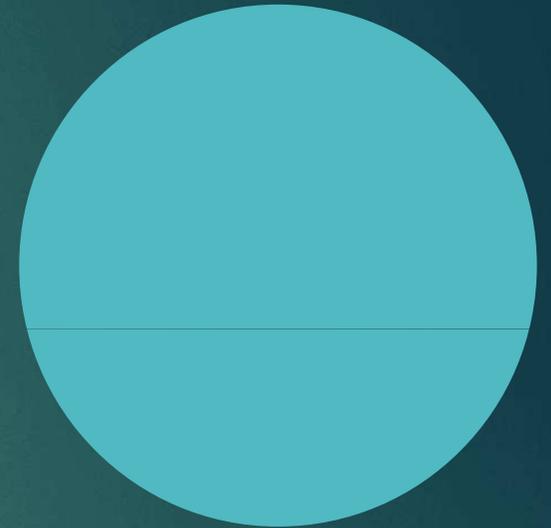


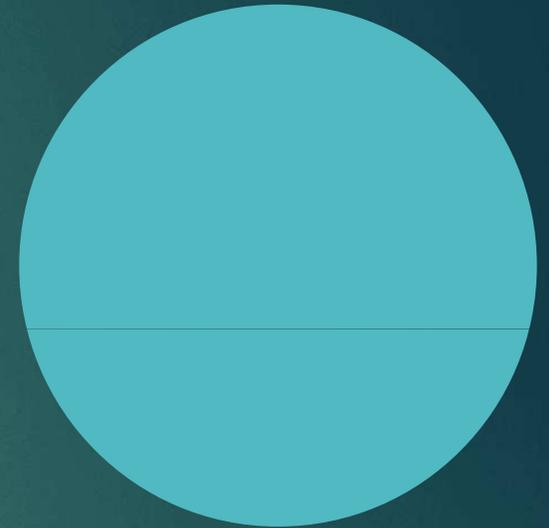
Case report

Luca Rozzini



D.G, male, 77 ys

- ▶ Education: 13 ys
- ▶ 180 cm, 80 kg, BMI 24,69
- ▶ Lives with his wife
- ▶ 2 sons in good health
- ▶ Dealer, business consultant
- ▶ prosthetic left knee, bilateral cataracts
- ▶ Pharmacological treatment: none
- ▶ Not neurological disease in family history



November 2013

- ▶ He was seen in consultation following a 2-year progressive cognitive decline
- ▶ Complaints of progressive memory and concentration problems, difficulties with multi-tasking and 'numbers'
- ▶ After retirement, he became increasingly withdrawn and refused to socialize.
- ▶ His wife states that his personality has changed from a kind, loving man to an argumentative, explosive, and moody individual
- ▶ He is not functionally impaired in all instrumental activities of daily living as well as in basic activities of daily living

Neurologic Examination



- **Mental Status Exam:** good orientation, normal receptive and expressive language, good confrontation-naming and repetition.
- **Cranial Nerves Exam:** I-XII cn normal
- **Motor Exam:** normal
- **Sensory Exam:** normal touch, pain, temperature, pallesthesia, position sense, double simultaneous stimulation
- **Gait Exam:** station, natural gait, heel and toe walking, tandem gait: normal
- **Coordination Exam:** Hand Rapid Alternating Movements, Finger-to-nose Heel-to-shin test correct bilaterally
- **Reflexes:** normal deep tendon reflexes to the 4 limbs, Babinski sign negative
- **Pathological reflexes-frontal release signs:** negative.

5 PAROLE DI DUBOIS

Dubois II, 2002

Ricordo spontaneo

FASE DI APPRENDIMENTO

Ricordo con cue



Bevanda
Limonata



Insetto
Cavalletta



CORCOTTERO



Edificio
Museo



Utensile da Cucina
Coltino



Mezzo di Trasporto
Camion



Punteggio di apprendimento: 4 / 5

Ricordo spontaneo

FASE DI MEMORIZZAZIONE

Ricordo con cue



Bevanda
Limonata



Insetto
Cavalletta



CORCOTTERO



Edificio
Museo



Utensile da Cucina
Coltino



Mezzo di Trasporto
Camion



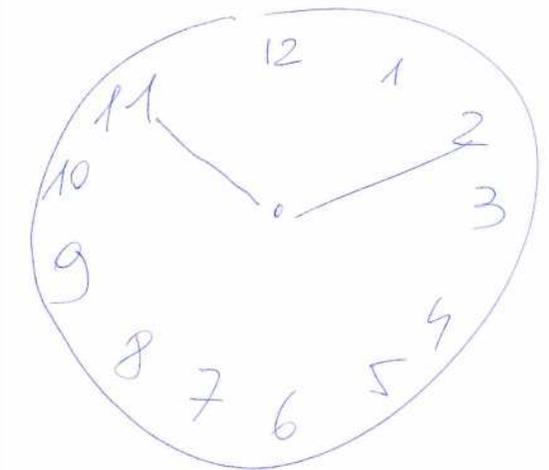
Punteggio di apprendimento: 4 / 5

PUNTEGGIO TOTALE: 8 / 10

Neuropsychological evaluation 4.11.13

MMSE: 29/30

TMA-TMB: nella norma



9/10

Parole	1	2	3	4	5
Tenda	1		1	1	1
Tambura	2	6	2	2	2
Caffè	3		3	3	3
Cintura					
Sole	4	4	8	4	
Giardino	5	3	4	5	4
Baffi		1	6	7	1
Finestra		5	7	8	6
Fiume					7
Paesano					
Colore				9	8
Tocchina					
Scuola			10	6	9
Casa	6		5		
Capello		2	9		
Totale	6/15	6/15	10/15	9/15	9/15
Falsi riconoscimenti					

BREVE RACCONTO

(Novelli, Papagno, Capitani, Lioacona, Cappa, Vallar, 1986)

Istruzioni: si presenta la prova al S, dicendo: "ora le leggerò un breve racconto, dopodiché dovrebbe ripetermi tutto ciò che si ricorda". Si deve specificare che non è necessaria la ripetizione letterale del racconto, ma che vanno ricordati quanti più elementi possibili. Alla fine della rievocazione spontanea si incoraggia il S. a ricordare altri elementi. Poi si legge una seconda volta il racconto. Si impegna il S. in una prova diversa (non di memoria verbale) e dopo 10 minuti si chiede una nuova rievocazione. Si trascrive fedelmente ciò che il S. dice.

Punteggi: media del numero di elementi rievocati nelle due ripetizioni (range 0-28).

Anna/Pesenti/di Bergamo/che lavora/come donna delle pulizie/in una ditta/di costruzioni/
riferi/al maresciallo/dei carabinieri/che la sera/precedente/mentre rincasava/era stata
aggredata/e derubata/di 150 euro./La poveretta/aveva quattro/ bambini/piccoli/che non
mangiavano/da due/giorni/e doveva pagare/l'affitto./I militari/commosi/fecero una colletta.

1° Ripetizione

Alc è stata aggredita e derubata
che aveva 4 bambini piccoli
che non mangiavano da due giorni
e doveva pagare l'affitto.

Totale:

6

2° Ripetizione

non ricordo da dove era stata aggredita
e derubata.

che aveva 4 bambini piccoli
che non mangiavano da due giorni
e doveva pagare l'affitto.

0

Totale/2:

3

TABELLE DI CORREZIONE

MASCHI

FEMMINE

4/5/28 perso

IADL 0/5 lost
BADL 0/6 lost
GAI: 2/20
GDS: 2/15

Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve

Massimo Nucci¹, Daniela Mapelli^{1,2} and Sara Mondini^{1,3}

¹Department of General Psychology, University of Padova, ²Centro Interdipartimentale CIRMANMEC, University of Padova, ³Casa di Cura Figlie di San Camillo, Cremona, Italy

- ▶ Brain Reserve
- ▶ Cognitive reserve

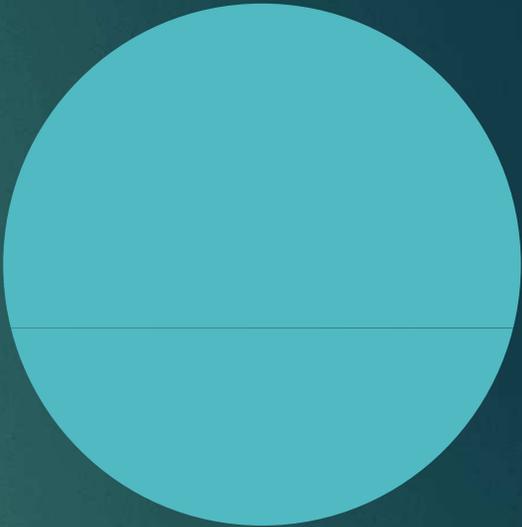
Cognitive Reserve Index

CRIq

questionnaire

M. Nucci, D. Mapelli & S. Mondini (2012)

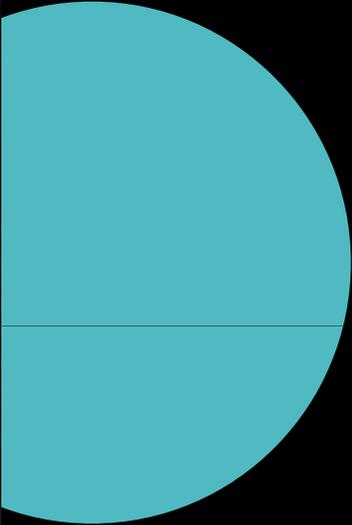
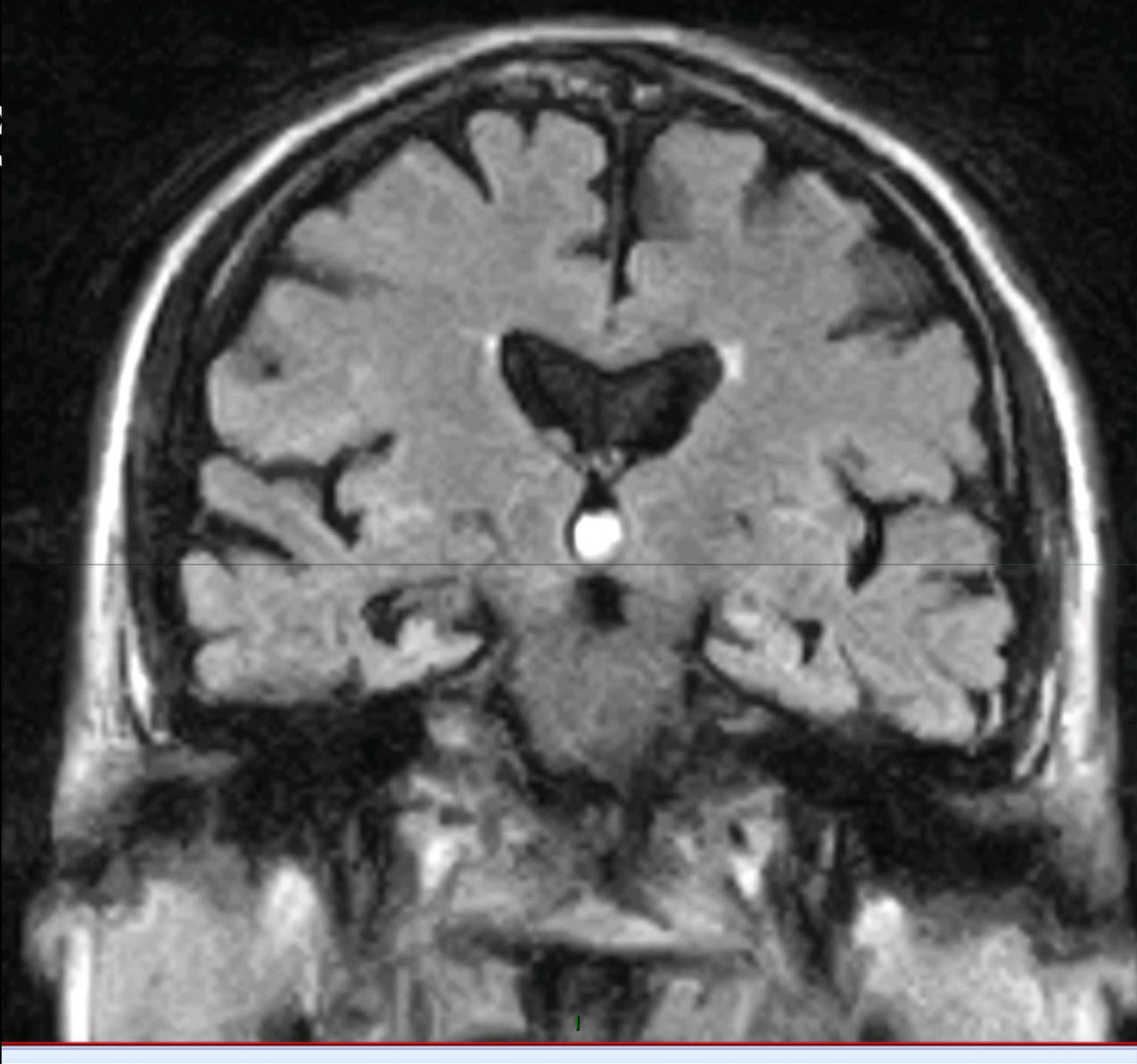
- ▶ il livello di scolarità: 115
- ▶ il tipo di professione svolta: 150
- ▶ lo stile di vita e le attività svolte durante il tempo libero: 143
 - ▶ Lettura di giornali e settimanali
 - ▶ Attività domestiche
 - ▶ Guida
 - ▶ Uso di nuove tecnologie
 - ▶ Attività sociali
 - ▶ Cinema/teatro
 - ▶ Attività di volontariato
 - ▶ Attività artistiche



