Neuropsicología y Envejecimiento: Una breve introducción

RANY™ HEALTH

Encuentro IV

Dr. Yunier Broche-Pérez, PhD.
Asesor Científico-RANY Health

DEMENCIA

Término “paraguas” empleado para describir un grupo de condiciones (más de 100) caracterizadas por alteraciones de la memoria, el comportamiento y el pensamiento.

Enfermedad de Parkinson

5% de todos los casos de demencia.

Demencia Frontotemporal

5% de todos los casos de demencia.

Demencia Vascular

Segunda forma más frecuente de demencia (**20%** del total de casos).

Enfermedad de Alzheimer

50-70% de todos los casos de demencia.

Demencia de los Cuerpos de Lewy

15% de todos los casos de demencia.

EUROPA
10.5
Millones

ÁMERICA
9.0
Millones

ÁFRICA
4.0
Millones

Asia
22.9
Millones

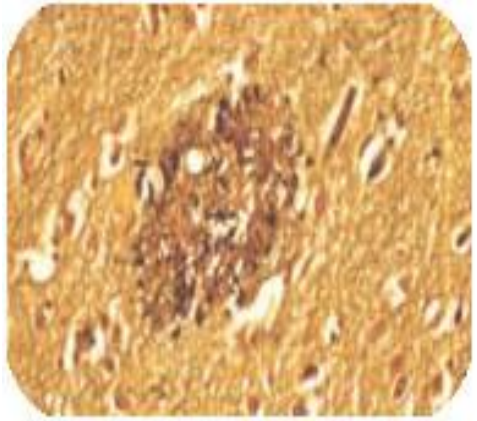
Estimados de prevalencia por regiones del mundo

World Alzheimer Report 2015

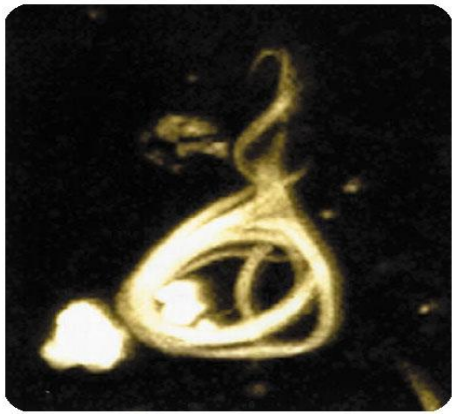
46, 800, 000
Personas padecen demencia a nivel mundial

Plaquetas y Ovillos: Los marcadores de la EA

El cerebro de las personas con EA son abundantes en dos estructuras anormales:



- Palquetas beta-amiloide (placas seniles): depocisiones densas de proteínas y material celular que se acumula fuera del axón celular.



- Ovillos neurofiblirales: fibras entrelazadas que se forman dentro de la neurona.

ALZHEIMER DISEASE

Alzheimer disease risk genes: 29 and counting

Lars Bertram and Rudolph E. Tanzi

The risk of Alzheimer disease is substantially influenced by genetic factors. A new genome-wide association study of more than 600,000 individuals identifies nine novel Alzheimer disease risk genes, raising the total count of independent risk loci to 29.

Refers to Jansen, I. E. et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer disease risk. *Nat. Genet.* https://doi.org/10.1038/s41588-018-0311-9 (2019).

Alzheimer disease (AD) is a debilitating neurodegenerative disorder that is characterized by progressive decline in cognitive functioning and ultimately leads to dementia and death. Pathogenetically, AD is triggered by

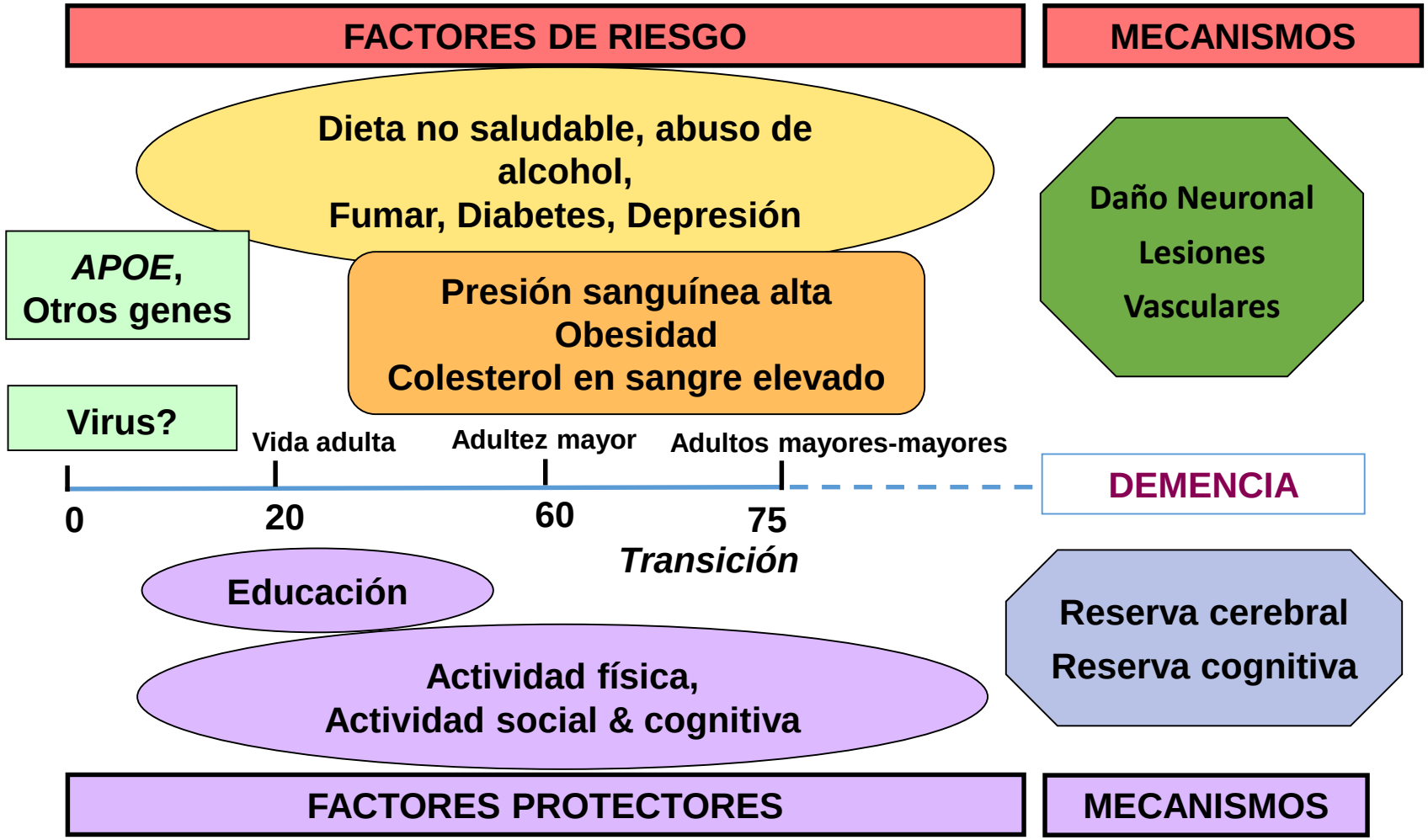
more than eightfold greater than that of the 2013 GWAS by accumulating the genetic data of ~635,000 individuals. This vast increase in number enabled the identification of nine novel AD risk loci, increasing the current total

At baseline, UKB participants were aged between 49 years and 69 years, and were therefore mostly too young to have developed AD, incidence of which peaks after the age of

posed[8] to be a valid approximation of future AD status in UKB individuals for whom genotype data were available but who had not (yet) developed AD themselves.

Second, Jansen et al.[4] used an impressive array of computational tools with the aim of integrating high-resolution transcriptomics and epigenomics data to aid the molecular and functional interpretation of their results. These analyses revealed that most DNA variants associated with AD are located in non-coding portions of the genome, especially in regions that have effects on gene transcription. This finding is in line with

"Genes de riesgo para la Enfermedad de Alzheimer: 29 y contando"



Modificado de Kivipelto, Mangialasche et al., Oxford Ger Text Medicine 2017, Nature Neurology (En prensa)

Si el principal factor de riesgo para el padecimiento de demencias es la edad, ¿qué tal si dejamos de envejecer?

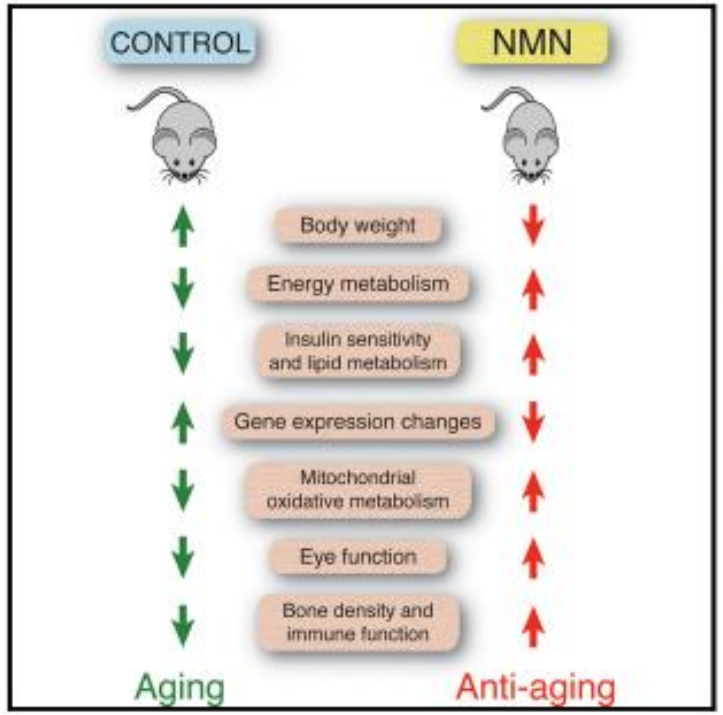
David Sinclair, PhD.
Harvard University
Escuela de Medicina

Article

Cell Metabolism

Long-Term Administration of Nicotinamide Mononucleotide Mitigates Age-Associated Physiological Decline in Mice

Graphical Abstract



Authors

Kathryn F. Mills, Shohei Yoshida, Liana R. Stein, ..., Koji Uchida, Jun Yoshino, Shin-ichiro Imai

Correspondence

jyoshino@wustl.edu (J.Y.), imaishin@wustl.edu (S.I.)

In Brief

Mills et al. conducted a 12-month-long administration of nicotinamide mononucleotide (NMN), a key natural NAD^+ intermediate, to normal wild-type mice, demonstrating that NMN effectively mitigates age-associated physiological decline in mice without any obvious toxicity. These results highlight the significant potential of NMN as an effective anti-aging intervention in humans.

Incorporando NMN en el agua de un grupo de ratones consiguieron:

- Disminuir el peso corporal
- Incrementar el metabolismo
- Disminuir el metabolismo occidativo.
- Mejorar la función visual.
- Incrementaron el metabolismo de los lípidos
- Incrementar la densidad ósea y el funcionamiento del sistema inmune

COGNICION
INICIATIVA CUBANA EN SALUD COGNITIVA

La Hipótesis de la Reserva Cognitiva

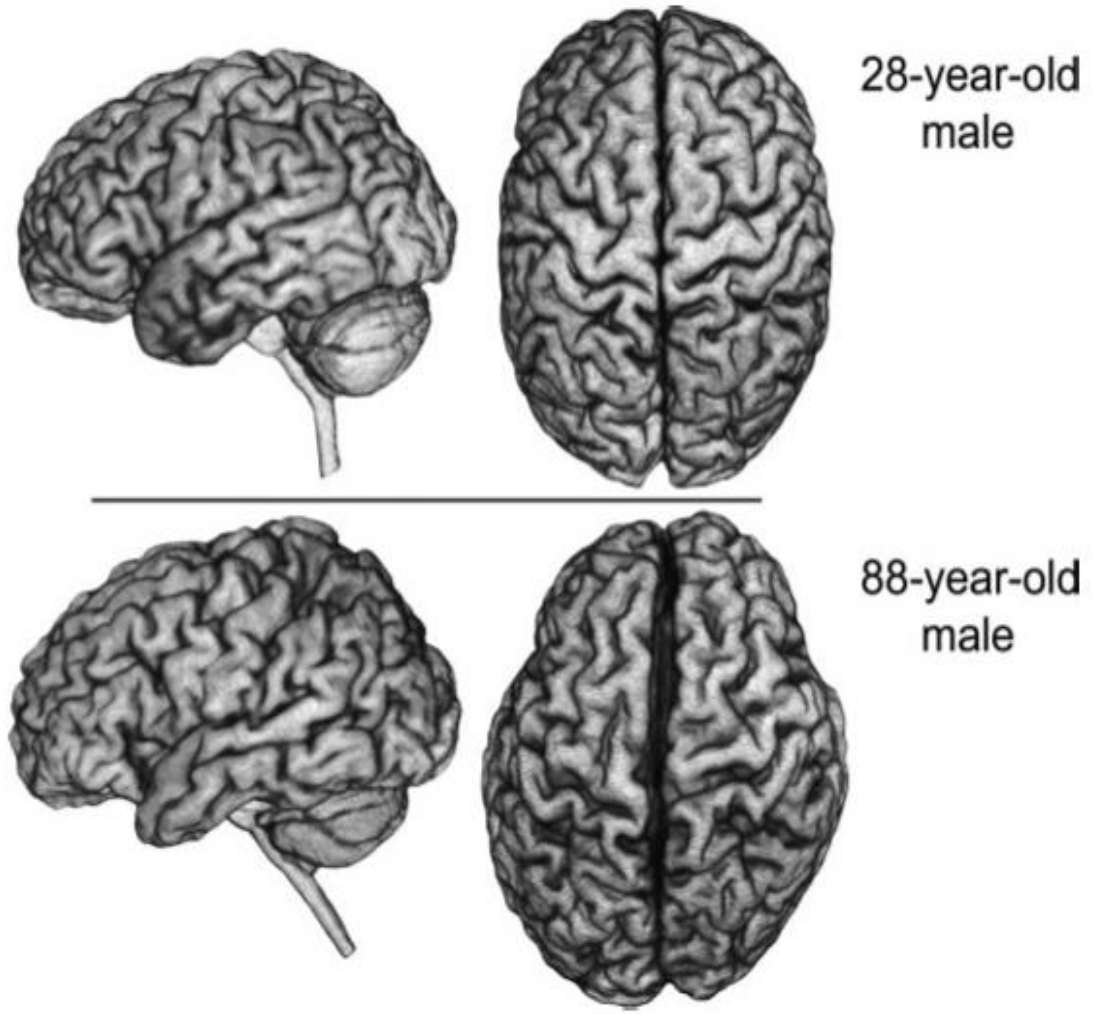
AMERICAN JOURNAL OF HUMAN BIOLOGY 17:673–689 (2005)

Feature Article

The Aging Brain: The Cognitive Reserve Hypothesis and Hominid Evolution

JOHN S. ALLEN,* JOEL BRUSS, AND HANNA DAMASIO
Department of Neurology, Division of Cognitive Neuroscience and Behavioral Neurology, University of Iowa College of Medicine, Iowa City, Iowa

ABSTRACT Compared to other primates, humans live a long time and have large brains. Recent theories of the evolution of human life history stages (grandmother hypothesis, intergenerational transfer of information) lend credence to the notion that selection for increased life span and menopause has occurred in hominid evolution, despite the reduction in the force of natural selection operating on older, especially post-reproductive, individuals. Theories that posit the importance (in an inclusive fitness sense) of the survival of older individuals require them to maintain a reasonably high level of cognitive function (e.g., memory, communication). Patterns of brain aging and factors associated with healthy brain aging should be relevant to this issue. Recent neuroimaging research suggests that, in healthy aging, human brain volume (gray and white matter) is well-maintained until at least 60 years of age; cognitive function also shows only nonsignificant declines at this age. The maintenance of brain volume and cognitive performance is consistent with the idea of a significant post- or late-reproductive life history stage. A clinical model, "the cognitive reserve hypothesis," proposes that both increased brain volume and enhanced cognitive ability may contribute to healthy brain aging, reducing the likelihood of developing dementia. Selection for increased brain size and increased cognitive ability in hominid evolution may therefore have been important in selection for increased lifespan in the context of intergenerational social support networks. Am. J. Hum. Biol. 17:673–689, 2005.



