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CLINICOPATHOLOGICAL CHARACTERISTICS OF NIGRAL NEURON DENSITY IN LEWY BODY SPECTRUM DISEASES

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ABSTRACT

Lewy body diseases are progressive neurodegenerative disorders that are clinically and pathologically heterogeneous. The combined base of the pathophysiology in Lewy body diseases is the pathological accumulation of α-synuclein, which forms Lewy bodies and Lewy neurites. The degeneration and Lewy pathology are particularly prominent in the substantia nigra, which is a crucial part of the dopaminergic system of the central nervous system. Lewy body disease patients usually have an individual spectrum of motor and nonmotor symptoms. The nonmotor symptoms, such as depression, may precede motor symptoms by several years. Substantial dopaminergic degeneration has already occurred by the time motor signs such as rigidity, bradykinesia and rest tremor emerge. The causative disease mechanism is unclear. Lewy body diseases decrease life quality and increase mortality.

This thesis focuses on the relationships between degeneration of the dopaminergic nuclei and clinical features in Lewy body disease patients. Cases were collected from neuropathologic records of the University Hospital of Turku between 2002 and 2016 retrospectively and the corresponding clinical records were then reviewed. The association between Tyrosine hydroxylase positive substantia nigra neuron or putaminal axon numbers and striatal dopamine transporter binding, depressive symptoms and height were examined in Lewy body disease patients. The number of neurons and axons were counted manually using midbrain sections, and mathematical corrections were applied in the last two studies.

The numbers of dopaminergic and tyrosine hydroxylase positive neurons in the substantia nigra or neurites in the striatum did not correlate with *in vivo* dopamine transporter binding. The results further demonstrate that neurodegeneration in the substantia nigra pars compacta in depressed Lewy body disease patients is more severe compared to non-depressed patients. The results also suggest that the height of Lewy body disease patients may be associated with neuron density in the substantia nigra pars compacta.

These results shed light on some factors which underlie the large interindividual variability of substantia nigra pars compacta degeneration.

KEYWORDS: Parkinson’s disease, Dementia with Lewy bodies, dopamine, substantia nigra, neurodegeneration, DAT SPECT, depression, height

TURUN YLIOPISTO
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LAURA SAARI: Mustatumakkeen hermosolutiheyden kliinispatologiset piirteet Lewyn kappale -kertymäsairauksissa
Väitöskirja, 158 s.
Turun kliininen tohtoriohjelma
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TIIVISTELMÄ

Lewyn kappale -kertymäsairaudet ovat heterogeenisia ja eteneviä hermostorappeumasairauksia. Näiden sairauksien yhteinen patofysiologinen piirre on α-synukleiinin kertyminen, mikä muodostaa Lewyn kappaleita ja Lewyn neuriitteja. Hermorappeuma ja Lewy-patologia ovat havaittavissa erityisesti mustatumakkeessa, joka on oleellinen osa keskushermoston dopaminergistä järjestelmää. Yleensä Lewyn kappale -kertymäsairaus potilaalla on yksilöllinen kirjo motorisia ja ei-motorisia oireita. Ei-motoriset oireet, kuten masennus, saattavat edeltää motorisia oireita useilla vuosilla. Motoristen oireiden, kuten jäykkyyden, hitauden ja lepovapinan, ilmetessä on havaittavissa jo merkittävää dopaminergisen hermoston rappeumaa. Taudin aiheuttava mekanismi on yhä epäselvä. Lewyn kappale -kertymäsairaudet alentavat potilaiden elämän laatua ja lisäävät kuolleisuutta.

Tässä väitöstutkimuksessa keskityttiin dopaminergisten tyvitumakkeiden ja Lewyn kappale -kertymäsairauksien kliinisten piirteiden yhteyksiin. Potilastapaukset kerättiin Turun yliopistollisen sairaalan neuropatologian arkistoista 2002 ja 2006 välillä retrospektiivisesti. Kliininen data kerättiin vastaavasti potilastietojärjestelmistä. Tyrosiinihydroksylaasi positiivisten mustatumakkeiden hermosolujen tai putamenin aksonien määrän suhdetta aivojuovion dopamiinitransportterin sitoutumiseen, masennusoireisiin ja pituuteen tutkittiin Lewyn kappale -tautia sairastavilla potilailla. Hermosolujen ja aksonien määrä laskettiin manuaalisesti keskiaivoleikkeistä, ja matemaattista korjausta hyödynnettiin jälkimmäisissä tutkimuksissa.

Tulokset osoittivat, että neuromelaniini- ja tyrosiinihydroksylaasipositiivisten mustatumakkeen hermosolujen ja aivokuorukan hermohaarakkeiden määrä ei korreloi dopamiinin takaisinottajan sitovuuteen. Lisäksi tulokset viittasivat siihen, että hermostorappeuma mustatumakkeessa on vaikeampaa masentuneilla kuin ei-masentuneilla potilailla. Lisäksi vaikuttaa siltä, että aikuispituus saattaisi liittyä mustatumakkeen hermosolutiheyteen.

Yhteenvedettynä tulokset auttavat ymmärtämään suurta yksilökohtaista vaihtelua mustatumakkeen hermorappeumassa, eli keskeisessä Lewyn kappale -kertymäsairauksien tautimekanismissa.

AVAINSANAT: Parkinsonin tauti, Lewyn kappale -tauti, dopamiini, substantia nigra, hermostorappeuma, DAT SPECT, masennus, pituus

Table of Contents

Abbreviations

[^{123}I]β-CIT	^{123}I-2β-carbomethoxy-3β-(4-iodophenyl)tropane
[^{123}I]FP-CIT	[^{123}I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane
5-HT	5-hydroxytryptamine or serotonin
α-Syn	α-synuclein
AADC	Aromatic L-amino acid decarboxylase
AD	Alzheimer's disease
BG	Basal ganglia
BMI	Body mass index
CBD	Corticobasal degeneration
CSF	Cerebrospinal fluid
CN	Caudate nucleus
COMT	Catechol-o-methyltransferase
DA	Dopamine
DA βH	Dopamine β–hydroxylase
DAT	Dopamine transporter
DAT SPECT	Dopamine transporter single-photon emission computed tomography
DLB	Dementia with Lewy bodies
DOPA DEC	Levodopa decarboxylase
DOPAC	3,4-dihydroxyphenylacetic acid
DSM-5	the Diagnostic and Statistical Manual of Mental Disorders, fifth edition
fMRI	Functional magnetic resonance imaging
GABA	γ-aminobutyric acid
GP	Globus pallidus
GBA	Glucocerebrosidase
GPe	External segment of globus pallidus
GPi	Internal segment of globus pallidus
GH	Growth hormone
ICD-10	International Classification of Diseases, Tenth Revision

IGF-1	Insulin-like growth hormone 1
L-dopa	Levodopa
LB	Lewy body
LBD	Lewy body disease
LC	Locus coeruleus
LDB	Levodopa + Benserazide
LDC	Levodopa + Carbidopa
LDCE	Levodopa + Carbidopa + Entacapone
LEDD	Levodopa equivalent daily dose
LFB	Luxol fast blue
MAO	Monoamine oxidase
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
MSA	Multiple system atrophy
NE	Norepinephrine
PCR	Polymerase chain reaction
PD	Parkinson's disease
PET	Positron emission tomography
PH	Phenylalanine hydroxylase
PNS	Peripheral nervous system
PSP	Progressive supranuclear palsy
Put	Putamen
REM	Rapid eye movement
ROI	Region of interest
SBR	Spesific binding ratio
SN	Substantia nigra
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
STN	Subthalamic nucleus
TDP-43	Transactive response DNA binding protein 43 kDa
TH	Tyrosine hydroxylase

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Saari L, Kivinen K, Gardberg M, Joutsa J, Noponen T, Kaasinen V. Dopamine transporter imaging does not predict the number of nigral neurons in Parkinson disease. *Neurology*, 2017;88(15):1461-1467.

II Honkanen EA, Saari L, Orte K, Gardberg M, Noponen T, Joutsa J, Kaasinen V. No link between striatal dopaminergic axons and dopamine transporter imaging in Parkinson's disease. *Movement Disorders*, 2019;34(10):1562-1566.

III Saari L, Heiskanen L, Gardberg M, Kaasinen V. Depression and Nigral Neuron Density in Lewy Body Spectrum Diseases. *Annals of Neurology*, 2021;89(5):1046-1050.

IV Saari L, Backman EA, Wahlsten P, Gardberg M, Kaasinen V. Height and nigral density in Parkinson's disease. *BMC Neurology,* 2022;22:254.

1 Introduction

Lewy body diseases (LBD) are common neurodegenerative diseases and movement disorders. The origin point for LBD research was likely the publication of "An Essay on the Shaking Palsy" by James Parkinson in 1817. He described a slowly progressive and disabling disease with rest tremor, flexed posture, and festination with remarkable details. He even noted some classic nonmotor symptoms of Parkinson's disease (PD), such as constipation, salivation, and sleep disturbances (Parkinson 2002). Jean-Martin Charcot brought the Essay to a broader audience and added significant observations on the diversity of PD. He advanced the theory by identifying rigidity as an essential feature of the disease and suggested changing the name to PD instead of the misleading "palsy" (Charcot 1877). Armand Trousseau was the first to describe bradykinesia in PD (Trousseau 1868).

The first suggestions of substantia nigra (SN) involvement in the pathology emerged in 1893 by Blocq and Marinesco. Their clinicopathological work suggested that a tubercle in SN might have been causing unilateral parkinsonism (Blocq and Marinesco 1893). Based on this finding Brissaud then raised the possibility that maladie de Parkinson might be due to ischaemia of the SN (Brissaud 1895). Cellular inclusion bodies were soon found in the neurons of parkinsonian patients by Friedrich Heinrich Lewy, and Konstantin Trétiakoff later connected the Lewy body (LBs) inclusions to PD pathology. The following decades of research focused on the central role of SN degeneration (Parent and Parent 2010). The cause of LDBs remains unclear.

Swedish pharmacologist Arvid Carlsson demonstrated that levodopa (L-dopa) alleviated parkinsonism in animal models (Carlsson, Lindqvist, and Magnusson 1957) and hypothesized about the relationship between DA and motor symptoms (Carlsson 1959). Hornykiewicz later demonstrated DA depletion in the striatum and his clinical colleague Birkmayer performed the first human L-dopa trials in PD (Birkmayer and Hornykiewicz 1961). Cotzias and colleagues were the first to demonstrate conclusively the beneficial effects of high dose L-dopa therapy (Cotzias, Van Woert, and Schiffer 1967). Despite its sustained symptomatic benefits, several limitations are associated with L-dopa treatment including

dyskinesias with long term therapy dyskinesia and psychiatric side effects (Bogetofte et al. 2020). There is now a variety of other adjunctive medical treatment options, including monoamine oxidase (MAO) type B inhibitors, catechol-o-methyl transferase (COMT) inhibitors and DA agonists although L-dopa remains the most efficacious treatment.

Motor symptoms are the major cause of reduced quality of life and physical handicap in PD (Postuma et al. 2015), but nonmotor symptoms such as depression, visual hallucinations and cognitive impairment also increase the burden of the disease. Prodromal symptoms including hyposmia, rapid eye movement (REM) sleep disorder and constipation occur in some patients before the motor symptoms emerge (Langston 2006). Symptomatic treatment of LBD demands a significant amount of healthcare resources (Sillanpää, Andlin-Sobocki, and Lönnqvist 2008; Gustavsson et al. 2011). Neuroimaging, especially functional imaging such as positron emission tomography (PET), single photon emission computed tomography (SPECT) and functional magnetic resonance imaging (fMRI), have provided new information on the patterns of LBD spectrum disorders and new techniques. Cryogenic electron microscopy and immunohistochemistry have demonstrated previously unrecognised cellular pathologies (Figure 1). The lack of disease-modifying therapies for PD combined with its predicted increased prevalence (Collaborators 2018) constitutes a significant public health issue. In most cases, LBD diagnosis can be made on clinical bases. DA transporter (DAT) SPECT may aid in some cases and immunohistochemistry aids in *postmortem* diagnostics. There is a need for reliable biomarkers to assist in early detection, prognosis, disease monitoring, and prediction of treatment response.

This thesis focused on clinicopathological characteristics of nigral neuron density in LBDs investigated by histological evaluation of SNc with immunohistochemical assessment, functions of basal ganglia (BG) evaluated by DAT imaging and observing clinical features of LBDs.

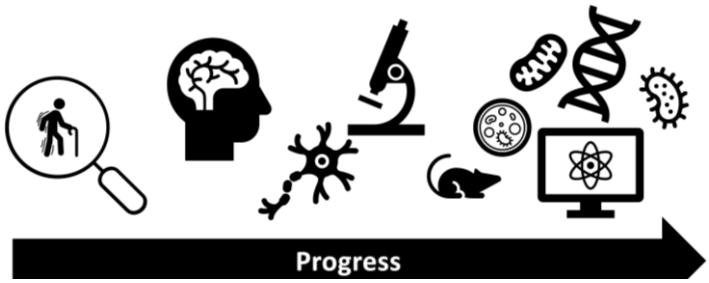

Figure 1. Timeline of research methodology on LBDs in chronological order. From the left: observations; autopsies; microscopy and basic staining; gene sequencing, functional imaging, immunohistochemical staining methods, electron microscopy as an example.

2 Review of the Literature

2.1 The basal ganglia anatomy and physiology

The basal ganglia (BG) are a group of subcortical nuclei situated at the base of the forebrain and top of the midbrain. The central nuclei of BG are the striatum, consisting of the dorsal striatum: caudate nucleus (CN) and putamen (Put), and the ventral striatum: nucleus accumbens and olfactory tubercle, the globus pallidus (GP), the ventral pallidum, the SN, and the subthalamic nucleus (STN). Figure 2 presents the anatomy. The BG neurons evolve from the neural tube during embryogenic development and differentiate by anatomical and biochemical pathways (Oliveira et al. 2017). The BG is supplied by the lenticulostriate arteries, which are branches of the middle cerebral artery (Young, Reddy, and Sonne 2021).

The BG receives inputs from various cortical areas, the thalamus, and the cerebellum on top of complex connectivity within the BG nuclei. The BG can be categorized into input nuclei: CN, Put, and nucleus accumbens, and output nuclei: the internal segment of GP (GPi) and SN pars reticulata (SNr), and intrinsic nuclei: the external segment of GP (GPe), STN, and SN pars compacta (SNc). (*Waldeyer - Anatomie des Menschen: Lehrbuch und Atlas in einem Band* 2012) Dopaminergic (DAergic) neurons of the ventrolateral region of SNc are the origin of the nigrostriatal pathway whereas the ventromedial DAergic neurons project to the nucleus accumbens and the ventral striatum (Fearnley and Lees 1991).

The BG are associated with various functions, including conditional learning, coordinating cognition and motor control (Stocco, Lebiere, and Anderson 2010; Yahya 2021). The motor function of BG has been studied far more than its other functions and associative areas because of its significant role in the motor symptoms of LBDs and other movement disorders such as dystonia or chorea.

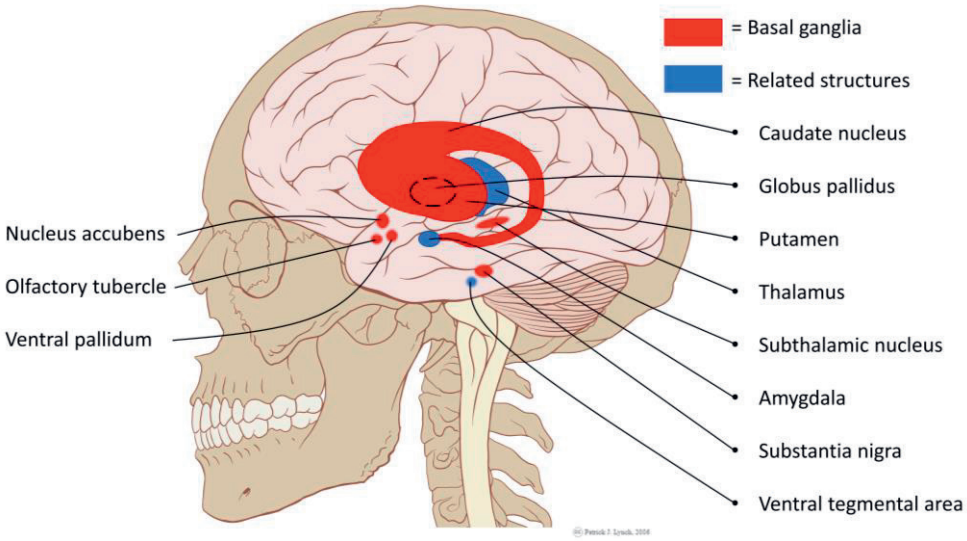

Figure 2. The BG and related structure. Modified from an image by Lynch 2006.

2.1.1 Neurotransmitters

Neurons use neurotransmitters to communicate with each other through synapses. This chemical synaptic communication is vital for the cooperative function of nervous systems, which enables and shapes movement and emotion (Rizo 2018). Disturbance in the balance of neurotransmitters can lead to brain disorders such as PD and Alzheimer's disease (AD), as demonstrated in Figure 3.

The chemical synaptic communication generally transmits either excitatory or inhibitory signals by releasing neurotransmitters from a presynaptic neuron to postsynaptic receptors, thus increasing or decreasing the actions in target cells. Action potential of the presynaptic neuron triggers calcium influx into the presynaptic cleft and activates the fusion of vesicles, thus releasing neurotransmitters (Rizo 2018). This process is one of the medication targets in brain disorders. The BG motor circuitry is mainly modulated by three transmitters: DA, glutamate, and γ-aminobutyric acid (GABA), but other neurotransmitters likely participate in the adjustment of circuitry (Jellinger 2019).

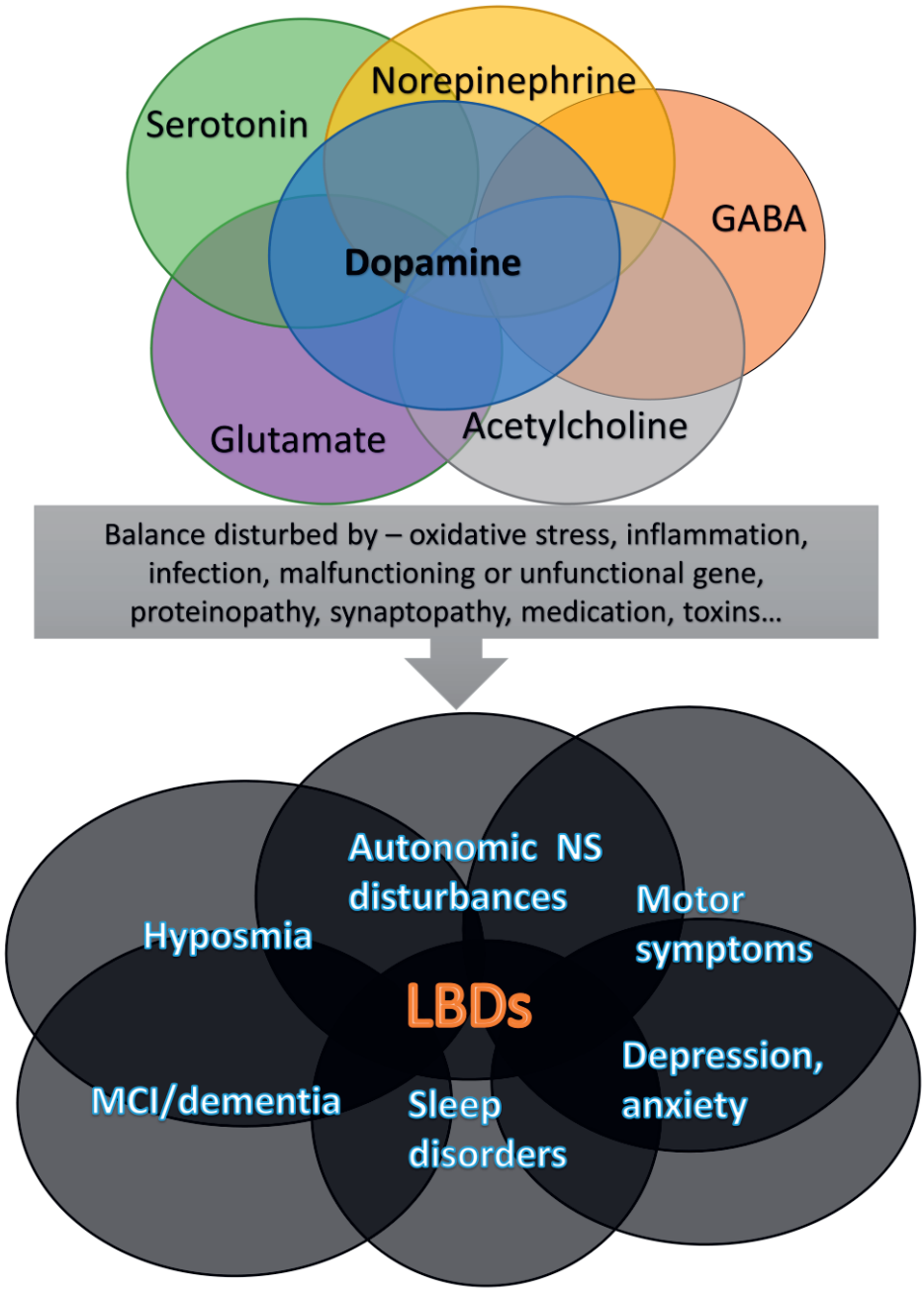

Figure 3. Neurotransmitter balance disturbances lead to combinations of LBD symptoms. Nervous system (NS), mild cognitive impairment (MCI).

