Cosa cambia con i nuovi criteri diagnostici?

Dr.ssa Laura Bracco

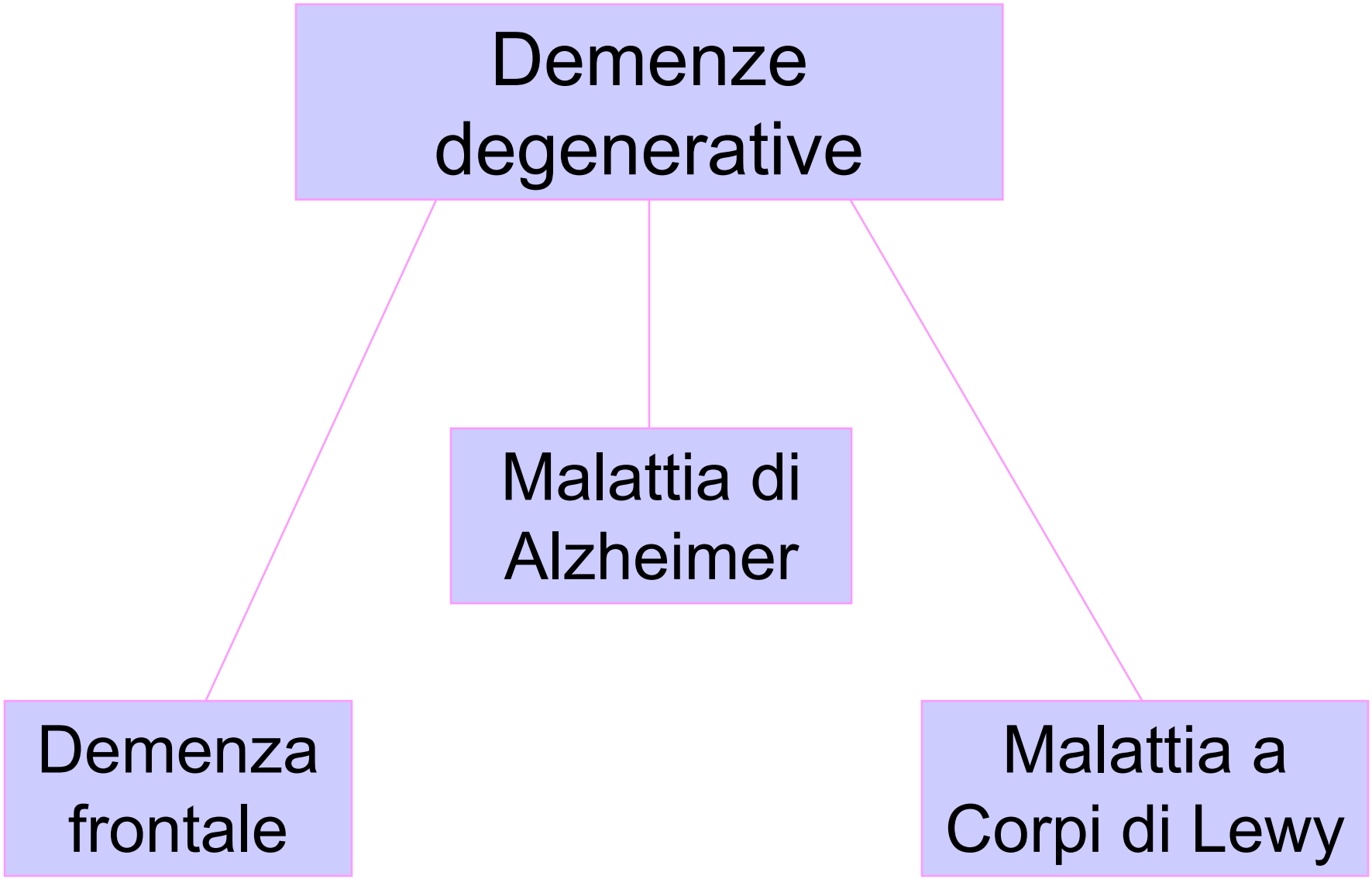
DEMENZA

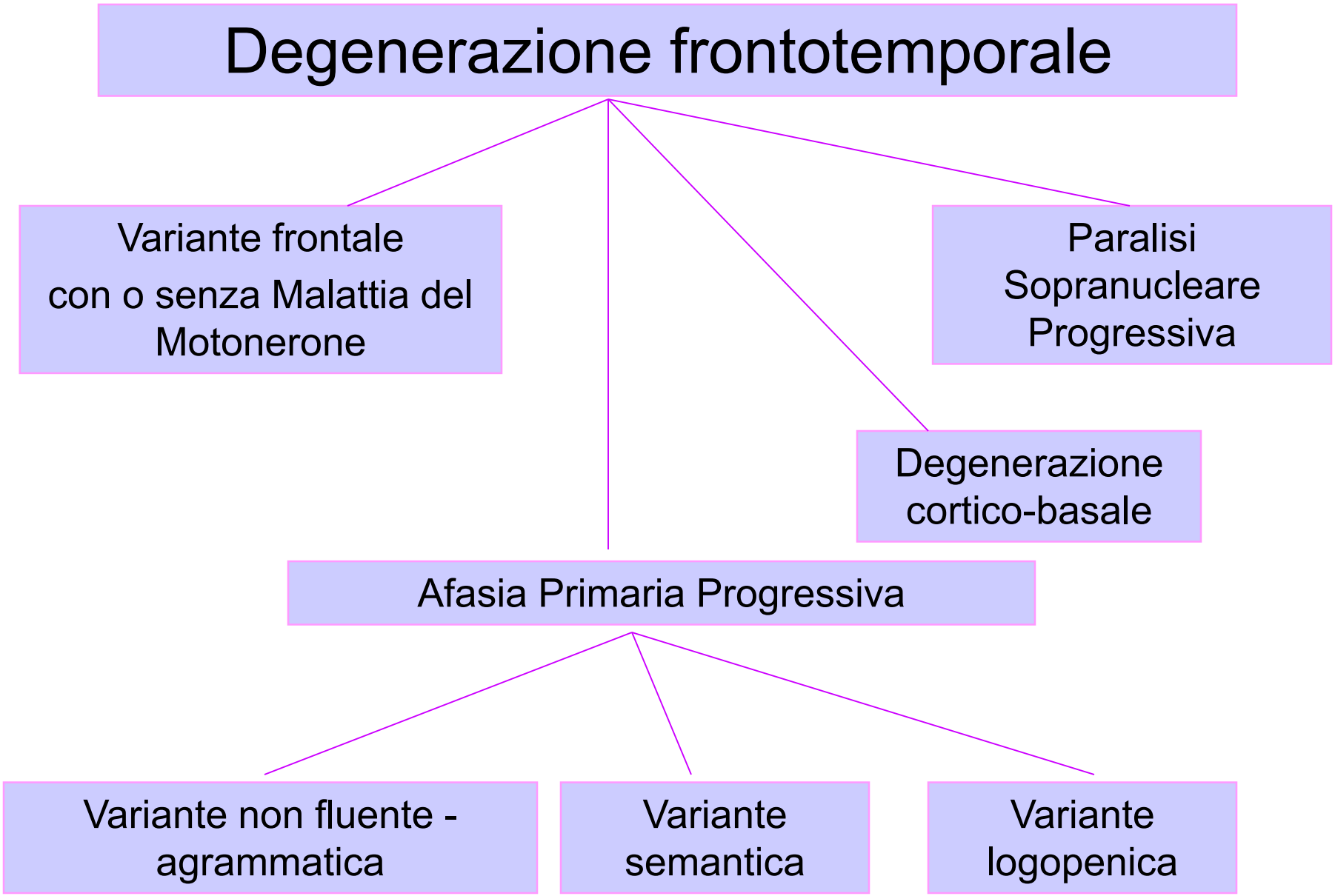
- **Sindrome clinica caratterizzata dal deterioramento della memoria e delle altre funzioni cognitive rispetto al livello di sviluppo cognitivo precedentemente raggiunto dal paziente**
- Il deterioramento è documentato da una storia clinica di riduzione di performance e da anomalie evidenziate dall'esame neurologico e dai test neuropsicologici

(McKhann et al., 1984)

- ….