□	□	□	□	□
basso	medio-basso	medio	medio-alto	alto
≤ 70	70 : 84	85 : 114	115 : 130	≥ 130

<http://cri.psy.unipd.it>

Brain MR



Atrophy of medial temporal lobes on MRI in “probable” Alzheimer’s disease and normal ageing: diagnostic value and neuropsychological correlates

Ph Scheltens, D Leys, F Barkhof, D Huglo, H C Weinstein, P Vermersch, M Kuiper, M Steinling, E Ch Wolters, J Valk

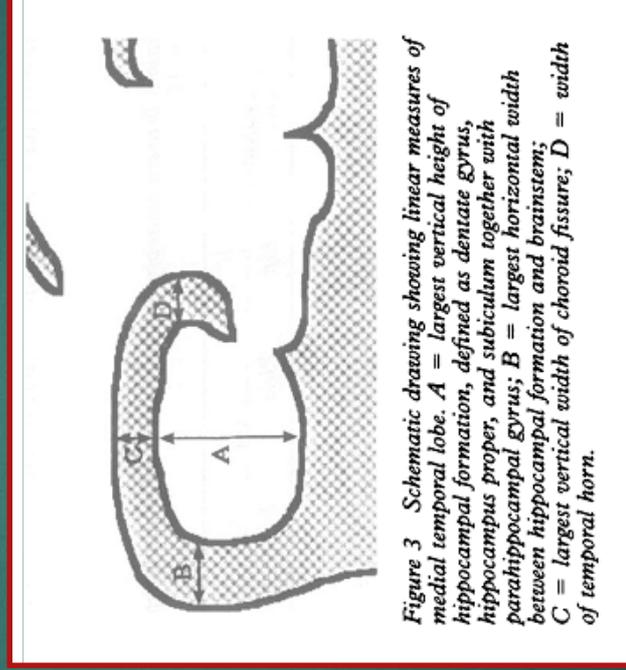
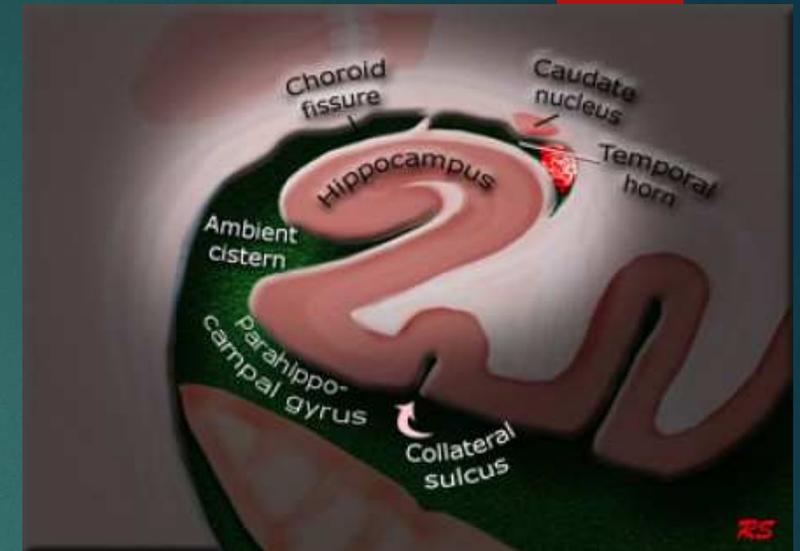
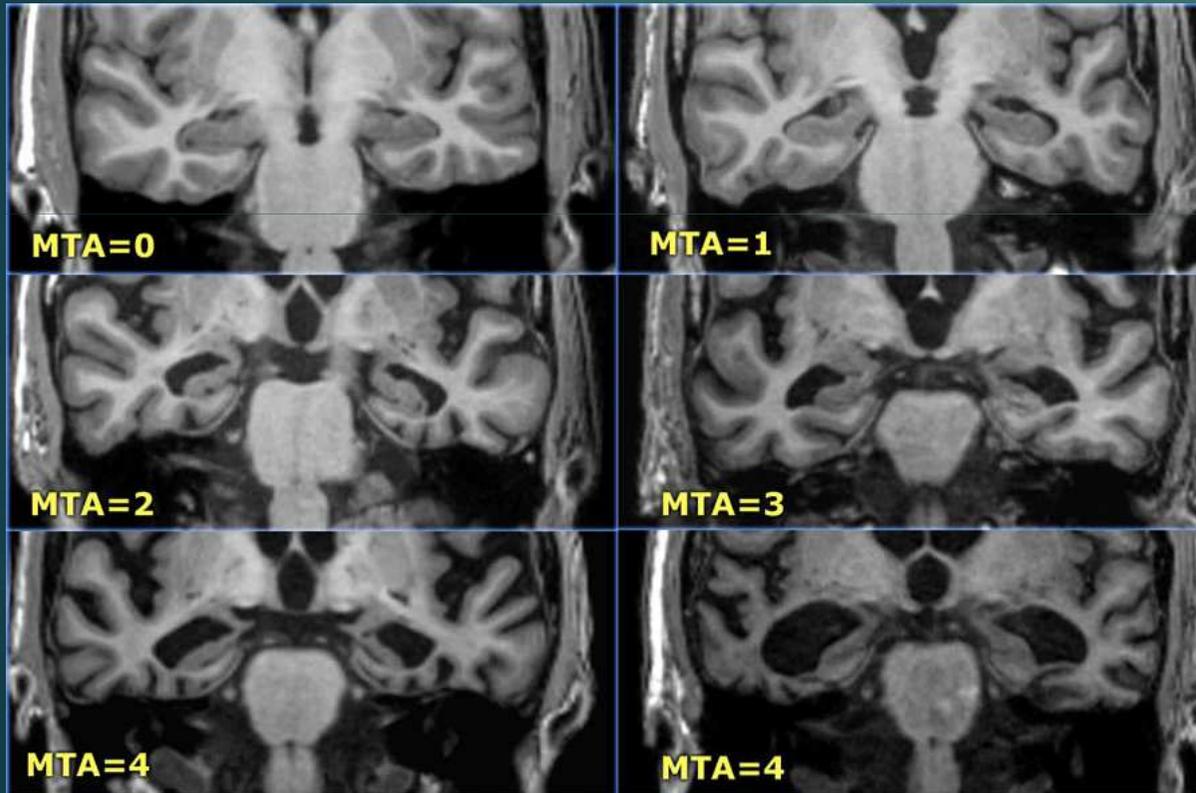


Figure 3 Schematic drawing showing linear measures of medial temporal lobe. A = largest vertical height of hippocampal formation, defined as dentate gyrus, hippocampus proper, and subiculum together with parahippocampal gyrus; B = largest horizontal width between hippocampal formation and brainstem; C = largest vertical width of choroid fissure; D = width of temporal horn.

Brain MRI

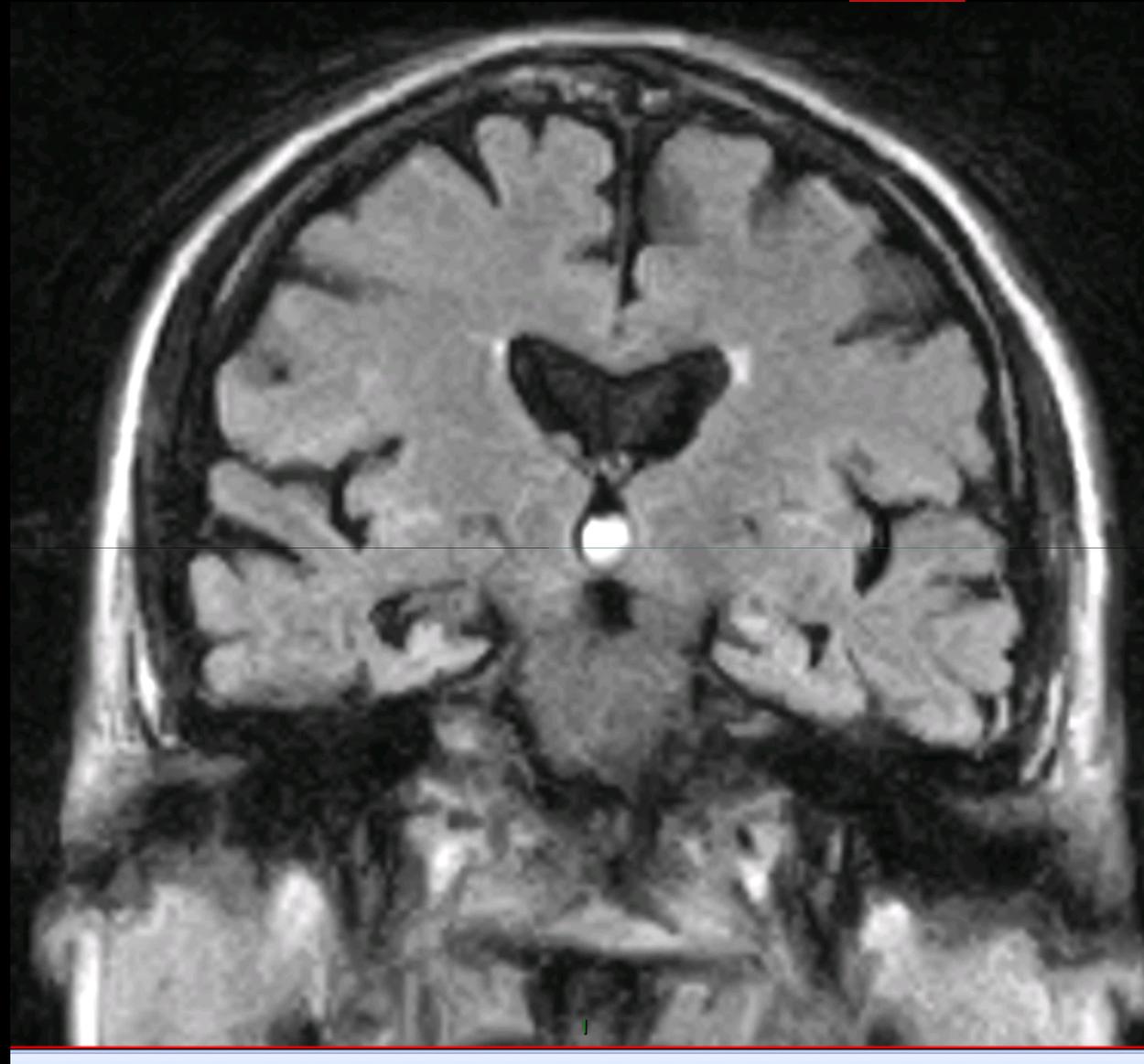
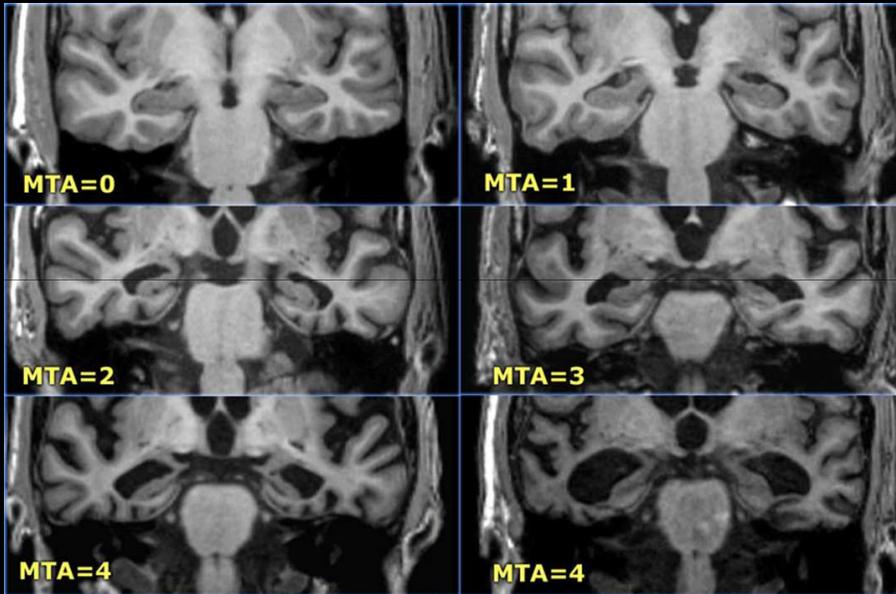


