Alzheimer's Disease

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Osher Lifelong Learning Institute
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Outline

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- Alzheimer's Disease Background and Epidemiology
- Biology and Biomarkers of Alzheimer's Disease
- Genetics of Alzheimer's Disease
- Initiatives at Vanderbilt Memory & Alzheimer's Center

Alzheimer's Disease

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- First described by Alois Alzheimer in 1908
- A diagnosis of Probable AD requires
  - Functional Impairment
  - Cognitive Impairment in at least 2 domains
  - Both must represent decline from previous levels
    - "Insidious onset" – symptoms are gradual rather than sudden
  - Not due to delirium or neuropsychiatric condition
  - Not due to other cerebrovascular or neural injury

Alzheimer's disease symptoms

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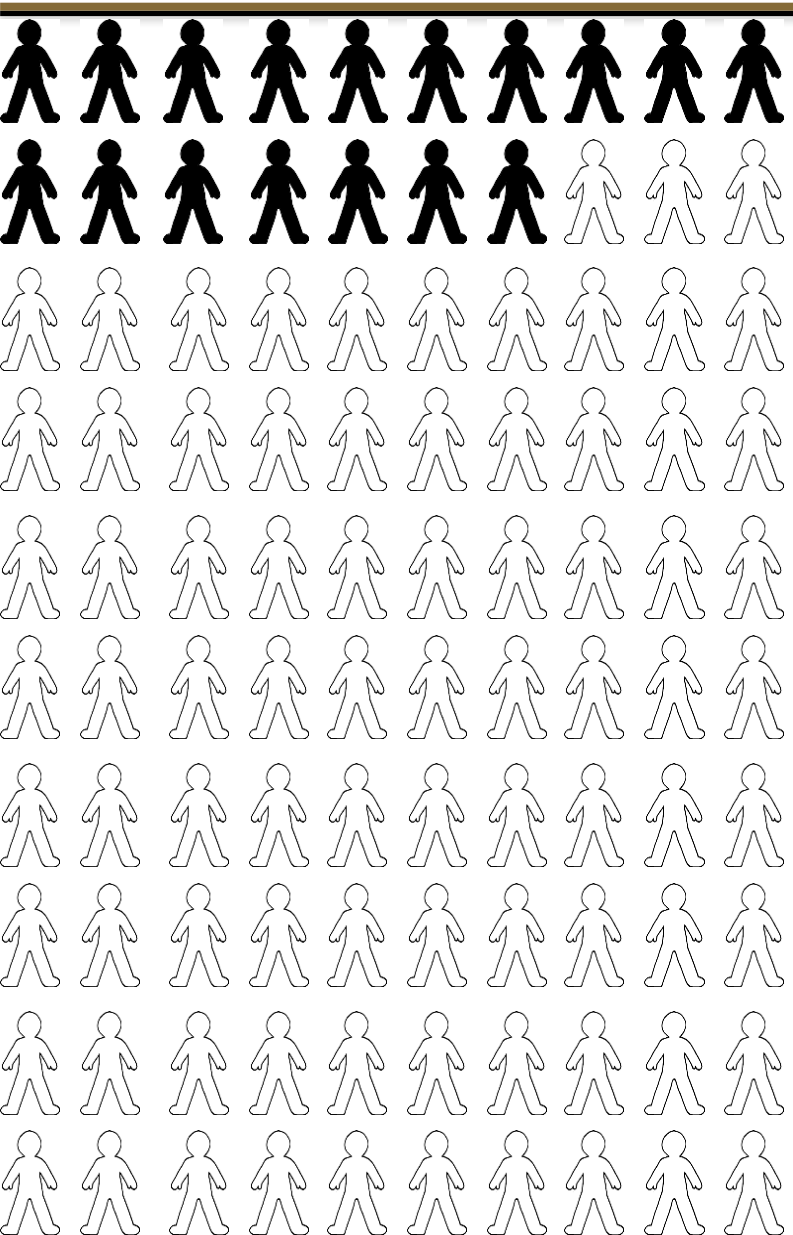
- Typically amnestic presentation
  - Primary impairment in learning and recall of recent information
- Can have non-amnestic presentations
  - Language, visuospatial, executive dysfunction
- Functional deficits
  - Handling finances, driving, bathing, dressing
- Personality and mood changes
  - Confusion, aggression, depression
  - *Makes diagnosis challenging!*

Alzheimer's Disease v. Age-Related Change

Signs of Alzheimer's/dementia	Typical age-related changes
Poor judgment and decision-making	Making a bad decision once in a while
Inability to manage a budget	Missing a monthly payment
Losing track of the date or the season	Forgetting which day it is and remembering it later
Difficulty having a conversation	Sometimes forgetting which word to use
Misplacing things and being unable to retrace steps to find them	Losing things from time to time

(Alz.org)

Alzheimer's Disease Prevalence

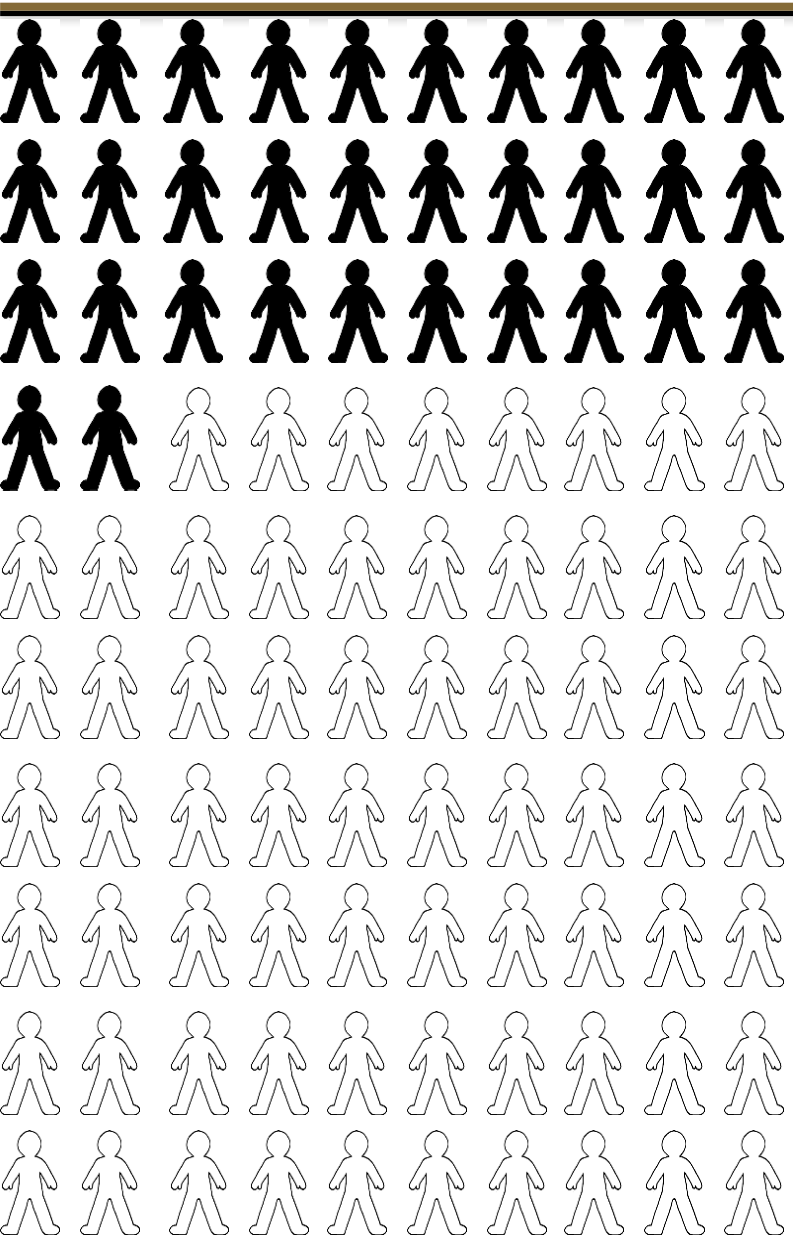


Prevalence of AD increases with age

- 3% of people age 65-74
- 17% of people age 75-84

Alzheimer's Association,
2013 Alzheimer's Disease Facts &Figures
Alzheimer's & Dementia, 9(2).

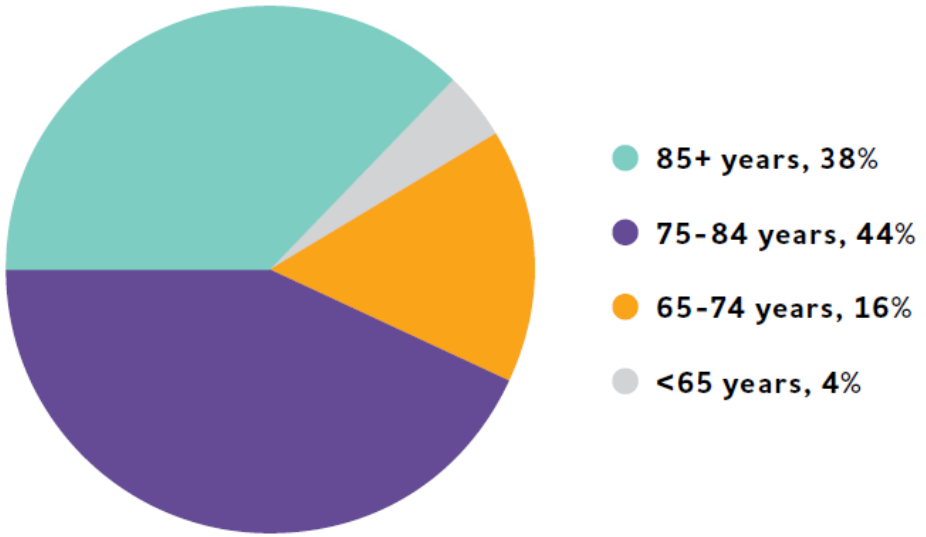
Alzheimer's Disease Prevalence



Prevalence of AD increases with age

- 3% of people age 65-74
- 17% of people age 75-84
- 32% of people age 85+

Ages of People with Alzheimer's Dementia in the United States, 2017



Created from data from Hebert et al.[A4, 31]

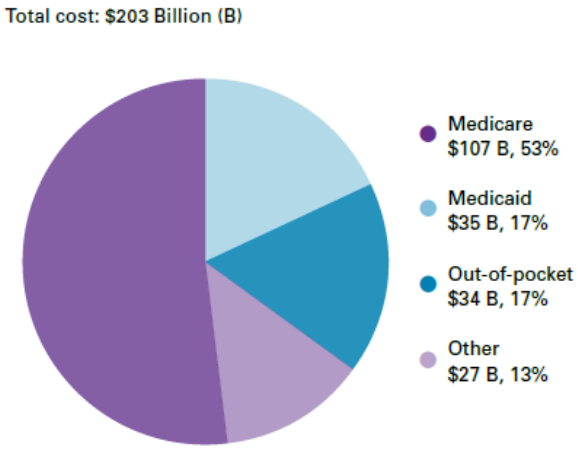
Percentages do not total 100 because of rounding.

Alzheimer's Association, 2013 Alzheimer's Disease Facts &Figures Alzheimer's & Dementia, 9(2).

Alzheimer's Disease Projections

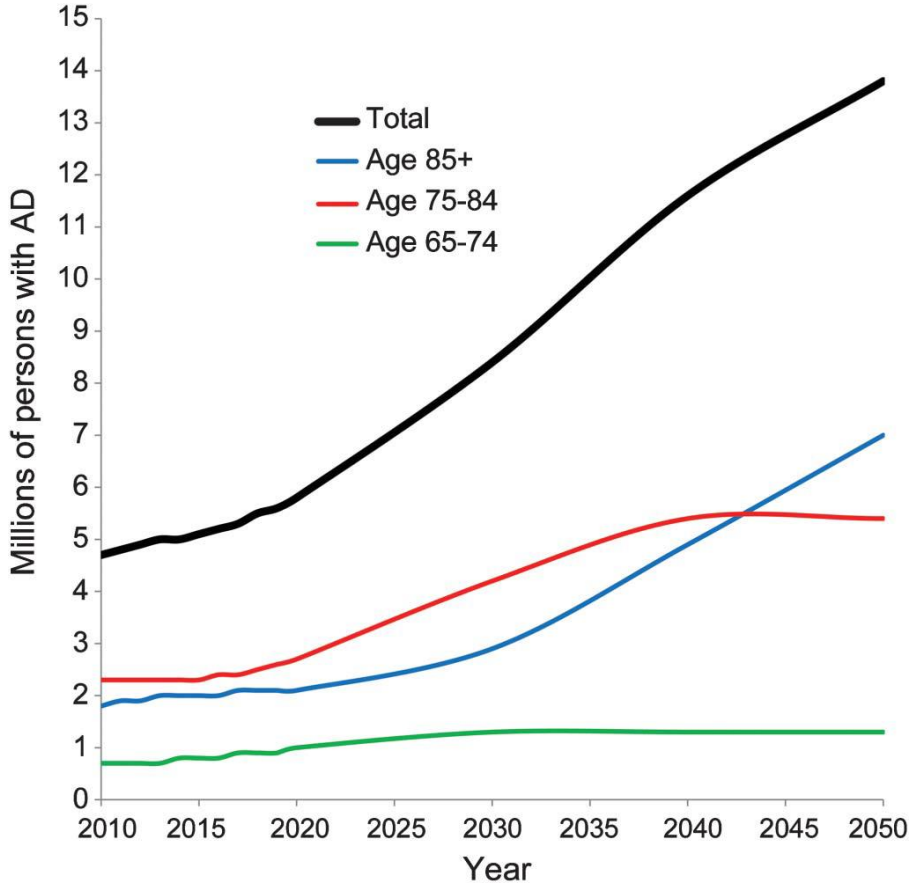
- 4.7 million cases of Late Onset Alzheimer's Disease (LOAD) in 2010
- 13.8 million cases by 2050
- Cost $203 Billion in 2012
- Estimated to reach

  $1.2 trillion by 2050



*Data are in 2013 dollars.

Alzheimer's Association,
2013 Alzheimer's Disease Facts and Figures
Alzheimer's & Dementia, 9(2).



