LE MALATTIE DI ALZHEIMER

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Clinica Neurologica, Università Tor Vergata, Roma
Fondazione I.R.C.C.S. S. Lucia, Roma

NEUROLOGICAL PROGRESS

Toward a Molecular Neuropsychiatry of Neurodegenerative Diseases

Jeffrey L. Cummings, MD

Annals of Neurology, 54, 147-154, 2003

…The molecular biology of neurodegenerative diseases is linked to the behavioral phenotype through selective regional vulnerability of cell populations. Cells exhibit differential vulnerability to abnormalities of protein metabolism resulting in protein-specific regional dysfunction, and the topography of the cellular dysfunction, in turn, determines the clinical phenotype…. Genetic and epigenetic factors modify the regional vulnerability to create disease-specific diagnostic phenotypes.

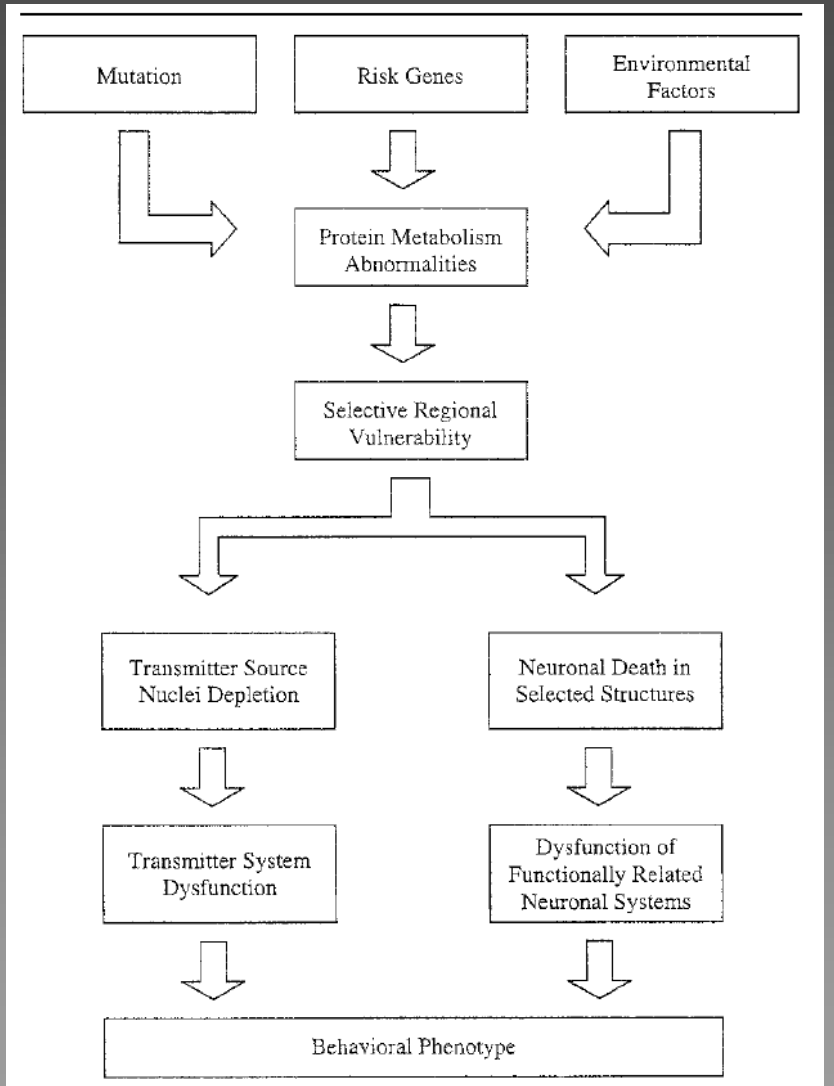


Fig. Schematic of relationship between causative factors, proteotypes, and phenotype.

Degenerative dementias as proteinopathies

Proteinopathy

↓

Neuropathological lesion

↓

Selective regional vulnerability neurodegeneration

↓

Phenotype

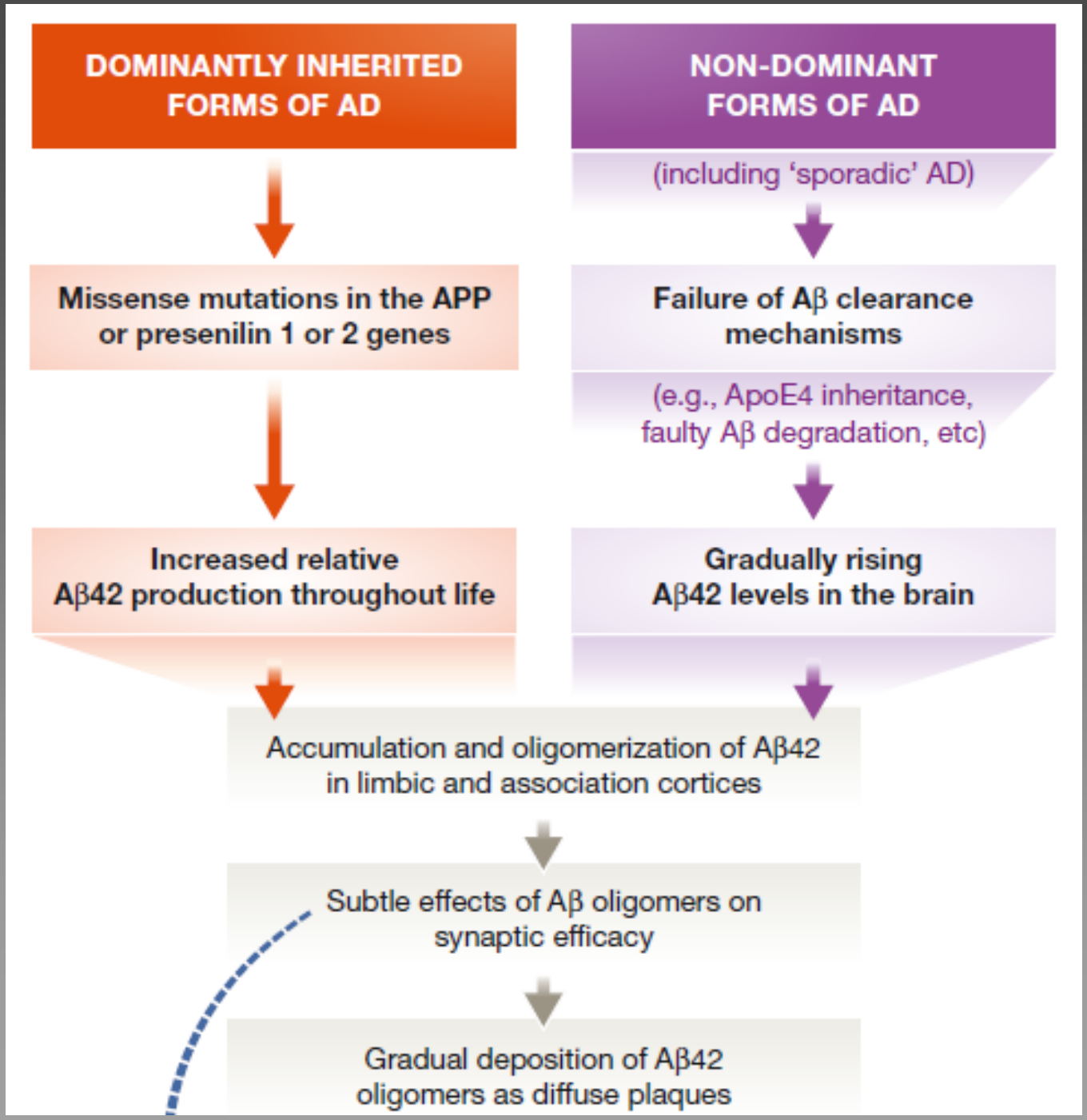
ALZHEIMER'S DISEASE

Proteinopathy 1

Amyloid-β protein

Neuropathological lesion 1

Amyloid plaques


DOMINANTLY INHERITED FORMS OF AD
NON-DOMINANT FORMS OF AD
(including 'sporadic' AD)
Missense mutations in the APP or presenilin 1 or 2 genes
Failure of Aβ clearance mechanisms
(e.g., ApoE4 inheritance, faulty Aβ degradation, etc)
Increased relative Aβ42 production throughout life
Gradually rising Aβ42 levels in the brain
Accumulation and oligomerization of Aβ42 in limbic and association cortices
Subtle effects of Aβ oligomers on synaptic efficacy
Gradual deposition of Aβ42 oligomers as diffuse plaques

