# Overview of Clinical and Post-Mortem Data Elements in the Religious Orders Study

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An important scientific innovation rarely makes its way gradually winning over and converting its opponents…What does happen is that its opponents gradually die out and the growing generation is familiarized with the idea from the beginning.

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***Max Planck***

*The philosophy of physics*

***Francis Harry Compton Crick***
*1916 - 2004*

*What Mad Pursuit:*
*A Personal View of Science.*
Basic Books, New York, 1988

**Francis Harry Compton Crick**
1916 - 2004

Some scientists work so hard there is no time left for serious thinking.

*What Mad Pursuit:*
*A Personal View of Science.*
Basic Books, New York, 1988

In some sciences accurate measurement is possible and important, in others it is difficult to find anything to measure which appears to have a fundamental bearing on the problem.

***Sir George Thomson***
*The Inspiration of Science, 1968*

The scientist is not a person who gives the right answers, he's one who asks the right questions.

***Claude Lévi-Strauss***
*Le Cru et le cuit*, *1964*

# Objectives:

- Review clinical data collection elements
  - Cognitive function tests
  - Clinical diagnoses
- Review post-mortem data collection elements
  - AD pathology
  - Cerebrovascular disease
  - Lewy body disease

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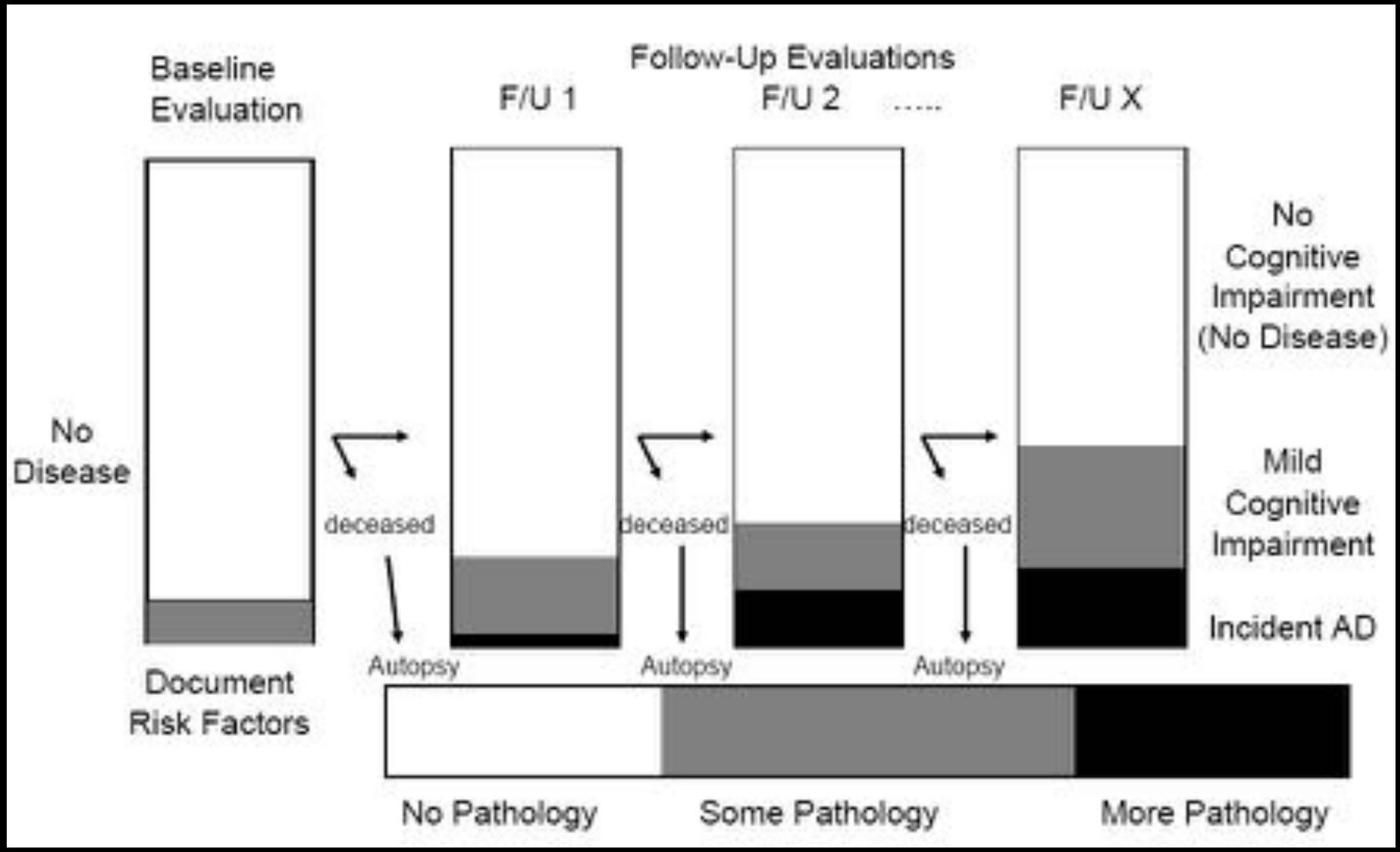
# The Rush Memory and Aging Project: Study Design and Baseline Characteristics of the Study Cohort




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

# Religious Orders Study: Participating Sites


Antioch
Zion
Lindenhurst
Beach Park
Waukegan
Spring Grove
Fox Lake Hills
Round Lake Beach
Gurnee
North Chicago
Cherry
McHenry
Grass Lake
BOONE
M C H E N R Y
L A K E
Woodstock
Liberty
Belvidere
Fremont Center
Mundelein
Lake Michigan
Marengo
Fox River Grove
Lake Barrington
Highwood
Crystal Lake
Lake in the Hills
Algonquin
Lake Zuch
Highland Park
Northbrook
Carpentersville
West Dundee
Palatine
Glencoe
Wilmette
Geneva
Hoffman Estates
Arlington Heights
Evanston
Elgin
Schaumburg
Niles
Lincolnwood
Sycamore
Bartlett
Park Ridge
Roselle
DeKalb
I L L I N O I S
Melrose Park
Carol Stream
Chicago
Cortland
St. Charles
Lombard
Oak Park
DEKALB
Wheaton
Maywood
Cicero
Batavia
Downers Grove
Berwyn
K A N E
Hinckley
Sugar Grove
Aurora
Westmont
Naperville
Burbank
Shabbona
Little Rock
Bolingbrook
Oak Lawn
East Chicago
Bristol
Sandwich
Plano
Oswego
W I L L
Yorkville
Romeoville
Orland Park
Leland
Somonauk
LASALLE
KENDALL
Plainfield
Harvey
Hammond
Gary
Crest Hill
Lockport
Tinley Park
Manster
Highland
Sheridan
Shorewood
Joliet
Chicago Heights
INDIANA

# Cost-Efficient Operation

- >2,300 participants
- Rolling admission with up to 15 years of data (1/94)
- > 15,000 detailed (~4 hr) clinical evaluations as home visits across the US
- About $1000 per person per year
  - Direct computer entry makes data rapidly available to study staff; computer scores and summarizes cognitive tests for clinicians; reduces training time
  - Computer-based actuarial decision tree enhances uniformity of diagnostic decisions across clinicians, time, and space
  - No routine informant interviews
  - No routine or special laboratory studies
  - No routine neuroimaging
  - No routine case conferences

# Decision Rules Guiding the Clinical Diagnosis of Alzheimer's Disease in Two Community-Based Cohort Studies Compared to Standard Practice in a Clinic-Based Cohort Study

1. History of cognitive decline by structured interview with participant
2. Education (not age) adjusted cutoff scores on 11 cognitive tests
3. Neuropsychologist rates impairment on five cognitive domains (orientation, attention, memory, language, visuospatial ability)
4. Clinician assigns diagnoses of dementia and its principal causes (e.g., AD, stroke, dementia due to stroke, PD)
5. MCI refers to persons with cognitive impairment who are not demented

Bennett DA, et al. *Neuroepidemiology* 2006;27:169-76.

# Memory complaints are related to Alzheimer disease pathology in older persons

1) How often do you have trouble remembering things, with responses ranging from 5 = very often to 1 = never;
2) How is your memory compared to 10 years ago, with responses ranging from 5 = much worse to 1 = much better.

| Model term* | Estimated effect of AD pathology | SE | *p* Value |
|---|---|---|---|
| Model A: AD pathology | 0.88 | 0.28 | 0.002 |
| Model B: Adjustment for depressive symptoms | 0.87 | 0.28 | 0.003 |
| Model C: Adjustment for chronic health problems | 0.83 | 0.29 | 0.006 |

Barnes LL, et al. *Neurology.* 2006;67:1581-5.

# Natural history of mild cognitive impairment in older persons

| Cognitive test | Cognitive domain | Maximum score | <8 | 8–11 | 12–16 | >16 |
|---|---|---|---|---|---|---|
| MMSE 1–10 | Orientation | 10 | <7 | <8 | <8 | <9 |
| Digits Backward | Attention | 12 | <3 | <4 | <5 | <5 |
| Symbol Digit | Attention | 110 | <8 | <16 | <21 | <25 |
| Logical Memory IIa | Memory | 25 | <3 | <5 | <5 | <9 |
| Word List Recall | Memory | 10 | <3 | <5 | <5 | <5 |
| Word List Recognition | Memory | 10 | <8 | <9 | <9 | <9 |
| Boston Naming | Language | 15 | <9 | <10 | <11 | <13 |
| Category Fluency | Language | NA | <9 | <10 | <10 | <12 |
| Complex Ideas | Language | 8 | <7 | <7 | <7 | <7 |
| Line Orientation | Visuospatial | 15 | <3 | <5 | <7 | <8 |
| Progressive Matrices | Visuospatial | 9 | <5 | <6 | <7 | <8 |

Bennett DA, et al. *Neurology.* 2000;59:198-205.

NEUROLOGISTS IMPRESSION OF CLINICAL EVALUATION DATA

[EXAMINER: REVIEW CLINICAL EVALUATION SUMMARY DATA PRIOR TO SEEING SUBJECT.]

Record whether subject asserts that (s)he has experienced loss of memory or other cognitive function(s).

- (●) 1. Yes
- ( ) 2. No

Record number of [POSSIBLE, MILD, MODERATE or SEVERE] impaired cognitive domains.

- ( ) 1. NO impaired or possible impaired domains
- ( ) 2. ONE or more possible impaired domains with NO impaired domains
- (●) 3. ONE impaired domain
- ( ) 4. TWO impaired domains
- ( ) 5. THREE impaired domains
- ( ) 6. FOUR impaired domains
- ( ) 7. FIVE impaired domains

Record the presence of memory impairment.

- ○ 1. No memory impairment
- ○ 2. Possible memory impairment
- ◉ 3. MILD, MODERATE OR SEVERE memory impairment

[EXAMINER: RENDER YOUR OPINION REGARDING COGNITIVE DECLINE AFTER REVIEWING THE CLINICAL EVALUATION SUMMARY DATA AND SPEAKING WITH SUBJECT]

Based on review of all available data and your interaction with the subject, in your opinion, has (s)he experienced a meaningful decline in cognitive function relative to a previous level of performance?

- ◉ 1. Yes
- ○ 2. Possible
- ○ 3. No

For Dementia: the algorithmic diagnosis is Possible

Do you agree with it?

- (•) 1. Yes
- ( ) 2. No

For Alzheimer's disease: the algorithmic diagnosis is Possible

Do you agree with it?

- (•) 1. Yes
- ( ) 2. No

SUMMARY OF ALL ALGORITHMIC DIAGNOSES FOR: 72659872 Eval. Date: 12/18/2006

| | Disease | Algorithmic Dx | Doc Agreed? | Doc's Dx |
|---|---|---|---|---|
| 1. | Dementia | Possible | Yes | Possible |
| 2. | Alzheimers Disease | Possible | Yes | Possible |
| 3. | Parkinsonism | Not Present | Yes | Not Present |
| 4. | Parkinson's Disease | Not Present | Yes | Not Present |
| 5. | Stroke | Not Present | Yes | Not Present |
| 6. | CI due to Stroke | Not Present | Yes | Not Present |
| 7. | Depression | Possible | Yes | Possible |

Cog. Impairment: One; Mem. Impairment: Definite; Pcpnt. evaluated: Yes

<<<< Hit ENTER to go to comment screen >>>>

SUMMARY OF ALL ALGORITHMIC DIAGNOSES FOR: 00000136 Eval. Date: 10/4/2007

| | Disease | Algorithmic Dx | Doc Agreed? | Doc's Dx |
|---|---|---|---|---|
| 1. | Dementia | Possible | Yes | Possible |
| 2. | Alzheimers Disease | Possible | Yes | Possible |
| 3. | Parkinsonism | Not Present | Yes | Not Present |
| 4. | Parkinson's Disease | Not Present | Yes | Not Present |
| 5. | Stroke | Not Present | Yes | Not Present |
| 6. | CI due to Stroke | Not Present | Yes | Not Present |
| 7. | Depression | Not Present | Yes | Not Present |

Cog. Impairment: Three Mem. Impairment: Definite; Pcpnt. evaluated: Yes

<<<< Hit ENTER to go to comment screen >>>>

For Dementia: the algorithmic diagnosis is Possible

Do you agree with it?