Hebert et al., 2013

Sex Differences in Alzheimer's Disease

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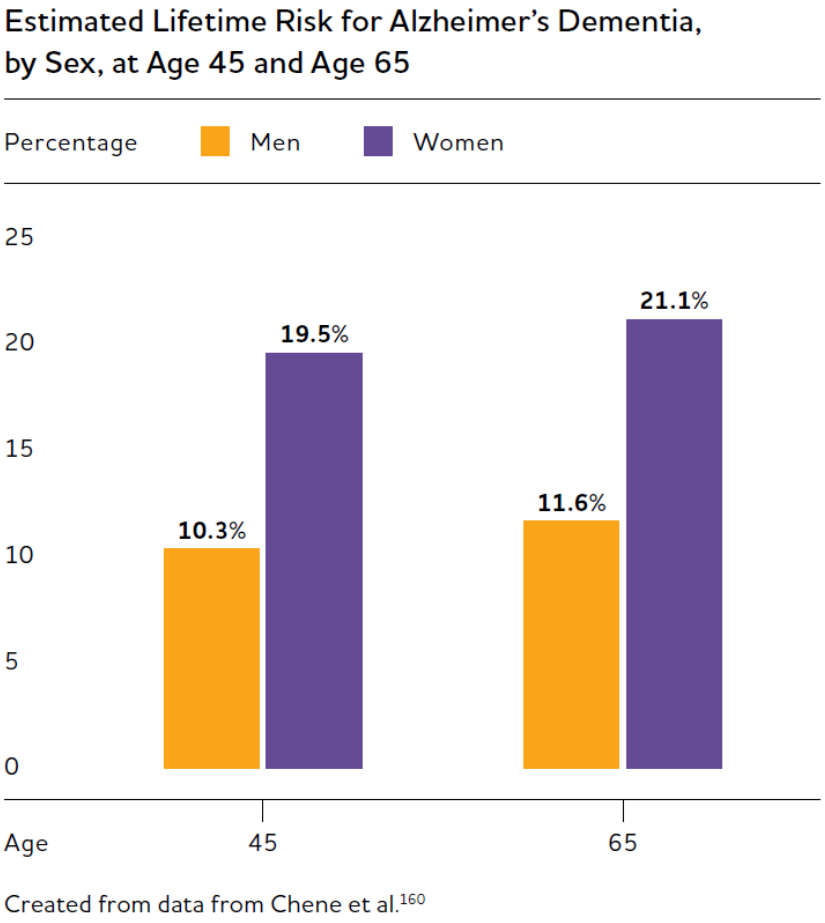
- Almost two-thirds of AD cases in the US are **women**



Alzheimer's Association. 2017 Alzheimer's Disease Facts And Figures. www.alz.org/facts/

Racial/Ethnic Differences in AD

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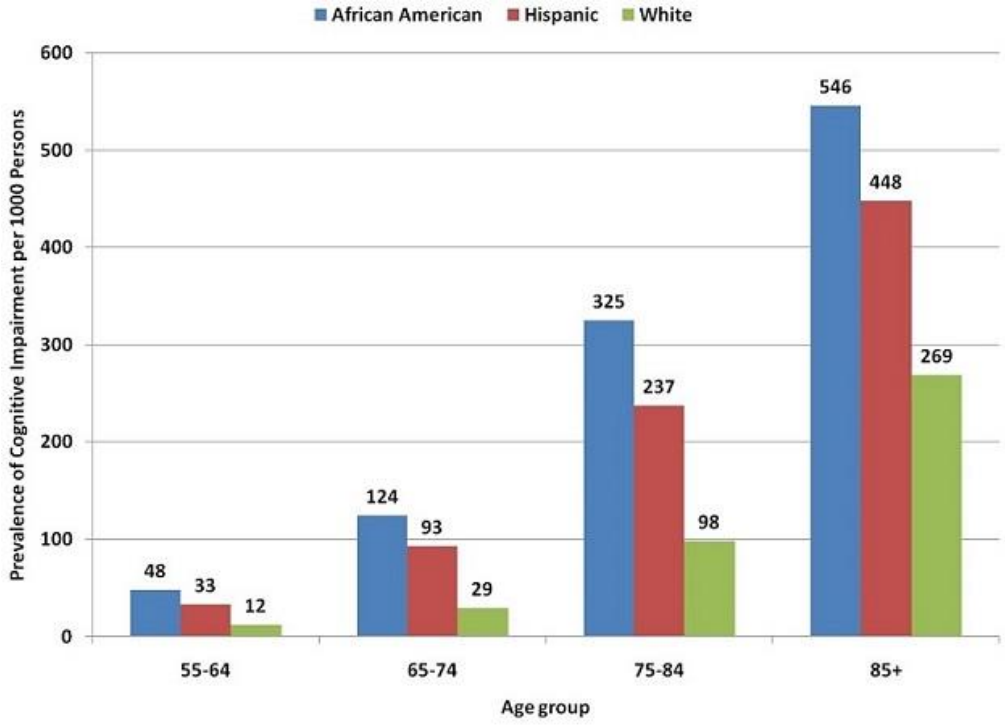
- Compared to older white individuals
  - **African Americans** are ~2x more likely to have AD
  - **Hispanics** are ~1.5x more likely to have AD



Adapted from Alzheimer's Association, 2010. https://aspe.hhs.gov/report/racial-and-ethnic-disparities-alzheimers-disease-literature-review

Racial/Ethnic Differences in AD

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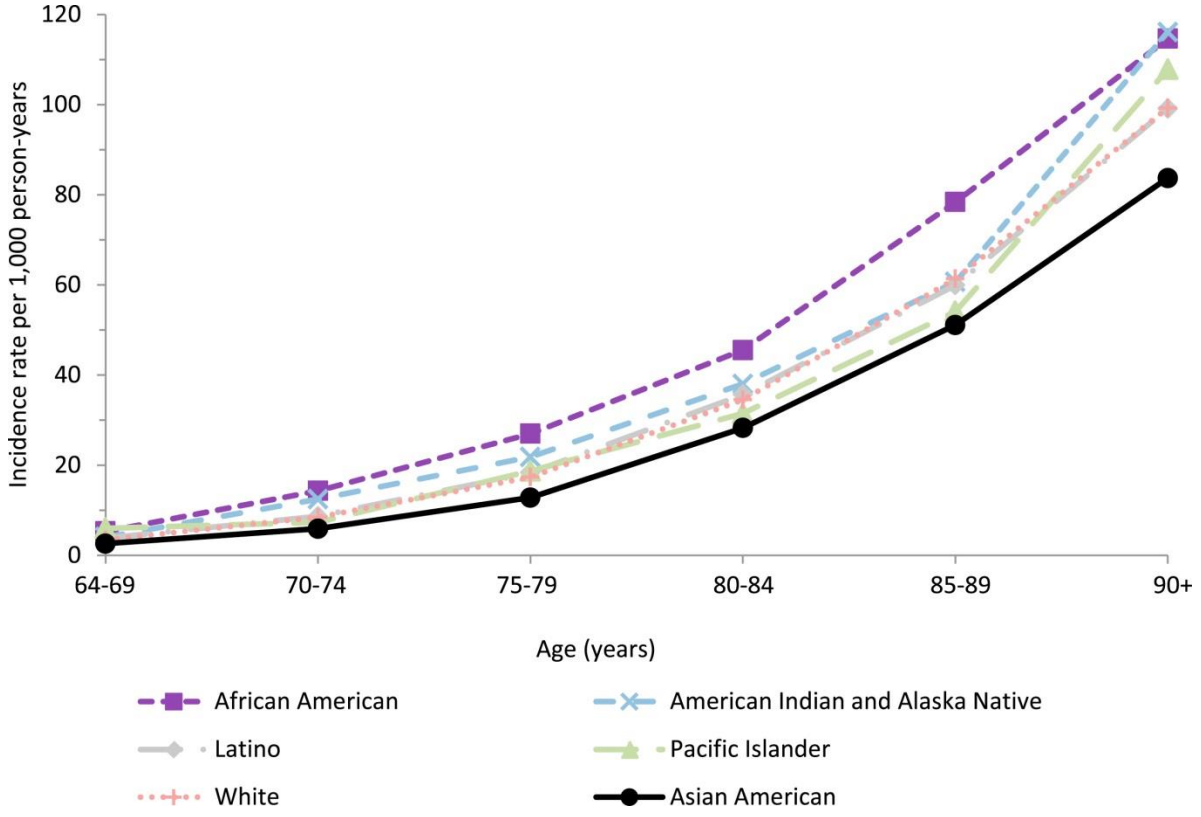
Disparities Increase with Age

- 6 racial/ethnic groups
- 274,000+ members of Kaiser Permanente
  - a large, integrated healthcare delivery system in Northern California
- Used electronic health records from 2000 to 2013

First Study of Dementia Risk in a Population Representative of the diversity in the US



Mayeda et al. *Alzheimer's & Dementia.* 2016

Costs of Health Care

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- African-Americans elders had significantly higher costs of care than whites or Hispanics
  - primarily due to more inpatient care and more comorbidities.

Average Annual Per-Person Payments by Type of Service and Race/Ethnicity for Medicare Beneficiaries Age 65 and Older, with and without Alzheimer's or Other Dementias, 2014, in 2016 Dollars

	Total Medicare Payments per Person	Hospital Care	Physician Care	Skilled Nursing Facility Care	Home Health Care	Hospice Care
White	$19,734	$5,163	$1,611	$3,367	$1,695	$3,128
African-American	26,686	8,690	2,185	4,174	2,072	2,316
Hispanic	21,151	6,986	1,900	3,209	1,787	1,724
Other	25,675	7,858	2,137	3,362	3,671	2,549

Created from unpublished data from the National 5% Sample Medicare Fee-for-Service Beneficiaries for 2014.[188]

Alzheimer's Association. 2017 Alzheimer's Disease Facts And Figures. www.alz.org/facts/

Summary

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- AD includes functional and cognitive deficits
- Risk of AD increases with age
- Females are at higher risk of AD than males
- Lower SES and Education are associated with higher risk
- African Americans and Hispanics populations are at higher risk than Caucasians and Asians
- These disparities increase over the lifespan

Outline

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- Alzheimer's Disease Background and Epidemiology
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Alzheimer's Disease Pathological Cascade

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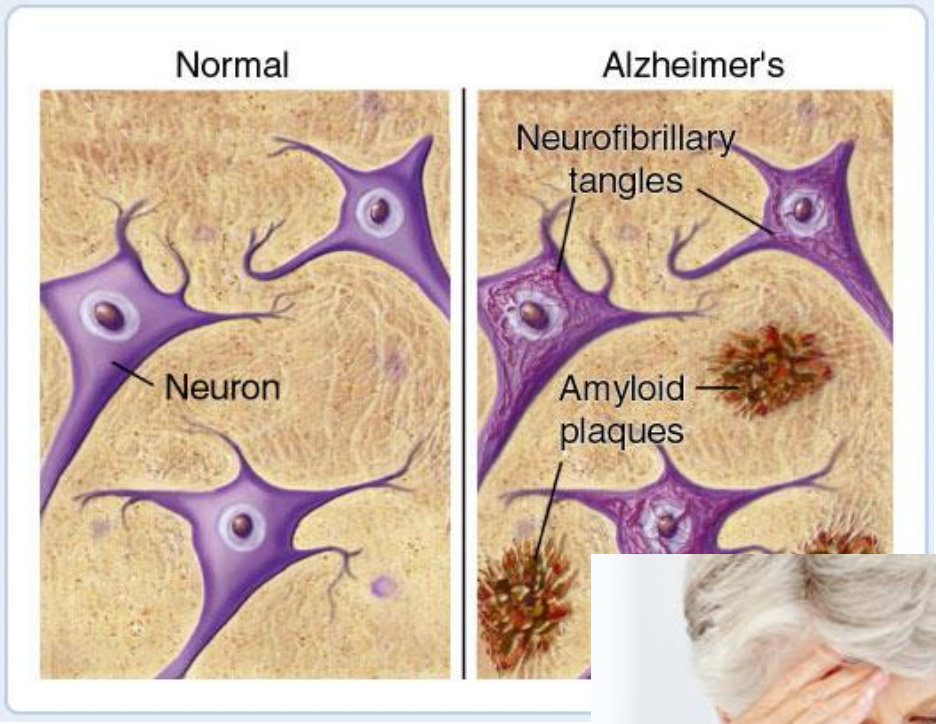
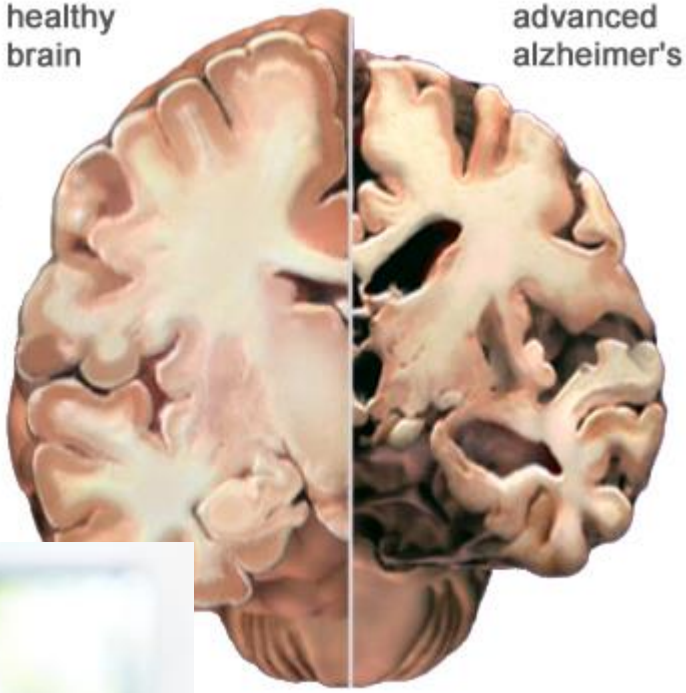
Neuropathology

