Neuropsicología y Envejecimiento: Una breve introducción

RANY™ HEALTH

Encuentro III

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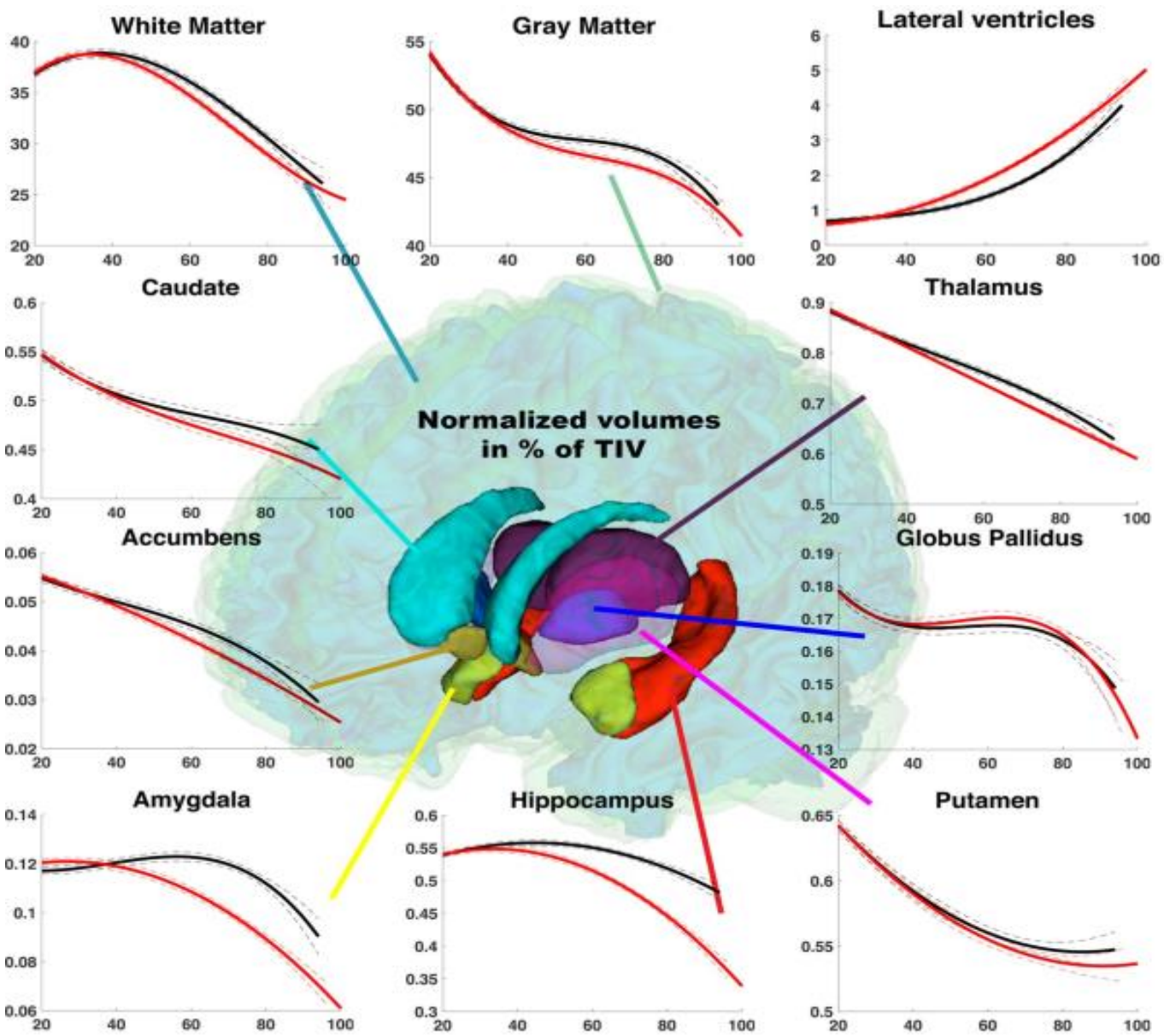
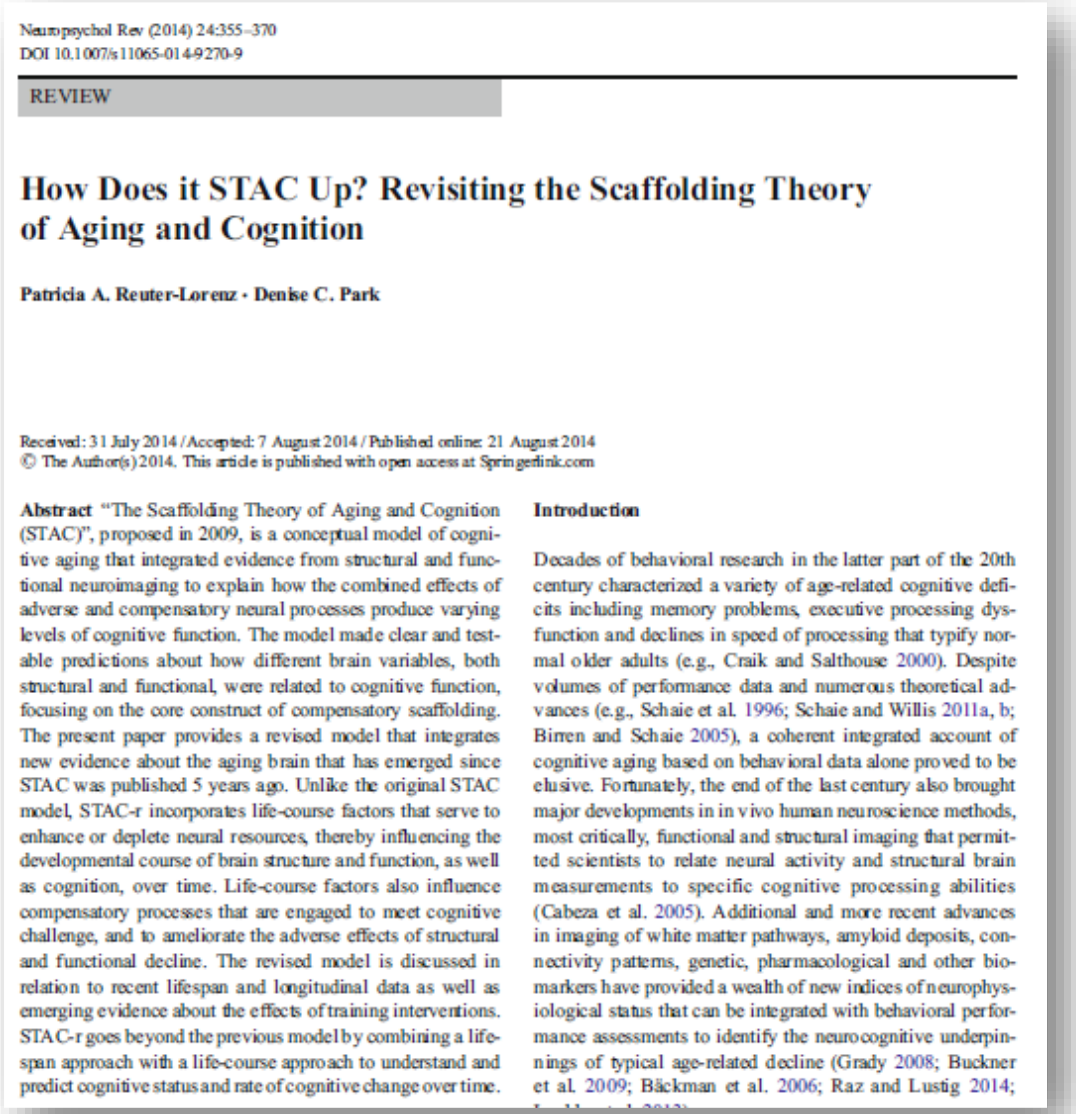
Asesor Científico-RANY Health



