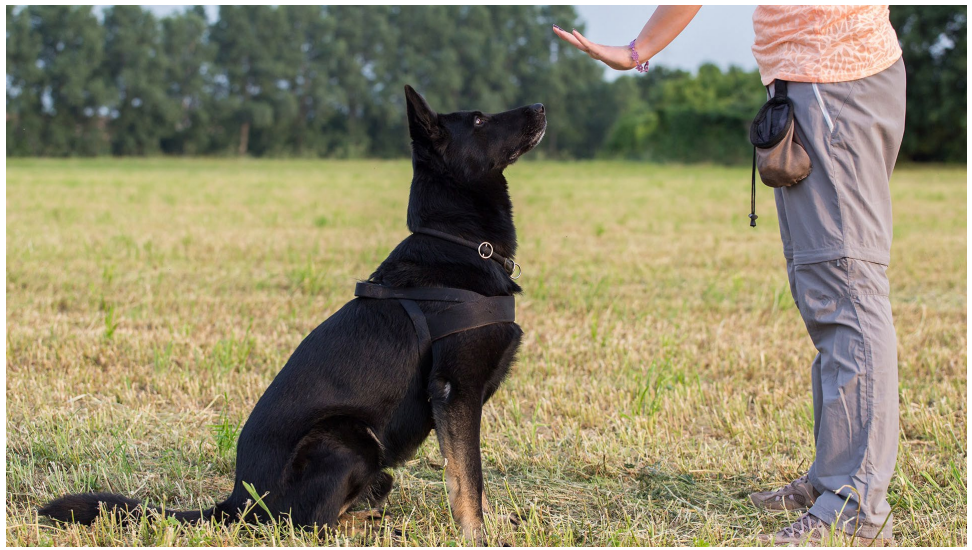
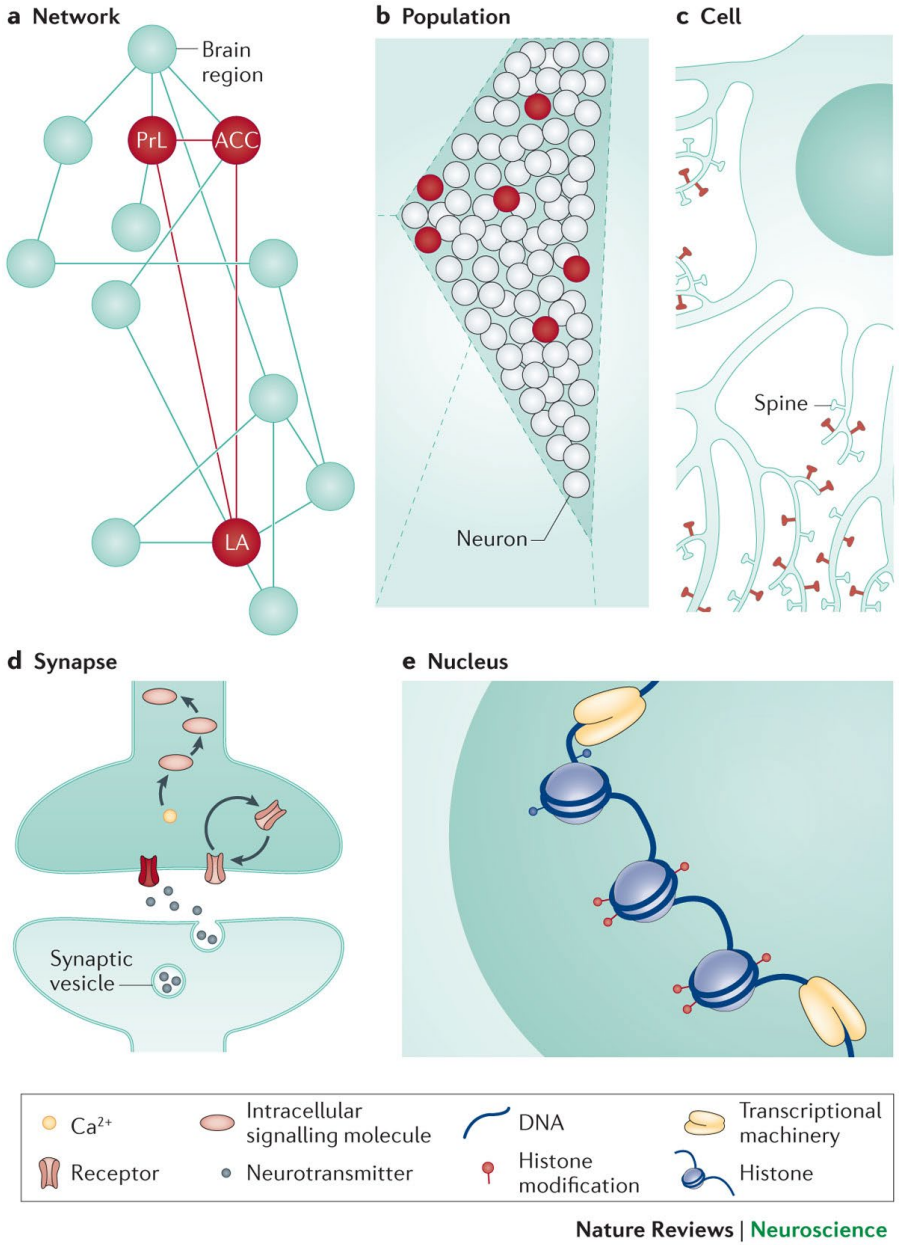
# Alzheimer Disease-2

Pathogenesis and

Some Clinical Concepts

# Learning and Memory






Nature Reviews Neuroscience 16, 521–534 (2015)

# Case Vignette

- A 74 year-old man is brought to the ED with “altered mental status”. His wife reports that he has been fighting with invisible men for weeks and accuses her of infidelity. He got into an argument with a neighbor, claiming they stole his eye-glasses. He has fallen 4 times within the last month. He is more “moody” than usual, does not sleep at all at night and naps most of the day.
- On physical exam, he is alert but argumentative. He knows his name and the year but is confused about the date and believes he is at a “sick ward” in Arizona. He has no focal neurological deficits. The cognitive exam is documented simply as “A/Ox2”.
- A head CT is interpreted as “no acute abnormality”, EKG and laboratory tests are WNL except 10 WBC/HPF and (+) leukocyte esterase in the urine.

# Chart Review

- PMHx: HTN, OA, COPD, insomnia, back pain, overweight, GERD
- PΨHx: unspecified anxiety
- Meds: Lisinopril, ibuprofen, albuterol, hydroxyzine, cyclobenzaprine, trazodone, melatonin, amitriptyline, ranitidine
- Substance use: EtOH “socially”, past smoker
- Social hx: Married, lives with wife, retired after 45 years of gainful employment 8 years ago

- What is the most likely diagnosis?

- A psychotic disorder or encephalopathy is suspected and psychiatry and neurology are consulted.

- IV hydration and antibiotics are administered. Hydroxyzine, cyclobenzaprine, and amitriptyline are held. An EEG shows generalized slowing.

- The next morning, Pt is calmer, oriented to person and place and off by a few days on the date. The still reports suspicions about his wife and neighbor but denies any memory problems. He reports he lets his wife take care of most chores due to “lack of time”.

- What is the next step?

- His daughter is contacted and she provides further history:
  - Pt had no neuropsychiatric complaints when he retired 8 years ago. Since then, he gradually withdrew from social interactions.
  - About 5 years ago, his wife took over their finances after he forgot to pay some bills.
  - He was driving until about 3 years ago but stopped after a couple of uncharacteristic accidents.
  - He used to enjoy cooking and gardening but his wife “doesn’t let him” anymore after he repeatedly misplaced cookware and fertilizer.
- His wife reports:
  - his mood has been more irritable for 6 months but does not recall any hopeless statements or crying spells.
  - She states his memory is “just fine, I wish he didn’t keep talking about his time in the Navy” but got concerned in the last few months due to his paranoia.

# Bedside cognitive testing and Depression screen

- MOCA:
  - Visuospatial/Executive: **1/5**
  - Naming: 3/3
  - Attention: 4/6
  - Language: 2/3
  - Abstraction: 2/2
  - Delayed Recall: **0/5**, improves to 1/5 with multiple choice
  - Orientation: 5/6
  - TOTAL: **17/30** (12+ years of education)
- PHQ9: 7 (3 points for sleep, 2 points for anhedonia)

# Approach to Dementia

Dementia = progressive cognitive decline from baseline + functional impairment in iADLs (DSM term: Major neurocognitive disorder)

**Dementia in an old adult with classic presentation and no focal deficits**

- Limited DDx
  - Alzheimer or other neurodegenerative dementias
  - Vascular dementia
- "Reversible" causes of dementia are rare in real life
- A basic w/u sufficient
  - B-12, TSH
  - PHQ9 (or similar depression screen)
  - MRI probably reasonable

**Dementia in a young patient**

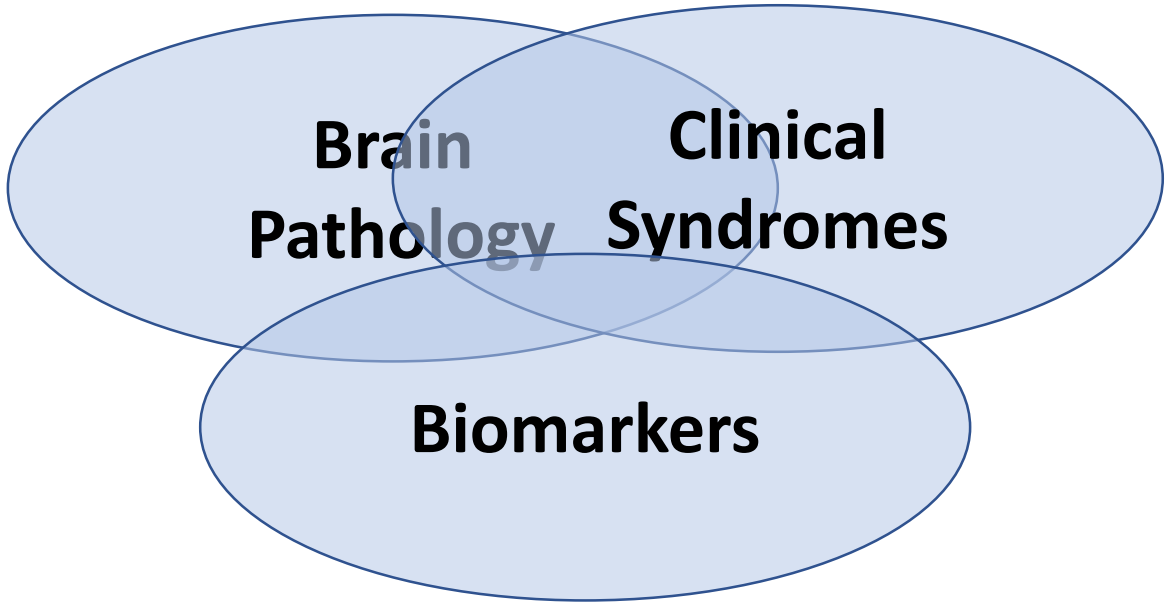
**Rapidly progressive dementia**

**Unusual symptoms/focal deficits**

- Very wide DDx
- Reversible and less common etiologies are possible (e.g. prion disease, tumor, etc)
- Extensive w/u may be necessary

