

Atypical Parkinsonian Syndromes

Progressive supranuclear palsy • Corticobasal degeneration • Multiple system atrophy

Neuropathology and clinicopathologic correlation

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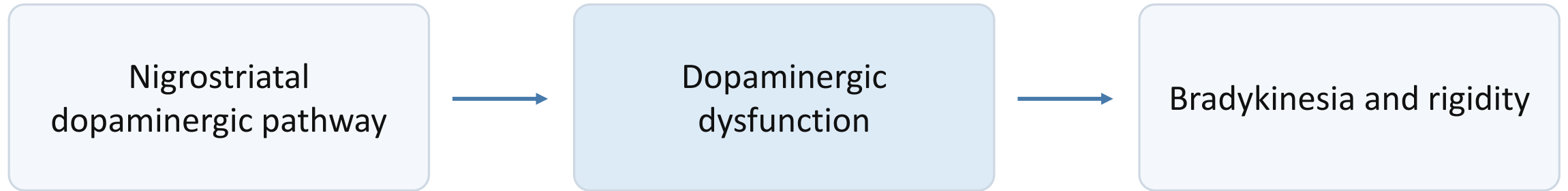
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Learning objectives

- Define atypical parkinsonism relative to Parkinson disease (PD).
- Differentiate PSP, CBD, and MSA by dominant clinical systems and protein aggregates.
- Correlate pathologic distribution and affected cell types with clinical phenotypes.
- Interpret representative clinicopathologic vignettes without treating them as definitive diagnoses.

Parkinsonism begins with nigrostriatal dysfunction



- The syndrome describes a motor phenotype, not a single disease.
- Multiple neurodegenerative conditions share this motor phenotype.

“Atypical” means additional neurologic systems

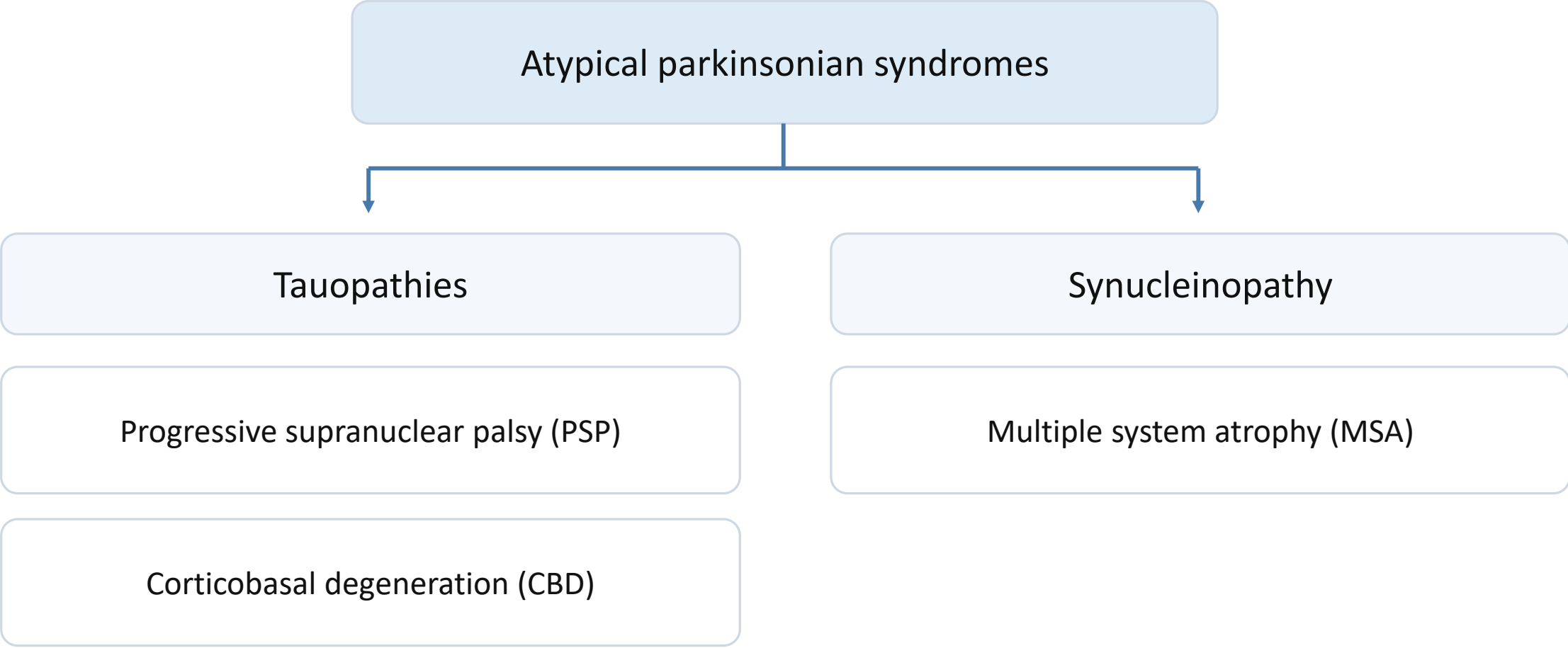
- Parkinsonism is only part of the clinical picture in PSP, CBD, and MSA.
- Prominent eye-movement, cortical, cerebellar, or autonomic findings extend beyond the core PD phenotype.
- The “Parkinson-plus” designation captures these accompanying abnormalities.

Levodopa response: A discriminating clue

Typical PD (source comparison)	Atypical parkinsonian syndromes
Dopamine replacement can improve motor symptoms, especially early	Generally minimally responsive to L-DOPA
Nigrostriatal dopamine deficit contributes strongly to motor features	Additional degenerating systems contribute non-dopaminergic deficits
Response is not a permanent arrest of degeneration	Limited response does not identify a particular atypical syndrome

Three entities, two protein families

Atypical parkinsonian syndromes



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graph TD; A[Atypical parkinsonian syndromes] --> B[Tauopathies]; A --> C[Synucleinopathy]; B --> D[Progressive supranuclear palsy (PSP)]; B --> E[Corticobasal degeneration (CBD)]; C --> F[Multiple system atrophy (MSA)];
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The diagram is a hierarchical flowchart. At the top is a light blue box with the text 'Atypical parkinsonian syndromes'. A horizontal line with two downward-pointing arrows branches from this box to two separate light blue boxes: 'Tauopathies' on the left and 'Synucleinopathy' on the right. Below 'Tauopathies' are two white boxes with light blue borders: 'Progressive supranuclear palsy (PSP)' and 'Corticobasal degeneration (CBD)'. Below 'Synucleinopathy' is one white box with a light blue border: 'Multiple system atrophy (MSA)'.

Tauopathies

Progressive supranuclear palsy (PSP)

Corticobasal degeneration (CBD)

Synucleinopathy

Multiple system atrophy (MSA)

Protein–cell–territory signature

Entity	Dominant aggregate	Topographic emphasis
PSP	Tau in neurons and glia	Brainstem and deep gray matter
CBD	Tau in neurons and glia	Cerebral cortex prominent
MSA	α -Synuclein in oligodendrocytes	White matter pathways and multiple circuits

PSP and CBD overlap FTLD-tau

- Both disorders combine parkinsonian features with frontotemporal degeneration.
- PSP and CBD as subtypes of frontotemporal lobar degeneration with tau pathology (FTLD-tau).
- Protein class alone cannot distinguish PSP from CBD; Distribution and lesion pattern matter.

Clinicopathologic orientation map

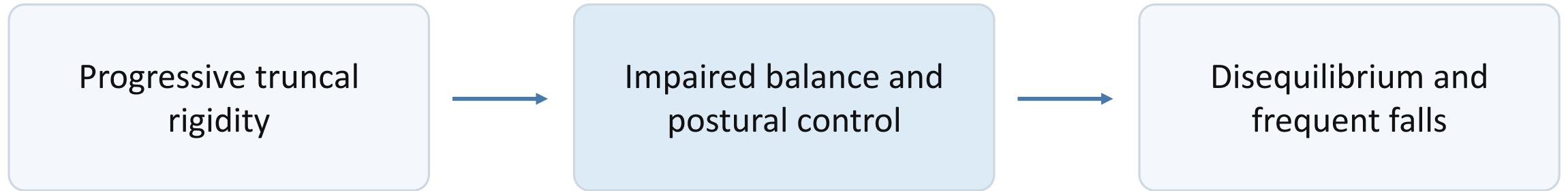
Entity	Motor / ocular pattern	Cortical dysfunction	Autonomic / cerebellar
PSP	Truncal rigidity, falls, ocular difficulty	Progressive dementia	Not the defining pattern
CBD	Asymmetric rigidity and jerks	Apraxia; later cognitive decline	Not the defining pattern
MSA	Parkinsonism among presentations	Not emphasized in source	Ataxia and orthostatic hypotension

Progressive supranuclear palsy

PSP: Characteristic clinical constellation

- Progressive truncal rigidity and disequilibrium produce frequent falls.
- Voluntary eye movements become difficult.
- Nuchal dystonia, pseudobulbar palsy, and progressive dementia may accompany the motor syndrome.

From axial motor disturbance to falls



- Truncal rather than predominantly distal dysfunction is emphasized.
- This constellation should redirect evaluation away from uncomplicated PD.

PSP: Disturbance of voluntary eye movements

- Difficulty with voluntary eye movements is a characteristic component of PSP.
- Eye-movement involvement occurs alongside truncal rigidity and postural disequilibrium.
- The combination carries greater discriminative value than parkinsonism alone.

PSP: Associated bulbar and cervical findings

- Nuchal dystonia adds a distinctive axial motor abnormality.
- Pseudobulbar palsy reflects dysfunction affecting voluntary bulbar control.
- These findings expand the phenotype beyond a pure nigrostriatal syndrome.

PSP: Progressive cognitive impairment

- Progressive dementia among the common clinical manifestations.
- Cognition must be assessed together with motor and ocular deficits.
- Combined motor and cognitive deficits are compatible with the FTLD-tau disease context.

PSP: Clinical tempo

- Typical onset is between the fifth and seventh decades.
- Males affected approximately twice as frequently as females.
- Death often occurring within 5–7 years of disease onset; This is a source-specific estimate.

PSP: Tissue compartments with greatest burden

Tau-positive neuronal and glial inclusions

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graph TD; A[Tau-positive neuronal and glial inclusions] --> B[Brainstem]; A --> C[Deep gray and cerebellar nuclei]; B --> D[Substantia nigra]; B --> E[Colliculi]; B --> F[Periaqueductal gray]; C --> G[Globus pallidus]; C --> H[Subthalamic nucleus]; C --> I[Dentate nucleus];
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Brainstem

Substantia nigra

Colliculi

Periaqueductal gray

Deep gray and cerebellar nuclei

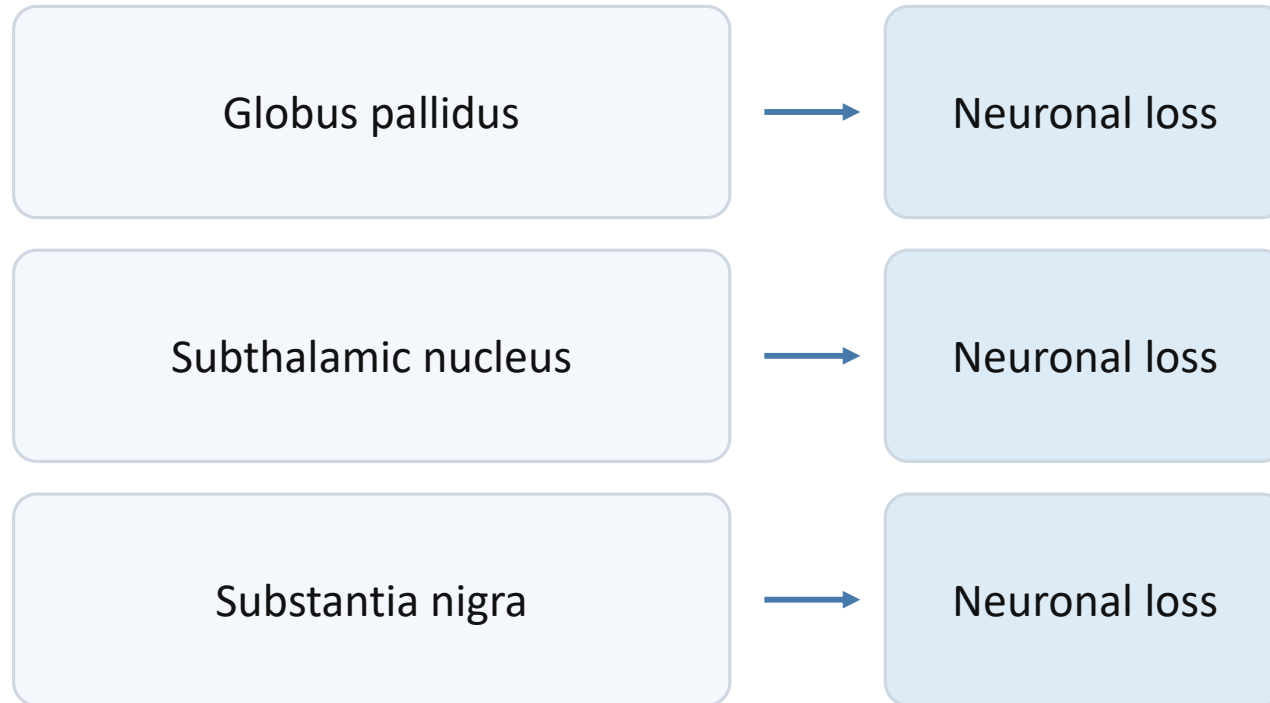
Globus pallidus

Subthalamic nucleus

Dentate nucleus

PSP: Deep gray matter involvement

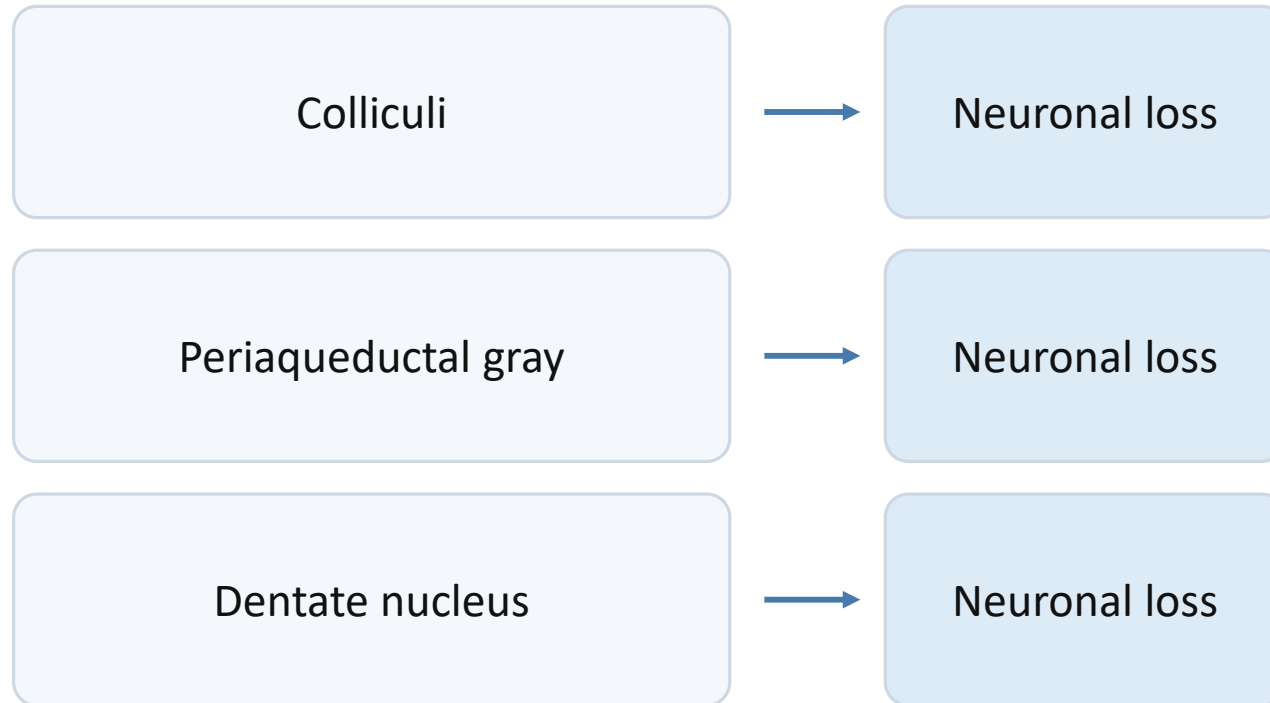
Regional involvement — conceptual map



- Multiple motor-associated deep gray structures are affected.
- The lesion distribution is broader than isolated nigral dysfunction.
- Source describes widespread neuronal loss rather than a single focal injury.

PSP: Brainstem and cerebellar nuclei

Regional involvement — conceptual map



- Affected structures extend through brainstem and cerebellar circuitry.
- Anatomic distribution helps explain the multisystem phenotype.
- No precise one-region–one-symptom mapping is asserted by the textbook excerpt.

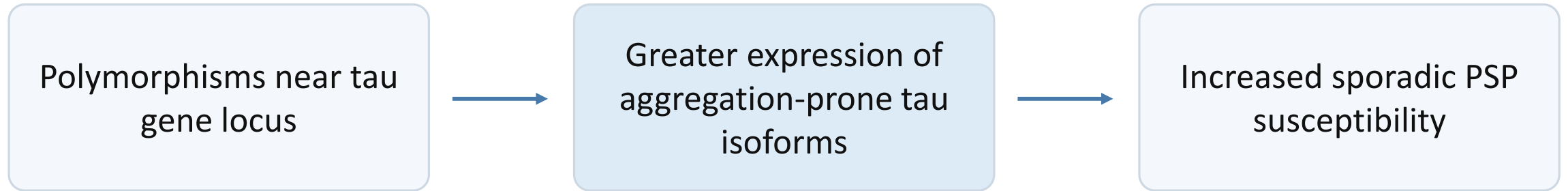
PSP aggregates are not Alzheimer-type tangles

PSP tau tangles	Alzheimer disease tangles (textbook comparison)
Globular appearance	More filamentous appearance
Neurons and glia in affected regions	Compared morphologically; not asserted to have identical cell distribution
Regional emphasis: brainstem and deep gray	Different broader disease context

PSP: Neuronal and glial tau pathology

- Tau-containing inclusions involve both neurons and glial cells.
- Inclusions concentrate most heavily in brainstem and deep gray matter.
- The coexistence of aggregate pathology and neuronal loss is the morphologic core of PSP in this chapter.

PSP genetic susceptibility: MAPT-linked risk



- The source describes a risk association, not a deterministic Mendelian rule.
- Causative tau-gene mutations are identified in only a few PSP cases.

PSP: Genetic evidence has distinct levels

- Causative tau-gene mutations are uncommon among described PSP cases.
- Common susceptibility is linked to tau-locus polymorphisms.
- Additional genome-wide association risk alleles exist; Their mechanistic contributions remain uncertain.

PSP: Clinical evidence versus morphologic evidence

Clinical observation	Pathologic observation
Truncal rigidity, falls	Neuronal loss across multiple motor-associated nuclei
Voluntary eye-movement difficulty	Brainstem/deep-gray involvement
Progressive cognitive symptoms	Tauopathy with frontotemporal degeneration context
Limited L-DOPA response (group-level)	Broader pathology beyond dopamine-specific circuitry

Illustrative case: PSP pattern

Teaching vignette (illustrative)

A patient develops progressive trunk rigidity, repeated falls, impaired voluntary eye movements, and nuchal dystonia.

Which protein family and predominant anatomic compartment best fit this pattern?

Tauopathy; Highest aggregate burden in brainstem and deep gray matter.

Corticobasal degeneration

CBD: Key clinical features

- Extrapyrarnidal rigidity and asymmetric motor disturbances characterize the disorder.
- Jerking movements of limbs may be present.
- Higher cortical function is impaired, commonly producing apraxia.

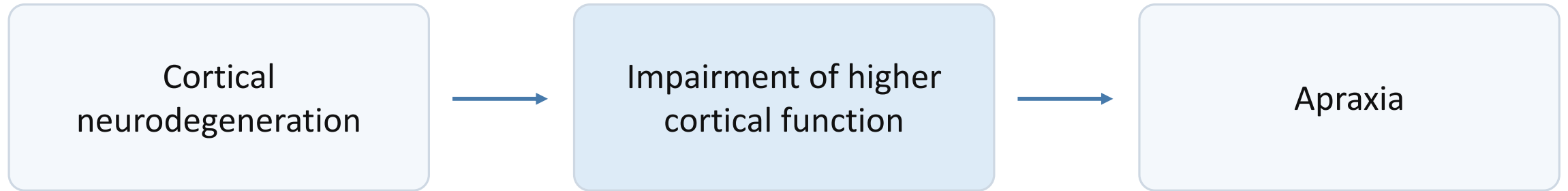
CBD combines movement and cortical deficits

Motor component	Cortical component
Rigidity	Impaired higher cortical function
Asymmetric limb disturbances	Apraxia is particularly typical
Jerking movements	Cognitive decline may develop later

CBD: Why asymmetry matters

- Asymmetric motor disturbance in CBD.
- Rigidity alone is nonspecific within the atypical-parkinsonism group.
- A lateralized motor presentation coupled with apraxia is especially suggestive in a teaching comparison.

CBD: Apraxia and cortical dysfunction



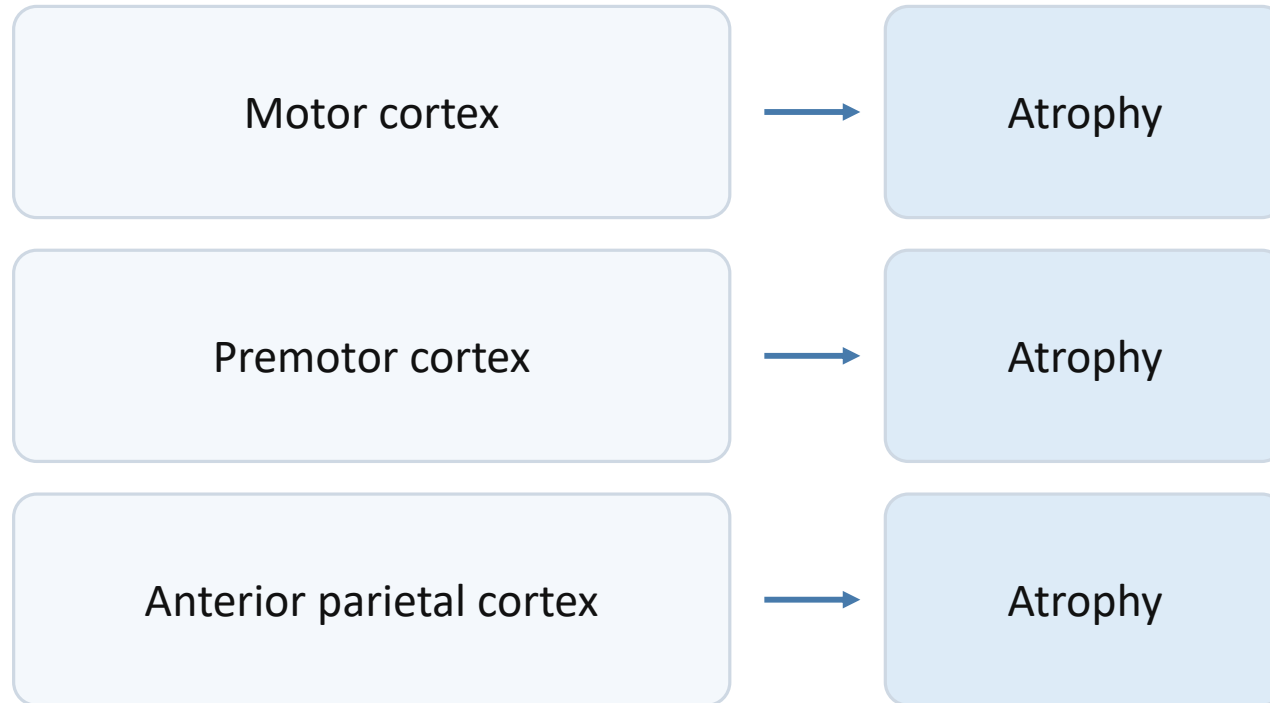
- Apraxia is highlighted as the typical higher cortical deficit.
- This link is clinicopathologic interpretation, not a claim of a uniquely localized lesion.

CBD: Cognition across progression

- Cognitive decline may occur during the illness.
- Decline is typically later in CBD than the early motor phenotype.
- Cognition should not be used in isolation to distinguish CBD from PSP.

CBD: Selective cortical atrophy

Regional involvement — conceptual map



- Cortical atrophy is concentrated in motor-associated and anterior parietal regions.
- This distribution supports combined motor and higher-cortical deficits.
- A schematic is used; No actual gross specimen is available for this deck.

CBD: Cortex shows neuron loss and gliosis

- Affected cerebral cortex undergoes severe neuronal depletion.
- Gliosis accompanies neuronal loss.
- Ballooned neurons are an additional conspicuous pathologic finding.

CBD: Ballooned neurons in the cortex

- Ballooned neurons in markedly affected cortical regions.
- This feature is interpreted in the setting of neuronal loss and gliosis.
- It does not, on its own, reproduce the full histopathologic diagnosis.

CBD: Tau-positive cell populations

Cell / compartment	Textbook observation	Use in interpretation
Astroglia	Tau immunoreactivity	Glial involvement
Oligodendroglia	Coiled bodies	Glial tau accumulation
Basal ganglia neurons	Tau immunoreactivity	Extrapyramidal involvement
Cortical neurons	Variable positivity	Cortical disease association

CBD: Astrocytic plaques and tau threads

- Clusters of tau-positive processes surround astrocytes, forming astrocytic plaques.
- Tau-positive threads occur in gray and white matter.
- These findings as potentially the most specific pathologic features of CBD.

CBD: Distinguish plaque from thread

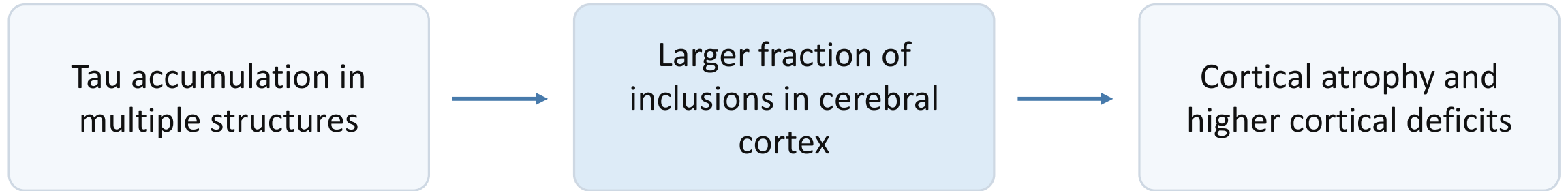


- A plaque is a cluster of processes organized around an astrocyte.
- Threads denote tau-positive processes distributed through gray and white matter.
- These are conceptual definitions; Not replacements for microscopy.

CBD: Additional subcortical neuronal injury

- Substantia nigra and locus ceruleus show neuronal loss.
- Ballooned neurons and tangles also occur in those structures.
- Thus, cortical predominance does not imply disease restriction to cortex.

CBD: Cortical predominance of tau inclusions



- The relative cortical burden in CBD with PSP.
- The final link is a clinicopathologic association, not proof of molecular causality.

CBD and PSP share MAPT-linked susceptibility

- Tau-gene variants associated with PSP are also strongly linked to CBD.
- Shared genetic association reinforces their grouping among tauopathies.
- Regional pathology and aggregate characteristics differentiate these related diseases.

PSP versus CBD: Dominant distributions

PSP	CBD
Brainstem and deep gray matter: greatest burden	Greater relative cortical tau burden
Truncal rigidity, disequilibrium, eye-movement difficulty	Asymmetric limb motor signs and apraxia
Globular tau tangles in neurons and glia	Astrocytic plaques, tau threads, ballooned neurons
Both tauopathies within FTLD-tau	Both associated with tau-locus variants

PSP and CBD have distinct tau folds

- Tau aggregates in PSP and CBD adopt distinct molecular folds in vitro.
- Shared tau protein does not imply identical aggregate conformation.
- Molecular fold is presented as a pathologic property—not as a routine clinical diagnostic assay.

Illustrative case: CBD pattern

Teaching vignette (illustrative)

A patient has progressive asymmetric rigidity and limb jerks accompanied by loss of a learned purposeful motor skill (apraxia).

Which pathology distribution is most strongly favored among the three syndromes?

Corticobasal degeneration; Prominent cortical atrophy and cortical tau pathology.

Multiple system atrophy

MSA: Defining histopathologic concept

- MSA is described as a sporadic neurodegenerative disorder.
- α -Synuclein aggregates accumulate in oligodendroglial cytoplasm.
- White matter tract degeneration and accompanying neuronal loss coexist.

“Multiple” refers to three systems

MSA: Multisystem circuit involvement

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graph TD; A[MSA: Multisystem circuit involvement] --> B[Motor circuits]; A --> C[Autonomic circuits]; B --> D[Striatonigral → parkinsonism]; B --> E[Olivopontocerebellar → ataxia]; C --> F[Central and peripheral autonomic involvement]; C --> G[Orthostatic hypotension prominent];
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Motor circuits

Striatonigral → parkinsonism

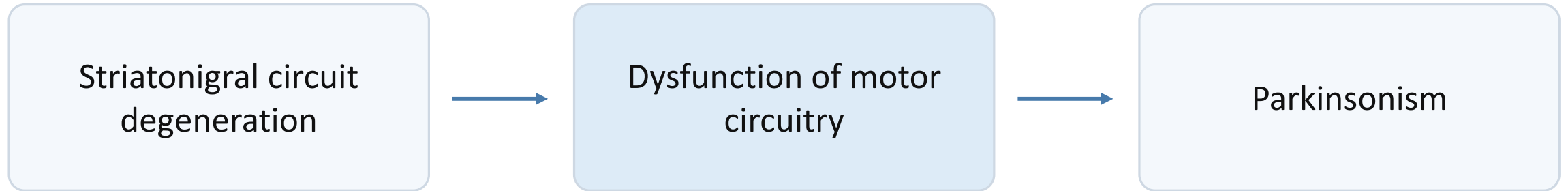
Olivopontocerebellar → ataxia

Autonomic circuits

Central and peripheral autonomic involvement

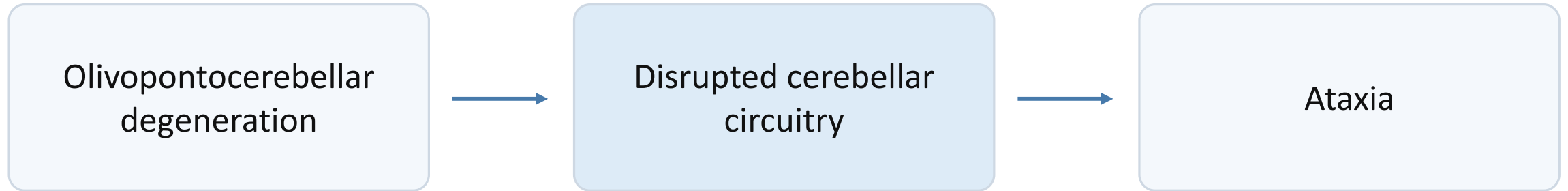
Orthostatic hypotension prominent

MSA: Striatonigral involvement



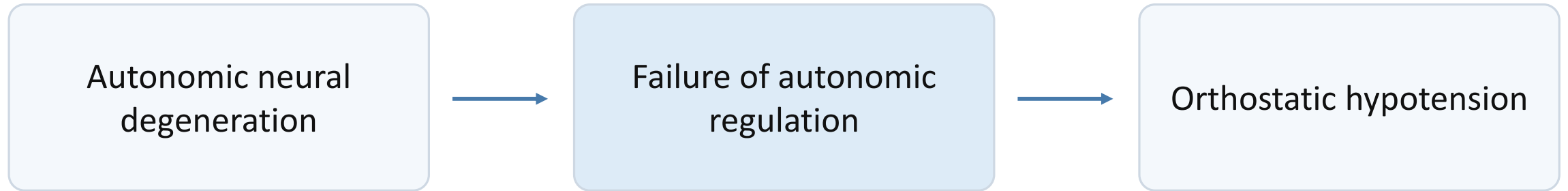
- Substantia nigra and striatum are prominent in parkinsonian forms.
- The putamen is highlighted within the striatum.

MSA: Olivopontocerebellar involvement



- Cerebellum, peduncles, pons, and inferior olive may be atrophic.
- This is the characteristic anatomic distribution of cerebellar forms.

MSA: Autonomic system involvement



- Robbins especially emphasizes orthostatic hypotension.
- Central medullary and spinal autonomic structures are implicated.

MSA phenotype evolves beyond the first system

- One system may dominate at onset of illness.
- Other involved circuits typically manifest as disease progresses.
- Therefore, an initial parkinsonian, cerebellar, or autonomic phenotype can evolve into multisystem disease.

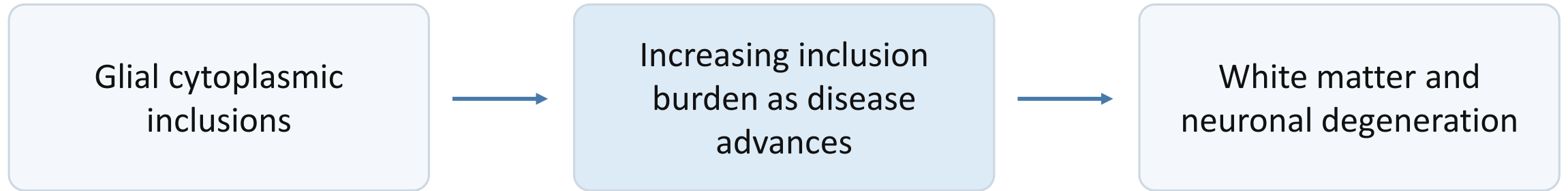
MSA: Predominant onset versus later illness

At presentation	During progression
Parkinsonism may dominate	Ataxic and autonomic features may emerge
Ataxia may dominate	Parkinsonian and autonomic features may emerge
Autonomic symptoms may dominate	Additional motor systems often become affected
Patterns are not mutually exclusive	Anatomic overlap is central to the disease concept

MSA: Glial pathology is the primary emphasis

- The major histopathologic alterations are located in glial cells.
- Oligodendrocytes contain characteristic glial cytoplasmic inclusions.
- Unlike typical Lewy-body disorders, neuronal degeneration often occurs without neuronal inclusions.

MSA: Inclusion burden and neuronal loss



- The observations support an early or primary glial pathologic role.
- The temporal sequence is suggested, not conclusively demonstrated, by the cited findings.

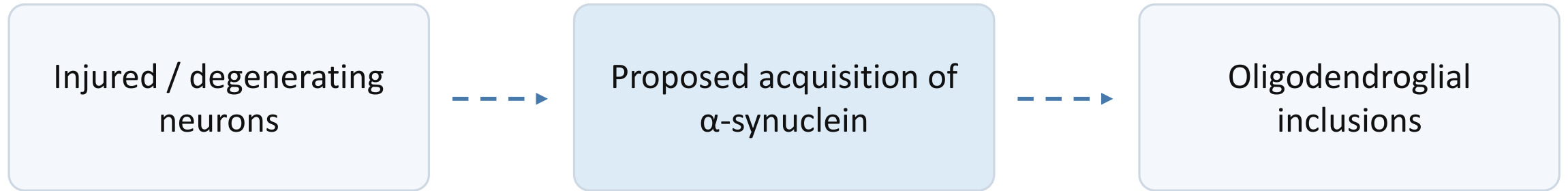
MSA: Evidence for early glial involvement

- Glial cytoplasmic inclusion burden increases with progression.
- Inclusions may be seen where neuronal loss has not yet occurred.
- Together, these observations suggest inclusions can be an early pathologic event.

MSA: Origin of oligodendroglial α -synuclein is uncertain

- α -Synuclein is normally associated with neuronal synaptic vesicles.
- No up-regulation of α -synuclein expression in oligodendrocytes or white matter.
- Transfer of aggregates from damaged neurons to oligodendrocytes is a proposed explanation, not established proof.

MSA: Proposed intercellular protein transfer



- Dashed conceptual hypothesis: Cellular origin remains unresolved.
- No mechanistic transport route is specified by the textbook.

MSA: Oligodendroglial stress responses

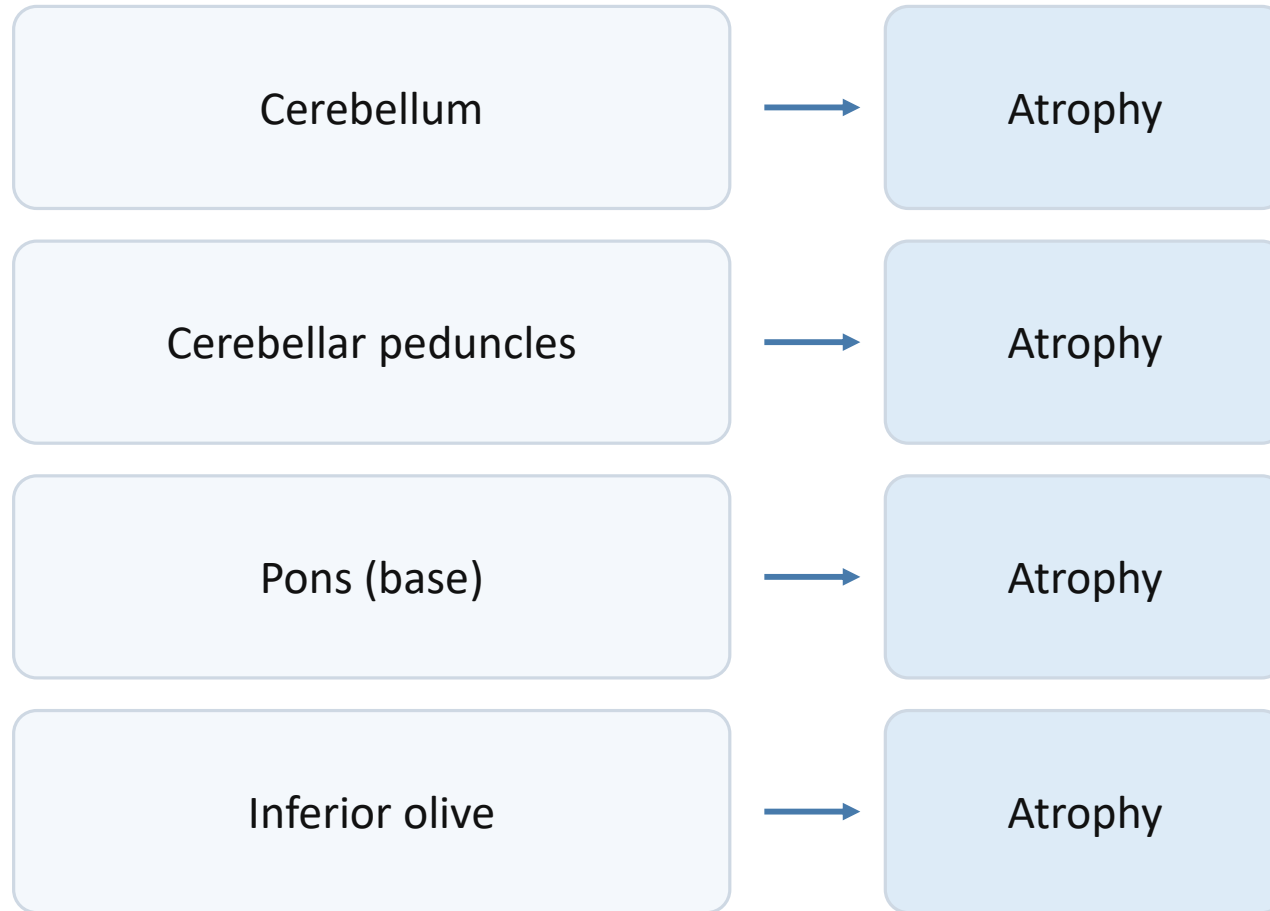
- Oligodendrocytes containing α -synuclein show increased susceptibility to oxidative stress.
- Their interaction with extracellular matrix is impaired.
- These cellular effects offer a possible link to white matter tract damage.

MSA: Genetic association is not causal proof

- No causative α -synuclein gene mutation is identified in the cited textbook account of MSA.
- Polymorphisms near the gene may influence susceptibility.
- A risk association should not be misrepresented as a diagnostic genetic test.

MSA cerebellar form: Gross atrophy

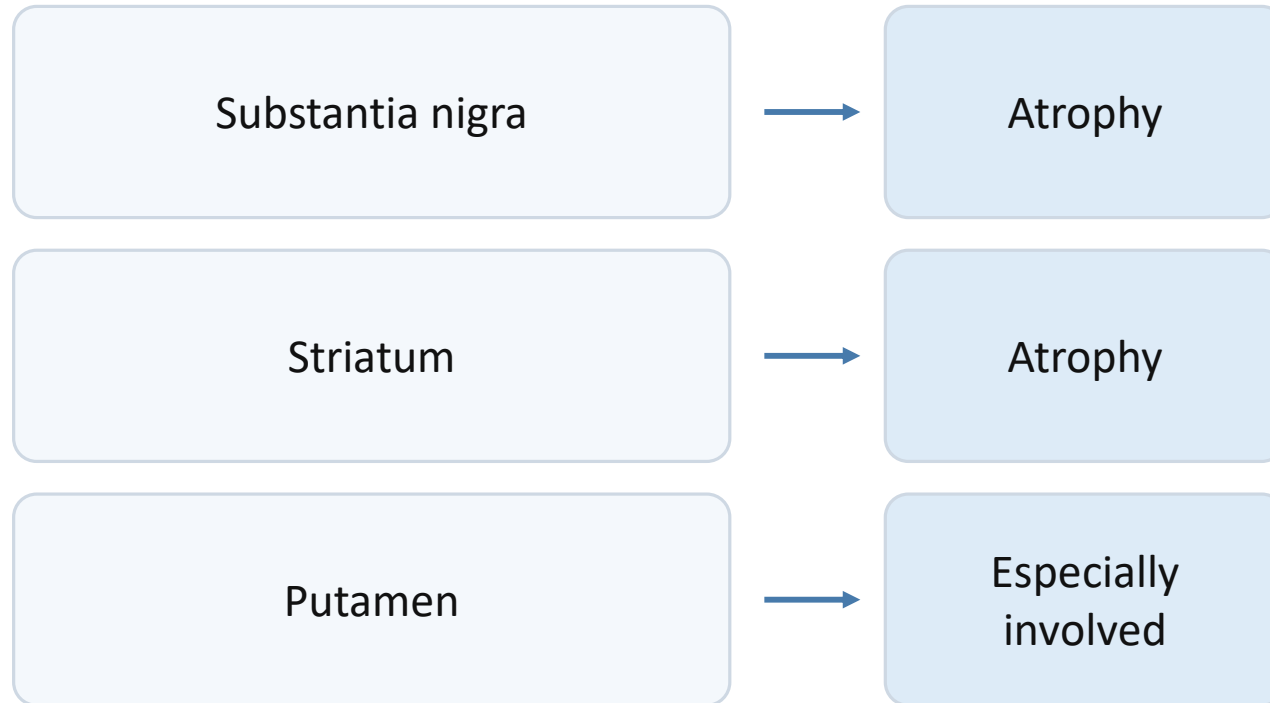
Regional involvement — conceptual map



- Atrophy extends through the olivopontocerebellar network.
- The pons, especially its base, is specifically highlighted.
- Region labels are conceptual; No source photomicrograph is reproduced.

MSA parkinsonian form: Gross atrophy

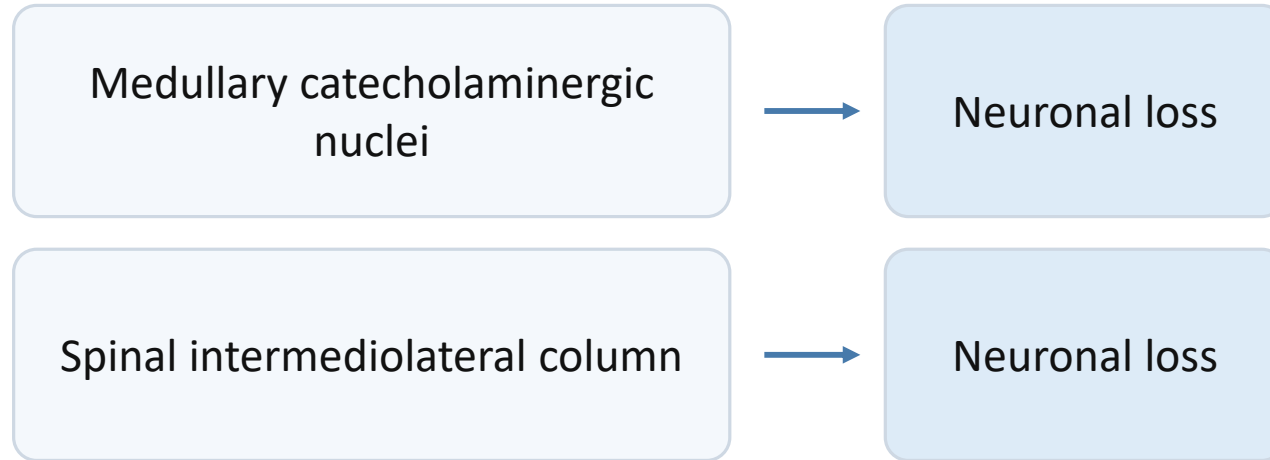
Regional involvement — conceptual map



- This distribution corresponds to a dominant parkinsonian phenotype.
- Putaminal injury is included within striatal pathology.
- Affected regions also show neuronal loss.

MSA autonomic form: Anatomic correlates

Regional involvement — conceptual map



- These structures participate in autonomic regulation.
- Loss correlates with autonomic dysfunction and orthostatic hypotension.
- Atrophy may be distributed rather than confined to one isolated center.

MSA: Direct morphology–clinical mapping

Circuit	Typical anatomic changes	Dominant feature
Striatonigral	Nigra and striatum, especially putamen	Parkinsonism
Olivopontocerebellar	Cerebellum, peduncles, pontine base, inferior olive	Ataxia
Autonomic	Medullary catecholaminergic nuclei; spinal intermediolateral column	Autonomic failure / orthostatic hypotension

MSA: Inclusion composition and detection

- The diagnostic glial cytoplasmic inclusions reside in oligodendrocytes.
- They contain α -synuclein and ubiquitin.
- They were originally demonstrated using silver impregnation methods.

MSA versus PD: Same protein, different cell emphasis

PD / dementia with Lewy bodies	MSA
α -Synuclein inclusions predominantly neuronal	α -Synuclein inclusions characteristically oligodendroglial
Lewy bodies and Lewy neurites described	Glial cytoplasmic inclusions are diagnostic
Substantia nigra neuronal loss; additional distribution varies	White matter tract degeneration and multiple circuits
Robbins reports a distinct α -synuclein fold	Fold differs from PD/DLB in textbook account

Illustrative case: MSA pattern

Teaching vignette (illustrative)

A patient develops parkinsonism with prominent orthostatic hypotension; Later, impaired coordination and gait ataxia appear.

Which primary aggregate protein and cell type best fit this multisystem pattern?

α -Synuclein in oligodendroglial cytoplasmic inclusions.

Integrated clinicopathologic comparison

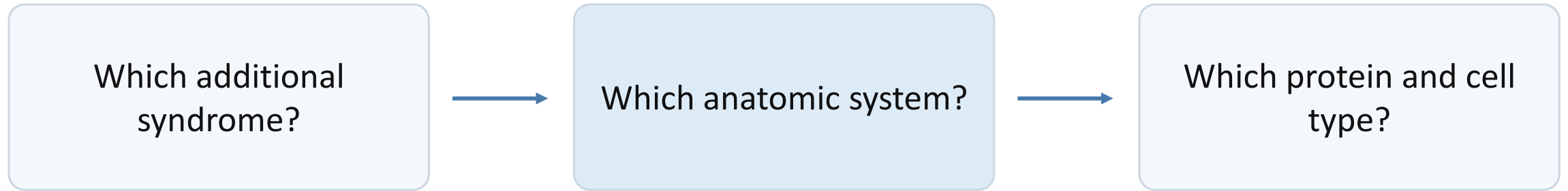
Distinguishing clinical signatures

Disorder	Early or prominent clue	Additional feature
PSP	Truncal rigidity with falls	Difficulty with voluntary eye movements
CBD	Asymmetric rigidity / jerking limb movements	Apraxia
MSA	Parkinsonism, ataxia or autonomic failure	Other systems commonly become involved

Distinguishing morphologic signatures

Disorder	Neural topography	Dominant inclusion
PSP	Brainstem and deep gray nuclei	Globular tau tangles; neuron and glia
CBD	Motor, premotor, anterior parietal cortex	Tau; astrocytic plaques and threads
MSA	White matter / striatonigral / olivopontocerebellar	Oligodendroglial α -synuclein inclusions

A three-question interpretation framework



- Clinical presentation directs the likely entity.
- Gross/neuroanatomic findings test that hypothesis.
- Aggregate identity and cellular location strengthen neuropathologic classification.

Avoid common classification errors

Tempting oversimplification	More accurate interpretation
“Parkinsonism means PD.”	Parkinsonism appears in multiple degenerative disorders.
“All α -synucleinopathies have neuronal Lewy bodies.”	MSA is characterized by oligodendroglial inclusions.
“All tauopathies share one morphologic pattern.”	PSP and CBD have different tissue distributions and folds.
“L-DOPA response alone identifies the syndrome.”	Group-level poor response is supportive, not individually specific.

Integrated recognition exercise

Teaching vignette (illustrative)

A neuropathologic examination shows severe cortical neuronal loss, gliosis, ballooned neurons, and tau-positive astrocytic plaques in association with an asymmetric motor–apraxic syndrome.

Which entity is most concordant, and why?

CBD; Cortical-predominant degeneration and tau-positive astrocytic plaques match the described morphology.

Integrated recognition: Contrasting example

Teaching vignette (illustrative)

A brain shows oligodendroglial α -synuclein/ubiquitin inclusions with degeneration of pontine and cerebellar structures in a patient with ataxia.

What syndrome and pathologic circuit are supported?

MSA; Olivopontocerebellar circuitry in the cerebellar phenotype.

Synthesis: Three testable distinctions

- PSP: Axial–ocular phenotype with brainstem and deep-gray tau pathology.
- CBD: Asymmetric motor–apraxic phenotype with pronounced cortical tau pathology.
- MSA: Oligodendroglial α -synuclein and combined parkinsonian, cerebellar, and autonomic systems.

Primary source and editorial boundaries

Core reference

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. (2026). Chapter 28: The Central Nervous System, pp. 1168–1170.

Scope and source caveats

- The lecture is based on project-provided textbook Markdown and adjacent Parkinson disease context; this is not an external-guideline update.
- Original chapter PDF and permission-cleared microscopy were not available; no authentic histology specimens or source figures are reproduced.