Resultados claves:

- **ANTES** de los 40 años comienza a aparecer una divergencia en las mediciones volumétricas del **hipocampo**, siendo menores los volúmenes en personas que luego son diagnosticadas con **MCI** o **Alzheimer**.
- **Alrededor** de los 40 se muestra un patrón similar para la **amígdala** y los **ventrículos laterales**.
- El modelo indica que la **ATROFIA TEMPORAL** y y el **ALARGAMIENTO VENTRICULAR** podrían ser dos eventos fisiopatológicos que caracterizan el cerebro de los pacientes con AD.



Neuropsychol Rev (2014) 24:355–370
DOI 10.1007/s11065-014-9270-9

REVIEW

How Does it STAC Up? Revisiting the Scaffolding Theory of Aging and Cognition

Patricia A. Reuter-Lorenz · Denise C. Park

Received: 31 July 2014 / Accepted: 7 August 2014 / Published online: 21 August 2014

Abstract "The Scaffolding Theory of Aging and Cognition (STAC)", proposed in 2009, is a conceptual model of cognitive aging that integrated evidence from structural and functional neuroimaging to explain how the combined effects of adverse and compensatory neural processes produce varying levels of cognitive function. The model made clear and testable predictions about how different brain variables, both structural and functional, were related to cognitive function, focusing on the core construct of compensatory scaffolding. The present paper provides a revised model that integrates new evidence about the aging brain that has emerged since STAC was published 5 years ago. Unlike the original STAC model, STAC-r incorporates life-course factors that serve to enhance or deplete neural resources, thereby influencing the developmental course of brain structure and function, as well as cognition, over time. Life-course factors also influence compensatory processes that are engaged to meet cognitive challenge, and to ameliorate the adverse effects of structural and functional decline. The revised model is discussed in relation to recent lifespan and longitudinal data as well as emerging evidence about the effects of training interventions. STAC-r goes beyond the previous model by combining a lifespan approach with a life-course approach to understand and predict cognitive status and rate of cognitive change over time.

Introduction

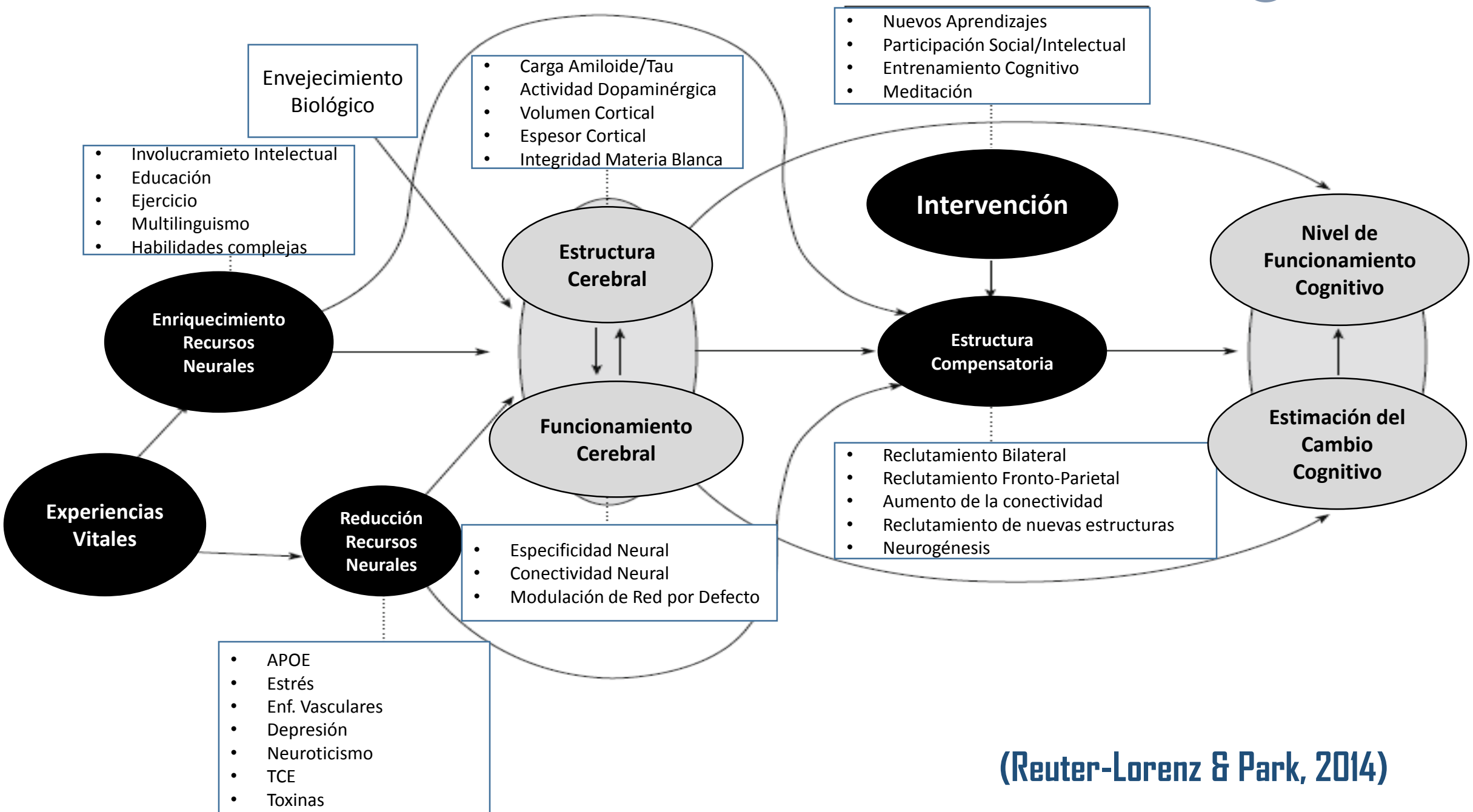
Decades of behavioral research in the latter part of the 20th century characterized a variety of age-related cognitive deficits including memory problems, executive processing dysfunction and declines in speed of processing that typify normal older adults (e.g., Craik and Salthouse 2000). Despite volumes of performance data and numerous theoretical advances (e.g., Schaie et al. 1996; Schaie and Willis 2011a, b; Birren and Schaie 2005), a coherent integrated account of cognitive aging based on behavioral data alone proved to be elusive. Fortunately, the end of the last century also brought major developments in in vivo human neuroscience methods, most critically, functional and structural imaging that permitted scientists to relate neural activity and structural brain measurements to specific cognitive processing abilities (Cabeza et al. 2005). Additional and more recent advances in imaging of white matter pathways, amyloid deposits, connectivity patterns, genetic, pharmacological and other biomarkers have provided a wealth of new indices of neurophysiological status that can be integrated with behavioral performance assessments to identify the neurocognitive underpinnings of typical age-related decline (Grady 2008; Buckner et al. 2009; Bäckman et al. 2006; Raz and Lustig 2014;