MTA visual rating scale

Score	Width of choroid fissure	Width of temporal horn	Height of hippocampal formation
0	N	N	N
1	↑	N	N
2	↑↑	↑↑	↓
3	↑↑↑	↑↑↑	↓↓
4	↑↑↑	↑↑↑	↓↓↓

> 75 years : MTA-score 3 or more is abnormal (i.e. 2 can still be normal at this age)

Brain MRI



MCI (Petersen, 1995)

- Cognitive complaint, usually memory, corroborated by an informant
- Cognitive screening test in normal range for age (eg MMSE)
- 1.5 SDs below age-appropriate norms on **memory tests or memory component** of other cognitive tests
- Not meeting DSM dementia criteria
- ADLs not significantly affected

Revised Criteria for Mild Cognitive Impairment: Validation within a Longitudinal Population Study

Sylvaine Artero^a Ronald Petersen^c Jacques Touchon^b Karen Ritchie^a

A) Disturbo cognitivo definito come uno dei seguenti:

- Riferito dal soggetto
- Riferito dal medico
- Riferito dai familiari

B) Presenza di tutte le seguenti caratteristiche:

- Cambiamento dal normale grado di funzionamento
- Declino in una qualsiasi area cognitiva
- Mantenimento nel funzionamento generale ma possibilmente con maggiore difficoltà nel compiere le attività quotidiane
- Assenza di demenza

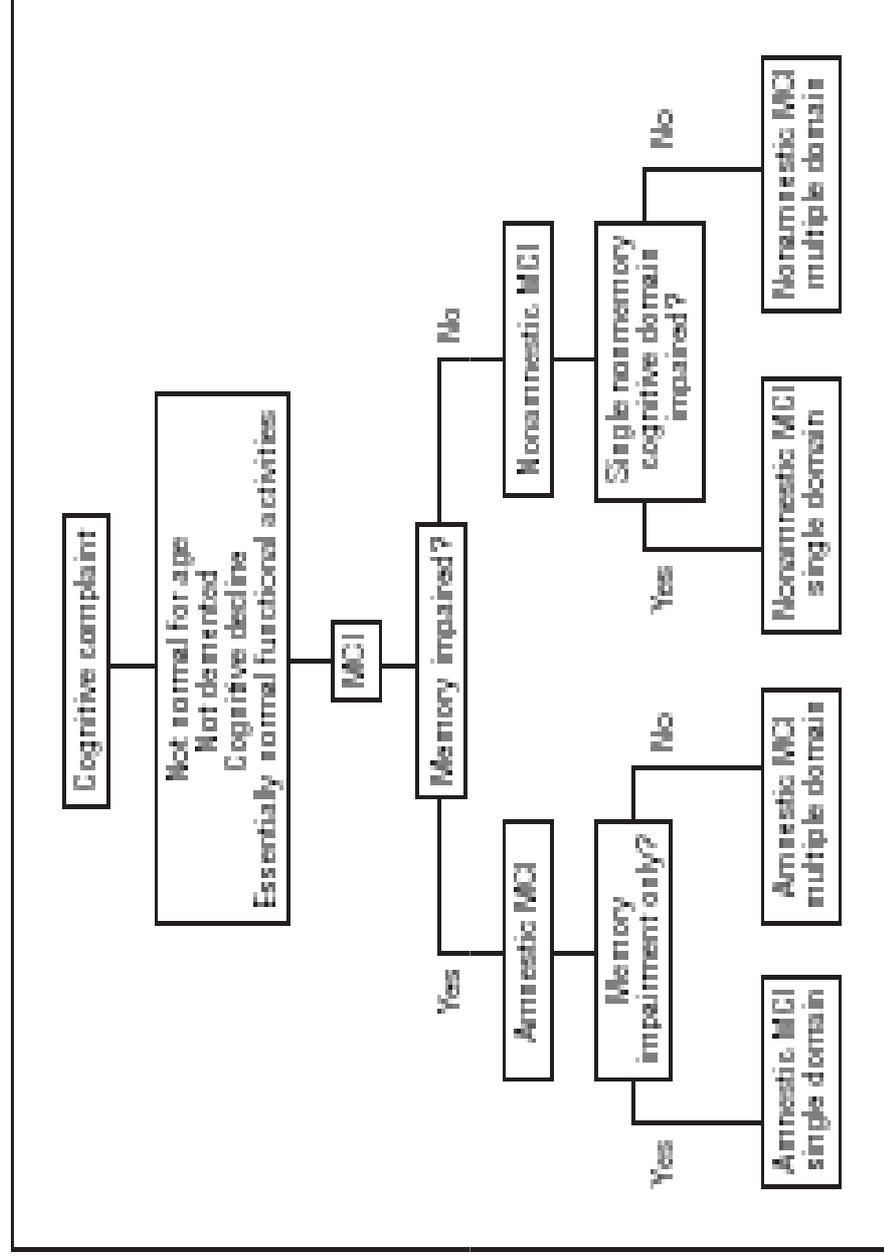


Figure 2. Current flowchart for the diagnosis of mild cognitive impairment (MCI) and its subtypes.¹⁰ Reprinted with permission from Blackwell Publishing.

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup

Marilyn S. Albert^{a,*}, Steven T. DeKosky^{b,c}, Dennis Dickson^d, Bruno Dubois^e,
Howard H. Feldman^f, Nick C. Fox^g, Anthony Gamst^h, David M. Holtzman^{i,j}, William J. Jagust^k,
Ronald C. Petersen^l, Peter J. Snyder^{m,n}, Maria C. Carrillo^o, Bill Thies^o, Creighton H. Phelps^p

Table 1

Summary of clinical and cognitive evaluation for MCI due to AD

Establish clinical and cognitive criteria

Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)

Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)

Preservation of independence in functional abilities

Not demented

Examine etiology of MCI consistent with AD pathophysiological process

Rule out vascular, traumatic, medical causes of cognitive decline, where possible

Provide evidence of longitudinal decline in cognition, when feasible

Report history consistent with AD genetic factors, where relevant

Disturbo neurocognitivo lieve

DIAGNOSTIC AND STATISTICAL
MANUAL OF
MENTAL DISORDERS

FIFTH EDITION

DSM-5™

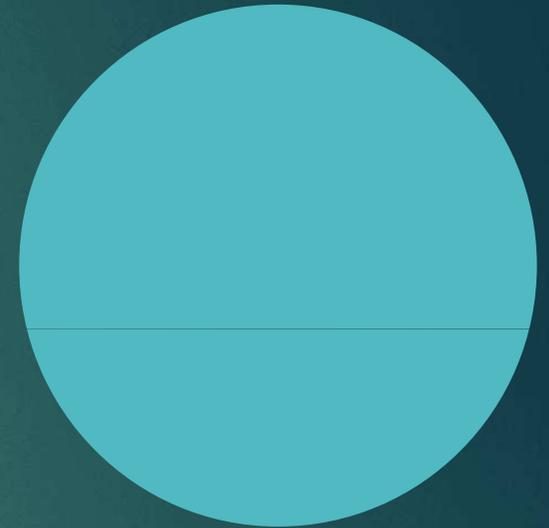
Criteria diagnostici

- a) Evidenza di un **modesto** declino cognitivo da un precedente livello di prestazioni in uno o più domini cognitivi (attenzione complessa, funzione esecutiva, apprendimento e memoria, linguaggio, funzione percettivo-motoria o cognizione sociale) basato su:
- 1) Preoccupazione dell'individuo, di un informatore attendibile o del clinico che vi è stato un **lieve** declino delle funzioni cognitive **e**
 - 2) Una **modesta** compromissione della performance cognitiva, preferibilmente documentata da test neuropsicologici standardizzati o, in loro assenza, da un'altra valutazione clinica quantificata .
- b) I deficit cognitivi interferiscono con l'indipendenza nelle attività quotidiane (per es., attività strumentali complesse della vita quotidiana, come pagare le bollette o gestire i farmaci, sono conservate ma richiedono uno sforzo maggiore, strategie compensatorie o adattamento).
- c) I deficit cognitivi non si verificano esclusivamente nel contesto di un delirium.
- d) I deficit cognitivi non sono meglio spiegati da un altro disturbo mentale (per es., disturbo depressivo maggiore, schizofrenia).

Disturbo neurocognitivo lieve

Specificare

- se dovuto a malattia di Alzheimer, Malattia vascolare ecc.
- senza alterazione comportamentale
- con alterazione comportamentale



Neuropsychological evaluation

17.11.14

- ▶ MMSE 27/30
- ▶ IADL 1/5 lost, BADL 0/6 lost



Alzheimer's & Dementia ■ (2011) 1–10

Alzheimer's
&
Dementia

The diagnosis of mild cognitive impairment due to Alzheimer's disease:
Recommendations from the National Institute on Aging and Alzheimer's
Association workgroup

Marilyn S. Albert^{a,*}, Steven T. DeKosky^{b,e}, Dennis Dickson^d, Bruno Dubois^e,
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Ronald C. Petersen^l, Peter J. Snyder^{m,n}, Maria C. Carrillo^o, Bill Thies^o, Creighton H. Phelps^p

2.2.3. Longitudinal cognitive evaluation

Evidence of progressive decline in cognition provides additional evidence that the individual has “MCI due to AD,” as noted earlier in the text. Thus, it is important to obtain longitudinal assessments of cognition, whenever possible. It is recognized that a diagnosis will likely need to be given without the benefit of this information; however, obtaining objective evidence of progressive declines in cognition over time is important for establishing the accuracy of the diagnosis, as well as for assessing any potential treatment response.

February 2014

- ▶ As part of a clinical research study, he was given one PET with an amyloid tracer (florbetapir).



Research

Original Investigation

Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia A Meta-analysis

Willemijn J. Jansen, MSc; Rik Ossenkoppele, PhD; Dirk L. Knol, PhD; Betty M. Tijms, PhD;
Philip Scheltens, MD, PhD; Frans R. J. Verhey, MD, PhD; Pieter Jelle Visser, MD, PhD;
and the Amyloid Biomarker Study Group

STUDY SELECTION Studies were included if they provided individual participant data for participants without dementia and used an a priori defined cutoff for amyloid positivity.

DATA EXTRACTION AND SYNTHESIS Individual records were provided for 2914 participants with normal cognition, 697 with SCI, and 3972 with MCI aged 18 to 100 years from 55 studies.

