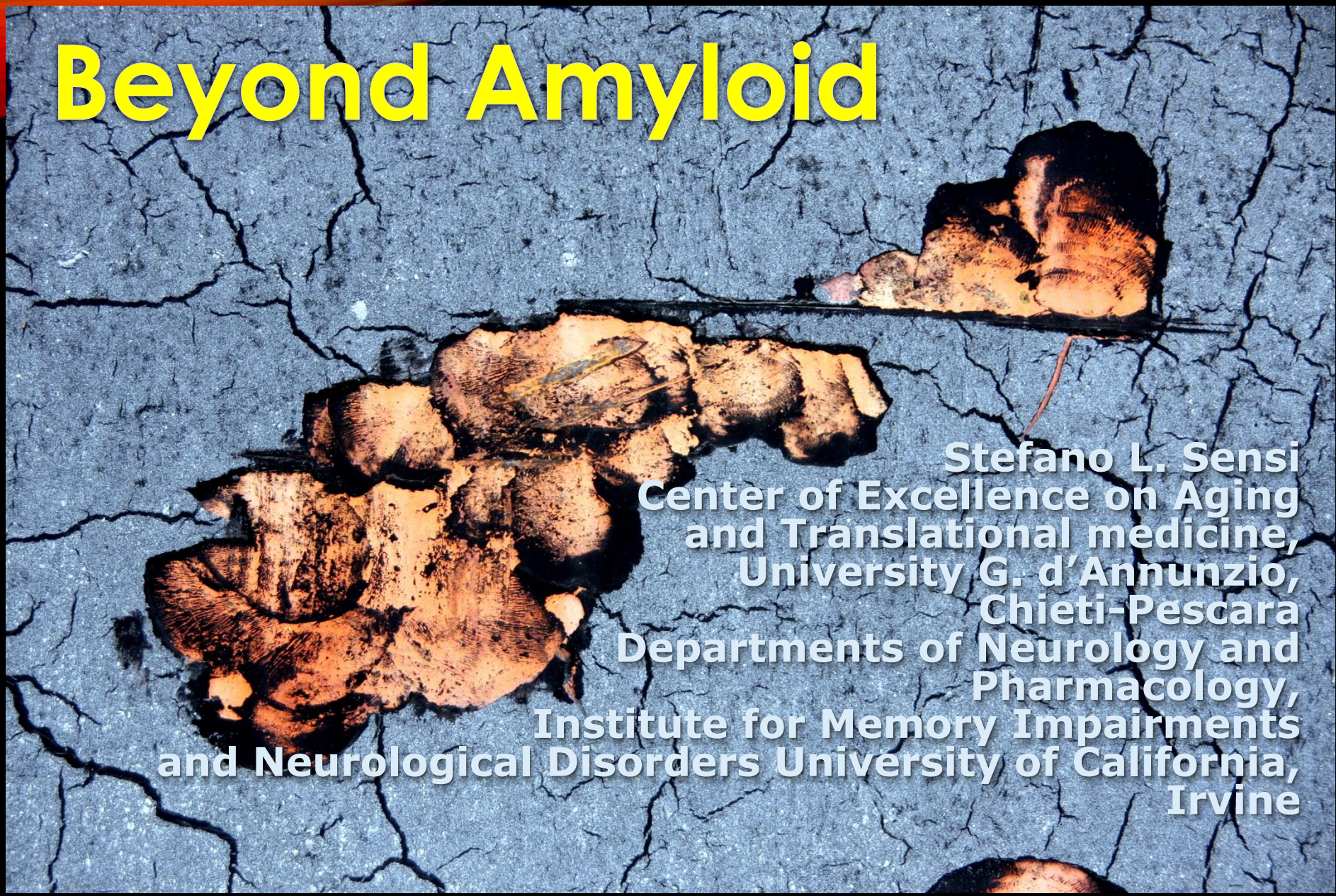
Beyond Amyloid



Stefano L. Sensi
Center of Excellence on Aging and Translational medicine, University G. d'Annunzio, Chieti-Pescara
Departments of Neurology and Pharmacology, Institute for Memory Impairments and Neurological Disorders University of California, Irvine

PERSPECTIVE

nature neuroscience

The case for rejecting the amyloid cascade hypothesis

Karl Herrup[1,2]

Acta Neuropathologica (2018) 136:663–689
https://doi.org/10.1007/s00401-018-1918-8

REVIEW

Questions concerning the role of amyloid-β in the definition, aetiology and diagnosis of Alzheimer's disease

Gary P. Morris[1,2] · Ian A. Clark[3] · Bryce Vissel[1,2]

Received: 30 July 2018 / Revised: 28 September 2018 / Accepted: 30 September 2018 / Published online: 22 October 2018

JAMA Neurology | Original Investigation

Prevalence of Biologically vs Clinically Defined Alzheimer Spectrum Entities Using the National Institute on Aging–Alzheimer's Association Research Framework

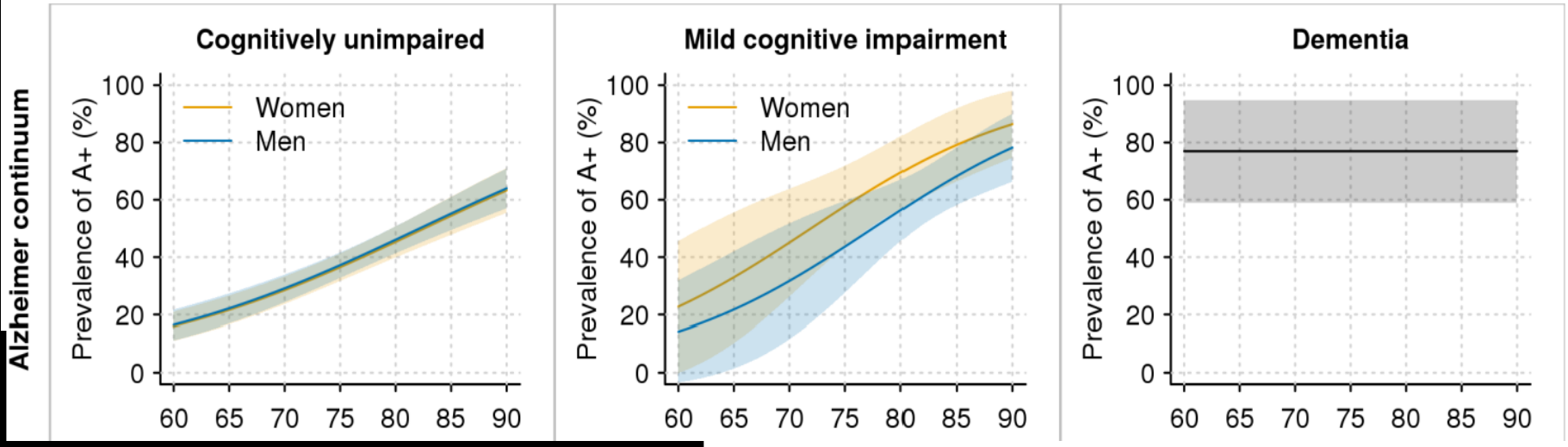
Clifford R. Jack Jr, MD; Terry M. Therneau, PhD; Stephen D. Weigand, MS; Heather J. Wiste, BA; David S. Knopman, MD; Prashanthi Vemuri, PhD; Val J. Lowe, MD; Michelle M. Mielke, PhD; Rosebud O. Roberts, MB, ChB; Mary M. Machulda, PhD; Jonathan Graff-Radford, MD; David T. Jones, MD; Christopher G. Schwarz, PhD; Jeffrey L. Gunter, PhD; Matthew L. Senjem, MS; Walter A. Rocca, MD; Ronald C. Petersen, MD, PhD

Key Points

Question How does the prevalence of 3 imaging biomarker–based definitions of the Alzheimer disease spectrum from the National

Figure 3. Prevalence of Biologically and Clinically Defined Diagnostic Entities

Figure 1. Prevalence of Biologically Defined Alzheimer Disease Spectrum Entities by Clinical Group



doi:10.1093/brain/awz037 BRAIN 2019: 0; 1–14 | 1

BRAIN
A JOURNAL OF NEUROLOGY

The metabolic brain signature of cognitive resilience in the 80+: beyond Alzheimer pathologies

Eider M. Arenaza-Urquijo,[1] Scott A. Przybelski,[2] Timothy L. Lesnick,[2] Jonathan Graff-Radford,[3] Mary M. Machulda,[4] David S. Knopman,[3] Christopher G. Schwarz,[1] Val J. Lowe,[1] Michelle M. Mielke,[2,3] Ronald C. Petersen,[3] Clifford R. Jack Jr.[1] and Prashanthi Vemuri[1]

	Full 80+ sample (n = 475)[a] Mean (SD)	Cognitively stable 80+ (n = 192) Mean (SD)
Age	83.5 (3.21)	82.7 (2.8)
Sex, % male	58	53
Education, years	14.4 (2.99)	14.8 (2.81)
Vascular risk (CMC)	2.74 (1.5)	2.7 (1.5)
Global cognition z-score	−0.74 (1.2)	−0.007 (0.79)
Amyloid positive, %	59	47
APOE4 positive, %	27.2	20

Characteristics of the cognitively stable subset of participants are provided separately.
[a]Of the full sample, 25% were cognitively impaired.
CMC = cardiac metabolic chronic conditions score.

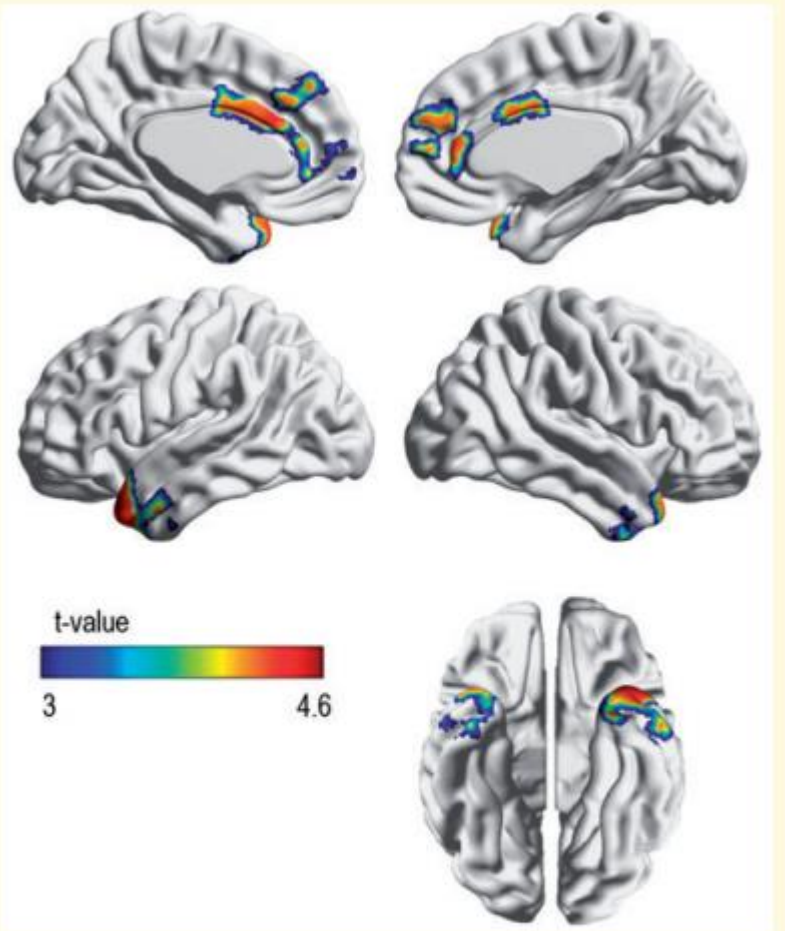
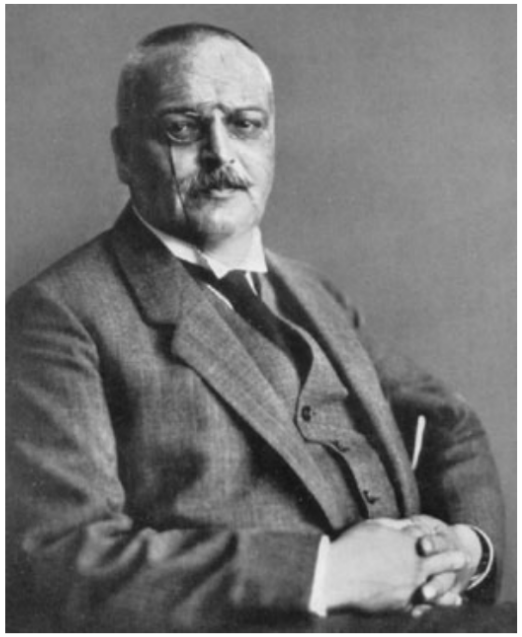


Figure 2 Results from the voxel-wise multiple regression analysis between global cognition and FDG-PET uptake in cognitively stable 80+ participants. Maps were thresholded at FDR $P < 0.05$ and $K > 1500$ mm^3. Note the lack of association between cognition and FDG in Alzheimer's disease signature regions.

"So we have to come to the conclusion that the plaques are not the cause of senile dementia, but only an accompanying feature of senile involution of the central nervous system."

Alois Alzheimer, 1911



Translation: On certain peculiar diseases of old age. History of Psychiatry, 1991

Rethinking the paradigm

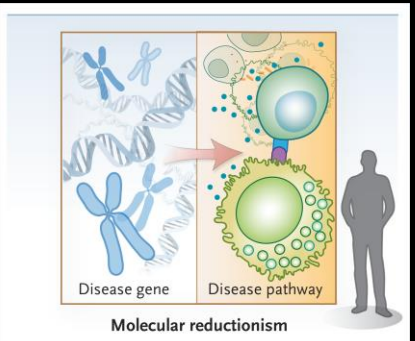
The NEW ENGLAND JOURNAL of MEDICINE

MEDICINE AND SOCIETY

Debra Malina, Ph.D., *Editor*

Putting the Patient Back Together — Social Medicine, Network Medicine, and the Limits of Reductionism

Jeremy A. Greene, M.D., Ph.D., and Joseph Loscalzo, M.D., Ph.D.

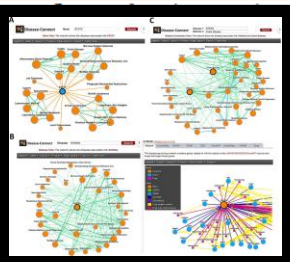


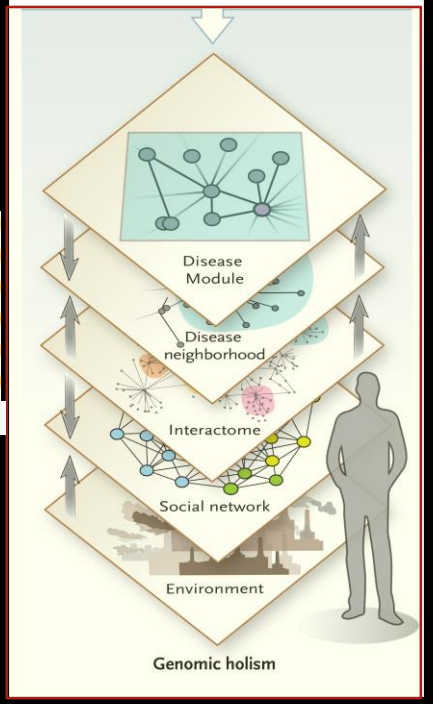
Molecular reductionism

Pathophenotype reflects the action of a deterministic, defective molecular network within a stochastic environmental context that modulates network function.

Another property of biologic networks is "emergence": their behavior cannot be predicted on the basis of a reductionist understanding of their component parts. Like an electrical circuit's behavior, that of a biologic network depends on the architectural connections among its elements. For decades, investigators have focused on one gene, transcription factor, or enzyme, gleaning a thorough understanding of its function but rarely in the context in which it normally operates. Before the -omic revolution, this approach reflected our limited knowledge of biologic networks' elements and the limitations of quantitative and computing methods. In the past decade, however, these limitations have diminished, and a holistic study of network medicine has become more achievable.[3,19]

It is thus important to reconceive biologic and pathobiologic phenomena in terms of complex networks of interacting genes or gene products and layers of environmental modulators. Network science has roots in sociology, which explores the behavior of social networks,[23] and in the mathematical field of graph theory.[24]





Genomic holism

Heart

Circulation

Kidney

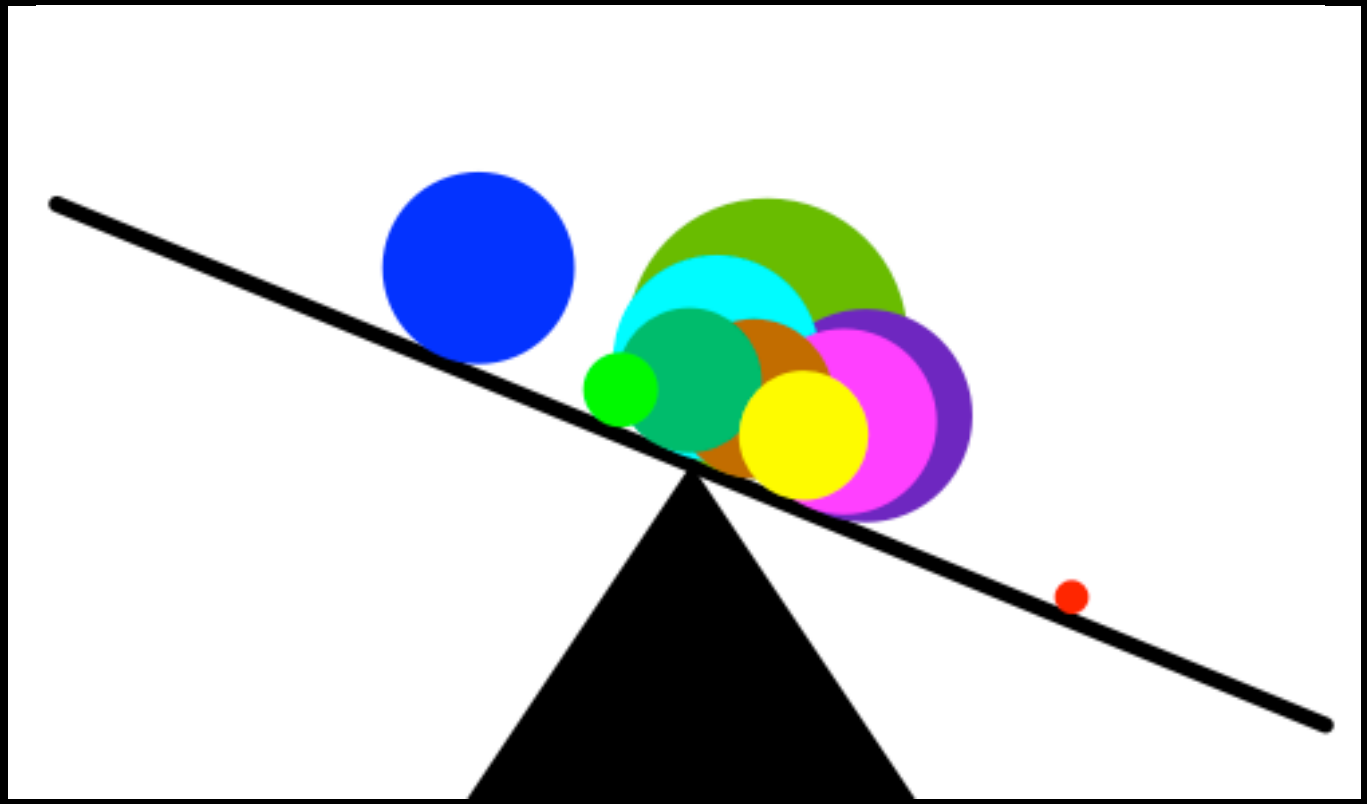
Lung functioning

Cell division

Cell death

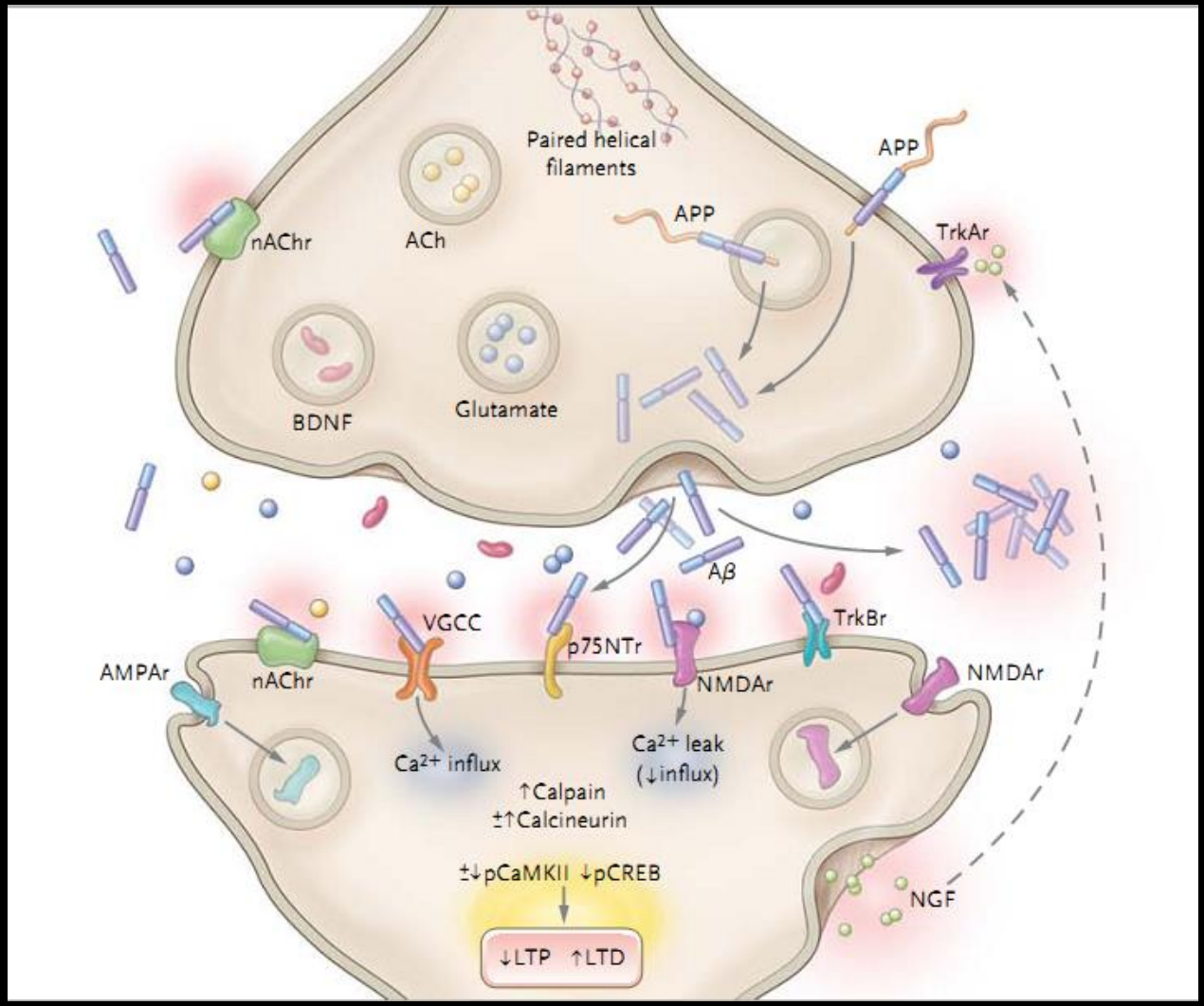
Metabolism

Immunitary system

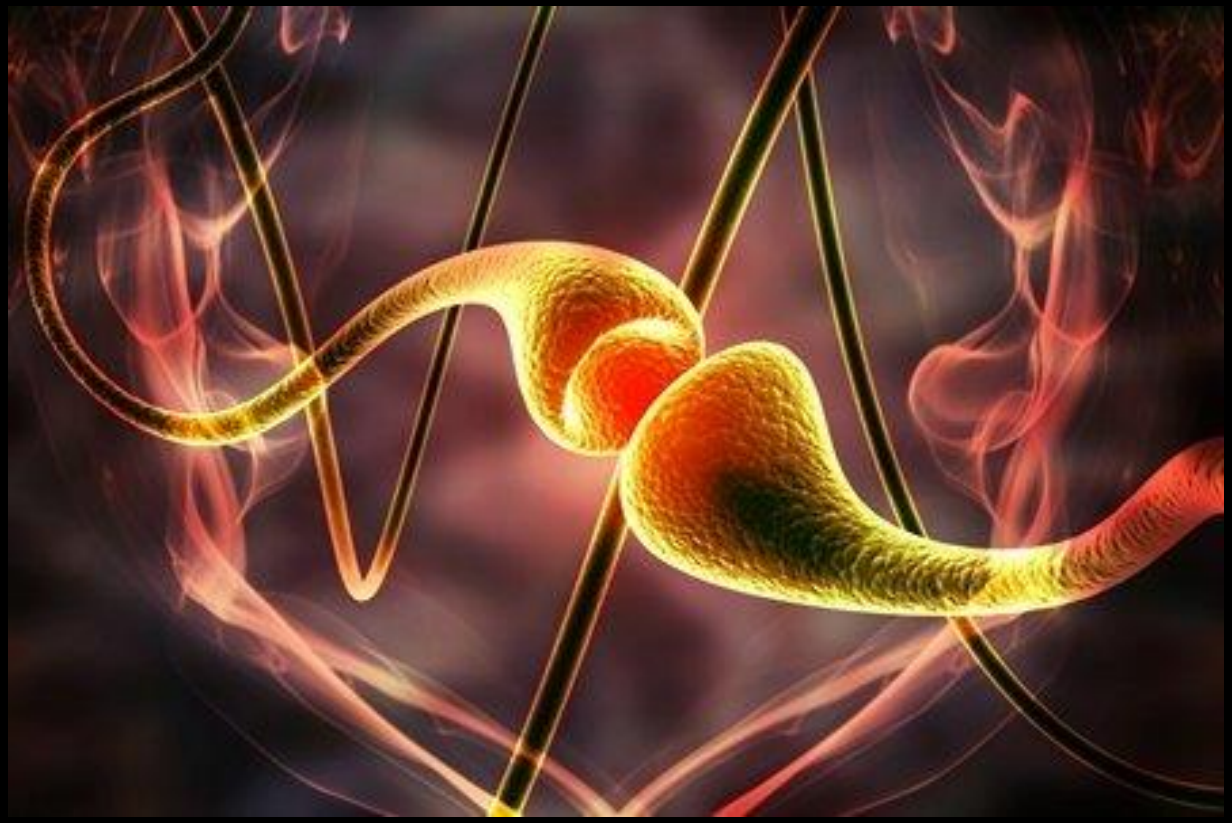


Death by multiple cuts

Synaptic dysfunction and dystrophy



The sweet trail to neuroprotection



The role of insulin receptor signaling in the brain

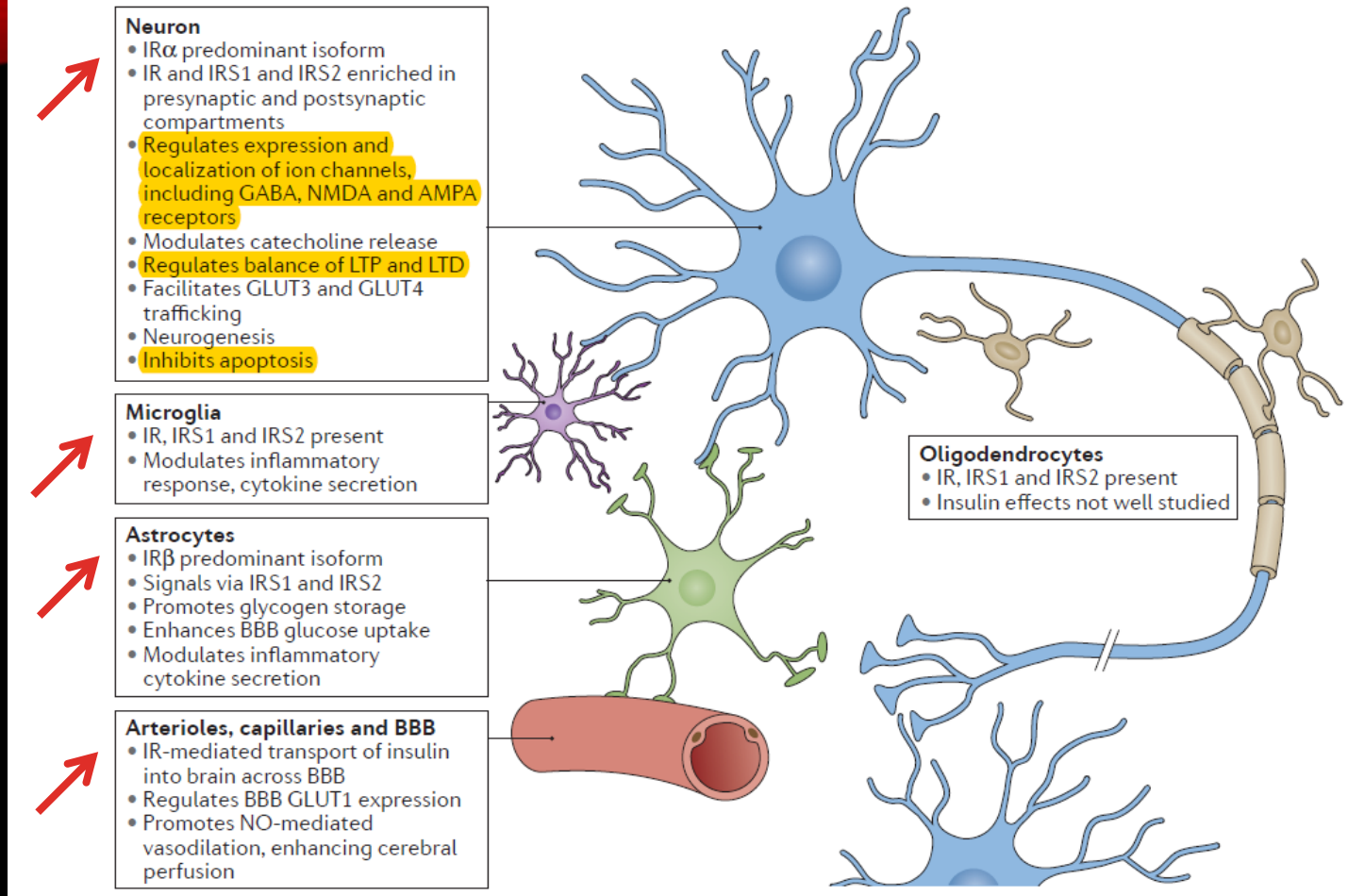
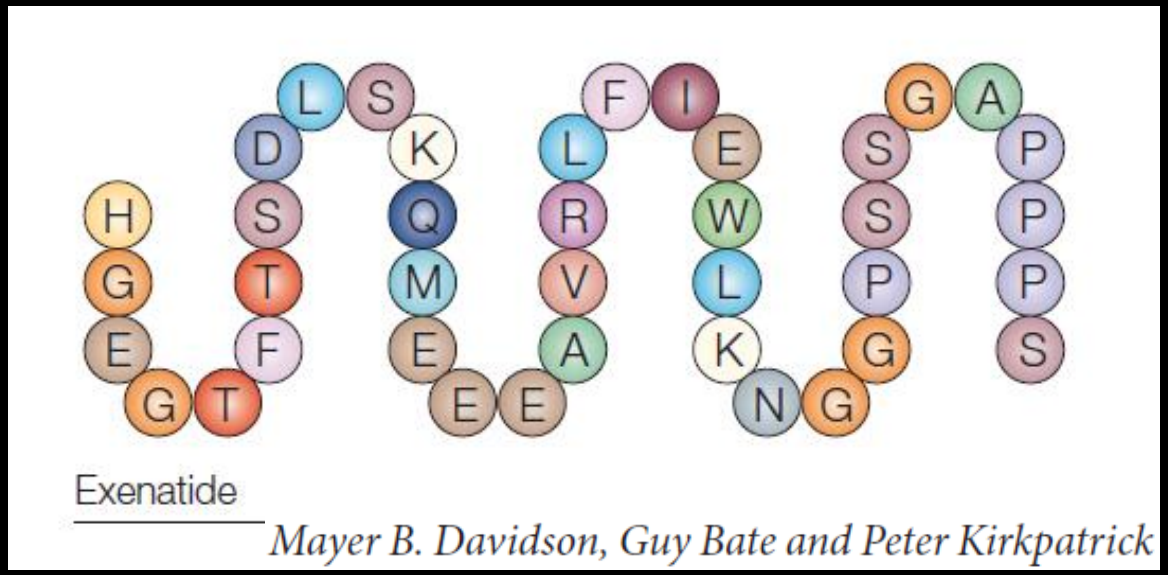


Figure 2 | **Insulin effects in major cell types of the brain.** Main characteristics of insulin signalling in neurons, astrocytes, microglia and the vascular system. AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BBB, blood–brain barrier; GLUT, glucose transporter type protein; IR, insulin receptor; IRS, insulin receptor substrate; LTD, long-term depression; LTP, long-term potentiation; NMDA, *N*-methyl-D-aspartate; NO, nitric oxide.

Glucagone Like Peptide (GLP-1) agonists- Exenatide, Liraglutide…

Can the stimulation of incretin signaling improve energetic metabolism and cognitive functions in preclinical models of neuronal dysfunction?



NEWS & VIEWS

PARKINSON DISEASE

Exenatide – a drug for diabetes and Parkinson disease?

Joseph Jankovic

Preventing the misfolding, aggregation, accumulation and propagation of α-synuclein — pivotal mechanisms that contribute to neurodegeneration in Parkinson disease (PD) and other synucleinopathies — is the goal of research into neuroprotective therapies. Exenatide, a glucagon-like peptide-1 (GLP-1) agonist, has been shown to ameliorate the severity of motor symptoms and

Refers to Athauda, D. *et al.* Exenatide once weekly versus placebo in P double-blind, placebo-controlled trial. *Lancet* http://dx.doi.org/10.1

than to directly treat certain symptoms. Exenatide crosses the blood–brain barrier (median reported cerebrospinal fluid concentrations were ~11 pg/ml — ~2% of the typical serum concentration), and has neuroprotective and regenerative effects, presumably via activation of GLP-1 receptors, in various animal models of PD[4]. However, no evidence is available from preclinical studies indicating that doses similar to those used in patients with T2DM provide clinically meaningful effects on dopaminergic symptoms.

Articles

Exenatide once weekly versus placebo in Parkinson's disease: a randomised, double-blind, placebo-controlled trial

Dilan Athauda, Kate Maclagan, Simon S Skene, Martha Bajwa-Joseph, Dawn Letchford, Kashfia Chowdhury, Steve Hibbert, Natalia Budnik, Luca Zampedri, John Dickson, Yazhou Li, Iciar Aviles-Olmos, Thomas T Warner, Patricia Limousin, Andrew J Lees, Nigel H Greig, Susan Tebbs, Thomas Foltynie

Lancet 2017; 390: 1664–75

Published Online August 3, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31585-4

See Comment page 1628

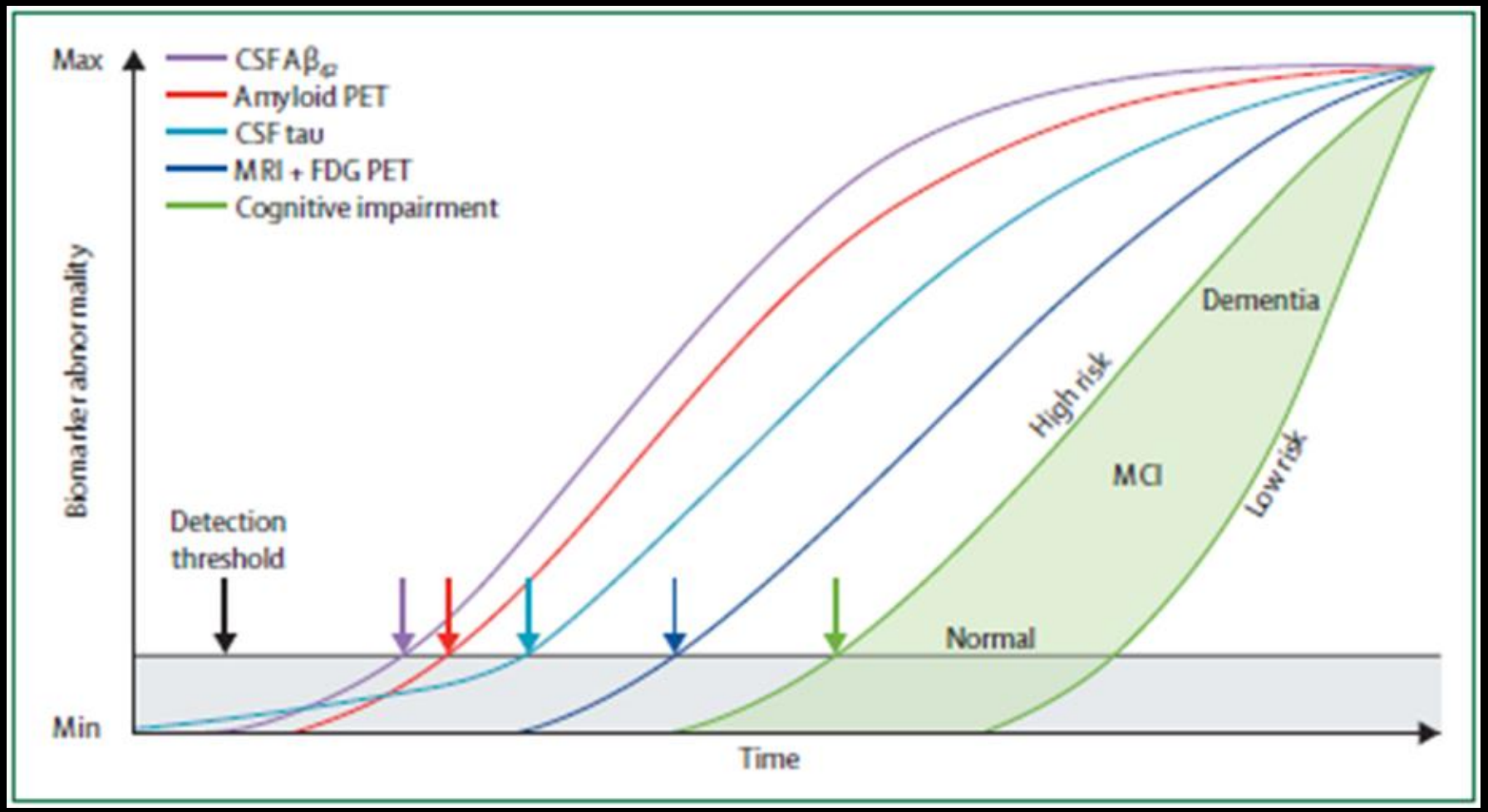
Sobell Department of Motor Neuroscience, University College London Institute of Neurology and the National Hospital for Neurology and Neurosurgery, London, UK (D Athauda MRCP, I Aviles-Olmos PhD, Prof P Limousin MD, Prof A J Lees FRCP, Prof T Foltynie PhD);

Summary

Background Exenatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, has neuroprotective effects in preclinical models of Parkinson's disease. We investigated whether these effects would be apparent in a clinical trial.

Methods In this single-centre, randomised, double-blind, placebo-controlled trial, patients with moderate Parkinson's disease were randomly assigned (1:1) to receive subcutaneous injections of exenatide 2 mg or placebo once weekly for 48 weeks in addition to their regular medication, followed by a 12-week washout period. Eligible patients were aged 25–75 years, had idiopathic Parkinson's disease as measured by Queen Square Brain Bank criteria, were on dopaminergic treatment with wearing-off effects, and were at Hoehn and Yahr stage 2·5 or less when on treatment. Randomisation was by web-based randomisation with a two strata block design according to disease severity. Patients and investigators were masked to treatment allocation. The primary outcome was the adjusted difference in the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) motor subscale (part 3) in the practically defined off-medication state at 60 weeks. All efficacy analyses were based on a modified intention-to-treat principle, which included all patients who completed any post-randomisation follow-up assessments. The study is registered at ClinicalTrials.gov (NCT01971242) and is completed.

Early intervention



Jack et al., Lancet Neurology, 2013

Patient M.

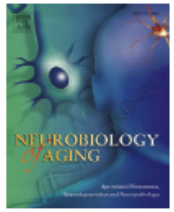
Exenatide acts as cognitive enhancer in adult mice

Neurobiology of Aging 64 (2018) 33–43

Contents lists available at ScienceDirect

Neurobiology of Aging

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



Exenatide exerts cognitive effects by modulating the BDNF-TrkB neurotrophic axis in adult mice

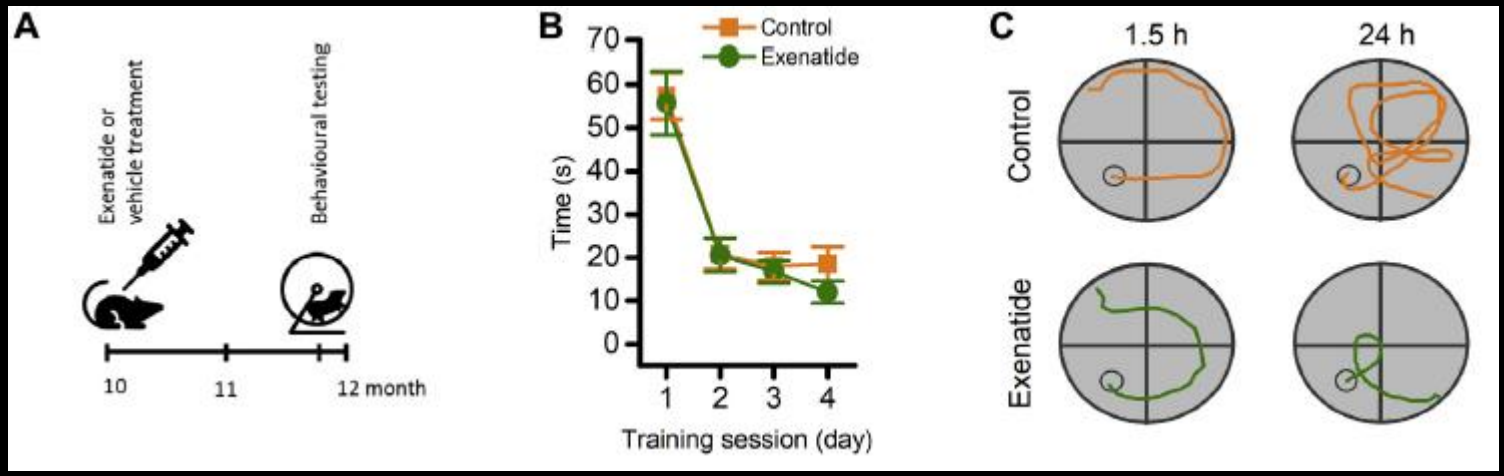
Manuela Bomba [a,b,1], Alberto Granzotto [a,b,1], Vanessa Castelli [c], Noemi Massetti [a], Elena Silvestri [d], Lorella M.T. Canzoniero [d], Annamaria Cimini [c,e,f], Stefano L. Sensi [a,b,g,*]

[a] Center of Excellence on Aging and Translational Medicine - CeSI-MeT, University G. d'Annunzio of Chieti-Pescara, Italy
[b] Department of Neuroscience, Imaging, and Clinical Sciences, University G. d'Annunzio of Chieti-Pescara, Italy
[c] Department of Life, Health and Environmental Sciences, University of L'Aquila, Italy
[d] Division of Pharmacology, Department of Science and Technology, University of Sannio, Benevento, Italy
[e] Sbarro Institute for Cancer Research and Molecular Medicine and Center for Biotechnology, Temple University, Philadelphia, USA
[f] National Institute for Nuclear Physics (INFN), Gran Sasso National Laboratory (LNGS), Assergi, Italy
[g] Departments of Neurology and Pharmacology, Institute for Mind Impairments and Neurological Disorders, University of California - Irvine, Irvine, USA

Experimental Paradigm

MICE ENROLLED

- 22 adult mice

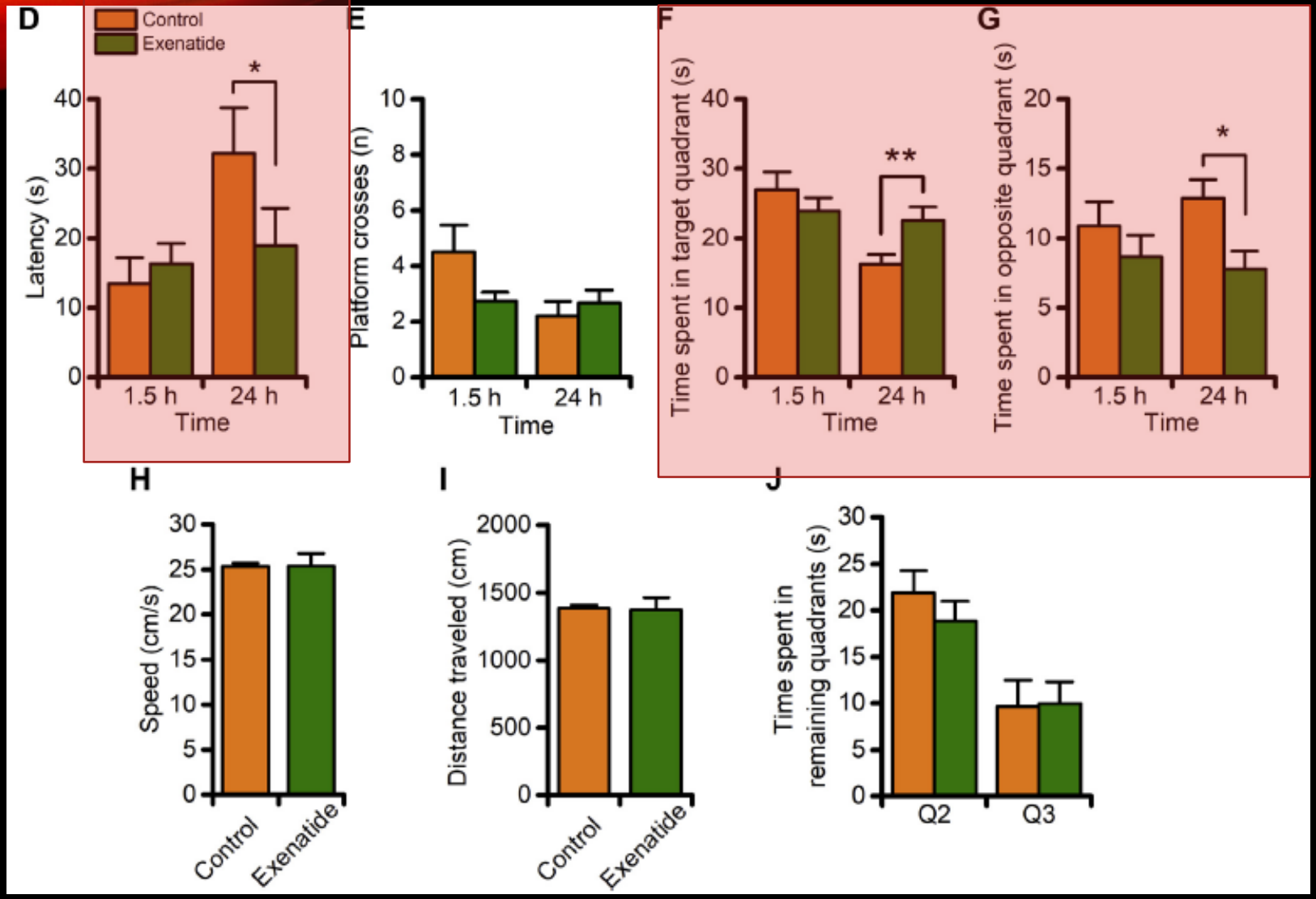


WEEKLY:
Animals weight, food consumption fasting glycaemia

MONTHLY:
Serum sampling
&
IPGTT

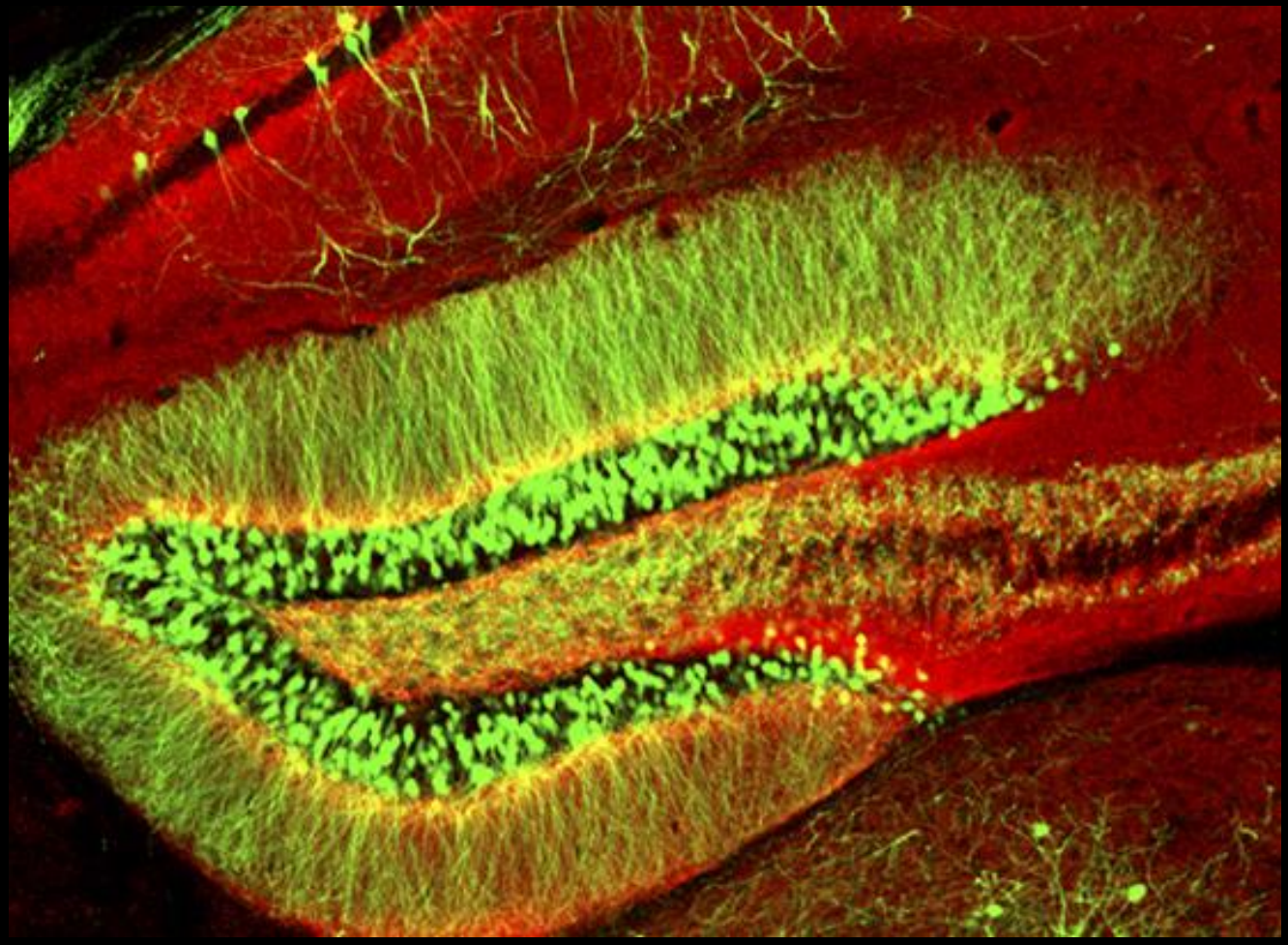
Assessment of COGNITIVE-BEHAVIORAL FUNCTIONS

Exenatide improves long-term memory

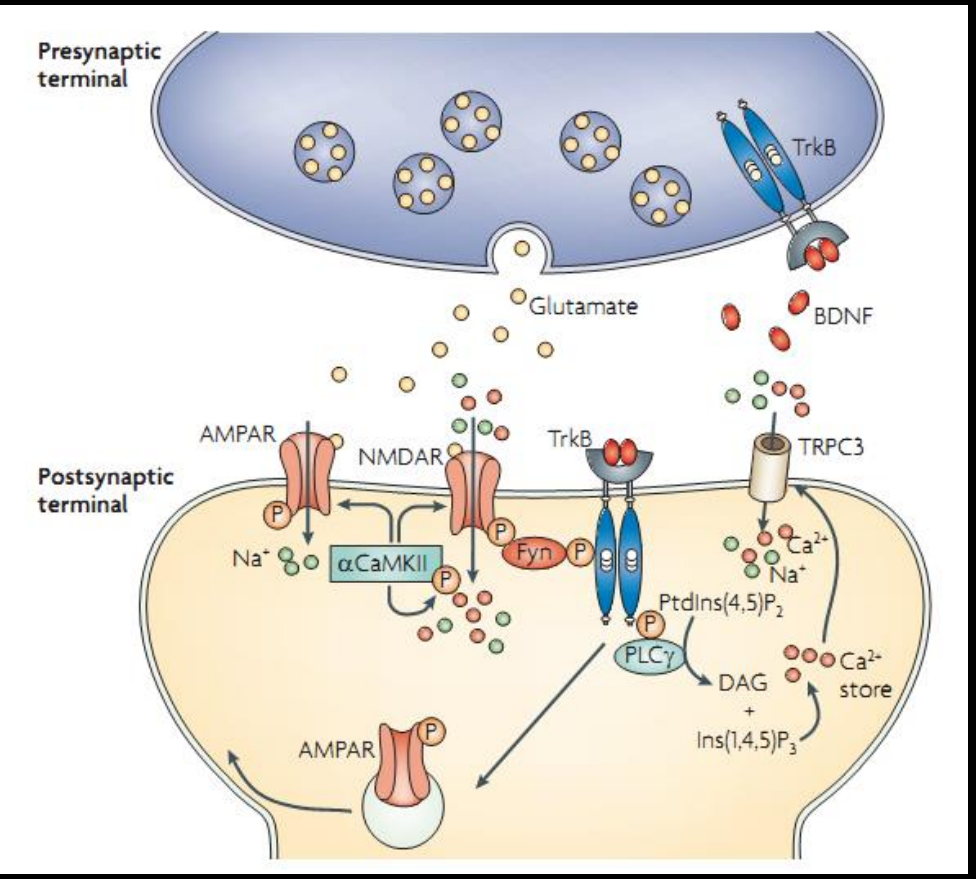


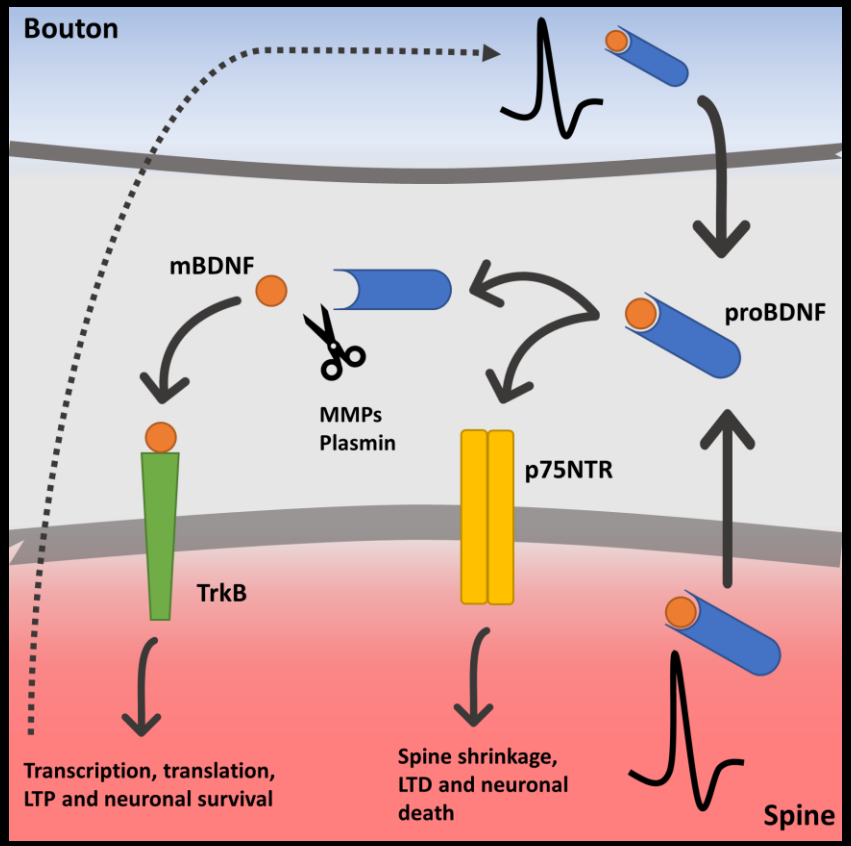
Bomba et al., Neurobiology of Aging, 2018

BDNF SIGNALING AND COGNITION



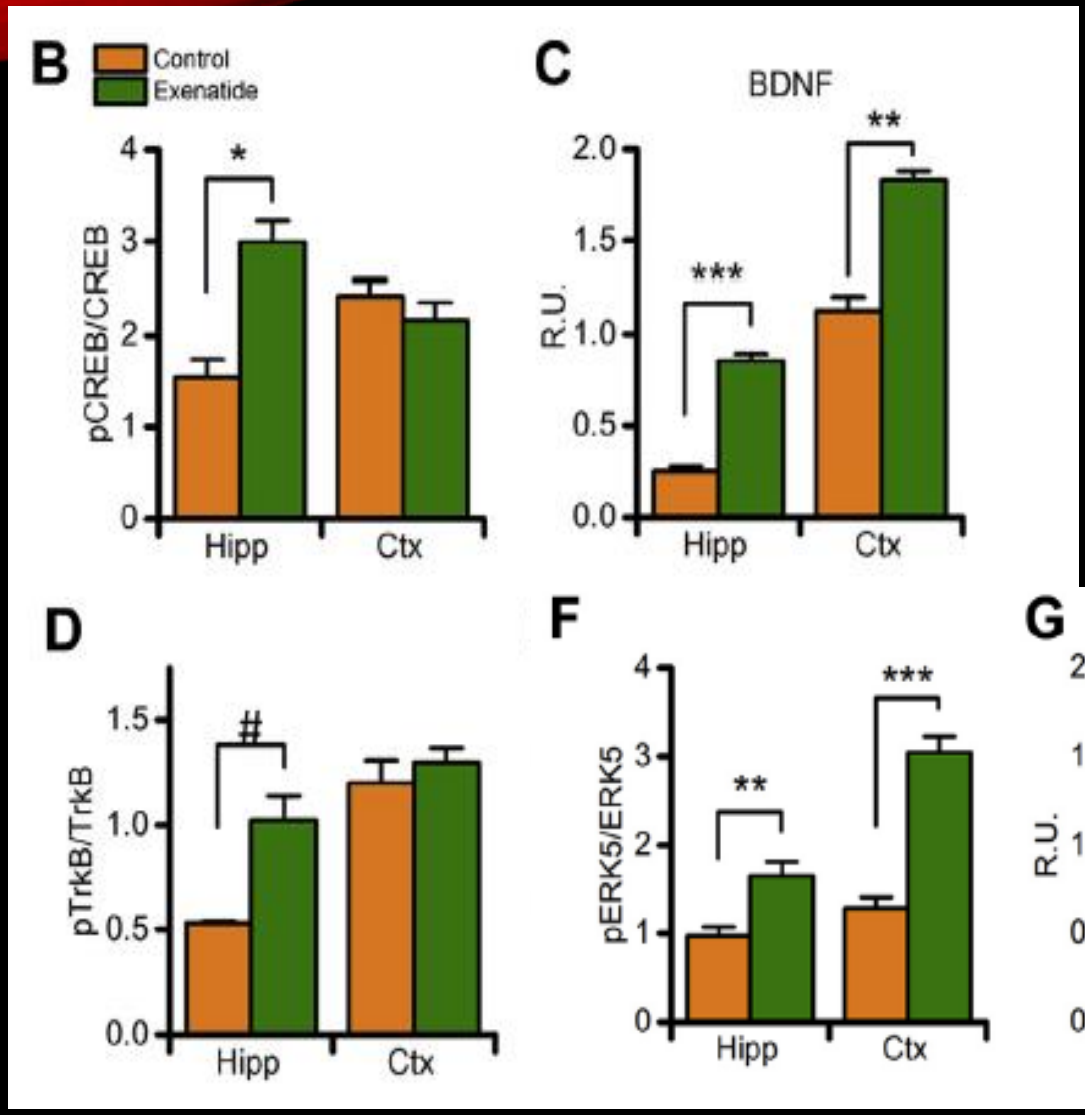
BDNF SIGNALING AT NEURONAL SYNAPSES

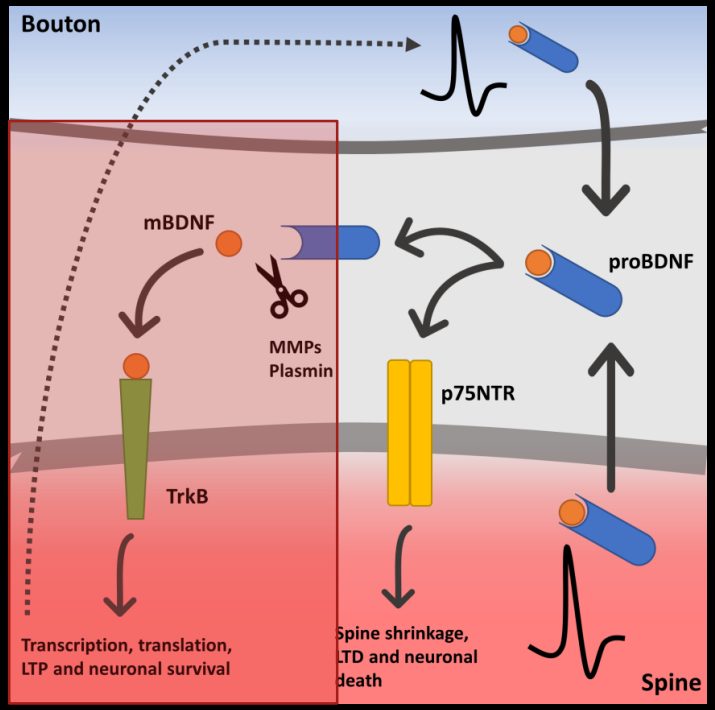




Minichiello T., Nature Rev Neurosci, 2009

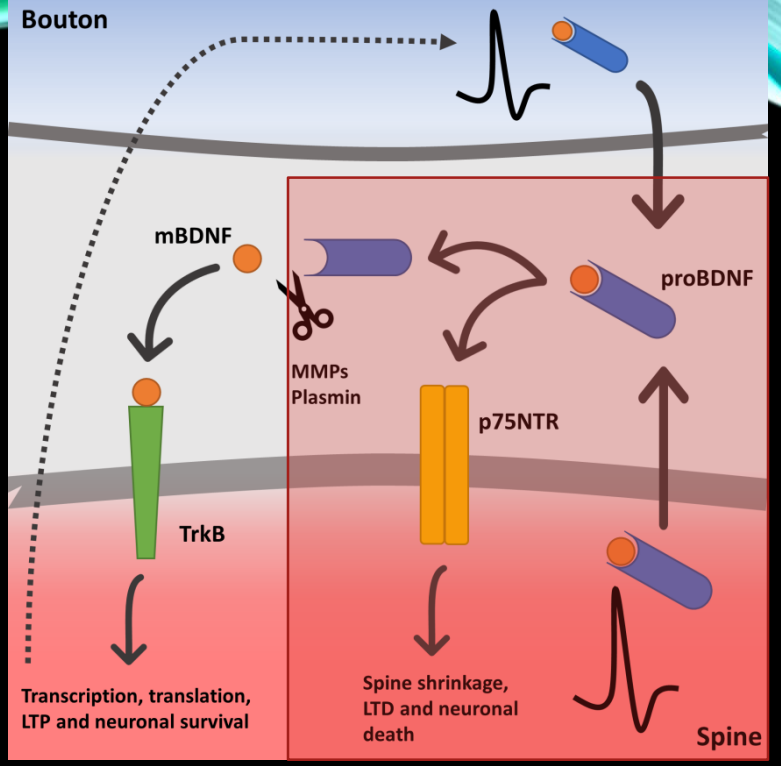
Exenatide activates survival- and plasticity-related pathways

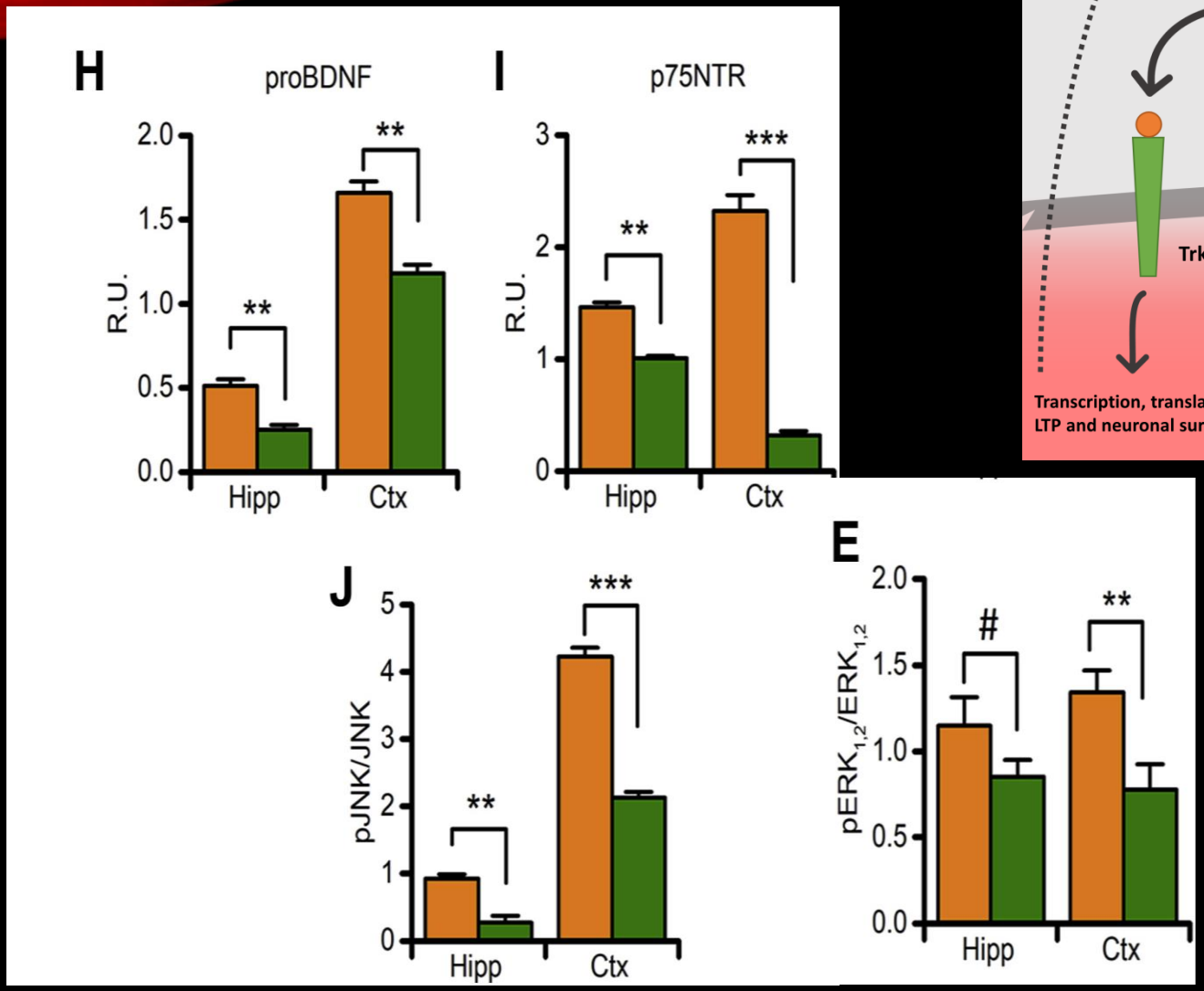




Bomba et al., Neurobiology of Aging, 2018

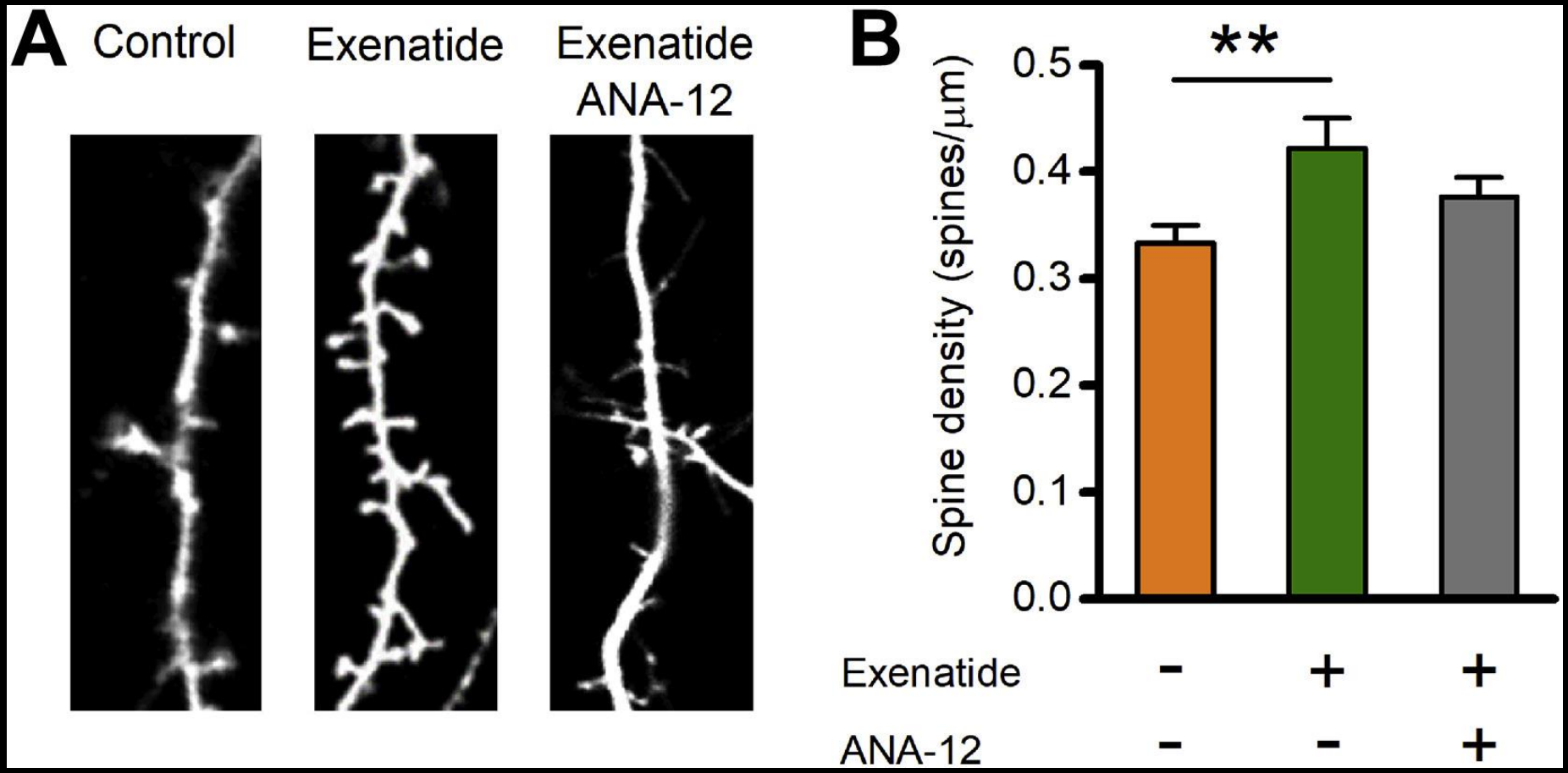
Exenatide decreases neuronal death-related pathways





Bomba et al., Neurobiology of Aging, 2018

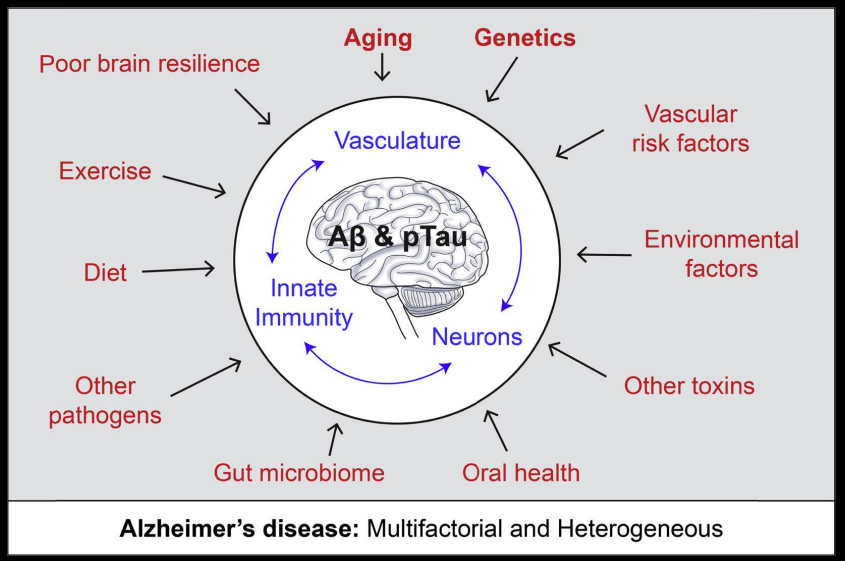
Exenatide increases synaptic plasticity



Bomba et al., Neurobiology of Aging, 2018

Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease

Miia Kivipelto[1,2,3,4], Francesca Mangialasche[2,5] and Tiia Ngandu[1,2]*



Alzheimer's disease: Multifactorial and Heterogeneous

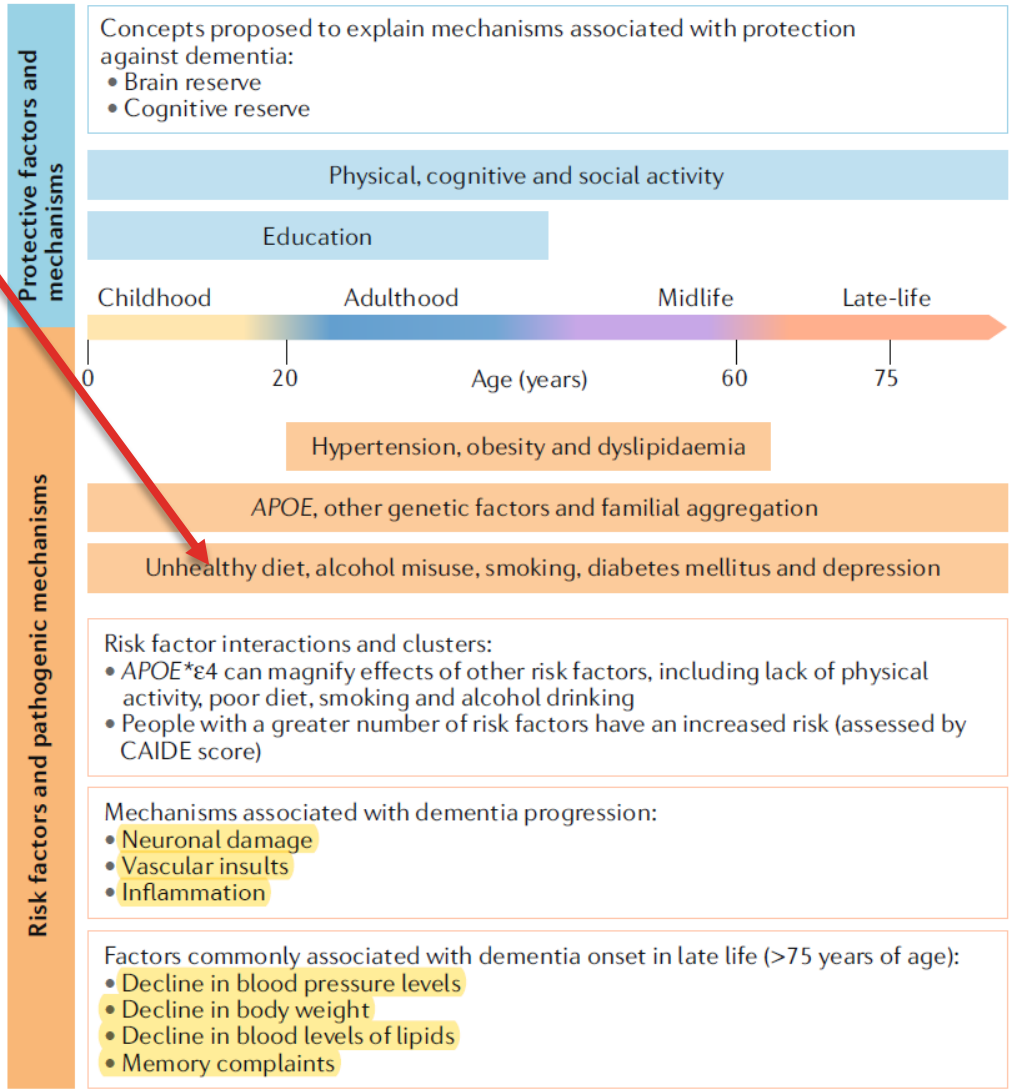
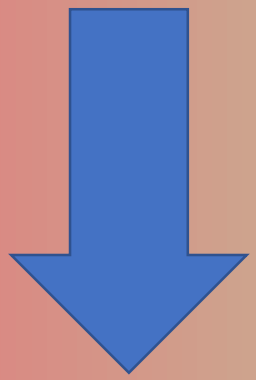
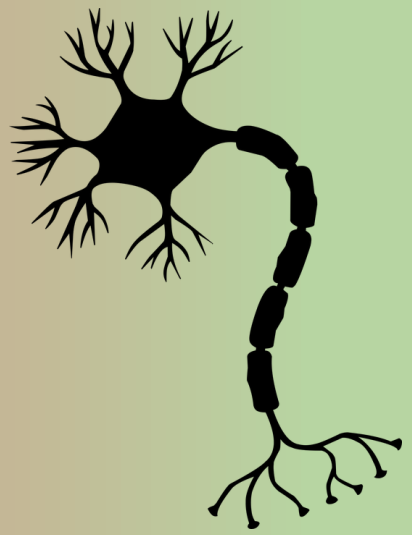
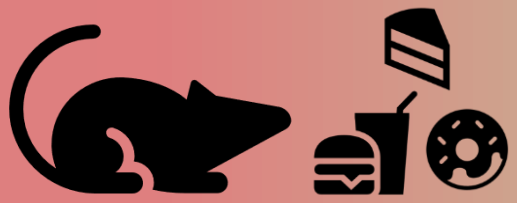


Fig. 1 | **Risk and protective factors for dementia and Alzheimer disease across the lifespan.** Some factors can differentially affect the risk of dementia and Alzheimer disease in an individual depending on the time of exposure within the life course. For example, hypertension, obesity and dyslipidaemia increase dementia risk when a person is exposed during midlife. By contrast, other factors such diet affect risk across the lifespan. CAIDE, Cardiovascular Risk Factors, Aging and Dementia.

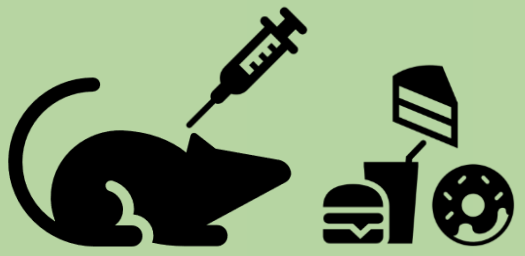
3xTg-AD-HFD
pro-AD background
+ stressor metabolico



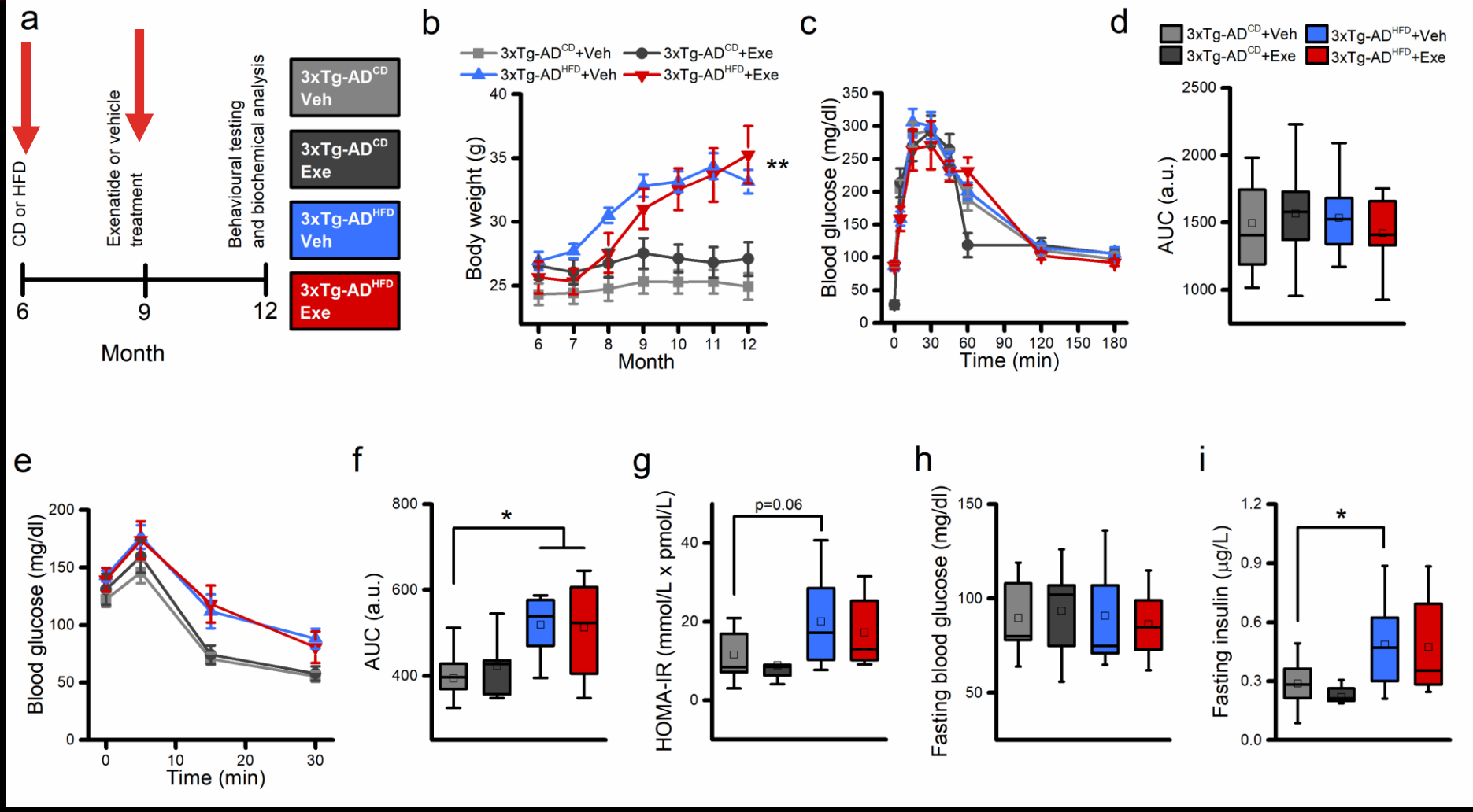




Exenatide

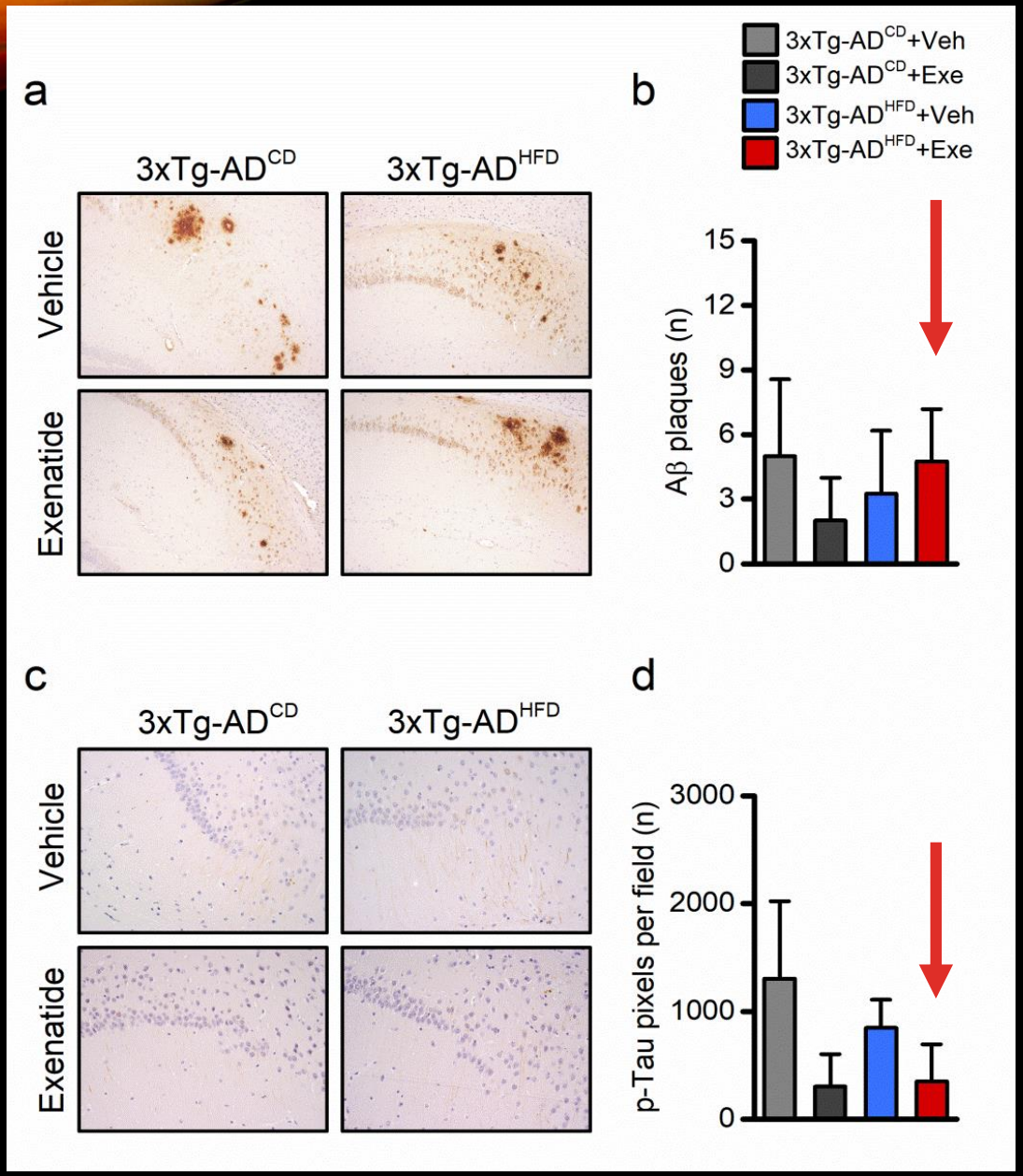


Effects of HFD and exenatide on systemic metabolism



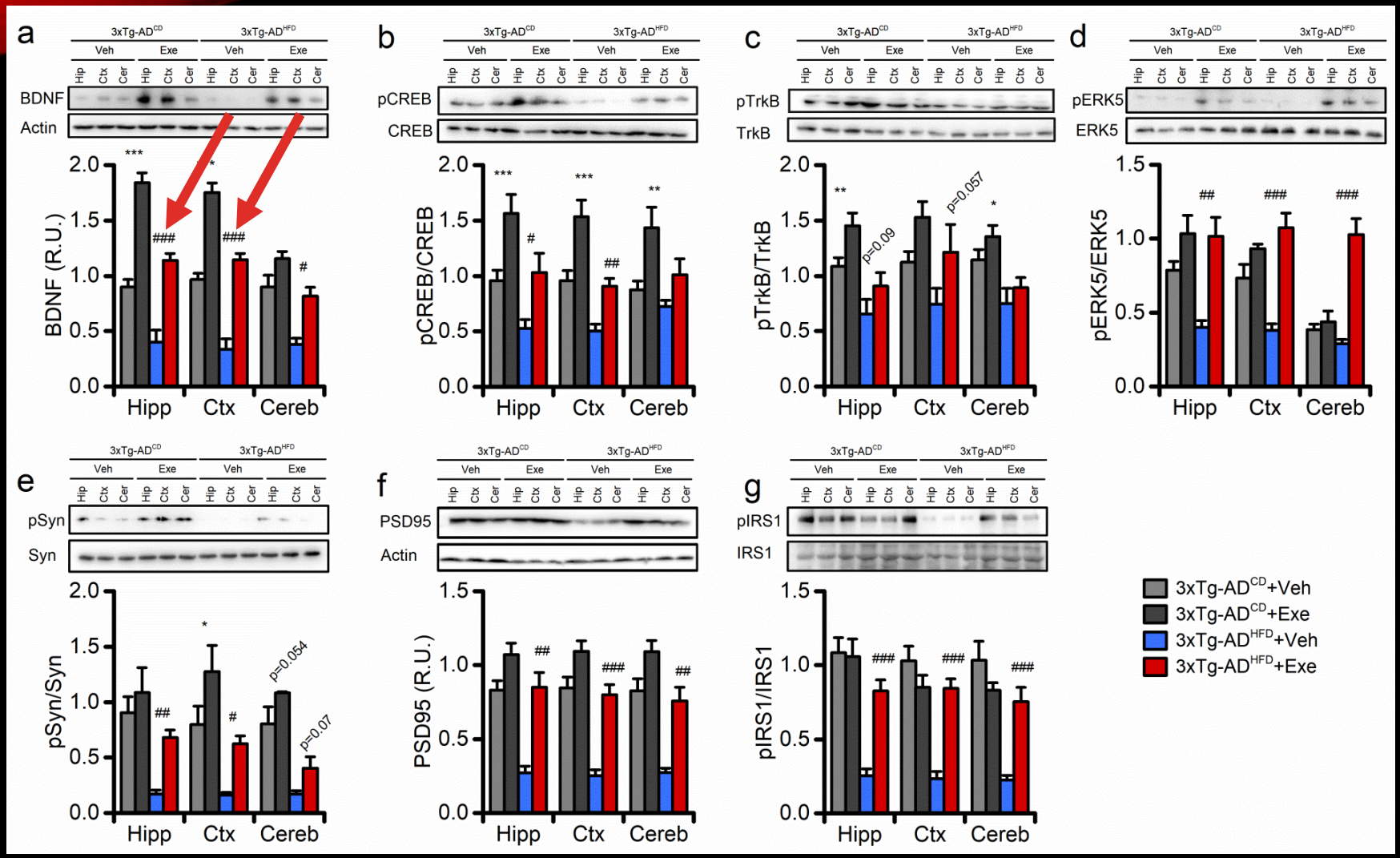
Bomba et al., JAD 2019

Effects of HFD and exenatide on Aβ and tau pathology



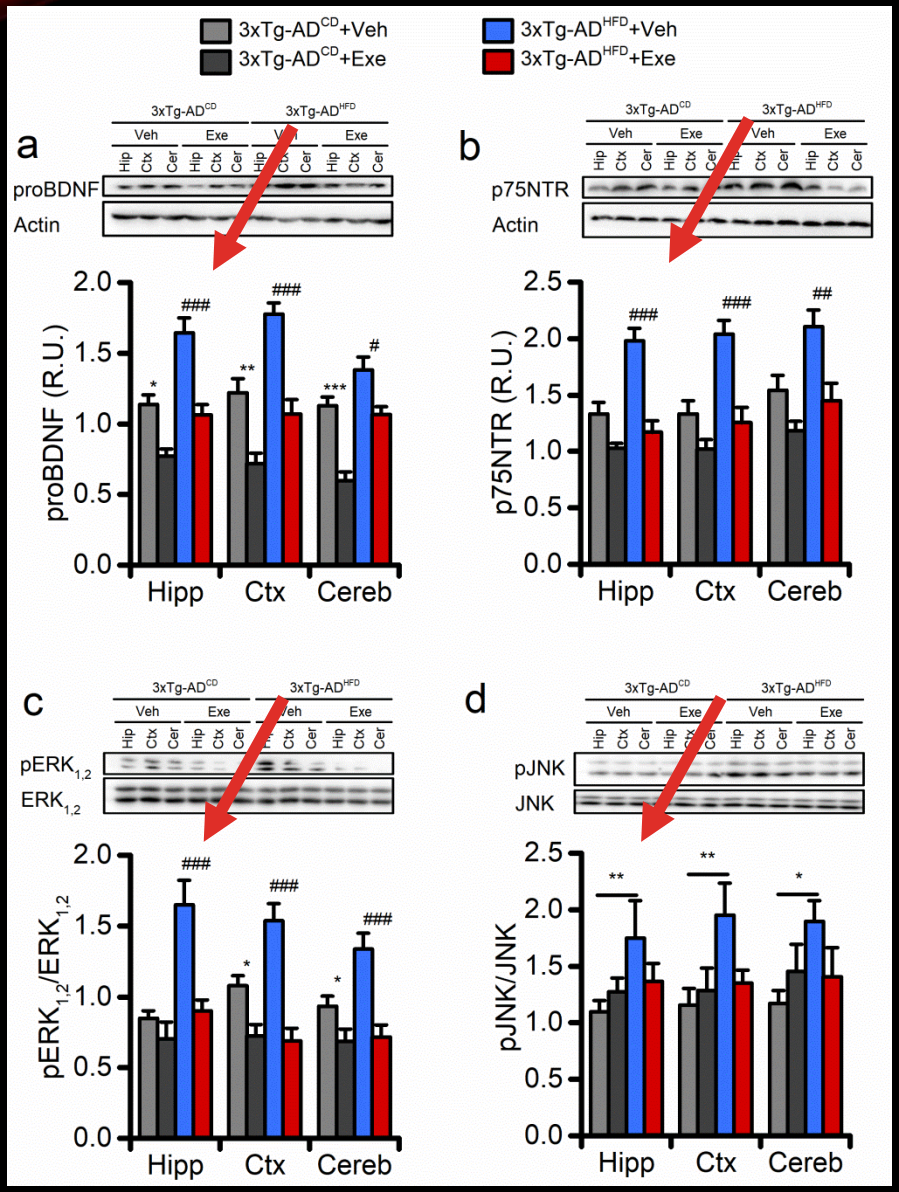
Bomba et al., JAD 2019

Effects of HFD and exenatide on plasticity-related signaling



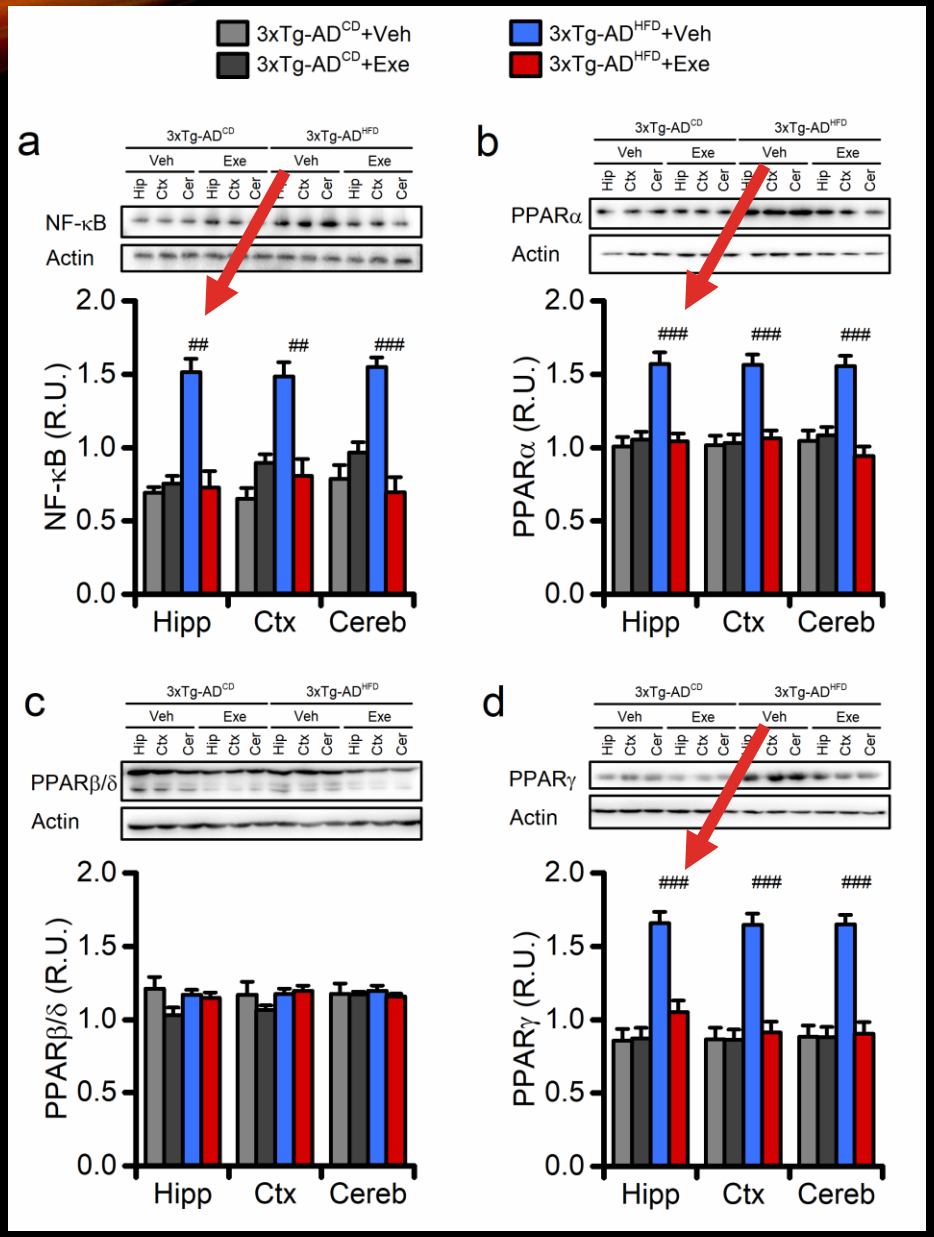
Bomba et al., JAD 2019

Effects of HFD and exenatide on pro-BDNF mediated neurotoxic signaling

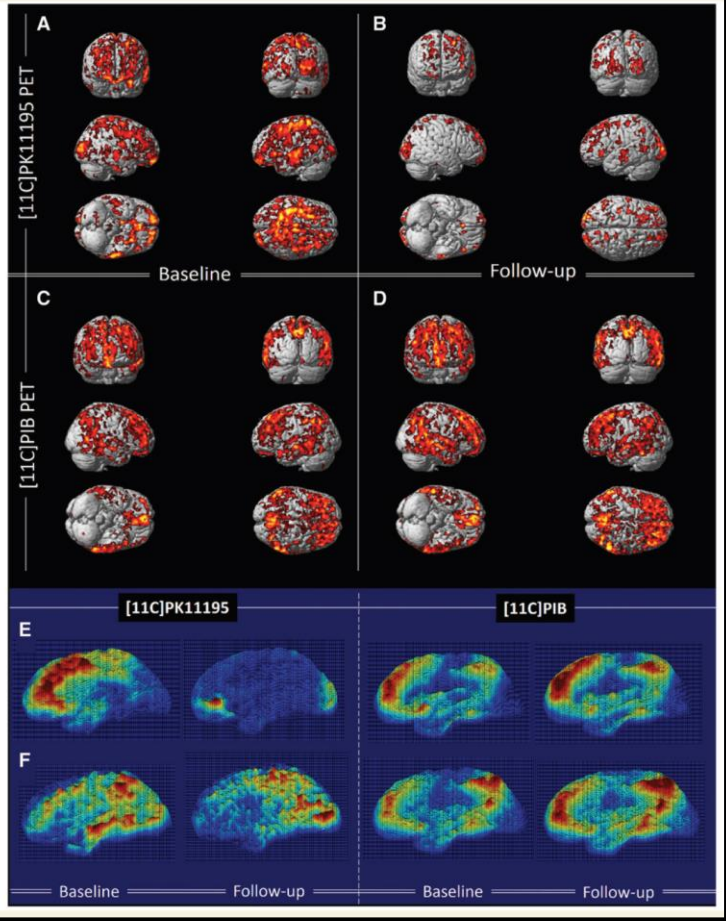


Bomba et al., JAD 2019

Effects of HFD and exenatide on brain inflammation



Bomba et al., JAD 2019

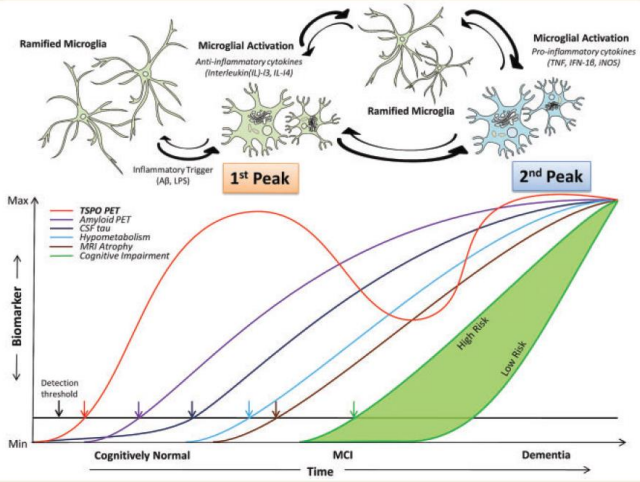


doi:10.1093/brain/aww349 BRAIN 2017: 140; 792–803 | 792

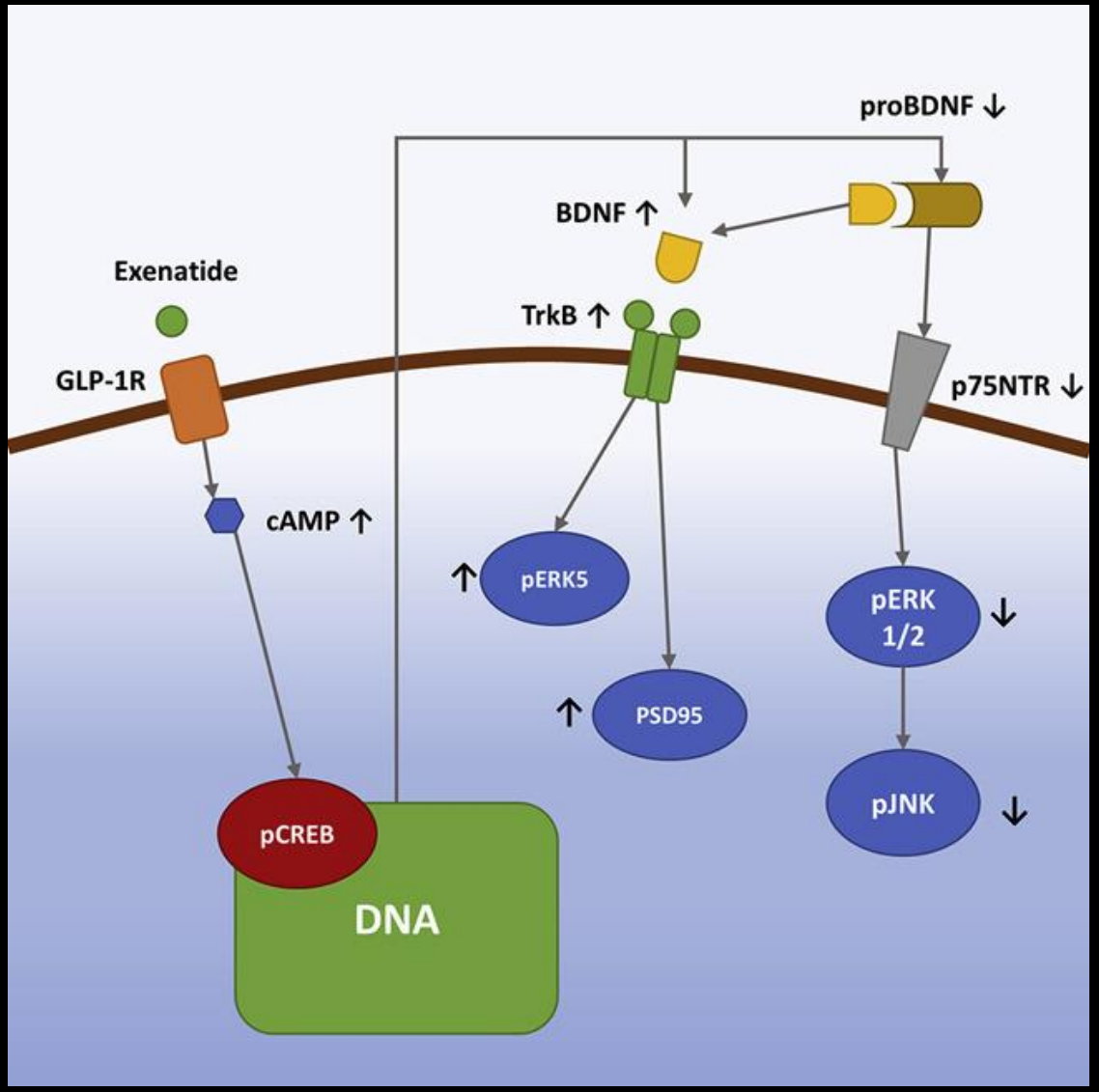
BRAIN
A JOURNAL OF NEUROLOGY

An early and late peak in microglial activation in Alzheimer's disease trajectory

Zhen Fan,[1] David J. Brooks,[1,2] Aren Okello[1] and Paul Edison[1]



Exenatide proposed mode of action



Original Investigation

Serum Brain-Derived Neurotrophic Factor and the Risk for Dementia
The Framingham Heart Study

Galit Weinstein, PhD; Alexa S. Beiser, PhD; Seung Hoan Choi, MS; Sarah R. Preis, ScD, MPH; Tai C. Chen, PhD; Demetrios Vorgas, MSc; Rhoda Au, PhD; Aleksandra Pikula, MD; Philip A. Wolf, MD; Anita L. DeStefano, PhD; Ramachandran S. Vasan, MD; Sudha Seshadri, MD

IMPORTANCE In animal studies, brain-derived neurotrophic factor (BDNF) has been shown to impact neuronal survival and function and improve synaptic plasticity and long-term memory. Circulating BDNF levels increase with physical activity and caloric restriction, thus BDNF may mediate some of the observed associations between lifestyle and the risk for dementia. Some prior studies showed lower circulating BDNF in persons with Alzheimer disease (AD) compared with control participants; however, it remains uncertain whether reduced levels precede dementia onset.

OBJECTIVE To examine whether higher serum BDNF levels in cognitively healthy adults protect against the future risk for dementia and AD and to identify potential modifiers of this association.

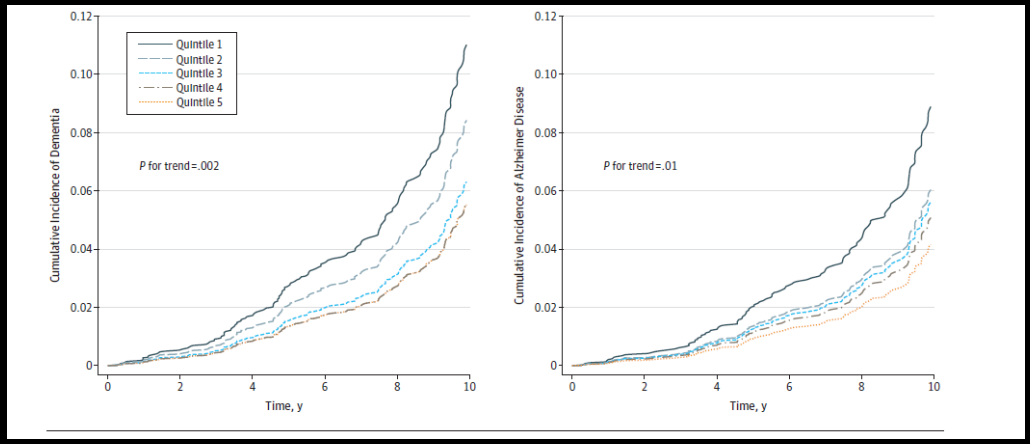
DESIGN, SETTING, AND PARTICIPANTS Framingham Study original and offspring participants were followed up from 1992 and 1998, respectively, for up to 10 years. We used Cox models to relate BDNF levels to the risk for dementia and AD and adjusted for potential confounders. We also ran sensitivity analyses stratified by sex, age, and education, as well as related BDNF genetic variants to AD risk. This community-based, prospective cohort study involved 2131 dementia-free participants aged 60 years and older (mean [SD] age, 72 [7] years; 56% women).

MAIN OUTCOMES AND MEASURES Ten-year incidence of dementia and AD.

RESULTS During follow-up, 140 participants developed dementia, 117 of whom had AD. Controlling for age and sex, each standard-deviation increment in BDNF was associated with a 33% lower risk for dementia and AD ($P = .006$ and $P = .01$, respectively) and these associations persisted after additional adjustments. Compared with the bottom quintile, BDNF levels in the top quintile were associated with less than half the risk for dementia and AD (hazard ratio, 0.49; 95% CI, 0.28-0.85; $P = .01$; and hazard ratio, 0.46; 95% CI, 0.24-0.86; $P = .02$, respectively). These associations were apparent only among women, persons aged 80 years and older, and those with college degrees (hazard ratios for AD: 0.65, [95% CI, 0.50-0.85], $P = .001$; 0.63 [95% CI, 0.47-0.85], $P = .002$; and 0.27 [95% CI, 0.11-0.65], $P = .003$, respectively). Brain-derived neurotrophic factor genetic variants were not associated with AD risk.

CONCLUSIONS AND RELEVANCE Higher serum BDNF levels may protect against future occurrence of dementia and AD. Our findings suggest a role for BDNF in the biology and possibly in the prevention of dementia and AD, especially in select subgroups of women and older and more highly educated persons.

JAMA Neurol. 2014;71(1):55-61. doi:10.1001/jamaneurol.2013.4781
Published online November 25, 2013.



RESULTS During follow-up, 140 participants developed dementia, 117 of whom had AD. Controlling for age and sex, each standard-deviation increment in BDNF was associated with a 33% lower risk for dementia and AD ($P = .006$ and $P = .01$, respectively) and these associations persisted after additional adjustments. Compared with the bottom quintile, BDNF levels in the top quintile were associated with less than half the risk for dementia and AD (hazard ratio, 0.49; 95% CI, 0.28-0.85; $P = .01$; and hazard ratio, 0.46; 95% CI, 0.24-0.86; $P = .02$, respectively). These associations were apparent only among women, persons aged 80 years and older, and those with college degrees (hazard ratios for AD: 0.65, [95% CI, 0.50-0.85], $P = .001$; 0.63 [95% CI, 0.47-0.85], $P = .002$; and 0.27 [95% CI, 0.11-0.65], $P = .003$, respectively). Brain-derived neurotrophic factor genetic variants were not associated with AD risk.

CONCLUSIONS AND RELEVANCE Higher serum BDNF levels may protect against future occurrence of dementia and AD. Our findings suggest a role for BDNF in the biology and possibly in the prevention of dementia and AD, especially in select subgroups of women and older and more highly educated persons.

Higher brain *BDNF* gene expression is associated with slower cognitive decline in older adults

Aron S. Buchman, MD
Lei Yu, PhD
Patricia A. Boyle, PhD
Julie A. Schneider, MD
Philip L. De Jager, MD, PhD
David A. Bennett, MD

Correspondence to Dr. Buchman: Aron_S_Buchman@rush.edu

ABSTRACT

Objectives: We tested whether brain-derived neurotrophic factor (*BDNF*) gene expression levels are associated with cognitive decline in older adults.

Methods: Five hundred thirty-five older participants underwent annual cognitive assessments and brain autopsy at death. *BDNF* gene expression was measured in the dorsolateral prefrontal cortex. Linear mixed models were used to examine whether *BDNF* expression was associated with cognitive decline adjusting for age, sex, and education. An interaction term was added to determine whether this association varied with clinical diagnosis proximate to death (no cognitive impairment, mild cognitive impairment, or dementia). Finally, we examined the extent to which the association of Alzheimer disease (AD) pathology with cognitive decline varied by *BDNF* expression.

Results: Higher brain *BDNF* expression was associated with slower cognitive decline ($p < 0.001$); cognitive decline was about 50% slower with the 90th percentile *BDNF* expression vs 10th. This association was strongest in individuals with dementia. The level of *BDNF* expression was lower in individuals with pathologic AD ($p = 0.006$), but was not associated with macroscopic infarcts, Lewy body disease, or hippocampal sclerosis. *BDNF* expression remained associated with cognitive decline in a model adjusting for age, sex, education, and neuropathologies ($p < 0.001$). Furthermore, the effect of AD pathology on cognitive decline varied by *BDNF* expression such that the effect was strongest for high levels of AD pathology ($p = 0.015$); thus, in individuals with high AD pathology (90th percentile), cognitive decline was about 40% slower with the 90th percentile *BDNF* expression vs 10th.

Conclusions: Higher brain *BDNF* expression is associated with slower cognitive decline and may also reduce the deleterious effects of AD pathology on cognitive decline. *Neurology*® 2016;86:1–7

Figure 1 Brain *BDNF* expression level and the rate of cognitive decline

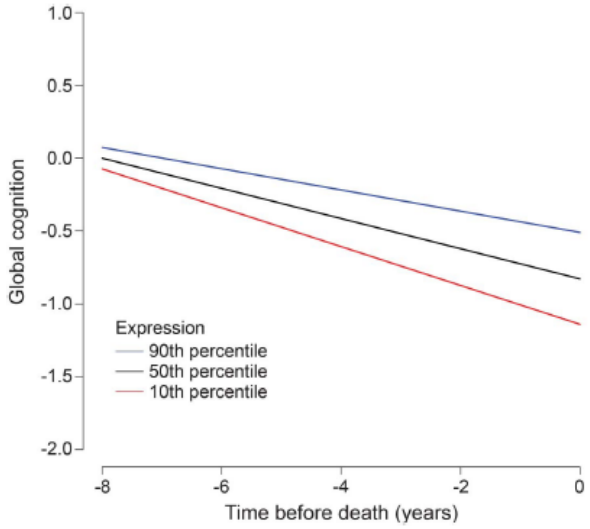
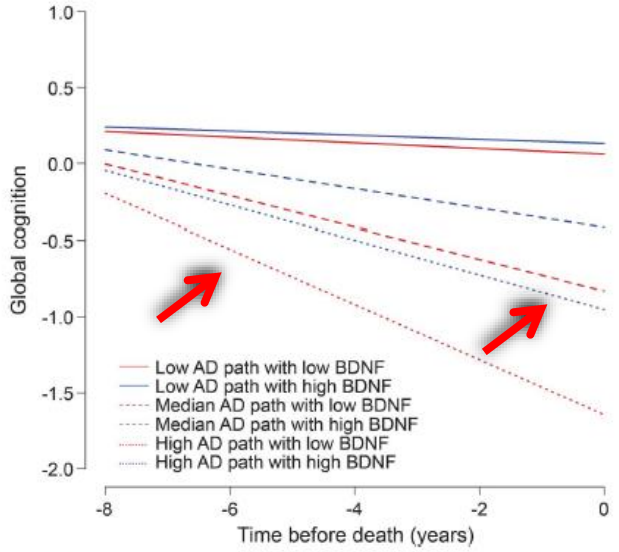


Figure 2 Brain *BDNF* expression level modifies the association of AD pathology and the rate of cognitive decline



Opinion TRENDS in Neurosciences Vol.25 No.1

Exercise: a behavioral intervention to enhance brain health and plasticity

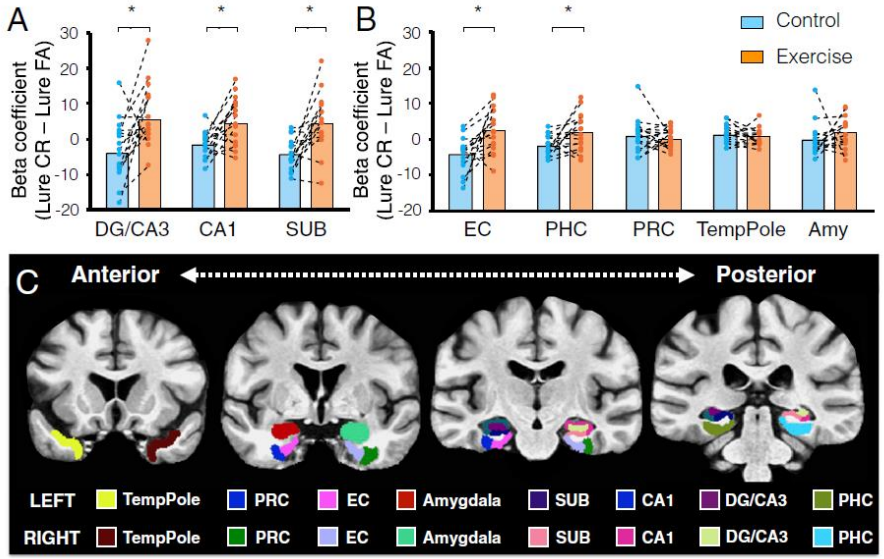
Carl W. Cotman and Nicole C. Berchtold

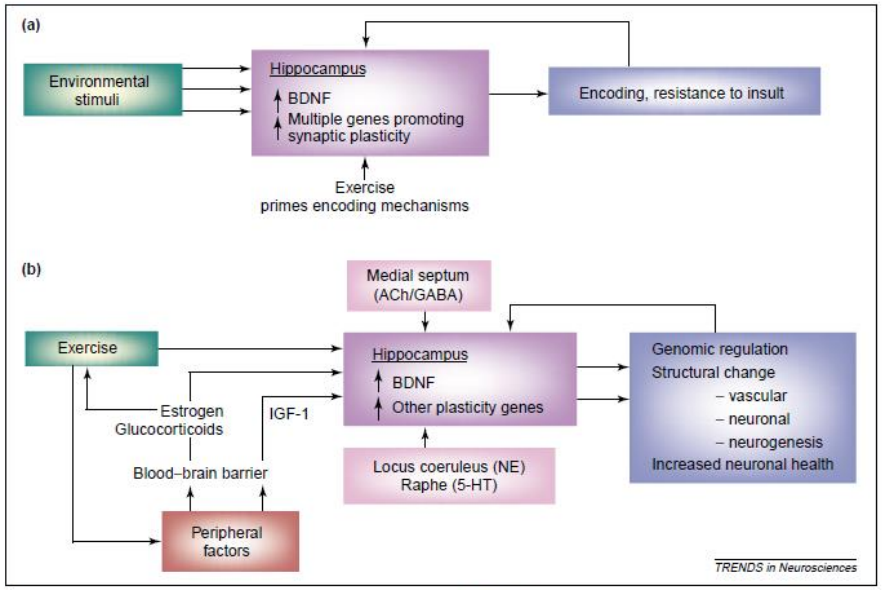
Extensive research on humans suggests that exercise could have benefits for overall health and cognitive function, particularly in later life. Recent studies using animal models have been directed towards understanding the neurobiological bases of these benefits. It is now clear that voluntary exercise can increase levels of brain-derived neurotrophic factor (BDNF) and other growth factors, stimulate neurogenesis, increase resistance to brain insult and improve learning and mental performance. Recently, high-density oligonucleotide microarray analysis has demonstrated that, in addition to increasing levels of BDNF, exercise mobilizes gene expression profiles that would be predicted to benefit brain plasticity processes. Thus, exercise could provide a simple means to maintain brain function and promote brain plasticity.

Rapid stimulation of human dentate gyrus function with acute mild exercise

Kazuya Suwabe[a,b,1], Kyeongho Byun[b,c,1], Kazuki Hyodo[a], Zachariah M. Reagh[c,d], Jared M. Roberts[c,d], Akira Matsushita[e,f], Kousaku Saotome[e], Genta Ochi[a], Takemune Fukuie[a], Kenji Suzuki[e], Yoshiyuki Sankai[e], Michael A. Yassa[b,c,d,2], and Hideaki Soya[a,b,2]

[a]Laboratory of Exercise Biochemistry and Neuroendocrinology, Faculty of Health and Sport Sciences, University of Tsukuba, 305-8574 Ibaraki, Japan; [b]Sports Neuroscience Division, Advanced Research Initiative for Human High Performance (ARIHHP), Faculty of Health and Sport Sciences, University of Tsukuba, 305-8574 Ibaraki, Japan; [c]Department of Neurobiology and Behavior, University of California, Irvine, CA 92697-3800; [d]Center for the Neurobiology of Learning and Memory, University of California, Irvine, CA 92697-3800; [e]Center for Cybernics Research, University of Tsukuba, 305-8574 Ibaraki, Japan; and [f]Department of Neurology, Ibaraki Prefectural University of Health Sciences, 300-0394 Ibaraki, Japan





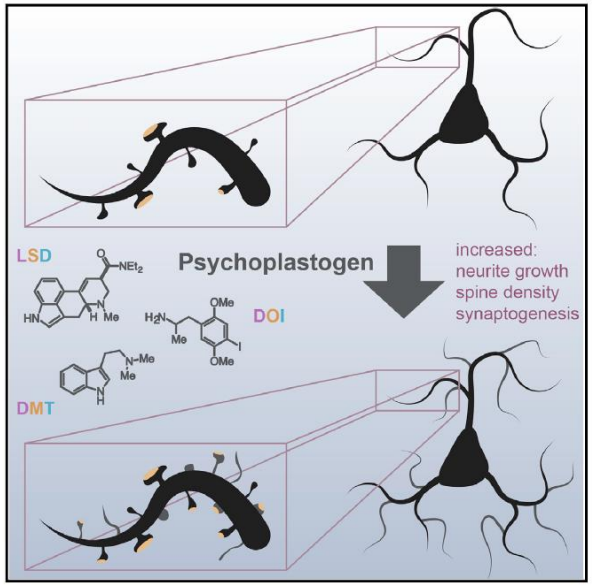
New targets for old pals

Article

Cell Reports

Psychedelics Promote Structural and Functional Neural Plasticity

Graphical Abstract



Authors

Calvin Ly, Alexandra C. Greb, Lindsay P. Cameron, ..., Kassandra M. Ori-McKenney, John A. Gray, David E. Olson

Correspondence

deolson@ucdavis.edu

In Brief

Ly et al. demonstrate that psychedelic compounds such as LSD, DMT, and DOI increase dendritic arbor complexity, promote dendritic spine growth, and stimulate synapse formation. These cellular effects are similar to those produced by the fast-acting antidepressant ketamine and highlight the potential of psychedelics for treating depression and related disorders.

Highlights

- Serotonergic psychedelics increase neuritogenesis, spinogenesis, and synaptogenesis
- Psychedelics promote plasticity via an evolutionarily conserved mechanism
- TrkB, mTOR, and 5-HT2A signaling underlie psychedelic-induced plasticity
- Noribogaine, but not ibogaine, is capable of promoting structural neural plasticity

Prevention: Cognitive Stimulation

LETTER

doi:10.1038/nature12486

Video game training enhances cognitive control in older adults

J. A. Anguera[1,2,3], J. Boccanfuso[1,3], J. L. Rintoul[1,3], O. Al-Hashimi[1,2,3], F. Faraji[1,3], J. Janowich[1,3], E. Kong[1,3], Y. Larraburo[1,3], C. Rolle[1,3], E. Johnston[1] & A. Gazzaley[1,2,3,4]

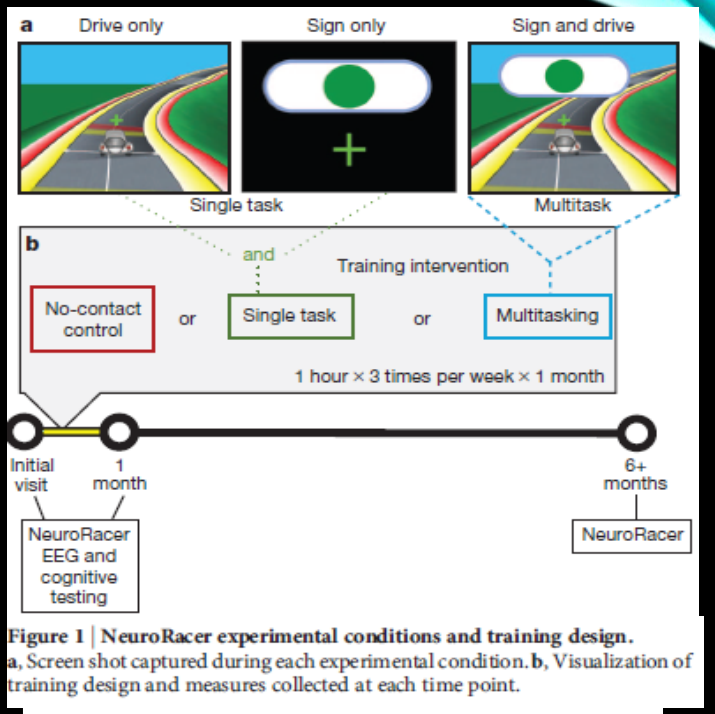
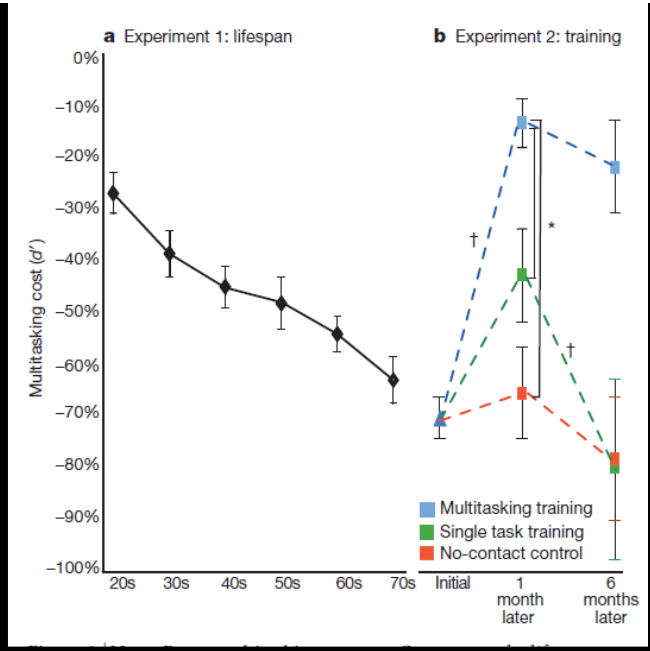


Figure 1 | NeuroRacer experimental conditions and training design. **a**, Screen shot captured during each experimental condition. **b**, Visualization of training design and measures collected at each time point.



Residents at the Easton Home engage in reminiscence therapy with Jennifer Woolley (centre).

SYMPTOMATIC TREATMENT

Treating the whole

In the absence of drugs that tackle the biological causes of Alzheimer's disease, some doctors are taking a more holistic approach.

Combination Training in Aging Individuals Modifies Functional Connectivity and Cognition, and Is Potentially Affected by Dopamine-Related Genes

Valentina Pieramico[1,2], Roberto Esposito[1], Francesca Sensi[2], Franco Cilli[2], Dante Mantini[1,3], Peter A. Mattei[1], Valerio Frazzini[1,2], Domenico Ciavardelli[2,4], Valentina Gatta[5,6], Antonio Ferretti[1], Gian Luca Romani[1], Stefano L. Sensi[1,2,7]*

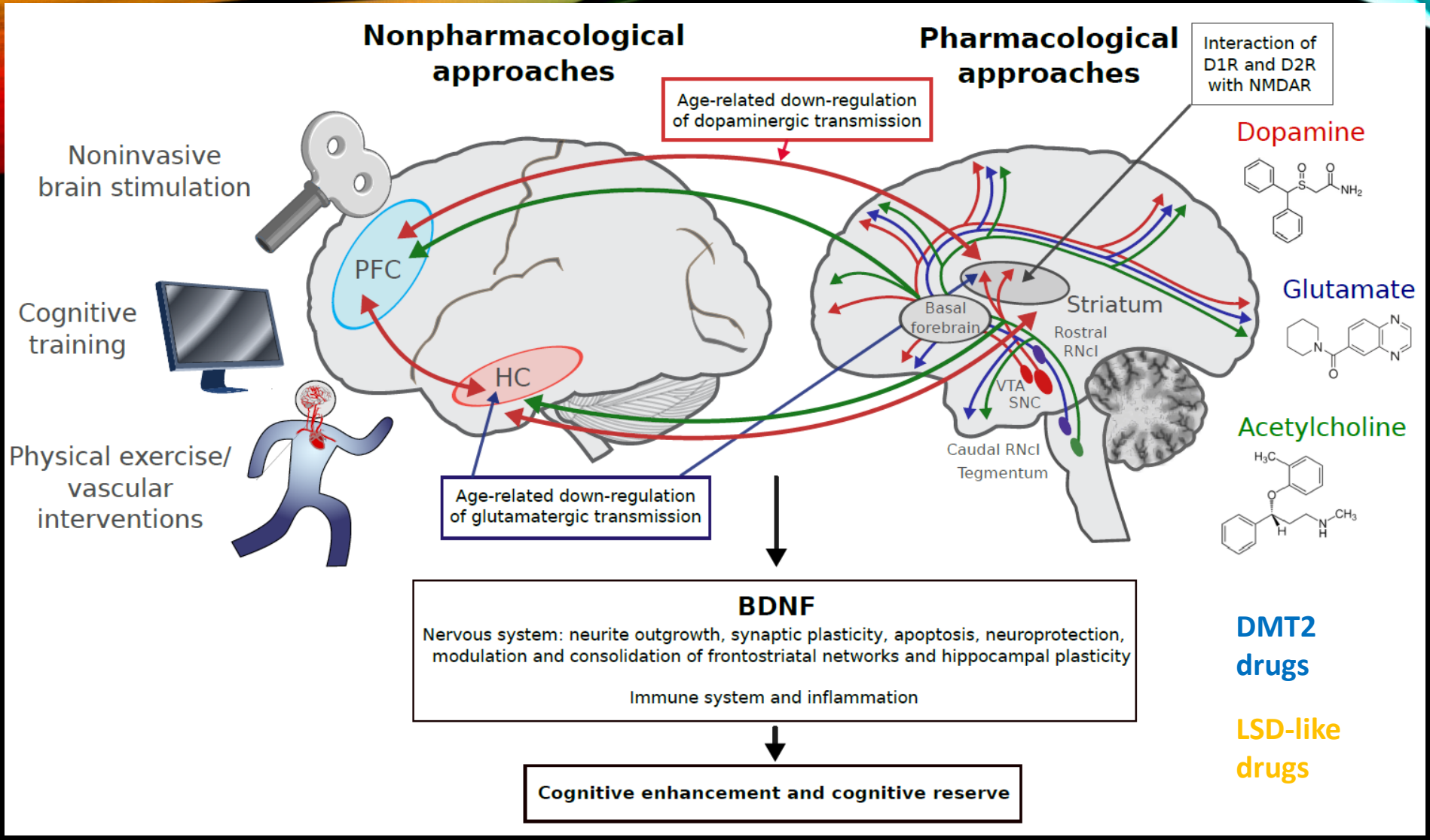
PLOS ONE | www.plosone.org
August 2012 | Volume 7 | Issue 8 | e43901

AIM OF THE STUDY

To evaluate effects of a set of structured multimodal activities (combined training) on the cognitive and occupational performances and brain plasticity of a group of 30 healthy elderly subjects

END POINTS:

Neuropsychological testing
Occupational performances
fMRI (resting state)
Connectivity
Cortical thickness
Genotyping DOPA axis



Towards Combinatorial Approaches for Preserving Cognitive Fitness in Aging
Brem & Sensi *Trends in Neuroscience 2018*

Manuela Bomba

Miriam Punzi

Francesca Masciopinto

Stefano Delli Pizzi

Mariangela Iorio

Alberto Granzotto

Alessandra Mosca

Valerio Frazzini

Domenico Ciavardelli

Noemi Massetti

Valentina D’Orazio

Valentina Pieramico

NEURODEGENERATION

A brain boost to fight Alzheimer's disease

A mouse model of Alzheimer's disease provides clues about why exercise is good for memory

By **Tara L. Spires-Jones**[1] *and* **Craig W. Ritchie**[2]

RESEARCH

RESEARCH ARTICLE SUMMARY

NEURODEGENERATION

Combined adult neurogenesis and BDNF mimic exercise effects on cognition in an Alzheimer's mouse model

Se Hoon Choi, Enjana Bylykbashi, Zena K. Chatila, Star W. Lee, Benjamin Pulli, Gregory D. Clemenson, Eunhee Kim, Alexander Rompala, Mary K. Oram, Caroline Asselin, Jenna Aronson, Can Zhang, Sean J. Miller, Andrea Lesinski, John W. Chen, Doo Yeon Kim, Henriette van Praag, Bruce M. Spiegelman, Fred H. Gage, Rudolph E. Tanzi*

Published Ahead of Print on December 19, 2018 as 10.1212/WNL.0000000000006784

ARTICLE CLASS OF EVIDENCE

Lifestyle and neurocognition in older adults with cognitive impairments

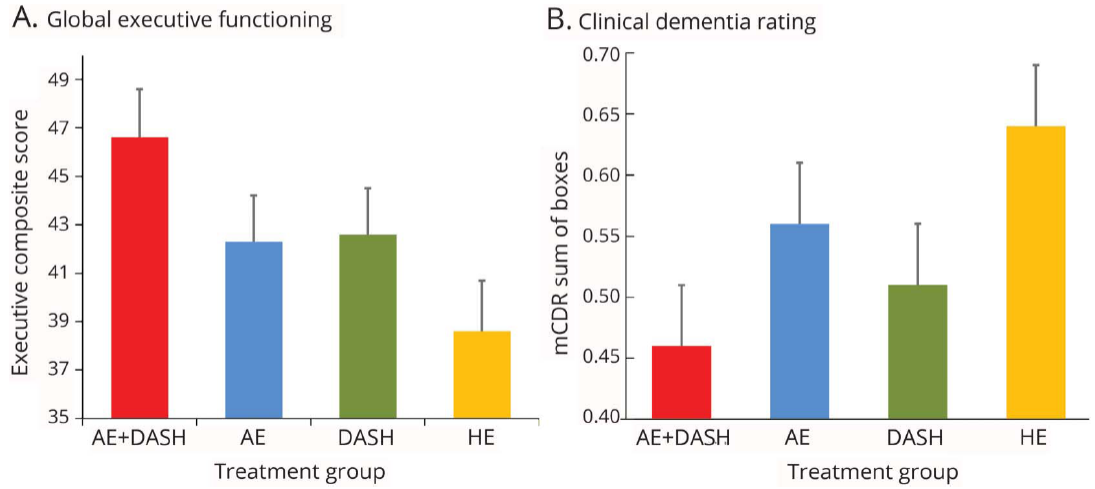
A randomized trial

James A. Blumenthal, PhD, Patrick J. Smith, PhD, Stephanie Mabe, MS, Alan Hinderliter, MD, Pao-Hwa Lin, PhD, Lawrence Liao, MD, Kathleen A. Welsh-Bohmer, PhD, Jeffrey N. Browndyke, PhD, William E. Kraus, MD, P. Murali Doraiswamy, MBBS, James R. Burke, MD, PhD, and Andrew Sherwood, PhD

Correspondence
Dr. Blumenthal
James.Blumenthal@duke.edu

Neurology® 2019;92:e1-e12. doi:10.1212/WNL.0000000000006784

Figure 2 Intervention effects for (A) global executive function and (B) mCDR




The Future
NEXT EXIT

COGNITIVE ENHANCING DRUGS and AGING

S2 | NATURE | VOL 531 | 3 MARCH 2016

SMART DRUGS

A dose of intelligence

As mind sports becomes the new frontier for doping concerns, research is exploring whether users really get any value from 'smart drugs'.

Opinion

CellPress REVIEWS

Towards Combinatorial Approaches for Preserving Cognitive Fitness in Aging

Anna-Katharine Brem[1,2,*] and Stefano L. Sensi[3,4,5,*]

REVIEW

Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: A systematic review

R.M. Battleday[a,*], A.-K. Brem[a,b]

European Neuropsychopharmacology (2015) 25, 1865-1881

Modafinil stands out as a non-amphetamine-like wake-promoting drug:

- **In preclinical settings, modafinil has been shown to promote hippocampal neurogenesis** *(Brandt et al., 2014)* **and synaptic plasticity** *(Tsanovetal., 2010)*
- **The compound shows lower risks of inducing addiction and a favorable side-effects profile** *(Malcolm et al., 2002)*
- **Not much evidence is available on CED activities exerted on the aging brain**

Modafinil-Induced Changes in Functional Connectivity in the Cortex and Cerebellum of Healthy Elderly Subjects

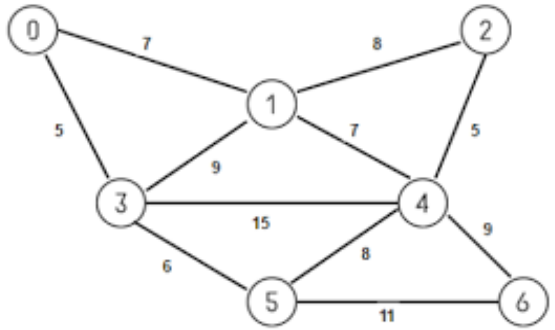
Miriam Punzi[1,2‡], Tommaso Gili[3,4‡], Laura Petrosini[4,5], Carlo Caltagirone[4,6], Gianfranco Spalletta[4†] and Stefano L. Sensi[1,2,7*†]*

[1] Department of Neurosciences, Imaging and Clinical Sciences, "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy, [2] Molecular Neurology Unit, Center of Excellence on Aging and Translational Medicine (Ce.S.I.-Me.T.), "G. d'Annunzio" University of Chieti-Pescara, Chieti, Italy, [3] Museo Storico della Fisica e Centro Studi e Ricerche Enrico Fermi, Rome, Italy, [4] Santa Lucia Foundation, Rome, Italy, [5] Department of Psychology, Section of Neuroscience and "Daniel Bovet" Neurobiology Research Center, Sapienza University of Rome, Rome, Italy, [6] Department of Medicine of Systems, University of Rome Tor Vergata, Rome, Italy, [7] Departments of Neurology and Pharmacology, Institute for Mind Impairments and Neurological Disorders, University of California, Irvine, Irvine, CA, USA

frontiers in Aging Neuroscience

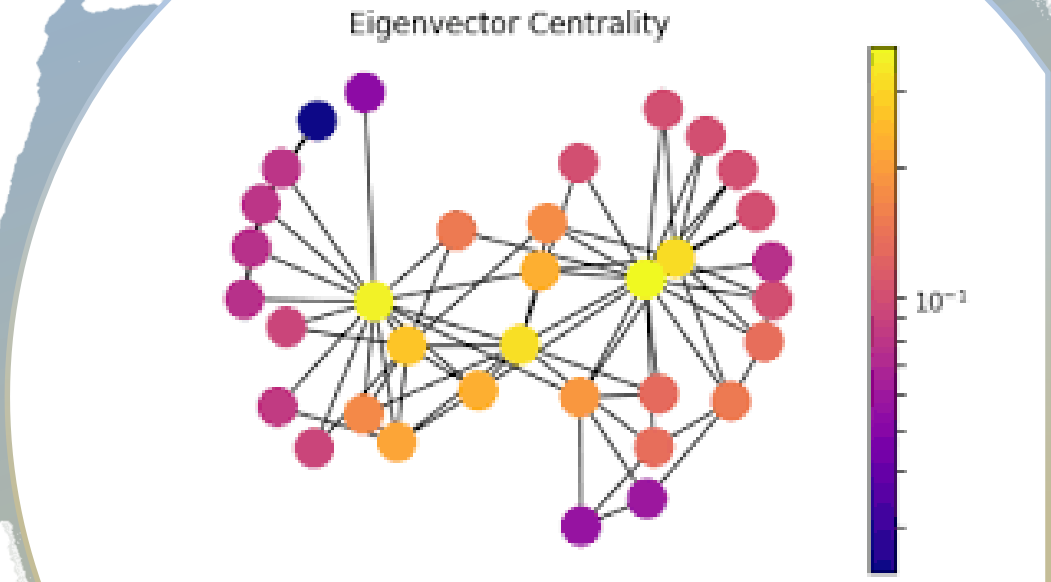
ORIGINAL RESEARCH
published: 30 March 2017
doi: 10.3389/fnagi.2017.00085

Network Analysis



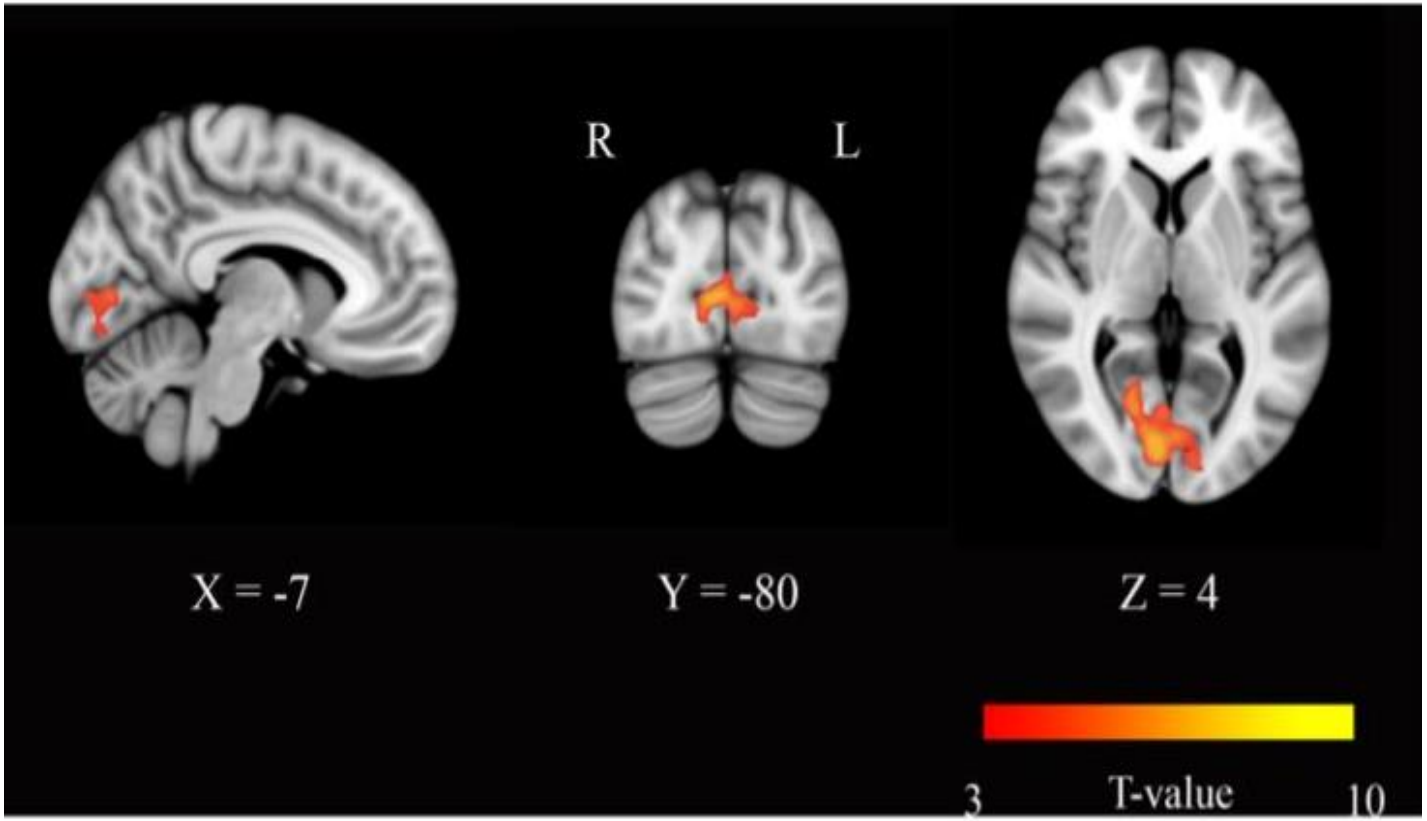
To investigate changes in functional brain network organization induced by drug administration, we modeled resting state FC as a complex network *(Caldarelli, 2007):*

- **A functional connection between two brain areas was considered as an undirected and weighted graph link**
- ***Eigenvector Centrality*** **(EC) was chosen as a topological metric to disclose brain nodes that were functionally connected to other highly functionally connected nodes** *(Rubinov and Sporns, 2010)*
- **The analysis modeled the interaction of the effect of treatment, namely baseline pre-treatment (B) and end of treatment (E), and the effect of condition, namely D (drug) and P (placebo). The interaction is described by the contrast (ED–BD) – (EP–BP)**



CENTRALITY CHANGES INDUCED BY ACUTE ADMINISTRATION OF MODAFINIL

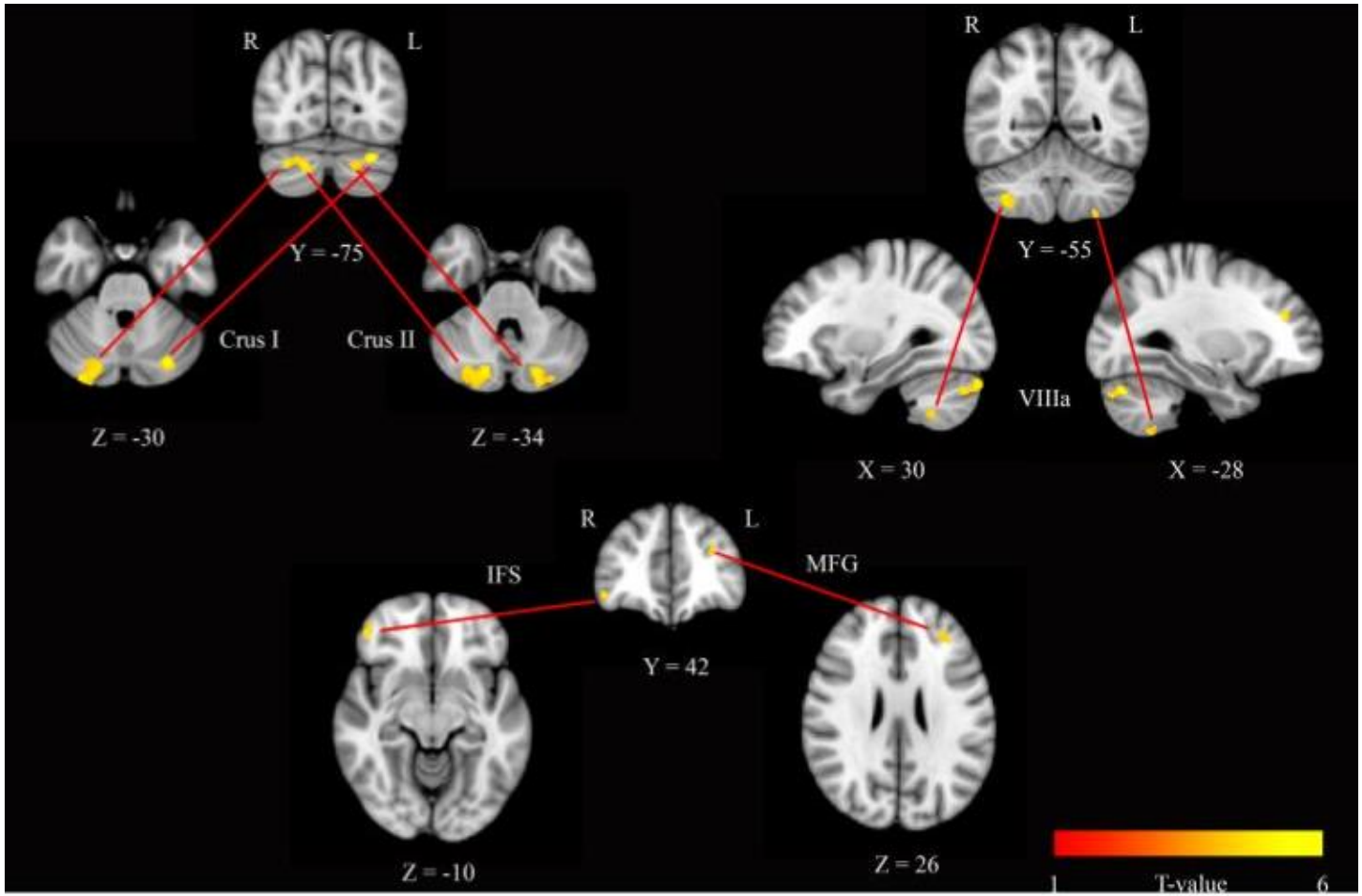
Increased centrality occurred bilaterally in the BA17



FUNCTIONAL NETWORK CHANGES INDUCED BY ACUTE ADMINISTRATION OF MODAFINIL

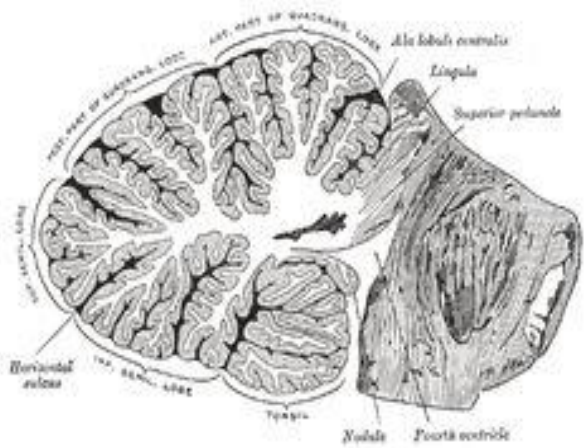
ROI-based FC analysis

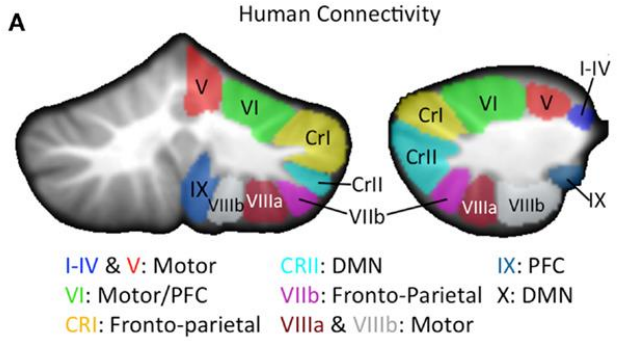
FC analysis revealed connectivity increase within the cerebellar Crus I, Crus II areas, and VIIIa lobule, the right inferior frontal sulcus (IFS), and the left middle frontal gyrus (MFG)

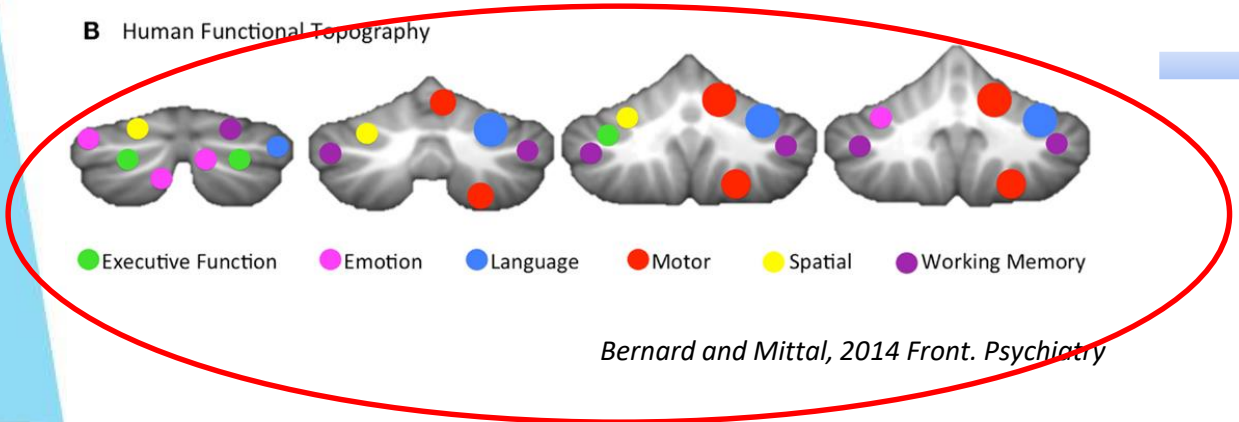


Cerebellum in cognition: beyond coordination in the CNS

- **It contains around 70% of the brain neurons**
- **Long considered as a motor structure**
- **Ignored by most neuroimaging study**
- **Largely neglected by AD and brain aging-related studies**
- **It is an emerging region for the control of a wide range of cognitive functions** (*Stoodley & Schmahmann, 2010; Buckner, 2013; Schmahmann, 2018*)







Bernard and Mittal, 2014 Front. Psychiatry

- **Cerebrocerebellar connections confer functional topography on cerebellar organization**
- **Cognition is subserved by the cerebellar posterior lobe**
- **Cerebellum contributes to higher-level cognition**

doi:10.1093/brain/awx194 BRAIN 2018: 141; 37–47 | 37

BRAIN
A JOURNAL OF NEUROLOGY

UPDATE

The cerebellum in Alzheimer's disease: evaluating its role in cognitive decline

Heidi I. L. Jacobs,[1,2,3] David A. Hopkins,[4,5] Helen C. Mayrhofer,[2] Emiliano Bruner,[6] Fred W. van Leeuwen,[4] Wijnand Raaijmakers[2] and Jeremy D. Schmahmann[7]

- **Early studies of the histopathology of Alzheimer's disease in humans focused on the cerebrum, and amyloid plaques were only occasionally detected in the cerebellum. This likely reflected limitations of classical staining techniques. Numerous studies over the past three decades, using more sensitive staining techniques, reveal that β-amyloid deposits in the cerebellum are a frequent finding in early-onset Alzheimer's disease**

- **The cerebellum receives modulatory input from the inferior olivary nuclei and The locus coeruleus, which contribute to sensorimotor and memory functions and has been postulated to be the initial site of tau pathology,**

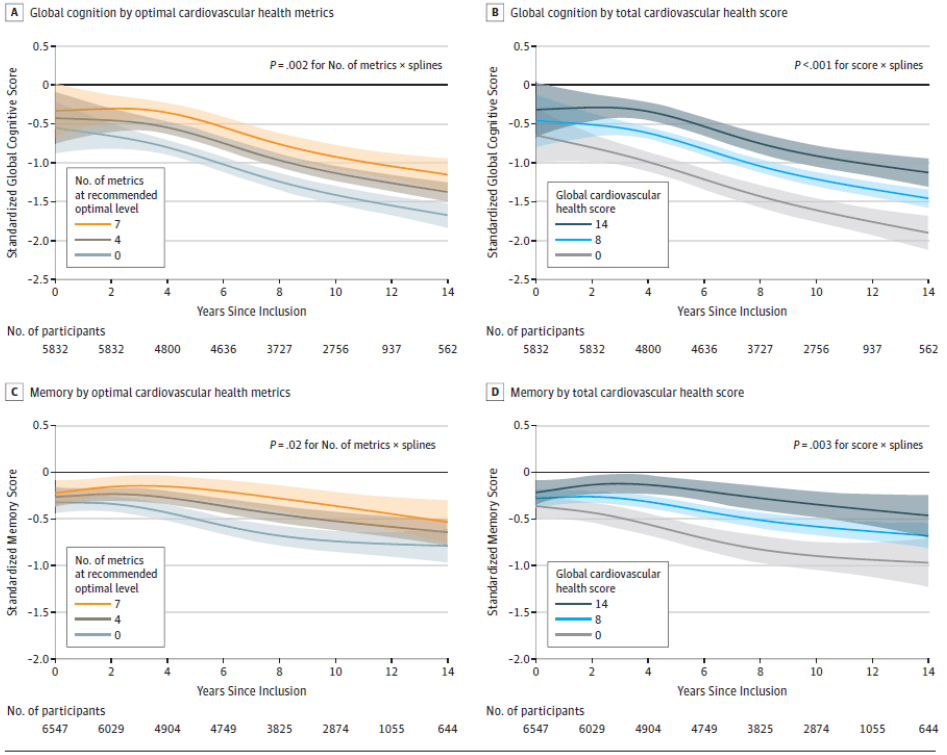
- **Noradrenalin, a neuromodulator produced in the locus coeruleus, has been suggested to have a central role in modulating cerebellar learning**

JAMA | Original Investigation

Association of Cardiovascular Health Level in Older Age With Cognitive Decline and Incident Dementia

Cécilia Samieri, PhD; Marie-Cécile Perier, MSc; Bamba Gaye, PhD; Cécile Proust-Lima, PhD; Catherine Helmer, MD, PhD; Jean-François Dartigues, MD, PhD; Claudine Berr, MD, PhD; Christophe Tzourio, MD, PhD; Jean-Philippe Empana, MD, PhD

Figure 2. Mean Trajectories of Change in Global Cognition and Memory Predicted by a Multivariable Linear Mixed Model for a Specific Profile of Covariates, by Increasing Number of Recommended Optimal Cardiovascular Health Metrics and by Higher Total Cardiovascular Health Score



IMPORTANCE Evidence is limited regarding the relation between cardiovascular health level and dementia risk.

OBJECTIVE To investigate the association between cardiovascular health level, defined using the 7-item tool from the American Heart Association (AHA), and risk of dementia and cognitive decline in older persons.

DESIGN, SETTING, AND PARTICIPANTS Population-based cohort study of persons aged 65 years or older from Bordeaux, Dijon, and Montpellier, France, without history of cardiovascular diseases or dementia at baseline who underwent repeated in-person neuropsychological testing (January 1999–July 2016) and systematic detection of incident dementia (date of final follow-up, July 26, 2016).

EXPOSURES The number of the AHA's Life's Simple 7 metrics at recommended optimal level (nonsmoking, body mass index <25, regular physical activity, eating fish twice a week or more and fruits and vegetables at least 3 times a day, cholesterol <200 mg/dL [untreated], fasting glucose <100 mg/dL [untreated], and blood pressure <120/80 mm Hg [untreated]; score range, 0-7) and a global cardiovascular health score (range, 0-14; poor, intermediate, and optimal levels of each metric assigned a value of 0, 1, and 2, respectively).

MAIN OUTCOMES AND MEASURES Incident dementia validated by an expert committee and change in a composite score of global cognition (in standard units, with values indicating distance from population means, 0 equal to the mean, and +1 and −1 equal to 1 SD above and below the mean).

RESULTS Among 6626 participants (mean age, 73.7 years; 4200 women [63.4%]), 2412 (36.5%), 3781 (57.1%), and 433 (6.5%) had 0 to 2, 3 to 4, and 5 to 7 health metrics at optimal levels, respectively, at baseline. Over a mean follow-up duration of 8.5 (range, 0.6-16.6) years, 745 participants had incident adjudicated dementia. Compared with the incidence rate of dementia of 1.76 (95% CI, 1.38-2.15) per 100 person-years among those with 0 or 1 health metrics at optimal levels, the absolute differences in incident dementia rates for 2, 3, 4, 5, and 6 to 7 metrics were, respectively, −0.26 (95% CI, −0.48 to −0.04), −0.59 (95% CI, −0.80 to −0.38), −0.43 (95% CI, −0.65 to −0.21), −0.93 (95% CI, −1.18 to −0.68), and −0.96 (95% CI, −1.37 to −0.56) per 100 person-years. In multivariable models, the hazard ratios for dementia were 0.90 (95% CI, 0.84-0.97) per additional optimal metric and 0.92 (95% CI, 0.89-0.96) per additional point on the global score. Furthermore, the gain in global cognition associated with each additional optimal metric at baseline was 0.031 (95% CI, 0.009-0.053) standard units at inclusion, 0.068 (95% CI, 0.045-0.092) units at year 6, and 0.072 (95% CI, 0.042-0.102) units at year 12.

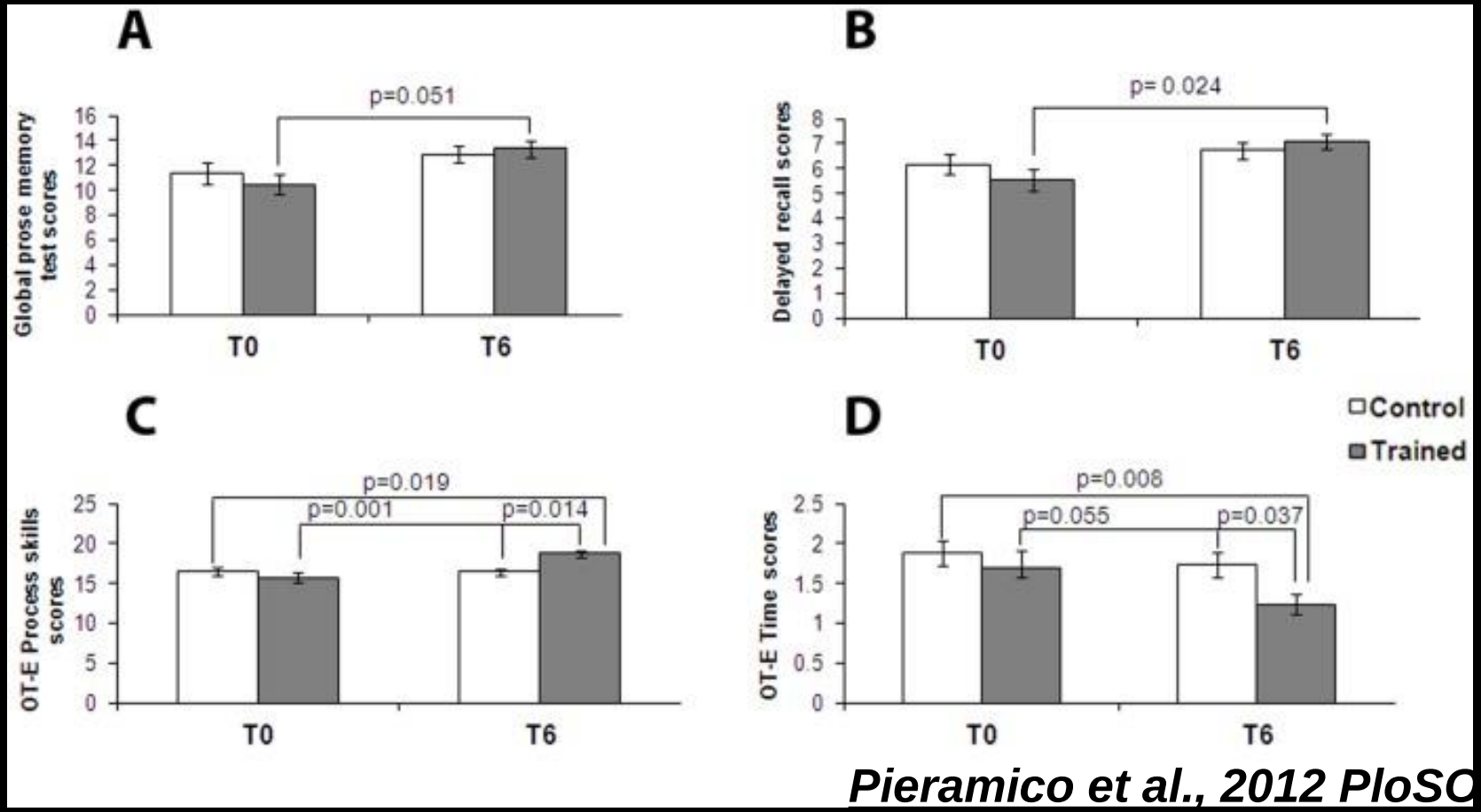
CONCLUSIONS AND RELEVANCE In this cohort of older adults, increased numbers of optimal cardiovascular health metrics and a higher cardiovascular health score were associated with a lower risk of dementia and lower rates of cognitive decline. These findings may support the promotion of cardiovascular health to prevent risk factors associated with cognitive decline and dementia.

JAMA. 2018;320(7):657-664. doi:10.1001/jama.2018.11499

Brem & Sensi *Trends in Neuroscience 201*

Combination Training increases cognitive and functional performances in healty aging individuals

CT positively affects neuropsychological and occupational performances

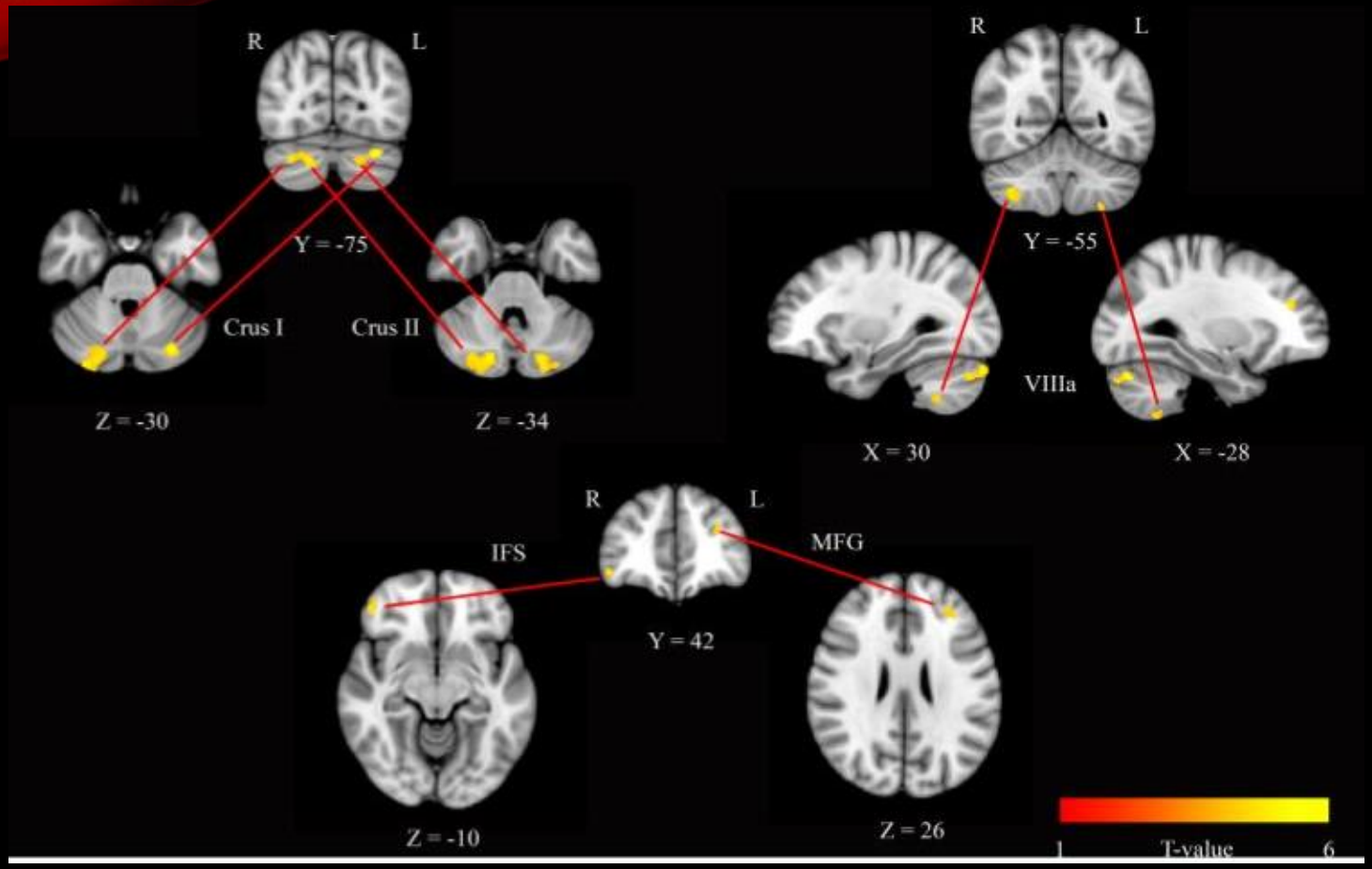


Pieramico et al., 2012 PloSO

1) (**A**) global prose memory test and (**B**) delayed recall subtest

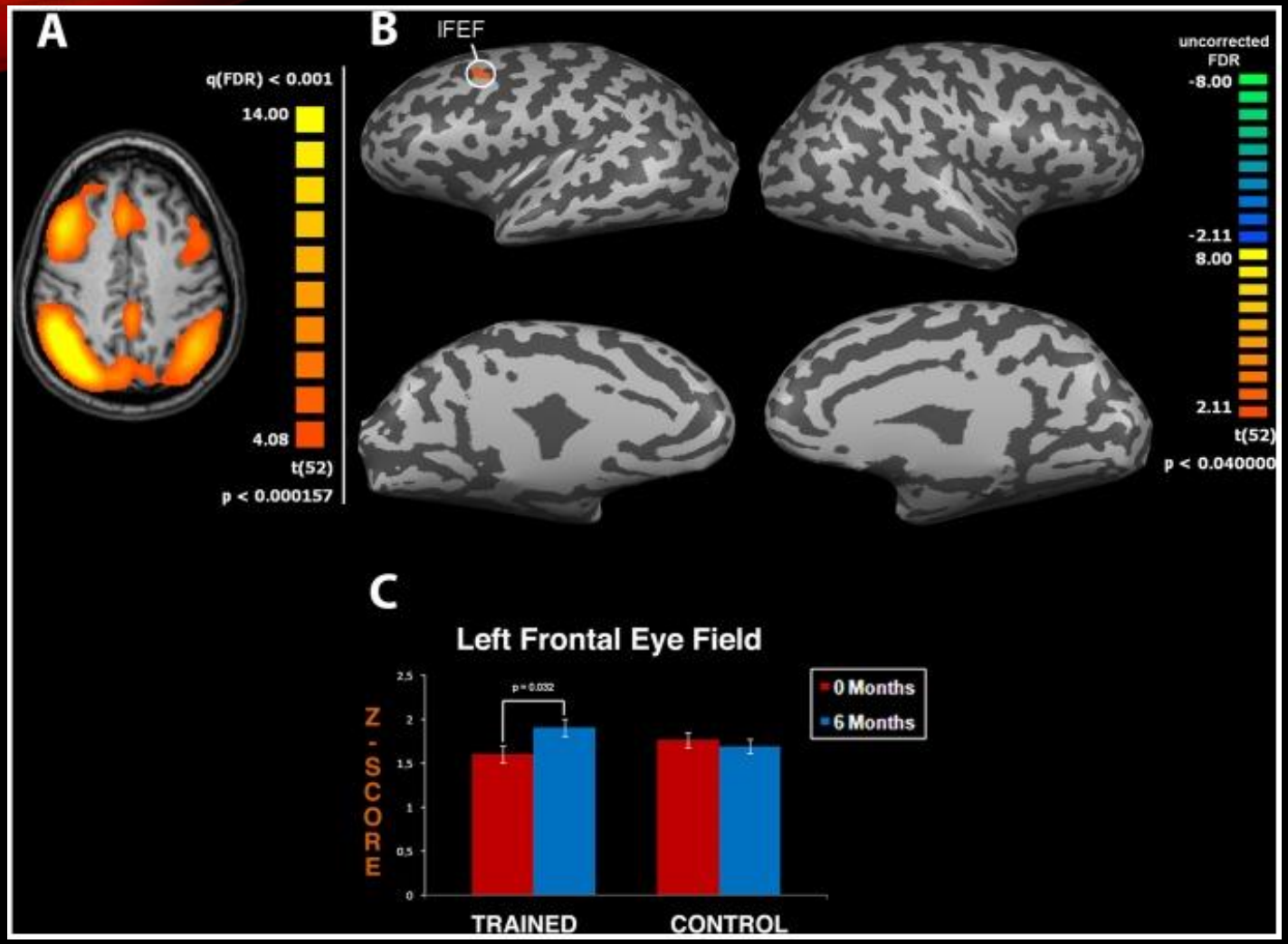
2) OT- Evaluation: C) OTE Processing skills and D) OTE Time

FUNCTIONAL NETWORK CHANGES INDUCED BY ACUTE ADMINISTRATION OF MODAFINIL



To further investigate these modafinil-driven centrality changes, ROI-based FC analysis was performed using BA17 as resulted from the group statistics of EC maps. FC analysis revealed connectivity increase within the cerebellar Crus I, Crus II areas, and VIIIa lobule, the right inferior frontal sulcus (IFS), and the left middle frontal gyrus (MFG).

CT improves neuronal connectivity: effects on the Dorsal Attention Network (DAN)



Panel (**A**) DAN Panel (**B**) shows t-maps obtained by extrapolating the T6-T0 difference for the trained group. (**C**) means ± SEM of z-scores of lFEF.

Pieramico et al., 2012 PloSONE

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Review

Can transcranial direct current stimulation counteract age-associated functional impairment?

Garon Perceval [a], Agnes Flöel [b], Marcus Meinzer [a,*]

[a] The University of Queensland, Centre for Clinical Research, Brisbane 4029, Australia
[b] Charité University Medicine, Department of Neurology, NeuroCure Clinical Research Center, and Center of Stroke Research Berlin, Berlin, Germany

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Contents lists available at ScienceDirect

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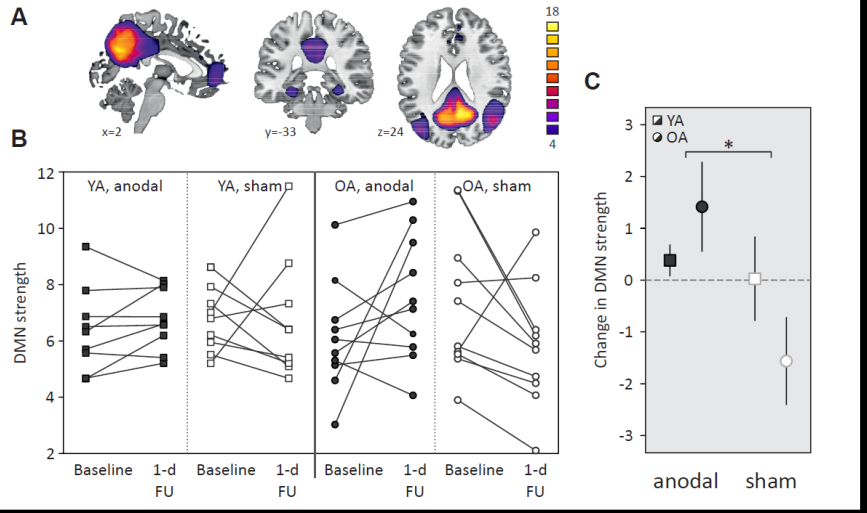
journal homepage: www.elsevier.com/locate/neuaging

Neuronal and behavioral effects of multi-day brain stimulation and memory training

Daria Antonenko [a,b,*,1], Nadine Külzow [a,1], Angelica Sousa [a], Kristin Prehn [a], Ulrike Grittner [c,d], Agnes Flöel [a,b,c,**]

[a] Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Department of Neurology, NeuroCure Clinical Research Center, Berlin, Germany
[b] Department of Neurology, Universitätsmedizin Greifswald, Greifswald, Germany
[c] Center for Stroke Research, Charité – Universitätsmedizin, Berlin, Germany
[d] Department of Biostatistics and Clinical Epidemiology, Charité – Universitätsmedizin, Berlin, Germany

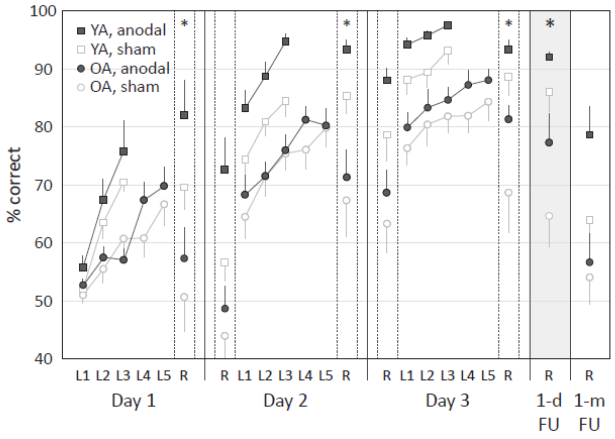


Behavioral/Cognitive

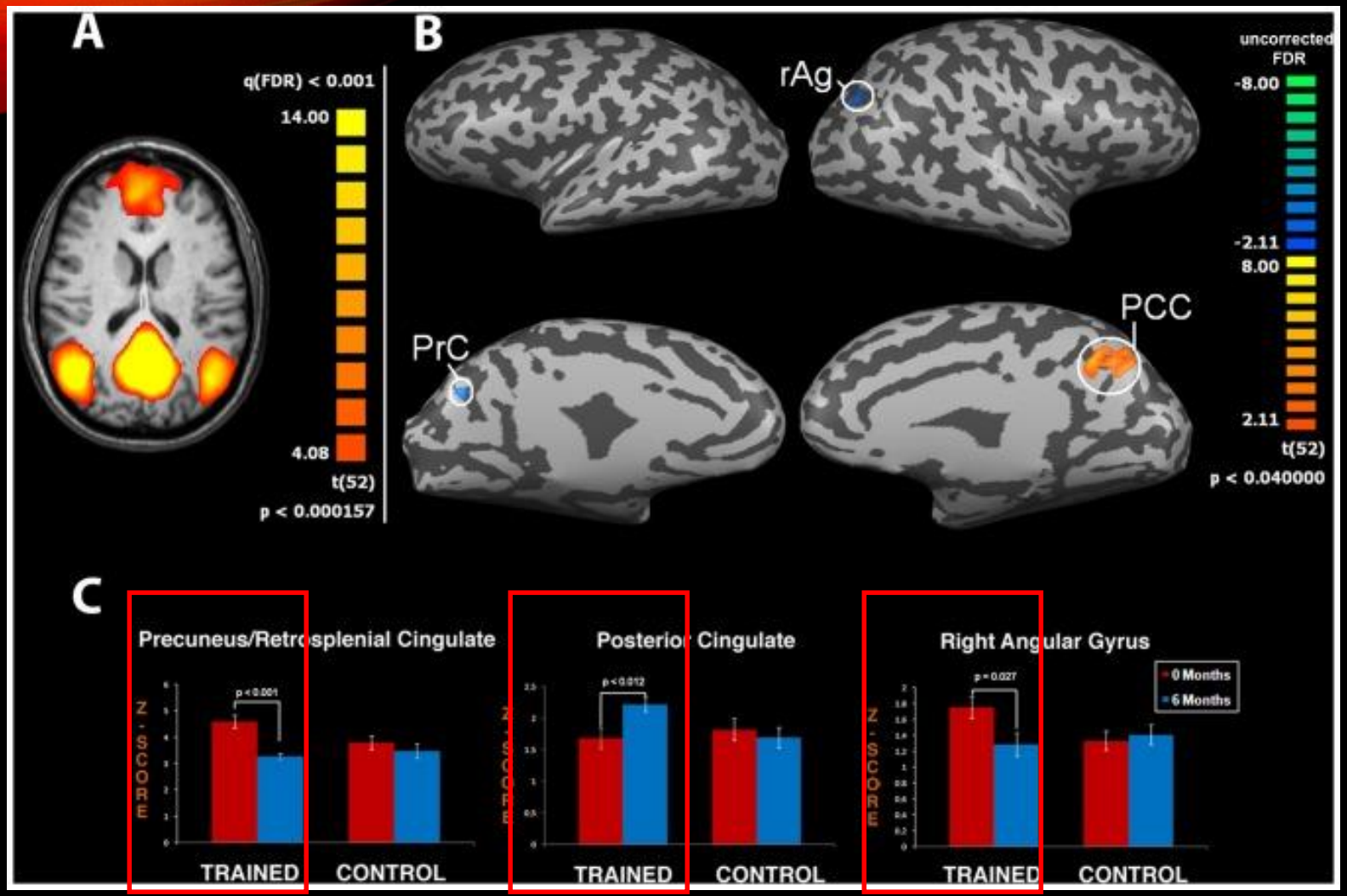
Anodal Transcranial Direct Current Stimulation Temporarily Reverses Age-Associated Cognitive Decline and Functional Brain Activity Changes

Marcus Meinzer,[1,2] Robert Lindenberg,[1] Daria Antonenko,[1] Tobias Flaisch,[3] and Agnes Flöel[1]

[1]Department of Neurology, Charité University Medicine, 10117 Berlin, Germany, [2]Center for Clinical Research, University of Queensland, Brisbane 4029, Australia, and [3]Department of Psychology, University of Konstanz, 78464 Konstanz, Germany



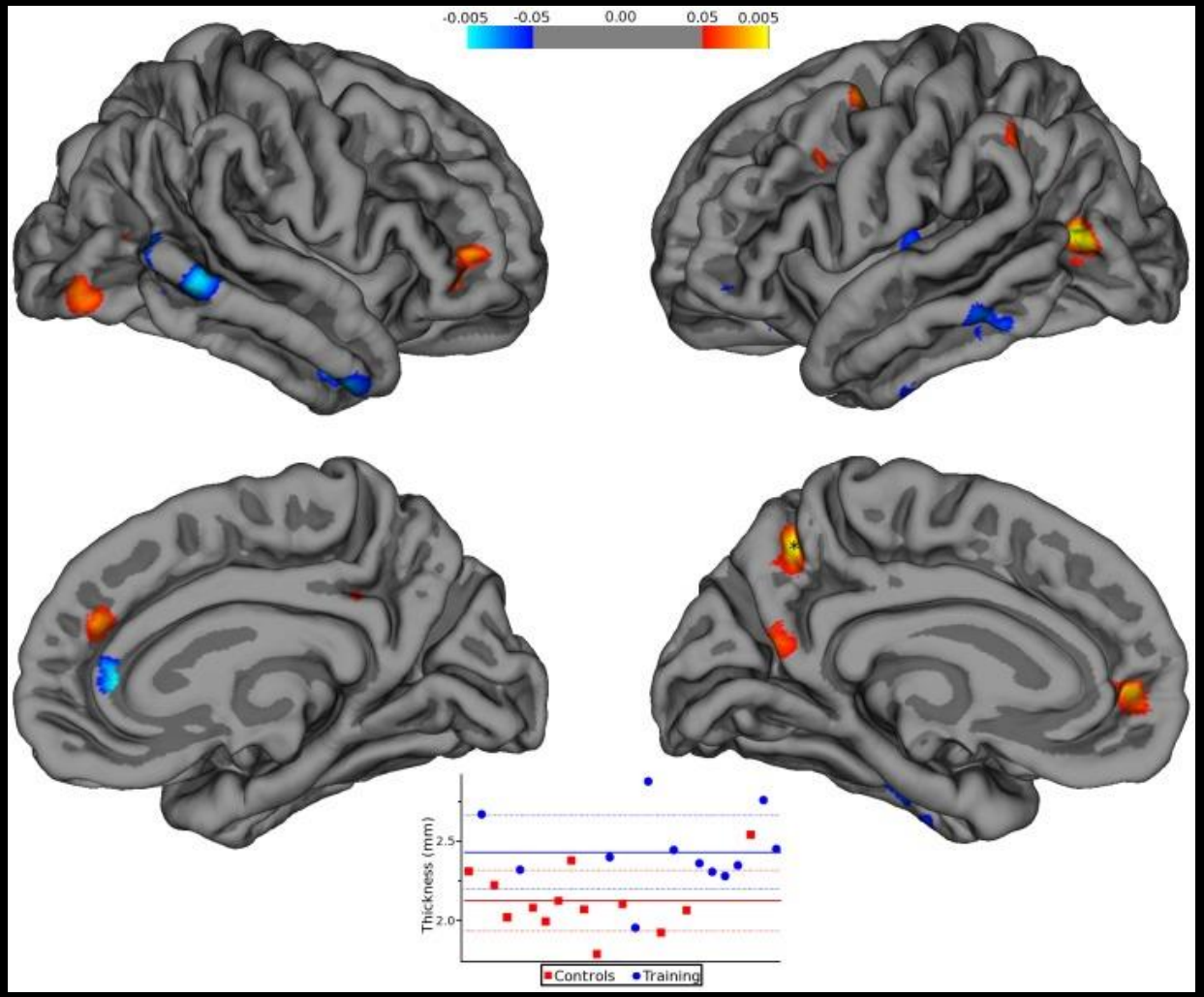
CT improves neuronal connectivity: effects on the Default Mode Network (DMN)



Panel (**A**) DMN (**B**) t-maps obtained by extrapolating the T6–T0 difference for the trained group. significant changes in the Precuneus (PrC,), the Right Angular Gyrus (rAg), and the Posterior Cingulate Cortex (PCC,). Graphs (**C**) show means ± SEM of z-scores of specific DMN areas (PrC, rAg and PCC).

Pieramico et al., 2012 PloSONE

CT positively affects cortical thickness



In the **right hemisphere**: **the middle temporal, rostral anterior cingulated, pars orbitalis, superior frontal, supramarginal, lateral occipital, isthmus cingulate, superior temporal, and lateral orbitofrontal**.

In the **left hemisphere**: **the inferior parietal, precuneus, inferior temporal, superior frontal, caudal middle frontal, middle temporal, supramarginal, insula, lateral occipital, pars orbitalis, and inferior parietal**.

The changing prevalence and incidence of dementia over time — current evidence

Yu-Tzu Wu[1], Alexa S. Beiser[2], Monique M. B. Breteler[3], Laura Fratiglioni[4], Catherine Helmer[5], Hugh C. Hendrie[6], Hiroyuki Honda[7], M. Arfan Ikram[8], Kenneth M. Langa[9], Antonio Lobo[10], Fiona E. Matthews[11], Tomoyuki Ohara[12], Karine Pérès[5], Chengxuan Qiu[4], Sudha Seshadri[13], Britt-Marie Sjölund[4], Ingmar Skoog[14] and Carol Brayne[15]

Abstract | Dementia is an increasing focus for policymakers, civil organizations and multidisciplinary researchers. The most recent descriptive epidemiological research into dementia is enabling investigation into how the prevalence and incidence are changing over time. To establish clear trends, such comparisons need to be founded on population-based studies that use similar diagnostic and research methods consistently over time. This narrative Review synthesizes the findings from 14 studies that investigated trends in dementia prevalence (nine studies) and incidence (five studies) from Sweden, Spain, the UK, the Netherlands, France, the USA, Japan and Nigeria. Besides the Japanese study, these studies indicate stable or declining prevalence and incidence of dementia, and some provide evidence of sex-specific changes. No single risk or protective factor has been identified that fully explains the observed trends, but major societal changes and improvements in living conditions, education and healthcare might have favourably influenced physical, mental and cognitive health throughout an individual's life course, and could be responsible for a reduced risk of dementia in later life. Analytical epidemiological approaches combined with translational neuroscientific research could provide a unique opportunity to explore the neuropathology that underlies changing occurrence of dementia in the general population.

Dementia has become an important public health, economic, social and political issue, and attracts increasing investment into research. According to estimates from the World Alzheimer Report 2015, 46.8 million people worldwide have dementia, and this number is expected to increase to 74.7 million by 2030 and 131.5 million by 2050 (REF. 1). In light of this predicted dementia 'epidemic' and consequent economic burden, the G8 dementia summit in 2013 and the WHO Ministerial Conference in 2015 resulted in calls for global action against dementia. The summit established a goal to identify a cure or disease-modifying therapy by 2025 (REFS 2,3). To date, most dementia research has focused on the neurological features, pathophysiological mechanisms, and drug discovery. This basic science approach has provided knowledge about dementia at the individual or biological level, but a predominantly reductionist approach that focuses on single mechanisms does not suffice to provide an understanding of the full spectrum of dementia in the general population and to identify risk factors across different populations and life courses[4]. These aspects can only be investigated fully with population-based epidemiological research.

Investigation of the changes in dementia incidence and prevalence over time is challenging, as changes in diagnostic criteria and other methodological variation can affect the prevalence and incidence estimates. Primary evidence must, therefore, be founded on population-based studies that have consistent study designs and measurement methods over time. In the past 5 years, several population-based studies of dementia have been published in which consistent research methods were used, providing new insight into the descriptive epidemiology of dementia and challenging the accepted forecasts of increasing prevalence and incidence.

Correspondence to C.B. Department of Public Health and Primary Care, Cambridge Institute of Public Health, Forvie Site, University of Cambridge, School of Clinical Medicine, Cambridge Biomedical Campus, Cambridge CB2 0SR, UK.
carol.brayne@medschl.cam.ac.uk

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Prevention: Exercise

SCIENCE AND SOCIETY

Be smart, exercise your heart: exercise effects on brain and cognition

Charles H. Hillman, Kirk I. Erickson and Arthur F. Kramer

Aerobic exercise effects on cognitive and neural plasticity in older adults

K I Erickson[1] and A F Kramer[2]
[1] University of Pittsburgh, Department of Psychology, Pittsburgh, Pennsylvania, USA
[2] Beckman Institute and Department of Psychology, University of Illinois at Urbana-Champaign, Illinois, USA

Opinion

Exercise: a behavioral intervention to enhance brain health and plasticity

Carl W. Cotman and Nicole C. Berchtold

Extensive research on humans suggests that exercise could have benefits for overall health and cognitive function, particularly in later life. Recent studies using animal models have been directed towards understanding the neurobiological bases of these benefits. It is now clear that voluntary exercise can increase levels of brain-derived neurotrophic factor (BDNF) and other growth factors, stimulate neurogenesis, increase resistance to brain insult and improve learning and mental performance. Recently, high-density oligonucleotide microarray analysis has demonstrated that, in addition to increasing levels of BDNF, exercise mobilizes gene expression profiles that would be predicted to benefit brain plasticity processes. Thus, exercise could provide a simple means to maintain brain function and promote brain plasticity.

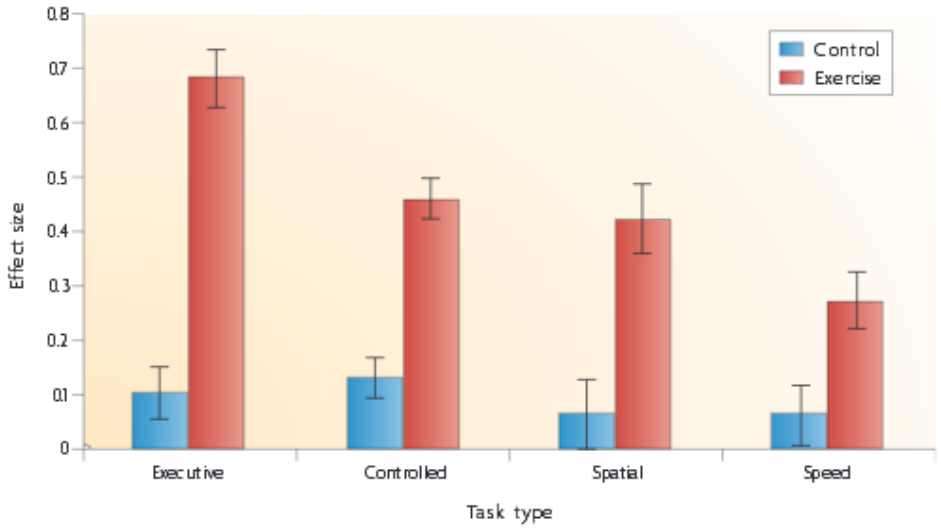
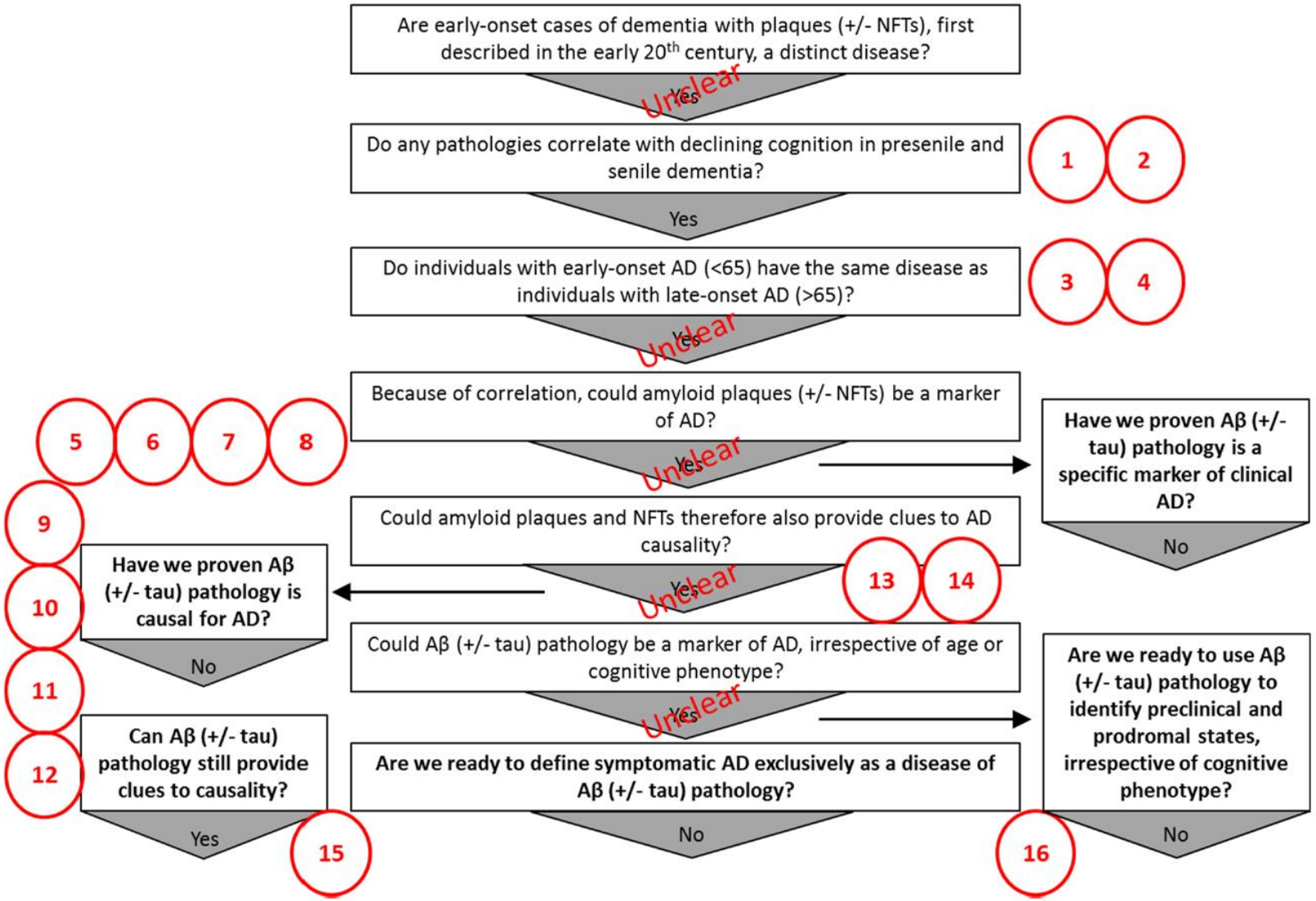


Figure 1 | **Meta-analytic findings of exercise-training effects on cognition in older adults.** The results of a meta-analysis of the effects of fitness training on cognition showed that the benefits of fitness training on four different cognitive tasks were significant. As illustrated in the figure, fitness training has both broad and specific effects. The effects are broad in the sense that individuals in aerobic fitness training groups (represented by the red bars) showed larger fitness training effects across the different categories of cognitive processes illustrated on the x-axis. They are specific in the sense that fitness training effects were larger for some cognitive processes, in particular executive control processes, than for other cognitive processes. Figure reproduced, with permission, from REF. 32 © (2003) Blackwell Publishers.


Are early-onset cases of dementia with plaques (+/- NFTs), first described in the early 20th century, a distinct disease?
Yes
Unclear
Do any pathologies correlate with declining cognition in presenile and senile dementia?
1
2
Yes
Do individuals with early-onset AD (<65) have the same disease as individuals with late-onset AD (>65)?
3
4
Yes
Unclear
Because of correlation, could amyloid plaques (+/- NFTs) be a marker of AD?
5
6
7
8
Yes
Unclear
Have we proven Aβ (+/- tau) pathology is a specific marker of clinical AD?
No
Could amyloid plaques and NFTs therefore also provide clues to AD causality?
9
13
14
Yes
Unclear
Have we proven Aβ (+/- tau) pathology is causal for AD?
10
No
Could Aβ (+/- tau) pathology be a marker of AD, irrespective of age or cognitive phenotype?
11
Yes
Unclear
Are we ready to use Aβ (+/- tau) pathology to identify preclinical and prodromal states, irrespective of cognitive phenotype?
Can Aβ (+/- tau) pathology still provide clues to causality?
12
Yes
15
Are we ready to define symptomatic AD exclusively as a disease of Aβ (+/- tau) pathology?
No
16
No

JAMA Neurology | Original Investigation

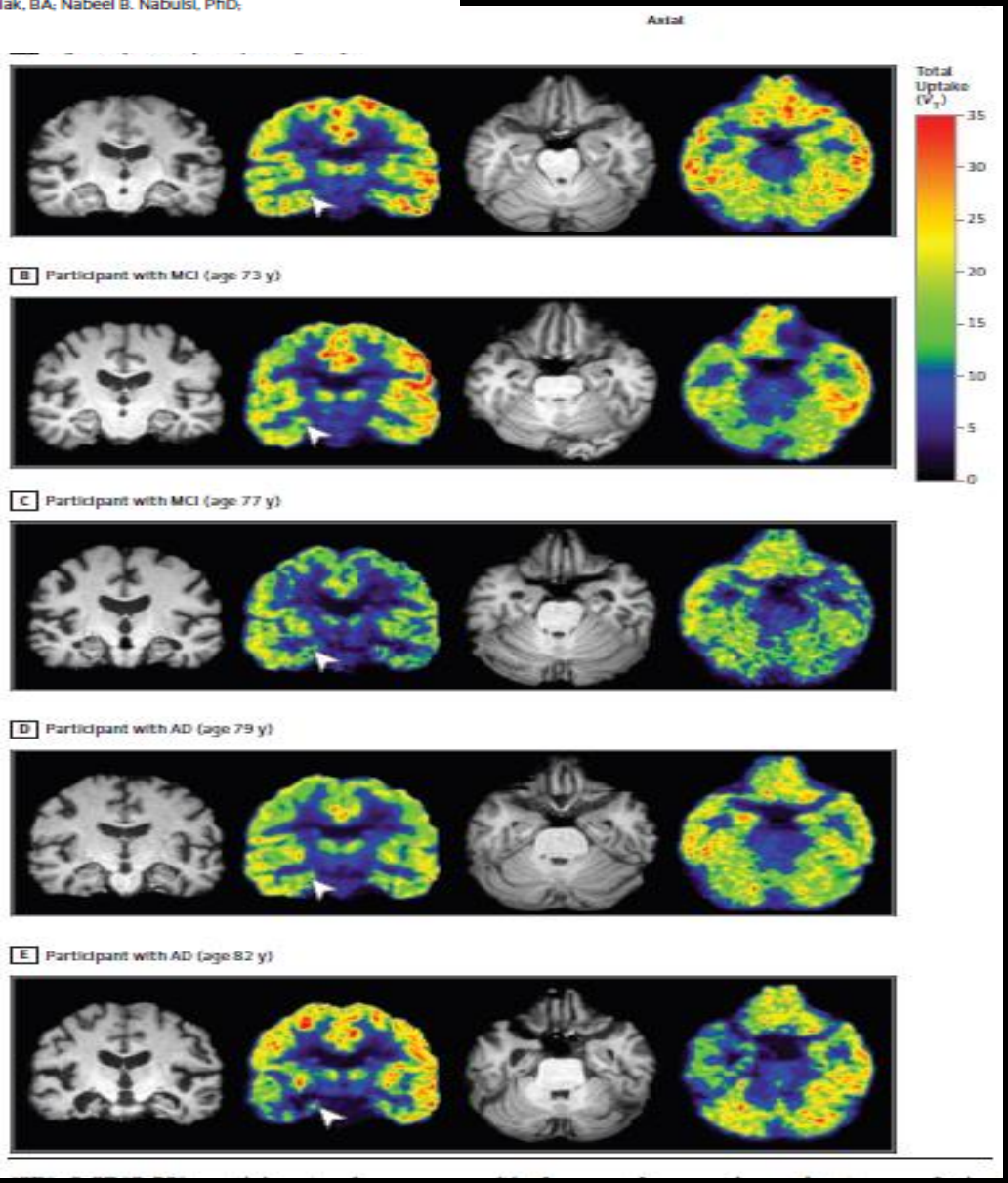
Assessing Synaptic Density in Alzheimer Disease With Synaptic Vesicle Glycoprotein 2A Positron Emission Tomographic Imaging

Ming-Kai Chen, MD, PhD; Adam P. Mecca, MD, PhD; Mika Naganawa, PhD; Sjoerd J. Finnema, PhD; Takuya Toyonaga, MD, PhD; Shu-fei Lin, PhD; Sohella Najafzadeh, MS; Jim Ropchan, PhD; Yihuan Lu, PhD; Julia W. McDonald, BA; Hannah R. Michalak, BA; Nabeel B. Nabulsi, PhD; Amy F. T. Arnsten, PhD; Yiyun Huang, PhD; Richard E. Carson, PhD; Christopher H. van Dyck, MD

EDITORIAL

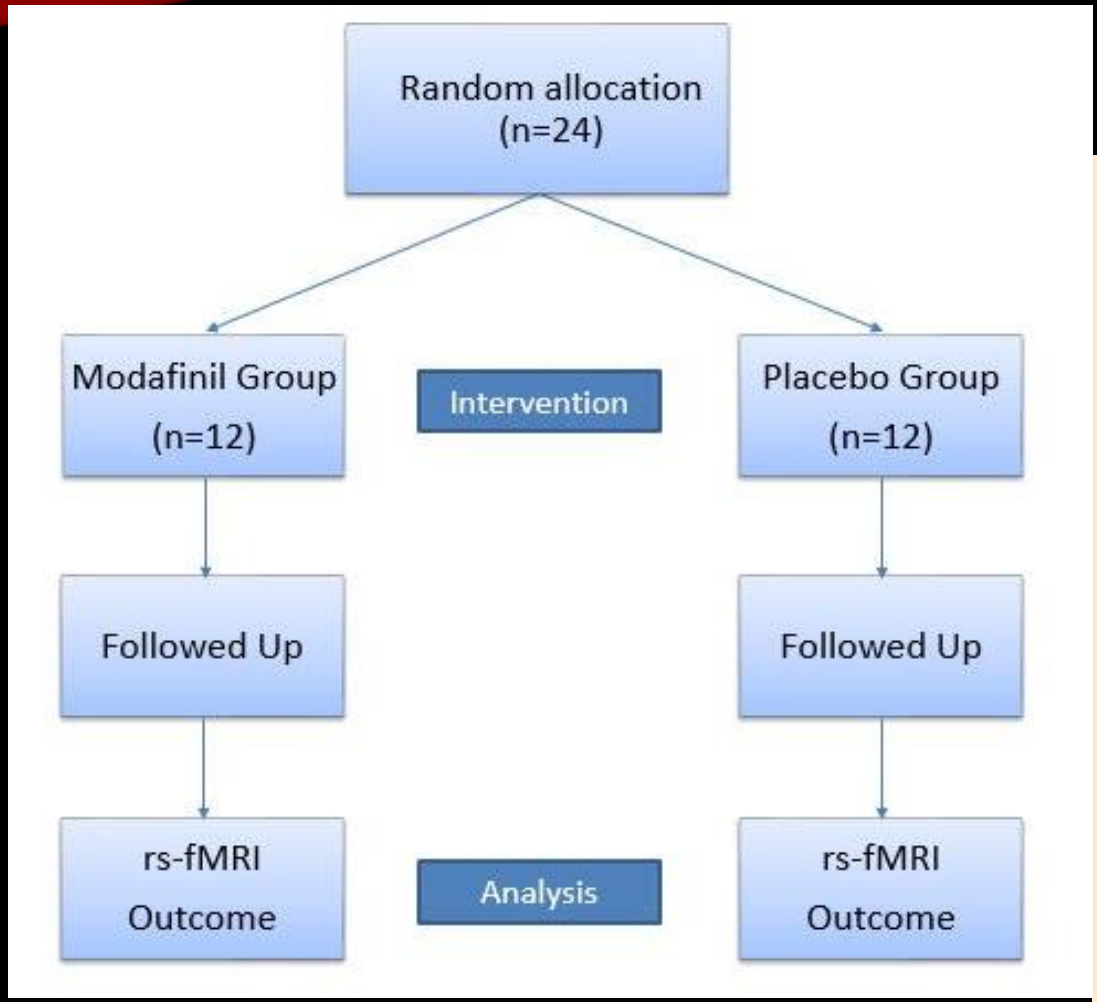
A New Tool for Clinical Neuroscience —Synaptic Imaging

Elizabeth C. Mormino, PhD; William J. Jagust, MD



STUDY DESIGN

Randomized, Double-Blind, Placebo-Controlled Study



- **Study participants received a single-dose of modafinil (n = 12) or a placebo pill identical to the drug pill (n = 12).**
- **All subjects then underwent two 3 T rs-fMRI scans, performed before and 3 h after drug (or placebo) administration, to achieve a plateau phase in drug levels in line with the compound pharmacokinetic profile** *(Robertson and Hellriegel, 2003)***.**
- **Subjects were asked to relax and fix a central point in the middle of a background screen. Upon rs-fMRI acquisitions, participants were instructed to stay still, keep their eyes open on a fixation cross.**

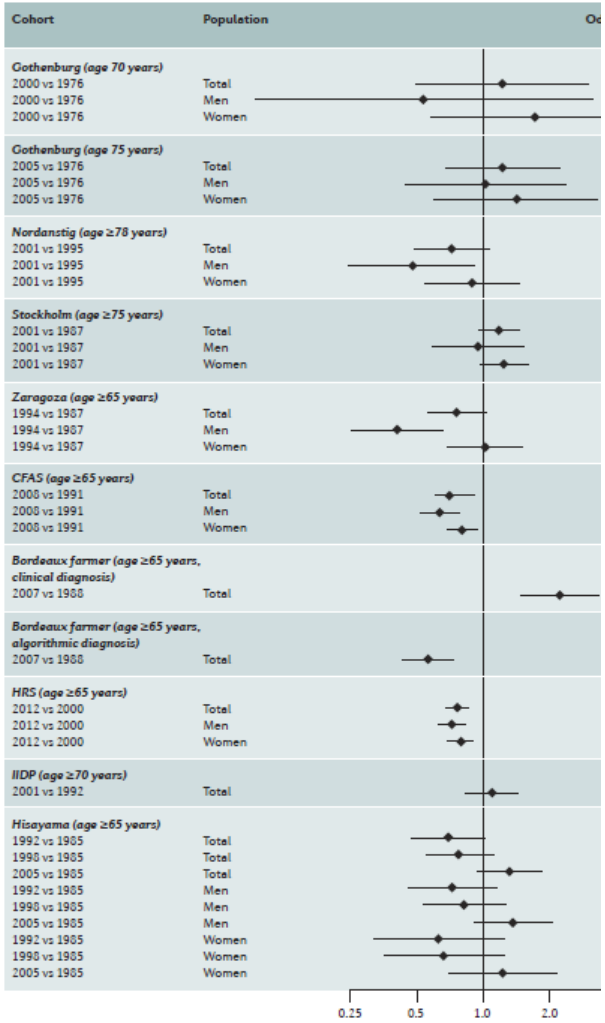


Figure 1 | **Odds ratios and prevalence ratios reported in nine studies of dementia prevalence.** Repo ratios of the prevalence estimate for new cohorts to those for old cohorts. If prevalence estimates remai cohorts, the ratio is 1.0. If estimates are higher in the new cohort than the old cohort, the ratio is greater are adjusted as follows: Gothenburg study and HRS, unadjusted; IIDP, adjusted for age; Nordanstig, Zara Hisayama studies, adjusted for age and sex; Stockholm study, adjusted for age, sex and education; CFA sex, area and deprivation. In the Bordeaux study, clinical diagnosis was made by neuropsychologists usir Diagnostic and Statistical Manual III revised, and algorithmic diagnosis was based on cognitive and functional ability tests. CFAS, Cognitive Function and Ageing Study; HRS, Health and Retirement Study; IIDP, Indianapolis–Ibadan Dementia Project.

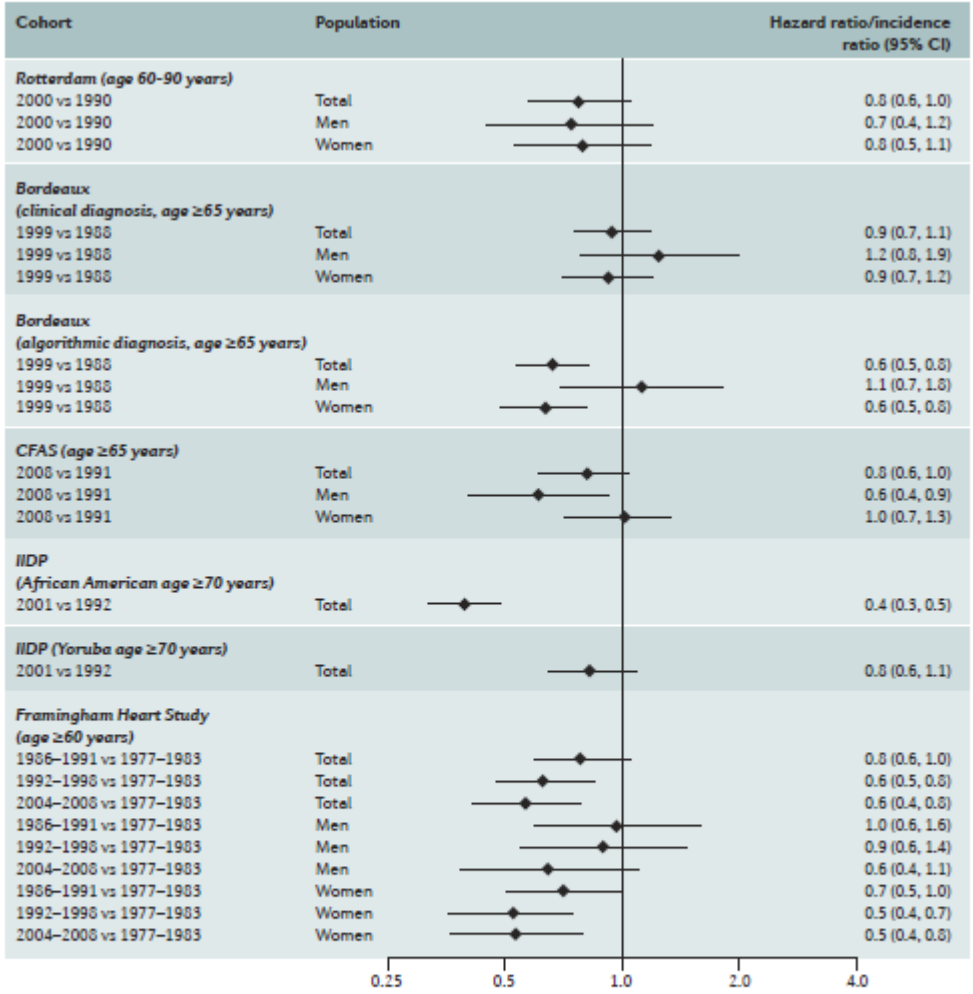


Figure 2 | **Hazard ratio and incidence rate ratio from five studies of dementia incidence.** Reported figures are the ratios of the incidence estimate in new cohorts to that in old cohorts. If incidence estimates remain the same across two cohorts, the ratio is 1.0. If estimates are higher in new cohorts than old cohorts, the ratio is greater than 1.0. Estimates are adjusted as follows: Rotterdam study, IIDP and Bordeaux study adjusted for age; Framingham Heart Study adjusted for age and sex; CFAS adjusted for age, sex, area and deprivation. In the Bordeaux study, clinical diagnosis was made by neuropsychologists and neurologists using criteria from the Diagnostic and Statistical Manual III revised and V, and algorithmic diagnosis was based on cognitive and functional ability tests. CFAS, Cognitive Function and Ageing Study; IIDP, Indianapolis–Ibadan Dementia Project.

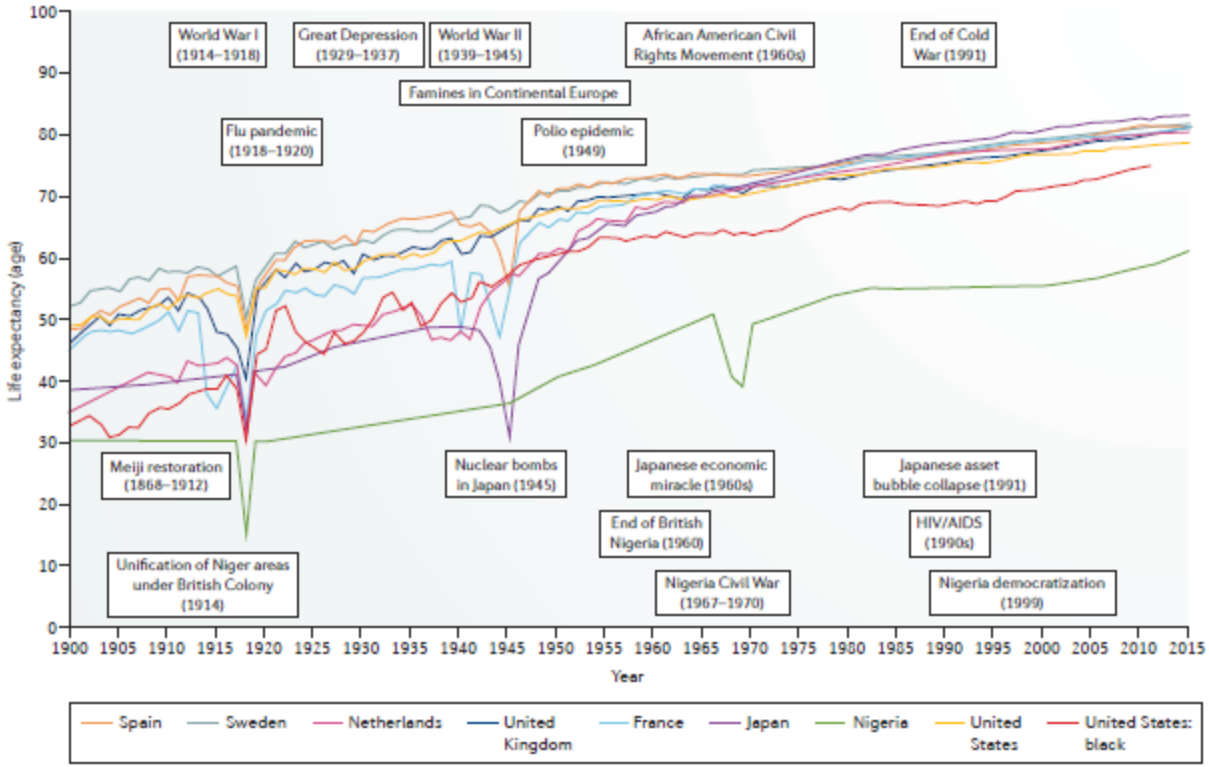


Figure 3 | **Life expectancy at birth in all countries included in population-based studies of dementia incidence and prevalence.** Data obtained from from Gapminder, the National Center for Health Statistics, USA[84] and Wu, Y.-T. *et al.*[5].

LETTER

doi:10.1038/nature10849

An epigenetic blockade of cognitive functions in the neurodegenerating brain

Johannes Gräff[1,2,3], Damien Rei[1,2], Ji-Song Guan[1,2,3], Wen-Yuan Wang[1,2,3], Jinsoo Seo[1,2], Krista M. Hennig[3,4], Thomas J. F. Nieland[3], Daniel M. Fass[3,4], Patricia F. Kao[5], Martin Kahn[1], Susan C. Su[1,2], Alireza Samiei[1], Nadine Joseph[1,2,3], Stephen J. Haggarty[3,4], Ivana Delalle[5] & Li-Huei Tsai[1,2,3]

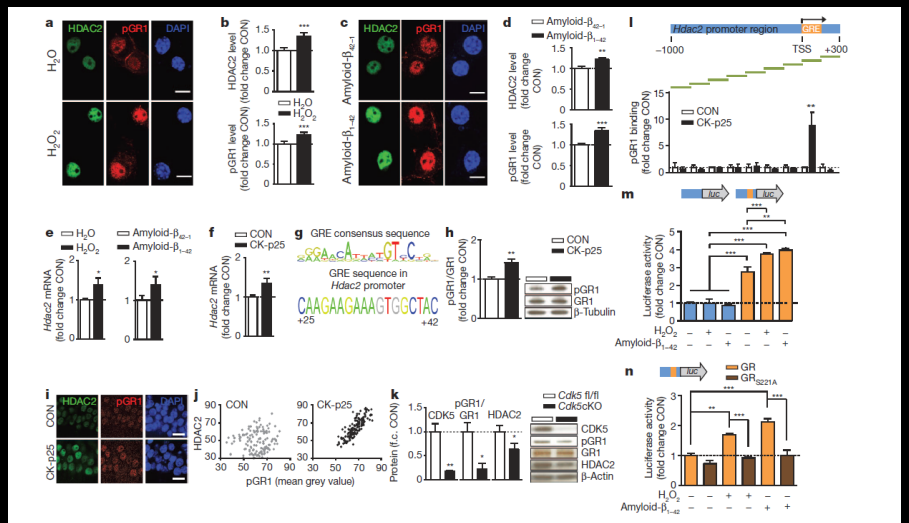


Figure 3 | Neurotoxic insults increase HDAC2 through stress elements in its promoter. **a**, **c**, Representative pictures of HDAC2 and pGR1 labelling of primary hippocampal neurons treated with (**a**) H_2O_2 and (**c**) amyloid-β-oligomers ($n = 20–40$ neurons per group); scale bar, 10 μm. **b**, **d**, Quantification of **a** and **c**. **e**, **f**, Quantitative RT–PCR results showing *Hdac2* expression in (**e**) H_2O_2- and amyloid-β-treated primary hippocampal neurons, and (**f**) in the CK-p25 hippocampus ($n = 7–9$ mice each). **g**, Alignment of the vertebrate GRE consensus sequence with the GRE in the proximal promoter of mouse *Hdac2*. **h**, Quantification and representative western blot images of hippocampal extracts of CK-p25 versus control mice ($n = 3$ each). **i**, Representative images of immunohistochemical labelling of pGR1 and HDAC2 in the CK-p25 hippocampus ($n = 3–6$ slices from three mice each); scale bar, 20 μm. **j**, Regression analysis of **i** showing a significant correlation between pGR1 and HDAC2 in CK-p25 ($R^2 = 0.686$, $P \leq 0.001$), but not control mice ($R^2 = 0.019$, not significant). **k**, Quantification and representative western blot images of *Cdk5*cKO and control *Cdk5*fl/fl forebrain extracts ($n = 3$ each). f.c., fold change. **l**, Quantitative PCR results of pGR1-immunoprecipitated chromatin around the GRE in a 1.3-kb-wide *Hdac2* promoter region (schematically shown above the graph; TSS, transcriptional start site) in the CK-p25 and control hippocampus ($n = 3–6$ animals each); green lines represent fragments amplified by primer pairs. **m**, Luciferase activity of CAD cells transfected with the *Hdac2* promoter with (orange) or without (blue) GRE (schematic of constructs shown above graph), and treated with H_2O_2 and amyloid-β_{1-42}. **n**, Luciferase activity of CAD cells transfected with *Hdac2*-GRE in the presence of endogenous glucocorticoid receptor or of cotransfected GR_{S211A}. *In vitro* results are from at least three independent experiments. $^*P \leq 0.05$; $^{**}P \leq 0.01$; $^{***}P \leq 0.001$; values are mean ± s.e.m.

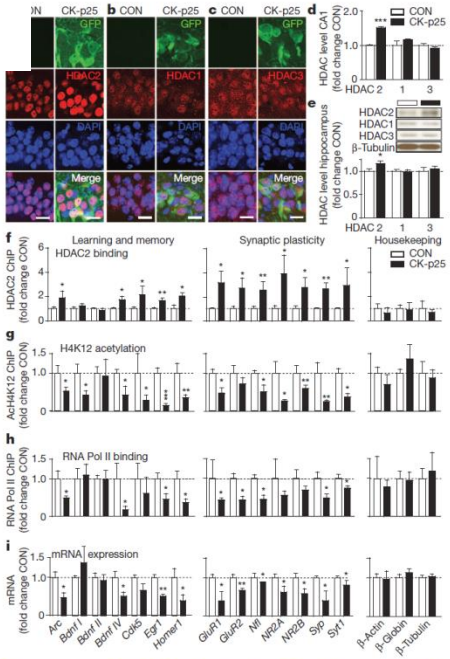


Figure 1 | Elevated HDAC2 levels epigenetically block the expression of neuroplasticity genes during neurodegeneration. **a**–**c**, Representative immunohistochemical images depicting HDAC1–3 levels in area CA1 of CK-p25 mice and control littermates; scale bar, 20 μm. **d**, Quantitative assessment of **a**–**c** ($n = 3–6$ slices from three or four mice each). **e**, Representative western blot images and quantification of HDAC1–3 in the CK-p25 and control hippocampus ($n = 6–9$ mice each). **f**–**h**, Quantitative PCR results of (**f**) HDAC2-, (**g**) AcH4K12- and (**h**) RNA Pol II-immunoprecipitated chromatin at the promoter of neuroplasticity and housekeeping genes in the CK-p25 and control hippocampus. **i**, Quantitative RT–PCR results of the same genes (**f**–**i**, $n = 4–8$ animals each). $^*P \leq 0.05$; $^{**}P \leq 0.01$; $^{***}P \leq 0.001$; values are mean ± s.e.m.

We next assessed the acetylation of several histone (H) residues in the promoter region of these genes, for which acetylation has been shown to be important for learning, memory, and synaptic plasticity, such as H2B lysine (K) 5, H3K14, H4K5 and H4K12 (ref. 4). ChIP analyses revealed a hypoacetylation for all residues at the neuroplasticity genes (Fig. 1g and Supplementary Fig. 6c–e), albeit to different extents. Importantly, the acetylation of housekeeping genes was not altered. The effects of elevated HDAC2 levels further appear to be restricted to histones, as

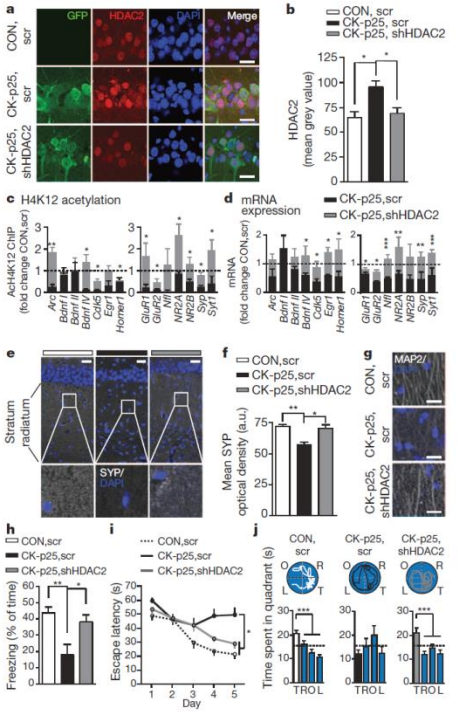


Figure 2 | Reducing HDAC2 levels alleviates memory deficits. **a**, Representative immunohistochemical images depicting HDAC2 in hippocampal area CA1 of CK-p25, shHDAC2, CK-p25, scr and CON, scr animals; scale bar, 20 μm. **b**, Quantitative assessment of **a**, $n = 4$ or 5 sections from four mice each. **c**, Quantitative PCR results of AcH4K12-immunoprecipitated chromatin in CK-p25, scr and CK-p25, shHDAC2 compared with CON, scr mice. **d**, Quantitative RT–PCR results of the same genes. (**c**, **d**, $n = 4–6$ animals each.) **e**, **g**, Representative immunohistochemical images depicting (**e**) SYP and (**g**) MAP2 immunoreactivity in the hippocampus stratum radiatum; scale bars: **e**, 25 μm; **g**, 20 μm. **f**, Quantitative assessment of **e**, $n = 4$ mice each; a.u., arbitrary units. **h**, Freezing responses of CON, scr ($n = 18$), CK-p25, scr ($n = 16$) and CK-p25, shHDAC2 ($n = 16$) mice 24 h after contextual fear conditioning. **i**, Escape latencies in a water maze task of CON, scr ($n = 19$), CK-p25, scr ($n = 17$) and CK-p25, shHDAC2 ($n = 19$) animals. Data points are averages of two trials per day. **j**, Representative swim traces and time spent per quadrant during the water maze test (T, target quadrant; R, right; O, opposite; L, left of target). $^*P \leq 0.05$; $^{**}P \leq 0.01$; $^{***}P \leq 0.001$; values are mean ± s.e.m.

Combination Training increases cognitive and functional performances in healty aging individuals

Methods

Combination Training

First three months	*Brain training*	*Aerobic training*	*Music Training*[3]
Monday	Crossword	Activit walkir	
Tuesday	Reading book		
Wednesday	Sudoku	ADL: c relatio	
Thursday	preparing for structured discussion or preparation activities for the fun-ricreation project		
Friday	word searches	ADL: c	
Saturday[2]	Fun-ricreation project		

Last three months[1]	*Brain training*	*Aerobic training*	*Music Training*[3]
Monday	Logical greed	Activity daily living(ADL): walking	Listening to music
Tuesday	Reading book		
Wednesday	Sudoku	ADL: choice of subject in relation to OPHI-II	Listening to music
Thursday	preparing for structured discussion or preparation activities for the fun-ricreation project		
Friday	Transfer	ADL: dancing	Listening to music
Saturday[2]	Fun-ricreation project		

- Activities of the last 3 months were of increased complexity
- "***fun recreation project***" :
  - Card games
  - Cognitive stimulating software
  - Structured group activities
- ***Music Training***: "***supermind compilation***" (Vivaldi, Chopin, Debussy, Mozart, Wagner, The Queen, Presley, Rolling Stones)

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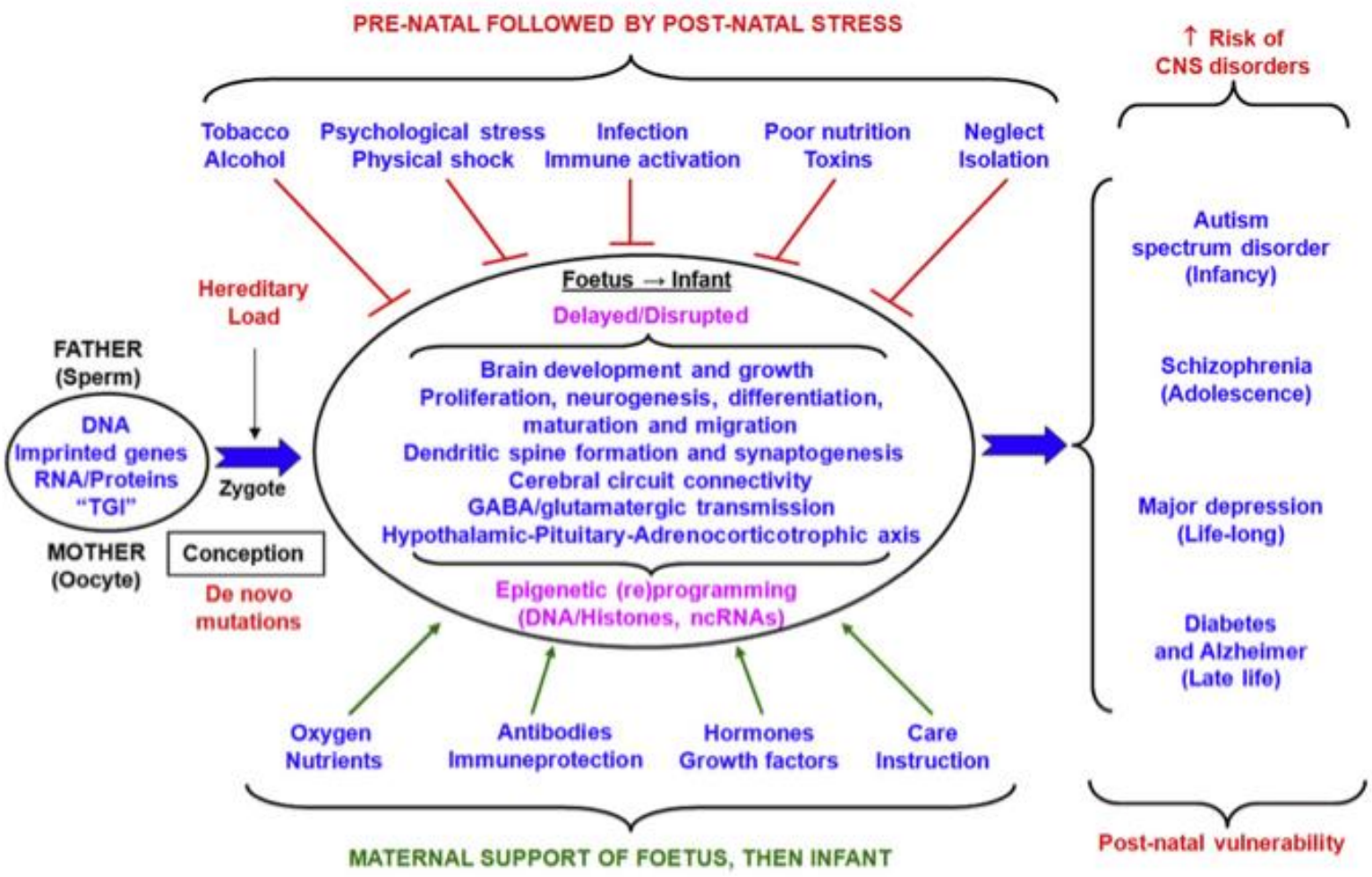
Epigenetics

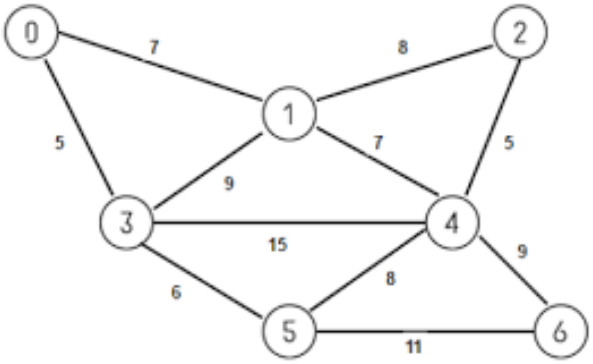
Invited review

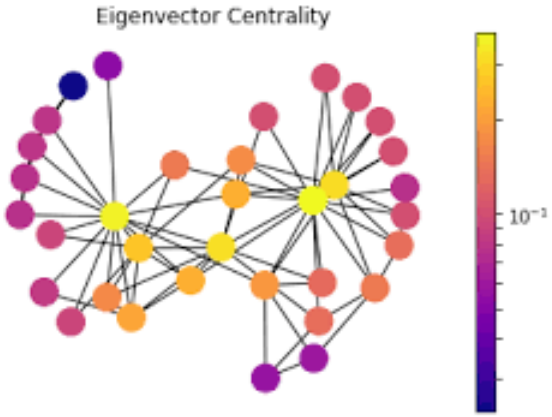
An epigenetic framework for neurodevelopmental disorders: From pathogenesis to potential therapy

Mark J. Millan*

Unit for Research and Discovery in Neuroscience, IDR Servier, 125 chemin de ronde, 78290 Croissy sur Seine, Paris, France







Network Analysis

To investigate changes in functional brain network organization induced by drug administration, we modeled resting state FC as a complex network *(Caldarelli, 2007):*

- **A functional connection between two brain areas was considered as an undirected and weighted graph link. The applied threshold is very conservative (s= 2)**
- ***Eigenvector Centrality*** **(EC) was chosen as a topological metric to disclose brain nodes that were functionally connected to other highly functionally connected nodes** *(Rubinov and Sporns, 2010)*
- **The analysis modeled the interaction of the effect of treatment, namely baseline pre-treatment (B) and end of treatment (E), and the effect of condition, namely D (drug) and P (placebo). The interaction is described by the contrast (ED–BD) – (EP–BP)**

Altered Histone Acetylation Is Associated with Age-Dependent Memory Impairment in Mice

Shahaf Peleg,[1*] Farahnaz Sananbenesi,[1*] Athanasios Zovoilis,[1*] Susanne Burkhardt,[1] Sanaz Bahari-Javan,[1] Roberto Carlos Agis-Balboa,[1] Perla Cota,[1] Jessica Lee Wittnam,[1†] Andreas Gogol-Doering,[2] Lennart Opitz,[3] Gabriella Salinas-Riester,[3] Markus Dettenhofer,[4] Hui Kang,[2] Laurent Farinelli,[5] Wei Chen,[2] André Fischer[1‡]

As the human life span increases, the number of people suffering from cognitive decline is rising dramatically. The mechanisms underlying age-associated memory impairment are, however, not understood. Here we show that memory disturbances in the aging brain of the mouse are associated with altered hippocampal chromatin plasticity. During learning, aged mice display a specific deregulation of histone H4 lysine 12 (H4K12) acetylation and fail to initiate a hippocampal gene expression program associated with memory consolidation. Restoration of physiological H4K12 acetylation reinstates the expression of learning-induced genes and leads to the recovery of cognitive abilities. Our data suggest that deregulated H4K12 acetylation may represent an early biomarker of an impaired genome-environment interaction in the aging mouse brain.

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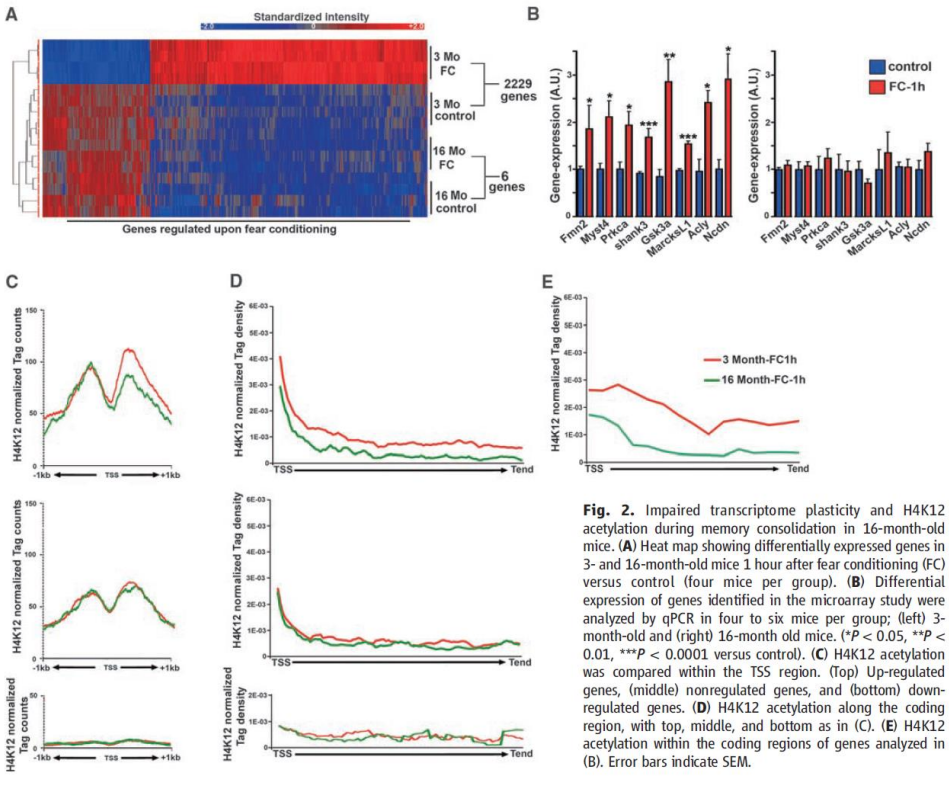


Fig. 2. Impaired transcriptome plasticity and H4K12 acetylation during memory consolidation in 16-month-old mice. (**A**) Heat map showing differentially expressed genes in 3- and 16-month-old mice 1 hour after fear conditioning (FC) versus control (four mice per group). (**B**) Differential expression of genes identified in the microarray study were analyzed by qPCR in four to six mice per group; (left) 3-month-old and (right) 16-month old mice. (*$P < 0.05$, **$P < 0.01$, ***$P < 0.0001$ versus control). (**C**) H4K12 acetylation was compared within the TSS region. (Top) Up-regulated genes, (middle) nonregulated genes, and (bottom) down-regulated genes. (**D**) H4K12 acetylation along the coding region, with top, middle, and bottom as in (C). (**E**) H4K12 acetylation within the coding regions of genes analyzed in (B). Error bars indicate SEM.

Opinion

Systems biology and the future of medicine

Joseph Loscalzo[1]* and Albert-Laszlo Barabasi[1,2]

Contemporary views of human disease are based on simple correlation between clinical syndromes and pathological analysis dating from the late 19th century. Although this approach to disease diagnosis, prognosis, and treatment has served the medical establishment and society well for many years, it has serious shortcomings for the modern era of the genomic medicine that stem from its reliance on reductionist principles of experimentation and analysis. Quantitative, holistic systems biology applied to human disease offers a unique approach for diagnosing established disease, defining disease predilection, and developing individualized (personalized) treatment strategies that can take full advantage of modern molecular pathobiology and the comprehensive data sets that are rapidly becoming available for populations and individuals. In this way, systems pathobiology offers the promise of redefining our approach to disease and the field of medicine. *WIREs Syst Biol Med* 2011 3 619–627 DOI: 10.1002/wsbm.144

In the arc of Western understandings of disease that began with the holism of the sick person and then atomized it into units of pathology, we are attempting a reassembly or reconstruction. The task of putting the patient back together again will be complex, arduous, and time consuming, but it promises a new articulation of the biologic and social sciences that are inextricably linked and essential to the advancement of medicine.

The range of possible applications of systems pathobiology to medicine is vast, yet, is in its very early stages. The advantages of using an holistic, network-based approach to characterize human disease will, at last, begin to move medicine from a field of simple associations rooted in semi-empiric reductionism in search of the 'cure' for each disease to one that recognizes the power of the molecular networks upon which human biology is based as a highly rational paradigm by which to identify disease cures. The emergent behavior of these networks dictates that reductionist approaches will, by definition, fail to ascertain the complexity implicit in these scale-free systems, and will, therefore, fail to appreciate commonalities among diseases, unique treatment approaches that will likely require combinations of therapies, and the many molecular consequences that environmental or pharmacological perturbations can evoke. Although there are clear examples of the successful application of systems principles to medicine reviewed in this article, the breadth of the success of this approach has yet to be realized but will, no doubt, revolutionize the science and practice of medicine.

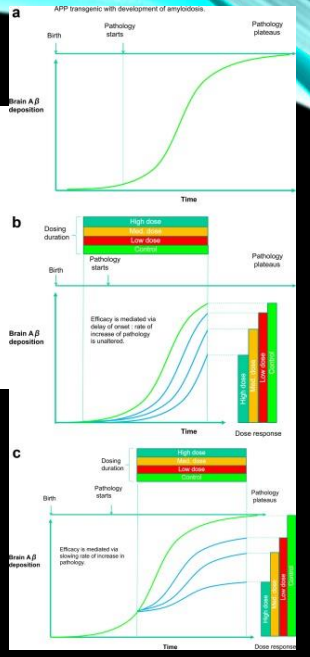
TABLE 1. Outcomes of Phase 3 Clinical Trials of Amyloidocentric Drugs

Drug Name and Proposed Mechanism of Action	Phase 2 Results	Phase 3 Results
Tramiprosate, Aβ aggregation inhibitor.	58 mild–moderate AD patients randomized to 4 groups: placebo, 50, 100, 150mg/kg tramiprosate b.i.d. for 3 months. Drug mediated a significant lowering of Aβ42 in CSF samples.[21]	1,052 mild–moderate AD patients randomized to 3 groups: placebo, 100, 150mg/kg b.i.d. for 78 weeks. No significant effects on primary outcome measures on ADAS-cog and CDR-SB.[25]
Tarenflurbil, γ-secretase modulator.	210 mild–moderate AD patients randomized to placebo, 400, 800mg b.i.d. tarenflurbil for 12 months. Some evidence of an improvement ADCS-ADL at the 800mg b.i.d. dose.[46]	1,684 mild AD patients randomized to placebo, 800mg b.i.d. tarenflurbil for 18 months. No significant effects on primary outcome measures on ADAS-cog and ADCS-ADL.[47]
Semagacestat, γ-secretase inhibitor.	51 mild–moderate AD patients randomized to placebo, 100, 140mg o.d. semagacestat following dose escalation for a total duration of 18 weeks. Significant reduction in plasma Aβ40 peptide.[77]	2,600 mild–moderate AD patients randomized to placebo, 100, 140mg semagacestat o.d. for 76 weeks in 2 trials (ClinicalTrials.gov identifiers NCT00594568, NTC00762411). Trials were halted after interim analysis showed increased incidence of skin cancer and worsening of cognition and activities of daily living.[78]
Bapineuzumab, humanized monoclonal antibody directed at amino acids 1–5 of Aβ peptide. Amyloid plaque clearance mediated by microglial activation.	234 mild–moderate AD patients, randomized to placebo, 0.15, 0.5, 1.0, or 2.0mg/kg bapineuzumab i.v. infusions every 13 weeks for 78 weeks. Some evidence of an improvement in cognitive and functional endpoints in study completers and *APOE4* noncarriers.[106]	4,500 mild–moderate AD patients randomized to placebo and 0.5mg/kg i.v. every 13 weeks for 18 months in *APOE4* carriers, and randomized to placebo, 0.5, 1.0mg/kg i.v. every 13 weeks for 18 months in *APOE4* noncarriers in 4 trials (ClinicalTrials.gov identifiers lNCT00575055, NCT00574132, NCT00676143, NCT00667810). Trials were halted after completion of 2 trials demonstrated a failure to meet primary outcome measures on ADAS-cog and activities of daily living.[109]
Solanezumab, humanized monoclonal antibody directed at amino acids 16–24 of Aβ peptide. Amyloid plaque clearance mediated via peripheral sink mechanism.	52 mild–moderate AD patients were randomized to placebo, 100mg every 4 weeks, 100mg weekly, 400mg every 4 weeks, 400mg weekly i.v. solanezumab for 12 weeks. There was a significant dose-dependent increase in Aβ42 peptide in CSF.[132]	2,000 mild–moderate AD patients randomized to placebo and 400mg solanezumab monthly i.v. for 18 months (ClinicalTrials.gov identifiers NCT00905372, NCT00904683). Trials failed to meet their primary outcome measures on ADAS-cog and ADCS-ADL. A secondary analysis of mild AD patients pooled from both trials showed a significant effect on cognition.[115]
Gammagard, intravenous immunoglobulin.	55 mild–moderate AD patients randomized to placebo, 0.2, 0.5, 0.8g/kg/4 weeks, or 0.1, 0.25, 0.4g/kg/2 weeks for 24 weeks. There was no increase in Aβ40 peptide in plasma at any dose.[129]	Trial data currently unpublished. 390 mild–moderate AD patients randomized to 0.2g/kg/2 weeks and 0.4g/kg/2 weeks vs placebo for 18 months (ClinicalTrials.gov Identifier NCT00818662). Gammagard failed to reach its coprimary outcomes of ADAS-cog and ADCS-ADL.

AD = Alzheimer disease; ADAS-cog = Alzheimer's Disease Assessment Scale–Cognitive Subscale; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; b.i.d. = twice daily; CDR-SB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebrospinal fluid; i.v. = intravenous; o.d. = once per day.

A Critique of the Drug Discovery and Phase 3 Clinical Programs Targeting the Amyloid Hypothesis for Alzheimer Disease

Eric Karran, PhD[1,2,3] and John Hardy, PhD[2,3]



	In vitro assays	Cell assays	In vivo models	Phase 1	Phase 2	Phase 3
Tramiprosate	Data on primary mechanism of action & potency unclear. Some reported studies fail to replicate anti-Aß aggregation properties.	Data on prevention of Aß-induced cell toxicity but mechanism unclear & not clearly related to in vitro data.	Some semi-quantitative evidence for reduction in Aß plaque, but free drug levels not measured.	Not reported.	Dose selection rationale unclear. CSF [drug] were > 20-fold Aß levels. CSF Aß levels were lowered dose-dependently, inconsistent with the mechanism of action.	No significant effects on primary outcome measures of ADAS-cog and CDR-sum of boxes. Target engagement not confirmed.
Tarenflurbil	No data.	Data on mechanism of action defined, dose responses published giving EC50 ~250uM. Data replicated by several groups.	Most data fail to support in vivo efficacy via the postulated mechanism of action. Brain levels of tarenflurbil when measured are below the EC50 level.	CSF levels of compound at highest dose are ~250-fold lower than EC50 levels. No reduction in CSF Aß42.	Subgroup analysis reveals a potential treatment effect on ADCS-ADL in mild AD; no significant effect on ADAS-cog or CDR-SB. Effects on CSF Aß42 not reported.	No significant effects on primary outcome measures of ADAS-cog and ADCS –ADL. Target engagement not confirmed.
Semagacestat	No data available before phase 3 trial. Subsequent data confirm mechanism of action and dose responses.	Data on mechanism of action and dose responses published. Data replicated by several groups.	Dose-dependent reduction in Aß40/42 demonstrated by multiple groups. No data on reduction of Aß plaque in a therapeutic dosing paradigm.	SILK technology confirmed reduction of brain Aß production in a dose-related manner. Proof of mechanism established.	Safety and tolerability study confirmed. Highest dose was tolerated although Notch inhibition effects were evident.	Significant worsening of disease. Target engagement confirmed.
Bapineuzumab	Antibody has nanomolar affinity for soluble Aß and binds deposited Aß. Epitope is Aß 1-5.	Mechanism of action determined to be mediated via antibody binding and microglial activation.	Data demonstrate robust prevention of Aß deposition, but no definitive data that existing Aß plaque can be removed. Evidence of microhaemorrhage as a potential adverse event.	No data.	Safety and tolerability study confirmed ARIA to be dose limiting. Pooled analysis of all doses show some evidence for cognitive benefit. Evidence for reduction in brain Aß and CSF ptau.	No significant effects on primary outcome measures of ADAS-cog and DAD. Significant reduction in ptau. No evidence for reduction of brain Aß. Target engagement not confirmed.
Solanezumab	Antibody has picomolar affinity for soluble Aß. Epitope is Aß 16-24. Antibody sequesters Aß in mixed solutions with ApoE and albumin.	No data.	Data demonstrate robust capture of peripheral Aß, but data on clearance of deposited Aß is weak and not replicated. No evidence for microhaemorrhage as a potential adverse event.	No data.	Safety, tolerability and biomarker studies confirmed capture of all peripheral Aß and evidence for reduction in soluble Aß40 and mobilization of plaque. No ARIA detected.	No significant effects on primary outcome measures of ADAS-cog and ADCS-ADL. No effects on brain Aß or CSF ptau. Target engagement confirmed.
IVIg/ Gammagard©	Anti- Aß antibodies purified from IVIg inhibit Aß fibril formation.	High anti-Aß antibody concentrations activate microglial mediated clearance of Aß plaque ex vivo.	Some evidence that IVIg administration to APP/PS1 transgenic mice results in human antibody reaching the brain parenchyma, but no evidence for binding to Aß plaque or plaque clearance.	No data.	Several clinical studies were in very small numbers of patients, without placebo controls. A dose ranging study showed no significant capture of peripheral Aß at any dose.	No significant effects on primary outcome measures of ADAS-cog and ADCS-ADL (data not published). Target engagement not confirmed.

Combination Training increases cognitive and functional performances in healty aging individuals

Table 2. Genotyping.

Polymorphisms	dbSNP ID	Primers	Restriction enzymes	Digestion fragments (bp)
DRD1–48A/G	rs 686	5′-GGC TTT CTG GTG CCC AAG ACA GTG-3′ 5′-AGC ACA GAC CAG CGT GTT CCC CA-3′	DdeI	A: 146,42,217 G: 146 259
DRD2-TAQ-IA	rs 1800497	5′-CCG TCG ACG GCT GGC CAA GTT GTC TA-3′ 5′-CCG TCG ACC CTT CCT GAG TGT CAT CA-3′	Taq I	A1:310 A2:180,130
DRD3-Ser9Gly	rs 6280	5′-GCT CTA TCTCCA ACT CTC ACA-3′ 5′-AAG TCT ACT CAC CTC CAG GTA-3′	MscI	Ser: 304,111, 47 Gly: 206, 111, 98,47
DRD4-521C/T	rs1800955	5′-ATG AGC TAG GCG TCG GCG G-3′ 5′-GCA TCG ACG CCA GCG CCA TCC TAC C -3′	FspI	C: 108, 176 T: 284
DRD5 promoter (TC)n repeat	–	5′-FAM_ATC CAC CCA CCT CGG CCT CCC AAA-3′ 5′-ATG CAA GGT CTT TTC CTC ATA TTG- 3′	–	*TC12:450 TC13:452
COMT-Val158Met	rs4680	5′- GGA GCT GGG GGC CTA CTG TG -3′ 5′- GGC CCT TTT TCC AGG TCT GAC A -3′	NlaIII	Val: 114,36,35 bp Met: 96,36,35,18 bp
DAT1 VNTR	–	5′- TGT GGT GTA GGG AAC GGC CTG AG -3′ 5′- CTT CCT GGA GGT CAC GGC TCA AGG -3′	–	9-r: 440 bp, 10-r: 480 bp 11-r: 520 bp

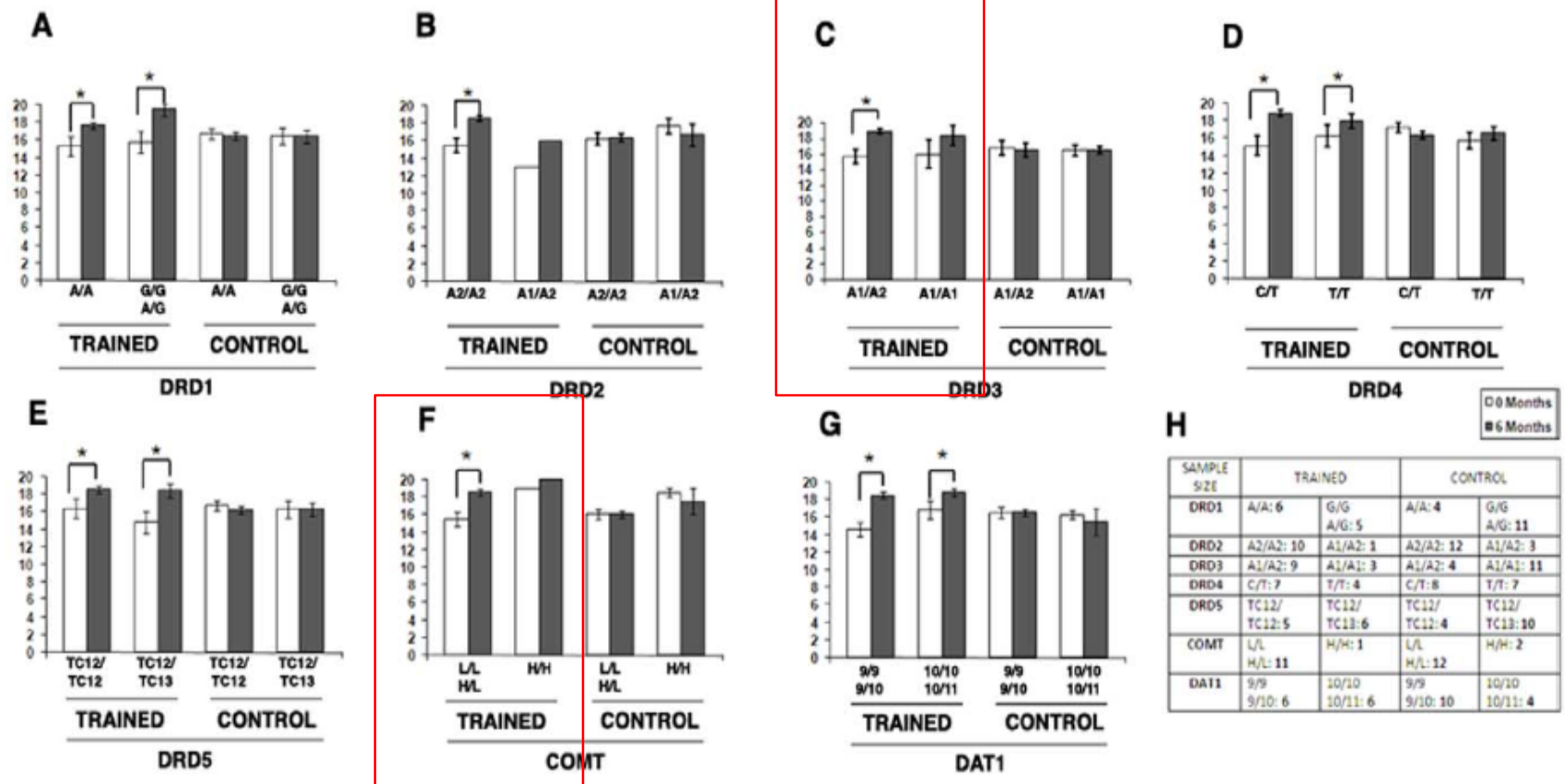
*allele repeat size.

Analysis of dopamine polymorphisms. List of investigated dopamine polymorphisms and the employed primers, restriction enzymes, and digestion fragments.

doi:10.1371/journal.pone.0043901.t002

Combination Training increases cognitive and functional performances in healty aging individuals

DOPA-related polymorphisms affect CT responses



SAMPLE SIZE	TRAINED		CONTROL	
DRD1	A/A: 6	G/G A/G: 5	A/A: 4	G/G A/G: 11
DRD2	A2/A2: 10	A1/A2: 1	A2/A2: 12	A1/A2: 3
DRD3	A1/A2: 9	A1/A1: 3	A1/A2: 4	A1/A1: 11
DRD4	C/T: 7	T/T: 4	C/T: 8	T/T: 7
DRD5	TC12/ TC12: 5	TC12/ TC13: 6	TC12/ TC12: 4	TC12/ TC13: 10
COMT	L/L H/L: 11	H/H: 1	L/L H/L: 12	H/H: 2
DAT1	9/9 9/10: 6	10/10 10/11: 6	9/9 9/10: 10	10/10 10/11: 4

Figure 5. Influence of dopaminergic gene functional polymorphisms on OT-E process skills performance. Bar graphs show the results of the OT-E Process Skills performance in study participants expressing different dopamine-related gene polymorphisms. No differences were found among carriers of different *DRD1* (**A**), *DRD2* (**B**), *DRD4* (**D**), *DRD5* (**E**), and *DAT1* (**G**) polymorphisms in the trained group. Compared to individuals carrying the *DRD3 A1/A1(Ser/Ser)* genotype, *DRD3 A1/A2(Ser/Gly)* carriers showed an increased response to CT (**C**). *COMT L/L-H/L (Val/Val-Val/Met)* carriers also benefitted the most from CT (**F**). Table (**H**) shows sample size.

doi:10.1371/journal.pone.0043901.g005

CONCLUSIONS

- Our study indicates that the human brain, even when aging, maintains important levels of neuronal plasticity. This plasticity is positively modulated by the Combination Training

- The Combination training (CT) is effective in preserving cognitive performances and promoting enhanced memory skills.

- CT positively affects the brain resting state.

- CT- driven cognitive improvements resulted in higher performance in daily living tasks as assessed by the OT-Evaluation test.

- Our results are in line with recent reports indicating that cognitive enrichment can counteract cognitive and behavioral decline as well as the brain atrophy found in neurodegenerative diseases like AD and PD

ARTICLE

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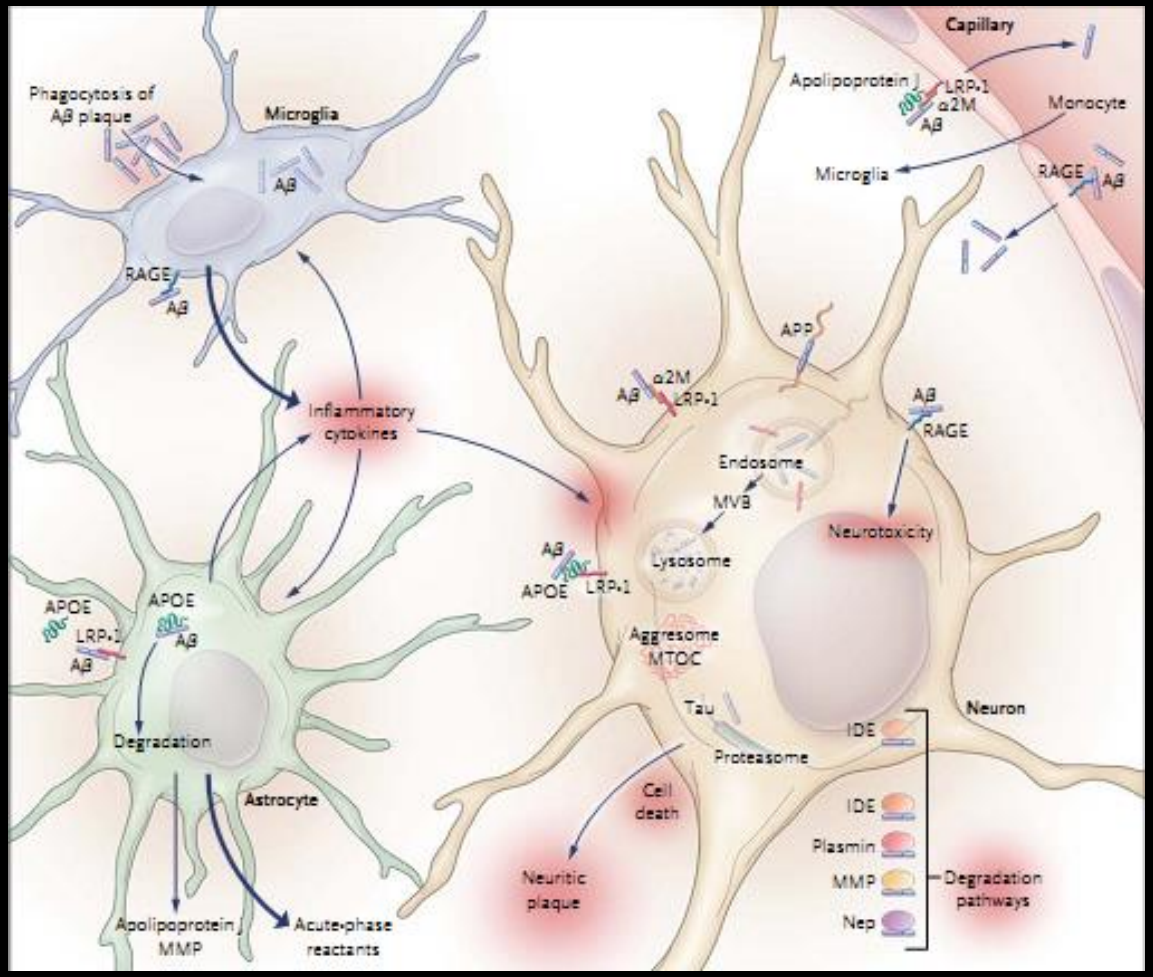
Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease

Sandro Da Mesquita[1,2,10]*, Antoine Louveau[1,2,10], Andrea Vaccari[3,4], Igor Smirnov[1,2], R. Chase Cornelison[4], Kathryn M. Kingsmore[4], Christian Contarino[1,2,5], Suna Onengut-Gumuscu[6], Emily Farber[6], Daniel Raper[1,2,7], Kenneth E. Viar[1,2], Romie D. Powell[1,2], Wendy Baker[1,2], Nisha Dabhi[1,2], Robin Bai[1,2], Rui Cao[4], Song Hu[4], Stephen S. Rich[6], Jennifer M. Munson[4,8], M. Beatriz Lopes[9], Christopher C. Overall[1,2], Scott T. Acton[3,4] & Jonathan Kipnis[1,2]*

Ageing is a major risk factor for many neurological pathologies, but its mechanisms remain unclear. Unlike other tissues, the parenchyma of the central nervous system (CNS) lacks lymphatic vasculature and waste products are removed partly through a paravascular route. (Re)discovery and characterization of meningeal lymphatic vessels has prompted an assessment of their role in waste clearance from the CNS. Here we show that meningeal lymphatic vessels drain macromolecules from the CNS (cerebrospinal and interstitial fluids) into the cervical lymph nodes in mice. Impairment of meningeal lymphatic function slows paravascular influx of macromolecules into the brain and efflux of macromolecules from the interstitial fluid, and induces cognitive impairment in mice. Treatment of aged mice with vascular endothelial growth factor C enhances meningeal lymphatic drainage of macromolecules from the cerebrospinal fluid, improving brain perfusion and learning and memory performance. Disruption of meningeal lymphatic vessels in transgenic mouse models of Alzheimer's disease promotes amyloid-β deposition in the meninges, which resembles human meningeal pathology, and aggravates parenchymal amyloid-β accumulation. Meningeal lymphatic dysfunction may be an aggravating factor in Alzheimer's disease pathology and in age-associated cognitive decline. Thus, augmentation of meningeal lymphatic function might be a promising therapeutic target for preventing or delaying age-associated neurological diseases.

Several pathogenic mechanisms have been postulated

Inflammation and Aβ Clearance



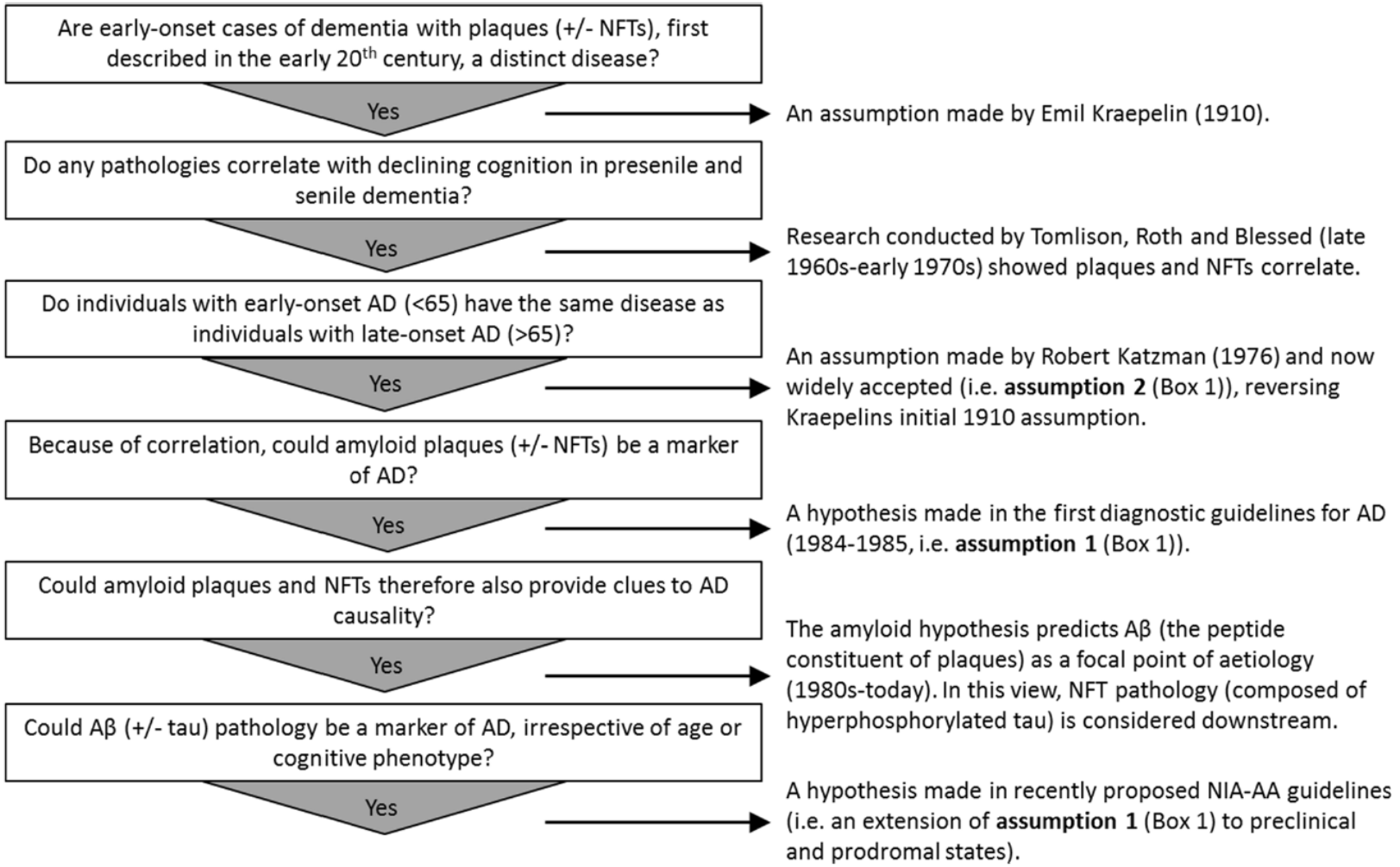
doi:10.1093/brain/aww016 BRAIN 2016: 139; 1265–1281 | 1265

BRAIN
A JOURNAL OF NEUROLOGY

Eliminating microglia in Alzheimer's mice prevents neuronal loss without modulating amyloid-β pathology

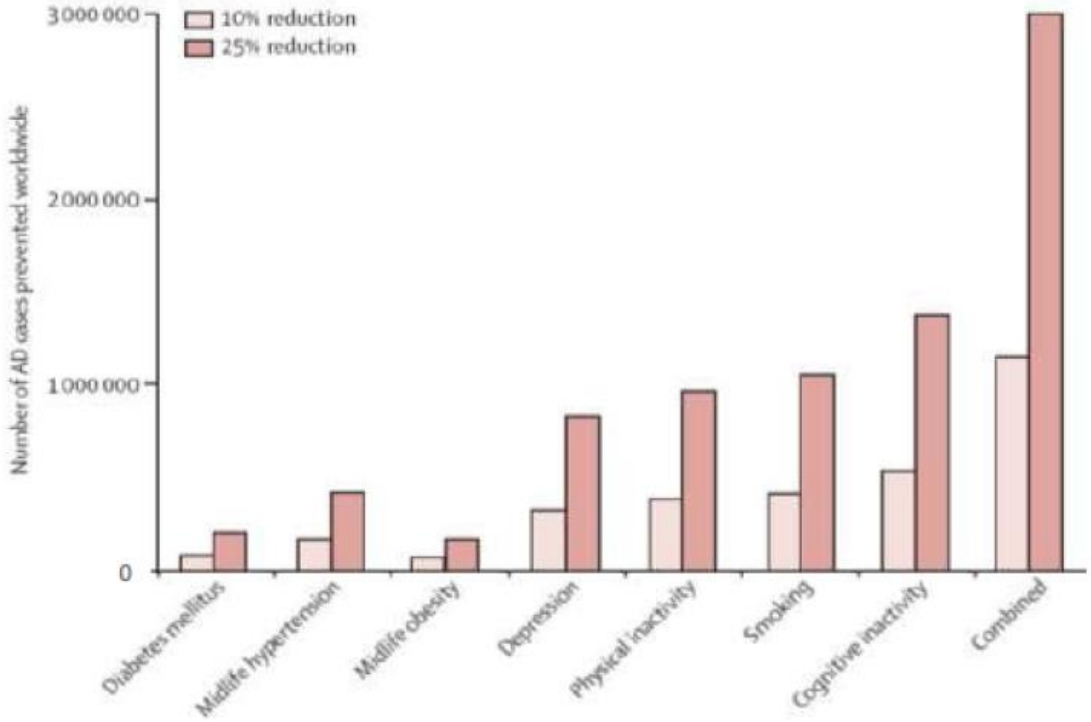
Elizabeth E. Spangenberg,[1] Rafael J. Lee,[1] Allison R. Najafi,[1] Rachel A. Rice,[1] Monica R. P. Elmore,[1] Mathew Blurton-Jones,[1] Brian L. West[2] and Kim N. Green[1]

In addition to amyloid-β plaque and tau neurofibrillary tangle deposition, neuroinflammation is considered a key feature of Alzheimer's disease pathology. Inflammation in Alzheimer's disease is characterized by the presence of reactive astrocytes and activated microglia surrounding amyloid plaques, implicating their role in disease pathogenesis. Microglia in the healthy adult mouse depend on colony-stimulating factor 1 receptor (CSF1R) signalling for survival, and pharmacological inhibition of this receptor results in rapid elimination of nearly all of the microglia in the central nervous system. In this study, we set out to determine if chronically activated microglia in the Alzheimer's disease brain are also dependent on CSF1R signalling, and if so, how these cells contribute to disease pathogenesis. Ten-month-old 5xfAD mice were treated with a selective CSF1R inhibitor for 1 month, resulting in the elimination of ~80% of microglia. Chronic microglial elimination does not alter amyloid-β levels or plaque load; however, it does rescue dendritic spine loss and prevent neuronal loss in 5xfAD mice, as well as reduce overall neuroinflammation. Importantly, behavioural testing revealed improvements in contextual memory. Collectively, these results demonstrate that microglia contribute to neuronal loss, as well as memory impairments in 5xfAD mice, but do not mediate or protect from amyloid pathology.


Are early-onset cases of dementia with plaques (+/- NFTs), first described in the early 20th century, a distinct disease?
Yes
An assumption made by Emil Kraepelin (1910).
Do any pathologies correlate with declining cognition in presenile and senile dementia?
Yes
Research conducted by Tomlison, Roth and Blessed (late 1960s-early 1970s) showed plaques and NFTs correlate.
Do individuals with early-onset AD (<65) have the same disease as individuals with late-onset AD (>65)?
Yes
An assumption made by Robert Katzman (1976) and now widely accepted (i.e. assumption 2 (Box 1)), reversing Kraepelins initial 1910 assumption.
Because of correlation, could amyloid plaques (+/- NFTs) be a marker of AD?
Yes
A hypothesis made in the first diagnostic guidelines for AD (1984-1985, i.e. assumption 1 (Box 1)).
Could amyloid plaques and NFTs therefore also provide clues to AD causality?
Yes
The amyloid hypothesis predicts Aβ (the peptide constituent of plaques) as a focal point of aetiology (1980s-today). In this view, NFT pathology (composed of hyperphosphorylated tau) is considered downstream.
Could Aβ (+/- tau) pathology be a marker of AD, irrespective of age or cognitive phenotype?
Yes
A hypothesis made in recently proposed NIA-AA guidelines (i.e. an extension of assumption 1 (Box 1) to preclinical and prodromal states).

The projected effect of risk factor reduction on Alzheimer's disease prevalence

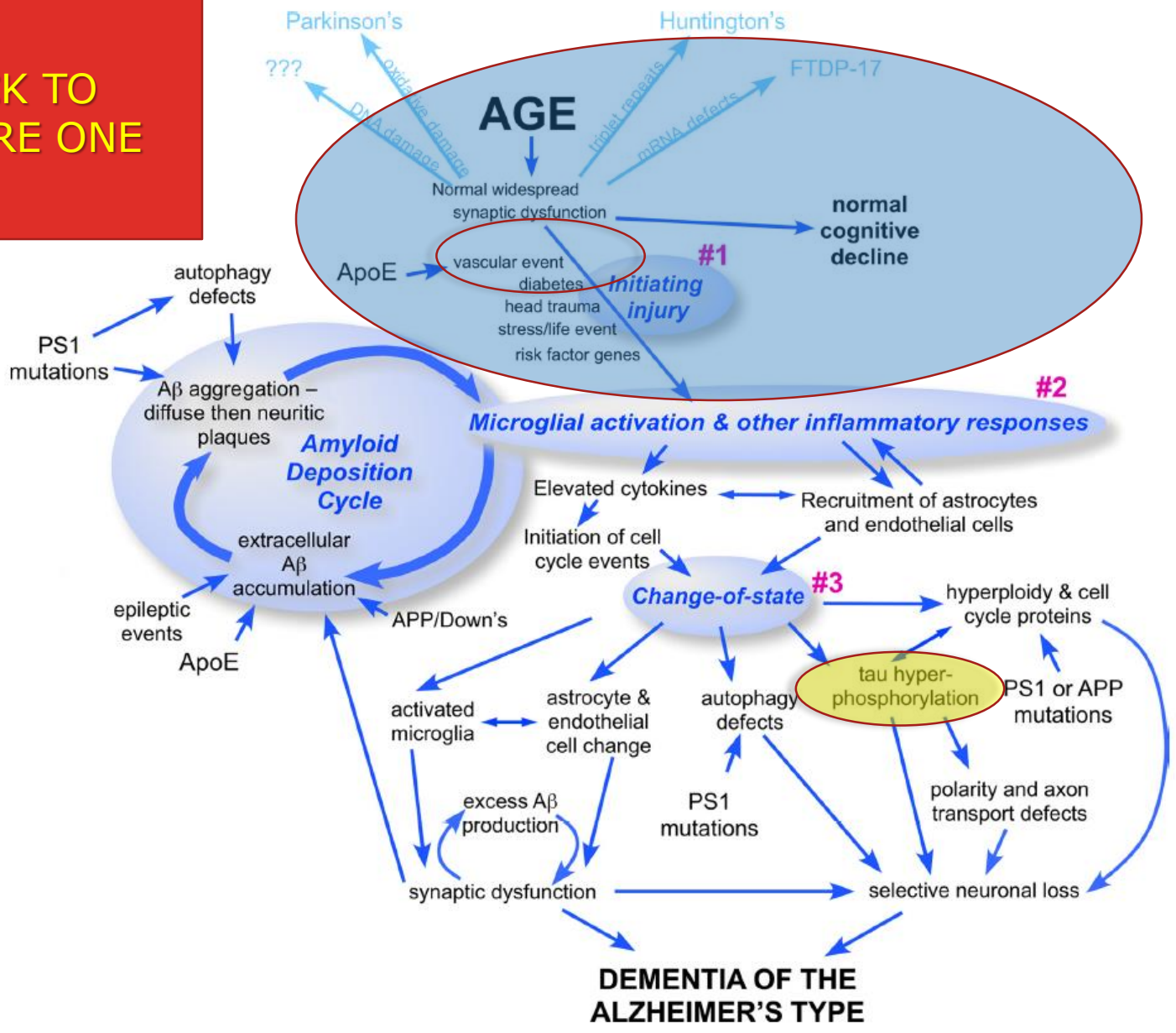
Deborah E Barnes, Kristine Yaffe

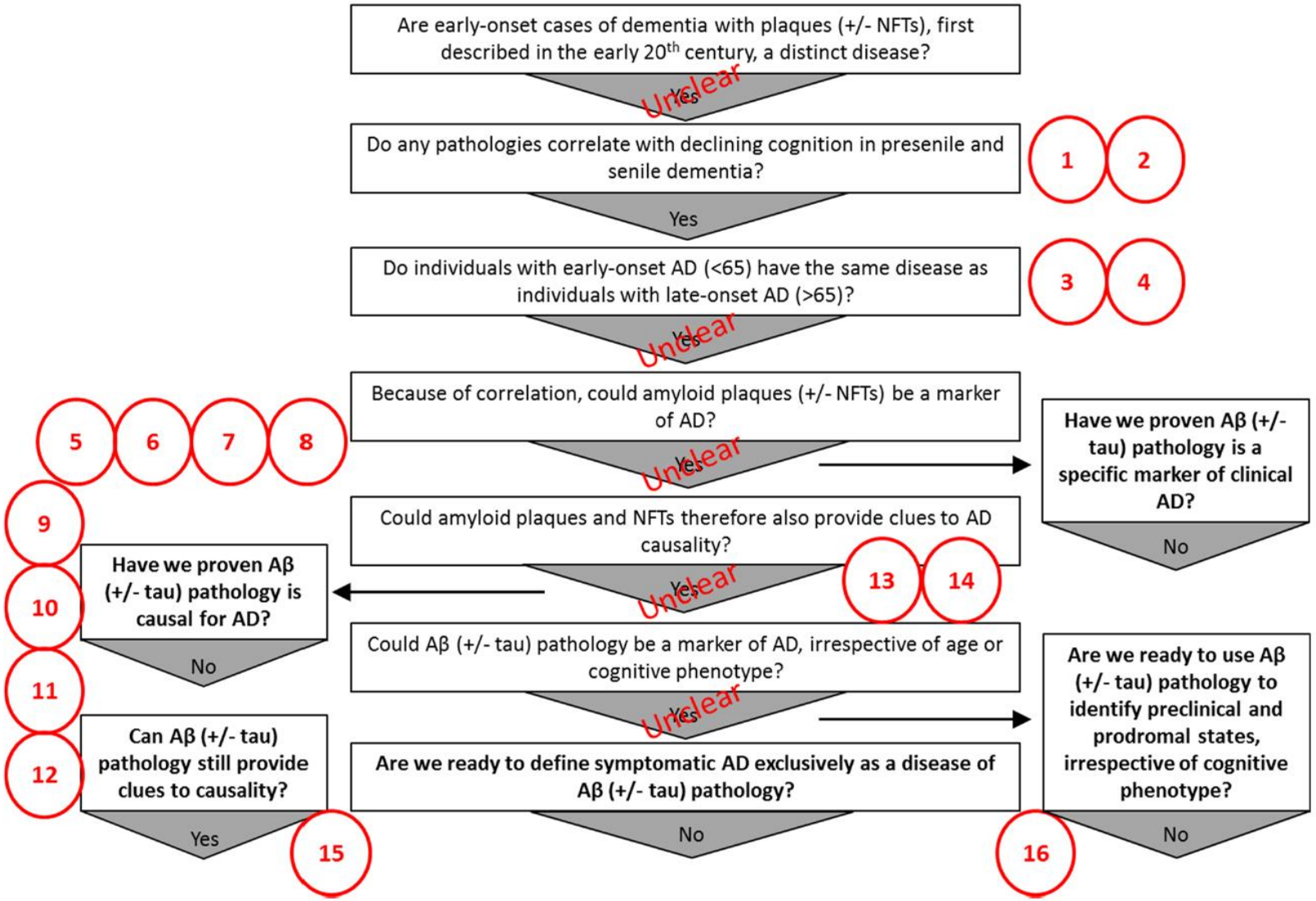


A 10–25% reduction in all seven risk factors could potentially prevent 1.1–3.0 million AD cases worldwide.

THE LANCET Neurology **July 2011**

BACK TO SQUARE ONE




Are early-onset cases of dementia with plaques (+/- NFTs), first described in the early 20th century, a distinct disease?
Yes
Unclear
Do any pathologies correlate with declining cognition in presenile and senile dementia?
1
2
Yes
Do individuals with early-onset AD (<65) have the same disease as individuals with late-onset AD (>65)?
3
4
Yes
Unclear
Because of correlation, could amyloid plaques (+/- NFTs) be a marker of AD?
5
6
7
8
Yes
Unclear
Have we proven Aβ (+/- tau) pathology is a specific marker of clinical AD?
No
Could amyloid plaques and NFTs therefore also provide clues to AD causality?
9
13
14
Yes
Unclear
Have we proven Aβ (+/- tau) pathology is causal for AD?
10
No
Could Aβ (+/- tau) pathology be a marker of AD, irrespective of age or cognitive phenotype?
11
Yes
Unclear
Are we ready to use Aβ (+/- tau) pathology to identify preclinical and prodromal states, irrespective of cognitive phenotype?
Can Aβ (+/- tau) pathology still provide clues to causality?
12
Yes
15
Are we ready to define symptomatic AD exclusively as a disease of Aβ (+/- tau) pathology?
No
16
No

doi:10.1093/brain/awt273 Brain 2013: 136; 3738–3752 | 3738

BRAIN
A JOURNAL OF NEUROLOGY

Cell number changes in Alzheimer's disease relate to dementia, not to plaques and tangles

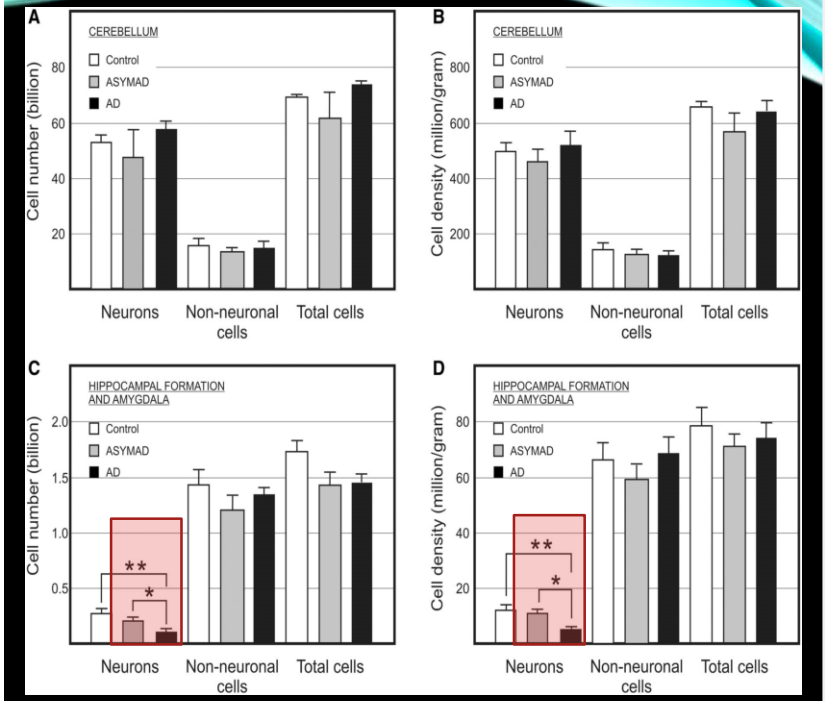
Carlos Humberto Andrade-Moraes,[1] Ana V. Oliveira-Pinto,[1] Emily Castro-Fonseca,[1] Camila G. da Silva,[1] Daniel M. Guimarães,[1] Diego Szczupak,[1] Danielle R. Parente-Bruno,[1] Ludmila R. B. Carvalho,[1] Lívia Polichiso,[2,3] Bruna V. Gomes,[1] Lays M. Oliveira,[1] Roberta D. Rodriguez,[2] Renata E. P. Leite,[2] Renata E. L. Ferretti-Rebustini,[2,4] Wilson Jacob-Filho,[2,5] Carlos A. Pasqualucci,[2] Lea T. Grinberg[2,3] and Roberto Lent[1,6]

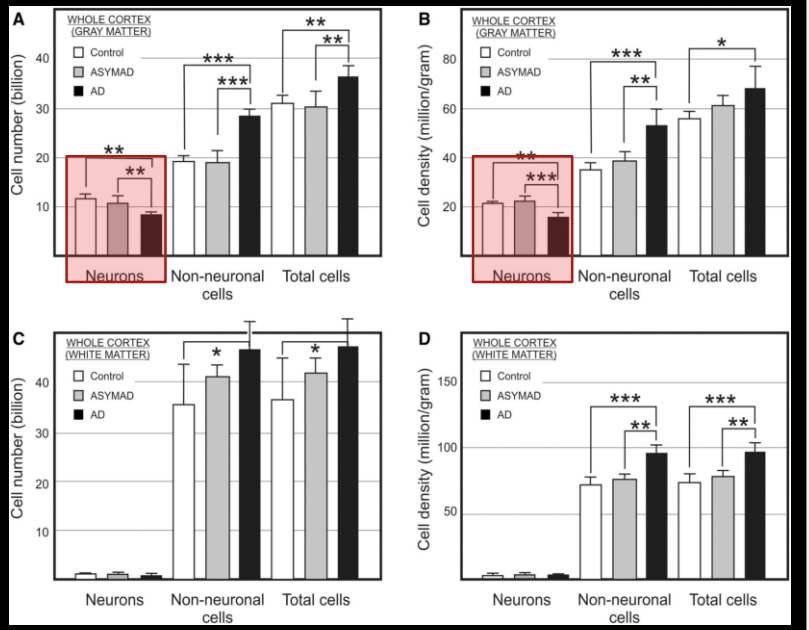
1 Institute of Biomedical Sciences, Federal University of Rio de Janeiro, Brazil
2 Ageing Brain Study Group, Department of Pathology, LIM 22, University of São Paulo Medical School, São Paulo, Brazil
3 Department of Neurology, University of California, San Francisco, USA
4 University of São Paulo Nursing School, São Paulo, Brazil
5 Division of Geriatrics, University of São Paulo, Brazil
6 National Institute of Translational Neuroscience, Ministry of Science and Technology, Brazil

Correspondence to: Prof. Roberto Lent,
Instituto de Ciências Biomédicas,
Universidade Federal do Rio de Janeiro,
Av. Carlos Chagas 373, Sl. F1-31,
Ilha do Fundão, Rio de Janeiro,
CEP 21941-902, Brazil
E-mail: rlent@icb.ufrj.br

Alzheimer's disease is the commonest cause of dementia in the elderly, but its pathological determinants are still debated. Amyloid-β plaques and neurofibrillary tangles have been implicated either directly as disruptors of neural function, or indirectly by precipitating neuronal death and thus causing a reduction in neuronal number. Alternatively, the initial cognitive decline has been attributed to subtle intracellular events caused by amyloid-β oligomers, resulting in dementia after massive synaptic dysfunction followed by neuronal degeneration and death. To investigate whether Alzheimer's disease is associated with changes in the absolute cell numbers of ageing brains, we used the isotropic fractionator, a novel technique designed to determine the absolute cellular composition of brain regions. We investigated whether plaques and tangles are associated with neuronal loss, or whether it is dementia that relates to changes of absolute cell composition, by comparing cell numbers in brains of patients severely demented with those of asymptomatic individuals—both groups histopathologically diagnosed as Alzheimer's—and normal subjects with no pathological signs of the disease. We found a great reduction of neuronal numbers in the hippocampus and cerebral cortex of demented patients with Alzheimer's disease, but not in asymptomatic subjects with Alzheimer's disease. We concluded that neuronal loss is associated with dementia and not the presence of plaques and tangles, which may explain why subjects with histopathological features of Alzheimer's disease can be asymptomatic; and exclude amyloid-β deposits as causes for the reduction of neuronal numbers in the brain. We found an increase of non-neuronal cell numbers in the cerebral cortex and subcortical white matter of demented patients with Alzheimer's disease when compared with asymptomatic subjects with Alzheimer's disease and control subjects, suggesting a reactive glial cell response in the former that may be related to the symptoms they present.

Keywords: ageing; amyloid-β; dementia; neuronal loss; isotropic fractionator





Brain. 2013;136(12):3738-3752. doi:10.1093/brain/awt273

INSULIN AND DEMENTIA

Can Alzheimer Disease Be a Form of Type 3 Diabetes?

Giulia Accardi,[1] Calogero Caruso,[1] Giuseppina Colonna-Romano,[1] Cecilia Camarda,[2]
Roberto Monastero,[2] and Giuseppina Candore[1]

REJUVENATION RESEARCH
Volume 15, Number 2, 2012

DOI: 10.1089/rej.2011.1289

REVIEWS

Fernanda G. De Felice and Sergio T. Ferreira

Inflammation, Defective Insulin Signaling, and Mitochondrial Dysfunction as Common Molecular Denominators Connecting Type 2 Diabetes to Alzheimer Disease

Diabetes 2014;63:2262–2272 | DOI: 10.2337/db13-1954

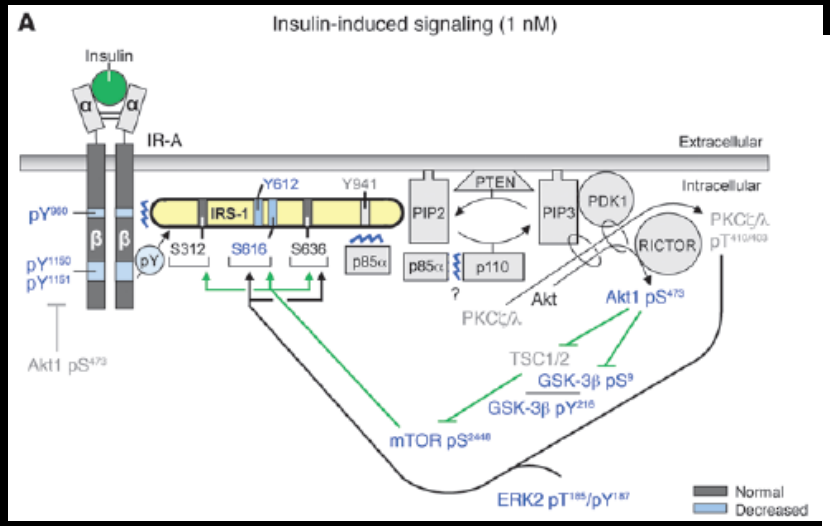
Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums

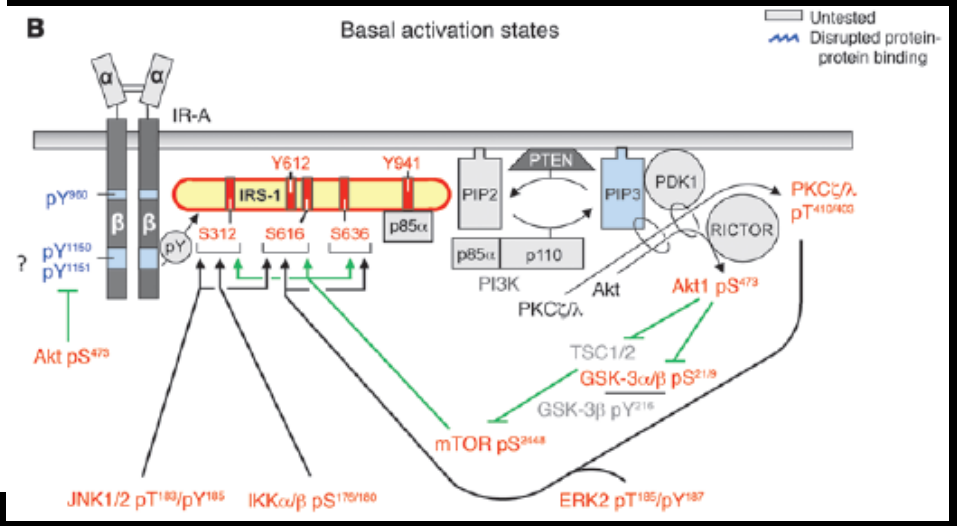
Steven E. Arnold[1], Zoe Arvanitakis[2], Shannon L. Macauley-Rambach[3], Aaron M. Koenig[1], Hoau-Yan Wang[4], Rexford S. Ahima[5], Suzanne Craft[6], Sam Gandy[7], Christoph Buettner[8], Luke E. Stoeckel[9], David M. Holtzman[3] and David M. Nathan[9]

Abstract | Considerable overlap has been identified in the risk factors, comorbidities and putative pathophysiological mechanisms of Alzheimer disease and related dementias (ADRDs) and type 2 diabetes mellitus (T2DM), two of the most pressing epidemics of our time. Much is known about the biology of each condition, but whether T2DM and ADRDs are parallel phenomena arising from coincidental roots in ageing or synergistic diseases linked by vicious pathophysiological cycles remains unclear. Insulin resistance is a core feature of T2DM and is emerging as a potentially important feature of ADRDs. Here, we review key observations and experimental data on insulin signalling in the brain, highlighting its actions in neurons and glia. In addition, we define the concept of 'brain insulin resistance' and review the growing, although still inconsistent, literature concerning cognitive impairment and neuropathological abnormalities in T2DM, obesity and insulin resistance. Lastly, we review evidence of intrinsic brain insulin resistance in ADRDs. By expanding our understanding of the overlapping mechanisms of these conditions, we hope to accelerate the rational development of preventive, disease-modifying and symptomatic treatments for cognitive dysfunction in T2DM and ADRDs alike.

Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline

Konrad Talbot,[1] Hoau-Yan Wang,[2] Hala Kazi,[1] Li-Ying Han,[1] Kalindi P. Bakshi,[2] Andres Stucky,[2] Robert L. Fuino,[1] Krista R. Kawaguchi,[1] Andrew J. Samoyedny,[1] Robert S. Wilson,[3] Zoe Arvanitakis,[3] Julie A. Schneider,[3] Bryan A. Wolf,[4,5] David A. Bennett,[3] John Q. Trojanowski,[5] and Steven E. Arnold[1]





The Journal of Clinical Investigation Volume 122 Number 4 April 2012

Understanding Conflicting Neuropathological Findings in Patients Clinically Diagnosed as Having Alzheimer Dementia

Stephen Salloway, MD, MS; Reisa Sperling, MD, MMSc

How accurate is the clinical diagnosis of Alzheimer disease (AD), and can we identify factors that predict other etiologies for dementia? In this issue of *JAMA Neurology*, Monsell et al[1] report that 25% of individuals clinically diagnosed as having mild to moderate Alzheimer dementia with a Mini-Mental State Examination score of 16 to 26 at their last visit at a National Institute on Aging–funded AD research center had no more than sparse neuritic amyloid plaques on postmortem examination. The percentage of individuals with low amyloid levels was much higher in apolipoprotein E ε4 (*APOE4*) noncarriers (37%) vs carriers (13%). The finding of low amyloid levels in a substantial segment of individuals diagnosed as having AD in experienced centers is consistent with a series of recent reports from the National Alzheimer's Coordinating Center neuropathology database and biomarker evidence from large phase 3 clinical trials.[2-5] Serrano-Pozo et al[2] found that 22 of 161 individuals (14%) diagnosed as having mild to moderate AD (Mini-Mental State Examination score of 16-26) in the National Alzheimer's Coordinating Center neuropathology data set had no more than sparse neuritic plaques at autopsy. In 2 large phase 3 clinical trials of bapineuzumab for mild to moderate Alzheimer dementia, Salloway et al[4] reported that 36% of *APOE4* noncarriers and 6% of *APOE4* carriers did not meet the amyloid positron emission tomography (PET) cutoff for amyloid positivity, percentages nearly identical to the neuropathological results reported by Monsell and colleagues.

Related article page 1124

Monsell and colleagues also found that 43% of individuals with low amyloid levels had Braak stage III to VI neurofibrillary tangles (NFTs), primarily stages III and IV, compared with 95% in the group with high amyloid levels. In a compara-

In summary, a substantial proportion of individuals clinically diagnosed as having mild to moderate Alzheimer dementia have low levels of amyloid. Many elderly individuals, both cognitively normal and impaired, have some NFTs, although the clinical relevance of NFTs restricted to the MTL remains to be elucidated. Thoughtful use of biomarkers will help improve diagnostic accuracy, and advances in tau PET imaging will help investigate the role of tau pathology in cognitively normal and impaired elderly individuals. Distinguishing between AD and non-AD pathologies will become increasingly important as more targeted treatments become available for intervention in the preclinical and early clinical stages of AD.[9]

PERSPECTIVE

nature neuroscience

The case for rejecting the amyloid cascade hypothesis

Karl Herrup[1,2]

Acta Neuropathologica (2018) 136:663–689
https://doi.org/10.1007/s00401-018-1918-8

REVIEW

Questions concerning the role of amyloid-β in the definition, aetiology and diagnosis of Alzheimer's disease

Gary P. Morris[1,2] · Ian A. Clark[3] · Bryce Vissel[1,2]

Received: 30 July 2018 / Revised: 28 September 2018 / Accepted: 30 September 2018 / Published online: 22 October 2018

Amyloid cascade hypothesis

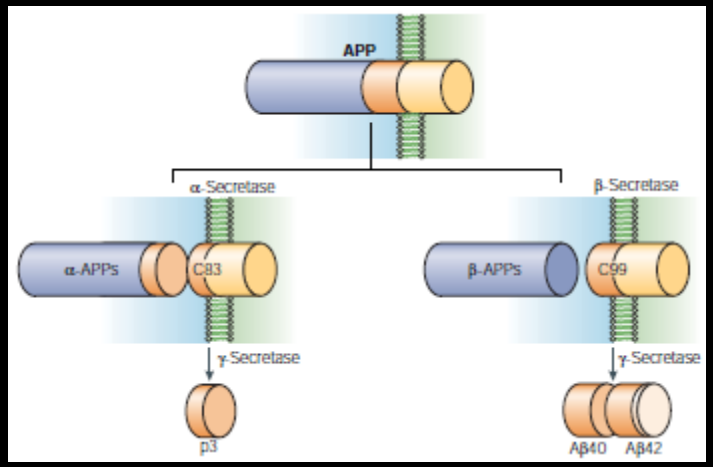
Overproduction, decreased clearance or enhanced aggregation of Aβ42

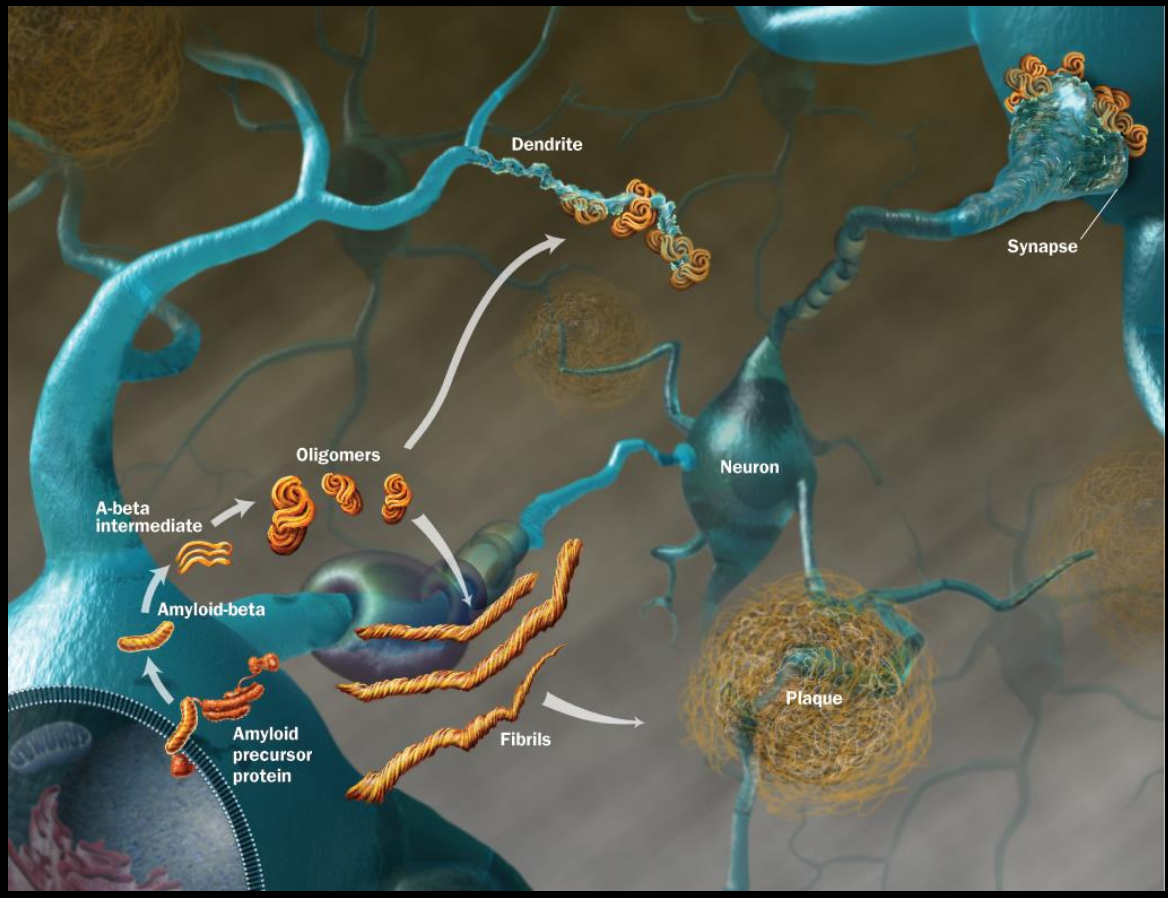
↓

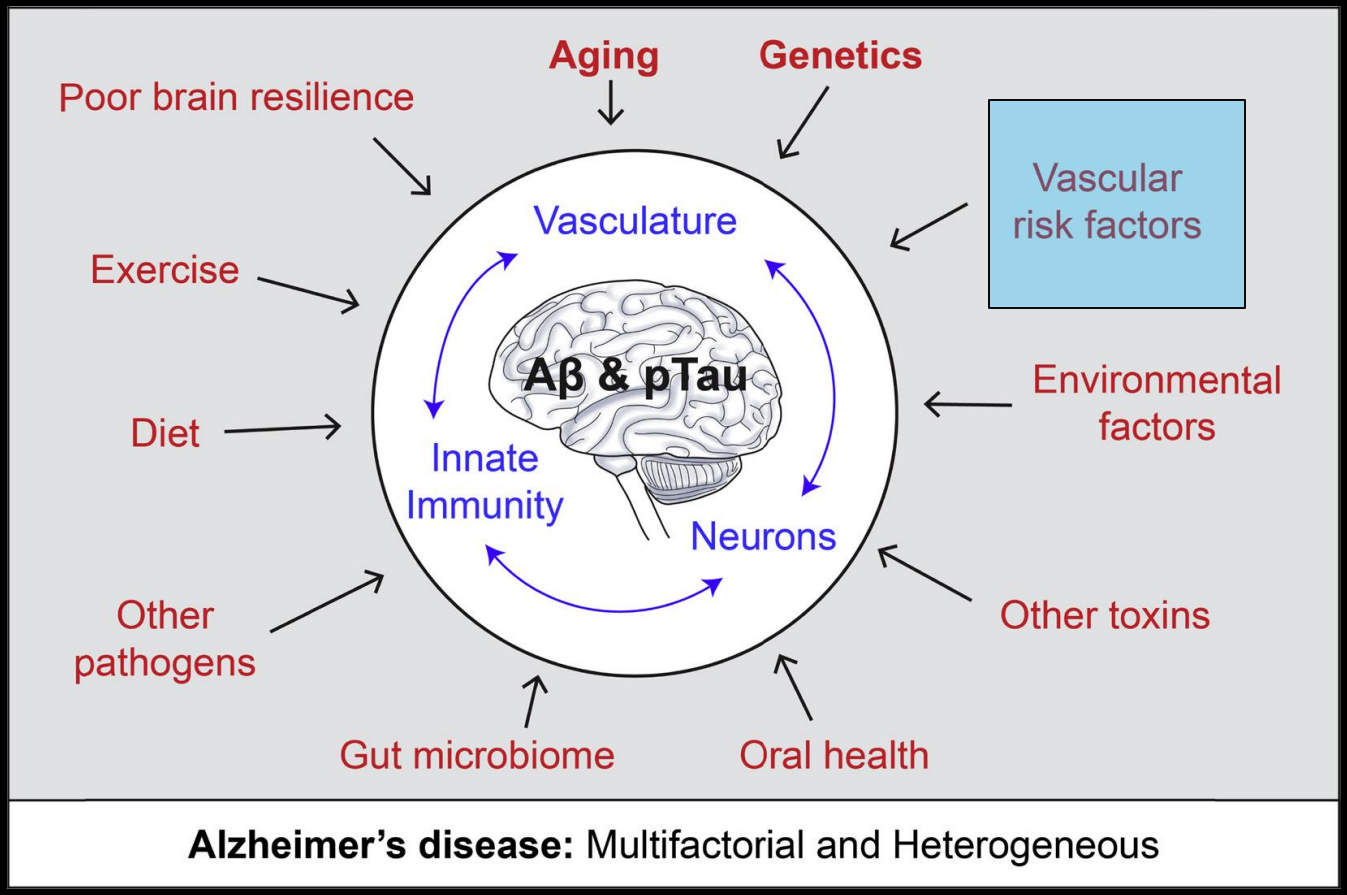
Aβ42 oligomerization and deposition as diffuse plaques

↓

Subtle effects of Aβ42 oligomers on synapses



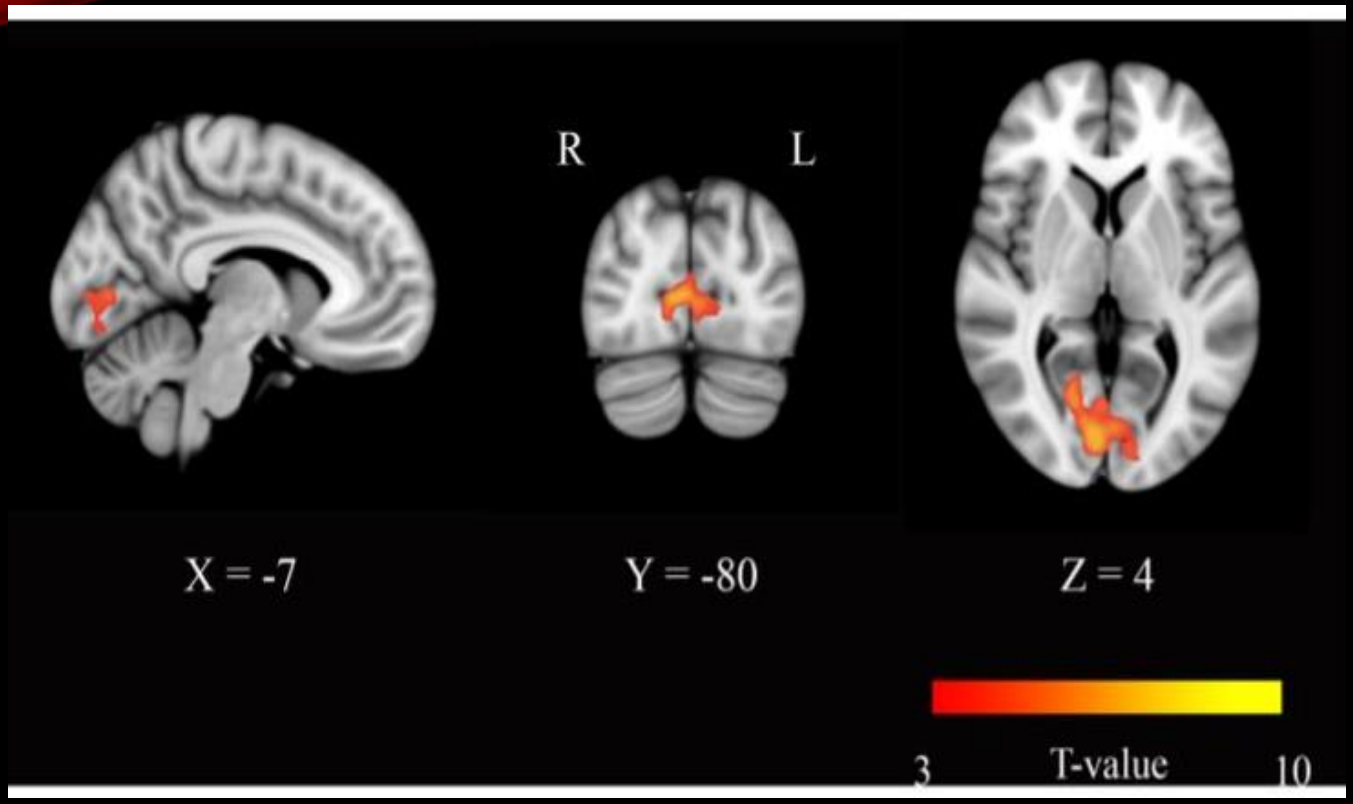




Alzheimer's disease: Multifactorial and Heterogeneous

Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2019 15, 158-167DOI: (10.1016/j.jalz.2018.07.222)

CENTRALITY CHANGES INDUCED BY ACUTE ADMINISTRATION OF MODAFINIL



Paired t-tests were performed across the study group [(ED-BD) > (EP-BP)], in the modafinil group, in the post-drug period, we found an increase of centrality that occurred bilaterally in the BA17, thereby suggesting an increase of the FC of the visual cortex with other brain regions due to drug action.

OPEN

Citation: Cell Death and Disease (2013) 4, e612; doi:10.1038/cddis.2013.139

www.nature.com/cddis

Exenatide promotes cognitive enhancement and positive brain metabolic changes in PS1-KI mice but has no effects in 3xTg-AD animals

M Bomba[1,2,8], D Ciavardelli[1,3,4,8], E Silvestri[5], LMT Canzoniero[5], R Lattanzio[4], P Chiappini[4], M Piantelli[4], C Di Ilio[4], A Consoli[6] and SL Sensi*[,1,2,7]

Bomba et al., Cell Death and Disease, 2013

Discussion and Conclusions

Present findings support that:

- **Acute administration of modafinil induces greater centrality in the bilateral primary visual cortex in elderly subjects;**
- **Modafinil-driven increased functional connectivity occurs between the V1 and prefrontal (IFS and MFG) and cerebellar (Crus I/II and VIIIa) areas;**
- **The drug can be employed to modulate cortico-cerebellar connectivity in the aging brain**

→ Potential therapeutic implication of modafinil use in aging- or Alzheimer's disease-dependent cognitive deficits. Upon brain aging, cognitive deficiency can result from failure of inhibitory processes and the dysfunctional interplay between the WM and the attentional systems *(Luis et al., 2015)*.

nature neuroscience

FOCUS | REVIEW ARTICLE

https://doi.org/10.1038/s41593-018-0234-x

The role of brain vasculature in neurodegenerative disorders

Melanie D. Sweeney[1,3], Kassandra Kisler[1,3], Axel Montagne[1,3], Arthur W. Toga[2] and Berislav V. Zlokovic[1*]

Adequate supply of bl other hand, cerebral bl in humans and animal ing cerebral blood flow rier in the pathogenes multiple sclerosis. We dysfunction in this dis disease biomarkers to common pathway linki

Special Topic Section: Responses to the NIA-AA Research Framework

Vascular dysfunction—The disregarded partner of Alzheimer's disease

Melanie D. Sweeney[a], Axel Montagne[a], Abhay P. Sagare[a], Daniel A. Nation[b,c], Lon S. Schneider[c,d,e], Helena C. Chui[c,d], Michael G. Harrington[f], Judy Pa[g], Meng Law[c,h], Danny J. J. Wang[g], Russell E. Jacobs[a], Fergus N. Doubal[i], Joel Ramirez[j,k,l], Sandra E. Black[m], Maiken Nedergaard[n,o], Helene Benveniste[p], Martin Dichgans[q], Costantino Iadecola[r], Seth Love[s], Philip M. Bath[t,u], Hugh S. Markus[v], Rustam A. Salman[i], Stuart M. Allan[w], Terence J. Quinn[x], Rajesh N. Kalaria[y], David J. Werring[z], Roxana O. Carare[aa], Rhian M. Touyz[bb], Steve C. R. Williams[cc], Michael A. Moskowitz[dd], Zvonimir S. Katusic[ee], Sarah E. Lutz[ff], Orly Lazarov[ff], Richard D. Minshall[gg,hh], Jalees Rehman[ii,jj], Thomas P. Davis[kk], Cheryl L. Wellington[ll], Hector M. González[mm], Chun Yuan[nn], Samuel N. Lockhart[oo,pp], Timothy M. Hughes[oo,pp], Christopher L. H. Chen[qq,rr], Perminder Sachdev[ss], John T. O'Brien[tt], Ingmar Skoog[uu], Leonardo Pantoni[vv], Deborah R. Gustafson[ww], Geert Jan Biessels[xx], Anders Wallin[yy], Eric E. Smith[zz], Vincent Mok[aaa,bbb], Adrian Wong[aaa], Peter Passmore[ccc], Frederick Barkof[ddd,eee], Majon Muller[fff], Monique M. B. Breteler[ggg,hhh], Gustavo C. Román[iii], Edith Hamel[iij], Sudha Seshadri[kkk,lll], Rebecca F. Gottesman[mmm], Mark A. van Buchem[nnn], Zoe Arvanitakis[ooo,ppp], Julie A. Schneider[ooo,ppp], Lester R. Drewes[qqq], Vladimir Hachinski[rrr], Caleb E. Finch[sss], Arthur W. Toga[c,g], Joanna M. Wardlaw[i,l], Berislav V. Zlokovic[a,c,*,l]

Exenatide reverts the high-fat-diet-induced impairment of BDNF signaling and inflammatory response in an animal model of Alzheimer's disease

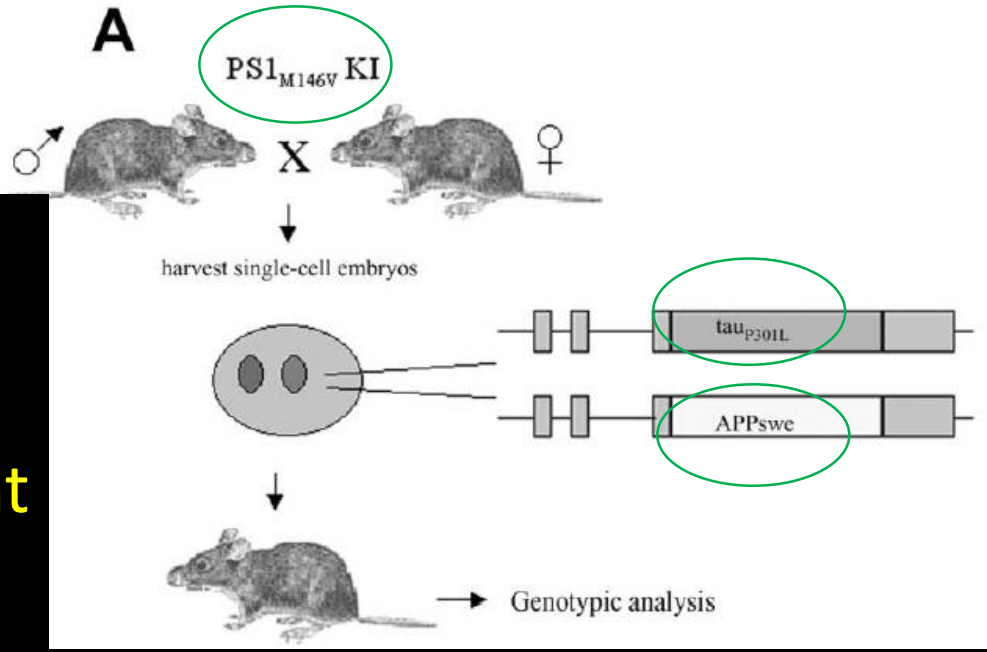
Bomba et al., bioRxiv 487629; doi: https://doi.org/10.1101/487629

Neuron, Vol. 39, 409–421, July 31, 2003, Copyright ©2003 by Cell Press

Triple-Transgenic Model of Alzheimer's Disease with Plaques and Tangles: Intracellular Aβ and Synaptic Dysfunction

Salvatore Oddo,[1] Antonella Caccamo,[1,5]
Jason D. Shepherd,[1,5] M. Paul Murphy,[3]
Todd E. Golde,[3] Rakez Kayed,[2]
Raju Metherate,[1] Mark P. Mattson,[4]
Yama Akbari,[1] and Frank M. LaFerla[1,*]
[1]Department of Neurobiology and Behavior

- mitochondrial and cation deregulation
- amyloid- and tau-dependent pathology
- cognitive decline



ANN NEUROL 2018;83:74–83

RESEARCH ARTICLE

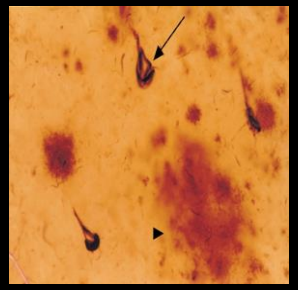
Person-Specific Contribution of Neuropathologies to Cognitive Loss in Old Age

Patricia A. Boyle, PhD,[1,2] Lei Yu, PhD,[1,3] Robert S. Wilson, PhD,[1,2,3] Sue E. Leurgans, PhD,[1,3] Julie A. Schneider, MD, MS,[1,3,4] and David A. Bennett, MD[1,3]

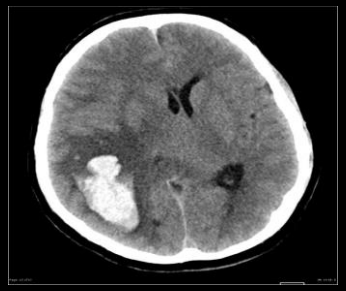
Subjects were 1,079 older persons, who completed at least 2 cognitive evaluations, died, and underwent uniform neuropathologic examinations. **Participants were followed annually for up to 22 years.**

Evaluations of patterns of neuropathologic comorbidity and quantification of the contribution of **9 age-related neuropathologies to pathologic cognitive loss at a person-specific level.**

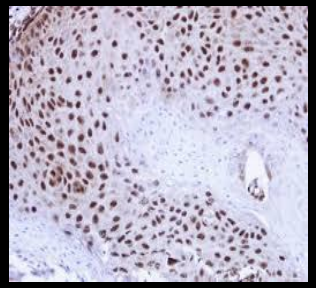
AD



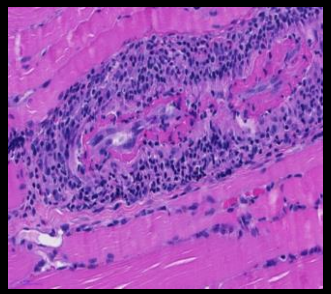
Cerebral Amyloid Angiopathy



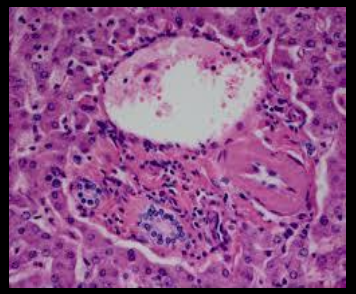
TDP-43



Atherosclerosis

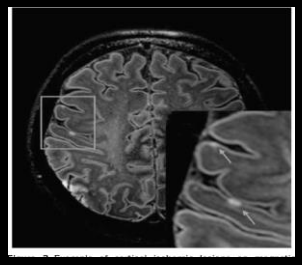


Arteriolosclerosis

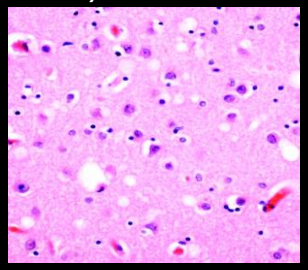


Macroscopic Infarcts

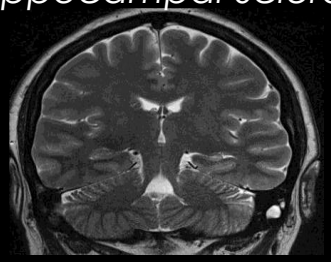
Microinfarcts



Lewy Bodies



Hippocampal Sclerosis



- The neuropathology was ubiquitous (**with nearly all participants having at least 1 neuropathology, more than three-quarters having 2 or more, more than one-half having 3 or more, and more than one-third having 4 or more**)
- AD was the most frequent neuropathology but rarely occurred in isolation **(>230 combinations of neuropathology were observed)**
- AD was the most virulent neuropathology, accounting for an average of >50% of the cognitive loss observed, but its relative contribution varied widely at a person-specific level, ranging from about 20% to 100% depending on the other neuropathologies present
- These findings suggest that there is considerably greater heterogeneity in both the comorbidity and relative impact of age-related neuropathologies than currently recognized. **These findings highlight an urgent need for novel approaches that embrace the heterogeneity of disease**

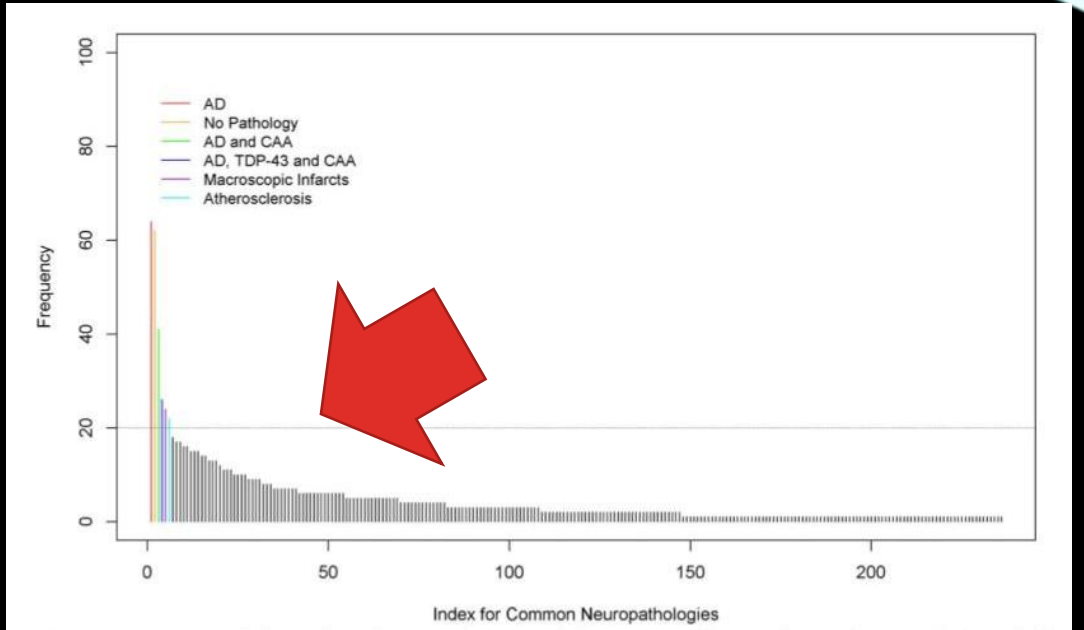


FIGURE 1: Frequencies of observed combinations of neuropathologies. AD = Alzheimer disease; CAA = cerebral amyloid angiopathy.

Neuropathology	No.	Mean	SD
AD	704	57.9%	19.9%
Gross infarcts	388	28.8%	23.7%
Cerebral amyloid angiopathy	386	20.6%	19.0%
TDP-43	377	30.5%	19.3%
Atherosclerosis	358	27.4%	23.1%
Arteriolosclerosis	338	27.5%	21.5%
Cortical Lewy bodies	143	45.1%	17.2%
Hippocampal sclerosis	112	28.1%	12.6%

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BRAIN
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Tau hyperphosphorylation induces oligomeric insulin accumulation and insulin resistance in neurons

Patricia Rodriguez-Rodriguez,[1] Anna Sandebring-Matton,[1] Paula Merino-Serrais,[1] Cristina Parrado-Fernandez,[1] Alberto Rabano,[2,3] Bengt Winblad,[1] Jesús Ávila,[2,4] Isidre Ferrer[2,5] and Angel Cedazo-Minguez[1]

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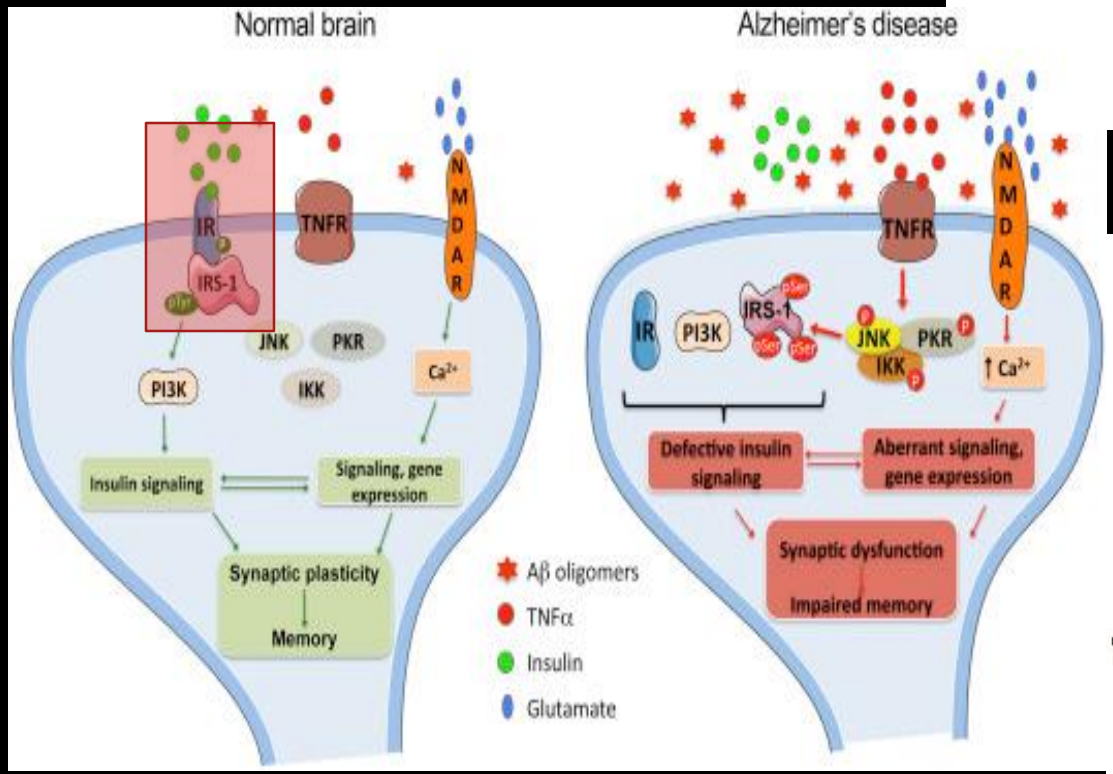

ALZHEIMER DISEASE

Is p-tau the missing link between insulin resistance and AD?