Il ruolo dell'esercizio fisico nella prevenzione delle malattie neurodegenerative

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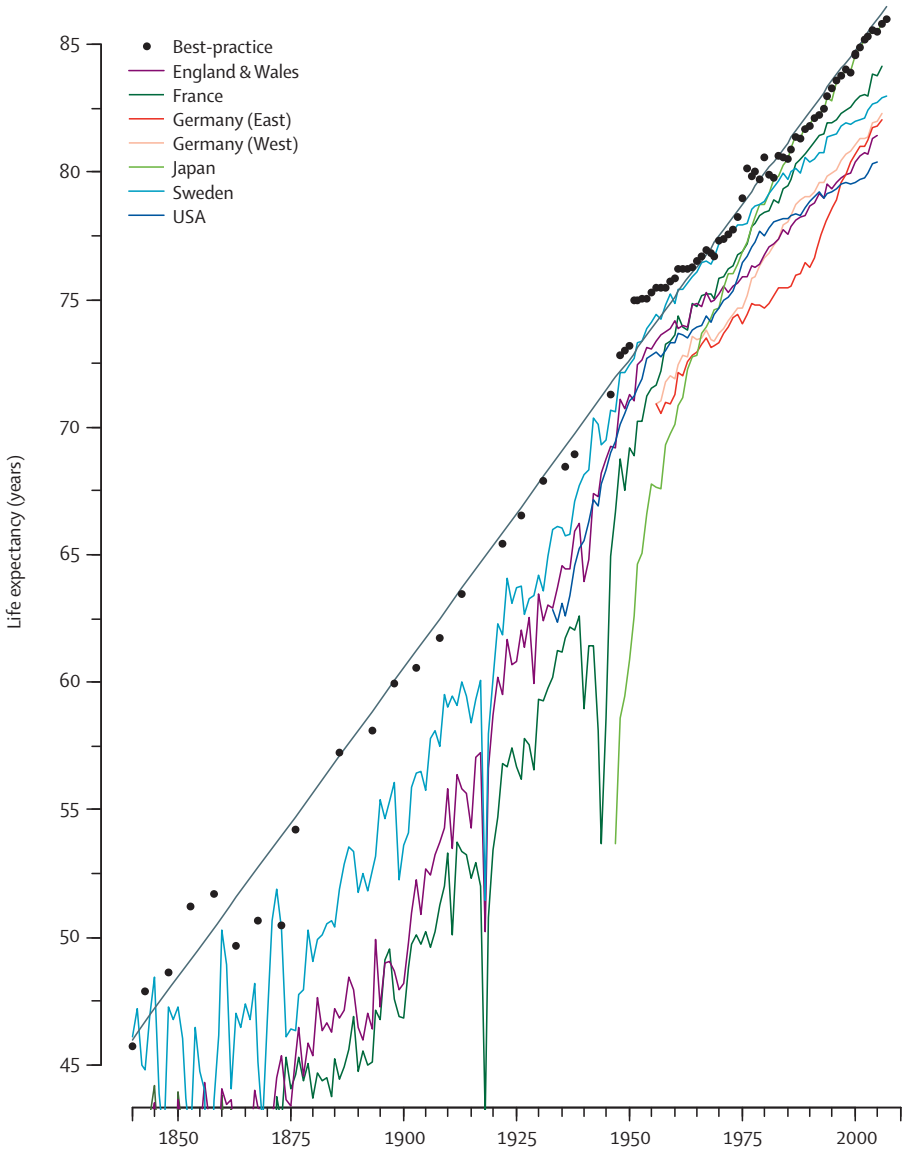
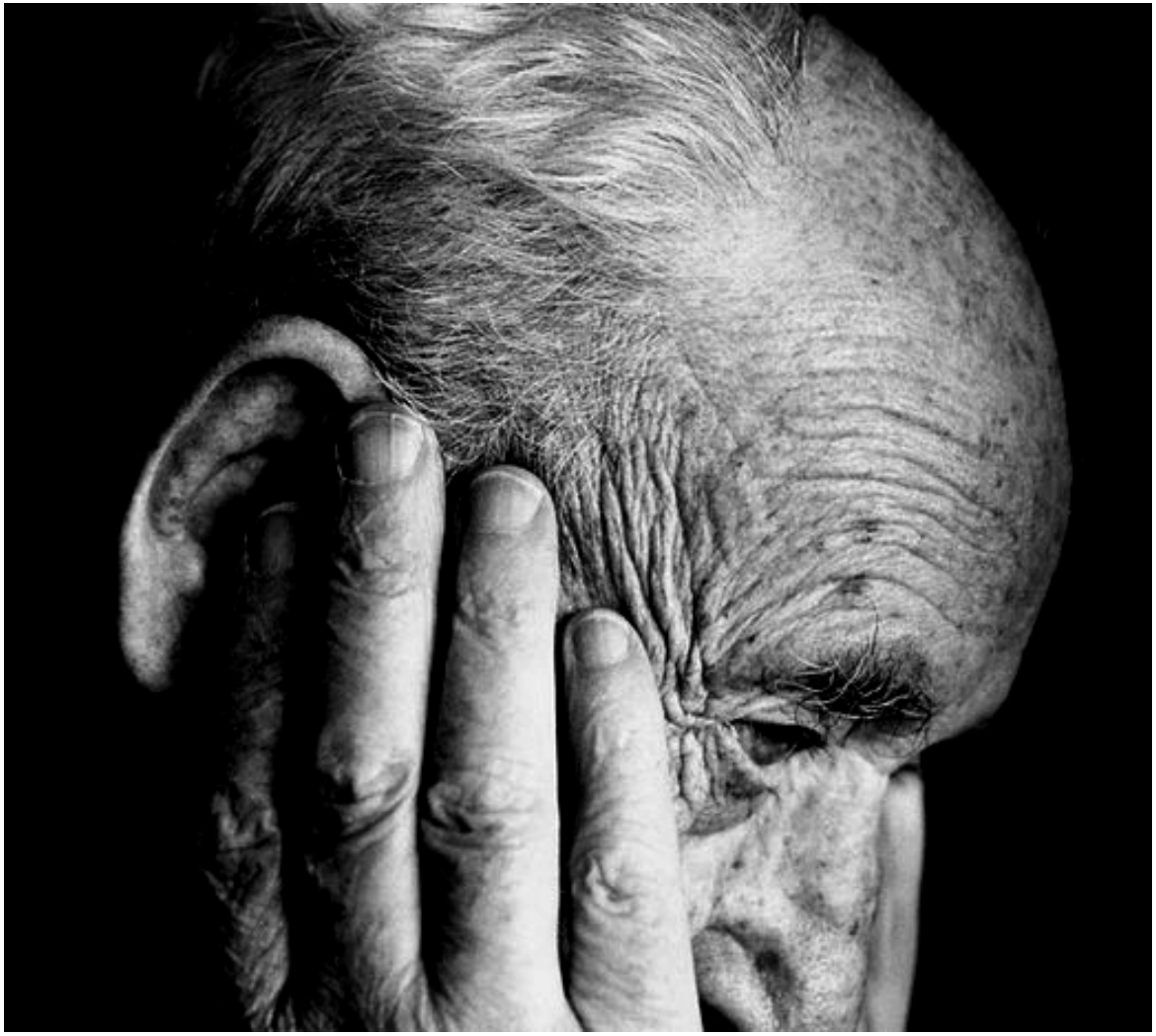
Life expectancy … but …



Christensen K. *Lancet*. 2009

Alzheimer’s disease most common type of dementia, 50% of the cases.



Alzheimer Association, 2012

- Gradually worsening ability to remember new information.
- Several cognitive deficits.
- Progressive deterioration in functional ability.
- Increased disability and mortality.

- Frequently AD patients exhibit a remarkable weight loss.
- Considered one of the diagnoses of dementia.
- Direct cause of mobility limitation, bed-bound, and increased mortality.

Deterioramento cognitivo …. demenza

Demenza è il termine usato per descrivere i sintomi di un numeroso gruppo di malattie che provocano il deterioramento progressivo delle funzioni mentali di una persona.

Tante demenze …. quali demenze

La Malattia di Alzheimer la più comune (50-70%)

Nelle fasi iniziali i sintomi sono quasi impercettibili

La Demenza Vascolare (multi-infartuale)

problemi della circolazione sanguigna cerebrale

Il Morbo di Parkinson

Nelle ultime fasi della malattia si può sviluppare demenza

Demenza con corpi di Lewy

Piccolissime strutture sferiche che contribuiscano alla morte delle cellule cerebrali

Il Morbo di Pick

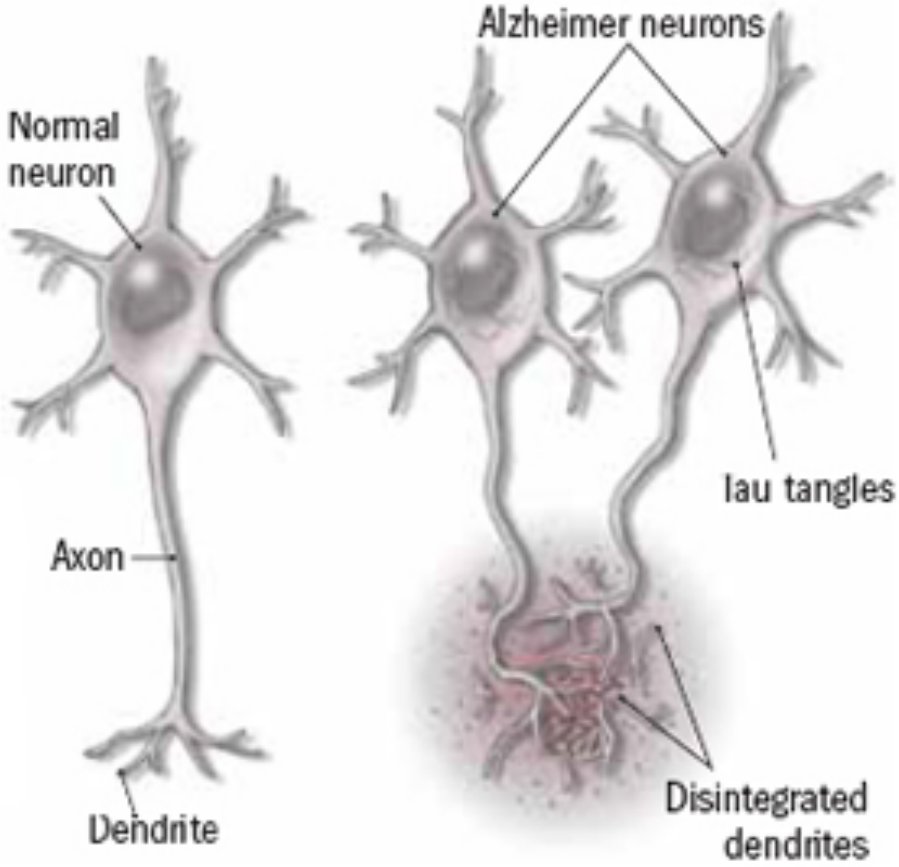
Deterioramento progressivo capacità mentali

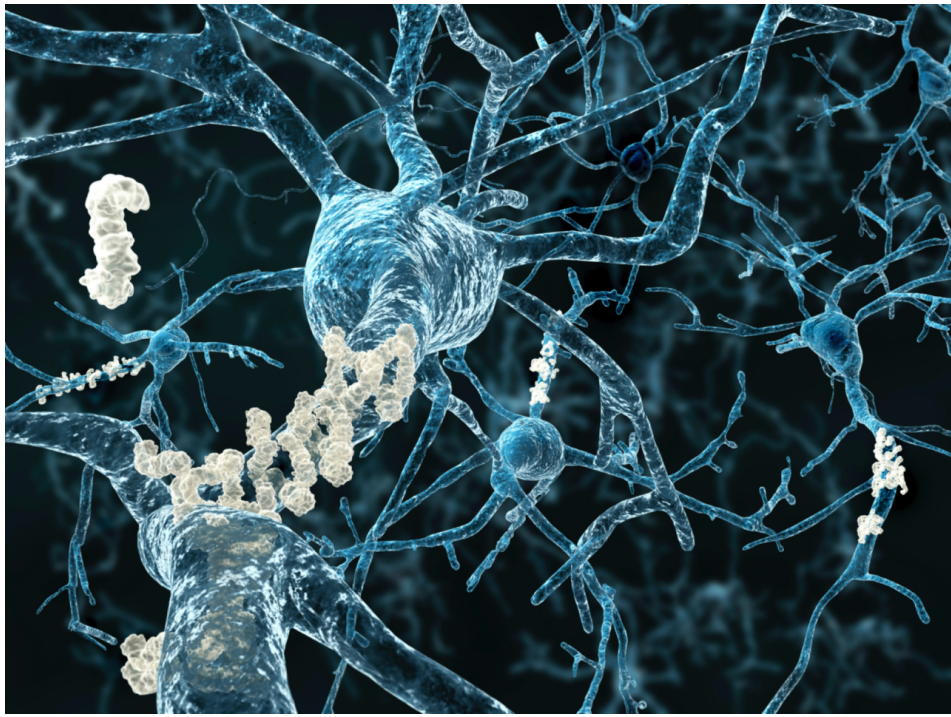
La Corea di Huntington

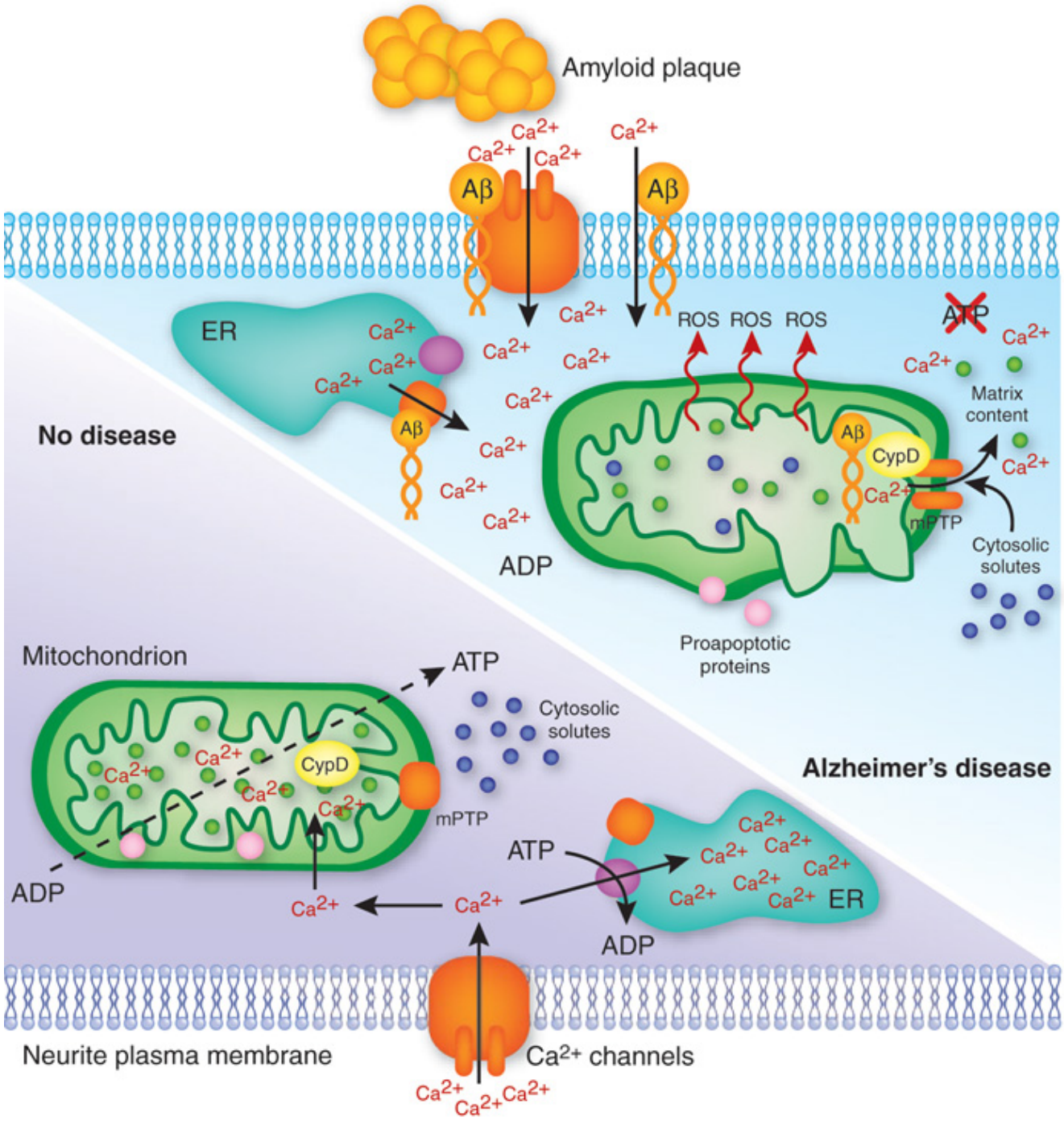
Malattia degenerativa ereditaria del cervello