IF TWO COGNITIVE DOMAINS ARE IMPAIRED AND YOUR DIAGNOSIS DIFFERS FROM THE NEUROPSYCHOLOGISTS DIAGNOSIS, PRESS CTRL F4 [COMMENT BOX] AND SPECIFY WHY YOUR DIAGNOSIS IS DIFFERENT.

For Dementia, please enter your own diagnosis.

- ○ 1. Yes
- ◉ 2. No

For DEMENTIA:

The Algorithmic Diagnosis is: Possible
Doctor's Diagnosis is: Probable

PLEASE specify why your diagnosis is different.

- ○ 1. Highly Probable
- ◉ 2. Probable
- ○ 3. Possible
- ○ 4. Not Present

SUMMARY OF ALL ALGORITHMIC DIAGNOSES FOR: 22865387 Eval. Date: 12/18/2006

| | Disease | Algorithmic Dx | Doc Agreed? | Doc's Dx |
|---|---|---|---|---|
| 1. | Dementia | Possible | No | Probable |
| 2. | Alzheimers Disease | Possible | No | Probable |
| 3. | Parkinsonism | No | Possible | |
| 4. | Parkinson's Disease | No | Possible | |
| 5. | Stroke | No | Not Present | |
| 6. | CI due to Stroke | Possible | No | Not Present |
| 7. | Depression | Not Present | Yes | Not Present |

Cog. Impairment: Two; Mem. Impairment: Definite; Pcpnt. evaluated: Yes

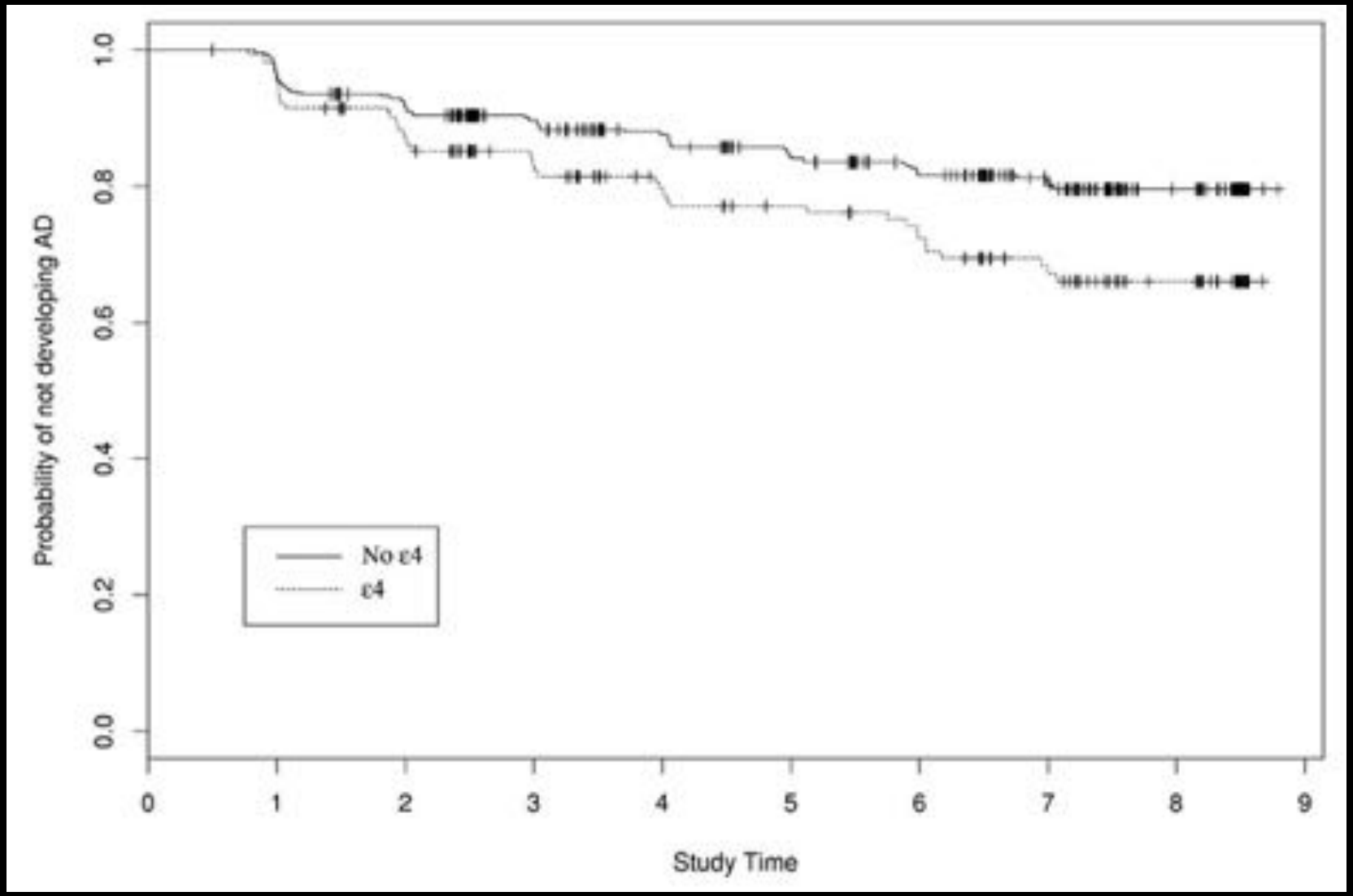
<<<< Hit ENTER to go to comment screen >>>>

**Decision Rules Guiding the Clinical Diagnosis of Alzheimer's Disease in Two Community-Based Cohort Studies Compared to Standard Practice in a Clinic-Based Cohort Study**

| | RADC | ROS/MAP |
|---|---|---|
| N | 306 | 141 |
| CERAD | .94 | .92 |
| NIA-Reagan | .94 | .91 |

Bennett DA, et al. *Neuroepidemiology* 2006;27:169-76.

# The Apolipoprotein E ε4 Allele and Decline in Different Cognitive Systems During a 6-Year Period



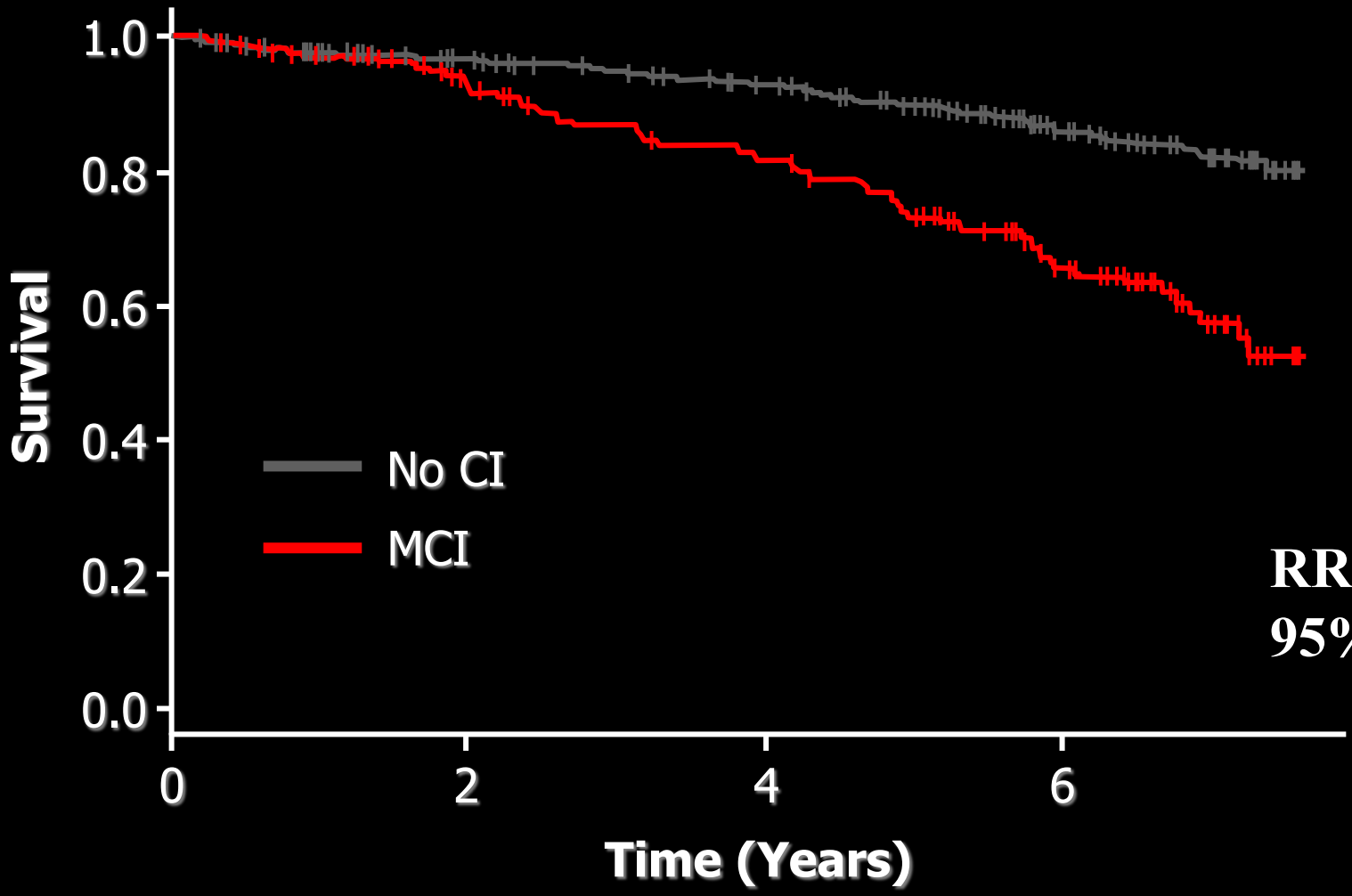

Wilson RS, et al. *Arch Neurol* 2002;59:1154-1160.

# Natural history of mild cognitive impairment in older persons

| Test | Mild cognitive impairment | No cognitive impairment |
|---|---|---|
| Logical Memory Ia | 9.6 (3.7) | 12.8 (3.6) |
| Logical Memory IIa | 7.2 (3.4) | 11.3 (3.9) |
| Immediate Story Recall | 9.2 (1.7) | 10.0 (1.7) |
| Delayed Story Recall | 8.5 (2.2) | 9.7 (1.7) |
| Word List Memory | 15.4 (4.1) | 18.9 (3.6) |
| Word List Recall | 4.1 (2.2) | 6.3 (1.7) |
| Word List Recognition | 9.9 (0.7) | 9.2 (1.4) |
| Boston Naming Test | 16.9 (2.3) | 18.5 (1.7) |
| Verbal Fluency | 29.7 (7.8) | 36.7 (8.9) |
| Extended Range Vocabulary | 9.7 (3.5) | 11.2 (3.2) |
| Reading Test | 12.3 (4.2) | 14.0 (4.0) |
| Digits Forward | 7.7 (1.8) | 8.4 (2.0) |
| Digits Backward | 5.6 (1.9) | 6.6 (2.0) |
| Digit Ordering | 5.9 (2.8) | 7.3 (2.6) |
| Alpha Span | 4.4 (1.6) | 5.2 (1.7) |
| Symbol Digit Modalities | 34.0 (10.6) | 42.1 (10.0) |
| Number Comparison | 22.5 (6.4) | 26.4 (7.2) |
| Line Orientation | 8.3 (3.3) | 10.6 (2.9) |
| Progressive Matrices | 7.8 (2.8) | 11.2 (3.1) |

Bennett DA, et al. *Neurology.* 2000;59:198-205.

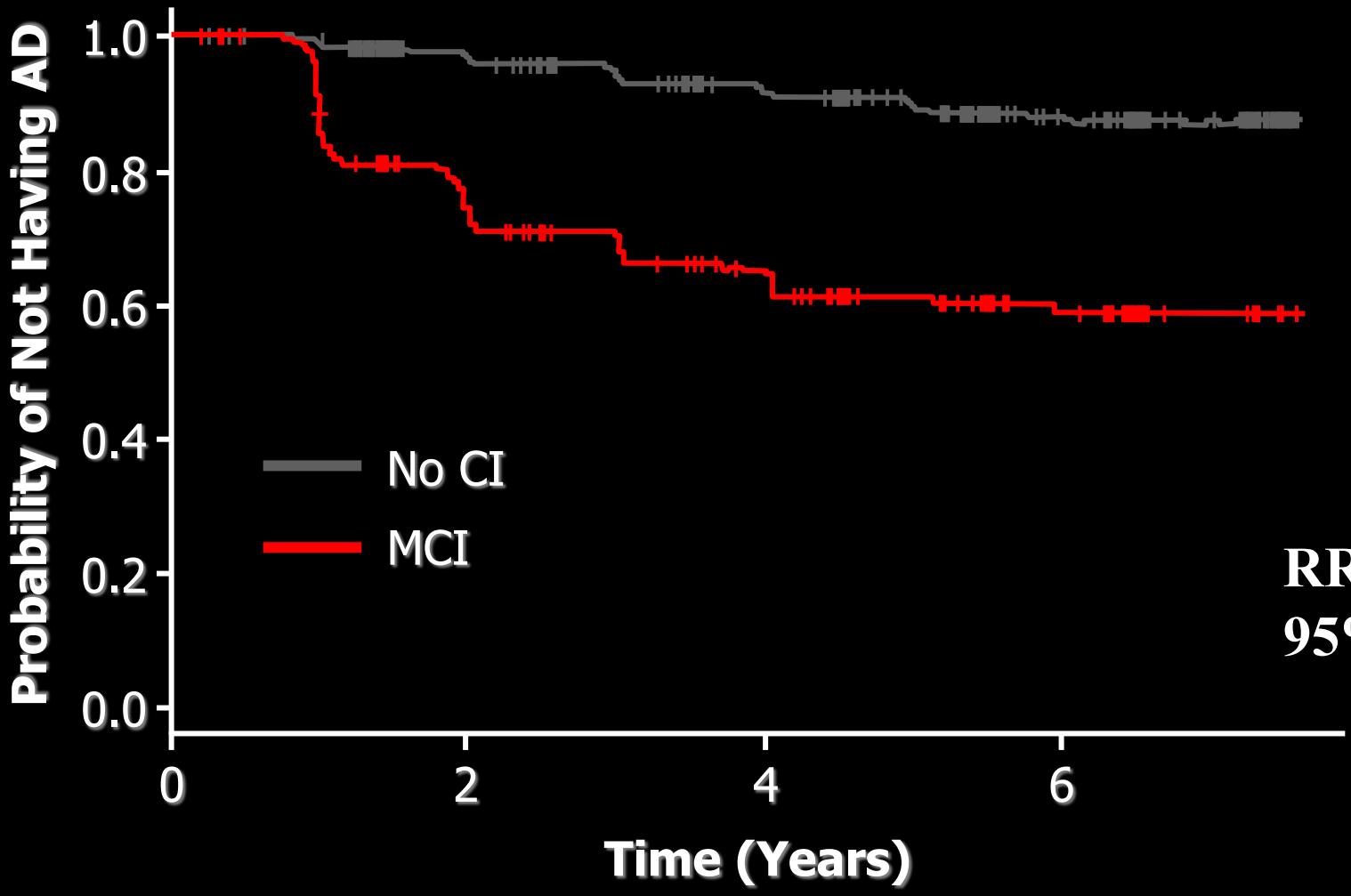
# Natural history of mild cognitive impairment in older persons




**RR: 1.7**
**95% CI: 1.2-2.5**

Bennett DA, et al. *Neurology.* 2002;59:198-205.

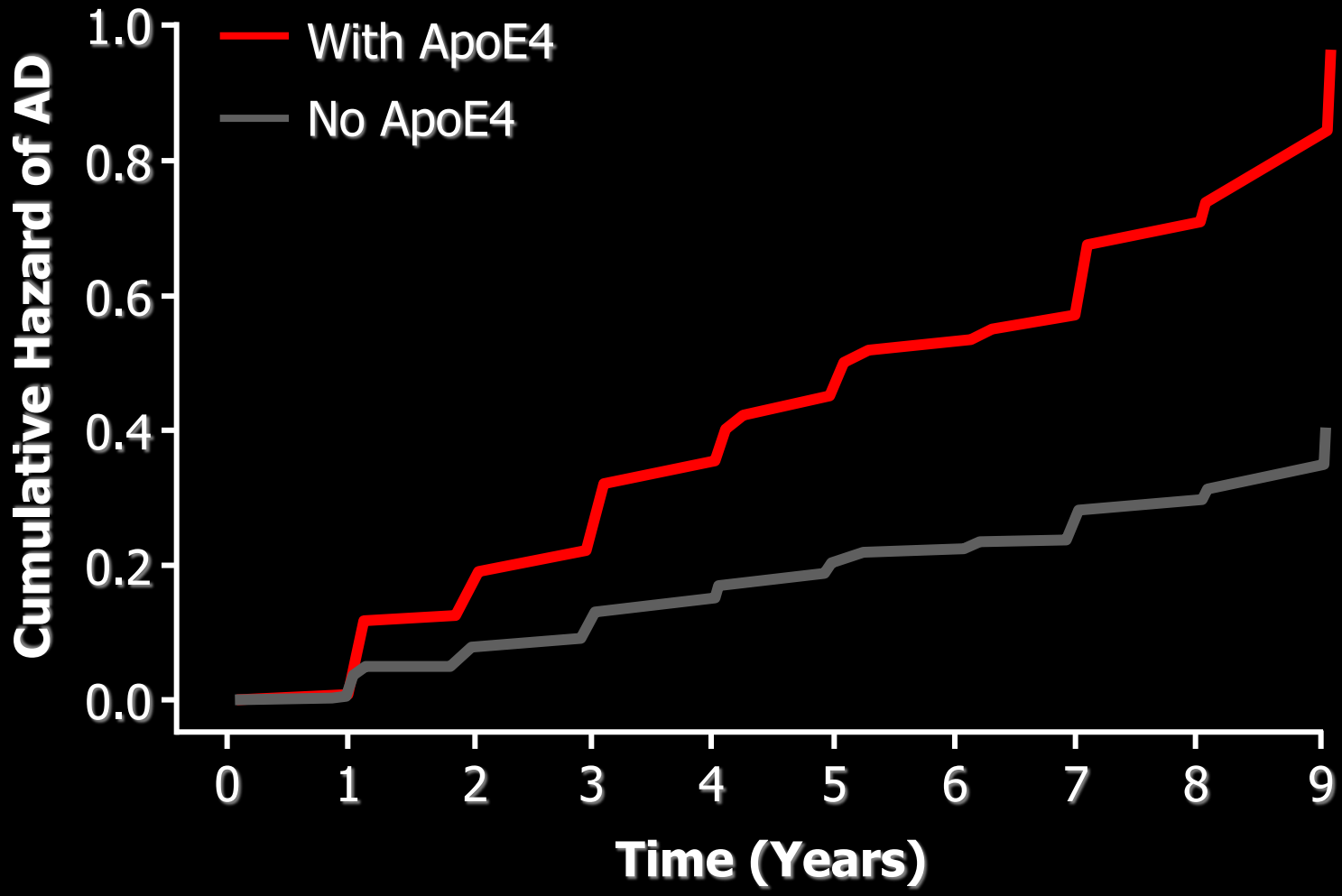
# Natural history of mild cognitive impairment in older persons




**RR: 3.1**
**95% CI: 2.1-4.5**

Bennett DA, et al. *Neurology.* 2002;59:198-205.

# The apolipoprotein E ε4 allele and incident Alzheimer's disease in person's with mild cognitive impairment




**RR: 1.62**
**95% CI: 1.02-2.63**

Aggarwal NT, et al. *Neurocase*. 2005;11:3-7.

# Individual Differences in Rates of Change in Cognitive Abilities of Older Persons

| Test | *M* | *SD* | Hypothesized cognitive domain[a] | | Factor loading[b] | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Grouping 1 | Grouping 2 | 1 | 2 | 3 | 4 | 5 |
| Logical Memory Ia | 11.8 | 3.9 | Episodic memory | Story retention | **.52** | .06 | .06 | .39 | .46 |
| Logical Memory IIa | 10.0 | 4.2 | Episodic memory | Story retention | **.62** | .11 | .09 | .34 | .42 |
| Immediate story recall | 9.8 | 1.7 | Episodic memory | Story retention | .11 | .14 | .11 | .07 | **.87** |
| Delayed story recall | 9.4 | 1.9 | Episodic memory | Story retention | .21 | .13 | .15 | .00 | **.84** |
| Word List Memory | 17.7 | 4.1 | Episodic memory | Word retention | **.76** | .26 | .24 | .04 | .03 |
| Word List Recall | 5.6 | 2.1 | Episodic memory | Word retention | **.82** | .13 | .12 | .06 | .10 |
| Word List Recognition | 9.6 | 1.0 | Episodic memory | Word retention | **.69** | .00 | −.01 | −.08 | .11 |
| Boston Naming Test | 18.1 | 2.0 | Semantic memory | Word generation | .23 | .38 | .10 | .47 | .09 |
| Verbal Fluency | 35.0 | 9.1 | Semantic memory | Word generation | .45 | .41 | .27 | .09 | .11 |
| Extended Range Vocabulary Test | 10.9 | 3.3 | Semantic memory | Word knowledge | .04 | .13 | .24 | **.82** | .07 |
| Reading test | 13.6 | 4.1 | Semantic memory | Word knowledge | .00 | .09 | .26 | **.81** | .04 |
| Digit Span Forward | 8.2 | 1.9 | Working memory | Working memory | .02 | .05 | **.78** | .18 | .10 |
| Digit Span Backward | 6.3 | 2.0 | Working memory | Working memory | .06 | .11 | **.75** | .19 | .12 |
| Digit ordering | 7.7 | 1.7 | Working memory | Working memory | .15 | .41 | **.50** | .15 | .10 |
| Alpha span | 5.0 | 1.7 | Working memory | Working memory | .27 | .23 | **.70** | .13 | .04 |
| Symbol Digit Modalities Test | 39.5 | 10.8 | Perceptual speed | Perceptual speed | .25 | **.79** | .19 | −.01 | .12 |
| Number Comparison | 25.2 | 7.1 | Perceptual speed | Perceptual speed | .07 | **.77** | .13 | .00 | .10 |
| Judgment of Line Orientation | 9.9 | 3.2 | Visuospatial ability | Visuospatial ability | −.09 | .48 | .03 | .30 | .08 |
| Standard Progressive Matrices | 10.3 | 3.4 | Visuospatial ability | Visuospatial ability | .22 | **.62** | .13 | .31 | .03 |

Wilson RS, et al. *Psych & Aging* 2002;17:179-193.

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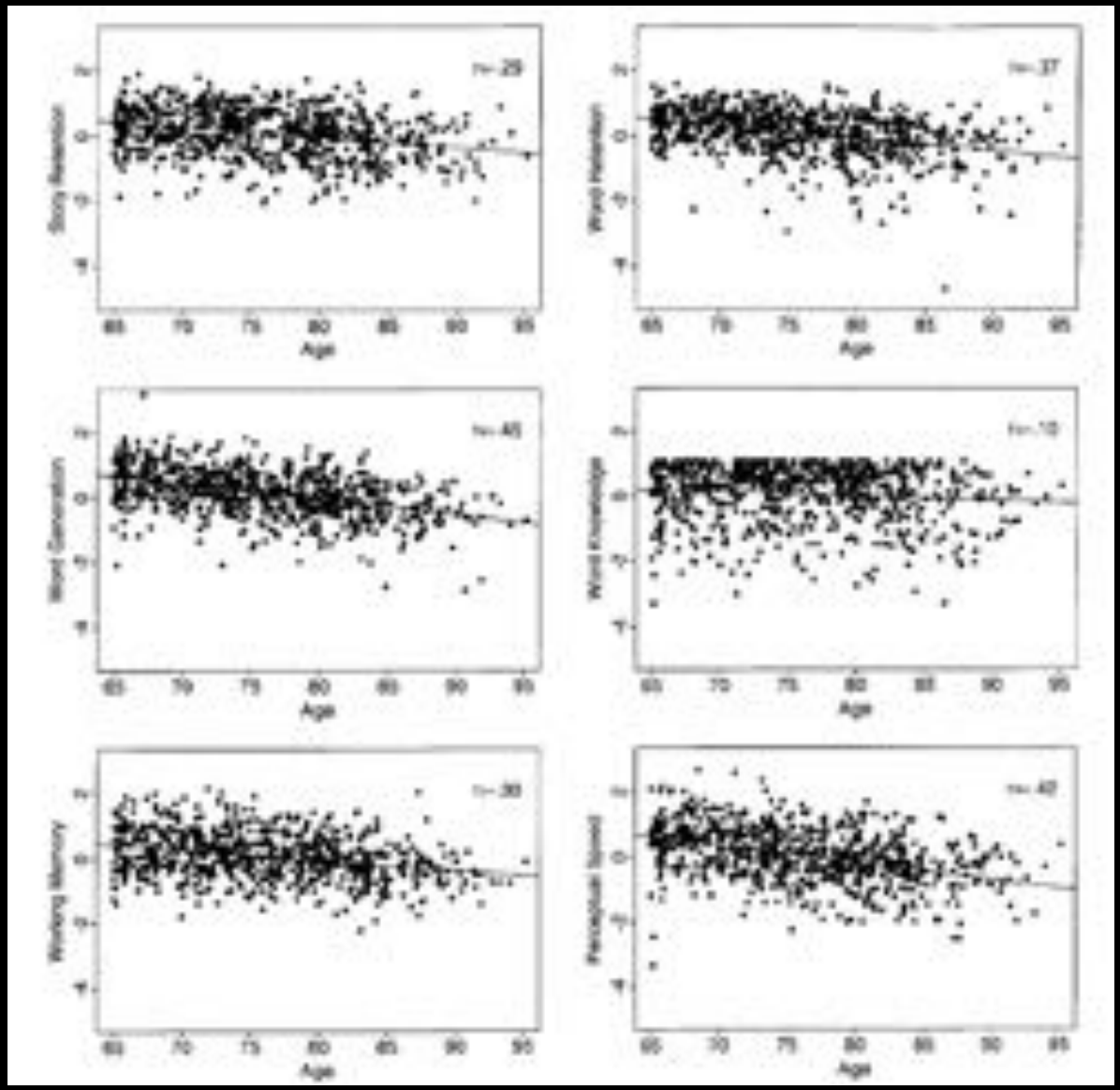

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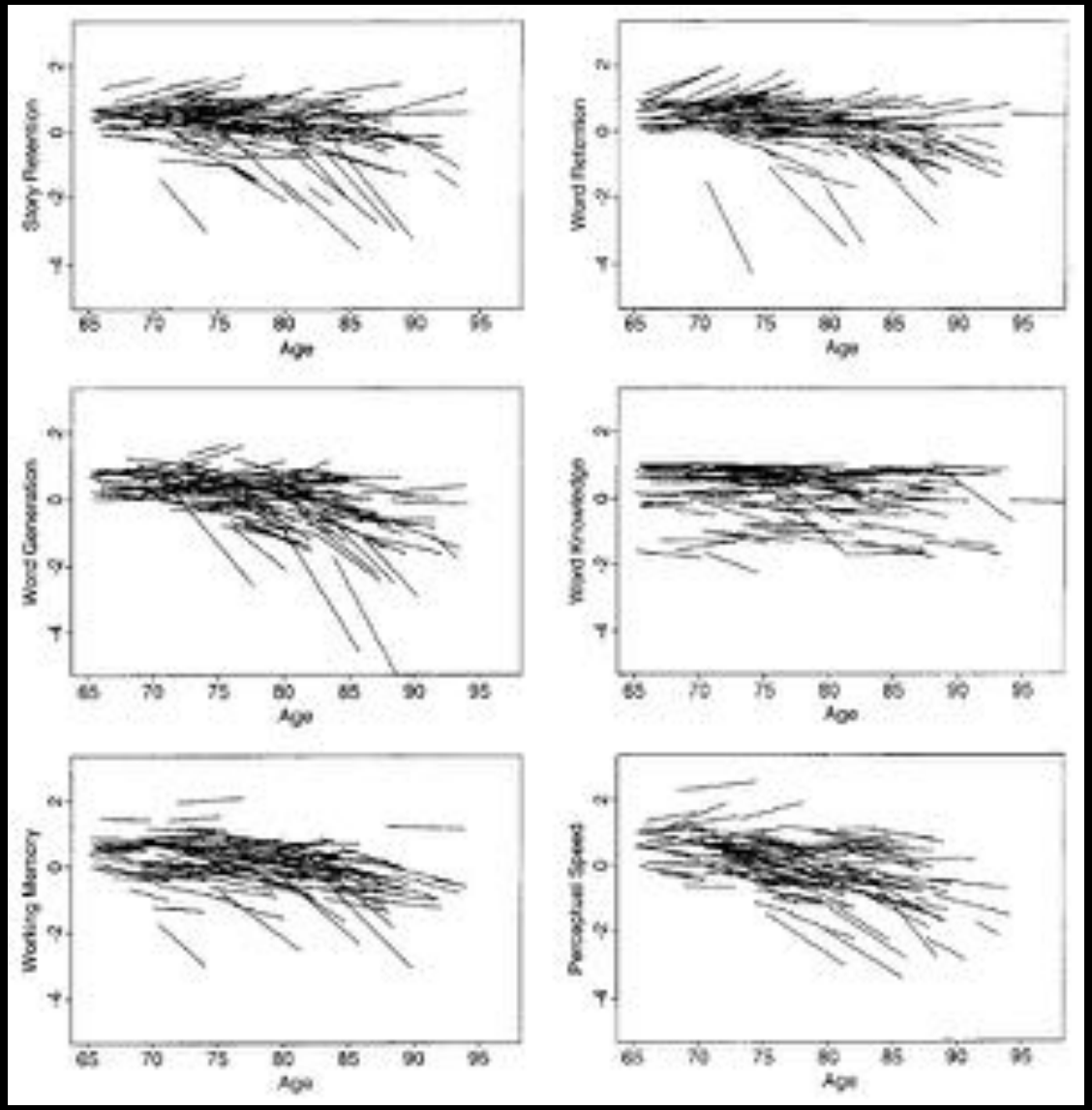


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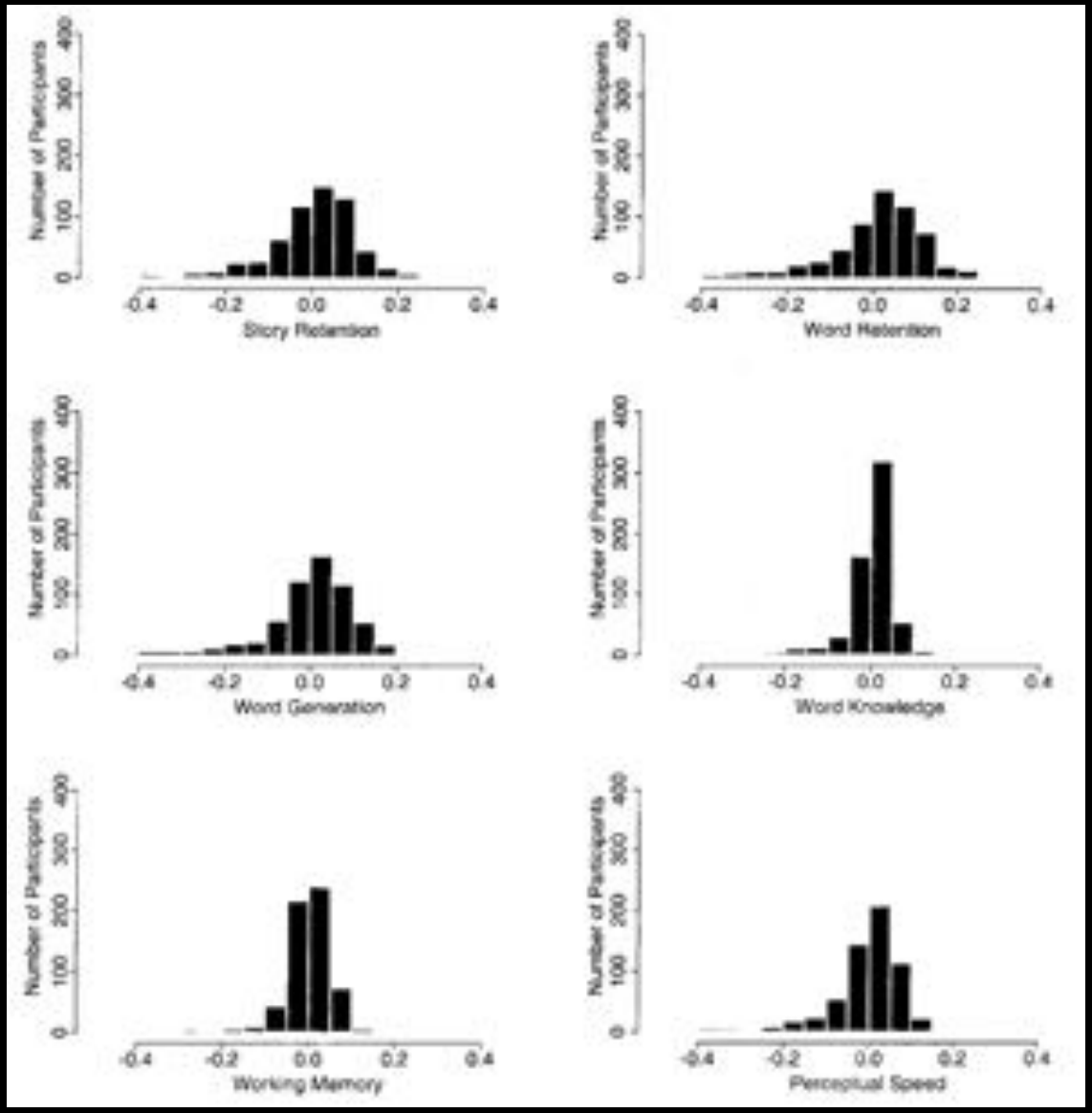


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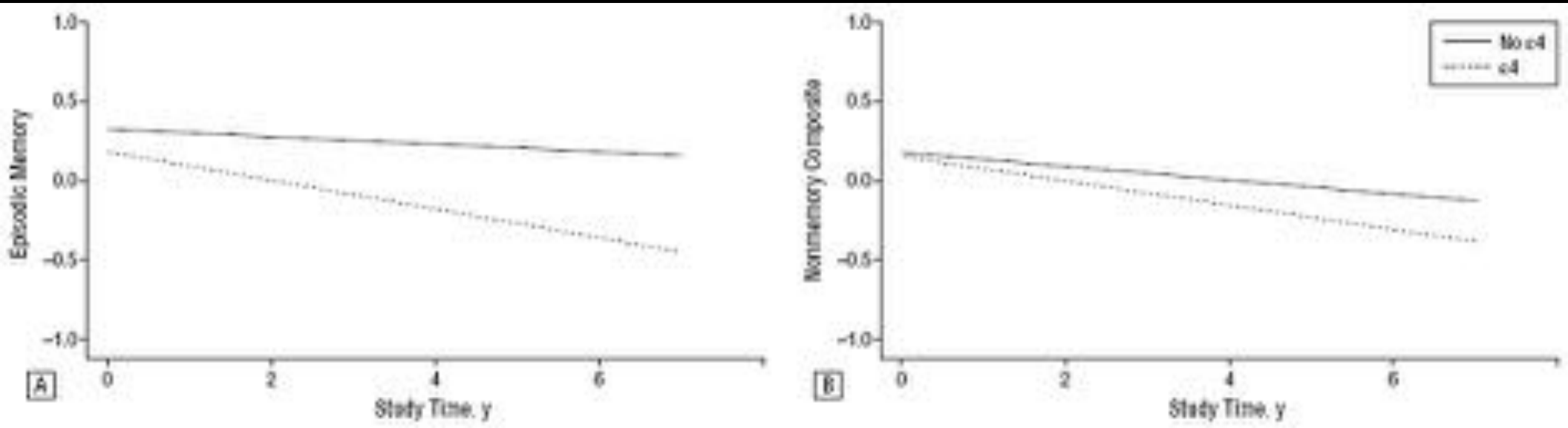
# The Apolipoprotein E ϵ4 Allele and Decline in Different Cognitive Systems During a 6-Year Period

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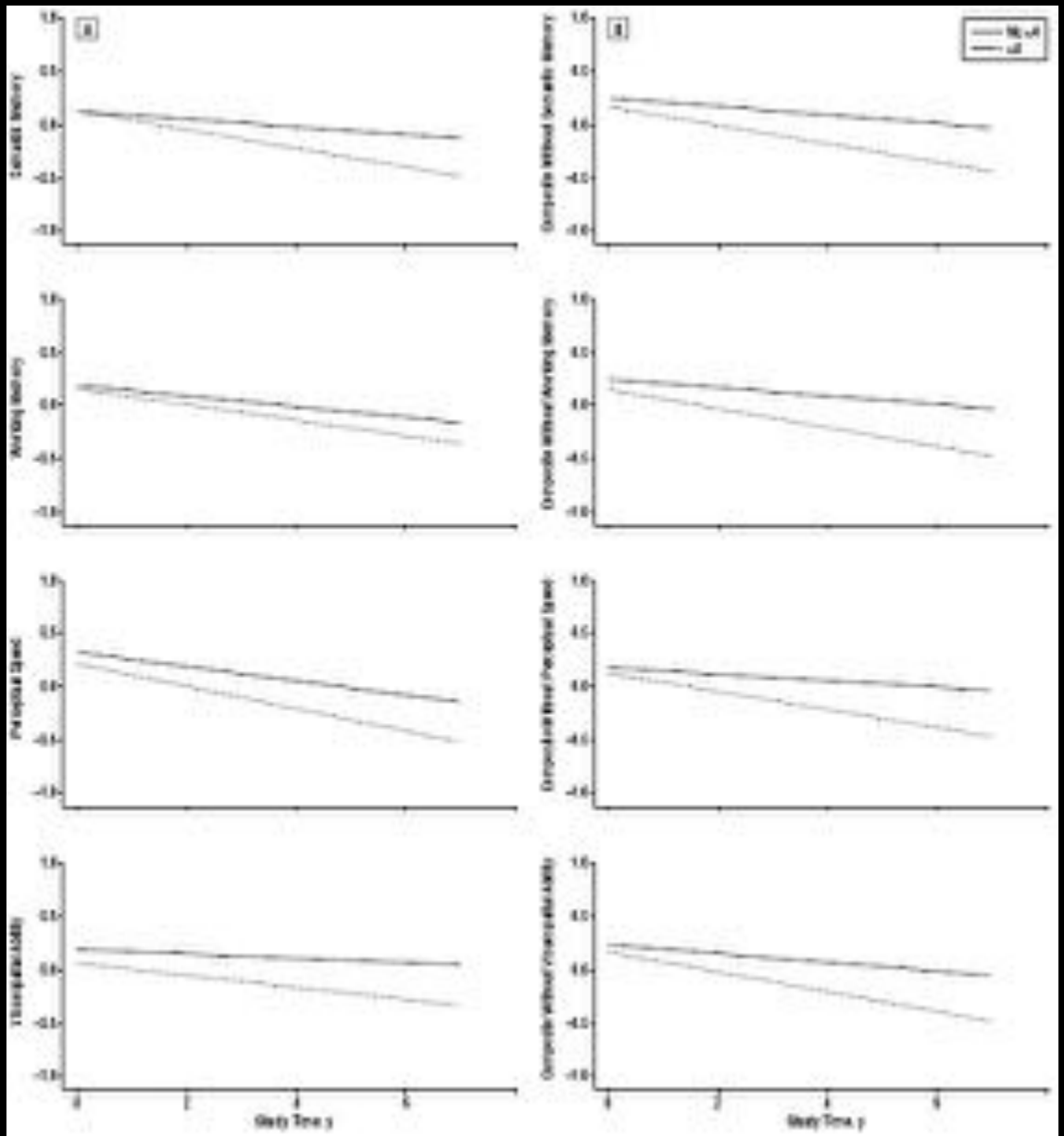
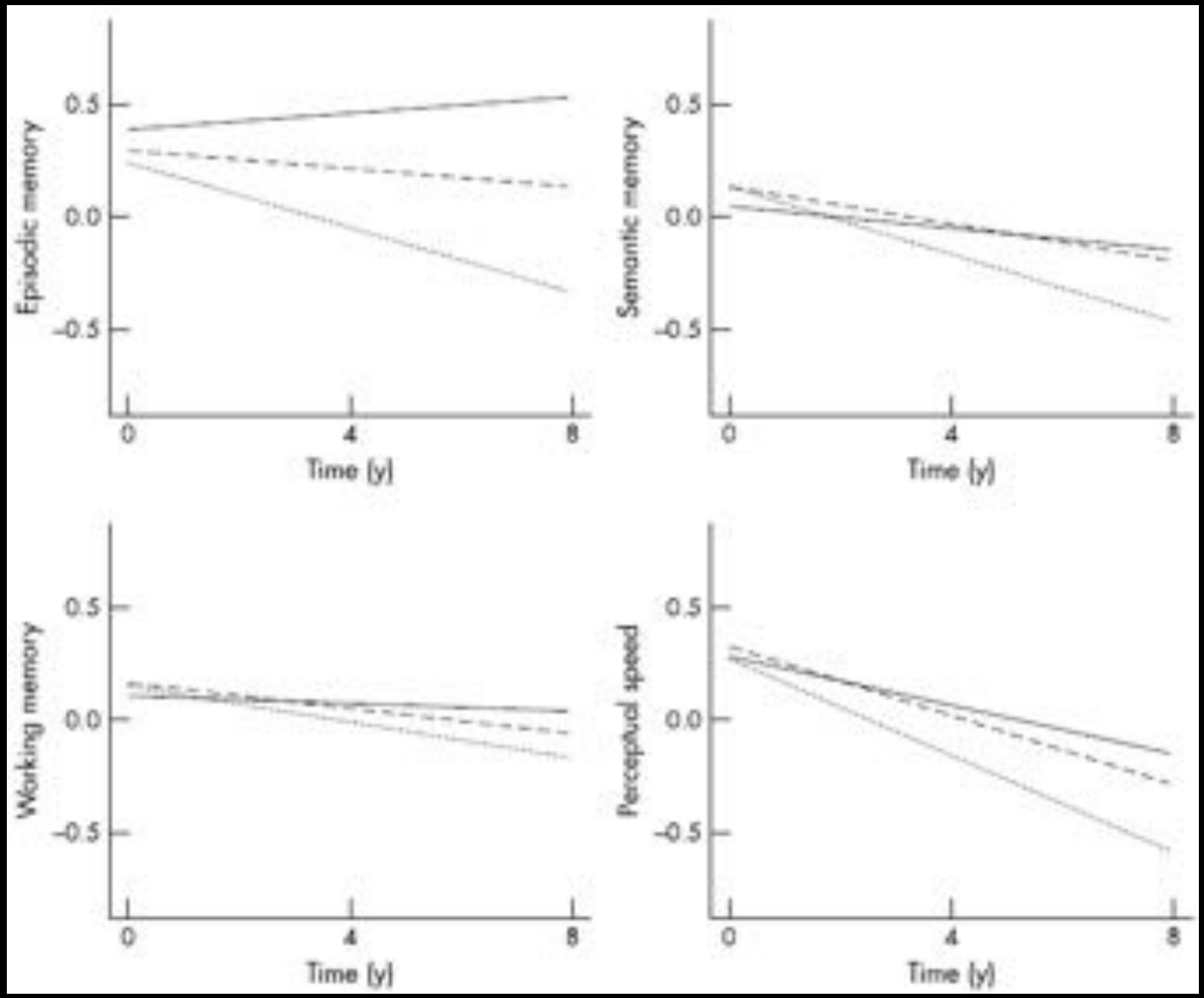


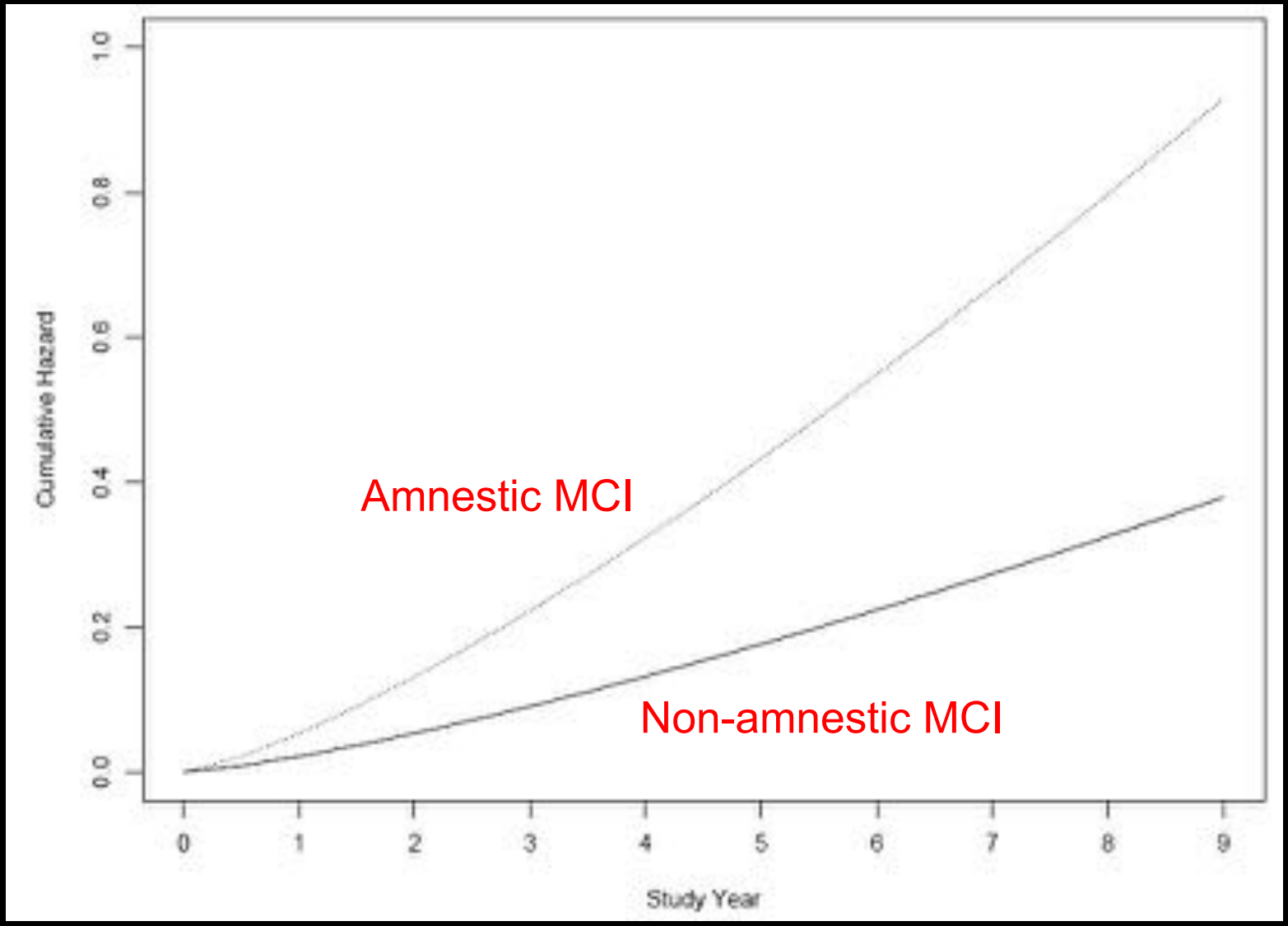
Wilson RS, et al. *Arch Neurol* 2002;59:1154-1160.

# The apolipoprotein E ϵ2 allele and decline in episodic memory




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

# Mild cognitive impairment in different functional domains and incident Alzheimer's disease




Aggarwal NT, et al. *JNNP* 2005;76;1479-1484.

# Assessment of Cognitive Decline in Old Age with Brief Tests Amenable to Telephone Administration

| Test | No dementia (mean ± SD) | Dementia (mean ± SD) | Hypothesized cognitive domain |
|---|---|---|---|
| Immediate story | 9.7 ± 1.8 | 7.1 ± 2.5 | episodic memory |
| Delayed story | 9.3 ± 2.0 | 5.3 ± 3.3 | episodic memory |
| Animal fluency | 17.4 ± 5.2 | 10.9 ± 4.0 | semantic memory |
| Fruit/veg. fluency | 17.4 ± 4.9 | 11.0 ± 4.7 | semantic memory |
| Digits Forward | 8.3 ± 2.0 | 6.7 ± 2.2 | working memory |
| Digits Backward | 6.3 ± 2.0 | 4.4 ± 1.9 | working memory |
| Digit Ordering | 7.0 ± 2.6 | 4.4 ± 3.1 | working memory |

| Model term | d.f. | Mean square | F value | p value |
|---|---|---|---|---|
| Group | 1, 82 | 0.13 | 0.09 | 0.761 |
| Test occasion | 2, 164 | 0.08 | 0.69 | 0.496 |
| Group × test occasion | 2, 164 | 0.03 | 0.24 | 0.774 |

Wilson RS, et al. *Neuroepi* 2005;25:19-25.

# Assessment of Cognitive Decline in Old Age with Brief Tests Amenable to Telephone Administration

| Outcome measure | Model term | Estimate | SE | p value |
|---|---|---|---|---|
| Episodic memory | time | –0.073 | 0.011 | <0.001 |
| | APOE ε4 | –0.063 | 0.061 | 0.303 |
| | APOE ε4 × time | –0.078 | 0.018 | <0.001 |
| Semantic memory | time | –0.069 | 0.007 | <0.001 |
| | APOE ε4 | –0.073 | 0.063 | 0.243 |
| | APOE ε4 × time | –0.026 | 0.011 | 0.019 |
| Working memory | time | –0.018 | 0.005 | <0.001 |
| | APOE ε4 | –0.028 | 0.052 | 0.597 |
| | APOE ε4 × time | –0.021 | 0.008 | 0.008 |
| Global cognition | time | –0.044 | 0.006 | <0.001 |
| | APOE ε4 | –0.051 | 0.041 | 0.212 |
| | APOE ε4 × time | –0.036 | 0.009 | <0.001 |

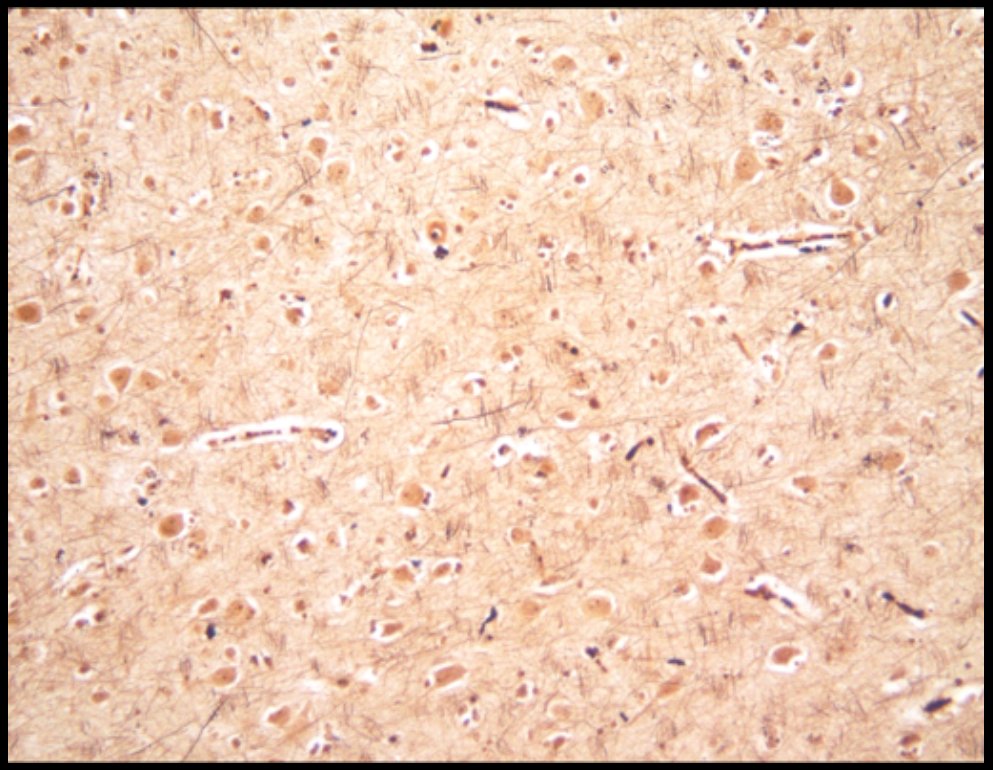
Data from mixed models adjusted for age, sex and education. SE = Standard error.

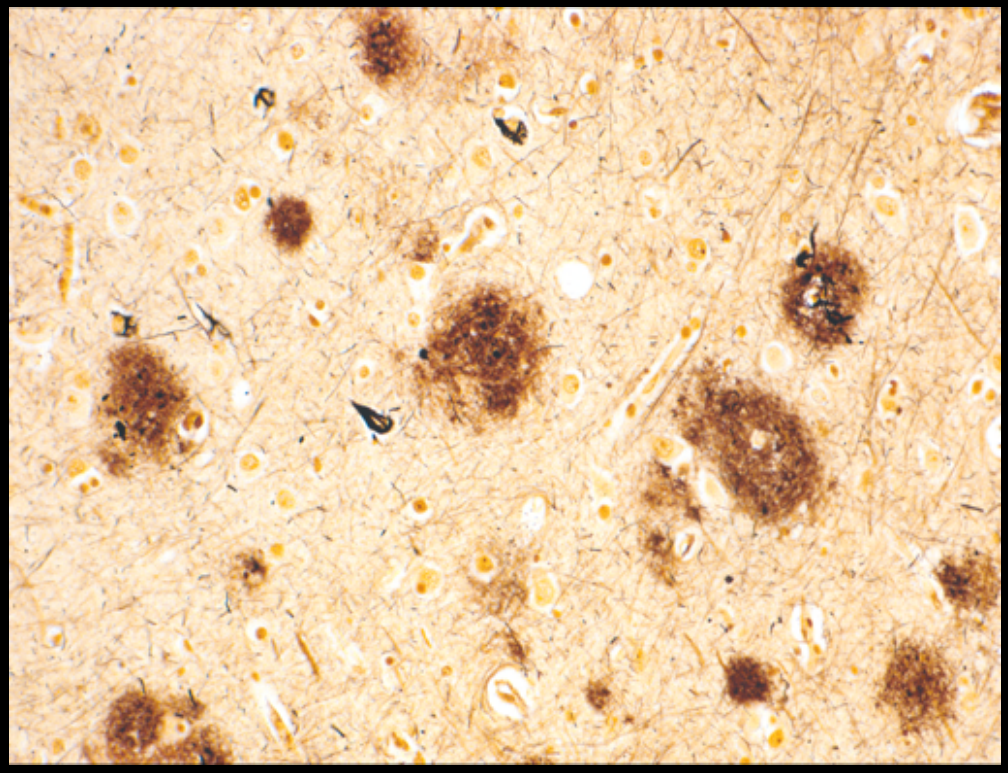
Wilson RS, et al. *Neuroepi* 2005;25:19-25.

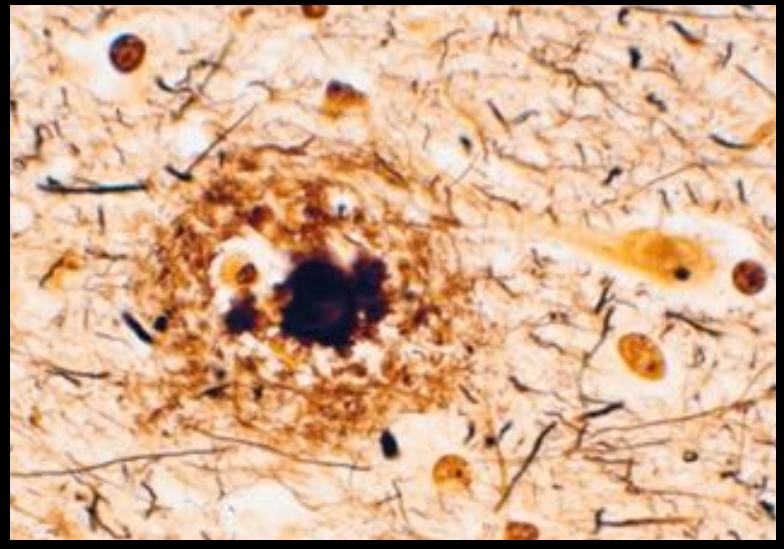

I specialize in theoretical math. My appointment is 50% research, 50% teaching and 25% administration.

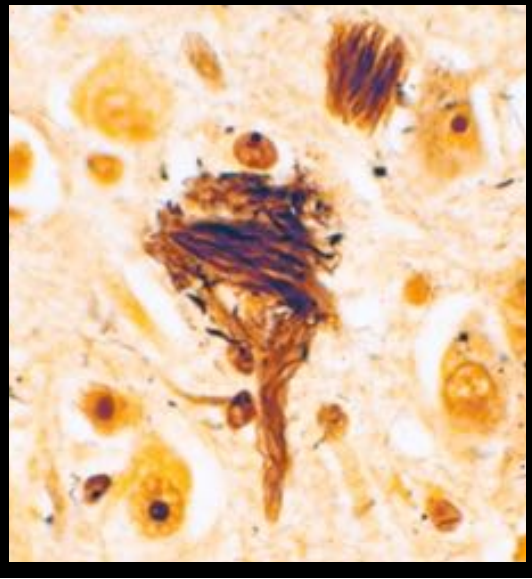
# Objectives:

- Review clinical data collection elements
  - Cognitive function tests
  - Clinical diagnoses
- Review post-mortem data collection elements
  - AD pathology
  - Cerebrovascular disease
  - Lewy body disease









# Apolipoprotein E ϵ4 allele, AD pathology, and the clinical expression of Alzheimer's disease

*Table 1 Mean, SD, and range of the raw counts and of the standardized scores for each of the 12 pathologic indices*

| | Raw data | | | Standardized score | | |
|---|---|---|---|---|---|---|
| Variable | Mean | SD | Range | Mean | SD | Range |
| Frontal neuritic plaques | 9.55 | 11.47 | 0–81 | 0.86 | 1.03 | 0–7.27 |
| Temporal neuritic plaques | 10.03 | 12.54 | 0–88 | 0.82 | 1.03 | 0–7.24 |
| Parietal neuritic plaques | 9.30 | 10.25 | 0–49 | 0.93 | 1.03 | 0–4.91 |
| Entorhinal neuritic plaques | 5.78 | 7.60 | 0–18 | 0.78 | 1.03 | 0–6.10 |
| Frontal diffuse plaques | 23.80 | 27.30 | 0–193 | 0.90 | 1.03 | 0–7.29 |
| Temporal diffuse plaques | 25.80 | 25.34 | 0–134 | 1.04 | 1.02 | 0–5.39 |
| Parietal diffuse plaques | 19.05 | 22.23 | 0–122 | 0.88 | 1.02 | 0–5.62 |
| Entorhinal diffuse plaques | 12.03 | 11.13 | 0–43 | 1.09 | 1.01 | 0–3.91 |
| Frontal neurofibrillary tangles | 1.94 | 4.57 | 0–28 | 0.44 | 1.04 | 0–6.38 |
| Temporal neurofibrillary tangles | 5.93 | 9.48 | 0–43 | 0.65 | 1.03 | 0–4.67 |
| Parietal neurofibrillary tangles | 2.47 | 5.22 | 0–34 | 0.49 | 1.04 | 0–6.78 |
| Entorhinal neurofibrillary tangles | 16.67 | 15.47 | 0–74 | 1.09 | 1.01 | 0–4.84 |

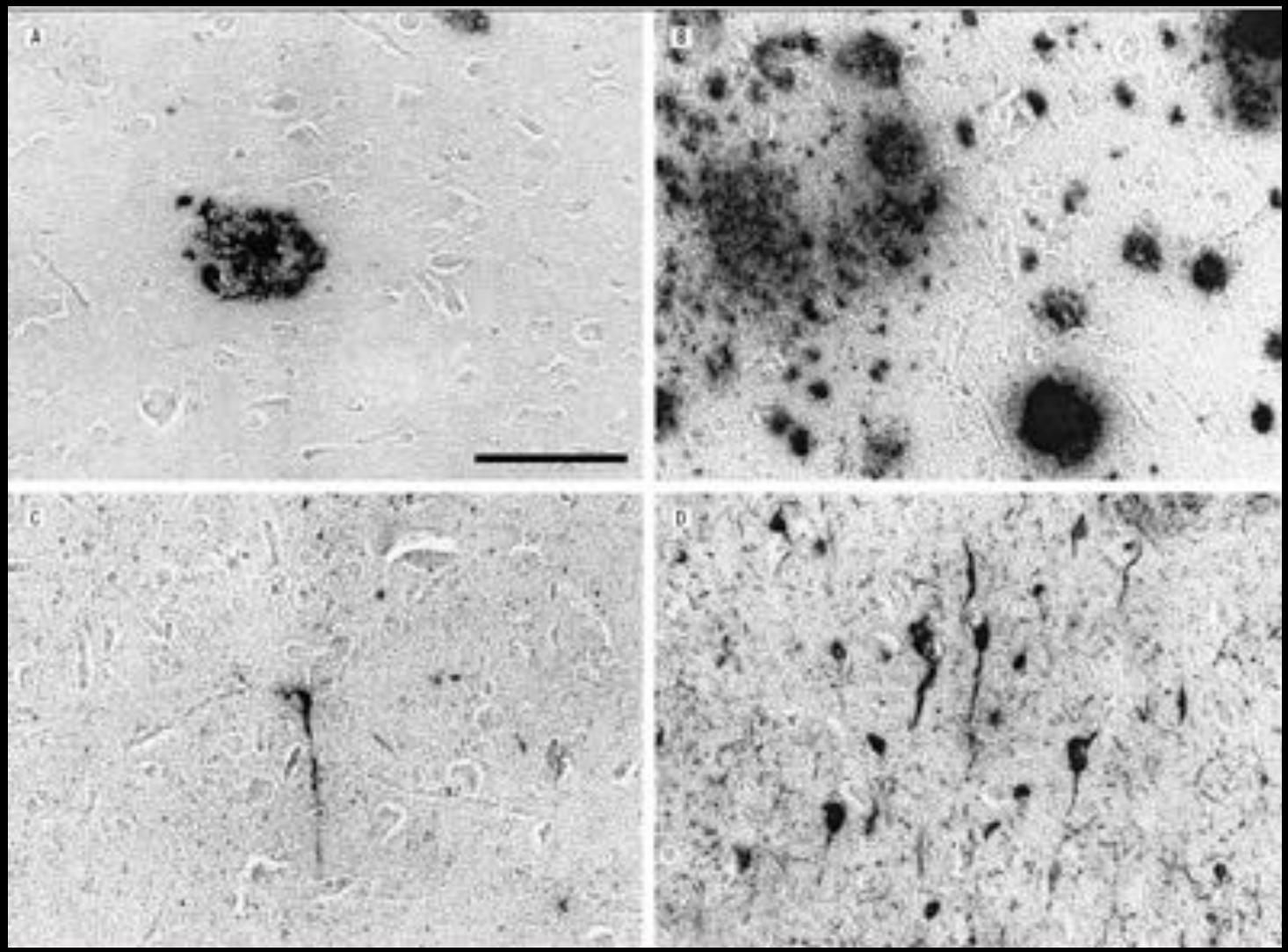
Bennett DA, et al. *Neurology* 2003;60:246-253

# Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions

| Characteristics | NCI | MCI | Dementia | Total |
|---|---|---|---|---|
| Demographic | | | | |
| n | 60 | 37 | 83 | 180 |
| Men, % | 50.0 | 40.5 | 44.6 | 45.6 |
| Mean age at death, y (SD) | 81.8 (6.6) | 85.0 (5.6) | 87.2 (6.2) | 84.9 (6.6) |
| Mean education, y (SD) | 18.7 (3.4) | 18.5 (4.1) | 17.4 (3.2) | 18.1 (3.5) |
| Mean MMSE (SD) | 28.2 (1.4) | 26.8 (2.1) | 16.8 (7.8) | 22.6 (7.7) |
| Global cognitive score (SD) | 0.08 (0.42) | −0.52 (0.41) | −1.79 (0.97) | −0.91 (1.11) |
| Interval, mo (SD) | 5.9 (3.5) | 7.2 (3.7) | 6.7 (3.6) | 6.5 (3.6) |
| Pathologic | | | | |
| AD pathology measure (SD) | 0.45 (0.40) | 0.67 (0.54) | 1.15 (0.72) | 0.82 (0.67) |
| Neuritic plaques (SD) | 0.44 (0.57) | 0.59 (0.60) | 1.28 (0.99) | 0.86 (0.88) |
| Diffuse plaques (SD) | 0.64 (0.69) | 0.91 (0.74) | 1.24 (0.90) | 0.97 (0.85) |
| Neurofibrillary tangles (SD) | 0.26 (0.27) | 0.50 (0.58) | 0.94 (0.99) | 0.62 (0.80) |
| Macroscopic infarctions, % | 22.0 | 32.4 | 45.8 | 35.2 |
| Lewy body disease, % | 11.7 | 8.1 | 21.7 | 15.6 |

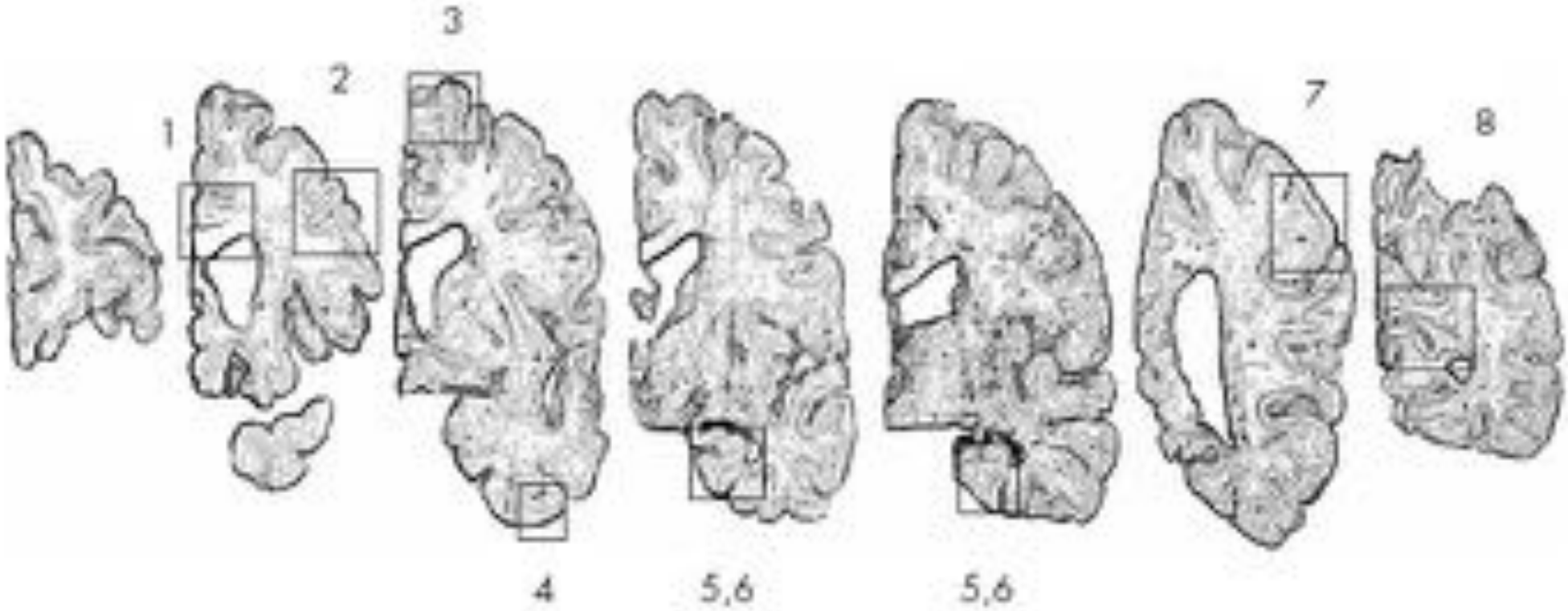
Bennett DA, et al. *Neurology* 2005;64:834-842.

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




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

# The relationship between cerebral Alzheimer's disease pathology and odour identification in old age



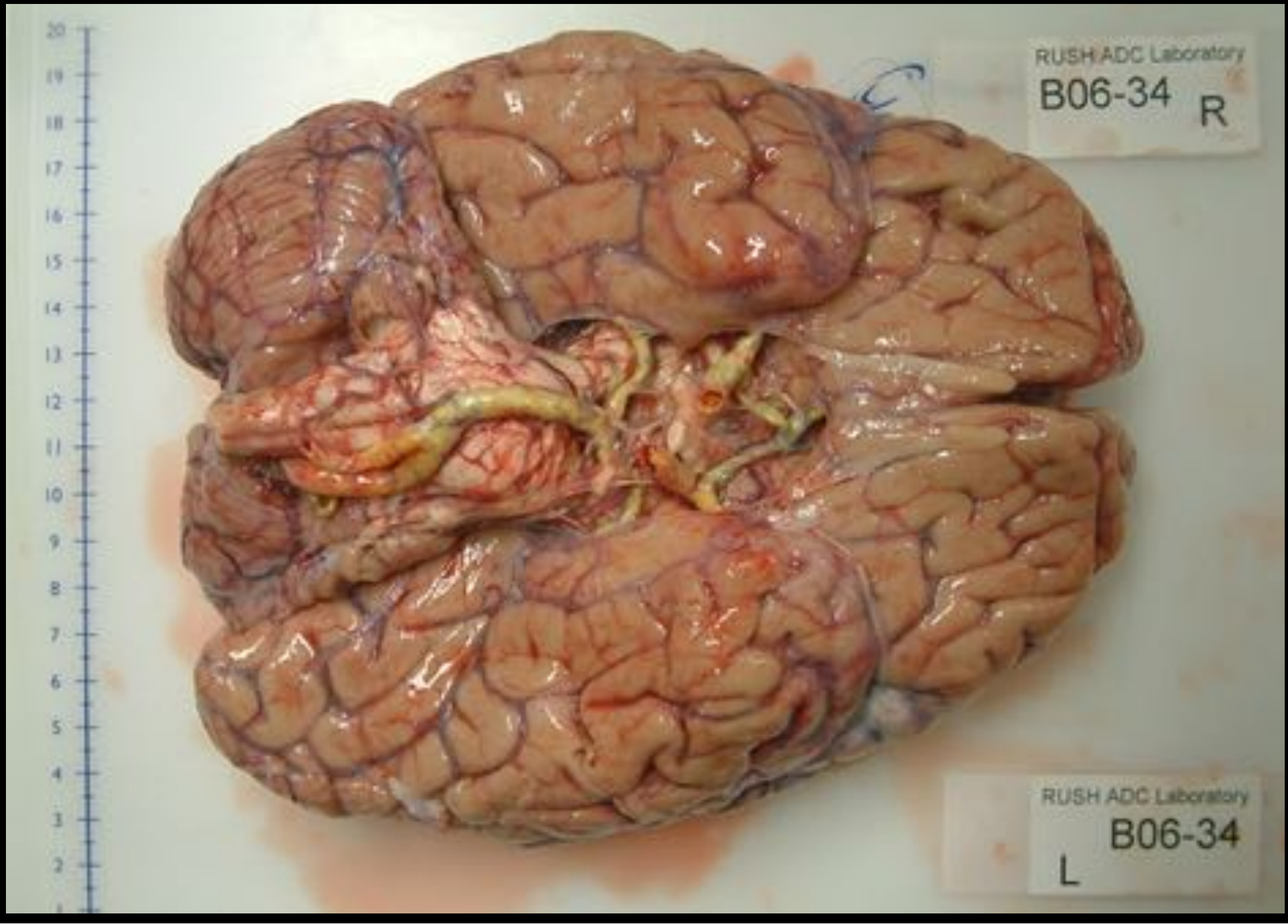

(1) anterior cingulate cortex (Brodmann area (BA) 24)
(2) dorsal lateral prefrontal cortex (BA 46/9)
(3) superior frontal cortex (BA 6/8)
(4) inferior temporal cortex (BA 20)
(5) hippocampus (CA1/subiculum)
(6) entorhinal cortex proper (BA 28)
(7) angular/supramarginal gyrus (BA 39/40)
(8) primary visual cortex (BA 17)

Wilson RS, et al. *JNNP* 2007;78:30-35.

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

| Characteristic | No Dementia (n = 53) | Alzheimer Disease (n = 44) | Total (N = 97) |
|---|---|---|---|
| Male, No. (%) | 24 (45.3) | 17 (38.6) | 41 (42.3) |
| Age at death, y | 82.4 ± 6.5 | 88.1 ± 5.3 | 85.0 ± 6.6 |
| Education, y | 18.7 ± 3.3 | 17.3 ± 3.0 | 18.1 ± 3.2 |
| MMSE score | 27.66 ± 1.89 | 16.07 ± 7.38 | 22.4 ± 7.75 |
| Global cognition | −0.07 ± 0.53 | −1.82 ± 0.83 | −0.87 ± 1.11 |
| Median interval, mo | 8.0 | 8.6 | 8.2 |
| Amyloid load, % | 1.83 ± 1.84 | 3.81 ± 2.47 | 2.73 ± 2.35 |
| Tangles/mm$^2$ | 3.51 ± 3.64 | 14.22 ± 12.38 | 8.37 ± 10.23 |

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


RUSH ADC Laboratory
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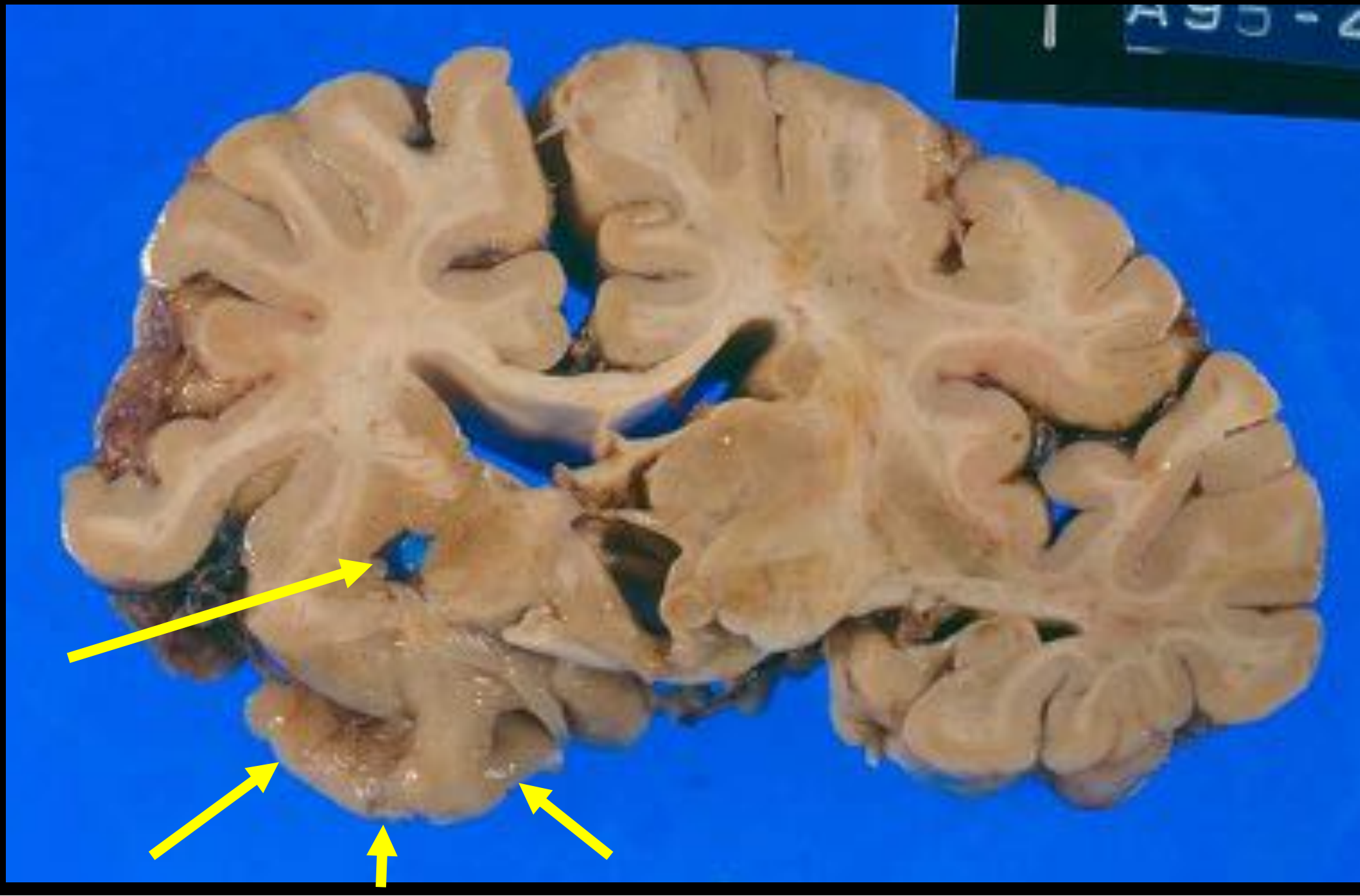
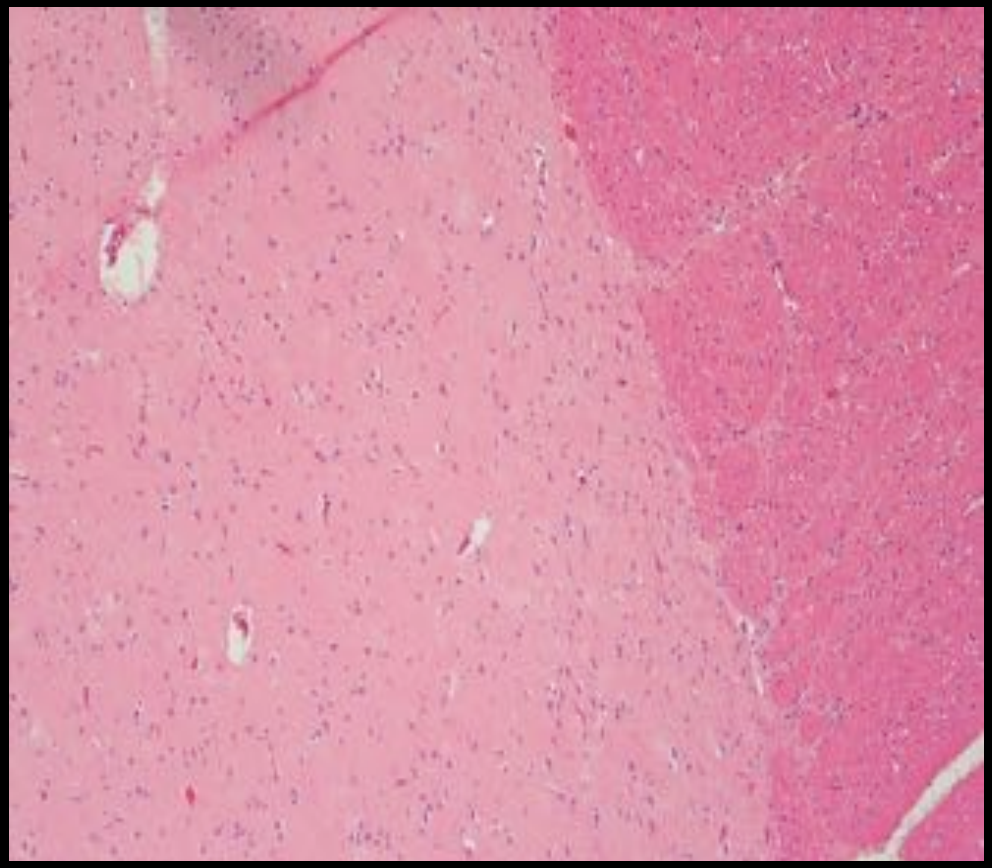
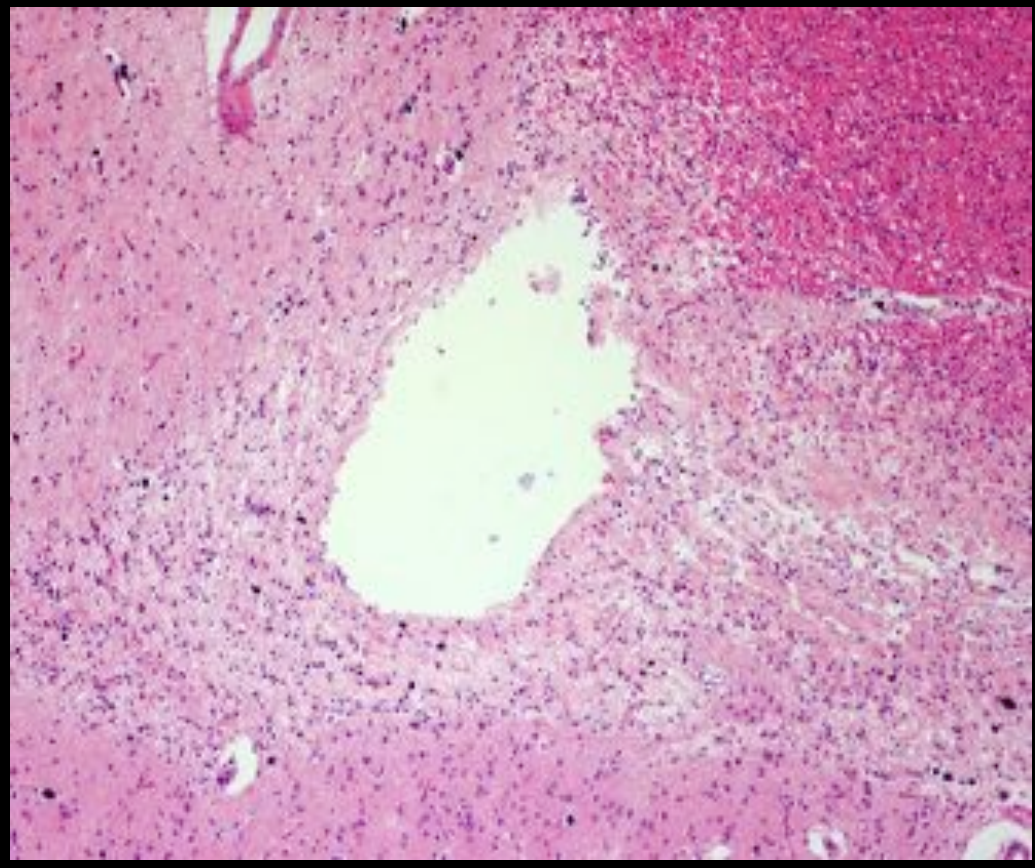




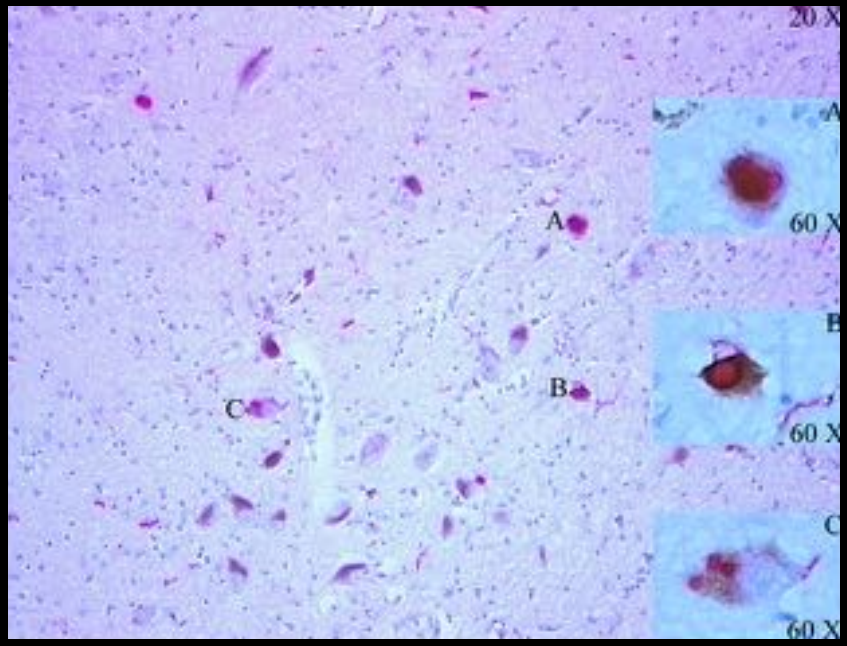


# Cerebral Infarctions and the Relationship of Depression Symptoms to Level of Cognitive Functioning in Older Persons

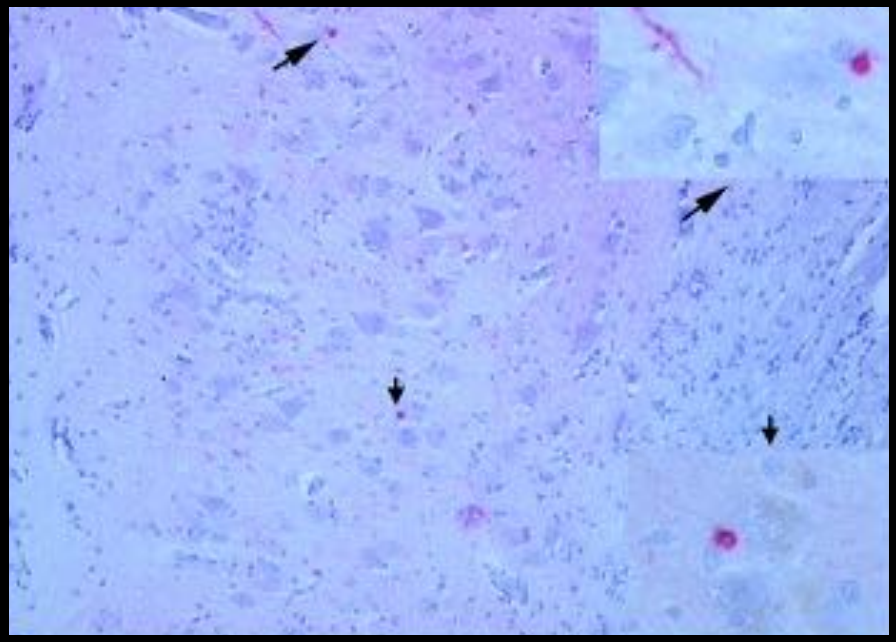
| | | | |
|---|---|---|---|
| Global AD pathology measure | 0.55 (0.48) | 1.15 (0.77) | 0.82 (0.69) |
| Number of infarctions, % | | | |
| 1 | 13 (15.1) | 13 (19.4) | 26 (17.0) |
| >1 | 10 (11.6) | 19 (28.4) | 29 (19.0) |
| Volume of infarction, % | | | |
| 1st quartile | 7 (8.1) | 5 (7.5) | 12 (7.8) |
| 2nd quartile | 5 (5.8) | 10 (14.9) | 15 (9.8) |
| 3rd quartile | 5 (5.8) | 8 (11.9) | 13 (8.5) |
| 4th quartile | 6 (7.0) | 9 (13.4) | 15 (9.8) |
| Location of infarction, % | | | |
| Cortical | 7 (8.1) | 10 (14.9) | 17 (11.1) |
| Subcortical | 19 (22.1) | 28 (41.8) | 47 (30.7) |
| Frontal | 5 (5.8) | 6 (9.0) | 11 (7.2) |
| Non-frontal | 18 (20.9) | 26 (38.8) | 44 (28.8) |
| Left | 12 (14.0) | 18 (26.9) | 30 (19.6) |
| Right | 16 (18.6) | 21 (31.3) | 37 (24.2) |

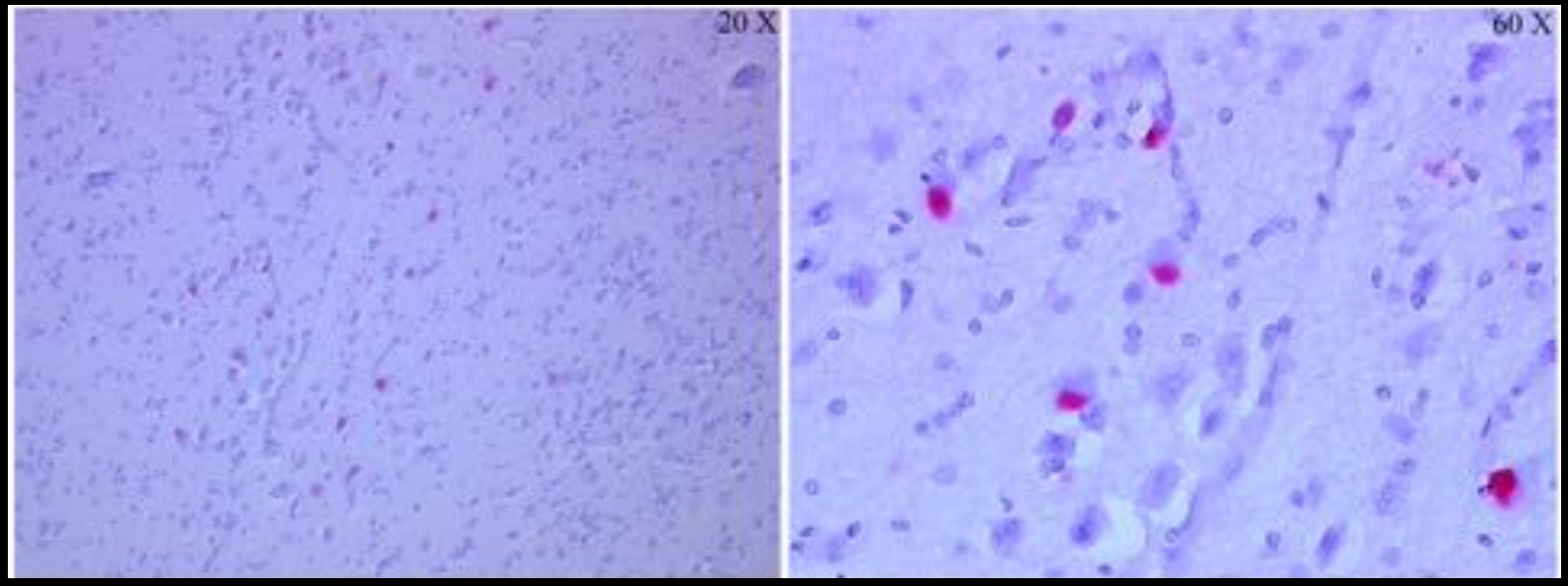
Bennett DA, et al. *Am J Geri Psych* 2004;12:211-219.

Alpha-Synuclein in substantia nigra




Alpha-Synuclein in hippocampus






Alpha-Synuclein in neocortex

# Mild cognitive impairment is related to Alzheimer disease pathology and cerebral infarctions

| Characteristics | NCI | MCI | Dementia |
|---|---|---|---|
| Lewy body disease | | | |
| Nigra predominant | 5 (8.3) | 2 (5.4) | 1 (1.2) |
| Limbic type | 2 (3.3) | 0 | 3 (3.6) |
| Neocortical type | 0 | 1 (2.7) | 14 (16.9) |

Bennett DA, et al. *Neurology* 2005;64:834-842.