- I deficit cognitivi devono essere tali da interferire con lo svolgimento delle abituali attività lavorative e sociali

DSM IV


Demenze degenerative
Malattia di Alzheimer
Demenza frontale
Malattia a Corpi di Lewy


Degenerazione frontotemporale
Variante frontale
con o senza Malattia del Motonerone
Paralisi Sopranucleare Progressiva
Degenerazione cortico-basale
Afasia Primaria Progressiva
Variante non fluente - agrammatica
Variante semantica
Variante logopenica

DEMENZA

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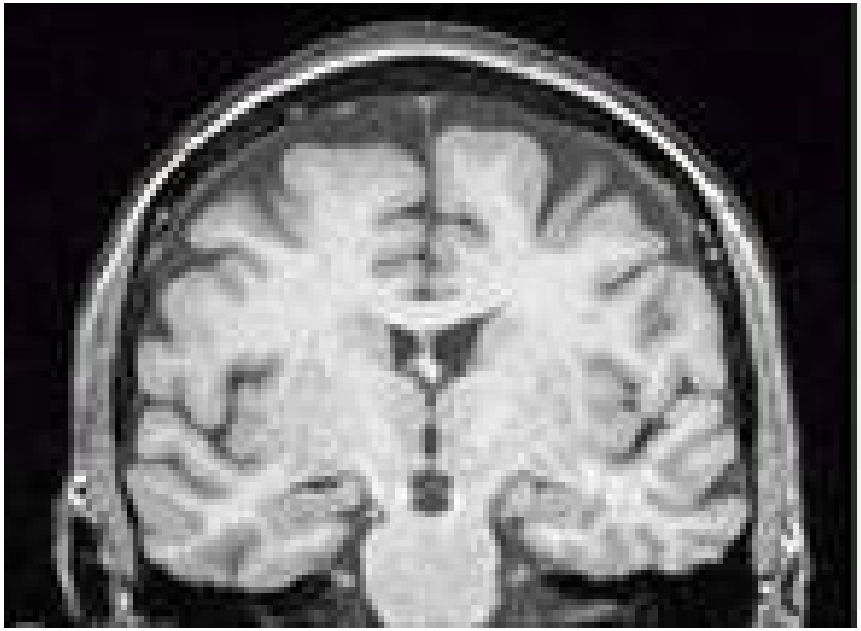
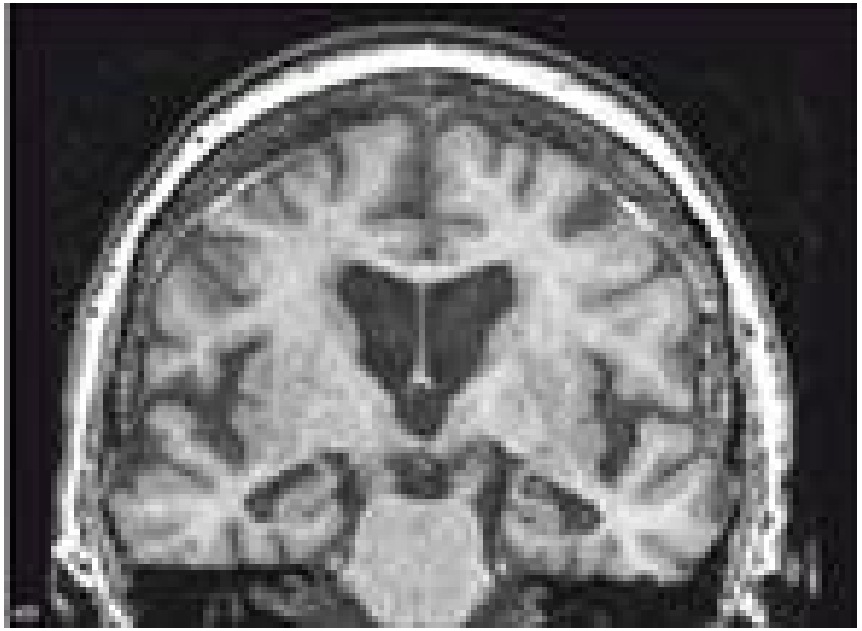
DSM IV