Segni e sintomi

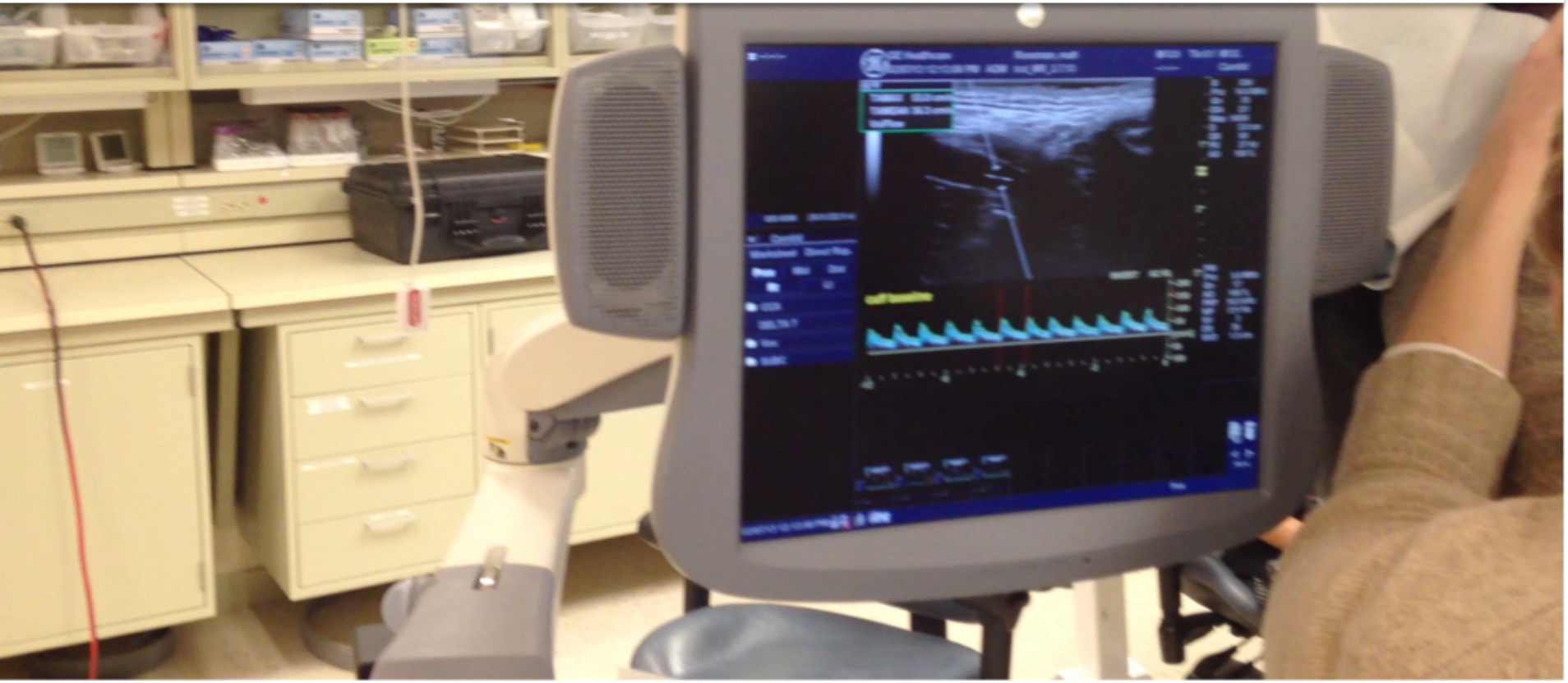
Perdita della memoria a breve termine	Difficoltà nel compiere le ADL	Problemi di linguaggio	Disorientamento spazio temporale wandering
Diminuzione della capacità di giudizio	La cosa giusta al posto sbagliato	Cambiamenti di umore e personalità	Controllo dell'alvo e minzione


Alzheimer neurons
Normal neuron
Iau tangles
Axon
Dendrite
Disintegrated dendrites

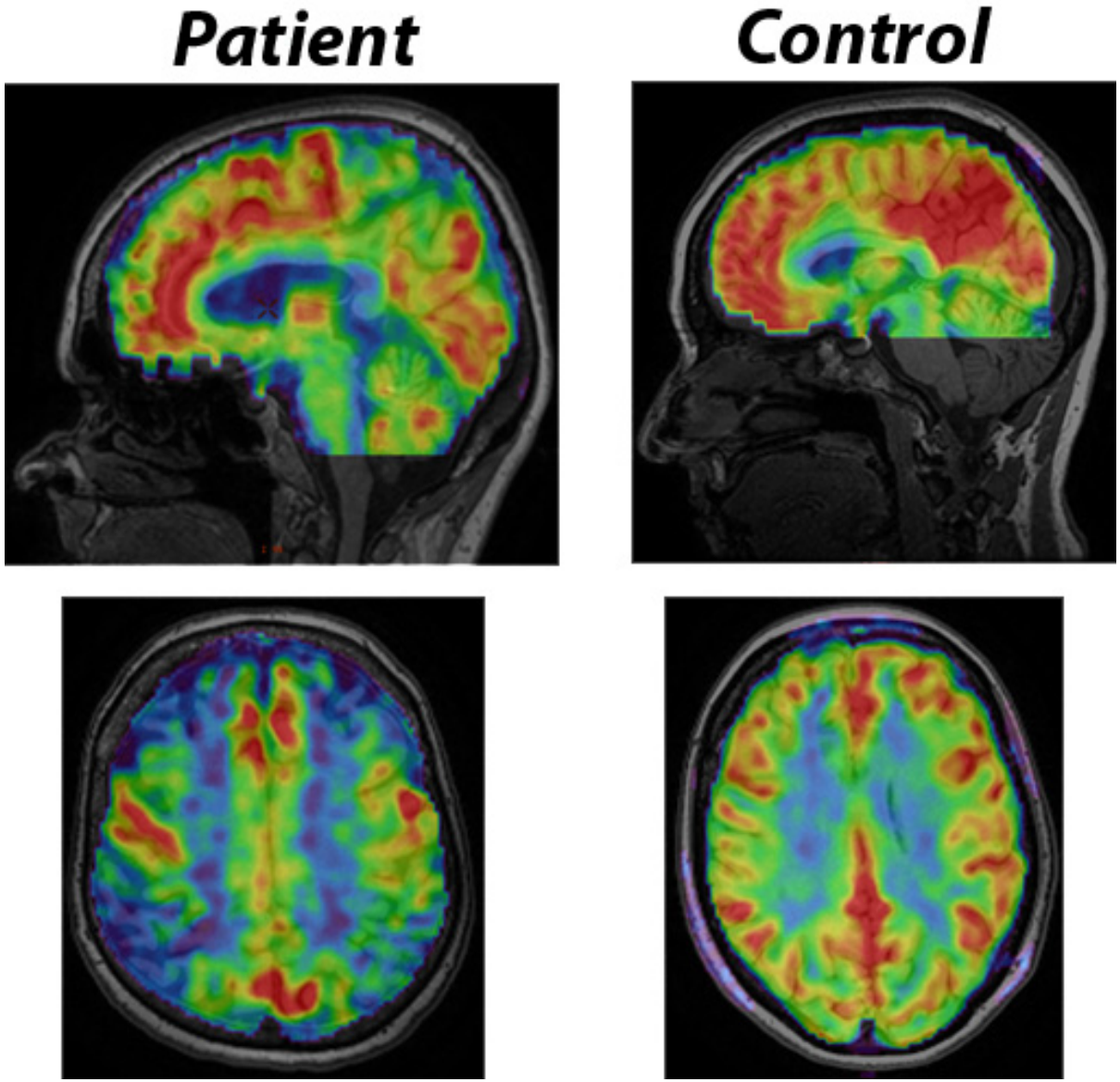



Amyloid plaque
Aβ
Ca2+
ER
No disease
ROS
ATP
Matrix content
CypD
mPTP
Cytosolic solutes
ADP
Proapoptotic proteins
Mitochondrion
Alzheimer's disease
Neurite plasma membrane
Ca2+ channels

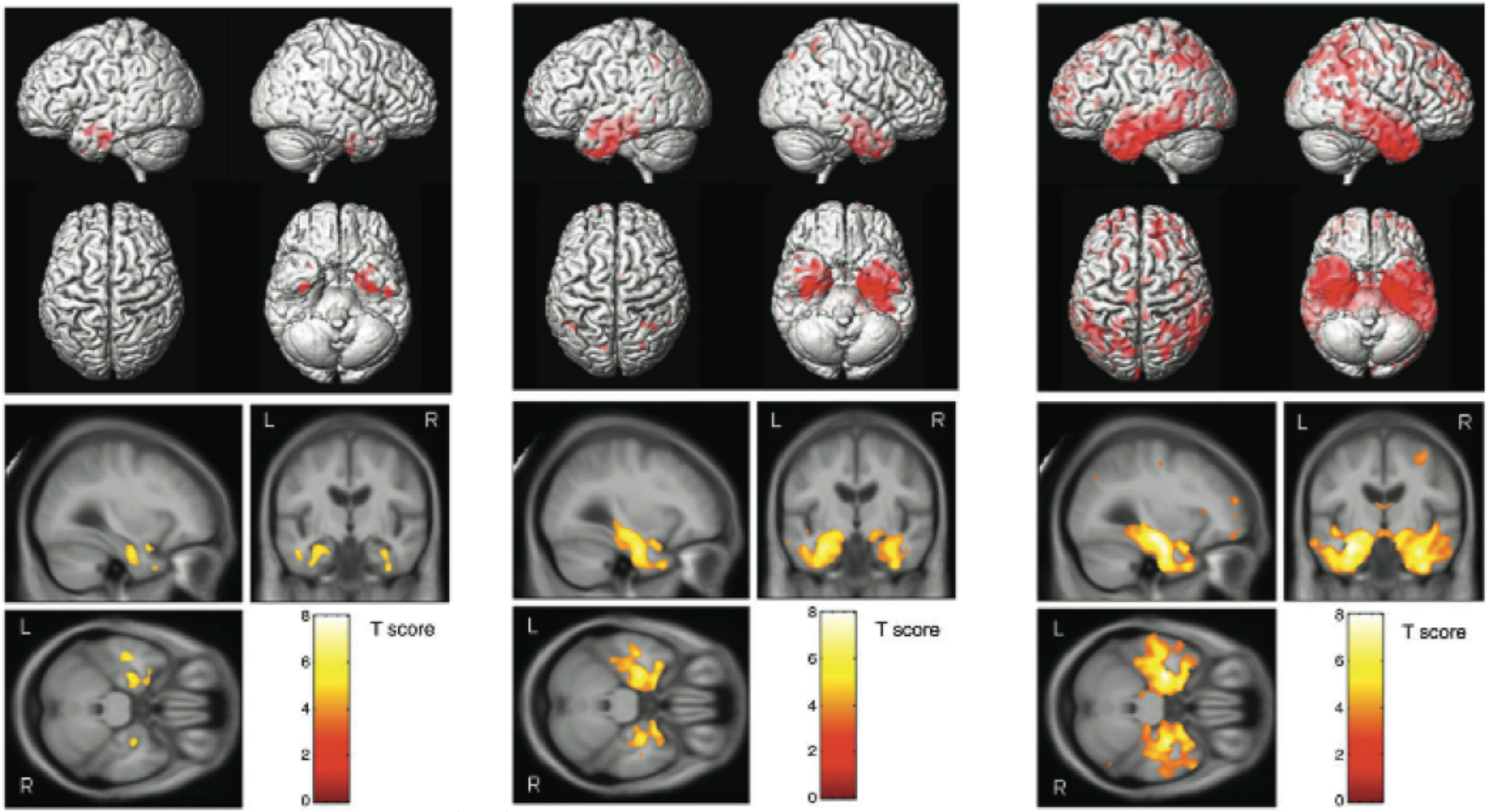
Transracial Doppler



Arterial spin labeling (MRI)



Microcirculation



MCI

12 mesi prima della diagnosi di AD

Diagnosi di AD

Whitwell J. Brain 2007

Test clinici predittivi

	3 anni prima della diagnosi di AD	1 anno prima della diagnosi di AD	Diagnosi di AD
MMSE	27	25	24
CDR	1.0	2.0	3.5
DRS	132	125	120

Whitwell J. Brain 2007

Demenza: quali fattori di rischio ?

Variabile	Non sviluppo della demenza	Sviluppo della demenza
età	78	80 *
sesso	63	67
entia	92	91
Scolarizzazione elevata	74	84 *
Capacità funzionali	10,9	11,5 *
Attività fisica precedente	13,6	12,8
Livello cognitivo	10,6	7,5 *
ipertensione	52	45
diabete	11	12
infarto	7	3
Patologie cardiache	29	23
Disfunzioni tiroidee	14	9
depressione	17	19

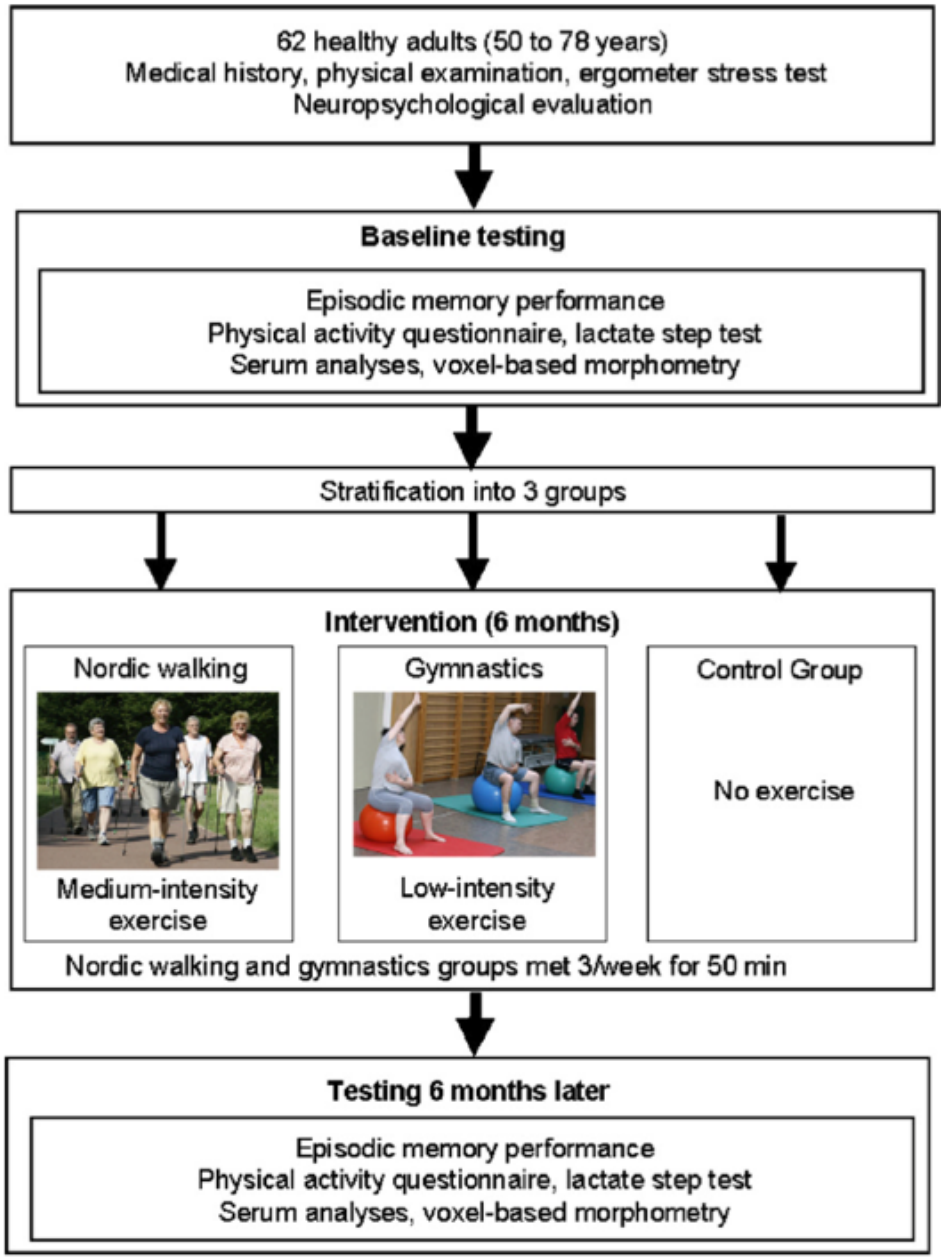
Verghese J. N Engl J Med 2003

Demenza: quali fattori preventivi ?

- Studio prospettico 21 anni
- Correlazione significativa tra:
  - Partecipazione all'attività fisica nel tempo libero e decremento del rischio di demenza (Alzheimer e vascolare)
  - La partecipazione ad una attività settimanale corrisponde ad una riduzione del 7% dell'insorgenza della malattia

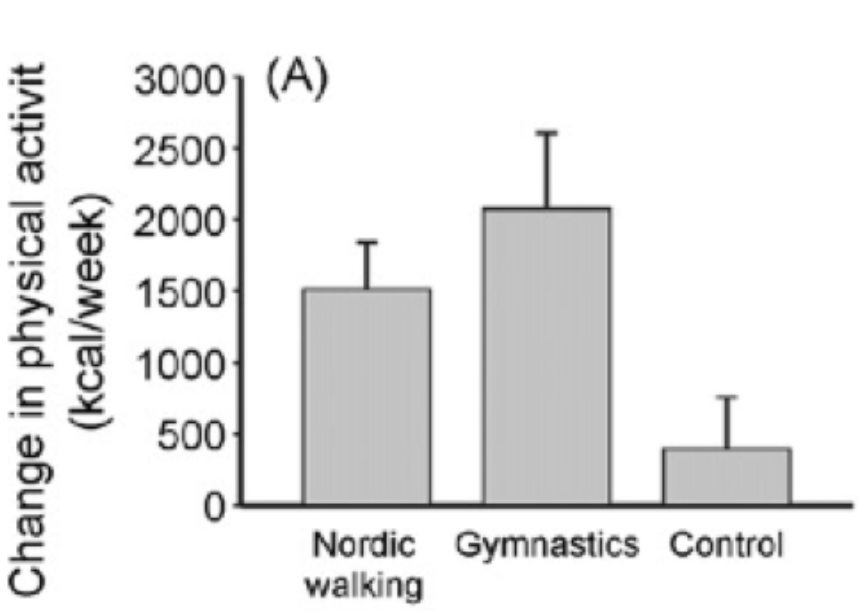
Verghese J. N Engl J Med 2003

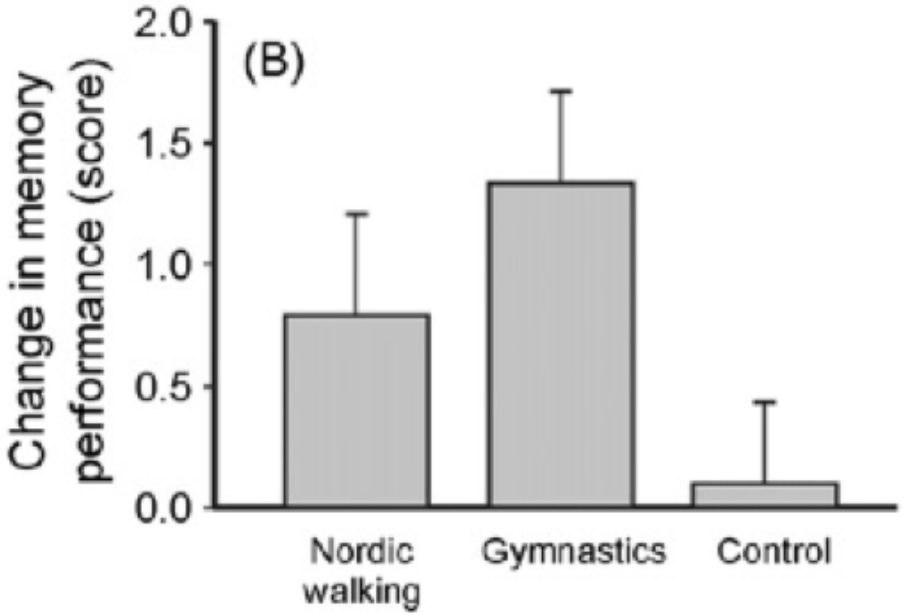
Demenza … e gli interventi di attività fisica

