Società Medico Chirurgica di Ferrara dal 1846


RENDICONTO
DELLE ADUNANZE
MEDICO-CHIRURGICA
DI FERRARA

Deficit sensoriali e disturbi cognitivi

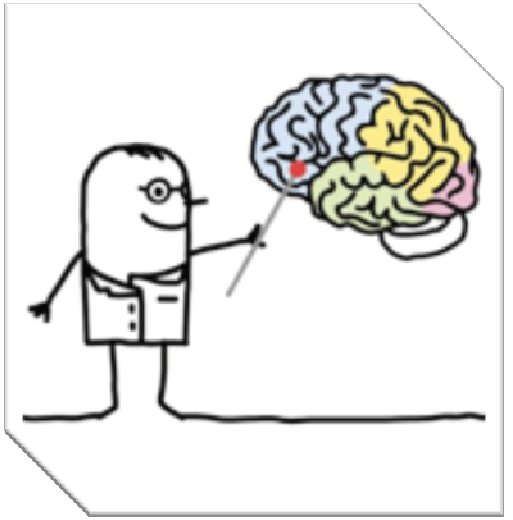
Sabato 5 marzo 2016

Aula Magna Nuovo Arcispedale S. Anna
Cona, Ferrara

Malattie neurologiche e deficit cognitivi

Valeria Tugnoli
U.O.C. di Neurologia
D.A.I. Neuroscienze-Riabilitazione – Ferrara
v.tugnoli@ospfe.it

Disordini Cognitivi



Funzioni Cognitive di Base

- **Attenzione**→isolare le informazioni pertinenti e rilevanti rispetto a un problema o a un contesto, fra le infinite informazioni in arrivo sia da dentro sia da fuori di noi
- **Memoria**→ riceve dai sistemi di apprendimento, ordina e archivia, recupera le informazioni
- **Percezione**→ elabozione degli stimoli interni e esterni che arrivano dai canali sensoriali
- **Ragionamento**→ responsabile dei processi logici, tra cui il linguaggio.

Funzioni Cognitive Complesse

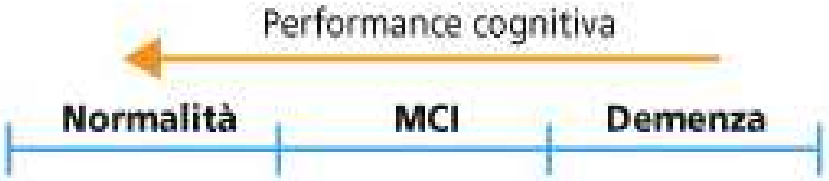
- **Orientamento** nello spazio, nel tempo, nelle relazioni con sè e con gli altri
- **Linguaggio** come competenza di gestire sistemi logici e simbolici
- **Abilità prassiche** sia come pianificazione, sia come esecuzione di prodotti finiti
- **Funzioni esecutive** che supervisionano tutte le funzioni cognitive dei livelli inferiori, se danneggiate, causano disturbi della intenzionalità
- **Intelligenza** è in realtà molte intelligenze ovvero molte funzioni che risolvono problemi complessi.

AGENDA

1. ***<u>Malattie Neurologiche</u>***
   - degenerative
   - infiammatorie
   - vascolari

2. ***<u>Deafferentazione/Paralisi</u>*** → Plasticità

Continuum tra declino cognitivo lieve (MCI) e demenza



MCI si riferisce allo stato cognitivo e funzionale compreso tra invecchiamento normale e malattia di Alzheimer molto lieve *(Petersen, 2004)*.

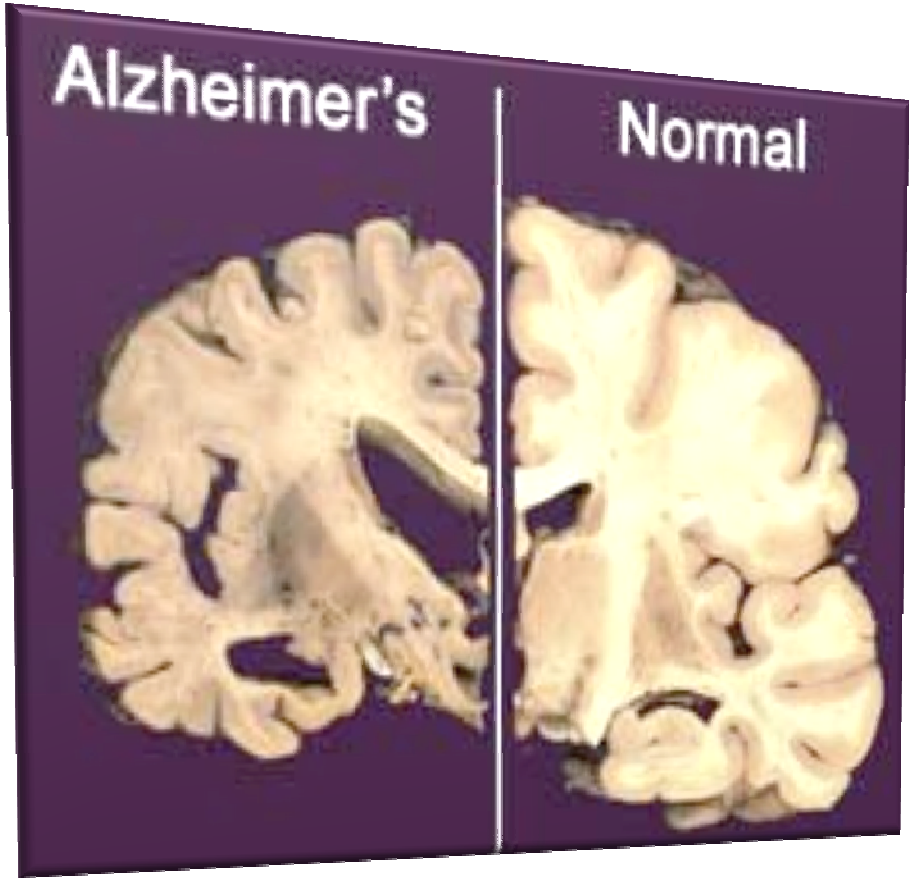
Ambiti (domini)

Almeno 2 dei seguenti domini comportamentali o cognitivi

- Deficit di apprendimento e di memoria di nuove informazioni
- Deficit di ragionamento, pianificazione, decisione
- Deficit visuospaziale o aprassici
- Deficit delle funzioni linguistiche
- Alterazioni della personalità e del comportamento, fra le quali
  - insolite variazioni dell'umore, agitazione, deficit di motivazione, iniziativa, apatia, ritiro sociale, perdita di interesse per le attività svolte in precedenza, comportamenti ossessivi o compulsivi, comportamenti socialmente inaccettabili

La differenziazione demenza/MCI si basa sulla compromissione delle ADL

(McKhann GM et al, 2011)



- **Malattia di Alzheimer**
- **DCL**
- **Malattia di Pick (FTD)**

CORTICALE

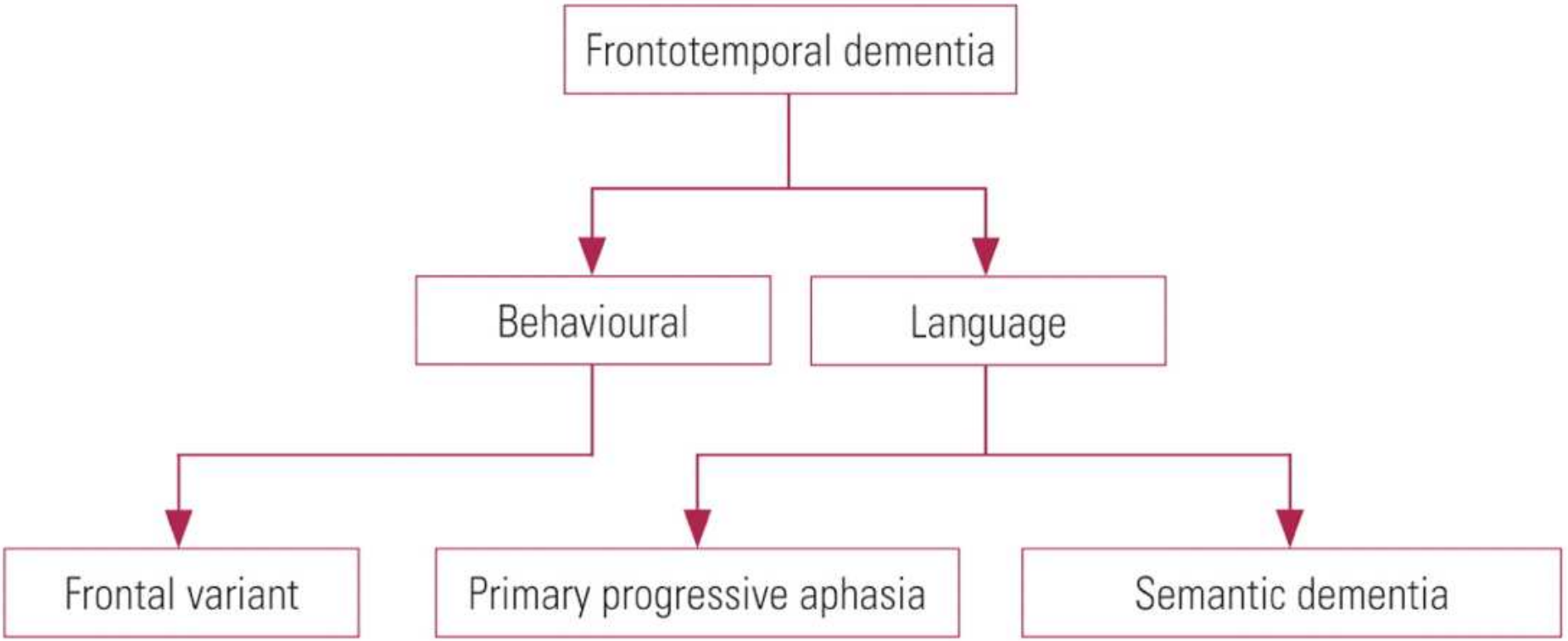
memoria: disturbo di apprendimento

cognitività: deficit corticali (aprassia, acalculia, agnosia, deficit pensiero astratto, critica e giudizio)

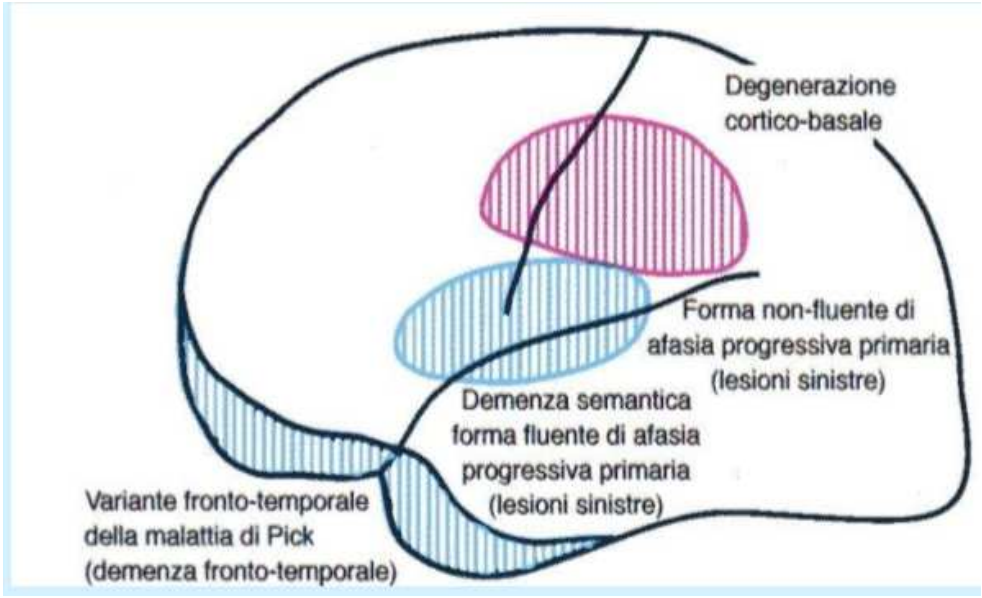
affettività: disinibizione/indifferenza

motilità: normale

linguaggio: afasia



Variants of frontotemporal dementia.



- **Demenza Vascolare**
- **Malattia di Parkinson**
- **Corea di Huntington**

- **Degen. Cortico-basale**
- **PSP**

SOTTOCORTICALE

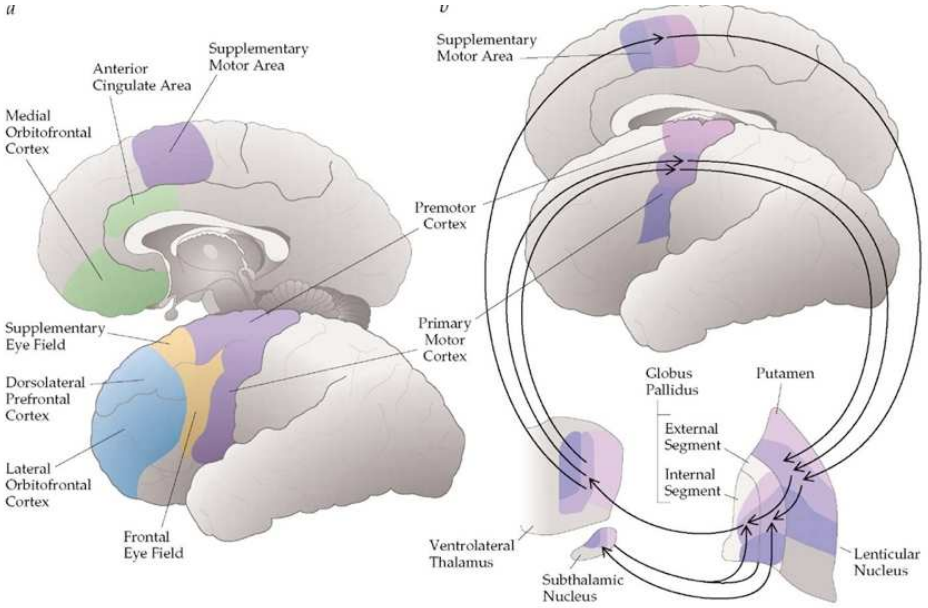
memoria: disturbo di richiamo del materiale mnesico; apprendimento discreto