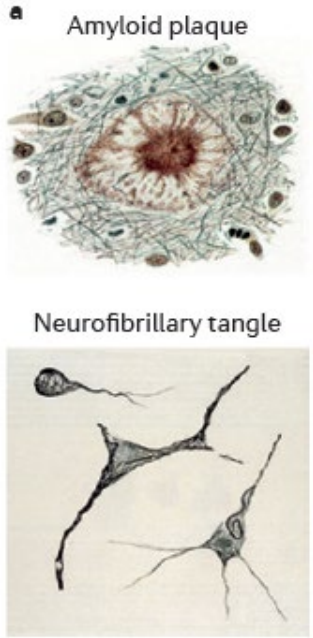
- What is the Gold Standard diagnostic test for dementias?

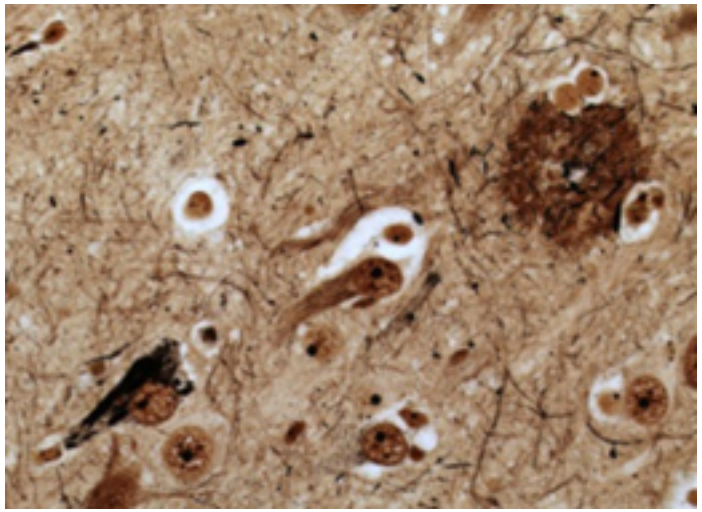
- Autopsy

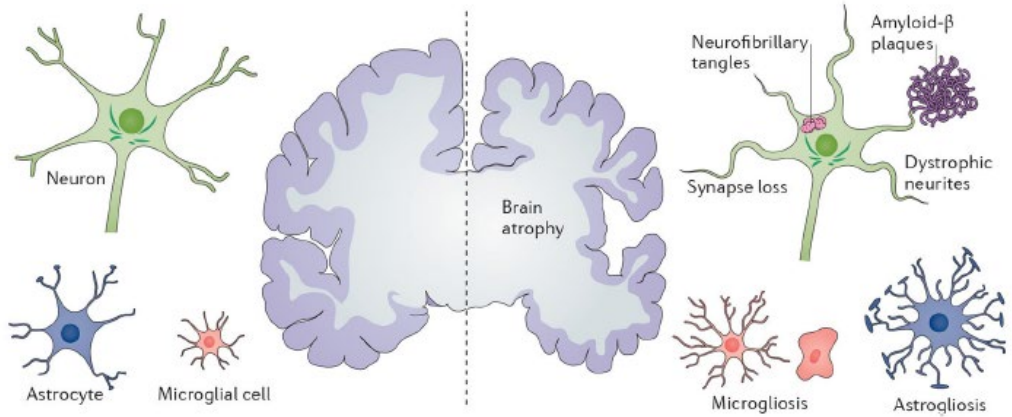


# Alzheimer Disease - Definition

- Dementia + Classic pathology in the brain
  - Extracellular Amyloid deposition (Amyloid-β)
  - Neurofibrillary tangles (P-tau)
  - Neuritic plaques: Amyloid-β + dystrophic neurites +  P-tau






Nat Rev Neurol. 2018 July ; 14(7): 399–415.. UpToDate®

# Alzheimer Disease – Natural History

- Preclinical phase (10-20 years before symptoms)
  - No objective cognitive decline
  - No impairment in iADLs
  - Biomarkers detectable
- Prodromal phase
  - Objective cognitive decline
  - No impairment in iADLs
  - Biomarkers detectable
  - aka MCI, or mild neurocognitive disorder
- Dementia phase
  - Objective cognitive decline + impairment in iADLs
  - Duration: 3-20 years, median 8-10 years

The Lancet Neurology VOLUME 19, ISSUE 11, P951-962, NOVEMBER 01, 2020

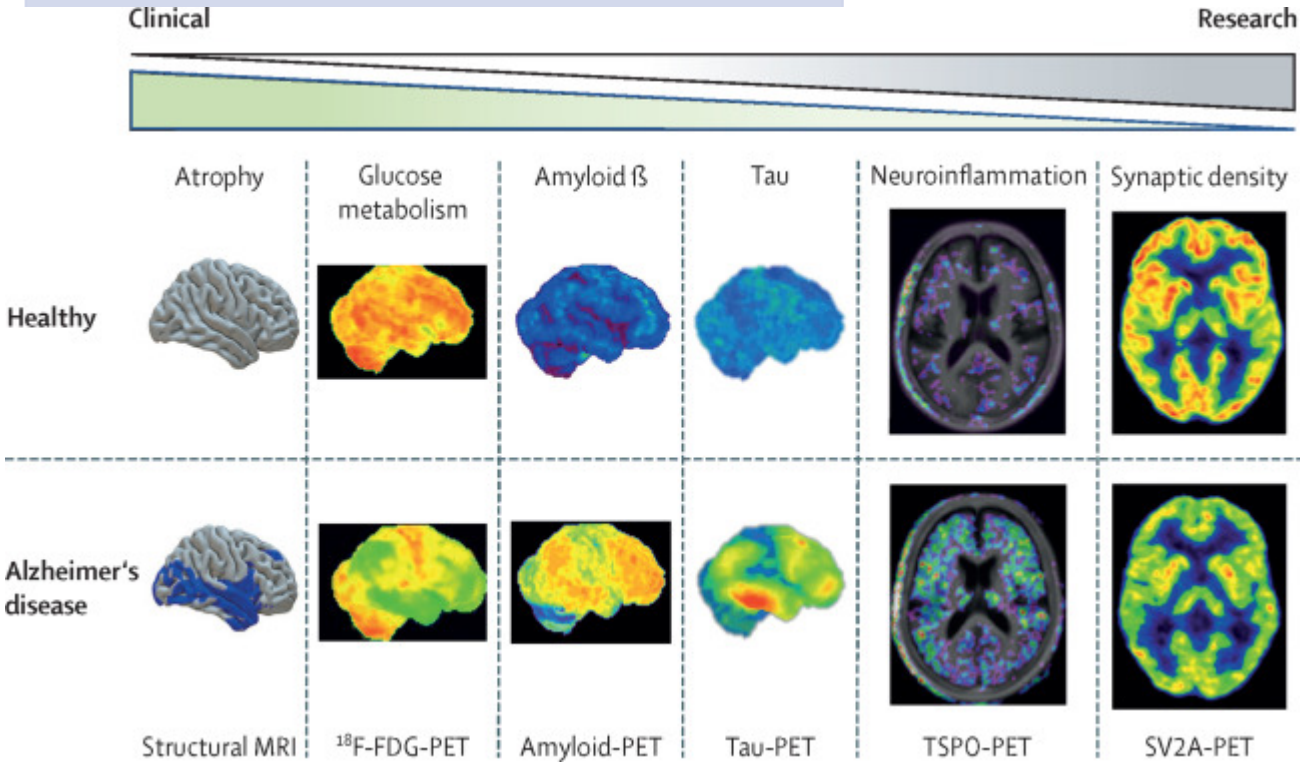
# Biomarkers

## Imaging

- Structural MRI
  - ↓hippocampal volume
- FDG-PET and SPECT
  - Hypometabolism and hypoperfusion
    - Hippocampus, precuneus, temporoparietal cortex
- Amyloid PET imaging
  - Florbetapir F-18, flutemetamol F-18, florbetaben F-18
- Tau PET imaging

## CSF

- $A\beta_{42}$ (low) or $A\beta_{42}/A\beta_{40}$ ratio (low)
- Total tau, or P-tau (high)



# Genetics

## Familial, Early-onset
Mendelian w/ high penetrance

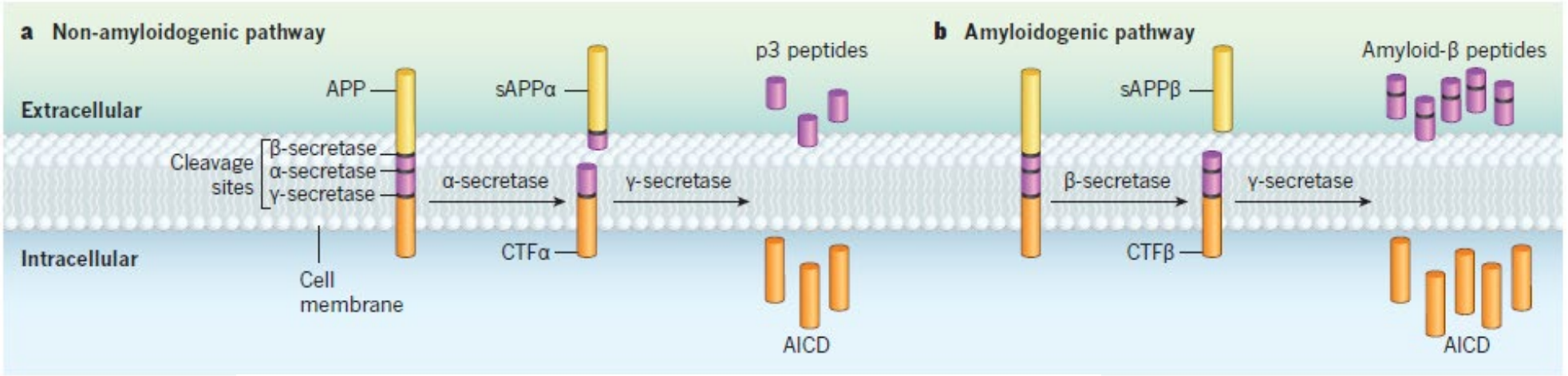
(~1% of cases)