Risonanza Magnetica dell’Encefalo

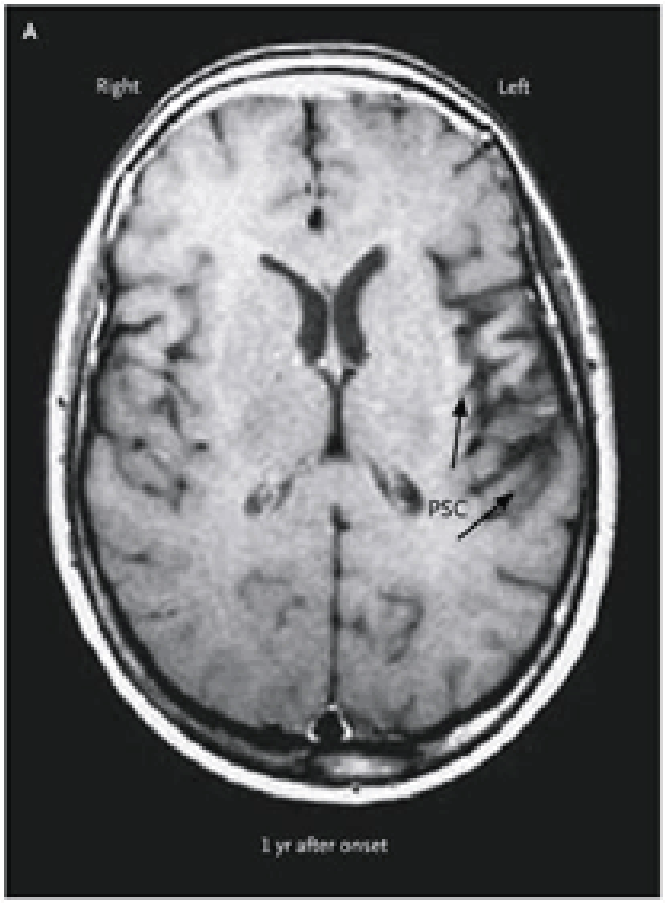


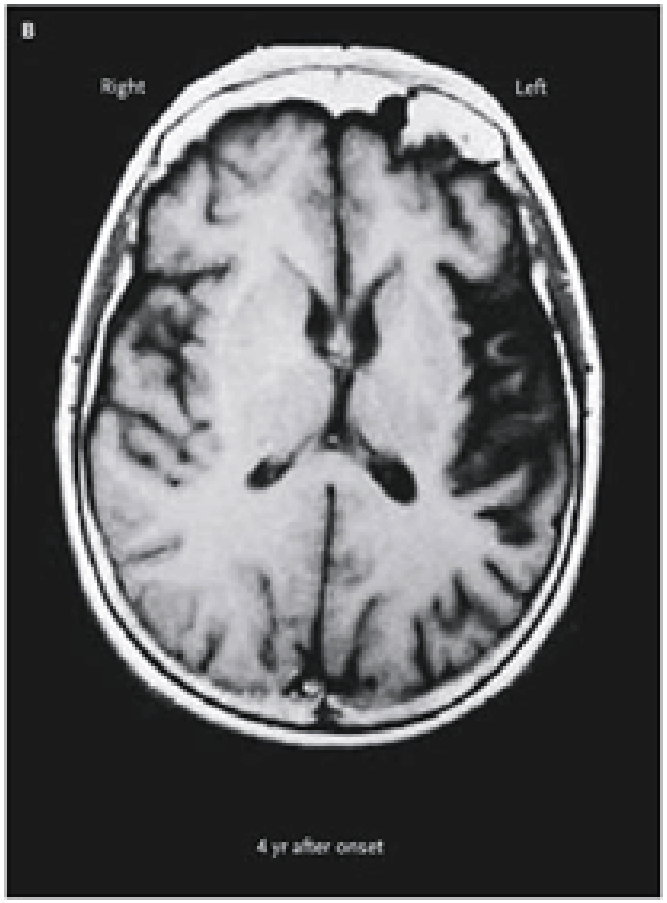
Soggetto sano



Paziente affetto da Malattia di Alzheimer

RM in paziente affetto da Afasia Primaria Progressiva, variante non fluente-agrammatica





