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Clinical Significance of Nigral Neuropathology in Parkinsonian Disorders

A Comparative Clinicopathological Study

Emmilotta Backman

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University of Turku

Faculty of Medicine
Department of Clinical Medicine
Clinical Neurosciences
Doctoral Programme in Clinical Research

Supervised by

Professor Valtteri Kaasinen
Clinical Neurosciences (Neurology)
University of Turku and
Neurocenter
Turku University Hospital
Turku, Finland

Adjunct Professor Maria Gardberg
Department of Pathology
Turku University Hospital and
Institute of Biomedicine
University of Turku
Turku, Finland

Reviewed by

Associate Professor Eino Solje
University of Eastern Finland and
Neurocenter
Kuopio University Hospital
Kuopio, Finland

Docent Olli Tynninen
Department of Pathology
Helsinki University Hospital and
University of Helsinki
Helsinki, Finland

Opponent

Professor Laura Parkkinen
Nuffield Department of Clinical Neurosciences
University of Oxford
Oxford, United Kingdom

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To the loving memory of my grandmother

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ABSTRACT

Parkinson's disease (PD) and atypical parkinsonisms are neurodegenerative disorders marked by overlapping motor symptoms such as stiffness, slow movements, and tremor, collectively termed parkinsonism. In PD, progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) leads to striatal dopamine depletion, driving the classical motor phenotype. Non-motor symptoms, including cognitive decline, mood and sleep disturbances, and autonomic dysfunction, further impair quality of life. Atypical parkinsonisms, including multiple system atrophy (MSA), and progressive supranuclear palsy (PSP), share core motor features with PD but are distinguished by faster progression, poor levodopa response, and a broader neuropathology, together with severe nigral degeneration.

This thesis investigated neuroinflammation and neural density in the SNc by comparing PD with MSA and PSP. Immunohistochemial analyses, clinical features, medication, and computed tomography (CT) imaging evaluation were assessed. Brain tissue and corresponding clinical records from the University Hospital Turku (between 2002 and 2021) were examined. Tyrosine hydroxylase (TH) positive neurons were manually quantified, while neuroinflammatory cells were assessed via automated analysis.

Results revealed pronounced T cell infiltration in PSP, with elevated CD3+, CD4+, and CD8+ T cell counts relative to PD, MSA, and controls, whereas microglial activity was most pronounced in PD. Levodopa was not associated with neurotoxicity or inflammation. Moreover, depressed PD patients exhibited more severe cortical atrophy than non-depressed counterparts.

These findings support existing evidence of distinct inflammatory and neuronal signatures across the disorders, suggesting potential disease-specific mechanisms and therapeutic targets. Moreover, depression, a common non-motor symptom in PD, appears to be associated with cortical atrophy, while levodopa, the golden standard medical treatment for parkinsonian syndromes, does not affect nigral neuronal survival or neuroinflammatory activity in PD, PSP, or MSA.

KEYWORDS: Parkinson's disease, progressive supranuclear palsy, multiple system atrophy, substantia nigra, neuroinflammation, neuropathology, dopamine, levodopa, depression, CT-imaging

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TIIVISTELMÄ

Parkinsonin tauti ja epätyypilliset parkinsonismit, kuten monisysteemiatrofia (MSA) ja etenevä supranukleaarinen halvaus (PSP), ovat neurodegeneratiivisia sairauksia, joihin liittyy motorisia oireita, kuten jäykkyyttä, liikkeiden hitautta ja lepovapinaa, joita kutsutaan yhteisnimellä parkinsonismi. Parkinsonin taudissa dopaminergisten hermosolujen etenevä rappeutuminen mustatumakkeessa johtaa dopamiinin vähenemiseen aivojen tyvitumakkeissa ja klassisten motoristen oireiden kehittymiseen. Motoristen häiriöiden lisäksi potilailla esiintyy tiedonkäsittelyn heikentymistä, mielialahäiriöitä, unihäiriöitä ja autonomisen hermoston toimintahäiriöitä, jotka heikentävät merkittävästi elämänlaatua. Epätyypillisissä parkinsonismeissa motoriset oireet ovat samankaltaisia kuin Parkinsonin taudissa, mutta sairaudet etenevät nopeammin, reagoivat heikosti levodopahoitoon ja sairauksiin liittyy laajempia neuropatologisia muutoksia, joissa mustatumakkeen rappeutuminen on voimakasta.

Tässä väitöskirjatutkimuksessa tutkittiin mustatumakkeen neuroinflammaatiota ja hermosolutiheyttä vertaamalla Parkinsonin tautia epätyypillisiin parkinsonismeihin. Menetelminä käytettiin immunohistokemiallisia analyyseja, kliinisten piirteiden ja lääkevasteen arviointia sekä tietokonetomografia (TT) kuvantamista. Aineisto koostui Turun yliopistollisen keskussairaalan neuropatologian arkistoista välillä 2002 ja 2021 kerätyistä aivoleikkeistä ja niihin liittyvistä kliinisistä potilastiedoista. Tyrosiini-hydroksylaasipositiiviset hermosolut laskettiin manuaalisesti, kun taas neuroinflammatoriset solut arvioitiin automatisoiduilla analyyseilla.

Tulokset osoittivat, että PSP:ssä T solujen (CD3+, CD4+, CD8+) määrä mustatumakkeessa oli kohonnut verrattuna Parkinsonin tautiin, MSA:han ja terveisiin verrokkeihin. Mikroglia-solujen aktiivisuus puolestaan oli korostuneinta Parkinsonin taudissa. Levodopalla ei havaittu olevan neurotoksista tai neuroinflammaatioon kohdistuvaa vaikutusta. Lisäksi masentuneilla Parkinson potilailla todettiin vahvempi kortikaalinen atrofia kuin ei-masentuneilla.

Nämä havainnot korostavat sairauksien välisiä eroja aivojen tulehdusreaktioissa ja hermoston rappeutumisessa, ja voivat tarjota potentiaalisia hoitokohteita. Lisäksi masennus vaikuttaa olevan yhteydessä aivokuoren surkastumiseen. Sen sijaan levodopan käytöllä ei ole vaikutusta mustatumakkeen hermosolukatoon tai neuroinflammatoriseen aktiivisuuteen Parkinsonin taudissa, PSP:ssa tai MSA:ssa.

AVAINSANAT: Parkinsonin tauti, PSP, MSA, mustatumake, neuroinflammaatio, neuropatologia, dopamiini, levodopa, masennus, TT-kuvantaminen

Table of Contents

Abbreviations

AADC	Aromatic I-amino acid decarboxylase
AD	Alzheimer's disease
AI	Artificial intelligence
ALS	Amyotrophic lateral sclerosis
ANCOVA	Analysis of covariance
APC	Antigen-presenting cell
ATP	Adenosine triphosphate
BBB	Blood-brain barrier
BG	Basal ganglia
CBD	Corticobasal degeneration
CD	Cluster of differentiation
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CN	Caudate nucleus
CNNs	Convolutional neural networks
CNS	Central nervous system
COMT	Catechol-O-methyltransferase
CSAI	Continuous subcutaneous apomorphine infusion
CSF	Cerebrospinal fluid
CT	Computed tomography
CTE	Chronic traumatic encephalopathy
DBS	Deep brain stimulation
DLB	Dementia with Lewy bodies
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
GABA	γ-aminobutyric acid
GCA	Global cortical atrophy
GCI	Glial cytoplasmic inclusion
GP	Globus pallidus
GPe	Globus pallidus externus
GPi	Globus pallidus internus
GWAS	Genome-wide association study

HLA	Human leukocyte antigen
HY	Hoehn and Yahr
ICC	Intraclass correlation coefficient
ICD-10	International Classification of Diseases Tenth Revision
IL	Interleukin
LB	Lewy body
LCIG	Levodopa-carbidopa intestinal gel
LECIG	Levodopa-entacapone-carbidopa intestinal gel
LED	Levodopa daily dose
LEDD	Levodopa equivalent daily dose of dopaminergic medications
LFB	Luxol fast blue
LLRK2	Leucine-rich repeat kinase 2
LN	Lewy neurite
LPS	Lipopolysaccharide
MAO-B	Monoamine oxidase-B
MDS	Movement Disorder Society
MHC	Major histocompatibility complex
MMSE	Mini-Mental State Examination
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSA	Multiple system atrophy
MSA-C	MSA cerebellar type
MSA-P	MSA parkinsonian type
MTA	Medial temporal lobe atrophy
NSAID	Non-steroidal anti-inflammatory drug
PD	Parkinson’s disease
PDD	Parkinson’s disease dementia
PET	Positron emission tomography
PSP	Progressive supranuclear palsy
PSP-C	PSP with predominant cerebellar ataxia
PSP-CBS	PSP-Corticobasal Syndrome
PSP-F	PSP-Frontal Presentation
PSP-P	PSP parkinsonian type
PSP-PGF	PSP with progressive gait freezing
PSP-RS	PSP-Richardson syndrome
PSP-SL	PSP-Speech and Language
Put	Putamen
REM	Rapid eye movement
ROS	Reactive oxygen species

SN	Substantia nigra
SNc	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
SPECT	Single-photon emission computed tomography
SSRI	Selective serotonin reuptake inhibitor
STN	Subthalamic nucleus
TD	Tremor dominant
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor alpha
WMH	White matter hyperintensity
WML	White matter lesion

List of Original Publications

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

I Backman EA, Gardberg M, Luntamo L, Peurla M, Vahlberg T, Borghammer P, Stefanova N, Wenning G, Kaasinen V. Nigral Neuroinflammation and Dopaminergic Neurons in Parkinson's Disease and Atypical Parkinsonisms. *Ann Neurol*. 2025 Jun;97(6):1096–1109. https://doi.org/10.1002/ana.27202

II Backman EA, Luntamo L, Vahlberg T, Gardberg M, Kaasinen V. Levodopa Exposure and Nigral Neuroinflammation in Parkinsonian Disorders: A Postmortem Study of 63 Cases. *Scientific Reports.* 2025 Nov 11;15(1):39516. https://doi.org/10.1038/s41598-025-23376-2

III Backman EA, Luntamo L, Parkkola R, Koikkalainen J, Gardberg M, Kaasinen V. Early cortical atrophy is related to depression in patients with neuropathologically confirmed Parkinson's disease. *J Neurol Sci*. 2023 Dec 15;455:122804. https://doi.org/10.1016/j.jns.2023.122804

1 Introduction

Parkinson's disease (PD) is one of the most prevalent neurodegenerative disorders, first described by Dr. James Parkinson in 1817 in his seminal essay *An Essay on the Shaking Palsy* (Parkinson, 1817). In this essay, he detailed six individuals who exhibited the characteristic clinical features of the disease. After 60 years, the condition was officially named "Parkinson's disease," a term recommended by the French neurologist Jean-Martin Charcot (Charcot, 1877). Charcot and his students further expanded the clinical understanding of PD. He distinguished PD from other neurological disorders, such as multiple sclerosis (MS), and introduced terms like "bradykinesia."

The core pathology of PD is the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), a key midbrain structure. The first case linking PD to the substantia nigra (SN) was published in 1893 by Blocq and Marinesco (Blocq & Marinesco, 1893). In 1912, Frederic Lewy identified abnormal protein aggregates in the brains of PD patients, now known as Lewy bodies (LBs) (Lewy, 1912). In 1919, Tretiakoff further reinforced this connection by identifying SN degeneration as a defining feature of the disease (Tretiakoff, 1919). Later, in the 1950s and 1960s, Swedish scientist Arvid Carlsson discovered the role of dopamine in movement control, leading to the development of levodopa, the first effective treatment for PD (Carlsson, 1959; Carlsson et al., 1957). Oleh Hornykiewicz was the first to suggest using levodopa to treat PD, and in 1961, the first successful clinical trial demonstrated levodopa's remarkable efficactiveness in relieving PD symptoms (Birkmayer & Hornykiewicz, 1961). George Cotzias further refined its use for patients (Cotzias et al., 1967).

In the late 20th and early 21st centuries, treatments advanced with deep brain stimulation (DBS), pioneered by Alim-Louis Benabid in the 1980s, significantly improving motor symptoms (Benabid et al., 1987). DBS, together with multiple possible infusion-therapies, remains a critical intervention for patients with advanced PD. Research into genetics, environmental factors, and neuroprotective therapies continues, but a cure has yet to be invented. **Figure 1** presents a timeline highlighting the most significant historical milestones in PD.

While PD is the most common form of parkinsonism, a group of disorders known as atypical parkinsonisms present with overlapping motor symptoms. They are, however, distinguished by unique clinical features, pathological findings, and often more rapid progression. Atypical parkinsonisms include multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). These conditions lack the classic response to dopaminergic therapy observed in PD and are associated with distinct patterns of neuronal degeneration and pathology (Levin et al., 2016). For instance, PSP is marked by tau protein accumulation, while MSA features glial cytoplasmic inclusions (GCIs) composed of α-synuclein. The distinction between PD and atypical parkinsonisms remains a significant clinical challenge, especially in early stages of the disease due to their overlapping symptoms. Advanced imaging techniques and histopathological studies of brain structures like the SN are invaluable tools for improving diagnostic accuracy and understanding disease mechanisms.

Neuroinflammation is increasingly recognized as a contributing factor in these diseases, especially in the pathogenesis of PD (Pajares et al., 2020). For example, studies of the brains of PD patients have revealed heightened microglial activation in the SNc and other regions (Imamura et al., 2003). Positron emission tomography (PET) studies have further supported these findings (Gerhard, Pavese, et al., 2006). Although research on MSA and PSP is more limited, similar results have been observed in these conditions (Gerhard et al., 2003; Gerhard, Trender-Gerhard, et al., 2006; Refolo & Stefanova, 2019).

This thesis focused on nigral neuroinflammation and neuron density in the SNc, comparing PD with MSA and PSP through immunohistochemial analysis, clinical features and medication assessments, and CT-imaging evaluation. By exploring the interplay between neuroinflammation, neuronal loss, and clinical presentation, this work aims to contribute to the growing body of knowledge that seeks to improve the diagnosis and treatment of these disorders.

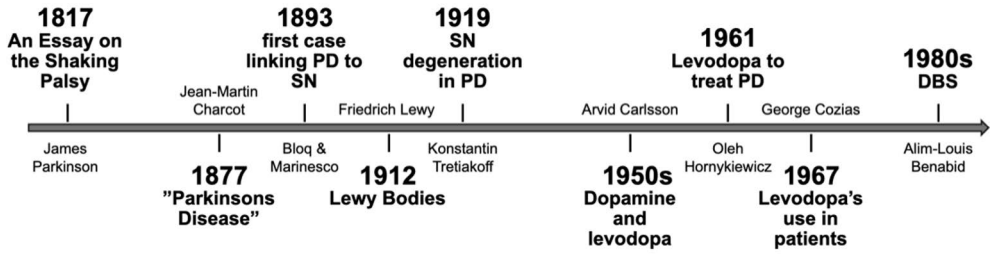

Figure 1. Historical timeline illustrating major scientific and medical advances in the understanding of PD.

2 Review of the Literature

2.1 The basal ganglia

The basal ganglia (BG) are a group of interconnected nuclei located at the base of the forebrain and the top of the midbrain. These structures are critical for regulating voluntary movements, facilitating motor control, and influencing conditional learning (Albin et al., 1989; Stocco et al., 2010). The BG consist of the dorsal striatum: caudate nucleus (CN) and putamen (Put), the ventral striatum: nucleus accumbens and olfactory tubercle, the globus pallidus (GP), the ventral pallidum, the subthalamic nucleus (STN), and the substantia nigra (SN). **Figure 2** presents the anatomy in a sagittal section, and **Figure 3** presents the anatomy in a coronal section.

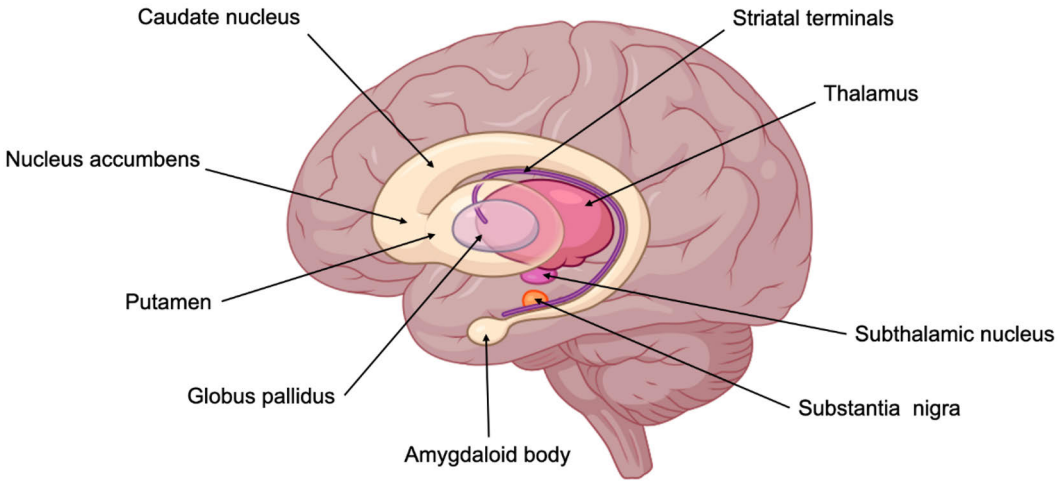

Figure 2. Anatomy of the Basal ganglia in sagittal brain section. Created in https://BioRender.com.

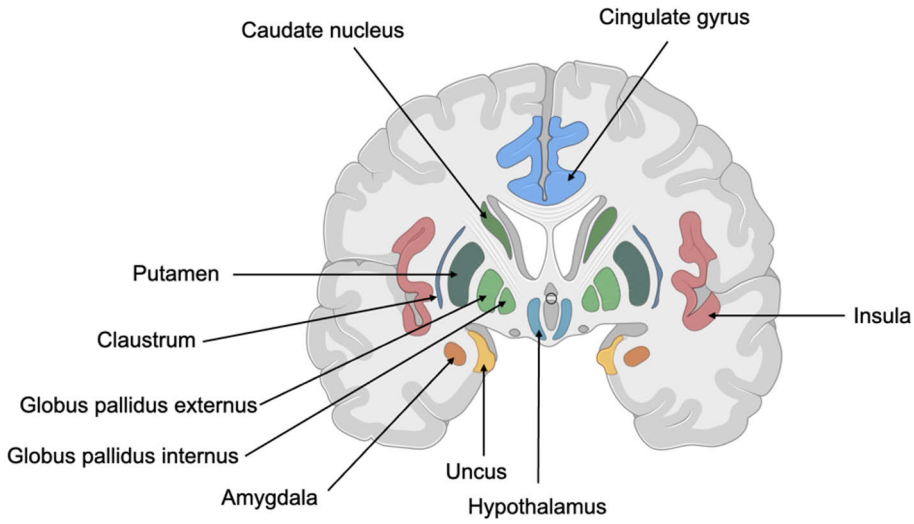

Figure 3. Basal ganglia anatomy in coronal section, illustrated in shades of green. Created in https://BioRender.com.

The BG nuclei are functionally divided into input, output, and intrinsic nuclei. The input nuclei include the CN, Put, and nucleus accumbens. They receive signals from the cerebral cortex, thalamus, and nigral nuclei. The output nuclei include the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr). They regulate the thalamus, which then projects back to the cortex, completing the cortico-basal ganglia-thalamo-cortical loop. The intrinsic nuclei, positioned between the input and output regions, include the external segment of the globus pallidus (GPe), the STN, and the substantia nigra pars compacta (SNc) (Lanciego et al., 2012). The physiological function of the basal ganglia revolves around two primary pathways. The direct pathway facilitates movement by reducing inhibition of the thalamus, which in turn enhances motor cortex activity, and the indirect pathway suppresses unwanted or excessive movements by increasing inhibition of the thalamus. **Figure 4** presents the pathways.

By coordinating these pathways, the basal ganglia maintain motor precision and contribute to learning, and habit formation. Disruptions to these systems can result in a variety of movement disorders, including PD, Huntington's disease, and dystonia.

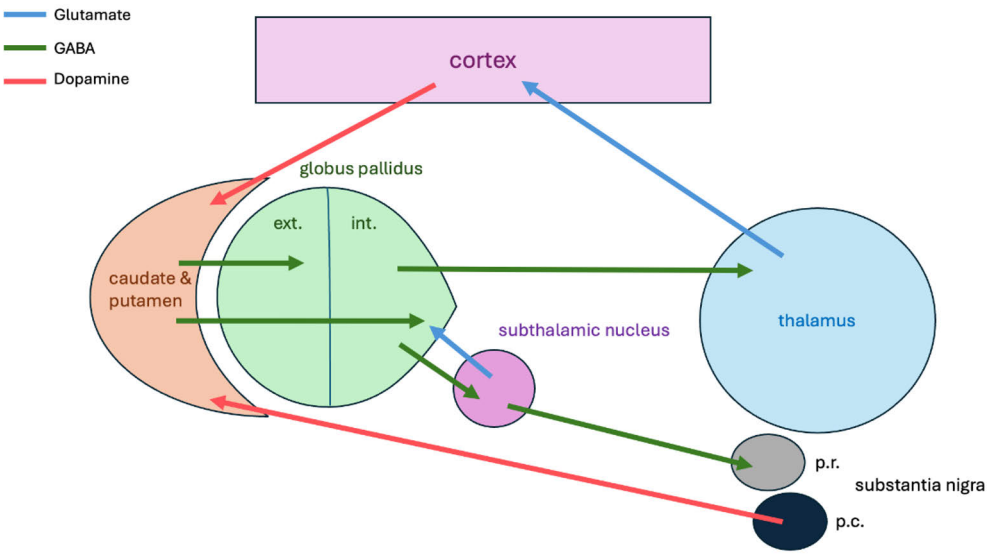

Figure 4. Main signal pathways within the basal ganglia with corresponding primary neurotransmitters. GABA = inhibitatory, Glutamate = exitatory.

2.1.1 Substantia Nigra

The SN is a vital structure located in the midbrain that plays an essential role in modulating movements and reward functions as part of the BG circuitry. The SN is divided into two main parts: the SNc and the SNr. The SNc is primarily known for its production of dopamine, which is a neurotransmitter critical for motor function and reward signaling. In gross anatomical dissections, the SNc appears dark due to its the high neuromelanin content, which is a byproduct of dopamine synthesis from its precursor, levodopa (Fabbri et al., 2017). The dopaminergic neurons in this region project to the striatum, forming the nigrostriatal pathway. The nigrostriatal pathway is essential in balancing the direct and indirect pathways that regulate voluntary movement. The loss of dopaminergic neurons in the SNc is a hallmark of PD, leading to motor deficits such as bradykinesia, rigidity, and tremor. Also, in atypical parkinsonisms, like MSA and PSP, degeneration of the SNc has been observed. **Figure 5** shows the SNc anatomy of a PSP patient and a patient without a neurodegenerative disease at death.

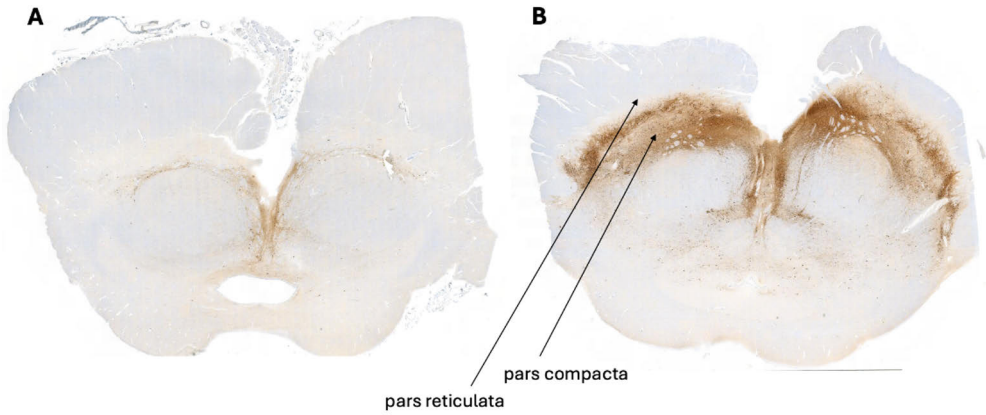

Figure 5. Midbrain section at the level of the third cranial nerve of a PSP patient (A) and a patient without a neurodegenerative disease (B) at death. Note the loss of the dopaminergic neurons in the SN region. Brown tyrosine hydroxylase staining highlights neuromelanin-laden dopaminergic neurons in the substantia nigra pars compacta.

The SNr, in contrast, contains primarily γ-aminobutyric acid- (GABA)ergic neurons and serves as an output nucleus of the BG (Chevalier & Deniau, 1990). It sends inhibitory signals to the thalamus and brainstem motor nuclei, thereby influencing motor control and coordination. The SNr also receives input from other BG components, including the striatum and STN, integrating information to regulate motor activity (Obeso et al., 2008; Redgrave et al., 2010). The SNr plays a crucial role in suppressing involuntary movements and maintaining the precision of motor commands.

The SN is richly vascularized and relies on a steady supply of oxygen and nutrients to support its high metabolic activity. The integrity of its dopaminergic neurons is critical for maintaining normal motor and cognitive function. Dopamine is synthetized from dietary amino acid phenylalanine via enzyme-driven pathway. Dopamine also oxidizes spontaneously, forming free radicals and dopamine quinone, which may lead to neuromelanin production – the pigment responsible for the coloration of the SNc. The pathways of dopamine biosynthesis and dopamine degradation are presented in **Figure 6**. While neuromelanin's exact role is unclear, it may contribute to the vulnerability of dopaminergic neurons (Franco et al., 2021).

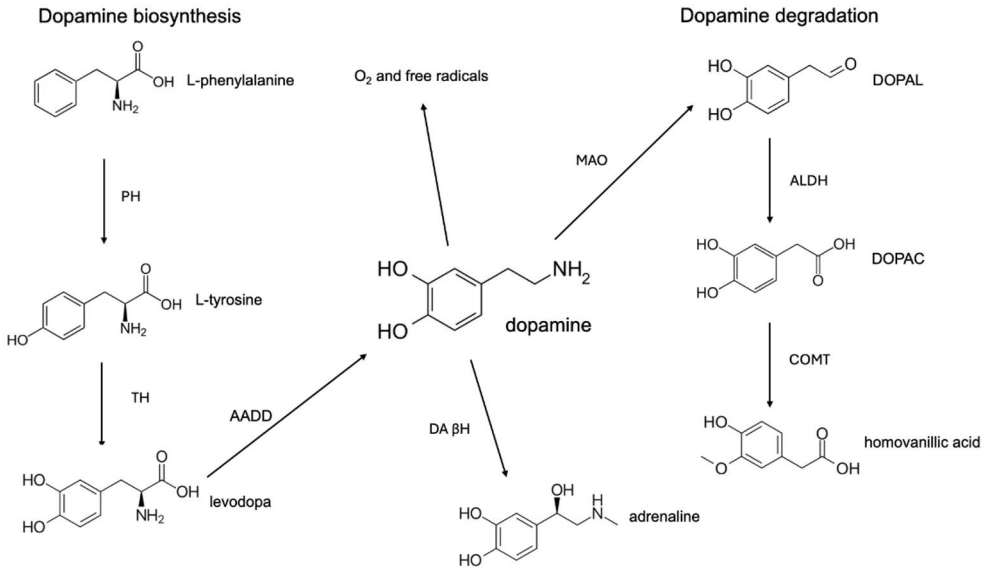

Figure 6. Main metabolic pathway of dopamine synthesis and clearance. PH=phenylalanine hydroxylase, TH=tyrosine hydroxylase, AADD=aromatic L-amino acid decarboxylase, DOPAL=3,4-dihydroxyphenylacetaldehyde, DOPAC=3,4-dihydroxyphenylacetic acid, ALDH=aldehyde dehydrogenase, DA βH=DA β-hydroxylase, MAO=monoamine oxidase, COMT=catechol-O-methyltransferase.

Dopamine is released by the SNc, and binds to specific receptors in the striatum, modulating the activity of the direct and indirect pathways. In the direct pathway, dopamine stimulates D1 receptors, enhancing excitatory signals that promote movement. Neurons in the direct pathway project from Put to GPi/SNr. In the indirect pathway, dopamine inhibits D2 receptors, reducing inhibitory signals and facilitating motor activity. Neurons in the indirect pathway project to the GPe which influence the GPi/SNr. This dual action ensures a balance between movement initiation and suppression (Obeso et al., 2008).

Disorders of the SN are associated with a range of neurological and neuropsychiatric conditions. PD is characterized by the progressive degeneration of dopaminergic neurons in the SNc, resulting in motor impairments. Also, non-motor symptoms such as depression have been associated with degeneration of the SNc in PD (Saari et al., 2021). Additionally, the SN has been implicated in Huntington's disease and conditions involving reward-processing abnormalities (Schultz, 1997; Waldvogel et al., 2015). Furthermore, dysfunction of dopaminergic pathways is central to the pathogenesis of psychotic disorders, particularly through dysregulation of dopaminergic signaling in limbic and cortical circuits (Rawani et al., 2024). In PD, psychotic symptoms such as visual hallucinations and delusions are common, especially in later stages of the disease and in association with dopaminergic treatment and widespread neurodegeneration, indicating that altered dopamine and

other neurotransmitter systems contribute to psychosis across different clinical contexts (González-Usigli et al., 2023; Samudra et al., 2016).

2.1.2 Neuropathology of substantia nigra

Histologically, SN is composed of neurons and glial cells. It is divided into 2 regions; SNc contains dopaminergic neurons, whereas SNr contains inhibitory GABAergic neurons (**Figure 5**). Neurons transmit and relay signals through the nervous system and consist of a cell body, axon, dendrites and a myelin sheath. Glial cells serve various functions, including protecting the nervous system from infections and producing the myelin sheath that insulates neuronal axons.

Degenerative parkinsonian disorders are typically characterized by selective loss of dopaminergic neurons in the SN that project to the BG. The most vulnerable are the ventrolateral cell groups (A9 or nigrostriatal pathway) (Fearnley & Lees, 1991), while the dorsal and medial cell groups (A10 or mesolimbic pathway) are more resistant (Dickson et al., 2009).

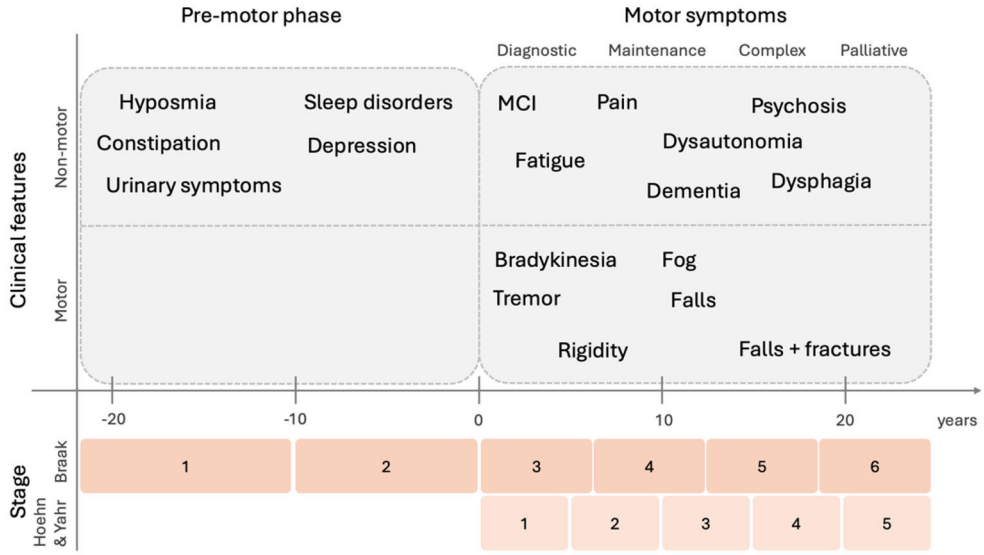

Figure 7. Braak staging together with Hoehn and Yahr (H&Y) scale, and clinical diagnostic criteria. Modified from Bamford et al 2021. MCI=mild cognitive impairment, FOG=freezing of gate. Braak stages neuroanatomically: 1=olfactory bulb, dorsal motor nucleus of the vagus (medulla), 2=locus coreruleus (pons), 3=substantia nigra (midbrain), 4=entorhinal cortex, amygdala (limbic lobe), 5=association cortex (neocortex), 6=primary sensory and motor cortices.

PD and MSA are characterized by α-synuclein pathology, whereas PSP is associated with tau pathology, with globose neurofibrillary tangles rather than LBs

in affected nigral neurons. Neuropathologically, PSP is classified within the frontotemporal lobar degeneration (FTLD) spectrum (Burrell et al., 2014), in contrast to PD and MSA. In MSA, the primary pathology occurs in oligodendroglia rather than neurons, with inclusions that differ in appearance and distribution from the LBs seen in PD (Cykowski et al., 2015). In PD, LB pathology extends beyond the SN. According to Braak staging (Braak et al., 2004), the earliest pathology appears in the dorsal motor nucleus of the vagus in the medulla and the anterior olfactory nucleus in the olfactory bulb. It then progresses to the locus ceruleus neurons in the pons and the dopaminergic neurons in the SN. In later stages, pathology spreads to the basal forebrain, amygdala and the medial temporal lobe structures. PD progression is divided into six neuropathological Braak stages. **Figure 7** illustrates the Braak staging together with H&Y scale, and clinical diagnostic criteria.

2.2 Parkinsonism

Parkinsonism is a clinical syndrome characterized by a combination of motor symptoms, including bradykinesia, rigidity, resting tremor, and postural instability. It is a broad term encompassing a range of conditions that manifest these characteristic motor dysfunctions. Idiopathic PD is the most common cause of parkinsonism, accounting for approximately 75% of cases. However, several other conditions and factors can also lead to parkinsonism, collectively referred to as atypical or secondary parkinsonism. The underlying causes of parkinsonism can be categorized into neurodegenerative, vascular, toxic, and drug-induced origins. Parkinsonism can also be observed in other neurodegenerative disorders, including frontotemporal dementia (FTD) and, in some cases, amyotrophic lateral sclerosis (ALS).

PD is a progressive neurodegenerative disorder primarily associated with the loss of dopamine-producing neurons in the SNc. Atypical parkinsonisms, also known as Parkinson-plus syndromes, include a group of neurodegenerative disorders that share some features with PD but exhibit distinct clinical and pathological characteristics. These conditions include MSA, PSP, corticobasal degeneration (CBD) and dementia with Lewy bodies (DLB). Secondary parkinsonism can result from other causes, such as vascular insults (e.g., stroke), exposure to neurotoxic agents (e.g., MPTP), or the use of certain medications, particularly antipsychotic drugs that block dopamine receptors. Studies suggest that PD and DLB are not distinct diseases, but rather different clinical expressions of single underlying condition known as Lewy Body disease. While traditionally differentiated by the timing of cognitive and motor symptoms, studies indicate that PD dementia (PDD) and DLB share similar symptoms, imaging findings, and neuropathological features (Borghammer et al., 2024).

2.2.1 Parkinson's disease

2.2.1.1 Epidemiology and risk factors

PD is the leading neurodegenerative cause of parkinsonism, affecting millions worldwide. It is the second most prevalent neurodegenerative disorder after Alzheimer's disease (AD) (Alzheimer's Association, 2015).

In 2021, an estimated 11.77 million people worldwide were living with PD, with age-standardized prevalence rates increasing substantially over the past three decades. Globally, age-standardized incidence rates were approximately 15.6-16.9 per 100 000 in 2021, with incidence and prevalence rising consistently since 1990 (Yang et al., 2026). Age remains the strongest risk factor for PD, with both incidence and prevalence increasing sharply with age, particularly after the age of 60 (de Lau & Breteler, 2006). However, early-onset PD can manifest in rare cases, often due to genetic mutations. The number of individuals diagnosed with PD has risen significantly and is projected to continue increasing (Dorsey et al., 2018). The increasing prevalence is thought to result from several converging factors, which include ageing and increased life expectancy, which have led to a larger proportion of individuals reaching the age at which PD most commonly develops. In addition, improvements in clinical awareness and diagnostic methods have contributed to more frequent and earlier detection. Current projections suggest that the global number of people living with PD will more than douple by 2050, reaching an estimated 25.2 million cases (Yang et al., 2026).

The etiology of PD remains unclear, though it is widely accepted that multiple factors contribute to disease risk. In addition to increasing age and sex, ethnicity has been implicated as a potential risk factor. In the United States, the highest incidence of PD is observed among individuals of Hispanic descent, followed by non-Hispanic Whites, Asians, and Blacks (Van Den Eeden et al., 2003). Notably, smoking has been associated with a reduced risk of developing PD, although the underlying mechanisms remain controversial (Ritz et al., 2007). Several environmental and lifestyle factors have also been linked to PD risk. Factors associated with increased risk, in descending order of strength of association, include pesticide exposure, prior head injury, rural living, β-blocker use, agricultural occupations, and consumption of well water. Conversely, factors associated with a decreased risk include tobacco smoking, coffee consumption, use of non-steroidal anti-inflammatory drugs (NSAID), calcium channel blockers, and alcohol intake (Noyce et al., 2012).

Genetic contributions to PD have become increasingly recognized, with monogenic causes estimated to account for 5-10% of cases (Lill, 2016). While historically considered rare, genetic mutations such as those in the leucine-rich

repeat kinase 2 (*LRRK2*) gene have since been identified as significant contributors to familial PD (Gilks et al., 2005).

2.2.1.2 Pathogenesis

The pathophysiology of PD is complex and multifaceted, involving dopaminergic neurodegeneration, α-synuclein aggregation, neuroinflammation, and genetic factors. The hallmark feature of PD is the selective loss of dopaminergic neurons in the SNc, leading to a significant reduction in dopamine levels within the striatum. This neurodegeneration disrupts the normal functioning of the BG circuitry, leading to the characteristic motor symptoms, including bradykinesia, rigidity, tremor, and postural instability.

A key pathological hallmark of PD is the accumulation of misfolded alpha-synuclein protein, forming the LBs (Spillantini et al., 1997). LBs are central to the disease and accumulate in various brain regions. However, Lewy pathology is also commonly observed in individuals who appear otherwise healthy (Parkkinen et al., 2005). Mutations in α-synuclein accelerate aggregation, indicating its role in both familial and likely sporadic PD. Pathological α-synuclein aggregates at synapses may trigger early synaptic dysfunction (Calo et al., 2016; Tozzi et al., 2021). Cryo-electron microscopy shows that α-synuclein filament structures are similar in PD, PDD, and DLB but differ in MSA (Schweighauser et al., 2020; Yang, 2022). The Braak hypothesis suggests that PD pathology begins in peripheral systems and spreads to the brain, but variations in disease progression and LB distribution exist (Braak et al., 2003; Dickson et al., 2009). Evidence supports α-synuclein spread from the gut and brain to other organs, contributing to early symptoms like constipation and rapid eye movement (REM) sleep behaviour disorder (Arotcarena et al., 2020; Bohnen & Hu, 2019; Luk et al., 2012; Ruffmann & Parkkinen, 2016; Schrag et al., 2015). The “gut-first” and “brain-first” hypothesis in PD suggests two distinct pathways for disease onset. In the gut-first subtypes, pathological α-synuclein aggregates originate in the enteric nervous system and ascend the brain via the vagus nerve. This form is typically associated with early autonomic symptoms. The brain-first subtype begins with α-synuclein pathology in the central nervous system, particularly in the SN, leading to motor symptoms before autonomic involvement (Borghammer & Van Den Berge, 2019; Borghammer et al., 2021). Research suggests that prion-like mechanisms contribute to the propagation of α-synyclein pathology (Hansen et al., 2011; Li et al., 2008).

Mitochondrial dysfunction is a critical contributor to PD pathology, regulating cellular energy and survival. Early synaptic damage and mitochondrial dysfunction lead to increased reactive oxygen species (ROS), abnormal calcium levels, and reduced adenosine triphosphate (ATP) production (Nicoletti et al., 2021). Genetic

and environmental factors, including pesticide exposure and MPTP toxicity, contribute to mitochondrial complex I inhibition, linking mitochondrial dysfunction to PD (Langston, 2017). Mutations in genes like *SNCA*, *PINK1*, and *LRRK2* disrupt mitochondrial energy production and quality control (Li et al., 2021). Mitophagy helps to remove damaged mitochondria, but mutations, such as *LRRK2* and *Gly2019Ser*, might impair this process (Singh & Ganley, 2021). Aggregated α-synuclein disrupts mitochondrial membranes and the electron transport chain, increasing oxidative stress and neuronal apoptosis (Haque et al., 2022). Mitochondrial dysfunction and ROS promote α-synuclein aggregation, further driving neurodegeneration in PD (Picca et al., 2021).

Inflammation was linked to PD in the 1980s when studies found microglial activation and elevated inflammatory cytokines in post-mortem patient brains (McGeer, Itagaki, Boyes, et al., 1988; Mogi, Harada, Kondo, et al., 1994). Inflammation occurs in both the central nervous system (CNS) and blood, with elevated cytokines linked to faster disease progression (Qin et al., 2016; Williams-Gray et al., 2016). Monocytes shift to a pro-inflammatory state (Konstantin Nissen et al., 2022), the neutrophil-to-lymphocyte ratio increases (Muñoz-Delgado et al., 2021), and changes in T cells include bias towards pro-inflammatory Th1 and Th17 subsets (Contaldi et al., 2022). Infiltrating immune cells and activated microglia contribute to chronic neuroinflammation, though early immune activation may aid protein clearance. Genetic and epidemiological studies support a primary immune role, with human leukocyte antigen (HLA) variation and immune-related genes like *LRRK2* implicated (Magistrelli et al., 2022; Nalls et al., 2019). Environmental factors, including gut microbiome changes and infections, may trigger inflammation (Matheoud et al., 2019). Mitochondrial dysfunction further promotes immune activation (Mishra et al., 2025). Immune alterations appear early, but their long-term evolution remains unclear, highlighting the need for further research.

Although most cases of PD are sporadic, genetic mutations have been linked to familial forms of the disease. Twin studies and statistical genetic methods estimate the heritability of PD to be between 22% and 40% (Ben-Shlomo et al., 2024). Three autosomal dominant genes (*SNCA, LRRK2,* and *VPS35*) and three autosomal recessive genes (*PRKN, PINK1,* and *DJ1*) are known to cause PD, along with several other genes implicated in a limited number of cases or families. Numerically, *LRRK2* is the most important mendelian cause of PD. Common single variants in the *GBA1* gene are associated with PD but typically do not segregate in autosomal dominant families (Gegg et al., 2022). *LRRK2* is also involved in the development of Crohn's disease, leprosy, and mycobacterial infections, suggesting potential pleiotropic effects at the *LRRK2* locus that influence susceptibility and resistance to infectious and inflammatory diseases as well as neurodegeneration (Kluss et al., 2019). *SNCA* mutations are a rare cause of autosomal dominant PD. The discovery of pathogenic

SNCA gene multiplications demonstrated that increased *SNCA* mRNA expression and elevated α-synuclein levels can be sufficient to cause the disease (Singleton & Hardy, 2011). A total of 90 independent variants across 74 genomic loci have been associated with PD, each conferring a modest increase in risk (Blauwendraat et al., 2020). The strongest genome-wide associations with PD in European populations are found at the *SNCA* and *MAPT* loci. *MAPT* encodes the microtubule-associated protein tau, though the specific causal genes at this locus in PD remain unclear. However, evidence suggests that *KANSL1*, a gene involved in mitochondrial regulation at the *MAPT* locus, may play a role (Soutar et al., 2022). Recent evidence indicates that the *MAPT* H1 is associated with enhanced α-synuclein deposition in synucleinopathies, suggesting a genetic and pathological interplay between tau and α-synuclein aggregation (Colom-Cadena et al., 2013; Leveille et al., 2021).

2.2.1.3 Symptoms

Clinically, PD is characterized by progressive slowness of movement (bradykinesia), muscular rigidity, rest tremor and postural and gait impairment (Bloem et al., 2021; Gibb & Lees, 1988; Kalia & Lang, 2015). The symptoms emerge due to the progressive loss of dopaminergic neurons and the formation of α-synuclein-containing proteinaceous aggregates in neurons of the SNc (Gibb & Lees, 1988; Lewy, 1912). The diagnosis is clinical and is made based on a detailed medical interview and clinical examination. The symptoms of PD sometimes overlap with other diseases, such as atypical parkinsonisms, and there are no reliable biomarkers to distinguish the diseases.

The Queen Square Brain Bank clinical diagnostic criteria defined PD primarily based on the levodopa-responsive motor phenotype, which is linked to cell loss in the SNc and dopaminergic denervation in the SNc and Put (Gibb & Lees, 1988). Today, Movement Disorder Society (MDS) clinical diagnostic criteria serve as the standard for guiding clinical diagnosis (Postuma et al., 2015). Motor symptoms are the hallmark of PD and mostly result from dopamine depletion affecting motor control circuits. Bradykinesia manifests as slowness and reduced amplitude of movement due to impaired striatal dopamine signaling. Resting tremor, typically starting unilaterally in the hand at 4–6 Hz, is associated with abnormal oscillatory activity in basal ganglia-thalamocortical circuits. Rigidity is caused by increased muscle tone, and results from abnormal recruitment of motor units, leading to resistance to passive movement. Postural instability arises due to impaired integration of sensory and motor signals, increasing fall risk. These motor deficits typically begin asymmetrically and progress bilaterally over time. Disease severity is often assessed using the HY scale, which stages PD based on motor disability and balance impairment (Hoehn & Yahr, 1967). **Figure 8** presents the HY scale.

Stage I	Unilateral involvement only Usually with minimal or no functional disability
Stage II	Bilateral symptoms No impairment of balance
Stage III	Bilateral disease Mild to moderate disease Physically independent
Stage IV	Severe disability Still able to walk or stand assisted
Stage V	Wheelchair-bound or bedridden unless assisted

Figure 8. HY scale from I to V based on Hoehn & Yahr 1967.

James Parkinson described the motor problems of the PD patients accurately, while also recognizing the presence of several non-motor features (Parkinson, 1817). Non-motor symptoms may appear years before motor onset. They are linked to widespread neurodegeneration beyond the dopaminergic system, including involvement of the noradrenergic, serotonergic, and cholinergic pathways. Non-motor symptoms include cognitive impairment that in PD range from mild executive dysfunction to dementia, psychiatric symptoms such as depression and anxiety, autonomic dysfunction, including orthostatic hypotension, constipation, and urinary disturbances, sleep disorders such as REM sleep behavior disorder, and sensory deficits, particularly olfactory dysfunction (Chaudhuri et al., 2006). PD reduces patients' quality of life and places a substantial economic burden on society. While the cardinal motor symptoms define PD, non-motor manifestations significantly contribute to disease burden. Inadequate recognition of non-motor symptoms increases the overall cost of care for patients with the disease within society.

2.2.1.4 Neuropathological criteria of Parkinson's disease

A neuropathological diagnosis of PD requires the presence of neuronal loss in the SN and at least one LB in either the SN or the locus coeruleus (LC) (Daniel & Lees, 1993; Gelb et al., 1999). Neurodegeneration is most pronounced in the ventral part of the SN (Fearnley & Lees, 1991). Evidence of other parkinsonism causing diseases, such as PSP or MSA, are regarded as exclusion criteria (Gelb et al., 1999).

The neuropathological diagnosis of PD is based on immunohistochemical assessment and McKeith staging of α-synuclein–positive LBs and Lewy neurites (LN) (McKeith et al., 2017). While this approach seems straightforward, it can be complex in practice, as some patients may exhibit typical symptoms and SN neuron loss without the presence of LBs (Forno, 1996). Additionally, incidental LBs can occur with normal aging in 5–55% of the elderly population (Jellinger, 2019). Standardized methods for assessing neuronal loss in the SNc use a semiquantitative grading system, typically involving a transverse midbrain slice at the level of the third cranial nerve. This section allows the evaluation of relevant nuclear groups, with neuronal loss assessed through hematoxylin and eosin or similar stains, comparing neuronal density to schematic examples of varying severity.

2.2.2 Multiple system atrophy (MSA)

The origins of MSA trace back to the early 20th century. In 1900, J. Dejerine and A. Thomas described patients with sporadic ataxia who later developed extrapyramidal and autonomic symptoms, with neuropathology revealing olivopontocerebellar atrophy (Quinn, 1989). In 1925, S. Bradbury and C. Egglestone described neurogenic orthostatic hypotension, a clinical entity later recognized as part of the spectrum of MSA (Bradbury, 1925). In 1960, G.M. Shy and G.A. Drager described a syndrome of autonomic failure, parkinsonism, and ataxia, later linked to striatonigral and cerebellar degeneration (Adams et al., 1961; Shy & Drager, 1960). Recognizing a common pathological basis, J.G. Graham and D.R. Oppenheimer introduced the term "multiple system atrophy" in 1969 (Graham & Oppenheimer, 1969).

Glial cytoplasmic inclusions and their identification as α-synuclein deposits in MSA were discovered in 1989 (Papp et al., 1989; Spillantini et al., 1998). Recent research has highlighted early disease markers, such as isolated autonomic failure and REM sleep behavior disorder, years before full MSA onset (Giannini et al., 2018; Iranzo et al., 2006; Kaufmann et al., 2017; Singer et al., 2017).

2.2.2.1 Epidemiology and risk factors

MSA is classified as an orphan disease. Its estimated mean incidence is 0.6 to 3 cases per 100,000 person-years (Poewe et al., 2022). In individuals over 50 years of age, the incidence rate is higher. The estimated point prevalence ranges from 1.9 to 4.9 cases per 100,000 people, increasing to 7.8 per 100,000 in individuals over 40 years of age (Fanciulli & Wenning, 2015; Poewe et al., 2022; Schrag et al., 1999). The parkinsonian subtype (MSA-P) is more common than the cerebellar subtype (MSA-C) in most countries (Gilman et al., 2005; Kim et al., 2011; Köllensperger et al., 2010).

However, in Japan, the cerebellar subtype is more prevalent, possibly due to genetic or epigenetic influences (Watanabe et al., 2002). The disease typically manifests in the sixth decade of life and affects both sexes equally (Ben-Shlomo et al., 1997). Average survival from symptom onset is 6 to 10 years (Klockgether et al., 1998; Wenning et al., 2013), with only a few patients living beyond 15 years (Petrovic et al., 2012).

MSA is generally considered a sporadic disorder, but rare familial cases suggest the existence of monogenic MSA with autosomal dominant or recessive inheritance (Hara et al., 2007; Tseng et al., 2023; Wüllner et al., 2004). For example, functionally impaired variants in the coenzyme Q2 (CoQ2) gene, essential for coenzyme Q10 (CoQ10) biosynthesis, have been identified (Multiple System Atrophy Research Collaboration, 2013), and independent studies have suggested an association between single-nucleotide polymorphisms in SNCA and an increased risk of MSA (Al-Chalabi et al., 2009; Scholz et al., 2009). No environmental factors are known to influence the risk of MSA.

2.2.2.2 Pathogenesis

The mechanisms underlying MSA pathogenesis remain incompletely understood. Evidence from preclinical and postmortem studies suggests that both neuronal and glial dysfunction contribute to the disease, recently classified as an oligodendroglioneural α-synucleinopathy (Jellinger, 2018).

α-Synuclein is a small protein involved in synaptic vesicle transport, and is not typically expressed in adult oligodendrocytes, including those in MSA (Miller et al., 2005; Monzio Compagnoni & Di Fonzo, 2019). Early pathogenic events in MSA include the mislocalization of p25α, a myelin stabilizer, leading to oligodendrocyte swelling (Song et al., 2007). This is followed by increased α-synuclein accumulation, which neighboring neurons cannot degrade (Bukhatwa et al., 2010; Reyes et al., 2014). Interaction between p25α and α-synuclein promotes its aggregation into insoluble oligomers and glial cytoplasmic inclusions. These inclusions activate microglia, triggering inflammation and oxidative stress (Fellner et al., 2013; Stefanova et al., 2012). Dysfunctional oligodendrocytes release misfolded α-synuclein into the extracellular space, forming fibril-shaped aggregates that induce neuronal cytoplasmic inclusions (Peng et al., 2018). Neuroinflammation, loss of glial-derived neurotrophic support, and mitochondrial dysfunction further drive neuronal degeneration (Monzio Compagnoni & Di Fonzo, 2019; Ubhi et al., 2009). In a prion-like manner, toxic α-synuclein species propagate to functionally connected brain regions (Watts et al., 2013). This cascade of events leads to the characteristic degeneration of the basal ganglia, cerebellum, and autonomic nervous system, resulting in the motor and autonomic symptoms of MSA.

2.2.2.3 Symptoms

MSA is classified into MSA-P and MSA-C subtypes, with overlapping clinical features (Wenning et al., 2022; Krismer & Wenning, 2017). MSA-P is characterized by rapidly progressive parkinsonism with poor or transient levodopa response (Krismer & Wenning, 2017). The motor findings are usually symmetrical but, in some patients, asymmetrical. Unlike in –PD, classical "pill-rolling" rest tremor is rare, whereas irregular postural and action tremors with jerky movements are seen in up to 50% of cases (Köllensperger et al., 2010). Drug-induced dyskinesias, including dystonia, may develop in some cases (Boesch et al., 2002). MSA-C primarily presents with cerebellar ataxia (Bensimon et al., 2009; Köllensperger et al., 2010), leading to a wide-based gait, limb incoordination, action tremor, and nystagmus (Wenning et al., 2022). Hyperreflexia and a Babinski sign are seen in 30–50% of patients (Köllensperger et al., 2010). Abnormal postures, including antecollis, bent spine, and limb dystonia, are common (Köllensperger et al., 2008). As the disease progresses, patients develop dysarthria, dysphagia, and frequent falls.

MSA patients have a prodromal phase in 20–75% of cases, with symptoms such as sexual dysfunction, urinary incontinence or retention, orthostatic hypotension, inspiratory stridor, and REM sleep behavior disorder appearing months to years before motor symptoms emerge (Jecmenica-Lukic et al., 2012).

Autonomic failure is a hallmark of MSA and can be present early in the disease course. Urogenital dysfunction is common, including erectile dysfunction in men and genital hyposensitivity in women, as well as urinary urgency, incontinence, nocturia, and incomplete bladder emptying. Severe orthostatic hypotension is the main feature of cardiovascular autonomic failure and may be asymptomatic or cause syncope, dizziness, weakness, and nausea (Wenning et al., 2022). Respiratory complications, including inspiratory stridor and sleep apnea, affect a substantial portion of patients, often in later disease stages (Köllensperger et al., 2008; Fanciulli & Wenning, 2015; Wenning et al., 2022). Other autonomic disturbances include constipation, impaired thermoregulation, and reduced sweating (Fanculli & Wenning, 2015; Lipp et al., 2009; Sakakibara et al., 2004).

Cognitive impairment is uncommon, but frontal-lobe dysfunction with attention deficits, depression, anxiety, and panic attacks can occur (Köllensperger et al., 2008; Stankovic et al., 2014). Dementia or visual hallucinations should prompt consideration of DLB rather than MSA (Gilman et al., 2008; Wenning et al., 2022).

MSA is characterized by a steadily worsening disease course, with a median survival of 6–10 years (Wenning et al., 2013). Within three years, half of patients require walking aids (Watanabe et al., 2002), and by five years, 60% need a wheelchair (Klockgether et al., 1998). The median time before the patient is bedridden is 6 to 8 years (Watanabe et al., 2002). Death often results from bronchopneumonia, urosepsis, or sudden respiratory failure due to brainstem

dysfunction. Factors predicting rapid progression include older age, a parkinsonian phenotype, and early autonomic failure, whereas a cerebellar subtype predicts slower progression (Wenning et al., 2013).

2.2.2.4 Neuropathological criteria of MSA

The definitive diagnosis of MSA relies on neuropathological examination. The Movement Disorder Society (MDS) neuropathological criteria require widespread α-synuclein–positive glial cytoplasmic inclusions alongside neurodegeneration in striatonigral and olivopontocerebellar systems for a definitive diagnosis (Wenning et al., 2022). Neuropathological changes vary by subtype: MSA-P shows degeneration in the SN and Put, while MSA-C primarily affects pontocerebellar structures. Though clinical criteria have improved, neuropathological confirmation remains essential to distinguish MSA from other neurodegenerative disorders like PD.

2.2.3 Progressive supranuclear palsy (PSP)

PSP was first described in 1964 by Steele, Richardson, and Olszewski as a distinct neurodegenerative disorder characterized by postural instability, vertical gaze palsy, and cognitive impairment (Steele et al., 1964). At that time, PSP was often misdiagnosed as PD or other movement disorders due to overlapping symptoms. Over time, research has expanded the understanding of PSP, revealing multiple clinical subtypes with varying presentations. Despite advances in diagnostic tools such as imaging and biomarkers, PSP remains a challenging disease to diagnose early. No disease-modifying treatments exist, making symptom management the primary focus of care (Lamb et al., 2016).

2.2.3.1 Epidemiology and risk factors

The epidemiology of PSP has been primarily studied in cases of PSP-Richardson syndrome (PSP-RS). The prevalence of PSP is generally estimated at around 5–6.4 per 100 000, with incidence rates ranging from approximately 0.16 to 2.6 per 100 000 person-years depending on the diagnostic criteria and population studied (Kukkle et al., 2025; Lyons et al., 2023). The median survival time is about 7 years (Golbe & Ohman-Strickland, 2007).

The discovery of multiple PSP subtypes suggests the disease is more common than previously believed. An autopsy study of 100 PSP cases found that nearly half did not present with PSP-RS (Respondek et al., 2014). A broader epidemiological study reported a PSP prevalence of 17.9 per 100,000, with PSP-RS accounting for

14.3 per 100,000 (Takigawa et al., 2016). Additionally, forensic and community autopsy series reveal PSP pathology in 3–6.7% of cases, raising questions about its true frequency, particularly when occurring alongside other neurodegenerative diseases (Dugger, Hentz, et al., 2014; Kovacs et al., 2013; Yoshida et al., 2017).

PSP is a sporadic neurodegenerative disorder of unknown etiology (Boxer et al., 2017). Environmental factors have been hypothesized to contribute to its development, with early suspicions arising from a PSP-like syndrome in Guadeloupe linked to the consumption of Annona Muricata, a fruit containing neurotoxic alkaloids (Champy et al., 2004; Champy et al., 2005; Lannuzel et al., 2003). However, case-control studies have yielded inconsistent results regarding pesticide exposure as a risk factor, while drinking well water has been implicated in one large study (Litvan et al., 2016). Due to the rarity of PSP, identifying environmental risks remains challenging.

Although familial cases are rare, mutations in the *MAPT* gene can cause PSP pathology (Höglinger et al., 2017; Im et al., 2015). The strongest genetic risk factor is the *MAPT* H1 haplotype, particularly its H1c sub-haplotype, which is significantly more common in PSP patients (Baker et al., 1999; Pittman et al., 2005). Genome-wide association studies (GWAS) have corroborated the *MAPT* gene's importance and identified additional risk loci, including *STX6*, *MOBP*, and *EIF2AK3* (Höglinger et al., 2011). Other genetic variants in *CXCR4*, *EGFR*, and *GLDC* may also contribute. Furthermore, genetic factors appear to influence PSP phenotypes and disease onset (Jabbari et al., 2019).

2.2.3.2 Pathogenesis

PSP is classified as a primary tauopathy, both genetically and neuropathologically (Höglinger et al., 2011), characterized by the accumulation of hyperphosphorylated tau in neurons and glial cells, particularly in the basal ganglia, brainstem, and frontal cortex (Kovacs, 2015). This tau pathology disrupts cellular function, and leads to neuronal loss, gliosis, and widespread brain atrophy.

The molecular mechanisms underlying tau aggregation in PSP involve dysfunction in tau phosphorylation, clearance, and interactions with microtubules. Additionally, oxidative stress, mitochondrial dysfunction, and neuroinflammation contribute to disease progression by exacerbating tau pathology and neuronal damage (Haque et al., 2019; Nilson et al., 2017).

Unlike in AD, where tau pathology primarily affects the temporal lobes, PSP predominantly targets frontal regions and brainstem (Heikkinen et al., 2022; Kovacs et al., 2020). Despite advances in understanding PSP's pathogenesis, no disease-modifying therapies exist.

2.2.3.3 Symptoms

Like PD and MSA, neurodegenerative diseases often begin with a presymptomatic phase where pathology accumulates without clinical symptoms. Evidence suggests a similar process in PSP, as mild PSP pathology has been found in some asymptomatic elderly individuals, indicating that many cases may not progress to overt disease (Dugger, Hentz, et al., 2014; Nogami et al., 2015; Yoshida et al., 2017).

Presymptomatic PSP occurs in individuals who are asymptomatic but at risk of developing PSP symptoms. The MDS PSP criteria (Höglinger et al., 2017), which focus on clinical diagnosis, do not account for the presymptomatic phase, though they align with this concept. Autopsy studies support the existence of presymptomatic PSP. For example, one community-based study using brain autopsies detected PSP pathology in 2.1% of 233 individuals (Kovacs et al., 2013). Two similar autopsy studies found PSP pathology in 4.2% of 119 clinically healthy elderly individuals (Dugger, Hentz, et al., 2014) and in 4.6% of 626 people over 60 years (Yoshida et al., 2017). These findings contrast with the low estimated prevalence of clinically diagnosed PSP-RS (Coyle-Gilchrist et al., 2016), suggesting that many individuals with PSP pathology may never develop symptoms. At early symptomatic phase individuals show mild clinical signs of PSP but do not meet full diagnostic criteria. Symptoms may include isolated saccadic slowing or unexplained postural instability (Respondek et al., 2014).

PSP presents with distinct clinical phenotypes, the most common being PSP-RS. PSP-RS is the classic and most recognized form, originally defined in the 1996 National Institute for Neurological Disorders and Society for PSP research criteria (Litvan, Agid, et al., 1996). It typically begins with unexplained falls, unsteady gait, and bradykinesia. Subtle personality changes, including apathy and disinhibition, often accompany early cognitive slowing and executive dysfunction, making daily tasks increasingly challenging. Speech becomes slow, ataxic, spastic, and hypophonic, and dysphagia progressively impairs swallowing (Williams & Lees, 2009). Ocular motor dysfunction is a hallmark of PSP-RS. Early signs include slowing of vertical saccades, difficulty reading, and apraxia of eyelid opening. The defining feature, vertical supranuclear gaze palsy, emerges later, typically 3–4 years after onset.

The parkinsonism variant of PSP (PSP-P), associated with a less severe course of the disease, is the second most common and is diagnosed in 14–35% cases of PSP (Caso et al., 2018). PSP-P mimics PD with asymmetric tremor, bradykinesia, and initial levodopa responsiveness. However, it progresses faster than PD, with fewer levodopa-induced dyskinesias and less autonomic dysfunction (Ling, 2016). Most PSP-P cases eventually develop PSP-RS features.

PSP with progressive gait freezing (PSP-PGF) presents as isolated gait freezing and start hesitation, often preceding other PSP symptoms by years (Owens et al.,

2016). Unlike PD, PSP-PGF lacks early tremor or rigidity, but it is strongly predictive of PSP pathology (Williams & Lees, 2009). Over time, additional PSP features emerge, confirming the diagnosis.

PSP-Corticobasal Syndrome (PSP-CBS) shares clinical features with CBD, including progressive limb rigidity, apraxia, cortical sensory loss, and alien limb phenomena. Due to substantial overlap with CBD, distinguishing PSP-CBS from CBD before autopsy remains difficult (Ling et al., 2010).

PSP-Speech and Language (PSP-SL) manifests initially as nonfluent speech and language impairments, including agrammatism and apraxia of speech (Gorno-Tempini et al., 2011). These deficits progressively worsen before motor symptoms of PSP-RS emerge (Josephs et al., 2014; Santos-Santos et al., 2016). Most cases exhibit tau pathology post-mortem, supporting their classification as a PSP variant (Spinelli et al., 2017).

PSP-Frontal Presentation (PSP-F) is a rare phenotype. PSP-F mimics behavioral variant frontotemporal dementia (bvFTD), presenting with personality, behavioral, and cognitive changes (Rascovsky et al., 2011). Early symptoms include apathy, disinhibition, compulsivity, and social inappropriateness. As the disease progresses, motor dysfunction consistent with PSP-RS becomes apparent, confirming the diagnosis. In a Mayo Clinic study, only 4.5% of 66 autopsy-confirmed PSP cases exhibited these symptoms (Hassan et al., 2012). However, a European study reported a higher prevalence, with 12% of 100 autopsy-confirmed PSP cases presenting FTD-like features at disease onset (Respondek et al., 2014).

PSP with predominant cerebellar ataxia (PSP-C) is a rare phenotype presenting with cerebellar ataxia before developing PSP-RS features. A study identified only five PSP-C cases among 1,085 autopsy-confirmed PSP patients, with four clinically misdiagnosed as multiple system atrophy type C (Koga et al., 2016). Due to diagnostic challenges, PSP-C is not included in the new MDS PSP criteria.

Some PSP patients have additional neuropathologies influencing their clinical presentation, including AD or PD, TDP-43 deposition, and cerebrovascular disease. In a study of 64 PSP cases, for example, 36% had Alzheimer's pathology, 20% had Parkinson's, and 44% had argyrophilic grain disease (Dugger, Adler, et al., 2014). Eventually, most PSP patients need a wheelchair and often die after an average of 8 years as a result of aspiration. PSP patients often show significant clinical and diagnostic overlap with FTD syndromes, in addition to other parkinsonian disorders, highlighting the need for more accurate and specific diagnostic criteria (Heikkinen et al., 2025).

2.2.3.4 Neuropathological criteria of PSP

The 1996 National Institute of Neurological Disorders and Stroke criteria for PSP require tau-based neurofibrillary tangles or neuropil threads in the basal ganglia and brainstem (Litvan, Hauw, et al., 1996). PSP pathology includes neuronal loss, gliosis, tufted astrocytes, and oligodendroglial coiled bodies (Dickson et al., 2010). Recently, the PSP neuropathological criteria have been updated to stipulate detection methods (phosphorylated tau immunohistochemistry) and glial tau pathology (Roemer et al., 2022). The regional distribution of tau pathology contributes to clinical heterogeneity, with more cortical involvement in PSP-CBS (Ling et al., 2014), PSP-SL (Spinelli et al., 2017), and PSP-F, and brainstem-predominant pathology in PSP-P and PSP-PGF. PSP-P and PSP-PGF, show less cortical tau pathology but greater degeneration in the globus pallidus, subthalamic nucleus, and substantia nigra than PSP-RS (Williams & Lees, 2009). Studies suggest different PSP phenotypes arise from tau's selective spread through functionally connected brain networks (Gardner et al., 2013). Experiments with tau transgenic mice show that PSP-associated tau strains can spread in a prion like manner (Clavaguera et al., 2013; Sanders et al., 2014).

2.2.4 The treatment of parkinsonism

The treatment of Parkinsonism encompasses many strategies, including pharmacological therapy, device-aided therapies, physical interventions, and supportive care tailored to the specific disorder (Hayes, 2019; Levin et al., 2016; Seppi et al., 2011). PD, MSA, and PSP each require an individualized approach to management, though they share some common therapeutic principles.

At early stages, PD responds well to dopaminergic medications, particularly levodopa combined with aromatic L-amino acid decarboxylase (AADC) inhibitors, such as carbidopa or benserazide, which prevents peripheral breakdown of levodopa, thereby enhancing its brain availability while reducing side effects like nausea. Levodopa remains the most effective treatment for PD, and nearly all patients require it at some stage. As a precursor to dopamine, it crosses the blood-brain barrier (BBB), allowing surviving dopaminergic neurons to boost dopamine production and alleviate symptoms. Other drugs, such as dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors, help manage motor symptoms by directly acting on the dopamine receptor or making more dopamine available in the brain. Advanced cases may benefit from DBS, and infusion therapies, such as continuous intrajejunal delivery of levodopa-carbidopa intestinal gel (LCIG) infusion, levodopa-entacapone-carbidopa intestinal gel (LECIG) infusion, and continuous subcutaneous apomorphine infusion (CSAI) (van Laar et al., 2023). Foslevodopa/foscarbidopa is a novel, water-soluble formulation of levodopa and carbidopa prodrugs,

administered via a continuous 24-hour subcutaneous infusion using an infusion set and a portable pump (Rosebraugh et al., 2021). Non-motor symptoms like depression and cognitive impairment require additional therapies (Seppi et al., 2011).

MSA is less responsive to dopaminergic therapy. Approximately one-third of patients with MSA-P experience an improvement in hypokinetic-rigid symptoms with levodopa treatment (Constantinescu et al., 2007). Currently, no effective treatment is available for ataxia. Treatment focuses on managing autonomic dysfunction, and other vegetative symptoms, as these significantly impact patients' quality of life (Schrag et al., 2006). Additionally, speech therapy, occupational therapy, and physiotherapy are advised.

PSP also has limited response to medication, and its treatment remains purely symptomatic (Stamelou et al., 2010). Key therapeutic targets include akinetic-rigid symptoms, oculomotor impairments, neuropsychological deficits, as well as occasional dystonia and sleep disturbances. Additionally, speech therapy and physiotherapy are recommended to reduce the risk of aspiration and falls.

2.2.4.1 Levodopa

Levodopa has been central to PD treatment for over half a century. Its therapeutic journey began in the early 20th century when it was first isolated from seedlings of the Vicia faba plant between 1910 and 1913 (Guggenheim, 1913). The discovery of levodopa decarboxylase in 1938 (Holtz et al., 1938), the enzyme responsible for converting levodopa to dopamine, was pivotal in understanding its potential role in neurochemistry. By 1957, dopamine was identified in the brain (Montagu, 1957; Weil-Malherbe & Bone, 1957), and two years later, it was found to be concentrated in the basal ganglia (Bertler & Rosengren, 1959), suggesting its involvement in motor control. These findings led to the hypothesis that dopamine deficiency might underlie PD symptoms (Carlsson, 1959). In 1960, postmortem analyses confirmed a significant dopamine deficit in the striatum of PD patients (Ehringer & Hornykiewicz, 1960), providing a rationale for dopamine replacement therapy using levodopa. The first successful clinical trial in 1961 demonstrated levodopa's remarkable efficacy in alleviating PD symptoms (Birkmayer & Hornykiewicz, 1961). Subsequent advancements included the introduction of chronic high-dose oral levodopa regimens in 1967 (Cotzias et al., 1967) and the combination of levodopa with dopa decarboxylase inhibitors, such as carbidopa, in the early 1970s to enhance its effectiveness and reduce side effects (Birkmayer et al., 1974; Markham et al., 1974; Papavasiliou et al., 1972; Yahr et al., 1971). Today, levodopa remains the gold standard in PD treatment, offering significant symptomatic relief despite ongoing challenges such as motor complications associated with long-term use.

Levodopa's absorption is variable and oral bioavailability low, primarily due to extensive presystemic metabolism. After oral administration, levodopa is absorbed quickly primarily in the proximal small intestine via a saturable transport system that also handles large neutral amino acids, making it susceptible to competition from dietary proteins. Only 30% of the orally administered dose enters the systemic circulation (Contin & Martinelli, 2010). Consequently, food intake, especially protein-rich meals, can lead to inconsistent absorption and plasma concentration fluctuations. Fasting significantly speeds up levodopa absorption, with peak plasma levels (t_{max}) reached in 15-60 minutes (Baruzzi et al., 1987; Nutt et al., 1984). Taking levodopa 30 minutes after a meal delays t_{max} by two- to threefold and lowers peak plasma concentration by about 30% (Baruzzi et al., 1987). Consistently dosing at least 30 minutes before meals help stabilize plasma levels and reduces variability in bioavailability.

Levodopa is also subject to extensive peripheral metabolism. Once absorbed, levodopa undergoes rapid peripheral metabolism by AADC and catechol-O-methyltransferase (COMT), resulting in a short plasma half-time of approximately 50 minutes when administered alone. Therefore, levodopa is commonly administered in combination with a peripheral AADC inhibitor, such as carbidopa, and in some treatment regimens with COMT inhibitors like entacapone. However, levodopa's half-life is short even when administered with concomitant peripheral inhibitors, ranging from 0.7 to 1.4 h in chronically treated patients (Contin et al., 1990). The short half-life of levodopa results in pulsatile stimulation of dopamine receptors, which is thought to contribute to the development of motor complications such as the wearing-off phenomenon and dyskinesias in patients receiving long-term therapy, although the mechanism remains unclear (Nutt, 1987, 1990). To address these issues, various strategies have been developed. These include altering the timing of levodopa administration in relation to meals, using controlled-release formulations, and implementing continuous intestinal infusions in advanced cases to stabilize plasma drug levels (Contin et al., 1996; Nyholm, 2006; Olanow et al., 2020).

Levodopa, as the precursor to dopamine, alleviates motor symptoms in PD by replenishing dopamine levels in the brain. A significant and lasting response to treatment strongly supports a PD diagnosis. While various therapeutic options exist for early-stage PD, nearly all patients will ultimately require levodopa as the disease progresses. However, not all PD symptoms respond equally to levodopa. Bradykinesia and rigidity tend to show the most significant improvement with dopaminergic therapy, whereas tremor exhibits a more variable response. In contrast, symptoms such as postural instability, micrographia, and speech disturbances are generally less responsive to dopaminergic treatment, suggesting they may result from deficits in other neurotransmitter systems. As PD progresses, patients often require more frequent and higher doses of levodopa. This change is not due to

tolerance but reflects the disease's impact on the brain's ability to store and utilize dopamine (Chou et al., 2018). As the disease advances, patients lose the long-duration response to dopaminergic medications, necessitating more frequent dosing.

However, long-term high-dose use of levodopa in PD, is associated with motor complications, including dyskinesias (abnormal involuntary movements) and motor "wearing-off" fluctuations. These complications affect 75% of patients after 6 years of levodopa therapy (Fahn, 1992). Multiple studies have identified the dosage (Fahn et al., 2004; Poewe et al., 1986) of levodopa therapy as key risk factors for developing motor complications. Studies also suggests that dopamine agonists are significantly less likely to cause these issues (Montastruc et al., 1994; Przuntek et al., 1996; Rinne et al., 1998). The exact mechanism behind levodopa-induced motor complications remains unclear. One hypothesis suggests that levodopa's higher potency and shorter half-life, compared to dopamine agonists, contribute to these effects. Since motor complications are dose-dependent (Fahn et al., 2004), using the lowest effective levodopa dose is recommended. Pulsatile levodopa administration may also play a role (Chase, 1998; Mouradian et al., 1990; Zappia et al., 2000), supporting the use of extended-release formulations or COMT inhibitors to prolong its half-life. However, clinical trials comparing regular and long-acting levodopa preparations have shown no difference in motor fluctuation rates (Block et al., 1997; Koller et al., 1999), and no studies have yet confirmed whether early COMT inhibitor use delays these complications.

For MSA, one diagnostic criterion is "poorly levodopa-responsive parkinsonism" (Litvan et al., 2003; Wenning et al., 2022). However, studies indicate that 30–40% of MSA patients experience at least temporary benefit from levodopa (Colosimo et al., 2005; Maaß et al., 2016). MSA and PD patients differ in levodopa tolerability. MSA patients are more prone to worsening orthostatic hypotension (Burns & McFarland, 2020; Colosimo et al., 2005; Wenning et al., 2005) but less likely to develop levodopa-induced psychiatric effects or motor fluctuations (Wenning et al., 2000). When motor complications occur in MSA, they typically appear within the first five years, often as facial dystonia rather than limb dyskinesias. Notably, some MSA patients develop levodopa-induced involuntary movements even without therapeutic benefit (Wenning et al., 2005).

Levodopa responsiveness in PSP is generally poor, and a marked or prolonged benefit is considered an exclusion criterion for diagnosis (Höglinger et al., 2017; Litvan et al., 2003). Studies indicate that about one-third of PSP patients experience some improvement with levodopa, though the response is typically minimal and short-lived (Lang, 2005; Martin et al., 2021; Nieforth & Golbe, 1993). Levodopa-induced dyskinesias and psychosis have been reported rare. A clinicopathological study identified two PSP subtypes with differing levodopa responses; PSP-RS (54% of cases) showed poor response, while PSP-P (32%) exhibited a moderate initial

benefit, particularly in patients with asymmetric motor features and tremor (Williams et al., 2005). Some PSP patients may experience levodopa-induced worsening of motor symptoms, including exacerbation of parkinsonism, bulbar dysfunction, and gaze palsy (Kompoliti et al., 1998).

One of the most debated issues in PD's treatment has been whether levodopa has neurotoxic effects. Although early in vitro studies suggested potential harm to dopaminergic neurons (Fahn, 1996), clinical evidence is inconclusive. The ELLDOPA study, a placebo-controlled trial, sought to clarify levodopa's impact (Fahn et al., 2004). After 42 weeks, patients on levodopa had better clinical outcomes than those on placebo, suggesting it is not neurotoxic and may even be neuroprotective. However, higher doses were linked to increased motor complications, and imaging data again showed greater declines in dopamine transporter markers with levodopa use, raising concerns about its long-term effects. Nevertheless, more recent studies suggest that levodopa is a good and safe treatment option (Gray et al., 2014; Frequin er al., 2024). Epidemiological and clinical studies, including long-term follow-ups, have not shown that levodopa treatment worsens disease trajectory compared with other dopaminergic therapies, and levodopa is widely regarded as the most effective symptomatic treatment for motor symptoms in all stages of PD (Riederer et al., 2025; Scheperjans, 2024). Improvements in understanding levodopa response have also shown that delaying its initiation does not confer long-term protective effects and may, in fact, delay optimal symptomatic control. While levodopa is associated with motor complications such as dyskinesia and fluctuations, these are pharmacodynamic consequences of long-term therapy rather than evidence of underlying neurotoxicity.

2.2.4.2 Other symptom relieving medication

Pharmacologic treatments for PD primarily target dopamine pathways. Levodopa, dopamine agonists, and MAO-B inhibitors are common initial therapies (Fox et al., 2018). Anticholinergics may help young patients with tremor but require caution due to cognitive risks (Fox et al., 2018).

Dopamine agonists (pramipexole, ropinirole, rotigotine) stimulate dopaminergic receptors in the CNS, alleviating PD's symptoms. While less potent than levodopa, they are preferred for their lower risk of dyskinesias and longer half-life. Their reduced D2 receptor stimulation may explain the decreased dyskinesia risk. However, their broader receptor stimulation can increase the risk of hallucinations, hypotension, somnolence (including sleep attacks), leg edema, and compulsive behaviors like excessive gambling or sexual activity (Garcia-Ruiz et al., 2014), especially in the elderly. It is advisable to consider carbidopa/levodopa in the elderly to minimize complications.

Peripheral COMT inhibitors (entacapone, opicapone, tolcapone) and central MAO-B inhibitors (rasagiline, selegiline) prevent the breakdown of levodopa and dopamine, extending the effects of carbidopa/levodopa (Fabbri et al., 2022; Tan et al., 2022). However, they may increase levodopa side effects, including hallucinations, dyskinesia, and nausea. MAO-B inhibitors can also interact with certain drugs, raising the risk of serotonin syndrome.

In cases of severe "off" periods, therapies like subcutaneous apomorphine injections (Pessoa et al., 2018) or inhaled/soluble levodopa (LeWitt et al., 2019) can provide quicker responses. These medications can be administered multiple times a day to address fluctuating symptoms. For managing dyskinesias, reducing dopaminergic medication doses or adding amantadine may be effective (Fox et al., 2018). Amantadine, particularly in its extended-release form, is FDA-approved for treating dyskinesias in PD (Pahwa et al., 2017). However, the EMA has not granted a centralised marketing extended-release authorisation for this indication in the EU.

While dopaminergic therapies address motor symptoms, nonmotor symptoms require treatments targeting different neurotransmitter systems. For PD dementia, rivastigmine is considered clinically useful (Seppi et al., 2019). Other cholinesterase inhibitors, such as donepezil and galantamine, have more limited supporting evidence. Memantine, commonly used for AD, lacks efficacy for PD dementia. Antidepressants, including selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants, can help manage depression in PD, with pramipexole, also providing benefits for some patients (Seppi et al., 2019).

For treating PD psychosis, the first step is to reduce medications that may contribute to the symptoms, such as dopamine agonists, amantadine, or levodopa. If psychosis persists, medications like pimavanserin, clozapine, or quetiapine may be considered (Seppi et al., 2019). Pimavanserin is the only FDA-approved drug for PD psychosis, though its long-term safety remains uncertain (Cummings et al., 2014; Seppi et al., 2019). However, the drug is not available in Europe. Clozapine has proven effective, but its use requires careful monitoring for severe side effects, including neutropenia. Quetiapine, while commonly prescribed due to its convenience, lacks robust evidence supporting its efficacy for PD psychosis.

Sleep disturbances, fatigue, and excessive daytime sleepiness are frequent and disabling in PD. However, there are no pharmacological treatments with established efficacy for these issues (Elbers et al., 2015; Seppi et al., 2019). Non-drug approaches, including cognitive-behavioral therapy, may be useful. For REM sleep behavior disorder, melatonin and clonazepam are first-line treatments, though evidence remains limited (Howell & Schenck, 2015). Autonomic symptoms like orthostatic hypotension and constipation are common in PD and especially in MSA. Fludrocortisone, midodrine, and droxidopa may help manage orthostatic hypotension, while various laxatives and prokinetic agents are used to address constipation (Seppi et al., 2019).

There is limited evidence for treatments specific to PD-related urinary symptoms, though sildenafil is helpful for sexual dysfunction. Botulinum toxin injections remain the most effective therapy for sialorrhea (Seppi et al., 2019).

2.2.4.3 Other treatment modalities

Different exercise modalities benefit various motor symptoms, improving mobility, balance, and function. Physiotherapy, occupational therapy, and speech therapy (for speech and swallowing difficulties) are also valuable in managing PD and atypical parkinsonisms (Fox et al., 2018; Mak et al., 2017; Tomlinson et al., 2013). Interdisciplinary therapy referrals are essential for comprehensive care.

Advanced treatment options such as DBS, magnetic resonance imaging- (MRI) guided focused ultrasound, and levodopa-carbidopa enteral suspension therapy require evaluation at specialty centres. These interventions are suitable for patients with medication-responsive motor symptoms who experience complications like dyskinesias or off periods despite medication adjustments. DBS and focused ultrasound targeting the thalamus can help treat medication-refractory tremors. DBS involves surgically implanting leads into the subthalamic nucleus or globus pallidus interna, which are connected to a battery in the chest, similar to a pacemaker. After recovery, patients undergo programming visits to optimize stimulation parameters and medication regimens. DBS helps manage motor fluctuations, tremors, and dyskinesias (Fox et al., 2018). For tremor-predominant PD, ventralis intermedius nucleus (thalamic) DBS, MRI-guided focused ultrasound, or traditional thalamotomy may be used (Bond et al., 2017). Focused ultrasound creates a lesion in the thalamus to reduce tremors, improving on-medication tremor scores by 62% (Bond et al., 2017). However, it is currently performed unilaterally due to potential adverse effects on speech and balance. Factors associated with poorer DBS outcomes include advanced age (≥75 years), cognitive impairment, and levodopa-unresponsive symptoms such as balance disturbances (Moro et al., 2016). Screening tools, including questionnaires and online assessments, can help identify suitable candidates (Okun et al., 2004).

2.3 The role of neuroinflammation in neurodegenerative diseases

In 1975, immune-related proteins were first detected in senile plaques of AD patients (Rogers et al., 1988). By the 1980s, microglial activation was recognized in several neurodegenerative diseases, including AD, PD, and ALS (McGeer, Itagaki, Boyes, et al., 1988; McGeer, Itagaki, & McGeer, 1988; McGeer et al., 1987), though inflammation was seen as a secondary effect rather than a cause. In the 1990s, studies

showed long-term NSAIDs use reduced AD risk by up to 50%, sparking interest in neuroinflammation's role (Kinney et al., 2018). Research on microglia's origin, function, and toxicity has deepened understanding of their link to neurodegeneration (Banati et al., 1993; Dickson et al., 1993; Ling & Wong, 1993; McGeer et al., 1993).

2.3.1 Neuroinflammation

Inflammation is the body's natural response mechanism against infections, injuries, and harmful stimuli. It involves immune cells, cytokines, and signaling pathways that help eliminate threats and promote tissue repair. Acute inflammation is a short-term response characterized by swelling, redness, heat, and pain, while chronic inflammation can lead to persistent tissue damage and contribute to diseases such as arthritis, cardiovascular disorders, cancer, and neurodegenerative diseases (Fernandez et al., 2019; Karin, 2006).

Chronic inflammation is increasingly recognized as a key element in neurodegenerative diseases (Hammond et al., 2019). Previously considered a consequence of protein buildup, immune signaling is now believed to actively drive protein aggregation early in neurodegenerative disease (Hong et al., 2016; Shi et al., 2017; Sosna et al., 2018). While the immune system typically maintains homeostasis and resolves inflammation after clearing threats (Bernier et al., 2020; Hanisch & Kettenmann, 2007), persistent stimuli can lead to chronic inflammation and the release of neurotoxic factors. These stimuli include internal factors like protein aggregates (Hammond et al., 2019), environmental triggers such as infections, gut dysbiosis, aging, and diet (Fairley et al., 2022; Mou et al., 2022; Park & Kim, 2021), and genetic risks like *PGRN* and *APOE4* mutations (Duro et al., 2022; Zheng et al., 2022).

The CNS is populated by neurons and neuroglial cells, which contribute to the mechanisms of neuroinflammation. Neuroglial cells include astrocytes, oligodendrocytes, microglia and ependymal cells. Microglia are the resident immune cells of the CNS. In a resting state, they constantly survey the CNS for signals of damage or infection (Colonna & Butovsky, 2017). When triggered by stimuli such as neuronal injury, amyloid-β, or α-synuclein aggregates, they become activated and shift into different phenotypes (Gao et al., 2023). The pro-inflammatory M1 phenotype releases cytokines tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β), and IL-6, along with ROS contributing to neuronal damage (Lull & Block, 2010). Conversely, the M2 phenotype supports tissue repair through anti-inflammatory signals like IL-10 and transforming growth factor-beta (TGF-β). The balance between these states is vital, as sustained M1 activation is linked to neurodegenerative diseases. Key regulators such as NF-κB drive pro-inflammatory responses, while pathways like STAT6 promote repair.

Astrocytes are the most abundant glial cells in the CNS. They are recognized as active participants in the immune response. They become reactive in response to injury or disease, adopting proinflammatory or anti-inflammatory phenotypes (Giovannoni & Quintana, 2020). Activated astrocytes release pro-inflammatory cytokines such as IL-1, IL6, and TNF- α influencing neurons and microglia. Microglial signals—particularly IL-1α, TNF-α, and C1q—can drive astrocytes into a neurotoxic "A1" state. These A1 astrocytes exacerbate inflammation and contribute to neuronal death, shifting from supportive roles to drivers of neurodegeneration.

Although the CNS is traditionally considered immune-privileged, pathological conditions can disrupt the BBB, allowing peripheral immune cells like T cells, B cells, and macrophages to infiltrate and contribute to neuroinflammation (Zang et al., 2022). In diseases such as MS, autoreactive Th1 and Th17 cells cross the BBB, promoting demyelination through cytokines like IFN-γ and IL-17. Also, peripheral macrophages, when recruited to CNS, can contribute by releasing pro-inflammatory cytokines and phagocytosing neuronal debris (Goverman, 2009; Kamma et al., 2022). In contrast, regulatory T cells (Treg) help control inflammation by suppressing effector T cells and releasing IL-10 and TGF-β.

Neuroinflammation is driven by key molecular pathways that regulate immune cell activation in the CNS. These include NF-κB, JAK-STAT, MAPK, and the NLRP3 inflammasome, which respond to triggers like infections, misfolded proteins, and cellular stress, and amplify inflammatory responses and exacerbate neuronal damage (Zhang et al., 2023). **Figure 9** presents the neuroinflammatory mechanisms contributing to neurodegeneration.

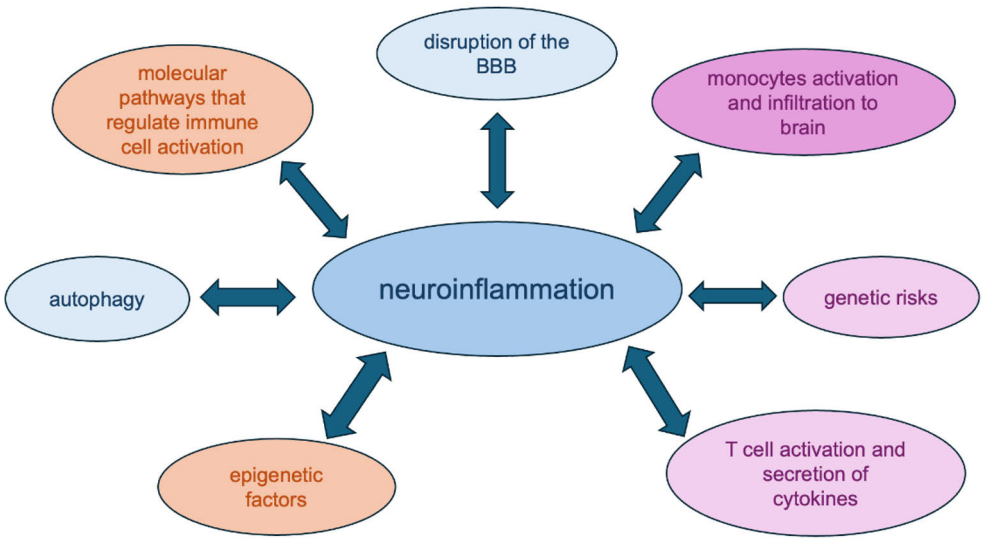

Figure 9. Neuroinflammatory mechanisms and factors contributing to neurodegeneration.

2.3.2 T cells

T cells are a type of white blood cell known as lymphocytes and are essential to the immune response. They constitute a central component of the adaptive immune system, which is characterized by antigen specificity, immunological memory, and tightly regulated cellular responses. Two main types of T cells are cytotoxic T cells that kill infected or abnormal cells, and helper T cells which coordinate the immune response by signaling other cells like B cells, macrophages, and cytotoxic T cells (Zhu & Paul, 2008). T cells express the cell membrane marker cluster of differentiation (CD)3. Among T cells, the subgroups cytotoxic and helper T cells can be identified by the expression of CD8 and CD4, respectively. An essential role in the immune system plays also Treg cells, which help prevent excessive immune activity and protect the body from attacking its own healthy cells. **Figure 10** presents the T cells.

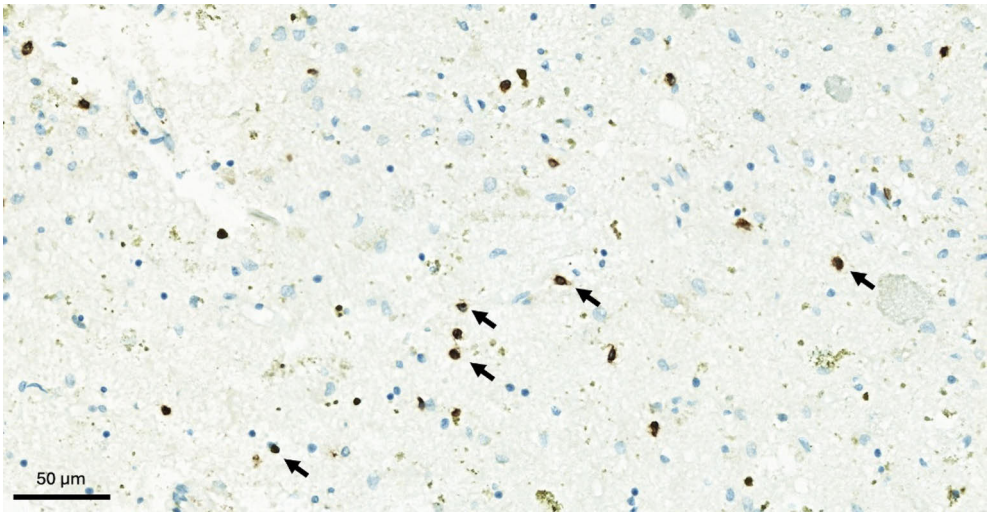

Figure 10. CD3+ T cells (arrows) from the SNc of a PSP patient. CD3 immunohistochemical staining.

T cell activation begins when an antigen-presenting cell (APC) detects a threat and displays a fragment of it on a major histocompatibility complex (MHC) molecule (Davis & Dustin, 2004; Grakoui et al., 1999). Cytotoxic T cells recognize antigens on MHC-I via their CD8 receptor, while helper T cells bind MHC-II via CD4. This specific interaction activates the T cell, triggering its immune function.

T cells originate in the bone marrow and migrate to the thymus, where they mature and undergo rigorous selection to ensure they respond only to threats and not to healthy cells (Koch & Radtke, 2011). Once matured as either CD4+ or CD8+ T

cells, they travel to lymphatic tissues like lymph nodes, spleen, and tonsils, or circulate in the bloodstream, staying on alert for infection. Under normal conditions, BBB restricts T cell entry into the brain (Abbott et al., 2010; Galea et al., 2007). However, during inflammation, infection, or injury, the BBB can become more permeable, allowing activated T cells to enter the brain and participate in immune defense or, in some cases, contribute to neuroinflammation (Varatharaj & Galea, 2017).

In neurodegenerative diseases like AD and PD, antigen-specific T cells migrate from the peripheral immune system into the CNS, where they engage with resident immune glial cells, influencing neuroinflammation and impacting neuronal survival. Additionally, multiple alleles and variants of HLA genes have been identified as risk factors for both AD and PD (Hamza et al., 2010; Wang et al., 2020). GWAS have uncovered a shared genetic pathway between PD and autoimmune disorders, involving HLA-DR and various inflammatory genes (Pierce & Coetzee, 2017; Witoelar et al., 2017). Multiple studies have also demonstrated the role of T cells in PD, both in human patients and in mouse models (Brochard et al., 2009; Yan et al., 2021). In MSA, evidence of T cell infiltration into the CNS has also been demonstrated in a mouse model (Williams et al., 2020). Regarding PSP, research on T cell infiltration in the brain is more limited.

2.3.3 Microglia

Microglia are the resident immune cells of the CNS and constitute the brain's principal component of the innate immune system, playing pivotal roles in maintaining brain homeostasis, synaptic remodeling, and responding to injury or disease (Nayak et al., 2014). Microglia make up approximately 10–15% of all glial cells and are commonly known as the resident macrophages of the CNS. Microglia originate from yolk sac progenitors during early embryonic development, and lodge CNS via the circulatory system (Ginhoux et al., 2010). Resting microglia in the adult brain have a small cell body and a highly ramified morphology that differentiates them from macrophages and dendritic cells (Nayak et al., 2014). Resting microglial cells can be activated by various pathological stimuli in the CNS, such as infection, brain trauma, stroke, and neurodegeneration. Upon activation, they transform from their ramified form into amoeboid, reactive cells. **Figure 11** represents the anatomy of a resting and an activated microglial cell. Activated microglia proliferate rapidly and release of a broad range of cytokines, chemokines, and other immune mediators in response to the injury or insult (Ajami et al., 2007; Lawson et al., 1992; Perry, 2004). **Figure 12** presents the microglial cells in an immunohistochemical staining.

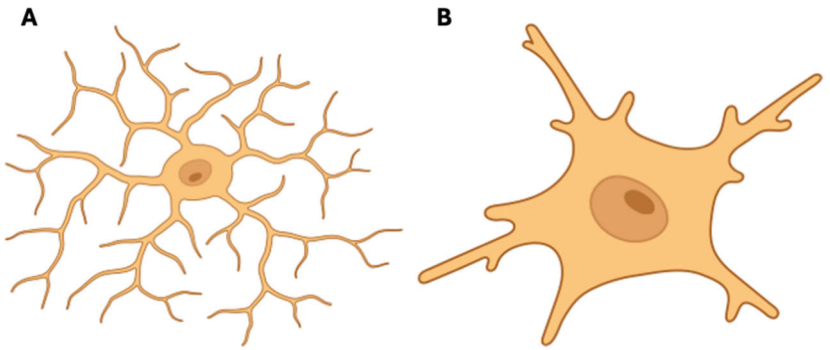

Figure 11. Anatomy microglial cells: A) resting and B) activated. In the resting state, microglial cells exhibit a branched morphology, whereas in the activated state they adopt an ameboid shape that changes in response to injury or disease. Created in https://BioRender.com.

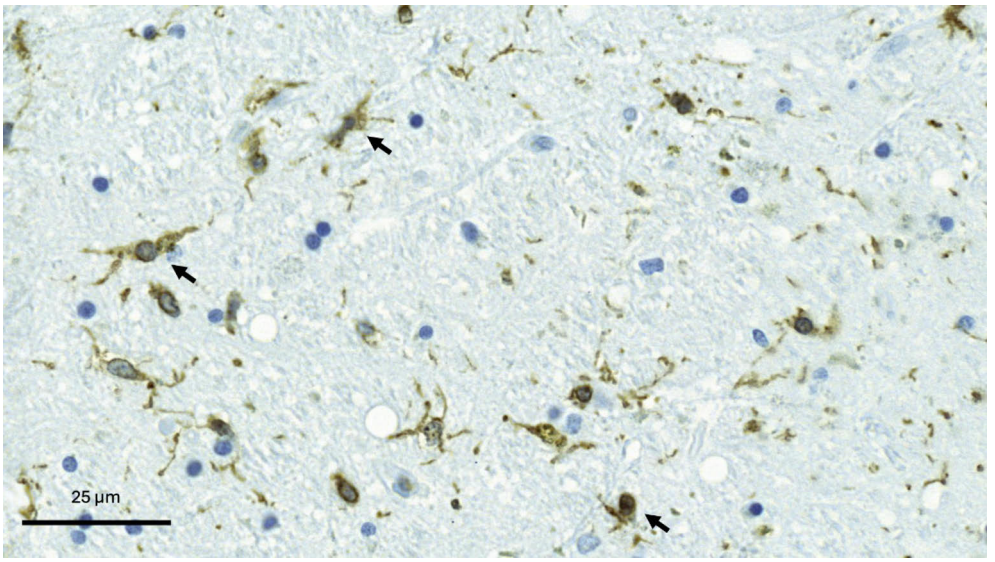

Figure 12. Microglial cells (arrows) from the SNc. Iba1 immunohistochemical staining.

Postmortem analyses of PD patients have revealed significant microglial activation in the SNc, evidenced by strong expression of the MHC class II receptor, HLA-DR (McGeer, Itagaki, Boyes, et al., 1988). Activated microglia produce various pro-inflammatory mediators, which contribute to the sustained loss of dopaminergic neurons (Imamura et al., 2003; Mogi, Harada, Kondo, et al., 1994; Mogi, Harada, Riederer, et al., 1994). PET imaging has confirmed microglial activation and dopaminergic neuron death in living PD patients, not only in the SNc but also in regions like the pons and basal ganglia (Gerhard, Pavese, et al., 2006; Ouchi et al., 2005). While it remains unclear whether

microglial activation initiates neuronal death or responds to it, experimental evidence indicates a causative role. Neurotoxins such as lipopolysaccharide (LPS) (Gao et al., 2002) and aggregated α-synuclein (Zhang et al., 2005) have been shown to drive dopaminergic neuron degeneration through microglia-dependent mechanisms. In familial PD, misfolded α-synuclein aggregates can activate microglia and undergo harmful post-translational modifications through microglia-derived nitric oxide, further contributing to neurodegeneration (Giasson et al., 2000; Zhang et al., 2005).

Research on microglia in atypical parkinsonisms remains low. PET studies have found widespread microglial activation in the brains of MSA patients. Studies have also suggested that microglia become activated in response to the accumulation of misfolded α-synuclein proteins within neurons and glial cells, supporting the role of microglia in the pathogenesis of MSA (Sanchez-Guajardo et al., 2015). The role of microglial activation in PSP remains more unclear. The microglial activation in PSP is suggested to be associated with the pathogenic deposition of tau (Alster et al., 2020).

2.4 Imaging of neurodegeneration

The main imaging modalities in the diagnosis and differential diagnosis of PD and atypical parkinsonisms include MRI, PET, single-photon emission computed tomography (SPECT), and computed tomography (CT) (Politis 2014). MRI is a noninvasive imaging technique that generates cross-sectional images of internal structures using strong magnetic field and radio waves. Unlike CT, MRI does not use ionizing radiation. CT and MRI have limited utility in detecting dopaminergic deficits in the brains of patients with PD. However, MRI is valuable for identifying structural abnormalities associated with other forms of parkinsonism, such as those resulting from vascular lesions or brain tumors (Mahlkneht et al., 2010). MRI is also useful for evaluating the extent and distribution of brain atrophy. PET and SPECT imaging use ionising radioactive ligands to assess presynaptic dopamine transporter function and availability in the striatum. PET provides higher spatial resolution, but SPECT imaging is more widely available and cost-effective (Schillaci et al., 2007).

2.4.1 CT-imaging

Brain CT is a widely available and fast neuroimaging technique that uses X-rays to create cross-sectional images. During CT scan, a narrow X-ray beam rotates around the patients, capturing multiple angles. When multiple slides are combined, they form a three-dimensional reconstruction of the scanned area.

CT is an important imaging tool, particularly for ruling out secondary causes of parkinsonism and alternative diagnoses, such as brain tumors, normal pressure hydrocephalus, cerebrovascular diseases or subdural hematomas (Carroll et al., 2017; Keong et al., 2016; Pantano et al., 2008; Perkins & Liu, 2016). Its use in the diagnosis of PD and atypical parkinsonisms remains limited. In PD, CT scans typically appear normal, as the structural changes in the early stages of the disease are not easily detectable by this modality. Unlike functional imaging methods, like PET and SEPCT, CT cannot visualize dopaminergic deficits or metabolic changes. Although MRI offers superior soft tissue contrast and more detailed visualization of brain structures, CT remains a valuable option in emergency settings due to its speed, accessibility, and lower cost. CT remains also a commonly used method, particularly when MRI is not available or contraindicated.

2.4.2 Machine-learning -based imaging analysis

Computer-aided image analysis and machine learning are playing an increasingly important role in modern medicine. Recent advancements, particularly in deep learning, have improved the ability to detect, measure, and classify complex patterns in medical images (Shen et al., 2017). Convolutional neural networks (CNNs) have emerged as the leading method for medical image analysis. CNNs are designed to automatically learn and extract features from images using convolutional operations.

Combinostics is a Finnish company specializing in artificial intelligence (AI) solutions aimed at enhancing the early detection, diagnosis, and management of neurological disorders. One of Combinostic's key components is cMRI, a cloud-based AI software that provides fully automated quantification of brain MRI scans. They have also developed an automated method, using CNNs (Kaipainen et al., 2021; Pitkänen et al., 2020), to evaluate medial temporal lobe atrophy (MTA), global cortical atrophy (GCA), and the severity of white matter lesions (WMLs)/ white matter hyperintensities (WMHs) from CT scans. WML is a broad pathological term, whereas WMH refer specifically to MRI-visible white matter changes appearing hyperintense on T2- and FLAIR-weighted sequences. This automated approach to assess brain atrophy from CT scans has been shown to be as precise as the technique used for evaluating brain atrophy from MRI scans (Kaipainen et al., 2021).

2.5 Depression in parkinsonism

Depression is a mental health disorder characterized by low mood and energy, hopelessness, and a diminished interest or pleasure in previously enjoyed activities.

It is a significant and growing health issue. In 2015 depressive disorders were estimated to be the third leading cause of disability worldwide (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators, 2016). Depressive disorders have a high impact on suicide rates, and the incidence of suicide is associated with depression more than 50% of the time (Henriksson et al., 1993). The global point prevalence is estimated to be 5% and incidence 3% (Ferrari et al., 2013). Depression diagnosis is based on the criteria of the International Classification of Diseases, Tenth Revision (ICD-10), as described in Komulainen et al. (2012). According to the criteria, the degree of the disease depends on the amount and quality of the typical symptoms.

ICD-10 diagnostic criteria for depression.

	Criteria
A	The depressive episode has lasted for at least two weeks.
B	The person has not previously had a hypomanic or manic episode.
C	The most common exclusion diagnoses: Symptoms are not due to substance use or a physical mental disorder.
D (core symptoms)	1 Depressed mood occurring most of the day and on most days of the episode, which is unusual for the person. This mood is not dependent on external factors and has lasted for at least two weeks.
	2 Lost of interest or pleasure in things that a person used to be interested in or that gave them pleasure.
	3 Decreased energy levels or exceptional fatigue.
E (additional key symptoms)	1 Decreased self-confidence of self-esteem.
	2 Unfounded or unreasonable self-accusations.
	3 Recurrent thoughts of death or suicide, or self-destructive behaviour.
	4 Difficulty concentrating, which may manifest as indecision or rushing through things.
	5 Psychomotor changes (agitation or retardation).
	6 Sleep disorders.
	7 Increase or decrease in appetite accompanied by weight change.

For the diagnosis to be made, criteria A, B, C, D, and E must be fulfilled, and symptom severity is classified as follows: Mild: At least 4 symptoms (2 core symptoms), Moderate: At least 6 symptoms (2 core symptoms), Severe: At least 7 symptoms (3 core symptoms).

The pathophysiology of depression is complex and not fully understood. Traditionally, it has been linked to reduced activity of monoamine neurotransmitters – serotonin, norepinephrine, and dopamine – with antidepressants aiming to restore their balance. Current research highlights the broader role of neuroplasticity, involving both structural and functional brain changes in response to environmental and experimental factors (Krishnan & Nestler, 2008). The treatment focuses on pharmacotherapy and psychotherapy, both of which are reasonable treatment options for moderate depression. The most effective treatment for severe depression is electroconvulsive therapy (van Diermen et al., 2018).

Depression is one of the most common and disabling non-motor symptoms associated with PD and atypical parkinsonisms. It affects patients' quality of life and can precede the onset of motor symptoms by several years. For patients and their families, these neuropsychiatric symptoms are often more challenging and distressing than the physical motor impairments (Hely et al., 2005). In clinical settings, depressive disturbances are underrecognized and, even when identified, frequently undertreated (Ravina et al., 2007; Shulman et al., 2002; Weintraub et al., 2003).

The global frequency of depressive disorders in PD is 30-38% (Aarsland et al., 2011; Chendo et al., 2022). The mechanism underlying depression in PD is multifactorial. While psychological stressors and major life events contribute, depression in PD is not solely a reaction to disability or disease burden (Chaudhuri et al., 2006). Depression often predates motor symptoms, suggesting that early neurodegeneration – particularly affecting monoaminergic system – may play a causal role. Degeneration occurs also in the serotonergic and noradrenergic neurons, which regulate mood and reward pathways. Their dysfunction has been implicated in PD-related depression (Mayberg & Solomon, 1995). Neuroimaging studies support this showing reduced dopamine transporter activity and abnormal frontal-limbic circuit function in depressed PD patients (Kostić et al., 2010). Neuroimaging studies have also shown structural brain changes in patients with PD and depression, including grey matter reduction in the prefrontal, parietal, and temporal regions, notably the cingulate gyrus, hippocampus, and thalamus (Hanganu et al., 2017; Pink et al., 2017). Severe white matter loss in the orbitofrontal and cingulate areas has been observed (Kostić & Filippi, 2011). Disruptions in multiple brain network connections further suggest that altered functional connectivity plays a role in the neural basis of depression in PD (Huang et al., 2020; Wei et al., 2018). Treatment for depression in PD is necessary when symptoms are persistent and impair functioning or cause distress. There is still, however, insufficient evidence for making recommendations for several treatments (Taylor et al., 2020). Studies have demonstrated the effectiveness of both antidepressant medications and cognitive behavioral therapy in treating depression in PD (Armento et al., 2012).

Patients with MSA exhibit a higher prevalence of depressive disorders compared to controls. The average prevalence in MSA ranges from 38% to 41% (Benrud-Larson et al., 2005; Köllensperger et al., 2010). However, depression is even more common and typically more severe in PSP, with reported rates between 55% and 59.7% (Bower et al., 2022; Flavell & Nestor, 2022; Schrag et al., 2010). Neuroimaging data on depression in MSA and other atypical parkinsonisms remain limited. In MSA-P, cortical thinning in fronto-temporal-parietal regions and atrophy of the periaqueductal grey matter, left pallidum, and putamen have been observed, independent of cognitive decline (Caso et al., 2020). Early MSA also shows widespread white matter microstructural changes, more prominent than grey matter loss (Dash et al., 2019). Despite established diagnostic criteria, depression in MSA and other movement disorders remain frequently underdiagnosed and undertreated. Although antidepressants are used, evidence for their effectiveness in MSA is limited, and management often focuses on supportive care and symptom relief.

Depression in PSP is common and may occur regardless of disease duration or motor symptom severity (Almeida et al., 2017). There are no significant qualitative differences in depression across the various clinical subtypes of PSP (Picillo et al., 2019). Neuroimaging data on depression in PSP remain also limited. Studies have shown grey matter loss in frontotemporal and temporo-parieto-occipital regions, particularly in the right hemisphere (Urso et al., 2022). Earlier findings also revealed hypometabolism in the frontal cortex, thalamus, and midbrain, with depression severity linked to reduced dorsolateral prefrontal metabolism, supporting a role for prefrontal dysfunction in PSP-related depression (Herting et al., 2007). The pathogenic factors contributing to depression in PSP are not well understood due to the absence of relevant human post-mortem or experimental data. In PSP, evidence supporting the effectiveness of antidepressants is limited and, treatment primarily focuses on mainly symptom relief. No controlled studies have specifically investigated the treatment of depression and other neuropsychiatric disorders in PSP.

3 Aims

This thesis focuses on SNc neuroinflammation and dopaminergic neurodegeneration in PD, MSA, and PSP, with the aim of investigating their associations with depression, brain atrophy, and levodopa use.

Specific aims of the thesis were:

I. To investigate SNc neuroinflammation in PD, PSP, and MSA by assessing dopaminergic neuron loss, T cell infiltration and microglial activation.

II. To assess the link between lifetime levodopa exposure and nigral neuroinflammation in PD, PSP, and MSA.

III. To examine cortical atrophy and WMHs in autopsy-confirmed parkinsonism, with a focus on their association with clinical depression.

4 Materials and Methods

4.1 Subjects

The included subjects had undergone a neuropathological examination between 2002 and 2021 at the Department of Pathology, Turku University Hospital, Finland. 67 cases who had received a neuropathological diagnosis of PD, MSA, or PSP, had a representative formalin-fixed, paraffin-embedded block available from the SN were included in the studies. They were re-evaluated by neuropathologists using neuropathological diagnostic criteria for PD (Gelb et al., 1999), MSA (Trojanowski et al., 2007), and PSP (Roemer et al., 2022). All in all, 79 individuals were included in the studies. Study I used 12 individuals who died without known neurological diseases as controls. **Table 1** presents the demographic characteristics of the studied subjects.

All PD patients had correctly received a PD diagnosis antemortem based on their clinical phenotype and levodopa treatment response based on the UK Brain Bank criteria (Gibb & Lees, 1988). Six MSA patients had been diagnosed with MSA antemortem, three had been diagnosed with PD, four had been diagnosed with undetermined parkinsonism, and one had been clinically diagnosed with motor neuron disease. Among the PSP patients, six had been correctly diagnosed with PSP antemortem, five had been diagnosed with undetermined parkinsonism, two had a diagnosis of PD, and two had been diagnosed with corticobasal syndrome.

A subsample of 63 patients was used in study II, and a subsample of 50 was used in study III. Antemortem CT imaging data was unavailable for 17 patients from Study III, and in Study II, four were excluded due to incomplete medical data.

Table 1. Demographic characteristics of studied subjects.

Study	I	II	III
PD n	38	38	30
MSA n	14	12	10
PSP n	15	13	10
Control n	12	-	-
Total n	79	63	50
PD age at death [IQR] or (SD)	80.3 [9.2]	80.3 [9.2]	80.1 (6.7)
PD females n (%)	8 (21.1)	8 (21.1)	5 (16.7)
MSA age at death [IQR] or (SD)	70.3 [19.2]	70.3 [22.6]	68.7 (14.5)
MSA females n (%)	8 (57.1)	7 (58.3)	4 (40.0)
PSP age at death [IQR] or (SD)	73.6 [8.0]	71.3 [11.6]	73.2 (6.8)
PSP females n (%)	6 (40.0)	5 (38.5)	3 (30.0)
Control age at death [IQR] or (SD)	69.5 [16.7]	-	-
Control females n (%)	5 (41.7)	-	-

PD = Parkinson's disease, PSP = progressive supranuclear palsy, MSA = multiple system atrophy

In all studies, a clinical PD diagnosis was neuropathologically confirmed when Lewy body disease of Braak stages 3–6 was present in combination with a loss of pigmented neurons in the SN (Braak et al., 2003). The clinical diagnosis was required to match the neuropathological diagnosis. The diagnosis of MSA was made when glial cytoplasmic inclusions positive for alpha-synuclein in immunohistochemical analyses were present, according to the MSA criteria proposed by the Neuropathology Working group on MSA (Trojanowski et al., 2007). For the diagnosis of PSP, phospho-tau positive neurofibrillary tangles and tufted astrocytes were required in characteristic locations according to the Rainwater Charitable Foundation criteria (Roemer et al., 2022).

4.2 Methods

4.2.1 Neuropathological examination

The brains included in all studies were collected retrospectively from autopsies conducted at Turku University Hospital between 2002 and 2021. A smaller portion, including controls without neurodegenerative diseases, originated from medicolegal autopsies carried out by the Finnish Institute for Health and Welfare (forensic pathology) and from regional hospital autopsies.

The histological sampling followed modified CERAD guidelines (Mirra et al., 1991). Brains were fixed in 4% phosphate-buffed formaldehyde for at least two weeks and examined macroscopically externally and from thin slabs. Tissue samples were taken from various brain regions, though only midbrain sections at the level of

the third cranial nerve were used for this study. Microscopic analysis was performed on hematoxylin- and eosin stained 3,5 µm sections, with neurodegenerative changes assessed using immunohistochemistry.

4.2.1.1 Staining and neuron counting

In each study, neuron counts and the area of the SNc were measured from paraffin-embedded midbrain tissue at the level where the third cranial nerve emerges. Tissues were sectioned at 8 µm for tyrosine hydroxylase (TH) staining, and 3.5 µm for other stainings. These sections were then stained with Luxol fast blue (LFB) or Substance P immunohistochemistry to define the borders of the SNc. The SNc outline was annotated on the LFB or Substance P-stained slides at 1x magnification and the area calculated using CaseViewer software version 2.4.0.119028 (3D HISTECH Ltd, Budapest, Hungary). The outline was then accurately transferred to the corresponding TH-stained sections by aligning anatomical landmarks such as vessels, section contours, and other histological features. **Figure 13** demonstrates the outline annotation. Due to the regions being transferred manually from one specimen to another using anatomical landmarks, the surface areas vary between specimens.

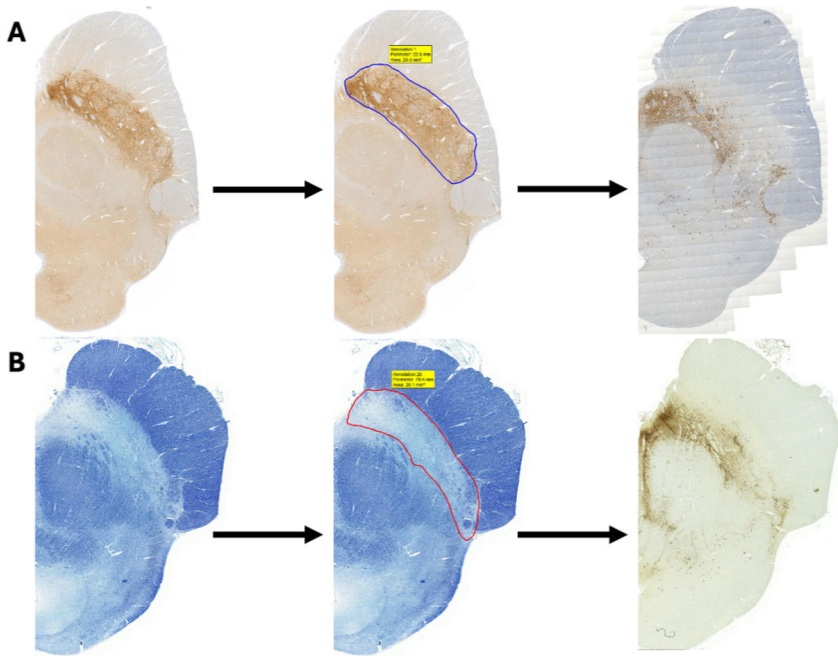

Figure 13. Demonstration of the SNc outlining method, in which the SNc outline was defined on (A) Substance P- or (B) LFB-stained sections and then transferred to TH-stained section using anatomic landmarks.

TH immunohistochemistry was used to identify dopaminergic neurons. Immunohistochemistry for CD3, CD4 and CD8 were used to detect all T lymphocytes, T helper cells or cytotoxic T cells, respectively. Microglia were detected using Iba1 immunohistochemistry. Details of the Immunohistochemical staining methods are summarized in **Table 2**. The slides were scanned with a Pannoramic P250 Flash slide scanner using Zeiss Plan-Apochromat 20×/0.8 NA objective, CIS VCC-F52U25CL camera (Vital Vision Technology Pte Ltd, Singapore) and control software version 1.18.2 and analysed with CaseViewer software. TH-positive neurons in the SNc were manually counted at high magnification. Neurons with visible nuclei were counted. Since counting in two dimensional sections can lead to errors due to overcount especially when counting objects that are large in relation to section thickness, neuron counts were corrected with the Abercrombie method (Guillery, 2002), which depends on section thickness and nuclear diameter along the appropriate axis. **Figure 14** demonstrates a TH+ neuron with a visible nucleus.

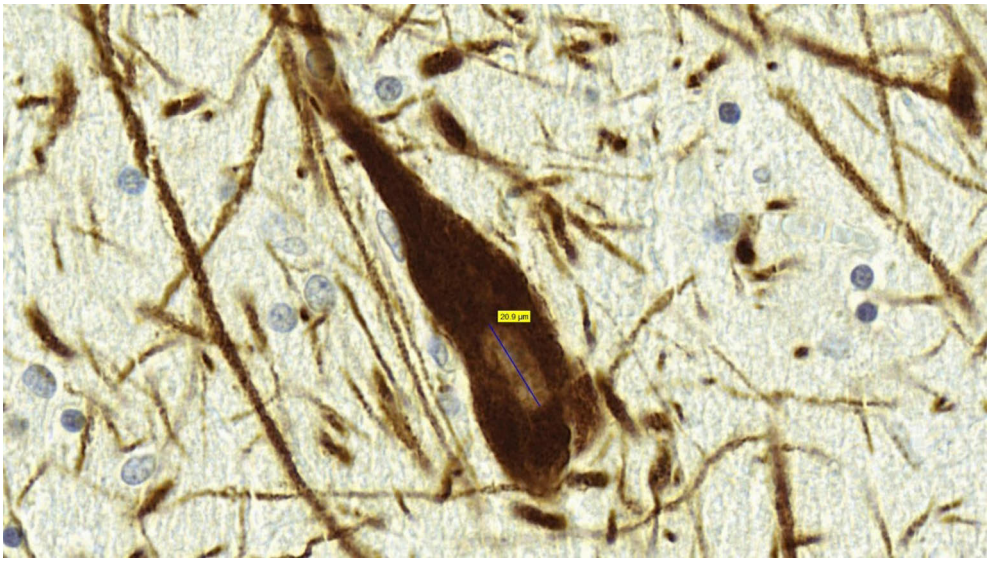

Figure 14. TH+ neuron with a visible nucleus. Nuclei diameters were used for the Abercrombie correction.

Table 2. Summary of immunohistochemical methods.

Antibody, source	clone/catalogue number	Dilution	Autostainer	Detection
Substance P (Abcam, Cambridge, UK)	EPR3959/ab133240	1:100	Labvision (Thermo-Fisher Scientific, Fremont, CA, USA)	BrightVision DPVB110HRP + BrightDAB (WellMed, Duiven, the Netherlands)
TH (Novocastra, Newcastle, UK)	1B5/NCL-TH	1:50	Labvision	BrightVision DPVB110HRP + BrightDAB
CD3 (Ventana Co., Tucson, AZ, USA)	2GV6/CONFIRM CD3 790-4341	ready to use	Ventana BenchMark ULTRA (Ventana)	Ultraview IHC DAB (Ventana)
CD4 (Ventana)	SP35/CONFIRM CD4 790-4423	ready to use	Ventana BenchMark ULTRA	Optiview IHC DAB, (Ventana)
CD8 (Novocastra)	4B11/NCL-L-CD8-4B11	1:100	Ventana BenchMark ULTRA	Optiview IHC DAB
Iba1 (Cell Signaling Technology, Danvers, MA, USA)	AIF-1/17198	1:2000	Labvision	BrightVision DPVB110HRP + BrightDAB

4.2.1.2 Computational image analyses

Bioimage analysis was performed using QuPath version 0.5.0 (https://qupath.github.io), an open-source platform. T cell quantification and Iba1 expression analysis were conducted within the SNc, which was defined as the region of interest based on outlines derived from LFB or Substance P staining. For T cell quantity counting within these delineated regions, all cells were first detected by Stardist Qupath extension version 0.4 using model dsb2018_heavy_augment.pb. (Schmidt et al., 2018). Stardist was run using modified version of Universal StarDist for QuPath script version 1.0.0. Stardist detection was done on the DAB color channel after stain vector optimization. Large detected neuromelanin-containing neurons were excluded by filtering the Stardist cell detections by nucleus size and stain intensity. A random forest object classifier was trained in QuPath to distinguish T cells from small neuromelanin fragments and other brown background features, using a collage of training images annotated by a pathologist. The classifier incorporated features such as detection area size and shape, hematoxylin and DAB color intensity, and Stardist detection probability. Separate classifiers were trained for CD3, CD4, and CD8 stainings, and analysis was performed on 79 images for each staining. After these exclusions, the remaining CD3+, CD4+ and CD8+ stained T cells were counted.

Due to the morphological variability and highly ramified structure of Iba1-positive microglial, which lack well-defined cell borders, manual counting or application of the T cell analysis pipeline was not feasible (Prinz et al., 2019). Instead, Iba1 expression was quantified as the total area of positive DAB staining within defined regions of interest, following a previously described approach (Green et al., 2022) with minor modifications. A pixel classifier was trained in QuPath to separate neuromelanin from Iba1 positive stained signal. A random forest classifier was trained on a collage of training images annotated by a pathologist showing typical variation in the appearance of neuromelanin. Gaussian filter, weighted deviation, and structure tensor eigenvalues were used as features on the hematoxylin and DAB channel pixel intensities at image resolution scales 1 and 4. Prior to measuring Iba1 coverage, areas identified by the classifier as neuromelanin were excluded from the analysis. The DAB-positive pixel count was then determined by thresholding the Gaussian-prefiltered DAB channel. Due to inter-slide variability in background staining, thresholds were visually optimized for each image. Iba1 coverage was calculated by dividing the number of pixels above the threshold by the total number of pixels in the region of interest under investigation. In total, 79 images from 79 patients were analyzed blinded to the clinical diagnosis.

To validate the accuracy of the automated counting method, all SNc CD3+ T cells from each subject were also manually counted by one of the investigators. Additionally, a random subset of ten samples from the CD4 and CD8 T cell stainings underwent manual cell counting to assess the reliability of the automated method.

4.2.2 Patient medical history

Clinical and medical histories were systematically reviewed using the hospital's electronic medical record system and archived patient charts to find possible correlations between clinical symptoms, imaging analyses and nigral neuron and inflammatory cell counts. Clinical symptoms or signs were considered present if they were recorded in the patient's records by the treating physician. The following clinical data were collected and categorized as available (last documented value): levodopa equivalent daily dose of dopaminergic medications (LEDD, mg), Mini-Mental State Examination (MMSE) total score, body measurements (height and weight) and HY stage. Demographic data, including sex, age at death, and disease duration - defined as the interval between the reported onset of motor symptoms to death – were collected. In addition, information about various clinical symptoms that had arisen during the course of the disease was recorded (present/not present), including depression, constipation, urinary incontinence, urinary retention, swallowing difficulties, voice problems, sleep disorders, hyposmia, orthostatism and hallucinations (**Table 3**). A patient was classified as depressed if a code for an ICD-

10 depression diagnosis (F32) was present in their record, the treating physician had recorded depression at clinical visits and/or the patient had been prescribed antidepressive medications for a mood disorder. Descriptive data related to rigidity, bradykinesia, resting tremor, and cognitive problems were also collected. A structured data collection approach, incorporating standardized checklists, was employed to ensure consistency and completeness.

Table 3. Clinical characteristics of the studied PD, PSP, and MSA patients in study with the largest sample sizes (Study I).

Variable	PD	PSP	MSA	p value
n	38	15	14	-
Sleep disorder n (%)	10 (26.3)	6 (40.0)	6 (42.9)	ns
Depression n (%)	7 (18.4)	6 (40.0)	4 (28.6)	ns
Hyposmia n (%)	6 (15.8)	0 (0.0)	0 (0.0)	ns
Orthostatic hypotension n (%)	14 (36.8)	1 (6.7)	8 (57.1)	0.015
Constipation n (%)	12 (31.6)	4 (26.7)	7 (50.0)	ns
Urinary incontinence n (%)	12 (31.6)	4 (26.7)	8 (57.1)	ns
Urinary retention n (%)	7 (18.4)	6 (40.0)	4 (28.6)	ns
Dysphagia n (%)	8 (21.1)	8 (53.3)	9 (64.3)	0.006
Antipsychotic drugs n (%)	18 (47.4)	3 (20.0)	0 (0.0)	0.001
Hallucinations n (%)	19 (50.0)	3 (20.0)	0 (0.0)	<0.001
Dysarthria or speech difficulties n (%)	10 (26.3)	12 (80.0)	12 (85.7)	<0.001

4.2.3 Levodopa data

Levodopa treatment data were systematically extracted from patient charts to assess usage patterns throughout each patient's disease course. Due to changes in dosing over time and occasional missing data, three key metrics were calculated to capture cumulative and time-specific levodopa exposure:

1. Cumulative lifetime dose of levodopa (formula 1): This measure was adapted from Parkkinen et al. and O'Sullivan et al., calculated using the following equation:

(LED [mg] at 1 year after commencement × 365) + ½ (maximum LED + LED at 1 year after commencement × 365) × (interval from 1 year after commencement to reaching maximum LED in years) + (maximum LED × 365) × (interval from reaching maximum LED to death in years).

LED = levodopa daily dose

2. Cumulative lifetime dose of levodopa not taking into account the multipliers (formula 2): This measure considers only the average daily levodopa dose and the duration of the disease, calculated using the following equation:

([LED at 1 year after commencement + maximum LED + LED at death]/3) x disease duration in years.

3. The mean levodopa dose (formula 3): This measure considers only levodopa daily doses at different time points, calculated using the following equation:

(LED at 1 year after commencement + maximum LED + LED at death)/3.

4.2.4 CT-imaging

CT imaging was used to assess brain changes due to its greater availability in clinical practice. MTA, GCA and WMHs were evaluated computationally from CT scans using an image quantification tool based on CNNs (Kaipainen et al., 2021; Pitkänen et al., 2020). CT scans were skullstripped and registered to a common template space. Two CNNs were trained using a separate training set of 214 CT scans to segment cerebrospinal fluid (CSF) and WMHs. MTA and GCA were computed based on the CSF volume in the medial temporal lobe and cortex, respectively. WMHs were quantified using the Fazekas score measuring the WMH volume in the deep white matter. MTA was assessed on a scale of 0–4, GCA on a scale of 0–3, and the Fazekas scale on a scale of 0–3.

4.3 Statistical analyses

Statistical analyses were conducted using SPSS Statistics 29 for Macintosh (IBM Corp., Armonk, NY, USA). The normality of the data was evaluated using histograms and the Kolmogorov-Smirnov test. A significance level of $p<0.05$ was generally applied, while a stricter statistical threshold of $p<0.01$ was used in Studies I and II for correlations involving multiple clinical variables.

In Study I and II, nonparametric Kurskal-Wallis tests were used to assess differences in continuous variables among the groups, with the post hoc Bonferroni correction for multiple comparisons. In Study I, an analysis of covariance (ANCOVA) model was applied to investigate clinical variables, using logarithmic values for cell counts and densities, with covariates (sex, disease duration and/or group) specified per analysis. β values with 95% confidence intervals were calculated, and possible interactions between covariates and groups were assessed. Reliability of automated vs. manual cell counts were assessed using intraclass

correlation coefficient (ICC). Catechorical variables were assessed using chi-square or Fisher's exact test, and correlations between neuropathological measurements were examined by determining Spearman's correlation coefficients.

In Study II, ANCOVA was used to assess relationships between levodopa exposure and neuropathological markers in PD patients, with log-transformed value transformations to cell counts and densities and specifying covariates for each analysis (age at death, sex, HY stage, disease duration and/or diagnostic group). For PSP and MSA cohorts, due to smaller sample sizes, partial Spearman correlation analyses were used to assess the relationship between levodopa exposure and neuropathological markers. Disease duration was controlled as a covariate.

In Study III, group differences were analyzed using one-way ANOVA, Kruskall-Wallis or the chi-square tests, with Bonferroni corrected post hoc tests. Residuals from the linear models met normality assumptions. ANCOVA assessed changes in CT-based GCA, MTA (mean separately left and right) and WMHs, using age, symptom duration, and group as covariates.

4.4 Ethics

All studies were conducted in accordance with the principles of the Declaration of Helsinki and complied with applicable national legislation and institutional guidelines. The research protocols were approved by the Ethics Committee of Turku University Hospital (Decision nr. 86/1803/2018).

All sub-studies were retrospective *postmortem* investigations based on previously collected clinical and pathological data and tissue samples. Due to the retrospective nature of the studies and the fact that all material was obtained after death, informed consent from the study subjects could not be obtained.

All data were handled in accordance with data protection regulations, and patient confidentiality was strictly maintained throughout the research process. Personal identifiers were removed prior to analysis, and all results are reported in an anonymized form, ensuring that individual subjects cannot be identified.

5 Results

5.1 Nigral neuroinflammation (Study I)

Baseline demographic, clinical, and neuropathological characteristics of the studied subjects are presented in **Table 4**. The median time from death to autopsy was 4.5 days, with a range of 0 to 18 days. Data were unavailable for 7 patients. PD patients were older at the time of death compared to patients in the other groups ($p<0.02$, Bonferroni corrected). No significant differences were found between groups in terms of sex distribution. The median disease duration from the onset of motor symptoms to death was 5.5 years longer in PD patients than in those with MSA ($p=0.01$). Motor disease severity, as measured by the the HY scale at the last assessment before death, was higher with patients with PSP and MSA (median score 5) compared to those with PD (median score 4) ($p<0.01$). The last LEDD before death was higher in patients with PD than those with PSP ($p=0.004$).

T cell infiltration was most pronounced in PSP, where SNc CD3+, CD4+, and CD8+ T cell counts were elevated by 89.4–212% compared to MSA ($p<0.04$), and CD3+/CD4+ T cell counts were 125–178% higher than in controls ($p<0.002$). PSP patients also had 94.9% more CD4+ T cells than PD patients ($p=0.001$). Similar PSP-specific increases were observed in T cell densities. **Figure 15** demonstrates CD3+ T cell counts and densities in different parkinsonian disorders. The increases persisted after adjusting for age and sex, with PSP patients consistently showing higher CD3+, CD4+, and CD8+ T cell counts and densities compared to all other groups ($p<0.045$).

Table 4. Group differences in baseline demographic, clinical, and neuropathological characteristics. Data are presented as the median [interquartile range] or n.

Variable	PD	PSP	MSA	Controls	p value
n	38	15	14	12	-
Age at death (years)	80.3 [9.2] *†	73.6 [8.0]	70.3 [19.2]	69.5 [16.7]	<0.001
Sex: female (%)	30/8 †	9/6	6/8	7/5	ns
Disease duration (years)	9.8 [7.0] †	7.0 [8.1]	4.3 [4.6]	-	0.009
HY score	4 [2] *†	5 [1]	5 [0]	-	<0.001
LEDD at death	574 [455] *	0 [520]	496 [1039]	-	0.006
Motor phenotype: tremor n (%)	24 (77.4)*	5 (33.3)	7/7	-	0.011
Asymmetry of motor symptoms: symmetrical n (%)	0 (0.0)*†	6 (54.5)†	11 (100%)	-	<0.001
SNc TH+ neuron count (n)	70.0 [43.2]	29.7 [31.3]	23.4 [18.7]	108 [54.8]	<0.001
SNc area (mm^2)	31.0 [10.8]	25.4 [7.9]	23.7 [6.76]	28.8 [11.1]	0.002
SNc TH+ neuron density (n/mm^2)	2.10 [1.89]	1.23 [0.74]	0.93 [0.65]	4.24 [1.0]	<0.001
Brain weight (g)	1420 [218]	1366 [116]	1373 [276]	1398 [239]	ns
SNc CD3+ count (n)	209 [129]	375 [382]	198 [161]	135 [124]	0.003
SNc CD3+ area (mm^2)	32.2 [10.3]	27.6 [9.8]	24.0 [7.1]	29.6 [12.5]	0.01
SNc CD3+ density (n/mm^2)	6.80 [3.73]	15.5 [11.2]	8.17 [6.47]	4.84 [3.92]	0.002
SNc CD4+ count (n)	136 [152]	265 [256]	131 [118]	118 [124]	<0.001
SNc CD4+ area (mm^2)	31.3 [8.9]	29.6 [9.1]	25.4 [7.4]	27.8 [8.0]	0.02
SNc CD4+ density (n/mm^2)	5.30 [3.51]	9.16 [9.92]	6.01 [5.10]	5.01 [1.94]	<0.001
SNc CD8+ count (n)	91.8 [79.3]	187 [192]	60.0 [37.3]	85.8 [73.3]	0.018
SNc CD8+ area (mm^2)	33.3 [10.8]	27.6 [7.9]	24.7 [6.7]	29.0 [10.4]	0.001
SNc CD8+ density (n/mm^2)	3.01 [2.51]	7.05 [7.25]	2.46 [1.94]	2.75 [2.93]	0.03
SNc Iba1 expression (%)	2.29 [1.53]	0.96 [2.29]	0.85 [1-26]	1.63 [1.55]	0.004
Crus cerebri Iba1 expression (%)	2.46 [1.24]	2.55 [2.93]	1.96 [1.93]	1.91 [2.17]	ns

PD = Parkinson's disease, PSP = progressive supranuclear palsy, MSA = multiple system atrophy. HY = Hoehn and Yahr, LEDD = levodopa equivalent daily dose, SNc = substantia nigra pars compacta, TH = tyrosine hydroxylase, ns = non-significant. P values are from the Kruskal–Wallis test, chi–square test or Fisher's exact test. [A] (lower/higher side neuron count) × 100.

* Significantly different ($p<0.05$) compared to PSP after Bonferroni correction, † Significantly different ($p<0.05$) compared to MSA after Bonferroni correction.

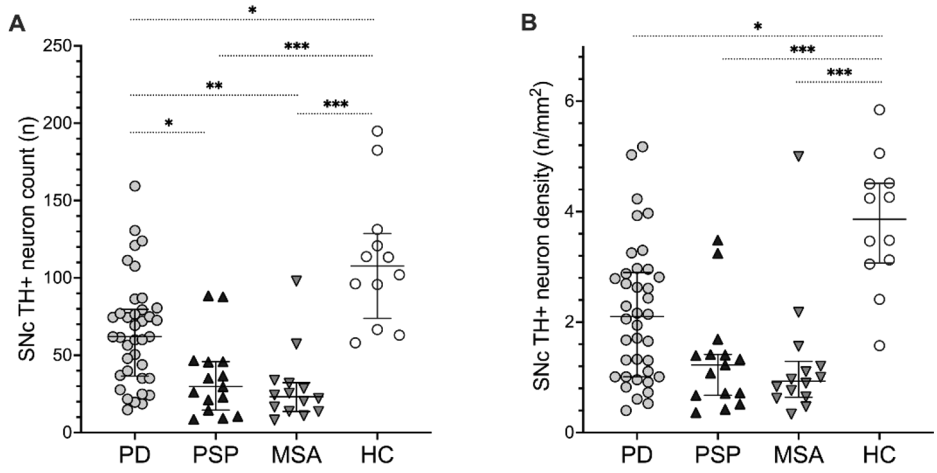

Figure 15. CD3+ T cell counts and densities in different parkinsonian disorders. (A) CD3+ T-cell count, (B) CD3+ T-cell density. *p<0.05, **p<0.01, ***p<0.001.

Compared to controls, patients with PSP or MSA and patients with PD had substantially fewer (by 72.5–78.3%) and moderately fewer (35.2%) TH+ neurons in the SNc, respectively ($p<0.05$ for both). Compared with the PD group, the PSP and MSA groups had 57.6% and 66.6% fewer SNc TH+ neurons, respectively ($p<0.05$ for both). The SNc TH+ neuron density was 50.5–78.1% lower in all patient groups than in the healthy control group ($p<0.02$). No differences were observed among the PD, PSP and MSA groups. **Figure 16** demonstrates the differences between the groups in TH+ neuron count and density. The differences remained significant after adjusting for age and sex. The key result is demonstrated in **Figure 17**.

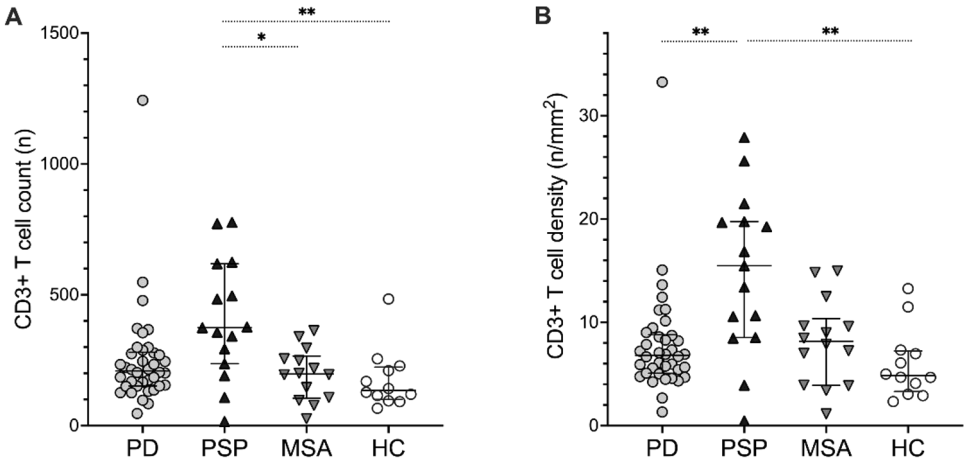

Figure 16. SNc TH+ neuron count (A) and TH+ neuron density (B) across patient groups. *p<0.05, **p<0.01, ***p<0.001.

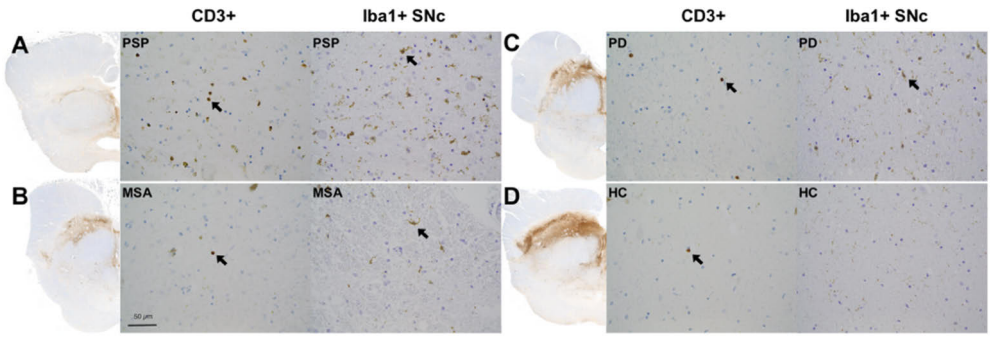

Figure 17. Representative histopathological sections of SNc from different patient groups. (A) A 76-year-old male patient diagnosed with PSP (B) A 65-year-old female patient diagnosed MSA (C) A 76-year-old male patient diagnosed with PD and (D) A 72-year-old male control without a degenerative parkinsonian disorder. Brown staining highlights dopaminergic neurons in the SNc. The immune cells (CD3+ and Iba1+) are shown at 60x magnification in the following columns (arrows), and the brown staining in the third and last columns indicates Iba1 expression (arrows).

Iba1 expression, a marker of microglial activation, was significantly elevated in PD patients compared to MSA (169% increase, $p=0.004$), but no other group differences were found. These findings did not hold after adjusting for covariates, likely due to the older age of PD patients ($p>0.56$). Extranigral Iba1 levels did not differ significantly across the conditions.

In the full sample ($n=79$), no significant correlations emerged between TH+ neuron count and T cell measures. However, a weak positive correlation was noted between TH+ neuron density and Iba1 expression ($r>0.24$, $p<0.03$). In PD specifically, TH+ neuron density correlated positively with CD3+ and CD8+ T cell densities and Iba1 expression in the SNc and crus cerebri. Strong intercorrelations were observed among T cell subtypes ($r>0.43$, $p>0.001$) and between nigral and extranigral Iba1 expression ($r>0.73$, $p<0.001$). CD8+ T cell density was also positively associated with Iba1 expression in the SNc ($r=0.29$, $p=0.009$) and crus cerebri ($r=0.34$, $p=0.002$).

Age did not correlate with neuropathological markers ($p>0.41$), but male sex was associated with higher extranigral Iba1 expression and increased SNc CD3+ and CD4+ T cell counts ($p<0.005$) and was thus included as a covariate. Longer disease duration was linked to lower SNc CD3+ and CD8+ T cell densities and counts ($p<0.005$); see **Figure 18**. Depression and sleep disorders were associated with reduced TH+ neuron density and counts ($p<0.01$), and depressed patients more often experienced sleep problems (58.8% vs. 24.0%, $p=0.008$). No differences in neuropathological markers were observed between clinical subtypes of MSA (MSA-P vs. MSA-C) or PSP (PSP-RS vs. other variants) ($p>0.23$).

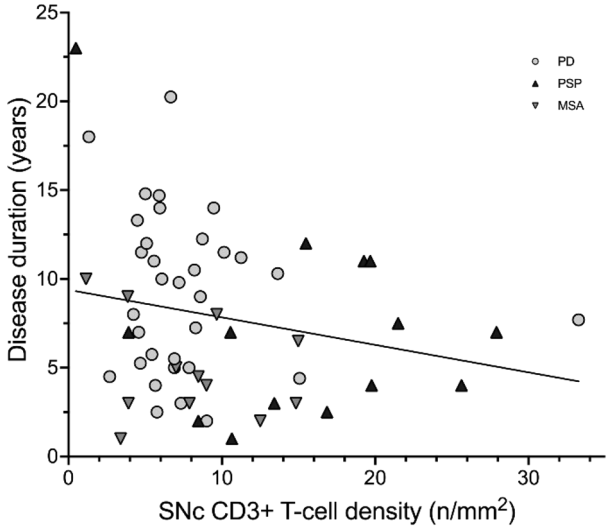

Figure 18. Correlation between disease duration and CD3+ T-cell density across patient groups. Longer disease duration was linked to lower SNc CD3+ T cell densities. *p<0.05, **p<0.01.

5.2 Nigral neuroinflammation and levodopa (Study II)

Table 5 summarizes the primary demographic and clinical characteristics of the participants. Levodopa was administered during the disease course in 97% of PD patients (n=37/38), 67% with MSA (n=8/12), and 54% with PSP (n=7/13). Dyskinesia occurred in four PD patients, but the anatomical locations were only partially described. Positive correlations among cumulative dose, mean dose, and dose at death confirmed internal consistency across exposure metrics.

Table 5. Group differences in baseline demographic, and clinical characteristics. Data are presented as median [IQR] for continuous variables and n for categorical variables.

Variable	PD	PSP	MSA	p value
n	38	13	12	-
Age at death (y)	80.3 [9.2]*†	71.3 [11.6]	70.3 [22.6]	<0.001
Sex: female n (%)	8 (21.1%)†	5 (38.5%)	7 (58.3%)	0.045
Disease duration (y)	9.8 [7.0]†	7.0 [8.3]	4.3 [4.6]	0.011
HY score	4 [2]*†	5 [1]	5 [0]	<0.001
LEDD at death	525 [438]*	0 [380]	496 [1056]	0.008
Motor phenotype: tremor n (%)	24 (77.4%)*	5 (38.5%)	6 (50.0%)	0.031
Asymmetry of motor symtoms: symmetrical n (%)	0 (100%)*†	6 (54.5%)†	10 (100%)	<0.001
Lifetime levodopa dose (formula 1) (kg)	0.68 [1.10]*	0.11 [0.49]	0.27 [1.09]	0.021
Lifetime levodopa dose (formula 2) (kg)	1.2 [1.9]*	0.049 [1.01]	0.35 [0.93]	0.005
Daily mean levodopa dose (formula 3) (mg)	467 [206]*	200 [325]	367 [646]	0.004
Daily levodopa dose at death (mg)	500 [300]*	0 [350]	350 [800]	0.008
Duration of levodopa use (years)	6.6 [7.1]	5.5 [7.1]	3.1 [4.4]	ns
Duration of dopamine agonist use (years)	7.2 [7.9]	6.6 [7.6]	3.7 [4.0]	ns

* Significantly different ($p<0.05$) compared to PSP after Bonferroni correction, † Significantly different ($p<0.05$) compared to MSA after Bonferroni correction.
PD = Parkinson's disease, PSP = progressive supranuclear palsy, MSA = multiple system atrophy, HY = Hoehn and Yahr, LEDD = levodopa equivalent daily dose, SNc = substantia nigra pars compacta, TH = tyrosine hydroxylase, ns = non-significant. P values are from the Kruskal–Wallis test, chi–square test or Fisher's exact test. [A] (lower/higher side neuron count) × 100

In PD patients, no significant associations were found between levodopa exposure and neuronal density or neuroinflammatory markers in the SNc or crus cerebri, after adjusting for age at death and sex ($p>0.17$). **Figure 19** demonstrates the results. This included lifetime cumulative levodopa dose (formulas 1 and 2), mean levodopa dose (formula 3), and dose at death. Additional analyses controlling for disease duration and HY stage confirmed these findings. Neuroinflammatory marker levels did not differ between dyskinetic and non-dyskinetic PD patients ($p>0.14$).

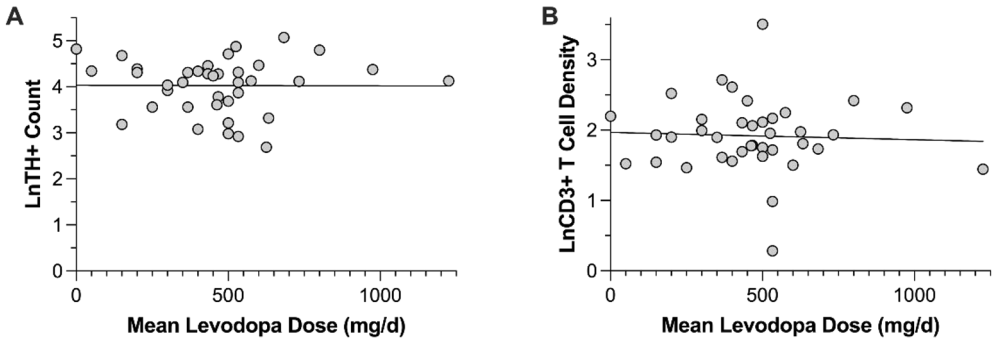

Figure 19. The relationships between mean daily levodopa dose over the disease course and neuropathological measures in the SNc in PD patients. (A) Tyrosine hydroxylase-positive (TH+) neuron count vs mean daily levodopa dose, (B) CD3+ T-cell density vs mean daily levodopa dose. No significant associations were observed between mean daily levodopa dose and any neuropathological measure. Similar results were found for lifetime cumulative levodopa dose and levodopa dose at death.

Lifetime levodopa exposure was positively correlated with disease duration ($r=0.38$-0.75, $p<0.004$) but not with age at death ($r=-0.47$ to 0.18, $p>0.2$). Levodopa doses did not vary significantly across HY stages ($p>0.78$), and lifetime cumulative dose showed no sex-based differences ($p>0.18$). Men received higher mean daily doses (median=456 mg vs. 200 mg; $p=0.047$) and higher doses at death (median=450 mg vs. 200 mg; $p=0.037$) compared to women.

In PSP and MSA patients, levodopa exposure was not significantly associated with neuronal or inflammatory markers after adjusting for disease duration ($p>0.012$). Age at death did not correlate with any measure of levodopa exposure ($p>0.026$), and no sex-based differences in dosing were observed in either PSP or MSA groups ($p>0.5$).

5.3 Cortical atrophy and depression in PD (Study III)

The main demographic and clinical characteristics of the studied PD, PSP, and MSA patients are presented in **Table 6**. Depressed patients exhibited significantly more severe MTA than non-depressed patients, after adjusting for age at scan, motor symptom duration, and diagnostic group (mean MTA: 2.30 [95% CI 1.56–3.03] vs. 1.01 [0.55–1.48]; $F(1,39)=8.62$, $p=0.006$). **Figure 20** presents the main results. This held true for both right and left hemispheres ($p=0.007$ each). MTA severity increased with age ($F=9.85$, $p=0.003$), but not with symptom duration or diagnostic group. The relationship remained significant when restricting analysis to PD patients ($p=0.021$). MTA was also associated with antidepressant use ($F=5.52$, $p=0.024$) but showed no link to dementia, MMSE scores, psychosis, antipsychotic use, or substantia nigra TH-positive neuron density at death.

Table 6. Main demographic and clinical characteristics of PD, PSP, and MSA patients.

Variable	PD	PSP	MSA	p value
n	30	10	10	-
Age at motor symptom onset (years)	70.4 [14.1]	68.0 [14.8]	62.0 [29.0]	0.37
Age at imaging (years)	76.2 (7.3)	71.3 (7.6)	66.9 (14.9)	0.024*
Age at death (years)	80.1 (6.7)	73.2 (6.8)	68.7 (14.5)	0.002*
Sex: female n (%)	5 (16.7)	3 (30.0)	4 (40.0)	0.29
LEDD (mg)	500 [400]	100 [540]	496 [1089]	0.029*
Disease duration at imaging (years)	3.2 [5.5]	2.8 [5.1]	1.0 [5.5]	0.31
Total disease duration (years)	9.3 (4.6)	5.1 (3.5)	4.8 (14.1)	0.006**
Clinical phenotype	TD (n=18) PIGD (n=9) Unknown (n=3)	PSP-RS (n=7) PSP-PGF (n=1) PSP-P (n=1) PSP-F (n=1)	MSA-P (n=7) MSA-C (n=3)	-
Global cortical atrophy (GCA)	1.52 (1.16)	1.78 (1.01)	1.06 (1.17)	0.36
Medial temporal cortex atrophy (MTA)	1.28 (1.14)	1.45 (1.36)	0.97 (1.26)	0.67
WMHs (Fazekas)	1.79 [0.87]	1.04 [1.42]	1.34 [1.94]	0.051
Depression n (%)	5 (16.7)	4 (40.0)	4 (40.0)	0.18
Dementia n (%)	12 (40.0)	2 (20.0)	0 (0.0)	0.042

LEDD = levodopa equivalent daily dose, TD = tremor dominant, PIGD = postural instability gait disorder, PSP-RS = Richardson syndrome subtype, PSP-PGF = progressive gait freezing subtype, PSP-P = parkinsonism subtype, PSP-F = frontal subtype, MSA-P = parkinsonism subtype, MSA-C = cerebellar subtype. Values are median [IQR], mean (SD) or n. p values are from the Kruskall–Wallis test, one-way ANOVA or the chi-square test. GCA scale 0–3, MTA scale 0–4, Fazekas scale 0–3.

GCA was more pronounced in depressed patients than non-depressed individuals (mean GCA: 2.20 [1.58–2.82] vs. 1.29 [0.90–1.68]; F=6.07, p=0.018). Age positively correlated with GCA (F=20.5, p<0.001), but symptom duration and diagnostic group did not. Unlike MTA, GCA was not significantly associated with antidepressant use or any cognitive or pathological variables.

There were no significant differences in vascular lesion load between depressed and non-depressed patients, in the overall sample (F=0.45, p=0.51) or in the PD subgroup (F=1.20, p=0.29). WMHs were not related to antidepressant use, dementia, MMSE scores, psychosis, antipsychotic use, or SNc neuron density.

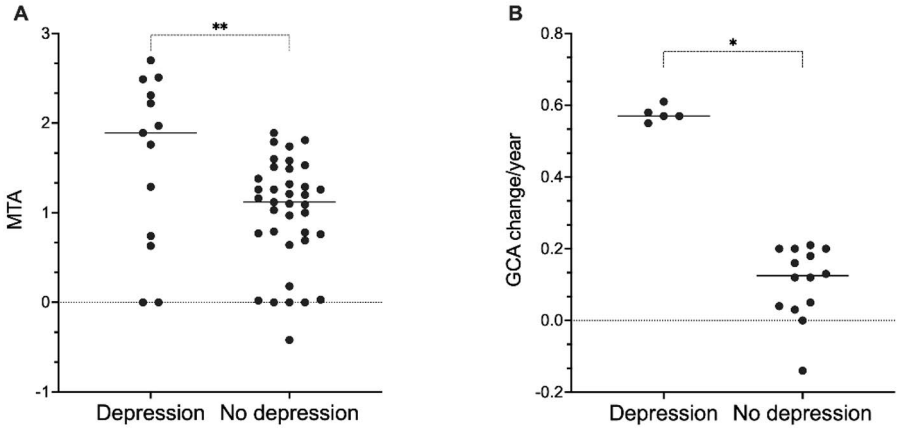

Figure 20. Differences in cortical atrophy between patients with depression and patients without depression. A. MTA in patients with and without depression. B. GCA yearly predicted progression in patients with and without depression. *p<0.05, **p<0.01.

Among PD patients, those with a tremor dominant phenotype had lower WMH burden than those with a postural instability gait disorder (PIGD) phenotype (mean: 1.34 vs. 2.10; F=5.31, p=0.031). However, phenotype was not linked to MTA or GCA. Subgroup analyses of MSA and PSP variants were not conducted due to small sample sizes. Longitudinal analysis showed that GCA worsened more rapidly in depressed patients (mean annual change: 0.58 vs. 0.11; p=0.029), while no such differences were observed for MTA or WMHs. No sex differences were found in MTA, GCA, or vascular lesion load (p>0.83).

6 Discussion

The purpose of this thesis project was to investigate nigral neuroinflammation and neuron density in the SNc, comparing PD with MSA and PSP, as well as to examine the association between long-term levodopa use and neuroinflammation and the relationship between non-motor symptoms and imaging detected brain atrophy. This was achieved through immunohistochemial analysis, clinical feature and medication assessment, and CT-imaging evaluation. The main results demonstrated the following: 1. T cell infiltration in the SNc is significantly increased in PSP. 2. Chronic of levodopa use does not have a toxic effect on nigral neurons or contribute to neuroinflammation. 3. Depression in PD is linked to a more rapid progression of cortical atrophy.

Together, these results support the concept that parkinsonian disorders are characterized by distinct neuroinflammatory profiles, challenge the long-standing concern regarding levodopa neurotoxicity, and highlight depression as an early clinical marker linked to neurodegenerative burden.

6.1 T cell mediated neuroinflammation in PSP (Study I)

In this study, MSA and PSP patients showed greater nigral dopaminergic neuron loss – by 58-67% – compared to PD despite having shorter disease durations, indicating accelerated degeneration. An intermediate reduction in dopaminergic neurons was observed in PD patients compared to individuals without neurodegenerative disease, aligning with the known susceptibility of these neurons across such conditions, as demonstrated by functional imaging (Kaasinen et al., 2019; Kaasinen & Vahlberg, 2017). While prior comparative studies are limited, some suggest broader A10 neuron loss in PSP compared to PD (McRitchie et al., 1997; Murphy et al., 2008), with similar A9 loss across both conditions (Hardman et al., 1997). Additionally, MSA has been associated with substantially greater nigral neuronal loss than in controls (Salvesen et al., 2015). It appears that only one previous small study directly compared nigral dopaminergic neuron loss across PD, PSP, and MSA (n=35), and its semi-quantitive grading scale (mild/moderate/severe) was unable to detect disease-specific differences (Song et al., 2011).

The very high number of tissue infiltrating CD3+, CD4+, and CD8+ T cells in the SNc of PSP patients represents one of the most striking findings of this study, with the amount of T cells exceeding that in MSA, PD and control patients by 89.4% to 212%. A recent study, using stereological approach, further confirmed this finding (Couto et al., 2025). This PSP-specific neuroinflammatory signature likely reflects fundamental pathophysiological differences between tauopathies and synucleinopathies (Langworth-Green et al., 2023).

An important question arising from these findings is whether the heightened neuroinflammatory activity observed in PSP represents a late-stage phenomenon or is already present in early stages of the disease. Although the current study cannot directly resolve this issue, it is noteworthy that PSP and MSA patients did not differ with respect to nigral dopaminergic neuronal loss, demographic variables, or indicators of disease severity. Despite these similarities, PSP patients exhibited markedly higher numbers of CD3+, CD4+, and CD8+ T cells in SNc than MSA patients, suggesting that the increased T cell infiltration cannot be explained by overall disease severity or the extent of nigral neuronal loss.

The inverse correlation between disease duration and CD3+ T cell counts suggests that T cell infiltration may be an early pathological event, rather than a feature of late-stage disease. This is further supported by the positive correlation observed between nigral TH+ neuron counts and densities and multiple neuro-inflammatory markers in PD patients, suggesting that inflammation is less pronounced in individuals with advanced nigral neuronal loss. An alternative interpretation is that elevated T cell presence marks a more aggressive disease variant, accelerating disease progression.

The prominence of adaptive immune cells in PSP invites comparison with chronic traumatic encephalopathy (CTE) and AD. CTE occurs as a consequence of repetitive mild traumatic brain injury and is characterized by accumulation of hyperphosphorylated tau, accompanied by long-lasting microglial activation and lymphocytic infiltration (Cherry et al., 2016; McKee et al., 2013). Studies have indicated that repetitive brain injury induces chronic immune activation, which can promote tau hyperphosphorylation, misfolding, and aggregation (Johnson et al., 2013; Cherry et al., 2016). Although PSP is not trauma-associated, the overlap in tau-dominant pathology, subcortical vulnerability, and immune involvement raises the possibility that partially shared inflammatory mechanisms may contribute to tau misfolding and disease propagation.

Similarly, in AD, increasing evidence supports a role for adaptive immunity in neurodegeneration. In tauopathy models and human AD tissue, microglia-dependent T cell recruitment is increased in tau-rich regions and correlates with neuronal loss, and experimental reduction of microglia or T cells mitigates tau-driven neurodegeneration (Chen et al., 2023). Moreover, a recent report focusing on the

frontal cortex demonstrated correlation between CD8+ T cells and phosphorylated tau in FTLD, potentially mediated by microglial and astroglial activation (Hartnell et al., 2024). These observations further support a link between adaptive immune responses and tau pathology across distinct tauopathies. Together, these parallels between PSP, CTE, and AD support a speculative view that PSP may not present purely primary tauopathy, but rather a disorder in which immune dysregulation participates in disease initiation or amplification.

This interpretation is further supported by the prion-like properties of tau. Both tau and α-synuclein are now widely recognised to spread via templated misfolding and transneuronal transmission (Clavaguera et al., 2009; Goedert, 2015; Mudher et al., 2017). Some evidence indicates that neuroinflammation modulates this process. Activated microglia internalize and release tau species via exosomes, thereby facilitating tau spread (Asai et al., 2015), and inflammatory signalling promotes tau phosphorylation and aggregation (Ising et al., 2019). Comparable bidirectional interactions have been demonstrated for α-synuclein. Elevated T-cell infiltration may therefore facilitate tau propagation, impair clearance mechanisms, or amplify neurotoxicity, establishing a self-reinforcing loop between immune activation and protein pathology.

Importantly, direct apposition of T cells to neurons is a recognized hallmark of immune-mediated neurological disorders, and is considered indicative of antigen-specific, potentially cytotoxic immune interactions (Bien et al., 2012). Consistent with this concept, a recent neuropathological study reported CD8+ T cells in close proximity to surviving neurons in PSP, suggesting that immune-mediated mechanisms may operate in at least a subset of cases (Couto et al., 2025). The authors proposed that this pattern resembles autoimmune brain disorders and raises the possibility that heterogeneous aetiologies, including autoimmune-like processes, may converge on the shared histopathological hallmarks currently classified as PSP-type pathology.

One possible explanation for the increased T cell infiltration could also be early and sustained BBB dysfunction, which may facilitate the entry of peripheral immune cells into the central nervous system. Vascular pathology and BBB impairment have been reported in tauopathies and could enable lymphocyte trafficking into vulnerable brain regions (Sweeney et al., 2018). Finally, the magnitude and selectivity of the T-cell response raise the possibility of autoimmune-like processes in PSP, in which loss of immune tolerance to neuronal or tau-related antigens sustains a chronic, antigen-driven adaptive immune response. If confirmed, this would have major implications for disease stratification and for the development of immunomodulatory or antigen-specific therapeutic approaches.

In contrast, microglial/macrophage activity, measured by Iba1 expression, was higher in PD patients than those with MSA, aligning with previous findings of

microglial involvement in PD (McGeer, Itagaki, Boyes, et al., 1988; Ouchi et al., 2005). Iba1 expression was not significantly different between the PSP and other groups, including controls. Although this contrasts with earlier reports, such as McGeer et al. (McGeer, Itagaki, Boyes, et al., 1988), other investigations have reported similar findings regarding PD (Gerhard, Trender-Gerhard, et al., 2006; Kouli et al., 2020). It is also possible that increased microglial activity is more prominent in early stages of PSP but declines as degeneration progresses, leaving T cell activity more prominent in later stages. Discrepancies across studies may stem from methodological differences, disease stages, or regional specificity of inflammation. Although both T cells and microglia contribute to neuroinflammation, our findings indicate that they play distinct roles in PD and PSP. While correlations between T cell density and microglial activity suggest interaction between these immune components, their contributions to neurodegeneration appear to differ between disorders.

Finally, reduced SNc dopaminergic neuron density was associated with depression and sleep disorders across all patient groups. While previously shown in PD (Saari et al., 2021), our results extend this link to atypical parkinsonisms, which are frequently linked to depressive symptoms (Belvisi et al., 2018), though the effect was less pronounced. No significant correlations were observed between symptomatology and T cell or Iba1 expression, likely due to categorical clinical data and the advanced disease of the cohort.

The study has several limitations. As it reflects end-stage pathology, we cannot determine when neuroinflammatory changes first appear. The lack of clinical differences between MSA and PSP despite distinct immune profiles, and the inverse correlation between T cell count and disease duration, suggest these changes are not solely severity-driven. Only midbrain sections were analyzed, and future studies should include broader brain regions. Small sample sizes limited subtype comparisons, and retrospective clinical data lacked validated severity scales. Additionally, we used Abercrombie correction for neuron counts, which is less precise than stereology. Nonetheless, robust diagnostics, validated methods, and multiple markers strengthen our findings.

To summarize, the progression from symptom onset to death in PD, MSA, and PSP involves substantial loss of nigral neurons, with degeneration notably more severe in atypical parkinsonisms. Neuroinflammatory profiles differ markedly between disorders: PSP is defined by a pronounced T cell -mediated response, while PD is characterized by microglia-driven inflammation. These distinct patterns highlight the dynamic and disease-specific nature of neuroinflammation, suggesting that each disorder engages unique immune mechanisms contributing to neurodegeneration. T cell response observed in PSP reflects a disease mechanism in which adaptive immunity plays a more central role than in synucleinopathies.

Whether immune activation constitutes a primary trigger or a disease-modifying process in PSP remains unresolved. However, the present data supports a model in which neuroinflammation is not merely secondary to tau accumulation, but may actively shape disease onset, protein propagation, and progression.

6.2 No evidence of chronic levodopa toxicity on nigral neuroinflammation (Study II)

The primary goal of this study was to evaluate whether chronic levodopa treatment affects nigral neuronal survival or neuroinflammatory activity in PD, PSP, and MSA. Our results indicate no association between cumulative levodopa exposure and either dopaminergic neuron loss or neuroinflammatory markers in the SNc across these disorders. These findings support the conclusion that levodopa does not worsen underlying neuropathological changes in parkinsonian syndromes.

While preclinical studies have suggested that chronic levodopa use may trigger neuroinflammatory responses – especially in models of levodopa-induced dyskinesias – our postmortem analysis did not reveal elevated T cell infiltration or microglial activation in relation to levodopa exposure. Although earlier experimental work reported microglial activation and increased proinflammatory cytokines in association with levodopa-induced dyskinesias following long-term levodopa treatment (Barnum et al., 2008; Mulas et al., 2016), we found no significant difference between dyskinetic and non-dyskinetic PD cases. However, only four PD patients in our cohort had documented dyskinesia, likely reflecting underreporting rather than true absence. Nevertheless, our findings suggest that levodopa neither drives nor suppresses chronic nigral neuroinflammation in parkinsonian disorders.

Importantly, these findings reflect end-stage pathology. While transient immune responses during earlier disease stages cannot be excluded, our results suggest no sustained neuroinflammatory effects from levodopa. Moreover, no relationship was observed between cumulative levodopa dose and SNc dopaminergic neuron counts. This supports existing clinicopathological and imaging data refuting the idea of levodopa-induced neurotoxicity (Fahn et al., 2004; Parkkinen et al., 2011).

Our findings extend prior observations to atypical parkinsonisms. Even in PSP and MSA, levodopa exposure showed no impact on neuronal survival or neuroinflammation. Although the average levodopa dose in our PD group (0.68 kg) was lower than in Parkkinen et al. (3.3 kg) (Parkkinen et al., 2011), this likely reflects differences in age at onset and disease duration – our cohort was older and had shorter disease durations. Given that older patients may be more susceptible to cellular stress, these findings further reinforce levodopa's safety profile.

Limitations include relatively small PSP and MSA sample sizes and potential underreporting in clinical records, particularly regarding dyskinesia. Incomplete

medical data may have affected dose estimates. Despite this, the variability in levodopa exposure without corresponding neuropathological differences strengthens our conclusions.

In summary, chronic levodopa use does not contribute to nigral neuroinflammation or neuronal loss in PD, PSP, or MSA. These results reaffirm levodopa's safety as a symptomatic treatment and argue neurotoxic concerns, while underscoring the need for future longitudinal studies to explore its immunological effects in earlier disease stages.

6.3 Early cortical atrophy is related to depression in PD (Study III)

This study found that MTA and GCA were significantly associated with depression in patients with neurodegenerative movement disorders, particularly in those with PD. Depression correlated with faster progression of cortical atrophy over an average disease duration of 2.7 years.

Compared to earlier MRI-based studies linking depression with cortical atrophy and disrupted functional connectivity in PD (Huang et al., 2016; Luo et al., 2016), this study offers two important strengths. First, all diagnoses were confirmed postmortem, ensuring complete diagnostic accuracy. This is critical, as clinical misclassification of PD and atypical parkinsonian syndromes is common, especially in early disease stages (Joutsa et al., 2014). Second, the use of an automated CT-based method for assessing atrophy demonstrated strong reliability, matching MRI assessments with 84-90% accuracy (Pitkänen et al., 2020). Since CT imaging is more accessible and frequently used in clinical settings, this method has strong potential broader application in identifying patients at risk of depression.

However, the retrospective and cross-sectional design limits conclusions about causability. It remains unclear whether atrophy leads to depression, vice versa, or whether a third factor influences both. Moreover, some data, including depression severity scales, were missing from clinical records. The relatively small sample size for PSP and MSA further restricts conclusions about these groups.

The study found no association between cognitive performance and MTA, GCA, or WMHs within three years of motor symptom onset, even though MTA and GCA are commonly linked to cognitive deficits. The association between cognition and cortical atrophy may become more apparent in later stages of neurodegeneration, when both brain atrophy and cognitive impairment or dementia are more prevalent. The PIGD phenotype of PD was linked with higher WMH burden, aligning with prior MRI studies (Moccia et al., 2016; Wan et al., 2019), and may reflect greater vascular contributions to motor severity in this subgroup.

The longitudinal component revealed that depressed patients exhibited a faster rate of cortical atrophy than non-depressed patients. This may reflect underlying neuroinflammatory processes implicating in both depression and neurodegeneration. Elevated cytokines (e.g. IL-1β, IL-6) and microglia activation have been reported in depressed PD patients (Troubat et al., 2021; Wang et al., 2022), though such mechanisms were beyond the scope of this study.

In summary, MTA and GCA are early imaging markers associated with depression in parkinsonian disorders. There findings emphasize the need for integrated neuropsychiatric evaluation and support the utility of CT-based atrophy measures in routine clinical care.

6.4 Clinical implications

The findings of this thesis have several potential clinical implications. First, the demonstration of a pronounced and disease-specific T cell-mediated immune response in PSP provides support for reframing PSP as a disorder with a substantial immunopathological component, rather than a purely primary tauopathy. Importantly, these observations require confirmation in independent and preferably longitudinal cohorts, and several key questions remain unsolved. It is still unclear, for example, whether autoimmune mechanisms contribute to PSP in a subset of patients, or whether specific T cell responses may directly promote tau misfolding, aggregation, or propagation.

Nevertheless, these results can open avenues for further research on the mechanisms of PSP, such as investigating immunological biomarkers to resolve the possibility of autoimmune mechanisms. Such research could eventually lead to novel therapeutic strategies, including immunomodulatory approaches aimed at limiting pathological T cell infiltration, altering maladaptive immune responses, or suppressing chronic inflammatory signalling. Such interventions could potentially slow tau propagation or neurodegeneration. Additionally, the identification of disease-specific immune signatures highlights the potential for developing diagnostic and prognostic biomarkers. Peripheral or CNS immune markers, combined with imaging or other molecular assays, could improve early detection, and monitoring of disease-modifying treatments. Future longitudinal studies are needed to determine the temporal dynamics of T cell infiltration, microglial activity, and tau accumulation in PSP. It is necessary to determine whether immune activation occurs before tau pathology or develops alongside it and accelerates its spread. Extended analyses across additional brain regions are also necessary.

Second, the demonstration that chronic levodopa exposure does not exacerbate nigral neuron loss or neuroinflammation reinforces its safety profile and supports current treatment guidelines recommending early initiation in PD and atypical

parkinsonisms. These results provide neuropathological confirmation that levodopa remains a cornerstone symptomatic therapy without contributing to disease progression. Future studies could focus on whether levodopa interacts with immune pathways at prodromal or earlier disease stages, or whether its effects interact with emerging immunotherapies.

Third, the observed link between depression and accelerated cortical atrophy suggests that neuropsychiatric symptoms may serve as early markers of cortical vulnerability. Clinically, this underscores the importance of proactive neuropsychiatric screening and management. Structural imaging may aid in identifying patients at higher risk for cognitive and mood complications, potentially guiding personalized interventions.

Together, the findings of this thesis position neuroinflammation not only as a pathological hallmark but also a promising entry point for biomarker development, patient stratification, and disease-modifying therapeutic innovation across parkinsonian disorders, particularly in PSP. They also reinforce the continued central role of levodopa as a safe symptomatic therapy, while underscoring the importance of neuroimaging for identifying clinically meaningful brain changes linked to neuropsychiatric symptoms.

7 Summary/Conclusions

This thesis is based on three clinicopathological postmortem studies, each examining the relationship between clinical features and underlying neuropathology on PD, PSP, and MSA. Study I examined neuroinflammation in the SNc across 67 individuals with different parkinsonian disorders, aiming to characterize disorder-specific inflammatory profiles. Study II investigated the association between cumulative lifetime levodopa exposure and nigral neuroinflammation in 63 patients diagnosed with PD, PSP, or MSA. Study III focused on 50 individuals with parkinsonian syndromes, analyzing cortical atrophy and WMHs with a particular emphasis on the presence of clinical depression.

Study I revealed a pronounced T cell mediated inflammatory response in the SNc of PSP patients compared to other patient groups. In PD, the inflammation was predominantly microglia-mediated. Both PSP and MSA exhibited more extensive dopaminergic neuron loss in the SNc compared to PD. Notably, neuroinflammatory activity appeared to peak during earlier stages and declined as neuronal degeneration progressed.

Study II found no significant associations between cumulative levodopa exposure and neuronal density or neuroinflammatory markers in the SNc or crus cerebri across patients with PD, PSP, or MSA. Additional analyses accounting for disease duration and HY stage reinforced these findings, showing no meaningful correlation. Furthermore, no significant differences were detected between PD patients with or without a history of dyskinesia.

Study III demonstrated that both MTA and GCA are associated with depression in patients with PD, PSP, and MSA, even when cognitive status is taken into account. Additionally, longitudinal analysis revealed that progression of GCA correlates with the presence of depression, after adjusting for motor symptom duration at the time of scanning. In contrast, no similar associations were found for MTA progression or WMHs.

In summary, the main conclusions of this thesis are as follows:

I Despite shorter disease duration, PSP and MSA show more severe degeneration in the SNc, indicating an accelerated dopaminergic

neurodegenerative process. PSP exhibits a T cell -mediated inflammatory response in the SNc, whereas PD is associated with predominantly microglia-driven neuroinflammation. These findings highlight the disease-specific nature of neuroinflammation and suggest distinct underlying immune mechanisms across parkinsonian disorders.

II Cumulative levodopa exposure does not affect nigral neuronal survival or neuroinflammatory activity in PD, PSP, or MSA, supporting the long-term safety of levodopa in clinical use.

III MTA and GCA are associated with clinical depression in PD, PSP and MSA patients even when cognitive capacity is taken into account. The progression of GCA is linked with depression, supporting the role of structural changes in mood disturbances in parkinsonian syndromes.

Together, these findings from Study I highlight the differential inflammatory signatures underlying each disorder, offering insights into disease mechanisms and potential therapeutic targets. Study II provides further reassurance regarding the safety of long-term levodopa therapy, addressing longstanding concerns about its potential neurotoxicity. Study III contributes to a growing understanding of the neuroanatomical correlates of depression in neurodegenerative diseases and suggests that imaging markers of cortical atrophy may aid in identifying patients at greater risk for affective symptoms.

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References

Aarsland, D., Påhlhagen, S., Ballard, C. G., Ehrt, U., & Svenningsson, P. (2011). Depression in Parkinson disease--epidemiology, mechanisms and management. *Nat Rev Neurol*, *8*(1), 35-47. https://doi.org/10.1038/nrneurol.2011.189

Abbott, N. J., Patabendige, A. A., Dolman, D. E., Yusof, S. R., & Begley, D. J. (2010). Structure and function of the blood-brain barrier. *Neurobiol Dis*, *37*(1), 13-25. https://doi.org/10.1016/j.nbd.2009.07.030

Adams, R., Van Bogaert, L., & Van Der Eecken, H. (1961). [Nigro-striate and cerebello-nigro-striate degeneration. (Clinical uniqueness and pathological variability of presenile degeneration of the extrapyramidal rigidity type]. *Psychiatr Neurol (Basel)*, *142*, 219-259.

Ajami, B., Bennett, J. L., Krieger, C., Tetzlaff, W., & Rossi, F. M. (2007). Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. *Nat Neurosci*, *10*(12), 1538-1543. https://doi.org/10.1038/nn2014

Al-Chalabi, A., Dürr, A., Wood, N. W., Parkinson, M. H., Camuzat, A., Hulot, J. S.,…Group, N. G. S. (2009). Genetic variants of the alpha-synuclein gene SNCA are associated with multiple system atrophy. *PLoS One*, *4*(9), e7114. https://doi.org/10.1371/journal.pone.0007114

Albin, R. L., Young, A. B., & Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends Neurosci*, *12*(10), 366-375. https://doi.org/10.1016/0166-2236(89)90074-x

Almeida, L., Ahmed, B., Walz, R., De Jesus, S., Patterson, A., Martinez-Ramirez, D.,…McFarland, N. R. (2017). Depressive Symptoms are Frequent in Atypical Parkinsonian Disorders. *Mov Disord Clin Pract*, *4*(2), 191-197. https://doi.org/10.1002/mdc3.12382

Alster, P., Madetko, N., Koziorowski, D., & Friedman, A. (2020). Microglial Activation and Inflammation as a Factor in the Pathogenesis of Progressive Supranuclear Palsy (PSP). *Front Neurosci*, *14*, 893. https://doi.org/10.3389/fnins.2020.00893

Alzheimer's Association. s. (2015). 2015 Alzheimer's disease facts and figures. *Alzheimers Dement*, *11*(3), 332-384. https://doi.org/10.1016/j.jalz.2015.02.003

Armento, M. E., Stanley, M. A., Marsh, L., Kunik, M. E., York, M. K., Bush, A. L., & Calleo, J. S. (2012). Cognitive behavioral therapy for depression and anxiety in Parkinson's disease: a clinical review. *J Parkinsons Dis*, *2*(2), 135-151. https://doi.org/10.3233/JPD-2012-12080

Arotcarena, M. L., Dovero, S., Prigent, A., Bourdenx, M., Camus, S., Porras, G.,…Bezard, E. (2020). Bidirectional gut-to-brain and brain-to-gut propagation of synucleinopathy in non-human primates. *Brain*, *143*(5), 1462-1475. https://doi.org/10.1093/brain/awaa096

Asai, H., Ikezu, S., Tsunoda, S., Medalla, M., Luebke, J., Haydar, T., Wolozin, B., Butovsky, O., Kügler, S., & Ikezu, T. (2015). Depletion of microglia and inhibition of exosome synthesis halt tau propagation. *Nature neuroscience*, *18*(11), 1584–1593. https://doi.org/10.1038/nn.4132

Baker, M., Litvan, I., Houlden, H., Adamson, J., Dickson, D., Perez-Tur, J.,…Hutton, M. (1999). Association of an extended haplotype in the tau gene with progressive supranuclear palsy. *Hum Mol Genet*, *8*(4), 711-715. https://doi.org/10.1093/hmg/8.4.711

Bamford, A., Henderson, EJ. (2021). Parkinson's Disease in older people. *Medicine*, 49:56-61. https://doi.org/10.1016/j.mpmed.2020.10.008

Banati, R. B., Gehrmann, J., Schubert, P., & Kreutzberg, G. W. (1993). Cytotoxicity of microglia. *Glia*, *7*(1), 111-118. https://doi.org/10.1002/glia.440070117

Barnum, C. J., Eskow, K. L., Dupre, K., Blandino, P., Deak, T., & Bishop, C. (2008). Exogenous corticosterone reduces L-DOPA-induced dyskinesia in the hemi-parkinsonian rat: role for interleukin-1beta. *Neuroscience*, *156*(1), 30-41. https://doi.org/10.1016/j.neuroscience.2008.07.016

Baruzzi, A., Contin, M., Riva, R., Procaccianti, G., Albani, F., Tonello, C.,…Martinelli, P. (1987). Influence of meal ingestion time on pharmacokinetics of orally administered levodopa in parkinsonian patients. *Clin Neuropharmacol*, *10*(6), 527-537. https://doi.org/10.1097/00002826-198712000-00004

Belvisi, D., Berardelli, I., Suppa, A., Fabbrini, A., Pasquini, M., Pompili, M., & Fabbrini, G. (2018). Neuropsychiatric disturbances in atypical parkinsonian disorders. *Neuropsychiatr Dis Treat*, *14*, 2643-2656. https://doi.org/10.2147/NDT.S178263

Ben-Shlomo, Y., Darweesh, S., Llibre-Guerra, J., Marras, C., San Luciano, M., & Tanner, C. (2024). The epidemiology of Parkinson's disease. *Lancet*, *403*(10423), 283-292. https://doi.org/10.1016/S0140-6736(23)01419-8

Ben-Shlomo, Y., Wenning, G. K., Tison, F., & Quinn, N. P. (1997). Survival of patients with pathologically proven multiple system atrophy: a meta-analysis. *Neurology*, *48*(2), 384-393. https://doi.org/10.1212/wnl.48.2.384

Benabid, A. L., Pollak, P., Louveau, A., Henry, S., & de Rougemont, J. (1987). Combined (thalamotomy and stimulation) stereotactic surgery of the VIM thalamic nucleus for bilateral Parkinson disease. *Appl Neurophysiol*, *50*(1-6), 344-346. https://doi.org/10.1159/000100803

Benrud-Larson, L. M., Sandroni, P., Schrag, A., & Low, P. A. (2005). Depressive symptoms and life satisfaction in patients with multiple system atrophy. *Mov Disord*, *20*(8), 951-957. https://doi.org/10.1002/mds.20450

Bensimon, G., Ludolph, A., Agid, Y., Vidailhet, M., Payan, C., Leigh, P. N., & Group, N. S. (2009). Riluzole treatment, survival and diagnostic criteria in Parkinson plus disorders: the NNIPPS study. *Brain*, *132*(Pt 1), 156-171. https://doi.org/10.1093/brain/awn291

Bernier, L. P., York, E. M., Kamyabi, A., Choi, H. B., Weilinger, N. L., & MacVicar, B. A. (2020). Microglial metabolic flexibility supports immune surveillance of the brain parenchyma. *Nat Commun*, *11*(1), 1559. https://doi.org/10.1038/s41467-020-15267-z

Bertler, A., & Rosengren, E. (1959). Occurrence and distribution of catechol amines in brain. *Acta Physiol Scand*, *47*, 350-361.

Bien, C. G., Vincent, A., Barnett, M. H., Becker, A. J., Blümcke, I., Graus, F., Jellinger, K. A., Reuss, D. E., Ribalta, T., Schlegel, J., Sutton, I., Lassmann, H., & Bauer, J. (2012). Immunopathology of autoantibody-associated encephalitides: clues for pathogenesis. *Brain : a journal of neurology*, *135*(Pt 5), 1622–1638. https://doi.org/10.1093/brain/aws082

Birkmayer, W., & Hornykiewicz, O. (1961). [The L-3,4-dioxyphenylalanine (DOPA)-effect in Parkinson-akinesia]. *Wien Klin Wochenschr*, *73*, 787-788.

Birkmayer, W., Linauer, W., Mentasti, M., & Riederer, P. (1974). [2-year experiences with a combination treatment of Parkinsonism with L-dopa and a decarboxylase inhibitor (Benserazid, Ro 4-4602)]. *Wien Med Wochenschr*, *124*(22), 340-344.

Blauwendraat, C., Nalls, M. A., & Singleton, A. B. (2020). The genetic architecture of Parkinson's disease. *Lancet Neurol*, *19*(2), 170-178. https://doi.org/10.1016/S1474-4422(19)30287-X

Block, G., Liss, C., Reines, S., Irr, J., & Nibbelink, D. (1997). Comparison of immediate-release and controlled release carbidopa/levodopa in Parkinson's disease. A multicenter 5-year study. The CR First Study Group. *Eur Neurol*, *37*(1), 23-27. https://doi.org/10.1159/000117399

Blocq, P., & Marinesco, G. (1893). Sur un cas de tremblement parkinsonien hémiplégique symptomatique d'une tumeur du pédoncule cérébral. In: Paris: Mémoire lu à la Société de Biologie.

Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *Lancet*, *397*(10291), 2284-2303. https://doi.org/10.1016/S0140-6736(21)00218-X

Boesch, S. M., Wenning, G. K., Ransmayr, G., & Poewe, W. (2002). Dystonia in multiple system atrophy. *J Neurol Neurosurg Psychiatry*, *72*(3), 300-303. https://doi.org/10.1136/jnnp.72.3.300

Bohnen, N. I., & Hu, M. T. M. (2019). Sleep Disturbance as Potential Risk and Progression Factor for Parkinson's Disease. *J Parkinsons Dis*, *9*(3), 603-614. https://doi.org/10.3233/JPD-191627

Bond, A. E., Shah, B. B., Huss, D. S., Dallapiazza, R. F., Warren, A., Harrison, M. B.,…Elias, W. J. (2017). Safety and Efficacy of Focused Ultrasound Thalamotomy for Patients With Medication-Refractory, Tremor-Dominant Parkinson Disease: A Randomized Clinical Trial. *JAMA Neurol*, *74*(12), 1412-1418. https://doi.org/10.1001/jamaneurol.2017.3098

Borghammer, P., Horsager, J., Andersen, K., Van Den Berge, N., Raunio, A., Murayama, S., Parkkinen, L., & Myllykangas, L. (2021). Neuropathological evidence of body-first vs. brain-first Lewy body disease. *Neurobiology of disease*, *161*, 105557. https://doi.org/10.1016/j.nbd.2021.105557

Borghammer, P., Okkels, N., & Weintraub, D. (2024). Parkinson's Disease and Dementia with Lewy Bodies: One and the Same. *J Parkinsons Dis*, *14*(3), 383-397. https://doi.org/10.3233/JPD-240002

Borghammer, P., & Van Den Berge, N. (2019). Brain-First versus Gut-First Parkinson's Disease: A Hypothesis. *J Parkinsons Dis*, *9*(s2), S281-S295. https://doi.org/10.3233/JPD-191721

Bower, S. M., Weigand, S. D., Ali, F., Clark, H. M., Botha, H., Stierwalt, J. A.,…Josephs, K. A. (2022). Depression and Apathy across Different Variants of Progressive Supranuclear Palsy. *Mov Disord Clin Pract*, *9*(2), 212-217. https://doi.org/10.1002/mdc3.13396

Boxer, A. L., Yu, J. T., Golbe, L. I., Litvan, I., Lang, A. E., & Höglinger, G. U. (2017). Advances in progressive supranuclear palsy: new diagnostic criteria, biomarkers, and therapeutic approaches. *Lancet Neurol*, *16*(7), 552-563. https://doi.org/10.1016/S1474-4422(17)30157-6

Braak, H., Del Tredici, K., Rüb, U., de Vos, R. A., Jansen Steur, E. N., & Braak, E. (2003). Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging*, *24*(2), 197-211. https://doi.org/10.1016/s0197-4580(02)00065-9

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res*, *318*(1), 121-134. https://doi.org/10.1007/s00441-004-0956-9

Bradbury, S. E., Cary. (1925). Postural hypotension. A report of three cases. In (Vol. 1, pp. Pages 73 - 86). American Heart Journal.

Brochard, V., Combadière, B., Prigent, A., Laouar, Y., Perrin, A., Beray-Berthat, V.,…Hunot, S. (2009). Infiltration of CD4+ lymphocytes into the brain contributes to neurodegeneration in a mouse model of Parkinson disease. *J Clin Invest*, *119*(1), 182-192. https://doi.org/10.1172/JCI36470

Bukhatwa, S., Zeng, B. Y., Rose, S., & Jenner, P. (2010). A comparison of changes in proteasomal subunit expression in the substantia nigra in Parkinson's disease, multiple system atrophy and progressive supranuclear palsy. *Brain Res*, *1326*, 174-183. https://doi.org/10.1016/j.brainres.2010.02.045

Burns, M. R., & McFarland, N. R. (2020). Current Management and Emerging Therapies in Multiple System Atrophy. *Neurotherapeutics*, *17*(4), 1582-1602. https://doi.org/10.1007/s13311-020-00890-x

Burrell, J. R., Hodges, J. R., & Rowe, J. B. (2014). Cognition in corticobasal syndrome and progressive supranuclear palsy: a review. *Movement disorders : official journal of the Movement Disorder Society*, *29*(5), 684–693. https://doi.org/10.1002/mds.25872

Calo, L., Wegrzynowicz, M., Santivañez-Perez, J., & Grazia Spillantini, M. (2016). Synaptic failure and α-synuclein. *Mov Disord*, *31*(2), 169-177. https://doi.org/10.1002/mds.26479

Carlsson, A. (1959). The occurrence, distribution and physiological role of catecholamines in the nervous system. *Pharmacol Rev*, *11*(2, Part 2), 490-493.

Carlsson, A., LINDQVIST, M., & MAGNUSSON, T. (1957). 3,4-Dihydroxyphenylalanine and 5-hydroxytryptophan as reserpine antagonists. *Nature*, *180*(4596), 1200. https://doi.org/10.1038/1801200a0

Carroll, J. J., Lavine, S. D., & Meyers, P. M. (2017). Imaging of Subdural Hematomas. *Neurosurg Clin N Am*, *28*(2), 179-203. https://doi.org/10.1016/j.nec.2016.11.001

Caso, F., Agosta, F., Ječmenica-Lukić, M., Petrović, I., Meani, A., Kostic, V. S., & Filippi, M. (2018). Progression of white matter damage in progressive supranuclear palsy with predominant parkinsonism. *Parkinsonism Relat Disord*, *49*, 95-99. https://doi.org/10.1016/j.parkreldis.2018.01.001

Caso, F., Canu, E., Lukic, M. J., Petrovic, I. N., Fontana, A., Nikolic, I.,…Agosta, F. (2020). Cognitive impairment and structural brain damage in multiple system atrophy-parkinsonian variant. *J Neurol*, *267*(1), 87-94. https://doi.org/10.1007/s00415-019-09555-y

Champy, P., Höglinger, G. U., Féger, J., Gleye, C., Hocquemiller, R., Laurens, A.,…Ruberg, M. (2004). Annonacin, a lipophilic inhibitor of mitochondrial complex I, induces nigral and striatal neurodegeneration in rats: possible relevance for atypical parkinsonism in Guadeloupe. *J Neurochem*, *88*(1), 63-69. https://doi.org/10.1046/j.1471-4159.2003.02138.x

Champy, P., Melot, A., Guérineau Eng, V., Gleye, C., Fall, D., Höglinger, G. U.,…Hocquemiller, R. (2005). Quantification of acetogenins in Annona muricata linked to atypical parkinsonism in guadeloupe. *Mov Disord*, *20*(12), 1629-1633. https://doi.org/10.1002/mds.20632

Charcot, J. M. J. M. (1877). Lectures on the diseases of the nervous system, delivered at La Salpêtrière. In (Vol. v.2): London : The New Sydenham Society.

Chase, T. N. (1998). The significance of continuous dopaminergic stimulation in the treatment of Parkinson's disease. *Drugs*, *55 Suppl 1*, 1-9. https://doi.org/10.2165/00003495-199855001-00001

Chaudhuri, K. R., Healy, D. G., Schapira, A. H., & Excellence, N. I. f. C. (2006). Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurol*, *5*(3), 235-245. https://doi.org/10.1016/S1474-4422(06)70373-8

Chen, X., Firulyova, M., Manis, M., Herz, J., Smirnov, I., Aladyeva, E., Wang, C., Bao, X., Finn, M. B., Hu, H., Shchukina, I., Kim, M. W., Yuede, C. M., Kipnis, J., Artyomov, M. N., Ulrich, J. D., & Holtzman, D. M. (2023). Microglia-mediated T cell infiltration drives neurodegeneration in tauopathy. *Nature*, *615*(7953), 668–677. https://doi.org/10.1038/s41586-023-05788-0

Chendo, I., Silva, C., Duarte, G. S., Prada, L., Vian, J., Quintão, A.,…Ferreira, J. J. (2022). Frequency of Depressive Disorders in Parkinson's Disease: A Systematic Review and Meta-Analysis. *J Parkinsons Dis*, *12*(5), 1409-1418. https://doi.org/10.3233/JPD-223207

Cherry, J. D., Tripodis, Y., Alvarez, V. E., Huber, B., Kiernan, P. T., Daneshvar, D. H., Mez, J., Montenigro, P. H., Solomon, T. M., Alosco, M. L., Stern, R. A., McKee, A. C., & Stein, T. D. (2016). Microglial neuroinflammation contributes to tau accumulation in chronic traumatic encephalopathy. *Acta neuropathologica communications*, *4*(1), 112. https://doi.org/10.1186/s40478-016-0382-8

Chevalier, G., & Deniau, J. M. (1990). Disinhibition as a basic process in the expression of striatal functions. *Trends Neurosci*, *13*(7), 277-280. https://doi.org/10.1016/0166-2236(90)90109-n

Chou, K. L., Stacy, M., Simuni, T., Miyasaki, J., Oertel, W. H., Sethi, K.,…Stocchi, F. (2018). The spectrum of "off" in Parkinson's disease: What have we learned over 40 years? *Parkinsonism Relat Disord*, *51*, 9-16. https://doi.org/10.1016/j.parkreldis.2018.02.001

Clavaguera, F., Akatsu, H., Fraser, G., Crowther, R. A., Frank, S., Hench, J.,…Tolnay, M. (2013). Brain homogenates from human tauopathies induce tau inclusions in mouse brain. *Proc Natl Acad Sci U S A*, *110*(23), 9535-9540. https://doi.org/10.1073/pnas.1301175110

Clavaguera, F., Bolmont, T., Crowther, R. A., Abramowski, D., Frank, S., Probst, A., Fraser, G., Stalder, A. K., Beibel, M., Staufenbiel, M., Jucker, M., Goedert, M., & Tolnay, M. (2009). Transmission and spreading of tauopathy in transgenic mouse brain. *Nature cell biology*, *11*(7), 909–913. https://doi.org/10.1038/ncb1901

Multiple System Atrophy Research Collaboration. (2013). Mutations in COQ2 in familial and sporadic multiple-system atrophy. *N Engl J Med*, *369*(3), 233-244. https://doi.org/10.1056/NEJMoa1212115

GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*, *388*(10053), 1545-1602. https://doi.org/10.1016/S0140-6736(16)31678-6

Colom-Cadena, M., Gelpi, E., Martí, M. J., Charif, S., Dols-Icardo, O., Blesa, R., Clarimón, J., & Lleó, A. (2013). MAPT H1 haplotype is associated with enhanced α-synuclein deposition in dementia with Lewy bodies. *Neurobiology of aging*, *34*(3), 936–942. https://doi.org/10.1016/j.neurobiolaging.2012.06.015

Colonna, M., & Butovsky, O. (2017). Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annu Rev Immunol*, *35*, 441-468. https://doi.org/10.1146/annurev-immunol-051116-052358

Colosimo, C., Tiple, D., & Wenning, G. K. (2005). Management of multiple system atrophy: state of the art. *J Neural Transm (Vienna)*, *112*(12), 1695-1704. https://doi.org/10.1007/s00702-005-0379-0

Constantinescu, R., Richard, I., & Kurlan, R. (2007). Levodopa responsiveness in disorders with parkinsonism: a review of the literature. *Mov Disord*, *22*(15), 2141-2148; quiz 2295. https://doi.org/10.1002/mds.21578

Contaldi, E., Magistrelli, L., & Comi, C. (2022). T Lymphocytes in Parkinson's Disease. *J Parkinsons Dis*, *12*(s1), S65-S74. https://doi.org/10.3233/JPD-223152

Contin, M., & Martinelli, P. (2010). Pharmacokinetics of levodopa. *J Neurol*, *257*(Suppl 2), S253-261. https://doi.org/10.1007/s00415-010-5728-8

Contin, M., Riva, R., Albani, F., & Baruzzi, A. (1996). Pharmacokinetic optimisation in the treatment of Parkinson's disease. *Clin Pharmacokinet*, *30*(6), 463-481. https://doi.org/10.2165/00003088-199630060-00004

Contin, M., Riva, R., Martinelli, P., Procaccianti, G., Cortelli, P., Avoni, P., & Baruzzi, A. (1990). Response to a standard oral levodopa test in parkinsonian patients with and without motor fluctuations. *Clin Neuropharmacol*, *13*(1), 19-28. https://doi.org/10.1097/00002826-199002000-00002

Cotzias, G. C., Van Woert, M. H., & Schiffer, L. M. (1967). Aromatic amino acids and modification of parkinsonism. *N Engl J Med*, *276*(7), 374-379. https://doi.org/10.1056/NEJM196702162760703

Couto, B., Forrest, S. L., Fearon, C., Lee, S., Knott, S., Li, J.,…Kovacs, G. G. (2025). Midbrain cytotoxic T cells as a distinct neuropathological feature of progressive supranuclear palsy. *Brain*. https://doi.org/10.1093/brain/awaf135

Coyle-Gilchrist, I. T., Dick, K. M., Patterson, K., Vázquez Rodríquez, P., Wehmann, E., Wilcox, A.,…Rowe, J. B. (2016). Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes. *Neurology*, *86*(18), 1736-1743. https://doi.org/10.1212/WNL.0000000000002638

Cummings, J., Isaacson, S., Mills, R., Williams, H., Chi-Burris, K., Corbett, A.,…Ballard, C. (2014). Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. *Lancet*, *383*(9916), 533-540. https://doi.org/10.1016/S0140-6736(13)62106-6

Cykowski, M. D., Coon, E. A., Powell, S. Z., Jenkins, S. M., Benarroch, E. E., Low, P. A.,…Parisi, J. E. (2015). Expanding the spectrum of neuronal pathology in multiple system atrophy. *Brain*, *138*(Pt 8), 2293-2309. https://doi.org/10.1093/brain/awv114

Daniel, S. E., & Lees, A. J. (1993). Parkinson's Disease Society Brain Bank, London: overview and research. *J Neural Transm Suppl*, *39*, 165-172.

Dash, S. K., Stezin, A., Takalkar, T., George, L., Kamble, N. L., Netravathi, M.,…Pal, P. K. (2019). Abnormalities of white and grey matter in early multiple system atrophy: comparison of parkinsonian and cerebellar variants. *Eur Radiol*, *29*(2), 716-724. https://doi.org/10.1007/s00330-018-5594-9

Davis, D. M., & Dustin, M. L. (2004). What is the importance of the immunological synapse? *Trends Immunol*, *25*(6), 323-327. https://doi.org/10.1016/j.it.2004.03.007

de Lau, L. M., & Breteler, M. M. (2006). Epidemiology of Parkinson's disease. *Lancet Neurol*, *5*(6), 525-535. https://doi.org/10.1016/S1474-4422(06)70471-9

Dickson, D. W., Ahmed, Z., Algom, A. A., Tsuboi, Y., & Josephs, K. A. (2010). Neuropathology of variants of progressive supranuclear palsy. *Curr Opin Neurol*, *23*(4), 394-400. https://doi.org/10.1097/WCO.0b013e32833be924

Dickson, D. W., Braak, H., Duda, J. E., Duyckaerts, C., Gasser, T., Halliday, G. M.,…Litvan, I. (2009). Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. *Lancet Neurol*, *8*(12), 1150-1157. https://doi.org/10.1016/S1474-4422(09)70238-8

Dickson, D. W., Lee, S. C., Mattiace, L. A., Yen, S. H., & Brosnan, C. (1993). Microglia and cytokines in neurological disease, with special reference to AIDS and Alzheimer's disease. *Glia*, *7*(1), 75-83. https://doi.org/10.1002/glia.440070113

Dorsey, E. R., Sherer, T., Okun, M. S., & Bloem, B. R. (2018). The Emerging Evidence of the Parkinson Pandemic. *J Parkinsons Dis*, *8*(s1), S3-S8. https://doi.org/10.3233/JPD-181474

Dugger, B. N., Adler, C. H., Shill, H. A., Caviness, J., Jacobson, S., Driver-Dunckley, E.,…Consortium, A. P. s. D. (2014). Concomitant pathologies among a spectrum of parkinsonian disorders. *Parkinsonism Relat Disord*, *20*(5), 525-529. https://doi.org/10.1016/j.parkreldis.2014.02.012

Dugger, B. N., Hentz, J. G., Adler, C. H., Sabbagh, M. N., Shill, H. A., Jacobson, S.,…Beach, T. G. (2014). Clinicopathological outcomes of prospectively followed normal elderly brain bank volunteers. *J Neuropathol Exp Neurol*, *73*(3), 244-252. https://doi.org/10.1097/NEN.0000000000000046

Duro, M. V., Ebright, B., & Yassine, H. N. (2022). Lipids and brain inflammation in APOE4-associated dementia. *Curr Opin Lipidol*, *33*(1), 16-24. https://doi.org/10.1097/MOL.0000000000000801

Elbers, R. G., Verhoef, J., van Wegen, E. E., Berendse, H. W., & Kwakkel, G. (2015). Interventions for fatigue in Parkinson's disease. *Cochrane Database Syst Rev*, *2015*(10), CD010925. https://doi.org/10.1002/14651858.CD010925.pub2

Fabbri, M., Ferreira, J. J., & Rascol, O. (2022). COMT Inhibitors in the Management of Parkinson's Disease. *CNS Drugs*, *36*(3), 261-282. https://doi.org/10.1007/s40263-021-00888-9

Fabbri, M., Reimão, S., Carvalho, M., Nunes, R. G., Abreu, D., Guedes, L. C.,…Ferreira, J. J. (2017). Substantia Nigra Neuromelanin as an Imaging Biomarker of Disease Progression in Parkinson's Disease. *J Parkinsons Dis*, *7*(3), 491-501. https://doi.org/10.3233/JPD-171135

Fahn, S. (1992). Adverse effects of levodopa. In (pp. 89-112): In: Olanow CW, Lieberman AN (eds) The Scientific Basis for the Treatment of Parkinson's disease. Carnforth, England; Parthenon Publishing Group.

Fahn, S. (1996). Is levodopa toxic? *Neurology*, *47*(6 Suppl 3), S184-195. https://doi.org/10.1212/wnl.47.6_suppl_3.184s

Fahn, S., Oakes, D., Shoulson, I., Kieburtz, K., Rudolph, A., Lang, A.,…Group, P. S. (2004). Levodopa and the progression of Parkinson's disease. *N Engl J Med*, *351*(24), 2498-2508. https://doi.org/10.1056/NEJMoa033447

Fairley, A., Stewart, C. J., Cassidy, A., Woodside, J. V., & McEvoy, C. T. (2022). Diet Patterns, the Gut Microbiome, and Alzheimer's Disease. *J Alzheimers Dis*, *88*(3), 933-941. https://doi.org/10.3233/JAD-220205

Fanciulli, A., & Wenning, G. K. (2015). Multiple-system atrophy. *N Engl J Med*, *372*(3), 249-263. https://doi.org/10.1056/NEJMra1311488

Fearnley, J. M., & Lees, A. J. (1991). Ageing and Parkinson's disease: substantia nigra regional selectivity. *Brain*, *114 (Pt 5)*, 2283-2301. https://doi.org/10.1093/brain/114.5.2283

Fellner, L., Irschick, R., Schanda, K., Reindl, M., Klimaschewski, L., Poewe, W.,…Stefanova, N. (2013). Toll-like receptor 4 is required for α-synuclein dependent activation of microglia and astroglia. *Glia*, *61*(3), 349-360. https://doi.org/10.1002/glia.22437

Fernandez, D. M., Rahman, A. H., Fernandez, N. F., Chudnovskiy, A., Amir, E. D., Amadori, L.,…Giannarelli, C. (2019). Single-cell immune landscape of human atherosclerotic plaques. *Nat Med*, *25*(10), 1576-1588. https://doi.org/10.1038/s41591-019-0590-4

Ferrari, A. J., Somerville, A. J., Baxter, A. J., Norman, R., Patten, S. B., Vos, T., & Whiteford, H. A. (2013). Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychol Med*, *43*(3), 471-481. https://doi.org/10.1017/S0033291712001511

Flavell, J., & Nestor, P. J. (2022). A Systematic Review of Apathy and Depression in Progressive Supranuclear Palsy. *J Geriatr Psychiatry Neurol*, *35*(3), 280-292. https://doi.org/10.1177/0891988721993545

Forno, L. S. (1996). Neuropathology of Parkinson's disease. *J Neuropathol Exp Neurol*, *55*(3), 259-272. https://doi.org/10.1097/00005072-199603000-00001

Fox, S. H., Katzenschlager, R., Lim, S. Y., Barton, B., de Bie, R. M. A., Seppi, K.,…Committee, M. D. S. E.-B. M. (2018). International Parkinson and movement disorder society evidence-based medicine review: Update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*, *33*(8), 1248-1266. https://doi.org/10.1002/mds.27372

Franco, R., Reyes-Resina, I., & Navarro, G. (2021). Dopamine in Health and Disease: Much More Than a Neurotransmitter. *Biomedicines*, *9*(2). https://doi.org/10.3390/biomedicines9020109

Frequin, H. L., Verschuur, C. V. M., Suwijn, S. R., Boel, J. A., Post, B., Bloem, B. R., van Hilten, J. J., van Laar, T., Tissingh, G., Munts, A. G., Dijk, J. M., Lang, A. E., Dijkgraaf, M. G. W., Hoogland, J., de Bie, R. M. A., & LEAP Study Group (2024). Long-Term Follow-Up of the LEAP Study: Early Versus Delayed Levodopa in Early Parkinson's Disease. *Movement disorders : official journal of the Movement Disorder Society*, *39*(6), 975–982. https://doi.org/10.1002/mds.29796

Galea, I., Bechmann, I., & Perry, V. H. (2007). What is immune privilege (not)? *Trends Immunol*, *28*(1), 12-18. https://doi.org/10.1016/j.it.2006.11.004

Gao, C., Jiang, J., Tan, Y., & Chen, S. (2023). Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. *Signal Transduct Target Ther*, *8*(1), 359. https://doi.org/10.1038/s41392-023-01588-0

Gao, H. M., Jiang, J., Wilson, B., Zhang, W., Hong, J. S., & Liu, B. (2002). Microglial activation-mediated delayed and progressive degeneration of rat nigral dopaminergic neurons: relevance to Parkinson's disease. *J Neurochem*, *81*(6), 1285-1297. https://doi.org/10.1046/j.1471-4159.2002.00928.x

Garcia-Ruiz, P. J., Martinez Castrillo, J. C., Alonso-Canovas, A., Herranz Barcenas, A., Vela, L., Sanchez Alonso, P.,…Mahillo Fernandez, I. (2014). Impulse control disorder in patients with Parkinson's disease under dopamine agonist therapy: a multicentre study. *J Neurol Neurosurg Psychiatry*, *85*(8), 840-844. https://doi.org/10.1136/jnnp-2013-306787

Gardner, R. C., Boxer, A. L., Trujillo, A., Mirsky, J. B., Guo, C. C., Gennatas, E. D.,…Seeley, W. W. (2013). Intrinsic connectivity network disruption in progressive supranuclear palsy. *Ann Neurol*, *73*(5), 603-616. https://doi.org/10.1002/ana.23844

Gegg, M. E., Menozzi, E., & Schapira, A. H. V. (2022). Glucocerebrosidase-associated Parkinson disease: Pathogenic mechanisms and potential drug treatments. *Neurobiol Dis*, *166*, 105663. https://doi.org/10.1016/j.nbd.2022.105663

Gelb, D. J., Oliver, E., & Gilman, S. (1999). Diagnostic criteria for Parkinson disease. *Arch Neurol*, *56*(1), 33-39. https://doi.org/10.1001/archneur.56.1.33

Gerhard, A., Banati, R. B., Goerres, G. B., Cagnin, A., Myers, R., Gunn, R. N.,…Brooks, D. J. (2003). [11C](R)-PK11195 PET imaging of microglial activation in multiple system atrophy. *Neurology*, *61*(5), 686-689. https://doi.org/10.1212/01.wnl.0000078192.95645.e6

Gerhard, A., Pavese, N., Hotton, G., Turkheimer, F., Es, M., Hammers, A.,…Brooks, D. J. (2006). In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease. *Neurobiol Dis*, *21*(2), 404-412. https://doi.org/10.1016/j.nbd.2005.08.002

Gerhard, A., Trender-Gerhard, I., Turkheimer, F., Quinn, N. P., Bhatia, K. P., & Brooks, D. J. (2006). In vivo imaging of microglial activation with [11C](R)-PK11195 PET in progressive supranuclear palsy. *Mov Disord*, *21*(1), 89-93. https://doi.org/10.1002/mds.20668

Giannini, G., Calandra-Buonaura, G., Asioli, G. M., Cecere, A., Barletta, G., Mignani, F.,…Cortelli, P. (2018). The natural history of idiopathic autonomic failure: The IAF-BO cohort study. *Neurology*, *91*(13), e1245-e1254. https://doi.org/10.1212/WNL.0000000000006243

Giasson, B. I., Duda, J. E., Murray, I. V., Chen, Q., Souza, J. M., Hurtig, H. I.,…Lee, V. M. (2000). Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. *Science*, *290*(5493), 985-989. https://doi.org/10.1126/science.290.5493.985

Gibb, W. R., & Lees, A. J. (1988). The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *J Neurol Neurosurg Psychiatry*, *51*(6), 745-752. https://doi.org/10.1136/jnnp.51.6.745

Gilks, W. P., Abou-Sleiman, P. M., Gandhi, S., Jain, S., Singleton, A., Lees, A. J.,…Wood, N. W. (2005). A common LRRK2 mutation in idiopathic Parkinson's disease. *Lancet*, *365*(9457), 415-416. https://doi.org/10.1016/S0140-6736(05)17830-1

Gilman, S., May, S. J., Shults, C. W., Tanner, C. M., Kukull, W., Lee, V. M.,…Group, N. A. M. S. A. S. (2005). The North American Multiple System Atrophy Study Group. *J Neural Transm (Vienna)*, *112*(12), 1687-1694. https://doi.org/10.1007/s00702-005-0381-6

Gilman, S., Wenning, G. K., Low, P. A., Brooks, D. J., Mathias, C. J., Trojanowski, J. Q.,…Vidailhet, M. (2008). Second consensus statement on the diagnosis of multiple system atrophy. *Neurology*, *71*(9), 670-676. https://doi.org/10.1212/01.wnl.0000324625.00404.15

Ginhoux, F., Greter, M., Leboeuf, M., Nandi, S., See, P., Gokhan, S.,…Merad, M. (2010). Fate mapping analysis reveals that adult microglia derive from primitive macrophages. *Science*, *330*(6005), 841-845. https://doi.org/10.1126/science.1194637

Giovannoni, F., & Quintana, F. J. (2020). The Role of Astrocytes in CNS Inflammation. *Trends Immunol*, *41*(9), 805-819. https://doi.org/10.1016/j.it.2020.07.007

Goedert M. (2015). Neurodegeneration. Alzheimer's and Parkinson's diseases: The prion concept in relation to assembled Aβ, tau, and α-synuclein. *Science (New York, N.Y.)*, *349*(6248), 1255555. https://doi.org/10.1126/science.1255555

Golbe, L. I., & Ohman-Strickland, P. A. (2007). A clinical rating scale for progressive supranuclear palsy. *Brain*, *130*(Pt 6), 1552-1565. https://doi.org/10.1093/brain/awm032

González-Usigli, H. A., Ortiz, G. G., Charles-Niño, C., Mireles-Ramírez, M. A., Pacheco-Moisés, F. P., Torres-Mendoza, B. M. G., Hernández-Cruz, J. J., Delgado-Lara, D. L. D. C., & Ramírez-Jirano, L. J. (2023). Neurocognitive Psychiatric and Neuropsychological Alterations in Parkinson's Disease: A Basic and Clinical Approach. *Brain sciences*, *13*(3), 508. https://doi.org/10.3390/brainsci13030508

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F.,…Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology*, *76*(11), 1006-1014. https://doi.org/10.1212/WNL.0b013e31821103e6

Goverman, J. (2009). Autoimmune T cell responses in the central nervous system. *Nat Rev Immunol*, *9*(6), 393-407. https://doi.org/10.1038/nri2550

Graham, J. G., & Oppenheimer, D. R. (1969). Orthostatic hypotension and nicotine sensitivity in a case of multiple system atrophy. *J Neurol Neurosurg Psychiatry*, *32*(1), 28-34. https://doi.org/10.1136/jnnp.32.1.28

Grakoui, A., Bromley, S. K., Sumen, C., Davis, M. M., Shaw, A. S., Allen, P. M., & Dustin, M. L. (1999). The immunological synapse: a molecular machine controlling T cell activation. *Science*, *285*(5425), 221-227. https://doi.org/10.1126/science.285.5425.221

Green, T. R. F., Murphy, S. M., & Rowe, R. K. (2022). Comparisons of quantitative approaches for assessing microglial morphology reveal inconsistencies, ecological fallacy, and a need for standardization. *Sci Rep*, *12*(1), 18196. https://doi.org/10.1038/s41598-022-23091-2

Guggenheim, M. (1913). Dioxyphenylalanin, eine neue Aminosäure aus Vicia faba. In (Vol. 88, pp. 276 – 284). *Hoppe-Seyler's Zeitschr Physiol Chem.*

Guillery, R. W. (2002). On counting and counting errors. *J Comp Neurol*, *447*(1), 1-7. https://doi.org/10.1002/cne.10221

Ehringer, H & Hornykiewicz, O. (1960). Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Mensachen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. In (Vol. 38, pp. 1238 – 1239). *Klin Wochenschr*.

Hammond, T. R., Marsh, S. E., & Stevens, B. (2019). Immune Signaling in Neurodegeneration. *Immunity*, *50*(4), 955-974. https://doi.org/10.1016/j.immuni.2019.03.016

Hamza, T. H., Zabetian, C. P., Tenesa, A., Laederach, A., Montimurro, J., Yearout, D.,…Payami, H. (2010). Common genetic variation in the HLA region is associated with late-onset sporadic Parkinson's disease. *Nat Genet*, *42*(9), 781-785. https://doi.org/10.1038/ng.642

Hanganu, A., Bruneau, M. A., Degroot, C., Bedetti, C., Mejia-Constain, B., Lafontaine, A. L.,…Monchi, O. (2017). Depressive symptoms in Parkinson's disease correlate with cortical atrophy over time. *Brain Cogn*, *111*, 127-133. https://doi.org/10.1016/j.bandc.2016.11.001

Hanisch, U. K., & Kettenmann, H. (2007). Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat Neurosci*, *10*(11), 1387-1394. https://doi.org/10.1038/nn1997

Hansen, C., Angot, E., Bergström, A. L., Steiner, J. A., Pieri, L., Paul, G., Outeiro, T. F., Melki, R., Kallunki, P., Fog, K., Li, J. Y., & Brundin, P. (2011). α-Synuclein propagates from mouse brain to grafted dopaminergic neurons and seeds aggregation in cultured human cells. *The Journal of clinical investigation*, *121*(2), 715–725. https://doi.org/10.1172/JCI43366

Haque, M. E., Akther, M., Azam, S., Kim, I. S., Lin, Y., Lee, Y. H., & Choi, D. K. (2022). Targeting α-synuclein aggregation and its role in mitochondrial dysfunction in Parkinson's disease. *Br J Pharmacol*, *179*(1), 23-45. https://doi.org/10.1111/bph.15684

Haque, M. M., Murale, D. P., Kim, Y. K., & Lee, J. S. (2019). Crosstalk between Oxidative Stress and Tauopathy. *Int J Mol Sci*, *20*(8). https://doi.org/10.3390/ijms20081959

Hara, K., Momose, Y., Tokiguchi, S., Shimohata, M., Terajima, K., Onodera, O.,…Tsuji, S. (2007). Multiplex families with multiple system atrophy. *Arch Neurol*, *64*(4), 545-551. https://doi.org/10.1001/archneur.64.4.545

Hardman, C. D., Halliday, G. M., McRitchie, D. A., Cartwright, H. R., & Morris, J. G. (1997). Progressive supranuclear palsy affects both the substantia nigra pars compacta and reticulata. *Exp Neurol*, *144*(1), 183-192. https://doi.org/10.1006/exnr.1997.6415

Hartnell, I. J., Woodhouse, D., Jasper, W., Mason, L., Marwaha, P., Graffeuil, M., Lau, L. C., Norman, J. L., Chatelet, D. S., Buee, L., Nicoll, J. A. R., Blum, D., Dorothee, G., & Boche, D. (2024). Glial reactivity and T cell infiltration in frontotemporal lobar degeneration with tau pathology. *Brain : a journal of neurology*, *147*(2), 590–606. https://doi.org/10.1093/brain/awad309

Hassan, A., Parisi, J. E., & Josephs, K. A. (2012). Autopsy-proven progressive supranuclear palsy presenting as behavioral variant frontotemporal dementia. *Neurocase*, *18*(6), 478-488. https://doi.org/10.1080/13554794.2011.627345

Hayes, M. T. (2019). Parkinson's Disease and Parkinsonism. *Am J Med*, *132*(7), 802-807. https://doi.org/10.1016/j.amjmed.2019.03.001

Heikkinen, S., Cajanus, A., Katisko, K., Hartikainen, P., Vanninen, R., Haapasalo, A., Krüger, J., Remes, A. M., & Solje, E. (2022). Brainstem atrophy is linked to extrapyramidal symptoms in frontotemporal dementia. *Journal of neurology*, *269*(8), 4488–4497. https://doi.org/10.1007/s00415-022-11095-x

Heikkinen, S., Katisko, K., Haapasalo, A., Portaankorva, A., Hartikainen, P., & Solje, E. (2025). Overlap in the diagnostic criteria of frontotemporal dementia syndromes with parkinsonism. *J Alzheimers Dis*, *104*(2), 374-381. https://doi.org/10.1177/13872877251316804

Hely, M. A., Morris, J. G., Reid, W. G., & Trafficante, R. (2005). Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. *Mov Disord*, *20*(2), 190-199. https://doi.org/10.1002/mds.20324

Henriksson, M. M., Aro, H. M., Marttunen, M. J., Heikkinen, M. E., Isometsä, E. T., Kuoppasalmi, K. I., & Lönnqvist, J. K. (1993). Mental disorders and comorbidity in suicide. *Am J Psychiatry*, *150*(6), 935-940. https://doi.org/10.1176/ajp.150.6.935

Herting, B., Beuthien-Baumann, B., Pöttrich, K., Donix, M., Triemer, A., Lampe, J. B.,…Holthoff, V. A. (2007). Prefrontal cortex dysfunction and depression in atypical parkinsonian syndromes. *Mov Disord*, *22*(4), 490-497. https://doi.org/10.1002/mds.21237

Hoehn, M. M., & Yahr, M. D. (1967). Parkinsonism: onset, progression and mortality. *Neurology*, *17*(5), 427-442. https://doi.org/10.1212/wnl.17.5.427

Holtz, P., Heise, R., & Lüdtke, K. (1938). Fermentativer Abbau von Ldioxyphenylalanin (Dopa) durch Niere. In (Vol. 191, pp. 87 – 118). *Naunyn-Schmiedeberg's Arch Exp Path Pharmak*.

Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., Ramakrishnan, S.,…Stevens, B. (2016). Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*, *352*(6286), 712-716. https://doi.org/10.1126/science.aad8373

Howell, M. J., & Schenck, C. H. (2015). Rapid Eye Movement Sleep Behavior Disorder and Neurodegenerative Disease. *JAMA Neurol*, *72*(6), 707-712. https://doi.org/10.1001/jamaneurol.2014.4563

Huang, P., Guan, X., Guo, T., Zeng, Q., Xuan, M., Gu, Q.,…Zhang, M. (2020). Damaged Insula Network Contributes to Depression in Parkinson's Disease. *Front Psychiatry*, *11*, 119. https://doi.org/10.3389/fpsyt.2020.00119

Huang, P., Lou, Y., Xuan, M., Gu, Q., Guan, X., Xu, X.,…Zhang, M. (2016). Cortical abnormalities in Parkinson's disease patients and relationship to depression: A surface-based morphometry study. *Psychiatry Res Neuroimaging*, *250*, 24-28. https://doi.org/10.1016/j.pscychresns.2016.03.002

Höglinger, G. U., Melhem, N. M., Dickson, D. W., Sleiman, P. M., Wang, L. S., Klei, L.,…Group, P. G. S. (2011). Identification of common variants influencing risk of the tauopathy progressive supranuclear palsy. *Nat Genet*, *43*(7), 699-705. https://doi.org/10.1038/ng.859

Höglinger, G. U., Respondek, G., Stamelou, M., Kurz, C., Josephs, K. A., Lang, A. E.,…Group, M. D. S.-e. P. S. (2017). Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Mov Disord*, *32*(6), 853-864. https://doi.org/10.1002/mds.26987

Im, S. Y., Kim, Y. E., & Kim, Y. J. (2015). Genetics of Progressive Supranuclear Palsy. *J Mov Disord*, *8*(3), 122-129. https://doi.org/10.14802/jmd.15033

Imamura, K., Hishikawa, N., Sawada, M., Nagatsu, T., Yoshida, M., & Hashizume, Y. (2003). Distribution of major histocompatibility complex class II-positive microglia and cytokine profile of Parkinson's disease brains. *Acta Neuropathol*, *106*(6), 518-526. https://doi.org/10.1007/s00401-003-0766-2

Iranzo, A., Molinuevo, J. L., Santamaría, J., Serradell, M., Martí, M. J., Valldeoriola, F., & Tolosa, E. (2006). Rapid-eye-movement sleep behaviour disorder as an early marker for a neurodegenerative disorder: a descriptive study. *Lancet Neurol*, *5*(7), 572-577. https://doi.org/10.1016/S1474-4422(06)70476-8

Ising, C., Venegas, C., Zhang, S., Scheiblich, H., Schmidt, S. V., Vieira-Saecker, A., Schwartz, S., Albasset, S., McManus, R. M., Tejera, D., Griep, A., Santarelli, F., Brosseron, F., Opitz, S., Stunden, J., Merten, M., Kayed, R., Golenbock, D. T., Blum, D., Latz, E., … Heneka, M. T. (2019). NLRP3 inflammasome activation drives tau pathology. *Nature*, *575*(7784), 669–673. https://doi.org/10.1038/s41586-019-1769-z

Jabbari, E., Woodside, J., Tan, M. M. X., Pavese, N., Bandmann, O., Ghosh, B. C. P.,…Morris, H. R. (2019). The genetic and clinico-pathological profile of early-onset progressive supranuclear palsy. *Mov Disord*, *34*(9), 1307-1314. https://doi.org/10.1002/mds.27786

Jecmenica-Lukic, M., Poewe, W., Tolosa, E., & Wenning, G. K. (2012). Premotor signs and symptoms of multiple system atrophy. *Lancet Neurol*, *11*(4), 361-368. https://doi.org/10.1016/S1474-4422(12)70022-4

Jellinger, K. A. (2018). Multiple System Atrophy: An Oligodendroglioneural Synucleinopathy1. *J Alzheimers Dis*, *62*(3), 1141-1179. https://doi.org/10.3233/JAD-170397

Jellinger, K. A. (2019). Neuropathology and pathogenesis of extrapyramidal movement disorders: a critical update-I. Hypokinetic-rigid movement disorders. *J Neural Transm (Vienna)*, *126*(8), 933-995. https://doi.org/10.1007/s00702-019-02028-6

Johnson, V. E., Stewart, J. E., Begbie, F. D., Trojanowski, J. Q., Smith, D. H., & Stewart, W. (2013). Inflammation and white matter degeneration persist for years after a single traumatic brain injury. *Brain : a journal of neurology*, *136*(Pt 1), 28–42. https://doi.org/10.1093/brain/aws322

Josephs, K. A., Duffy, J. R., Strand, E. A., Machulda, M. M., Senjem, M. L., Gunter, J. L.,…Whitwell, J. L. (2014). The evolution of primary progressive apraxia of speech. *Brain*, *137*(Pt 10), 2783-2795. https://doi.org/10.1093/brain/awu223

Joutsa, J., Gardberg, M., Röyttä, M., & Kaasinen, V. (2014). Diagnostic accuracy of parkinsonism syndromes by general neurologists. *Parkinsonism Relat Disord*, *20*(8), 840-844. https://doi.org/10.1016/j.parkreldis.2014.04.019

Kaasinen, V., Kankare, T., Joutsa, J., & Vahlberg, T. (2019). Presynaptic Striatal Dopaminergic Function in Atypical Parkinsonism: A Metaanalysis of Imaging Studies. *J Nucl Med*, *60*(12), 1757-1763. https://doi.org/10.2967/jnumed.119.227140

Kaasinen, V., & Vahlberg, T. (2017). Striatal dopamine in Parkinson disease: A meta-analysis of imaging studies. *Ann Neurol*, *82*(6), 873-882. https://doi.org/10.1002/ana.25103

Kaipainen, A. L., Pitkänen, J., Haapalinna, F., Jääskeläinen, O., Jokinen, H., Melkas, S.,…Julkunen, V. (2021). A novel CT-based automated analysis method provides comparable results with MRI in measuring brain atrophy and white matter lesions. *Neuroradiology*, *63*(12), 2035-2046. https://doi.org/10.1007/s00234-021-02761-4

Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *Lancet*, *386*(9996), 896-912. https://doi.org/10.1016/S0140-6736(14)61393-3

Kamma, E., Lasisi, W., Libner, C., Ng, H. S., & Plemel, J. R. (2022). Central nervous system macrophages in progressive multiple sclerosis: relationship to neurodegeneration and therapeutics. *J Neuroinflammation*, *19*(1), 45. https://doi.org/10.1186/s12974-022-02408-y

Karin, M. (2006). Nuclear factor-kappaB in cancer development and progression. *Nature*, *441*(7092), 431-436. https://doi.org/10.1038/nature04870

Kaufmann, H., Norcliffe-Kaufmann, L., Palma, J. A., Biaggioni, I., Low, P. A., Singer, W.,…Consortium, A. D. (2017). Natural history of pure autonomic failure: A United States prospective cohort. *Ann Neurol*, *81*(2), 287-297. https://doi.org/10.1002/ana.24877

Keong, N. C., Pena, A., Price, S. J., Czosnyka, M., Czosnyka, Z., & Pickard, J. D. (2016). Imaging normal pressure hydrocephalus: theories, techniques, and challenges. *Neurosurg Focus*, *41*(3), E11. https://doi.org/10.3171/2016.7.FOCUS16194

Kim, H. J., Jeon, B. S., Lee, J. Y., & Yun, J. Y. (2011). Survival of Korean patients with multiple system atrophy. *Mov Disord*, *26*(5), 909-912. https://doi.org/10.1002/mds.23580

Kinney, J. W., Bemiller, S. M., Murtishaw, A. S., Leisgang, A. M., Salazar, A. M., & Lamb, B. T. (2018). Inflammation as a central mechanism in Alzheimer's disease. *Alzheimers Dement (N Y)*, *4*, 575-590. https://doi.org/10.1016/j.trci.2018.06.014

Klockgether, T., Lüdtke, R., Kramer, B., Abele, M., Bürk, K., Schöls, L.,…Dichgans, J. (1998). The natural history of degenerative ataxia: a retrospective study in 466 patients. *Brain*, *121 (Pt 4)*, 589-600. https://doi.org/10.1093/brain/121.4.589

Kluss, J. H., Mamais, A., & Cookson, M. R. (2019). LRRK2 links genetic and sporadic Parkinson's disease. *Biochem Soc Trans*, *47*(2), 651-661. https://doi.org/10.1042/BST20180462

Koch, U., & Radtke, F. (2011). Mechanisms of T cell development and transformation. *Annu Rev Cell Dev Biol*, *27*, 539-562. https://doi.org/10.1146/annurev-cellbio-092910-154008

Koga, S., Josephs, K. A., Ogaki, K., Labbé, C., Uitti, R. J., Graff-Radford, N.,…Dickson, D. W. (2016). Cerebellar ataxia in progressive supranuclear palsy: An autopsy study of PSP-C. *Mov Disord*, *31*(5), 653-662. https://doi.org/10.1002/mds.26499

Koller, W. C., Hutton, J. T., Tolosa, E., & Capilldeo, R. (1999). Immediate-release and controlled-release carbidopa/levodopa in PD: a 5-year randomized multicenter study. Carbidopa/Levodopa Study Group. *Neurology*, *53*(5), 1012-1019. https://doi.org/10.1212/wnl.53.5.1012

Kompoliti, K., Goetz, C. G., Litvan, I., Jellinger, K., & Verny, M. (1998). Pharmacological therapy in progressive supranuclear palsy. *Arch Neurol*, *55*(8), 1099-1102. https://doi.org/10.1001/archneur.55.8.1099

Komulainen, J., Lehtonen, J., Mäkelä, M., & Kampman, O. (2012). Psykiatrian luokituskäsikirja : Suomalainen tautiluokitus ICD-10:n psykiatriaan liittyvät koodit.

Konstantin Nissen, S., Farmen, K., Carstensen, M., Schulte, C., Goldeck, D., Brockmann, K., & Romero-Ramos, M. (2022). Changes in CD163+, CD11b+, and CCR2+ peripheral monocytes relate to Parkinson's disease and cognition. *Brain Behav Immun*, *101*, 182-193. https://doi.org/10.1016/j.bbi.2022.01.005

Kostić, V. S., Agosta, F., Petrović, I., Galantucci, S., Spica, V., Jecmenica-Lukic, M., & Filippi, M. (2010). Regional patterns of brain tissue loss associated with depression in Parkinson disease. *Neurology*, *75*(10), 857-863. https://doi.org/10.1212/WNL.0b013e3181f11c1d

Kostić, V. S., & Filippi, M. (2011). Neuroanatomical correlates of depression and apathy in Parkinson's disease: magnetic resonance imaging studies. *J Neurol Sci*, *310*(1-2), 61-63. https://doi.org/10.1016/j.jns.2011.05.036

Kouli, A., Camacho, M., Allinson, K., & Williams-Gray, C. H. (2020). Neuroinflammation and protein pathology in Parkinson's disease dementia. *Acta Neuropathol Commun*, *8*(1), 211. https://doi.org/10.1186/s40478-020-01083-5

Kovacs, G. G. (2015). Invited review: Neuropathology of tauopathies: principles and practice. *Neuropathol Appl Neurobiol*, *41*(1), 3-23. https://doi.org/10.1111/nan.12208

Kovacs, G. G., Lukic, M. J., Irwin, D. J., Arzberger, T., Respondek, G., Lee, E. B., Coughlin, D., Giese, A., Grossman, M., Kurz, C., McMillan, C. T., Gelpi, E., Compta, Y., van Swieten, J. C., Laat, L. D., Troakes, C., Al-Sarraj, S., Robinson, J. L., Roeber, S., Xie, S. X., … Höglinger, G. U. (2020). Distribution patterns of tau pathology in progressive supranuclear palsy. *Acta neuropathologica*, *140*(2), 99–119. https://doi.org/10.1007/s00401-020-02158-2

Kovacs, G. G., Milenkovic, I., Wöhrer, A., Höftberger, R., Gelpi, E., Haberler, C.,…Budka, H. (2013). Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series. *Acta Neuropathol*, *126*(3), 365-384. https://doi.org/10.1007/s00401-013-1157-y

Krishnan, V., & Nestler, E. J. (2008). The molecular neurobiology of depression. *Nature*, *455*(7215), 894-902. https://doi.org/10.1038/nature07455

Krismer, F., & Wenning, G. K. (2017). Multiple system atrophy: insights into a rare and debilitating movement disorder. *Nature reviews. Neurology*, *13*(4), 232–243. https://doi.org/10.1038/nrneurol.2017.26

Kukkle, P. L., Neupane, R., Pantelyat, A., Wills, A. M., Jabbari, E., Dopper, E. G. P., Kovacs, G. G., Hoglinger, G., Aiba, I., Litvan, I., Ganguly, J., Whitwell, J. L., Ma, J., Okeng'O, K., Skakibara, R., Forrest, S., Lorenzl, S., Zewde, Y. Z., Compta, Y., Morris, H. R., … MDS-PSP Study Group (2025). Progressive Supranuclear Palsy-A Global Review. *Movement disorders clinical practice*, 10.1002/mdc3.70338. Advance online publication. https://doi.org/10.1002/mdc3.70338

Köllensperger, M., Geser, F., Ndayisaba, J. P., Boesch, S., Seppi, K., Ostergaard, K.,…EMSA-SG. (2010). Presentation, diagnosis, and management of multiple system atrophy in Europe: final analysis of the European multiple system atrophy registry. *Mov Disord*, *25*(15), 2604-2612. https://doi.org/10.1002/mds.23192

Köllensperger, M., Geser, F., Seppi, K., Stampfer-Kountchev, M., Sawires, M., Scherfler, C.,…Group, E. M. S. (2008). Red flags for multiple system atrophy. *Mov Disord*, *23*(8), 1093-1099. https://doi.org/10.1002/mds.21992

Lamb, R., Rohrer, J. D., Lees, A. J., & Morris, H. R. (2016). Progressive Supranuclear Palsy and Corticobasal Degeneration: Pathophysiology and Treatment Options. *Curr Treat Options Neurol*, *18*(9), 42. https://doi.org/10.1007/s11940-016-0422-5

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional neuroanatomy of the basal ganglia. *Cold Spring Harb Perspect Med*, *2*(12), a009621. https://doi.org/10.1101/cshperspect.a009621

Lang, A. E. (2005). Treatment of progressive supranuclear palsy and corticobasal degeneration. *Mov Disord*, *20 Suppl 12*, S83-91. https://doi.org/10.1002/mds.20545

Langston, J. W. (2017). The MPTP Story. *J Parkinsons Dis*, *7*(s1), S11-S19. https://doi.org/10.3233/JPD-179006

Langworth-Green, C., Patel, S., Jaunmuktane, Z., Jabbari, E., Morris, H., Thom, M.,…Duff, K. (2023). Chronic effects of inflammation on tauopathies. *Lancet Neurol*, *22*(5), 430-442. https://doi.org/10.1016/S1474-4422(23)00038-8

Lannuzel, A., Michel, P. P., Höglinger, G. U., Champy, P., Jousset, A., Medja, F.,…Ruberg, M. (2003). The mitochondrial complex I inhibitor annonacin is toxic to mesencephalic dopaminergic neurons by impairment of energy metabolism. *Neuroscience*, *121*(2), 287-296. https://doi.org/10.1016/s0306-4522(03)00441-x

Lawson, L. J., Perry, V. H., & Gordon, S. (1992). Turnover of resident microglia in the normal adult mouse brain. *Neuroscience*, *48*(2), 405-415. https://doi.org/10.1016/0306-4522(92)90500-2

Leveille, E., Ross, O. A., & Gan-Or, Z. (2021). Tau and MAPT genetics in tauopathies and synucleinopathies. *Parkinsonism & related disorders*, *90*, 142–154. https://doi.org/10.1016/j.parkreldis.2021.09.008

Levin, J., Kurz, A., Arzberger, T., Giese, A., & Höglinger, G. U. (2016). The Differential Diagnosis and Treatment of Atypical Parkinsonism. *Dtsch Arztebl Int*, *113*(5), 61-69. https://doi.org/10.3238/arztebl.2016.0061

LeWitt, P. A., Hauser, R. A., Pahwa, R., Isaacson, S. H., Fernandez, H. H., Lew, M.,…Investigators, S.-P. S. (2019). Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Neurol*, *18*(2), 145-154. https://doi.org/10.1016/S1474-4422(18)30405-8

Lewy, F. (1912). “Paralysis agitans,” in Handbuch der Neurologie, ed. Lewandowsky M. In: Berlin: Julius Springer.

Li, J. Y., Englund, E., Holton, J. L., Soulet, D., Hagell, P., Lees, A. J., Lashley, T., Quinn, N. P., Rehncrona, S., Björklund, A., Widner, H., Revesz, T., Lindvall, O., & Brundin, P. (2008). Lewy bodies in grafted neurons in subjects with Parkinson's disease suggest host-to-graft disease propagation. *Nature medicine*, *14*(5), 501–503. https://doi.org/10.1038/nm1746

Li, W., Fu, Y., Halliday, G. M., & Sue, C. M. (2021). Genes Link Mitochondrial Dysfunction and Alpha-Synuclein Pathology in Sporadic Parkinson's Disease. *Front Cell Dev Biol*, *9*, 612476. https://doi.org/10.3389/fcell.2021.612476

Lill, C. M. (2016). Genetics of Parkinson's disease. *Mol Cell Probes*, *30*(6), 386-396. https://doi.org/10.1016/j.mcp.2016.11.001

Ling, E. A., & Wong, W. C. (1993). The origin and nature of ramified and amoeboid microglia: a historical review and current concepts. *Glia*, *7*(1), 9-18. https://doi.org/10.1002/glia.440070105

Ling, H. (2016). Clinical Approach to Progressive Supranuclear Palsy. *J Mov Disord*, *9*(1), 3-13. https://doi.org/10.14802/jmd.15060

Ling, H., de Silva, R., Massey, L. A., Courtney, R., Hondhamuni, G., Bajaj, N.,…Revesz, T. (2014). Characteristics of progressive supranuclear palsy presenting with corticobasal syndrome: a cortical variant. *Neuropathol Appl Neurobiol*, *40*(2), 149-163. https://doi.org/10.1111/nan.12037

Ling, H., O'Sullivan, S. S., Holton, J. L., Revesz, T., Massey, L. A., Williams, D. R.,…Lees, A. J. (2010). Does corticobasal degeneration exist? A clinicopathological re-evaluation. *Brain*, *133*(Pt 7), 2045-2057. https://doi.org/10.1093/brain/awq123

Lipp, A., Sandroni, P., Ahlskog, J. E., Fealey, R. D., Kimpinski, K., Iodice, V.,…Low, P. A. (2009). Prospective differentiation of multiple system atrophy from Parkinson disease, with and without autonomic failure. *Arch Neurol*, *66*(6), 742-750. https://doi.org/10.1001/archneurol.2009.71

Litvan, I., Agid, Y., Calne, D., Campbell, G., Dubois, B., Duvoisin, R. C.,…Zee, D. S. (1996). Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. *Neurology*, *47*(1), 1-9. https://doi.org/10.1212/wnl.47.1.1

Litvan, I., Bhatia, K. P., Burn, D. J., Goetz, C. G., Lang, A. E., McKeith, I.,…Committee, M. D. S. S. I. (2003). Movement Disorders Society Scientific Issues Committee report: SIC Task Force appraisal of clinical diagnostic criteria for Parkinsonian disorders. *Mov Disord*, *18*(5), 467-486. https://doi.org/10.1002/mds.10459

Litvan, I., Hauw, J. J., Bartko, J. J., Lantos, P. L., Daniel, S. E., Horoupian, D. S.,…Anderson, D. W. (1996). Validity and reliability of the preliminary NINDS neuropathologic criteria for progressive supranuclear palsy and related disorders. *J Neuropathol Exp Neurol*, *55*(1), 97-105. https://doi.org/10.1097/00005072-199601000-00010

Litvan, I., Lees, P. S., Cunningham, C. R., Rai, S. N., Cambon, A. C., Standaert, D. G.,…ENGENE-PSP, f. (2016). Environmental and occupational risk factors for progressive supranuclear palsy: Case-control study. *Mov Disord*, *31*(5), 644-652. https://doi.org/10.1002/mds.26512

Luk, K. C., Kehm, V., Carroll, J., Zhang, B., O'Brien, P., Trojanowski, J. Q., & Lee, V. M. (2012). Pathological α-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. *Science*, *338*(6109), 949-953. https://doi.org/10.1126/science.1227157

Lull, M. E., & Block, M. L. (2010). Microglial activation and chronic neurodegeneration. *Neurotherapeutics*, *7*(4), 354-365. https://doi.org/10.1016/j.nurt.2010.05.014

Luo, C., Song, W., Chen, Q., Yang, J., Gong, Q., & Shang, H. F. (2016). Cortical thinning in drug-naive Parkinson's disease patients with depression. *J Neurol*, *263*(10), 2114-2119. https://doi.org/10.1007/s00415-016-8241-x

Lyons, S., Trépel, D., Lynch, T., Walsh, R., & O'Dowd, S. (2023). The prevalence and incidence of progressive supranuclear palsy and corticobasal syndrome: a systematic review and meta-analysis. *Journal of neurology*, *270*(9), 4451–4465. https://doi.org/10.1007/s00415-023-11791-2

Maaß, S., Levin, J., & Höglinger, G. (2016). Current Treatment of Multiple System Atrophy. *Curr Treat Options Neurol*, *18*(12), 51. https://doi.org/10.1007/s11940-016-0435-0

Magistrelli, L., Contaldi, E., Vignaroli, F., Gallo, S., Colombatto, F., Cantello, R., & Comi, C. (2022). Immune Response Modifications in the Genetic Forms of Parkinson's Disease: What Do We Know? *Int J Mol Sci*, *23*(7). https://doi.org/10.3390/ijms23073476

Mahlknecht, P., Hotter, A., Hussl, A., Esterhammer, R., Schocke, M., & Seppi, K. (2010). Significance of MRI in diagnosis and differential diagnosis of Parkinson's disease. *Neuro-degenerative diseases*, *7*(5), 300–318. https://doi.org/10.1159/000314495

Mak, M. K., Wong-Yu, I. S., Shen, X., & Chung, C. L. (2017). Long-term effects of exercise and physical therapy in people with Parkinson disease. *Nat Rev Neurol*, *13*(11), 689-703. https://doi.org/10.1038/nrneurol.2017.128

Markham, C., Diamond, S. G., & Treciokas, L. J. (1974). Carbidopa in Parkinson disease and in nausea and vomiting of levodopa. *Arch Neurol*, *31*(2), 128-133. https://doi.org/10.1001/archneur.1974.00490380076010

Martin, W. R. W., Miles, M., Zhong, Q., Hartlein, J., Racette, B. A., Norris, S. A.,…Perlmutter, J. S. (2021). Is Levodopa Response a Valid Indicator of Parkinson's Disease? *Mov Disord*, *36*(4), 948-954. https://doi.org/10.1002/mds.28406

Matheoud, D., Cannon, T., Voisin, A., Penttinen, A. M., Ramet, L., Fahmy, A. M.,…Desjardins, M. (2019). Intestinal infection triggers Parkinson's disease-like symptoms in Pink1. *Nature*, *571*(7766), 565-569. https://doi.org/10.1038/s41586-019-1405-y

Mayberg, H. S., & Solomon, D. H. (1995). Depression in Parkinson's disease: a biochemical and organic viewpoint. *Adv Neurol*, *65*, 49-60.

McGeer, P. L., Itagaki, S., Boyes, B. E., & McGeer, E. G. (1988). Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains. *Neurology*, *38*(8), 1285-1291. https://doi.org/10.1212/wnl.38.8.1285

McGeer, P. L., Itagaki, S., & McGeer, E. G. (1988). Expression of the histocompatibility glycoprotein HLA-DR in neurological disease. *Acta Neuropathol*, *76*(6), 550-557. https://doi.org/10.1007/BF00689592

McGeer, P. L., Itagaki, S., Tago, H., & McGeer, E. G. (1987). Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci Lett*, *79*(1-2), 195-200. https://doi.org/10.1016/0304-3940(87)90696-3

McGeer, P. L., Kawamata, T., Walker, D. G., Akiyama, H., Tooyama, I., & McGeer, E. G. (1993). Microglia in degenerative neurological disease. *Glia*, *7*(1), 84-92. https://doi.org/10.1002/glia.440070114

McKee, A. C., Stern, R. A., Nowinski, C. J., Stein, T. D., Alvarez, V. E., Daneshvar, D. H., Lee, H. S., Wojtowicz, S. M., Hall, G., Baugh, C. M., Riley, D. O., Kubilus, C. A., Cormier, K. A., Jacobs, M. A., Martin, B. R., Abraham, C. R., Ikezu, T., Reichard, R. R., Wolozin, B. L., Budson, A. E., … Cantu, R. C. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain : a journal of neurology*, *136*(Pt 1), 43–64. https://doi.org/10.1093/brain/aws307

McKeith, I. G., Boeve, B. F., Dickson, D. W., Halliday, G., Taylor, J. P., Weintraub, D.,…Kosaka, K. (2017). Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology*, *89*(1), 88-100. https://doi.org/10.1212/WNL.0000000000004058

McRitchie, D. A., Cartwright, H. R., & Halliday, G. M. (1997). Specific A10 dopaminergic nuclei in the midbrain degenerate in Parkinson's disease. *Exp Neurol*, *144*(1), 202-213. https://doi.org/10.1006/exnr.1997.6418

Miller, D. W., Johnson, J. M., Solano, S. M., Hollingsworth, Z. R., Standaert, D. G., & Young, A. B. (2005). Absence of alpha-synuclein mRNA expression in normal and multiple system atrophy oligodendroglia. *J Neural Transm (Vienna)*, *112*(12), 1613-1624. https://doi.org/10.1007/s00702-005-0378-1

Mirra, S. S., Heyman, A., McKeel, D., Sumi, S. M., Crain, B. J., Brownlee, L. M.,…Berg, L. (1991). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology*, *41*(4), 479-486. https://doi.org/10.1212/wnl.41.4.479

Mishra, Y., Kumar, A., & Kaundal, R. K. (2025). Mitochondrial Dysfunction is a Crucial Immune Checkpoint for Neuroinflammation and Neurodegeneration: mtDAMPs in Focus. *Molecular neurobiology*, *62*(6), 6715–6747. https://doi.org/10.1007/s12035-024-04412-0

Moccia, M., Tedeschi, E., Ugga, L., Erro, R., Picillo, M., Caranci, F.,…Brunetti, A. (2016). White matter changes and the development of motor phenotypes in de novo Parkinson's Disease. *J Neurol Sci*, *367*, 215-219. https://doi.org/10.1016/j.jns.2016.06.015

Mogi, M., Harada, M., Kondo, T., Riederer, P., Inagaki, H., Minami, M., & Nagatsu, T. (1994). Interleukin-1 beta, interleukin-6, epidermal growth factor and transforming growth factor-alpha are elevated in the brain from parkinsonian patients. *Neurosci Lett*, *180*(2), 147-150. https://doi.org/10.1016/0304-3940(94)90508-8

Mogi, M., Harada, M., Riederer, P., Narabayashi, H., Fujita, K., & Nagatsu, T. (1994). Tumor necrosis factor-alpha (TNF-alpha) increases both in the brain and in the cerebrospinal fluid from parkinsonian patients. *Neurosci Lett*, *165*(1-2), 208-210. https://doi.org/10.1016/0304-3940(94)90746-3

Montagu, K. A. (1957). Catechol compounds in rat tissues and in brains of different animals. *Nature*, *180*(4579), 244-245. https://doi.org/10.1038/180244a0

Montastruc, J. L., Rascol, O., Senard, J. M., & Rascol, A. (1994). A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow up. *J Neurol Neurosurg Psychiatry*, *57*(9), 1034-1038. https://doi.org/10.1136/jnnp.57.9.1034

Monzio Compagnoni, G., & Di Fonzo, A. (2019). Understanding the pathogenesis of multiple system atrophy: state of the art and future perspectives. *Acta Neuropathol Commun*, *7*(1), 113. https://doi.org/10.1186/s40478-019-0730-6

Moro, E., Schüpbach, M., Wächter, T., Allert, N., Eleopra, R., Honey, C. R.,…Stoevelaar, H. (2016). Referring Parkinson's disease patients for deep brain stimulation: a RAND/UCLA appropriateness study. *J Neurol*, *263*(1), 112-119. https://doi.org/10.1007/s00415-015-7942-x

Mou, Y., Du, Y., Zhou, L., Yue, J., Hu, X., Liu, Y.,…Dong, B. (2022). Gut Microbiota Interact With the Brain Through Systemic Chronic Inflammation: Implications on Neuroinflammation, Neurodegeneration, and Aging. *Front Immunol*, *13*, 796288. https://doi.org/10.3389/fimmu.2022.796288

Mouradian, M. M., Heuser, I. J., Baronti, F., & Chase, T. N. (1990). Modification of central dopaminergic mechanisms by continuous levodopa therapy for advanced Parkinson's disease. *Ann Neurol*, *27*(1), 18-23. https://doi.org/10.1002/ana.410270105

Mudher, A., Colin, M., Dujardin, S., Medina, M., Dewachter, I., Alavi Naini, S. M., Mandelkow, E. M., Mandelkow, E., Buée, L., Goedert, M., & Brion, J. P. (2017). What is the evidence that tau pathology spreads through prion-like propagation?. *Acta neuropathologica communications*, *5*(1), 99. https://doi.org/10.1186/s40478-017-0488-7

Mulas, G., Espa, E., Fenu, S., Spiga, S., Cossu, G., Pillai, E.,…Carta, A. R. (2016). Differential induction of dyskinesia and neuroinflammation by pulsatile versus continuous l-DOPA delivery in the 6-OHDA model of Parkinson's disease. *Exp Neurol*, *286*, 83-92. https://doi.org/10.1016/j.expneurol.2016.09.013

Murphy, K. E., Karaconji, T., Hardman, C. D., & Halliday, G. M. (2008). Excessive dopamine neuron loss in progressive supranuclear palsy. *Mov Disord*, *23*(4), 607-610. https://doi.org/10.1002/mds.21907

Muñoz-Delgado, L., Macías-García, D., Jesús, S., Martín-Rodríguez, J. F., Labrador-Espinosa, M., Jiménez-Jaraba, M. V.,…Mir, P. (2021). Peripheral Immune Profile and Neutrophil-to-Lymphocyte Ratio in Parkinson's Disease. *Mov Disord*, *36*(10), 2426-2430. https://doi.org/10.1002/mds.28685

Nalls, M. A., Blauwendraat, C., Vallerga, C. L., Heilbron, K., Bandres-Ciga, S., Chang, D.,…Consortium, I. P. s. D. G. (2019). Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol*, *18*(12), 1091-1102. https://doi.org/10.1016/S1474-4422(19)30320-5

Nayak, D., Roth, T. L., & McGavern, D. B. (2014). Microglia development and function. *Annu Rev Immunol*, *32*, 367-402. https://doi.org/10.1146/annurev-immunol-032713-120240

Nicoletti, V., Palermo, G., Del Prete, E., Mancuso, M., & Ceravolo, R. (2021). Understanding the Multiple Role of Mitochondria in Parkinson's Disease and Related Disorders: Lesson From Genetics and Protein-Interaction Network. *Front Cell Dev Biol*, *9*, 636506. https://doi.org/10.3389/fcell.2021.636506

Nieforth, K. A., & Golbe, L. I. (1993). Retrospective study of drug response in 87 patients with progressive supranuclear palsy. *Clin Neuropharmacol*, *16*(4), 338-346. https://doi.org/10.1097/00002826-199308000-00006

Nilson, A. N., English, K. C., Gerson, J. E., Barton Whittle, T., Nicolas Crain, C., Xue, J.,…Kayed, R. (2017). Tau Oligomers Associate with Inflammation in the Brain and Retina of Tauopathy Mice and in Neurodegenerative Diseases. *J Alzheimers Dis*, *55*(3), 1083-1099. https://doi.org/10.3233/JAD-160912

Nogami, A., Yamazaki, M., Saito, Y., Hatsuta, H., Sakiyama, Y., Takao, M.,…Murayama, S. (2015). Early Stage of Progressive Supranuclear Palsy: A Neuropathological Study of 324 Consecutive Autopsy Cases. *J Nippon Med Sch*, *82*(6), 266-273. https://doi.org/10.1272/jnms.82.266

Noyce, A. J., Bestwick, J. P., Silveira-Moriyama, L., Hawkes, C. H., Giovannoni, G., Lees, A. J., & Schrag, A. (2012). Meta-analysis of early nonmotor features and risk factors for Parkinson disease. *Ann Neurol*, *72*(6), 893-901. https://doi.org/10.1002/ana.23687

Nutt, J. G. (1987). On-off phenomenon: relation to levodopa pharmacokinetics and pharmacodynamics. *Ann Neurol*, *22*(4), 535-540. https://doi.org/10.1002/ana.410220415

Nutt, J. G. (1990). Levodopa-induced dyskinesia: review, observations, and speculations. *Neurology*, *40*(2), 340-345. https://doi.org/10.1212/wnl.40.2.340

Nutt, J. G., Woodward, W. R., Hammerstad, J. P., Carter, J. H., & Anderson, J. L. (1984). The "on-off" phenomenon in Parkinson's disease. Relation to levodopa absorption and transport. *N Engl J Med*, *310*(8), 483-488. https://doi.org/10.1056/NEJM198402233100802

Nyholm, D. (2006). Pharmacokinetic optimisation in the treatment of Parkinson's disease : an update. *Clin Pharmacokinet*, *45*(2), 109-136. https://doi.org/10.2165/00003088-200645020-00001

O'Sullivan, S. S., Massey, L. A., Williams, D. R., Silveira-Moriyama, L., Kempster, P. A., Holton, J. L.,…Lees, A. J. (2008). Clinical outcomes of progressive supranuclear palsy and multiple system atrophy. *Brain*, *131*(Pt 5), 1362-1372. https://doi.org/10.1093/brain/awn065

Obeso, J. A., Rodríguez-Oroz, M. C., Benitez-Temino, B., Blesa, F. J., Guridi, J., Marin, C., & Rodriguez, M. (2008). Functional organization of the basal ganglia: therapeutic implications for Parkinson's disease. *Mov Disord*, *23 Suppl 3*, S548-559. https://doi.org/10.1002/mds.22062

Okun, M. S., Fernandez, H. H., Pedraza, O., Misra, M., Lyons, K. E., Pahwa, R.,…Foote, K. D. (2004). Development and initial validation of a screening tool for Parkinson disease surgical candidates. *Neurology*, *63*(1), 161-163. https://doi.org/10.1212/01.wnl.0000133122.14824.25

Olanow, C. W., Calabresi, P., & Obeso, J. A. (2020). Continuous Dopaminergic Stimulation as a Treatment for Parkinson's Disease: Current Status and Future Opportunities. *Movement disorders : official journal of the Movement Disorder Society*, *35*(10), 1731–1744. https://doi.org/10.1002/mds.28215

Ouchi, Y., Yoshikawa, E., Sekine, Y., Futatsubashi, M., Kanno, T., Ogusu, T., & Torizuka, T. (2005). Microglial activation and dopamine terminal loss in early Parkinson's disease. *Ann Neurol*, *57*(2), 168-175. https://doi.org/10.1002/ana.20338

Owens, E., Josephs, K. A., Savica, R., Hassan, A., Klassen, B., Bower, J.,…Ahlskog, J. E. (2016). The clinical spectrum and natural history of pure akinesia with gait freezing. *J Neurol*, *263*(12), 2419-2423. https://doi.org/10.1007/s00415-016-8278-x

Pahwa, R., Tanner, C. M., Hauser, R. A., Isaacson, S. H., Nausieda, P. A., Truong, D. D.,…Stempien, M. J. (2017). ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson Disease (EASE LID Study): A Randomized Clinical Trial. *JAMA Neurol*, *74*(8), 941-949. https://doi.org/10.1001/jamaneurol.2017.0943

Pajares, M., I Rojo, A., Manda, G., Boscá, L., & Cuadrado, A. (2020). Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. *Cells*, *9*(7). https://doi.org/10.3390/cells9071687

Pantano, P., Totaro, P., & Raz, E. (2008). Cerebrovascular diseases. *Neurol Sci*, *29 Suppl 3*, 314-318. https://doi.org/10.1007/s10072-008-1006-2

Papavasiliou, P. S., Cotzias, G. C., Düby, S. E., Steck, A. J., Fehling, C., & Bell, M. A. (1972). Levodopa in Parkinsonism: potentiation of central effects with a peripheral inhibitor. *N Engl J Med*, *286*(1), 8-14. https://doi.org/10.1056/NEJM197201062860102

Papp, M. I., Kahn, J. E., & Lantos, P. L. (1989). Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). *J Neurol Sci*, *94*(1-3), 79-100. https://doi.org/10.1016/0022-510x(89)90219-0

Park, J., & Kim, C. H. (2021). Regulation of common neurological disorders by gut microbial metabolites. *Exp Mol Med*, *53*(12), 1821-1833. https://doi.org/10.1038/s12276-021-00703-x

Parkinson, J. (2002). An essay on the shaking palsy. 1817. *J Neuropsychiatry Clin Neurosci*, *14*(2), 223-236; discussion 222. https://doi.org/10.1176/jnp.14.2.223

Parkkinen, L., Kauppinen, T., Pirttilä, T., Autere, J. M., & Alafuzoff, I. (2005). Alpha-synuclein pathology does not predict extrapyramidal symptoms or dementia. *Annals of neurology*, *57*(1), 82–91. https://doi.org/10.1002/ana.20321

Parkkinen, L., O'Sullivan, S. S., Kuoppamäki, M., Collins, C., Kallis, C., Holton, J. L.,…Lees, A. J. (2011). Does levodopa accelerate the pathologic process in Parkinson disease brain? *Neurology*, *77*(15), 1420-1426. https://doi.org/10.1212/WNL.0b013e318232ab4c

PD Med Collaborative Group, Gray, R., Ives, N., Rick, C., Patel, S., Gray, A., Jenkinson, C., McIntosh, E., Wheatley, K., Williams, A., & Clarke, C. E. (2014). Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet (London, England)*, *384*(9949), 1196–1205. https://doi.org/10.1016/S0140-6736(14)60683-8

Peng, C., Gathagan, R. J., Covell, D. J., Medellin, C., Stieber, A., Robinson, J. L.,…Lee, V. M. (2018). Cellular milieu imparts distinct pathological α-synuclein strains in α-synucleinopathies. *Nature*, *557*(7706), 558-563. https://doi.org/10.1038/s41586-018-0104-4

Perkins, A., & Liu, G. (2016). Primary Brain Tumors in Adults: Diagnosis and Treatment. *Am Fam Physician*, *93*(3), 211-217.

Perry, V. H. (2004). The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. *Brain Behav Immun*, *18*(5), 407-413. https://doi.org/10.1016/j.bbi.2004.01.004

Pessoa, R. R., Moro, A., Munhoz, R. P., Teive, H. A. G., & Lees, A. J. (2018). Apomorphine in the treatment of Parkinson's disease: a review. *Arq Neuropsiquiatr*, *76*(12), 840-848. https://doi.org/10.1590/0004-282X20180140

Petrovic, I. N., Ling, H., Asi, Y., Ahmed, Z., Kukkle, P. L., Hazrati, L. N.,…Lees, A. J. (2012). Multiple system atrophy-parkinsonism with slow progression and prolonged survival: a diagnostic catch. *Mov Disord*, *27*(9), 1186-1190. https://doi.org/10.1002/mds.25115

Picca, A., Guerra, F., Calvani, R., Romano, R., Coelho-Júnior, H. J., Bucci, C., & Marzetti, E. (2021). Mitochondrial Dysfunction, Protein Misfolding and Neuroinflammation in Parkinson's Disease: Roads to Biomarker Discovery. *Biomolecules*, *11*(10). https://doi.org/10.3390/biom11101508

Picillo, M., Cuoco, S., Tepedino, M. F., Cappiello, A., Volpe, G., Erro, R.,…group, P. S. s. (2019). Motor, cognitive and behavioral differences in MDS PSP phenotypes. *J Neurol*, *266*(7), 1727-1735. https://doi.org/10.1007/s00415-019-09324-x

Pierce, S., & Coetzee, G. A. (2017). Parkinson's disease-associated genetic variation is linked to quantitative expression of inflammatory genes. *PLoS One*, *12*(4), e0175882. https://doi.org/10.1371/journal.pone.0175882

Pink, A., Przybelski, S. A., Krell-Roesch, J., Stokin, G. B., Roberts, R. O., Mielke, M. M.,…Geda, Y. E. (2017). Cortical Thickness and Depressive Symptoms in Cognitively Normal Individuals: The Mayo Clinic Study of Aging. *J Alzheimers Dis*, *58*(4), 1273-1281. https://doi.org/10.3233/JAD-170041

Pitkänen, J., Koikkalainen, J., Nieminen, T., Marinkovic, I., Curtze, S., Sibolt, G.,…Melkas, S. (2020). Evaluating severity of white matter lesions from computed tomography images with convolutional neural network. *Neuroradiology*, *62*(10), 1257-1263. https://doi.org/10.1007/s00234-020-02410-2

Pittman, A. M., Myers, A. J., Abou-Sleiman, P., Fung, H. C., Kaleem, M., Marlowe, L.,…de Silva, R. (2005). Linkage disequilibrium fine mapping and haplotype association analysis of the tau gene in progressive supranuclear palsy and corticobasal degeneration. *J Med Genet*, *42*(11), 837-846. https://doi.org/10.1136/jmg.2005.031377

Poewe, W. H., Lees, A. J., & Stern, G. M. (1986). Low-dose L-dopa therapy in Parkinson's disease: a 6-year follow-up study. *Neurology*, *36*(11), 1528-1530. https://doi.org/10.1212/wnl.36.11.1528

Poewe, W., Stankovic, I., Halliday, G., Meissner, W. G., Wenning, G. K., Pellecchia, M. T., Seppi, K., Palma, J. A., & Kaufmann, H. (2022). Multiple system atrophy. *Nature reviews. Disease primers*, *8*(1), 56. https://doi.org/10.1038/s41572-022-00382-6

Politis M. (2014). Neuroimaging in Parkinson disease: from research setting to clinical practice. *Nature reviews. Neurology*, *10*(12), 708–722. https://doi.org/10.1038/nrneurol.2014.205

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A. E., Halliday, G., Goetz, C. G., Gasser, T., Dubois, B., Chan, P., Bloem, B. R., Adler, C. H., & Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Movement disorders : official journal of the Movement Disorder Society*, *30*(12), 1591–1601. https://doi.org/10.1002/mds.26424

Prinz, M., Jung, S., & Priller, J. (2019). Microglia Biology: One Century of Evolving Concepts. *Cell*, *179*(2), 292-311. https://doi.org/10.1016/j.cell.2019.08.053

Przuntek, H., Welzel, D., Gerlach, M., Blümner, E., Danielczyk, W., Kaiser, H. J.,…Uberla, K. (1996). Early institution of bromocriptine in Parkinson's disease inhibits the emergence of levodopa-associated motor side effects. Long-term results of the PRADO study. *J Neural Transm (Vienna)*, *103*(6), 699-715. https://doi.org/10.1007/BF01271230

Qin, X. Y., Zhang, S. P., Cao, C., Loh, Y. P., & Cheng, Y. (2016). Aberrations in Peripheral Inflammatory Cytokine Levels in Parkinson Disease: A Systematic Review and Meta-analysis. *JAMA Neurol*, *73*(11), 1316-1324. https://doi.org/10.1001/jamaneurol.2016.2742

Quinn, N. (1989). Multiple system atrophy--the nature of the beast. *J Neurol Neurosurg Psychiatry*, *Suppl*(Suppl), 78-89. https://doi.org/10.1136/jnnp.52.suppl.78

Rascovsky, K., Hodges, J. R., Knopman, D., Mendez, M. F., Kramer, J. H., Neuhaus, J.,…Miller, B. L. (2011). Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*, *134*(Pt 9), 2456-2477. https://doi.org/10.1093/brain/awr179

Ravina, B., Camicioli, R., Como, P. G., Marsh, L., Jankovic, J., Weintraub, D., & Elm, J. (2007). The impact of depressive symptoms in early Parkinson disease. *Neurology*, *69*(4), 342-347. https://doi.org/10.1212/01.wnl.0000268695.63392.10

Rawani, N. S., Chan, A. W., Dursun, S. M., & Baker, G. B. (2024). The Underlying Neurobiological Mechanisms of Psychosis: Focus on Neurotransmission Dysregulation, Neuroinflammation, Oxidative Stress, and Mitochondrial Dysfunction. *Antioxidants (Basel, Switzerland)*, *13*(6), 709. https://doi.org/10.3390/antiox13060709

Redgrave, P., Rodriguez, M., Smith, Y., Rodriguez-Oroz, M. C., Lehericy, S., Bergman, H.,…Obeso, J. A. (2010). Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. *Nat Rev Neurosci*, *11*(11), 760-772. https://doi.org/10.1038/nrn2915

Refolo, V., & Stefanova, N. (2019). Neuroinflammation and Glial Phenotypic Changes in Alpha-Synucleinopathies. *Front Cell Neurosci*, *13*, 263. https://doi.org/10.3389/fncel.2019.00263

Respondek, G., Stamelou, M., Kurz, C., Ferguson, L. W., Rajput, A., Chiu, W. Z.,…Group, M. D. S.-e. P. S. (2014). The phenotypic spectrum of progressive supranuclear palsy: a retrospective multicenter study of 100 definite cases. *Mov Disord*, *29*(14), 1758-1766. https://doi.org/10.1002/mds.26054

Reyes, J. F., Rey, N. L., Bousset, L., Melki, R., Brundin, P., & Angot, E. (2014). Alpha-synuclein transfers from neurons to oligodendrocytes. *Glia*, *62*(3), 387-398. https://doi.org/10.1002/glia.22611

Riederer, P., Strobel, S., Nagatsu, T., Watanabe, H., Chen, X., Löschmann, P. A., Sian-Hulsmann, J., Jost, W. H., Müller, T., Dijkstra, J. M., & Monoranu, C. M. (2025). Levodopa treatment: impacts and mechanisms throughout Parkinson's disease progression. *Journal of neural transmission (Vienna, Austria : 1996)*, *132*(6), 743–779. https://doi.org/10.1007/s00702-025-02893-4

Rinne, U. K., Bracco, F., Chouza, C., Dupont, E., Gershanik, O., Marti Masso, J. F.,…Marsden, C. D. (1998). Early treatment of Parkinson's disease with cabergoline delays the onset of motor complications. Results of a double-blind levodopa controlled trial. The PKDS009 Study Group. *Drugs*, *55 Suppl 1*, 23-30. https://doi.org/10.2165/00003495-199855001-00004

Ritz, B., Ascherio, A., Checkoway, H., Marder, K. S., Nelson, L. M., Rocca, W. A.,…Gorell, J. (2007). Pooled analysis of tobacco use and risk of Parkinson disease. *Arch Neurol*, *64*(7), 990-997. https://doi.org/10.1001/archneur.64.7.990

Roemer, S. F., Grinberg, L. T., Crary, J. F., Seeley, W. W., McKee, A. C., Kovacs, G. G.,…Dickson, D. W. (2022). Rainwater Charitable Foundation criteria for the neuropathologic diagnosis of

progressive supranuclear palsy. *Acta Neuropathol*, *144*(4), 603-614. https://doi.org/10.1007/s00401-022-02479-4

Rogers, J., Luber-Narod, J., Styren, S. D., & Civin, W. H. (1988). Expression of immune system-associated antigens by cells of the human central nervous system: relationship to the pathology of Alzheimer's disease. *Neurobiol Aging*, *9*(4), 339-349. https://doi.org/10.1016/s0197-4580(88)80079-4

Rosebraugh, M., Liu, W., Neenan, M., & Facheris, M. F. (2021). Foslevodopa/Foscarbidopa Is Well Tolerated and Maintains Stable Levodopa and Carbidopa Exposure Following Subcutaneous Infusion. *J Parkinsons Dis*, *11*(4), 1695-1702. https://doi.org/10.3233/JPD-212813

Ruffmann, C., & Parkkinen, L. (2016). Gut Feelings About α-Synuclein in Gastrointestinal Biopsies: Biomarker in the Making?. *Movement disorders : official journal of the Movement Disorder Society*, *31*(2), 193–202. https://doi.org/10.1002/mds.26480

Saari, L., Heiskanen, L., Gardberg, M., & Kaasinen, V. (2021). Depression and Nigral Neuron Density in Lewy Body Spectrum Diseases. *Ann Neurol*, *89*(5), 1046-1050. https://doi.org/10.1002/ana.26046

Sakakibara, R., Odaka, T., Uchiyama, T., Liu, R., Asahina, M., Yamaguchi, K.,…Hattori, T. (2004). Colonic transit time, sphincter EMG, and rectoanal videomanometry in multiple system atrophy. *Mov Disord*, *19*(8), 924-929. https://doi.org/10.1002/mds.20165

Salvesen, L., Ullerup, B. H., Sunay, F. B., Brudek, T., Løkkegaard, A., Agander, T. K.,…Pakkenberg, B. (2015). Changes in total cell numbers of the basal ganglia in patients with multiple system atrophy - A stereological study. *Neurobiol Dis*, *74*, 104-113. https://doi.org/10.1016/j.nbd.2014.11.008

Samudra, N., Patel, N., Womack, K. B., Khemani, P., & Chitnis, S. (2016). Psychosis in Parkinson Disease: A Review of Etiology, Phenomenology, and Management. *Drugs & aging*, *33*(12), 855–863. https://doi.org/10.1007/s40266-016-0416-8

Sanchez-Guajardo, V., Tentillier, N., & Romero-Ramos, M. (2015). The relation between α-synuclein and microglia in Parkinson's disease: Recent developments. *Neuroscience*, *302*, 47-58. https://doi.org/10.1016/j.neuroscience.2015.02.008

Sanders, D. W., Kaufman, S. K., DeVos, S. L., Sharma, A. M., Mirbaha, H., Li, A.,…Diamond, M. I. (2014). Distinct tau prion strains propagate in cells and mice and define different tauopathies. *Neuron*, *82*(6), 1271-1288. https://doi.org/10.1016/j.neuron.2014.04.047

Santos-Santos, M. A., Mandelli, M. L., Binney, R. J., Ogar, J., Wilson, S. M., Henry, M. L.,…Gorno-Tempini, M. L. (2016). Features of Patients With Nonfluent/Agrammatic Primary Progressive Aphasia With Underlying Progressive Supranuclear Palsy Pathology or Corticobasal Degeneration. *JAMA Neurol*, *73*(6), 733-742. https://doi.org/10.1001/jamaneurol.2016.0412

Schillaci, O., Filippi, L., Manni, C., & Santoni, R. (2007). Single-photon emission computed tomography/computed tomography in brain tumors. *Seminars in nuclear medicine*, *37*(1), 34–47. https://doi.org/10.1053/j.semnuclmed.2006.08.003

Schmidt, U., Weigert M., Broaddus C., Myers G. (2018). Cell Detection with Star-convex Polygons. In W. M (Ed.).

Scholz, S. W., Houlden, H., Schulte, C., Sharma, M., Li, A., Berg, D.,…Gasser, T. (2009). SNCA variants are associated with increased risk for multiple system atrophy. *Ann Neurol*, *65*(5), 610-614. https://doi.org/10.1002/ana.21685

Schrag, A., Ben-Shlomo, Y., & Quinn, N. P. (1999). Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. *Lancet*, *354*(9192), 1771-1775. https://doi.org/10.1016/s0140-6736(99)04137-9

Schrag, A., Geser, F., Stampfer-Kountchev, M., Seppi, K., Sawires, M., Köllensperger, M.,…Group, E. M.-S. (2006). Health-related quality of life in multiple system atrophy. *Mov Disord*, *21*(6), 809-815. https://doi.org/10.1002/mds.20808

Schrag, A., Horsfall, L., Walters, K., Noyce, A., & Petersen, I. (2015). Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol*, *14*(1), 57-64. https://doi.org/10.1016/S1474-4422(14)70287-X

Schrag, A., Sheikh, S., Quinn, N. P., Lees, A. J., Selai, C., Mathias, C.,…Jahanshahi, M. (2010). A comparison of depression, anxiety, and health status in patients with progressive supranuclear palsy and multiple system atrophy. *Mov Disord*, *25*(8), 1077-1081. https://doi.org/10.1002/mds.22794

Schultz, W. (1997). Dopamine neurons and their role in reward mechanisms. *Curr Opin Neurobiol*, *7*(2), 191-197. https://doi.org/10.1016/s0959-4388(97)80007-4

Schweighauser, M., Shi, Y., Tarutani, A., Kametani, F., Murzin, A. G., Ghetti, B.,…Goedert, M. (2020). Structures of α-synuclein filaments from multiple system atrophy. *Nature*, *585*(7825), 464-469. https://doi.org/10.1038/s41586-020-2317-6

Seppi, K., Ray Chaudhuri, K., Coelho, M., Fox, S. H., Katzenschlager, R., Perez Lloret, S., Weintraub, D., Sampaio, C., & the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine Committee (2019). Update on treatments for nonmotor symptoms of Parkinson's disease-an evidence-based medicine review. *Movement disorders : official journal of the Movement Disorder Society*, *34*(2), 180–198. https://doi.org/10.1002/mds.27602

Seppi, K., Weintraub, D., Coelho, M., Perez-Lloret, S., Fox, S. H., Katzenschlager, R.,…Sampaio, C. (2011). The Movement Disorder Society Evidence-Based Medicine Review Update: Treatments for the non-motor symptoms of Parkinson's disease. *Mov Disord*, *26 Suppl 3*(0 3), S42-80. https://doi.org/10.1002/mds.23884

Shen, D., Wu, G., & Suk, H. I. (2017). Deep Learning in Medical Image Analysis. *Annu Rev Biomed Eng*, *19*, 221-248. https://doi.org/10.1146/annurev-bioeng-071516-044442

Scheperjans, F. (2024). *Näin hoidan: Levodopan käyttö Parkinsonin taudin hoidossa.* Duodecim, 140(17), 17120. https://www.duodecimlehti.fi/xmedia/duo/duo17120.pdf

Shi, Q., Chowdhury, S., Ma, R., Le, K. X., Hong, S., Caldarone, B. J.,…Lemere, C. A. (2017). Complement C3 deficiency protects against neurodegeneration in aged plaque-rich APP/PS1 mice. *Sci Transl Med*, *9*(392). https://doi.org/10.1126/scitranslmed.aaf6295

Shulman, L. M., Taback, R. L., Rabinstein, A. A., & Weiner, W. J. (2002). Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord*, *8*(3), 193-197. https://doi.org/10.1016/s1353-8020(01)00015-3

Shy, G. M., & Drager, G. A. (1960). A neurological syndrome associated with orthostatic hypotension: a clinical-pathologic study. *Arch Neurol*, *2*, 511-527. https://doi.org/10.1001/archneur.1960.03840110025004

Singer, W., Berini, S. E., Sandroni, P., Fealey, R. D., Coon, E. A., Suarez, M. D.,…Low, P. A. (2017). Pure autonomic failure: Predictors of conversion to clinical CNS involvement. *Neurology*, *88*(12), 1129-1136. https://doi.org/10.1212/WNL.0000000000003737

Singh, F., & Ganley, I. G. (2021). Parkinson's disease and mitophagy: an emerging role for LRRK2. *Biochem Soc Trans*, *49*(2), 551-562. https://doi.org/10.1042/BST20190236

Singleton, A., & Hardy, J. (2011). A generalizable hypothesis for the genetic architecture of disease: pleomorphic risk loci. *Hum Mol Genet*, *20*(R2), R158-162. https://doi.org/10.1093/hmg/ddr358

Song, Y. J., Huang, Y., & Halliday, G. M. (2011). Clinical correlates of similar pathologies in parkinsonian syndromes. *Movement disorders : official journal of the Movement Disorder Society*, *26*(3), 499–506. https://doi.org/10.1002/mds.23336

Song, Y. J., Lundvig, D. M., Huang, Y., Gai, W. P., Blumbergs, P. C., Højrup, P.,…Jensen, P. H. (2007). p25alpha relocalizes in oligodendroglia from myelin to cytoplasmic inclusions in multiple system atrophy. *Am J Pathol*, *171*(4), 1291-1303. https://doi.org/10.2353/ajpath.2007.070201

Sosna, J., Philipp, S., Albay, R., Reyes-Ruiz, J. M., Baglietto-Vargas, D., LaFerla, F. M., & Glabe, C. G. (2018). Early long-term administration of the CSF1R inhibitor PLX3397 ablates microglia and reduces accumulation of intraneuronal amyloid, neuritic plaque deposition and pre-fibrillar

oligomers in 5XFAD mouse model of Alzheimer's disease. *Mol Neurodegener*, *13*(1), 11. https://doi.org/10.1186/s13024-018-0244-x

Soutar, M. P. M., Melandri, D., O'Callaghan, B., Annuario, E., Monaghan, A. E., Welsh, N. J.,…Plun-Favreau, H. (2022). Regulation of mitophagy by the NSL complex underlies genetic risk for Parkinson's disease at 16q11.2 and MAPT H1 loci. *Brain*, *145*(12), 4349-4367. https://doi.org/10.1093/brain/awac325

Spillantini, M. G., Crowther, R. A., Jakes, R., Cairns, N. J., Lantos, P. L., & Goedert, M. (1998). Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson's disease and dementia with Lewy bodies. *Neurosci Lett*, *251*(3), 205-208. https://doi.org/10.1016/s0304-3940(98)00504-7

Spillantini, M. G., Schmidt, M. L., Lee, V. M., Trojanowski, J. Q., Jakes, R., & Goedert, M. (1997). Alpha-synuclein in Lewy bodies. *Nature*, *388*(6645), 839-840. https://doi.org/10.1038/42166

Spinelli, E. G., Mandelli, M. L., Miller, Z. A., Santos-Santos, M. A., Wilson, S. M., Agosta, F.,…Gorno-Tempini, M. L. (2017). Typical and atypical pathology in primary progressive aphasia variants. *Ann Neurol*, *81*(3), 430-443. https://doi.org/10.1002/ana.24885

Stamelou, M., de Silva, R., Arias-Carrión, O., Boura, E., Höllerhage, M., Oertel, W. H.,…Höglinger, G. U. (2010). Rational therapeutic approaches to progressive supranuclear palsy. *Brain*, *133*(Pt 6), 1578-1590. https://doi.org/10.1093/brain/awq115

Stankovic, I., Krismer, F., Jesic, A., Antonini, A., Benke, T., Brown, R. G.,…Group, M. D. S. M. M. S. (2014). Cognitive impairment in multiple system atrophy: a position statement by the Neuropsychology Task Force of the MDS Multiple System Atrophy (MODIMSA) study group. *Mov Disord*, *29*(7), 857-867. https://doi.org/10.1002/mds.25880

Steele, J. C., Richardson, J. C., & Olszewski, J. (1964). Progressive Supranuclear Palsy. A Heterogenous Degeneration Involving The Brain Stem, Basal Ganglia and Cerebellum With Vertical Gaze And Pseudobulbar Palsy, Nuchal Dystonia And Dementia. *Arch Neurol*, *10*, 333-359. https://doi.org/10.1001/archneur.1964.00460160003001

Stefanova, N., Kaufmann, W. A., Humpel, C., Poewe, W., & Wenning, G. K. (2012). Systemic proteasome inhibition triggers neurodegeneration in a transgenic mouse model expressing human α-synuclein under oligodendrocyte promoter: implications for multiple system atrophy. *Acta Neuropathol*, *124*(1), 51-65. https://doi.org/10.1007/s00401-012-0977-5

Stocco, A., Lebiere, C., & Anderson, J. R. (2010). Conditional routing of information to the cortex: a model of the basal ganglia's role in cognitive coordination. *Psychol Rev*, *117*(2), 541-574. https://doi.org/10.1037/a0019077

Sweeney, M. D., Sagare, A. P., & Zlokovic, B. V. (2018). Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nature reviews. Neurology*, *14*(3), 133–150. https://doi.org/10.1038/nrneurol.2017.188

Takigawa, H., Kitayama, M., Wada-Isoe, K., Kowa, H., & Nakashima, K. (2016). Prevalence of progressive supranuclear palsy in Yonago: change throughout a decade. *Brain Behav*, *6*(12), e00557. https://doi.org/10.1002/brb3.557

Tan, Y. Y., Jenner, P., & Chen, S. D. (2022). Monoamine Oxidase-B Inhibitors for the Treatment of Parkinson's Disease: Past, Present, and Future. *J Parkinsons Dis*, *12*(2), 477-493. https://doi.org/10.3233/JPD-212976

Taylor, J. P., McKeith, I. G., Burn, D. J., Boeve, B. F., Weintraub, D., Bamford, C.,…O'Brien, J. T. (2020). New evidence on the management of Lewy body dementia. *Lancet Neurol*, *19*(2), 157-169. https://doi.org/10.1016/S1474-4422(19)30153-X

Tomlinson, C. L., Patel, S., Meek, C., Herd, C. P., Clarke, C. E., Stowe, R.,…Ives, N. (2013). Physiotherapy versus placebo or no intervention in Parkinson's disease. *Cochrane Database Syst Rev*, *2013*(9), CD002817. https://doi.org/10.1002/14651858.CD002817.pub4

Tozzi, A., Sciaccaluga, M., Loffredo, V., Megaro, A., Ledonne, A., Cardinale, A.,…Calabresi, P. (2021). Dopamine-dependent early synaptic and motor dysfunctions induced by α-synuclein in the nigrostriatal circuit. *Brain*, *144*(11), 3477-3491. https://doi.org/10.1093/brain/awab242

Tretiakoff, K. (1919). Contribution à l'étude de l'anatomie du Locus Niger de Soemmerin: g avec Quelques Déductions Relatives à la Pathogenie des Troubles du tonus Musculaire et de la Maladie de Parkinson. In: Paris: Thèse de.

Trojanowski, J. Q., Revesz, T., & MSA, N. W. G. o. (2007). Proposed neuropathological criteria for the post mortem diagnosis of multiple system atrophy. *Neuropathol Appl Neurobiol*, *33*(6), 615-620. https://doi.org/10.1111/j.1365-2990.2007.00907.x

Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B.,…Camus, V. (2021). Neuroinflammation and depression: A review. *Eur J Neurosci*, *53*(1), 151-171. https://doi.org/10.1111/ejn.14720

Tseng, F. S., Foo, J. Q. X., Mai, A. S., & Tan, E. K. (2023). The genetic basis of multiple system atrophy. *Journal of translational medicine*, *21*(1), 104. https://doi.org/10.1186/s12967-023-03905-1

Ubhi, K., Lee, P. H., Adame, A., Inglis, C., Mante, M., Rockenstein, E.,…Masliah, E. (2009). Mitochondrial inhibitor 3-nitroproprionic acid enhances oxidative modification of alpha-synuclein in a transgenic mouse model of multiple system atrophy. *J Neurosci Res*, *87*(12), 2728-2739. https://doi.org/10.1002/jnr.22089

Urso, D., Tafuri, B., De Blasi, R., Nigro, S., Logroscino, G., & Initiative, -. R. T. N. (2022). Imaging correlates of depression in progressive supranuclear palsy. *J Neurol*, *269*(7), 3522-3528. https://doi.org/10.1007/s00415-021-10939-2

Van Den Eeden, S. K., Tanner, C. M., Bernstein, A. L., Fross, R. D., Leimpeter, A., Bloch, D. A., & Nelson, L. M. (2003). Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am J Epidemiol*, *157*(11), 1015-1022. https://doi.org/10.1093/aje/kwg068

van Diermen, L., van den Ameele, S., Kamperman, A. M., Sabbe, B. C. G., Vermeulen, T., Schrijvers, D., & Birkenhäger, T. K. (2018). Prediction of electroconvulsive therapy response and remission in major depression: meta-analysis. *Br J Psychiatry*, *212*(2), 71-80. https://doi.org/10.1192/bjp.2017.28

van Laar, T., Chaudhuri, K. R., Antonini, A., Henriksen, T., & Trošt, M. (2023). Infusion Therapies in the Treatment of Parkinson's Disease. *J Parkinsons Dis*, *13*(5), 641-657. https://doi.org/10.3233/JPD-225112

Varatharaj, A., & Galea, I. (2017). The blood-brain barrier in systemic inflammation. *Brain Behav Immun*, *60*, 1-12. https://doi.org/10.1016/j.bbi.2016.03.010

Waldvogel, H. J., Kim, E. H., Tippett, L. J., Vonsattel, J. P., & Faull, R. L. (2015). The Neuropathology of Huntington's Disease. *Curr Top Behav Neurosci*, *22*, 33-80. https://doi.org/10.1007/7854_2014_354

Wan, Y., Hu, W., Gan, J., Song, L., Wu, N., Chen, Y., & Liu, Z. (2019). Exploring the association between Cerebral small-vessel diseases and motor symptoms in Parkinson's disease. *Brain Behav*, *9*(4), e01219. https://doi.org/10.1002/brb3.1219

Wang, H., He, Y., Sun, Z., Ren, S., Liu, M., Wang, G., & Yang, J. (2022). Microglia in depression: an overview of microglia in the pathogenesis and treatment of depression. *J Neuroinflammation*, *19*(1), 132. https://doi.org/10.1186/s12974-022-02492-0

Wang, Z. X., Wan, Q., & Xing, A. (2020). HLA in Alzheimer's Disease: Genetic Association and Possible Pathogenic Roles. *Neuromolecular Med*, *22*(4), 464-473. https://doi.org/10.1007/s12017-020-08612-4

Watanabe, H., Saito, Y., Terao, S., Ando, T., Kachi, T., Mukai, E.,…Sobue, G. (2002). Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. *Brain*, *125*(Pt 5), 1070-1083. https://doi.org/10.1093/brain/awf117

Watts, J. C., Giles, K., Oehler, A., Middleton, L., Dexter, D. T., Gentleman, S. M.,…Prusiner, S. B. (2013). Transmission of multiple system atrophy prions to transgenic mice. *Proc Natl Acad Sci U S A*, *110*(48), 19555-19560. https://doi.org/10.1073/pnas.1318268110

Wei, L., Hu, X., Yuan, Y., Liu, W., & Chen, H. (2018). Abnormal ventral tegmental area-anterior cingulate cortex connectivity in Parkinson's disease with depression. *Behav Brain Res*, *347*, 132-139. https://doi.org/10.1016/j.bbr.2018.03.011

Weil-Malherbe, H., & Bone, A. D. (1957). Intracellular distribution of catecholamines in the brain. *Nature*, *180*(4594), 1050-1051. https://doi.org/10.1038/1801050a0

Weintraub, D., Moberg, P. J., Duda, J. E., Katz, I. R., & Stern, M. B. (2003). Recognition and treatment of depression in Parkinson's disease. *J Geriatr Psychiatry Neurol*, *16*(3), 178-183. https://doi.org/10.1177/0891988703256053

Wenning, G. K., Ben-Shlomo, Y., Hughes, A., Daniel, S. E., Lees, A., & Quinn, N. P. (2000). What clinical features are most useful to distinguish definite multiple system atrophy from Parkinson's disease? *J Neurol Neurosurg Psychiatry*, *68*(4), 434-440. https://doi.org/10.1136/jnnp.68.4.434

Wenning, G. K., Geser, F., Krismer, F., Seppi, K., Duerr, S., Boesch, S.,…Group, E. M. S. A. S. (2013). The natural history of multiple system atrophy: a prospective European cohort study. *Lancet Neurol*, *12*(3), 264-274. https://doi.org/10.1016/S1474-4422(12)70327-7

Wenning, G. K., Geser, F., & Poewe, W. (2005). Therapeutic strategies in multiple system atrophy. *Mov Disord*, *20 Suppl 12*, S67-76. https://doi.org/10.1002/mds.20543

Wenning, G. K., Stankovic, I., Vignatelli, L., Fanciulli, A., Calandra-Buonaura, G., Seppi, K.,…Kaufmann, H. (2022). The Movement Disorder Society Criteria for the Diagnosis of Multiple System Atrophy. *Mov Disord*, *37*(6), 1131-1148. https://doi.org/10.1002/mds.29005

Williams, D. R., de Silva, R., Paviour, D. C., Pittman, A., Watt, H. C., Kilford, L.,…Lees, A. J. (2005). Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism. *Brain*, *128*(Pt 6), 1247-1258. https://doi.org/10.1093/brain/awh488

Williams, D. R., & Lees, A. J. (2009). Progressive supranuclear palsy: clinicopathological concepts and diagnostic challenges. *Lancet Neurol*, *8*(3), 270-279. https://doi.org/10.1016/S1474-4422(09)70042-0

Williams, G. P., Marmion, D. J., Schonhoff, A. M., Jurkuvenaite, A., Won, W. J., Standaert, D. G.,…Harms, A. S. (2020). T cell infiltration in both human multiple system atrophy and a novel mouse model of the disease. *Acta Neuropathol*, *139*(5), 855-874. https://doi.org/10.1007/s00401-020-02126-w

Williams-Gray, C. H., Wijeyekoon, R., Yarnall, A. J., Lawson, R. A., Breen, D. P., Evans, J. R.,…group, I.-P. s. (2016). Serum immune markers and disease progression in an incident Parkinson's disease cohort (ICICLE-PD). *Mov Disord*, *31*(7), 995-1003. https://doi.org/10.1002/mds.26563

Witoelar, A., Jansen, I. E., Wang, Y., Desikan, R. S., Gibbs, J. R., Blauwendraat, C.,…International Parkinson's Disease Genomics Consortium (IPDGC), N. r. A. B. E. C. N., and United Kingdom Brain Expression Consortium (UKBEC) Investigators. (2017). Genome-wide Pleiotropy Between Parkinson Disease and Autoimmune Diseases. *JAMA Neurol*, *74*(7), 780-792. https://doi.org/10.1001/jamaneurol.2017.0469

Wüllner, U., Abele, M., Schmitz-Huebsch, T., Wilhelm, K., Benecke, R., Deuschl, G., & Klockgether, T. (2004). Probable multiple system atrophy in a German family. *J Neurol Neurosurg Psychiatry*, *75*(6), 924-925. https://doi.org/10.1136/jnnp.2003.025155

Yahr, M. D., Duvoisin, R. C., Mendoza, M. R., Schear, M. J., & Barrett, R. E. (1971). Modification of L-dopa therapy of Parkinsonism by alpha-methyldopa hydrazine (MK-486). *Trans Am Neurol Assoc*, *96*, 55-58.

Yan, Z., Yang, W., Wei, H., Dean, M. N., Standaert, D. G., Cutter, G. R.,…Qin, H. (2021). Dysregulation of the Adaptive Immune System in Patients With Early-Stage Parkinson Disease. *Neurol Neuroimmunol Neuroinflamm*, *8*(5). https://doi.org/10.1212/NXI.0000000000001036

Yang, Y. (2022). Cryo-EM structures of α-synuclein filaments from Parkinson's disease and dementia with Lewy bodies. In: bioRxiv.

Yang, R., Sun, M., Chen, W., Feng, H., Chen, B., Liu, Y., He, Q., Wang, L., Zou, C., Luo, X., Li, Z., Fu, A., Qiao, F., Tang, H., Yang, J., & Ren, H. (2026). Global, regional and national burden of Parkinson's disease, 1990-2021: Update from the GBD 2021 study. *Journal of the neurological sciences*, *480*, 125703. https://doi.org/10.1016/j.jns.2025.125703

Yoshida, K., Hata, Y., Kinoshita, K., Takashima, S., Tanaka, K., & Nishida, N. (2017). Incipient progressive supranuclear palsy is more common than expected and may comprise clinicopathological subtypes: a forensic autopsy series. *Acta Neuropathol*, *133*(5), 809-823. https://doi.org/10.1007/s00401-016-1665-7

Zang, X., Chen, S., Zhu, J., Ma, J., & Zhai, Y. (2022). The Emerging Role of Central and Peripheral Immune Systems in Neurodegenerative Diseases. *Front Aging Neurosci*, *14*, 872134. https://doi.org/10.3389/fnagi.2022.872134

Zappia, M., Oliveri, R. L., Bosco, D., Nicoletti, G., Branca, D., Caracciolo, M.,…Quattrone, A. (2000). The long-duration response to L-dopa in the treatment of early PD. *Neurology*, *54*(10), 1910-1915. https://doi.org/10.1212/wnl.54.10.1910

Zhang, W., Wang, T., Pei, Z., Miller, D. S., Wu, X., Block, M. L.,…Zhang, J. (2005). Aggregated alpha-synuclein activates microglia: a process leading to disease progression in Parkinson's disease. *FASEB J*, *19*(6), 533-542. https://doi.org/10.1096/fj.04-2751com

Zhang, W., Xiao, D., Mao, Q., & Xia, H. (2023). Role of neuroinflammation in neurodegeneration development. *Signal Transduct Target Ther*, *8*(1), 267. https://doi.org/10.1038/s41392-023-01486-5

Zheng, X., Mi, T., Wang, R., Zhang, Z., Li, W., Zhao, J.,…Mao, Q. (2022). Progranulin deficiency promotes persistent neuroinflammation and causes regional pathology in the hippocampus following traumatic brain injury. *Glia*, *70*(7), 1317-1336. https://doi.org/10.1002/glia.24175

Zhu, J., & Paul, W. E. (2008). CD4 T cells: fates, functions, and faults. *Blood*, *112*(5), 1557-1569. https://doi.org/10.1182/blood-2008-05-078154

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