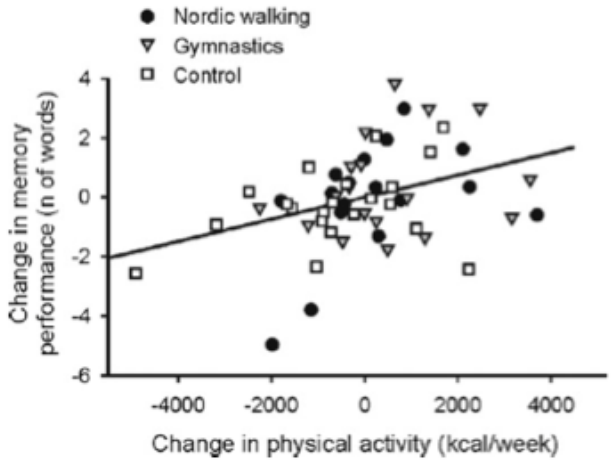


Ruscheweyh R. *Neurobiology of Aging*. 2009

Demenza … e gli interventi di attività fisica







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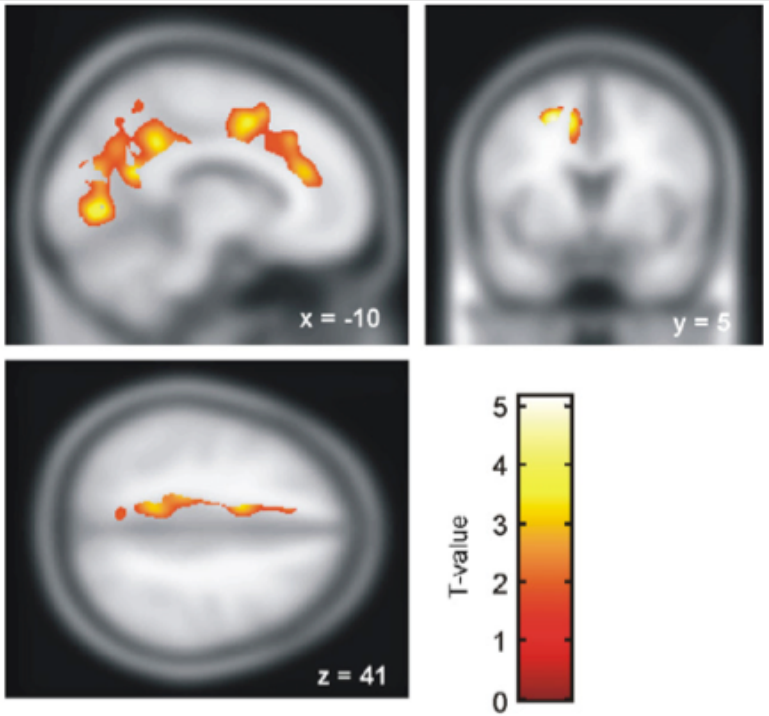
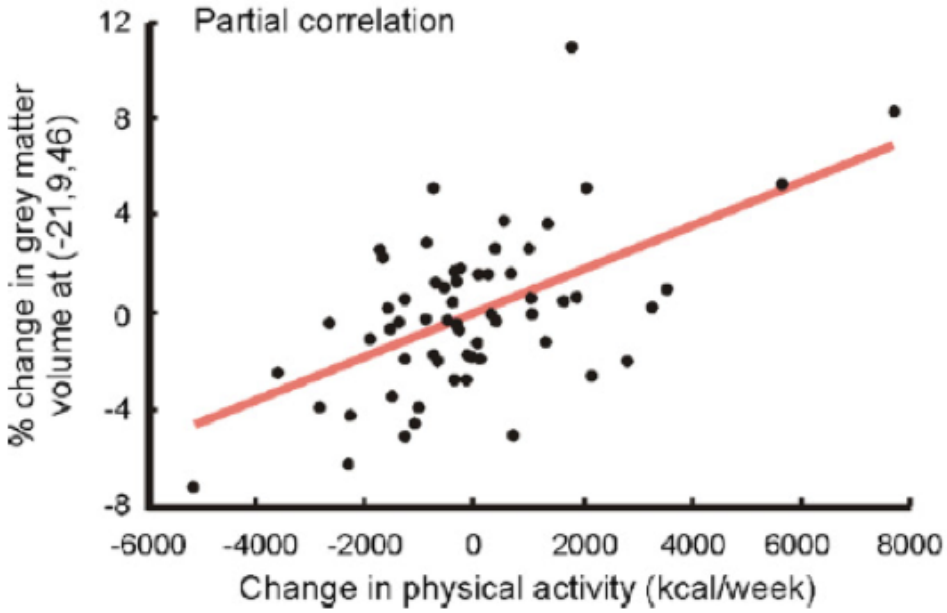
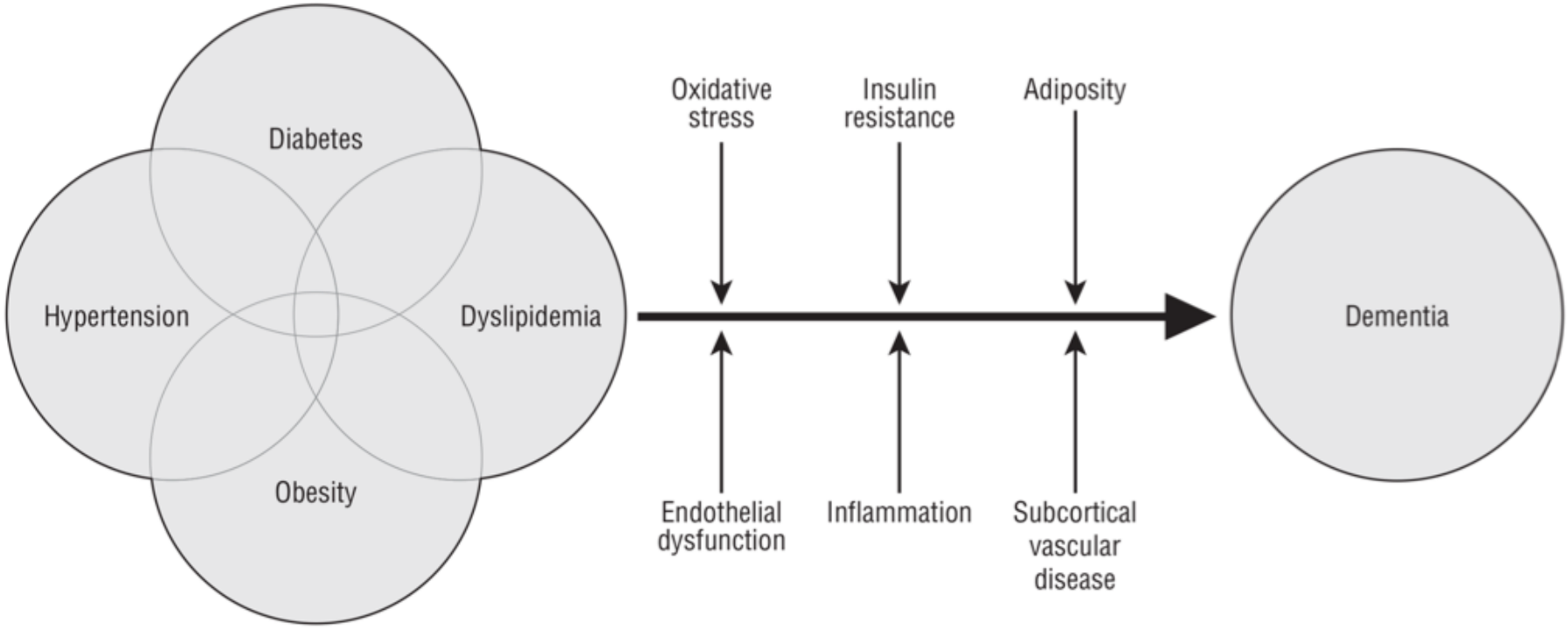
Demenza … e gli interventi di attività fisica





Ruscheweyh R. *Neurobiology of Aging*. 2009

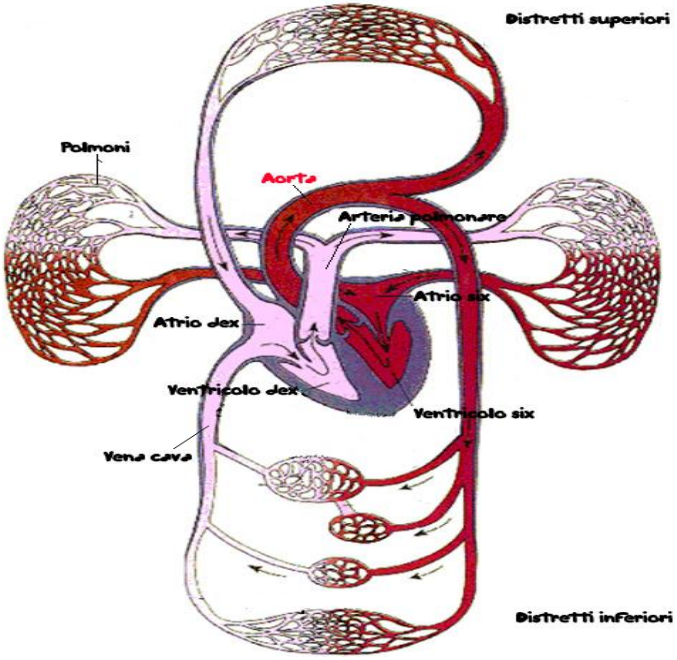
Altri fattori associati all'insorgenza della demenza



Middleton L. *Arch Neurol* 2009

Componenti cardiovascolari

Prevention Strategy	Observational Studies	Controlled Trials	Future Directions for Research
Vascular risk factors	Older adults with diabetes, hypertension, dyslipidemia, obesity, and metabolic syndrome have a higher risk of dementia and cognitive decline in most studies	Antihypertensives have not consistently reduced the risk of dementia or cognitive impairment among people with hypertension	Trials examining the effect of interventions for diabetes and obesity (in progress)
	These risk factors at midlife are also associated with increased risk of dementia	Statins have not consistently reduced the risk of dementia among people with dyslipidemia	Trials identifying the mechanistic link between vascular risk factors and dementia and determining whether modification is possible through behavior or treatment
	Midlife hypertension is associated with increased risk of dementia in late life; the association between late-life hypertension and dementia is less consistent	Initial trials with diabetes medications show improved cognitive performance in some domains	



Middleton L. *Arch Neurol* 2009

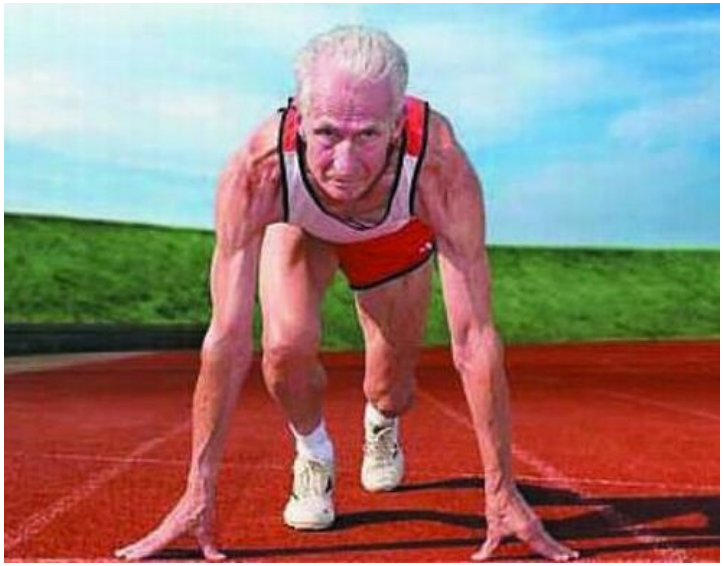
Attività ad elevato impatto cognitivo

Prevention Strategy	Observational Studies	Controlled Trials	Future Directions for Research
Cognitive activity	Greater education and/or participation in cognitively engaging activities at younger or older ages is associated with a lower risk of dementia	Several trials demonstrate better cognitive function and less decline with cognitive interventions	Further trials examining cognitive interventions (in progress)
		The effects of training appear to be domain specific	Controlled trial investigating whether a multifaceted intervention involving cognitive, physical, and social components leads to improved cognitive function

Middleton L. *Arch Neurol* 2009

Attività fisica

Prevention Strategy	Observational Studies	Controlled Trials	Future Directions for Research
Physical activity	People who engage in high levels of physical activity in midlife or late life have a lower risk of dementia	Improved cognitive performance in people with and without cognitive impairment after exercise interventions	Further trials examining physical activity interventions (in progress)



Middleton L. *Arch Neurol* 2009

Rapporti sociali

Prevention Strategy	Observational Studies	Controlled Trials	Future Directions for Research
Social engagement	Most studies suggest that people with limited social networks and low social engagement have a higher risk of dementia	No interventions specifically addressing social engagement	Trials examining social interventions (in progress)

Middleton L. *Arch Neurol* 2009

Alimentazione

Prevention Strategy	Observational Studies	Controlled Trials	Future Directions for Research
Diet	Higher intake of antioxidants and polyunsaturated fatty acids is generally associated with a lower risk of dementia	Interventions with antioxidants and polyunsaturated fatty acids have benefited cognitive performance and the risk of dementia	Additional controlled trials investigating whether nutritional education and diet modification are beneficial to cognitive function

Middleton L. *Arch Neurol* 2009

Depressione

Prevention Strategy	Observational Studies	Controlled Trials	Future Directions for Research
Depression	People with depression or high depressive symptoms have a higher risk of dementia	Initial evidence suggests that treatment improves cognition in people with depression	Randomized controlled trial investigating whether treatment of depression benefits cognitive function and reduces the risk of dementia

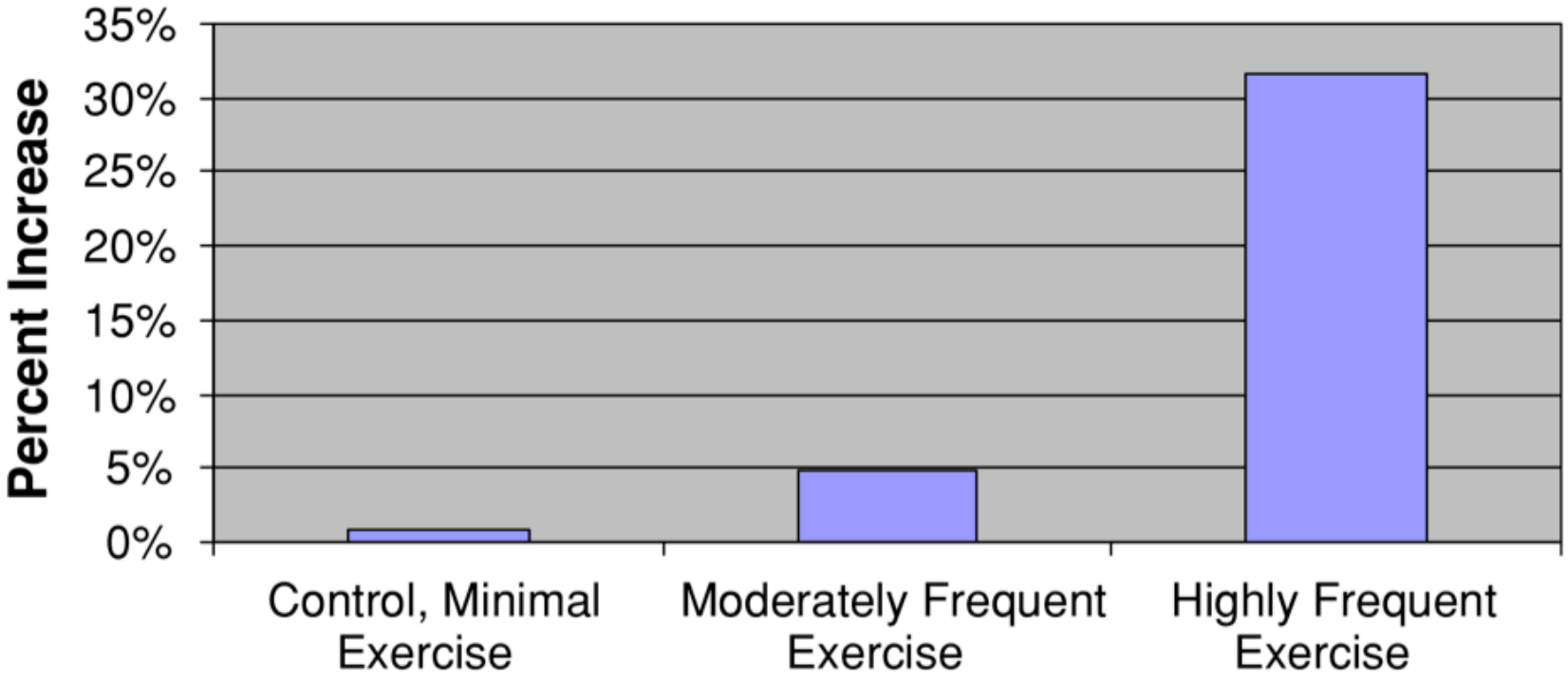
Middleton L. *Arch Neurol* 2009

Allenamento aerobico e performance cognitive

	Controls		Moderate exercise		Intense exercise	
	t	*p*	*t*	*p*	*t*	*p*
Memory	.940	.359	.442	.662	−2.408	.021
Psychomotor speed	−1.385	.182	−2.929	.007	−4.432	<.001
Reaction time	2.111	.048	.637	.529	4.060	.001
Cognitive flexibility	−.048	.962	−2.062	.048	−5.197	<.001
Attention	.361	.722	.381	.706	3.577	.001

Masley F. *J Clin Psychol Med Settings*. 2009

Allenamento aerobico e performance cognitive



Masley F. *J Clin Psychol Med Settings*. 2009

Ma l'intensità dell'attività fisica è importante ?

