FONDAZIONE CASSA DI RISPARMIO DI PISTOIA E PESCIA

Centro Monteoliveto

"Casa dell'Anziano"

15 - 16 Maggio 2015

6° CONVEGNO NAZIONALE SUI CENTRI DIURNI ALZHEIMER

Longevity

Sessione Attività fisica e training cognitivo nella demenza

TRAIN the BRAIN

Le basi neurobiologiche e la sperimentazione clinica

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Consiglio Nazionale delle Ricerche

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The *World Alzheimer Report* estimates that in 2010 the number of people with dementia worldwide was 35.6 million and that this will increase to 65.7 million by 2030 and 115.4 million by 2050 unless effective means of reducing the incidence of this disease are introduced.

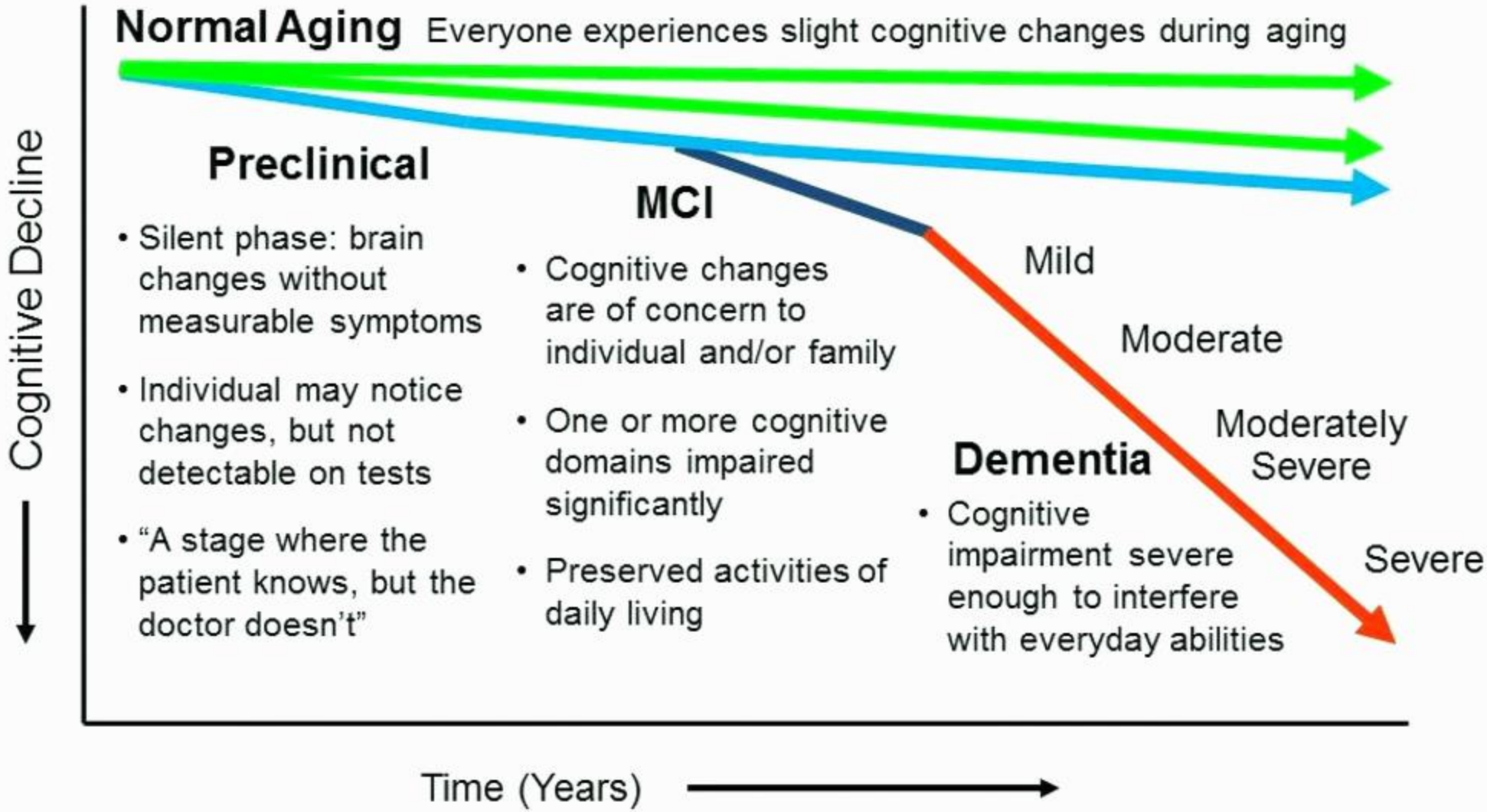
Mangialasche et al., 2012

La complessa patofisiologia della demenza di Alzheimer inizia molti anni prima che i sintomi della malattia appaiano.

In modelli animali, oligomeri solubili della proteina amiloide producono già deficit cognitivi

Converging evidence from the experimental and clinical literature indicate that moderate levels of cognitive impairment and the presence of subtle cerebral alterations, detectable with techniques such as structural and functional neuroimaging, precede by several years the clinical onset of dementia (Jones et al., 2004; Garrett et al., 2004 a e b; Bowler e Hachinsky, 2003, Bowler, 2005; DeCarli et al., 2007; Pike et al., 2007; Garibotto et al., 2008; Sterling et al., 2013).

This condition is referred to as mild cognitive impairment (MCI).



It is now hypothesised that MCI is preceded by a silent stage of AD—when the disease has begun in the brain but symptoms are not yet clinically evident— a stage termed 'preclinical AD'. Sterling et al., 2013

MCI affects a vast number of people and is characterized by objective deficits in one single domain (e.g. memory) or multiple domains of cognition, which do not yet configure as overt dementia (Petersen et al., 1999, 2001 a e b, 2004).

The rate of yearly progression to dementia of MCI subjects is much higher than in the non-MCI elderly: in particular, the amnestic subtype of MCI (aMCI) may represent a prodromal form of AD (Scheltens et al., 2002; Petersen et al. 1999 and 2003). Rate of conversion correlates with MTL atrophy.

However, a good proportion of MCI subjects not only does not develop dementia, but can also recover from the initial slight impairments that characterizes them as MCI subjects (Petersen et al 1999, 2001; Jack et al 2001, 2005; Frisoni et al 2004; Small et al. 2007)

Is it possible to impact on disease progression by starting at early stages of the road to AD?

Can we reduce Aβ production and/or increase Aβ degradation and clearance?

Can we harness brain plasticity and exploit it to steer the brain towards healthy aging?

The “environmental enrichment” approach

What is an enriched environment

The first formal definition has been given by Rosenzweig: “a combination of complex inanimate and social stimulation ” (Rosenzweig et al., 1978).

Environmental enrichment: experimental conditions

- Impoverished condition

- Standard laboratory condition (non EE).

- Enriched environment with possibility to do voluntary physical exercise (EE).

Effects of EE or physical activity alone on brain and behaviour:

Early studies: Increase in cortical thickness, increase in dendritic spine density, increase in the complexity of the dendritic tree, increase in parameters related to neuromodulatory systems;

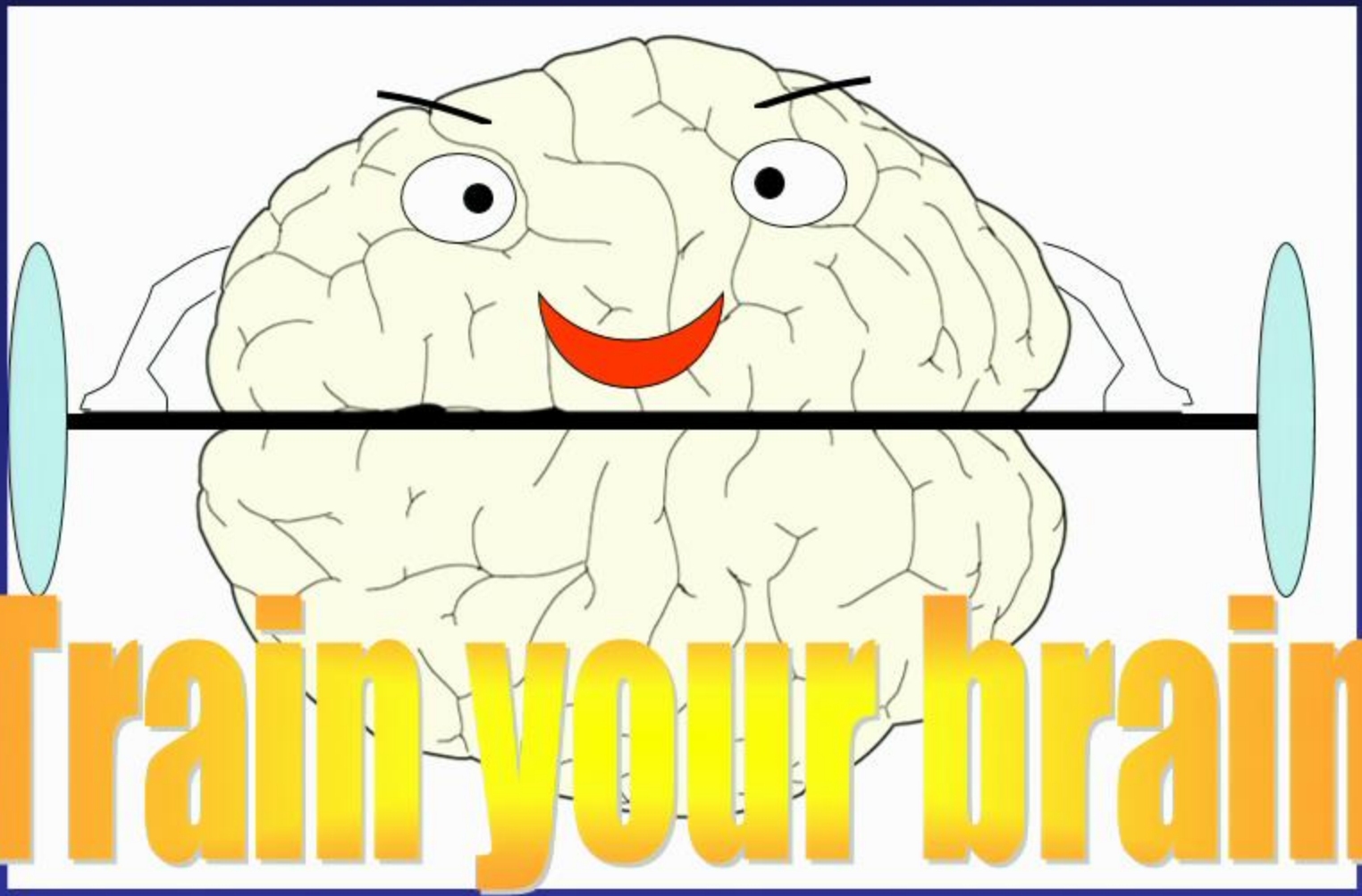
Recent studies: Enhancement of neural plasticity, enhancement of learning and memory processes, neuroprotection and brain repair, particularly evident in aged animals.