1 anno dopo l'esordio

4 anni dopo l'esordio

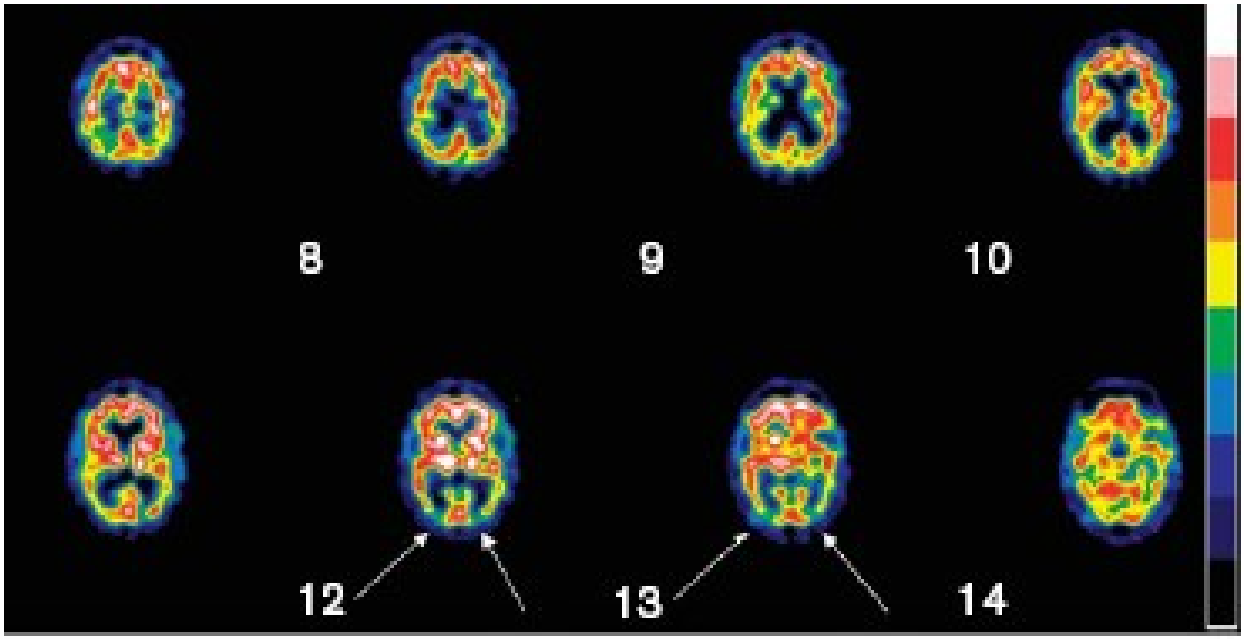
Markers liquorali di AD

ß42 amiloide

Proteina Tau totale

Proteina Tau fosforilata

PET in DLB



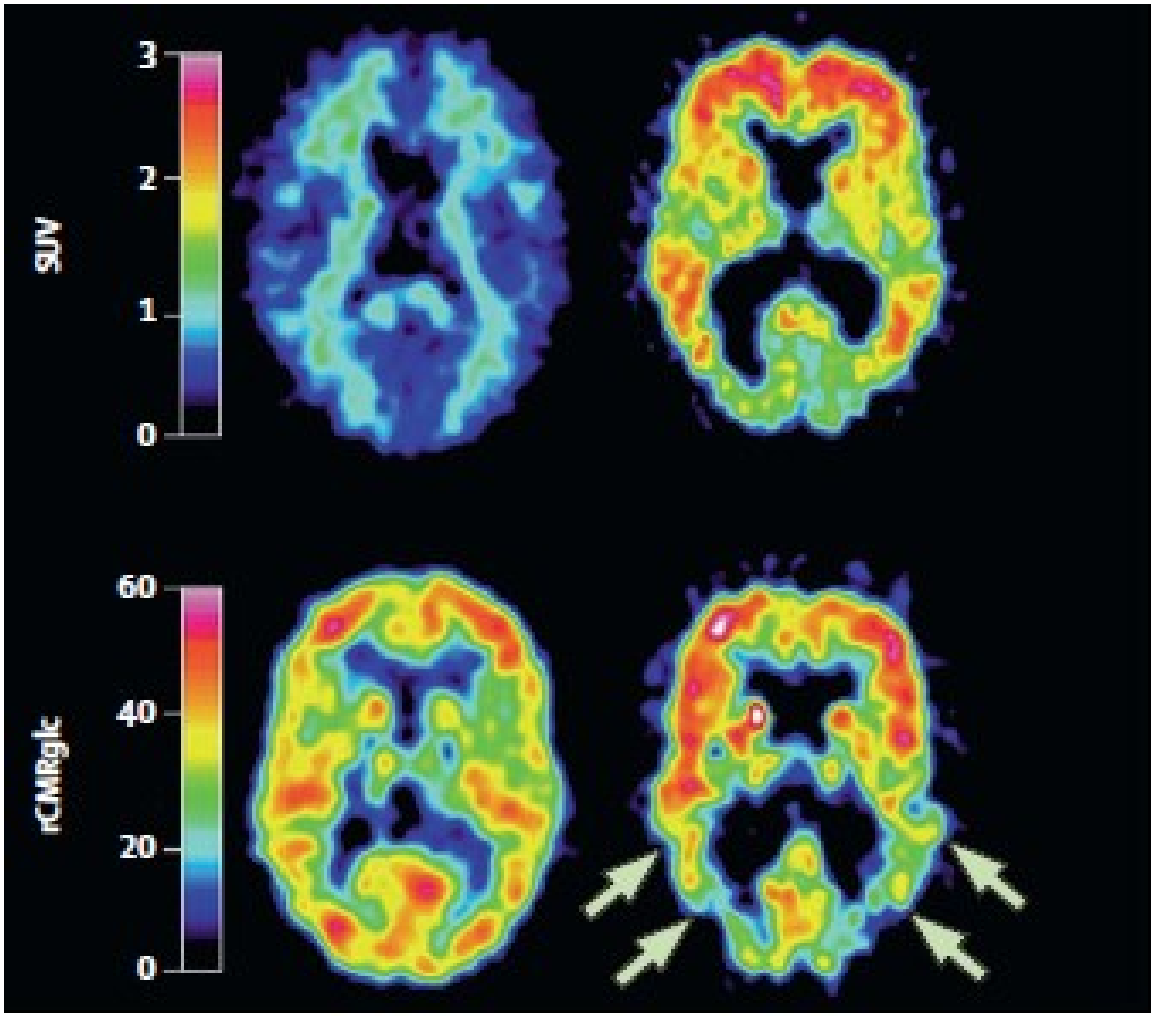
Ridotta perfusione nelle cortecce associative posteriori con evidente interessamento occipitale bilaterale