Teoría Estructural del Envejecimiento Cognitivo (STAC)

- La teoría STAC concibe el funcionamiento cerebral y la cognición en un sentido tanto positivo como negativo

- Publicado por primea vez en 2009, toma en consideración los cambios que de manera normativa deben ocurrir a nivel cerebral y cognitivo, considerando además los facores que actúan como moduladores

- La primera descripción gráfica del modelo describía las vaiables consideradas "intervinientes" en el procesos de envejecimiento en la adultez mayor



(Reuter-Lorenz & Park, 2014)

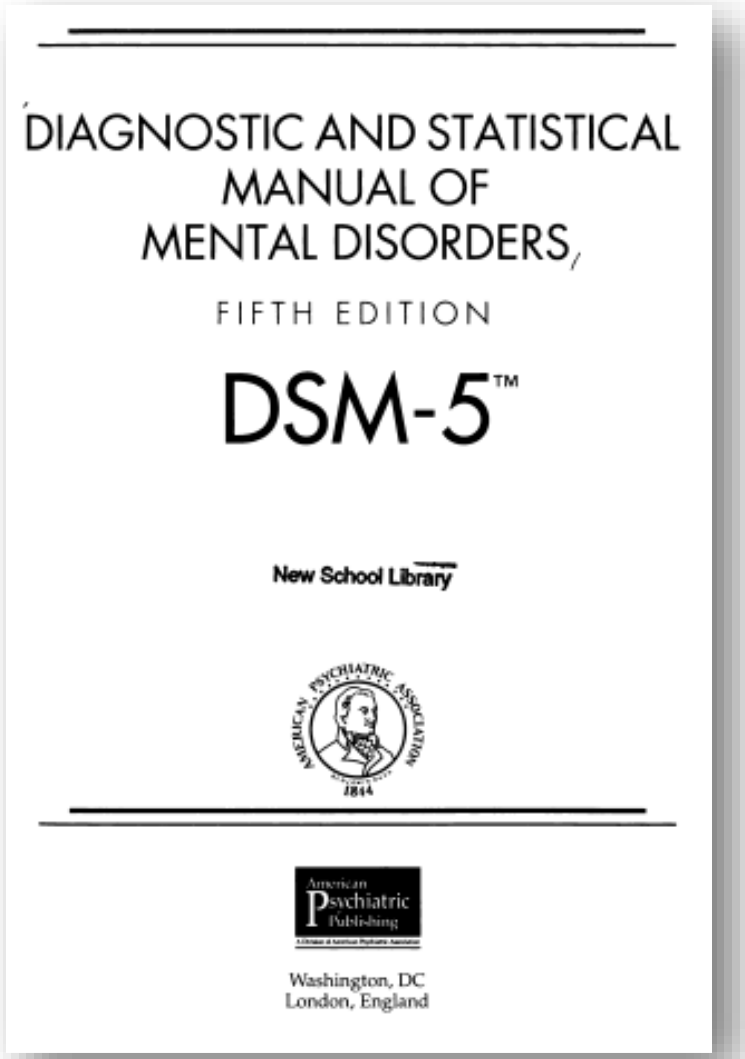
Cambios Cognitivos Normales Relacionados con el Envejecimiento

Estadios Preclínicos

Deterioro Cognitivo Ligero

Síndrome Demencial

Esquema Diagnóstico Contemporáneo (Smith, 2016)



Criterios Diagnósticos

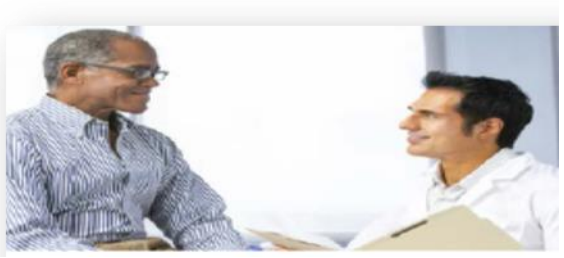
1. Evidencia de declive cognitivo en uno o más dominios, obtenido a partir a partir del estudio del paciente, un informante, o un especialista, o luego de evaluación objetiva;

2. Preservación de la independencia funcional;

3. El deterioro no se limita únicamente a episodios de delirium;

4. El deterioro no se explica por la presencia de otras condiciones, por ejemplo , depressión;

5. Ausencia de Demencia



DCL

Alteraciones Mnémicas

SÍ

NO

DCL Amnésico

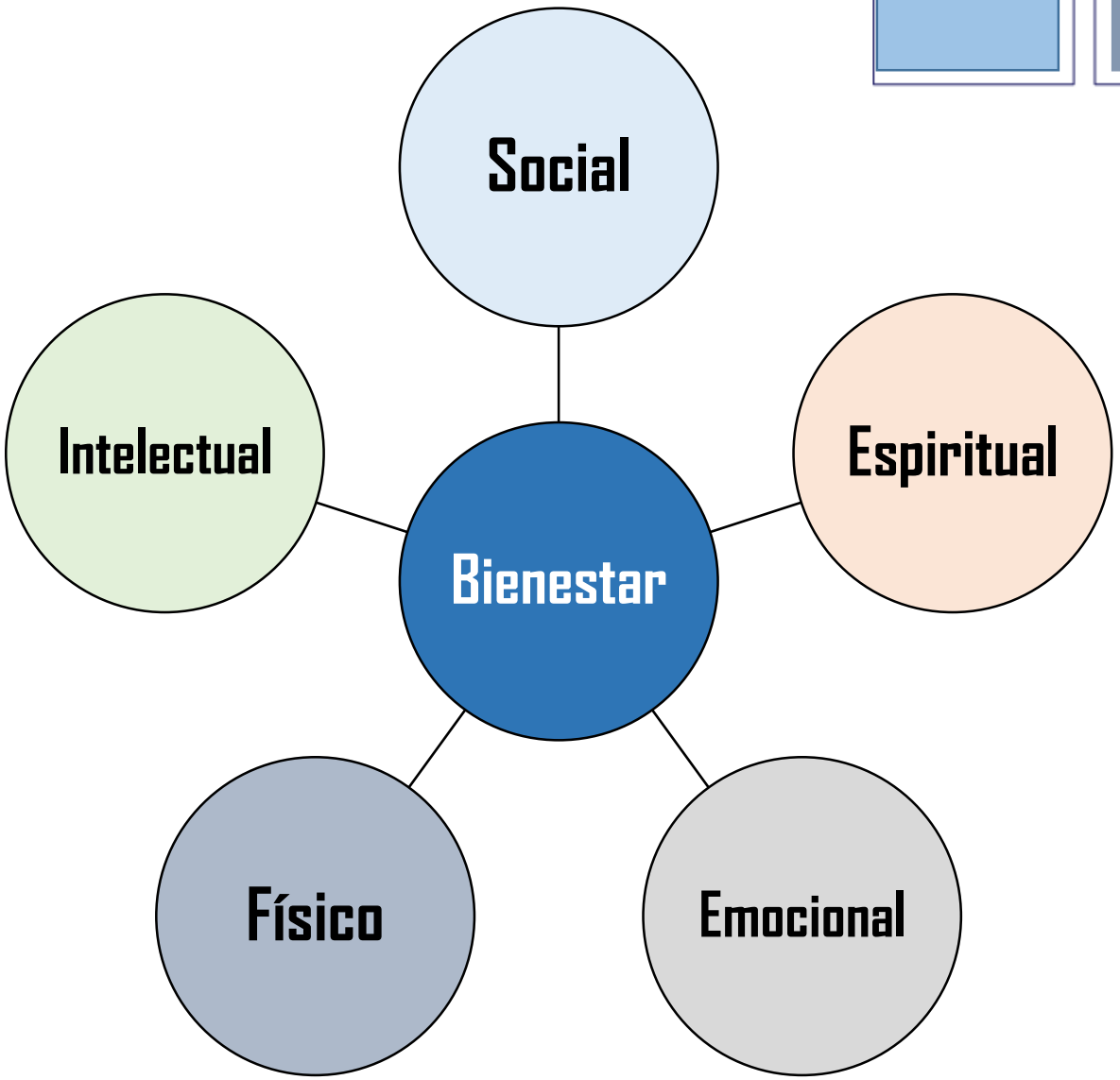
- DCL Amnésico Dominio Único
- DCL Amnésico Multidominio