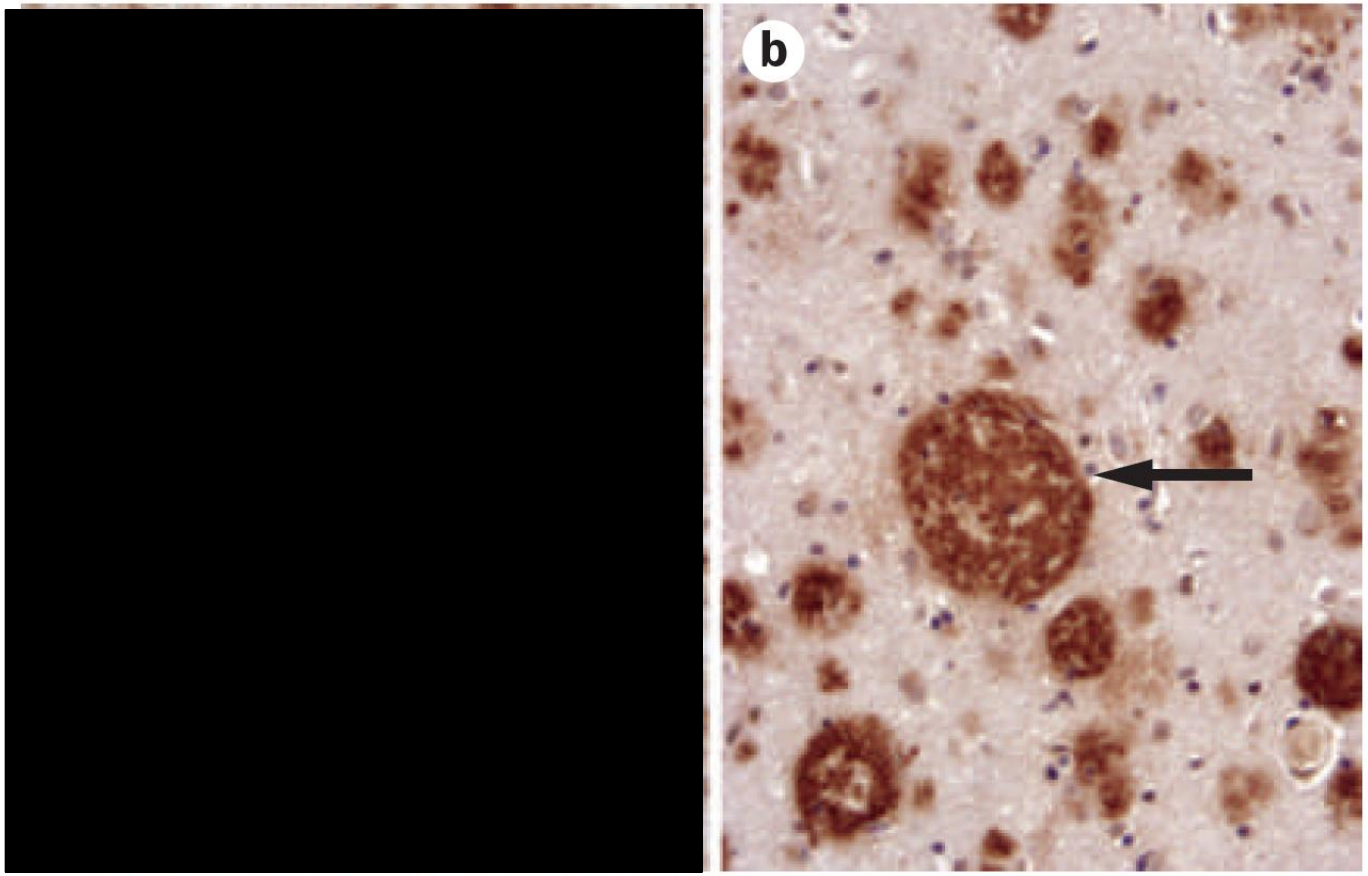


Figure 2 | Alzheimer disease pathology. **a** | Neurofibrillary tangle (arrow). **b** | Neuritic plaque (arrow). ×400 magnification. Images courtesy of Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, PA, USA.

BIOMARKER DEI DEPOSITI DI AMILOIDE CEREBRALE

- ✓ Riduzione della beta-amiloide nel LCS
- ✓ Depositi di amiloide alla PIB-PET

ALZHEIMER'S DISEASE

Proteinopathy 1

Amyloid-β protein

↓

Neuropathological lesion 1

Amyloid plaques

↓

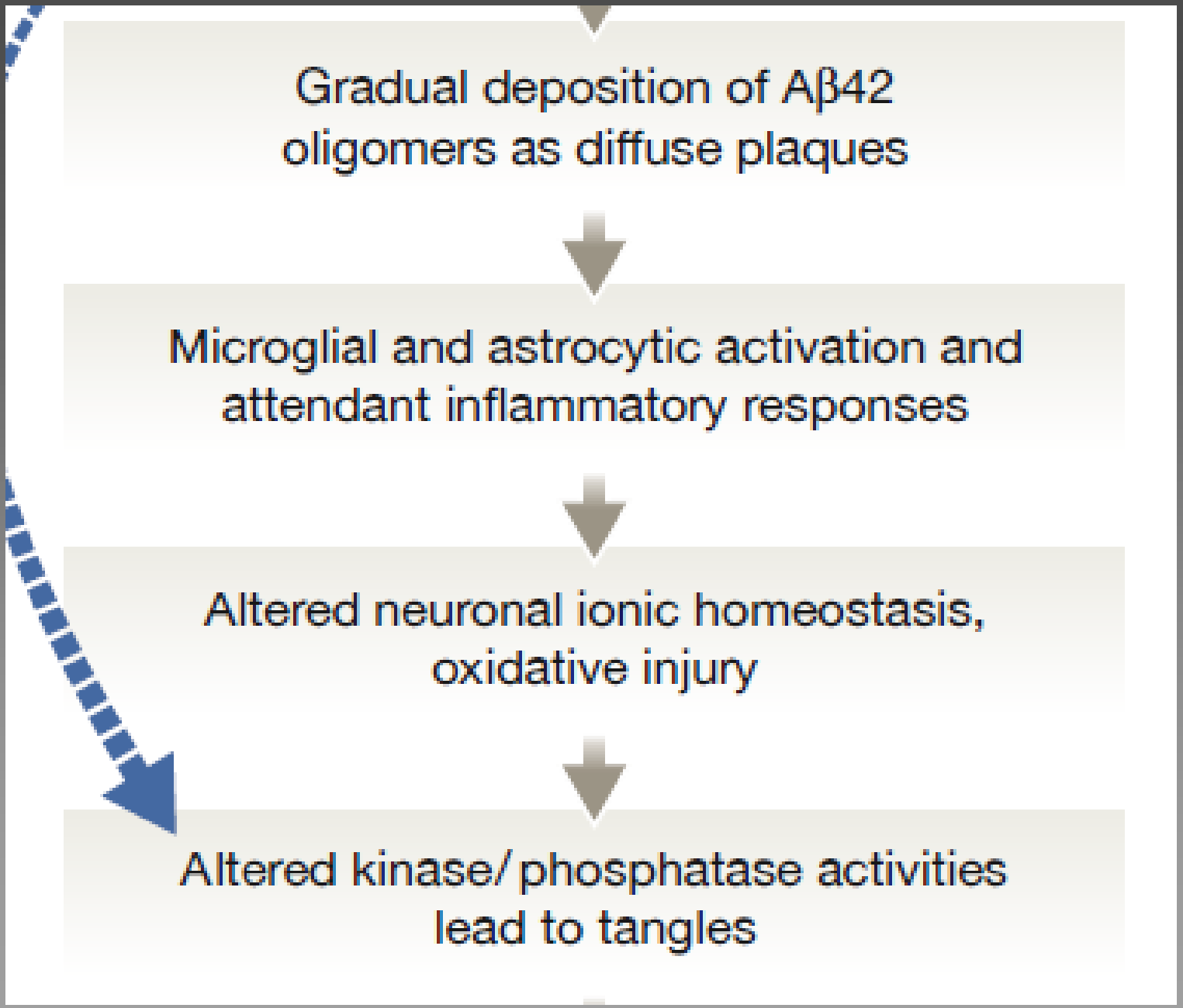
Proteinopathy 2

Tau protein

↓

Neuropathological lesion 2

Neurofibrillary tangles
(hyperphosphorylated tau)


Gradual deposition of Aβ42 oligomers as diffuse plaques
Microglial and astrocytic activation and attendant inflammatory responses
Altered neuronal ionic homeostasis, oxidative injury
Altered kinase/phosphatase activities lead to tangles