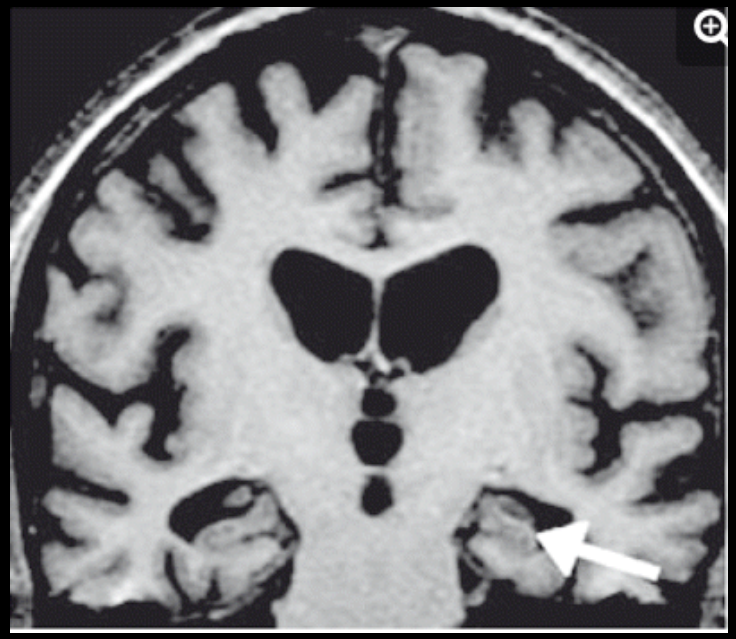
cognitività: rallentamento dei processi cognitivi; incapacità di utilizzo di conoscenze acquisite

affettività: apatia

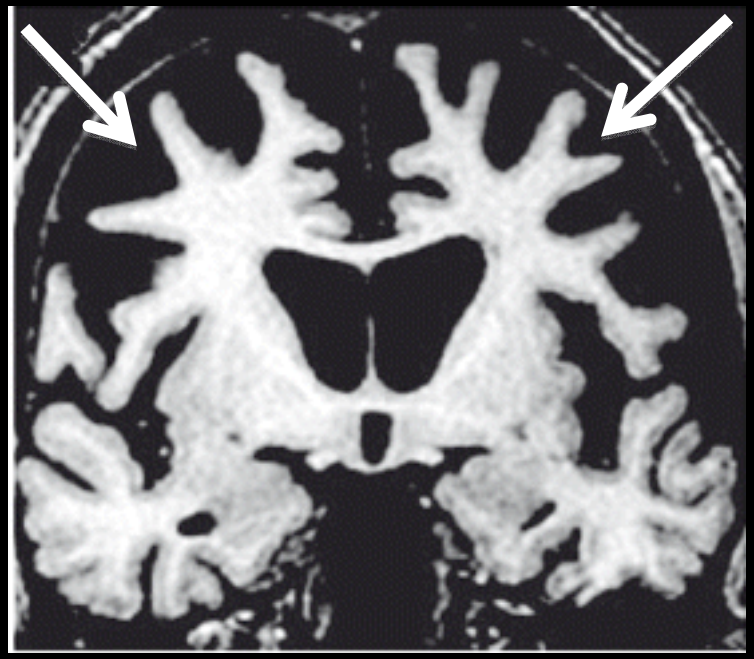
motilità: segni extrapiramidali

linguaggio: disartria e ipofonia

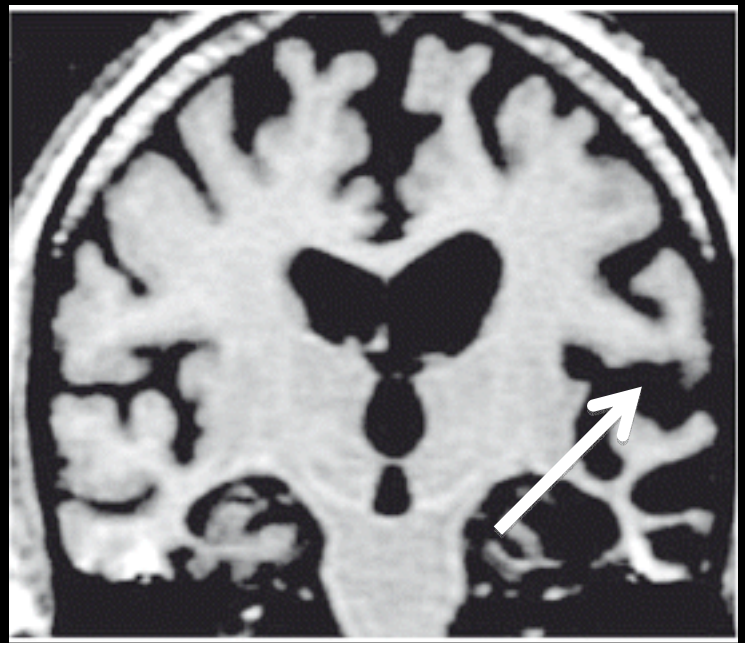




ALZHEIMER DISEASE



FRONTO-TEMPORAL DISEASE (PICK)



PRIMARY PROGRESSIVE APHASIA

Demenze degenerative	Demenze vascolari	Demenze post-infettive e\o infiammatorie	Demenze da sostanze tossiche e farmaci	Demenze da malattie endocrine e metaboliche	Demenze Post-traumatiche
-Malattia di Alzheimer	D. multinfartuale	-da meningo-encefaliti	-da Alcol	-della tiroide, delle paratiroidi,dell'asse ipofisi-surreni,	Demenze da tumori, ematomi, ascessi cerebrali
-Demenza con corpi di Lewy	-D. da singoli infarti in sedi strategiche	-da Sclerosi multipla e Malattie demielinizzanti di altro tipo	-da metalli pesanti	-da ipoglicemia (in diabete mellito non equilibrato, da insulinoma ecc.)	Demenze da stati carenziali
-Demenza Fronto-Temporale o Pick-Complex	-D. da patologia dei piccoli vasi	-da malattie autoimmunitarie sistemiche	-da composti organici	-da insufficienza renale cronica	Demenze paraneoplastiche
-Parkinson-Demenza, Demenza-SLA e Parkinson-Demenza-SLA	-D. da ipoperfusione (anche da terapia ipotensiva incongrua : vedi sopra)	-da Prioni (Mal. di Creutzfeldt-Jakob e Variante della "mucca pazza"	-da farmaci vari (fra cui psicofarmaci, soprattutto se abbinati ad alcol, anticolinergici ecc.	-da disidratazione (gli anziani ! soprattutto se sono febbrili o assumono diuretici !)	
-Paralisi sopranucleare progressiva o Mal. di Steele-Richardson-Olszewski	-D. da emorragia (e)	-da HIV (AIDS)			
-Idrocefalo c.d. normoteso primitivo					
-Corea di ntington					

Etiologia

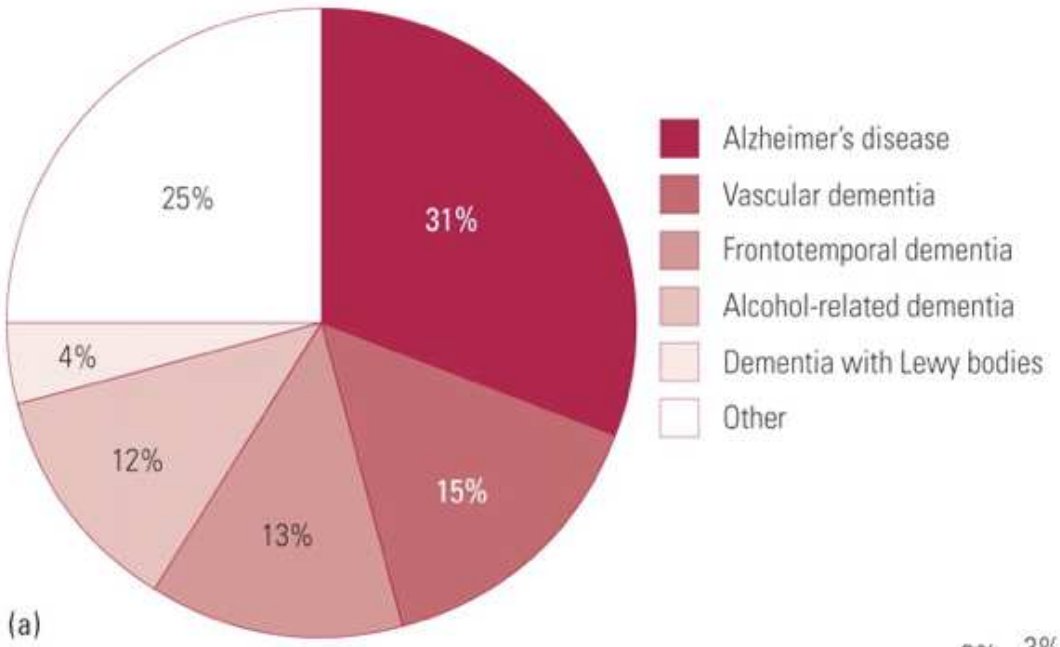
Prognosi - Demenze

Reversibili

- **metabolica** (ipotiroidismo, iperparatiroidismi, malassorbimento, deficit vit.B12, m.epatica, pancreatica, alcool)
- iatrogena
- **ematoma subdurale**
- **idrocefalo normoteso**
- encefaliti

Irreversibili

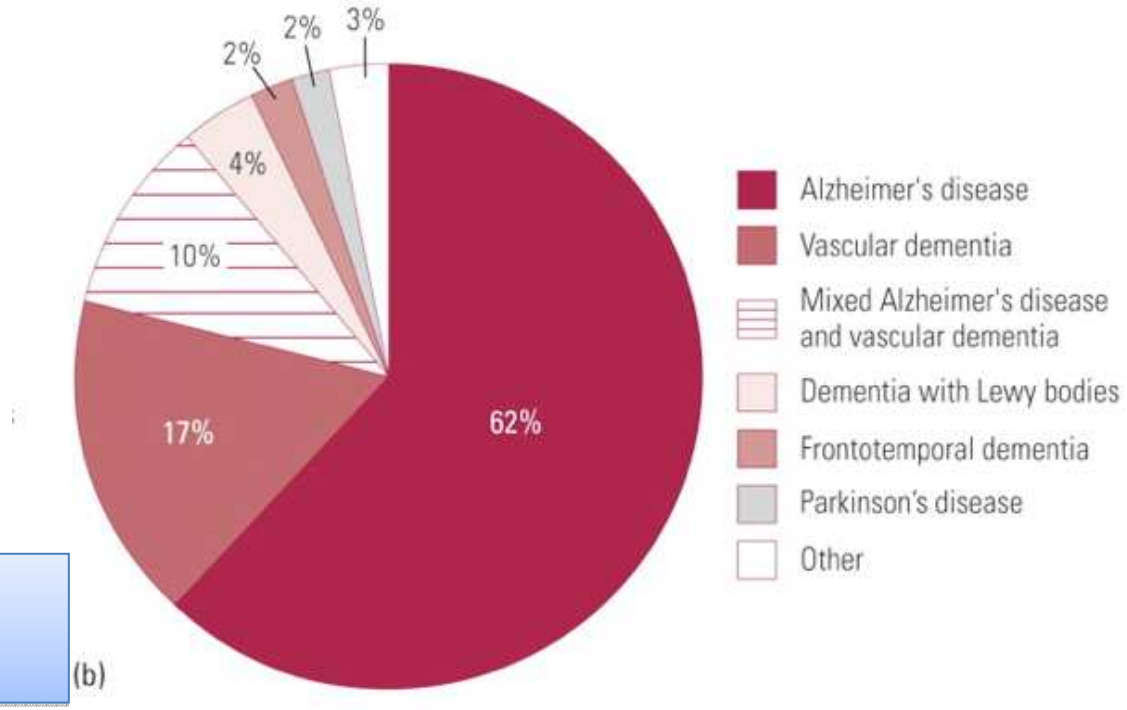
- m.Alzheimer
- d.vascolare
- MP, PSP, CB, DCL
- Sindrome di Pick
- m.Creutzfeld-Jacob
- m.Huntigton
- SM, Neuro-LES
- post-traumatiche
- AIDS dementia complex



young-onset dementia

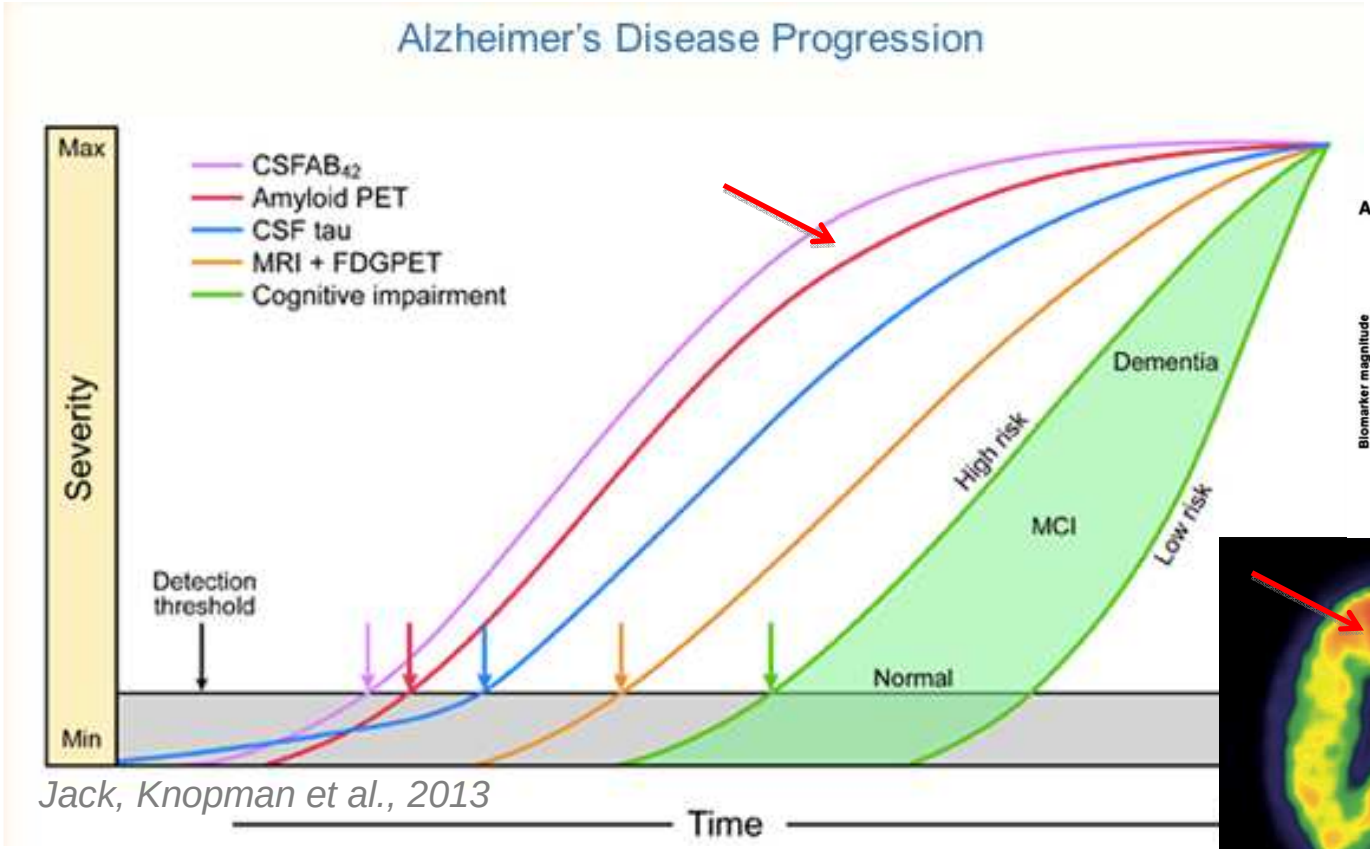
Sampson et al 2004

30-64 yrs=78.2/100 000 men and 56.4/100 000 women.