DCL No-Amnésico

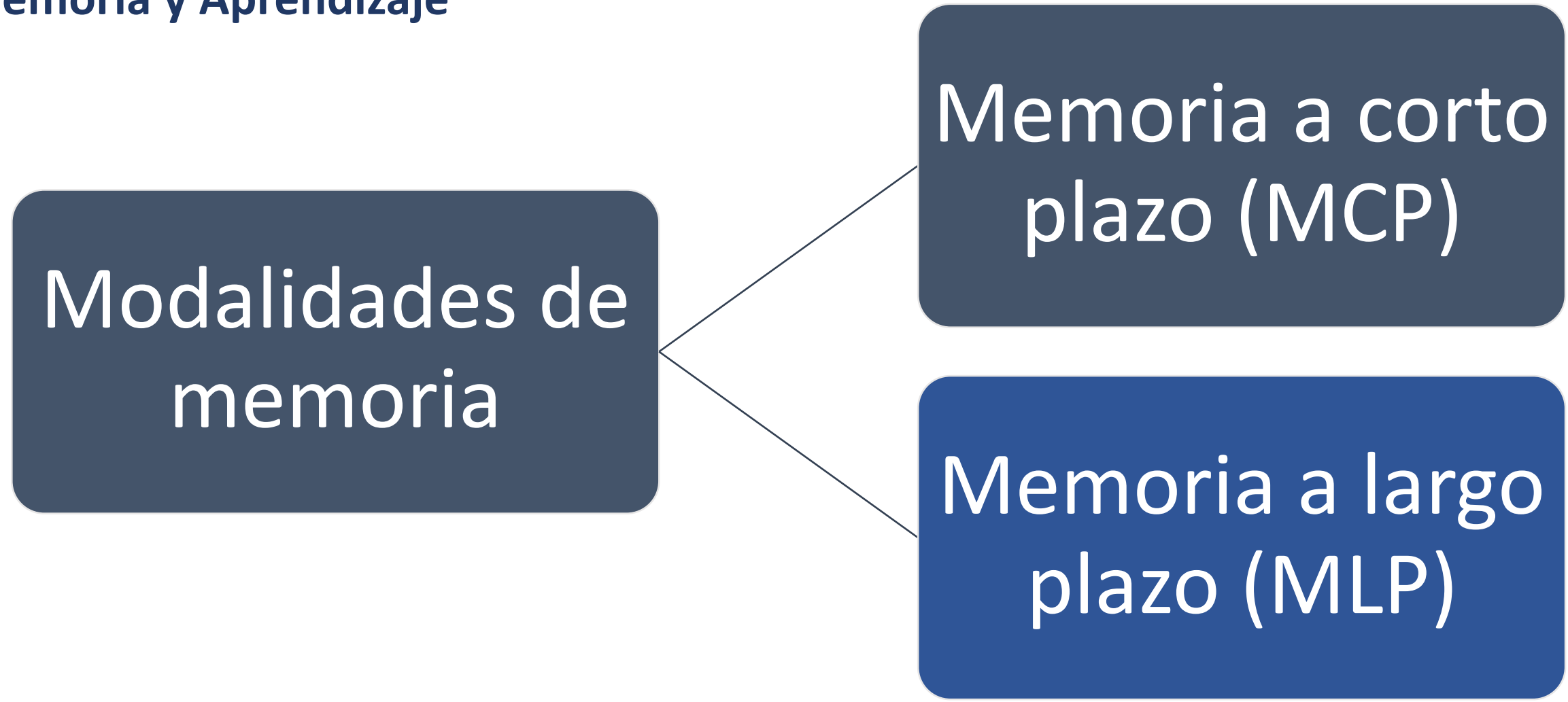
- DCL No- Amnésico Dominio Único
- DCL No- Amnésico Multidominio

Trastorno Neurocognitivo Menor (DSM-5)

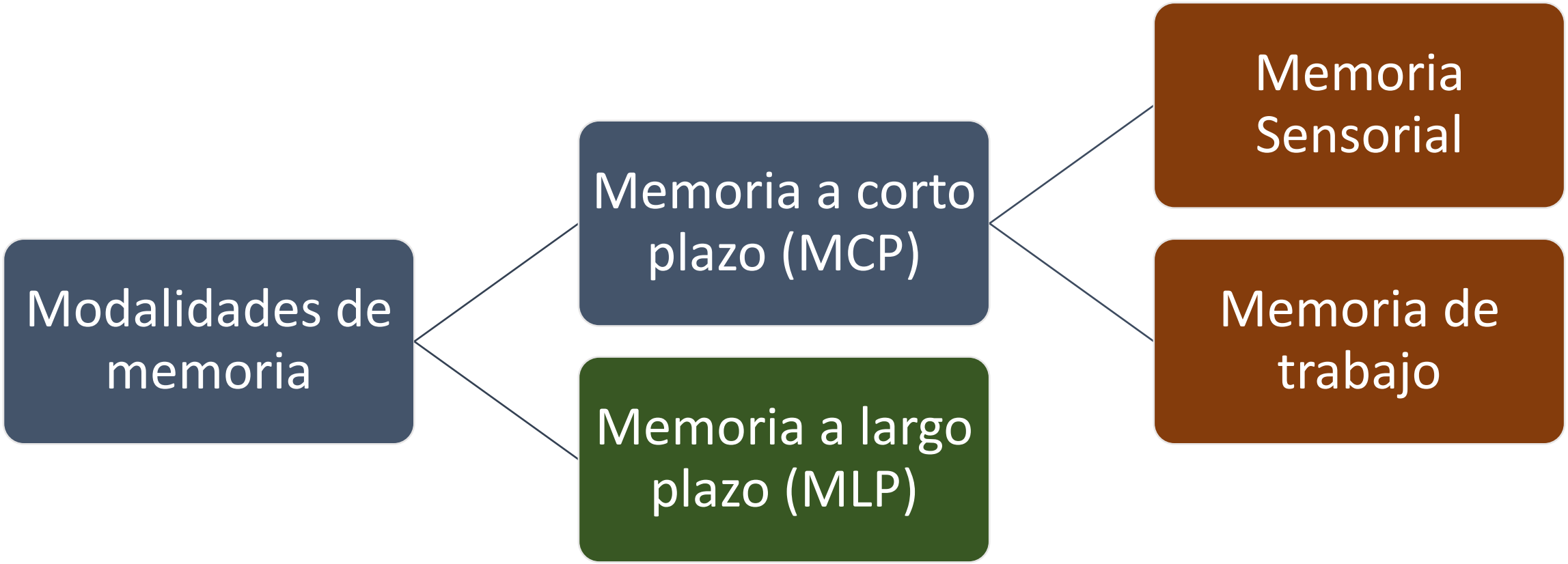
Cinco dimensiones del Modelo de Bienestar de Hettler (2015)