Glutamate is the major excitatory neurotransmitter in the brain and is responsible for various activities. The excitatory pathways continuously release and recapture glutamate through the "glutamate-glutamine cycle". Released glutamate excites postsynaptic neurons by binding to ionotropic and metabotropic receptors, after which glutamate is quickly removed by transporters expressed in both neurons and glial cells. Then astrocytes convert glutamate into inert glutamine and release it for neurons to be reused. Disturbed glutamate homeostasis has been connected with neurological or neurodegenerative disorders such as epilepsy, multiple sclerosis, AD and PD (Iovino, Tremblay, and Civiero 2020).

Acetylcholine is mainly a transmitter in the neuromuscular junction and parasympathetic NS (Tiwari et al. 2013), but it is also a neuromodulator and neurotransmitter of the brain. The central cholinergic system includes the basal forebrain nuclei (innervate the cortex), projecting to the cortex, the mesopontine tegmental nuclei (innervate thalamus and subcortical structures) and other clusters of neurons. The cholinergic interneurons contribute a small percentage of the striatal neurons and interact with DAergic innervation arising from the SNc and the ventral tegmental area (Zhou, Wilson, and Dani 2002). Acetylcholine acts through the muscarinic and nicotinic receptors. Both are found in presynaptic and postsynaptic terminals of the striatum. The effect is regulated by complex interactions between these receptors. This cholinergic system regulates sleep, locomotion and cognition among many functions (Pasquini, Brooks, and Pavese 2021).

Norepinephrine (NE) is both a neurotransmitter and a hormone throughout the body, including the brain. A nucleus in the pons, locus coeruleus (LC), is the leading site of NE synthesis in the brain, and its neurons widely innervate the whole brain (Pasquini, Brooks, and Pavese 2021). NE binds to adrenergic receptors, which are a class of G-protein-coupled receptors. α and β (β1, β2 and β3) are the main adrenergic receptor groups. The NE or adrenaline binding into the adrenergic receptors generally stimulates the sympathetic nervous system. LC is associated with various functions in the central nervous system such as wakefulness, memory, and modulation of motor control (Gesi et al. 2000; Giorgi et al. 2020).

Serotonin (5-HT) is a neurotransmitter, and it binds 5-HT receptors widely present in the brain. There are seven families and at least 14 different subtypes of 5-HT receptors, including G-protein-coupled receptor subtypes and ligand-gated ion channels. Neuronal uptake by the 5-HT reuptake transporter or enzymatic metabolism transformation ends the 5-HT action. The raphe nuclei are the main centre of 5-HT neurons, which innervate almost the whole brain, including the BG, whose activity the 5-HT system modulates. The 5-HT system is a remarkable

modulator of multiple functions such as sleep, mood, appetite and motor activity. The system is also connected to the aetiology of various neuropsychiatric disorders such as depression and anxiety (Vegas-Suarez et al. 2019).

GABA is the primary inhibitory transmitter in the BG circuitry and the brain. High concentrations of GABA are found in the SN, GP and STN. There is a substantial amount of GABA receptors in the BG, hypothalamus, hippocampus and dorsal horn of the spinal cord (Jellinger 2019). There are two major GABA receptor subtypes, ionotropic GABAA and metabotropic GABAB. The postsynaptic GABAA receptor quickly executes the inhibitory effects mainly by altering the membrane permeability to chloride ions. The GABAB receptor mediates prolonged slower inhibitory neurotransmission via presynaptic and postsynaptic G-protein-coupled receptors. Both receptors are targeted to treat many clinically significant diseases, including epilepsy and anxiety disorders (Jembrek and Vlainic 2015).

DA is the neurotransmitter that partakes in virtually any higher executive action, but it also maintains homeostasis as a paracrine hormone. DA is a biosynthetic product of phenylalanine. Humans obtain this essential amino acid from nutrition. DA synthesis is processed via an enzyme-induced pathway, presented in Figure 4. The oxidation of tyrosine to L-dopa is an exothermic reaction with tyrosine hydroxylase (TH) induction and cofactors iron and tetrahydropteridine. The continuous production of DA may lead to oxidative stress via production of oxygen radicals. DA is widely distributed throughout the brain, but high densities are found in the DAergic SNc and the nigrostriatal pathway. DA in the fine terminal branches of striatal neurons is derived from the DAergic neurons of the SNc. All these DAergic structures contain TH so that DA can also be synthesized directly at the terminal parts of neurons. Thus, TH can be used to identify DAergic neurons with immunohistochemistry (Franco, Reyes-Resina, and Navarro 2021).

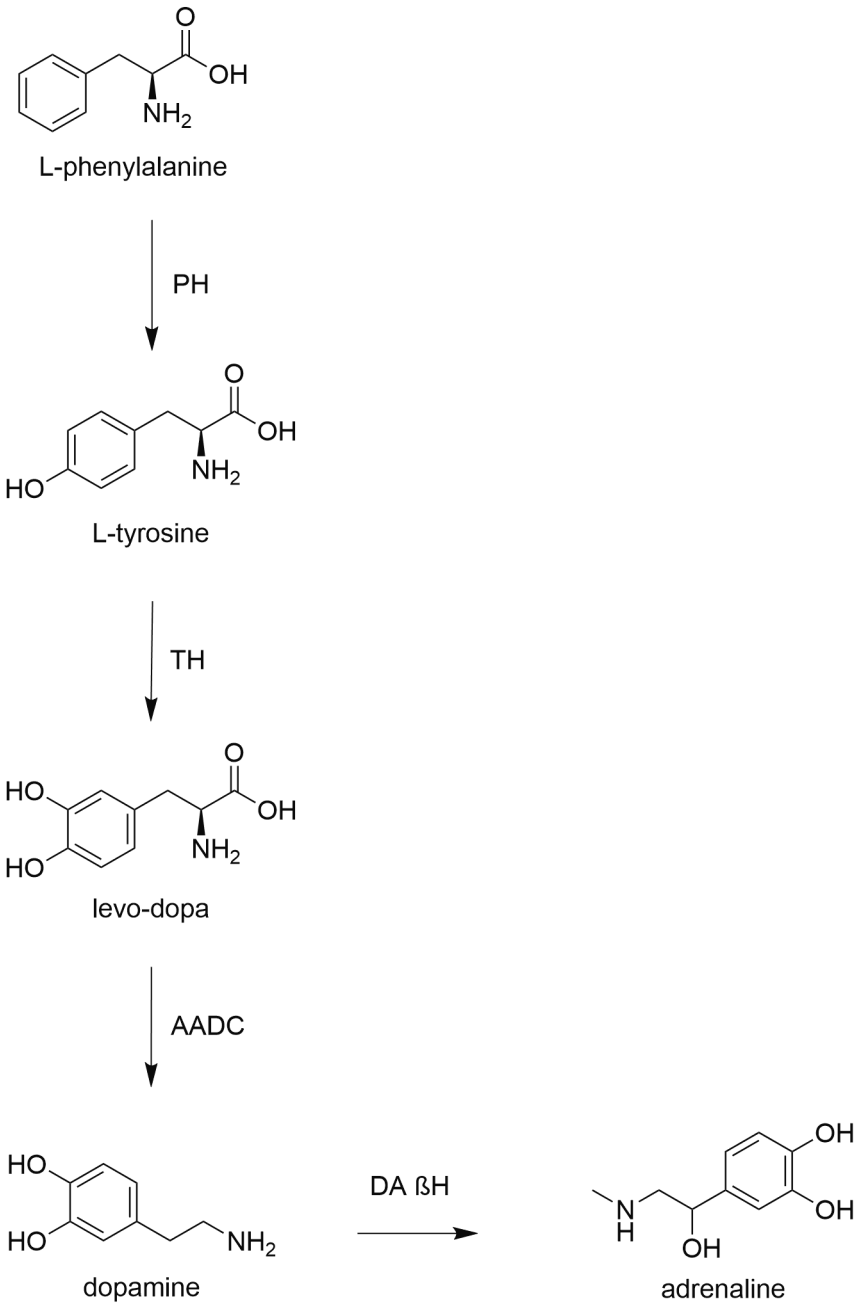

Figure 4. Main pathways of DA synthesis. PH, phenylalanine hydroxylase; AADC, aromatic L-amino acid decarboxylase; DA βH, DA β–hydroxylase.

DA is the final product in the DAergic cells that can be re-used via uptake mechanism or degraded. DA synthesis is a consuming process; thus, energy is saved when the DA is re-used after releasing it to the synaptic cleft. DA transporter (DAT) regulates DA levels in the synaptic clefts by transporting DA back to the presynaptic neuron (Giros et al. 1996). DA is converted to NE in cells containing DA β–hydroxylase. Figure 5 presents the main pathways of DA degeneration. Major products include 3-methoxytyramine, 3,4-dihydroxyphenylacetic acid (DOPAC) and 4-hydroxy-3-methoxyphenylacetic acid, or homovanillic acid (HVA). The main DA degenerating enzymes are COMT and MAO. MAO has two forms, MAO type A and MAO type B, which are present in the outer membrane of the mitochondria. COMT mainly reacts with substrates from MAO-induced degeneration. The degeneration process is very efficient in the human brain, and only minimal quantities of DOPAC are typically found in the striatum but considerable amounts of homovanillic acid. homovanillic acid is excreted in the urine, where it can be identified (Franco, Reyes-Resina, and Navarro 2021). Homovanillic acid levels in the cerebrospinal fluid can be used as a marker for DA catabolism in the brain, although it is not very sensitive (Marín-Valencia et al. 2008).

DA also degenerates spontaneously via oxidation and thus produces free radicals and DA quinone. This pathway is thought to eventually lead to the formation of neuromelanin, which gives the characteristic pigmentation to SNc. The possible function of neuromelanin remains unidentified, but it might associate with the vulnerability of these DAergic neurons (Franco, Reyes-Resina, and Navarro 2021).

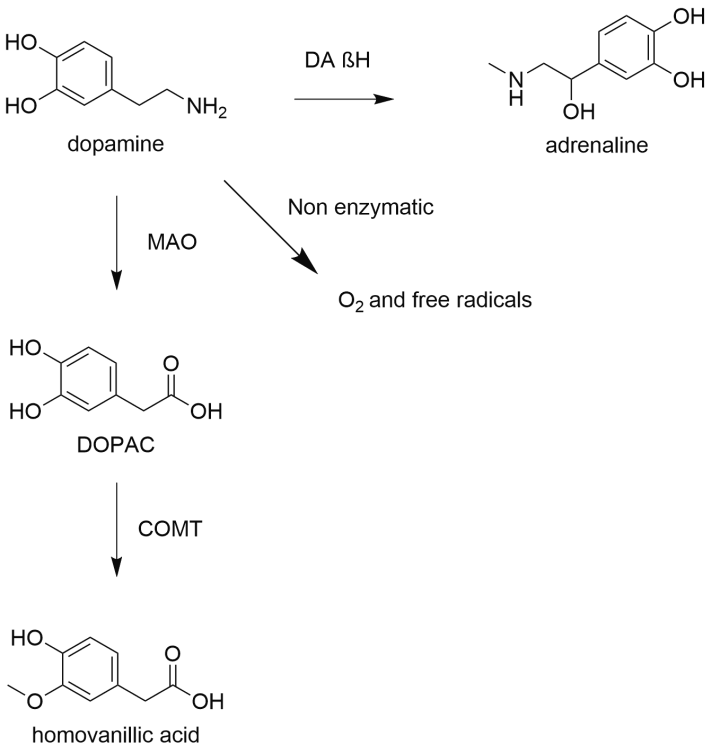

Figure 5. Main pathways of DA degradation. DA βH, DA β–hydroxylase; MAO, monoamine oxidase; DOPAC, levodopa decarboxylase.

DA affects mainly via two different mechanisms: by releasing DA into the synaptic cleft and thus affecting the postsynaptic DA receptors, and by diffusion where the DA binds into receptors of different cells that are not in direct contact with the DA releasing cell (Fuxe and Borroto-Escuela 2016). DAergic neurons in the striatum release DA regularly to sustain a tonic DA level, which is associated with normal BG function. For example, unexpected rewards fire phasic bursts, which are thought to participate in reinforcement learning (DeLong 1990; Obeso et al. 2017). DA acts by binding to five different types of G-protein-coupled receptors: D1, D2, D3, D4 and D5. These receptors are present in synapses of

DAergic neurons and extrasynaptically in neurons and many other types of cells throughout the human body.

Moreover, DA receptors often form heteromers with DA or other receptors, thus rising multiform and varying patterns of DA expression. Each receptor heteromer has its role and pharmaceutical features (Franco and Franco 2014). Structural deviations in the DA receptors can cause differential signalling and cause disturbances in the normal signal pathways. Some individual variants are associated with addiction risks (Franco, Reyes-Resina, and Navarro 2021). The effect of DA in a particular cell depends on the expression of different DA binding receptors and of the complexes formed by the receptors (Franco, Reyes-Resina, and Navarro 2021). For example, D4-receptor heteromers involving adrenergic receptors participates in circadian regulation (González et al. 2012). DA acts as a major modulator of the BG circuitry within the BG by altering the activity of striatal neurons (DeLong 1990).

As previously stated, DA acts widely as a paracrine hormone in the human body. DA is produced by various cells, like cells in Peyer's patches in the gut, where DA influences the composition of the microbiota and binds the DA receptors of surrounding cells including immune cells. DA has a clear and certain role as a regulator of dendritic cells and lymphocytes and a role in the development of autoimmune diseases. Moreover, DA volume is much higher in the periphery than in the central nervous system. There is evidence that DA links the gut and the brain. The mechanism is not clear yet, but it is believed that the DA modulated immune system activation in the gut could mediate inflammation in the central nervous system, where the immune system (Franco, Reyes-Resina, and Navarro 2021).

2.1.2 Striatal circuits

The BG are viewed as components of segregated but parallel networks that process and refine information from particular cortical areas divided into the motor, associative and limbic areas. The information passes through the BG and ventral thalamus and returns to the frontal cortex. The information interacts on the way with internal circuits linked to the control of behaviour and movement (Klaus, Alves da Silva, and Costa 2019).

A constant level of inhibition in the striatum and brainstem is the common base for most of the BG models. Inhibition is provided from GPi and SNr by high-frequency GABAergic neurons (Chevalier and Deniau 1990). These networks are modulated by the amount of striatal DA, thus facilitating adaptable motor and behaviour control (Neumann et al. 2018). Abnormality in these networks or

functions leads to movement disorders, obsessive-compulsive disorders, and mood alterations. Hyperkinetic and hypokinetic movement disorders are assumed to be due to a disturbance in the balance between excitation and inhibition firing in the BG (Lanciego, Luquin, and Obeso 2012).

The classical but overly simplified model of motor BG circuitry describes separate opponent pathways: The direct D1-like DA receptor-expressing striatal–GPi/SNr pathway facilitates movement by disinhibiting the thalamus. The indirect D2 DA receptor-expressing striatal–GPe–GPi/SNr pathway suppresses movement by inhibiting the thalamus. DA is suggested to have opposing effects on these pathways in this model (Young, Reddy, and Sonne 2020). Other BG nuclei, cortical loops and likely other structures are involved in the information processing. For example, STN is involved in the hyperdirect pathway, which is assumed to participate in the cancellation of an inappropriate movement (Figure 6) (Nambu 2004).

Studies tracing individual axons and immunohistochemical assays with animal models have also provided evidence against the classical two separate pathways model (Lévesque and Parent 2005; Rico et al. 2017). A different model presents that the two pathways are not distinct parallel systems but functionally intertwined inside and outside the striatum by collaterals (Papa and Wichmann 2015; Simonyan et al. 2017). Other models assume that circuits are simultaneously active, and the coordinated activity regulates the initiation and execution of movement (Tecuapetla et al. 2016). The classical model predicts that the BG output increase excessively inhibits the thalamus and cortex, and thus leads to a paucity of movement. However, manipulations of the BG in animal models suggest that other measures of activity, such as pattern and synchrony, play a role in PD motor symptoms (Meissner et al. 2005; McGregor and Nelson 2019).

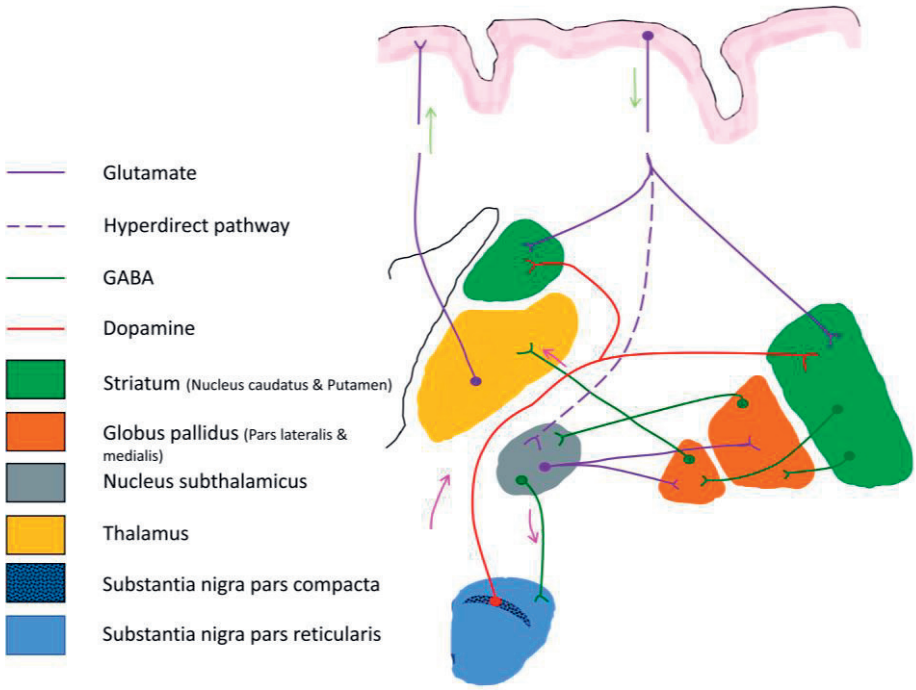

Figure 6. Schematic diagram of the key motor pathways of BG. Drawn based on Waldeyer Anatomie des Menschen.

2.2 Lewy body diseases

LBDs are chronic and progressive multisystem diseases, that significantly affect the quality of life and life expectancy (Barone, Erro, and Picillo 2017; Palma and Kaufmann 2018). LBDs are pathologically and clinically heterogeneous disorders characterized by pathologic accumulation of α-synuclein (α-Syn) in neurons in the form of Lewy bodies, Lewy neurites and neuronal cytoplasmic inclusions (pale bodies). In practice clinical presentations of LBDs are categorized into distinct entities: PD, PD with dementia, and DLB based on the time of appearance of cognitive symptoms and motor symptoms (Berg et al. 2014; Jellinger and Korczyn 2018). Even though speculated to be the causative disease mechanism, it is not

known how α-Syn is linked to a distinct molecular pathological mechanism or factors determining the vulnerability of the DAergic system.

