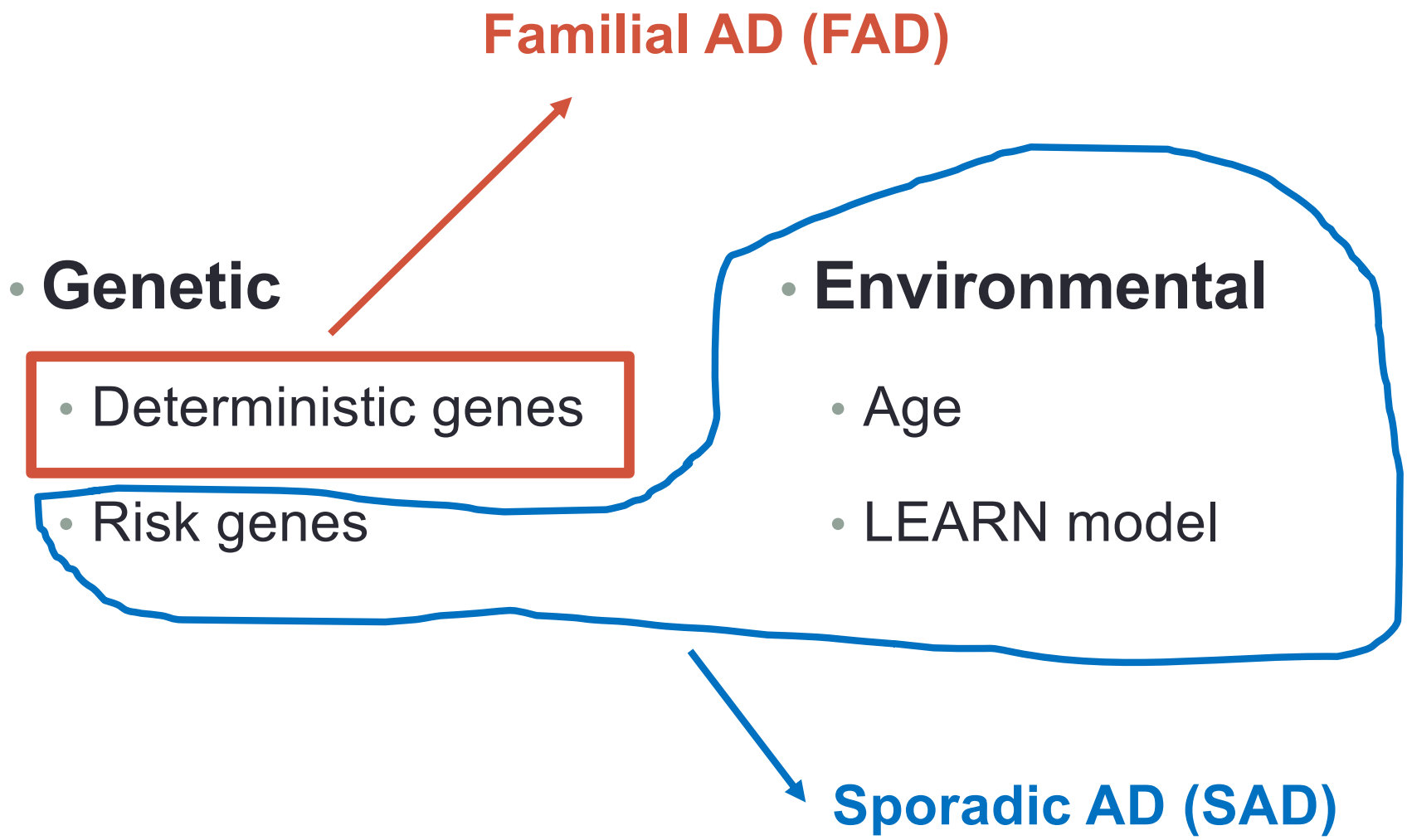
WEEK 8

ALZHEIMER'S DISEASE

Alzheimer's Disease – Overview

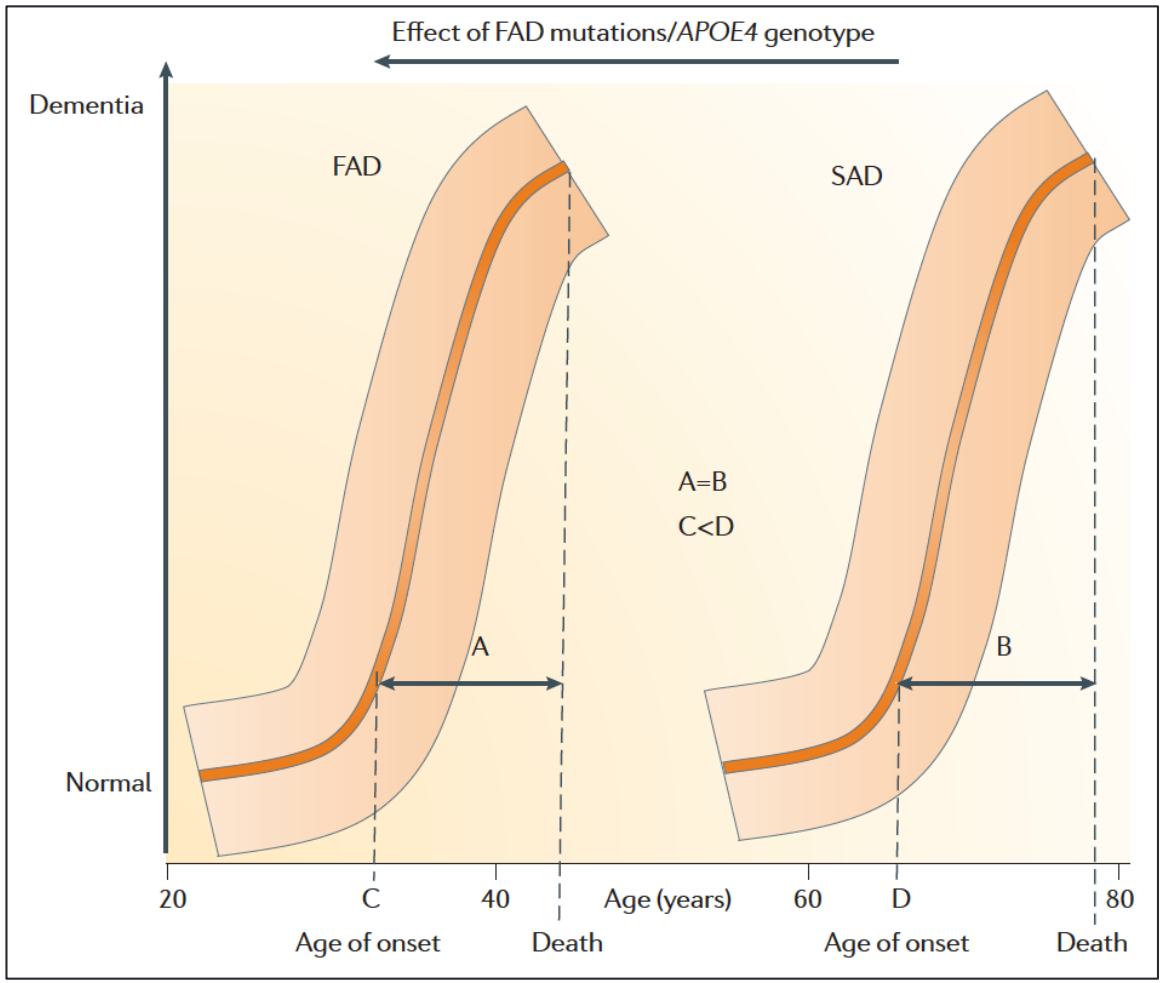
1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) **Risk factors**
   - Genes
   - Environment
6) Treatment approaches
7) Diagnostics and biomarkers

Risk factors for AD



Familial vs sporadic AD:

Familial AD (FAD)



Sporadic AD (LOAD)

LOAD=Late-onset Alzheimer's disease

Genetic risk factors for AD

- **Deterministic vs risk genes**:

1. **Deterministic genes**

= Directly cause a disease, everyone inheriting them will develop the disorder.

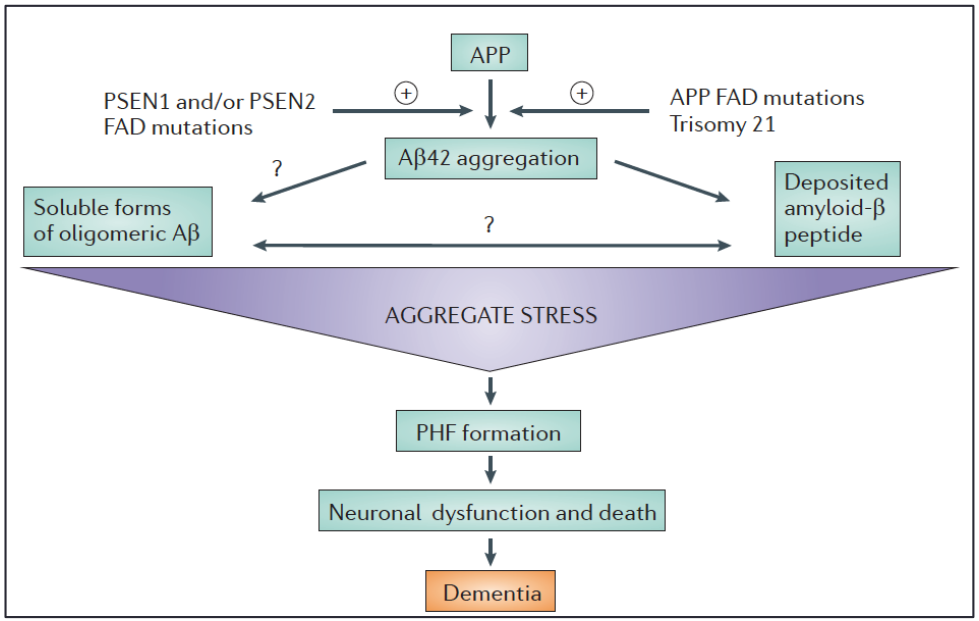
- Rare genes that directly cause Alzheimer's in only a few hundred extended families worldwide.
- These genes cause an early-onset of the disease
- This type is known as **"Familial Alzheimer's disease" (FAD)**
- **BUT**: True familial AD accounts for **less than 5%** of the cases.
  - The majority of cases do not have a genetic underpinning with high penetrance
  - This type of the disease is known as **"Sporadic Alzheimer's disease"**

Genetic risk factors for AD

- **Deterministic, early-onset genes**:
  - APP mutations
  - Mutations in PSEN1 and/or PSEN2:
    - Code for γ-secretase complex

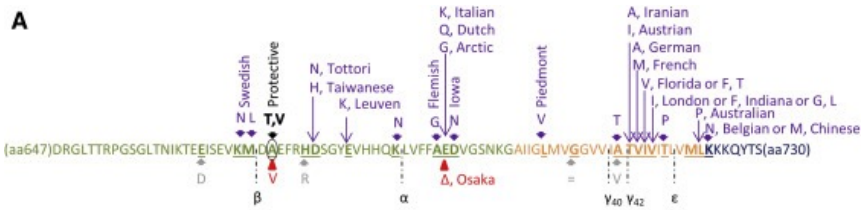
AD-Mutations

Chromosome 21	Chromosome 14	Chromosome 1
Abnormal **amyloid precursor protein (APP).**	Abnormal **presenilin 1**	Abnormal **presenilin 2**

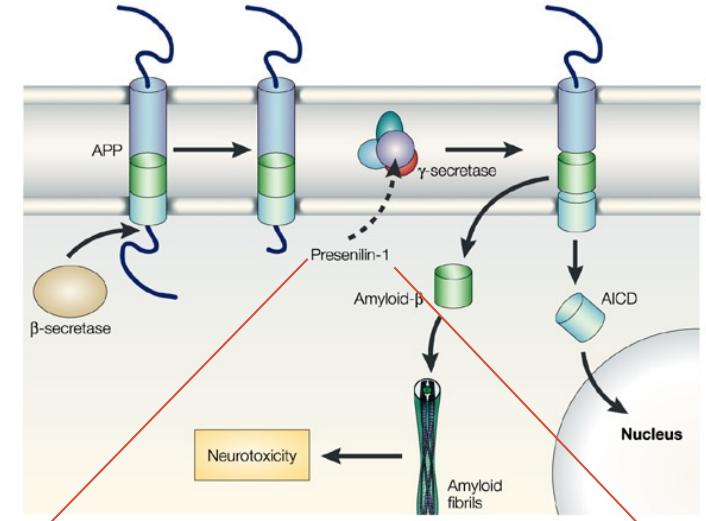


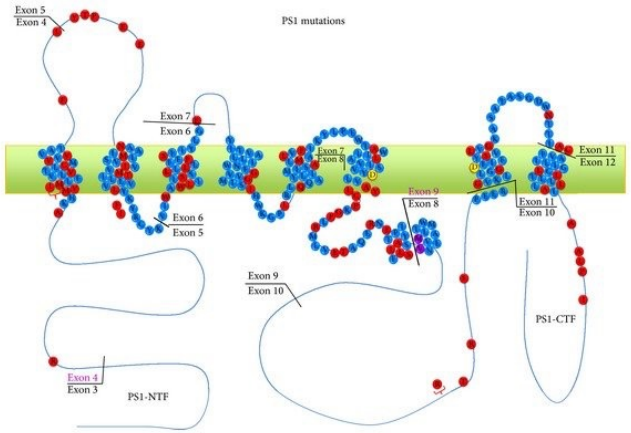
Genetic risk factors for AD

- APP mutations:



- PSEN mutations



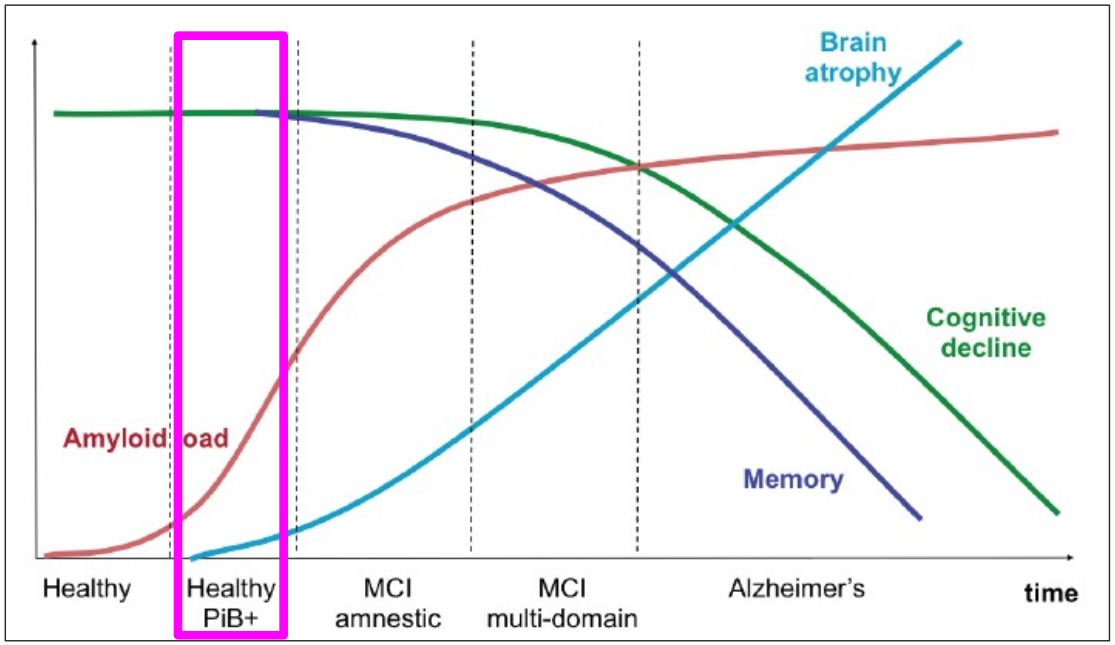


Familial AD

- The case of a Columbian village (video):
  - Yarumal, Columbia and its surroundings are home to the world's largest group of individuals with a hereditary form of AD
  - Members of 25 extended families, with 5,000 members, developed early onset Alzheimer's, if they have the mutated E280A in *PSEN1*
  - This population is the basis for an approach that will test drugs in patients **before the first signs of dementia appear**.

Familial AD

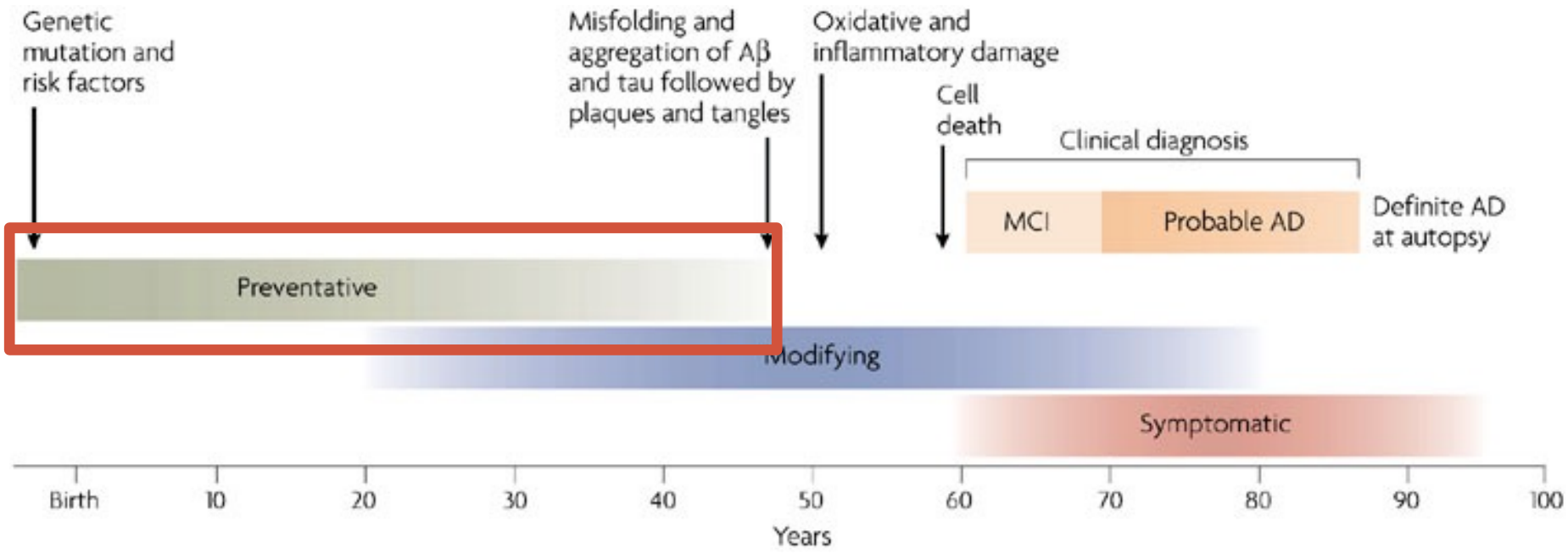
- The case of a Columbian village – The advantage of a clear trajectory:



Major issues with plaques in AD:
1) They appear (too) early for AD diagnosis, at non-symptomatic stages
2) They don't always correlate AD

Familial AD

- The case of a Columbian village – The advantage of an early treatment:



- Testing the amyloid cascade hypothesis

Genetic risk factors for AD

2. **Risk Genes**

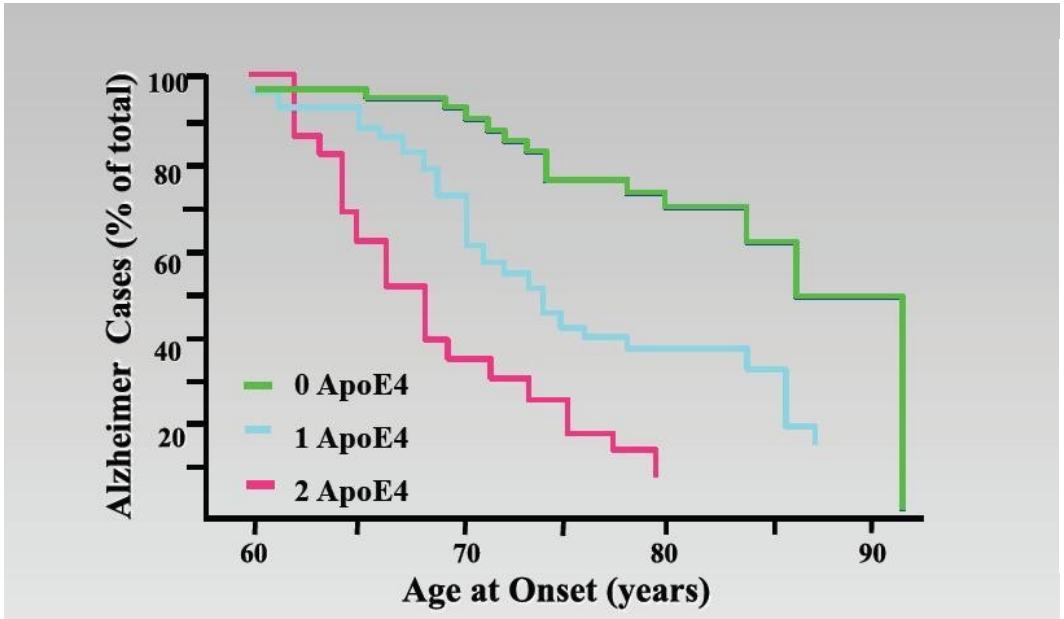
- Risk genes increase the likelihood of developing a disease but do not guarantee it will happen.
- **APOE-e4**

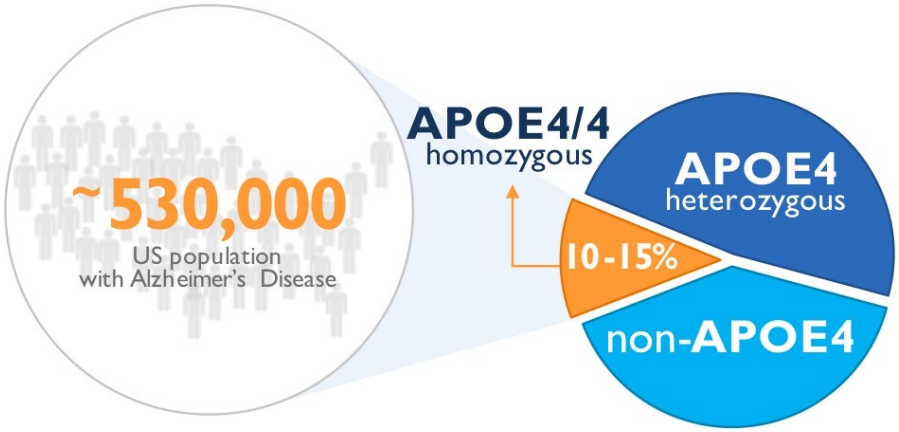
= one of three common forms of the APOE (apolipoprotein) gene.

- Those who inherit one copy of APOE-e4 have an increased risk of developing Alzheimer's.
- Those who inherit two copies have an even higher risk.
- In addition to raising risk, APOE-e4 may tend to make symptoms appear at a younger age than usual.

APOE4 is the strongest genetic risk factor for patients with late-onset (sporadic) Alzheimer's disease

Survival Curve



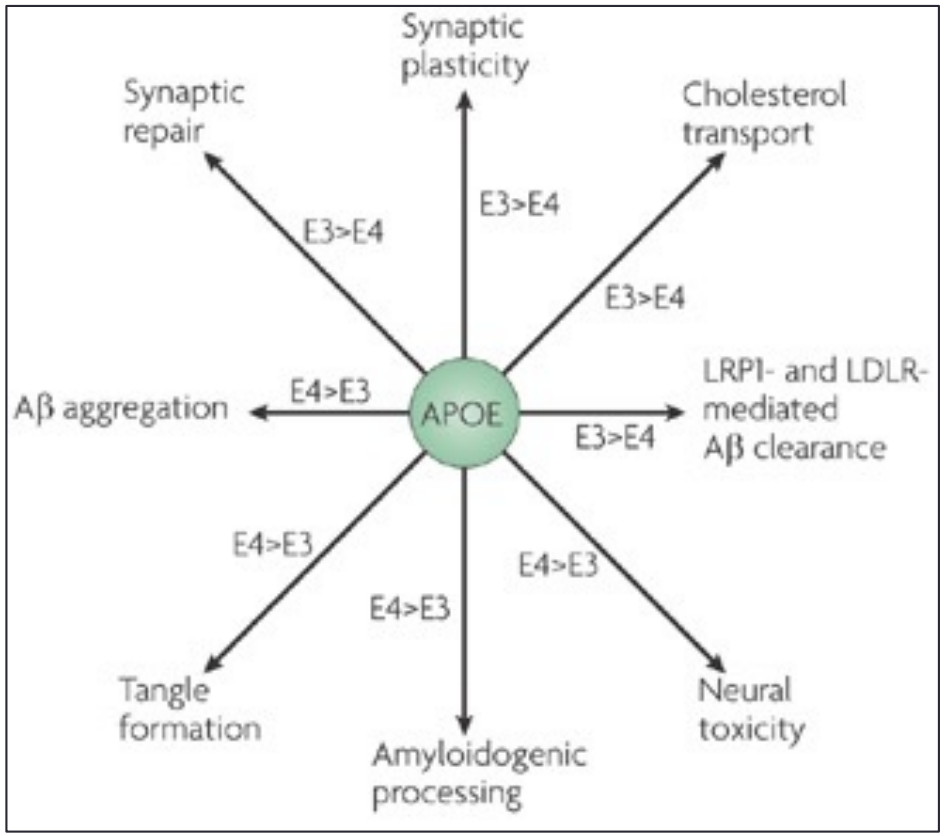


There are three major isoforms (ApoE2, ApoE3, and ApoE4) in humans.

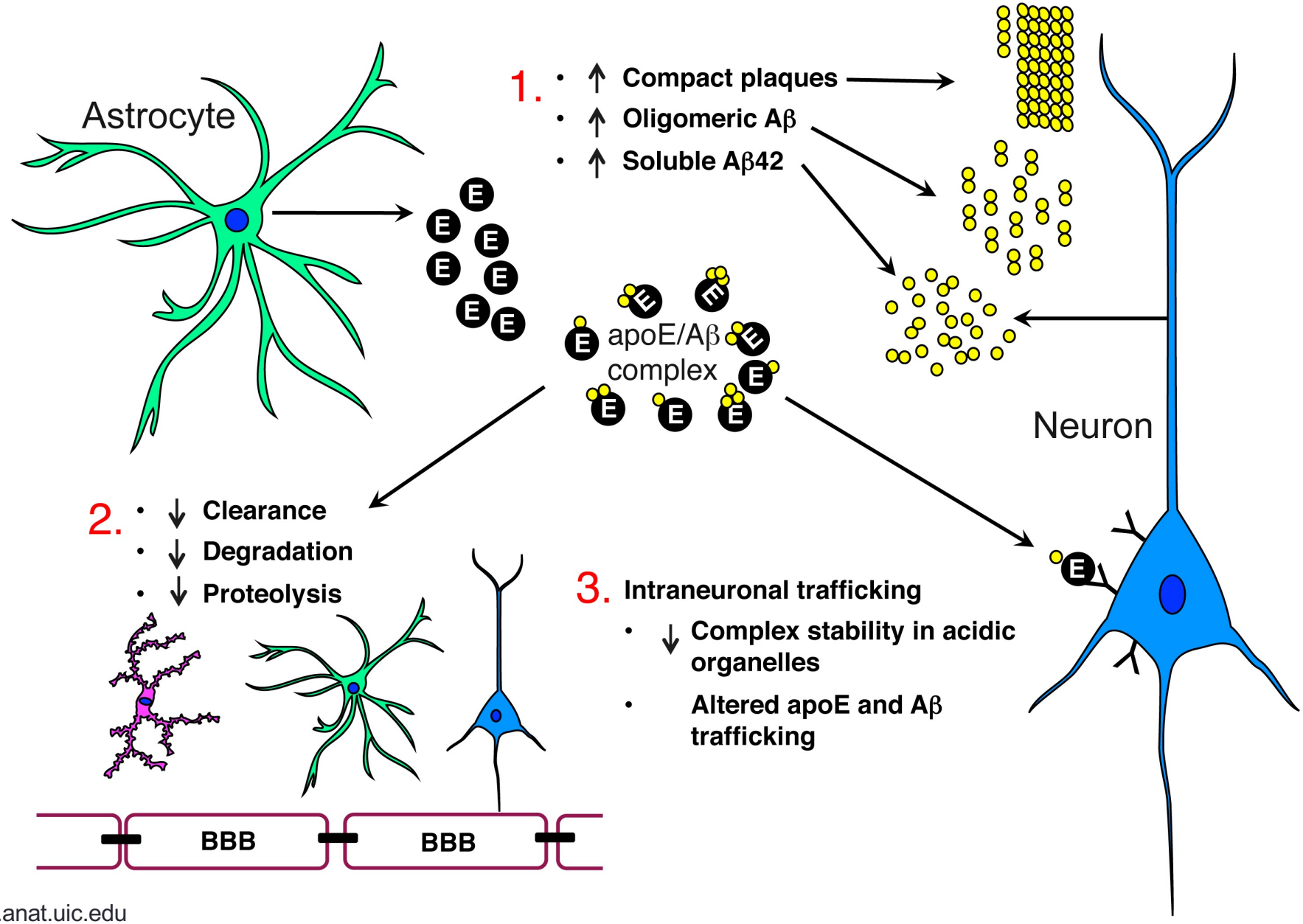
- ApoE is produced predominantly by astrocytes and to some extent microglia
- ApoE is also expressed in neurons in response to excitotoxic injury
- ApoE plays important role in the transport of HDL-like particles cholesterol and phospholipid between cells.

Genetic risk factors for AD: APOE4

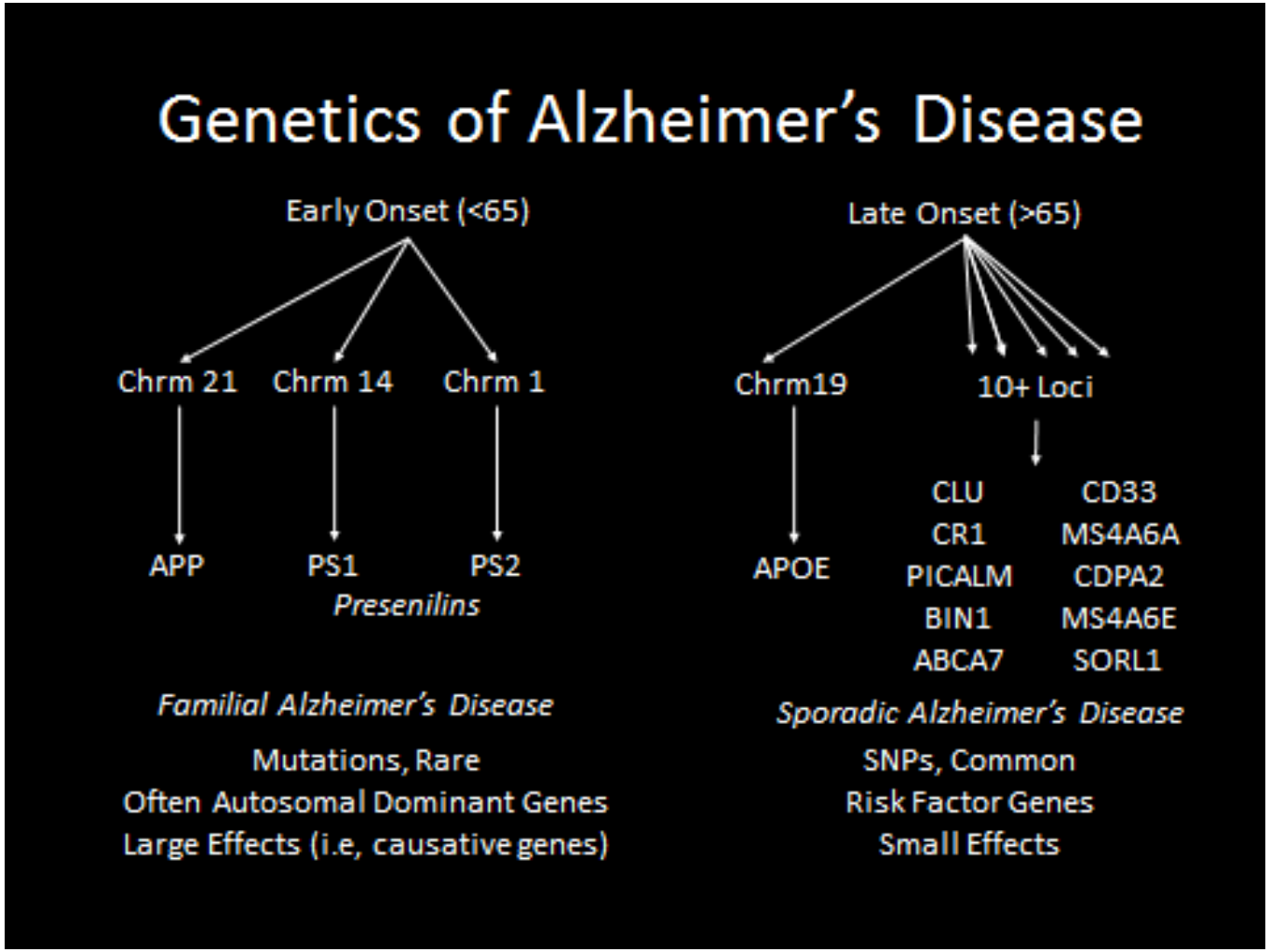
- Mechanism of Action:



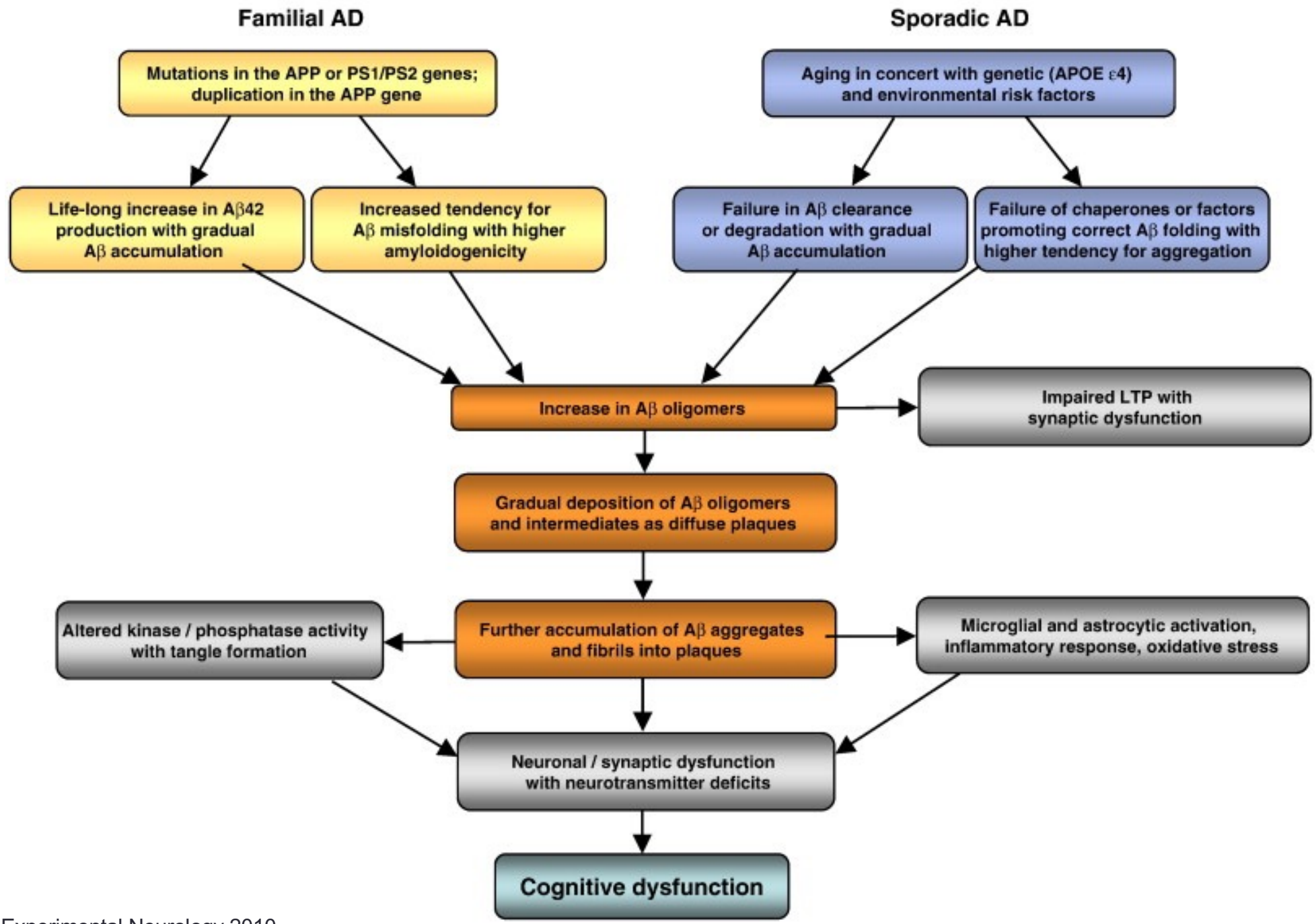
Proposed mechanism: APOE4/Aβ complex



Summary genetic risk factors:

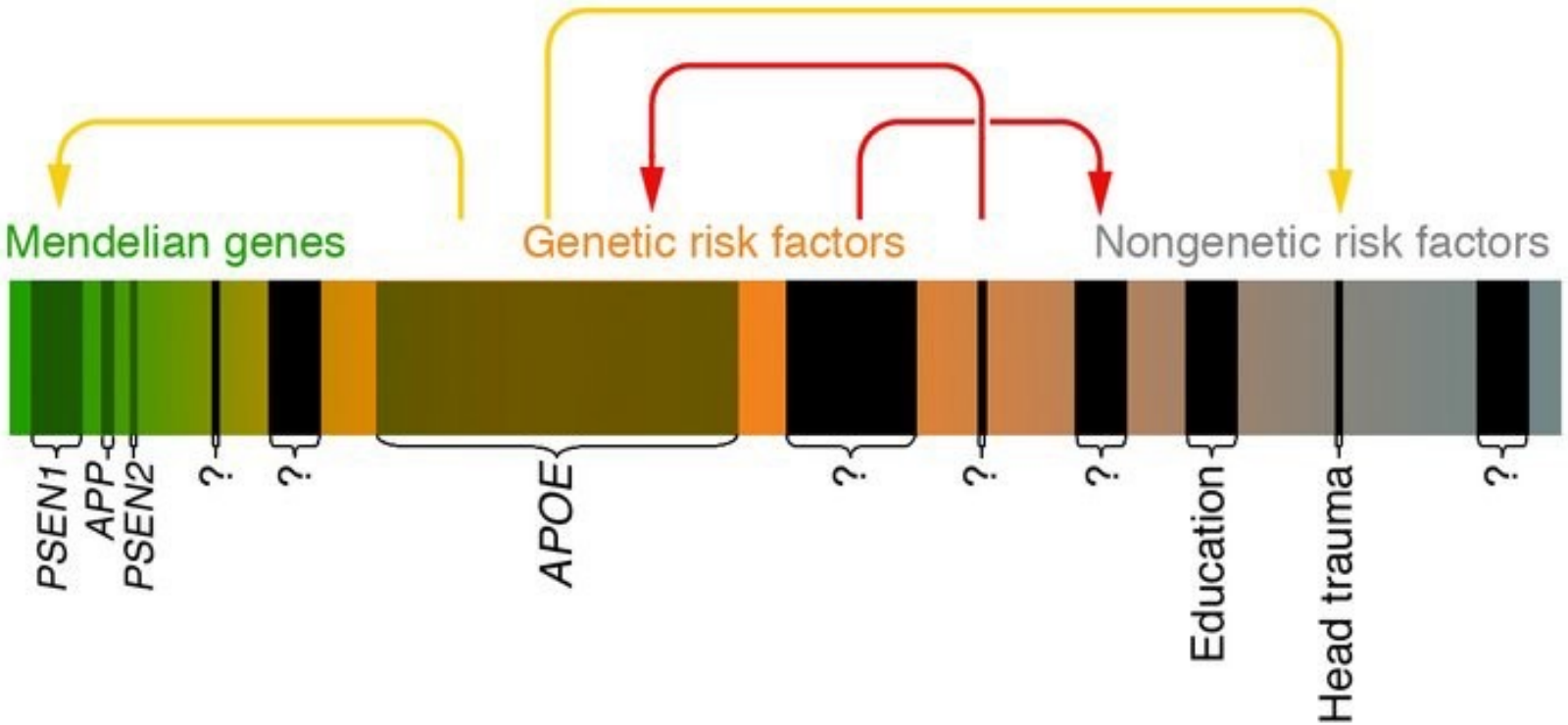


Alzheimer's Disease: FAD vs SAD



The (genetic) etiology of AD

The **risk spectrum** predisposing to AD as one continuum



- The width of these boxes approximately represents the relative contribution to the overall risk
- Colored arrows indicate possible gene-gene and gene-environment interaction patterns

Environmental risk factors for AD

- Age
- Carrying a risk gene (APOE4 and others)
- Others:
  - Diabetes mellitus
  - Midlife hypertension
  - Midlife obesity
  - Midlife inactivity
  - Depression
  - Smoking
  - Low educational attainment

Low educational attainment and AD:

- Cognitive Reserve Hypothesis

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Relation of Education and Occupation-based Socioeconomic Status to Incident Alzheimer's Disease

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Low educational attainment and AD:

- Cognitive Reserve Hypothesis

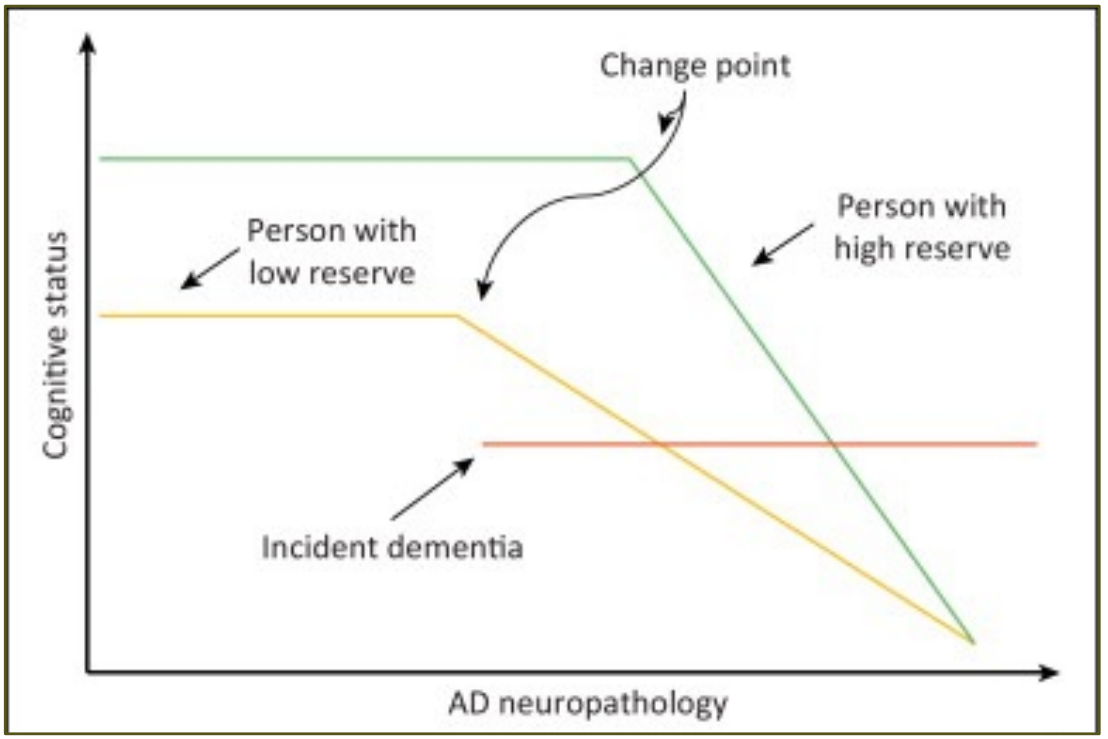
TABLE 3. Relative risks of clinically diagnosed Alzheimer's disease or dementia associated with combinations of education and occupation-based socioeconomic status (lifetime longest-held job), The Kungsholmen Project, Stockholm, Sweden, 1987–1993

	All subjects (no.)	Alzheimer's disease					All types of dementia				
		No. of cases	RR*,†	95% CI*	RR‡	95% CI	No. of cases	RR†	95% CI	RR‡	95% CI
High education/high SES*	353	14	1		1		22	1		1	
High education/low SES	36	1	0.6	0.1, 4.7	0.7	0.1, 5.5	3	1.2	0.4, 4.1	1.3	0.4, 4.4
Low education/high SES	220	25	3.1	1.6, 6.0	3.2	1.6, 6.1	30	2.4	1.4, 4.2	2.3	1.3, 4.1
Low education/low SES	301	36	3.2	1.7, 5.9	3.1	1.6, 5.7	46	2.6	1.6, 4.4	2.4	1.5, 4.0

* RR, relative risk; CI, confidence interval; SES, socioeconomic status.
† Relative risks were estimated after adjustment for age and gender.
‡ Relative risks were estimated after adjustment for age, gender, vascular diseases index, and alcohol data.

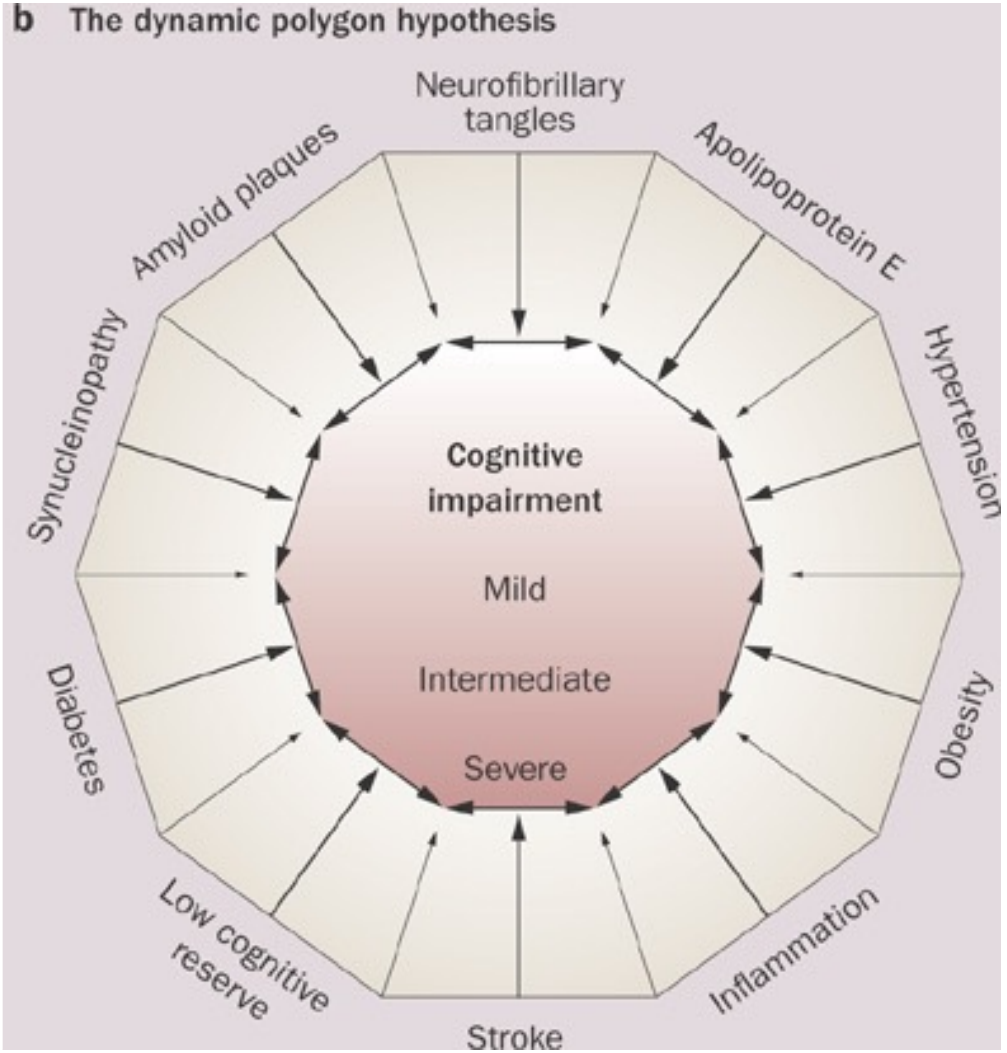
Low educational attainment and AD:

- Cognitive Reserve Hypothesis



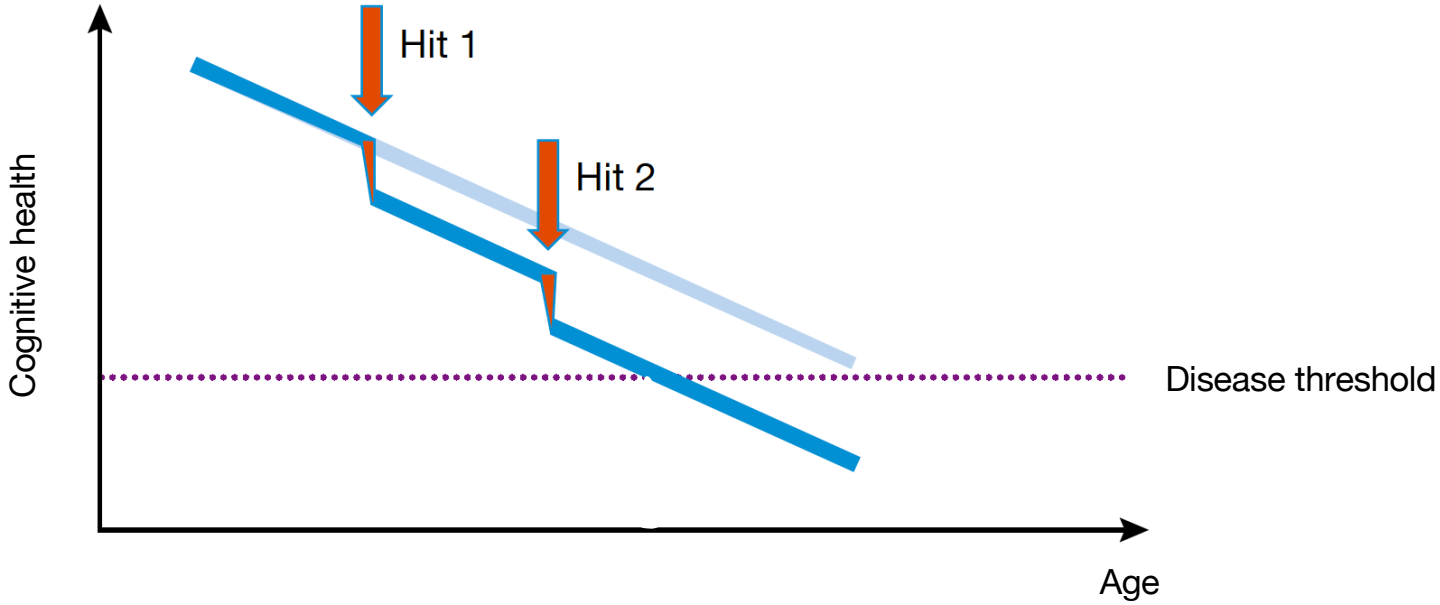
Risk factors for AD

- The dynamic polygon hypothesis:

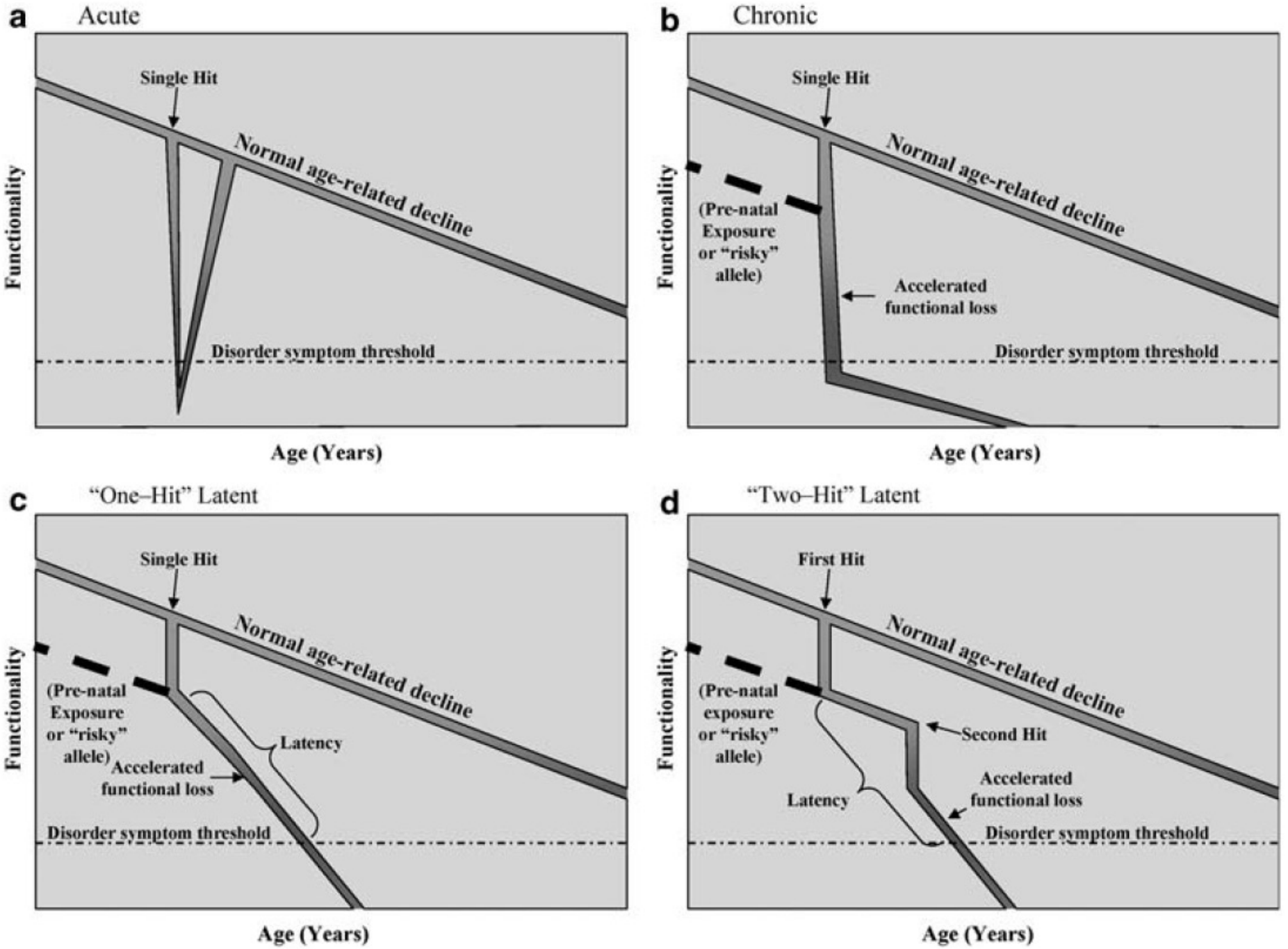


The LEARn model:

- =Latent Early-Life Associated Regulation
- Not a single hit can explain the disease
- "Multiple hit hypothesis" for idiopathic neurodegenerative disorders:



Alzheimer's Disease



Alzheimer's Disease is a monogenetic disorder.

A. True
B. False

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Alzheimer's disease is genetic disorder.

A. True
B. False
C. It depends...

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What are differences between familial and sporadic AD?

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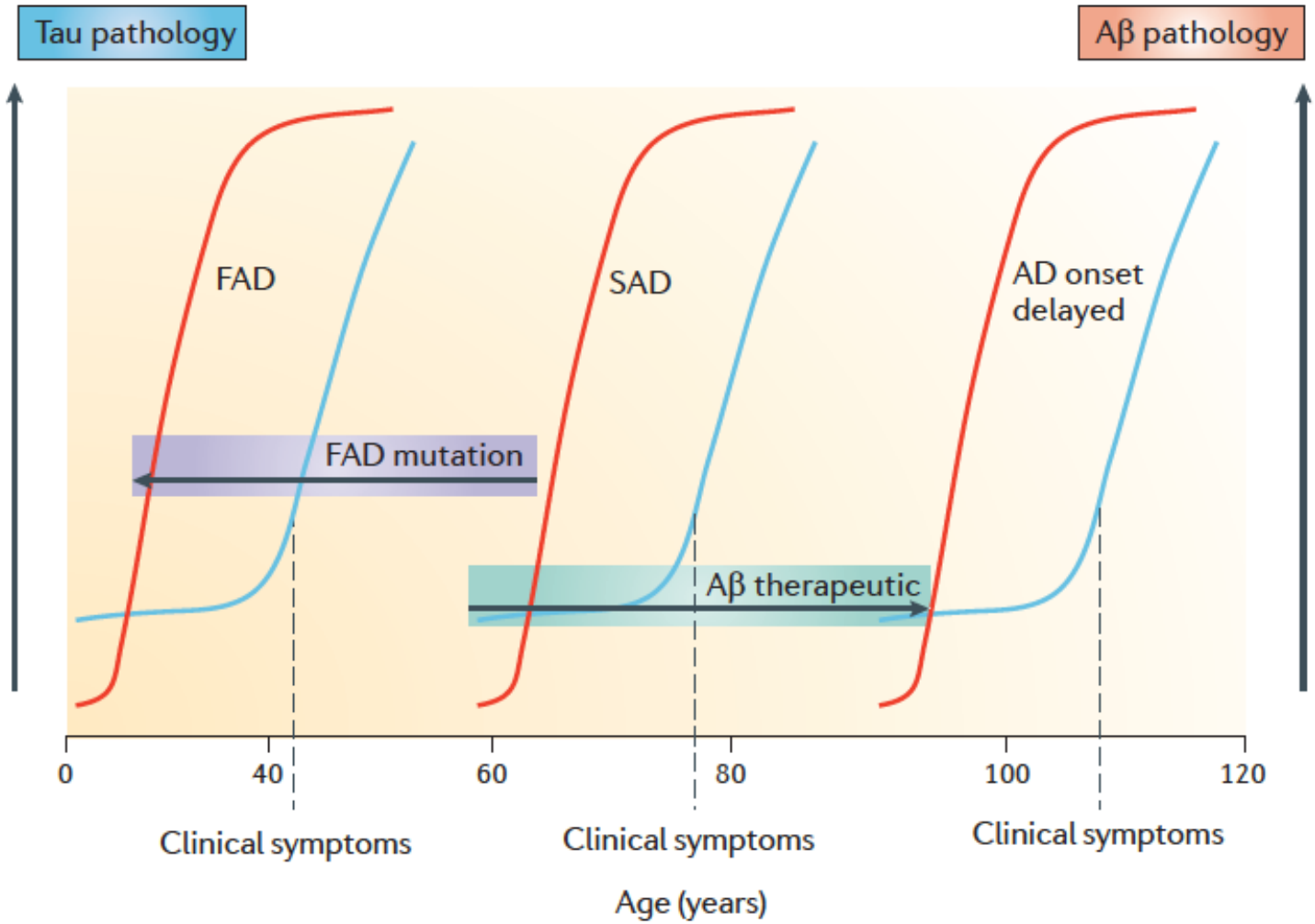
Alzheimer's Disease – Overview

1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) Risk factors
   - Genes
   - Environment
6) **Treatment approaches**
7) Diagnostics and biomarkers

Treatment approaches for AD:

- Goal:



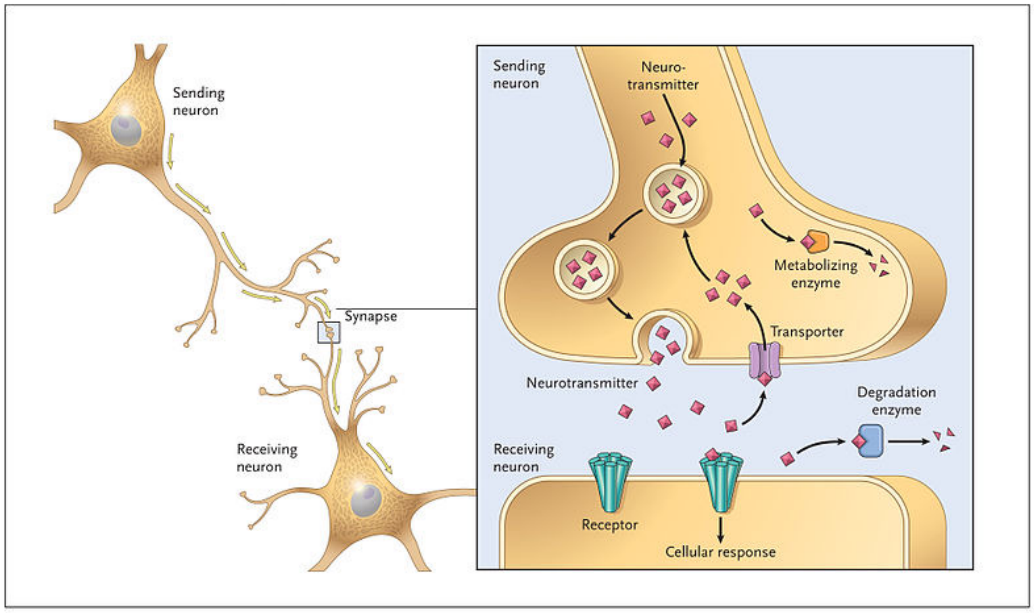
Treatment approaches for AD:

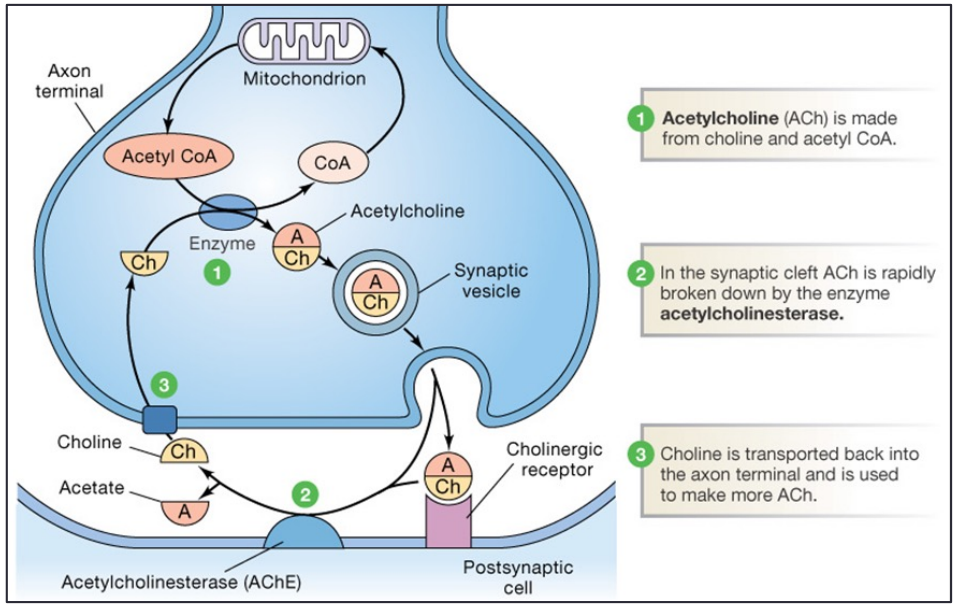
- 2 types of FDA approved drugs against cognitive symptoms
  - **Cholinesterase inhibitors**
    - Donepezil (Aricept)
    - Rivastigmine (Exelon)
    - Galantamine (Razadyne)
    - Tacrine (Cognex)

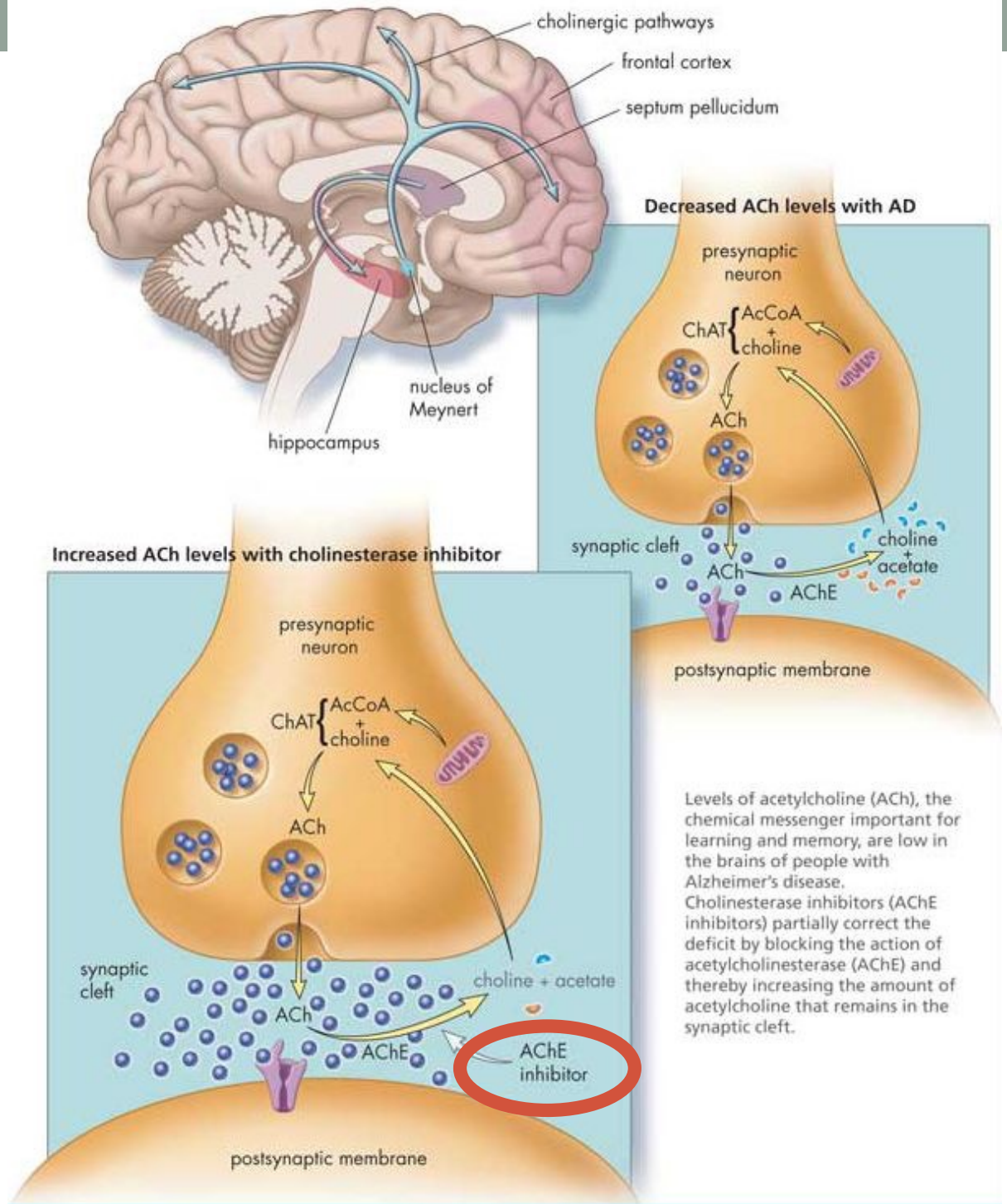
  - **NMDA receptor antagonist:**
    - Maintenance of glutamatergic synaptic transmission, thereby increasing learning and memory capacities
      - Memantine (Ebixa)

Treatment approaches for AD:

- **Cholinesterase inhibitors**
  - Prevent the breakdown of acetylcholine, a chemical messenger important for learning and memory.

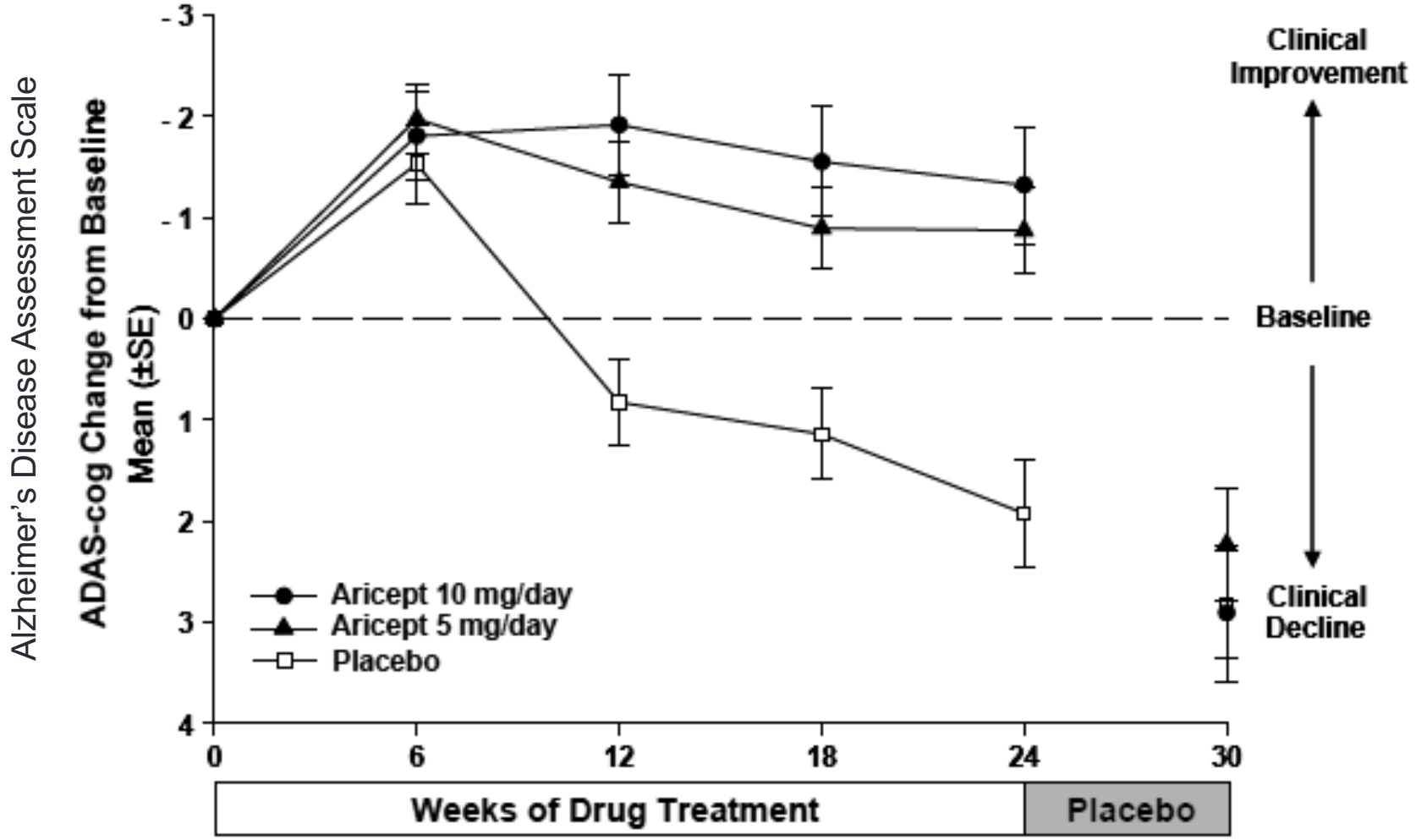






Treatment approaches for AD:

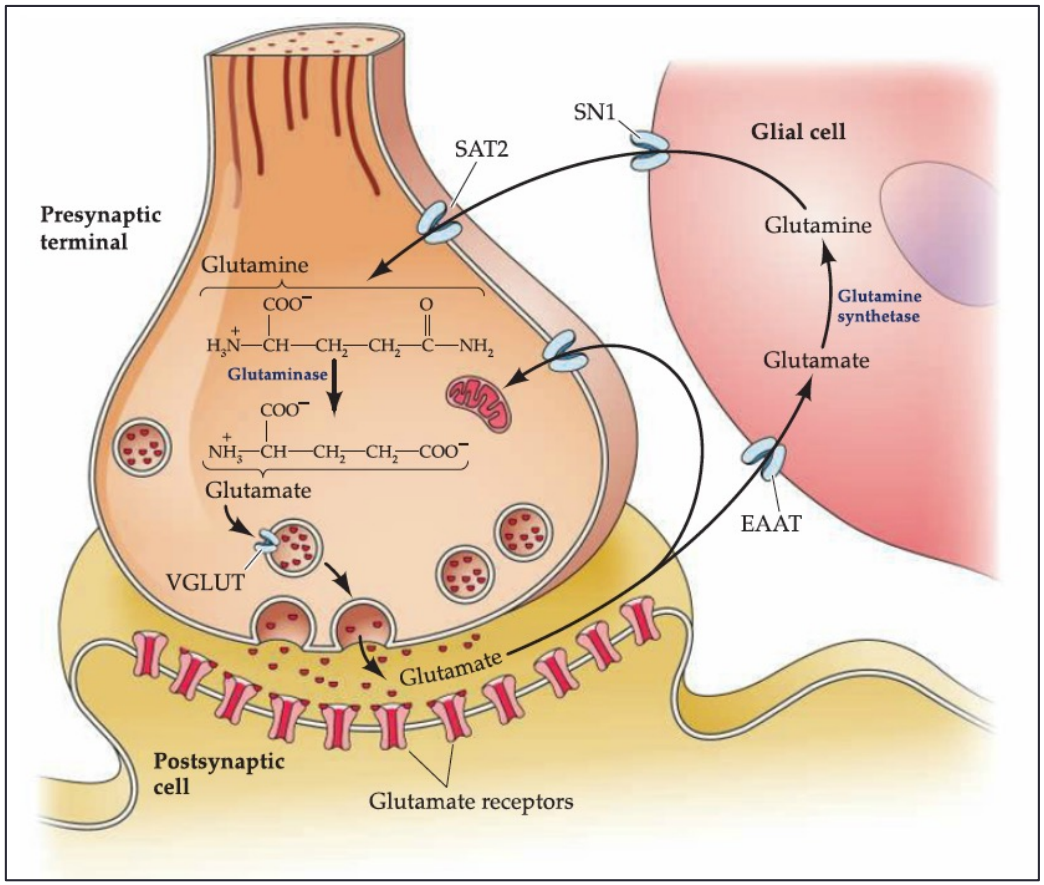
- Cholinesterase inhibitors, e.g., Aricept:



Treatment approaches for AD:

- **NMDA receptor antagonist**
  - Mode of action:
    1) Maintenance of glutamatergic synaptic transmission, thereby increasing learning and memory capacities

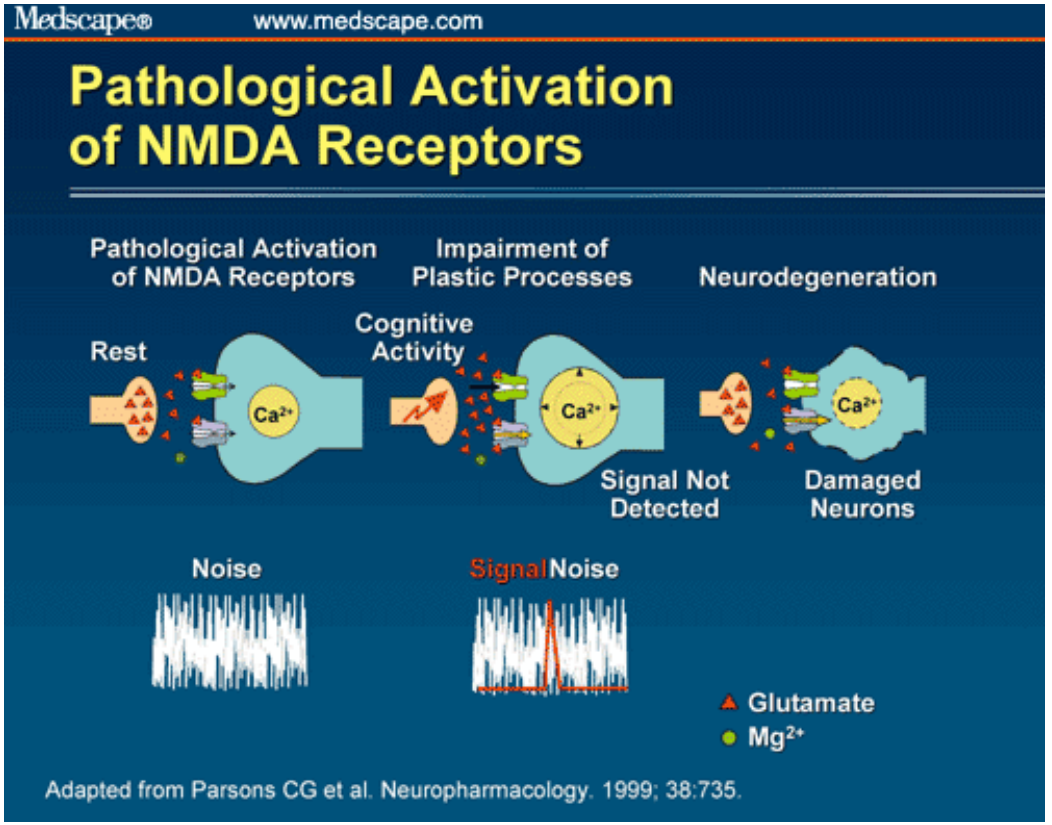
       (glutamate is the major excitatory neurotransmitter in the brain)



EAAT= Excitatory amino acid transporter VGLUT= Vesicular glutamate transporter

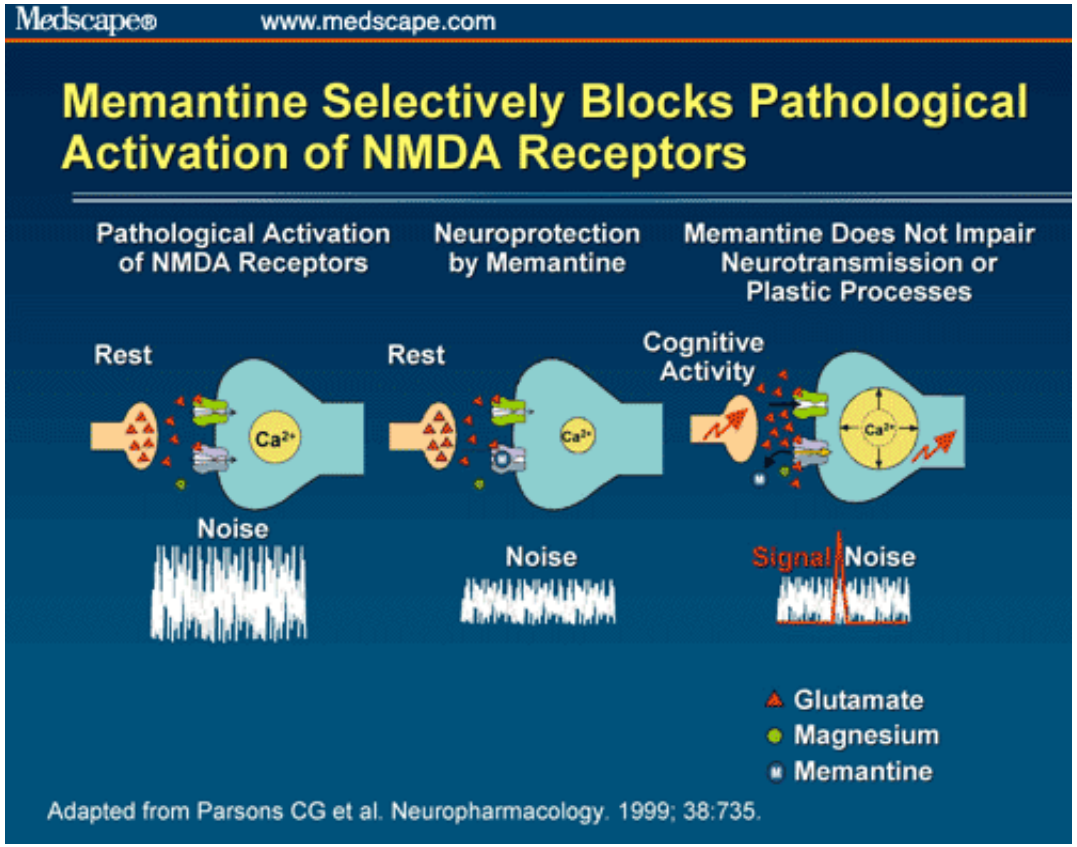
Treatment approaches for AD:

- **NMDA receptor antagonist**
  - Mode of action:
    2) <u>Reduction</u> of excessive excitatory glutamatergic neurotransmission



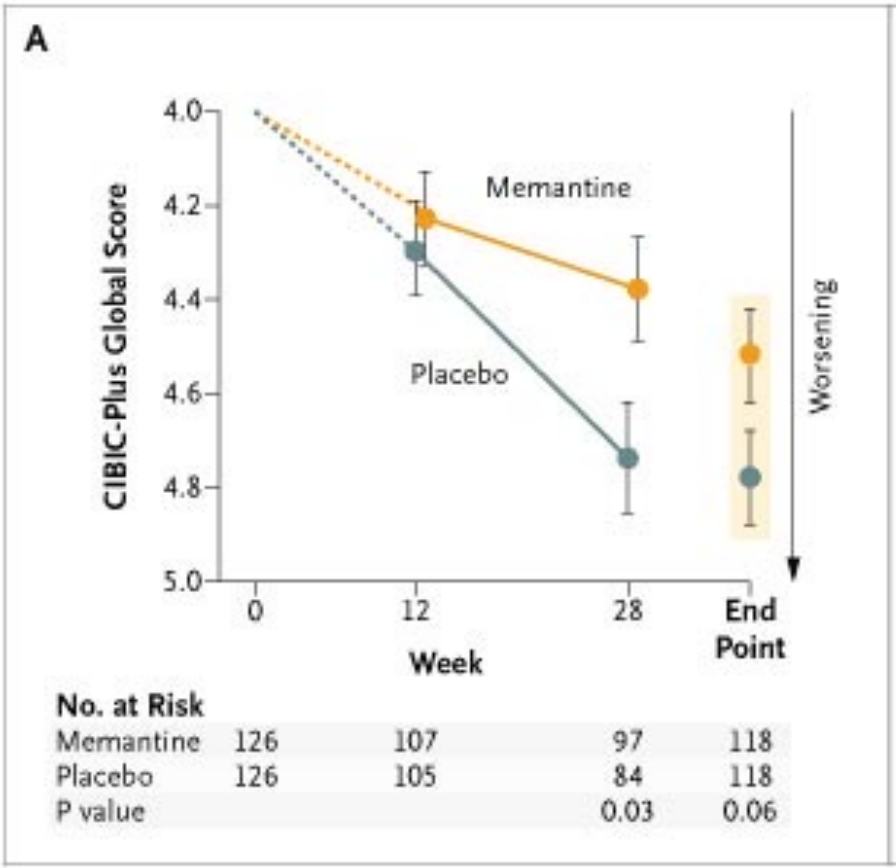
Treatment approaches for AD:

- **NMDA receptor antagonist**
  - Mode of action:
    2) <u>Reduction</u> of excessive excitatory glutamatergic neurotransmission

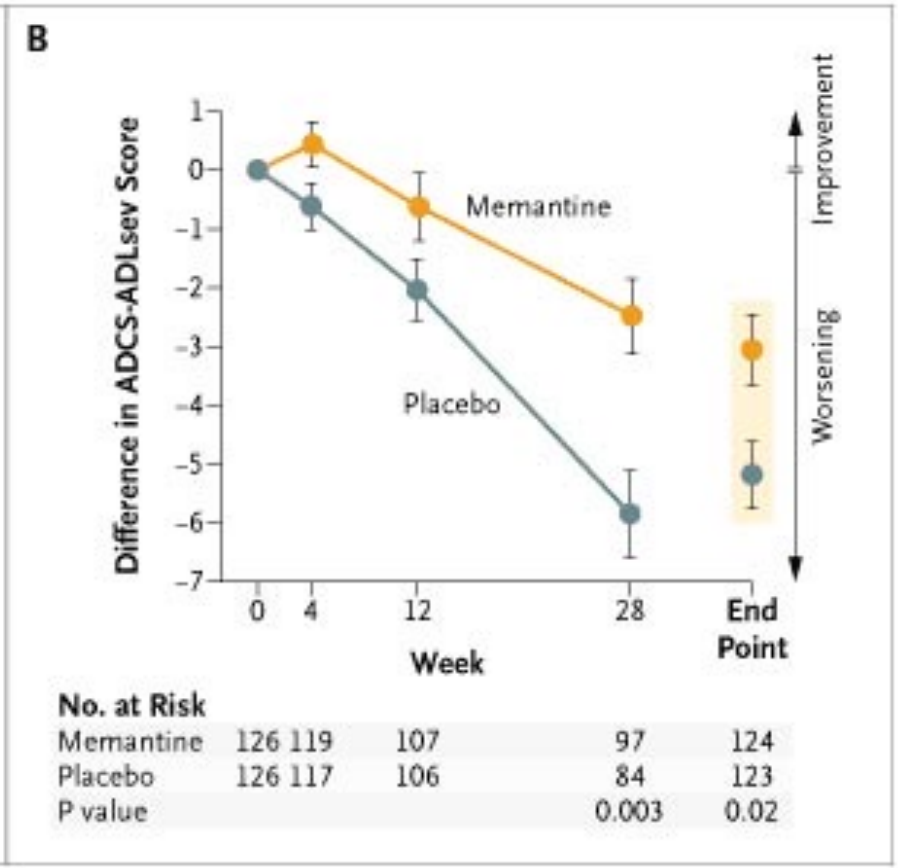


Treatment approaches for AD:

- NMDA receptor antagonist, e.g., memantine:



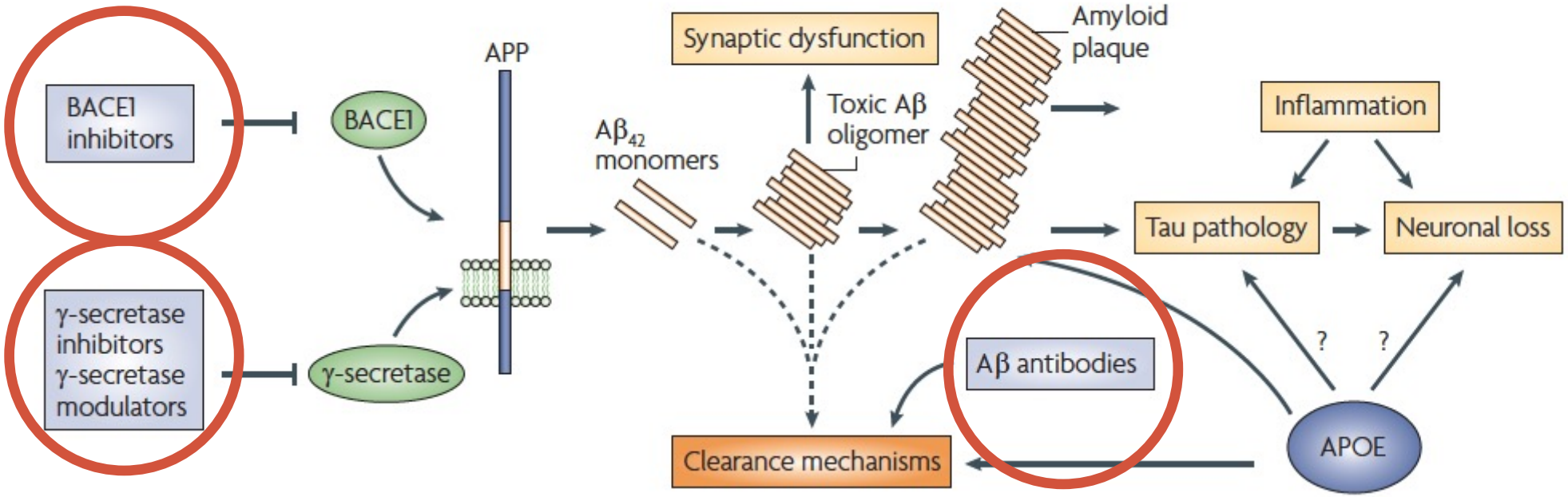
Clinician's interview based impression of change



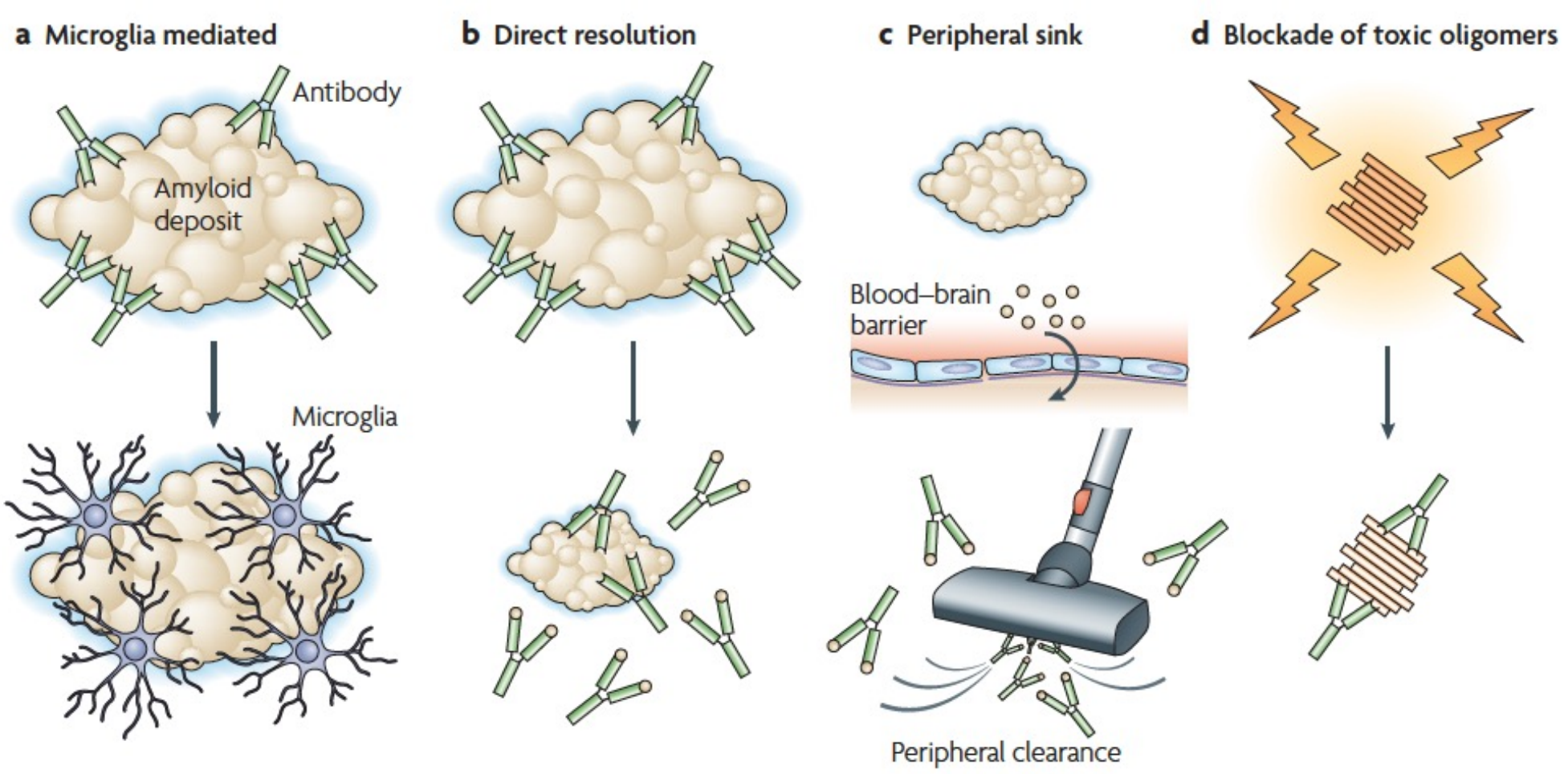
Activities of Daily Living

Treatment approaches for AD:

- 2 types of FDA approved drugs against cognitive symptoms
  - They only work symptomatically!
- **Prevention approaches against AD:**

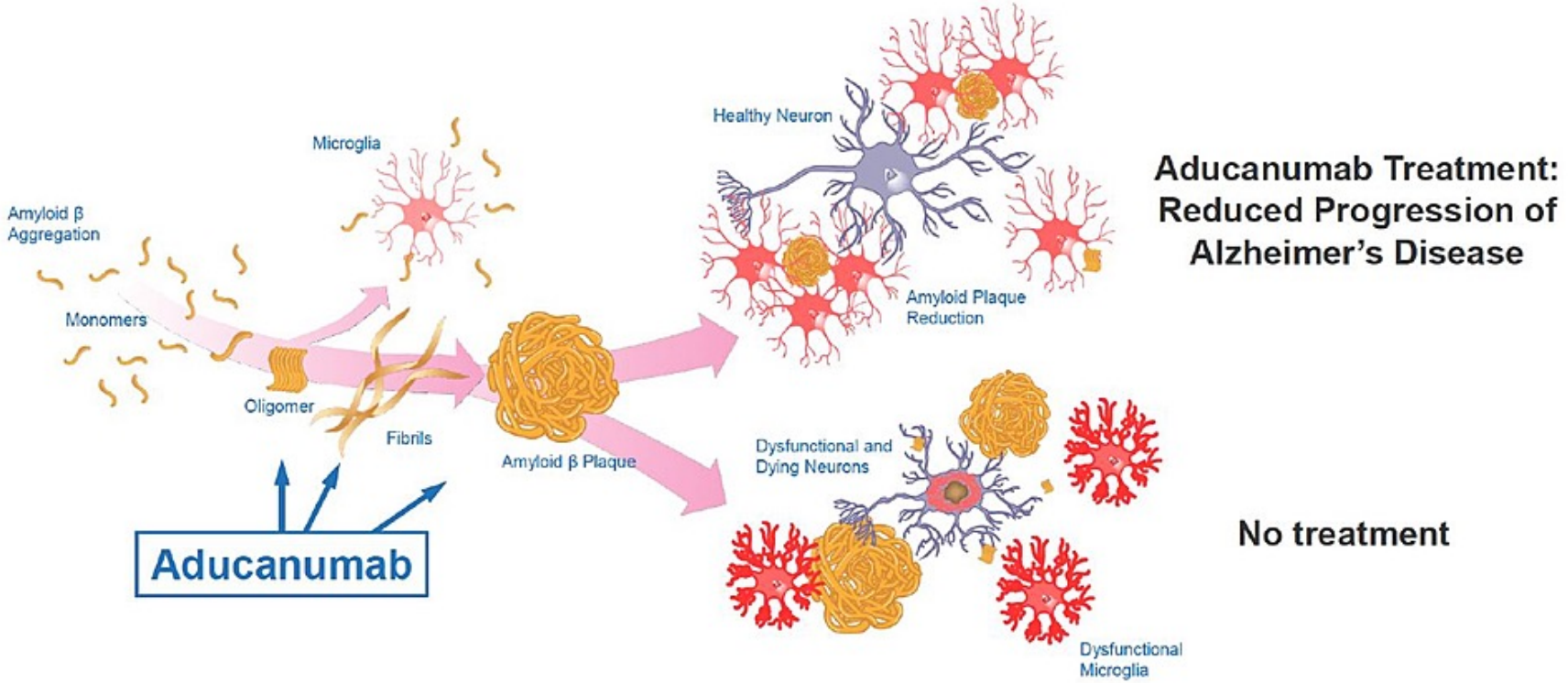


Antibody-mediated amyloid clearance:



Antibody-mediated amyloid clearance:

- Example of aducanumab (Biogen, approved 2020):



Antibody-mediated amyloid clearance:

- Example of lecanemab:

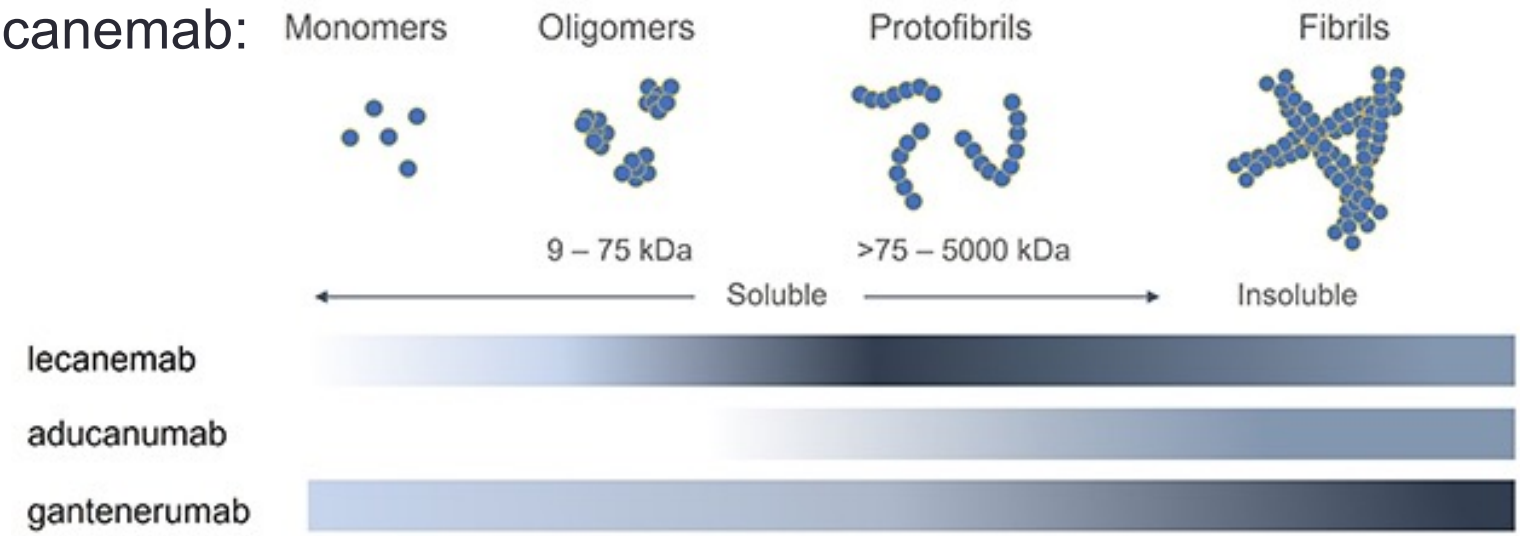


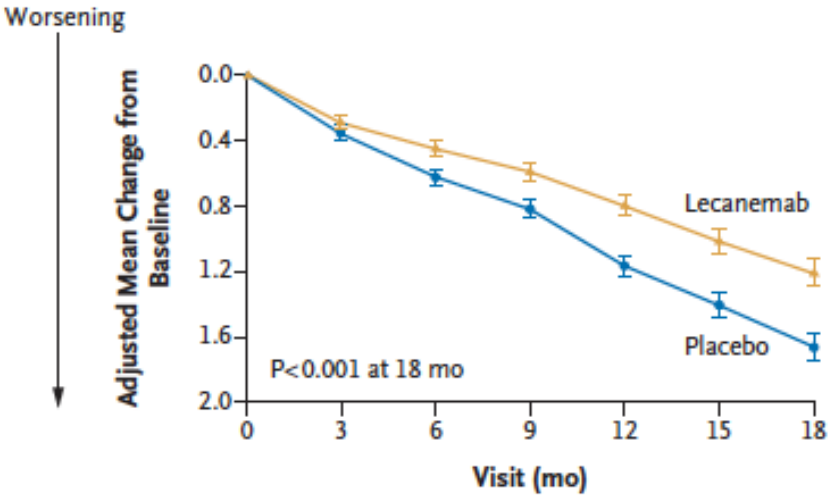
TABLE. BINDING OF ANTIAMYLOID MONOCLONAL ANTIBODIES TO DIFFERENT SPECIES OF AMYLOID β

Antibody	Targets	Off-target binding
Aducanumab	Plaque	Fibrils, none to oligomer
Donanemab	Plaque	None
Gantenerumab	Plaque	Fibrils>protofibrils, monomers
Lecanemab	Protofibril	Protofibrils, oligomers>fibrils, monomers

Antibody-mediated amyloid clearance:

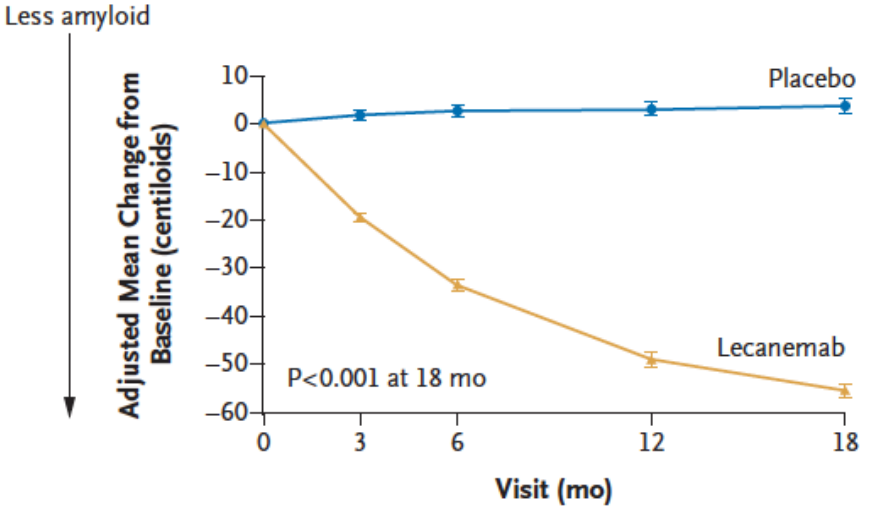
- Example of lecanemab:

- **Cognition:**



No. of Participants							
Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

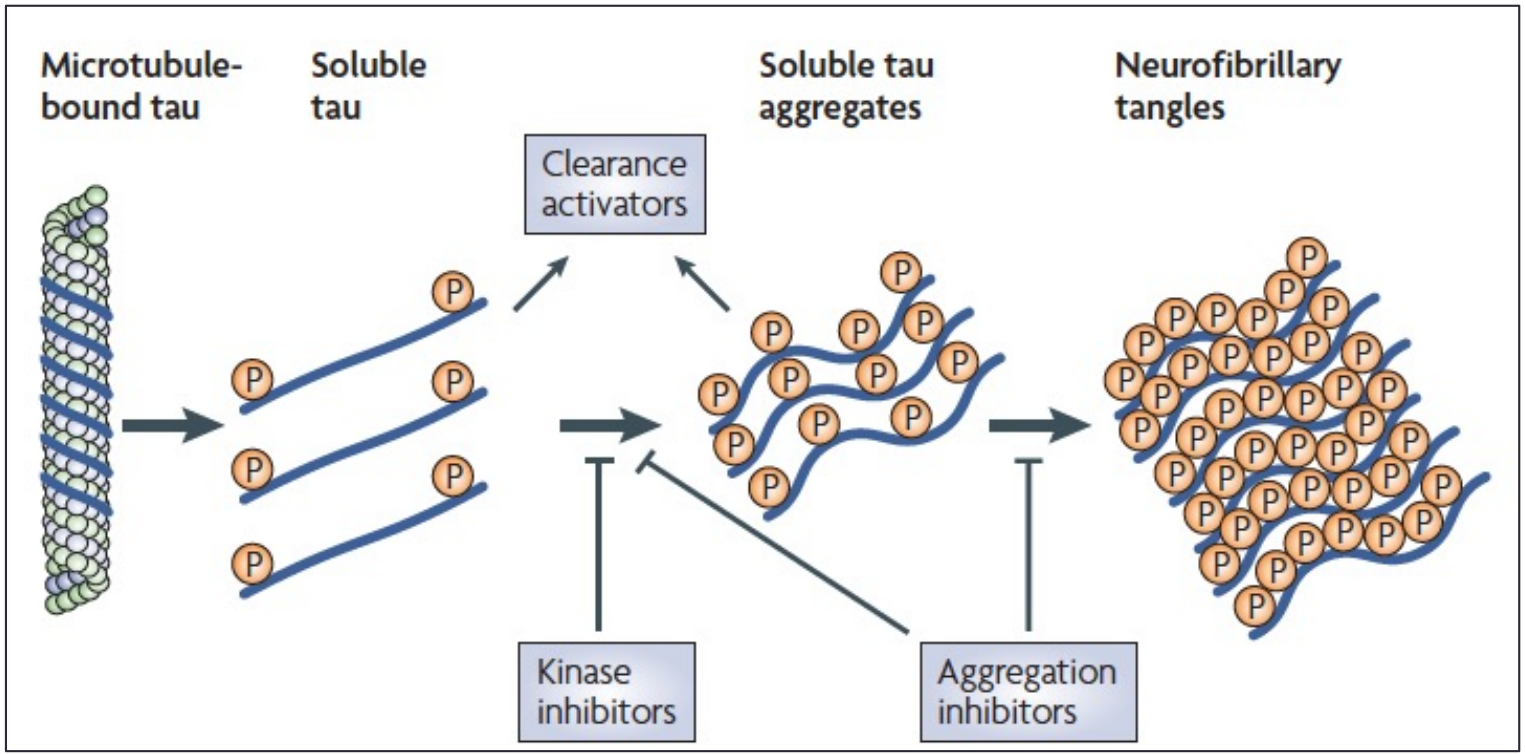
Amyloid burden:

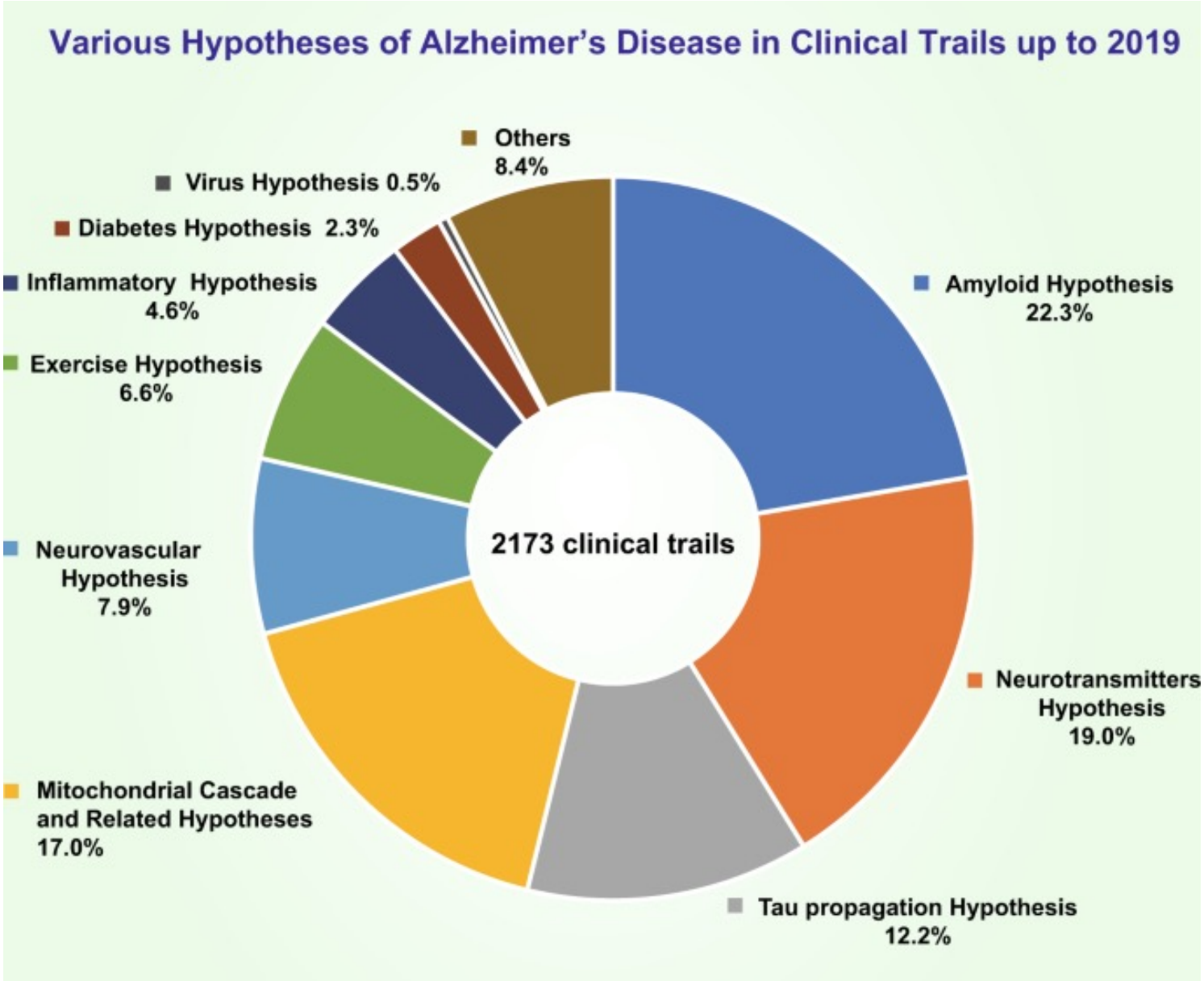


No. of Participants					
Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

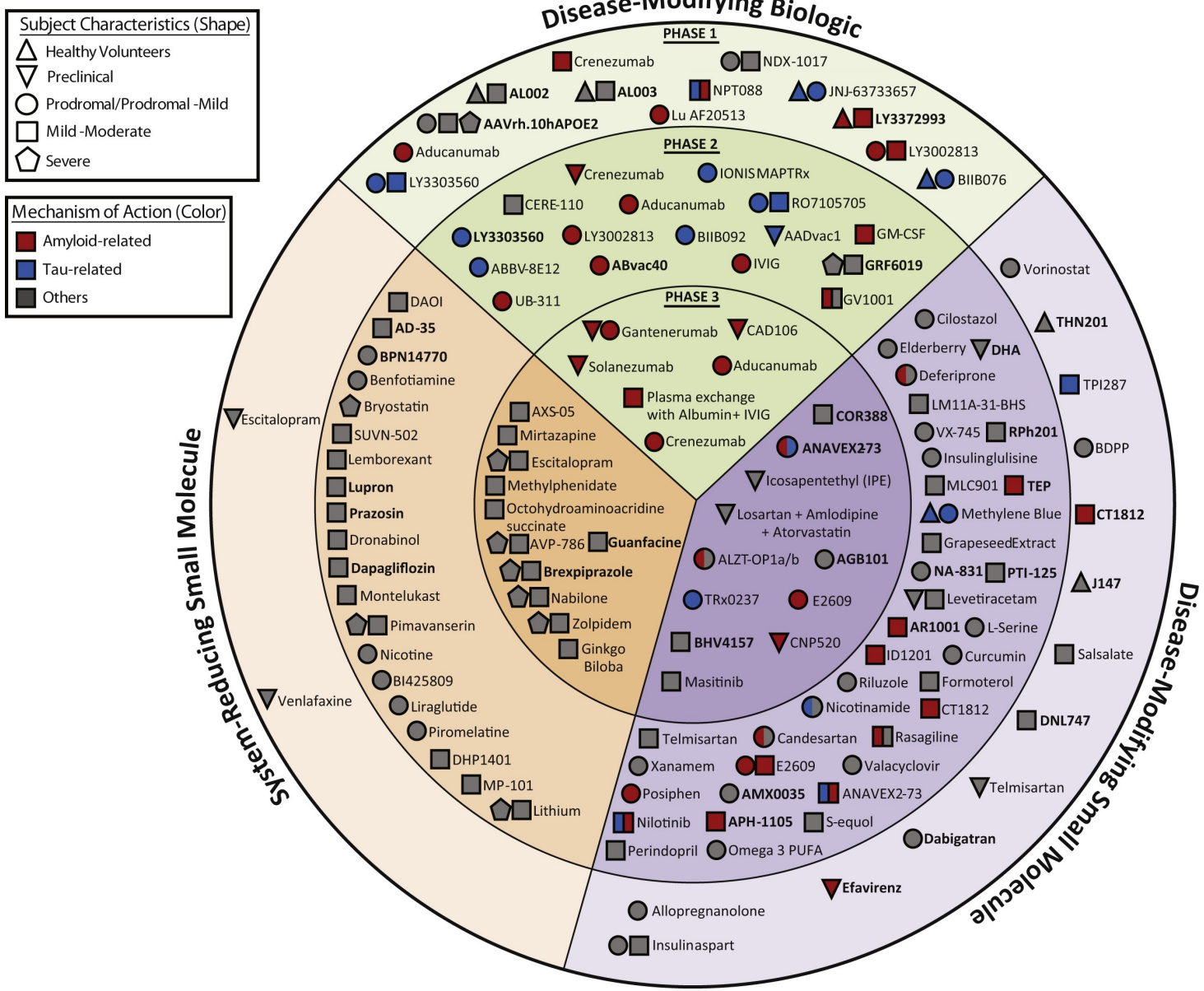
Tau-based approaches:

- Hyperphosphorylation of tau protein leads to aggregation

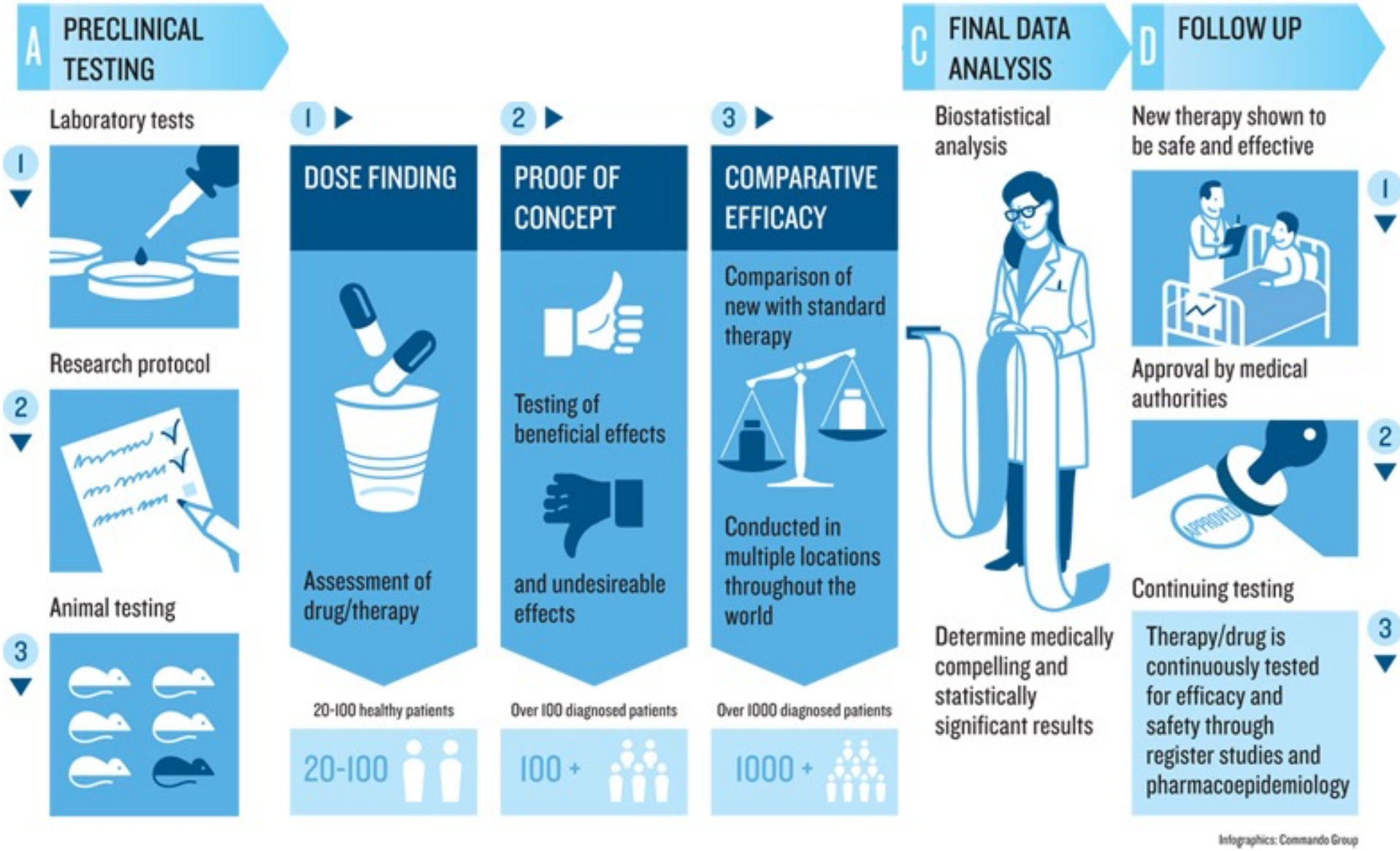



Various Hypotheses of Alzheimer's Disease in Clinical Trails up to 2019
Others
8.4%
Virus Hypothesis 0.5%
Diabetes Hypothesis 2.3%
Inflammatory Hypothesis
4.6%
Exercise Hypothesis
6.6%
Neurovascular
Hypothesis
7.9%
Mitochondrial Cascade
and Related Hypotheses
17.0%
Amyloid Hypothesis
22.3%
Neurotransmitters
Hypothesis
19.0%
Tau propagation Hypothesis
12.2%
2173 clinical trails

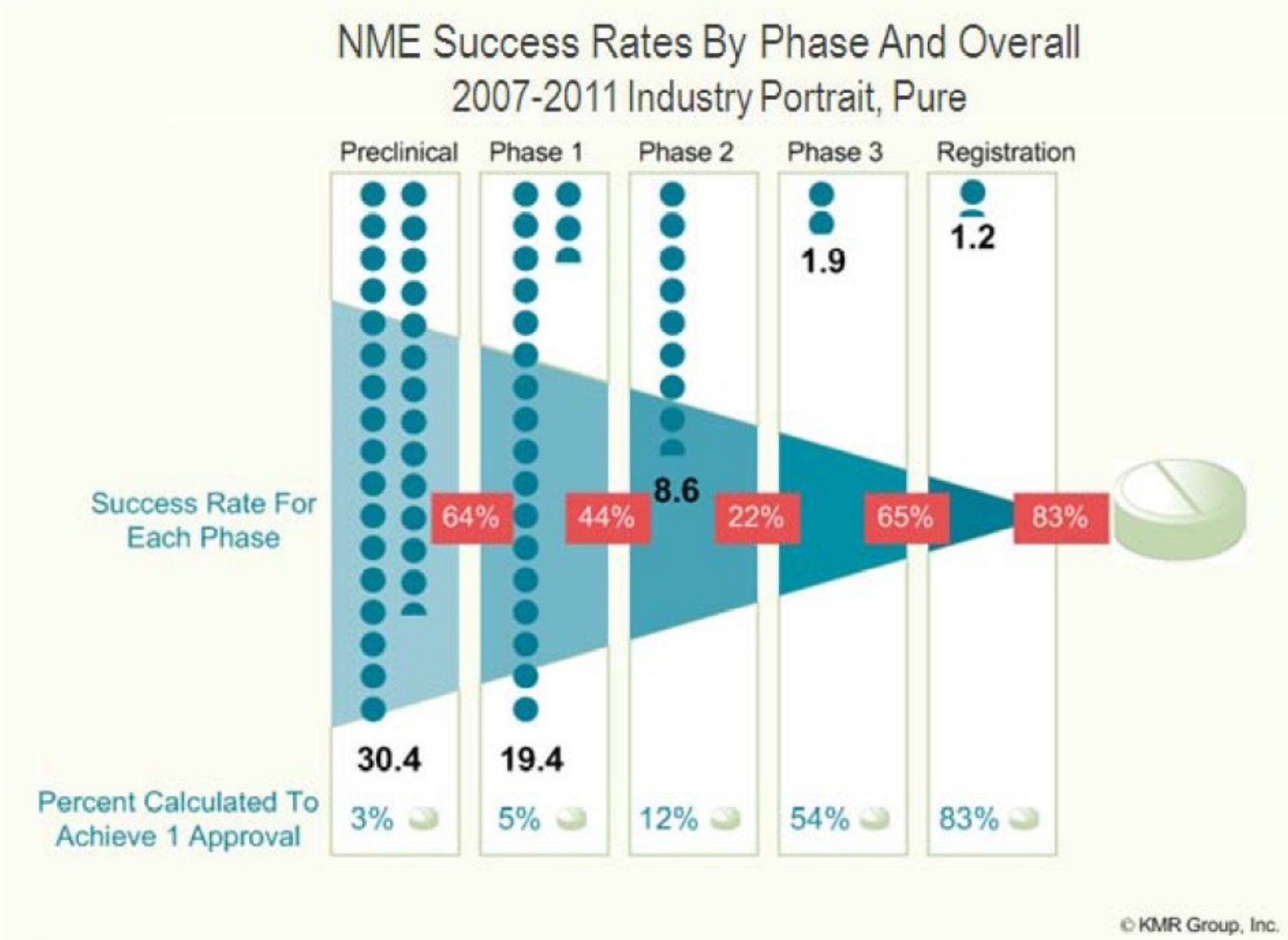
Overview clinical trials:



Phases of Clinical trials:



Success rate of clinical trials:

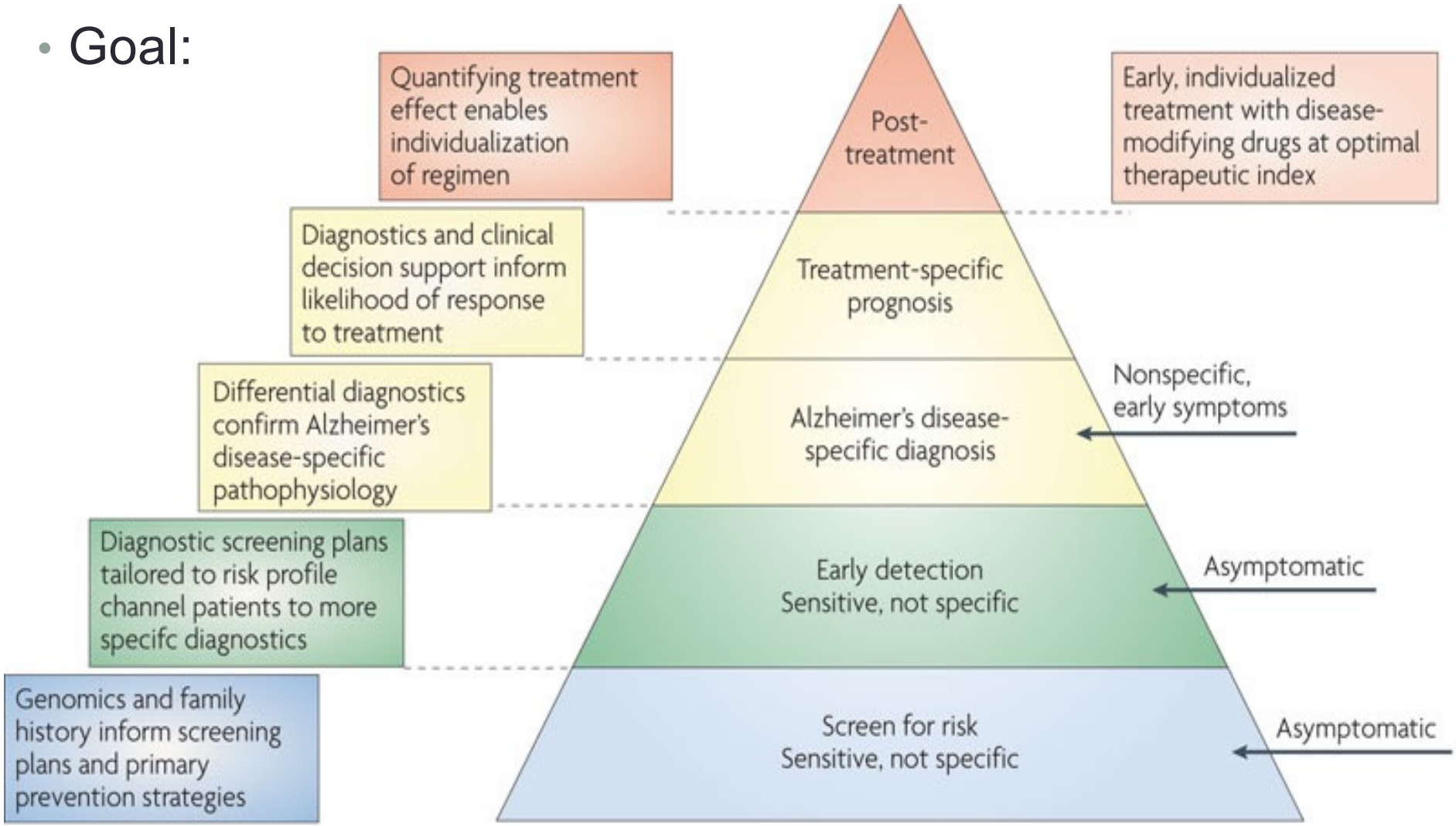


Alzheimer's Disease – Overview

1) Check your knowledge about AD
2) Prevalence and history
3) Symptomatology
4) Pathophysiological hallmarks
   - Tau tangles
   - Amyloid plaques
5) Risk factors
   - Genes
   - Environment
6) Treatment approaches
7) **Diagnostics and biomarkers**

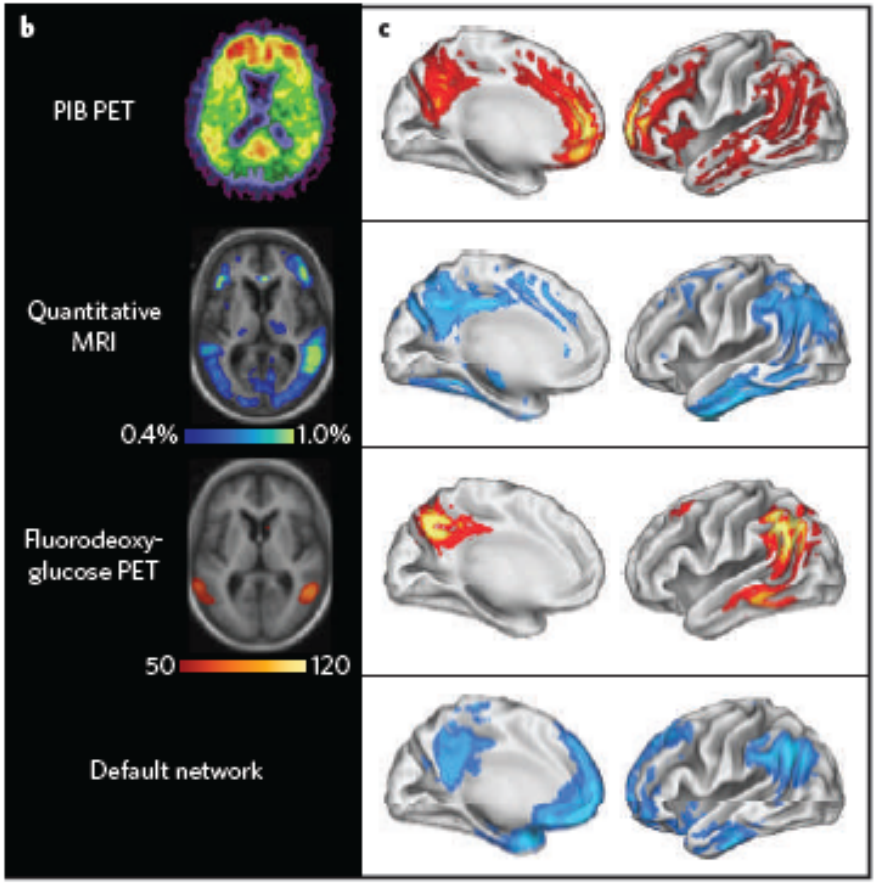
AD Diagnostics

- Goal:



AD Diagnostics

- Diagnostic tools:
  - Mental examination
  - PIB PET
  - Quantitative MRI
  - Fluorodeoxyglucose PET
  - More experimental approaches



AD Diagnostics

- PIB PET
  - PIB=Pittsburgh Compound B
    - ^{11}C-PIB is a fluorescent derivative of thioflavin T
  - Type of measurement: Amyloid plaques
    - PIB preferentially targets and binds to fibrillar Aβ forms found in dense core plaques with high affinity and specificity
  - no binding to tau
  - Problem: Amyloid plaques don't necessarily predict AD

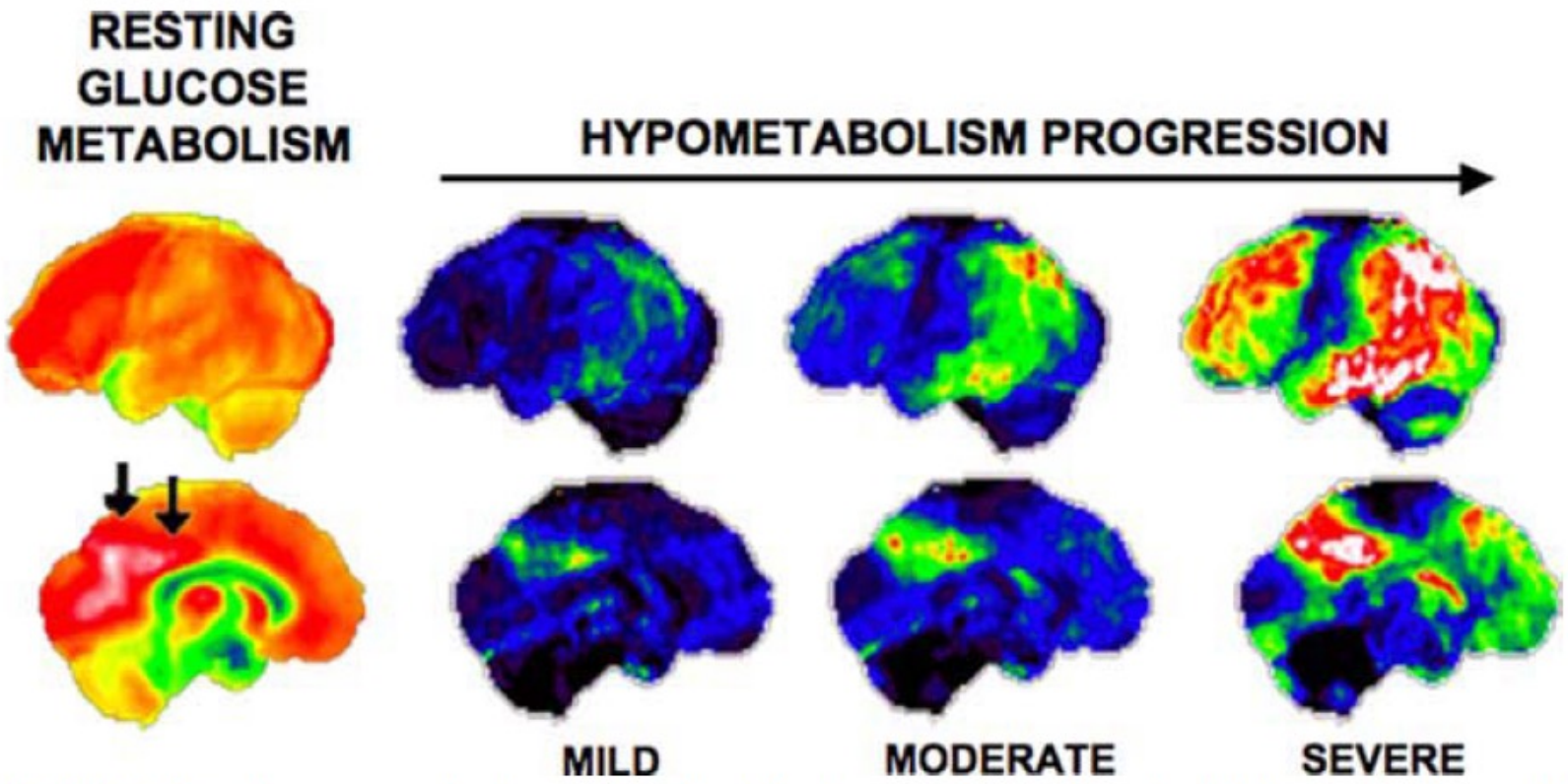
AD Diagnostics

- Quantitative MRI
  - Type of measurement: Neurodegeneration
    - Sensitive to neurodegeneration that occurs in mild and preclinical AD
    - Predictive of decline to dementia in individuals with mild cognitive impairment

AD Diagnostics

- Fluorodeoxyglucose PET
  - ^{18}F-glucose
  - Type of measurement: Neuronal activity
    - The uptake of ^{18}F-FDG is a marker for a tissue's metabolism
    - Particularly relevant for disorganized brain activity in the default mode network (DMN)
      - Active at wakeful rest
      - Earliest brain area affected in AD:
        - Medial temporal cortex
        - Posterior cingulate cortex
        - Parietal cortex

The Default Mode Network and AD (Glucose metabolism):



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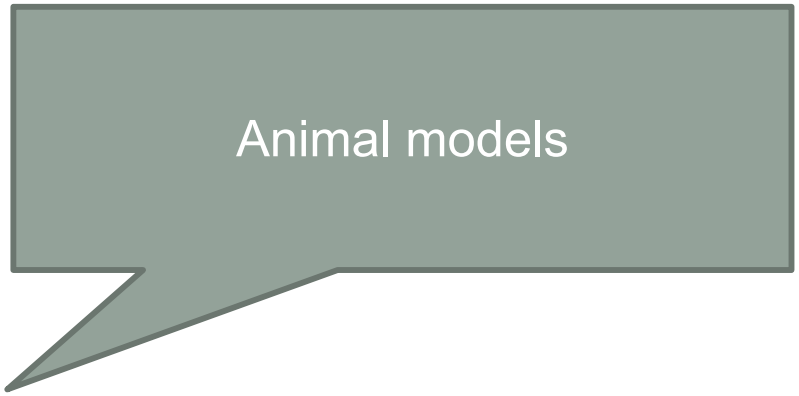
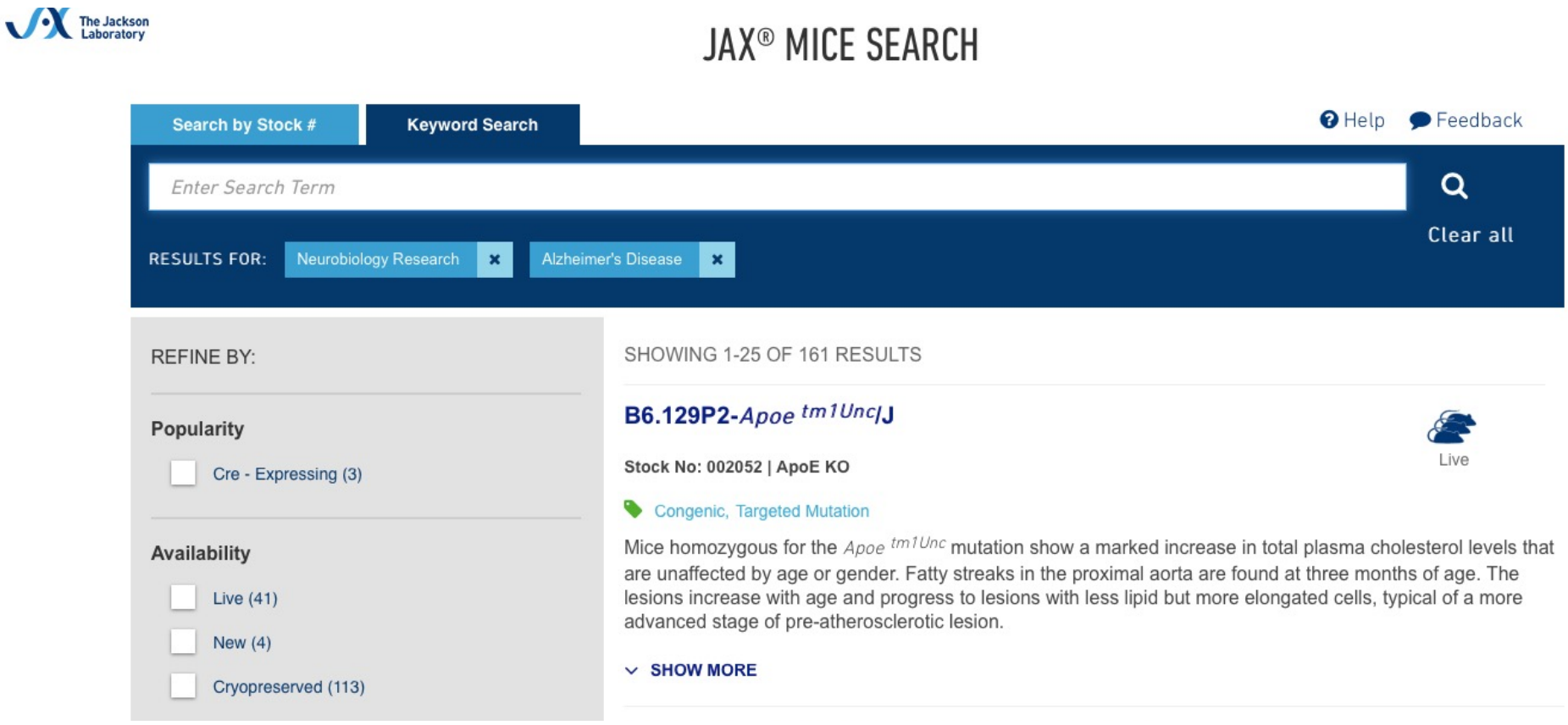
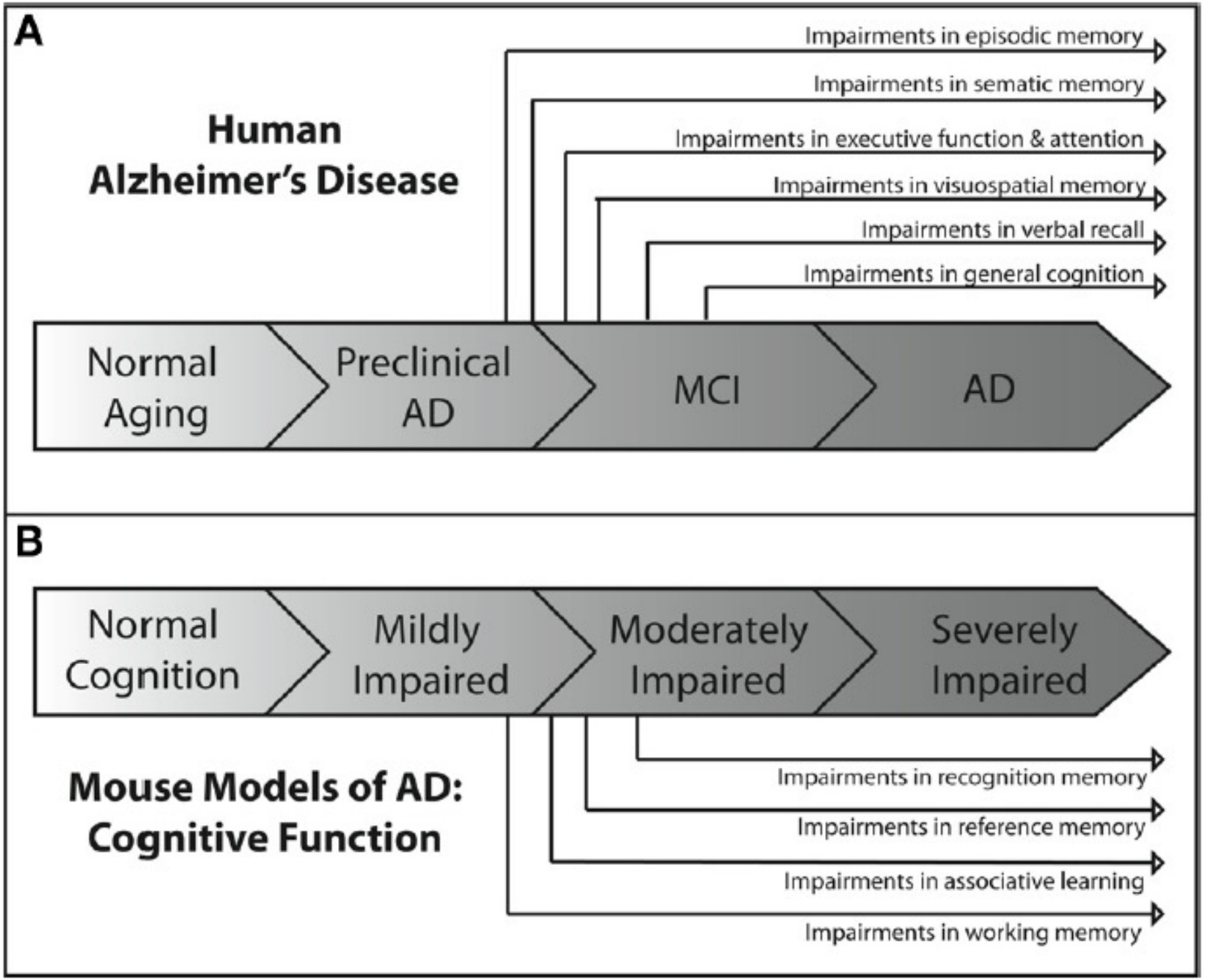


How to study AD outside humans:





How to study AD outside humans:

frontiers in GENETICS

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Using mice to model Alzheimer's dementia: an overview of the clinical disease and the preclinical behavioral changes in 10 mouse models

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Animal models

- Limitations of mouse models:
  - Incomplete recapitulation of the pathology
  - Based on fAD
    - Wild type mice do not develop AD
- Other (animal) models?
  - *C.elegans*
  - *D.melanogaster*
  - Rats
  - Marmosets
  - Brain organoids/cellular culture