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HIGH IMPACT REVIEW IN NEUROSCIENCE, NEUROLOGY OR PSYCHIATRY - REVIEW ARTICLE

Neuropathology and pathogenesis of extrapyramidal movement disorders: a critical update—I. Hypokinetic-rigid movement disorders

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Abstract

Extrapyramidal movement disorders include hypokinetic rigid and hyperkinetic or mixed forms, most of them originating from dysfunction of the basal ganglia (BG) and their information circuits. The functional anatomy of the BG, the cortico-BG–thalamocortical, and BG–cerebellar circuit connections are briefly reviewed. Pathophysiologic classification of extrapyramidal movement disorder mechanisms distinguish (1) parkinsonian syndromes, (2) chorea and related syndromes, (3) dystonias, (4) myoclonic syndromes, (5) ballism, (6) tics, and (7) tremor syndromes. Recent genetic and molecular–biologic classifications distinguish (1) synucleinopathies (Parkinson's disease, dementia with Lewy bodies, Parkinson's disease–dementia, and multiple system atrophy); (2) tauopathies (progressive supranuclear palsy, corticobasal degeneration, FTLD-17; Guamian Parkinson–dementia; Pick's disease, and others); (3) polyglutamine disorders (Huntington's disease and related disorders); (4) pantothenate kinase-associated neurodegeneration; (5) Wilson's disease; and (6) other hereditary neurodegenerations without hitherto detected genetic or specific markers. The diversity of phenotypes is related to the deposition of pathologic proteins in distinct cell populations, causing neurodegeneration due to genetic and environmental factors, but there is frequent overlap between various disorders. Their etiopathogenesis is still poorly understood, but is suggested to result from an interaction between genetic and environmental factors. Multiple etiologies and noxious factors (protein mishandling, mitochondrial dysfunction, oxidative stress, excitotoxicity, energy failure, and chronic neuroinflammation) are more likely than a single factor. Current clinical consensus criteria have increased the diagnostic accuracy of most neurodegenerative movement disorders, but for their definite diagnosis, histopathological confirmation is required. We present a timely overview of the neuropathology and pathogenesis of the major extrapyramidal movement disorders in two parts, the first one dedicated to hypokinetic-rigid forms and the second to hyperkinetic disorders.

Keywords Movement disorders · Proteinopathies · Parkinsonism · Lewy body pathology · Tauopathies · Polyglutamine repeat disorder · Genetics · Neuropathology · Pathophysiology

Abbreviations

AGs	Argyrophilic grains
ALS	Amyptrophic lateral sclerosis
ALS/PDC	Guamanian ALS–Parkinson's disease complex
AP	Astroglial plaque
APP	Amyloid precursor protein
AR-PD	Akinesia-and-rigidity type PD
AS	α-Synuclein
AutD	Autosomal dominant
AutR	Autosomal recessive
βSyn	β-Synuclein
BG	Basal ganglia
BHC	Benign hereditary chorea
BIBD	Basophilic inclusion body disease
CAA	Cerebral amyloid angiopathy
CAG	Polyglutamine
CBD	Corticobasal degeneration
CBGTC	Cortico-BG-thalamocortical
CBS	Corticobasal syndrome
ChAc	Chorea-acanthocytosis
ChAT	Choline-acetyl transferase
CI	Cognitive impairment
CN	Caudate nucleus

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CNS	Central nervous system
CS–TD	Cortico-striatal–temporal difference
DA	Dopamine
DLB	Dementia with Lewy bodies
DLB-AD	Dementia with Lewy bodies and Alzheimer's disease
DRD	Dopa-responsive dystonia
DRPLA	Dentatorubral-pallidoluysian atrophy
DS	Dystonia syndrome
ENK	Enkephalin
ET	Essential tremor
FTDP-17	Frontotemporal degeneration and parkinsonism linked to chromosome 17
FTLD	Frontotemporal lobar degeneration
GABA	γ-Aminobutyric acid
GBA	Glucocerebrosidase gene
GCase	Glucocerebrosidase
GCIs	Glial cytoplasmic inclusions
GDNF	Glia-derived neurotrophic factor
GNIs	Glial nuclear inclusions
GPe	External segment of globus pallidus
GPi	Internal segment of globus pallidus
GTP	Guanosine triphosphate
HD	Huntington's disease
HTT	Huntingtin
iLBD	Incidental Lewy body disease
IT	Intratelencephalic
LB	Lewy body
LC	Locus ceruleus
LID	L-Dopa-induced dyskinesia
LP	Lewy body pathology
MCI	Mild cognitive impairment
MD	Menkes' disease
MJD	Machado-Joseph disease
MSA	Multiple system atrophy
MSA-C	Multiple system atrophy with predominant cerebellar features
MSA-P	Multiple system atrophy with predominant parkinsonism
MSN	Medium spiny projection neuron
NA	Neuroacanthocytosis
NBIA	Neurodegeneration with brain iron accumulation
NBM	Nucleus basalis of Meynert
NCIs	Neuronal cytoplasmic inclusions
NFTs	Neurofibrillary tangles
NIID	Neuronal intranuclear inclusion disease
NM	Neuromelanin
NNIs	Neuronal nuclear inclusions
NT	Neuropil threads
OCD	Obsessive-compulsive disorder
OPC	Olivopontocerebellar
OPCA	Olivopontocerebellar atrophy
OS	Oxidative stress
pAS	Phosphorylated α-synuclein
PC	Purkinje cell
PD	Parkinson's disease
PDC	Parkinson's disease complex
PDD	Parkinson's disease dementia
PEP	Postencephalitic parkinsonism
PGF	PSP with progressive gait freezing
PHFs	Paired helical filaments
PiD	Pick's disease
PKAN	Pantothenate-kinase associated neurodegeneration
PPN	Pedunculopontine nucleus
PPT	Pedunculo-pontine tegmental
PSP	Progressive supranuclear palsy
PSP-CBS	PSP presenting with corticobasal syndrom
PSP-P	Progressive supranuclear palsy-parkinsonism
PSP-RS	Richardson's syndrome
Put	Putamen
SCA3	Spinocerebellar ataxia type 3
SN	Substantia nigra
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
SP	Substance P
STN	Subthalamic nucleus
TA	Tufted astrocyte
TDPD	Tremor-dominant type of PD
TH	Tyrosine hydoxylase
TS	Tourette's syndrome
VaP	Vascular parkinsonism
VM	Ventromedial
VTA	Ventral tegmental area
WD	Wilson's disease
XDP	X-linked dystonia-parkinsonism

Introduction

Extrapyramidal movement disorders are divided into hypokinetic rigid, hyperkinetic, and mixed forms, most of which have their origin in dysfunction of the dorsal basal ganglia (BG), which have a multitude of functions associated with cognition and reward, but are primarily involved in motor control. Dysfunction of the cortico-BG–thalamocortical (CBGTC) circuits due to disruption of downstream network activities in cortex, thalamus, and brainstem result in a number of landmark motor disorders such as Parkinson's and Huntington's diseases, which disturb motor control in markedly different contexts.

Structure and function of the basal ganglia

The BG are a cluster of subcortical nuclei which include (1) input nuclei [caudate nucleus (CN), putamen (Put), and nucleus accumbens], (2) output nuclei [internal segment of globus pallidus (GPi) and substantia nigra pars reticulata (SNr)], and (3) intrinsic nuclei/external segment of globus pallidus (GPe), subthalamic nucleus (STN), and substantia nigra pars compacta (SNc). According to the current model of the BG circuitry, they are viewed as components of segregated networks that emanate from special cortical areas, traverse the BG and ventral thalamus, and return to the frontal cortex, interacting with internal re-entering circuits engaging motor, associative, and limbic cortical territories in the control of movement, behavior, planning, and emotions, related to a functional interconnection of these areas (Klaus et al. 2019).

The fundamental understanding of the essential anatomical pathways—CBGTC—and the alterations of the neurotransmitter systems located in these circuits are essential for understanding potential pathophysiological mechanisms in the landmark extrapyramidal motor disorders. The functions of these networks are modulated by three main transmitter systems: dopamine (DA), glutamate, and γ-aminobutyric acid (GABA). Normal movement is controlled by the CBGTC circuits. The striatum integrates motor behavior using well-defined circuits, whose individual components are independently affected in various movement disorders. It receives excitatory glutamatergic input from the cerebral cortex, thalamus, and brainstem, mainly from DAergic cells and releases GABAergic output to SNc, SNr, GPi, and GPi, which project to specific nuclei in thalamus and the brainstem tegmentum. The involved thalamic nuclei have an excitatory glutamatergic output to specific regions of the motor cortex. The GABAergic output of SNc and GPi reduces glutamatergic projections from thalamus back to the cortex. Other cortical regions project to subthalamic nucleus (STN), SN, thalamus, ventral tegmental area (VTA) and via pontine nuclei to the cerebellum. GPe, DAergic SNc, and STN modulate the main flow of information through the BG. The classical model of the involved circuits describes a dynamic web of interlinked pathways with inhibitory and excitatory functions providing multiple sites of influence (Young and Sonne 2018) (Fig. 1). Similar to the body regions within the sensory motor cortex, the BG nuclei are somatotopically organized (Simonyan 2019).

Five BG–thalamocortical circuits form a topographically organized functional network: motor and oculomotor circuits, dorsolateral prefrontal, lateral orbitofrontal, and anterior cingulate or limbic circuits involving different parts of the striatum, pallidonigral complex, and medial and ventral thalamus (Simonyan 2019). The functions of these networks are strongly modulated by the release of DA in the striatum.

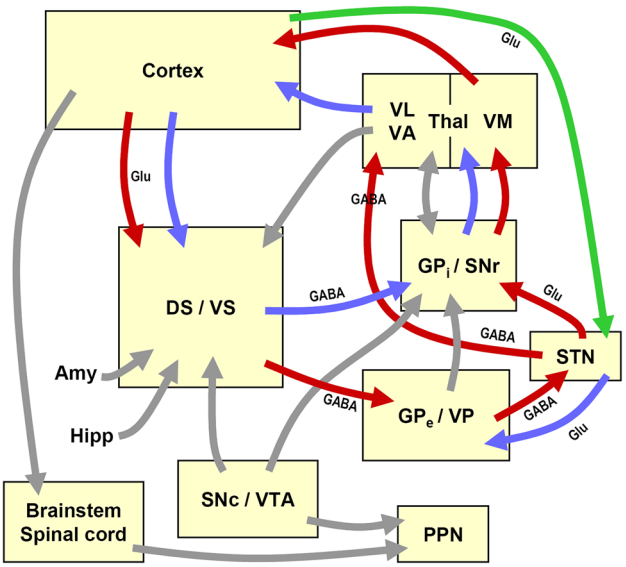

Fig. 1 Schematic representation of key structures and pathways of the basal ganglia. Blue arrows: direct pathway; red arrows: indirect pathway; yellow arrow: hyperdirect pathway. *Amy* amygdala, *DS* dorsal striatum, *GPi* globus pallidus, internal segment, *GPe* globus pallidus, external segment, *Hipp* hippocampus, *PPN* pedunculopontine nucleus, *SNc* substantia nigra compacta, *SNr* substantia nigra reticulata, *STN* subthalamic nucleus, *Thal* thalamus, *VA* ventral anterior, *VM* ventral median, *VP* ventral pallidum, *VS* ventral striatum, *VTA* ventral tegmental area, *Glu* glutamatergic, *GABA* gabaergic. Modified from (Haber 2016) with permission from Association La Conférence Hippocrate-Servier. © AICH-Servier

It alters the activity of striatal neurons which, in turn, influences the (inhibitory) BG output.

A nigrostriatal circuit in which SNc gets a GABAergic inhibitory projection from striatum feeds back to striatum as the major source of its DAergic innervation. The medial SN connects with limbic striatal and cortical regions: the ventral SN with associative regions of cortex and striatum and the lateral SN with somatomotor regions of striatum and cortex encoding different functions (Zhang et al. 2017). The retrorubral field (A8) and ventral tegmental area (A10) are integrated in the mesostriatal and mesolimbic DAergic projections. DA induces excitation of striatal neurons that project to GPi and SNr and inhibits thalamic nuclei to maintain normal movements. It inhibits neurons that project to GPe or STN to moderate the normal negative effect on motor speed and tone associated with high output from STN. Its outputs project to GPi, SNr, GPe, striatum, and PPN. DA modulates BG functions, but also acts outside of the striatum, thus contributing to the symptoms of PD and other disorders (Wichmann et al. 2018). GPe receives GABAergic input from striatum and projects to STN, which in turn sends glutamatergic projections to SNr, GPi, and GPe to inhibit glutamatergic excitation of the cortex. Excitatory glutamatergic drive of STN neurons along the cortico-subthalamic pathway triggers

GABAergic inhibition of pallidothalamic inputs (Chu et al. 2015). The STN-GPe system is a major input relais station receiving projections from various cortical and subcortical regions, thus modulating the downstream effects of the BG that control both motor function and emotion (Suryanarayana et al. 2019). Many PD symptoms result directly from neurodegeneration; others are driven by aberrant activity patterns in surviving neurons. This latter phenomenon, PD circuit dysfunction, is an area of intense study in view of currently incurable neurodegeneration (McGregor and Nelson 2019).

A commonly presented but overly simplistic model of motor function suggests that BG output structures are controlled by two opposing striatal motor loops, originating from distinct populations of medium-sized spiny projection neurons (MSNs) and projecting to different output structures (Young and Sonne 2018). The direct pathway is a monosynaptic inhibitory projection from the glutamatergic cortex to the GABAergic MSNs, containing DA-D1 receptor neurons projecting to GABAergic neurons in GPi and SNr. Activation of striatal MSNs leads to inhibition of the inhibitory GPi/SNr output and to disinhibition of BG target structures in thalamus and midbrain, thus promoting movement and behavior. The indirect pathway contains disinhibitory projections from the glutamatergic cortex to striatal MSNs (containing GABA and expressing the DA-D2 receptor), with striatal projections to GPe, GABAergic GPe projections to STN, and glutamatergic STN projections to GPi and SNr. The STN as part of the indirect pathway drives pallidal GABAergic output through glutamatergic synapses. The GPi sends inhibitory projections to the ventral anterior and ventral lateral nuclei of the thalamus and will disinhibit motor output by thalamic stimulation of the motor cortex. A signal through the indirect pathway (cortex–striatum–GPe–STN–GPi) ultimately terminates a movement. The SNr, an inhibitory GABAergic nucleus, works together with the GPi as the final output of the BG's direct and indirect pathways. In turn, both pathways have a reverse effect on spontaneously firing thalamocortical neurons and ultimate motor activity, i.e., activation of the direct pathway facilitates motor activity via disinhibition of thalamocortical neurons, whereas activation of the indirect pathway reduces motor activity by increasing inhibition of the thalamocortical neurons. The thalamus is a neural integrator for the activities of the forebrain, but all the cortico-cerebellocortical loops make relay in the thalamus (Habas et al. 2019).

The parallel circuit model of the BG (Fig. 1) describes how information progresses through the BG in anatomically and functionally distinct channels. Balance between these two pathways at the level of GP and SN is essential for normal functioning of the BG–thalamocortical circuits, the disruption of which is the major locus of PD-related dysfunction (McGregor and Nelson 2019). Increased inhibition of the thalamocortical pathway results in hypokinetic disorders, while decreased inhibition of thalamocortical output induces hyperkinetic disorders (Lanciego et al. 2012). These networks are modulated by the release of DA in the striatum, thus enabling flexible motor and behaviour control (Neumann et al. 2018). In parkinsonism, the loss of striatal DA results in the emergence of oscillatory burst patterns of firing of BG output neurons, increased synchrony of the discharge of neighbouring BG neurons and an overall increase in BG output, thus inhibiting their thalamic and midbrain targets. In PD, DA loss is predicted to cause imbalanced activity between the two pathways.

The reduced activity in the "direct" striato-cortical–nigral–GPi pathway induces akinesia (Beck et al. 2018; Wichmann et al. 2018), which may also be associated with abnormalities outside the DAergic pathways (Spay et al. 2018). The two pathways are not separate parallel systems, but functionally intertwined in- and outside the striatum, collaterals bridging the two pathways (Papa and Wichmann 2015; Simonyan et al. 2017). Other models suggest that they are not alternatively but concomitantly active, and coordinated activity across the two pathways regulates movement initiation and execution (Tecuapetla et al. 2016). While the classical model predicts that increased BG output induces excessive inhibition of thalamus and cortex, leading to a paucity of movement, manipulations of the BG in parkinsonian and healthy animals suggest that other measures of activity such as pattern and synchrony play a role in driving PD motor symptoms. According to the "center-surround" model of the BG, cortical input activates STN neurons that excite GPI neurons, suppressing actions. Concurrently, cortical input to the striatum activates indirect MSNs that shape STN activity through the GPe, as well as direct MSNs that converge and inhibit a subset of GPi neurons to permit selective execution of movement. At the striatal level, inhibitory connections between MSNs may contribute to consensually similar center-surround patterns (McGregor and Nelson 2019).

A different hypothesis of the BG pathways and DA, named the cortico-striatal–temporal-difference (CS–TD) model proposes a new modality that integrates the OpAL and CS–TD models. It suggests that the intratelencephalic (IT–BG pathways represent goodness/badness of current options, while the PT-indirect pathway represents the overall value of the previous option, and both these have influence on the DA neurons, through the BG output. A key assumption is that opposite directions of plasticity are induced upon phasic activation of DA neurons in the IT-indirect pathway and PT-indirect pathway because of different profiles of IT and PT inputs. At PT → indirect MSN synapses, sustained glutamatergic inputs generate rich adenosine, which prevents DA-D2 receptor signaling and instead favors adenosine–A2A receptor signaling. Then, DA-induced phasic

adenosine, which reflects TD-RPE, causes long-term synaptic potentiation. In contrast, at IT → indirect MSN synapses, where adenosine is scarce, phasic DA causes long-term synaptic depression via D2 receptor signaling. This new model provides new predictions, part of which is in line with recently reported activity patterns of GPe neurons in the "indirect" pathway (Morita and Kawaguchi 2019).

There are, however, other actions within the BG including communication between DA-D1 and DA-D2 receptor striatal MSNs, with collaterals in both GPi and GPe: GPe projections going back to the striatum, GPi/SNr ones not only to the thalamus, but to pedunculo-pontine tegmental nucleus (PPT), habenula and superior colliculus, as well as a balanced dynamic system regulated by mesolimbic and DAergic neuronal circuits (Cazorla et al. 2015; Hegeman et al. 2016; Schmidt and Berke 2017).

Two "hyperdirect" pathways include a direct cortico–subthalamic–pallidal pathway that increases GPi activity and inhibits thalamocortical targets, thus causing supression of all movements (Wichmann et al. 2018), while three parallel but independent neurotrophic circuits between SN and GABAergic and cholinergic striatal interneurons may exist (Ortega-de San Luis et al. 2018). The hyperdirect and indirect pathways, converging in the STN, are differentially involved in cognitive aspects of motor preparation and gait control during motor performance (Neumann et al. 2018). The thalamostriatal system is a dual system, one originating from midline and intralaminar nuclei, another one from ventral and relais nuclei using glutamate transporters. The source of thalamostriatal projections is highly organized in striatal compartments that are influenced by their cortical and thalamic afferents (Fujiyama et al. 2019). The midbrain locomotor region with the cholinergic PPN that is interconnected with BG, thalamic and brainstem nuclei, spinal effectors, and cerebellum, is crucial for motor and cognitive control (Mori et al. 2016; Vitale et al. 2018). BG and cerebellum are reciprocally interconnected with the neocortex via oligosynaptic loops (Hintzen et al. 2018) as substrate of integrated functional networks between them (Pelzer et al. 2017). They are topographically organized, so that motor, cognitive, and affective territories in the network are interconnected, abnormalities in each node can have network-wide effects (Bostan and Strick 2018). The dorsal motor nucleus of the vagus and SN is connected in a recently discovered monosynaptic nigro–vagal pathway, which is dysfunctional in rodent models of PD (Bove and Travagli 2019).

Classification of major movement disorders

Most extrapyramidal disorders related to BG dysfunction are neurodegenerative diseases featured by neuronal degeneration and astrocytosis in many parts of the nervous system. A classical pathophysiological classification distinguishes: (A) hypokinetic-rigid syndromes: parkinsonian syndromes with rigidity, akinesia/bradykinesia, resting tremor, and postural instability; (B) hyperkinetic syndromes: (1) chorea syndromes with irregular movements; (2) dystonia characterized by involuntary muscle spasms and abnormal posture; (3) ballism with high amplitude movements of the proximal extremities; (4) myoclonus with brief, quick movements; (5) tremor syndromes with rhythmic involuntary movements; and (6) tic disorders with rapid involuntary movements.

Recent genetic and molecular–biologic classification of movement disorders distinguishes (Table 1): (1) Synucleinopathies, a heterogeneous group of neurodegenerative disorders caused by misfolded α-synuclein (α-Syn) protein that forms amyloid-like filamentous inclusions (Alafuzoff and Hartikainen 2017; Goedert et al. 2017b). They include Lewy body (LB) disorders—sporadic and rare familial forms of PD, dementia with Lewy bodies (DLB), pure autonomic failure (PAF), and multiple system atrophy (MSA). Neurodegeneration with brain iron accumulation type I (NBIA-I) or pantothenate kinase-associated neurodegeneration (PKAN) is no longer considered a synucleinopathy (Li et al. 2013). (2) Tauopathies, featured by neurofibrillary tau pathology, include progressive supranuclear palsy (PSP), cortico-basal degeneration (CBD), and frontotemporal lobe degeneration with tau pathology (FTLD/TAU); (3) polyglutamine disorders linked to CAG trinucleotide repeats, such as Huntington's disease (HD); and (4) paraneoplastic forms (Poplawska-Domaszewicz et al. 2018); those associated with neuronal antibodies (Dash and Pandey 2019) or without hitherto detected genetic or specific disease markers. The various phenotypes are associated with the deposition of pathologic (misfolded) proteins and cytoskeletal abnormalities in distinct neuronal populations, which represent important diagnostic signposts. Recent consensus criteria for their clinical and neuropathologic diagnosis have been established (Ali and Josephs 2018a; Gilman et al. 2008; Hoglinger et al. 2018; Jellinger 2016; McKeith et al. 2017). The first part of this review is dedicated to the hypokinetic-rigid syndromes, the second part to the hyperkinetic disorders.

