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Anstalt öffentlichen Rechts

# Neuropathologie WiSe 24/25

# Neurodegenerative Erkrankungen

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Paul-Flechsig-Institut - Zentrum für Neuropathologie und Hirnforschung

# Lernziele

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- Überblick zu neurodegenerativen Erkrankungen
- Typische histomorphologische Merkmale des M. Alzheimer
- Typische histomorphologische Merkmale des M. Parkinson

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# Was sind neurodegenerative Erkrankungen?

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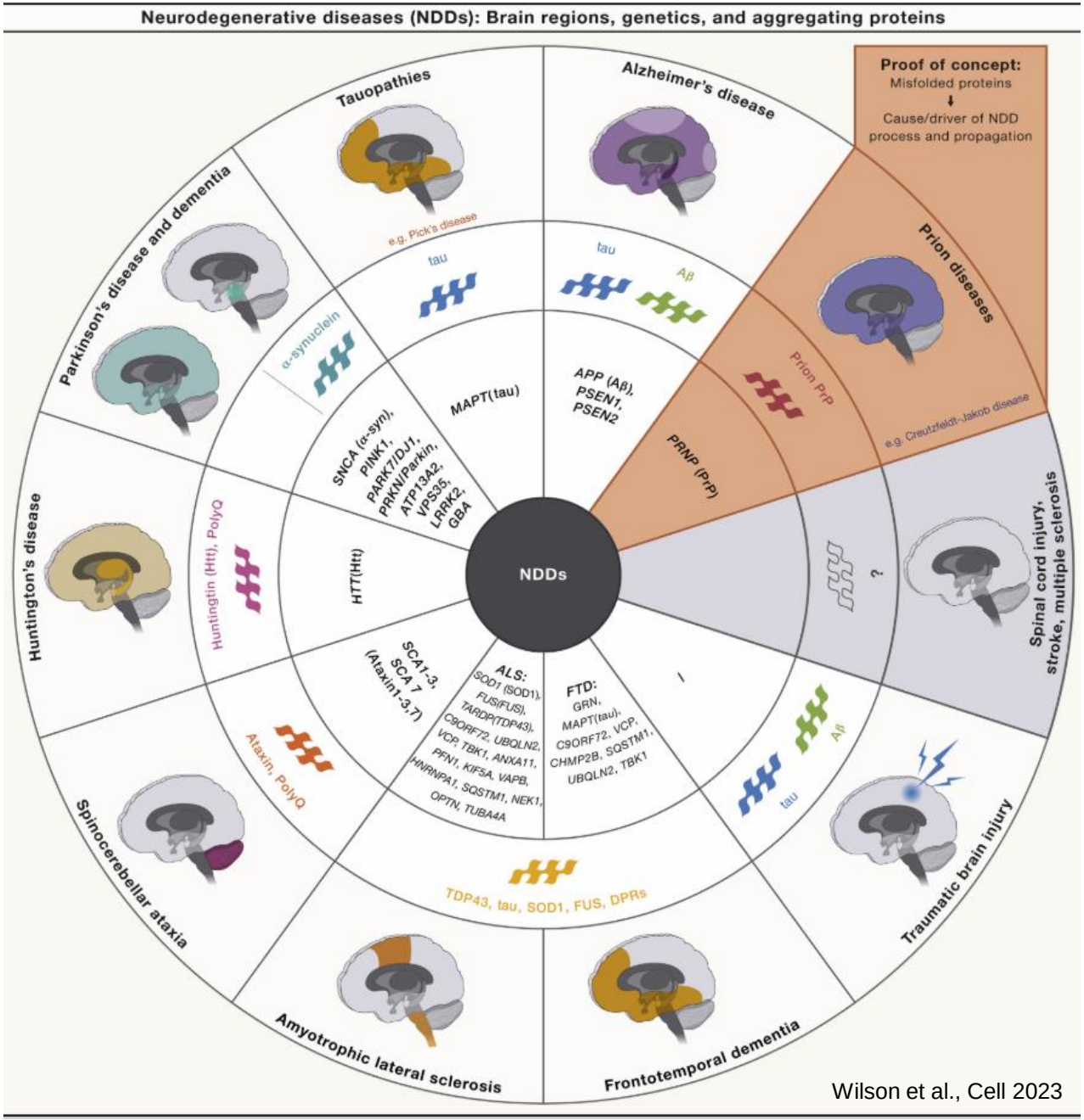
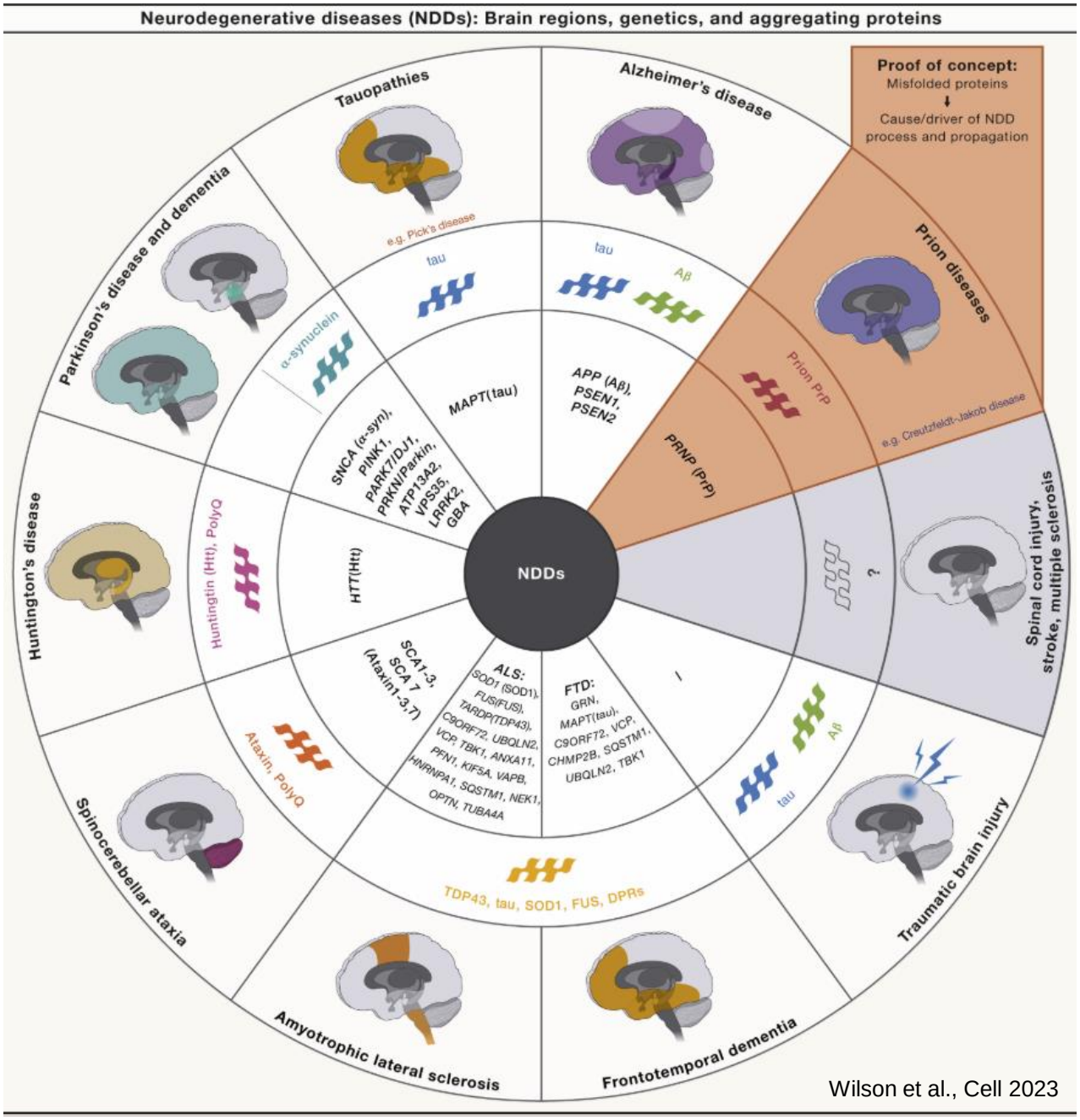
- Progrediente neuronale Dysfunktion und neuronaler Verlust
- Sehr unterschiedliche Definitionen und Klassifikationen

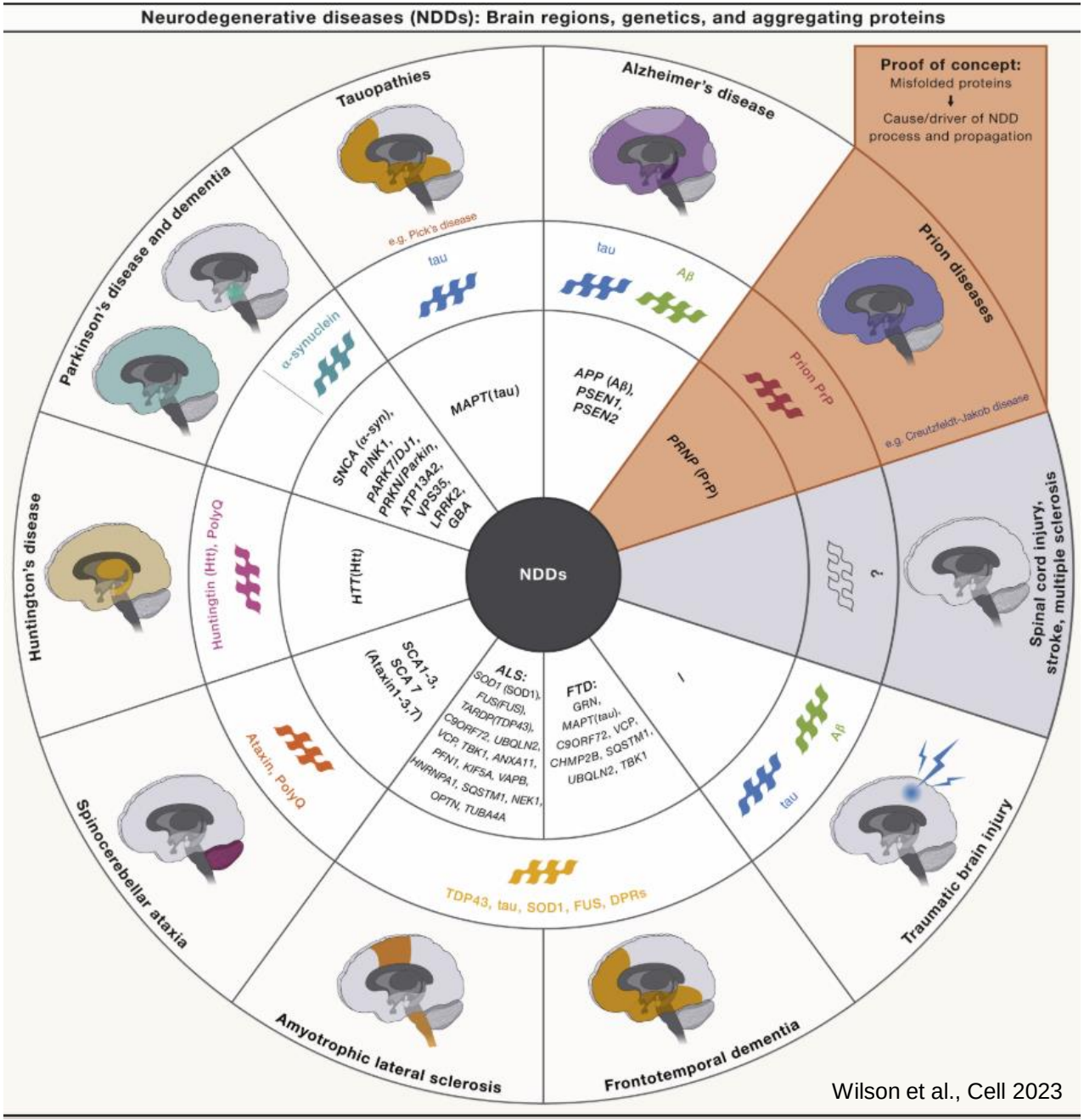



Wilson et al., Cell 2023




Wilson et al., Cell 2023

**Klinisch:**
Demenz *vs*
Motorische Störung




Wilson et al., Cell 2023

**Klinisch:**
Demenz *vs*
Motorische Störung

| Movement disorders |
|---|
| Akinetic and rigid |
| Hyperkinetic |
| Ataxic |
| Motor neuron disorders |
| **Cognitive disturbance (dementia)** |
| Temporal and parietal degenerations |
| Frontotemporal degenerations |
| Multifocal degenerations |

# Selektiver Nervenzellverlust in Neurodegeneration

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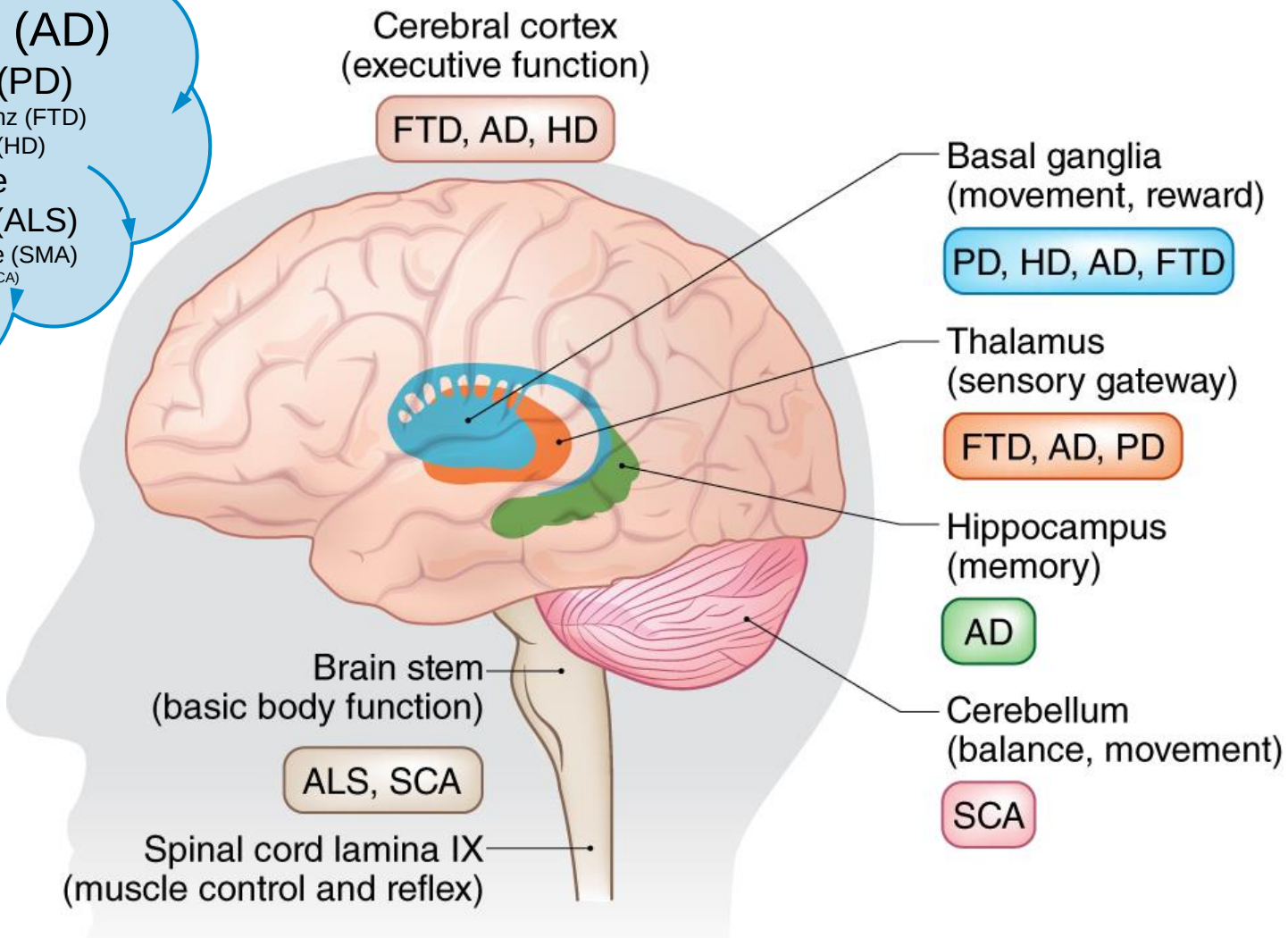
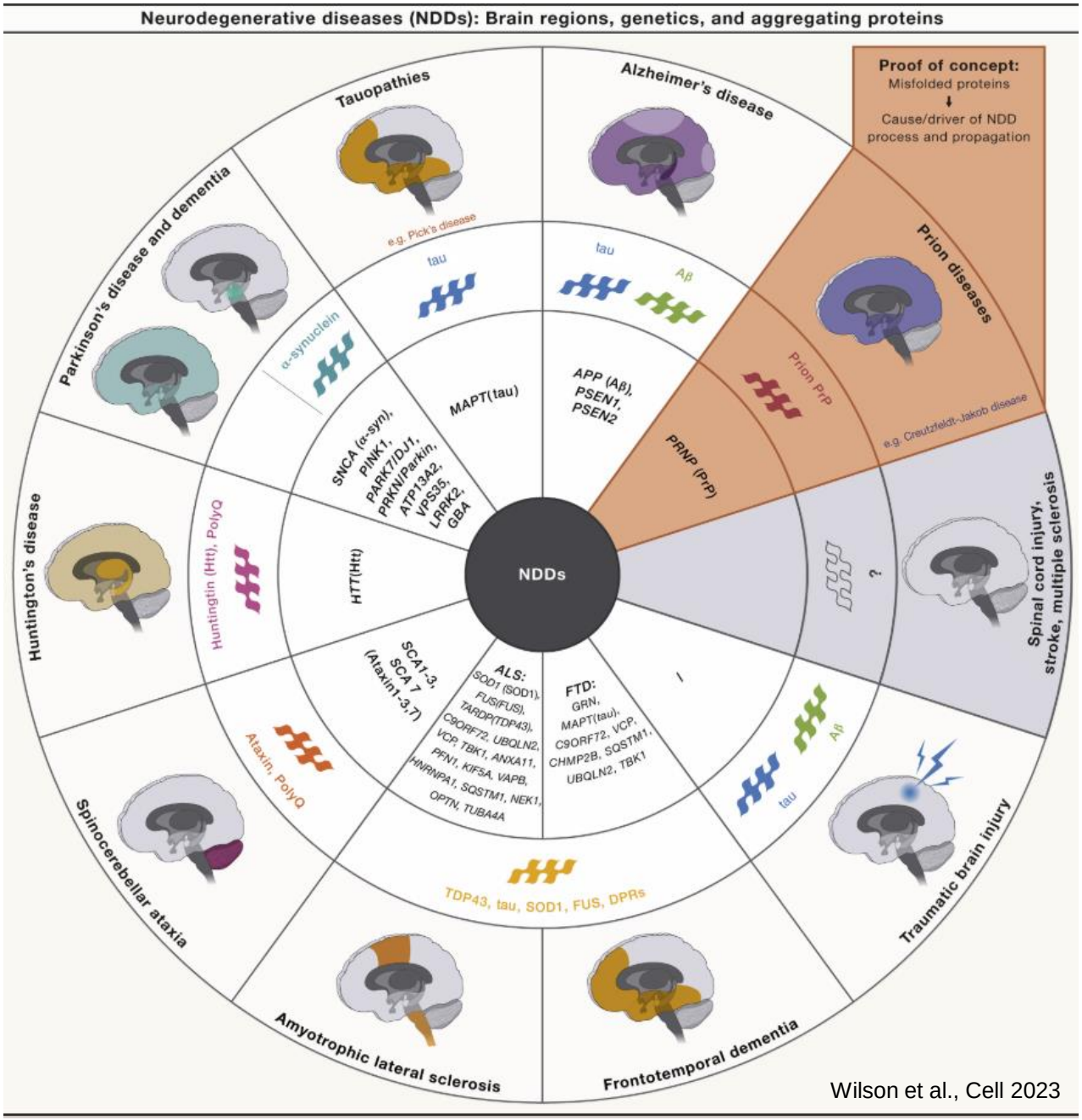
M. Alzheimer (AD)
M. Parkinson (PD)
Frontotemporale Demenz (FTD)
Chorea Huntington (HD)
Amyotrophe Lateralsklerose (ALS)
Spinale Muskelatrophie (SMA)
Spinocerebelläre Ataxien (SCA)
und andere