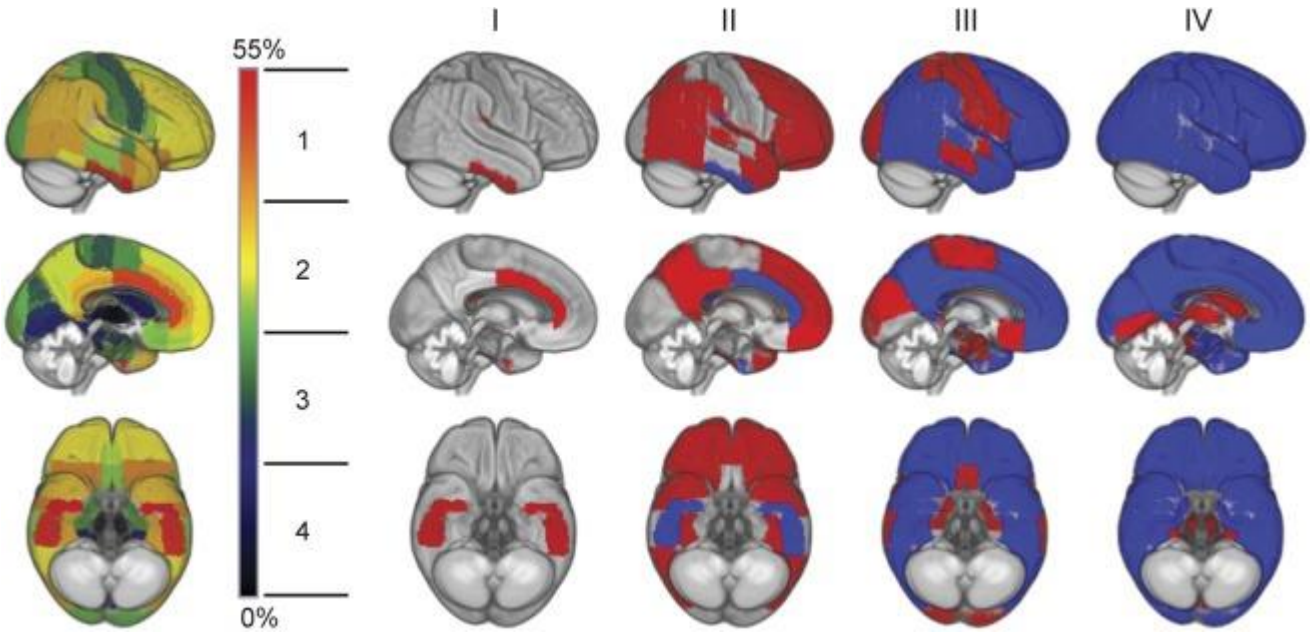


Neurodegeneration



Cognitive Impairment

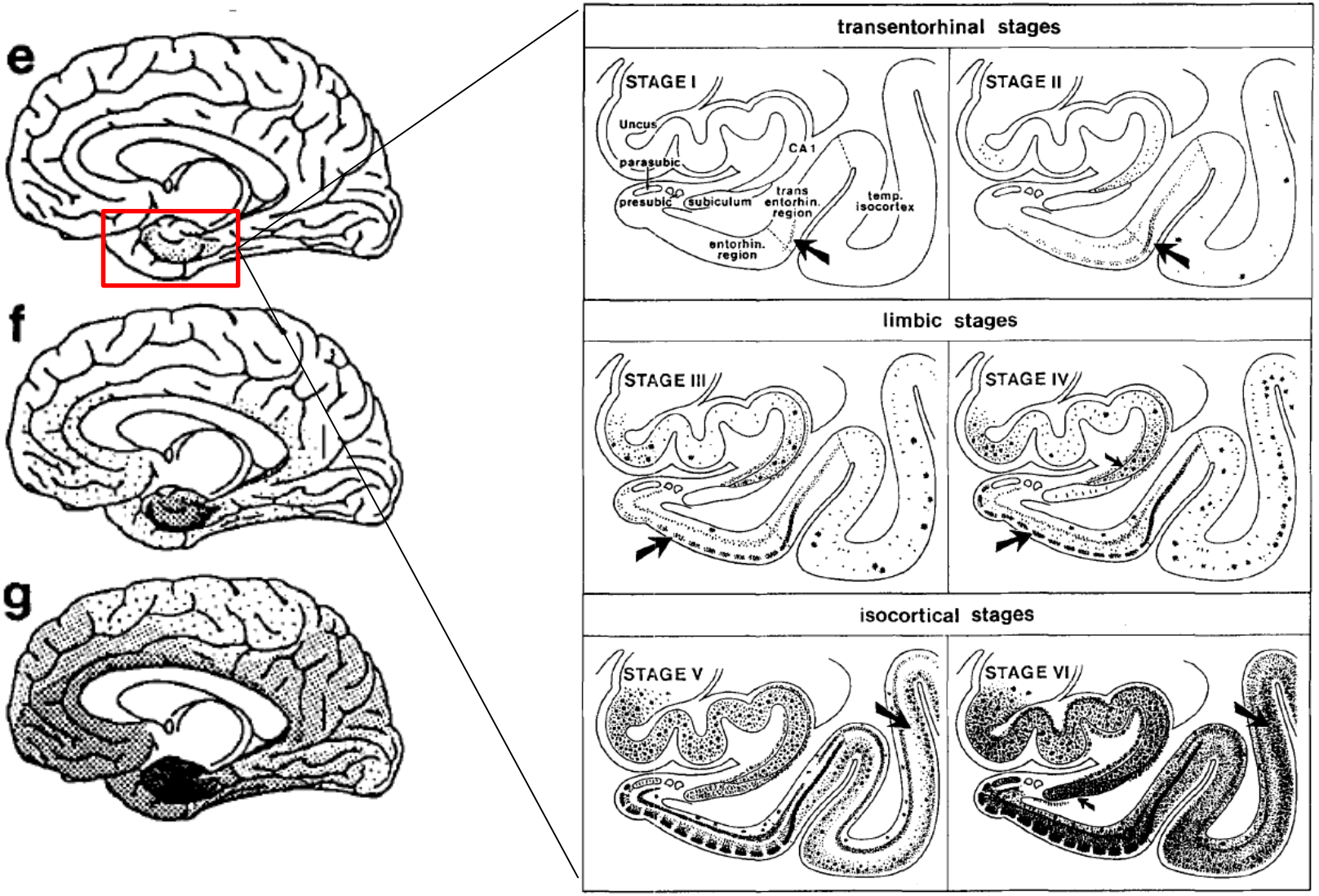
Spread of Plaques



Red regions represent new regions in stage, blue regions represent regions that continue from previous stage.

Grothe et al., *Neurology,* 2017

Spread of Tangles



Braak & Braak, *Neurobiology of Aging*, 1995

Atrophy, Glucose Metabolism, Amyloid

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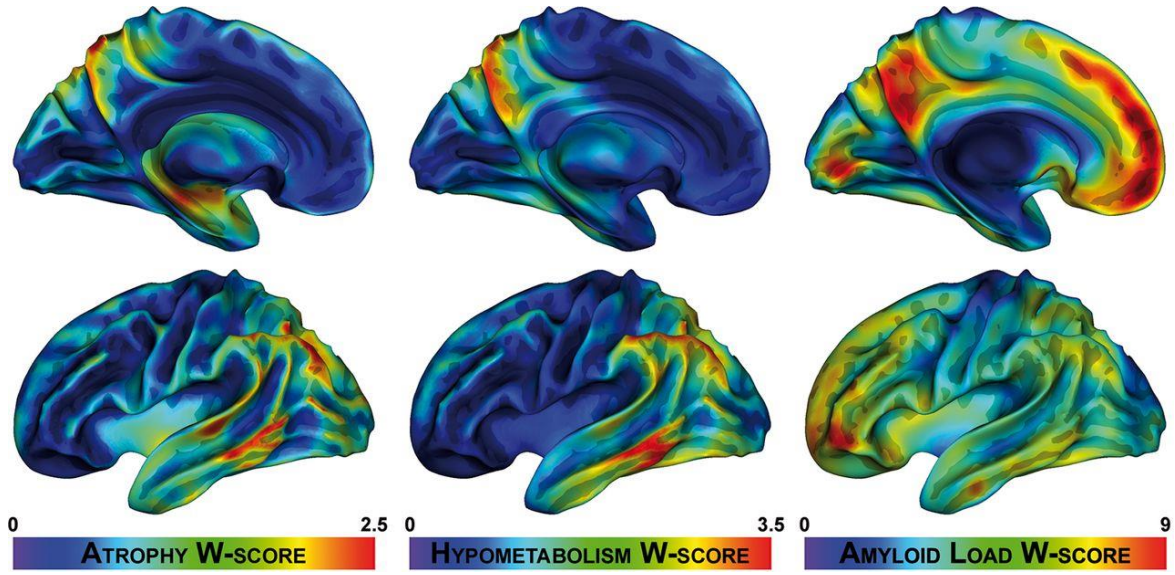
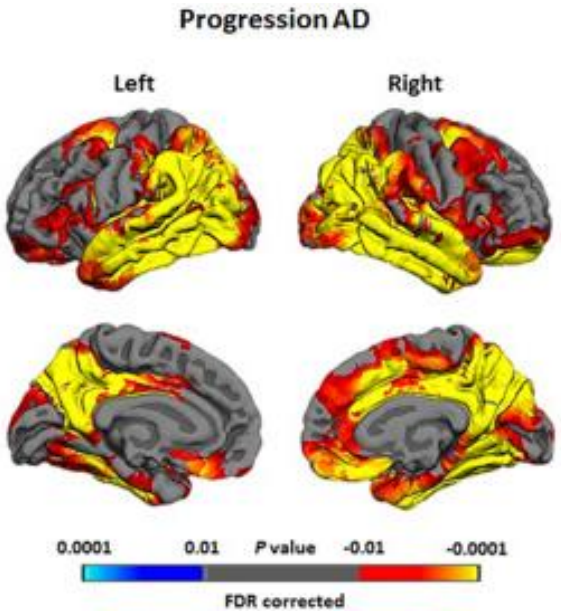
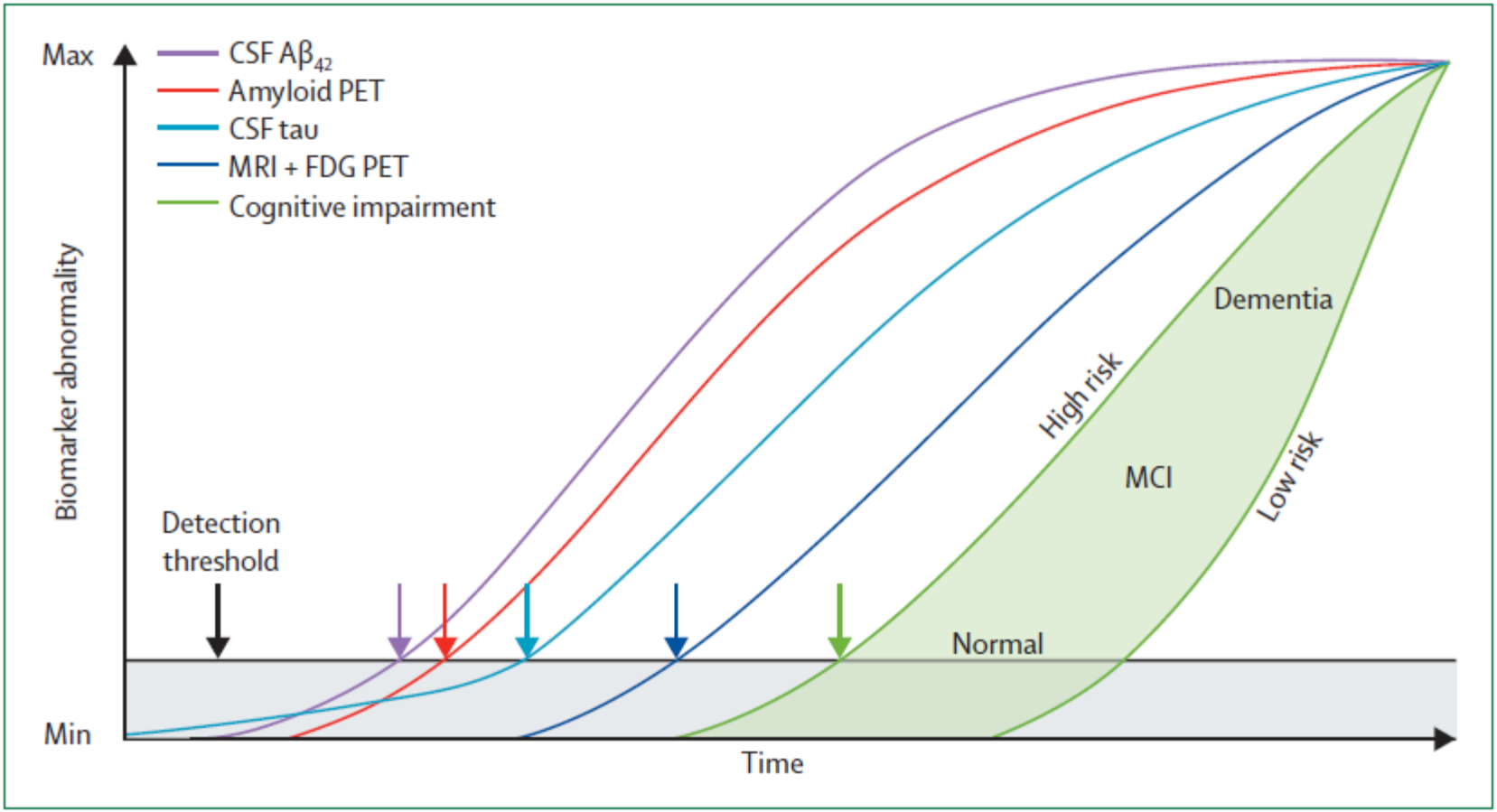
Neuropathology and Atrophy in Alzheimer's Disease





La Joie, *Journal of Neuroscience, 2012*
Landin-Romero, Neuroimage, 2017

Alzheimer's Disease Background



Alzheimer's Disease Background

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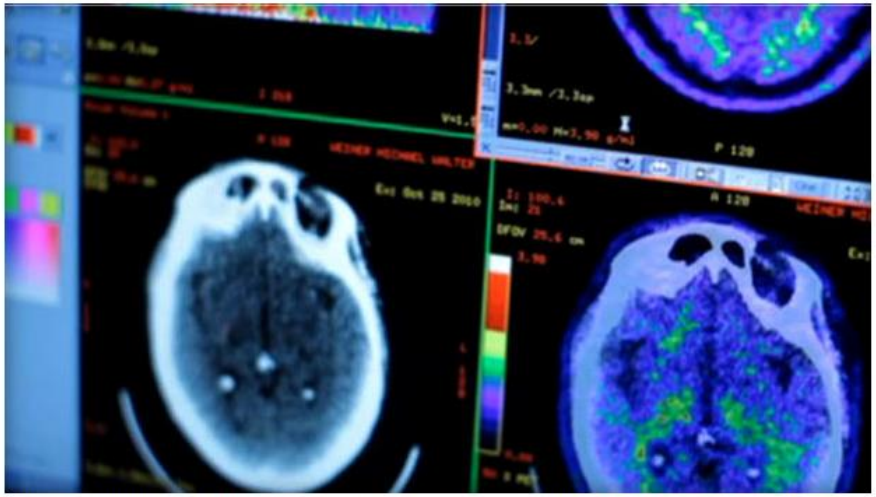
By MICHELLE CASTILLO / CBS NEWS / *August 7, 2012, 4:47 PM*