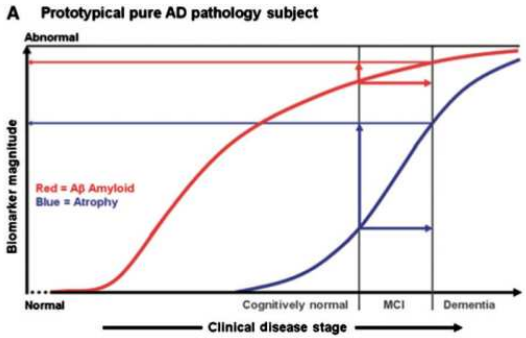


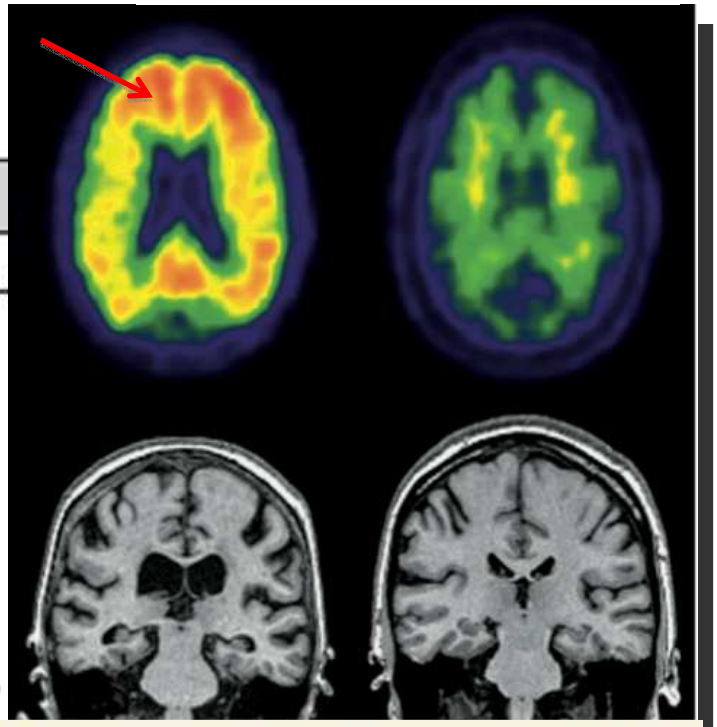
late-onset dementia

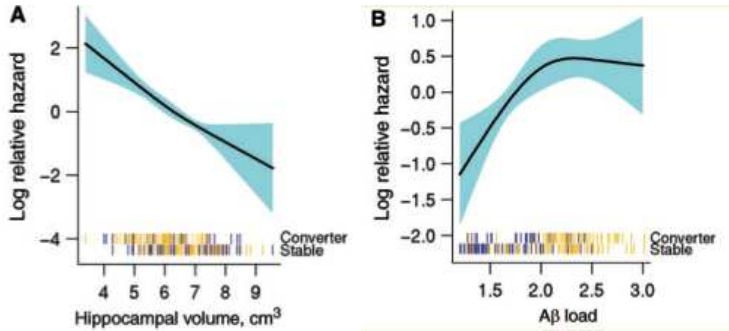
Knapp et al 2007



Jack, Knopman et al., 2013

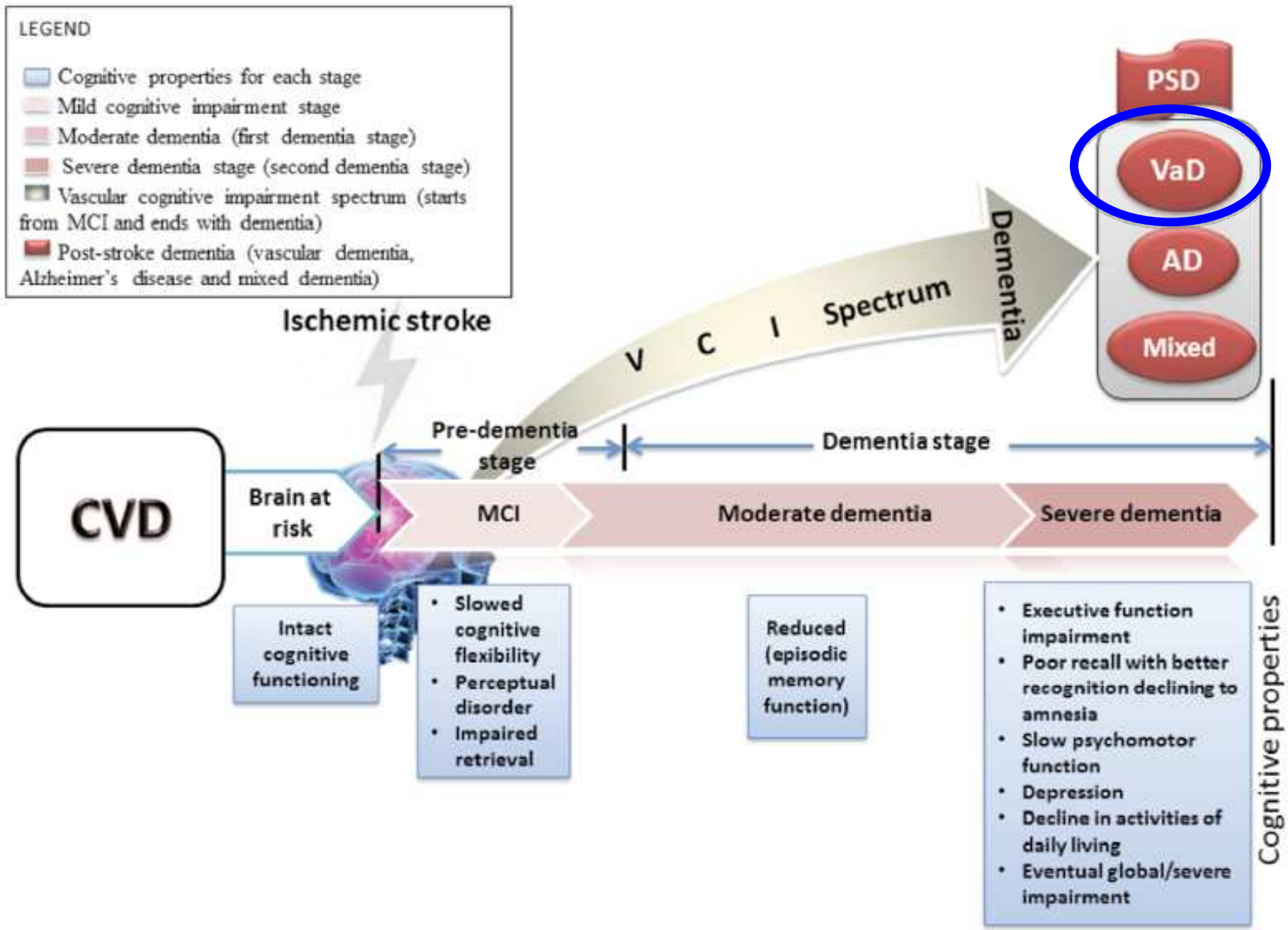






Jack et al., 2010

Figure 1 Illustrative images. *Left*: Mild cognitive impairment progressor, *Top*: positive PIB PET. *Bottom*: MRI illustrating atrophic hippocampi and ventricular enlargement. *Right*: Mild cognitive impairment non-progressor. *Top*: negative PIB PET with non-specific white matter retention but no cortical retention. *Bottom*: MRI illustrating normal hippocampi and no ventricular enlargement.


LEGEND
Cognitive properties for each stage
Mild cognitive impairment stage
Moderate dementia (first dementia stage)
Severe dementia stage (second dementia stage)
Vascular cognitive impairment spectrum (starts from MCI and ends with dementia)
Post-stroke dementia (vascular dementia, Alzheimer's disease and mixed dementia)
Ischemic stroke
V C I Spectrum
Dementia
PSD
VaD
AD
Mixed
CVD
Brain at risk
Pre-dementia stage
Dementia stage
MCI
Moderate dementia
Severe dementia
Intact cognitive functioning
Slowed cognitive flexibility
Perceptual disorder
Impaired retrieval
Reduced (episodic memory function)
Executive function impairment
Poor recall with better recognition declining to amnesia
Slow psychomotor function
Depression
Decline in activities of daily living
Eventual global/severe impairment
Cognitive properties

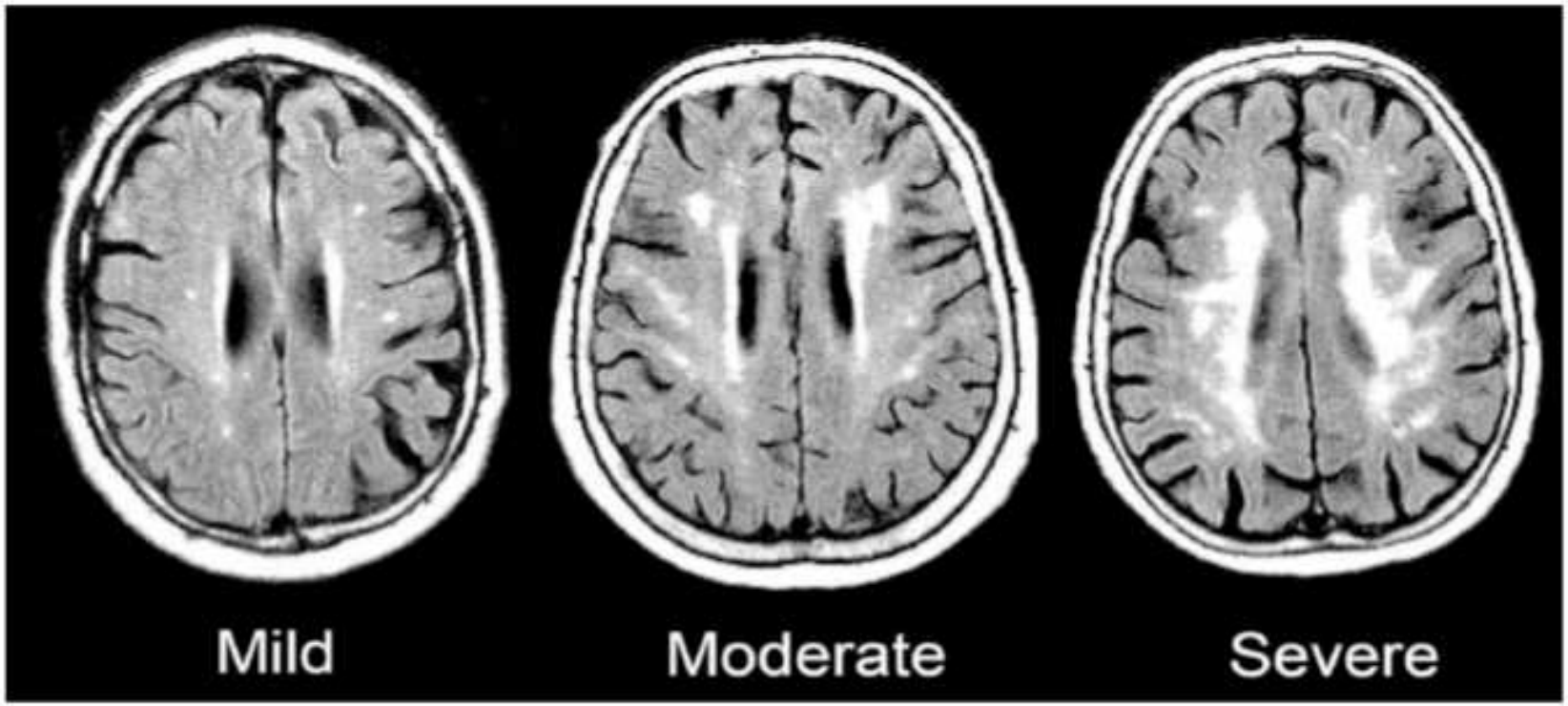
BMJ

RESEARCH

Changes in white matter as determinant of global functional decline in older independent outpatients: three year follow-up of LADIS (leukoaraiosis and disability) study cohort

Alterazioni età-correlate della sostanza bianca alla risonanza: leucoaraiosi (TC), aree iperintense in T2 alla RM, focali lievi o ampie confluenti, in circa 1/3 dei casi

Deficit cognitivo,moderato-severo, depressione, turbe della marcia, incontinenza urinaria sono i principali determinanti di perdita di indipendenza funzionale negli anziani



Microinfarti, deficit cognitivo, e deficit neurologici

Microinfarti

Sono frequenti in riscontri autoptici di pazienti con demenza vascolare o mista, MP o malattia Lewy body