Table 1. Descriptive Statistics for All Measures for the Overall Sample

Variable and time point	*M*	*SD*
Physical activity at baseline	156.44	70.89
Physical activity at Month 12	137.59	64.78
Physical activity at Month 24	128.84	60.12
Variables measured at baseline only		
Walking self-efficacy	71.75	31.80
Lifestyle self-efficacy	90.91	13.20
FDI: advanced lower extremity function	17.90	4.85
FDI: basic lower extremity function	23.63	2.30
Outcome expectations for exercise (Resnick, Zimmerman, Orwig, Furstenberg, & Magaziner, 2000)	4.35	0.59
Outcome expectations for exercise (Conn, 1997)	4.63	0.44
Outcome expectations (Kim, Horan, Gendler, & Patel, 1991)	4.13	0.69

Note: FDI = *Function and Disability Instrument.*

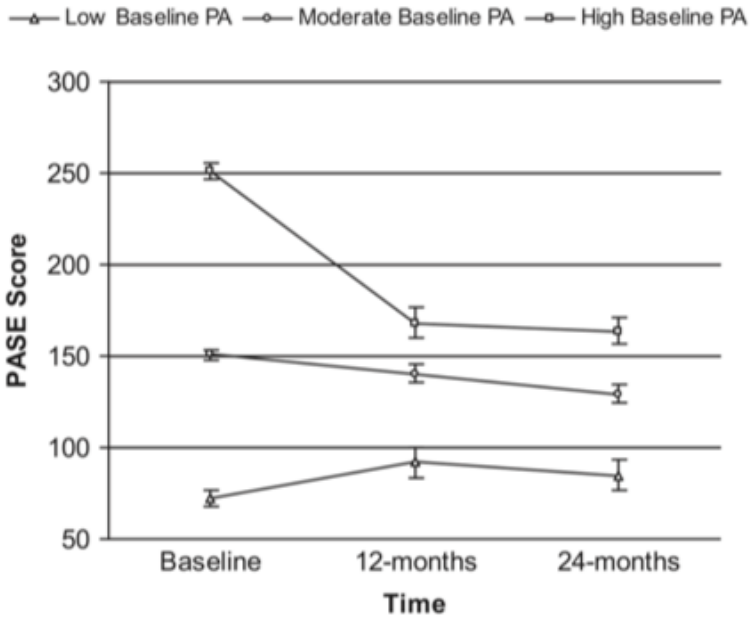


Figure 1. Trajectories of change in physical activity for individuals with high, medium, and low activity scores at baseline.

McAuley, E. *Journal of Gerontology.* 2009

Malattie durante l'esercizio fisico

Table 6. Adverse Events and Discontinuation of Intervention During Active (First 24 Weeks) or After Active (24 Weeks to 18 Months) Period

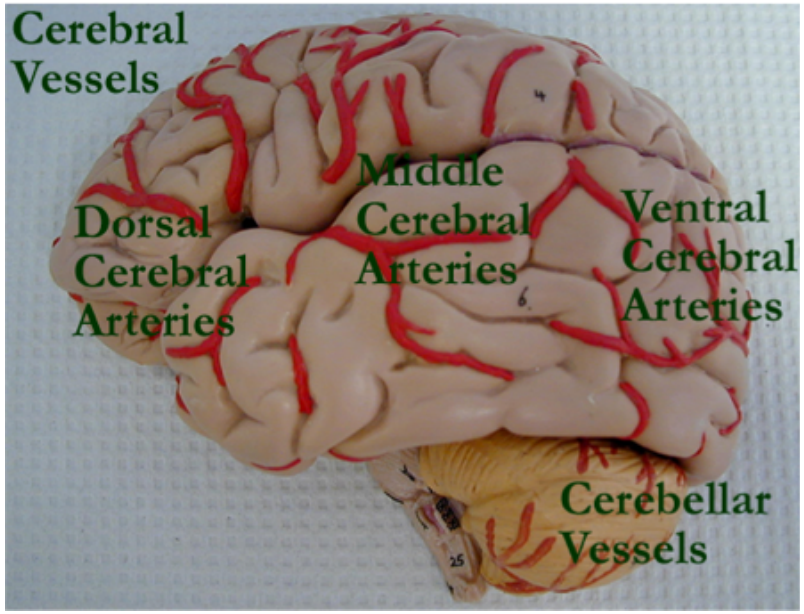
	Control Group	Intervention Group During Active Phase	Intervention Group After Active Phase
Total adverse events reported	2	3	5
Cardiovascular problem	1	1[a]	2
Stroke or transient ischemic attack	1	0	1[d]
Inoperable lung cancer	0	1[b]	0
Foot pain and gout	0	1[c]	0
Disorientation episodes	0	0	1
Shoulder operation needing 8-wk recovery	0	0	1[d]

Lautenschlager, N.T. *JAMA* 2008

Meccanismi fisiologici

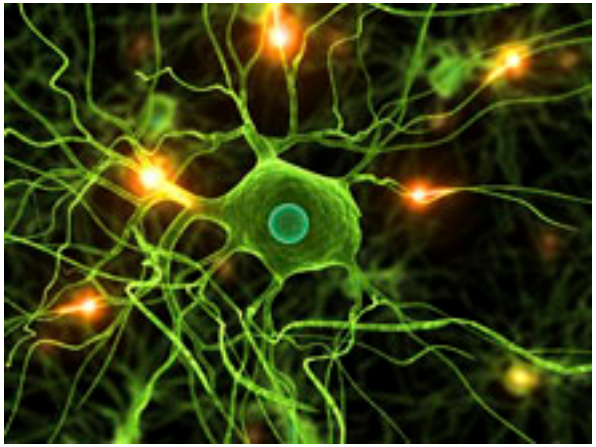
Chodzko-Zajko & Moore, 1994; Poon, 2006 hanno proposto alcune ipotesi che spiegano la correlazione positiva tra l'attività fisica e le performance cognitive:

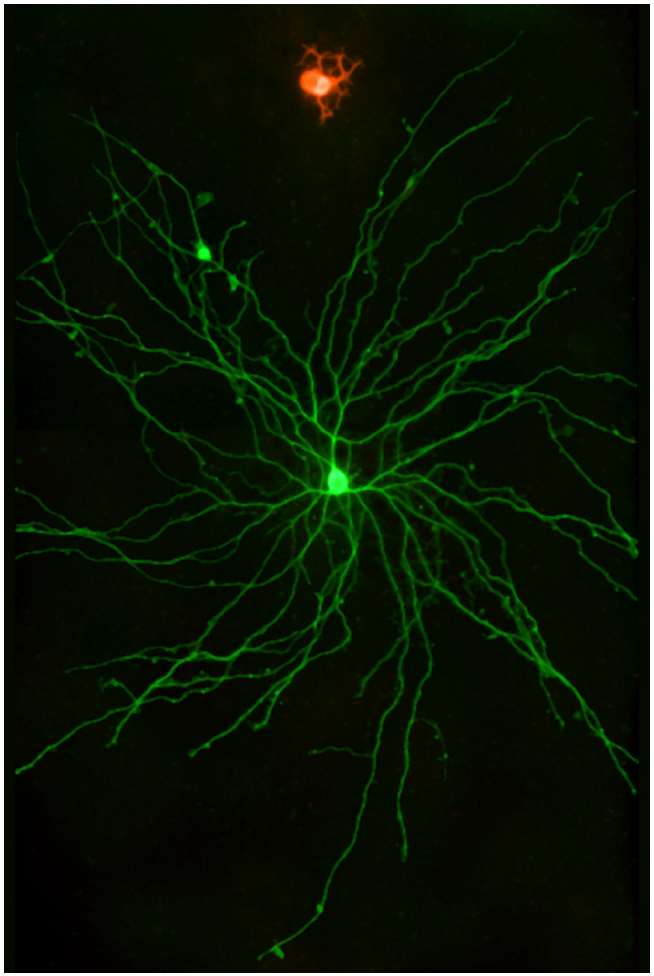
Miglioramento del flusso ematico celebrale



Meccanismi fisiologici

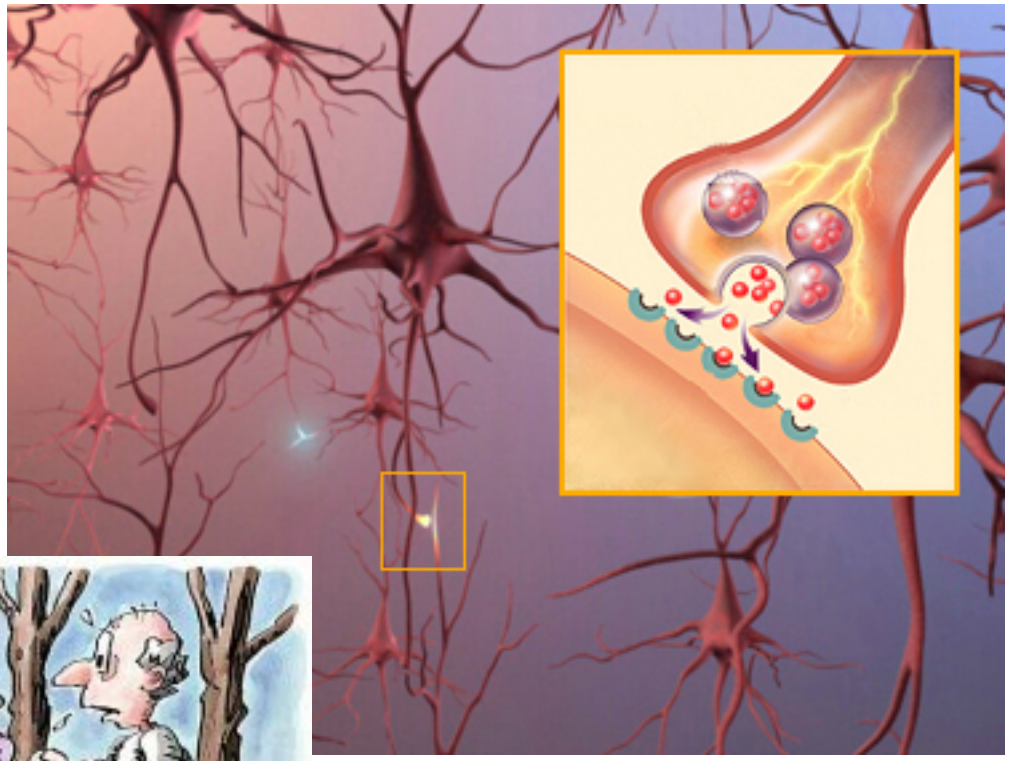
Rigenerazione dei neuroni e delle sinapsi





Meccanismi fisiologici

Modificazioni nella sintesi e degradazione di neurotrasmettitori



Esercizio fisico e demenza di Alzheimer ….
Esiste una relazione?

Exercise programs for people with dementia (Review)

Forbes D, Thiessen EJ, Blake CM, Forbes SC, Forbes S

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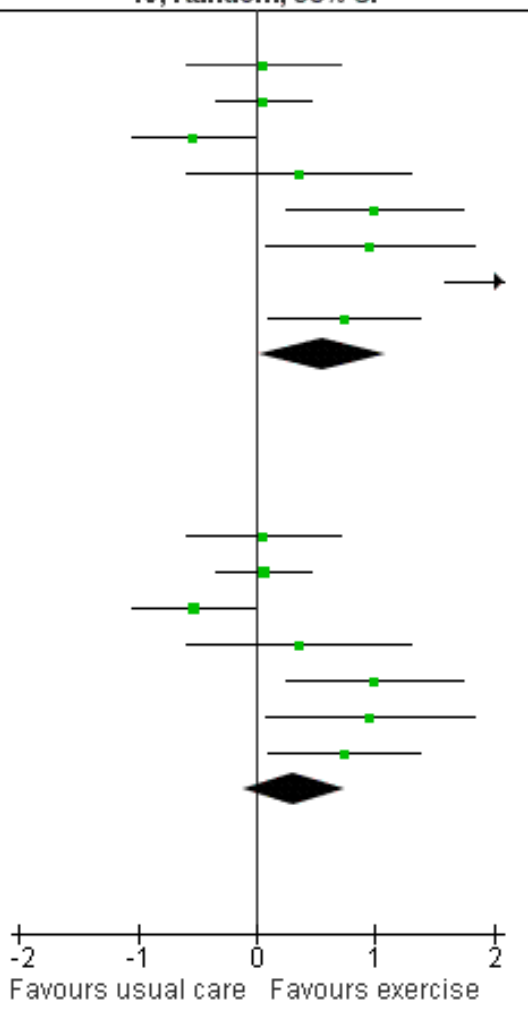
COLLABORATION®

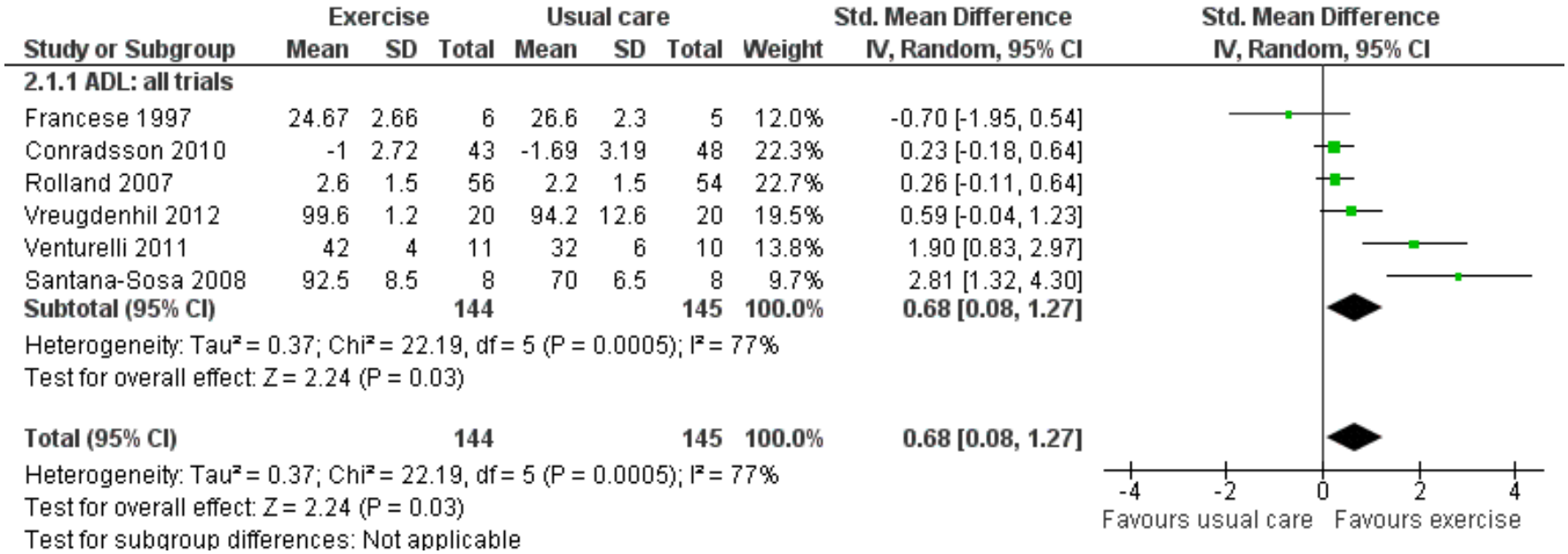
Figure 4. Forest plot of comparison 1: Physical activity vs usual care: cognition

Study or Subgroup	Exercise Mean	Exercise SD	Exercise Total	Usual care Mean	Usual care SD	Usual care Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Cognition: all trials								
Christofoletti 2008	14.9	2.2	17	14.8	1.3	20	13.4%	0.06 [-0.59, 0.70]
Eggermont 2009a	0.24	0.78	51	0.2	0.63	46	15.2%	0.06 [-0.34, 0.45]
Eggermont 2009b	0.07	0.37	30	0.47	0.97	31	14.4%	-0.53 [-1.05, -0.02]
Hwang 2010	28.9	11.86	10	24	14.68	8	11.0%	0.35 [-0.58, 1.29]
Kemoun 2010	30.38	7.66	16	22.23	8.37	15	12.5%	0.99 [0.24, 1.74]
Van de Winckel 2004	15.33	4.44	15	11	4.3	9	11.5%	0.95 [0.08, 1.83]
Venturelli 2011	12	2	11	6	2	10	8.5%	2.88 [1.59, 4.17]
Vreugdenhil 2012	23.9	5	20	19	7.7	20	13.4%	0.74 [0.10, 1.38]
Subtotal (95% CI)			**170**			**159**	**100.0%**	**0.55 [0.02, 1.09]**
Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 34.67$, df = 7 (P < 0.0001); $I^2 = 80\%$								
Test for overall effect: Z = 2.03 (P = 0.04)								
1.1.2 Cognition: excluded moderate-severe dementia								
Christofoletti 2008	14.9	2.2	17	14.8	1.3	20	14.7%	0.06 [-0.59, 0.70]
Eggermont 2009a	0.24	0.78	51	0.2	0.63	46	18.6%	0.06 [-0.34, 0.45]
Eggermont 2009b	0.07	0.37	30	0.47	0.97	31	16.8%	-0.53 [-1.05, -0.02]
Hwang 2010	28.9	11.86	10	24	14.68	8	10.7%	0.35 [-0.58, 1.29]
Kemoun 2010	30.38	7.66	16	22.23	8.37	15	13.1%	0.99 [0.24, 1.74]
Van de Winckel 2004	15.33	4.44	15	11	4.3	9	11.4%	0.95 [0.08, 1.83]
Vreugdenhil 2012	23.9	5	20	19	7.7	20	14.7%	0.74 [0.10, 1.38]
Subtotal (95% CI)			**159**			**149**	**100.0%**	**0.31 [-0.11, 0.74]**
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 18.49$, df = 6 (P = 0.005); $I^2 = 68\%$								
Test for overall effect: Z = 1.45 (P = 0.15)								

