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# Overview and Current Status of Alzheimer´s Disease

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# Alzheimer´s Disease

First described by Dr. Alois Alzheimer in 1906, when conducting an autopsy on Augste Deter, who presented 5 years earlier with rapidly increasing memory impairment and behavioral changes.

He described the 2 defining pathological features of AD: amyloid plaques and neurofibrillary tangles.

# The **NINCDS-ADRDA Alzheimer's Criteria 1984**

Proposed in 1984 by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association) and are among the most used in the diagnosis of Alzheimer's disease (AD).

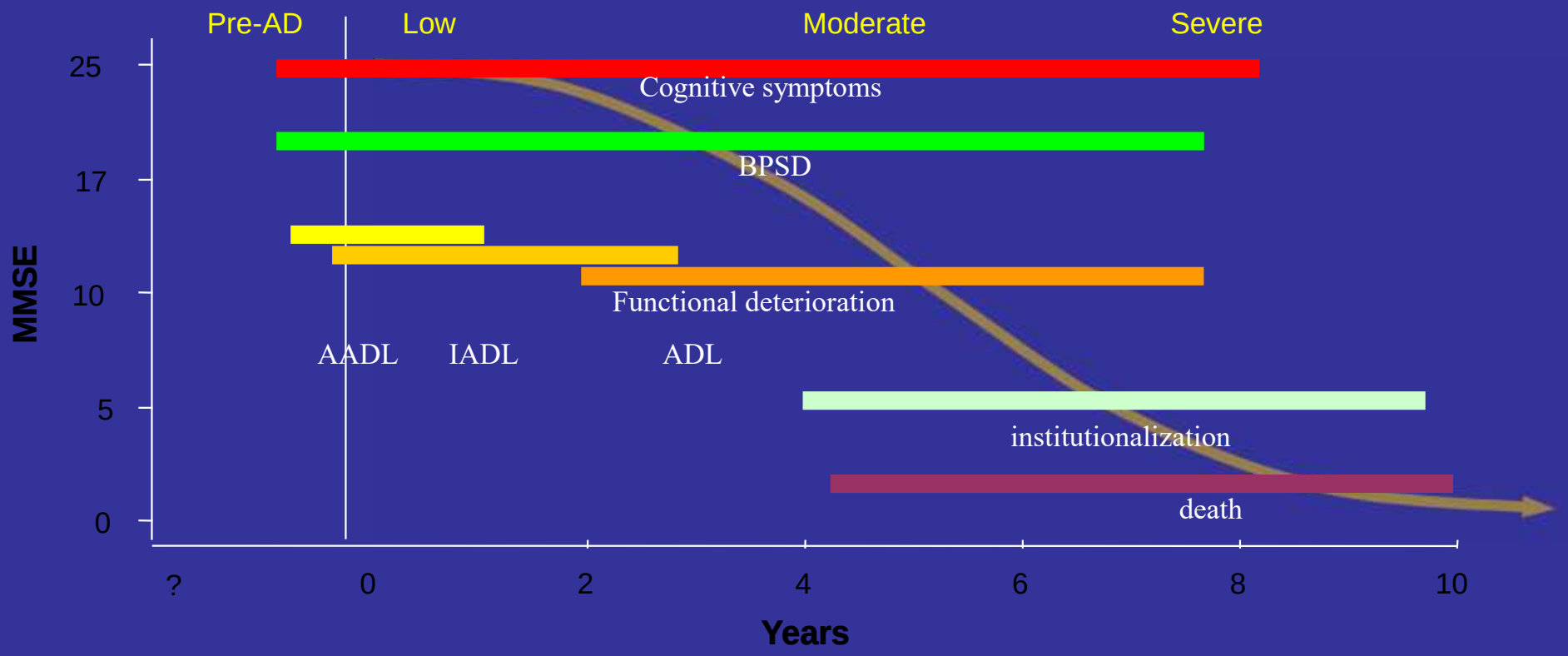
These criteria require that the presence of cognitive impairment and a suspected dementia syndrome be confirmed by neuropsychological testing for a clinical diagnosis of possible or probable AD; while they need histopathologic confirmation for the definitive diagnosis. They specify as well eight cognitive domains that may be impaired in AD. These criteria have shown good reliability and validity. The NINCDS-ADRDA Alzheimer's Criteria specify eight cognitive domains that may be impaired in AD: memory, language, perceptual skills, attention, constructive abilities, orientation, problem solving and functional abilities.

**Definite Alzheimer's disease**: The patient meets the criteria for probable Alzheimer's disease and has histopathologic evidence of AD via autopsy or biopsy.
**Probable Alzheimer's disease**: Dementia has been established by clinical and neuropsychological examination. Cognitive impairments also have to be progressive and be present in two or more areas of cognition. The onset of the deficits has been between the ages of 40 and 90 years and finally there must be an absence of other diseases capable of producing a dementia syndrome.
**Possible Alzheimer's disease**: There is a dementia syndrome with an atypical onset, presentation or progression; and without a known etiology; but no co-morbid diseases capable of producing dementia are believed to be in the origin of it.
**Unlikely Alzheimer's disease**: The patient presents a dementia syndrome with a sudden onset, focal neurologic signs, or seizures or gait disturbance early in the course of the illness.

# Alzheimer’s disease is the most common cause of dementia in old people

- AD is the most frequent neurodegenerative disease with roughly 44 million people affected and growing.
- AD is highly heritable, with estimates ranging between 60% and 80% .
- Lifetime prevalence 5-10%
- Major risk factor is age
    - Prevalence rises from less than 1% at age 65 to over 30% at age 90
- Over 90% of patients are above age 65
- Significantly reduced life expectancy of AD patients
    - 7-10 yrs after diagnosis

# Natural History of AD




Modificata da Gauthier S. ed. Clinical Diagnosis and Management of Alzheimer's Disease. 1996.

# Ten Warning Signs of AD

**Alzheimer's Association: Ten Warning Signs for AD**

- Memory loss that affects job skills
- Difficulty performing familiar tasks
- Problems with language
- Disorientation to time and place
- Poor or decreased judgment
- Problems with abstract thinking
- Misplacing things
- Changes in mood and behavior
- Changes in personality
- Loss of initiative

# Brain Reserve

- **Neurological BR**
  - **Large brain size**
  - **Neuronal numbers**
  - **Complexity of circuitry**
- **Behavioral brain reserve**
  - **Education**
  - **Occupation & its complexity**
  - **Mental activity through life span**

# Vascular risk factors are linked with an increased risk of AD

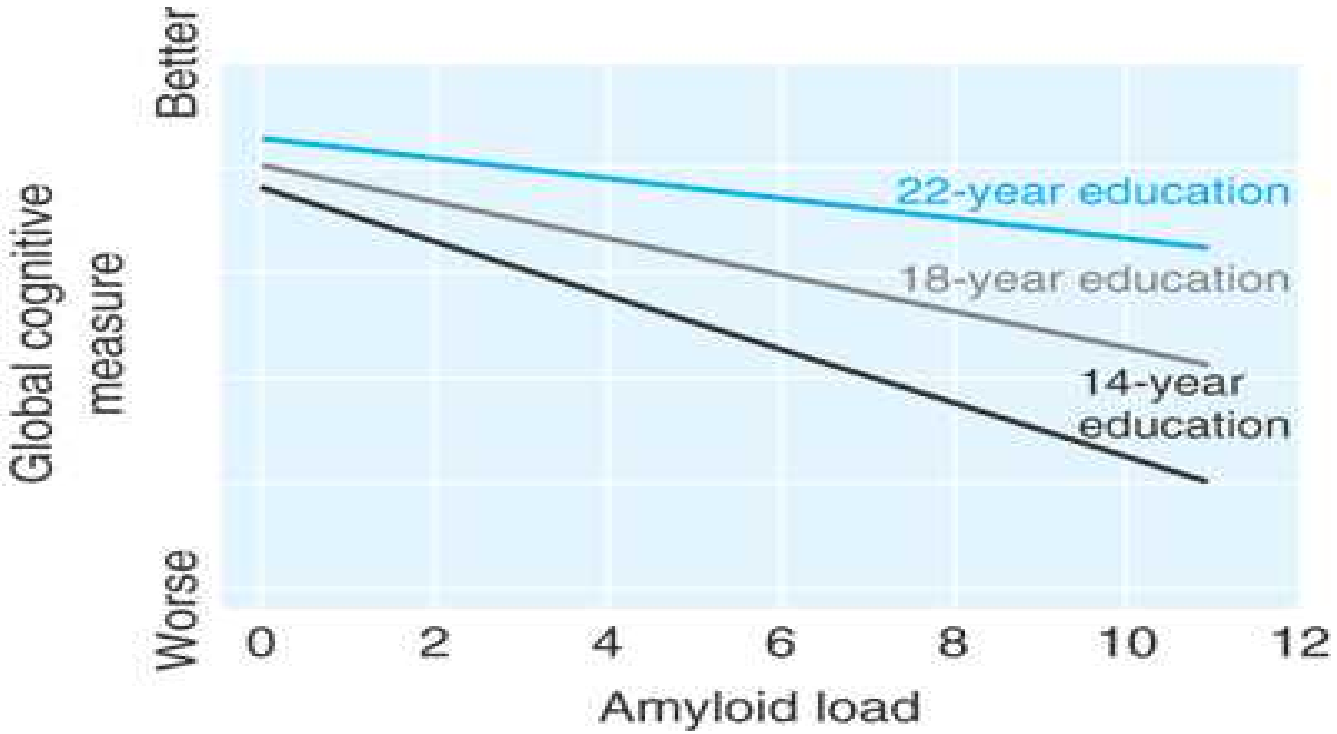
- Midlife hypertension has a stronger association with dementia than late-life blood pressure levels.
- Elevated serum cholesterol levels in midlife also increase the risk of developing AD decades later.
- Risk of AD is also elevated in the presence of diabetes, in particular type 2 diabetes and hyperinsulinemia.

# Influence of education and occupation on the incidence of AD

- The risk of dementia was increased in subjects with either
  - low education RR, 2.02 (1.33-3.06)
  - low lifetime occupational attainment RR, 2.25 (1.32-3.84)

Y. Stern, B. Gurland, T.K. Tatemichi, M.X. Tang, D. Wilder and R. Mayeux, JAMA 1994: 271;1004–1010

# The cognitive impairment associated with amyloidosis is minimized by increasing years of education.

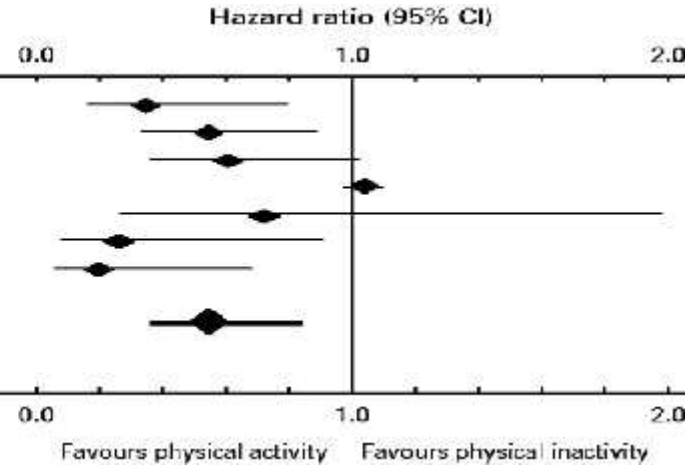



***It is estimated that the difference between 15 years of education and 22 years is equivalent to approximately 2.6 years of amyloid progression***

*Bennett DA et al. Neurology. 2005;65[6]:953–955.*

# The association between physical activity and Alzheimer's disease

| | Author (year) | Exposure | Sample size | Hazard ratio (95% CI) |
|---|---|---|---|---|
| 1 | Ravio *et al.* (2005) ♂♀ | × 2 times/week | 1449 | 0.35 (0.16–0.80) |
| 2 | Podewils *et al.* (2005) ♂♀ | × 2 times/week | 3375 | 0.55 (0.34–0.88) |
| 3 | Abbott *et al.* (2004) ♂ | > 2 miles/day walking | 2257 | 0.61 (0.36–1.02) |
| 4 | Wilson *et al.* (2002) ♂ | × 5 h/week | 1249 | 1.04 (0.98–1.10) |
| 5a | Laurin *et al.* (2001) ♂ | × 3 times/week vigorous | 1831 | 0.73 (0.27–1.98) |
| 5b | Laurin *et al.* (2001) ♀ | × 3 times/week vigorous | 2784 | 0.27 (0.08–0.90) |
| 6b | Yoshitake *et al.* (1995) ♂♀ | Daily physical activity | 826 | 0.20 (0.06–0.68) |
| Total | | | 13 771 | 0.55 (0.36–0.84) |
| Test for heterogeneity | | | | $\chi^2(6) = 29.12$, $p < 0.001$ |
| Test for overall effect | | | | $\chi^2(1) = 7.63$, $p = 0.006$ |