Positive effects linked to changes in expression of plasticity and neuroprotective factors.

Plasticità neurale e invecchiamento

La plasticità neurale declina con l'invecchiamento nelle strutture nervose alla base della memoria dichiarativa e delle funzioni esecutive (strutture del lobo temporale mediale e corteccia prefrontale).

Tuttavia, vi sono esempi di "plasticità compensativa", particolarmente evidente negli anziani che mantengono un buono stato cognitivo con l'età.



Aricchimento ambientale/esercizio fisico: una strategia per potenziare la plasticità cerebrale a la neuroprotezione nel cervello che inveccia agendo su fattori **endogeni**?

L’ipotesi della riserva cognitiva

Evans, Wilson, Katzman: l’ipotesi della **“riserva cognitiva”:** l’effetto dell’educazione in età scolare ed universitaria sull’incidenza della demenza

Il concetto di riserva cognitiva si basa sulle osservazioni cliniche (epidemiologiche) che soggetti con un elevato grado di scolarità, sembrano far fronte meglio all’inizio della patologia, mantenendo un livello funzionale normale per un tempo più lungo rispetto a soggetti con un livello di scolarità inferiore

Snowdon: the Nun study

Ammassi neurofibrillari e placche amiloidi sono risultate più rare nelle suore che mostravano una maggiore ricchezza linguistica rispetto alle suore con una più bassa ricchezza linguistica.

Riley et al., 2005

On the basis of epidemiological studies in humans, risk and protective factors for developing major cognitive decline and dementia with age have been pointed out, which include cardiovascular factors, genetic factors, such as the presence of APOE4 allele or familiarity for the disease, **education** and lifestyle factors, such as being engaged in **cognitively stimulating and social activities** and **practicing physical exercise**, key components of an "enriched environment" (e.g. Laurin et. al, 2001; Fratiglioni et al., 2004; Podewils et al., 2005; Marx, 2005; Kramer and Erickson, 2007; Paillard-Borg et al., 2012; Mangialasche et al., 2012).

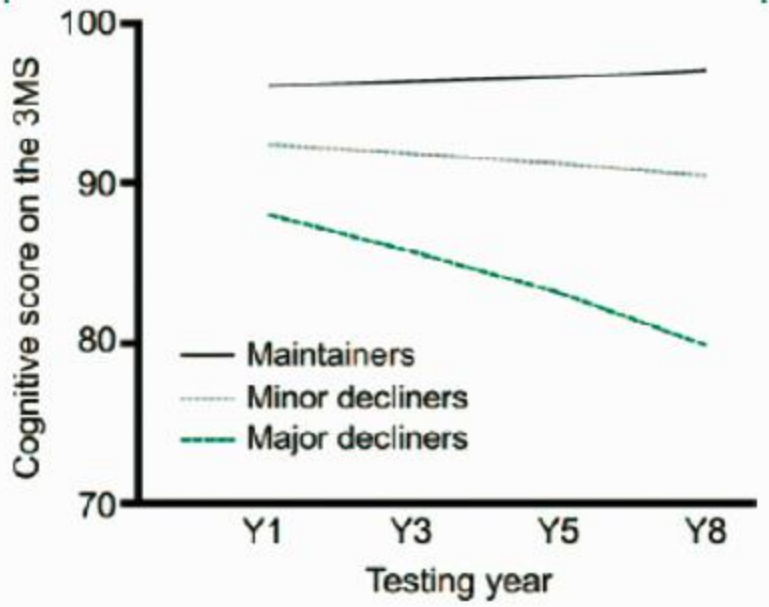
Esercizio fisico e declino cognitivo nell'anziano

Laurin et al., 2001; Weuve et al., 2005; Podewils et al., 2005; Larson et al.,2007;

Predictors of maintaining cognitive function in older adults: The Health ABC (Aging and Body Composition) Study

Yaffe et al., Neurology, 2009

Figure Cognitive score over time by cognitive group



Cognitive group was determined by change in score on the Modified Mini-Mental State Examination (3MS) over 7 years, resulting in the classification of participants as cognitive maintainers (cognitive change slope ≥0), minor decliners (slope <0 and >1 SD below mean), or major decliners (slope ≤1 SD below mean). 2509 subjects

In the final multivariate-adjusted model characteristics that remained **significant predictors of being a maintainer** vs a minor decliner were age, having a high school education level or greater and a ninth grade literacy level or greater, engaging in weekly moderate to vigorous exercise, and not smoking at baseline. At the statistical trend level ($P<0.10$) cognitive maintenance was associated with **working or volunteering**, **living with someone,** and absence of the APOE 4 gene.

Elders who maintain cognitive function have a unique profile that differentiates them from those with minor decline. Importantly, some of these factors are **modifiable** and thus may be implemented in **prevention programs** to promote **successful cognitive aging**.

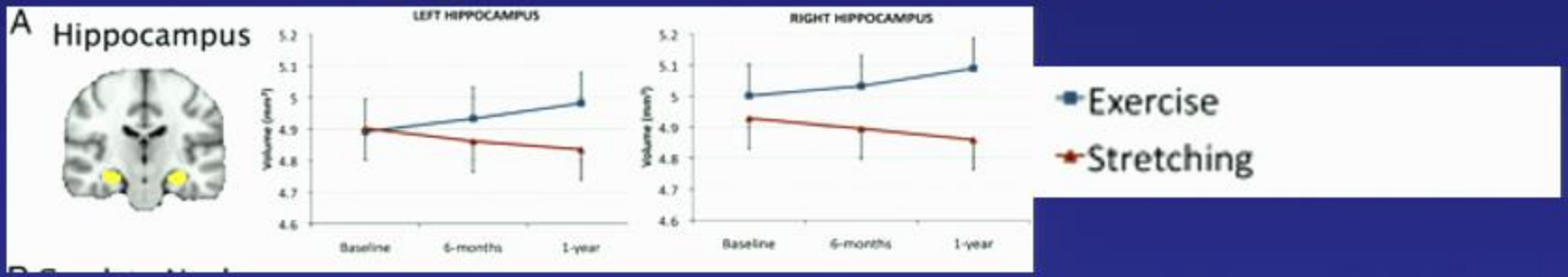
Physical and cognitive activity intervention studies in humans

A Cochrane survey (Angevaren et al., 2008) specifically reviewed the evidence that aerobic fitness is necessary for improved cognitive function: all published randomised controlled trials comparing aerobic physical activity programmes with any other intervention or no intervention with participants older than 55 years of age were included in the survey.

Conclusion: aerobic physical activities which improve cardiorespiratory fitness are beneficial for cognitive function in healthy older adults,

(warning: the data were insufficient to show that the improvements in cognitive function which could be attributed to physical exercise were due to improvements in cardiovascular fitness, although the temporal association suggests that this might be the case, and that larger studies were required).

Erickson et al. (2011) showed, in a randomized controlled trial with 120 older adults, that aerobic exercise training increases the size of the anterior hippocampus, leading to improvements in spatial memory (position of dots on computer screen).

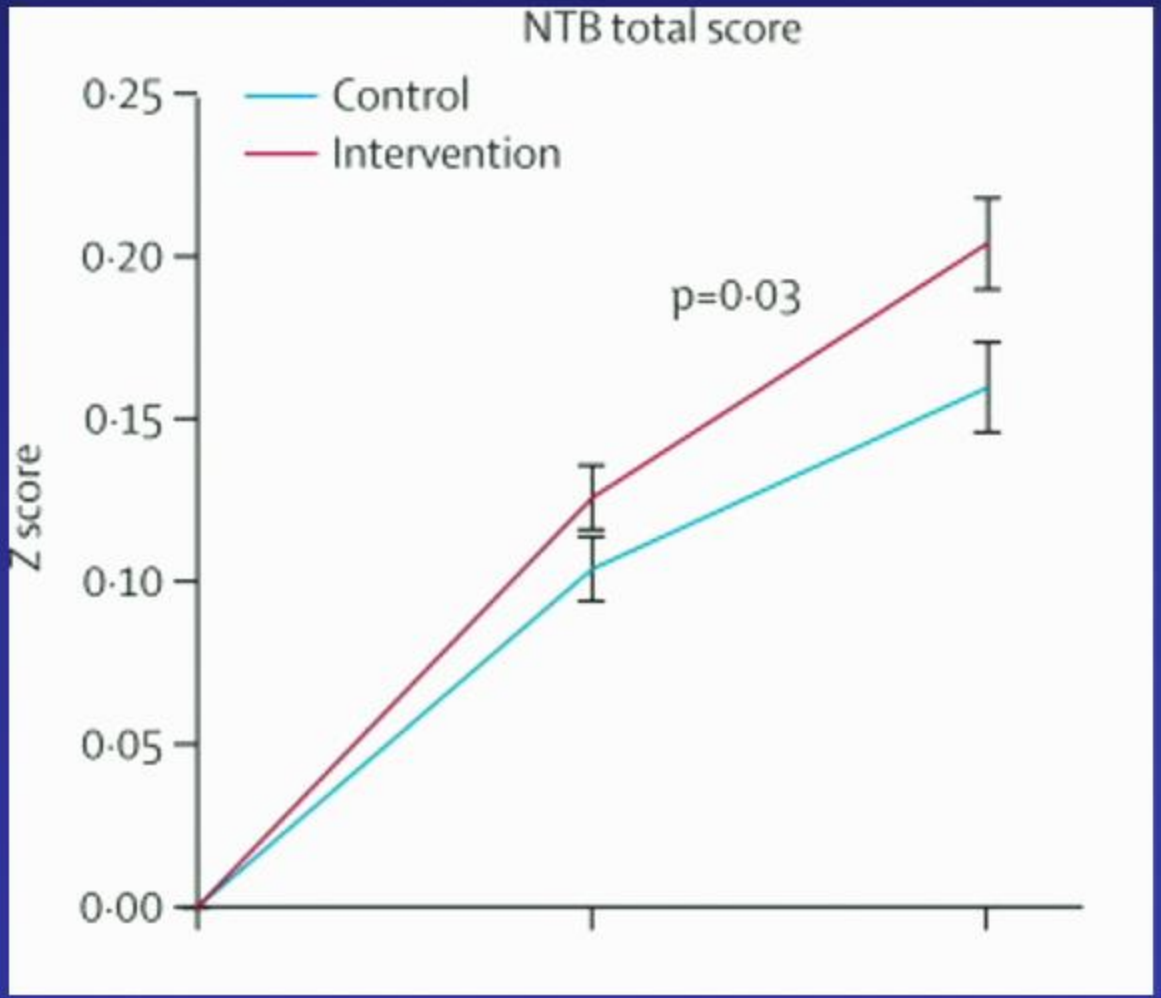


Exercise training increased hippocampal volume by 2%, effectively reversing age-related loss in volume by 1 to 2 y.

