Come si inquadrano le demenze in ambito neuro-psico-geriatrico. Quali sono i percorsi diagnostico-terapeutico-assistenziali idonei per un paziente con decadimento cognitivo e disturbi psico-comportamentali.

Andrea Arighi, MD

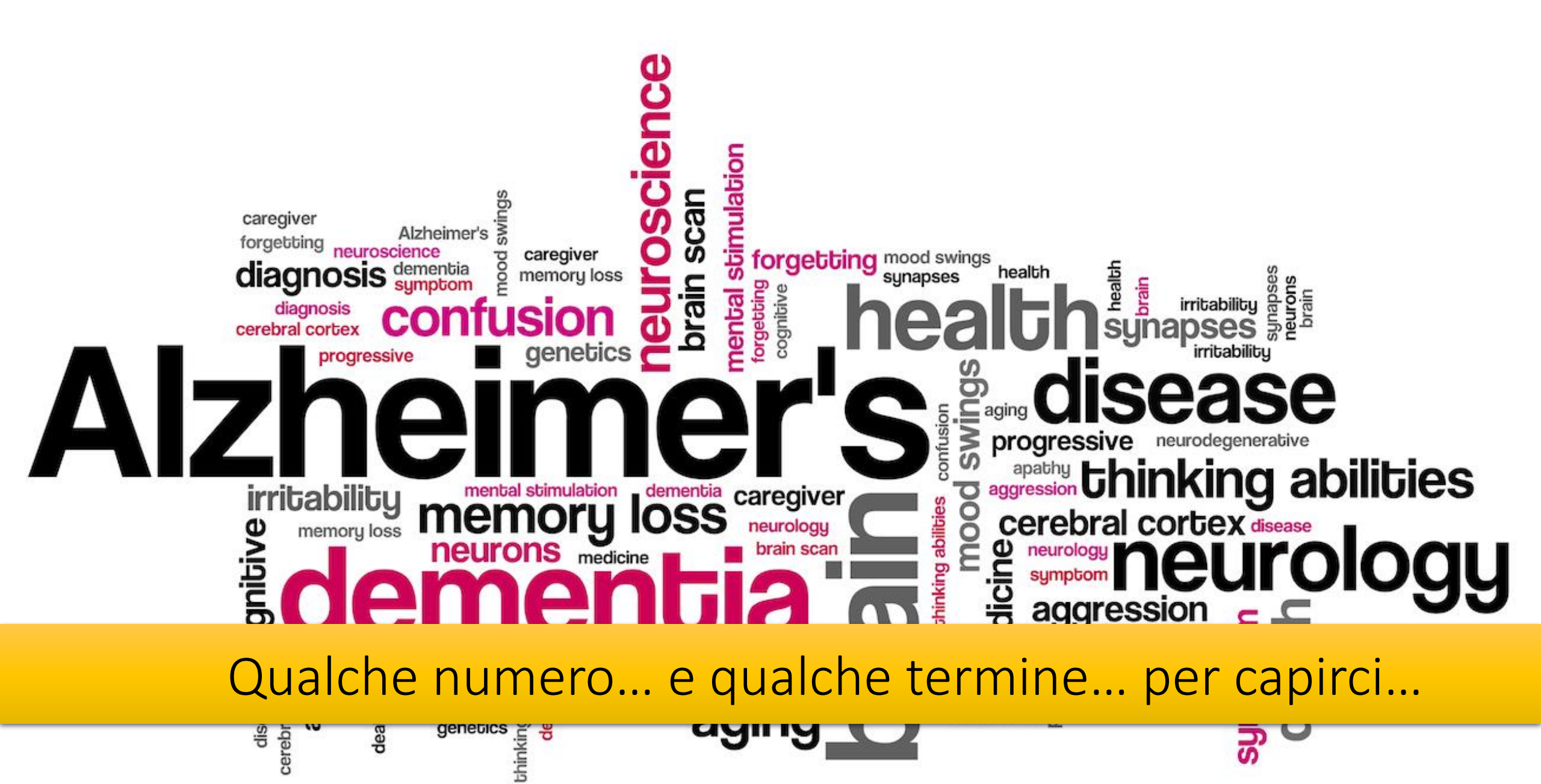
andrea.arighi@policlinico.mi.it

@neurodoc83

FONDAZIONE IRCCS CA' GRANDA
OSPEDALE MAGGIORE POLICLINICO

Outline

- Qualche numero… e qualche termine… per capirci…
- «Ci ha mandati il medico di famiglia…»
- «Ma allora è demenza senile?»
- «Dottore, cosa possiamo fare?»
- «C'è una medicina?»
- «Ma è trasmissibile? È genetica?»
- «E noi figli? Ci dobbiamo preoccupare?»
- «Ma… perché?»
- Il nostro PDTA Neuro-Psico-Geriatrico



Qualche numero… e qualche termine… per capirci…

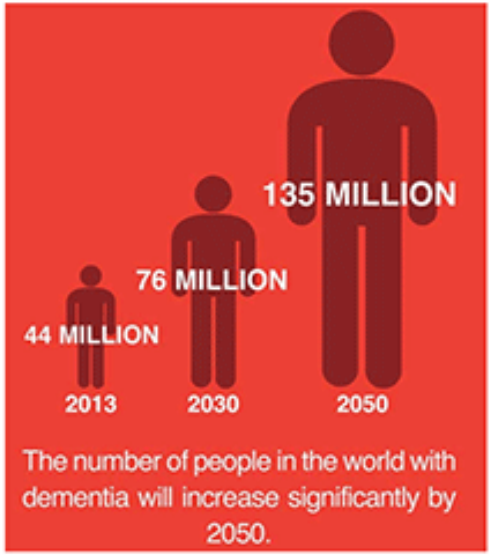
Epidemiologia

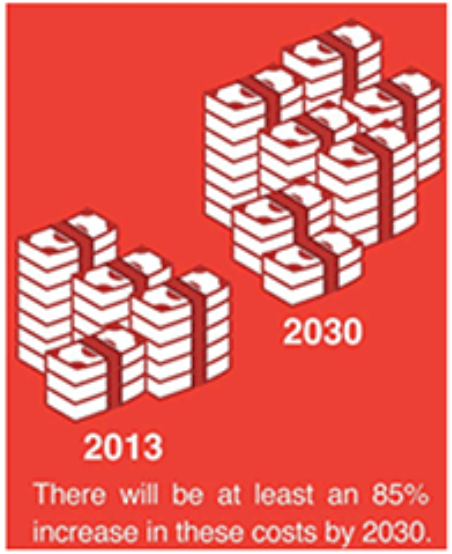
Nel mondo
46.6 milioni pz con demenza
9.9 milioni di nuovi casi all'anno (1 / 4 secondi)

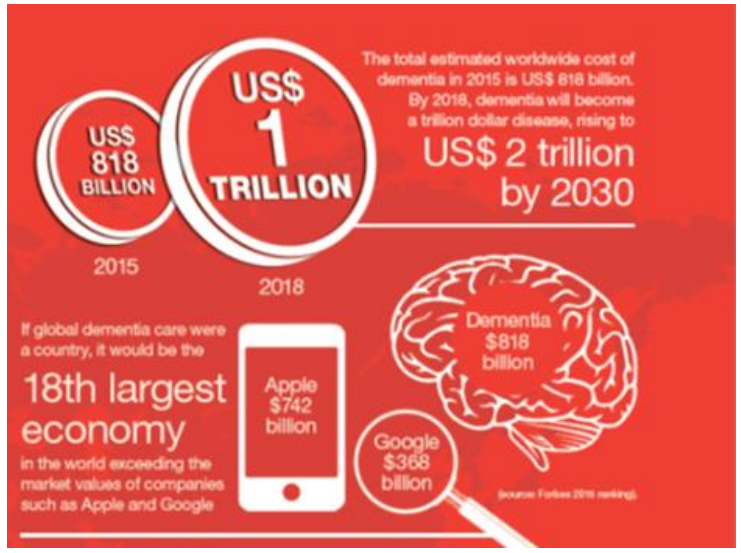
In Italia
1.2 milioni pz con demenza
269.000 nuovi casi all'anno (737 / giorno)

In Lombardia
115 mila pz con demenza

A Milano
25 mila pz con demenza







Dementia

2. Criteria for all-cause dementia: Core clinical criteria

In this section, we outline core clinical criteria to be used in all clinical settings. Because there are many causes of dementia, we will first outline the criteria for all-cause dementia.

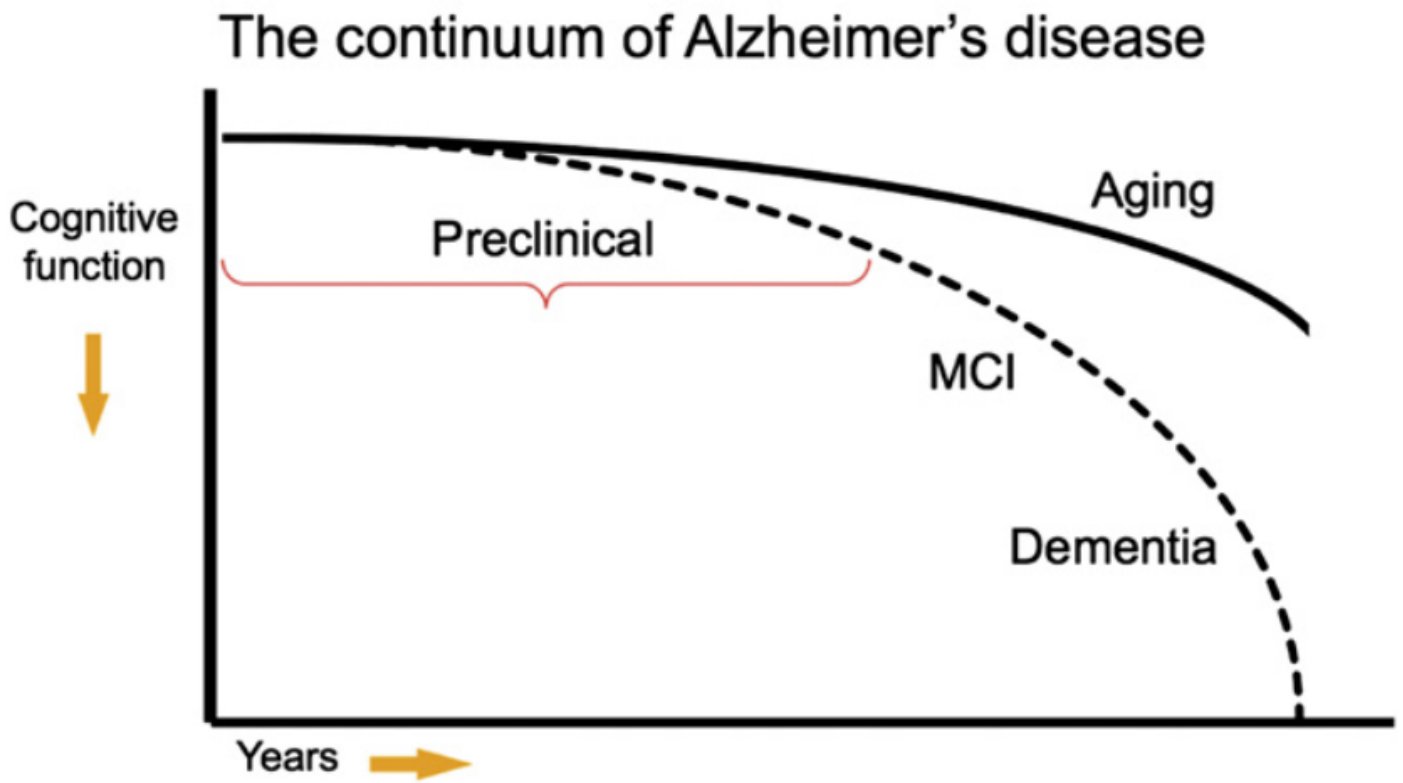
The diagnosis of dementia is intended to encompass the spectrum of severity, ranging from the mildest to the most severe stages of dementia. The methodology for staging of dementia severity was beyond the charge of the workgroup. Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder;
4. Cognitive impairment is detected and diagnosed through a combination of (1) history-taking from the patient and a knowledgeable informant and (2) an objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.
5. The cognitive or behavioral impairment involves a minimum of two of the following domains:
   a. Impaired ability to acquire and remember new information—symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
   b. Impaired reasoning and handling of complex tasks, poor judgment—symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
   c. Impaired visuospatial abilities—symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
   d. Impaired language functions (speaking, reading, writing)—symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
   e. Changes in personality, behavior, or comportment—symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

McKhann G et al, 2011

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

Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack, Jr.[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o], Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison-Bogorad[r], Molly V. Wagster[r], Creighton H. Phelps[r]

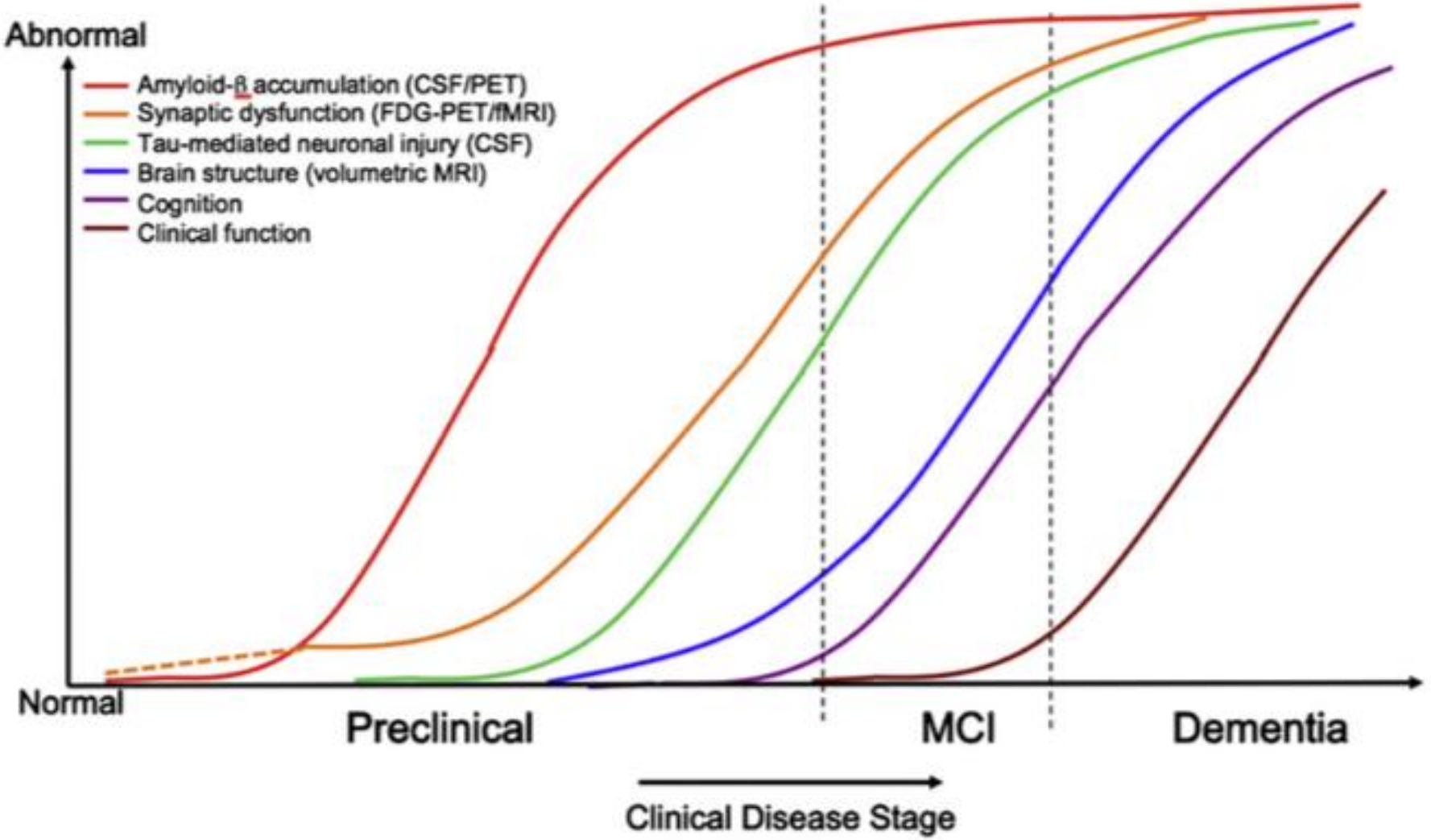


Sperling RA et al, 2011

MCI (Mild Cognitive Impairment)

- Problemi cognitivi
- Non all'interno del fisiologico invecchiamento
- Che non soddisfano i criteri per demenze specifiche
- Che non impattano in maniera significativa sulle attività della vita quotidiana
- La memoria può essere o non essere compromessa → a - na MCI
- Distinzione tra compromissione di un singolo dominio e multipli domini cognitivi → sd – md MCI

Biomarkers



Sperling RA et al, 2011

MCI evolution

Mild Cognitive Impairment

Petersen et al., 1999

Prodromal AD

Dubois et al., 2010

MCI due to AD

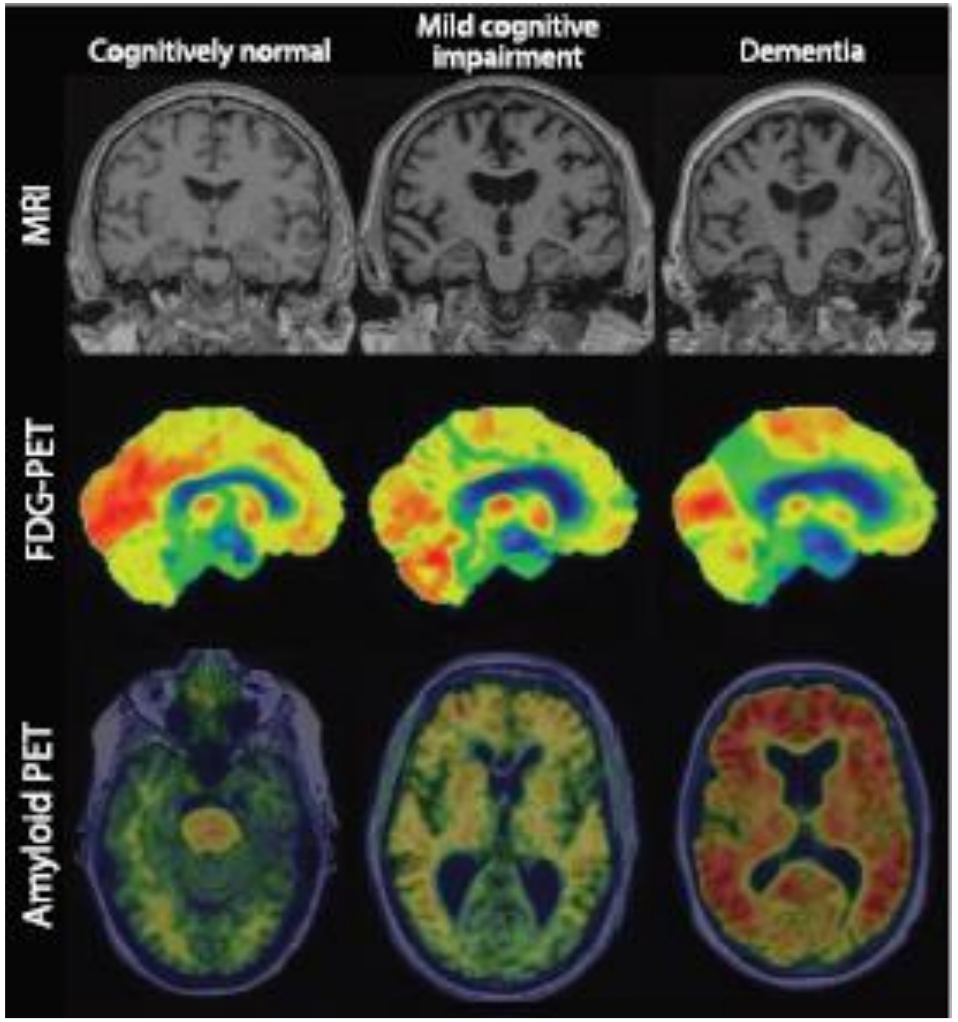
Albert et al, 2011

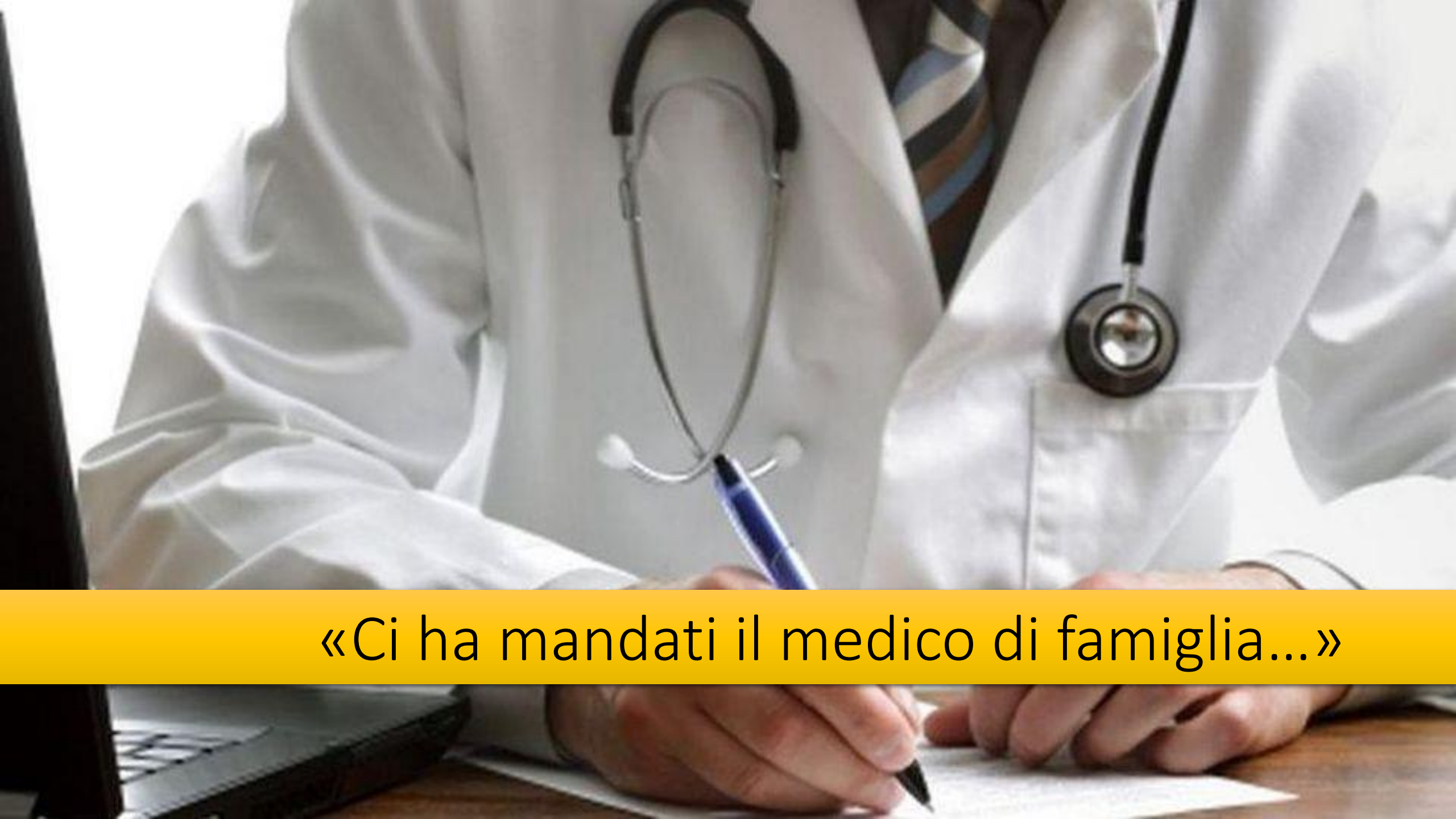
Alzheimer disease

Asymptomatic at risk for AD

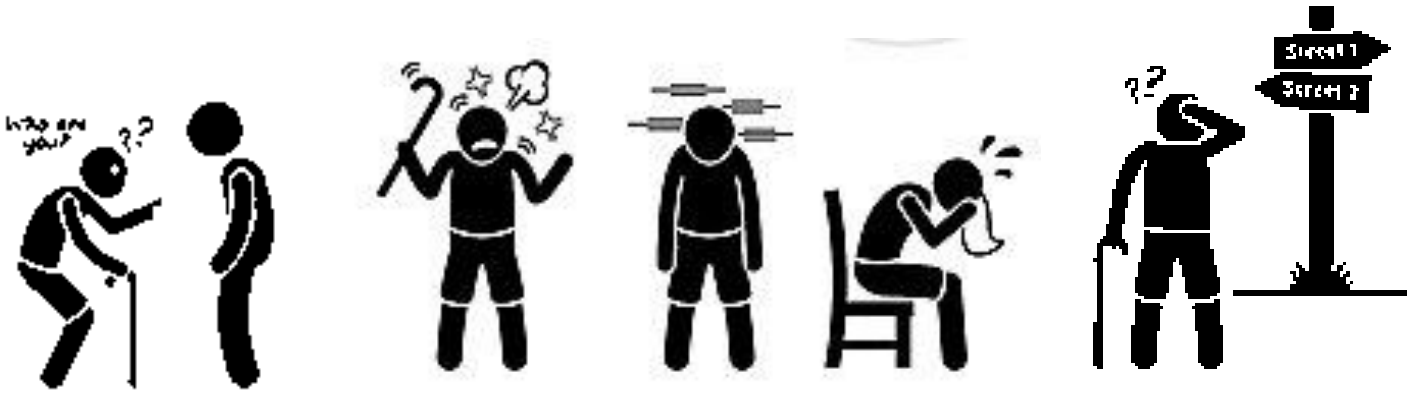
Presymptomatic AD

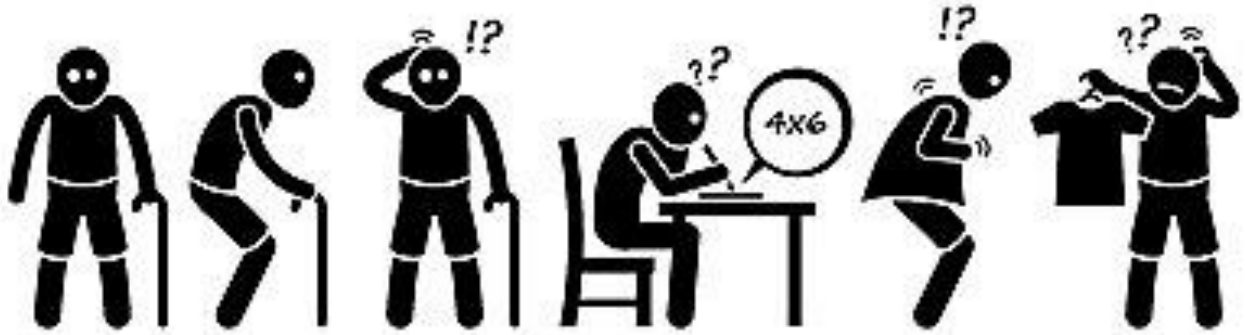
Dubois et al. 2014





«Ci ha mandati il medico di famiglia…»


Street 1
Street 2


4X6

Ma cosa vuol dire «problema di memoria»?

- Spesso indica un qualsiasi problema cognitivo
- Portare esempi!
  - perde gli oggetti
  - ripete più volte le stesse domande
  - non riconosce persone
  - si perde per strada
  - non trova le parole
- Chi lo dice? Il paziente o il caregiver?
- Solo ansia o problema significativo?

Cosa indagare

- Qual è stato il primo sintomo? (memoria, linguaggio, comportamento)
- Da quanto tempo ci sono questi problemi
- Esordio graduale o lentamente progressivo?
- Fluttuazioni?
- Qual è il problema principale adesso?

Cosa indagare

- Ci sono problemi coi soldi? Controlla bene i resti?
- Cambiamento di personalità
- Cambiamenti nell’alimentazione / potus
- Riduzione delle attività / riposizionamento al lavoro
- Allucinazioni / deliri / agitazione
- Umore
- Disturbi del sonno

Caregiver

- Fondamentale
- Paziente può essere anosognosico o minimizzante
- Se il paziente viene solo chiedere di portare un conoscente alla prossima visita
- Se possibile parlateci separatamente
- È più preoccupato il paziente o il caregiver?
- Prestate attenzione alle interazioni tra loro

Familiarità

- Considerate come possibile familiarità qualsiasi disturbo cognitivo e/o malattia neurologica/psichiatrica di genitori e fratelli
- Non basta avere uno zio con la demenza
- In casi selezionati disegnare un albero genealogico
- Importante chiedere età di esordio

Obiettività neurologica

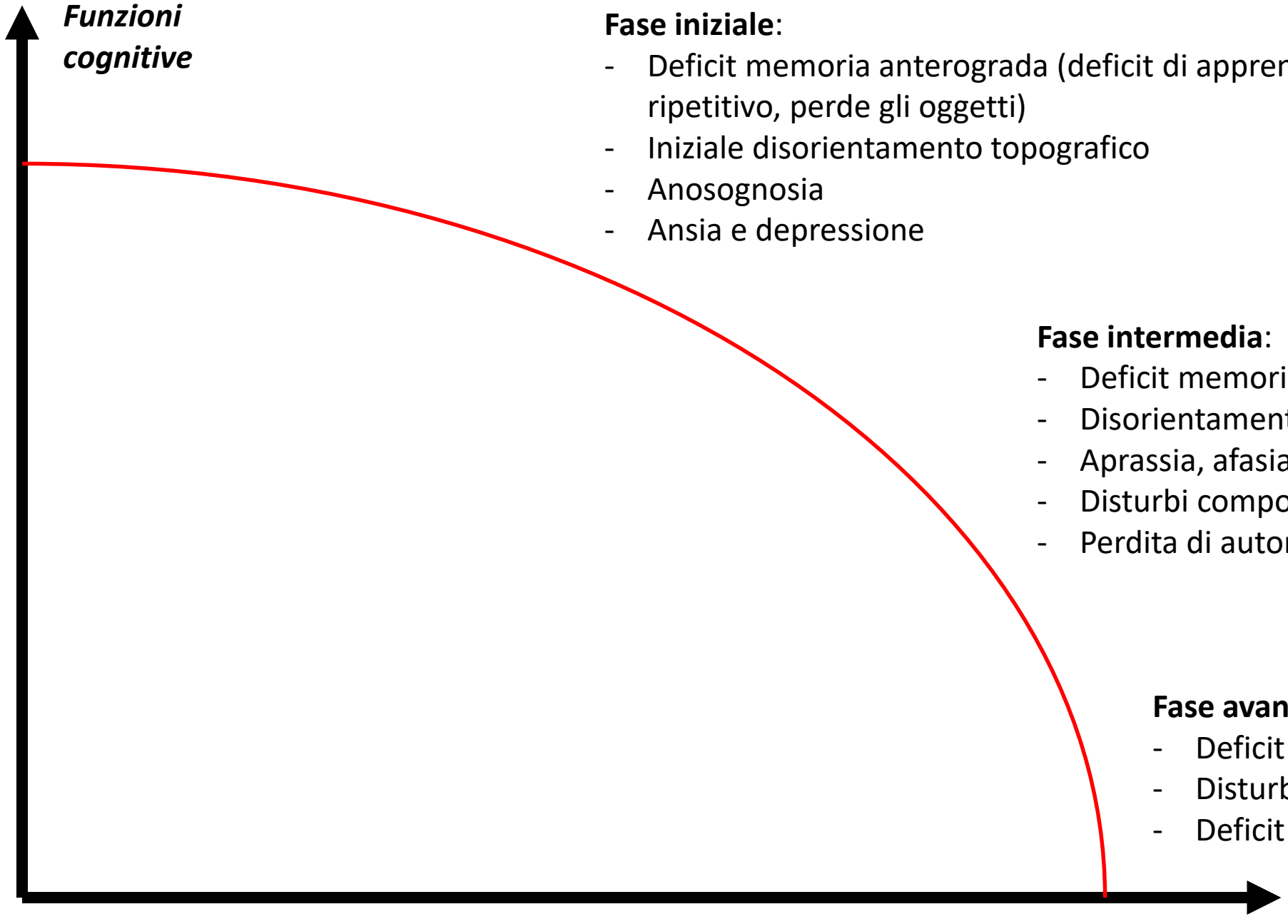
- EON con particolare attenzione a valutazione funzioni cognitive superiori, cammino, riflessi di liberazione
- MMSE (Mini Mental State Examination) / MOCA (MOntreal Cognitive Assessment) / ACE-R (Addenbrooke Cognitive Examination)

Localizzazione del deficit cognitivo

- Sottocorticale → vigilanza ed orientamento
- Sensibilità primarie → vista / udito
- Emisfero sinistro → linguaggio
- Temporale mesiale → memoria verbale
- Temporale destro → memoria visiva / riconoscimento volti
- Parietale destro → visuospaziale / visuopercettivo
- Parietale sinistro → calcolo/ prassia
- Frontale → funzioni esecutive

Esami di I livello

- Esami ematici (VitB12, Folati, TSH, Ab anti-Treponema)
- Test neuropsicologici
- Imaging (TC encefalo o RM encefalo)



Fase iniziale:

- Deficit memoria anterograda (deficit di apprendimento, ripetitivo, perde gli oggetti)
- Iniziale disorientamento topografico
- Anosognosia
- Ansia e depressione

Fase intermedia:

- Deficit memoria retrograda
- Disorientamento spazio temporale
- Aprassia, afasia, prosopoagnosia
- Disturbi comportamnetali
- Perdita di autonomia

Fase avanzata:

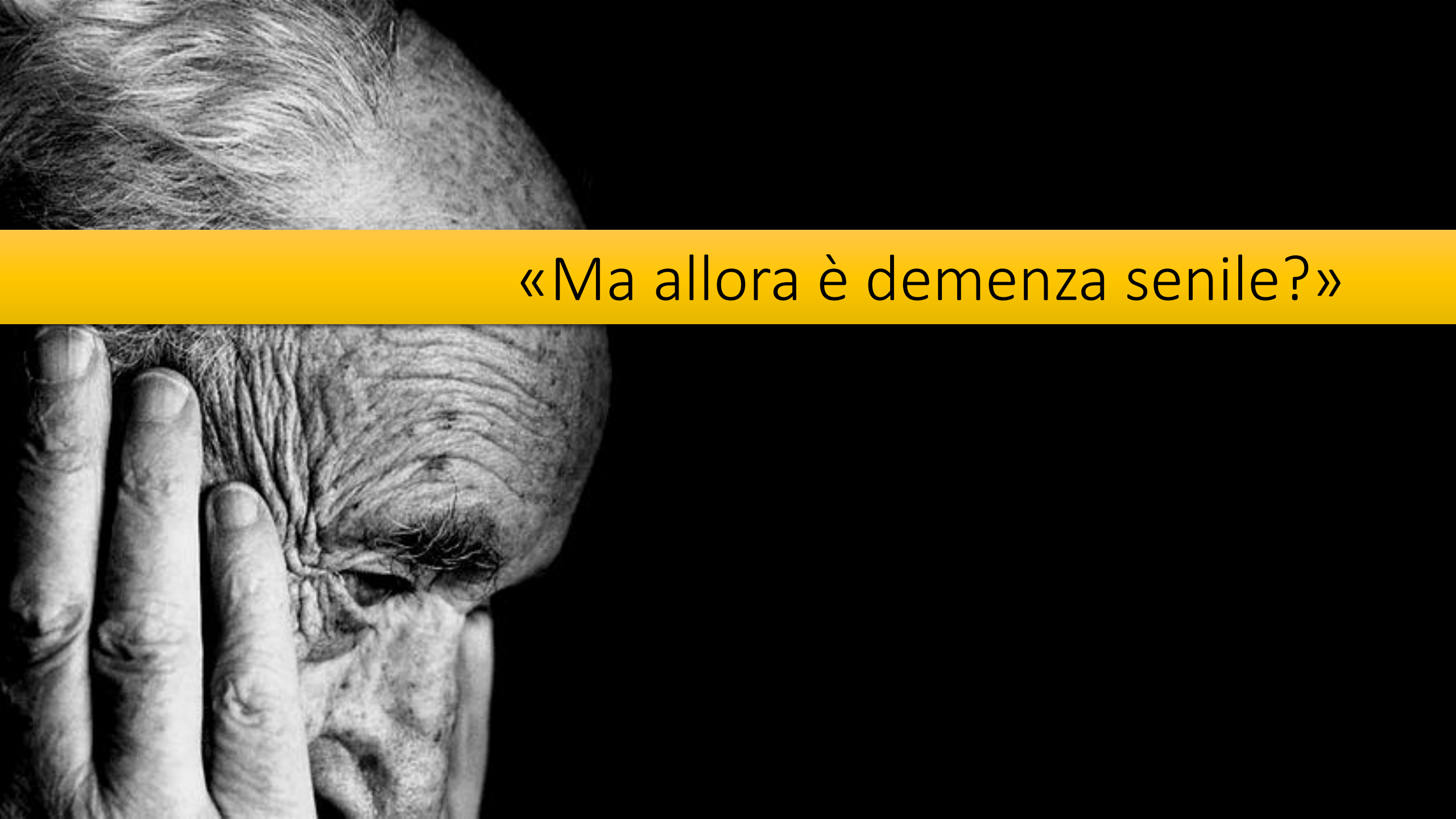
- Deficit di tutte le funzioni cognitive
- Disturbi comportamentali (BPSD)
- Deficit delle funzioni motorie

Behavioural and Psychological Symptoms of Dementia (BPSD)

- DEPRESSIONE: tristezza, ansia, perdita dell'autostima
- APATIA: perdita di interesse e motivazione
- PSICOSI: allucinazioni, deliri, false identificazioni
- AGITAZIONE PSICOMOTORIA: disturbi del sonno, irrequietezza, atti ripetitivi, vocalizzazioni, vagabondaggio
- AGGRESSIVITA': resistenza oppositiva, aggressività verbale, talora anche fisica

Subclasses of Misidentification Syndrome	Clinical Features
Capgras delusion	Familiar person replaced by identical impostor
Fregoli syndrome	Unfamiliar people or places misidentified as familiar
Phantom boarder syndrome	Someone uninvited living in patient's home
TV sign misidentification	Events on television perceived as occurring in external, 3-dimensional space
Nurturing syndrome	Deceased family members believed as still living
Reduplicative paramnesia	Belief that oneself has been replaced into an identical or near identical duplicated person
Clonal pluralization of the self	Belief to be cloned
Reduplication of a person	Belief that a double of another person exists
Intermetamorphosis	Familiar or unfamiliar people change both physical and mental identity
Delusional hermaphroditism	Belief that oneself and a friend of the opposite sex have been incorporated in the same body
Mirror sign	Misidentification of oneself in the mirror

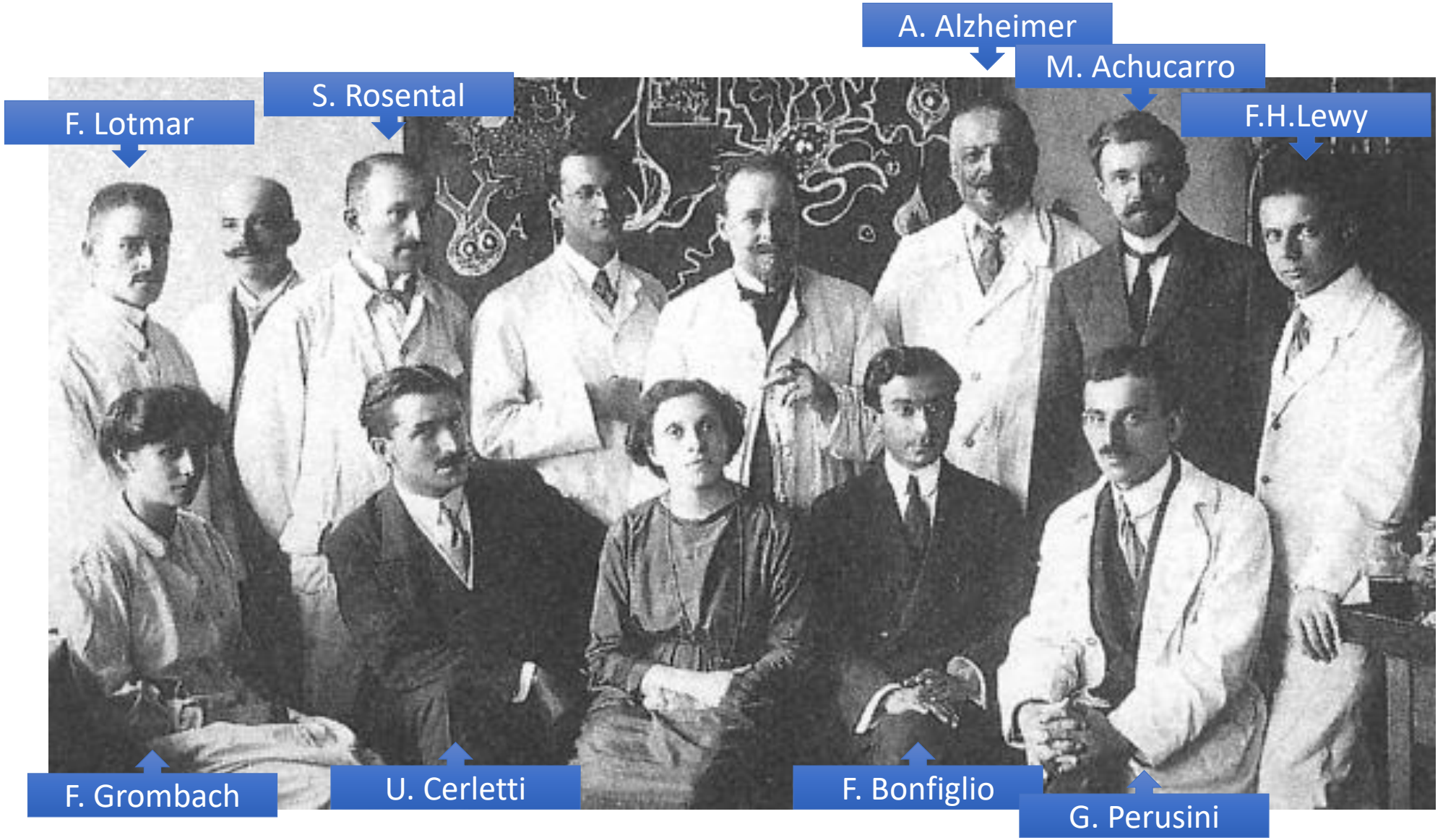
Cipriani G et al, 2013



«Ma allora è demenza senile?»


Hypolimnas dexithea, Madagascar
Delias nakula, ♂ Indonesia
Inachis io, Italia
Phoebis argante, Peru
Anthocaris cardamines, ♂ Italia
Papilio machaon, Italia
Callicore aelgina, Peru
Sasakia funebris, ♂ Cagayone
Heliconius leucippe, ♂ Matese
Papilio androgeos, ♂ Colombia
Iturna genus, Peru
Melanargia galathea, Italia
Cymothoe aramis, ♂ Rep. C. Africana
Morpho achilles, Brasile

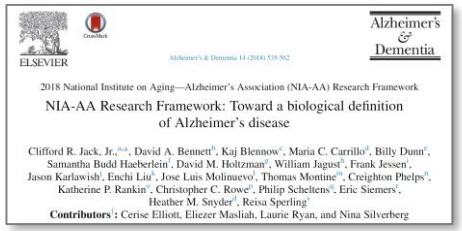
Laboratorio neuro-patologico
Clinica psichiatrica di Monaco diretta da Emil Kraepelin



Alois Alzheimer
(1863-1915)

Gaetano Perusini
(1879-1915)

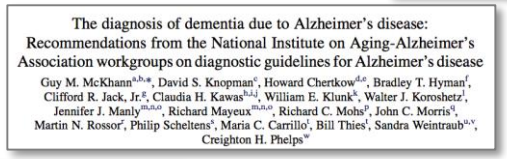
1906: Auguste Deter, 51 aa

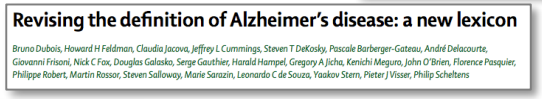

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

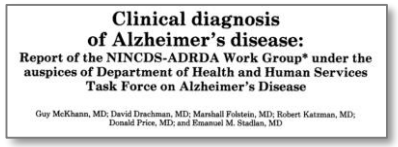
NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease


Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria


The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease


Revising the definition of Alzheimer's disease: a new lexicon


Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria


Clinical diagnosis of Alzheimer's disease:
Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

NINCS-ADRDA 1984

IWG-1 2007

IWG 2010

NIA-AA 2011

IWG-2 2014

NIA-AA 2018

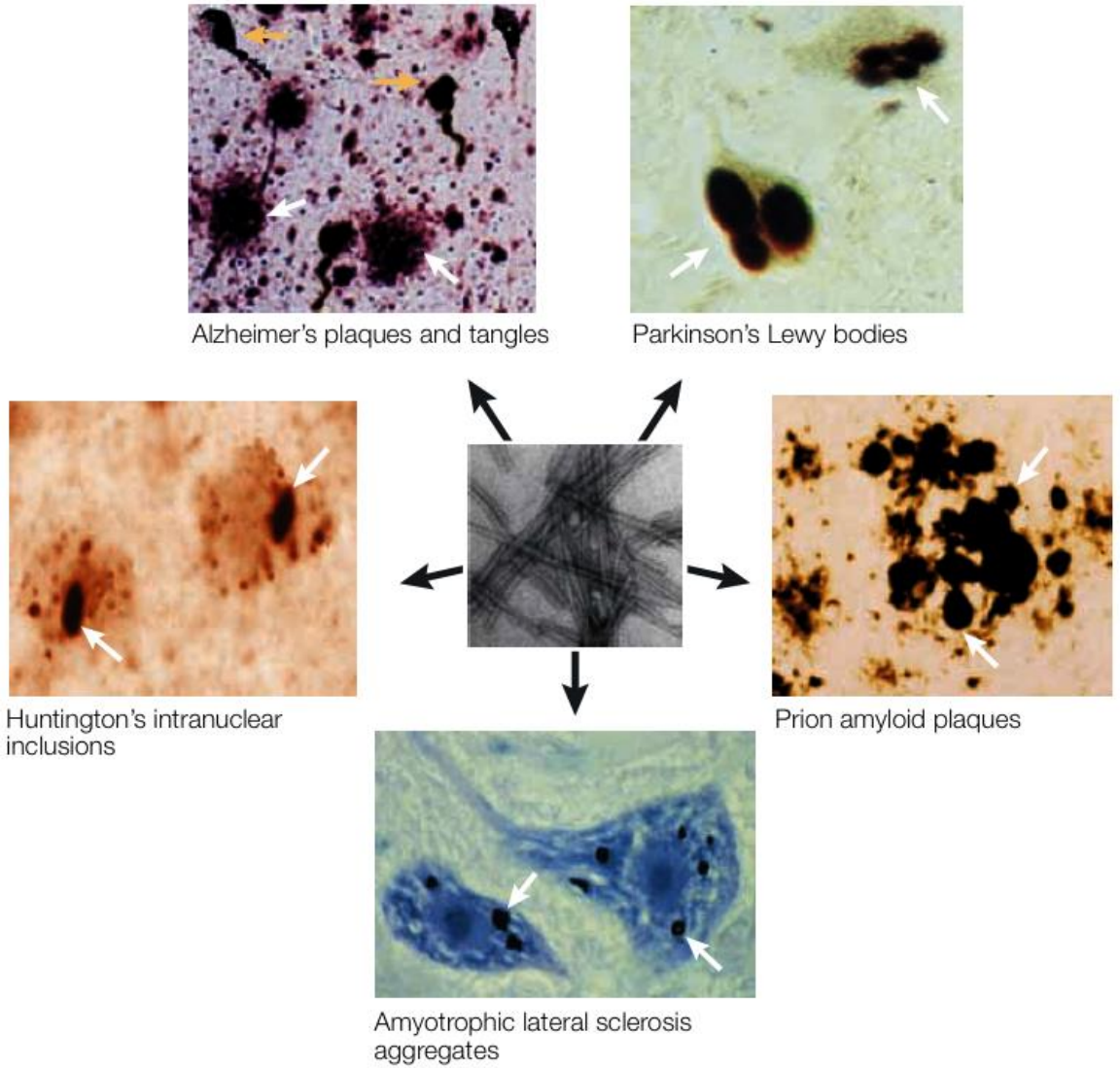
Time line AD criteria

Clinical Pathological

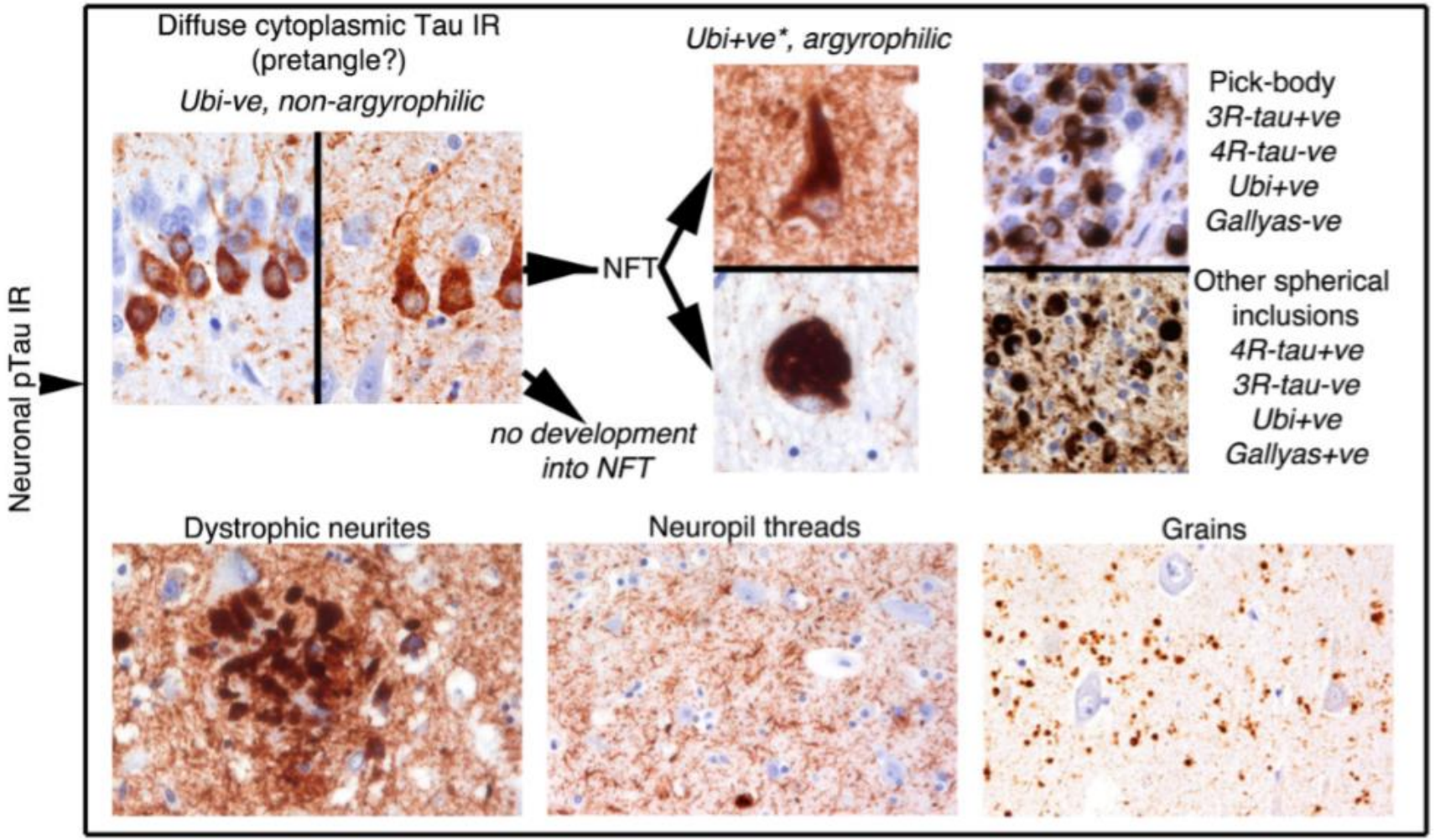
Clinical Biomarker

Biological

Neurodegeneration: what?

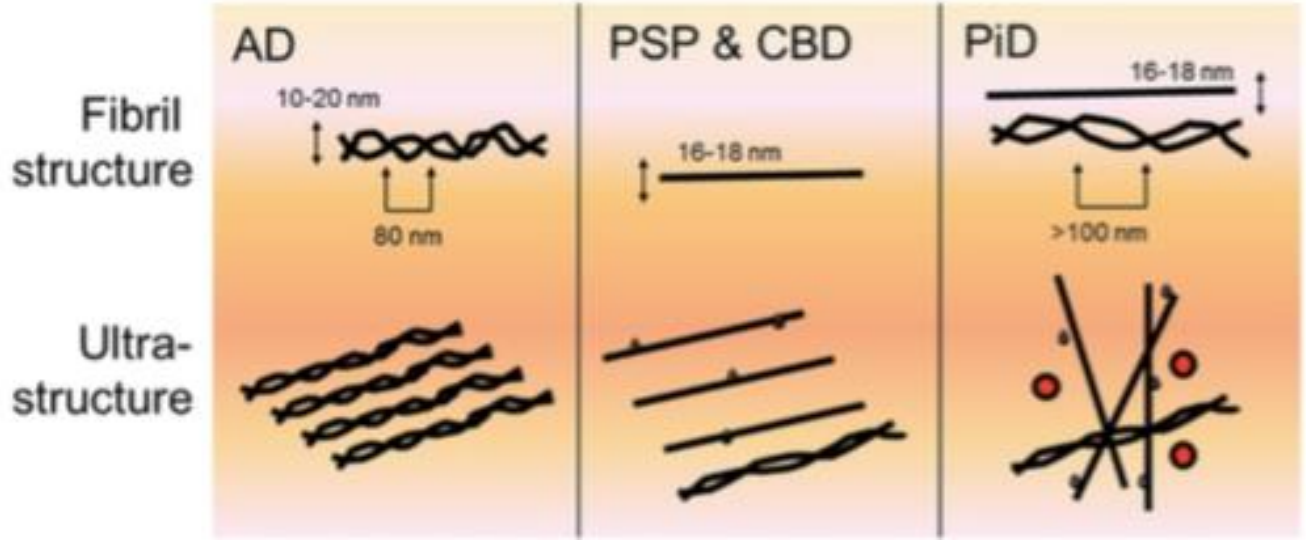


C Soto, 2003



IR structure	*Definition*	*4R*	*3R*	*Gallyas*	*Biel*	*Ubi/p62*
Pretangle	Diffuse fine granular staining of neuronal cytoplasm	+	–	–	–	–
NFT	Fibrillar intracellular cytoplasmic structures	+	+/–*	+	+	+/–*
Pick body	Cytoplasmic fibrillar spherical structures	–	+	–	+	+
Other spherical inclusions (Pick-body-like)	Globular cytoplasmic structures that are various sized, and the staining pattern does not match the current definition of a Pick body	+	–	+	+/–	+
Dystrophic neurite	Rounded, oval or elongated thick profiles accumulating mostly around amyloid plaques	+/–	+/–	+	+	+
Threads	A segment of a thin neuronal process usually associated to axons	+/–	+/–	+	+/–	+/–
Grains	4–9 μm spindle, coma or dot-like structures in the neuropil that are associated with dendrites	+	–	+	+/–	+

Kovacs GG, 2015



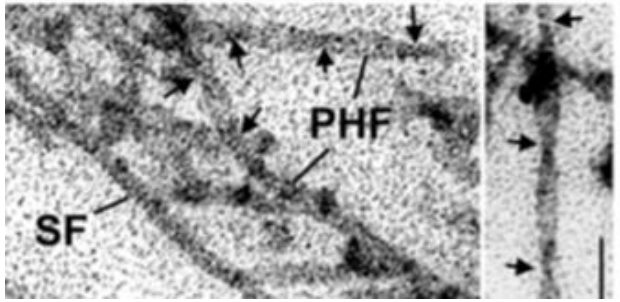


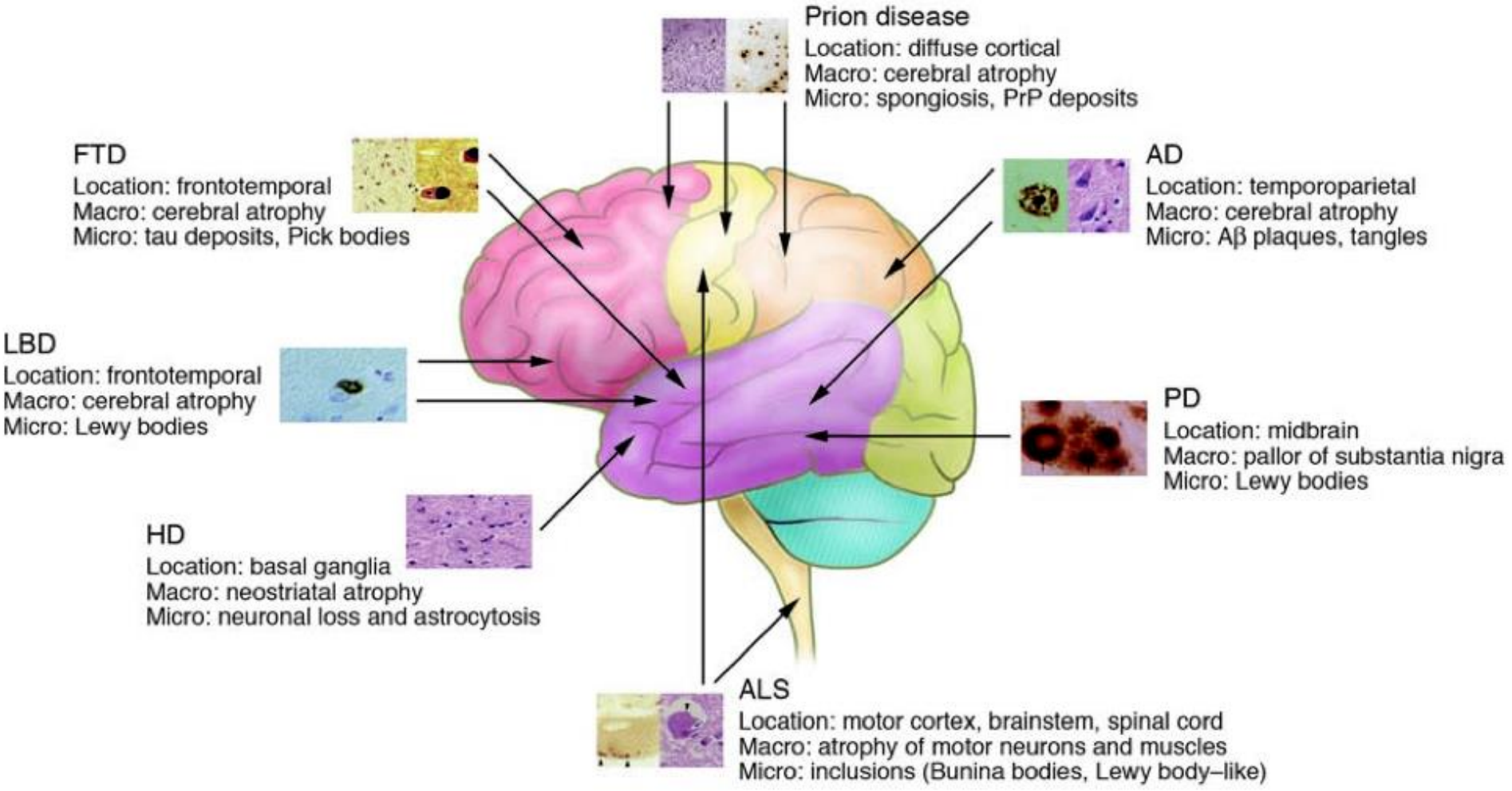
Table 2 Biochemical and ultrastructural characteristics of Alzheimer's disease and frontotemporal lobar degeneration tauopathies

	Tau repeat	Filaments (width)	Periodicity	Reference
AD	3R≈4R	PHF (10 to 20 nm) >> SF (~15 nm)	80 nm	[6]
PSP	4R >3R	SF (15 nm); rare twisted filament (15 to 30 nm)	>100 nm	[7]
CBD	4R >3R	SF >> twisted filament (15 to 30 nm)	160 nm	[8]
PiD	3R >4R	SF (15 nm) >> twisted filament (15 to 30 nm)	160 nm	[9]

Abbreviations: AD – Alzheimer's disease; PSP - progressive supranuclear palsy; CBD - corticobasal degeneration; PiD - Pick's disease; PHF - paired helical filament; SF – straight filament; nm - nanometer

Murray ME et al., 2014

Neurodegeneration: where?



Bertram & Tanzi, 2005

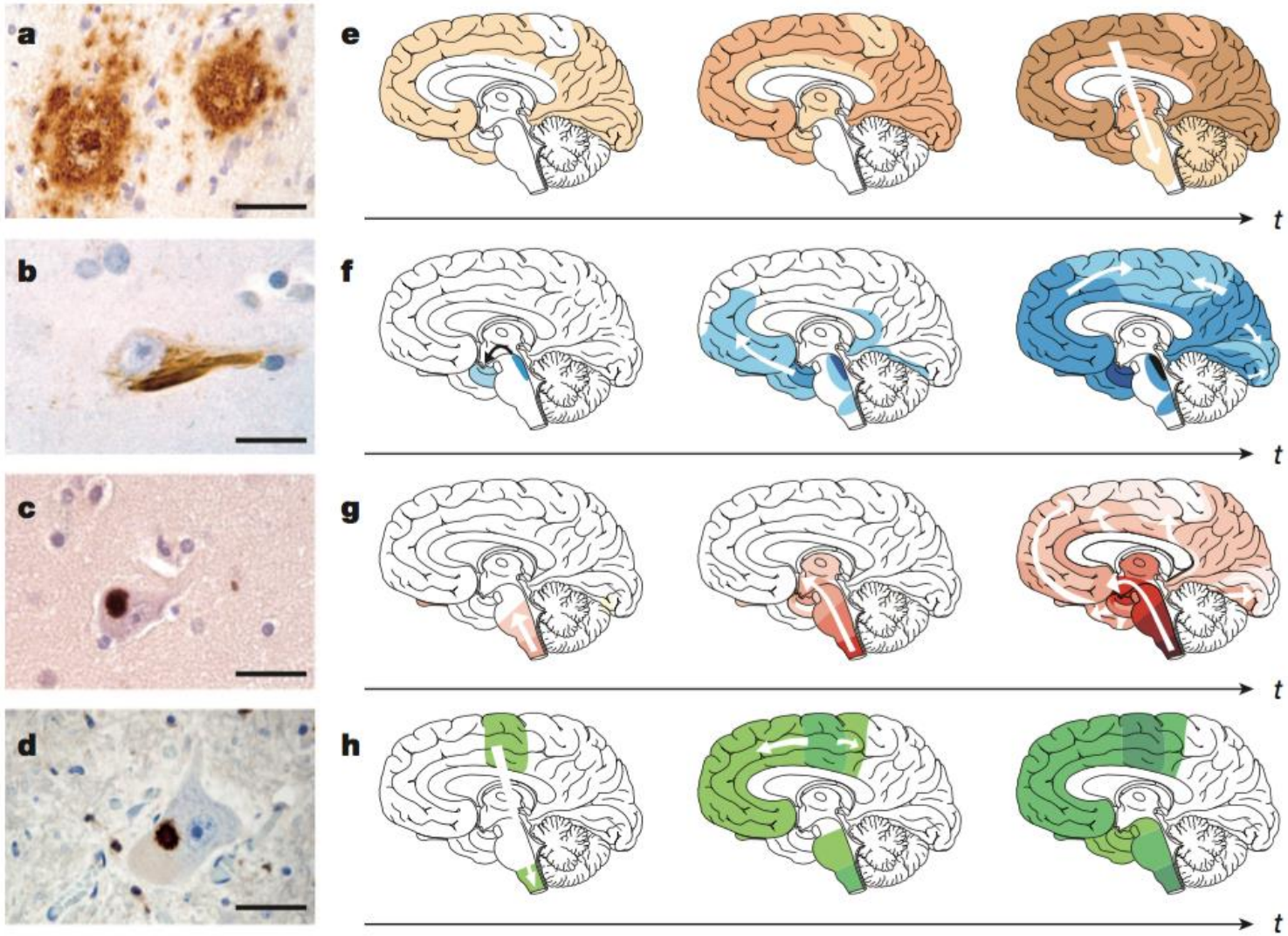
Neurodegeneration: when?

Amyloid-β deposits
(senile plaques)
in Alzheimer's disease

Tau inclusion
(neurofibrillary tangle)
in Alzheimer's disease

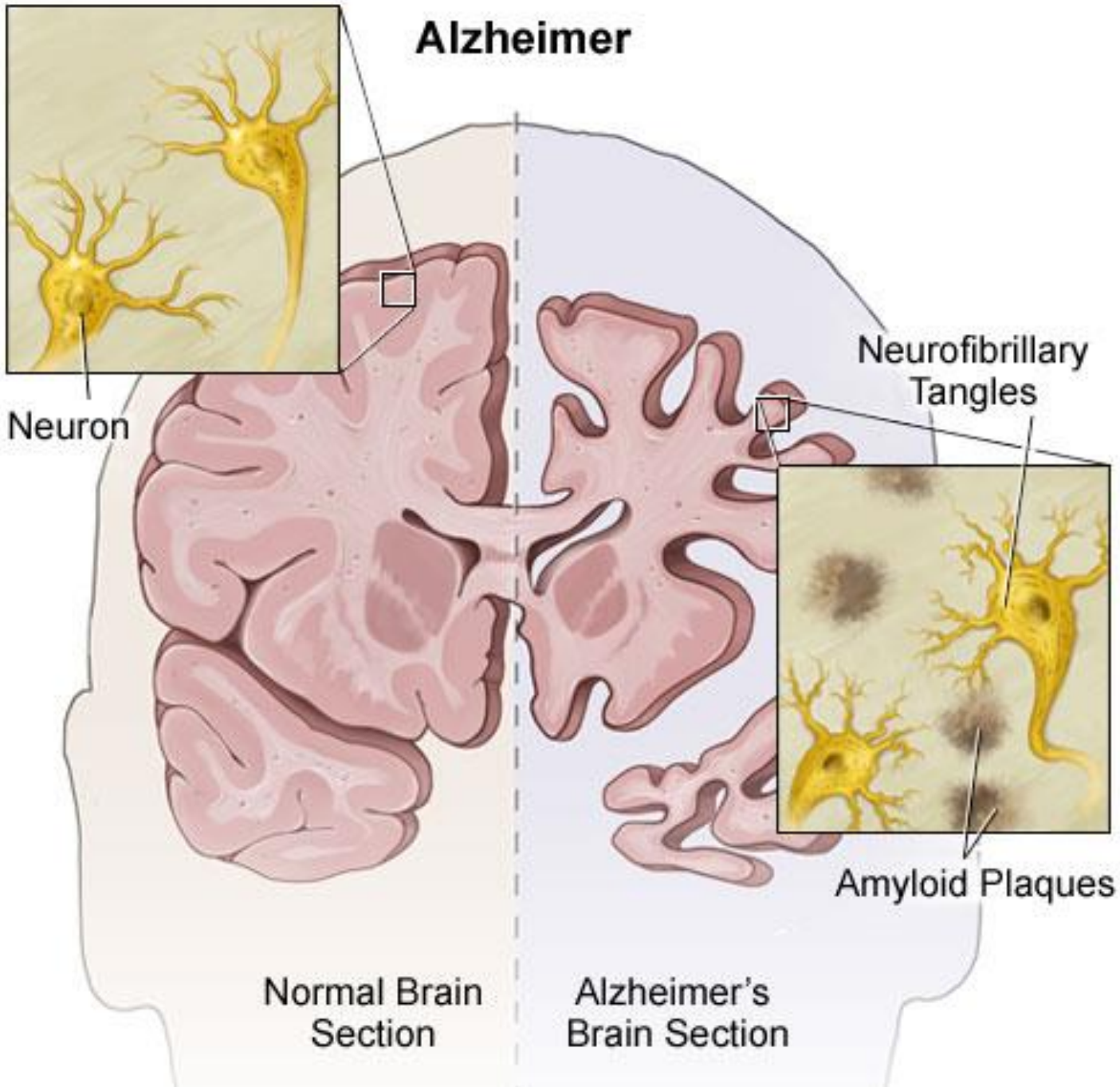
α-Synuclein inclusion
(Lewy body)
in Lewy body dementia

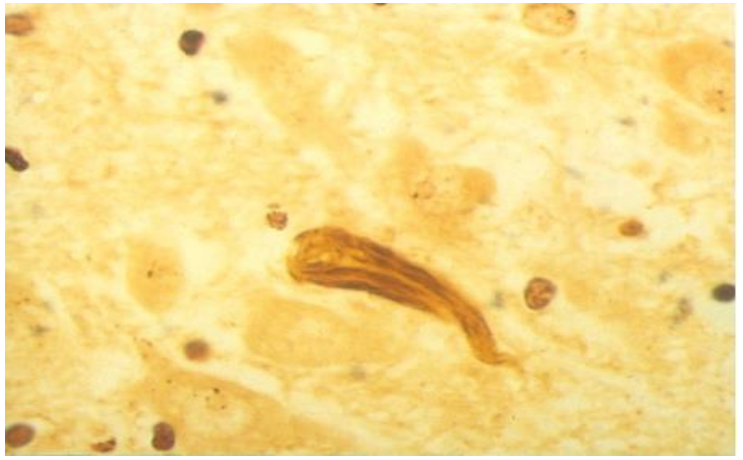
TDP-43 inclusion
in amyotrophic lateral
sclerosis

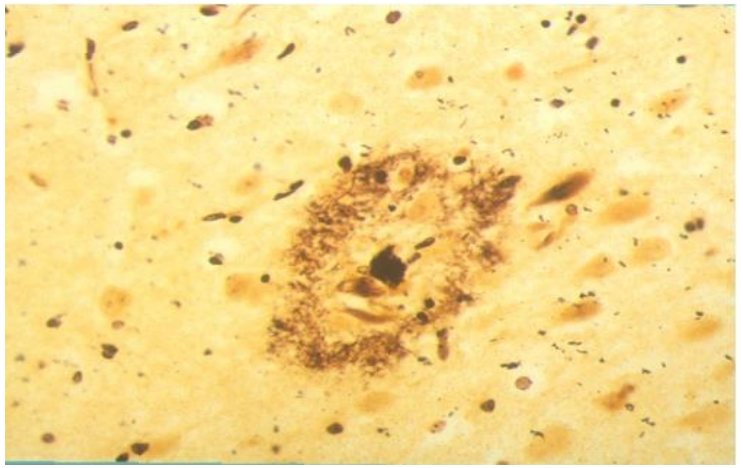


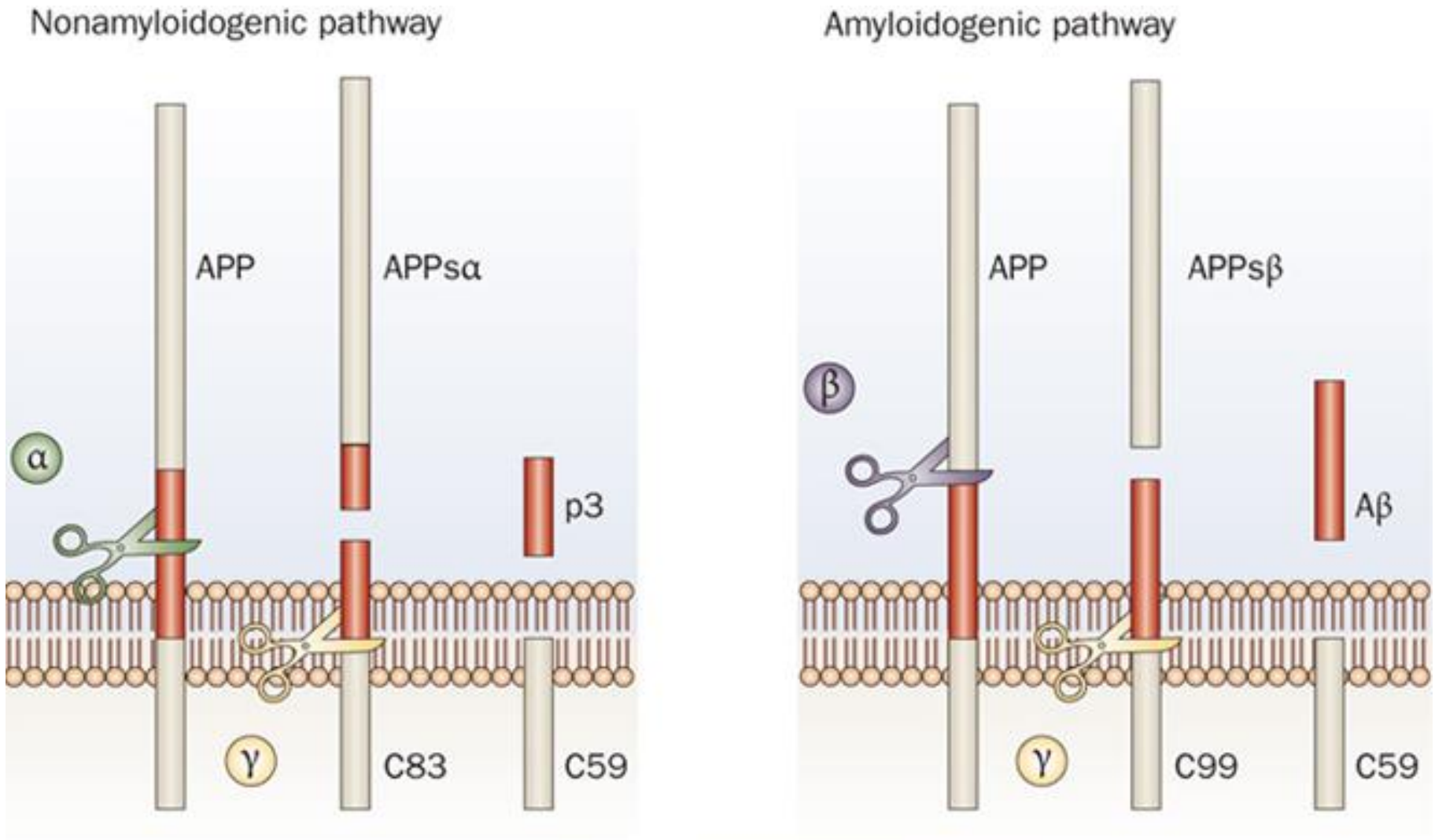
Jucker M and Walker LC, 2013

Alzheimer's dementia

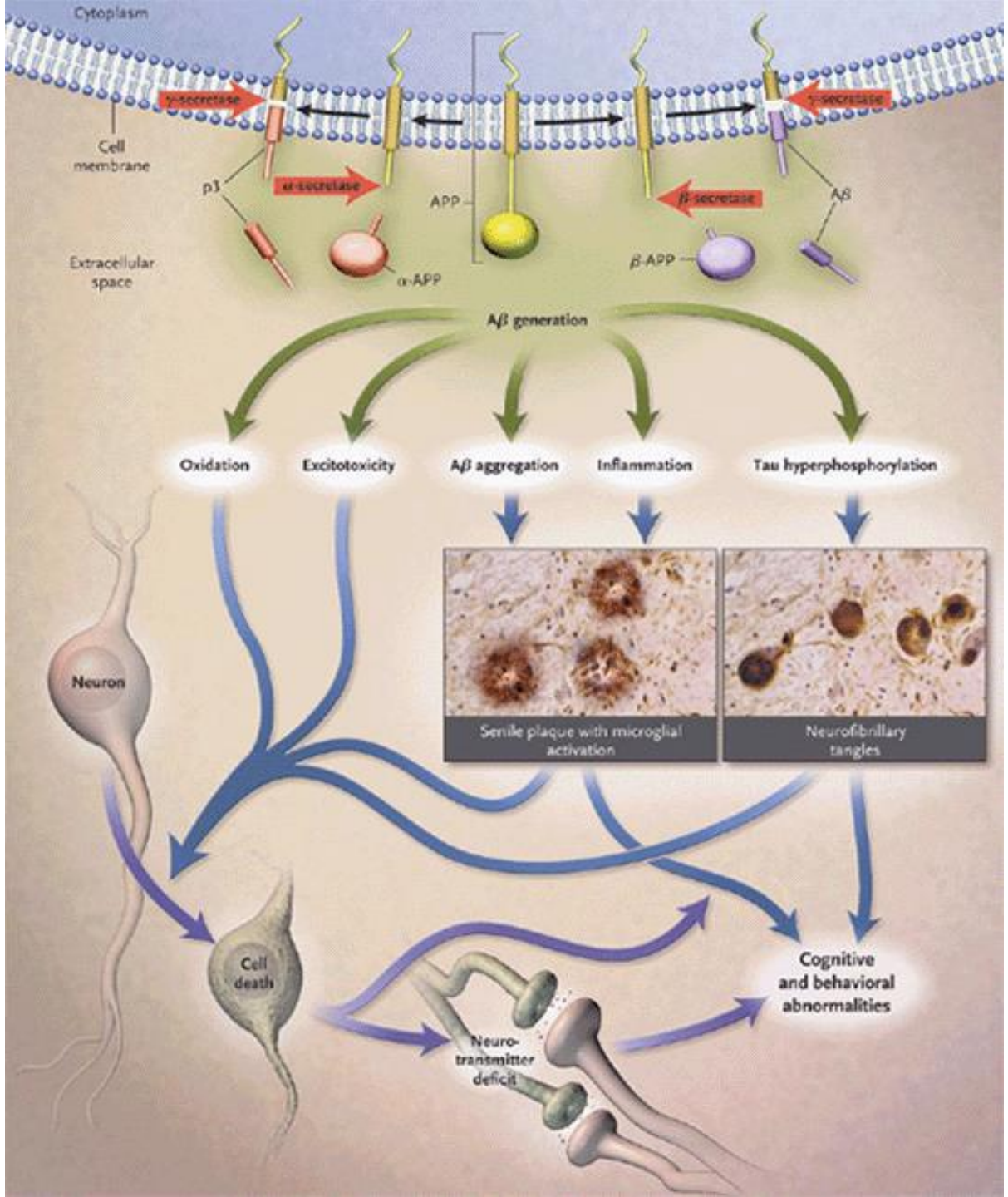

Alzheimer
Neuron
Neurofibrillary Tangles
Amyloid Plaques
Normal Brain Section
Alzheimer's Brain Section

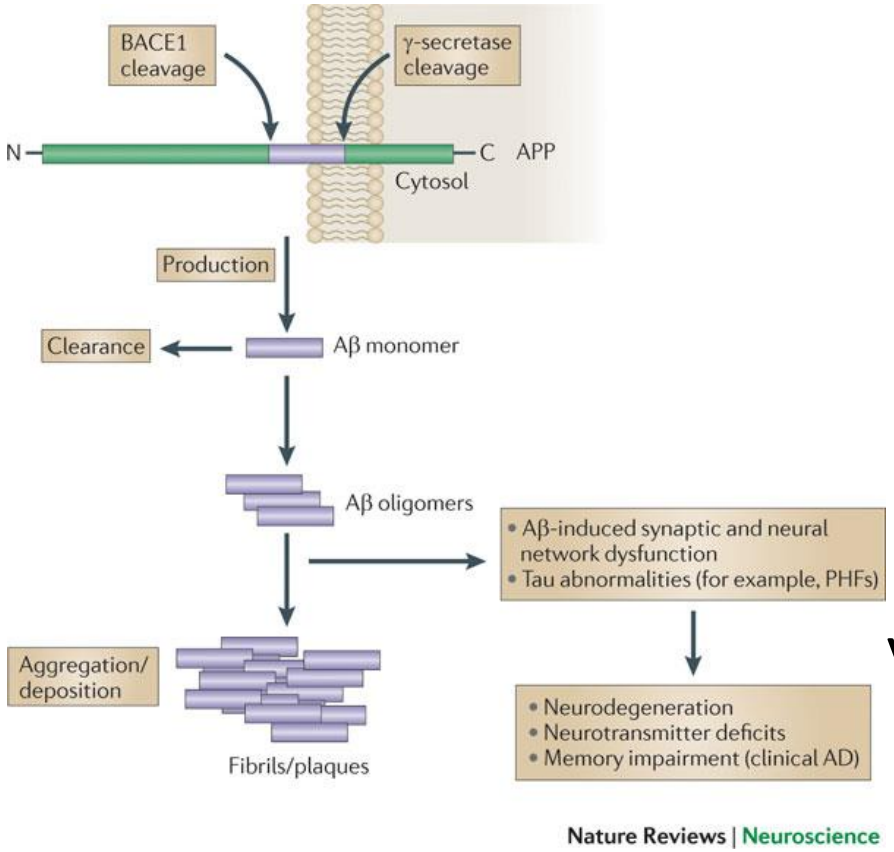





Nonamyloidogenic pathway
APP
APPsα
α
p3
γ
C83
C59
Amyloidogenic pathway
APP
APPsβ
β
Aβ
γ
C99
C59

Frank M, 2007


Cytoplasm
γ-secretase
γ-secretase
Cell membrane
p3
α-secretase
APP
β-secretase
Aβ
Extracellular space
α-APP
β-APP
Aβ generation
Oxidation
Excitotoxicity
Aβ aggregation
Inflammation
Tau hyperphosphorylation
Neuron
Senile plaque with microglial activation
Neurofibrillary tangles
Cell death
Neuro-transmitter deficit
Cognitive and behavioral abnormalities



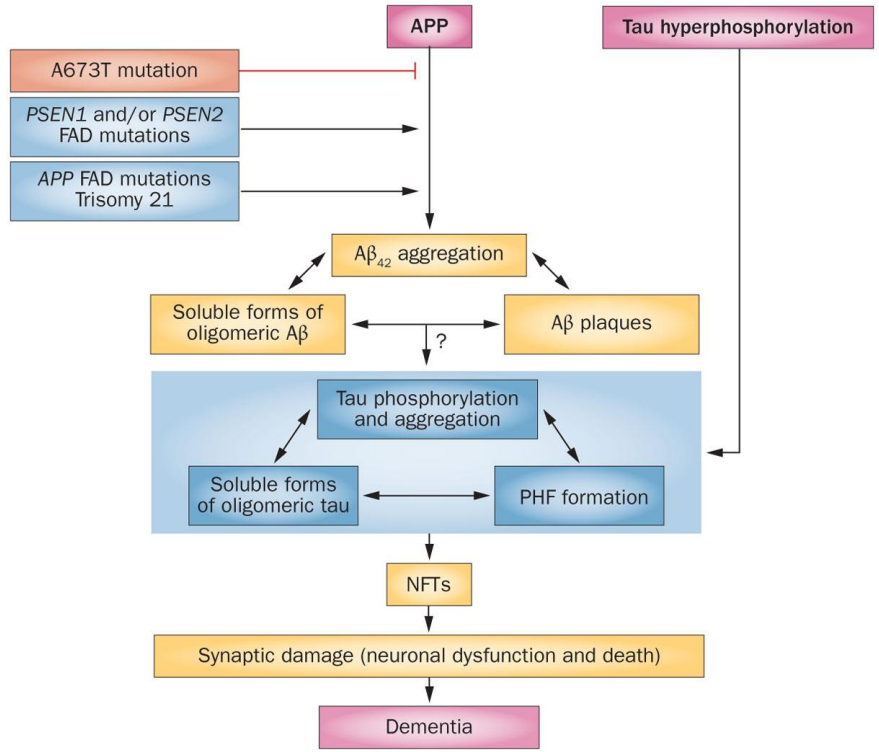
Amyloid

VS

Alzheimer disease therapy—moving from amyloid-β to tau

Ezio Giacobini and Gabriel Gold

Tau

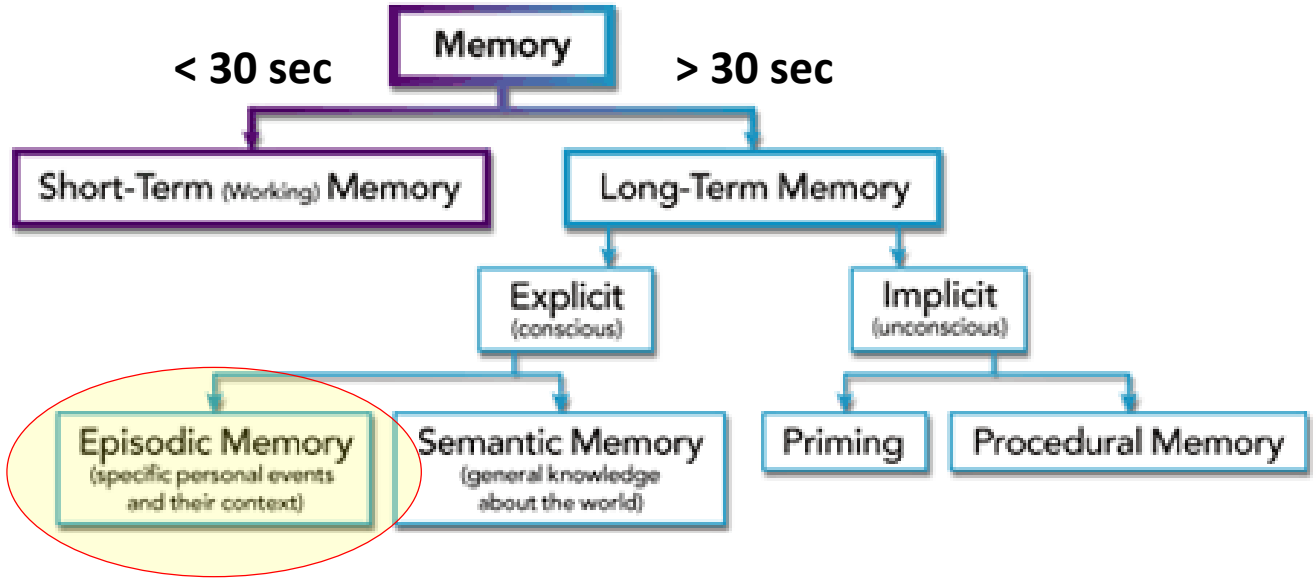


Typical Alzheimer's disease

Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:

- Gradual and progressive change in memory function reported by patient or informant over more than 6 months
- Objective evidence of an amnestic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

Dubois B, 2014



Amnestic syndrome of the medial temporal type identifies prodromal AD

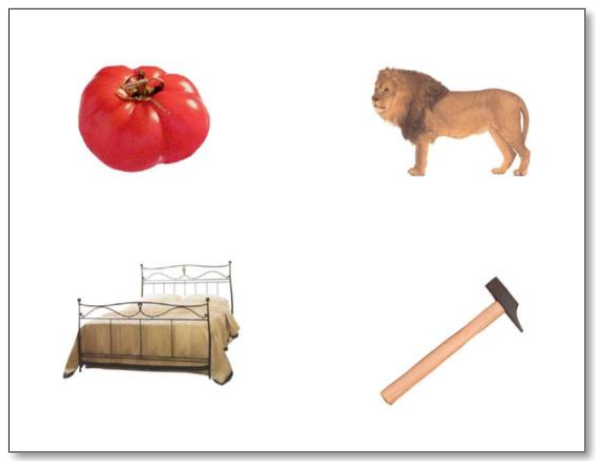
A longitudinal study

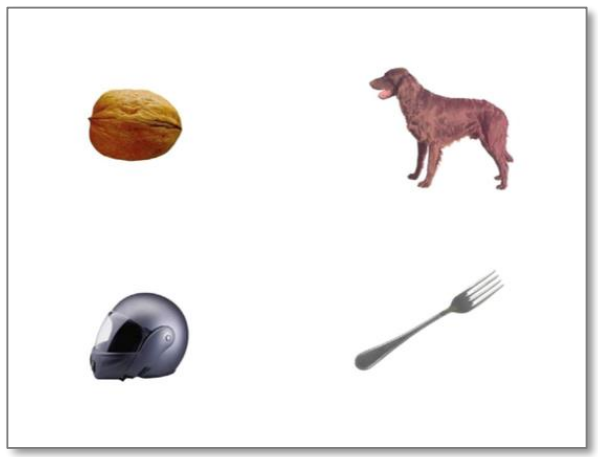
Sarazin M, 2007

Free and cued selective reminding test: an Italian normative study

P. Frasson · R. Ghiretti · E. Catricalà · S. Pomati · A. Marcone · L. Parisi · P. M. Rossini · S. F. Cappa · C. Mariani · N. Vanacore · F. Clerici

Frasson P, 2011





Journal of Alzheimer's Disease 61 (2018) 47–52
DOI 10.3233/JAD-170712
IOS Press

Short Communication

Word and Picture Version of the Free and Cued Selective Reminding Test (FCSRT): Is There Any Difference?