Kemp and Holmes, 2007

Neuroimaging funzionale in soggetto di controllo
ed in paziente affetto da Malattia di Alzheimer

PET con marcatore per l’amiloide

PET con fluoro-desossiglucosio



Aspetti genetici della Malattia di Alzheimer

Geni Causativi

Gene	Cromosoma	effetto genetico	Quadro clinico
APP	21	mutazione (n=32)	Aut.Dom., esordio precoce Aut. Rec. 1 caso, 36 anni
Presenilina 1	14	mutazione (n=177)	Aut. Dom., esordio precoce
Presenilina 2	1	mutazione (n=14)	Aut. Dom., esordio precoce e tardivo

Geni di Suscettibilità

Gene	Cromosoma	effetto genetico	Quadro clinico
Apolipoporteina E	19	suscettibilità	AD familiare ad esordio tardivo e sporadica

Altri possibili geni candidati per una aumentata suscettibilità alla malattia:
SORL-1 **(proteina coinvolta nel riciclaggio dell'APP),** ***CH25H*** **(coinvolto nel processing dell'APP),** ***ACE*** **(coinvolto nella regolazione della pressione arteriosa e nella degradazione di Abeta),** ***GAB2*** **(nella iperfosforilazione della tau),** ***CHRNB2*** **(recettore nicotinico, media l'effetto tossico di Abeta),** ***Transferrina*** **(ferro ruolo nella aggregazione della tau iperfosforilata in filamenti insolubili).**
Recentemente associati alla malattia (*CR1, CLU*, coinvolti nella *clearance* di Abeta dalla barriera ematoencefalica e *PICALM*, ruolo nella plasticità sinaptica).

DEMENZA

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(McKhann et al., 1984)

I deficit cognitivi devono essere tali da interferire con lo svolgimento delle abituali attività lavorative e sociali

DSM IV

Mild Cognitive Impairment

- Disturbo soggettivo di memoria, preferibilmente confermato da un familiare
- Altre funzioni cognitive nella norma
- Non difficoltà rilevanti nella vita quotidiana
- Assenza di demenza e disturbi psichiatrici
- Deficit mnesico obiettivabile, per età e scolarità

Petersen, 1999-2001

MCI: eterogeneità clinica

MCI
(amnestico)

→ Malattia di Alzheimer

MCI
(lieve compromissione di più domini cognitivi)

→ Malattia di Alzheimer
Demenza Vascolare

MCI
(compromissione di un solo dominio cognitivo, non la memoria)