MAIN OUTCOMES AND MEASURES Prevalence of amyloid pathology on positron emission tomography or in cerebrospinal fluid according to AD risk factors (age, apolipoprotein E [APOE] genotype, sex, and education) estimated by generalized estimating equations.

Research

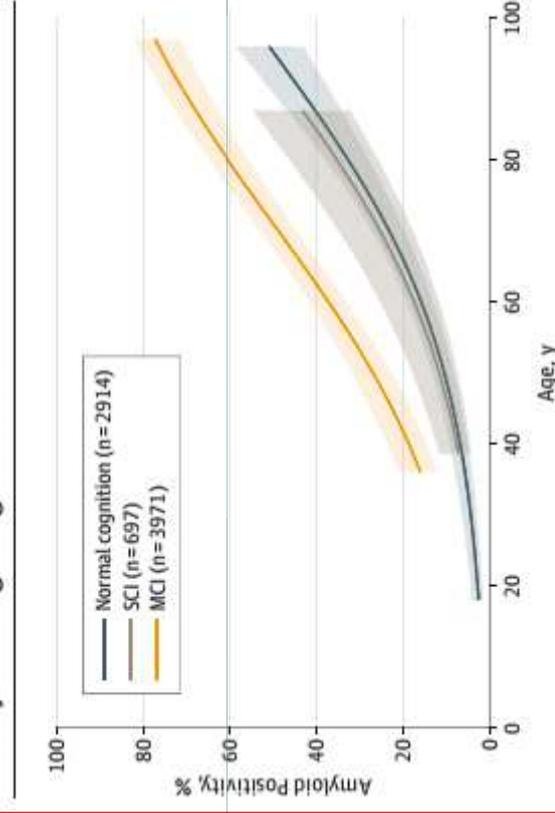
Original Investigation

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JAMA. 2015;313(19):1924-1938. doi:10.1001/jama.2015.4668
Corrected on May 19, 2015.

Figure 2. Association of Age With Prevalence Estimates of Amyloid Positivity According to Cognitive Status



The prevalence estimates were generated from generalized estimating equations. The model included age and cognitive status as predictors. Shading indicates 95% CIs; SCl, subjective cognitive impairment; MCl, mild cognitive impairment.

Research

Original Investigation

Prevalence of Cerebral Amyloid Pathology in Persons Without Dementia A Meta-analysis

Willemijn J. Jansen, MSc; Rik Ossenkoppele, PhD; Dirk L. Knol, PhD; Betty M. Tijms, PhD;
Philip Scheltens, MD, PhD; Frans R. J. Verhey, MD, PhD; Pieter Jelle Visser, MD, PhD;
and the Amyloid Biomarker Study Group

CONCLUSIONS AND RELEVANCE Among persons without dementia, the prevalence of cerebral amyloid pathology as determined by positron emission tomography or cerebrospinal fluid findings was associated with age, APOE genotype, and presence of cognitive impairment. These findings suggest a 20- to 30-year interval between first development of amyloid positivity and onset of dementia.

Research

Original Investigation

Prevalence of Amyloid PET Positivity in Dementia Syndromes A Meta-analysis

Rik Ossenkoppele, PhD; Willemijn J. Jansen, MSc; Gil D. Rabinovici, MD; Dirk L. Knol, PhD; Wiesje M. van der Flier, PhD; Philip Scheltens, MD, PhD; Pieter Jelle Visser, MD, PhD; and the Amyloid PET Study Group

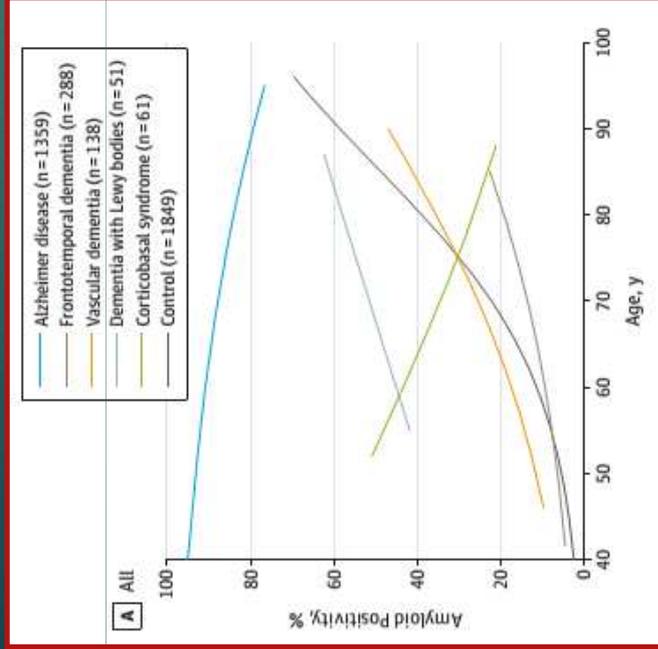


Figure 2. Prevalence of Amyloid Positivity on PET According to Age for the Different Dementia Diagnostic Groups

RESULTS The likelihood of amyloid positivity was associated with age and APOE ε4 status. In AD dementia, the prevalence of amyloid positivity decreased from age 50 to 90 years in APOE ε4 noncarriers (86% [95% CI, 73%-94%] at 50 years to 68% [95% CI, 57%-77%] at 90 years; n = 377) and to a lesser degree in APOE ε4 carriers (97% [95% CI, 92%-99%] at 50 years to 90% [95% CI, 83%-94%] at 90 years; n = 593; P < .01). Similar associations of age and APOE ε4 with amyloid positivity were observed in participants with AD dementia at autopsy. In most non-AD dementias, amyloid positivity increased with both age (from 60 to 80 years) and APOE ε4 carriage.

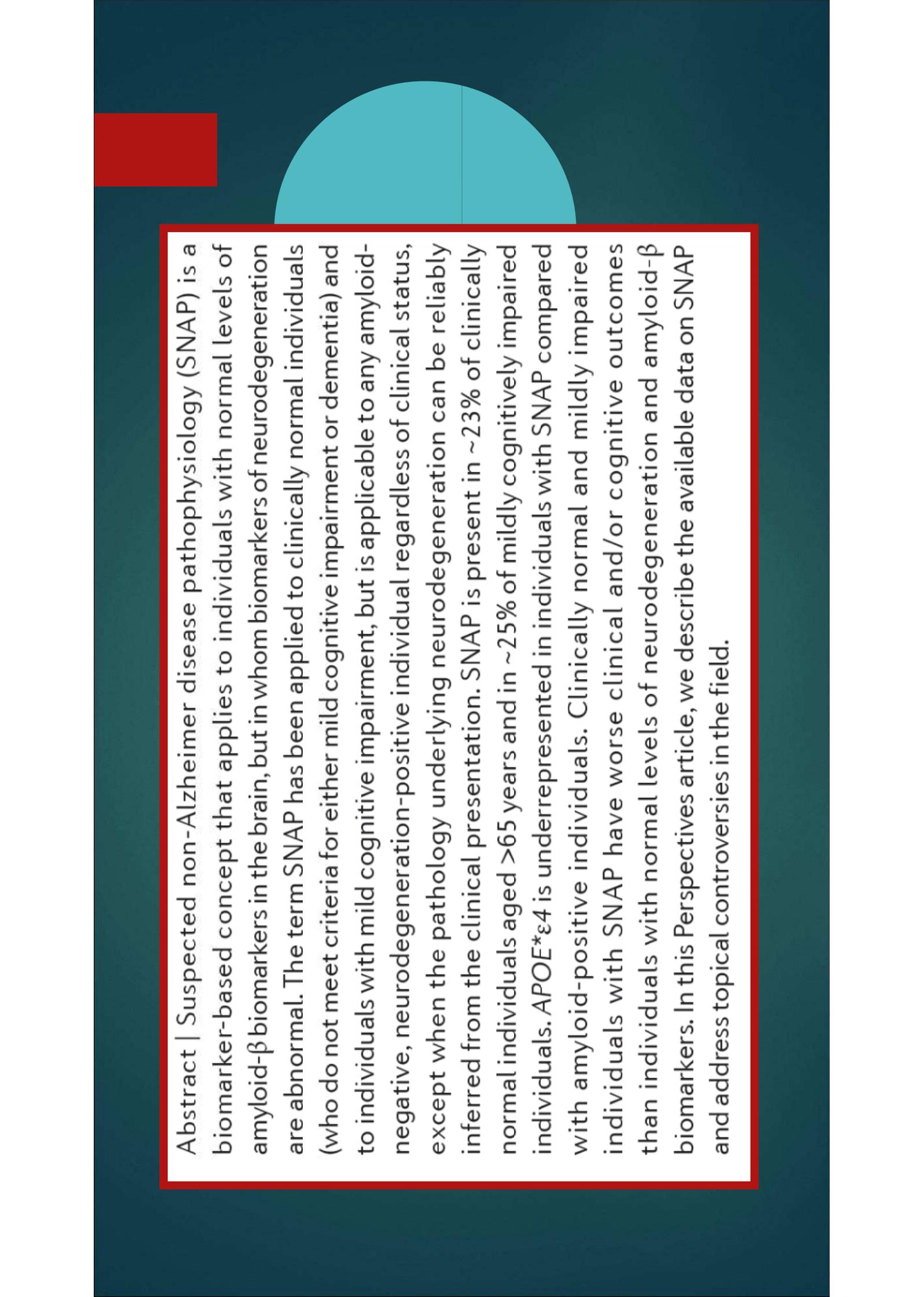
	Total Participants	Amyloid Positivity, % (95% CI)	
		Age 60 y	Age 80 y
Dementia with Lewy bodies			
APOE ε4 carrier	16	63 (48-80)	83 (67-92)
APOE ε4 noncarrier	18	29 (15-50)	54 (30-77)
Frontotemporal dementia			
APOE ε4 carrier	48	19 (12-28)	43 (35-50)
APOE ε4 noncarrier	160	5 (3-8)	14 (11-18)
Vascular dementia			
APOE ε4 carrier	30	25 (9-52)	64 (49-77)
APOE ε4 noncarrier	77	7 (3-18)	29 (17-43)

CONCLUSIONS AND RELEVANCE Among participants with dementia, the prevalence of amyloid positivity was associated with clinical diagnosis, age, and APOE genotype. These findings indicate the potential clinical utility of amyloid imaging for differential diagnosis in early-onset dementia and to support the clinical diagnosis of participants with AD dementia and noncarrier APOE ε4 status who are older than 70 years.

OPINION

Suspected non-Alzheimer disease pathophysiology — concept and controversy

Clifford R. Jack Jr, David S. Knopman, Gaël Chételat, Dennis Dickson, Anne M. Fagan, Giovanni B. Frisoni, William Jagust, Elizabeth C. Mormino, Ronald C. Petersen, Reisa A. Sperling, Wiesje M. van der Flier, Victor L. Villemagne, Pieter J. Visser and Stephanie J. B. Vos



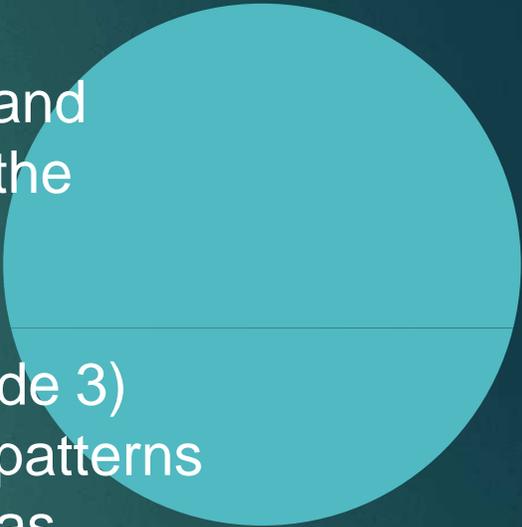
Abstract | Suspected non-Alzheimer disease pathophysiology (SNAP) is a biomarker-based concept that applies to individuals with normal levels of amyloid- β biomarkers in the brain, but in whom biomarkers of neurodegeneration are abnormal. The term SNAP has been applied to clinically normal individuals (who do not meet criteria for either mild cognitive impairment or dementia) and to individuals with mild cognitive impairment, but is applicable to any amyloid-negative, neurodegeneration-positive individual regardless of clinical status, except when the pathology underlying neurodegeneration can be reliably inferred from the clinical presentation. SNAP is present in ~23% of clinically normal individuals aged >65 years and in ~25% of mildly cognitively impaired individuals. *APOE** ϵ 4 is underrepresented in individuals with SNAP compared with amyloid-positive individuals. Clinically normal and mildly impaired individuals with SNAP have worse clinical and/or cognitive outcomes than individuals with normal levels of neurodegeneration and amyloid- β biomarkers. In this Perspectives article, we describe the available data on SNAP and address topical controversies in the field.