Increased hippocampal volume is associated with greater serum levels of BDNF (crucial for EE and exercise effect on hippocampal neurogenesis).

Caudate nucleus and thalamus volumes were unaffected by the intervention.

A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial.



Ngandu et al., Lancet. 2015

Which factors and mechanisms underly the effects of EE/physical exercise on aging related cognitive decline and dementia?

Animal models:

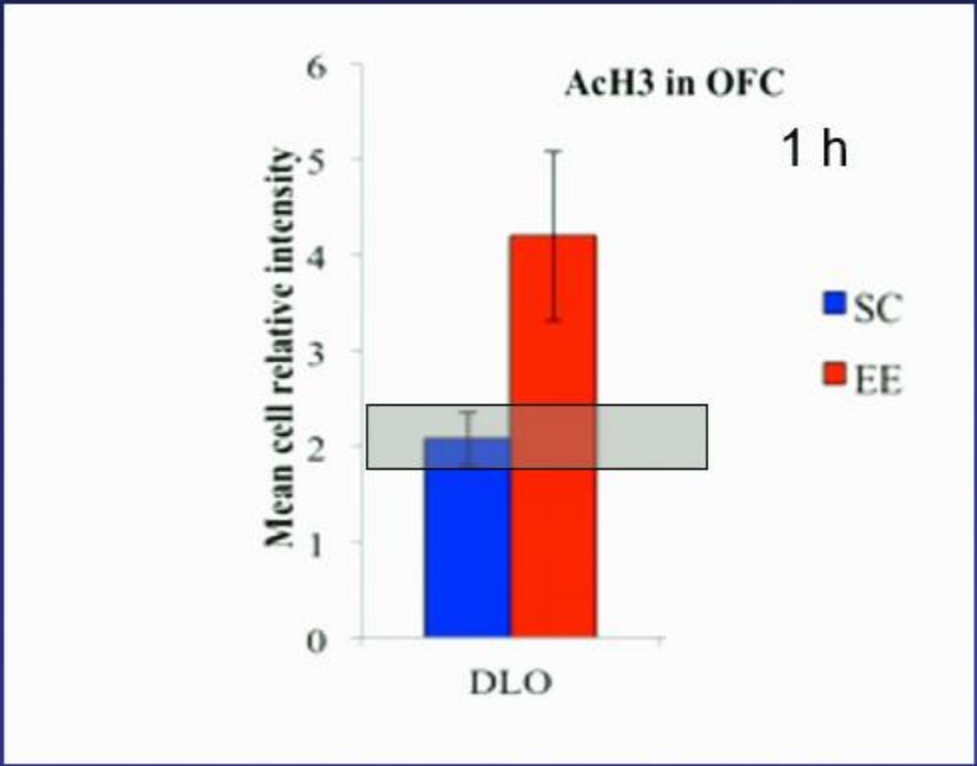
Positive effects of EE and physical exercise on cognitive processes in aging animals have been related to an action on hippocampal neurogenesis, brain neurotrophic factors (BDNF), Nerve Growth Factor (NGF), IGF-1, synaptic density, function and plasticity, neurotransmitter systems and, more recently, on epigenetic factors and on neuroinflammation.

EE effects on neural plasticity underlying long term declarative memory: system consolidation in aged mice

Social Transmission of Food Preference (STFP)

Cintoli et al., in preparation

EE increases Histone acetylation in prefrontal cortex



Failure of system consolidation in aging?

Male and female C57BL/6 mice of 16 months of age, EE from 14 to 16 months of age.

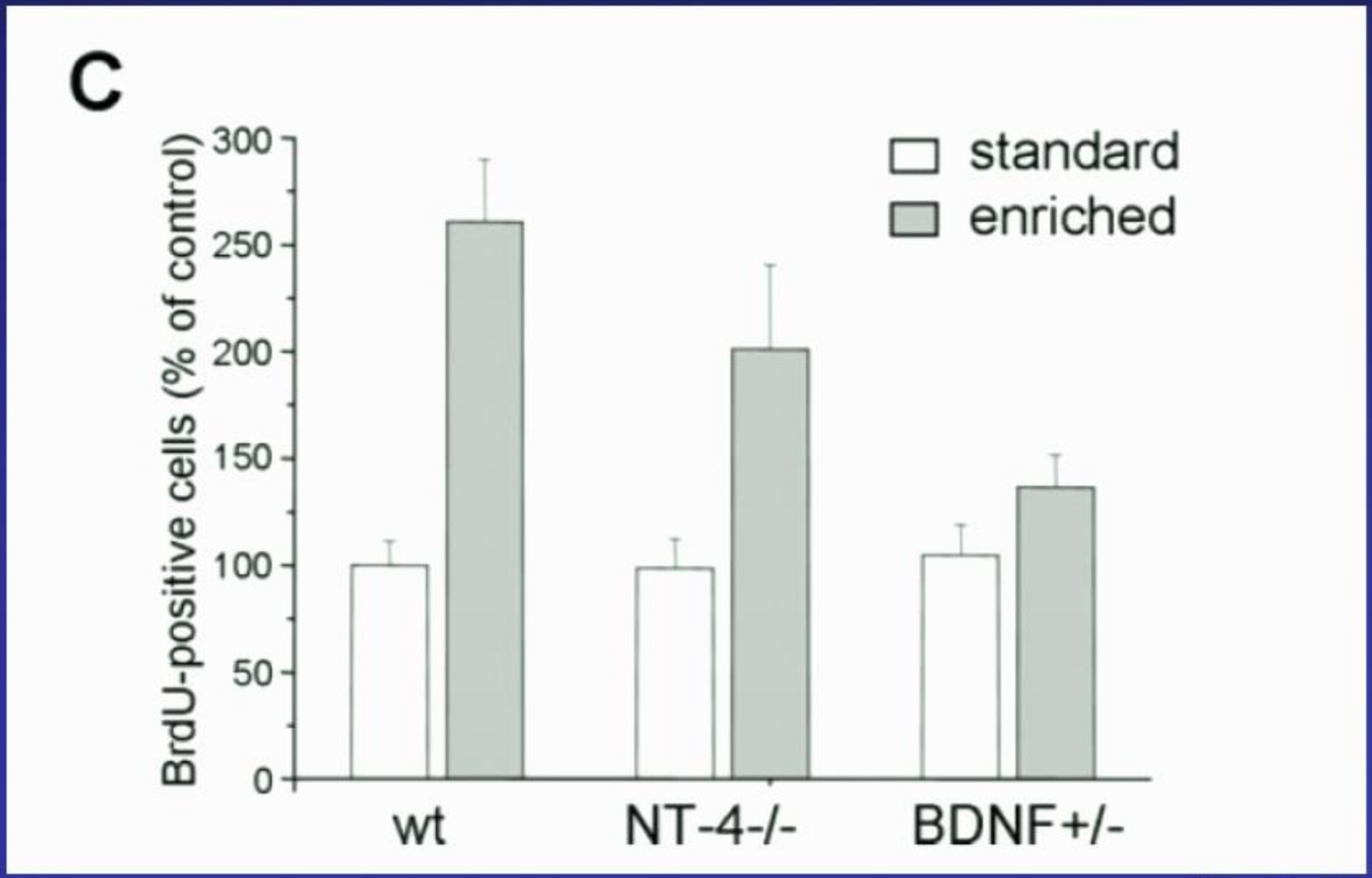
Positive effects of EE

Cintoli et al., in preparation

L’invecchiamento riduce la neurogenesi nel giro dentato dell’ippocampo, sia in modelli animali che nell’uomo (Knoth et al. (2010); Spalding et al., (2013), evidenza diretta)

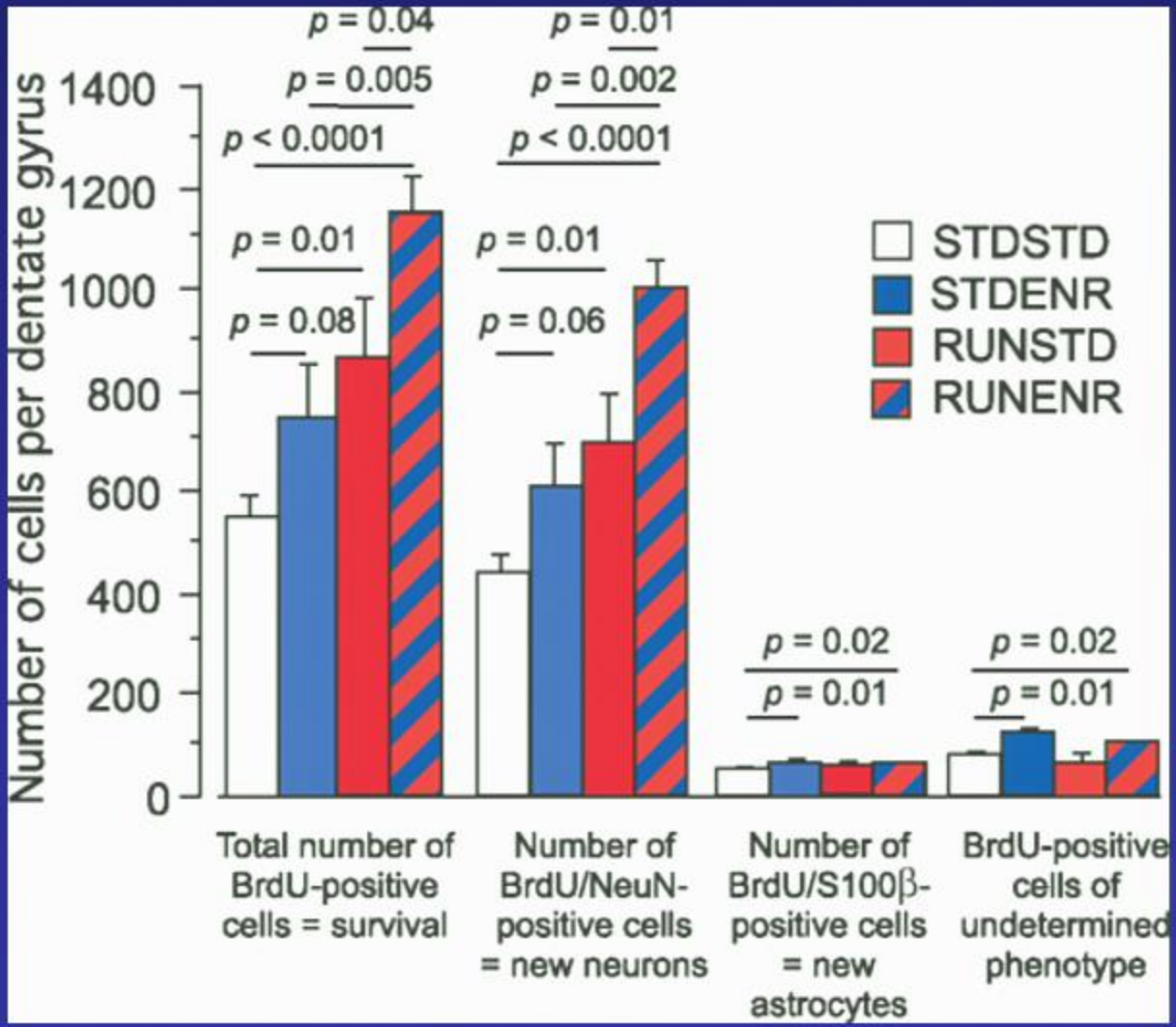
Arricchimento ambientale ed esercizio fisico aumentano fortemente la neurogenesi nell’ippocampo