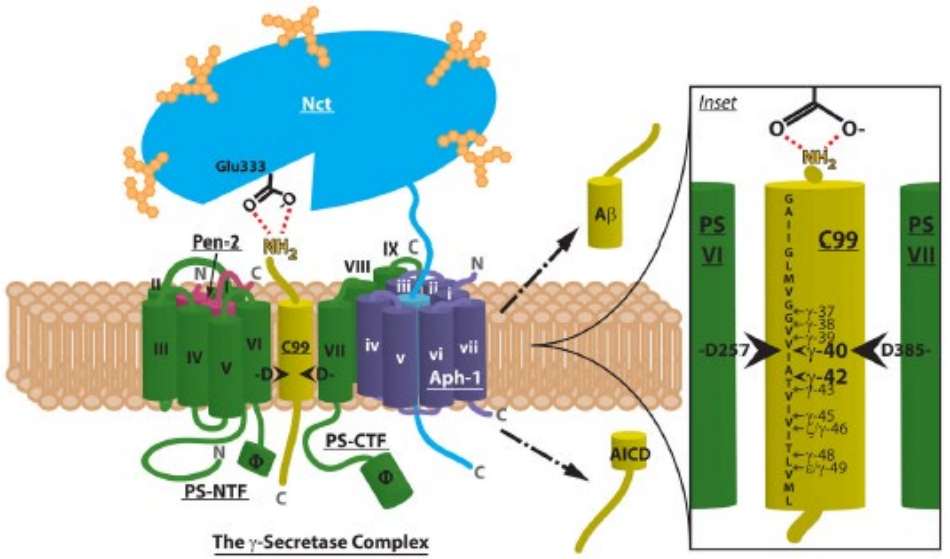
- *APP*
- *PSEN1*
- *PSEN2*

## Sporadic
(Non-mendelian risk genes)

- *APOE*
- *TREM2*
- *Possibly others*

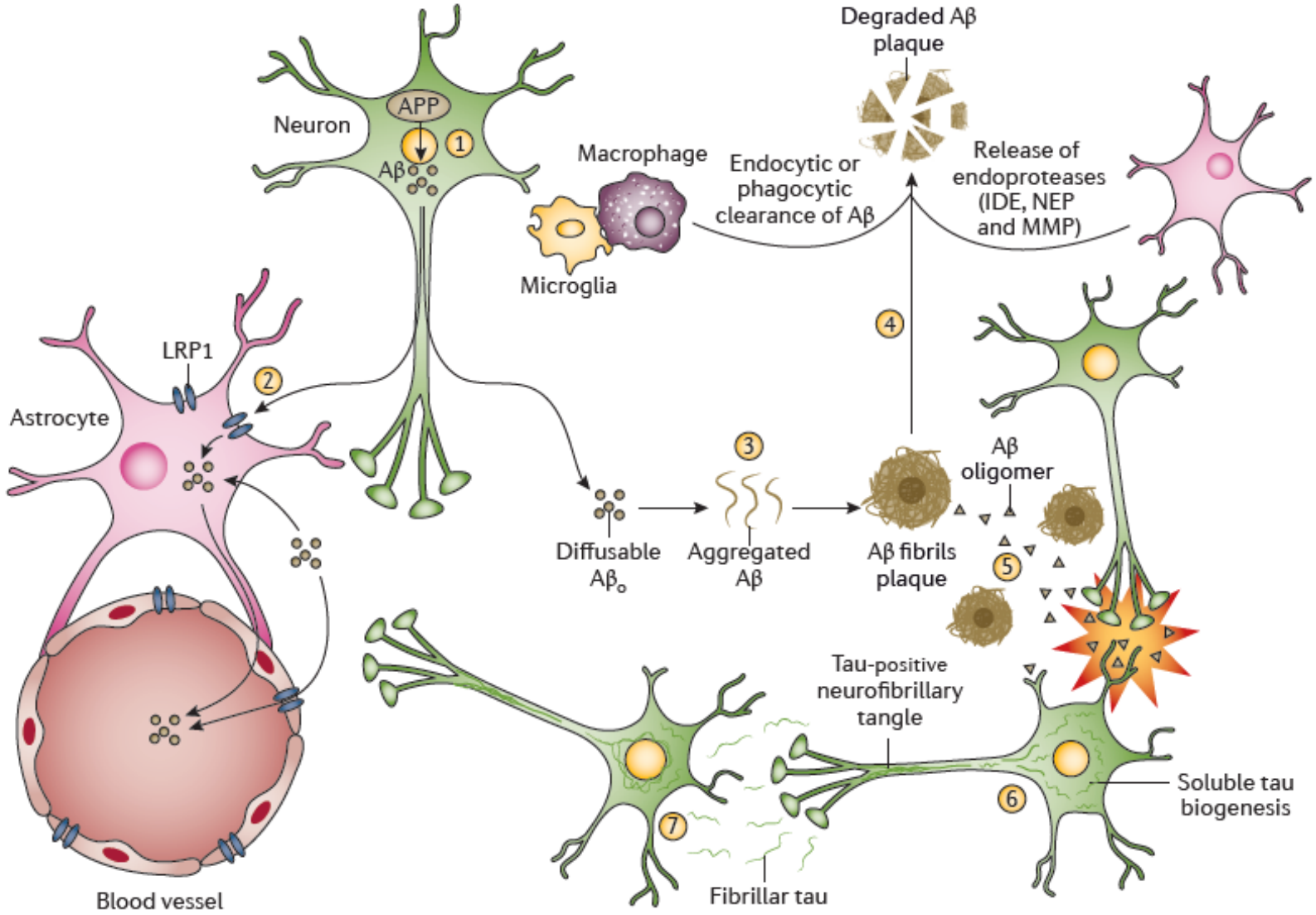
# APP



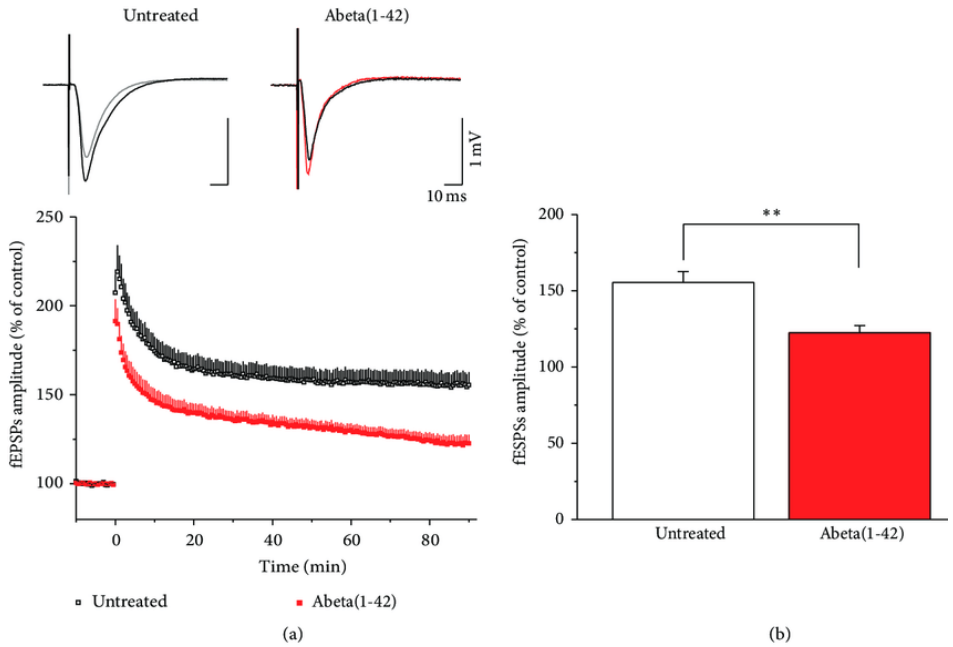



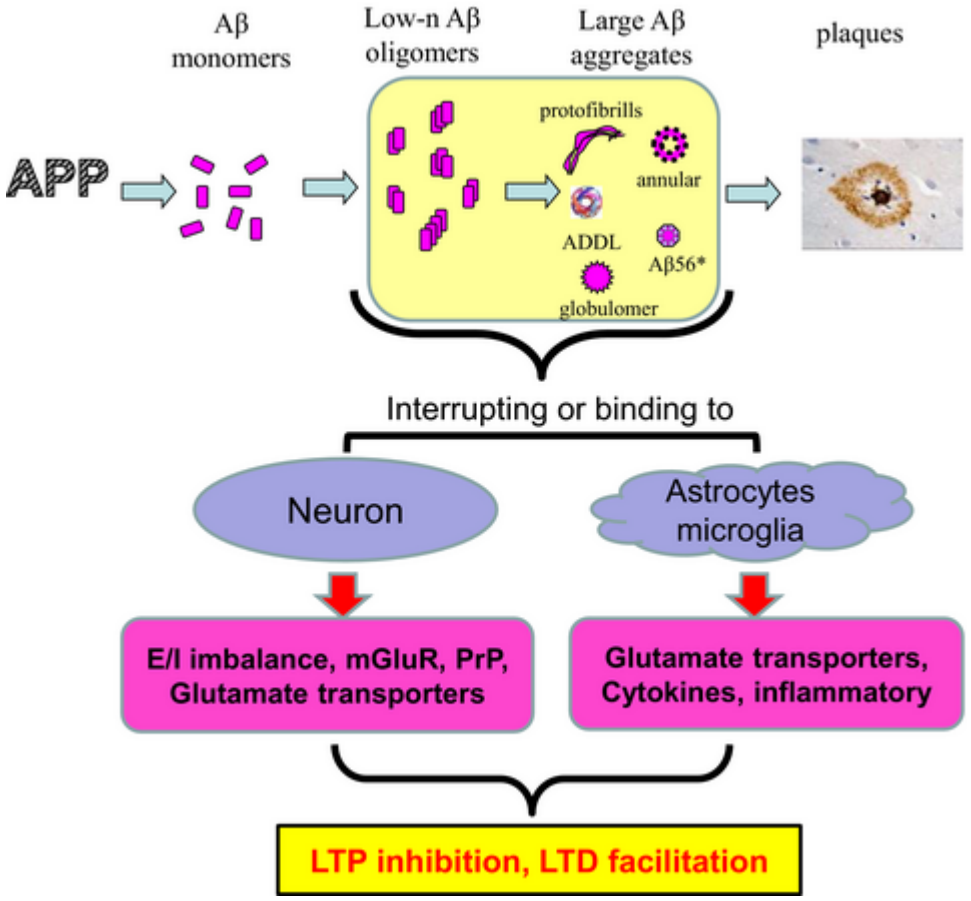

*Curr Alzheimer Res*. 2008 April ; 5(2): 132–146.