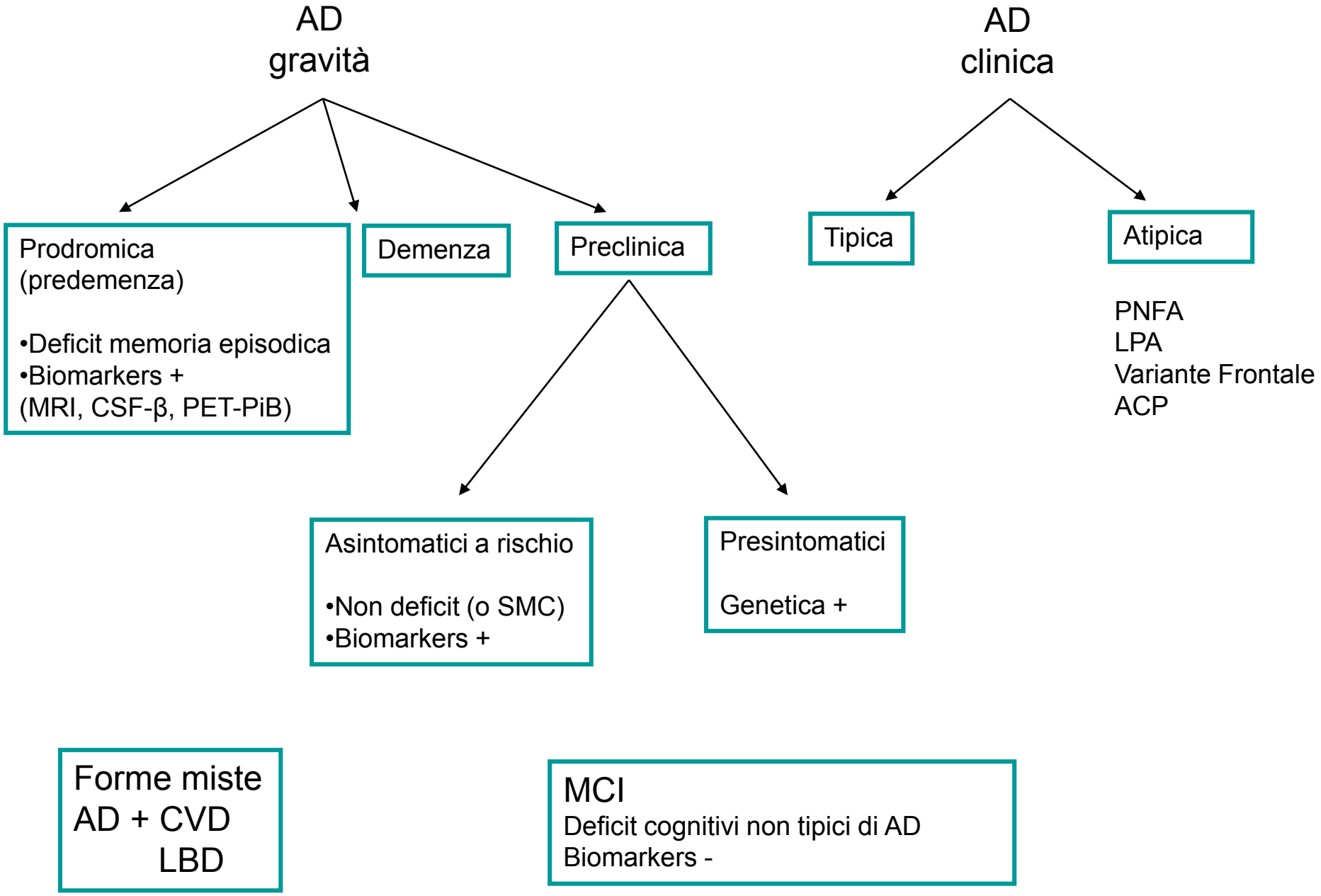
→ Demenza Vascolare
Demenza a Corpi di Lewy
Malattia di Parkinson
Malattia di Alzheimer
Demenza Frontotemporale
Afasia Primaria Progressiva

