common are dementia and depression. However, hallucinations, delusions, irritability, apathy, and anxiety have also been reported (Aarsland, et al. 1999). Cognitive decline in the course of PD is of particular importance for the progression of overall disability in PD. Aarsland and co-workers (Aarsland, et al. 1996) identified dementia in 28% of PD patients. In another study, 65% of the surviving members of a cohort of patients over the age of 85 had dementia (Mayeux, et al. 1990). Dementia has been associated with a faster progression of disability and is a major risk factor for nursing home placement in PD. Therefore, there is a highly important potential and target for disease modification strategies in PD. Depression is reported in 40% of patients with PD (Cummings. 1992). The vegetative symptoms of depression, such as psychomotor retardation, lack of energy, poor concentration and sleep disturbance, can often be difficult to separate from PD. Unique features of depression in the PD population include increased dysphoria, irritability, anxiety and brooding. In addition to neurologic signs and symptoms, PD patients often have disturbing sensory problems and pain in the affected limbs. Many PD patients also have signs of autonomic failure, including orthostatic hypertension, constipation, urinary hesitancy, and impotence in men (Koike and Takahashi. 1997, Mathias. 1998, Quigley. 1996).

Because of the known difficulty in making a clinical diagnosis of PD, various sets of clinical criteria have been put forward. One popular criteria applied in clinical trial is the set devised by the United Kingdom Parkinson's Disease Society Brain Bank (Calne, et al. 1992) (Table 1). First the diagnosis of a parkinsonian syndrome (defined as bradykinesia and at least one of either muscular rigidity, 4-6 Hz rest tremor, or postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction) is required. The second step is a checklist of exclusion criteria, such as a history of definite encephalitis or the presence of cerebellar signs. The third step is to look for supportive prospective

features for PD, such as unilateral onset and levodopa response for 5 years or more. The disability of the symptoms is usually evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn, et al. 1987). The UPDRS is a composite scale consisting of six sections. Part I of the UPDRS consists of four items that assess mentation, behaviour, and mood. Part II consists of 13 items and assesses the performance of activities of daily living. Part III is a 14-item rating of motor signs. Part IV rates complications of therapy. Part V is a modified version of the Hoehn and Yahr staging system; overall disease severity is divided into unilateral (stage I), bilateral, but without a gait or balance disorder (stage II), and bilateral disease with progressively more difficulty with mobility and balance (stage III-V). Half points are allowed between stages I-II and II-III (1.5, unilateral and axial involvement; 2.5, mild bilateral disease with recovery on the pull test). Part VI is a disability scale based on a scale reported by Schwab and England (Martinez-Martin. 1993).

Table 1. Three-step approach to diagnosis, recommended by the UK Parkinson's Disease Society Brain Bank (Adapted from Hughes, et al. 1992b).

Step 1. Diagnosis of Parkinsonian Syndrome
● Bradykinesia
● At least one of the following
- Muscular rigidity
- 4-6 Hz rest tremor
- postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction
Step 2 Exclusion criteria for Parkinson's disease
● history of repeated strokes with stepwise progression of parkinsonian features
● history of repeated head injury
● history of definite encephalitis
● oculogyric crises
● neuroleptic treatment at onset of symptoms
● more than one affected relative
● sustained remission
● strictly unilateral features after 3 years
● supranuclear gaze palsy
● cerebellar signs
● early severe autonomic involvement
● early severe dementia with disturbances of memory, language, and praxis
● Babinski sign
● presence of cerebral tumor or communication hydrocephalus on imaging study
● negative response to large doses of levodopa in absence of malabsorption
● MPTP exposure
Step 3 supportive prospective positive criteria for Parkinson's disease
Three or more required for diagnosis of definite Parkinson's disease in combination with step one
● Unilateral onset
● Rest tremor present
● Progressive disorder
● Persistent asymmetry affecting side of onset most
● Excellent response (70-100%) to levodopa
● Severe levodopa-induced chorea
● Levodopa response for 5 years or more
● Clinical course of ten years or more

Although a diagnosis of PD can be straightforward, clinical exercise in patients with typical presentations of the cardinal signs and an excellent response to levodopa treatment, the differential diagnosis versus other forms of parkinsonism can be challenging, especially early in the disease when signs and symptoms of different forms of parkinsonism have a greater overlap. Error rates in clinicopathological series have been as high as 24%, even though most of the patients in these studies had been treated by movement-disorder specialists (Hughes, et al. 1992b). With the use of standard clinical criteria, such as the UK Parkinson's Disease Brain Bank Criteria, accuracy of a clinical diagnosis of the disease can be improved significantly. However, up to 10% of patients diagnosed with the disease in life will still have to be reclassified at the post-mortem examination (Hughes, et al. 2001b). In clinicopathological studies, the most common misdiagnoses relate to other forms of degenerative parkinsonism, such as progressive supranuclear palsy, multisystem atrophy, or corticobasal degeration (Hughes, et al. 2002). Clinically based studies have shown that other common errors include essential tremor, drug-induced parkinsonism, and vascular parkinsonism (Meara, et al. 1999). There is also an ongoing debate on the distinction between PD with dementia and dementia with Lewy bodies (Emre. 2003, McKeith, et al. 2004).

2.2.5. Clinical progression and treatment

Initially, symptoms are likely to affect one side of the body only, often appearing in one hand, but then progressing slowly to both sides of the body. The onset and progression tend to be slow. In the majority of cases, symptoms appear gradually and sporadically and increase in severity, over a period of years.

Owing to the success of pharmacological treatment, assessment of the natural progression of the key features of PD over the whole disease course is impossible at present. Studies from the pre-levodopa era have not provided details on the rate of progression of motor impairment using validated scores or rating scales (Hoehn and Yahr. 1967, Marttila and Rinne. 1977, Muller, et al. 2001), and it has now become impossible to assess the true natural progression of tremor, rigidity or akinesia in untreated patients in the long-term. The results of these studies suggested a fast progression of motor disability, reaching Hoehn and Yahr stage 5, which indicates a bedridden state, usually after 10-14 years. Data on the short-term rate of progression of cardinal motor features are available from recent placebo-controlled studies, which have provided information of the short-term decline of motor-function as assessed by combined UPDRS part II and III scores in PD patients receiving placebo treatment for 6 to 18 months (Fahn, et al. 2004b, Parkinson Study Group. 2004, The Parkinson Study Group. 1993, The Parkinson Study Group. 1996). These data suggest the fast progression of motor dysfunction in the first years of disease duration (about 5 years), with annual rates of progression of the total unified Parkinson's disease rating scale (UPDRS) score from 7.8 to 14 points, and of the UPDRS III (motor) score from 5.2 to 8.9 points. This fast decline would inevitably lead to severe disability after about 10 years of disease duration, and is thus comparable to the data from the studies

on untreated PD (Hoehn and Yahr. 1967, Marttila and Rinne. 1977). The heterogeneity of disease progression is enourmous and could be associated with several factors. In addition, the progression of motor impairment is likely non-linear in PD, with steeper declines earlier vs. later in the disease. This was originally suggested by Fearnley and Lees (Fearnley and Lees. 1991) who reported an exponential decline of neuronal cell counts in the SN of PD brains over time, and is supported by clinical observations of faster rates of progression of UPDRS motor scores in the first vs. the 10th year of disease (Lee, et al. 1994), or the plateauing of OFF-period motor scores with disease durations of 9 years and above as observed in cross-sectional studies (Bonnet, et al. 1987). These observations highlight the need for early intervention when attempting to modify disease progression in PD. Most studies in the post-levodopa era have found reduced excess mortality, but mortality ratios were still around 2 (Berger, et al. 2000, Ebmeier, et al. 1990, Herlofson, et al. 2004). Cognitive decline and dementia, as well as older age, at the onset have been identified as predictors of decreased survival in several studies. Others have also found improved survival in patients presenting with a tremor-dominant disease. In a series of 200 cases with pathologically confirmed PD, the impact of clinical dementia and Alzheimer pathology on survival was investigated. Mean survival was around 10 years in patients whose brains were free of Alzheimer type pathology, but only 4.9 years in patients with AD pathology of CERAD grade B or C (Jellinger, et al. 2002). Pneumonia is the leading cause of death in PD followed by cardiovascular events, stroke and cancer in most surveys (Ben-Shlomo, et al. 1998, Hely, et al. 1999, Louis, et al. 1997).

Many reports have subtyped patients and compared the projected course among the subgroups based on a small number of evaluations (Marras, et al. 2002). In a previous 39-year clinicopathological study where the patients were classified into tremor dominant (TD), akinetic/rigid (AR), and mixed (MX) based on the entire clinical course it was found that the outcome is most favorable in TD cases, who have the least biochemical abnormalities (Rajput, et al. 2008)and the worst in AR subtype, where the brain biochemical pathology is the most pronounced (Rajput, et al. 2009). As the PD progresses there is a progressive nigrostriatal denervation and progressive neurodegeneration in multiple brain areas and the peripheral autonomic nervous system. This is clinically reflected by increasing severity over time of cardinal motor features as well as the evolution of poorly Ldopa-responsive axial motor symptoms such as postural instability, freezing of gait, dysarthria and dysphagia. In addition, a wide range of non-motor disturbances including dementia, psychosis, autonomic failure and sleep-wake-cycle dysregulation may develop and contribute substantially to disability in PD (Poewe and Mahlknecht. 2009).

Although PD is still an incurable progressive disease, treatment substantially improves the quality of life and functional capacity. The management of PD can be subdivided into three categories: protective or preventive treatment, symptomatic treatment with dopaminergic or non-dopaminergic therapy, and treatment of non-motor symptoms. L-dopa, in combination with a peripheral dopa decarboxylase inhibitor (benserazide or carbidopa), is the most effective therapy. During the past two decades, substantial

evidence has accumulated indicating that levodopa-related motor complications in PD are associated with the non-physiological, discontinuous, or pulsatile stimulation of striatal dopamine receptors, and can be prevented or reversed by long acting dopaminergic drugs that theoretically provide a more continuous stimulation of the striatal dopamine neurons (Olanow. 2004). Central to this concept are observations indicationg that dopamine neurons in the substantia nigra pars compacta (SNc) fire tonically at a nearly constant rate (Grace and Bunney. 1984, Grace. 1991), that striatal dopamine is maintained at a fairly constant concentration (Abercrombie, et al. 1990, Venton, et al. 2003), and that there is a continuous activation of striatal dopamine receptors.

The goal of therapeutics in PD (and other neurodegerative disorders) is the development of drugs that slow or halt the progression of the disease – so-called neuroprotection or disease modification. Ideally, a neuroprotective agent would modify the underlying pathophysiology that causes neurodegeration and cell death. To that end, a variety of agents, targeted at hypothesized pathogenic or protective mechanisms including extitotoxity (riluzole), apoptosis/programmed cell death (TCH346, CEP-1347, minocycline), oxidative stress/mitochondrial dysfunction (vitamin E, coenzyme Q10, creatine), and neurotrophic factors (glial-derived neurotrophic factor, neurturin) have been tested in clinical trials in PD. None has had a clear impact on clinical outcomes in initial studies, although some agents (creatine, CoQ10) have shown sufficient promise to warrant larger phase III trials. Though considered mainstays of symptomatic therapy, drugs that directly (levodopa, dopamine agonists) or indirectly (monoamine oxidase [MAO-B] inhibitors) influence dopamine signalling have also been evaluated for neuroprotective activity, but with controversial results (Lohle and Reichmann. 2010). A previous study showed that early treatment with rasagiline at a dose of 1 mg per day provided benefits that were consistent with a possible disease-modifying effect, but early treatment with rasagiline at a dose of 2 mg per day did not (Olanow, et al. 2009).

The current therapeutic approach to PD is of a symptomatic type. If the patient needs treatment for motor symptoms, efficacious agents for initial therapy include levodopa, dopamine agonists, anticholinergic agents, amantadine, and selective monoamine oxidase B (MAO-B) inhibitors. Levodopa, a dopamine precursor, is considered the most effective antiparkinsonian agent. Levodopa, combined with a peripheral decarboxylase inhibitor, such as carbidopa or benserazide to reduce the decarboxylation of levodopa before it reaches the brain, is available as an immediate-release and controlled-release formulation. Carbidopa plus levodopa combined with a catechol 0-methyltransferase (COMT) inhibitor, entacapone, is another preparation designed to prolong the action of levodopa by preventing its 0-methylation. Dopamine agonists (bromocriptine, lisuride, pergolide, ropinirole, cabergoline, pramipexole, rotigotine, apomorphine) are alternative first-line agents for PD, although they are slightly less effective than levodopa. Non-ergot derivatives (pramipexole, ropinirole, rotigotine) should be favoured over ergot compounds because of an increased risk to pleuritis or pulmonary or heart valve fibrosis by the latter. Dopamine agonists are avoided in the treatment of patients with dementia because of the drugs' propensity to

produce hallucinations. A variety of anticholinergic drugs (benzhexol, procyclidine and others) have been used in the treatment of PD. Anticholinergics have more effect on tremor and rigidity than they do on bradykinesia. The reason these drugs work at all is most likely because they block intrastriatal cholinergic transmission. Confusion and urinary retention are both common side-effects especially in elderly patients. Amantadine, developed as an antiviral agent, was long ago recognized to have some benefit in PD patients. It is a weak N-methyl-D-aspartate (NMDA) antagonist, and this is presumed to be the basis of its antiparkinsonian activity. Selegiline and rasagiline are inhibitors of monoamine oxidase type B (MAO-B). There are two strings to the logic of using MAO-B inhibitors for the treatment of PD. Firstly, MAO-B is responsible (along with COMT) for the intrastriatal catabolism of dopamine after its release in the course of neurotransmission. So blocking brain MAO-B acts to potentiate the effect of both endogenous dopamine and any dopamine formed in the brain as a consequence of levodopa administration. MAO-B inhibitors have therefore been shown to prolong the efficacy of single doses of levodopa, and it also has a small symptomatic treatment in its own right. The second reason for prescribing a MAO-B inhibitor is tied closely to the MPTP story. Since MPTP is not itself a neurotoxin, but rather it depends upon toxification by MAO-B to MPP+ (which is a powerful nigral toxin), it has been suggested that if PD is caused by the toxic effect of an environmental substance then perhaps MAO-B is necessary for the toxification of that agent too. So a MAO-B inhibitor could be a neuroprotective agent, not just a drug with symptomatic effect.

Surgical therapy, such as thalamotomy and thalamic stimulation – deep-brain stimulation (DBS) with the use of implanted electrodes – can be efficacious in treating the tremor of PD when it is severe and unresponsive to medication. Pallidotomy, pallidal deep-brain stimulation, and subthalamic deep-brain stimulation can improve all features of PD in patients in whom the response to antiparkinsonian medication is complicated by severe motor fluctuations and dyskinesias. Overall, the benefits of DBS must be balanced with the risk of adverse events, particularly an increased risk of falls and cognitive dysfunction. Furthermore, patients should understand that DBS treats a fairly specific set of symptoms (mostly levodopa-induced), has no effect on other important problems, such as postural instability, and does not alter the natural history of PD.

Non-motor manifestations affecting neuropsychiatric, neuropsychologic, sleep, and autonomic and sensory domains occur in up to 88% of PD patients and can be an important source of disability. The non-motor symptoms of PD play a significant role in the impairment of the quality of life. The causes of the non-motor manifestations of PD are non-dopaminergic neuropathological changes and treatment with dopaminergic agents. It is important to recognize these phenomena, because some non-motor signs may precede motor impairment. The high impact of non-motor symptoms on the management of PD led the American Academy of Neurology's Quality Standards Subcommittee to review the literature and issue a set of guidelines for practitioners (Zesiewicz, et al. 2010). Evidence-based recommendations included the consideration of sildenafil for erectile dysfunction, polyethylene glycol for constipation, methylphenidate for fatigue,

modafinil for excessive daytime somnolence, and carbidopa/levodopa (Sinemet) for the periodic limb movements of sleep. A prior Practice Parameter supported the use of cholinesterase inhibitors, such as donepezil (Aricept) and rivastigmine (Exelon), for the treatment of cognitive dysfunction associated with PD.

2.3. Cognitive dysfunction

Recent findings, supplemented by advances in neuroimaging and genetic research, reveal substantial heterogeneity in the range of cognitive deficits in patients with PD. Cognitive impairment, in the form of executive deficits, visuospatial and memory deficits, and clinically evident dementia, seems to be an independent non-motor aspect of the disorder that has an important role in establishing functional outcome; PD dementia is a crucial determinant of reduced life expectancy in patients with this movement disorder (Levy, et al. 2002a). Patients who have been newly diagnosed with PD are twice as likely to develop mild cognitive impairment than the healthy elderly individuals (Aarsland, et al. 2009, Foltynie, et al. 2004). PD patients suffer from selective cognitive impairments, including difficulties with attention, concentration, problem solving, set-shifting, and memory, which are thought to reflect the dysfunction of cortical circuits subserving frontal brain regions. These impairments are most frequently reported by patients in terms of the disabilities they cause, such as difficulties in paying attention at work; problems handling more than one project at a time; inability to sequence, plan, and organize tasks at work and home; and problems completing tasks that have been started. Increasing evidence suggests that the neuropsychological deficits seen early in the course of the disease might also be a powerful predictor of the overall progression of cognitive dysfunction to dementia, with implications for early pharmacological intervention.

2.3.1. Fronto-striatal syndrome

The frontal lobes are enormous and comprise more than one-third of the volume of the human brain. This region is anatomically complex with diverse connections to most other cortical and subcortical regions. The frontal lobes are divided into two major functional subdivisions: the motor and premotor cortex and the prefrontal cortex. The prefrontal cortex consists of the heteromodal association cortex, as well as limbic cortex (anterior cingulate and posterior orbitofrontal area). The prefrontal cortex is divided into three regions: lateral prefrontal cortex, orbitofrontal cortex and basomedial cortex, which includes the anterior cingulate cortex (Figure 6). The more differentiated granular areas of the lateral prefrontal cortex connect extensively with parietal and temporal heteromodal association areas, thus receiving information that originated in primary somatic, auditory, visual, olfactory, and gustatory areas. All prefrontal areas connect reciprocally with the dorsomedial thalamic nucleus. The prefrontal cortex is relatively unique, projecting into the subcortical monoaminergic and cholinergic sources (ventral tegmental area, dorsal raphe, locus ceruleus, basal nucleus of Meynert) (Arnsten and

Goldman-Rakic. 1984). These projections permit the prefrontal cortex to influence more global behavioral patterns, such as attention and arousal. The orbitofrontal cortex is divided into an anterior granular region, a posterior agranular region that forms part of the limbic system, and a transitional dysgranular segment in between (Babcock and Salthouse. 1990, Barbas and Pandya. 1989, Hof, et al. 1995, Morecraft, et al. 1992). The posterior agranular and dysgranular cortices strongly connect to the brain stem reticular formation, limbic cortices (entorhinal and anterior cingulated cortices), amygdale, and midline thalamic nuclei. The anterior granular cortex strongly connects to the association cortex and thalamic association nuclei (Van Hoesen, et al. 1996). The anterior cingulate cortex is part of a large structural-functional matrix within the limbic system, including the amygdala, periaqueductal gray, ventral striatum, and orbitofrontal and anterior insular cortices. It also connects extensively with the posterior cingulated cortex. Both anterior and posterior cingulated cortices connect with the heteromodal association and limbic cortices. The anterior cingulate cortex has stronger connections with the amygdale and temporal pole, and receives more diverse thalamic inputs than the posterior cingulate. In summary, the prefrontal cortex has efferent connections to most areas of the association cortex in the parietal, temporal, and occipital lobes. In addition, it connects to the premotor cortex; the limbic cortex (including the cingulated gyrus, amygdale and hippocampus; the basal ganglia (the caudate and putamen); the thalamus; the hypothalamus; and the midbrain. The human prefrontal cortex is privileged to communicate with almost every brain area and plays a vital role in diverse cognitive and behavioral function.
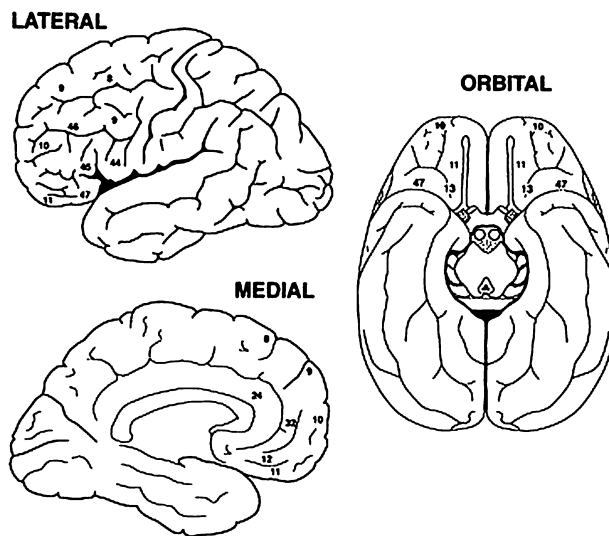
Figure 6. Three views (lateral, orbital and medial) of the cerebral hemispheres with the areas of the prefrontal cortex numbered in accord with Brodmann's cytoarcitectonic map. A Brodmann area is a region of the cerebral cortex defined on its cytoarchitectonics, or structure and organization of cells. Lateral prefrontal cortex, areas 9 and 46; orbitofrontal cortex, areas 11 and 12; basomedial cortex, areas 24 and 32. (Adapted from Fuster. 2002)

The heterogeneous morphology and connectivity patterns within the prefrontal cortex can be resolved into three functional circuits: dorsolateral frontal, orbitofrontal, and medial frontal (Cummings and Miller. 2007) (Figure 7). All three circuits originate in the prefrontal cortex and projects into striatal structures, which in turn project into the globus pallidus and substantia nigra, which feed to the thalamus and then complete a loop back to the prefrontal cortex. The dorsolateral, orbital, and medial prefrontal regions project into unique regions of the basal ganglia and thalamus and create segregated parallel circuits. These circuits, when damaged, produce signature behavioral or cognitive syndromes. Damage to the dorsolateral prefrontal circuit impairs executive function, causing inflexibility of thought in generating solutions to novel problems, planning and regulating adaptive and goal-directed behavior. Damage to the orbitofrontal circuit causes significant affective and social changes and instinctual behaviors, failure to appreciate the consequences of one's actions, emotional lability with euphoria or dysphoria, and increased aggressiveness. The medial frontal circuit originates in the anterior cingulate cortex and projects into the ventral striatum. Hippocampal and amygdalar neurons also project into the ventral striatum, which projects into the rostrolateral globus pallidus and subtantia nigra. These regions in turn project into paramedian portions of the medial dorsal nucleus of the thalamus before returning to the anterior cingulate cortex. Bilateral damage to the medial frontal circuit can cause the dramatic syndrome of akinetic mutism. This behavioral syndrome is characterized by profound apathy and lack of impulse for speech, action, and psychic initiative. In addition to associating anterior cingulate cortex disruption with affective and behavioral alterations, there is ample evidence to suggest that the anterior cingulate cortex also mediates cognitive functions (e.g. in cingulotomy patients (Cohen, et al. 1999) and in PD patients (Grossman, et al. 1992)). In these studies, impairment generally reflects deficits in attention, such as response intention, sustained attention, spontaneous response production, and response monitoring. The intimate relationship between the frontal lobes, basal ganglia, and thalamus explains why selective damage to the striatum, or thalamus, can cause behavioral and cognitive deficits.
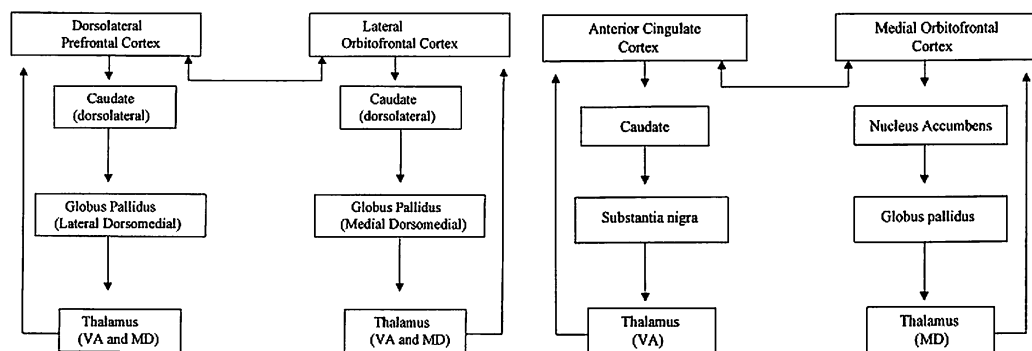

Figure 7. The anatomy (direct pathways) of dorsolateral prefrontal, lateral orbitofrontal, medial orbitofrontal and anterior cingulated circuits. VA = ventral anterior; MD = mediodorsal. (Adapted from Tekin and Cummings. 2002)

2.3.1.1. Dopaminergic nature of the fronto-striatal dysexecutive syndrome

Frontal/executive functions are relatively compromised in PD and are regarded as the primary cognitive sequelae in this disease (Barbosa, et al. 1997, Dubois and Pillon. 1997, Levin, et al. 1992). PD patients with or without dementia have been shown, for example, to exhibit impairments in working memory (Owen, et al. 1997), trial-and-error learning (Owen AM, Sahakian BJ, Hodges JR, et al. Dopamine-dependant frontostriatal planning deficits in Parkinson's disease. Neuropsychology. 1995;9:126-140), response monitoring (Cooper, et al. 1994), set sifting (Hsieh, et al. 1995, Owen, et al. 1992, Raskin, et al. 1992a, Richards, et al. 1993) and attentional control(Brown and Marsden. 1988a). Alteration of the neuronal loops connecting the frontal cortex, thalamus and basal ganglia (frontostriatal circuitry) are suggested to play a role in the executive dysfunction of PD (Owen. 2004). This notion is largely based on the concept of basal ganglia organization, of which frontostriatal circuits are structurally and functionally segregated into "motor", "limbic" and "associative" (including prefrontal) domains (Alexander, et al. 1986, Alexander, et al. 1990). The neurochemical basis of frontostriatal and cognitive dysfunction in PD (particularly in the early stages) is hypothesised to be linked predominately to dopaminergic dysfunction within neural networks linking the dorsal striatum (i.e. dorsolateral putamen and dorsal caudate nucleus) to the dorsolateral prefrontal cortex (Cools. 2006, Owen. 2004). In PD, tests sensitive to dorsal frontostriatal dysfunction (so-called executive processes), such as planning and set-shifting, were impaired following L-dopa (L-3,4-dihydroxyphenylalanine) withdrawal (Cools, et al. 2003, Hayes, et al. 1998, Lange, et al. 1992), and improved with L-dopa treatment(Bowen, et al. 1975, Lange, et al. 1993), suggesting a primarily dopaminergic substrate. Further, a cerebral blood flow sudy in PD patients demonstrated dopaminergic modulation of frontostriatal networks during planning (Cools, et al. 2002). Results from early studies indicated that dopaminergic medication can impair some aspects of cognition, mostly by overdosing the caudate nucleus and ventral striatum, which are generally less dopaminergically depleted early in the disease (Kish, et al. 1988b). Whereas drug-induced cognitive deficits are mainly associated with the context of depleted versus intact striatal regions, other deficits, such as distractibility, might stem from upregulated frontal dopaminergic transmission in early PD in response to reductions in striatal dopamine (Pycock, et al. 1980). The U-shaped dose-response curve shows that a specific dosage produces optimal performance on working memory tasks (Arnsten. 1997). This observation suggests that "more" is not "better" and that an optimal dopamine concentration is necessary for the optimal function of the prefrontal cortex.

2.3.2. Other cognitive deficits

Althtough the most common deficits described are related to executive functions (Caviness, et al. 2007, Elgh, et al. 2009, Emre, et al. 2007, Goetz, et al. 2008, Muslimovic, et al. 2005, Williams-Gray, et al. 2009), visuospatial (Goetz, et al. 2008, Levin, et al. 1991, Zgaljardic, et al. 2003), attentional (Goetz, et al. 2008, Rippon and Marder. 2005),

memory (Caviness, et al. 2007, Elgh, et al. 2009, Emre. 2003, Muslimovic, et al. 2005), and language (Gurd and Ward. 1989, Williams-Gray, et al. 2009) impairments have also been observed in PD patients. Some of these disorders have been detected even in the early stages of the disease (Levy, et al. 2002b, Mahieux, et al. 1998), while others appear in later stages. In an attempt to put order to the cognitive heterogeneity present in PD patients, signs of cognitive impairment have been proposed to cluster into two main groups (Aarsland and Kurz. 2010). Thus, whereas some of the patients with PD present reduced attention and executive capacities, others show a pattern of impairment that is primarily characterized by memory loss. These two cognitive impairment profiles would be the result of frontal lobe- and temporal lobe-dependent pathology, respectively (Aarsland and Kurz. 2010). However, it has also been suggested that the executive deficit is the primary cause of the other symptoms, including the language and memory impairments (Zgaljardic, et al. 2003).

Memory deficits exhibited by PD patients are characterized by impairments of delayed recall, temporal ordering, and conditional associate learning (Lichter. 2000). PD patients who tend to maintain normal rates of decay demonstrate preserved encoding of information and recognition and benefit from external cueing (Brown and Marsden. 1988b, Cummings. 1986, Levin, et al. 1992). This profile contrasts with that of patients with AD (Huber, et al. 1989, Mahler and Cummings. 1990), who tend to exhibit increased forgetting (due to impaired encoding), poor recognition, and an inability to benefit from external cueing (Cummings. 1986). PD patients may have difficulties in initiating and maintainin search strategies effectively, despite preserved encoding and recognition. This particular series of functions is reportedly mediated by the dorsolateral prefrontal cortex (DLPFC) (Lichter. 2000), supporting the notion that memory impairments described in PD most likely reflects an executive deficit possibly indicative of select frontostriatal circuit disruption.

Patients with PD have exhibited selected impairments in linquistic ability. Word list generation, using semantic and/or phonemic cueing, has been found to be impaired in PD patients with and without dementia (Bayles, et al. 1993, Raskin, et al. 1992b, Troster, et al. 1998). Non-demented PD patients have demonstrated impairments on tasks assessing complex comprehension and grammar relative to normal controls (Cummings, et al. 1988). Research evidence also suggests that PD patients can demonstrate sentence processing deficits (Grossman. 1999). This particular deficit may be attributed to dysfunctional attentional mechanisms (involving the anterior cingulate cortex) necessary to attend to sentence structure (Grossman, et al. 1992). These reported deficits in sentence processing in PD may not necessarily be related to alterations in dopamine levels/or deficits in working memory (Skeel, et al. 2001). However, recent findings using functional magnetic resonance imaging (Grossman, et al. 2003) revealed that non-demented PD patients had reduced recruitment of striatal regions in comparison with normal controls when asked to process sentences with a high demand on working memory.

There have been mixed findings regarding attentional deficits in PD assessed by neuropsychological tasks in the literature. There is some indication that select areas of attention are better preserved than others. Digit span, representative of vigilance or sustained attention, remains fairly intact, while performance on attentional tasks that demand speeded cognitive processing or require the patient to internally guide their attentional resources appear to be impaired (Pahwa, et al. 1998, Raskin, et al. 1990, Ridenour and Dean. 1999).

Cognitive slowing has also been reported to be a typical feature of PD. The speed of information processing in PD has mainly been studied using reaction-time (RT) tasks. PD patients have been shown to be slower than controls in simple reaction time (SRT), but not disproportionately slower in choice reaction time (Evarts, et al. 1981). Computerised tests have been used to measure both automatic and controlled cognitive processing in PD, and it has been suggested that the slowness of controlled processing in the PD patients is a manifestation of a decreased amount of connections in a neural network (Revonsuo, et al. 1993). Cognitive slowing has been found mainly in patients with longer disease duration and more marked general cognitive decline (Revonsuo, et al. 1993). It has been reported that PD patients with severe executive deficits were also cognitively slower (Berry, et al. 1999).

Results from early psychopharmacological studies have indicated that, compared with dopaminergic therapy, anticholinergic drugs lead to similar motor improvements after chronic treatment in newly diagnosed PD patients, but impaired short-term memory (Cooper, et al. 1992) and frontal-like executive dysfunction after acute treatment (Dubois, et al. 1990), a pattern similar to that seen in PD patients, but not controls, after treatment with hyoscine (Dubois, et al. 1987). Cholinergic deficits at the level of the frontal and temporal cortex are well documented, even early in the course of PD (Dubois, et al. 1983, Rinne, et al. 1989a, Ruberg, et al. 1986), owing to the degeneration of the basal forebrain cholinergic nuclei and ascending cholinergic pathways, which occurs in parallel with the main dopaminergic pathological changes. Increasing evidence (Kehagia, et al. 2010) suggests that also norepinephrine might be implicated in higher-order cognitive flexibility, which is consistent with the early and profound degeneration of the locus coeruleus, the main source of cortical norepinephrine (Baloyannis, et al. 2006), seen in PD patients. The distribution of serotonergic projections into the cortex and the association between depression and serotonin levels in PD (Mayeux, et al. 1988) suggest that the serotonergic system in PD might also have a role in cognitive symptoms in PD.

Patients with PD are three to five times more likely to develop dementia compared with healthy individuals (de Lau, et al. 2005, Hobson and Meara. 2004). Aarsland and co-workers (Aarsland, et al. 1996) identified dementia in 28% of PD patients. In another study, 65% of surviving members of a cohort of patients over the age of 85 had dementia (Mayeux, et al. 1990).

Several studies based on prevalent PD samples have suggested that the incidence of dementia in a defined PD cohort is 100 per 1000 person-years, meaning that approximately 10% of PD patients convert to dementia every year (Aarsland, et al. 2001). There is evidence that the early occurrence of cognitive impairment is associated with a more rapid decline (Janvin, et al. 2006, Uc, et al. 2009). Although PD patients share some of the features of cognitive impairment seen in patients without dementia in terms of executive and mnemonic features (Dubois and Pillon. 1997), the range, complexity, and severity of cognitive and psychiatric symptoms clearly differentiate these patients. The diagnosis of dementia in patients with PD is a complex undertaking despite its clear differentiation from the dementia of AD, as recently highlighted by the Movement Disorder Society task force (Dubois, et al. 2007, Emre, et al. 2007). The defining feature of PD dementia is that dementia develops in the context of established PD. Hence, diagnosis of idiopathic PD before the development of dementia symptoms is the essential first step in the diagnosis. Diagnosis of dementia must be based on the presence of deficits in at least two of the four core cognitive domains (attention, memory, executive and visuo-spatial functions) as shown in clinical and cognitive examination, and be severe enough to affect normal functioning. Although there are some differences in the extent and profile of deficits in individiual cognitive domains compared to patients with AD (more prominent memory impairment in AD, more prominent executive dysfunction in PD dementia), these may vary from patient to patient and cannot be used as the sole basis of diagnosis. Neuropsychiatric and behavioral symptoms are frequent, but are not invariable. The profile of cognitive and behavioral symptoms in PD dementia and DLB are very similar (Emre, et al. 2007). Although PD dementia (PDD) is associated with many types of cognitive impairment, it still remains unclear whether dementia itself is indicative of further cognitive deterioration along the same impairment as mild cognitive impairment in patients without dementia (Foltynie, et al. 2004, Girotti, et al. 1988), or whether it is a separate clinical disorder (McFadden, et al. 1996) or an interaction between PD and age.

Previous studies have indicated that the profile of impairment in patients who eventually develop dementia might differ from the typical frontostriatal executive dysfunction seen in early PD (Williams-Gray, et al. 2007), emphasizing the role of visuospatial and language deficits in these patients that are indicative of early Lewy body load in the occipito-parietal cortex and the temporal lobe. Lewy bodies are present in small numbers in almost all cases of PD (Halliday, et al. 2008) and they are especially common in the temporal, frontal, parietal, insular cortices, cingulum, and entorhinal cortex. Extensive neocortical Lewy body pathology is common in patients with severe memory loss when additional Alzheimer-type changes are frequently seen (Apaydin, et al. 2002, Braak, et al. 2005, Hurtig, et al. 2000, Jellinger and Attems. 2008, Kosaka, et al. 1984, Tsuboi and Dickson. 2005). A substantial proportion of non-demented patients with PD (NDPD) also have widespread cortical Lewy body pathology. Therefore, neocortical Lewy bodies are not necessarily the pathological correlate of dementia in PD (Parkkinen, et al. 2005a, Parkkinen, et al. 2005b). Lewy bodies, plaques, and vascular changes are

present in both PD with dementia and dementia with Lewy bodies. These disorders are, however, characterized by different temporal profiles, but whether they are separate non-converging clinical diseases remains a matter of debate (McKeith. 2009).

The amount of associated cortical β-amyloid may be the key factor for the cognitive decline in PD (Ballard, et al. 2006, Halliday, et al. 2008, Kalaitzakis, et al. 2008, Lashley, et al. 2008). Alzheimer-type pathology is common in PD with dementia, and it is now possible to assess this in living patients with amyloid imaging methods (Klunk, et al. 2004). These methods permit the assessment of amyloid deposits in the brain of PD and PD with dementia, and some studies show an increased frequency of amyloid in some demented compared to non-demented (Edison, et al. 2008).

The occurrence of dementia in PD seems to be multifactorial, although there is increasing evidence that α-synuclein pathology beyond the nigrostriatal dopaminergic system is critically involved in both the presymptomatic and late-developing cognitive dysfunction of PD. The distribution of serotonergic projections into the cortex and the association between depression and serotonin levels in PD (Mayeux, et al. 1988) suggest that the serotonergic system in PD might also have a role in some cognitive symptoms in the disease. PET studies of the resting state cerebral glucose metabolism has become a major functional imaging tool for investigating the age related brain pathology such as PD or AD, and it has been suggested that widespread glucose hypometabolism in the cerebral cortex may be associated with dementia in PD (Ma, et al. 2008b, Sasaki, et al. 1992b). In addition, structural imaging with an MRI has shown that, when compared to age-matched healthy controls, non-demented patients with PD have a significant rate of median or global brain volume loss and these changes correlated with global measures of cognitive decline (Hu, et al. 2001).

2.4.   Positron emission tomography (PET)

2.4.1. PET basics

Positron emission tomography (PET) provides unprecedented insights into human brain function in both health and disease, but is a complex endeavour involving many scientific disciplines. PET is a nuclear medicine technique that provides quantitative cross-sectional images of several physiological and biochemical processes *in vivo* such as oxygen consumption, blood flow, metabolism and ligand-receptor interactions. It is based on the utilization of artificially produced positron-emitting radionuclides (tracers). The tracer is chemically incorporated into a biologically active molecule and then injected into the living subject (usually into the blood circulation). The most used radionuclides in PET are ^{11}C, ^{18}F, and ^{15}O (half-lives 20.4 min, 109.8 min and 2.0 min, respectively).

The unstable nucleus of the radionuclide emits a positively charged positron, which travels a short distance in the tissue. After losing most of its kinetic energy, a positron

interacts with an electron in such a fashion that the masses of two particles are converted into electromagnetic radiation in the form of two photons, each carrying an energy of approximately 511 keV and travelling nearly collinearly in opposite directions. This process is called annihilation. The average distance which positron travels in tissue before depositing all its kinetic energy and annihilates with an electron sets the limit to the absolute theoretical spatial resolution of PET. For example, ^{18}F emit positrons with a very low energy that only travel on average 0.35 mm (maximum 2.3 mm), while positrons emitted by 15O have greater energy, thus travelling a longer distance (1.1 mm and 8.1 mm respectively). The PET camera system includes multiple rings of detectors, which consist of scintillation crystals coupled with photomultiplier tubes. The ring design utilizes the concept that two photons detected within an electronic time window (e.g. 12 ns) by two opposed detectors in the ring are likely to have originated from a single annihilation event in the body, somewhere along a line between the two detectors. Such a simultaneous detection is called a "coincidence". All of the coincidence events detected during an imaging period are recorded by the PET computer system as a raw data set. The coincidence data in PET is reconstructed by a computer to produce cross-sectional images in the axial, sagittal, and coronal planes.

2.4.2. [^{18}F]FDOPA as a PET tracer

The most widely used tracer for the dopaminergic system is L-6-^{18}F-fluoro-3,4-dihydroxyphenylalanine (FDOPA) (Garnett, et al. 1983). FDOPA is transported across the blood-brain barrier by the large neutral amino acid carrier (Yee, et al. 2001), and is then decarboxylated by aromatic amino acid decarboxylase (AADC) to ^{18}F-dopamine, which is stored in dopamine vesicles. In a similar way to dopamine, it is metabolized further by catechol-0-methyltransferase (COMT) and by monoamine oxidase (MAO) (Firnau, et al. 1987). The metabolites leave the brain slowly (Cumming, et al. 2001), and thus activity accumulates during measurement times of typically up to 90 min. Accumulation is highest in brain regions rich in aromatic amino acid decarboxylase (AADC), these being the midbrain, caudate and putamen. FDOPA uptake mainly reflects the transport of FDOPA into nigrostriatal nerve terminals, dopa decarboxylation by AADC activity, conversion to and storage as ^{18}F-dopamine within vesicles in presynaptic nerve terminals (Firnau, et al. 1987), and the number of functioning nerve terminals (Snow, et al. 1993). FDOPA uptake is not strictly specific for dopaminergic cells but also includes many regions with relatively high concentrations of norepinephrine and serotonin (Brown, et al. 1999).

2.4.3. [^{18}F]FDOPA uptake in PD

Positron emission tomography with FDOPA as the tracer has been used to demonstrate and to quantify presynaptic dopaminergic function. Decreased FDOPA uptake has been reported in the striatum in PD (Garnett, et al. 1984b, Leenders, et al. 1986b, Nahmias, et al. 1985b) (see Figure 8 for example). Post mortem studies have shown that there is an

uneven pattern of dopamine loss in the striatum in PD. The depletion is more severe in the putamen than in the caudate nucleus and most prominent in the caudal parts of the putamen due to the topographical organization of the nigrostriatal projection (Kish, et al. 1988b). Accordingly, subregional analysis of striatal Fdopa uptake in PD has revealed predominately posterior putamen impairment (Morrish, et al. 1996b, Nurmi, et al. 2001b, Rinne, et al. 2001). The posterior putamen receives dopaminergic projections especially from the ventrolateral part of the substantia nigra, which is the most severely degenerated nigral subregion (Damier, et al. 1999b). A longitudinal FDOPA study over 5 years confirmed that the disease process in PD first affects the posterior putamen, followed by the anterior putamen and the caudate nucleus (Nurmi, et al. 2001b). The FDOPA uptake deficit in putamen is related to indices of motor function in PD, such as clinical Hoehn and Yahr grades (Antonini, et al. 1995) and finger tapping (Pal, et al. 2001). The deficit in the caudate heads seems to be related more to the speed of mental function (Bruck, et al. 2001) and to memory (Holthoff-Detto, et al. 1997, Rinne, et al. 2000). This is consistent with the view that this part of the striatum, with its intense connections to the frontal cortex, mainly supports mental rather than motor function. PD is characterized by the unilateral appearance of symptoms which can be seen also with Fdopa. Patients in the early stage of PD have at least a 30% loss of FDOPA uptake in the putamen contralateral to the side with clinical symptoms (Morrish, et al. 1995, Rinne, et al. 2001). At very late stages of the disease, a 60-70% or more drop in FDOPA striatal uptake may be observed. FDOPA PET also permits objective monitoring of disease progression in PD. The striatal FDOPA uptake clearly correlates with the duration of PD (Broussolle, et al. 1999), and the FDOPA uptake has been found to decrease in the putamen annually by 8-9% (Morrish, et al. 1998, Nurmi, et al. 2001b), which is significantly greater than the normal age-related decline (Vingerhoets, et al. 1994). Over the course of the disease, functional impairment of the remaining neurons appears to proceed at a constant rate. FDOPA was used in a study demonstrating that the dopamine agonist ropinirole may slow disease progression more than L-DOPA treatment (Whone, et al. 2003c). Because many neurodegerative disorders are associated with some degree of decreased FDOPA uptake, it is not possible to distinguish between PD and other disorders with parkinsonian symptoms on the basis of FDOPA studies alone (Burn, et al. 1994). However, in families with several cases of PD, detection of asymptomatic patients may be possible with a FDOPA PET. In a PET study of 32 "at-risk" asymptomatic subjects from seven families (Piccini, et al. 1997), putamen FDOPA uptake was decreased by more than 2.5 SDs in 11 cases, three of whom had developed clinical signs within two years of the PET study. PET investigations with FDOPA in twins, one of which being parkinsonian, show that asymptomatic cases are frequent, with a concordance in a FDOPA influx rate of 55% and 18% in monozycotic and dizycotic twins respectively (Piccini, et al. 1999).
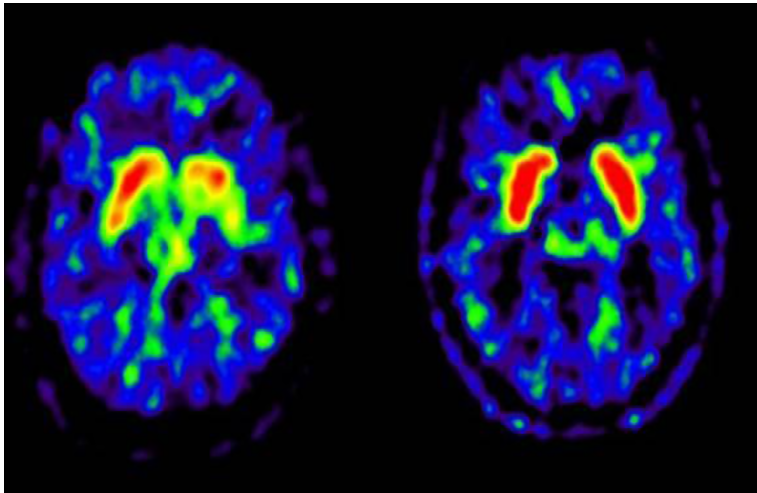
Figure 8. FDOPA PET images of a PD patient and control. PD patient on the left and control on the right. PD patient has dopaminergic hypofunction in the striatum (the red areas in the center of the picture).

The pathophysiological significance of extratriatal changes of dopamine turnover in the course of PD is widely unknown as yet. Because of the development of high-resolution PET scanners and 3D-MRI based methods, extrastriatal cerebral regions have become the subject of recent imaging studies in PD. In the internal segment of pallidum a compensatory increase of FDOPA uptake was observed in PD (Whone, et al. 2003a). Fdopa is also taken up by the pineal gland, and this uptake is even increased in PD, which may indicate compensatory up-regulation of monoaminergic transmitter systems outside the basal ganglia (Ghaemi, et al. 2001). Ito and colleagues found decreased FDOPA uptake bilaterally in the SNc of PD patients, whereas Rakshi and co-workers demonstrated significant increases of midbrain activity in early, but significant reductions of radiotracer binding in advanced PD patients compared with controls (Ito, et al. 1999, Rakshi, et al. 1999). FDOPA uptake in the midbrain may be due not only to dopaminergic, but also to noradrenergic and serotonergic, cells (Rakshi, et al. 1999). Several studies have reportedly measured cortical FDOPA upatake in PD patients (Bruck, et al. 2005b, Ito, et al. 2002, Kaasinen, et al. 2001, Rakshi, et al. 1999, Rinne, et al. 2000) or normal elderly controls (Nagano, et al. 2000) using the cerebellum or occipital cortex as a reference region. Such studies have reported increases (Bruck, et al. 2005b, Kaasinen, et al. 2001, Rakshi, et al. 1999) and decreases (Ito, et al. 2002, Rinne, et al. 2000) in FDOPA uptake in the cortex, which has been interpreted as reflecting either increased or decreased dopamine synthesis. The observations of increased extrastriatal uptake have been made only in patients at the early stage of PD, and not in advanced cases. The increased uptake of FDOPA in the cortex might be a compensatory process in the cortical-subcortical DA loops or since AADC is present also in other monoaminergic systems the increased values can present changes in the serotonergic or noradrenergic neurotransmitter systems in addition to dopaminergic system.

A variety of analytical methods have been developed to quantify FDOPA PET images to discriminate reliably patients with PD from controls. A striatal-to-occipital ratio (SOR) and influx constant using the graphical tissue reference approach (Ki^{ref}) are commonly used as quantitative parameters in FDOPA PET studies. They have been measured non-invasively in a dynamic mode using region-of-interest (ROI) based approaches (Hoshi, et al. 1993, Morrish, et al. 1998, Takikawa, et al. 1994, Vingerhoets, et al. 1996). Both SOR and Ki^{ref} have been used to quantify regional dopamine metabolism and to reflect disease severity in PD (DeJesus, et al. 1997, Ishikawa, et al. 1996a, Ishikawa, et al. 1996b, Morrish, et al. 1996b, Nakamura, et al. 2001). It has been observed that both SOR and Ki^{ref} successfully discriminate patients with moderate PD from healthy subjects and are also equally sensitive as descriptors of disease severity (Dhawan, et al. 2002). Determining Ki^{ref} requires dynamic scans over a longer time than determining SOR, which can be determined with a shorter static data acquisition. A long study poses a compliance issue, may increase potential bias because of subject movement, and may diminish the cost-effectiveness of the cameras and tracers used. SOR may offer a practical advantage because it is a simple measure and would be the easiest to apply in clinical studies quantifying nigrostriatal dopamine function in PD and related disorders.

2.4.4. Cognitive functions and the dopamine system in PD studied with PET

The cortico-striato-thalamo-cortical loops connect the basal ganglia with the cerebral cortex. The putamen is closely connected with the supplementary motor cortex and is thought to be involved mainly in motor functions and not to cognitive performance (Broussolle, et al. 1999, Holthoff-Detto, et al. 1997, Rinne, et al. 2000). A few, however, have reported an association between decreased putamen FDOPA uptake and a worse performance on tests of memory (Marie, et al. 1999) and executive function and fluency (Muller, et al. 2000, van Beilen, et al. 2008), which may in part be related to motor actions required after some test of frontal lobe function (van Beilen, et al. 2008). The caudate nucleus, in turn, is connected with the dorsolateral prefrontal cortex and the lateral orbitofrontal cortex, and it has been suggested that the dysfunction in this system contribute to the cognitive impairment in PD. Positron emission tomographic (PET) studies showed that the reduced FDOPA uptake (Holthoff, et al. 1994, Holthoff-Detto, et al. 1997), especially in the caudate nucleus (Rinne, et al. 2000), is associated with the impaired cognitive performance in patients with PD. This suggests the role of the caudate nucleus via connections to frontal areas in the cognitive impairment in PD. To support this, a connection between the caudate nucleus FDOPA uptake and the performance in tests measuring verbal memory or delayed recall (Holthoff, et al. 1994, Holthoff-Detto, et al. 1997) or frontal lobe functioning (Stroop. 1992) has been found in PD. In particular decreased Fdopa uptake in the caudate nucleus and the impairment in tests measuring verbal fluency, working memory and attentional functioning reflecting frontal lobe function were related (Stroop. 1992). In addition previous studies have shown that the impaired performance in tests requiring suppressed attention, planning and set-

shifting is related to the dopaminergic hypofunction in the caudate nucleus, especially on the right side (Bruck, et al. 2001, Marie, et al. 1999), indicating that the disturbances in the dopaminergic system are involved in the cognitive impairments found in the early stages of PD. These findings are consistent with reports of explicit memory and executive deficits in PD (Dubois and Pillon. 1997) and the demonstration that executive dysfunction in PD is accompanied by reduced activity within the caudate nucleus and prefrontal regions (Lewis, et al. 2003). However, contrary to these reports and to the caudate nucleus-cognition model, three studies have failed to show an association between caudate nucleus FDOPA uptake and cognitive performance in non-demented PD patients (Broussolle, et al. 1999, Bruck, et al. 2005b, Nagano-Saito, et al. 2004).

The involvement of the frontal cortex and limbic system in cognitive functions have stressed the importance of measuring the FDOPA uptake in extrastriatal regions receiving mesolimbic dopaminergic projections (e.g. the frontal and cingulate cortex, amygdala, the nucleus accumbens) in PD patients with cognitive impairment. The neurochemical basis of frontostriatal and cognitive dysfunction has been hypothesised to be linked predominately to dopaminergic dysfunction within neural networks linking dorsal striatum (i.e. the dorsolateral putamen and dorsal caudate nucleus) to the dorsolateral prefrontal cortex (Cools. 2006, Owen. 2004). In PD patients, tests sensitive to dorsal frontostriatal dysfunction (executive processes) such as planning and set-shifting were impaired following L-dopa withdrawal (Cools, et al. 2003, Hayes, et al. 1998, Lange, et al. 1992) and improved with L-dopa treatment (Bowen, et al. 1975, Lange, et al. 1993), suggesting a primarily dopaminergic substrate. An association between reduced FDOPA uptake in the frontal cortex and deficits in working and immediate memory and executive strategies has been found (Rinne, et al. 2000). In another study, FDOPA reductions in the anterior cingulated were observed in PD patients with dementia (Ito, et al. 2002), although AADC is also present in noradrenergic and serotonergic neurons (Tison, et al. 1991), the cortical FDOPA reductions might be a composite of DAergic, serotonergic, and noradrenergic systems, which also degerate in advanced PD. Contrary to these reports, early, non-demented and non-medicated PD patients were recently reported to show increased FDOPA uptake in cortical areas covering the dorsolateral prefrontal cortex, anterior cingulate, and medial frontal cortex (Bruck, et al. 2005b), replicating previous findings of increased cortical FDOPA uptake in early, medicated (Rakshi, et al. 1999), and unmedicated (Kaasinen, et al. 2001) PD patients. Interestingly, an increase in dopamine tracer uptake in the frontal lobe of early stage, drug naive PD subjects was associated with a worse performance on the test of sustained attention (DLPFC), but improved performance on the test of suppressed attention (anterior cingulate, medial frontal cortex). Greater FDOPA uptake in the dorsal anterior cingulate has recently been associated with reduced interference on the Stroop task (reflecting decreased processing time to suppress attention) in medicated male schizophrenic patients and control subjects (McGowan, et al. 2004), providing support for the involvement of anterior cingulate DA function in the suppressed attention/response inhibition processes. These observations

could represent an early compensatory mechanism brought on by striatal dopaminergic dysfunction, or may reflect changes in other neurotransmitter systems (Bruck, et al. 2005b). Another possible explanation could be that the effect of DA on cognitive performance might be dependant on the nature of the cognitive task and the basal level of DA in the underlying fronto-striato-thalamic circuitry, as has been proposed by others (Cools, et al. 2003). In addition the FDOPA signal-to-noise ratio is quite low in cortex, and it has been questioned whether FDOPA uptake can be reliably quantified in cortical areas (Cropley, et al. 2008). The pathophysiological significance of extrastriatal changes of dopamine turnover in the course of PD is widely unknown yet.

2.4.5. [^{18}F]FDG PET and PD

The widely used tracer for the measurement of the cerebral metabolic rate of glucose (GMR) is 18F-labeled glucose analogue 2-[18F]-fluoro-2-deoxy-D-glucose ([18F] FDG) (Reivich, et al. 1979). Both glucose and [18F]FDG enter the cells via facilitated diffusion by glucose transporters. Inside the cell, [18F]FDG is phosphorylated by hexokinase to 18F-fluodeoxyglucose-6-phosphate, which is not metabolized further. Thus, it accumulates in the brain in proportion to local GMR. Due to the positron emitting 18F-isotope, the brain regions of glucose uptake can be detected with PET. After the first 10-20 min following an i.v. bolus injection, during which transport effects dominate tracer distribution, the distribution of [^{18}F]FDG in the brain approximates local GMR. A variety of methods for the quantification of GMR based on physiological modelling has been used. In this thesis an automated region of interest (ROI) analysis was performed to obtain the quantitative regional values of [^{18}F]FDG. A late scan (30–45 min) target region-to-pons ratio as an outcome measure was chosen, since previous results have indicated that relative region-to-pons ratio measures are suitable for clinical and research purposes in mild AD, particularly in studies aimed at detecting group differences (Mosconi, et al. 2007).

PET studies of the resting state cerebral glucose metabolism using [^{18}F]FDG has become a major functional imaging tool for investigating the age related brain pathology such as PD or AD (Eidelberg, et al. 1995, Thobois, et al. 2001). Glucose metabolism as measured with [^{18}F]FDG is generally normal in most patients with PD.There may be a tendency for it to be elevated in the putamen (Antonini, et al. 1995) and reduced in the mesial frontal cortex (Eidelberg, et al. 1990), but these alterations rarely reach significance (Rougemont, et al. 1984). Putamen [^{18}F]FDG increase is probably the result of more complex feedback mechanisms that are primarily induced by a striatal dopamine deficiency (Antonini, et al. 1995). On the other hand, hypometabolism very similar to that seen in AD in frontal and temporo-parieto-occipital asoociation cortices may develop with advancing PD. In contrast to AD, the reduction of GMR in the association cortex is not generally associated with dementia or other cognitive impairment (Berding, et al. 2001, Hu, et al. 2000, Kuhl, et al. 1984, Metter, et al. 1990, Wu, et al. 2000). Although, it has been suggested that widespread glucose hypometabolism in the cerebral

cortex may be associated with dementia in PD (Ma, et al. 2008b, Sasaki, et al. 1992b). In demented PD patients metabolic deficits tend to be more severe and more focused in the temporoparietal, frontal and occipital cortex (Vander Borght, et al. 1997, Yong, et al. 2007) (Peppard, et al. 1992). In nondemented patients there is relatively little correlations between cognitive functions and GMR (Holthoff-Detto, et al. 1997, Turjanski and Brooks. 1997). However, it has been demonstrated that there is an association of parieto-occipital hypometabolism with a mild impairment of memory and associative visual processing (Mentis, et al. 2002).

Compared to the non-demented patients with PD, both PDD and DLB patients show a similar pattern of decreased metabolism in the bilateral inferior and medial frontal lobes, and the right parietal lobe (Yong, et al. 2007). Preserved metabolism on medial temporal structures is suggested to be a GMR feature in separating PDD from AD (Vander Borght, et al. 1997), and impaired glucose metabolism in the occipital cortex is suggested to distinguish a metabolic pattern in dementia with Lewy bodies from that seen in AD (Albin, et al. 1996, Gilman, et al. 2005, Imamura, et al. 1997, Minoshima, et al. 2001, Vander Borght, et al. 1997).

2.4.6. [^{11}C]PIB PET and PD

Patients with idiopathic PD have more frequently AD pathology in the entorhinal cortex (ERC) and hippocampus than controls (Alvord, et al. 1974, Ince, et al. 1991, Perry, et al. 1985, Perry, et al. 1990). The presence and severity of dementia in PD have been reported to correlate with the intensity of cortical AD-type lesions, particularly neurofibrillary tangles in both the frontal cortex (Jellinger. 1987, Vermersch, et al. 1993) and the hippocampus (Braak and Braak. 1990, Duyckaerts, et al. 1993, Jellinger. 1987, Quinn, et al. 1986) and thus dementia in PD could be attributable to co-existent AD pathology (Gaspar and Gray. 1984, Jellinger, et al. 2002). However, there are PD patients with severe dementia who have no significant Alzheimer's disease (AD) pathology, suggesting other underlying pathology for intellectual deterioration (Jellinger. 1987). The estimates of AD pathology in PD have varied from 42 % to 91 % (Boller, et al. 1980, Gaspar and Gray. 1984, Hakim and Mathieson. 1979). Clinicopathological studies have shown that cognitive impairment and dementia in PD are related to the number of limbic and cortical Lewy bodies (Bertrand, et al. 2004, Gibb, et al. 1989), even when the possible co-existing AD-pathology has been taken into account (Mattila, et al. 1998). Thus, the pathophysiological basis of cognitive impairment and dementia in PD may be heterogenous involving cortical Lewy bodies, concomitant AD pathology, or the degeneration of subcortical projection nuclei of neurotransmitter systems (such as dopamine, noradrenaline, serotonin), or a combination of these brain changes.