→ Sono considerati predittori independenti di deficit cognitivo

Hanno prevalenza quasi doppia in paz. con demenza rispetto a paz. senza demenza

Si associano a infarti visibili, soprattutto infarti lacunari

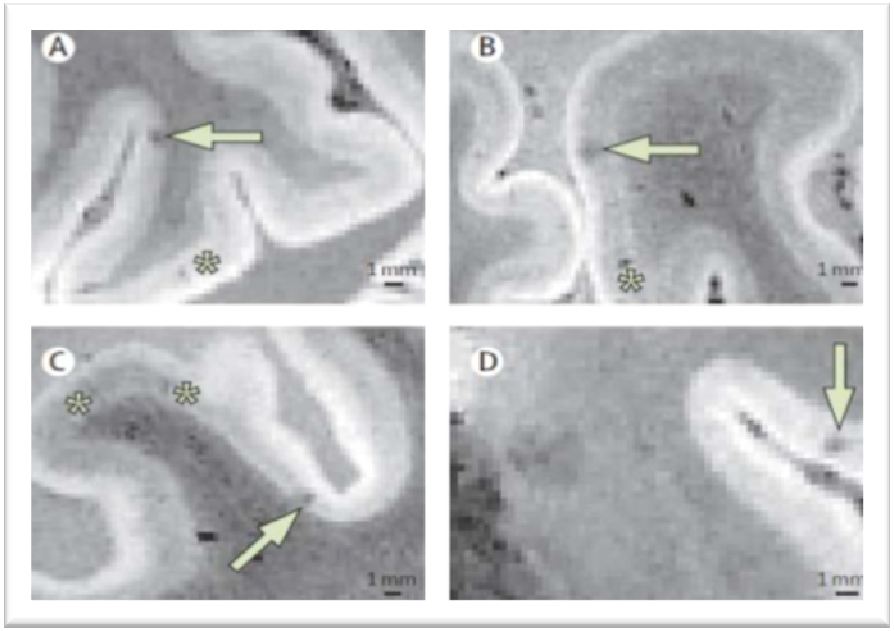
→ I microinfarti corticali sono associati a demenza più frequentemente di quelli sottocorticali

Le manifestazioni cliniche associate a microinfarti sono:

→ deficit cognitivo

disturbi della deambulazione

parkinsonismo



Patogenesi dei microinfarti

Meccanismi principali:

malattia vascolare occlusiva

ipoperfusione

embolie

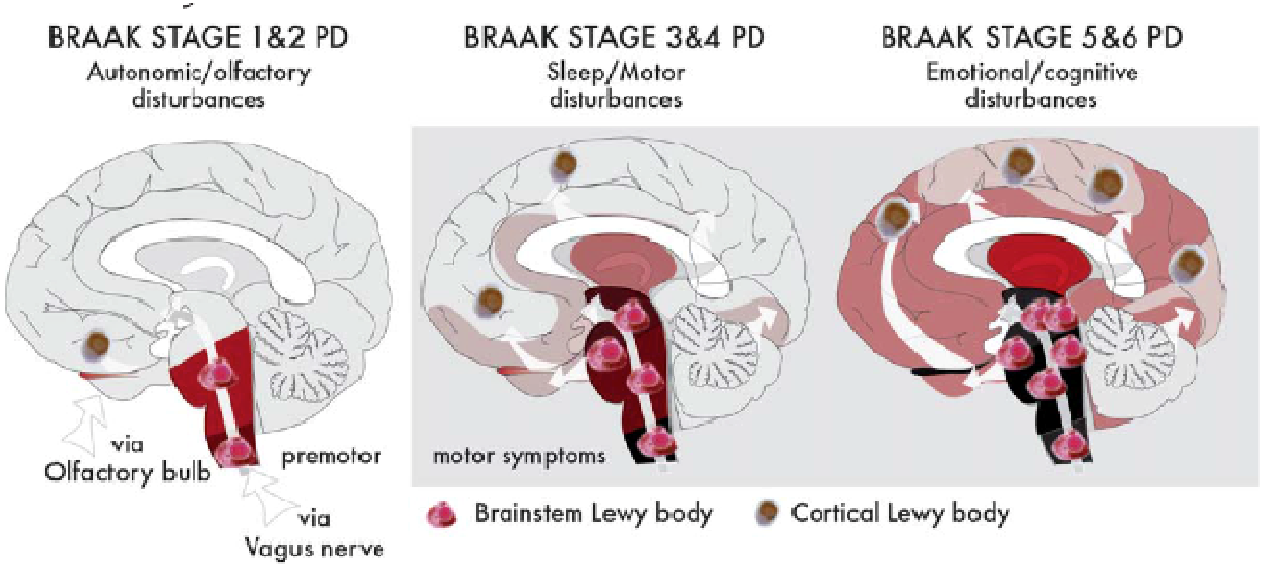
alterazioni della BEE

stress ossidativo

infiammazione

1 Brundin P, et al. Nat Rev Neurosci. 2008;9:741–745.

Gli stadi Braak e Braak



la sinnucleina si può trasferire per via sinaptica da cellula a cellula

La PDD è un'entità clinica caratterizzata da:

- progressione tipica (inizia con PD per molti anni prima che compaia la demenza)
- **deficit esecutivi, attentivi, mnestici e funzionali**
- disturbi neuropsichiatrici di tipo **psicotico**

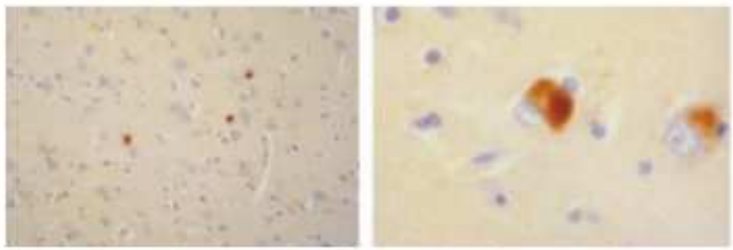
La PDD si associa ad un deficit di trasmissione colinergica

- Gli inibitori della colinesterasi sono i farmaci di prima scelta

Profilo cognitivo del PDD

(Emre M Lancet Neurol 2003)

- **Deficit attentivo** con fluttuazioni, concentrazione, dual-tasking
- **Bradifrenia**
- **Deficit delle funzioni esecutive**
    - ragionamento astratto, soluzione dei problemi, pianificazione, prendere decisioni
    - elaborazione, mantenimento e modificazione di regole
    - difficoltà nei comportamenti “internally cued”
    - poco comuni gli errori di perseverazione (diff con PSP)
- **Deficit di memoria**
    - deficit di rievocazione libera, memoria procedurale, prospettica e di lavoro
    - beneficio da suggerimenti esterni
    - preservato il riconoscimento
- **Deficit visuospaziali**
- Linguaggio preservato (eccetto fluenza verbale)
- Prassia preservata
- Alterazioni comportamentali e di personalità



Corpi di Lewy in un pz con PD che sviluppò successivamente PDD

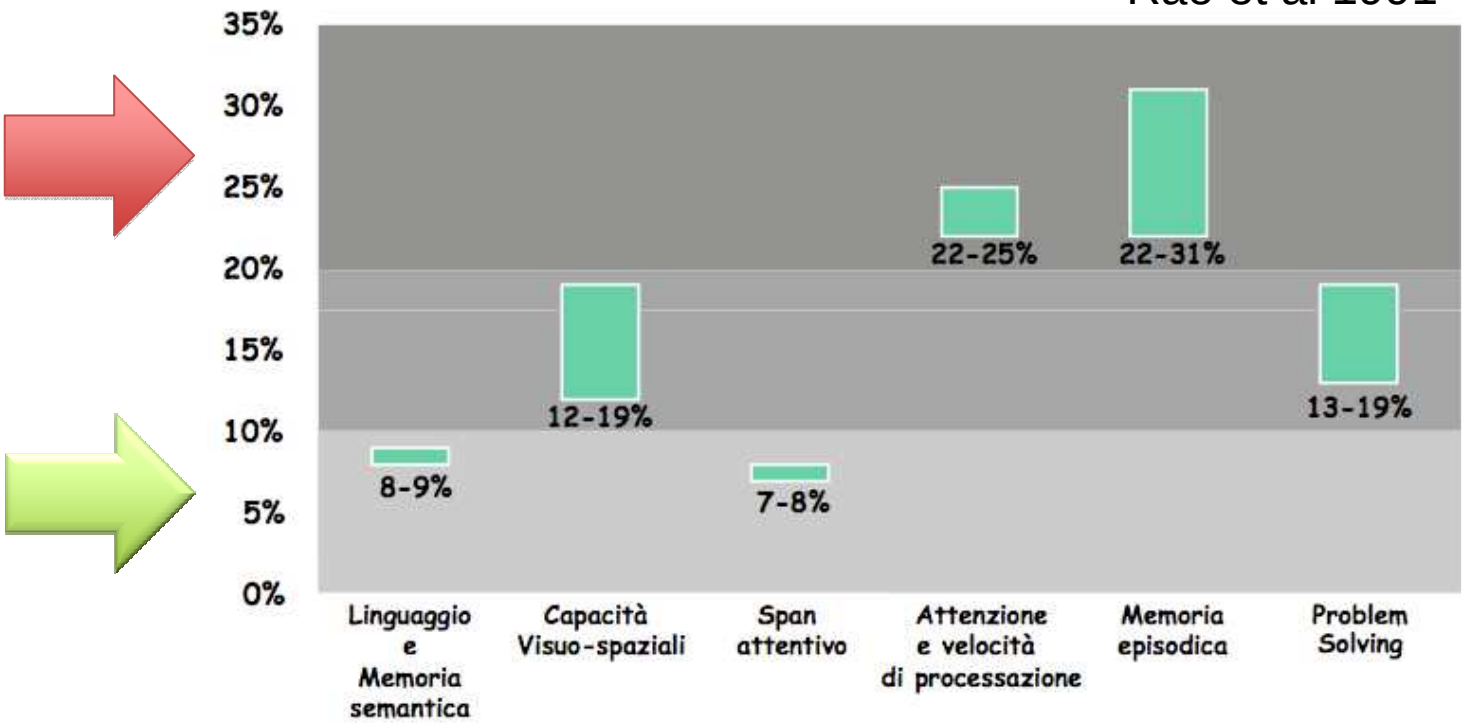
Disordini Cognitivi e SM

- “...la memoria è diminuita, i pensieri si formano lentamente e le facoltà intellettive ed emozionali sono indebolite nella loro globalità...”

Charcot 1877

- Cognitive impairment affects a large proportion of patients with multiple sclerosis (MS), with a **prevalence rate ranging from 40% to 70%.**
- Although cognitive deficits have been observed from the early stages of the disease, they are more frequent and pronounced in **chronic progressive MS and tend to worsen over time.**
- **SP>RR>PP**
- Neurological disability and disease duration primarily moderated performance on tasks assessing memory and learning.

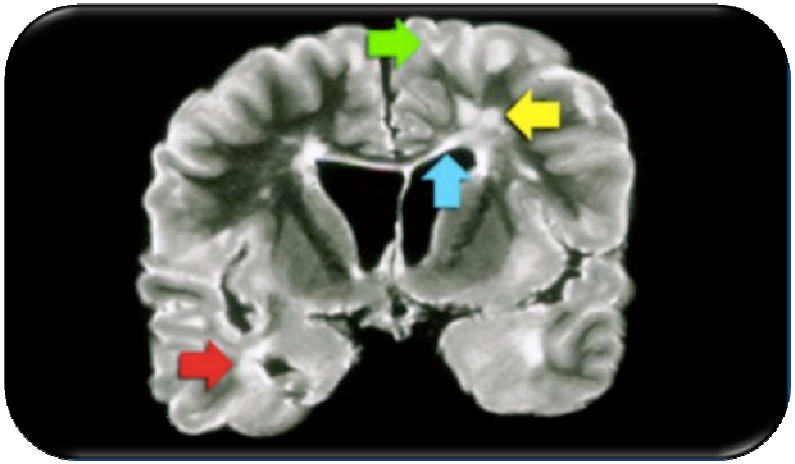
Rao et al 1991

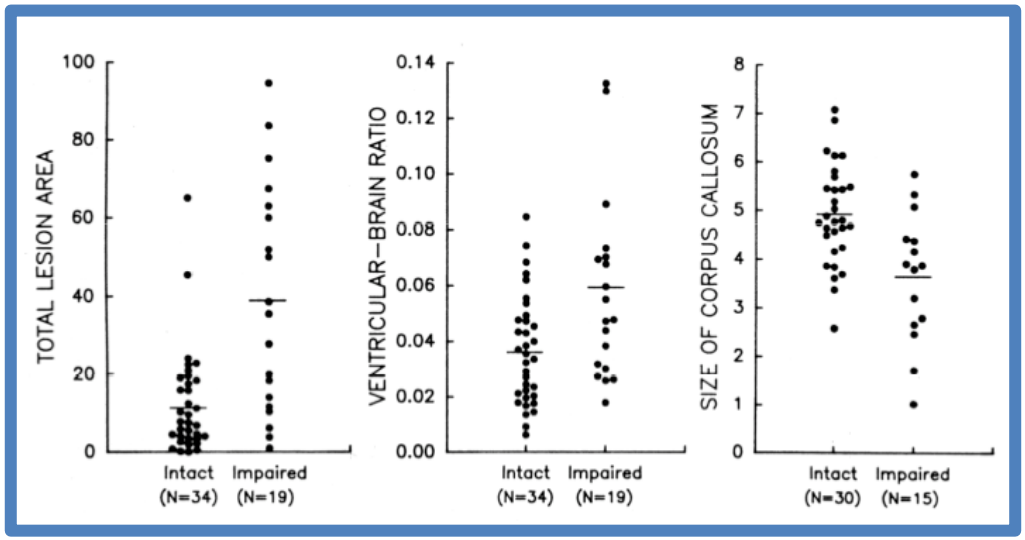


The contribution of MRI in assessing cognitive impairment in multiple sclerosis

Filippi et al 2010

- different aspects of MS-related pathology (inflammatory lesions and changes in normal-appearing brain tissue) involving the 1) **cortex** and 2) **connecting WM tracts** that rely on rapid transfer of information (e.g., attention, information processing, and executive function) are relevant in determining **cognitive impairment.**





e ancora.....