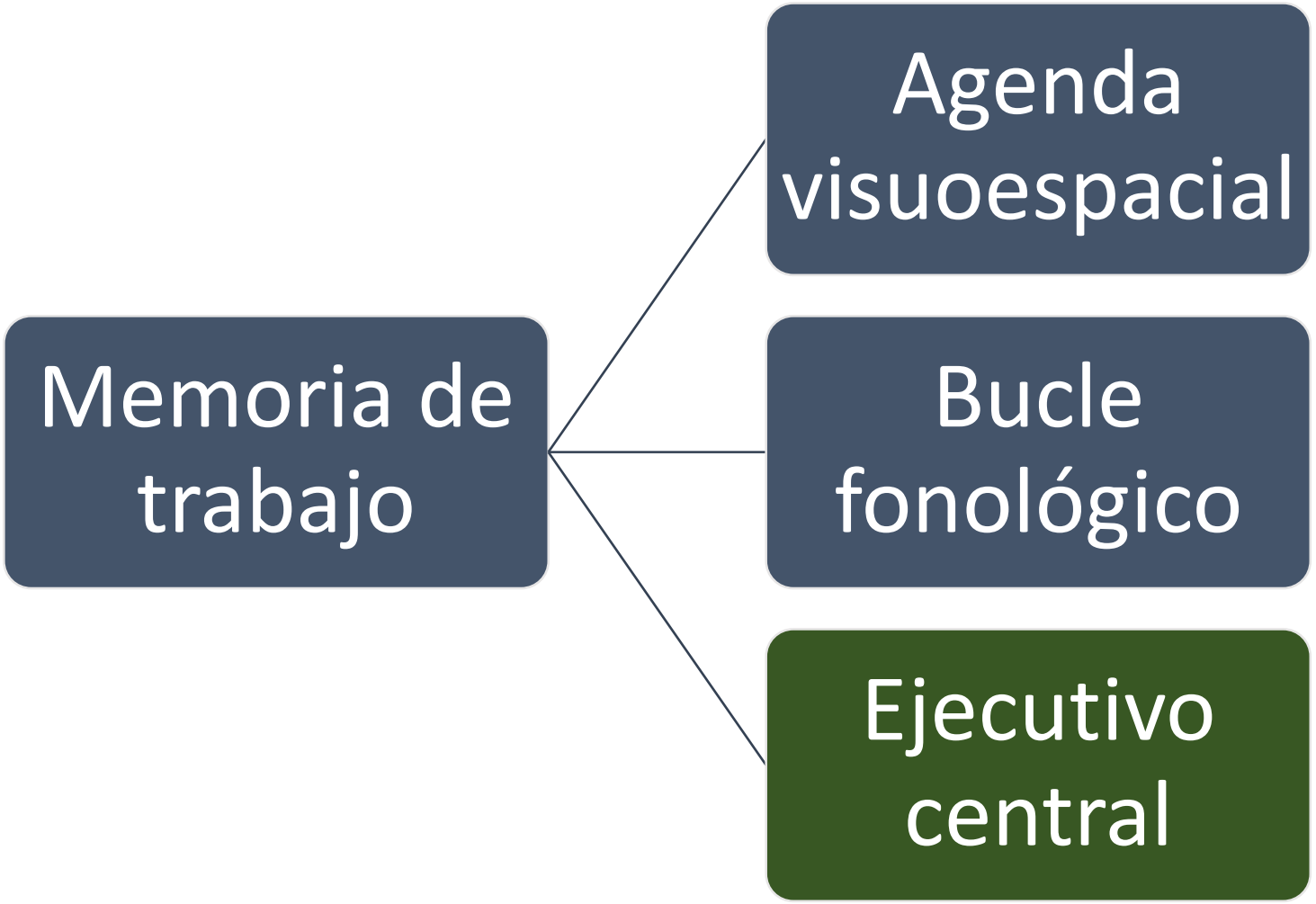
Memoria y Aprendizaje



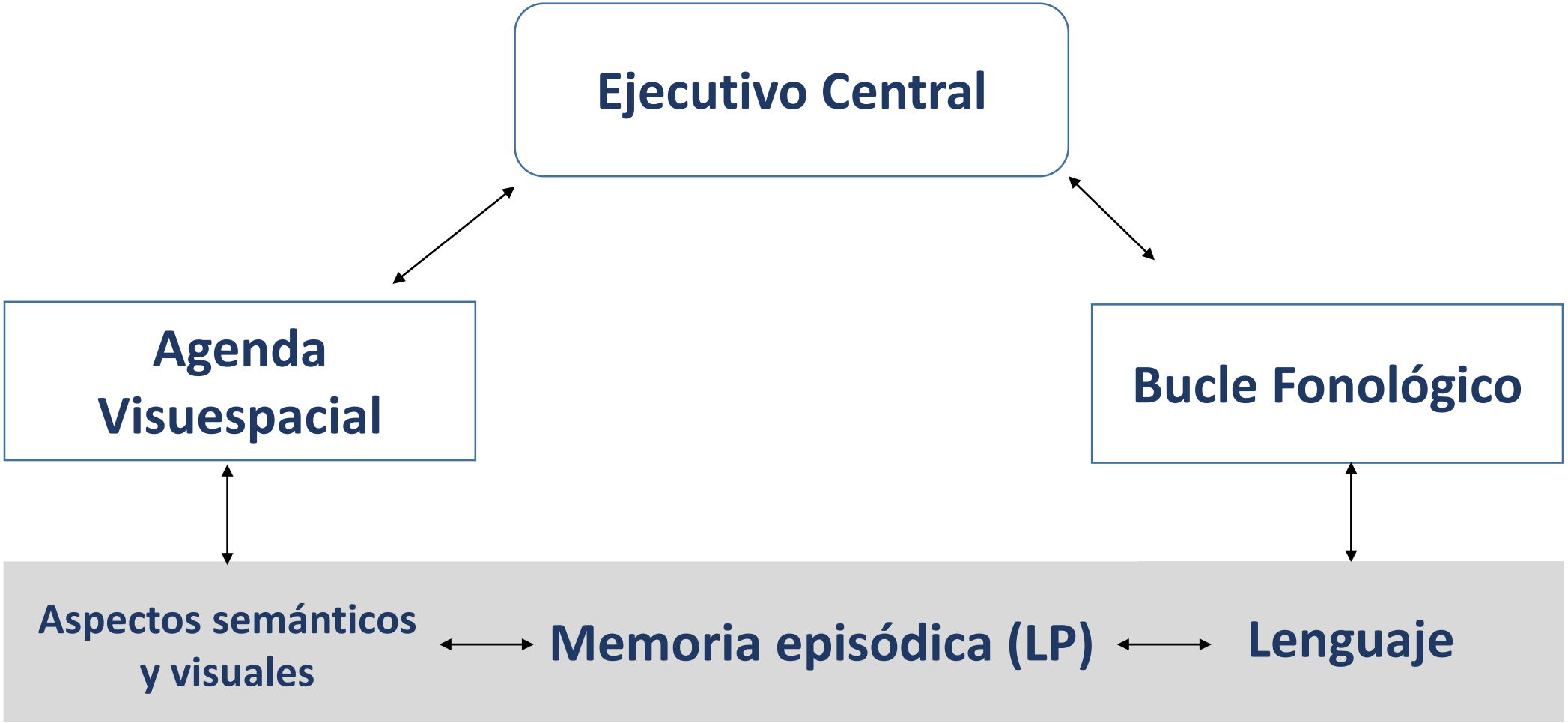
Memoria y Aprendizaje



Modelo de Memoria de Trabajo (Baddeley & Hitch, 1974)



Modelo de Memoria de Trabajo (Baddeley & Hitch, 1974)

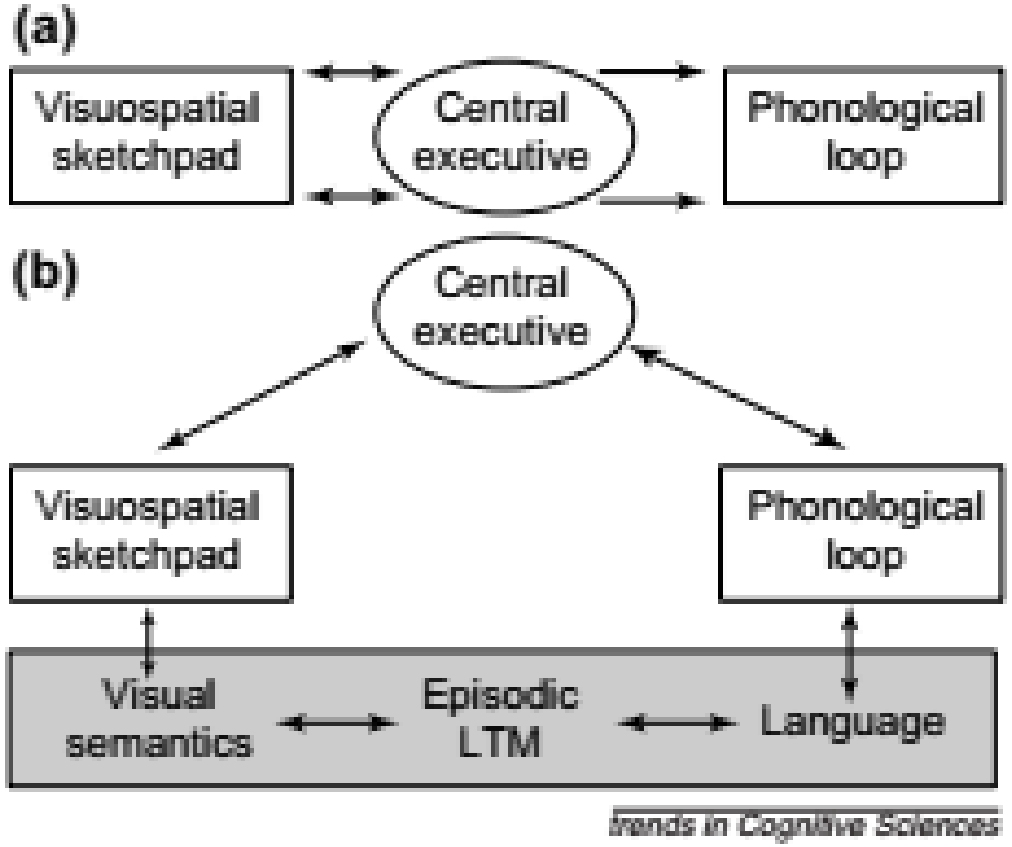


Review

The episodic buffer: a new component of working memory?