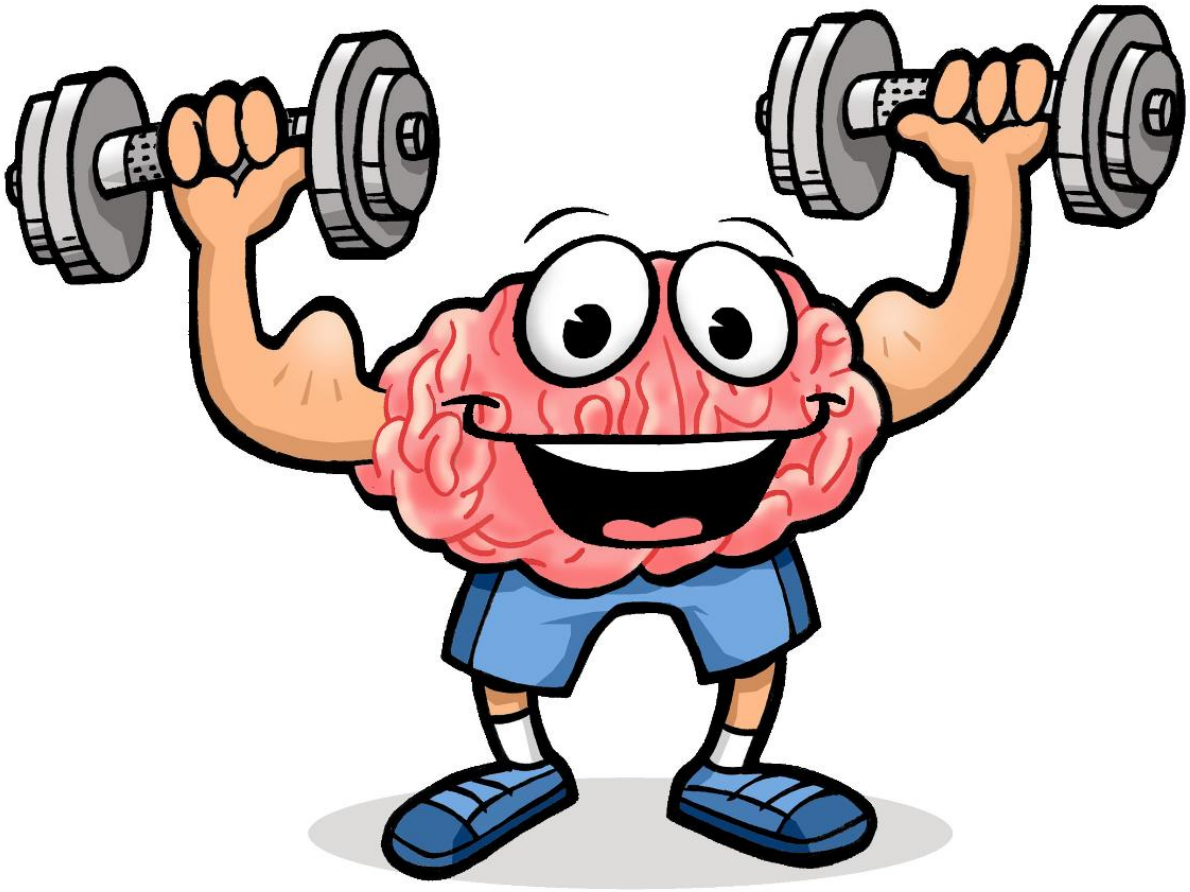


Forbes et al. 2013

Figure 5. Forest plot of comparison 2: Physical activity vs usual care: Activities of daily living (ADLs)



Forbes et al. 2013



…. Ma perchè esiste questa relazione positiva?

Neurovascular unit

Acta Physiol 2014, **210,** 790–798

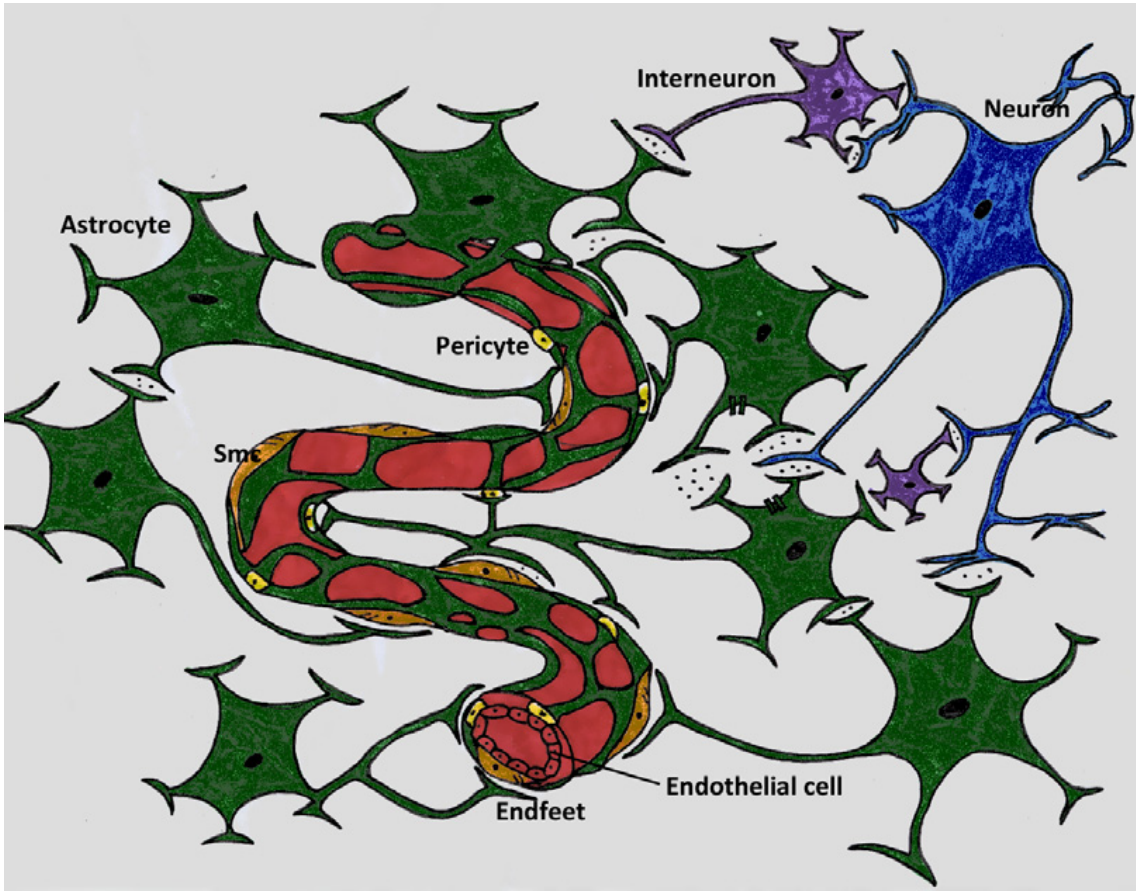
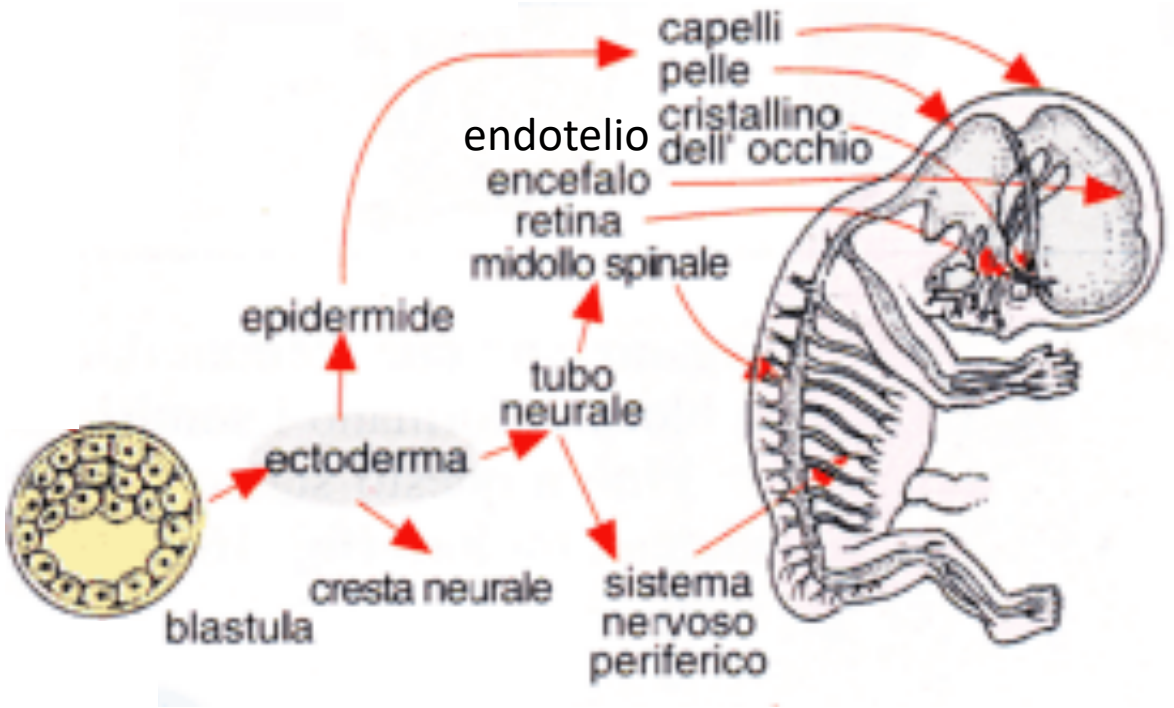


Figure 1 The figure above shows the components of the neurovascular unit: The neurone (blue) establishes synapses with interneurones (purple) and with astrocytes (green), sending information through neurotransmitters on their oxygen requirements and commands contraction or vascular relaxation. Astrocytes, through calcium waves, transmit the order to the vessels. The point of contact between astrocytes and the vasculature is the endfeet, which can be in touch directly with endothelial cells (red), pericytes (yellow) or myocytes/Smc (orange).

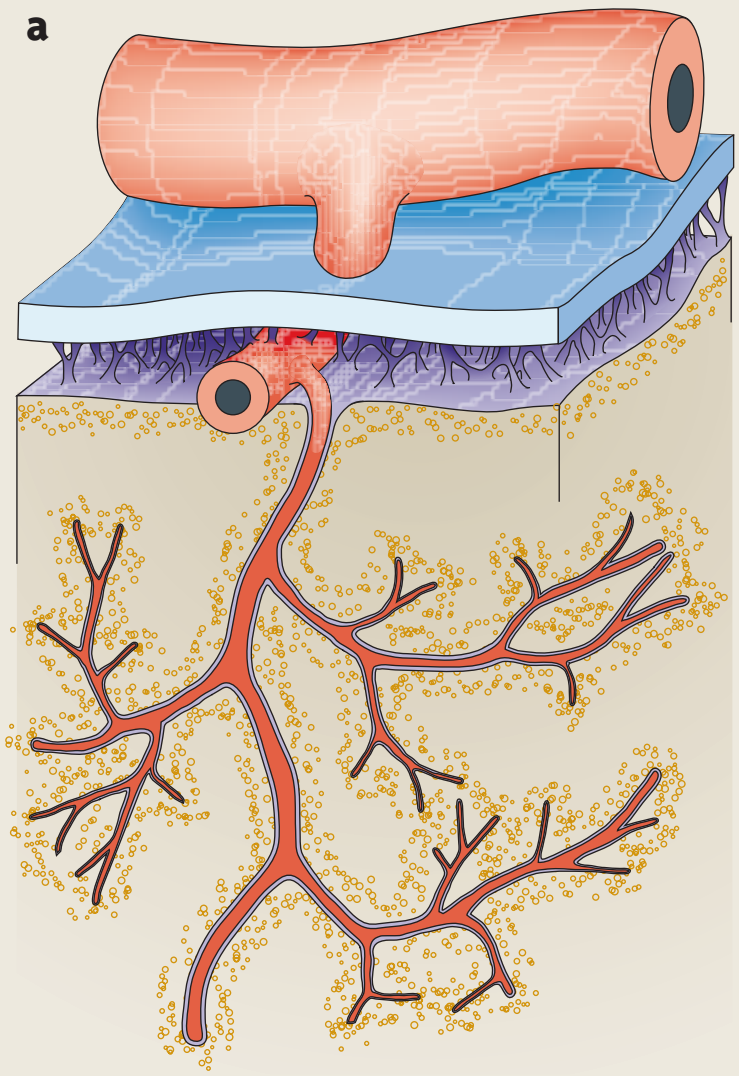
1 relazione anatomico funzionale

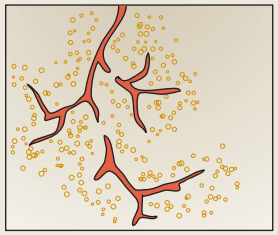
Human embryogenesis



2 stessa origine embrionale

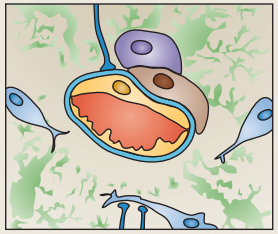
Box 2 | **Vascular defects in neurodegenerative disease**



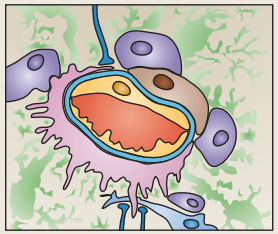


Vessel regression, hypoperfusion, endothelial degeneration

Abnormal vessel growth, size and shape. Blood–brain-barrier disruption, leakiness, impaired clearance of toxins



Healthy blood vessel, showing an endothelial cell (yellow), a pericyte (brown), a glial cell (purple) and the basement membrane (blue)



Microvessel angiopathy: amyloid deposition (pink), basement-membrane thickening, impaired O_2 diffusion and vasoregulation, inflammation

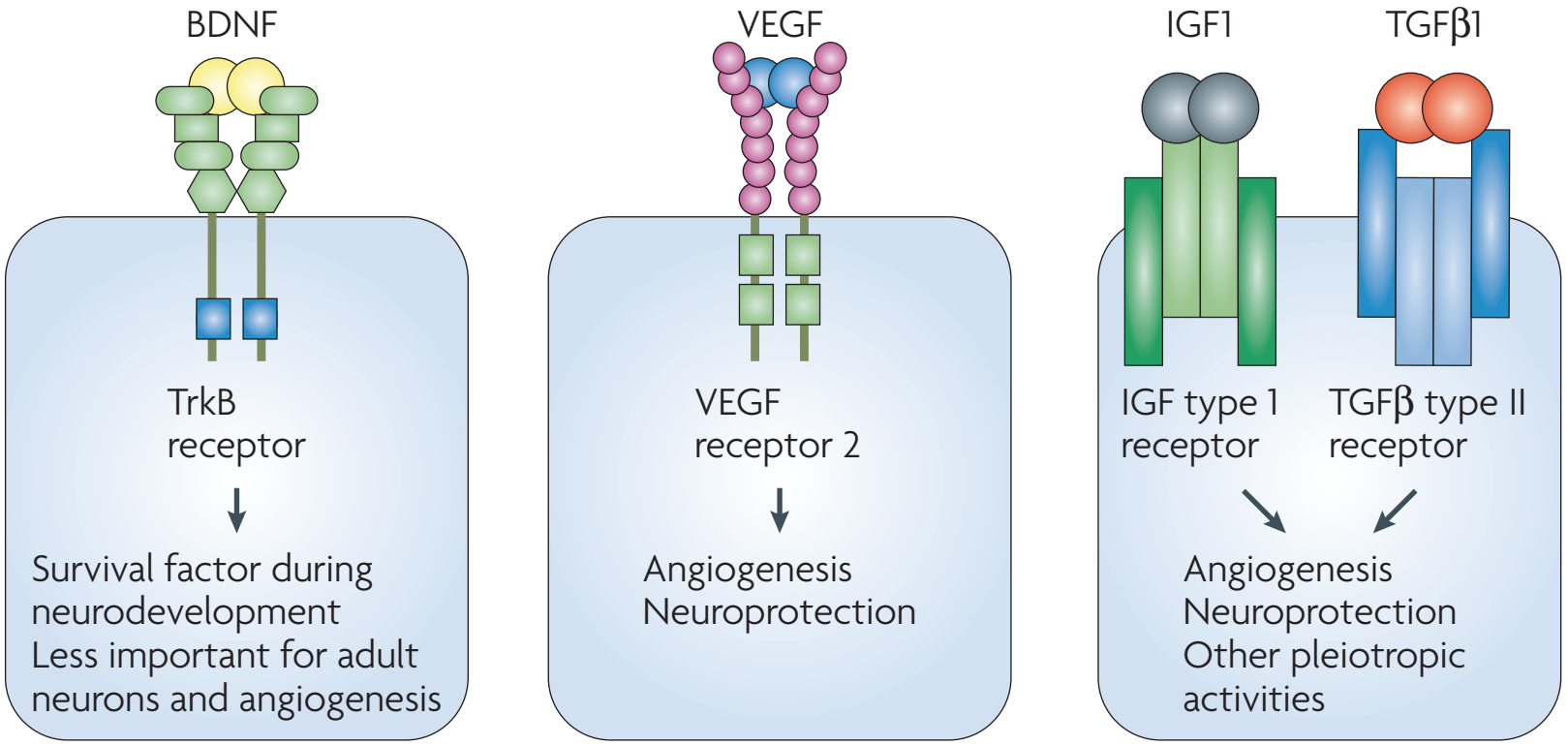
Zacchigna et al. Nature Reviews 2008

Angioneurine

Angioneurins discovered through their neuronal effects
(NGF, BDNF, NT3, NT4)

Angioneurins discovered as angiogenic factors
(VEGF, PDGF, ANG)

Other angioneurins
(TGFβ1, EPO, FGF2, HGF, EGF, IGF1, PGRN)