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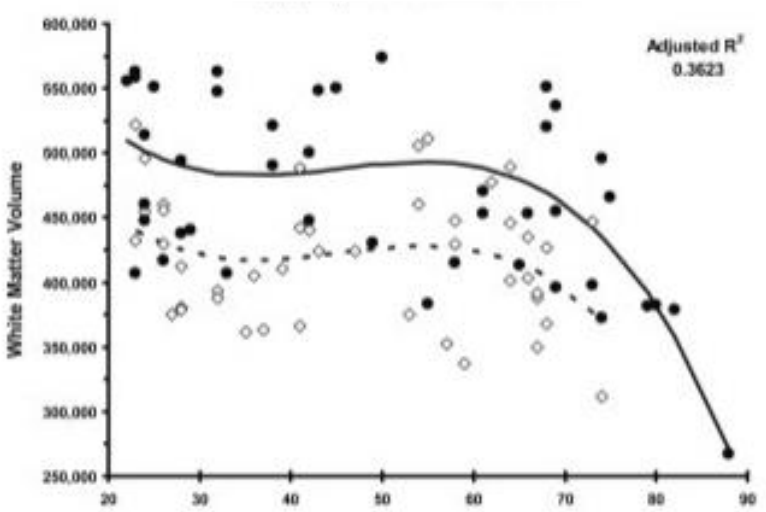
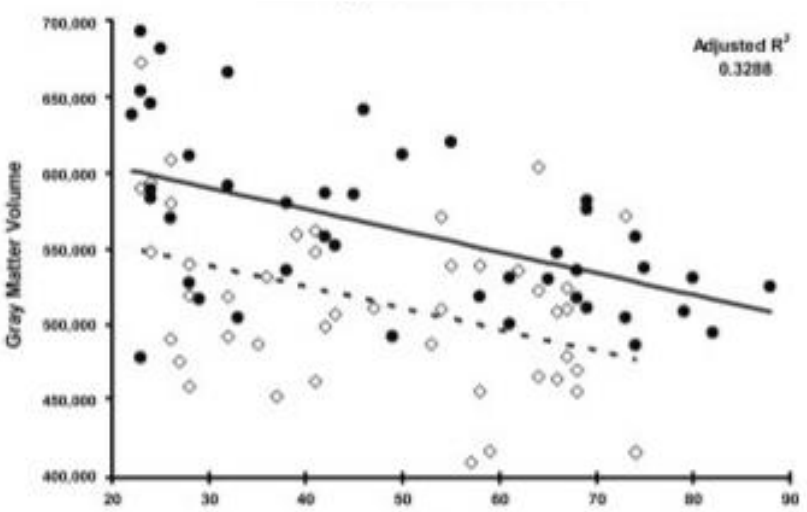
Volumen de Materia Blanca



Edad

Volumen de Materia Gris



Edad

Cognitive reserve in ageing and Alzheimer's disease

Yaakov Stern

The concept of cognitive reserve provides an explanation for differences between individuals in susceptibility to age-related brain changes or pathology related to Alzheimer's disease, whereby some people can tolerate more of these changes than others and maintain function. Epidemiological studies suggest that lifelong experiences, including educational and occupational attainment, and leisure activities in later life, can increase this reserve. For example, the risk of developing Alzheimer's disease is reduced in individuals with higher educational or occupational attainment. Reserve can conveniently be divided into two types: brain reserve, which refers to differences in the brain structure that may increase tolerance to pathology, and cognitive reserve, which refers to differences between individuals in how tasks are performed that might enable some people to be more resilient to brain changes than others. Greater understanding of the concept of cognitive reserve could lead to interventions to slow cognitive ageing or reduce the risk of dementia.

Introduction

The possibility of a connection between life experience and the prevalence of dementia has long been discussed. In 1982, Gurland[1] wrote "It is still an open matter whether there is an important sociocultural contribution to the prevalence of Alzheimer's and other forms of dementia occurring in the senium, but evidence now available is sufficiently intriguing to warrant further study of the issue". Kittner and colleagues[2] suggested that adjustment should be made for level of education when screening for dementia to avoid ascertainment bias, whereas Berkman[3] suggested that we must remain open to the view that "educational level and/or socioeconomic behavior correlated with it may be a genuine risk factor for senile dementia and are worthy of scientific exploration in their own right". Zhang and colleagues[4] reported that a low level of education was associated with increased prevalence of Alzheimer's disease and dementia in a probability sample survey of 5055 older people not admitted to care facilities in Shanghai, China. These observations sparked my interest in studying the association between aspects of life experience and dementia; subsequently I have undertaken a long-term research programme to investigate cognitive reserve. In this Personal View I present a theoretical account of cognitive reserve, summarise epidemiological research that has lent support to the concept, and describe imaging studies that have attempted to identify the neural substrates of cognitive reserve. I will also discuss the potential clinical implications of the concept of cognitive reserve. Although I discuss cognitive reserve in the context of Alzheimer's disease and normal ageing, it has also been reported to provide benefit in patients with vascular injury,[5–7] Parkinson's disease,[8] traumatic brain injury,[9] HIV,[10] neuropsychiatric disorders,[11] and multiple sclerosis.[12]

Brain reserve and cognitive reserve

The concept of reserve has been put forward to account for differences between individuals in susceptibility to age-related brain changes and pathology, such as that seen in Alzheimer's disease. Reserve is purported to act as a moderator between pathology and clinical outcome, thus accounting for the discontinuity. A convenient, although somewhat artificial, way to view cognitive reserve is to separate it into two main features: brain reserve and cognitive reserve.

The original concept of brain reserve was quantitative, for example the number of neurons or synapses available to be lost differs among individuals. This idea was supported by study findings that suggested the prevalence or incidence of dementia was lower in individuals with larger brains than in those with smaller brains.[13,14] I suggest that this is a passive model of brain reserve—ie, a large brain might simply be able to tolerate more pathology before it reaches the critical threshold for clinical symptoms to appear. By contrast, cognitive reserve is an active form of reserve in which brain function rather than brain size is the relevant variable. The concept of cognitive reserve suggests that the brain actively attempts to cope with pathology by using pre-existing cognitive-processing approaches or compensatory mechanisms.[15,16] Therefore, an individual with high cognitive reserve would cope better with the same amount of pathology than an individual with low cognitive reserve, even when brain size is the same.

Although the initial concept of brain reserve was entirely quantitative, several studies have suggested wider underlying biological features. For example, stimulating environments have been associated with neurogenesis[17,18] and upregulation of BDNF, which fosters neural plasticity and could impart reserve.[19] Brain reserve and cognitive reserve, therefore, seem to make independent and synergistic contributions to our understanding of individual differences in clinical resilience to brain pathology. Whether the two components of reserve interact remains unresolved.

Cognitive reserve was initially posited as a moderator between brain change and clinical outcome, but life experience may also prevent or minimise brain pathology. On a simple level, physical exercise has long been recognised to help prevent vascular disease. Likewise, participation in cognitively stimulating activities has been suggested to slow the rate of hippocampal atrophy in normal ageing,[20] and perhaps even to prevent

Cognitive reserve in ageing and Alzheimer's disease

Yaakov Stern

Proceso de **adaptabilidad** que ayuda a explicar los **diferentes grados de suceptibilidad** de las habilidades cognitivas y del funcionamiento cotidiano en relación con el envejecimiento cerebral y en presencia de procesos patológicos.

Current Neurology and Neuroscience Reports (2019) 19:1
https://doi.org/10.1007/s11910-019-0917-z

DEMENTIA (K MARDER, SECTION EDITOR)

CrossMark

Defining Cognitive Reserve and Implications for Cognitive Aging

Dentro de la Hipótesis de la Reserva Cognitiva existen tres constructos que deben ser diferenciados:

- Reserva Cerebral
- Reserva Cognitiva
- Mantenimiento Cerebral

COGNICION
INICIATIVA CUBANA EN SALUD COGNITIVA

• Reserva Cerebral

Journal of the International Neuropsychological Society (2002), **8**, 448–460.

DOI: 10.1017.S1355617701020240

CRITICAL REVIEW

What is cognitive reserve? Theory and research application of the reserve concept

YAAKOV STERN
Cognitive Neuroscience Division, G.H. Sergievsky Center, The Taub Institute, and Departments of Neurology, Psychiatry, and Psychology, Columbia University College of Physicians and Surgeons

La reserva cerebral (modelo pasivo) es definida en términos de la cantidad de daño que es asimilado por el sistema antes de expresarse clínicamente.

Modelo Pasivo

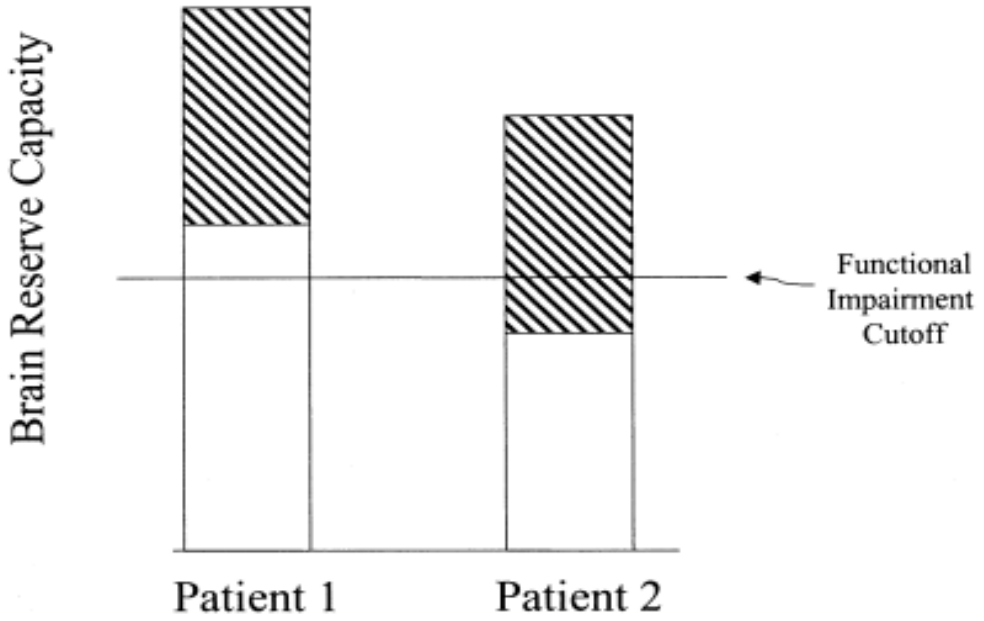


Fig. 1. The threshold or brain reserve model. In 2 patients with different amounts of brain reserve capacity (BRC), a lesion of a particular size results in a clinical deficit in a person with less BRC (Patient 2), because it exceeds the threshold of brain damage sufficient to produce that deficit. However, an individual with greater BRC could remain unaffected.

COGNICION
INICIATIVA CUBANA EN SALUD COGNITIVA

• Reserva Cognitiva •

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La reserva cognitiva (modelo activo) es definida en términos de resiliencia cognitiva, o el uso eficiente del "software".

Modelo Activo

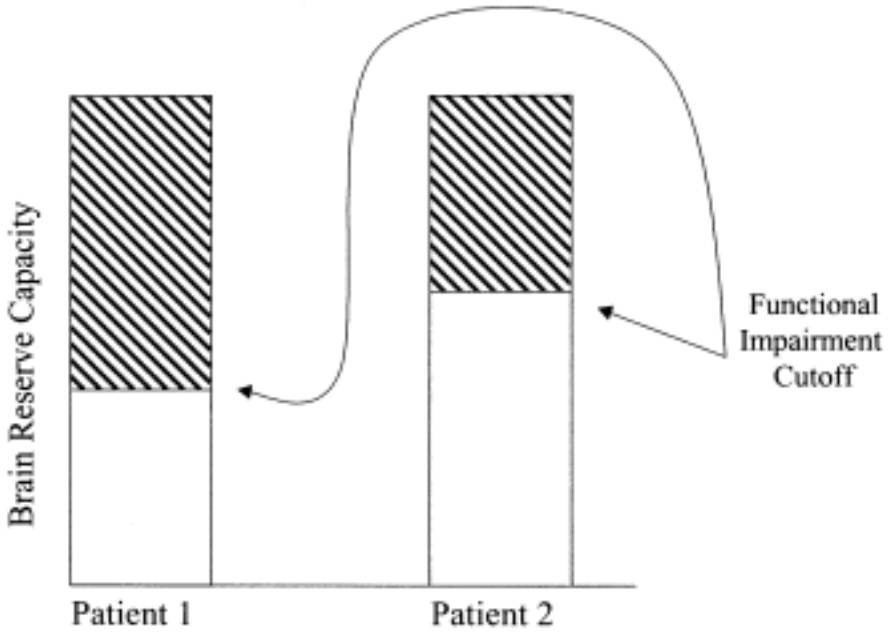

Fig. 4. The cognitive reserve model. Two patients have the *same* amount of brain reserve. However, Patient 1 has more cognitive reserve than Patient 2, in that Patient 1 uses more efficient processing mechanisms. As a result, Patient 1 can tolerate a *larger* lesion than Patient 2 before functional impairment is apparent.

COGNICION
INICIATIVA CUBANA EN SALUD COGNITIVA

• Mantenimiento Cerebral

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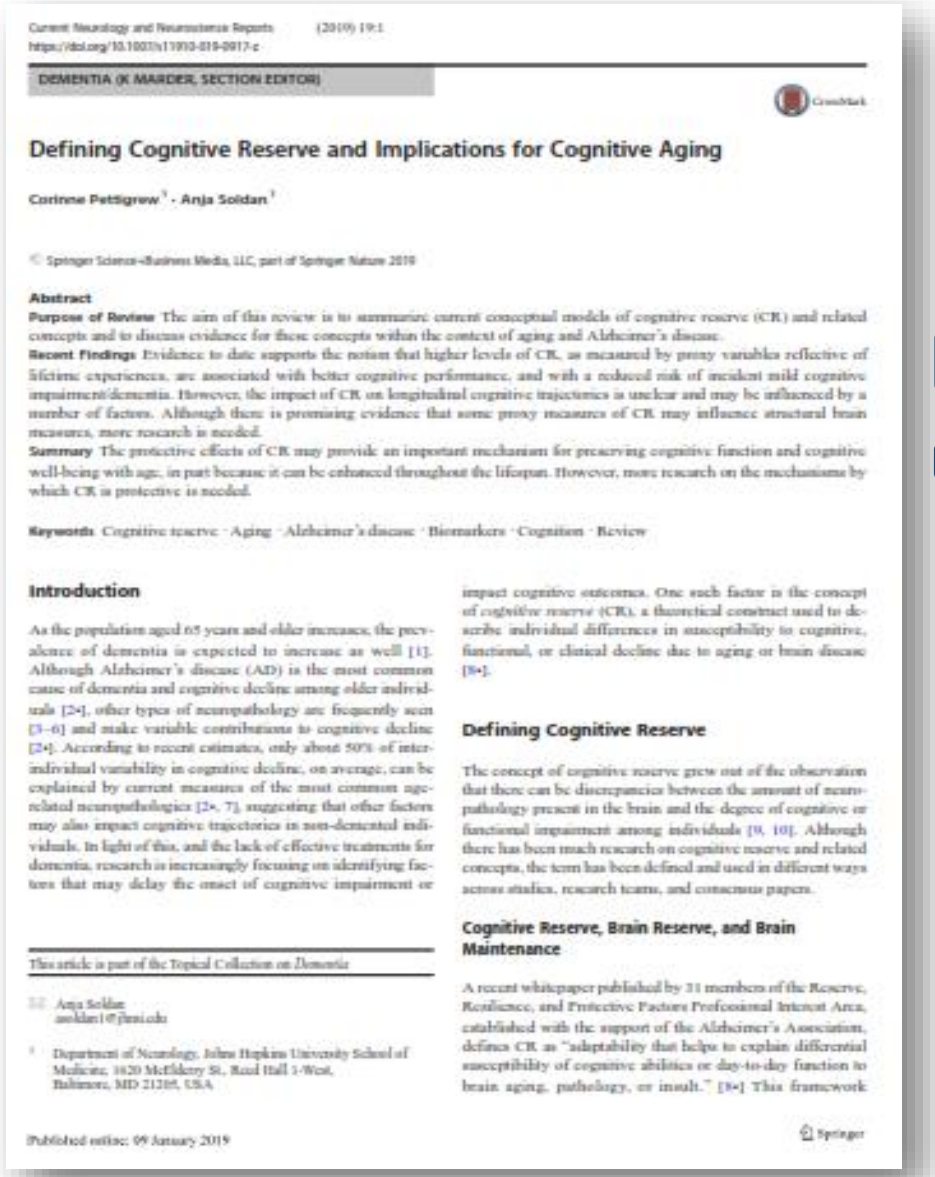
Hace refrencia al proceso de preservar y/o potenciar el funcionamiento cerebral y cognitivo a través de la vida, tomando en consideración las interacciones genéticas.