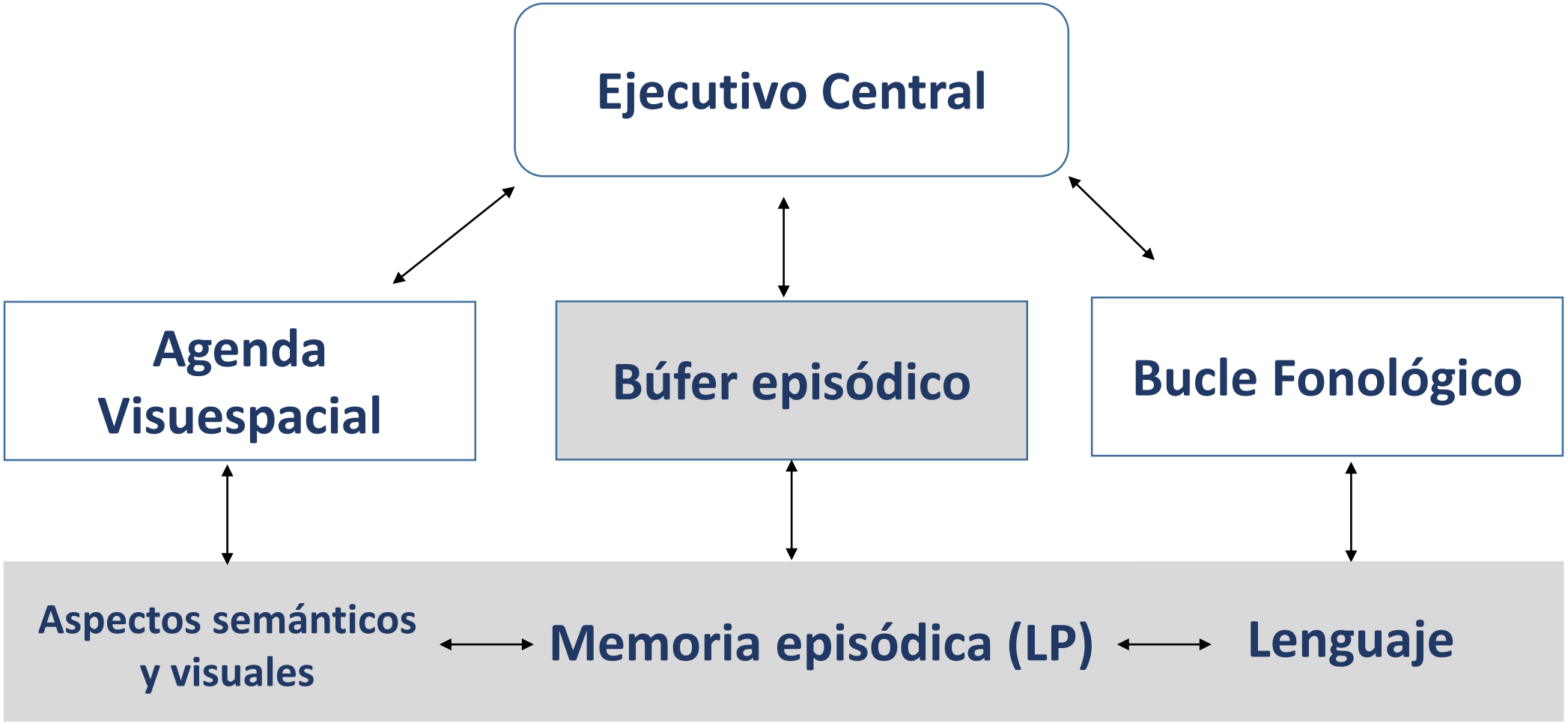
Alan Baddeley

In 1974, Baddeley and Hitch proposed a three-component model of working memory. Over the years, this has been successful in giving an integrated account not only of data from normal adults, but also neuropsychological, developmental and neuroimaging data. There are, however, a number of phenomena that are not readily captured by the original model. These are outlined here and a fourth component to the model, the episodic buffer, is proposed. It comprises a limited capacity system that provides temporary storage of information held in a multimodal code, which is capable of binding information from the subsidiary systems, and from long-term memory, into a unitary episodic representation. Conscious awareness is assumed to be the principal mode of retrieval from the buffer. The revised model differs from the old principally in focussing attention on the processes of integrating information, rather than on the isolation of the subsystems. In doing so, it provides a better basis for tackling the more complex aspects of executive control in working memory.