Since most dementia researchers regard amyloid deposition as the most important and specific pathophysiological events in AD, newly developed tracers that label amyloid plaques and neurofibrillary tangles have been developed. The Pittsburg compound B

([^{11}C]PIB, N-methyl-^{11}C-2-(4'-methylaminophenyl)-6-hydroxybenzothiazole) is the most widely studied amyloid tracer in PD patients. This tracer binds with nanomolar affinity to amyloid and is being used to study amyloid deposition in the brain. PET with [^{11}C]PIB (Pittsburgh Compound B) demonstrates an increased retention of the tracer, probably reflecting parenchymal and vascular amyloid-β (Aβ) (Klunk, et al. 2004) (for example see Figure 9). In AD, up to twofold increases in the cortical uptake of [^{11}C]PIB have been reported compared with healthy controls (Archer, et al. 2006, Edison, et al. 2007, Engler, et al. 2006, Fagan, et al. 2006, Kemppainen, et al. 2006, Klunk, et al. 2004, Mintun. 2005, Verhoeff, et al. 2004, Ziolko, et al. 2006).
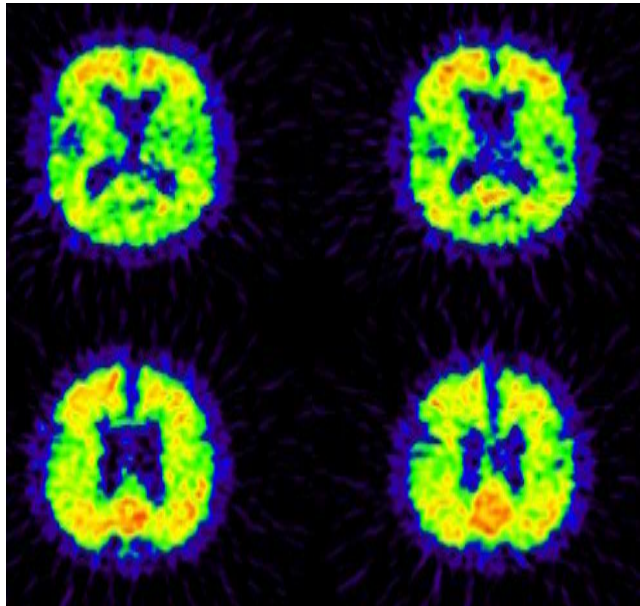

Figure 9. [^{11}C]PIB PET images of a subject. Note the increased tracer signal on the frontal and parietal cortex.

A clinicopathological case description showed that the binding of [^{11}C]PIB in a patient with a neuropathological diagnosis of DLB was to amyloid plaques and not to Lewy bodies (Fodero-Tavoletti, et al. 2007). A study with autopsy-confirmed Parkinson's disease with dementia suggests that PIB PET is specific for fibrillar Aß molecular pathology, but not for the pathologic diagnosis of comorbid AD in individuals with PD (Burack, et al. 2010). [^{11}C]PIB studies in PD have shown that non-demented patients have an uptake comparable to that of healthy controls. Some demented patients with PD show increased cortical [^{11}C]PIB uptake, which is however much more common in patients with dementia with Lewy bodies (DLB) (Edison, et al. 2008, Gomperts, et al. 2008, Rowe, et al. 2007). In addition the "PIB positivity" in patients with PDD might be coincidental, since also healthy elderly individuals show increased [^{11}C]PIB uptake, the percentage of subjects showing increased uptake varying between 5 -20%

in different studies (Kemppainen, et al. 2006, Klunk, et al. 2004, Mintun, et al. 2006, Rowe, et al. 2007). Anyhow, the cortical deposition of amyloid in PD may be a risk factor for dementia (Jellinger, et al. 2002), but more studies are needed to understand the usefulness of [^{11}C]PIB as a diagnostic agent in this respect.

A variety of methods for the quantification of [^{11}C]PIB uptake based on physiological modelling has been used. In this thesis, an automated region of interest (ROI) analysis was performed to obtain the quantitative regional values of [^{11}C]PIB. A late scan (60–90 min) target region-to-cerebellum ratio was chosen as an outcome measure, since this has been shown to give the best effect size in separating AD patients from controls, and it also shows the best correlation with results obtained with quantification using a metabolite purified arterial input function (Lopresti, et al. 2005).

2.5. Magnetic resonance imaging (MRI)

2.5.1. MRI basics

Magnetic resonance imaging (MRI) is a unique medical imaging technique used in radiology to visualise detailed internal structures. It is based on the phenomenon that hydrogen nuclei, which are abundant in living tissue, respond to a magnetic field by aligning with or against it. This process is called magnetisation. An MRI machine uses a powerful magnetic field to align the magnetisation of hydrogen nuclei in the body, and radio frequency fields to systematically alter the alignment of this magnetisation. This causes the nuclei to produce a rotating magnetic field detectable by the scanner and this information is recorded to construct a tomographic image of the scanned area of the body. The number of nuclei aligned with the magnetic field is slightly greater than that aligned against it. Thus, the magnetization vector is oriented in the direction of the magnetic field, which is designated the longitudinal direction. The direction of this magnetization vector can be altered by the addition of energy in the form of radio wave pulse of appropriate frequency. In the most common type of MRI, a radio wave pulse with enough energy to rotate the magnetisation vector 90 degrees from the static magnetic field is applied. This pulse changes the direction of the vector from the longitudinal plane into the transverse plane. When the radio wave pulse is terminated, the hydrogen nuclei will begin to realign in the direction of the external magnetic field. Two phenomena occur, the longitudinal magnetisation gradually increases (T1 relaxation) and the transverse magnetisation gradually decreases (T2 relaxation). The hydrogen nuclei in different tissues return to their equilibrium state at different rates, which is a difference that can be detected and an image can be constructed.

2.5.2. PD and MRI

MRI is more widely available than PET and most commonly used in clinical practice to differentiate idiopathic PD from secondary causes of parkinsonism, such as vascular

disease and other structural lesions. To better understand the anatomical substrate for cognitive impairment in PD, several studies have analysed atrophic patterns using various MR methods. A MRI study found that non-demented patients with PD had a significant rate of median/global brain volume loss with no significant loss seen in age-matched controls, and these changes correlated with global measures of cognitive decline (Hu, et al. 2001). In non-demented PD patients, greater atrophy in the frontal lobe has been reported (Bruck, et al. 2004, Burton, et al. 2004, Nagano-Saito, et al. 2005, Summerfield, et al. 2005), with an association observed between the smaller prefrontal cortex and poorer performance on tests of executive function (Bruck, et al. 2004, Nagano-Saito, et al. 2005). When compared with controls, greater temporal lobe atrophy has also been found in non-demented PD patients (Beyer, et al. 2007b, Summerfield, et al. 2005). MRI studies reporting hippocampal volumes have shown that PD is associated with hippocampal atrophy (Laakso, et al. 1996), and related to impaired memory even in non-demented patients (Camicioli, et al. 2003, Riekkinen, et al. 1998). The patients in these studies were on antiparkinsonian medication and had had PD for at least 5 years. The association between brain atrophy and cognitive impairment is further supported by a previous study (Laakso, et al. 1996) in which the hippocampal volumes of patients with AD, vascular dementia, PD with dementia, and PD without cognitive impairment were compared. It was found that the cognitively unimpaired patients with PD had atrophy when compared with controls, but to a lesser extent than patients with PD who also had dementia. The more recent studies have shown that the hippocampal head may be affected to a greater degree than the posterior hippocampal region, and that atrophy of the hippocampal head is associated with poorer performance on delayed recall testing and visual hallucinations in PD subjects without dementia (Bouchard, et al. 2008, Ibarretxe-Bilbao, et al. 2008). Atrophy of the amygdale that is associated with delayed recall performance has also been reported in demented (Junque, et al. 2005) and non-demented (Bouchard, et al. 2008) PD patients.

In demented PD patients, substantial atrophy is seen throughout the brain, particularly in the frontal, temporal, and occipital cortices and in subcortical regions (Beyer and Aarsland. 2008, Burton, et al. 2005, Junque, et al. 2005, Ramirez-Ruiz, et al. 2005, Summerfield, et al. 2005). In a previous study, reductions of the grey matter in the occipital cortex bilaterally differentiated PD patients with dementia from non-demented PD patients (Burton, et al. 2004). In one longitudinal study tracking lobar atrophy over time it was reported that there are significantly greater rates of cerebral atrophy in PD patients with dementia (1.2% per year) when compared with non-demented PD patients (0.3% per year) and controls (0.4% per year) with no difference in cortical atrophy rates between non-demented PD patients and controls (Burton, et al. 2005). There is a discrepancy between this and an earlier study in which a greater annual rate of cortical atrophy was seen in non-demented PD patients (0.8% per year) compared with controls (0.04% per year).

3. OBJECTIVES OF THE STUDY

Parkinson's disease (PD), whose etiology is unknown, is one of the most common neurodegenerative disorders and a progressive neurological disease. There is no known way to prevent Parkinson's disease and disease-modifying drugs are not available. The characteristic movement symptoms are tremor, rigidity, bradykinesia and postural instability. Non-movement symptoms include, for example, anxiety, depression, executive dysfunction, and impaired memory, which may lead to dementia, urinary incontinence and weight loss. PD is characterized by a progressive loss of dopaminergic neurons in the substantia nigra leading to decreased dopamine levels in the striatum. The pathopsyiological basis of cognitive symptoms and dementia in PD is unclear, and thus their management is difficult. Lewy bodies, coexisting Alzheimer's disease, brain atrophy and dysfunction in different neurotransmitter systems have all been linked to the cognitive symptoms and these are indeed considered to be multifactorial in origin. The present and increasing burden of suffering that dementing disorders impose on patients, their caregivers and the health care system, makes the research for the assessment of these conditions very important. To explore these issues, we performed a neuropsychological evaluation, structural brain MRI, FDOPA-, [18F]FDG- and [11C]PIB PET in patients with PD and healthy elderly volunteers, and the specific objectives were:

I   To study the relation between dopaminergic dysfunction and the cognitive symptoms in PD patients with FDOPA PET, and to evaluate the association between atrophy in brain regions essential for cognitive functions with structural MRI.

II   To evaluate whether a simple ratio analysis of a single 15-min FDOPA PET scan 75 min after tracer injection in striatal subregions is feasible for distinguishing patients with early PD from healthy controls. FDOPA PET scanning, which takes normally 60 to 90 minutes, poses a compliance issue, may increase potential bias because of subject movement, and may diminish the cost-effectiveness of the cameras and tracers used.

III To identify possible group differences between PD patients with dementia and those without dementia by combining different functional ([11C]PIB, [18F]FDG) and structural imaging (MRI) methods in vivo, which might provide an opportunity to disentangle the pathophysiological correlates of cognitive impairment and dementia in PD.

IV   To evaluate the relationship between the frontostriatal dopaminergic function and cognitive performance, especially cognitive processing speed by performing a FDOPA PET and computerized tests of cognitive processing speed. It is unknown whether dopaminergic frontostriatal loops are involved in relatively automatic processing, such as two-choice reaction time, and more controlled cognitive processing, such as mental calculation.

4. SUBJECTS AND METHODS

4.1. Subjects

The patients were diagnosed at the Turku University hospital and they fulfilled the UK Brain Bank clinical criteria for PD. They had at least two of the main symptoms of PD: tremor, rigidity and hypokinesia, and none of the patients exhibited atypical symptoms (Hughes, et al. 1993). All patients had a brain MRI showing no findings incompatible with the diagnosis of PD. The severity of motor symptoms was evaluated using the motor examination part of the UPDRS. In Study II, none of the PD patients were taking antiparkinsonian medications at the time of the PET scan. In Studies I, II and IV, all PD patients were on antiparkinsonian medication, which was stopped for at least 12 hours before the UPDRS motor evaluation and FDOPA PET scan. In PD patients with dementia in Study III, the diagnosis of PD preceded the development of dementia by at least 1 year (Emre, et al. 2007). All PD patients with dementia fulfilled the suggested clinical criteria for probable dementia associated with PD (Emre, et al. 2007). The control subjects were healthy volunteers and none had a history of neurological or psychiatric disorders. The clinical characteristics of the PD patients and the controls are shown in Table 1.

All patients and controls gave their written consent, which was obtained according to the Declaration of Helsinki. The study protocol was approved by the Joint Ethics Committee of Turku University and Turku University Central Hospital.

4.2. Neuropsychological tests

In Studies I, III and IV, the subjects underwent a comprehensive cognitive testing to evaluate their overall cognitive performance.

The test batteries included following tests; The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery, which consists of different subtests and these tests assess memory, language, praxis, and orientation; The Wechsler Memory Scale (WMS), which is a neuropsychological test designed to measure different memory functions; The Wechsler Adult Intelligence Scale WAIS, which is the primary clinical instrument used to measure adult and adolescent intelligence; The Trail-making test, which is a neuropsychological test of visual attention and task switching. It is known to be associated with many types of brain impairment; in particular frontal lobe lesions; The Geriatric Depression Scale (GDS), which is a 30-item self-report assessment used to identify depression in the elderly; The Frontal Assessment Battery (FAB), which is a short, bedside, cognitive battery assessing frontal lobe functions. It comprises six subtests mainly exploring cognitive functions such as conceptualization/similarities, verbal fluencies, motor programming, sensitivity to interference, inhibitory control, and environmental anatomy; The Stroop test, which is considered to measure selective

attention, cognitive flexibility and processing speed, and it is used as a tool in the evaluation of executive functions; The mini–mental state examination (MMSE), which is a brief 30-point questionnaire test that is used to screen for cognitive impairment. It includes seven-ordered subsections assessing orientation, visual registeration, attention, verbal fluency, visual recall, set-shfting, and concept processing; Cognispeed, which is an easy and accurate measurement of cognitive performance in a variety of tasks that tap attention, working memory, automatic visual processing, and object recognition.

In Study I, special attention was paid to the so-called frontal lobe tests measuring suppressing attention, shifting, and attention and concept formation. Other functions tested were memory, naming and visuomotor performance. The tests included CERAD, Wechsler Memory Scale-Revised (WMS-R), Wechsler Adult Intelligence Scale-Revised (WAIS-R) subtests block design, digit symbol and similarities, Trail Making Test A and B (TMT-A, TMT-B), GDS, Attention/Concentration (ATT/C), FAB (Dubois, et al. 2000, Matsui, et al. 2006), the Stroop test (Stroop. 1992) and MMSE (Folstein, et al. 1975). In addition to individual CERAD subtests (Morris, et al. 1989), CERAD total scores were obtained by calculating a total composite, which could be used together with the normative data to provide an index of the overall level of cognitive functioning (Chandler, et al. 2005).

In Study III, a comprehensive cognitive testing was performed to evaluate the overall cognitive performance of the patients, and to categorize the patients into PDD and PD groups. Tests included CERAD, WMS-R, WAIS-R subtests block design, digit symbol and similarities, Trail Making Test A and B (TMT-A, TMT-B), GDS, Attention/Concentration (ATT/C), The Stroop test and the MMSE. A subtraction value (TMT-B - TMT-A) was calculated reflecting the executive demands of the TMT. In Study IV, the PD patients underwent MMSE and Cognispeed. Cognispeed is a computerized neuropsychological test programme that has been described in more detail previously (Revonsuo, et al. 1993).

4.3.   PET imaging

4.3.1. Scanning protocol

In Studies I, II and IV, all the patients and controls underwent a 90-min dynamic PET scan with a GE Advance PET Scanner (General Electric Medical Systems, Milwaukee, WI, USA) in the 3D scanning mode. The axial field of view is 15.2cm. The in-plane spatial resolution (in FWHM) is 3.8mm and the axial resolution is 4.0 mm in the centre. For the scanning the subjects were positioned in the PET scanner with three-dimensional laser alignment with reference to the orbito-meatal line. A transmission scan for 8 to 10 minutes was performed prior to the emission scan to correct the photon attenuation. FDOPA was used as the tracer to examine the presynaptic dopaminergic function and it was synthesized according to previously described methods (Bergman. 1994, Namavari,

et al. 1992). The radiochemical purity exceeded at least 95% in every case. All subjects were given 150 mg of carbidopa before the scan to block the peripheral decarboxylation of FDOPA.

In Study III, all subjects underwent a 90-min dynamic PET image using [^{11}C]PIB as a radiotracer. A GE Advance PET scanner (General Electric Medical Systems, Milwaukee, Wisc., USA) was used in the 3D scanning mode. The mean injected activity for the controls was 432.8±102.9 MBq (SD), 444.1±76.5 MBq (SD) for the PD patients, and 379.1±112.1 MBq (SD) for the PDD patients. There were no significant differences in these values between the groups. The acquired imaging data was corrected for attenuation, scatter, accidental coincidence and dead time, and reconstructed for analyses. Imaging data was reconstructed into a 128 X 128 matrix using a transaxial Hann filter with a 4.6-mm cut-off and an axial ramp filter with an 8.5-mm cut-off. In addition to PIB imaging all subjects in Study III underwent up to 55-min dynamic PET imaging using [^{18}F]FDG as a radiotracer. Before imaging cannulas were placed in both antecubital veins; one for injection of the FDG bolus and the other for blood sample drawing. Subjects were scanned with a protocol including an up to 55-min-long dynamic PET scan with 17 frames and 21 arterialized venous blood samples to measure plasma activity concentration. The [^{18}F]FDG was synthesized automatically using a modified Hamacher method (Hamacher, et al. 1986) so that the radiochemical purity exceeded 95%. The subjects had been fasting for at least 4 h before the PET scan. A GE Advance PET scanner (General Electric Medical Systems, Milwaukee, Wisc., USA) was used in the 3D scanning mode. The mean injected activity for the controls was 260.9±46.3 MBq (SD), 275.0±31.2 MBq (SD) for the PD patients, and 265.4±40.0 MBq (SD) for the PDD patients. There was no significant difference in these values between the groups. The corrections and reconstruction parameters of the imaging data were the same as above for PIB imaging.

4.3.2. Image analyses

In Study I, an automated region of interest (ROI) analysis was conducted because it enables reliable quantitative estimation of Ki (influx constant) values. The automated ROI analysis was performed in accordance with a validation study (Nagano, et al. 2000) and using a procedure described elsewhere (Bruck, et al. 2005b). Striatal ROIs were defined on the mean MRI template bilaterally on the caudate nucleus and the putamen. A dorsal and ventral ROI were drawn on the head of the caudate at its midpoint. Only one ROI was traced on the putamen. The cerebellum was used as a reference area.

In Study II, the MRI scans were matched with the PET images by use of the surface fitting method (Pellizari, et al. 1989) and resliced according to the PET scans using trilinear interpolation. The ROIs were drawn on the MR images and copied to the PET images. The ROIs were located bilaterally at the head of the caudate nucleus, the putamen (divided into the anterior and posterior parts along the longitudinal axis of

the transaxial plane), the ventral striatum, and the occipital cortex. The occipital cortex ROI was used as a reference. The average of the radioactivity concentrations of the ROIs in 2 planes was calculated before statistical analysis. The uptake of [^{18}F]FDOPA was calculated by use of a graphical analysis method with data from 15 to 90 min after 18F-FDOPA injection (Patlak and Blasberg. 1985). This method (Patlak method) yields the Ki^{ref}, which mainly represents the decarboxylation of FDOPA to and storage as fluorodopamine, reflecting presynaptic dopaminergic function. SORs were generated for each structure from (bilaterally averaged) occipital ROI data. SORs were calculated for a 15-min time frame starting 75 min after injection.

In Study III, to obtain quantitative regional values of [^{18}F]FDG, an automated region of interest (ROI) analysis was performed as described earlier (Bruck, et al. 2005b)(Bruck, et al. 2005a). Briefly, parametric images representing [^{18}F]FDG uptake in each pixel were calculated as a region-to-pons ratio of the radioactivity concentration over 30–45 min, the ROI being drawn on the pons cortex of a spatially normalised MRI template image. Spatial normalisation of parametric images was performed using a ligand-specific [^{18}F] FDG template as described in detail earlier (Virta, et al. 2009). The ROIs were bilaterally defined using Imadeus software version 1.50 (Forima, Turku, Finland) on a spatially normalised MRI template image representing brain anatomy in the common stereotactic Montreal Neurological Institute space (see Figure 10 for examples). ROIs were drawn on the anterior and posterior cingulate, lateral and medial frontal cortex, caudate nucleus, putamen, amygdala, hippocampus, parahippocampal area, thalamus, occipital cortex, parietal cortex and temporal cortex. The average regional ratio values of [^{18}F]FDG uptake were calculated using these ROIs from spatially normalised parametric ratio images. We chose a late scan (30–45 min) target region-to-pons ratio as an outcome measure, since previous results have indicated that relative region-to-pons ratio measures are suitable for clinical and research purposes in mild AD, particularly in studies aimed at detecting group differences (Mosconi, et al. 2007). To obtain quantitative regional values of [^{11}C] PIB uptake, an automated region of interest (ROI) analysis was performed as described earlier (Kemppainen, et al. 2006, Kemppainen, et al. 2007). Briefly, parametric images representing [^{11}C]PIB uptake in each pixel were calculated as a region-to-cerebellum ratio of the radioactivity concentration over 60–90 min, the cerebellar ROI being drawn on cerebellar cortex of a spatially normalised MRI template image. Spatial normalization of parametric images was performed using a ligand-specific [^{11}C]PIB template prepared as described in detail earlier (Kemppainen, et al. 2006). The ROIs were bilaterally defined using Imadeus software version 1.50 (Forima, Turku, Finland) on a spatially normalised MRI template image representing the brain anatomy in the common stereotactic Montreal Neurological Institute space. ROIs were drawn on the posterior cingulate, lateral frontal cortex, hippocampus, parietal cortex and temporal cortex. The average regional ratio values of [^{11}C]PIB uptake were calculated using these ROIs from spatially normalised parametric ratio images. A late scan (60–90 min) target region-to-cerebellum ratio was chosen as an outcome measure, since this has been shown to give the best effect size

in separating AD patients from controls, and it also shows the best correlation with the results obtained with quantification using metabolite purified arterial input function (Lopresti, et al. 2005).
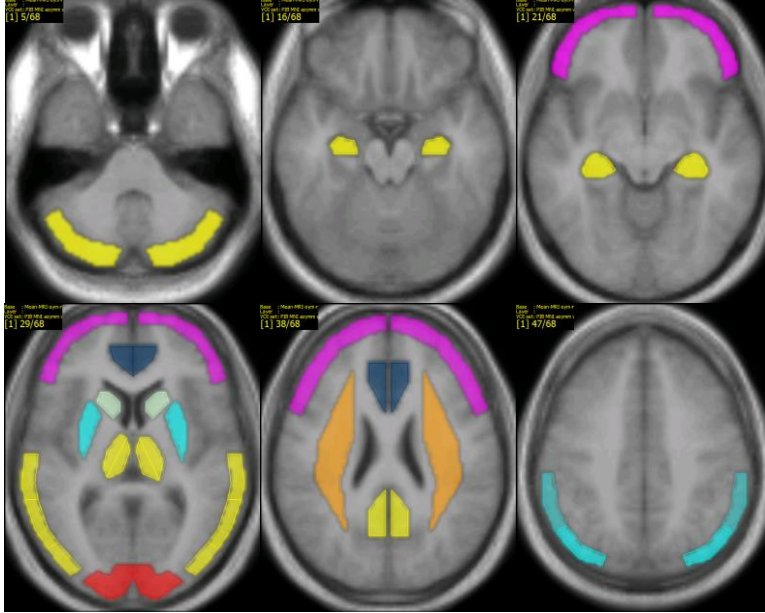

Figure 10. Examples of ROIs used in studies. ROIs are drawn on the cerebellar cortex, medial temporal cortex, lateral frontal cortex, anterior cingulate, occipital cortex, caudate nucleus, putamen, thalamus, lateral temporal cortex, posterior cingulate, parietal cortex.

In Study IV both auto ROI and voxel-based analysis were performed. Frame-to-frame realignment and magnetic resonance imaging-to-PET coregisteration was involved in the auto ROI analysis processing FDOPA images. Algorithms implemented in SPM8 were utilized in these steps (Friston, et al. 1995), with in-house modification. To correct for frame misalignment caused by head motion during the emission scan, frames within a dynamic emission scan were realigned to a reference frame, which was calculated as an average of the first frames. T1-weighted 3D magnetic resonance images (MRI) were co-registered to an average image of frame-to-frame corrected summated PET images using SPM8. The PET images were analysed using an automated region of interest (ROI) analysis based on the spatial normalisation of dynamic PET images into a common stereotactic space and an ROI template (Hirvonen, et al. 2006). No spatial smoothing was applied to the dynamic PET images to retain spatial resolution. First, a ligand specific template in a common stereotactic space was created (Meyer, et al. 1999). Second, spatial normalisation parameters for the automated ROI analysis were estimated from the mean images of summed and preprocessed (see above) PET images and the ligand-specific template. Third, T1-weighted 3D MRIs and the dynamic PET images were transformed frame by frame into the standard space using SPM8 and in-house software. The ROIs

were bilaterally defined using Imadeus software version 1.50 (Forima, Turku, Finland) on a spatially normalised MRI template image representing the brain anatomy in the common stereotactic Montreal Neurological Institute space. To assure the common stereotactic space, the mean images of twenty spatially normalized MRIs were used instead of a single MR-image. ROIs were drawn using Imadeus (version 1.20, Forima Inc., Turku, Finland). ROIs were drawn bilaterally on the anterior cingulate, lateral and medial frontal cortex, caudate nucleus, posterior and anterior putamen, thalamus and occipital cortex. The average regional ratio values of [^{18}F]Fdopa uptake were calculated using these ROIs from spatially normalised parametric ratio images. We chose late scan (75-90 min) target region-to-occipital cortex ratio as an outcome measure, since previous results have indicated that relative region-to-occipital ratio measures are suitable for clinical and research purposes in PD, particularly in studies aimed at detecting group differences.

In medical imaging and more generally in biological imaging such as PET scanning when a single voxel contains a mixture of multiple tissue values the partial volume effect can occur. As a result of limitations in spatial resolution there is a loss of accuracy in quantitation of the activity in small structures. A higher resolution would decrease this effect, as it better resolves the tissue. For example in patient studies, a selected region-of-interest will include contributions from regions around the structure as well as from the area of interest. The activity in small structures with high levels of activity surrounded by areas with lower activity will be underestimated; the activity in structures with low activity concentration surrounded by areas of high concentration will be overestimated. In addition the FDOPA signal-to-noise ratio is quite low in cortex, and it has been questioned whether FDOPA uptake can be reliably quantified in cortical areas (Cropley, et al. 2008).

In voxel-based analysis using statistical parametric mapping (SPM), the regions of statistically significant differences in tracer uptake can be visualised as a demonstrative brain map, and using additional automated ROI analysis of parametric images, tracer uptake can be regionally quantified. Although SPM analysis has been widely used in recent Fdopa studies, automated ROI analysis enable accurate estimation of the effects (Nagano, et al. 2000). A voxel based statistical analysis was performed using Statistical Parametric Mapping (Friston, et al. 1995) version 8 (SPM8) and Matlab 6.5 for Windows (Math Works, Natick, MA). Parametric ratio images in which each voxel indicates the region-to-occipital ratio value of FDOPA were calculated from dynamic and spatially normalised PET images by using the in-house software imgki_1_5_5. A late scan (75-90 min) target region-to-occipital cortex ratio was chosen as in the automated ROI analysis. The smoothing of the ratio images was performed with SMP8. Fdopa uptake images at early time points reflect mainly blood flow and since early images have greater activity than late images, a portion of the summed up images from the entire scan reflect merely blood flow but not the metabolism of [^{18}F]Fdopa to [^{18}F]Fdopamine. The correlation analysis in the PD group was made with multiple regression model testing the correlation

between neuropsychological variable and Fdopa ratio values at the voxel level. The correlation analyses were restricted to the frontal cortical area and striatum because of our hypothesis. In all SPM analyses, the multiple comparison corrected p-value below 0.05 was considered as significant. For localisation, the co-ordinates of the local maxima of the clusters resulting from statistical analyses were converted into Talairach coordinates (Talairach and Tournoux. 1988) using the Yale non-linear MNI to Talairach conversion software (http://www.bioimagesuite.org/Mni2Tal/index.html) (Lacadie, et al. 2008) and localised using the Talairach Deamon Software (Lancaster, et al. 2000).

4.4.   MR imaging

To exclude structural abnormalities in all the studies and to evaluate atrophic changes in Studies I and III, all subjects were scanned with 1.5T MRI GE Signa Horizon LX (General Electric Medical Systems, Milwaukee, WI, USA). A three-dimensional FSPGR (fast spoiled gradient echo) sequencing was used for image analysis. The degree of atrophy was evaluated separately on both sides by an experienced neuroradiologist (RP) on a GE workstation (GE AW3.1, General Electric Medical Systems, Milwaukee, WI, USA). The evaluator was blinded to the identity, sex, age, and diagnosis of the subjects. Hippocampal atrophy scored from 0 to 4 was evaluated from coronal T1 images according to Scheltens et al. (Scheltens, et al. 1992), a highly reliable method for hippocampal atrophy rating (Wahlund, et al. 2000). Atrophy of the prefrontal cortex was similarly evaluated by a 0-4-visual scale from axial T1 images. The visual evaluation of atrophy has previously been used in the frontal cortex and has been found to be reliable (Victoroff, et al. 1994). In both scales, zero corresponded to no atrophy and four to very severe atrophy. Subjects with massive white matter changes were excluded from these studies.

4.5.   Statistical analyses

In Studies I, III and IV, to evaluate the correlation between the FDOPA uptake of the ROIs (Study I), or the FDOPA uptake ratio (Study IV), or the [18F]FDG uptake ratio (Study III) and the cognitive performances of the patients, we used Spearman's non-parametric rank correlation test. It is well suited for small samples and makes no assumptions about the linearity of the relationship. In Studies I and IV, the between-group analysis of both striatal Ki (Study I) or [18F]FDOPA uptake ratio (Study IV) and neuropsychological tests was performed by two-sample t-test. In Study III, the [11C]PIB and [18F]FDG results in the three groups were compared for each anatomical region using the Kruskal-Wallis test and the significance level was set to $p < 0.05$. When the Kruskal-Wallis test was significant, groups were then compared using the Mann-Whitney U test. In Studies I and III, the Mann-Whitney U test was used to compare the atrophy scores between the patients with PD and the controls. Exact p-values were used in Mann-Whitney U tests.

To test whether atrophy was related to performance in neuropsychological tests we used a one-way ANOVA and Tukey's studentized range (HSD) test. p-Values less than 0.05 were considered significant. All statistical analysis was conducted using SAS Enterprise Guide 3.0 (SAS Institute Inc., Cary, NC, USA).