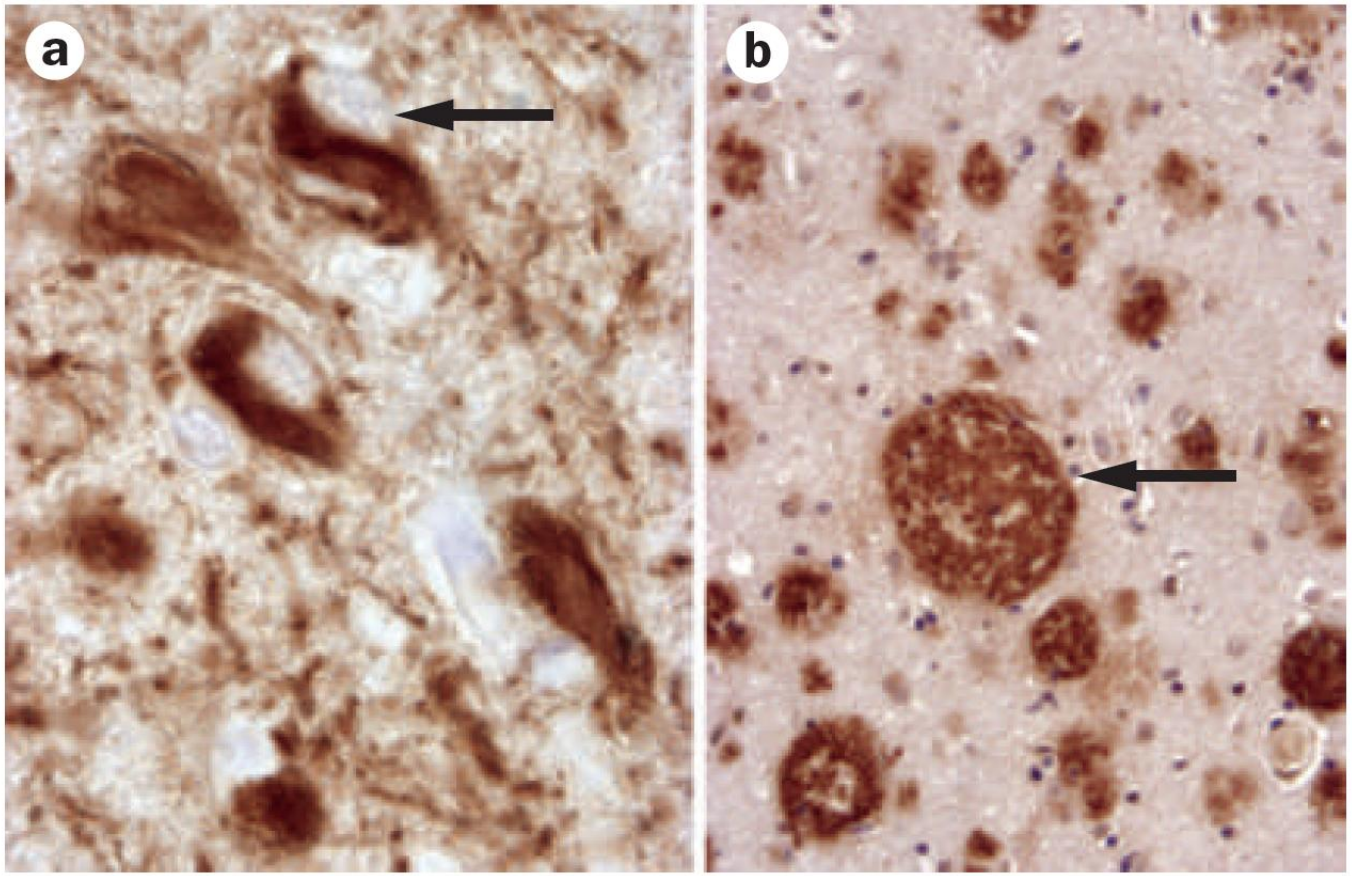


Figure 2 | Alzheimer disease pathology. **a** | Neurofibrillary tangle (arrow). **b** | Neuritic plaque (arrow). ×400 magnification. Images courtesy of Center for Neurodegenerative Disease Research, University of Pennsylvania, Philadelphia, PA, USA.

BIOMARKER DI NEUROFIBRILLARY TANGLES

- ✓ Aumento della proteina tau fosforilata nel LCS
- ✓ Positività dei tracciatori di proteina tau alla PET cerebrale

ALZHEIMER'S DISEASE

Proteinopathy 2

Tau protein

Neuropathological lesion 2

Neurofibrillary tangles (hyperphosphorylated tau)

Neurodegeneration

Neuronal death

Altered kinase/phosphatase activities
lead to tangles

Widespread neuronal/synaptic dysfunction
and selective neuronal loss with
attendant neurotransmitter deficits

BIOMARKER DI NEURODEGENERAZIONE 2

- ✓ Aumento della proteina tau totale nel LCS
- ✓ Atrofia corticale alla TC o RMN
- ✓ Ipometabolismo temporo-parietale al FDG-PET

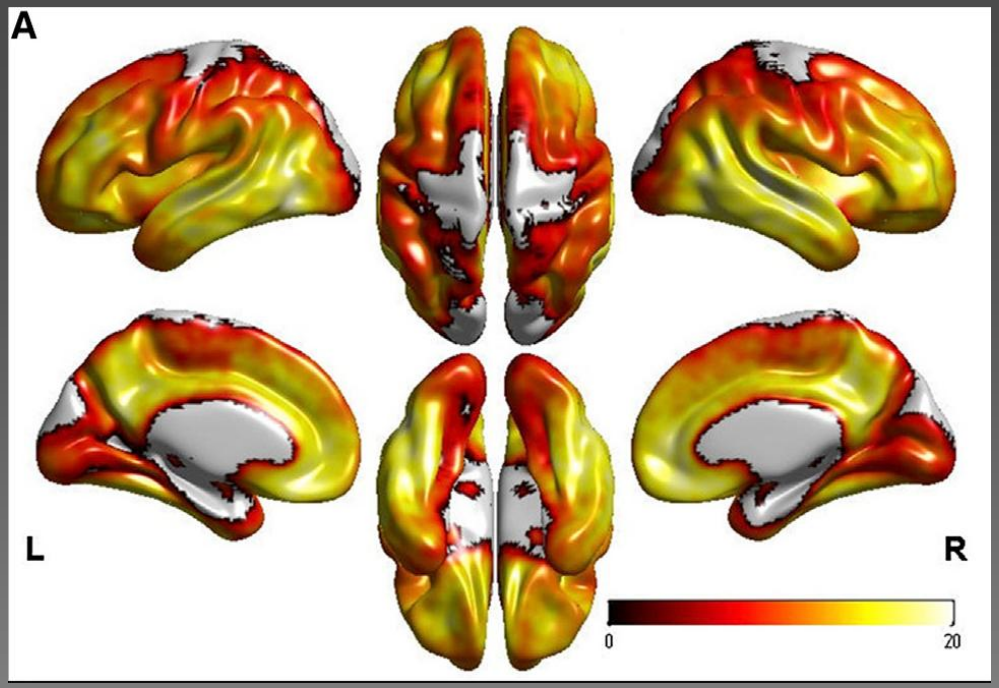
TYPICAL ALZHEIMER'S DISEASE

Proteinopathy → Amyloid-β + Tau protein

Neuropathological lesion → Amyloid plaques + NFT

Neurodegeneration → Hippocampus

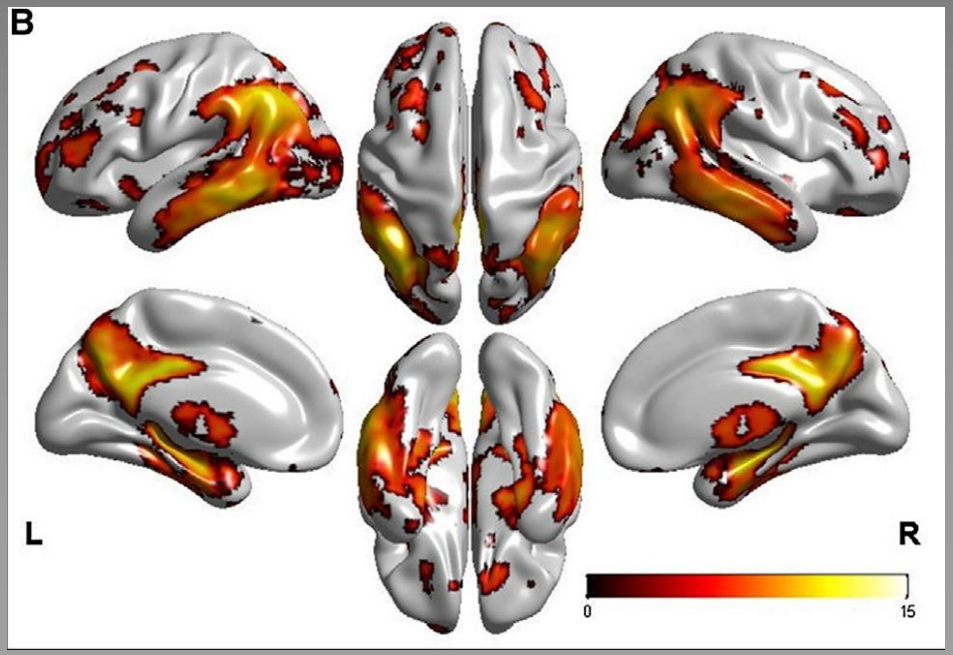
Phenotype → Amnesic syndrome

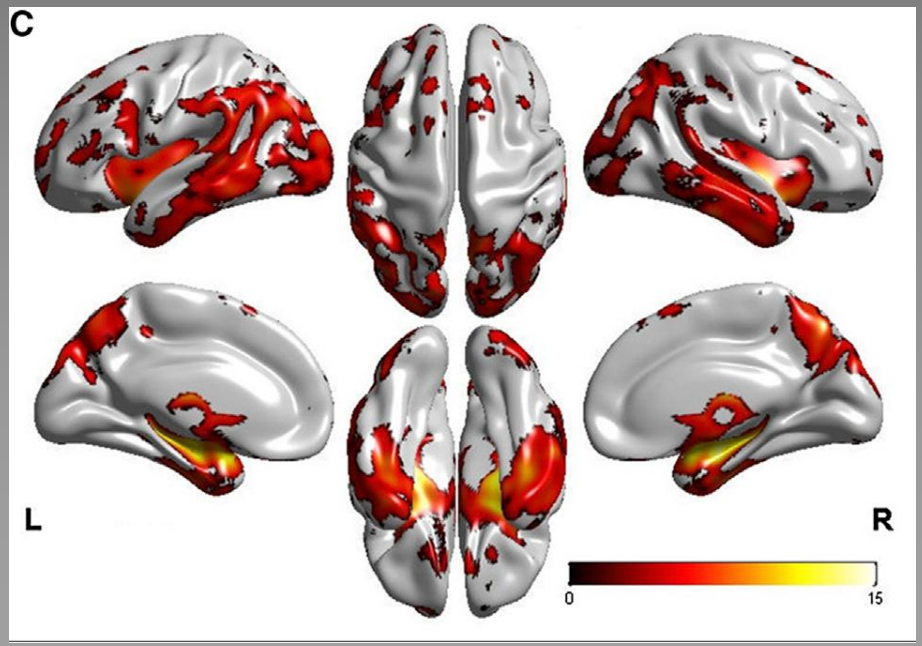


PIB-PET

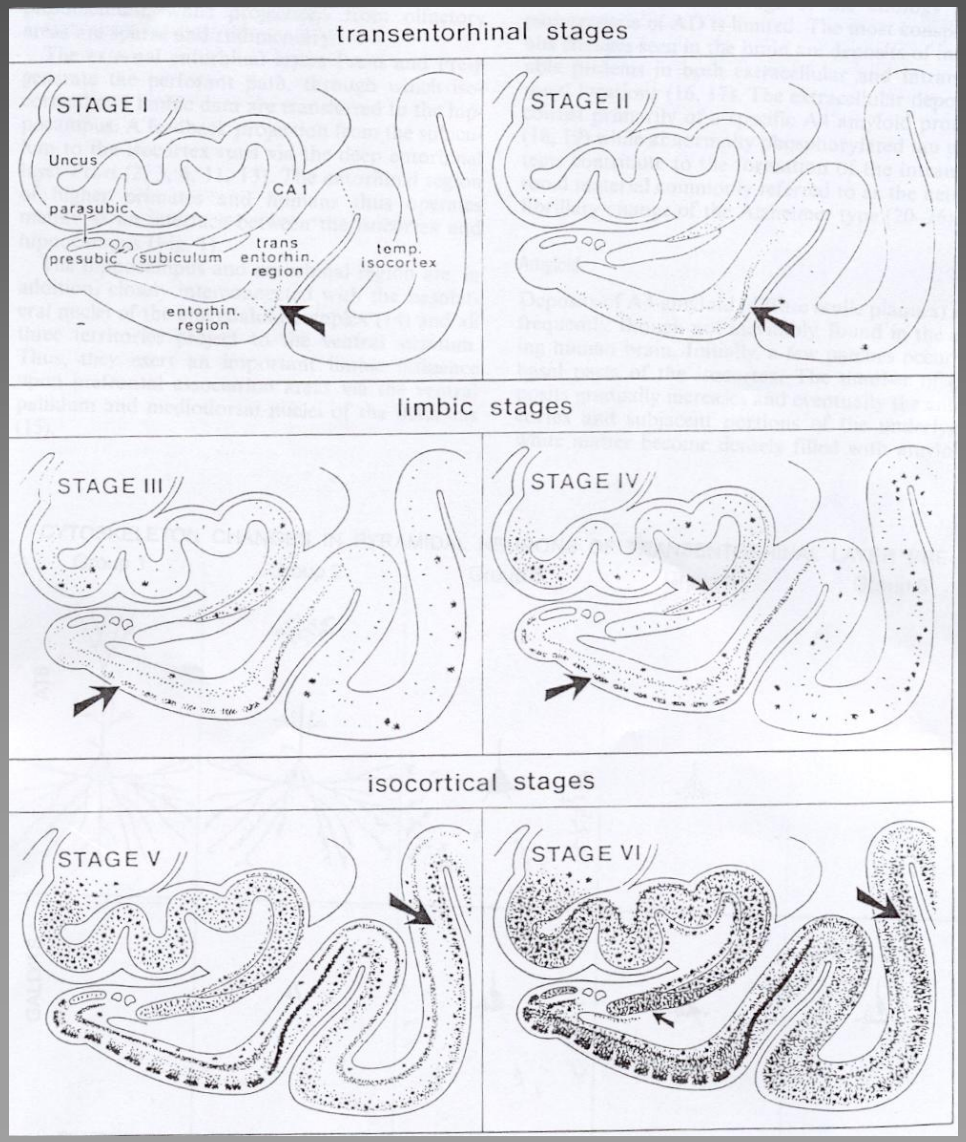
FDG-PET

MRI

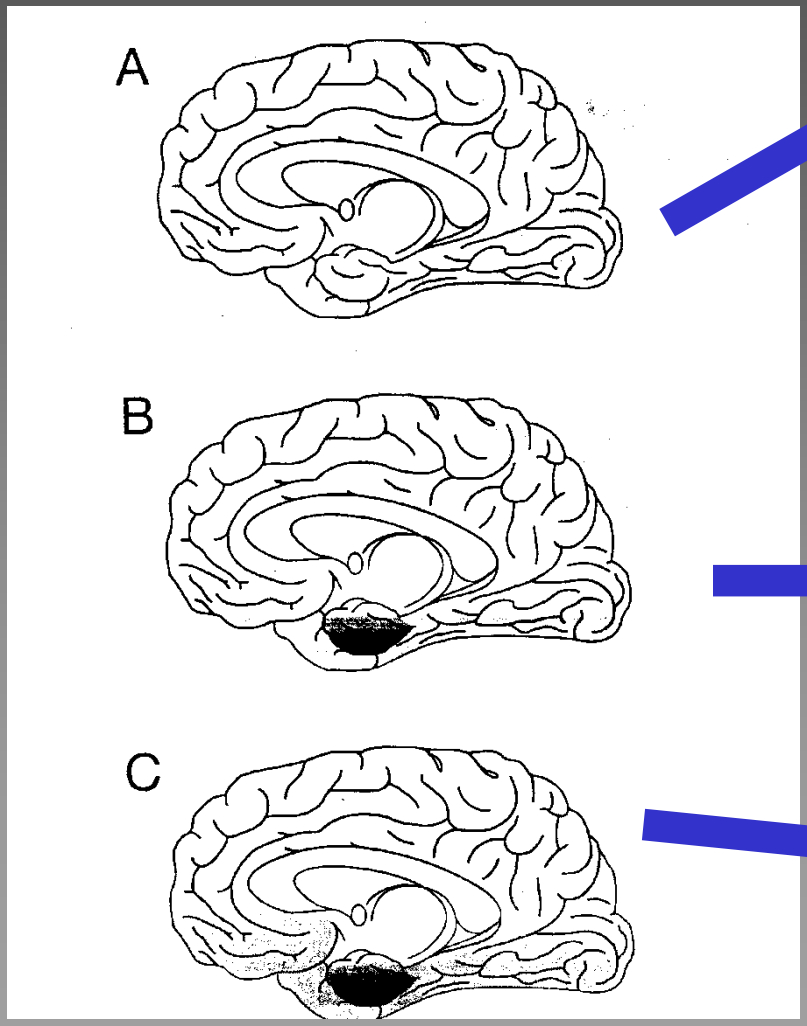




Localization of Alzheimer's neuropathological changes in the mesial temporal lobe (Braak and Braak, Acta Neurol Scand, 1993)



Localizzazione tipica delle alterazioni neuropatologiche nella malattia di Alzheimer



Braak and Braak's stages I-II:
lesioni confinate alla regione transentorinale

Nessun evidente deficit cognitivo

Braak and Braak's stages III-IV:
Coinvolgimento della corteccia entorinale/ippocampo

Solo deficit di memoria

Braak and Braak's stages V-VI:
Diffusione all'isocortex

Sindrome amnesico-afasico-agnosico-aprassica

EXPERT REVIEWS

Distinguishing Alzheimer's disease from other major forms of dementia

Expert Rev. Neurother. 11(11), 1579–1591 (2011)

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Alzheimer's disease (AD) is the most common and most studied cause of dementia. Significant advances have been made since the first set of clinical criteria for AD were put forth in 1984 that are now captured in the new criteria for AD published in 2011. Key features include recognition of a broad AD spectrum (from preclinical to mild cognitive impairment to AD dementia) and requirement of AD biomarkers for diagnosis. Correctly diagnosing dementia type is increasingly important in an era when potential disease-modifying agents are soon to be marketed. The typical AD dementia syndrome has at its core, an amnestic syndrome of the hippocampal type, followed by associated deficits in word-finding, spatial cognition, executive functions and neuropsychiatric changes. Atypical presentations of AD have also been identified that are presumed to have a different disease course. It can be difficult to distinguish between the various dementia syndromes given the overlap in many common clinical features across the dementias. The clinical difficulty in diagnosis may reflect the underlying pathology, as AD often co-occurs with other pathologies at autopsy, such as cerebrovascular disease or Lewy bodies. Neuropsychological evaluation has provided clinicians and researchers with profiles of cognitive strengths and weaknesses that help to define the dementias. There is yet no single behavioral marker that can reliably discriminate AD from the other dementias. The combined investigation of cognitive and neurobehavioral symptoms coupled with imaging markers could provide a more accurate approach for differentiating between AD and other major dementia syndromes in the future.

KEYWORDS: Alzheimer's disease • cognition • dementia • depression • differential diagnosis • frontotemporal dementia • Lewy body • vascular

CARATTERISTICHE DEL DISTURBO DI MEMORIA EPISODICA 'HIPPOCAMPAL TYPE' NEI PAZIENTI AD

- ✓ Non miglioramento prestazionale in test di memoria dalla disponibilità di supporto in fase di encoding e/o retrieval
- ✓ Oblio accelerato

ATYPICAL ALZHEIMER'S DISEASE

Proteinopathy → Amyloid-β + Tau protein

Neuropathological lesion → Amyloid plaques + NFT

Neurodegeneration → Frontal lobes, Left Temporal lobe, Parietal/Temporal/Occipital

Phenotype → Behavioral/Disexecutive Aphasic, Apraxic/Agnosic

BRAIN RESEARCH REVIEWS 51 (2006) 176–211

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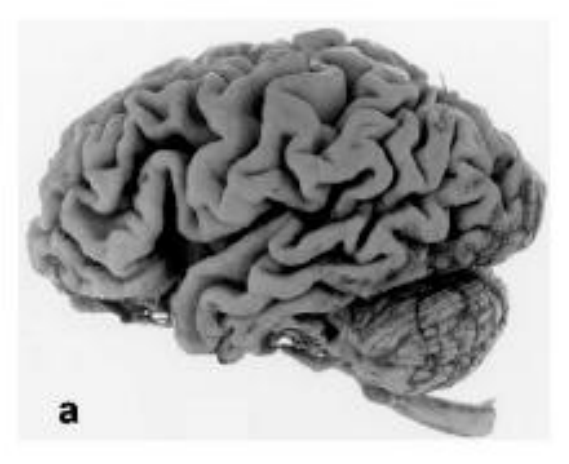
BRAIN RESEARCH REVIEWS

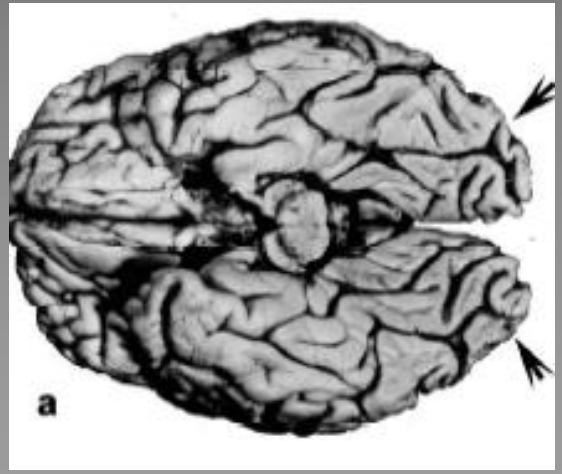
Review

Neural substrates of cognitive and behavioral deficits in atypical Alzheimer's disease

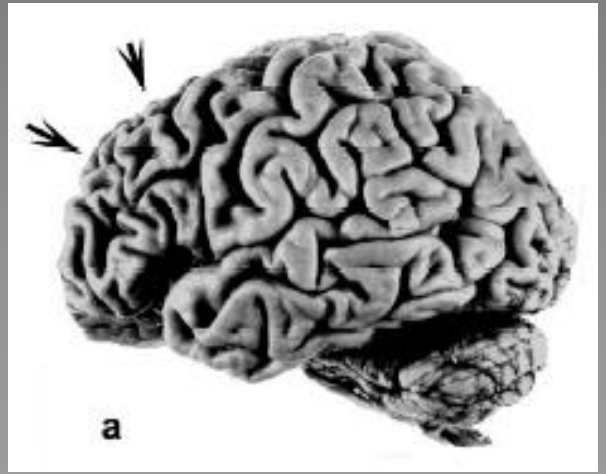
Armin von Gunten[a,*], *Constantin Bouras*[b], *Enikö Kövari*[b], *Panteleimon Giannakopoulos*[a,b], *Patrick R. Hof*[c,d]



Typical AD



Posterior cortical atrophy/AD



AD frontal variant

doi:10.1093/brain/awm213 *Brain* (2007), **130**, 2636–2645

Focal cortical pre

S. Alladi,[1] J. Xuereb,[2] T. Bak,[1] P. N

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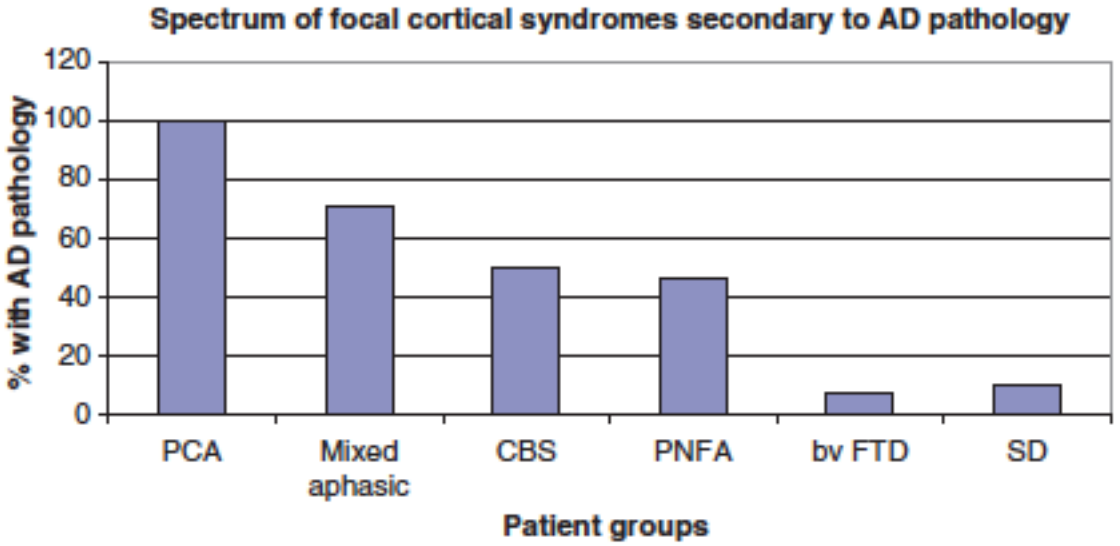


Fig. 1 Spectrum of focal cortical syndromes secondary to AD pathology ($n = 29$).

To determine the frequency of A gressive focal cortical syndromes, notably vioural variant frontotemporal dementia ia) and semantic dementia (SD); and to co cortical presentations of AD versus more typical AD and those with non AD pathology. From a total of 200 patients with comprehensive prospective clinical and pathological data we selected 120:100 consecutive cases with focal cortical syndromes and 20 with clinically typical AD. Clinical files were reviewed blind to pathological diagnosis. Of the 100 patients with focal syndromes, 34 had AD as the primary pathological diagnosis with the following distribution across clinical subtypes: all 7 of the PCA (100%); 6 of 12 with CBS (50%); 2 of 28 with bvFTD (7.1%); 12 of 26 with PNFA (44.1%); 5 of 7 with mixed aphasia (71.4%) and 2 of 20 with SD (10%). Of 20 with clinically typical AD, 19 had pathological AD. Age at both onset and death was greater in the atypical AD cases than those with non-AD pathology, although survival was equivalent. AD is a much commoner cause of focal cortical syndromes than previously recognised, particularly in PCA, PNFA and CBS, but rarely causes SD or bvFTD. The focal syndrome may remain pure for many years. Patients with atypical AD tend to be older than those with non-AD pathology.

Posterior cortical atrophy

Sebastian J Crutch, Manja Lehmann, Jonathan M Schott, Gil D Rabinovici, Martin N Rossor, Nick C Fox

Lancet Neurol 2012; 11: 170–78

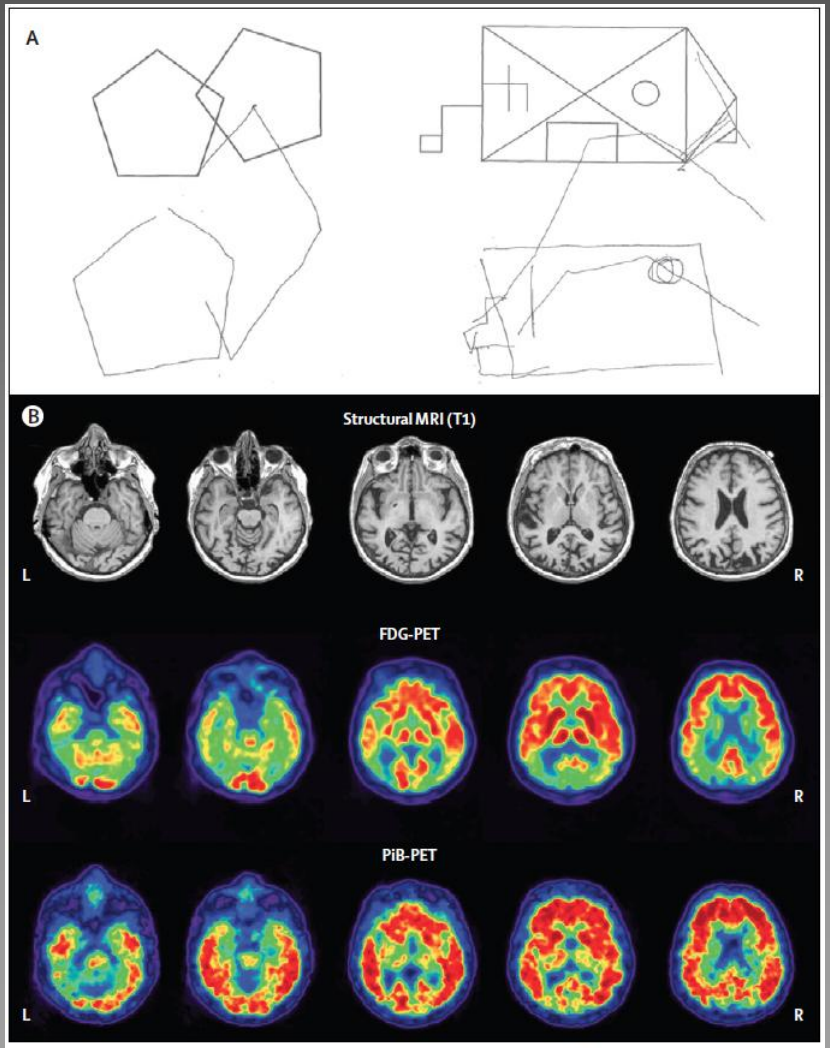
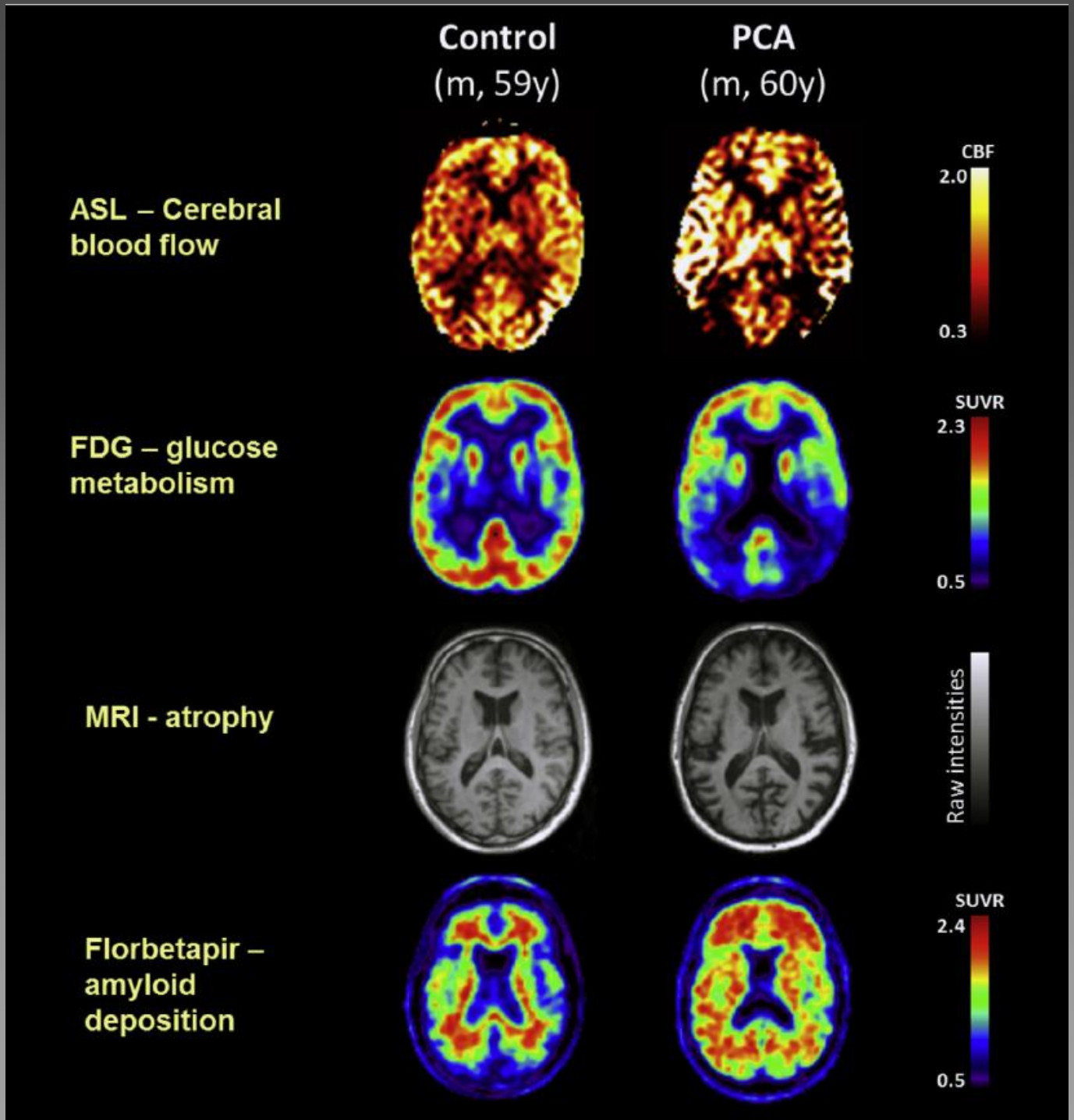


Figure 2: **Neuropsychological and neuroimaging evidence of posterior cortical atrophy**
Neurological testing (A) and brain imaging (B) of a 62-year-old woman with visuospatial dysfunction. Images are in neurological orientation. See the panel for a description of the case history and imaging findings.


Control
(m, 59y)
PCA
(m, 60y)
ASL – Cerebral blood flow
CBF
2.0
0.3
FDG – glucose metabolism
SUVR
2.3
0.5
MRI - atrophy
Raw intensities
Florbetapir – amyloid deposition
SUVR
2.4
0.5

Atypical Alzheimer's disease: posterior cortical atrophy

- ✓ Primary progressive occipito-temporal syndromes:
  - Alexia, agraphia, transcortical sensory aphasia
  - Cortical blindness, achromatopsia, hemianopsia
  - Impairment in motion perception and target tracing
  - Visual agnosia, prosopagnosia
  - Spatial disorientation (landmark agnosia)

- ✓ Primary progressive parieto- occipital syndromes:
  - Apraxia
  - Alien hand sign
  - Hemineglect

Primary progressive aphasia: clinicopathological correlations

Murray Grossman

Box 2 | Characteristics of primary progressive aphasia syndromes

Progressive nonfluent aphasia

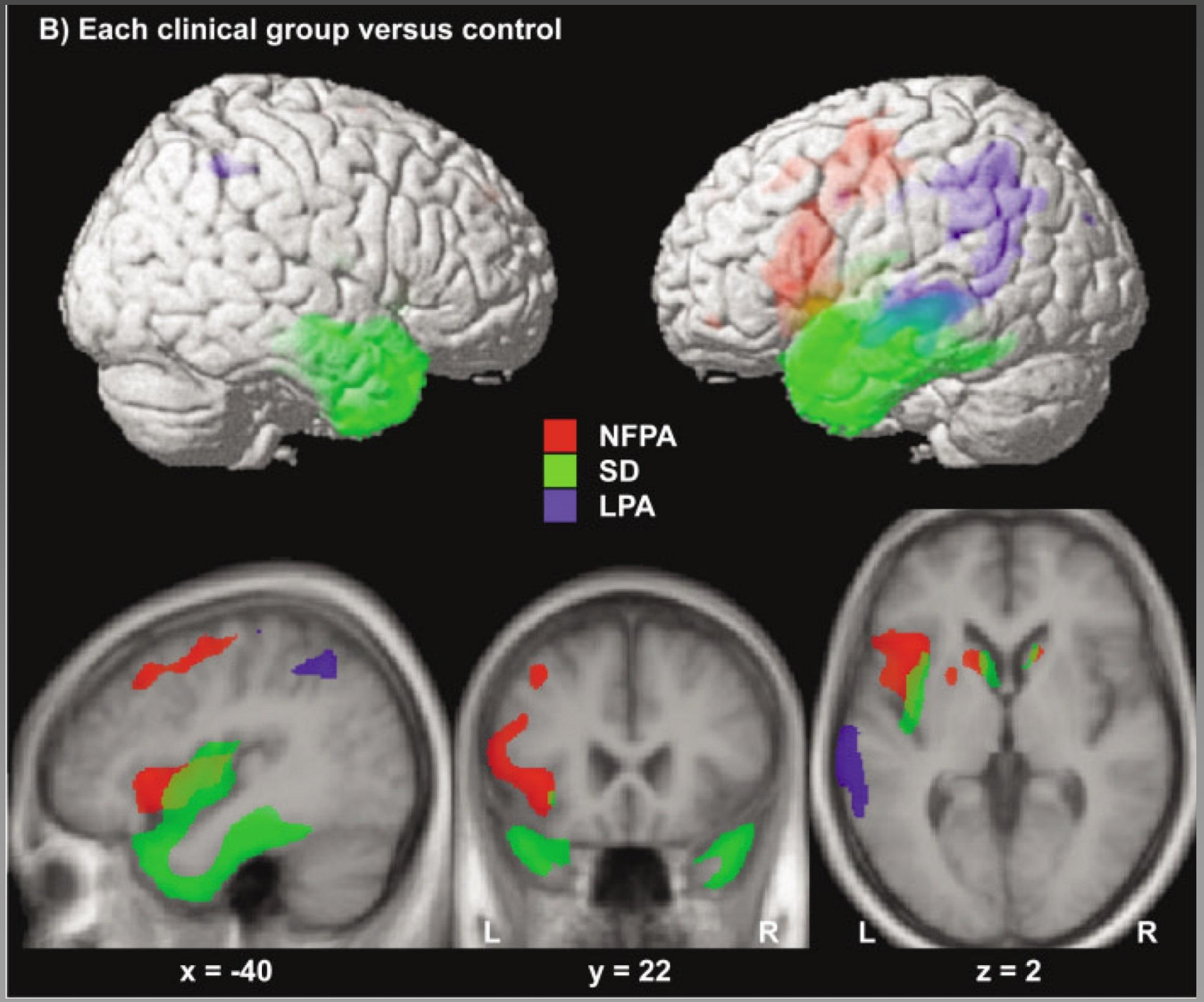
- Grammatical simplification and errors in language production
- Effortful, halting speech with speech sound errors
- Two or more of the following: impaired syntactic comprehension; spared content word comprehension; spared object knowledge

Semantic dementia

- Poor confrontation naming
- Impaired single word comprehension
- Three or more of the following: poor object and/or person knowledge; surface dyslexia: spared repetition; spared motor speech

Logopenic progressive aphasia

- Impaired single word retrieval
- Impaired repetition of phrases and sentences
- Three or more of the following: speech sound errors; spared motor speech; spared single word comprehension and object knowledge; absence of agrammatism


B) Each clinical group versus control
NFPA
SD
LPA
L
R
L
R
x = -40
y = 22
z = 2

ORIGINAL CONTRIBUTION

Clinical and Pathological Evidence for a Frontal Variant of Alzheimer Disease

Julene K. Johnson, PhD; Elizabeth Head, PhD; Ronald Kim, MD; Arnold Starr, MD; Carl W. Cotman, PhD

Arch Neurol. 1999;56:1233-1239

Table 2. Neuropsychological Test Results*

	Alzheimer Disease Group		
	Typical	Frontal	*P*
Mini–Mental State Examination	23.33 (20, 22, 28)	20.33 (18, 21, 22)	.33
Trail Making Test A (seconds to complete)	56.00 (47, 52, 69)	140.67 (100, 155, 167)	.002†
FAS fluency‡	40.67 (32, 45, 45)	19.00 (13, 17, 27)	.02†
WAIS-R Digit Span			
Forward digits	9.00 (8, 8, 11)	5.67 (4, 6, 7)	.08
Reverse digits	6.00 (4, 6, 8)	3.00 (2, 3, 4)	.17
Symbol Digit Modalities Test§	22.67 (11, 22, 35)	6.00 (0, 8, 10)	.14
CERAD Word List			
Trials 1-3 (total)	11.00 (5, 12, 16)	7.33 (4, 5, 13)	.22
5-min delayed recall	1.33 (0, 1, 3)	0.33 (0, 0, 1)	.33
Boston Naming Test (30-item version)	17.00 (10, 14, 27)	22.00 (12, 25, 29)	.87
CERAD Animal Naming‖	10.67 (8, 11, 13)	8.33 (2, 9, 14)	.21
WAIS-R Vocabulary (scaled score)	9.67 (8, 8, 13)	10.33 (7, 12, 12)	.96
CERAD Constructional Praxis	10.00 (9, 10, 11)	7.67 (7, 8, 8)	.06
WAIS-R Block Design (scaled score)	5.67 (5, 5, 7)	1.00 (1, 1, MD)	.01†
Kendrick Digit Copy¶	93.33 (80, 100, 100)	67.00 (43, 66, 92)	.29

**Scores are given as means (individual scores). WAIS-R indicates Wechsler Adult Intelligence Scale–Revised; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; and MD, missing data.*

†Significant group differences (analysis of variance, Scheffé post hoc adjustment, P<.05).

‡The number of words beginning with F, A, S in 1 minute.

§Written test of the number of symbol-number pairs in 90 seconds.

‖The number of animals in 1 minute.

¶The number of numbers copied in 2 minutes.

REVIEW

Selective vulnerability in neurodegeneration: insights from clinical variants of Alzheimer's disease

Niklas Mattsson,[1] Jonathan M Schott,[2] John Hardy,[3] Martin R Turner,[4] Henrik Zetterberg[3,5]

…. Aggregation of Aβ is driven by the total neuronal activity in highly connected cortical hubs (which explains the diffuse and symmetric patterns of amyloid pathology), while τ pathology develops in specific vulnerable networks…. As τ-mediated injury patterns more closely correlate both with specific functional networks and neuronal loss, this provides a means of explaining the clinical variability. If this model is correct, then the different AD variants arise due to different localisations of τ-related neuronal injury in specific functional networks. The next logical step is to identify factors that predispose specific networks to τ-mediated injury…..

Grazie per l'attenzione

The NEW ENGLAND JOURNAL of MEDICINE

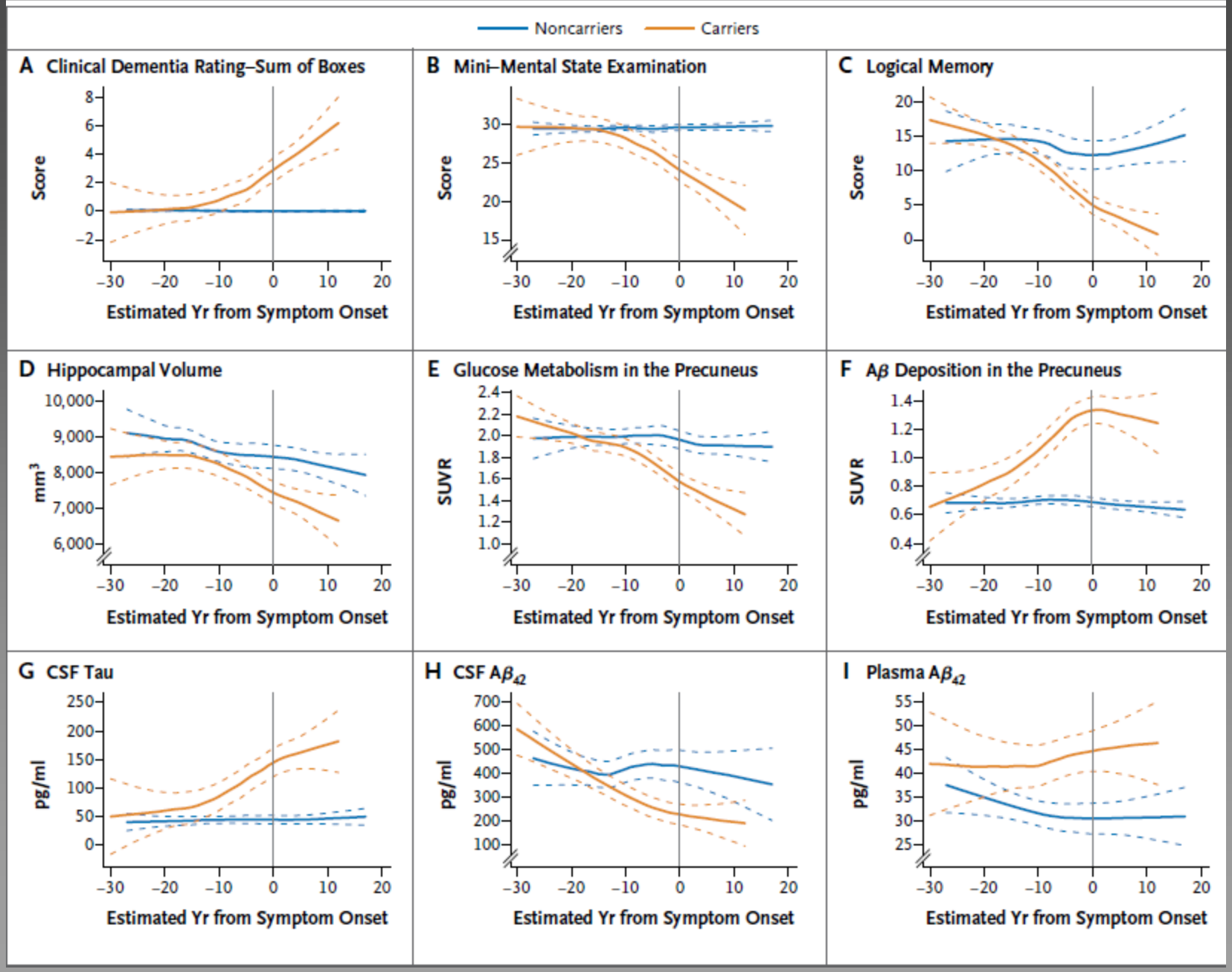
ESTABLISHED IN 1812 AUGUST 30, 2012 VOL. 367 NO. 9

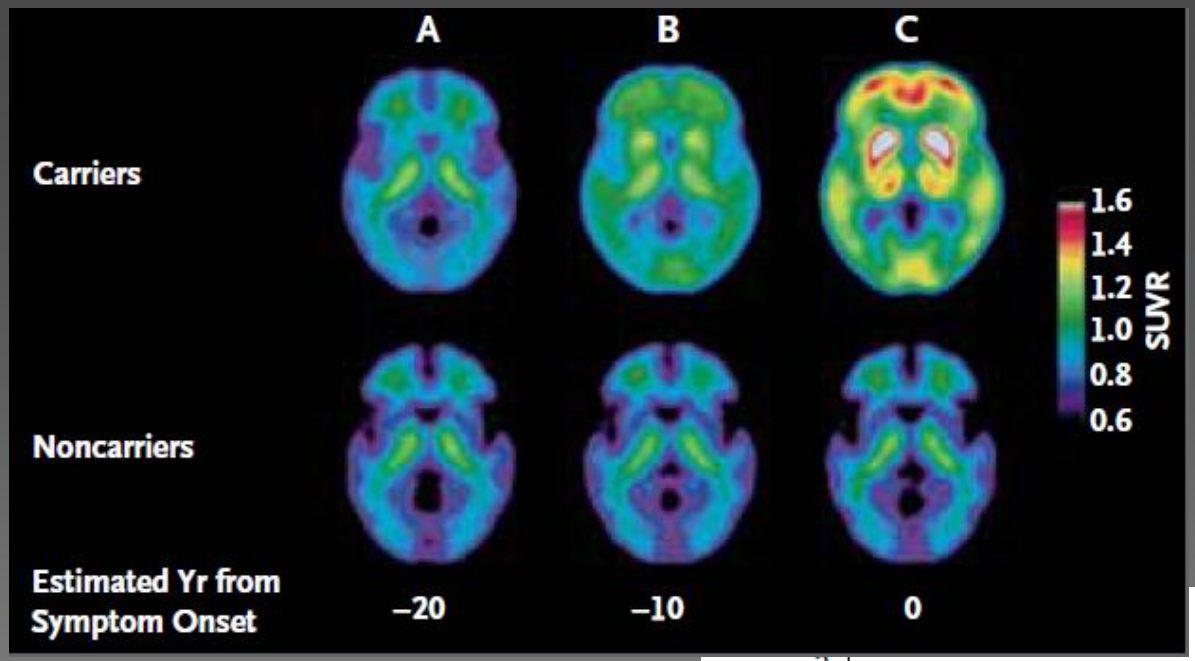
Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

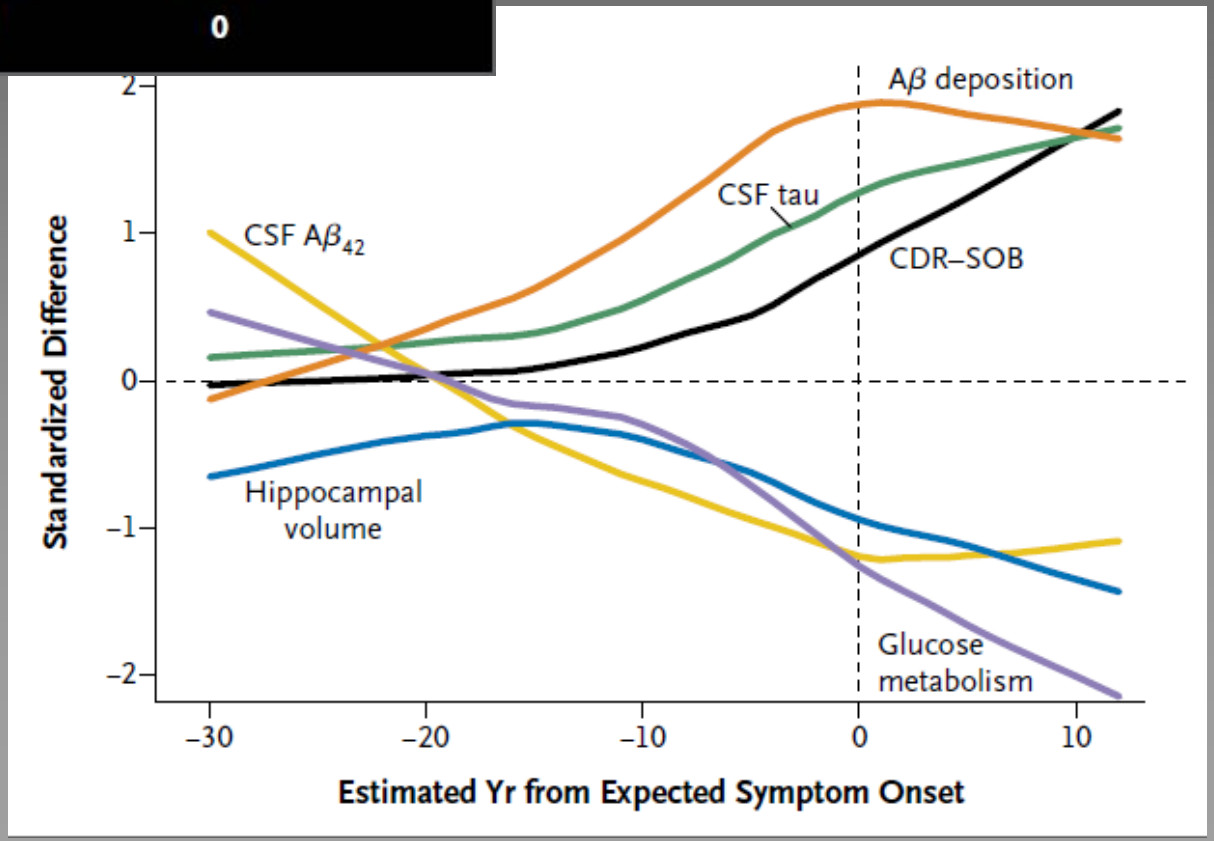
Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network