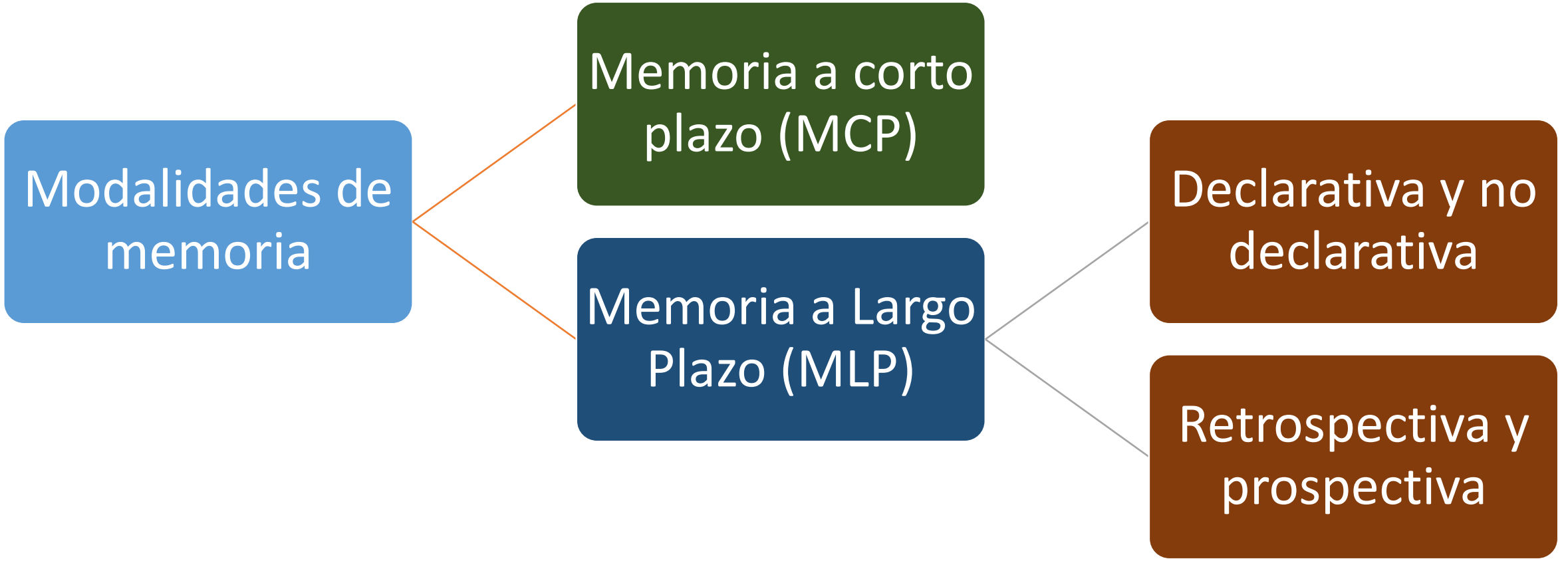


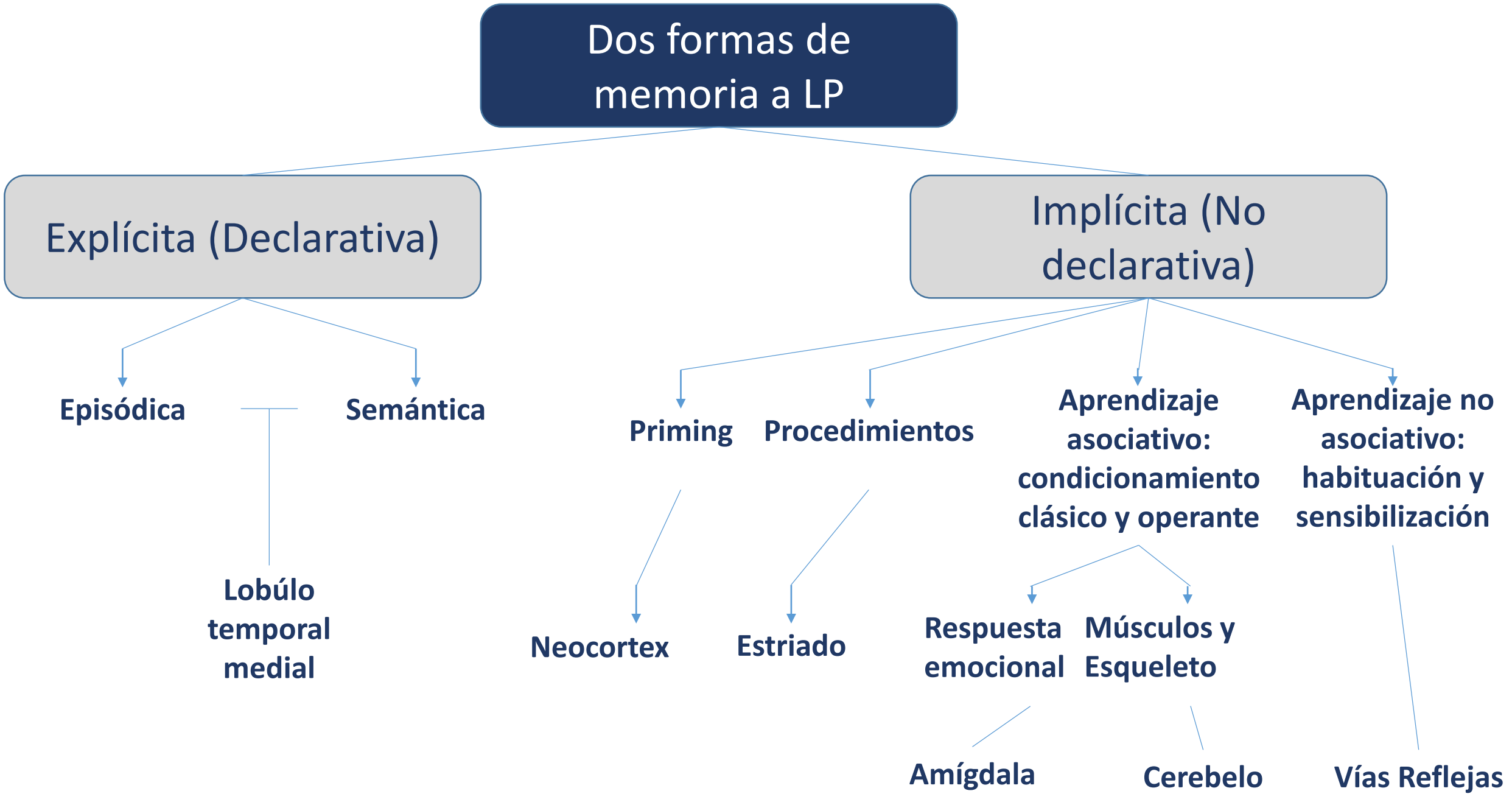
Trends in Cognitive Sciences

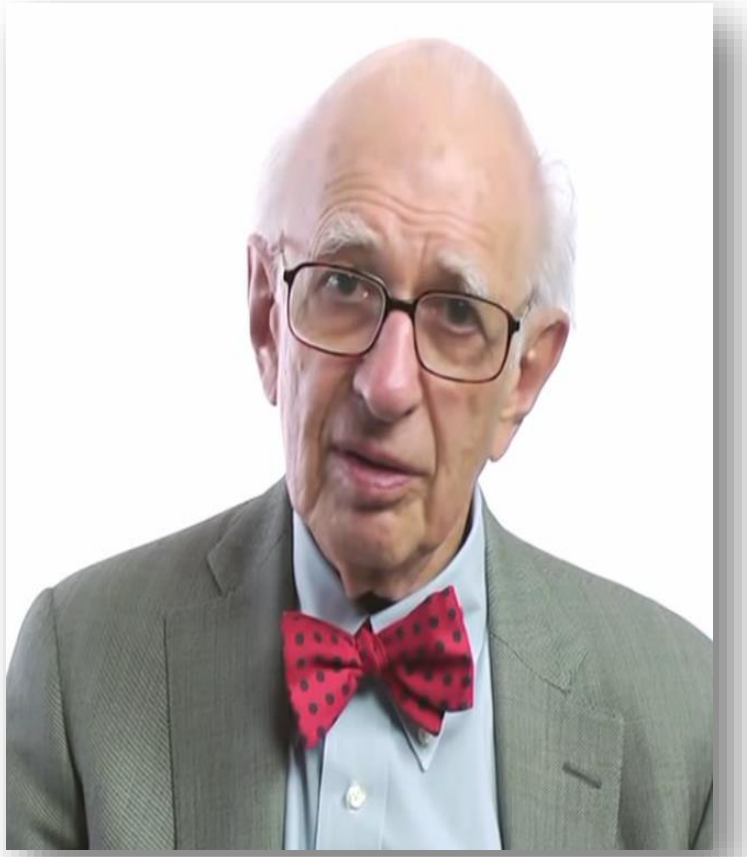
Modelo de Memoria de Trabajo (Baddeley, 2000)



Memoria y Aprendizaje

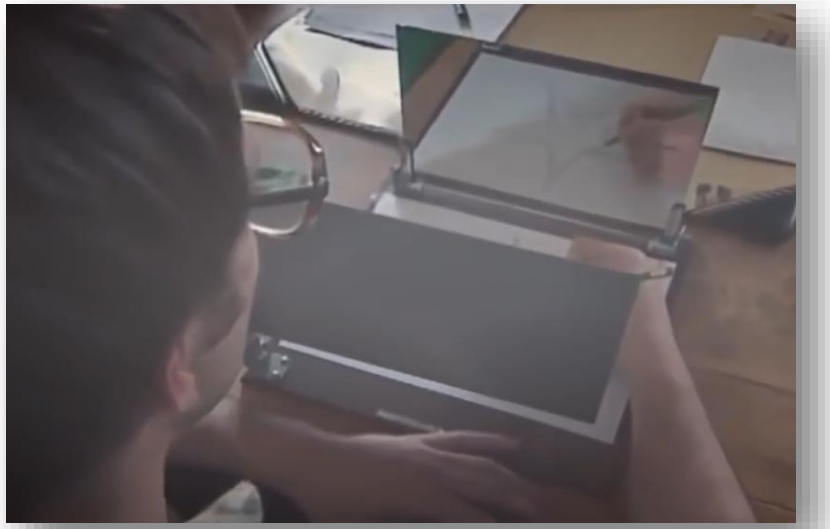



Dos formas de memoria a LP
Explícita (Declarativa)
Implícita (No declarativa)
Episódica
Semántica