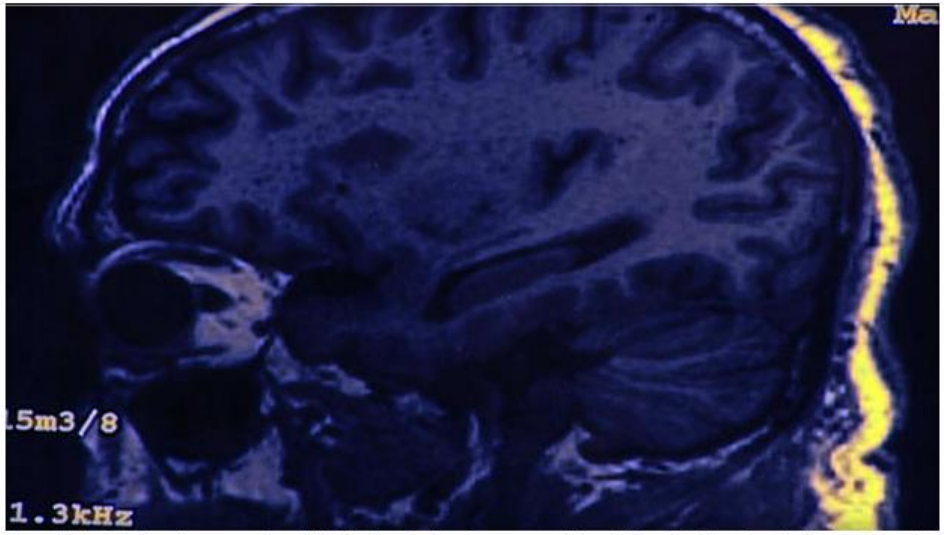
Poor results halt production, studies on promising Alzheimer's drug bapineuzumab



President Obama pledged $130 million for Alzheimer's disease research over the next two years, and an additional $26 million to support caregivers. But, will that funding be enough to make a difference? Dr. Jon LaPook reports

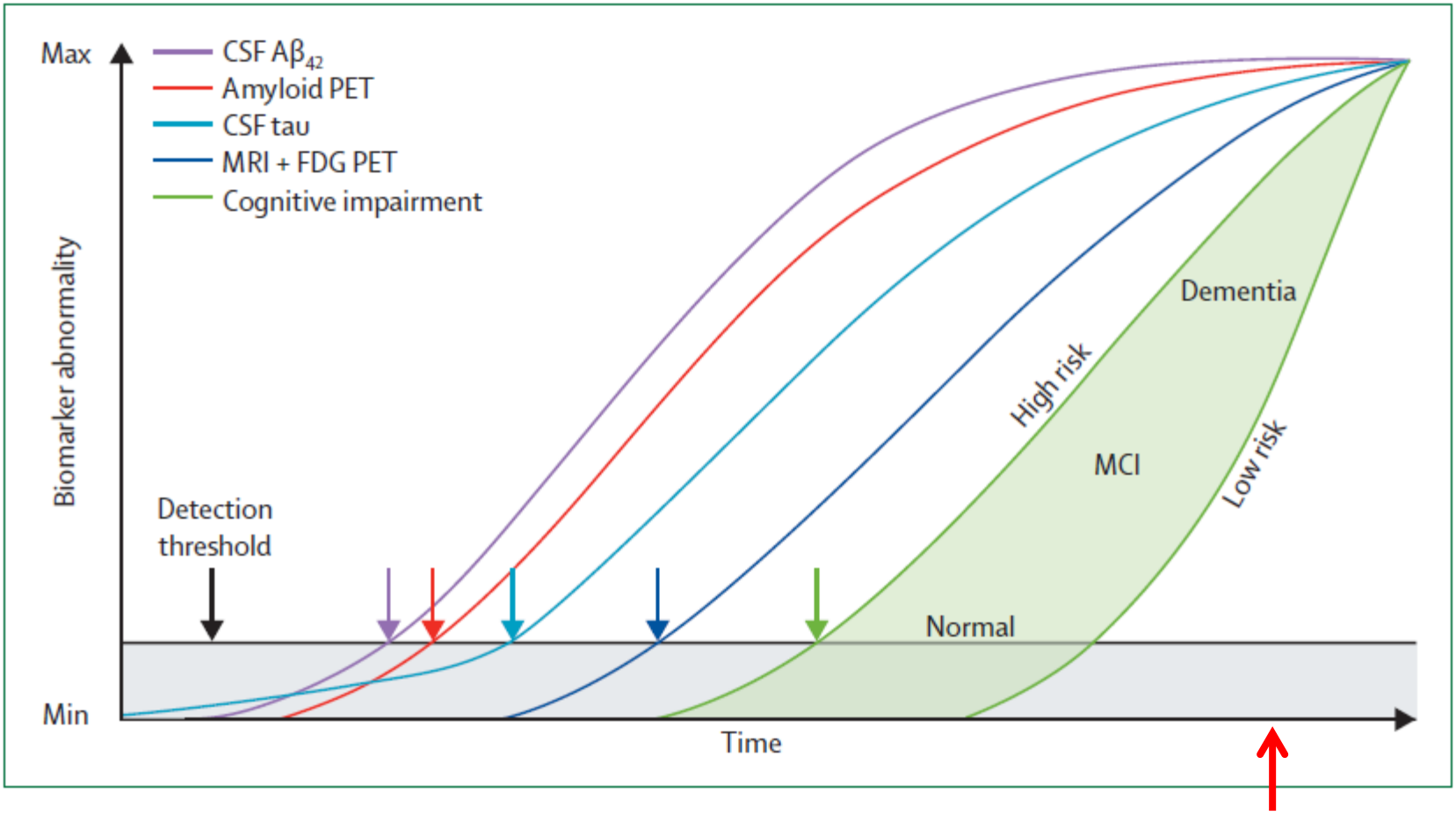
CBS NEWS / *August 24, 2012, 4:19 PM*

Eli Lilly's experimental Alzheimer's drug solanezumab fails study but shows potential



A new trial of the leading experimental Alzheimer's drug Crenezumab is set to begin; Also, Dr. Jon LaPook reports on what is behind the recent whooping cough outbreak; And, The man who runs the hometown bank in Cattaraugus, New York feels he has a responsibility to his town to hold the community together.

Moving back the treatment window



Heterogeneity and Concomitant Pathology

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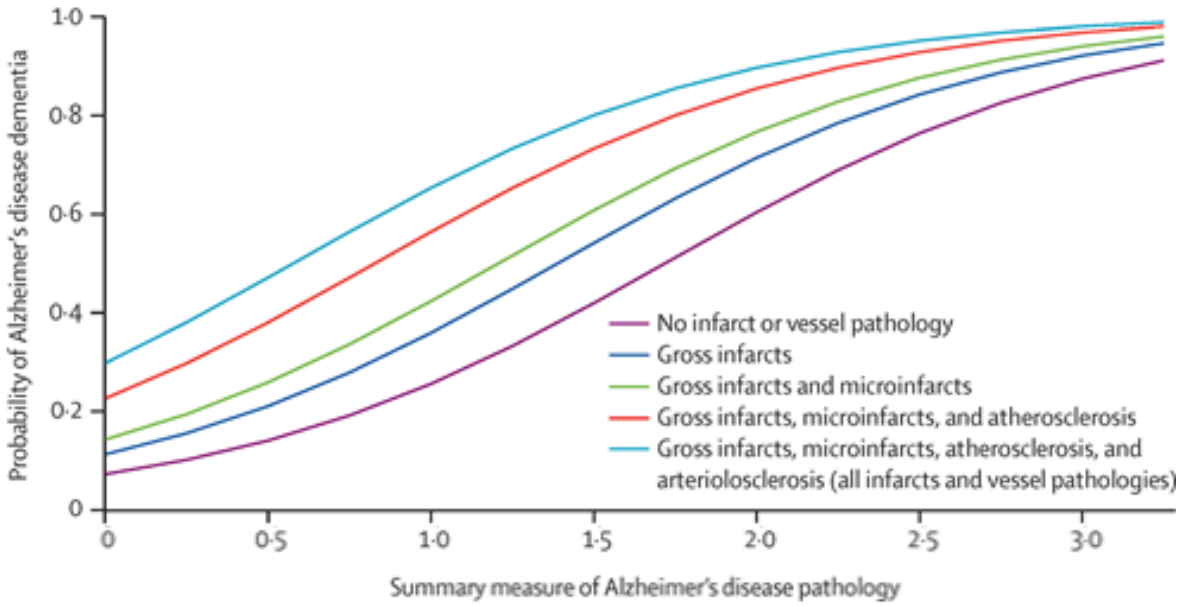
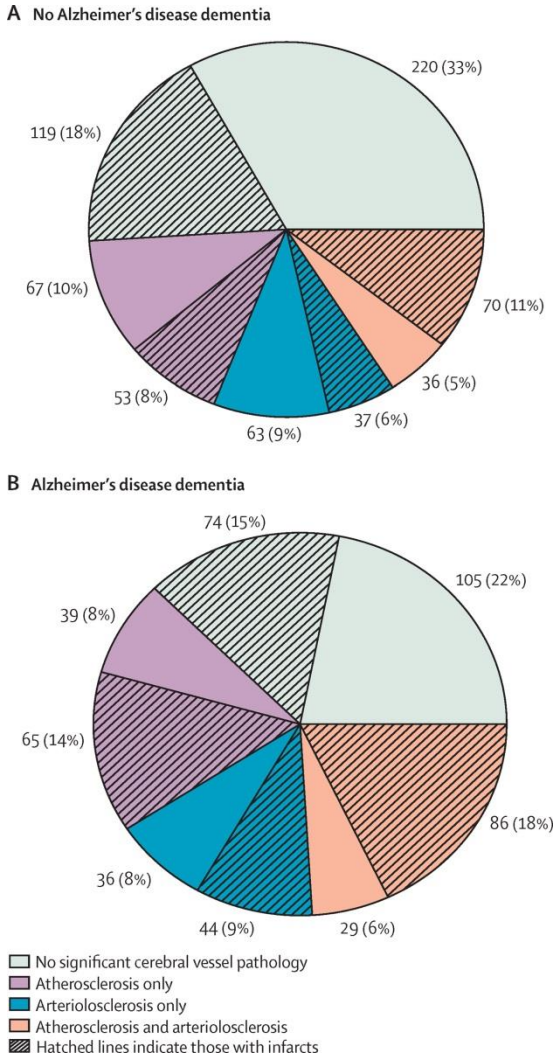
- It's not just plaques and tangles!





- And that matters:

9896 • The Journal of Neuroscience, September 21, 2016 • 36(38):9896 –9907

Neurobiology of Disease

Reduced Efficacy of Anti-Aβ Immunotherapy in a Mouse Model of Amyloid Deposition and Vascular Cognitive Impairment Comorbidity

Erica M. Weekman,[1,2] Tiffany L. Sudduth,[1,2] Carly N. Caverly,[1,2] Timothy J. Kopper,[2] Oliver W. Phillips,[1,2] Dave K. Powell,[3,4] and Donna M. Wilcock[1,2]
[1]Sanders-Brown Center on Aging, [2]Department of Physiology, [3]Magnetic Resonance Imaging and Spectroscopy Center, [4]Department of Biomedical Engineering, University of Kentucky, Lexington, Kentucky 40536

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- Alzheimer's Disease Background and Epidemiology
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Genetics of AD: Past

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- Early Onset Alzheimer's Disease (EOAD)
  - Before the age of 65
  - Dominantly inherited
  - ~1% of AD Cases
  - *APP*
    - *Amyloid Precursor Protein: Membrane Protein at Synapse*
    - *Mutations result in* ↑*A*β Production
  - *PSEN1*
    - *Gamma Secratase: APP Cleavage resulting in* ↑*A*β Production
  - *PSEN2*
    - *Gamma Secratase: APP Cleavage resulting in* ↑*A*β Production

Genetics of AD: Past

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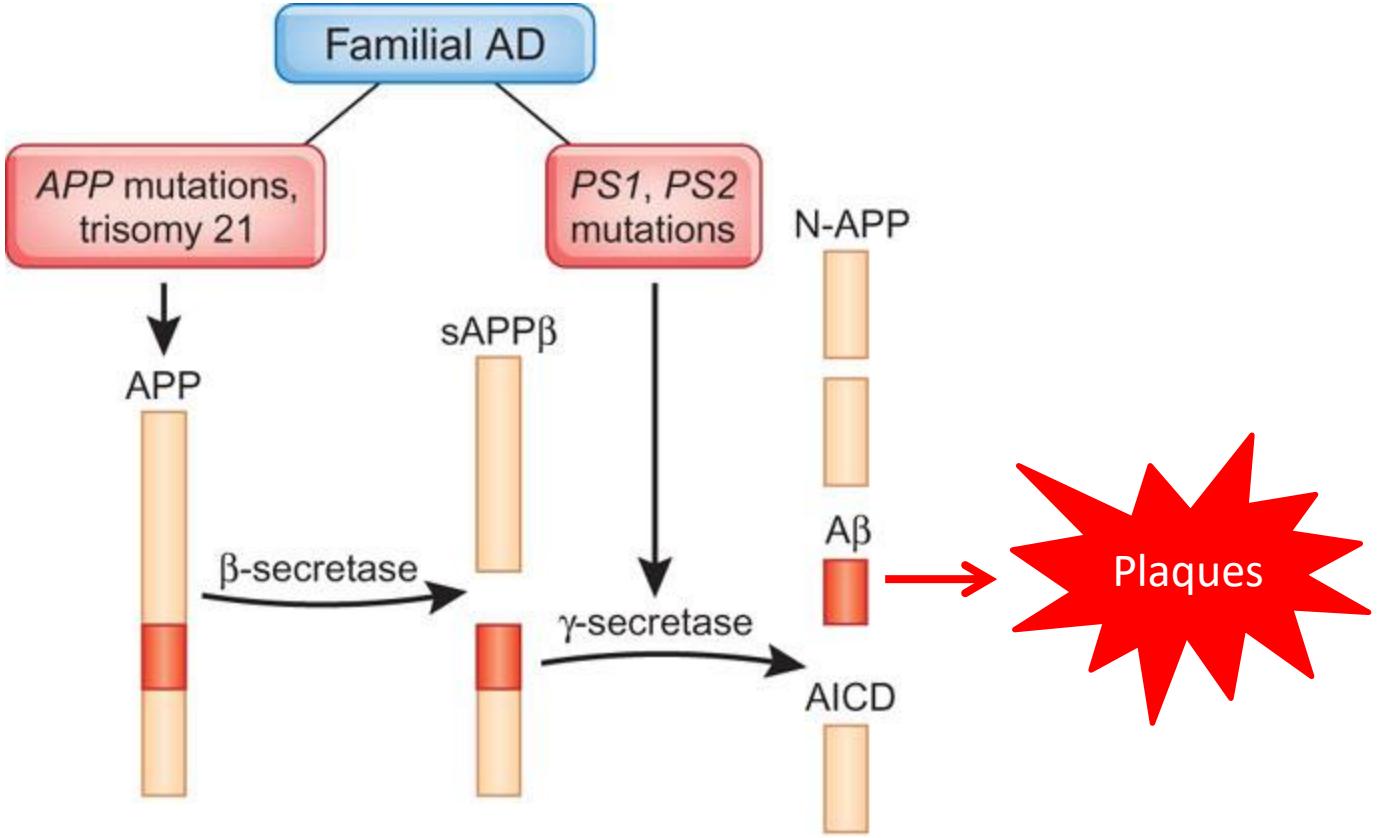
- Early Onset Alzheimer's



Van Es & Van den Berg, 2009. *Nature Genetics,* 41, Figure 1.

Genetics of AD: Past

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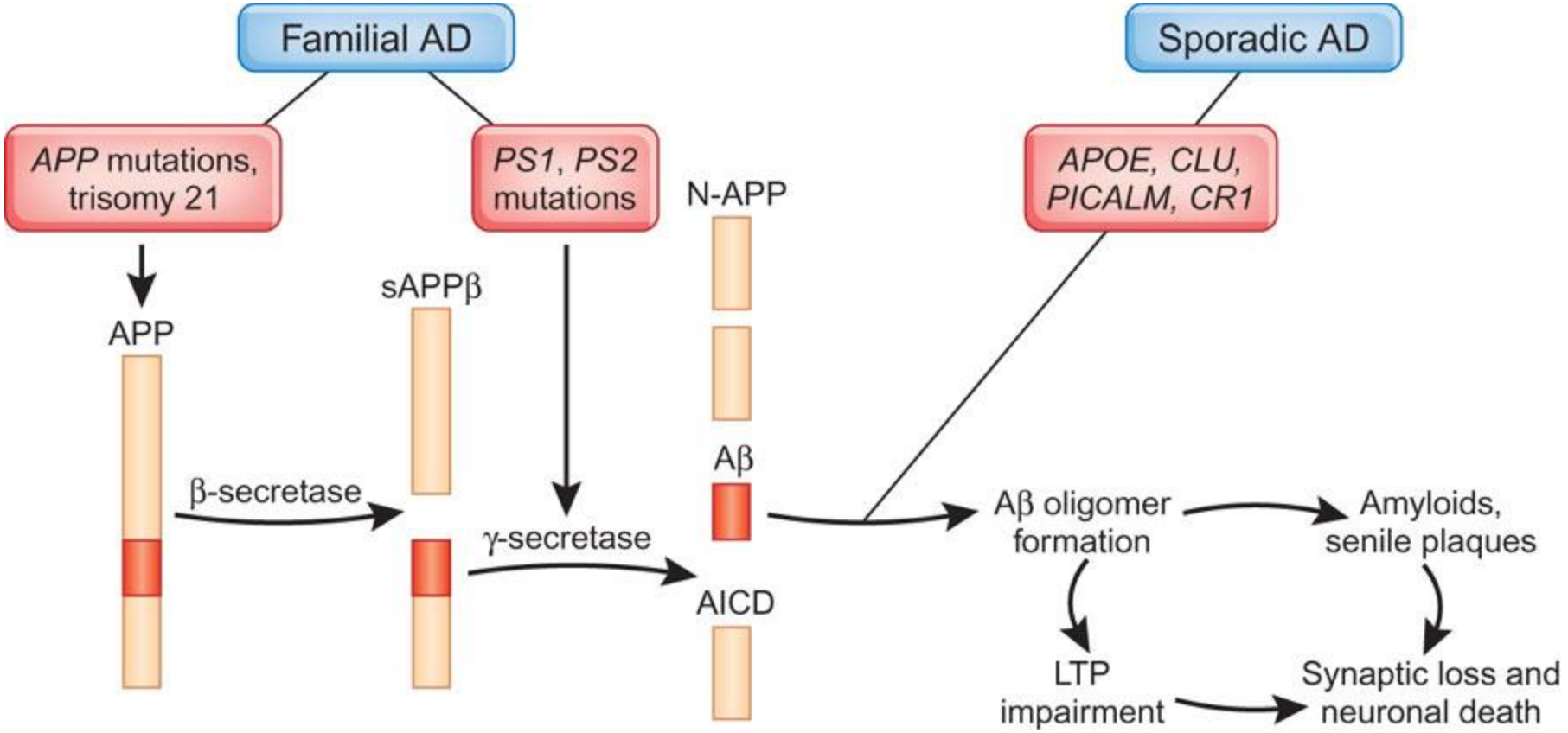
- Late Onset Alzheimer's Diseae (LOAD)
  - Heritability estimated between 60-80% (Gatz et al., 2006)
  - Known loci explain ~25% of heritability (Hon-Cheong et al, 2011)
  - *APOE*
    - ε4 dose dependent effect (Corder et al, 1993)
    - Mechanism unknown
    - OR = 3.68
    - ε2 protective effect
  - Other loci
    - *BIN1, CLU, ABCA7, CR1, PICALM, MS4A6A, CD33, MS4A4E, CD2AP, EPHA1 (alzgene.org)*
    - *Odds ratios between .85 and 1.25*

Genetics of AD: Past

- Early Onset Alzheimer's and Late Onset Alzheimer's



Van Es & Van den Berg, 2009. *Nature Genetics,* 41, Figure 1.

Apolipoprotein E

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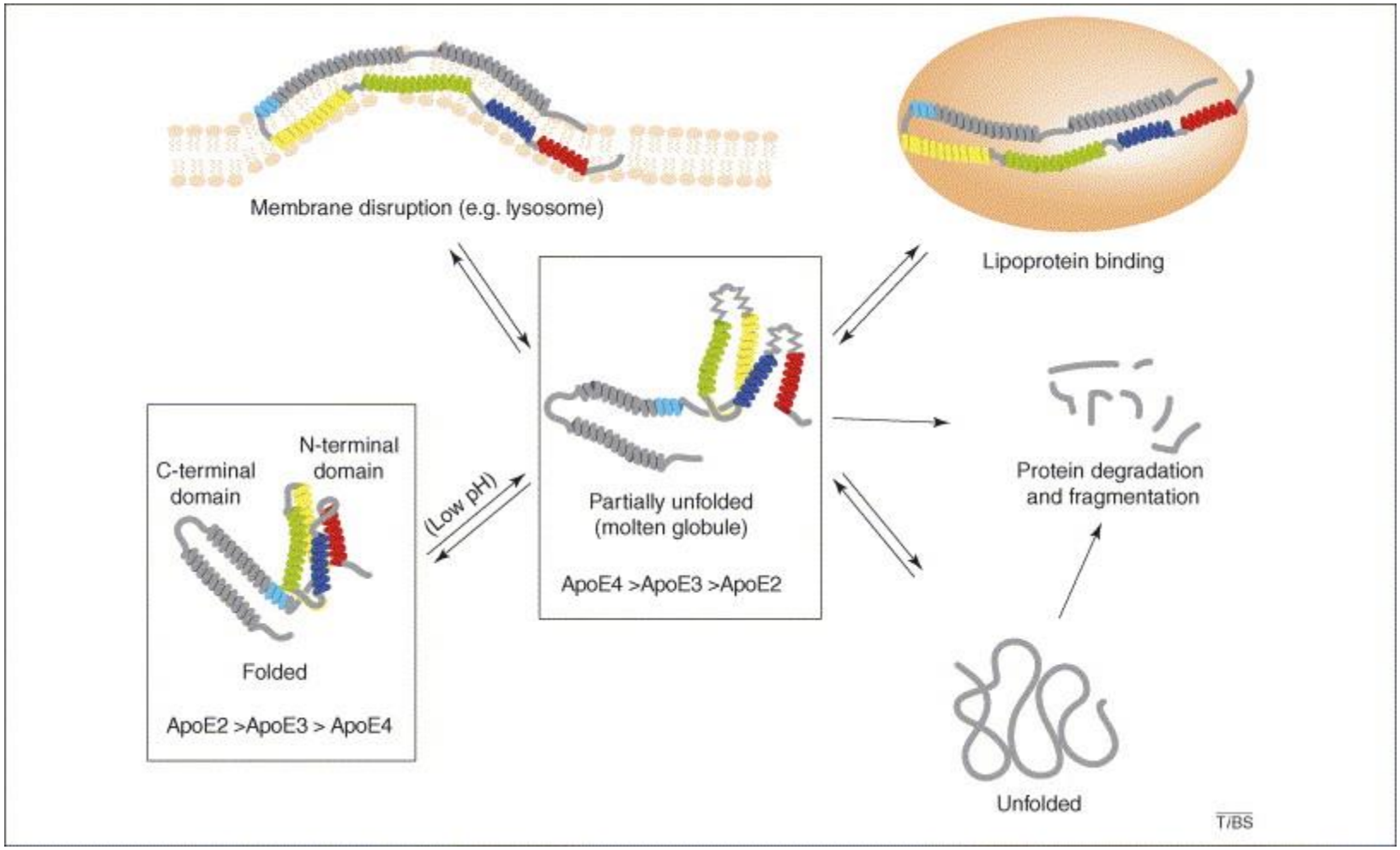
- Structure (299 amino acids)
  - Polymorphic, differs at position 112 and 158
    - E3 – cys112(-), arg158(+)
      - Common, normal function
    - E4 – arg112 (+), arg158(+)
      - Preferentially binds large lower-density lipoproteins
      - Positive charge at 112 leads to conformation change in N-terminal and an interaction between N and C terminal
        - » Interacts with Glu255 (residue), preferential binding reverts when glutamine is changed to alanine.
    - E2 – cys112(-), cys158(-)
      - Alters conformation, reducing ability to interact with Low-Density Lipoprotein (LDL) receptor
  - Implications
    - E4 is less stable, E2 is extremely stable (2 state equilibrium)
    - Increases likelihood of binding larger lipoproteins
    - Little is known about how these structural differences alter binding potential for lipid-bound APOE molecules
- Observed effects of E4
  - Associated with enhanced inflammatory response
  - Amyloid clearance (released from astroglia)
  - Associated with higher levels of plaques and tangles post-mortem and in vivo
  - May regulate tau phosphorylation via GSK-3 through interaction with LRP5 and LRP6

Apolipoprotein E



Hatters et al., Trends in Biochemical Sciences, 2006

GWAS Era Findings

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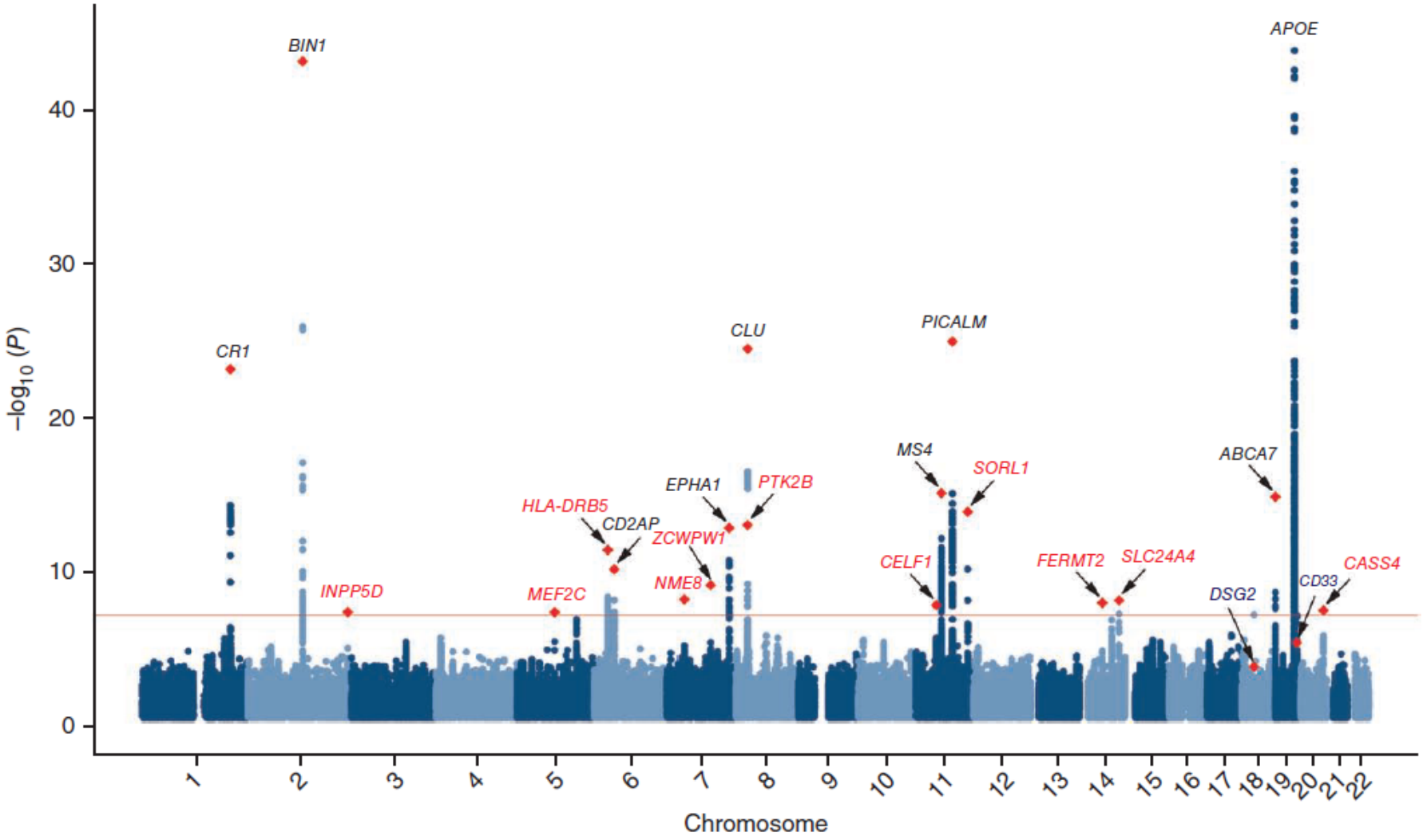
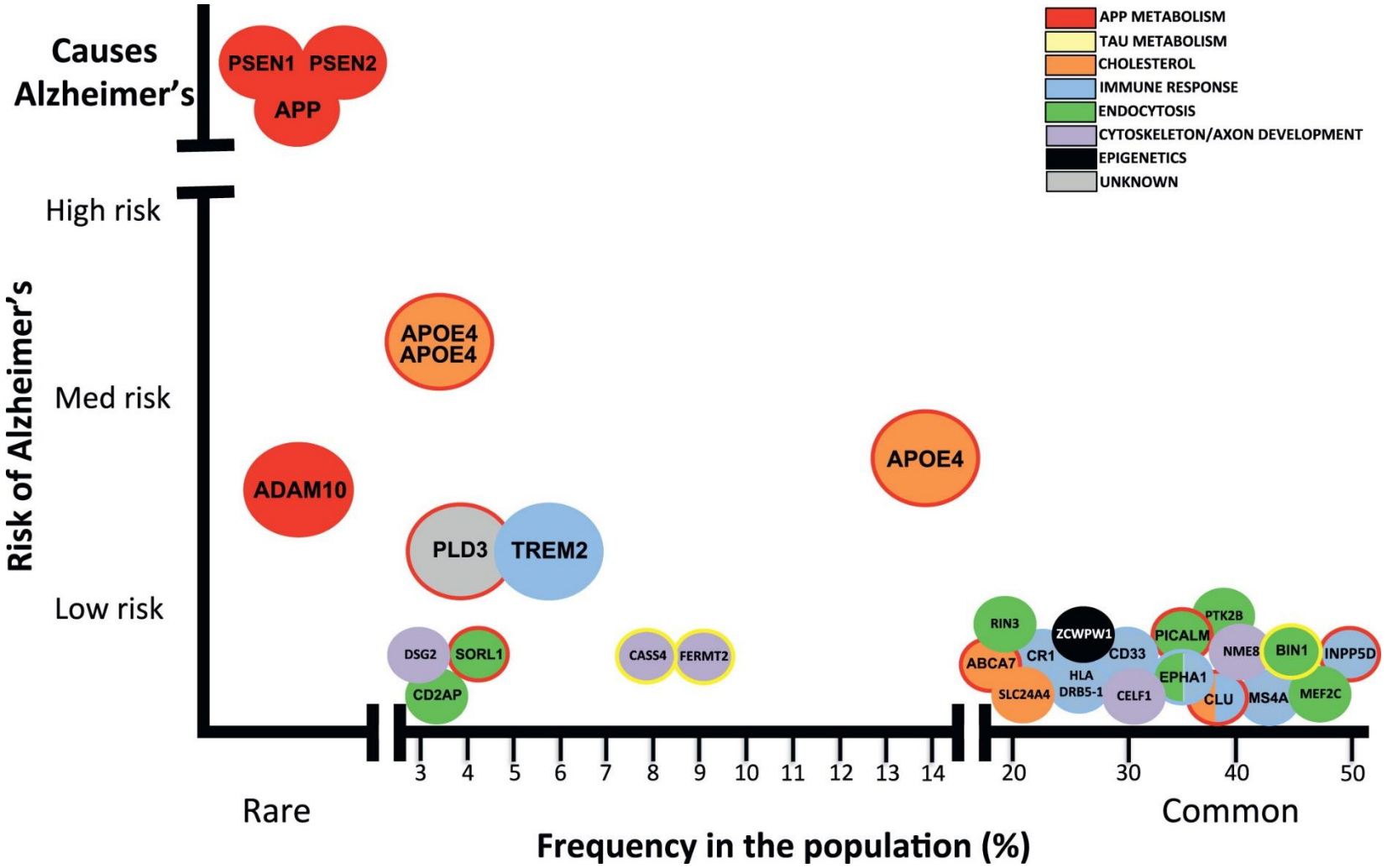


Rare and Common Variants



Biological Psychiatry 2015 77, 43-51DOI: (10.1016/j.biopsych.2014.05.006)

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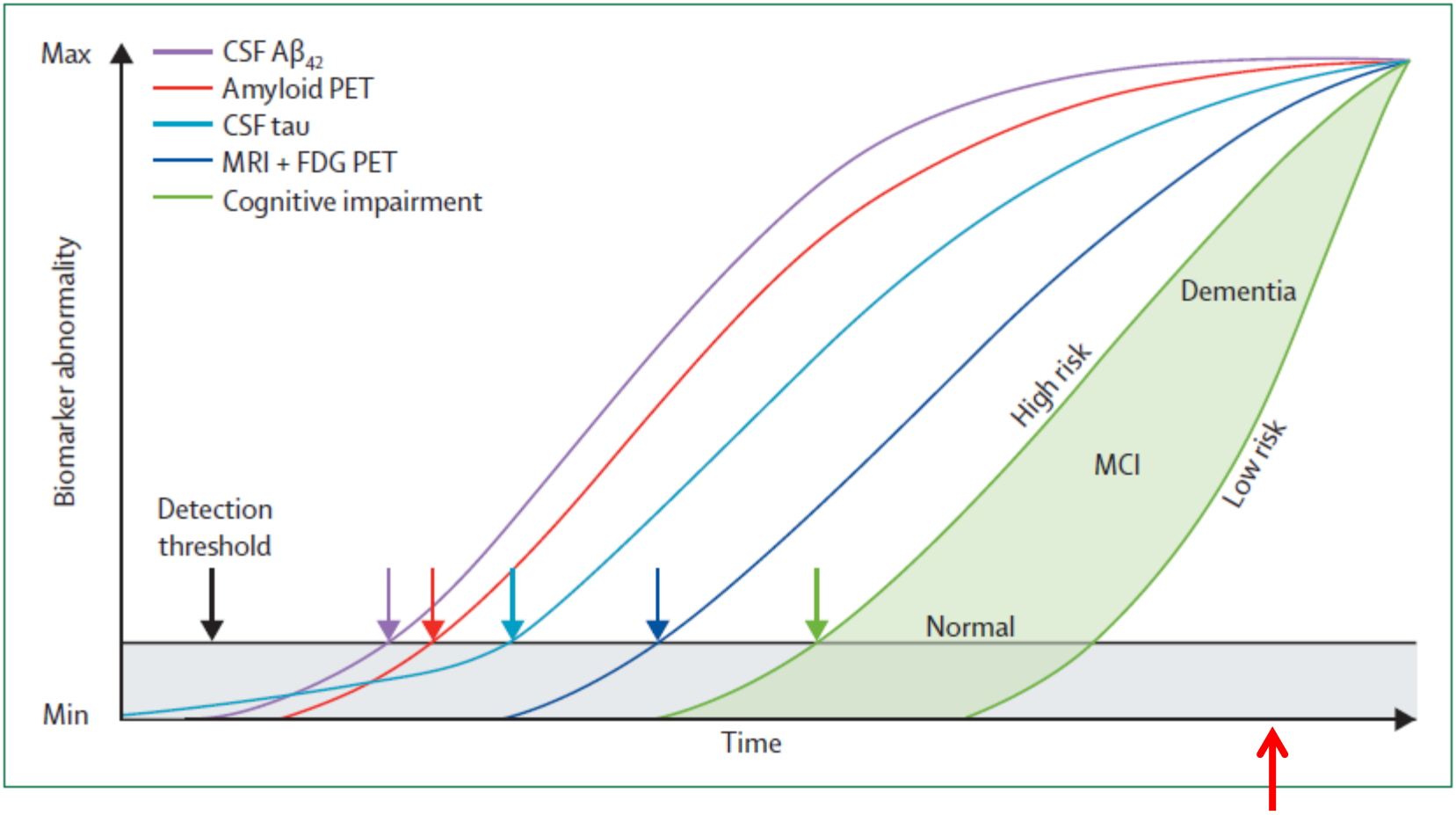
Reminder: Timing



Jack et. al, Lancet Neurology, 2013

Vanderbilt Memory & Alzheimer's Center

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https://medschool.vanderbilt.edu/vmac/

- Early Detection Initiative
  - Developing robust screening tools for primary care settings

Forging Ahead: Concomitant Pathology

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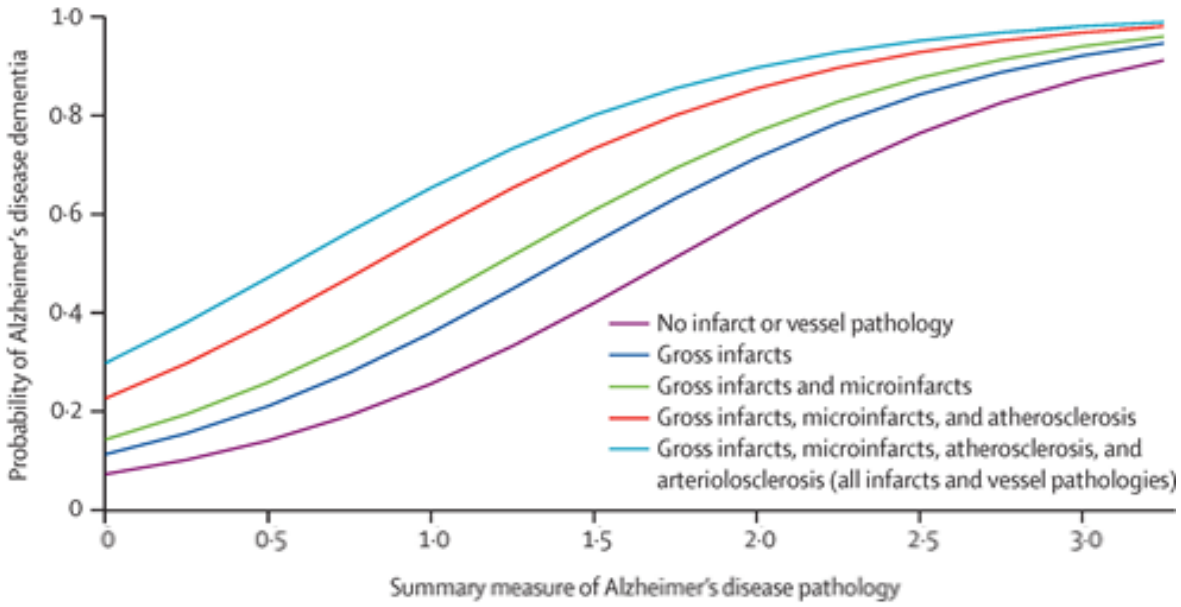
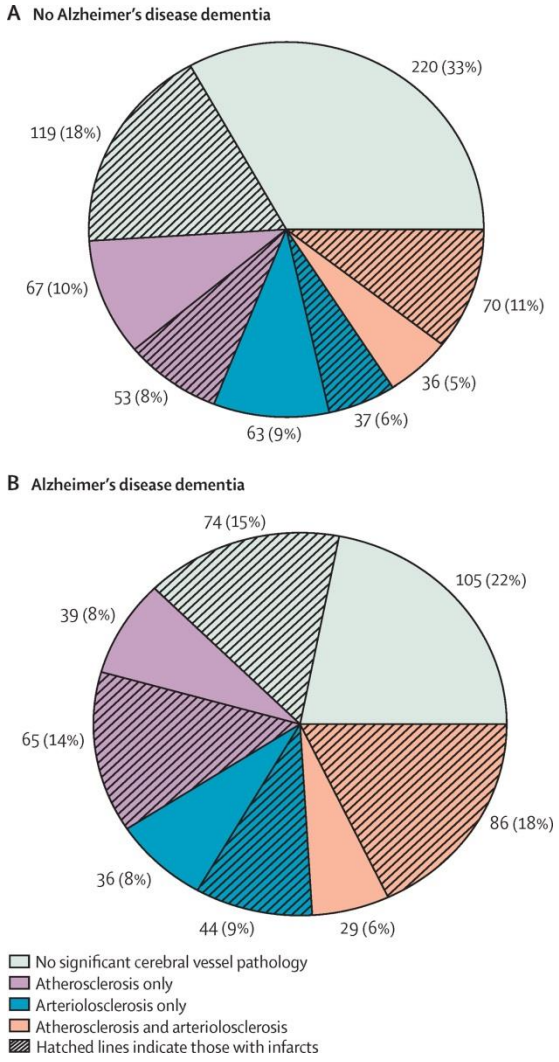
- It's not just plaques and tangles!





Arvanitakis et al, The Lancet, 2016

- And that certainly matters:

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Reduced Efficacy of Anti-Aβ Immunotherapy in a Mouse Model of Amyloid Deposition and Vascular Cognitive Impairment Comorbidity

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Vanderbilt Memory & Alzheimer's Center

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https://medschool.vanderbilt.edu/vmac/

- Early Detection Initiative
  - Developing robust screening tools for primary care settings
- Risk & Prevention Initiative
  - Vascular health and Alzheimer's disease

Resilience as a Pathway to New Targets

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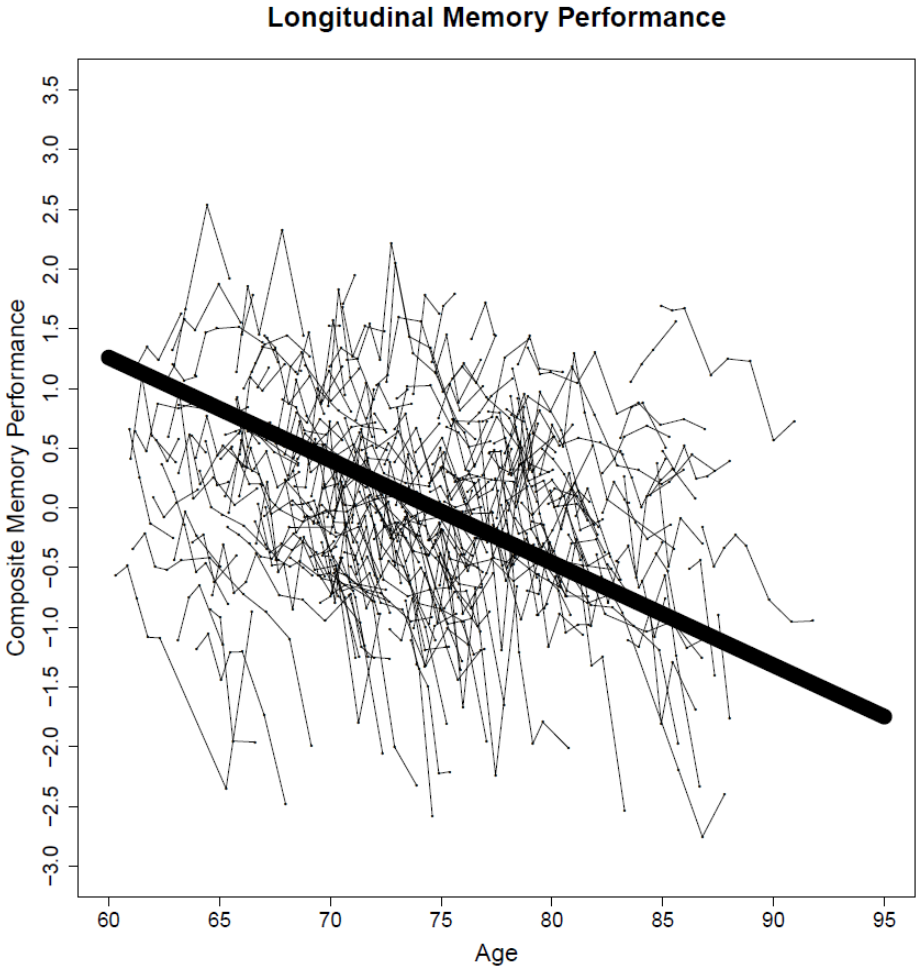
- Pathology ≠ Impairment



Resilience as a Pathway to New Targets

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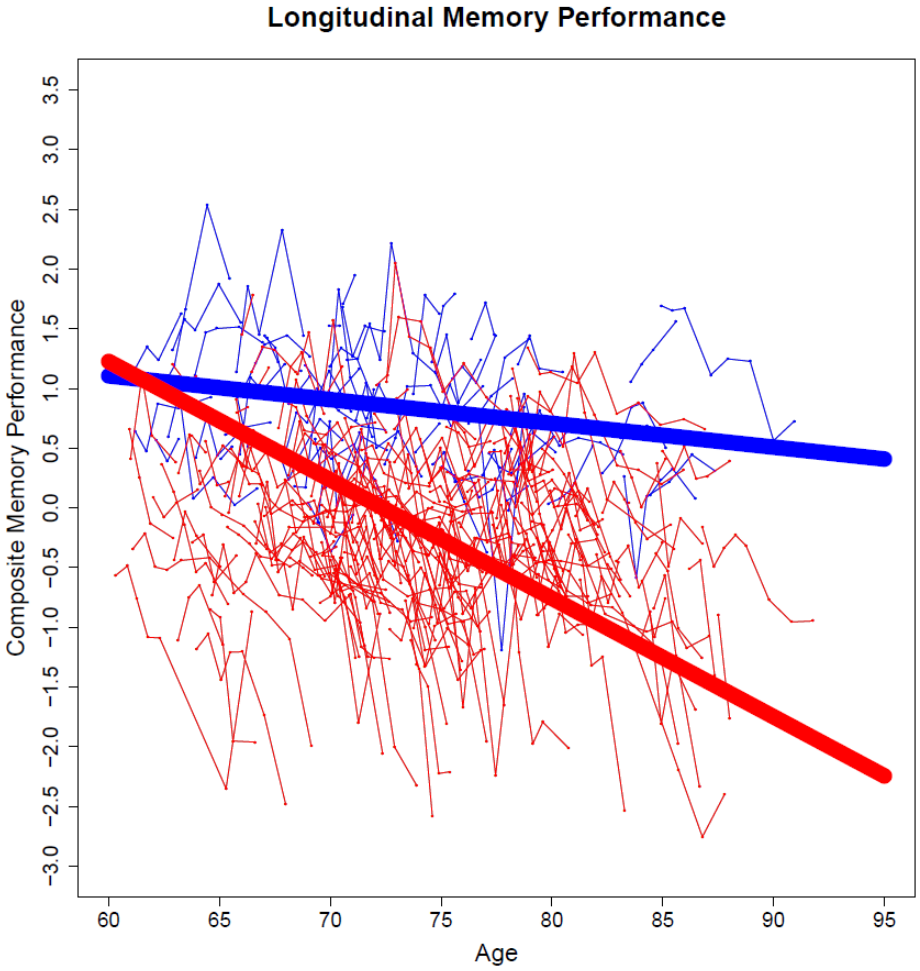

All Participants:

- Amyloid^{+}
- Tau^{+}
- *APOE* ε4^{+}

Vanderbilt Memory & Alzheimer's Center

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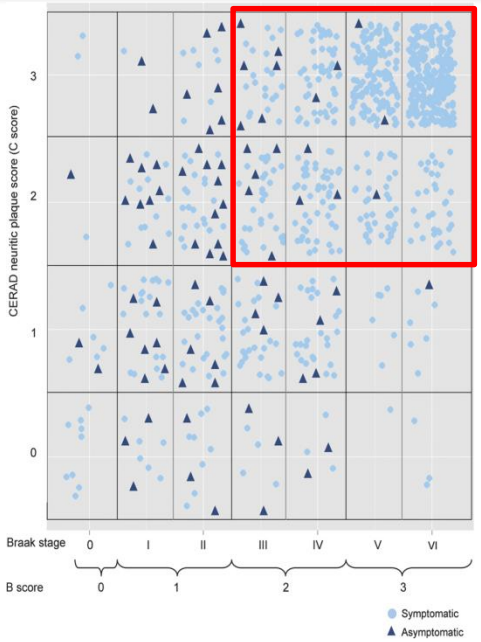
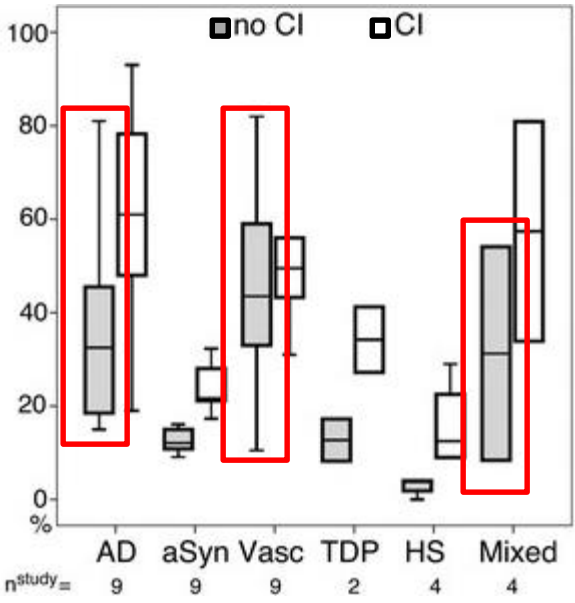
https://medschool.vanderbilt.edu/vmac/

- Early Detection Initiative
  - Developing robust screening tools for primary care settings
- Risk & Prevention Initiative
  - Vascular health and Alzheimer's disease
- Resilience Initiative
  - Identify the molecular drivers of resilience

Asymptomatic Alzheimer's Disease

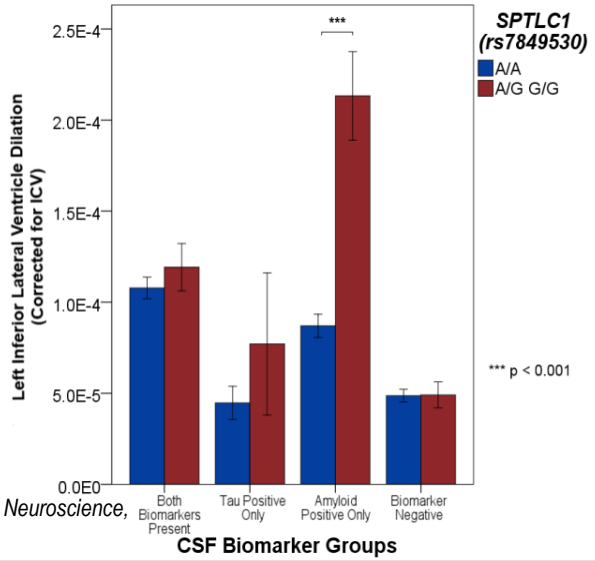
- Reported by Braak & Braak (1997)
- Approximately 10% of NACC autopsy cases
- Approximately 30% in cohort studies (BLSA, ROS/MAP)





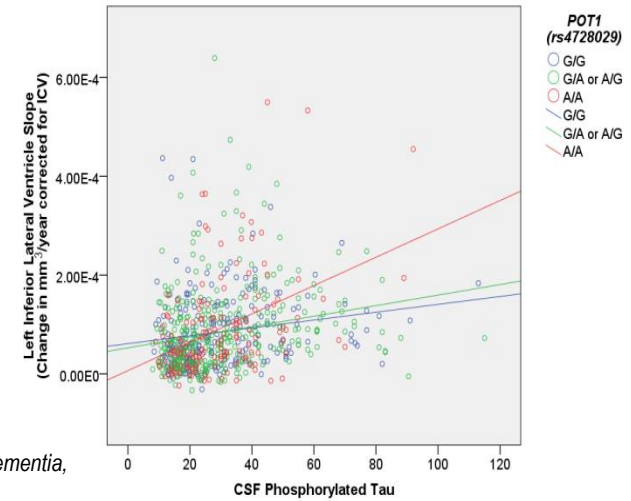
Identifying Markers of Resilience in ADNI

SNP x Biomarker Group Interactions



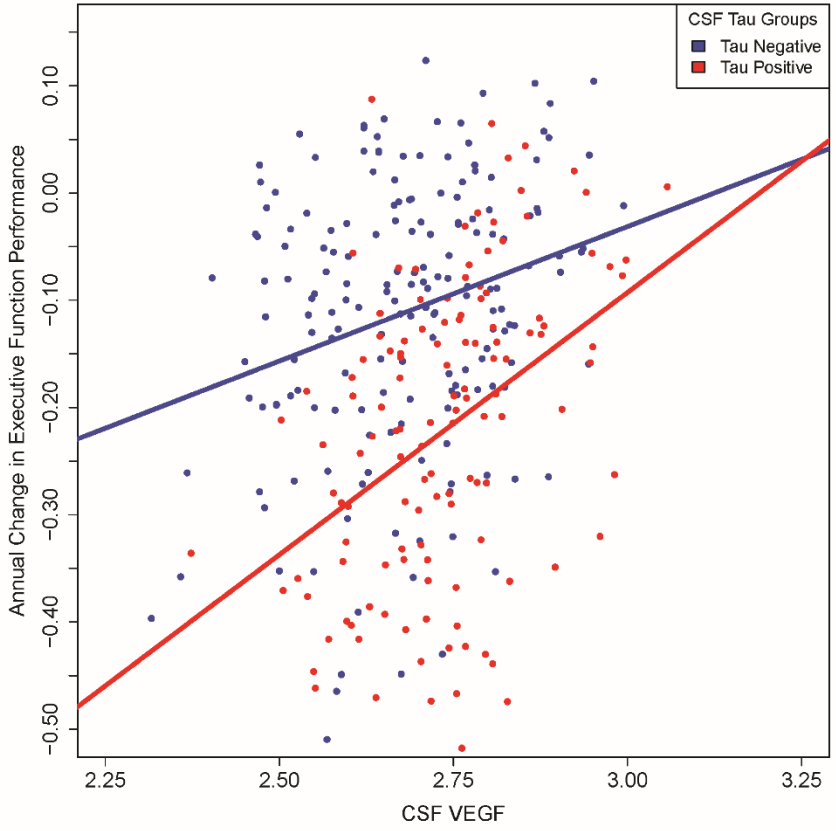
(Hohman et al., Frontiers in Aging Neuroscience, 2015)

SNP x Continuous Biomarker Interactions



(Hohman et al., Alzheimer's & Dementia, 2014)

VEGF x Biomarker Interactions



(Hohman et al., JAMA Neurology, 2015)

Identifying Markers of Resilience in ADNI

- Prokineticin 1 in the Coronary Artery and the Aorta

Neuropharmacology 116 (2017) 82–97

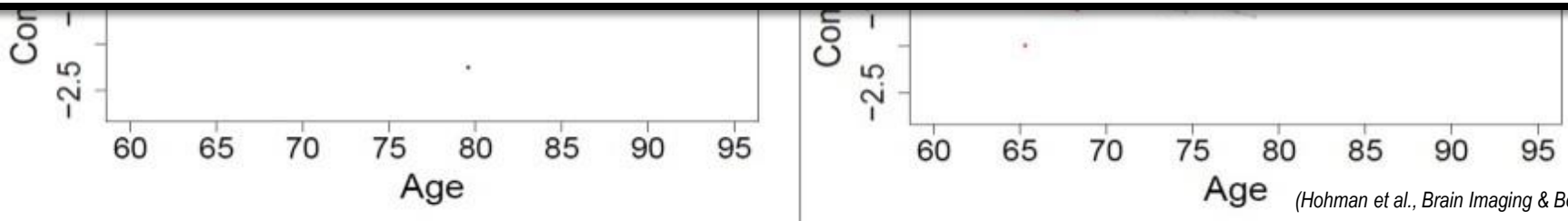
Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

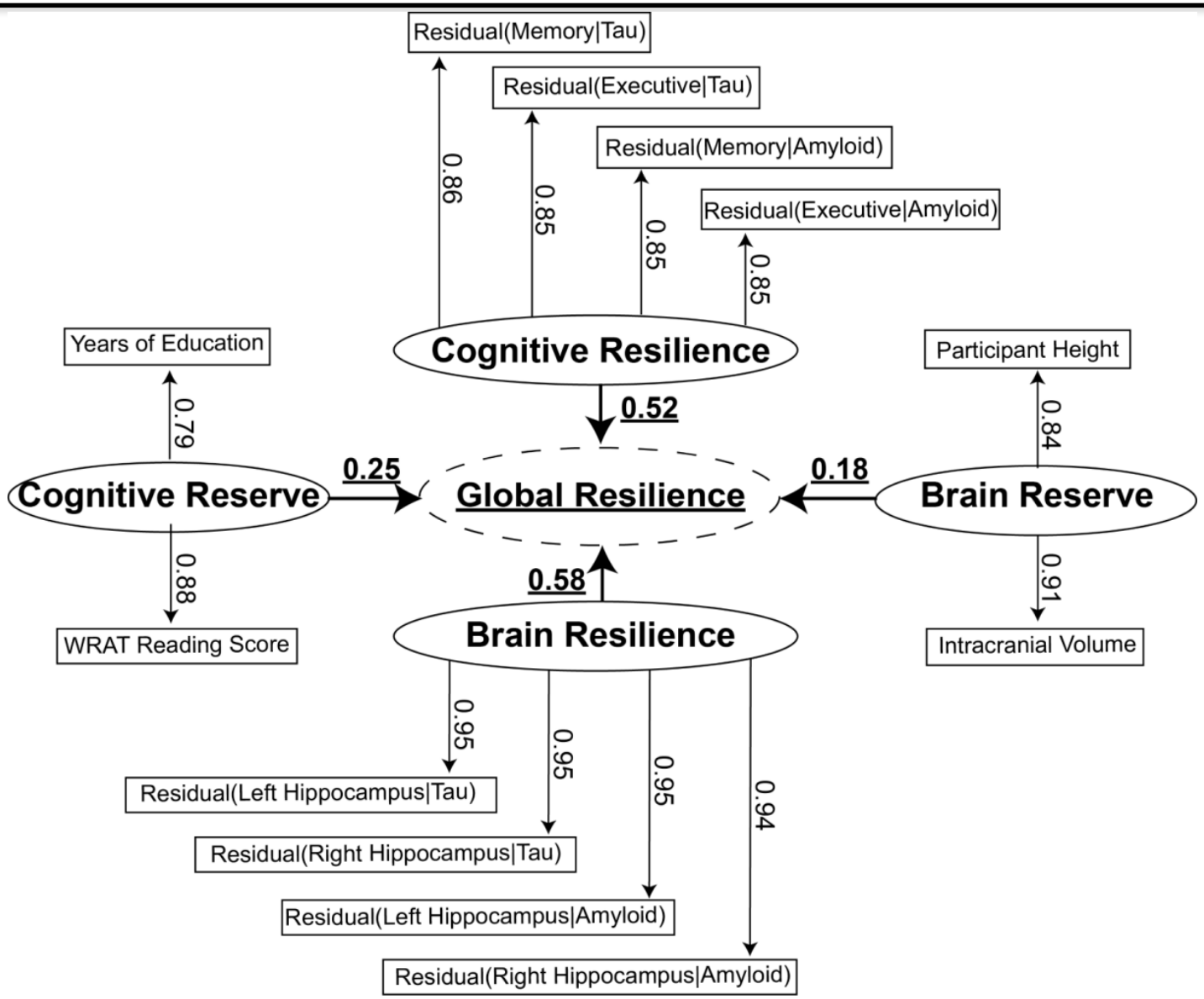
Prokineticin system modulation as a new target to counteract the amyloid beta toxicity induced by glutamatergic alterations in an *in vitro* model of Alzheimer's disease

Silvia Caioli [a], Cinzia Severini [b], Teresa Ciotti [c], Fulvio Florenzano [c], Domenico Pimpinella [a], Pamela Petrocchi Passeri [b], Gianfranco Balboni [d], Patrizio Polisca [e], Roberta Lattanzi [f], Robert Nisticò [c, g], Lucia Negri [f], Cristina Zona [a, h, *]



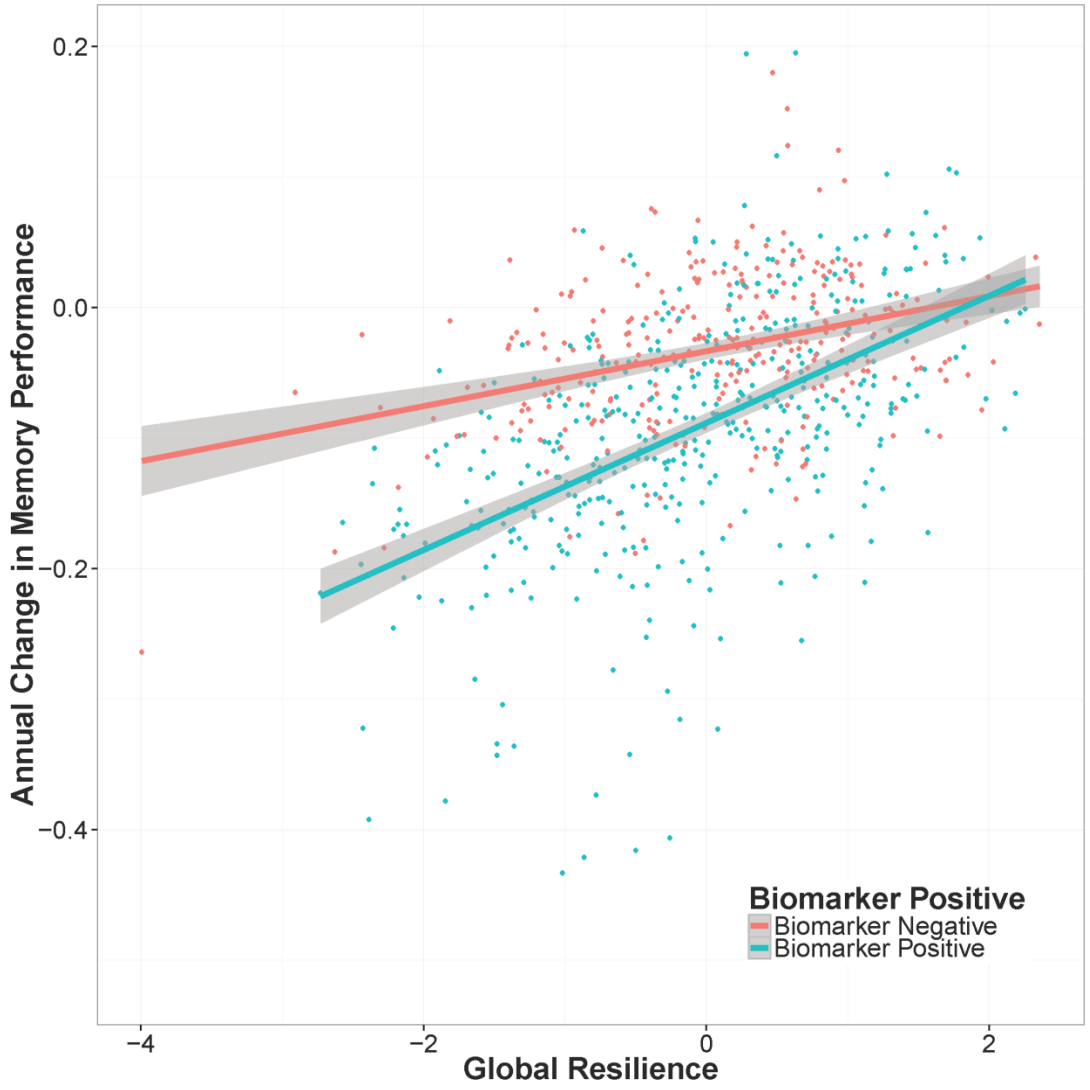
(Hohman et al., Brain Imaging & Behavior, 2016)

Resilience in ADNI (Built from Baseline Data)



(Hohman et al., Neurology, 2016)

Resilience in ADNI



(Hohman et al., Neurology, 2016)

Resilience from Alzheimer's Disease (RAD)

VANDERBILT UNIVERSITY MEDICAL CENTER

Drs. Hohman (PI), Cox, Ruderfer, Jefferson, & Gifford
- Project Coordination
- Phenotype Development
- Compiling of Data Sources
- Data Management
- Genetic Analyses

CASE WESTERN RESERVE UNIVERSITY EST. 1826

Dr. William Bush
- Variant Annotation
- PrediXcan Reference Panels

RUSH UNIVERSITY MEDICAL CENTER

Drs. Bennett & Schneider
- ROS/MAP
- Data Sharing

KAISER PERMANENTE®

Dr. Eric Larson
- ACT Dataset
- Data Sharing

UNIVERSITY of WASHINGTON

Dr. Paul Crane
- ACT Dataset
- Data Harmonization

JOHNS HOPKINS SCHOOL of MEDICINE

Dr. Marilyn Albert
- BIOCARD Dataset

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON

Dr. Sterling Johnson
- WRAP Dataset

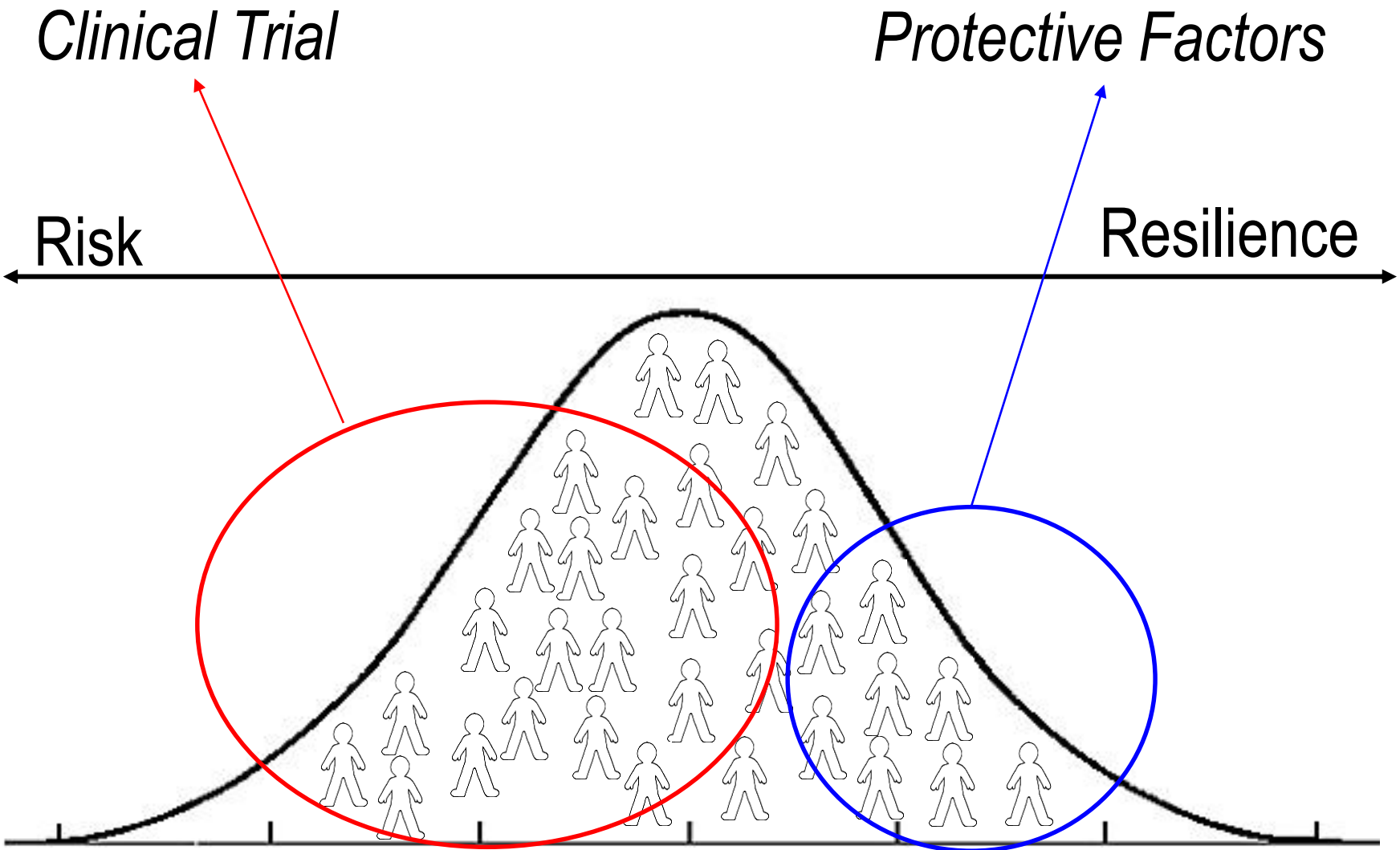
NIH National Institute on Aging

Dr. Susan Resnick
- BLSA Dataset

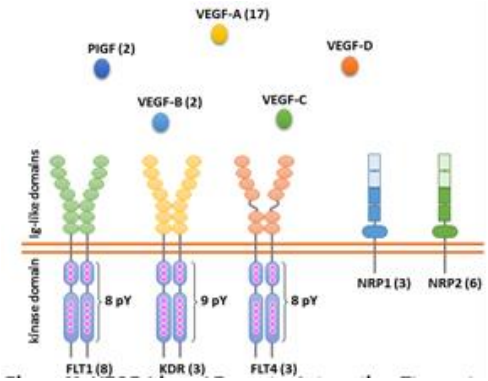
NACC National Alzheimer's Coordinating Center

Dr. Walter Kukull
- NACC Dataset

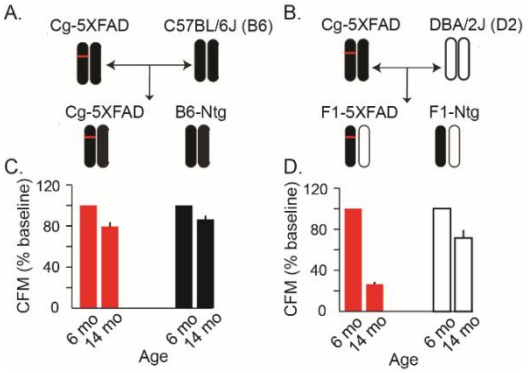
Future Goals



Future Goals of Resilience Initiative

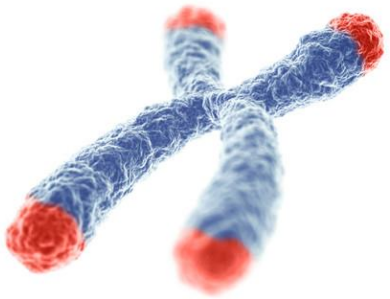


Isoform-Specific Effects of VEGF

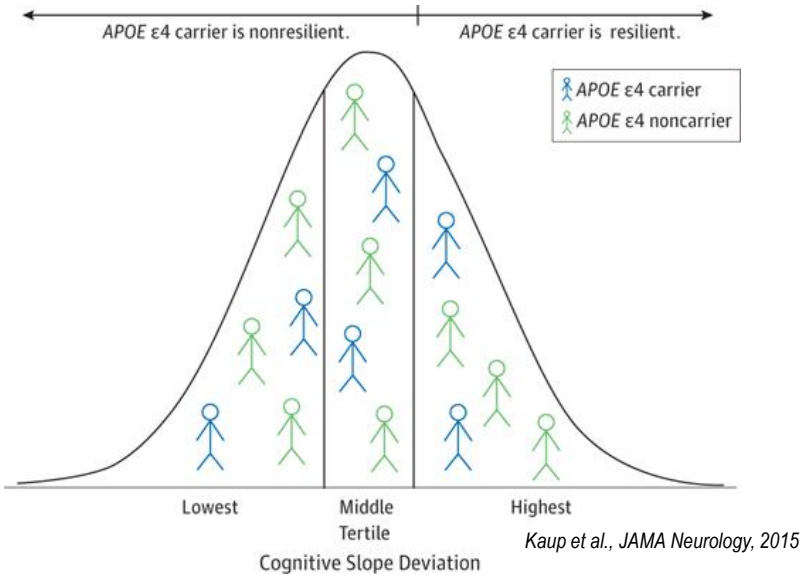


Translational Resilience Models

Model System ↔ Human



Telomere Length and Resilience



Kaup et al., JAMA Neurology, 2015

Resilience Among *APOE* ε4 Carriers

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alzheimer's association
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The National Cell Repository for Alzheimer's Disease
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SOUTHWESTERN MEDICAL CENTER
MASSACHUSETTS alzheimer's disease research center
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