2.2.1 Neuropathology of Lewy body diseases

In PD macroscopical examination shows paleness in the SN and the LC within an often normal-sized brain or with mild cortical atrophy and modest enlargement of ventricles. Histological inspection reveals severe depletion of melanized neurons and DAergic neurons of the ventrolateral part of the SNc (Koga et al. 2021b).

LBDs are characterized by the presence of LBs, pale bodies and Lewy neurites. LBD pathology is viewed as a continuum of progressive findings, where the extremities are incidental LBs or PD and PD with dementia and dementia with LBs (DLB). Concomitant proteinopathies, particularly AD pathology, are common and often accompany LB pathology also with continuum trend. The distribution of LBs determines the LBD pathological phenotype (Hughes et al. 1993; Koga et al. 2021b). The LBs are intracytoplasmic eosinophilic inclusions primarily composed of fibrillary-aggregated and phosphorylated α-Syn along with

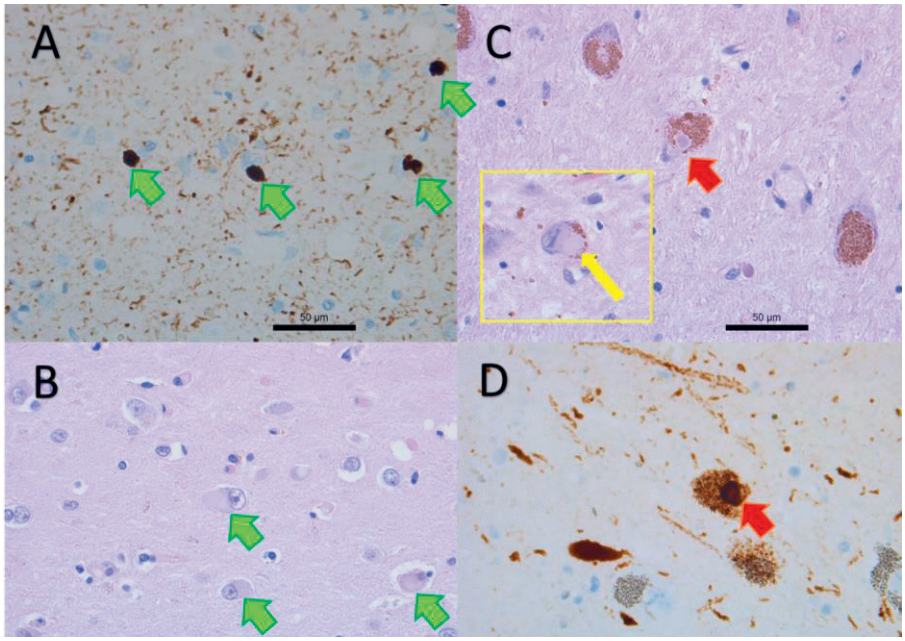

Figure 7. Typical Lewy pathology findings: cortical LBs in α-Syn (A) and Hematoxylin and eosin stain (B) (green arrows), classical midbrain LBs in Hematoxylin and eosin stain (C) and α-Syn (D) stain (red arrows). In panel C, a pale body (yellow arrow) on the same scale (yellow square).

other proteins including neurofilament and ubiquitin (Fujiwara et al. 2002; Wakabayashi et al. 2013). Lewy neurites are mostly axonal cell processes with α-Syn accumulations and are typically found in the CA2-3 sectors of the hippocampus (Dickson et al. 1991). Pathological α-Syn inclusions are widely distributed through the central and peripheral nervous systems. Besides α-Syn related pathology, there may be spongiform vacuolization changes in the amygdala, limbic and temporal cortexes. The aetiology of these changes is still unclear, but it is associated with the rapid degeneration of large pyramidal neurons of the entorhinal cortex (Sherzai et al. 2013). Figure 7 presents typical LBs.

2.2.1.1 Hypotheses of pathogenesis

Deposition of α-Syn is considered by some authorities to be central to the pathogenic mechanisms underlying PD (Spillantini et al. 1997; Rocha, De Miranda, and Sanders 2018). lα-Synuclein is a small soluble protein composed of 140 amino acids encoded by *Synuclein Alpha* (Touchman et al. 2001). It is a widely expressed neuronal protein involved in interaction with phospholipids and involved in vesicle and microtubule formations and neurotransmitter release (Burré, Sharma, and Südhof 2018). A neuroanatomical analysis of SN in animal models indicated that the complex axonal architecture makes the nigral neurons particularly susceptible to cell death (Bolam and Pissadaki 2012). The complex axon net needs efficient trafficking of organelles and vesicles within these neurons. Accumulated α-Syn can impair synaptic DA release and lead to impairment of protein trafficking, autophagy, and mitochondrial function (Plowey and Chu 2011; Michel, Hirsch, and Hunot 2016; Longhena et al. 2017).

One hypothesis of pathogenesis is that misfolded α-Syn triggers endogenous alpha-synuclein to seed further protein aggregation in new neurons in a prion-like fashion (Ma et al. 2019). However, not all studies have confirmed the accumulation of α-Syn as a critical factor in disease causation because no correlation between nigral neuron density and LB pathology has been demonstrated (Parkkinen et al. 2011; Dijkstra et al. 2014).

The role of the immune system in PD is of contemporary interest. The main features of the inflammatory response in PD are microglial and astrocyte activation and increased gene expression of proinflammatory factors in the central nervous system, and the infiltration of immune cells from the periphery into the central nervous system (Duffy et al. 2018; Caggiu et al. 2019; Iovino, Tremblay, and Civiero 2020; MacMahon Copas et al. 2021). A suggested trigger for this immune activation is α-Syn accumulation because α-Syn is both a neurotoxin and pro-inflammatory compound (Caggiu et al. 2019; Cardinale et al. 2021). Evidence

that adaptive immune reaction precedes synucleinopathy and cell death has recently been provided. T-lymphocytes accumulate in the SN and induce neuronal cell death by cytokine secretion and activation of ambient immune cells (Galiano-Landeira et al. 2020). A disturbed immune reaction might also explain the proposed link between gut and brain in LBDs (Franco, Reyes-Resina, and Navarro 2021).

The Braak's method of staging PD based on LB distribution has been extended to a hypothesis postulating an ascending progression of PD from the lower brain stem to the cerebral cortex (Braak et al. 2003), presented in Figure 8. This hypothesis has gained some support from further pathological studies (Beach et al. 2009; Dickson et al. 2010), although there is a weak clinical correlation and it is impossible to predict from the pathology whether dementia was present in life (Jellinger 2009; Kon, Tomiyama, and Wakabayashi 2020; Attems et al. 2021). LB-pathology can be identified through the nervous system but also in many visceral organs of prodromal and late-stage LDB patients; thus, the pattern of the pathology spreading is unclear (Beach et al. 2010; Gelpi et al. 2014; Jellinger 2019). Horsager and colleagues demonstrated signs of both spreading types, the "body first" and the "brain first", with a functional imaging study (Horsager et al. 2020). A significant number of people dying without signs of PD or dementia in life, have extensive LB pathology in their brains (furtherly discussed in chapter 2.2.4).

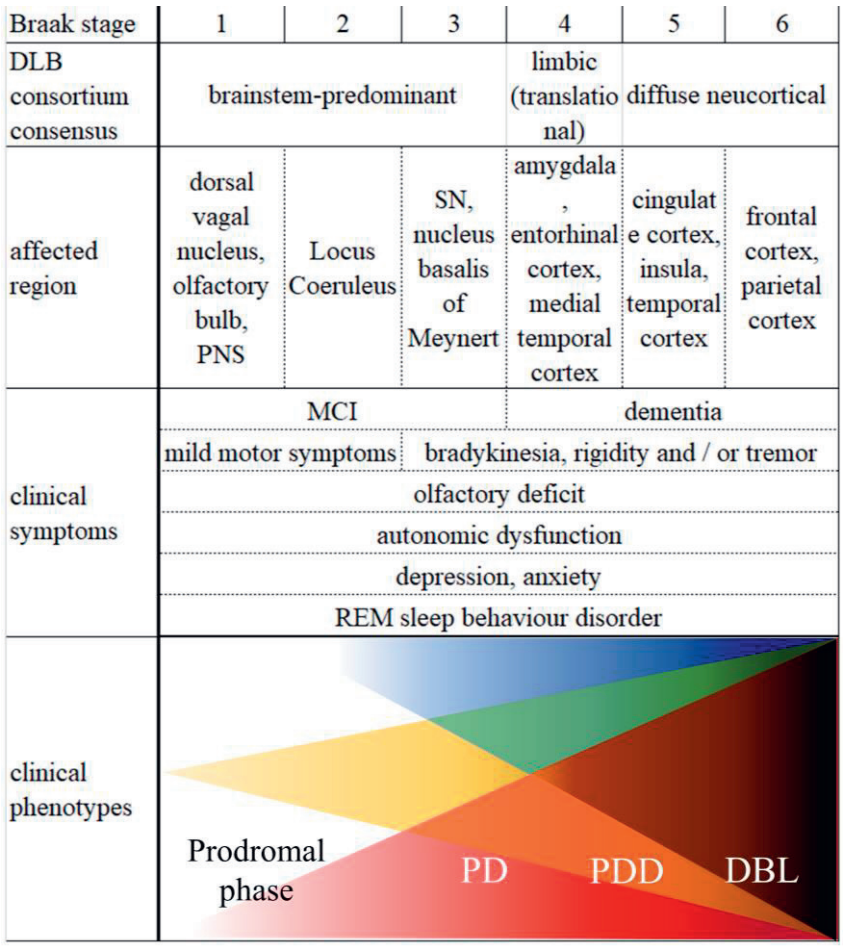

Figure 8. Braak staging presented as a progressive spectrum of LBD. Motor symptoms (red colour, degree of saturation presents severity of symptoms), cognitive dysfunction (blue), nonmotor symptoms (yellow). Peripheral nervous system (PNS), rapid eye movement (REM), Substantia nigra (SN), mild cognitive impairment (MCI). Modified from Kon et al 2020.

2.2.1.2 Pathophysiology of Lewy body disease

SNc neuron loss and decline in TH and DAT immunoreactivity in the corresponding Put, later in CN, has been correlated with the duration of disease in PD (Bernheimer et al. 1973). Bradykinesia and rigidity are correlated with the loss

of DAergic neurons of the ventrolateral tier of SNc (Fearnley and Lees 1991; Greffard et al. 2006). It is hypothesized that a breakdown of compensatory mechanisms in the surviving nigral neurones results in the first motor features of PD (Lee et al. 2004). The ventrolateral SNc neuron clusters are nearly obliterated at the time of diagnosis, yet there might be only partial loss of neurons in the dorsal tier and other DAergic and GABAergic neurons are spared (Surmeier, Obeso, and Halliday 2017). SNc neuron loss continues in a ventrodorsal pattern affecting the related striatal projections as the disease progresses (Kordower et al. 2013). DA loss occurs first and progresses faster in the dorsal Put but molecular imaging studies have revealed that 50% of Putaminal DA is still present after a few years of the motor symptom onset (Kaasinen and Vahlberg 2017; Sung et al. 2017). Functional studies also indicate that the destruction of the DAergic system is not total even after decades of neurodegeneration (Djaldetti et al. 2011).

Functional molecular imaging studies have demonstrated several possible compensatory mechanisms. The DAT expression has been shown to decrease as a reaction to declining DA levels (Lee et al. 2000). Increased serotonergic system density with DA output with extrastriatal plasticity has been shown in a degenerated striatum of parkinsonian animal models (Kozina et al. 2017; Jiménez-Sánchez et al. 2020). It is hypothesized that the early compensatory mechanisms could have long-term effects on BG and even contribute to the risk or development of motor complications of PD (Sossi et al. 2007; Hong et al. 2014; Palermo et al. 2020).

Nigrostriatal DAergic depletion causes bradykinesia and rigidity. Motor symptom severity has been shown to correlate with the degree of SNc neuron loss (Greffard et al. 2006). Bradykinesia also correlates with reduced striatal DA terminals in molecular imaging (Vingerhoets et al. 1997), and molecular imaging of DAT is reported to have a loose correlation with the severity of bradykinesia and rigidity (Spiegel et al. 2007). Results with other motor symptoms, such as tremor, are less congruent. Tremor seems to be associated not only with abnormal interactions between the BG and cerebellum (Obeso et al. 2017; Helmich 2018) but also with dysfunction of the serotoninergic system (Qamhawi et al. 2015). Postural disturbances have been connected to both the cholinergic and glutamatergic systems (Bohnen et al. 2009; Hamani et al. 2016).

DA deficiency also plays an important role in the modulation of some nonmotor symptoms such as gastrointestinal and urinary difficulties both of which are improved by effective DA replacement (Bodis-Wollner 2009; Chaudhuri and Schapira 2009; Jellinger 2015; Chung et al. 2020; Northoff et al. 2021). Cognitive impairment in PD has been associated with greater caudate DA reduction in molecular imaging studies (Palermo et al. 2021). Cognitive decline in PD has also

been linked to abnormalities in extrastriatal 5-HT transporter binding in functional imaging (Joling et al. 2019) and with α-Syn deposition to nucleus basalis of Meynert, thus causing loss of acetylcholine esterase-rich producing neurons (Liu et al. 2015). Abnormalities in the cholinergic (Acharya and Kim 2021), serotonergic (Vegas-Suarez et al. 2019; Wilson et al. 2019), glutaminergic (Iovino, Tremblay, and Civiero 2020), adrenergic (Hopfner et al. 2020) and noradrenergic systems (Gesi et al. 2000; Giorgi et al. 2020) occur in LBDs and contribute either directly or by interconnections with DAergic pathways to the pathology.

2.2.2 Parkinson's disease

2.2.2.1 Epidemiology and risk factors

PD is a common disease that most commonly presents in the seventh decade of life. It is the second most common neurodegenerative disorder after AD. It is the commonest cause of a bradykinetic-rigid clinical syndrome, which is a clinical syndrome characterized by rigidity, tremor, and bradykinesia (Kalia and Lang 2015).

In 2016, 6.1 million individuals worldwide had PD, of whom 47.5% were women and 52.5% were men. The incidence and prevalence of PD appear to be slightly greater in men than in women (Collaborators 2018). The incidence and prevalence increase with age (de Lau et al. 2004; Darweesh et al. 2016), and affect about 1% of over 60-year-olds (de Rijk et al. 1995). Age-standardised prevalence rates increased by 21.7% from 1990 to 2014, and it has been claimed that the global burden of PD has more than doubled largely as a result of increasing numbers of elderly people and is likely to increase further in the next 50 years (Collaborators 2018). The age-standardized overall incidence has remained at a

stable level of 44.5 per 100,000 person-years between 1994 to 2019 (Sipilä and Kaasinen 2020) in Finland. See Figure 9 for the age-specific incidence.

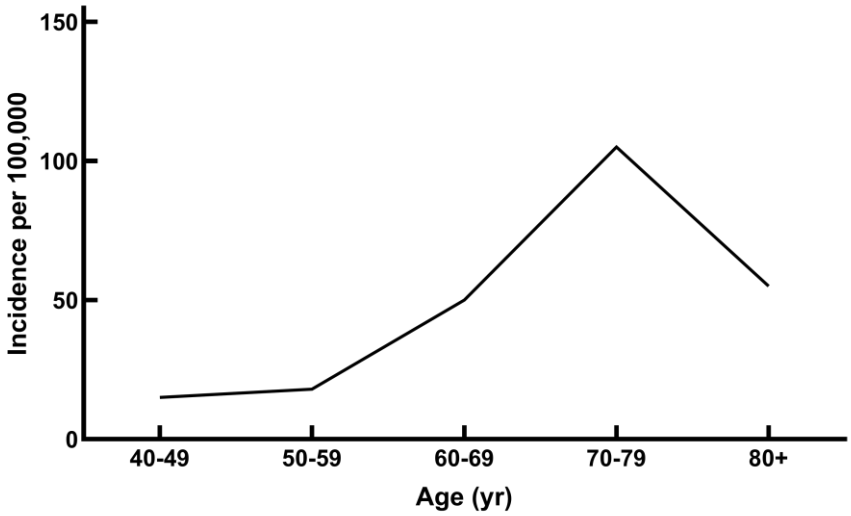

Figure 9. Age-specific incidence rates in 1992 in southwestern Finland. Based on data of Kuopio et al 1999.

The cause of PD is unknown but after age and genetic factors, the strongest risk factor identified so far is related to non-smoking tobacco (Goldman et al. 2019). Pesticide exposure has been claimed to be a risk factor based in part on epidemiological studies and known neurotoxic effects of compounds such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine that cause selective damage to DAergic neurons in the nigrostriatal pathway by mitochondrial poisoning of complex I (Ballard, Tetrud, and Langston 1985). Head injury has also been implicated as a risk factor (Chen et al. 2021).

About 5 per cent of cases of Parkinsonism have a monogenic cause. The most known genetic causes of PD are the mutations of a gene coding lysosomal enzyme glucocerebrosidase (GBA) (Gan-Or, Liong, and Alcalay 2018). Rare autosomal dominant and recessive familial forms have been identified. Several genetic variants have been mapped, and several involving genes have been identified, for example, *Synuclein Alpha*, *Leucine-rich repeat kinase 2*, *Parkin*, *Phosphatase and*

tensin homolog-induced putative kinase. These genes code for proteins, some of which are believed to be involved in the cascades leading to neurodegeneration through disruption of mitochondrial and lysosomal function (Cherian and Divya 2020).

2.2.2.2 Clinical features

PD is a clinically heterogeneous disorder characterized by the presence of bradykinesia and rigidity (Kalia and Lang 2015). These symptoms are due to DAergic degeneration (Langston 2006). The diagnosis is made on clinical grounds dependent upon a detailed medical interview and clinical examination. Diagnostic criteria have been introduced to aid clinicians with diagnosis (Hughes et al. 1992; Postuma et al. 2015). Other disorders with evident signs and symptoms of parkinsonism, such as postencephalitic, drug-induced, vascular and atypical parkinsonism can usually be distinguished clinically (Gelb, Oliver, and Gilman 1999; Joutsa et al. 2014). There are no reliable biomarkers, but neuroimaging may provide additional helpful information in selected cases.

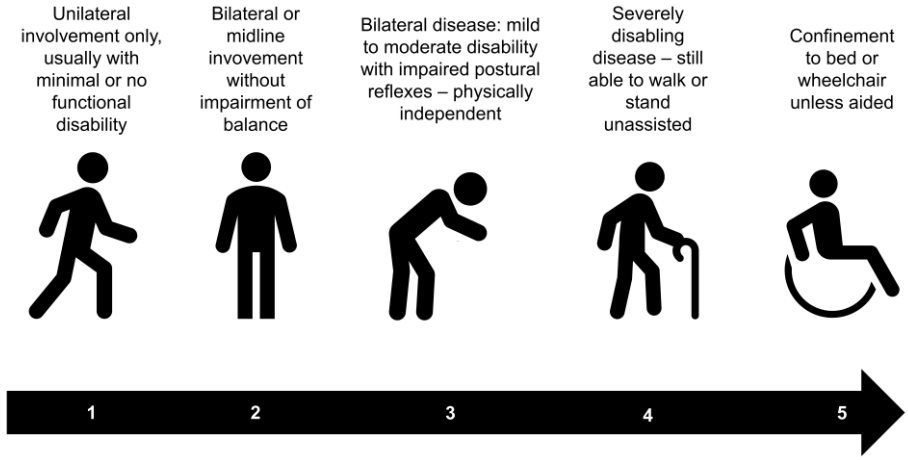

Figure 10 Hoehn and Yahr scale presented from 1 to 5. Based on Hoehn & Yahr 1967. Arrow demonstrates progression of disability in PD.

Characteristic motor symptoms in PD are bradykinesia, which is defined as a progressive reduction in the speed and amplitude of sequential self-paced voluntary movements, muscular rigidity, rest tremor of 4 to 6 Hz and in the later

stages postural instability (Obeso et al. 2017). The symptoms usually have a unilateral onset beginning in an arm or leg but become bilateral and involve axial and bulbar musculature (Lee et al. 1995; Vu, Nutt, and Holford 2012). Clinical deterioration is often more rapid in the early phases (Vu, Nutt, and Holford 2012). The Hoehn and Yahr scale is an internationally used, simple way to numerically rate the disease by motor features (Martinez-Martin et al. 2018), presented in Figure 10. Prodromal symptoms involving motor and non-motor systems may be detected in hindsight in a minority of patients after definitive diagnosis (Berg et al. 2015) and nonmotor symptoms such as depression and pain may contribute considerably to reduced quality of life (Schapira, Chaudhuri, and Jenner 2017). PD dementia is often present at PD's end stage (McKeith 2009). Patients who are diagnosed for the first time over seventy years of age are at greater risk of earlier cognitive impairment (Weintraub et al. 2018). Chapter 2.2.4.2 further examines the pathophysiology of the symptoms. Figure 11 presents the most common nonmotor symptoms (Schapira, Chaudhuri, and Jenner 2017).

L-dopa, DA agonists, MAO and COMT inhibitors, amantadine and anticholinergic drugs are efficacious treatments for both motor and some nonmotor symptoms (Armstrong and Okun 2020). For example, depression responds to pramipexole treatment (Leentjens et al. 2009; Barone et al. 2010; Barone 2011), and optimizing antiparkinsonian medication can relieve some types of pain with the disorders (Quinn et al. 1986; Buhmann, Kassubek, and Jost 2020). With long-term symptomatic treatment disabling motor fluctuations, also known as an on-off phenomenon, and L-dopa induced dyskinesias (Aquino and Fox 2015; Vijayakumar and Jankovic 2016) become increasingly common and require treatment with device assisted therapies such as continuous apomorphine pump therapy, enteral dopa and deep brain stimulation of the STN or GPi (Marsili et al. 2021).

Tremor-dominant and non-tremor-dominant subtypes are distinguished by some neurologists, and the non-tremor-dominant form is associated with a poorer prognosis with this division (Kalia and Lang 2015). Clinical division by age of onset is associated with L-dopa responsiveness and dementia; the younger onset (< 60 years) is associated with better responsiveness to L-dopa and older onset (> 60 years) with has been associated more with dementia. The earlier onset typically features classical limb presentation and a good L-dopa response. The later onset typically bradykinesia dominant with early axial involvement and cognitive impairment (Foltynie, Brayne, and Barker 2002). The division between age onsets and L-dopa responsiveness can be explained by age dependant neurochemistry rather than by pathological differences, since in clinic-pathological studies at least

the final stage of the disease is quite similar in both groups (Kempster et al. 2007; Kempster et al. 2010).

A division to quantify endophenotypes (parkinsonism-predominant, parkinsonism + dementia and dementia-predominant) has been associated with the state of nigrostriatal degeneration, which could not be explained by PD genetic risk variants (Kasanuki et al. 2017). An extensive longitudinal study exploiting over 400 PD patients and biomarkers also recognized an endophenotype division of distinct clinical subtypes of PD: "mild motor-predominant", "intermediate" and "diffuse malignant", in which the types were associated with different spectra of

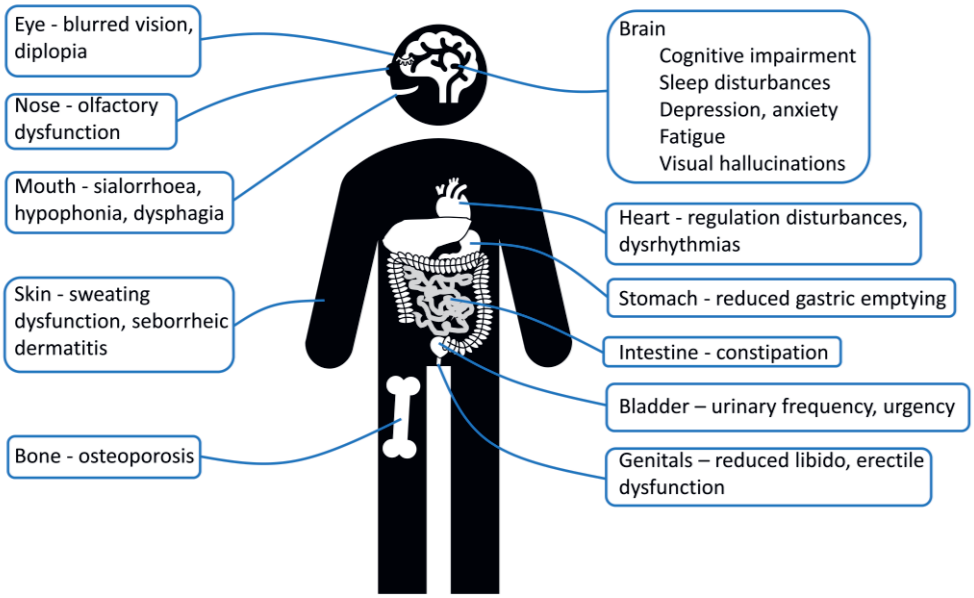

Figure 11. Nonmotor features in PD. Drawn based on Schapira et al 2017.

cerebrospinal fluid (CSF) pathology, imaging findings and progression (Fereshtehnejad et al. 2017). The priority aim of the subtyping is to elucidate the pathogenesis and thus aid in predicting progression and developing personalized and efficient treatments (Berg et al. 2014; Sieber et al. 2014).

2.2.2.3 Neuropathological criteria of Parkinson's disease

A neuropathological diagnosis requires neuron loss in the SN and the presence of LBs (at least 1) in the SN or the LC (Gelb, Oliver, and Gilman 1999).

Neurodegeneration is typically most prominent in the ventrolateral part of the SN (Fearnley and Lees 1991), but close ventral and dorsal neurons are affected by the disease's progression (Kordower et al. 2013; Surmeier, Obeso, and Halliday 2017). There should be no pathologic evidence for other parkinsonism causing diseases, such as progressive supranuclear palsy (PSP) or multiple system atrophy (MSA), which are regarded as exclusion criteria (Gelb, Oliver, and Gilman 1999).

Nowadays neuropathological diagnosis is based on immunohistochemical assessment and McKeith staging by the LBs and Lewy neurites (McKeith et al. 2017a). A neuropathological diagnosis of PD is fairly straightforward in theory, but the reality is often more complex. Patients may have a typical clinical phenotype and SN neuron loss but no LBs, for example (Forno 1996). However, incidental LBs may feature as part of normal ageing, even for 5–55% of the elderly (Jellinger 2019). The neuropathological diagnosis has remained a probability statement of the clinical syndrome despite improved staining and methods (Dickson et al. 2009).

2.2.3 Dementia with Lewy bodies

2.2.3.1 Epidemiology and risk factors

DLB is common neurodegenerative dementia. It is the second most common type after AD, thus causing approximately 5–10% of all dementias (Arnaoutoglou, O'Brien, and Underwood 2019). Its incidence is approximately 3.5 to 100,000 persons per year (Savica et al. 2013). DLB typically affects over 70-year-olds and men over women (Savica et al. 2017). The DLB-related mortality is significantly higher compared to the general population and PD, giving a life expectancy of five to seven years (Savica et al. 2017). DLB's aetiology remains unclear. Age and male sex are acknowledged risk factors (Sanford 2018). There are also genetic risk factors, such as apolipoprotein E and glucocerebrosidase A coding gene variants, which overlap with PD and other dementias (Arnaoutoglou, O'Brien, and Underwood 2019).

2.2.3.2 Clinical features

DLB is broadly underdiagnosed (Sanford 2018). Differentiating DLB from other dementias, especially from PD dementia, is a challenge, and it is debatable whether DLB and PD dementia are distinct entities or rather two phenotypes of the LBD spectrum (Postuma et al. 2016; McKeith et al. 2017b; Cao et al. 2022). Some *postmortem* studies suggest that over 50% of the DLBs have been

misdiagnosed (Palmqvist et al. 2009), but this may be explained by the frequent occurrence of multiple brain pathologies including Alzheimer's change and cerebrovascular disease (Sanford 2018). Clinical diagnosis is based on medical interviews and physical examination, and imaging may support the diagnosis (McKeith et al. 2017b; Hamed et al. 2018; Thomas et al. 2019). Like PD, DLB is a widespread disease causing a variety of symptoms that range widely from autonomic symptoms and motor dysfunction to neuropsychiatric complications. Table 1 presents clinical criteria by the DLB consortium (McKeith et al. 2017b). The core symptoms of DLB are visual hallucinations, fluctuating cognition, rapid eye movement sleep behavioural disorder (RBD) and parkinsonism (Sanford 2018).

There are no disease-modifying therapies (Sanford 2018). The evidence-based management of DLB symptoms was reviewed recently (Taylor et al. 2020) and includes a recommendation for the trial of acetylcholinesterase inhibitors, such as rivastigmine, donepezil and galantamine, and the N-methyl-d-aspartate receptor antagonist memantine (Stinton et al. 2015). Complex, frightening and visual hallucinations may respond to cholinesterase inhibitors and atypical neuroleptics such as clozapine, quetiapine and pimvanserin (Ricci et al. 2009; Taylor et al. 2020). Antiparkinsonian medications may improve Parkinsonian symptoms, but run the risk of enhancing neuropsychiatric symptoms (Goldman et al. 2008).

Table 1 Criteria for the clinical diagnosis of probable and possible DLB. Modified from McKeith et al. 2017.

Essential for diagnosis	Dementia: Progressive cognitive decline, which interferes with normal social or occupational functions, or daily activities. In the early phase of the disease, there might be only prodromal features, such as deficits in attention, executive function and visuoperceptual ability.
Core clinical features	Fluctuating cognition, with variations in attention and alertness.
	Recurrent visual hallucinations are typically well-formed and detailed.
	RBD, which may precede cognitive impairment and dementia.
	At least one of the core features of parkinsonism
Supportive clinical features	Severe sensitivity to antipsychotic medicines
	Postural instability
	syncope or other transient episodes of unresponsiveness
	Severe autonomic dysfunction: orthostatic hypotension, constipation, urinary incontinence
	hypersomnia

	hyposmia
	neuropsychiatric features: hallucinations (other than visual), apathy, anxiety, depression, systematic delusions
Indicative biomarkers	Reduced DAT binding in the BG in molecular imaging
	Cardiac [^{123}I] metaiodobenzylguanidine scintigraphy reflecting postganglionic cardiac autonomic denervation
	Polysomnographic confirmation of non-atonic REM
Supportive biomarkers	Relative preservation of medial temporal lobe structures on a brain scan
	Generalized low uptake on molecular imaging perfusion/metabolism scan, with reduced occipital activity and the possible cingulate sign on a glucose-metabolism scan.
	Prominent posterior slow-wave activity in electroencephalography with periodic fluctuations in the pre-alpha/theta range.
Probable DLB diagnosis	Two or more core clinical features of DLB are present
	Only one core feature is present, and at least one indicative biomarker
Possible DLB diagnosis	Only one core feature is present, no indicative biomarker support
	At least one indicative biomarker is present
Red flags	Other physical illness or brain disorder is likely to account for the clinical picture
	If the parkinsonian features are the only core clinical feature and appear at the stage of severe dementia for the first time
DLB should be diagnosed when dementia occurs before or concurrently with parkinsonism. The PD dementia should be diagnosed when dementia occurs in the context of well-established parkinsonism. For research purposes, the 1-year role is still recommended (McKeith et al. 2005).	

2.2.3.3 Neuropathological criteria of Dementia with Lewy bodies

The neuropathological findings are heterogenous in DLB patients. The anatomical distribution and severity of LB pathology are variable, as well as the concomitant AD pathology. An additional challenge for classification systems is that LB pathology may be found in the brains of elderly individuals without cognitive decline.

Several neuropathological classification systems have been developed to harmonize neuropathology protocols, facilitate research and identify clinicopathological correlations. Classifications are primarily based on a neuropathological assessment of defined anatomical regions and semi-quantitative analysis of LBs and LNs. One of the existing classification systems

for Lewy body pathology is the Braak LB stages (Braak et al. 2003). The Braak LB stages I–VI present a predictable progression of pathology from medullary and olfactory nuclei to cortical areas. The two first stages are incidental or associated with nonmotor symptoms, mid-stages with parkinsonism and higher stages with cognitive impairment (Figure 8). Another classification system is the DLB consortium consensus criteria by McKeith and colleagues (McKeith et al. 2005): the distribution of LB pathology is the basis for three distinct subtypes: brainstem predominant, limbic (transitional), and diffuse neocortical. In this system, the concurrent AD pathology is evaluated.

The Braak LB stages and McKeith criteria from 2005 were not able to classify cases with predominant LB pathology in the amygdala, often found in association with AD neuropathological change (Uchikado et al. 2006). Recent evidence from a population based study supports that this is a distinct subtype where LB pathology originates in the amygdala and caudo-rostral propagation does not occur (Raunio et al. 2019). More recent classification systems aim to recognize a subtype with amygdala-based LB pathology.

Leverenz and colleagues redefined the staging from topographic spreading to the location of the LB pathology burden: brainstem, amygdala, limbic or neocortical (Leverenz et al. 2008). This scheme was able to classify the LB pathology in a vast majority of brains of dementia patients. Soon after, Beach et colleagues published a unified staging system for LBDs with stages: olfactory bulb only, brainstem predominant, limbic predominant, brainstem and limbic, neocortical. With this system, they were able to correlate Lewy pathology burden with clinical features in a diverse study population (Beach et al. 2009). A new dichotomic evaluation of LB-related pathology has recently been released to cut bias related to inter-rater reliability (Attems et al. 2021), and it has shown promising tentative results for accuracy (Koga et al. 2021a).

The DLB consortium consensus criteria by McKeith et al were revised in 2017. The LB pathological findings were now classified to types olfactory bulb only, amygdala predominant, brainstem predominant, limbic (transitional), and diffuse neocortical, with AD pathology assessment according to Braak stages I–VI. Taken together, the findings can be used to assess the probability of typical clinical DLB (Table 2). Olfactory, amygdala and brainstem predominant findings indicate a low probability of clinical DLB. Clinically typical DLB is associated with the diffuse neocortical and limbic type. However, with increasing AD pathological change, the probablility of clinically typical DLB decreases.

A definitive diagnosis of LBD can only be made at autopsy (McKeith et al. 2017a; Sanford 2018). The neuropathological diagnosis of DLB is lucid in theory,

but in the presence of multiple neuropathological findings it may be challenging and only a statement of probability can be made.

Table 2. Tool for estimating whether pathologic findings are associated with a typical clinical DLB. Modified from McKeith et al. 2017. Here AD refers to AD-related pathology and LB to LB-related pathology.

AD / LB	none / low (Braak stage 0-II)	intermediate (Braak stage III- IV)	high (Braak stage V-VI)
Diffuse neocortical	High	High	Intermediate
Limbic (transitional)	High	Intermediate	Low
Brainstem-predominent	Low	Low	Low
Amygdala-predominant	Low	Low	Low
Olfactory bulb only	Low	Low	Low

SN neuronal loss was assessed for the likelihood of parkinsonism.

2.2.4 Mixed neuropathological findings

Dual or multiple pathologies involving different proteins are a rule rather than an exception in both the healthy and demented elderly (Robinson et al. 2018). This leads to considerable difficulties in trying to determine the primary pathology (Savica et al. 2019). Age, the severity of neurodegenerative disease and genetic factors including the *ε4* allele at the *apolipoprotein E* increase the risk of interaction of co-pathologies (Robinson et al. 2018).

The simultaneous appearance of α-Syn, tau, β-amyloid and transactive response DNA binding protein 43 kDa (TDP-43) proteins promotes protein aggregation, accentuating the risk of neuronal damage (Visanji, Lang, and Kovacs 2019; Kovacs 2019). LBs are the hallmarks of LBDs but are found in a considerable number of elderly people who die without signs and symptoms of PD or dementia (Wakisaka et al. 2003; Jellinger 2019; Beach and Malek-Ahmadi 2021). The α-Syn has been suggested as the driver for the neurodegeneration in LBD comorbidities and it is known in animal models to increase amyloid and tau accumulation, whereas conversely tau and β-amyloid increase α-Syn aggregation and toxicity (Visanji, Lang, and Kovacs 2019). Some *in vitro* and animal models

have intriguingly demonstrated contradictory results with α-Syn, leading to both induction and inhibition of Aβ deposition (Kallhoff, Peethumnongsin, and Zheng 2007; Bachhuber et al. 2015; Roberts, Schneider, and Brown 2017).

Concomitant neuropathology complicates the interpretability of possible biomarkers and makes accurate diagnosis even at *postmortem* difficult. A method applying Mini-Mental Status Exam, protein levels of CSF, and genotype at the H1 haplotype at the gene locus encoding *tau* and *ε4* allele at the *apolipoprotein E* loci has been claimed to predict cognitive phenotypes (Cornblath et al. 2020).

2.2.5 Atypical Parkinson's syndromes (Parkinson's plus syndromes)

Atypical parkinsonian syndromes can have overlapping signs and symptoms with PD. The atypical Parkinsonism disorders include DLB (in chapter 2.2.2), PSP, corticobasal degeneration (CBD) and MSA. The differentiation of the atypical parkinsonian syndromes is important because atypical parkinsonian syndromes often progress and life quality decline rapidly compared to the typical PD. Standard therapies for PD often benefit only partially or wane. The gold standard for atypical parkinsonism diagnosis is a neuropathologic examination (Rizzo et al. 2016).

MSA is a rare and sporadic neurodegenerative disease. Symptoms and signs of the disease often are a combination of autonomic disturbances, parkinsonism, and cerebellar and pyramidal signs (Gilman et al. 1999). MSA is α-synucleinopathy, like LBDs, but evidence suggests that the α-Syn accumulations in glial cells are distinct from the α-Syn of LBDs (Koga et al. 2021a). The prevalence rate of MSA is approximately three per 100,000 (Tison et al. 2000). The incidence is approximately three cases per 100,000 in over 50-year-olds (Bower et al. 1997). The prognosis is fairly poor compared to typical PD because there is a rapid decline in several neurologic functions and a mean life expectancy of ten years (Low et al. 2015).

PSP is also an adult-onset, rare and sporadic neurodegenerative disease manifesting typically with supranuclear gaze palsy, parkinsonian motor signs and frontolimbic cognitive dysfunction. PSP motor symptoms usually appear symmetrically with axial rigidity and falls within the first year. The symptoms usually do not respond to L-dopa (Williams and Lees 2009). Its neuropathology is characterized by abnormal 4R tau distribution in the brain (Armstrong 2018). The mean age at onset for PSP is 63 years, and the mean survival is 6–9 years. The prevalence of PSP in over 50-year-olds is estimated to be three per 100,000 with an annual incidence of 5.3 per 100,000 (Coyle-Gilchrist et al. 2016).

CBD is a rare, progressive 4R tauopathy. CBD is generally considered a sporadic disorder (Ali and Josephs 2018), manifesting with a combination of rigid and asymmetric motor symptoms and a poor response to L-dopa. Agnosia, sensory loss, apraxia and alien limb phenomena are typical of CBD (Armstrong et al. 2013; Alexander et al. 2014). CBD typically onsets between the ages of 51 to 69. The mean survival is 6–7 years (Coyle-Gilchrist et al. 2016).

2.3 Functional SPECT imaging

Molecular imaging is used in the clinical practice of nuclear medicine and medical research to better understand the biochemical processes that underlie human disease. Two examples of molecular imaging are PET and single-photon emission computed tomography (SPECT). In both PET and SPECT imaging, patients are given a radioactive compound with a pharmacokinetic behavior that targets a molecular pathway related to the pathology of a certain disease.

PET and SPECT imaging allow a highly sensitive and selective measurement of specific biologic changes in the human body. SPECT imaging has much greater availability and lower costs, while PET achieves a higher resolution. The radioactive ligands used are administered in amounts too small to cause pharmacologic effects (“trace” doses) to avoid perturbation of the biochemical pathway being studied (Louis, Mayer, and Rowland 2015).

2.3.1 SPECT imaging physics

SPECT imaging depends on the physical phenomenon of radioactive decay, which occurs in radionuclides that are unstable due to an incompatible number of protons and neutrons, or excess energy. Radionuclides exist in a metastable state in SPECT imaging and decay from their excited state to the ground state, resulting in the emission of a single photon. The gamma-emitting Tc and 123 I are commonly used for SPECT. Radionuclides are combined with a pharmaceutical through a series of synthetic steps to create a radiopharmaceutical SPECT ligand. The radiation exposure to the patient is a function of the radionuclide used and the amount of radiopharmaceutical administered.