Andrea Arighi[a,*], Tiziana Carandini[a], Matteo Mercurio[a], Giovanni Carpani[a], Anna Margherita Pietroboni[a], Giorgio Fumagalli[a,b], Laura Ghezzi[a], Paola Basilico[a], Alberto Calvi[a], Marta Scarioni[a], Milena De Riz[a], Chiara Fenoglio[a], Elisa Scola[c], Fabio Triulzi[c], Daniela Galimberti[a] and Elio Scarpini[a]

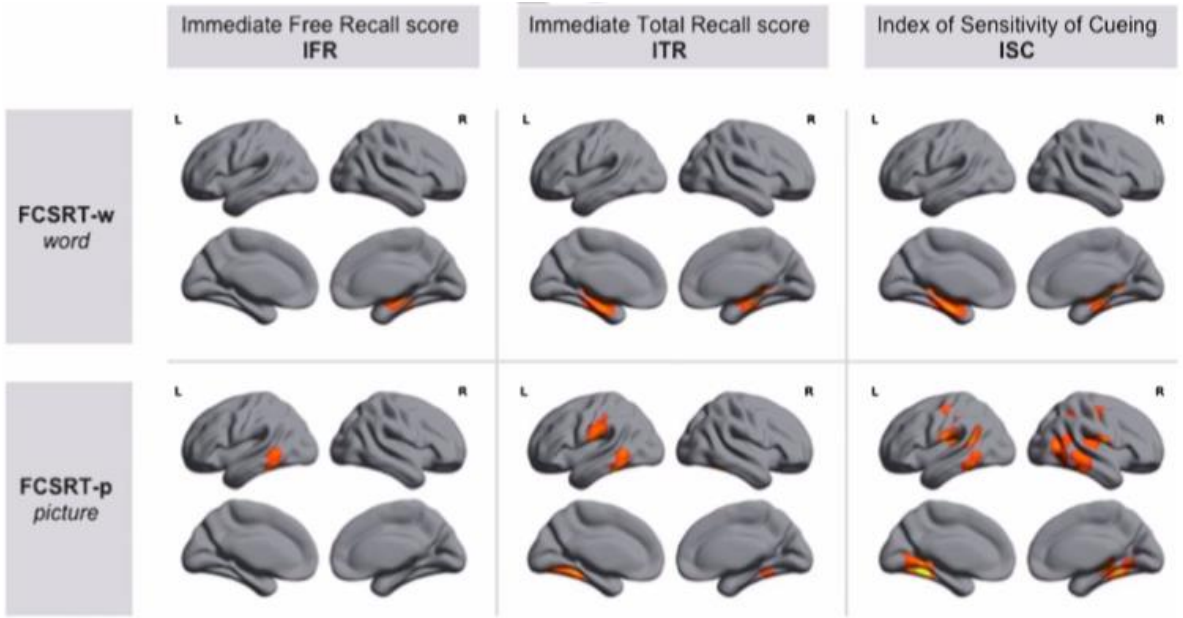


Fig. 2. VBM analysis: correlation between FCSRT scores and gray matter atrophy. FCSRT-w scores: IFR resulted associated to the degree of atrophy of the right hippocampus, while ITR and ISC scores were related with the degree of atrophy of both hippocampi. FCSRT-p: IFR score showed an association with atrophy of the left fusiform gyrus in Brodmann area (BA)-37, ITR score with atrophy of left and right fusiform gyri and ISC score with atrophy of the left fusiform gyrus in BA-37 and right BA-19. Statistical threshold: $p < 0.05$ Family Wise Error (FWE) corrected at cluster level. See text for further details.

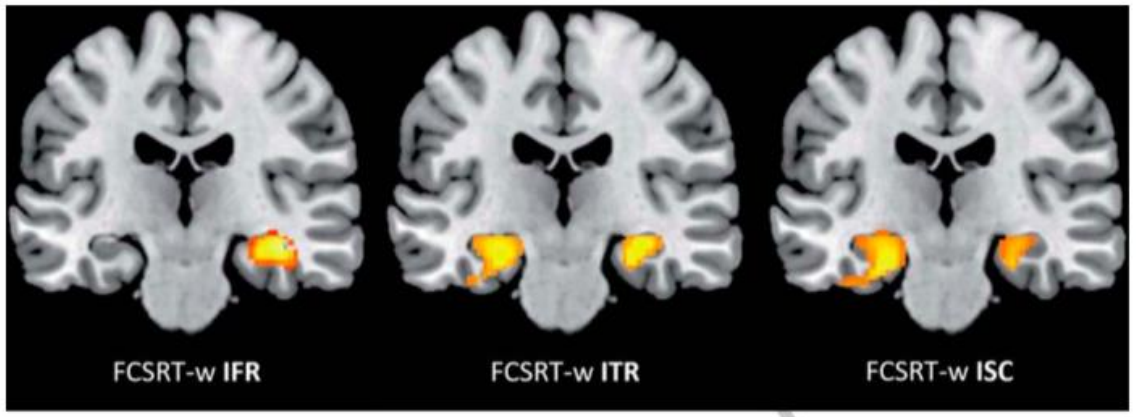


Fig. 3. VBM analysis: correlation between FCSRT-w scores and gray matter atrophy. Coronal slices showing hippocampal atrophy (IFR resulted associated to the degree of atrophy of the right hippocampus, while ITR and ISC scores were related with the degree of atrophy of both hippocampi).

Arighi A et al, 2018

4. Probable AD dementia: Core clinical criteria

4.1. Probable AD dementia is diagnosed when the patient

1. Meets criteria for dementia described earlier in the text, and in addition, has the following characteristics:

A. Insidious onset. Symptoms have a gradual onset over months to years, not sudden over hours or days;

B. Clear-cut history of worsening of cognition by report or observation; and

C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories.

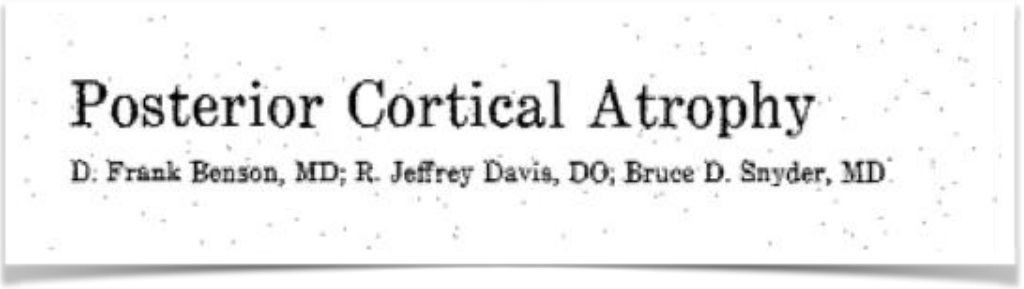
a. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.

b. Nonamnestic presentations:

- Language presentation: The most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
- Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
- Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.

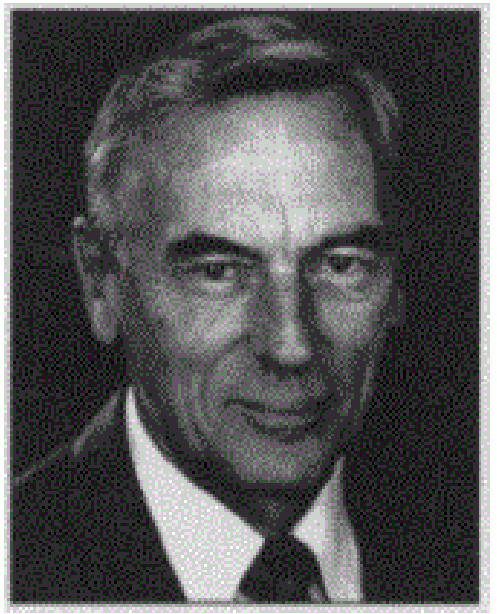
D. The diagnosis of probable AD dementia ***should not*** be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of Dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

McKhann G et al, 2011



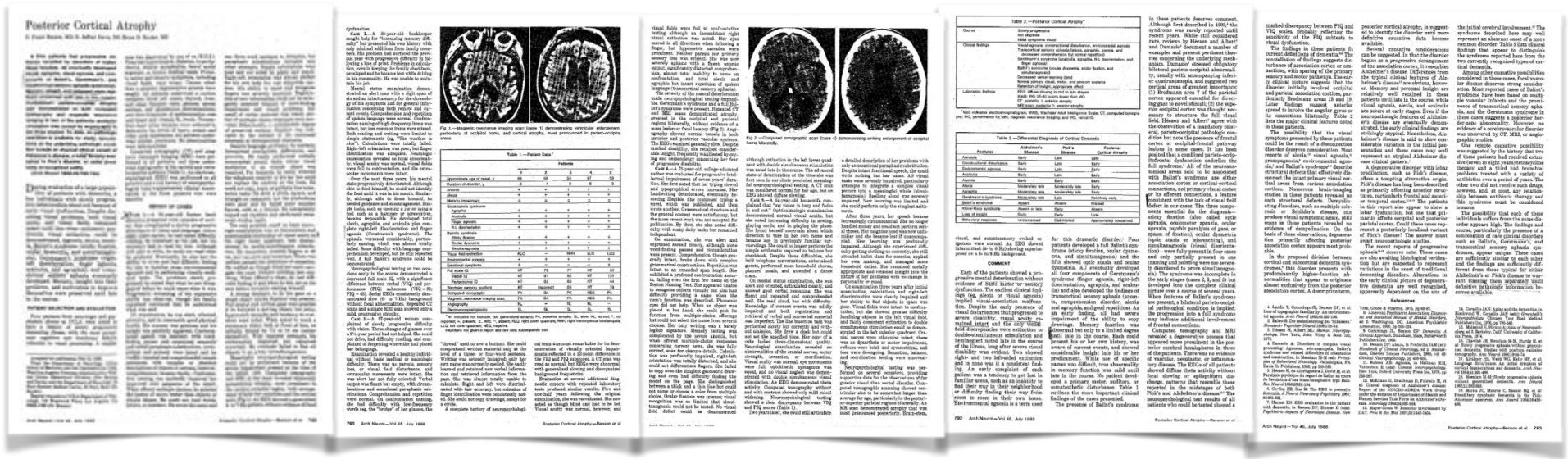
Posterior Cortical Atrophy

D. Frank Benson, MD; R. Jeffrey Davis, DO; Bruce D. Snyder, MD

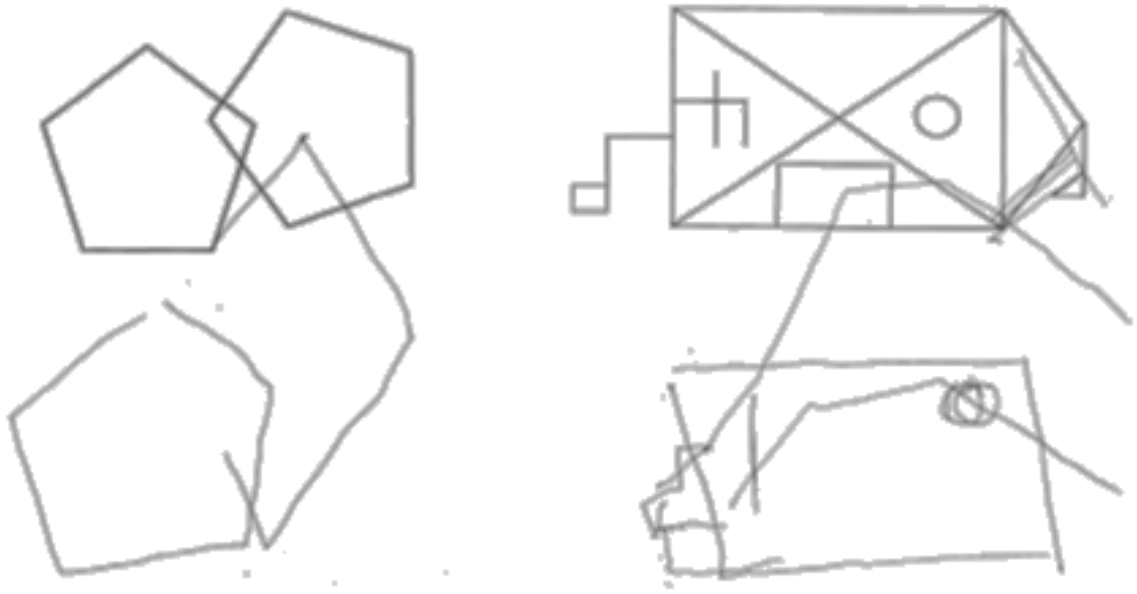


D. Frank Benson, MD

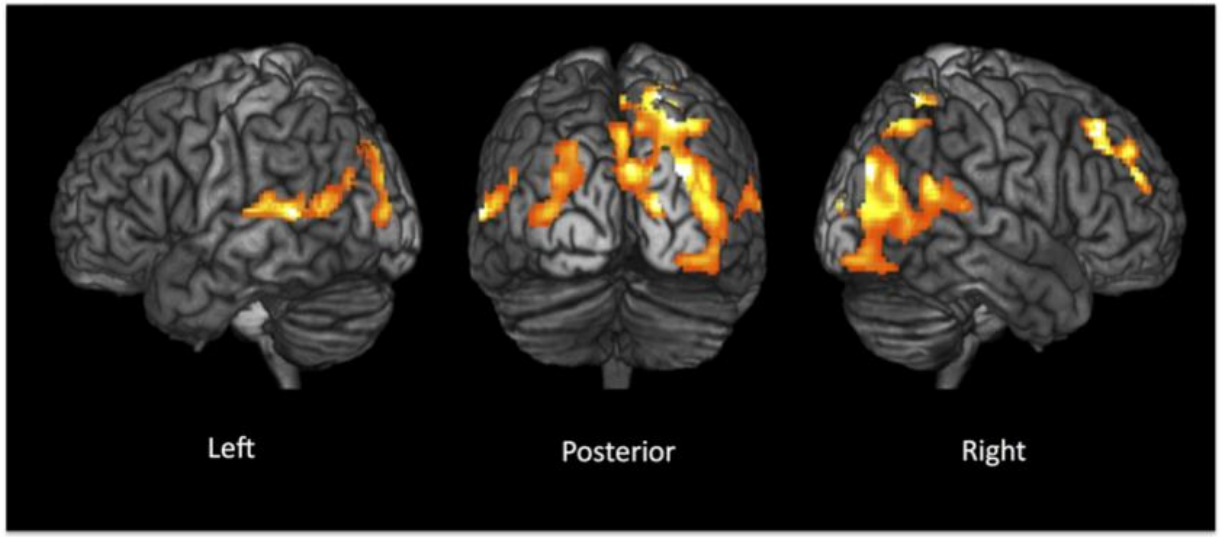
Posterior Cortical Atrophy (PCA) was first described in 1988 when Benson et al. reported five patients with prominent visual complaints, who exhibited both Balint's and Gerstmann's syndromes.



Benson DF, Davis RJ, Snyder BD. Posterior cortical atrophy. Arch Neurol 1988; 45: 789–93.

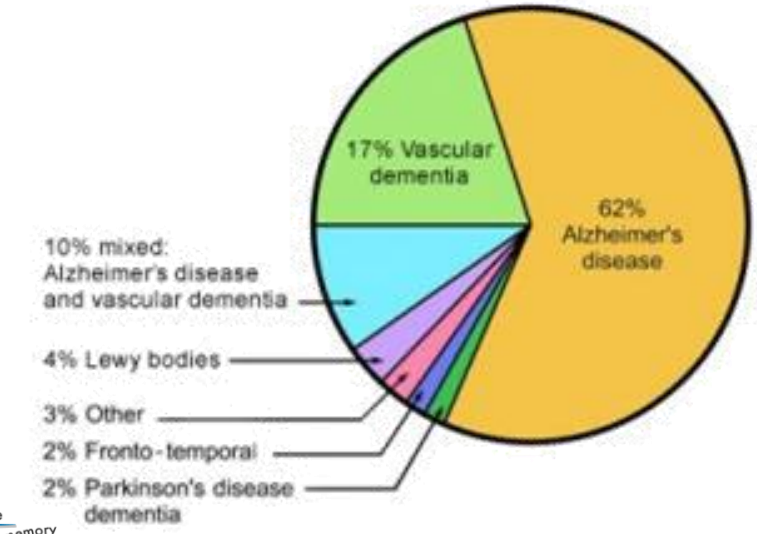


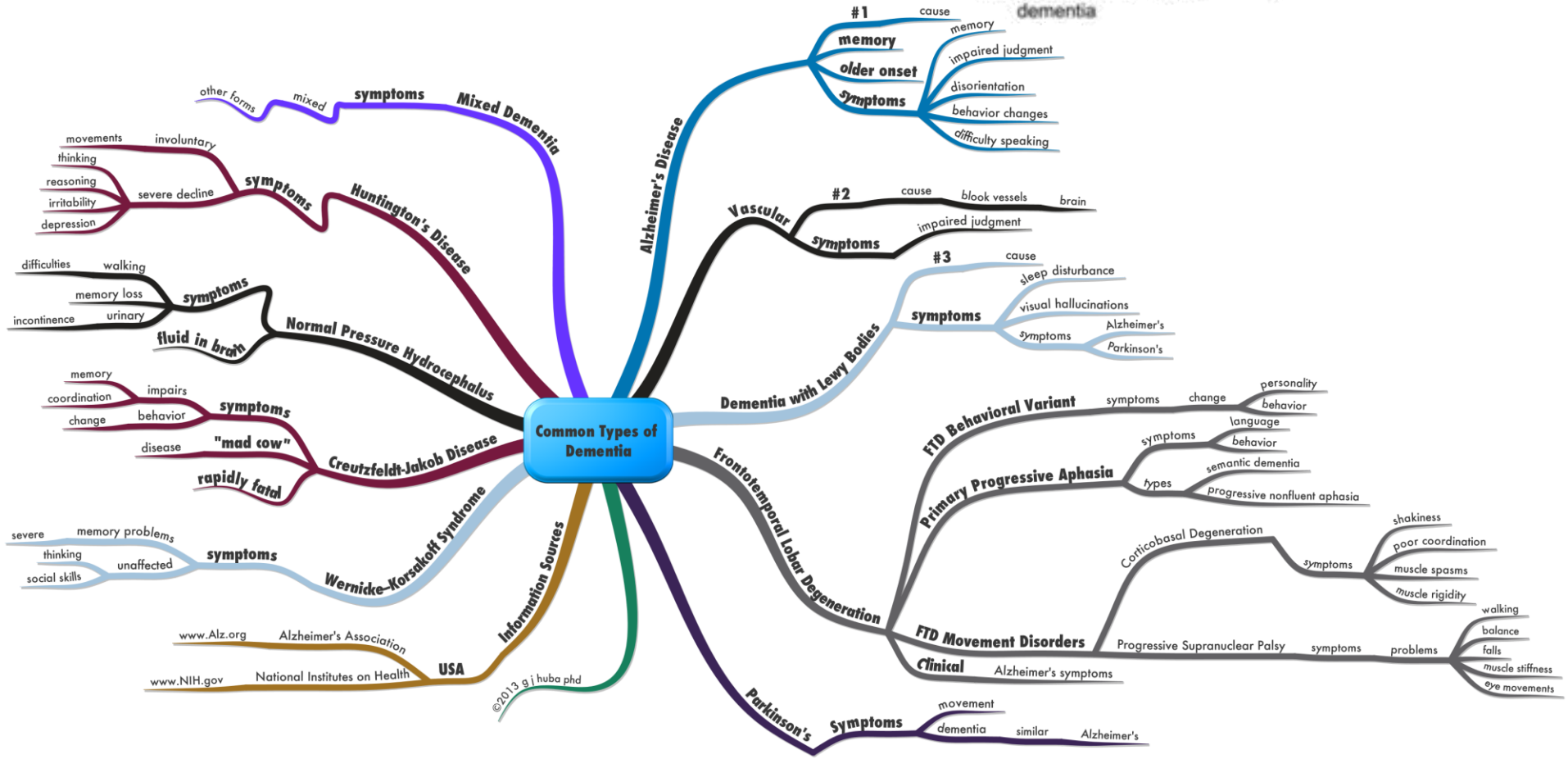
Crutch SJ, 2012



Arighi A et al, 2015

Types of dementia





Classificazione

Demenze primarie o degenerative:

- Demenza di Alzheimer
- Demenze fronto-temporali
- Demenza a corpi di Lewy
- Parkinson-demenza
- Corea di huntington
- Paralisi sopranuclare progressiva
- Degenerazione cortico-basale

Demenze secondarie:

- Demenza vascolare ischemica
- Disturbi endocrini e metabolici
- Malattie metaboliche ereditarie
- Malattie infettive e infiammatorie SNC
- Stati carenziali
- Sostanze tossiche
- Processi espansivi intracranici
- Idrocefalo normoteso

di interesse neurochirurgico:

- idrocefalo normoteso
- tumori endocranici
- ematoma cronico subdurale
- fistole durali arterovenose

da insufficienza d'organo:

- epatica
- respiratoria
- renale
- cardiaca

da causa endocrina:

- ipotiroidismo
- ipertiroidismo,
- ipoparatiroidismo
- Addison
- ipercortisolismo

carenziali:

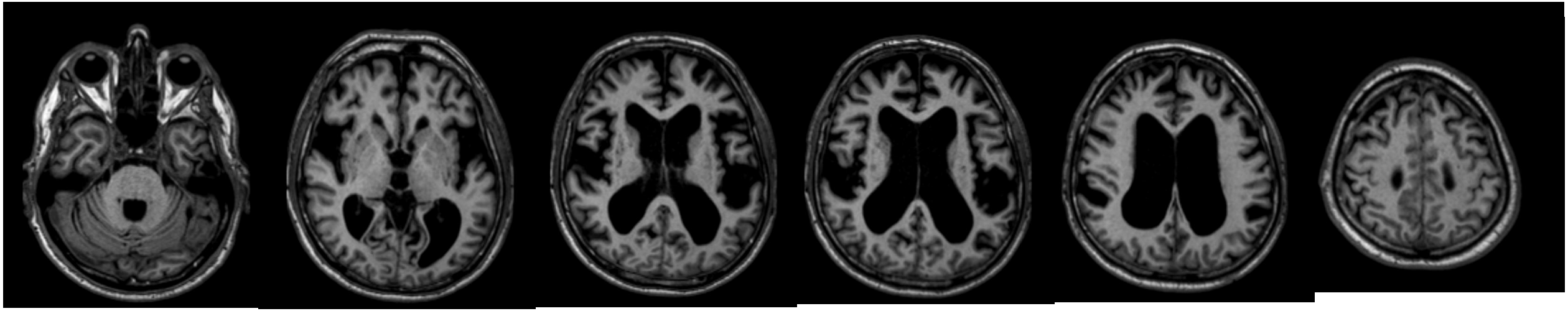
- Vit B12
- folati
- Vit B1

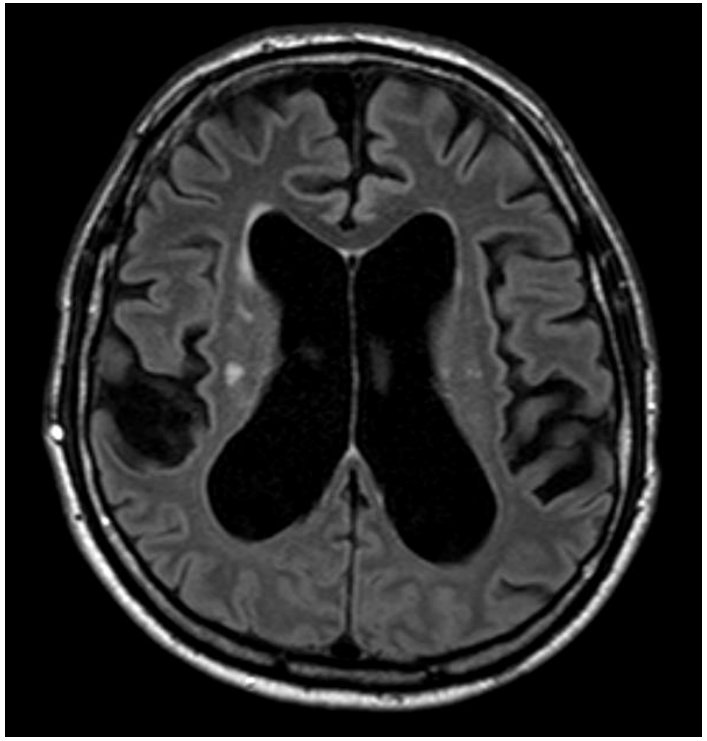
da farmaci

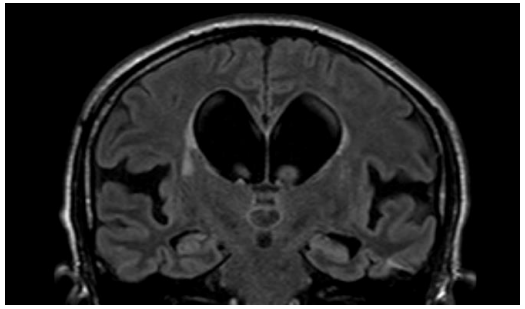
da patologia infettiva

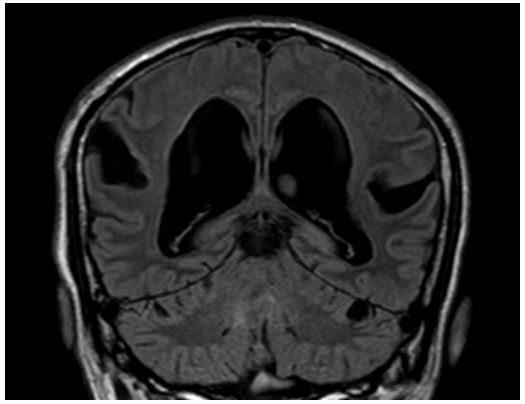
da depressione

Demenze reversibili

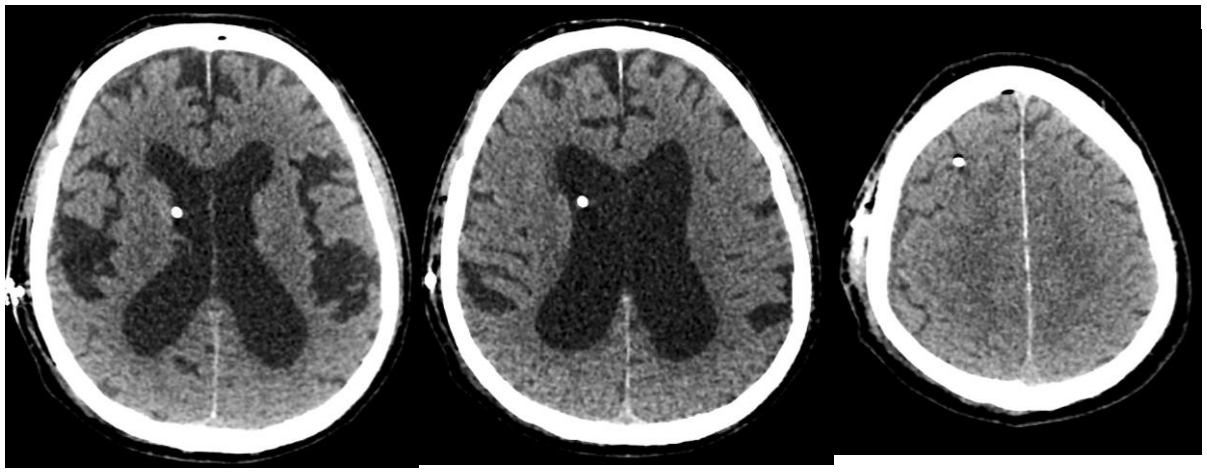


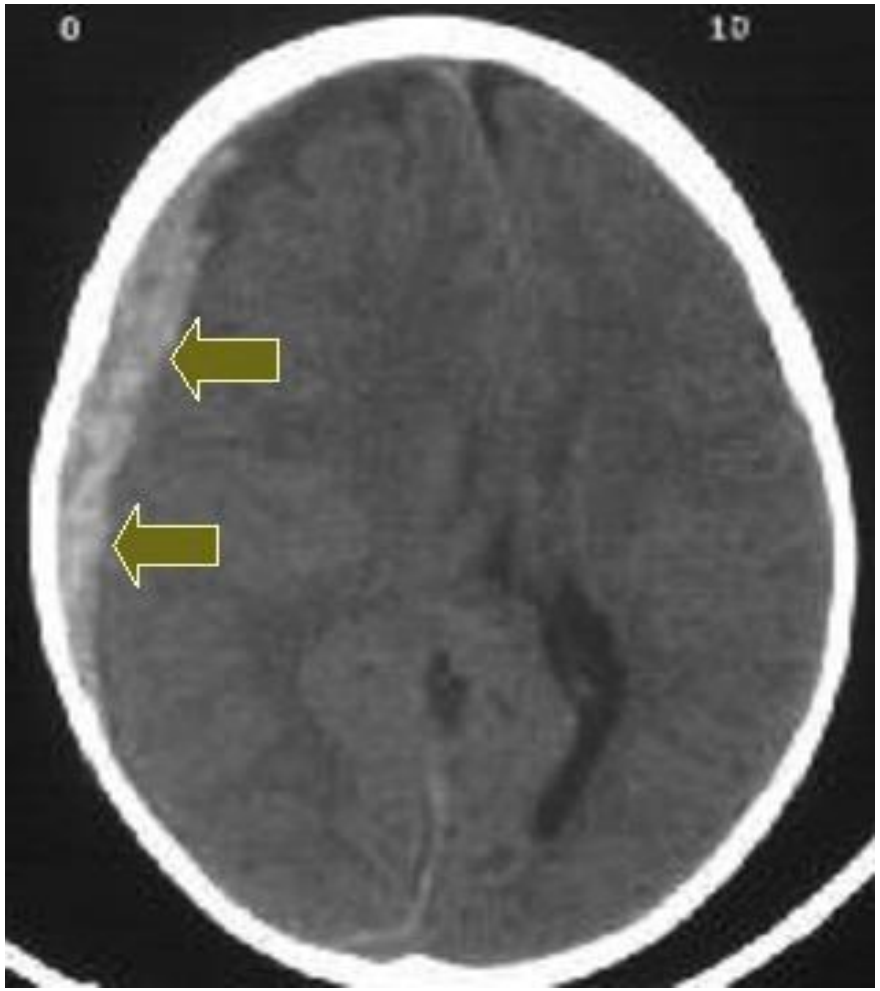






Pz di 70 aa
Disturbo della deambulazione, deficit cognitivo lieve, incontinenza urinaria

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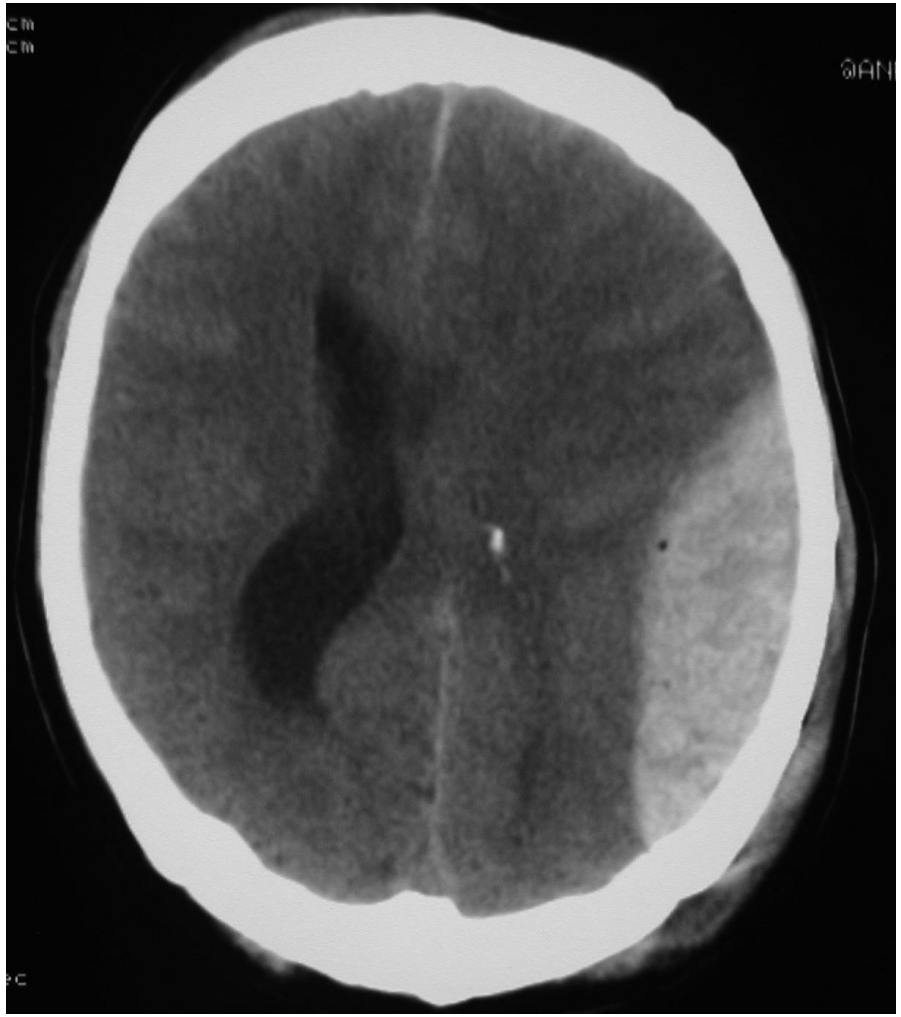
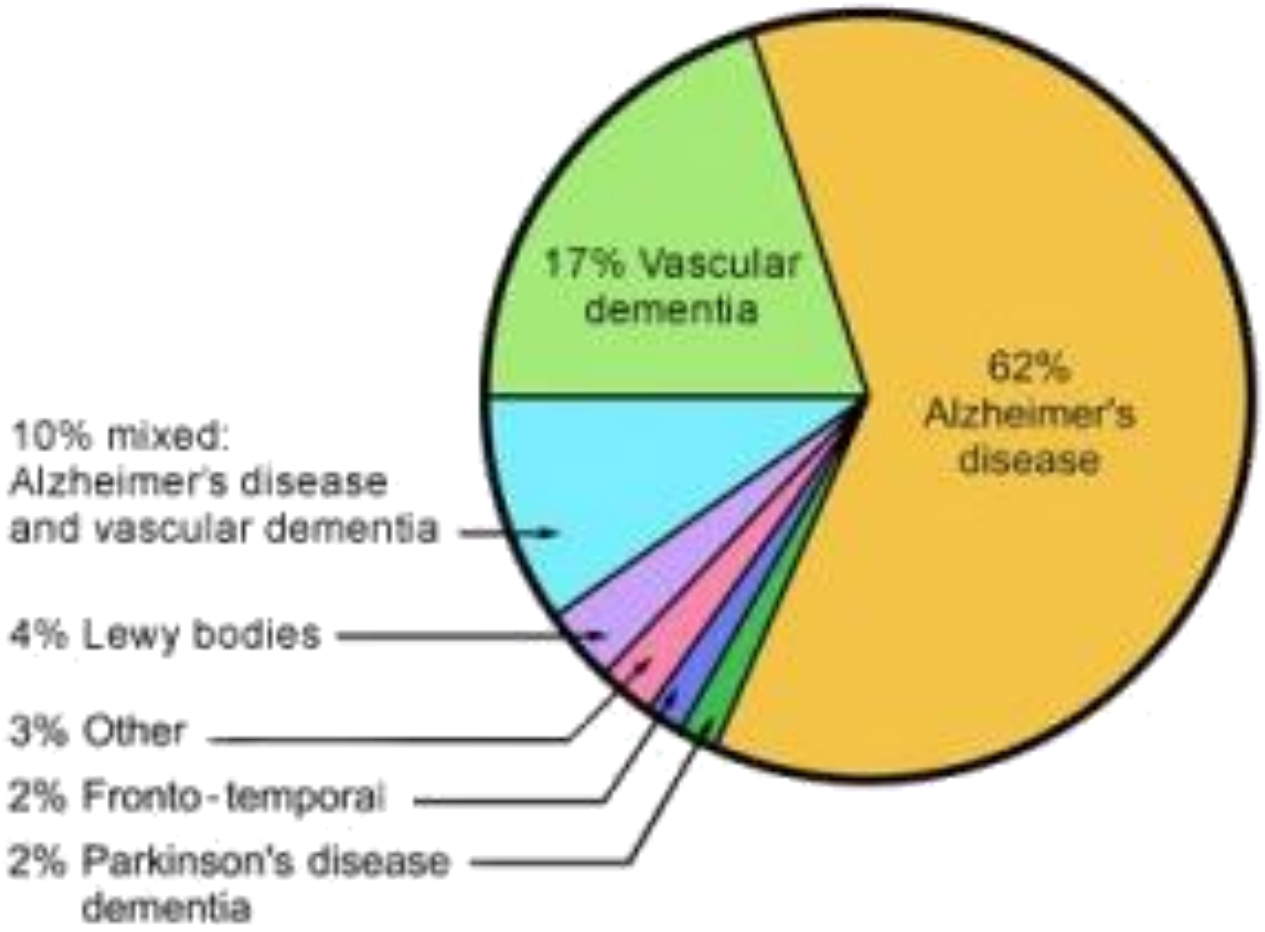
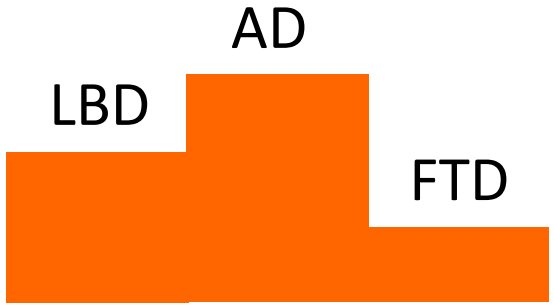