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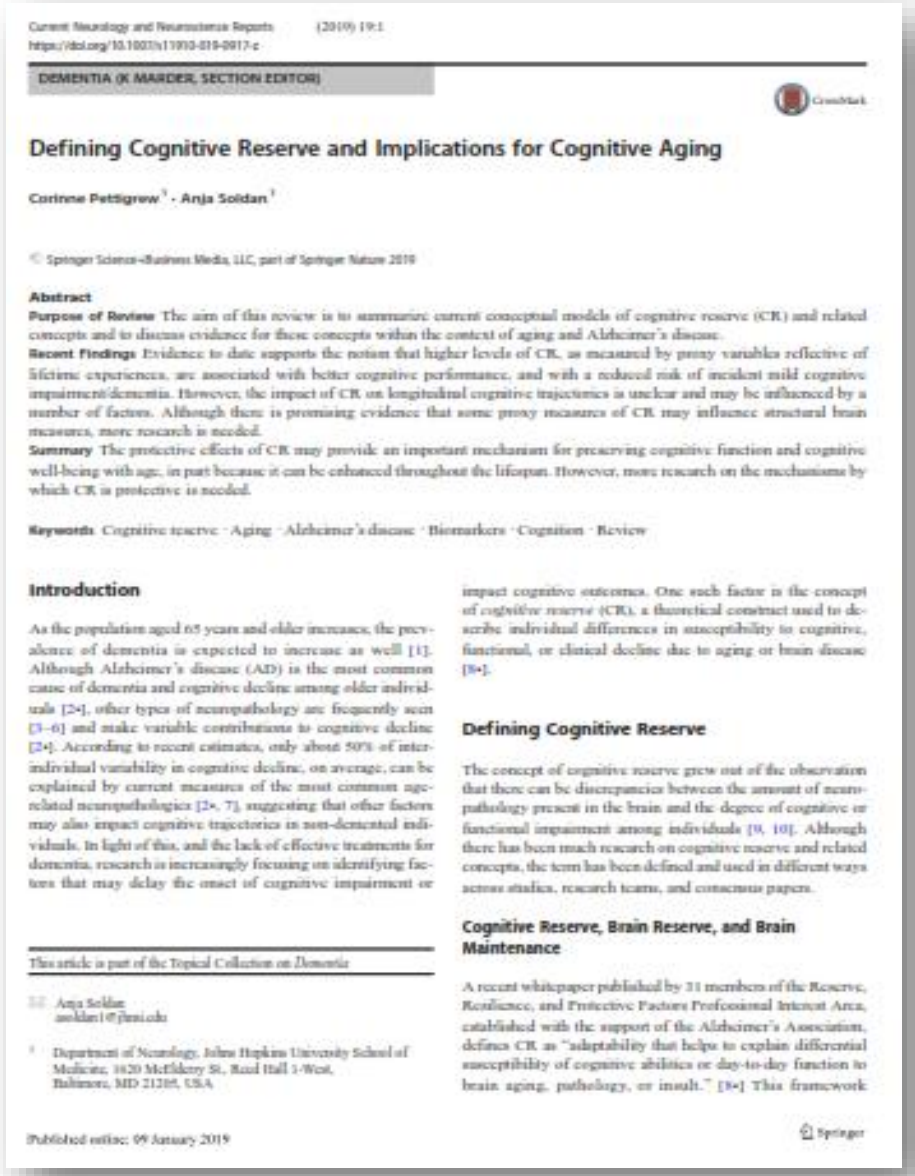
DEMENTIA (K MARDER, SECTION EDITOR)

Defining Cognitive Reserve and Implications for Cognitive Aging

Otros dos conceptos también deben ser diferenciados dentro del modelo (hipótesis) de la Reserva Cognitiva:

- Resistencia Cerebral
- Resiliencia Cerebral



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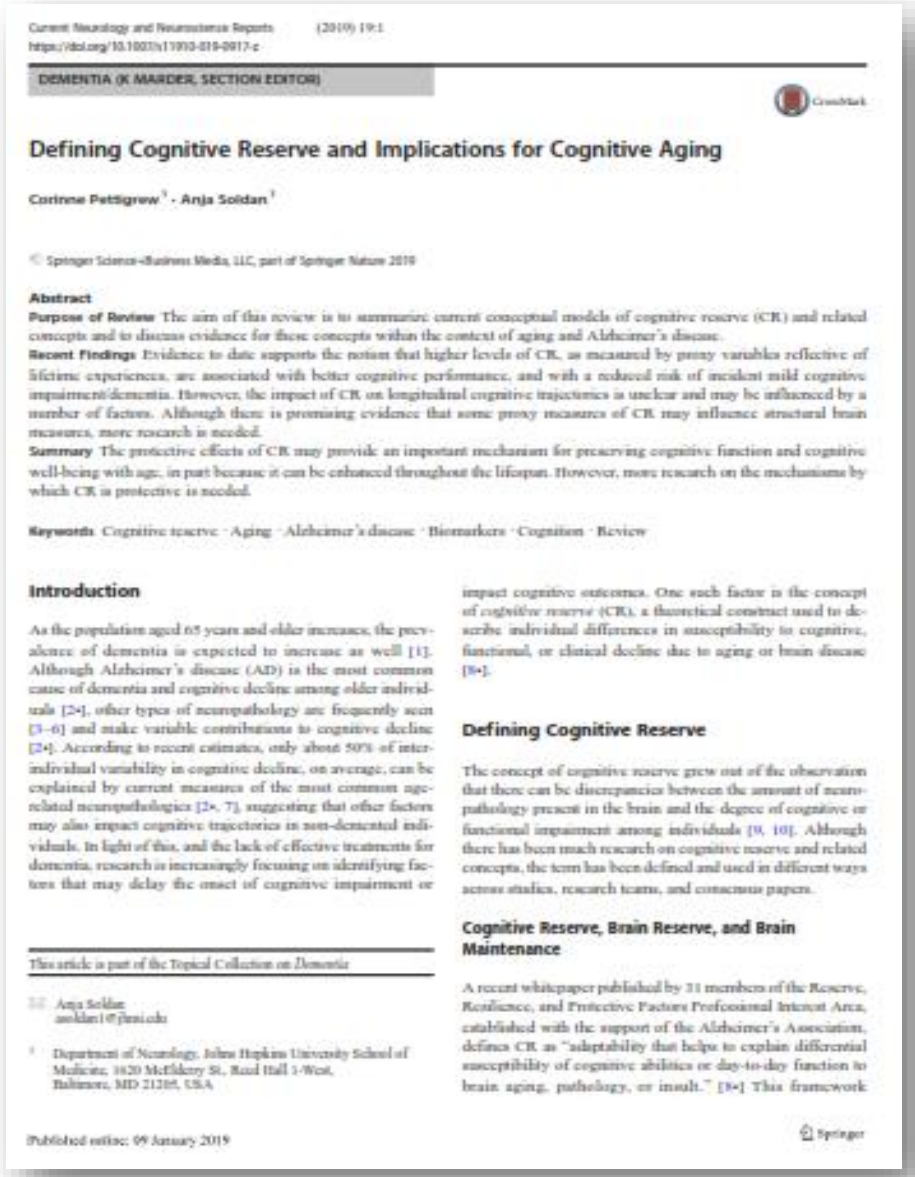
CrossMark

Defining Cognitive Reserve and Implications for Cognitive Aging

- **Resistencia Cerebral**

Mecanismo cerebral que subyace a la habilidad para resistir los procesos patológicos



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DEMENTIA (K MARDER, SECTION EDITOR)

CrossMark

Defining Cognitive Reserve and Implications for Cognitive Aging

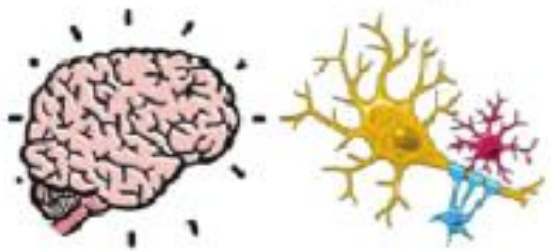
- **Resiliencia Cerebral**

Habilidad para manejar los efectos de la patología cerebral (por ejemplo la Enfermedad de Alzheimer) y que se expresa en un funcionamiento cognitivo superior al esperado

CEREBRO

- Cerebro Mayor
- Mayor Número de Neuronas
- Mayor Densidad Dendrítica

- Daño Cerebral Traumático
- Encefalitis
- Enfermedades Psiquiátricas
- Trastornos del Desarrollo

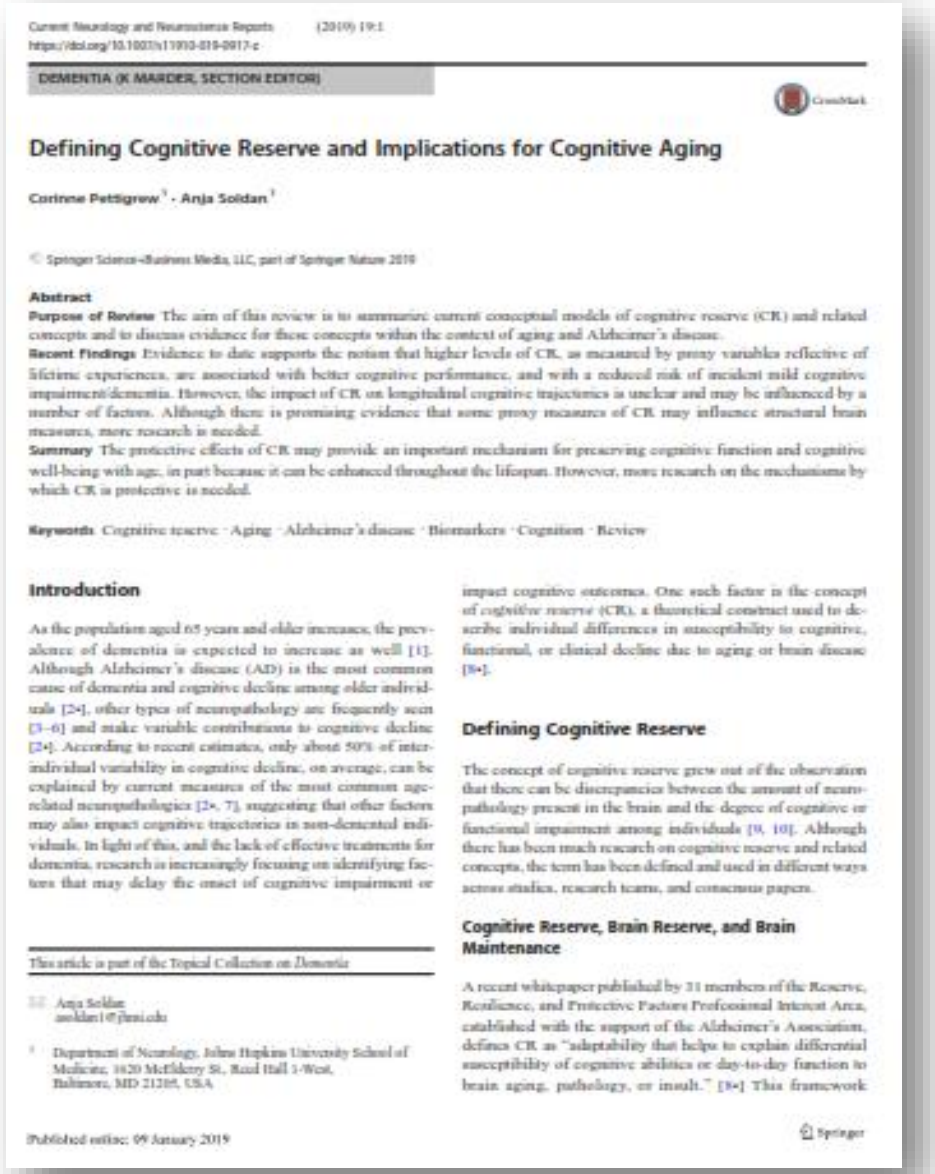


- Involucramiento Cognitivo
- Remediación Cognitiva
- Educación
- Actividades de Ocio
- Nutrición
- Estimulación Social

- Sedentarismo Cognitivo
- Nutrición Inadecuada
- Bajo Nivel de Instrucción
- Aislamiento Social

RESERVA CEREBRAL

RESERVA COGNITIVA



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DEMENTIA (K MARDER, SECTION EDITOR)

Defining Cognitive Reserve and Implications for Cognitive Aging

Corinne Pettigrew[1] · Anja Soldan[1]

Abstract

Purpose of Review The aim of this review is to summarize current conceptual models of cognitive reserve (CR) and related concepts and to discuss evidence for these concepts within the context of aging and Alzheimer's disease.

Recent Findings Evidence to date supports the notion that higher levels of CR, as measured by proxy variables reflective of lifetime experiences, are associated with better cognitive performance, and with a reduced risk of incident mild cognitive impairment/dementia. However, the impact of CR on longitudinal cognitive trajectories is unclear and may be influenced by a number of factors. Although there is promising evidence that some proxy measures of CR may influence structural brain measures, more research is needed.

Summary The protective effects of CR may provide an important mechanism for preserving cognitive function and cognitive well-being with age, in part because it can be enhanced throughout the lifespan. However, more research on the mechanisms by which CR is protective is needed.

Keywords Cognitive reserve · Aging · Alzheimer's disease · Biomarkers · Cognition · Review

Introduction

As the population aged 65 years and older increases, the prevalence of dementia is expected to increase as well [1]. Although Alzheimer's disease (AD) is the most common cause of dementia and cognitive decline among older individuals [2•], other types of neuropathology are frequently seen [3–6] and make variable contributions to cognitive decline [2•]. According to recent estimates, only about 50% of inter-individual variability in cognitive decline, on average, can be explained by current measures of the most common age-related neuropathologies [2•, 7], suggesting that other factors may also impact cognitive trajectories in non-demented individuals. In light of this, and the lack of effective treatments for dementia, research is increasingly focusing on identifying factors that may delay the onset of cognitive impairment or impact cognitive outcomes. One such factor is the concept of *cognitive reserve* (CR), a theoretical construct used to describe individual differences in susceptibility to cognitive, functional, or clinical decline due to aging or brain disease [8•].

Defining Cognitive Reserve

The concept of cognitive reserve grew out of the observation that there can be discrepancies between the amount of neuropathology present in the brain and the degree of cognitive or functional impairment among individuals [9, 10]. Although there has been much research on cognitive reserve and related concepts, the term has been defined and used in different ways across studies, research teams, and consensus papers.

Cognitive Reserve, Brain Reserve, and Brain Maintenance

A recent whitepaper published by 31 members of the Reserve, Resilience, and Protective Factors Professional Interest Area, established with the support of the Alzheimer's Association, defines CR as "adaptability that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult." [8•] This framework

This article is part of the Topical Collection on Dementia

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Published online: 09 January 2019

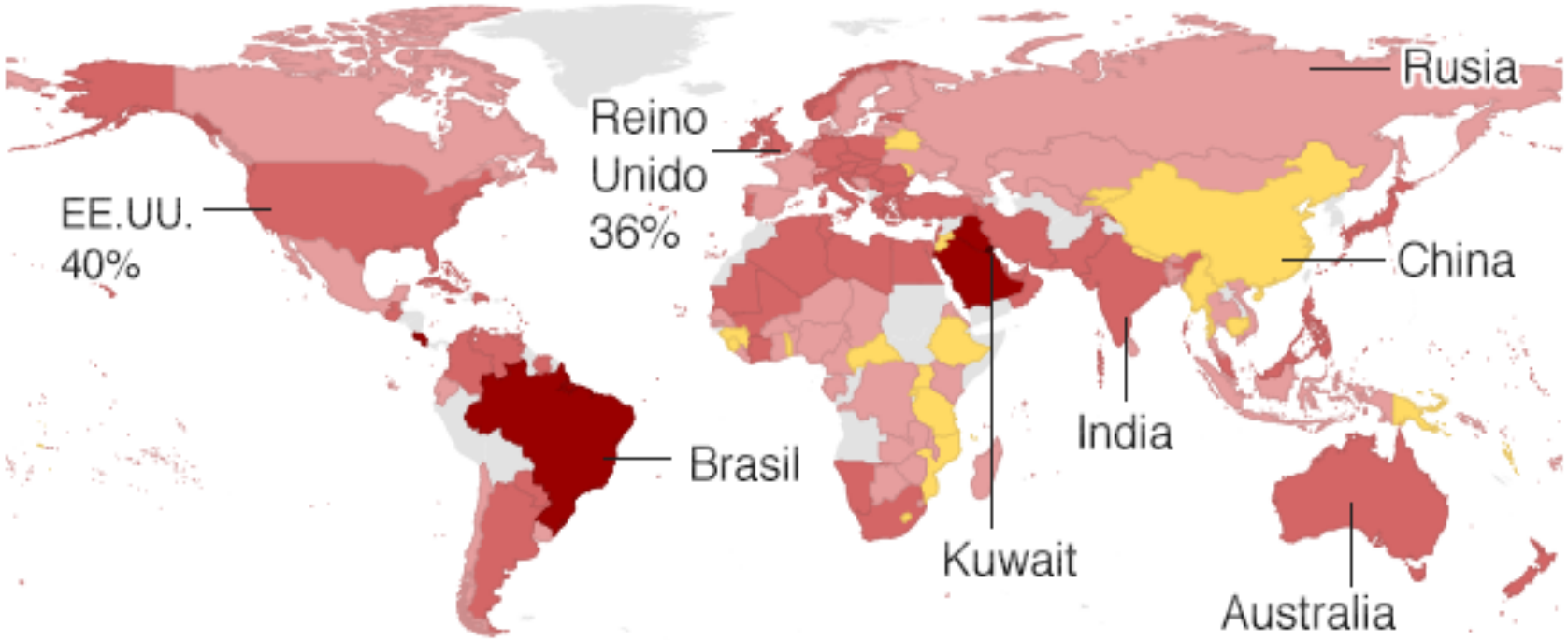
- La reserva cognitiva es un constructo teórico y como cualquier constructo no puede ser observado directamente
- La medida más común de la RC son los denominados "proxys", variables descriptivas que describen experiencias acumuladas a lo largo de la vida
- Dentro de los proxys más estudiados están la educación, ocupación, inteligencia, actividades de ocio, vínculos sociales, estatus socioeconómico