Gli effetti dell'arricchimento ambientale e dell'esercizio fisico sulla neurogenesi ippocampale dipendono dal BDNF



Rossi et al., 2006

Of particular interest, also in relation to intervention in humans, is the finding that the effects of exercise and environmental enrichment on adult neurogenesis seem to be **additive**



Sequentially combining the effects of physical activity on precursor cell proliferation with the survival promoting effects of environmental enrichment resulted in a much greater effect with respect to that caused by enrichment or exercise alone.

(Fabel et al., 2009)

J Alzheimers Dis. 2012;31(4):835-42. doi: 10.3233/JAD-2012-120724.

An active lifestyle postpones dementia onset by more than one year in very old adults.

Paillard-Borg S, Fratiglioni L, Xu W, Winblad B, Wang HX.

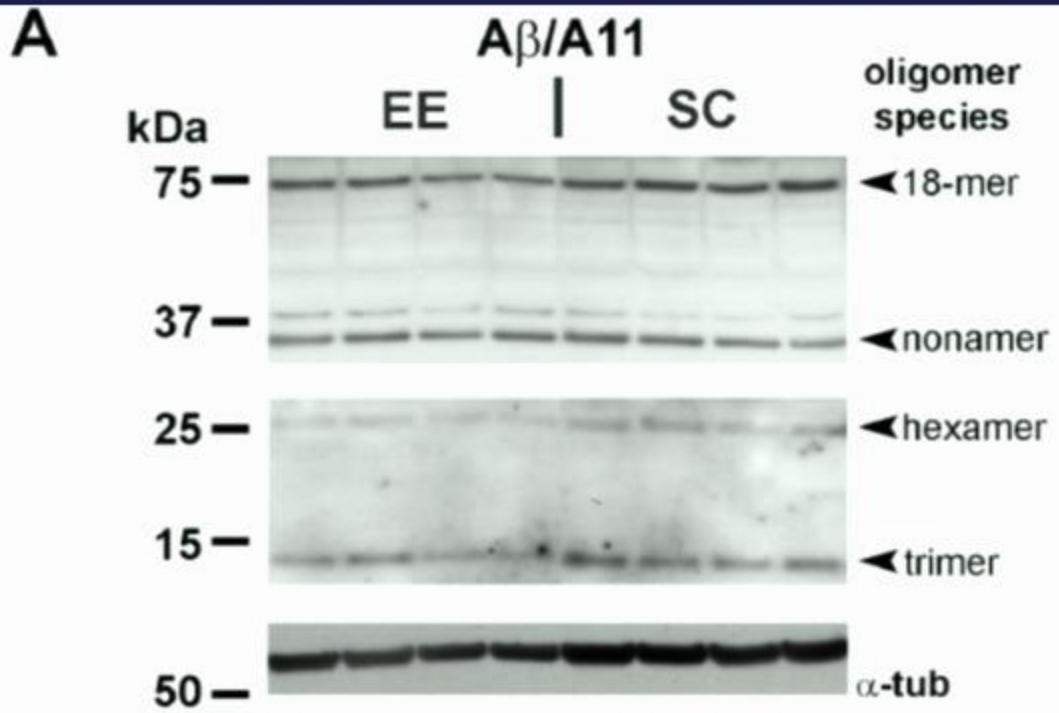
This study included 388 incident dementia cases (DSM-III-R criteria) that developed over a 9-year follow-up period among 1,375 baseline dementia-free community dwellers with good cognitive function (MMSE >23) (mean age = 81.2) from the Kungsholmen Project. An active lifestyle was defined as participation in mental, physical, or social activity.

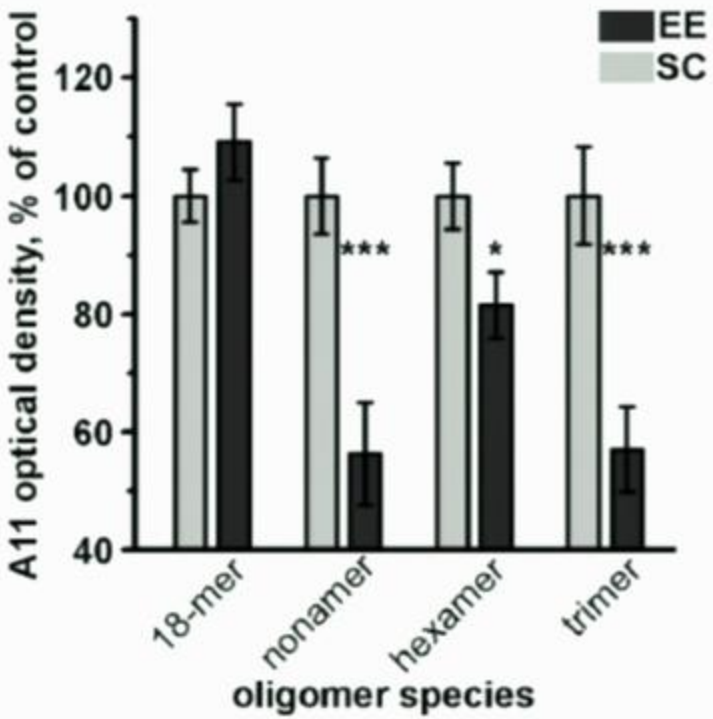
Age at onset of dementia was significantly older in persons who had higher levels of participation in mental, physical, or social activity independent of education, medical condition, functional status, and other confounders including APOE.

When the three types of activities were integrated into an index, it was found that the broader the spectrum of participation in the activities, the later the onset of disease ($p = 0.01$ for participating in two activities, and $p < 0.001$ for three activities).

There were 17 months difference in mean age at dementia onset between the inactive group and the most active group.

EE on Aβ oligomers in aged mice





EE effects on diffuse Abeta. Mediators: increase in nep, igf1

Mainardi et al, 2014

Landau et al. (2012) assessed the association between lifestyle practices (cognitive and physical activity) and Aβ deposition, measured with positron emission tomography using carbon 11–labeled Pittsburgh Compound B ([11C]PiB), in healthy older individuals.

The results showed that greater participation in cognitively stimulating activities across the lifespan, but particularly in early and middle life, was associated with reduced [11C]PiB uptake (physical activity alone was not a significant predictor).

EE protects neural circuits from Aβ oligomers effects

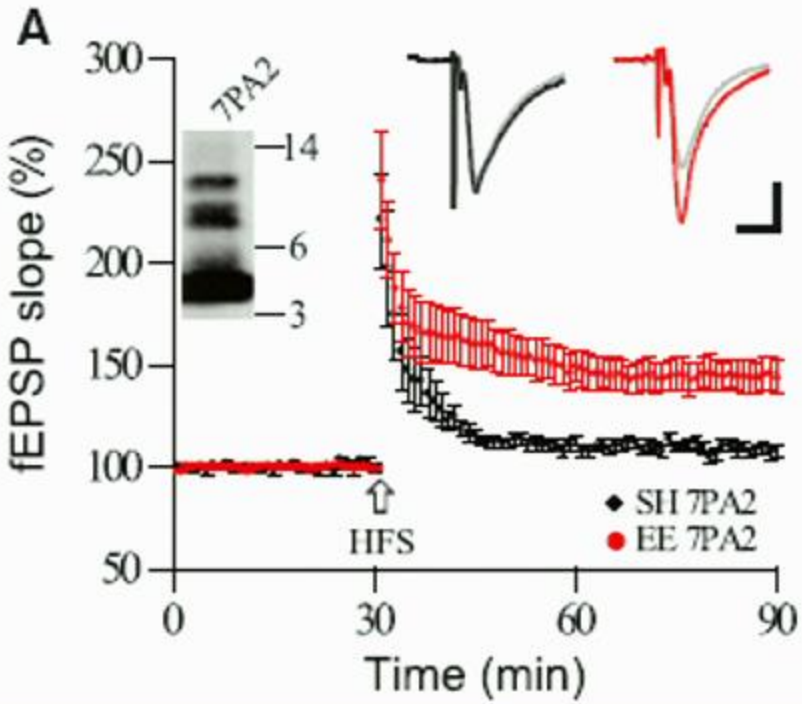


Figure 3. EE Exposure Prevents the Impairment of Hippocampal LTP and Decrease in Certain Signaling Molecules by Soluble Aβ Oligomers

(A) 7PA2 CM containing soluble human Aβ oligomers significantly inhibited HFS-induced LTP in hippocampal slices of SH mice (black diamonds, n = 9 slices/8 mice), but this was prevented in slices of EE-trained mice (red circles, n = 12/10). Inset: WB (Aβ mAbs 6E10+2G3) of the CM shows the soluble Aβ monomers (4 kDa) and SDS-stable low-n oligomers.

EE-Enhanced LTP Requires Activation of β_2-Adrenergic Receptors

Shaomin Li et al., 2012

EE and physical exercise in animal models of AD

Studies in animals models of AD have strengthened the relevance of EE/physical exercise protocols in relation to pathological aging (Sale et al., 2014).

Most studies have employed protocols of EE starting in very young animals, long before the onset of cognitive deficits, thus modelling the effects of cognitive reserve in delaying the onset of clinical manifestations, but there are also studies employing EE protocols starting after cognitive deficits and neurodegeneration are evident, thus modelling the effects of environmental stimulation in rescuing cognitive deficits.