PSEUDODEMENZA DEPRESSIVA

	Demenza	Pseudodemenza depressiva
Insorgenza	**Insidiosa**	Improvvisa
Progressione	Lenta	Rapida
Consapevolezza	Scarsa, sminuisce il deficit	**Mantenuta, enfatizza il deficit**
Comportamnento	Congruo ad entità deficit	Non congruo ad entità del deficit
Risposte	Mancanti o confabulazioni	**Risposte generiche o “non so”**
Umore	**Poco congruo**	Deflesso
Sintomi vegetativi	Scarsi	Frequenti
Precedenti psichiatrici	Non frequenti	Rilevanti
Rischio suicidio	Basso	Alto

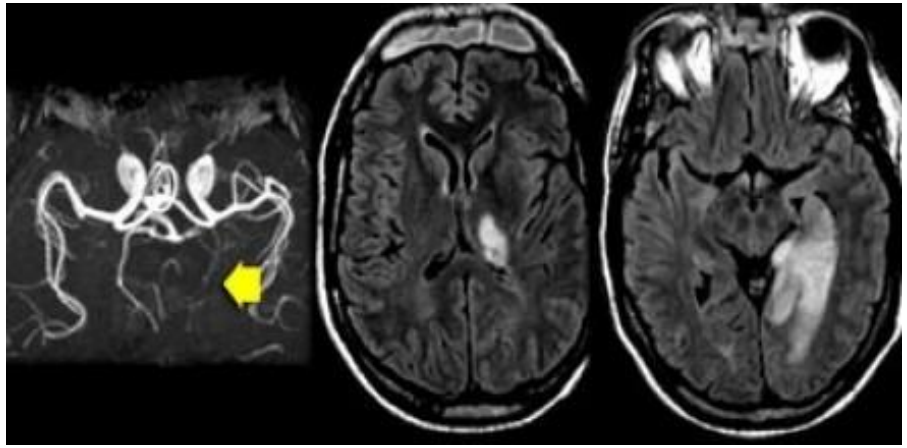
Neurodegenerative dementia



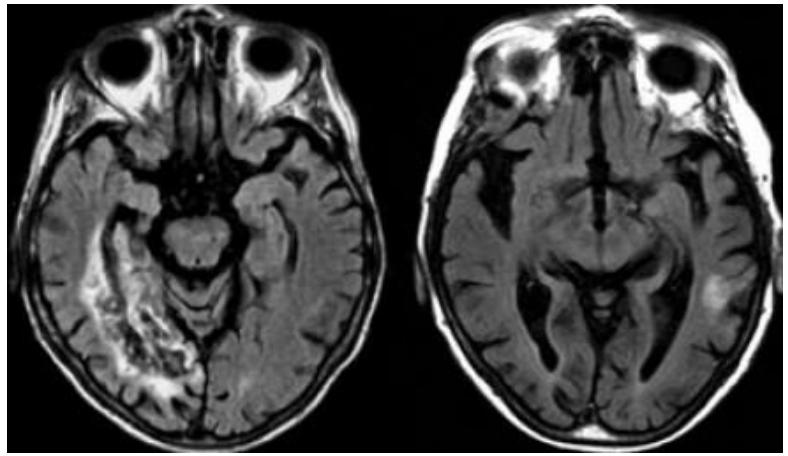


Demenza vascolare

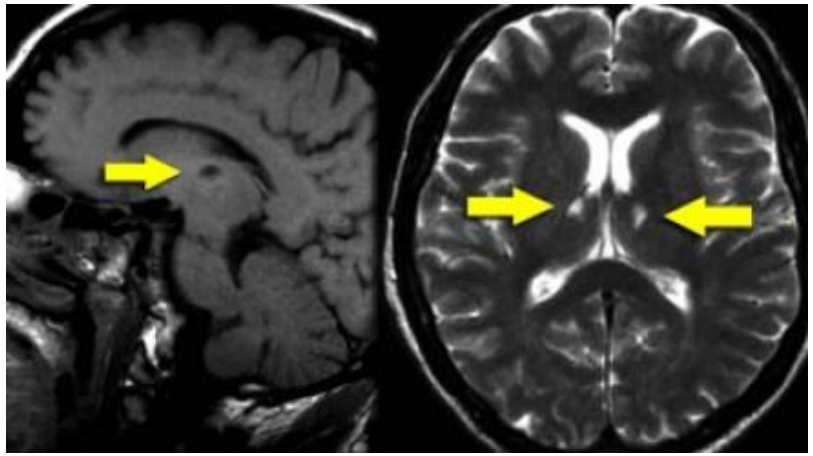
- ✓ **Demenza multiinfartuale**



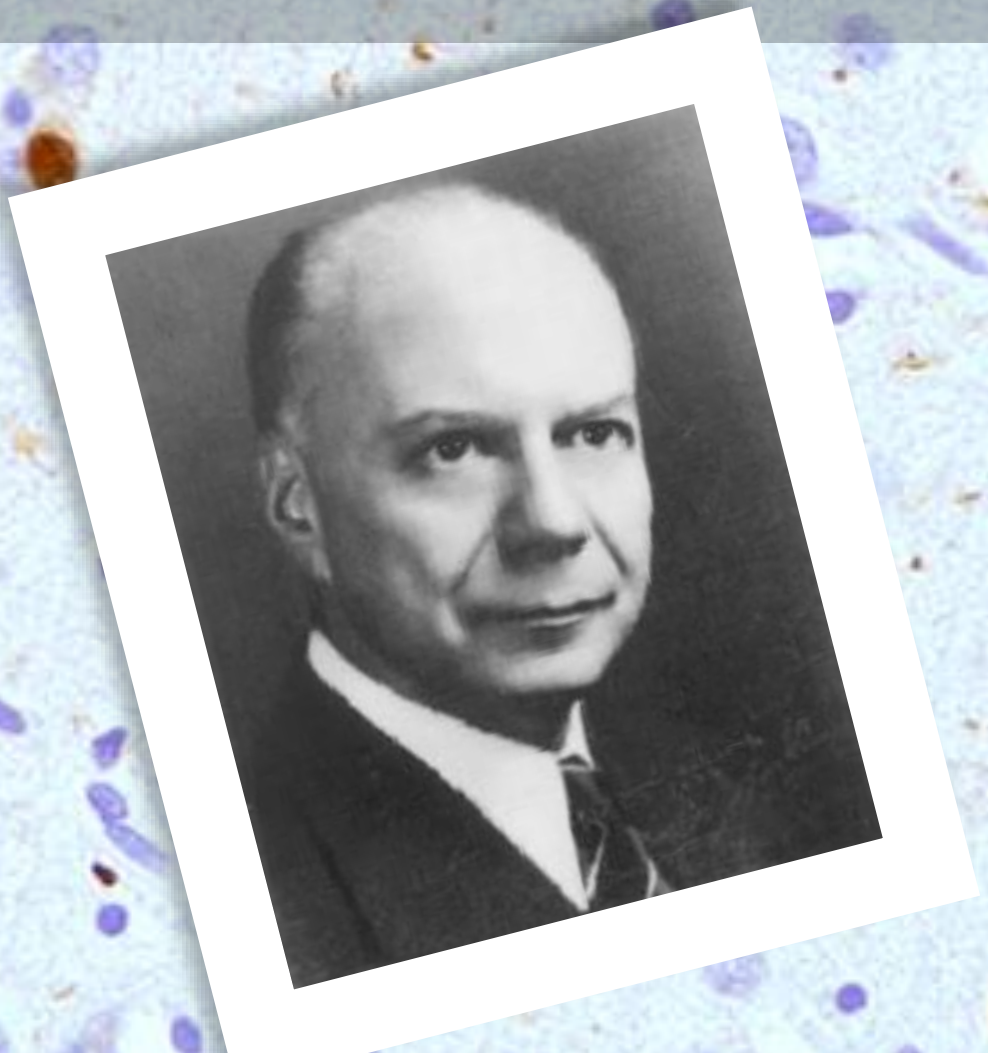
- ✓ **Demenza da infarti strategici**
  - Territorio dell'arteria cerebrale anteriore bilateralmente
  - Aree associative parieto-temporali e temporo-occipitali dell'emisfero dominante
  - Territorio dell'arteria cerebrale posteriore coinvolgente talamo o lobo temporale mesiale bilateralmente

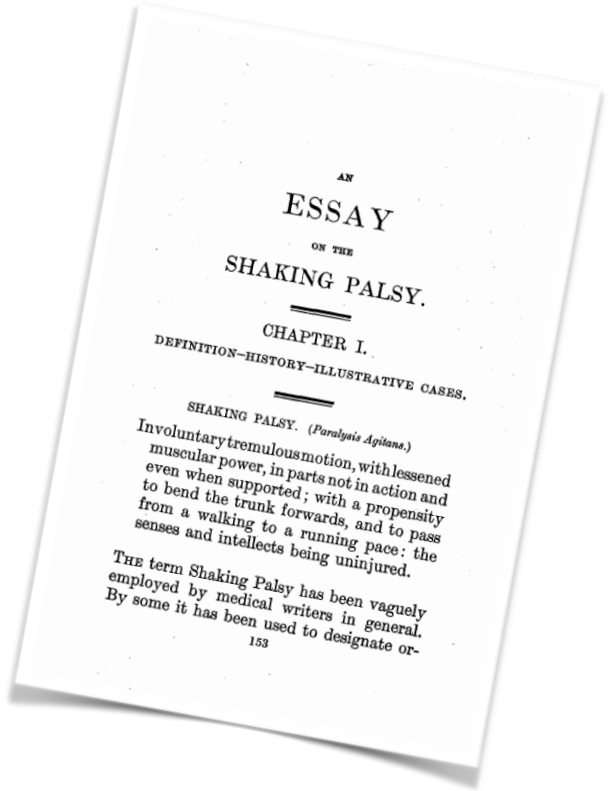


- ✓ **Demenza da patologia dei piccoli vasi**
  - Carico vascolare > 25 % della sostanza bianca (malattia di Binswanger)
  - Forme genetiche (es. CADASIL)



Lewy body dementia





AN

ESSAY

ON THE

SHAKING PALSY.

CHAPTER I.

DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING PALSY. (*Paralysis Agitans.*)

Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

THE term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-

153

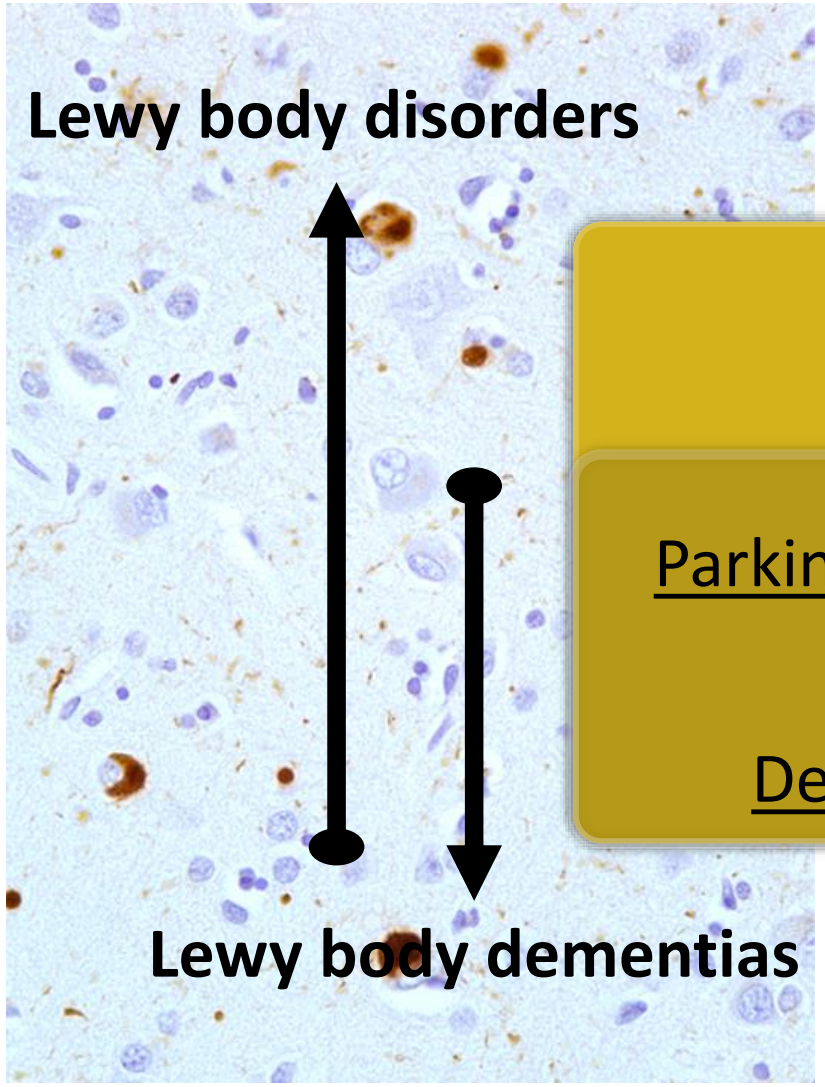
James Parkinson (1755-1824)

‘‘the sense and intellects being uninjured"

Jean-Martin Charcot (1825-1893)

‘‘the mind becomes clouded and the memory is lost’’

Lewy Body Dementias



Parkinson's disease (PD)

Parkinson's disease with dementia (PDD)

Dementia with Lewy bodies (DLB)

Lippa CF et al, 2007

2005

HIGH LIGHT
CME

Diagnosis and management of dementia with Lewy bodies

Third report of the DLB consortium

I.G. McKeith, MD, FMedSci; D.W. Dickson, MD; J. Lowe, DM; M. Emre, MD; J.T. O'Brien, DM; H. Feldman, MDCM; J. Cummings, MD; J.E. Duda, MD; C. Lippa, MD; E.K. Perry, DSc; D. Aarsland, MD; H. Arai, MD; C.G. Ballard, MD; B. Boeve, MD; D.J. Burn, FRCP; D. Costa, MD; T. Del Ser, MD, PhD; B. Dubois, MD; D. Galasko, MD; S. Gauthier, MD, FRCPC; C.G. Goetz, MD; E. Gomez-Tortosa, MD, PhD; G. Halliday, PhD; L.A. Hansen, MD; J. Hardy, PhD; T. Iwatsubo, MD; R.N. Kalaria, FRCPath; D. Kaufer, MD; R.A. Kenny, MD; A. Korczyn, MD; K. Kosaka, MD; V.M.-Y. Lee, PhD, MBA; A. Lees, MD; I. Litvan, MD; E. Londos, MD, PhD; O.L. Lopez, MD; S. Minoshima, MD, PhD; Y. Mizuno, MD; J.A. Molina, MD; E.B. Mukaetova-Ladinska, MD, PhD; F. Pasquier, MD, PhD; R.H. Perry, DSc; J.B. Schulz, MD; J.Q. Trojanowski, MD, PhD; and M. Yamada, MD, PhD, for the Consortium on DLB*

2017

Published Ahead of Print on June 7, 2017 as 10.1212/WNL.0000000000004058

VIEWS & REVIEWS

Diagnosis and management of dementia with Lewy bodies

Fourth consensus report of the DLB Consortium

OPEN

Essential for a diagnosis of DLB is dementia, defined as a progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or with usual daily activities. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuoperceptual ability may be especially prominent and occur early.

Core clinical features (*The first 3 typically occur early and may persist throughout the course.*)

Fluctuating cognition with pronounced variations in attention and alertness.
Recurrent visual hallucinations that are typically well formed and detailed.
REM sleep behavior disorder, *which may precede cognitive decline.*
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.

Supportive clinical features

Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematized delusions; apathy, anxiety, and depression.

Indicative biomarkers

Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Abnormal (low uptake) ^{123}iodine-MIBG myocardial scintigraphy.
Polysomnographic confirmation of REM sleep without atonia.

Supportive biomarkers

Relative preservation of medial temporal lobe structures on CT/MRI scan.
Generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging.
Prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range.

Essenziale:
Declino cognitivo progressivo
(attenzione, f esecutive, f visuospaziali)

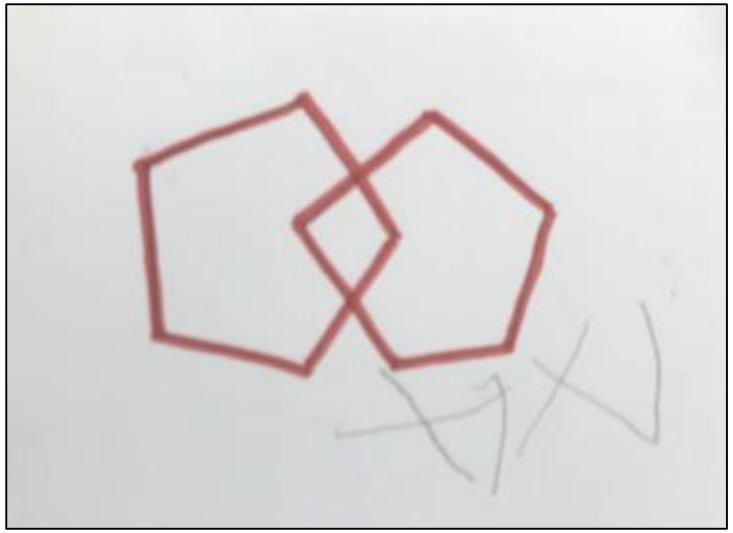
Core clincial features:

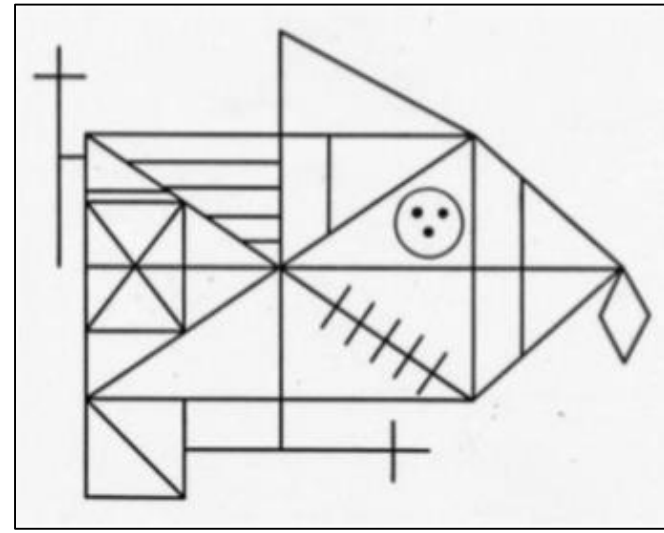
- Fluttuazioni
- Allucinazioni visive
- RSBD
- Parkinsonismo

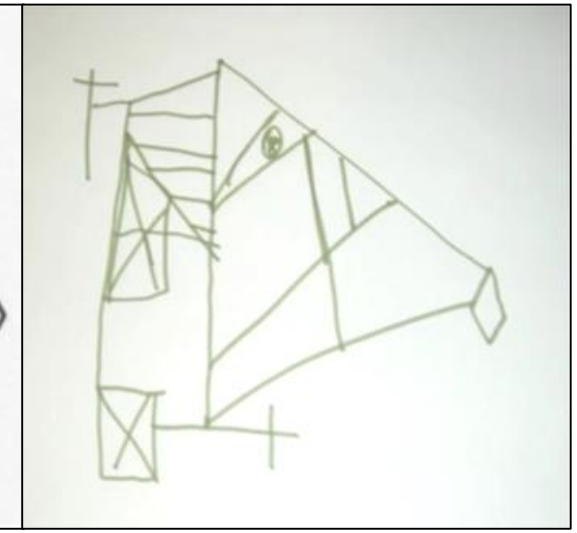
Indicative biomarkers:

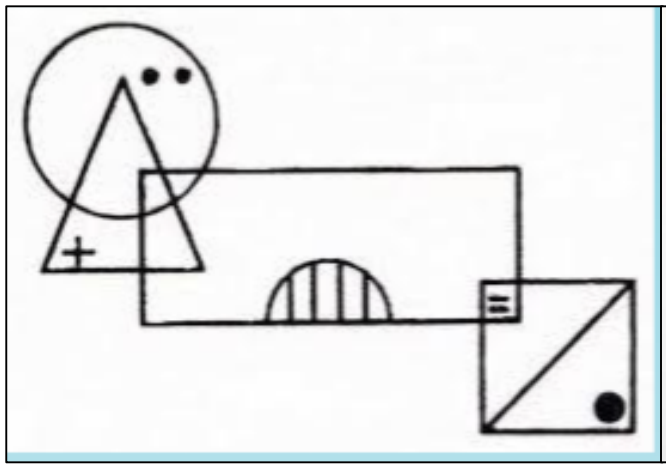
- DAT-scan
- SPECT miocardica
- Polisonnografia

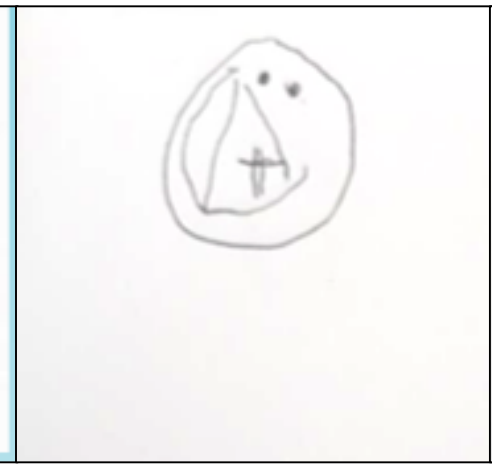
LG Mc Keith, 2017

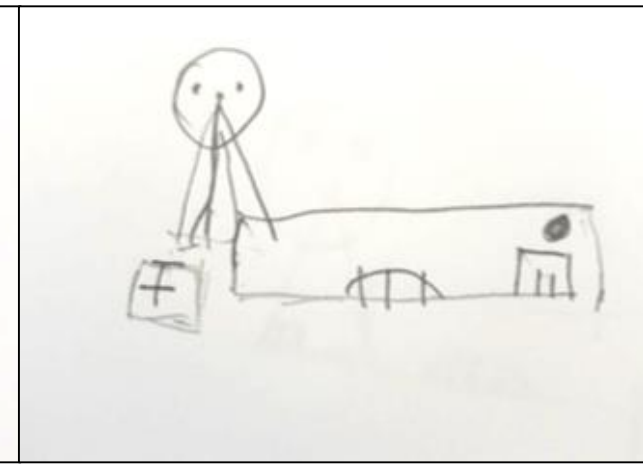










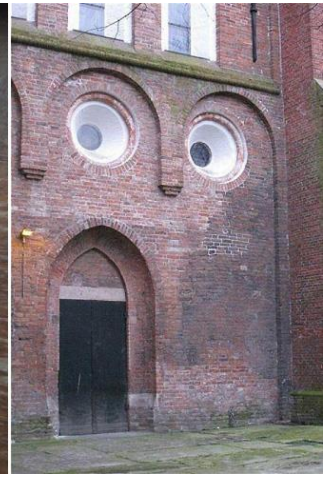


Allucinazioni visive

- Ben formate e animate
- Adulti o piccoli bambini

Fenomeni visivi

- Sensazione di passaggio
- Sensazione di presenza
- Illusioni
- Pareidolie



Frontotemporal dementia

Clinica neurologica di Praga

Caso A → August H, 71 aa (1892)
Caso B → Anna H, 41 aa (1904)

Arnold Pick (1851-1924)

Über die Beziehungen der senilen Hirnatrophie zur Aphasie.
Prag Med Wochenschr. 1892; 17:165-167.

Über primare progressive Demenz bei Erwachsenen.
Prag Med Wochenschr. 1904;29:417-420.

Alois Alzheimer (1864-1915)

Über einen eigenartigen, schweren Erkrankungsprozeß der Hirnrinde
37th Meeting of South-West German Psychiatrists
Tubingen - November 3, 1906

Über eigenartige Krankheitsfalle des spateren Alters.
Z Gesamte Neurol Psychiatr. 1911; 4:356-385.

Pick bodies

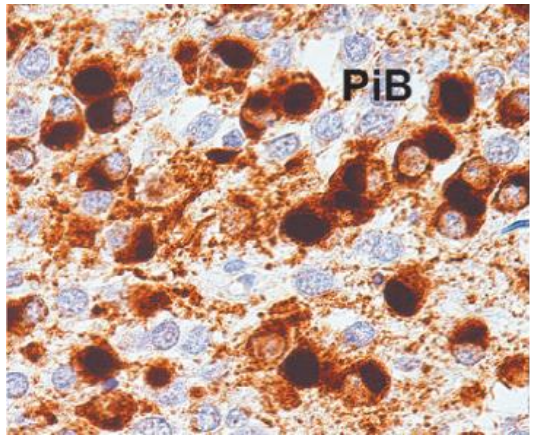
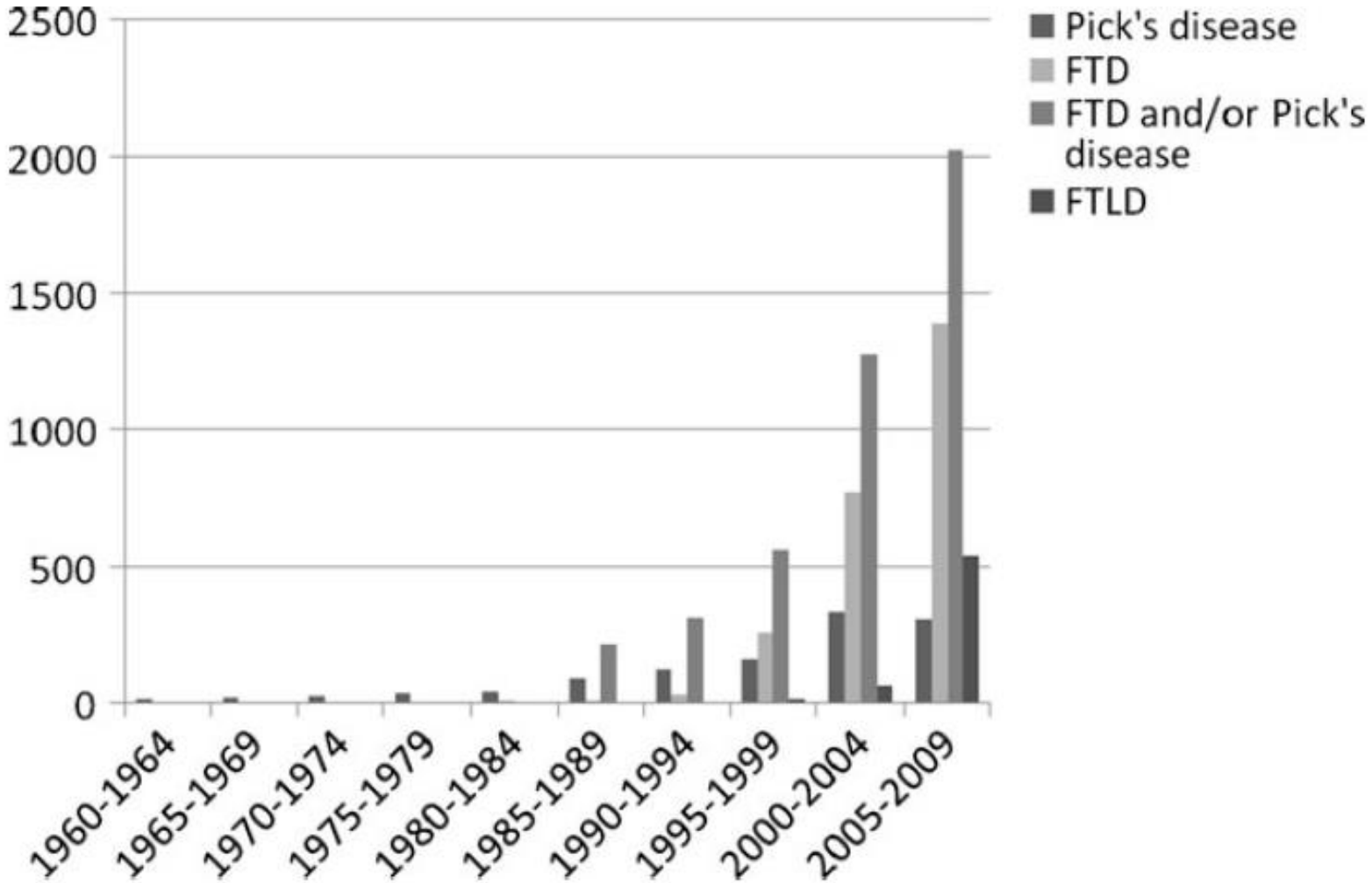


Fig. 1 Publications on frontotemporal dementias in PubMed (Medline) in 5-year intervals, 1960–2009



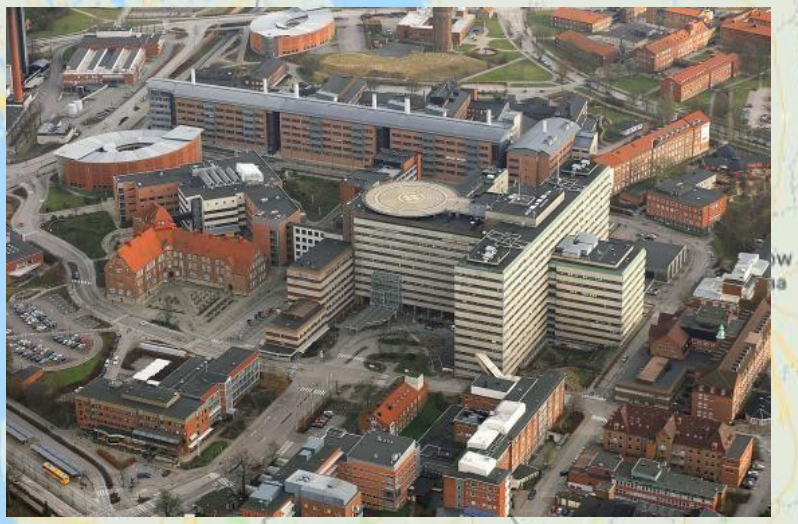
Brun A and Gustafson L, 2011

Lund – Svezia

International conferences on frontotemporal dementia (FTD)

Lund dementia research group

1986 – 1992 – 1998 – 2003



Lund University Hospital

1994

CONSENSUS STATEMENT

Clinical and neuropathological criteria for frontotemporal dementia

The Lund and Manchester Groups

1998

Frontotemporal lobar degeneration

A consensus on clinical diagnostic criteria

D. Neary, MD; J.S. Snowden, PhD; L. Gustafson, MD; U. Passant, MD; D. Stuss, PhD; S. Black, MD; M. Freedman, MD; A. Kertesz, MD; P.H. Robert, MD, PhD; M. Albert, PhD; K. Boone, PhD; B.L. Miller, MD; J. Cummings, MD; and D.F. Benson, MD

2011

doi:10.1093/brain/awr179 Brain 2011: 134; 2456–2477 | 2456

BRAIN
A JOURNAL OF NEUROLOGY

Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia

Katya Rascovsky,[1] John R. Hodges,[2] David Knopman,[3] Mario F. Mendez,[4,5] Joel H. Kramer,[6] John Neuhaus,[7] John C. van Swieten,[8] Harro Seelaar,[8] Elise G. P. Dopper,[8] Chiadi U. Onyike,[9] Argye E. Hillis,[10] Keith A. Josephs,[3] Bradley F. Boeve,[3] Andrew Kertesz,[11] William W. Seeley,[6] Katherine P. Rankin,[6] Julene K. Johnson,[12] Maria-Luisa Gorno-Tempini,[6] Howard Rosen,[6] Caroline E. Prioleau-Latham,[6] Albert Lee,[6] Christopher M. Kipps,[13,14] Patricia Lillo,[2] Olivier Piguet,[2] Jonathan D. Rohrer,[15] Martin N. Rossor,[15] Jason D. Warren,[15] Nick C. Fox,[15] Douglas Galasko,[16,17] David P. Salmon,[16] Sandra E. Black,[18] Marsel Mesulam,[19] Sandra Weintraub,[19] Brad C. Dickerson,[20] Janine Diehl-Schmid,[21] Florence Pasquier,[22] Vincent Deramecourt,[22] Florence Lebert,[22] Yolande Pijnenburg,[23] Tiffany W. Chow,[24,25] Facundo Manes,[26] Jordan Grafman,[27] Stefano F. Cappa,[28,29] Morris Freedman,[24,30] Murray Grossman[1,*] and Bruce L. Miller[6,*]

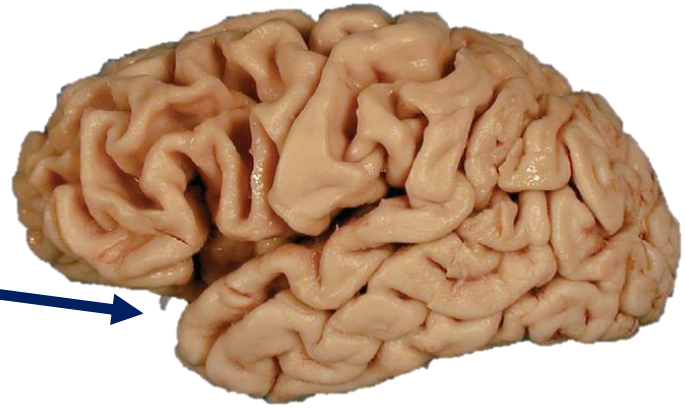
2011

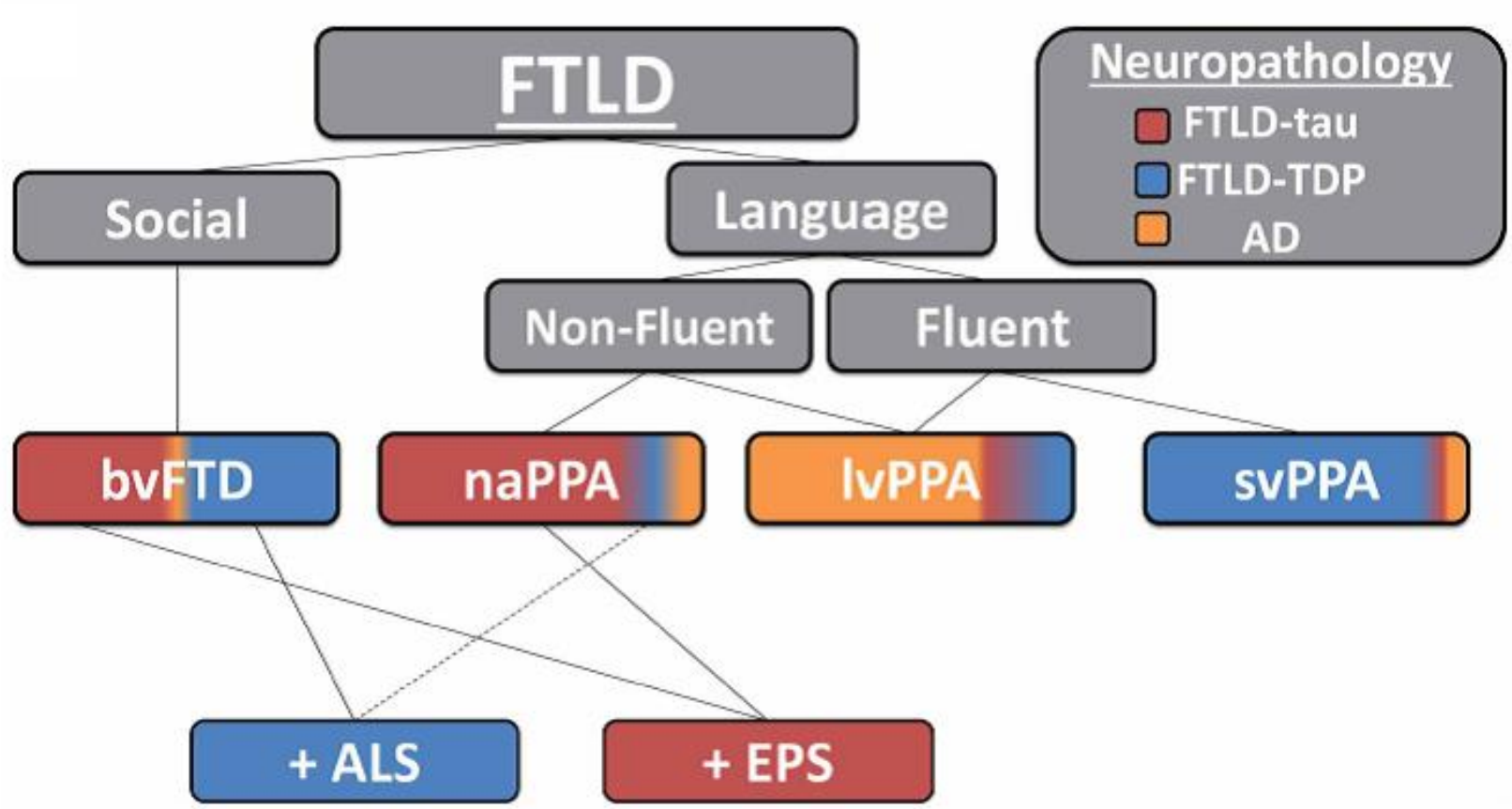
VIEWS & REVIEWS

Classification of primary progressive aphasia and its variants

M.L. Gorno-Tempini, MD, PhD
A.E. Hillis, MD
S. Weintraub, PhD
A. Kertesz, MD
M. Mendez, MD
S.F. Cappa, MD
J.M. Ogar, MS
J.D. Rohrer, MD
S. Black, MD
B.F. Boeve, MD
F. Manes, MD
N.F. Dronkers, PhD
R. Vandenberghe, MD, PhD
K. Rascovsky, PhD
K. Patterson, PhD
B.L. Miller, MD
D.S. Knopman
J.R. Hodges, MD*
M.M. Mesulam, MD*
M. Grossman, MD*

Malattia neurodegenerativa
che coinvolge i lobi **frontali**
e i lobi **temporali**





Irwin et al., 2013

Behavioral variant FTD (bv-FTD)

I. Neurodegenerative disease

The following symptom must be present to meet criteria for bvFTD

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant).

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A–F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events.

A. Early* behavioural disinhibition [one of the following symptoms (A.1–A.3) must be present]:
   - A.1. Socially inappropriate behaviour
   - A.2. Loss of manners or decorum
   - A.3. Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1–B.2) must be present]:
   - B.1. Apathy
   - B.2. Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1–C.2) must be present]:
   - C.1. Diminished response to other people's needs and feelings
   - C.2. Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1–D.3) must be present]:
   - D.1. Simple repetitive movements
   - D.2. Complex, compulsive or ritualistic behaviours
   - D.3. Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1–E.3) must be present]:
   - E.1. Altered food preferences
   - E.2. Binge eating, increased consumption of alcohol or cigarettes
   - E.3. Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and visuospatial functions [all of the following symptoms (F.1–F.3) must be present]:
   - F.1. Deficits in executive tasks
   - F.2. Relative sparing of episodic memory
   - F.3. Relative sparing of visuospatial skills

Rascovsky et al, 2011

Essenziale:
Declino comportamentale/cognitivo progressivo

Sintomi comportamentali/cognitivi:

- Disinibizione
- Apatia
- Perdita di empatia
- Compulsioni/ritualismi
- Iperoralità e cambiamenti della dieta
- Deficit delle funzioni esecutive

Biomarkers:

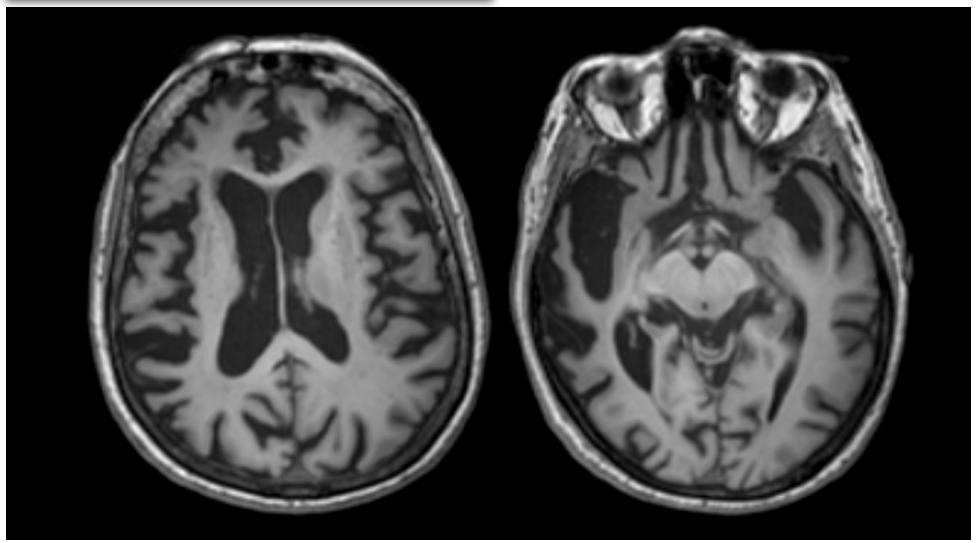
- RM
- FDG-PET

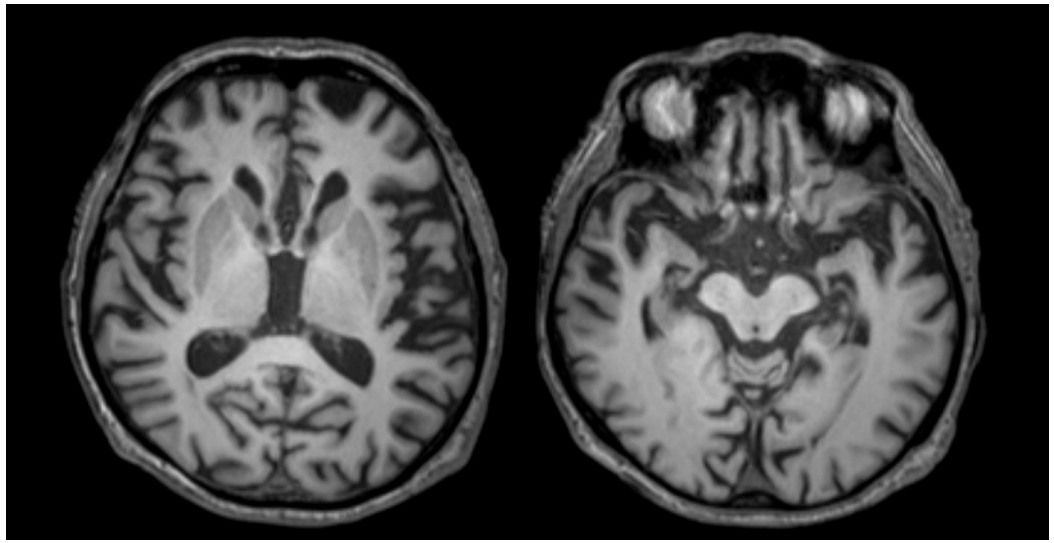
bvFTD patients received a **prior psychiatric diagnosis** significantly more often (**52.2%**) than patients with AD (23.1%), SemD (24.4%), or PNFA (11.8%), and were more likely to receive **diagnoses of bipolar affective disorder or schizophrenia** than patients with other NDs ($p<0.001$).

Woolley JD et al, 2011

RM

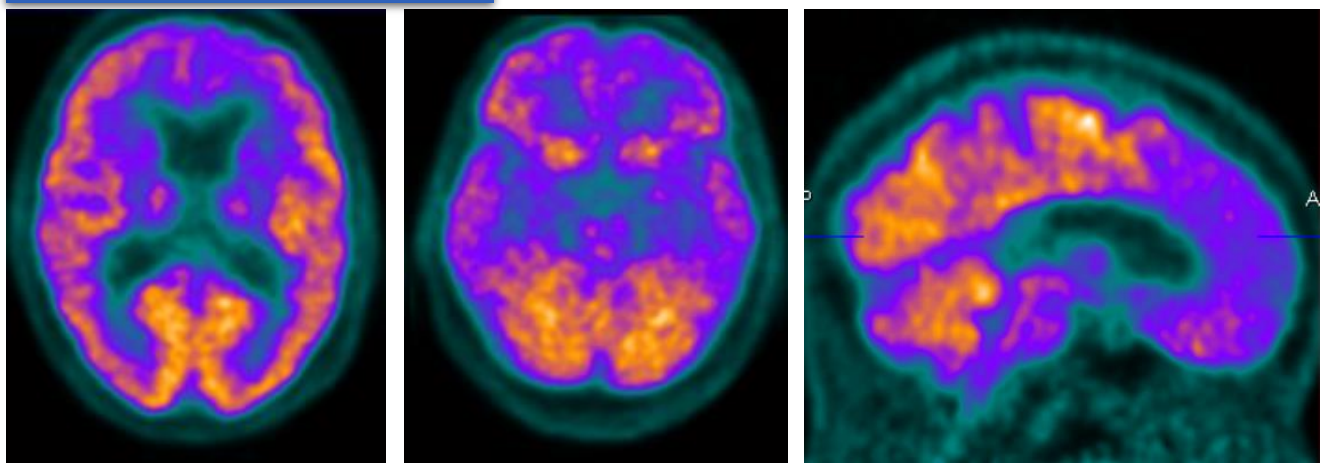
Atrofia





FDG-PET

Ipometabolismo



Corteccia frontale

- Orbitofrontale
- Dorsolaterale
- Mesiale

Corteccia temporale anteriore

Psychiatric Symptoms in Frontotemporal Dementia: Epidemiology, Phenotypes, and Differential Diagnosis

Daniela Galimberti, Bernardo Dell'Osso, A. Carlo Altamura, and Elio Scarpini

Table 1. Possible Critical Areas in Differential Diagnosis between FTD and Specific Psychiatric Disorders Warranting Further Neurologic/Psychiatric Investigation

Late-onset and/or long-lasting depressive disorder/BD with progressive (not episodic) course, prominent cognitive impairment, and poor antidepressant/mood stabilizer response
Late-onset psychotic spectrum disorder (e.g., delusional disorder, brief psychotic disorder, paraphrenia) with prominent cognitive impairment and poor antipsychotic response
Late-onset obsessive/compulsive and impulsive behaviors with cognitive alterations and poor treatment response
Early-onset sporadic FTD with prominent behavioral alterations mimicking symptoms characteristic of other psychiatric disorders
Cases of real cross-sectional and longitudinal comorbidity (e.g., patient with previous BD who subsequently develops FTD)

BD, bipolar disorder; FTD, frontotemporal dementia.

Table 2. Differential Diagnosis between FTD and Depressive Disorder/BD

Likely Psychiatric Disorder (i.e., Depressive/BD)	Likely Frontotemporal Dementia (FTD)
– Early acute/subacute onset (i.e., 15-30 years)	
– Positive family history for mood disorders	
– History of multiple mood episodes	– Later, insidious onset (> 40-45 years)
– Presence of comorbidity (anxiety and substance use disorders)	– Positive family history for dementia (for familial forms)
– Suicidal ideation and previous suicide attempts	– Progressive and continuous course
– Inter-episodic complete or partial recovery	– Enduring and progressive cognitive impairment
– Cognitive impairment mostly limited to affective episodes	– Genetics and neuroimaging evidence
– Episodic wake-sleep cycle alterations	– Poor response to psychiatric treatments

BD, bipolar disorder; FTD, frontotemporal dementia.

Galimberti D et al, 2015

Primary Progressive Aphasia

- Mesulam M-M. Slowly progressive aphasia without generalized dementia. Ann Neurol. 1982;11:592–598.

Inclusion: criteria 1–3 must be answered positively
1. Most prominent clinical feature is difficulty with language
2. These deficits are the principal cause of impaired daily living activities
3. Aphasia should be the most prominent deficit at symptom onset and for the initial phases of the disease

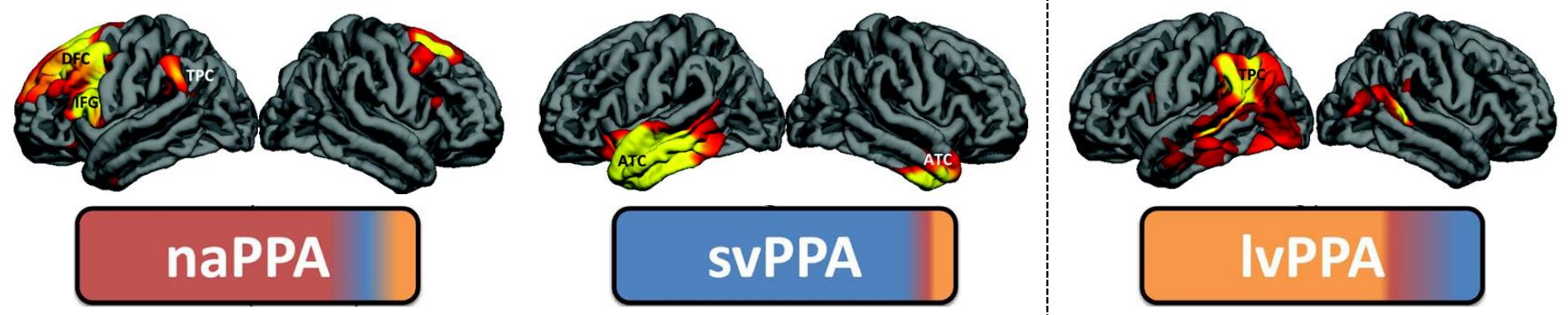
Exclusion: criteria 1–4 must be answered negatively for a PPA diagnosis
1. Pattern of deficits is better accounted for by other nondegenerative nervous system or medical disorders
2. Cognitive disturbance is better accounted for by a psychiatric diagnosis
3. Prominent initial episodic memory, visual memory, and visuoperceptual impairments
4. Prominent, initial behavioral disturbance

Classification of primary progressive aphasia and its variants

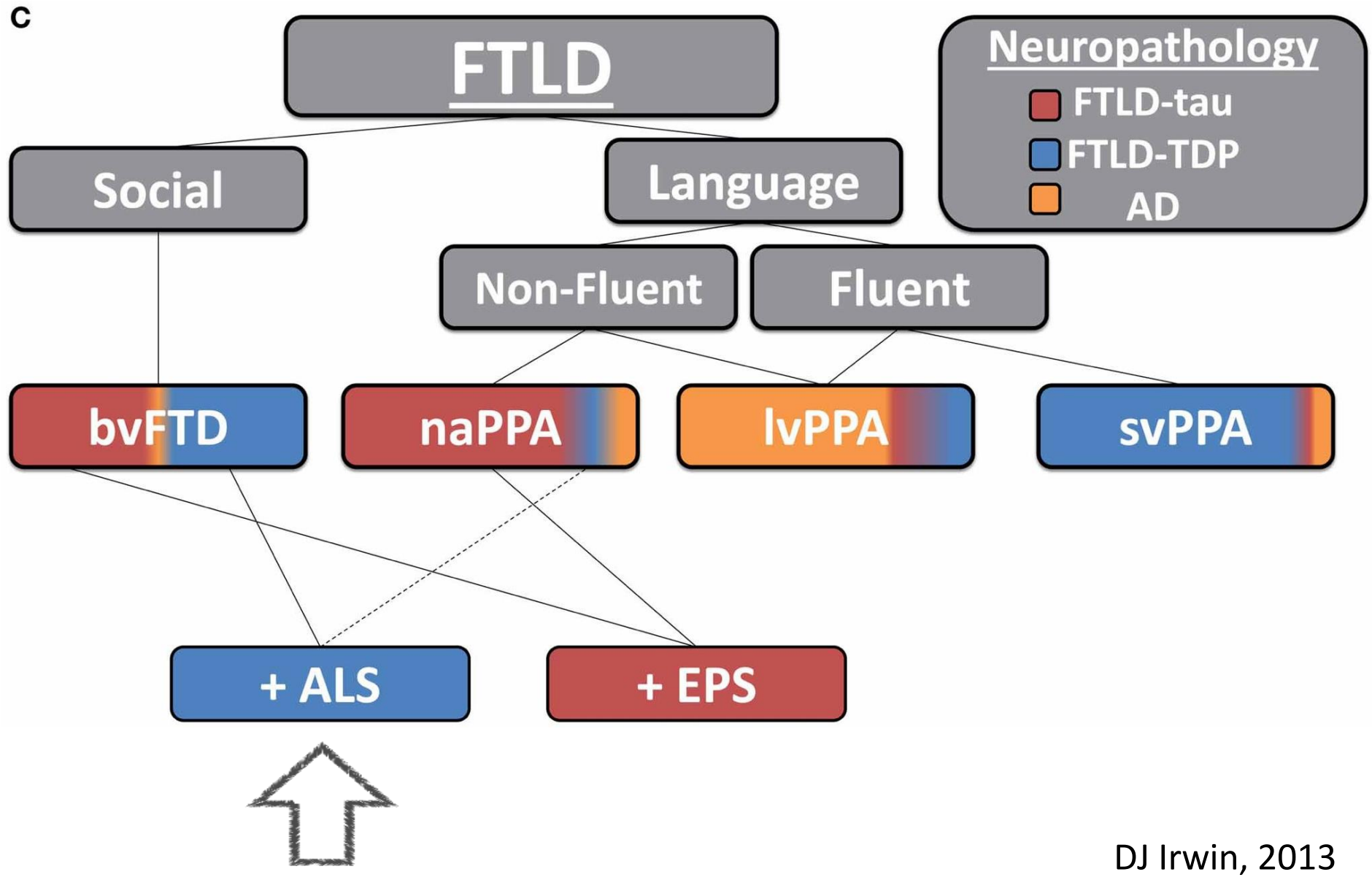
I. Clinical diagnosis of nonfluent/agrammatic variant PPA
At least one of the following core features must be present:
1. Agrammatism in language production
2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech)
At least 2 of 3 of the following other features must be present:
1. Impaired comprehension of syntactically complex sentences
2. Spared single-word comprehension
3. Spared object knowledge

I. Clinical diagnosis of semantic variant PPA
Both of the following core features must be present:
1. Impaired confrontation naming
2. Impaired single-word comprehension
At least 3 of the following other diagnostic features must be present:
1. Impaired object knowledge, particularly for low-frequency or low-familiarity items
2. Surface dyslexia or dysgraphia
3. Spared repetition
4. Spared speech production (grammar and motor speech)

I. Clinical diagnosis of logopenic variant PPA
Both of the following core features must be present:
1. Impaired single-word retrieval in spontaneous speech and naming
2. Impaired repetition of sentences and phrases
At least 3 of the following other features must be present:
1. Speech (phonologic) errors in spontaneous speech and naming
2. Spared single-word comprehension and object knowledge
3. Spared motor speech
4. Absence of frank agrammatism

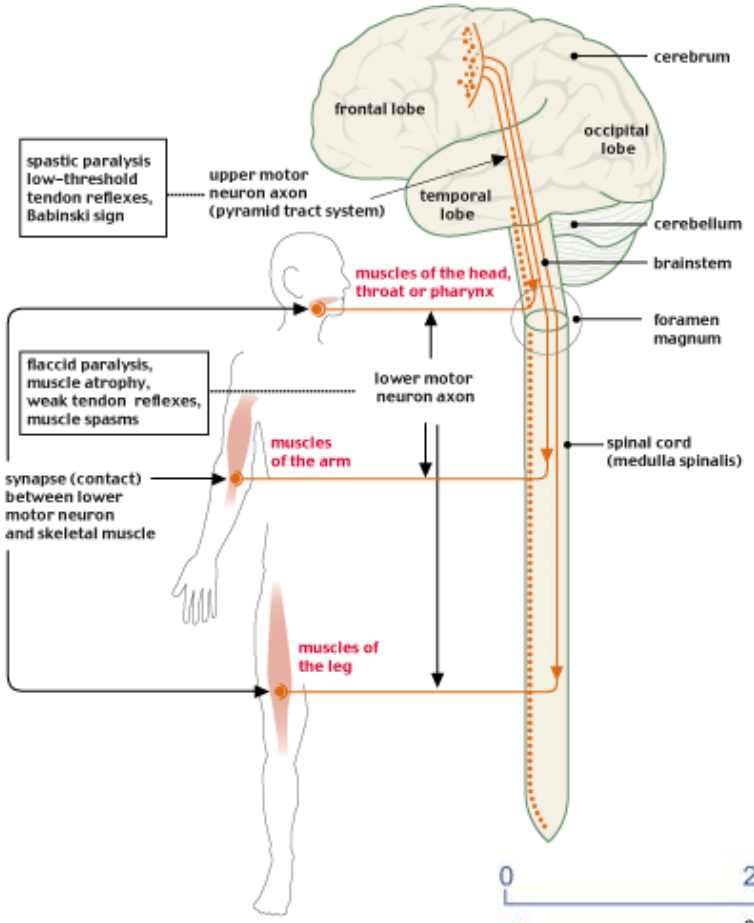


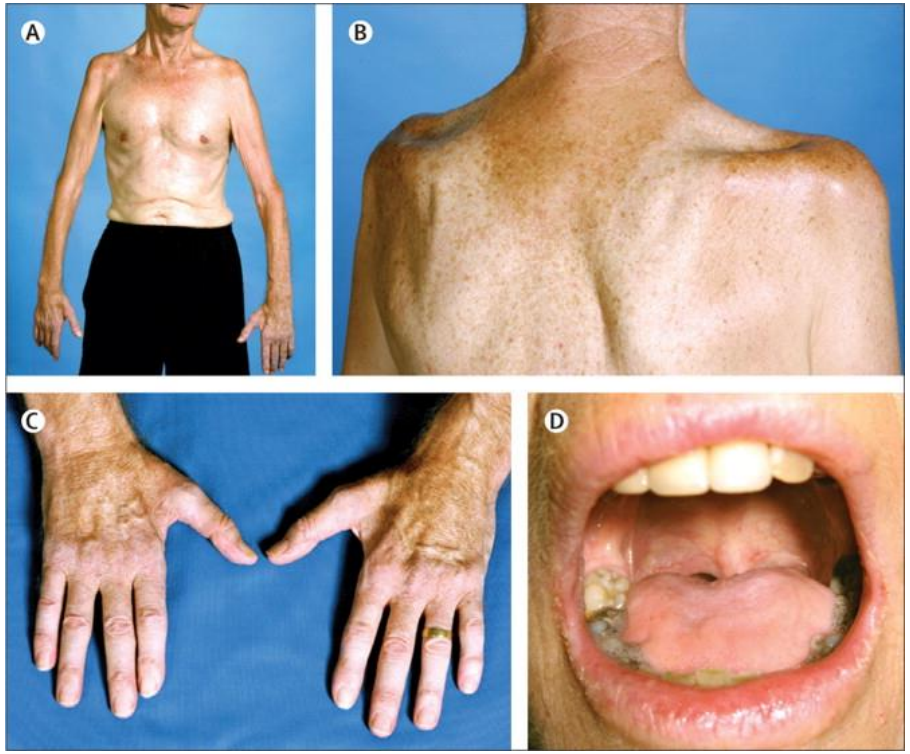
Gorno-Tempini ML, 2011

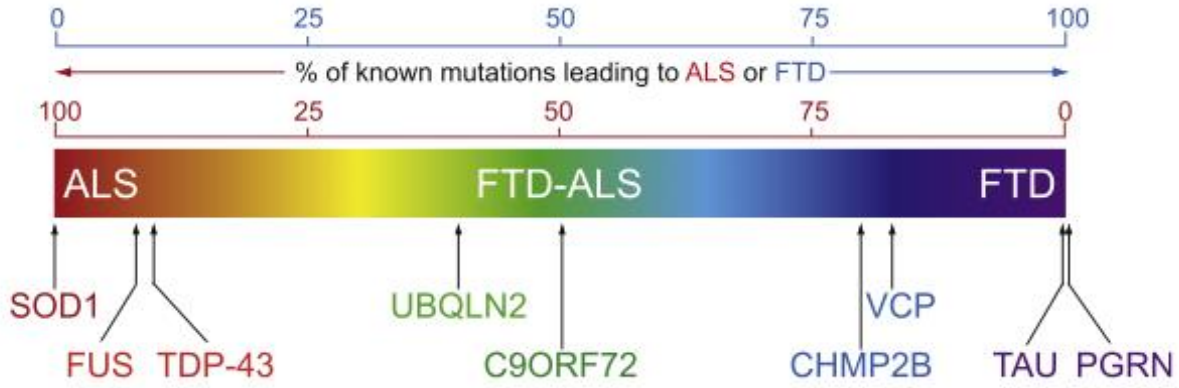


DJ Irwin, 2013

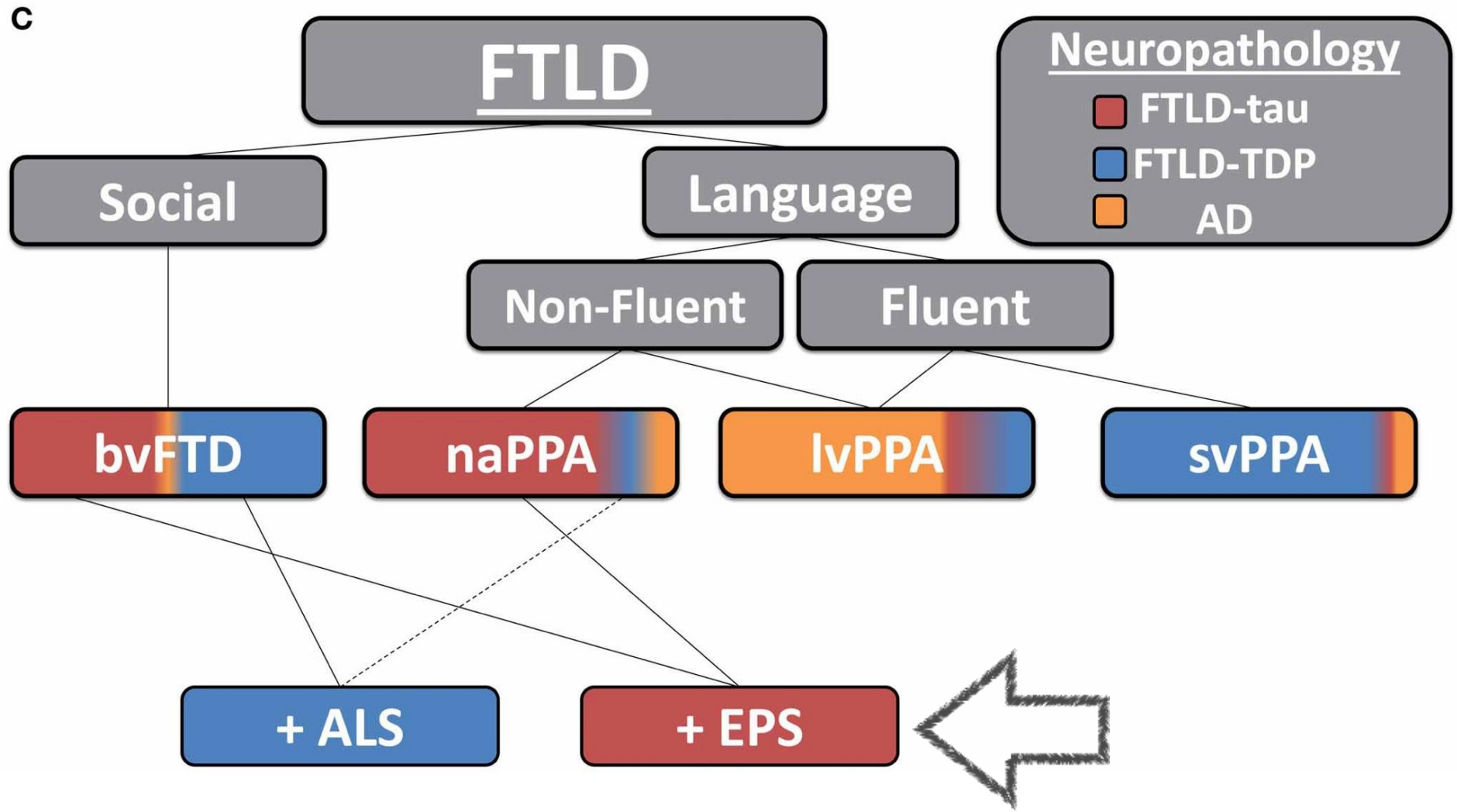
Amyotrophic Lateral Sclerosis



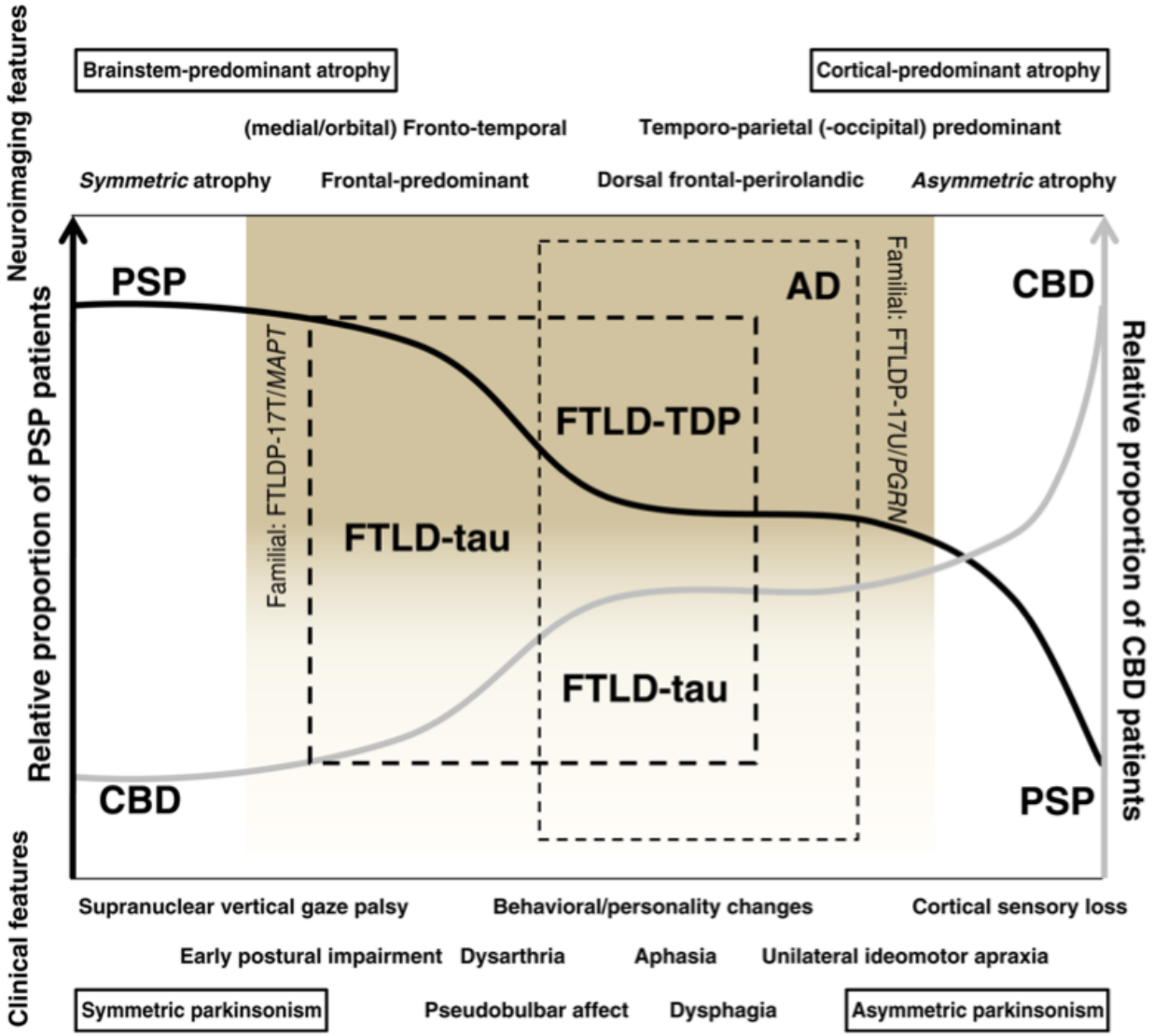




Ling S, 2013



DJ Irwin, 2013



AJ Espay, I Litvan, 2011

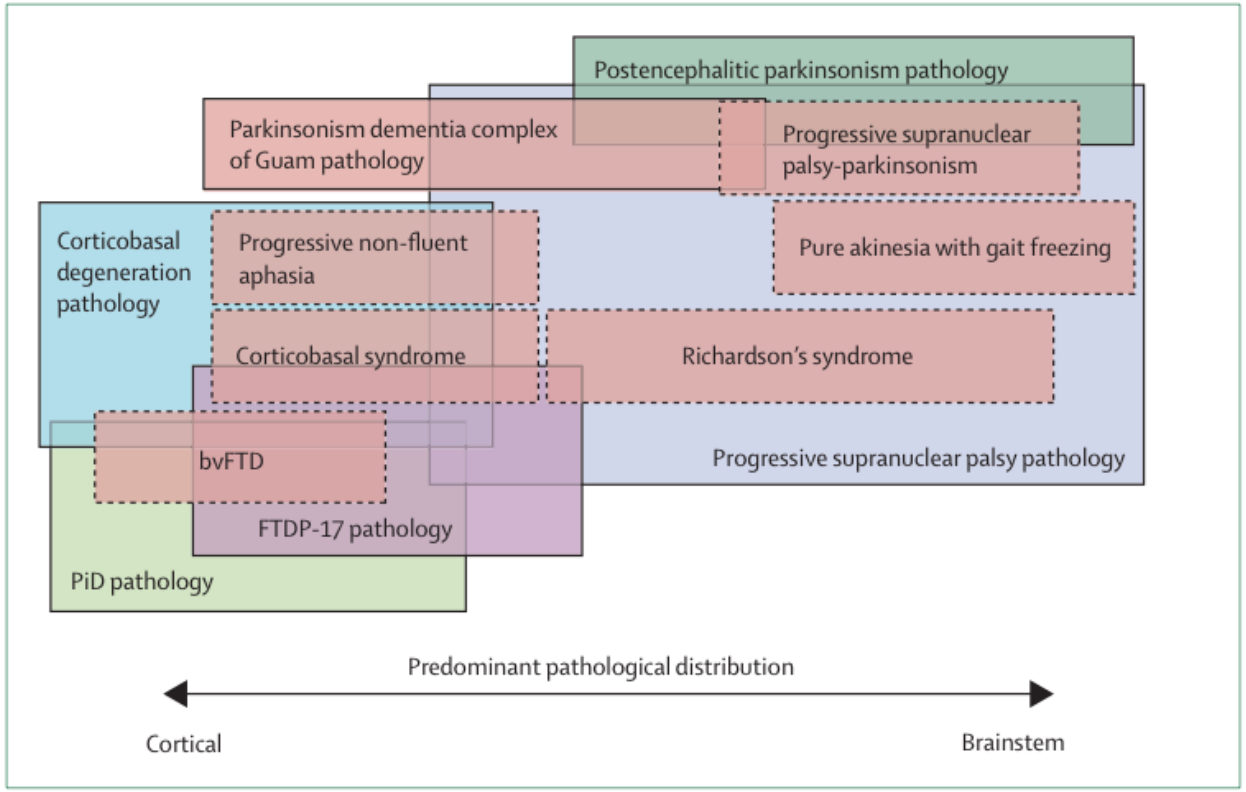
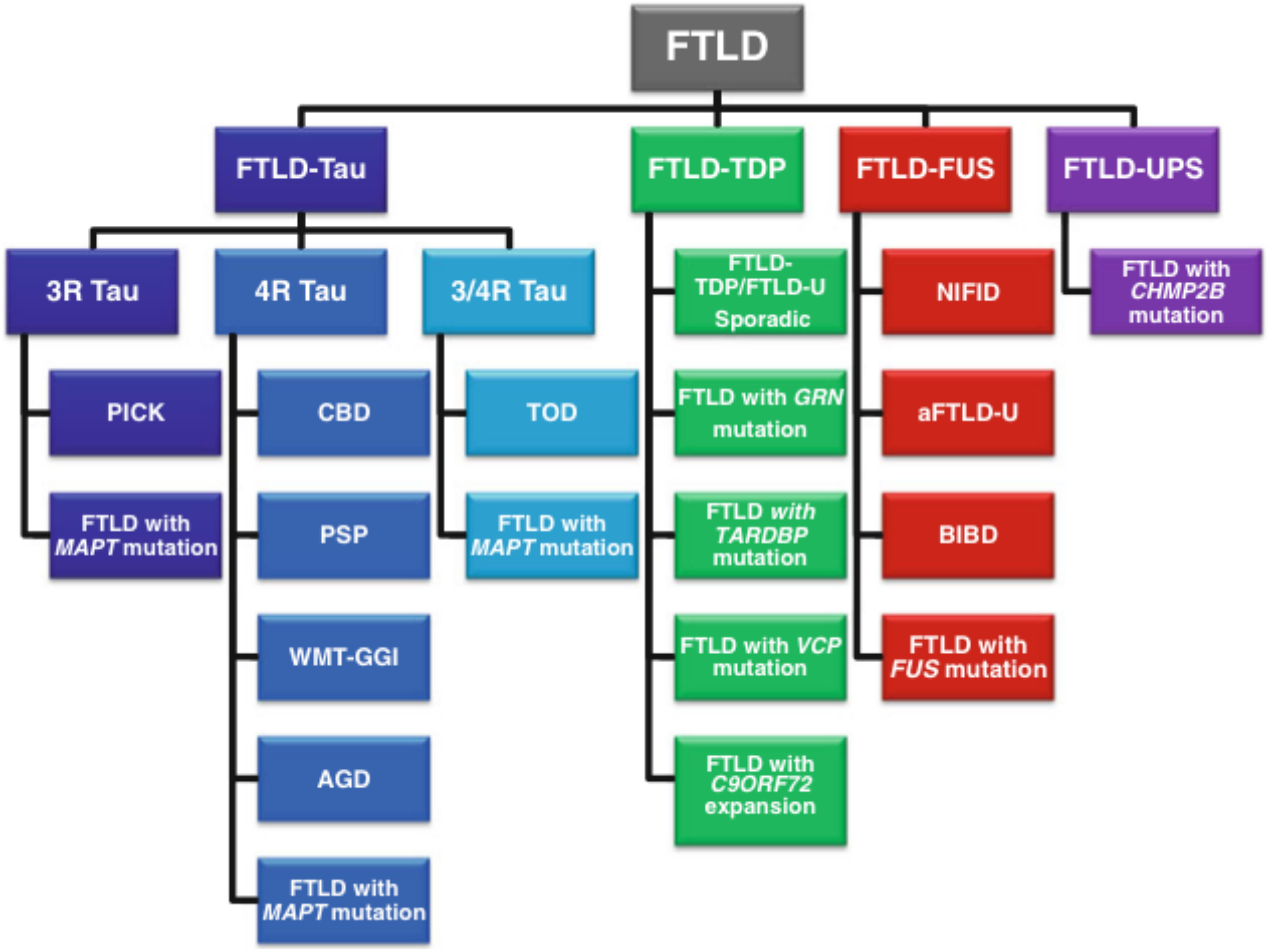


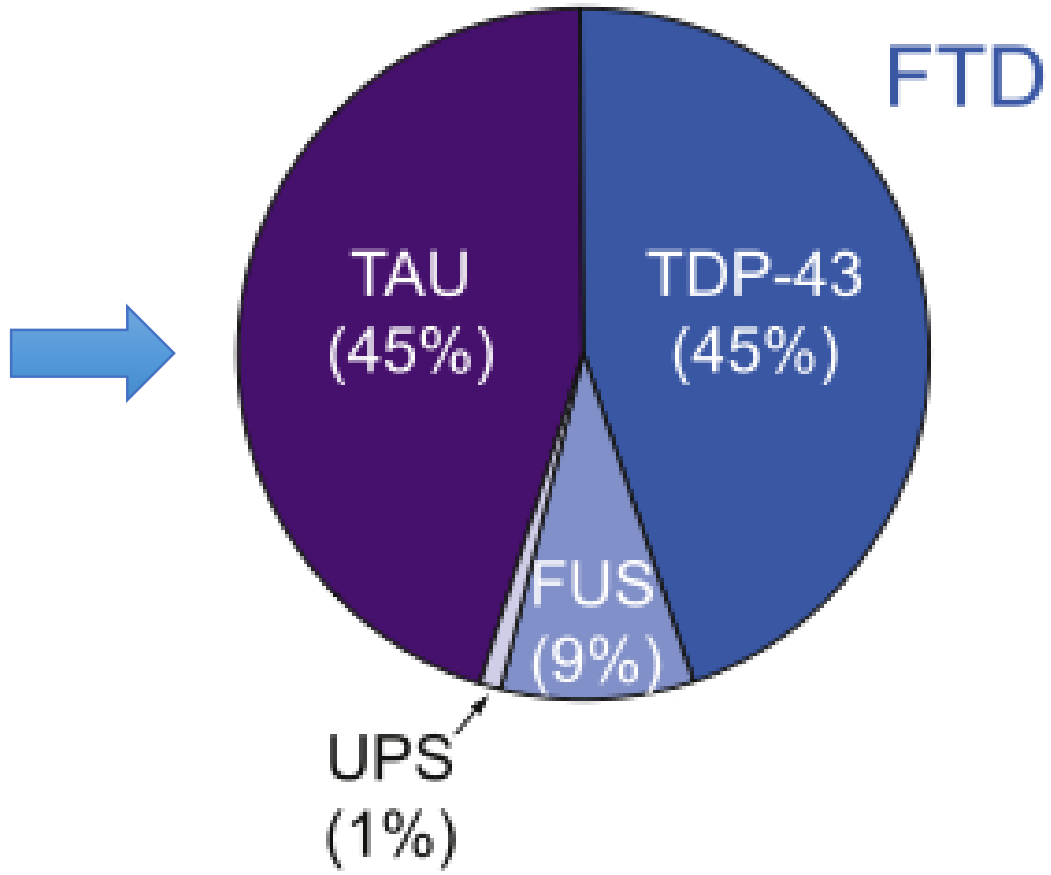
***Figure 1*: Distribution of tau pathology in clinical and pathological nosological syndromes of progressive supranuclear palsy**

Dashed boxes=clinical syndromes. Solid boxes=pathologically defined diseases. PiD=Pick's disease. FTDP-17=frontotemporal dementia with parkinsonism-17. bvFTD=behavioural variant of frontotemporal dementia.[3,6,45,60,65]

DR Williams, 2009

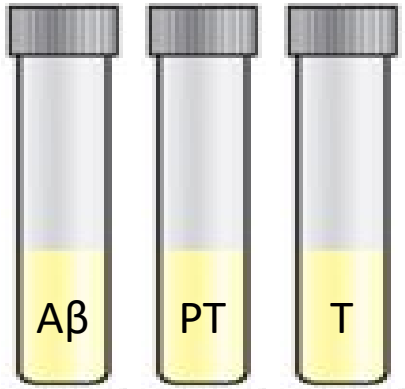
FTLD pathology





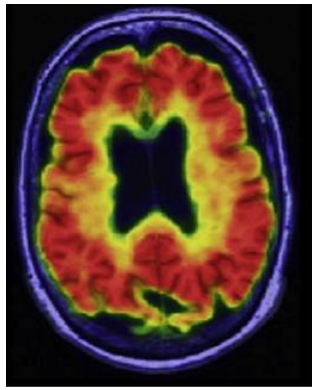
«Dottore, cosa facciamo?»

WHAT?

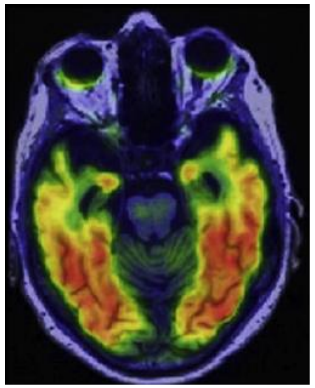


CSF biomarkers

Genetic test



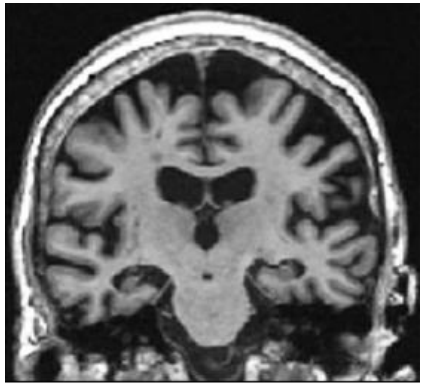
Amyloid PET



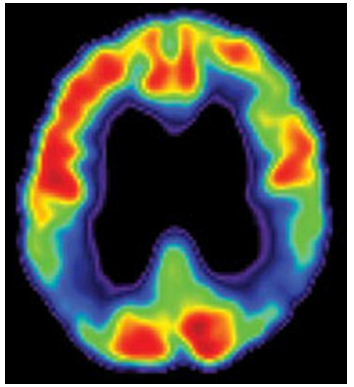
Tau PET

WHERE?
WHEN?