45% less likely to develop dementia if physically active

M. Hamer and Y. Chida, Psychol Med 2009;39:3–11

# Are the neuroprotective effects of exercise training systemically mediated?

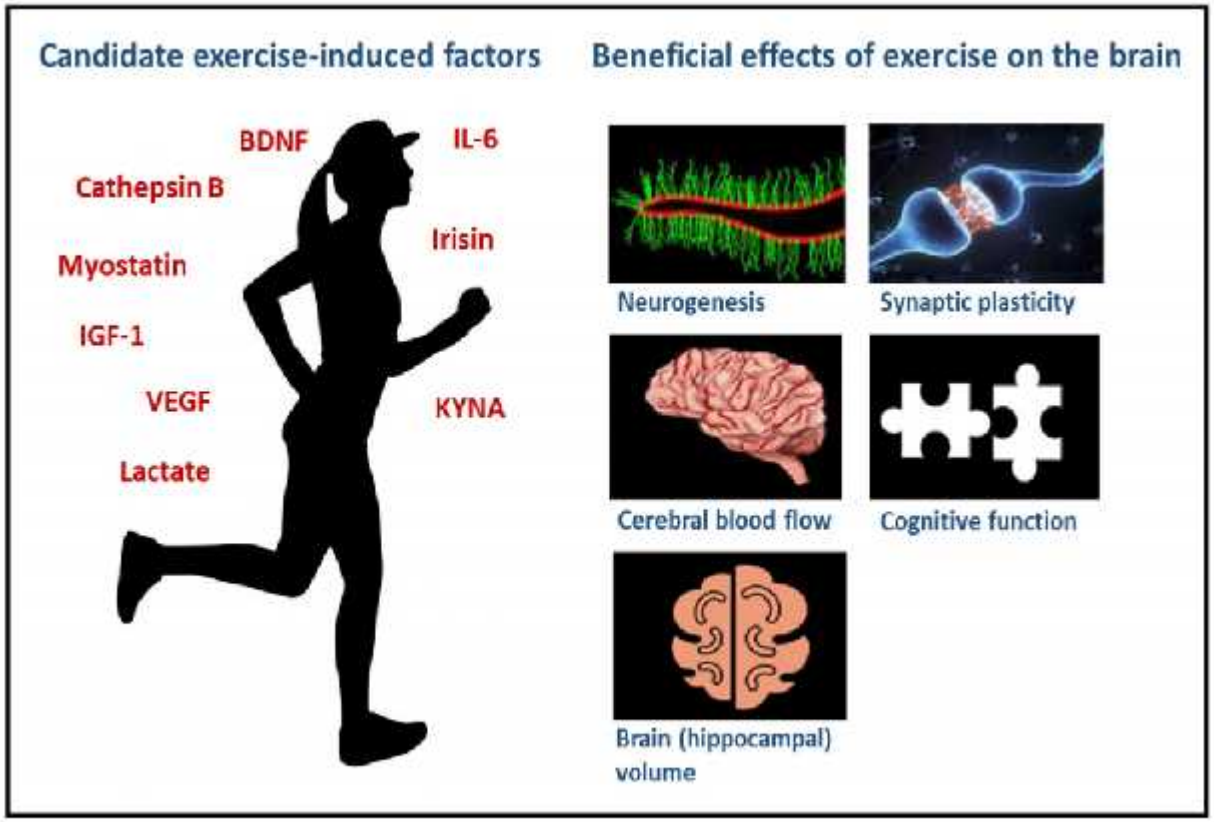



Fig. 1. Candidate factors for PA-induced neuroprotection.

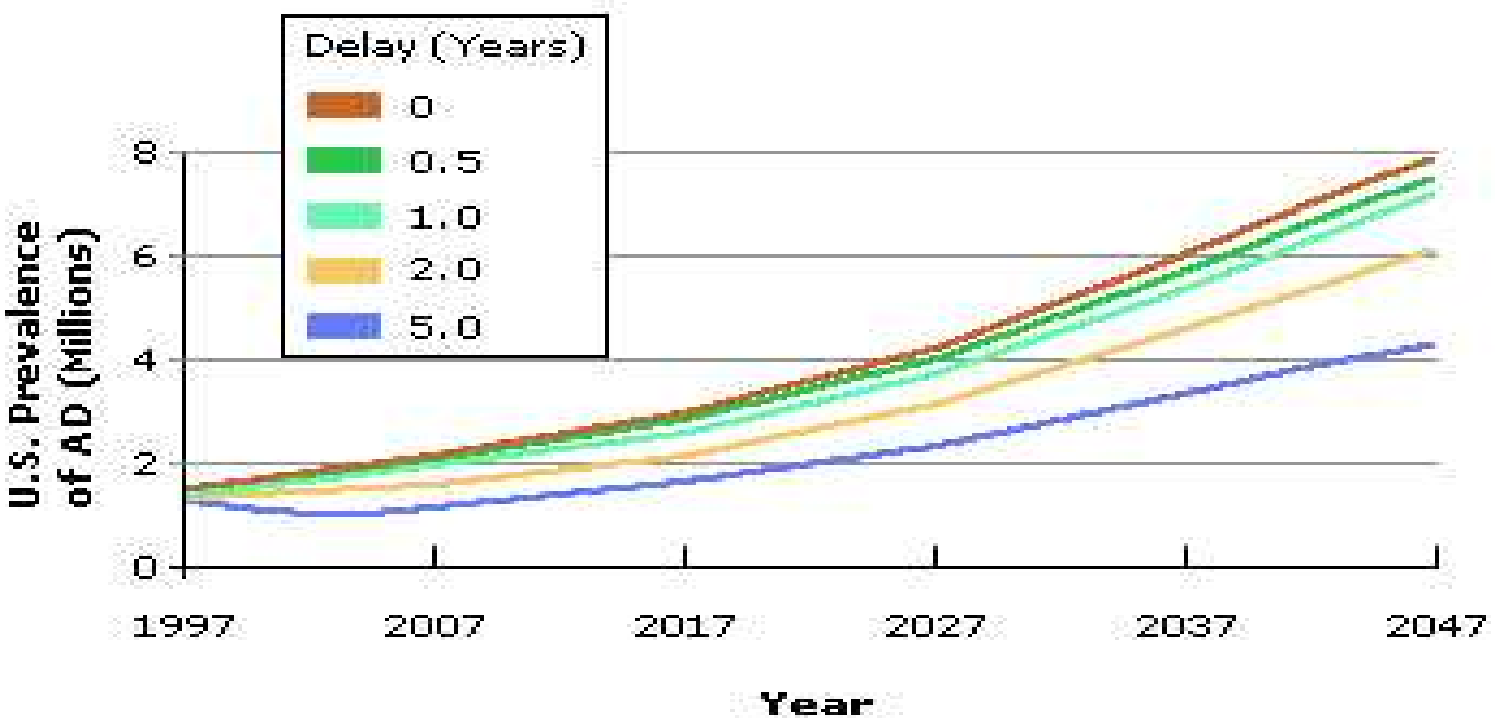
Current literature provides initial evidence that

exercise-induced, blood-borne biomolecules, such as BDNF and FNDC5/irisin, may be powerful agents mediating the benefits of exercise on cognitive function

and may form the basis for new therapeutic strategies to better prevent and treat dementia

A.R. Tari et al. / Progress in Cardiovascular Diseases 62 (2019) 94–101

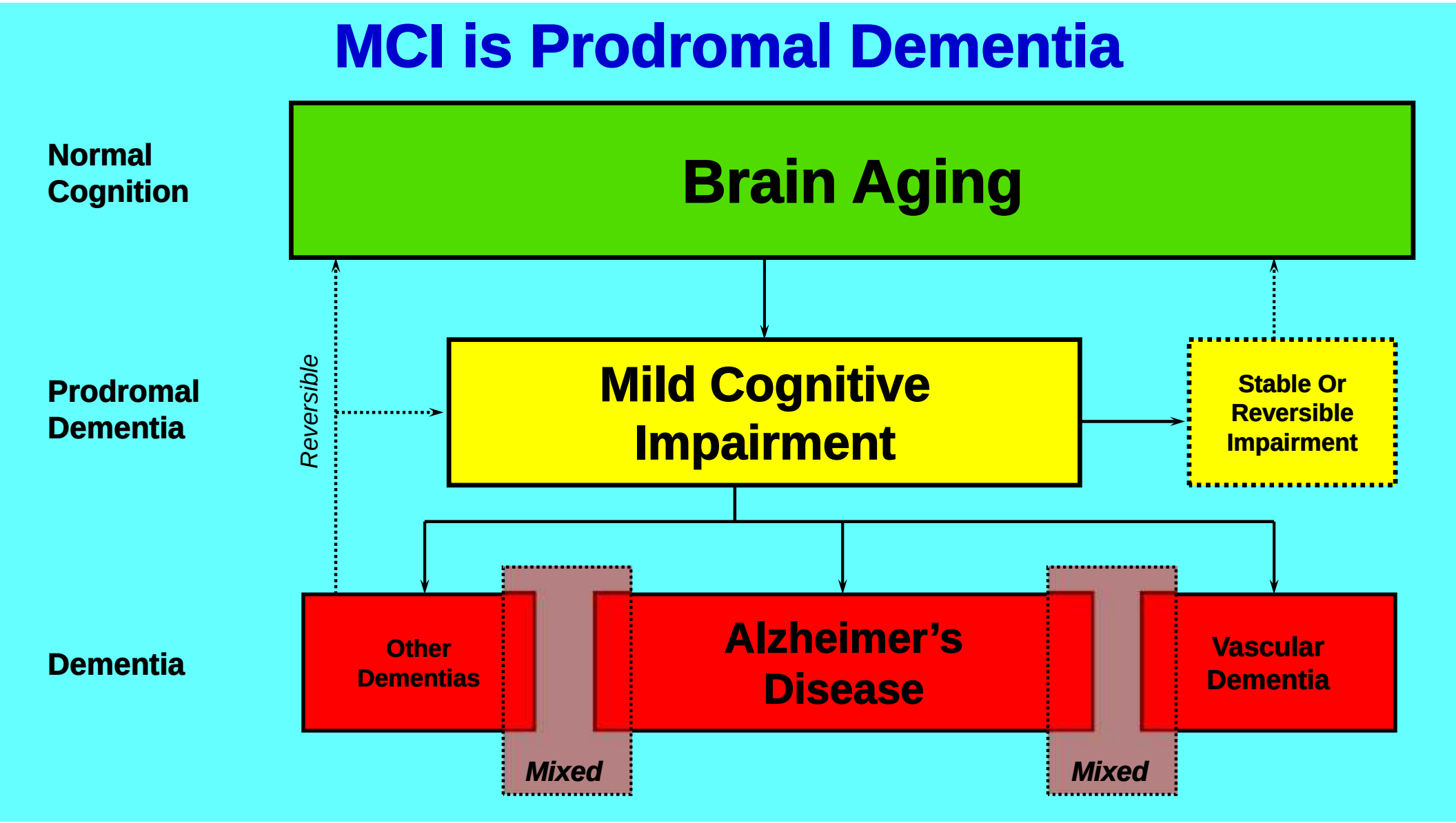
# Delay AD onset ⟶ Prevent AD cases




**50% Reduction**

Brookmeyer et al, 1998

# MCI is Prodromal Dementia



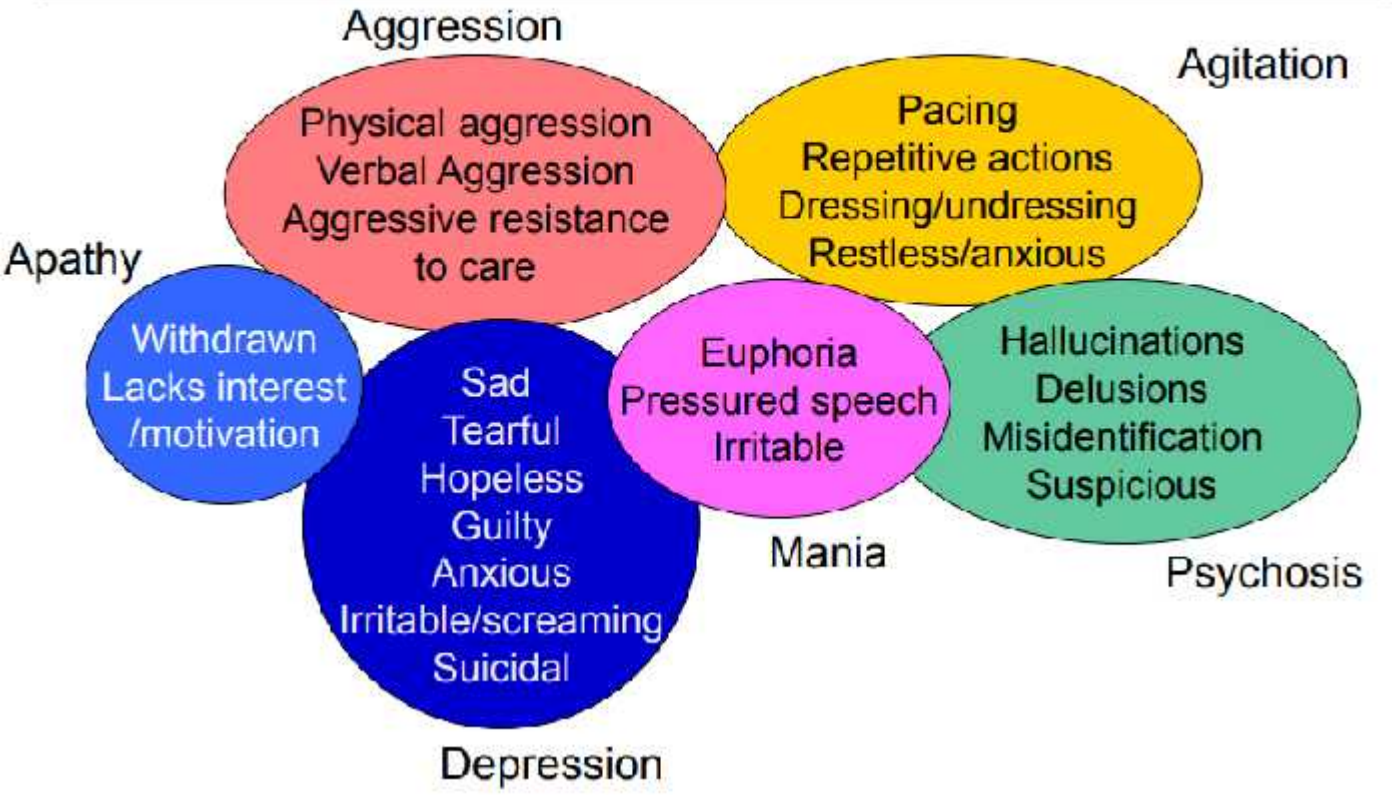
# Cognitive impairment in AD

- Cognitive decline is manifested as the 4As
  - **Amnesia**
  - **Aphasia**
  - **Agnosia**
  - **Apraxia**
- Visiospatial impairment
- Personality Change

