Pathophysiology of nervous system III:
Neurodegenerative diseases and dementias

Complex Brain Functions: Associational Cortex

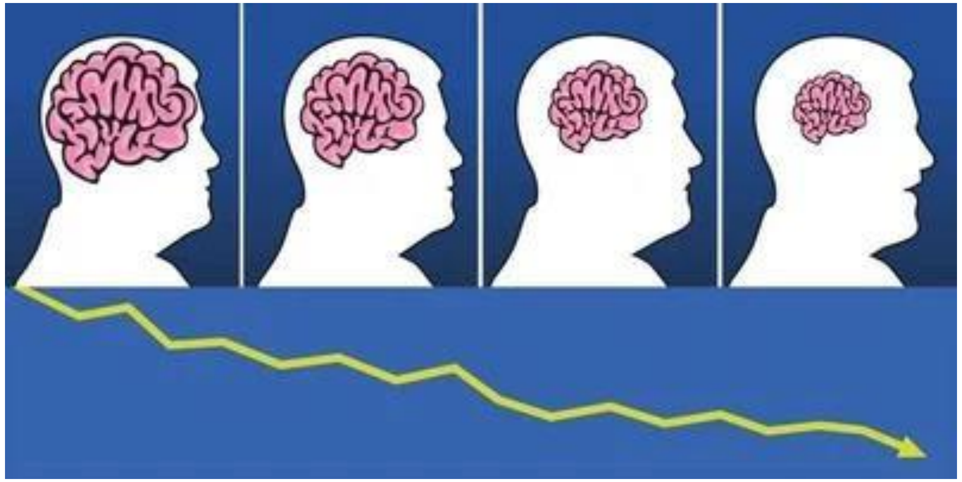
Human cognition and cognitive functions

Brain aging – mild cognitive impairment

Dementias - definition, signs

Neurodegeneration as a proteinopathy – mechanisms

Alzheimer's disease



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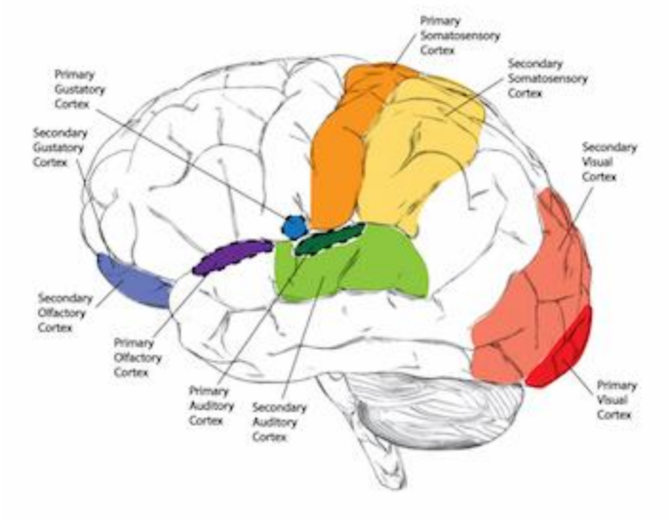
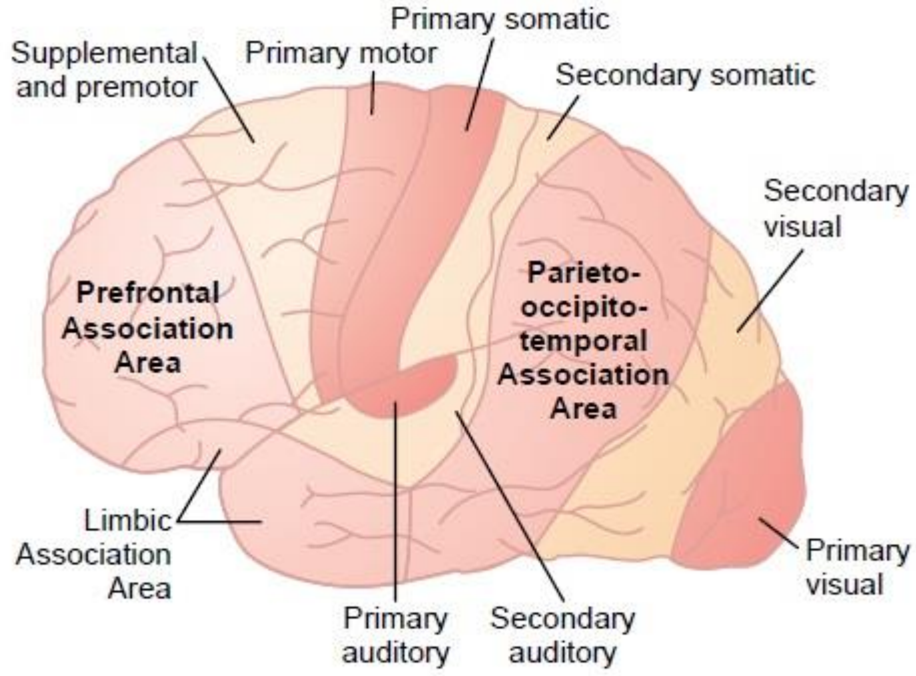
Complex Brain Functions: Associational Cortex

- only 25% of the cerebral cortex is accounted for by the modal sensory and motor cortical areas
  - i.e. primary and secondary motor and sensory areas

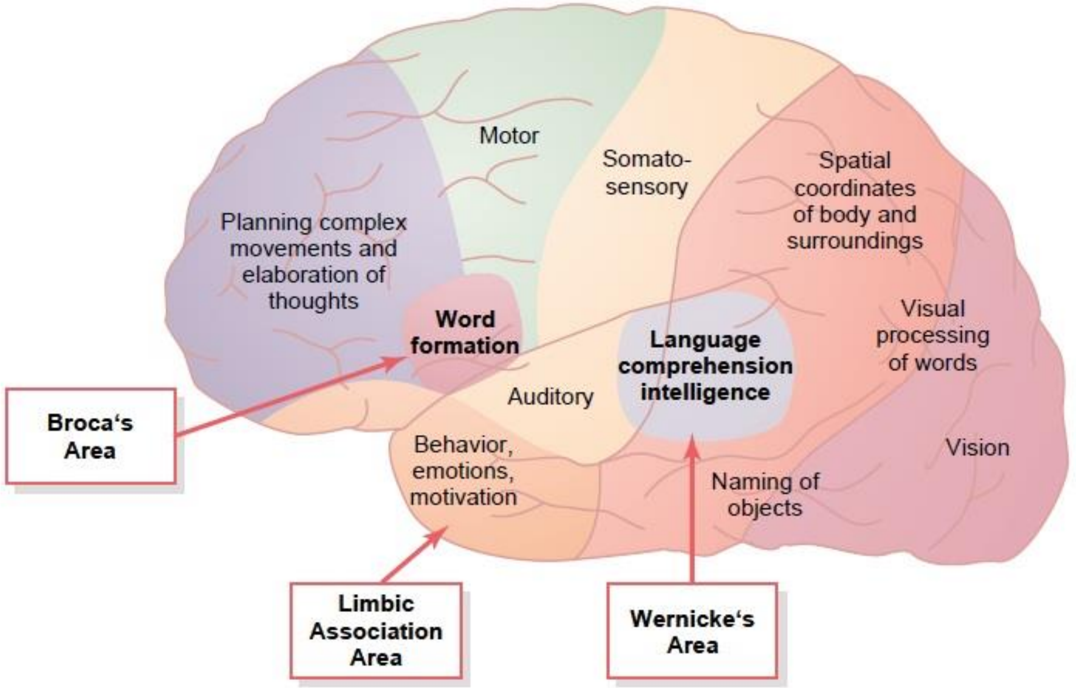


- the majority of the human cerebral cortex (approx. 75% of the entire cerebral mantle) is multi-modal cortex that associates signals derived from one or more modal systems
    - these areas are called **association areas** because they receive and analyze signals simultaneously from multiple regions of both the motor and sensory cortices as well as from subcortical structures
    - yet even the association areas have their specializations
  - (1) the parieto-occipito-temporal association area
  - (2) the prefrontal association area
  - (3) the limbic association area



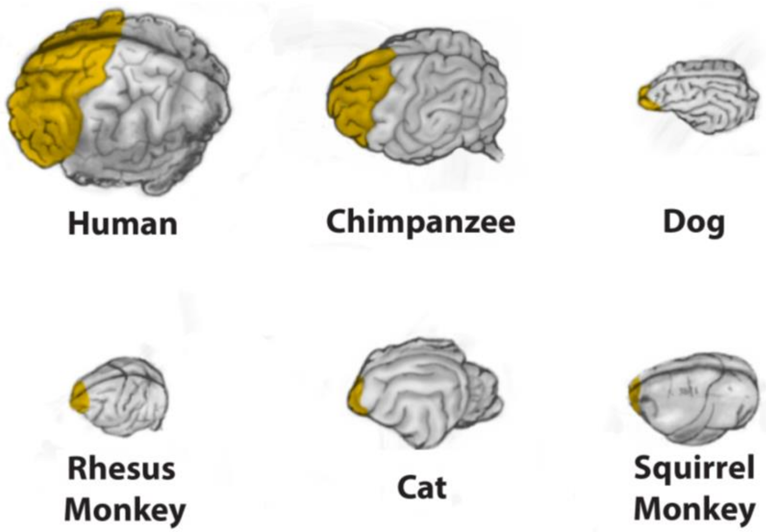
Complex Brain Functions: Associational Cortex

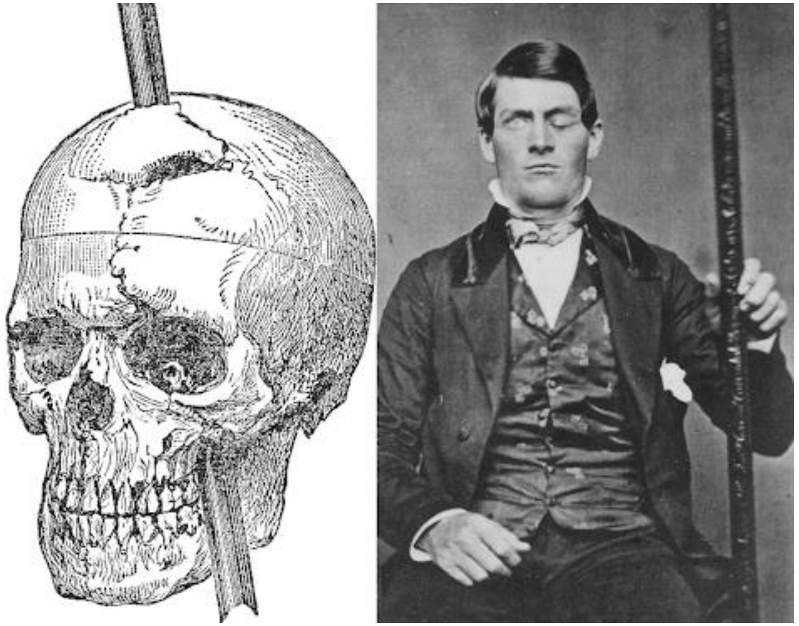
- most inferences about their function were derived from observations of patients with cortical lesions
  - recently PET (positron emission tomography), MRI (magnetic resonance imaging), EEG (electroencephalography), TMS (transcranial magnetic stimulation), TES (transcranial electrical stimulation), MEG (magnetoencephalography) and NIRS (near infrared spectroscopy) has significantly advanced our understanding of the neural basis of cognitive control
- lesions
  - the **parietal** association cortex governs **attention** and perceptual **awareness**
    - patients with parietal lobe lesions experience an inability to attend to objects in a portion of space, even though their visual, somatosensory and motor systems are intact
      - **contralateral neglect syndrome**
  - the **temporal** association cortex is responsible for the recognition and **identification** of stimuli
    - unlike patients with neglect syndromes, patients with damage to the temporal cortex are aware of objects on the side contralateral to the lesion, but experience difficulty recognising and naming them
    - these disorders are collectively known as **agnosias**
    - damage to a particular part of the inferior temporal cortex results in an inability to identify faces, a condition known as **prosopagnosia**
  - the **frontal** association cortex is responsible for **planning and decision making** and integrates information from sensory and motor cortices, as well as from the parietal and temporal association cortices
    - part of frontal cortex is called **pre-frontal cortex**



Human prefrontal cortex

- the brain structure within the human frontal cortex that evolved the most from our ancestors
- the prefrontal cortex plays a critical role in **cognitive control** , and governs what we call an individual's **"personality"**
- functions carried out by the prefrontal cortex area are called executive functions
    - executive function relates to abilities to differentiate among conflicting thoughts, determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal, prediction of outcomes, expectation based on actions, and social "control" (the ability to suppress urges that, if not suppressed, could lead to socially unacceptable outcomes)
  - planning complex cognitive behaviours
    - orchestration of thoughts and actions in accordance with internal goals
  - personality expression
  - decision making
  - moderating social behaviour





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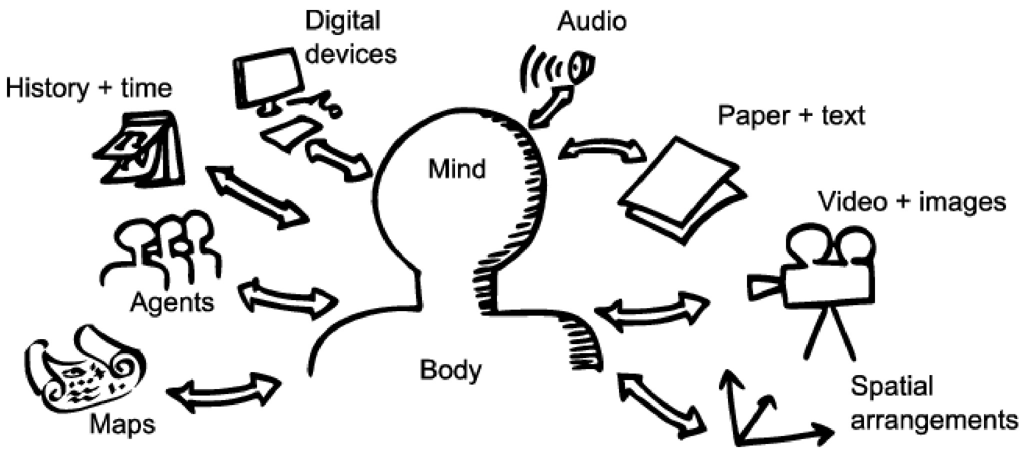
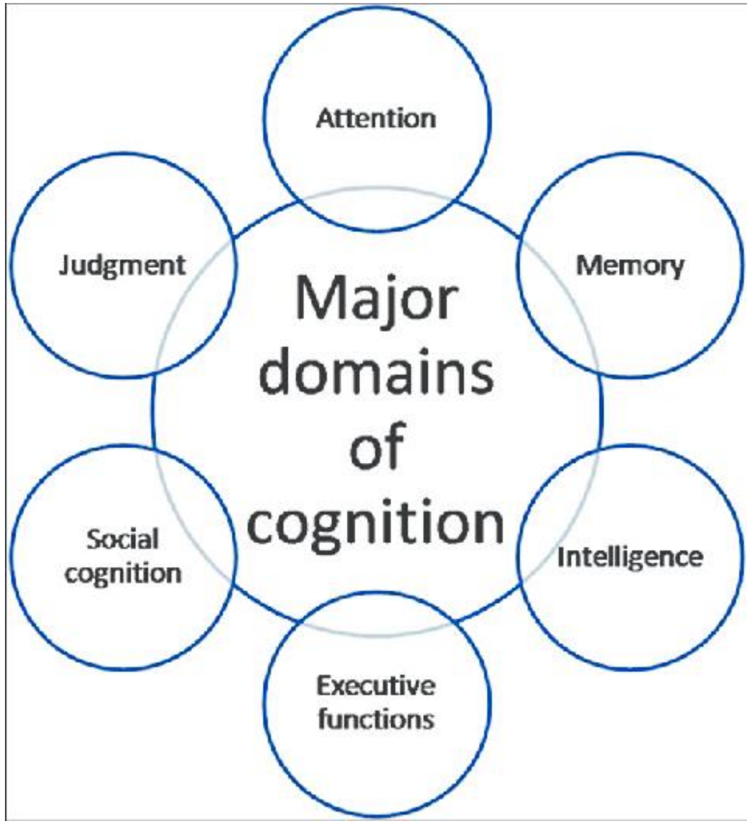
Human cognition

- lay-person definition: the process of **knowing**
- more sophisticated definition: the mental/neural brain action or process of **acquiring knowledge, awareness, understanding and appropriate behaviour** through thought, experience, and the senses (integrating stimuli and internal motivations)
- it encompasses many aspects of intellectual functions and processes such as:
  - perception/attention
  - the formation of knowledge, memory and working memory
  - judgment and evaluation
  - reasoning and "computation", problem solving
  - decision making
  - comprehension and production of language
- cognitive processes use existing knowledge to discover new knowledge
  - human **intelligence** is a mental quality that consists of the abilities to learn from experience, adapt to new situations, understand and handle abstract concepts, and use knowledge to manipulate one's environment
    - **IQ** as a measure of intelligence?
- cognition may by altered by various disease states





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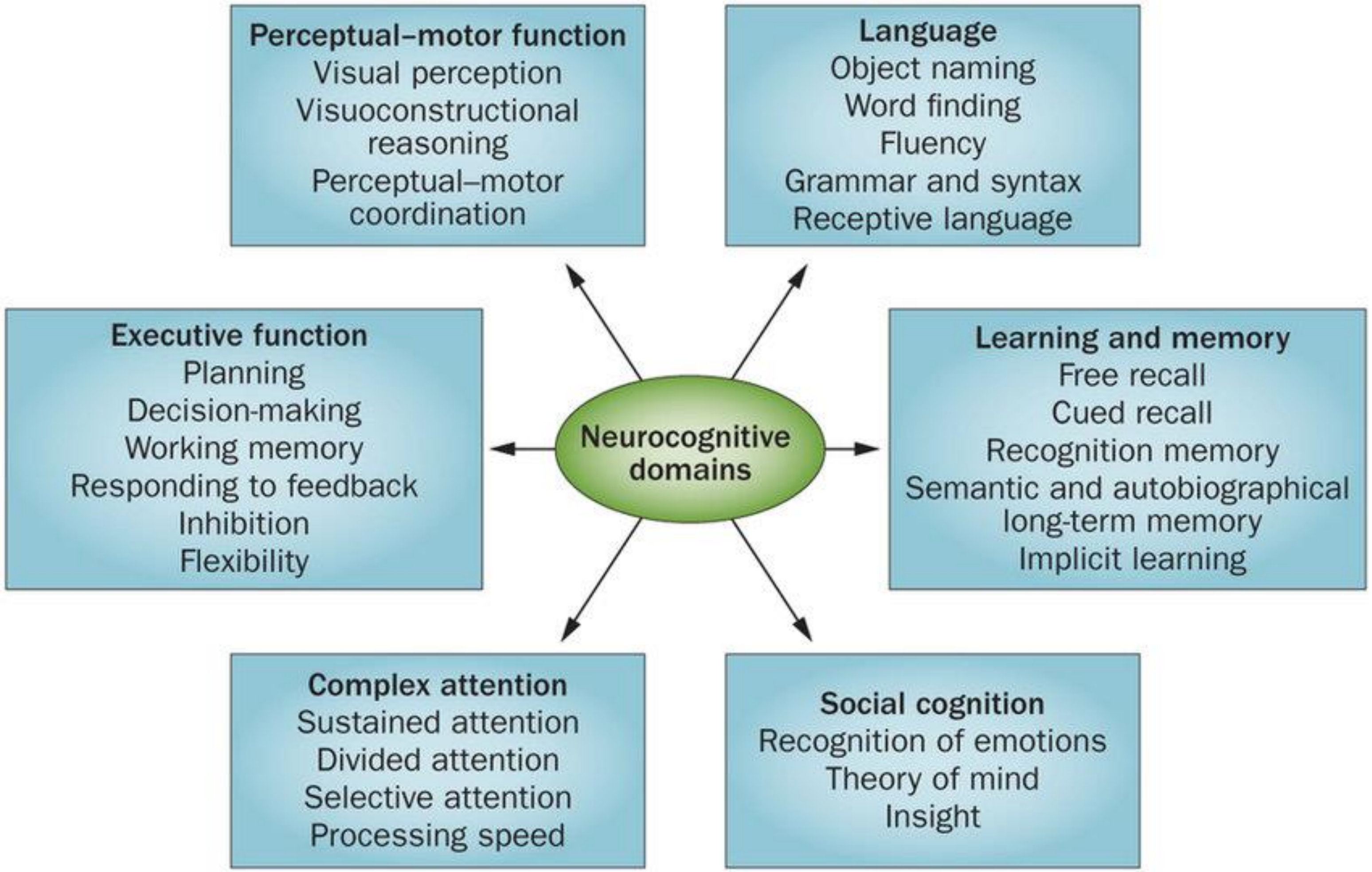
Six neurocognitive domains according to the 5the of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)



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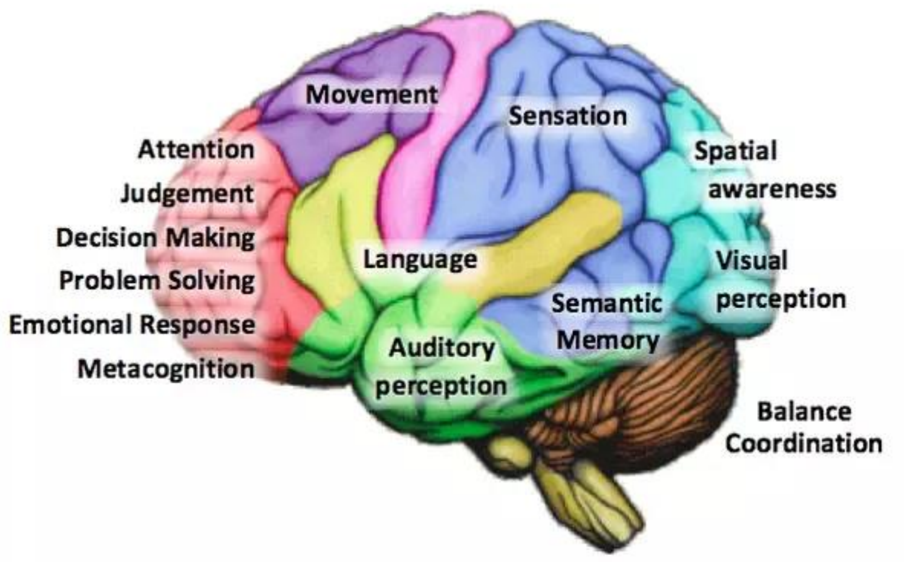
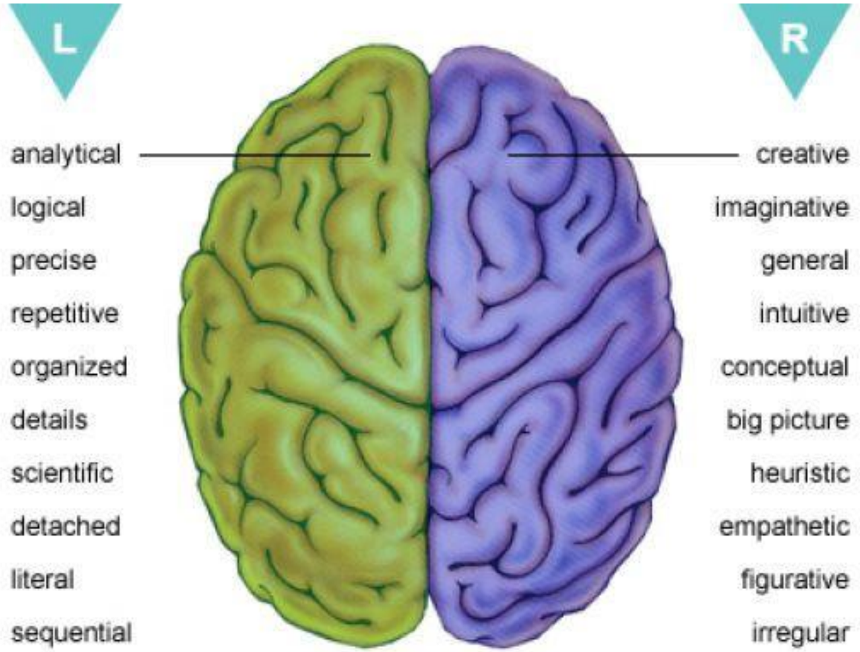
Cognitive functions

- cognitive functions are inherent features of CNS aiming to recognize and understand both external and internal environment and to properly react to it
- categories
  - memory
    - declarative – can be expressed by words (related to hippocampus)
      - semantic – what we learned
        - affected in FTD
      - episodic – what we experienced (defines our identity)
        - affected by AD, WKD
    - non-declarative — difficult to express (related to hippocampus, basal ganglia, cerebellum and neocortex)
      - emotional memory, conditional reflexes, procedural memory (incl. motor programmes)
        - affected in PD
  - attention, concentration
  - executive functions (planning, decision making, problem solving) incl. emotions and self-regulation
  - speech, expression, understanding
  - spatial orientation
- disorders
    - complex severe – in dementia
    - mild cognitive impairment – aging
    - temporary - delirium
    - isolated amnestic syndromes – strokes





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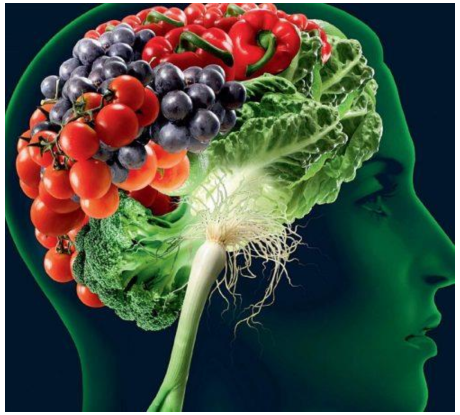
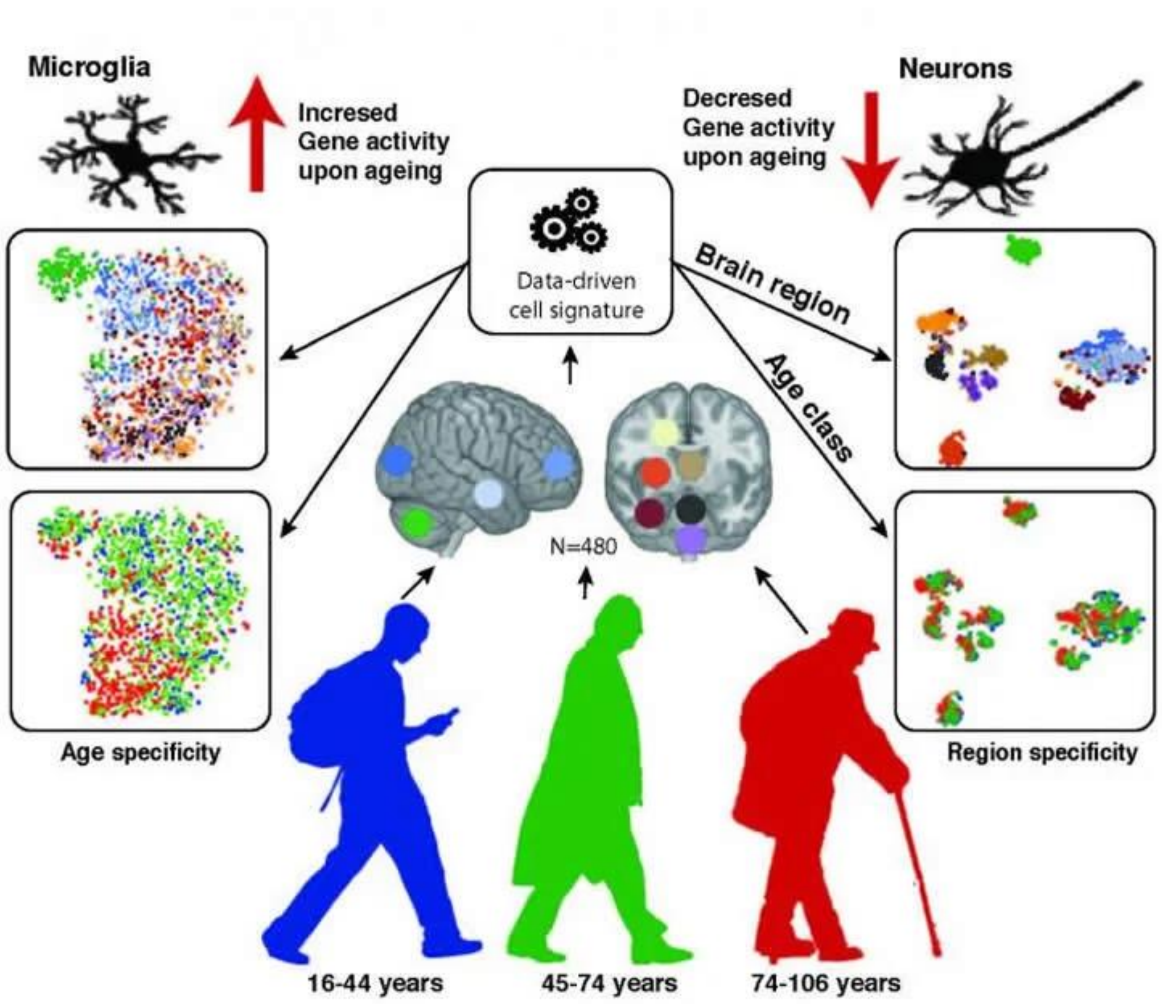
Brain aging – mild cognitive impairment (MCI)

- human brain shrinks with increasing age (not homogenously though)
  - cerebral ventricles expand as a function of age
- changes accompanying aging brain
  - loss of neural circuits and brain plasticity
    - not due to neuronal death but due to synaptic alterations
  - white matter lesions
    - loss of oligodendroglia and myelin and general dendrite reduction
  - deposition of material similar to AD or DLB
    - beta-amyloid, Lewy bodies in minor amounts
  - vascular – small strokes
  - changes in brain metabolism (glucose)
  - neuroinflammation (activation of microglia)
    - oxidative stress
- MCI of certain degree is typical for aging brain – it comprises
  - forgetting things more often, forgetting important events such as appointments or social engagements
  - loosing a train of thought or the thread of conversations, books or movies
  - feeling increasingly overwhelmed by making decisions, planning steps to accomplish a task or understanding instructions
  - having trouble finding a way around familiar environments
  - becoming more impulsive or having increasingly poor judgment
  - eventually accompanied by
    - depression
    - irritability and aggression
    - anxiety
    - apathy
- preventive strategies are emerging that might be usable also in the prevention of dementias
  - cognitive training!
  - aerobic exercise
  - diet?





Dementia

Definition, signs, types and mechanisms

Alzheimer's disease

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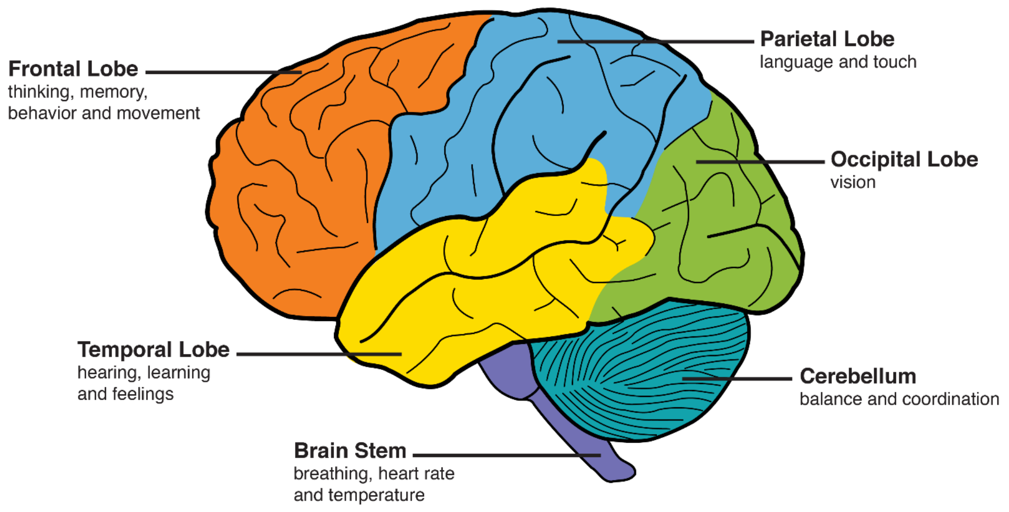
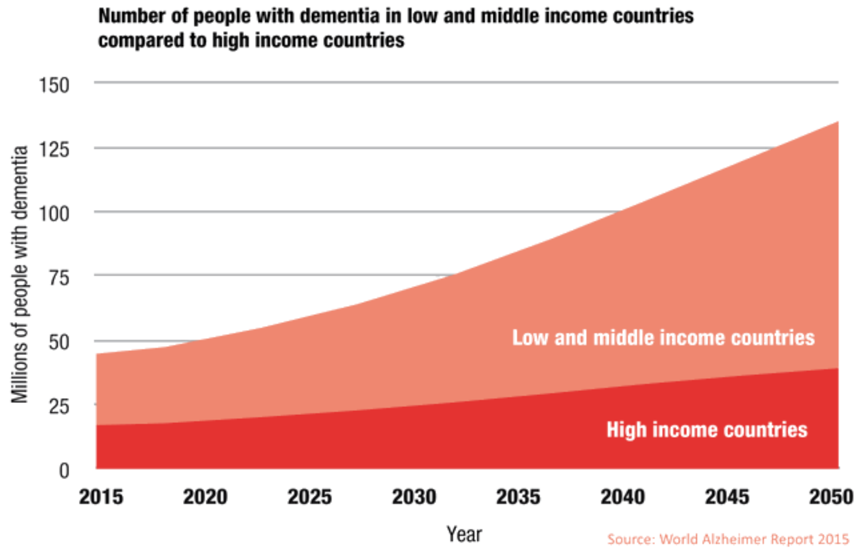
Dementia as a consequence of neurodegeneration

- general term for any disease that causes a long-term and gradual change in **ability to think** and remember (**memory**) and is severe enough to impair a person's daily functioning
  - while some mild changes in cognition are considered a part of the normal aging process, dementia is not
  - consciousness is usually not affected
- symptoms – might differ in different aetiologies of dementias
  - memory loss
  - trouble planning and organizing, doing familiar tasks
  - impaired visual-spatial orientation
  - poor judgment, trouble and making decisions
  - confusion or agitation
  - changes in personality and mood
  - later problems with walking, swallowing, apathy, frequent falls
- time course of dementia:
  - cognitive functions impaired
  - impaired behaviour and emotions
  - impaired daily activities (eating, dressing, hygiene, sleep etc.)
  - mortality – mute, incontinent, bed ridden, feeding failure, aspiration pneumonia
- prevalence
  - about 3% of people between the ages of 65–74 have dementia
  - 19% between 75 and 84
  - nearly half of those over 85 years of age
- diagnosis is usually based on history of the illness and cognitive testing with medical imaging
  - the mini mental state examination is one commonly used cognitive test





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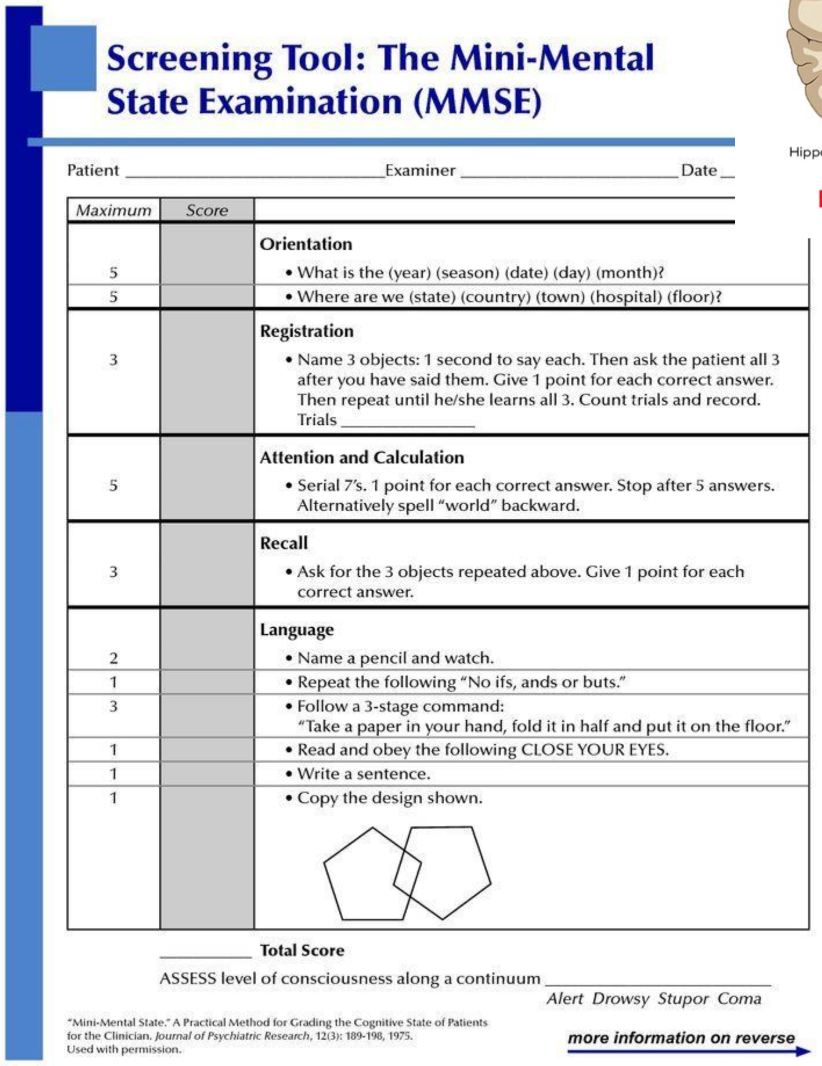
Types and aetiologies of dementia

- Alzheimer's disease (60%)
  - typical hippocampal atrophy
- Vascular dementia (25%)
  - not gradual but abrupt or stepwise
    - with or without stroke in personal history
      - focal neurological deficits
    - emotional instability, impulsivity, depression
- Dementia with Lewy bodies (15%)
  - dementia develops together with motor symptoms
  - visual hallucination!
- Parkinson's disease
  - dementia develops relatively late after motor symptoms
- Frontotemporal dementia
  - socially inappropriate behaviour (disinhibition)
  - apathy
- Huntington disease dementia
- Creutzfeld Jacob disease
  - spongiform encefalopathy
- normal pressure hydrocephalus
- Wernicke-Korsakoff Syndrome
  - severe shortage of thiamine (vitamin B-1) in the body
  - most commonly happens in people who are long-term heavy drinkers
- NOTE: unrecognised and untreated depression can mimic dementia



Screening Tool: The Mini-Mental State Examination (MMSE)

Patient ______________________ Examiner ______________________ Date __

Maximum	Score	
		Orientation
5		• What is the (year) (season) (date) (day) (month)?
5		• Where are we (state) (country) (town) (hospital) (floor)?
		Registration
3		• Name 3 objects: 1 second to say each. Then ask the patient all 3 after you have said them. Give 1 point for each correct answer. Then repeat until he/she learns all 3. Count trials and record. Trials ______
		Attention and Calculation
5		• Serial 7's. 1 point for each correct answer. Stop after 5 answers. Alternatively spell "world" backward.
		Recall
3		• Ask for the 3 objects repeated above. Give 1 point for each correct answer.
		Language
2		• Name a pencil and watch.
1		• Repeat the following "No ifs, ands or buts."
3		• Follow a 3-stage command: "Take a paper in your hand, fold it in half and put it on the floor."
1		• Read and obey the following CLOSE YOUR EYES.
1		• Write a sentence.
1		• Copy the design shown.

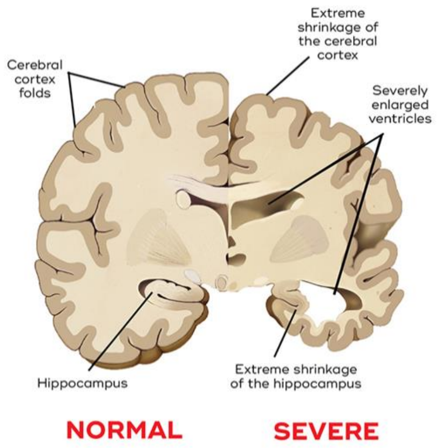
______ **Total Score**

ASSESS level of consciousness along a continuum ______________________

Alert Drowsy Stupor Coma

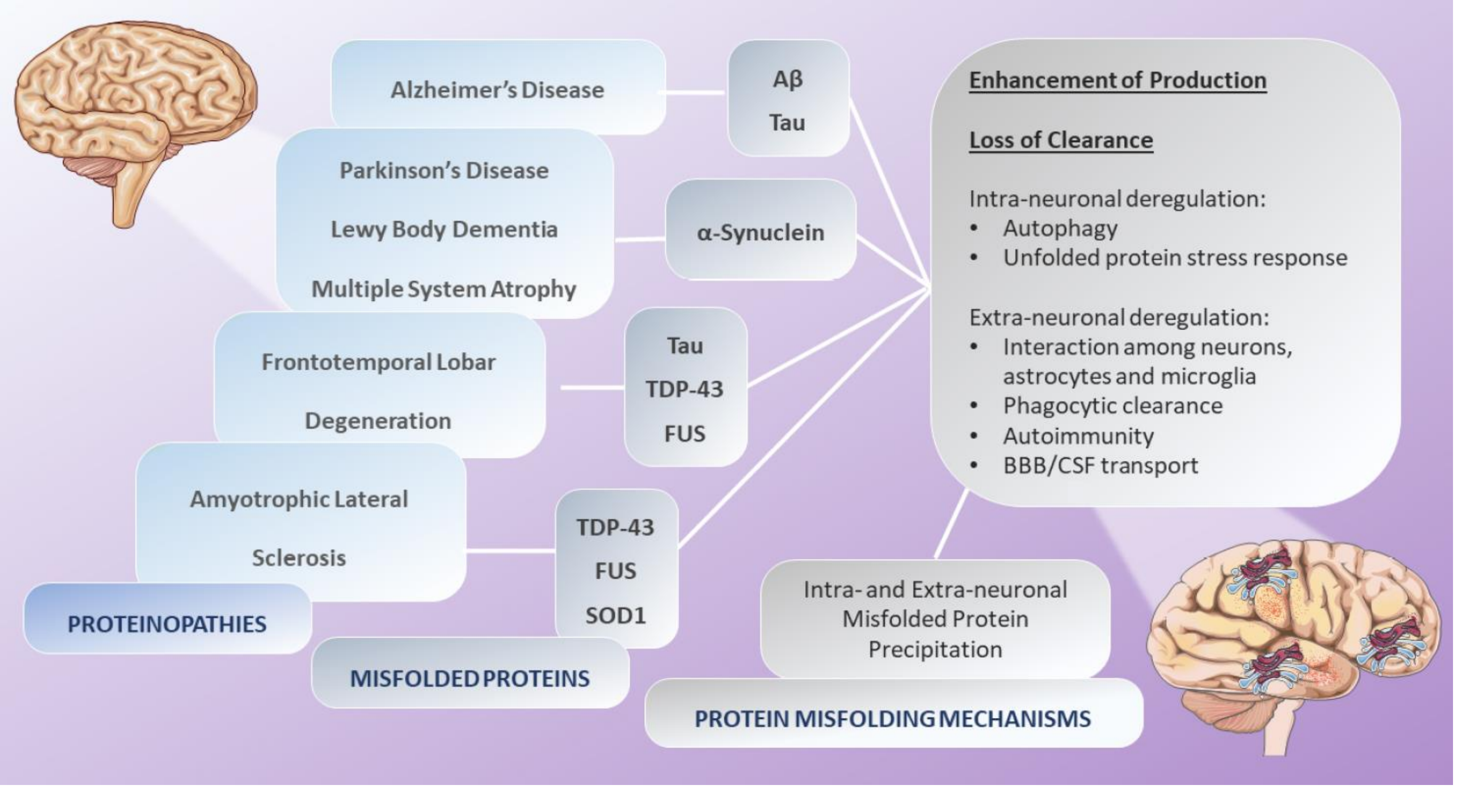
"Mini-Mental State." A Practical Method for Grading the Cognitive State of Patients for the Clinician. *Journal of Psychiatric Research*, 12(3): 189-198, 1975. Used with permission.

more information on reverse



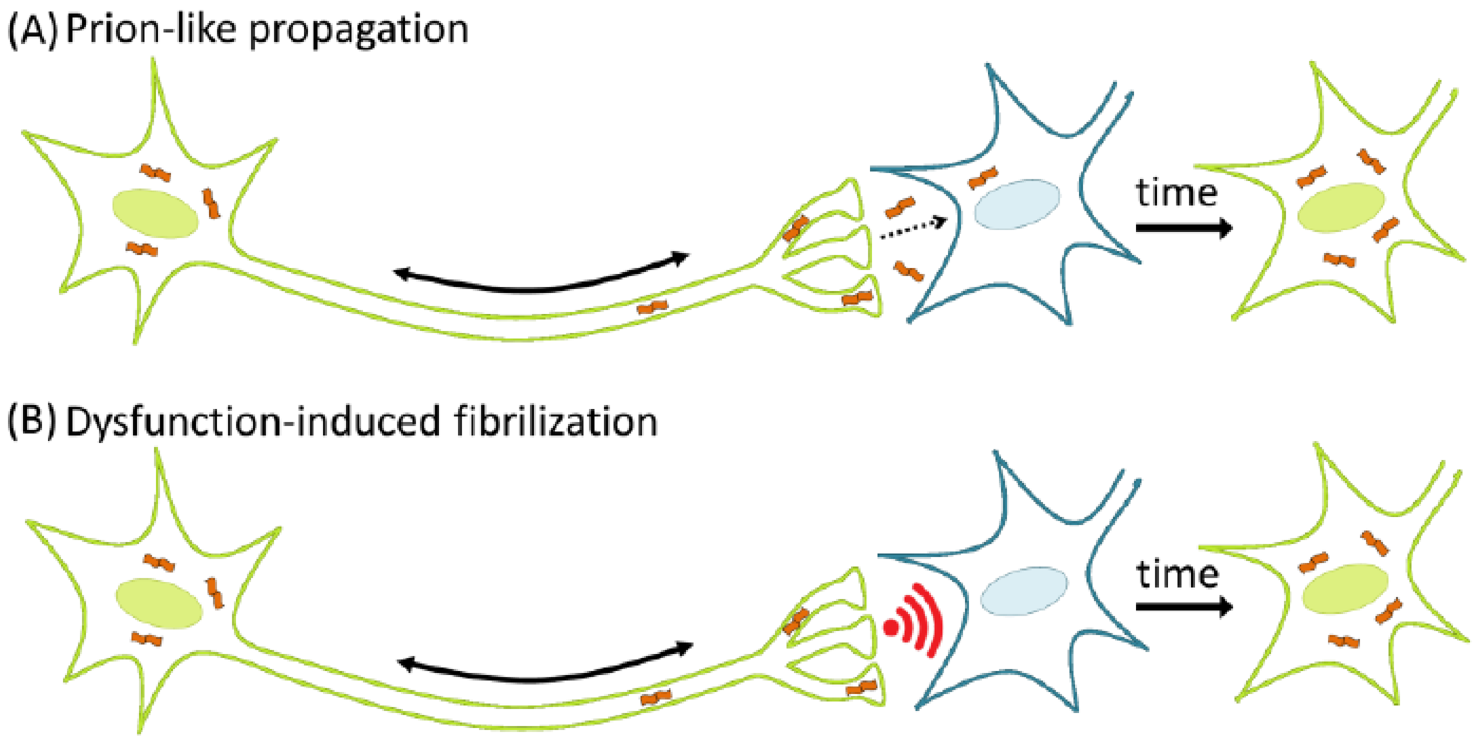
Neurodegenerative diseases as proteinopaties

- mechanisms of neurodegeneration in general
    - build-up of abnormal/misfolded proteins and their aggregation in the brain that interferes with the brain functions
        - different protein build-up in different types of dementia though
            - beta-amyloid and tau in AD, alpha-synuclein in DLW, prions in CJD
- neurodegeneration could therefore be consider as a proteinopathy
    - cumulated protein in toxic doses or mutated is prone to misfolding and aggregation
    - resistance or concomitant dysfunction in systems degrading the proteins
        - ubiquitin-proteasom
        - autophagy
    - ER stress (UPR) and apoptosis
    - protein-propagation/spreading
        - prion-like?
    - role of chaperons



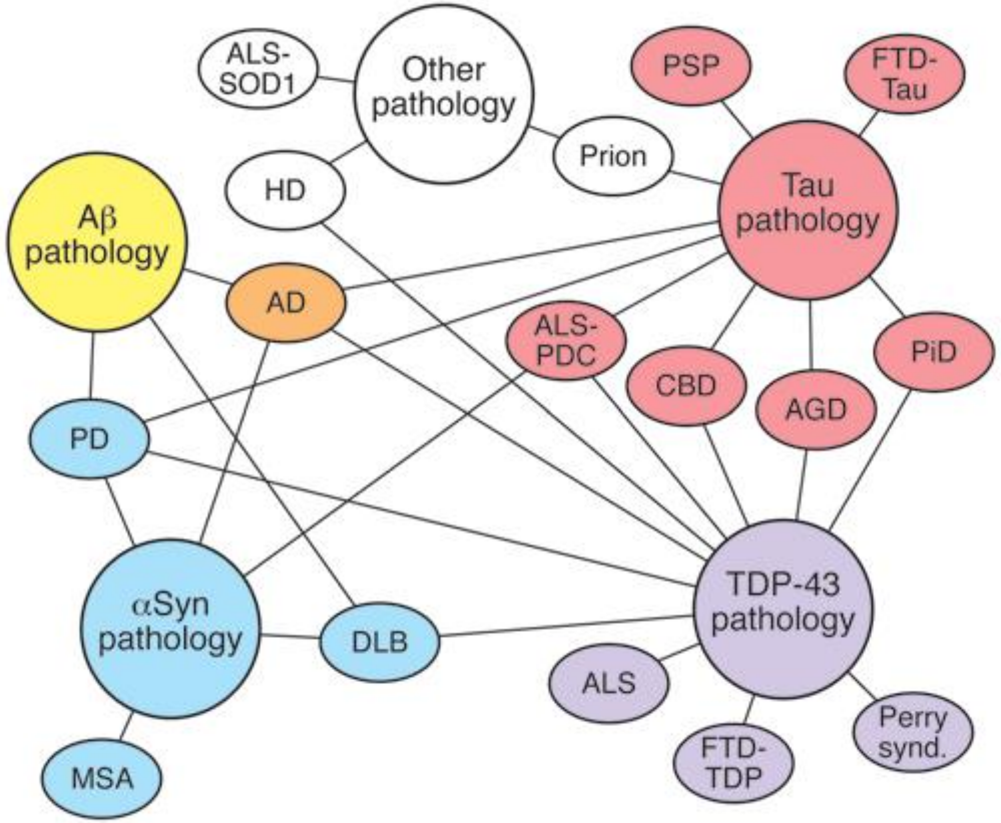
- In most neurodegenerative disorders, proteins that are unstructured in healthy brains, undergo modifications in their structural folding, forming small oligomeric or large fibrillary aggregates
- These changes lead to their self-association, elongation and intra- and extra-neuronal precipitation
- The molecular mechanisms resulting in misfolded protein conformational changes tend to be the same in all the proteinopathies and may include different mechanisms, such as post-translational modifications, the loss of protein clearance or the enhancement of protein production

Prion-like transmission of protein aggregates in neurodegenerative diseases



- Competing hypotheses for the causative mechanism of disease pathogenesis.
  - (A) The “prion-like” hypothesis of tauopathies suggests that strains of tau fibrils pass from dysfunctioning neurons (green) into healthy neurons (blue) and recruit native tau, resulting in dysfunction of the healthy neuron over time.
  - (B) An alternate hypothesis is that dysfunctioning neurons induce a state of stress in healthy neurons through signaling, causing tau fibrillization as a downstream effect, e.g. through disruption of protein homeostasis or induction of apoptosis
    - this hypothesis is akin to the amyloid cascade hypothesis in AD.
    - the observation that tau strains are conserved throughout the brain as they spread supports the first hypothesis

Schematic of the interrelated neurodegenerative proteinopathies



- Diseases are organized in color blocks that indicate their primary proteinaceous aggregate. AD has primary proteinaceous aggregates of both Aβ (yellow) and tau (red) and is therefore designated orange. Diseases are connected to proteinaceous aggregates that can be observed in at least some cases of the disease with lines. AGD, argyrophilic grain disease; CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; HD, Huntington's disease; MSA, multiple system atrophy; Perry synd., Perry syndrome; PDC, parkinsonism-dementia complex; PiD, Pick's disease; PSP, progressive supranuclear palsy; αSyn, α-synuclein.

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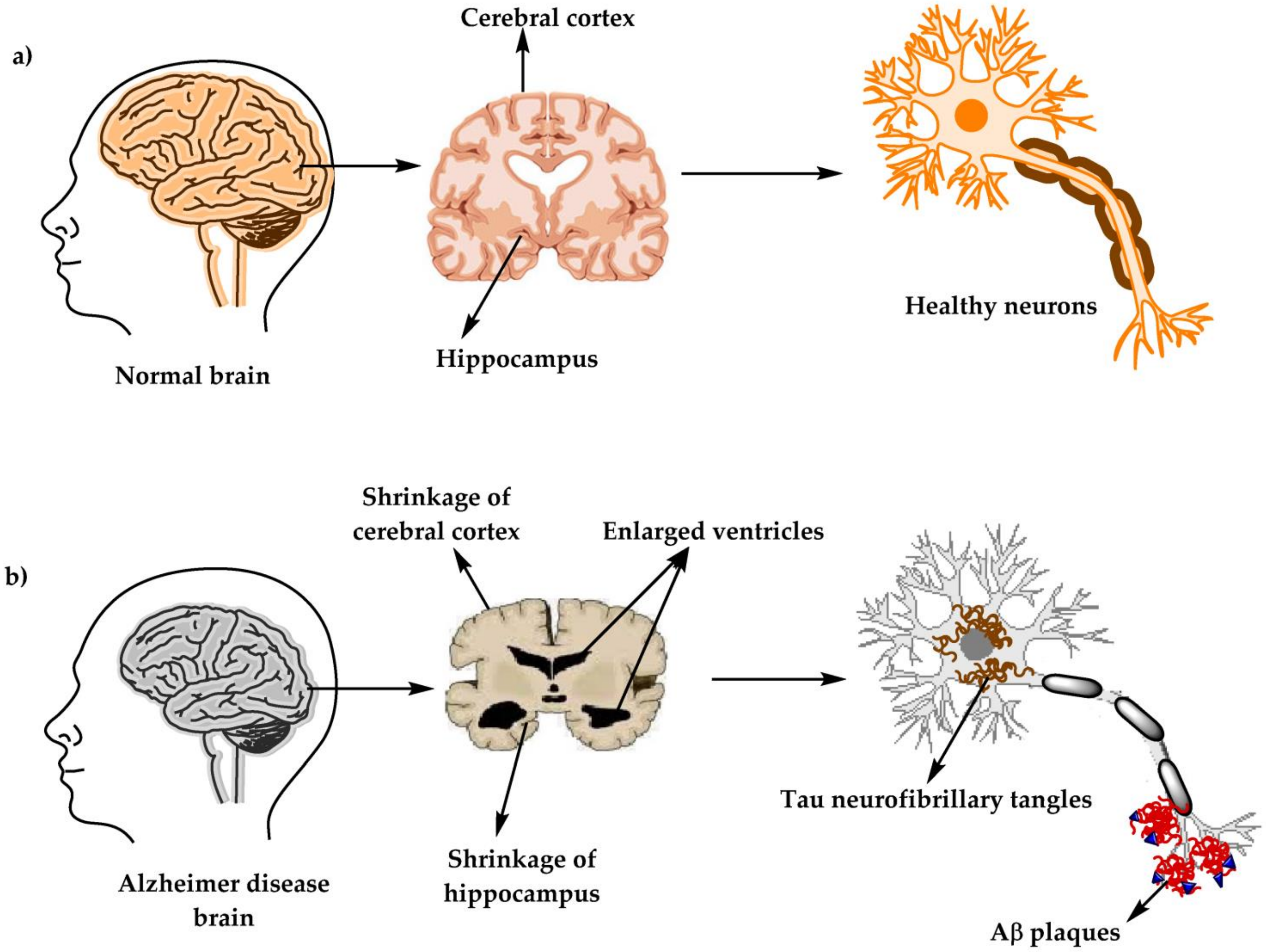
Alzheimer's disease as the most common form of dementia

Alzheimer's disease = β-amyloidopathy + Tauopathy



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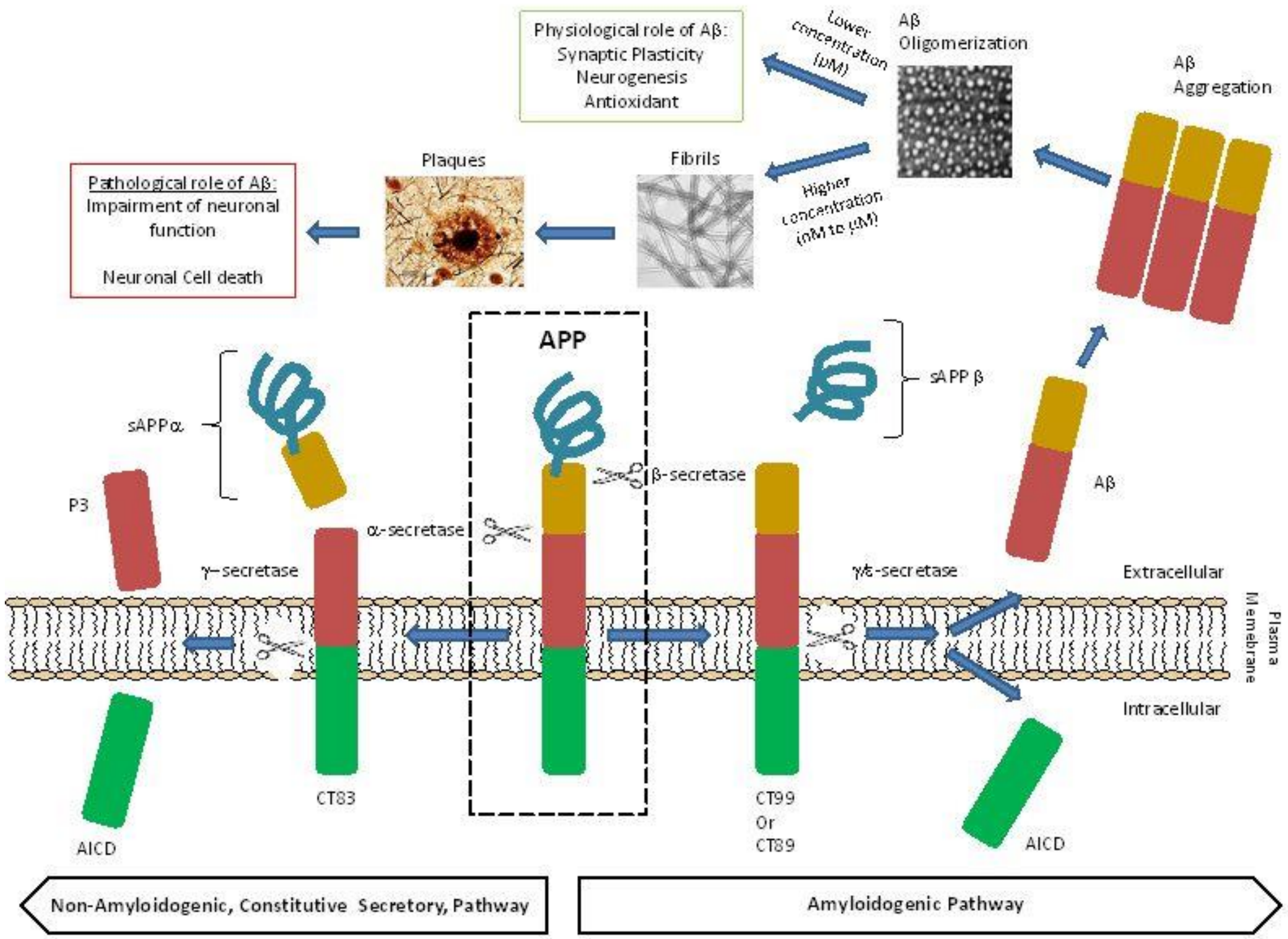
Amyloid B production and breakdown in normal brain



- **Amyloid**-beta **precursor protein** (**APP**) is an integral **membrane protein** expressed in many tissues and concentrated **in the synapses of neurons**
  - it functions as a cell surface receptor and has been implicated as a regulator of synapse formation, neural plasticity, antimicrobial activity, and iron export
  - like all other proteins it wears out and has to be recycled
- There are two pathways for processing APP:
  - **(1) non-amyloidogenic**, constitutive secretory pathway
    - small APP fragments are generated after sequential cleavage by α- and γ-secretase
      - part of the extracellular domain of APP is cleaved by the α-secretases, that belong to the disintegrin and metalloproteinase (ADAM, including ADAM9, ADM10 and ADAM17, also known as TACE), releasing a soluble extracellular fragment know as sAPP-α, that has **neurotrophic and neuroprotective functions**
      - then γ-secretase that is present at the plasma membrane, can generate an intracellular APP fragment that is known as APP intracellular C-terminal domain (AICD)
    - these fragments are easy to dispose of
  - **(2) amyloidogenic pathway**
    - In the amyloidogenic pathway, APP is cleaved by β-secretase (BACE1) at its extracellular domain, giving rise to two fragments; sAPP-β (N-terminal fragment) and CT99 or CT89. Then CT99 could be cleaved by the γ-secretase complex (including Nicastrin, Anterior Pharynx defective 1, Presenilin enhancer 2, Presenilin 1 and or Presenilin 2) within the plasma membrane.
    - These two cleavages (β-secretase and γ-secretase cleavages) generate Amyloid beta (Aβ) and more AICD fragment.
    - The length of the AICD fragment could vary due to heterogeneous γ-secretase cleavage, and subsequent ε-secretase and ζ-secretase activity.
    - AICD has physiological and pathological actions, particularly in signaling from the membrane to the nucleus through epigenetic modulation of gene expression.
    - Moreover inside the cell, AICD fragment can undergo more processing by caspases giving rise to a fragment called CT31, which is a potent inducer of apoptosis

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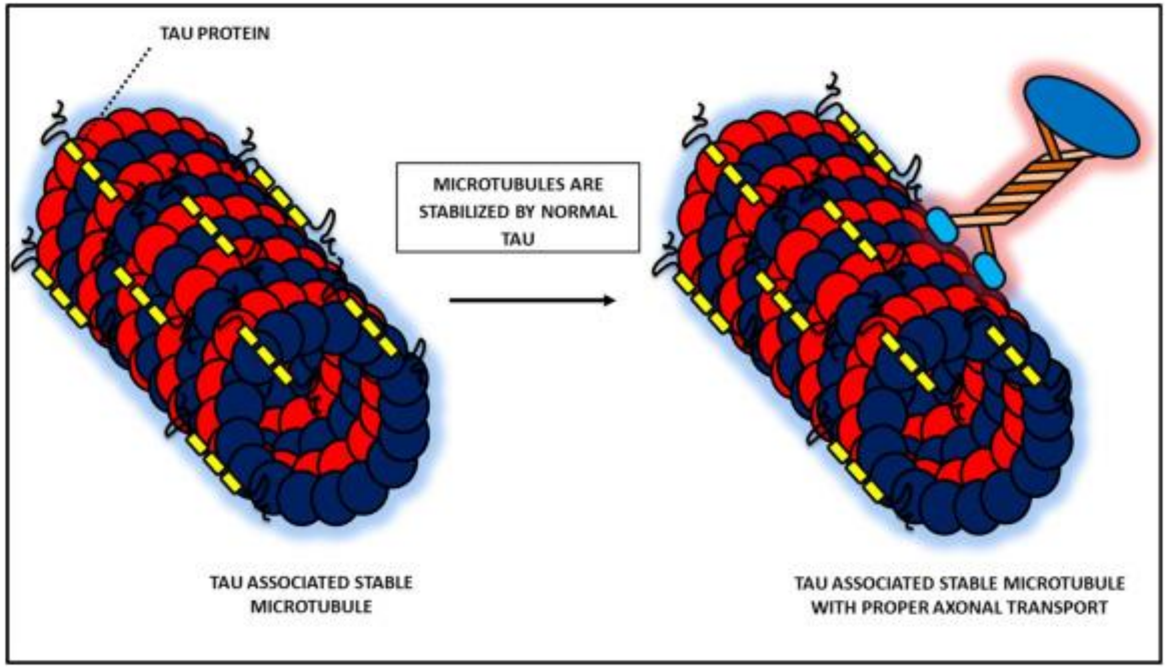
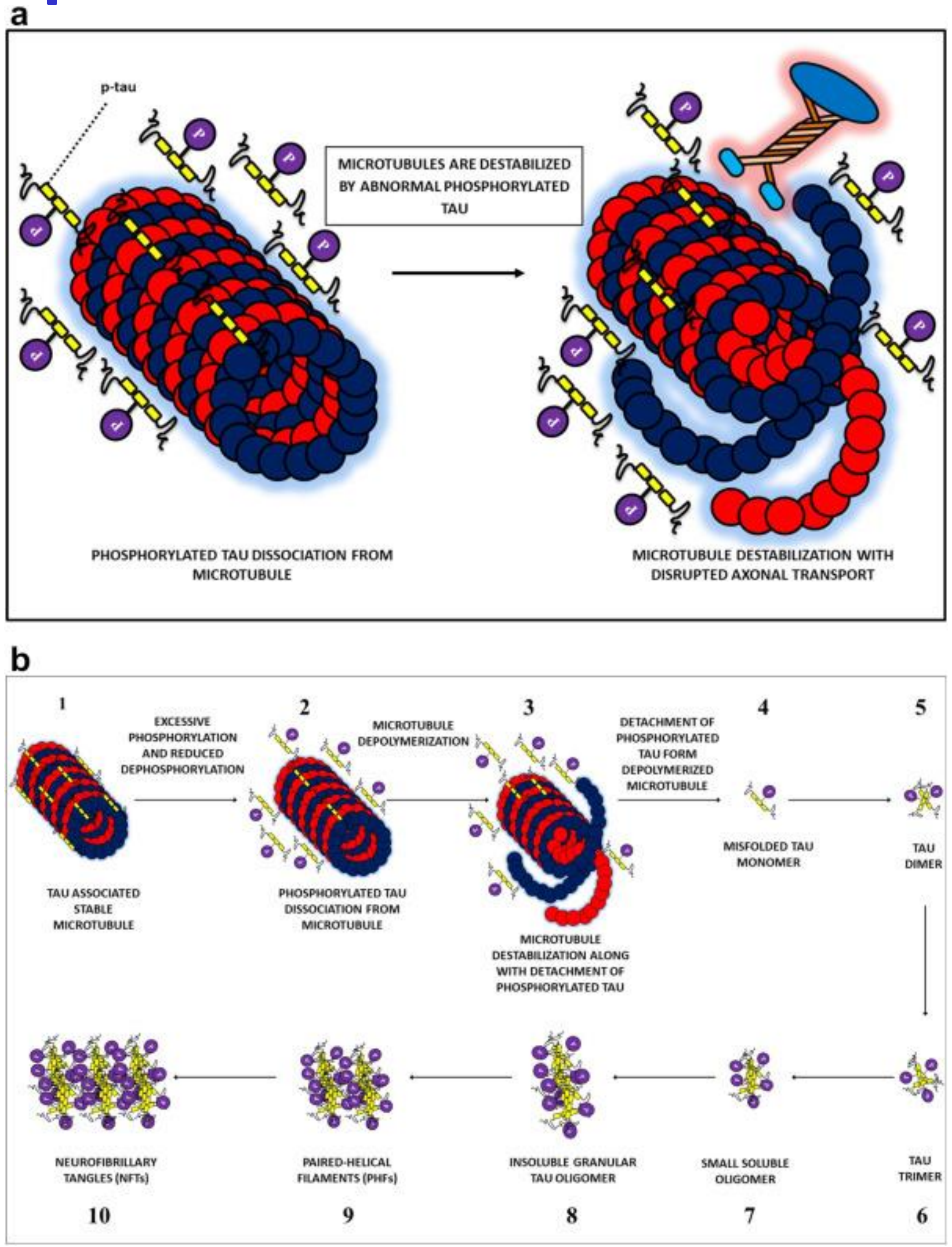
Physiological function of tau protein and its abnormalities





- https://doi.org/10.1016/j.ijbiomac.2020.07.327

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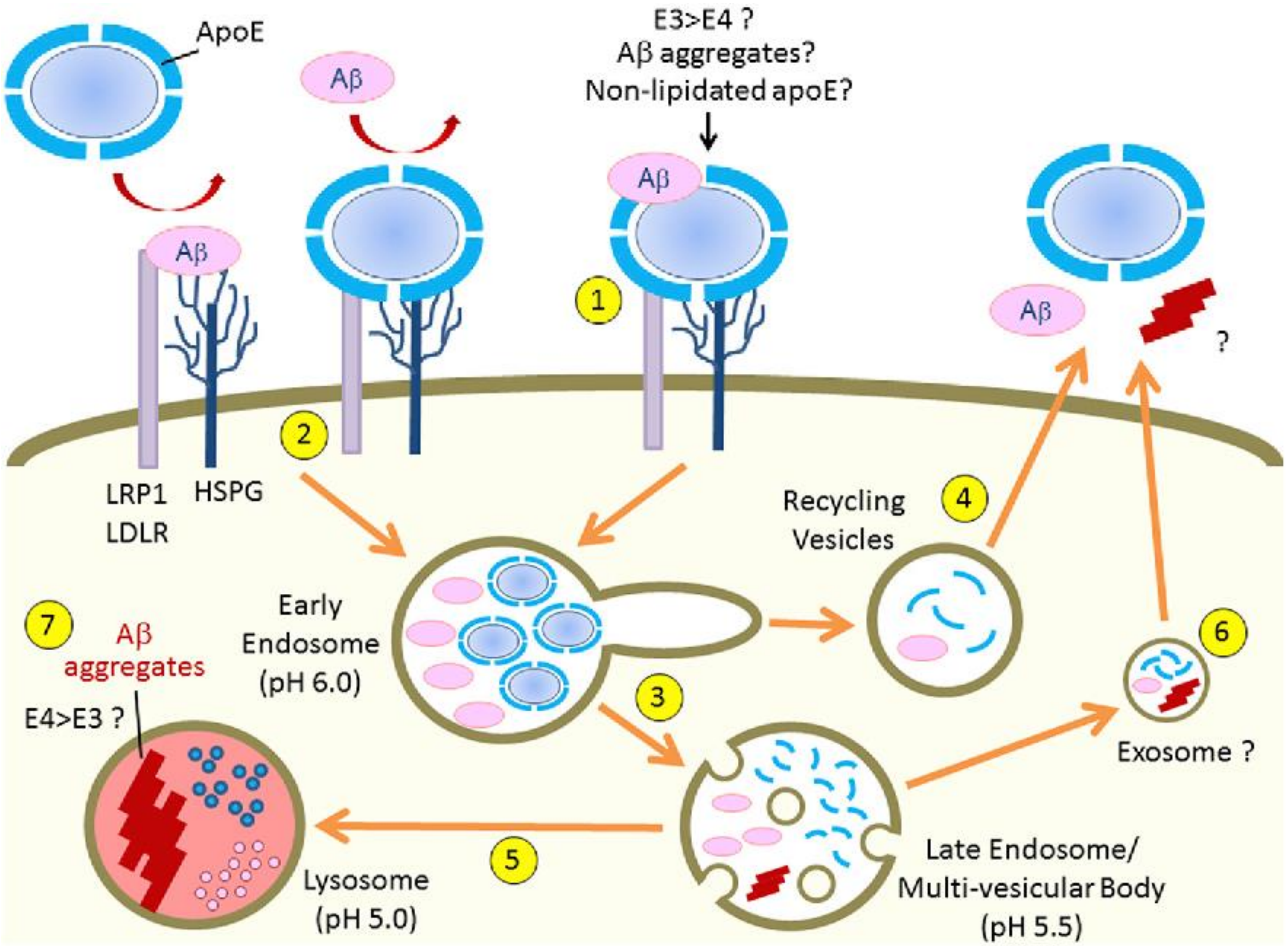
Clearance of Aβ requires ApoE lipoprotein



- There are 3 ApoE alleles in [population
    - ApoE4 confers the risk for AD
- Cell Surface Binding and Endocytic Trafficking of apoE and Ab ApoE probably binds to Ab in an isoform-dependent manner with apoE3 forming more stable apoE/Ab complexes than apoE4
- LRP1, LDLR, and HSPG are major cell surface receptors that bind apoE, Ab, and apoE/Ab complexes
- In addition to forming a stable complex with Ab (1), apoE probably competes with Ab to common cell surface receptors (2)
- Endocytosed apoE either dissociates from lipid components within the early endosomes due to lower pH (3) and recycles (4) or is transported to lysosomes for degradation (5)
- Endocytosed Ab is typically delivered to lysosomes for degradation (5), although a small amount of Ab can be recycled (4)
- In some conditions, apoE and Ab may be transferred through exosomes from the late endosomes/multivesicular body (6)
- When Ab accumulation overwhelms the capacity of lysosomes for degradation, the low pH in the lysosomes provides a suitable environment to initiate Ab aggregation (7) , which could injure lysosomes and also provide seeding for further Ab aggregation

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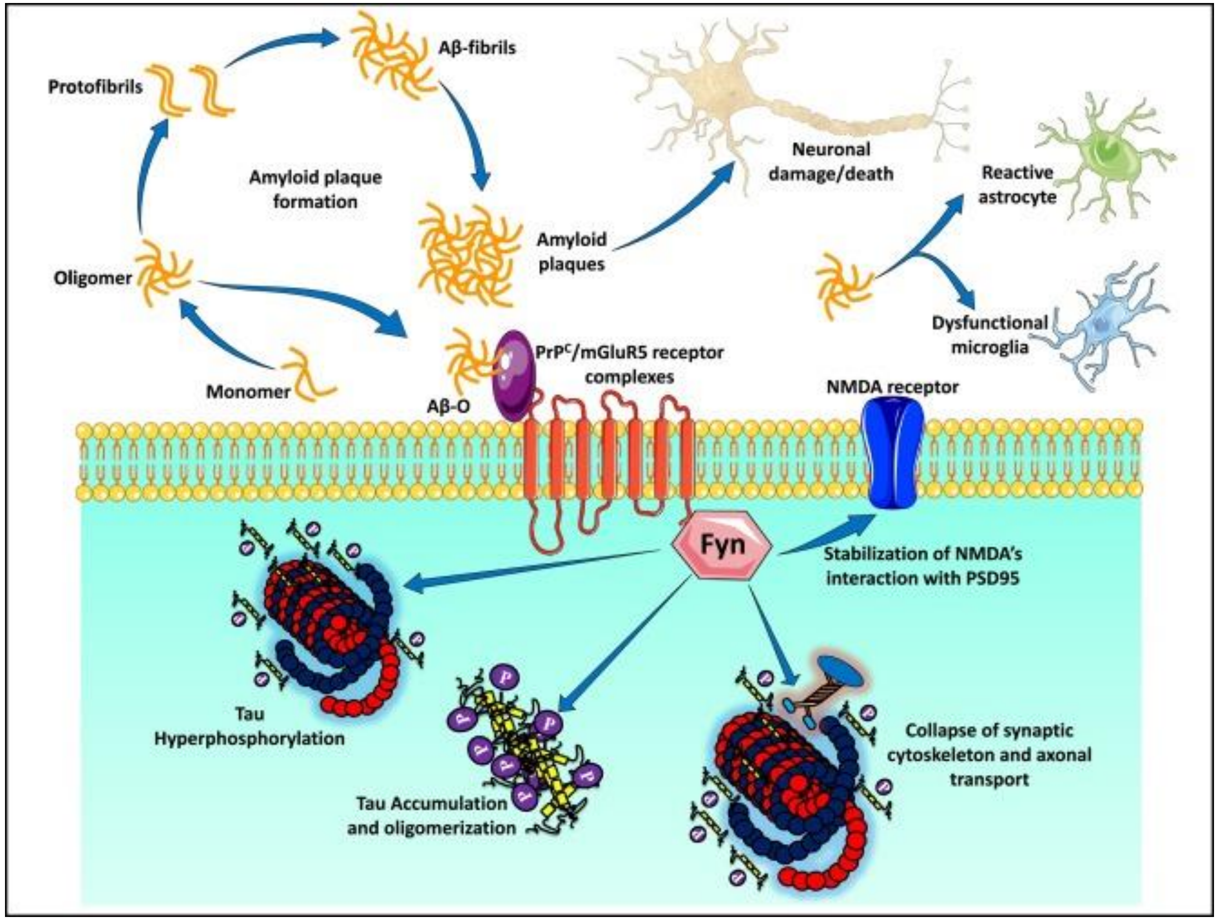
Aβ production and breakdown in normal brain

- Widespread deposition of Aβ plaques in the neocortex (particularly in medial prefrontal and medial parietal regions) and a hierarchically organized pattern of neurofibrillary tangles (composed largely of tau aggregates) in limbic and cortical association areas are the neuropathologic hallmarks of AD
- cortical plaques are widespread 10–20 years before clinical symptoms emerge, and both autopsy-based and recent Aβ positron emission tomography (PET) studies suggest that up to 40% of cognitively normal individuals have profuse plaque deposition in the brain
- current disease models
  - ‘linear’ model
    - suggest that Aβ—either as plaques or as non-fibrillar, soluble, oligomeric forms—initiates a pathophysiological cascade leading to tau misfolding and assembly that spreads throughout the cortex, ultimately resulting in neural system failure, neurodegeneration and cognitive decline.
  - both pathologies have synergistic effects



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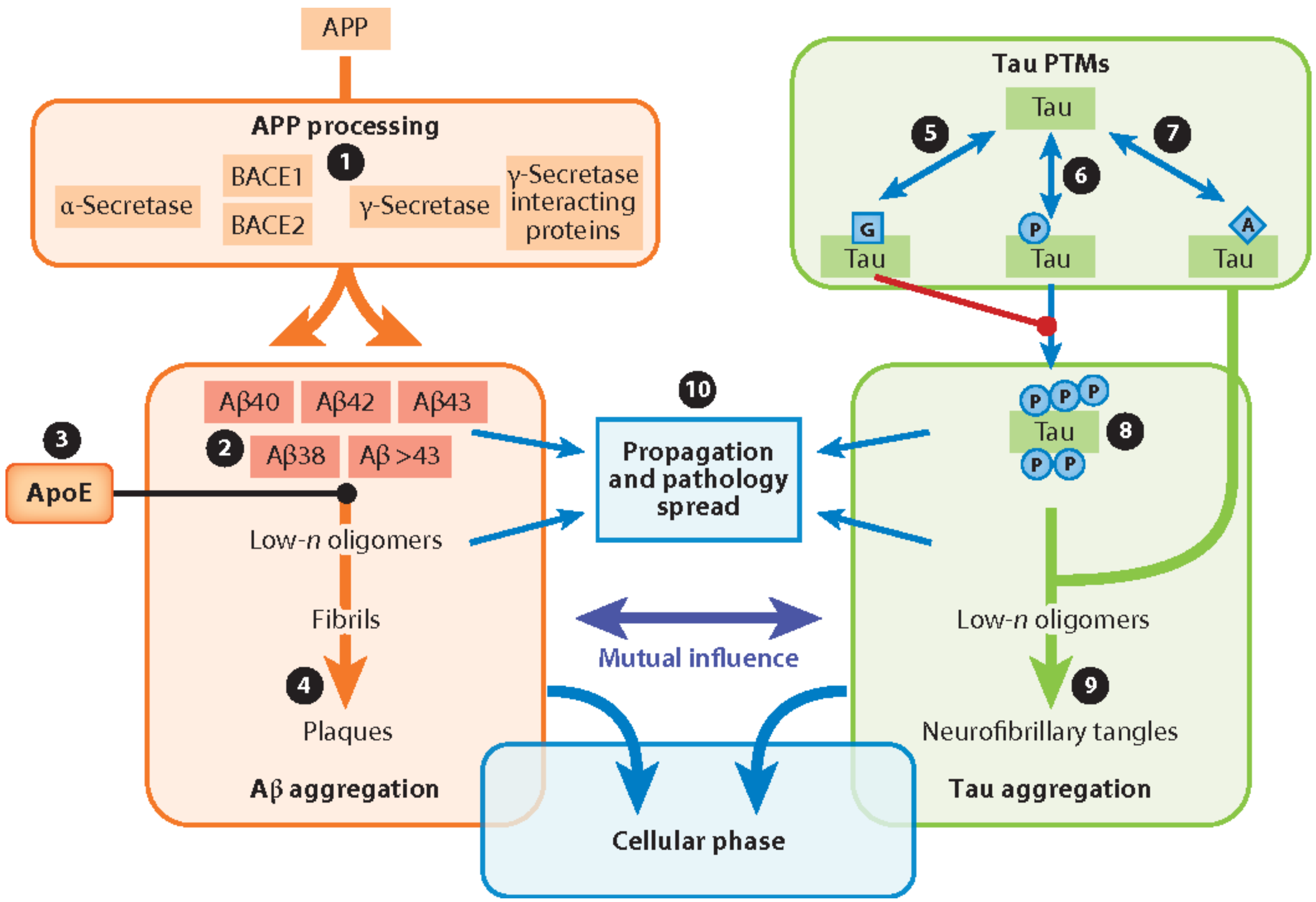
AD = beta-amyloid and Tau-proteinopathies



- The amyloid cascade hypothesis posits that Aβ aggregation is the starting point of a series of events ultimately leading to AD.
- Aβ originates from the sequential cleavage of APP by BACE1 and γ-secretase.
- Gradual formation of Aβ low-*n* oligomers and their build up into dynamic, higher-order aggregates impacts synaptic function first and leads progressively to tau hyperphosphorylation, aggregation, and intracellular deposition; elicits neuroinflammation; and ultimately leads to neurodegeneration and dementia.
- Although these steps are proposed to proceed in a mostly linear timeline, researchers increasingly appreciate the fact that Aβ and tau pathology may well start and proceed independently, eventually feeding into each other

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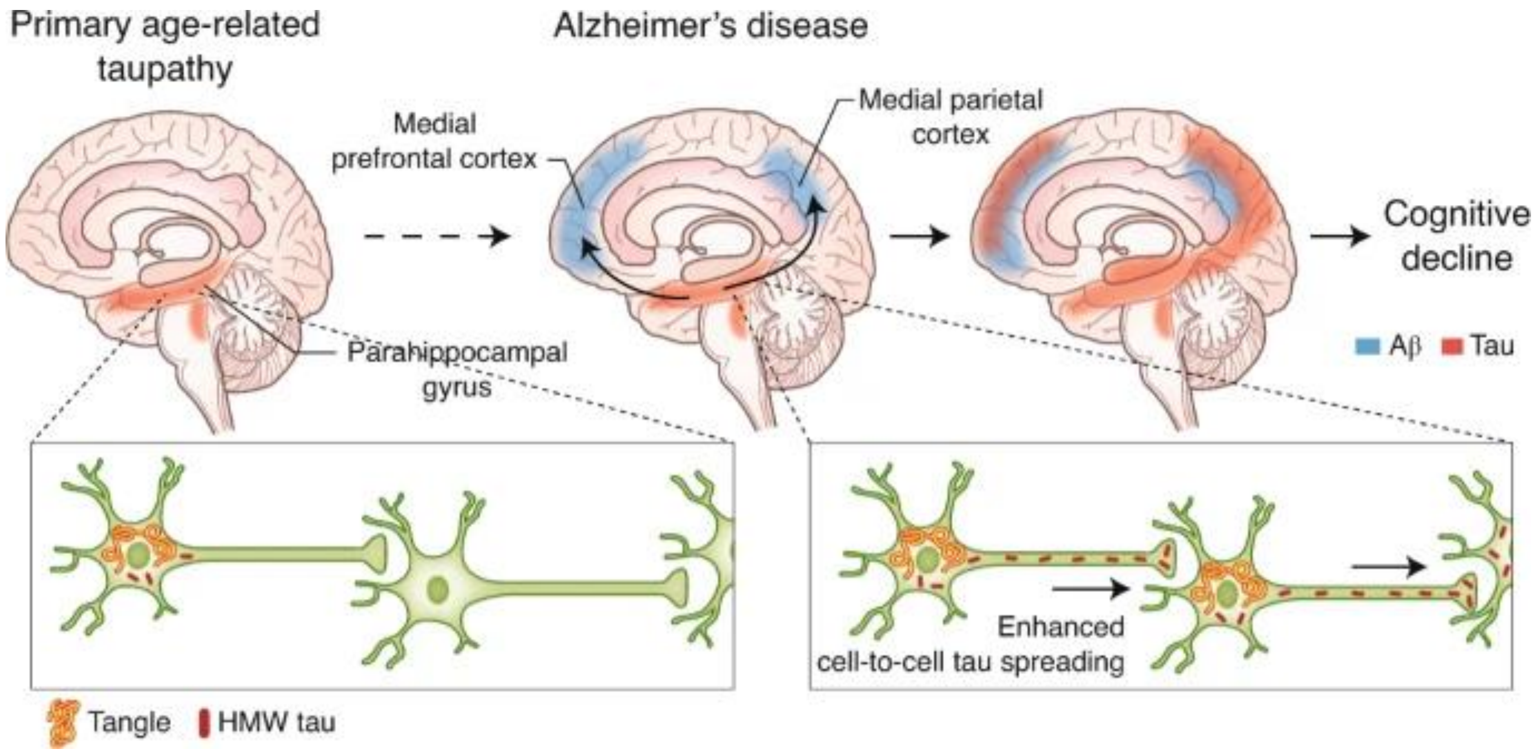
Mechanism of protein spreading in AD



- tau tangles (red) in the absence of concurrent cortical plaques are present in brain stem nuclei (for example, locus coeruleus) and the parahippocampal gyrus, which includes the EC, of many cognitively normal aged individuals (i.e., those with primary age-related tauopathy).
- In AD, the presence of cortical plaques (blue) correlates with neuronal tau propagation from the parahippocampal gyrus into neocortical areas, including medial parietal and medial prefrontal cortex
- Bottom: human AD cases with plaques and tangles show a dramatically enhanced formation and propagation of bioactive, HMW forms of tau (right) relative to human cases with tangles alone

Busche, M.A., Hyman, B.T. Synergy between amyloid-β and tau in Alzheimer's disease. *Nat Neurosci* **23,** 1183–1193 (2020). https://doi.org/10.1038/s41593-020-0687-6

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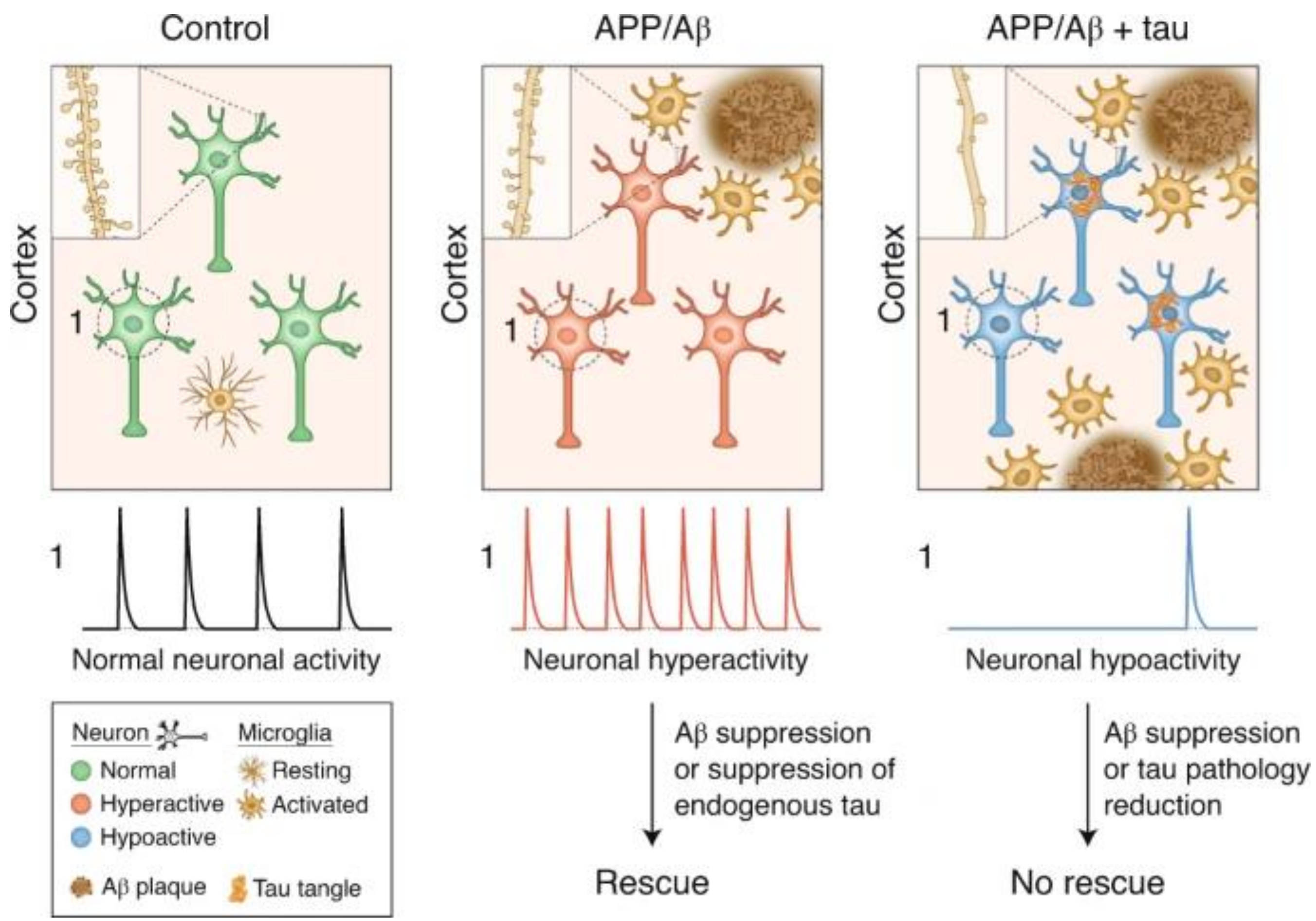
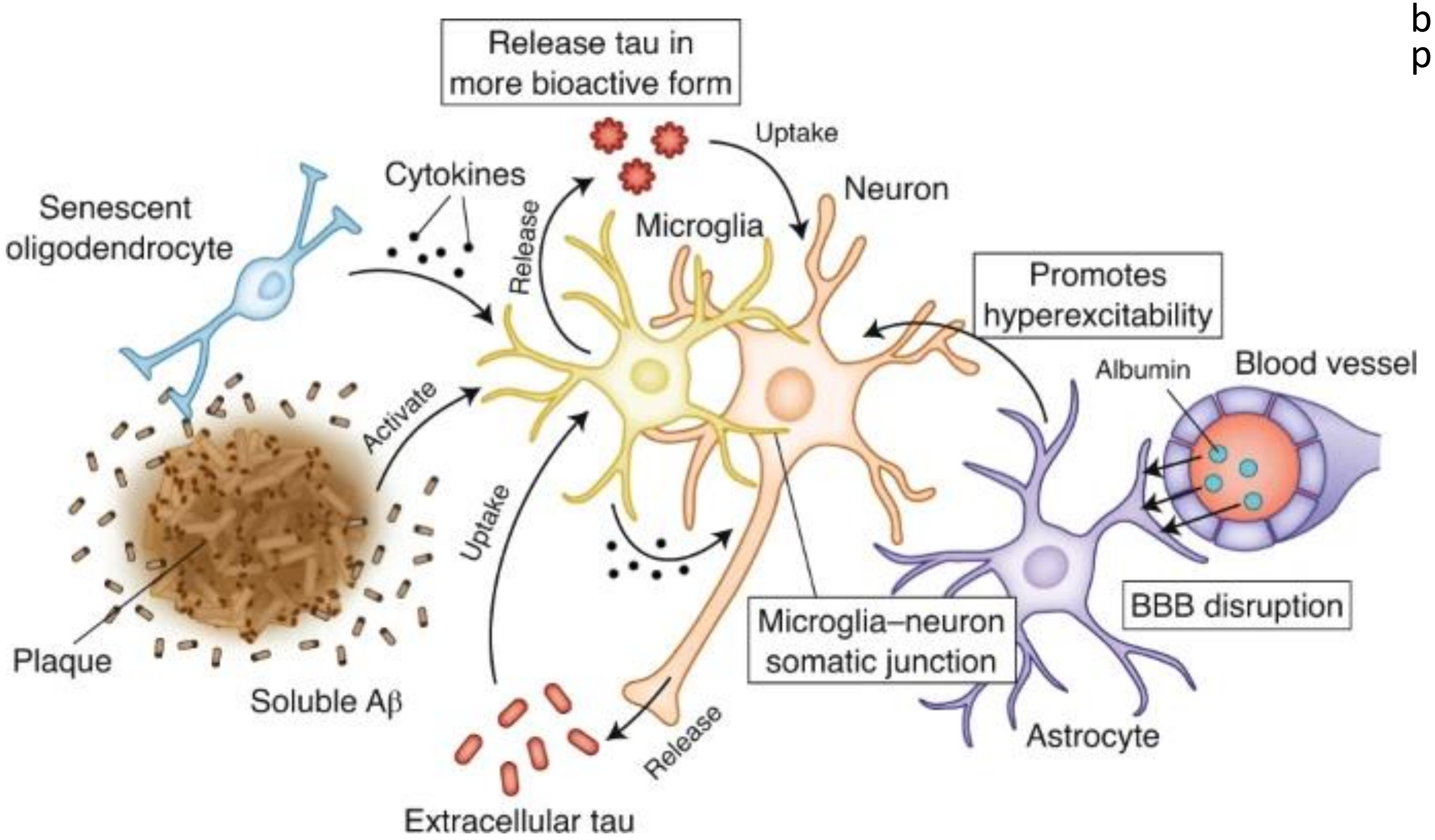
The interaction between Aβ and tau enhances neural circuit impairment – both lesions are necessary!!!



- Compared to the healthy brain (left), the cellular microenvironment adjacent to plaques (middle) is characterized by hyperactive neurons, microglia activation and spine loss (inset)
- The impairments are largely reversible following suppression of Aβ or endogenous tau
- In vivo multiphoton imaging has revealed that the combined presence of Aβ and tau pathology in the neocortex (right) is associated with suppressed neuronal activity, as well as with enhanced microglia activation and spine loss
- Suppression of Aβ or tau pathology alone is not effective in rescuing these functional impairments

Busche, M.A., Hyman, B.T. Synergy between amyloid-β and tau in Alzheimer's disease. *Nat Neurosci* **23,** 1183–1193 (2020). https://doi.org/10.1038/s41593-020-0687-6

Microglia may be critical intermediaries of Aβ–tau synergy



- Depicted are mechanisms by which microglia might contribute to enhanced bioactivity and spreading of tau in the presence of Aβ
  - Soluble Aβ and other factors, such as release of cytokines by senescent oligodendrocytes near plaques, can activate microglia
  - Activated microglia may take up tau, process it and release it in a more bioactive form
  - Neurons may take up released tau (possibly through an interaction with LRP1) and, in turn, release tau into the neuropil in an activity-dependent manner
  - Neuronal activity is enhanced by multiple mechanisms, including Aβ-mediated block of glutamate reuptake, impaired synaptic inhibition or blood–brain barrier (BBB) breakdown resulting in extravasation of neurotoxic products (for example, albumin, illustrated) and activation of astrocytic TGF-β signalling
  - Additional mechanisms by which microglia might contribute to tau seeding and propagation include the release of cytokines, chemokines and nitric oxide that enhance tau phosphorylation and perhaps direct transfer through microglia–neuron somatic junctions

Busche, M.A., Hyman, B.T. Synergy between amyloid-β and tau in Alzheimer's disease. *Nat Neurosci* **23,** 1183–1193 (2020). https://doi.org/10.1038/s41593-020-0687-6

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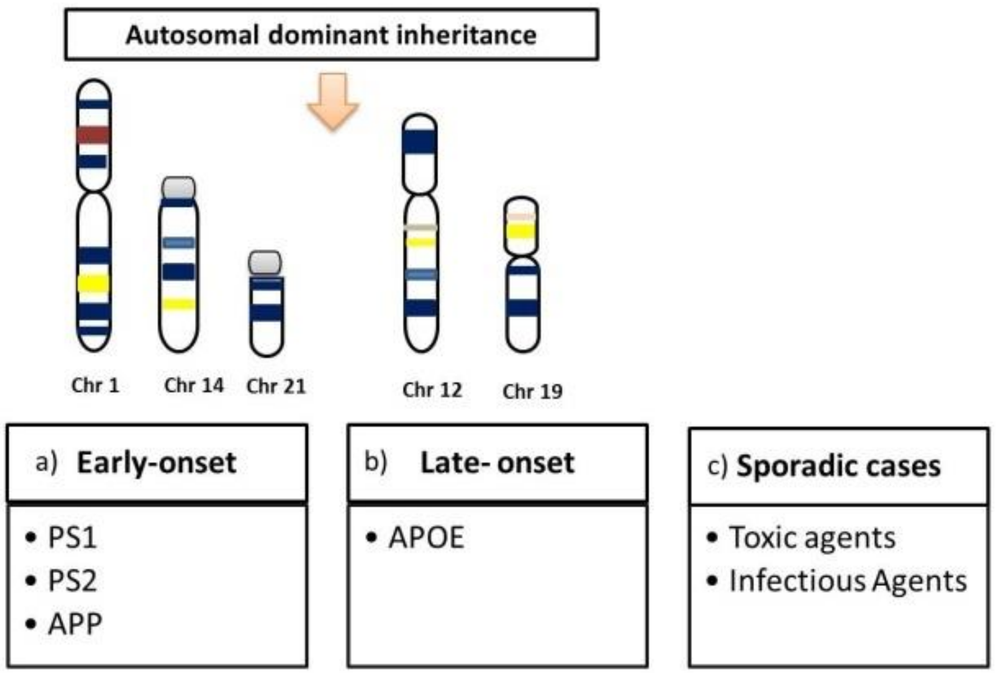
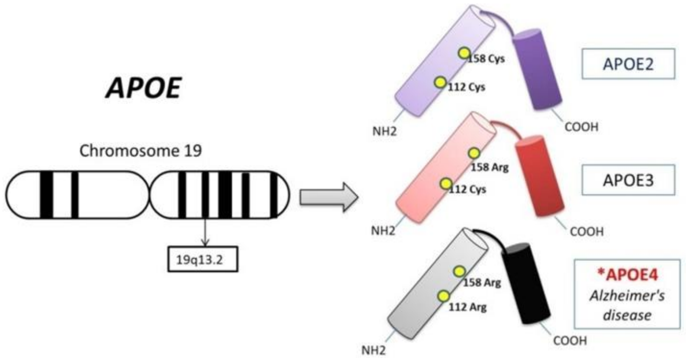
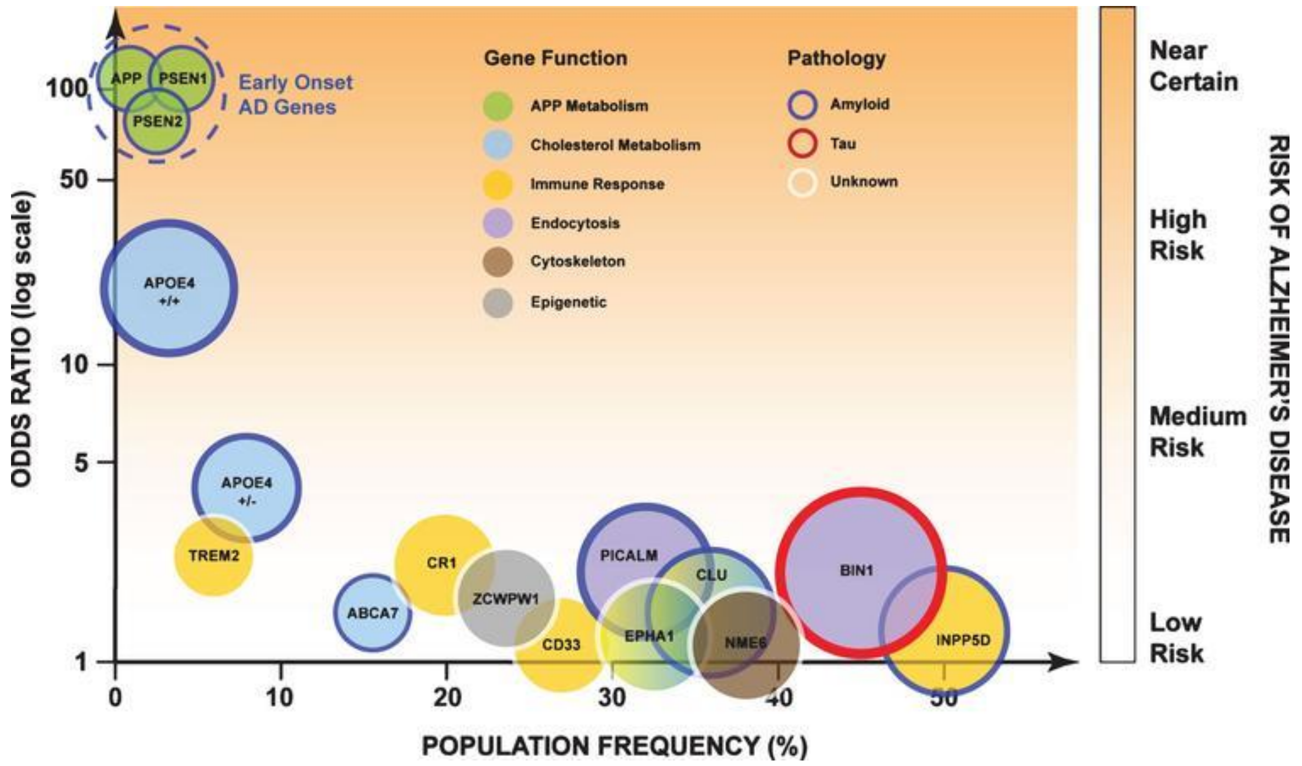
Genetics of AD



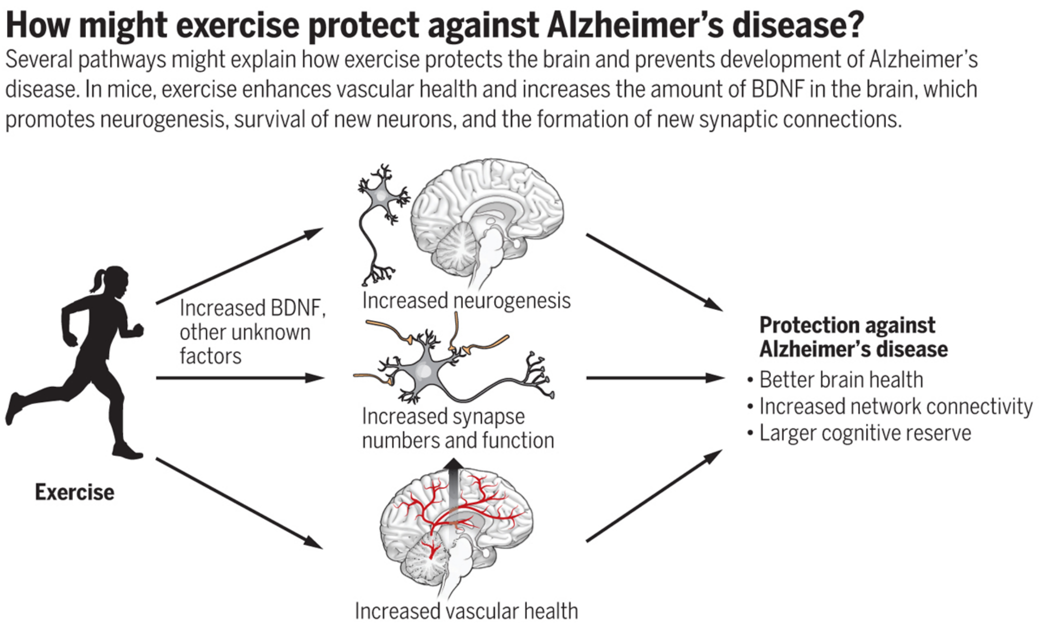




Genetic risk factors for AD according to GWAS and their general role in physiological function. High risk genes are associated with increased severity of the disease and earlier age of onset, with low risk genetic factors age of onset is delayed and disease severity is less. The area of each circle is proportional to each genes' population attributable fraction (PAF). "Larger" genes have a greater influence of AD within the population.

Alzheimer’s disease - symptoms

- **Memory**
  - memory loss is the key symptom of AD
  - repeated statements and questions, lost in conversations, forgotten appointments or events, routinely misplaced possessions, getting lost in familiar places, forgetting the names of family members and everyday objects, trouble finding the right words to identify objects, express thoughts or take part in conversations
- **Thinking and reasoning**
  - especially about abstract concepts such as numbers, multitasking is especially difficult, challenge to manage finances
- **Making judgments and decisions**
  - making poor or uncharacteristic choices in social interactions, wearing inappropriate clothes, food burning on the stove or unexpected driving situations
- **Planning and performing familiar tasks**
  - planning and cooking a meal or playing a favorite game, inability to perform basic tasks such as dressing and bathing
- **Changes in personality and behaviour**
  - depression, apathy, social withdrawal, mood swings, distrust in others, irritability and aggressiveness, changes in sleeping habits, wandering, loss of inhibitions, delusions (such as believing something has been stolen)
- **Preserved skills**
  - reading or listening to books, telling stories and reminiscing, singing, listening to music, dancing, drawing, or doing crafts



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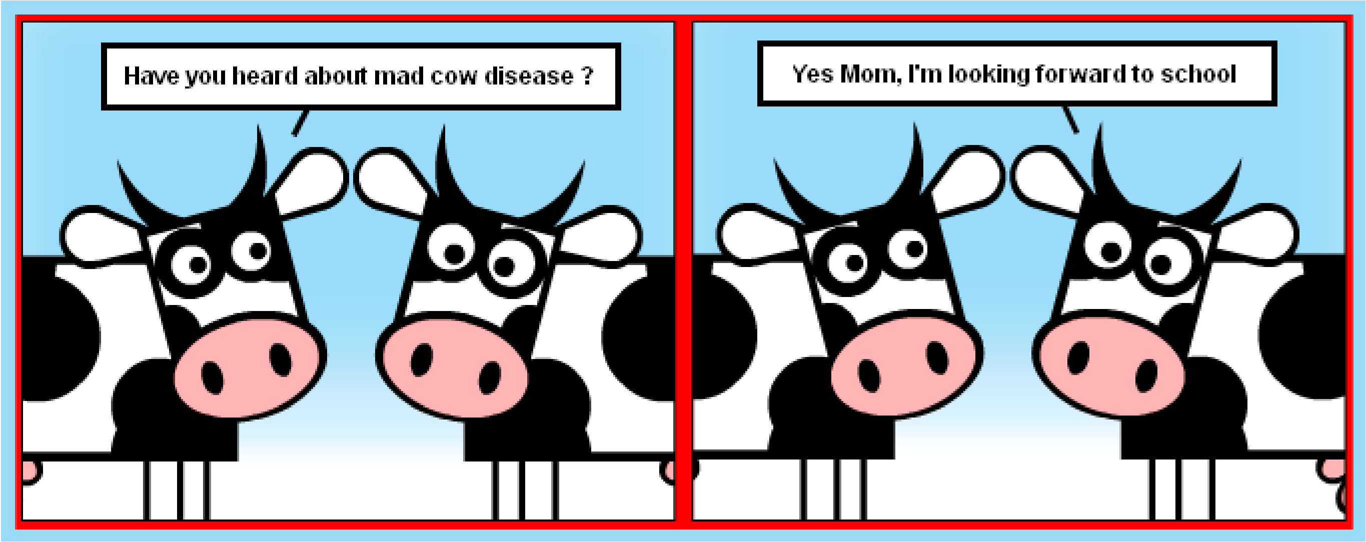
Have you heard about mad cow disease ?
Yes Mom, I'm looking forward to school