Reducing Your Risk of Alzheimer's Disease: Building a Better Brain as We Age

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ADC Administrators Meeting
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Rush Memory & Aging Project
Religious Orders Study

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K23AG23675

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Illinois Department Public Health
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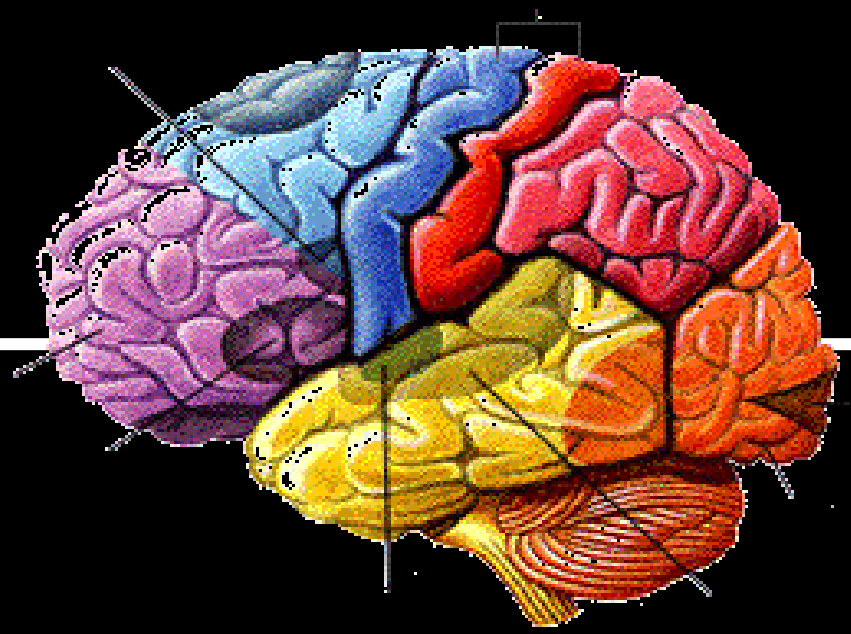
Robert C. Borwell Endowment Fund

How do we Prevent AD?

Risk Factors
Genetic
Lifestyle



Alzheimer's Disease

- Identify risk factors for AD
- Determine biologic pathways linking risk factors to disease
- Develop strategies to prevent AD

Need Studies that Include:

- Large numbers of people without dementia
- Agree to:
  - Donation of blood for genetic testing
  - Detailed assessment of potential risk factors for AD
  - Annual testing to
    - Identify the occurrence of AD
    - Document diagnoses and cognition proximate to death
- How do we get measures of changes in the brain?
  - Brain imaging
  - Brain autopsy

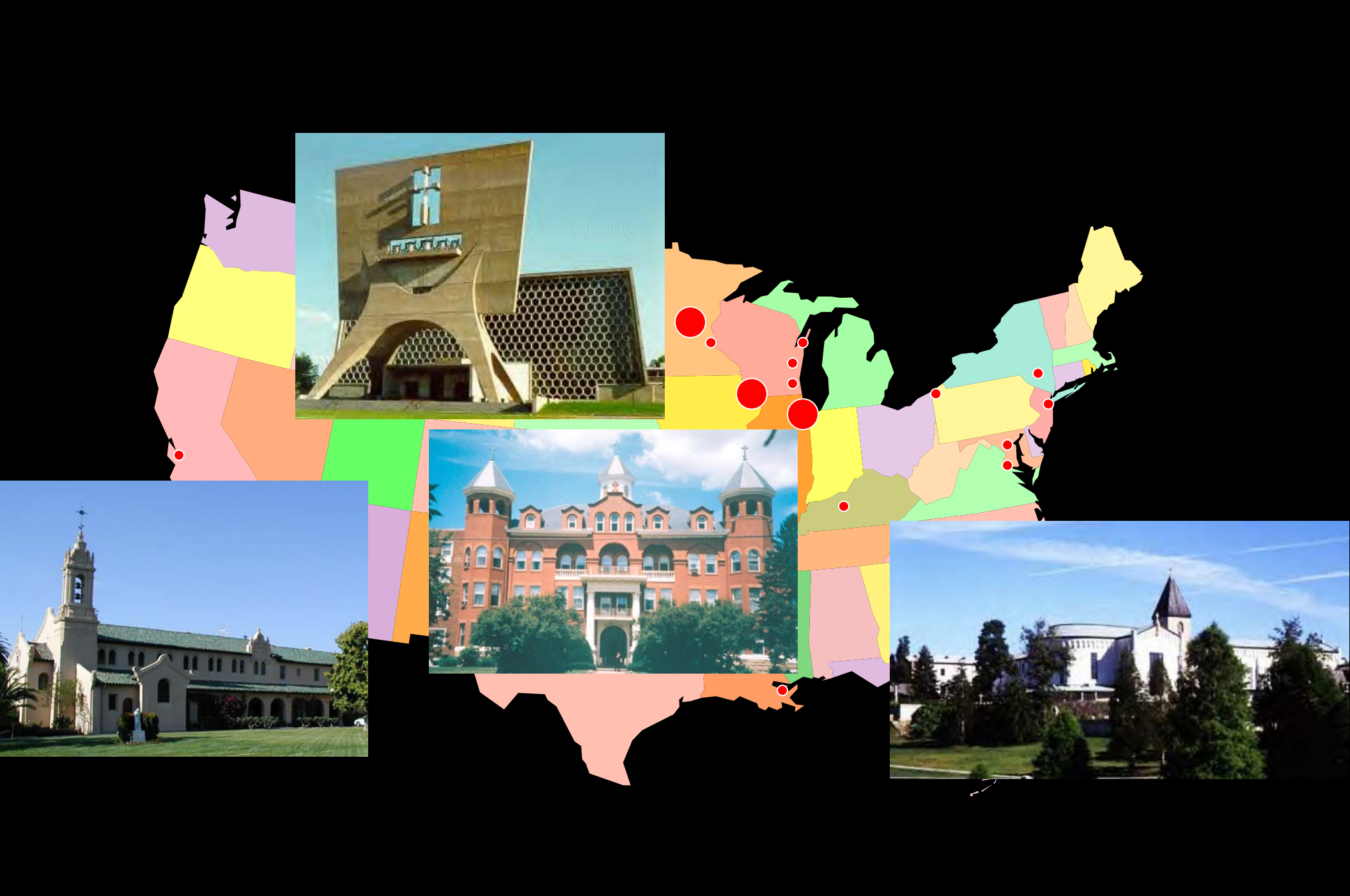
Objectives

- Two clinical-pathologic studies of aging and AD
  - Religious Orders Study
  - Rush Memory and Aging Project
- Common age-related brain pathology
- Implications of mixed pathologies for AD prevention
- Concept of neural reserve
- How to build a better brain as we age

The Religious Orders Study

- Began in 1993
- > 1,135 older nuns, priests, and brothers without known dementia from across the U.S.
- All agreed to annual cognitive and motor testing
- All agreed to brain donation at the time of death
- > 260 have developed AD
- > 360 have developed MCI
- > 485 brain autopsies

Religious Orders Study: Participating Sites



The Rush Memory and Aging Project

… because memories should last a lifetime

- Began in 1997
- > 1,335 residents from about 40 retirement communities and senior housing from across the Chicago area
- All agreed to annual cognitive and motor testing, and blood draw.
- All agreed to donate brain, spinal cord, muscle, and nerve at the time of death
- > 200 have developed AD
- > 300 have developed MCI
- > 345 autopsies


MapPoint .net
Antioch
Lindenhurst
Zion
Beach Park
Waukegan
North Chicago
Gurnee
Round Lake Beach
Fox Lake Hills
Alden
Spring Grove
Chemung
McHenry
Gages Lake
Libertyville
Mundelein
Fremont Center
Woodstock
Belvidere
Marengo
Crystal Lake
Lake in the Hills
Algonquin
Fox River Grove
Lake Barrington
Lake Zurich
Highwood
Highland Park
Lake Michigan
Northbrook
Glencoe
Wheeling
Palatine
Hoffman Estates
Arlington Heights
Wilmette
Evanston
Niles
Lincolnwood
Park Ridge
Melrose Park
Chicago
Oak Park
Cicero
Berwyn
Oak Brook
Maywood
Villa Park
Lombard
Schaumburg
Elgin
Bartlett
Roselle
Carpentersville
West Dundee
Genoa
Sycamore
De Kalb
Cortland
Carol Stream
Wheaton
St. Charles
Batavia
Downers Grove
Warrenville
Aurora
Westmont
Naperville
Darien
Willowbrook
Burbank
Oak Lawn
Calumet
East Chicago
Hammond
Gary
Highland
Munster
Dolton
Harvey
Robbins
Worth
Lemont
Bolingbrook
Romeoville
Orland Park
Tinley Park
Lockport
Joliet
Chicago Heights
Crest Hill
Plainfield
Yorkville
Oswego
Sandwich
Plano
Bristol
Little Rock
Shabbona
Hinckley
Sugar Grove
Leland
Somonauk
Sheridan
Shorewood
BOONE
MCHENRY
LAKE
DEKALB
KANE
DUPAGE
WILL
LASALLE
KENDALL
COOK
ILLINOIS
INDIANA
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12565
Grand Victorian

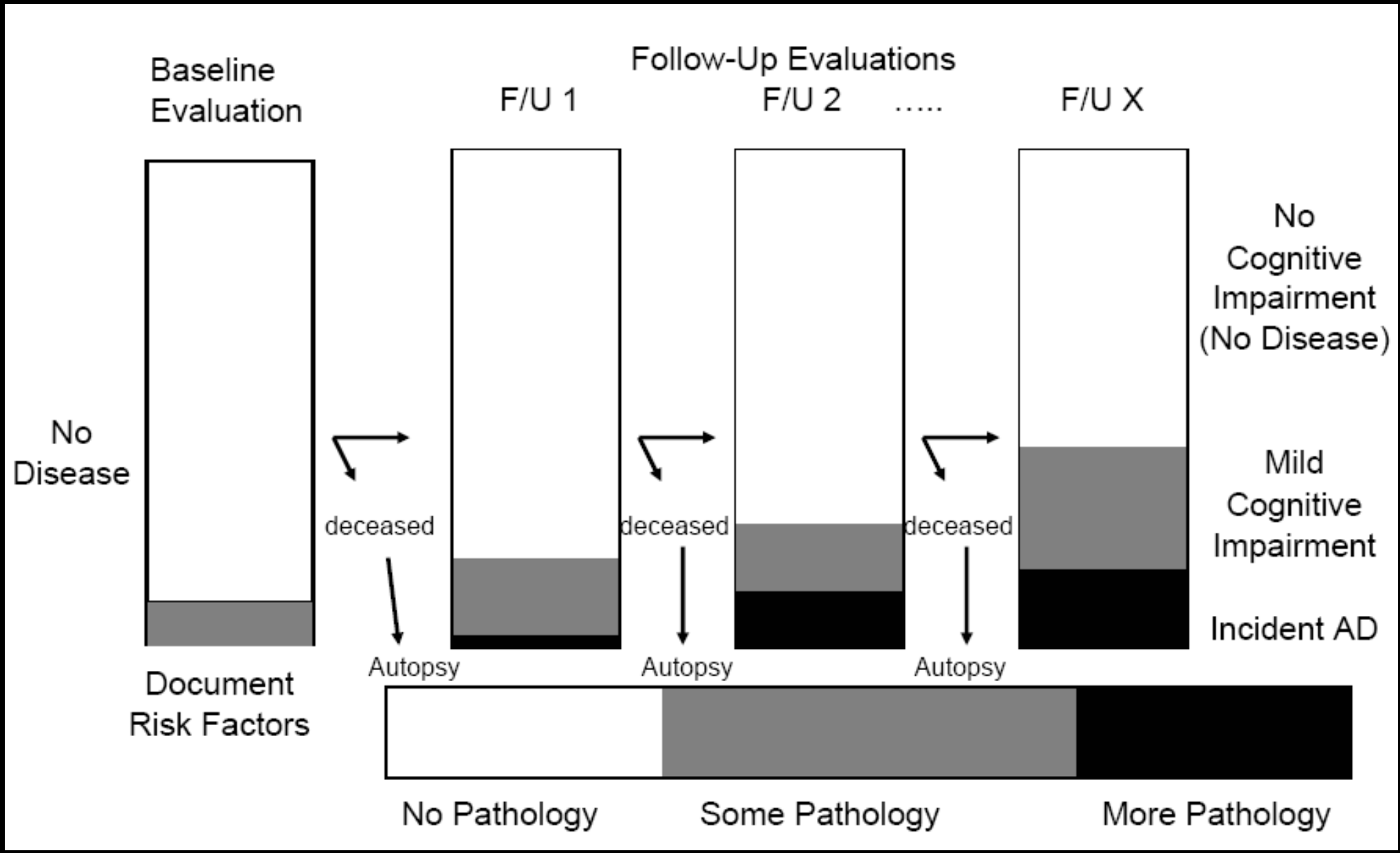

EXIT
02/22/2009 23:20


Can Do


VINEYARD

Two Studies Include:

- Nearly 2600 people without dementia who agreed to:
  - Donation of blood for genetic testing
  - Detailed assessment of potential risk factors for AD
  - Annual testing to
    - Identify the occurrence of AD
    - Document diagnoses and cognition proximate to death
  - Brain donation
    - More than 830 autopsies to date

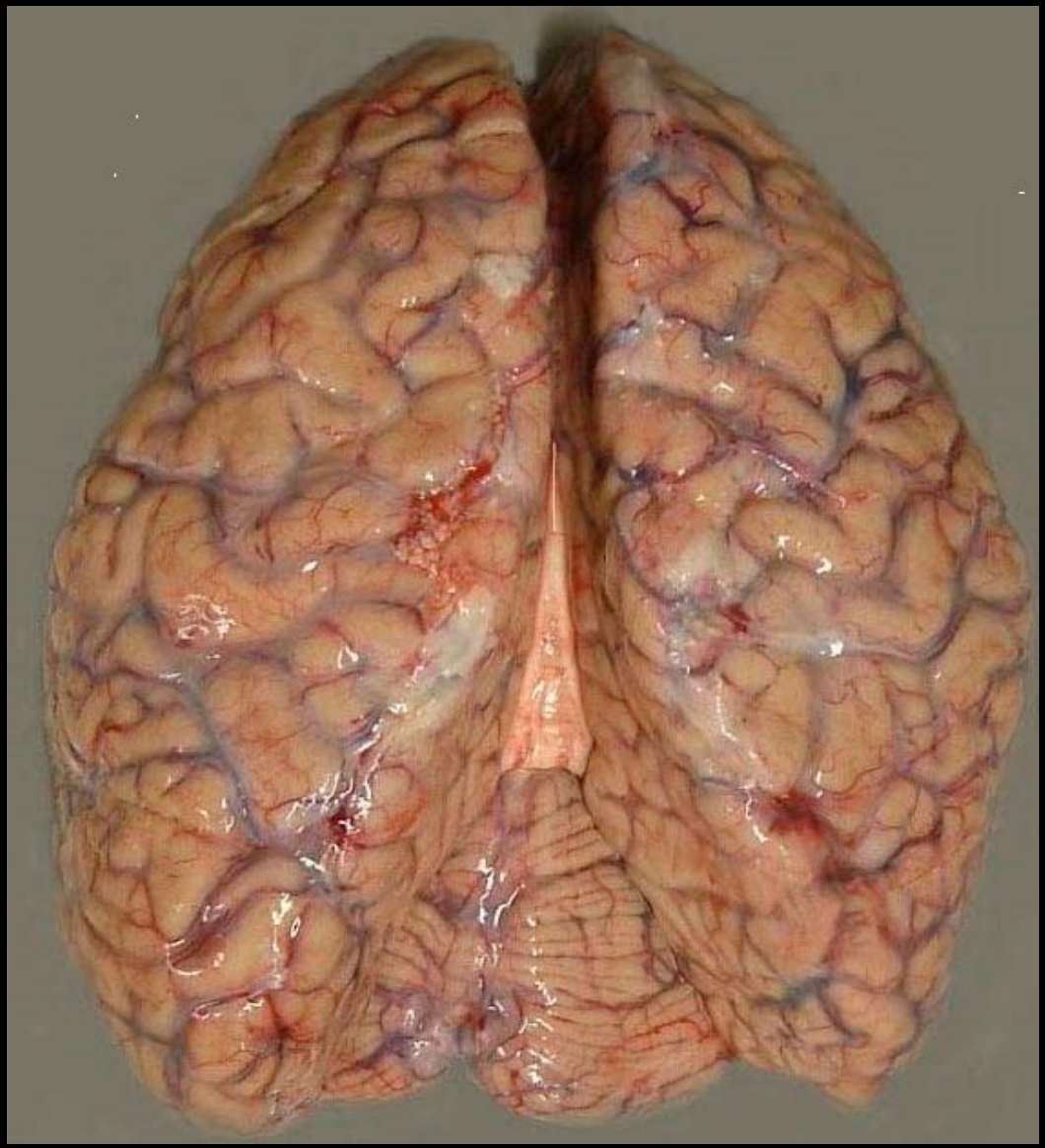


Bennett DA, et al. *Neuroepidemiology.* 2005;25:163–175.

Objectives

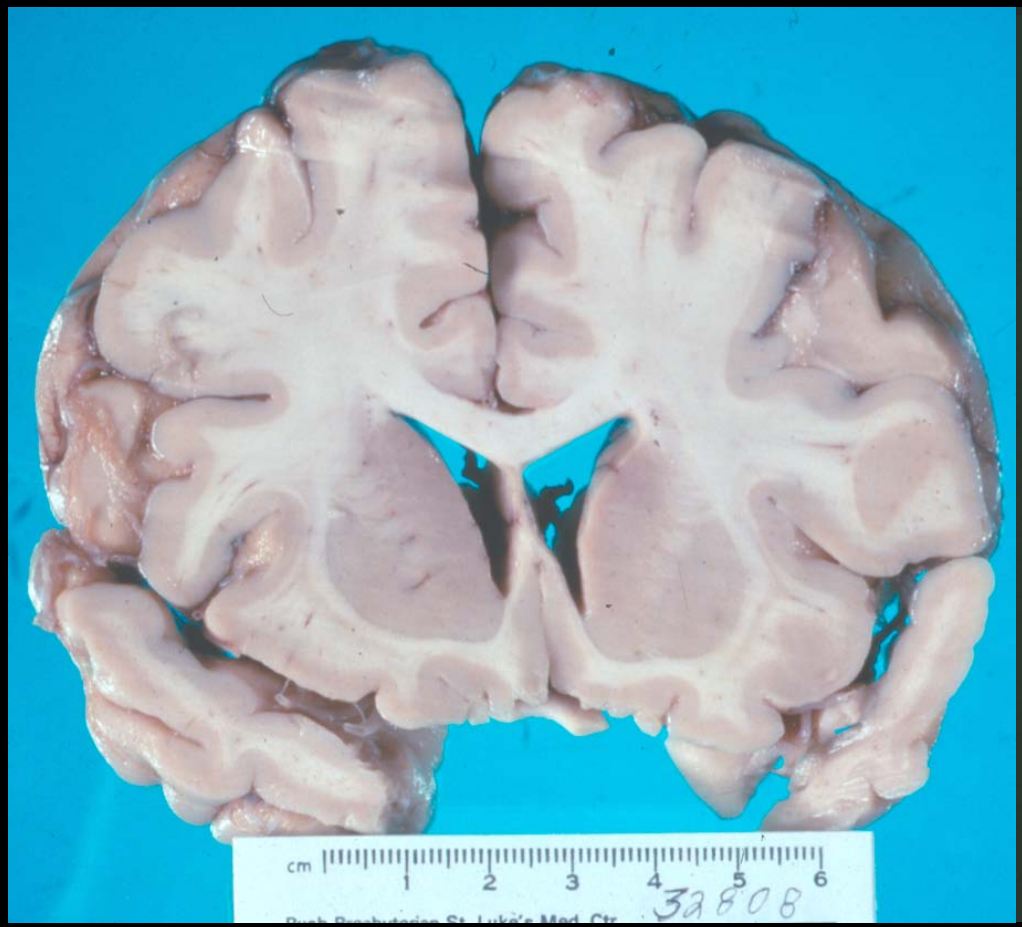
- Two clinical-pathologic studies of aging and AD
- Common age-related brain pathology
  - AD
  - Cerebral Infarctions
  - Lewy bodies
- Implications of mixed pathologies for AD prevention
- Concept of neural reserve
- How to build a better brain as we age

Normal Brain

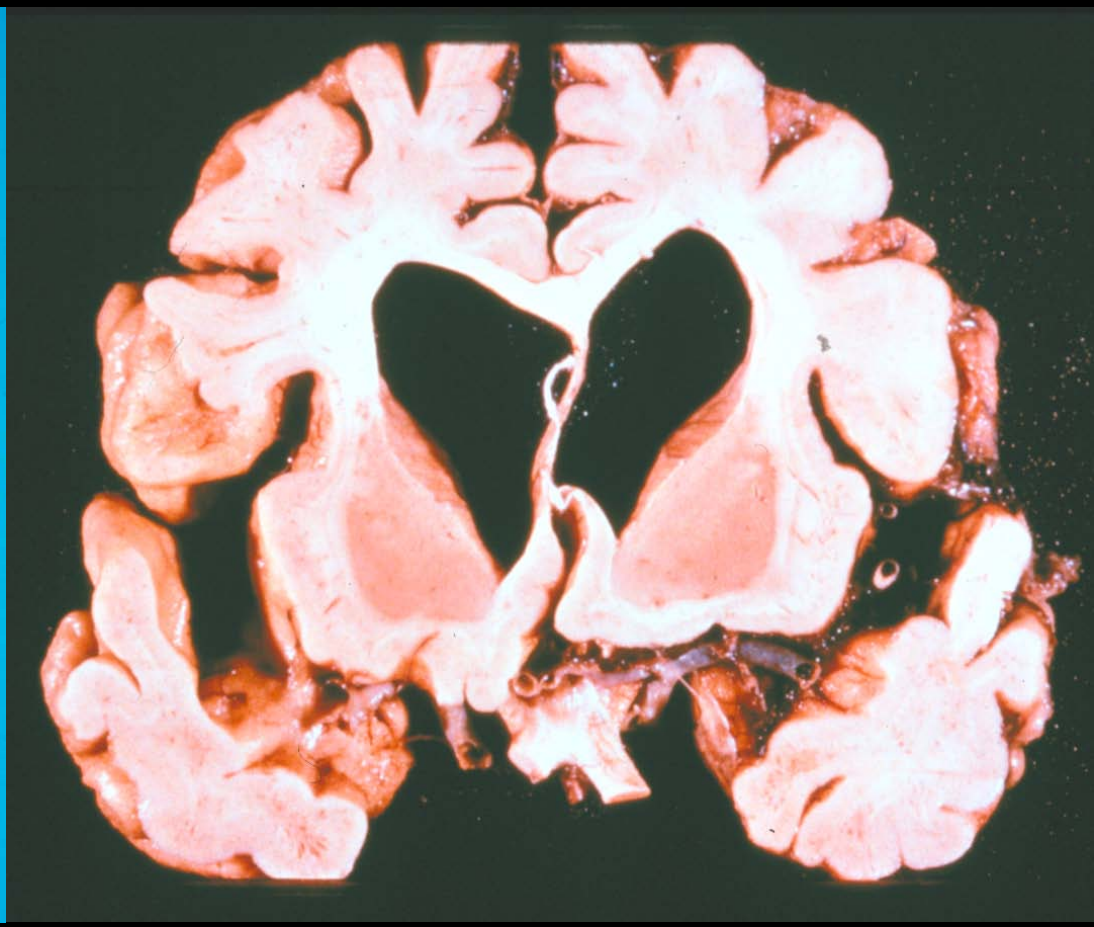


Alzheimer’s Disease

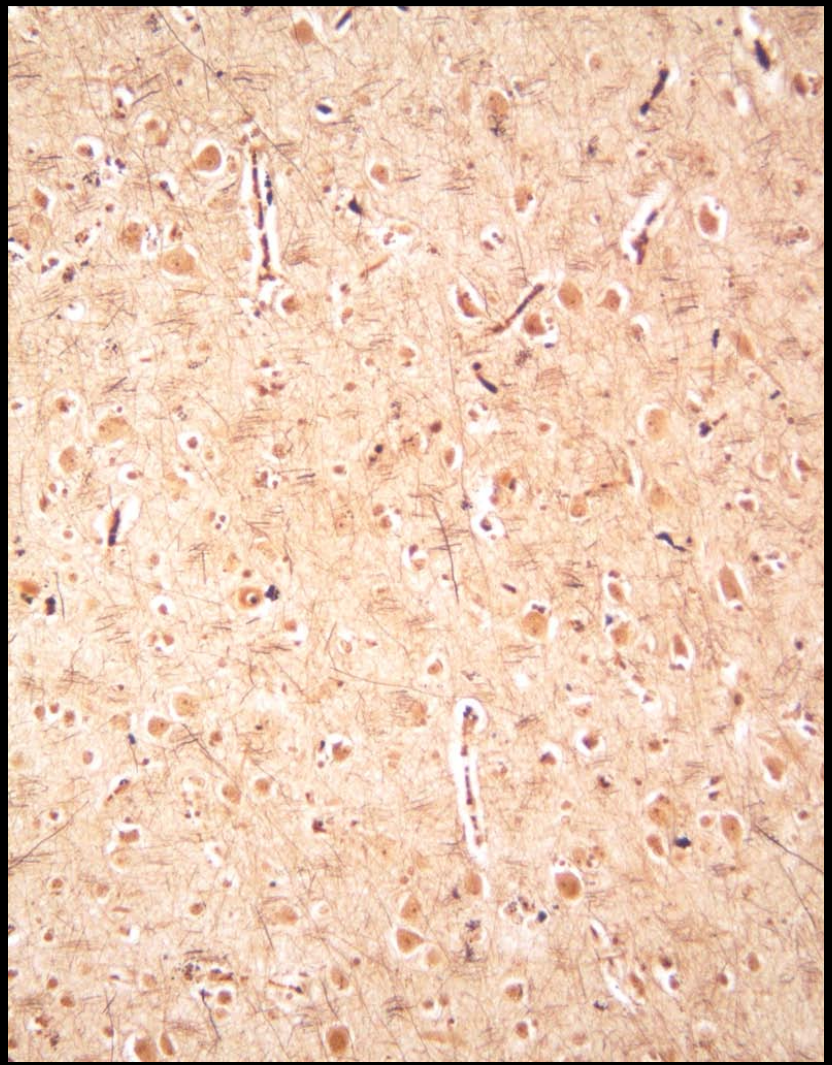
Normal Brain



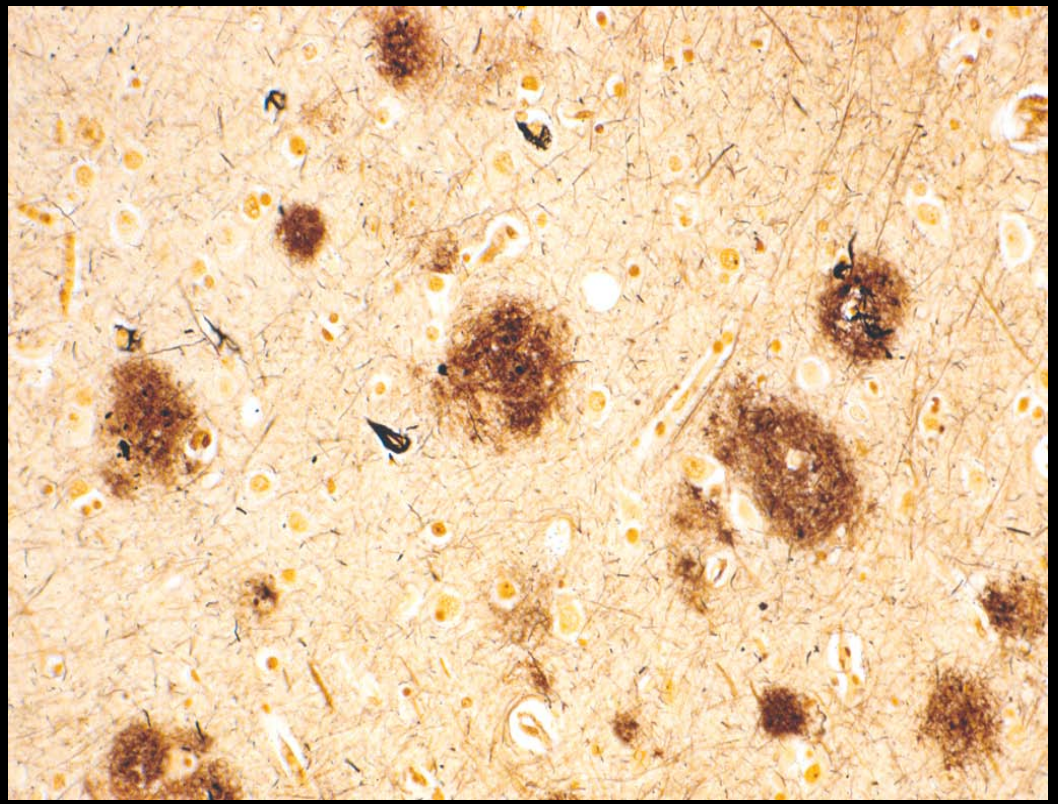
Alzheimer's Disease

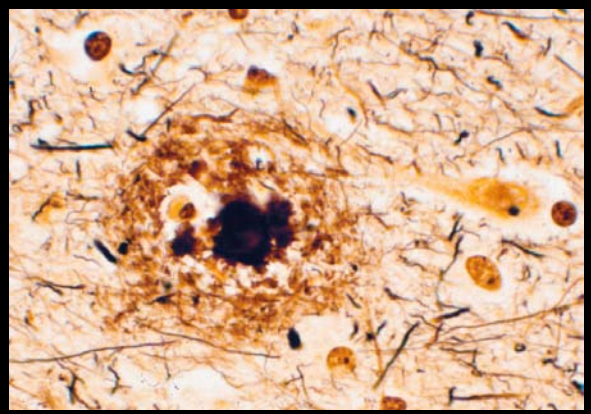


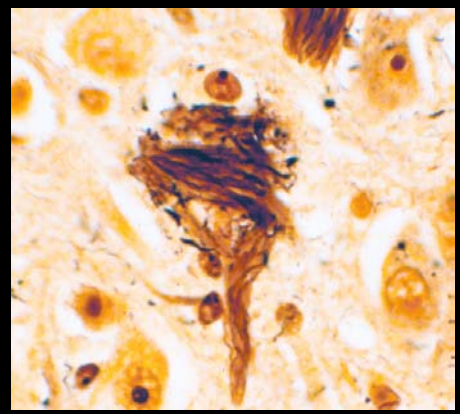
Modified Bielschowsky silver stain



Normal Brain



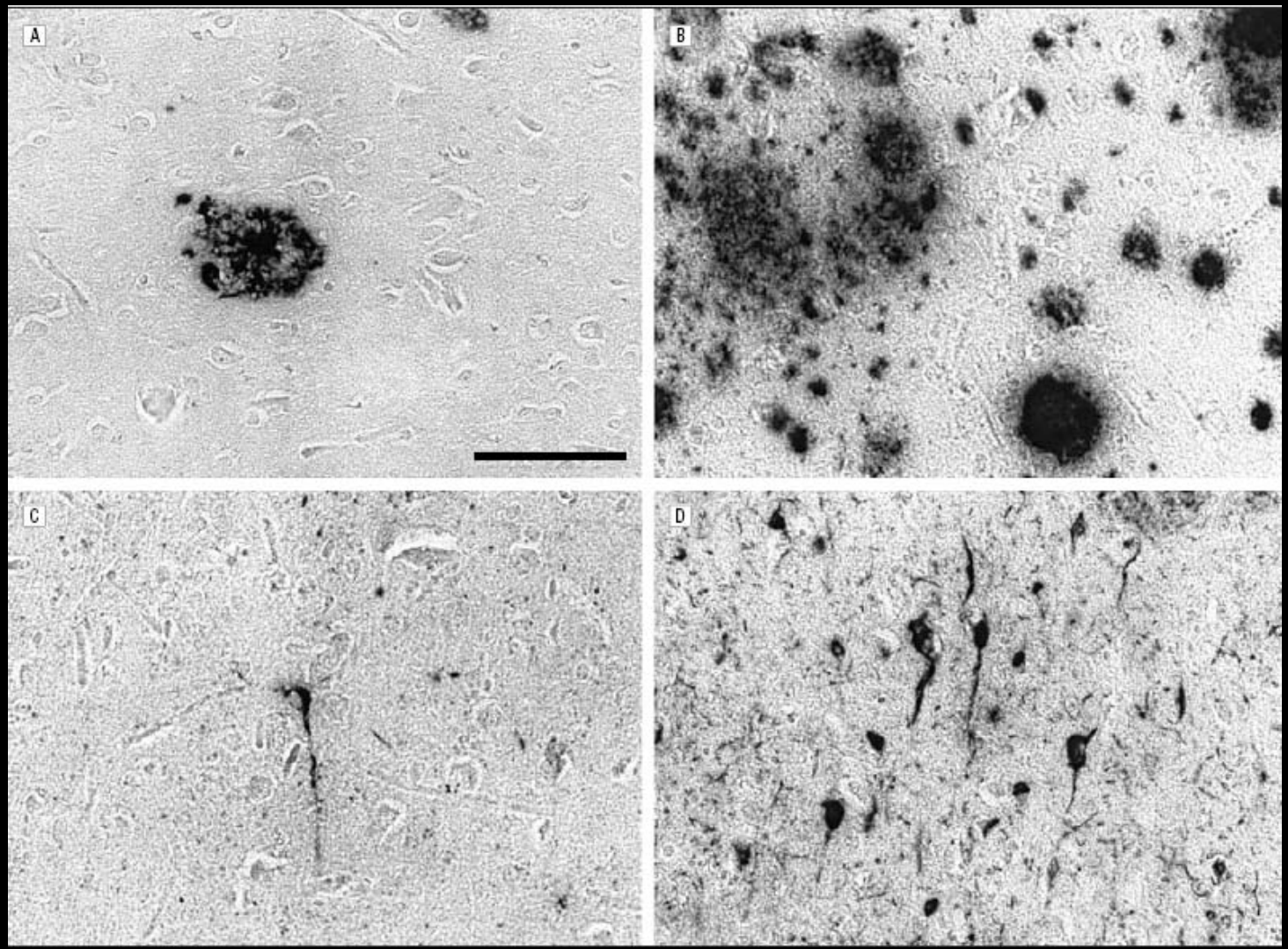




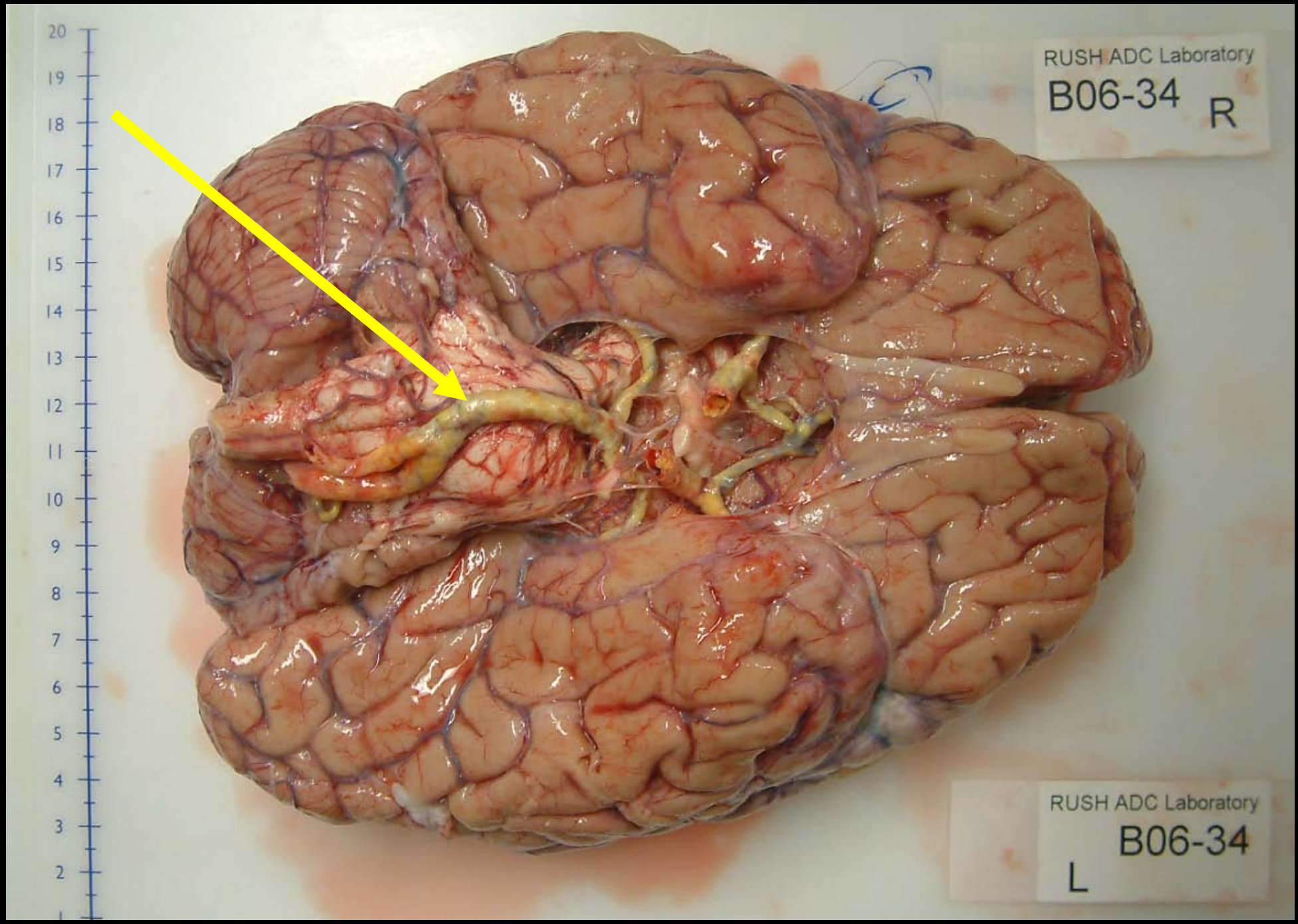
Neurofibrillary Tangles Mediate the Association of Amyloid Load With Clinical Alzheimer Disease and Level of Cognitive Function

Low and high amyloid

One and many tangles



Bennett DA, et al. *Arch Neurol.* 61:378-384


RUSH ADC Laboratory
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R
RUSH ADC Laboratory
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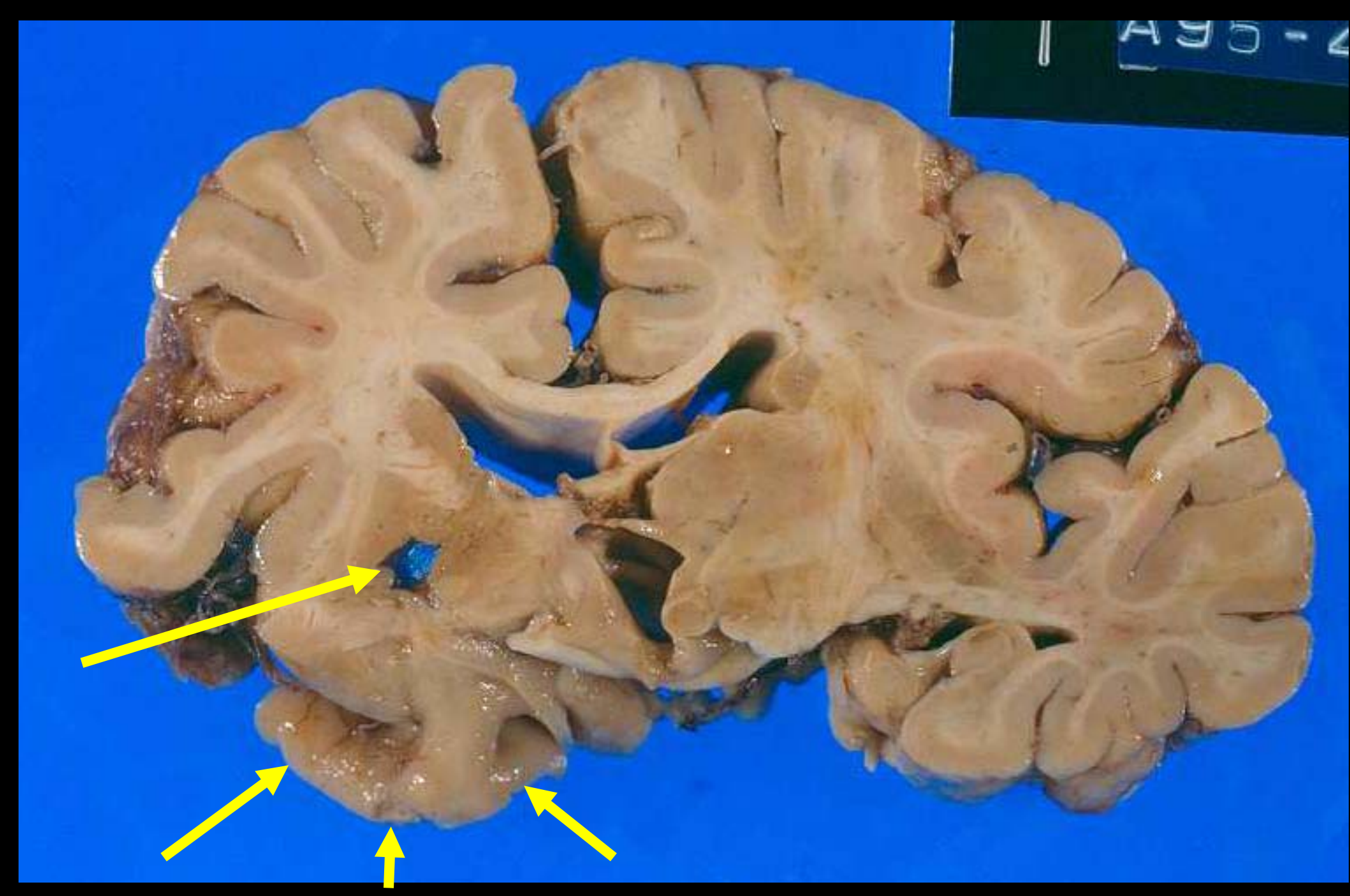
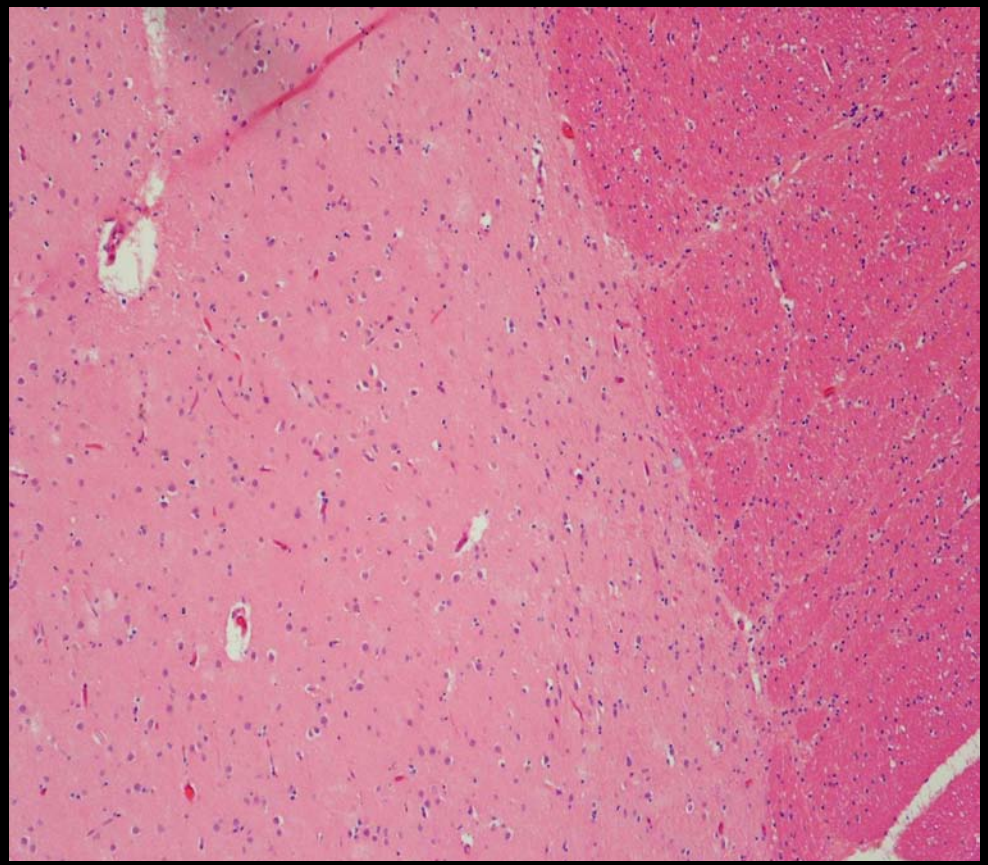
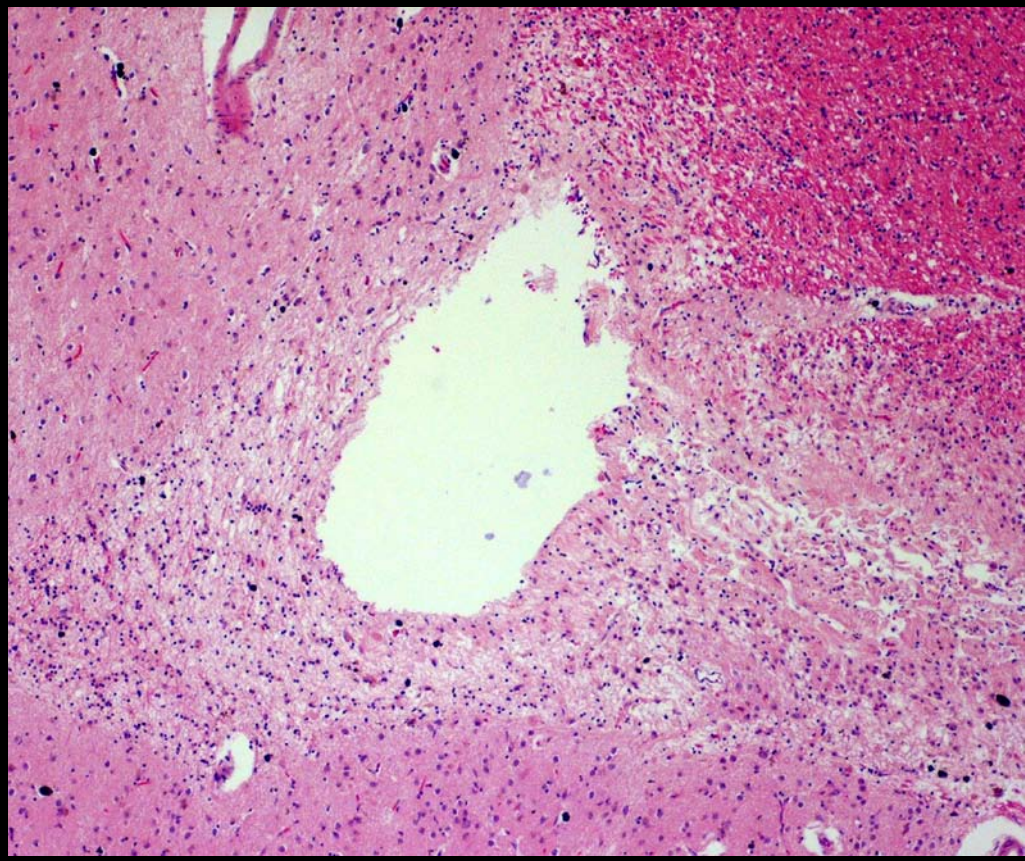
L



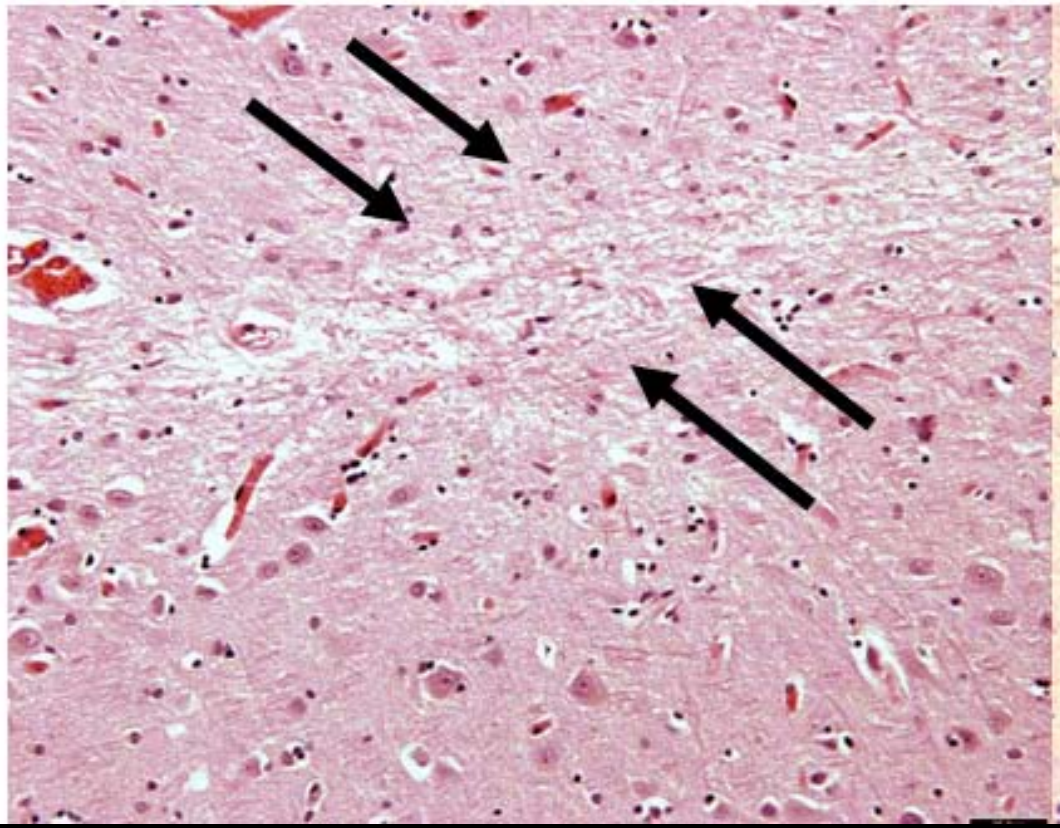
Normal brain

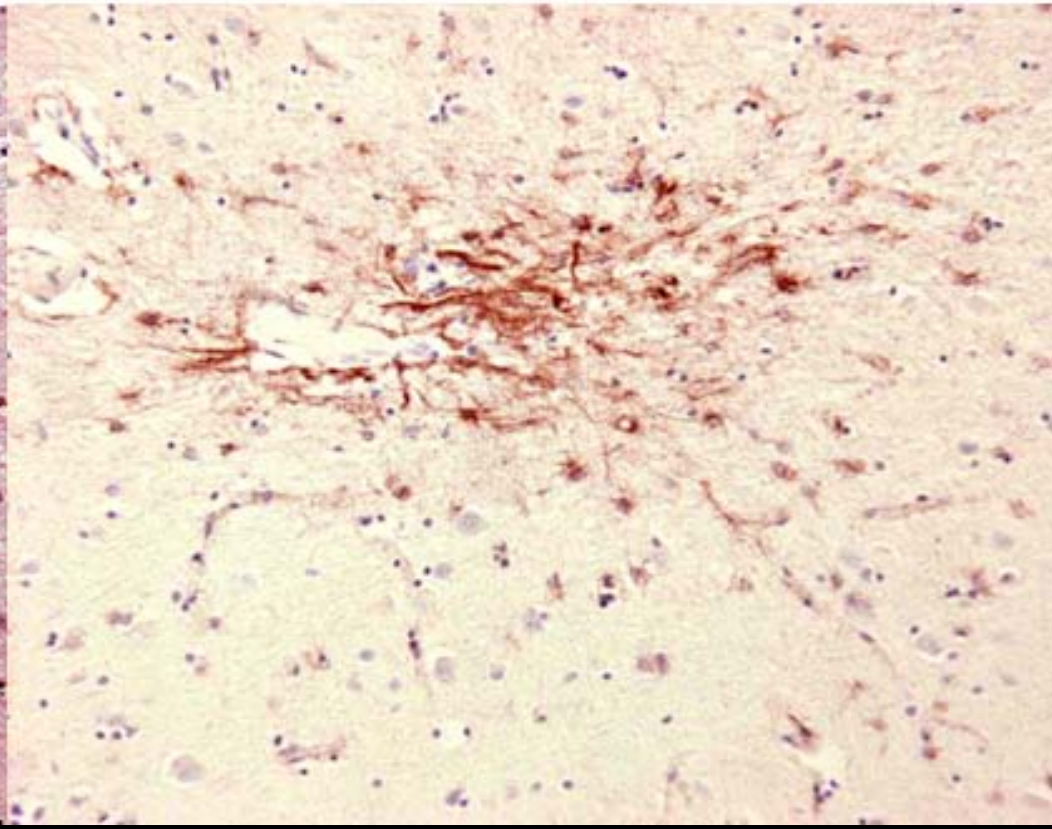


Cerebral infarction (stroke)

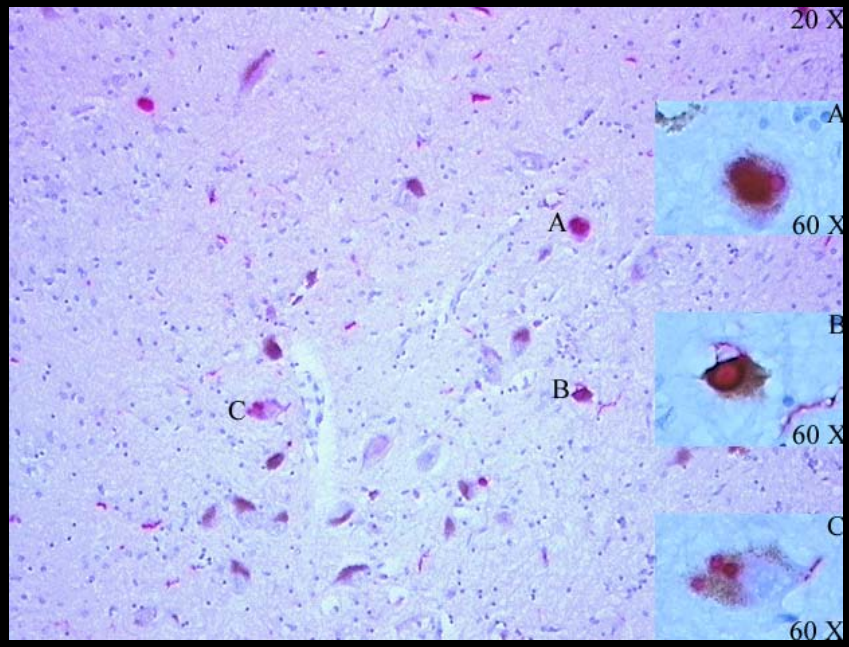


Cortical microinfarct

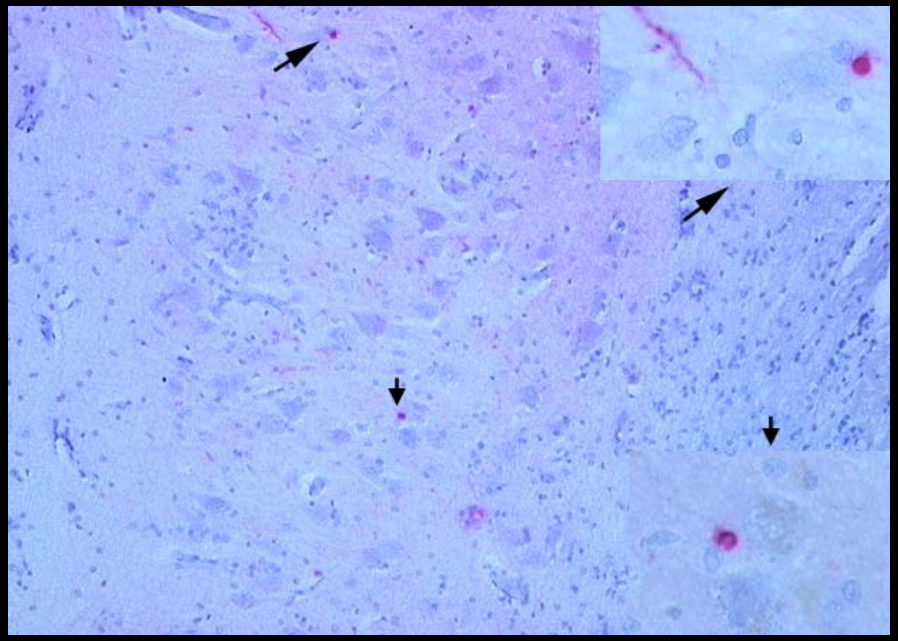


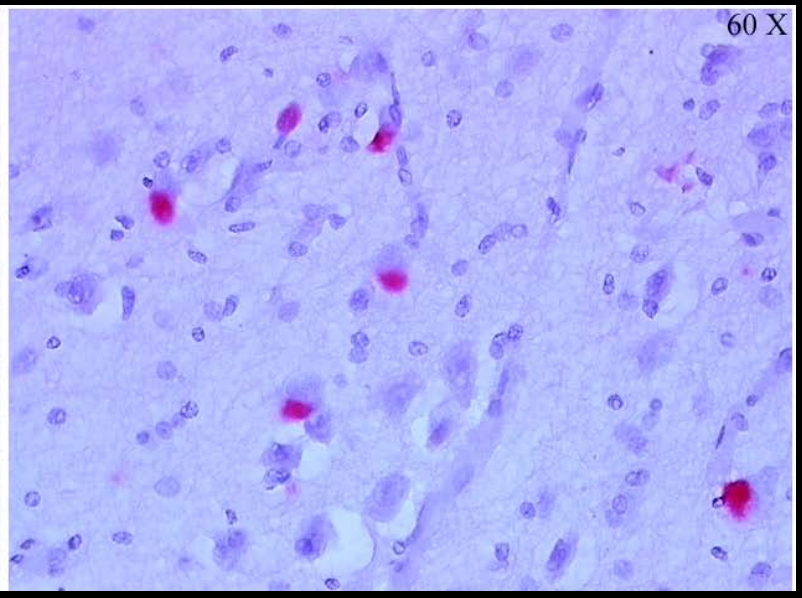


Lewy bodies in substantia nigra



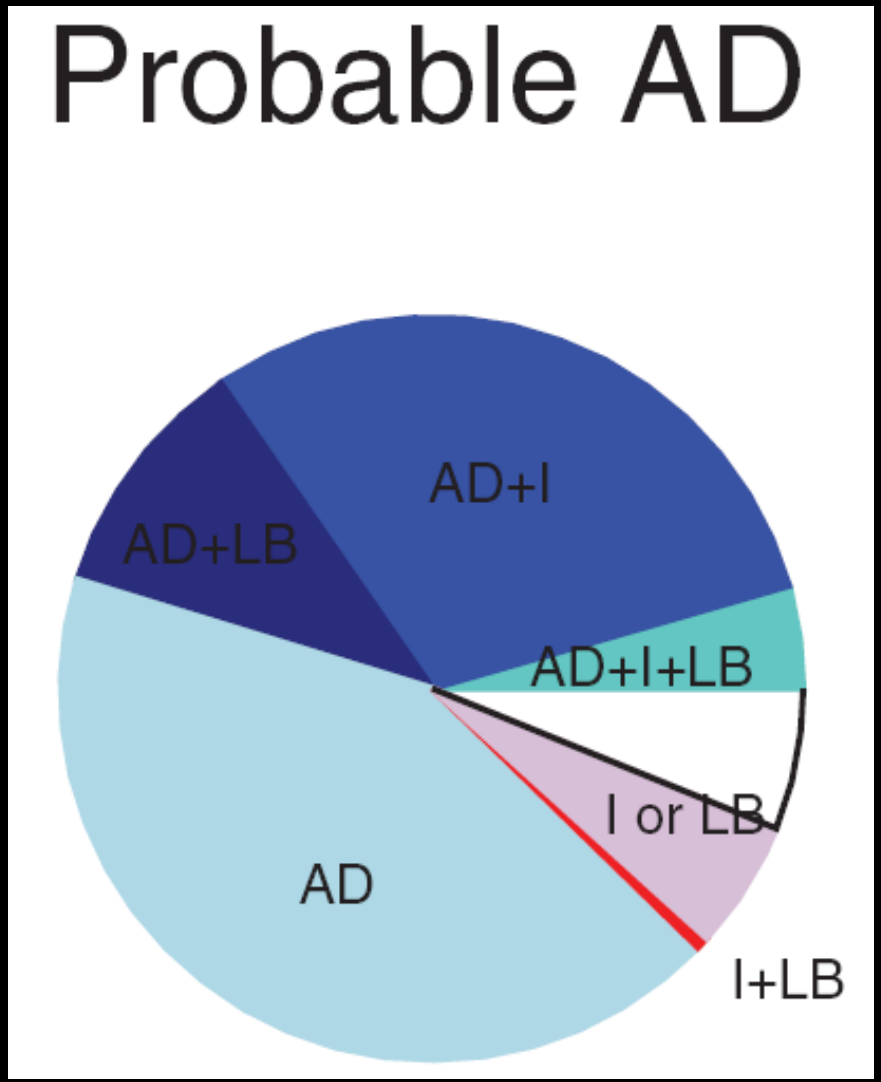
Lewy bodies in hippocampus





Lewy bodies in neocortex

The Neuropathology of Probable Alzheimer Disease and Mild Cognitive Impairment

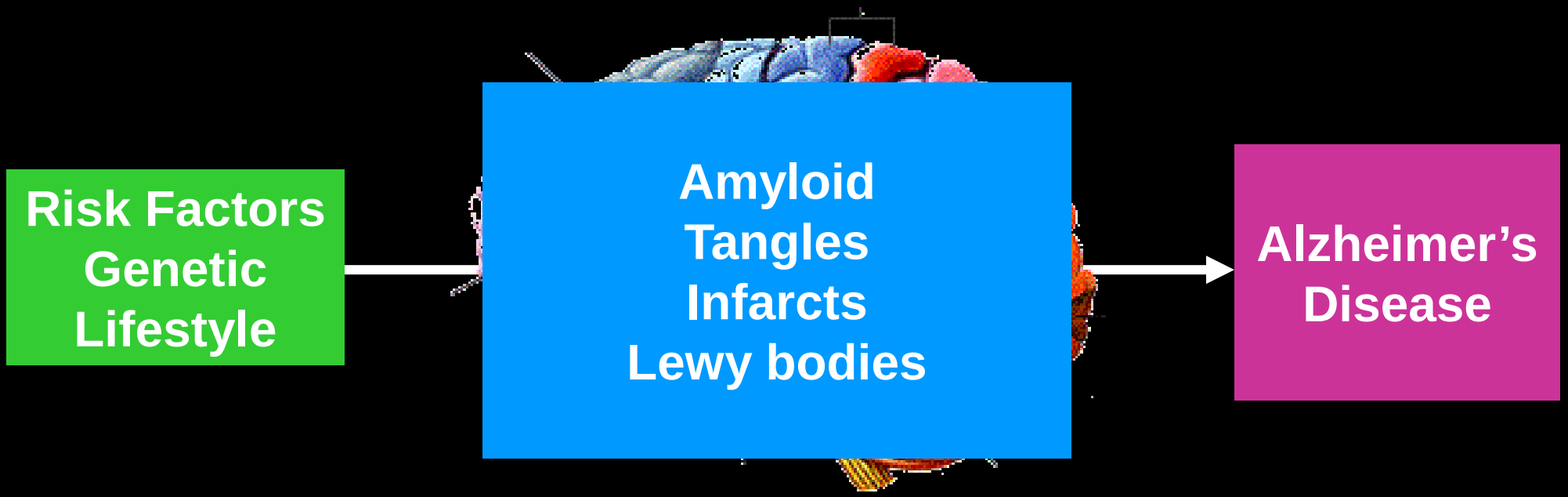


Mixed pathology is most common cause of AD.

Schneider JA, et al. *Annals Neurology.* 2009;66:200-208.

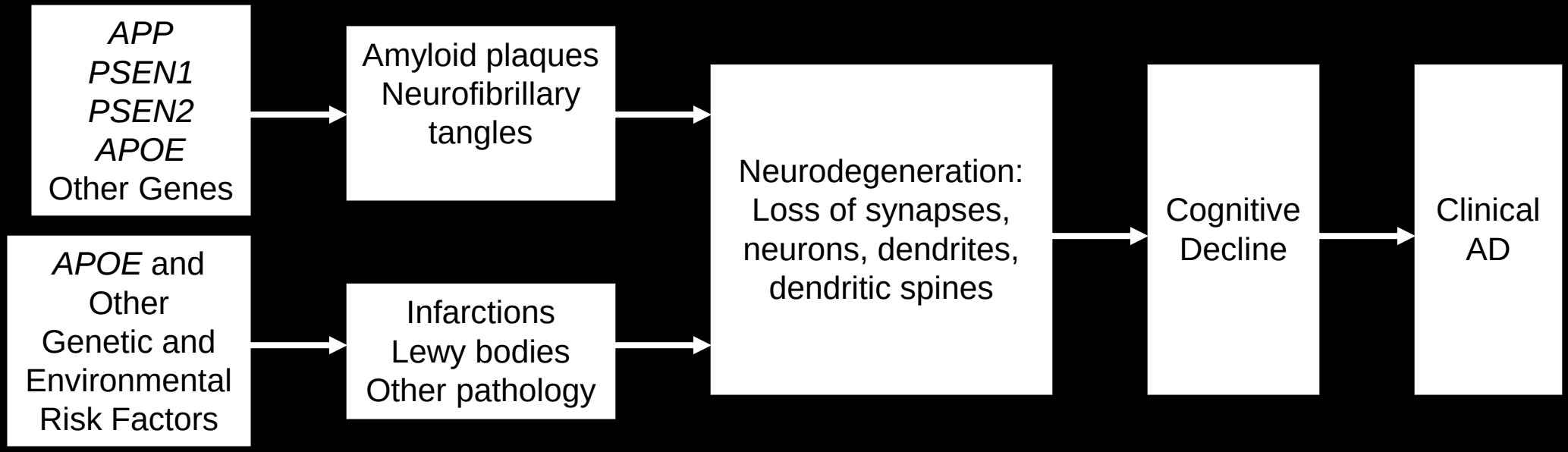
Objectives

- Two clinical-pathologic studies of aging and AD
- Common age-related brain pathology
- Implications of mixed pathologies for AD prevention
  - Not all risk factors for clinical AD are related to AD pathology
- Concept of neural reserve
- How to build a better brain as we age



•Implications for the prevention of AD

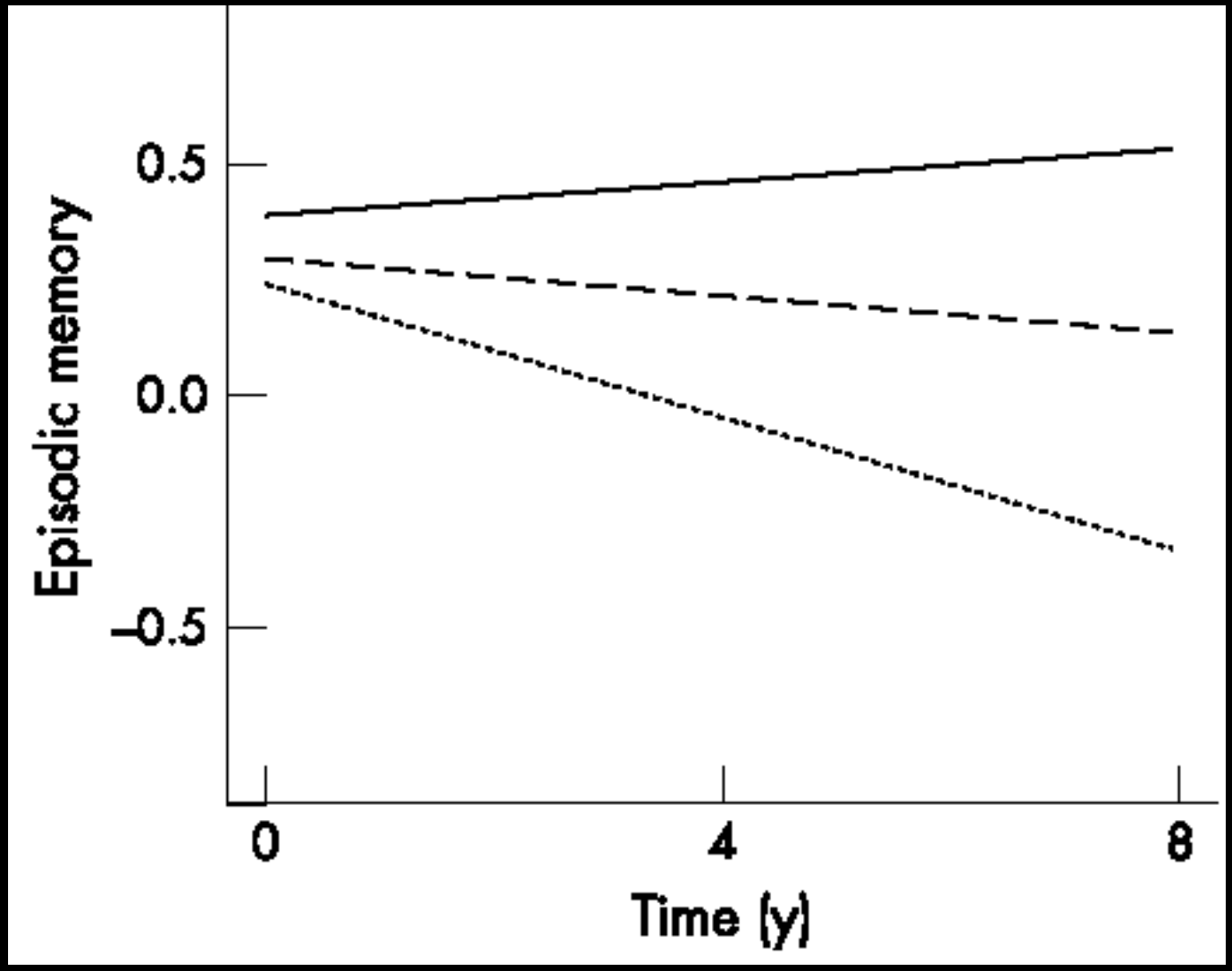
Neuropathologic intermediate phenotypes enhance association to Alzheimer susceptibility alleles



- Can prevent AD by preventing:
  - AD pathology
  - Infarcts or Lewy bodies

Bennett DA, et al. *Neurology*. 2009;72:1495-1503.

The apolipoprotein E ε2 allele and decline in episodic memory



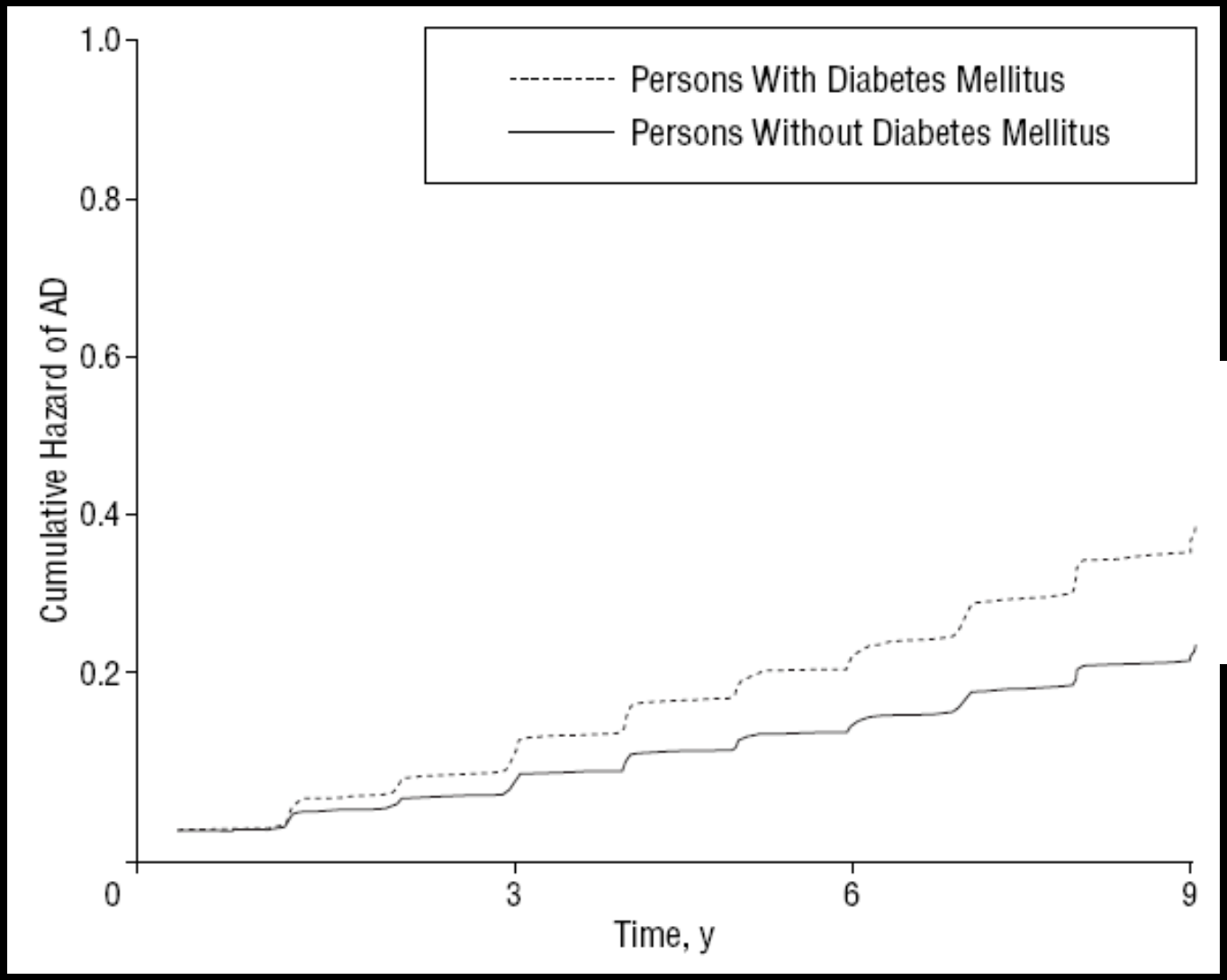
Wilson, et al. *JNNP.* 2002;73:672-677.

Neuropathologic intermediate phenotypes enhance association to Alzheimer susceptibility alleles

	AD PATHOLOGY
Any *APOE* ε4	0.365 (0.0363) 9×10^{-24}
Any *APOE* ε2	−0.200 (0.0461) 1×10^{-5}

Bennett DA, et al. *Neurology*. 2009;72:1495-1503.

Diabetes Mellitus and Risk of Alzheimer Disease and Decline in Cognitive Function



Diabetes

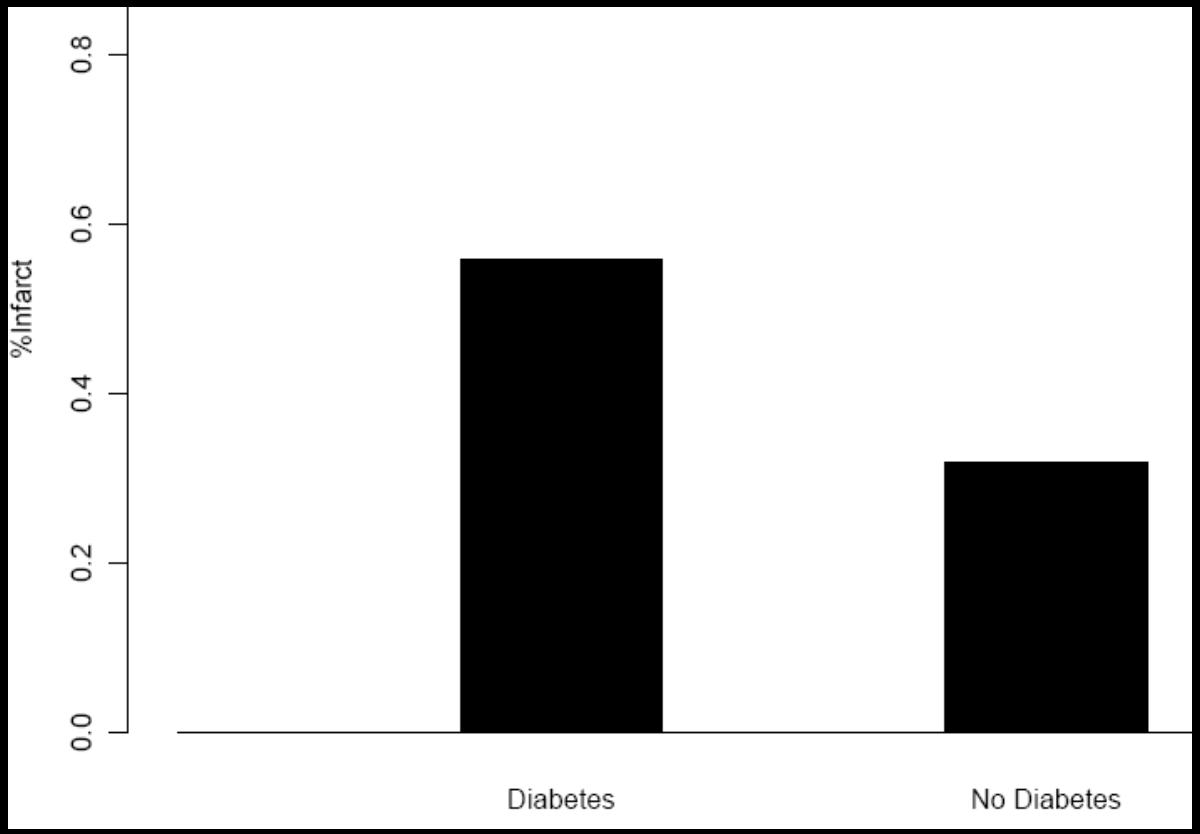
yes

no

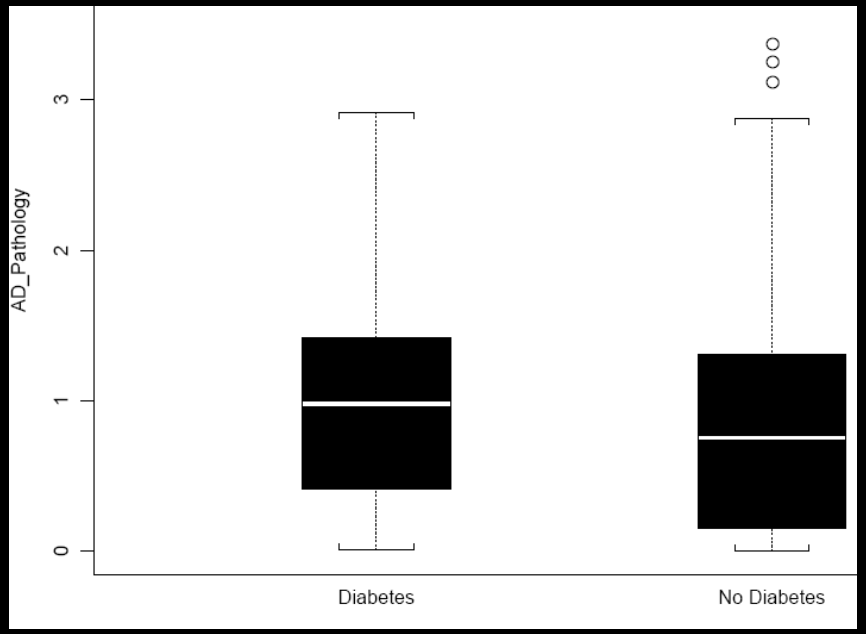
Arvanitakis Z, et al. *Archives Neurology.* 2004;61:661-666.

Diabetes is related to cerebral infarction but not to AD pathology in older persons

% Infarcts

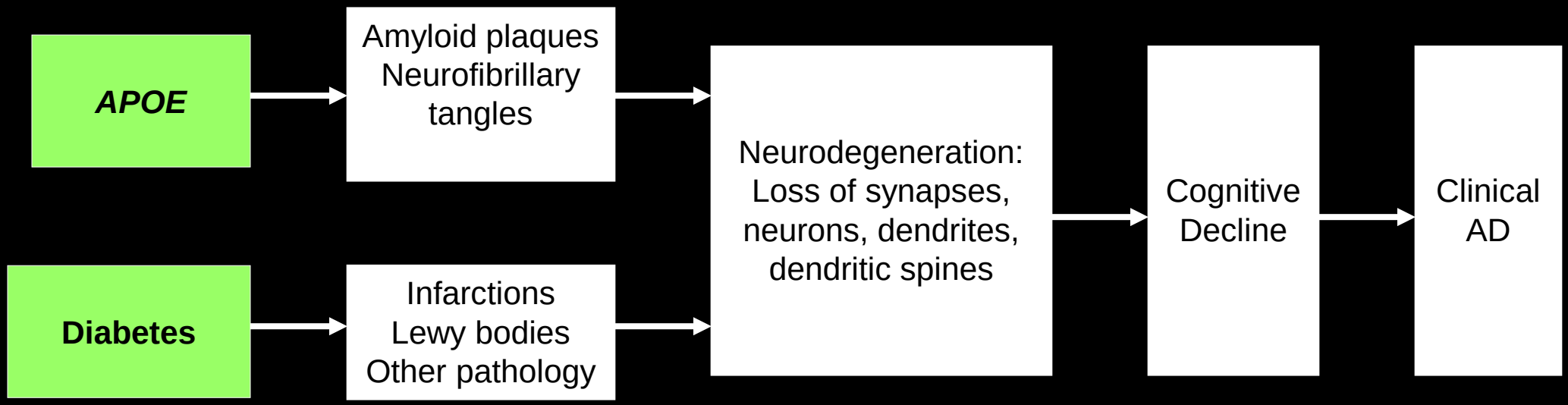


AD Pathology



Arvanitakis Z, et al. *Neurology.* 2006;67:1960–1965.

Neuropathologic intermediate phenotypes enhance association to Alzheimer susceptibility alleles



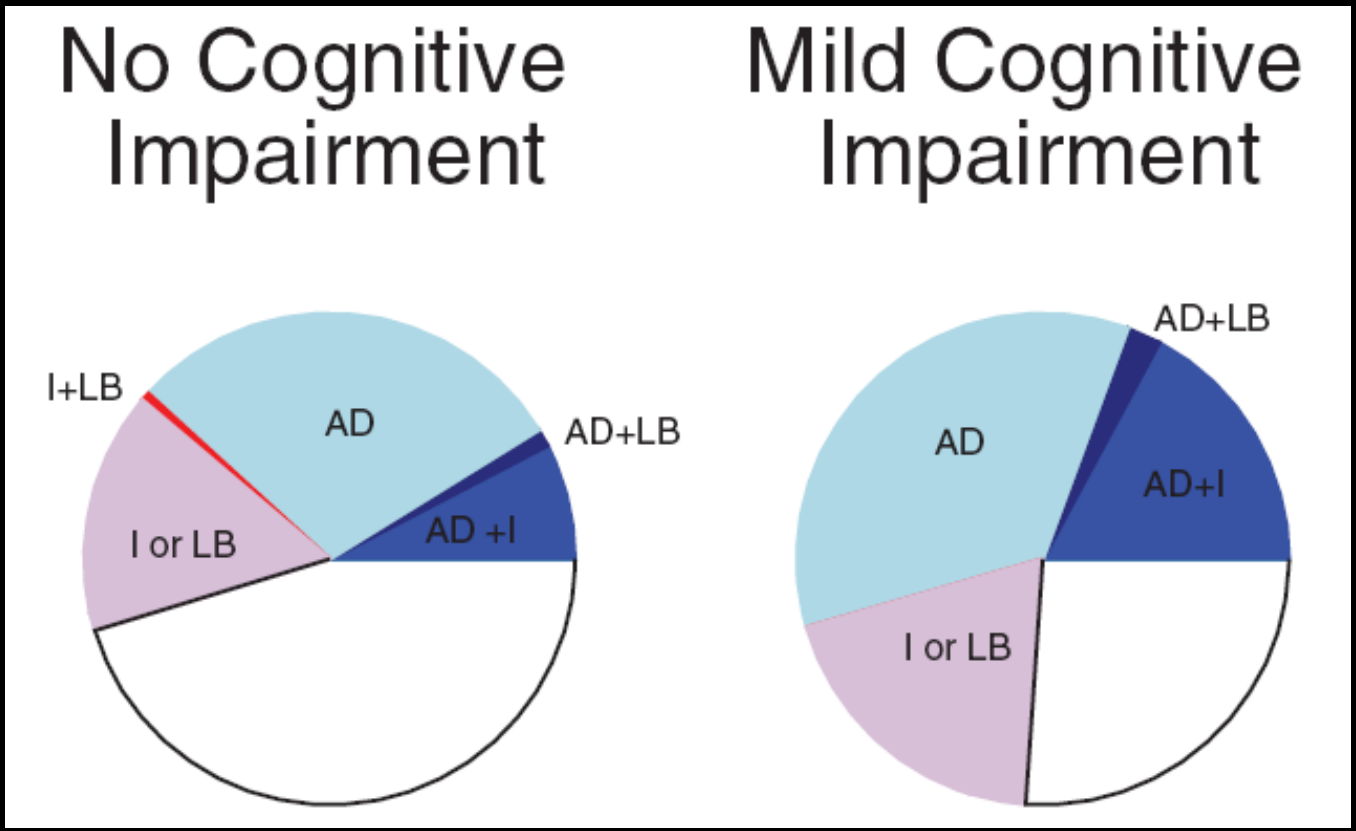
- *APOE* leads to clinical AD through AD pathology
- Diabetes leads to clinical AD through infarctions

Bennett DA, et al. *Neurology*. 2009;72:1495-1503.

Objectives

- Two clinical-pathologic studies of aging and AD
- Common age-related brain pathology
- Implications of mixed pathologies for AD prevention
- Concept of neural reserve
  - Neuropathology in persons without dementia
- How to build a better brain as we age

The Neuropathology of Probable Alzheimer Disease and Mild Cognitive Impairment



Pathology common in persons with MCI and those without dementia or MCI.

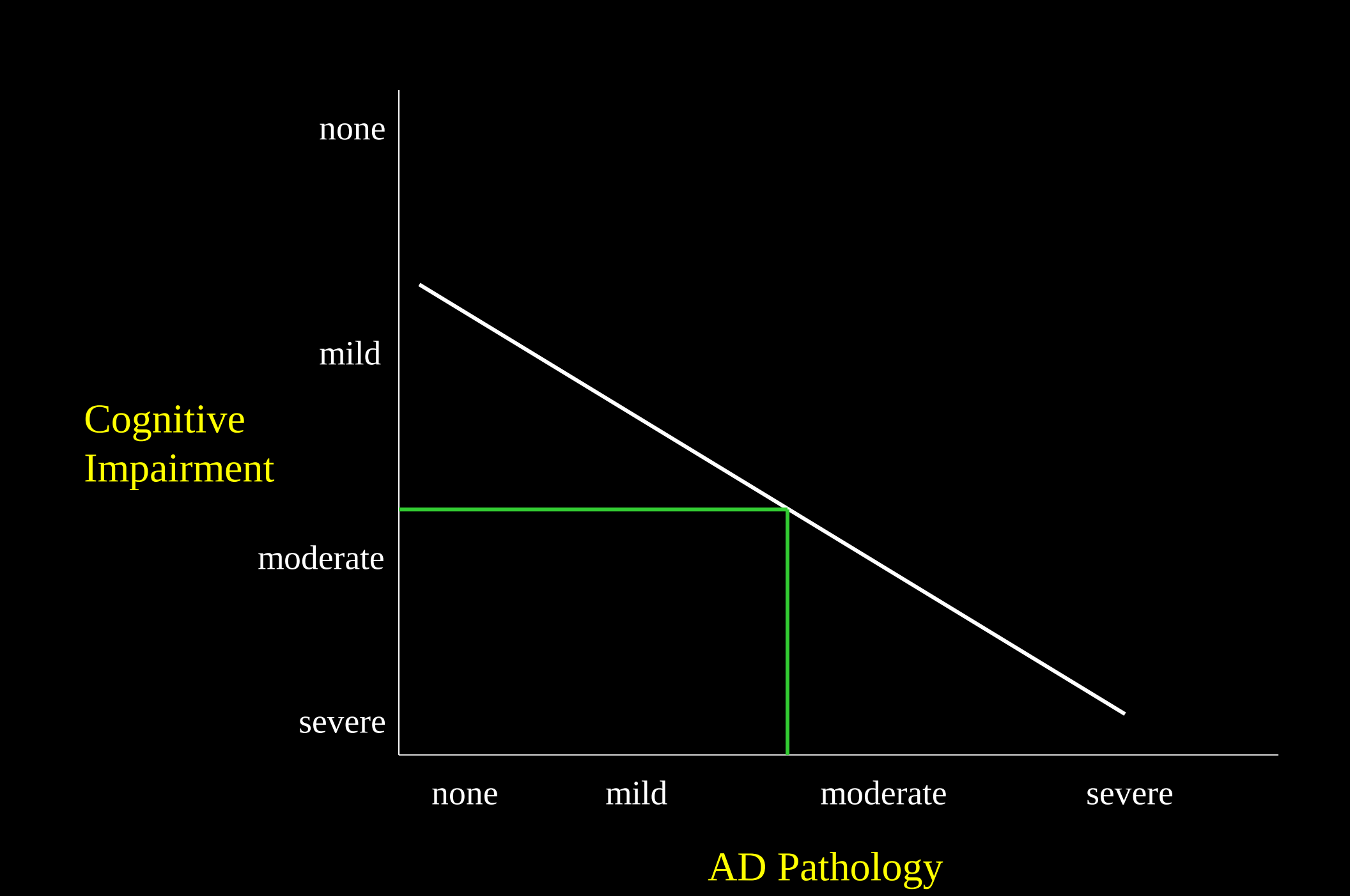
Schneider JA, et al. *Annals Neurology.* 2009;66:200-208.

Concept of neural reserve:

- Individual brains differ in their ability to withstand the effects of brain pathology

Concept of neural reserve:

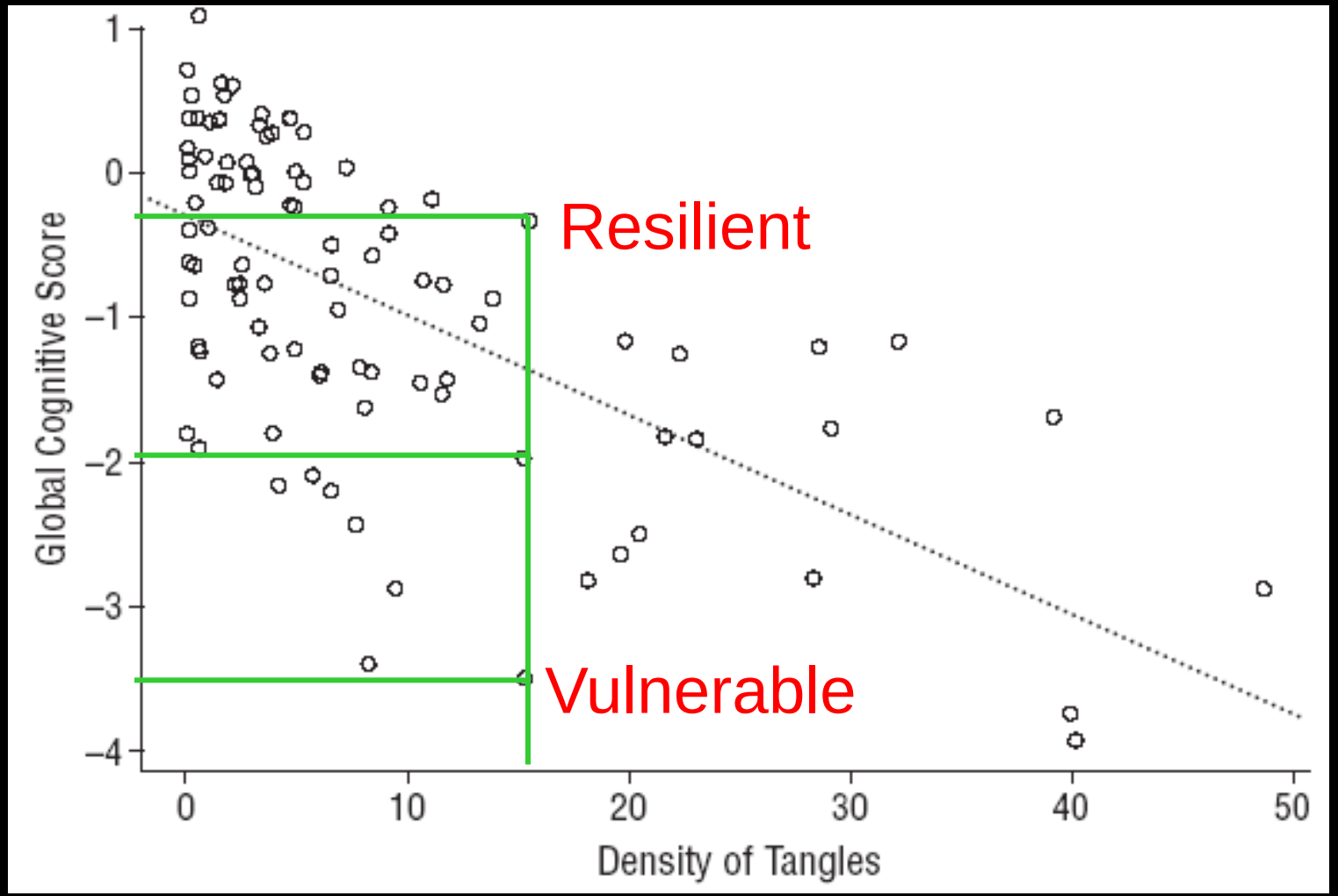
- Individual brains differ in their ability to withstand the effects of brain pathology
- The same amount of brain pathology does not result in the same amount of memory loss in different people


none
mild
moderate
severe
Cognitive Impairment
none
mild
moderate
severe
AD Pathology

Neurofibrillary Tangles Mediate the Association of Amyloid Load With Clinical Alzheimer Disease and Level of Cognitive Function

Bennett DA, et al. *Arch Neurol.* 2004;61:378-384.

Neurofibrillary Tangles Mediate the Association of Amyloid Load With Clinical Alzheimer Disease and Level of Cognitive Function

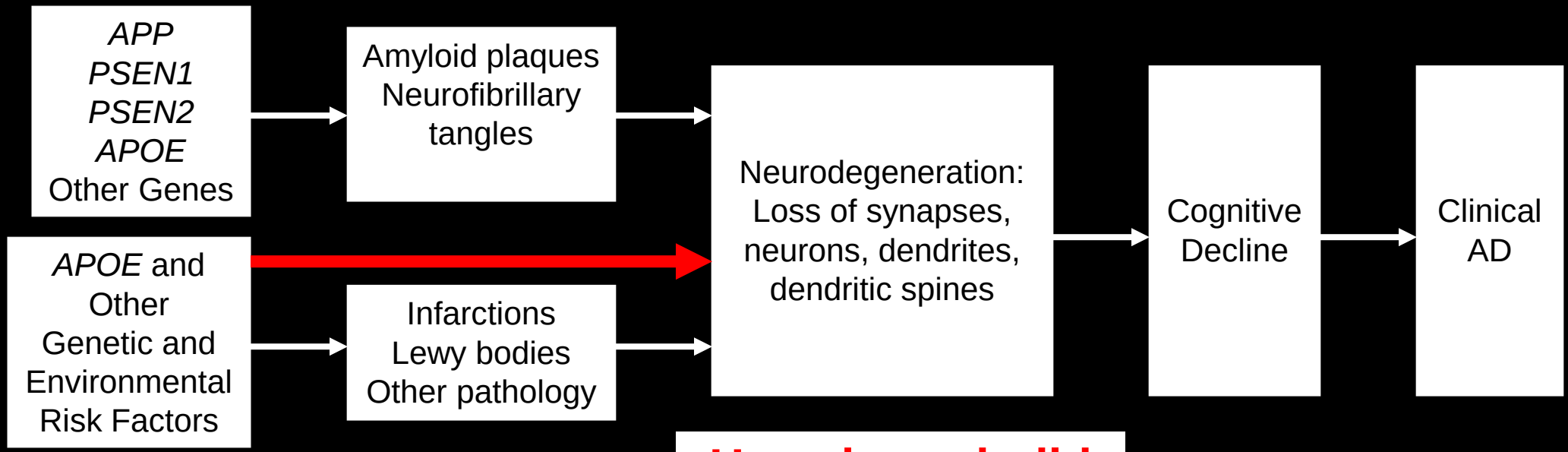


Bennett DA, et al. *Arch Neurol.* 2004;61:378-384.

Objectives

- Two clinical-pathologic studies of aging and AD
- Common age-related brain pathology
- Implications of mixed pathologies for AD prevention
- Concept of neural reserve
- How to build a better brain as we age
  - Factors related to vulnerability or resiliance

Neuropathologic intermediate phenotypes enhance association to Alzheimer susceptibility alleles



How do we build a better brain as we age?

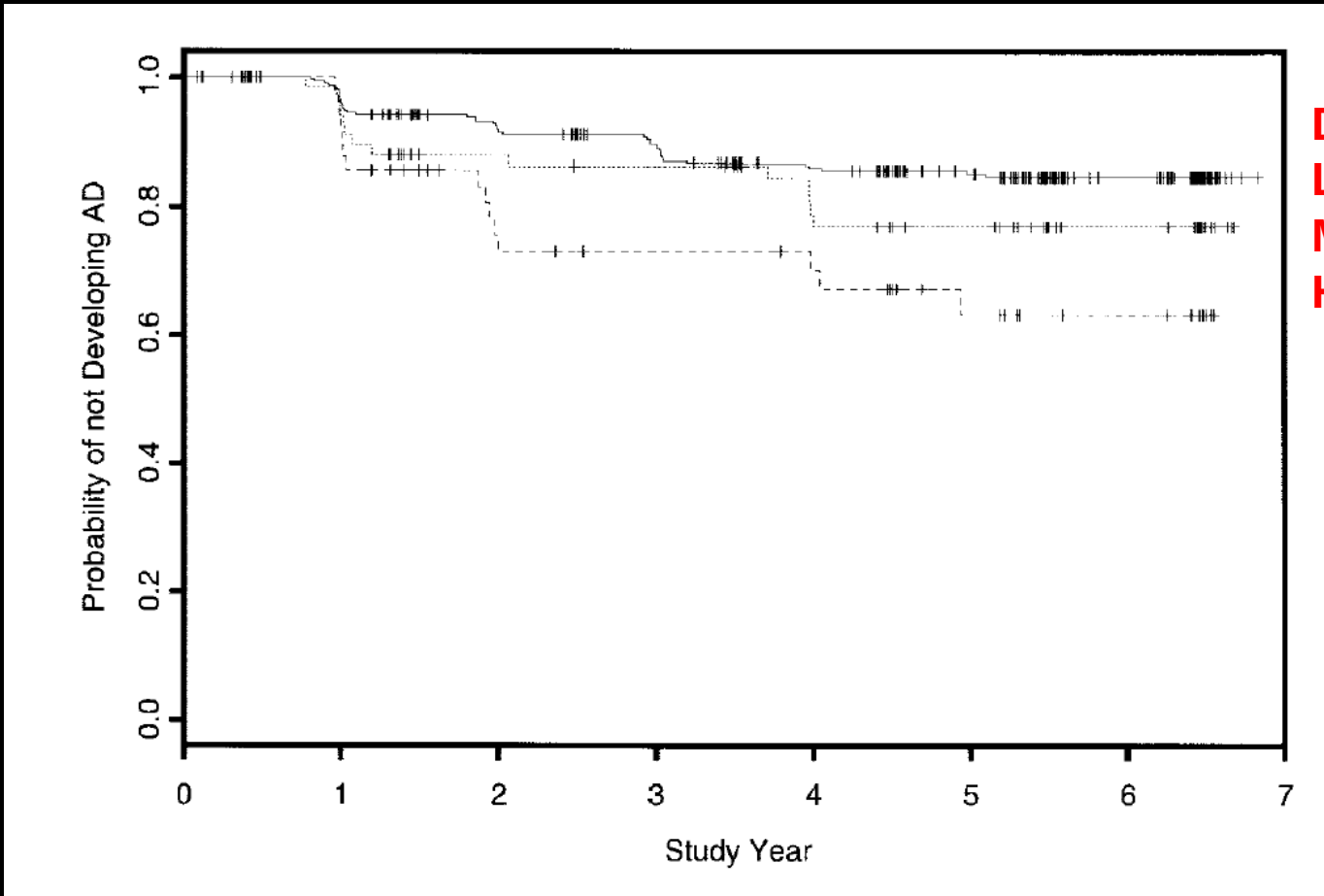
Bennett DA, et al. *Neurology*. 2009;72:1495-1503.

Building a Better Brain

- Vulnerable
  - Depressive symptoms
  - Anxiety
  - Distress proneness
  - Loneliness
  - Harm avoidance
- Resilient
  - Years of education
  - Cognitive activities
  - Physical activities
  - Social activities
  - Conscientiousness
  - Social networks
  - Processing resources
  - Purpose in life
  - Life space

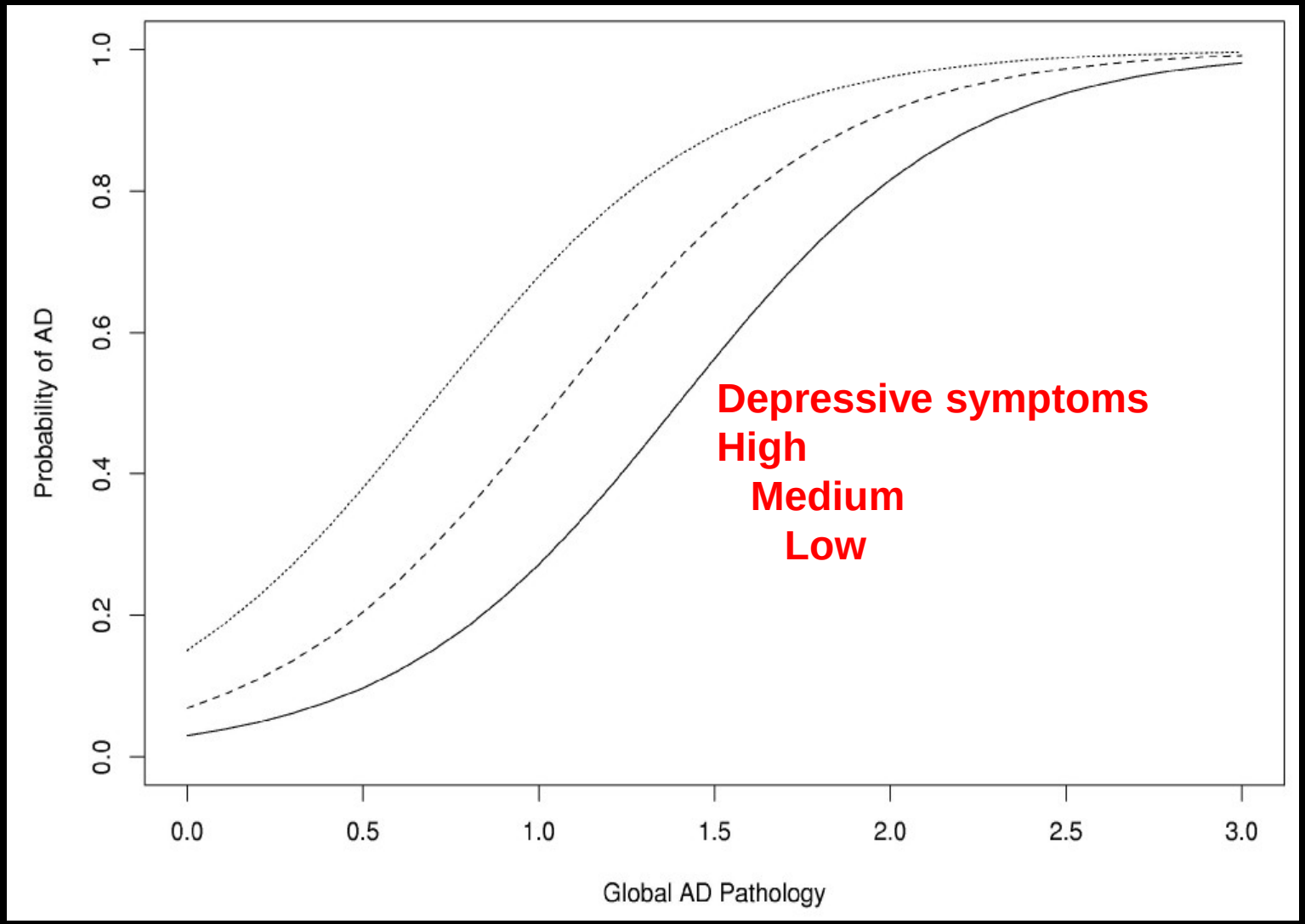
Depressive symptoms, cognitive decline, and risk of AD in older persons

Depressive symptoms (CES-D) (e.g., I felt like everything was an effort, I felt depressed, I felt sad, I could not “get going”).



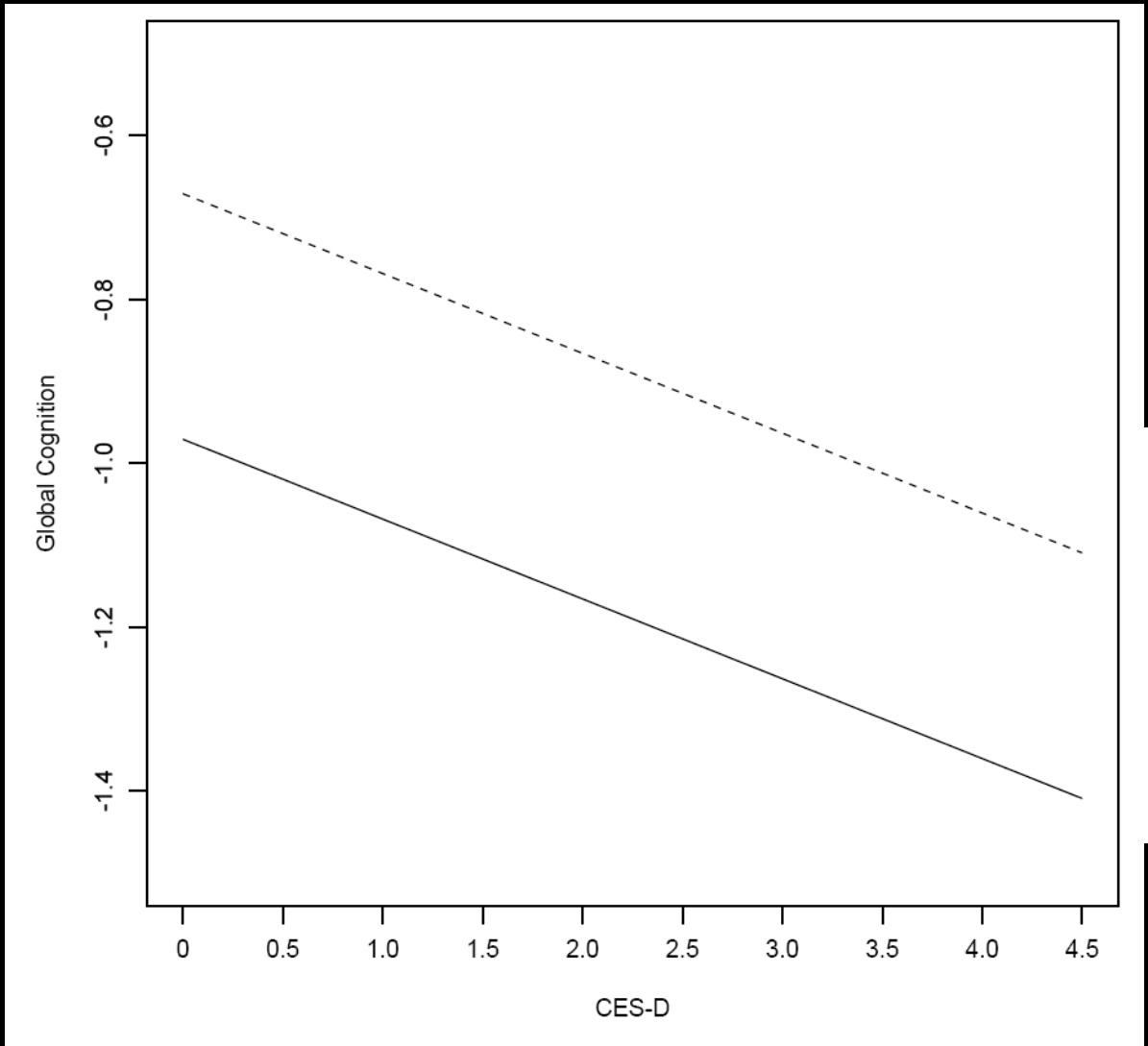
Wilson RS, et al. *Neurology.* 2002;59:364-370.

Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons



Wilson RS, et al. *Neurology.* 2003;61:364-370.

Cerebral Infarctions and the Relationship of Depression Symptoms to Level of Cognitive Functioning in Older Persons



Depressive symptoms

No infarcts

Infarcts

Bennett DA, et al. *Am J Geri Psych.* 2004;12:211-219.

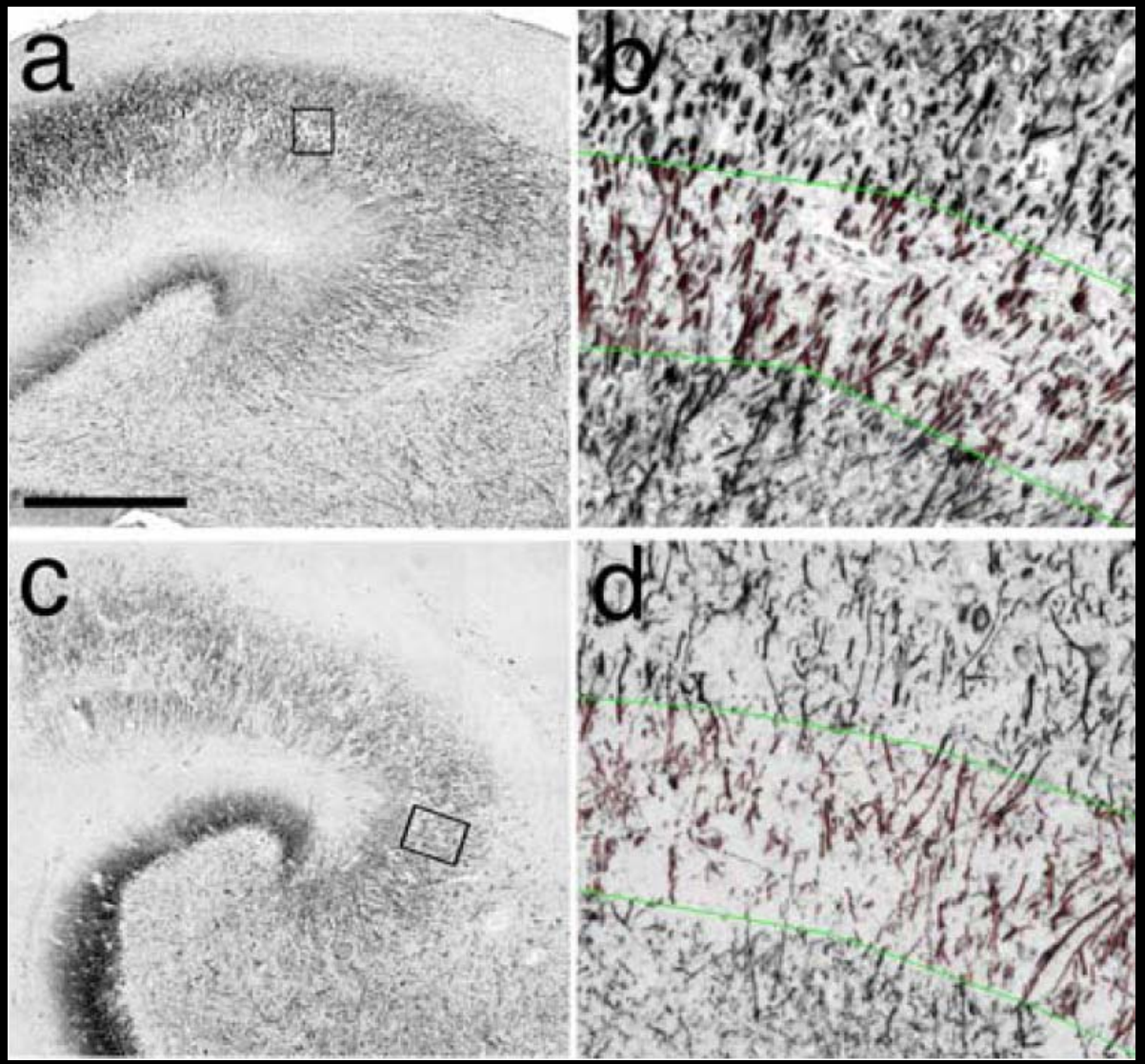
Chronic Distress, Age-Related Neuropathology, and Late-Life Dementia

Anxiety was assessed with the State-Trait Anxiety Inventory which queries about feelings of anxiety thought to be relatively stable over time

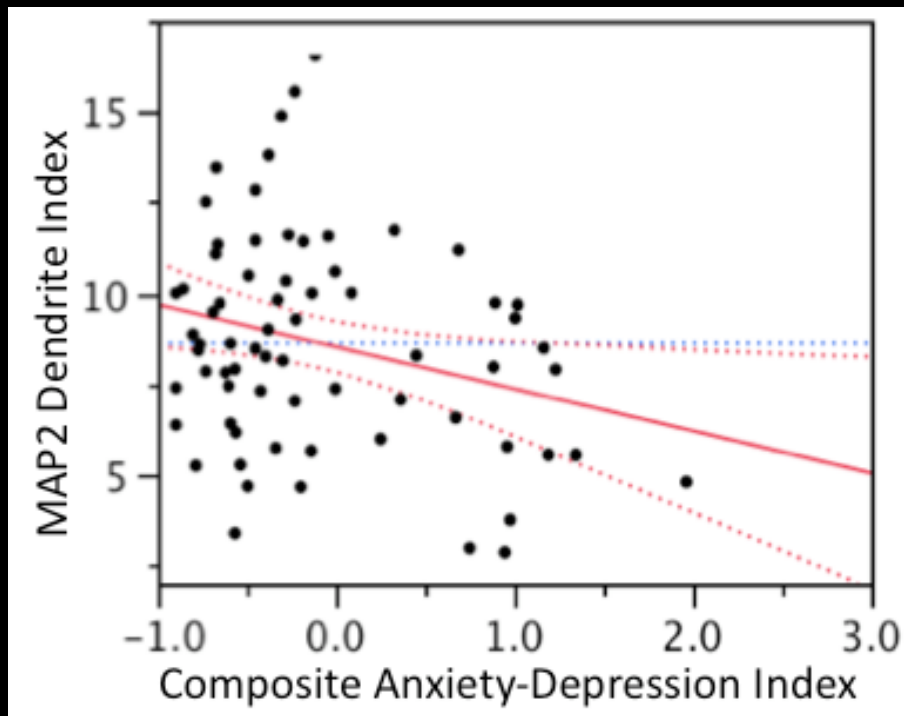
I feel nervous and restless

Wilson RS, et al. *Psychosomatic Med.* 2007;69:47-53.

Anxiety and Depression Are Associated with Hippocampal CA3 Dendrite and Spine Density in Older Humans

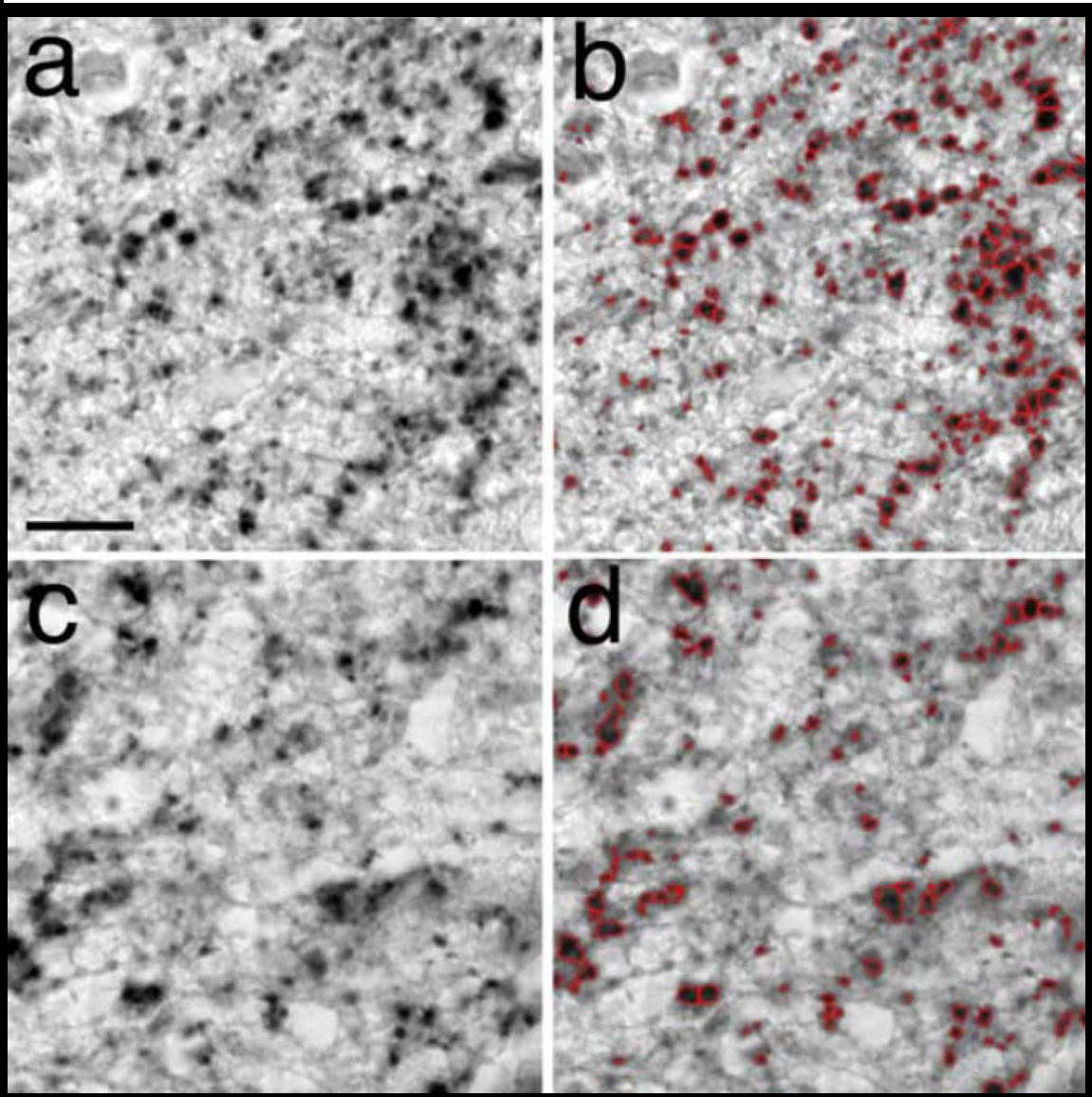


Dendrites in hippocampus

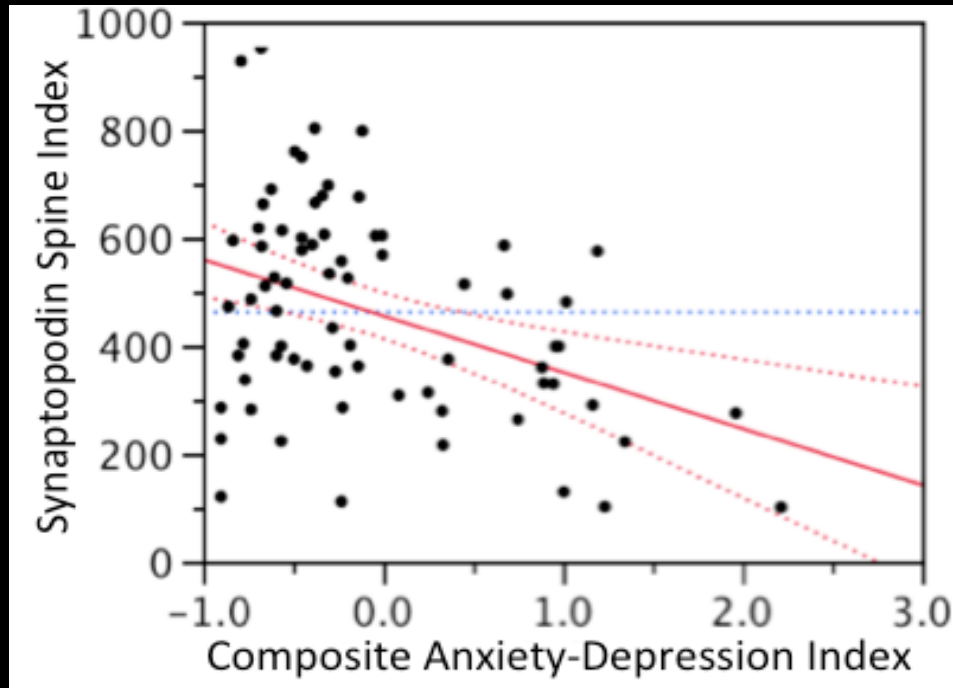


Soetento A, et al. *Arch Gen Psych*. In press.

Anxiety and Depression Are Associated with Hippocampal CA3 Dendrite and Spine Density in Older Humans



Dendritic spines in hippocampus



Soetento A, et al. *Arch Gen Psych*. In press.

Proneness to psychological distress is associated with risk of Alzheimer's disease

Neuroticism refers to the disposition to experience psychological distress

I am a worrier;
I often feel tense and jittery;
I often get angry at the way people treat me;
I often feel helpless and want someone else to solve my problems

Wilson RS, et al. *Neurology.* 2003;61:1479-1485.

Loneliness and Risk of Alzheimer Disease

Loneliness is a measure of the feeling of social isolation

I experience a general sense of emptiness,
I miss having people around,
I feel like I don’t have enough friends,
I often feel abandoned,
I miss having a really good friend

Wilson RS, et al. *Arch Gen Psych.* 2007;64:234-240.

Harm Avoidance and Risk of Alzheimer's Disease

Loneliness is a trait associated with behavioral inhibition, i.e., a tendency to avoid new situations and aversive stimuli.

Four Subscales:
anticipatory worry; e.g., "Things often go wrong for me unless I'm careful"
fear of uncertainty; e.g., "I usually feel tense and worried when I have to do something new and unfamiliar."
shyness; e.g., "I am more shy than most people."
fatigability; e.g., "I have less energy and tire more quickly than most people."

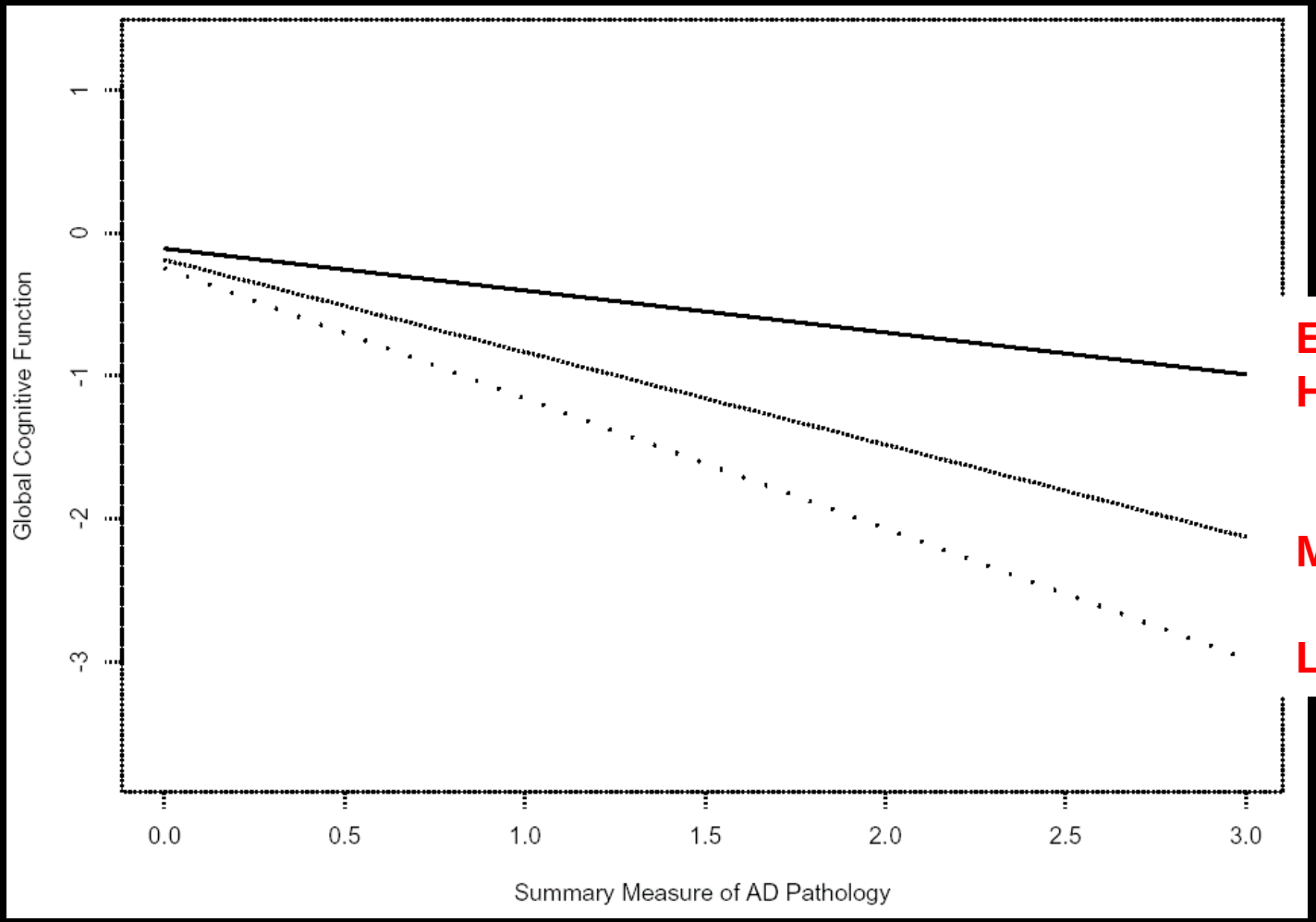
Wilson RS, et al. *Under review.*

Building a Better Brain

- Vulnerable
  - Depressive symptoms
  - Anxiety
  - Distress proneness
  - Loneliness
  - Harm avoidance
- Resilient
  - Years of education
  - Cognitive activities
  - Physical activities
  - Social activities
  - Conscientiousness
  - Social networks
  - Processing resources
  - Purpose in life
  - Life space

CME

Education modifies the relation of AD pathology to level of cognitive function in older persons



Bennett DA, et al. *Neurology.* 2003;60:1909-1915.

CME

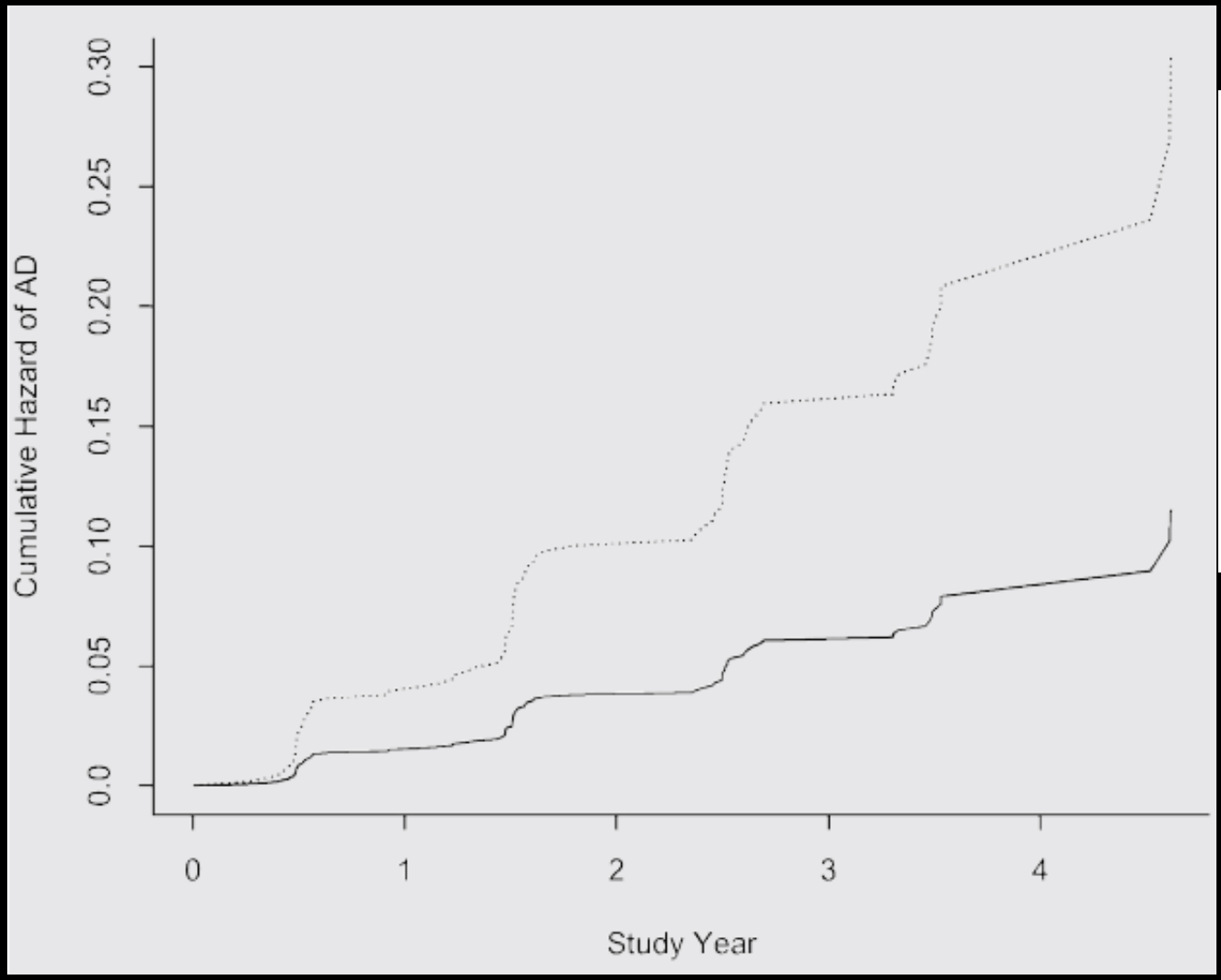
Education modifies the relation of AD pathology to level of cognitive function in older persons

An example of the cognitive scores of two older women (scale: mean = 100, SD = 10, from baseline).

Education	plaques	score	plaques	score
18 years	0	98.1	18	96.2
15 years	0	96.8	18	82.0

Bennett DA, et al. *Neurology.* 2003;60:1909-1915.

The relation of cognitive activity to risk of developing Alzheimer's disease



Cognitive activities
Low

High

Wilson RS, et al. *Neurology.* 2007;69:1911-20.

The relation of cognitive activity to risk of developing Alzheimer's disease

	Model A			Model B		
Model term	Estimate	SE	*p*	Estimate	SE	*p*
Time	−0.019	0.010	0.053	−0.010	0.012	0.403
Time squared	−0.014	0.003	<0.001	−0.015	0.003	<0.001
Current cognitive activity	0.256	0.024	<0.001			
Current activity × time	0.019	0.008	0.017			
Past cognitive activity				0.183	0.034	<0.001
Past activity × time				0.027	0.011	0.017

Wilson RS, et al. *Neurology.* 2007;69:1911-20.

Cognitive Activities

	Age 6	Age 12	Age 18	Age 40	Current
Read to	X				
Told stories	X				
Play games	X	X	X	X	X
Time reading/day		X			
Time on homework/day		X			
Visit library		X	X	X	X
Read newspaper		X	X	X	X
Read magazine		X	X	X	X
Read books		X	X	X	X
Write letter		X	X	X	X
Music instruction			X		
Kept a diary			X	X	X
Visit museum			X	X	X
Attend concert, play			X	X	X

The relation of cognitive activity to risk of developing Alzheimer's disease

Table 4 Relation of neuropathology to frequency of participation in cognitively stimulating activities at study onset*

Model term	Estimate	SE	p
Amyloid burden	0.002	0.028	0.943
Tangle density	−0.016	0.014	0.229
Braak stage	0.003	0.066	0.964
Lewy bodies	−0.130	0.222	0.561
One infarction	−0.304	0.229	0.188
Multiple infarction	−0.037	0.206	0.859

Wilson RS, et al. *Neurology.* 2007;69:1911-20.

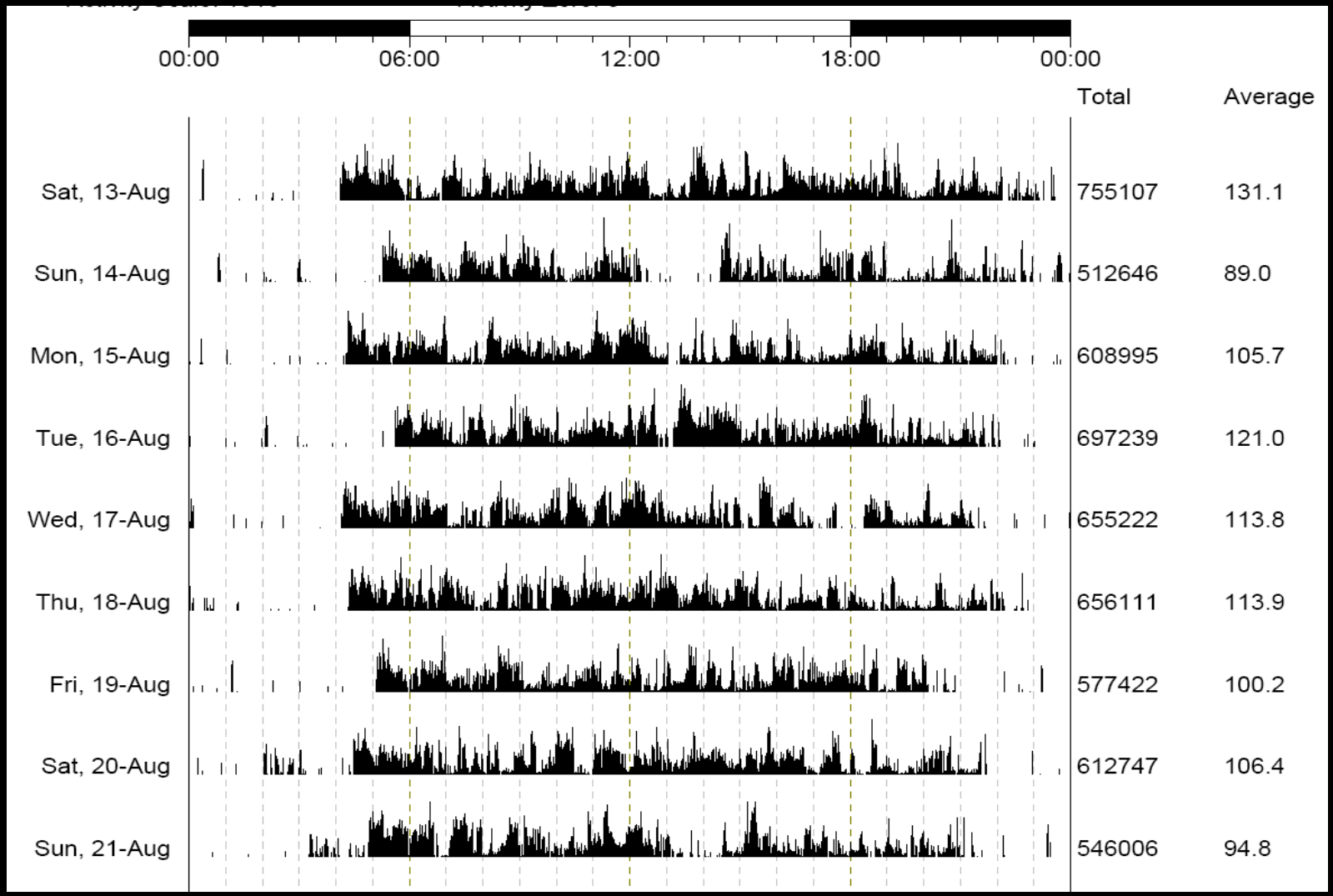
SOCIAL ENGAGEMENT AND COGNITIVE FUNCTION IN OLD AGE

How often during the past year did you

Go to restaurants, sporting events, play bingo
on day trips or overnight trips
do unpaid community/volunteer work
visit relatives or friends houses
participate in groups, such as senior center, social club

Krueger KR, et al. *Exp Aging Research.* 2009;35:45-60.

Total Daily Activity is Associated With Cognition in Older Persons



Buchman AS, et al. *Am J Geriatr Psych*. 2008;16:697-701.

Conscientiousness and the Incidence of Alzheimer Disease and Mild Cognitive Impairment

Conscientiousness refers to a tendency to be self-disciplined, scrupulous, and purposeful

I am a productive person who always gets the job done

Wilson RS, et al. *Arch Gen Psych.* 2007;64:1204-12.

The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study

Number of relatives (besides spouse and children) and other friends that they saw each month that they felt close to and at ease with and could talk to about private matters and could call upon for help.

Bennett DA, et al. *Lancet Neurology.* 2006;5:406-412.

Processing resources reduce the effect of Alzheimer pathology on other cognitive systems

Processing resources:

Perceptual speed refers to the speed with which mental comparisons are made

Working memory involves the ability to hold and manipulate information in short-term memory stores

Boyle PA, et al. *Neurology.* 2008;70:1534-42.

Participation in Cognitively Stimulating Activities and Risk of Incident Alzheimer Disease

Cognitive Measure	Model Terms	Estimate (SE)	*P* Value
Episodic memory	Cognitive activity	0.100 (0.037)	.007
	Time	−0.037 (0.008)	<.001
	Cognitive activity × time	0.020 (0.012)	.10
Semantic memory	Cognitive activity	0.221 (0.038)	<.001
	Time	−0.048 (0.007)	<.001
	Cognitive activity × time	0.010 (0.010)	.36
Working memory	Cognitive activity	0.082 (0.041)	.05
	Time	−0.035 (0.005)	<.001
	Cognitive activity × time	0.021 (0.008)	.007
Perceptual speed	Cognitive activity	0.211 (0.052)	<.001
	Time	−0.087 (0.008)	<.001
	Cognitive activity × time	0.026 (0.012)	.02
Visuospatial ability	Cognitive activity	0.133 (0.048)	.005
	Time	−0.020 (0.007)	.002
	Cognitive activity × time	0.015 (0.010)	.14

Wilson RS, et al. *JAMA* 2002;287:742-748.

Purpose in Life is Associated with Incident AD Among Community-Dwelling Older Persons

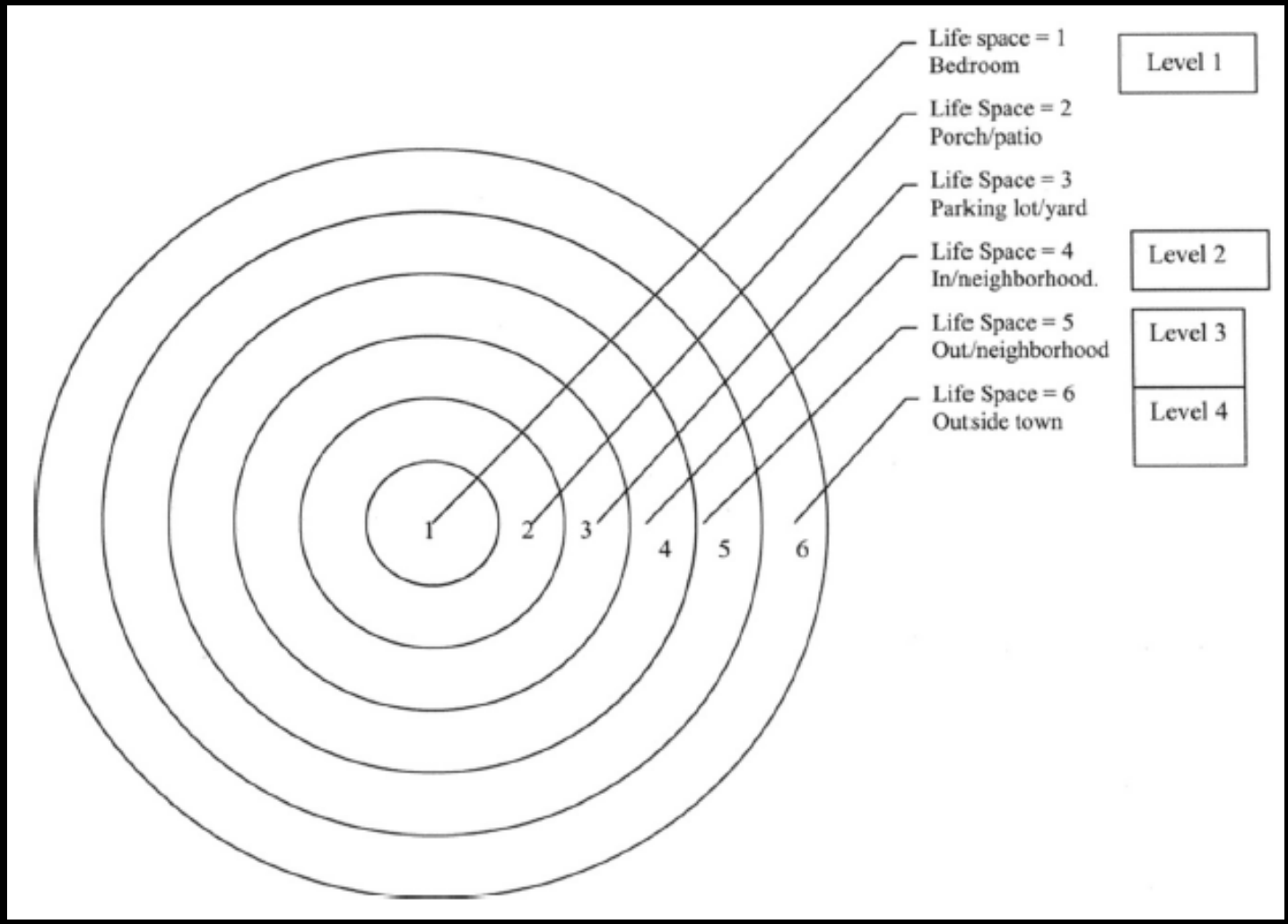
Tendency to derive meaning from life's experiences and possess a sense of intentionality and goal directedness that guides behavior.

I feel good when I think of what I've done in the past and what I hope to do in the future;
I am an active person in carrying out the plans I set for myself

Boyle PA, et al. *Arch Gen Psych*. 2010;67:304-10.

Life space and risk of Alzheimer's disease, mild cognitive impairment, and cognitive decline in older adults: prospective cohort study

Six zones in the past week



James BD, et al.
Under review.

CORRELATES OF LIFE SPACE IN A VOLUNTEER COHORT OF OLDER ADULTS

Barnes LL, et al. *Exp Aging Res.* 2007;33:77-93.

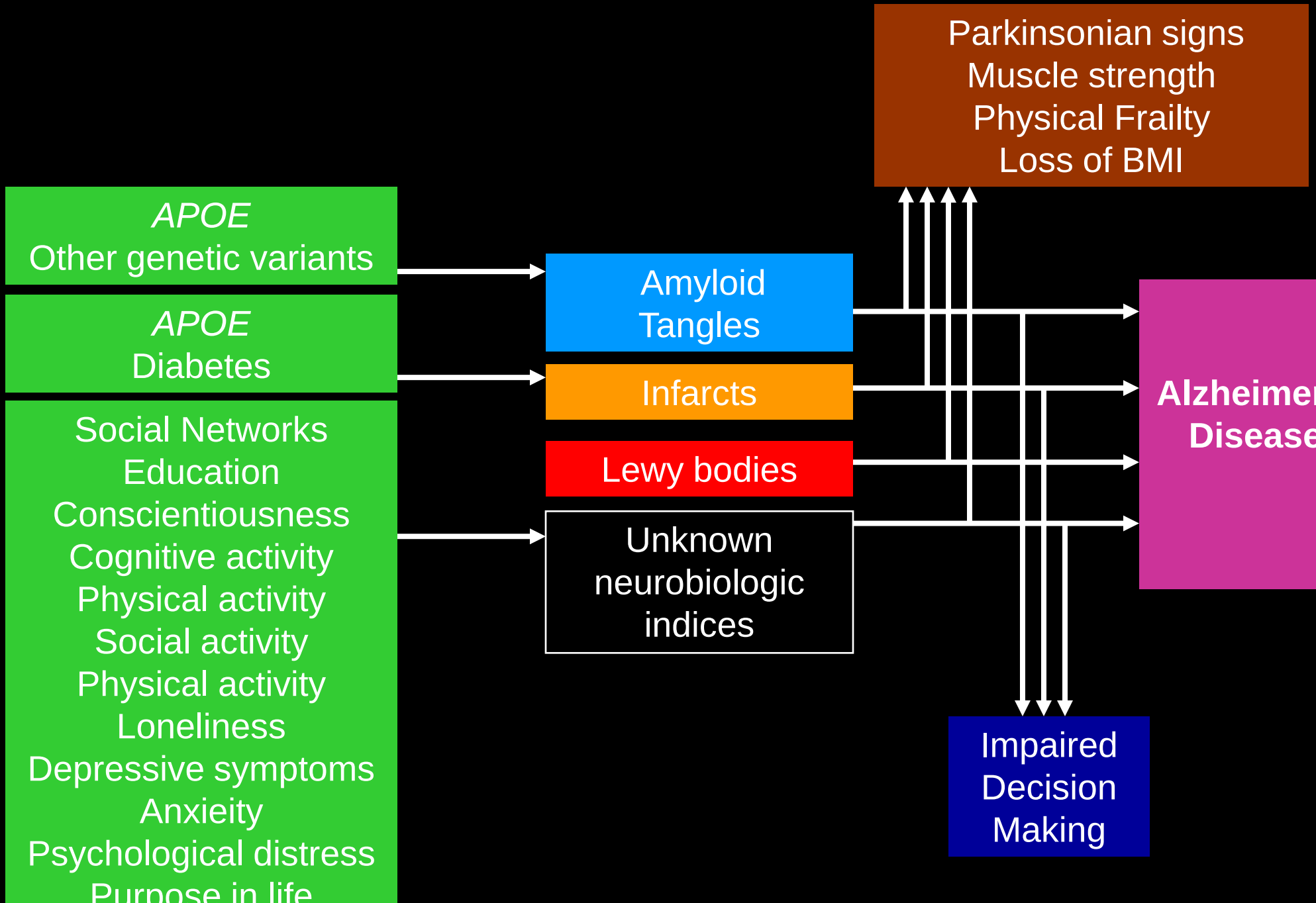
Summary

- AD pathology is common in persons without dementia, and in persons without mild cognitive impairment
- Many factors in addition to AD pathology determine the likelihood of dementia in old age
  - Coexisting brain pathology
    - Infarcts
    - Lewy bodies
  - Life experiences and psychological factors
    - Some increase vulnerability
    - Some increase resilience
- AD is a disease of a lifetime; there are many ways to build a better brain as we age


SCORE

Future Directions and Other ongoing work:

- Relation of AD pathology to healthcare and financial decision making in persons without dementia
  - Impaired decision making results in part from subclinical AD
- Relation of AD pathology to mobility
  - AD is a poorly recognized cause of gait disturbance
- Relation of genetic factors to AD pathology
  - Genes more strongly related to pathology than cognition
- Nutrition survey
  - You are what you eat
- Relation of factors associated with neural reserve to
  - brain elements needed for cognitive function (e.g., neurons, synapses, dendrites, spines)
  - brain proteins
  - brain epigenome
  - brain imaging


Parkinsonian signs
Muscle strength
Physical Frailty
Loss of BMI
APOE
Other genetic variants
APOE
Diabetes
Social Networks
Education
Conscientiousness
Cognitive activity
Physical activity
Social activity
Physical activity
Loneliness
Depressive symptoms
Anxieity
Psychological distress
Purpose in life
Amyloid
Tangles
Infarcts
Lewy bodies
Unknown
neurobiologic
indices
Alzheimer's Disease
Impaired
Decision
Making

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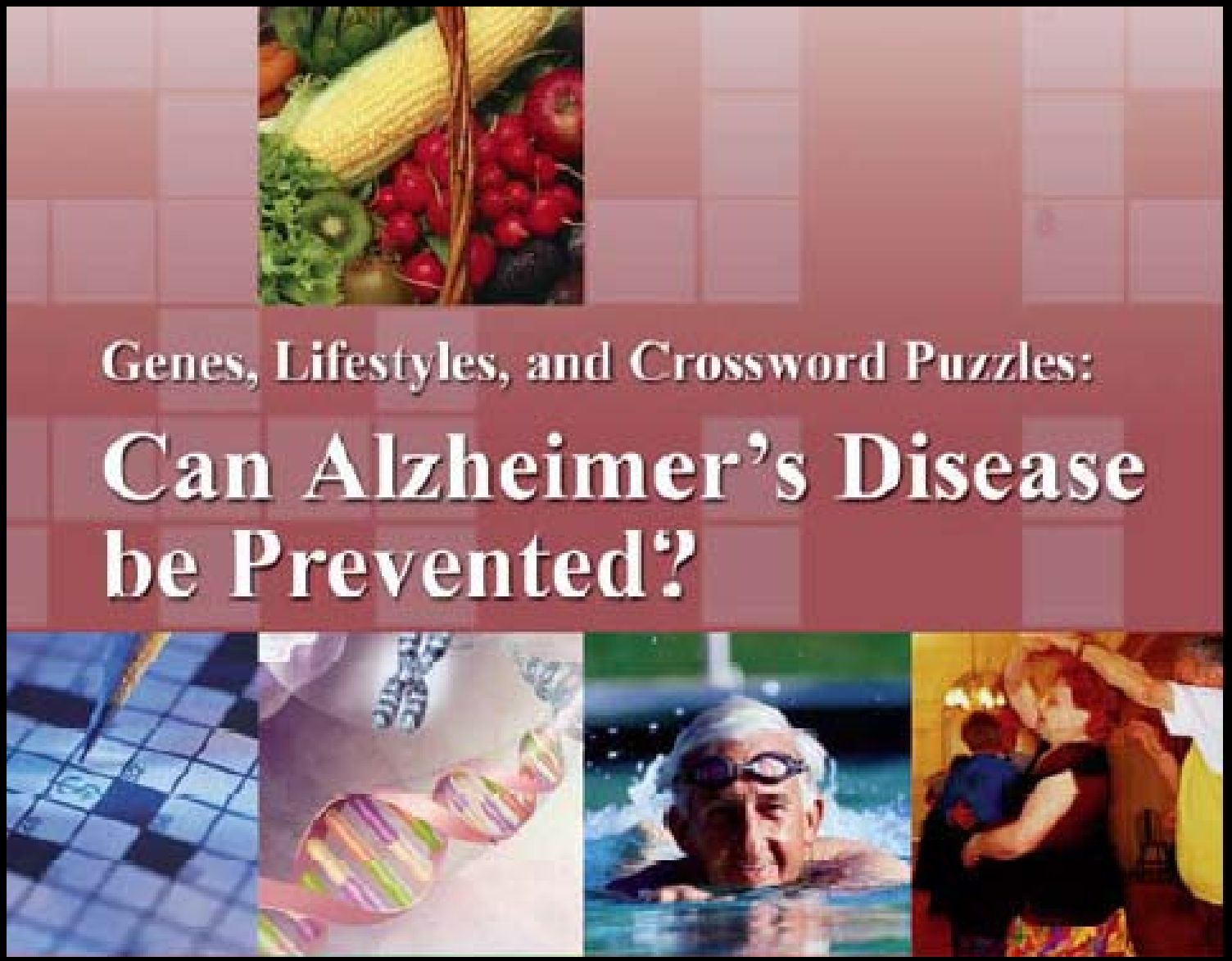

National Institute on Aging, Alzheimer's Disease Education and Referral Center

What can you do to prevent AD?

- Control diabetes and high blood pressure
- Relax, be happy
- Get out and do something new
- Engage in regular:
  - Cognitive activities
  - Physical activities
  - Social activities
- Maintain social ties
- Engage in meaningful, goal directed behavior
- Be diligent
- Start early


OLD AGE
SPARE
BRAIN