# Pathogenesis – Amyloid “hypothesis”



# Aβ at the synapse

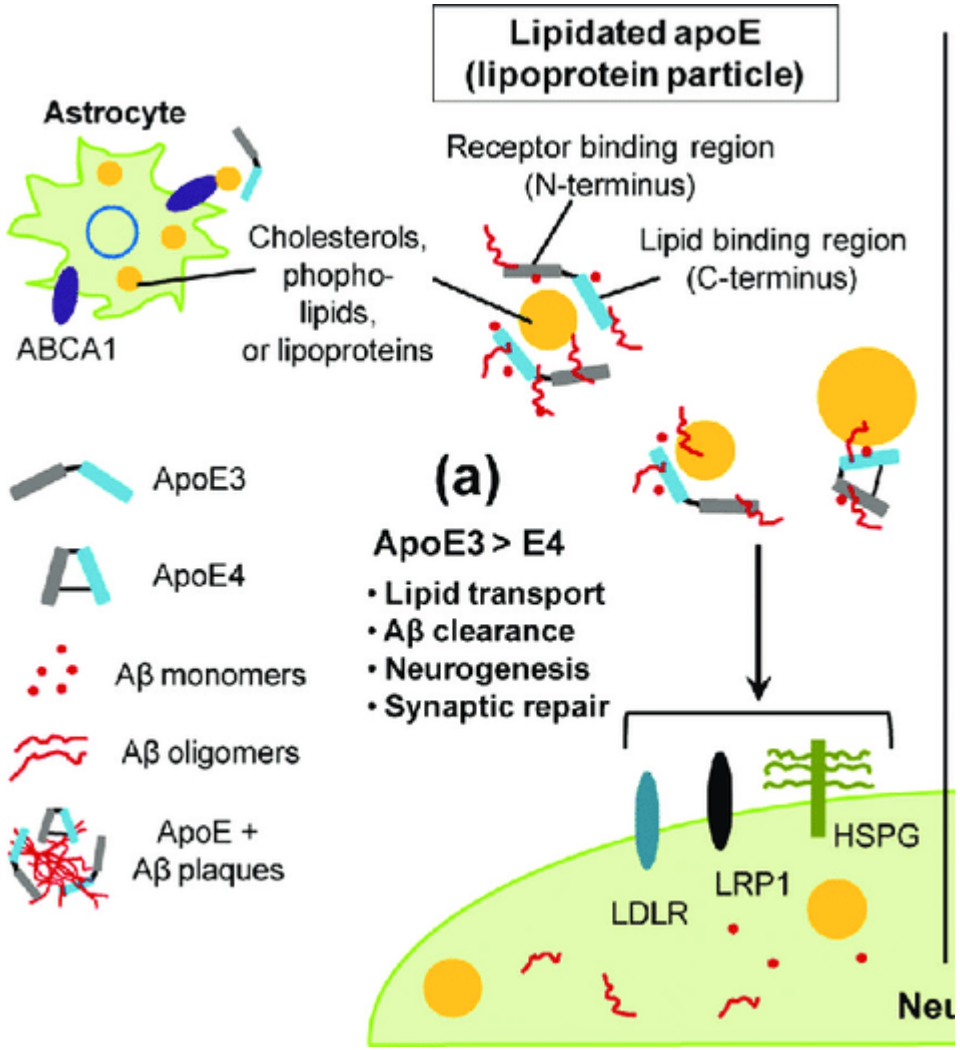



*Journal of Neurochemistry.* 2020;154:583–597.

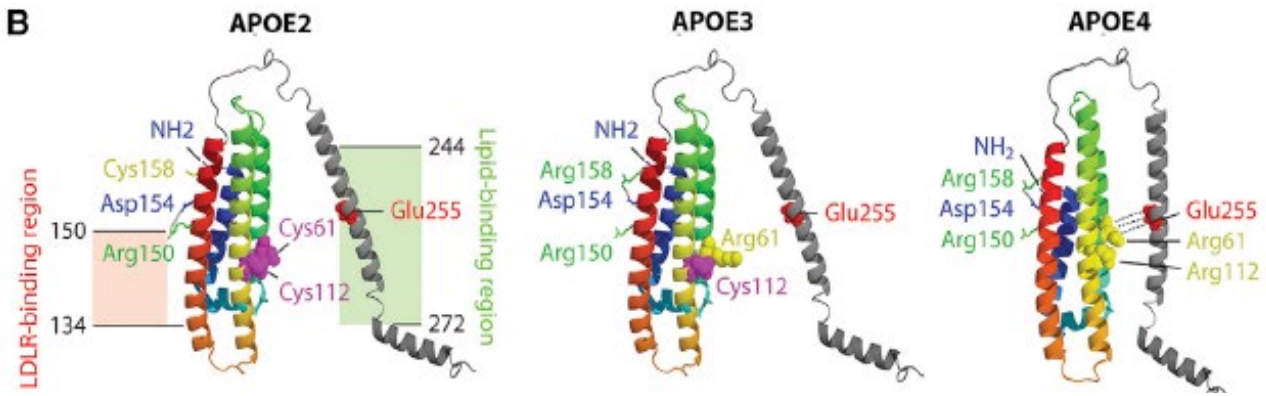
•Neural Plasticity 2014(3)

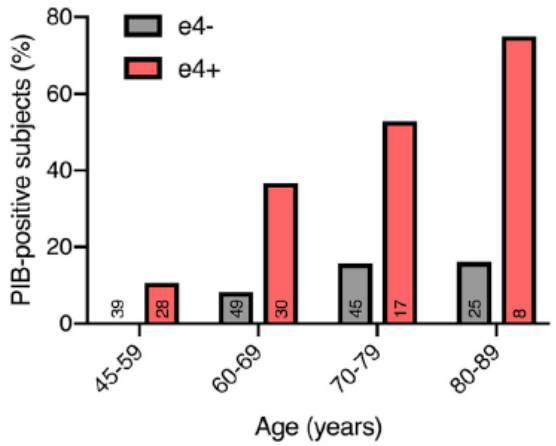
# APOE




A

| | Variant allele frequency | | Isoform amino acid (AA) differences | |
|---|---|---|---|---|
| | *Control* | *AD* | *AA 112* | *AA 158* |
| APOE2 | 8% | 4% | Cys | Cys |
| APOE3 | 78% | 59% | Cys | Arg |
| APOE4 | 14% | 37% | Arg | Arg |