Zacchigna et al. Nature Reviews 2008

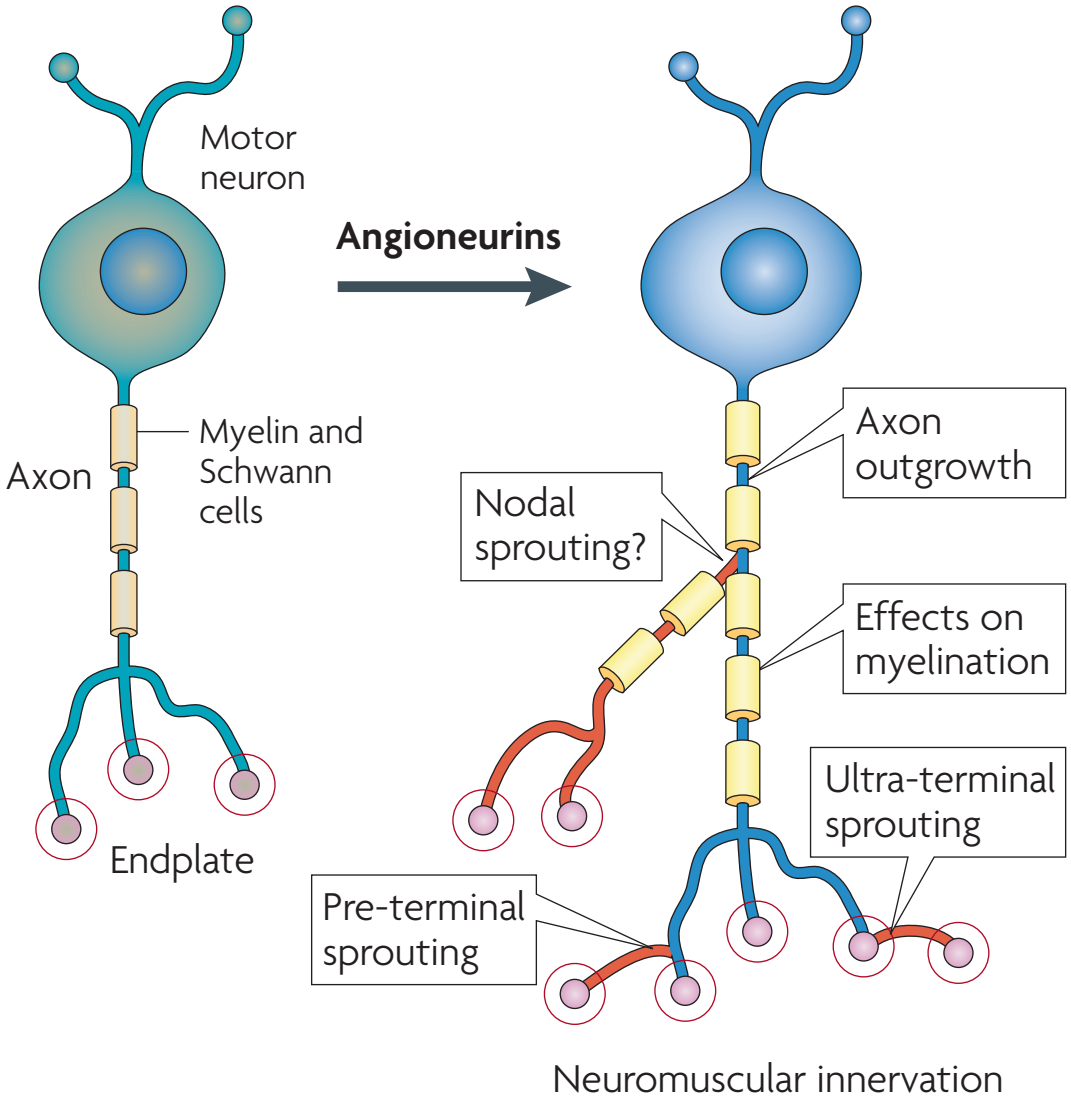
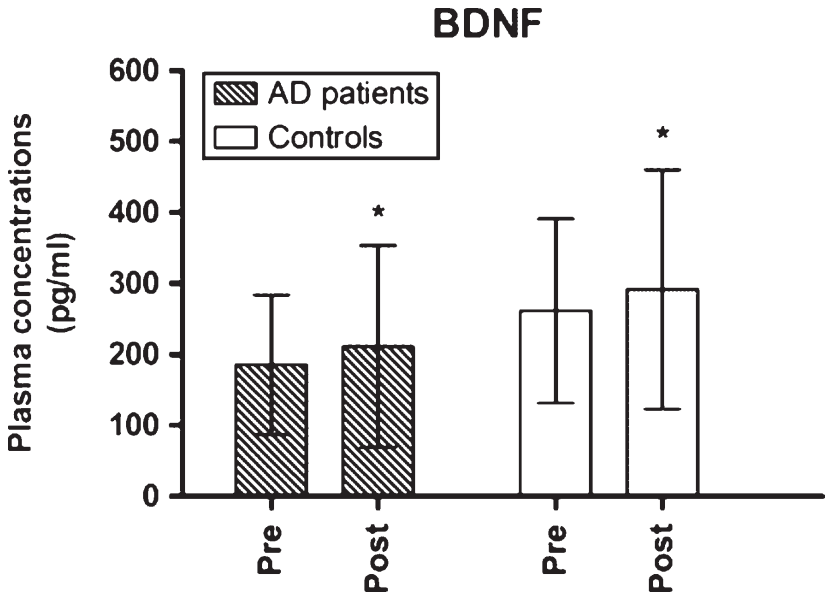
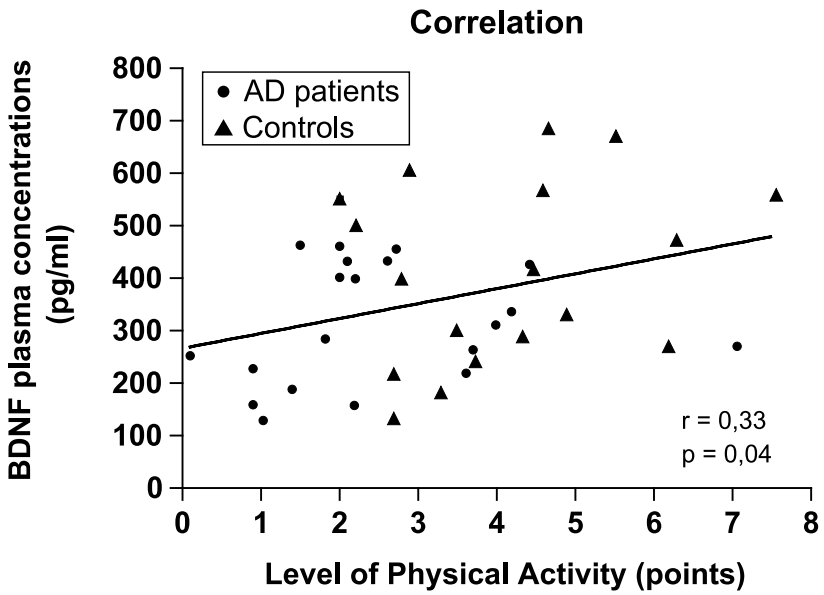


Figure 5 | **Angioneurins promote innervation and axon sprouting.** The repair of neurodegeneration and nerve

Zacchigna et al. Nature Reviews 2008


BDNF
Plasma concentrations (pg/ml)
600
500
400
300
200
100
0
AD patients
Controls
*
*
Pre
Post
Pre
Post


Correlation
BDNF plasma concentrations (pg/ml)
800
700
600
500
400
300
200
100
0
AD patients
Controls
r = 0,33
p = 0,04
0
1
2
3
4
5
6
7
8
Level of Physical Activity (points)

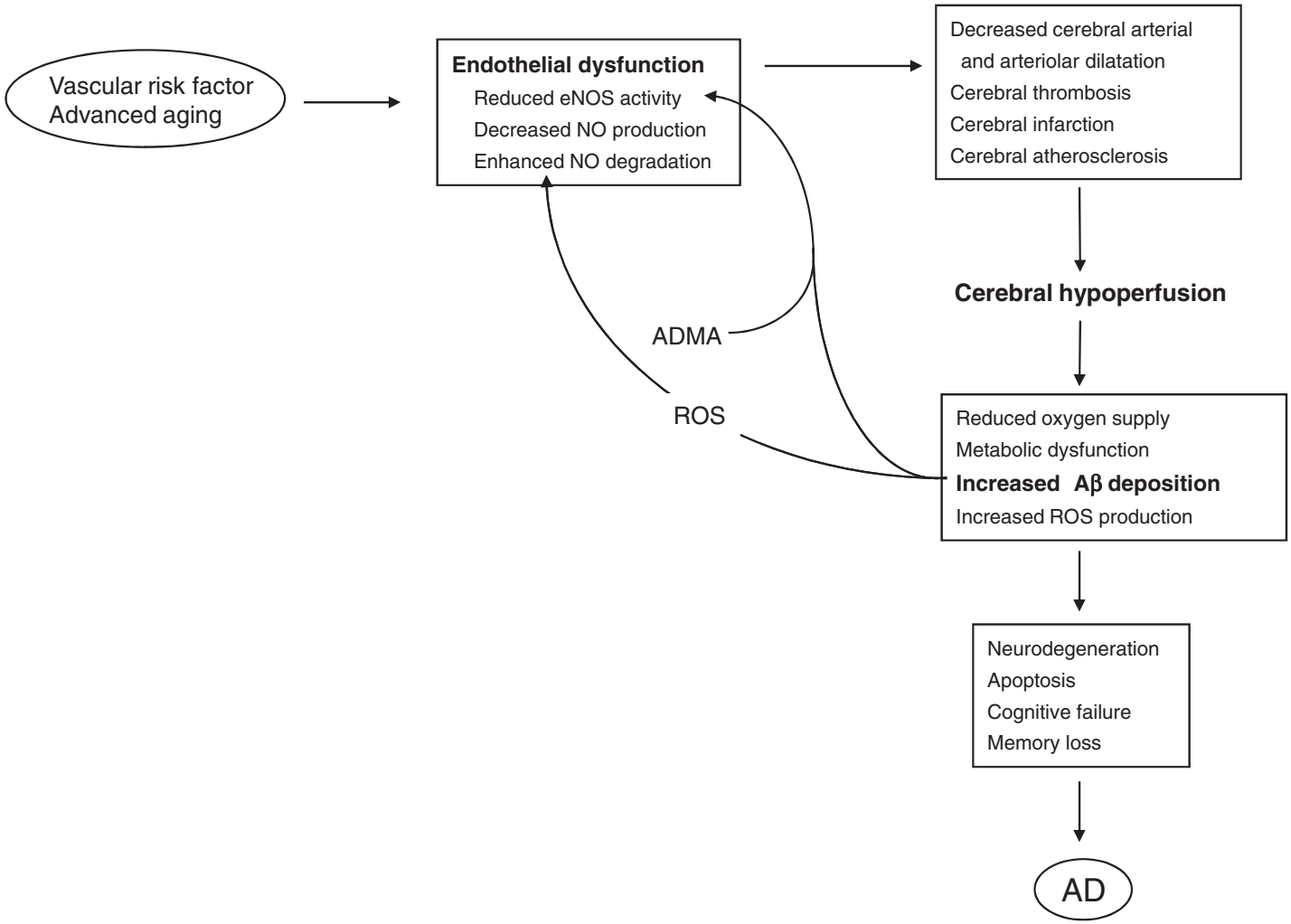


Fig. 2. Possible roles of endothelial dysfunction, cerebral hypoperfusion, and Aβ in the pathogenesis of Alzheimer's disease (AD). Plasma ADMA (asymmetric dimethylarginine) levels are increased in many of the diseases regarded as vascular risk factors.

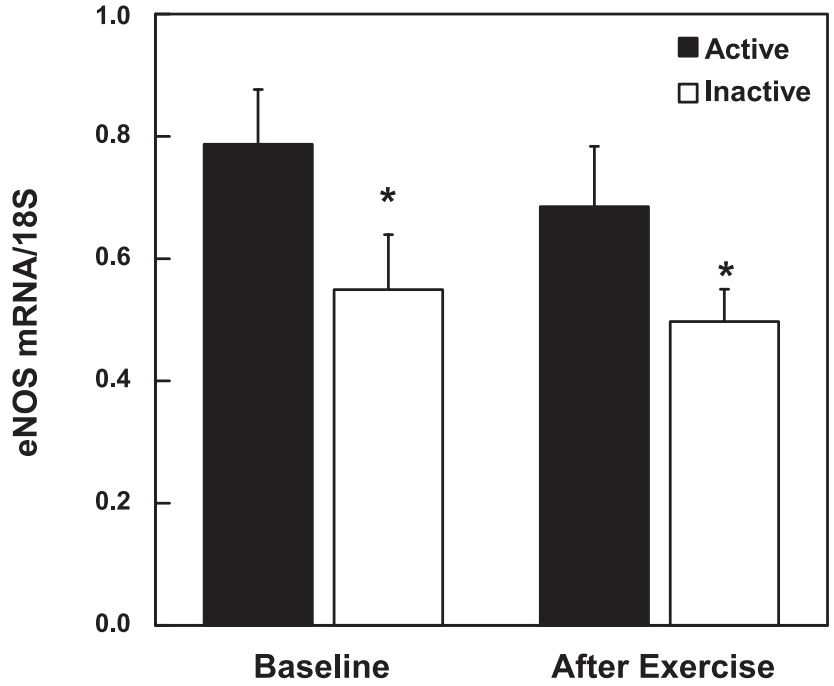
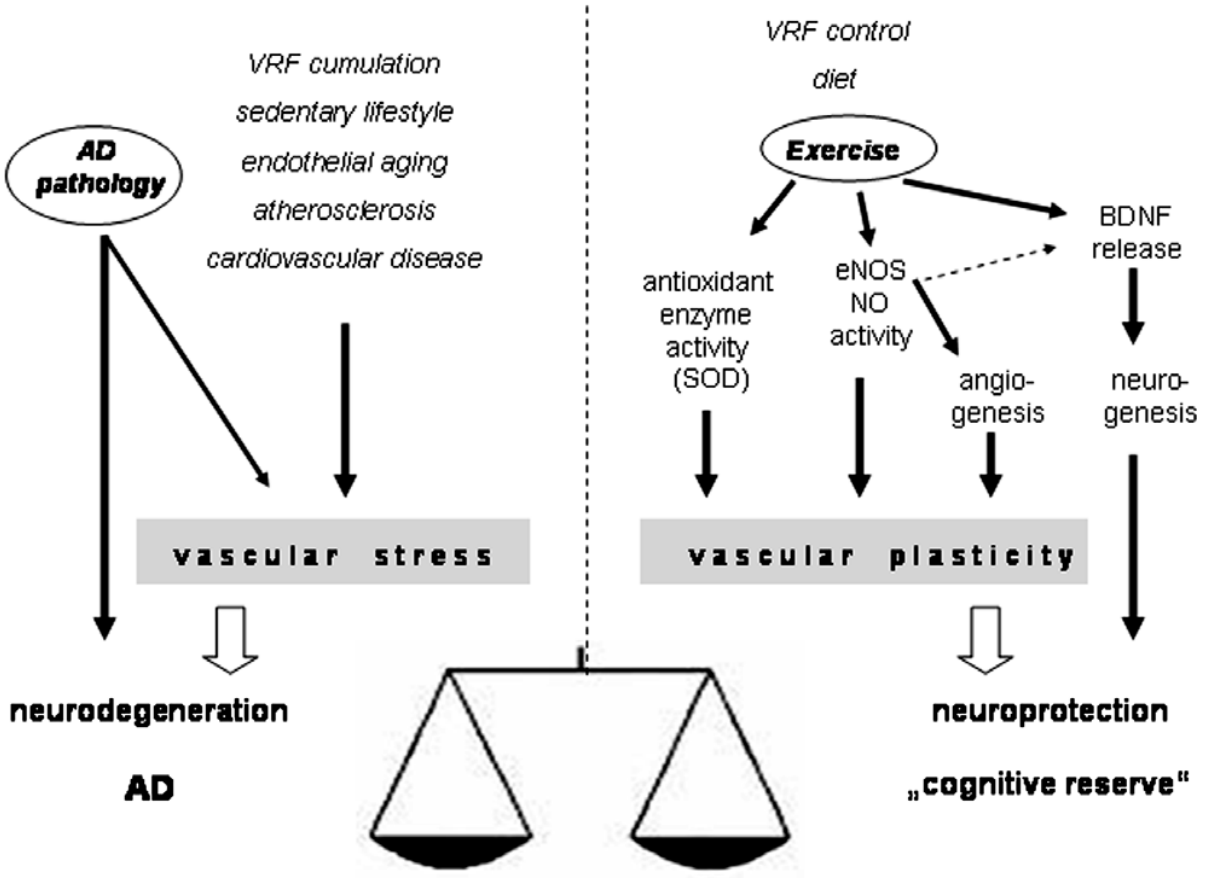


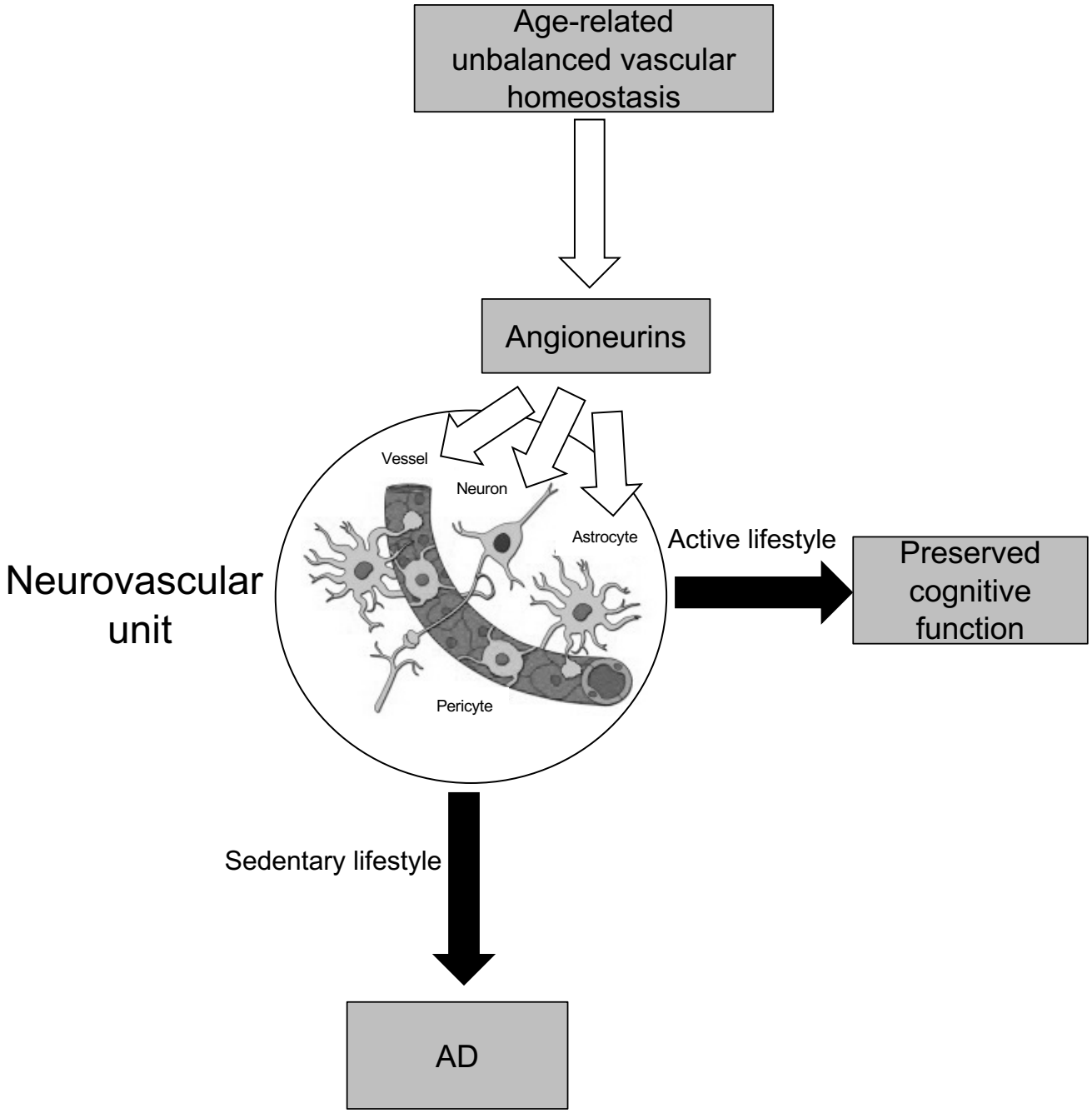
Fig. 2. Endothelial nitric oxide synthase (eNOS) mRNA as measured by semiquantitative RT-PCR in active and inactive men. *Significant difference between groups ($P < 0.05$).

Jenkins et al. AJP Heart and circ 2009

Paradigma della riserva vascolare



Lange-Asschenfeldt et al. exp Geront


Age-related unbalanced vascular homeostasis
Angioneurins
Vessel
Neuron
Astrocyte
Pericyte
Neurovascular unit
Active lifestyle
Preserved cognitive function
Sedentary lifestyle
AD

Experimental Aging Research, 36: 190–205, 2010

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POSITIVE EFFECTS OF PHYSICAL TRAINING IN ACTIVITY OF DAILY LIVING–DEPENDENT OLDER ADULTS

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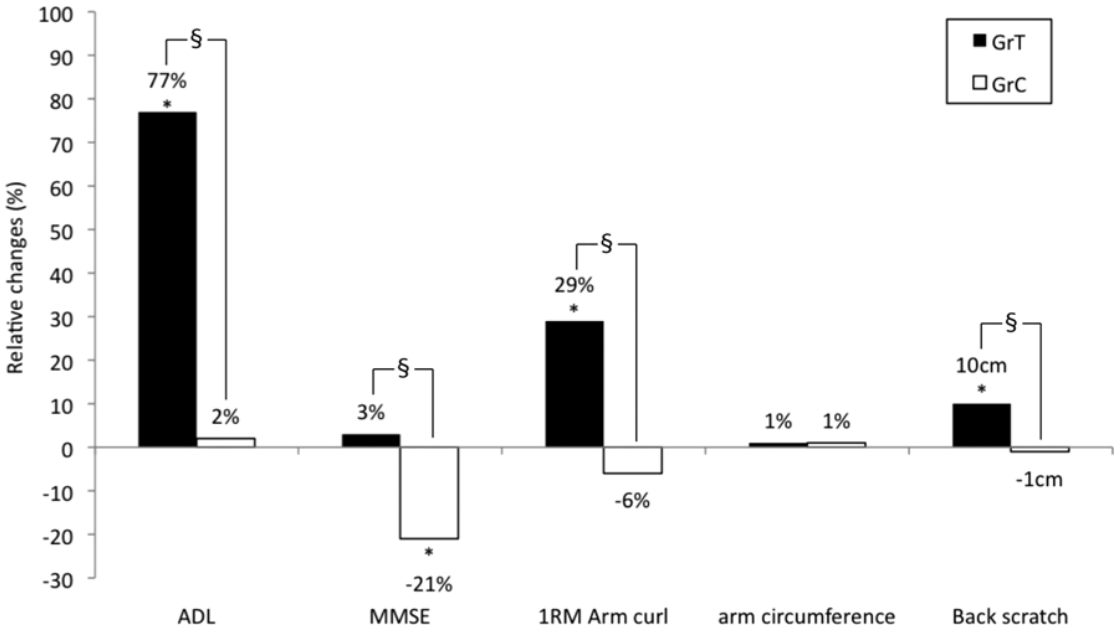

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Six-Month Walking Program Changes Cognitive and ADL Performance in Patients With Alzheimer

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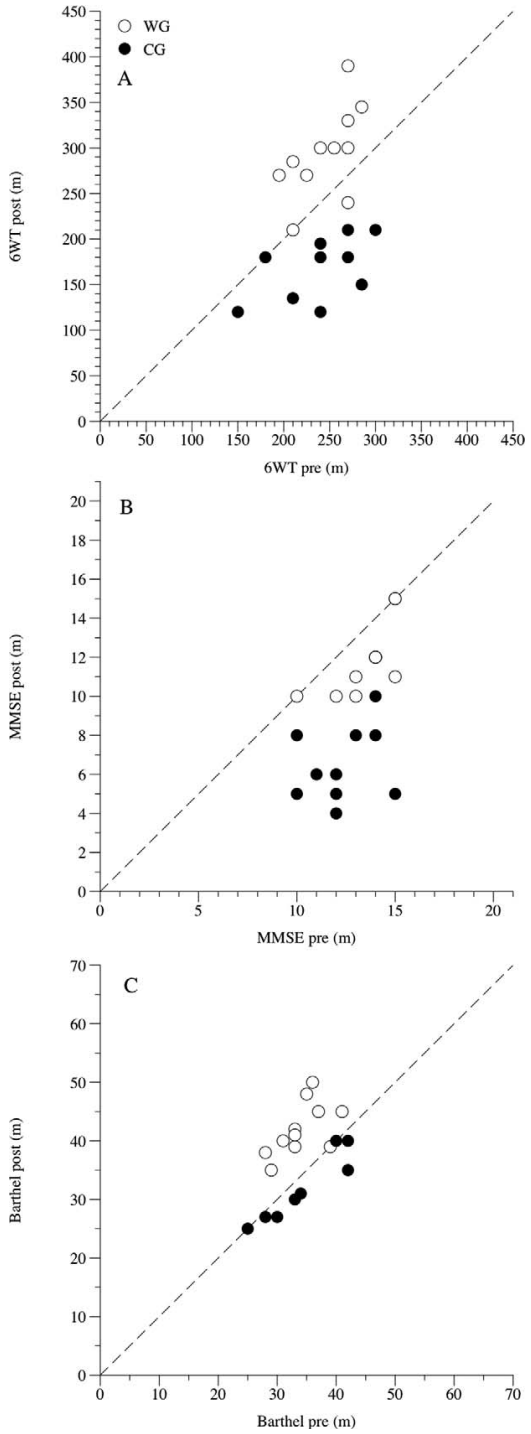
Massimo Venturelli, PhD[1,2,3], Renato Scarsini, MD[2], and Federico Schena, MD, PhD[1]

Abstract

Motor inactivity is typical in the later stages of Alzheimer's disease although there is evidence that physical exercise can reduce depression and enhance performance of daily activities. The aim of this study was to determine whether a walking program could reduce the functional and cognitive decline of elderly nursing home residents in the later stages of Alzheimer's disease. A total of 21 patients (84 $\pm$ 5 years) were randomly assigned to a walking program (WG) or to a control group (CG). A 6-minute walking test (6WT), the Barthel index of activities of daily living (ADLs), and Mini-Mental State Examination (MMSE) tests were performed before and after 24 weeks of the program. The WG showed significant improvement in the 6WT (20%) and ADLs (23%), while the CG decreased in MMSE (−47%), the WG had a slower decline (−13%). This study indicates that it is possible to stabilize the progressive cognitive dysfunctions in nursing home residents with Alzheimer's disease through a specific walking program.



From Alzheimer's Disease Retrogenesis A New Care Strategy for Patients With Advanced Dementia

American Journal of Alzheimer's Disease & Other Dementias®
00(0) 1-7

DOI: 10.1177/1533317512459794
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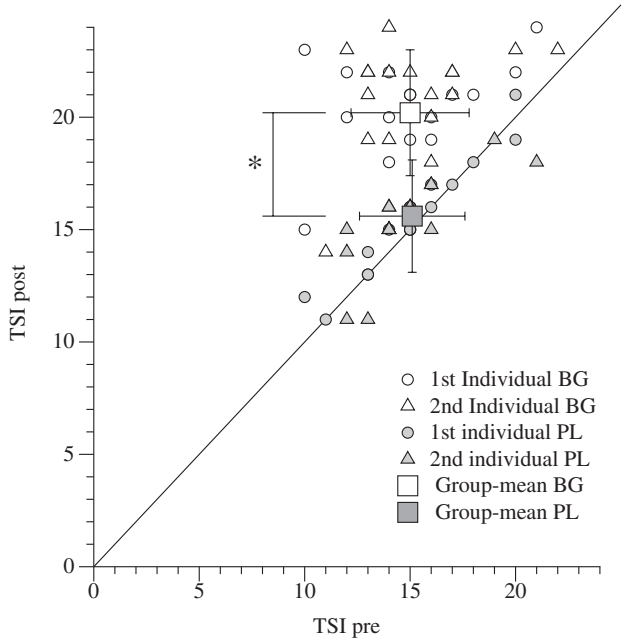
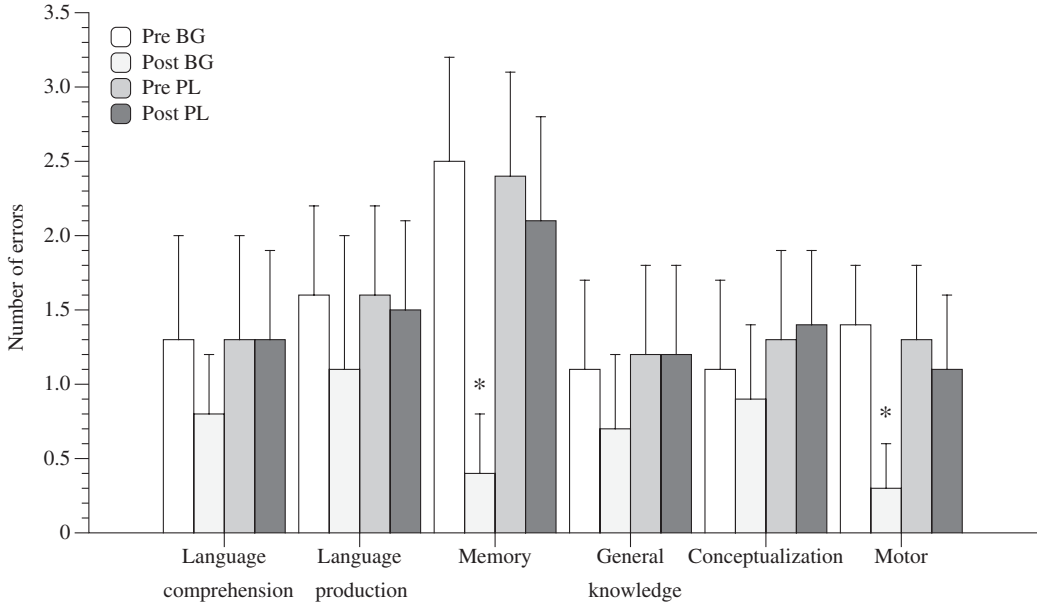
SAGE

Massimo Venturelli, PhD[1,2,3], Alessandra Magalini, MdS[1], Renato Scarsini, MD[2] and Federico Schena, MD, PhD[1]

Abstract

There is evidence that exercise may reduce the progressive cognitive dysfunction of Alzheimer's disease (AD). However, no previous investigation has studied the acute effects of adapted games (AG) on patients with AD. The aim of this study was to examine the acute effects of AG on the agitated behavior (rating scale Agitated Behavior Rating Scale [ABRS]) and cognitive performance (Test for Severe Impairment [TSI]) of patients with advanced dementia. Twenty patients (83 ± 4 yrs) participated in AG and placebo activities (PL). Agitated behavior and cognitive performance were compared before and after 30 minutes of AG and PL. In the hour after the AG, agitated behavior decreased by ~4 ABRS points and cognitive performance increased by ~5 TSI points. On the contrary, after PL we found no change in agitated behavior or cognitive performance. Our data indicate that AG can momentarily reduce agitated behavior and increase the cognitive performance in participants with AD.





Alzheimer's diseases related neuro-endocrine dysfunction

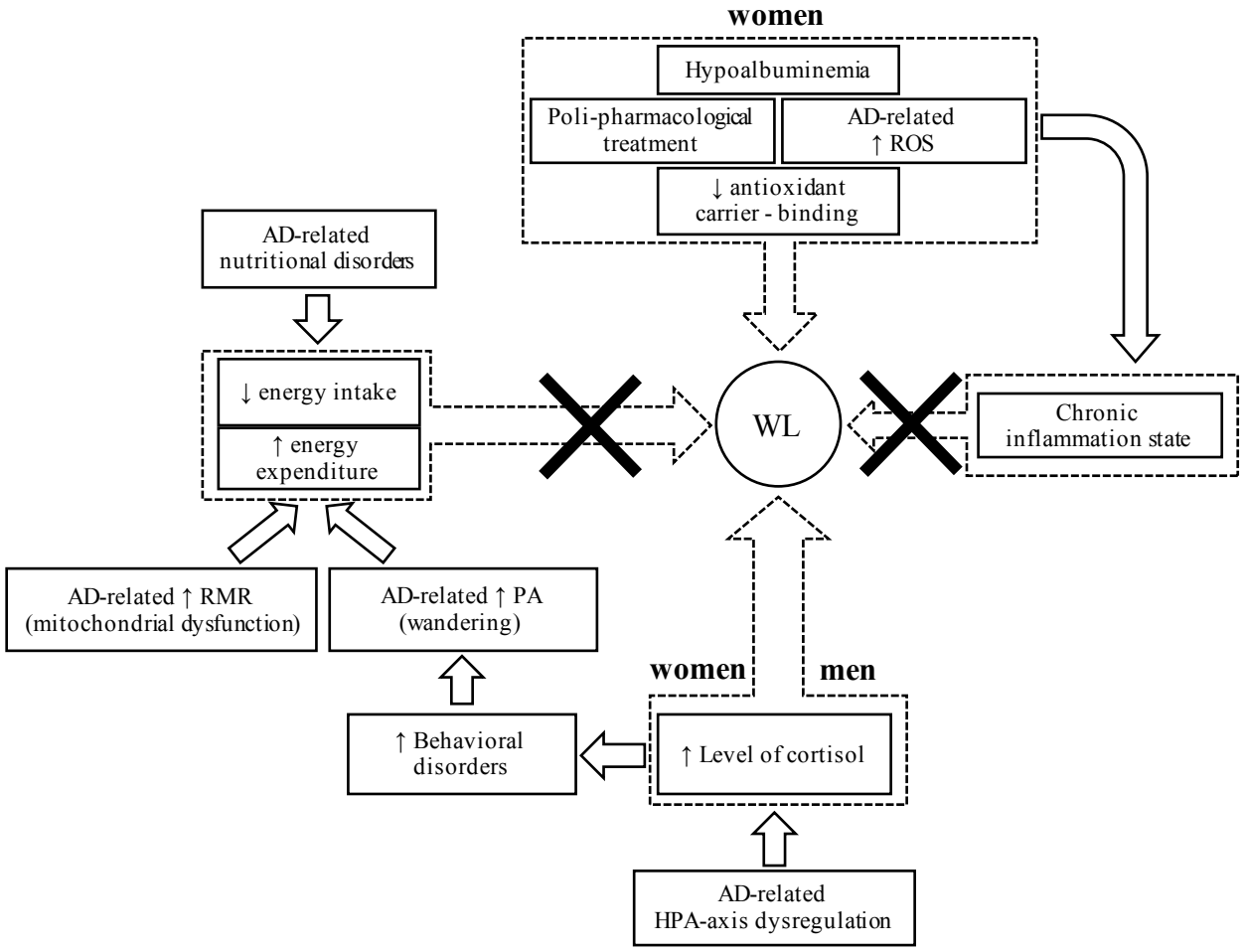


Figure 5. Causal mechanisms linking Alzheimer's disease (AD) and involuntary weight loss (WL). Resting metabolic rate (RMR); daily physical activity (PA); hypothalamic–pituitary–adrenal axis (HPA-axis); reactive oxygen species (ROS).

Venturelli et al. *PlosOne,* 2016

Behavioral disorders and neuro-endocrine dysfunction

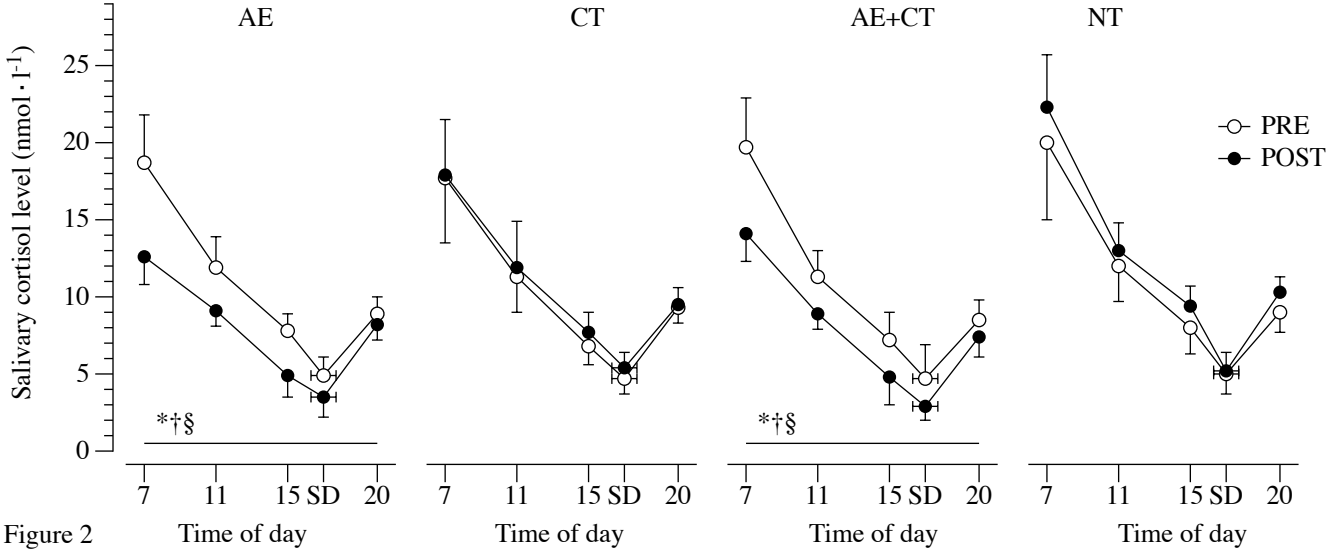


Figure 2

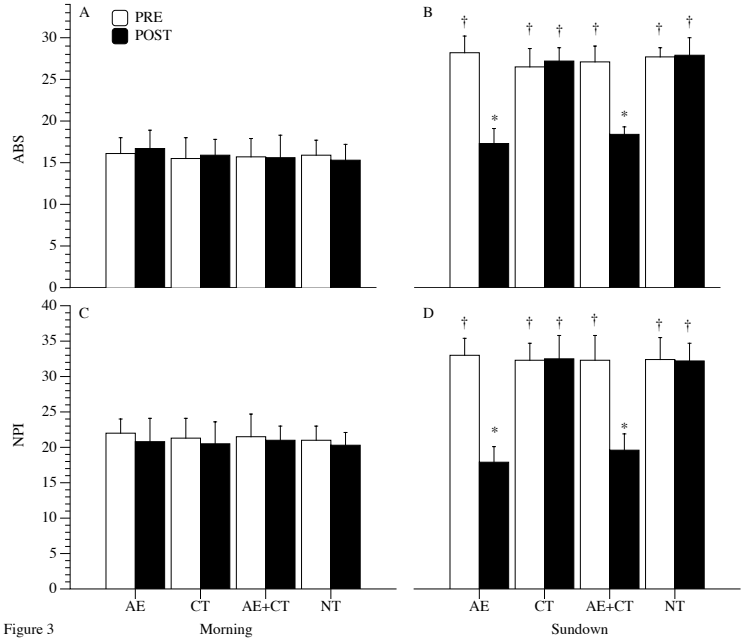


Figure 3

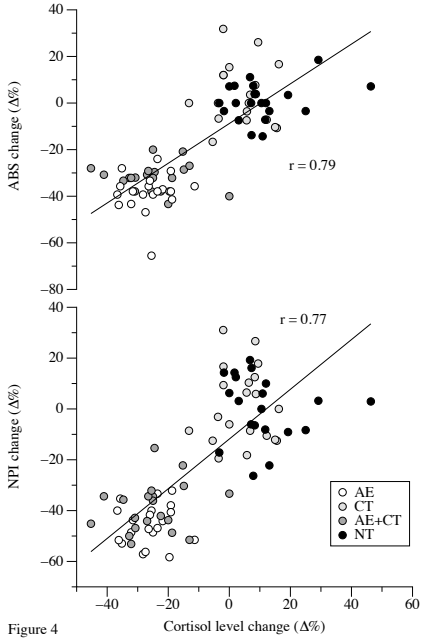
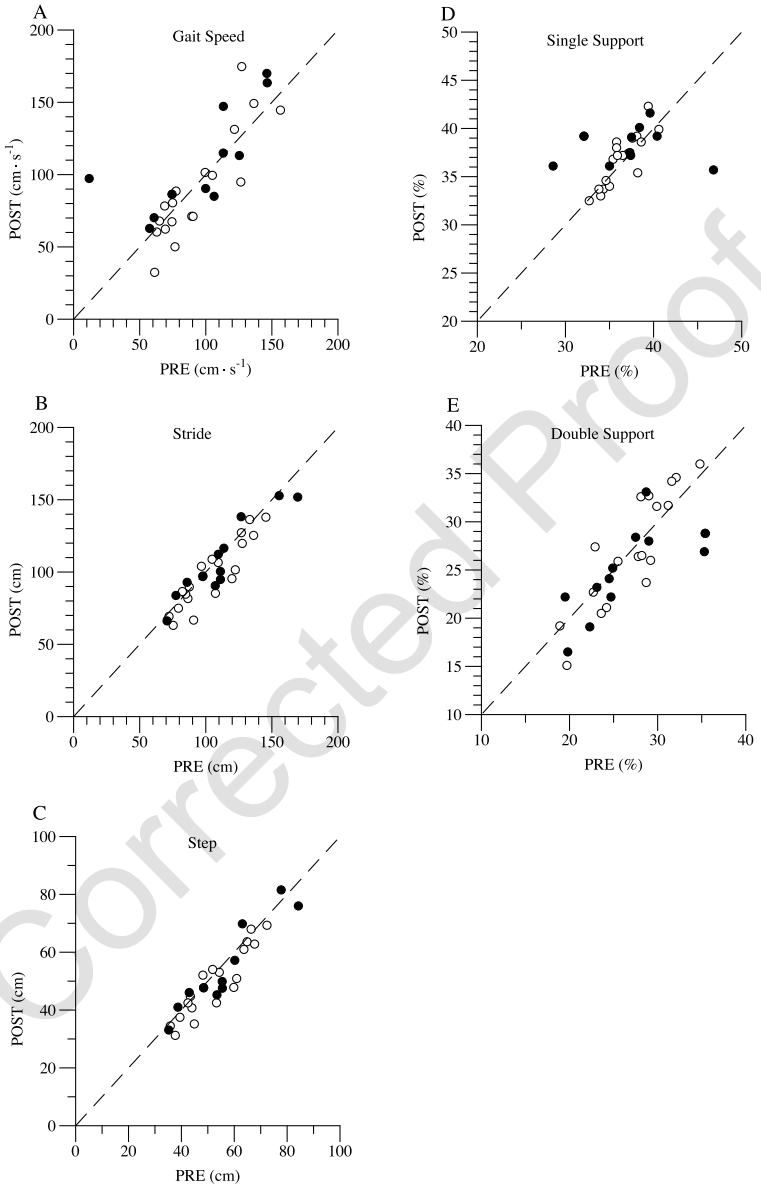
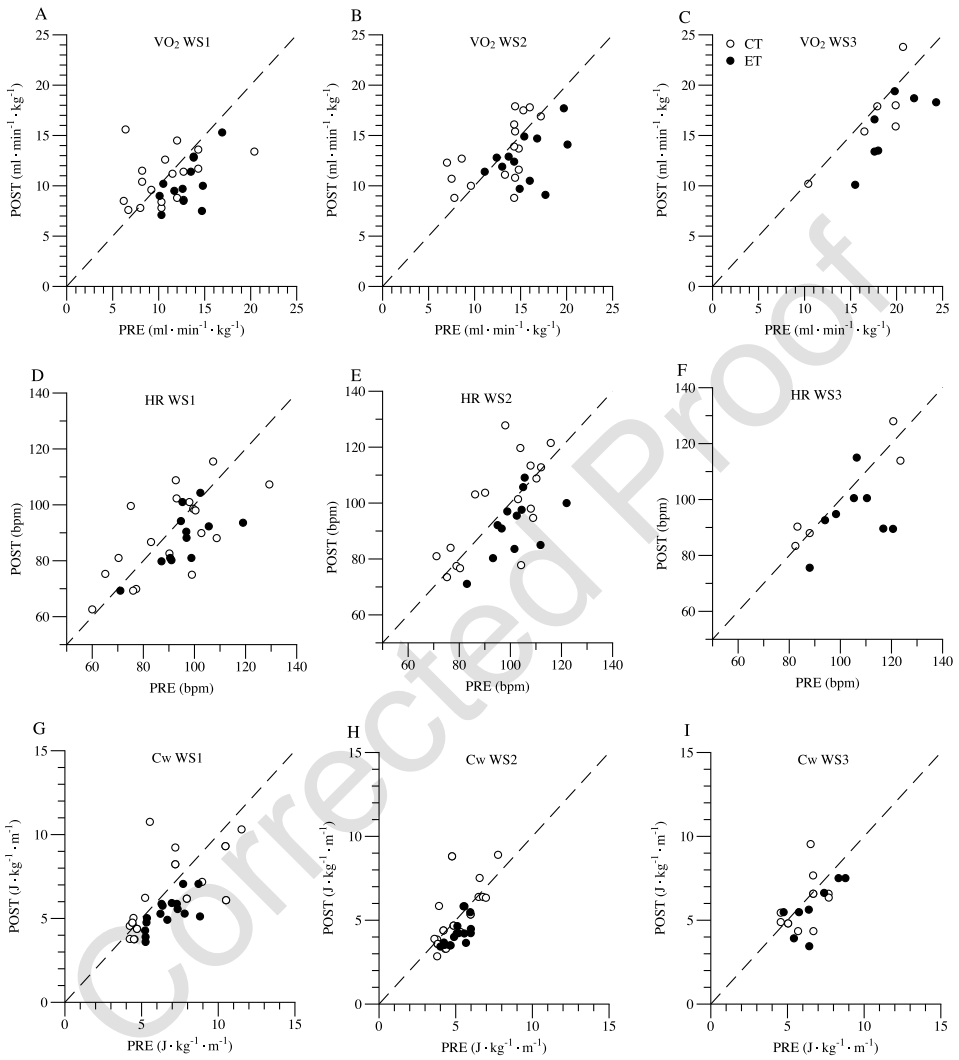


Figure 4

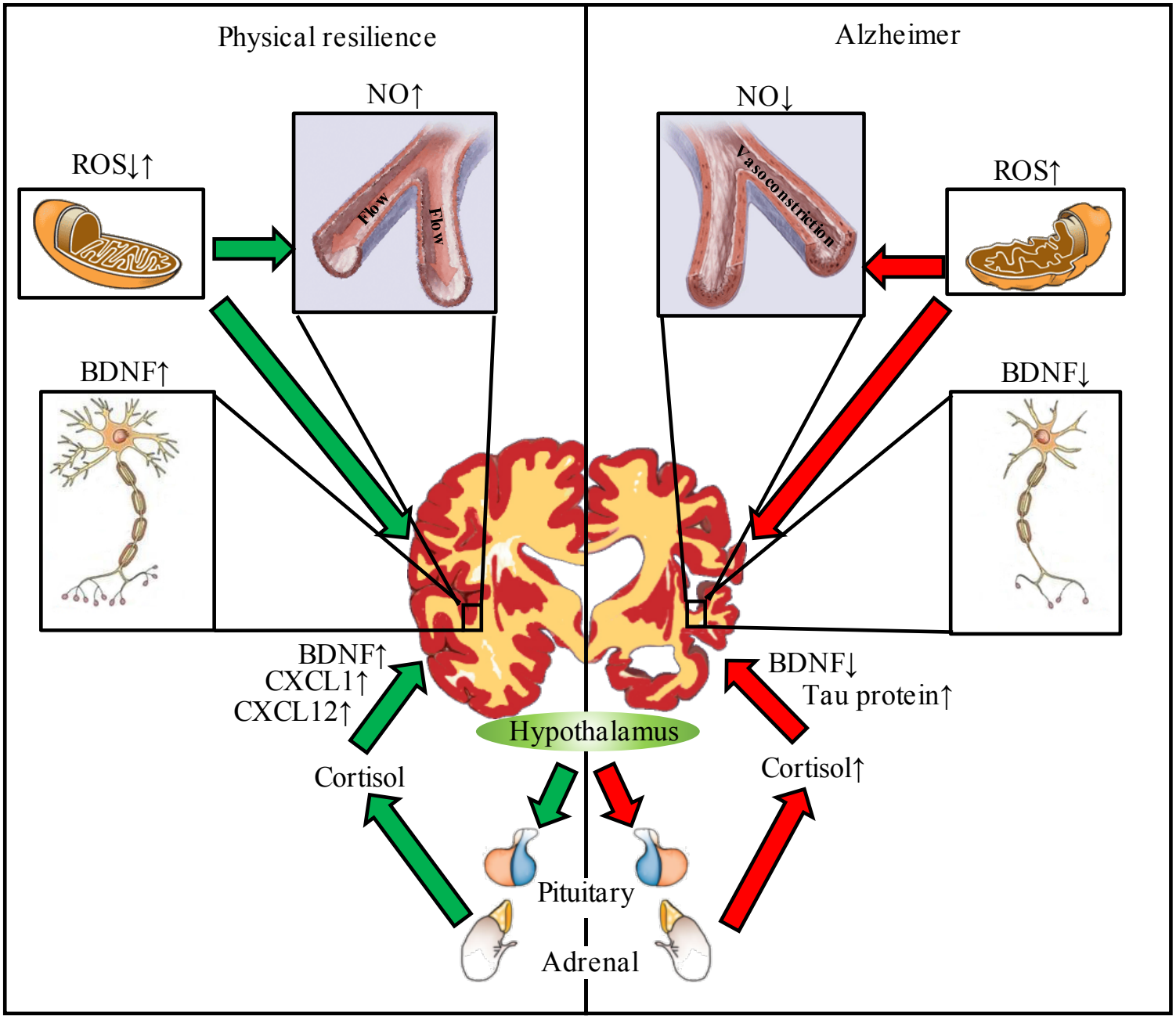
Venturelli et al. *JAD,* 2016

Exercise Training on Locomotion in Patients with Alzheimer's Disease: A Feasibility Study





Pedrinolla et al. *JAD,* 2018



Pedrinolla et al. *Current Alzheimer's research,* 2017

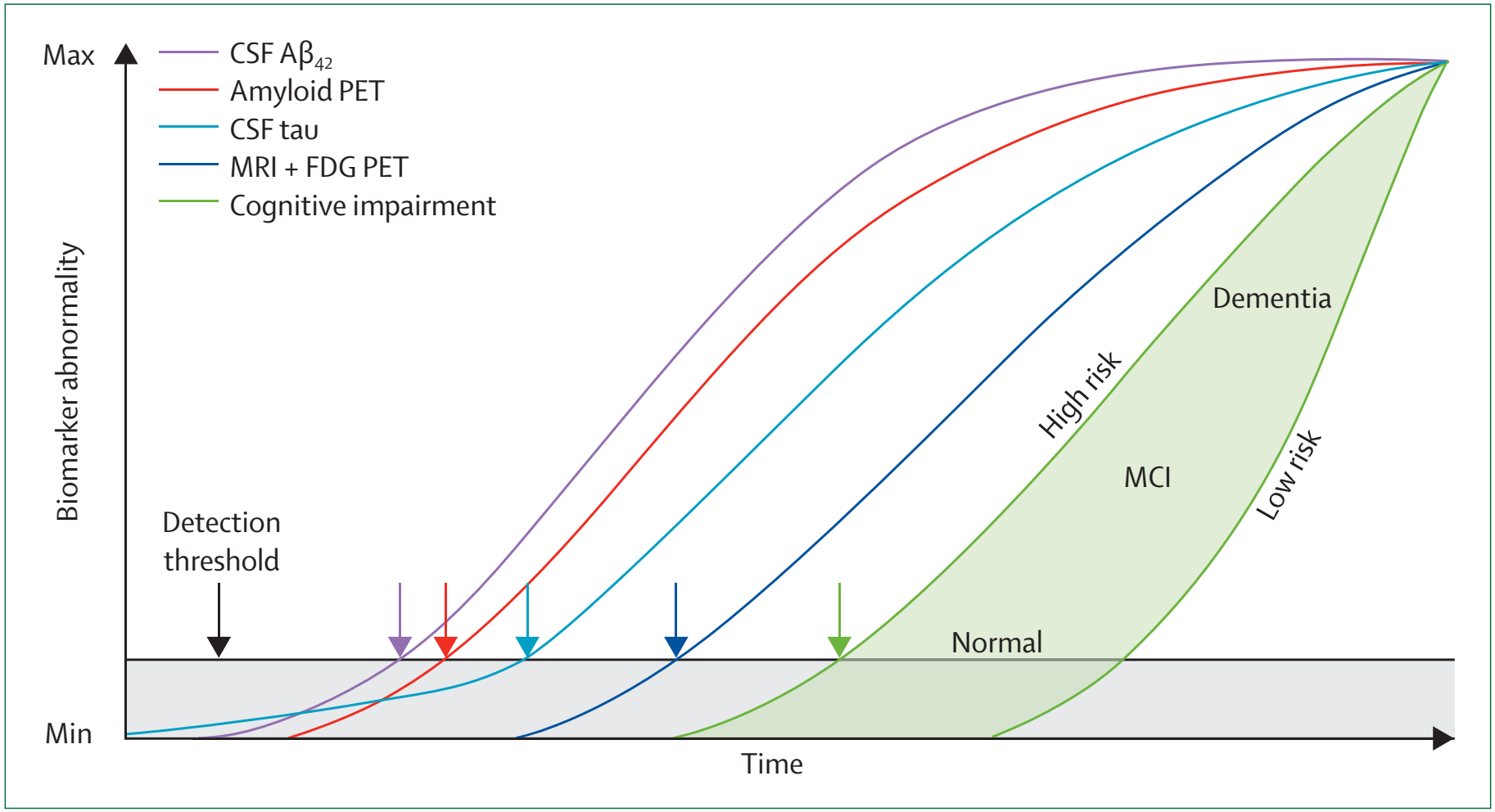


Figure 6: **Model integrating Alzheimer's disease immunohistology and biomarkers**

Clifford et al. Lancet Neurol 2013