Five biomarkers are used in the NIA–AA classification.

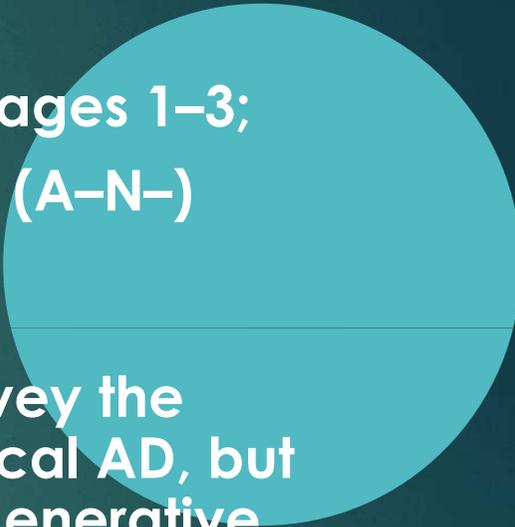
1) Biomarkers of fibrillary A β deposition include high ligand retention on amyloid-PET and 2) low levels of A β 42 in the cerebrospinal fluid (CSF).

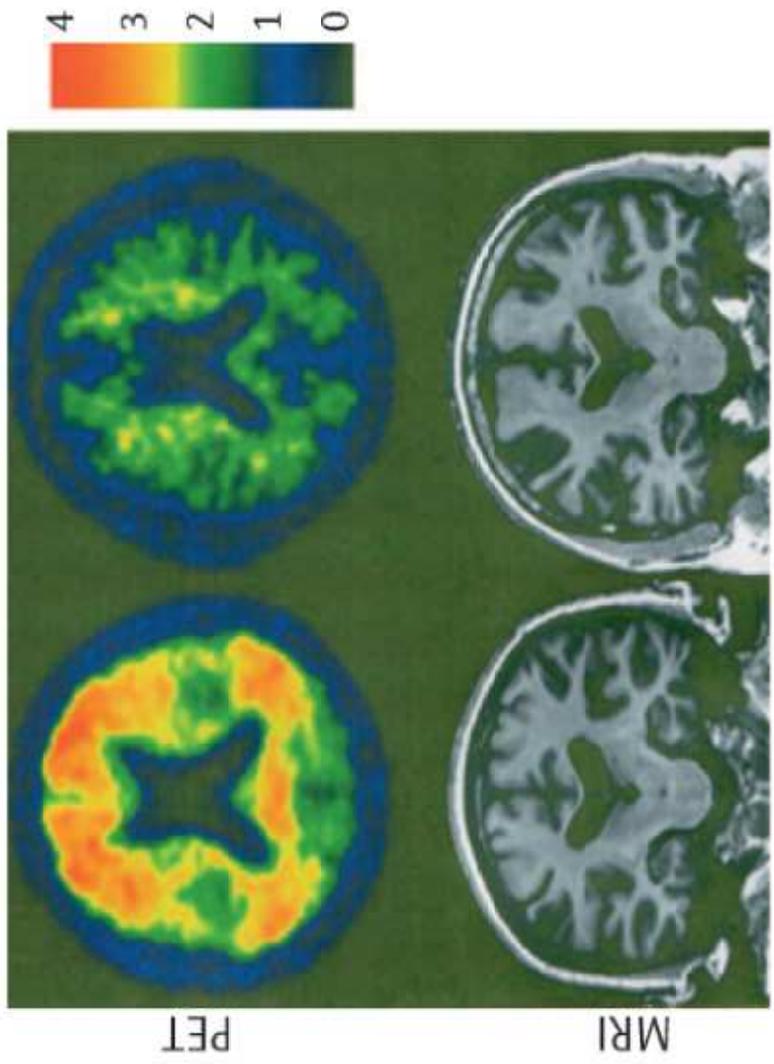
The biomarkers of AD-related neurodegeneration include 3) high levels of tau in the CSF, 4) signature topographic patterns characteristic of AD-associated brain hypometabolism as assessed by 18F-FDG–PET, and 5) atrophy as assessed by structural MRI.





The NIA-AA preclinical AD workgroup that proposed the concept of preclinical AD operated under the assumption that the term 'AD' referred to the pathological condition and that clinical symptoms resulting from the pathological condition are not required in the definition of AD.

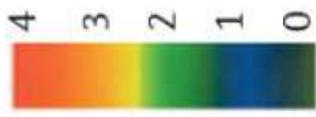
- 
- 
- ▶ 450 clinically normal individuals aged >70 years were classified using amyloid plaque density assessed by PET, brain metabolism assessed by ^{18}F -FDG-PET and hippocampal volume assessed by MRI.
 - ▶ 31% of participants were at NIA-AA preclinical AD stages 1–3;
 - ▶ 43% had neither amyloidosis nor neurodegeneration (A–N–) and were classified as being at stage 0
 - ▶ 23% of participants had neurodegeneration without amyloidosis (A–N+). The term SNAP was used to convey the notion that the latter group did not represent preclinical AD, but rather had biomarker evidence of non-AD neurodegenerative processes.
 - ▶ The proportion of *APOE** ϵ 4 carriers in the SNAP group was 13%, much lower than that in individuals with preclinical AD (~40%), and half that in individuals at stage 0 (24%).



Preclinical AD stage 1 SNAP

PET

MRI





'Clinically normal' rather than "cognitively normal' to describe an elderly individual who does not meet criteria for either mild cognitive impairment or dementia.

Box 1 | Terminology for classification

- A⁻N⁻: NIA-AA preclinical stage 0
- A⁺N⁻: NIA-AA preclinical stage 1
- A⁺N⁺: NIA-AA preclinical stages 2 and 3
- A⁻N⁺: SNAP

A, amyloidosis; N, neurodegeneration; NIA-AA, National Institute on Ageing-Alzheimer disease Association; SNAP, suspected non-Alzheimer disease pathophysiology.

- 
- 
- ▶ Men are more likely to have SNAP than women
 - ▶ SNAP also tend to be older than those at preclinical AD stages 0 or 1.
 - ▶ $APOE^*\epsilon 4$ is markedly less common in SNAP than in preclinical AD (A+N- and A+N+).
 - ▶ One study that examined the changes in the frequency of biomarker-based groups with age found that the frequency of SNAP was 0 in the 50–60 years age range and then increased monotonically, reaching 24% by 89 years of age.

SNAP is a biomarker-based concept that is independent of any particular level of cognitive impairment.

SNAP was found in

- ▶ 17% of participants in the Alzheimer disease Disease Neuroimaging Initiative,
- ▶ 17% of those in the study by Caroli *et al.*,
- ▶ 20% of those in the study by Prestia *et al.*
- ▶ 29% of those in the study by Vos *et al.*
- ▶ 29% of those in the Mayo Clinic Study of Ageing
- ▶ 35% of those in the study by Duara *et al.*

Cognitive trajectories in SNAP



- ▶ In individuals with MCI, the risk of cognitive decline is lowest in A–N– and A+N– individuals, intermediate in those with SNAP, and is highest in A+N+ individuals.
- ▶ In clinically normal individuals, the risk of decline is lowest in A–N– individuals, intermediate in those with SNAP and in A+N– individuals, and is highest in A+N+ individuals.

Mild cognitive impairment with suspected nonamyloid pathology (SNAP)

Prediction of progression

Anna Caroli, PhD
Annapaola Prestia, PsyD
Samantha Galluzzi, MD
Clarissa Ferrari, PhD
Wiesje M. van der Flier, PhD
Rik Ossenkoppele, PhD
Bart Van Berckel, MD
Frederik Barkhof, MD, PhD
Charlotte Teunissen, PhD
Anders E. Wall, PhD
Stephen F. Carter, PhD
Michael Schöll, PhD
Il Han Choo, MD, PhD
Timo Grimmer, MD
Alberto Redolfi, MSc
Agneta Nordberg, MD, PhD
Philip Scheltens, MD, PhD
Alexander Drzezga, MD
Giovanni B. Frisoni, MD
For the Alzheimer's Disease Neuroimaging Initiative

ABSTRACT

Objectives: The aim of this study was to investigate predictors of progressive cognitive deterioration in patients with suspected non-Alzheimer disease pathology (SNAP) and mild cognitive impairment (MCI).

Methods: We measured markers of amyloid pathology (CSF β -amyloid 42) and neurodegeneration (hippocampal volume on MRI and cortical metabolism on ^{18}F -fluorodeoxyglucose-PET) in 201 patients with MCI clinically followed for up to 6 years to detect progressive cognitive deterioration. We categorized patients with MCI as A+/A- and N+/N- based on presence/absence of amyloid pathology and neurodegeneration. SNAPs were A-N+ cases.

Results: The proportion of progressors was 11% (8/41), 34% (14/41), 56% (19/34), and 71% (60/85) in A-N-, A+N-, SNAP, and A+N+, respectively; the proportion of APOE ϵ 4 carriers was 29%, 70%, 31%, and 71%, respectively, with the SNAP group featuring a significantly different proportion than both A+N- and A+N+ groups ($p \leq 0.005$). Hypometabolism in SNAP patients was comparable to A+N+ patients ($p = 0.154$), while hippocampal atrophy was more severe in SNAP patients ($p = 0.002$). Compared with A-N-, SNAP and A+N+ patients had significant risk of progressive cognitive deterioration (hazard ratio = 2.7 and 3.8, $p = 0.016$ and $p < 0.001$), while A+N- patients did not (hazard ratio = 1.13, $p = 0.771$). In A+N- and A+N+ groups, none of the biomarkers predicted time to progression. In the SNAP group, lower time to progression was correlated with greater hypometabolism ($r = 0.42$, $p = 0.073$).

Conclusions: Our findings support the notion that patients with SNAP MCI feature a specific risk progression profile. *Neurology*® 2015;84:1-8

GLOSSARY

A β = β -amyloid; A β ₄₂ = β -amyloid 1-42; AD = Alzheimer disease; ADNI = Alzheimer's Disease Neuroimaging Initiative; EU = European Union; FDG = ^{18}F -fluorodeoxyglucose; FTD = frontotemporal dementia; KUHH = Karolinska University Hospital Huddinge; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; MUCH = Klinikum rechts der Technischen Universität München; SNAP = suspected non-Alzheimer disease pathology; TOMC = Translational Outpatient Memory Clinic; VUMC = VU University Medical Center.

201 patients with clinical diagnosis of MCI amnesic, multiple domain

They measured markers of amyloid pathology (CSF β -amyloid 42) and neurodegeneration (hippocampal volume on MRI and cortical metabolism on ^{18}F -fluorodeoxyglucose-PET)

MCI:

41 A+/N-

85 A+/N+

41 A-/N-

34 A-/N+ → SNAP

^a CSF A β ₄₂ concentration was determined by commercial ELISAs in Brescia, Amsterdam, Stockholm, and Munich samples and xMAP Luminex platform with Innogenetics immunoassay kit-based reagents in ADNI samples, and was expressed in z scores, computed as deviation from the threshold in SD units. For European memory clinics, thresholds for abnormality were as follows: <500 pg/mL in Brescia, <550 pg/mL in Amsterdam, <450 pg/mL in Stockholm, and <643 pg/mL in Munich. Thresholds were rescaled to <500 pg/mL before transformation into z scores (for details see text).