Contents lists available at ScienceDirect

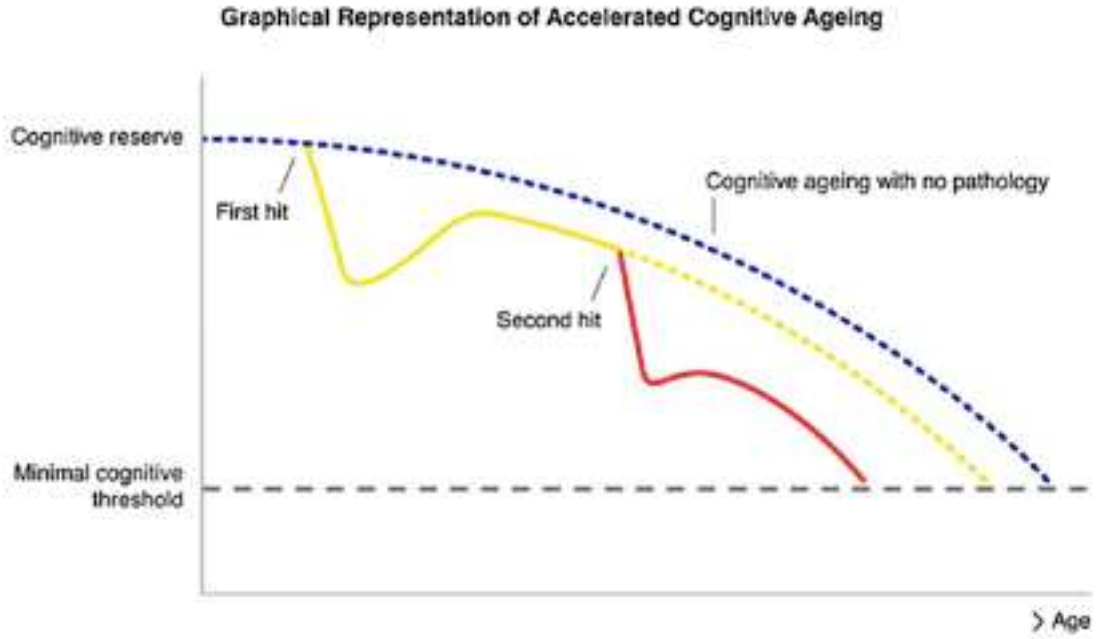
Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Cognitive deterioration in adult epilepsy: Does accelerated cognitive ageing exist?

L.E.M. Breuer[a,b,*], P. Boon[a,c], J.W.M. Bergmans[b], W.H. Mess[d], R.M.H. Besseling[b], A. de Louw[a,b], A.G. Tijhuis[b], S. Zinger[b], A. Bernas[b], D.C.W. Klooster[b], A.P. Aldenkamp[a,b,c,d]



Disabilità e Disordini Cognitivi

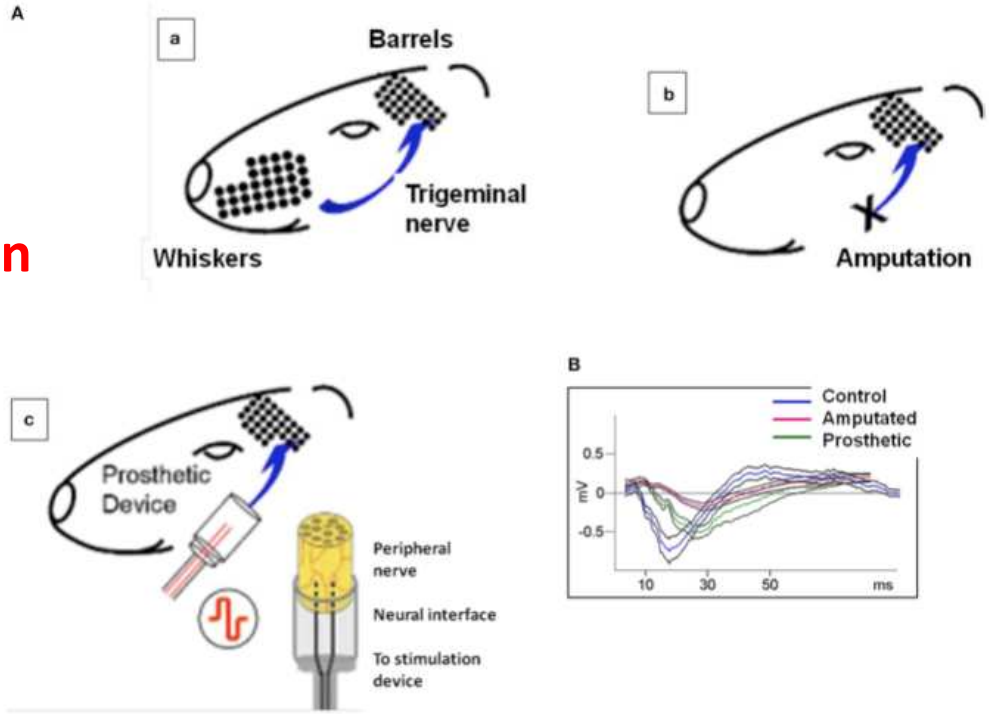
frontiers in
CELLULAR NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 14 November 2014
doi: 10.3389/fncel.2014.00385

Substitution of natural sensory input by artificial neurostimulation of an amputated trigeminal nerve does not prevent the degeneration of basal forebrain cholinergic circuits projecting to the somatosensory cortex

Celia Herrera-Rincon[1,2,3] *and Fivos Panetsos*[1,2,3,4]*

- **Peripheral deafferentation downregulates acetylcholine** (ACh) synthesis in sensory cortices
- Rat **infraorbital nerve transected** and implanted neuroprosthetic microdevices for proximal stump stimulation,
- Stimulation of the cut nerve does not affect the decrease in cholinergic fibers in **basal forebrain modality-specific cortex-MBN**-cortex circuit for **cognitive information processing.**



Clinical Research Article

Reduced Dual-Task Performance in MS Patients Is Further Decreased by Muscle Fatigue

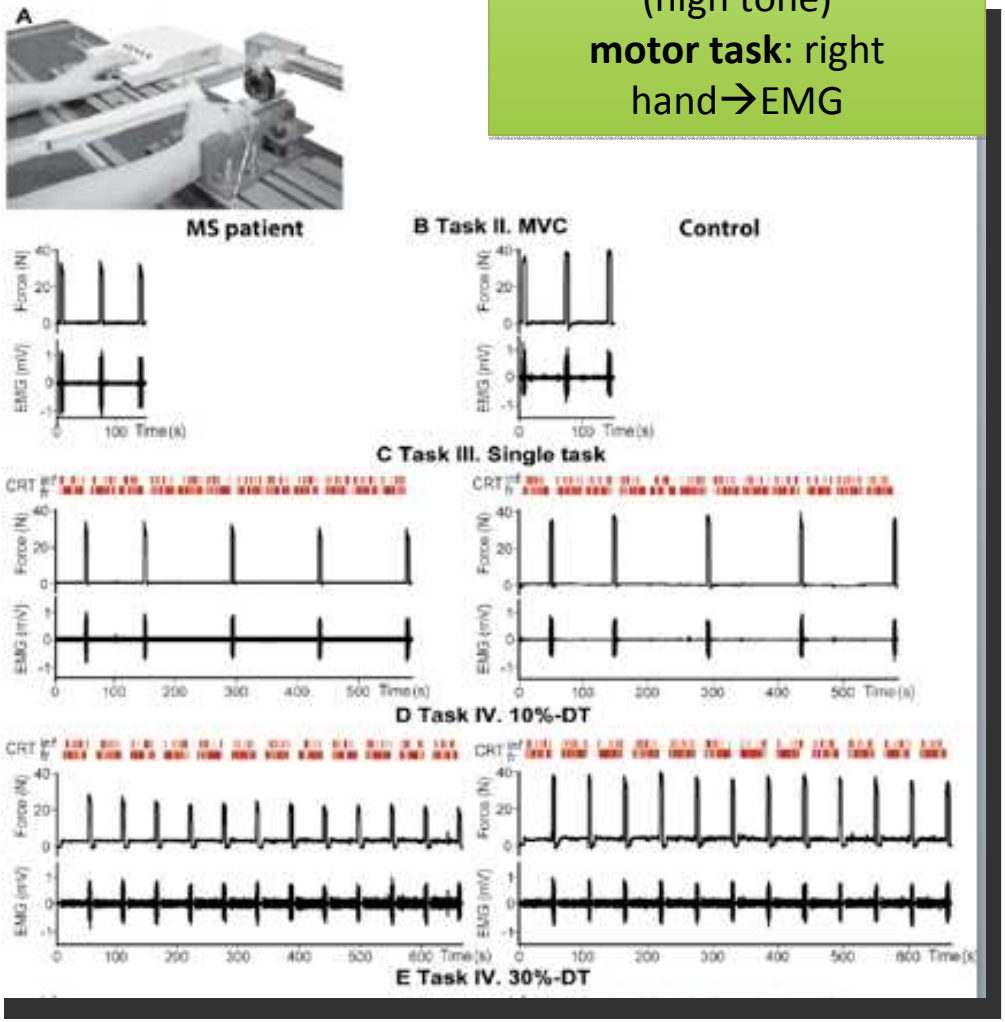
Neurorehabilitation and Neural Repair
2015, Vol. 29(5) 424–435

DOI: 10.1177/1545968314552529
nnr.sagepub.com
SAGE

Ria Wolkorte, MSc[1], Dorothea J. Heersema, MD, PhD[2], and Inge Zijdewind, PhD[1]

cognitive task: low (500Hz) and high (900Hz) tone, frequent (70%) and rare(30%)→ press a button with left index (low) or middle finger (high tone)
motor task: right hand→EMG

- compared with controls, MS pts performed less well on dual-tash, with reduction both in cognitive and motor performances
- the decrease is stronger under fatiguing conditions and related to the sense of fatigue of MS pts.



Social activity, cognitive decline and dementia risk: a 20-year prospective cohort study

Riccardo E. Marioni[1,2*], Cecile Proust-Lima[3,4], Helene Amieva[3,4,5], Carol Brayne[1], Fiona E. Matthews[6], Jean-Francois Dartigues[3,4,5] and Helene Jacqmin-Gadda[3,4]

Marioni et al. BMC Public Health (2015) 15:1089

Results: In the whole population, we found associations between increased engagement in social, physical, or intellectual pursuits and increased cognitive ability (but not decline) and decreased risk of incident dementia, and between feeling understood and slower cognitive decline. There was evidence for three sub-populations of cognitive aging: fast, medium, and no cognitive decline. The social-environment measures at baseline did not help explain the heterogeneity of cognitive decline and incident dementia diagnosis between these sub-populations.

Conclusions: We observed a complex series of relationships between social-environment variables and cognitive decline and dementia. In the whole population, factors such as increased engagement in social, physical, or intellectual pursuits were related to a decreased risk of dementia. However, in a sub-population analysis, the social-environment variables were not linked to the heterogeneous patterns of cognitive decline and dementia risk that defined the sub-groups.

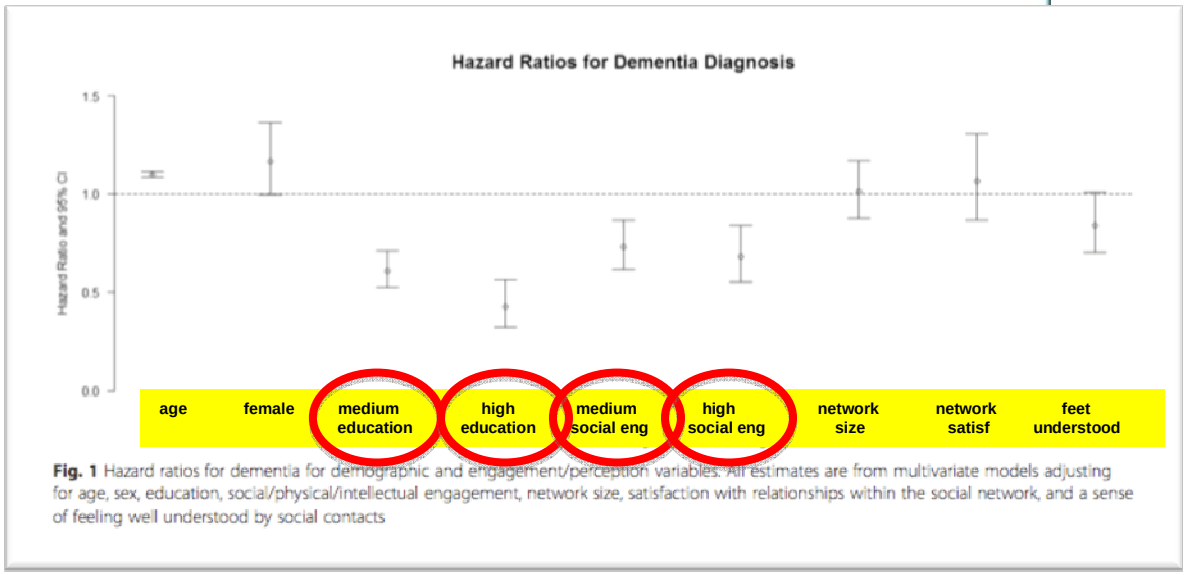


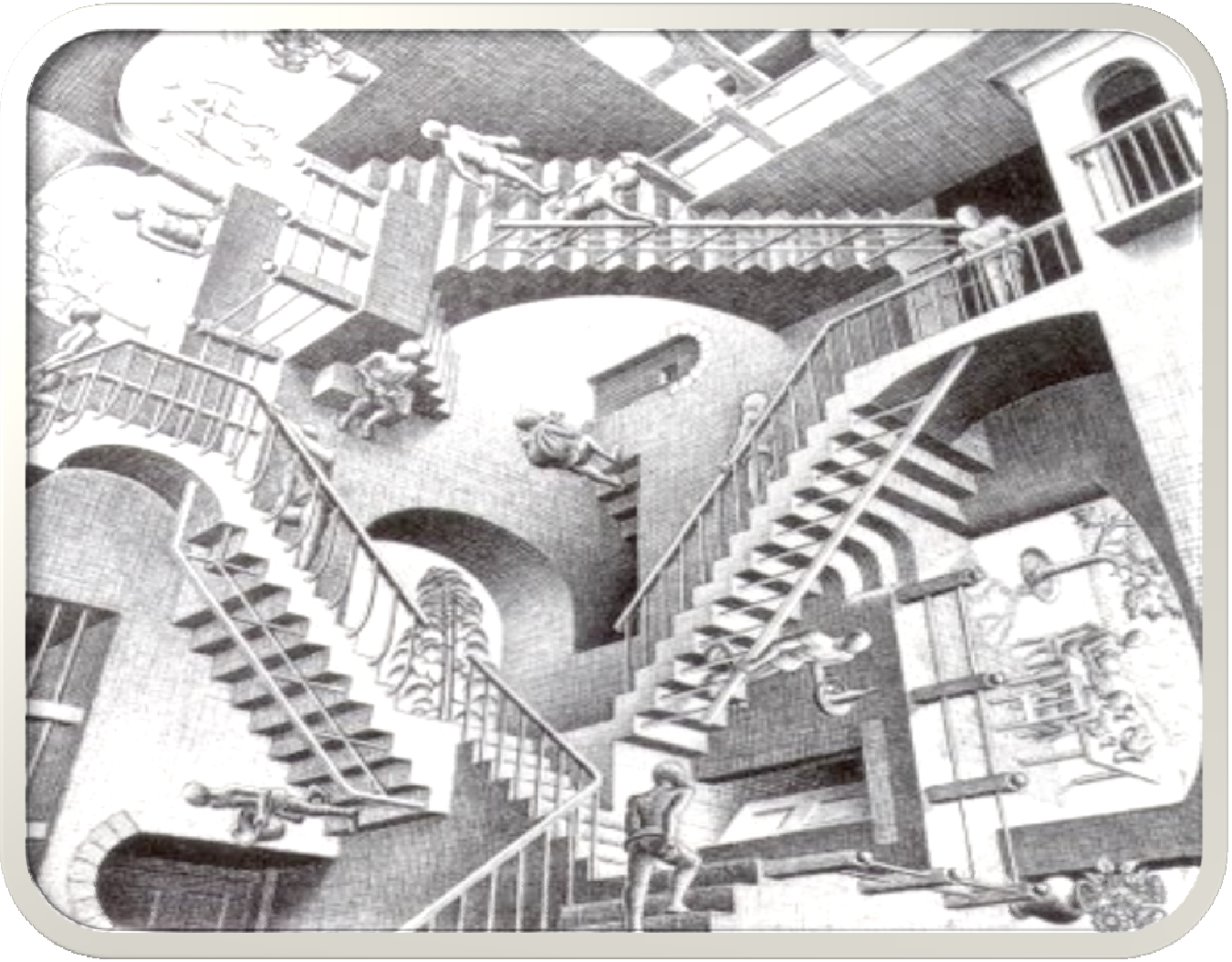
Fig. 1 Hazard ratios for dementia for demographic and engagement/perception variables. All estimates are from multivariate models adjusting for age, sex, education, social/physical/intellectual engagement, network size, satisfaction with relationships within the social network, and a sense of feeling well understood by social contacts