In Study II, the data were characterized by calculating the mean and SD. Comparisons of the mean values for the PD and control groups were done with a 2-sample t test. The eligibility of SOR and Ki^{ref} measurements for the diagnosis of PD were studied with a logistic regression analysis. In this analysis, the dichotomic variable indicating PD or the control group was the response variable, and the SOR or Ki^{ref} measurement was the predictor. The strength of the association in the logistic regression analysis was quantified by the calculating odds ratios (ORs) with 95% confidence intervals (95% CIs). For each variable, the OR, corresponding to the change equal to the coefficient of variation (CV) (calculated as SD/mean) of the variable, was calculated. ORs calculated in this way are comparable among different variables because the differences in the original measurement units do not confuse the comparisons. Exact tests and CIs for ORs were used in the logistic regression analysis. The estimated logistic regression models were illustrated by graphs of prediction probabilities (Agresti. 2002). The diagnostic ability to predict PD with SOR or Ki^{ref} measurements was also studied, with an analysis of receiver operating characteristic (ROC) curves. The area under the curve was used to quantify the results of the ROC analysis. The diagnostic abilities of different measurements were compared by testing the differences in the areas under the empiric ROC curves with nonparametric techniques (DeLong, et al. 1988). A value of 0.05 was used as a cutoff for statistical significance. Statistical analysis was performed with the SAS System for Windows, release 9.2/2007 (SAS Institute Inc.).

In Study IV, SPM correlation analysis in the PD group was made with the multiple regression model testing the correlation between the neuropsychological variable and Fdopa ratio values at the voxel level. The correlation analyses were restricted to the frontal cortical area and striatum because of our hypothesis. In all SPM analyses, a multiple comparison corrected p-value below 0.05 was considered as significant.

5. RESULTS

5.1. FDOPA PET in PD patients and controls

The automated ROI analysis showed that the mean striatal Ki (Study I) and ratio values (Study IV) in the PD group were significantly smaller than in controls (Table 2, Table 3). There were no statistically significant differences in the frontal or thalamic Fdopa ratio values between PD patients and controls (Study IV). In Study IV, FDOPA ratio values in the caudate nucleus correlated statistically significantly with the FDOPA region to the occipital ratio values of the thalamus and anterior cingulate gyrus (p<0.0001). (Table 4).

Table 2. Results of the automated ROI analysis. The mean Fdopa±SD.s of influx constants ($Ki x 10^{-3} min^{-1}$) in PD patients and controls. (Study I).

	PD	Controls	p
Dorsal caud left	8.8 ± 2.7	11.4 ± 0.8	0.007
Dorsal caud right	8.6 ± 2.3	11.2 ± 1.0	0.003
Ventral caud left	9.3 ± 2.2	11.9 ± 1.7	0.005
Ventral caud right	8.7 ± 1.6	10.8 ± 1.4	0.003
Put left	4.4 ± 1.3	11.2 ± 0.8	<0.001
Put right	4.2 ± 1.1	11.0 ± 1.0	<0.001

p-values of statistic testing difference in means are given.
Abbreviations: Caud, caudate nucleus; Put, putamen.

Table 3. Results of the automated ROI analysis. The mean Fdopa ± SD.s target to occipital ratio in PD patients and controls. (Study IV).

	PD	Controls	*t*-value	*p*-value
ACC right	1.043 ± 0.097	1.063 ± 0.116	0.56	0.597
ACC left	1.036 ± 0.101	1.064 ± 0.103	0.83	0.415
Cau right	1.681 ± 0.233	1.816 ± 0.168	1.88	0.049
Cau left	1.578 ± 0.208	1.745 ± 0.191	2.44	0.019
Lfc right	0.971 ± 0.059	0.951 ± 0.088	-0.8	0.475
Lfc left	0.945 ± 0.081	0.906 ± 0.066	-1.5	0.123
Mfc right	1.052 ± 0.092	1.053 ± 0.107	0.04	0.971
Mfc left	1.033 ± 0.086	1.043 ± 0.102	0.33	0.757
Puta right	1.968 ± 0.277	2.286 ± 0.219	3.65	<0.001
Puta left	1.849 ± 0.286	2.194 ± 0.242	3.76	<0.001
Putp right	1.595 ± 0.214	2.083 ± 0.238	6.44	<0.001
Putp left	1.673 ± 0.286	2.254 ± 0.236	6.38	<0.001
Thal right	1.109 ± 0.107	1.104 ± 0.102	-0.15	0.878
Thal left	1.083 ± 0.103	1.080 ± 0.090	-0.07	0.944

t-values and p-values of statistic testing difference in means are given.
Abbreviations: ACC, anterior cingulate gyrus; caud, caudate nucleus; Lfc, lateral frontal cortex; Mfc, medial frontal cortex; Puta, anterior putamen; Putp, posterior putamen; thal, thalamus

Table 4. Correlation (Spearman's non-parametric rank correlation) between the Fdopa region to occipital ratio values in the caudate nucleus and thalamus, and anterior cingulate gyrus in PD patients (Study IV).

	n	*r*	*p*
ACC	23	0.74	<0.0001
Thal	23	0.76	<0.0001

Abbreviations: ACC, anterior cingulate gyrus; thal, thalamus

In study II all of the results were calculated separately for brain regions ipsilateral and contralateral to the side with predominant symptoms. The between-group analysis showed that the mean striatal SOR and Ki^{ref} values in the PD group were significantly smaller than those in the control group.

The decrease was most severe in the putamen and more intense on the contralateral side than on the ipsilateral side. The decreases in the putamen, expressed as a percentage of the control mean, varied from 18% to 31% for SOR and from 33% to 64% for Ki^{ref}. The magnitudes of reduction in the caudate nucleus ranged from 9% to 13% for SOR and from 9% to 18% for Ki^{ref}. The decrease in the ventral striatum was approximately 10% for both SOR and Ki^{ref} (Table 5).

Table 5. The mean SOR and Ki^{ref} uptake values of controls and Parkinson's disease (PD) patients (Study II).

Region	SOR				Ki^{ref}			
	PD mean; SD	Controls mean; SD	p-value	Δ%	PD mean; SD	Controls mean; SD	p-value	Δ%
Anterior putamen								
ipsilateral	2.12; 0.26	2.59; 0.18	<0.0001	18	0.008; 0.002	0.012; 0.001	<0.0001	33
contralateral	1.93; 0.23	2.62; 0.20	<0.0001	27	0.006; 0.002	0.012; 0.001	<0.0001	50
Posterior putamen								
ipsilateral	1.91; 0.27	2.43; 0.22	<0.0001	21	0.006; 0.002	0.010; 0.002	<0.0001	40
contralateral	1.71; 0.21	2.47; 0.19	<0.0001	31	0.005; 0.002	0.011; 0.001	<0.0001	55
Putamen								
ipsilateral	1.89; 0.25	2.46; 0.19	<0.0001	23	0.006; 0.002	0.011; 0.002	<0.0001	45
contralateral	1.68; 0.21	2.44; 0.22	<0.0001	31	0.004; 0.002	0.011; 0.002	<0.0001	64
Caudate								
ipsilateral	2.05; 0.21	2.26; 0.14	<0.0001	9	0.010; 0.002	0.011; 0.001	<0.0001	9
contralateral	1.96; 0.21	2.26; 0.15	<0.0001	13	0.009; 0.002	0.011; 0.001	<0.0001	18
Ventral striatum								
ipsilateral	2.03; 0.24	2.20; 0.27	0.003	8	0.009; 0.002	0.010; 0.003	0.02	10
contralateral	1.96; 0.20	2.19; 0.22	<0.0001	10	0.009; 0.002	0.010; 0.002	<0.0001	1

Δ% denotes decrease in PD group relative to control group. Units for Ki^{ref} are 1/min.

We performed an ROC analysis of both SOR and Ki^{ref} to evaluate how well these measures could separate PD patients from healthy controls. An ROC curve is a plot of the sensitivity of a measurement against one minus specificity. The overall accuracy of the measurement can be described as the area under the ROC curve: the larger the area, the better the tool. An area under the ROC curve of 1.00 indicates a perfect diagnostic tool. The contralateral posterior putamen showed the largest areas under the ROC curve: 0.994 for SOR and 0.998 for Ki^{ref}; these values indicated excellent diagnostic accuracy. The ROC curves for the ipsilateral and contralateral SOR and Ki^{ref} values in each striatal subregion are shown in Figure 11. For each subregion, the area under the ROC curve for the contralateral side was larger than that for the ipsilateral side. In addition, the ROC analysis revealed that the SOR and Ki^{ref} values in the caudate nucleus and the ventral striatum, both ipsilateral and contralateral, had lower diagnostic accuracy than the values in the putamen.

We also applied a logistic regression model to calculate the prediction probabilities of SOR and Ki^{ref} for PD in the ipsilateral and contralateral striatal regions. In addition to the analysis of the association between the binary outcome (i.e., PD patient or control) and continuous predictor variables (i.e., SOR or Ki^{ref}), the logistic regression model provided estimates of outcome probability at various levels of the predictor variable. It has been suggested that the logistic regression model is a useful method for determining the decision level with less ambiguity than ROC curves (DeBari. 2006). The ORs, corresponding to the change equal to the CV (SD/mean) of the variable, were calculated for SOR and Ki^{ref} in the substriatal structures. ORs calculated in this way are comparable among different variables because the differences in the original measurement units do not confuse the comparisons. Almost identical prediction probability curves were obtained for Ki^{ref} and SOR. The curves were dependent on both striatal subregions and the laterality of the predominant symptoms. Figure 12 shows that for the contralateral subregions of the putamen, the curves were steep, indicating that when a certain threshold was reached, the probability of being a PD patient rose dramatically. A change of one CV for SOR and Ki^{ref} in the contralateral posterior putamen increased the risk of being a PD patient approximately 30- and 4-fold, respectively ($P < 0.0001$) (Table 6). Five patients (5.6%) with PD had FDOPA uptake within the control range on both the contralateral and the ipsilateral sides.
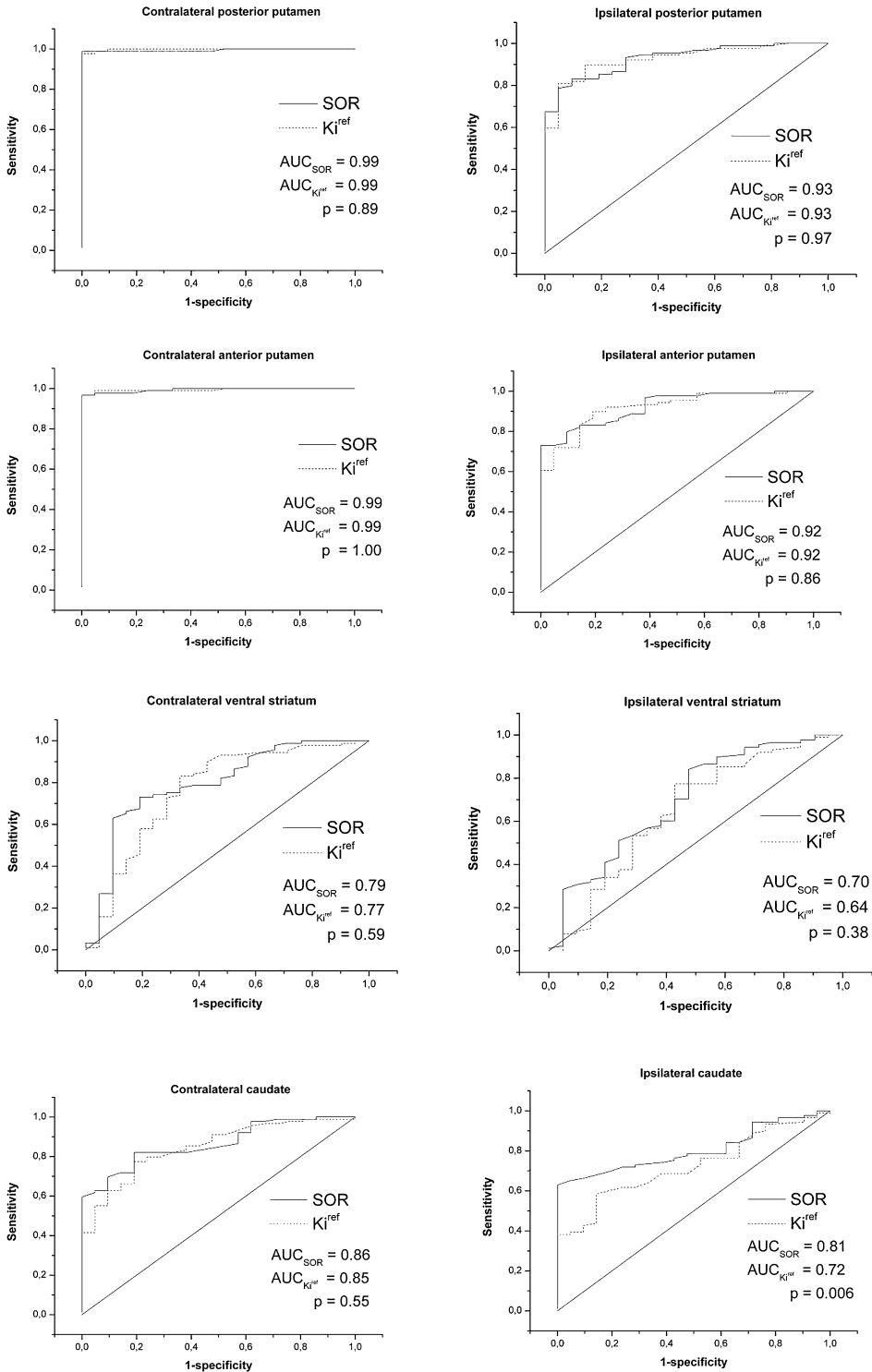
Figure 11. ROC curves for SOR and Ki[ref] in substriatal structures. The larger the *P* value, the smaller the difference between SOR and Kiref. AUC = area under curve (Study II).
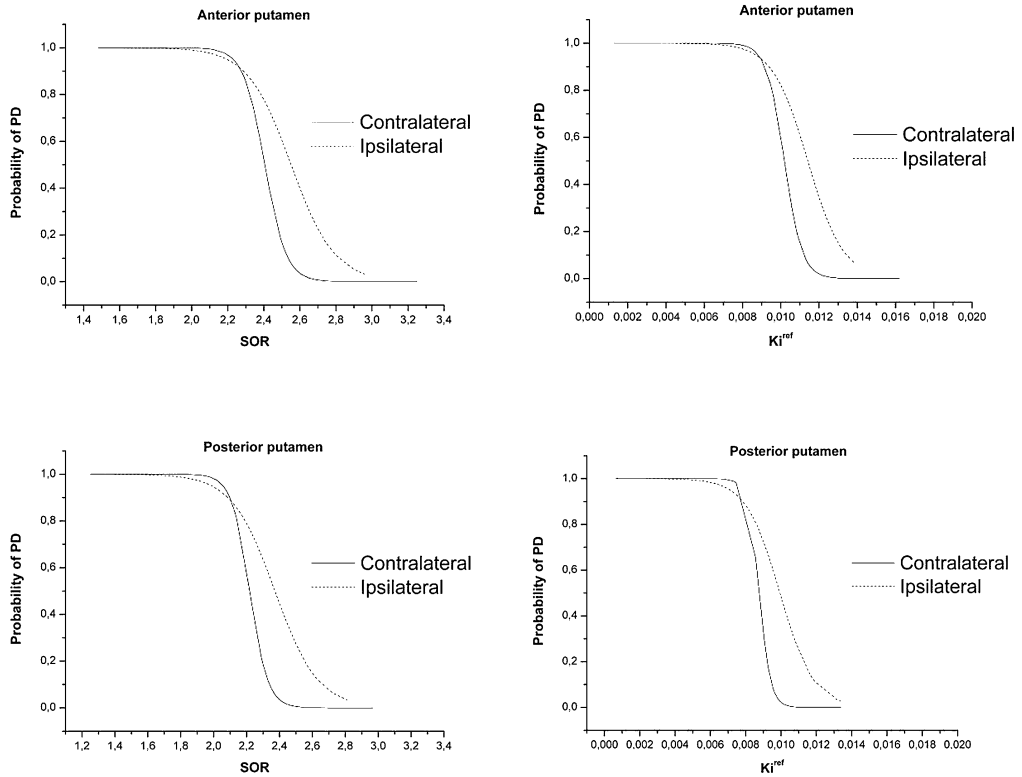
Figure 12. Probability of receiving a positive diagnosis (PD) at a given substriatal SOR and Ki^{ref} ipsilateral and contralateral to the side with predominant symptoms (Study II).

Table 6. The odds ratios (OR) in putaminal subregions for SOR and Ki^{ref} evaluated by the logistic regression model (Study II).

Region	SOR			Ki^{ref}		
	CV	OR (95% CI)[a]	p-value	CV	OR (95% CI)[a]	p-value
Anterior putamen						
ipsilateral	0.1	2.3 (1.6-3.4)	<0.0001	0.3	1.4 (1.2-1.6)	<0.0001
contralateral	0.2	24.2 (6.2-175.9)	<0.0001	0.4	2.3 (1.6-4.1)	<0.0001
Posterior putamen						
ipsilateral	0.2	4.5 (2.5-9.2)	<0.0001	0.4	1.5 (1.3-1.9)	<0.0001
contralateral	0.2	29.6 (5.9-495.5)	<0.0001	0.5	4.0 (1.8-26.9)	<0.0001

For each variable the odds ratio was calculated corresponding to the change which was equal to the coefficient of variation (CV) (SD/Mean) of the variable. [a] CI, confidence interval.

5.2.   [¹¹C]PIB PET in PD patients and controls

[¹¹C]PIB region-to-cerebellum ratios (Study III) did not differ significantly between groups in any regions (Kruskall-Wallis, p>0.05). When expressed as a percentage of the mean of the control group, the [¹¹C]PIB uptake in non-demented PD patients varied from 93% to 102%, and in PDD patients from 99% to 118% (Table 7). In three of the 11 PDD patients (27%) and two of the 24 controls (8.3%), [¹¹C]PIB binding was elevated in cortical areas when uptake ratios of 1.5 or above were considered to be increased (Figure 13). The two controls with elevated [¹¹C]PIB binding were the oldest of the control group, but had no subjective memory impairment and were cognitively normal according to neuropsychological evaluation. Excluding these individuals gave essentially identical results as the full subject population. The MMSE score of both of these controls was 28. In addition there has been no evidence of cognitive decline or impairment in the daily functioning of these two individuals during the follow-up.

Table 7. Results from the automated region-of-interest analysis of [¹¹C]PIB uptake: mean±SD region-to-cerebellum   ratio at 60 to 90 minutes in PD patients, PDD patients and control subjects and percentage of PD and PDD mean of control mean. There were no statistically significant differences between the groups in any brain area.

Brain area	PDD (n = 11)	PD (n = 8)	Control (n = 24)	% PDD vs Control	% PD vs Control	% PDD vs PD
Lateral frontal cortex	1.30±0.26	1.25±0.05	1.24±0.16	105	101	104
Posterior cingulate	1.63±0.48	1.28±0.09	1.38±0.32	118	93	127
Hippocampus	1.20±0.16	1.24±0.10	1.21±0.10	99	102	97
Parietal cortex	1.28±0.24	1.20±0.17	1.25±0.16	102	96	107
Temporal cortex	1.33±0.24	1.21±0.11	1.27±0.14	105	95	110
Caudate nucleus	1.28±0.28	1.20±0.12	1.24±0.22	103	97	107
Putamen	1.52±0.25	1.44±0.11	1.40±0.17	109	103	106

PD = Parkinson's disease without dementia
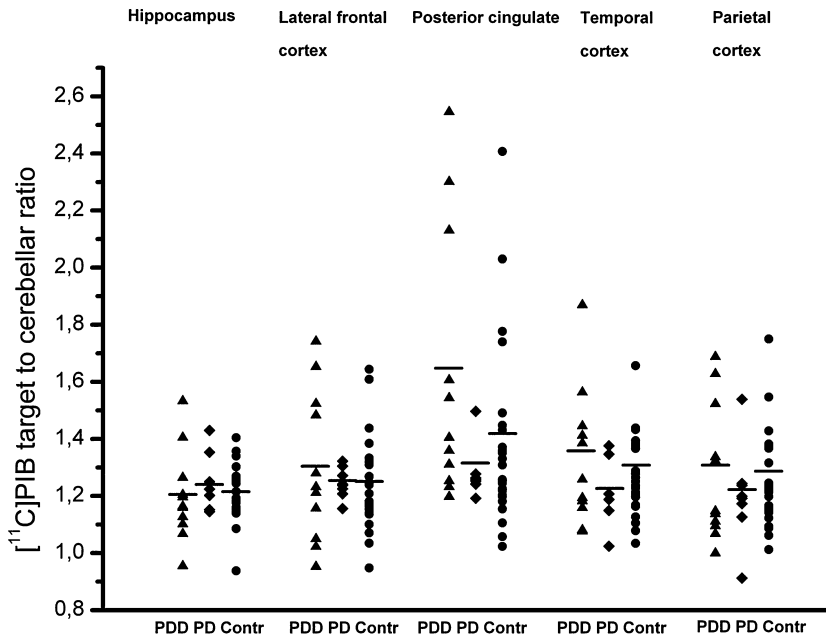PDD = Parkinson's disease with dementia

Figure 13. [¹¹C]PIB uptake ratio in the posterior cingulate, temporal cortex, hippocampus, lateral frontal cortex and parietal cortex. Individually, two of 24 controls showed significant [¹¹C]PIB uptake in more than one cortical areas, while three of the PDD patients showed a significant uptake ratio. None of the patients with PD showed significant [¹¹C]PIB uptake. PD = Parkinson's disease without dementia, PDD = Parkinson's disease with dementia, Contr = Controls. The horizontal lines show the group mean values. [¹¹C]PIB uptake ratios did not differ significantly between groups in any region (Study III).

5.3.   [¹⁸F]FDG PET in PD patients and controls

Automated ROI analysis showed that the [¹⁸F]FDG region-to-pons values in the PDD group were smaller than in controls or non-demented PD patients. Table 8 shows the brain regions with statistically significant decreases ($p < 0.05$, Kruskal-Wallis analysis followed by Mann-Whitney U-test) in glucose metabolism in the non-demented PD and PDD patients compared with the controls. In the patients with PDD, cerebral glucose metabolism was significantly decreased in the lateral frontal cortex, posterior and anterior cingulate, inferior parietal lobe, caudate nucleus, cerebellum, medial frontal cortex, occipital cortex, parahippocampal area and thalamus. As compared to the control mean, the decrease varied between 78% to 94%. In the non-demented PD patients, the cerebral glucose metabolism was significantly decreased (by 8%) only in the occipital cortex when compared to controls. Figure 14 shows the [¹⁸F]FDG region-to-pons values in the PD and PDD compared with those in the controls.

Table 8. Results from the automated region-of-interest analysis of [^{18}F]FDG uptake: mean±SD region-to-pons ratio at 30 to 45 minutes in PD patients, PDD patients and control subjects and percentage of PD and PDD mean of control mean (Study III).

	PDD (n = 9)	PD (n = 8)	Control (n = 24)	*p* PDD vs Control	*p* PD vs Control	*p* PDD vs PD	% PDD vs Control	% PD vs Control	% PDD vs PD
Lateral frontal cortex	0.98±0.10	1.13±0.07	1.11±0.08	0.003	NS	0.005	88	102	87
Medial frontal cortex	0.99±0.14	1.17±0.12	1.21±0.09	<0.001	NS	0.009	82	97	85
Temporal cortex	1.06±0.10	1.17±0.12	1.25±0.08	<0.001	NS	0.043	85	94	91
Parietal cortex	0.96±0.14	1.14±0.15	1.23±0.07	<0.001	NS	0.027	78	93	84
Occipital cortex	1.13±0.11	1.22±0.14	1.32±0.08	<0.001	0.045	NS	86	92	93
Anterior cingulate	1.00±0.16	1.20±0.12	1.19±0.10	0.002	NS	0.012	84	101	83
Posterior cingulate	1.26±0.16	1.50±0.16	1.55±0.10	<0.001	NS	0.012	81	97	84
Hipppocampus	0.85±0.10	0.91±0.06	0.91±0.05	NS	NS	NS	93	100	93
Parahippocampal area	0.90±0.09	0.99±0.07	1.00±0.06	0.004	NS	NS	90	99	91
Amygdala	0.89±0.14	0.97±0.07	0.95±0.06	NS	NS	NS	94	102	92
Caudate nucleus	1.00±0.21	1.24±0.13	1.26±0.12	<0.001	NS	0.016	79	98	81
Putamen	1.36±0.16	1.45±0.10	1.44±0.07	NS	NS	NS	94	101	94
Thalamus	1.19±0.12	1.32±0.08	1.32±0.07	0.004	NS	0.027	90	100	90
Cerebellum	1.09±0.11	1.19±0.09	1.22±0.07	0.003	NS	0.021	89	98	92

PD = Parkinson's disease without dementia
PDD = Parkinson's disease with dementia
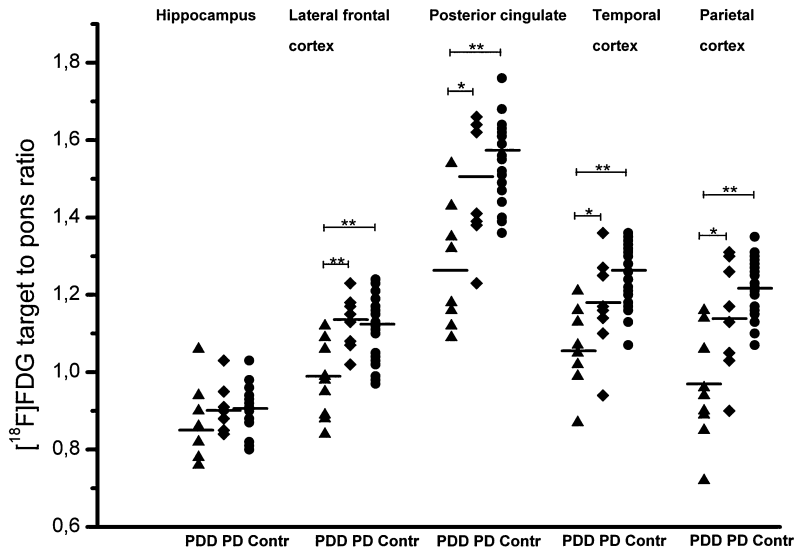NS = Not statistically significant

Figure 14. [^{18}F]FDG uptake ratio in the posterior cingulate, temporal cortex, hippocampus, lateral frontal cortex and parietal cortex. PD = Parkinson's disease without dementia, PDD = Parkinson's disease with dementia, Contr = Controls. The horizontal lines show the group mean values and p values. * p < 0.05, ** p ≥0.005 (Study III).

5.4. Neuropsychological tests and correlates

5.4.1. Cognitive performance and FDOPA

The patients had worse cognitive test scores in many neuropsychological tests compared to controls. In Study I, statistically significant differences were found in the subtests of FAB, CERAD, WAIS-R, VIM and DEL. The FAB global score (p = 0.012) and subscore 5 (p = 0.016) exploring inhibitory control were statistically significantly lower in the PD patients compared to the controls. (Table 9.) There were no statistically significant correlations between FAB and other frontal neuropsychological tests, FDOPA PET or MRI atrophy changes. To test the hypothesis that the caudate nucleus dopaminergic function is involved in controlling frontal lobe-related behaviour, we calculated the correlation between striatal FDOPA uptake and cognitive performance in tests thought to be related to the frontal lobe function (Stroop, ATT/C, Fluency, Trail Making Test A and B, FAB). To test the hypothesis that the caudate nucleus dopaminergic function is involved in tests measuring verbal memory or delayed recall, we calculated the correlation between striatal Fdopa uptake and VEM, VIM, DEL, CERAD word list savings%. A clear-cut positive correlation was found between the Fdopa uptake of the ventral caudate nucleus and the verbal memory (VEM), the visual memory (VIM) and the word list savings% of CERAD (Table 10). FDOPA uptake of the dorsal caudate nucleus showed a statistically significant positive correlation with the delayed memory (DEL) (Table 10). The positive correlation indicates that the weaker the dopaminergic activity, the poorer the result in tests that require special cognitive performance. We found no statistically significant correlations between the Fdopa uptake in the caudate nucleus and the classic Stroop test or the FAB, neither did we find any statistically significant correlations between the performances in these tests and the Fdopa uptake in the putamen.

Table 9. Scores on the neuropsychological tests in controls and patients with Parkinson's disease (PD). (Study I).

	Controls	PD	*p*
FAB global score	17.1 ± 1.7	13.2 ± 3.0	0,003
VIM Sum score	55.3 ± 12.8	42.5 ± 15.3	0.045
DEL Sum score	76.5 ± 19.6	57.6 ± 8.4	0.032
VEM Sum score	52.9 ± 14.5	67.8 ± 20.5	0.072
CERAD Verbal fluency	27.4 ± 4.7	21.5 ± 6.8	0.025
CERAD Word list learning	24.6 ± 3.5	19.7 ± 4.4	0.008
CERAD Word list recognition%	99.0 ± 2.1	94.2 ± 7.0	0.041
CERAD Constructional praxis	10.5 ± 1.3	7.5 ± 3.2	0.012
CERAD Constructional praxis savings%	97.4 ± 12.2	73.0 ± 27.1	0.017
CERAD Clock drawing	6.0 ± 0.0	5.2 ± 1.0	0.020
CERAD Total score	90.9 ± 6.1	79.1 ± 10.9	0.010
WAIS-R Block design	32.7 ± 6.8	18.6 ± 5.7	<0.001
WAIS-R Digit symbol	39.0 ± 11.3	28.4 ± 9.4	0.032
WAIS-R Similarities	28.8 ± 2.4	23.7 ± 5.5	0.010

Figures indicate mean values±standard deviation. *P* refers to significant differences between groups.

Table 10. Correlation (Spearman´s non-parametric rank correlation) between neuropsychological tests and [^{18}F]fluorodopa uptake in the caudate nucleus[a] (Study I).

	n	*r*	*p*
VEM Logical memory			
Ventral cau left	12	0.68	0.017
VEM Linguistic learning			
Ventral cau left	11	0.67	0.023
VEM Sum score			
Ventral cau left	12	0.72	0.009
VIM Visual recognition			
Ventral cau right	12	0.61	0.037
CERAD Word list savings%			
Ventral cau right	12	0.77	0.003
DEL Verbal learning			
Dorsal cau left	12	0.65	0.022

[a]In the putamen no significant correlations were found. n = number of patients.

Speed of information processing in PD has mainly been studied using reaction-time (RT) tasks. PD patients have been shown to be slower than controls in simple reaction time (SRT), but not disproportionately slower in choice reaction time (Brown and Marsden. 1986, Evarts, et al. 1981). In our Study IV, the choice reaction times (2-CRT, 10-CRT) were significantly slower in PD patients when compared to controls. In Subtraction test, measuring concentrating attention and working memory, the PD patients performed worse compared to the controls. The results showed that the patients with PD were significantly slower than the controls in controlled processing. (Table 11)

Table 11. Scores on the neuropsychological tests in patients with Parkinson's disease (PD) and controls (Study IV).

	n (PD)	*n* (Controls)	PD	Controls	*p*
MMSE	23		26.6± 1.8		
2-CRT	23	14	637.4±160.6	534.8± 76.4	0.013
10-CRT	23	14	1216.1±381.6	944.9±141.6	0.004
SUB	23	14	2181.7±924.5	1446.6±320.3	0.002
SUB – 10-CRT	23	14	965.6±671.6	494.6±211.0	0.004

Figures indicate mean values ± standard deviation. *p* refers to significant differences between groups.

To test the hypothesis that the frontostriatal dopaminergic function is involved in cognitive impairment in PD, we calculated the correlations between the Fdopa target to occipital ratio values and cognitive tests. An overall cognitive impairment (MMSE) was associated with reduced dopaminergic function in the anterior cingulate gyrus, caudate nucleus and thalamus. A clear cut negative correlation was found between the Fdopa target to region uptake values of the anterior cingulate gyrus and caudate nucleus,

and choice reaction times 2-CRT and 10-CRT. The subtraction task (working memory, concentrating attention) correlated negatively with the Fdopa target to region uptake values of the anterior cingulate gyrus, caudate nucleus and thalamus. Slowed controlled processing was associated with reduced dopaminergic function in the caudate nucleus. (Table 12, Figure 15)

The positive correlation in MMSE indicates that the weaker the dopaminergic activity, the poorer the results in tests that require special cognitive performance. The negative correlation in other tests indicates that the weaker the dopaminergic activity, the poorer the results in tests (more time needed to finish the test) that require special cognitive performance.

Table 12. Correlations (Spearman's non-parametric rank correlation) between neuropsychological tests and Fdopa target to occipital ratio values[a] (Study IV).

	r	p
MMSE		
ACC right	0.60	0.004
ACC left	0.61	0.003
Cau right	0.50	0.021
Cau left	0.49	0.023
Thal left	0.45	0.041
2-CRT		
ACC right	-0.58	0.004
ACC left	-0.62	0.002
Cau right	-0.44	0.037
10-CRT		
ACC right	-0.57	0.004
ACC left	-0.54	0.008
Cau right	-0.51	0.012
Cau left	-0.55	0.007
SUB		
ACC right	-0.44	0.035
ACC left	-0.49	0.018
Cau right	-0.53	0.009
Cau left	-0.58	0.004
Thal right	-0.42	0.047
Thal left	-0.45	0.031
SUB – 10-CRT		
Cau right	-0.42	0.045
Cau left	-0.49	0.019

[a]In the putamen no significant correlations were found.
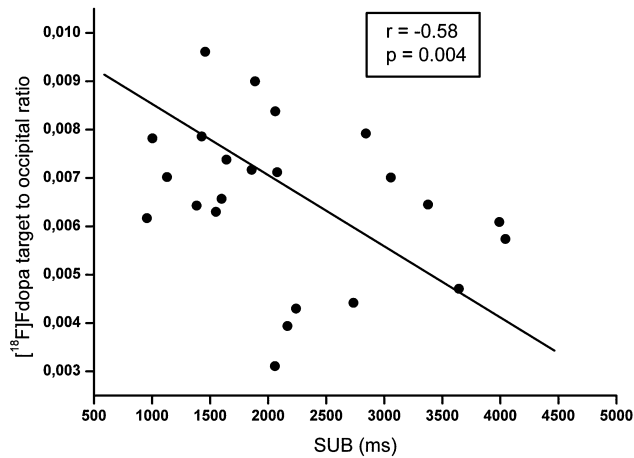Abbreviations: ACC, anterior gyrus cinculate; caud, caudate nucleus; thal, thalamus

Figure 15. The correlation (Spearman's non-parametric rank correlation) between the [^{18}F]Fdopa uptake ratio in the left caudate nucleus and the score of the subtraction test (SUB). Each dot denotes an individual patient with PD.

Using statistical parametric mapping (SPM), the correlations of statistically significant differences between cognitive tests and automated ROI analysis could be visualized and confirmed as a demonstrative brain map. The SPM analysis confirmed the statistically significant correlations between the following brain regions and neuropsychological tests; the anterior cingulate gyrus vs 2-CRT, 10-CRT, SUB and MMSE; caudate nucleus vs. 2-CRT, 10-CRT, SUB - 10-CRT, SUB; thalamus vs 2-CRT and SUB (Table 13, Table 14, Figure 16).

Table 13. Statistically significant correlations in SPM and/or automated ROI analysis between cognitive tests and the Fdopa target to occipital ratio values (Study IV).

	ACC right	ACC left	Caud right	Caud left	Thal right	Thal left
2-CRT	auto-ROI, SPM	auto-ROI, SPM	auto-ROI, SPM	auto-ROI only	auto-ROI, SPM	auto-ROI only
10-CRT	auto-ROI, SPM	auto-ROI, SPM	auto-ROI, SPM	auto-ROI, SPM	auto-ROI only	auto-ROI only
SUB-10-CRT	auto-ROI only	auto-ROI only	auto-ROI, SPM	auto-ROI, SPM	auto-ROI only	auto-ROI only
SUB	auto-ROI, SPM	auto-ROI, SPM	auto-ROI, SPM	auto-ROI, SPM	auto-ROI, SPM	auto-ROI, SPM
MMSE	auto-ROI, SPM	auto-ROI, SPM	auto-ROI only	auto-ROI only	auto-ROI only	auto-ROI only

Abbreviations: caud, caudate nucleus; ACC, anterior cingulated gyrus; thal, thalamus

Table 14. The results of the SPM analysis, testing the correlations between the Fdopa target to occipital ratio values and neuropsychological tests in PD patients (Study IV).

	MNI co-ordinates			Cluster size	*t*-value	*p*
	x	y	z			
R02						
ACC right	13	28	16	22	4.58	0.01
	1	33	6	3	3.89	0.037
ACC left	0	26	15	59	4.23	0.019
	-6	16	-5	2	4.07	0.026
Cau right	15	21	9	112	5.03	0.004
	19	-23	22	9	3.97	0.032
	11	0	20	3	3.82	0.043
Cau left	-12	19	7	343	5.15	0.003
	-13	-12	20	19	4.51	0.011
Thal right	4	-17	10	466	6.87	
	7	-7	10	466	6.18	0.001
Thal left	-13	-14	17	466	4.86	0.009
	-17	-28	12	89	5.25	0.004
R10						
ACC left	-6	16	-5	1	4	0.03
ACC right	1	33	6	5	3.9	0.036
Cau right	13	18	11	114	4.35	0.016
	3	3	-2	2	3.97	0.033
Cau left	-4	7	-7	97	4.59	0.01
	-5	-1	11	42	4.04	0.029
	-8	5	9	42	3.96	0.034
SUB-R10						
Cau right	9	18	1	7	3.84	0.038
Cau left	-13	-8	16	2	3.75	0.046
	-13	-9	17	1	3.73	0.047
SUB						
ACC left	0	26	17	28	4.07	0.024
Caud left	-4	3	-7	35	4.81	0.006
	-4	-1	11	108	4.69	0.008
	-13	-12	20	108	4.67	0.008
Caud right	9	0	10	165	4.72	0.008
	3	3	-2	165	4.09	0.026
Thalamus right	4	-15	10	85	4.76	0.009
	17	-18	17	4	3.98	0.038
Thalamus left	-13	-12	17	18	4.61	0.012
	-5	-7	11	4	4.24	0.023
MMSE						
ACC right	7	22	16	177	4.66	0.008
	3	29	10	177	3.93	0.031
ACC left	0	24	17	177	4.61	0.008
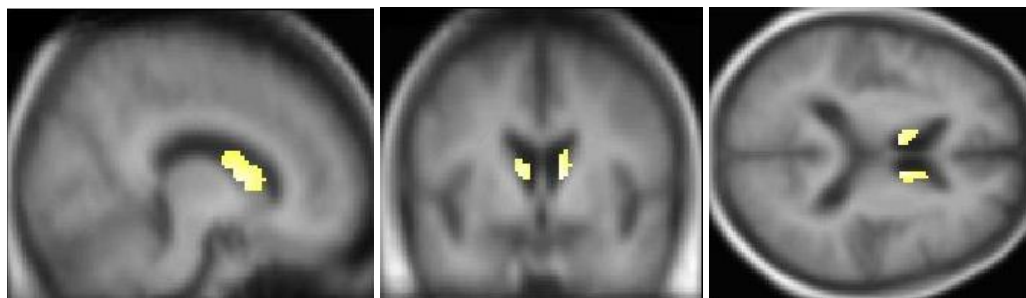
Figure 16. Visualization of the SPM analyses testing the correlation between the [18F]Fdopa uptake ratio and performance in the Subtraction test (SUB). The [18F]Fdopa target to occipital ratio values in the caudate nucleus correlated negatively with the performance in the SUB in Parkinson's disease (PD) patients.

5.4.2. Cognitive performance and [18F]FDG

In Study III, hypotheses relating regional cerebral glucose metabolism with specific tests of cognitive performance across non-demented PD and PDD groups were assessed. Our hypothesis was that verbal memory tests would be associated with the left temporal glucose metabolism, frontal lobe tests (verbal fluency, trail making test) with the frontal metabolism and visuoconstructive tests with the parietal metabolism. We found that the glucose metabolism rate (GMR) in the lateral frontal cortex correlated significantly with MMSE, CERAD Verbal fluency, TMT-B and TMT-B – TMT-A. A clear-cut correlation was found between the medial frontal cortex GMR and MMSE, CERAD Verbal fluency, TMT-A, TMT-B, TMT-B – TMT-A. GMR in the temporal cortex correlated significantly with MMSE and CERAD wordlist learning. GMR in the parietal cortex correlated significantly with CERAD figure copying, CERAD constructional recall and CERAD constructional praxis recall (Table 15). The positive correlation indicates that the weaker the GMR, the poorer the results in tests that require special cognitive performance. The negative correlation in trail making tests indicates that the weaker the GMR, the poorer the results in tests (more time needed to finish the test) that require special cognitive performance.

Table 15. Statistically significant correlations (Spearman´s non-parametric rank correlations) in PD patients with and without dementia between neuropsychological tests and 18F-FDG uptake ratios in the lateral and medial frontal cortex, gyrus temporalis and inferior parietal lobule (Study III).

	n	r	p
Lateral frontal cortex			
MMSE	16	+0.60	0.015
CERAD Verbal fluency	16	+0.53	0.035
TMT-B	14	−0.54	0.045
TMT-B - TMT-A	14	−0.57	0.034
Medial frontal cortex			
MMSE	16	+0.66	0.005
CERAD Verbal fluency	16	+0.63	0.009
S-Fluency	16	+0.54	0.030
TMT-A	16	−0.59	0.017
TMT-B	14	−0.67	0.008
TMT-B - TMT-A	14	−0.68	0.007
Temporal cortex			
MMSE	16	+0.55	0.027
CERAD Wordlist learning	16	+0.54	0.029
Parietal cortex			
CERAD Copying test	16	+0.59	0.015
CERAD Constructional recall	16	+0.65	0.007
CERAD Constructional praxis recall	16	+0.54	0.030

5.5.   MRI

In Study I, we found that the patients with PD had more atrophy in the hippocampus and the prefrontal cortex compared with controls: these differences were seen in both hemispheres. Table O shows the mean atrophy scores. In Study III, the patients with PDD had more atrophy both in the hippocampus and in the frontal cortex compared with non-demented PD patients and with controls. Differences in hippocampal atrophy were seen in both hemispheres. We found no significant differences in atrophy values between non-demented PD patients and controls. Table 16 and 17 show the mean atrophy scores.

Table 16. The atrophy values for patients with Parkinson's disease and controls (Study I).

	N	PFC right[a]	PFC left[a]	Hippocampus right[a]	Hippocampus left[a]
Patients	11	1.18; 0.87; 1; 0-2	1.18; 0.87; 1; 0-2	1.09; 0.53; 1; 0-2	0.91; 0.70; 1; 0-2
Controls	9	0.22; 0.44; 0; 0-1	0.22; 0.44; 0; 0-1	0.22; 0.44; 0; 0-1	0.22; 0.44; 0; 0-1
p value		0.015	0.015	0.003	0.040

[a]values are mean, SD, median and range. PFC, prefrontal cortex.

Table 17. The atrophy values for patients with Parkinson's disease and controls (Study III).

	n	Hippocampus right[a]	Hippocampus left[a]	Frontal Cortex[a]
PD	8	0.63; 0.76; 0.5; 0-2	0.5; 0.76; 0; 0-2	0.5; 0.76; 0; 0-2
PDD	11	1.72; 1.01; 1; 1-4	1.55; 0.52; 2; 1-2	1; 0.77; 1; 0-2
Control	24	0.38; 0.65; 0; 0-2	0.42; 0.72; 0; 0-2	0.5; 0.83; 0; 0-3
p (PDD vs Control)		<0.001	<0.001	0.028
p (PD vs Control)		>0.05	>0.05	>0.05
p (PD vs PDD)		0.013	0.005	>0,05

PDD = Parkinson's disease with dementia

PD = Parkinson's disease with dementia

[a] Values are mean, SD, median and range

In Study I, to test whether hippocampal atrophy was related to performance in tests related to memory, we calculated the one-way analysis of variance between hippocampal atrophy and the performance in VEM, VIM, DEL, word list savings% and FAB. A similar one-way analysis of variance was calculated between prefrontal cortex atrophy and the Attention/Concentration, Trail Making Test, the Stroop test, FAB and verbal fluency, functions thought to be mainly under frontal control. An overall effect of VIM sum score ($p < 0.034$) and word list savings% ($p < 0.015$) was found in the one-way ANOVA between groups with left hippocampal atrophy scores 0-2. Post hoc testing for VIM sum score and word list savings% were significant for score 1 vs 2 and 1 vs 2, 0 vs 2, respectively. An overall effect of VEM logical memory and right hippocampal atrophy scores 0-2 was also found ($p < 0.020$). Post hoc testing was significant for scores 0 vs 1 and 0 vs 2. No significant findings were found in the one-way analysis of variance between prefrontal atrophy and neuropsychological tests.

In Study III, to test whether hippocampal atrophy was related to performance in neuropsychological tests related to memory, we calculated the one-way analysis of variance between hippocampal atrophy and the performance in MMSE, word list learning, word list savings% and the naming test of CERAD. We found that hippocampal atrophy was related to impaired memory. An overall effect of MMSE ($p = 0.023$) and word list learning was found in the one-way ANOVA between groups with left hippocampal atrophy scores 0-2. Post hoc testing for MMSE and word list learning were significant for atrophy scores 0 vs.1, 0 vs 2 and 0 vs 2, respectively.

6. DISCUSSION

PD, one of the most common neurodegerative disorders, is a progressive neurological disease, whose etiology is unknown. There is no known way to prevent Parkinson's disease and disease-modifying drugs are not available. The characteristic movement symptoms are tremor, rigidity, bradykinesia and postural instability. Non-movement symptoms include, for example, anxiety, depression, executive dysfunction, impaired memory, which may lead to dementia, urinary incontinence and weight loss. PD is characterized by a progressive loss of dopaminergic neurons in the substantia nigra leading to decreased dopamine levels in the striatum. The prevalence is around 170 per 100 000, and it is expected to increase in the future when the population ages. In Finland there are over 10 000 PD patients.

The pathopsyiological basis of cognitive symptoms in PD is unclear and thus their management is difficult. Lewy bodies, coexisting Alzheimer's disease, brain atrophy and dysfunction in different neurotransmitter systems have all been linked to the cognitive symptoms, and the symptoms are indeed considered to be multifactorial in origin.

The present study was designed to identify possible neural and structural factors that may be involved in the aetiology and cognitive impairment of PD, to improve the diagnostics of PD and to help in developing new medical treatments and diagnostic methods for dementing disorders. The present and increasing burden of suffering that dementing disorders impose on patients, their caregivers and the health care system, makes the research for the assessment of these conditions very important.

6.1. FDOPA uptake in PD patients

In Studies I, II and IV, the results showed that the PD patients have decreased [^{18}F]FDOPA uptake bilaterally in the striatum as compared to controls. The decrease was clearly more pronounced in the putamen than in the caudate nucleus. In Study II, we investigated also the contra- and ipsilateral sides to the predominant symptoms separately and divided the striatum into subregions. A Fdopa uptake decrease was greater in the contralateral striatum, which is understandable considering that the motor symptoms have been shown to be more severe on the contralateral side of the striatum with lower dopaminergic activity. Accordingly, we found that separation of PD patients from healthy controls was most obvious using FDOPA values of striatal structures contralateral to the predominant symptoms, especially those of the posterior putamen. In study IV we did not find any statistically significant differences in frontal or thalamic FDOPA uptake between PD patients and controls.

Decreased FDOPA uptake has been reported in the striatum in PD (Garnett, et al. 1984a, Leenders, et al. 1986a, Nahmias, et al. 1985a). Post mortem studies have shown that

there is an uneven pattern of dopamine loss in the striatum in PD. The depletion is more severe in the putamen than in the caudate nucleus, and most prominent in the caudal parts of the putamen due to the topographical organisation of the nigrostriatal projection (Kish, et al. 1988a).

Our findings are consistent with the PD imaging studies, which have suggested that the dopamine depletion starts from the posterior parts of the putamen and proceeds during the disease to the caudate nucleus and other parts of the dopaminergic system (Brooks, et al. 1990, Bruck, et al. 2006, Morrish, et al. 1996a, Nurmi, et al. 2001a). The posterior putamen receives dopaminergic projections, especially from the ventrolateral part of the substantia nigra, which is the most severely degenerated nigral subregion (Damier, et al. 1999a). Although in study IV there were no statistically significant differences in frontal or thalamic Fdopa target to occipital ratio values between PD patients and controls, the correlations between cognitive tests and Fdopa uptake of the ACC and thalamus could be explained by the strong dopaminergic cortico-basal ganglia-thalamo-cortical connections modulated by dopamine. We found that the Fdopa uptake of the caudate nucleus, which was significantly decreased when compared to the controls, correlated statistically significantly with the Fdopa uptake of the ACC and thalamus ($p < 0.0001$).

In Study II, analysing the contra- and ipsilateral side of the predominant symptoms separately and the division of the striatum into its subregions gave the possibility to find out the most sensitive striatal subregions to differentiate PD patients from controls. It was found that the values of the contralateral posterior putamen showed the greatest area under the ROC curve being 0.994 for SOR and 0.998 for Ki^{ref} indicating an excellent separation of the groups. The caudate nucleus and ventral striatum performed less well in this respect. In the contralateral putamen probability curves were the steepest indicating that when reaching a certain threshold the probability of being a PD patient rises dramatically. Actually, the probability curves for SOR and Ki^{ref} were comparable indicating that the probability of being a PD patient can be equally accurately estimated by the use of either of the analytical methods. Different slopes in the probability curves may indicate different diagnostic patterns of PD; a steep curve, like found both in the anterior and posterior putamen, would indicate a PD diagnosis easily linked to low levels of SOR or Ki^{ref} values. A more flat curve in contrast, would indicate a difficulty to link even very low SOR or Ki^{ref} values to a PD diagnosis as was seen in the caudate nucleus and ventral striatum. It has been suggested that the logistic regression model provides a useful method to determine the decision level with less ambiguity than those obtained from ROC curves, as well as provide measures of dispersion for the decision level (DeBari. 2006).

Underdiagnosis and misdiagnosis of PD are common because of the variety of syndromes with parkinsonism (Hughes, et al. 1992a) although it has been shown that with the current clinical criteria, an accuracy of 90% can be obtained in the clinical diagnosis of PD (Hughes, et al. 2001a). Neuropathological examination at autopsy is currently the

definitive diagnostic gold standard, but one would benefit from biomarkers that would improve the diagnostic accuracy. Interestingly, in Study II there were five patients (5.6%) with a clinical diagnosis of PD in whom FDOPA uptake was within the control range. Four of them still have the diagnosis of PD and they all are on levodopa medication. Such patients are sometimes referred to as "SWEDDs" (scans without evidence of dopaminergic deficit) (Marek, et al. 2005). In large clinical series such individuals have represented around 11 to 15 % of patiens with PD (Eckert, et al. 2007, Fahn, et al. 2004a, Whone, et al. 2003b). Clinical follow-up has shown that the final diagnoses of these SWEDDs were diverse, pointing to secondary forms of Parkinsonism, as well as psychogenic causes (Eckert, et al. 2007, Eerola, et al. 2005).

Even though the diagnosis of PD is still done clinically, the imaging techniques like FDOPA PET using SOR and Ki^{ref} as analytic parametres would provide a unique aid in the diagnosis and differential diagnosis of PD. In daily clinical practice, helping to differentiate between PD and a healthy state will be especially interesting in patients with mild or debatable clinical symptoms. Verification of dopaminergic hypofunction may warrant a early treatment initiation as recently suggested (Schapira and Obeso. 2006), although contradictory views are equally justified (Aminoff. 2006). The early detection of dopaminergic hypofunction and treatment initiation will become important when disease-modifying therapies are becoming available. Our study shows that both SOR and Kiref can be used to measure the presynaptic dopaminergic function in vivo, and they show equally good ability to distinguish PD patients from healthy subjects. A single 15-min scan 75 min after a tracer injection seems to be sufficient in a clinical research environment dealing with patients with PD, which provides a powerful and economical alternative for the research of disease mechanisms and differential diagnosis.

6.2. Cerebral glucose metabolism and beta-amyloid deposition in PD

Many elderly individuals, or PD patients without dementia, or with only mild cognitive impairment, have neuritic Alzheimer-type changes (neurofibrillary tangles and/or neuropil threads) in the entorhinal cortex (ERC) (Jellinger, et al. 1991). On the other hand, there are PD patients with severe dementia who have no significant AD pathology, suggesting other underlying pathology for intellectual deterioration (Jellinger. 1987). The pathophysiological basis of cognitive impairment and dementia in PD may be heterogenous involving cortical Lewy bodies, concomitant AD pathology or the degeneration of subcortical projection nuclei of neurotransmitter systems (such as dopamine, noradrenaline, serotonin), or a combination of these brain changes. It has also been suggested that widespread glucose hypometabolism in the cerebral cortex may be associated with dementia in PD (Ma, et al. 2008a, Sasaki, et al. 1992a).

In Study III, we combined different imaging methods in the same patients to provide an opportunity to disentangle the pathophysiological correlates of cognitive impairment and

dementia in PD. PET imaging with [^{11}C]PIB and [^{18}F]FDG was performed to evaluate amyloid accumulation and glucose metabolism in both demented and non-demented patients with PD, and healthy controls.

We found that [^{11}C]PIB region-to-cerebellum ratios did not differ significantly between the groups in any brain region (p > 0.05). In addition, PDD patients showed impaired glucose metabolism in the cortical brain regions and this reduction was associated with the degree of cognitive impairment.

As compared to the controls, patients with PDD showed decreased GMR in the frontal cortex, posterior and anterior cingulate, inferior parietal lobe, caudate nucleus, cerebellum, occipital cortex, parahippocampal area and the thalamus. The metabolic deficits were much more extensive in patients with PDD than in non-demented patients with PD. In comparison with the non-demented PD patients, those with PDD showed greater metabolic deficits in all the brain regions examined. In fact, non-demented PD patients showed an impaired glucose metabolism only in the occipital cortex when compared to controls. The findings are in agreement with previous PET studies demonstrating reductions in GMR in the parietal, occipital and frontal regions (Vander Borght, et al. 1997, Yong, et al. 2007). It is of interest that an impaired glucose metabolism in non-demented PD patients was seen in the occipital cortex, a feature suggested to distinguish metabolic pattern in dementia with Lewy bodies from that seen in AD (Albin, et al. 1996, Gilman, et al. 2005, Imamura, et al. 1997, Minoshima, et al. 2001, Vander Borght, et al. 1997). It is tempting to speculate that this can be taken as an additional evidence that the functional and pathological features of PD and dementia with Lewy bodies ultimately represent different ends of a common pathology. Interestingly, in our study PDD patients had decreased GMR also in the parahippocampal area, since a preserved metabolism on medial temporal structures is suggested to be a GMR feature in separating PDD from AD (Vander Borght, et al. 1997). Our findings suggest that the functional substrate for dementia in PD may be associated with the global progression of metabolic deficits.

In general there was no difference in [^{11}C]PIB uptake between the non-demented PD patients, PDD patients and controls. However, we found that three of the 11 (27%) PDD patients had clearly raised amyloid accumulation in at least one cortical region, while that was true for none of the non-demented PD patients. In addition, two (8.3%) of the 24 healthy controls had increased [^{11}C]PIB uptake. The three PDD patients with a raised amyloid load had not suffered significantly longer from dementia or from PD than the other PDD patients. Furthermore, we were not able to find relevant clinical or neuropsychological differences between these three PDD patients with an AD-like [^{11}C]PIB uptake pattern and the rest of the PDD patients. However, the three patients had the lowest GMR values in the hippocampus and parahippocampal area among the PD patients, and also had pronounced hippocampal atrophy (scores (left/right): 4/2, 3/2, 2/2 for individual patients). Both these features are typically seen in early AD, suggesting possible concomitant AD pathology in these patients. We are currently following-

up these patients to find out whether they will develop typical clinical AD features, such as prominent episodic memory impairment. Thus, there are several possible explanations. First, the PDD patients with the AD-like [^{11}C]PIB PET pattern may suffer from concomitant AD, or at least have concomitant AD pathology (Aβ plaques), as also reported in post mortem studies (Mattila, et al. 1998). Second, it could be that the combination of a parkinsonian syndrome, and an AD-like [^{11}C]PIB binding reflects, at least from a neuropathological point of view, a disease entity which is distinct from pure PDD and comparable with the large subgroup of LBD patients who also showed increased, AD-like cortical [^{11}C]PIB binding (Edison, et al. 2008, Rowe, et al. 2007) or Aβ plaques in the post mortem examination (Jellinger, et al. 2003). As stated in the consensus paper on the clinical diagnosis of DLB, the distinction between PDD and DLB may sometimes be difficult (McKeith, et al. 2005). The cortical deposition of amyloid in PD may therefore be a risk factor for dementia (Jellinger, et al. 2002), but more studies are needed to understand the usefulness of [^{11}C]PIB as a diagnostic agent in this respect. Third, the "PIB positivity" in patients with PDD might be coincidental, since also healthy elderly individuals show increased [^{11}C]PIB uptake, the percentage of subjects showing increased uptake varying between 5 -20% in different studies (Kemppainen, et al. 2006, Klunk, et al. 2004, Mintun, et al. 2006, Rowe, et al. 2007). The small number of PDD patients in Study III does not allow reliable estimation of the prevalence of "PIB-positivity" in PDD. In addition, a large patient population is needed to find out whether there might be clinical or neurobiological features that would predict the concomitant AD process. Such features could include pronounced episodic memory impairment, hipppocampal atrophy or an apolipoprotein E epsilon 4 genotype. Although Lewy bodies can be widespread in cognitively normal PD patients (Colosimo, et al. 2003), the probability of having widespread Lewy bodies, or Aβ, or both is greater in cognitively impaired or demented patients. Pathological studies have shown that Lewy body densities in the cortex, especially in the temporal neocortex, correlated significantly with the cognitive impairment in PD independent of or in addition to Alzheimer-type pathology (Mattila, et al. 1998).

Our Study III shows that the occurrence of dementia in PD seems to be multifactorial and related to cortical and subcortical hypometabolism, but only rarely with AD-like [^{11}C]PIB binding. More studies are needed to understand the underlying brain pathology and aetiology of dementia in PD.

6.3. Cognitive impairment and FDOPA uptake in PD

It has been observed that patients at the early stage of PD already show impaired performance in tests measuring frontal lobe functions, such as attention, planning and working memory [1]. Especially set-shifting, suppressing attention and other attentional deficits are among the first cognitive domains to show deterioration in PD (Dubois and Pillon. 1997, Dujardin, et al. 1999, Hart, et al. 1998). As the disease progresses there is

an apparent increase in the severity and a broadening of cognitive impairments to affect also other domains (Owen, et al. 1992).

The cortico-striato-thalamo-cortical loops connect the basal ganglia with the cerebral cortex. The putamen is closely connected with the supplementary motor cortex and is thought to be involved mainly in motor functions. The caudate nucleus, in turn, is connected with the dorsolateral prefrontal cortex and the lateral orbitofrontal cortex, and it has been suggested that the dysfunction in this system contributes to the cognitive impairment in PD. PET studies showed that the reduced Fdopa (Holthoff, et al. 1994, Holthoff-Detto, et al. 1997)uptake, especially in the caudate nucleus (Rinne, et al. 2000), is associated with the impaired cognitive performance in patients with PD. This suggests the role of the caudate nucleus via connections to frontal areas in the cognitive impairment in PD.

In Studies I and IV, neuropsychological performance, frontal lobe functions in particular, in patients with PD in relation to striatal and frontostriatal dopaminergic function was investigated. In Study I, it was found that PD patients had worse cognitive test scores in many neuropsychological tests compared to the controls, not limiting only to frontal lobe function tests. Caudate FDOPA uptake correlated positively with performance in the memory subtests of WMS-R and CERAD. In Study IV, it was found that PD patients were slower than the controls in all the CogniSpeed measures studied, and the dopaminergic dysfunction within the neural networks linking the striatum to the prefrontal cortex was involved in the slowing of cognitive processing in PD patients. The fact that slowing was seen at all levels (automatic and controlled), and irrespective of whether the motor component was included, supports the previous findings that motor and cognitive slowing may be intertwined and occur in parallel in PD (Sawamoto, et al. 2002).

In Study I, the performance of the PD patients in verbal (immediate and delayed) and visual memory correlated positively with the FDOPA uptake in the caudate nucleus. There was no correlation between Fdopa and attentional tasks. In previous PET studies (Holthoff, et al. 1994, Holthoff-Detto, et al. 1997, Rinne, et al. 2000), a connection between the caudate nucleus Fdopa uptake and the performance in tests measuring verbal memory or delayed recall (Holthoff, et al. 1994, Holthoff-Detto, et al. 1997) or frontal lobe functioning (Stroop. 1992) was found in PD. In particular, decreased FDOPA uptake in the caudate nucleus and the impairment in tests measuring verbal fluency, working memory and attentional functioning reflecting frontal lobe function were related (Stroop. 1992). In addition, previous studies have shown that the impaired performance in tests requiring suppressed attention, planning and set-shifting is related to the dopaminergic hypofunction in the caudate nucleus, especially on the right side (Bruck, et al. 2001, Marie, et al. 1999), indicating that the disturbances in the dopaminergic system are involved in the cognitive impairments found already at the early stages of PD. Our Study IV further supports these suggestions by showing that the FDOPA uptake in the

caudate nucleus correlated negatively with the performance in the choice reaction times, subtraction task measuring working memory and concentrating attention, and controlled processing. This means that the weaker the dopaminergic activity, the poorer the results in tests (more time needed to finish the test) that require special cognitive performance.

The spatiotemporal progression of dopamine degeneration in the striatum and its cortical afferents has been suggested as being responsible for the evolving pattern of cognitive impairment observed in PD patients (Grahn, et al. 2008). In this study, cortical presynaptic dopaminergic activity of the anterior cingulate gyrus was related to cognitive functions in PD. We found that the worse performance in choice reaction times, subtraction task measuring working memory and concentrating attention was related to reduced Fdopa uptake in the anterior cingulate gurus. Slowed controlled processing was associated with a reduced dopaminergic function in ACC only in the automated ROI analysis. These findings are in concordance with a previous study showing that the anterior cingulate gyrus mediates cognitive functions in PD patients (Grossman, et al. 1992). ACC has also been implicated in various other cognitive functions (for a review see Faw. 2003). Interestingly, in a previous study it was suggested that the effect of caudate nucleus dopamine depletion on the anterior cingulate gyrus metabolism could be a possible early pathophysiological and functional substrate for the impairment of executive functions in PD (Polito, et al. 2010).

The basic flow of information through the basal ganglia is topographically organized from the cortex through basal ganglia structures to the thalamus, and back to the cortex. It has been long thought that the primary role for the thalamus is a simple relay of information processed in the basal ganglia to the cortex. However, recent studies have indicated a more dynamic role for the thalamus in basal ganglia information processing than just a passive relay (for a review see Haber and McFarland. 2001). Damage to the thalamic regions appears to impact on cognition, awareness and perception, and the direct pathology of the thalamus contributes to the symptoms of PD (Halliday. 2009). In a previous study using diffusion-based tractography, it was found that the thalamus closely interacts with the ACC, and this interaction is of great functional importance for performance monitoring and subsequent adjustments (Seifert, et al. 2011). Our study supports the role of the thalamus in cognitive functions, since we found that the worse performance in the subtraction task measuring working memory and concentrating attention was associated with reduced dopaminergic function in the thalamus. Although there were no statistically significant differences in the frontal or thalamic FDOPA target to occipital ratio values between PD patients and controls, the correlations between the cognitive tests and Fdopa uptake of the anterior cingulate gurys and thalamus could be explained by the strong dopaminergic cortico-basal ganglia-thalamo-cortical connections. We found that the Fdopa uptake of the caudate nucleus, which was significantly decreased when compared to the controls, correlated statistically significantly with the Fdopa uptake of the ACC and thalamus ($p<0.0001$).

In PD patients, tests sensitive to dorsal frontostriatal dysfunction (executive processes) such as planning and set-shifting were impaired following L-dopa withdrawal (Cools, et al. 2003) and improved with L-dopa treatment (Lange, et al. 1993), suggesting a primarily dopaminergic substrate. The effect of dopamine on cognitive performance might also be dependant on the nature of the cognitive task and the basal level of dopamine in the underlying fronto-striato-thalamic circuitry, as has been proposed by others (Cools, et al. 2003). Although in Study IV we found that the reduced dopaminergic activity in the frontostriatal regions is associated with the impaired cognitive performance, and the Study I (and previous studies) suggests that the reduced dopaminergic activity in the caudate nucleus is not only related to the classic frontal lobe functions, but is also associated with the tests measuring verbal and visual memory, one must bear in mind that the presence of correlation does not necessarily imply causality. FDOPA uptake is not strictly specific for dopaminergic cells, but also includes many regions with relatively high concentrations of norepinephrine and serotonin (Brown, et al. 1999). Thus, the cortical FDOPA reductions might be a composite of dopaminergic, serotonergic, and noradrenergic systems, which also degenerate in PD. Even though the dopaminergic, noradrenergic and serotonergic systems all have projections to the cortical areas, there are some differences in their distribution. Especially, the dopaminergic system has strong mesocortico-prefrontal projections wheras the noradrenergic and the serotonergic projections are much more evenly distributed throughout the cortex (Javoy-Agid, et al. 1989). In addition, the FDOPA signal-to-noise ratio is quite low in the cortex, and it has been questioned whether FDOPA uptake can be reliably quantified in cortical areas (Cropley, et al. 2008). Later, during the progression of PD, cognitive impairment is more widespread and the basis of generalized cognitive impairment in PD is probably multifactoring, involving various cortical areas and their connections, which also might explain the poor response of the levodopa medication on cognitive symptoms in the advanced PD patients.

Studies I and IV show that the reduced dopaminergic activity in the frontostriatal regions is associated with the impaired cognitive performance, such as attention, verbal, visual and working memory and different levels of cognitive processing in non-demented patients with PD. Further research on understanding the driving pathology for the cognitive impairment in PD is highly important in order to develop more relevant therapeutic options for cognitive impairment in patients with PD.

6.4. Hypometabolism, brain atrophy and cognitive impairment in PD

The underlying brain pathology of the cognitive deficits in PD is not yet fully understood. PET studies of the resting state cerebral glucose metabolism has become a major functional imaging tool for investigating the age-related brain pathology, such as PD or AD, and it has been suggested that widespread glucose hypometabolism in the cerebral cortex may be associated with dementia in PD (Ma, et al. 2008b, Sasaki, et al. 1992b). A

MRI study found that non-demented patients with PD had a significant rate of median/ global brain volume loss with no significant loss seen in age-matched controls, and these changes correlated with global measures of cognitive decline (Hu, et al. 2001). In Study III, we found that impairment in cortical GMR was associated with worse cognitive performance in patients with PD. In Studies I and III, patients with PD had more atrophy, both in the hippocampus and the prefrontal cortex compared, with controls. We also found that the hippocampal atrophy in PD patients was related to impaired memory.

When comparing [^{18}F]FDG uptake and cognitive performance, it was found that impairment in cortical GMR was associated with general cognition (evaluated by a MMSE score) in patients with PD. More specifically, the association between cognition and GMR showed regional and cognitive domain specificity in the sense that performance in typical "frontal lobe" cognitive tests was associated with impairment in the frontal (medial and lateral) cortical metabolism. On the other hand, impairment in verbal word list learning was associated with hypometabolism in the temporal cortex and impairment in visuoconstructive tests of CERAD with parietal hypometabolism. Similar to AD, reduced GMR in PD assessed by PET has been discussed to be related to the dementing process (Hoffman, et al. 2000). The aetiology of dementia in PD is still unclear and under investigation. There is increasing evidence that the occurrence and severity of dementia is primarily related to cortical changes rather than to alterations of subcortical structures (Harding and Halliday. 2001, Hurtig, et al. 2000). However, the underlying brain pathology of hypometabolism is not yet fully understood. Cortical Lewy body pathology (Aarsland, et al. 2005), Alzheimer pathology (Mastaglia, et al. 2003) and deficits in different non-dopaminergic neurotransmitter systems, primarily cholinergic (Hilker, et al. 2005) or combination of these processes may play a role.

In our Study III, PD patients with dementia had more brain atrophy both in the hippocampus and the frontal cortex compared with non-demented PD patients and controls. On the other hand, Study I showed that PD patients without dementia had more atrophy both in the hippocampus and the prefrontal cortex compared with controls, but the atrophy was mild, since in the visual scale the atrophy scores (max. score 4) ranged from 0 to 2 in the hippocampal and prefrontal cortex. In both studies we also found that hippocampal atrophy in PD patients was related to impaired memory, which is logical considering the role of the hippocampus in learning and memory. In Study I, we did not find any association between the prefrontal atrophy and neuropsychological test performance, maybe because of the small number of subjects and narrow range of atrophy scores. Previous studies have indicated that brain atrophy in PD is related to cognitive impairment. This has been shown in medicated PD patients using volumetric MRI between global brain volume loss and global measures of cognitive decline (Hu, et al. 2001), between hippocampal atrophy and impaired memory (Riekkinen, et al. 1998), and impaired recognition memory and MMSE (Camicioli, et al. 2003). The association between brain atrophy and cognitive impairment is further supported by a previous study in which the hippocampal volumes of patients with Alzheimer's disease, vascular

dementia, PD with dementia, and PD without cognitive impairment were compared. It was found that the cognitively unimpaired patients with PD had atrophy when compared with the controls, but to a lesser extent than patients with PD who also had dementia (Laakso, et al. 1996).

Advances in imaging have made it possible to detect functional and structural changes in Parkinson's disease, and there is general agreement in the value of identifying the stage of mild cognitive impairment before the onset of functional impairments that characterise dementia. Understanding the pathogenesis of Parkinson's disease have stimulated greater interest in the development of potential disease-modifying therapies. There is a more urgent need for the use of imaging as a biomarker to detect early disease and identify the results of interventions. Investigations employing structural MRI analysed by visual inspection, region of interest and whole brain voxel based morphometry (VBM) methods have reported grey matter atrophy associated with dementia in PD in the basal ganglia, medial temporal and limbic areas, as well as other cortical regions (Beyer, et al. 2007a, Bouchard, et al. 2008, Burton, et al. 2004, Summerfield, et al. 2005, Tam, et al. 2005). Some studies defining a single 'non-dementia' group of PD subjects have reported atrophy in the medial temporal lobe (Bouchard, et al. 2008, Bruck, et al. 2004, Nishio, et al. 2010, Summerfield, et al. 2005, Tam, et al. 2005), amygdale (Bouchard, et al. 2008), frontal regions (Burton, et al. 2004, Nishio, et al. 2010) and cerebellum (Camicioli, et al. 2009). In contradistinction, others have found no significant atrophy in PD without dementia (Feldmann, et al. 2008, Ghaemi, et al. 2002, Martin, et al. 2009, Tessa, et al. 2008). In a previous study, it was found that marked grey matter atrophy occurs in PD with dementia, but far less extensive changes are evident in PD with mild cognitive impairment. Grey matter loss in PD correlated with global cognitive score, but not motor impairment in most of the regions examined. It was concluded that some grey matter atrophy precedes the development of dementia but may be accelerated once frank dementia begins (Melzer, et al. 2011).

The primary objective of these studies was not to explore associations between cortical metabolism or brain atrophy and neuropsychological test performance. These correlations obtained should be interpreted with caution because of the relatively small number of patients. In addition, one must bear in mind that the presence of correlation does not necessarily imply causality. Thus, impairment in cortical GMR and hippocampal atrophy may both be markers of more advanced disease, which may in turn be associated with more severe cognitive impairment.

7. CONCLUSIONS

On the basis of the present investigation, the following conclusions can be made:

I   The impaired dopaminergic function of the caudate nucleus is related to the impairment in cognitive functions, such as verbal memory, visual memory and delayed recall in non-demented PD patients. Structural MRI shows that PD patients have atrophy both in the prefrontal cortex and in the hippocampus, and the hippocampal atrophy is related to impaired memory.

II Both SOR and K_i^{ref} can be used to measure the presynaptic dopaminergic function *in vivo* and they show equally good ability to distinguish PD patients from healthy subjects. The contralateral anterior and posterior putamen have the greatest ability to distinguish PD patients from controls. A single 15-min scan 75 min after tracer injection seems to be sufficient in a clinical research environment dealing with patients with PD, which provides a powerful and economical alternative for the research of disease mechanisms and differential diagnosis.

III The occurrence of dementia in PD seems to be multifactorial, and associated with an extensive spread of hypometabolism beyond the occipital cortex and with hippocampal and frontal atrophy, but not beta-amyloid deposition consistent with a unique biological process related to PD rather than the co-incidental development of AD in persons with PD.

IV The reduced dopaminergic activity in the frontostriatal regions is associated with the impairment and the slowing in tests tapping different levels of cognitive processing from basic, relatively automatic choice-reaction tasks to mental arithmetic tasks requiring a working memory and attention in non-demented patients with PD.

V   In general, impairment in frontal lobe functions and the slowing of information processing in PD seems to be related to dopaminergic hypofunction in the caudate nucleus and anterior cingulate gyrus. However, more widespread cognitive impairment and dementia in PD is associated with cortical hypometabolism and hippocampal and frontal atrophy, but rarely with concomitant beta-amyloid (Alzheimer's disease) pathology.

8. ACKNOWLEDGEMENTS

I wish to thank the official reviewers of this thesis, Professor Aapo Ahonen and Professor Tapani Keränen for their valuable and constructive criticism and comments. I am grateful to Henno Parks for skilful linguistic revision of this manuscript.

I am sincerely thankful to my fellow researchers; Terhi Tuokkola, Noora Scheinin, Anna Brück, Jaana Koivunen, Timo Suotunen, Jere Virta and Juho Joutsa for pleasant discussions and great atmosphere. I am also grateful for their methodological advice and sharing the scanning workload. I also owe my thanks to my colleagues Esa Kotilainen, Antti Puntala, Ville Vuorinen, Janek Frantzen, Melissa Rahi, Anna Kotkansalo, Katariina Korhonen, Jussi Posti and Matti Sankinen, at Turku neurosurgery department. They have inspired me by showing me the strength of the human spirit.

I want to express my warm thanks to all patients and healthy individuals who participated in these studies. I hope that this work will benefit them and others.

I'm grateful to my dear friends, Jaakko and Jonna, Mika and Kaisa, Tommi and Maija, Klaus and Jukka, Juho and Kaisa, Mari and Petteri, Vesa and Piia, Tuomas and Aida, Aki and Saara, Jukka and Eeva, Jonna and Oskari, and others, for supporting me through these years. I have shared great moments with you, and you have provided me important perspectives outside science and clinical work. I have been priviledged to get to know your little children as well. My triathlon friends, Pasi, Ilkka, Tatu, Maria, Arttu, Mikax2, and others are warmly thanked for keeping me in relatively good shape. I also want to thank my singing teacher Johanna and the students of music school for the enjoyable and relaxing concerts.

I wish to thank my parents Merja and Jouko for the encouragement and support throughout my life. They have raised me, supported me, taught me, believed in me, and most of all, loved me. I am grateful for my brother, Santtu, and his wife Taru for being always there and believing that I could get through this. My parents-in-law Jaakko and Kaija are warmly thanked for their enthusiastic attitude and sharing enjoyable moments outside work. I am also grateful to Pauliina's sister and brothers Karoliina, Olli and Anssi and their spouses Erling, Maria and Helena for friendship and unforgettable memories. I owe my thanks to our godchildren Kauri, Heikki and Elias and also Heikki's brother Kalle who have brought so much happiness and joy to our life.

I owe my deepest gratitude to my wife Pauliina. She is the love of my life, my soul mate and the most beautiful (on the inside and outside) wife in the world. Without her love, great advice, support and patience this work would have not been possible. I am eternally and overwhelming grateful, fortunate and blessed for my perfect and precious princess daughter Emma.

9. REFERENCES

Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. Brain Pathol 2010; 20: 633-9.

Aarsland D, Tandberg E, Larsen JP, Cummings JL. Frequency of dementia in parkinson disease. Arch Neurol 1996; 53: 538-42.

Aarsland D, Perry R, Brown A, Larsen JP, Ballard C. Neuropathology of dementia in Parkinson's disease: A prospective, community-based study. Ann Neurol 2005; 58: 773-6.

Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G, Norwegian ParkWest Study Group. Cognitive impairment in incident, untreated parkinson disease: The norwegian ParkWest study. Neurology 2009; 72: 1121-6.

Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sorensen P. Risk of dementia in Parkinson's disease: A community-based, prospective study. Neurology 2001; 56: 730-6.

Aarsland D, Larsen JP, Lim NG, Janvin C, Karlsen K, Tandberg E, et al. Range of neuropsychiatric disturbances in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1999; 67: 492-6.

Abercrombie ED, Bonatz AE, Zigmond MJ. Effects of L-dopa on extracellular dopamine in striatum of normal and 6-hydroxydopamine-treated rats. Brain Res 1990; 525: 36-44.

Agresti A. Categorical data analysis. New York ; Chichester: Wiley-Interscience; 2002.

Albin RL, Minoshima S, D'Amato CJ, Frey KA, Kuhl DA, Sima AA. Fluoro-deoxyglucose positron emission tomography in diffuse lewy body disease. Neurology 1996; 47: 462-6.

Alexander GE, Crutcher MD. Functional architecture of basal ganglia circuits: Neural substrates of parallel processing. Trends Neurosci 1990; 13: 266-71.

Alexander GE, Crutcher MD, DeLong MR. Basal ganglia-thalamocortical circuits: Parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 1990; 85: 119-46.

Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu Rev Neurosci 1986; 9: 357-81.

Allam MF, Campbell MJ, Hofman A, Del Castillo AS, Fernandez-Crehuet Navajas R. Smoking and Parkinson's disease: Systematic review of prospective studies. Mov Disord 2004; 19: 614-21.

Alvord EC,Jr, Forno LS, Kusske JA, Kauffman RJ, Rhodes JS, Goetowski CR. The pathology of parkinsonism: A comparison of degenerations in cerebral cortex and brainstem. Adv Neurol 1974; 5: 175-93.

Aminoff MJ. Treatment should not be initiated too soon in Parkinson's disease. Ann Neurol 2006; 59: 562,4; discussion 564-5.

Antonini A, Vontobel P, Psylla M, Gunther I, Maguire PR, Missimer J, et al. Complementary positron emission tomographic studies of the striatal dopaminergic system in Parkinson's disease. Arch Neurol 1995; 52: 1183-90.

Apaydin H, Ahlskog JE, Parisi JE, Boeve BF, Dickson DW. Parkinson disease neuropathology: Later-developing dementia and loss of the levodopa response. Arch Neurol 2002; 59: 102-12.

Archer HA, Edison P, Brooks DJ, Barnes J, Frost C, Yeatman T, et al. Amyloid load and cerebral atrophy in alzheimer's disease: An 11C-PIB positron emission tomography study. Ann Neurol 2006; 60: 145-7.

Arnsten AF. Catecholamine regulation of the prefrontal cortex. J Psychopharmacol 1997; 11: 151-62.

Arnsten AF, Goldman-Rakic PS. Selective prefrontal cortical projections to the region of the locus coeruleus and raphe nuclei in the rhesus monkey. Brain Res 1984; 306: 9-18.

Ascherio A, Chen H, Schwarzschild MA, Zhang SM, Colditz GA, Speizer FE. Caffeine, postmenopausal estrogen, and risk of Parkinson's disease. Neurology 2003; 60: 790-5.

Ascherio A, Weisskopf MG, O'Reilly EJ, McCullough ML, Calle EE, Rodriguez C, et al. Coffee consumption, gender, and Parkinson's disease mortality in the cancer prevention study II cohort: The modifying effects of estrogen. Am J Epidemiol 2004; 160: 977-84.

Aston-Jones G. The locus coeruleus, A5 and A7 noradrenergic cell groups. In: Paxinos G, editor. The rat Nervous System. San Diego: Academic Press; 1995. p. 183-213.

Babcock RL, Salthouse TA. Effects of increased processing demands on age differences in working memory. Psychol Aging 1990; 5: 421-8.

Ballard C, Ziabreva I, Perry R, Larsen JP, O'Brien J, McKeith I, et al. Differences in neuropathologic characteristics across the lewy body dementia spectrum. Neurology 2006; 67: 1931-4.

Baloyannis SJ, Costa V, Baloyannis IS. Morphological alterations of the synapses in the locus coeruleus in Parkinson's disease. J Neurol Sci 2006; 248: 35-41.

Barbas H, Pandya DN. Architecture and intrinsic connections of the prefrontal cortex in the rhesus monkey. J Comp Neurol 1989; 286: 353-75.

Barbosa ER, Limongi JC, Cummings JL. Parkinson's disease. Psychiatr Clin North Am 1997; 20: 769-90.

Bayles KA, Trosset MW, Tomoeda CK, Montgomery EB,Jr, Wilson J. Generative naming in parkinson disease patients. J Clin Exp Neuropsychol 1993; 15: 547-62.

Beckstead RM. Complementary mosaic distributions of thalamic and nigral axons in the caudate nucleus of the cat: Double anterograde labeling combining autoradiography and wheat germ-HRP histochemistry. Brain Res 1985; 335: 153-9.

Ben-Shlomo Y, Churchyard A, Head J, Hurwitz B, Overstall P, Ockelford J, et al. Investigation by Parkinson's disease research group of united kingdom into excess mortality seen with combined levodopa and selegiline treatment in patients with early, mild Parkinson's disease: Further results of randomised trial and confidential inquiry. BMJ 1998; 316: 1191-6.

Berding G, Odin P, Brooks DJ, Nikkhah G, Matthies C, Peschel T, et al. Resting regional cerebral glucose metabolism in advanced Parkinson's disease studied in the off and on conditions with [(18)F]FDG-PET. Mov Disord 2001; 16: 1014-22.

Berendse HW, Groenewegen HJ. Organization of the thalamostriatal projections in the rat, with special emphasis on the ventral striatum. J Comp Neurol 1990; 299: 187-228.

Berger K, Breteler MM, Helmer C, Inzitari D, Fratiglioni L, Trenkwalder C, et al. Prognosis with Parkinson's disease in europe: A collaborative study of population-based cohorts. neurologic diseases in the elderly research group. Neurology 2000; 54: S24-7.

Bergman J. Electrophilic synthesis of 6-[18F]fluoro-L-dopa, starting from aqueous [18F]-fluoride. 1994; 35: 476-7.

Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of parkinson and huntington. clinical, morphological and neurochemical correlations. J Neurol Sci 1973; 20: 415-55.

Berry EL, Nicolson RI, Foster JK, Behrmann M, Sagar HJ. Slowing of reaction time in Parkinson's disease: The involvement of the frontal lobes. Neuropsychologia 1999; 37: 787-95.

Bertrand E, Lechowicz W, Szpak GM, Lewandowska E, Dymecki J, Wierzba-Bobrowicz T. Limbic neuropathology in idiopathic Parkinson's disease with concomitant dementia. Folia Neuropathol 2004; 42: 141-50.

Beyer MK, Aarsland D. Grey matter atrophy in early versus late dementia in Parkinson's disease. Parkinsonism Relat Disord 2008; 14: 620-5.

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. J Neurol Neurosurg Psychiatry 2007a; 78: 254-9.

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. J Neurol Neurosurg Psychiatry 2007b; 78: 254-9.

Björklund A, Lindvall O. Dopamine-containing systems in the CNS. In: Björklund A, Hokfelt T, editors. Handbook of chemical neuroanatomy. Amsterdam: Elsevier; 1984. p. 55-122.

Blandini F, Nappi G, Tassorelli C, Martignoni E. Functional changes of the basal ganglia circuitry in Parkinson's disease. Prog Neurobiol 2000; 62: 63-88.

Boller F, Mizutani T, Roessmann U, Gambetti P. Parkinson disease, dementia, and alzheimer disease: Clinicopathological correlations. Ann Neurol 1980; 7: 329-35.

Bonnet AM, Loria Y, Saint-Hilaire MH, Lhermitte F, Agid Y. Does long-term aggravation of Parkinson's disease result from nondopaminergic lesions? Neurology 1987; 37: 1539-42.

Bouchard TP, Malykhin N, Martin WR, Hanstock CC, Emery DJ, Fisher NJ, et al. Age and dementia-associated atrophy predominates in the hippocampal head and amygdala in Parkinson's disease. Neurobiol Aging 2008; 29: 1027-39.

Bowen FP, Kamienny RS, Burns MM, Yahr M. Parkinsonism: Effects of levodopa treatment on concept formation. Neurology 1975; 25: 701-4.

Bower JH, Maraganore DM, McDonnell SK, Rocca WA. Incidence and distribution of parkinsonism in olmsted county, minnesota, 1976-1990. Neurology 1999; 52: 1214-20.

Braak H, Del Tredici K. Invited article: Nervous system pathology in sporadic parkinson disease. Neurology 2008; 70: 1916-25.

Braak H, Braak E. Cognitive impairment in Parkinson's disease: Amyloid plaques, neurofibrillary tangles, and neuropil threads in the cerebral cortex. J Neural Transm Park Dis Dement Sect 1990; 2: 45-57.

Braak H, Rub U, Jansen Steur EN, Del Tredici K, de Vos RA. Cognitive status correlates with neuropathologic stage in parkinson disease. Neurology 2005; 64: 1404-10.

Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's

disease-related pathology. Cell Tissue Res 2004; 318: 121-34.

Braak H, de Vos RA, Jansen EN, Bratzke H, Braak E. Neuropathological hallmarks of alzheimer's and Parkinson's diseases. Prog Brain Res 1998; 117: 267-85.

Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003; 24: 197-211.

Brooks DJ, Ibanez V, Sawle GV, Quinn N, Lees AJ, Mathias CJ, et al. Differing patterns of striatal 18F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. Ann Neurol 1990; 28: 547-55.

Broussolle E, Dentresangle C, Landais P, Garcia-Larrea L, Pollak P, Croisile B, et al. The relation of putamen and caudate nucleus 18F-dopa uptake to motor and cognitive performances in Parkinson's disease. J Neurol Sci 1999; 166: 141-51.

Brown RG, Marsden CD. Internal versus external cues and the control of attention in Parkinson's disease. Brain 1988a; 111 (Pt 2): 323-45.

Brown RG, Marsden CD. An investigation of the phenomenon of "set" in Parkinson's disease. Mov Disord 1988b; 3: 152-61.

Brown RG, Marsden CD. Visuospatial function in Parkinson's disease. Brain 1986; 109 (Pt 5): 987-1002.

Brown WD, Taylor MD, Roberts AD, Oakes TR, Schueller MJ, Holden JE, et al. FluoroDOPA PET shows the nondopaminergic as well as dopaminergic destinations of levodopa. Neurology 1999; 53: 1212-8.

Bruck A, Aalto S, Nurmi E, Bergman J, Rinne JO. Cortical 6-[18F]fluoro-L-dopa uptake and frontal cognitive functions in early Parkinson's disease. Neurobiol Aging 2005a; 26: 891-8.

Bruck A, Aalto S, Nurmi E, Bergman J, Rinne JO. Cortical 6-[18F]fluoro-L-dopa uptake and frontal cognitive functions in early Parkinson's disease. Neurobiol Aging 2005b; 26: 891-8.

Bruck A, Kurki T, Kaasinen V, Vahlberg T, Rinne JO. Hippocampal and prefrontal atrophy in patients with early non-demented Parkinson's disease is related to cognitive impairment. J Neurol Neurosurg Psychiatry 2004; 75: 1467-9.

Bruck A, Aalto S, Nurmi E, Vahlberg T, Bergman J, Rinne JO. Striatal subregional 6-[18F]fluoro-L-dopa uptake in early Parkinson's disease: A two-year follow-up study. Mov Disord 2006; 21: 958-63.

Bruck A, Portin R, Lindell A, Laihinen A, Bergman J, Haaparanta M, et al. Positron emission tomography shows that impaired frontal lobe functioning in

Parkinson's disease is related to dopaminergic hypofunction in the caudate nucleus. Neurosci Lett 2001; 311: 81-4.

Burack MA, Hartlein J, Flores HP, Taylor-Reinwald L, Perlmutter JS, Cairns NJ. In vivo amyloid imaging in autopsy-confirmed parkinson disease with dementia. Neurology 2010; 74: 77-84.

Burn DJ, Sawle GV, Brooks DJ. Differential diagnosis of Parkinson's disease, multiple system atrophy, and steele-richardson-olszewski syndrome: Discriminant analysis of striatal 18F-dopa PET data. J Neurol Neurosurg Psychiatry 1994; 57: 278-84.

Burton EJ, McKeith IG, Burn DJ, O'Brien JT. Brain atrophy rates in Parkinson's disease with and without dementia using serial magnetic resonance imaging. Mov Disord 2005; 20: 1571-6.

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.

Calne DB, Snow BJ, Lee C. Criteria for diagnosing Parkinson's disease. Ann Neurol 1992; 32 Suppl: S125-7.

Camicioli R, Moore MM, Kinney A, Corbridge E, Glassberg K, Kaye JA. Parkinson's disease is associated with hippocampal atrophy. Movement Disorders 2003; 18: 784-90.

Camicioli R, Gee M, Bouchard TP, Fisher NJ, Hanstock CC, Emery DJ, et al. Voxel-based morphometry reveals extra-nigral atrophy patterns associated with dopamine refractory cognitive and motor impairment in parkinsonism. Parkinsonism Relat Disord 2009; 15: 187-95.

Caviness JN, Driver-Dunckley E, Connor DJ, Sabbagh MN, Hentz JG, Noble B, et al. Defining mild cognitive impairment in Parkinson's disease. Mov Disord 2007; 22: 1272-7.

Chandler MJ, Lacritz LH, Hynan LS, Barnard HD, Allen G, Deschner M, et al. A total score for the CERAD neuropsychological battery. Neurology 2005; 65: 102-6.

Clark IE, Dodson MW, Jiang C, Cao JH, Huh JR, Seol JH, et al. Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. Nature 2006; 441: 1162-6.

Cohen RA, Kaplan RF, Moser DJ, Jenkins MA, Wilkinson H. Impairments of attention after cingulotomy. Neurology 1999; 53: 819-24.

Colosimo C, Hughes AJ, Kilford L, Lees AJ. Lewy body cortical involvement may not always predict dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 2003; 74: 852-6.

Cools R. Dopaminergic modulation of cognitive function-implications for L-DOPA treatment in Parkinson's disease. Neurosci Biobehav Rev 2006; 30: 1-23.

Cools R, Barker RA, Sahakian BJ, Robbins TW. L-dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with Parkinson's disease. Neuropsychologia 2003; 41: 1431-41.

Cools R, Stefanova E, Barker RA, Robbins TW, Owen AM. Dopaminergic modulation of high-level cognition in Parkinson's disease: The role of the prefrontal cortex revealed by PET. Brain 2002; 125: 584-94.

Cooper JA, Sagar HJ, Tidswell P, Jordan N. Slowed central processing in simple and go/no-go reaction time tasks in Parkinson's disease. Brain 1994; 117 (Pt 3): 517-29.

Cooper JA, Sagar HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. Brain 1992; 115 (Pt 6): 1701-25.

Crocker D. Dopamine - mechanism of action. Aust Prescr 1994: 17-21.

Cropley VL, Fujita M, Bara-Jimenez W, Brown AK, Zhang XY, Sangare J, et al. Pre- and post-synaptic dopamine imaging and its relation with frontostriatal cognitive function in parkinson disease: PET studies with [11C]NNC 112 and [18F]FDOPA. Psychiatry Res 2008; 163: 171-82.

Cumming P, Munk OL, Doudet D. Loss of metabolites from monkey striatum during PET with FDOPA. Synapse 2001; 41: 212-8.

Cummings JL. Depression and Parkinson's disease: A review. Am J Psychiatry 1992; 149: 443-54.

Cummings JL. Subcortical dementia. neuropsychology, neuropsychiatry, and pathophysiology. Br J Psychiatry 1986; 149: 682-97.

Cummings JL, Miller BL. Conceptual and clinical aspects of the frontal lobes. In: Miller BL, Cummings JL, editors. The human frontal lobes. New York: The Guilford Press; 2007. p. 12-25.

Cummings JL, Darkins A, Mendez M, Hill MA, Benson DF. Alzheimer's disease and Parkinson's disease: Comparison of speech and language alterations. Neurology 1988; 38: 680-4.

Dagher A, Nagano-Saito A. Functional and anatomical magnetic resonance imaging in Parkinson's disease. Mol Imaging Biol 2007; 9: 234-42.

Damier P, Hirsch EC, Agid Y, Graybiel AM. The substantia nigra of the human brain. II. patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain 1999a; 122 (Pt 8): 1437-48.

Damier P, Hirsch EC, Agid Y, Graybiel AM. The substantia nigra of the human brain. II. patterns of loss of dopamine-containing neurons in Parkinson's disease. Brain 1999b; 122 (Pt 8): 1437-48.

de Lau LM, Schipper CM, Hofman A, Koudstaal PJ, Breteler MM. Prognosis of parkinson disease: Risk of dementia and mortality: The rotterdam study. Arch Neurol 2005; 62: 1265-9.

de Rijk MC, Breteler MM, Graveland GA, Ott A, Grobbee DE, van der Meche FG, et al. Prevalence of Parkinson's disease in the elderly: The rotterdam study. Neurology 1995; 45: 2143-6.

DeBari VA. Computation of decision levels from differentiated logistic regression probability curves. Ann Clin Lab Sci 2006; 36: 194-200.

DeJesus OT, Endres CJ, Shelton SE, Nickles RJ, Holden JE. Evaluation of fluorinated m-tyrosine analogs as PET imaging agents of dopamine nerve terminals: Comparison with 6-fluoroDOPA. J Nucl Med 1997; 38: 630-6.

DelleDonne A, Klos KJ, Fujishiro H, Ahmed Z, Parisi JE, Josephs KA, et al. Incidental lewy body disease and preclinical parkinson disease. Arch Neurol 2008; 65: 1074-80.

DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics 1988; 44: 837-45.

Dhawan V, Ma Y, Pillai V, Spetsieris P, Chaly T, Belakhlef A, et al. Comparative analysis of striatal FDOPA uptake in Parkinson's disease: Ratio method versus graphical approach. J Nucl Med 2002; 43: 1324-30.

Dick FD, De Palma G, Ahmadi A, Scott NW, Prescott GJ, Bennett J, et al. Environmental risk factors for Parkinson's disease and parkinsonism: The geoparkinson study. Occup Environ Med 2007; 64: 666-72.

Dickson DW, Fujishiro H, DelleDonne A, Menke J, Ahmed Z, Klos KJ, et al. Evidence that incidental lewy body disease is pre-symptomatic Parkinson's disease. Acta Neuropathol 2008; 115: 437-44.

Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. J Neurol 1997; 244: 2-8.

Dubois B, Slachevsky A, Litvan I, Pillon B. The FAB - A frontal assessment battery at bedside. Neurology 2000; 55: 1621-6.

Dubois B, Pilon B, Lhermitte F, Agid Y. Cholinergic deficiency and frontal dysfunction in Parkinson's disease. Ann Neurol 1990; 28: 117-21.

Dubois B, Ruberg M, Javoy-Agid F, Ploska A, Agid Y. A subcortico-cortical cholinergic system is affected in Parkinson's disease. Brain Res 1983; 288: 213-8.

Dubois B, Danze F, Pillon B, Cusimano G, Lhermitte F, Agid Y. Cholinergic-dependent cognitive deficits in Parkinson's disease. Ann Neurol 1987; 22: 26-30.

Dubois B, Burn D, Goetz C, Aarsland D, Brown RG, Broe GA, et al. Diagnostic procedures for Parkinson's disease dementia: Recommendations from the movement disorder society task force. Mov Disord 2007; 22: 2314-24.

Dujardin K, Degreef JF, Rogelet P, Defebvre L, Destee A. Impairment of the supervisory attentional system in early untreated patients with Parkinson's disease. J Neurol 1999; 246: 783-8.

Duyckaerts C, Gaspar P, Costa C, Bonnet AM, Hauw JJ. Dementia in Parkinson's disease. morphometric data. Adv Neurol 1993; 60: 447-55.

Ebmeier KP, Calder SA, Crawford JR, Stewart L, Besson JA, Mutch WJ. Mortality and causes of death in idiopathic Parkinson's disease: Results from the aberdeen whole population study. Scott Med J 1990; 35: 173-5.

Eckert T, Feigin A, Lewis DE, Dhawan V, Frucht S, Eidelberg D. Regional metabolic changes in parkinsonian patients with normal dopaminergic imaging. Mov Disord 2007; 22: 167-73.

Edison P, Rowe CC, Rinne JO, Ng S, Ahmed I, Kemppainen N, et al. Amyloid load in Parkinson's disease dementia and lewy body dementia measured with [11C]PIB positron emission tomography. J Neurol Neurosurg Psychiatry 2008; 79: 1331-8.

Edison P, Archer HA, Hinz R, Hammers A, Pavese N, Tai YF, et al. Amyloid, hypometabolism, and cognition in alzheimer disease: An [11C]PIB and [18F]FDG PET study. Neurology 2007; 68: 501-8.

Eerola J, Tienari PJ, Kaakkola S, Nikkinen P, Launes J. How useful is [123I]beta-CIT SPECT in clinical practice? J Neurol Neurosurg Psychiatry 2005; 76: 1211-6.

Eidelberg D, Moeller JR, Ishikawa T, Dhawan V, Spetsieris P, Chaly T, et al. Early differential diagnosis of Parkinson's disease with 18F-fluorodeoxyglucose and positron emission tomography. Neurology 1995; 45: 1995-2004.

Eidelberg D, Moeller JR, Dhawan V, Sidtis JJ, Ginos JZ, Strother SC, et al. The metabolic anatomy of Parkinson's disease: Complementary [18F] fluorodeoxyglucose and [18F]fluorodopa positron emission tomographic studies. Mov Disord 1990; 5: 203-13.

Elbaz A, Tranchant C. Epidemiologic studies of environmental exposures in Parkinson's disease. J Neurol Sci 2007; 262: 37-44.

Elgh E, Domellof M, Linder J, Edstrom M, Stenlund H, Forsgren L. Cognitive function in early Parkinson's disease: A population-based study. Eur J Neurol 2009; 16: 1278-84.

Emre M. Dementia associated with Parkinson's disease. Lancet Neurol 2003; 2: 229-37.

Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 2007; 22: 1689,707; quiz 1837.

Engler H, Forsberg A, Almkvist O, Blomquist G, Larsson E, Savitcheva I, et al. Two-year follow-up of amyloid deposition in patients with alzheimer's disease. Brain 2006; 129: 2856-66.

Evarts EV, Teravainen H, Calne DB. Reaction time in Parkinson's disease. Brain 1981; 104: 167-86.

Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR, et al. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. Ann Neurol 2006; 59: 512-9.

Fahn S, Elton R, and the members of the UPDRS Development Committee. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinson's disease. Macmillan, Florham Park NJ; 1987. p. 153-163.

Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004a; 351: 2498-508.

Fahn S, Oakes D, Shoulson I, Kieburtz K, Rudolph A, Lang A, et al. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004b; 351: 2498-508.

Faw B. Pre-frontal executive committee for perception, working memory, attention, long-term memory, motor control, and thinking: A tutorial review. Conscious Cogn 2003; 12: 83-139.

Fearnley JM, Lees AJ. Ageing and Parkinson's disease: Substantia nigra regional selectivity. Brain 1991; 114 (Pt 5): 2283-301.

Feldmann A, Illes Z, Kosztolanyi P, Illes E, Mike A, Kover F, et al. Morphometric changes of gray matter in Parkinson's disease with depression: A voxel-based morphometry study. Mov Disord 2008; 23: 42-6.

Firnau G, Sood S, Chirakal R, Nahmias C, Garnett ES. Cerebral metabolism of 6-[18F]fluoro-L-3,4-dihydroxyphenylalanine in the primate. J Neurochem 1987; 48: 1077-82.

Fodero-Tavoletti MT, Smith DP, McLean CA, Adlard PA, Barnham KJ, Foster LE, et al. In vitro characterization of pittsburgh compound-B binding to lewy bodies. J Neurosci 2007; 27: 10365-71.

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189-98.

Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. the CamPaIGN study. Brain 2004; 127: 550-60.

Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith C, Frackowiak RSJ. Statistical parametric maps in functional imaging: A general linear approach. In: Anonymous Hum Brain Mapp 2. ; 1995. p. 189-210.

Fuster JM. Frontal lobe and cognitive development. J Neurocytol 2002; 31: 373-85.

Fuxe K, Agnati LF. Receptor-receptor interactions in the central nervous system. A new integrative mechanism in synapses. Med Res Rev 1985; 5: 441-82.

Gaig C, Tolosa E. When does Parkinson's disease begin? Mov Disord 2009; 24 Suppl 2: S656-64.

Garnett ES, Nahmias C, Firnau G. Central dopaminergic pathways in hemiparkinsonism examined by positron emission tomography. Can J Neurol Sci 1984a; 11: 174-9.

Garnett ES, Nahmias C, Firnau G. Central dopaminergic pathways in hemiparkinsonism examined by positron emission tomography. Can J Neurol Sci 1984b; 11: 174-9.

Garnett ES, Firnau G, Nahmias C. Dopamine visualized in the basal ganglia of living man. Nature 1983; 305: 137-8.

Gaspar P, Gray F. Dementia in idiopathic Parkinson's disease. A neuropathological study of 32 cases. Acta Neuropathol 1984; 64: 43-52.

Ghaemi M, Hilker R, Rudolf J, Sobesky J, Heiss WD. Differentiating multiple system atrophy from Parkinson's disease: Contribution of striatal and midbrain MRI volumetry and multi-tracer PET imaging. J Neurol Neurosurg Psychiatry 2002; 73: 517-23.

Ghaemi M, Rudolf J, Hilker R, Herholz K, Heiss WD. Increased pineal fdopa uptake is related to severity of Parkinson's disease--a PET study. J Pineal Res 2001; 30: 213-9.

Gibb WR, Lees AJ. Anatomy, pigmentation, ventral and dorsal subpopulations of the substantia nigra, and differential cell death in Parkinson's disease. J Neurol Neurosurg Psychiatry 1991; 54: 388-96.

Gibb WR, Lees AJ. The relevance of the lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 745-52.

Gibb WR, Luthert PJ, Janota I, Lantos PL. Cortical lewy body dementia: Clinical features and classification. J Neurol Neurosurg Psychiatry 1989; 52: 185-92.

Gilman S, Koeppe RA, Little R, An H, Junck L, Giordani B, et al. Differentiation of alzheimer's disease from dementia with lewy bodies utilizing positron emission tomography with [18F]fluorodeoxyglucose and neuropsychological testing. Exp Neurol 2005; 191 Suppl 1: S95-S103.

Girotti F, Soliveri P, Carella F, Piccolo I, Caffarra P, Musicco M, et al. Dementia and cognitive impairment in Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 1498-502.

Goetz CG, Emre M, Dubois B. Parkinson's disease dementia: Definitions, guidelines, and research perspectives in diagnosis. Ann Neurol 2008; 64 Suppl 2: S81-92.

Goker-Alpan O, Schiffmann R, LaMarca ME, Nussbaum RL, McInerney-Leo A, Sidransky E. Parkinsonism among gaucher disease carriers. J Med Genet 2004; 41: 937-40.

Gomperts SN, Rentz DM, Moran E, Becker JA, Locascio JJ, Klunk WE, et al. Imaging amyloid deposition in lewy body diseases. Neurology 2008; 71: 903-10.

Grace AA. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: A hypothesis for the etiology of schizophrenia. Neuroscience 1991; 41: 1-24.

Grace AA, Bunney BS. The control of firing pattern in nigral dopamine neurons: Single spike firing. J Neurosci 1984; 4: 2866-76.

Grahn JA, Parkinson JA, Owen AM. The cognitive functions of the caudate nucleus. Prog Neurobiol 2008; 86: 141-55.

Greffard S, Verny M, Bonnet AM, Seilhean D, Hauw JJ, Duyckaerts C. A stable proportion of lewy body bearing neurons in the substantia nigra suggests a model in which the lewy body causes neuronal death. Neurobiol Aging 2010; 31: 99-103.

Grossman M. Sentence processing in Parkinson's disease. Brain Cogn 1999; 40: 387-413.

Grossman M, Crino P, Reivich M, Stern MB, Hurtig HI. Attention and sentence processing deficits in Parkinson's disease: The role of anterior cingulate cortex. Cereb Cortex 1992; 2: 513-25.

Grossman M, Cooke A, DeVita C, Lee C, Alsop D, Detre J, et al. Grammatical and resource components of sentence processing in Parkinson's disease: An fMRI study. Neurology 2003; 60: 775-81.

Gurd JM, Ward CD. Retrieval from semantic and letter-initial categories in patients with Parkinson's disease. Neuropsychologia 1989; 27: 743-6.

Haber S, McFarland NR. The place of the thalamus in frontal cortical-basal ganglia circuits. Neuroscientist 2001; 7: 315-24.

Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. J Neurosci 2000; 20: 2369-82.

Hakim AM, Mathieson G. Dementia in parkinson disease: A neuropathologic study. Neurology 1979; 29: 1209-14.

Halliday G, Harding A, Paxinos G. Serotonin and tachykinin system. In: Paxinos G, editor. The Rat Nervous System. San Diego: Academic Press; 1995. p. 929-974.

Halliday G, Hely M, Reid W, Morris J. The progression of pathology in longitudinally followed patients with Parkinson's disease. Acta Neuropathol 2008; 115: 409-15.

Halliday GM. Thalamic changes in Parkinson's disease. Parkinsonism Relat Disord 2009; 15 Suppl 3: S152-5.

Hamacher K, Coenen HH, Stocklin G. Efficient stereospecific synthesis of no-carrier-added 2-[18F]-fluoro-2-deoxy-D-glucose using aminopolyether supported nucleophilic substitution. J Nucl Med 1986; 27: 235-8.

Harding AJ, Halliday GM. Cortical lewy body pathology in the diagnosis of dementia. Acta Neuropathol 2001; 102: 355-63.

Hart RP, Wade JB, Calabrese VP, Colenda CC. Vigilance performance in Parkinson's disease and depression. Journal of Clinical and Experimental Neuropsychology 1998; 20: 111-7.

Hayes AE, Davidson MC, Keele SW, Rafal RD. Toward a functional analysis of the basal ganglia. J Cogn Neurosci 1998; 10: 178-98.

Healy DG, Falchi M, O'Sullivan SS, Bonifati V, Durr A, Bressman S, et al. Phenotype, genotype, and worldwide genetic penetrance of LRRK2-associated Parkinson's disease: A case-control study. Lancet Neurol 2008; 7: 583-90.

Hely MA, Morris JG, Traficante R, Reid WG, O'Sullivan DJ, Williamson PM. The sydney multicentre study of Parkinson's disease: Progression and mortality at 10 years. J Neurol Neurosurg Psychiatry 1999; 67: 300-7.

Herlofson K, Lie SA, Arsland D, Larsen JP. Mortality and parkinson disease: A community based study. Neurology 2004; 62: 937-42.

Hernan MA, Zhang SM, Rueda-deCastro AM, Colditz GA, Speizer FE, Ascherio A. Cigarette smoking and the incidence of Parkinson's disease in two prospective studies. Ann Neurol 2001; 50: 780-6.

Hilker R, Thomas AV, Klein JC, Weisenbach S, Kalbe E, Burghaus L, et al. Dementia in parkinson disease: Functional imaging of cholinergic and dopaminergic pathways. Neurology 2005; 65: 1716-22.

Hirvonen J, van Erp TG, Huttunen J, Nagren K, Huttunen M, Aalto S, et al. Striatal dopamine D1 and D2 receptor balance in twins at increased genetic risk for schizophrenia. Psychiatry Res 2006; 146: 13-20.

Hobson P, Meara J. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the united kingdom. Mov Disord 2004; 19: 1043-9.

Hoehn MM, Yahr MD. Parkinsonism: Onset, progression and mortality. Neurology 1967; 17: 427-42.

Hof PR, Mufson EJ, Morrison JH. Human orbitofrontal cortex: Cytoarchitecture and quantitative immunohistochemical parcellation. J Comp Neurol 1995; 359: 48-68.

Hoffman JM, Welsh-Bohmer KA, Hanson M, Crain B, Hulette C, Earl N, et al. FDG PET imaging in patients with pathologically verified dementia. J Nucl Med 2000; 41: 1920-8.

Holthoff VA, Vieregge P, Kessler J, Pietrzyk U, Herholz K, Bonner J, et al. Discordant twins with Parkinson's disease: Positron emission tomography and early signs of impaired cognitive circuits. Ann Neurol 1994; 36: 176-82.

Holthoff-Detto VA, Kessler J, Herholz K, Bonner H, Pietrzyk U, Wurker M, et al. Functional effects of striatal dysfunction in parkinson disease. Arch Neurol 1997; 54: 145-50.

Hoshi H, Kuwabara H, Leger G, Cumming P, Guttman M, Gjedde A. 6-[18F]fluoro-L-dopa metabolism in living human brain: A comparison of six analytical methods. J Cereb Blood Flow Metab 1993; 13: 57-69.

Hsieh S, Lee CY, Tai CT. Set-shifting aptitude in Parkinson's disease: External versus internal cues. Psychol Rep 1995; 77: 339-49.

Hu MT, White SJ, Chaudhuri KR, Morris RG, Bydder GM, Brooks DJ. Correlating rates of cerebral atrophy in Parkinson's disease with measures of cognitive decline. J Neural Transm 2001; 108: 571-80.

Hu MT, Taylor-Robinson SD, Chaudhuri KR, Bell JD, Labbe C, Cunningham VJ, et al. Cortical dysfunction in non-demented Parkinson's disease patients: A combined (31)P-MRS and (18)FDG-PET study. Brain 2000; 123 (Pt 2): 340-52.

Huber SJ, Shuttleworth EC, Freidenberg DL. Neuropsychological differences between the dementias of alzheimer's and Parkinson's diseases. Arch Neurol 1989; 46: 1287-91.

Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of lewy body Parkinson's disease. Neurology 2001a; 57: 1497-9.

Hughes AJ, Daniel SE, Lees AJ. Improved accuracy of clinical diagnosis of lewy body Parkinson's disease. Neurology 2001b; 57: 1497-9.

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: 861-70.

Hughes AJ, Daniel SE, Blankson S, Lees AJ. A clinicopathologic study of 100 cases of Parkinson's disease. Arch Neurol 1993; 50: 140-8.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992a; 55: 181-4.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: A clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992b; 55: 181-4.

Hurtig HI, Trojanowski JQ, Galvin J, Ewbank D, Schmidt ML, Lee VM, et al. Alpha-synuclein cortical lewy bodies correlate with dementia in Parkinson's disease. Neurology 2000; 54: 1916-21.

Ibarretxe-Bilbao N, Ramirez-Ruiz B, Tolosa E, Marti MJ, Valldeoriola F, Bargallo N, et al. Hippocampal head atrophy predominance in Parkinson's disease with hallucinations and with dementia. J Neurol 2008; 255: 1324-31.

Imamura T, Ishii K, Sasaki M, Kitagaki H, Yamaji S, Hirono N, et al. Regional cerebral glucose metabolism in dementia with lewy bodies and alzheimer's disease: A comparative study using positron emission tomography. Neurosci Lett 1997; 235: 49-52.

Ince P, Irving D, MacArthur F, Perry RH. Quantitative neuropathological study of alzheimer-type pathology in the hippocampus: Comparison of senile dementia of alzheimer type, senile dementia of lewy body type, Parkinson's disease and non-demented elderly control patients. J Neurol Sci 1991; 106: 142-52.

Ishikawa T, Dhawan V, Chaly T, Margouleff C, Robeson W, Dahl JR, et al. Clinical significance of striatal DOPA decarboxylase activity in Parkinson's disease. J Nucl Med 1996a; 37: 216-22.

Ishikawa T, Dhawan V, Kazumata K, Chaly T, Mandel F, Neumeyer J, et al. Comparative nigrostriatal dopaminergic imaging with iodine-123-beta CIT-FP/SPECT and fluorine-18-FDOPA/PET. J Nucl Med 1996b; 37: 1760-5.

Ito K, Morrish PK, Rakshi JS, Uema T, Ashburner J, Bailey DL, et al. Statistical parametric mapping with 18F-dopa PET shows bilaterally reduced striatal and nigral dopaminergic function in early Parkinson's disease. J Neurol Neurosurg Psychiatry 1999; 66: 754-8.

Ito K, Nagano-Saito A, Kato T, Arahata Y, Nakamura A, Kawasumi Y, et al. Striatal and extrastriatal dysfunction in Parkinson's disease with dementia: A 6-[18F]fluoro-L-dopa PET study. Brain 2002; 125: 1358-65.

Janvin C, Aarsland D, Larsen JP, Hugdahl K. Neuropsychological profile of patients with Parkinson's disease without dementia. Dement Geriatr Cogn Disord 2003; 15: 126-31.

Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: Progression to dementia. Mov Disord 2006; 21: 1343-9.

Javoy-Agid F, Scatton B, Ruberg M, L'Heureux R, Cervera P, Raisman R, et al. Distribution of monoaminergic, cholinergic, and GABAergic markers in the human cerebral cortex. Neuroscience 1989; 29: 251-9.

Jellinger K. Overview of morphological changes in Parkinson's disease. Adv Neurol 1987; 45: 1-18.

Jellinger K, Braak H, Braak E, Fischer P. Alzheimer lesions in the entorhinal region and isocortex in Parkinson's and alzheimer's diseases. Ann N Y Acad Sci 1991; 640: 203-9.

Jellinger KA, Attems J. Prevalence and impact of vascular and alzheimer pathologies in lewy body disease. Acta Neuropathol 2008; 115: 427-36.

Jellinger KA, Seppi K, Wenning GK. Clinical and neuropathological correlates of lewy body disease. Acta Neuropathol 2003; 106: 188,9; author reply 190.

Jellinger KA, Seppi K, Wenning GK, Poewe W. Impact of coexistent alzheimer pathology on the natural history of Parkinson's disease. J Neural Transm 2002; 109: 329-39.

Joel D, Weiner I. The connections of the dopaminergic system with the striatum in rats and primates: An analysis with respect to the functional and compartmental organization of the striatum. Neuroscience 2000; 96: 451-74.

Junque C, Ramirez-Ruiz B, Tolosa E, Summerfield C, Marti MJ, Pastor P, et al. Amygdalar and hippocampal MRI volumetric reductions in Parkinson's disease with dementia. Mov Disord 2005; 20: 540-4.

Kaasinen V, Nurmi E, Bruck A, Eskola O, Bergman J, Solin O, et al. Increased frontal [(18)F]fluorodopa uptake in early Parkinson's disease: Sex differences in the prefrontal cortex. Brain 2001; 124: 1125-30.

Kalaitzakis ME, Graeber MB, Gentleman SM, Pearce RK. Striatal beta-amyloid deposition in parkinson disease with dementia. J Neuropathol Exp Neurol 2008; 67: 155-61.

Kehagia AA, Murray GK, Robbins TW. Learning and cognitive flexibility: Frontostriatal function and monoaminergic modulation. Curr Opin Neurobiol 2010; 20: 199-204.

Kelley AE, Domesick VB, Nauta WJ. The amygdalostriatal projection in the rat--an anatomical study by anterograde and retrograde tracing methods. Neuroscience 1982; 7: 615-30.

Kemp JM, Powell TP. The structure of the caudate nucleus of the cat: Light and electron microscopy.

Philos Trans R Soc Lond B Biol Sci 1971; 262: 383-401.

Kemppainen NM, Aalto S, Wilson IA, Nagren K, Helin S, Bruck A, et al. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. Neurology 2007; 68: 1603-6.

Kemppainen NM, Aalto S, Wilson IA, Nagren K, Helin S, Bruck A, et al. Voxel-based analysis of PET amyloid ligand [11C]PIB uptake in alzheimer disease. Neurology 2006; 67: 1575-80.

Kempster PA, Hurwitz B, Lees AJ. A new look at james Parkinson's essay on the shaking palsy. Neurology 2007; 69: 482-5.

Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. pathophysiologic and clinical implications. N Engl J Med 1988a; 318: 876-80.

Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease. pathophysiologic and clinical implications. N Engl J Med 1988b; 318: 876-80.

Kita H, Kitai ST. Efferent projections of the subthalamic nucleus in the rat: Light and electron microscopic analysis with the PHA-L method. J Comp Neurol 1987; 260: 435-52.

Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in alzheimer's disease with pittsburgh compound-B. Ann Neurol 2004; 55: 306-19.

Koike Y, Takahashi A. Autonomic dysfunction in Parkinson's disease. Eur Neurol 1997; 38 Suppl 2: 8-12.

Kosaka K, Yoshimura M, Ikeda K, Budka H. Diffuse type of lewy body disease: Progressive dementia with abundant cortical lewy bodies and senile changes of varying degree--a new disease? Clin Neuropathol 1984; 3: 185-92.

Kuhl DE, Metter EJ, Riege WH. Patterns of local cerebral glucose utilization determined in Parkinson's disease by the [18F]fluorodeoxyglucose method. Ann Neurol 1984; 15: 419-24.

Kuopio AM, Marttila RJ, Helenius H, Rinne UK. Changing epidemiology of Parkinson's disease in southwestern finland. Neurology 1999; 52: 302-8.

Laakso MP, Partanen K, Riekkinen P, Lehtovirta M, Helkala EL, Hallikainen M, et al. Hippocampal volumes in alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: An MRI study. Neurology 1996; 46: 678-81.

Lacadie CM, Fulbright RK, Rajeevan N, Constable RT, Papademetris X. More accurate talairach coordinates for neuroimaging using non-linear registration. Neuroimage 2008; 42: 717-25.

Lancaster JL, Woldorff MG, Parsons LM, Liotti M, Freitas CS, Rainey L, et al. Automated talairach atlas labels for functional brain mapping. Hum Brain Mapp 2000; 10: 120-31.

Lang AE, Lozano AM. Parkinson's disease. first of two parts. N Engl J Med 1998a; 339: 1044-53.

Lang AE, Lozano AM. Parkinson's disease. second of two parts. N Engl J Med 1998b; 339: 1130-43.

Lange KW, Paul GM, Robbins TW, Marsden CD. L-dopa and frontal cognitive function in Parkinson's disease. Adv Neurol 1993; 60: 475-8.

Lange KW, Robbins TW, Marsden CD, James M, Owen AM, Paul GM. L-dopa withdrawal in Parkinson's disease selectively impairs cognitive performance in tests sensitive to frontal lobe dysfunction. Psychopharmacology (Berl) 1992; 107: 394-404.

Lashley T, Holton JL, Gray E, Kirkham K, O'Sullivan SS, Hilbig A, et al. Cortical alpha-synuclein load is associated with amyloid-beta plaque burden in a subset of Parkinson's disease patients. Acta Neuropathol 2008; 115: 417-25.

Lee CS, Schulzer M, Mak EK, Snow BJ, Tsui JK, Calne S, et al. Clinical observations on the rate of progression of idiopathic parkinsonism. Brain 1994; 117 (Pt 3): 501-7.

Leenders KL, Palmer AJ, Quinn N, Clark JC, Firnau G, Garnett ES, et al. Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. J Neurol Neurosurg Psychiatry 1986a; 49: 853-60.

Leenders KL, Palmer AJ, Quinn N, Clark JC, Firnau G, Garnett ES, et al. Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. J Neurol Neurosurg Psychiatry 1986b; 49: 853-60.

Levin BE, Tomer R, Rey GJ. Cognitive impairments in Parkinson's disease. Neurol Clin 1992; 10: 471-85.

Levin BE, Llabre MM, Reisman S, Weiner WJ, Sanchez-Ramos J, Singer C, et al. Visuospatial impairment in Parkinson's disease. Neurology 1991; 41: 365-9.

Levy G, Tang MX, Louis ED, Cote LJ, Alfaro B, Mejia H, et al. The association of incident dementia with mortality in PD. Neurology 2002a; 59: 1708-13.

Levy G, Jacobs DM, Tang MX, Cote LJ, Louis ED, Alfaro B, et al. Memory and executive function impairment predict dementia in Parkinson's disease. Mov Disord 2002b; 17: 1221-6.

Lewis D, Seasack S. Dopamine systems in the primate brain. In: Bloom F, Björklund A, Hökfelt T, editors. Handbook of chemical neuroanatomy. Amsterdam: Elsevier; 1997. p. 263-275.

Lewis SJ, 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. J Neurosci 2003; 23: 6351-6.

Lichter DG. Movement disorders and frontal-subcortical circuits. In: Lichter DJ, Cummings JL, editors. Frontal-subcortical Circuits in Psychiatric and neurological disorders. New York: Guilford Press; 2000. p. 260-313.

Lilienfeld DE, Perl DP. Projected neurodegenerative disease mortality in the united states, 1990-2040. Neuroepidemiology 1993; 12: 219-28.

Lohle M, Reichmann H. Clinical neuroprotection in Parkinson's disease - still waiting for the breakthrough. J Neurol Sci 2010; 289: 104-14.

Lopresti BJ, Klunk WE, Mathis CA, Hoge JA, Ziolko SK, Lu X, et al. Simplified quantification of pittsburgh compound B amyloid imaging PET studies: A comparative analysis. J Nucl Med 2005; 46: 1959-72.

Louis ED, Marder K, Cote L, Tang M, Mayeux R. Mortality from parkinson disease. Arch Neurol 1997; 54: 260-4.

Ma AJ, Zhang BS, Pan XD, Gao S, Li ZG. Cerebral glucose metabolism in Parkinson's disease with dementia. Zhonghua Yi Xue Za Zhi 2008a; 88: 2623-8.

Ma AJ, Zhang BS, Pan XD, Gao S, Li ZG. Cerebral glucose metabolism in Parkinson's disease with dementia]. Zhonghua Yi Xue Za Zhi 2008b; 88: 2623-8.

Mahieux F, Fenelon G, Flahault A, Manifacier MJ, Michelet D, Boller F. Neuropsychological prediction of dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 1998; 64: 178-83.

Mahler ME, Cummings JL. Alzheimer disease and the dementia of parkinson disease: Comparative investigations. Alzheimer Dis Assoc Disord 1990; 4: 133-49.

Marek K, Jennings D, Seibyl J, Group tPS. Long-term follow-up of patients with scans without evidence of dopaminergic deficit (SWEDD) in the ELLDOPA study [abstract]. Neurology 2005: A274.

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. Neurosci Lett 1999; 260: 77-80.

Marras C, Rochon P, Lang AE. Predicting motor decline and disability in parkinson disease: A systematic review. Arch Neurol 2002; 59: 1724-8.

Marshall VL, Patterson J, Hadley DM, Grosset KA, Grosset DG. Two-year follow-up in 150 consecutive cases with normal dopamine transporter imaging. Nucl Med Commun 2006; 27: 933-7.

Martin WR, Wieler M, Gee M, Camicioli R. Temporal lobe changes in early, untreated Parkinson's disease. Mov Disord 2009; 24: 1949-54.

Martinez-Martin P. Rating scales in Parkinson's disease. In: Jankovic J, Tolosa E, editors. Parkinson's disease and movement disorders. Baltimore: Williams & Wilkins; 1993. p. 218-292.

Marttila RJ, Rinne UK. Disability and progression in Parkinson's disease. Acta Neurol Scand 1977; 56: 159-69.

Mastaglia FL, Johnsen RD, Byrnes ML, Kakulas BA. Prevalence of amyloid-beta deposition in the cerebral cortex in Parkinson's disease. Mov Disord 2003; 18: 81-6.

Mathias CJ. Cardiovascular autonomic dysfunction in parkinsonian patients. Clin Neurosci 1998; 5: 153-66.

Matsui H, Udaka F, Miyoshi T, Hara N, Tamura A, Oda M, et al. Frontal assessment battery and brain perfusion image in Parkinson's disease. J Geriatr Psychiatry Neurol 2006; 19: 41-5.

Mattila PM, Roytta M, Torikka H, Dickson DW, Rinne JO. Cortical lewy bodies and alzheimer-type changes in patients with Parkinson's disease. Acta Neuropathol 1998; 95: 576-82.

Mayeux R, Stern Y, Sano M, Williams JB, Cote LJ. The relationship of serotonin to depression in Parkinson's disease. Mov Disord 1988; 3: 237-44.

Mayeux R, Chen J, Mirabello E, Marder K, Bell K, Dooneief G, et al. An estimate of the incidence of dementia in idiopathic Parkinson's disease. Neurology 1990; 40: 1513-7.

McFadden L, Mohr E, Sampson M, Mendis T, Grimes JD. A profile analysis of demented and nondemented Parkinson's disease patients. Adv Neurol 1996; 69: 339-41.

McGeorge AJ, Faull RL. The organization of the projection from the cerebral cortex to the striatum in the rat. Neuroscience 1989; 29: 503-37.

McGowan S, Lawrence AD, Sales T, Quested D, Grasby P. Presynaptic dopaminergic dysfunction in schizophrenia: A positron emission tomographic [18F]fluorodopa study. Arch Gen Psychiatry 2004; 61: 134-42.

McKeith I. Commentary: DLB and PDD: The same or different? is there a debate? Int Psychogeriatr 2009; 21: 220-4.

McKeith I, Mintzer J, Aarsland D, Burn D, Chiu H, Cohen-Mansfield J, et al. Dementia with lewy bodies. Lancet Neurol 2004; 3: 19-28.

McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of

dementia with lewy bodies: Third report of the DLB consortium. Neurology 2005; 65: 1863-72.

Meara J, Bhowmick BK, Hobson P. Accuracy of diagnosis in patients with presumed Parkinson's disease. Age Ageing 1999; 28: 99-102.

Melzer TR, Watts R, Macaskill MR, Pitcher TL, Livingston L, Keenan RJ, et al. Grey matter atrophy in cognitively impaired Parkinson's disease. J Neurol Neurosurg Psychiatry 2011.

Mentis MJ, McIntosh AR, Perrine K, Dhawan V, Berlin B, Feigin A, et al. Relationships among the metabolic patterns that correlate with mnemonic, visuospatial, and mood symptoms in Parkinson's disease. Am J Psychiatry 2002; 159: 746-54.

Metter EJ, Kuhl DE, Riege WH. Brain glucose metabolism in Parkinson's disease. Adv Neurol 1990; 53: 135-9.

Meyer JH, Gunn RN, Myers R, Grasby PM. Assessment of spatial normalization of PET ligand images using ligand-specific templates. Neuroimage 1999; 9: 545-53.

Minoshima S, Foster NL, Sima AA, Frey KA, Albin RL, Kuhl DE. Alzheimer's disease versus dementia with lewy bodies: Cerebral metabolic distinction with autopsy confirmation. Ann Neurol 2001; 50: 358-65.

Mintun MA. Utilizing advanced imaging and surrogate markers across the spectrum of alzheimer's disease. CNS Spectr 2005; 10: 13-6.

Mintun MA, Larossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, et al. 11C]PIB in a nondemented population: Potential antecedent marker of alzheimer disease. Neurology 2006; 67: 446-52.

Morecraft RJ, Geula C, Mesulam MM. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol 1992; 323: 341-58.

Morris JC, Heyman A, Mohs RC, Hughes JP, Vanbelle G, Fillenbaum G, et al. The consortium to establish A registry for alzheimers-disease (cerad) .1. clinical and neuropsychological assessment of alzheimers-disease. Neurology 1989; 39: 1159-65.

Morrish PK, Sawle GV, Brooks DJ. Regional changes in [18F]dopa metabolism in the striatum in Parkinson's disease. Brain 1996a; 119 (Pt 6): 2097-103.

Morrish PK, Sawle GV, Brooks DJ. Regional changes in [18F]dopa metabolism in the striatum in Parkinson's disease. Brain 1996b; 119 (Pt 6): 2097-103.

Morrish PK, Sawle GV, Brooks DJ. Clinical and [18F] dopa PET findings in early Parkinson's disease. J Neurol Neurosurg Psychiatry 1995; 59: 597-600.

Morrish PK, Rakshi JS, Bailey DL, Sawle GV, Brooks DJ. Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with

[18F]dopa PET. J Neurol Neurosurg Psychiatry 1998; 64: 314-9.

Mosconi L, Tsui WH, Rusinek H, De Santi S, Li Y, Wang GJ, et al. Quantitation, regional vulnerability, and kinetic modeling of brain glucose metabolism in mild alzheimer's disease. Eur J Nucl Med Mol Imaging 2007; 34: 1467-79.

Muller J, Wenning GK, Verny M, McKee A, Chaudhuri KR, Jellinger K, et al. Progression of dysarthria and dysphagia in postmortem-confirmed parkinsonian disorders. Arch Neurol 2001; 58: 259-64.

Muller U, Wachter T, Barthel H, Reuter M, von Cramon DY. Striatal [123I]beta-CIT SPECT and prefrontal cognitive functions in Parkinson's disease. J Neural Transm 2000; 107: 303-19.

Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed parkinson disease. Neurology 2005; 65: 1239-45.

Nagano AS, Ito K, Kato T, Arahata Y, Kachi T, Hatano K, et al. Extrastriatal mean regional uptake of fluorine-18-FDOPA in the normal aged brain--an approach using MRI-aided spatial normalization. Neuroimage 2000; 11: 760-6.

Nagano-Saito A, Washimi Y, Arahata Y, Kachi T, Lerch JP, Evans AC, et al. Cerebral atrophy and its relation to cognitive impairment in parkinson disease. Neurology 2005; 64: 224-9.

Nagano-Saito A, Kato T, Arahata Y, Washimi Y, Nakamura A, Abe Y, et al. Cognitive- and motor-related regions in Parkinson's disease: FDOPA and FDG PET studies. Neuroimage 2004; 22: 553-61.

Nahmias C, Garnett ES, Firnau G, Lang A. Striatal dopamine distribution in parkinsonian patients during life. J Neurol Sci 1985a; 69: 223-30.

Nahmias C, Garnett ES, Firnau G, Lang A. Striatal dopamine distribution in parkinsonian patients during life. J Neurol Sci 1985b; 69: 223-30.

Nakamura T, Dhawan V, Chaly T, Fukuda M, Ma Y, Breeze R, et al. Blinded positron emission tomography study of dopamine cell implantation for Parkinson's disease. Ann Neurol 2001; 50: 181-7.

Namavari M, Bishop A, Satyamurthy N, Bida G, Barrio JR. Regioselective radiofluorodestannylation with [F-18] F2 and [F-18] Ch3Coof - A high-yield synthesis of 6-[F-18]fluoro-L-dopa. Applied Radiation and Isotopes 1992; 43: 989-96.

Nicola SM, Surmeier J, Malenka RC. Dopaminergic modulation of neuronal excitability in the striatum and nucleus accumbens. Annu Rev Neurosci 2000; 23: 185-215.

Nieoullon A. Dopamine and the regulation of cognition and attention. Prog Neurobiol 2002; 67: 53-83.

Nieuwenhuys R. Chemoarchitecture of the brain. Dordrecht: Kluwer Academic Publishers; 1985.

Nishio Y, Hirayama K, Takeda A, Hosokai Y, Ishioka T, Suzuki K, et al. Corticolimbic gray matter loss in Parkinson's disease without dementia. Eur J Neurol 2010; 17: 1090-7.

Nurmi E, Ruottinen HM, Bergman J, Haaparanta M, Solin O, Sonninen P, et al. Rate of progression in Parkinson's disease: A 6-[18F]fluoro-L-dopa PET study. Mov Disord 2001a; 16: 608-15.

Nurmi E, Ruottinen HM, Bergman J, Haaparanta M, Solin O, Sonninen P, et al. Rate of progression in Parkinson's disease: A 6-[18F]fluoro-L-dopa PET study. Mov Disord 2001b; 16: 608-15.

Olanow CW. The scientific basis for the current treatment of Parkinson's disease. Annu Rev Med 2004; 55: 41-60.

Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, et al. A double-blind, delayed-start trial of rasagiline in Parkinson's disease. N Engl J Med 2009; 361: 1268-78.

Owen AM. Cognitive dysfunction in Parkinson's disease: The role of frontostriatal circuitry. Neuroscientist 2004; 10: 525-37.

Owen AM, Iddon JL, Hodges JR, Summers BA, Robbins TW. Spatial and non-spatial working memory at different stages of Parkinson's disease. Neuropsychologia 1997; 35: 519-32.

Owen AM, 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 (Pt 6): 1727-51.

Pahwa R, Paolo A, Troster A, Koller W. Cognitive impairment in Parkinson's disease. Eur J Neurol 1998; 5: 431-41.

Paisan-Ruiz C, Jain S, Evans EW, Gilks WP, Simon J, van der Brug M, et al. Cloning of the gene containing mutations that cause PARK8-linked Parkinson's disease. Neuron 2004; 44: 595-600.

Pal PK, Lee CS, Samii A, Schulzer M, Stoessl AJ, Mak EK, et al. Alternating two finger tapping with contralateral activation is an objective measure of clinical severity in Parkinson's disease and correlates with PET. Parkinsonism Relat Disord 2001; 7: 305-9.

Parent A. Extrinsic connections of the basal ganglia. Trends Neurosci 1990; 13: 254-8.

Park J, Lee SB, Lee S, Kim Y, Song S, Kim S, et al. Mitochondrial dysfunction in drosophila PINK1 mutants is complemented by parkin. Nature 2006; 441: 1157-61.

Parkinson Study Group. A controlled, randomized, delayed-start study of rasagiline in early parkinson disease. Arch Neurol 2004; 61: 561-6.

Parkkinen L, Pirttila T, Tervahauta M, Alafuzoff I. Widespread and abundant alpha-synuclein pathology in a neurologically unimpaired subject. Neuropathology 2005a; 25: 304-14.

Parkkinen L, Kauppinen T, Pirttila T, Autere JM, Alafuzoff I. Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. Ann Neurol 2005b; 57: 82-91.

Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data. generalizations. J Cereb Blood Flow Metab 1985; 5: 584-90.

Pellizari CA, Chen GTY, Spelbring DR, Weichselbaum RR, Chen CT. Accurate three-dimensional registration of CT, PET, and/or MR images of the brain. J Comput Assist Tomogr 1989: 20-26.

Peppard RF, Martin WR, Carr GD, Grochowski E, Schulzer M, Guttman M, et al. Cerebral glucose metabolism in Parkinson's disease with and without dementia. Arch Neurol 1992; 49: 1262-8.

Perry EK, Marshall E, Perry RH, Irving D, Smith CJ, Blessed G, et al. Cholinergic and dopaminergic activities in senile dementia of lewy body type. Alzheimer Dis Assoc Disord 1990; 4: 87-95.

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. J Neurol Neurosurg Psychiatry 1985; 48: 413-21.

Piccini P, Burn DJ, Ceravolo R, Maraganore D, Brooks DJ. The role of inheritance in sporadic Parkinson's disease: Evidence from a longitudinal study of dopaminergic function in twins. Ann Neurol 1999; 45: 577-82.

Piccini P, Morrish PK, Turjanski N, Sawle GV, Burn DJ, Weeks RA, et al. Dopaminergic function in familial Parkinson's disease: A clinical and 18F-dopa positron emission tomography study. Ann Neurol 1997; 41: 222-9.

Poewe W, Mahlknecht P. The clinical progression of Parkinson's disease. Parkinsonism Relat Disord 2009; 15 Suppl 4: S28-32.

Polito C, Berti V, Ramat S, Vanzi E, De Cristofaro MT, Pellicano G, et al. Interaction of caudate dopamine depletion and brain metabolic changes with cognitive dysfunction in early Parkinson's disease. Neurobiol Aging 2010.

Polymeropoulos MH, Lavedan C, Leroy E, Ide SE, Dehejia A, Dutra A, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. Science 1997; 276: 2045-7.

Pycock CJ, Kerwin RW, Carter CJ. Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. Nature 1980; 286: 74-6.

Quigley EM. Gastrointestinal dysfunction in Parkinson's disease. Semin Neurol 1996; 16: 245-50.

Quinn NP, Rossor MN, Marsden CD. Dementia and Parkinson's disease--pathological and neurochemical considerations. Br Med Bull 1986; 42: 86-90.

Rajput AH, Voll A, Rajput ML, Robinson CA, Rajput A. Course in parkinson disease subtypes: A 39-year clinicopathologic study. Neurology 2009; 73: 206-12.

Rajput AH, Sitte HH, Rajput A, Fenton ME, Pifl C, Hornykiewicz O. Globus pallidus dopamine and parkinson motor subtypes: Clinical and brain biochemical correlation. Neurology 2008; 70: 1403-10.

Rakshi JS, Uema T, Ito K, Bailey DL, Morrish PK, Ashburner J, et al. Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [(18)F]dopa-PET study. Brain 1999; 122 (Pt 9): 1637-50.

Ramirez-Ruiz B, Marti MJ, Tolosa E, Bartres-Faz D, Summerfield C, Salgado-Pineda P, et al. Longitudinal evaluation of cerebral morphological changes in Parkinson's disease with and without dementia. J Neurol 2005; 252: 1345-52.

Raskin SA, Borod JC, Tweedy JR. Set-shifting and spatial orientation in patients with Parkinson's disease. J Clin Exp Neuropsychol 1992a; 14: 801-21.

Raskin SA, Sliwinski M, Borod JC. Clustering strategies on tasks of verbal fluency in Parkinson's disease. Neuropsychologia 1992b; 30: 95-9.

Raskin SA, Borod JC, Tweedy J. Neuropsychological aspects of Parkinson's disease. Neuropsychol Rev 1990; 1: 185-221.

Reivich M, Kuhl D, Wolf A, Greenberg J, Phelps M, Ido T, et al. The [18F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. Circ Res 1979; 44: 127-37.

Revonsuo A, Portin R, Koivikko L, Rinne JO, Rinne UK. Slowing of information processing in Parkinson's disease. Brain Cogn 1993; 21: 87-110.

Richards M, Cote LJ, Stern Y. Executive function in Parkinson's disease: Set-shifting or set-maintenance? J Clin Exp Neuropsychol 1993; 15: 266-79.

Ridenour TA, Dean RS. Parkinson's disease and neuropsychological assessment. Int J Neurosci 1999; 99: 1-18.

Riekkinen P,Jr, Kejonen K, Laakso MP, Soininen H, Partanen K, Riekkinen M. Hippocampal atrophy is related to impaired memory, but not frontal functions in non-demented Parkinson's disease patients. Neuroreport 1998; 9: 1507-11.

Rinne JO, Lonnberg P, Marjamaki P, Rinne UK. Brain muscarinic receptor subtypes are differently affected in alzheimer's disease and Parkinson's disease. Brain Res 1989a; 483: 402-6.

Rinne JO, Rummukainen J, Paljarvi L, Rinne UK. Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. Ann Neurol 1989b; 26: 47-50.

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: 470-5.

Rinne OJ, Nurmi E, Ruottinen HM, Bergman J, Eskola O, Solin O. (18)F]FDOPA and [(18)F]CFT are both sensitive PET markers to detect presynaptic dopaminergic hypofunction in early Parkinson's disease. Synapse 2001; 40: 193-200.

Rippon GA, Marder KS. Dementia in Parkinson's disease. Adv Neurol 2005; 96: 95-113.

Rougemont D, Baron JC, Collard P, Bustany P, Comar D, Agid Y. Local cerebral glucose utilisation in treated and untreated patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1984; 47: 824-30.

Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G, et al. Imaging beta-amyloid burden in aging and dementia. Neurology 2007; 68: 1718-25.

Rubchinsky LL, Kopell N, Sigvardt KA. Modeling facilitation and inhibition of competing motor programs in basal ganglia subthalamic nucleus-pallidal circuits. Proc Natl Acad Sci U S A 2003; 100: 14427-32.

Ruberg M, Rieger F, Villageois A, Bonnet AM, Agid Y. Acetylcholinesterase and butyrylcholinesterase in frontal cortex and cerebrospinal fluid of demented and non-demented patients with Parkinson's disease. Brain Res 1986; 362: 83-91.

Rudow G, O'Brien R, Savonenko AV, Resnick SM, Zonderman AB, Pletnikova O, et al. Morphometry of the human substantia nigra in ageing and Parkinson's disease. Acta Neuropathol 2008; 115: 461-70.

Sasaki M, Ichiya Y, Hosokawa S, Otsuka M, Kuwabara Y, Fukumura T, et al. Regional cerebral glucose metabolism in patients with Parkinson's disease with or without dementia. Ann Nucl Med 1992a; 6: 241-6.

Sasaki M, Ichiya Y, Hosokawa S, Otsuka M, Kuwabara Y, Fukumura T, et al. Regional cerebral glucose metabolism in patients with Parkinson's disease with or without dementia. Ann Nucl Med 1992b; 6: 241-6.

Sawamoto N, Honda M, Hanakawa T, Fukuyama H, Shibasaki H. Cognitive slowing in Parkinson's disease: A behavioral evaluation independent of motor slowing. J Neurosci 2002; 22: 5198-203.

Schapira AH. Evidence for mitochondrial dysfunction in Parkinson's disease--a critical appraisal. Mov Disord 1994; 9: 125-38.

Schapira AH, Obeso J. Timing of treatment initiation in Parkinson's disease: A need for reappraisal? Ann Neurol 2006; 59: 559-62.

Scheltens P, Leys D, Barkhof F, Huglo D, Weinstein HC, Vermersch P, et al. Atrophy of medial temporal lobes on MRI in "probable" alzheimer's disease and normal ageing: Diagnostic value and neuropsychological correlates. J Neurol Neurosurg Psychiatry 1992; 55: 967-72.

Seifert S, von Cramon DY, Imperati D, Tittgemeyer M, Ullsperger M. Thalamocingulate interactions in performance monitoring. J Neurosci 2011; 31: 3375-83.

Shulman JM, De Jager PL, Feany MB. Parkinson's disease: Genetics and pathogenesis. Annu Rev Pathol 2011; 6: 193-222.

Singleton AB, Farrer M, Johnson J, Singleton A, Hague S, Kachergus J, et al. Alpha-synuclein locus triplication causes Parkinson's disease. Science 2003; 302: 841.

Skeel RL, Crosson B, Nadeau SE, Algina J, Bauer RM, Fennell EB. Basal ganglia dysfunction, working memory, and sentence comprehension in patients with Parkinson's disease. Neuropsychologia 2001; 39: 962-71.

Snow BJ, Tooyama I, McGeer EG, Yamada T, Calne DB, Takahashi H, et al. Human positron emission tomographic [18F]fluorodopa studies correlate with dopamine cell counts and levels. Ann Neurol 1993; 34: 324-30.

Stroop JR. Studies of interference in serial verbal reactions (reprinted from journal experimental-psychology, vol 18, pg 643-662, 1935). Journal of Experimental Psychology-General 1992; 121: 15-23.

Summerfield C, Junque C, Tolosa E, Salgado-Pineda P, Gomez-Anson B, Marti MJ, et al. Structural brain changes in parkinson disease with dementia: A voxel-based morphometry study. Arch Neurol 2005; 62: 281-5.

Takahashi H, Wakabayashi K. The cellular pathology of Parkinson's disease. Neuropathology 2001; 21: 315-22.

Takikawa S, Dhawan V, Chaly T, Robeson W, Dahl R, Zanzi I, et al. Input functions for 6-[fluorine-18] fluorodopa quantitation in parkinsonism: Comparative studies and clinical correlations. J Nucl Med 1994; 35: 955-63.

Talairach F, Tournoux P. Co-planar stereotaxic atlas of the human brain. : New York Thieme; 1988.

Tam CW, Burton EJ, McKeith IG, Burn DJ, O'Brien JT. Temporal lobe atrophy on MRI in parkinson disease with dementia: A comparison with alzheimer disease and dementia with lewy bodies. Neurology 2005; 64: 861-5.

Tanner CM. Is the cause of Parkinson's disease environmental or hereditary? evidence from twin studies. Adv Neurol 2003; 91: 133-42.

Tanner CM, Aston DA. Epidemiology of Parkinson's disease and akinetic syndromes. Curr Opin Neurol 2000; 13: 427-30.

Taylor KS, Counsell CE, Gordon JC, Harris CE. Screening for undiagnosed parkinsonism among older people in general practice. Age Ageing 2005; 34: 501-4.

Tekin S, Cummings JL. Frontal-subcortical neuronal circuits and clinical neuropsychiatry: An update. J Psychosom Res 2002; 53: 647-54.

Tessa C, Giannelli M, Della Nave R, Lucetti C, Berti C, Ginestroni A, et al. A whole-brain analysis in de novo parkinson disease. AJNR Am J Neuroradiol 2008; 29: 674-80.

Thacker EL, Chen H, Patel AV, McCullough ML, Calle EE, Thun MJ, et al. Recreational physical activity and risk of Parkinson's disease. Mov Disord 2008; 23: 69-74.

The Parkinson Study Group. Effect of lazabemide on the progression of disability in early Parkinson's disease. Ann Neurol 1996; 40: 99-107.

The Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. N Engl J Med 1993; 328: 176-83.

Theuns J, Van Broeckhoven C. Alpha-synuclein gene duplications in sporadic parkinson disease. Neurology 2008; 70: 7-9.

Thobois S, Guillouet S, Broussolle E. Contributions of PET and SPECT to the understanding of the pathophysiology of Parkinson's disease. Neurophysiol Clin 2001; 31: 321-40.

Tison F, Normand E, Jaber M, Aubert I, Bloch B. Aromatic L-amino-acid decarboxylase (DOPA decarboxylase) gene expression in dopaminergic and serotoninergic cells of the rat brainstem. Neurosci Lett 1991; 127: 203-6.

Troster AI, Fields JA, Testa JA, Paul RH, Blanco CR, Hames KA, et al. Cortical and subcortical influences on clustering and switching in the performance of verbal fluency tasks. Neuropsychologia 1998; 36: 295-304.

Tsuboi Y, Dickson DW. Dementia with lewy bodies and Parkinson's disease with dementia: Are they different? Parkinsonism Relat Disord 2005; 11 Suppl 1: S47-51.

Turjanski N, Brooks DJ. PET and the investigation of dementia in the parkinsonian patient. J Neural Transm Suppl 1997; 51: 37-48.

Twelves D, Perkins KS, Counsell C. Systematic review of incidence studies of Parkinson's disease. Mov Disord 2003; 18: 19-31.

Uc EY, McDermott MP, Marder KS, Anderson SW, Litvan I, Como PG, et al. Incidence of and risk

factors for cognitive impairment in an early parkinson disease clinical trial cohort. Neurology 2009; 73: 1469-77.

van Beilen M, Portman AT, Kiers HA, Maguire RP, Kaasinen V, Koning M, et al. Striatal FDOPA uptake and cognition in advanced non-demented Parkinson's disease: A clinical and FDOPA-PET study. Parkinsonism Relat Disord 2008; 14: 224-8.

Van Hoesen GE, Morecraft RJ, Semendeferi K. Functional neuroanatomy og the limbic system and prefrontal cortex. In: Fogel BS, Schiffer RB, RAO SM, editors. Neuropsychiatry. Baltimore: Williams & Wilkins; 1996. p. 113-143.

Vander Borght T, Minoshima S, Giordani B, Foster NL, Frey KA, Berent S, et al. Cerebral metabolic differences in Parkinson's and alzheimer's diseases matched for dementia severity. J Nucl Med 1997; 38: 797-802.

Venton BJ, Zhang H, Garris PA, Phillips PE, Sulzer D, Wightman RM. Real-time decoding of dopamine concentration changes in the caudate-putamen during tonic and phasic firing. J Neurochem 2003; 87: 1284-95.

Verhoeff NP, Wilson AA, Takeshita S, Trop L, Hussey D, Singh K, et al. In-vivo imaging of alzheimer disease beta-amyloid with [11C]SB-13 PET. Am J Geriatr Psychiatry 2004; 12: 584-95.

Vermersch P, Delacourte A, Javoy-Agid F, Hauw JJ, Agid Y. Dementia in Parkinson's disease: Biochemical evidence for cortical involvement using the immunodetection of abnormal tau proteins. Ann Neurol 1993; 33: 445-50.

Victoroff J, Mack WJ, Grafton ST, Schreiber SS, Chui HC. A method to improve interrater reliability of visual inspection of brain MRI scans in dementia. Neurology 1994; 44: 2267-76.

Vingerhoets FJ, Schulzer M, Ruth TJ, Holden JE, Snow BJ. Reproducibility and discriminating ability of fluorine-18-6-fluoro-L-dopa PET in Parkinson's disease. J Nucl Med 1996; 37: 421-6.

Vingerhoets FJ, Snow BJ, Lee CS, Schulzer M, Mak E, Calne DB. Longitudinal fluorodopa positron emission tomographic studies of the evolution of idiopathic parkinsonism. Ann Neurol 1994; 36: 759-64.

Virta JJ, Aalto S, Jarvenpaa T, Karrasch M, Kaprio J, Koskenvuo M, et al. Voxel-based analysis of cerebral glucose metabolism in mono- and dizygotic twins discordant for alzheimer disease. J Neurol Neurosurg Psychiatry 2009; 80: 259-66.

Wahlund LO, Julin P, Johansson SE, Scheltens P. Visual rating and volumetry of the medial temporal lobe on magnetic resonance imaging in dementia: A comparative study. J Neurol Neurosurg Psychiatry 2000; 69: 630-5.

Wakabayashi K, Tanji K, Mori F, Takahashi H. The lewy body in Parkinson's disease: Molecules implicated in the formation and degradation of alpha-synuclein aggregates. Neuropathology 2007; 27: 494-506.

Whone AL, Moore RY, Piccini PP, Brooks DJ. Plasticity of the nigropallidal pathway in Parkinson's disease. Ann Neurol 2003a; 53: 206-13.

Whone AL, Watts RL, Stoessl AJ, Davis M, Reske S, Nahmias C, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. Ann Neurol 2003b; 54: 93-101.

Whone AL, Watts RL, Stoessl AJ, Davis M, Reske S, Nahmias C, et al. Slower progression of Parkinson's disease with ropinirole versus levodopa: The REAL-PET study. Ann Neurol 2003c; 54: 93-101.

Wichmann T, DeLong MR. Functional and pathophysiological models of the basal ganglia. Curr Opin Neurobiol 1996; 6: 751-8.

Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain 2007; 130: 1787-98.

Williams-Gray CH, Evans JR, Goris A, Foltynie T, Ban M, Robbins TW, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain 2009; 132: 2958-69.

Wu JC, Iacono R, Ayman M, Salmon E, Lin SD, Carlson J, et al. Correlation of intellectual impairment in Parkinson's disease with FDG PET scan. Neuroreport 2000; 11: 2139-44.

Yee RE, Cheng DW, Huang SC, Namavari M, Satyamurthy N, Barrio JR. Blood-brain barrier and neuronal membrane transport of 6-[18F]fluoro-L-DOPA. Biochem Pharmacol 2001; 62: 1409-15.

Yong SW, Yoon JK, An YS, Lee PH. A comparison of cerebral glucose metabolism in Parkinson's disease, Parkinson's disease dementia and dementia with lewy bodies. Eur J Neurol 2007; 14: 1357-62.

Zesiewicz TA, Sullivan KL, Arnulf I, Chaudhuri KR, Morgan JC, Gronseth GS, et al. Practice parameter: Treatment of nonmotor symptoms of parkinson disease: Report of the quality standards subcommittee of the american academy of neurology. Neurology 2010; 74: 924-31.

Zgaljardic DJ, Borod JC, Foldi NS, Mattis P. A review of the cognitive and behavioral sequelae of Parkinson's disease: Relationship to frontostriatal circuitry. Cogn Behav Neurol 2003; 16: 193-210.

Ziolko SK, Weissfeld LA, Klunk WE, Mathis CA, Hoge JA, Lopresti BJ, et al. Evaluation of voxel-based methods for the statistical analysis of PIB PET amyloid imaging studies in alzheimer's disease. Neuroimage 2006; 33: 94-102.