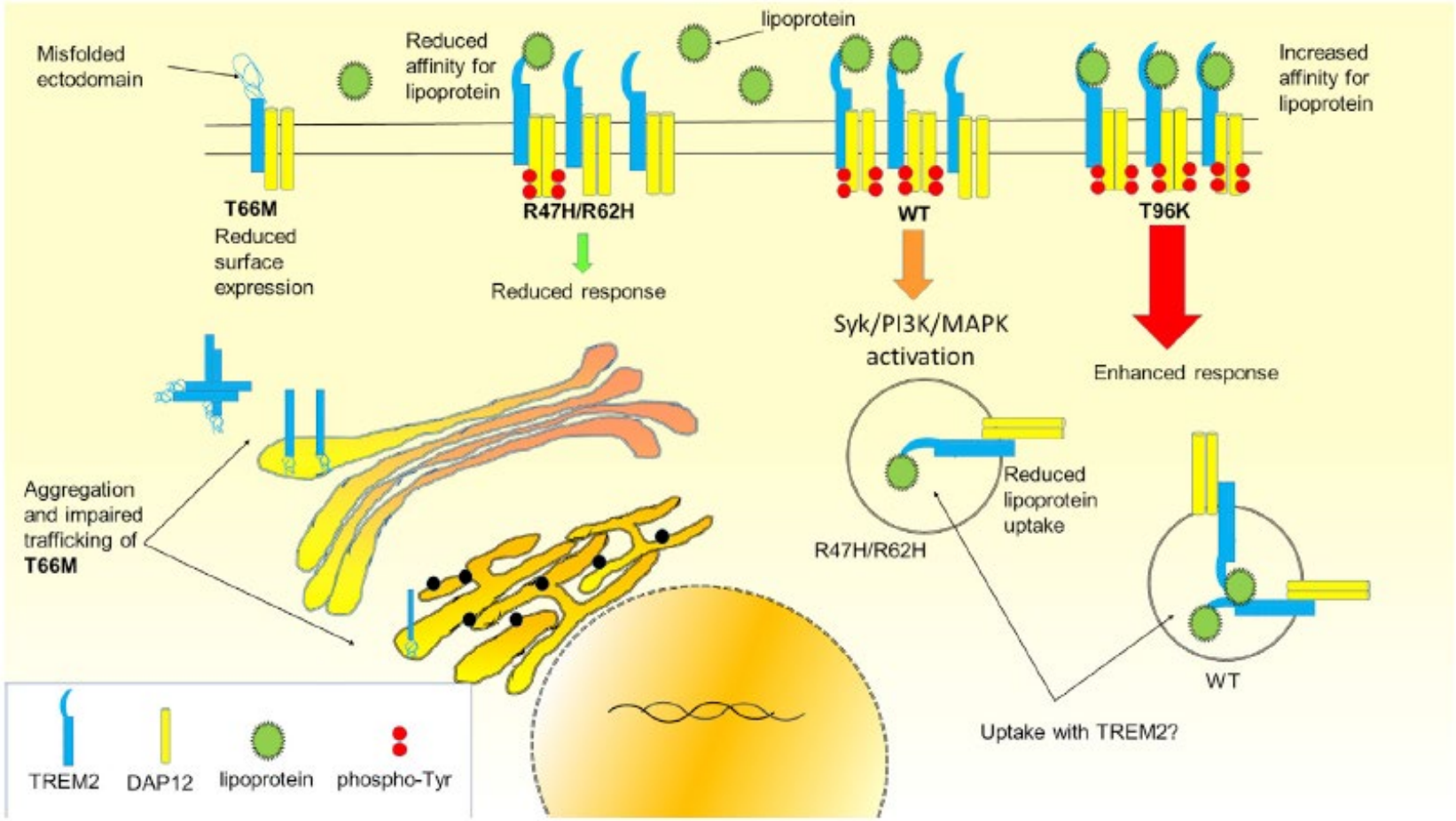



Kim, Kwang-Min & Palmore, G.. (2017). Lipoproteins and Diseases of the Brain. 10.5772/67053.