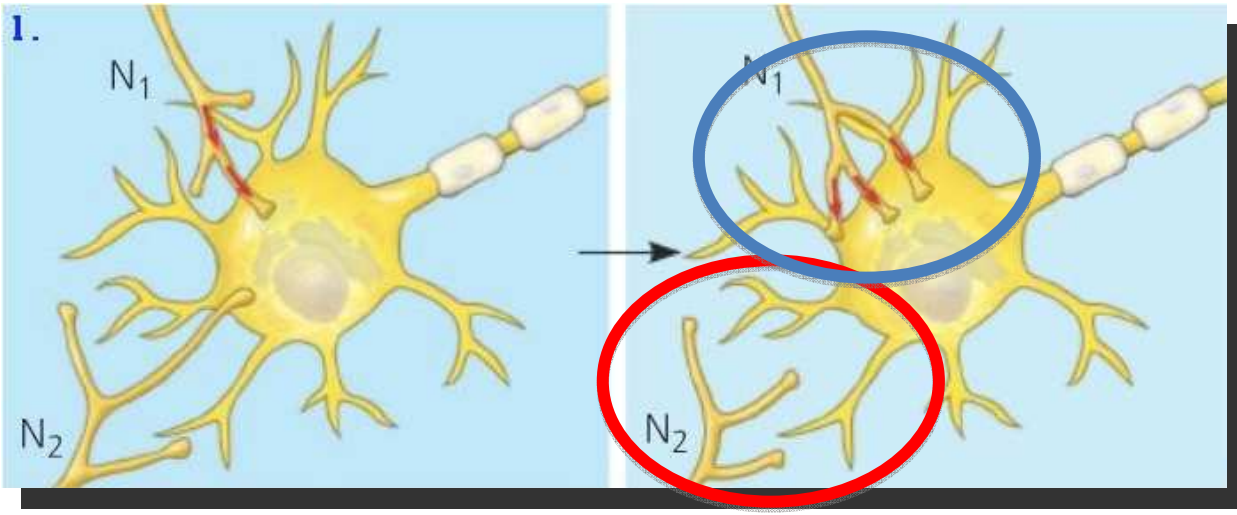
Riabilitazione Cognitiva

- ri-orientamento nella realtà → Rot therapy
- memory training
- tecnica di spaced retrieval
- ausili mnesici esterni
- terapia di reminiscenza
- terapia di validazione
- terapia di ri-motivazione

- **Quale ruolo ha il movimento nel recupero cognitivo???**

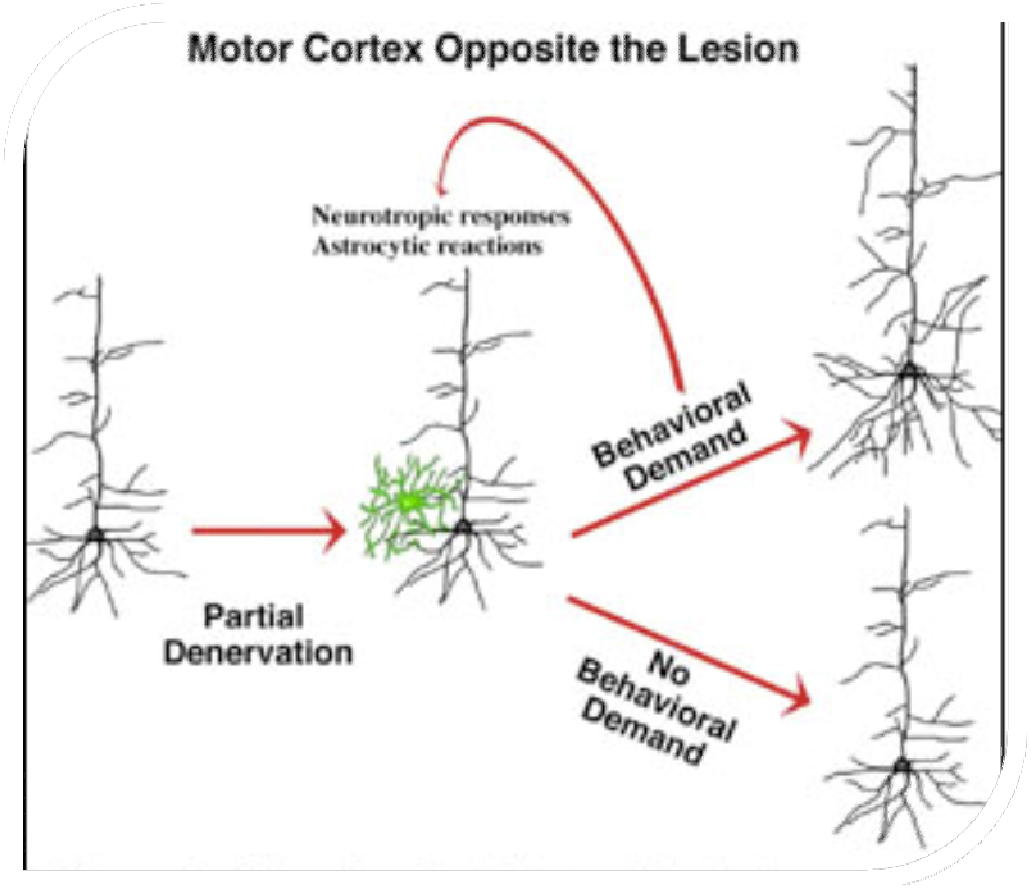
Riabilitazione Cognitiva e Plasticità
Tecniche di Valutazione NFS



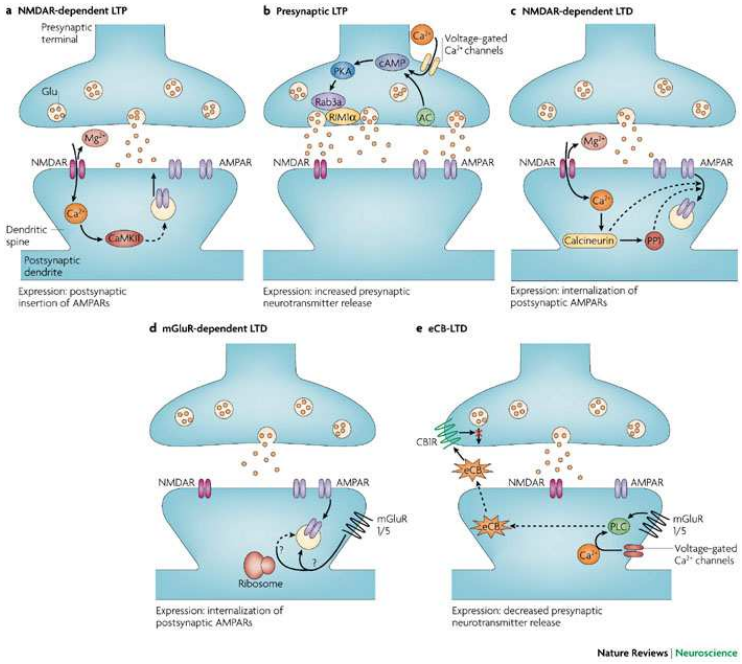


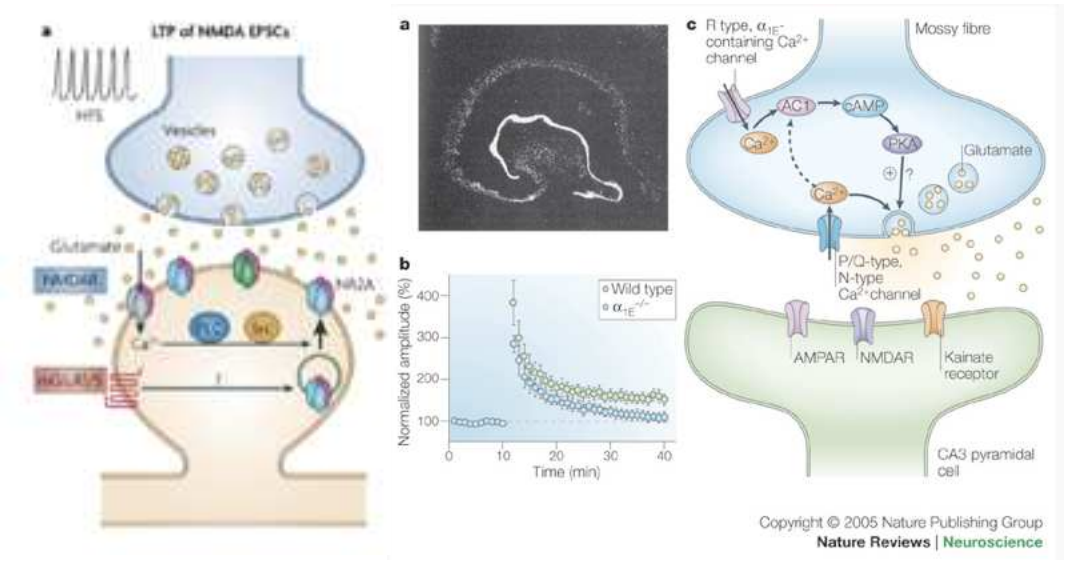
..Capacity of neurons and of neural circuit to change, structurally and functionally, in response to experience.
This property is fundamental for the adaptability of our behavior, for learning and memory processes, brain development, and brain repair

Neural Plasticity



Long term potentation→ LTP



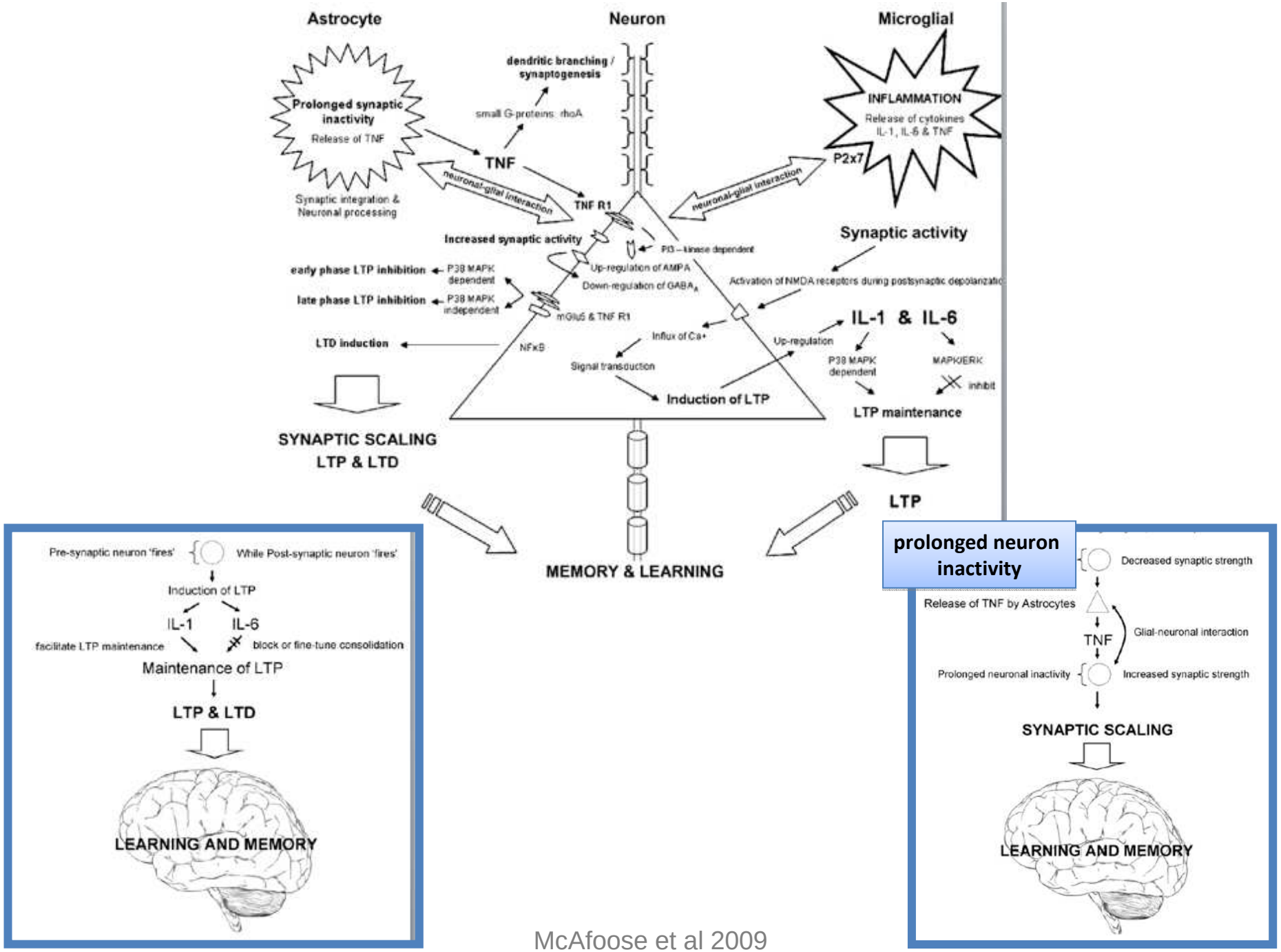


inibita da:

- infiammazione
- β -amiloide
- memantina (| NMDA)

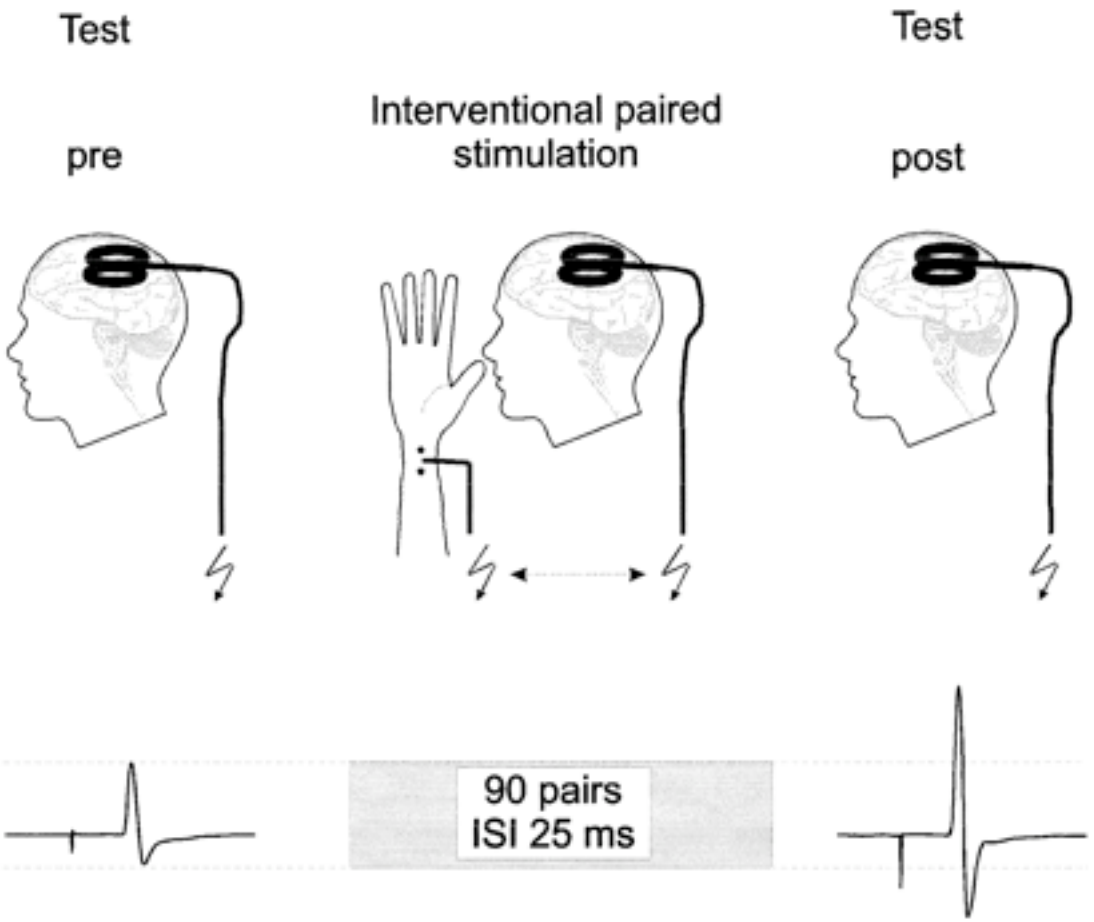
facilitata da:

- BDNF
- cannabinoidi
- DA-agonisti D1
- SSRI
- neuromodulazione
- attività



McAfoose et al 2009

PAS e Riserva Sinaptica



Research Paper

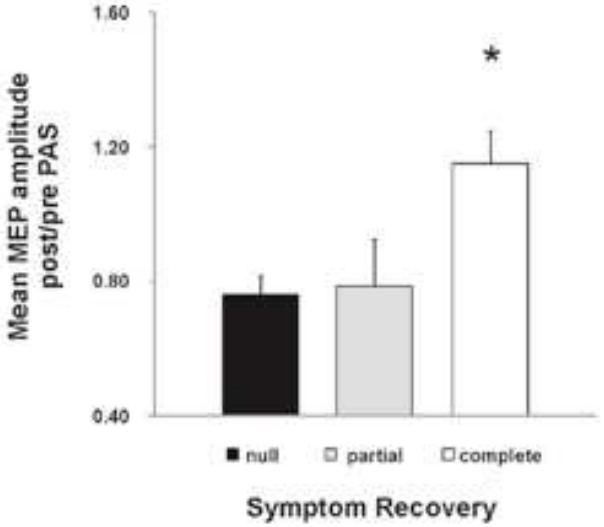
MULTIPLE SCLEROSIS JOURNAL | MSJ

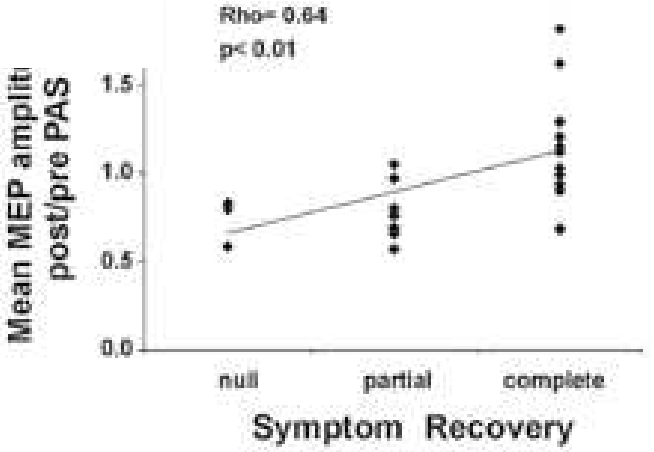
Cortical plasticity predicts recovery from relapse in multiple sclerosis

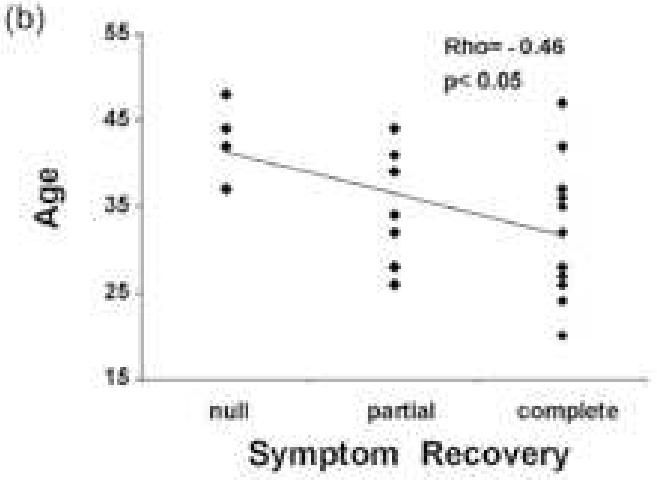
Multiple Sclerosis Journal
2014, Vol. 20(4) 451–457

DOI: 10.1177/1352458513512541
msj.sagepub.com
SAGE

Francesco Mori[1,2], Hajime Kusayanagi[1,2], Carolina Gabri Nicoletti[1,2], Sagit Weiss[1,2], Maria Grazia Marciani[1,2] and Diego Centonze[1,2]



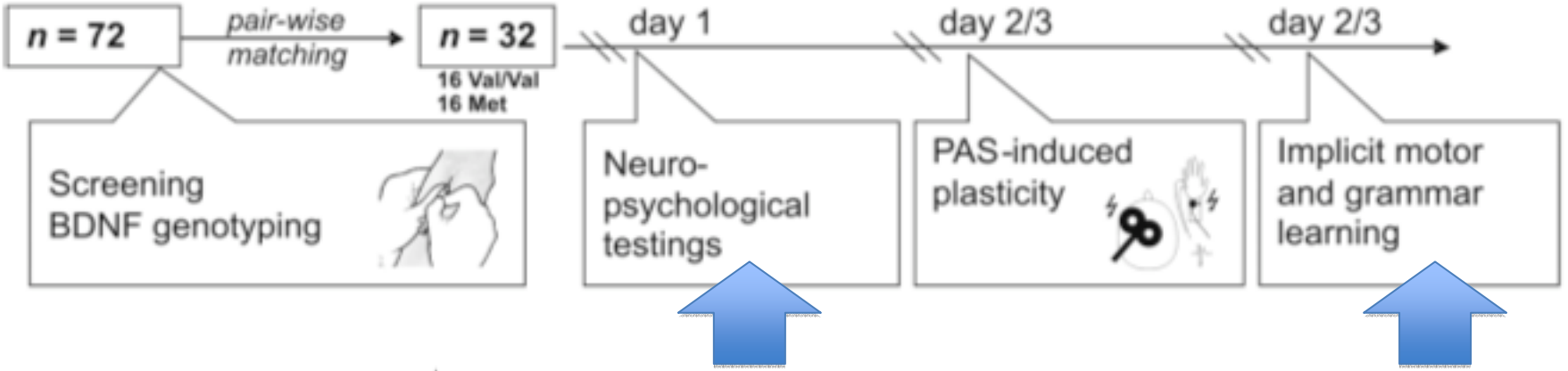


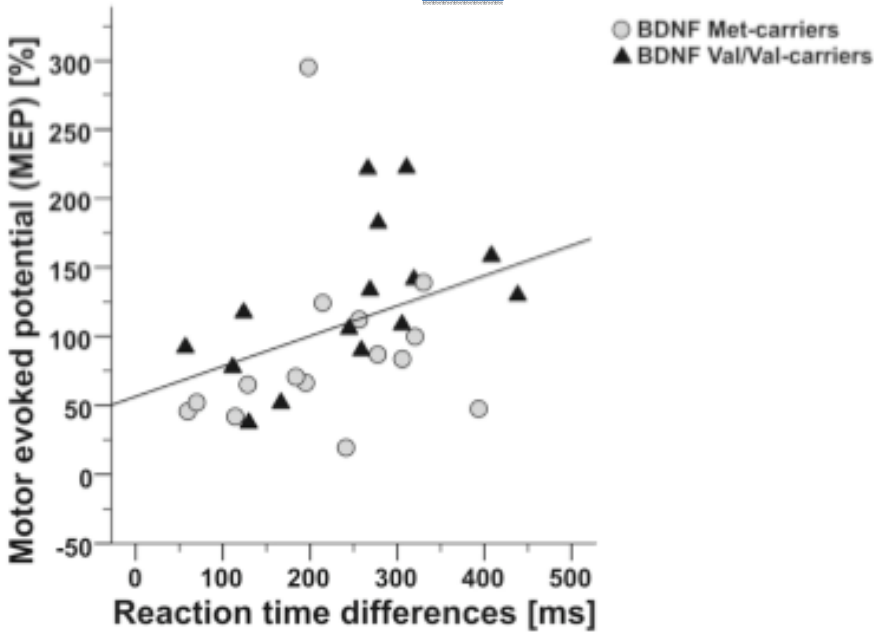


- better symptoms recovery is associated with increased LTP

Interaction of BDNF and COMT Polymorphisms on Paired-Associative Stimulation-Induced Cortical Plasticity

A. Veronica Witte,[1,2] Julia Kürten,[4] Stefanie Jansen,[4] Anja Schirmacher,[4] Eva Brand,[5] Jens Sommer,[6] and Agnes Flöel[1,2,3]

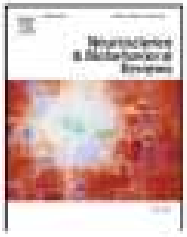




Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev



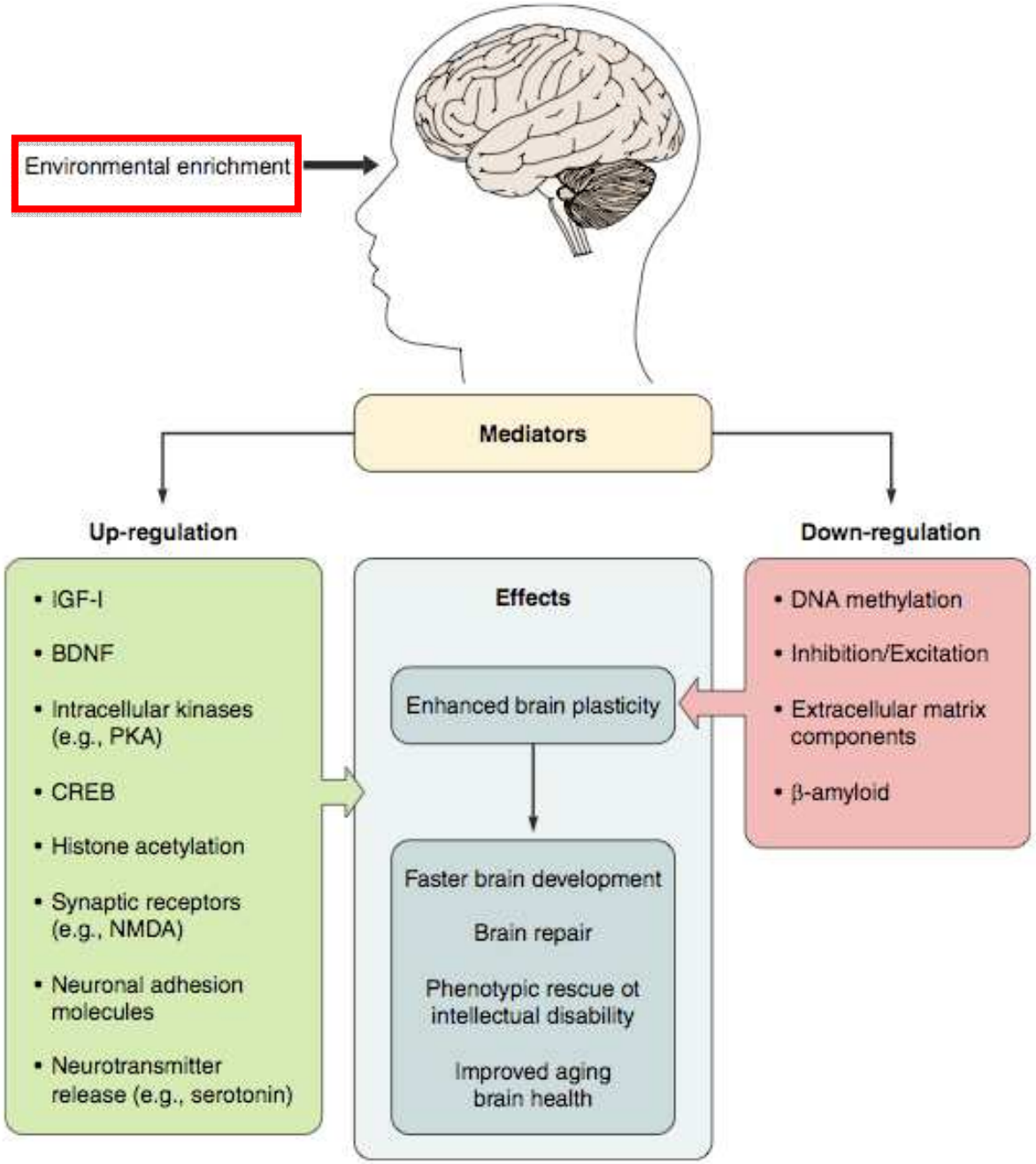
Review

Exercise and cognition in multiple sclerosis: The importance of acute exercise for developing better interventions