Synucleinopathies

This heterogeneous group of neurodegenerative disorders caused by misfolded α-synuclein that forms amyloid-like filamentous aggregations in many central nervous system (CNS) areas, include (1) Lewy body diseases (LBD)—Parkinson's disease (PD) with and without dementia, dementia with Lewy bodies (DLB), and pure autonomic failure (PAF), all morphologically characterized by α-Syn-positive cytoplasmic inclusions in neurons (Lewy bodies/LBs/) and dystrophic neurites (LN) and (2) multiple system atrophy (MSA), the morphological hallmarks of which are

Table 1 Morphologic and biochemical classification of degenerative diseases with movement disorders

α-Synucleinopathies
Invariable forms (consistent α-synuclein deposition)
Parkinson's disease (brainstem type of Lewy body disease)
Sporadic
Familial with α-synuclein mutation
Familial with other mutations
Incidental Lewy body disease (subclinical Parkinson's disease)
Pure autonomic failure
Lewy body dysphagia
Dementia with Lewy bodies; diffuse Lewy body disease
Multiple system atrophy
Striatonigral degeneration (MSA-P)
Olivopontocerebellar atrophy (MSA-C)
Pantothenate kinase–associated neurodegeneration (Hallervorden-Spatz disease) (no longer classified as synucleinopathy)
Variable forms (inconsistent α-synuclein deposition)
Parkinson's disease with parkin- and LRRK2-linked mutations
Alzheimer's disease (and other tauopathies)
Tauopathies
Progressive supranuclear palsy (4R-tau doublet + exon 19)
Corticobasal degeneration (same)
Amyotrophic lateral sclerosis and parkinsonism-dementia complex of Guam (3R + 4R triplet)
Postencephalitic parkinsonism (3R + 4R triplet)
Frontotemporal lobar degeneration-tau (FTLD-tau) (formerly referred to as frontotemporal dementia and parkinsonism linked to chromosome 17/FTDP-17)
Pallidopontonigral degeneration (4R-tau)
Pick's disease (3R-tau doublet without exon 10)
Advanced Alzheimer's disease with subcortical neurofibrillary tangles
Amyotrophic lateral sclerosis and parkinsonism-dementia complex of Guam
Perry's syndrome
Frontotemporal lobe degeneration with *MAPT* mutation (FTLD-MAPT)
Polyglutamine repeat (CAG) disorders
Huntington's disease—rigid type (CAG triplet repeat)
Choreoacanthocytosis (neuroacanthocytosis)
Machado-Joseph disease (spinocerebellar ataxia type 3 + type 2)
Dentatorubral-pallidoluysian atrophy
X-linked dystonia parkinsonism (Lubag's disease)
Fragile X-associated tremor and ataxia syndrome (FXTAS)
Spinocerebellar ataxia
Other hereditary degenerative disorders
Hereditary striatal degeneration
Pallidal degeneration and related variants
Hallervorden-Spatz disease (without α-synucleinopathy)
Inherited metabolic disorders (e.g., Wilson's disease, Menkes' disease)
Neuronal intranuclear inclusion and basophilic inclusion disease
Inherited dystonias and dyskinesias
Hereditary ferritinopathies

FTLD frontotemporal lobe degeneration, *LLRK2* leucine-rich repeat kinase 2, *MSA-C* multiple system atrophy with predominant cerebellar features, *MSA-P* multiple system atrophy with predominant parkinsonism, *TDP-43* transactive response DNA-binding protein 43 kD

α-Syn-positive glial cytoplasmic inclusions (GCI) in oligodendroglia and less frequent neuronal inclusions. Synucleinopathies account for 73–83% of cases of parkinsonism, including 42–63% PD, whereas other degenerative disorders mimicking PD account for 9–33% (Dickson 2018; Horvath et al. 2013a; Savica et al. 2013a).

α-Syn is a 14 kDa intrinsically disordered presynaptic protein with potential for self-oligomerization and fibrillary aggregation under pathologic conditions. Increasing phosphorylation of α-Syn at serine 129 enhances the accumulation and toxicity (Prasad et al. 2019). Pathological α-Syn has the capacity to self-seed and propagate between cells; its intercellular transfer has been implicated in the progression of synucleinopathies (Dehay 2014; Karpowicz et al. 2019; Reyes et al. 2019). For its molecular basis, functions, interaction with DA metabolites, and relevant animal models, see (Alegre-Abarrategui et al. 2019; Benskey et al. 2016; Burre et al. 2018; Das and Eliezer 2019; Dettmer et al. 2016; Ghiglieri et al. 2018; Goedert et al. 2017b; Grozdanov and Danzer 2018; Huang et al. 2019; Jellinger 2013a; Stefanis 2012; Wong and Krainc 2017). α-Syn assembles into oligomers, which lead to impairment of axonal transport (Prots et al. 2018; Volpicelli-Daley 2017), synaptic dysfunction and neuronal death (Calo et al. 2016; McCormack et al. 2019; Mehra et al. 2019; Mor et al. 2017; Snead and Eliezer 2014). Lipid alterations in membranous compartments may have an effect on α-Syn misfolding and neurotoxicity (Canerina-Amaro et al. 2019). Interaction of α-Syn aggregate species with phospholipid membranes causes disruption and cell death (Iyer and Claessens 2019). α-Syn is a multifunctional player in the regulation of exocytosis, endocytosis, and vesicle recycling (Huang et al. 2019), and a major component of LBs, dystrophic Lewy neurites (LNs), and glia in PD and DLB (Spillantini et al. 1998; Wakabayashi et al. 2013), in neuronal and glial inclusions in MSA (Jellinger and Wenning 2016). Elevated levels of soluble α-Syn oligomers were seen in postmortem PD and DLB brains (Tong et al. 2010) with higher intensity in MSA (Sekiya et al. 2019). They mediate early synaptic pathology and cellular dysruption (Bengoa-Vergniory et al. 2017; Roberts and Brown 2015; Rockenstein et al. 2014). Clearance mechanisms of α-Syn are complex and multifaceted in particular related to exosomes (Stefanis et al. 2019).

Co-occurrence of α-Syn, tau, β-amyloid (Aβ) and other proteins, and interaction between their oligomeric forms, promote their mutual aggregation, thereby inducing neuronal damage (Bourdenx et al. 2017; Foguem and Manckoundia 2018; Spires-Jones et al. 2017). Interaction of α-Syn, tau, and Aβ (with metal ions) is responsible for the overlapping pathology of different proteinopathies that are considered a continuum depending upon genetic and environmental factors (Bengoa-Vergniory et al. 2017; Colom-Cadena et al. 2017a; Godini et al. 2019; Spires-Jones et al. 2017; Walker et al. 2015; Yan et al. 2018). Modification of α-Syn may induce both Lewy and tau pathologies, and enhances amyloid and tau accumulation, while tau and Aβ enhance α-Syn aggregation and toxicity (Gerson et al. 2018; Irwin et al. 2013c; Yan et al. 2018). Interaction between Aβ and α-Syn leads to inhibition of Aβ deposition (Bachhuber et al. 2015). In PD and DLB brains, concentrations of soluble pSer129 α-Syn correlated with the levels of Aβ (Swirski et al. 2014). Distinct strains of α-Syn are responsible for propagation and regional distribution of lesions in synucleinopathies (Alegre-Abarrategui et al. 2019; Candelise et al. 2019; Karpowicz et al. 2019), and are involved in their heterogeneity (Peelaerts et al. 2018; Peng et al. 2018b; Tanaka et al. 2019), as observed after the injection of α-Syn aggregates into animal models (Goedert et al. 2017c; Ko and Bezard 2017; Peng et al. 2018a; Polinski et al. 2018; Thakur et al. 2017).

Lewy body disorders

This group of neurodegenerative disorders is morphologically featured by the presence of α-Syn-positive inclusions. Lewy bodies (LBs), α-Syn-positive cytoplasmic inclusions, are the morphological hallmarks of PD and DLB, but are also found in a variety of disorders, e.g., in 7–71% of sporadic and familial forms of AD (Cairns et al. 2015; Savica et al. 2019), in a small proportion of cases of frontotemporal lobar degeneration (FTLD) with parkinsonism (Forrest et al. 2019a), and in 2–61% of aged individuals with or without dementia (Buchman et al. 2018; Jellinger 2004; Markesbery et al. 2009).

LBs occur in two types: the classical brainstem and the cortical type. Classical LBs are spherical cytoplasmic intraneuronal inclusions 8–30 μm in diameter with a hyaline eosinophilic core and a narrow pale-stained halo. Ultrastructurally, classical LBs are non-membrane-bound, granulofilamentous structures composed of radially arranged, 7–20 nm intermediate filaments with electron-dense granule material and vesicular structures: the core shows densely packed filaments and dense granular material, the periphery radially arranged 10-nm filaments (Forno 1996; Tercjak et al. 2014). Cortical LBs, eosinophilic, rounded, angular, or reniform structures without a halo, are poorly organized, granulofibrillary structures with a felt-like arrangement composed of 7–27 nm wide filaments (Ishiyama et al. 2006). They are found in small neurons in lower cortical layers, particularly in insular and entorhinal cortex, amygdala, hippocampal sector CA2/3, and cingulate gyri (Armstrong et al. 2014; Wakabayashi et al. 2013). Similar granular, pale-staining eosinophilic materials displacing neuromelanin (NM) in brainstem neurons—"pale bodies"—are precursors of LBs (Dale et al. 1992).

Both types of LBs share immuno- and biochemical characteristics (Jellinger 2012b; Rocha Cabrero and Morrison

2019). Their major components are α-Syn, ubiquitin (Ub), phosphorylated Ub, and others such as structural fibrillary elements, α-Syn-binding proteins, those implicated in the Ub–proteasome system, synphilin-1, aggresome- and mitochondria-related, cytoskeletal, cytosolic, cellular response proteins, etc. (Kalia and Kalia 2015; Voronkov et al. 2018). LBs have a central Parkin- and Ub-positive domain with peripheral α-Syn. Colocalization of α-Syn, synphilin, and Parkin suggests that Parkin plays a role in ubiquitination and modification of α-Syn, its oligomers inducing Parkin nitrosylation (Wilkaniec et al. 2019). Synapsin III, a key component of α-Syn fibrils, TH, and choline-acetyl transferase (ChAT) are co-localized in cortical LBs (Longhena et al. 2018). Brainstem LBs show TH and ChAT reactivity with peripheral α-Syn (Dugger and Dickson 2010). LBs and pale bodies are reactive for autophagic proteins p62 and NBR1 (Kuusisto et al. 2003; Odagiri et al. 2012), and for TIGAR protein regulating TP53, which is absent in MSA inclusions (Lopez et al. 2019). LBs further contain 14-3-3 proteins that interact with α-Syn and have multiple cellular functions. Leucine-rich repeat kinase 2 (LRRK2) is not a major component of LBs. Purified inclusions contain approximately 50 isoforms of α-Syn (McCormack et al. 2016). Proteomic analysis of cortical LBs revealed 296 proteins related to multiple or unknown functions (Leverenz et al. 2007) and 204 proteins in PD brainstem (Licker et al. 2014). Different conformations of α-Syn fibrils correspond to different stages of maturity of LBs (Covell et al. 2017), but none of the detected α-Syn variants were LB-specific (Bhattacharjee et al. 2019), while phosphorylated NUB1 (an adaptor protein) distinguishes α-Syn in LBs from that in GCIs in MSA (Tanji et al. 2019). Recent studies showed that LBs are rich in protein–lipid structures found in other parts of the brain (Shahmoradian et al. 2018).

The formation of classical LBs begins with intraneuronal dust-like particles related to neuromelanin (NM) or lipofuscin that are cross-linked to α-Syn, with granular or diffuse deposition of α-Syn and Ub in the center, followed by condensation of dense filamentous inclusions, forming "early LBs" later developing to LBs. Extraneuronal LBs after disappearance of the affected neuron are degraded by astroglia (Wakabayashi et al. 2013).

Cortical LBs show diffuse α-Syn and Ub labeling, whereas subcortical LBs have a central Ub-positive domain with peripheral deposition of α-Syn. Initial granular accumulation of α-Syn is followed by accumulation of dense filaments, spreading to dendrites, later deformation of LBs, and final degradation by astrocytes. Coarse, dystrophic neurites (LNs) with α-Syn and Ub inclusions in axonal processes, which may evolve into LBs (Kanazawa et al. 2008). LBs and LNs occur in virtually all brainstem nuclei and fiber tracts, with significant correlations between LBs and LNs, in both PD and DLB (Seidel et al. 2015).

Most toxin animal models of PD, e.g., 6-OHDA and MPTP, lacked LB pathology, although chronic low doses of MPTP occasionally induced α-Syn-positive inclusions (Meredith and Rademacher 2011). However, trichloroethylene caused SN neuron loss, DA depletion in striatum, and accumulation of intraneuronal α-Syn (Liu et al. 2010). On the other hand, most of the α-Syn tg models exhibit key features of human PD including α-Syn-positive inclusions similar to human LBs (Dehay and Fernagut 2016; Feany and Bender 2000). Injection of α-Syn preformed fibrils (PFF), which mimick α-Syn oligomers found in LBs, into the striatum or other brain areas induced PD-like α-Syn pathologies and robust LB and LN formations (Ko and Bezard 2017; Nouraei et al. 2018; Polinski et al. 2018). Intracellular injection of synthetic α-Syn fibrils in marmosets produced robust LB-like inclusions in TH-positive neurons (Shimozawa et al. 2017), whereas no LBs were seen in monkeys with over 10 years of MPTP parkinsonism (Halliday et al. 2009).

Marinesco bodies, intranuclear inclusions in pigmented neurons of SN and locus ceruleus (LC), frequently found in elderly individuals in the presence of AD, are rare in PD and their frequency declines with duration of PD (Abbott et al. 2017). Higher LP has been shown to be associated with lower prevalence of atherosclerotic cardiovascular disease risk factors in PD patients (Driver-Dunckley et al. 2019).

Functional role of Lewy bodies

The pathobiological significance of LBs is poorly understood. As a consequence of α-Syn misfolding, they could represent indicators of toxicity or of neuronal protection or end products or epiphenomena of unknown responses to cellular stress (Chartier and Duyckaerts 2018; Espay et al. 2019; Rocha Cabrero and Morrison 2019; Sian-Hulsmann et al. 2015). LBs interact with DNA to cause nuclear degeneration and cell death (Power et al. 2017). Mitochondrial DNA deletion was highest in LB positive neurons, indicating increased mitochondrial damage (Muller et al. 2013), while accumulation of mitochondrial DNA deletions triggers neuroprotective mechanisms (Ammal Kaidery and Thomas 2018; Michel et al. 2016). Nuclear localization of α-Syn, the effect on gene expression, and its toxicity is modulated by phosphorylation on serine 129 (Prasad et al. 2019), which indicates an interplay between subcellular location, phosphorylation, and toxicity (Pinho et al. 2019). Aggregated forms of Ser129-phosphorylated α-Syn can no longer be degraded by the proteasome and eventually accumulate within LBs (Arawaka et al. 2017). Small α-Syn intermediates termed "soluble oligomers" lead to synaptic dysfunction (Gadad et al. 2011). Their oligomerization in early stages of PD (Kalia and Kalia 2015) induces protein aggregation, disrupts cellular function, and leads to neuronal death due to mitochondrial dysfunction and oxidative stress (OS) (Michel

et al. 2016; Mullin and Schapira 2013; Rosborough et al. 2017; Stefanis 2012; Tzoulis et al. 2016; Yasuda et al. 2013; Zeng et al. 2018). The Ub–proteasome system (UPS) and the autophagy–liposome pathway (ALP) that render damaged proteins less toxic than their soluble forms contribute to α-Syn turnover, while alterations in these proteolytic pathways result in the accumulation of pathological proteins due to impaired clearance (Liu et al. 2019c). Ubiquitinated proteins in LBs may be a manifestation of a cytoprotective response to eliminate damaged cellular components and to delay the onset of neuronal degeneration (Grunblatt et al. 2018). LBs could be interpreted as markers of surviving neurons, since they are present in the remaining neurons at post-mortem in PD patients or in tissues of asymptomatic individuals, thus reflecting the inability of cells to clear waste proteins due to dysfunction of clearing mechanisms (e.g., autophagy) with subsequent induction of LP and lysosomal stress (Alegre-Abarrategui et al. 2019). All major brain cell types are able to internalize and degrade extracellular α-Syn, but glial cells appear to be the most efficient scavengers. Impairment of clearance leads to accumulation of toxic α-Syn, and dysfunctions of glia, that is involved in the progression of neurodegeneration (Brück et al. 2016; Chavarria et al. 2018; di Domenico et al. 2019; Filippini et al. 2019).

Sporadic Parkinson's disease

PD, the second-most frequent neurodegenerative movement disorder (prevalence 100–572/100,000; incidence 4.5–21/100,000 person/year (Marras et al. 2018); proposed twofold rise within the next 20 years (Dorsey et al. 2018)), is clinically featured by bradykinesia, rigidity, resting tremor, postural imbalance, and various nonmotor features. Subtle cognitive dysfunction and depression often occur early in the disease (Lees et al. 2009), dementia being common in later stages (Emre et al. 2007). Progressive degeneration of the DAergic nigrostriatal system and many cortical and subcortical networks are associated with widespread α-Syn pathology. This causes striatal DA deficiency and related biochemical deficits that produce a heterogeneous clinical phenotype (Fereshtehnejad et al. 2017; Lawton et al. 2015, 2018; Selikhova et al. 2009; Thenganatt and Jankovic 2014). Diagnostic accuracy of clinical diagnosis is 73.8–79.6%, according to a recent metaanalysis 82.7% (Rizzo et al. 2016). For the diagnosis of definite PD, histopathological confirmation is required. Although LBs are not specific to PD and occur in a variety of conditions, a positive diagnosis of PD is possible by the demonstration of neuronal loss and the demonstration of LBs in the midportion of the SN. If no LBs are found, two further sections should be examined. Cell loss in SN and LC in the absence of LBs or other α-Syn-positive inclusions suggests an alternative cause of parkinsonism (Dickson et al. 2009).

Neuropathology of Parkinson's disease

Gross inspection of the brain shows mild cortical atrophy, enlargement of the ventricles, and pallor of SN and LC. Widespread α-Syn-immunoreactive deposits in neurons (LBs) and LNs throughout the nervous system, including the brainstem and many visceral organs are present indicating a multisystem involvement by α-Syn pathology (Beach et al. 2010; Gelpi et al. 2014; Jellinger 2012b; Sulzer and Surmeier 2013; Wakabayashi et al. 2010).

LP is associated with variable neuronal loss in midbrain, other subcortical nuclei and other neuronal systems. Depletion of melanized neurons (45–66%) and DAergic neurons immunoreactive for TH, the key enzyme of DA synthesis (60–85%), affects the ventrolateral part of the A9 group of SNc (91–97% cell loss) projecting to striatum. This corresponds to a somatotopic pattern of DAergic terminal loss being more severe in the dorsal and caudal Put with later involvemen of ventral Put and CN. SN cell degeneration is preceded by loss of neurofilament protein, neuronal TH, and DAT immunoreactivity, indicating functional neuronal damage. Later, extracellular released NM is taken up by macrophages, with rare neuronophagy, and only minor astroglial response. Microglial activation occurs even prior to nigral damage (Duffy et al. 2018). The ventrolateral SNc cell clusters are nearly wiped out, while DAergic neuron loss in the dorsal tier may be as little as 25% (Surmeier et al. 2017), and other DAergic and GABAergic neurons are spared at this time. As the disease processes, the nearby ventral and then dorsal SN cell clusters and their striatal projections are affected (Kordower et al. 2013).

In SN, the proportion of LB-bearing neurons appears to be stable throughout the disease duration, between 3.6 and 15% of surviving SN neurons containing LBs (Greffard et al. 2010). SNc cell loss and the reduction of TH and DAT immunoreactivity in Put followed by CN and NAC correlate with the duration and severity of motor dysfunction (Bernheimer et al. 1973). At 4 year post-diagnosis and thereafter, DAT staining in dorsal Put is almost completely lost with only an occasional DAergic fiber in SNc and a 50–90% loss of TH-positive neurons in striatum (Kordower et al. 2013), whereas in end-stage PD, a stable proportion of LB-bearing SN neurons remains (Greffard et al. 2010). Despite a massive loss of SN neurons with atrophy of the remaining cells (Rudow et al. 2008), degeneration of the striatonigral system is not total, even after many years of illness (Djaldetti et al. 2011). Stereological studies showed no overall loss of neocortical neurons in endstage PD, despite many cortical LBs (Pedersen et al. 2005).

The A10 group of DAergic neurons—VTA, nucleus parabrachialis, and nucleus parabrachialis pigmentosus—projecting to the striatal matrix, thalamus, cortical, and limbic areas (mesocorticolimbic system) show only an average 53% cell loss (Alberico et al. 2015), whereas the periretrorubral A8 region, which contains only a few DAergic but CAB-rich neurons, and the central periventricular gray matter show little or no involvement (Geibl et al. 2019). Cholinergic neurons in the basal forebrain and PNP are lost, but not glutamatergic and GABAergic PPN neurons, while there is a modest loss of glutamatergic neurons in the intralaminar nuclei of the thalamus and basolateral amygdala (Double et al. 2010).

Degeneration of the nigrostriatal system causes denervation in striatum with DA loss ranging from 44 to 98% and progressing from the ventrorostal to posterior Put and CN. In earlier disease stages, an increased number of striatal DAergic neurons, representing a compensatory mechanism, are more efficient in younger PD patients (de la Fuente-Fernandez et al. 2011). More severe nigrostriatal neuron loss occurs in early onset rather than in late-onset PD. At the time of motor symptom onset, the extent of striatal DA marker loss exceeds that of DAergic SN neurons. Neuron loss is more severe in Put (−98.4%) than in CN (−89%), whereas in GPi (−89%) and GPe (−51%), it is not related to the pattern of Put DA loss (Rajput et al. 2008). The concept that PD motor symptoms first appear when more that 50% of DAergic SN neurons are lost (Bernheimer et al. 1973) has been changed by the notion that at that time only around 30% of DAergic SN neurons, but 50–60% of their axon terminals have been lost (Cheng et al. 2010). This is preceded by loss of DA markers in the nigrostriatal terminals in early PD, while melanin-containing SN neurons may persist for a longer time (Kordower et al. 2013). The duration and severity of motor dysfunction, the corresponding decrease of DA, TH, and vesicular monoamine transporter-2 (VAT2) in striatum are negatively correlated with the total SN α-Syn burden and neuronal loss (Cheng et al. 2010). It shows neither correlation with LB formation (Mori et al. 2006) nor with morphological LB stages, clinical severity of PD, and age at death (Burke et al. 2008), whereas SNc cell loss and α-Syn accumulation are closely related. A significant correlation between the nigral α-Syn burden and DAT immunoreactivity in striatum suggests that the severity of neurodegeneration and local α-Syn burden is closely coupled, whereas nigral TH immunoreactivity did not correlate with α-Syn positivity, which supports the concept of synaptic dysfunction or impairment of axonal transport (Chu et al. 2012). Nigral pigmentation and nigral DAT density show no significant association, wereas pigmentation of the ventral SN tier and DAT binding in related striatal areas are closely related (Martin-Bastida et al. 2019). LP may or may or may not be related to nigral DAergic cell loss (Beach et al. 2009; Colloby et al. 2012; Parkkinen et al. 2011). This suggests that both lesions are not interchangeable hallmarks for disease progression or severity, but could be complementing to each other (Rietdijk et al. 2017). While there are normal levels in the cytosolic fraction of α-Syn without correlation with nigral LB density (Tong et al. 2010), PD brains show a significant increase in soluble and phosphorylated α-Syn (pα-Syn) over the disease course, with progressive decrease of soluble α-Syn (Quinn et al. 2012) and changes of serin 129 pα-Syn (Walker et al. 2013).

Increased pα-Syn precedes its aggregation followed by the formation of LBs and LNs, but it does not necessarily correlate with LP, that shows an inconsistent relationship with clinical disease progression (Lue et al. 2012). Lower neuron densities in SN occur before LB deposition, suggesting that cellular dysfunction precedes LP related to a dying-back mechanism, in which dysfunction is caused by accumulation of small α-Syn aggregates at presynaptic terminals (Schulz-Schaeffer 2015). Accumulation of α-Syn is triggered by presynaptic dysfunction (Nakata et al. 2012), and mediates early synaptic pathology by disrupting synaptic vesicles by retrograde degeneration (Tagliaferro and Burke 2016). α-Syn and synapsin III are suggested to cooperatively regulate DA neuron synaptic function (Zaltieri et al. 2015a), and synapsins have been shown to regulate α-Syn formation (Atias et al. 2019). Early intraaxonal aggregation of α-Syn as "pale neurites" at axon collaterals extending centripetally into proximal segments (Kanazawa et al. 2012) damages the parental neurons by interfering with axonal transport (O'Keeffe and Sullivan 2018; Volpicelli-Daley 2017). Axonopathy in presymptomatic PD is followed by neuronal degeneration (Longhena et al. 2017), suggesting that the loss of DAergic neurons might be a consequence of synaptic loss (Yasuda et al. 2013), defining PD as a "synaptopathy" (Bridi and Hirth 2018; Imbriani et al. 2018; Longhena et al. 2017).

Parkinson disease: a multiorgan disorder

LB/α-Syn pathology in PD is not restricted to DAergic brainstem nuclei, but it is associated with degenerative lesions affecting the central, autonomic, and peripheral system (Beach et al. 2010; Braak and Del Tredici 2009; Wakabayashi and Miki 2018), including the cholinergic basal forebrain, and other neurotransmitter systems (Kalia and Lang 2015; Politis et al. 2010). The extranigral lesions correlate with early premotor symptoms (olfactory, autonomic, sensory symptoms, sleep disturbances, pain, and neuropsychiatric dysfunction), later non-motor fluctuations, and advanced non-DA-responsive nonmotor features (Coon et al. 2018; De Pablo-Fernandez et al. 2017; Jellinger 2015, 2017a, b; Klingelhoefer and Reichmann 2017; Lang 2011; Schapira et al. 2017; Titova et al. 2017). LP involves the spinal cord (Del Tredici and Braak 2012; Nardone et al. 2019), the

autonomic and peripheral nervous system, sympathetic and parasympathetic ganglia and plexuses, intramural enteric nervous system, skin, retina, uterus, submandibular gland, bladder, cardiac nervous system, and adrenals (Adler et al. 2016; Braak and Del Tredici 2008; Ma et al. 2019; Orimo et al. 2008; Ortuno-Lizaran et al. 2018; Veys et al. 2019; Wakabayashi and Miki 2018). The musculoskeletal system, and major parts of the sensory nervous system are generally spared (Beach et al. 2009; Cersosimo and Benarroch 2012a, b; Obeso et al. 2017; Oinas et al. 2010), whereas peripheral sympathetic nerves are affected very early (Donadio 2018; Donadio et al. 2019).

Among the earliest involved areas are the olfactory bulb and related olfactory brain nuclei (amygdala and perirhinal cortex), suggesting that olfactory dysfunction in PD is related to the involvement of central pathways rather than peripheral sensory nerve fibers (Attems et al. 2014; Dickson et al. 2009). α-Syn aggregation in the olfactory system and its spreading to the brain may contribute to PD initiation (Cersosimo 2018; Lema Tomé et al. 2013; Rey et al. 2018) by inducing lesions in related brain areas (Niu et al. 2018). Preferential involvement of the olfactory bulb, dmX, and the peripheral autonomic nervous system by LP (Attems et al. 2014; Beach et al. 2010) is related to an increase of pα-Syn in the olfactory bulb and brainstem (Beach et al. 2009; Halliday et al. 2012). Affection of the autonomic nervous system and gastrointestinal tract before involvement of the CNS has suggested a route for spreading α-Syn via the vagus nerve to the brain (Braak and Del Tredici 2008; Holmqvist et al. 2014), confirmed by intragastric rotenone administration or α-Syn inoculation into the mouse gastrointestinal tract (Pan-Montojo et al. 2010). Resection of the vagal nerve interrupted the disease progression to the CNS (Uemura et al. 2018), and appendectomy were associated with reduced risk of PD (Svensson et al. 2015), suggesting a possible role of the gut-brain axis in the pathogenesis of PD (Bove and Travagli 2019; Bu et al. 2019; Perez-Pardo et al. 2017), which has been critically discussed recently (Breen et al. 2019; Kujawska and Jodynis-Liebert 2018; Lionnet et al. 2018). On the other hand, the appearance of α-Syn aggregates in both the submucosal and myenteric plexuses of the enteric nervous system, prior to their appearance in the brain, indicates a possible gut to brain route of α-Syn spread (Felice et al. 2016), and a better understanding of the brain-gut microbiota axis could bring a new insight in the pathophysiology of PD (Fitzgerald et al. 2019; Mulak and Bonaz 2015).

Incidental Lewy body disease (iLBD)

The term iLBD is used when LBs are present in the nervous system in subjects without clinical parkinsonism. Their distribution is similar to that in PD, but often LBs are limited to the limbic cortex, whereas in definite PD cases, LP is present in all regions. A 70% SN cell loss and decreased TH immunoreactivity involve striatum and epicardial nerve fibers, but not to the same extent as in PD (Adler et al. 2010b; Beach et al. 2008; DelleDonne et al. 2008; Dickson et al. 2008), suggesting that it is a preclinical form of PD and that the lack of symptoms is due to subthreshold pathology (Dickson 2018).

Between 5 and 55% of neurologically unremarkable elderly people showed abundant LP with a distribution pattern similar to that seen PD, but relative preservation of pigmented SN neurons (DelleDonne et al. 2008; Jellinger 2004; Markesbery et al. 2009), while LP may be confined to the olfactory bulb. Some had sparse, but widespread LP involving the cortex (Frigerio et al. 2011), which would violate the theory of upward progress from brainstem and would suggest a multicentric disease progress from the onset (Dickson 2012). LP in the spinal cord and dorsal root ganglia in elderly persons was associated with LP in lower brainstem due to retrograde spread (Sumikura et al. 2015).

Staging of Lewy pathology

Three major staging systems currently exist for LB disorders: (1) for PD (Braak et al. 2006; Braak and Del Tredici 2017); (2) for DLB (McKeith et al. 2017); and (3) revised guidelines for LB disease (Zaccai et al. 2008). Based on semiquantitative assessment of LB distribution in a large autopsy series, a staging of the presumed spread of LP was proposed to designate the sequence of lesions in the nervous system (Table 2). LP initially involves the olfactory bulb and related olfactory brain nuclei, the peripheral autonomic system, and adrenal medulla in neurologically unimpaired subjects referred to as iLBD (Beach et al. 2008; DelleDonne et al. 2008; Dickson et al. 2008; Frigerio et al. 2011). In stage 1, the dmX and intermediate reticular zone are involved, while the NBM and midbrain regions are preserved. In stage 2, LNs involve the enteric nervous system, parasympathetic and sympathetic nerves, and medullary nuclei of the level setting system (lower raphe nuclei, gigantocellular reticular nucleus, and ceruleus–subceruleus complex). These a- or presymptomatic stages may explain nonmotor (olfactory and autonomic, e.g., gastrointestinal and urinary) symptoms that precede motor dysfunctions (Cersosimo and Benarroch 2012b; Dickson et al. 2009; Halliday and McCann 2010). In stage 3, LNs and LBs involve PPN, LC, amygdala, upper raphe nuclei, magnocellular nuclei of the basal forebrain, hypothalamic tuberomammillary nucleus, posterolateral/posteromedial SNc, and spinal cord, whereas the allocortex and isocortex are preserved. This stage is associated with disturbed sleep, early motor dysfunction, and several non-motor symptoms. In stage 4, midline and intralaminar thalamic nuclei, anteromedial temporal limbic cortex

Table 2 Neuropathological staging of Lewy body disease

Kosaka LBD stage	Braak PD stage	Anatomical distribution of Lewy bodies
Brainstem-predominent type	1	Medulla oblongata: dorsal IX/X motor nucleus, intermediate reticular zone; enteric and peripheral autonomic nervous system, spinal cord and anterior olfactory nucleus
	2	Medulla oblongata and pontine tegmentum: stage 1 plus lesions in the caudal raphe nuclei, gigantocellular reticular nucleus, and ceruleus-subceruleus complex; olfactory bulb
	3	Midbrain: stage 2 plus midbrain lesions, pars compacta of the substantia nigra and basal forebrain
Transitional (limbic) type	4	Basal prosencephalon and mesocortex: stage 3 plus prosencephalic lesions. Cortical involvement confined to temporal mesocortex (transentorhinal region) and allocortex (CA2)
Diffuse cortical type	5	Neocortex: stage 4 plus lesions in high order sensory association areas of the neocortex and prefrontal neocortex
	6	Advanced neocortex: stage 5 plus lesions in first-order sensory association areas of the neocortex and premotor areas

(transentorhinal and entorhinal region), hippocampus, and the second sector of the Ammon's horn are affected, associated with severe motor dysfunction. In stage 5, LNs and LBs in cortical areas for regulation of autonomic functions, in higher order sensory association areas and prefrontal fields, are associated with late phase motor disability, and fluctuations. In stage 6, sensory association areas and premotor fields, primary sensory, and motor areas or the entire neocortex are involved (Braak and Del Tredici 2009), causing late motor disability, fluctuations, and cognitive impairment. An increase in the density of α-Syn aggegates and LBs from stages 3–6 correlated negatively with the decrease in neuronal density (Dijkstra et al. 2014).

The validity of the Braak staging scheme, which corresponds roughly to the original classification of LB disorders into three phenotypes—brainstem predominant, limbic/transitional, and diffuse neocortical (Kosaka et al. 1988)—has gained acceptance (Dickson et al. 2010b; Kingsbury et al. 2010), but has been debated (Beach et al. 2010; Burke et al. 2008; Dickson 2012; Jellinger 2009a; Kempster et al. 2010; Parkkinen et al. 2008; Sestini et al. 2019). 51–83% of PD and DLB cases were compatible with this staging (Beach et al. 2009; Jellinger 2009a), but between 6.3% and 47% of autopsy-proven PD cases did not not conform to it (Attems and Jellinger 2008; Beach et al. 2009; Leverenz et al. 2008; Parkkinen et al. 2008). In large autopsy samples, 49–55% of individuals with widespread α-Syn pathology lacked clinical symptoms (Kalaitzakis and Pearce 2009; Leverenz et al. 2008; Zaccai et al. 2008), the determination of cases as atypical being dependent on the staging system applied (Coughlin et al. 2019).

The Braak hypothesis, suggesting predictable caudo-rostral spreading of LP is based exclusively on distribution of LBs but not on neuronal loss, that are not correlated, and it is not identical with α-Syn spreading (Alafuzoff et al. 2009; Rietdijk et al. 2017). While the Braak staging shows only indirect correlations, another scheme based on a limited number of PD cases offered a strong correlation between SN neuronal loss and α-Syn pathology in Braak stages 3–6 ($p < 0.001$), but no correlation between Hoehn and Yahr and Braak stages (van de Berg et al. 2012). A negative correlation between neuronal density and α-Syn burden was observed in SN, but no relationship with Hoehn and Yahr stage or disease duration (Dijkstra et al. 2014). The Braak staging is valid for PD patients with young onset and long duration with motor symptoms (Halliday et al. 2008), but not for those with late onset and rapid disease course (Jellinger 2019). 10–15% of PD cases associated with genetic mutations show a pattern of LP that is distinct from the Braak scheme (Schneider and Alcalay 2017).

A new unifying system for LB disorders correlates with nigrostriatal degeneration, cognitive impairment, and motor dysfunction (Beach et al. 2009). Whereas the previous systems left 42–50% of elderly individuals unclassified, this new one allowed all cases to be classifiable into one of the following stages: I, olfactory bulb only; IIa, brainstem predominant; IIb, limbic predominant; III, brainstem and limbic; and IV, neocortical. Progression through these stages accompanied by stepwise reduction of striatal TH and SN pigmented cell loss showed significant correlation with clinical and psychometric data (Table 3).

Neuronal vulnerability

There is a close relationship between differential expression profiles of α-Syn and selective vulnerability of certain neuronal populations (Taguchi et al. 2019). Degeneration in PD shows a selective vulnerability of neurons located in the caudal and mediolateral region of SNc (area A9), which have an anatomical, physiological, and biochemical phenotype that predisposes them to α-Syn pathology and mitochondrial dysfunction (Surmeier et al. 2017; Surmeier 2018). Some of

Table 3 Causes of Parkinsonism

Common causes of neurodegenerative parkinsonism
Idiopathic Parkinson's disease (sporadic, familial)
Multiple system atrophy
Dementia with Lewy bodies
Progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome)
Genetic Parkinson's disease (PINK1, PRKN, LRRK2)
Uncommon neurodegenerative causes of parkinsonism
Vascular pseudoparkinsonism
Corticobasal degeneration
Alzheimer's disease, Pick's disease
Frontotemporal lobe degeneration type 17
Parkinson-dementia complex of Guam
Metal storage disorder (Wilson's disease; PKAN, HH, etc.)
Neuroacanthocytosis
Huntington's disease, rigid type
Spinocerebellar ataxia type 3
Dentatorubral-pallidoluysian atrophy
Lubag's disease (X-linked dystonia-parkinsonism)
Dopa-responsive dystonia
Pallidal degenerations, pallidonigroluysian atrophy
Neuronal inclusion body and neurofilament inclusion body disease
TDP-43 Perry syndrome
Guam Parkinson dementia syndrome
Secondary causes of parkinsonism (symptomatic forms)
Vascular (pseudo-) parkinsonism (lacunar state, leukoaraiosis)
Drug-induced parkinsonism (dopamine receptor blockers, neuroleptics)
Toxin-induced disease (e.g., manganese, carbon monoxide, carbon disulfide, MPTP, rotenone)
Infections and postinfectious diseases (influenza virus, HIV encephalopathy, Creutzfeldt-Jakob disease, neurosyphilis, Japanese B encephalitis, herpes encephalitis, paraneoplastic encephalitis)
Anoxic brain injury
Inherited metabolic disorders:
Lysosomal storage diseases: Gaucher dis., Niemann-Pick dis., GM1 gangliosidosis
Disorders of metal metabolism: Wilson's dis., hemachromatosis, PKAN
Disorders of amino acid metabolism: phenylketonuria, maple syrup urine dis., methylmalonic aciduria
Mitochondrial disorders
Other disorders:
Normal pressure hydrocephalus
Space-occupying lesions (frontal lobe tumor, CNS lymphomas)
Posttraumatic parkinsonism (boxer's encephalopathy, chronic traumatic encephalopathy)
Basal ganglia calcification (Fahr's syndrome, hypoparathyroidism)
Brainstem tumors
Brainstem lesions due to increased intracranial pressure

CNS central nervous system, *HIV* human immunodeficiency virus, *HH* hereditary hemachromatosis, *MPTP* 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, *PKAN* pantothenate kinase-associated neurodegeneration

the factors which determine vulnerability to degeneration in synucleinopathies are best characterized in the DAergic SNc neurons that suffer from an enormous metabolic burden due to this architecture (long unmyelinated axons and large numbers of synapses), Ca^{2+} handling capacity, and DA itself being potentially toxic (Post et al. 2018). These neurons contain calbindin (CAB) and glycolytic enzymes, but are poor in DAT and arborize profusely in the striatum and extrastriatal components of the BG. NM lipid changes, upregulation of α-Syn, low intrinsic calcium buffering capacity, change in iron levels, long, poorly myelinated, highly branched axons, and various risk factors promote the susceptibility to selective death of these neurons due to disruption of nuclear membrane integrity (Giguere et al. 2018; Jiang et al. 2016;

Surmeier et al. 2017; Surmeier 2018). Calcium mediates the localization of α-Syn at the presynaptic terminal and an imbalance in calcium or α-Syn can cause synaptic vesicle clustering (Lautenschlager et al. 2018). Interaction between α-Syn, calcium ions and DA leads to imbalanced protein turnover of these neurons (Post et al. 2018), that show increased iron (Sian-Hulsmann et al. 2011), but much more in microglia obviously originating from phagocytosis of Fe-laden neurons (Horowitz and Greenamyre 2010). An inhibitory effect of α-Syn on proteasomal activities can contribute to the selective vulnerability of DAergic neurons in PD (Zondler et al. 2017). Dysfunctional synaptic vesicle endocytosis may contribute to selective vulnerability of DAergic midbrain neurons (Nguyen et al. 2019). Neurons in STN and GABAergic SNr, that are rich in calcium-binding proteins (calcineurin and parvalbumin), and glycolytic enzymes are either not affected or involved only in the terminal stages (Double et al. 2010). The confluence of disruption of the cellular metabolic state and α-Syn structural equilibrium, and anatomical connectivity as suggested factors to initiate cascades of pathological processes triggered by genetic, environmental, or stochastic events was reviewed recently (Alegre-Abarrategui et al. 2019).

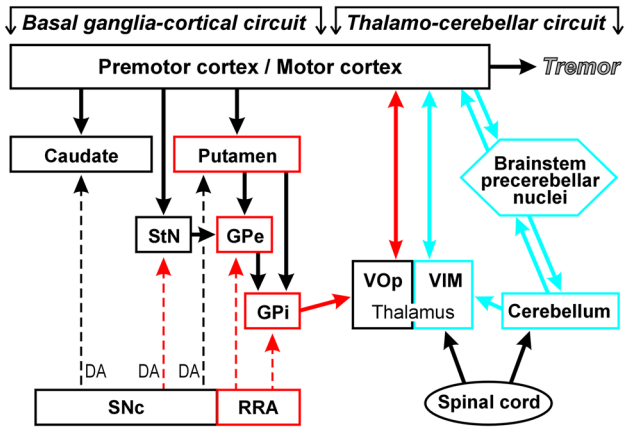

Fig. 3 Model of cerebral mechanisms underlying Parkinson's disease resting tremor. It emerges from the ventral intermediate nucleus of the thalamus (VIM)–motor cortex (MC)–cerebellum (CBLM) circuit (in blue), when triggered by transient pathological signals from the basal ganglia motor loop (in red). In tremor-dominant PD, the basal ganglia globus pallidus internus, globus pallidus externus and putamen) has increased connectivity with the VIM–MC–CBLM circuit through the MC (thick red line), and the basal ganglia is activated at critical times in the tremor cycle (onset/offset of tremor episodes). These alterations may be caused by loss of dopaminergic projections from retrorubral area 8 in red to the GPi and GPe. These alterations are different from the dopaminergic denervation of the striatum associated with bradykinesia and rigidity. *DA* dopamine, *SNc* substantia nigra pars compacta, *StN* subthalamic nucleus, *Vop* thalamic ventralis oralis posterior nucleus. Modified from (Helmich et al. 2011)

Lesion patterns in clinical subtypes of Parkinson's disease

Pathological variability of PD contributes to its clinical heterogeneity of the disease. Two major clinical subtypes of PD show specific morphologic patterns of pathophysiologic importance, with different involvements of striatal and cerebello-thalamo-cortical pathways (Figs. 2, 3). The two classical motor subtyping systems of PD poorly overlap, but their temporal instability undermines their prognostic value in the early stage of PD (Erro et al. 2019).

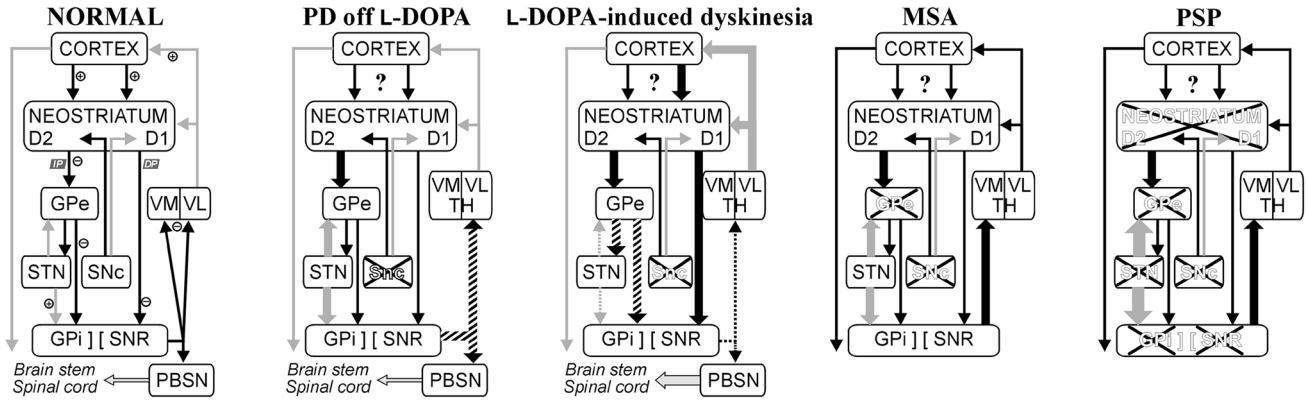

Fig. 2 Schematic diagram of the basal ganglia-thalamocortical circuitry under normal conditions and in hypokinetic movement disorders. The width of lines represents the relative change in activity versus normal. Disrupted lines represent altered patterns with an increase or decrease in neuronal activity; dashed arrow, reduced activity; solid arrow, increased activity. *D1 and D2* dopamine 1 and 2 receptor subtypes, *DYS* dystonia, *GPe and GPi* external and internal segment of the globus pallidus, *IP/DP* indirect/direct pathway, *MSA* multiple system atrophy; normal, normal conditions, *PD* Parkinson's disease, *PPN* pedunculopontine nucleus, *PSP* progressive supranuclear palsy, *SNc and SNr* substantia nigra pars compacta and reticulata, *STN* subthalamic nucleus, *TH* thalamus, *VL and VM* ventrolateral and ventromedial thalamic nuclei. From (Jellinger 2016)

In the *akinetic-rigid type* (about 50% of PD patients), the ventrolateral SNc projecting to dorsal Put degenerates more severely than the medial parts projecting to CN and anterior Put. Loss of TH- and DAT-reactive fibers and endings progressing from the dorsal to the ventral Put is associated with damage to the met-ENK and SP-rich AChE-poor striosomes projecting to the predominantly affected ventrolateral SNc, that correlates with DA loss in posterior Put and the severity of akinesia/rigidity (Bernheimer et al. 1973). DAergic denervation causes loss of dendrites on type I MSNs, the principal targets of DAergic input from the SN, and decline of nigrostriatal DA. DA modulation of glutamatergic synapses on the striato–pallidal GABA and striato–nigral pathways via heteroreceptor complexes (Borroto-Escuela et al. 2018) is due to the efficacy of inhibitory synaptic plasticity of these BG output nuclei (Milosevic et al. 2019). The beneficial effect of L-dopa on bradykinesia is associated with normalization of the striato–thalamo–cortical motor and STN–cortical motor pathways (Gao et al. 2017).

In early PD stages, overactivation of the BG as a compensation of the DA deficit in the striatal motor circuit (Reetz et al. 2009) and decreased excitation of D1-bearing neurons lead to reduced activity of the "direct" pathway, whereas reduced inhibition of D2-bearing neurons results in decreased activity in striatopallidal GPe projections. In later stages, this filtering mechanism is deranged, and DA depletion shifts the BG toward inhibiting movements by increased activity in the GABAegic "indirect" GPe–STN–GPi network and decreased activity in the "direct" cortico–Put–GPi circuit due to loss of D1 excitation (Calabresi et al. 2009). Excessive glutamatergic drive from GP/SNr leads to an akinetic–rigid syndrome through reduced cortical activation due to inhibition of thalamocortical and brainstem motor systems or due to loss of DA input to prefrontal or motor cortex (Fig. 2).

The *tremor-dominant type* (about 25% of PD patients) that shows a better prognosis and slower disease progression has less severe depletion of lateral SNc, but damage to the retrorubral A8 field, which is usually preserved in AR PD (Paulus and Jellinger 1991). It projects to the matrix of the dorsolateral striatum and VM thalamus, and influences striatal efflux via the SNc and thalamus-to-prefrontal cortex (Fig. 3). Resting tremor severity is inversely correlated with raphe serotonin transporter availability which, together with Put DA depletion may contribute to it (Pasquini et al. 2018). Resting tremor is associated with increased activity of the ventral intermediate (VIM) thalamus and dysfunction of cerebellar connections (Elias et al. 2008) and is produced by pathological interaction between BG and the cerebello–thalamo–cortical circuit in the presence of striatopallidal DAergic dysfunction (Dirkx et al. 2017; Helmich 2018). Deficits in cerebellar function with decreased excitability of the cerebello–thalamo–cortical pathway may generate postural tremor, indicating that resting and postural tremor in PD is mediated by different pathways (Ni et al. 2010).

Motor complications, dyskinesia, and freezing

α-Syn pathology in striatum, progressive loss of DAergic neurons and of TH- and DAT-reactive nigrostriatal fibers increase with progression of PD (Sorrentino et al. 2019), and are substrates for motor deficits and decreased efficacy of DAmimetic therapy in late stages of PD (Lane 2019). Prevalence of L-dopa-induced dyskinesia (LID) ranges from 3 to 94% (Rosqvist et al. 2018; Tran et al. 2018). LID can also be present in MSA and PSP, although less frequently, and with varying clinical manifestation (Jost et al. 2019). Dysregulation of striatal projecting neurons in advanced PD (Beck et al. 2018) and degeneration of striatal efferents with transgression to non-DAergic systems cause loss of postsynaptic D2, and muscarinic cholinergic receptors in striatum and of *N*-methyl-D-aspartate (NMDA) receptors and glutamatergic synapses degenerate, favoring drug resistance and motor complications (Picconi et al. 2008). Impairment of synaptic plasticity of striatal MSNs contributes to the development of motor fluctuations and dyskinesias (Bagetta et al. 2010).

Hyperstimulation of DAergic receptors and impairment of synaptic plasticity of striatal MSNs causing excessive striato-cortical connectivity in response to L-dopa produce aberrant signals that trigger involuntary movements (Herz et al. 2015) and overreaction of the mesocortical and mesolimbic systems results in hyperdopaminergism (Voon et al. 2017) (Fig. 2). Presynaptic dysregulation of DA release after L-dopa, causing stimulation of striatal intraneurons (D1-MSNs), may trigger LIDs (Klietz et al. 2016; Mosharov et al. 2015; Perez et al. 2017). It has become evident that striatal interneurons are major determinants of network activity and behavior in PD and LID (Zhai et al. 2019). Peak-dose dyskinesias are caused by the following mechanisms: (1) marked fluctuation of DA concentrations occur in synaptic clefts of striatal neurons after each L-dopa dose; (2) supersensitive cortico-striatal synapses of direct-pathway spiny neurons; (3) increased production of GABA in the spiny neurons and their axon terminals; (4) each L-dopa dose causes excessive release of GABA into the output nuclei of the BG, resulting in their abnormal firing (Tomiyama 2017); and (5) modifications in perisomatic GABAergic connectivity and neuronal activation of MSN, leading to an imbalance between excitation and inhibition in striatal activity (Gomez et al. 2019). Sprouting of DAergic terminals may contribute to increased DA release/turnover, and increased DA sensitivity of striatal cholinergig neurons, predisposes to motor complications (Bordia and Perez 2019; Perez et al. 2018). Pre- versus postsynaptic mechanisms, changes in DA receptor subtypes, glutamate receptors,

striatal spreading depolarization contributing to abnormal BG activity, and non-DAergic transmitter systems including serotonergic and cholinergic mechanisms are also related to LIDs (de Iure et al. 2019; Pagano et al. 2018; Politis et al. 2014). Monoaminergic dysregulation in limbic domains (Engeln et al. 2015) and structures outside the CBGTC circuit, as well as cerebellar dysfunction of the PPN-GB system, may also contribute to LID (Cenci et al. 2018; French and Muthusamy 2018). Since the PPN is densely connected with the BG and the brainstem dysfunctions of this system (Bohnen et al. 2019) or of cerebellar connections (Bhatia et al. 2018) lead to advanced symptomatic progression in PD (French and Muthusamy 2018). The recently described bidirectional connections between BG and cerebellum indicate a key role of the cerebellum in the generation of LID. This model suggests that aberrant neuronal synchrony in PD with LID may propagate from the STN to the cerebellum and "lock" the cerebellar cortex in a hyperactive state. The motor responses are worsened by the lack of normal subcortico-cortical inputs from cerebellum and BG due to of the aberrant plasticity at their own synapses (Kishore and Popa 2014). Animal models of LID in rats and mice with nigrostriatal 6-OHDA lesions treated with L-dopa developed involuntary movements with both hyperkinetic and dystonic components, which enabled insight into the mechanisms of LID (Cenci and Crossman 2018; Keber et al. 2015).

Freezing of gait (FOG), one of the most disabling motor symptoms in PD, reflects a combined motor and cognitive de-automatization deficit, which may be related to structural changes in the PPN network affecting prefrontal cortical areas involved in executive inhibition function (Fling et al. 2013; Snijders et al. 2016), a functional decoupling between the cognitive cortical control network and the BG (Shine et al. 2013), or specific changes in the frontostriatal pathways rather than brainstem lesions (Hall et al. 2014), while others found correlations between the severity of FOG and the density of cortical LB-containing neurons (Virmani et al. 2015).

Pathology of cognitive impairment in Parkinson's disease

Cognitive impairment (CI), which may precede the onset of dementia up to 10 years, was observed in 19–30% of untreated PD patients (Aarsland and Kurz 2010; Poletti et al. 2012), mild cognitive impairment (MCI), often progressing to dementia in 21–62%, and a mean of 25.8% (Aarsland and Kurz 2010; Jellinger 2013b). The point cumulative prevalence of dementia in PD (48 and 78%), with a mean of 75% after more than 10 years, of 83% after 20 years (Hely et al. 2008) is up to 95% by age 90 years (Rongve and Aarsland 2013). PD dementia (PDD) has a prevalence of 31.3% (95% CI 20.1–42.1) and incidence rates from 42.6 to 112.5/1000 person/years (Marder 2010), indicating that around 10% of a PD population develop dementia per year (Emre et al. 2007). The pathological substrate of CI in PD is heterogenous, related to both LB and AD pathologies, multiple neurotransmitter deficits, and changes in gray and white matter (Hall and Lewis 2019; Wilson et al. 2019). Neuropathology of MCI in PD (PD-MCI) with brainstem–limbic, and rare neocortical LB lesions, amyloid but only rare neuritic plaques in cerebral cortex, mild cerebral amyloid angiopathy (CAA), and lacunar state in BG (Adler et al. 2010a; Jellinger 2013b), or cortical or limbic predominant LB disease, but rare coexisting AD (Molano et al. 2010), is similar to that found in MCI cases without PD (Markesbery 2010; Petersen et al. 2006). Structural brain analyses found unilateral insula involvement in PDD-MCI extending to bilateral insula involvement in PDD indicating both increasing brain atrophy in PD with CI and suggesting the existence of sub-typing in PD-MCI (Mihaescu et al. 2018). In PD-MCI, cholinergic fiber depletion was evident, which was correlated with loss of neurons in hippocampal subfield CA2, whereas only PDD cases had significantly greater LP in CA2 (Liu et al. 2019a).

Cognitive deficits in early PD are associated with impaired striatal and extrastriatal DAergic function (Siepel et al. 2014), due to abnormal processing in the cortico–BG circuit with reduced prefrontal and parietal metabolism (Ekman et al. 2012) and dysfunction of the salience networks of the medial temporal lobe (Christopher et al. 2015). Dysfunction of subcortico–cortical networks is a result of neuronal loss in brainstem and limbic areas, cholinergic deficits in cortex, thalamus, and NBM, striatal DA loss, degeneration of the medial SN, and striatosubfrontal and mesocorticolimbic loops. Cortical cholinergic denervation and early posterior cortical atrophy contribute to CI in PD (Bohnen et al. 2015; Sampedro et al. 2019). Reduction of cholinergic markers is due to early degeneration of the corticopetal basal forebrain projection involving the NBM (70% loss of cholinergic neurons in PDD) (Liu et al. 2018; Ray et al. 2018; Schulz et al. 2018). Muscarinic acetylcholine receptors (mAChRs) are important in the regulation of the striatal network which may have implications in the motor and CI in PD (Ztaou and Amalric 2019). Galanin upregulation in the NBM as a response to loss of cholinergic neurons was higher in the transition between PD and PDD, but failed with increasing AD pathology, thus being uncommon in established AD and DLB (Alexandris et al. 2019). The noradrenergic LC, serotonergic DRN, and VTA are also involved (Del Tredici and Braak 2013; Espay et al. 2014; Halliday et al. 2014; Vermeiren and De Deyn 2017). Aβ pathology is not the primary driver of CI and dementia in PD (Melzer et al. 2019). A systemic review of autopsy studies of PDD was published recently (Smith et al. 2019).

PD patients without dementia may have AD pathology largely restricted to the limbic system (Braak neuritic stages < 4), whereas in 10–50% of PDD cases, it was severe

enough to attain the diagnosis of definite AD (Hepp et al. 2016). Neocortical or limbic LP was considered as the most significant correlate of dementia in PD (Horvath et al. 2013b), while recent studies revealed increasing evidence of tau pathology in PD (Whitwell 2018; Zhang et al. 2018b). PD patients with AD co-pathology harbor greater neocortical α-Syn pathology, the latter contributing uniquely to the heterogeneity of CI diseases (Coughlin et al. 2018), while both cognitive and gait disturbances in PD show common underlying pathological mechanisms related to AD pathology (Lim et al. 2018).

Molecular pathology of depression in Parkinson's disease

Depression is a predominant non-motor symptom involving 30–40% of PD patients (Reijnders et al. 2008). However, the neuropathology of this comorbitity is still unclear. Early neuropathological studies indicated a higher prevalence of lesions in depressed compared to non-depressed PD patients particularly in catecholaminergic brain areas (neuron loss in LC, DVN, and SNc), suggesting that depression in PD is related more to catecholaminergic than serotonergic systems (Frisina et al. 2009). Decreased DAT binding in the CN suggested that depressive symptoms in PD are associated with DA loss in this region related to degeneration of DAergic projections from the VTA (Vriend et al. 2014). Later, imaging studies presented conflicting data about the role of serotonergic degeneration in depression in PD: while some studies suggested that abnormalities in serotonin 1A receptor neurotransmission in the limbic system may be involved in the neural mechanisms underlying depression in PD patients (Ballanger et al. 2012) and emphasized a prominent role of the serotonergic degeneration in apathy, anxiety, and depression in de novo PD (Maillet et al. 2016), others found no association between raphe serotonin transporter availability and depression and other psychiatric symptoms in early drug-naive PD patients (Qamhawi et al. 2015). Other imaging studies demonstrated widespread abnormalities within the limbic circuits notably the orbitofrontal and anterior cingulate cortices, amygdala, thalamus, and ventral striatum involved in the pathophysiology of depression in PD (Thobois et al. 2017). Recent diffusion MRI connectometry studies suggested that the prominent circuits involved in emotion and recognition (fornices, fronto–occipital fasciculus, genu of corpus callosum, etc.) might be impaired in comorbid depressive symptoms in PD (Ansari et al. 2019). Other recent studies indicated that an abnormal mesocorticolimbic system may account for depressive symptoms in PD, suggesting that resting-state functional connectivity of midbrain DAergic nuclei might be useful for understanding the underlying pathology in PD with depression (Wei et al. 2018), while others suggested impaired interhemispheric synchrony as underlying neural mechanism of depression in PD (Zhu et al. 2016). Another study showed significant negative association between depression scores in PD patients and qualitative anisotropy (QA) of left cingulum, genu and splenium of corpus callosum, and anterior and posterior limbs of the right internal capsule (Ghazi Sherbaf et al. 2018). Others suggested a possible role of inflammation and neuromodulation as pathogenic mechanism of depression and cognitive impairment in PD (Pessoa Rocha et al. 2014). The inflammatory hypothesis states that depression in PD is caused by changes in the serotonergic systems induced by neuroinflammation (Santiago et al. 2016), whereas disturbances in monoaminergic transmission and the hypothalamic–pituitary–adrenal axis, increased oxidative and neuroinflammatory events, and impaired trophic transport may be implicated in the relationship between depression and neurodegeneration (Galts et al. 2019). Recent studies failed to verify the vascular depression hypothesis in PD (Ou et al. 2018).

Neuronal basis of drug-induced psychoses in Parkinson's disease

Psychotic symptoms in PD have a prevalence of 20–40% (Bizzarri et al. 2015) and are associated with high morbidity and mortality (Samudra et al. 2016), but their pathogenesis is unclear. Factors implicated include DAergic medications, neurotransmitter imbalances, neuroanatomic alterations, and genetic disposition (Ffytche et al. 2017). Other factors include LB deposition in the limbic system, cholinergic deficits and impairments of primary visual processing (Williams-Gray et al. 2006), or genetics (e.g., APOE ε4 allele and tau H1H1 genotype) (Zahodne and Fernandez 2008). Current theories on the pathophysiology of PD psychosis implicate pathways involving visual processing and executive function, including temporo-limbic structures and neocortical gray matter with altered neurotransmitter functioning (Chang and Fox 2016), while others described degeneration of specific hippocampal subfields in PD patients with psychosis (Lenka et al. 2018). Unlike patients with PD psychosis who have dementia, those without dementia have no higher LB load in amygdala and hippocampus (Harding et al. 2002; Kalaitzakis et al. 2009a). Definite neuropathological findings for drug-induced psychoses in PD, to the best of our knowledge, are not available.

Genetics of Parkinson's disease

Familial parkinsonism is rare (5–10%), but the importance of genetic factors is increasingly being recognized (Lill 2016). The heritable estimate of PD is between 23 and 34% (Chang et al. 2017). A minority present a Mendelian form with autosomal-dominant (AutD), e.g., SNCA, LRRK2, and VPS35 genes accounting for 0.1–30% of PD, or with

autosomal-recessive (AutR) transmission, e.g., PARK2 (Parkin), PARK7 (DJ-1), or PINK1 genes, depending on family history, age at onset, and population background (Trinh et al. 2018; Volta et al. 2015). Until to date, a total of 23 loci and 19 causative genes have been associated with PD, although some of the PARK loc (PARK3, 10, 12, and 16) have not yet been identified (Del Rey et al. 2018). PD GWAS confirmed 10 candidate genes previously selected and nominated 17 novel candidate gens for sporadic PD (Ferrari et al. 2018). PARK14 (D331Y) PLA2G6 mutation causes degeneration of SNc DAergic neurons by inducing mitochondrial dysfunction, elevated ER stress, mitophagy impairment, and transcriptional abnormality (Chiu et al. 2019). Seven novel candidate genes (VCAM1, BACH1, CALM3, EGR1, IKBKE, MYC, and YWHAG) may play important roles in PD pathogenesis (George et al. 2019). SNCA, the gene encoding α-Syn, is central to the pathogenesis of PD (Lubbe and Morris 2014; Singleton et al. 2013; Verstraeten et al. 2015). It is associated with hereditary AutD forms, and variations of the SNCA gene are associated with increased risk for sporadic PD (Nussbaum 2018). In cases harboring SNCA missense mutations, several mechanisms could lead to a loss of functional mechanisms including haploinsufficiency and epigenetic silencing (Voutsinas et al. 2010). A recently identified SNCA mutation, p.Ala53Glu (A53E), enriches α-Syn oligomers and fibrils dependent on the phosphorylation state (Picillo et al. 2018). Families with SNCA multiplications are rare and globally distributed (Book et al. 2018). A systematic Movement Disorder Society (MDS) gene review identified common variants in SNCA, LRRK2, MAPT and GBA genes contributing to increased PD susceptibility (Lill 2016; Marras et al. 2017). SNCA, TMEM175, SCARB2, BAG3, and GBA have all been shown to be implicated in α-Syn aggregation pathways, while other established risk loci, such as GCH1 and MAPT, show no effect on age at onset of PD (Blauwendraat et al. 2019). Mutations of PARK2 and LRRK2 cause early onset PD with AutR patterns of inheritance. The most common mutation of LRRK2, encoding dardarin, on chromosome 12, a heterozygous G2019S mutation, accounts for approximately 3–10% of familial and 1–8% of sporadic PD (Hernandez et al. 2005). LRRK2 levels are negatively correlated with disease duration; LRRK2 phosphorylation was reduced with clinical PD (Dzamko et al. 2017). Dysfunction or loss of LRRK2 decreased α-Syn aggregation and modifies α-Syn spread in mouse models and human neurons (Bieri et al. 2019), and may influence the accumulation of α-Syn and its pathology to alter cellular functions and signaling pathways (Rui et al. 2018). PRKN, PINK1 and DJ1 cases are associated with early onset PD with slow progression. Mutations in the PRKN gene (encoding parkin) are the most common cause of AutR familial PD, representing up to 50% of all early-onset cases (Schulte and Gasser 2011). PD patients with PARKIN mutation show dystonia at onset and dose-sensitive LID, which is suggested to be caused by other mechanisms than the well-established DA depletion. Since cortical and striatal neurons express PARKIN protein, which modulates the function of ionotropic glutamatergic receptors, PARKIN may have a potential role in controlling the glutamatergic corticostriatal synapse transmission. PARKIN transcript variants 3, 7, and 11 were over-expressed in striatum and cerebellar cortex, together with synphilin-1A and 1C, suggesting that alterations in the regulation of transcription events that may be important for the increased aggregation of α-Syn (Brudek et al. 2016). Patients with PARK2 mutations show increase in the expression of catechol-O-methyltransferase (COMT) and a reduction in DNA methylation in DAergic neurons, which may contribute to the initial neuronal dysfunction in PD (Kuzumaki et al. 2019). Loss of PARKIN function can dysregulate transmission at these synapses where they cause maladaptive changes that co-occur with changes due to DA loss. This suggests an early striatal synaptopathy as the potential cause of early LID in PARKIN mutations (Sassone et al. 2019). PD cases with heterozygous variants in AutR genes suggest that monogenic and idiopathic PD may have shared pathogenic mechanisms (Reed et al. 2019). GBA is a major PD risk factor (Davis et al. 2016; Lunati et al. 2018). GBA mutations influence the age of disease onset, disease severity, motor phenotype, and are associated with a significant risk of dementia (Seto-Salvia et al. 2012). Several α-Syn point mutations associated with familial PD prone to form oligomers tend to form fibrils to a lesser extent (Ruf et al. 2019). In autopsy-proven PD, mutations of the GBA1 gene located on chromosome 1q21 which encodes glucocerebrosidase (GCase) are the most common genetic factor (in 5–20% of PD cases) by interference with α-Syn homoeostasis pathways (Blandini et al. 2018; Mullin et al. 2019; Sidransky and Lopez 2012). GBA mutations induce α-Syn aggregation, lysosomal autophagy changes, and endoplasmic reticulum stress (Balestrino and Schapira 2018; Maor et al. 2019; O'Regan et al. 2017). GCase deficiency, most pronounced in SN, leads to mitochondrial dysfunction, decreased macroautophagy, neuronal ubiquitinopathy and axonal lesions (Gegg and Schapira 2018), and may promote the spread of α-Syn aggregates (Bae et al. 2014; Thomas et al. 2019). The GBA1-substrate glucosylceramide (GluCer) can induce α-Syn aggregation via conversion of physiological α-Syn oligomeric forms into neurotoxic oligomers that are also able to seed amyloid fibril formations (Zunke et al. 2018). No consensus exists regarding the pathogenic mechanism of GBA PD (Mullin et al. 2019). However, the interrelation between GCase, glucosylsphingosine and α-Syn parameters supports the hypothesis that GCase acts as a modulator of PD-DLB (Gundner et al. 2019). Overlap between monogenic and sporadic PD genes is seen for SNCA and LRRK2 loci, LRRK2 and α-Syn showing interaction in PD brains and in

cell models (Daher 2017). Mutations of GCH1 that encodes guanosine triphosphate (GTP) cyclohydrolase 1, essential for DA synthesis in nigrostriatal cells, may lead to PD and Dopa-responsive dystonia (Rudakou et al. 2019; Yoshino et al. 2018). Different mutations in a single gene exhibit considerable clinical and neuropathologic variables both within and between kindreds. COQ2 variants, associated with familial MSA, rarely may associate with familial PD (Mikasa et al. 2018). Recent meta-analyses of GWAS data for target genes of brain microRNAs that have been implicated in PD pathogenesis showed significant associations of genetic variants in nine loci (Schulz et al. 2019). PARK1 overexpression was shown to promote PD-like phenotypes by direct phosphorylation of α-Syn at the serine 129 site, inducing DA neuron degeneration in PD (Su et al. 2019). PD risk loci do not lie in specific cell types or brain regions, but rather in global cellular processes detectable across several cell types (Reynolds et al. 2019). DJ-1 (PARK7) can induce activation of transcriptional factors and change redox balance that may protect neurons against α-Syn aggregation and oligomer-induced neurodegeneration (Dolgacheva et al. 2019).

Neuropathology of genetic Parkinson's disease

Neuropathological features of AutD SNCA (PARK/PARK4) are similar, with LP in all cases. AutR PARKIN (PARK2) mutations usually showed more severe neuronal loss in SNc than in LC, most without LP. Many individuals with A53T mutations (e.g., in the Contursi kindred) had α-Syn neuritic pathology, tau-positive neuritic inclusions, and some had both tau and α-Syn lesions (Kotzbauer et al. 2004; Markopoulou et al. 2008; Polymeropoulos et al. 1997). LRP10 gene defects (at chromosome 14) are implicated in the development of familial PD and DLB, some showing severe LP (Quadri et al. 2018; Sestini et al. 2019). Several forms of PD do not have LBs (Jiang and Dickson 2018). DJ1 (PARK7) AutR cases showed severe SNc and LC neuronal loss with diffuse LP (Taipa et al. 2016) and most GBA PD cases showed LP involving cortical areas (Schneider and Alcalay 2017). LRP10 gene variants showed severe LP (Quadri et al. 2018). PINK1 (PARK6) and PRKN mutations cause AutR early onset PD, with neuronal loss, no LP and inconsistent tau pathology (Schneider and Alcalay 2017). In rare mutations in PLA2G6 (PARK14), cell loss in SN and LC with rare LBs were associated with spheroids and iron deposition in GP (Klein et al. 2016), DJ-1-associated pathology shows damage to SN and LC with diffuse LP (Taipa et al. 2016). TDP-43 pathology is rare in MAPT and SNCA gene mutations (Schneider and Alcalay 2017).

LRRK2 mutations (PARK8), the most common cause of late-onset and AutD PD, are pathologically comparable to sporadic PD (Marras et al. 2016; Pont-Sunyer et al. 2017), with cell loss in SNc and LC but inconsistent LP (Takanashi et al. 2018). LRRK2 is a complex multi-domain protein with kinase and GTPase enzymatic activity. It is associated with mitochondrial functions and autophagy (Gomez-Suaga et al. 2012). Mutations of α-Syn, LRRK2 and tau that have been associated with familial and sporadic forms of PD show a complex interplay (Outeiro et al. 2019a) and a range of tau and TDP-43 pathologies. LRRK2 phosphorylates both tau epitopes and amyloid precursor protein (APP), promotes neurotoxiciy in PD and tauopathy (Bailey et al. 2013; Chen et al. 2017), suggesting an overlap between both AD and PD. Neuropathology in familial PD due to A30P mutant α-Syn was identical to sporadic PD (Seidel et al. 2010). LP was described in heterozygous (R275W) mutations of the PARK2 gene (Ruffmann et al. 2012), and in a family with early-onset PD associated with a heterogenous PARKIN exon 3–4 deletion (Sharp et al. 2014). The MAPT H1 haplotype is related to a higher burden of neocortical LP (Robakis et al. 2016). Other AutD forms pathologically resemble PD with neuronal loss in SN, with or without LBs and NFTs (Tomiyama et al. 2007). G51D SNCA mutations showing neuronal α-Syn and oligodendroglial inclusions may represent a link between PD and MSA (Kiely et al. 2013). The APOE ε4 allele has been considered to be associated also with α-Syn and TDP-43 pathologies (Dickson et al. 2018; Yang et al. 2018).

Kufor-Rakeb disease (KRS/PARK9), a rare AutR young onset disease, the result of mutations of the ATP13A2 gene on chromosome 1p (Park et al. 2015), shows parkinsonism, pyramidal tract signs, supranuclear gaze palsy, dystonic spasms, myoclonus, autonomic dysfunctions, dementia, and good response to L-dopa (Kruer 2013), while other KRS siblings manifested myoclonus and seizure (Rohani et al. 2017). Postmortem studies are so far lacking. Sural nerve biopsy showed reduced myelin fiber density, axonal degeneration, and cytoplasmic inclusion bodies resembling primary lysosomes (Paisan-Ruiz et al. 2010); electron microscopy revealed dense lamellar deposits ca. 1 μm in size (Malandrini et al. 2013). A novel mutation was found in Ashkenazi cases (Inzelberg et al. 2018).

Perry's syndrome, a rare combination of AutD parkinsonism, depression, hypoventilation, and weight loss, is an early-onset, rapidly progressing disease with neuronal loss in SN without LBs and involvement of putative respiratory neurons in ventral medulla caused by mutations in dynactin p150(Glued) (DCTN1) (Konno et al. 2017; Mishima et al. 2017, 2018). TDP-43-positive, pleomorphic neuronal inclusions, dystrophic neurites, and axonal spheroids were seen in pallidonigral distribution. TDP-43 was neurochemically similar to that found in FTLD-U indicating that Perry's syndrome is a unique pallidonigral TDP-43 proteinopathy (Mishima et al. 2017; Wider et al. 2009). Three families

from distinct parts of the world have been reported (Tacik et al. 2014).

Dementia with Lewy bodies

DLB, accounting for 4.6–10.1% of all dementia cases (Arnaoutoglou et al. 2019; Kane et al. 2018), has an incidence of 3.5/100,000 person/year (Savica et al. 2013b), although it is widely underdiagnosed. A recent meta-analysis reported a pooled sensitivity, specificity, and accuracy of 60.2% (95% CI 30.9–83.7%), 93.8% (83.8–97.6%), and 79.7% (62.6–90.7%) for the diagnostic criteria of DLB, while about 20% of DLB diagnosis are incorrect (Rizzo et al. 2018; Skogseth et al. 2017). Diagnostic accuracy of DAergic imaging in prodromal DLB has a specificity of 89%, but a sensitivity of 61% (Thomas et al. 2019), while occipital hypometabolism has 91% sensitivity and 80% specificity (Hamed et al. 2018). ^{18F}FDG-PET hypometabolism in temporo-parietal and occipital cortex was highly consistent across DLB cases (Caminiti et al. 2019). Clinical features of DLB are spontaneous parkinsonism, recurrent visual hallucinations, fluctuating cognition, RBD, sensitivity to antipsychotic medication, and reduction in striatal DAT (Donaghy and McKeith 2014; Sanford 2018). According to international consensus, DLB is diagnosed when CI precedes parkinsonism, or begins within 1 year of parkinsonism; PDD when parkinsonian symptoms precede CI by more than 1 year (McKeith et al. 2005). Revised criteria for the clinical dagnosis of probable and possible DLB have been reviewed recently (Cousins et al. 2019; Outeiro et al. 2019b; Yousaf et al. 2019), as well as imaging in prodromal DLB (Durcan et al. 2019; Lin and Truong 2019). Complex visual hallucinations are the only symptoms which helped identification of DLB in the context of a mixed AD + DLB dementia (Thomas et al. 2018).

Genetics of Lewy body disease

Our present understanding of the genetic etiology of DLB is limited, although a few families with AutD inheritance and mutations in SNCA and SNCB have been reported (Nervi et al. 2011). The heritable component of DLB was estimated at about 36% (Guerreiro et al. 2018). GBA and APOE ε4 are the most prevalent risk factors for sporadic DLB (Vergouw et al. 2017) and PDD (Brockmann et al. 2015; Sun et al. 2019). PSEN1 and APP are also common (Geiger et al. 2016). GBA mutations are associated with cortical LBs but not with AD pathology (Geiger et al. 2016). The fact that many members of kindreds with mutations in the SNCA gene show some features of DLB, and the frequent occurrence of LBs in familial and sporadic AD, suggested an overlap in their genetic factors, which was not confirmed by GWAS metaanalyses (Moskvina et al. 2013; Orme et al. 2018). MAPT H1 haplotype is associated with enhanced α-Syn deposition, suggesting a genetic association between MAPT haplotype and synucleinopathies (Colom-Cadena et al. 2013b), confirmed by recent GWAS (Outeiro et al. 2019b). Another GWAS reported a wide variety of copy number variations in a large DLB cohort (Kun-Rodrigues et al. 2019). LRP10 (encoding the LDC receptor related protein 10) is a novel disease gene bridging PD and DLB (Quadri et al. 2018). Today, only three genes have been convincingly established to be involved in DLB: APOE, GBA, and SNCA (Orme et al. 2018).

Neuropathology of dementia with Lewy bodies

The DLB brain is macroscopically similar to that in PD. Unlike AD, it shows relative preservation of the medial temporal lobe (hippocampus) (Oppedal et al. 2019). The histologic hallmarks are α-Syn/Lewy pathology or a variable mixture of Lewy and AD pathologies, with three main patterns: (1) widespread LBs associated with cortical diffuse Aβ plaques and low neuritic Braak stages, (2) widespread LBs with neuropathological halmarks of AD, fulfilling the criteria for both diagnoses (mixed AD/DLB), and (3) "pure" LB disease involving widespread cortical areas without significant AD pathology (Irwin and Hurtig 2018). LB density is assessed semiquantitatively, using α-Syn immunohistochemistry, in five cortical regions. According to the density and distribution of LBs, patients are allocated to the brainstem-predominant (PD), limbic (or transitional) type, LBs relatively being restricted to limbic structures, and neocortical type with widespread cortical LBs (Fujishiro et al. 2008a; McKeith 2007). The pattern of LP in brainstem is similar to that of PD (Seidel et al. 2015), but the majority of DLB cases have advanced LB stages. Clinical features are related to the extent of LP and negatively to the severity of tau pathology (Ruffmann et al. 2016; Tiraboschi et al. 2015). Correlates of attentional dysfunction and visual hallucinations are impairment of orbitofrontal, anterior cingulate cortex and secondary visual areas (Heitz et al. 2015), neuronal loss and α-Syn pathology in the superior colliculus (Erskine et al. 2017), less in the pulvinar, which, however, showed decreased protein levels and astrogliosis associated with synaptic changes (Erskine et al. 2018). The striatum exhibits a variable reduction (more than in AD, less than in PD) in TH immunoreactivity, loss of DA markers, reflecting loss of SN neurons and low striatal DAT in DLB compared to AD. Cholinergic denervation is a result of neuronal loss in NBM and cholinergic basal forebrain (Alexandris et al. 2019; Nejad-Davarani et al. 2019). The insular cortex shows severe α-Syn involvement with sparing of insular TH neurons (Fathy et al. 2019). Recent studies showed upregulation of β-synuclein (βSyn) within the frontal cortex and its decrease in occipital cortex of DLB patients, while βSyn-containing neurons were

consistently devoid of oligomeric α-Syn in frontal cortex. There was no overall correlation between total βSyn and 5G4 levels (marker of oligomeric α-Syn). The autophagy markers LC3-II and p62 were increased in the areas of βSyn upregulation, which suggests that βSyn changes in DLB may exacerbate neuronal dysfunction caused by accumulation of α-Syn due to influencing protein degradation pathways (Evans et al. 2018).

LP levels were highest in the hippocampal CA2 subregion and entorhinal cortex, while correlation with memory performance was strongest with CA1 burden. This suggests that LP must reach a critical burden across hippocampal circuitry to contribute to memory dysfunction (Adamowicz et al. 2017). Phosphorylated α-Syn at the presynaptic terminals in the form of small aggregates may disrupt structure and function of synapses (Colom-Cadena et al. 2017b; Schulz-Schaeffer 2010). Levels of insoluble pS129-α-Syn are elevated in DLB, whereas increased levels of aqueous-soluble o-α-Syn and detergent-soluble pS129-α-Syn are observed in PD and AD, suggesting different changes across the spectrum of proteinopathies (Vaikath et al. 2018).

All brains in sporadic DLB cases showed important deposits of tau, Aβ and α-Syn that are similar in biochemical quality to those in AD, with less severe tau pathology in DLB and DLB + AD than in "pure" AD (Colom-Cadena et al. 2013a; Deramecourt et al. 2006). Aβ deposition in DLB was associated with more severe hippocampus and subiculum atrophy, reflecting an early process of superimposed AD pathology (Mak et al. 2019). Over 50% of all DLB cases have considerable AD pathology, which is associated with a shorter interval between onset of motor symptoms and development of dementia, and a shorter live span (Irwin and Hurtig 2018). They are classified as AD/DLB or LB variant of AD (LBV/AD) (Hansen et al. 1998). They should be distinguished from cases with more prominent AD pathology and LP limited to the amygdala referred to as AD with amygdala LBs, considered as a distinct form of α-synucleinopathy (Fujishiro et al. 2008b; Uchikado et al. 2006b). "Pure" DLB cases with diffuse Aβ plaques but few neuritic elements or only minimal cerebral Aβ deposition show no significant differences in neocortical synapse density and synaptophysin reactivity, whereas AD/DLB has severe synapse protein loss comparable to AD (Colom-Cadena et al. 2017b). Downregulation of the postsynaptic proteins synaptopodin (SYNPO) and neurogranin indicates defective neurotransmission as a major factor for CI (Bereczki et al. 2016) that is strongly correlated with the DLB hypometabolism pattern (Morbelli et al. 2019). Recent imaging studies suggested a loss of dynamic interactions between the BG-thalamic and large scale cortical networks, which may contribute to fluctuations of cognition in DLB (Schumacher et al. 2019). α-Syn is an important predictor of disease duration, both independently and synergistically with tau and Aβ (Ferman et al. 2018), but concomitant LP and AD involving widespread association cortices contribute to visouspatial dysfunction (Kang et al. 2019). Rapidly progressing DLB cases, clinically resembling Creutzfeldt-Jakob disease, showed higher neocortical α-Syn and Aβ load than those with low or no AD pathology (Geut et al. 2019). CAA in DLB is less severe than in AD, with frontal predominance of cortical microbleeds (De Reuck et al. 2018). Cerebrovascular lesions were lower in DLB than in PD (34.4 vs. 36.7%) (Jellinger 2003). TDP-43 deposition is common in DLB (23.3%) and mixed AD/DLB (52.6%) (McAleese et al. 2017). Grey matter aging-related tau astrogliopathy (ARTAG) has been reported in 36% of LBD (Kovacs et al. 2017).

Dementia with Lewy bodies versus Parkinson's disease dementia

According to DSM-5, DLB and PDD are major neurocognitive disorders with LP sharing many clinical, genetic, pathophysiological, and morphological features (American P, Association, Force D-T 2013; McKeith et al. 2017). A clear and objective distinction between the two entities other than the arbitrary timing of the appearance of cognitive and motor impairments (1-year rule) has not yet been established (Beach et al. 2009), while others merged the two entities (Berg et al. 2014) or considered them as one disease (Friedman 2018). The clinical features of both phenotypes, DLB (McKeith et al. 2017; Outeiro et al. 2019b) and PDD (Dubois et al. 2007; Emre et al. 2007; Goetz et al. 2008)], despite individual variability, show both overlapping and distinguishing features (Armstrong 2019; Elder et al. 2017; Gomperts 2016; Jellinger and Korczyn 2018; Joki et al. 2018). The latter are that DLB has less severe parkinsonism, and more profound cognitive deficits with higher frequency of visual hallucinations. Moreover, DLB has a unique genetic risk profile in comparison to PD and PDD (Guerreiro et al. 2018; Hansen et al. 2019). The way in which SNCA SNPs modulate risk is complex, and different patterns in PD and DLB show that the effect of each association signal is phenotype-specific: the strongest signal in PD is absent in DLB, while the second signal is significant in both (Pihlstrom et al. 2018). Morphology, molecular isoforms, histochemistry of LBs and the spreading pattern of α-Syn pathology do not significantly differ between both, the late LP stages 5 and 6 suggesting a transition between both phenotypes, although DLB has a higher density of cortical LBs and AD lesions than PDD (Hansen et al. 2019; McKeith et al. 2017).

Morphological differences include higher amyloid load in striatum (Halliday et al. 2011; Jellinger and Attems 2006; Kalaitzakis et al. 2011), in cortex (Fujishiro et al. 2010; Jellinger and Attems 2008; Ruffmann et al. 2016;

Walker et al. 2015), entorhinal cortex, amygdala, and putamen in DLB (Hepp et al. 2016), the GP being free of amyloid plaques. Moreover Aβ phases, neuritic plaque scores and CAA severity and frequency are higher in DLB compared to PDD (Halliday et al. 2011; Hepp et al. 2016; Ruffmann et al. 2016; Walker et al. 2015), indicating a hierarchy in both Aβ and tau burden (Bohnen et al. 2017; Kalaitzakis and Pearce 2009; Kalaitzakis et al. 2009b). More severe α-Syn load in hippocampal subareas CA 2/3 and in the entorhinal cortex (EC), implicated a role of the EC-CA 2 circuitry in DLB (Adamowicz et al. 2017). Other deviations are the severity and distribution pattern of SNc lesions (more severe in the ventrolateral cell groups in PDD (Dickson et al. 2009) compared to more severe damage in the dorsolateral SN in DLB). Less nigral neuronal loss causing less severe postsynaptic DAergic upregulation (Jellinger 2006) may be related to the risk for neuroleptic sensibility reaction in DLB. Significantly higher 5-HT1A receptor-binding density in cortex was seen in DLB compared to PDD (Francis and Perry 2007). Thus, DLB and PDD are likely to represent two subtypes of an α-Syn-associated disease spectrum (LBD), beginning with iLBD → PD-nondemented → PDD → DLB → DLB with AD (DLB-AD) at the most severe end, although DLB does not begin with PD and does not always progress to DLB-AD (Jellinger 2018b; Jellinger and Korczyn 2018). The pathology underlying PDD and DLB is heterogeneous, with some differences in the topography and severity of lesions between both phenotypes that need further confirmation. An overlap between FTP and DLB was discussed recently (Gallucci et al. 2019).

Pathogenetic implications

The etiopathogenesis of PD (and other LB diseases) is poorly understood, but the majority is suggested to result from complex interactions between genetic background and environmental factors (Gasser et al. 2011), multiple etiologies being more likely than a single factor (Fig. 4). Genetic susceptibility, e.g., related to mutations in mitochondria-related genes (PARKIN, PINK1) in early onset PD, may be determined through impaired metabolism of free radicals or complex I activity, which, in turn, may be the product of nuclear or mitochondrial genomic deficits (Mullin and Schapira 2013). α-Syn undergoes post-translational modifications that regulate its structure and function, and may be linked to aggregation and/or oligomer formation (Gonzalez et al. 2019). DA modified α-Syn aggregation results in unique DA-induced oligomeric conformations (Mor et al. 2019). α-Syn oligomers induce selective oxidation of the ATP synthase β subunit and mitochondrial lipid peroxidation. These events open the permeability transmission pore (PTP), triggering mitochondrial swelling and ultimately cell death (Ludtmann et al. 2018). Environmental interactions include exogenous compounds with uptake and conversion similar to MPTP, cyanide, 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo) (Bringmann et al. 1995), or endogenously generated neurotoxins, such as rotenone or tetraisoquinoline, which affect mitochondrial function, produce reactive oxidative species (ROS) (Jiang and Dickson 2018) and cause disruption of calcium homeostasis (Freestone et al. 2009). The neurodegenerative process in PD is thought to be related to a complex cascade of noxious factors (Fig. 4) (Lim and Zhang 2013): imbalanced proteostasis (in

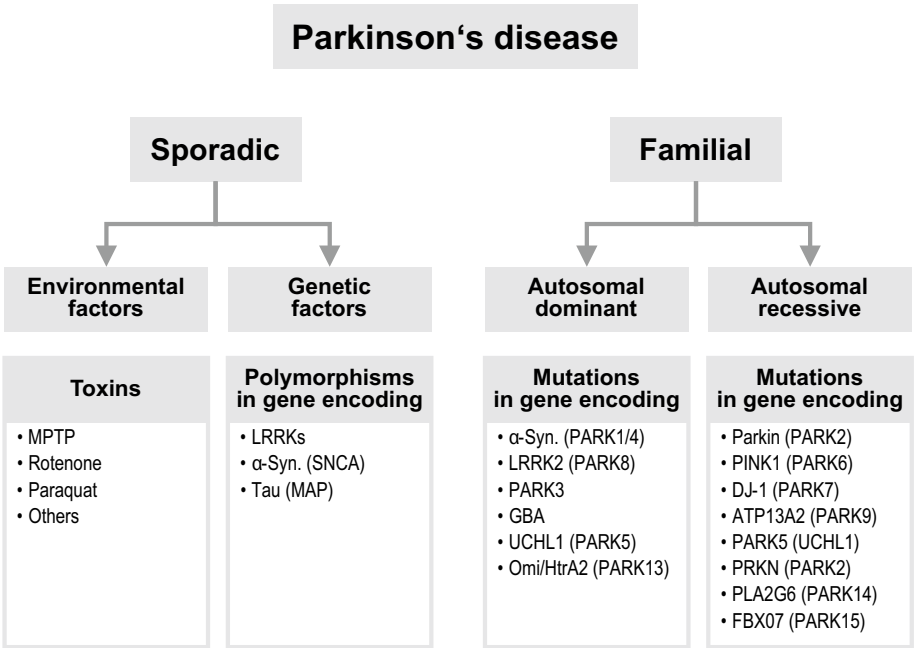

Fig. 4 Etiology of PD. Sporadic PD is a complex multifactorial disorder with variable contribution of environmental factors and genetic susceptibility. Mutations of various genes are associated with autosomal-dominant or autosomal-recessive parkinsonism. PARK 16–18: inheritance unknown. From (Jellinger 2012a)

particular misfolded α-Syn and its oligomers) (Lehtonen et al. 2019), perturbation of protein degradation systems (Maiti et al. 2017), endolysosomal dysfunctions (Kett and Dauer 2016; Klein and Mazzulli 2018), formation of free radicals, oxidative, nitritive, and proteolytic stress (Janda et al. 2012), production of ROS and advanced glycation products (Guerrero et al. 2013; Munch et al. 2000). There is compelling evidence that the endocytic membrane trafficking pathway plays a relevant role in the etiology of PD (Bandres-Ciga et al. 2019). Mitochondrial dysfunction (Aroso et al. 2016; Chen et al. 2019a; Rocha et al. 2018; Wang et al. 2019; Zaltieri et al. 2015b), impaired bioenergetics (Mullin and Schapira 2013), lipid peroxidation, nuclear RNA deficits, protein-iron and NM-iron interactions (Sian-Hulsmann et al. 2011; Zucca et al. 2017), cause iron-related nigral degeneration (Guan et al. 2019; Sun et al. 2018), and ferroptosis dysregulation inducing cell death (Van Do et al. 2016; Guiney et al. 2017). There is evidence for the existence of a connection between familial mutations of α-Syn, their distinct affinity to lipid membranes and the formation of toxic oligomers of the protein mediated by 3,4-dihydroxyphenylacetaldehyde (DOPAL) (Lima et al. 2019). A number of genetic risk factors of PD, such as PLA2G6 and SCARB2, which are involved in glycerophospholipid and sphingolipid metabolism either directly or indirectly are associated with risk of PD (Alecu and Bennett 2019). ROS-mediated transport impairment occurs early and induces axonal degeneration (Lu et al. 2014), while mitochondrial dysfunction is a common downstream pathogenic mechanism for α-Syn aggregation (Wang et al. 2019) (Fig. 5). Recent studies showed that α-Syn induces a selective loss of the mitochondrial protease ClpP in DA neurons of both α-Syn A53T tg mice and PD patients, which results in an overload of mitochondrial unfolded proteins and increased oxidative damage. Compensation for the loss of ClpP reduced mitochondrial oxidative damage and α-Syn-associated neuropathology. These findings revealed a novel mechanism by which α-Syn induces mitochondrial damage to proceed PD-associated neurodegeneration (Hu et al. 2019). Further mechanisms include transcriptional α-Syn dysregulation (Pinho et al. 2019), defects in intracellular transport pathways (Abeliovich and Gitler 2016), autophagy at presynaptic terminals (Pan et al. 2019), cell membrane disruptions (Iyer and Claessens 2019), disturbed proteasis processes (Zhou et al. 2019), excitotoxicity, neuroinflammation by activation of microglia and production of proinflammatory cytokines (Ferreira and Romero-Ramos 2018; Hirsch et al. 2013; Lema Tomé et al. 2013; Zhang et al. 2018a) and interactions between several noxious factors. Degradation of α-Syn by both UPS and ALP, and the fact that mutated α-Syn inhibits these pathways, support its role as an essential trigger for neurodegeneration (Pan et al. 2008; Puska et al. 2018). Poly(ADP-ribose) accelerates the formation of pathologic α-Syn (Kam et al. 2018), which may contribute to OS inducing microglial activation and antioxidant responses, that could modulate progression of PD (Scudamore and Ciossek 2018) (Fig. 6). Microglia is suggested to play a crucial role in α-Syn transmission via exosome pathways (Xia et al. 2019). Exosomes seem to be a common pathway in the microglia-mediated clearance of toxic aggregated proteins, e.g., Aβ and α-Syn

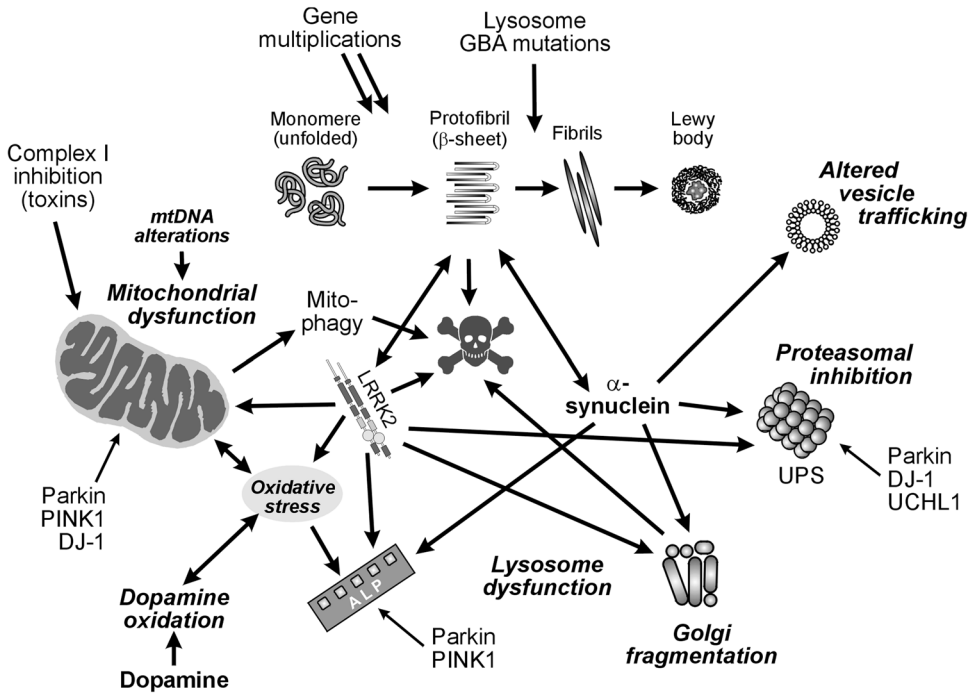

Fig. 5 Common pathways underlying PD pathogenesis. Schematic impairment by α-synuclein and gene mutations enhancing α-synuclein misfolding, fibril formation an Golgi fractionation; impairing proteasome and mitochondrial functions, altering vesicle traffic and translation. From (Jellinger 2012a)

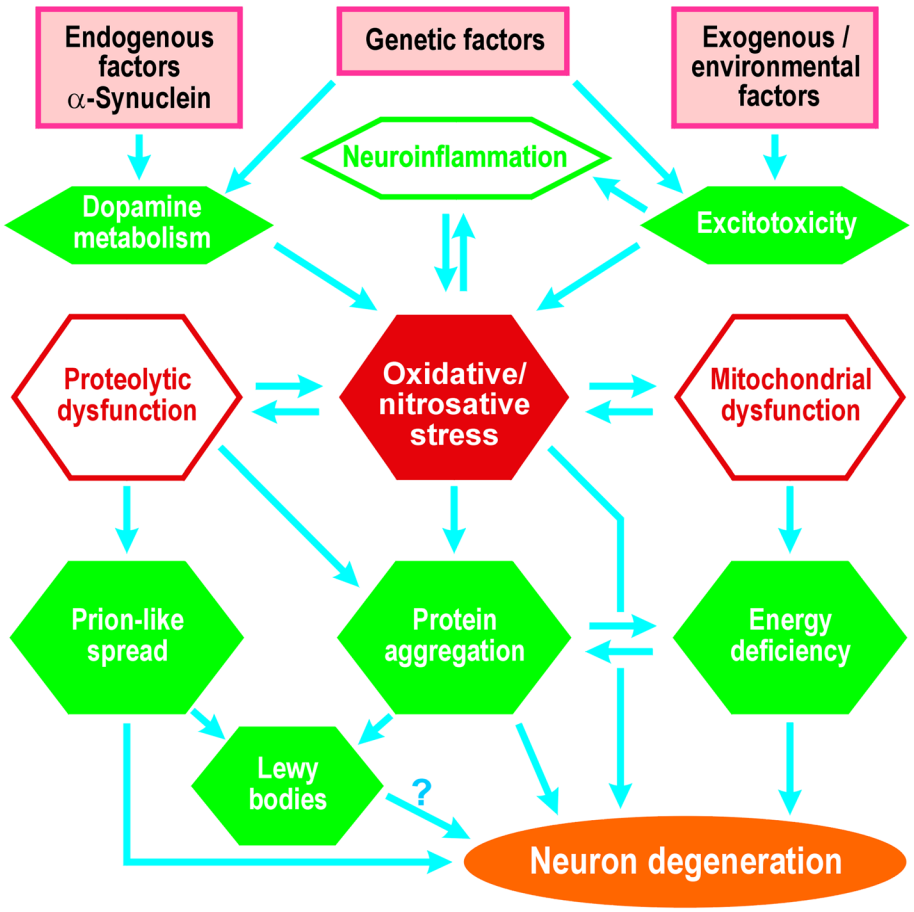

Fig. 6 Major pathways underlying Parkinson's disease pathogenesis related to α-synuclein and dopamine metabolism include proteolytic and mitochondrial dysfunction, oxidative/nitrosative stress, resulting in protein aggregation and reduced energy biosynthesis leading to neuronal degeneration. Modified from (Tsang and Chung 2009)

(Paolicelli et al. 2019), which can be affected by lysosomal deficits (Tremblay et al. 2019). In DAergic neurons, increased calcium conductance and greater production of ROS lead to mitochondrial damage. The burden caused by mitochondrial dysfunction will reach a pathological threshold, provoking neuronal dysfunction and death (Callizot et al. 2019). Disruption of the ceramide metabolism may affect endolysosomal and mitochondrial dysfunctions that are important in PD/parkinsonism (Lin et al. 2019). Lowering PARKIN levels by extracellular α-Syn oligomers may contribute to the propagation of neurodegeneration in PD (Wilkaniec et al. 2019). The major components inducing neuronal loss in PD are: (1) presynaptic and/or axonal α-Syn aggregation, synaptic and axon degeneration (2) mitochondrial dysfunction, (3) environmental OS, (4) neuroinflammation and interaction with other noxious factors (Jellinger 2013a; Kouli et al. 2018). Given that a sequence of molecular mechanisms including OS, apoptosis, neuroinflammation, microglia and astrocyte activation and aquaporin 4 (AQP4) are associated with progression of PD (Tamtaji et al. 2019), the role of chemokines in the pathogenesis of PD is of interest, since they may induce microglia activation and apoptosis (Liu et al. 2019b). Microglia activation may contribute to the development of α-Syn pathology, supporting the concept that microglia play an integral role in the propagation and spread of α-Syn pathology (Olanow et al. 2019). Several rodent models of PD showed impairment of major cellular functions (mitochondrial phosphorylation, autophagy-lysosomal changes, protein degradation, and endoplasmic reticulum stress/unfolded protein response) (Jiang and Dickson 2018). Complex cell interactions may induce "prion-like" spreading of α-Syn (Braak and Del Tredici 2017; Duyckaerts et al. 2019; Longhena et al.2017). Postmortem observation of α-Syn pathology within cell grafts in the striata of PD patients suggested that the spread of α-Syn as a main mechanism underlying disease progression in PD (Angot et al. 2012; Lema Tomé et al. 2013). The three antibodies aSyn-323.1, aSyn-336.1 and aSyn-338.1 that have the highest affinity to recombinant full-length α-Syn were able to neutralize the "seeding" of intracellular α-Syn aggregates in an in vitro assay (Li et al. 2019). α-Syn aggregates form sequence-dependent polymorphic fibrils upon spontaneous aggregation but become seed structure-dependent upon seeding (Tanaka et al. 2019). Transcellular spreading may be responsible for the propagation of neurodegeneration (Brundin et al. 2010; Davis et al. 2018; Freundt et al. 2012; Iljina et al. 2016; Henderson et al. 2019). Misfolded forms of α-Syn and tau can propagate from cell to cell

and throughout the brain, thereby templating the misfolding of native forms of the proteins (Vasili et al. 2019). 14-3-3 proteins reduce cell-to-cell transfer and propagation of pathogenic α-Syn (Wang et al. 2018), whereas 'aggravators' may induce impaired autophagy and cell-to-cell propagation of α-Syn pathology (Johnson et al. 2019). Rab-GTPase proteins have a fundamental role in the modulation of α-Syn and spreading in PD (Masaracchia et al. 2018). Recent studies provided evidence that the gap junction protein connexin-32 (Cx32) is centrally involved in the uptake and transfer of α-Syn oligomers in neurons and oligodendrocytes. Cx32 levels were significantly decreased in SN of PD and MSA, indicating a potential relationship between human α-Syn and Cx32 in the pathogenesis of both disorders (Reyes et al. 2019). Exocytosis can induce spreading (Emmanouilidou and Vekrellis 2016) and cell-to-cell seeding that explains the formation of LBs and LNs and their wide distribution (Karpowicz et al. 2019). The endocytosis of pathological α-Syn required to facilitate its transmission through synaptically connected neuronal networks has recently be reviewed (Valdinocci et al. 2018). However, recent findings indicate that cellular prion protein PrPC neither binds α-Syn oligomers nor mediates their detrimental actions, suggesting that other pathways may co-exist in PD (La Vitola et al. 2019), whereas the binding between PrP^{C} and α-Syn fibrils prevents the formation and accumulation of PrP^{Sc} (De Cecco and Legname 2018). Hence, the prion hypothesis of human synucleinopathies has to be reconsidered (Gelpi and Colom-Cadena 2019; Masaracchia et al. 2018; Tamguney and Korczyn 2018), and there is no evidence that proteins underlying PD (or AD) transmit disease to humans (Irwin et al. 2013a).

Multiple system atrophy

This adult-onset, progressive α-synucleinopathy of presumed sporadic origin, is morphologically characerized by prominent α-Syn inclusions with neuronal multisystem degeneration (Jellinger 2018b). It is clinically characterized by autonomic failure and motor impairment with poorly L-dopa-responsive parkinsonism, cerebellar ataxia, tremor, and corticospinal tract dysfunction (Krismer and Wenning 2017). MSA is an orphan disease (prevalence 1.9–4.9 up to 7.8/100,000, incidence 0.6–0.7/100,000 person-years (Fanciulli and Wenning 2015).

Clinical features of multiple system atrophy

Diagnostic criteria recommend classification into two subtypes: MSA-P (predominant parkinsonism, 70–80% in the Western world) and MSA-C (cerebellar features associated with olivopontocerebellar atrophy/OPCA/, 20–67%), more frequent in Asian populations (67–84%), with rather frequent mixed phenotypes (Ozawa and Onodera 2017; Yabe et al. 2006). Red flag categories—characteristic symptoms including inspiratory stridor, pyramidal signs, postural instability—had a specificity of 98.3% and sensitivity of 84.2% (Köllensperger et al. 2008). Revised criteria differentiate possible, probable, and definite MSA, the latter confirmed by postmortem examination (Gilman et al. 2008). The accuracy of clinical diagnosis of MSA with a positive predictive value even in later stages from 60 to 90% is still unsatisfactory (Joutsa et al. 2014; Koga et al. 2015; Osaki et al. 2009), but the true rate of over- or under-diagnosis is not known. Autonomic dysfunction (urogenital dysfunction, orthostatic hypotension) is common in both variants and reflects degeneration of the central and peripheral autonomic pathways (Ozawa 2007). Motor symptom onset is 56 ± 9 years but 40–75% of MSA cases have a prodromal phase with non-motor and autonomic symptoms (Fanciulli and Wenning 2015). Akinesia and rigidity are prominent in MSA-P but also occur in later stages of MSA-C. Tremor is not rare (Kaindlstorfer et al. 2013). Parkinsonian features are more severe in the MSA-STR group showing DAergic dysfunction than in the MSA-SNc group with predominant pre-synaptic tracer uptake loss in the posterior putamen (Ryu et al. 2019). The goal of a recently established MDS MSA Criteria Revision Task Force is to define principles for a revision of the second consensus criteria for an MSA diagnosis (Stankovic et al. 2019).

Subtypes of multiple system atrophy

MSA diversities are broader than previously considered (Koga and Dickson 2018). Various disorders may mimick MSA (Krismer and Wenning 2017), e.g. PD and PSP (Koga and Dickson 2018); MSA-C may resemble spinocerebellar ataxias (Li et al. 2018). A wide range of subtypes does not fit into the current classifications of MSA (Koga and Dickson 2018; Watanabe et al. 2016): "Minimal-change" MSA-P is a rare aggressive form with CGIs and neurodegeneration restricted to SN and Put ("pure SND") (Berciano et al. 2002; Ling et al. 2015; Wenning et al. 1994), while a case of "minimal" MSA-C showed widespread GCIs, NCIs and NNIs, and neuronal loss restricted to OPC areas (Wakabayashi et al. 2005). Another with limbic-predominant α-Syn pathology (Koga and Dickson 2019), and those with limbic-predominant α-Syn pathology, dementia and Pick-like inclusions were classified as FTD with α-Syn (FTLD-synuclein) (Aoki et al. 2015; Rohan et al. 2015). Incidental MSA with widespread GCIs without clinical disease is rare (Parkkinen et al. 2007; Wakabayashi et al. 2005; Wenning et al. 1994) as is coexistence of MSA and PSP (Uchikado et al. 2006a). Rare 'young-onset MSA' (YOMSA) before age 40 shows more common LID and minimal pathological changes (Batla et al. 2018), while others showed progressed pathological stages of MSA-P or MSA-Mix (Jellinger 2018c). MSA progresses

rapidly (Wenning et al. 2013), while MSA-P with slow progression and prolonged survival is an uncommon "benign" subgroup (Petrovic et al. 2012). "Benign" MSA cases show slowly progressing parkinsonism and prolonged survival up to 15 years or more in 2–3% of MSA patients (Kim and Jeon 2012; Petrovic et al. 2012), while others with clinical course of 18 years showed extensive distribution of GCIs (Masui et al. 2012).

Genetics of multiple system atrophy

Familial clustering of MSA is uncommon, but rare familial forms with AutR inheritance have been published (Fujioka et al. 2014a). A recent GWAS found an estimated heretability at 2–7% (Sailer et al. 2016), but unlike PD, no single gene mutation linked to familial forms and no definite risk factor have been identified. Screening for PD causal genes (MAPT, PDYN, Parkin, PINK1) did not reveal any association with MSA (Brooks et al. 2011; Yuan et al. 2015), while LRRK2 exonic variants may contribute to its susceptibility (Heckman et al. 2014). GBA variants were associated with autopsy-proven MSA (Sklerov et al. 2017; Sun et al. 2013), significantly with MSA-C (Mitsui et al. 2015), while others found no association (Srulijes et al. 2013). SNCA polymorphism as a risk factor for MSA (Al-Chalabi et al. 2009; Scholz et al. 2009) was not confirmed (Federoff et al. 2016; Sun et al. 2015). No association of the APOE locus or the prion PRPN with increased risk of MSA was observed (Chelban et al. 2017; Ogaki et al. 2018), and there is no evidence of AutD MSA or of de novo mutations in this disorder (Laurens et al. 2017). A British family with AutD inheritance and G51D SNCA mutation shared neuropathologic features of both PD and MSA (Kiely et al. 2013). They are distinct from PD patients carrying the H50Q or SNCA duplication (Kiely et al. 2015).

The link between V393A mutations in the COQ2 gene, encoding the coenzyme Q10 (COQ10) and familial or sporadic MSA in Japan and other Asian populations (Lin et al. 2015; MSA-Research-Collaboration and Collaboration 2013; Quinzii et al. 2014; Sun et al. 2016; Zhao et al. 2016) was not confirmed in other populations (Ferguson et al. 2014; Ronchi et al. 2016; Sailer et al. 2016; Sharma et al. 2014). Decreased COQ10 levels in cerebellum (Barca et al. 2016; Schottlaender et al. 2016), suggest that its deficiency may contribute to its pathogenesis due to cellular dysfunction (Nakamoto et al. 2018).

Neuropathology and molecular pathology of multiple system atrophy

The brain shows diffuse atrophy, green-gray discoloration of Put in MSA-P and atrophy of the cerebellum, middle cerebellar peduncles, and pons in MSA-C. The pigmented brainstem nuclei are pale. Histopathology shows: (1) selective neuronal loss and axonal degeneration involving multiple NS regions with brunt on the striatonigral and OPC systems; (2) cellular α-Syn-immunoreactive inclusions [glial cytoplasmic inclusions (GCIs) within oligodendrocytes, less frequent glial nuclear inclusions (CNIs), neuronal cytoplasmic inclusions (NCIs), neuronal nuclear inclusions (NNIs)]; (3) astroglial cytoplasmic inclusions and neuronal threads of similar composition; (4) myelin pallor with reduction of myelin basic protein (MBP); and (5) microglial activation. The histologic hallmarks are cytoplasmic α-Syn-immunoreactive GCIs within oligodendroglial cells, the demonstration of which is required for the diagnosis of definite MSA (Trojanowski and Revesz 2007).

GCIs are argyrophilic, triangular, sickle- or half moon-shaped or oval cytoplasmic aggregates composed of fibrillary α-Syn, Ub, and various multifunctional proteins, including 14-3-3 protein, LRRK2, aggresomal proteins (Jellinger and Lantos 2010; Jellinger 2018a). They form a meshwork of loosely packed filaments or tubules 15–30 nm in diameter with a periodicity of 70- to 90-nm and straight filaments, both consisting of polymerized α-Syn, granular material, and variable types of filaments. The central core is formed by phosphorylated (ser129) α-Syn (Gai et al. 2003). The soluble α-Syn in GCIs differs from the insoluble form in LBs (Campbell et al. 2001). Purification of α-Syn containing GCIs revealed 11.9% α-Syn, 2.8% αB-crystallin, and 1.7% 14-3-3 protein compared to 8.5, 2.0, and 1.5% in LBs (McCormack et al. 2016). In MSA brain, α-Syn 140 and 122 isoform levels were significantly increased, whereas α-Syn 126 was decreased in SN, striatum and cerebellum. Early accumulation of p25α (tubulin polymerization-promoting protein/TPPP), a potent stimulator of α-Syn aggregation, may decrease MBP, favoring both the deposition and fibrillation of α-Syn and changing myelin metabolism (Olah et al. 2017). TDP-43 pathology is rare in MSA, but colocalization with α-Syn suggests interaction between the two molecules (Koga et al. 2018b). Widespread accumulation of oligomeric α-Syn in neurons and oligodendrocytes in neocortex and Purkinje cells in MSA is more severe than in PD (Sekiya et al. 2019). α-Syn in brain-derived exosomes distinguishes MSA from PD (Bitan et al. 2019). Cathepsin-D, calpain-1 and kallikrein-6 were elevated in the Put, pontine basis, and cerebellar white matter, indicating that α-Syn accumulation is not due to reduced activity of these proteases, but their upregulation may be compensatory to increased α-Syn (Kiely et al. 2019). Decreased complex II/III activity and increased complex I and IV activity in MSA cerebellar white matter correspond with CoQ10 deficit in MSA and reflect the high regional pathological burden of GCIs, indicating mitochondrial dysfunction in MSA pathogenesis (Foti et al. 2019). Iron levels in BG and SN are higher in MSA than in

PD and controls, and resemble that in PSP (Kaindlstorfer et al. 2018; Lee and Lee 2019).

Neuronal cell loss, reactive gliosis, iron deposition, and demyelination involve pons, medulla, Put, cerebellum, SNc, spinal cord, and preganglionic autonomic structures (Ahmed et al. 2012; Holton et al. 2011; Jellinger 2014). The degree and pattern of neurodegeneration and demyelination correlate with the density and distribution of GCIs, and duration of illness, support a direct association, but there is no clear correlation between α-Syn glial burden and neuronal degeneration (Jellinger 2018a). Damage to the striatonigral system is most severe in dorsolateral caudal Put and lateral SN, suggesting transsynaptic degeneration of striatonigral fibers. Based on semiquantitative assessment of neuronal loss, astrocytosis, and GCIs, four degrees of severity were distinguished for both MSA phenotypes (Jellinger et al. 2005). This grading reflects the initial symptoms, disease progression, and clinical key features, but there was a low correlation between involvement of the two major systems and the natural history of the disorder. Postmortem MRI changes in Put (type 1, mild atrophy and isointensity; type 2, atrophy and diffuse hypointensity with a hyperintense putaminal rim [HPR]; type 3, putaminal atrophy and iso- or hypointensity with HPR) reflect various degrees of brain damage (Matsusue et al. 2008). There is an increasing overlap of α-Syn pathology with increasing duration of disease, and with the extent of α-Syn pathology (Brettschneider et al. 2018). Degeneration of GP and STN leads to dysfunction of these inhibitory nuclei projecting to the motor thalamus, a mechanism similar to that in PSP (Fig. 2). In MSA-C, GCIs are most prominent in cerebellum, pons, and medulla (Brettschneider et al. 2017). The cerebellar Purkinje cells are more severely affected in the vermis, with atrophy of olivary nucleus, cerebellopontine fibers, and pontine basis, causing disruption of specific cerebello-cortical circuits (Ren et al. 2019). The motor subnetwork in MSA-C has significant structural alterations in both BG and cerebellar connectivity (Shah et al. 2019). The motor neurons in spinal cord show only mild involvement. Involvement of the autonomic nervous system underlies the multidomain autonomic failure typical of MSA (Iodice et al. 2012; Ozawa 2007). The peripheral nervous system shows α-Syn aggregation in sympathetic ganglia, skin nerve fibres and Schwann cells (Doppler et al. 2015; Mori et al. 2002; Nakamura et al. 2015; Zange et al. 2015). Myelin lesions involve various brain regions, but also affect otherwise apparently normal areas (Matsuo et al. 1998). Demyelination is associated with reduction of myelin proteins by about 50% (Don et al. 2014). GCIs and microglial burden are greatest in mild to moderate white matter lesions and decrease with progression of myelin damage, but showed no correlation with the severity of gray matter damage. Early MSA stages show widespread increase of microglia (about 100%) in the white matter (Kübler et al. 2019) without concomitant astrogliosis or essential oligodendroglial degeneration (Nykjaer et al. 2017). Both microglial activation and α-Syn containing oligodendrocytes trigger neuroinflammation restricted to white matter regions (Hoffmann et al. 2019). MSA-C cases showed increased microglia in cerebellum, not observed in any other region (Kiely et al. 2018). In MSA-C, myoclonus was associated with more α-Syn in the anterior spinal horns and lateral corticospinal tracts (Hwang et al. 2019).

Cognitive impairment (CI) and visual hallucinations, characteristic for DLB, are rare symptoms in MSA (Gilman et al. 2008), although MCI and executive deficits may occur (Fanciulli and Wenning 2015). CI is induced by cortical and subcortical gray matter atrophy and neocortical neuronal loss (Kim et al. 2015; Lee et al. 2015; Salvesen et al. 2015), LB-like inclusions in neocortex (Cykowski et al. 2015), globular inclusion in the medial temporal region (Homma et al. 2016) or corpus callosum involvement (Hara et al. 2018). However, others found no pathological differences between MSA cases with and without cognitive impairment (Asi et al. 2014). Progressive retinal structure abnormalities were seen in visually asymptomatic MSA patients (Mendoza-Santiesteban et al. 2015).

LBs, a classical hallmark of PD, were seen in 10.7–22.7% of autopsy-proven MSA cases (Koga et al. 2017a), while GCI pathology occurred in familial PD cases with rapid disease progression (Houlden and Singleton 2012). α-Syn inclusions in astroglia and oligodendroglia, however, occur in both PD and DLB (Fellner et al. 2011; Ferrer 2018). Limbic TDP-43 pathology is rare in MSA (Koga and Dickson 2018; Koga et al. 2018a, b; Robinson et al. 2018). Grey matter ARTAG has been reported in 17.1% of MSA cases (Kovacs et al. 2017).

Pathogenesis of multiple system atrophy

The role of the neuronal endosomal-lysosomal system in the processing of α-Syn in PD is well established, while lysosomes contribute to the pathogenesis of MSA, enabling oligodendroglial and neuronal uptake of exogenous α-Syn (Puska et al. 2018). α-Syn, primarily generated by neurons, can be toxic once released to the extracellular environment (Guo and Lee 2014), and can spread throughout the brain in a "prion-like" manner like other pathological proteins (Dhillon et al. 2019b; Duyckaerts et al. 2019; Goedert et al. 2017a, c; Karpowicz et al. 2019). Extracellular α-Syn interacting with neuronal and non-neuronal cell types, mediates neuroinflammation, cell-to-cell spread (Davis et al. 2018; Valdinocci et al. 2018). Neuron-to-oligodendrocyte transfer of misfolded α-Syn plays a crucial role in the pathogenesis of MSA (Reyes et al. 2014). MSA and PD show different phosphorylation of α-Syn and distinct α-Syn seed characteristics indicating that distinct strains underlie these

diseases (Yamasaki et al. 2019). MSA prions show remarkable stability and resistance to inactivation (Woerman et al. 2018) and their transmission to transgenic mouse lines provided evidence that MSA is a prion disease (Woerman et al. 2019). Human α-Syn forms distinct inclusions and propagates within cultured tg astrocytes exposed to MSA prions, indicating that α-Syn expression determines the tropism of inclusion formation in certain cells (Krejciova et al. 2019). Brain lysates from MSA patients can induce α-Syn pathology similar to what is induced by preformed human α-Syn fibrils in tg mice. This reinforces the idea that the intrinsic traits of the tg mouse model dominates over any prion-like strain properties of MSA α-Syn seeds that can induce pathology (Dhillon et al. 2019a). However, there is currently no evidence of iatrogenic transmission or infectivity of MSA (De Pablo-Fernandez et al. 2018; Wenning et al. 2018).

The pathogenesis of MSA is not fully understood, but the crucial role of oligodendroglial pathology has been confirmed by animal models (Fellner et al. 2015; Stefanova 2014). Decreased expression of glia-derived neurotrophic factor (GDNF) in MSA brains (Ubhi et al. 2010) indicates that α-Syn expression in oligodendrocytes impacts their trophic transport to neurons. Oligodendroglial changes are more widespread than α-Syn-positive GCIs, suggesting that primary oligodendroglial pathology is the main driver of the disease process, inducing degeneration of the oligodendroglia-myelin-axon-neuron complex. Early events are an ectopic appearance of α-Syn in oligodendrocytes, loss of the cAMP-regulated phosphoprotein of 32 kDa (DARPP 32) and calbindin indicating calcium toxicity and disturbance of phosphorylated proteins (Hayakawa et al. 2013). Impaired protein degradation, autophagic and proteasomal dysfunction, alterations of the autophagic pathway (Monzio Compagnoni et al. 2018; Valera et al. 2017), perturbed iron homeostasis (Kaindlstorfer et al. 2018) and lipid dysfunction involved in myelin synthesis by oligodendrocytes (Bleasel et al. 2014; Grigoletto et al. 2017) are other pathogenic factors. Apoptosis and neuroinflammation (Valera et al. 2017) suggest that that multiple mechanisms interact to result in the system-specific pattern of neurodegeneration in MSA (Fellner et al. 2018; Ubhi et al. 2011) (Fig. 7). TNFα-dependent neuroinflammation may play a key role in MSA pathogenesis, and its relevance has been underlined in various models of MSA (Ndayisaba et al. 2019).

Recent animal model studies that only partly replicate the human disorder have provided some progress in our understanding of MSA pathogenesis (Bassil et al. 2017; Bleasel et al. 2016; Fellner et al. 2015; Heras-Garvin et al. 2019;

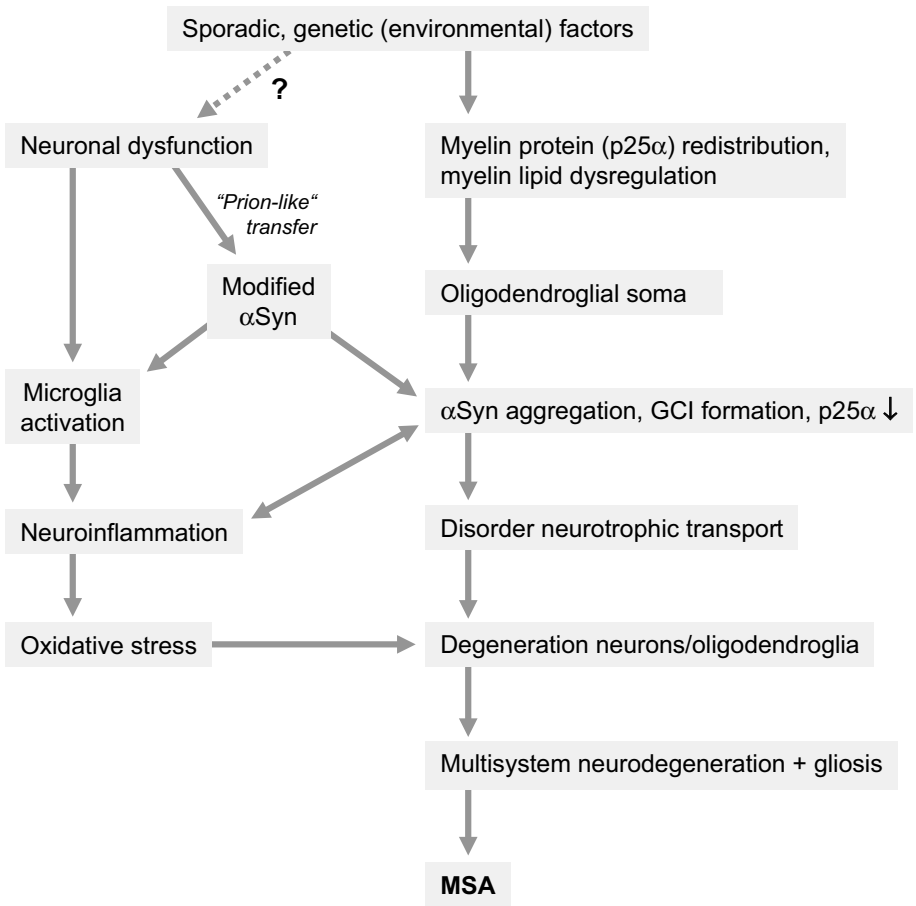

Fig. 7 Putative pathogenic pathways of multiple system atrophy. From (Jellinger and Wenning 2016)

Mandel et al. 2017; Overk et al. 2018; Refolo et al. 2018; Stefanova 2014; Valera et al. 2017). Relocation of p25α from the myelin sheaths to the oligodendroglial soma (due to mitochondrial dysfunction), with formation of cytoplasmic p25α inclusions precedes aggregation of transformed α-Syn in oligodendrocytes. Endogenous α-Syn and p25α orchestrate the formation of pathological α-Syn assemblies in oligodendrocytes and provide in vivo evidence of the contribution of oligodendroglial α-Syn to the pathogenesis of MSA (Mavroeidi et al. 2019). Although large inclusions appear at a late disease state, small, soluble assemblies of α-Syn promoted by p25α are pathogenic (Olah and Ovadi 2019). The source of α-Syn in oligodendroglia is unclear, but it contains α-Syn mRNA expression and α-Syn may be secreted by neurons and taken up by oligodendrocytes, which is facilitated by protein Cx32 (Reyes et al. 2019). 21% of proteins found consistently in GCIs and LBs were synaptic vesicle-related, which suggests that misfolded α-Syn may be targeted via vesicle-mediated transport, which also explains the presence of this neuronal protein within GCIs (McCormack et al. 2019). Secondary events include reduced trophic support to axons and neurons by reduced GDNF. Neuroinflammation, OS, proteasomal dysfunction, proteolytic dysbalance, dysregulation of myelin lipids and energy failure are important factors leading to neurodegeneration in MSA. The disease is currently viewed as a primary synucleinopathy with specific glia-neuronal degeneration developing via the oligo-myelin-axon-neuron complex (Jellinger and Wenning 2016). Thus, MSA represents a specific form of oligodendroglial proteinopathies (Rohan et al. 2016), while others suggest that it is a neuronal disease with secondary accumulation of α-Syn in oligodendrocytes (Cykowski et al. 2015).

Tauopathies

The morphological hallmarks of this heterogeneous group of neurodegenerative diseases are filamentous neuronal and glial tau inclusions associated with the degeneration of affected brain areas showing selective vulnerability (Ferrer et al. 2014; Murray et al. 2014; Spillantini and Goedert 2013). Human tau proteins are encoded by the MAPT gene consisting of 16 exons on chromosome 17q21. The adult human brain has six tau isoforms composed of either three (3R) or four (4R) carboxy-terminal tandem repeat sequences of 31–32 amino acids that are encoded by exons 9–12. The triplets of 3R- and 4R-tau isoforms differ as a result of alternative splicing to generate isoforms with 29 or 58 amino acid inserts (Mietelska-Porowska et al. 2014; Spillantini and Goedert 2013). In tauopathies, the tau protein is hyperphosphorylated, which causes it to lose its affinity for microtubules and becomes resistant to proteolysis; this results in its accumulation and the formation of NFTs (Birdi et al. 2002). Tau filaments comprise two types: straight filaments or tubules with 9–18 nm diameters and "twisted ribbons" composed of two parallel aligned components (Arima 2006). The structures of tau filaments were recently found to differ between distinct tauopathies, e.g., between AD and Pick's disease (Falcon et al. 2018; Goedert et al. 2019). The patterns of soluble and insoluble tau were the basis for biochemical classification of the major tauopathies (Goedert et al. 2017c; Gotz et al. 2019; Hoglinger et al. 2018; Spillantini and Goedert 2013): AD (as a secondary tauopathy), postencephalitic parkinsonism (PEP), Guamanian amyptrophic lateral sclerosis-Parkinson's disease complex (ALS/PDC) (3R and 4R triplets), and Pick's disease (PiD) (predominant 3R), while PSP and CBD contain predominantly 4R-tau doublets with two 68- and 64-kD insoluble tau bands at exon 10. The morphology of the neuronal and glial inclusions and the patterns of cellular vulnerability are specific, but there is frequent overlap between various tauopathies (Irwin et al. 2013b). This has lead to the suggestion that different molecular conformers or strains of aggregated tau exist (Goedert et al. 2017a), which are responsible for the heterogeneity and cell-type specificity of tauopathies. Tau pathology is suggested to spread through "prion-like" propagation (Ayers et al. 2018; Mudher et al. 2017), but does not have a high propensity to spread to peripheral tissues (Dugger et al. 2018). Seeding and spreading of tau occurs in oligodendrocytes, thereby supporting its spreading in the white matter in tauopathies (Ferrer et al. 2019). There are potential barriers in cross-seeding between 3R- and 4R-tau isoforms (Strang et al. 2018; Weismiller et al. 2018). Despite the similarities to prion proteins, there is no evidence that pathological tau is infectious (Gibbons et al. 2019).

Progressive supranuclear palsy

PSP, or Steele-Richardson-Olszewski syndrome, a predominantly sporadic movement disorder, is the most common atypical parkinsonian disease with incidence rates increasing with age from 1.7 to 14/100,000/year and an estimated prevalence of 6.2–74 1.4/100,000. The annual incidence increases with age from 1.7/100,000 at age 50–59 years to 14.7/100,000 at 80–89 years (Coyle-Gilchrist et al. 2016). Mean age at disease onset is 60–65 years, which is older than in IPD, and mean survival is 3–5 years (Ali and Josephs 2018a). PSP is clinically featured by progressive postural instability and falls, supranuclear vertical gaze palsy, frontal cognitive disturbances, and absence of resting tremor (Agarwal and Gilbert 2019). However, atypical cases with a variety of clinical syndromes indicate the heterogeneity of PSP. The new MDS PSP criteria outline 14 core clinical features and 4 clinical clues that combine to diagnose one of eight PSP phenotypes with probable, possible, or suggestive

certainty (Armstrong 2018; Hoglinger 2018). The following phenotypes have been established: (1) Richardson's syndrome (PSP-RS/classic PSP), with early postural instability, falls, vertical gaze palsy and a rapid course (Respondek et al. 2017); (2) PSP-parkinsonism (PSP-P), which often mimics PD; (3) gait freezing form (PSP-PGE), (4) PIGD (postural instability and gait disorder), (5) oculomotor dysfunction (PSP-OM), several others (Ali and Josephs 2018a, b), and overlap with both brFTD (PSP-F) and nfvPPA (PSP-SL) (Hoglinger et al. 2018). The clinical syndrome of PSP may arise through several pathologic processes: PSP-RS, PSP-P, FTLD, CBD, LBD, progressive subcortical gliosis, and MSA (Ali and Josephs 2018a; Respondek et al. 2017). Given these variants, it is not surprising that overall diagnostic accuracy is 70–85.7% (Ali et al. 2019). The proposed four rules for Multiple Allocations eXtinction (MAX) helped to standardize the application of the MDS criteria for PSP (Grimm et al. 2019). Incipient PSP comprises three subgroups with typical or only mild PSP pathology (Yoshida et al. 2017). Divergent brain gene expression patterns associated with distinct cell-specific tau neuropathology, suggest that specific PSP phenotypes may emerge from different tau strains (Narasimhan et al. 2017). Tau strains from human PSP brains showed transneuronal/transsynaptic spreading in a "prion-like" manner via exosomes, nanotubes and endocytosis from the extracellular space (Calafate et al. 2015; Tardivel et al. 2016; Wang et al. 2017).

Genetics of progressive supranuclear palsy

The major genetic risk factor for sporadic PSP, which represents around 85% of all cases, is a variant in the MAP gene, with prevalence of A0/A0 and the H1/H1 genotypes (Houlden et al. 2001). A GWAS study of autopsy-proven PSP identified SNPs mapping to MAPT, STX6, MOBP, STX6, and EIF2AK3 (Hoglinger et al. 2011). Rare monogenetic inheritance of PSP is associated with MAPT mutations (Forrest et al. 2018). Although PSP is defined as a sporadish condition, an increasing number of familial PSP with MAPT mutations have been reported (Donker Kaat et al. 2009; Fujioka et al. 2014b). An atypical PSP-P phenotype with rare variants in FBXO7 and VPS35 genes was associated with LP (Mensikova et al. 2019). PSP variants at MAPT and MOBP loci may confer PSP risk via gene expression and tau pathology (Allen et al. 2016). There is overlap between PSP and CBD in various genes, CXCR4 (chemokine receptor type 4), EGFR (epidermal growth factor), GLDC (glycine dehydrogenase), and MOBP (Yokoyama et al. 2017). Recent studies have identified three novel associations of MAPT H1 subhaplotypes with risk of PSP and their role in susceptibility to and severity of tau pathology (Heckman et al. 2019). A recent GWA analysis of copy number variants found MAPT duplications as a possible genetic cause of PSP, particularly in patients presenting with young age at onset (Chen et al. 2019b). Variation at the TRIM11 locus modifies PSP phenotype (Jabbari et al. 2018).

Neuropathology of progressive supranuclear palsy

Typical PSP cases show pallor of SN, atrophy of STN, midbrain, pontine tegmentum, and superior cerebral peduncle; with mild cortical atrophy (that differentiates PSP-RS from PSP-P) (Schofield et al. 2011). The histological hallmarks of PSP are globose tangles (different from the flame-shaped cortical NFTs), neuronal threads, and tau deposits in glia in BG, diencephalon, many brainstem regions, dentate, and inferior olivary nuclei, and spinal gray matter (Dickson et al. 2011a). Composed of 12- to 15-nm straight tubules/filaments containing 4R-tau with a sequence encoded on exon 10, they differ from those in AD or PEP. Swollen achromatic neurons in cortex and BG contain tau aggregates with straight filaments, which are also present in "tufted" or thorn-shaped astrocytes (with straight, irregular 22-nm filaments, in contrast to the "astrocytic plaques" of CBD) and in oligodendroglia as "coiled bodies" (straight 14-nm filaments) throughout the neuraxis, in particular, the white matter. Tau pathology predominates in precentral gyrus, entorhinal cortex, hippocampus, dentate granule cells, and A10 midbrain cell groups (Dickson et al. 2011a); the distribution of NFTs is similar to that in PEP and Guamanian ALS/PDC. Only few tangle-bearing neurons but many tau-positive oligodendrocytes occur in brainstem and pontine nuclei, not in SNc. Neuropil threads, short, tortouous, cell processes of neuronal and oligodendroglial origin, occur in both cortical and subcortical gray and white matter, the latter predominantly in typical PSP cases (Dickson et al. 2011a). Astrocytic tau pathology, the result of abnormal tau released from damaged axons (Armstrong 2013), and microglial activation correlate with NFT density and neuronal loss (Ito et al. 2008). Severe damage to GPi, GPe, SNr, and STN causes dysfunction of striatal efflux to motor thalamus, accounting for akinesia-rigidity and its resistance to DAergic treatment (Fig. 2).

Neuropathological criteria for clinical variants show significant morphologic and biochemical differences (Respondek et al. 2017): PSP-P and PSP with progressive gait freezing (PGF) have a lower tau pathology score with more restricted involvement of SN, STN, and Gpi and a mean 4R-/3R-tau ratio of 2.8, whereas PSP-RS has more severe and more widely distributed tau pathology in BG, brain stem, and prefrontal cortex, negatively correlated with disease duration (Jellinger 2008b; Williams et al. 2007). PSP-corticobasal syndrome (CBS) brains have greater cortical tau pathology than those with PSP-RS, while PSP-P and PGF have more severe BG degeneration (Dickson et al. 2010a). AD neuropathology is seen in about 26% of PSP cases (Robinson et al. 2018).

Cortical tau pathology in PSP, with the highest density in prefrontal and limbic areas and mainly in deeper cortical layers, differs from its bimodal distribution in AD, while a combination of PSP with AD is rare (Sakamoto et al. 2009). Although tau lesions in central grey matter, SN, and LC are found in both PSP and AD, 4R-selectivity with glial component suggests PSP origin (Ebashi et al. 2019). Hippocampal and amygdala pathology is usually minimal, but 20% of patients show ballooned neurons and argyrophilic grains (AGs) in the limbic region (Togo et al. 2002). TDP-43 pathology in hippocampus, and amygdala may occur in PSP (Koga et al. 2017b). Rare variants are PSP associated with pallidonigro-luysian degeneration and axonal dystrophy (Ahmed et al. 2008; Yokoyama et al. 2016) or presenting with CBS. More tau load in frontal and parietal cortices was seen in a "cortical" variant (PSP-CBS) (Ling et al. 2014). Tau pathology in spinal cord and pyramidal motor system structures is very common in PSP and may supplement the distinction between classical Richardson's syndrome from other PSP subtypes (Stejskalova et al. 2019).

Nigrostriatal dysfunction in PSP is associated with an 80–90% reduction in DA and 40–50% reduction in homovanillic acid in CN and Put, whereas the mesocortical and mesolimbic DAergic systems remain intact in comparison to PD. The cholinergic systems are severely affected, with a 40–80% reduction in ChAT activity, and 60% loss of neurons in the PPNc. Cognitive decline is related to dysfunction of striatofrontal or prefrontal circuits as a result of degeneration of BG and brainstem tegmental nuclei. Pathogenesis of PSP, in addition to genetic factors, is due to a cascade of events, such as inflammation and oxidative injury leading to tau aggregation in different neuronal populations. Cerebrovascular lesions in PSP are rare, although PSP has been described as a multiinfarct disorder (Josephs et al. 2002). LBs reported in approximately 20% of PSP may represent an independent disease process (Robinson et al. 2018; Uchikado et al. 2006a). Argyrophilic grains are frequent in PSP (18–80%) (Gil et al. 2018a, b) and show overlap with astroglial tau pathology and anatomical vulnerability with PSP (Yokota et al. 2008). NFTs are positively associated with a brain co-expression network enriched for synaptic and PSP candidate risk genes, but are negatively associated with immune system transcripts, indicating diverse molecular mechanisms that underlie cell-specific vulnerability and disease risks in PSP (Allen et al. 2018).

Corticobasal degeneration (CBD)

CBD, previously described as corticodentatonigral degeneration with neuronal achromatism (Rebeiz et al. 1968), is a rare, sporadic, late-onset progressive disorder of unknown etiology. This 4R tauopathy is clinically shows non-L-dopa-responsive rigidity with focal asymmetric cortical signs (apraxia and aphasia; "alien hand syndrome") and frontal lobe dementia (Wenning et al. 2011). The estimated incidence of CBD is 0.02–0.92/100,000/year and its prevalence 4.9–7.3/100,000 (Ali and Josephs 2018b). The syndrome is not specific, as clinical features of pathologically proven CBD include 4 phenotypes: CBS, frontal behavioral-spatial syndrome (FBS), nonfluent variant of primary progressive aphasia (naPPA), and PSP syndrome (PSP-S) (Shimohata et al. 2015). Current criteria distinguish possible and probable CBD; the diagnosis of probable CBD requires insidious onset, gradual progression for at least 1 year, age at onset > 50 years, no similar family history of known tau mutations, and a clinical phenotype with at least one CBS feature (Armstrong et al. 2013). These criteria, however, did not sufficiently improve the specificity of diagnosis (Alexander et al. 2014; Ali and Josephs 2018b). Their sensitivity for CBS was poor within 2 years of disease onset (Ouchi et al. 2014), which is between 5th and 7th decade; mean duration is 8 ± 2.65 years. Most CBD cases are sporadic, with only rare familial cases of AutD inheritance associated with mutations in tau genes (Kouri et al. 2014). Both CBD and PSP are characterized by accumulation of an isoform of tau containing four tandem repeats in its microtubule-binding domain and both are associated with increased frequency of MAPT H1/H1 genotype (Kouri et al. 2015). A GWAS identified new CBS susceptibility loci and showed that CBD and PSP share a genetic risk factor other than MAPT and MOBR (Kouri et al. 2015). There are shared risk factors between CBD, PSP and FTLD (Yokoyama et al. 2017). Novel GRN mutations were reported in CBS (Taghdiri et al. 2016), while a familial CBS was due to AD pathology and PSEN1 mutations (Lam et al. 2018).

Neuropathology of corticobasal degeneration

Pigment loss in SN and often asymmetric atrophy of the posterior frontal, parietal and perirolandic cortex, are associated with neuronal loss, superficial laminar spongiosis, and gliosis, temporal and occipital lobes being unaffected. Histological hallmarks are neuronal and glial cytoplasmic tau inclusions (ballooned/achromatic neurons) in cortex, BG, brainstem and cerebellum, and extensive accumulation of tau-positive thread-like processes throughout the brain, which are more widespread than in PSP. The ballooned neurons are similar to those seen in PiD and contain phosphorylated neurofilament protein and αB-crystallin. The aggregates composed of predominantly 4R-tau isoforms with exclusively exon 10 isoforms, identical to PSP and certain forms of FTLD-17, do not stain with antibodies to 3R isoforms and Ub (Dickson et al. 2011a). Ultrastructurally, they consist of 10- to 15-nm filaments, with fewer 25- to 30-nm filaments, granular material, and lipofuscin, resembling those in PSP with 20–24 nm. The twisted ribbons and shift from

4R to 3R tau in pretangles in CBD are different from the AD PHFs (Tatsumi et al. 2014b; Uchihara 2014). In the white matter, "astroglial plaques" (APs) and numerous inclusions involve both astrocytes and oligodendroglia ("coiled bodies"). They do not stain for α-Syn or Ub and thus differ from GCIs in MSA. APs, of diagnostic value in CBD, resemble the neuritic plaques in AD, but instead of clustering around amyloid cores, the tau-positive processes surround unstained neuropil. They involve prefrontal and orbital regions and striatum, but are uncommon in brainstem. The presence of tufted astrocytes (TA) and APs differentiates PSP and CBD: proximal-dominant aggregation of TAs and formation of filamentous NFTs in PSP vs. distal-dominant aggregation of APs and less filamentous pretangles in CBD (Yoshida 2014). Typical CBD displays asymmetrical frontoparietal cortical atrophy (with ballooned neurons), nigral degeneration and tau-positive neuronal and glial lesions, especially APs, in the affected cortex, while typical PSP shows loss of subcortical neurons, accumulation of tau-positive inclusions in neurons (NFTs) and in glia (tufted astrocytes). Systemic metaanalysis of the distribution of localized atrophies tried to distinguish between clinical features (CBS) and histopathological findings (CBD) (Albrecht et al. 2017). Brains with CBD or PSP show differences in amino-terminal truncated tau (37 kDa for CBD and 33 kDa for PSP) (Clavaguera et al. 2013), indicating differences in tau proteolytic processing. LBs have been reported in about 20% of CBD cases, comparable to age-matched controls (Robinson et al. 2018). Argyrophilic grains are thought to be a constant feature of CBD (Tatsumi et al. 2014a).

Pathological features of preclinical or early CBD showed significant differences in neuronal loss, cortical atrophy, white matter volume reduction, and asymmetrical cortical tau pathology (Nishida et al. 2015), while early prominence of APs suggests that CBD begins as an astrogliopathy and neuronal lesions occur later (Ling et al. 2016). Unusual variants include CBD with OPCA and TDP-43/CBD-OPCA (Kouri et al. 2013), with accumulation of α-Syn and TDP-43 (Yamashita et al. 2014), and CBD with TDP-43 pathology (45%) presenting with PSP syndrome (Ali and Josephs 2018b), were associated with lower MAPT H1/H1 genotype frequency than TPD-negative CBD (Koga et al. 2018a). AGs, which also have a predominance of 4R-tau, occur in both PSP and CBD more frequently than in controls, but are reliable disease-specific features to CBD (Tatsumi et al. 2014a). CBS with visual hallucinations and probable REM sleep behavior disorders was seen in an autopsy case of CBD with LBD confined to the brain stem (Naasan et al. 2019). Pathogenic factors of CBD are hyperphosphorylated tau, neuroinflammation and oxidative injury, but the role of MAPT-H1 remains unclear. A significant association between tau burden, post-mortem measures of neurodegeneration and in vivo volume loss was found in both PSP and CBD (Spina et al. 2019). Patients with "vascular CBS" have been reported based on MRI findings but none of them was confirmed at autopsy (Kim et al. 2009; Kreisler et al. 2007; Miyaji et al. 2013). Among 217 patients with an antemortem diagnosis of CBS, three were identified as vascular due to chronic cerebrovascular disease, with infarcts or white matter pathology (Koga et al. 2019).

Frontotemporal lobar degeneration-tau (FTLD-tau)

Frontotemporal dementia (FTD) is a heterogeneous clinical syndrome associated with frontotemporal lobar degeneration (FTLD) as a relatively consistent neuropathological hallmark feature. FTD is a diverse condition on the genetic and neuropathological basis. A novel molecular classification of these conditions distinguished three broad molecular subgroups: FTLD with tau, TAR DNA-binding protein 43 (FDP-43) and FET protein accumulation (FTLD-tau, FTLD-TDP and FTLD-FET respectively) (Neumann and Mackenzie 2019).

FTLD-tau, formerly referred to as frontotemporal degeneration and parkinsonism linked to chromosome 17 (FTDP-17), linked the P301L mutation in the MAPT gene, is caused by mutations in either the MAPT or the progranulin (PGRN) gene. The spectrum of sporadic FTLD associated with tau pathology includes PSP, CBD, PiD, and FTDP-17 MAPT (Taniguchi-Watanabe et al. 2016). Depending upon the specific mutation in MAPT, familial FTLD-tau can have 3R, 4R, or a combination of 3R and 4R tau (Dickson et al. 2011b). Positive family history was seen in 25%, 13% with AutD inheritance and 9% MAPT mutations (Forrest et al. 2019b). Mixed FTLD-tau and TDP-43 proteinopathy (FTLD-TDP) is rare (Kim et al. 2018). The tauopathy associated with FTDP-17 MAPT shows a wide range of pathological phenotypes. FTDP-17 mutations contribute to the pathogenesis via increased formation of tau oligomers (Maeda et al. 2018). Neuropathology shows focal symmetrical frontotemporal atrophy with rust-colored appearance of the GP due to increased iron pigment, and depigmented SN (Wszolek et al. 2005). Pretangles in neurons show diffuse tau immunoreactivity, while some cases have also AD-NFTs, globose tangles and astrocytic lesions similar to those in PSP or CBD, or tau-positive glial inclusions resembling those in PSP, CBD, and AG disease. Despite significant pathologic heterogeneity between different mutations, there is broad overlap with other sporadic tauopathies (AD, PSP, CBD, PiD). Ultrastructurally, the filaments vary in structure and appearance, with PHFs, 15- to 27-nm-wide twisted ribbons, and 12- to 15-nm or 15- to 20-nm straight tubules, which are either paired helical, slender or narrow twisted ribbons or straight filaments (Ghetti et al. 2011; van Swieten and Spillantini 2007). They cause cell dysfunction, due to abnormal proteostasis, impaired axonal transport and mitochondrial

damage (Irwin et al. 2015). Neuronal loss and astrogliosis affect the frontal, temporal cortical and subcortical gray matter and hippocampus. FTDP-17 with Pick body-like neuronal inclusions and swollen processes in white matter reactive to 3R and 4R tau was associated with a novel tau mutation, p.E372G. FTLD-tau-related pathological lesions in non-diseased individuals suggest that preclinical stages of FTLD-tau exist (Thal et al. 2015). Toxic tau accumulating in neuronal soma and dendrites leads to microtubule depolymerization and synaptic loss (Bodea et al. 2016). However, the hypothesized pathogenic mechanisms by which mutations in the MAPT gene promote tauopathy and the ability of mutant tau protein to support prion-like propagation do not give definite insights into the basis for the reactive vulnerability in FTLD-tau (Strang et al. 2019).

Postencephalitic parkinsonism

This progressive disorder, a sequela of encephalitis lethargica and other viral encephalitides, clinically shows rigid parkinsonism, oculomotor lesions (ocular palsy and oculogyric crises), and cognitive impairment (Jellinger 2011). Depigmentation of SN, marked neuronal loss and astrocytosis in brainstem—particularly in SN (diffuse and more marked than in PD)—, is associated with widespread occurrence of tau-positive globose NFTs, neuropil threads (NTs), glial inclusions in brainstem, BG, NBM, and amygdala, less severe in striatopallidum, thalamus, hypothalamus, and cerebellum. NFTs and NTs, composed of 22-nm twisted tubules with occasional straight filaments showing 3R- plus 4R-tau and Ub immunoreactivity, are identical to those in AD. Tau-immunoreactive astroglia are seen in affected areas, whereas TAs, APs, oligodendroglial inclusions, ballooned neurons or Pick bodies are absent. Perivascular lympho-plasmocytic aggregates and microglial activation can be found in the midbrain for many years after the initial encephalitic illness, but are sparse in long-surviving patients. Cortical pathology is common, with NFTs mainly in hippocampus and less often in cortical layers II and III, differs from that in AD. The distribution of lesions is similar to PSP, although there are subtle deviations: rare involvement of cranial nerves IV and XII, inferior olives, and striatopallidum, different cortical involvement, and less tau pathology in white matter in PEP (Jellinger 2011). Essential differences include PHF and 3 + 4 R tau in PEP, while PSP NFTs have straight filaments and 4R tau. TDP-43 pathology is present in most PEP brains, but there was no correlation between clinical features or hippocampal sclerosis (Ling et al. 2013). Lesions in cholinergic subcortical supranuclear centers of gaze movement cause gaze palsy and lid apraxia similar to that in PSP (Wenning et al. 1997). Amyloid-β deposits are rare. Neither LBs nor α-Syn pathology were detected, thus classifying PEP it as a "pure" tauopathy (Jellinger 2009b). Despite epidemiologic evidence of a viral infection, the etiopathogenesis is unknown, and molecular-biologic studies have failed to identify influenza virus in archival material from PEP brain (Vilensky 2011).

Pick's disease

This progressive dementia with personality deterioration and signs of frontal disinhibition exhibits rare extrapyramidal symptoms. Age of onset ranges between 40 and 80 years. The prevalence in autopsy series ranged from 8 to 30% of FTD (Munoz et al. 2011). The clinical presentation is often that of the behavioral variant of FTD or progressive non-fluent aphasia, while involvement of the amygdala may mimick Kluver-Bucy syndrome. Most cases are sporadic, but familial cases, usually with AutD inheritance as a result of MAPT mutations (prominently in exon 9) have been reported (Forrest et al. 2019b), while the extended haplotype (H1/H1) of the MAPT gene is not associated with PiD (Russ et al. 2001). Frontotemporal atrophy, often with a "knife blade" appearance of the cortical gyri, is associated with dilated ventricles, and degeneration of striatum and SN. Loss of neurons, astrocytosis, and spongiosis affect the outer cortical layers with swollen neurons ("Pick cells"), indistinguishable from the swollen achromatic (ballooned) neurons in other conditions. Some brains show extensive loss of pigmented SN neurons, in others the SN is preserved. Mature tau pathology is more abundant in frontotemporal mesolimbic regions than in neocortical regions (Irwin et al. 2016). Argyrophilic intraneuronal cytoplasmic inclusions (Pick bodies) are abundant in the granule neurons of dentate fascia and pyramidal neurons of hippocampus. Their major component is 3R-tau (Delacourte et al. 1996), with an occasional mixture of 3R-tau and 4R-tau (Zhukareva et al. 2002), due to the presence of concomitant NFT degeneration or rare AGRs (Kovacs et al. 2013). Ultrastructurally, they consist of narrow protofilaments and of wide filaments (the minority) composed of two narrow filaments packed against each other. The filamentous tau in PiD shows differences in phosphorylation and folding relative to those in AD, indicating the existence of distinct molecular conformers (Falcon et al. 2018; Goedert et al. 2019).

Guamanian and other forms of western Pacific parkinsonism

A high incidence of ALS and PDC was recognized in three regions of the Western Pacific, the Mariana islands of Guam and Rota, the Muro district on the Kii peninsula in Japan, and Western New Guinea. A doublet of pathological tau at 64 and 69 kDa was observed in brain tissue homogenates. The incidence of ALS/PDC in Guam has declined since the 1960s (Waring et al. 2004). Guamanian PDC and ALS/PDC

of the Chamorro population may appear clinically similar to FTLD-U and ALS, with extrapyramidal symptoms, olfactory dysfunction, oculomotor signs, and dementia. Neuropathology shows cerebral and BG atrophy, depigmentation of SN and LC, widespread loss of neurons and gliosis in hippocampus, amygdala, NBM, brainstem tegmentum, and dentate nucleus, with abundant NFTs, granulovacuolar degeneration, and Hirano bodies (Oyanagi et al. 2011). NFTs in cortex involve layers II and III, similar to that in PSP. NTs and tau-positive thread-like structures are sparse or absent. NFTs in both the Japanese and Guamanian forms of PDC show similarities to AD (Oyanagi et al. 2011), and marked deposition of 43-kDa TAR DNA-binding protein, indicating a role for proteostasis imbalance (Verheijen et al. 2018). Glial pathology is prominent in Guam PDC and includes granular astrocytes, coiled inclusions in oligodendroglia, and fine granules in motor cortex, frontal white matter, and amygdala, all composed of 3R + 4R-tau isoforms (Yamazaki et al. 2005). Numerous coiled body-like inclusions occur in cerebral white matter (Hasegawa et al. 2008).

The cortex in PDC is distinguished from that in PSP by the presence of α-Syn and LBs (Miklossy et al. 2008). α-Syn-positive aggregates in the amygdala often colocalize with neurons harboring NFTs, and spherical α-Syn-positive structures in the molecular layer of cerebellar cortex (Yamazaki et al. 2005). Guam PDC is associated with cortical tau-negative, TPD-43-positive dystrophic neurites and neuronoglial inclusions in gray and white matter. Biochemical analysis showed FTLD-U-like insoluble TPD-43, and spinal cord exhibited tau-positive tangles and TDP-43-positive inclusions, suggesting that ALS/PDC is a multiple proteinopathy (Mimuro et al. 2018). The Western Pacific disease clusters show factors similar to that causing AD and other tauopathies, but GWAS failed to identify a single gene locus for Guam PDC, supporting the hypothesis of a mixed genetic/environmental etiology. The cycad hypothesis suggesting that dietary consumption of cycad toxins or sterol glucosides is causative has not been confirmed (Steele and McGeer 2008). The etiopathogenesis remains enigmatic.

In ALS/PDC on the Kii peninsula, ALS and PDC clinically occur separately or in combination, and are considered as different manifestations of a single disease entity. The neuropathological hallmarks are widespread NFTs and NTs, most predominantly in medial temporal and frontal cortices, less in other cortices, subcortical nuclei, brainstem and spinal cord. Tau-positive astrocytes are also present in the white matter (Mimuro et al. 2018). NFTs are ultrastructurally characterized as helical filaments composed of all 6 tau isoforms, similar to those in α-Syn and Guamanian ALS/PDC (Itoh et al. 2003). Kii ALS/PDC differs from AD by differential NFT distribution and the lack of abundant senile plaques. In addition, various types of α-Syn-positive lesions, including NCIs, GCIs and dystrophic neurites are present, mainly in the limbic system and brainstem (Kokubo et al. 2012; Mimuro et al. 2018). A recent study showed phosphorylated tau pathology of various types in dentante nucleus and Purkinje and glia lcells in the cerebellum (Morimoto et al. 2018). Recent PET studies confirmed distinct distribution of tau pathology and lack of β-amyloid in Kii ALS/PDC patients (Shinotoh et al. 2019). Genetic and environmental factors are implicated in the pathogenesis of the disease (Hata et al. 2018).

Secondary parkinsonism

About 10% of all patients with parkinsonism have secondary forms with known specific causes, e.g. certain drugs and toxins, metabolic disorders, viral infections, multiple infarcts, brain tumors, trauma, or hydrocephalus (Table 2).

Vascular parkinsonism (pseudoparkinsonism)

Vascular parkinsonism (VaP) (arteriosclerotic pseudoparkinsonism) (Critchley 1981) is a rare akinetic-rigid syndrome resulting from cerebrovascular disease, with a variety of clinical and pathologic features distinct from those of sporadic PD. Its prevalence is estimated at 2–17% of all parkinsonian syndromes but it is difficult to diagnose with clinical certainty, based on the presence of clinical parkinsonism with variable signs and findings of cerebrovascular disease (Rektor et al. 2018). Three subtypes are considered: (1) acute/subacute post-stroke VaP presenting with acute/subacute onset of parkinsonism responding to DAergic drugs; (2) more frequent insidious onset with progressive parkinsonism and multiple other symptoms, particularly higher-level gait disorder; (3) mixed or overlapping syndrome of VaP with PD and other neurodegenerative parkinsonism (Rektor et al. 2018). Neuropathology shows multiple small ischemic lesions in BG, white matter, and less often the SN that involve the corticostriatopallidal-thalamic and thalamocortical loops (Jellinger 2008a; Zijlmans et al. 2004). Postmortem demonstration of LBs in 13% of patients with multi-infarct encephalopathy, an incidence twice as common as in age-matched controls, suggested subclinical PD, whereas vascular lesions were observed in 44–58% of individuals without dementia and in up to 94% of those with dementia (Jellinger and Attems 2008). Vascular lesions affecting the BG, subcortical and deep white matter changes suggest disruption of the striato-thalamo-cortical circuits leading to motor and cognitive impairment in VaP (Chen et al. 2014; Sibon and Tison 2004).

Drug- and toxin-related parkinsonism

Drug-induced parkinsonism, which can be clinically confused with AR PD, is often associated with neuroleptic

drugs, antipsychotics, calcium channel blocking agents, and other substances causing DA depletion, blockage of postsynaptic D1 and D2 receptors, or loss of striatonigral TH immunoreactivity (Wenning et al. 2011). Drug-induced parkinsonism affects 15–60% of patients treated with typical neuroleptics, depending on their type, dose, and the underlying susceptibility of the patients, but neuropathologial data are poor (Shuaib et al. 2016). The mechanisms of DIB and other extrapyramidal effects (dystonia, akathisia, etc.) are thought to be due to antagonistic binding of DAergic receptors in the BG and the mesolimbic and mesocortical pathways (Kamin et al. 2000). Frequent age-related SNc cell loss or iLBD are predisposed to adverse drug effects as a result of relative DA deficiency. Parkinsonism resulting from carbon monoxide, carbon disulfide intoxication or postnarcotic encephalopathy is caused by anoxic lesions with necrosis of GP and SN (Ginsberg 1985). Methamphetamine abuse is linked to injury of SN neurons and increased risk of PD (Rumpf et al. 2018). Methanol intoxication causes bilateral putaminal necrosis and necrosis of subcortical white matter (Franquet et al. 2012). Severe parkinsonism after poisoning with potassium cyanide is due to neuronal loss and gliosis in GP, Put, and SNr, while SNc was spared (Uitti et al. 1985). Chronic lead intoxication causes SN damage, and manganese encephalopathy, e.g., due to welding exposure, is associated with an L-dopa resistent akinetic-rigid syndrome (Racette et al. 2012), related to neuronal loss and gliosis, particularly in GPi, and in striatum with little or no SN damage and absence of LBs (Perl and Olanow 2007). Accumulation of manganese in BG associated with hepatic cirrhosis is a rare disorder with parkinsonism, ataxia, and cognitive impairment (Maffeo et al. 2014). Chronic exposure to trichlorethylene (TCE) and carbondisulfide (CS_2) can cause parkinsonism through mitochondrial complex I inhibition (Gash et al. 2008). Severe L-dopa-responsive parkinsonism developed after exposure to MPTP—a synthetic heroin drug that leads to mitochondrial damage and neuronal death—shows diffuse neuronal loss and gliosis in SN, extracellular NM and activated microglia but no typical LBs (Langston et al. 1999). Eosinophilic inclusion bodies resembling LBs have been seen in SN and LC of MPTP-treated aged monkeys, but their ultrastructure differed from that of human LBs (Forno et al. 1996). Other toxins that may cause parkinsonism include paraquat, rotenone, other herbicides and pesticides (Hoglinger et al. 2006; Taba 2017).

Other lesions causing parkinsonism

Parkinsonism has been observed in a wide variety of disorders involving the brainstem or SN, or both, that affect DAergic projections, such as destruction of the SN by bullet injury, after direct traumatic impact, herniation-contusion of the upper brainstem or midbrain damage caused by increased intracranial pressure, with loss of the nigrostriatal pathway (Formisano and Zasler 2014). Chronic traumatic encephalopathy (punch drunk, pugilistic encephalopathy, boxer's dementia), a consequence of repetitive mild traumatic brain injury, often accompanied by parkinsonian symptoms, is characterized by diffuse cortical atrophy; degeneration of corpus callosum and cerebellum; cell loss in SN, LC, and striatum, deposition of p-tau protein as NFTs, astrocytic tangles in superficial cortical layers, thread-like neurites and astrocytic inclusions around small blood vessels at the sulcal depths of the cortex (McKee et al. 2015, 2018). Parkinsonism has also been observed in rare cases of tuberculoma, brainstem tumors, solid tumors causing brainstem compression, calcification of the BG (Fahr's disease), viral encephalitis, including HIV infections, subacute sclerosing panencephalitis, multiple sclerosis, paraneoplastic syndromes (Grant and Graus 2009; Yap et al. 2017), normal-pressure hydrocephalus (Wenning et al. 2011), and cerebrovascular diseases (Grabli et al. 2011; Mehanna and Jankovic 2013). Parkinsonism may occur in a variety of inherited metabolic disorders, like Gaucher disease (linking GBA mutations to PD) (Mullin et al. 2019; Sidransky and Lopez 2012), Niemann-Pick disease (parkinsonism with mutated NPC1), lysosomal storage diseases, disorders of amino acid metabolism (phenylketonuria, maple syrup urine disease, methylmalonic acidemia) and inherited mitochondrial disorders, showing genetic evidence of common pathways with PD (Limphaibool et al. 2018). There are links between PD and metal storage disorders (Botsford et al. 2018), in particular iron accumulation causing nigral cell death (Pietracupa et al. 2017). The most frequent metal storage disorders associated with parkinsonism are hereditary hemochromatosis, PKAN and Wilson's disease (Botsford et al. 2018).

Vision for future research

Despite considerable clinical and pathologic overlapping, most types of movement disorders, particularly those of neurodegenerative origin, show characteristic pathologic pictures. The deposition of pathologic fibrillary proteins or the distribution patterns of CNS lesions may or may not be typical cytoskeletal signposts pointing to the correct diagnosis and to their pathophysiology. Because in vivo markers for most of these disorders (except those with known molecular genetic backgrounds) are still poor, the diagnosis usually depends on clinicomorphologic features. Specific identification and correct diagnosis of some of these disorders may be difficult because they share clinical and morphologic phenotypes with other neurodegenerative diseases or have considerable intrafamilial, interfamilial, and interindividual differences. Therefore, comprehensive morphologic studies using modern methods of neuropathobiology are needed to

distinguish the different disease entities. Consensus data on clinical and neuropathologic criteria, together with molecular genetic and biochemical data, will aid in correct classifying and diagnosing neurodegenerative movement disorders and provide further insight into their pathophysiology and pathogenesis as a basis for options of treatment and further directions of research.

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Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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