Mild cognitive impairment with suspected
nonamyloid pathology (SNAP)
Prediction of progression

Progression:

A-/N- < A+/N- < **SNAP** < A+/N+ → **progression is linked to
NEURODEGENERATION**

None of the biomarkers predicted time to progression

APOE ε4 carriers

A+/N- = A+/N+ = **70%** A-/N- = SNAP = **30%** → **APOE ε4 is linked to
AMYLOID DEPOSITION**

Mild cognitive impairment with suspected nonamyloid pathology (SNAP)

Prediction of progression

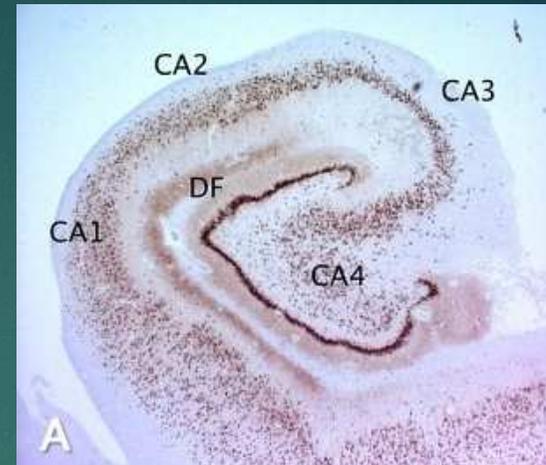
The pathophysiology of cognitive impairment in MCI-SNAP is still a matter of debate.

It can be hypothesized that the category represents a mixed bag of several different types of amyloid-unrelated pathologies that may resemble AD clinically, such as

- hippocampal sclerosis,
- argyrophilic grain disease,
- tangle-only dementia,
- frontotemporal degeneration, or
- Lewy body disease,

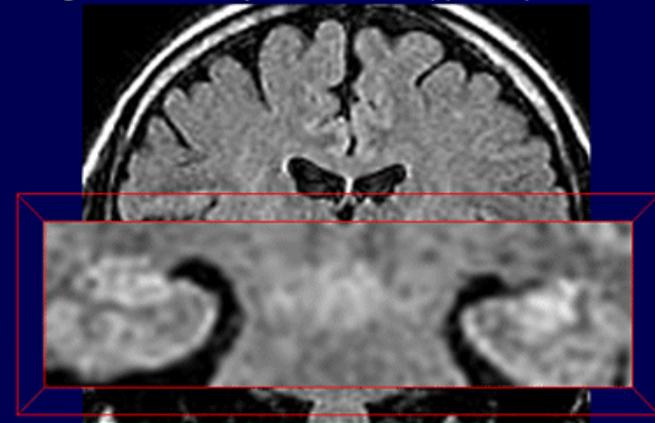
Hippocampal sclerosis?

- ▶ Hippocampal sclerosis (HS) is a neuropathological condition with severe neuronal cell loss and gliosis in the hippocampus, specifically in the CA-1.
- ▶ MRI scan commonly displays increased T2 signal and hippocampal atrophy.
- ▶ Strong association with complex partial temporal lobe epilepsy (cause? Sequelae?)



Hippocampal Sclerosis

Coronal FLAIR (T2-weighted, 3-mm slices)
T2 signal abnormality indicative of hippocampal sclerosis



Tauopathy?

▶ Other conditions in which neurofibrillary tangles are commonly observed include:

▶ Argyrophilic grain disease?

▶ Tangle-predominant dementia?

▶ Progressive supranuclear palsy?

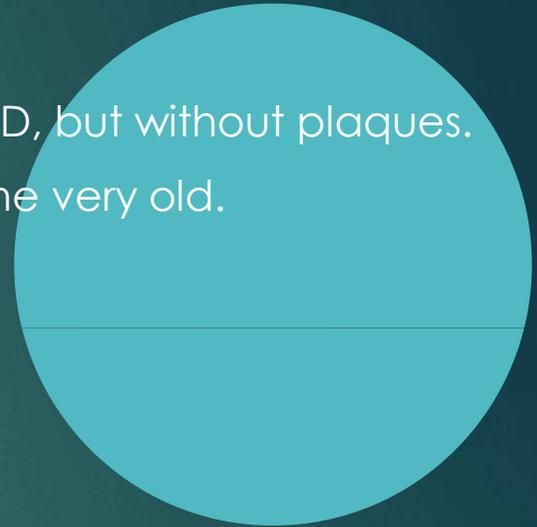
▶ Frontotemporal degeneration?

} with NFTs similar to AD, but without plaques.

} Tends to appear in the very old.

} Not suggestive

▶ Dementia pugilistica (chronic traumatic encephalopathy)



November 2015 Optical coherence tomography



REVIEW

Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome

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- ▶ The long-term consequences of repetitive head impacts have been described since the early 20th century.
- ▶ Terms such as punch drunk and dementia pugilistica were first used to describe the clinical syndromes experienced by boxers.
- ▶ A more generic designation, chronic traumatic encephalopathy (CTE), has been employed since the mid-1900s and has been used in recent years to describe a neurodegenerative disease found not just in boxers but in American football players, other contact sport athletes, military veterans, and others with histories of repetitive brain trauma, including concussions and subconcussive trauma

Chronic traumatic encephalopathy (CTE)

- ▶ CTE è una malattia neurodegenerativa caratterizzata da accumulo di proteina tau iperfosforilata (p-tau) in neuroni e astrociti in un modello che è unico rispetto ad altre taupatie, compresa la malattia di Alzheimer (AD) e alla degenerazione lobare frontotemporale.
- ▶ La deposizione p-tau inizialmente si verifica focalmente, con grovigli neurofibrillari perivascolari e neuriti nella profondità dei solchi cerebrali.
- ▶ Si diffonde fino a coinvolgere strati superficiali della corteccia adiacenti, eventualmente con conseguente diffusa degenerazione dei lobi temporali mediali, lobi frontali, diencefalo, tronco encefalico.
- ▶ Diversamente AD, vi è una scarsità di beta amiloide placche neuritiche.



The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy

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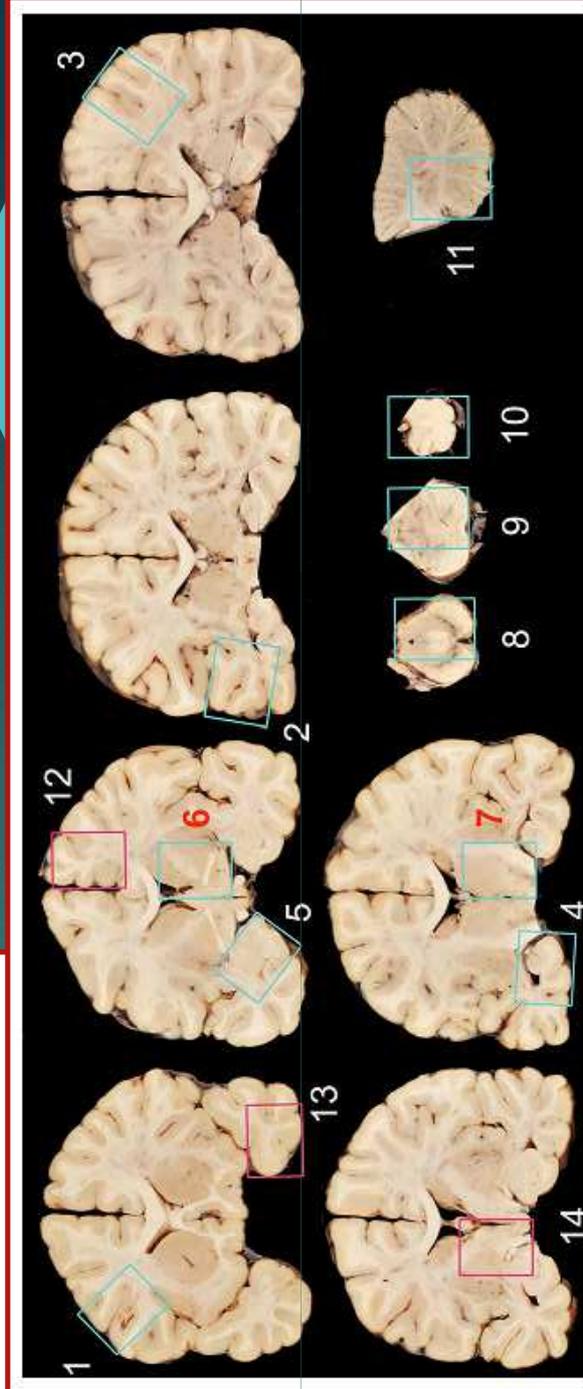


Fig. 6 Minimum recommended brain regions for evaluation for CTE. The following sections from the NIA-AA blocking scheme are recommended for p-tau immunostaining in evaluation for CTE (*blue rectangles*). In the cortical sections (blocks 1–5, 12, 13), the depths of the cortical sulci should be included in the section. 1 Middle frontal gyrus, 2 superior and middle temporal gyri, 3 inferior parietal lobule, 4 hippocampus, 5 amygdala and entorhinal cortex, 6 basal ganglia at

level of anterior commissure with basal nucleus of Meynert, 7 thalamus, 8 midbrain with substantia nigra, 9 pons with locus coeruleus, 10 medulla oblongata, 11 cerebellar cortex and dentate nucleus; additional sections if high suspicion of CTE (*red rectangles*): 12 superior frontal gyrus, 13 temporal pole, 14 hypothalamus and mammillary body

Table 2 Preliminary NINDS criteria for the pathological diagnosis of CTE

Required for diagnosis of CTE

1. The pathognomonic lesion consists of p-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci

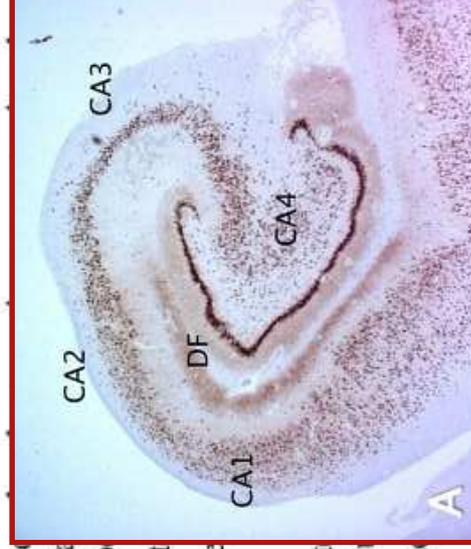
Supportive neuropathological features of CTE

p-Tau-related pathologies:

1. Abnormal p-tau immunoreactive pretangles and NFTs preferentially affecting superficial layers (layers II–III), in contrast to layers III and V as in AD
2. In the hippocampus, pretangles, NFTs or extracellular tangles preferentially affecting CA2 and pretangles and prominent proximal dendritic swellings in CA4. These regional p-tau pathologies differ from the preferential involvement of CA1 and subiculum found in AD (Fig. 3)
3. Abnormal p-tau immunoreactive neurons in the cerebral cortex, including the thalamic nuclei, amygdala, nucleus accumbens, subthalamic nucleus, thalamic nuclei, substantia nigra and locus coeruleus
4. p-Tau immunoreactive thorny astrocytes
5. p-Tau immunoreactive large grain-like inclusions

Non-p-tau-related pathologies:

1. Macroscopic features: disproportionate atrophy of the cerebral cortex and other signs of previous traumatic injury
2. TDP-43 immunoreactive neuronal cytoplasmic inclusions in the hippocampus, anteromedial temporal cortex and amygdala (Fig. 4)

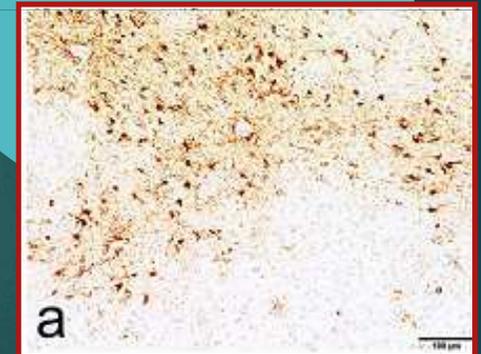


Diagnostic neuropathological features of CTE

The pathognomonic lesion of CTE consists of p-tau aggregates in neurons, astrocytes, and cell processes around small vessels in an irregular pattern at the depths of the cortical sulci

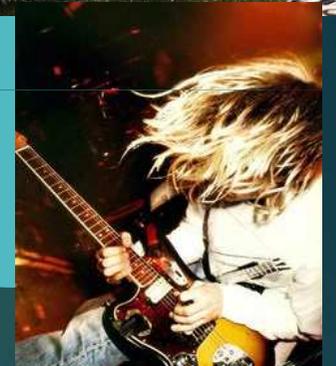


Fig. 1 Low magnification inspection of p-tau-stained slides often revealed the irregular spatial pattern of CTE pathology. AT8-stained slides of cerebral cortex in 3 cases of CTE showing irregular patches of p-tau pathology most dense at the depths of the sulci



Chronic traumatic encephalopathy (CTE)

- ▶ CTE è stata trovata più spesso in atleti professionisti coinvolti negli sport di contatto (ad esempio, la boxe e football americano), che sono stati sottoposti a testa a testa ripetitivo con conseguente trauma contusivo e subcontusivo.
- ▶ La conferma neuropatologica è stata riportata in individui giovani atleti che hanno praticato lo sport alla scuola superiore o all'università.
- ▶ Inoltre è stato trovato nei non-atleti che hanno sperimentato colpi al capo ripetuti, negli epilettici, persone disabile che Headbang, e vittime di abusi fisici.
- ▶ Inoltre, CTE è stata diagnosticata in neuropatologici membri del servizio militare in precedenza dispiegati in Iraq e in Afghanistan con storie di traumi cerebrali ripetitivi



- ▶ All cases of neuropathologically confirmed CTE reported to date have had a history of repetitive head impacts, although **there has been some suggestion that a single traumatic brain injury (TBI)** may also lead to the neuropathological changes of CTE (Johnson VE, Stewart W, Smith DH: Widespread tau and amyloid- β pathology many years after a single traumatic brain injury in humans. *Brain Pathol* 2012,22:142–149)
- ▶ Although head impacts appear to be necessary for the initiation of the pathogenetic cascade that eventually leads to neurodegeneration, the history of head impacts is not sufficient and additional risk factors (including genetic susceptibility markers) remain unknown.
- ▶ The incidence and prevalence of CTE are also unknown, although the number potentially affected could be quite large. Every year, between 1.6 and 3.8 million individuals in the US experience a sports-related concussion, and the number of youth sports-related concussions has grown in recent years.

Clinical presentation of chronic traumatic encephalopathy



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ABSTRACT

Objective: The goal of this study was to examine the clinical presentation of chronic traumatic encephalopathy (CTE) in neuropathologically confirmed cases.

Methods: Thirty-six adult male subjects were selected from all cases of neuropathologically confirmed CTE at the Boston University Center for the Study of Traumatic Encephalopathy. Subjects were all athletes, had no comorbid neurodegenerative or motor neuron disease, and were next-of-kin informants to provide retrospective reports of the subjects' histories and clinical presentations. These interviews were conducted blind to the subjects' neuropathologic findings.

Results: A triad of cognitive, behavioral, and mood impairments was common overall, with cognitive deficits reported for almost all subjects. Three subjects were asymptomatic at death. Consistent with earlier case reports of boxers, 2 relatively distinct clinical presentations emerged, with one group whose initial features developed at a younger age and involved primarily behavioral and mood disturbance (n = 22), and another group whose initial presentation developed at an older age and involved cognitive impairment (n = 11).

Conclusions: This suggests there are 2 major clinical presentations of CTE, one a behavioral variant and the other a cognitive variant. **Neurology**® 2013;81:1122-1129

Table 1 Description of sample by initial clinical presentation

Variable	All subjects (n = 36)	Behavior/mood group (n = 22) ^a	Cognition group (n = 11) ^a
Age at death, y, mean ± SD (range)	56.6 ± 21.9 (17-98)	51.4 ± 18.5 (21-84) ^b	69.2 ± 21.8 (34-98) ^b
Cause of death, %			
Systemic illness	41.8	49.8	27.3
Accidental overdose	13.9	18.2	9.1
Dementia-related	13.9	9.1	27.3
Suicide	16.7	18.2	18.2
Injury	8.4	4.5	18.2
Years of education, mean ± SD (range)	15.0 ± 2.4 (10-20)	14.5 ± 2.4 (10-18)	15.7 ± 1.4 (13-18)
Football as primary sport, %	80.6	72.7	90.9
Total years of football played, mean ± SD (range)	15.3 ± 6.4 (3-25)	14.4 ± 6.5 (3-25)	18.2 ± 5.9 (5-24)
Neuropathologic severity stage, %			
Stage I	8	9.1	0
Stage II	28	31.8	9.1
Stage III	31	31.8	36.4
Stage IV	33	27.3	54.5
APOE genotype, ^c %			
ε2/ε2	0	0	0
ε2/ε3	3	4.5	0
ε2/ε4	0	0	0
ε3/ε3	63	63.6	54.5
ε3/ε4	26	27.3	27.3
ε4/ε4	9	4.5	18.2

^a Three subjects were asymptomatic; percentages within initial feature group are based on the percent of asymptomatic subjects.

^b Statistically significant between-group difference, $p < 0.05$.

^c One subject did not have APOE genotyping.

Table 2 Summary of clinical features of chronic traumatic encephalopathy found in the literature

Behavioral features	Mood features	Cognitive features	Motor features
Explosivity	Depression	Dementia	Ataxia
Loss of control	Hopelessness	Memory impairment	Dysarthria
Short fuse	Suicidality	Executive dysfunction	Parkinsonism
Impulsivity	Anxiety	Lack of insight	Gait Disturbance
Aggression	Fearfulness	Perseveration	Tremor
Rage	Irritability	Impaired attention and concentration	Masked facies
Physical violence	Labile emotions	Language difficulties	Rigidity
Verbal violence	Apathy	Dysgraphia	Muscle weakness
Inappropriate speech	Loss of interest	Alogia	Spasticity
Boastfulness	Fatigue	Visuospatial difficulties	Clonus
Childish behavior	Flat affect		
Social inappropriateness	Insomnia		
Disinhibited speech	Mania		
Disinhibited behavior	Euphoria		
Paranoid delusions	Mood swings		
Personality changes	Prolix		
Psychosis			
Social isolation			
		General cognitive impairment	
		Reduced intelligence	

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Psychosis			
Social isolation			

- ▶ Symptom onset for the 'behavior/mood group' usually occurs at a significantly younger age than for the 'cognition group'.
- ▶ Significantly more subjects in the cognition group developed dementia than those in the behavior/mood group.

Traumatic encephalopathy syndrome is meant to be a diagnosis of a clinical syndrome associated with a history of repetitive brain trauma

General criteria for traumatic encephalopathy syndrome

All five criteria must be met for a diagnosis of TES:

1. **History of multiple impacts to the head (or to the body resulting in impulsive force transmitted to the head).** Multiple impacts are defined based upon (a) the types of injuries and (b) the source of exposure.

a. Types of injuries:

- i) Mild TBI or concussion, defined according to the Zurich 2012 Consensus Statement on Concussion in Sport [57] as a 'complex pathophysiological process affecting the brain, induced by biomechanical forces...caused either by a direct blow to the head, face, neck or elsewhere on the body with an "impulsive" force transmitted to the head...the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury' and, as such, **no abnormality** is seen on standard structural **neuroimaging studies**. Concussion results in a graded set of clinical symptoms that **may or may not involve loss of consciousness**. History of this form of trauma can be based on documented records from health-care providers or on self- or informant-reports, after being given an appropriate definition of 'concussion' [58]. If there is no reported exposure to other

repetitive hits to the head, there should be a minimum of four documented mild TBIs or concussions.

- ii) **Moderate/severe TBI**, defined as having loss of consciousness of at least 30 minutes, alteration of consciousness/mental state of more than 24 hours, post-traumatic amnesia of more than 24 hours, and Glasgow Coma Scale score of less than 13 [59]. If there is no reported exposure to other repetitive hits to the head, there should be a minimum of two moderate/severe TBIs.
 - iii) 'Subconcussive' trauma, defined as biomechanical force to the head or body similar to, or less than, that required for symptomatic concussion but without symptoms and clinical presentation consistent with concussion [3,4].
- b) Source of exposures:
- i. Involvement in **'high exposure' contact sports (including, but not limited to, boxing, American football, ice hockey, lacrosse, rugby, wrestling, and soccer)** for a minimum of **6 years, including at least 2 years at the college level (or equivalent) or higher**.
 - ii. Military service (including, but not limited to, combat exposure to blast and other explosions as well as non-combat exposure to explosives or to combatant or breach training).
 - iii. History of any other significant exposure to repetitive hits to the head (including, but not limited to, **domestic abuse, head banging, and vocational activities such as door breaching by police**).
 - iv. For moderate/severe TBI, any activity resulting in the injury (for example, **motor vehicle accident**).

- 2) **No other neurological disorder** (including chronic residual symptoms from a single TBI or persistent post-concussion syndrome) that likely accounts for all clinical features, although concomitant diagnoses of substance abuse, post-traumatic stress disorder (PTSD), mood/anxiety disorders, or other neurodegenerative diseases (**for example, AD** and frontotemporal dementia) or a combination of these can be present.
- 3) Clinical features must be present for a **minimum of 12 months**. However, if treatment (for example, 'antidepressant' medication) results in an improvement in select symptoms, the clinician should use her or his best judgment to decide whether the symptoms would have persisted or progressed if treatment had not been initiated.
- 4) At least one of the core clinical features must be present and should be considered a change from baseline functioning.
- 5) **At least two supportive features must be present**.

Traumatic encephalopathy syndrome is meant to be a diagnosis of a clinical syndrome associated with a history of repetitive brain trauma

Core clinical features of traumatic encephalopathy syndrome

At least **one of the core clinical features** must be present:

- 1) **Cognitive.** Difficulties in cognition:
 - a) as reported by self or informant, by history of treatment, or by clinician's report of decline; and
 - b) substantiated by impairment on standardized mental status or neuropsychological tests of episodic memory, executive function, and/or attention, as defined by scores at a level of at least 1.5 standard deviations below appropriate norms.
- 2) **Behavioral.** Being described as emotionally explosive (for example, having a 'short fuse' or being 'out of control'), physically violent, and/or verbally violent, as reported by self or informant, by history of treatment, or by clinician's report. A formal diagnosis of intermittent explosive disorder would meet this criterion but is not necessary.
- 3) **Mood.** Feeling overly sad, depressed, and/or hopeless, as reported by self or informant, by history of treatment, or by clinician's report. A formal diagnosis of major depressive disorder or persistent depressive disorder would meet this criterion but is not necessary.

Supportive features of traumatic encephalopathy syndrome

A **minimum of two** of the following features must be present for a diagnosis of TES:

- 1) **Impulsivity.** Impaired impulse control, as demonstrated by new behaviors, such as excessive gambling, increased or unusual sexual activity, substance abuse, excessive shopping or unusual purchases, or similar activities.
- 2) **Anxiety.** History of anxious mood, agitation, excessive fears, or obsessive or compulsive behavior (or both), as reported by self or informant, history of treatment, or clinician's report. A formal diagnosis of anxiety disorder would meet this criterion but is not necessary.
- 3) **Apathy.** Loss of interest in usual activities, loss of motivation and emotions, and/or reduction of voluntary, goal-directed behaviors, as reported by self or informant, history of treatment, or clinician's report.
- 4) **Paranoia.** Delusional beliefs of suspicion, persecution, and/or unwarranted jealousy.
- 5) **Suicidality.** History of suicidal thoughts or attempts, as reported by self or informant, history of treatment, or clinician's report.
- 6) **Headache.** Significant and chronic headache with at least one episode per month for a minimum of 6 months.
- 7) **Motor signs.** Dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other

features of parkinsonism. If present, the modifier 'with motor features' should be used (see below).

- with motor features should be used (see below).
- 8) **Documented decline.** Progressive decline in function and/or a progression in symptoms and/or signs, based upon repeated formal testing, clinician examination, or other formal measurement (for example, informant questionnaire) **for a minimum of 1 year.**
 - 9) **Delayed onset.** Delayed onset of clinical features after significant head impact exposure, usually at least 2 years and in many cases several years after the period of maximal exposure. It should be noted, however, that individual cases may begin to develop the clinical features of TES during their period of head impact exposure (for example, while still actively involved in a collision sport), especially older individuals or those who have been engaged in the high-exposure activity for many years. It may also be difficult to differentiate the clinical presentation of prolonged or persistent post-concussion syndrome (pPCS) from that of TES. Therefore, there could be cases for whom there is overlap of resolving pPCS and the initial features of TES, thus masking any delayed onset of TES.

Traumatic encephalopathy syndrome is meant to be a diagnosis of a clinical syndrome associated with a history of repetitive brain trauma

Traumatic encephalopathy syndrome diagnostic subtypes

- 1) TES **behavioral/mood** variant (TES-BMv)
 - a) Behavioral or mood core features (or both) without cognitive core features.
- 2) TES **cognitive** variant (TES-COGv)
 - a) Cognitive core features without behavioral or mood core features (or both).
- 3) TES **mixed** variant (TES-MIXv)
 - a) Both cognitive core features and behavioral or mood core features (or both).
- 4) TES **dementia** (TES-D)
 - a) Progressive course of cognitive core features with or without behavioral or mood core features (or both).
 - b) Evidence of **functional impairment**, defined as cognitive impairment (or cognitive impairment exacerbated by behavioral or mood impairment or both) that is severe enough to interfere with the ability to function independently at work or in usual activities, including hobbies, and instrumental activities of daily living. The determination of functional impairment is based on clinician's judgment, taking into account informant reports as well as consideration of individual differences with regard to level of expected responsibility and daily challenges.
 - c) If the **clinical presentation is not distinguishable from that of dementia due to AD or another neurodegenerative disease** (for example,

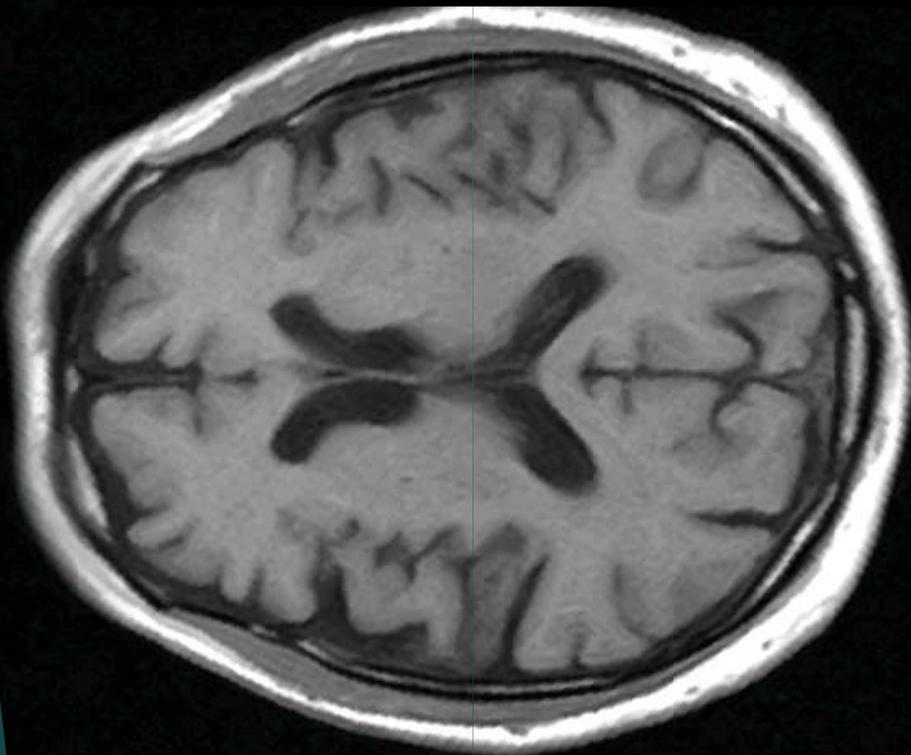
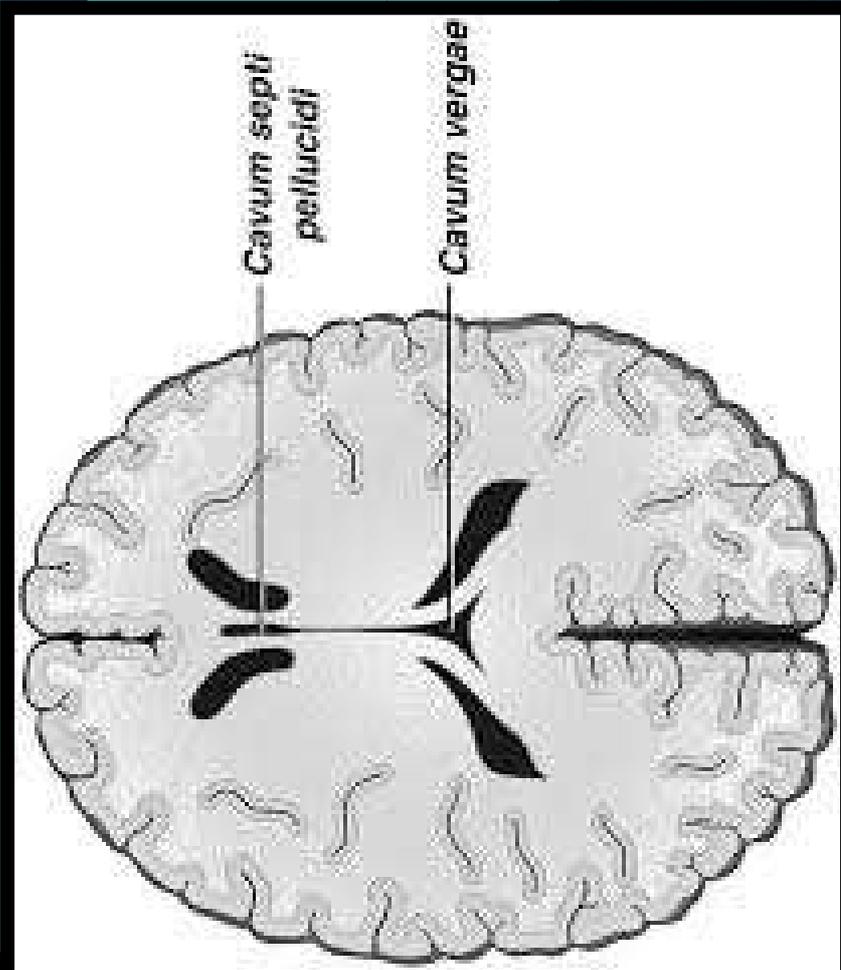
frontotemporal dementia), **both diagnoses may be given**, either with one being 'primary' and the other being 'secondary' or with the term 'mixed' used if neither is presumed primary.

'With motor features' modifier

For each TES subtype, the modifier **with motor features** should be added if the individual demonstrates dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism.

Potential biomarkers for the diagnosis of probable chronic traumatic encephalopathy

- 1) **Cavum septum pellucidum**. Report of cavum septum pellucidum, cavum vergae, or fenestrations based on neuroimaging study.
- 2) **Normal beta amyloid cerebrospinal fluid (CSF) levels**. CSF beta amyloid levels in the normal range for age and not diminished as would be suggestive of AD.
- 3) **Elevated CSF p-tau/tau ratio**. CSF p-tau/total tau ratio above the normal range for age.
- 4) **Negative amyloid imaging**. PET amyloid imaging (for example, florbetapir and flutemetamol) in the normal range, not suggestive of AD.
- 5) **Positive tau imaging**. PET paired helical filament tau imaging suggestive of abnormal tau deposition. It should be noted that this remains an experimental procedure and requires additional validation prior to its use as a research tool for diagnostic purposes.
- 6) **Cortical thinning**. Based on magnetic resonance imaging (MRI) measurement, evidence of abnormal cortical thinning indicative of neurodegeneration.
- 7) **Cortical atrophy**. Based on MRI or computed tomography, generalized cortical atrophy beyond what is expected for age, and, in particular, **frontal, thalamic, hippocampal, and/or amygdalar atrophy**.



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Traumatic encephalopathy syndrome diagnostic subtypes

- 1) TES **behavioral/mood** variant (TES-BMv)
 - a) Behavioral or mood core features (or both) without cognitive core features.
- 2) TES **cognitive** variant (TES-COGv)
 - a) Cognitive core features without behavioral or mood core features (or both).
- 3) TES **mixed** variant (TES-MIXv)
 - a) Both cognitive core features and behavioral or mood core features (or both).
- 4) TES **dementia** (TES-D)
 - a) Progressive course of cognitive core features with or without behavioral or mood core features (or both).
 - b) Evidence of **functional impairment**, defined as cognitive impairment (or cognitive impairment exacerbated by behavioral or mood impairment or both) that is severe enough to interfere with the ability to function independently at work or in usual activities, including hobbies, and instrumental activities of daily living. The determination of functional impairment is based on clinician's judgment, taking into account informant reports as well as consideration of individual differences with regard to level of expected responsibility and daily challenges.
 - c) If the **clinical presentation is not distinguishable from that of dementia due to AD or another neurodegenerative disease** (for example,

frontotemporal dementia), **both diagnoses may be given**, either with one being 'primary' and the other being 'secondary' or with the term 'mixed' used if neither is presumed primary.

'With motor features' modifier

For each TES subtype, the modifier **with motor features** should be added if the individual demonstrates dysarthria, dysgraphia, bradykinesia, tremor, rigidity, gait disturbance, falls, and/or other features of parkinsonism.

Chronic traumatic encephalopathy classification

- 1) **Probable CTE**. Meets classification for any TES subtype, progressive course; does not meet diagnostic criteria for another disorder more consistently than TES; and has a minimum of one positive potential biomarker for CTE.
- 2) **Possible CTE**. Meets classification for any TES subtype, progressive course, and (1) has not undergone any potential biomarker testing, (2) has had negative results on one or more biomarkers with the exception of PET tau imaging (that is, if a negative PET tau imaging finding, the current classification would be 'unlikely CTE'), or (3) meets the diagnostic criteria for another disorder that, on its own, could account for the clinical presentation.

Potential biomarkers for the diagnosis of probable chronic traumatic encephalopathy

- 1) **Cavum septum pellucidum**. Report of cavum septum pellucidum, cavum vergae, or fenestrations based on neuroimaging study.
- 2) **Normal beta amyloid cerebrospinal fluid (CSF) levels**. CSF beta amyloid levels in the normal range for age and not diminished as would be suggestive of AD.
- 3) **Elevated CSF p-tau/tau ratio**. CSF p-tau/total tau ratio above the normal range for age.
- 4) **Negative amyloid imaging**. PET amyloid imaging (for example, florbetapir and flutemetamol) in the normal range, not suggestive of AD.
- 5) **Positive tau imaging**. PET paired helical filament tau imaging suggestive of abnormal tau deposition. It should be noted that this remains an experimental procedure and requires additional validation prior to its use as a research tool for diagnostic purposes.
- 6) **Cortical thinning**. Based on magnetic resonance imaging (MRI) measurement, evidence of abnormal cortical thinning indicative of neurodegeneration.
- 7) **Cortical atrophy**. Based on MRI or computed tomography, generalized cortical atrophy beyond what is expected for age, and, in particular, **frontal, thalamic, hippocampal, and/or amygdalar atrophy**.

Diagnosis?

TES-MIXv, progressive course; possible CTE



CONCLUSIONI



- ▶ La diagnosi di Malattia di Alzheimer è e sarà sempre meno clinica
- ▶ Sarà sempre più precoce
- ▶ Con i nuovi strumenti di indagine non tutto è Alzheimer
- ▶ Una grossa fetta è non amiloide
- ▶ Difficile spiegare ai pazienti ed ai familiari che, sebbene i sintomi siano dell'Alzheimer, non si tratta di questo.
- ▶ Interessa ancora davvero la definizione diagnosi?