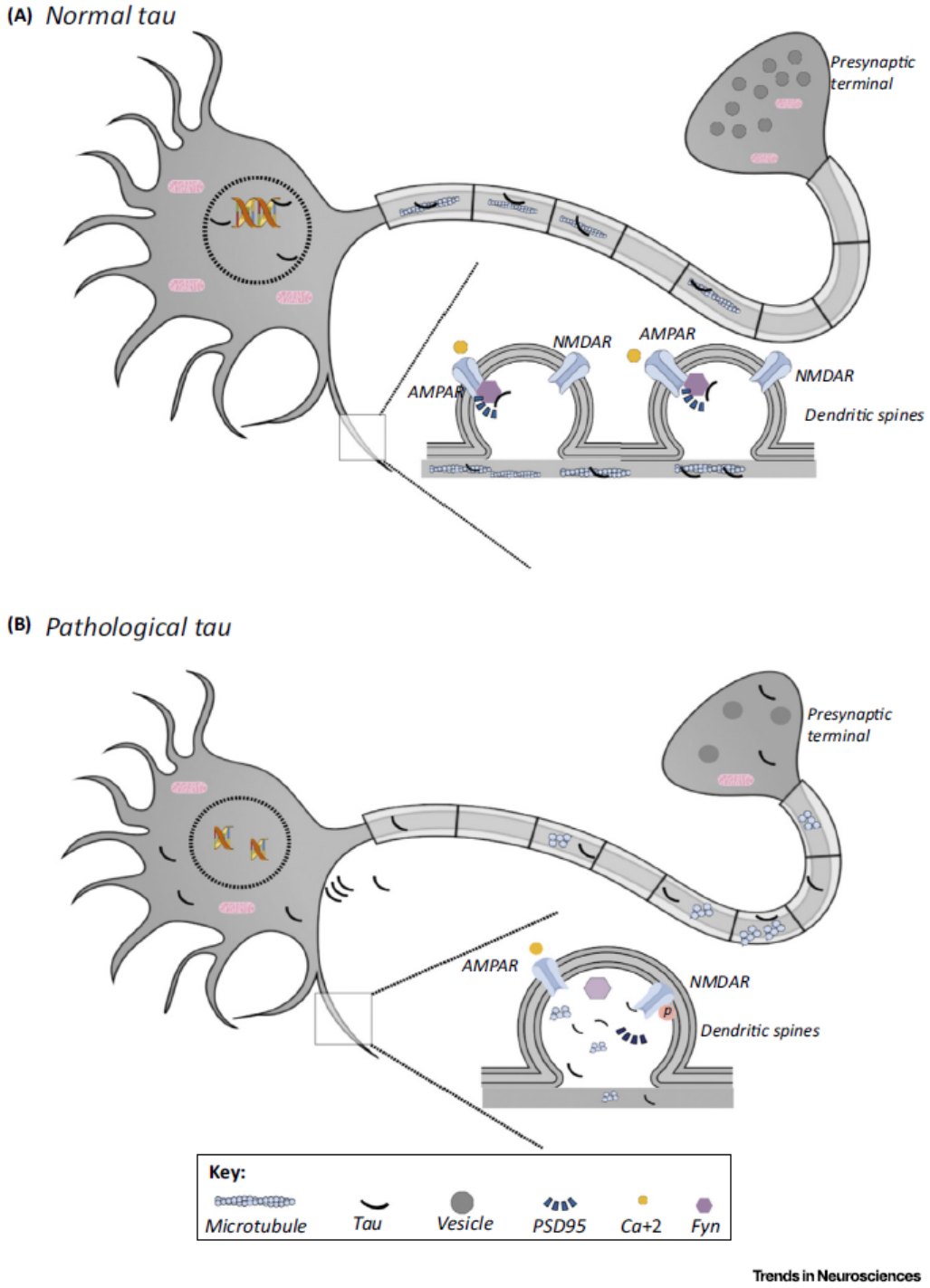
Neuron 101, March 6, 2019

# TREM2




Neuron 94, April 19, 2017

# Tau

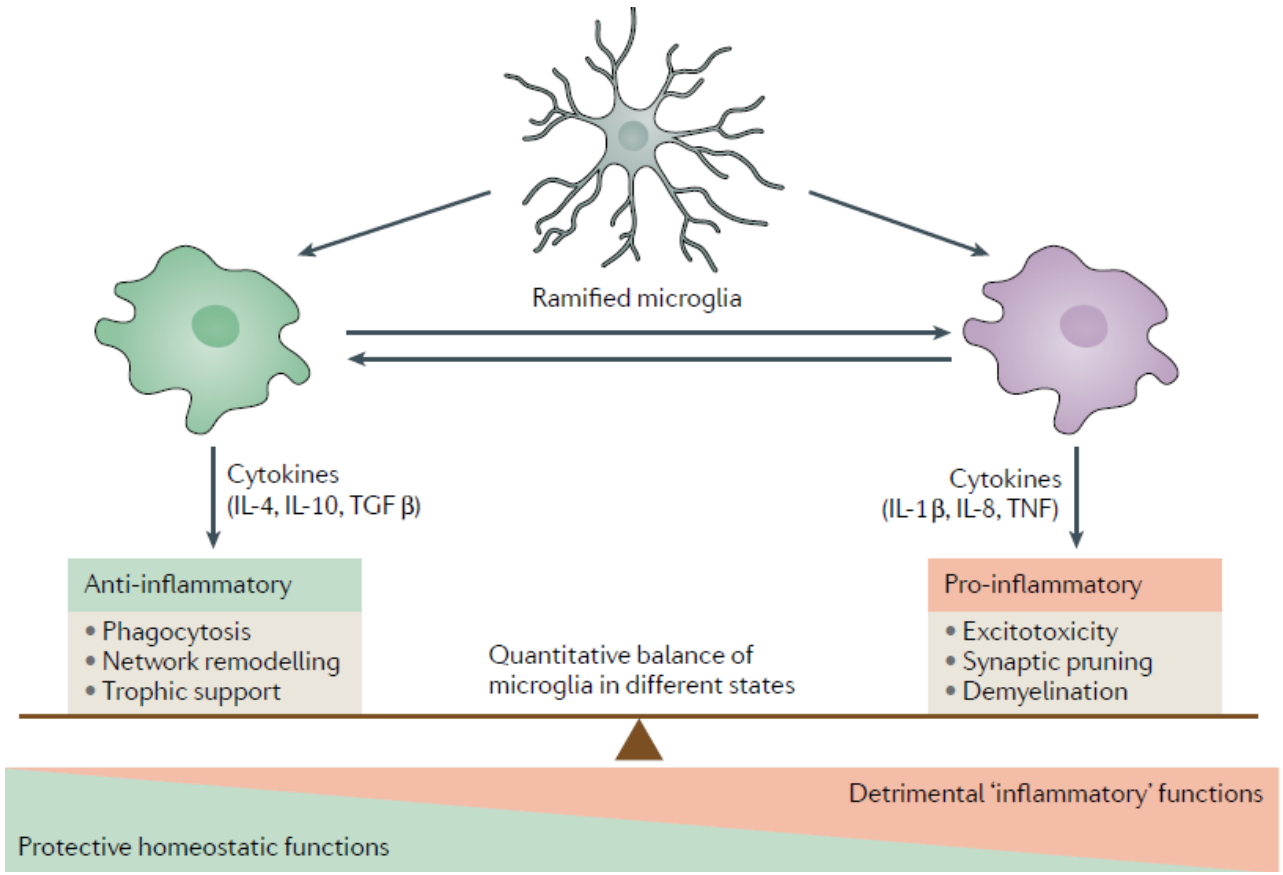


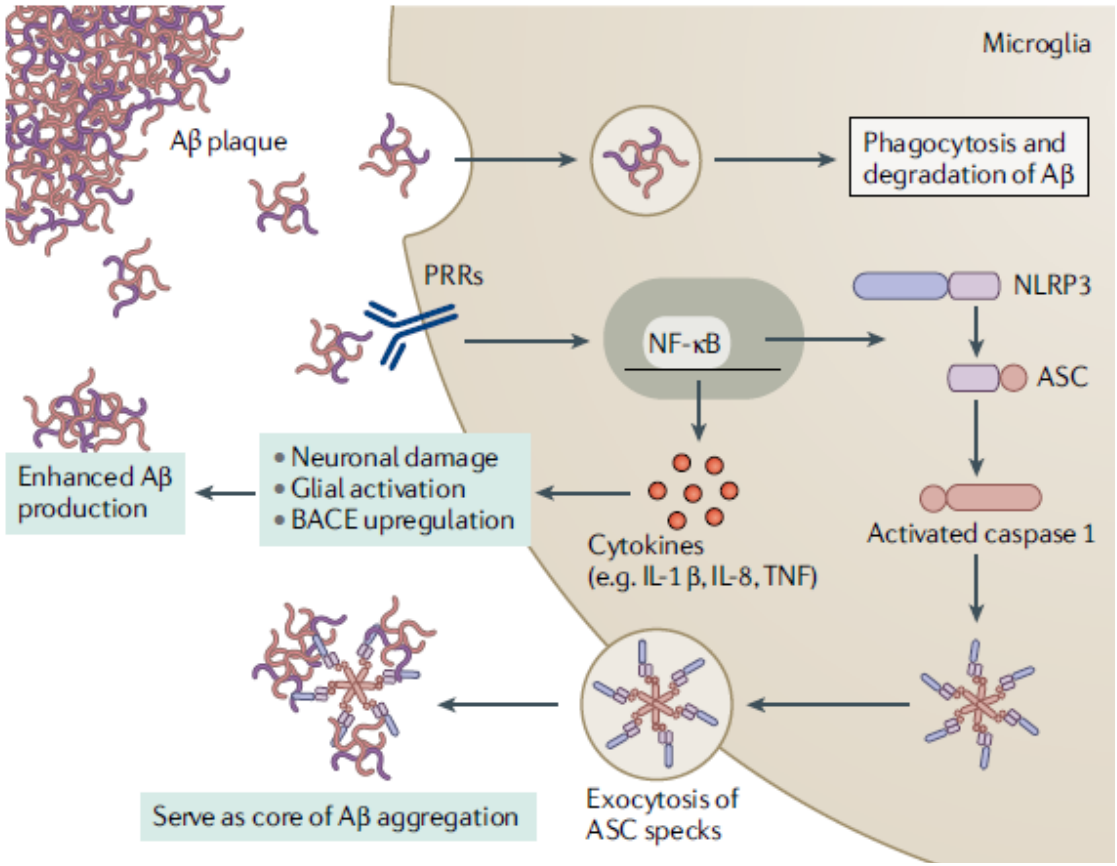

Trends in Neurosciences

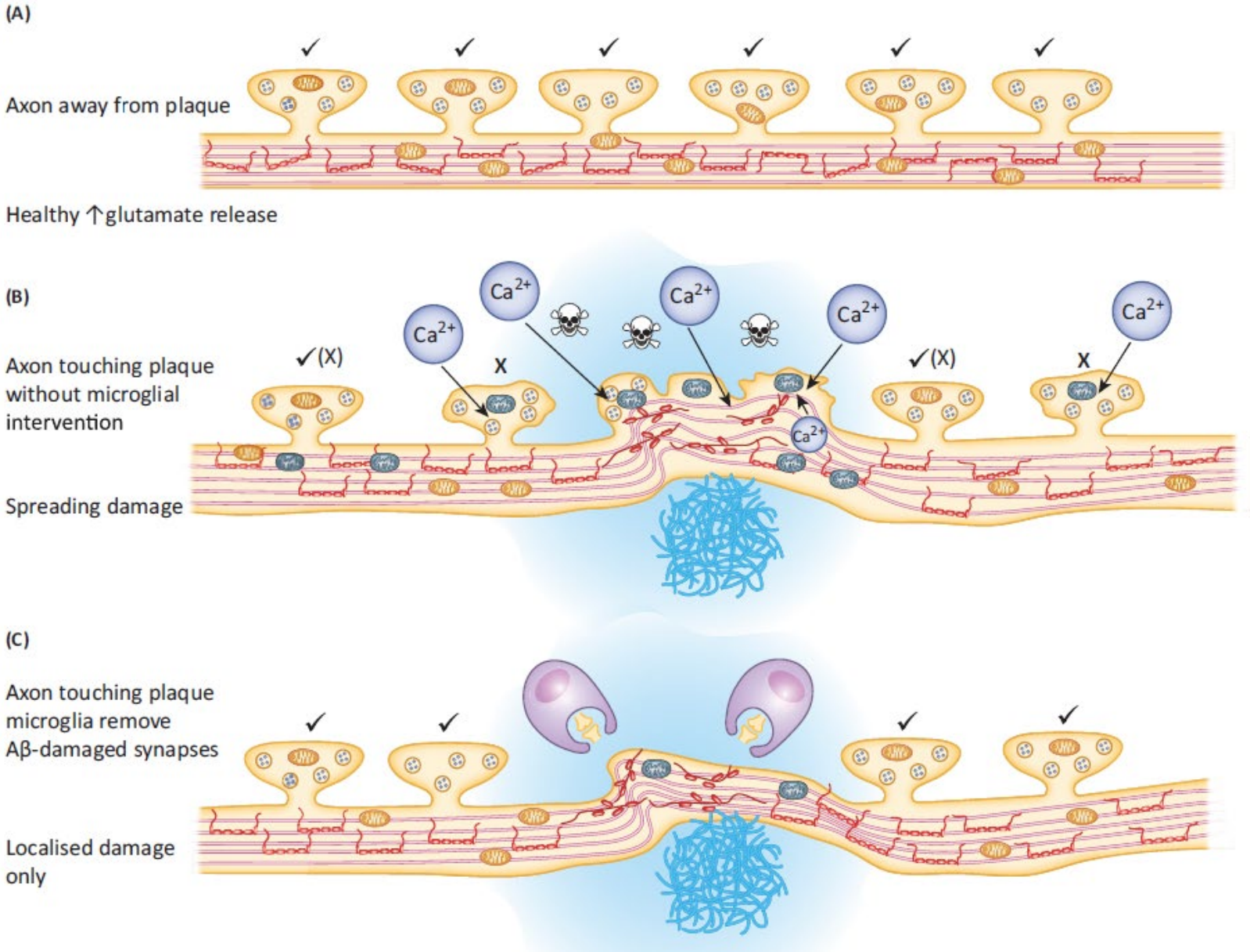
# Other “hypotheses”

- Vascular hypothesis
  - Risk factors for Alzheimer disease = Risk factors for atherosclerosis
  - (?) Atherosclerosis makes it more difficult to clear amyloid from the brain
  - (?) Amyloid pathology extends to intracranial vessels and causes a vascular component
- Metabolic/Insulin signaling hypothesis
- Excitotoxicity/$Ca^{++}$ toxicity/mitochondrial dysfunction hypotheses
  - NMDA antagonist memantine has small benefit
- Neuroinflammation/Microglia hypothesis

# Microglia “hypothesis”






Trends in Neurosciences, May 2019, Vol. 42, No. 5

# Are all neurodegenerative diseases Prion-(like) diseases?

**Like prions: the propagation of aggre and α-synuclein in neurodegeneratio**

Michel Goedert, Masami Masuda-Suzukake and Benjamin Falcon

*Neuropathology and Applied Neurobiology* (2020), 46, 522–545 doi: 10.1111/nan.125

**Invited Review: The role of prion-like mechanisms in neurodegenerative diseases**

Z. Jaunmuktane*† and S. Brandner*‡

Acta Neuropathol (2016) 132:577–592
DOI 10.1007/s00401-016-1582-9

**Human-to-mouse prion-like propagation of mutant huntingtin protein**

frontiers in Molecular Neuroscience

REVIEW
published: 01 November 2019
doi: 10.3389/fnmol.2019.00262

**Prion-like Properties of Pathological TDP-43 Aggregates from Diseased Brains**

Takashi Nonaka,[1,*] Masami Masuda-Suzukake,[1] Tetsuaki Arai,[2,3] Yoko Hasegawa,[1] Hiroyasu Akatsu,[4] Tomokazu Obi,[5] Mari Yoshida,[6] Shigeo Murayama,[7] David M.A. Mann,[8] Haruhiko Akiyama,[2] and Masato Hasegawa[1,*]

**Prion-Like Propagation of Protein Misfolding and Aggregation in Amyotrophic Lateral Sclerosis**

*Luke McAlary[1,2], Steven S. Plotkin[3,4], Justin J. Yerbury[1,2] and Neil R. Cashman[5]**

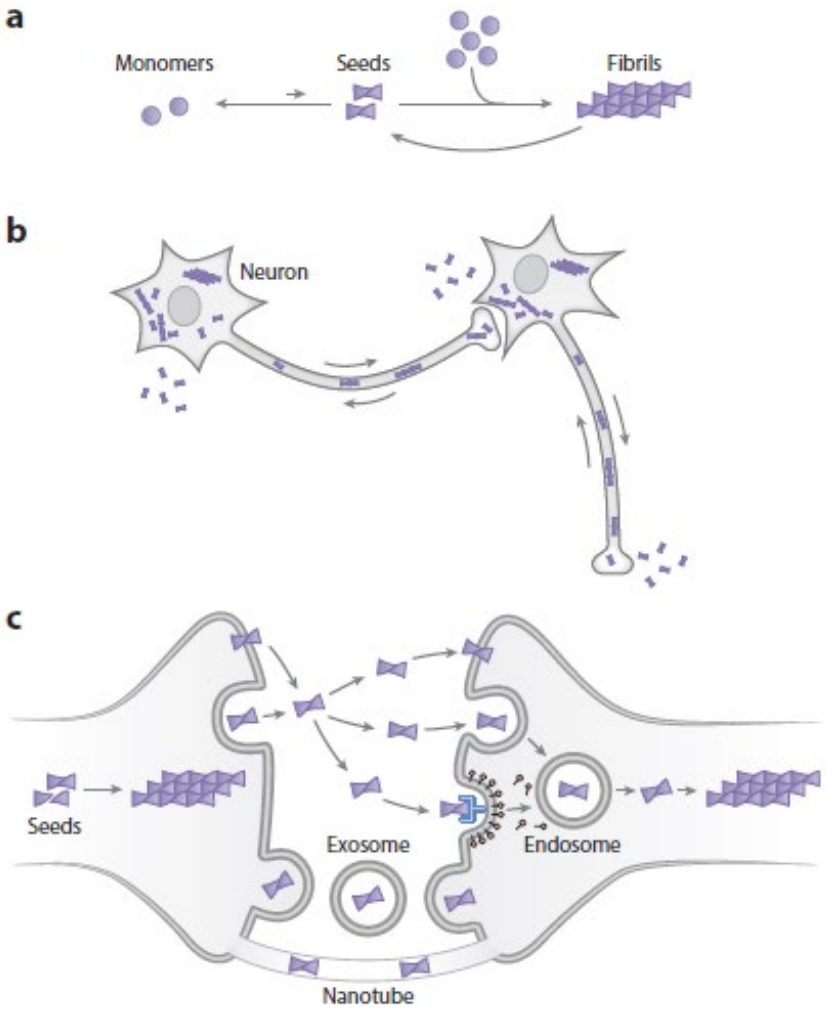
**The Prion-Like Properties of Amyloid-β Assemblies: Implications for Alzheimer's Disease**