Crystals in a scintillation detector absorb the photons and then emit pulses of light that are then amplified, sorted, and registered as a count when radiopharmaceutical decay events occur inside a SPECT scanner. The sum of these counts creates a tomographic map of all the decay events that occur within the scanner’s view. The result is an image that represents the different densities of radioactivity throughout the tissues captured by the scanner. The basis of SPECT

imaging is that most decay events occur in proximity to where the radiopharmaceutical is acting on the molecular target of interest (Louis, Mayer, and Rowland 2015). There is an increasing number of molecular targets and tracers for clinical and research use.

2.3.2 DAT imaging with SPECT

DAT imaging with SPECT is used for LBDs in clinical practice for diagnostic purposes and research. DAT availability reflects a compensatory decrease aiming to increase the synaptic DA in the striatum (Lee et al. 2000) and is a powerful investigation for estimating disturbances in the presynaptic nigrostriatal terminals in LBDs with parkinsonism phenotypes (Palermo et al. 2021).

Radioligand [^{123}I]-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane ([^{123}I]-FP-CIT) is a widely used DAT binding ligand because of its practical pharmacokinetic and pharmacodynamic properties (Booij et al. 1997). It also has an affinity for other transporters such as 5-HT, which are mainly found extrastriatally in the midbrain and diencephalon (Palermo et al. 2021). Other commonly used DAT ligands are [^{99}mTc]TRODAT, ^{123}I]2β-carbomethoxy-3 β-(4-iodo-phenyltropane) ([^{123}I]-β-CIT), [^{123}I]N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (^{18}F-FP-CIT) and [^{123}I]IPT. [^{123}I]-FP-CIT has been approved by the Food and Drug Administration and the European Medicines Agency for differential diagnostics of parkinsonian syndromes (Palermo et al. 2021). The interpretation of SPECT images is dichotomic and made by visual evaluation, but often striatal binding rations from a semi-quantitative striatal region of interests (ROIs) are analyzed to provide measurements and a cut-off range for normality. Only a few DATs are present in cortical areas and the cerebellum, and as a consequence, these areas are commonly used as reference regions (Joutsa, Johansson, and Kaasinen 2015). ROI- or voxel-based analysis or both are usually performed for research purposes (Palermo et al. 2021).

[^{123}I]-FP-CIT SPECT has high accuracy in differentiating PD from essential and indeterminate tremor and non-degenerative parkinsonisms such as is seen occasionally in L-dopa responsive dystonias (Palermo et al. 2021). It has been claimed to decrease healthcare costs and improve patient care (Antonini et al. 2008). In PD it is usual to find asymmetric DAT loss with greater involvement of the Put than the CN. The total binding diminishes as the disease progresses. However, the anterior-posterior gradient of DA depletion remains (Nandhagopal et al. 2009; Palermo et al. 2021). DAT SPECT imaging may aid clinicians in distinguishing atypical tremor from PD and in PD syndromes where there is no response to L-dopa and in distinguishing neuroleptic induced Parkinson's

syndrome from PD (Palermo et al. 2021). Additionally, DLB can be differentiated from AD and vascular dementias with high accuracy (Saeed et al. 2017; Palermo et al. 2021). There is continuing uncertainty over whether DAergic drugs affect DAT SPECT imaging but if there is an effect, it seems to be relatively small and nonsignificant for clinical purposes. There are also other confounders such as smoking tobacco or 5-HT reuptake inhibitors, which may affect the scan result (Palermo et al. 2021).

The SPECT's relation to neuropathology is unknown (Colloby et al. 2012; Brown et al. 2013; Karimi et al. 2013; Kraemmer et al. 2014) and reduced uptake correlates poorly with disease progression. DAT imaging is not an assessment tool of LBD pathology; it should instead be considered a functional measurement of the DAergic nigrostriatum reflecting axonal activity (Palermo et al. 2021). DAT SPECT correlates well with rigidity and bradykinesia in baseline scans. Additionally, it might have some prognostic value with mild cognitive impairment (MCI) and motor complications and as a prodromal marker, especially in patients suffering from LBD- related sleep disorders (Palermo et al. 2021).

2.4 Depression

2.4.1 Depression in general

Depression is a chronic and heterogeneous disease characterized by low mood and energy, sleep disturbances and an inability to enjoy life. Besides its effect on mood and thought, it may harm physical health (Belmaker and Agam 2008). The global point prevalence is estimated to be 5% and an incidence of 3% (Ferrari et al. 2013). One out of ten Finnish adults was reported to have depression in 2011. Depressive disorders have a significant impact on suicide rates and are associated with two-fold mortality risk (Markkula and Suvisaari 2017).

The aetiology of depression is multifactorial. Approximately 35% of cases are mediated by genes (Ormel, Hartman, and Snieder 2019). Chronic diseases, for example, neurodegenerative diseases, stroke, cancer, and chronic pain, have been associated with a higher risk for depression. Prior depressive symptoms and psychiatric comorbidities, especially personality disorders, increase the risk for depression. Life events and stress, such as financial problems, reproduction or the loss of a loved one, may also trigger the development of depression (Chand and Arif 2021).

Neurotransmitter abnormalities have been reported in depression but it remains uncertain if they are causative. The deficiency of cortical serotonergic

transmission is considered to be an important abnormality. Disturbed cholinergic, histaminergic, DAergic, GABAergic and glutamatergic systems have also been found (Nikolaus, Antke, and Müller 2009; Ashok et al. 2017). Abnormalities in Corticotrophin-releasing hormone and arginine vasopressin affect the hypothalamic-pituitary-adrenal axis and may be important possible pathogenic factors. There is evidence that brain-derived neurotrophic factor levels are lower in depressed patients' central nervous systems, and they are argued to be the link between stress, neurogenesis and depression (Hao et al. 2019). Oxidative stress and disturbances in immune systems are acknowledged as important factors in depression, as also in neurodegenerative diseases (Maes et al. 2011).

Depression diagnosis is based on the International Classification of Diseases, Tenth Revision (ICD-10) (Komulainen, Lehtonen, and Mäkelä 2012) or the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (*Diagnostic and statistical manual of mental disorders* 2013). In ICD-10 criteria, the degree of the disease depends on the amount and quality of the typical symptoms. Table 3 presents these criteria. It is noteworthy that neither age nor ageing are included in either diagnostic criteria. Major depression is not a part of normal ageing, although it may be associated with aspects of ageing like grief and physical illness. Thus, the depression of geriatric patients should be considered a treatable medical illness. Depression is a major cause of emotional suffering in the elderly and may compound the reduced quality of life of various diseases. The elderly may experience feelings of general unwellness or apathy instead of classical mood symptoms, thus making their depression more difficult to recognize. Specific geriatric questionnaires have been developed to aid assessment (Sheikh et al. 1991). Late life depression, like neurodegenerative diseases, is an increasingly important public health issue in elderly people in Finland (Tilastokeskus 2019 [cited: 7.12.2021]).

Table 3 ICD-10 criteria for major depression. A, B C, D and E criteria must meet for diagnosis: Mild 4 symptoms (2 core), moderate 6 symptoms (2 core) and severe at least 7 symptoms (3 core).

A		Depressive episode period of a fortnight at least
B		The patient has not had a manic or hypomanic period
C		The most common exclusion diagnoses are not the cause: a mental disorder due to a known physiological condition or psychogenic substance use
D		Core symptoms
	1	Depressed mood most of the time during at least fortnight. The mood is exceptional to the patient and is not dependent on external factors.

	2	Loss of interest or pleasure in things, that normally have been interesting or pleasuring.
	3	Exceptional fatigue
E		Additional key symptoms
	1	Decrease in self-confidence or conscience
	2	Unsubstantiated or unreasonable self-allegations
	3	Repeated thoughts related to death or suicide or self-destructive behaviour
	4	Difficulties in concentrating
	5	Change in psychomotorics (excitation or retardation)
	6	Sleep disturbances
	7	Change in appetite accompanied by a change in weight

Treatment focuses on antidepressants and psychotherapies. Antidepressants are overall more efficacious than placebos, but dropout rates are significant (Cipriani et al. 2018). Most antidepressants inhibit 5-HT or 5-HT and NE reuptake. Psychological therapies are effective for mild to moderate depression or as a supportive treatment for severe depression (Cuijpers et al. 2008). Both medication and psychological therapies may have negative effects (Cipriani et al. 2018; P. Cuijpers et al. 2018). The most effective treatment for severe depression is electroconvulsive therapy (van Diermen et al. 2018). More recognition has been given lately to physical activity and exercise, which can be used to reduce symptoms and improve the quality of life in mild to severe depression (Schuch and Stubbs 2019). Most patients with major depression recover fully, some even without any kind of intervention. 75% of the depressed patients recovered in a Finnish 10-year follow-up study with 10,000 randomly sampled adults (Markkula and Suvisaari 2017).

2.4.2 Depression in Lewy body spectrum diseases

Depression is common in LBD and may precede diagnosis by several years in some patients (Schapira, Chaudhuri, and Jenner 2017). The prevalence of depression is higher in LBDs than in healthy controls (Larsen et al. 2017). Approximately every third PD (Reijnders et al. 2008) patient and every second DLB patient (Ballard et al. 1999; Takahashi et al. 2009) have clinically significant depressive symptoms during the course of their disease. It is important to diagnose depression because it increases death risk and decreases life quality (Gallagher, Lees, and Schrag 2010; Kasten et al. 2012). Depression is commonly

accompanied by anxiety in LBDs, although both can exist independently (Castrioto et al. 2016).

Chronic disease-related stress may lead to depressive symptoms in LBDs (Even and Weintraub 2012; DeJean et al. 2013). And common LBD symptoms, such as sleep disturbances and progressive decline in motor functions can increase the risk for depression (Dissanayaka et al. 2011; Schapira, Chaudhuri, and Jenner 2017). Several studies also support the idea of depression in LBDs is a distinct biological entity (Even and Weintraub 2012; Kritzinger et al. 2015). In contrast to PD, essential tremor and indeterminate old age tremor have not been linked with depression (Aslam et al. 2017), supporting the idea that depression in LBDs is not only based on declining physical abilities. Dementia, prevalent in LBDs, is known to increase the risk for depressive symptoms (Kuring, Mathias, and Ward 2020) and, vice versa, depressive symptoms increase the risk of dementia (Kuring, Mathias, and Ward 2020). However, when compared to other neurodegenerative and dementia-causing diseases such as AD, LBDs seem to have a higher risk for depression (Andreasen, Lönnroos, and von Euler-Chelpin 2014).

The neuropathology of this comorbidity remains ambiguous. However, α-Syn-related pathology in the brainstem has been correlated to depression in elderly subjects without dementia or PD (Wilson et al. 2013) and in LBDs (Patterson et al. 2019). Key shared dysfunctions of cholinergic, noradrenergic and serotonergic systems in PD may be linked to the neuropathology of PD depression (Schapira, Chaudhuri, and Jenner 2017; Conio et al. 2020). Dissatisfaction or loss of enjoyment is seen more commonly than in primary depressive illness (Kasten et al. 2012; Kritzinger et al. 2015), which might be in keeping with depression's relationship to DA deficiency in LBD. This is also suggested because LBD-associated depression is shown to deepen during off periods and to respond to DA agonists (Barone et al. 2010; Barone 2011; Taylor et al. 2020). And is supported by the fMRI study, which demonstrated aberrant connectivity between the ventral tegmental area and the anterior cingulate cortex (Wei et al. 2018). Diffusion MRI connectometry studies have implied that emotion- and recognition-related circuits are involved in depressive symptoms in PD (Ansari et al. 2019). A recently published study demonstrated that PD with depression can be distinguished from healthy controls and PDs without depression with high-dimensional MRI with high accuracy (Cao et al. 2022).

Depression treatments have been inadequately evaluated and there is still insufficient evidence for making recommendations for several treatments (Taylor et al. 2020). 5-HT and noradrenaline reuptake inhibitors like nortriptyline and venlafaxine have decreased depressive symptoms in several studies. Antidepressants should be used with caution in LBDs because they might worsen

sleep disturbances. DA agonists have shown benefits in the short term, but the results are inconclusive. Cognitive-behavioural therapy is probably efficient and efficacious in the depression of LBD patients. Future studies are needed to address the effectiveness and safety of neuropsychiatric treatments in LDBs (Seppi et al. 2019; Taylor et al. 2020).

2.5 Height in health and disease

Height is an objective measure commonly used in healthcare and research (Lissauer et al. 2022). It has been widely used in research to evaluate welfare trends throughout history and the long-term impacts of childhood health and conditions. It is easy and inexpensive to measure and has an objective scale (Steckel 2008).

Genetic factors are responsible for up to 80% of divergence in body height (Wood et al. 2014). Whether an individual can reach the height predicted by genotype depends on various environment-related factors (Grasgruber et al. 2014). Growth is regulated by different hormone systems during an individual's development. The growth hormone (GH) / insulin-like GH 1 axis (IGF-1) axis is involved in a multitude of processes during the phases of life (Figure 12). Either GH or its metabolite IGF-I effects as a metabolic active hormone during the adulthood; by impairing insulin action or promoting protein anabolism depending

on the nutritional state (Olarescu et al. 2019 Oct 16). Sex steroids and thyroid hormones are other major hormones in growth (Lissauer et al. 2022).

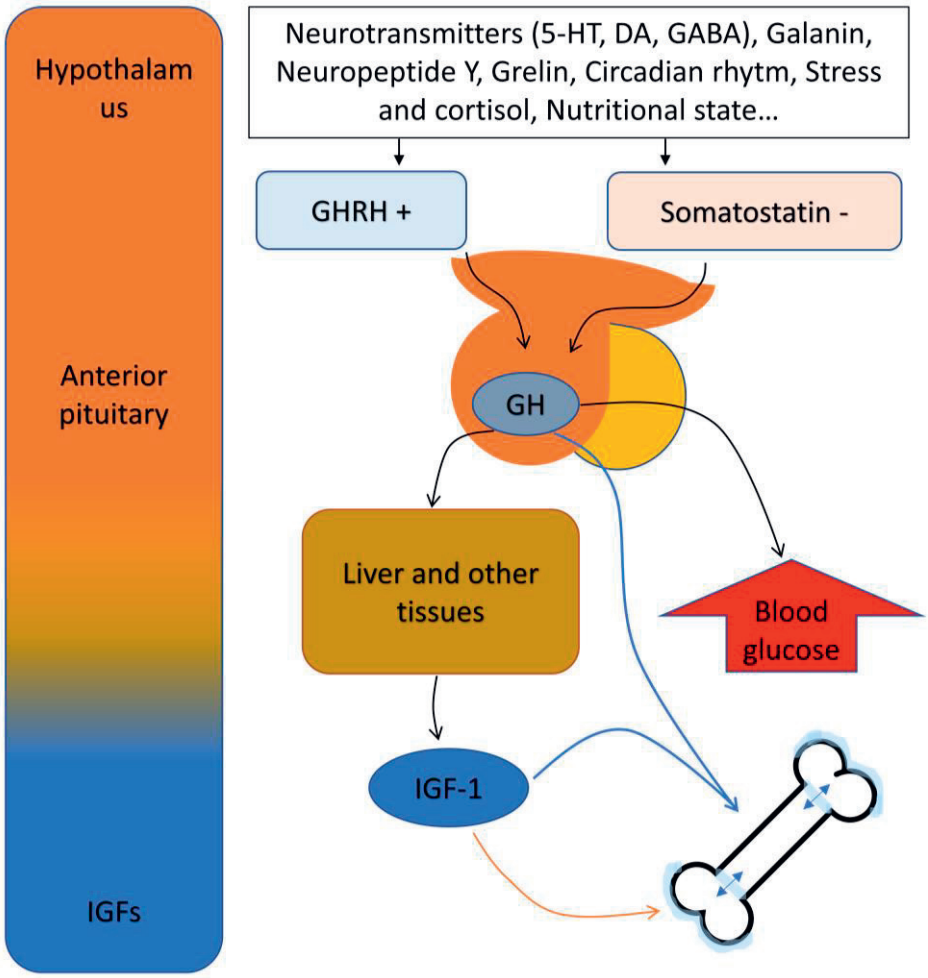

Figure 12. Chart of GH / IGF-1 axis. Gradient bar demonstrates distinct factors in the axis. GHRH induces whereas Somatostatin inhibits the release of GH. GH and IGF-1 stimulate bone and tissue growth (blue arrows). Supplementing IGF-1 stimulates cartilage growth (orange arrow). GHRH, Growth hormone-releasing hormone. Modified from Olarescu et al 2019.

The fastest phase of growth occurs during the foetal period and accounts for about 30% of the eventual height. Foetal growth is stimulated indirectly by raised levels of IGF-1. Genetic growth potential, maternal nutrition and the clinical state of the pregnancy determine the foetal growth. After birth, the length of growth depends on nutrition and general health and progresses in line with individual genetic growth patterns. The infancy phase is dependent on normal hormone levels, especially thyroid hormones. Growth during infancy accounts for approximately 15% of adult height. GH is the main determinant of growth during childhood, which induces an IGF-1 effect at the epiphyses, but nutrition, healthy state and other hormones are also important factors. This growth phase is characterized by steady and prolonged growth and corresponds to about 40% of adult height. When an individual reaches the pubertal growth spurt, testosterone and oestradiol, induce the secretion of GH, but they also cause the fusion of the growth plates and thus end the height growth. The pubertal spurt adds approximately 15% to the final height. The sex steroids also induce the fusion of the epiphyseal growth plates and the end of growth (Lissauer et al. 2022).

Shrinkage begins several years after the peak of height has been reached. According to a study by Fernihough and McGovern 2015 based on the British population, stature decline is approximately 2–4 centimetres over the life course and is a significant factor after reaching the age of 50. Moreover, their study associated shrinkage with a decline in health. Shrinkage has been associated with loss of weight and bone density in women. The decline in stature is recognized as an important predictor and covariate of health at older ages. Shrinkage is an often ignored factor in height-health studies because height has generally been assumed to be fixed after late adolescence (Fernihough and McGovern 2015; Jain and Ma 2020).

Height has been associatedwith risks for various diseases. There is evidence that taller stature is associated with a lower risk for coronary heart diseases and respiratory diseases (McCarron et al. 2002; Collaboration 2012). It has been shown that patients under 160.5 cm have up to a 50% higher risk for morbidity and mortality from coronary heart disease than taller individuals (Paajanen et al. 2010). Similar phenomena have been shown for mortality with mental disorders, gastrointestinal ulcers and liver disease (Collaboration 2012), whereas taller height has been associated with a higher risk for atrial fibrillation, pulmonary embolism and several cancers (Collaboration 2012). Lai et al.‘s 2018 genetical study has provided supportive evidence by using Mendelian randomisation. It concluded that taller height is associated with a higher risk for atrial fibrillation, thromboembolism, musculoskeletal disorders and overall cancer and a lower risk for coronary heart diseases, hypertension, and gastro-oesophageal reflux, but the

study was unable to find significant associations between genetically determined height and neurological diseases (Lai et al. 2018). There are contradictory results from an association between adult height and longevity, but some studies have found that the risk of death from any cause is slightly lower in tall individuals (Collaboration 2012), while there are several studies with contradictory results (Samaras 2012; Rohrmann et al. 2017). Biological mechanisms behind the height-disease risk association are still widely uncertain and need to be studied more.

3 Aims

This thesis focuses on BG nuclei DAergic neurodegeneration, one of the key neuropathological events in LBDs.

Specific aims of the thesis were:

I. To examine possible associations between *in vivo* brain DAT SPECT imaging and SNc neuronal survival in PD.
II. To investigate a possible correlation between DAT imaging and striatal DAergic axons in PD.
III. To investigate whether an association between depression and a lower density of DAergic neurons, previously demonstrated in nondemented elderly individuals, is also present in LBD patients.
IV. To study the possible relationship between adult body measurements and the SNc neuronal survival in PD.

4 Materials and Methods

4.1 Subjects

Table 4. Demographic characteristics of studied subjects.