# Functional impairment

- Although the cognitive decline in AD is the core symptom, it is the functional deterioration that has the most impact
  - on the person themselves and
  - necessitates most of the care needs of patients with AD, including nursing-home residency.
- In general, functional abilities decline alongside cognitive abilities.
  - Functional abilities are related to gender;
    - cooking abilities are rehearsed more frequently in women
    - home-improvement skills in men
- Instrumental ADLs are lost first and can be subtle.
- Self-care ADLs include dressing and personal hygiene and are also lost gradually

# BPSD Symptom Clusters




Residents with BPSD are more likely to[1]:

- be physically restrained
- receive antipsychotic medication
- negatively influence care staff
- negatively influence other residents

BPSD increase the cost of caring[2]

BPSD increase nurse stress, especially aggression[3]

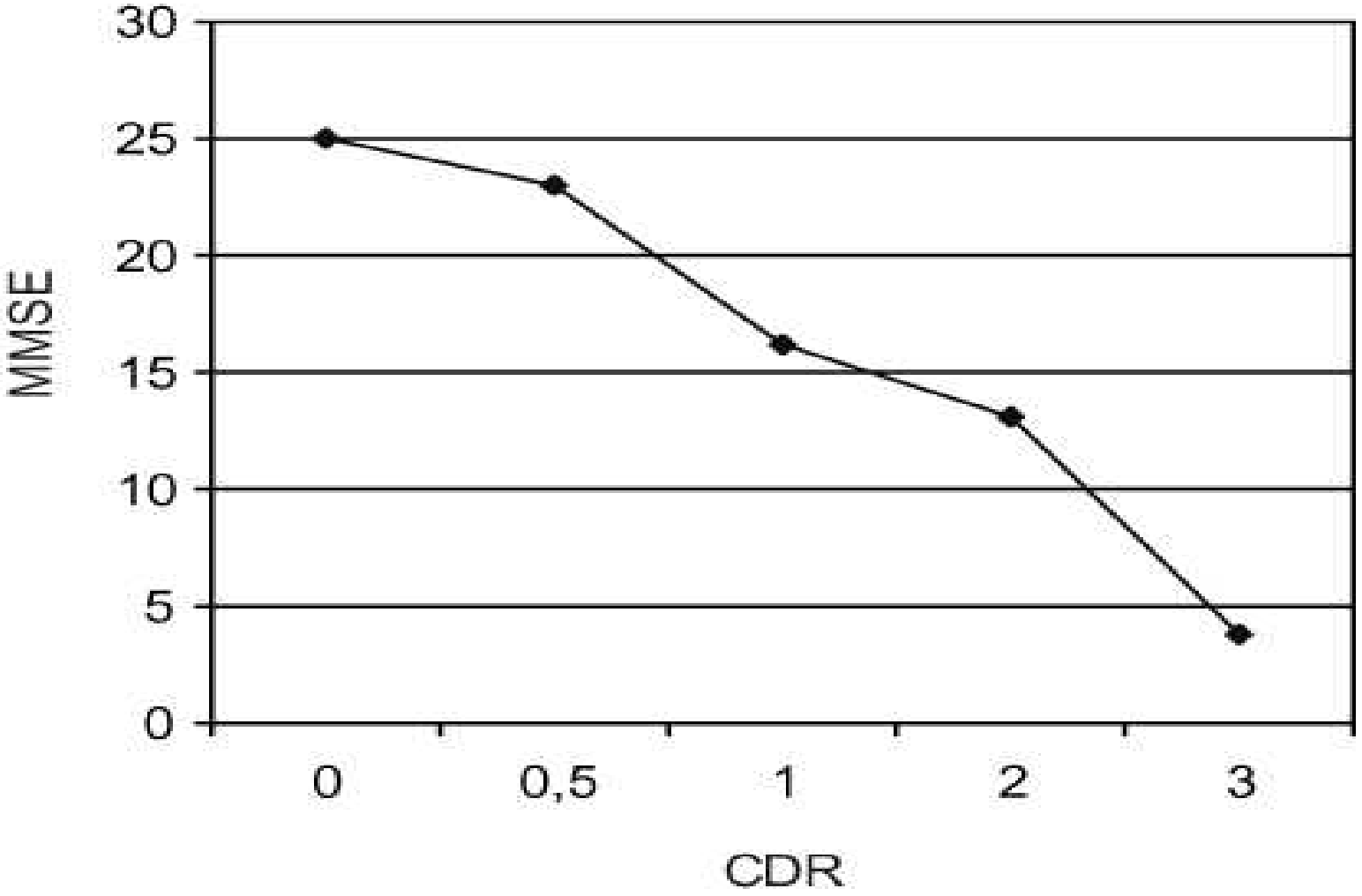
BPSD exacerbates cognitive and functional deficits[4]

BPSD increase morbidity and mortality[5]


1 Maslow K 1994
2 O'Brien JA, Shomphe LA,Caro JJ 2000
3 Rodney, 2000
4 J Clin Psychiatry 2004;65:5-10
5 Arch Neurol 2005;62:1601-8

# The AD progression

- AD is a relentlessly progressive disorder. There are no remissions.
- The first signs are marked by subtle decline in memory.
- As the disease advances, changes in personality and language skills develop.
- Eventually motor functions are impaired.
- Understanding the spread of the pathology of AD gives a greater appreciation of the changing clinical picture.
- The progression of the disease can be staged by the development and progression of neurofibrillary tangles.
  - In a landmark analysis of more than 2,500 brains in Germany over 10 years, Braak documented the insidious evolution of AD.




CDR: *Clinical Dementia Rating*
MMSE: *Mini-mental State Examination*

**Figure 2** - Mean scores on the MMSE according to the CDR classification.

Memory
Orientation
Judgment and
Problem solving
Community affairs
Home and hobbies
Personal care

# Stages of Dementia Described by the Global Deterioration Scale.

*Table 1.* **Stages of Dementia Described by the Global Deterioration Scale***

| Global Deterioration Scale Stage | General Features |
|---|---|
| 1 | No subjective symptoms or clinical evidence of memory deficit. |
| 2 | Subjective symptoms of memory deficit, such as forgetting the location of familiar objects or previously well-known names. |
| 3 | Early, clear-cut memory deficits, such as getting lost, poor work performance, problems with word or name finding, misplacing objects of value, or poor retention of written material. |
| 4 | Clear-cut memory deficits, such as poor knowledge of current events, difficulty remembering details of personal history, impaired concentration doing serial subtractions, and inability to handle finances or travel to new places. Frequently, there is no deficit in orientation to time and place, recognition of familiar faces, or travel to familiar locations. |
| 5 | Can no longer function without some assistance. Unable to recall major aspects of current life (e.g., address, telephone number, names of family members). May need assistance dressing, but still independent in eating and toileting. |
| 6 | Occasionally forgets name of primary caregiver (e.g., spouse). Largely unaware of recent personal events. Substantial assistance required with activities of daily living and travel to familiar locations. Often unaware of surroundings (e.g., year or season). Can still recall his or her own name and distinguish a familiar face. |
| 7 | Unable to recognize familiar faces, verbal abilities limited to <5 words, incontinent of urine and stool, total functional dependence, and unable to walk. |

* Information is from reference 12.

**Mitchell S L et al. Ann Intern Med 2012;156:45-51**

Annals of Internal Medicine

# Importance of Cognitive Screening

Establish a baseline level of functioning

Allows for objective documentation of cognition

Cognitive Impairment is often not documented

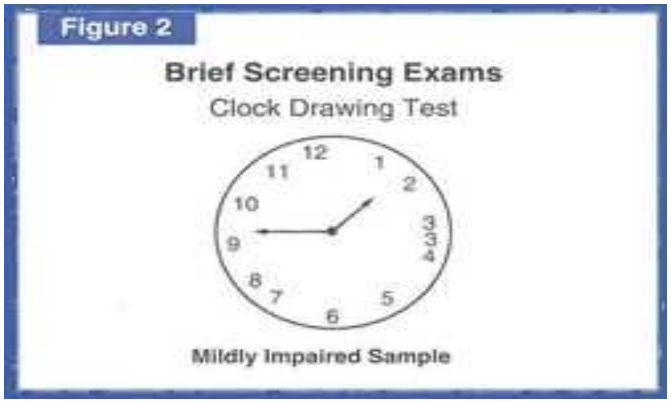
- Such patients are not evaluated for potentially reversible causes
- They also do not receive treatment

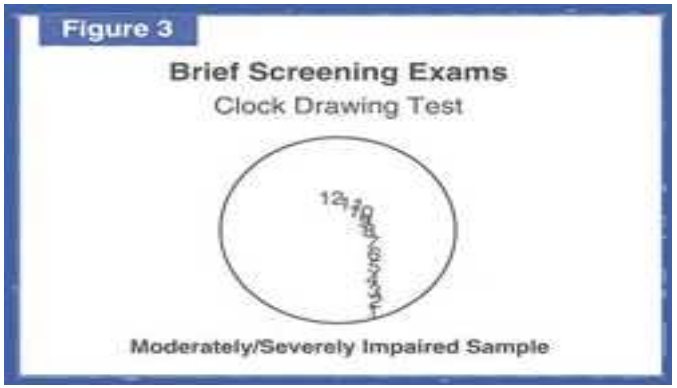
# Screening Tests

- Mini-Mental State Exam (MMSE)

- Pros
  - Widely used and therefore can track cognition over time and between clinicians
  - 5-10 minutes.
- Cons
  - False positives:  those with little education.
  - False negatives:  those with high premorbid intellectual functioning.
  - Psychologically stressful--makes people angry!

- Clock Drawing Test (CDT)



# Advanced diagnostic tests for Alzheimer´s disease

**CSF and Blood Biomarkers**

- β-Amyloid and tau protein levels in cerebrospinal fluid...and blood
- Genetic markers: apolipoprotein E gene (*APOE*)

**Imaging Biomarkers**

- MRI Hippocampal volume
- Positron Emission Tomography
  - Decreased focal brain function demonstrated
  - Pattern of amyloid plaque and tau deposition

**Neuropsychological tests**

- Batteries of several formal neuropsychological tests

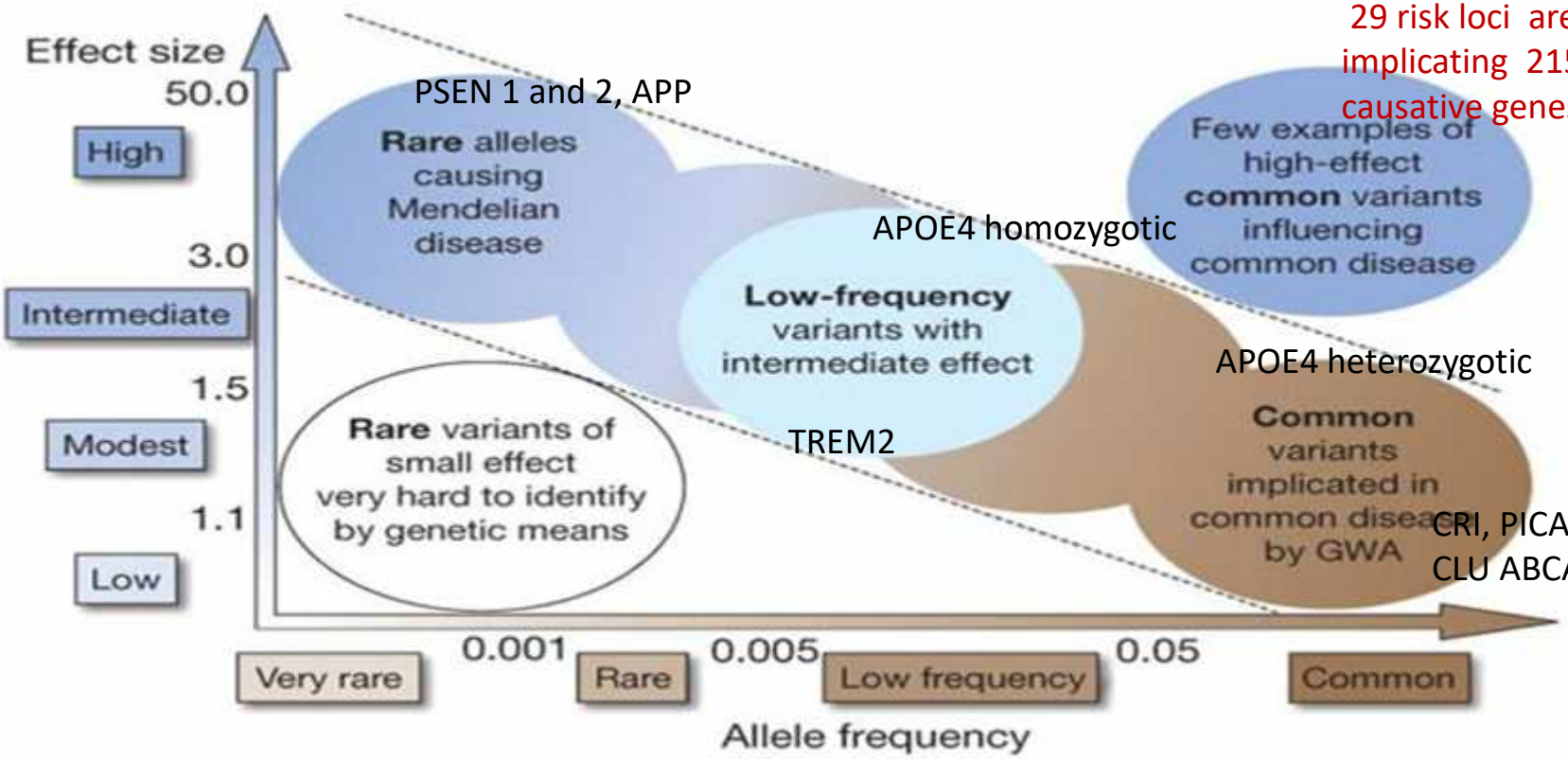

Pathogenesis of Alzheimer´´s disease

## AD is highly heritable, with estimates ranging between 60% and 80%

- First degree relatives (sibs, parents, children) have 3-4 fold increased risk of disease.
- Distant relatives are also at increased risk
- Concordance in monozygotic twins is high ( about 50%)
- Age of onset is more similar in monozygotic twins than dizygotic twins
- In some families the disease is inherited according to (almost) Mendelian inheritance
    - Usually early onset disease

# Genetics of Complex Diseases

29 risk loci are identified for AD implicating 215 potential causative genes



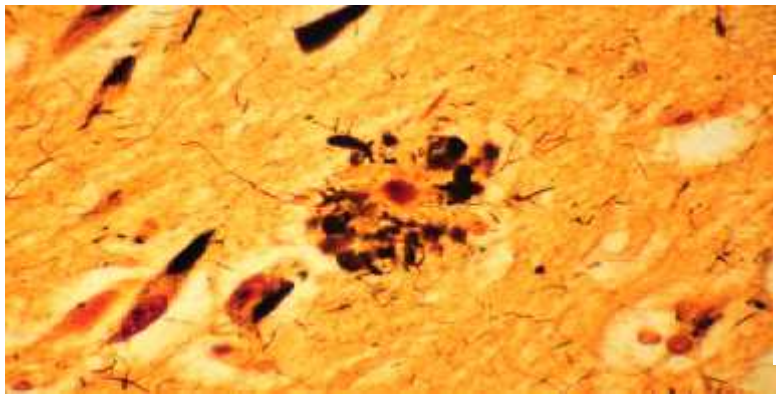

Over the past several years, it has become clear that common genetic variants with large effect sizes (such as the high-risk allele of *APOE*) for common diseases are rare, and that the majority of SNPs confer a more modest risk for disease (with odds ratios between 1.1 and 1.3).

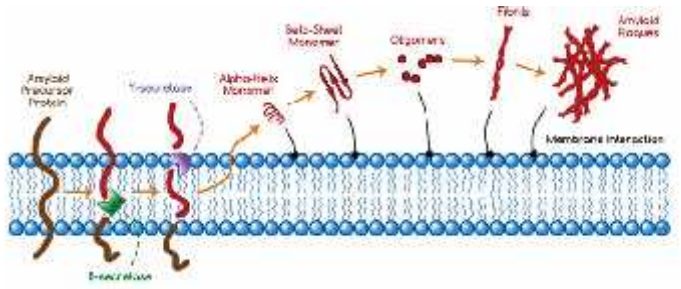
McCarthy et al., *Nat Rev Genetics*, 2008

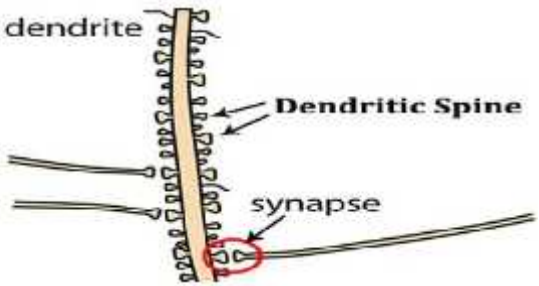
# Amyloid Precursor Protein (APP)

- *APP* gene cloned in 1987
- Located on chromosome 21
  - Trisomy 21 leads to Downs syndrome, which is characterized by early-onset AD
- First mutation in *APP* identified in 1991
- To date, over 30 mutations in about 85 families have been identified
- Most, very rare, found in one or very few families
- Lead to disease with an early onset in the $5^{th}$ or $6^{th}$ decade

# Neuritic (senile) plaque

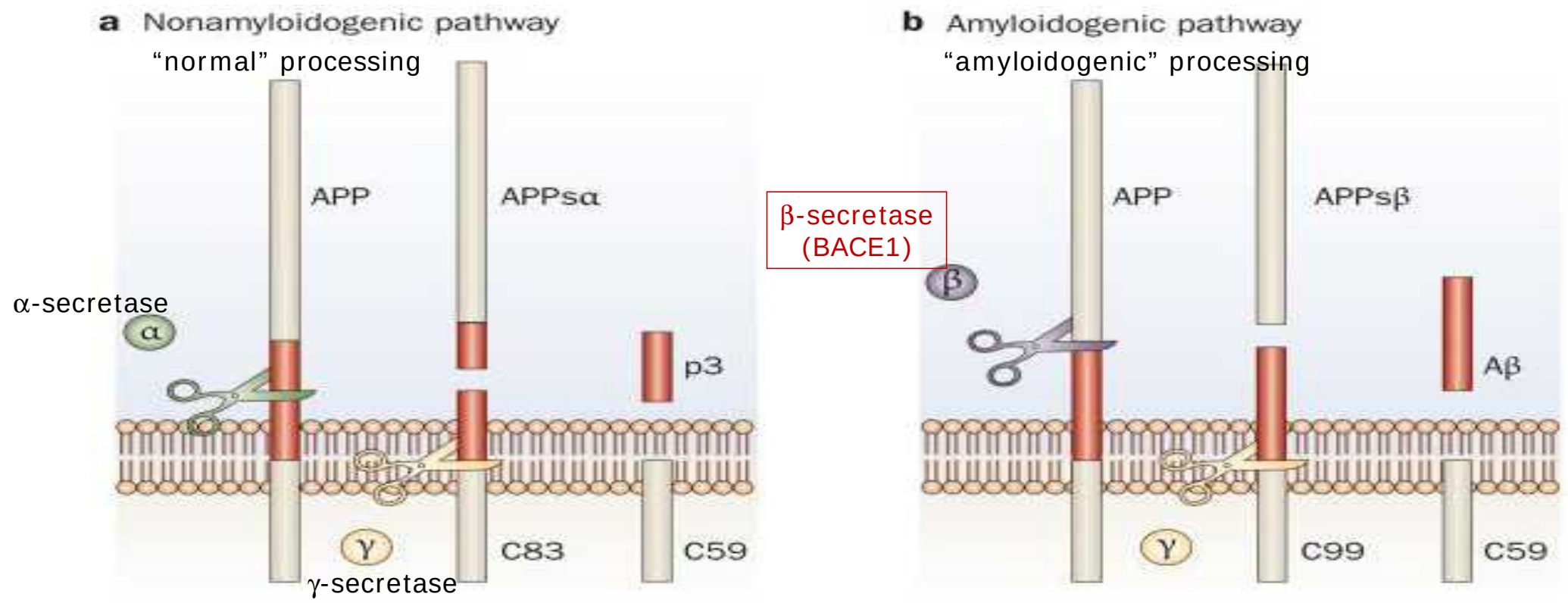




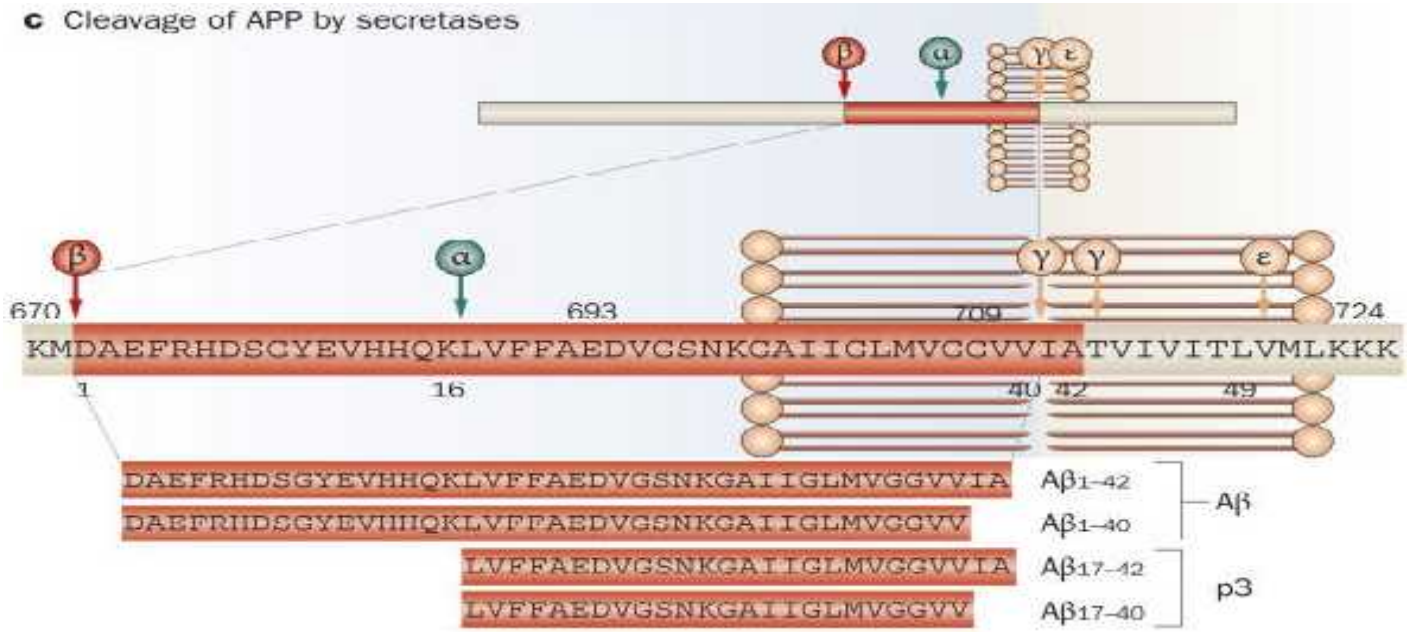

This is a silver stain (Bielschowsky) of a neuritic (senile) plaque. The plaque is composed of degenerating neurons and numerous chemical constituents and is a hallmark of Alzheimer's disease.

# Ab is formed by proteolytic degradation of APP




The benefits of a normal process: chelation of metal ions, regulation of cholesterol transport, vessel repair, antimicrobial function, and antioxidant activity meant to protect the brain with aging.

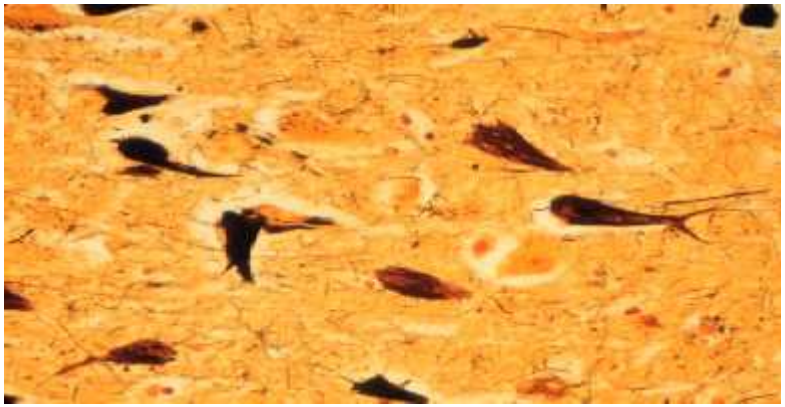
# Increased ratio of $Ab_{1-42}$ induces formation of Ab deposits (plaques)



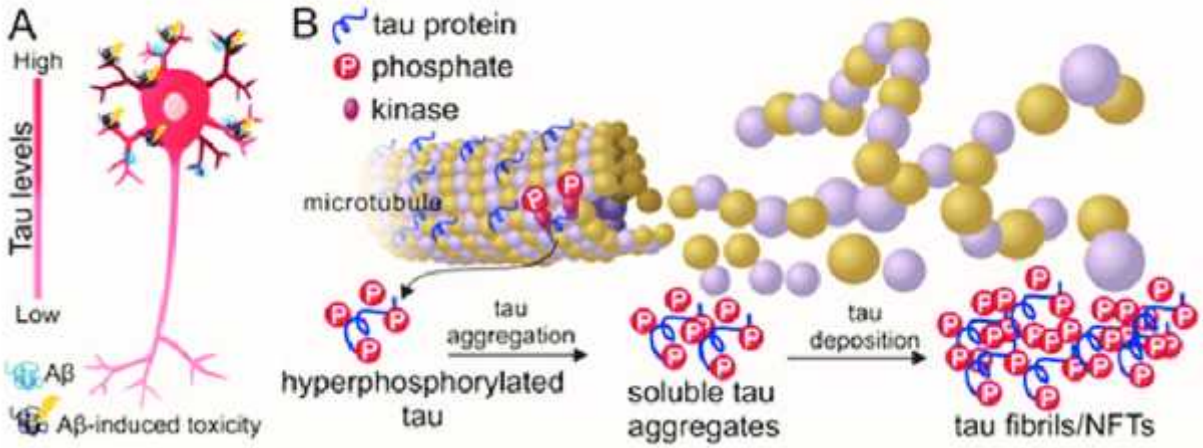

Beta-amyloid accumulates first in neocortex, then to allocortex to brainstem, eventually reaching cerebellum.

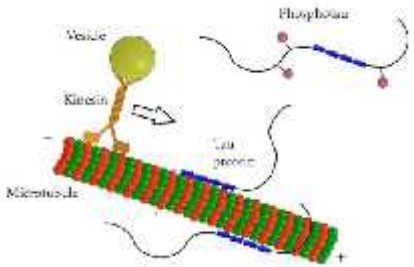
Beta-amyloid has less effect on hippocampus than tau protein.

# Neurofibrillary tangles



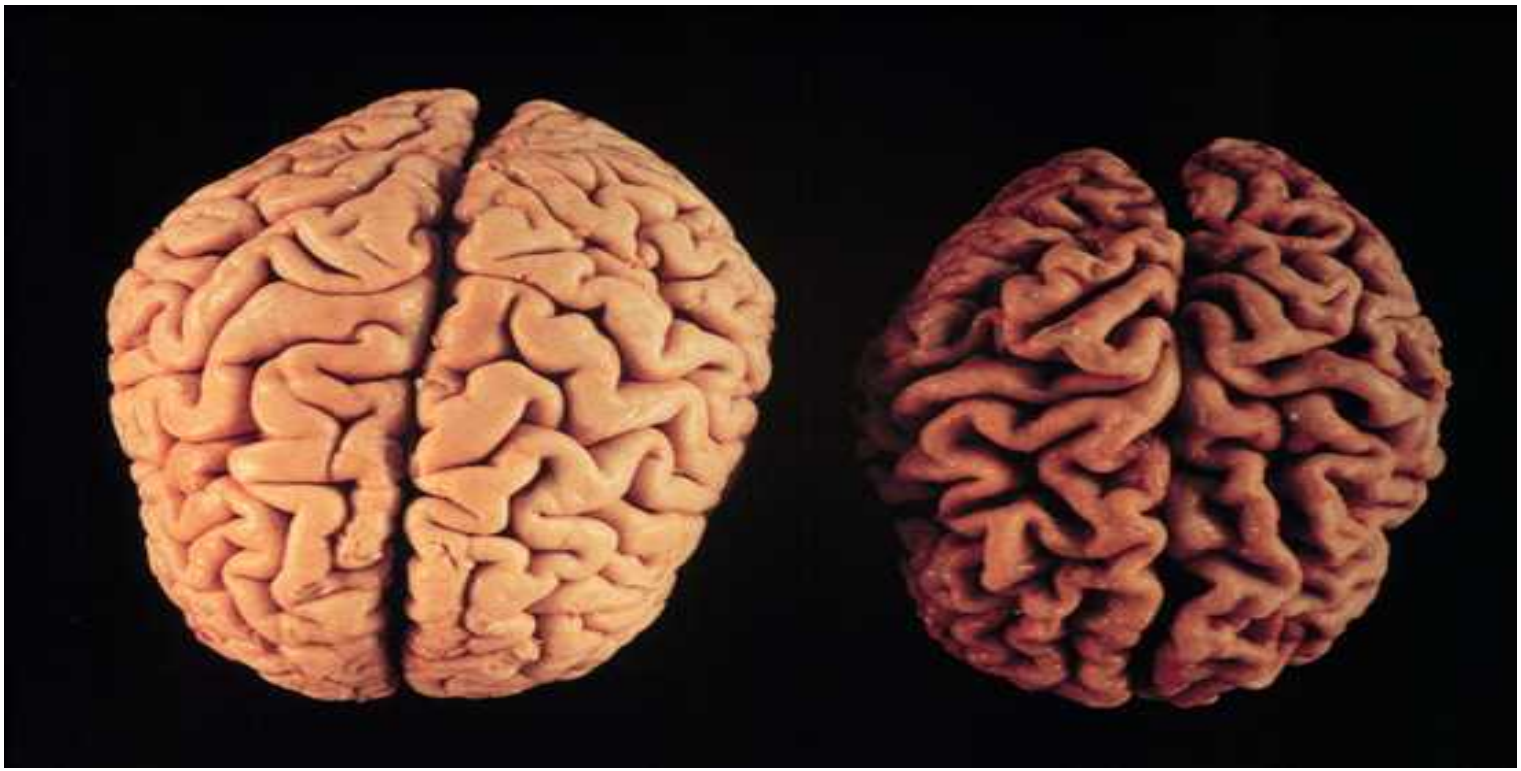
This Bielschowsky stain shows dark-staining neurofibrillary tangles in individual neurons.



Tau pathology begins in allocortex in medial temporal lobe and then spreads to limbic areas and from there to neocortex.

# Alzheimers Disease – Atrophy due to neurodegeneration



Both spatially and temporally tau pathology correlates much more strongly than A-beta pathology with neurodegeneration and cognitive impairment

# Apolipoprotein E

- APOE is a protein that transports the cholesterol needed by neurons for synapse development, dendrite formation, long-term potentiation, and axonal guidance
- Three polymorphisms 2,3,4
- 4 confers risk (65% of AD), 2 protective
- Moves age of onset earlier
- Not useful as a general screening tool
- E4 effect attenuated in some groups
- Increases specificity when used in patients with dementia (fewer false positives)

Mayeux et al., *NEJM*, 1998

# Amyloid-β-independent regulators of tau pathology in Alzheimer´s disease

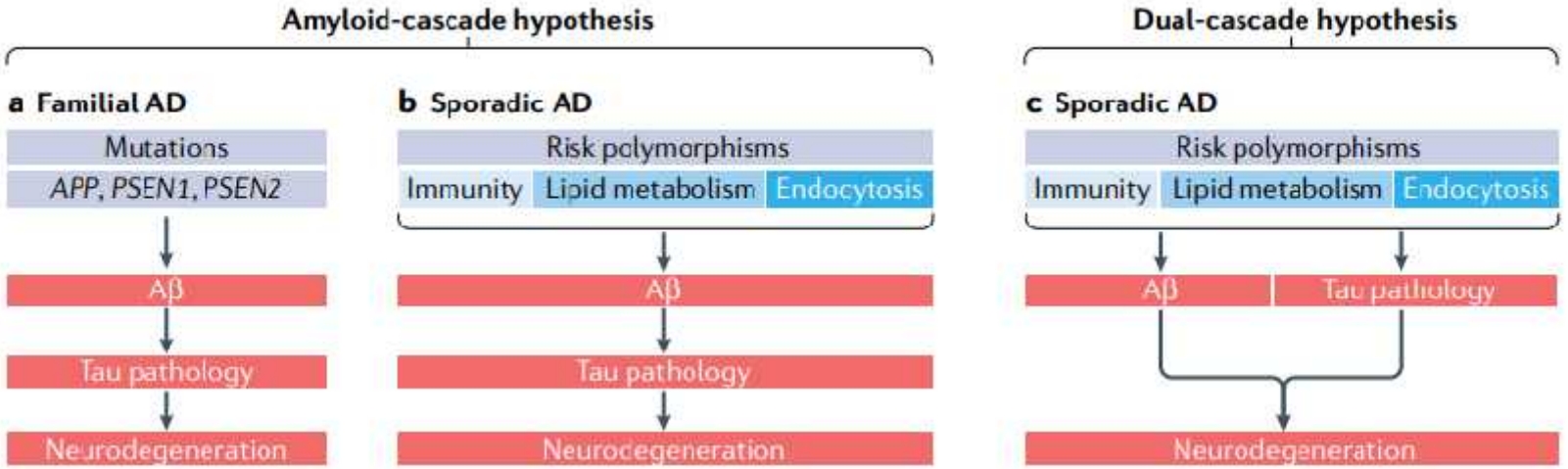
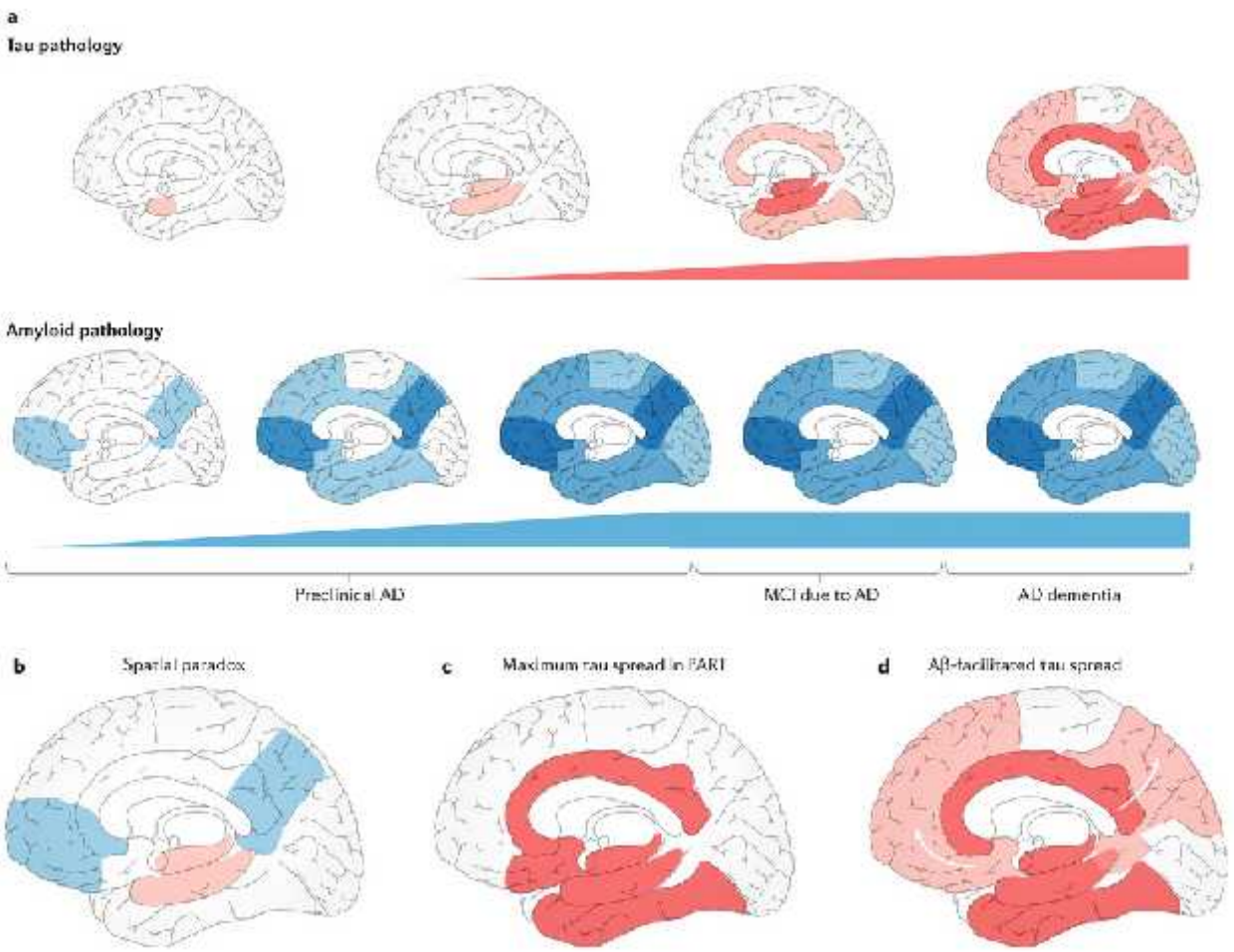



Fig. 1 | **The amyloid-cascade hypothesis and the dual-cascade hypothesis of AD. a** | Mutations in (or duplications of) *APP*, *PSEN1* or *PSEN2*, which respectively encode amyloid-β (Aβ) precursor protein (APP) and the APP-processing enzymes presenilin 1 and 2, alter amyloidogenic processing of APP and cause familial Alzheimer disease (AD). These findings led to the amyloid-cascade hypothesis, which predicts that initial changes in Aβ drive downstream tau pathology and tau-mediated neurodegeneration. **b** | Although mutations in APP or its processing enzymes are absent in patients with sporadic AD, the neuropathology of sporadic AD closely mirrors that of familial AD. Therefore, the amyloid-cascade hypothesis is suggested to also be applicable to sporadic AD. Polymorphisms in genes that regulate microglial immune activation, lipid metabolism and endocytosis are risk factors for sporadic AD. **c** | The dual-cascade hypothesis offers an alternative model to explain the pathogenesis of sporadic AD. This hypothesis predicts that the polymorphisms associated with the risk of sporadic AD contribute to Aβ and tau pathology through correlated but independent cellular pathways.

Rik van der Kant: Nature Reviews, Neuroscience , 2020, Jan 2020, p 21-35

# Progression of Aβ and tau pathology in AD.




Rik van der Kant: Nature Reviews, Neuroscience , 2020, Jan 2020, p 21-35

# Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria

**Probable AD: A plus one or more supportive features B, C, D, or E**

***Core diagnostic criteria***

A. Presence of an early and significant episodic memory impairment that includes the following features:

1. Gradual and progressive change in memory function reported by patients or informants over more than 6 months
2. Objective evidence of significantly impaired episodic memory on testing: this generally consists of recall deficit that does not improve significantly or does not normalise with cueing or recognition testing and after effective encoding of information has been previously controlled
3. The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances

***Supportive features***

B. Presence of medial temporal lobe atrophy
- Volume loss of hippocampi, entorhinal cortex, amygdala evidenced on MRI with qualitative ratings using visual scoring (referenced to well characterised population with age norms) or quantitative volumetry of regions of interest (referenced to well characterised population with age norms)

C. Abnormal cerebrospinal fluid biomarker
- Low amyloid $\beta_{1-42}$ concentrations, increased total tau concentrations, or increased phospho-tau concentrations, or combinations of the three
- Other well validated markers to be discovered in the future

D. Specific pattern on functional neuroimaging with PET
- Reduced glucose metabolism in bilateral temporal parietal regions
- Other well validated ligands, including those that foreseeably will emerge such as Pittsburg compound B or FDDNP

E. Proven AD autosomal dominant mutation within the immediate family

***Exclusion criteria***

History
- Sudden onset
- Early occurrence of the following symptoms: gait disturbances, seizures, behavioural changes

Clinical features
- Focal neurological features including hemiparesis, sensory loss, visual field deficits
- Early extrapyramidal signs

Other medical disorders severe enough to account for memory and related symptoms
- Non-AD dementia
- Major depression
- Cerebrovascular disease
- Toxic and metabolic abnormalities, all of which may require specific investigations
- MRI FLAIR or T2 signal abnormalities in the medial temporal lobe that are consistent with infectious or vascular insults

***Criteria for definite AD***

AD is considered definite if the following are present:
- Both clinical and histopathological (brain biopsy or autopsy) evidence of the disease, as required by the NIA-Reagan criteria for the post-mortem diagnosis of AD; criteria must both be present[3,9]
- Both clinical and genetic evidence (mutation on chromosome 1, 14, or 21) of AD; criteria must both be present

Duboi B et. al.Lancet Neurol 2007; 6: 734–46

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# Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

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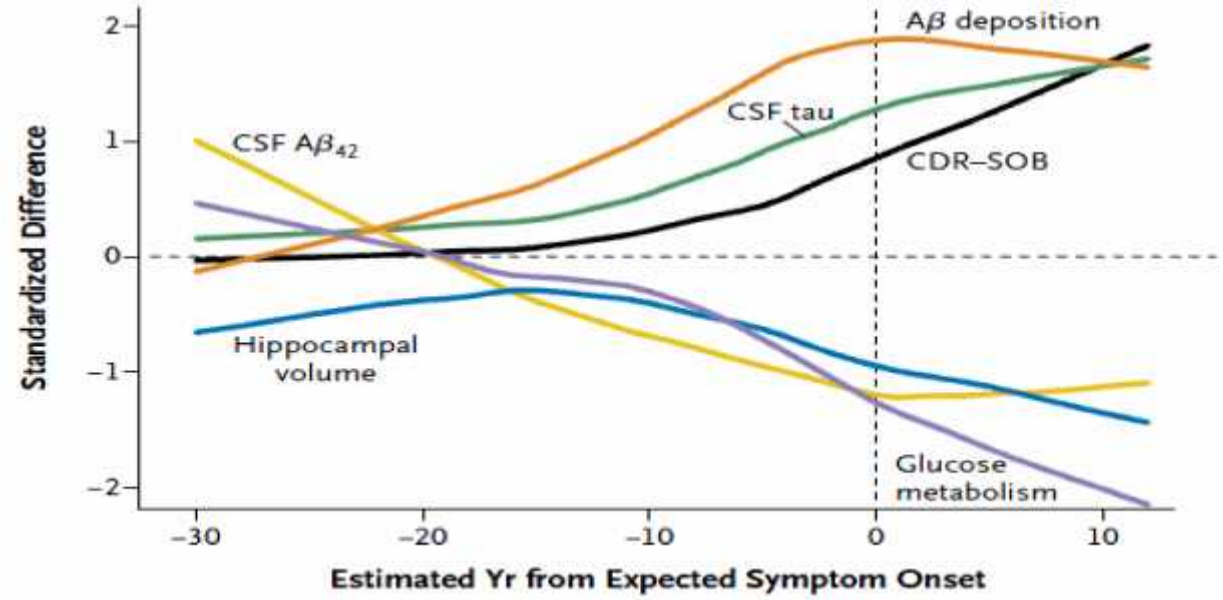
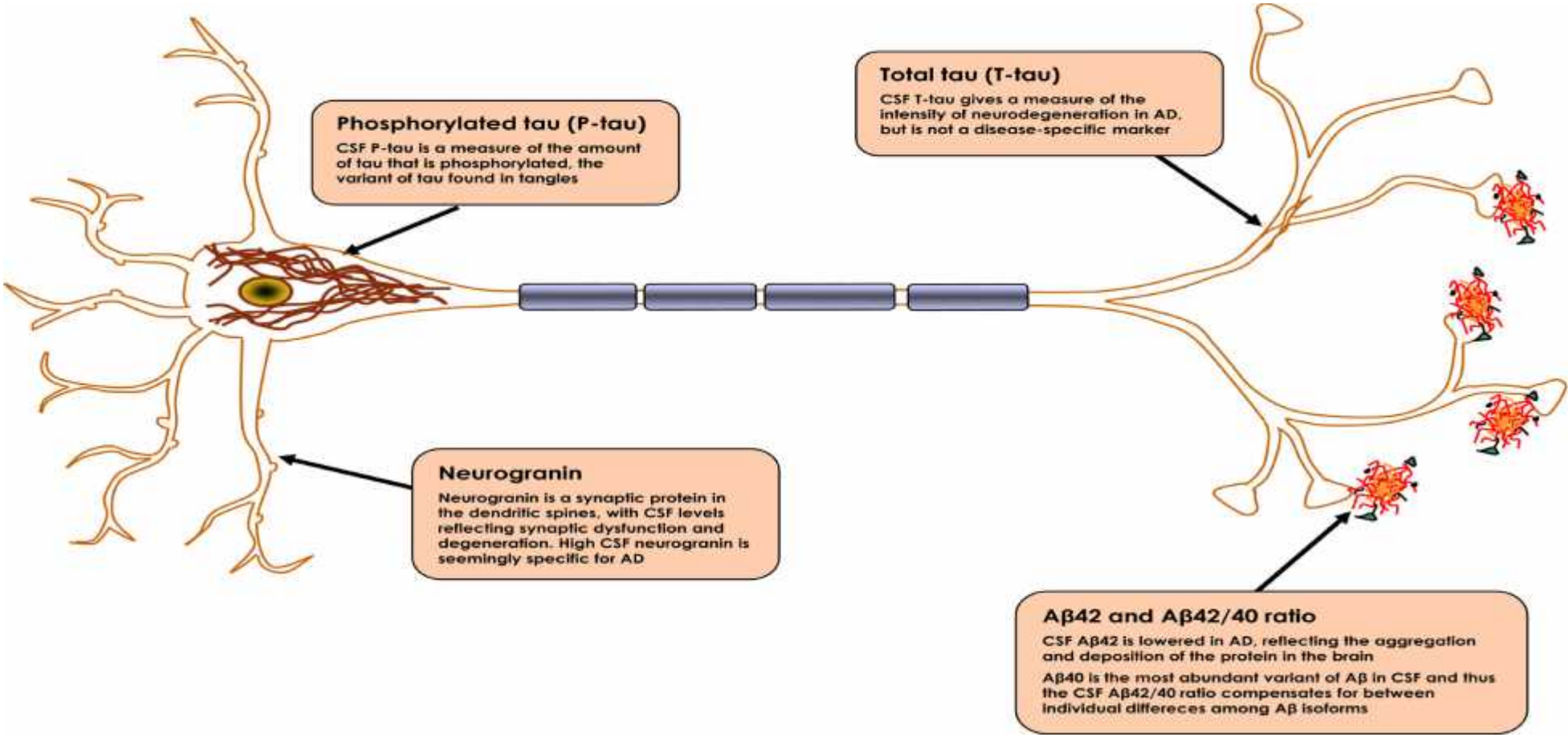



**<u>Bottom line:</u> AD develop over decades**

# Neuron with intracelllular neurofibrillary tangles and extracellular neuritic amyloid plaques




K. Blennow and H. Zetterbaerg Journal of Internal Medicine, Volume: 284, Issue: 6, Pages: 643-663

# Sensitivity and Specificity of CSF Biomarkers – amyloid PET or autopsy

Detection of Alzheimer Disease Pathology in Patients Using Biochemical Biomarkers: Prospects and Challenges for Use in Clinical Practice

January 2020 | 05:01 | 183–193 | JALM

Leslie M. Shaw,[1*] Magdalena Korecka,[1] Michal Figurski,[1] Jon Toledo,[2] David Irwin,[2] Ju Hee Kang,[3] and John Q. Trojanowski[1]

Now fully Automated Methods and Certified Reference material

**Table 2. Sensitivity and specificity of CSF biomarkers or ratios based on a systematic review of the literature. In each of these studies either amyloid PET or autopsy was the basis for detection of AD pathology.**

| | Sensitivity | Specificity | ROC AUC[ab] | Participants |
|---|---|---|---|---|
| 4 consecutive memory clinic studies; amyloid PET | | | | |
| Aβ42 | 87.6 | 85.2 | 0.90 | 748 |
| Aβ42/Aβ40 | 96.0 | 91.3 | 0.96 | 315 |
| 13 case control, multicenter, and cohort studies; amyloid PET | | | | |
| Aβ42 | 93.2 | 84.5 | 0.93 | 2346 |
| Aβ42/Aβ40 | 96.0 | 88.0 | 0.94 | 200 |
| 5 case control or cohort studies; autopsy diagnosis of AD | | | | |
| Aβ42 | 90.0 | 84.0 | 0.92 | 764 |
| Aβ42/t-tau | 88.7 | 88.3 | 0.93 | |
| Aβ42/p-tau181 | 92.3 | 82.3 | 0.91 | |

[a] ROC AUC, receiver operating characteristic area under the curve.
[b] Data from Shaw et al. (9)

# Biomarker profiles and categories of NIA/AA Framework

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**Table 4. Biomarker profiles and categories for the NIA/AA Framework, Jack et al. *(41)*.[a]**

| ATN profiles | Biomarker category | |
|---|---|---|
| A–T–N– | Normal AD biomarkers | |
| A+T–N– | AD pathologic change | AD continuum |
| A+T+N– | AD | AD continuum |
| A+T+N+ | AD | AD continuum |
| A+T–N+ | AD and concomitant suspected non-AD pathologic change | AD continuum |
| A–T+N– | Non-AD pathologic change | |
| A–T–N+ | Non-AD pathologic change | |
| A–T+N+ | Non-AD pathologic change | |

[a] A, amyloid plaque burden measured by CSF Aβ42 or Aβ42/Aβ40 or by amyloid PET; T, tau pathology measured by CSF p-tau181 or tau PET; N, neurodegeneration, measurable by FDG-PET or MRI. When blood-based biomarkers become validated, they may substitute for CSF biomarkers.

# Clinical indications for LP and CSF testing in dx. of AD

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- Patients with SCD who are considered to be at increased risk for AD
- Patient with MCI that is persistent, progressing, and unexplained
- Patients with symptoms that suggest possible AD
- Patient with MCI or dementia with an onset at an early age (less than 65)
- Patient meeting core clinical criteria for probable AD with typical age of onset
- Patients whose dominant symptoms is a change in behavior and where AD diagnosis is being considered.

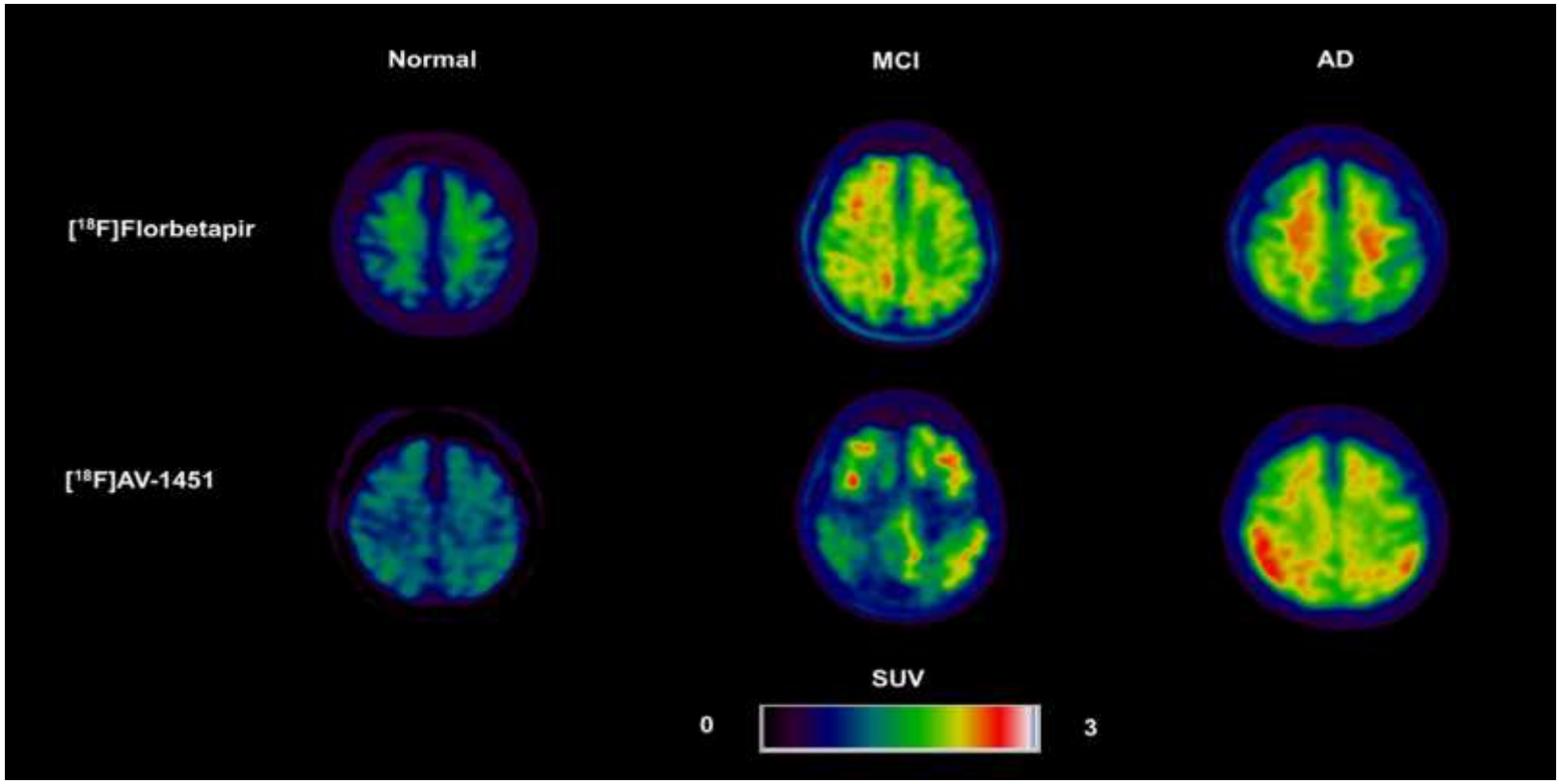
# Emerging blood-based AD biomarkers

Awaiting to be fully Automated Methods and with Certified Reference material

**Table 2.**
Emerging blood-based AD biomarkers.[a]

| Emerging blood (plasma) biomarkers | Analytical method | Cutoff or median AD biomarker concentration | | Clinical performance[b] | | | Manufacturer | Reference |
|---|---|---|---|---|---|---|---|---|
| | | AD pathology | Healthy control | AUC | Sensitivity | Specificity | | |
| *Predicting amyloid plaques* | | | | | | | | |
| Aβ42/Aβ40 | ECLIA | Ab42: 23 Ab40:380 | Ab42: 33 Ab40: 482 | 0.77 | 70% | 73% | Roche | (48) |
| | IP, LC-MS/MS | <0.1218 | | 0.88 | 88% | 76% | C2N Diagnostics | (10, 36) |
| Aβ40/Aβ42 | IP, MALDI-Mass Spectrometry | 27.656 | | 0.89 | 73% | 92% | Shimadzu | (37) |
| *Tau proteins* | | | | | | | | |
| T-tau | Simoa | 2.58–5.58 | 3.12–5.37 | [c] | | | Quanterix | (61) |
| | NT1 Simoa Assay | 2.5 | 3.5 | 0.75 | 70% | 78% | Quanterix | (61) |
| | ECLIA | 16.7 | 16.6 | NA[d] | | | Roche | (28) |
| *Neurofilament light chain* | | | | | | | | |
| NfL, Plasma | Simoa | 49 | 21 | 0.85 | 84% | 78% | Quanterix | (61) |
| | Simoa Homebrew | 49 | 34 | 0.87 | NA | | [b] | (59) |
| | ECLIA | 44 | 21 | NA | | | Roche | (48) |
| *Multibiomarker assays* | | | | | | | | |
| Aβ42, Aβ40 + APOE, age | IP, LC-MS/MS | NA | | 0.94 | NA | | C2N Diagnostics | (10, 36) |
| | IP, MALDI-Mass Spectrometry | 0.52 | | 0.89 | 83% | 84% | Shimadzu | (37) |
| Aβ42, Aβ40, T-Tau | ECLIA | NA | | 0.81 | 89% | 64% | Roche | (48) |
| Aβ42, Aβ40, T-Tau, NfL, APOE | ECLIA | NA | | NA | 73% | 86% | Roche | (48) |

# Applications of amyloid, tau, and neuroinflammation PET imaging to Alzheimer's




Human Brain Mapping, Chandra A. et.al. Volume: 40, Issue: 18, Pages: 5424-5442,

# Treatment of Alzheimer Disease -First:

- Disease modifying medications have not reached the market yet

- Treatment of cognitive symptoms is a symptomatic treatment

- Treat all co-morbidity
  - RO B12 deficiency, Hypothyroidism,
  - Treat all cardiovascular risk factors
    - hypertension
    - hypercholesterolemia
    - smoking
  - Optimize treatment of DM

- Treat depression

  Depression can begin before, with and after the diagnosis of Alzheimer´s disease

# Symptomatic treatment of Alzheimer´s disease

•Acetylcholinesterase inhibitors work by inhibiting acetylcholinesterase (the enzyme primarily responsible for synaptic recycling of acetylcholine in gray matter), thereby prolonging the action of endogenous acetylcholine.

•Three such inhibitors are currently in clinical use:
- •donepezil (Aricept)
- •rivastigmine (Exelon)
- •galantamine (Razadyne)

•Overall there is no convincing evidence that acetylcholinesterase inhibitors have any clinically meaningful disease modifying effects, and therefore the decision on timing of initiation of therapy should be individualized based on the preferences of the patient and family.

•However, all three acetylcholinesterase inhibitors have been shown to be safe and to maintain their cognitive benefits over multiple years.

•The acetylcholinesterase inhibitors maintain their efficacy in severe dementia

Cognitive symptoms of Alzheimer's disease: clinical management and prevention

BMJ 2019;367:l6217

# Symptomatic treatment of Alzheimer´s disease

Memantine is a low affinity N-methyl-D-aspartate (NMDA) receptor antagonist;

it has been hypothesized to involve mitigation of glutamate-induced excitotoxicity.

it is available as immediate and extended release formulations

A recent meta-analysis of 29 trials including 7885 patients with AD found with a high degree of certainty that memantine showed a clear but modest benefit on global impression, cognition, and activities of daily living for moderate to severe AD

The meta-analysis also found an effect on behavior with patients randomized to the memantine arm being significantly less likely to develop agitation during the treatment period compared with those randomized to placebo. However, this was only true for those without agitation at baseline

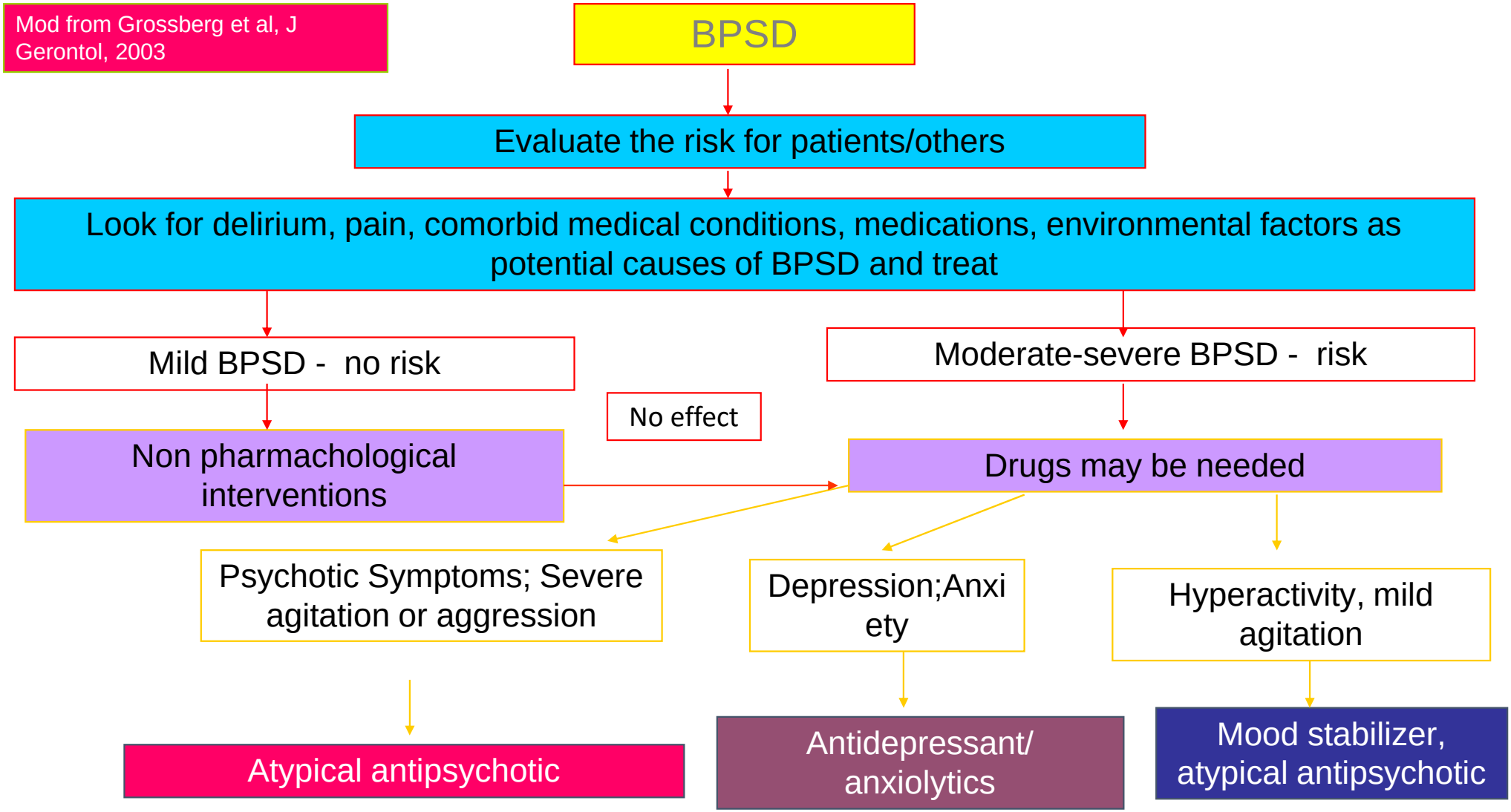
The clinical benefit of memantine is smaller than that of the acetylcholinesterase inhibitors. Effect size of 0.65-0.4 points/ MMSE

The benefit of adding memantine to acetylcholinesterase inhibitor therapy has been studied with mixed results.


BMJ 2019;367:l6217

## Psycho-social support

- Psycho- social support is important – several possibilities:
  - Support groups for spouses and children
  - Specialized day care
  - Respite care
  - Nursing Home
    - If BPSD symptoms are uncontrollable
    - If well into 5th stage of Dementia Global Deteriorating Scale


Mod from Grossberg et al, J Gerontol, 2003
BPSD
Evaluate the risk for patients/others
Look for delirium, pain, comorbid medical conditions, medications, environmental factors as potential causes of BPSD and treat
Mild BPSD - no risk
Moderate-severe BPSD - risk
No effect
Non pharmachological interventions
Drugs may be needed
Psychotic Symptoms; Severe agitation or aggression
Depression;Anxiety
Hyperactivity, mild agitation
Atypical antipsychotic
Antidepressant/ anxiolytics
Mood stabilizer, atypical antipsychotic

## Disease-Modifying Treatments for Alzheimer Disease

Despite all scientific efforts and many protracted and expensive clinical trials, **no new drug** has been approved by FDA for treatment of Alzheimer disease (AD) **since 2003**.

**More than 200 investigational programs have failed** or have been abandoned in the last decade.

**The most probable explanations for failures of disease-modifying treatments (DMTs) for AD may include:**

- Late initiation of treatments during the course of AD development,
- Inappropriate drug dosages,
- Erroneous selection of treatment targets,
- Mainly an inadequate understanding of the complex pathophysiology of AD, which may necessitate combination treatments rather than monotherapy.
- Clinical trials' methodological issues have also been criticized.

Konstantina KG et. al. Biomedicines 2019, 7, 97

**Drug-development research for AD is aimed to overcome these drawbacks.**

•Preclinical and prodromal AD populations, as well as traditionally investigated populations representing all the clinical stages of AD, are included in recent trials.

•Systematic use of biomarkers in staging preclinical and prodromal AD and of a single primary outcome in trials of prodromal AD are regularly integrated.

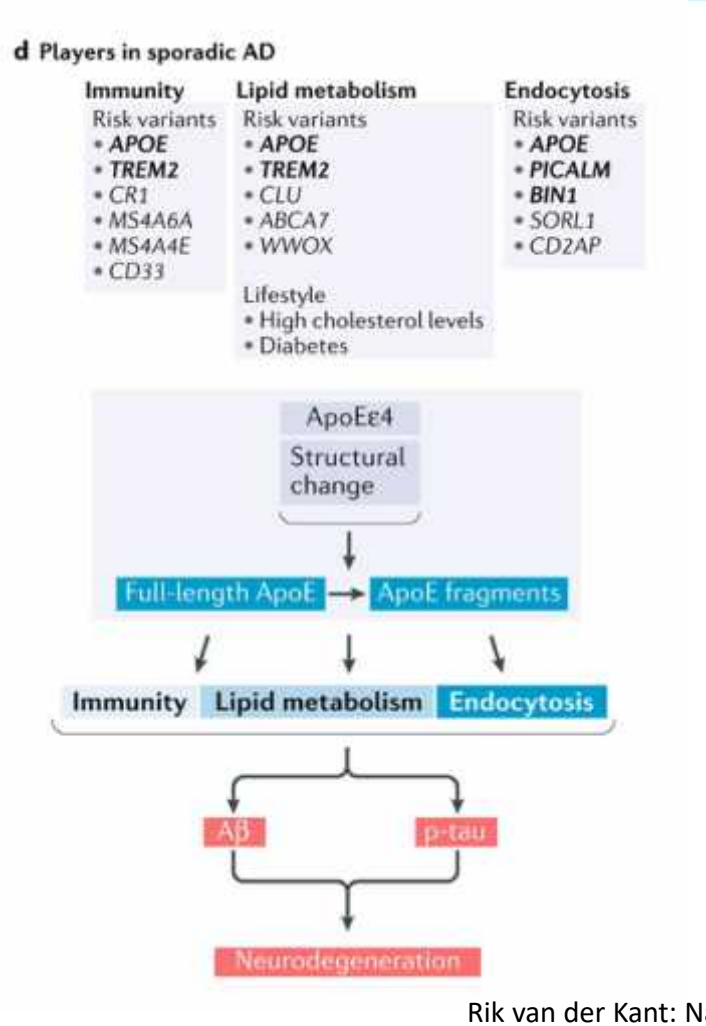
•The application of amyloid, tau, and neurodegeneration biomarkers, including new biomarkers—such as Tau positron emission tomography, neurofilament light chain (blood and Cerebrospinal fluid (CSF) biomarker of axonal degeneration) and neurogranin (CSF biomarker of synaptic functioning)—to clinical trials allows more precise staging of AD.

•Additionally, use of Bayesian statistics, modifiable clinical trial designs, and clinical trial simulators enrich the trial methodology.

•Besides, combination therapy regimens are assessed in clinical trials.

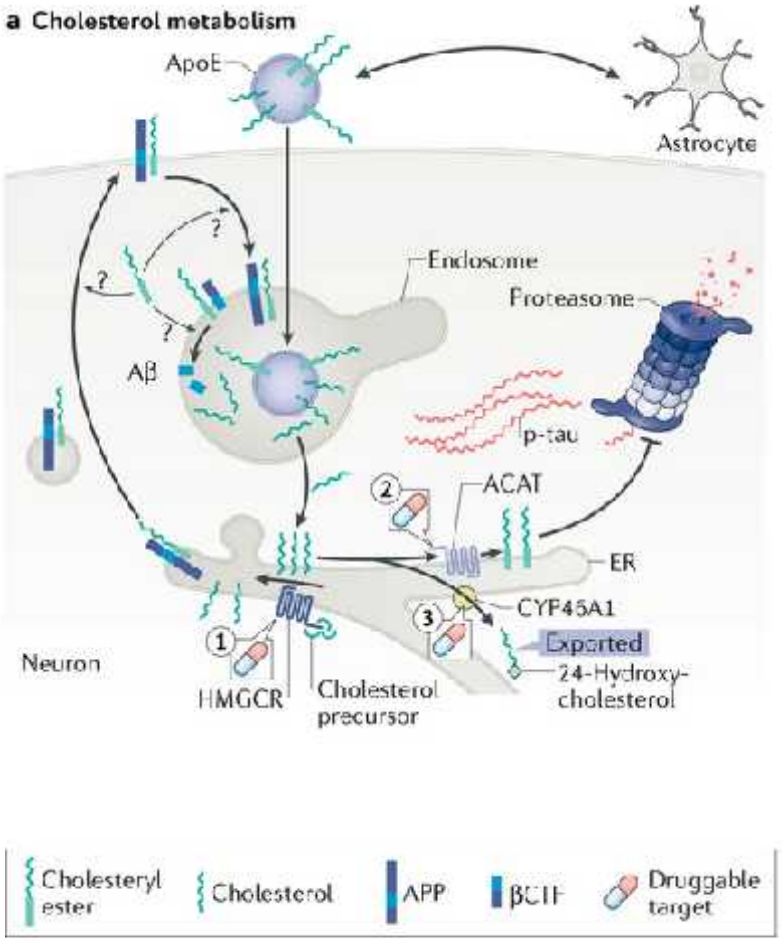
Konstantina KG et. al. Biomedicines 2019, 7, 97

# Players in sporadic AD




Rik van der Kant: Nature Reviews, Neuroscience , 2020, Jan 2020, p 21-35

# Cholesterol metabolism




The accumulation of cholesteryl esters inhibits proteasomal degradation of p-tau. In addition, cholesteryl esters enhance amyloidogenic processing of Aβ precursor protein (APP). The effect of cholesteryl esters on APP is mediated by a lipid-binding domain in APP.

Small-molecule inhibitors of HMGCR (step 1) and ACAT (step 2) prevent the generation of cholesteryl esters, reducing amyloidogenic processing of APP and enhancing proteasomal degradation of p-tau.

In the ER, conversion of cholesterol to 24-hydroxycholesterol by cholesterol 24-hydroxylase (also known as cytochrome P450 46A1 (CYP46A1)) also prevents the esterification of cholesterol by ACAT; hence, small-molecule activators of CYP46A1 (step 3) also reduce levels of cholesteryl esters, Aβ and p-tau.

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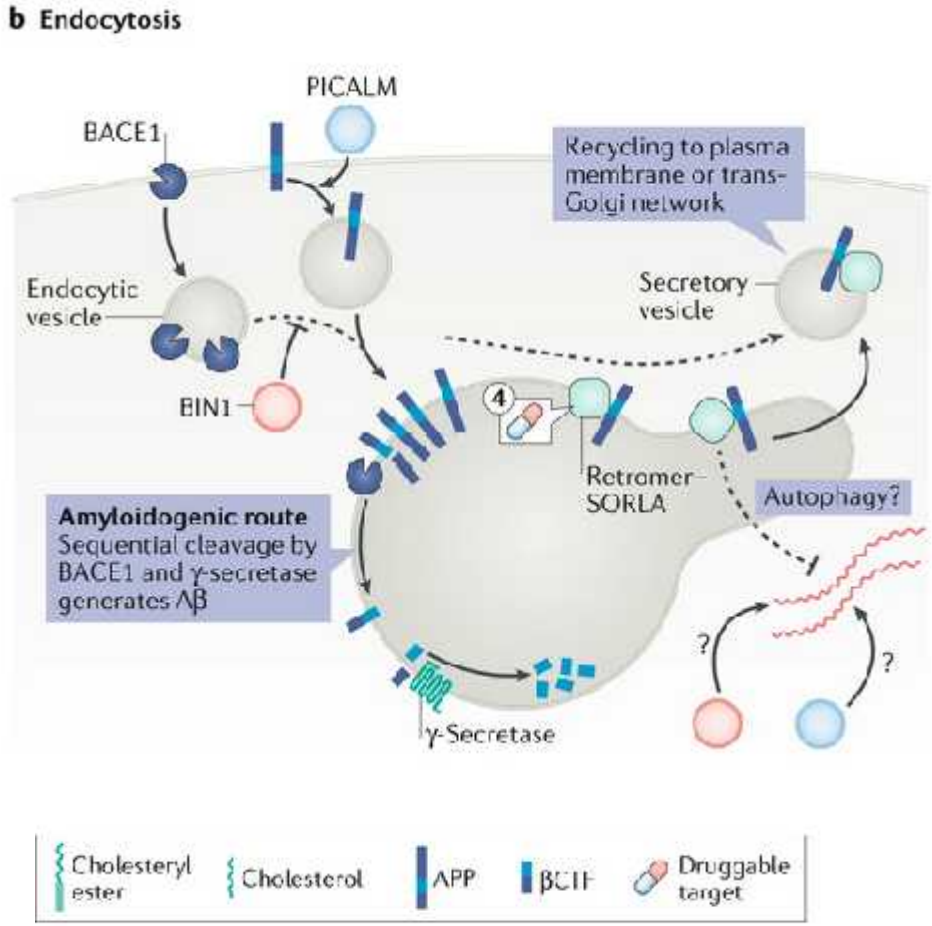
# Endocytosis




Overview of the role of endocytic regulators that might act through parallel and independent pathways upstream of both Aβ and p-tau in sporadic AD.

Retromer-stabilizing drugs (step 4) promote this step and thereby decrease amyloidogenic processing of APP.

Retromer, BIN1 and PICALM also regulate tau in a poorly understood, but seemingly Aβ-independent, manner that might involve autophagy

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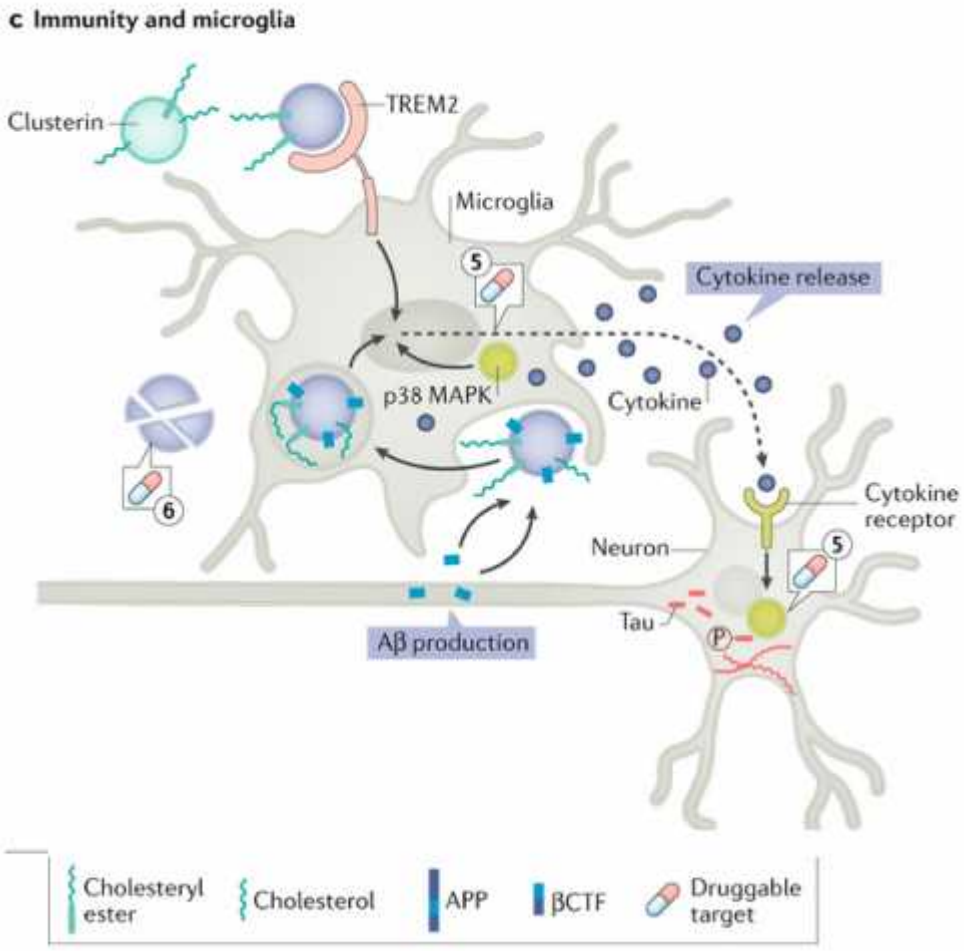
# Immunity and microglia




Schematic overview of the role of microglia in the regulation of Aβ and tau.
ApoE and clusterin (also known as ApoJ) bind to the microglial triggering receptor expressed on myeloid cells 2 (TREM2) to regulate microglial activation.

Activated microglia release cytokines that bind to neuronal cytokine receptors, activating p38 mitogen-activated protein kinase (p38 MAPK) and increasing tau (hyper) phosphorylation. p38 MAPK inhibitors (step 5) might directly reduce microglia-dependent tau hyperphosphorylation in neurons. In addition, p38 MAPK inhibitors decrease cytokine release from activated microglia.

Microglia also phagocytose complexes of ApoE and Aβ, and ApoEε4 is less efficient than other isoforms in clearing Aβ.

Treatment with ApoEε4 structure correctors, which stabilize ApoEε4 proteins (step 6), might increase microglial Aβ uptake and concomitantly prevent microglial activation upstream of tau pathology

Rik van der Kant: Nature Reviews, Neuroscience , 2020, Jan 2020, p 21-35