Neuropsychology



Magnetic resonance



FDG PET

Revising the definition of Alzheimer's disease: a new lexicon

Bruno Dubois, Howard H Feldman, Claudia Jacova, Jeffrey L Cummings, Steven T DeKosky, Pascale Barberger-Gateau, André Delacourte, Giovanni Frisoni, Nick C Fox, Douglas Galasko, Serge Gauthier, Harald Hampel, Gregory A Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Marie Sarazin, Leonardo C de Souza, Yaakov Stern, Pieter J Visser, Philip Scheltens

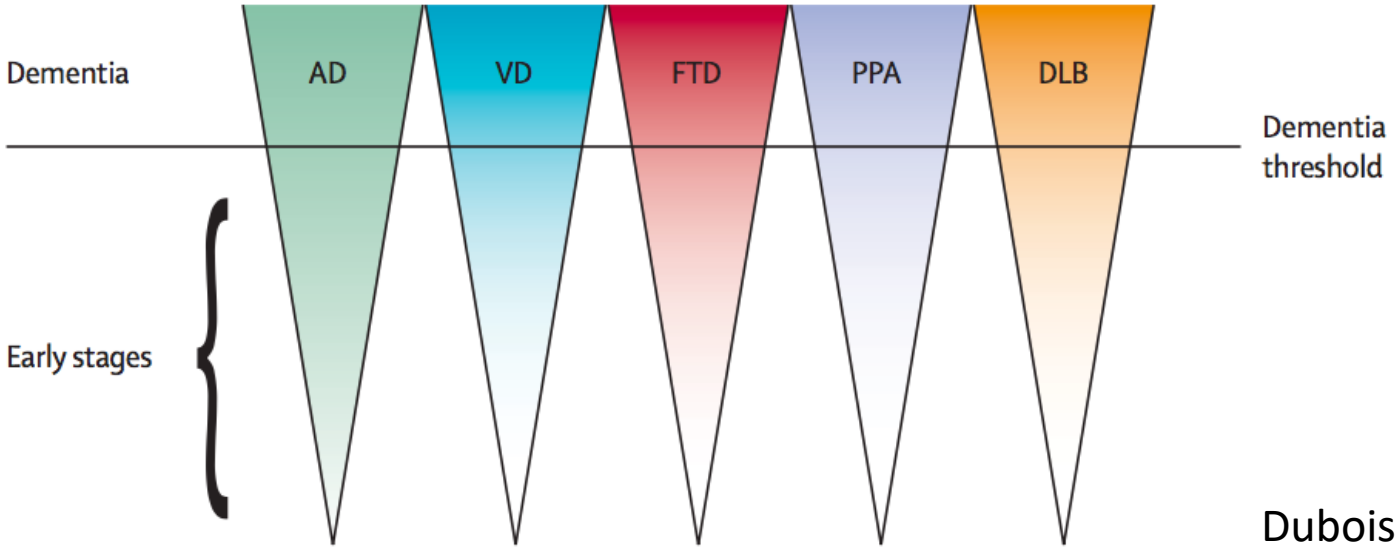
IWG
2010

Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria

Bruno Dubois, Howard H Feldman*, Claudia Jacova, Steven T DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J Visser, Philip Scheltens*

IWG-1
2007

Time line AD criteria



Dubois B et al, 2007

	Pathophysiological markers	Topographical markers
Cerebrospinal fluid		
Amyloid β_{42}	Yes	No
Total tau, phospho-tau	Yes	No
PET		
Amyloid tracer uptake	Yes	No
Fluorodeoxyglucose	No	Yes
Structural MRI		
Medial temporal atrophy	No	Yes

AD=Alzheimer's disease.

Table 1: **Categorisation of the current, most-validated AD biomarkers**

Dubois B et al, 2010

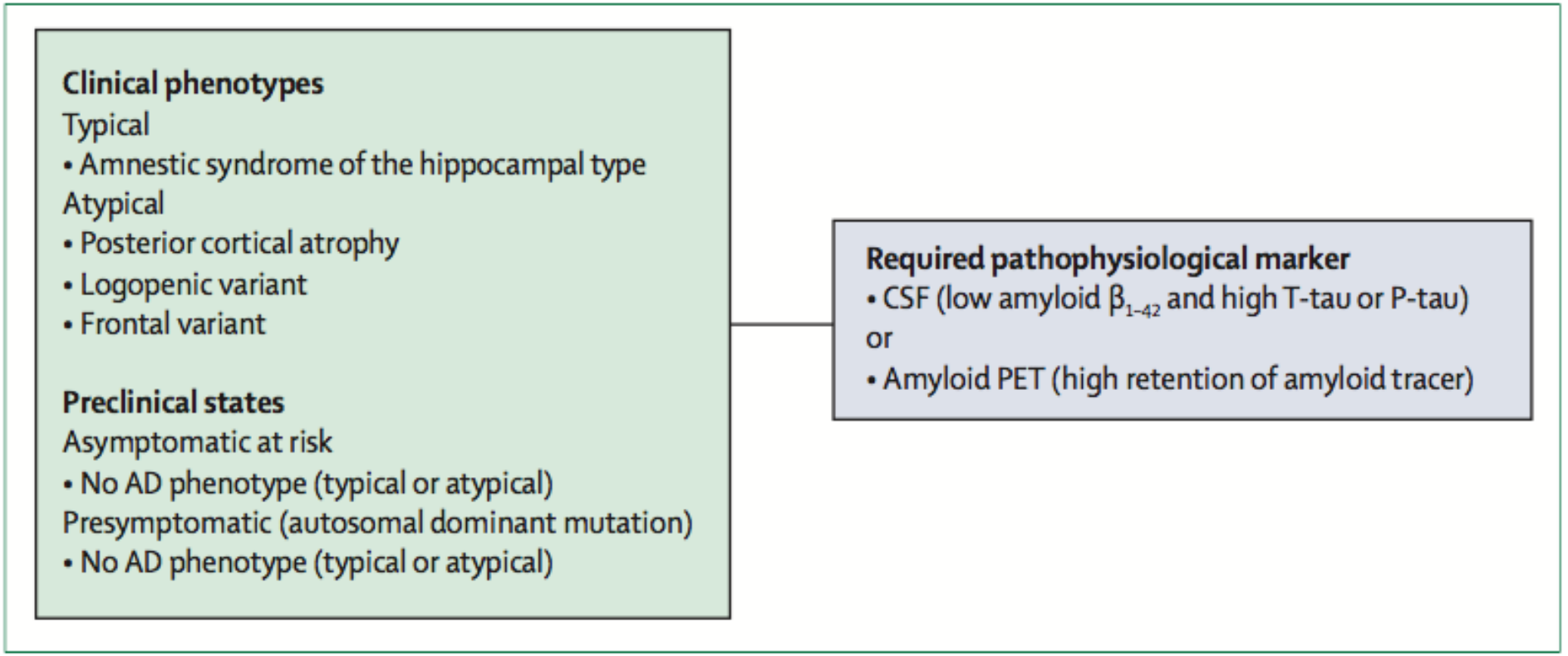
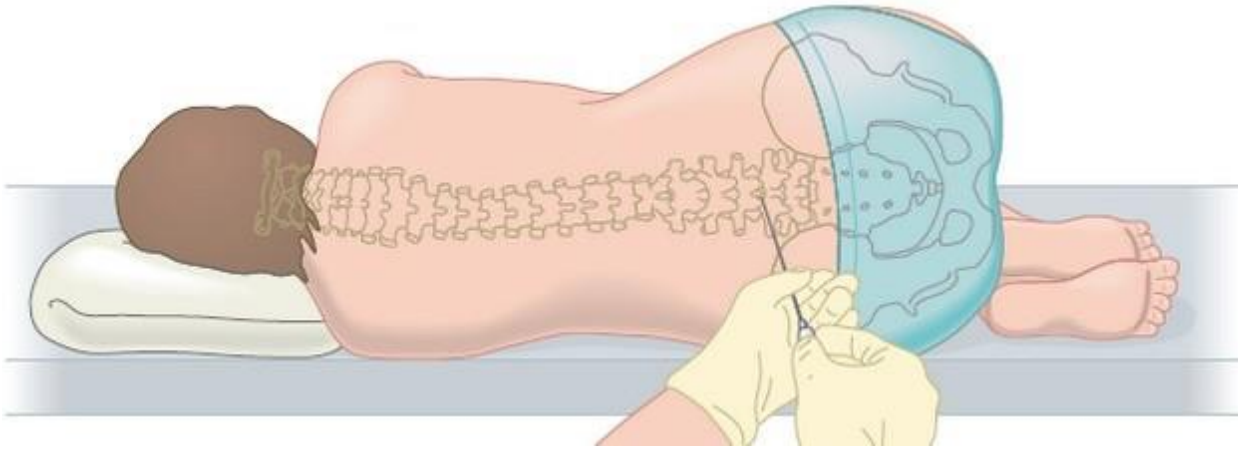


***Figure*: AD is defined as a clinicobiological entity**

A simplified algorithm is proposed: in any condition and at any stage of the disease, the diagnosis of AD relies on the presence of a pathophysiological marker. AD=Alzheimer's disease.

Dubois B, 2014

Cerebrospinal fluid



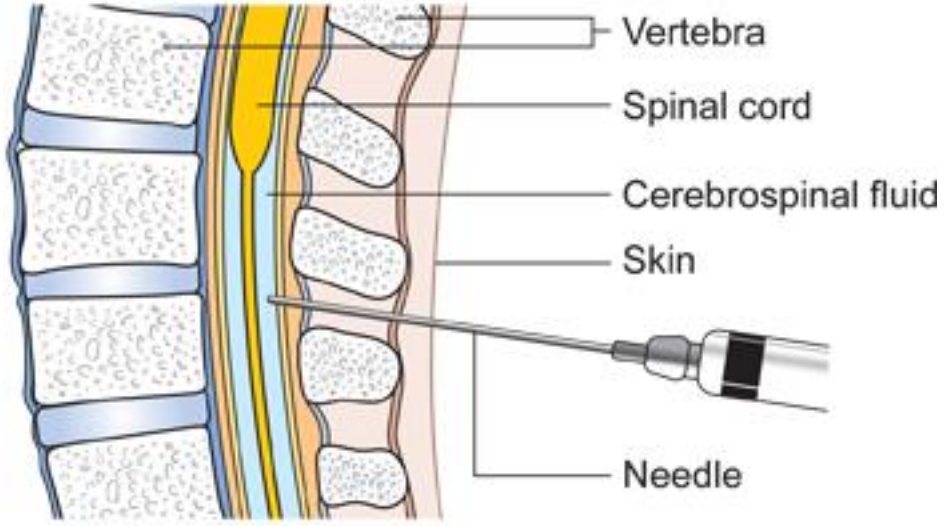


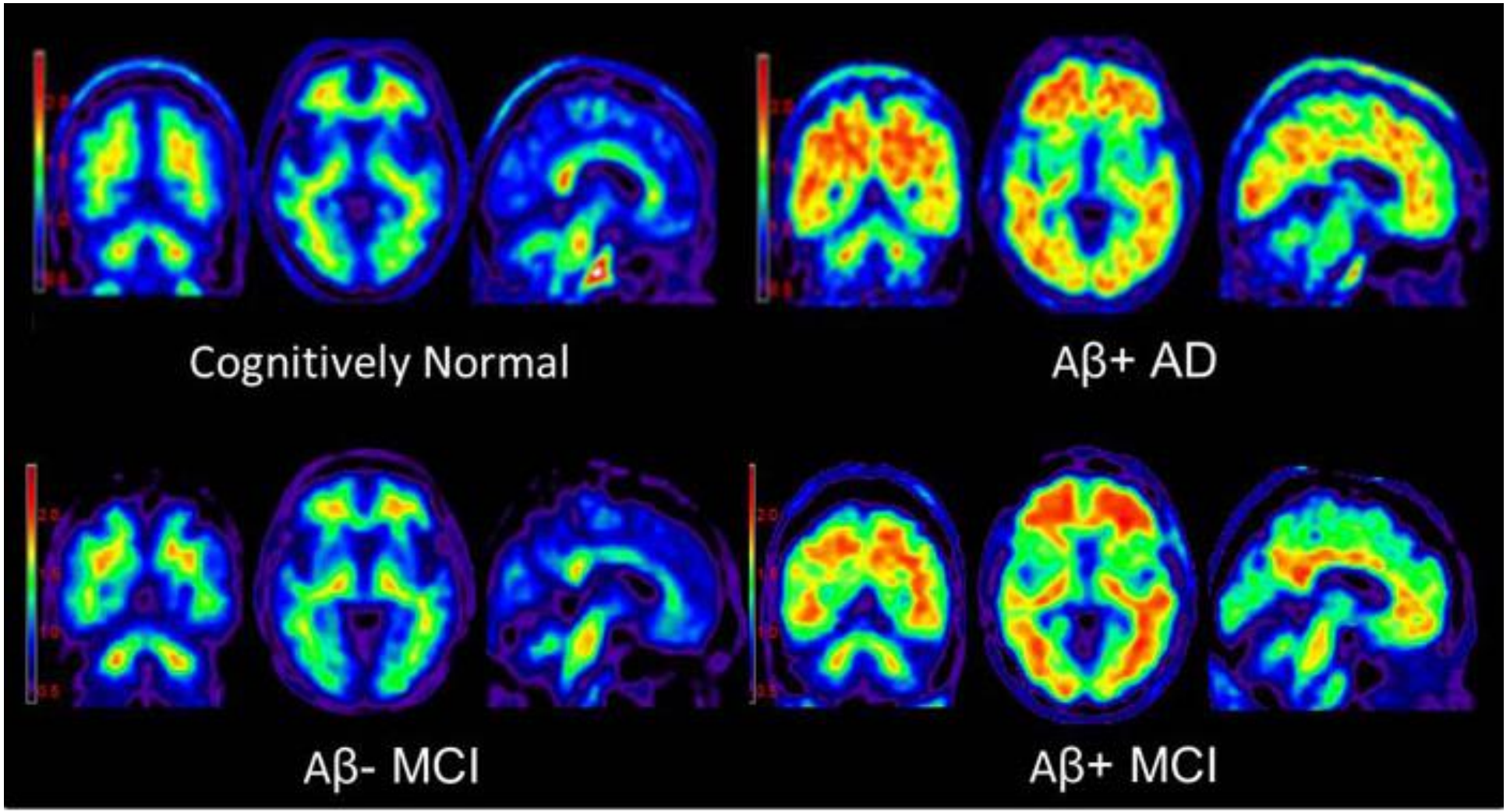
Diagram showing how you have a lumbar puncture

Beta amiloide ↓

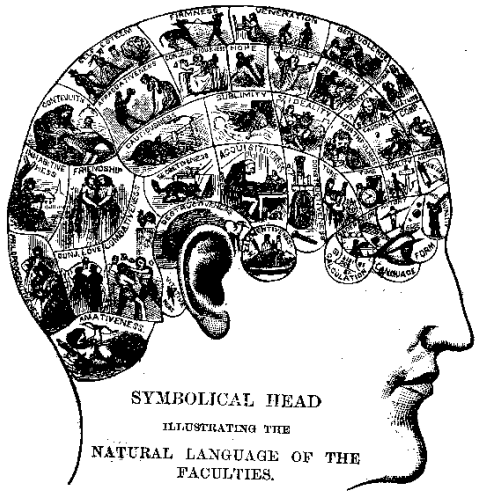
Tau ↑

P-Tau ↑

Amyloid PET

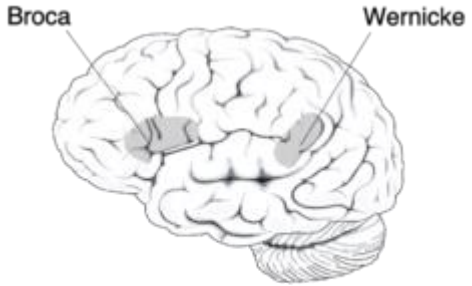


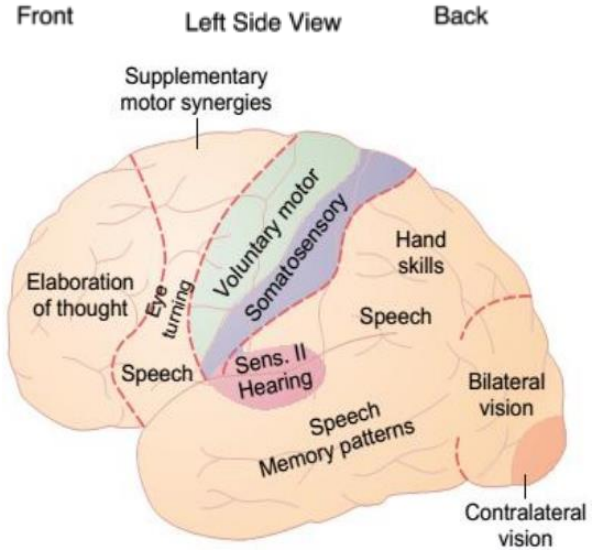
Cesare Lombroso
(1835-1909)



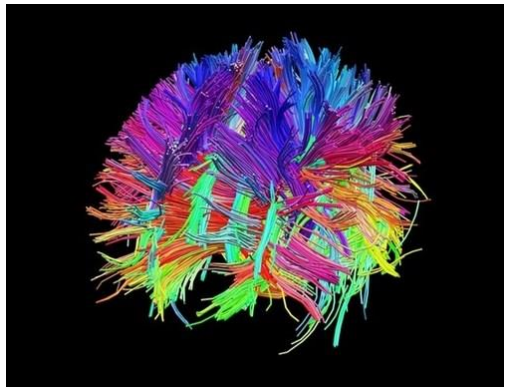
Paul Broca
(1824-1880)

Carl Wernicke
(1848-1905)



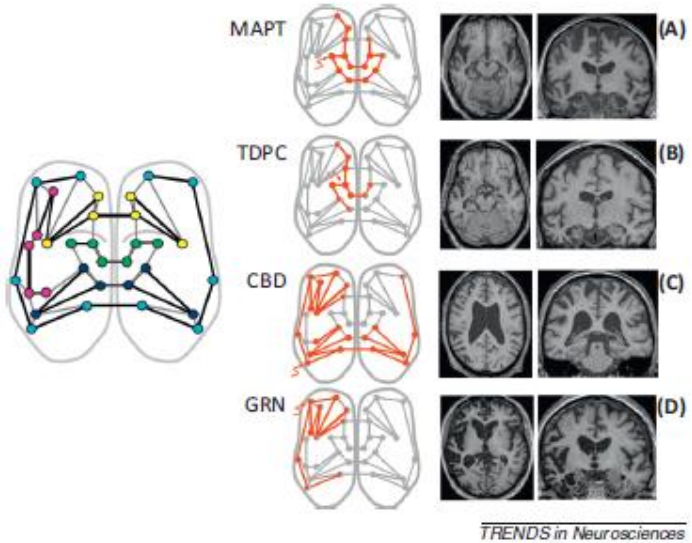


Brain connectome

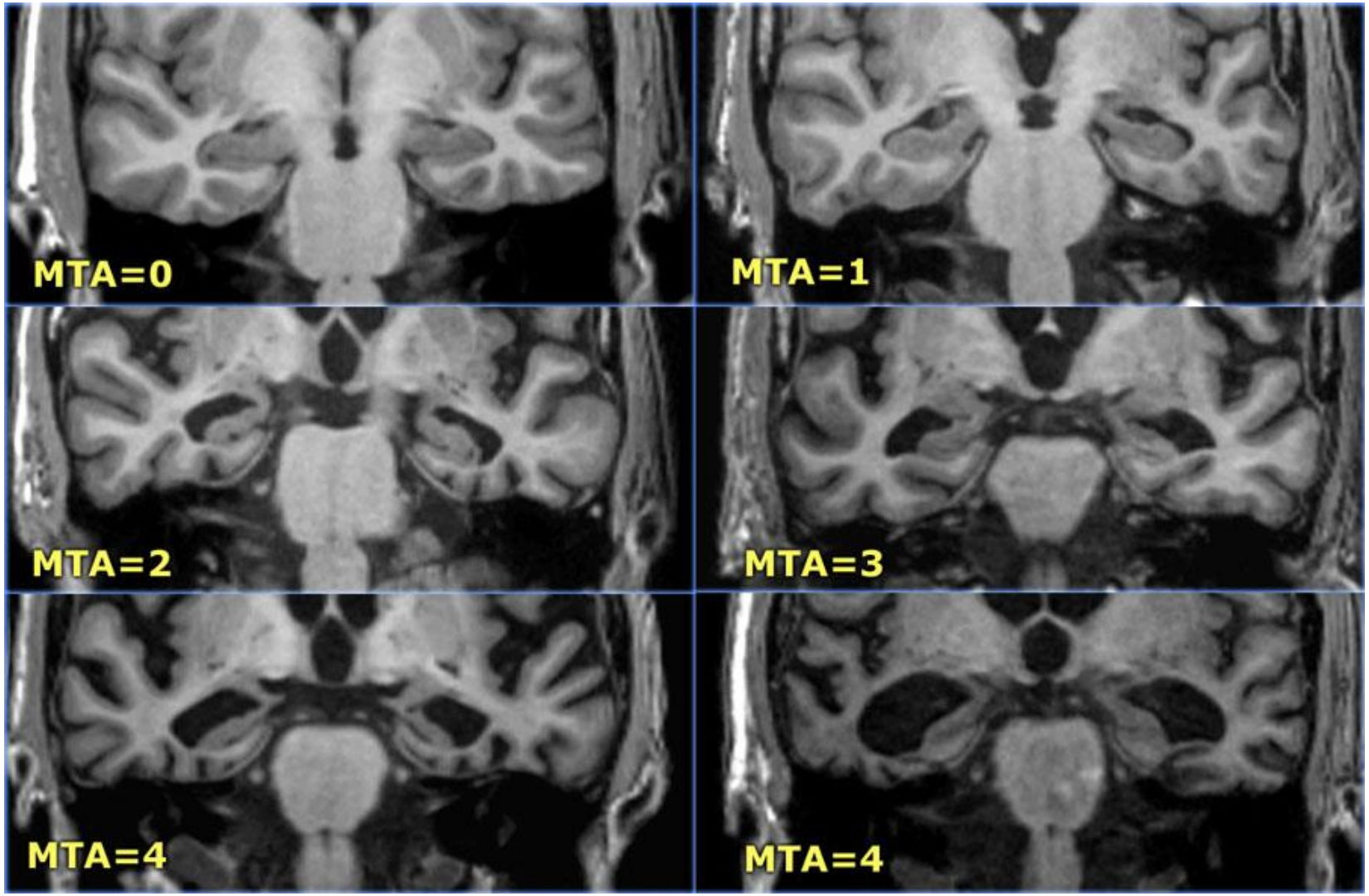


Molecular nexopathies: a new paradigm of neurodegenerative disease

Jason D. Warren[1], Jonathan D. Rohrer[1], Jonathan M. Schott[1], Nick C. Fox[1], John Hardy[2], and Martin N. Rossor[1]



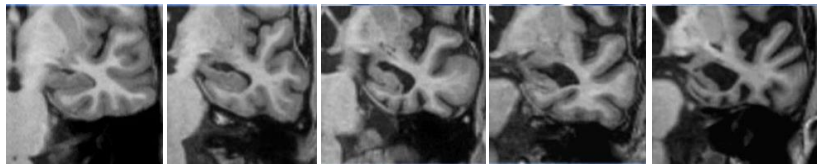
Structural MRI



Scale visive quantitative

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

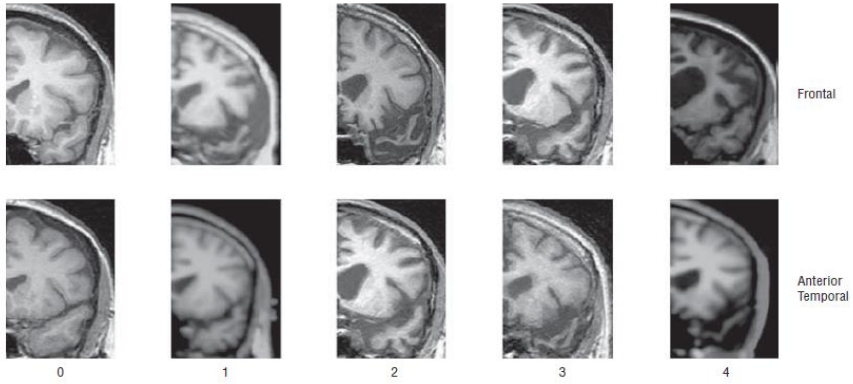
Ph Scheltens, D Leys, F Barkhof, D Huglo, H C Weinstein, P Vermersch, M Kuiper, M Steinling, E Ch Wolters, J Valk



Progression in Frontotemporal Dementia

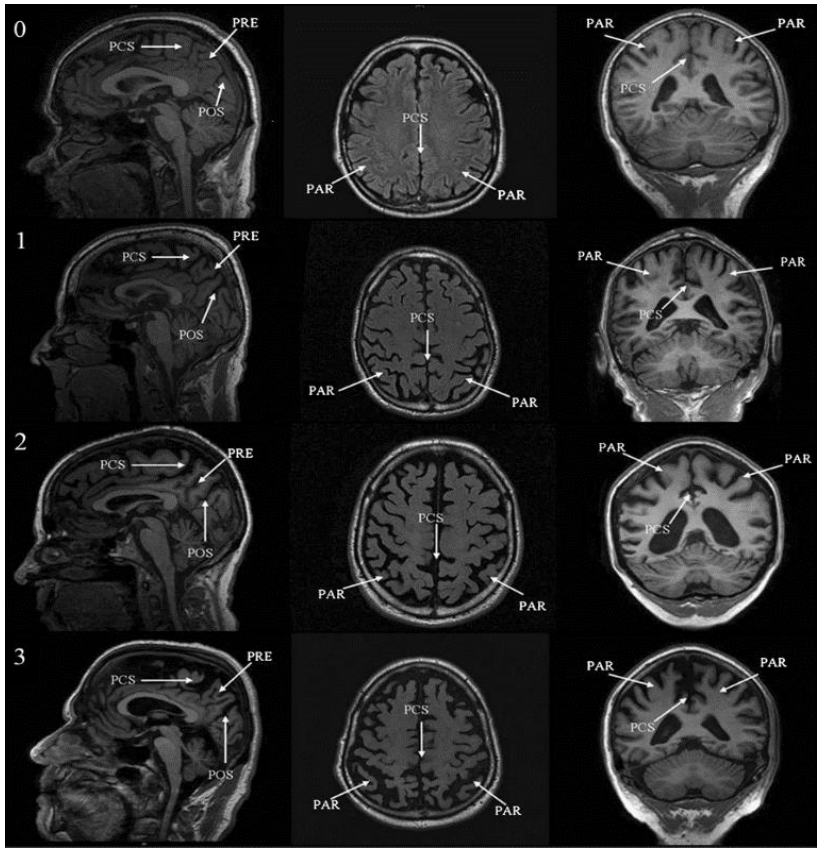
Identifying a Benign Behavioral Variant by Magnetic Resonance Imaging

Rhys R. Davies, MRCP; Christopher M. Kipps, FRACP; Joanna Mitchell, BSc; Jillian J. Kril, PhD; Glenda M. Halliday, PhD; John R. Hodges, FMedSci



Visual assessment of posterior atrophy development of a MRI rating scale

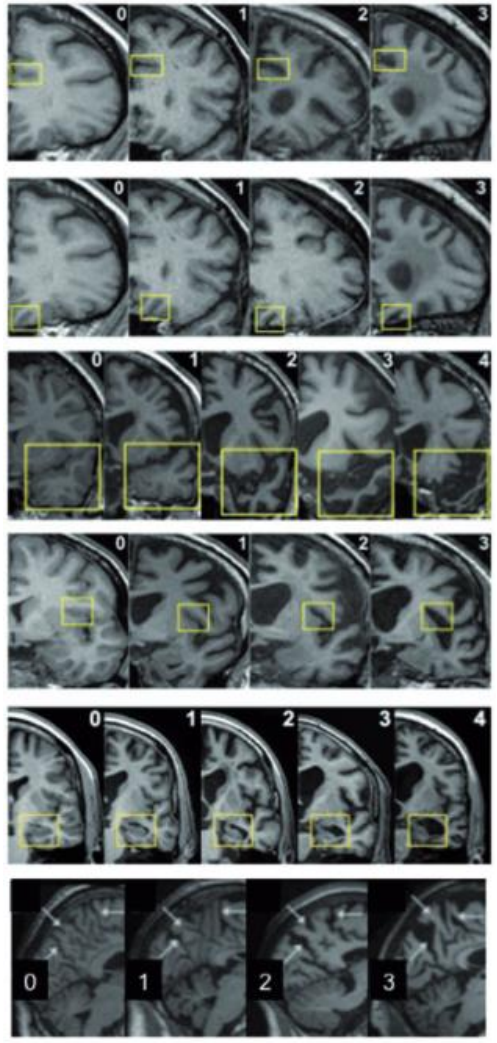
Esther L. G. E. Koedam · Manja Lehmann · Wiesje M. van der Flier · Philip Scheltens · Yolande A. L. Pijnenburg · Nick Fox · Frederik Barkhof · Mike P. Wattjes



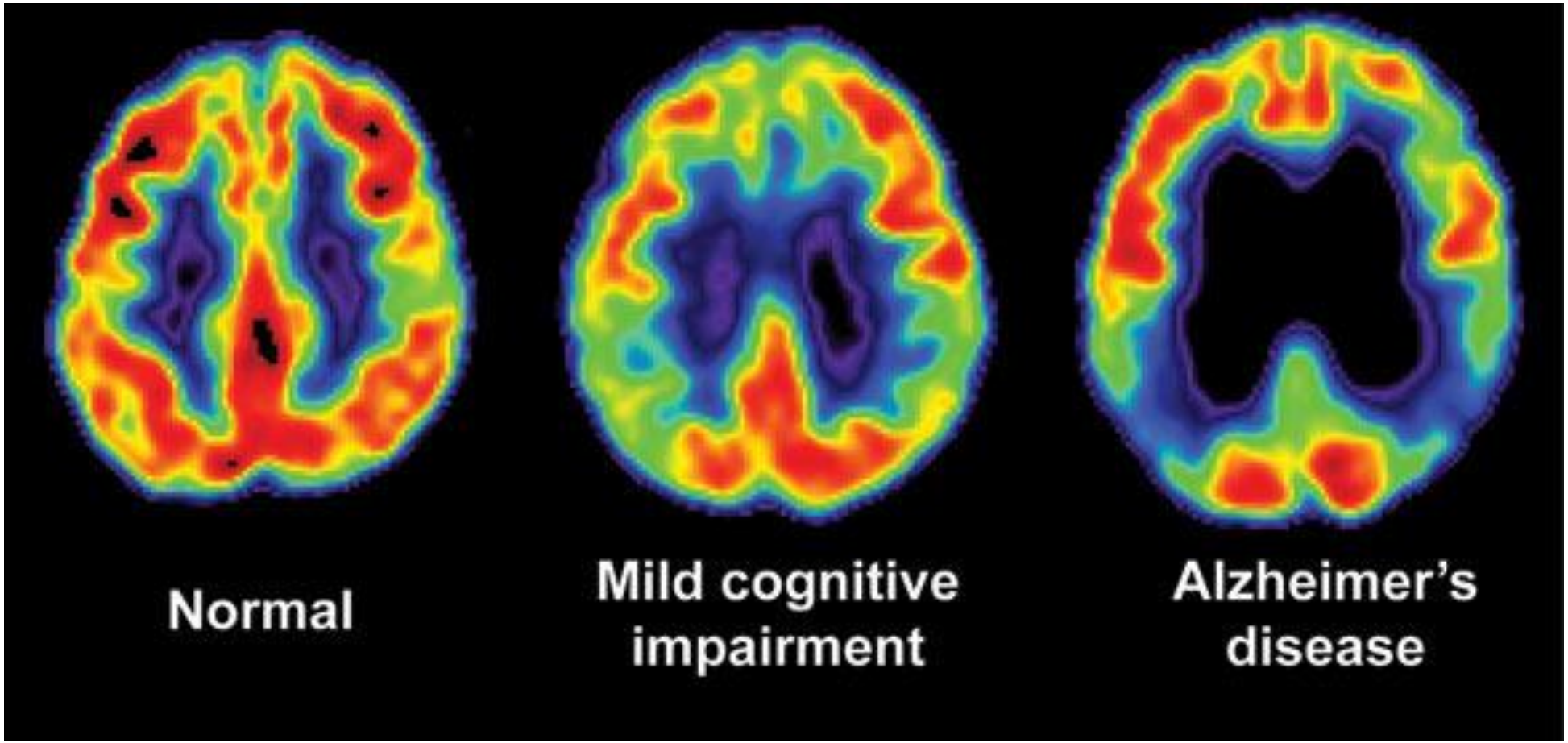
BRAIN
A JOURNAL OF NEUROLOGY

MRI visual rating scales in the diagnosis of dementia: evaluation in 184 post-mortem confirmed cases

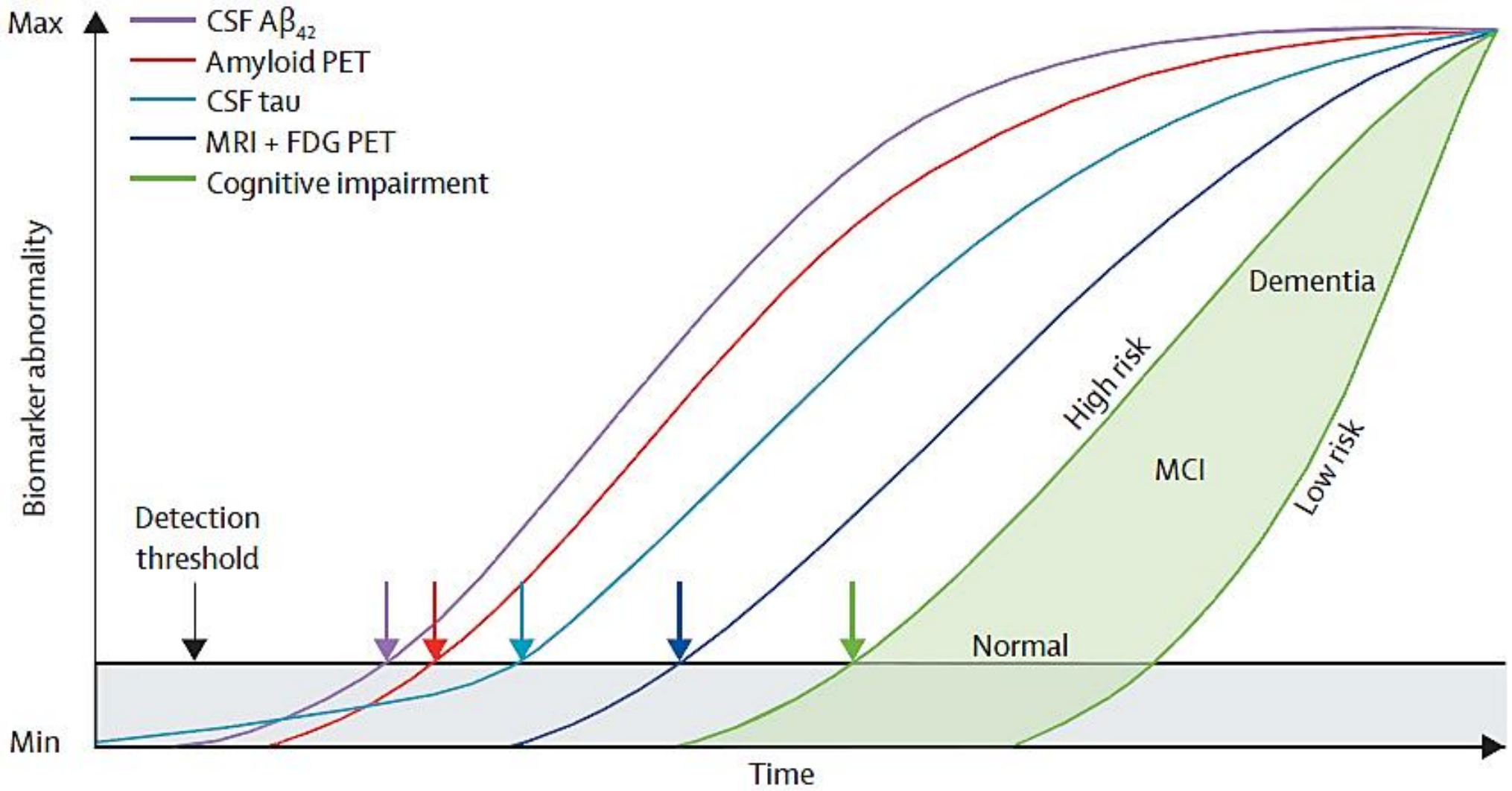
Lorna Harper,[1] Giorgio G. Fumagalli,[2] Frederik Barkhof,[3] Philip Scheltens,[4] John T. O'Brien,[5] Femke Bouwman,[4] Emma J. Burton,[6] Jonathan D. Rohrer,[1] Nick C. Fox,[1] Gerard R. Ridgway[7,8,*] and Jonathan M. Schott[1,*]



FDG PET



Diagnosi precoce



«Ma è trasmissibile? È genetica?»

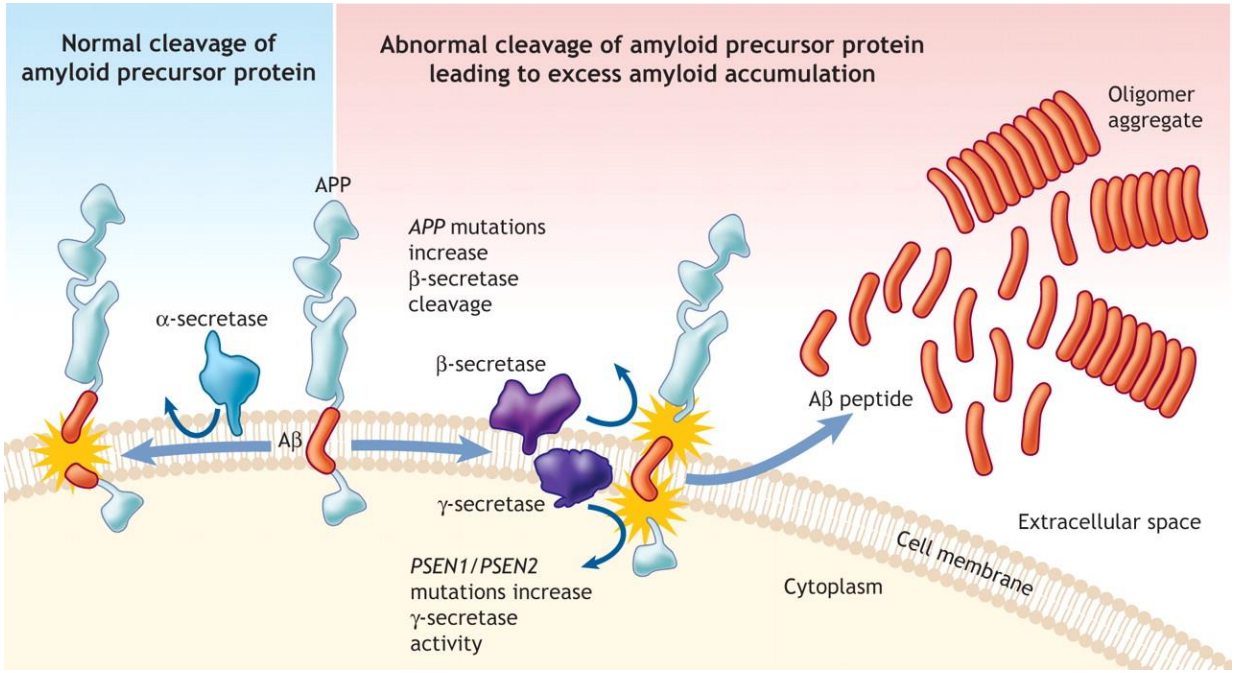
Genetica e Alzheimer

Geni mendeliani

- APP
- PSEN1
- PSEN2

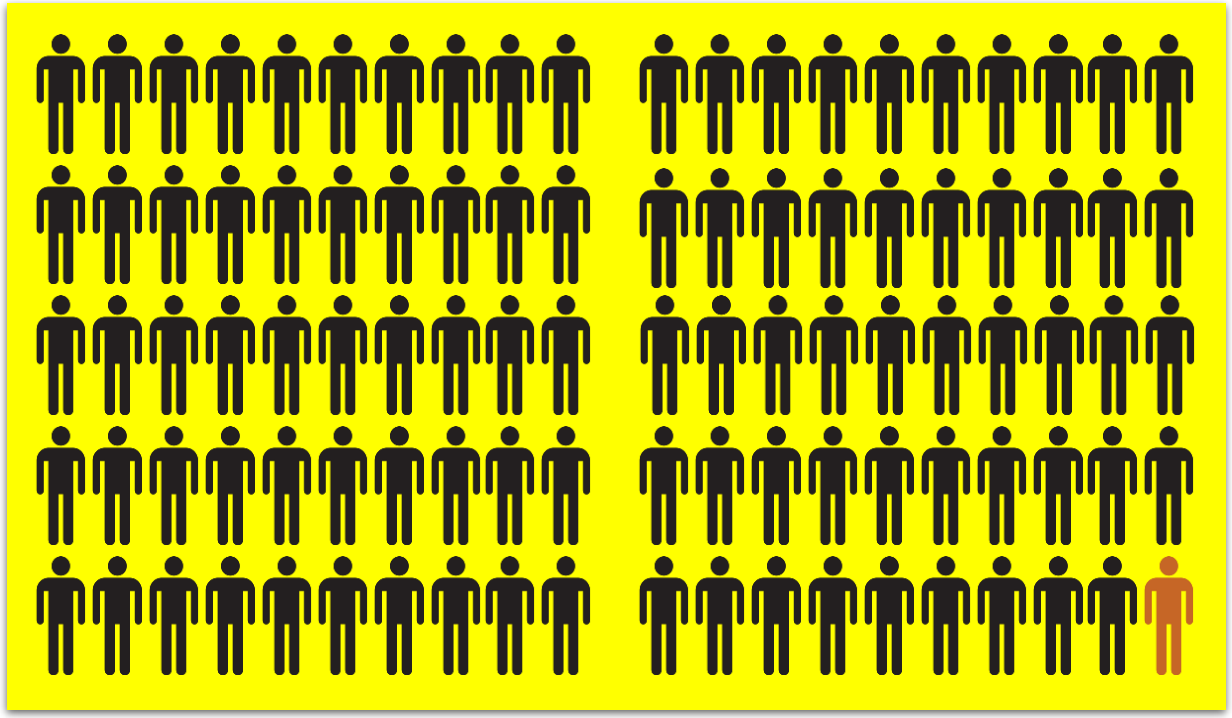
Geni di rischio

- APOE



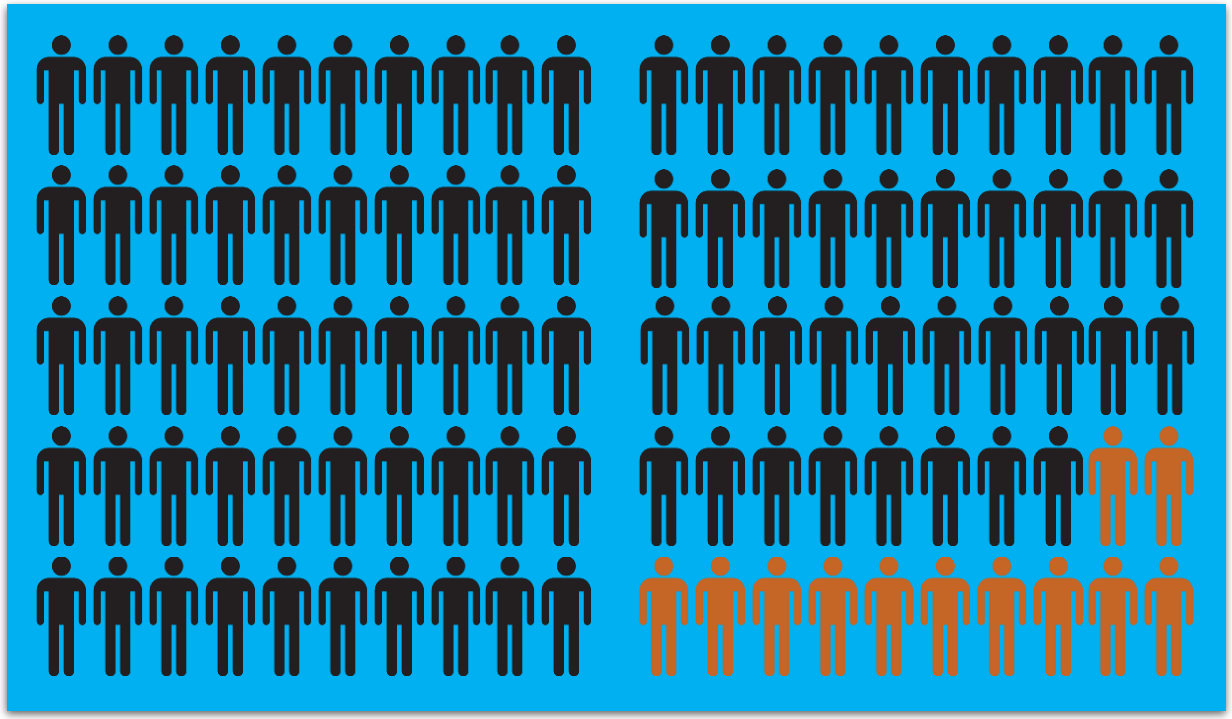
Genetic carriers in AD population

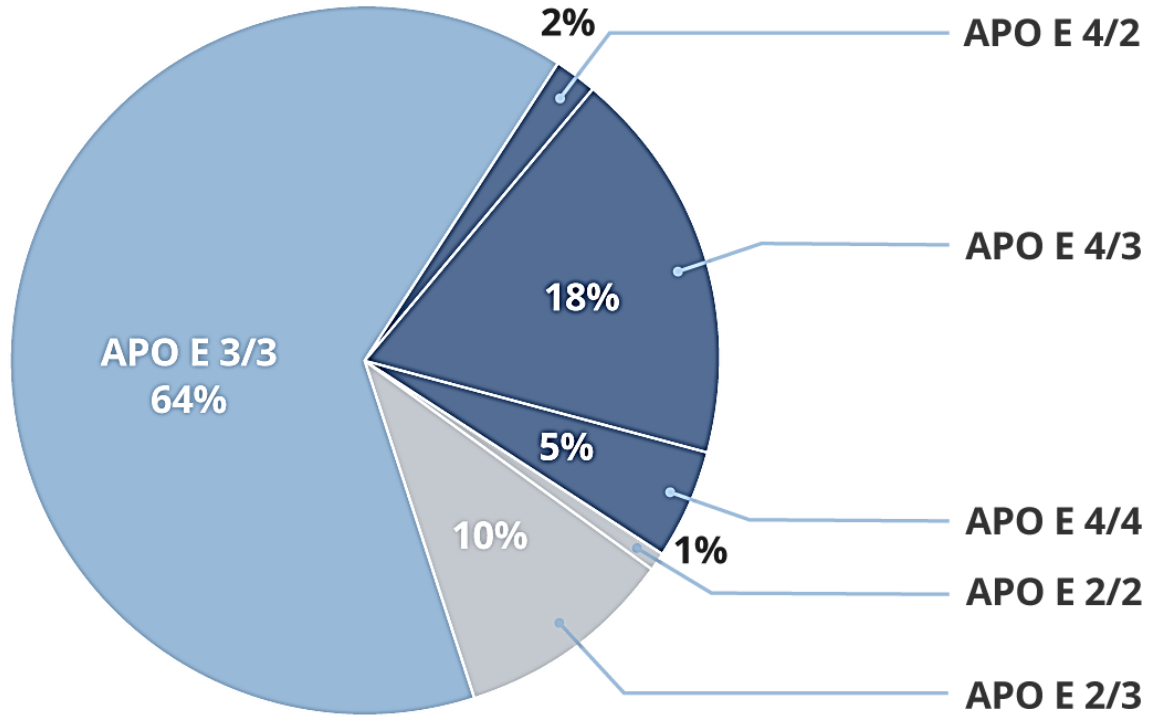
< 1%



Genetic carriers in early onset AD population (<65y)

13%





Genotype	E2/E2	E2/E3	E2/E4	E3/E3	E3/E4	E4/E4
Disease Risk	40% less likely	40% less likely	2.6 times more likely	Average risk	3.2 times more likely	14.9 times more likely

Pazienti FTLD

40 % familiarità
(almeno 1 familiare)

mutazione
13.4 %

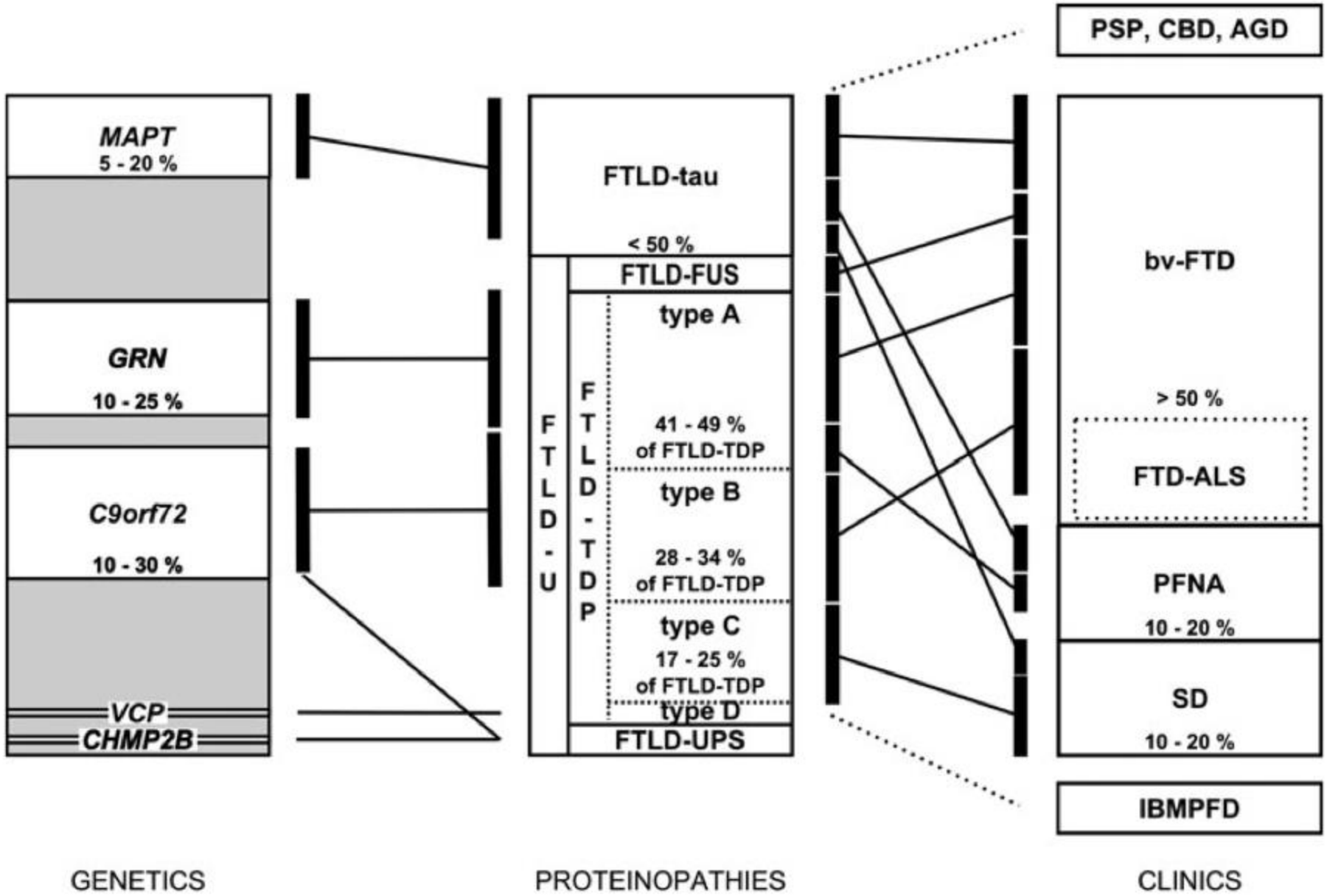
Table 3 FTLD – genes

Gene symbol	Chromosomal location	Gene name	Mutation frequency
C9orf72	9p21.2	Chromosome 9 open reading frame 21	14%–48%
GRN	17q21.32	Progranulin	3%–26%
MAPT	17q21.1	Microtubule-associated protein tau	0%–50%
CHMP2B	3p11.2	Charged multivesicular body protein 2B	<1%
VCP	9p13.3	Valosin-containing protein	<1%

Riedl L, 2014

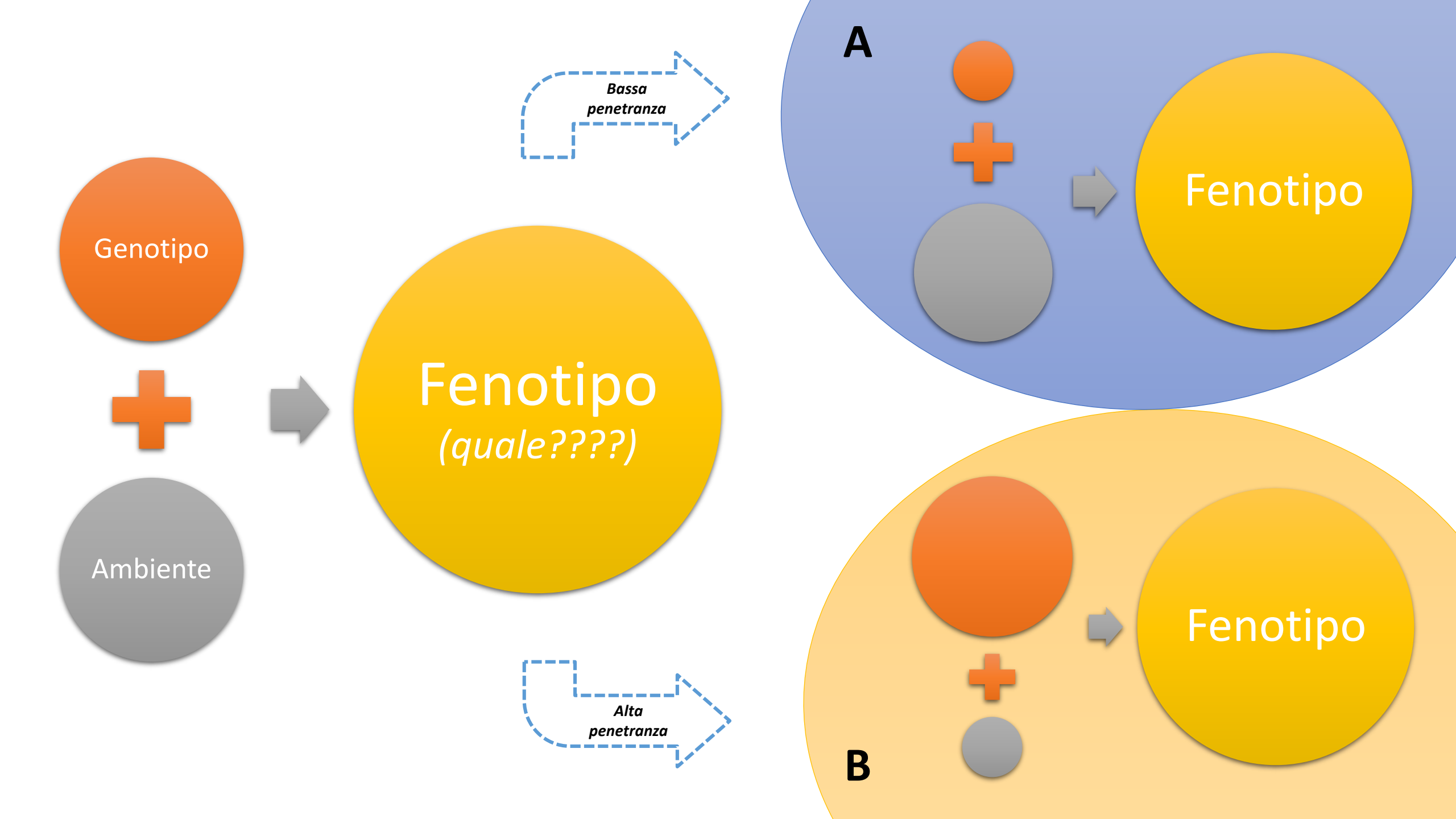
Psychosis in FTD may occur with a prevalence of about 10%. The percentage increases in carriers of C9ORF72 and GRN mutations and in patients with a TDP-43 pathology.

Shinigawa L et al, 2014



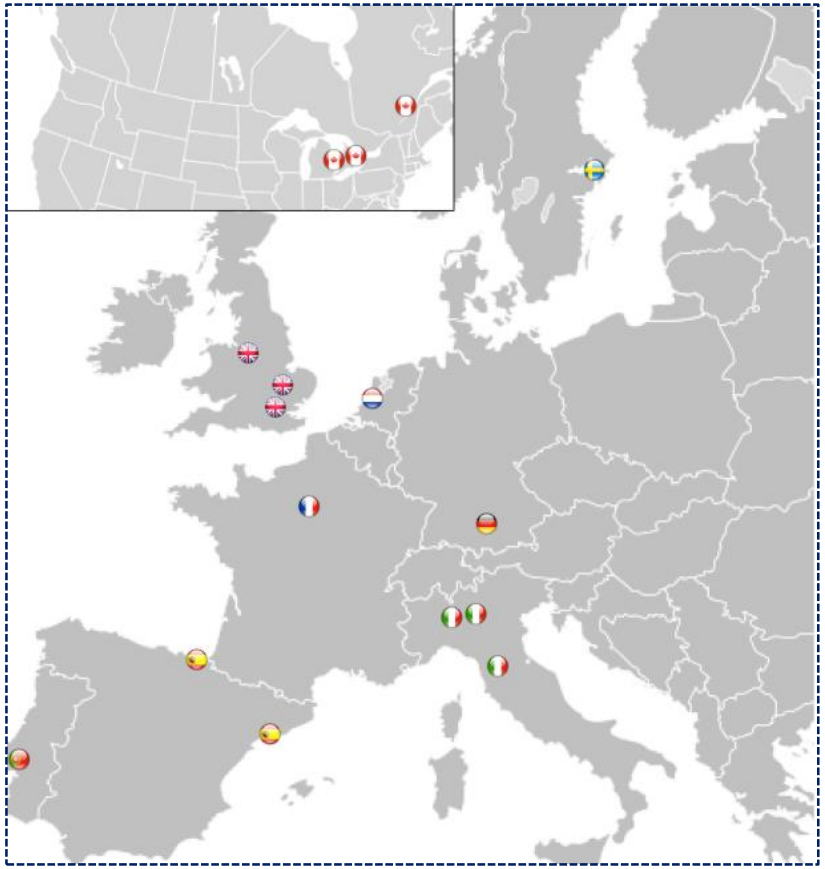
Sieben A, 2012

«E noi figli? Ci dobbiamo preoccupare?»


Genotipo
Ambiente
Fenotipo
(quale????)
Bassa penetranza
Alta penetranza
A
Fenotipo
B
Fenotipo

GENFI

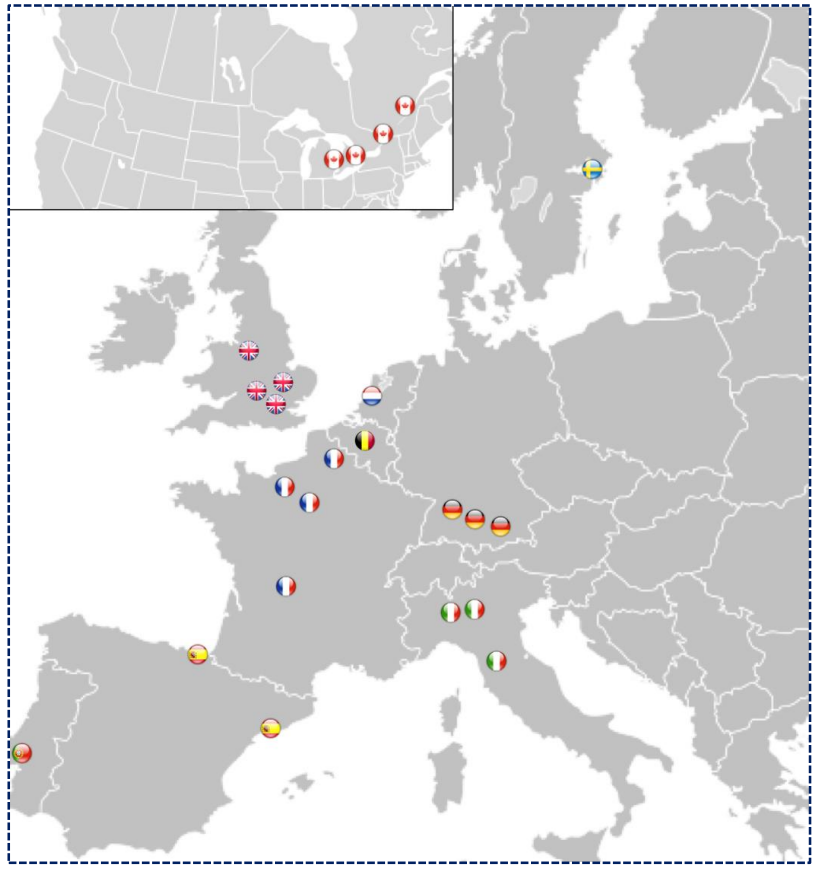
GENetic Ftd Initiative



http://genfi.org.uk/index.html

GENFI

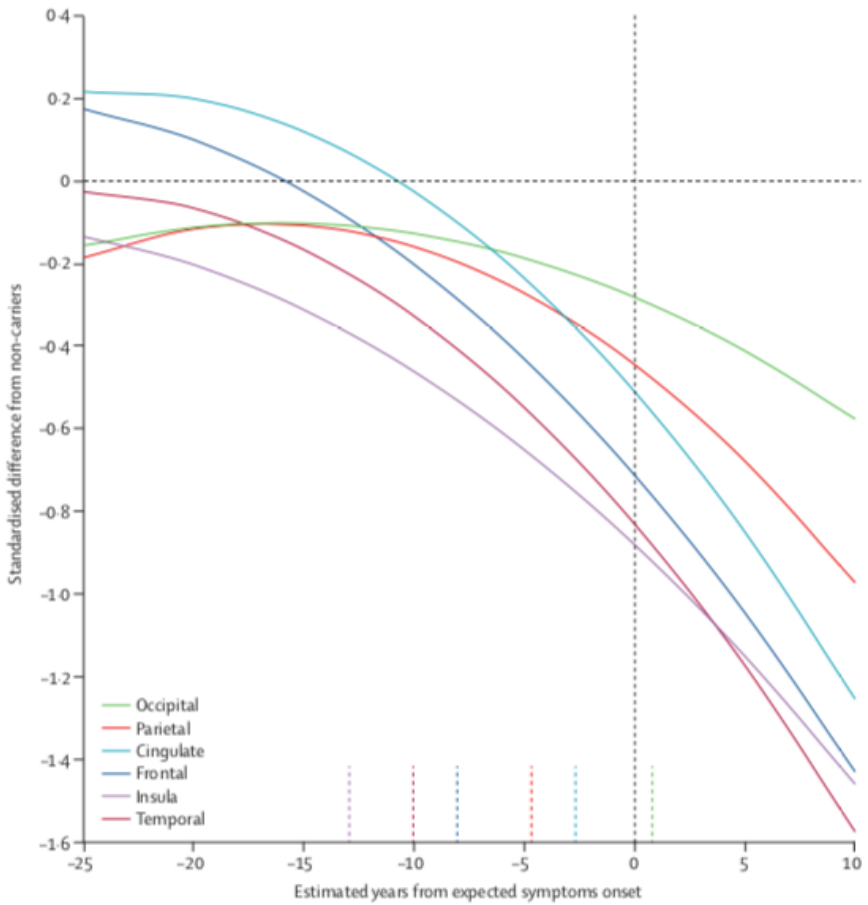
GENETIC FTD INITIATIVE



Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis

Jonathan D Rohrer, Jennifer M Nicholas, David M Cash, John van Swieten, Elise Dopper, Lize Jiskoot, Rick van Minkelen, Serge A Rombouts, M Jorge Cardoso, Shona Clegg, Miklos Espak, Simon Mead, David L Thomas, Enrico De Vita, Mario Masellis, Sandra E Black, Morris Freedman, Ron Keren, Bradley J MacIntosh, Ekaterina Rogaeva, David Tang-Wai, Maria Carmela Tartaglia, Robert Laforce Jr, Fabrizio Tagliavini, Pietro Tiraboschi, Veronica Redaelli, Sara Prioni, Marina Grisoli, Barbara Borroni, Alessandro Padovani, Daniela Galimberti, Elio Scarpini, Andrea Arighi, Giorgio Fumagalli, James B Rowe, Ian Coyle-Gilchrist, Caroline Graff, Marie Fallström, Vesna Jelic, Anne Kinhult Ståhlbom, Christin Andersson, Håkan Thonberg, Lena Lilius, Giovanni B Frisoni, Michela Pievani, Martina Bocchetta, Luisa Benussi, Roberta Ghidoni, Elizabeth Finger, Sandro Sorbi, Benedetta Nacmias, Gemma Lombardi, Cristina Polito, Jason D Warren, Sebastien Ourselin, Nick C Fox, Martin N Rossor

2015



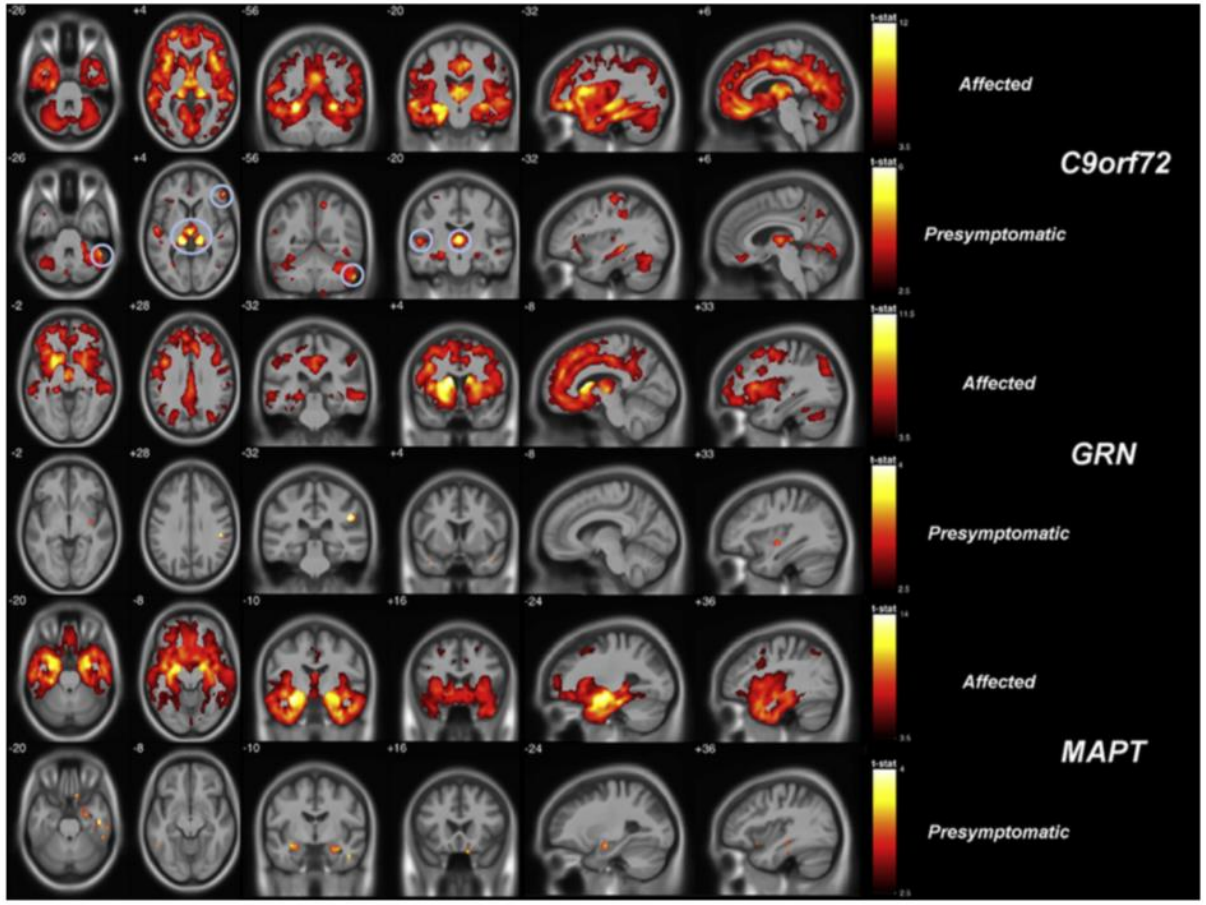
	-25 years	-20 years	-15 years	-10 years	-5 years	0 years	5 years	10 years
(Continued from previous page)								
Digit Symbol Task								
Non-carriers	0·8	0·7	0·5	0·3	0·1	-0·2	-0·4	-0·7
Carriers	0·8	0·6	0·3	<0·1	-0·4	-0·9	-1·4	-1·9
Difference	<0·1	-0·2	-0·2	-0·3	-0·5	-0·7	-0·9	-1·2
SE	0·2	0·2	0·2	0·2	0·2	0·2	0·2	0·3
p value	0·9036	0·7223	0·3033	0·0549	0·0017	<0·0001	<0·0001	<0·0001
Trail Making Test Part A								
Non-carriers	0·4	0·3	0·2	<0·1	-0·2	-0·4	-0·6	-0·8
Carriers	0·6	0·4	0·1	-0·2	-0·6	-1·0	-1·5	-2·0
Difference	0·2	0·1	-0·1	-0·2	-0·4	-0·6	-0·9	-1·2
SE	0·2	0·2	0·2	0·2	0·2	0·2	0·2	0·3
p value	0·4662	0·7470	0·7716	0·2832	0·0355	0·0012	0·0002	0·0006
Trail Making Test Part B								
Non-carriers	0·6	0·4	0·3	0·2	<0·1	-0·2	-0·3	-0·5
Carriers	0·9	0·7	0·4	<0·1	-0·5	-1·0	-1·7	-2·5
Difference	0·3	0·2	0·1	-0·2	-0·5	-0·9	-1·4	-1·9
SE	0·2	0·2	0·2	0·2	0·2	0·2	0·2	0·3
p value	0·1730	0·2639	0·7317	0·3799	0·0072	<0·0001	<0·0001	<0·0001
Letter Fluency								
Non-carriers	0·1	-0·1	-0·2	-0·3	-0·4	-0·5	-0·6	-0·6
Carriers	0·2	0·2	<0·1	-0·3	-0·6	-1·1	-1·7	-2·4
Difference	0·1	0·2	0·2	0·1	-0·2	-0·6	-1·1	-1·8
SE	0·2	0·2	0·2	0·2	0·2	0·2	0·2	0·3
p value	0·6629	0·3280	0·3592	0·7952	0·2746	0·0015	<0·0001	<0·0001
Category Fluency								
Non-carriers	0·5	0·4	0·2	0·1	-0·1	-0·3	-0·4	-0·6
Carriers	0·6	0·5	0·3	<0·1	-0·4	-0·8	-1·3	-2·0
Difference	0·1	0·1	0·1	-0·1	-0·3	-0·5	-0·9	-1·4
SE	0·2	0·2	0·2	0·2	0·2	0·2	0·2	0·3
p value	0·6632	0·4945	0·6544	0·7932	0·1226	0·0007	<0·0001	<0·0001
Boston Naming Test								
Non-carriers	<0·1	-0·1	-0·2	-0·3	-0·3	-0·3	-0·3	-0·3
Carriers	0·4	0·2	-0·2	-0·6	-1·0	-1·6	-2·2	-2·9
Difference	0·4	0·3	0·1	-0·3	-0·7	-1·2	-1·9	-2·6
SE	0·3	0·3	0·3	0·3	0·3	0·2	0·3	0·4
p value	0·1763	0·2871	0·7965	0·3202	0·0047	<0·0001	<0·0001	<0·0001
Block Design								
Non-carriers	0·4	0·3	0·2	<0·1	-0·2	-0·3	-0·5	-0·7
Carriers	0·7	0·5	0·2	-0·1	-0·5	-1·0	-1·4	-2·0
Difference	0·3	0·2	<0·1	-0·2	-0·4	-0·6	-0·9	-1·3
SE	0·2	0·2	0·2	0·2	0·2	0·2	0·2	0·3
p value	0·2220	0·3911	0·8839	0·4029	0·0284	0·0001	<0·0001	<0·0001

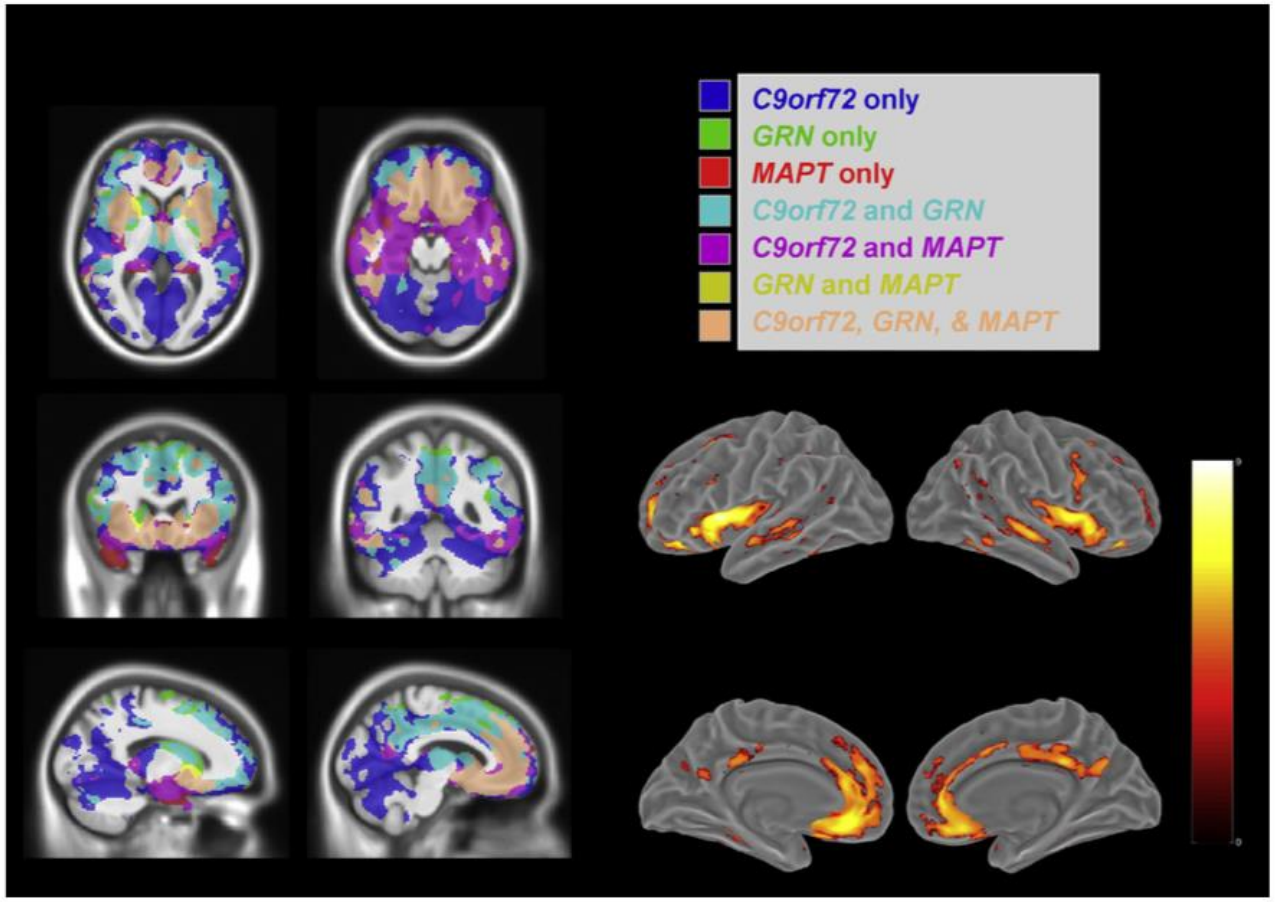
Patterns of gray matter atrophy in genetic frontotemporal dementia: results from the GENFI study

David M. Cash [a,b], Martina Bocchetta [a], David L. Thomas [a,b], Katrina M. Dick [a], John C. van Swieten [c], Barbara Borroni [d], Daniela Galimberti [e], Mario Masellis [f], Maria Carmela Tartaglia [g], James B. Rowe [h], Caroline Graff [i,j], Fabrizio Tagliavini [k], Giovanni B. Frisoni [l], Robert Laforce Jr [m], Elizabeth Finger [n], Alexandre de Mendonça [o], Sandro Sorbi [p,q], Martin N. Rossor [a], Sebastien Ourselin [a,b], Jonathan D. Rohrer [a,*], on behalf of the Genetic FTD Initiative, GENFI [1]

Shared network:

fronto-insula- anterior cingulate network





Cash DM et al, 2018

«C’è una medicina?»

Terapie

- Inibitori dell’acetilcolinesterasi
  - Donepezil
  - Galantamina
  - Rivastigmina
- Antagonista recettoriale NMDA non competitivo
  - Memantina

Soggetti a piano terapeutico AIFA nota 85

Quando prescriverli

Indicazioni:

- AD
- DLB
- Demenza vascolare

- MMSE tra 26 e 20 Donepezil/Rivastigmina/Galantamina
- MMSE tra 20 e 10 Donepezil/Rivastigmina/Galantamina/Memantina
- MMSE <10 Sospendere somministrazione (?)

- Memantina + AChEI assieme

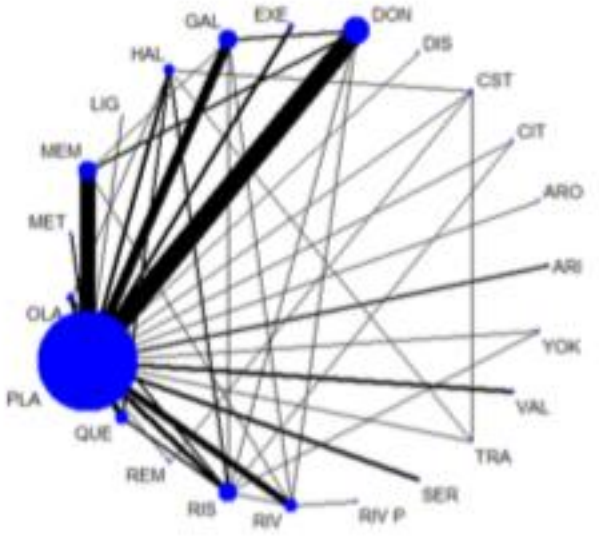
Comparative efficacy and safety of therapy for the behavioral and psychological symptoms of dementia: a systemic review and Bayesian network meta-analysis

Boru Jin[1] · Huayan Liu[1]

146 RCTs → 44873 patients

Result 146 RCTs comprising 44,873 patients with BPSD were included in this study. On NPI, aripiprazole (MD − 3.65, 95% credible interval (CrI) = − 6.92 to − 0.42), escitalopram (MD − 6.79, 95% CrI − 12.91 to − 0.60), donepezil (MD − 1.45, 95% CrI − 2.70 to − 0.20), galantamine (MD − 1.80, 95% CrI − 3.29 to − 0.32), memantine (MD − 2.14, 95% CrI − 3.46 to − 0.78), and risperidone (MD − 3.20, 95% CrI − 6.08 to − 0.31) were superior to placebo. On CMAI, aripiprazole (MD − 4.00, 95% CrI − 7.39 to − 0.54) and risperidone (MD − 2.58, 95% CrI − 5.20 to − 0.6) showed superiority to placebo. On the risk of total AEs, donepezil (OR 1.27, 95% CrI 1.07–1.50), galantamine (OR 1.91, 95% CrI 1.58–2.36), risperidone (OR 1.47, 95% CrI 1.13–1.97), and rivastigmine (OR 2.02, 95% CrI 1.53–2.70) owned higher risk than placebo.

Conclusion Pharmacological therapies should be the first choice for BPSD. Aripiprazole, haloperidol, quetiapine, and risperidone of antipsychotics showed the significant efficacy, while memantine, galantine, and donepezil may provide the modest effectiveness. The safety of all was thought to be acceptable.

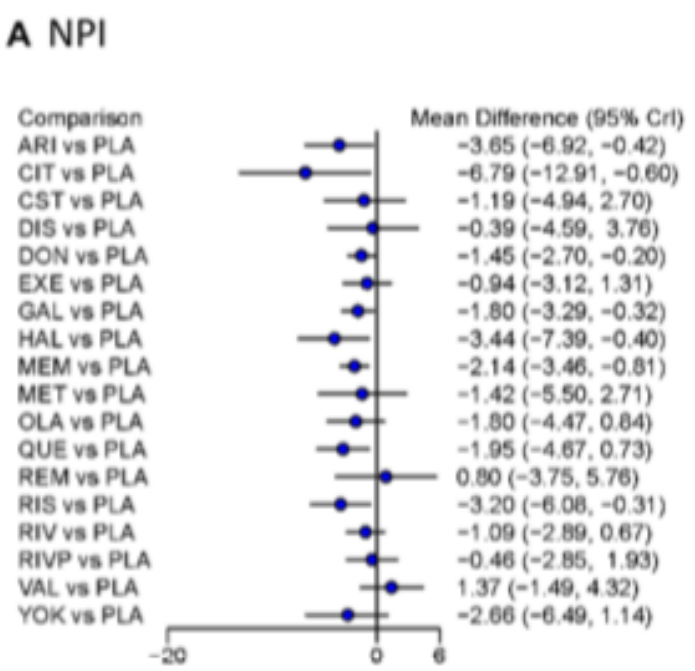


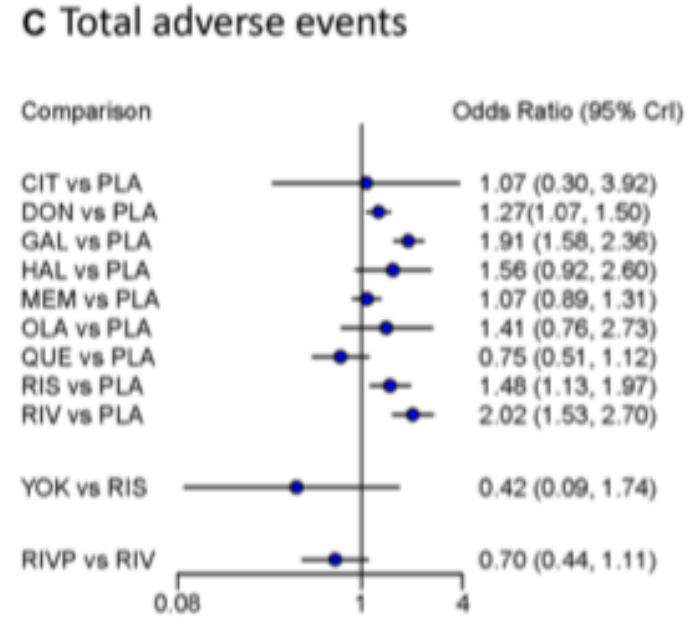
Effect on NPI

1. Aripiprazole
2. Escitalopram
3. Donepezil
4. Galantamine
5. Memantina
6. Risperidone

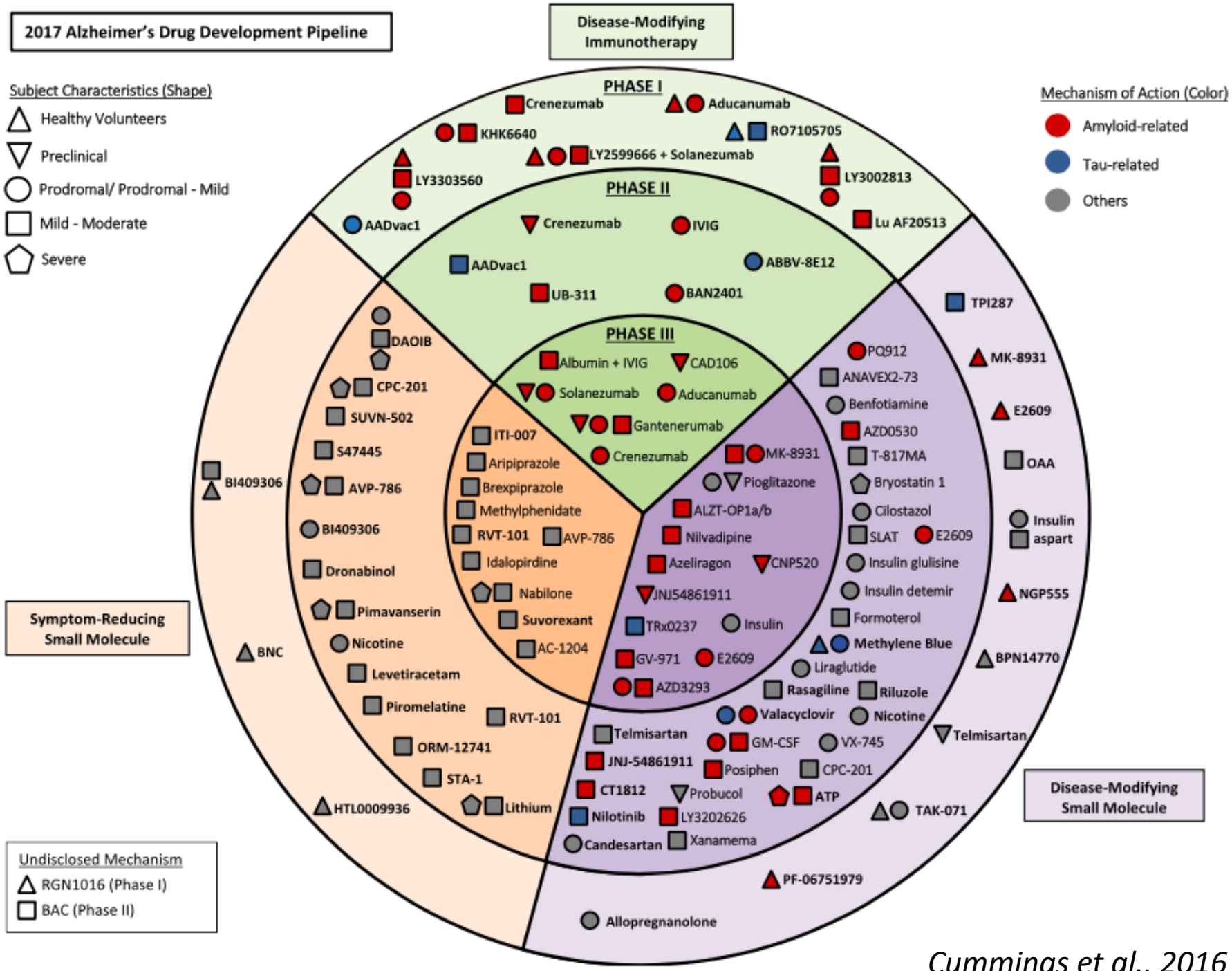
Adverse events

1. Donepezil
2. Galantamine
3. Risperidone
4. Rivastigmine





Boru J et al, 2019

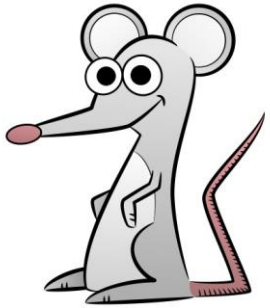


Strategie terapeutiche per farmaci sperimentali:

- Inibire la formazione di Amiloide
- Stimolare il sistema immunitario ad eliminarla
- Bloccare la proteina Tau

Cummings et al., 2016

Perché i farmaci sperimentali falliscono???