Study	I	II	III	IV
PD n	11	10	46	22
LBD n	-	-	20	11
PSP n	1	2	-	-
MSA n	5	1	-	-
CBD n	1	1	-	-
AD n	-	-	7	3
Control n	-	-	-	19
Total n	18	14	73	55
PD age (SD)	74.4 (6.5)	74.1 (6.7)	79.8 (7.1)	79.3 (5.7)
PD sex (m/f)	10 / 1	9 / 1	32 / 14	14 / 8
DLB age (SD)	-	-	77.4 (7.1)	78.4 (6.0)
LBD sex (m/f)	-	-	11 / 9	7 / 4

PD patients receiving L-dopa or other antiparkinsonian medication in this study were diagnosed by a neurologist based on clinical examination and the use of operational diagnostic criteria, either the Queen Square Brain Bank criteria (Hughes et al. 1992) or the Movement Disorder Society criteria (Postuma et al. 2015). Other atypical parkinsonian syndromes were diagnosed by neurologists. Geriatricians, neurologists or general practitioners evaluated and treated the other patients.

4.1.1 Studies I and II

Eighteen cases who had received a neuropathologic diagnosis of PD, CBD, PSP, or MSA from 2002 to 2016 and had been scanned with DAT SPECT for diagnostic purposes had a representative formalin-fixed, paraffin-embedded block available from the SN were identified from the hospital records of the Turku University Hospital, Finland. Two independent neuropathologists re-evaluated all 18 cases individually using neuropathological diagnostic criteria for PD (Gelb, Oliver, and Gilman 1999; Dickson et al. 2009), CBD (Dickson et al. 2002), PSP (Hauw et al. 1994) and MSA (Trojanowski, Revesz, and MSA 2007).

A subsample of this cohort was used in Study II. Put samples were unavailable for six patients from Study I. Two patients who had available Put samples but no SNc samples were included in Study II but excluded from Study I.

4.1.2 Studies III and IV

A database of *postmortem* cases (n = 168) with clinical parkinsonism due to neurodegenerative disease confirmed by a neuropathologic examination was used to identify cases for Studies III and IV. Seventy-three patients who had LB pathology from 2002 to 2016 were identified from the records of the Turku University Hospital, Finland.

Study III's inclusion criteria were sufficiently detailed clinical details to enable accurate phenotypic characterization (Kasanuki et al. 2017), as per clinical phenotypes Parkinsonism-predominant (n = 23), Parkinsonism + dementia (n = 30) and Dementia-predominant (n = 20). Study IV used a subsample of 36 patients from 168 *postmortem* cases. Inclusion criteria included height and weight measurements as well as clinical and autopsy data. The most common clinical diagnosis was PD (n = 22). The same phenotypical categorization mentioned in the previous chapter was applied: Parkinsonism-predominant (n = 13), Dementia-predominant (n = 11) and Parkinsonism + dementia (n = 12). Study IV used 19 individuals who died without known neurological diseases as controls. Figure 13 demonstrates a flowchart of the patient selection.

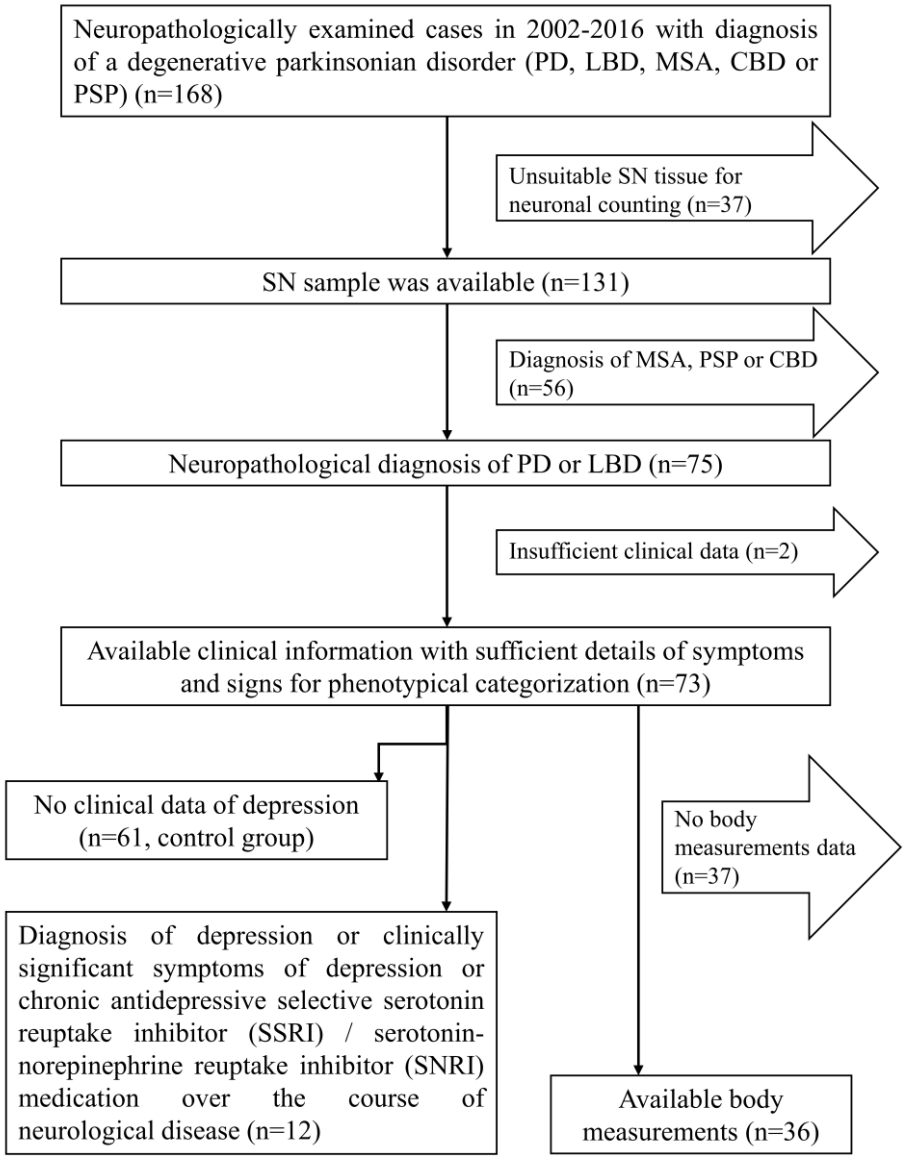

Figure 13. Flow chart of case selection for studies III and IV. Clinical categorization was made according to principles of Kasanuki et al 2017.

Table 5 Clinical characteristics of LBD patients with depressive symptoms, from the autopsy records or the last visit before death clinical records.

Case	Age at death (yr)	Sex	Clinical diagnosis	Clinical syndrome[a]	Symptom onset to death (yr)	HY	MMSE	Antiparkinsonian medication	LEDD (mg)
A	85	F	PD	Parkinsonism + dementia	5.25	-	-	LDC	150
B	68	M	PD	Parkinsonism	4.5	2	-	LDC, PRX	810
C	82	M	PD	Parkinsonism + dementia	8	5	18	LDC	600
D	75	M	PD	Parkinsonism + dementia	20	4	19	LDCE	599
E	81	F	PD	Parkinsonism + dementia	4	2	16	LDC	250
F	77	M	PD	Parkinsonism + dementia	-	4	-	LDC	400
G	68	F	Atypical parkinsonism	Parkinsonism + dementia	12	4	17	LDCE, PRX	906
H	74	M	-	Dementia	-	5	20	-	0
I	86	F	PD	Parkinsonism + dementia	-	4	14	LDB	250
J	67	F	-	Dementia	-	5	22	-	0
K	75	M	PD	Parkinsonism	6	4	-	LDC	500
L	80	M	PD	Parkinsonism + dementia	2.5	3	15	LDC	500
Mean (SD)	77 (6.6)	-	-	-	7.7 (5.8)	4 (1.1)	18 (2.7)	-	414 (293)

LDC = levodopa + carbidopa, PRX = pramipexole, LDCE = levodopa + carbidopa + entacapone, LDB = levodopa + benserazide, LEDD = levodopa equivalent daily dose of antiparkinsonian drugs, MMSE = Mini Mental State Examination.

4.2 Methods

4.2.1 SPECT imaging (Studies I and II)

The patients were scanned as part of the clinical investigation, and the data were retrospectively used for research purposes. The patients received a rapid 185-MBq bolus of the [123I]FP-CIT tracer and were then scanned four hours after the injection, or the scanning was performed 24 hours after the tracer injection for the [123I]β-CIT. The scan was performed either with [123I]FP-CIT (n = 13, PD n =9) or [123I]β-CIT (n = 5, PD n =2) SPECT at the Department of Nuclear Medicine, Turku University Hospital, Turku, Finland.

Ten patients were scanned with a Picker Irix gamma camera with 1.90-cm (0.75-in) crystals (Picker International Inc, Highland Heights, OH), five with an ADAC Vertex V60 gamma camera (ADAC Laboratories, Milpitas, Canada), and three patients with 2 GE Infinia II Hawkeye SPECT/CT camera (GE Medical Systems, Waukesha, WI). On average, the patients were scanned 1.5 (SD = 1.2) years after the onset of motor symptoms and died 5.2 (2.7) years after the scan.

The SPECT images were reconstructed using the three-dimensional ordered-subset expectation algorithm with 16 iterations, four subsets, and fixed radii of rotation in the Hybrid Recon Neurology, version 1.0F, software by Hermes Medical Solutions AB, Stockholm, Sweden. The Chang uniform attenuation correction of μa = 0.146 cm-1, a depth-dependent resolution-recovery correction, Monte Carlo–based scatter correction, and a gaussian post-filtering with a full-width-at-half-maximum of 0.70 cm, were applied in the reconstruction (Kaasinen et al. 2014).

Automated semi-quantitative analysis of the SPECT scans was carried out with the BRASS software version 3.6 by Hermes Medical Solutions AB, Stockholm, Sweden, to define ROIs. Scanner-specific corrections were applied except with the ADAC Vertex V60 data. Specific binding ratios (SBRs) were calculated for the left and right hemispheres and anterior and posterior Put using the occipital cortex as the reference region: SBR = (ROIPut – ROIoccipital) / ROIoccipital (Kaasinen et al. 2014). The means of the left and right values of the Put were used to assess correlations between SBRs and SNc neuron or Put axon counts.

The voxel-based analysis was also applied to the studies. A common occipital cortex ROI was used to estimate nonspecific binding, thus the SBR was smaller than one (Joutsa, Johansson, and Kaasinen 2015). SBR images were then calculated by dividing the images by the signal of the occipital cortex. Voxel-by-voxel general linear model analyses were performed correspondingly to ROI

analyses. The analyses were restricted to grey matter, midbrain and pons regions that showed specific binding. Midbrain SBR values were extracted with a 2-mm-radius spherical ROI centered to the maximum midbrain SBR of the average ratio image of the sample to evaluate DAT binding in the SN with Marsbar software (version 0.44; marsbar.sourceforge.net) (Brett et al. June 2-6, 2002). For the whole-brain voxel-by-voxel, the image processing was conducted with Statistical Parametric Mapping software (SPM8; fil.ion.ucl.ac.uk/spm/software/spm8/) running in Matlab 2011b by Mathworks Inc., Natick, MA, USA.

4.2.2 Patient medical history (Studies III and IV)

The patients' hospital records were studied to find clinical symptoms and signs that might correlate with nigral neuron counts. The following data were evaluated: rest tremor, rigidity, bradykinesia and problems with memory and orientation. Numeric data were collected, if available, including Mini-Mental State Examination (MMSE) scores, Beck Depression Inventory (BDI) scores, body measurements and L-dopa equivalent doses of medication (LEDD). Hoehn and Yahr scale scores were estimated based on clinical information available related to the symmetry of symptoms, balance, and mobility.

Study III patients were classified as clinically depressed if they had been diagnosed with depression or prescribed chronic antidepressive SSRI/SNRI medication during the course of their neurological illness. No severity threshold was used for depression.

Study IV patients' height and weight measurements were collected from the autopsies conducted in Turku University Hospital. The weight is measured by a floor scale with a standard-sized hospital bed and the height by a measuring stick from heels to the top of the head. Body measurements were unavailable from the autopsy for eight patients; thus, their height and weight were collected from Turku University Hospital's clinical records. The median (range) time from recorded *antemortem* body measurements to death was 4.0 (0.9–10.2) years in these eight cases. The 19 controls were examined by a forensic pathologist at the Finnish Institute for Health and Welfare, as described (Heiskanen et al. 2019).

4.2.3 Neuropathologic examination

The brains in this study were a retrospective hospital sample from Turku University Hospital from 2002 to 2016. The brains were from autopsies performed at Turku University Hospital, but a minority were from medicolegal autopsies

performed at the Finnish Institute for Health and Welfare/forensic pathology and autopsies at regional hospitals. Table 6 presents the delays between death and autopsy and autopsy and neuropathological examination.

Table 6 Examination delays in days are presented by medians (range)

Study	Death to autopsy	Autopsy to neuropathological examination
I	-	-
II	5 (1–8)	35 (18–51)
III	5 (1–18)	23 (10–91)
IV patients	5 (2–8)	23 (12–73)
IV controls	3 (1–8)	20 (11–56)

Brain fixation was performed for a minimum of two weeks in 4% phosphate-buffered formaldehyde. Macroscopically, the brains were examined externally and from thin slices.

The histological sampling was adapted from the CERAD recommendation (Mirra et al. 1991). Samples were obtained from the medulla oblongata, pons, midbrain (at the emergence of the third cranial nerve), cerebellum, thalamus, BG, both hippocampi, amygdala, cingulate gyrus, middle gyrus of the frontal lobe, superior and medial gyrus of the temporal lobe, inferior parietal lobule and medial occipital lobe. The specific location and hemisphere of the samples were selected by the neuropathologist during the routine examination. Further samples were taken when indicated after macroscopic or microscopic evaluation. The samples were processed to formalin-fixed, paraffin-embedded blocks.

Microscopic examination was performed from hematoxylin- and eosin-stained histological sections (6 μm). Neurodegenerative changes were evaluated from Bielschewsky and/or immunohistochemical stainings. Histology and immunohistochemistry were assessed from 2012 onwards by principles presented by Montine et al. 2012.

4.2.3.1 Staining procedures and neuron counting

The neuron numbers and area of the SNc were calculated from paraffin-embedded tissue from the midbrain at the level of emergence of the third cranial nerve for each case.

We used TH immunohistochemistry to identify DAergic neurons. Tissue sections were stained for this with an anti-TH antibody at 1:50 dilution (clone 1B5; product code NCL-TH, Novocastra, Newcastle, UK). We used a Lab Vision Autostainer 480 (Thermo-Fisher Scientific, Fremont, CA, USA) with detection performed applying PowerVision+polymer kit with diaminobenzidine as chromogen (DPVB+110HRO; Immunovision Technologies, Vision Biosystems, Norwell, MA, USA) according to standard protocol.

The slides were scanned using a Pannoramic P25 Flash slide scanner and analyzed using CaseViewer software version 1.4.0.50094 (3DHISTECH Ltd, Budapest, Hungary). This single section counting technique has weaknesses compared to full unbiased stereological counting, although it has been shown to provide a satisfactory estimate of neuronal loss in the SNc (Ma et al. 1995).

The midbrain of each case was consecutively sectioned at 20 micrometers for TH staining and Cresyl fast violet histochemistry for Studies I and II as previously described (Kraemmer et al. 2014). The outline of the SNc was annotated on the scanned slides, and the Pannoramic viewer software was used to calculate the SNc surface area. TH-positive or neuromelanin containing cells were independently quantified by two examiners, both blinded to the clinical data. The mean density of neurons in these samples was calculated per mm^2. The interrater agreement of the neuron counts between the two examiners was excellent (for TH-positive SNc neurons intraclass correlation coefficient = 0.92 m, consistency).

For Studies III and IV, the midbrain was sectioned at 8 micrometers for Luxol fast blue (LFB) and TH staining. The outline of the SNc was annotated on the LFB stained slides within a 1x magnification. The SNc area was calculated with CaseViewer software. The annotated SNc outline was transferred to the corresponding TH stains by using vessels, section outlines and other histological landmarks as references. Figure 15 demonstrates the outline annotation. TH-positive neurons were counted at high magnification from inside the outline. Only neurons with a visible nucleus were included. A similar protocol was followed with the control cases in Study IV. Studies III and IV used the diameters of the nuclei for the Abercrombie correction, which was calculated by dividing the section thickness with a sum of the section thickness and the mean of the nuclei diameters for each sample (Guillery 2002), Figure 14).

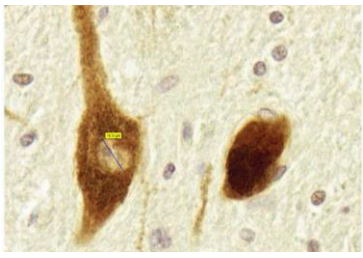

Figure 14. TH-positive neurons with a visible nucleus were included. Nuclei diameters were used for Abercrombie correction.

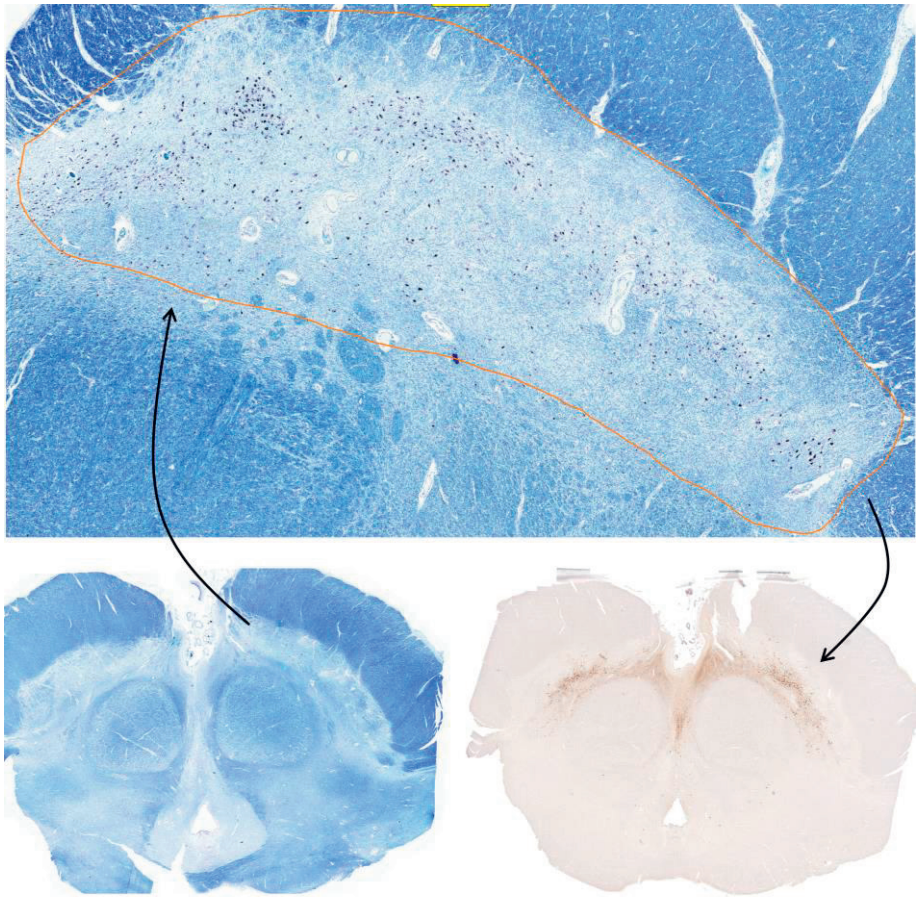

Figure 15. Demonstration of SNc outlining method. SNc outline was marked to LFB stained section and transferred to TH stain using anatomic structures such as veins and section outlines as landmarks.

4.2.3.2 Fiber counting (Study II)

Put samples were obtained from the coronal slices of the postcommisural striatum where GPi and GPe were present. The Put samples were sectioned at 8 micrometers thickness and stained for TH to identify DAergic axons. The margin of Put was annotated into sections, and the annotated area was divided into nine subregions for counting (Figure 16). Two independent examiners quantified TH-positive nerve fibers or cross sections of fibers from three standardized visual areas (20x magnification) in each of the subregions in each Put.

The interrater agreement of the fiber counts between the two examiners was good (intraclass correlation coefficient = 0.739, absolute agreement) or excellent (0.815, consistency). Fiber counts of the Put were reported by regions based on different axonal/neuronal densities: three in the medial-lateral and three in the rostrocaudal direction.

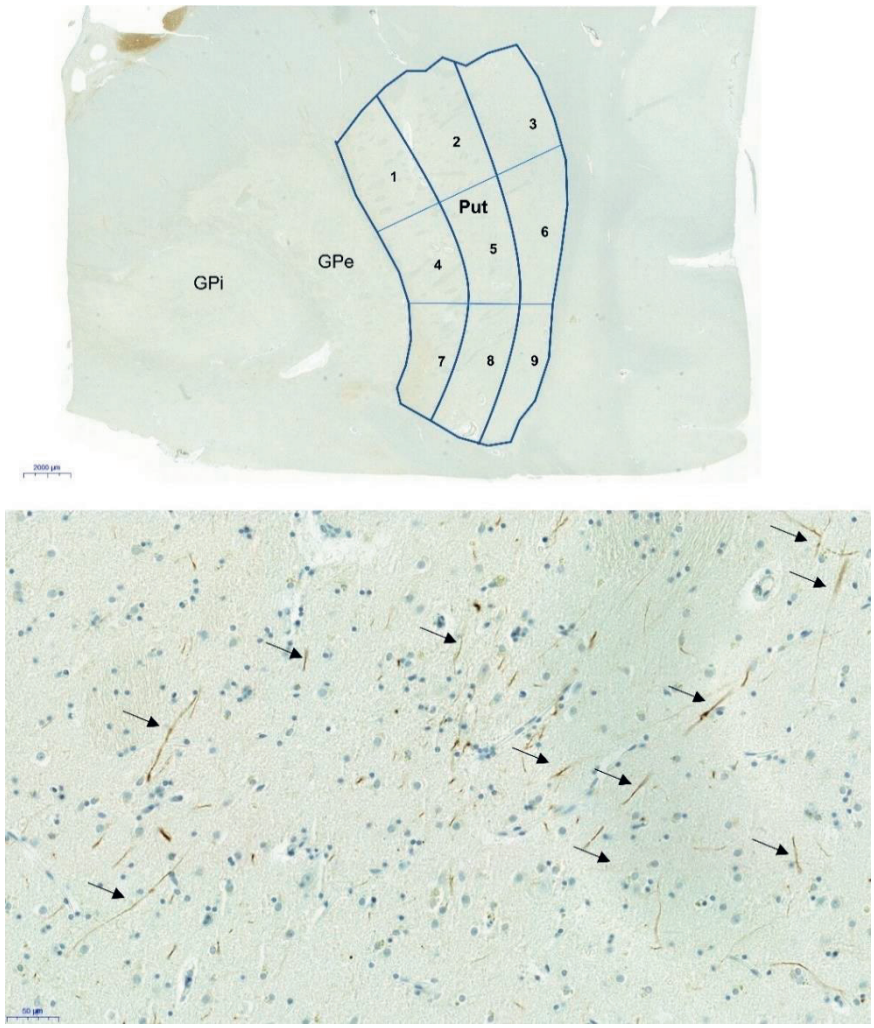

Figure 16. A section of the postcommisural striatum was stained for TH. Put was identified for fiber counts from the coronal section, that also included GPi and GPe. For practical reasons, Put was sectioned after outlining. As an example, a few of the counted fibers are marked with an arrow from the Put sample.

4.3 Statistical analyses

SPSS Statistics 25 for Windows (IBM Corp, Aonk, NY, USA) was used for statistical analyses. The data distribution was evaluated with histograms and the Shapiro-Wilk test. P-values less than 0.05 were considered to be statistically significant in all statistical analyses.

The mean Put SBRs in Studies I and II were correlated with the corresponding SNc neuron and total Put fiber counts. The correlations were evaluated with Spearman's correlation or Pearson's correlation coefficients, as appropriate. Interrater agreements were analyzed with both absolute agreement and consistency.

Differences between LBD patients without and with depressive symptoms were analyzed for Study III with independent samples t-test (parametric test) or Mann-Whitney U-test (nonparametric test) for continuous variables. Differences between three groups (Parkinsonism-predominant, Parkinsonism + dementia and Dementia-predominant) were analyzed with a 1-way analysis of variance or analysis of covariance, or Kruskal–Wallis test (nonparametric test). Chi-square test or Fisher exact test were applied for dichotomic variables as appropriate.

Correlations between SNc neuron numbers and clinical factors were evaluated in Study IV with Pearson's correlation or Spearman's correlation, as appropriate. Linear regression analysis by the enter method was performed within the correlating variables. Differences between LBD patients and controls were analyzed with independent sample t-tests or chi-square tests, as appropriate.

4.4 Ethics

All studies were conducted according to the principles of the Declaration of Helsinki, and the Ethics Committee of Turku University Hospital approved the protocols.

5 Results

5.1 Neuropathologic cell counts and SPECT (Study I and II)

Neither TH-positive SNc neuron counts (r = -0.11, p = 0.66) nor Put fiber counts (r = 0.00, p = 1.0) correlated with mean Put SBRs, Figure 17. Table 7 presents counts and SBRs among demographic data of the studied subjects.

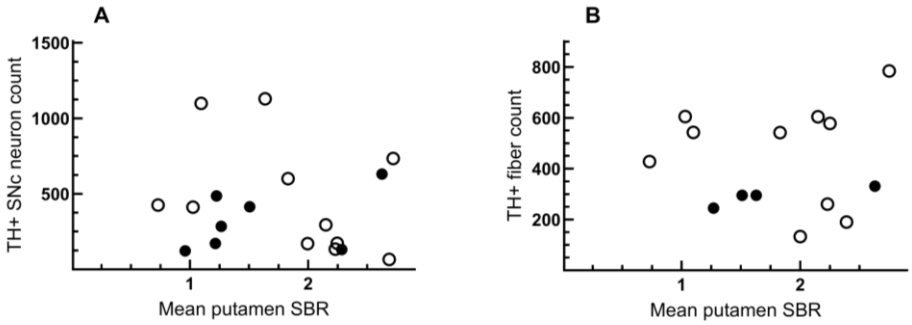

Figure 17. Correlations between mean Put DAT binding (SBR). Open circles = PD patient, solid circles = non-PD patient. A. SNc counts of TH-positive neurons (n = 18; r = -0.11, p = 0.66). B. TH-positive fiber counts of Put (n = 14, r = 0.00, p = 1.0)

Table 7. Demographic, clinical and neuropathologic data of the studied sample.

Case	Diagnosis (yr)	Age at death (yr)	Sex (m / f)	Parkinsonism onset to death (yr)	SNc neuron count (n)	Put fiber count (n)	Mean Put SBR
1	PD	74	M	5.1	412	605	1.03
2	PD	76	M	5.0	426	428	0.73
3	PD	68	M	4.5	735	784	2.75
4	PD	78	M	5.0	174	578	2.25
5	PD	77	M	7.1	1099	543	1.10
6	PD	75	M	5.5	601	542	1.83
7	PD	80	F	9.8	134	261	2.23
8	PD	58	M	7.8	295	604	2.15
9	PD	76	M	8.3	66	-	2.69
10	PD	74	M	10.8	170	133	2.00
11	PD	82	M	11.2	1130	-	1.63
12	PD	81	M	13.8	-	190	2.39
13	MSA	58	F	8.0	172	-	1.22
14	MSA	57	F	7.2	132	-	2.29
15	MSA	54	M	3.3	123	-	0.96
16	MSA	48	M	3.3	285	245	1.27
17	MSA	70	F	7.2	486	-	1.23
18	CBD	72	F	3.2	631	331	2.63
19	PSP	63	M	9.5	414	295	1.51
20	PSP	63	M	4.2	-	295	1.63
Mean (SD)	-	69 (9.9)	-	7.0 (3.0)	416 (320)	417 (193)	1.77 (0.63)

5.1.1 Nigral neurons and SPECT (Study I)

SNc neuron counts did not correlate with the mean Put SBR (count: TH-positive r = -0.11, p = 0.66; neuromelanin-containing r = -0.07, p = 0.78, or density: TH-positive r = -0.05, p = 0.86; neuromelanin-containing r = -0.21, p = 0.40). Figure 18 demonstrates the results. The result remained non-significant when only PD patients (n = 11) were included (r = -0.45, p = 0.17 and r = -0.44, p = 0.18).

No significant differences were found when plausible affecting covariates were applied: the scanner (r = -0.15, p = 0.57 and r = -0.05, p = 0.84), the scanner and tracer (n = 10; r = 0.04, p = 0.91 and r = -0.02, p = 0.96), and the interval between SPECT and death (r = -0.16, p = 0.55; r = 0.03, p = 0.90).

No significant correlation was found with a partial subject sample either, when short duration between SPECT and death patients (n = 11) were included (r = 0.38, p = 0.25; r = 0.35, p = 0.30), only data from the Picker Irix scanner (n = 10) were included (r = 0.04, p = 0.91 and r = -0.02, p = 0.96) and only FP-CIT SBRs (n = 13) were used (r = 0.14, p = 0.64; r = 0.12, p = 0.69).

There were no correlations between SNc neuron counts and the mean posterior Put SBRs (r = -0.37, p = 0.13 and r = -0.31, p = 0.21), when midbrain ROI SBRs were used (r = -0.07, p = 0.79; r = 0.02, p = 0.94), or when the two Putamina were examined separately (r = -0.05 to -0.15, p > 0.56).

The ratio of the lower to higher SNc TH-positive neuron density correlated with the corresponding ratio of Put SBR (r = 0.60, p = 0.025) but not in the quantitative correlation analysis (p > 0.29). The interval from symptom onset to SPECT scan correlated with mean Put SBRs (n = 18; r = -0.62, p = 0.006) and in PD patients (n = 11, r = -0.76, p = 0.007). There was also no correlation between symptom onset to death and SNc neuron counts (whole sample: r = -0.16, p = 0.52; r = -0.13, p = 0.60 or PD patients: r = -0.21, p = 0.53; r = -0.12, p = 0.73).

No significant correlation was found when the above analyses were also examined voxel by voxel over the entire brain.

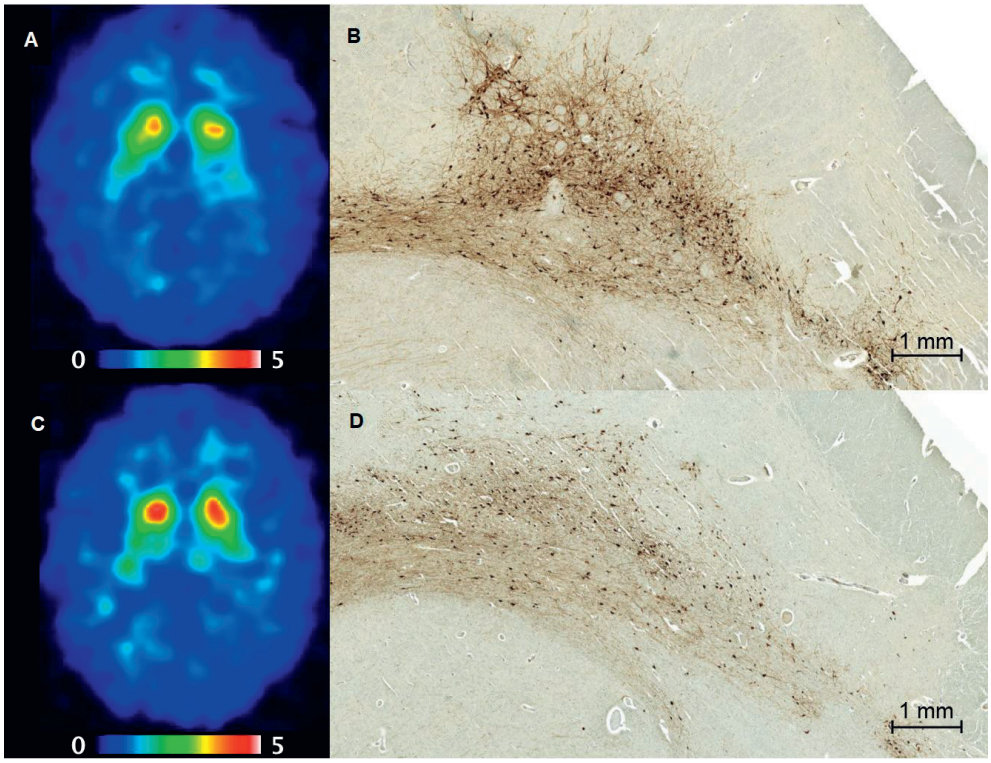

Figure 18. Transaxial SPECT images and a part of corresponding TH stained SNc sections from two PD patients. A. FP-CIT SPECT image of patient 5 with mean Put SBR (1.10) B. and SNc showing a high number of neurons (n = 1099). C. FP-CIT SPECT image of patient 1 with mean Put SBR (1.03) D. and SNc with a mediocre number of neurons (n = 413).

5.1.2 Putaminal fibers and SPECT (Study II)

No correlation was found between the total Putaminal TH+ fiber counts and the Put SBR in the sample ($r = 0.00$, $p = 1.0$) and also when only PD patients ($n = 10$) were included ($r = 0.07$, $p = 0.86$). The key result is demonstrated in Figure 19. No significant correlation was found when only patients with a short interval between the SPECT scan and death were included ($r = 0.21$; $p = 0.62$) and when only the FP-CIT SBRs ($n = 12$) were used ($r = 0.00$; $p = 1.0$; $n = 12$). The interval mean between motor symptom onset and SPECT scan was 1.7 (SD 1.3) years.

The result remained insignificant when correlated covariates were applied: interval between SPECT and death ($r = 0.27$; $p = 0.37$), interval between symptom

onset and SPECT scan (r = 0.07; p = 0.82), interval between death and autopsy (r = -0.02; p = 0.94), interval between death and neuropathologic examination (r = -0.04; p = 0.90) and scanner (r = 0.34; p = 0.31) were used as covariates. No correlation was found when the different Put SBRs were analyzed with all the Put subregions in the whole sample (r = -0.24 to 0.11; p > 0.42) or in PD patients (r = -0.29 to 0.23; p > 0.43). Compared to age-matched individuals, the studied subject had lost approximately half of the striatal DAT binding (Kaasinen and Vahlberg 2017).

The medial and central Put fiber count correlated with the SNc TH-positive neuron count in all patients (r = 0.65; p = 0.02) and also in the PD patients (r = 0.68 – 0.80, p < 0.04). There were no significant correlations between the fiber counts and the SNc neuromelanin-containing neuron counts (r = 0.25; p = 0.44).

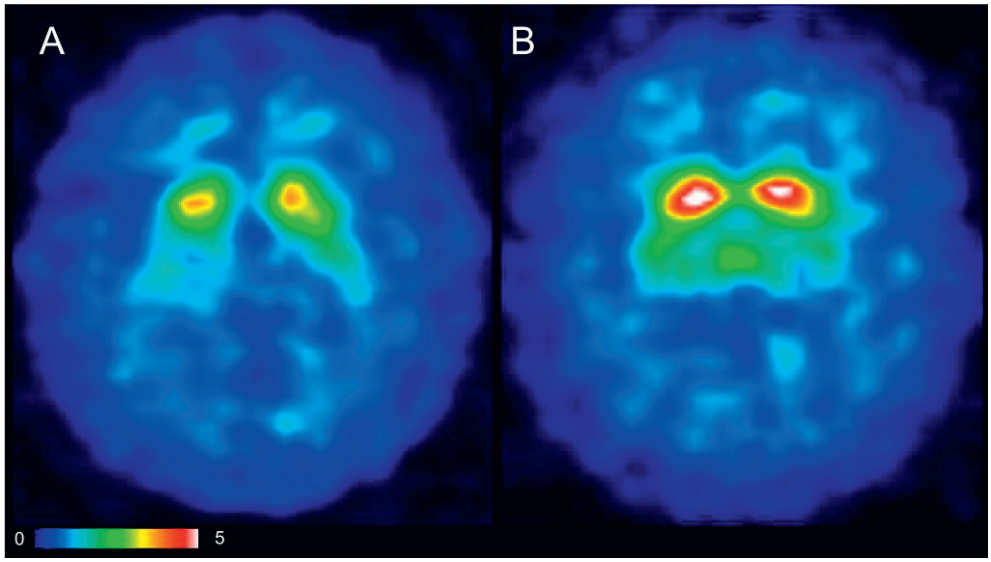

Figure 19. Representative transaxial FP-CIT SPECT images of two PD patient. A SPECT image of PD patient 5 with low mean Put SBR (1.10) and high fiber count (n = 543). B SPECT image of PD patient 10 with high mean Put SBR (2.00) and low fiber count (n = 133).

5.2 Nigral neurons and depression (Study III)

The SNc neuron density was 52.0% (p = 0.004) higher in LBD patients without depressive symptoms than in LBD patients with depression (n = 12). The key result is demonstrated in Figure 20. Other variables were non-significant. This

difference remained significant when patients without parkinsonism (n = 10; n = 43, p = 0.02) and patients with longer interval between recorded depressive symptoms and death (n = 3, p = 0.038) were analysed. Using MMSE scores as a covariate did not significantly change the result (F = 5.18, p = 0.029). Table 8 presents the demographic and clinical characteristics. The differences in clinical phenotypes are presented in Table 9.

Table 8. Demographic and clinical characteristics of patients with and without depression. Values are the mean (SD) [n]. Neuron counts and densities in the table are corrected with the Abercrombie method.

	Depression	**No depression**	**p-value[a]**
n	12	61	-
Age at death (yr)	77.0 (6.6) [12]	79.8 (7.5) [61]	0.220
Sex (m/f)	7 / 5	41 / 20	0.740
Parkinsonism onset to death (yr)	7.7 (5.8) [8]	8.6 (4.6) [39]	0.602
Diagnosis to death (yr)	4.8 (5.0) [9]	6.3 (4.1) [46]	0.200
HY score	3.8 (1.1) [10]	3.9 (1.1) [47]	0.771
LEDD (mg)	414 (294) [12]	377 (359) [54]	0.619
BMI (kg/m^2)	25.4 (4.3) [5]	23.7 (5.1) [31]	0.467
MMSE score	18 (2.7) [8]	20 (5.6) [33]	0.054
Brain weight (g)	1398 (141) [11]	1410 (166) [59]	0.800
Concurrent AD pathology (y/n)	6 / 12	37 / 61	0.534
SNc neuron count (n)	52.0 (23.0) [12]	72.9 (42.1) [61]	0.022*
SNc area (mm^2)	35.0 (6.4) [12]	32.3 (7.9) [61]	0.220
SNc neuron density (n/mm^2)	1.52 (0.65) [12]	2.32 (1.33) [61]	0.004*

[a] Independent samples t-test, Mann-Whitney U-test or Fisher exact test. BMI = body mass index

Table 9. Demographic, clinical and neuropathologic characteristics are categorized as clinical motor-cognitive phenotypes as described by Kasanuki and colleagues 2017. Values are the means (SD) [n] or n. Neuron counts and densities in the table are corrected with the Abercrombie method.

	All	Parkinsonism-predominant	Parkinsonism + Dementia	Dementia-predominant	p-value[a]
n	73	23	30	20	
Age at death (yr)	79.4 (7.4) [73]	81.4 (5.4) [23]	77.9 (7.8) [30]	79.4 (8.6) [20]	0.241
Sex (m / f)	48 / 25	18 / 5	18 / 12	12 / 8	0.334
Depression (y/n)	12 / 61	2 / 21	8 / 22	2 / 18	0.208
Parkinsonism onset to death (yr)	8.4 (4.8) [47]	8.5 (4.2) [19]	8.8 (5.2) [26]	3.5 (0.7) [2]	0.241
Diagnosis to death (yr)	6.1 (4.3) [55]	6.4 (3.7) [20]	5.6 (4.6) [26]	6.8 (4.8) [9]	0.492
HY score	3.9 (1.1) [57]	3.8 (1.1) [19]	3.8 (1.1) [29]	4.3 (0.7) [9]	0.750
LEDD (mg)	506 (316[b]) [42]	647 (300) [18]	454 (306) [24]	-	0.150
BMI (kg/m^2)	23.9 (5.0) [36]	23.6 (3.7) [13]	23.0 (6.7) [12]	25.3 (4.1) [11]	0.544
MMSE score	19.8 (5.2) [41]	28.0 (0) [5]	19.1 (4.3) [22][c]	18.1 (4.9) [14][c]	<0.0001*
Brain weight (g)	1408 (161) [70]	1444 (139) [22]	1390 (172) [30]	1395 (170) [18]	0.464
Concurrent AD pathology (y/n)	43/73	8/23	20/30	15/20	0.015*
SNc neuron count (n)	69.5 (40.3) [73]	67.9 (39.0) [23]	51.1 (29.2) [30]	98.8 (40.5) [20][d]	0.001*
SNc area (mm^2)	32.7 (7.7) [73]	32.8 (8.5) [23]	32.6 (7.9) [30]	32.9 (6.8) [20]	0.992
SNc neuron density (n/mm^2)	2.19 (1.28) [73]	2.21 (1.43) [23]	1.63 (0.948) [30]	2.99 (1.14) [20][d]	0.001*

*One-way ANOVA, Kruskal-Walls test, Fisher exact test or Chi-square test between 3 subgroups, equality of variances were evaluated with Levene's test in ANOVA, and post hoc tests were Tukey or Games Howell as appropriate. b median, c $p<0.01$ after multiple comparisons in pair-wise post hoc test as compared to parkinsonism+dementia d $p<0.001$ after multiple comparison ns in pair-wise post hoc test as compared to parkinsonism

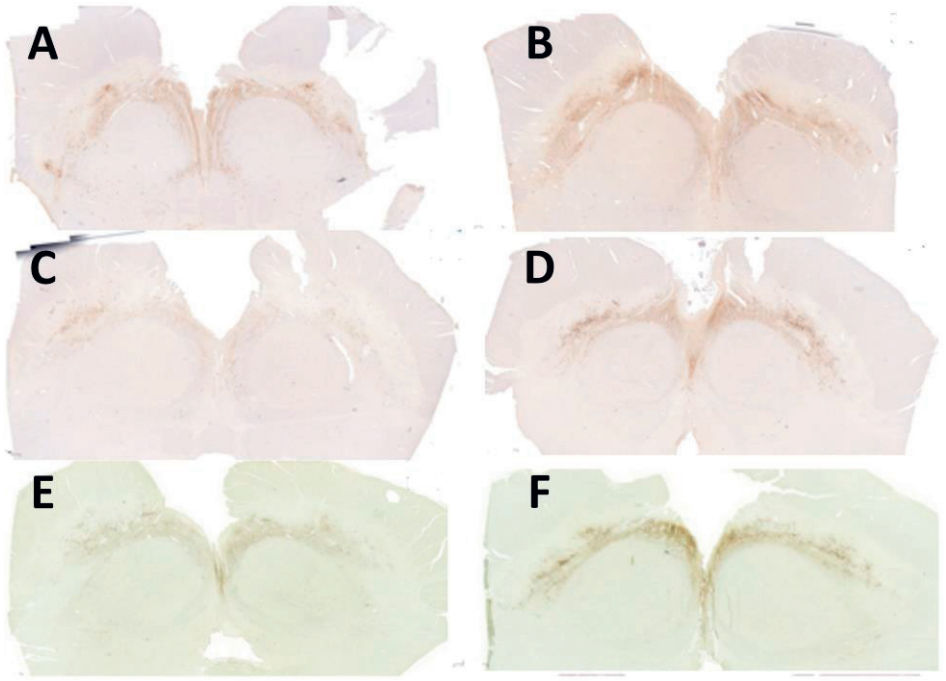

Figure 20. Representative TH stained SNc sections. LBD patients with depressive symptoms on the left A (corrected TH-positive neuron density n/mm^2 = 1.0), C (n/mm^2 = 1.1) and E (n/mm^2 = 1.3). Age and sex matched LBD patients without depressive symptoms on the right B (n/mm^2 = 3.5), D (n/mm^2 = 4.7) and F (n/mm^2 = 3.9).

5.3 Nigral neurons and height (Study IV)

A significant linear correlation of SNc neuron density and height was found in LDB patients (n = 36, F(1, 34) = 15.790, p < 0.0001, R2 = 0.317). The quadratic correlation model demonstrated a slightly stronger relationship (R2 = 0.351) (see Figure 21). A similar correlation was present in the PD patients (n = 22, F(1, 18) = 11.093, p = 0.004, R2 = 0.381). No other significant correlations with SNc neuron density were found in LBD patients (r = -0.09–0.20, p > 0.24) and none in the control group (n = 19, r = -0.27–0.143, p > 0.27).

The relationship between SNc pathology and height remained significant when patients with body measurements taken before autopsy were excluded (Pearson r = 0.584, p = 0.001) and when sex and age were used as covariates (r = 0.58, p = 0.004, β = 0.082, SD = 0.023). The correlation in LBD patients was slightly stronger when stature decline was corrected to the height (n =36, F(1, 34) = 16.760, p < 0.0001, R2 = 0.330), although the stature itself did not correlate to

SNc neuron density (r = -0.15, p = 0.392). Stature decline was calculated with the formula (k = K/(1 + (- i))n, where k is the height at the age of fifty, K is the final height, n is the years lived after fifty and i is an annual decline of height percentage in decimal (for females 0.13% and males 0.09%)). Table 10 presents the demographic and clinical characteristics.

Table 10 Demographic and clinical characteristics of the studied subjects. Values are means (SD) [n] or medians [interquartile range, IQR] [n]. Neuron counts and densities in the table are corrected with the Abercrombie method.

	All patients	**PD patients**	**Controls**
n	36	22	19
Sex (m / f)	23 / 13	14 / 8	11 / 8
Age at death (yr)	79.4 (6.2) [36]	79.1 (5.8) [22]	55.9 (18) [19]
Height (cm)	169.3 (9.0) [36]	169.0 (9.6) [22]	171.8 (9.7) [19]
Weight (kg)	68.9 (15.9) [36]	66.2 (15.9) [22]	84.9 (18) [19]
Parkinsonism onset to death (yr)	8.4 (5.1) [25]	9.2 (5.0) [20]	-
Diagnosis to death (yr)	4.3 [6] [29]	6.6 [7] [20]	-
HY score	4.1 (0.83) [26]	4.1 (0.85) [19]	-
LEDD (mg)	455 (372) [32]	520 (334) [21]	-
Brain weight (g)	1433 (153) [35]	1420 (169) [22]	-
SNc neuron count (n)	69.2 (41.5) [36]	63.2 (38.0) [22]	121 (43.6) [19]
SNc area (mm^2)	31.9 (7.3) [36]	31.9 (7.2) [22]	30.6 (5.9) [19]
SNc neuron density (n/mm^2)	2.17 (1.23) [36]	1.99 (1.17) [22]	3.94 (1.21) [19]

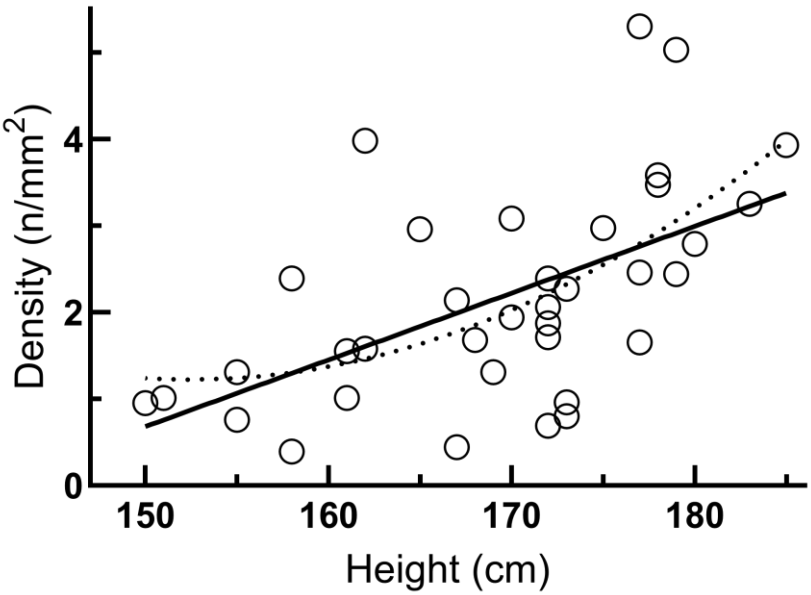

Figure 21. Correlation between height and SNc neuron density in LBD patients (n = 36). Two relationships are demonstrated: linear ($r = 0.563$, $p < 0.0001$) and quadratic ($r = 0.592$, $p = 0.001$).

6 Discussion

6.1 No relationship between nigral neuron numbers and DAT (Study I)

Striatal DAT imaging did not correlate with SNc DAergic neuron counts in PD. The result is in line with PD animal models indicating a predictive value of DAT SPECT to striatal DA levels but not with SNc neuron numbers (Alvarez-Fischer et al. 2007).

There are three previous studies which have compared SNc neuron counts to functional molecular imaging in humans. The first study suggested a strong correlation between neuron counts and striatal DA function based on the results of 5 patients (PSP = 2, PD = 1 and 2 normal) and [^{18}F]fluorodopa PET (Snow et al. 1993). DAT SPECT was performed in a larger sample of 23 patients (AD = 4, DLB = 7 and PD = 12) and the results demonstrated a strong correlation between SNc neurons and DAT (Colloby et al. 2012). However, the correlation might be confounded by the fact that the authors combined the entire sample population (also AD patients with normal DAT binding and normal SN neuron counts). The most recent study examined 9 patients (AD = 1, normal = 2, Creutzfeldt-Jakob = 1, parkinsonian syndrome = 7) with DAT SPECT and showed a clear positive correlation with SNc counts (Kraemmer et al. 2014). As with the study by Colloby and colleagues, the authors analyzed correlations across the whole group. It is reasonable to conclude that the findings in the three previous studies are methodologically limited due to combined samples of patients with various diagnoses.

Studies in non-human primate models of Parkinsonism where about half the nigral neurones have been destroyed have shown that the DAergic molecular imaging does not mirror the SNc neuron loss (Karimi et al. 2013). Non-human primate models have been demonstrated to have a lower threshold of nigrostriatal degeneration leading to observable signs of parkinsonism than is seen in PD (Tabbal et al. 2012).

A rapid decline of DAergic function in the first few years of PD due to a possibly exponential decline in pars compacta cell loss might be the reason for the

lack of correlation in this study (Fearnley and Lees 1991; Nandhagopal et al. 2009). The loss of SNc neurons might be reached in a few years after the PD diagnosis (Kordower et al. 2013), causing a floor effect and loss of any meaningful correlation with DAT binding. This is suggested by the correlation between motor symptom duration and DAT binding at the time of the scan without an association between symptom duration and SNc neuron counts at death. The function of surviving SNc neurons rather than the actual numbers is likely to be the critical factor. Damaged but viable SNc neurons have been demonstrated in PD (Kordower et al. 2013), possibly with decreased DAT expression (Uhl et al. 1994; Counihan and Penney 1998). Axonal dysfunction due to dying back terminals might also reduce striatal DAT binding without affecting the SNc neuron count.

The mean interval in this study between DAT scan and neuropathologic examination was 5.2 years but the results remained non-significant even in patients with a shorter interval of 3.5 years and when the interval between scan and death was used as a covariate. This interval is longer than in the three earlier studies in which the interval ranged between 2.4 and 3.7 years (Snow et al. 1993; Colloby et al. 2012; Kraemmer et al. 2014). Likely, the difference in the correlation of the DAT binding and SNc neuron counts between this study and the three previous studies are related to the inclusion of non-PD patients in the previous analyses. Although the number of PD patients in this study is not large the numbers are comparable to those in Colloby's study (Colloby et al. 2012) and larger than in the other two earlier studies (Snow et al. 1993; Kraemmer et al. 2014). Furthermore, it is conceivable the DAergic neuron terminal numbers in Put and CN might be preserved while DAT immunoreactivity is decreased (Porritt et al. 2005). Further studies are necessary to understand the relationships between the anatomic and functional nigrostriatal pathways and DAT binding.

The results of this study imply that the SNc neuron numbers are not associated with striatal DAT binding. However, it cannot be excluded that there may be a correlation between the two in the early or prodromal phases of PD.

6.2 No relationship between striatal dopaminergic axons and DAT imaging (Study II)

The DAergic TH-positive axon counts in the Put did not correlate with Put DAT binding, while the axon count correlated with the SNc TH-positive neuron counts. These findings do not support a relationship between DAT binding and striatal

axons or the dying-back hypothesis of PD, where the death of striatal terminals is considered to be the cause of nigral damage in PD.

Earlier results from PD animal model studies are in line with these findings. Stereologically assessed nigrostriatal fiber lengths in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treated monkeys correlated with SNc and with motor function but not with striatal terminals (Tian et al. 2014). Additionally, no correlations were found between three different striatal tracers and striatal fiber density or SN neurons, while diffusion MRI correlated with both (Shimony et al. 2018).

This study is limited by the small sample and the intervals between the SPECT scan and the putaminal fiber counts but is comparable with previous clinicopathologic imaging studies (Snow et al. 1993; Colloby et al. 2012; Kraemmer et al. 2014). Fiber counts were done manually rather than stereologically but the inter-rater reliability was good to excellent and the significant correlation found between putaminal fibers and SNc neurons suggests that the neuropathologic method was adequate. Additionally, the delay between scanning and death when used as covariates revealed no significant difference. The mean interval between symptom onset to death was 6.7 (SD 3.5) years so it remains possible that DAT scans may correlate with striatal axons, dendrites or nigral neurons in very early-stage PD.

DAT imaging might reflect DA or DAergic activity rather than neuronal structures. It may also measure DAT expression of synaptic DA levels because DAT seems to participate actively in the modulation of synaptic DA signalling and synaptic DA release (Blesa et al. 2012).

In summary, no correlation between nigrostriatal structures, striatal axons or SN neurons, and striatal DAT binding was found. The pathophysiology of DAT binding changes in PD remains unclear but might be more closely linked to synaptic DA rather than neuropathologic changes. Further clinicopathologic research with subjects in the early or prodromal phases of PD is required.

6.3 Dopaminergic neuron loss is greater with depression in LBDs (Study III)

LBD patients with depressive symptoms had significantly lower TH-positive SNc neuron densities than LBD patients without depression. The difference could not be explained by other variables, including cognition, motor symptoms, DA replacement therapy and disease duration.

SN has long been viewed as important in motor programming. However, it should not be considered purely a motor nucleus, because DA participates in the

modulation of mood and cognition (Chaudhuri and Schapira 2009). There are also functional interdependencies of the DAergic SN-related sub-cortical motor pathways with other neurotransmitter systems (Northoff et al. 2021), including depression-related interactions between DAergic SN and serotonergic raphe nucleus (Conio et al. 2020).

A study of 124 non-demented elderly subjects with no signs of PD showed a negative correlation between mesencephalic DAergic neuron density and the quantity of depressive symptoms (Wilson et al. 2013). Motivational deficits and affective impairments resembling PD depression and anxiety symptoms have also been observed in 6-hydroxydopamine lesioned rats (Drui et al. 2014).

This study has some limitations based on the retrospective data collection and some clinical variables were unavailable for every studied subject, and detailed and structured assessments such as the Patient Health Questionnaire-9 for depression or the Unified Parkinson's Disease Rating Scale were only occasionally performed. It should be noted that the studied subjects were examined in a specialized university hospital institute, and the results might not be comparable with common outpatient DLB.

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6.4 Dopaminergic neurons and height in LBDs (Study IV)

The results reveal a correlation between adult height and SNc TH-positive neuron density and, thus, suggest a link between late-age height and DAergic degeneration. The association was present in LBD patients and PD patients but not in subjects without any neurodegenerative disease. Short stature in LBD patients might be one of the factors that explain interindividual differences in nigral neuron numbers, although the mean heights in this study sample are comparable to adult heights of the reported same generation (male LBD 173 cm, SD 6.7, n = 23; male general 176 cm, SD 6.3, n = 5010; female LBD 164 cm, SD 9.8, n = 13; female general 163, SD 5.5, n = 5898) (Silventoinen et al. 2004).

An earlier study has demonstrated an increased risk of PD in association with shorter young adult height. The increase in risk was seen particularly in young males with short stature (Ragonese et al. 2007). The present study's results suggest that PD patients with low height may have lower TH-positive SNc neuron counts than taller patients, which could not be explained by other demographic or clinical differences. These two studies differed in perspective and methodology; Although the earlier study investigated a possible premorbid risk increase and this study

investigated SNc neurons *postmortem*, both studies point to a possible link between low height and greater risk for DAergic degeneration. There is also some preclinical data to support the relationship. For example, DA also seems to modulate body size in *Caenorhabditis elegans* (Nagashima et al. 2016), and DA D2 receptors regulate body size through GH secretion (Noaín et al. 2013). Additionally, 6-hydroxydopamine administration to rats at the perinatal stage causes nigrostriatal DAergic degeneration, but it also reduces the rats' growth (Kostrzewa et al. 2016). PD in the advanced stage often leads to inadequate nutritional status, weight loss and immobility increasing the risk of osteoporosis and reduced bone density (Figueroa and Rosen 2020). 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine treatment also seems to cause bone loss in mice, whereas L-dopa treatment further reduced bone mass, suggesting a DA-dependent mechanism (Handa et al. 2019). Thus, the results of the present study might be explained by an interaction between DAergic neurotransmission and GH secretion in human development.

Interestingly, the results did not show a relationship between body mass index (BMI) and SNc pathology, even though weight loss and low BMI have been associated with PD severity (Yong et al. 2020). This may be because most of the body measurements were recorded at autopsy and thus might not reflect adult life weight due to weight loss in the end stages before the death. The error caused by the age-related stature decline (Fernihough and McGovern 2015) was nevertheless corrected in this model.

To summarize, the results point to a possible link between adult height and DAergic neuronal density in patients with PD. Our results should be considered preliminary and need verification with larger samples, although they support a theory of shared factors determining adult height and vulnerability to neuronal degeneration.

7 Summary/Conclusions

This thesis is based on four Studies. All the Studies investigated the association between clinical characteristics and degeneration in the key structures in the DAergic system. Study I examined the proposed correlation between *in vivo* DAT binding and SNc TH-positive neuron counts in 18 patients. Study II investigated the association between DAT imaging and striatal DAergic axon counts in 14 patients. Study III compared TH positive neuron densities of SNc in 12 LBD patients with depressive symptoms against 61 LBD patients without known depressive symptoms. Study IV investigated the association between TH positive neuron densities of SNc and body measurements in 37 LBD patients and 19 controls. All studies were clinicopathological *postmortem* studies and thus have limitations such as delays, which need to be considered when drawing conclusions

Neither Study I neuron counts of the SNc nor Study II TH-positive fiber counts of Put demonstrated a significant correlation with the mean Put SBR. The correlations remained nonsignificant with both voxel by voxel and ROI-based analyses and when scanner and tracer were also used as covariates. No significant correlations were observed within specific subgroups either.

Study III showed a significant difference in the number of TH-positive neurons of the SNc between LBD patients with depressive symptoms and without evidence of depression. The neuron count and density of depressive LBD patients were smaller. The difference remained significant when only patients with recently recorded depressive symptoms were included. No significant differences between the two groups were found in disease duration, cognition, antiparkinsonian medications or motor disease severity.

Study IV demonstrated an inverse correlation between late-life height and TH-positive neuron counts of the SNc of all LBD patients and only PD patients. The correlation was not observed in the control group. The association could not be explained by sex, age, brain weight, antiparkinsonian medication, weight, or motor disease severity.

In brief, the main conclusions of this thesis are:

I DAT binding does not correlate with the density of DAergic neurons at SNc in PD. This finding suggests that the DAergic system is adaptable and has a buffering ability in PD.

II DAT binding does not correlate with the number of DAergic axons of the Put in PD, the other end of the nigrostriatal tract.

III LBD patients with depressive symptoms have decreased DAergic neuron density in SNc compared to LBD patients without depression. This finding demonstrates the crucial role of the substantial nigra not only in motor function modulation but also in mood regulation.

IV LBD patients with shorter stature have lower DAergic neuron density in SNc than taller patients. This finding suggests a link between height and the DAergic system.

The results of Studies I and II do not support the use of DAT scan as a surrogate marker of nigrostriatal degeneration, but more investigation is needed with patients in the early stage of the disease. Study III emphasises the relationship between LBDs and depression, but longitudinal studies and trials are needed to determine the interactions and to give treatment recommendations. Study IV results are preliminary and larger study samples, preferably with several height follow-up points could clarify the relationship between height and SN pathology in LBD. Further investigation is necessary in order to utilize these results to develop patient care in LBDs.

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