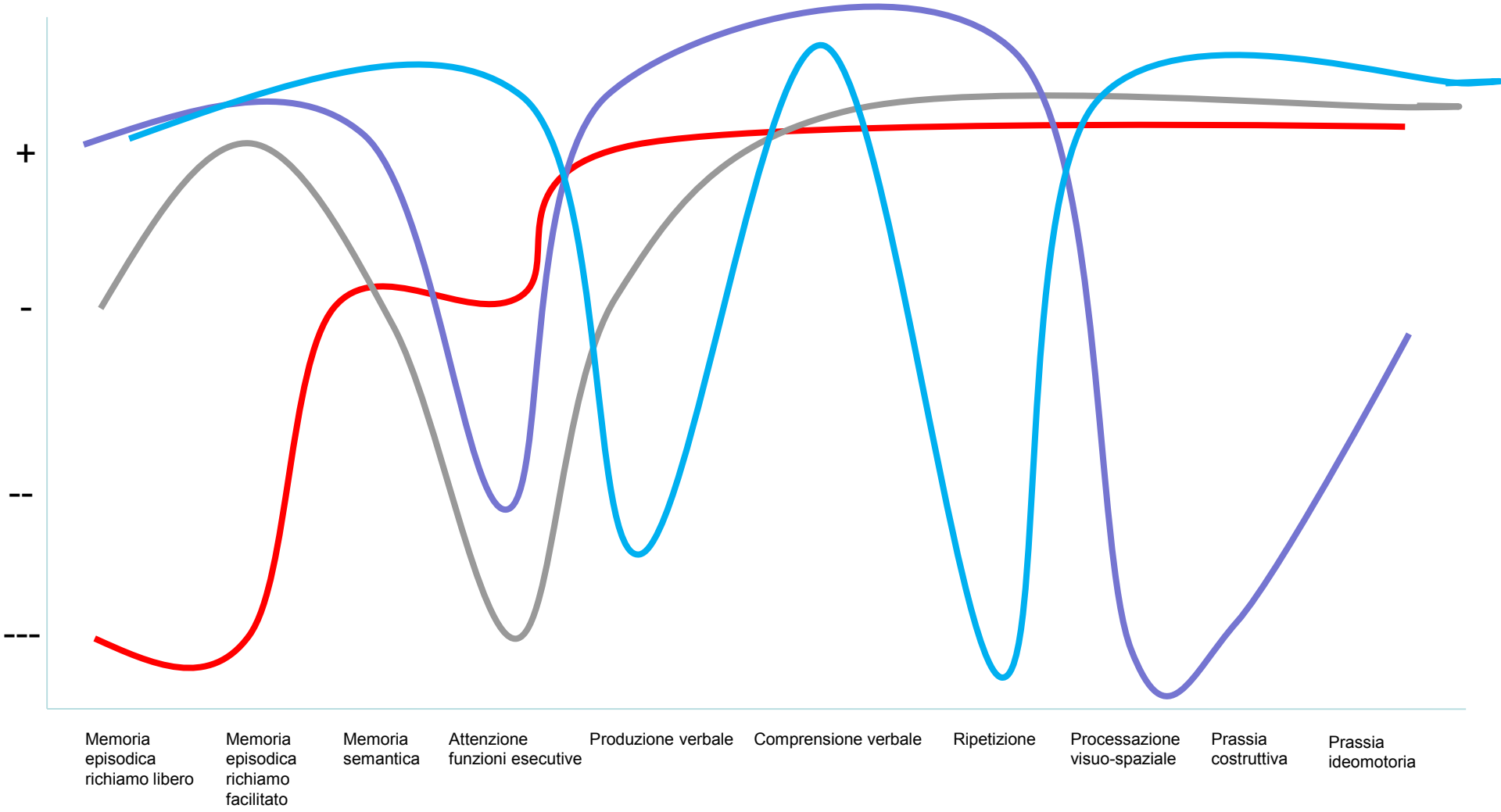
Petersen, 2001

Disturbo Neurocognitivo Minore

Deficit cognitivi associati a patologie mediche e neurologiche come il trauma cranico, l'HIV, le patologie da uso di sostanze psicotrope, il diabete, gli stadi precoce/lievi della malattia cerebrovascolare o di malattie neurodegenerative come la malattia di Alzheimer.

DSM V


AD
gravità
AD
clinica
Prodromica
(predemenza)
•Deficit memoria episodica
•Biomarkers +
(MRI, CSF-β, PET-PiB)
Demenza
Preclinica
Tipica
Atipica
PNFA
LPA
Variante Frontale
ACP
Asintomatici a rischio
•Non deficit (o SMC)
•Biomarkers +
Presintomatici
Genetica +
Forme miste
AD + CVD
LBD
MCI
Deficit cognitivi non tipici di AD
Biomarkers -



MCI/AD iniziale

FTD-variante frontale

Atrofia Corticale Posteriore

Afasia Logopenica

Alzheimer's Disease ≠ Alzheimer's pathology

Alzheimer's pathology

This term refers to the underlying neurobiological changes responsible for AD that span the earliest pathogenic events in the brain and that include specific neuronal brain lesions (senile neuritic plaques and neurofibrillary tangles), synaptic loss, and vascular amyloid deposits within the cerebral cortex. This term can be applied irrespective of the existence of clinical manifestation.

Alzheimer's disease (AD)

This diagnostic label is now restricted to the clinical disorder that starts with the onset of the first specific clinical symptoms of the disease, and encompasses both the predementia and dementia phases. AD thus refers to the whole spectrum of the clinical phase of the disease and is not restricted to the dementia syndrome. The diagnosis is now established in vivo and relies on a dual clinicobiological entity that requires the evidence of both specific memory changes and in-vivo markers of Alzheimer's pathology that can include: CSF amyloid β, total tau, and phospho-tau; retention of specific PET amyloid tracers; medial temporal lobe atrophy on MRI; and/or temporal/parietal hypometabolism on fluorodeoxyglucose PET. The clinical phenotype can be typical or atypical. Additionally, two different stages might still be meaningful: a prodromal and a dementia phase.

Prodromal AD (also called "predementia stage of AD")

This term refers to the early symptomatic, predementia phase of AD in which (1) clinical symptoms including episodic memory loss of the hippocampal type (characterised by a free recall deficit on testing not normalised with cueing) are present, but not sufficiently severe to affect instrumental activities of daily living and do not warrant a diagnosis of dementia; and in which (2) biomarker evidence from CSF or imaging is supportive of the presence of AD pathological changes. This phase is now included in the new definition of AD. The term of prodromal AD might disappear in the future if AD is considered to encompass both the predementia and dementia stages.

AD dementia

This term refers to the phase of AD during which cognitive symptoms are sufficiently severe to interfere with social functioning and instrumental activities of daily living, a threshold that is considered to define dementia in association with changes in episodic memory and in at least one other cognitive domain. It might still be meaningful to identify the dementia threshold for clinical trials or social/economic evaluations.

Preclinical states of AD (including both "asymptomatic at-risk state for AD" and "presymptomatic AD")

These terms refer to the long asymptomatic stage between the earliest pathogenic events/brain lesions of AD and the first appearance of specific cognitive changes. Traditionally, a preclinical or asymptomatic phase was recognised post mortem by evidence of histological changes typical of Alzheimer's pathology in individuals considered as cognitively normal before death. Today, two preclinical states can be isolated in vivo:

- *Asymptomatic at-risk state for AD*—this state can be identified in vivo by evidence of amyloidosis in the brain (with retention of specific PET amyloid tracers) or in the CSF (with changes in amyloid β, tau, and phospho-tau concentrations). In the absence of knowledge about the value of these biological changes to predict the further development of the disease, the asymptomatic phase of AD should still be referred to as an "at-risk state for AD".
- *Presymptomatic AD*—this state applies to individuals who will develop AD. This can be ascertained only in families that are affected by rare autosomal dominant monogenic AD mutations (monogenic AD).

Typical AD

This term refers to the most common clinical phenotype of AD, which is characterised by an early significant and progressive episodic memory deficit that remains dominant in the later stages of the disease, and is followed by or associated with other cognitive impairments (executive dysfunction, language, praxis, and complex visual processing impairments) and neuropsychiatric changes. The diagnosis is further supported by one or more in-vivo positive biomarkers of Alzheimer's pathology.

Atypical AD

This term refers to the less common and well characterised clinical phenotypes of the disease that occur with Alzheimer's pathology. These clinical syndromes include primary progressive non-fluent aphasia, logopenic aphasia, frontal variant of AD, and posterior cortical atrophy. In the presence of one of these clinical presentations, the diagnosis of AD is supported by in-vivo evidence of amyloidosis in the brain (with retention of specific amyloid labelling radioligands) or in the CSF (with changes characteristic of Alzheimer's pathology in amyloid β, tau, and phospho-tau concentrations).