Gan, L., Cookson, M.R., Petrucelli, L. et al. (2018) Nat Neurosci 21, 1300–1309

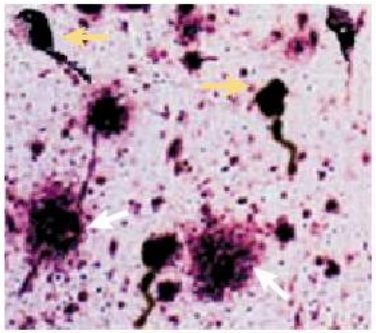



Wilson et al., Cell 2023

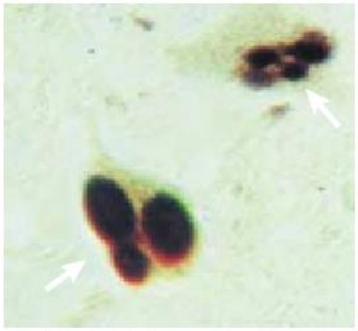
**Klinisch:**
Demenz *vs*
Motorische Störung

**Pathophysiologisch:**
Trauma
Entzündung
Demyelinisierung
Proteinaggregate
Genetisch
Betroffene Neurone und Hirnregionen

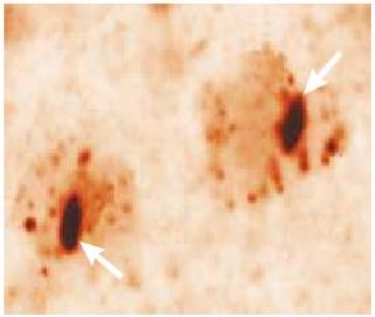
# Neurodegenerative Erkrankungen: Aggregopathien



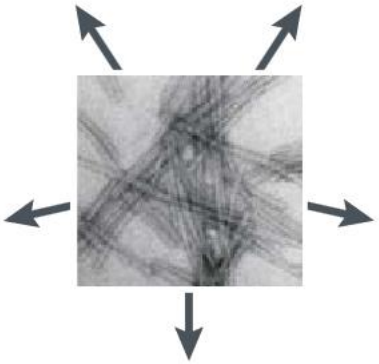
Alzheimer's plaques and tangles

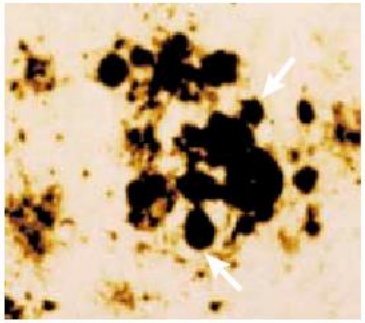


Parkinson's Lewy bodies

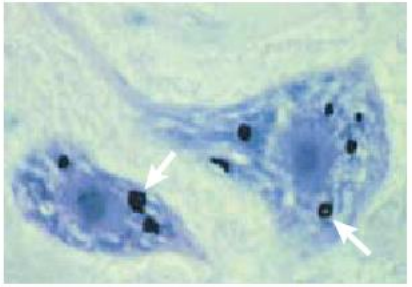


Huntington's intranuclear inclusions





Prion amyloid plaques



Amyotrophic lateral sclerosis aggregates

Soto C (2003) Nat Rev Neurosci 4: 49-60.

# Proteinfehlfaltung in neurodegenerativen Erkrankungen

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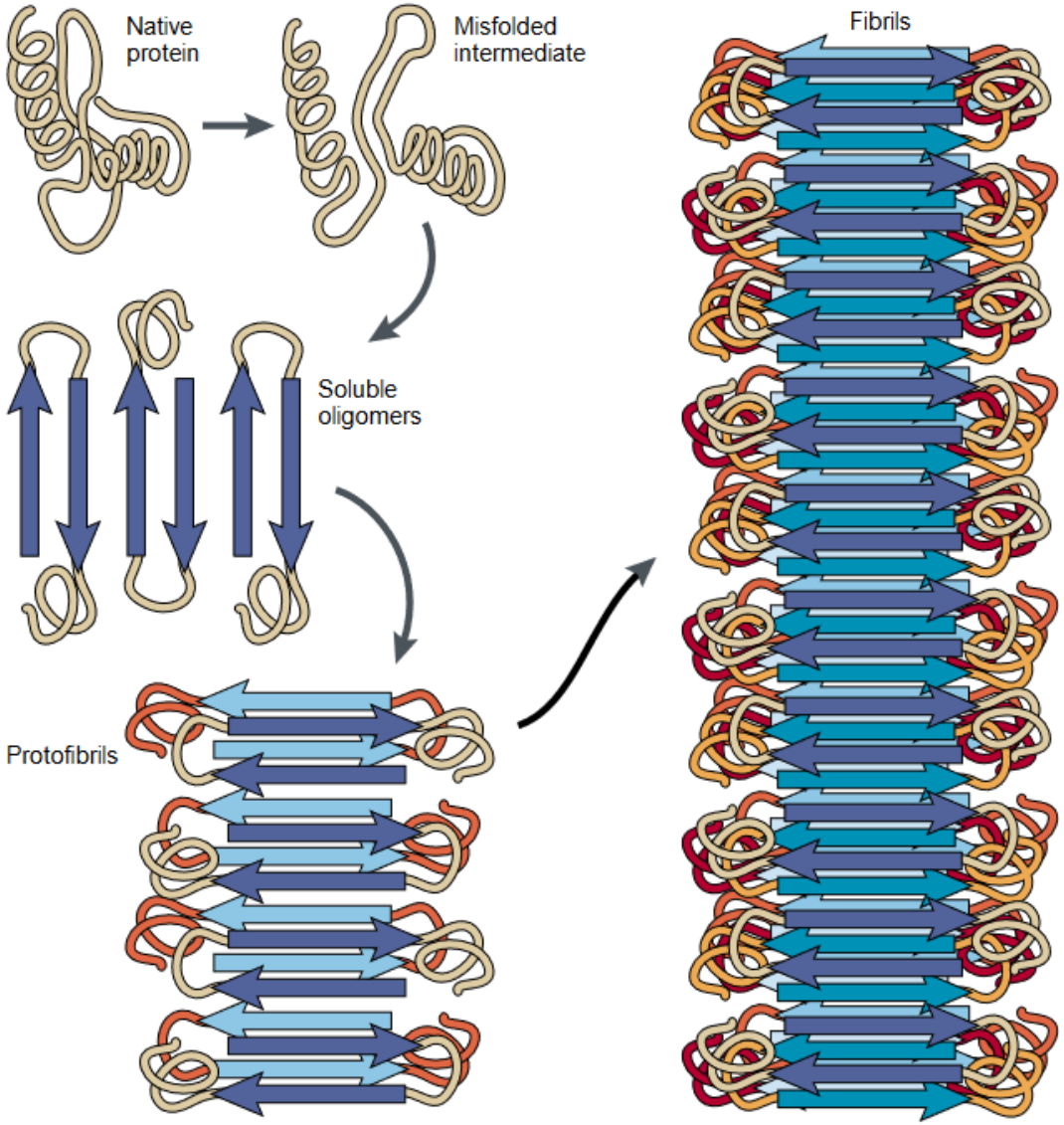
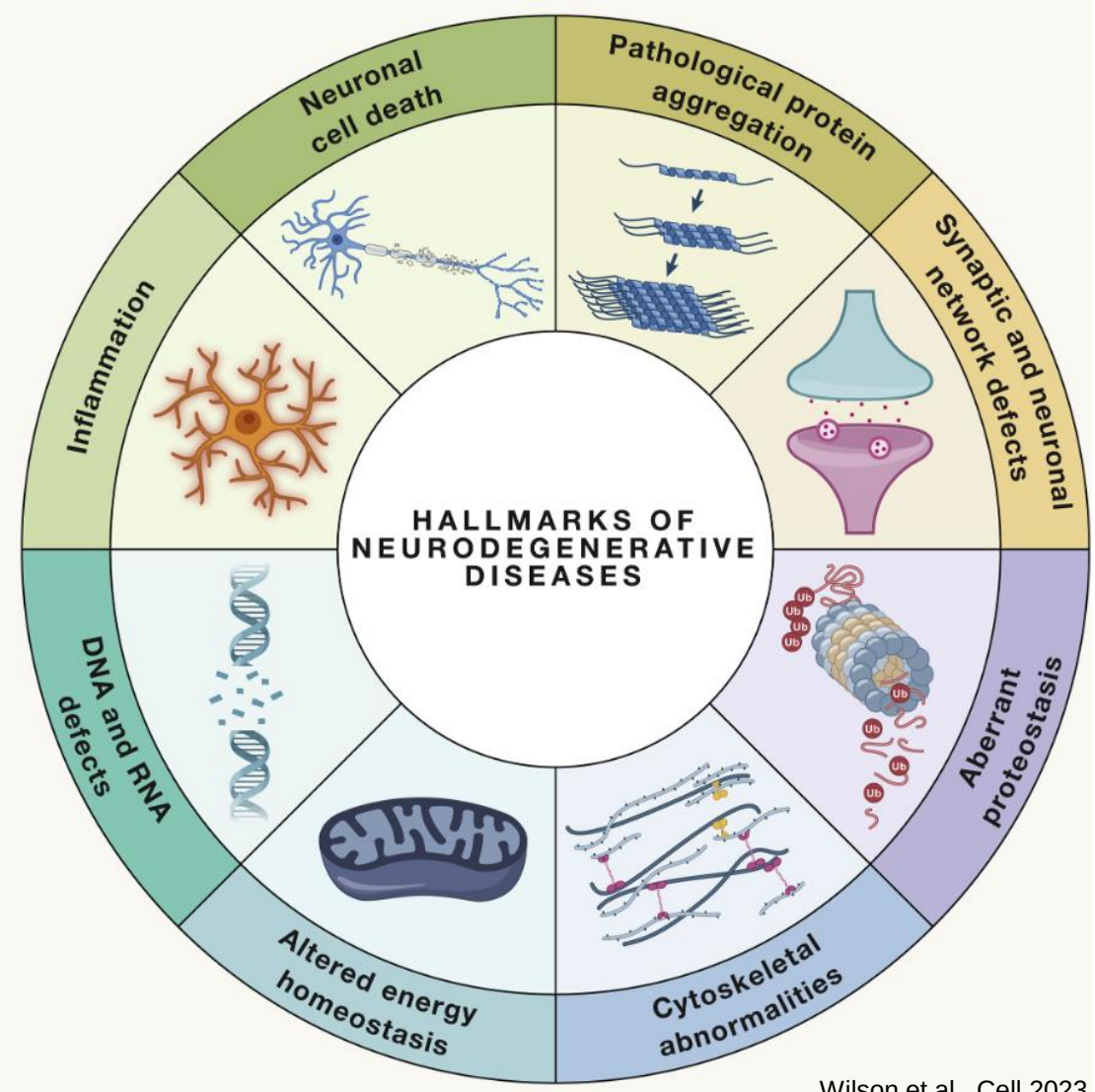



Soto C (2003) Nat Rev Neurosci 4: 49-60.

# Was sind neurodegenerative Erkrankungen?

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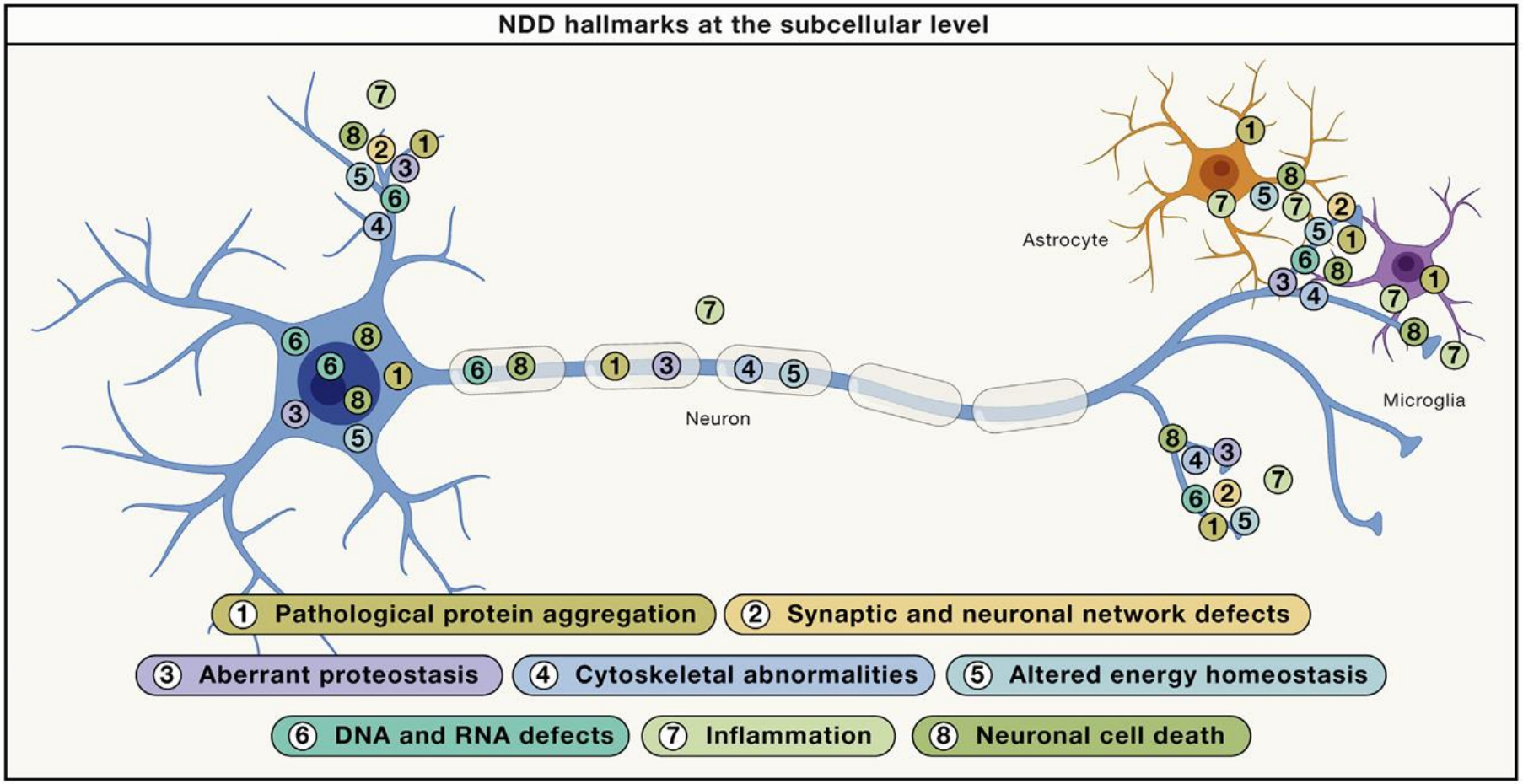


Wilson et al., Cell 2023

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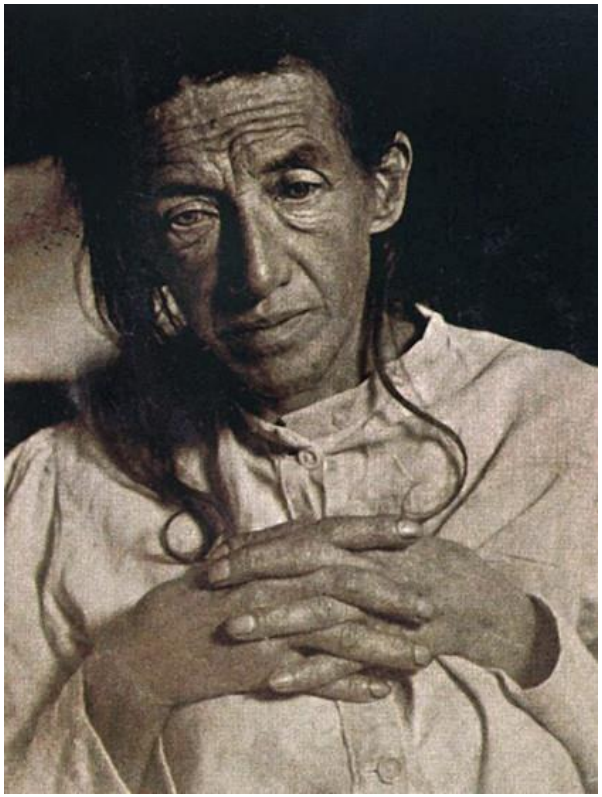
# Morbus Alzheimer



**Auguste Deter**: 1850-1906

„Über eine eigenartige Erkrankung der Hirnrinde“

Klinik:
Zeitlich-/räumlicher Orientierungsverlust
Vergesslichkeit, Aphasie, Paraphrasien

https://www.deutsche-alzheimer.de/die-krankheit/die-alzheimer-krankheit/alois-alzheimer.htm
http://abqnm.us/PerfImages/Hayworth,%20Rita,%20Alzheimers.html

# Klinik des M. Alzheimer

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**Demenz** nach ICD 10:

Störung des Gedächtnisses und mindestens einer weiteren kognitiven Teilleistung
Länger als 6 Monate anhaltend
Chronisch progredient
Bewusstseinsstörung muss ausgeschlossen sein
Störung der sozialen und/oder beruflichen Funktion

Ursachenspektrum demenzielles Syndrom

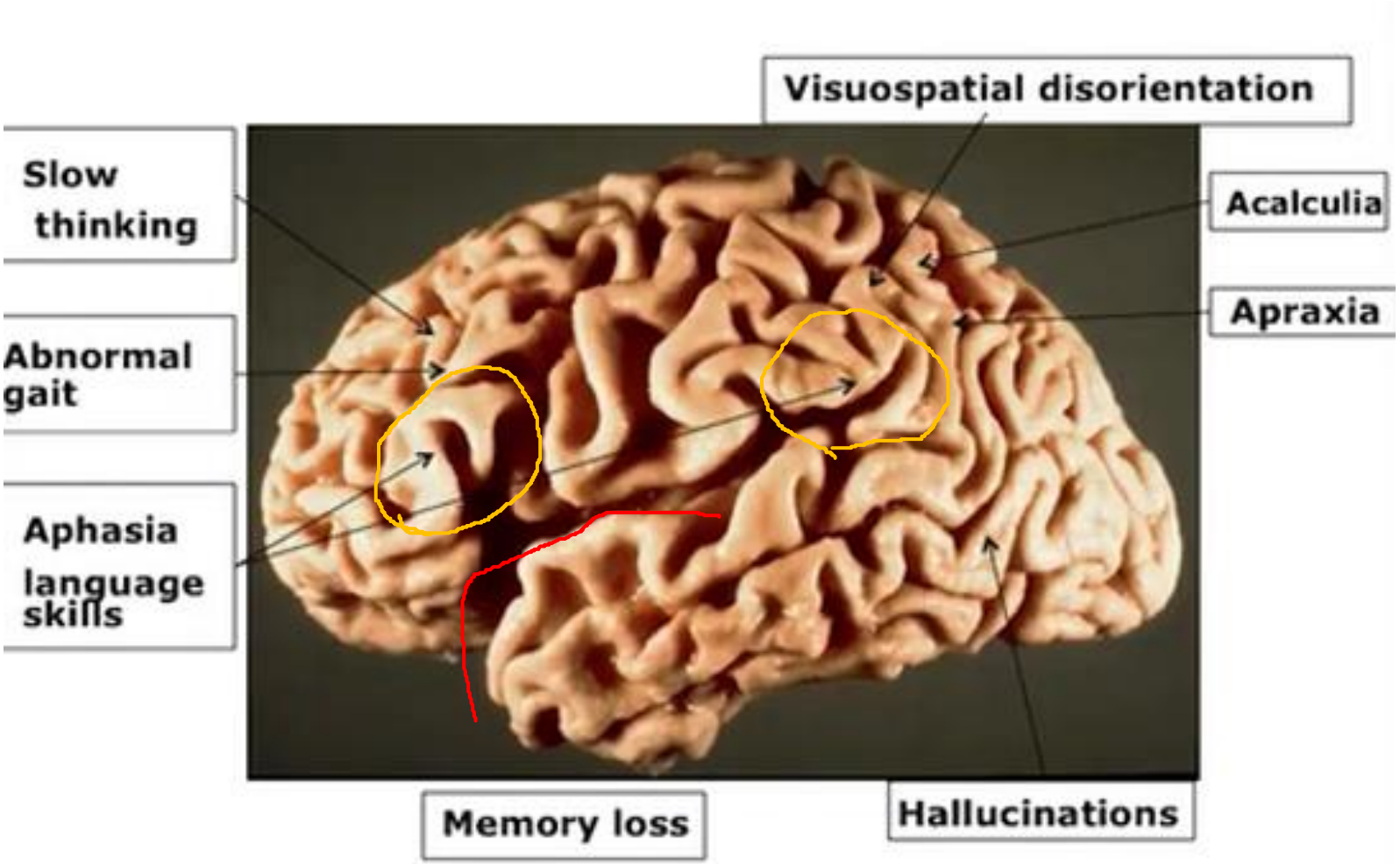
**Sekundär z.B.:**
Hypox. Hirnschaden
Tumor/Blutung/Trauma
Entzündlich
Metabolisch/ Toxisch
Normaldruckhydrocephalus

**Primär neurodegenerativ:**
M. Alzheimer >50 % aller Demenzen
Frontotemporale Demenz
M. Parkinson
Lewy-Body-Demenz
Chorea Huntington
Progressive nukleäre Blickparese
**Vaskulär** ~ 20% aller Demenzen

nicht jedes demenzielle Syndrom ist durch eine neurodegenerative Erkrankung bedingt

Neurodegenerative Erkrankungen gehen häufig mit demenziellem Syndrom einher

# Pathologie – Makroskopische Befunde




https://neuropathology-web.org/chapter9/chapter9bAD.html#ad

# Pathologie – Makroskopische Befunde

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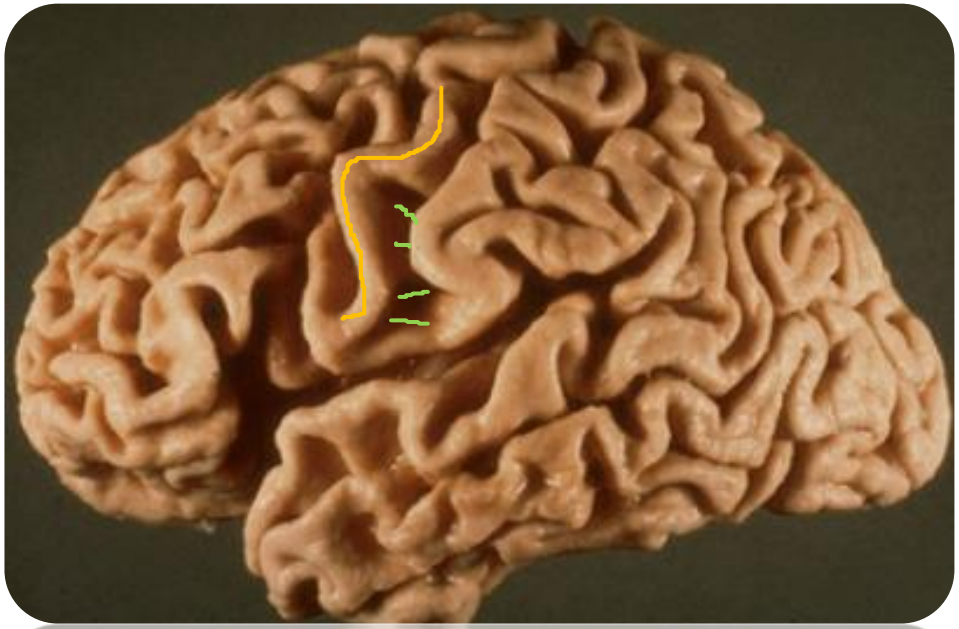
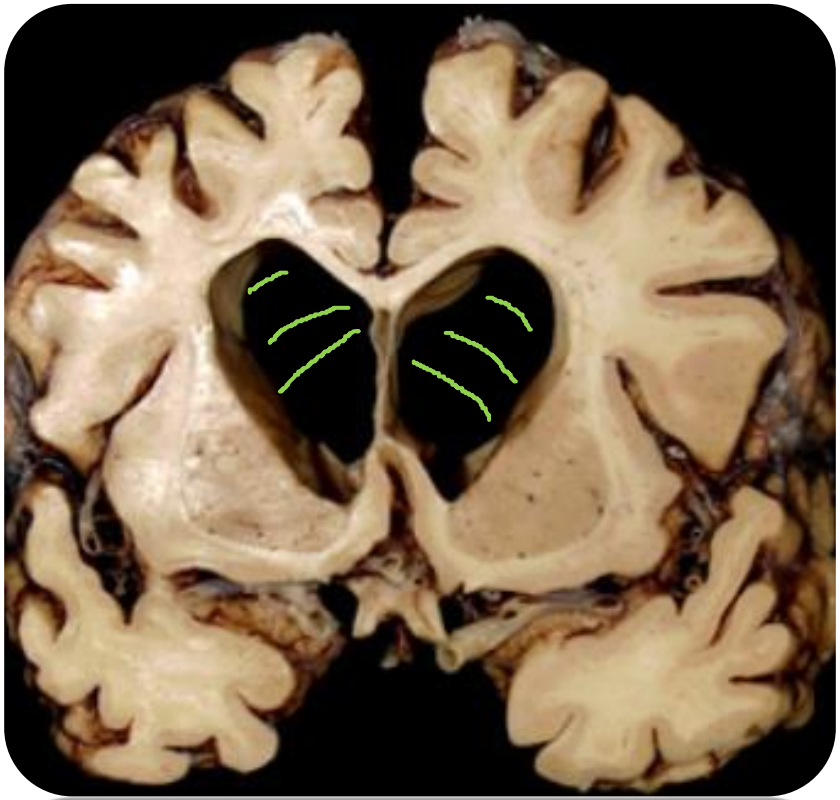
Äußere und innere- Hirnatrophie





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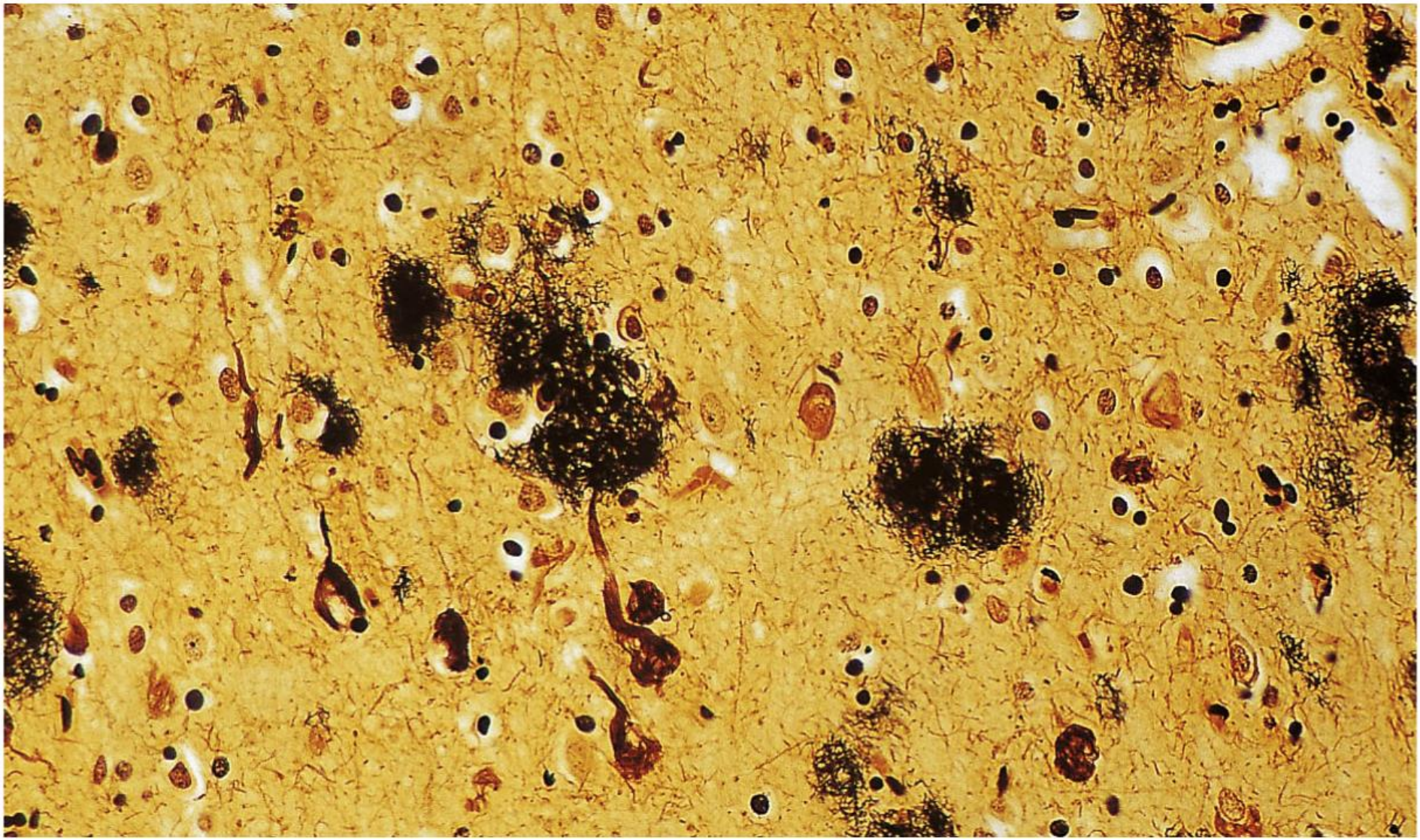
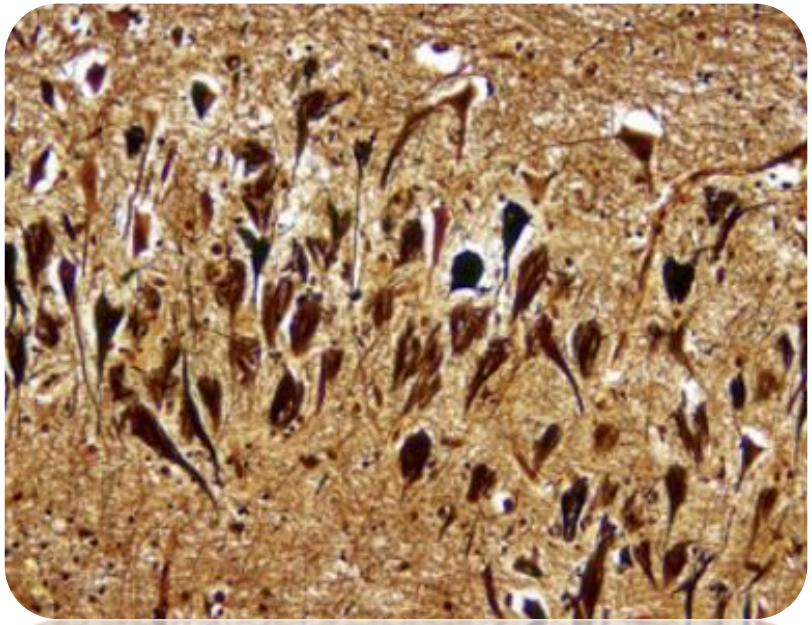
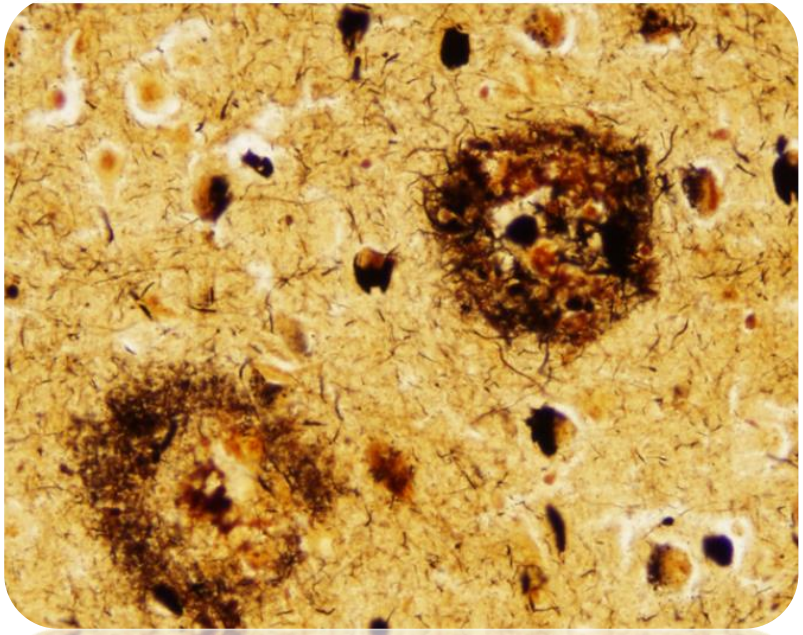


Love, Ellison, Neuropathology, Elsevier

# Pathologie – Mikroskopische Befunde



**Intrazelluläre neurofibrilläre Tangles (NFT)**



**Extrazelluläre Neuritische Plaques (NPs)**

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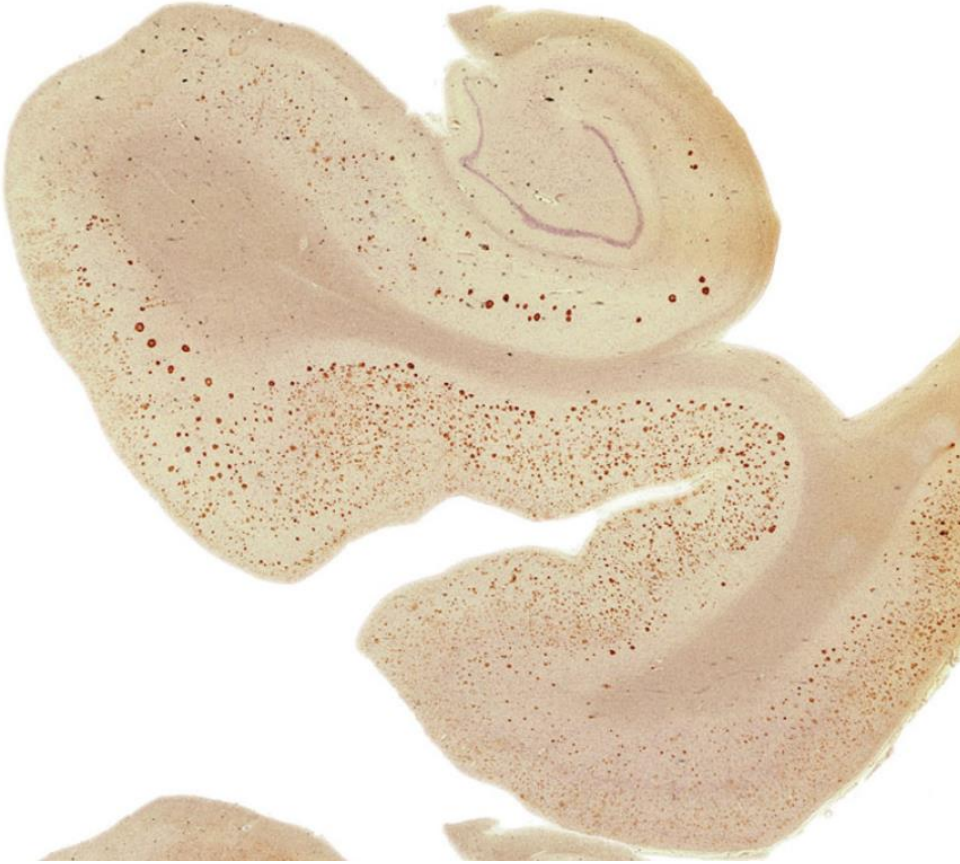

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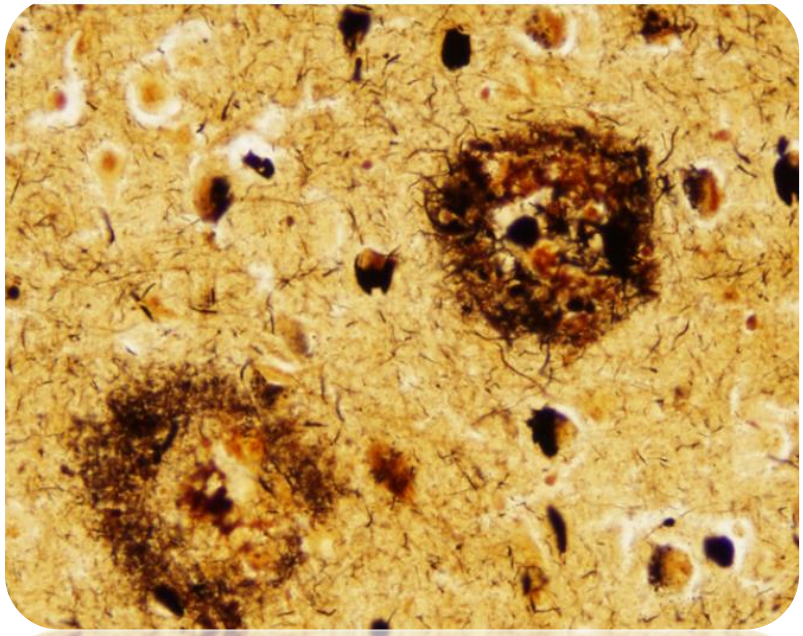

**Extrazelluläre Neuritische Plaques (NPs)**

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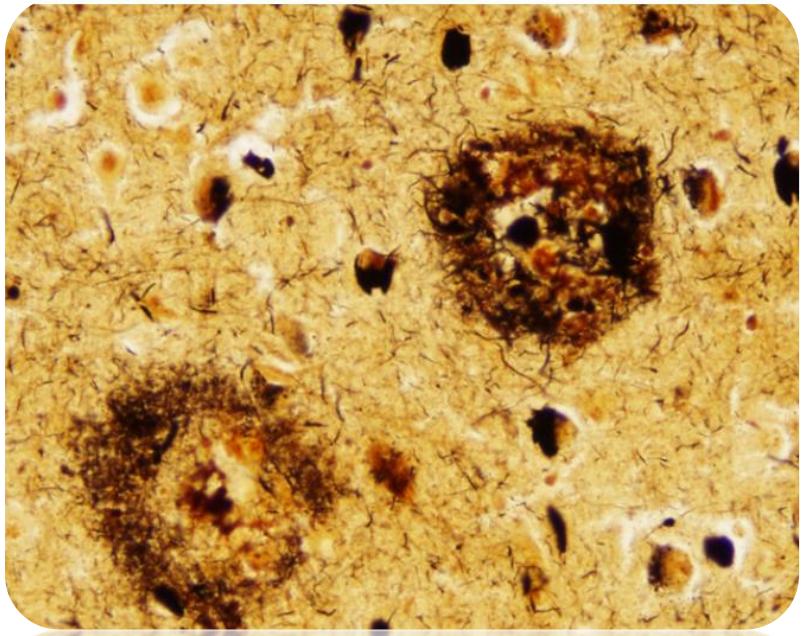
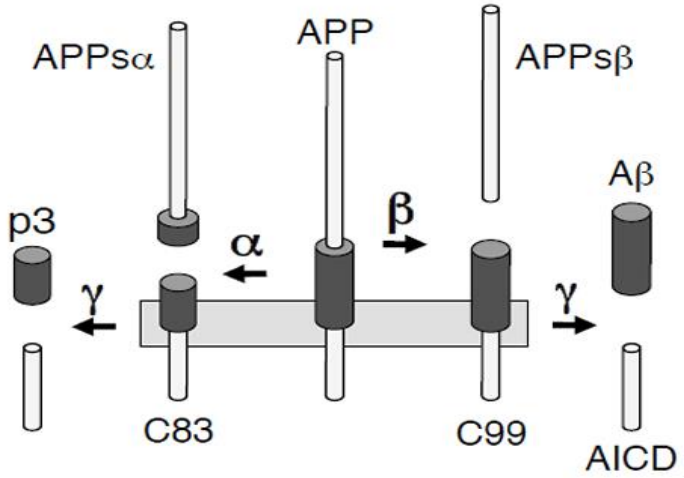


**Extrazelluläre Neuritische Plaques (NPs)**

## Amyloidablagerungen




APP = transmembranöses Glykoprotein
Gen auf Chromosom 21
Funktion unklar > Oberflächenrezeptor mit Funktionen in der Zell-Zell und Zell-Matrix Interaktion

Love, Ellison, Neuropathology, Elsevier

# Pathologie – Mikroskopische Befunde

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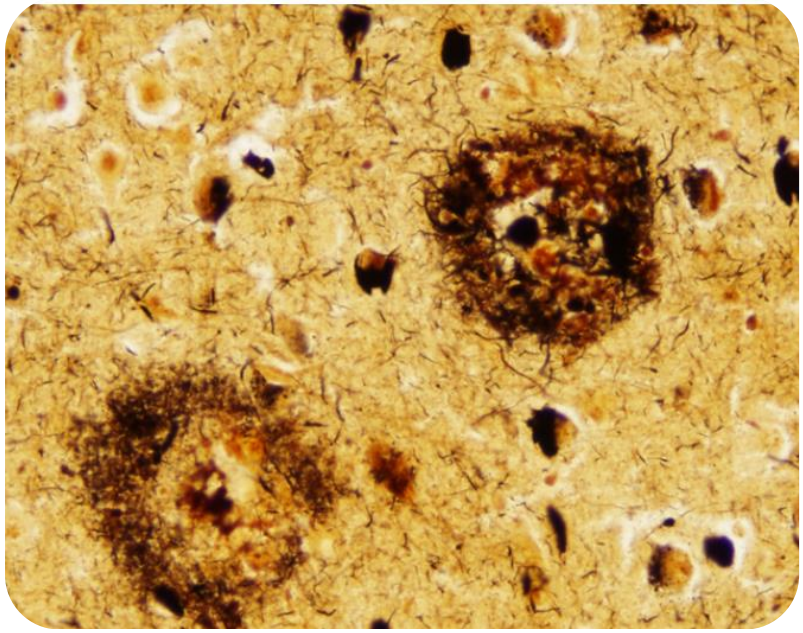
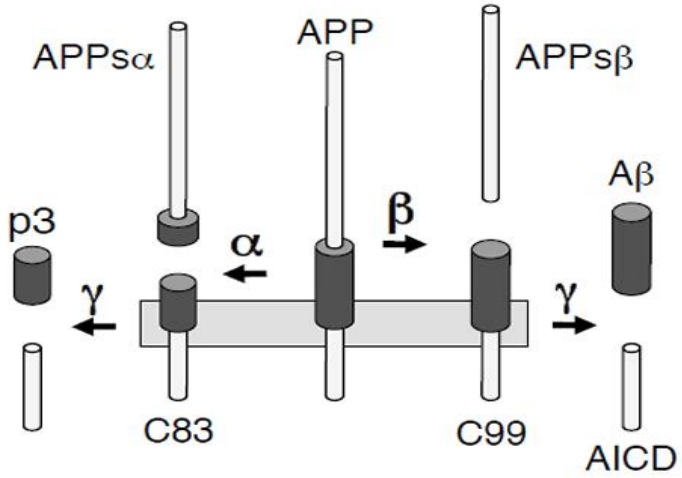
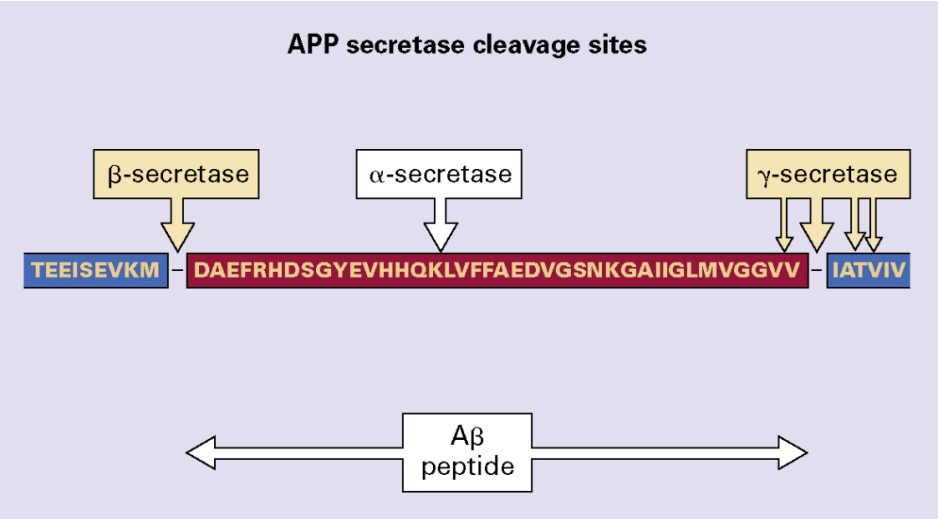
## Amyloidablagerungen

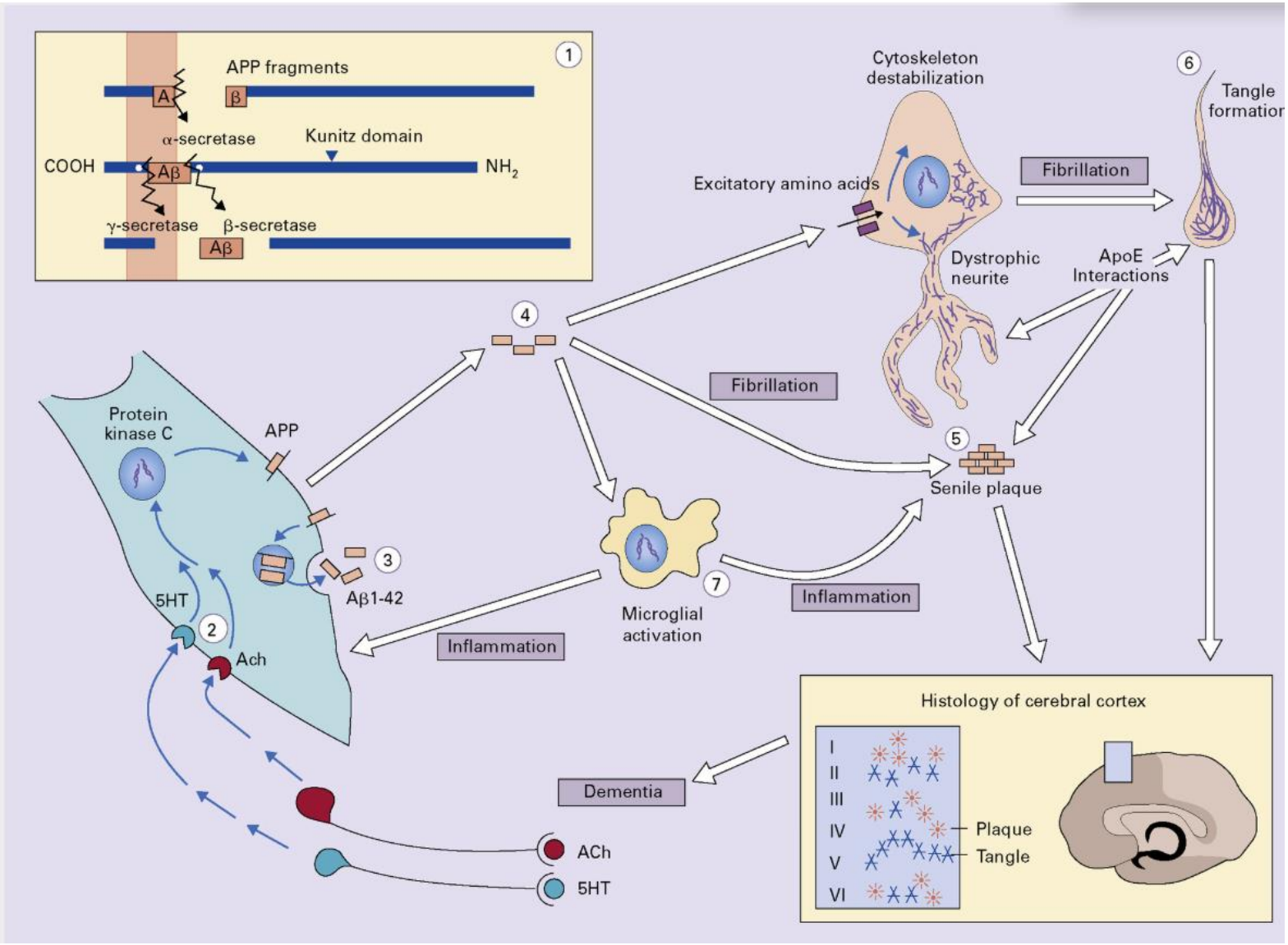


Aβ Peptid Fragmente: insb. 40 oder 42 Aminosäuren lang. Aβ Peptide in Plaques: hauptsächlich 42-residue Form of Aβ (Aβ42)



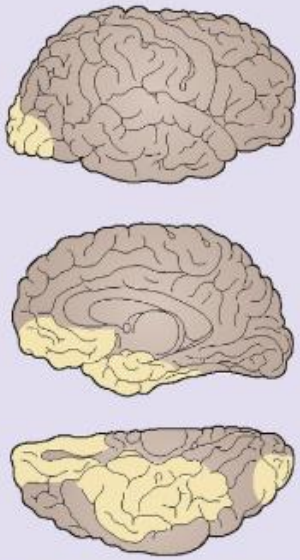




Love, Ellison, Neuropathology, Elsevier

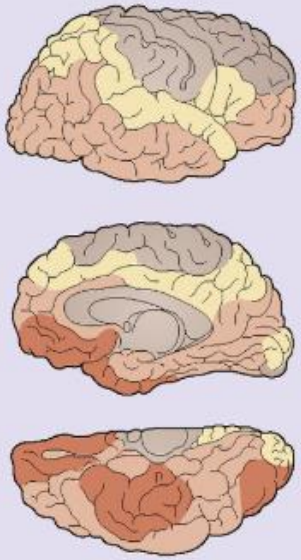



Love, Ellison, Neuropathology, Elsevier

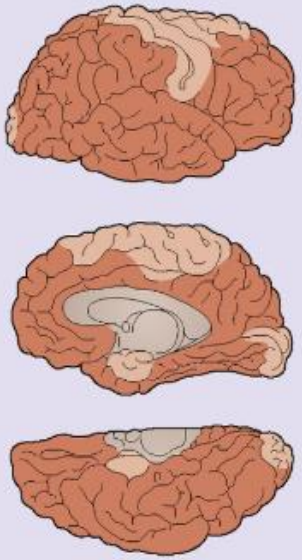
## Plaque stages: poor correlation with clinical severity of dementia



**Stage A**: Low density of plaques in neocortex, especially frontal, temporal and occipital lobes

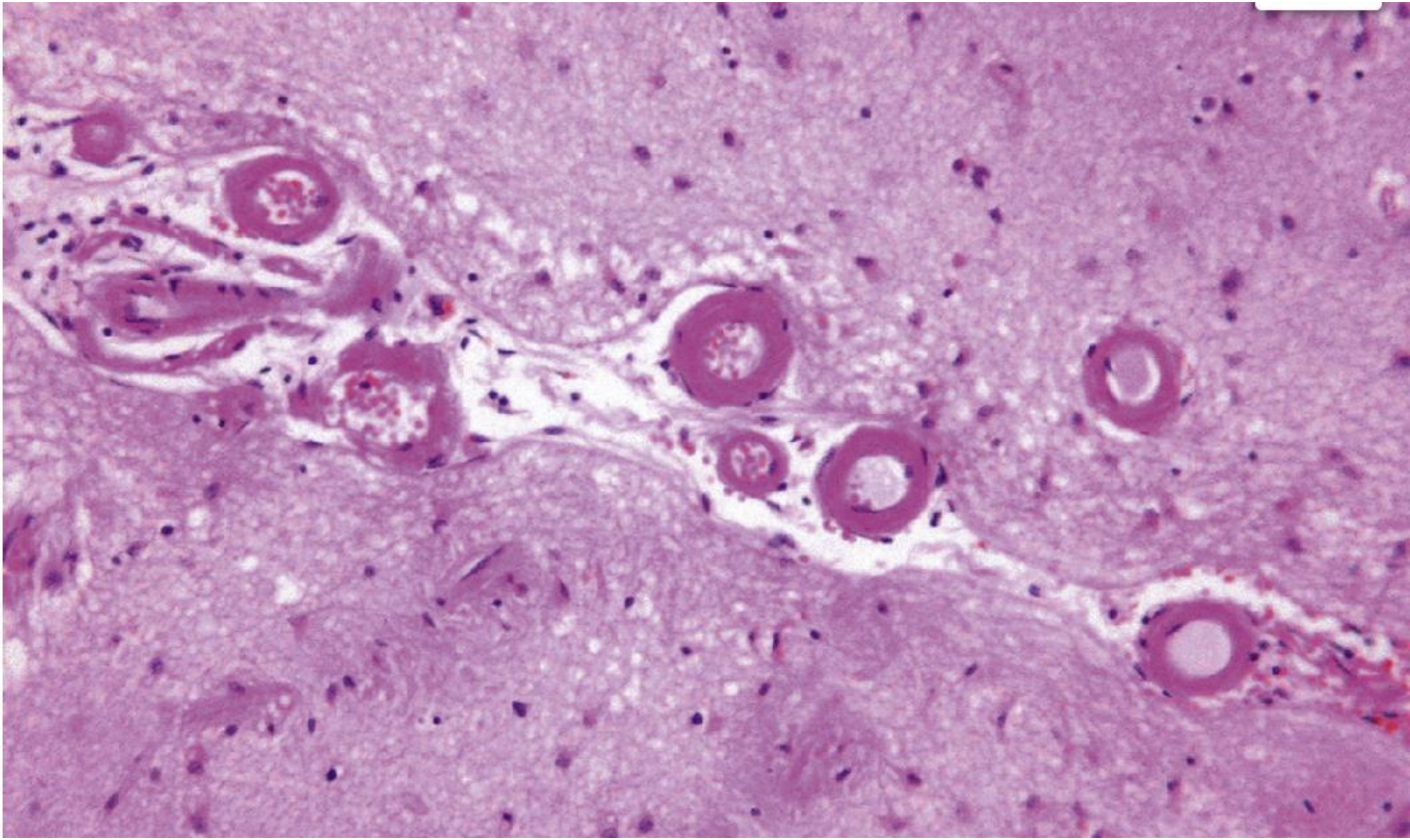


**Stage B**: Plaques present in neocortical association areas with moderate hippocampal involvement

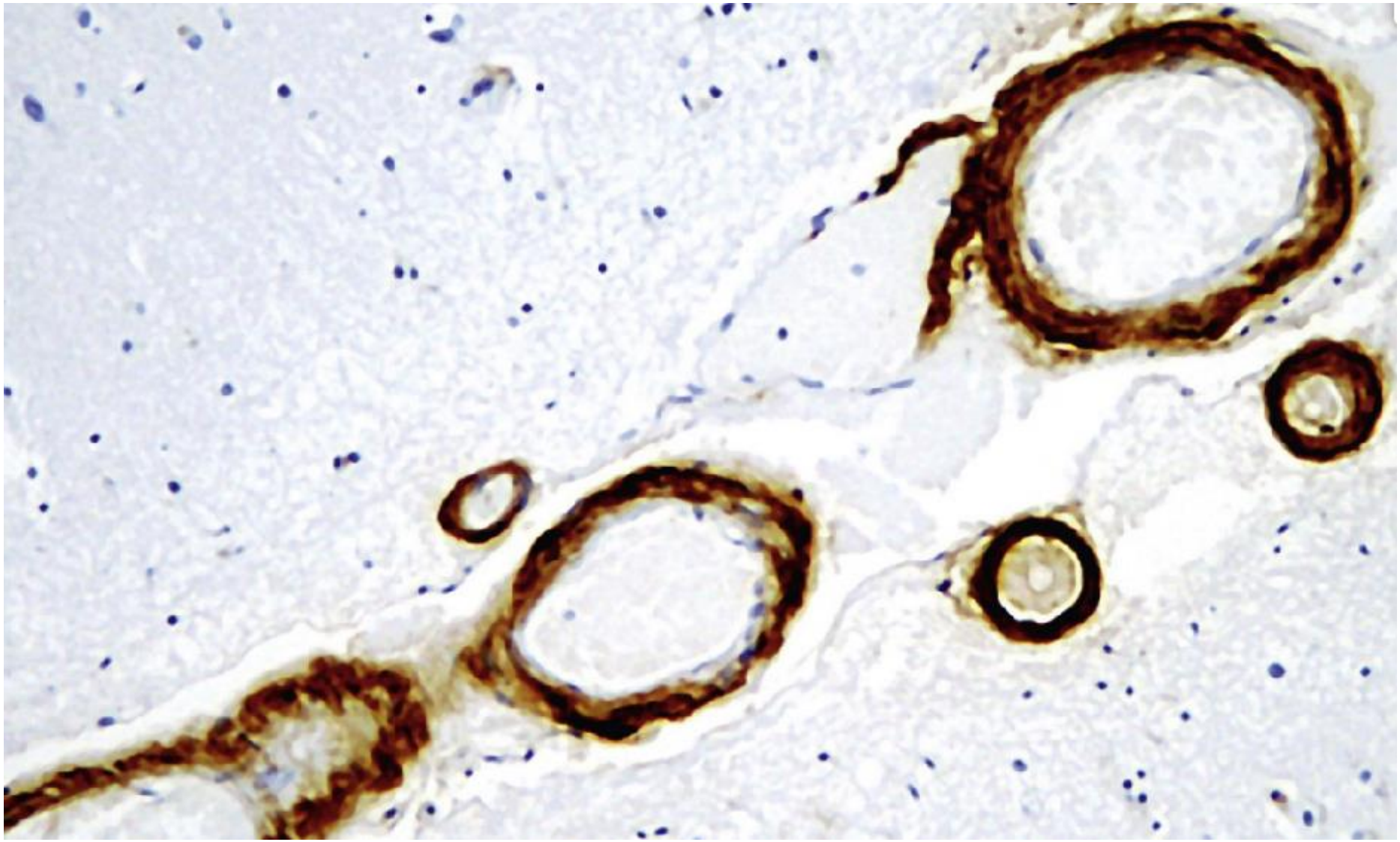


**Stage C**: Plaques present in primary sensory and motor areas in addition to other cortical areas


Love, Ellison, Neuropathology, Elsevier

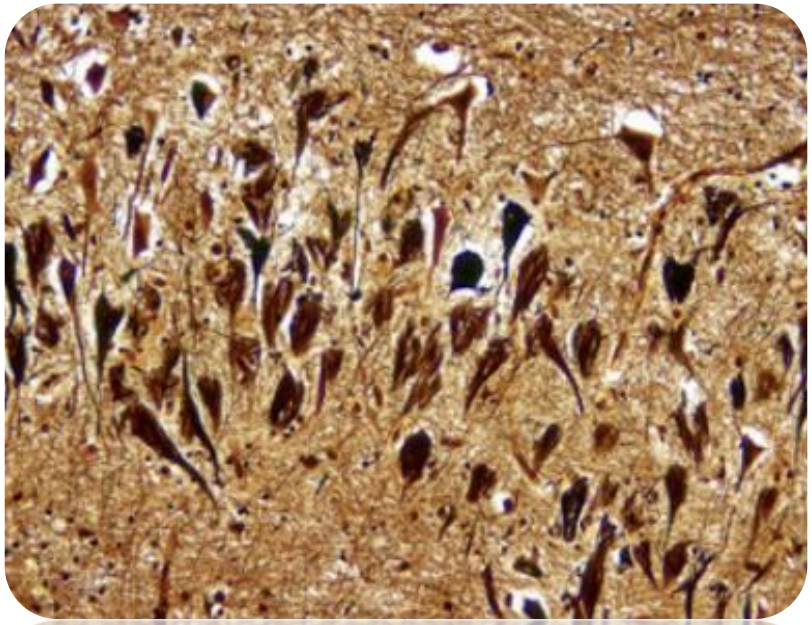


Love, Ellison, Neuropathology, Elsevier



Love, Ellison, Neuropathology, Elsevier

# Pathologie – Mikroskopische Befunde



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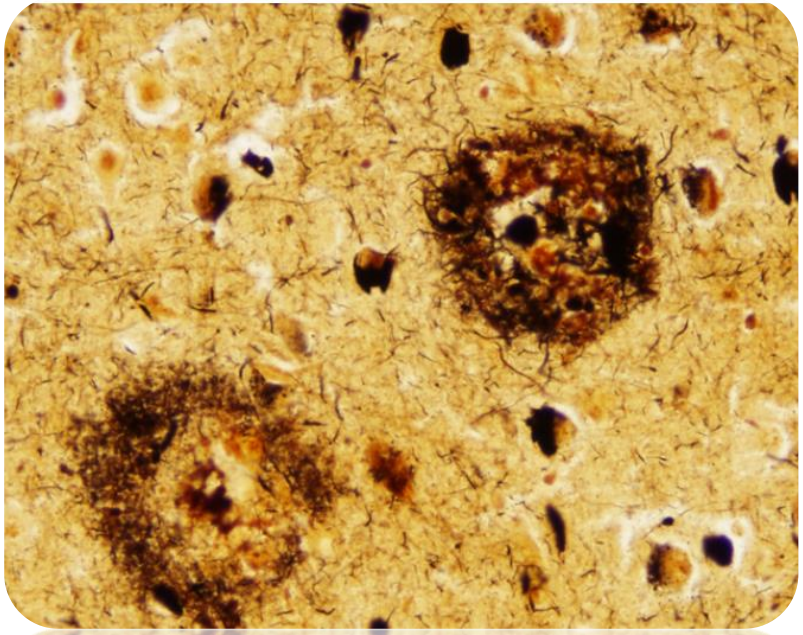
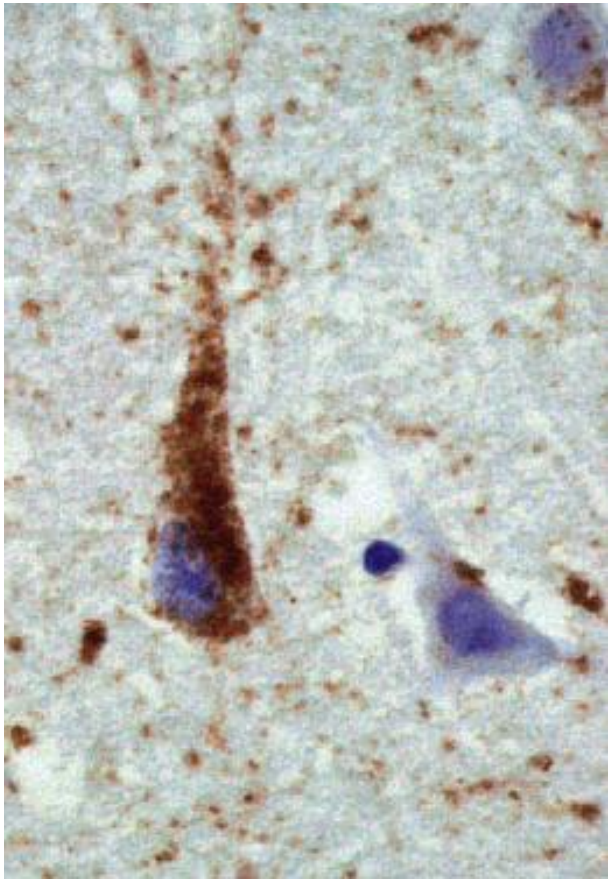
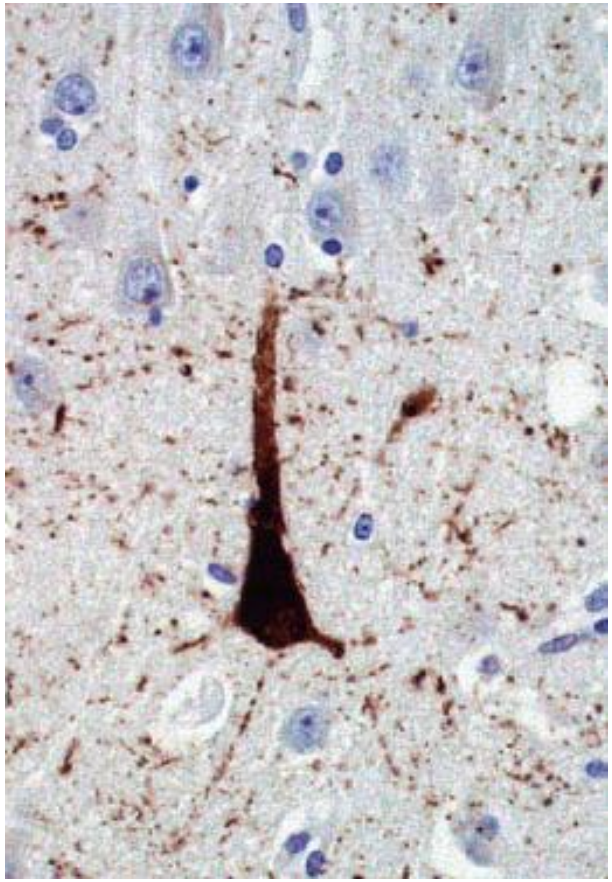
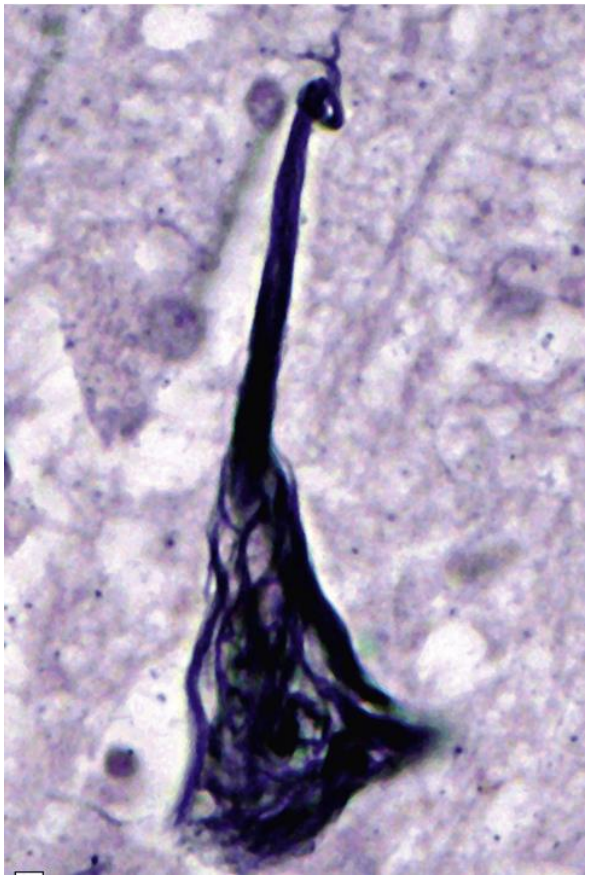


**Extrazelluläre Neuritische Plaques (NPs)**







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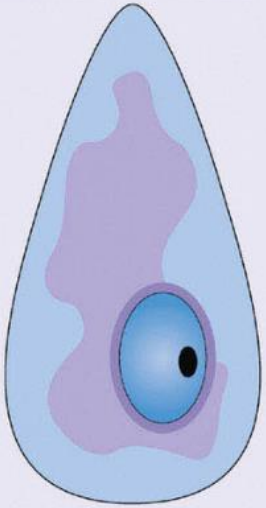
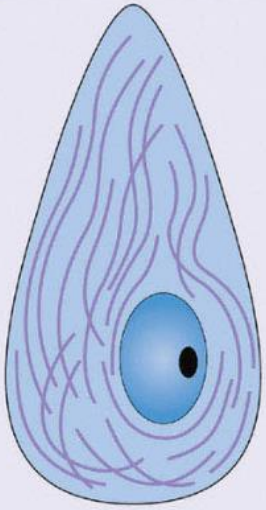
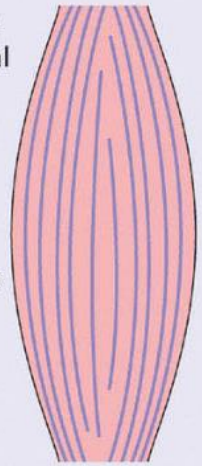


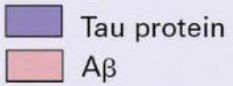
**Early stage:** There is accumulation of tau protein in neurons but in a dispersed form detectable only by immunohistochemistry for tau protein. There may be perinuclear accentuation of immunoreactivity. Silver staining does not reveal any abnormality.



**Established stage:** Tau protein is aggregated into paired helical filaments as well as a smaller number of straight filaments. There is ubiquitination of some of the tau protein in tangles rendering them immunoreactive for ubiquitin. Silver staining reveals classical tangles.

**Late stage:** There is death of the neuron and removal of cell debris by local phagocytes. The tangle structure remains as an eosinophilic extracellular 'tombstone' or ghost tangle. With time there is progressive loss of tau-protein immunoreactivity. Aβ-peptide is later deposited around these structures as amyloid, and there is infiltration by astroglial processes making these NFTs apparently immunoreactive for GFAP.






## Biologie des Tau-Proteins

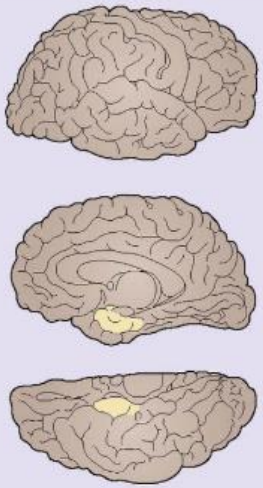
Tau-Protein:
Mikrotubuli- assoziiertes Protein und wichtig für die Funktionalität des Zytoskeletts

M. Alzheimer: Tau-Protein hyperphosphoryliert

Verdrängung von Zellorganellen
axonaler Transport ↓
Zytoplasmatische Zirkulation↓

Love, Ellison, Neuropathology, Elsevier

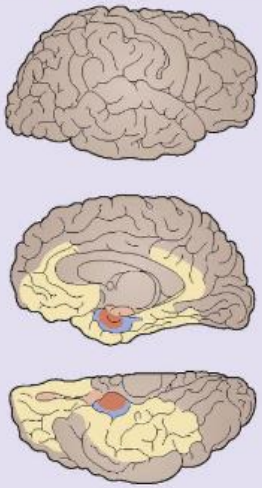
## Tangle stages: good correlation with clinical severity ratings



**TRANSENTORHINAL**
(Clinically asymptomatic)

**Stage I:** NFTs and NTs in small density, confined to transentorhinal cortex in pre-α cells.

**Stage II:** Tangles present in moderate density in pre-α cells of entorhinal cortex. Small numbers develop in CA1 region of hippocampus

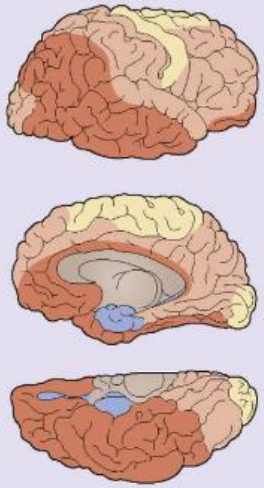


**LIMBIC**
(Incipient AD)

**Stage III:** There are modest numbers of NFTs and NTs throughout CA1 and in pyramidal cells in the subiculum. Small numbers appear in the fusiform gyrus lateral to the transentorhinal cortex as well as in the nucleus basalis of Meynert and amygdaloid complex.

There is now severe involvement of pre-α cells with neuronal loss and gliosis

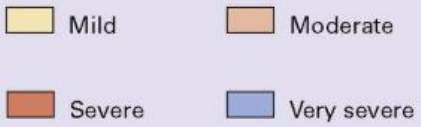
**Stage IV:** Severe involvement of areas affected in stage 3. Large numbers of ghost tangles in entorhinal and transentorhinal regions. Mild involvement of isocortex with sparing of primary sensory and motor cortices.



**ISOCORTICAL**
(Symptomatic AD)

**Stage V:** Tangles in all sectors of hippocampus and subiculum. Widespread, moderate to severe isocortical involvement but still relative sparing of primary sensory and motor cortices. Tangles in claustrum, thalamus, hypothalamus. Ghost tangles with neuronal loss and astrocytic gliosis involving pre-α cells, CA1, antero-dorsal thalamic nucleus.

**Stage VI:** Increased densities of tangles in regions affected in earlier stages. Tangles in dentate granule cell layer. Marked involvement of claustrum, thalamus, hypothalamus, substantia nigra




Love, Ellison, Neuropathology, Elsevier

# Gemeinsame Endstrecke!

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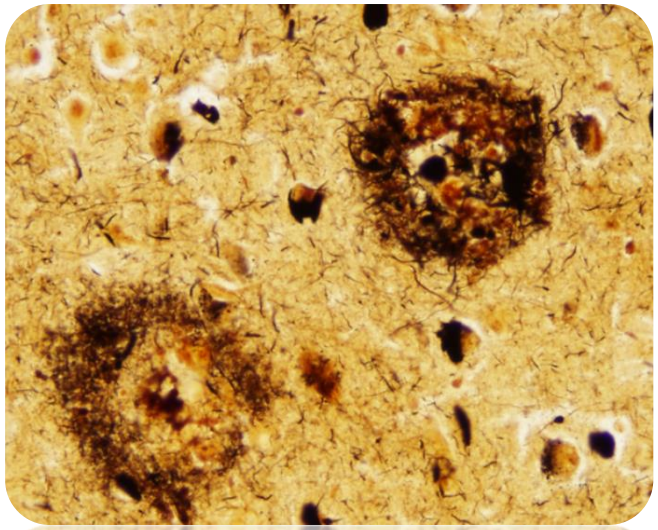
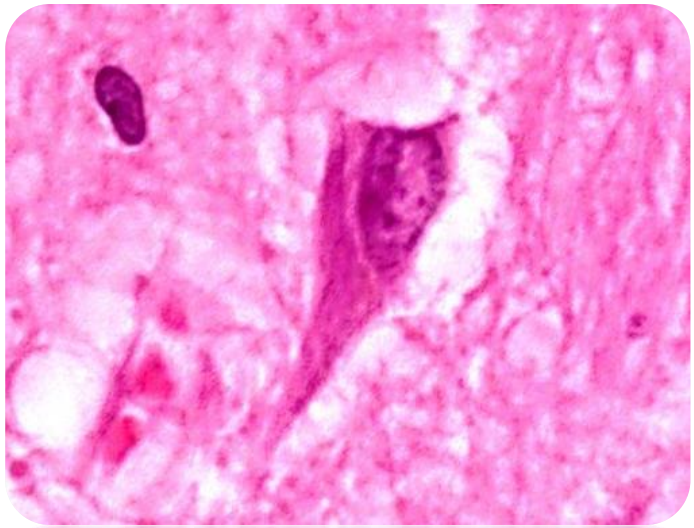


**Extrazelluläre Neuritische Plaques (NPs)**



**Intrazelluläre neurofibrilläre Tangles (NFT)**

Gemeinsame Endstrecke:
Neuronale Degeneration/ Untergang, Verlust von Synapsen, Hirnatrophie, Hydrocephalus e vacuo

# Genetik

**Early onset (vor dem 65. Lebensjahr)**

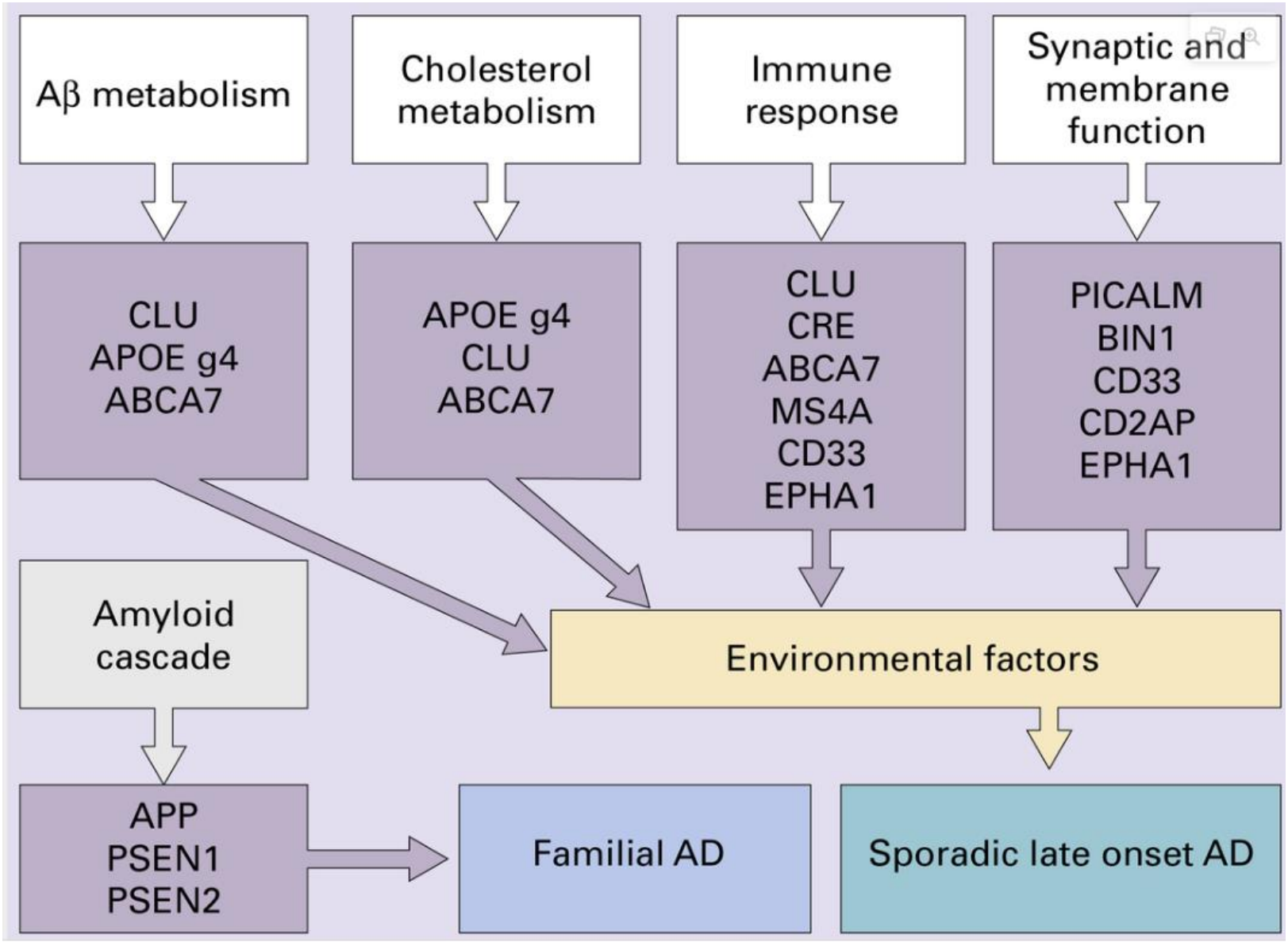
**Selten (~7%) und oft familiär**

Mutationen im APP (Amyloid Precursor Protein) (21q)
Mutationen in PSN1 (Presenilin 1) (14q23.3)
Mutationen in PSN2 (Presenilin 2) (1q13)

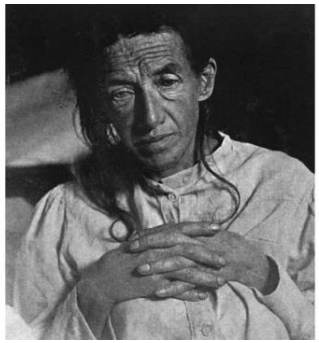
**Late onset (nach dem 65. Lebensjahr)**

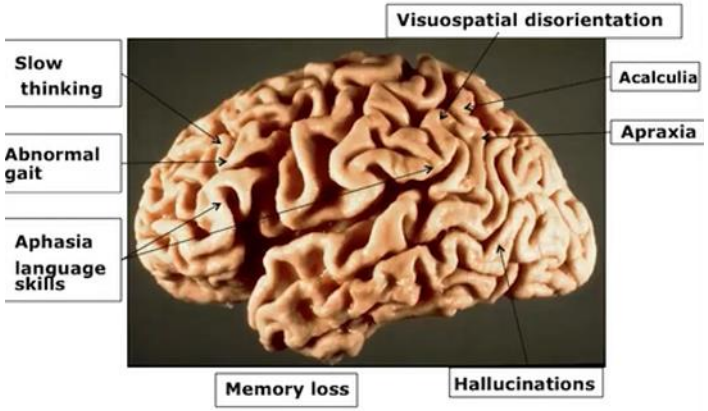
**Häufig und nicht familiär**

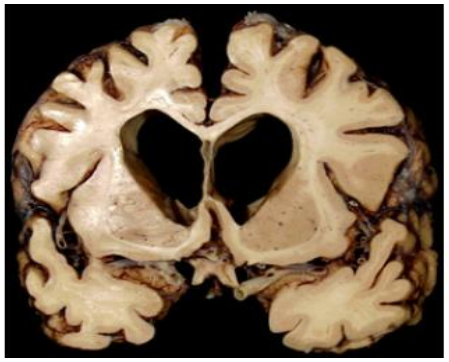
APOE e4 (19q13.2)



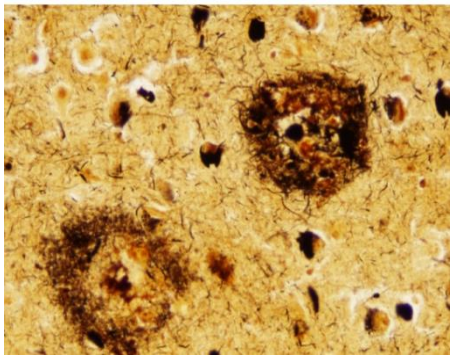

Love, Ellison, Neuropathology, Elsevier

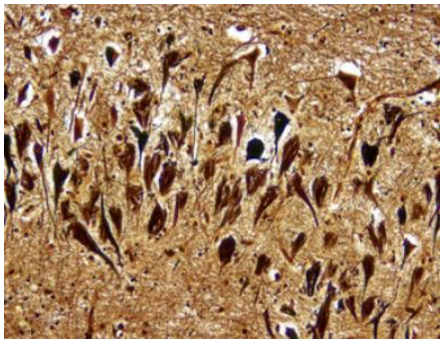


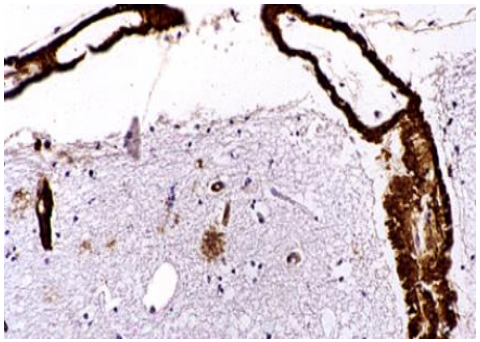


- Klinische Symptomatik
- äußere- und innere Hirnatrophie, verm. Hirngewicht
- Extrazelluläre Ablagerung von neuritischen Plaques; (NPs) Cerebrale Amyloidangiopathie (CAA)
- Intrazelluläre Akkumulation von Tau-Protein in Form von neurofibrillären Tangles (NFT)
- Neuronaler Degeneration und Nervenzellverlust, Gliose, granulovakuoläre Degeneration, Hirano-Körperchen







Postmortale Diagnostik kann zur Ursachenklärung der klinischen Symptomatik beitragen

# Lernziele

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- Überblick zu neurodegenerativen Erkrankungen
- Typische histomorphologische Merkmale des M. Alzheimer
- Typische histomorphologische Merkmale des M. Parkinson

# Klinik des M. Parkinson

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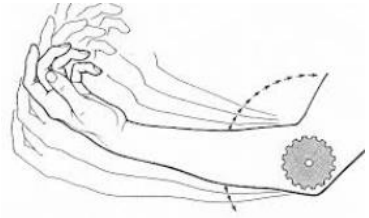
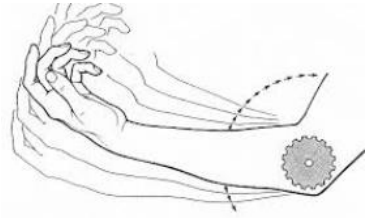
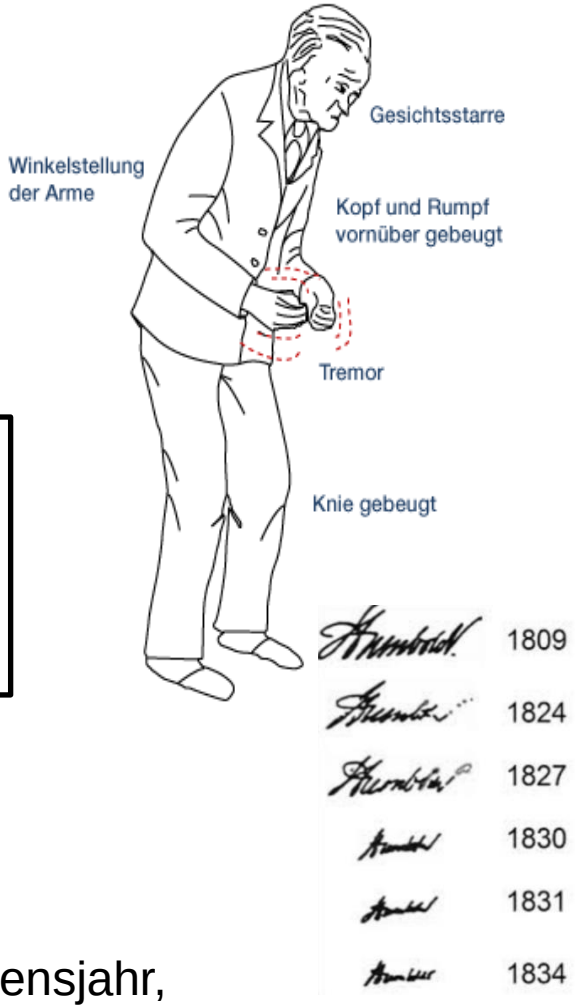



https://www.google.de/url?sa=i&url=http%3A%2F%2Fwww.ulmmed.de%2Fimages%2Fdownload%2Fthema_des_monats%2FParkinson-1-Krankheit.pdf&psig=AOvVaw0yBkPZ8tRuJQJFhTR6_1NQ&ust=1606411356954000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCIik3OSanu0CFQAAAAAdAAAAABAD
https://www.t-online.de/sport/boxen/id_78028822/tod-von-muhammad-ali-sprecher-nennt-die-todesursache.html

# Klinik des M. Parkinson



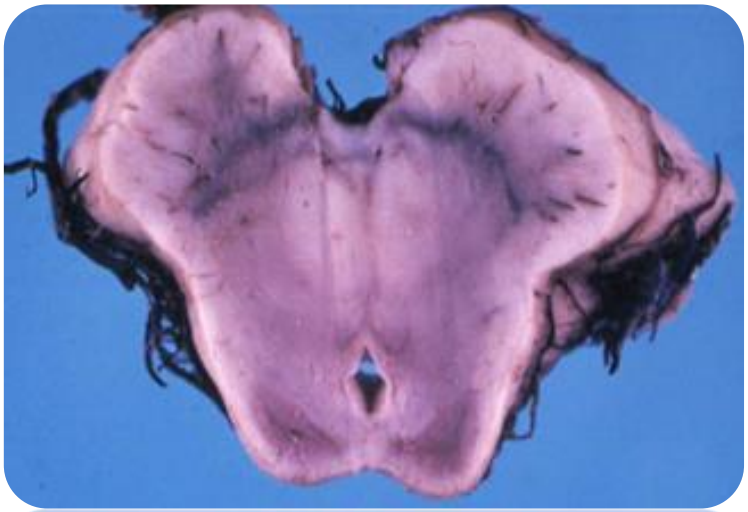


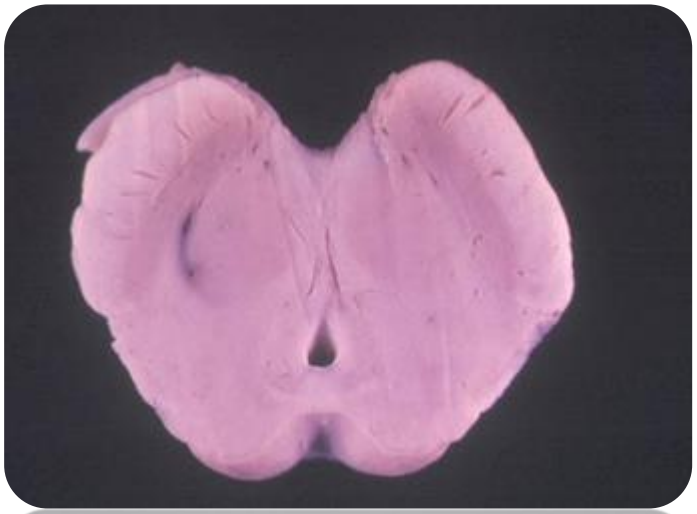

**T** remor
**R** igor
**A** kinese
**P** osturale Instabilität

Epidemiologie: Häufigkeitsgipfel 50.-60. Lebensjahr,
m=f, zu 70% idiopathisch

https://www.google.de/url?sa=i&url=http%3A%2F%2Fwww.ulmmed.de%2Fimages%2Fdownload%2Fthema_des_monats%2FParkinson-1-Krankheit.pdf&psig=AOvVaw0yBkPZ8tRuJQJFhTR6_1NQ&ust=1606411356954000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCIk3OSanu0CFQAAAAAdAAAAABAD
https://www.t-online.de/sport/boxen/id_78028822/tod-von-muhammad-ali-sprecher-nennt-die-todesursache.html

# Pathologie - Makroskopische Befunde





Verlust neuromelaninhaltiger dopaminerger
Neurone der Substantia nigra

# Pathophysiologie des M. Parkinsons

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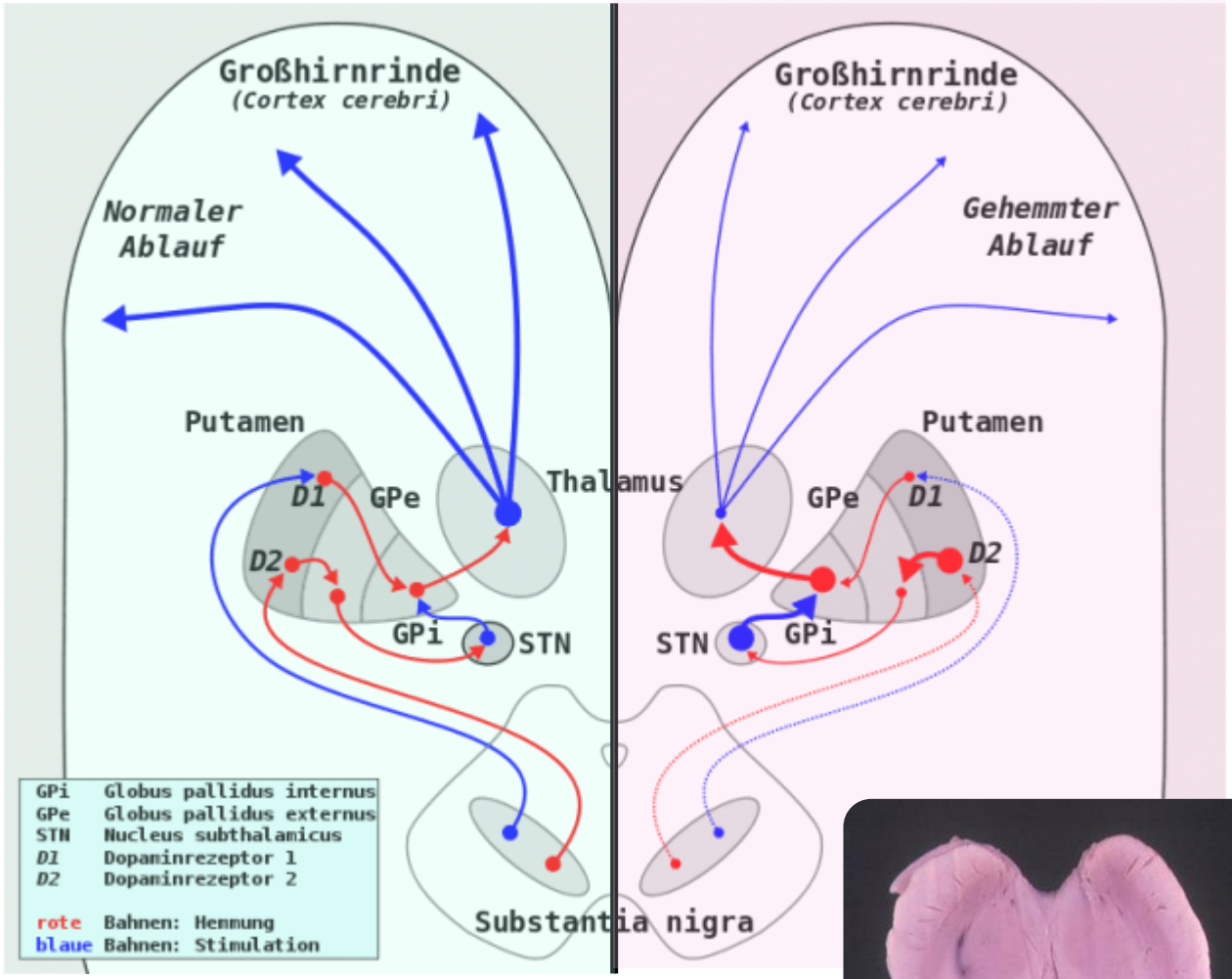
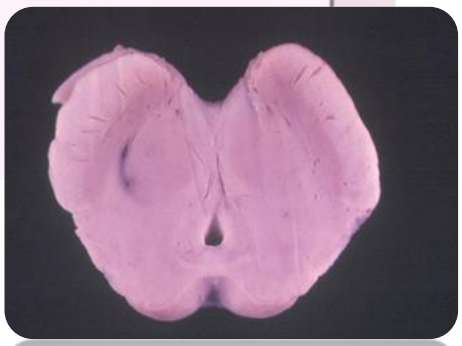
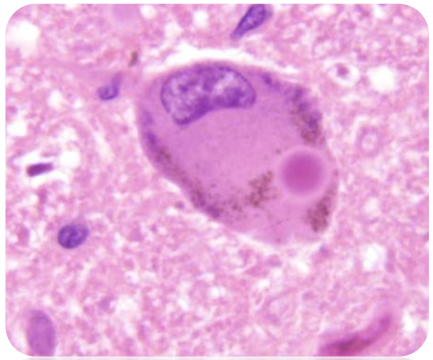



**Hemmende Wirkung** der SN auf die Basalganglienschleife **entfällt**

Enthemmte Basalganglienschleife **hemmt den Thalamus**

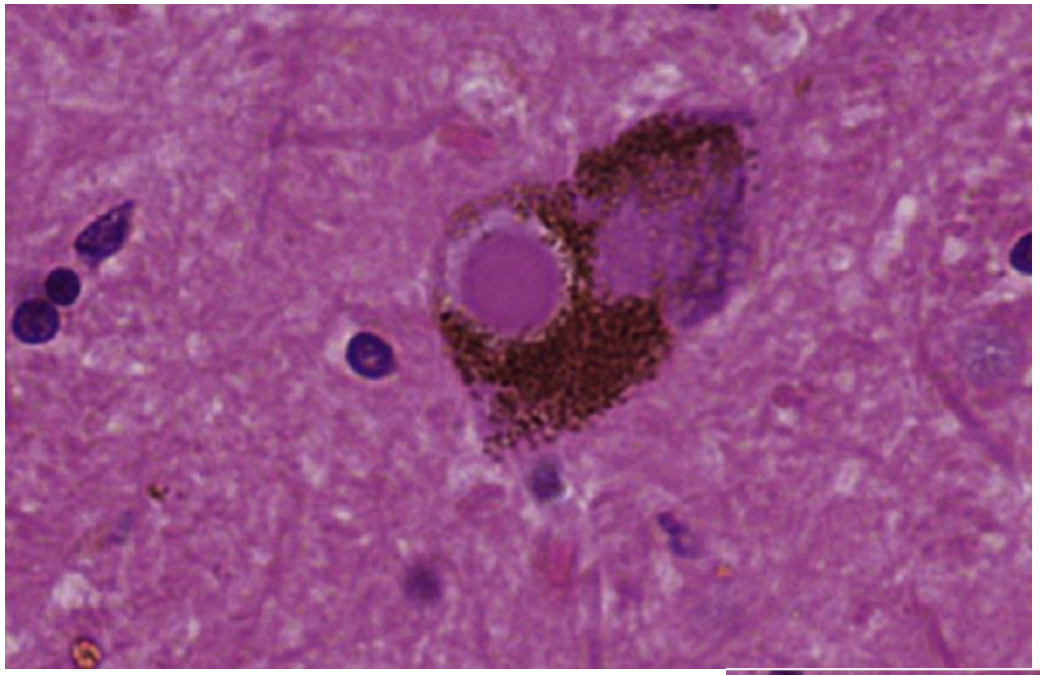
Autonome Störungen **(Vaguskerne, sympathische Ganglien)**

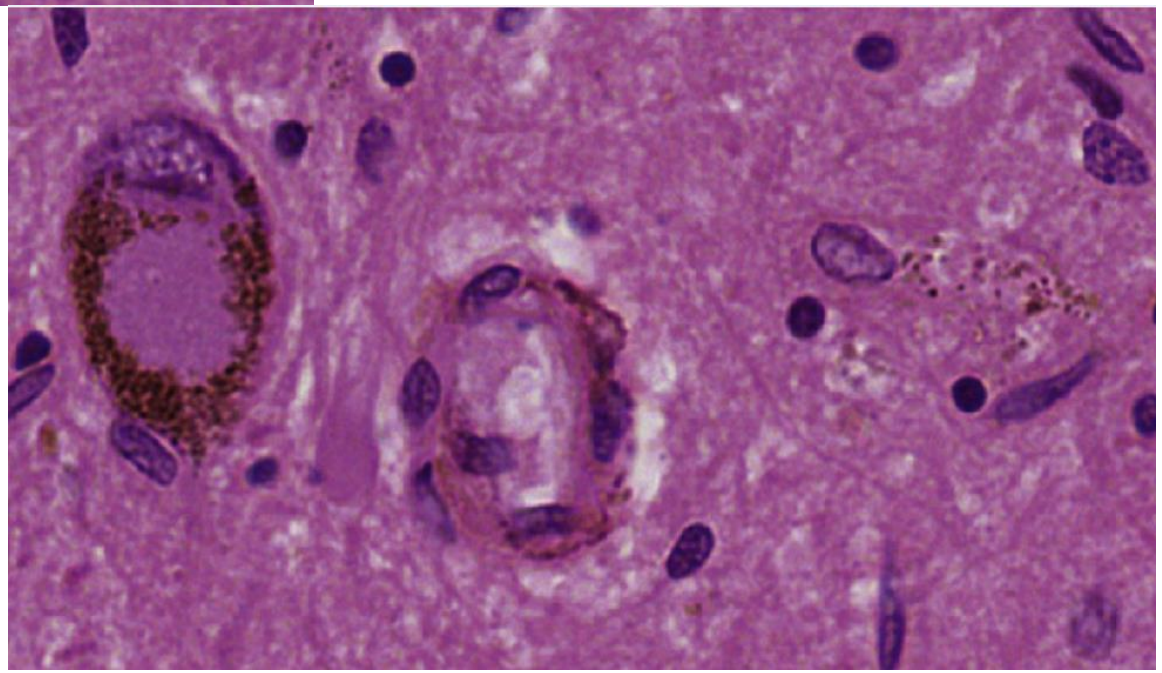




**Basalganglienschleife**
D1 Aktivierung : Direkter Weg
D2 Aktivierung und Hemmung des STN: Indirekter Weg

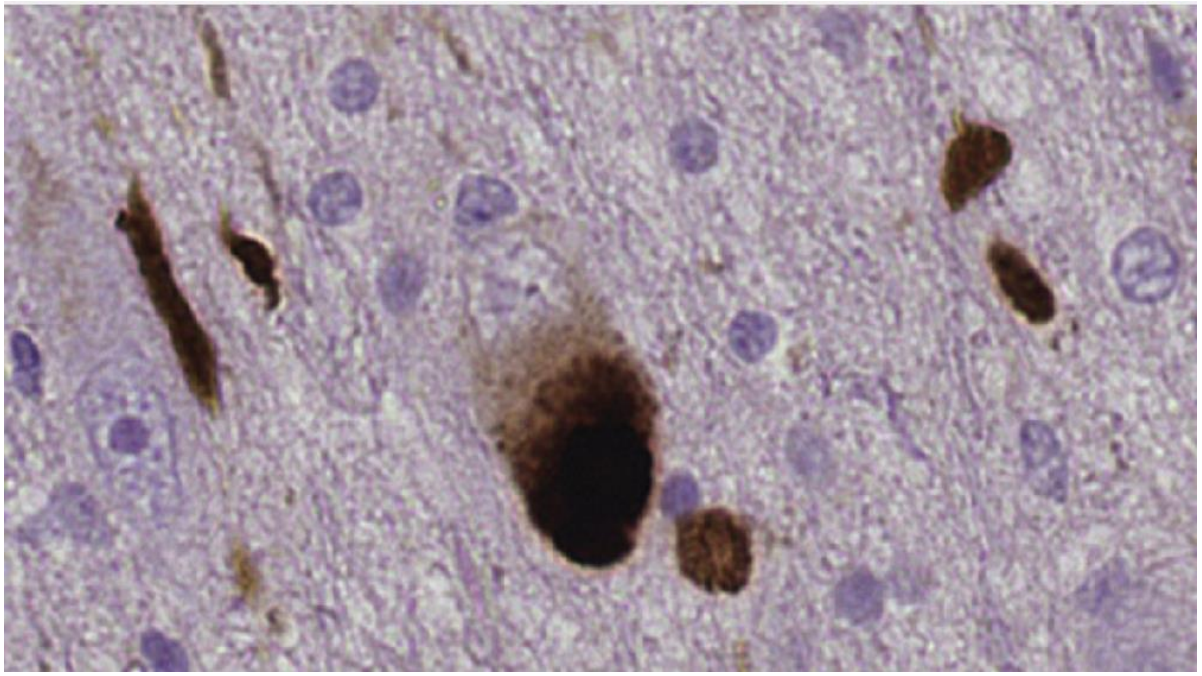
https://de.wikipedia.org/wiki/Parkinson-Krankheit#/media/Datei:Parkinson_-_Ablauf_auf_funktioneller_Ebene.svg





Love, Ellison, Neuropathology, Elsevier

# Biologie von Synuclein



3 Synucleine:

α-Synuclein (chr.4)
β-Synuclein (chr.5)
γ-Synuclein (chr.10)

α-Synuclein als synaptisches lösliches Protein in Nervenzellen, Bildung von Membrankanälen, Regulation der Dopaminausschüttung

→Lewy-Körperchen, neurotoxische Wirkung, Nervenzelluntergang

Love, Ellison, Neuropathology, Elsevier

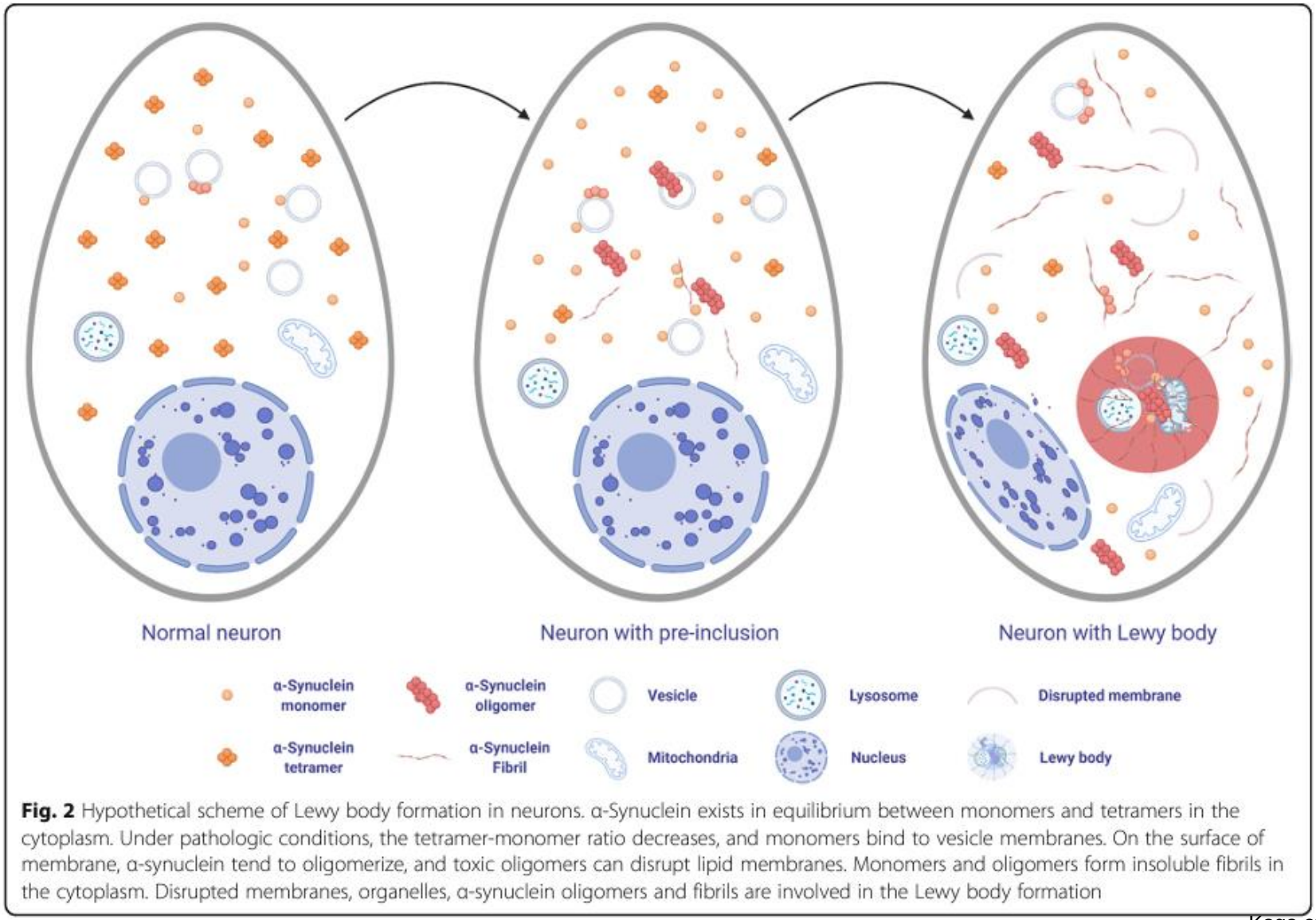
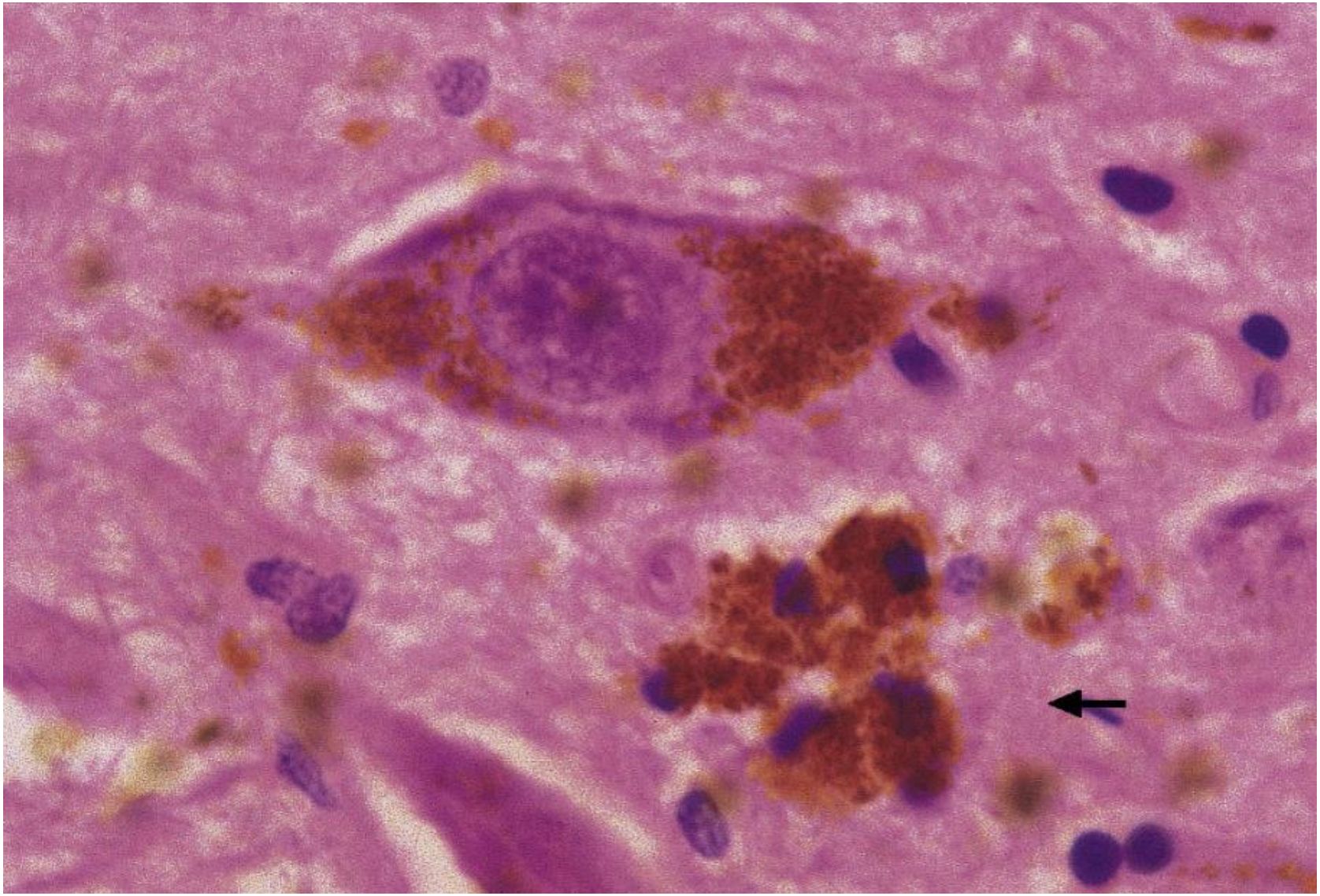