Inactividad global

MÁS INACTIVO
Kuwait
67%
de los adultos son inactivos

MÁS ACTIVO
Uganda
5.5%
de los adultos son inactivos

Adultos inactivos
- 0 - 15%
- 15 - 30%
- 30 - 45%
- 45 - 60%
- > 60%
- Sin datos



Fuente: The Lancet

BBC

Guía de actividad física

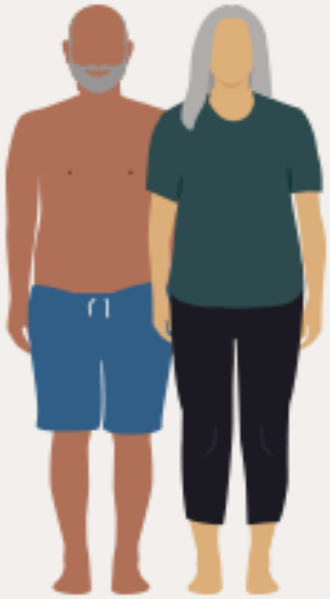
Niños 5-18

60 minutos de actividad física por día

Adultos 19-64

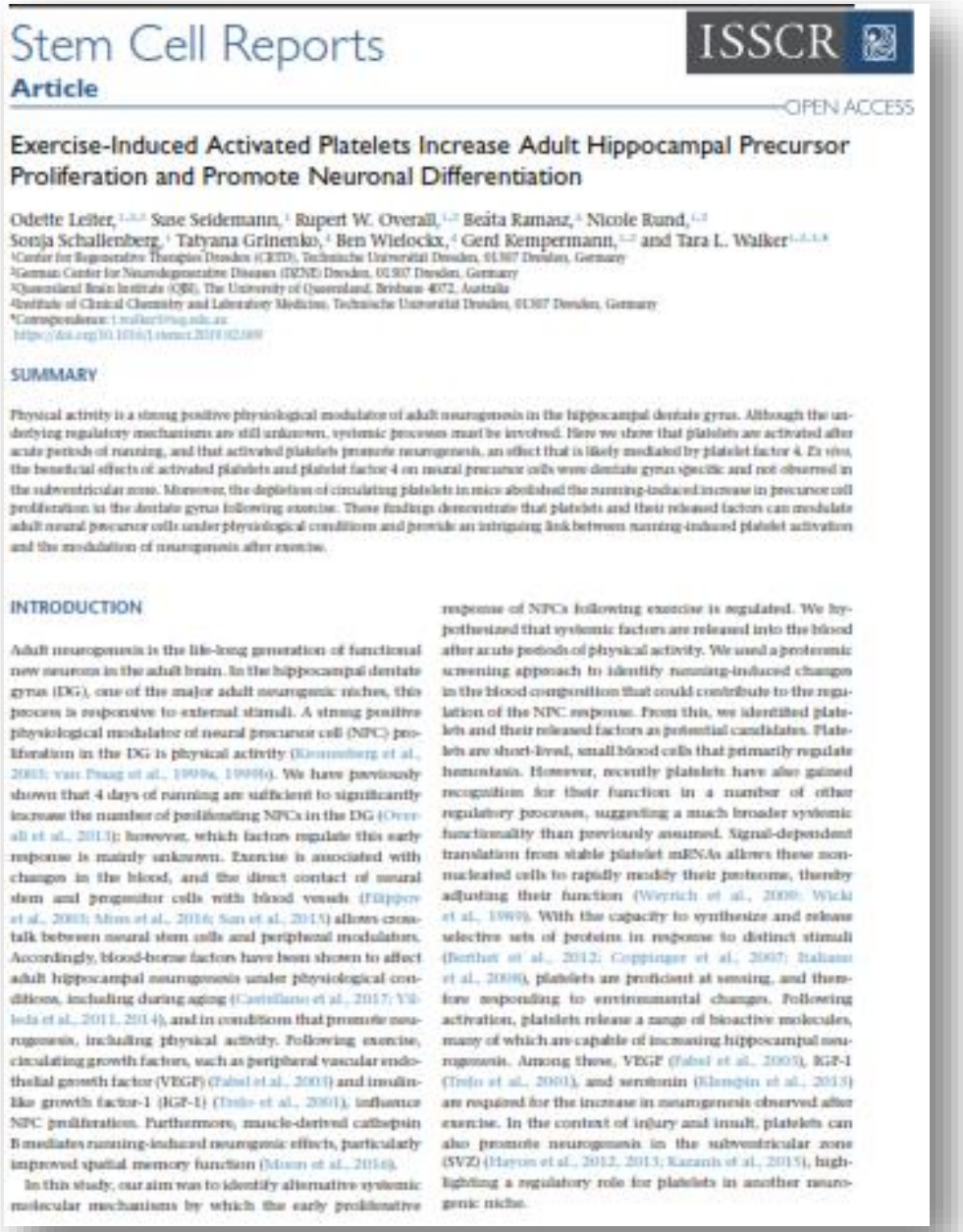
150 minutos de actividad aeróbica moderada por semana

Adultos +65



150 minutos de ejercicio aeróbico moderado por semana y ejercicios de fuerza dos veces por semana

Fuente: Public Health England



Stem Cell Reports

Article

OPEN ACCESS

Exercise-Induced Activated Platelets Increase Adult Hippocampal Precursor Proliferation and Promote Neuronal Differentiation

Odette Leiter,[1,2,3] Suse Seidemann,[1] Rupert W. Overall,[1,2] Beáta Ramasz,[4] Nicole Rund,[1,2] Sonja Schallenberg,[1] Tatyana Grinenko,[1] Ben Wielockx,[4] Gerd Kempermann,[1,2] and Tara L. Walker[1,2,3,5]

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https://doi.org/10.1016/j.stemcr.2018.02.009

SUMMARY

Physical activity is a strong positive physiological modulator of adult neurogenesis in the hippocampal dentate gyrus. Although the underlying regulatory mechanisms are still unknown, systemic processes must be involved. Here we show that platelets are activated after acute periods of running, and that activated platelets promote neurogenesis, an effect that is likely mediated by platelet factor 4. *In vivo*, the beneficial effects of activated platelets and platelet factor 4 on neural precursor cells were dentate gyrus specific and not observed in the subventricular zone. Moreover, the depletion of circulating platelets in mice abolished the running-induced increase in precursor cell proliferation in the dentate gyrus following exercise. These findings demonstrate that platelets and their released factors can modulate adult neural precursor cells under physiological conditions and provide an intriguing link between running-induced platelet activation and the modulation of neurogenesis after exercise.

INTRODUCTION

Adult neurogenesis is the life-long generation of functional new neurons in the adult brain. In the hippocampal dentate gyrus (DG), one of the major adult neurogenic niches, this process is responsive to external stimuli. A strong positive physiological modulator of neural precursor cell (NPC) proliferation in the DG is physical activity (Kronenberg et al., 2003; van Praag et al., 1999a, 1999b). We have previously shown that 4 days of running are sufficient to significantly increase the number of proliferating NPCs in the DG (Overall et al., 2013); however, which factors regulate this early response is mainly unknown. Exercise is associated with changes in the blood, and the direct contact of neural stem and progenitor cells with blood vessels (Filippov et al., 2003; Mirzadeh et al., 2010; Sun et al., 2015) allows cross-talk between neural stem cells and peripheral modulators. Accordingly, blood-borne factors have been shown to affect adult hippocampal neurogenesis under physiological conditions, including during aging (Castellano et al., 2017; Villeda et al., 2011, 2014), and in conditions that promote neurogenesis, including physical activity. Following exercise, circulating growth factors, such as peripheral vascular endothelial growth factor (VEGF) (Fabel et al., 2003) and insulin-like growth factor-1 (IGF-1) (Trejo et al., 2001), influence NPC proliferation. Furthermore, muscle-derived cathepsin B mediates running-induced neurogenic effects, particularly improved spatial memory function (Moon et al., 2016).

In this study, our aim was to identify alternative systemic molecular mechanisms by which the early proliferative response of NPCs following exercise is regulated. We hypothesized that systemic factors are released into the blood after acute periods of physical activity. We used a proteomic screening approach to identify running-induced changes in the blood composition that could contribute to the regulation of the NPC response. From this, we identified platelets and their released factors as potential candidates. Platelets are short-lived, small blood cells that primarily regulate hemostasis. However, recently platelets have also gained recognition for their function in a number of other regulatory processes, suggesting a much broader systemic functionality than previously assumed. Signal-dependent translation from stable platelet mRNAs allows these non-nucleated cells to rapidly modify their proteome, thereby adjusting their function (Weyrich et al., 2009; Wicki et al., 1989). With the capacity to synthesize and release selective sets of proteins in response to distinct stimuli (Berthet et al., 2012; Coppinger et al., 2007; Italiano et al., 2008), platelets are proficient at sensing, and therefore responding to environmental changes. Following activation, platelets release a range of bioactive molecules, many of which are capable of increasing hippocampal neurogenesis. Among these, VEGF (Fabel et al., 2003), IGF-1 (Trejo et al., 2001), and serotonin (Klempin et al., 2013) are required for the increase in neurogenesis observed after exercise. In the context of injury and insult, platelets can also promote neurogenesis in the subventricular zone (SVZ) (Hayon et al., 2012, 2013; Kazanis et al., 2015), highlighting a regulatory role for platelets in another neurogenic niche.

Stem Cell Reports

Article

OPEN ACCESS

Exercise-Induced Activated Platelets Increase Adult Hippocampal Precursor Proliferation and Promote Neuronal Differentiation

Cuando se disminuye experimentalmente la circulación de plaquetas se suprime el efecto beneficioso del ejercicio físico, interrumpiendo la proliferación de la neurogénesis en el giro dentado del impocampo

*Nuevas fronteras: Relación **Emoción-Cognición***

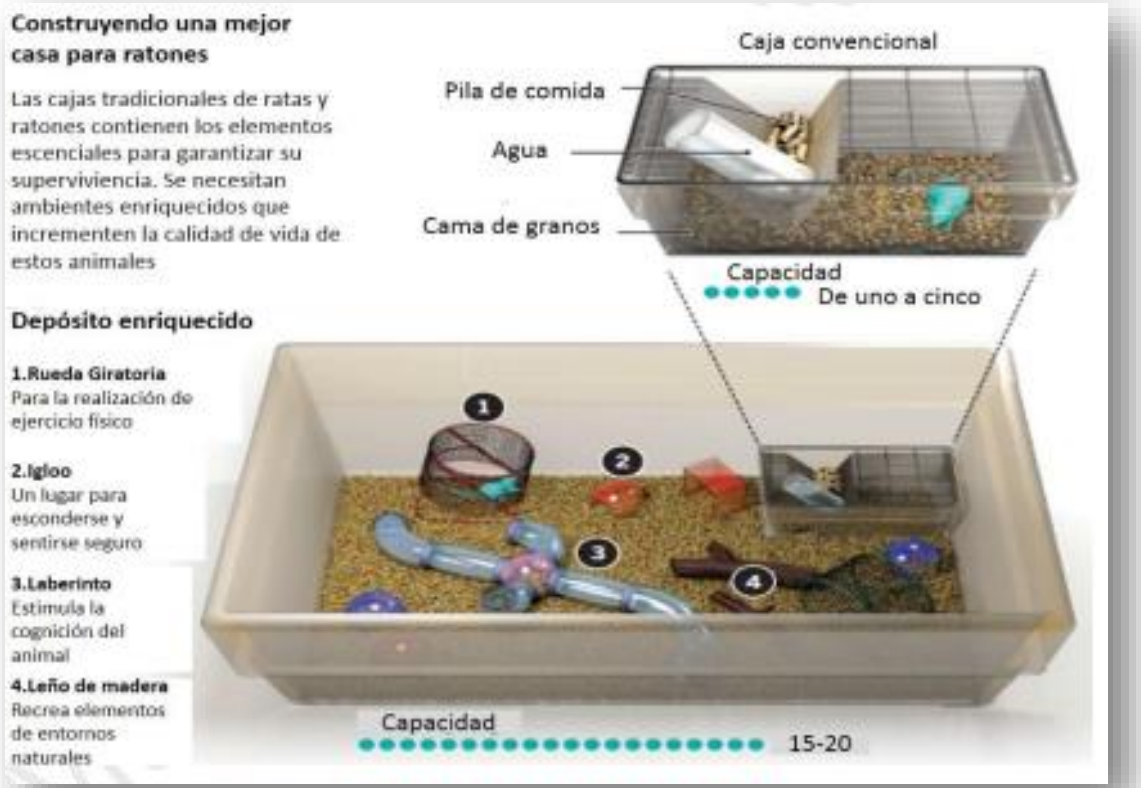
Contents lists available at ScienceDirect

Neuroscience Research

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

¿Emociones positivas y Cognición?

Neurogenesis in the dentate gyrus of the rat hippocampus enhanced by tickling stimulation with positive emotion



El fenómeno del Aislamiento Social

RESEARCH ARTICLE

Social isolation, cognitive reserve, and cognition in healthy older people

Isobel E. M. Evans[1]*, David J. Llewellyn[2], Fiona E. Matthews[3,4], Robert T. Woods[5], Carol Brayne[6], Linda Clare[1,2,7,8], on behalf of the CFAS-Wales research team[¶]

1 Centre for Research in Ageing and Cognitive Health (REACH), School of Psychology, University of Exeter, Exeter, United Kingdom, 2 University of Exeter Medical School, Exeter, United Kingdom, 3 Institute of Health and Society, Faculty of Medicine, Newcastle University, Newcastle, United Kingdom, 4 MRC Biostatistics Unit, Institute of Public Health, University of Cambridge, Cambridge, United Kingdom, 5 Dementia Services

- Luego de controlar la edad, el sexo, el nivel educacional y las limitaciones físicas, el aislamiento social mostró una asociación significativa con el funcionamiento cognitivo luego de un perido de 2 años.
- Los autores concluyeron que ***mantener un estilo de vida socialmente activo, incrementaba la reserva y beneficiaba el funcionamiento cognitivo global***.

RESEARCH ARTICLE

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OPEN ACCESS Freely available online

PLoS one

Lifespan Mental Activity Predicts Diminished Rate of Hippocampal Atrophy

Michael J. Valenzuela[1,2]*, Perminder Sachdev[1,2], Wei Wen[1,2], Xiaohua Chen[1,2], Henry Brodaty[1,3,4]

1 School of Psychiatry, University of New South Wales, Sydney, Australia, **2** The Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia, **3** Aged Care Psychiatry, Prince of Wales Hospital, Sydney, Australia, **4** Primary Dementia Collaborative Research Centre, University of New South Wales, Sydney, Australia

Abstract

Objective: Epidemiological studies suggest that complex mental activity may reduce the risk for dementia, however an underlying mechanism remains unclear. Our objective was to determine whether individual differences in lifespan complex mental activity are linked to altered rates of hippocampal atrophy independent of global measures of neurodegeneration.

Methods: Thirty seven healthy older individuals had their complex mental activity levels estimated using the Lifetime of Experiences Questionnaire (LEQ) and completed serial MRI investigations at baseline and three years follow-up. Hippocampal volume and semi-automatic quantitation of whole brain volume (WBV) and white matter hyperintensities (WMHs) were compared at both time points.

Results: Higher LEQ scores were correlated with hippocampal volume independent of covariates at the three year follow-up stage ($r = 0.43$, $p = 0.012$). Moreover, those with higher LEQ scores experienced less hippocampal atrophy over the follow-up period ($r = 0.41$, $p = 0.02$). High LEQ individuals had less than half the hippocampal volume decline of low LEQ individuals in a multivariate analysis ($F = 4.47$, $p = 0.042$). No parallel changes were found in measures of WBV and WMHs.

Conclusions: High level of complex mental activity across the lifespan was correlated with a reduced rate of hippocampal atrophy. This finding could not be explained by general differences in intracranial volume, larger hippocampi at baseline, presence of hypertensive disease, gender or low mood. Our results suggest that neuroprotection in medial temporal lobe may be one mechanism underlying the link between mental activity and lower rates of dementia observed in population-based studies. Additional studies are required to further explore this novel finding.

- **Evaluaron 37 adultos mayores saludables que realizaron el completamiento de actividades mentales en dos niveles: complejas y poco complejas.**

- **Realizaron un seguimiento de 3 años evaluando el volumen hipocampal, volumen cerebral global, así como la hiperintensidad de la materia blanca.**

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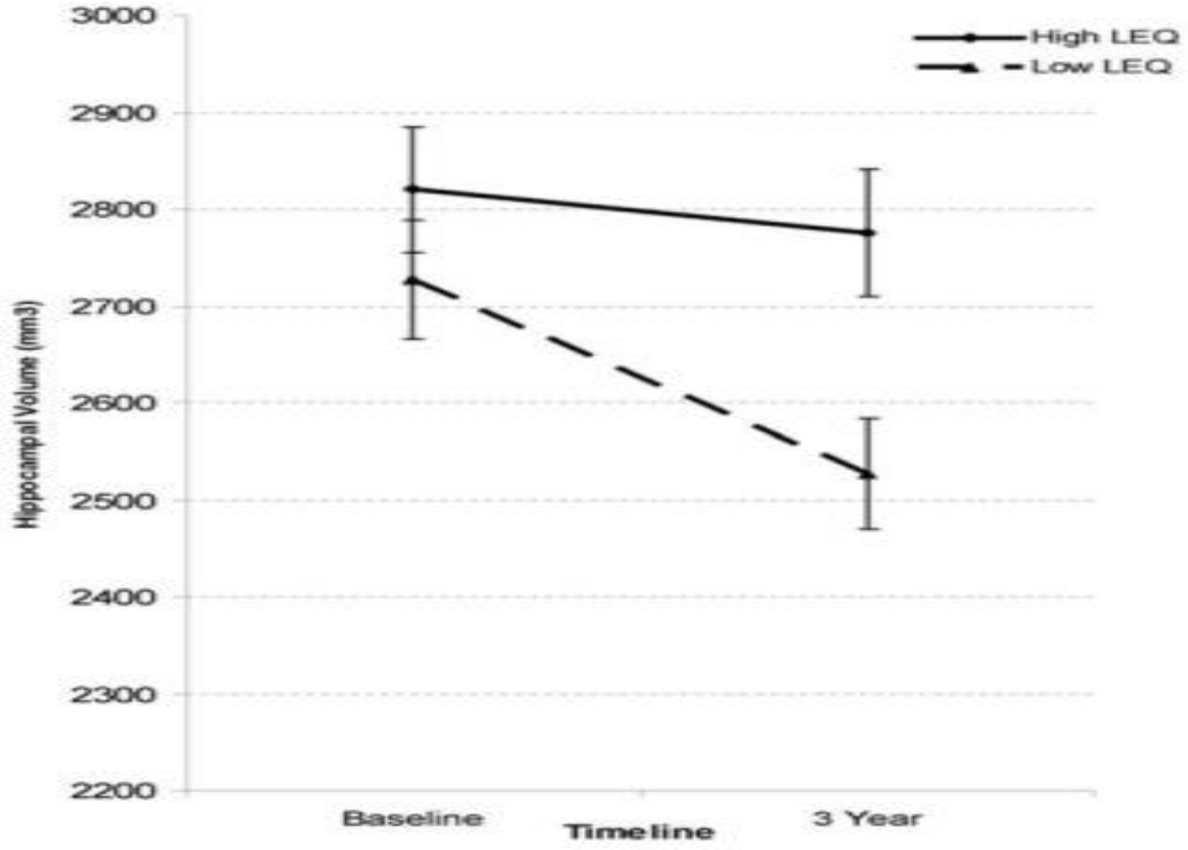


Figure 1. Average hippocampal volume (across right and left sides) in high (solid) and low (dashed) LEQ groups at baseline and 3 year follow-up. Error bars represent standard error of mean. *p-value after covariate control for age, gender, hypertension, baseline volume and total intracranial volume.
doi:10.1371/journal.pone.0002598.g001

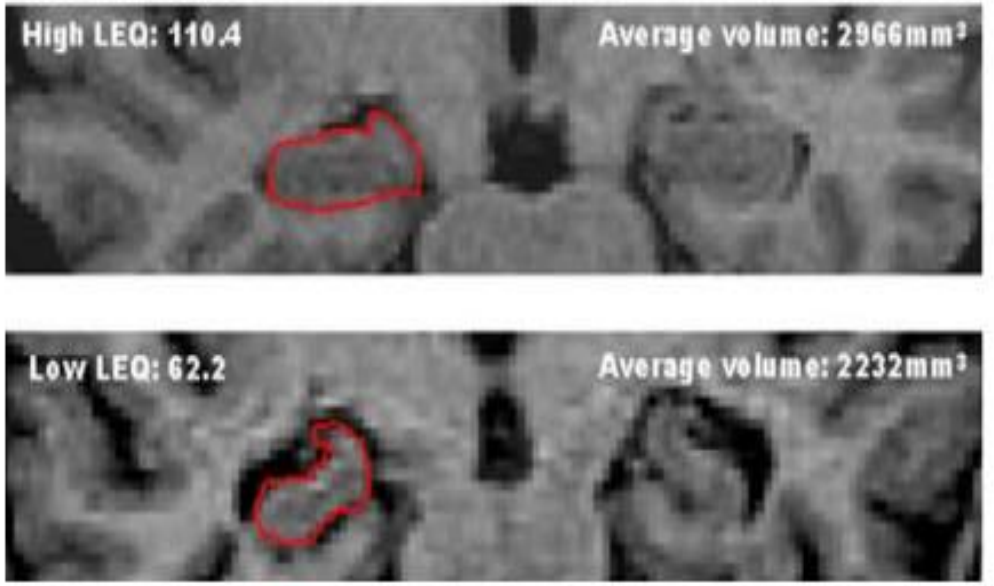
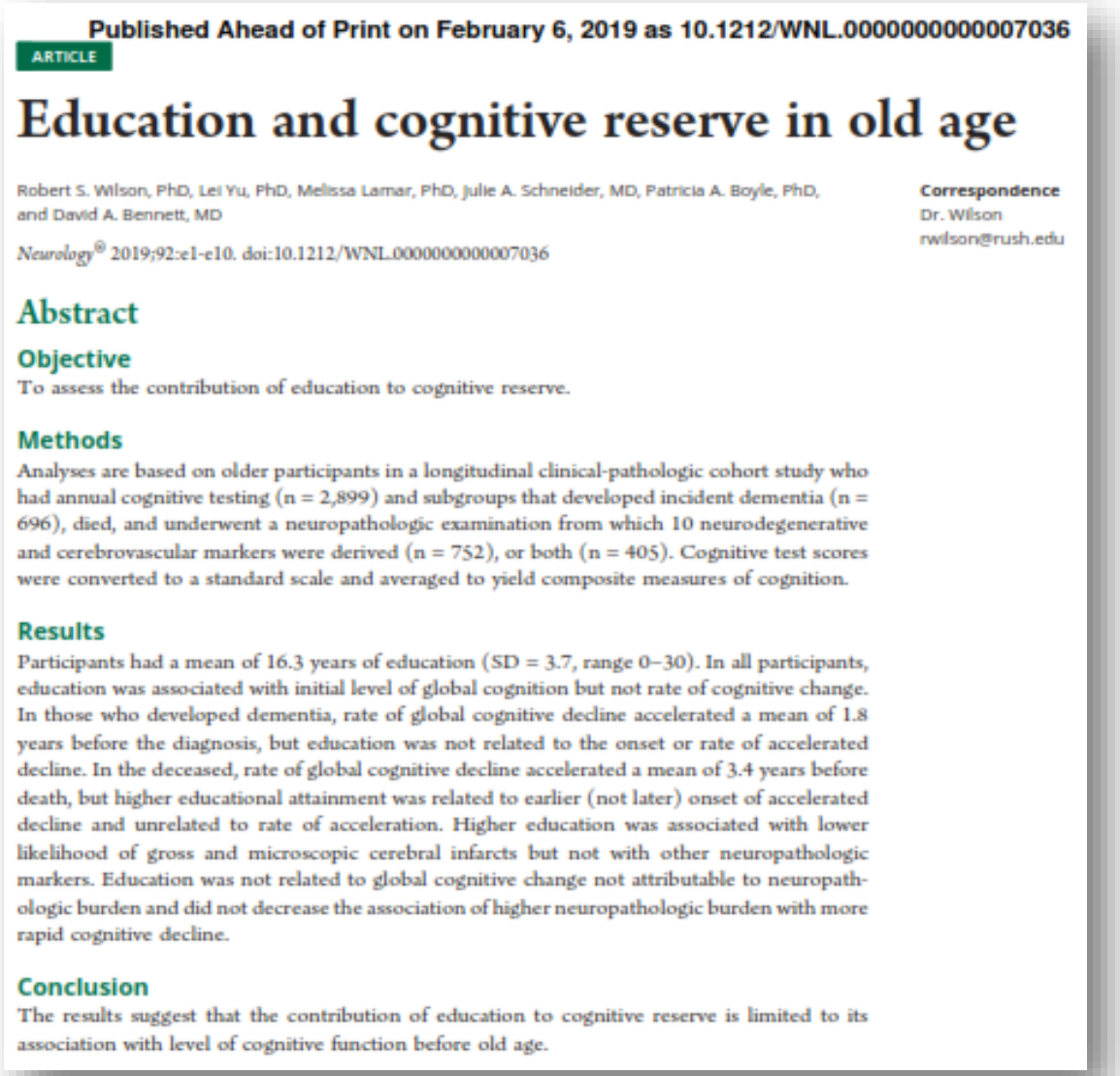


Figure 3. Examples of hippocampal volumes from a high and low LEQ individual at the 3 year follow-up stage. Note the relative increase in the volume of the inferior horn of the lateral ventricle. Average volumes refer to the mean across right and left sides. Right hippocampus tracing shown in red.
doi:10.1371/journal.pone.0002598.g003



Published Ahead of Print on February 6, 2019 as 10.1212/WNL.0000000000007036

ARTICLE

Education and cognitive reserve in old age

Robert S. Wilson, PhD, Lei Yu, PhD, Melissa Lamar, PhD, Julie A. Schneider, MD, Patricia A. Boyle, PhD, and David A. Bennett, MD

Correspondence
Dr. Wilson
rwilson@rush.edu

Neurology® 2019;92:e1-e10. doi:10.1212/WNL.0000000000007036

Abstract

Objective

To assess the contribution of education to cognitive reserve.

Methods

Analyses are based on older participants in a longitudinal clinical-pathologic cohort study who had annual cognitive testing (n = 2,899) and subgroups that developed incident dementia (n = 696), died, and underwent a neuropathologic examination from which 10 neurodegenerative and cerebrovascular markers were derived (n = 752), or both (n = 405). Cognitive test scores were converted to a standard scale and averaged to yield composite measures of cognition.

Results

Participants had a mean of 16.3 years of education (SD = 3.7, range 0–30). In all participants, education was associated with initial level of global cognition but not rate of cognitive change. In those who developed dementia, rate of global cognitive decline accelerated a mean of 1.8 years before the diagnosis, but education was not related to the onset or rate of accelerated decline. In the deceased, rate of global cognitive decline accelerated a mean of 3.4 years before death, but higher educational attainment was related to earlier (not later) onset of accelerated decline and unrelated to rate of acceleration. Higher education was associated with lower likelihood of gross and microscopic cerebral infarcts but not with other neuropathologic markers. Education was not related to global cognitive change not attributable to neuropathologic burden and did not decrease the association of higher neuropathologic burden with more rapid cognitive decline.

Conclusion

The results suggest that the contribution of education to cognitive reserve is limited to its association with level of cognitive function before old age.

- En 2019 se publiccará un importante artículo que explica la relación entre el progreso de la Enfermedad de Alzheimer y rendimiento cognitivo global.
- El artículo se realizó desde un diseño longitudinal con un tiempo mínimo de 4 años.

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- El estudio examinó los datos de forma longitudinal de un total de 2899 adultos mayores
- 1,239 procedentes del *Religius Orders Study* y 1660 del *Memory and Aging Project*
- El seguimiento fue de la menos 4 años
- 1044 individuos participantes fallecieron luego de los primeros 4 años de seguimiento
- Se realizó autopsia cerebral a 958% (958 personas)
- Edad media de inicio del estudio 87.7 años y al concluir 91.3 años
- Media de años de educación 16.3

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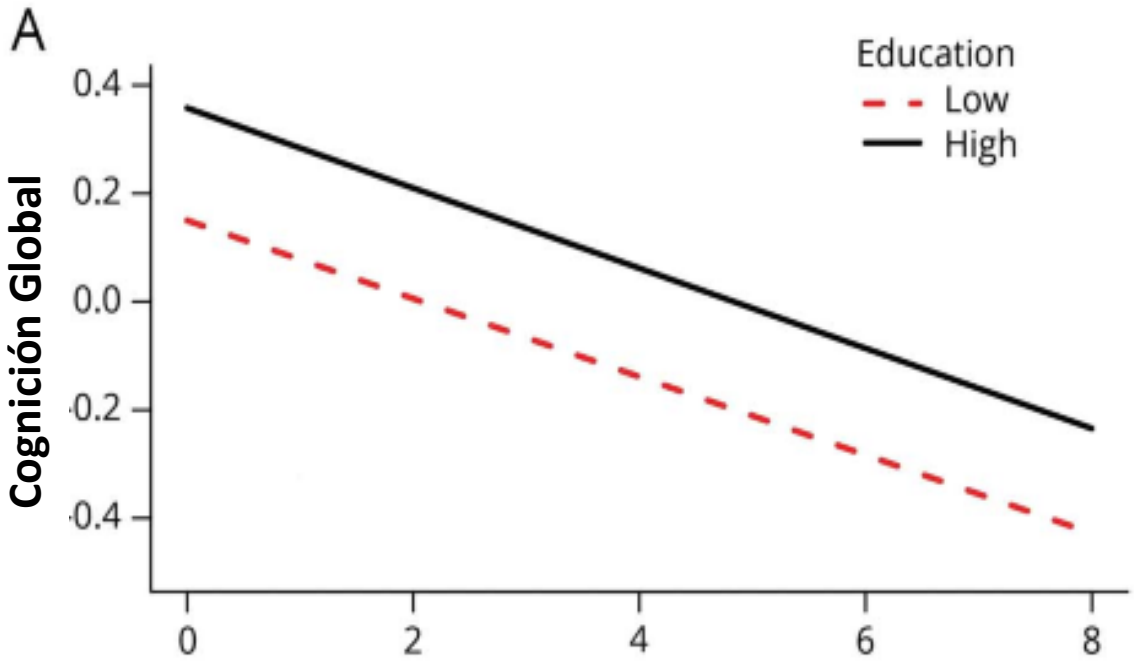
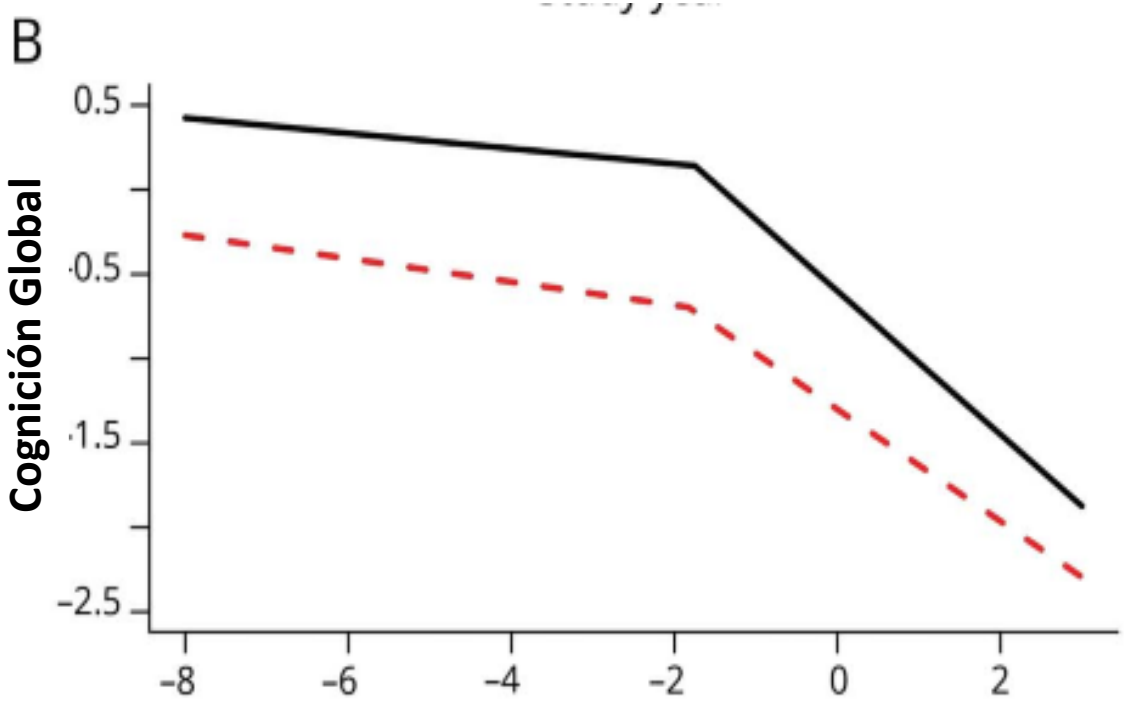


Duración del estudio



Años antes/después del diagnóstico de demencia

Published Ahead of Print on February 6, 2019 as 10.1212/WNL.0000000000007036

ARTICLE

Education and cognitive reserve in old age

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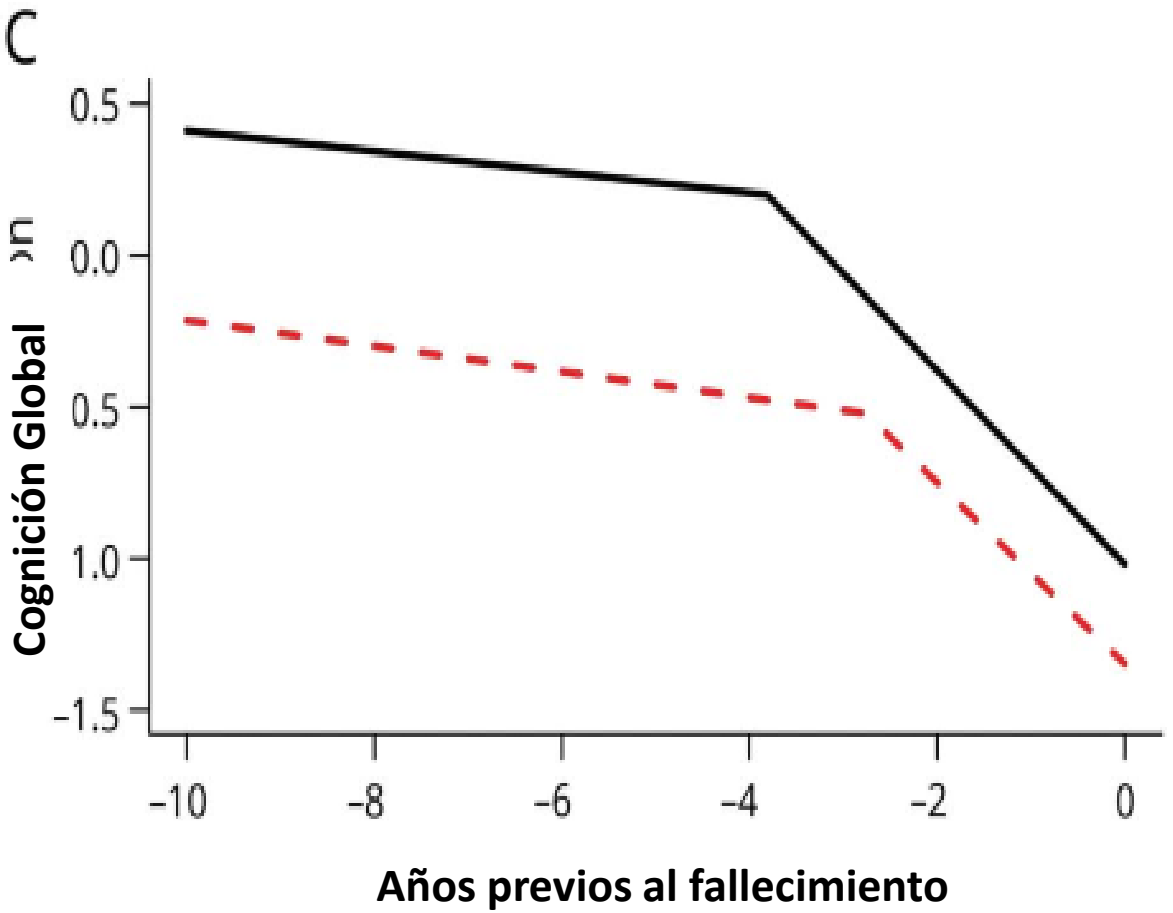
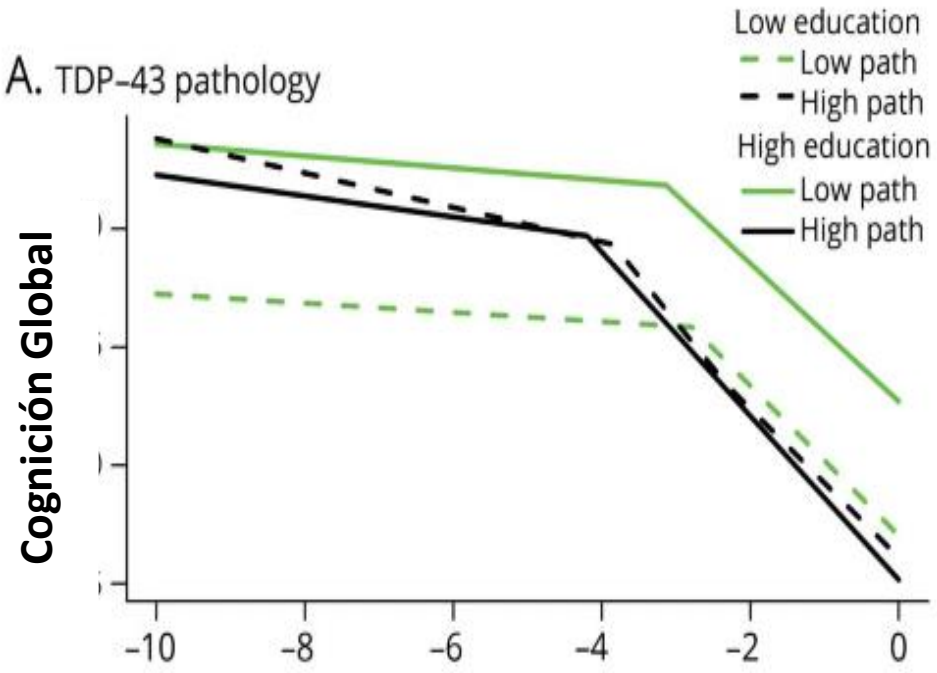
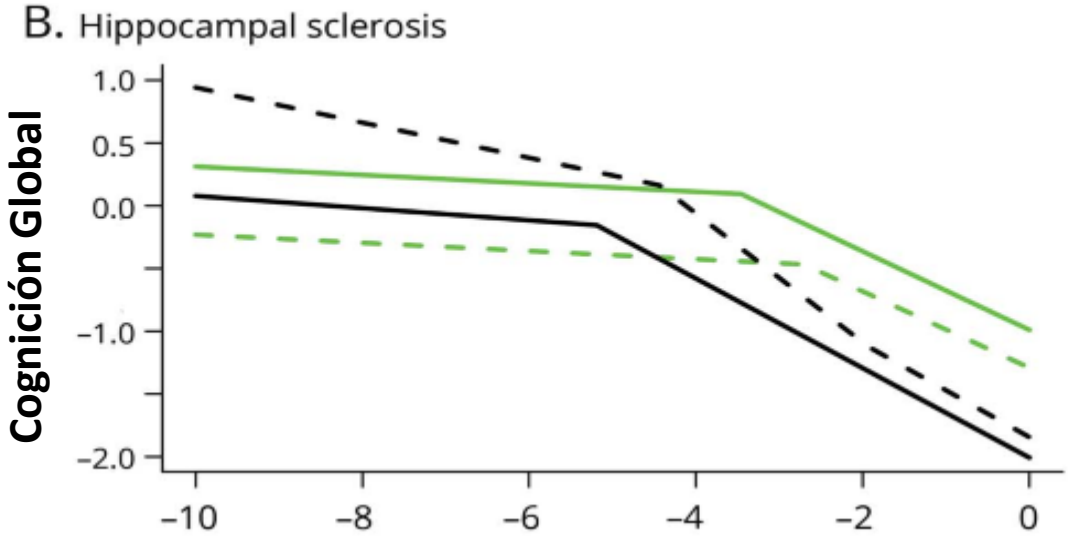
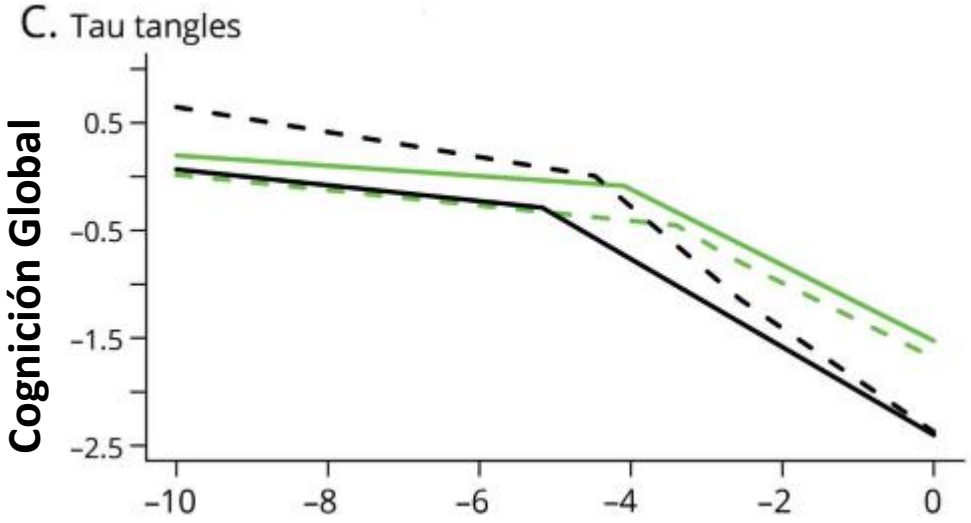








Marcadores biológicos de neurodegeneración en asociación con el nivel de educación

Cognitive reserve in ageing and Alzheimer's disease

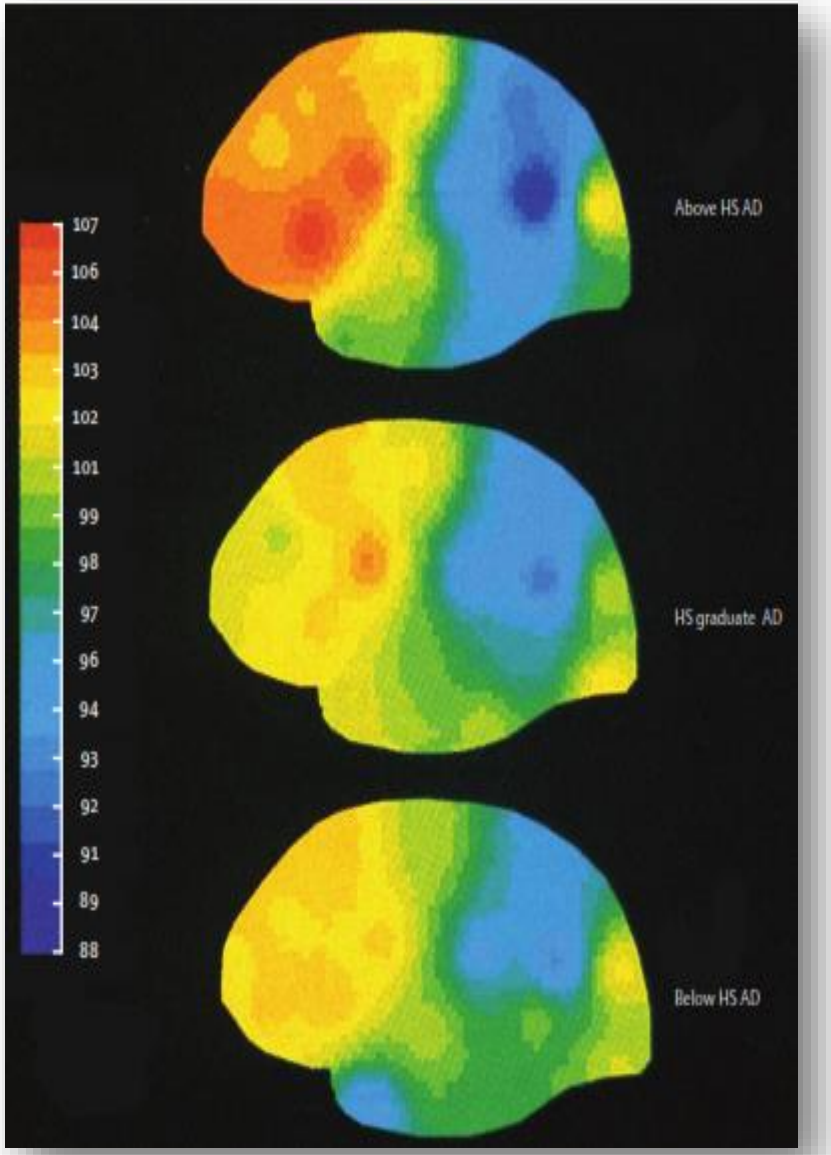
Yaakov Stern

Neuroimaging studies of cognitive reserve

Resting regional cerebral blood flow

Epidemiological studies suggest that at any given level of clinical severity in Alzheimer's disease, the degree of pathology will be greater in individuals with higher cognitive reserve than in those with lower cognitive reserve (figure 2). This idea was tested by assessment of resting regional cerebral blood flow as a surrogate for Alzheimer's disease pathology.[30,31] In patients matched for clinical severity, an inverse relation was found between resting regional cerebral blood flow and years of education.[32] Higher level of education was associated with greater depletion of blood flow in the parietotemporal area (figure 3), where PET changes are seen in patients with Alzheimer's disease. This observation provided an initial indication that patients with higher cognitive reserve had more Alzheimer's disease pathology than those with lower cognitive reserve even though they appeared clinically similar. Similar associations have

"Mayores niveles de educación fueron asociados con una disminución del flujo sanguíneo en la áreas parietotemporales...estas observaciones indican que en los pacientes con mayor reserva cognitiva existe mayor patología de Alzheimer que quienes tienen menos reserva cognitiva, a pesar de parecer similares clínicamente."

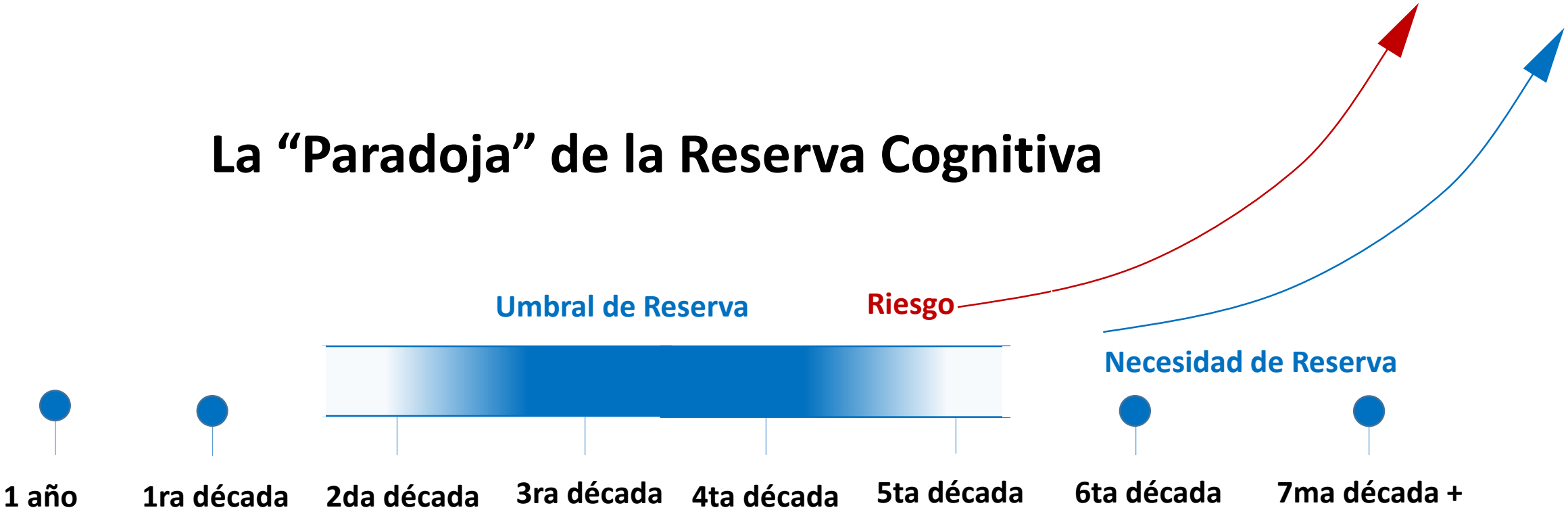


MMENTARY

Cognitive ability in old age is predetermined by age 20 y

Denise C. Park[a,1]

La “Paradoja” de la Reserva Cognitiva



¿Cómo evaluar la Reserva Cognitiva en el contexto clínico e investigativo?

ORIGINAL

Escala de reserva cognitiva: ajuste del modelo teórico y baremación

Irene León-Estrada, Juan García-García, Lola Roldán-Tapia

Introducción. La teoría de la reserva cognitiva contribuiría a explicar las diferencias en el rendimiento intelectual en sujetos con deterioro cognitivo similar y en sujetos sanos. Sin embargo, son necesarios más datos psicométricos que garanticen el uso de los instrumentos de medición de reserva cognitiva.

Objetivo. Aportar evidencias de validez respecto a la estructura interna de la escala de reserva cognitiva (ERC) y establecer un baremo de referencia para la interpretación de sus puntuaciones.

Sujetos y métodos. Un total de 172 sujetos completaron la ERC y fueron distribuidos en dos grupos en función de la edad: 18-64 años (n = 110) y 65-88 años (n = 62).

Resultados. El análisis factorial mediante modelos de ecuaciones estructurales exploratorios indicó un moderado ajuste de los datos al modelo propuesto. En general, los índices de discriminación fueron correctos (entre 0,21 y 0,50), y se registró congruencia entre los ítems a lo largo de los periodos de juventud, adultez y madurez para ambos grupos de edad. Se observaron valores adecuados del índice de fiabilidad (alfa de Cronbach: 0,80) y de los errores típicos de medida (medias: 51,80 ± 11,11).

Conclusiones. La ERC se enmarcaría dentro del modelo teórico hipotetizado y las puntuaciones podrían interpretarse mediante el baremo ofrecido, lo que avalaría su empleo en la investigación en este campo.

Palabras clave. Escala. Medición. Modelo teórico. Reserva cerebral. Reserva cognitiva. Validez.

Introducción

La teoría de reserva distingue entre reserva cerebral (modelo pasivo), que entiende que las personas se van a diferenciar en su capacidad para acumular patología en el cerebro hasta alcanzar un determinado umbral que desencadene el inicio de la manifestación de los síntomas, y reserva cognitiva (modelo activo), que postula que las diferencias entre los individuos se van a registrar en su capacidad para emplear procesos cognitivos ya existentes o mecanismos compensatorios que dilaten la manifestación del deterioro cognitivo [1]. Bajo esta última perspectiva, Stern [1] ha incluido los conceptos de reserva neural y compensación neural. De este modo, las personas sanas con mayor reserva neural van a realizar procesamientos cognitivos más eficientes ante la aparición de un daño cerebral. En el caso de la compensación neural, las diferencias individuales ante la neuropatología ya existente se asientan en la capacidad para hacer uso de circuitos alternativos que permitan mantener la destreza en la resolución de tareas. En definitiva, la reserva cognitiva se aplica a personas sanas y a personas con daño o lesión cerebral en la línea común de retrasar el deterioro cognitivo, y podría explicar las diferencias individuales ante una alteración cerebral o ante el propio envejecimiento sano.

El término 'reserva cognitiva' nace con la idea de ofrecer una explicación teórica a las discrepancias observadas entre patología cerebral y rendimiento cognitivo [2], esto es, a las diferencias individuales ante un daño o deterioro cerebral similar y la ejecución cognitiva mostrada. Según esta teoría, los sujetos con más reserva cognitiva harán frente de forma más eficaz a lesiones cerebrales y mostrarán más tardíamente la clínica correspondiente [3].

La relevancia del término reserva cognitiva recae en la repetida asociación entre una mayor reserva y una ejecución cognitiva mejor de la estimada, a pesar de la neuropatología o la afectación cerebral subyacente [4,5]. Además, se ha sugerido la capacidad predictiva de la reserva cognitiva en sujetos presintomáticos que posteriormente acaban desarrollando una demencia, como enfermedad de Alzheimer [6]. Por lo tanto, una adecuada medición de la reserva cognitiva junto con el empleo de otro tipo de técnicas, como de neuroimagen, podría favorecer el diagnóstico temprano de procesos neuropatológicos, supondría un avance en la investigación de la

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Aceptado tras revisión externa:
30.09.12.

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Escala de Reserva Cognitiva

Edad: _____ Sexo: _____

Años de educación formal (ej. desde 1º de E.G.B. a C.O.U.=12 años): _____

Máxima titulación obtenida (ej. graduado escolar, Ingeniero Técnico, etc.): _____

Profesión ejercida durante mayor tiempo (ej. Maestro Secundaria): _____

La Escala de Reserva Cognitiva pretende medir cómo de activo ha sido y es su estilo de vida. A continuación, se presenta una serie de actividades referidas a tres etapas de su vida:

JUVENTUD (18-35 años) **ADULTEZ (36-64 años)** **MADUREZ (A partir de los 65 años)**

Para responder **con qué frecuencia** realizaba y realiza cada una de las siguientes actividades en cada etapa de su vida, tenga en cuenta el siguiente código de respuesta:

0 = Nunca
1 = Una o varias veces al año
2 = Una o varias veces al mes
3 = Una o varias veces a la semana
4 = Tres veces o más a la semana, siempre que me surge la oportunidad

ACTIVIDADES DE LA VIDA DIARIA

Pregunta: ¿Con qué frecuencia realizaba (Juventud y Adultez) y realizo (Actualmente) cada una de las siguientes actividades?

	Juventud	Adultez	Madurez
***Ejemplo**: Controlar mis asuntos personales*.....	0 1 2 (3) 4	0 (1) 2 3 4	0 1 (2) 3 4

Aging Clinical and Experimental Research

Cognitive Reserve Index questionnaire (CRIq): a new instrument for measuring cognitive reserve

Massimo Nucci[1], **Daniela Mapelli**[1,2] **and Sara Mondini**[1,3]

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ABSTRACT. ***Background and aims:*** *The concept of "reserve" has been used to explain the difference between individuals in their capacity to cope with or compensate for pathology. Brain reserve refers to structural aspects of the brain, such as brain size and synapse count. Cognitive reserve is the ability to optimize and maximize performance through two mechanisms: recruitment of brain networks, and/or compensation by alternative cognitive strategies. The aim of the present research was to devise an instrument for comprehensive assessment and measurement of the quantity of cognitive reserve accumulated by individuals throughout their lifespan.* ***Methods:*** *A new approach using the Cognitive Reserve Index questionnaire (CRIq) was developed and tested in a sample of 588 healthy individuals, from 18 to 102 years old, stratified by age (Young, Adults, Elderly) and gender. The CRIq includes demographic data and items grouped into three sections: education, working activity and leisure time, each of which returns a subscore. The WAIS Vocabulary test and TIB were also administered.* ***Results:*** *The main descriptive features and some inferential results are described. Intelligence was only moderately correlated with cognitive reserve, stressing the distinction between these two concepts. Age and gender significantly affected CRIq scores, whereas no effect emerged from*

ability to cope with physiological or pathological cognitive decline. There is not always a direct relationship between the severity of brain pathologies or brain damage and the degree of deficit in performance. For many years, *Brain Reserve* (BR) was the prevalent construct of the potential ability of the brain to cope with neuronal damage. Katzman et al. (1) examined the brains of ten subjects who had documented post-mortem neuropathology of Alzheimer's dementia (AD), even though they had not expressed any sign of cognitive decline when alive. The authors attributed the absence of clinical signs of dementia to the higher-than-average weight of their brains. Later, BR was defined as the brain's resilience: that is, the possibility of the brain itself coping with increasing brain damage (2). The *Brain Reserve hypothesis* is primarily a passive-quantitative model related to individual differences (e.g., brain size and synapse count): a greater BR is considered as a protective factor, and a lower one indicates vulnerability.

The debate on BR and aging introduced and developed the concept of *Cognitive Reserve* (CR), a fascinating concept at the basis of brain plasticity. The *Cognitive Reserve hypothesis* suggests that the brain actively attempts to cope with damage by using pre-existing cognitive processes or enlisting compensatory strategies. Thus, people

Cognitive Reserve Index

CRIq

questionnaire

M. Nucci, D. Mapelli & S. Mondini (2012)

Instrucciones: En caso de alteración cognitiva o del comportamiento, aunque sea solamente sospechada, el cuestionario debe suministrarse a los familiares o a quién cuide del paciente, indicándolo al final del cuestionario en la casilla correspondiente.

Apellidos: ..... Nombre: .....

Fecha de nacimiento: ...../...../..... Lugar de nacimiento: ..... Edad: .....

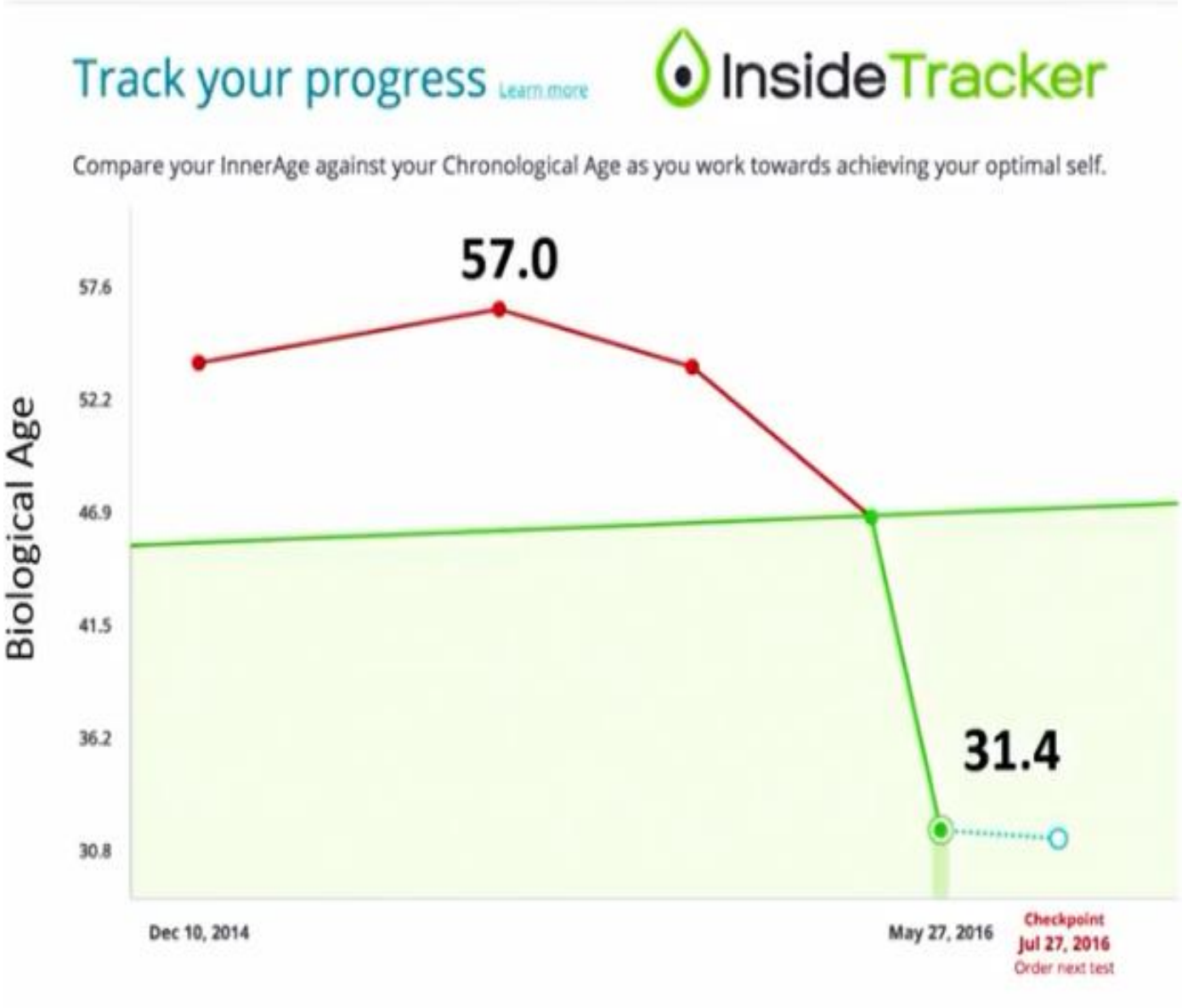
Lugar de residencia: ..... Nacionalidad: española ☐ otra ☐ .....

Estado civil: soltero ☐ casado ☐ divorciado ☐ viudo ☐

CRI-Escuela

Instrucciones: Contar los años de escuela superados más 0.5 por cada año en el que se haya repetido curso. Para cada curso de formación al que se haya asistido contar 0.5 cada 6 meses.

	Años
1. Años de escolaridad (incluida una eventual especialización)	.....
2. Cursos (0.5 cada 6 meses)	.....



	Nov 30, 2015	Apr 07, 2016	May 27, 2016
InnerAge	53.8	46.7	31.8
Chronological Age	46.4	46.8	46.9
Difference	7.4	0.1	15.1
Optimal Best	30.1	30.4	30.5
Potential Worst	71.4	71.8	71.9

- **Debemos realizar una distinción entre edad cronológica y edad biológica**
- **Nada puede hacerse con la primera…**

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Behavioral/Cognitive

Youthful Brains in Older Adults: Preserved Neuroanatomy in the Default Mode and Salience Networks Contributes to Youthful Memory in Superaging

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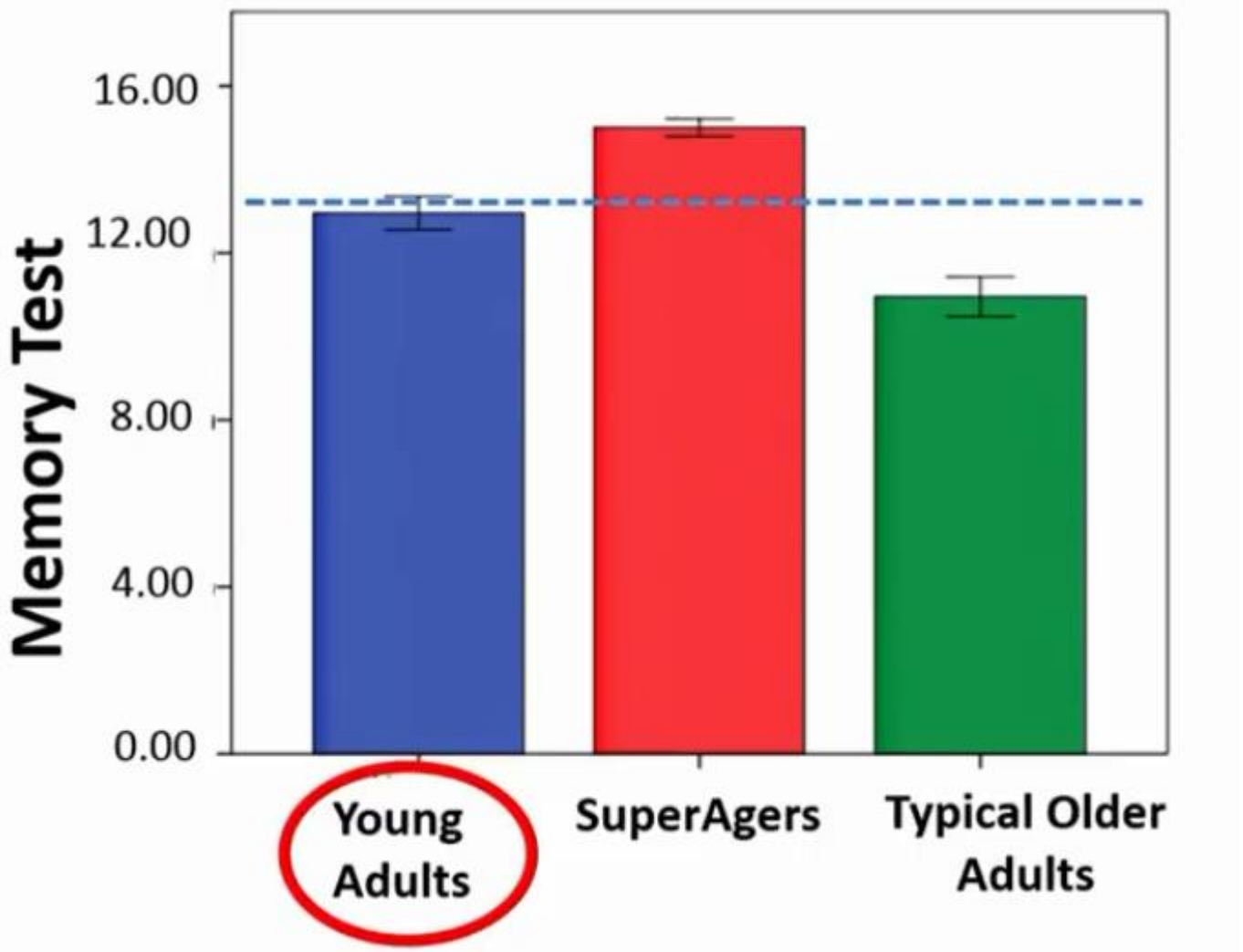
Decline in cognitive skills, especially in memory, is often viewed as part of "normal" aging. Yet some individuals "age better" than others. Building on prior research showing that cortical thickness in one brain region, the anterior midcingulate cortex, is preserved in older adults with memory performance abilities equal to or better than those of people 20–30 years younger (i.e., "superagers"), we examined the structural integrity of two large-scale intrinsic brain networks in superaging: the default mode network, typically engaged during memory encoding and retrieval tasks, and the salience network, typically engaged during attention, motivation, and executive function tasks. We predicted that superagers would have preserved cortical thickness in critical nodes in these networks. We defined superagers (60–80 years old) based on their performance compared to young adults (18–32 years old) on the California Verbal Learning Test Long Delay Free Recall test. We found regions within the networks of interest where the cerebral cortex of superagers was thicker than that of typical older adults, and where superagers were anatomically indistinguishable from young adults; hippocampal volume was also preserved in superagers. Within the full group of older adults, thickness of a number of regions, including the anterior temporal cortex, rostral medial prefrontal cortex, and anterior midcingulate cortex, correlated with memory performance, as did the volume of the hippocampus. These results indicate older adults with youthful memory abilities have youthful brain regions in key paralimbic and limbic nodes of the default mode and salience networks that support attentional, executive, and mnemonic processes subserving memory function.

Key words: aging; cerebral cortex; default mode network; memory; salience network



PLOS ONE

RESEARCH ARTICLE

Psychological well-being in elderly adults with extraordinary episodic memory

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Abstract

Objectives

The Northwestern University SuperAging Program studies a rare cohort of individuals over age 80 with episodic memory ability at least as good as middle-age adults to determine what factors contribute to their elite memory performance. As psychological well-being is positively correlated with cognitive performance in older adults, the present study examined whether aspects of psychological well-being distinguish cognitive SuperAgers from their cognitively average-for-age, same-age peers.

Method

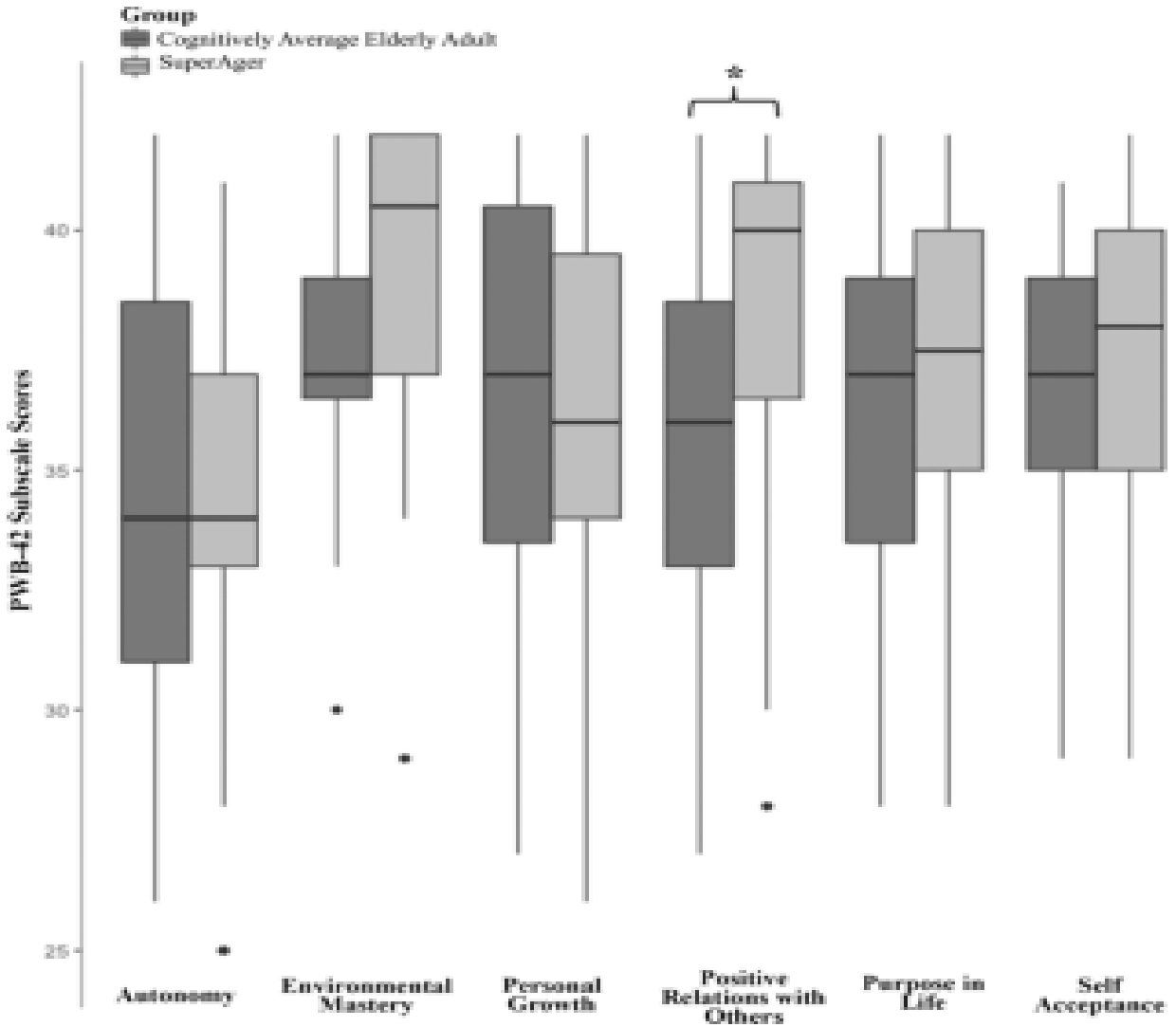
Thirty-one SuperAgers and 19 cognitively average-for-age peers completed the Ryff 42-item Psychological Well-Being questionnaire, comprised of 6 subscales: Autonomy, Positive Relations with Others, Environmental Mastery, Personal Growth, Purpose in Life, and Self-Acceptance.

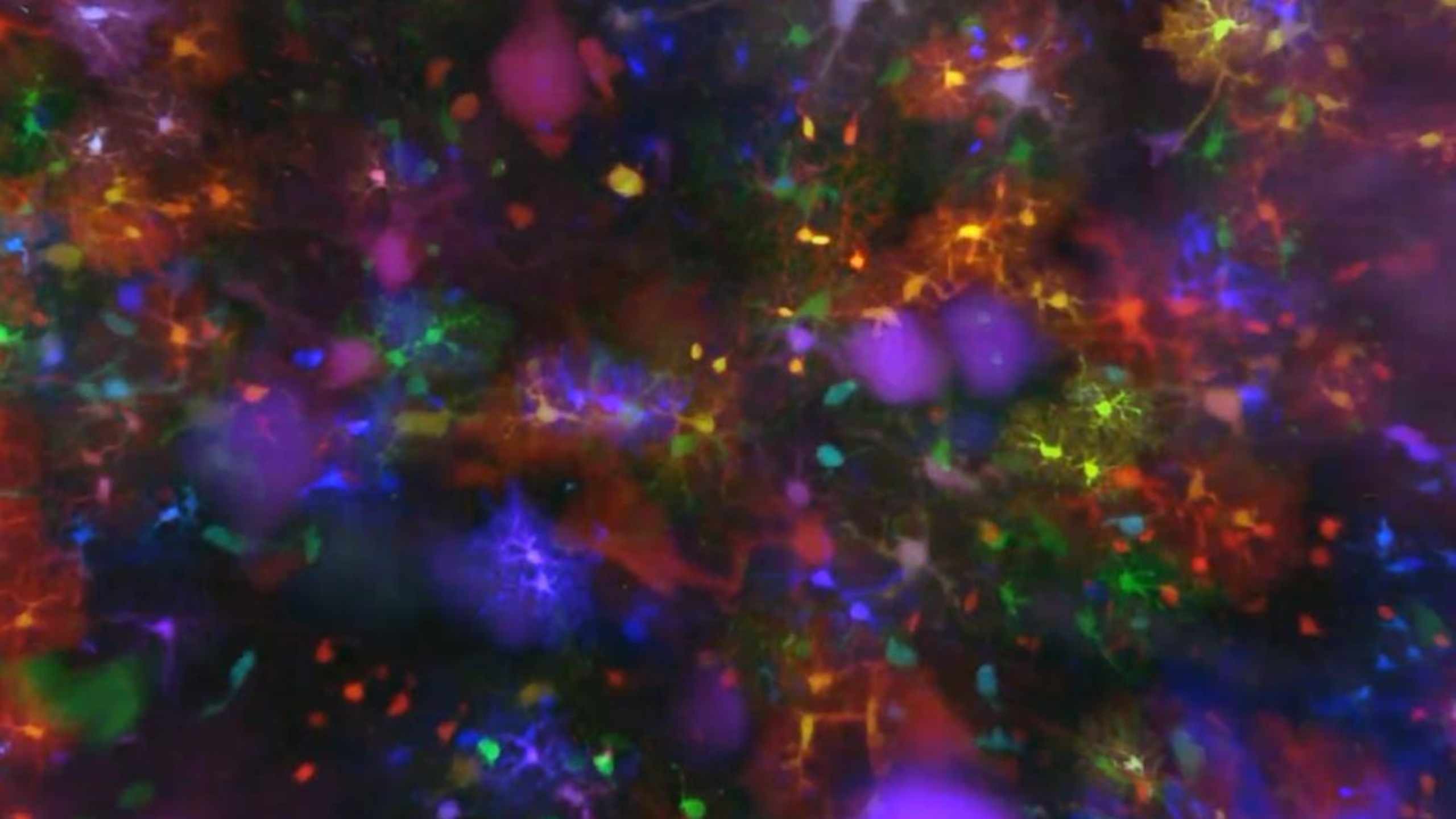
Results

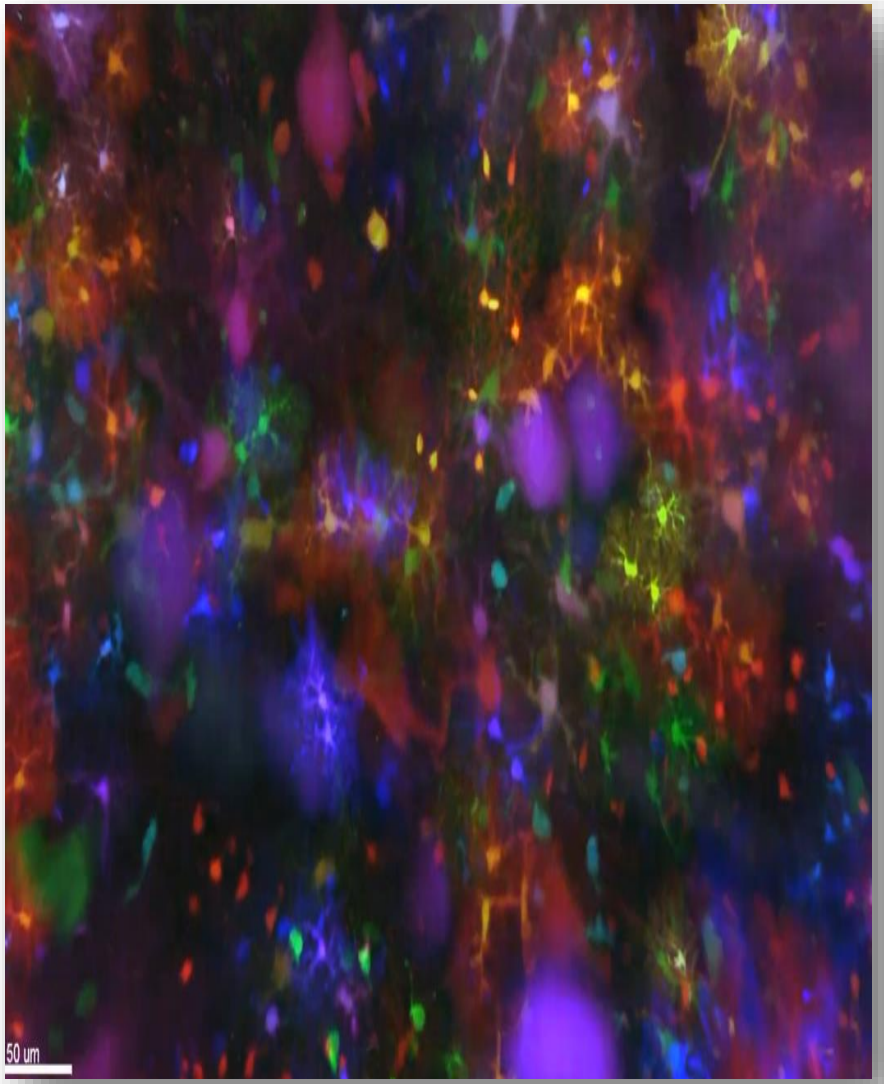
The groups did not differ on demographic factors, including estimated premorbid intelligence. Consistent with inclusion criteria, SuperAgers had better episodic memory scores. Compared to cognitively average-for-age peers, SuperAgers endorsed greater levels of Positive Relations with Others. The groups did not differ on other PWB-42 subscales.

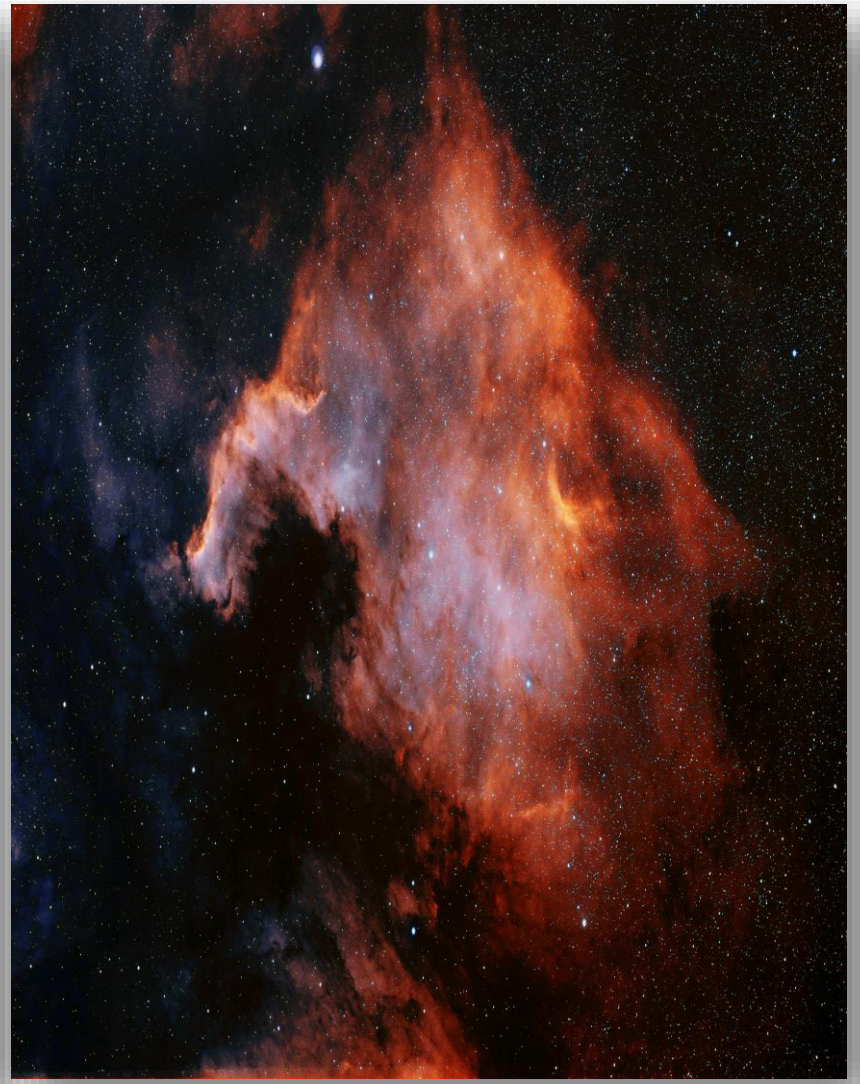
Discussion

While SuperAgers and their cognitively average-for-age peers reported similarly high levels of psychological well-being across multiple dimensions, SuperAgers endorsed greater levels of positive social relationships. This psychological feature could conceivably have a







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Neuropsicología y Envejecimiento: Una breve introducción

RANY™ HEALTH

Encuentro IV

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