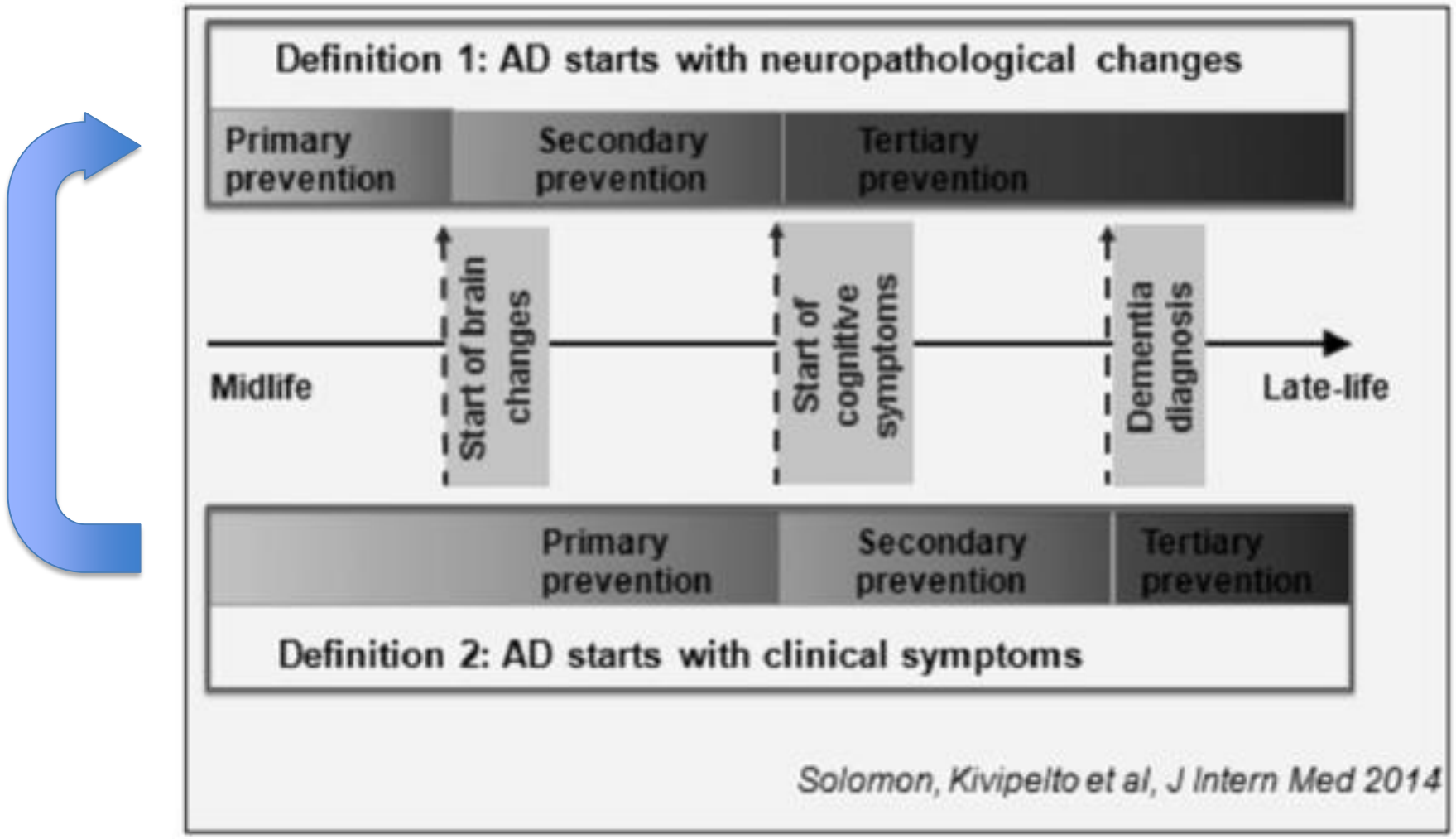


Modelli preclinici
modello animale
diverso da uomo

Popolazione
altre demenze
patologia avanzata

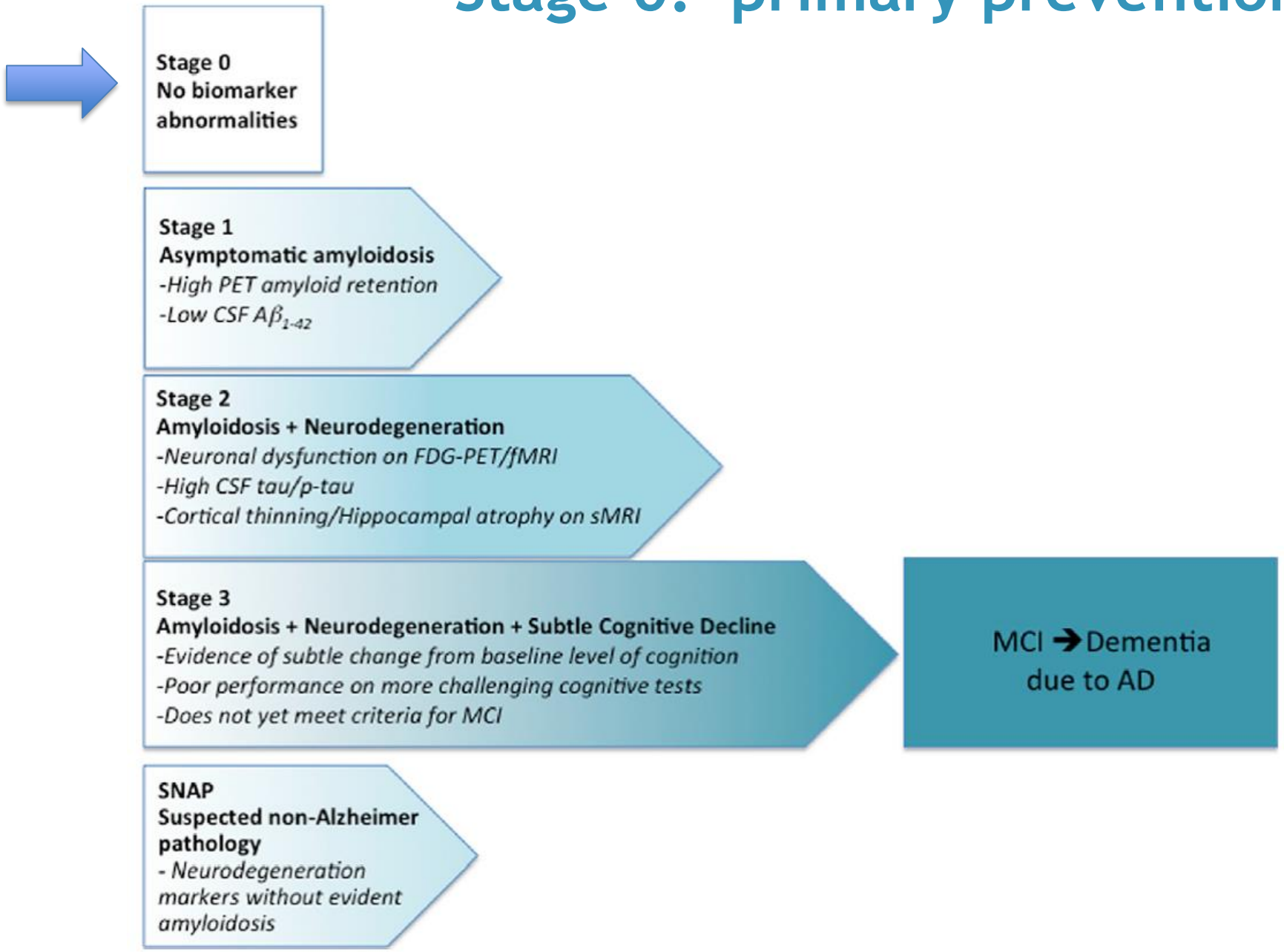
Cascata dell'amiloide
chi è il vero killer?

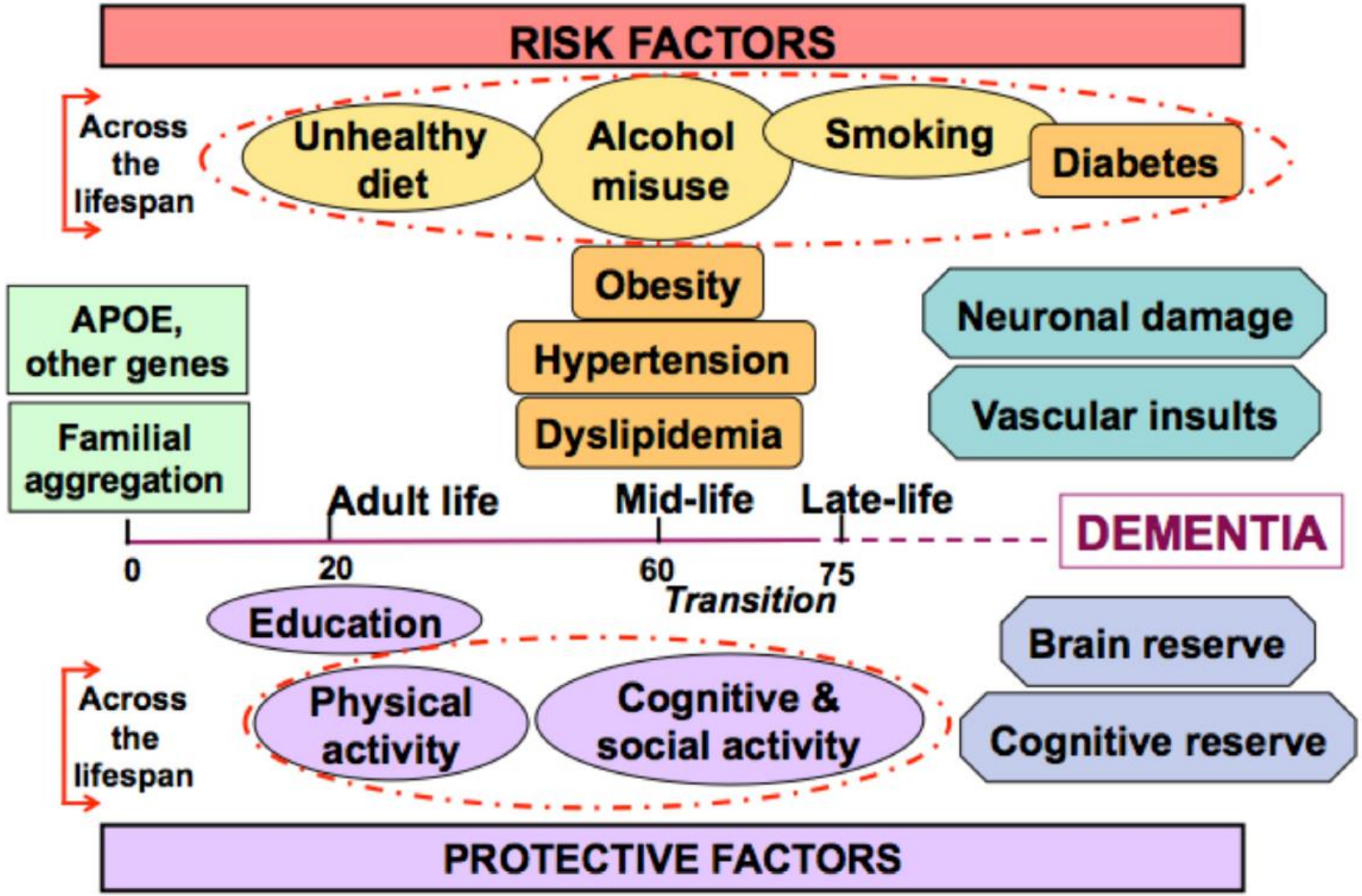
How disease definition affects prevention



Cavedo et al, 2014

Stage 0: primary prevention

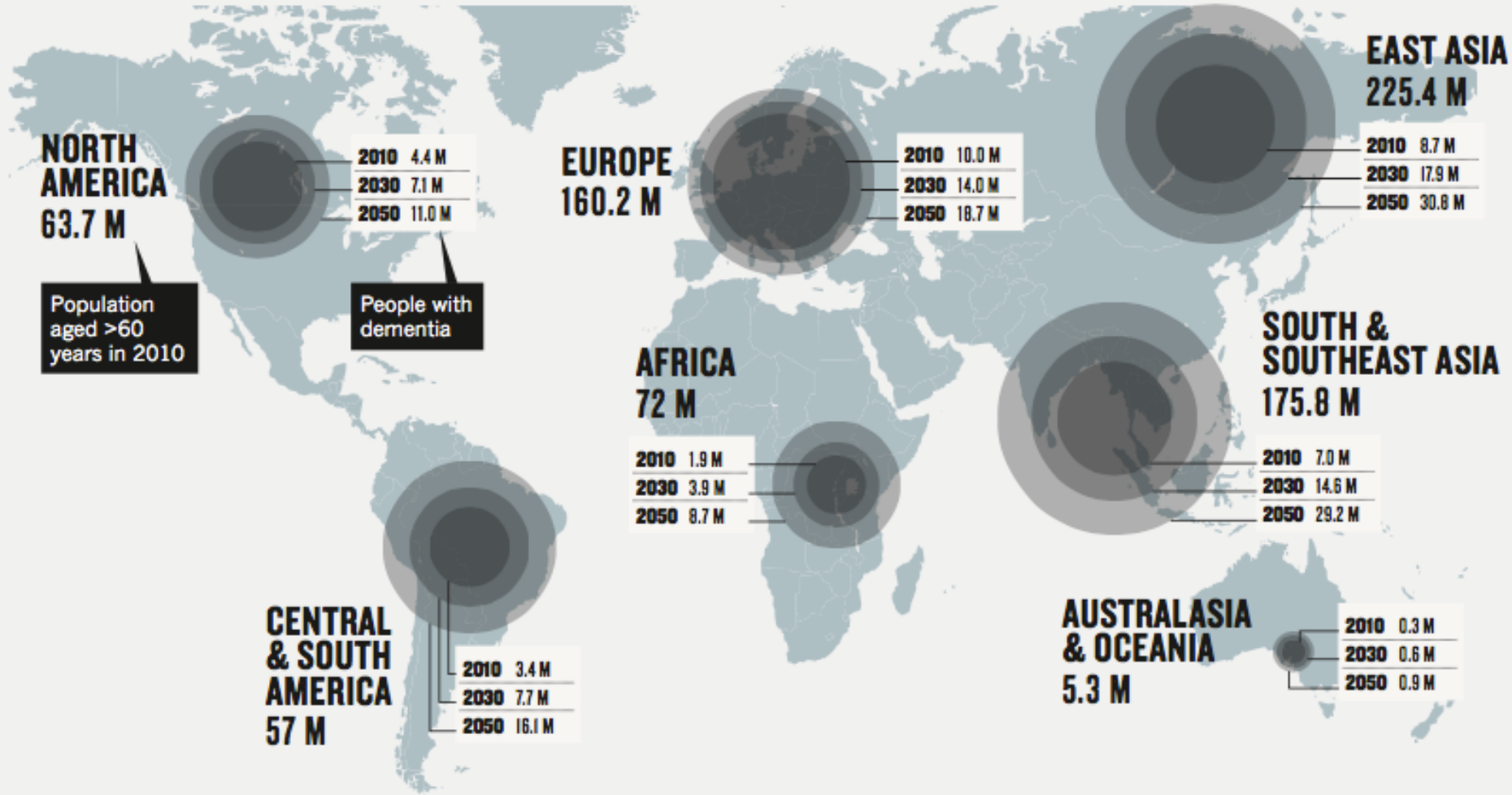




Sindi S et al, 2015

ESTIMATED GROWTH OF DEMENTIA

The number of people with dementia will roughly double every 20 years, with the biggest increases in developing countries.



La prevenzione

Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions

Sandrine Andrieu, Nicola Coley*, Simon Lovestone, Paul S Aisen, Bruno Vellas*

The projected effects of preventive interventions with even quite modest effects at the individual level are impressive, dramatically reducing the future burden of dementia. For example, an intervention that delays disease onset and progression by 1 year, or a reduction in the prevalence of several modifiable lifestyle risk factors of 10% per decade, could potentially reduce the number of Alzheimer's disease dementia cases worldwide in 2050 by around 9 million.[5,6]

Andrieu S, 2015

Potential for primary prevention of Alzheimer's disease: an analysis of population-based data

Sam Norton, Fiona E Matthews, Deborah E Barnes, Kristine Yaffe, Carol Brayne

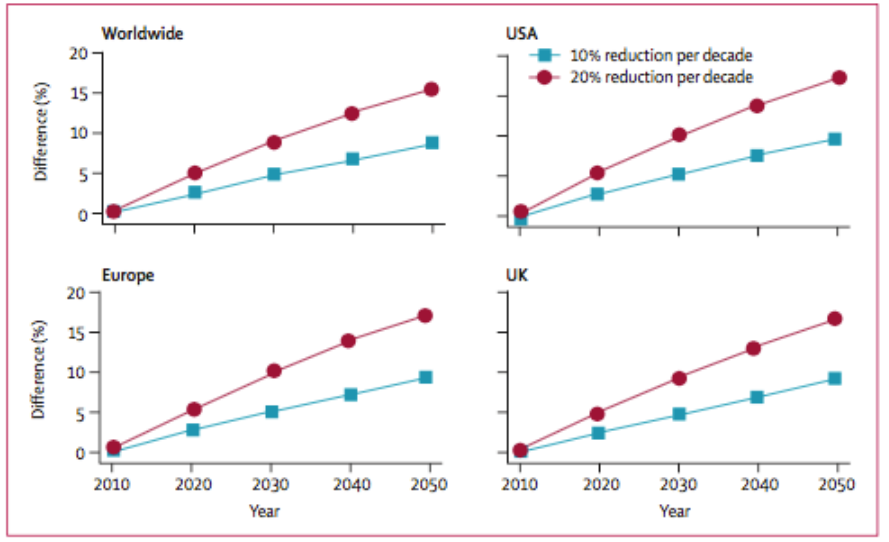


Figure: Projected percentages of Alzheimer's disease cases that could be prevented, with 10% or 20% reductions per decade in each risk factor

Norton S, 2014

Patient 1

- bvFTD
- Età esordio 73 aa
- CSF

  Amyloid 1096 pg/ml

  Total-TAU 342 pg/ml

  P-TAU 37 pg/ml

Patient 2

- bvFTD
- Età esordio 68 aa
- CSF

  Amyloid 680 pg/ml

  Total-Tau 713 pg/ml

  P-TAU 64 pg/ml

Test	Patient 1	Patient 2
MMSE (/30)	21	17
EXECUTIVE FUNCTION		
Matrici Raven colore	13	15
TMT A	44	120
TMT B	Interrotta	Interrotta
LANGUAGE		
Fonemic Fluency	7	13
Semantic Fluency	10.25	10.25
Token test	23	25.5
MEMORY		
Digit span	4	4
Corsi span	4	3
Breve racconto - Immediato	0	6
Breve racconto - Differito	5	5
Breve racconto - Totale	5	11
Fig Rey differita	8.5	2
ATTENTION		
Matrici Numeriche	37	38
VISUOCONSTRUCTIVE SKILLS		
Apraxia	11	10
Fig Rey Copia	14.5	Interrotta
VISUOSPATIAL SKILLS		
VOSP	18	20

GRN Thr272fs mutation

GRN Thr272fs mutation

Journal of Alzheimer's Disease xx (20xx) x–xx
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Short Communication

Monozygotic Twins with Frontotemporal Dementia Due To Thr272fs *GRN* Mutation Discordant for Age At Onset

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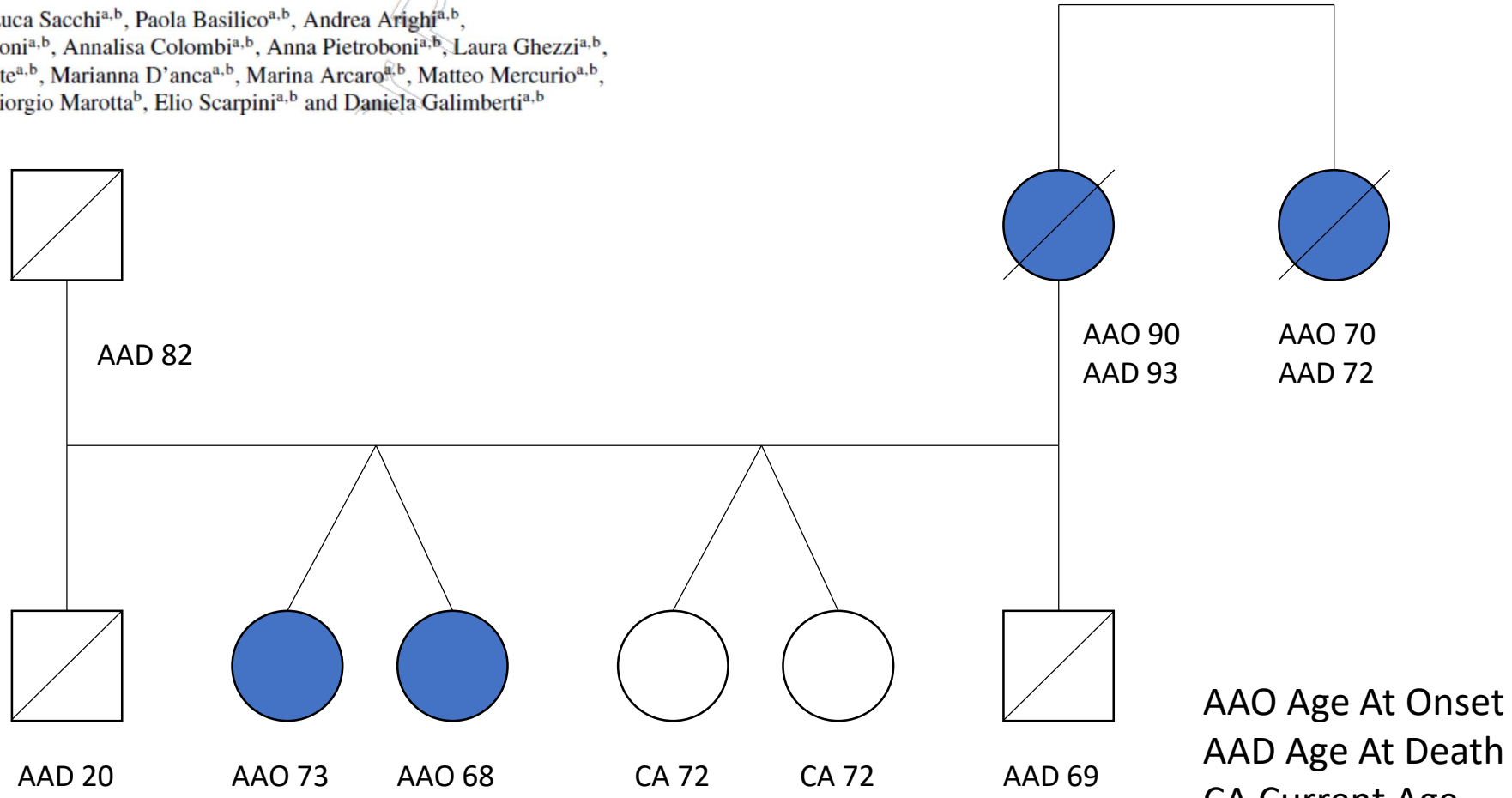
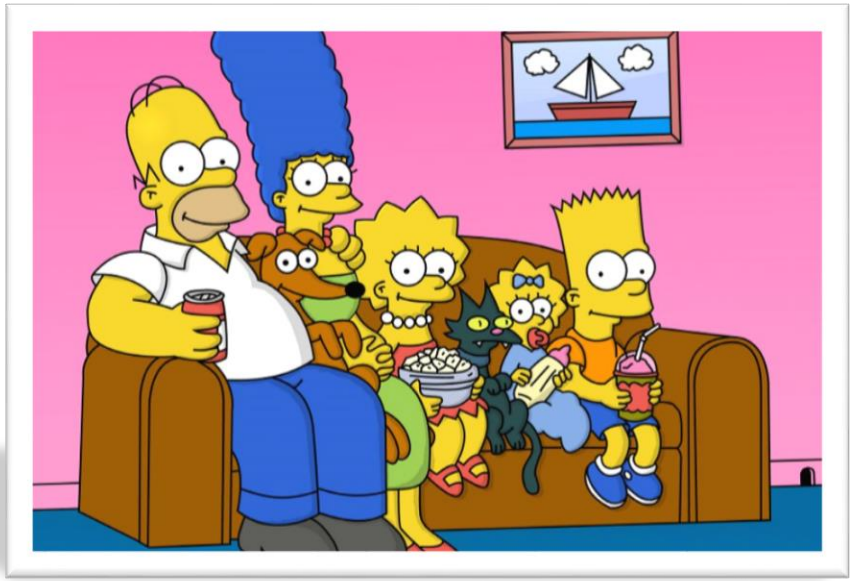


«Ma… perché?»


MATT
GROENING


Welcome to
SPRINGFIELD




L429

Hide Search | Start Over

Condition or disease | **Other terms**

Alzheimer Disease | x | | x

Country

| x

Search | Advanced Search

509 Studies found for: **Recruiting, Not yet recruiting Studies | Alzheimer Disease**

Also searched for **Disorders** and **Alzheimer Dementias**. See Search Details

Applied Filters: ☑ **Recruiting** ☑ **Not yet recruiting**

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Status

Recruitment :

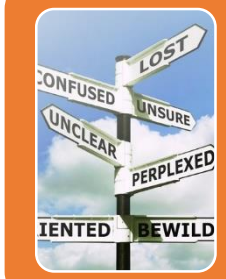
- ☑ Not yet recruiting
- ☑ Recruiting
- ☐ Enrolling by invitation
- ☐ Active, not recruiting

Row	Saved	Status	Study Title	Conditions	Interventions	Locations
1	☐	Not yet recruiting	Gamma Induction for **Alzheimer's Disease**	• **Alzheimer Disease**	• Device: Transcranial Alternating Current Stimulation (tACS) • Other: Sham Transcranial Alternating Current Stimulation	• Beth Israel Deaconess Medical Center Boston, Massachusetts, United States
2	☐	Recruiting	Early Onset **Alzheimer's Disease** Genomic Study	• **Alzheimer Disease**	• Genetic: Genetic Testing	• Baylor Scott & White AT&T Memory Center Dallas, Texas, United States
3	☐	Recruiting	Gut Microbiota and **Alzheimer's Diseases**	• **Alzheimer Disease**		• Shanghai Tenth People's Hospital Shanghai, Shanghai, China

Il nostro PDTA Neuro-Psico-Geriatrico

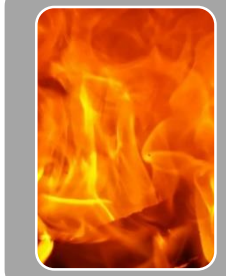
PERCORSO NEURO-PSICO-GERIATRICO DIAGNOSTICO, TERAPEUTICO E ASSISTENZIALE (PDTA) PER I PAZIENTI ADULTI ED ANZIANI AFFETTI DA DECADIMENTO COGNITIVO E DISTURBI PSICO-COMPORTAMENTALI

- Clinica: Neurologo – Geriatra – Psichiatra
- Neuropsicologia
- Neuroimaging
  - TC encefalo di base
  - RM encefalo: T13D – T2 – FLAIR – DWI – SWI
  - FDG PET encefalo
  - Amy PET encefalo
  - SPECT con DAT-scan
- Laboratorio
  - Analisi CSF (AB, T, PT)
  - Analisi genetiche: APOE, APP, ATP13A2, ATP7B, C19ORF12, CHCHD10, CHMP2B, CP, CSFR1, DCTN1, EIF2B1, EIF2B2, EIF2B3, EIF2B4, EIF2B5, FTL, FUS, GBA, GFAP, GRN, LRRK2, MAPT, MATR3, NOTCH3, NPC1, NPC2, PANK2, PFN1, PLA2G6, PRKAR1B, PSEN1, PSEN2, SNCA, SORL1, SQSTM1, TARDPB, TBK1, TMEM230, TREM2, UBE3A, UBQLN2, VCP



Problemi cognitivi

- Deficit mnesico
- Deficit di linguaggio
- Deficit funzioni esecutive
- Deficit visuo-spaziale
- ….



Problemi comportamentali

- Agitazione ed aggressività
- Disinibizione
- Apatia
- Ansia
- …

Problemi motori

- Bradicinesia
- Rigidità
- Tremore
- Instabilità posturale
- …

Problemi internistici

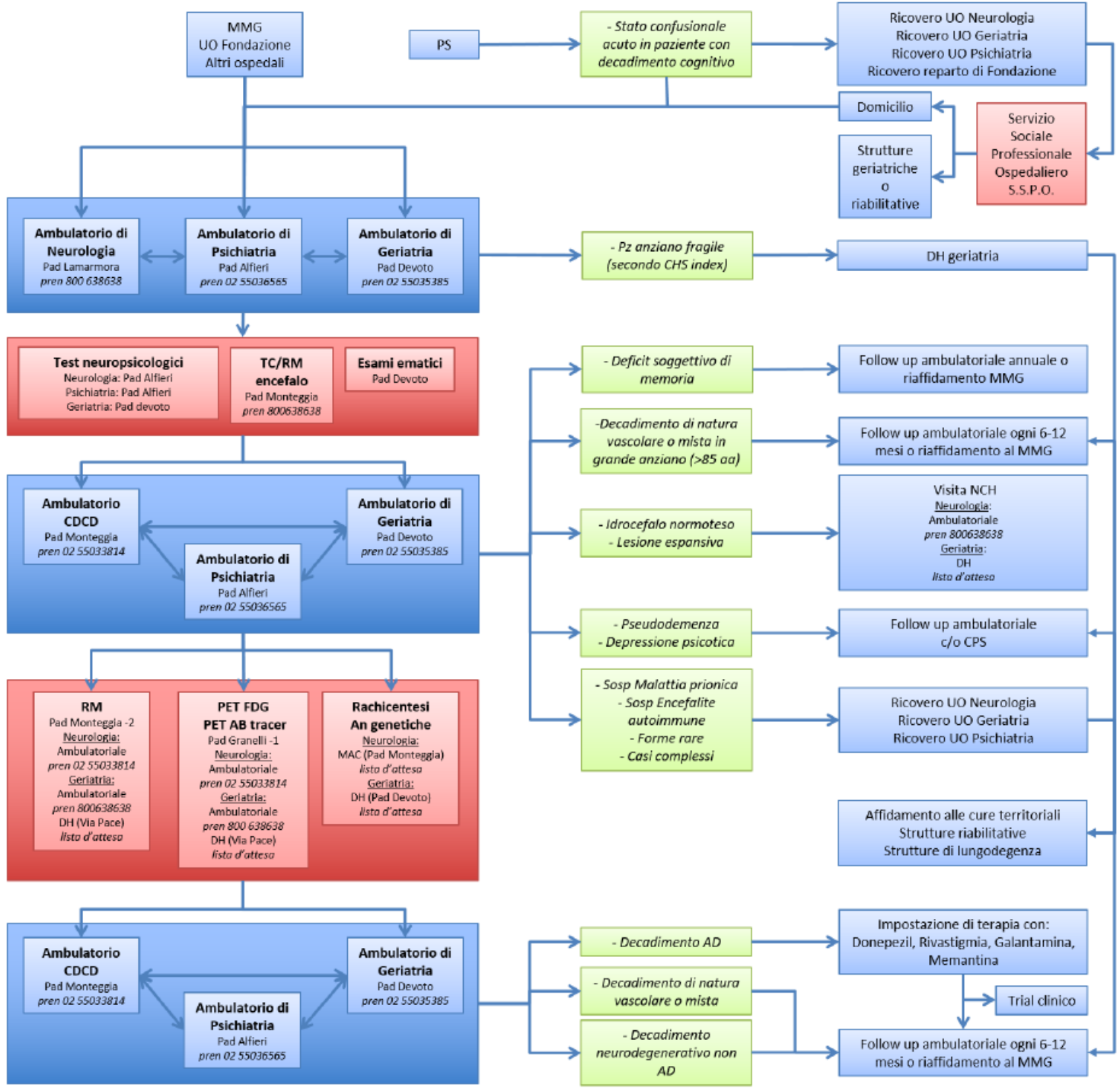
- Sindrome da allettamento
- Patologie legate all’invecchiamento
- …

Percorso

NEURO-PSICO-GERIATRICO

diagnostico, terapeutico ed assistenziale (PDTA)

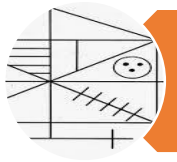
per i *pazienti adulti ed anziani* affetti da *decadimento cognitivo e disturbi psicocomportamentali*


MMG
UO Fondazione
Altri ospedali
PS
- Stato confusionale acuto in paziente con decadimento cognitivo
Ricovero UO Neurologia
Ricovero UO Geriatria
Ricovero UO Psichiatria
Ricovero reparto di Fondazione
Domicilio
Strutture geriatriche o riabilitative
Servizio Sociale Professionale Ospedaliero S.S.P.O.
Ambulatorio di Neurologia
Pad Lamarmora
pren 800 638638
Ambulatorio di Psichiatria
Pad Alfieri
pren 02 55036565
Ambulatorio di Geriatria
Pad Devoto
pren 02 55035385
- Pz anziano fragile (secondo CHS index)
DH geriatria
Test neuropsicologici
Neurologia: Pad Alfieri
Psichiatria: Pad Alfieri
Geriatria: Pad devoto
TC/RM encefalo
Pad Monteggia
pren 800638638
Esami ematici
Pad Devoto
- Deficit soggettivo di memoria
Follow up ambulatoriale annuale o riaffidamento MMG
-Decadimento di natura vascolare o mista in grande anziano (>85 aa)
Follow up ambulatoriale ogni 6-12 mesi o riaffidamento al MMG
Ambulatorio CDCD
Pad Monteggia
pren 02 55033814
Ambulatorio di Psichiatria
Pad Alfieri
pren 02 55036565
Ambulatorio di Geriatria
Pad Devoto
pren 02 55035385
- Idrocefalo normoteso
- Lesione espansiva
Visita NCH
Neurologia:
Ambulatoriale
pren 800638638
Geriatria:
DH
lista d'attesa
- Pseudodemenza
- Depressione psicotica
Follow up ambulatoriale c/o CPS
- Sosp Malattia prionica
- Sosp Encefalite autoimmune
- Forme rare
- Casi complessi
Ricovero UO Neurologia
Ricovero UO Geriatria
Ricovero UO Psichiatria
RM
Pad Monteggia -2
Neurologia:
Ambulatoriale
pren 02 55033814
Geriatria:
Ambulatoriale
pren 800638638
DH (Via Pace)
lista d'attesa
PET FDG
PET AB tracer
Pad Granelli -1
Neurologia:
Ambulatoriale
pren 02 55033814
Geriatria:
Ambulatoriale
pren 800 638638
DH (Via Pace)
lista d'attesa
Rachicentesi
An genetiche
Neurologia:
MAC (Pad Monteggia)
lista d'attesa
Geriatria:
DH (Pad Devoto)
lista d'attesa
Affidamento alle cure territoriali
Strutture riabilitative
Strutture di lungodegenza
Ambulatorio CDCD
Pad Monteggia
pren 02 55033814
Ambulatorio di Psichiatria
Pad Alfieri
pren 02 55036565
Ambulatorio di Geriatria
Pad Devoto
pren 02 55035385
- Decadimento AD
Impostazione di terapia con:
Donepezil, Rivastigmia, Galantamina, Memantina
Trial clinico
- Decadimento di natura vascolare o mista
- Decadimento neurodegenerativo non AD
Follow up ambulatoriale ogni 6-12 mesi o riaffidamento al MMG

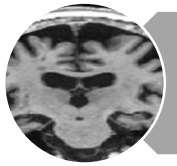
Neurologo

Geriatra

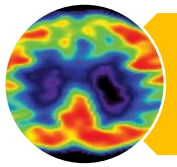
Psichiatra



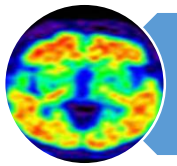
Test neuropsicologici



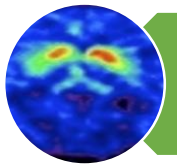
Risonanza magnetica



FDG-PET



PET con tracciante per amiloide



SPECT con DAT-scan

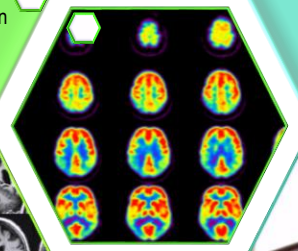
Analisi liquor cefalorachidiano

Analisi genetiche

Geriatra
- Visita ambulatoriale
- Valutazione neuropsicologica
- Visita multidisciplinare
- DH
- Ricovero

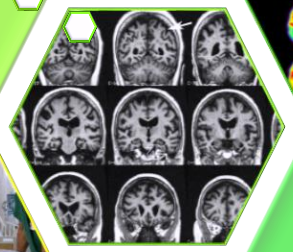
Neuroradiologo
- TC encefalo
- RM encefalo

Medico Nucleare
- FDG-PET
- PET per amiloide
- SPECT con DAT-scan



Assistente Sociale Ospedaliero
- Orientamento socio-sanitario
- Sostegno sociale
- Tutela giuridica

Psichiatra
- Visita ambulatoriale
- Visita multidisciplinare
- Ricovero



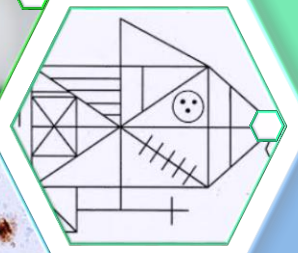
Neurologo
- Visita ambulatoriale
- Valutazione neuropsicologica
- MAC per rachicentesi
- Ricovero

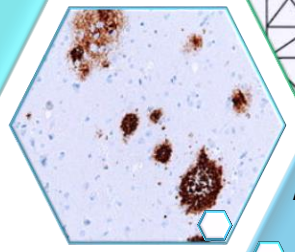
Neurochirurgo
- Visita ambulatoriale
- Ricovero

Biologo
- Esame del liquido cefalorachidiano
- Esami genetici (NGS)

Neuropsicologo
- Valutazione neuropsicologica
- Counseling per i caregivers

Infermiere
- Assistenza in reparto, MAC ed ambulatorio
- Educazione sanitaria per i caregivers





Fisiatra
- Riabilitazione cognitiva
- Riabilitazione motoria
- Logopedia
- Terapia occupazionale

Anatomo Patologo
- Riscontro autoptico

UOSD Malattie Neurodegenerative

Neurologi
Prof. Elio Scarpini
Milena De Riz
Anna Pietroboni
Andrea Arighi
Giorgio Fumagalli
Laura Ghezzi
Paola Basilico
Alberto Calvi
Marta Scarioni
Tiziana Carandini
Annalisa Colombi

Neuropsicologi
Emanuela Rotondo
Matteo Mercurio
Priscilla Corti
Roberto Vimercati

Biologi
Daniela Galimberti
Chiara Fenoglio
Maria Serpente
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