**Fig. 2** Hypothetical scheme of Lewy body formation in neurons. α-Synuclein exists in equilibrium between monomers and tetramers in the cytoplasm. Under pathologic conditions, the tetramer-monomer ratio decreases, and monomers bind to vesicle membranes. On the surface of membrane, α-synuclein tend to oligomerize, and toxic oligomers can disrupt lipid membranes. Monomers and oligomers form insoluble fibrils in the cytoplasm. Disrupted membranes, organelles, α-synuclein oligomers and fibrils are involved in the Lewy body formation

Koga et al., 2021



Love, Ellison, Neuropathology, Elsevier

# Pathologie - Zusammenfassung

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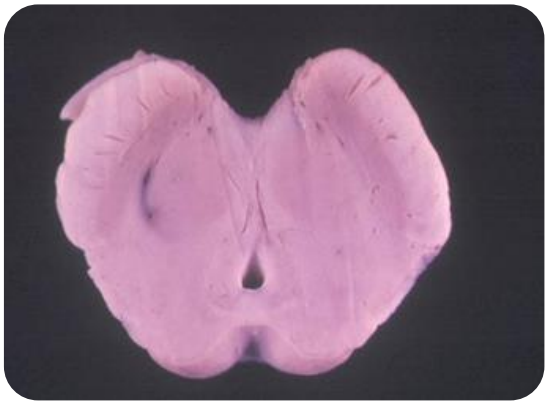
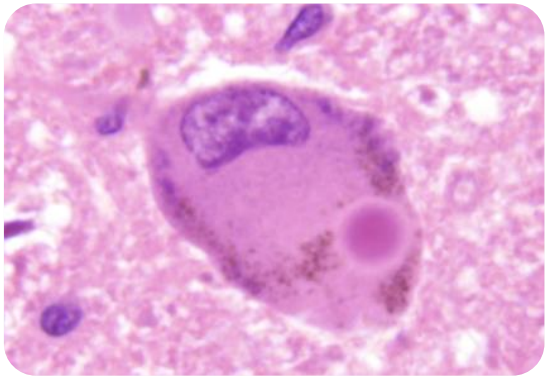
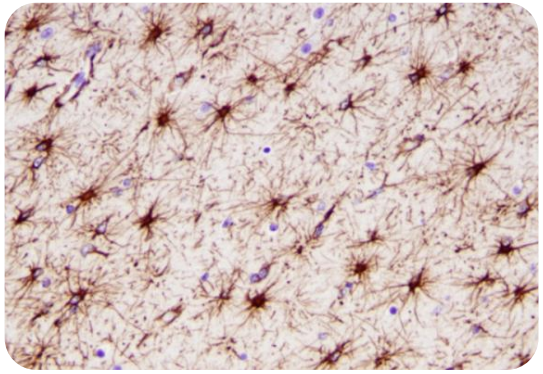
- Ausgeprägter Verlust melanin-pigmentierter, dopaminerger Nervenzellen in der Substantia nigra



- Konzentrische hyaline Einschlüsse (Lewy-Körper) in den pigmentierten Nervenzellen.



- Gliose und melaninhaltige Makrophagen



# Pathophysiologie

Genetische Formen

Idiopathisches (M. Parkinson)

Sekundäre Parkinsonsyndrome

-Medikamente: typ. Antipsychotica, Lithium, Valproat, Metoclopramid
- Traumatisch, Tumor, toxisch (CO, Mangan), metabolisch (M.Wilson)


Atypische Parkinsonsyndrome

Multisystematrophie
Lewy-Body-Demenz
Progressive supr. Blickparese
Kortikobasale Degeneration

Postmortale Diagnostik zur Diagnosesicherung und/oder weiteren Einordnung

# Synukleinopathien

## Lewy Body Erkrankungen

| Disorder | Main site of Lewy body pathology | Clinical correlate |
|---|---|---|
| Parkinson's disease (PD) | Substantia nigra | Akinetic–rigid syndrome |
| Parkinson's disease with dementia (PDD) | Substantia nigra, cerebral cortex | Dementia occurs ≥1 year after a clinical diagnosis of PD |
| Dementia with Lewy bodies (DLB) | Cerebral cortex, substantia nigra | Dementia with akinetic–rigid syndrome. Dementia occurs within a year of onset of parkinsonian features |
| Autonomic failure | Sympathetic neurons in spinal cord | Autonomic failure |
| Lewy body dysphagia | Dorsal vagal nucleus | Dysphagia |

# Lewy-Body-Demenz

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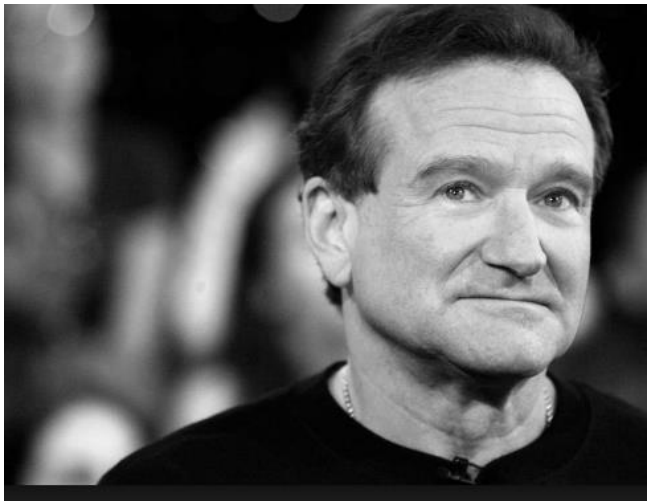
Epidemiologie: Prävalenz 0,4% der über 65 jährigen
Häufigstes atypisches Parkinsonsyndrom

Klinik: Bradykinese/Rigor mit
**führend neuropsychiatrische** Symptome:
- fluktuierend kognitive Defizite
- akustische/visuelle Halluzinationen
- Wahnhafte Episoden
- Depression und Angststörung



https://www.gala.de/stars/starportraets/robin-williams-20540186.html

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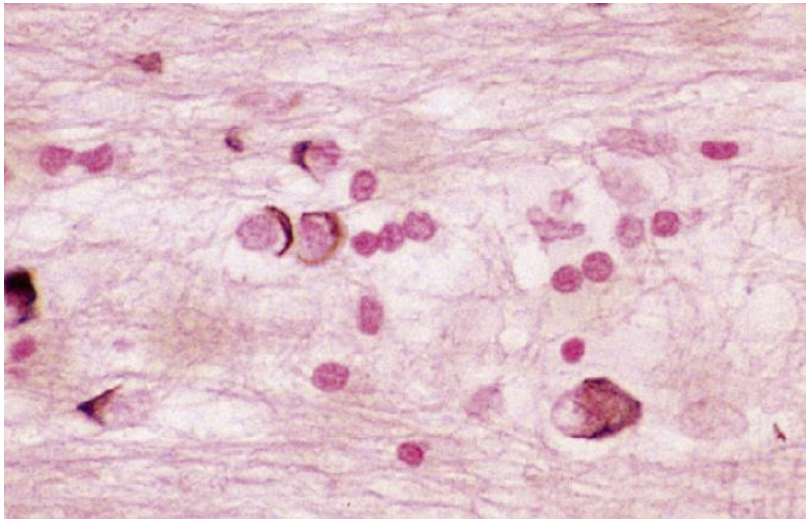
## Multisystematrophie

*Gliale Einschlüsse von alpha-Synuklein*



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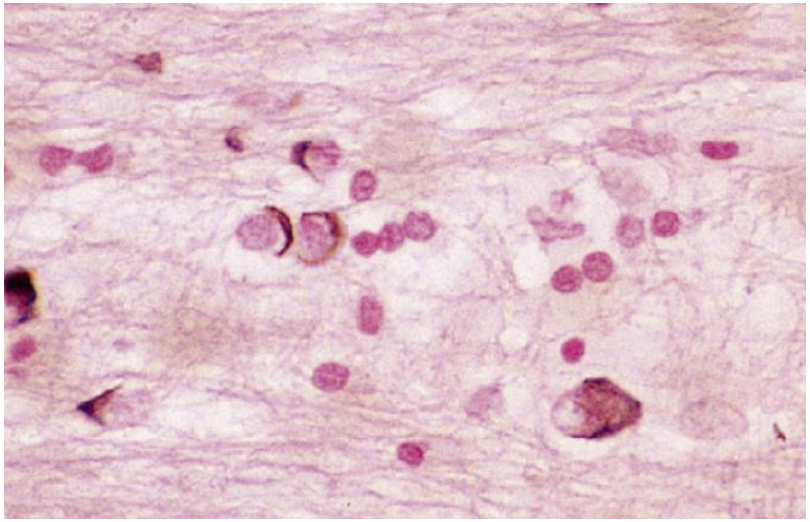
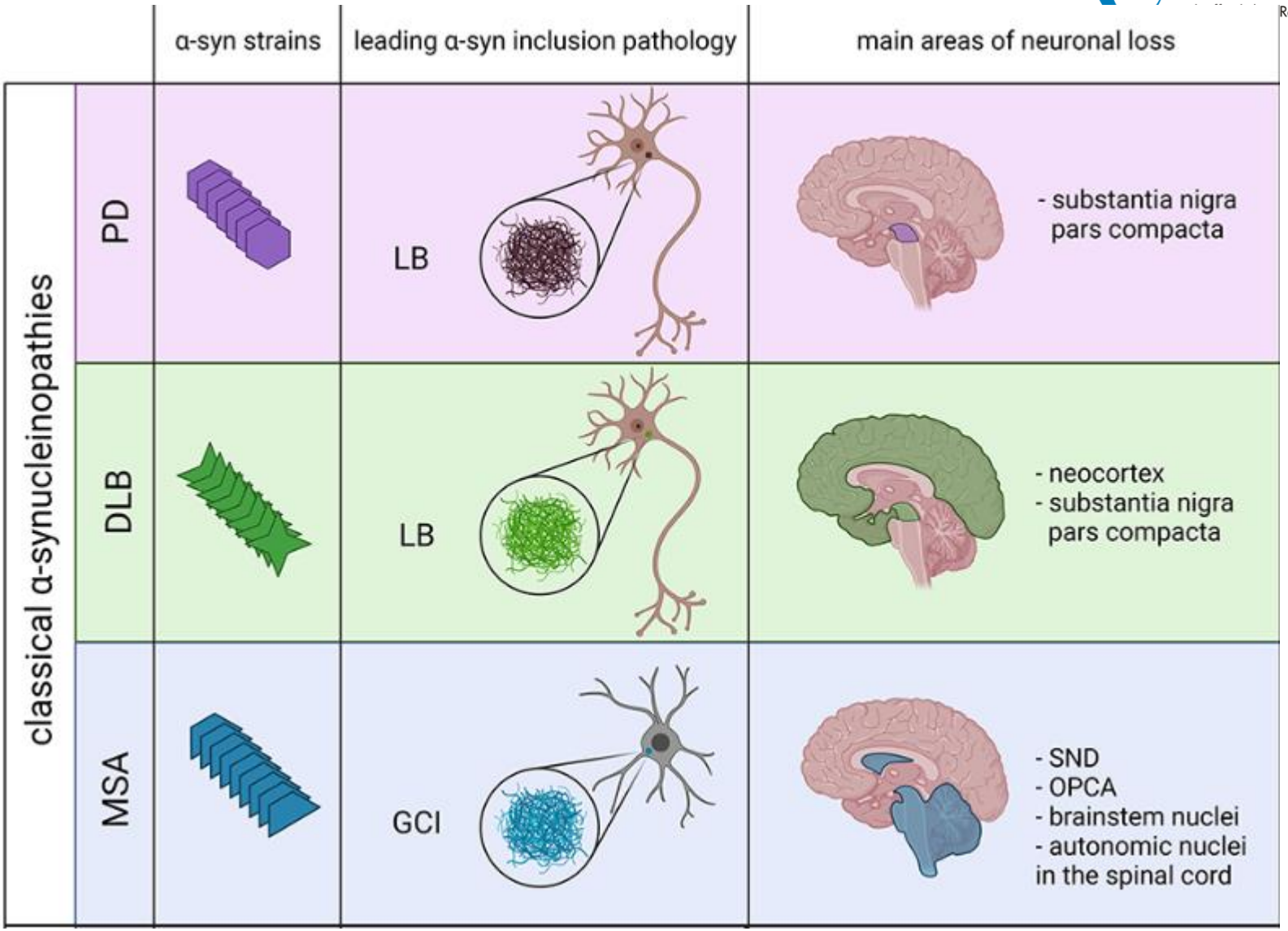
## Multisystematrophie

*Gliale Einschlüsse von alpha-Synuklein*

MSA – P:  Parkinson Symptomatik im Vordergrund
MSA – C: cerebelläre Symptomatik im Vordergrund

Olivopontocerebellar atrophy (OPCA)
Shy–Drager syndrome
Striatonigral degeneration.




α-syn strains
leading α-syn inclusion pathology
main areas of neuronal loss
classical α-synucleinopathies
PD
LB
- substantia nigra pars compacta
DLB
LB
- neocortex
- substantia nigra pars compacta
MSA
GCI
- SND
- OPCA
- brainstem nuclei
- autonomic nuclei in the spinal cord

# Die Herausforderung der Neurodegenerativen Erkrankungen

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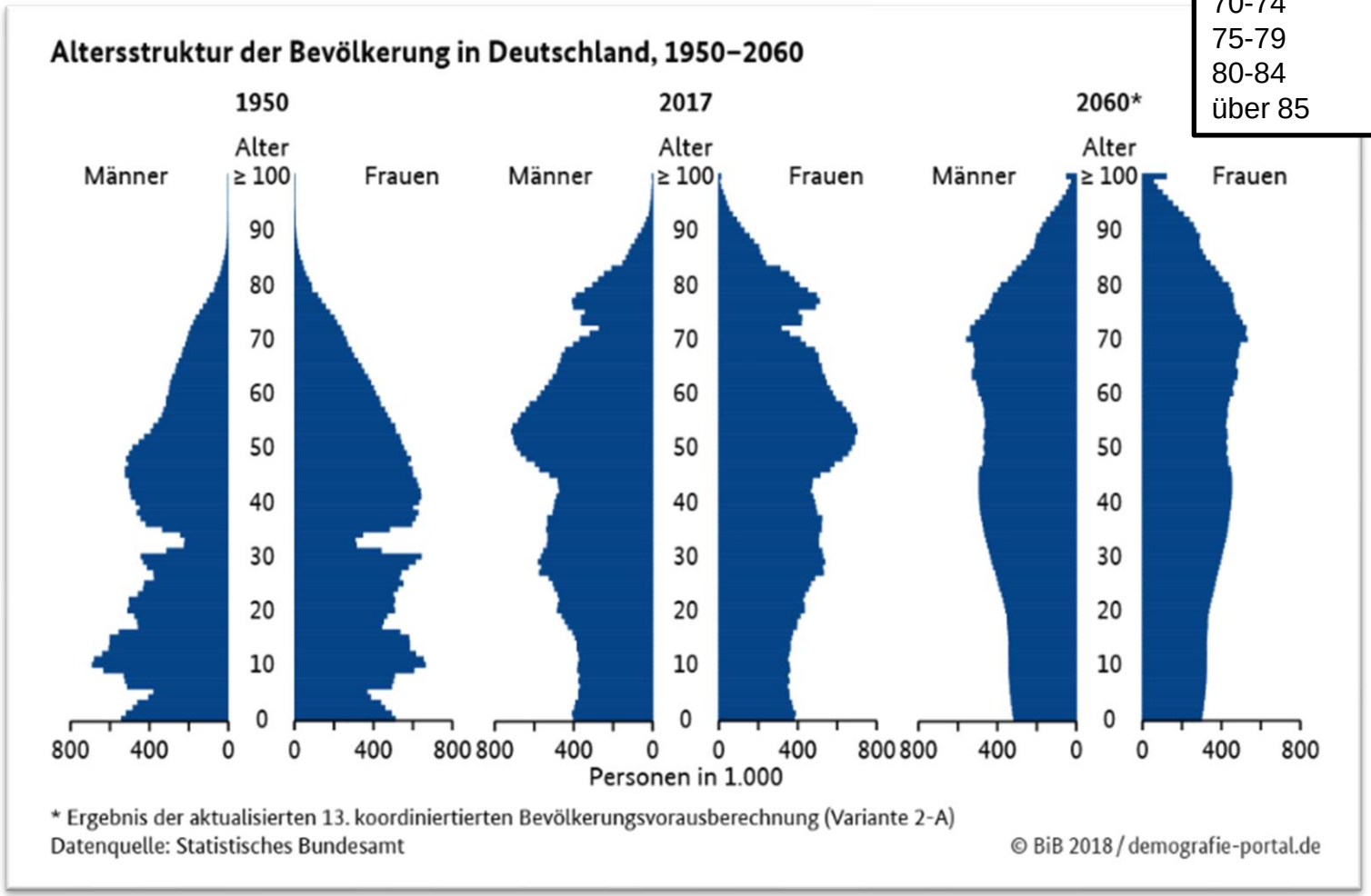
| Prävalenz M. Alzheimer | |
|---|---|
| 65-69 | 1% |
| 70-74 | 2% |
| 75-79 | 4% |
| 80-84 | 8% |
| über 85 | 20% - 50% |




Neurodegenerative Erkrankungen und Demenz 2060?

# Take-Home Messages

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- Neurodegeneration mit abnormer Proteinablagerung assoziiert
- Neurodegenerative Erkrankungen gehen häufig mit demenziellem Syndrom einher, ABER
- Nicht jedes demenzielles Syndrom ist durch neurodegenerative Erkrankung bedingt
- Histopathologie M. Alzheimer und M.Parkinson
- Postmortale Diagnostik zur Diagnosesicherung

und weiteren Einordnung

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# Vielen Dank für Ihre Aufmerksamkeit

Bei Fragen, Anmerkungen, Lob/ Kritik:

Ruth.Stassart@medizin.uni-leipzig.de