Mixed AD

This term refers to patients who fully fulfil the diagnostic criteria for typical AD and additionally present with clinical and brain imaging/biological evidence of other comorbid disorders such as cerebrovascular disease or Lewy body disease.

Mild cognitive impairment (MCI)

This term applies to individuals with measurable MCI in the absence of a significant effect on instrumental activities of daily living. This diagnostic label is applied if there is no disease to which MCI can be attributed. It remains a term of exclusion for individuals who are suspected to have but do not meet the proposed new research criteria for AD, in that they deviate from the clinicobiological phenotype of prodromal AD because they have memory symptoms that are not characteristic of AD or because they are biomarker negative.

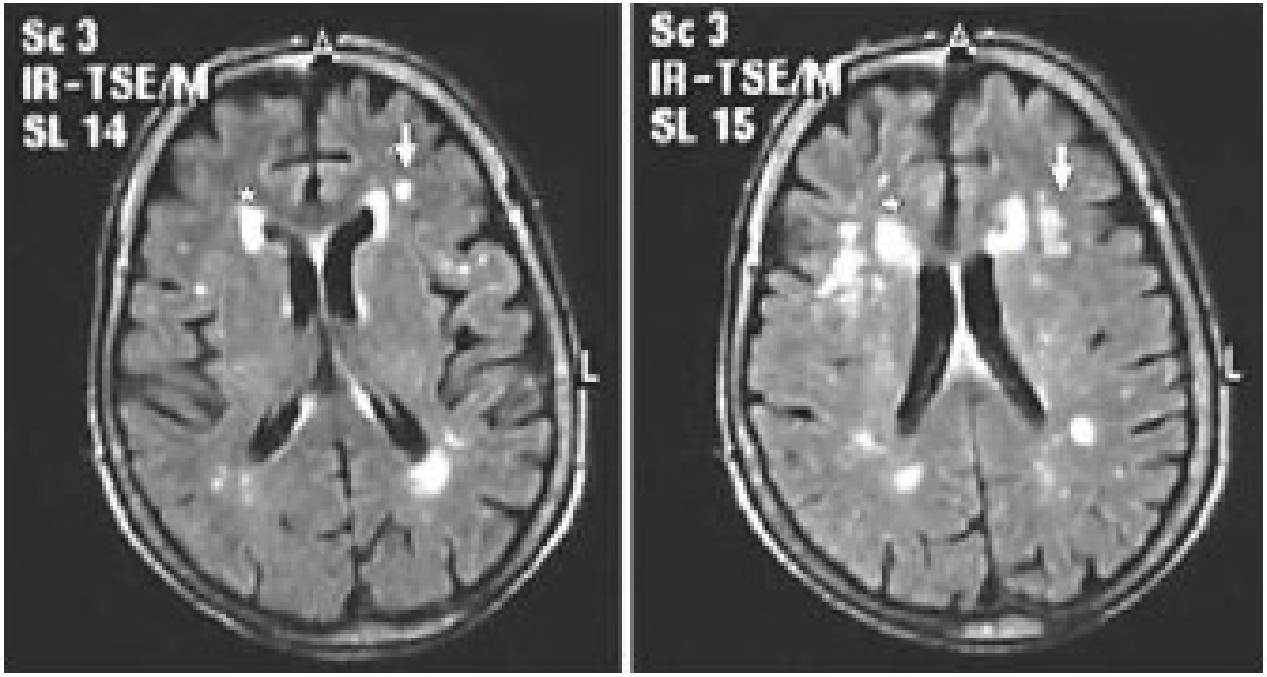
	AD diagnosis	Presence of impairment on specified memory tests	Evidence of biomarkers in vivo	Additional requirements
Typical AD	Yes	Required	Required	None
Atypical AD	Yes	Not required	Required	Specific clinical presentation
Prodromal AD	Yes	Required	Required	Absence of dementia
AD dementia	Yes	Required	Required	Presence of dementia
Mixed AD	Yes	Required	Required	Evidence of comorbid disorders
Preclinical AD				
Asymptomatic at risk for AD	No	Not present	Required	Absence of symptoms of AD
Presymptomatic AD	No	Not present	Not required	Absence of symptoms of AD and presence of monogenic AD mutation
Mild cognitive impairment	No	Not required	Not required	Absence of symptoms or biomarkers specific for AD

AD=Alzheimer's disease.

Table 2: **Comparative features of the different conditions described in the new lexicon according to the new research criteria framework[6]**

- Il fenotipo clinico appare determinato dalla disfunzione di strutture neuronali deputate allo svolgimento di specifici processi cognitivi e comportamentali
- Tale disfunzione è secondaria alla progressiva neurodegenerazione di specifiche aree o circuiti
- Il quadro clinico non dipende dalla natura della lesione, ma dalla sua sede

Alzheimer's Disease: Role of Size and Location of White Matter Changes in Determining Cognitive Deficits



86 AD patients

Fig. 1. FLAIR MRI images showing examples of periventricular (asterisks) and subcortical (arrows) white matter hyperintensities.

Bracco et al., 2005

Malattia di Alzheimer: nuovo lessico

- Deficit della memoria episodica
- Atrofia delle strutture temporo-mesiali alla RM
- Alterazioni dei biomarkers liquorali (beta-amiloide, tau totale, tau fosforilata)
- Neuroimaging funzionale: ipometabolismo temporo-parietale bilaterale alla PET/ visualizzazione dell'amiloide
- Intero spettro di malattia, comprese le fasi prodromica e preclinica

Dubois et al., 2007, 2011