Brian M. Sandroff*

- **Cognitive dysfunction is highly prevalent**, disabling and poorly-managed in persons with MS
- **update review** on the evidence describing exercise effects on cognition in MS
- the development of such successful interventions is based on examinations of **fitness, physical activity and acute excercise effects** (yoga, aerobic excercises) **on cognition**
- studies of **physical fitness** → cognitive **processing speed**, but not learning and memory
- **acute excercise** (treadmill walking) → improvement of **reaction time**, not accuracy
- excercise training represents a **promising behavioral approach** for managing cognitive dysfunction in persons with MS

- A Cochrane comprehensive survey specifically reviewed the evidence that **aerobic fitness** is necessary for **improved cognitive function**: it concluded that “aerobic physical activities which improve cardiorespiratory fitness are beneficial for cognitive function in healthy older adults



Aerobic Fitness is Associated with Gray Matter Volume and White Matter Integrity in Multiple Sclerosis

Ruchika Shaurya Prakash[1,*], **Erin M. Snook**[2], **Robert W. Motl**[3], and **Arthur F. Kramer**[1]

Alterations in gray and white matter have been well documented in individuals with multiple sclerosis. Severity and extent of such brain tissue damage have been associated with cognitive impairment, disease duration and neurological disability, making quantitative indices of tissue damage important markers of disease progression. In this study, we investigated the association between cardiorespiratory fitness and measures of gray matter atrophy and white matter integrity. Employing a voxel-based approach to analyses of gray matter and white matter, we specifically examined whether higher levels of fitness in multiple sclerosis participants were associated with preserved gray matter volume and integrity of white matter. We found a positive association between cardiorespiratory fitness and regional gray matter volumes and higher focal fractional anisotropy values. Statistical mapping revealed that higher levels of fitness were associated with greater gray matter volume in the midline cortical structures including the medial frontal gyrus, anterior cingulate cortex and the precuneus. Further, we also found increasing levels of fitness were associated with higher fractional anisotropy in the left thalamic radiation and right anterior corona radiata. Both preserved gray matter volume and white-matter tract integrity were associated with better performance on measures of processing speed. Taken together, these results suggest that fitness exerts a prophylactic influence on the cerebral atrophy observed early on preserving neuronal integrity in multiple sclerosis, thereby reducing long-term disability.

suggests a clear triple association between fitness, cognitive functioning and GM and WM structures

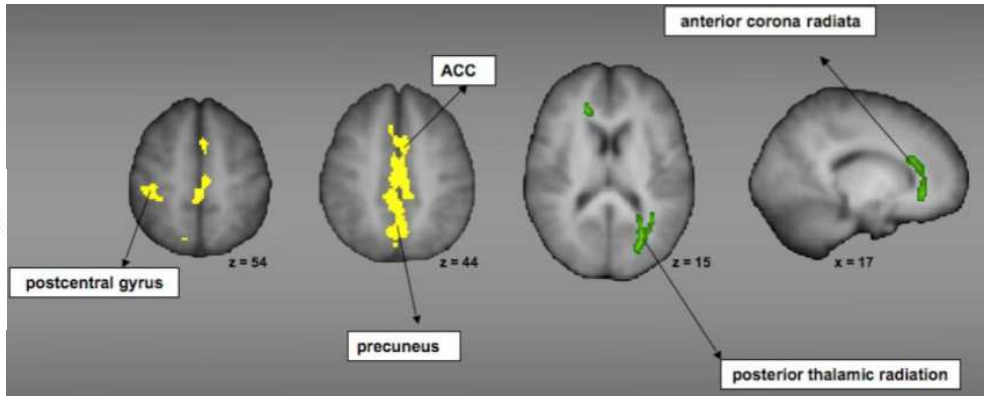


Figure III.
Represents regions of GM loss (displayed in yellow) and FA reductions (displayed in green) in MS participants that are preserved with higher levels of cardiorespiratory fitness. Partial volume estimates in the GM structures and FA values in the white matter tracts correlated positively with fitness levels.

Physiol Rev 94: 189–234, 2014
doi:10.1152/physrev.00036.2012

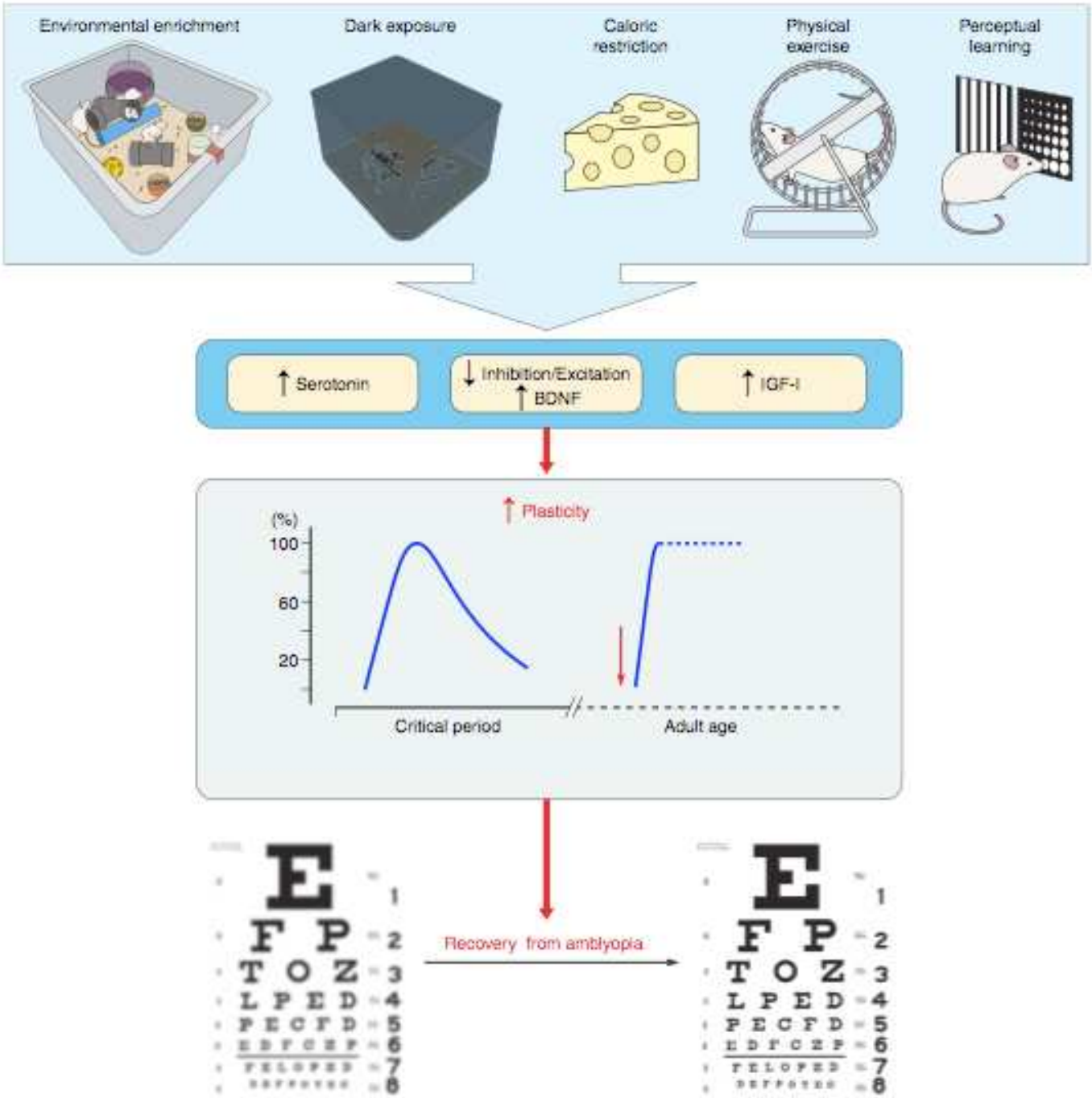
ENVIRONMENT AND BRAIN PLASTICITY: TOWARDS AN ENDOGENOUS PHARMACOTHERAPY

Alessandro Sale, Nicoletta Berardi, and Lamberto Maffei

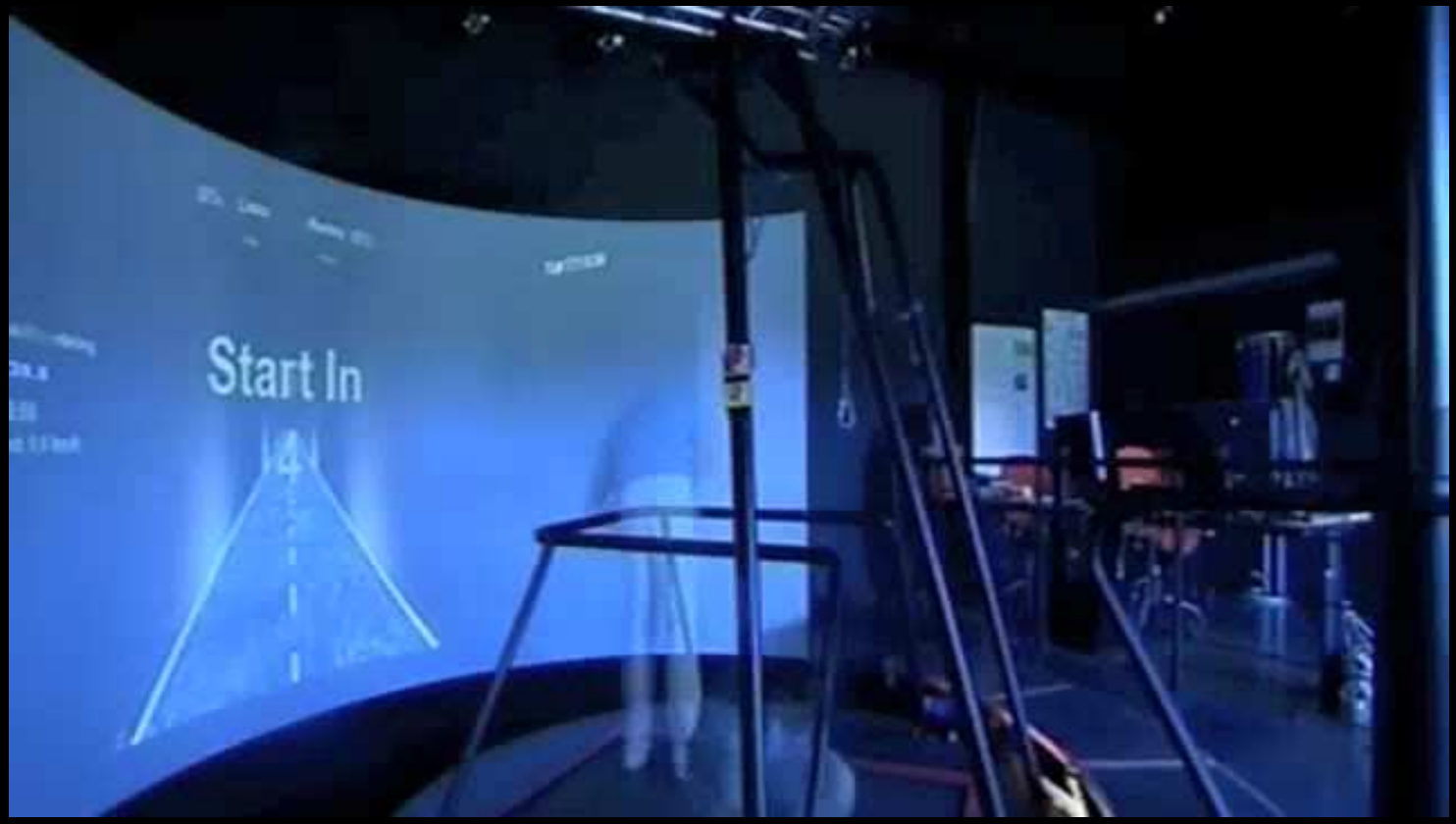
- ***Hippocampal adult neurogenesis*** is stimulated by **voluntary running** and by exposure to **sensory, cognitive, motor, and socially enriched conditions (enriched environment EE)**

- The newly generated neurons in Dentate Gyrus integrate with local circuits, receiving and establishing synaptic contacts, and are particularly susceptible to synaptic plasticity of the LTP type
- Very recent paper estimated that humans have at least as much adult hippocampal neurogenesis as mice, with one-third of adult hippocampal neurons turning over

- An essential component of the EE is sustained voluntary physical, Including **enhanced motor activity** is **more effective than exercise alone in enhancing memory functions**
- **Learning to juggle** and practicing it for 3 mo lead to a transient and **selective expansion in grey matter in the midtemporal area** and in **the left posterior intra- parietal sulcus**, which are regions involved in the processing and storage of complex visual motion


Environmental enrichment
Dark exposure
Caloric restriction
Physical exercise
Perceptual learning
↑ Serotonin
↓ Inhibition/Excitation
↑ BDNF
↑ IGF-I
↑ Plasticity
(%)
100
60
20
Critical period
Adult age
Recovery from amblyopia

Recent developments in computer assisted rehabilitation environments. Rob van der Meer 2014



È

Fondamentale

ricordare che: