

Review

Motor System Neurodegeneration in Aging and Synucleinopathies: Circuit Vulnerability and Neuroimaging Biomarkers

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ABSTRACT: Aging is the primary risk factor for synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), and independently contributes to motor dysfunction. This review summarizes motor system degeneration in aging and disease, focusing on the primary motor cortex (M1), its white matter tracts, and the nigrostriatal system. In healthy aging, M1 exhibits cortical thinning, myelin loss, reduced perfusion, and iron deposition. The motor cortex-derived corticospinal and corticostriatal pathways undergo microstructural decline, often linked to vascular factors. The substantia nigra (SN) demonstrates selective neuronal loss, oxidative stress, iron deposition, and synaptic reduction, contributing to motor impairment. In synucleinopathies, these age-related vulnerabilities are exacerbated by disease-specific pathology. In PD, progressive dopaminergic neuron loss in the SN is a core feature, detectable with advanced magnetic resonance imaging (MRI) markers of iron, neuromelanin, and microstructure. PD pathophysiology extends beyond the nigrostriatal system, involving M1 dysfunction and widespread white matter abnormalities linked to motor deficits and cognitive impairment. DLB is characterized by widespread involvement of cortex (especially posterior), limbic, basal ganglia, brainstem, and cholinergic system, accounting for its early cognitive impairment, neuropsychiatric, motor, and autonomic symptoms. In contrast, MSA is characterized by oligodendroglial α -synuclein inclusions, causing multi-system degeneration, with characteristic atrophy and microstructural disruption in the putamen, pons, and cerebellum that aid differential diagnosis. Multiparametric MRI offers in vivo insights into structural, microstructural, hemodynamic, metabolic, and pathological changes underlying motor dysfunction in aging and neurodegenerative disorders. Understanding the convergence of age-related motor neuron degeneration and disease-specific pathology is essential for elucidating disease mechanisms, identifying early biomarkers, and developing targeted therapies in synucleinopathies.

Keywords: aging, synucleinopathy, motor cortex, nigrostriatal, white matter tract, α -synuclein, iron, neuroimaging

1. Introduction

Aging is the strongest independent risk factor for synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), and exerts profound effects on motor system function [1, 2]. Epidemiological studies show that

the prevalence of PD is approximately 1% among individuals older than 60 years and rises to nearly 5% in those over 85 years, highlighting the critical role of aging in disease onset and progression [3-5]. Even in healthy older adults without overt neurodegenerative disorders, motor abilities decline gradually with age, manifesting as impairments in gait, balance, fine motor control, and

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coordination, ultimately affecting independence and quality of life [6, 7]. The primary motor cortex (M1), located in the precentral gyrus of the frontal lobe, is a core region for voluntary motor control and exhibits a somatotopic organization [8, 9]. M1 and its output pathways, together with the nigrostriatal system, play essential roles in motor execution and motor learning [10–12]. Investigating age-related alterations in these motor-related cortical and subcortical structures, as well as associated white matter pathways, is crucial for elucidating the neural mechanisms underlying the increased vulnerability to synucleinopathies in older adults.

Aging is increasingly recognized not only as a chronological risk factor but also as a biological process that promotes vulnerability to protein misfolding disorders [13]. Emerging evidence suggests that several hallmarks of brain aging, including mitochondrial dysfunction, oxidative stress, iron accumulation, neurovascular impairment, chronic neuroinflammation, myelin degeneration, and synaptic loss, converge to create a microenvironment conducive to α -synuclein misfolding and aggregation [14, 15]. Mitochondrial dysfunction and reactive oxygen species production can destabilize α -synuclein homeostasis [16], whereas age-related iron accumulation accelerates oxidative injury and promotes α -synuclein fibrillization [17]. Concurrently, impaired autophagy-lysosomal and proteasomal pathways reduce the clearance of misfolded proteins [18]. Neurovascular dysfunction may further compromise nutrient delivery and waste removal [19], while chronic activation of microglia and astrocytes amplifies inflammatory responses that facilitate neuronal injury [20]. Degeneration of myelin and synaptic networks may increase vulnerability to axonal dysfunction and enhance the trans-neuronal propagation of pathological α -synuclein species [21, 22]. These age-related alterations may lower the biological threshold for the emergence and progression of synucleinopathies, providing a mechanistic link between physiological aging and disease-specific neurodegeneration.

PD, DLB, and MSA differ in pathology, clinical features, and disease trajectories [23]. Pathologically, PD and DLB are Lewy body diseases, defined by α -synuclein aggregates (Lewy bodies and Lewy neurites) within neurons [24], whereas MSA is characterized by α -synuclein-positive glial cytoplasmic inclusions in oligodendrocytes [25]. Clinically, PD is a motor disorder with resting tremor, bradykinesia, rigidity, and postural instability as its core symptoms, often preceded by non-motor features [26, 27]; some patients later develop PD with dementia [28, 29]. DLB is characterized by progressive dementia accompanied by parkinsonism, fluctuating cognition, visual hallucinations, and rapid eye

movement (REM) sleep behavior disorder [30]. MSA features early cerebellar ataxia, autonomic failure, and poorly levodopa-responsive parkinsonism, with cognitive impairment typically less prominent [31]. PD generally has an earlier onset (around age 60), whereas DLB and PD with dementia present later (>70 years) [24, 32]. Nosologically, DLB and MSA are classified as atypical parkinsonian syndromes, marked by limited response to standard PD therapies and shorter survival [33].

Recent advancements in multiparametric neuroimaging, including structural magnetic resonance imaging (MRI), diffusion MRI, arterial spin labeling (ASL) perfusion imaging, quantitative susceptibility mapping (QSM), and positron emission tomography (PET), have enabled in vivo assessment of structural, microstructural, hemodynamic, metabolic, and pathological changes within the motor system. These methods provide critical tools for probing aging-related and disease-specific pathophysiological mechanisms, as summarized in Figure 1.

The objective of this review is to provide a comprehensive overview of motor system degeneration across physiological aging and synucleinopathies, including PD, DLB, and MSA. Specifically, we focus on key components of the motor network that are particularly vulnerable to aging and disease, including the M1, motor cortex-associated white matter pathways, and the nigrostriatal dopaminergic system. We further highlight the contributions of multimodal neuroimaging techniques to the *in vivo* characterization of structural, microstructural, hemodynamic, metabolic, and pathological alterations within these systems. By comparing aging-related changes with disease-specific patterns of neurodegeneration, this review aims to clarify shared and distinct mechanisms of motor-system vulnerability and to discuss potential imaging biomarkers relevant to early diagnosis, differential diagnosis, disease monitoring, and therapeutic development.

2. Motor System Degeneration in the Aging

2.1 Motor Cortex

The motor cortex undergoes progressive, hierarchical structural and functional degeneration with aging [34, 35]. From a neurobiological perspective, aging is accompanied by reductions in neuronal soma size, decreased dendritic branching, lower dendritic spine density, and diminished axonal conduction efficiency in the motor cortex. These alterations collectively weaken cortical excitability and the capacity for information integration [36, 37]. Although the overall number of neurons remains relatively stable during physiological aging, a growing imbalance emerges between neuronal

energy demand and mitochondrial energy supply. Declines in mitochondrial function, reduced oxidative phosphorylation efficiency, and the accumulation of reactive oxygen species are key drivers of neuronal

vulnerability. These changes disrupt cellular energy homeostasis and impair synaptic plasticity, ultimately affecting the efficiency of motor information encoding and network reorganization [38-41].

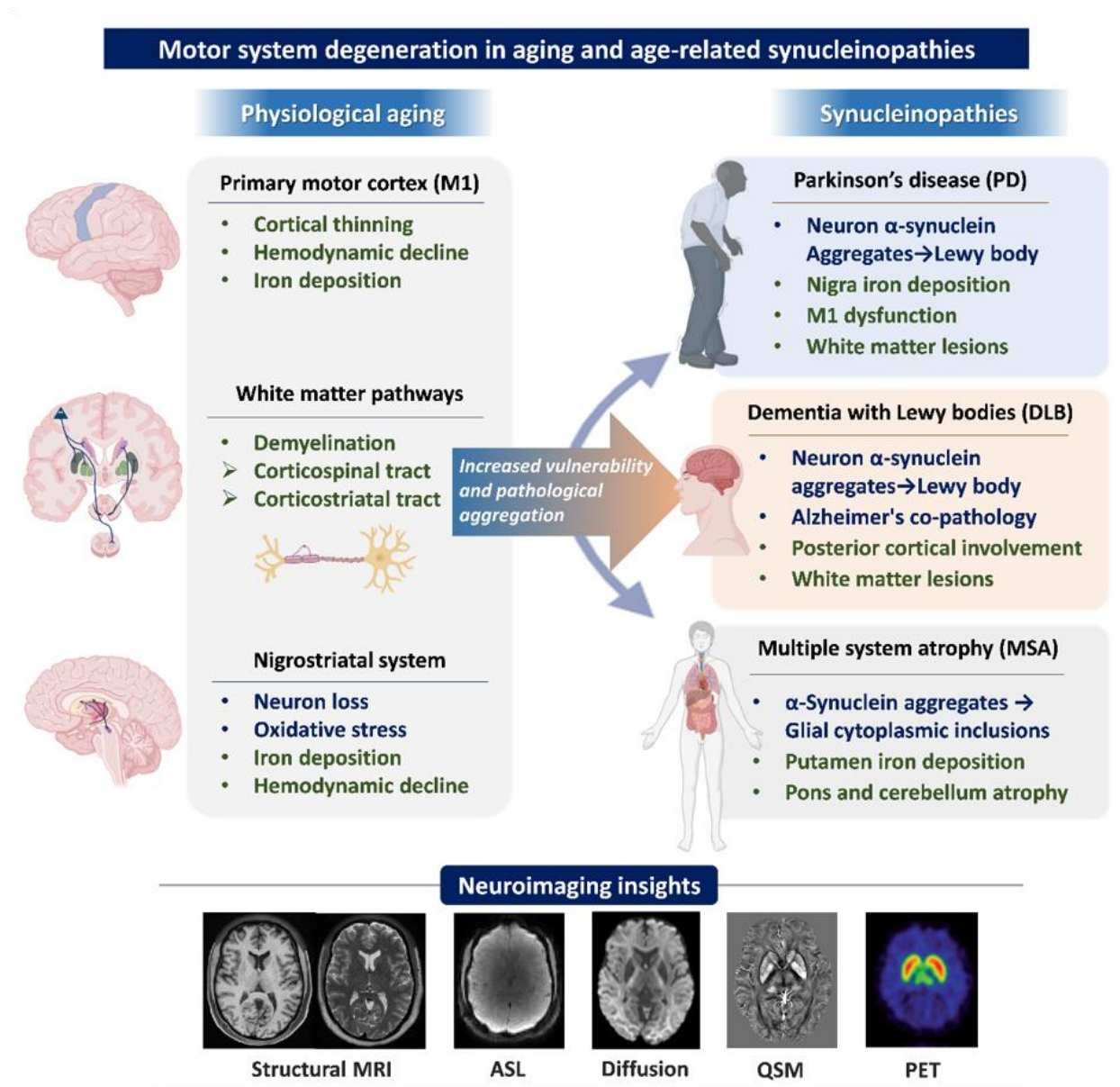


Figure 1. Overview of motor system degeneration in aging and age-related synucleinopathies. Aging affects multiple components of the motor system, including the primary motor cortex (M1), white matter pathways, and the nigrostriatal system, resulting in cortical atrophy, demyelination, neuronal loss, hemodynamic impairment, and iron deposition. These alterations are thought to increase susceptibility to α -synuclein pathology and neurodegeneration. In Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA), distinct pathological processes are superimposed on this aging-related vulnerability, producing characteristic patterns of neuronal or glial α -synuclein aggregation, regional neurodegeneration, and network dysfunction. Multimodal neuroimaging techniques, including structural magnetic resonance imaging (MRI), arterial spin labeling (ASL), diffusion MRI, quantitative susceptibility mapping (QSM), and positron emission tomography (PET), enable in vivo characterization of these structural, microstructural, hemodynamic, metabolic, and pathological changes. To distinguish different types of evidence, blue text denotes pathological and pathophysiological mechanisms, whereas green text indicates neuroimaging findings.

Previous studies have shown that the motor cortex is highly sensitive to age-related iron accumulation [42]. Excess iron can induce oxidative stress, damage mitochondrial structure and membrane integrity, and alter neuronal electrophysiological properties. These processes provide a molecular basis for reduced cortical excitability and impaired plasticity in aging [43]. At the level of the extracellular microenvironment, aging is accompanied by chronic low-grade inflammation and dysregulation of neuroimmune homeostasis [44, 45]. A decline in the remyelination capacity of oligodendrocytes and degeneration of myelin structure further reduce conduction velocity along cortical input and output pathways, compromising the coordination of motor circuits [46]. Moreover, aging leads to impaired neurovascular coupling and endothelial dysfunction, which limit the availability of energy substrates and metabolic support to the motor cortex during task performance. These vascular changes further accelerate cortical functional decline [47, 48]. Consequently, the aging motor cortex may provide a biologically permissive environment in which pathological α -synuclein can accumulate more readily and exert enhanced neurotoxic effects.

Multimodal neuroimaging studies have provided essential *in vivo* evidence for elucidating the mechanisms of motor cortex aging. Structural MRI has shown that cortical thinning in the motor cortex begins as early as mid-adulthood and continues to decline progressively with age [49]. Studies using the T1/T2 ratio have further demonstrated that myelin content in the M1 decreases at an accelerated rate after midlife [50]. Perfusion imaging research has revealed age-related reductions in cerebral blood flow within the motor cortex, prolonged arterial transit time, and declining microvascular efficiency. These hemodynamic alterations may exacerbate mitochondrial energy deficits and promote synaptic dysfunction, thereby accelerating cortical degeneration [50, 51]. Functional MRI findings indicate that aging is associated with reduced neural activity in M1, a change closely linked to diminished neuro-oxygen metabolism [52]. Susceptibility imaging studies have reported significant age-related increases in iron deposition in the motor cortex, particularly in layer V of M1 [42, 53-55]. This layer contains large pyramidal neurons (Betz cells) with high metabolic demands, which may increase susceptibility to iron overload [11, 54].

Taken together, aging of the motor cortex is not driven by a single factor but rather by the convergence of multiple processes, including structural deterioration, impaired synaptic function, reduced hemodynamic support, diminished network plasticity, and energy metabolic dysfunction. Many of these alterations emerge during midlife and continue to progress, ultimately

manifesting as declines in motor control, slower reaction time, reduced muscle strength, and impaired motor flexibility. Overall, the motor cortex is among the cortical regions most susceptible to age-related degeneration. Its vulnerability not only influences motor performance during normal aging but also provides critical insights into the mechanisms underlying the development of neurodegenerative diseases.

2.2 White Matter Pathways Connecting the Motor Cortex

With increasing age, key descending pathways of the motor cortex also exhibit pronounced age-related alterations. The corticospinal tract (CST), which serves as the primary output pathway for voluntary movement, undergoes age-associated demyelination, reduced axonal density, and decreased microstructural integrity. In diffusion tensor imaging (DTI), these changes manifest as reduced fractional anisotropy (FA) and increased mean diffusivity (MD), with multiple studies demonstrating a quadratic trajectory of age-related MD elevation [50, 56]. Such microstructural degeneration is closely linked to declines in motor performance among older adults, including impairments in fine motor skills, reduced grip strength, and slower gait speed. Evidence indicates that greater blood pressure variability among older individuals is associated with poorer CST microstructural integrity, thereby exacerbating downstream motor control deficits [57]. This observation suggests that vascular factors may accelerate motor system dysfunction by compromising white matter conduction pathways.

In addition to the CST, the corticostriatal tract (CStrT) conveys output signals from M1 to the striatum and plays a crucial role in motor planning, execution, and motor-related cognitive functions such as executive processing [11, 58, 59]. Studies have shown that aging-related atrophy of M1 is often accompanied by reduced integrity of the CStrT, and this structural degeneration constitutes a key mechanism underlying declines in both motor and motor-related cognitive performance [50]. Vascular factors exert additive effects on this process. Microinfarcts, a common form of ischemic injury in older adults, often occur in regions adjacent to the cortex [60-62]. Experimental evidence suggests that cortical microinfarcts induce long-range effects on white matter fiber integrity, providing a mechanistic link between vascular insufficiency and neurodegenerative changes [51, 63]. Tract-based analyses further indicate that the proximal segments of the CST and CStrT, located near the cortex, are more susceptible to aging-related degeneration than distal segments, and that reduced cortical perfusion further undermines the microstructural stability of these tracts [50]. These findings highlight the synergistic

contribution of vascular perfusion deficits and white matter degeneration in driving motor system aging. Moreover, among older adults with elevated vascular risk, CST dysfunction is associated with enlargement of perivascular spaces (PVS) in the juxtacortical white matter near the motor cortex, an imaging marker of cerebral small vessel disease (CSVD) [60].

In summary, age-related degeneration of motor cortex output pathways is driven by the combined effects of axonal aging, myelin damage, and cerebrovascular pathology. These changes ultimately manifest as reduced white matter tract integrity on neuroimaging and progressive decline in clinical motor function.

2.3 Nigrostriatal System

Current evidence consistently indicates that the substantia nigra (SN) in the midbrain is one of the brain regions exhibiting the most prominent neuronal loss during aging and is also a core structure affected early in synucleinopathies such as PD [3]. With advancing age, dopaminergic neurons in the substantia nigra pars compacta (SNc) decline progressively. Classic estimates suggest a loss rate of approximately 4.7% per decade [64], whereas assessments based on modern stereological techniques indicate that this rate may reach 9.8% per decade [65]. In a community-based cohort of more than 750 older adults with a mean age of approximately 88.5 years, nearly one third of participants without a clinical diagnosis of PD already exhibited varying degrees of nigral neuronal loss, and approximately 10% showed Lewy body-like pathology [66]. These findings suggest that aging alone can induce neurobiological alterations partially resembling those observed in synucleinopathies. However, age-related changes in the striatum appear relatively independent of molecular alterations in nigrostriatal dopaminergic pathways [67]. Unlike PD, reductions in tyrosine hydroxylase protein levels and striatal dopamine content during normal aging are generally modest and show substantial interindividual variability [68-74].

Collectively, these data illustrate the selective vulnerability of the SN during aging, driven by multiple interacting factors including oxidative stress, mitochondrial dysfunction, iron and neuromelanin (NM) accumulation, and the high metabolic burden associated with intrinsic pacemaking activity [75]. Accumulated metabolic and oxidative stress is considered one of the core mechanisms underlying neuronal susceptibility. Reactive oxygen species generated by mitochondrial respiration impose endogenous oxidative pressure, and dopaminergic neurons experience additional stress due to dopamine metabolism. Dopamine metabolism via monoamine oxidase produces reactive oxygen species and

hydrogen peroxide, and dopamine is also prone to auto-oxidation in the presence of metal ions such as iron, further exacerbating intracellular oxidative stress [76]. Under normal conditions, dopamine transporter (DAT) activity allows the reuptake of extracellular dopamine and storage in synaptic vesicles via vesicular monoamine transporters, thereby limiting cytosolic accumulation and oxidative damage. However, the number of DAT-immunoreactive neurons declines significantly with age [77], which may reduce the ability of aging neurons to defend against oxidative stress and increase susceptibility to metabolic and environmental insults. Studies using [¹¹C]UCB-J PET have further shown that mild motor impairment in healthy older adults is associated with reduced synaptic density in the SN, indicating that nigral circuit dysfunction plays an important role in age-related motor decline [78]. Another study using [¹¹C]DTBZ PET demonstrated a progressive reduction in nigrostriatal dopaminergic integrity with aging, with a more pronounced decline in individuals with PD [79].

Recent research integrating deep learning with QSM has confirmed continuous age-related iron deposition within the SN [80, 81]. Similar trends have been observed in the striatum of older adults [81, 82]. Excessive iron deposition not only aggravates oxidative stress but may also trigger iron-dependent cell death pathways and promote abnormal aggregation of α -synuclein. Additionally, aging is associated with marked reductions in the volumes of the SN and putamen [83, 84], whereas reports regarding age-related changes in the volume of the caudate nucleus have been less consistent [84, 85]. A multiparametric MRI study combining structural and functional imaging revealed that healthy aging is accompanied by coordinated structural and hemodynamic changes within the nigrostriatal system, which are associated with age-related declines in motor and cognitive performance [86].

The aging nigrostriatal system exhibits several characteristics that may directly facilitate α -synuclein pathology. Dopaminergic neurons in the SNc possess extensive axonal arborization, sustained pacemaking activity, and high metabolic demand, rendering them particularly vulnerable to mitochondrial dysfunction and oxidative stress [87, 88]. Iron accumulation, which increases progressively with age, can accelerate α -synuclein aggregation and may contribute to ferroptosis-related neurodegeneration [89]. In parallel, age-associated declines in proteostatic mechanisms reduce the capacity to remove misfolded α -synuclein species [90]. Neuroinflammatory activation further amplifies neuronal injury and may facilitate pathological protein propagation within interconnected motor networks [91]. These mechanisms provide a biological basis for the preferential

involvement of the nigrostriatal system in synucleinopathies.

In summary, the nigrostriatal system demonstrates multilayered structural and metabolic vulnerability during aging. Neuronal loss increased metabolic and oxidative burden from dopamine turnover, abnormal iron deposition, reduced antioxidant capacity, and altered hemodynamics collectively shape a highly vulnerable neural microenvironment. Neuroimaging studies further reveal progressive degeneration of this system across multiple dimensions with advancing age. Elucidating the mechanisms of physiological aging in the nigrostriatal system is essential not only for understanding the onset and progression of PD but also for identifying at-risk populations and developing early intervention strategies.

3. Degeneration of the Motor System in Synucleinopathies

PD and MSA are classified as synucleinopathies, for which aging is a prominent risk factor [92, 93]. The core pathological hallmark of PD and MSA involves the aggregation of misfolded α -synuclein within neurons and oligodendrocytes, respectively [94, 95], with the nigrostriatal system serving as a principal target [96]. Clinically, patients with PD and MSA exhibit similar motor symptoms, including bradykinesia, rigidity, and tremor. In addition, individuals with MSA generally show more severe autonomic dysfunction, faster disease progression, and shorter survival [97]. These observations highlight the overlapping pathological and clinical features shared by PD and MSA.

3.1 Motor System Degeneration in PD

3.1.1 Nigrostriatal Dopaminergic System

The core pathological hallmark of PD is the progressive loss of dopaminergic neurons in the SNc and consequent denervation of the striatum. Compared with physiological aging, dopaminergic neuronal loss in PD is accelerated and exhibits selective vulnerability. The cardinal motor symptoms of PD, including resting tremor, rigidity, bradykinesia, and postural instability, primarily result from significant impairment of the nigrostriatal dopaminergic pathway. With recent developments in neuroimaging, MRI-based measures have emerged as valuable noninvasive biomarkers for assessing degeneration within this system. While conventional MRI lacks sensitivity for early-stage PD, advanced imaging sequences have markedly improved visualization of subcortical structures, especially the SN within the brainstem [98, 99].

Abnormal iron deposition in the SN represents a key pathological component of PD. In vivo quantification of brain iron is commonly achieved using R2* relaxometry or QSM. Numerous studies have demonstrated elevated R2* or magnetic susceptibility values in the SN of PD patients relative to controls, and these increases correlate with clinical progression [100-104]. QSM offers greater sensitivity to iron overload than R2* [103, 105] and can capture asymmetries between hemispheres that parallel symptom lateralization [102]. In addition, QSM studies have shown that iron deposition in the SN may contribute to disease severity of PD through dysfunction of the basal ganglia network and hyperactivity within the visual network [106]. PD patients also exhibit a gradient of iron deposition across the SN, caudate nucleus, and putamen [81]. Subregional QSM values within the limbic, sensorimotor, and associative territories of the SN are selectively associated with disease severity, motor symptoms, and depressive scores [107]. Distinct iron deposition patterns across parkinsonian syndromes can also support differential diagnosis [108, 109].

NM is a paramagnetic pigment present within SNc dopaminergic neurons. In PD, neuronal loss leads to a marked reduction in neuromelanin-sensitive MRI (NM-MRI) signal within the SNc [110-113]. Signal reduction typically begins in the posterolateral motor region of the SNc and extends medially, serving as a biomarker of disease progression [114]. Based on NM-MRI, the event-based model, a probabilistic model that estimates the temporal sequence of biomarker abnormalities, identified the SN as the region most likely to be affected earliest in the sequence of PD progression [115]. NM-MRI can also aid in distinguishing PD subtypes and detecting prodromal changes such as idiopathic REM sleep behavior disorder [116-119].

DTI provides sensitivity to microstructural integrity within the SN. PD patients typically exhibit decreased FA, indicative of neuronal degeneration and disrupted tissue organization [120-123]. Furthermore, increased free water in the posterior SN correlates with disease severity, as well as motor and cognitive decline, making it a promising marker for monitoring disease progression [124, 125]. Additionally, reductions in FA and alterations in diffusivity have been observed along the nigrostriatal tract, corresponding to motor symptom severity in PD [126].

Molecular neuroimaging techniques have been shown to support the early and differential diagnosis of PD and enable in vivo tracking of PD-related pathology. DAT imaging using single-photon emission computed tomography (SPECT) has demonstrated that striatal DAT uptake correlates with motor symptom severity and can detect dopaminergic deficits in approximately 50% of individuals with REM sleep behavior disorder [127-130],

suggesting its potential for monitoring PD progression from the prodromal stage.

3.1.2 Motor Cortex

It is noteworthy that the pathological process of PD is hypothesized to originate in peripheral tissues or the olfactory bulb and subsequently propagate via synaptically connected networks to the brainstem, including the SN, ultimately ascending to influence widespread cortical and subcortical regions [131]. This prion-like propagation pattern of α -synuclein pathology may explain why, in late-stage PD, both motor and non-motor networks are extensively affected. Increasing evidence indicates that PD pathophysiology is not confined to the nigrostriatal pathway but extends progressively along the cortico-basal ganglia-thalamocortical loops, with M1 emerging as a key node that becomes increasingly affected during disease progression [132-135]. Loss of nigrostriatal dopaminergic neurons reduces thalamic excitatory output to the cortex, placing M1 under abnormal inhibitory control [136, 137]. Concurrently, PD patients exhibit aberrant neural oscillatory activity within cortical and subcortical motor networks, which have been closely associated with multiple motor symptoms [138-140].

Multimodal neuroimaging has provided an important window into the functional and structural alterations of M1 in PD [141-143]. PET studies indicate that, although resting-state perfusion in M1 may be comparable to that in healthy controls [144, 145], task-related activation during motor execution is attenuated [146, 147]. Additionally, studies using 18F-dopa PET and [11 C]MeNER PET have revealed impaired dopaminergic and noradrenergic projections to M1, with the latter deficit being more pronounced in advanced disease stages [148-150], suggesting that M1 dysfunction in PD reflects the combined influence of multiple neurotransmitter systems. Notably, some studies have observed functional hyperactivation in M1 during specific motor subtypes, such as tremor-dominant PD, or during tasks performed with the affected limb [151-154]. The degree of hyperactivation correlates with tremor severity and other hyperkinetic manifestations [152, 153]. Functional MRI further confirms abnormal activity patterns in the motor cortex. Multiple task-based fMRI studies in the medication-off state (defined as withdrawal of dopaminergic medications for at least 12 hours) report decreased M1 activation, supporting the basal ganglia-thalamocortical circuit model in which dopamine depletion reduces excitatory thalamic output to the cortical motor areas, thereby contributing to M1 functional impairment [155-161]. Conversely, some studies in the medicated state have observed task-related

hyperactivation in the parietal cortex and premotor regions, which negatively correlates with bradykinesia severity and likely reflects compensatory cortical responses to basal ganglia dysfunction [162-165]. QSM studies have demonstrated disrupted metal homeostasis, particularly iron homeostasis, in the motor cortex of PD patients [166]. Aberrant iron deposition may exacerbate oxidative stress and promote toxic aggregation of α -synuclein, directly impairing cortical neurons and synaptic function. Recent multimodal imaging evidence suggests that PD may involve dysfunction of distributed action-control networks. A large-scale study identified abnormal hyperconnectivity between the somato-cognitive action network and subcortical structures, which was reduced following effective interventions including levodopa, deep brain stimulation, transcranial magnetic stimulation, and MRI-guided focused ultrasound [167], highlighting the importance of network-level disturbances in PD pathophysiology and treatment response.

In summary, M1 dysfunction is widespread in PD and progresses with disease severity. Advances in multimodal neuroimaging have provided critical insights into these abnormalities, offering a theoretical basis for cortex-targeted interventions, such as noninvasive brain stimulation. While such interventions cannot reverse nigral neuronal loss, they may help improve motor function.

3.1.3 White Matter Lesions

White matter lesions occur in approximately 30% to 50% of patients with PD, with a lesion burden significantly higher than that observed in age-matched healthy individuals [168, 169]. Studies have shown that white matter lesions are strongly associated with axial motor deficits, freezing of gait, and postural instability in PD, independent of age-related loss of nigrostriatal dopaminergic neurons [170, 171]. Therefore, degeneration of dopaminergic neurons alone cannot fully account for all motor and non-motor impairments observed in PD, and the contribution of white matter alterations to disease pathology has received increasing attention. Clinically and in research settings, white matter lesions are primarily assessed using neuroimaging techniques, with MRI being the most commonly employed modality.

White matter hyperintensities (WMHs), visible on T2-weighted and fluid-attenuated inversion recovery sequences, are frequently observed in PD [172, 173], and greater WMH burden corresponds to more severe motor impairment, especially in axial motor control [174-176]. Regional lesion distribution contributes to distinct motor deficits: for example, left temporal WMHs increase fall

risk [177], deep white matter lesions are associated with bradykinesia, and periventricular hyperintensities correlate with both bradykinesia and axial symptoms [178]. Notably, damage to white matter tracts in the periventricular frontal regions, which are critical for postural control, may disrupt connections between the M1, supplementary motor areas, basal ganglia, and cerebellum, or impair central sensorimotor signal transmission, thereby contributing to postural instability and freezing of gait [174, 179-182]. DTI investigations have documented widespread microstructural white matter abnormalities in early PD, involving the corona radiata, CST, internal and external capsules, corpus callosum, cerebellar peduncles, and several longitudinal and fronto-occipital fasciculi [183-185]. Longitudinal imaging further shows that reductions in FA and increases in MD within the posterior corpus callosum and corona radiata are associated with motor symptom severity [186]. White matter lesions are independently associated with cognitive decline across multiple domains in PD [172, 187-189]. Their presence more than doubles the risk of developing dementia [190]. White matter involvement also varies across motor subtypes: tremor-dominant patients typically maintain relatively preserved white matter organization, whereas postural instability/gait disorder subtypes exhibit widespread microstructural damage accompanied by more severe cognitive impairment [191, 192]. The cognitive consequences of WMHs are location-dependent: frontal lesions mainly affect working memory and executive functions; periventricular lesions influence multiple domains; and temporal WMHs predominantly impair verbal memory [193, 194]. Reduced integrity of the basal forebrain cholinergic pathways originating from the nucleus basalis of Meynert, which are closely linked to cognition, can be detected up to 1 year before the onset of mild cognitive impairment in PD [195].

3.2 Motor System Degeneration in DLB

DLB is the second most common neurodegenerative dementia after Alzheimer's disease and is characterized by the widespread distribution of α -synuclein pathology throughout the central nervous system [196, 197]. While sharing the core pathological hallmark of neuronal α -synuclein aggregates with PD, DLB exhibits distinct patterns of regional involvement that account for its unique clinical phenotype [198]. The pathological burden in DLB extends beyond the nigrostriatal system to encompass extensive cortical regions, particularly posterior cortical areas, as well as limbic structures, basal ganglia, brainstem nuclei, and the cholinergic system [199-201]. This multisystem involvement explains the characteristic features of progressive dementia,

fluctuating cognition, visual hallucinations, and parkinsonism that define DLB clinically [202].

Motor system degeneration is a core clinical feature of DLB [203]. The parkinsonism in DLB typically manifests as bradykinesia, rigidity, and postural instability, whereas resting tremor is less frequent and often less prominent than in PD [204-206]. The distinction between DLB and Parkinson's disease dementia (PDD) is primarily based on the temporal sequence of symptom onset: DLB is diagnosed when cognitive symptoms precede or co-occur with parkinsonism within one year [207], whereas PDD is diagnosed when dementia develops in the setting of established PD (typically >1 year after motor onset) [28]. Notably, motor symptoms in DLB progress more rapidly than in PDD. Longitudinal data from autopsy-confirmed cohorts demonstrate that DLB patients with parkinsonism exhibit significantly faster progression on the Unified PD Rating Scale-III compared to PDD patients over an 8-year period, with gait impairment and limb bradykinesia showing the most accelerated deterioration [208].

Nigrostriatal dopaminergic dysfunction is a consistent feature of both DLB and PD, with [123 I]FP-CIT SPECT imaging revealing significant reductions in DAT binding in the caudate nucleus and putamen, which distinguishes DLB from AD with high diagnostic accuracy [209-211]. However, approximately 10% of DLB patients show normal DAT imaging, particularly those with significant AD co-pathology, highlighting the heterogeneous nature of nigrostriatal involvement in DLB [212]. Furthermore, a SPECT study demonstrated that the shift from an increased to a decreased bilateral putamen-thalamus-cortex connectivity might be a hallmark of transition from prodromal to dementia DLB stages [213]. Structural MRI studies reveal cortical atrophy patterns that differ from both normal aging and AD, with relative preservation of medial temporal lobe structures but pronounced atrophy in posterior cortical regions [214]. White matter abnormalities are also prevalent in DLB and contribute to deterioration of cognitive function, neuropsychiatric symptoms, and dementia stages [215-217].

The frequent co-occurrence of AD pathology, specifically amyloid β plaques and tau neurofibrillary tangles, substantially modifies the clinical presentation and progression of DLB [218]. DLB patients with significant amyloid co-pathology exhibit more rapid cognitive decline, greater cortical atrophy, and less prominent DAT deficits compared with those with pure DLB pathology [219, 220]. This pathological heterogeneity underscores the importance of multimodal biomarkers for accurate diagnosis and prognostication. [18 F]FDG PET reveals characteristic occipital hypometabolism and the "cingulate island sign" in DLB,

patterns that may be attenuated in the presence of concurrent Alzheimer's pathology [220-222]. The clinical heterogeneity of DLB further manifests in distinct onset variants, including patients presenting with idiopathic REM sleep behavior disorder who subsequently develop dementia and parkinsonism, those with mild cognitive impairment as a prodromal stage, and individuals with delirium onset or psychiatric onset presentations [223-225]. Understanding the interplay among α -synuclein pathology, co-pathologies, and age-related motor system degeneration is therefore essential for elucidating the mechanisms underlying the variable motor and cognitive manifestations in DLB.

3.3 Motor System Degeneration in MSA

As a synucleinopathy, MSA shares certain clinical and pathological characteristics with PD while also displaying distinct features. Clinically, MSA manifests with progressive cerebellar dysfunction, parkinsonism that responds poorly to levodopa, and pronounced autonomic failure [226]. Neuropathologically, the disorder is defined by cytoplasmic inclusions composed of abnormal α -synuclein aggregates within oligodendrocytes and neurons, which contribute to cellular degeneration and symptom expression. Although patients are typically categorized into the cerebellar (MSA-C) and parkinsonian (MSA-P) variants based on predominant regional involvement, recent findings indicate that these patterns may represent different phenotypic expressions along a shared disease continuum [227].

Early diagnosis of MSA remains challenging, and neuroimaging has become an indispensable supportive tool. Conventional MRI can reveal characteristic patterns of atrophy, such as prominent putaminal (especially posterior) atrophy and susceptibility-weighted hypointensity reflecting iron deposition in MSA-P, as well as pontine, middle cerebellar peduncle, and cerebellar atrophy in MSA-C. The "hot cross bun" sign, defined as a cruciform T2 hyperintensity in the pons, shows high specificity for MSA [228]. This radiological finding arises from selective loss of myelinated transverse pontocerebellar fibers and neurons in the pontine raphe with preservation of the pontine tegmentum and CST [229, 230]. In addition, diffusion MRI-based free-water imaging and neurite orientation dispersion and density imaging can distinguish MSA from PD at the microstructural level with high precision [231]. Integrating macrostructural and microstructural MRI features further strengthens differential diagnostic performance [232].

From a mechanistic perspective, multimodal neuroimaging has highlighted the extensive involvement of motor networks in MSA. Diffusion MRI studies show

that impairments in fine motor control, regardless of subtype, are linked to degeneration within the cerebellar–pontine pathways, suggesting a shared underlying pathophysiology across the disease spectrum [227]. Cognitive deficits in MSA appear to arise from a combination of heterogeneous cortical and subcortical atrophy and microstructural disruption of major white matter tracts, including the corpus callosum, indicating widespread network-level involvement [233-235]. DAT imaging, such as [123 I]FP-CIT SPECT, demonstrates severe loss of striatal dopaminergic terminals, particularly in the posterior putamen, in MSA-P patients, whereas DAT deficits in MSA-C are typically less severe or may be absent [236-239]. Glucose metabolism studies using [18 F]FDG PET show distinct hypometabolic patterns, with reduced metabolism in the putamen and posterior frontal regions in MSA-P, and in the pons and cerebellum in MSA-C [240]. These metabolic signatures have substantial diagnostic value [241].

In conclusion, degeneration of the motor system in MSA involves multiple interconnected brain circuits and is driven by α -synuclein pathology within oligodendrocytes. Multimodal neuroimaging enables progressive characterization of these changes and substantially enhances diagnostic accuracy. These imaging biomarkers improve understanding of disease heterogeneity and pathophysiology, support biologically informed subtyping and prognostication, and provide essential tools for future therapeutic evaluation.

4. Vascular and Small-Vessel Disease as Modifiers of Motor-System Vulnerability in Aging and Synucleinopathies

Aging is accompanied by progressive deterioration of the neurovascular unit (NVU), including endothelial dysfunction, blood–brain barrier disruption, impaired neurovascular coupling, reduced vascular compliance, and diminished cerebrovascular reserve [242]. These alterations contribute to CSVD, a spectrum of vascular pathologies characterized by WMHs, enlarged PVS, lacunes, and microbleeds [243], which represent important modifiers of disease expression and progression. By independently affecting gait, cognition, and white matter integrity, vascular pathology may interact synergistically with α -synuclein-mediated neurodegeneration and amplify motor-system vulnerability in older adults [244, 245].

The NVU has emerged as a key interface linking aging, cerebrovascular dysfunction, and synucleinopathies. A recent systematic review and meta-analysis demonstrated widespread evidence of NVU dysfunction in PD, including impaired cerebral perfusion, blood–brain barrier abnormalities, endothelial

dysfunction, and imaging markers of CSVD [246]. These findings suggest that vascular pathology is not merely an epiphenomenon of neurodegeneration but may actively contribute to disease pathogenesis and progression. Chronic hypoperfusion can impair metabolic support and waste clearance, thereby promoting oxidative stress, neuroinflammation, and α -synuclein aggregation. Conversely, α -synuclein pathology may further disrupt vascular integrity, creating a bidirectional cycle between neurodegeneration and vascular injury.

Among vascular imaging markers, WMHs have received particular attention because of their close relationship with motor and cognitive dysfunction [247]. In PD, increasing WMH burden has been consistently associated with gait impairment, postural instability, and freezing of gait [248, 249]. Furthermore, a quantitative MRI study has shown that WMHs exhibit microstructural heterogeneity, and lesion tissue properties vary according to cognitive status in PD [250]. Vascular dysfunction may also interact directly with degeneration of the dopaminergic system. A recent study in drug-naïve PD demonstrated that greater blood pressure variability was associated with increased WMH burden and more severe nigrostriatal dopaminergic deficits [251]. Similarly, DAT imaging studies have reported associations between WMH burden and reduced striatal dopaminergic availability in PD [252]. These observations suggest that cerebrovascular injury and dopaminergic degeneration may not occur independently but instead converge on shared neural networks involved in motor control.

In DLB, systematic reviews and biomarker studies have demonstrated substantial white matter abnormalities and frequent coexistence of cerebrovascular pathology [253, 254]. WMHs are common in DLB and are associated with cognitive impairment, motor dysfunction, and disease severity [255, 256]. In addition, cerebrovascular biomarkers often coexist with Alzheimer-type pathology in DLB, further contributing to clinical heterogeneity [257]. Therefore, WMHs observed in DLB should not be viewed solely as incidental age-related findings but rather as potential contributors to disease phenotypes.

Importantly, vascular pathology itself increases with advancing age and therefore represents a critical mechanistic link between aging and synucleinopathies. Periventricular and deep white matter regions are particularly vulnerable to chronic hypoperfusion and small-vessel disease [258, 259]. Recent work has demonstrated a characteristic periventricular gradient of white matter abnormalities across aging and multiple neurological disorders, which is associated with cognitive and physical performance [260], supporting the concept that vascular injury preferentially affects long-range white

matter connections that are essential for motor and cognitive network integrity.

Current evidence supports a conceptual framework in which vascular and small-vessel disease function as major modifiers of motor-system degeneration in aging and synucleinopathies. Future longitudinal multimodal imaging studies integrating vascular biomarkers with measures of α -synuclein-related neurodegeneration will be essential for clarifying these interactions and identifying potential therapeutic targets.

5. Strengths and Limitations of Multimodal Neuroimaging

Multimodal neuroimaging has substantially advanced our understanding of motor system degeneration in aging and synucleinopathies by enabling in vivo assessment of structural, microstructural, hemodynamic, metabolic, and molecular alterations. Each imaging modality provides distinct yet complementary information regarding disease-related changes.

Structural MRI is widely available and highly sensitive to macroscopic morphological changes, such as cortical atrophy and regional volume loss. However, it has limited sensitivity to early cellular and molecular abnormalities that may precede overt neurodegeneration [261]. Diffusion MRI enables the characterization of white matter microstructure and structural connectivity, providing valuable insights into axonal and myelin integrity. Nevertheless, diffusion-derived metrics are not pathologically specific and may be influenced by crossing fibers, partial-volume effects, and methodological variability across acquisition and processing pipelines [262]. ASL offers a noninvasive approach for quantifying cerebral perfusion without the need for exogenous tracers, making it particularly suitable for longitudinal studies. However, its relatively low signal-to-noise ratio and sensitivity to arterial transit time variations may affect measurement accuracy, especially in older adults and individuals with cerebrovascular dysfunction [263, 264]. QSM enables in vivo assessment of magnetic susceptibility and has emerged as a valuable tool for investigating iron accumulation in neurodegenerative disorders. Nonetheless, susceptibility measurements may also be influenced by other tissue components, including myelin and calcium, which can complicate biological interpretation [265]. PET imaging provides high molecular specificity for evaluating neurotransmitter systems, glucose metabolism, proteinopathies, and synaptic density [266]. As such, it offers unique insights into disease mechanisms that are not accessible with conventional MRI techniques. However, its widespread application is constrained by radiation exposure, high

cost, limited availability, and the need for specialized radiotracers.

Importantly, no single imaging modality can fully capture the complex interplay among structural degeneration, vascular dysfunction, metabolic impairment, neuroinflammation, and pathological protein accumulation that characterizes aging and synucleinopathies. Therefore, integrating complementary imaging techniques with molecular biomarkers and longitudinal study designs will be essential for improving mechanistic understanding, enhancing diagnostic accuracy, identifying early disease biomarkers, and facilitating the development of targeted therapeutic strategies.

6. Summary

Aging is the strongest risk factor for synucleinopathies and has widespread effects on the motor system. Beyond structural degeneration, aging promotes a biological environment characterized by mitochondrial dysfunction, oxidative stress, iron accumulation, neurovascular impairment, chronic neuroinflammation, myelin

degeneration, synaptic loss, and impaired proteostasis. These interconnected processes may facilitate α -synuclein misfolding, aggregation, impaired clearance, and network propagation, thereby lowering the threshold for disease development. Physiological aging therefore provides the substrate upon which disease-specific α -synuclein pathology emerges and progresses. In PD, the hallmark loss of SN dopaminergic neurons can propagate pathological effects to the motor cortex and white matter networks, resulting in complex motor dysfunction. In DLB, widespread cortical and subcortical α -synuclein pathology involving posterior cortical regions, limbic structures, brainstem nuclei, and the cholinergic system contributes to early cognitive impairment, visual hallucinations, fluctuating attention, and variable parkinsonism. Motor system involvement in DLB is heterogeneous and often influenced by coexisting Alzheimer's pathology. In MSA, oligodendroglial pathology drives multi-system damage, including the cerebellum, pons, and basal ganglia, and its distinctive imaging patterns aid in differential diagnosis. The main pathological, clinical, and neuroimaging characteristics of aging, PD, DLB, and MSA are summarized in Table 1.

Table 1. Comparative Summary of Motor System Degeneration in Aging, PD, DLB, and MSA.

Domain	Aging	PD	DLB	MSA
Primary Pathology	None (physiological process); mitochondrial dysfunction, oxidative stress, iron deposition, neuroinflammation, myelin degeneration, impaired proteostasis	Neuronal α -synuclein inclusions (Lewy bodies/neurites); progressive dopaminergic neuron loss in SNc	Neuronal α -synuclein aggregates with frequent coexisting AD pathology; widespread cortical (esp. posterior), limbic, basal ganglia, brainstem, and cholinergic involvement	Oligodendrocytic α -synuclein inclusions (glial cytoplasmic inclusions); multi-system degeneration (striatum, pons, cerebellum)
Motor Cortex	Cortical thinning (begins mid-adulthood); myelin loss; reduced perfusion; iron deposition (layer V, Betz cells); $\downarrow$ neuronal excitability & plasticity	M1 dysfunction via basal ganglia-thalamocortical loops; aberrant oscillatory activity; task-related hypoactivation or hyperactivation; iron deposition	Less characterized; cortical atrophy predominantly posterior (occipital); motor cortex involvement variable	Less prominent, M1 not a primary target
White Matter	CST & CStrT: demyelination (quadratic trajectory); $\downarrow$ axonal density; proximal segments more vulnerable; vascular factors (BP variability, PVS enlargement) contribute	Widespread microstructural WM abnormalities; WM lesions common (30-50%); WM lesions linked to axial deficits, freezing, postural instability, and cognitive decline	WM abnormalities prevalent; WMHs associated with cognitive impairment, neuropsychiatric symptoms, dementia severity	Cerebellar-pontine pathway degeneration; corpus callosum microstructural disruption; pontine transverse fiber loss ("hot cross bun" sign)
Nigrostriatal System	Progressive SNc neuron loss; modest $\downarrow$ tyrosine hydroxylase & striatal dopamine; iron deposition; $\downarrow$ DAT-immunoreactive neurons; synaptic density	Severe progressive dopaminergic neuron loss in SN (accelerated vs. aging); $\downarrow$ NM; iron deposition; striatal denervation	Nigrostriatal dopaminergic dysfunction ($\downarrow$ DAT binding on SPECT); $\sim$ 10% show normal DAT (if significant)	Severe striatal dopaminergic terminal loss (especially posterior putamen in MSA-P); less severe in MSA-C

	loss		AD co-pathology)	
Neurovascular Involvement	Impaired neurovascular coupling, endothelial dysfunction, reduced cerebrovascular reserve	NVU dysfunction, WMHs, BP variability, vascular contributions to motor decline and cognitive status	Frequent cerebrovascular pathology; contribute to clinical heterogeneity if coexist with AD pathology	Less extensively studied; vascular pathology may contribute to disease burden
Dominant Motor Manifestations	Gradual motor decline: impaired gait/balance, fine motor skills, coordination; slower reaction time; ↓muscle strength	Resting tremor, bradykinesia, rigidity, postural instability; levodopa-responsive; some progress to PDD	Parkinsonism (bradykinesia, rigidity, postural instability; resting tremor less prominent than PD); rapid motor progression (faster than PDD)	Parkinsonism (poorly levodopa-responsive) or cerebellar ataxia; early autonomic failure; MSA-P vs. MSA-C subtypes; shorter survival
Cognitive Involvement	Mild age-related decline	Cognitive impairment may develop with disease progression	Early dementia, fluctuating cognition, visual hallucinations	Mild and variable
Imaging Findings	Structural MRI: M1 thinning; DTI: ↓FA/↑MD in CST/CSTrT; Perfusion: ↓CBF; QSM: ↑iron in M1 & SN; PET: ↓synaptic density (SN)	NM-MRI: ↓signal in SNc; QSM: ↑SN iron; DTI: ↓FA, ↑free water (posterior SN); DAT-SPECT: ↓striatal DAT uptake; task-fMRI: M1 hypo/hyperactivation	Structural MRI: posterior cortical atrophy; FDG-PET: occipital hypometabolism, "cingulate island sign"; DAT-SPECT: ↓striatal DAT uptake	MRI: putamen atrophy & hypointensity (MSA-P), pontine/middle cerebellar peduncle/cerebellar atrophy, "hot cross bun" sign (MSA-C); DAT-SPECT: ↓posterior putamen DAT uptake (MSA-P); FDG-PET: putamen/frontal (MSA-P) or pons/cerebellum (MSA-C) hypometabolism

Abbreviations: AD, Alzheimer's disease; BP, blood pressure; CBF, cerebral blood flow; CST, corticospinal tract; CSTrT, corticostriatal tract; DAT, dopamine transporter; DLB, dementia with Lewy bodies; DTI, diffusion tensor imaging; FA, fractional anisotropy; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; M1, primary motor cortex; MD, mean diffusivity; MSA-C, multiple system atrophy-cerebellar subtype; MSA-P, multiple system atrophy-parkinsonian subtype; NM, neuromelanin; NVU, neurovascular unit; PD, Parkinson's disease; PDD, Parkinson's disease dementia; PET, positron emission tomography; PVS, perivascular spaces; QSM, quantitative susceptibility mapping; SN, substantia nigra; SNc, substantia nigra pars compacta; SPECT, single-photon emission computed tomography; WM, white matter; WMHs, white matter hyperintensities.

From a clinical perspective, the findings reviewed here have direct implications for the early diagnosis and management of synucleinopathies. Multimodal MRI biomarkers, including QSM for iron deposition, NM-MRI for nigral neuronal integrity, and diffusion MRI for white matter microstructural damage, hold promise for detecting prodromal pathology years before the emergence of overt motor symptoms. These tools may facilitate the identification of at-risk individuals in clinical settings and enable more accurate differential diagnosis among PD, DLB, and MSA, particularly when clinical presentations overlap. Moreover, the distinct patterns of motor system degeneration across these disorders may guide patient stratification for clinical trials, allowing for more homogeneous study cohorts based on biomarker-defined endophenotypes. The incorporation of imaging biomarkers into natural history studies and therapeutic trials offers the potential to objectively track disease

progression and evaluate treatment efficacy, especially as disease-modifying therapies targeting α -synuclein aggregation or neuroinflammation enter clinical development. Ultimately, integrating longitudinal multimodal neuroimaging with molecular biomarkers will be essential to clarify interactions between aging and disease-specific mechanisms, identify critical pathological thresholds and early degenerative windows, and inform the development of targeted therapeutic strategies.

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