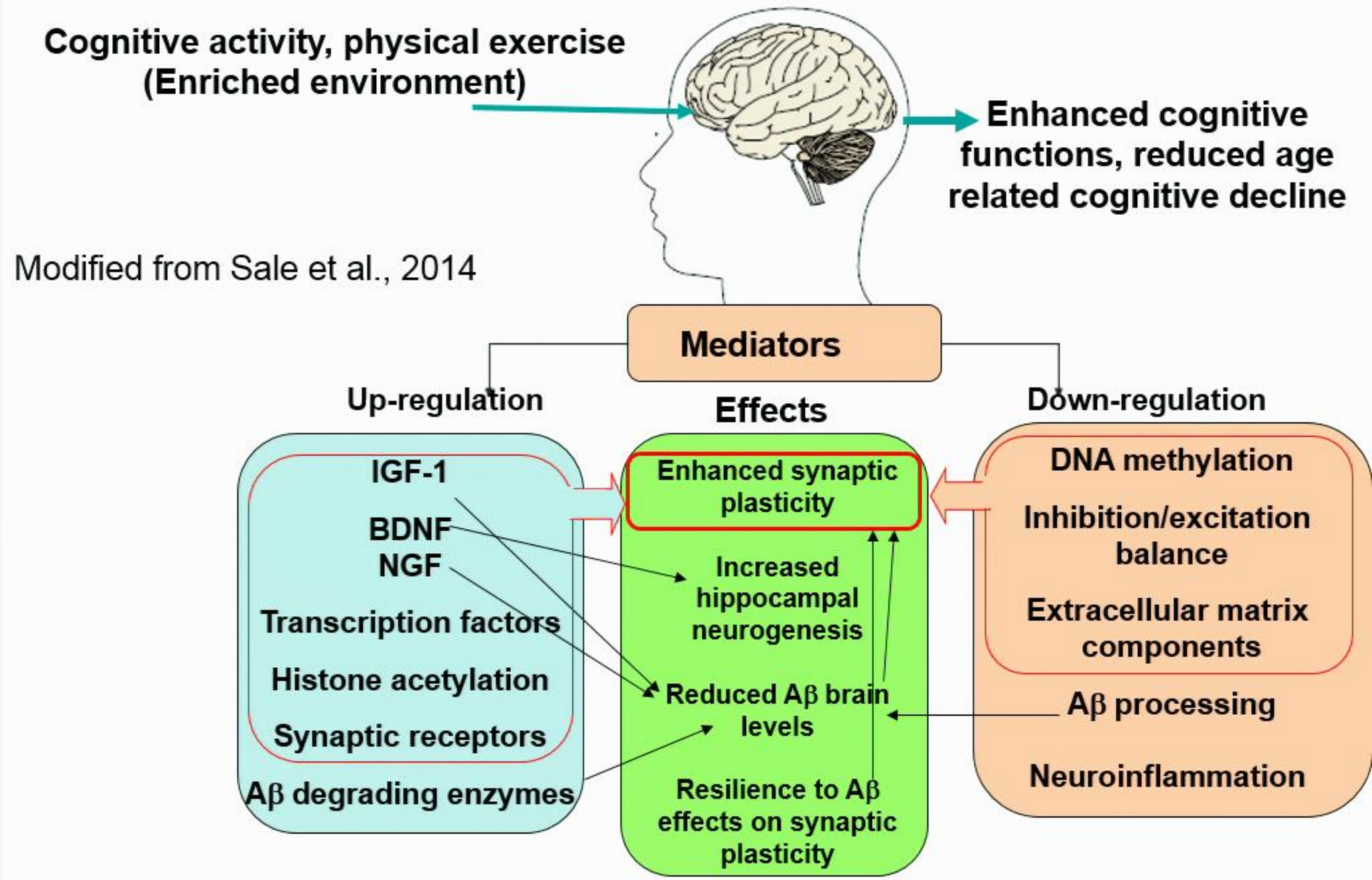


Fig. 3. The effects of Cognitive activity and physical exercise, key components of an Enriched Environment, on age related cognitive decline are mediated by several well-established key molecular factors. We have divided the factors through which EE acts into those that are upregulated and those that are downregulated. All factors within light red boxes enhance synaptic plasticity. In addition, BDNF increases hIppocampal neurogenesis and IGF-1 contributes to reduce Ab levels. Reduced Ab levels and resilience to Ab effects further contribute to increase synaptic plasticity.

EE: A richness that cures?

At present, few studies are available on the effects of training, cognitive or physical, on MCI or AD subjects.

Baker et al. (2010) investigated the effect of a 6 month program of aerobic exercise in thirty-three adults (17 women) with aMCI ranging in age from 55 to 85 years.
They found gender specific effects on cognition, with older women benefiting on a larger number of executive function tests than men, which had a limited benefit.

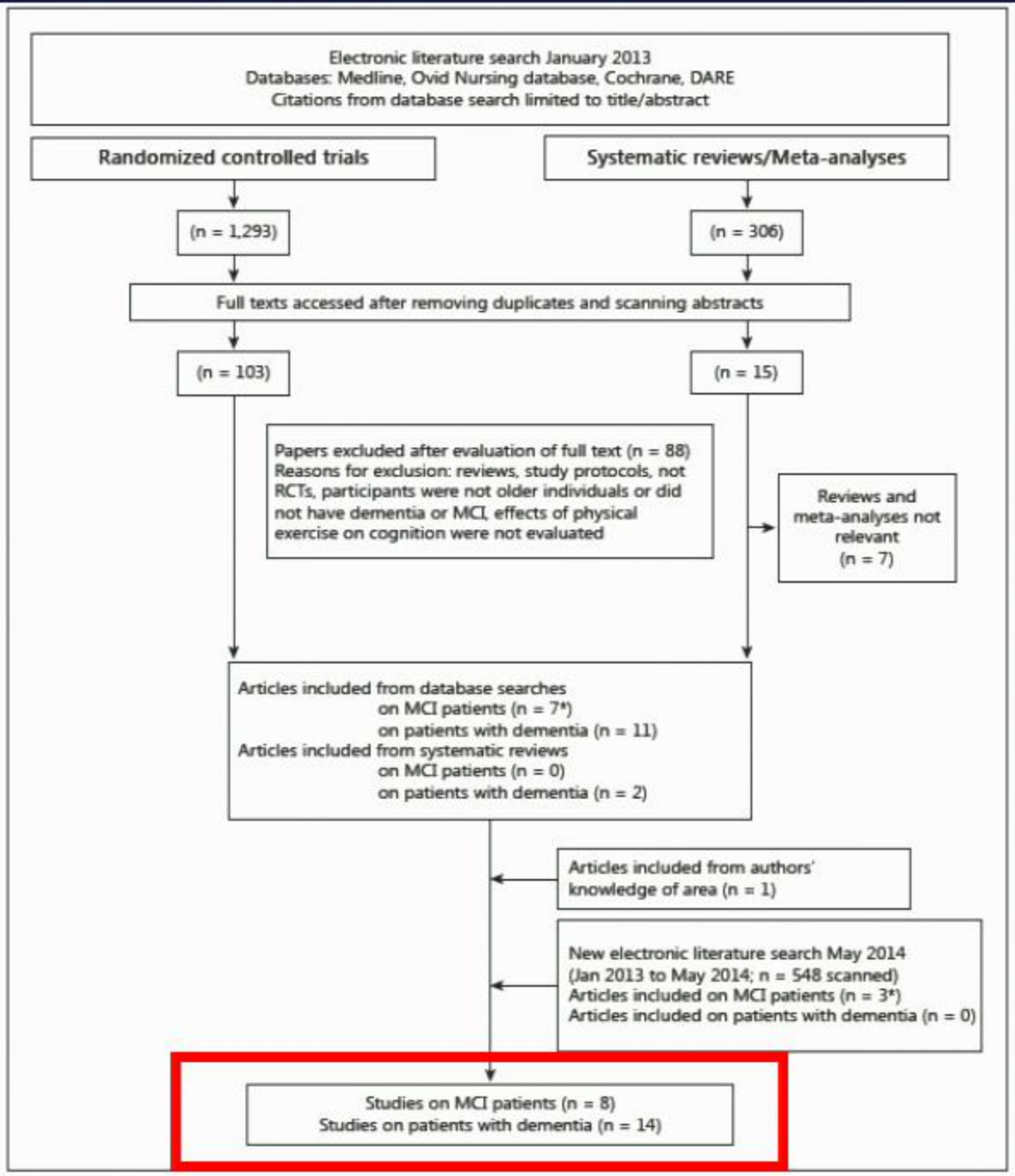


Fig. 1. Results of the research strategy using the terms cogniti* or demen* or Alzheimer* or mild cognitive impairment and physical activity or physical exercise or exercise or aerobic or strength or walk*. *One study was reported in two publications.

Ohman et al. 2014

Train the Brain project in Pisa

To assesses the efficacy of a combined cognitive and physical training on the progression of the disease in subjects with MCI or in the early stages of dementia.

Proposers and contractors:
two Institutes of the National Research Council (CNR), the Institute of Neuroscience and the Institute of Clinical Physiology (IN-CNR and IFC-CNR, Pisa)

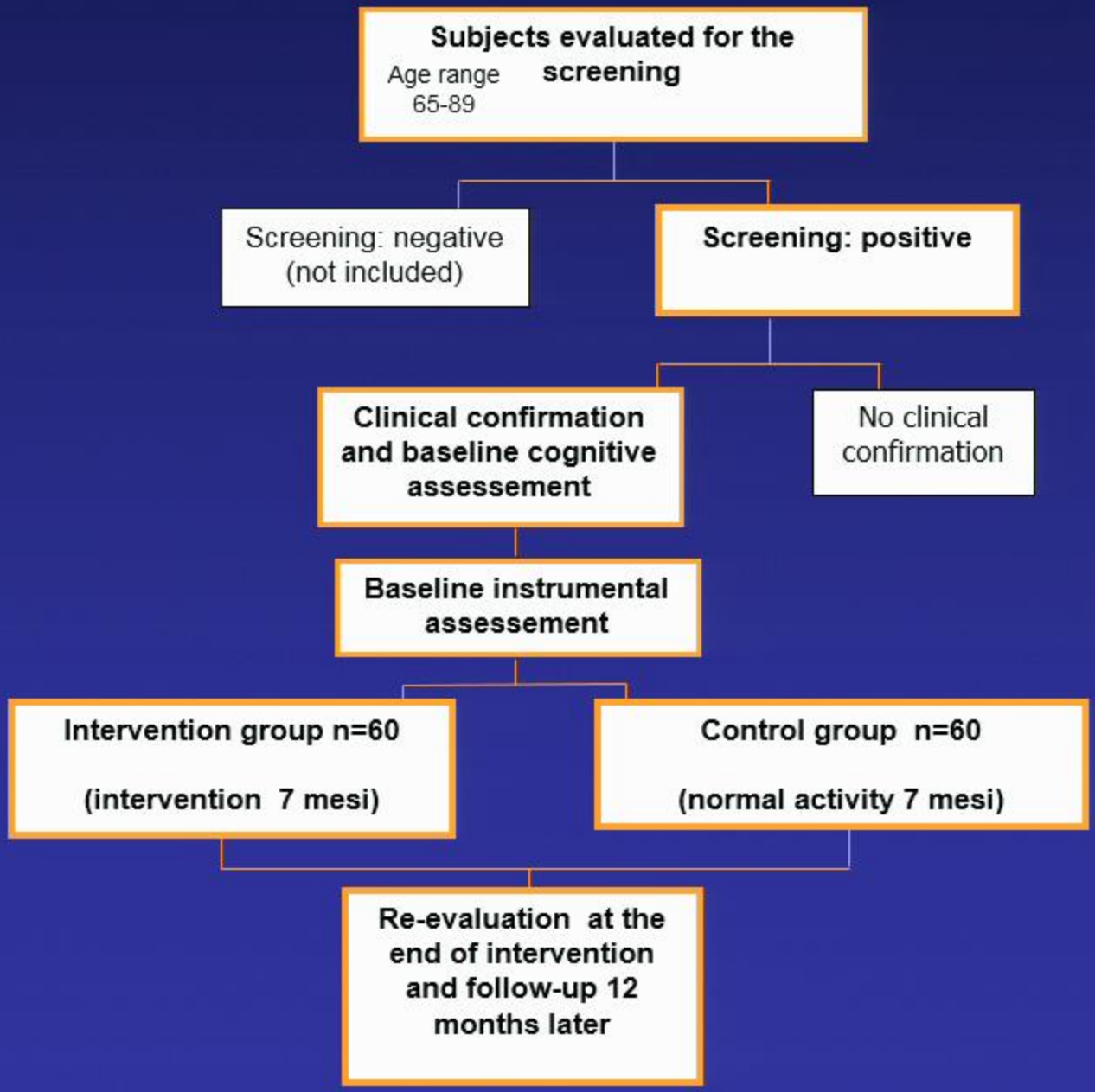
Collaborators: IRCCS Stella Maris, Pisa University and Azienda Ospedaliera Universitaria Pisana (Neurological, Cardiovascular, Clinical Biochemistry units)

Azienda Ospedaliero Universitaria Pisana

Università di Pisa

Funded by: CariPisa la FONDAZIONE

Project plan



TRAINING and NO TRAINING group did not differ for socio-demographical data, education, age, gender, screening and baseline cognitive assessments.

TtB space

- Reception

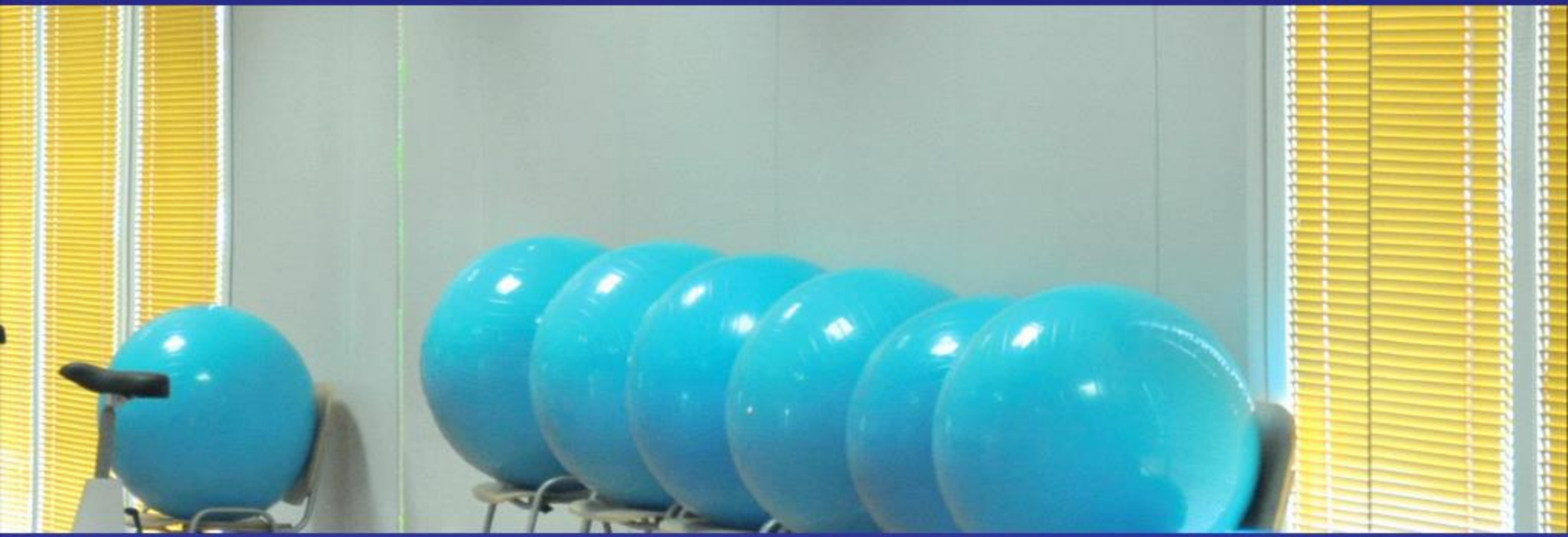
- Testing

- Music

- Cognitive training

TtB space

Physical training, 1 h/day, three days/week, incremental



SOMMINISTRAZIONE

Per mantenere elevato il grado di coinvolgimento da parte dei soggetti sperimentali la somministrazione del training giornaliero si è basata su una strategia mista.

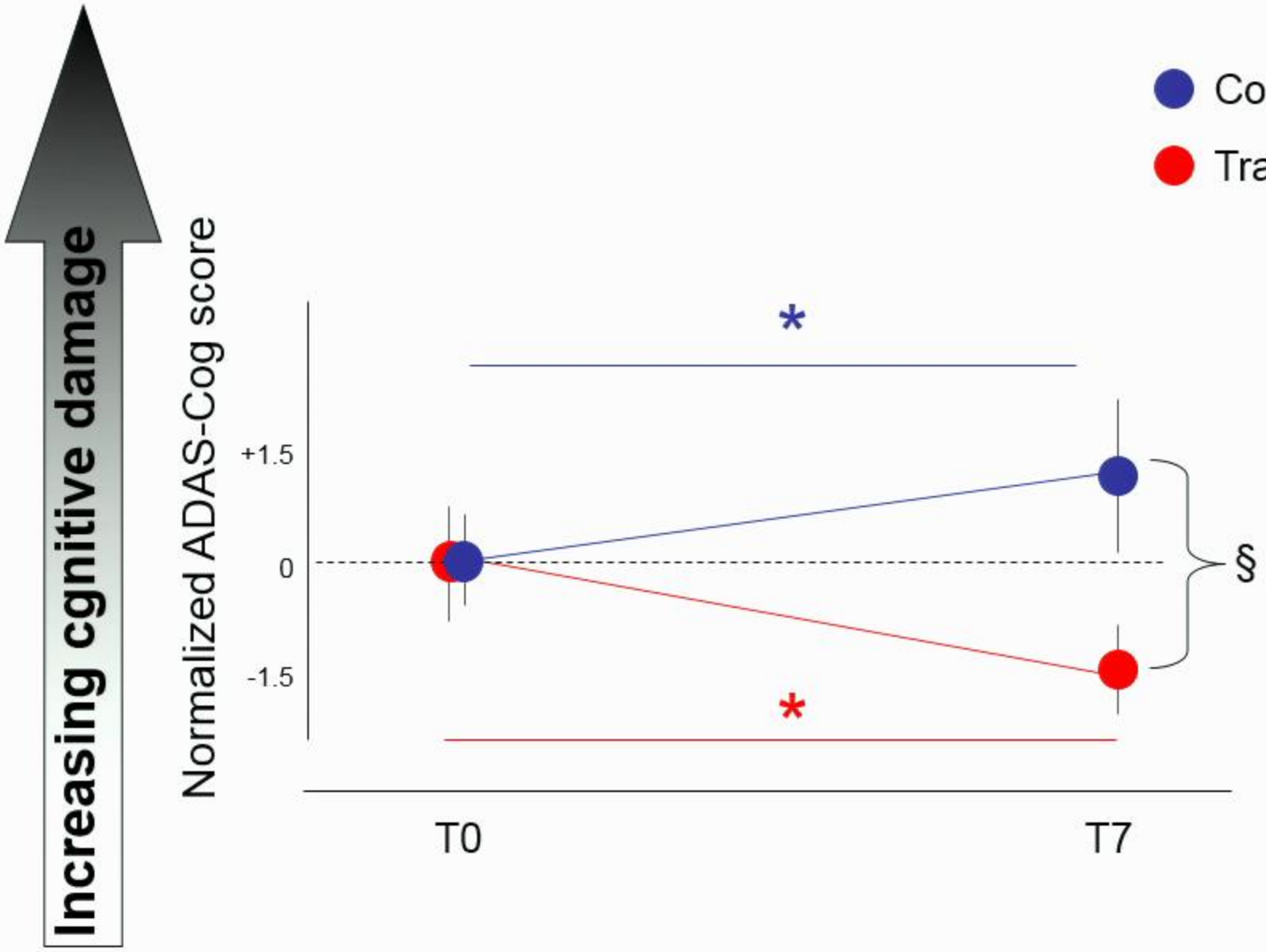
Le due sessioni giornaliere si componevano quindi:

- Sessioni di allenamento di singola modalità
- Sessioni di attività cognitive a carattere «ludico-ricreativo» e attività di gruppo.

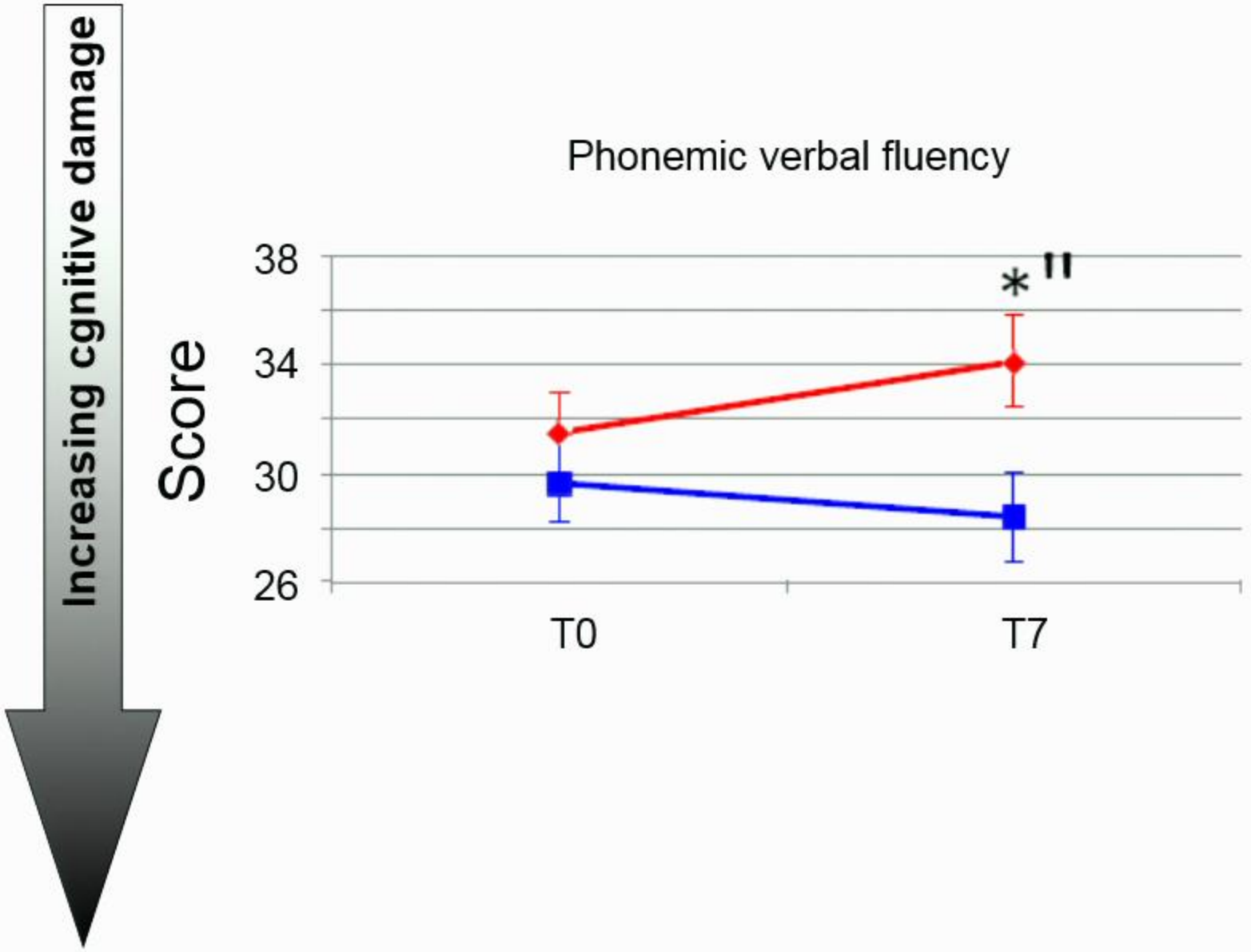
Compliance for the training

An intermediate goal was to study how patients adhere to the proposed protocols ("drop out" analysis).

Only **two subjects have abandoned the training**, suggesting a strong motivation and a good compliance with the protocol in the subjects but also a strong attractiveness of the proposed activities.

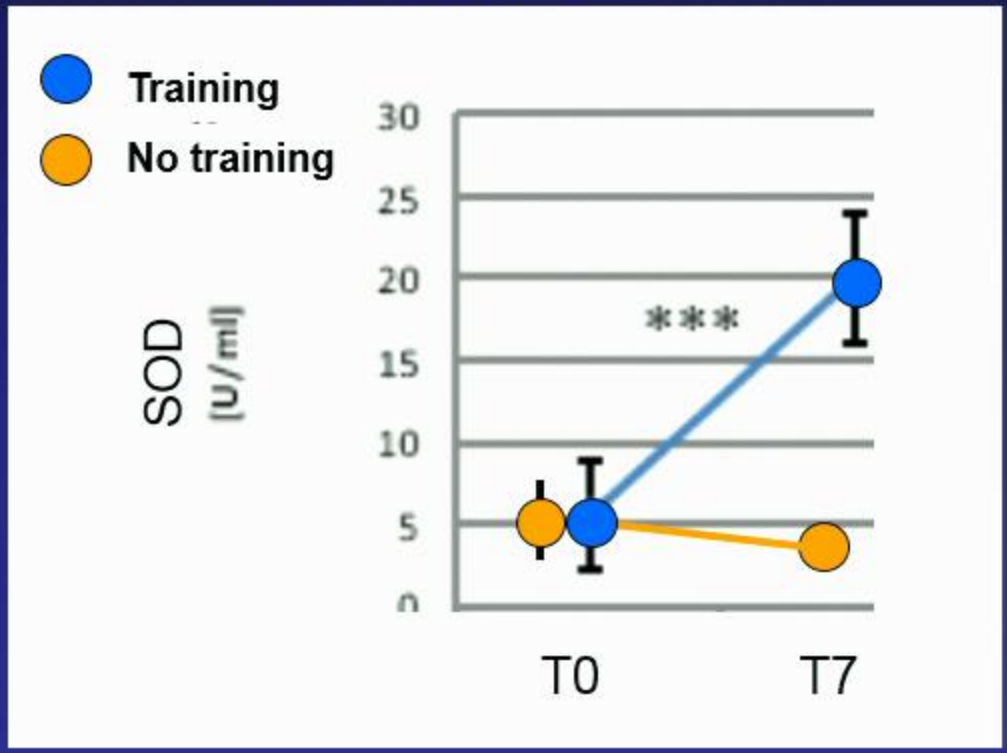


U. Bonuccelli, G. Tognoni, S. Cintoli, L. Volpi, C. Carlesi



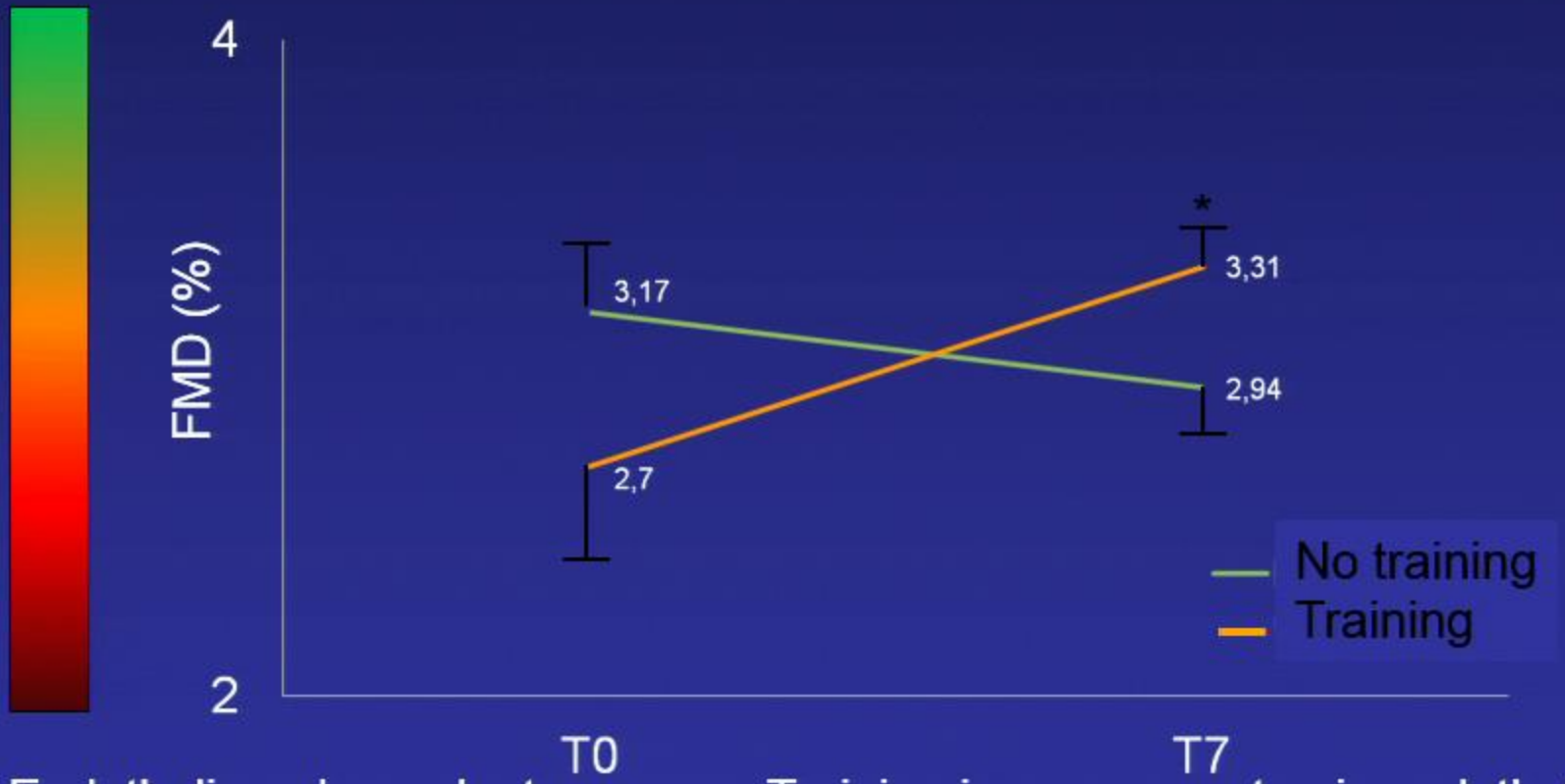
U. Bonuccelli, G. Tognoni, S. Cintoli, L. Volpi, C. Carlesi

Variazione dei livelli plasmatici dei biomarcatori di stress ossidativo



L. Chico, G. Siciliano

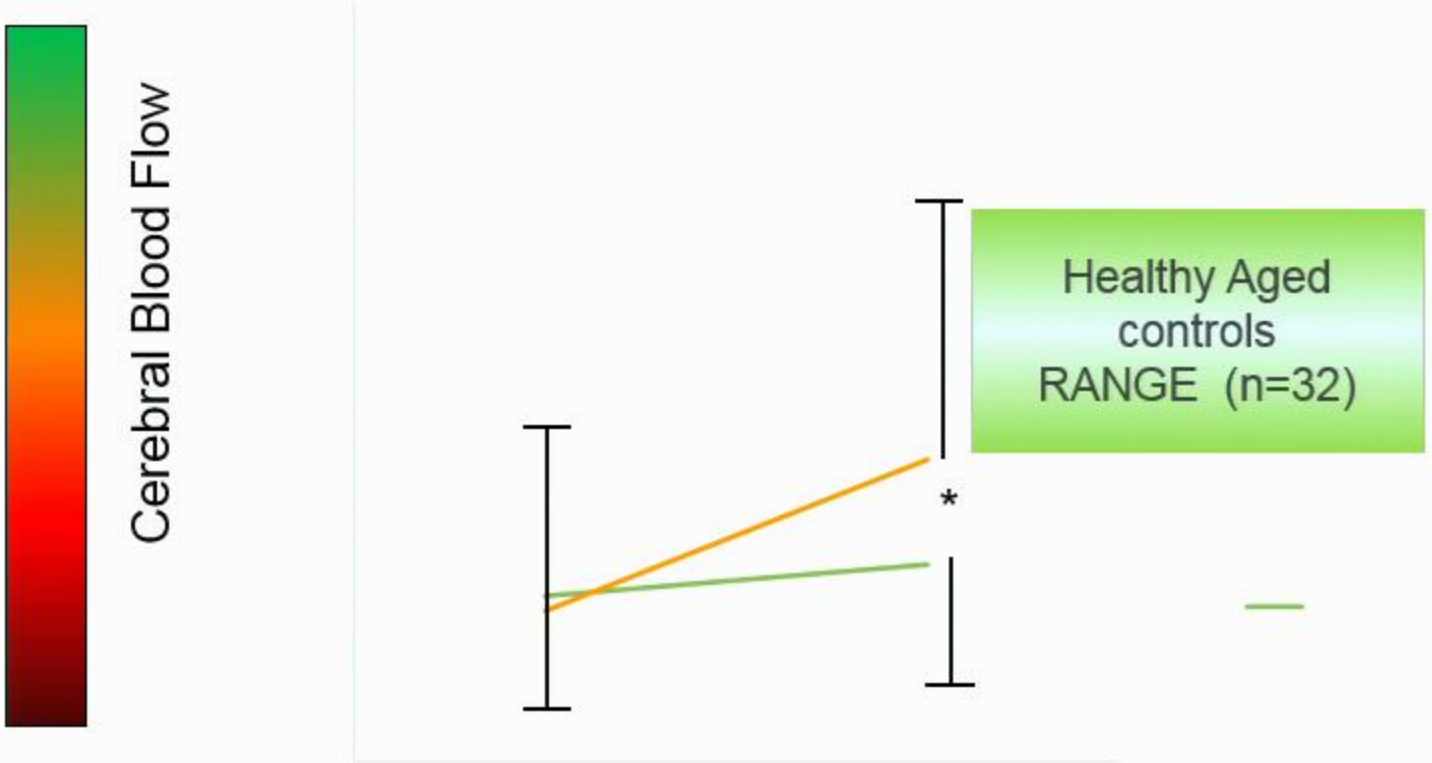
Mind the vessel - la funzione endoteliale



Endothelium dependent process. Training improves systemic endothelial function, which tends to worsen over time in non-trained MCI

Rosa Maria Bruno, Francesco Stea, Giulia Cartoni, Rosanna Iannarella, Alberto Marabotti, Gennaro D'Angelo, Luna Gargani, Lorenzo Ghiadoni, Stefano Taddei, Eugenio Picano, Rosa Sicari, Lorenza Pratali

CBF in whole para-hippocampus

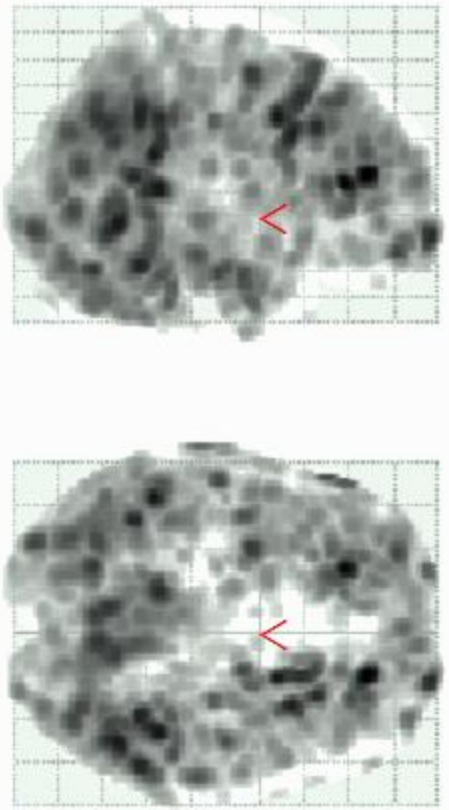


Training increases cerebral blood flow in para-hippocampal region (key to memory and learning), restoring values to normal range found in healthy aged controls

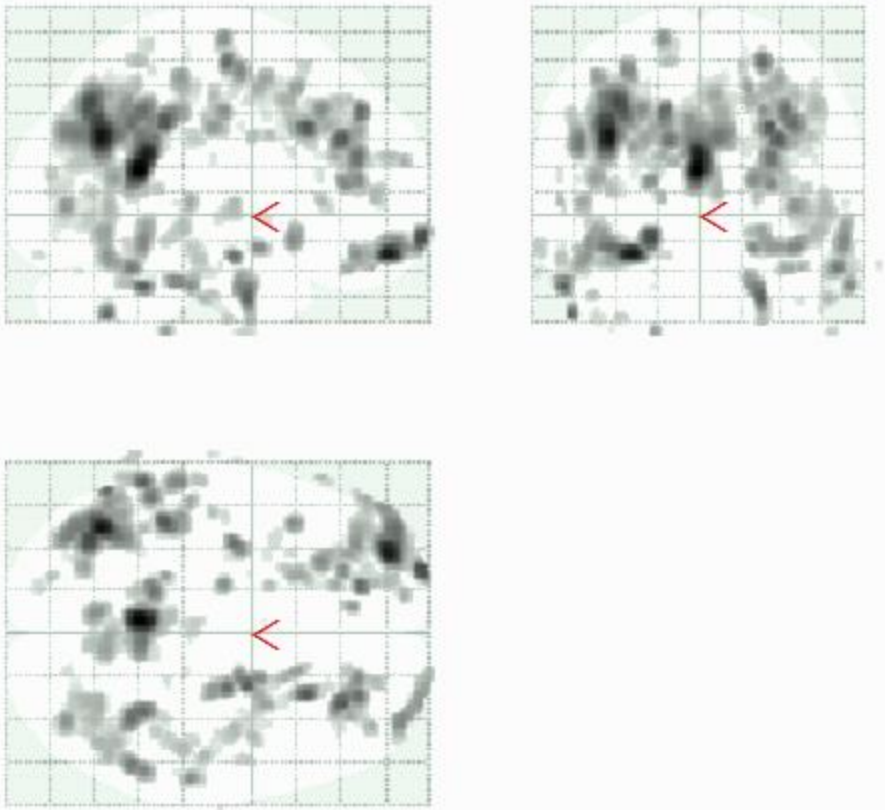
M. Tosetti, G. Cioni, D. Scelfo, L. Biagi, A. Retico, R. Paquariello, S. Beconcini

CBF

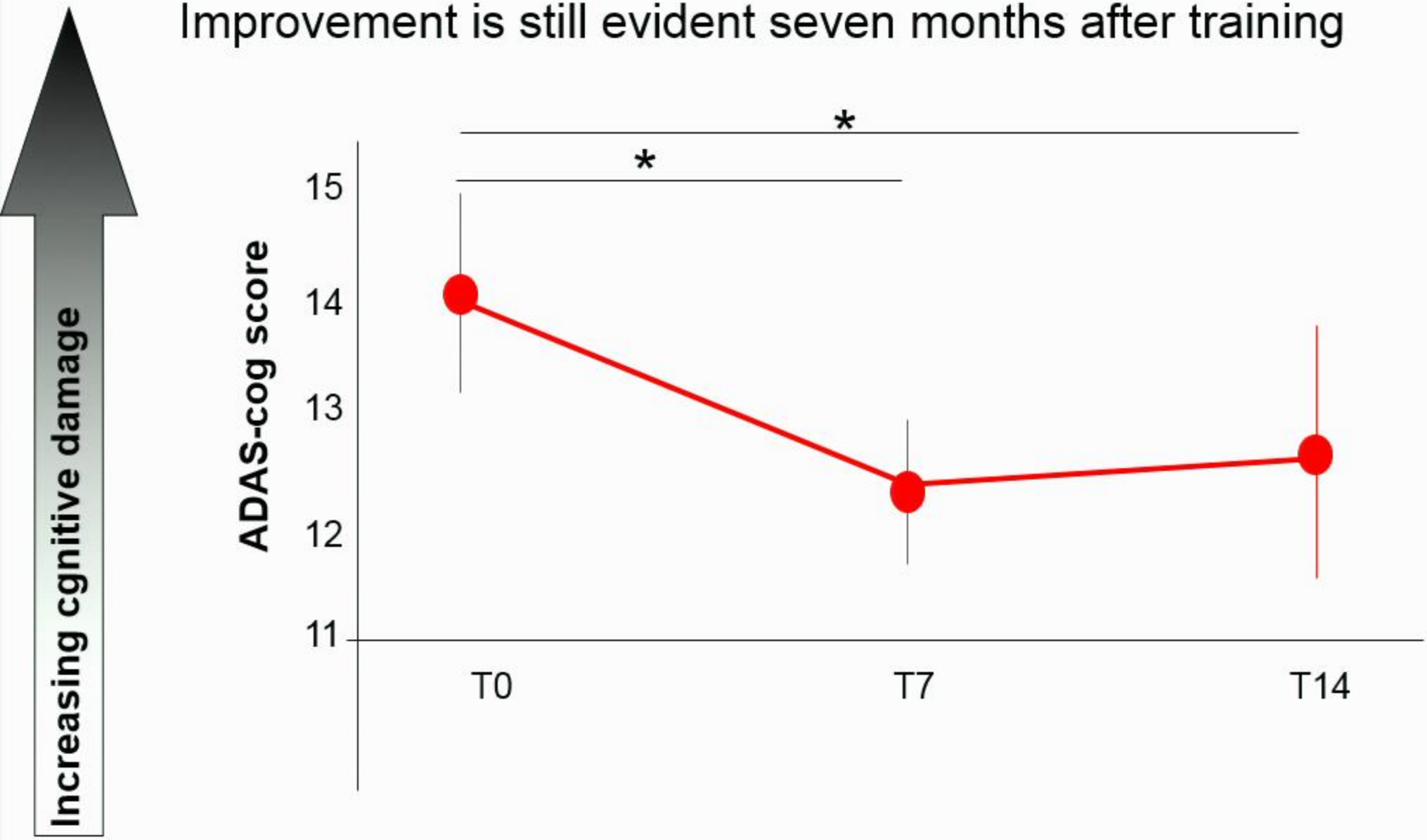
Reference healthy subjects > MCI subjects a T0



Reference healthy subjects > MCI subjects a T1



Improvement is still evident seven months after training



Preliminary data

There are more things in heaven and earth, Horatio,
Than are dreamt of in your philosophy.
Hamlet Act 1, scene 5, 159–167

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