Table 1. Characteristics of the Study Participants.*

Characteristic	Carriers (N=88)	Noncarriers (N=40)	P Value
Age — yr	39.1±10.3	39.5±8.9	0.92
Male sex — no. (%)	36 (41)	17 (42)	0.85
Education level — yr	13.9±2.5	15.0±2.5	0.04
Cognitive status — no. (%)†			
Symptomatic	43 (49)	1 (2)	0.29
Asymptomatic	45 (51)	39 (98)	
Positive for apolipoprotein E ε4 allele — no. (%)	22 (25)	9 (22)	0.69


Noncarriers
Carriers
A Clinical Dementia Rating–Sum of Boxes
Score
8
6
4
2
0
−2
−30 −20 −10 0 10 20
Estimated Yr from Symptom Onset
B Mini–Mental State Examination
Score
30
25
20
15
−30 −20 −10 0 10 20
Estimated Yr from Symptom Onset
C Logical Memory
Score
20
15
10
5
0
−30 −20 −10 0 10 20
Estimated Yr from Symptom Onset
D Hippocampal Volume
mm³
10,000
9,000
8,000
7,000
6,000
−30 −20 −10 0 10 20
Estimated Yr from Symptom Onset
E Glucose Metabolism in the Precuneus
SUVR
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
−30 −20 −10 0 10 20
Estimated Yr from Symptom Onset
F Aβ Deposition in the Precuneus
SUVR
1.4
1.2
1.0
0.8
0.6
0.4
−30 −20 −10 0 10 20
Estimated Yr from Symptom Onset
G CSF Tau
pg/ml
250
200
150
100
50
0
−30 −20 −10 0 10 20
Estimated Yr from Symptom Onset
H CSF Aβ42
pg/ml
700
600
500
400
300
200
100
−30 −20 −10 0 10 20
Estimated Yr from Symptom Onset
I Plasma Aβ42
pg/ml
55
50
45
40
35
30
25
−30 −20 −10 0 10 20
Estimated Yr from Symptom Onset


A
B
C
Carriers
Noncarriers
1.6
1.4
1.2
1.0
0.8
0.6
SUVR
Estimated Yr from Symptom Onset
–20
–10
0


Aβ deposition
CSF tau
CSF Aβ42
CDR–SOB
Hippocampal volume
Glucose metabolism
Standardized Difference
2
1
0
–1
–2
–30
–20
–10
0
10
Estimated Yr from Expected Symptom Onset

Published online: March 29, 2016

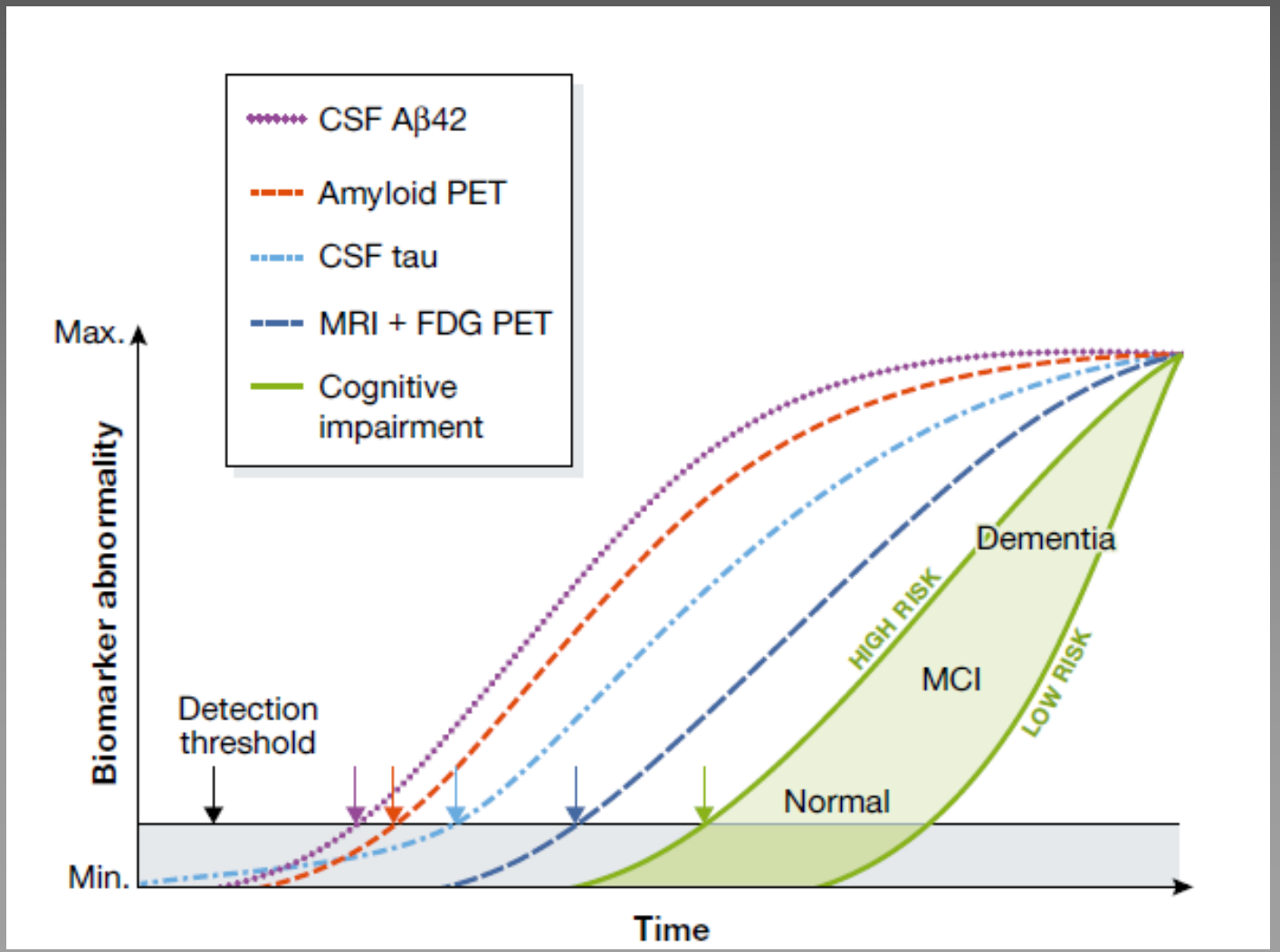
Review

OPEN ACCESS

EMBO Molecular Medicine

The amyloid hypothesis of Alzheimer's disease at 25 years

Dennis J Selkoe[1,†] & John Hardy[2,*,†]

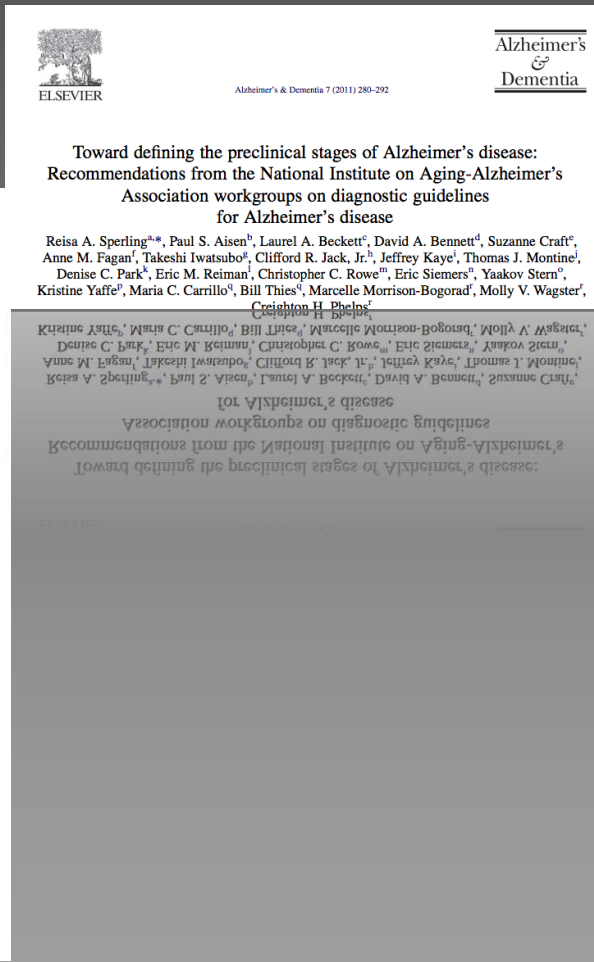


Stage 1: Asymptomatic amyloidosis
- *High PET amyloid tracer retention*
- *Low CSF Aβ42*

Stage 2: Amyloidosis + Neurodegeneration
- *Neuronal dysfunction on FDG-PET/fMRI*
- *High CSF tau/p-tau*
- *Cortical thinning/Hippocampal atrophy*

Stage 3: Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
- *Subtle change from baseline level of cognition*
- *Poor performance on challenging cognitive tests*
- *Does not yet meet criteria for MCI*

Mild cognitive impairment (MCI) →AD



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Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

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