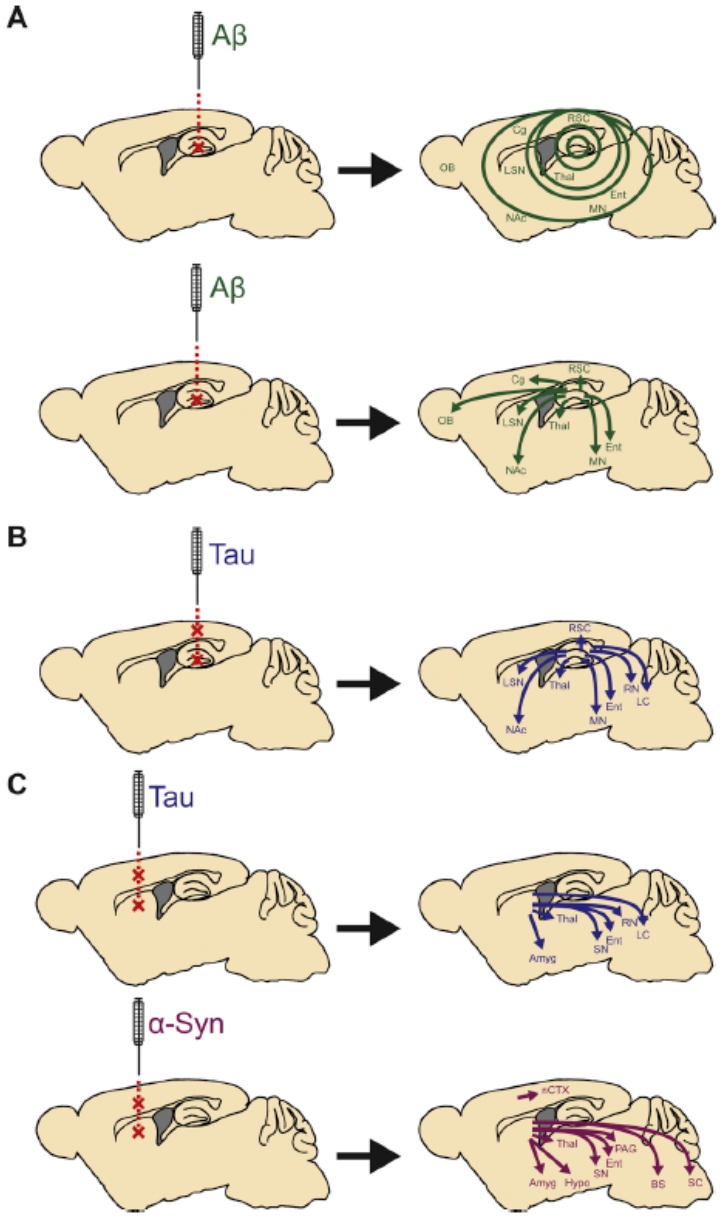
# Parkinson's Disease Is Not Simply a Prion Disorder

**D. James Surmeier,[1] José A. Obeso,[2,3] and Glenda M. Halliday[4,5]**

[1]Department of Physiology, Feinberg School of Medicine, Northwestern University, Chicago, Illinois 60611, [2]CINAC, HM Puerta del Sur, Hospitales de Madrid, Mostoles and CEU-San Pablo University, 28938 Madrid, Spain, [3]Network Center for Biomedical Research on Neurodegenerative Diseases, Instituto Carlos III, 28029 Madrid, Spain, [4]Brain and Mind Centre, Sydney Medical School, University of Sydney, Sydney, 2006 New South Wales, Australia, and [5]School of Medical Sciences, University of New South Wales and Neuroscience Research Australia, Sydney, 2052 New South Wales, Australia

The Journal of Neuroscience, October 11, 2017 • 37(41):9799–9807 • **9799**




Annu. Rev. Neurosci. 2017.40:189-210.

Neuroscience and Biobehavioral Reviews 112 (2020) 1–27

# Treatment of Dementias

1. Make a diagnosis if possible
    - Prognostic information
    - Valued by families and patients
    - May be important for pharmacological approaches, eg:
        - DLB
            - May benefit more from cholinesterase inhibitors
            - Avoid Haloperidol!
2. Control vascular risk factors

# Treatment of Alzheimer Disease

- No disease modifying treatments
- Symptomatic pharmacotherapy
  - Cholinesterase inhibitors (Donepezil, Galantamine, Rivastigmine)
    - Modest benefit in MMSE scores (+1-1.5 points, equivalent to ~3-9 months slowing of progression) and Global Impression Scales
    - ? Benefit for delaying nursing home placement, or caregiver QOL
    - Probably no benefit for patient QOL
    - Diarrhea and bradycardia can be limiting
  - Memantine (NMDA antagonist)
    - Only approved for moderate-severe dementia.
    - Modest benefit (+1 – 1.5 points) on MMSE scores
    - Probably no benefit for delaying nursing home placement

# Treatment of Neuropsychiatric Symptoms

- Pharmacotherapy is of limited benefit!
- Look for the cause!
  - Pain – may have to treat empirically!
  - Sleep deprivation – Circadian rhythm disturbance – “Sundowning”
  - Medication side effects
  - Changes to routine; strict, impersonal routines
  - Depression – may have to treat empirically!
  - Delirium (UTIs, drugs, insomnia, any non-trivial medical illness)
  - Hearing and vision problems – Hearing aids and eye-glasses!
  - Misperception, misunderstandings, caregiver fatigue/frustration

# Treatment of Agitated Behaviors

- Non-pharmacological methods are *moderately* effective. Encourage them at every opportunity
  - Caregiver education
  - Distraction and redirection
  - Structured but personalized routines
  - Exposure to sunlight in the morning (best option for sleep issues!)
  - Music therapy
  - Massage therapy
  - Aromatherapy
  - Exercise training

# Pharmacotherapy for Agitation

- Anti-dementia meds
  - No evidence of benefit for behavioral Sxs, reasonable to try if tolerated

- SSRIs
  - Citalopram (QTc prolongation!) and Sertraline have RCT evidence of slight benefit
  - Trazodone may have additional benefit of ↑ slow-wave sleep, no RCT evidence but some expert opinion recommendations for agitation

# Antipsychotics for Agitation in Dementia

- Often treatment of last resort for severe agitation
- BBW for increased mortality (believed to be due to excess CVD/strokes)
- Probably more effective if frank psychosis (hallucinations, delusions) exists
- 2nd generation (olanzapine, risperidone, quetiapine) preferred, start low, go slow

# Future Treatments

Table 1 | **Principal failed clinical studies on anti-Aβ therapies in AD and related disorders**

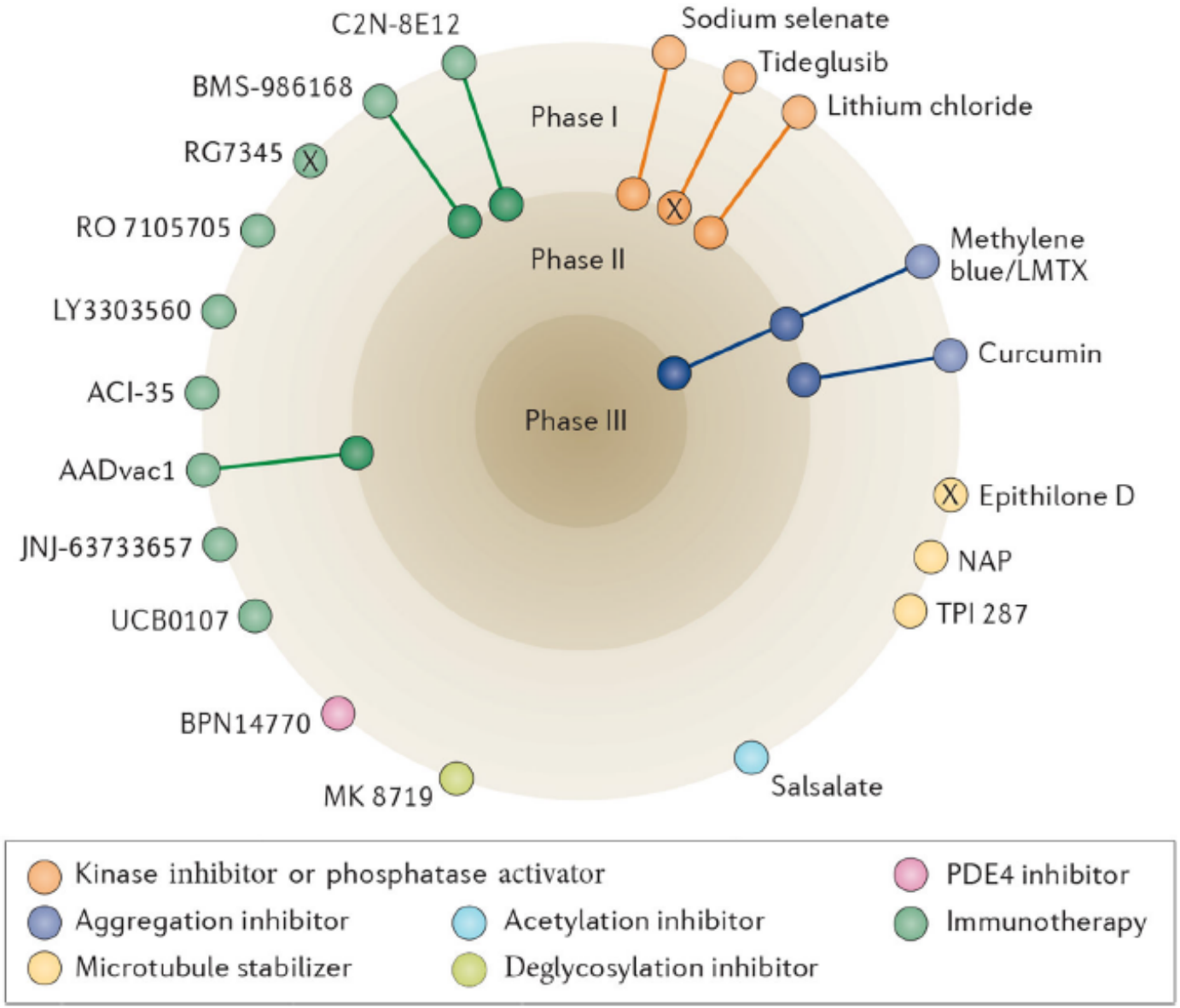
| Drug | Company | Mechanism of action | Patient population | Trial phase | Main reasons for failure | Remarks |
|---|---|---|---|---|---|---|
| 2002 | | | | | | |
| AN-1792 (REF.[35]) | Elan | Aβ antigen | Mild to moderate AD | II | Toxicity and lack of efficacy | – |
| 2007 | | | | | | |
| Tramiprosate[204] | Neurochem | Aβ aggregation inhibitor | Mild to moderate AD | III | Lack of efficacy | – |
| 2009 | | | | | | |
| Tarenflurbil[205] | Myriad Genetics/ Lundbeck | γ-Secretase modulator | Mild AD | III | Lack of efficacy | Worsens global status |
| Scyllo-inositol[206] | Transition Therapeutics/Elan | Aβ aggregation inhibitor | Mild to moderate AD | II | Toxicity and lack of efficacy | • Increases mortality<br>• Inactivates Aβ oligomers |
| 2010 | | | | | | |
| Begacestat[207] | Wyeth | γ-Secretase inhibitor | Mild to moderate AD | II | Toxicity and lack of efficacy | – |
| 2011 | | | | | | |
| Ponezumab[208] | Pfizer | Anti-Aβ monoclonal antibody | Mild to moderate AD | II | Lack of efficacy | – |
| Semagacestat[209] | Eli Lilly | γ-Secretase inhibitor | Mild to moderate AD | III | Toxicity and lack of efficacy | Worsens cognition |
| 2012 | | | | | | |
| Bapineuzumab[210] | Elan/Wyeth | Anti-Aβ monoclonal antibody | Mild to moderate AD | III | Lack of efficacy | – |
| Avagacestat[211] | Bristol-Myers Squibb | γ-Secretase inhibitor | Mild to moderate AD | II | Toxicity and lack of efficacy | Worsens cognition |
| Avagacestat[212] | Bristol-Myers Squibb | γ-Secretase inhibitor | Prodromal AD | II | Toxicity and lack of efficacy | Worsens cognition |
| 2013 | | | | | | |
| Solanezumab[49] | Eli Lilly | Anti-Aβ monoclonal antibody | Mild to moderate AD | III | Lack of efficacy | – |
| Vanutide[36] | Janssen | Aβ antigen | Mild to moderate AD | II | Lack of efficacy | – |
| Immunoglobulin[213] | Baxter | Anti-Aβ polyclonal antibody | Mild to moderate AD | III | Lack of efficacy | – |
| LY2886721 (REF.[214]) | Eli Lilly | β-Secretase inhibitor | Mild to moderate AD | II | Toxicity | – |
| AZD3839 (REF.[215]) | AstraZeneca | β-Secretase inhibitor | Healthy volunteers | I | Toxicity | – |
| 2014 | | | | | | |
| Affitope AD02 (REF.[216]) | Affiris/ GlaxoSmithKline | Aβ antigen | Early AD | II | Lack of efficacy | Worsens cognition |
| CAD106 (REF.[40]) | Novartis | Aβ antigen | Mild AD | II | Lack of efficacy | Worsens cognition |
| PBT2 (REF.[217]) | Prana Biotechnology | Aβ aggregation inhibitor | Prodromal AD | II | Lack of efficacy | – |
| Crenezumab[65] | Genentech/Roche | Anti-Aβ monoclonal antibody | Mild to moderate AD | II | Lack of efficacy | Binds oligomeric Aβ |
| Gantenerumab[57] | Chugai/Roche | Anti-Aβ monoclonal antibody | Prodromal AD | II | Lack of efficacy | Binds oligomeric Aβ |
| Gantenerumab[59] | Chugai/Roche | Anti-Aβ monoclonal antibody | Mild AD | II | Lack of efficacy | Binds oligomeric Aβ |
| 2016 | | | | | | |
| Solanezumab[50] | Eli Lilly | Anti-Aβ monoclonal antibody | Mild AD | III | Lack of efficacy | – |
| Solanezumab[218] | Eli Lilly | Anti-Aβ monoclonal antibody | Prodromal AD | III | Strategic | – |
| Verubecestat[80] | Merck | BACE inhibitor | Mild to moderate AD | III | Lack of efficacy | • Increases mortality<br>• Worsens cognition |
| 2018 | | | | | | |
| Verubecestat[82] | Merck | BACE inhibitor | Prodromal AD | III | Lack of efficacy | Worsens cognition |
| Atabecestat[96] | Janssen | BACE inhibitor | Asymptomatic at risk of AD | III | Toxicity | Worsens cognition |
| Lanabecestat[88] | • Astra<br>• Eli Lilly | BACE inhibitor | Early AD | III | Lack of efficacy | Worsens cognition |
| Lanabecestat[88] | • Astra<br>• Eli Lilly | BACE inhibitor | Mild AD | III | Lack of efficacy | Worsens cognition |

Studies are grouped by year of publication of the main results. Aβ, amyloid-β; AD, Alzheimer disease; BACE, β-secretase.

Table 2 | **Ongoing double-blind, placebo-controlled phase III studies of anti-Aβ therapies for AD and related disorders**

| Study and sponsor | Drug(s) | Mechanism of action | Study cohort and treatment duration | Primary outcomes | Expected completion |
|---|---|---|---|---|---|
| • AMBAR (NCT01561053)<br>• Grifols Biologicals | Immunoglobulin + albumin | Polyclonal antibodies | • 496 patients with mild to moderate AD<br>• 14 months | • ADAS-Cog<br>• ADCS-ADL | Completed[219] |
| • NCT02293915<br>• Shanghai Green Valley | Sodium oligo-mannurarate (GV-971) | Aβ aggregation inhibitor | • 818 patients with mild to moderate AD<br>• 72 weeks | ADAS-Cog | Completed[220] |
| • NCT02051608<br>• Roche–Genentech | Gantenerumab | Monoclonal antibody | • 1,000 patients with mild AD<br>• 100 weeks | • ADAS-Cog13<br>• ADCS-ADL | July 2020 |
| • MissionAD1 (NCT02956486)<br>• Eisai–Biogen | Elenbecestat | BACE inhibitor | • 1,330 patients with early AD<br>• 24 months | CDR-SB | December 2020 |
| • MissionAD2 (NCT03036280)<br>• Eisai–Biogen | Elenbecestat | BACE inhibitor | • 1,330 patients with early AD<br>• 24 months | CDR-SB | December 2020 |
| • API ADAD (NCT01998841)<br>• Roche–Genentech | Crenezumab | Monoclonal antibody | • 252 asymptomatic *PSEN1* Glu280Ala carriers<br>• 60 months | APCC | February 2022 |
| • EMERGE (NCT02477800)<br>• Biogen | Aducanumab | Monoclonal antibody | • 1,350 patients with early AD<br>• 78 weeks | CDR-SB | March 2022 |
| • ENGAGE (NCT02484547)<br>• Biogen | Aducanumab | Monoclonal antibody | • 1,350 patients with early AD<br>• 78 weeks | CDR-SB | April 2022 |
| • ADCS A4 (NCT02008357)<br>• Eli Lilly | Solanezumab | Monoclonal antibody | • 1,150 asymptomatic individuals at risk of AD<br>• 240 weeks | ADCS–PACC | July 2022 |
| • GRADUATE 1 (NCT03444870)<br>• Roche–Genentech | Gantenerumab | Monoclonal antibody | • 750 patients with early AD<br>• 104 weeks | CDR-SB | June 2023 |
| • GRADUATE 2 (NCT03443973)<br>• Roche–Genentech | Gantenerumab | Monoclonal antibody | • 750 patients with early AD<br>• 104 weeks | CDR-SB | June 2023 |
| • DIAN-TU (NCT01760005)<br>• Eli Lilly, Roche–Genentech and Janssen | • Solanezumab<br>• Gantenerumab<br>• Atabecestat | • Monoclonal antibody<br>• Monoclonal antibody<br>• BACE inhibitor | • 438 asymptomatic *APP* or *PSEN* mutation carriers<br>• 208 weeks | DIAN-TU composite score | December 2023 |
| • API Generation S1 (NCT02565511)<br>• Novartis | • CAD106<br>• CNP520 | • Aβ antigen<br>• BACE inhibitor | • 1,340 asymptomatic homozygous *APOE*ε4* carriers<br>• 60 months | • MCI diagnosis<br>• APCC | May 2024 |
| • API Generation S2 (NCT03131453)<br>• Novartis | CNP520 | BACE inhibitor | • 2,000 asymptomatic homozygous *APOE*ε4* carriers and heterozygous *APOE*ε4* carriers with brain amyloid accumulation<br>• 60 months | • MCI diagnosis<br>• APCC | July 2024 |

The table shows the status of studies on 10 July 2018, as reported in ClinicalTrials.gov. Aβ, amyloid-β; AD, Alzheimer disease; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive subscale; ADAS-Cog13, 13-item ADAS-Cog; ADCS-ADL, AD Cooperative Study–Activities of Daily Living; ADCS–PACC, Alzheimer's Disease Cooperative Study–Preclinical Alzheimer Cognitive Composite; APCC, Alzheimer disease Prevention Initiative Composite Cognitive; *APOE*, apolipoprotein E gene; *APP*, amyloid precursor protein gene; BACE, β-secretase; CDR-SB, Clinical Dementia Rating scale–Sum of Boxes; DIAN-TU, Dominantly Inherited Alzheimer Network–Trials Unit; MCI, mild cognitive impairment; *PSEN*, presenilin gene.

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