Lobúlo temporal medial
Priming
Procedimientos
Aprendizaje asociativo: condicionamiento clásico y operante
Aprendizaje no asociativo: habituación y sensibilización
Neocortex
Estriado
Respuesta emocional
Músculos y Esqueleto
Amígdala
Cerebelo
Vías Reflejas

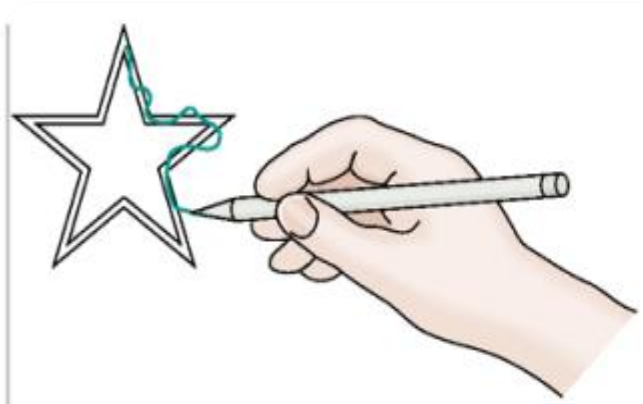


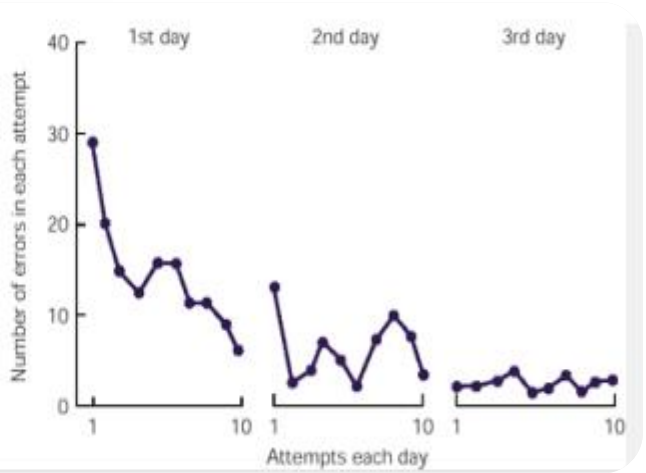
Eric Kandel

Aplysia

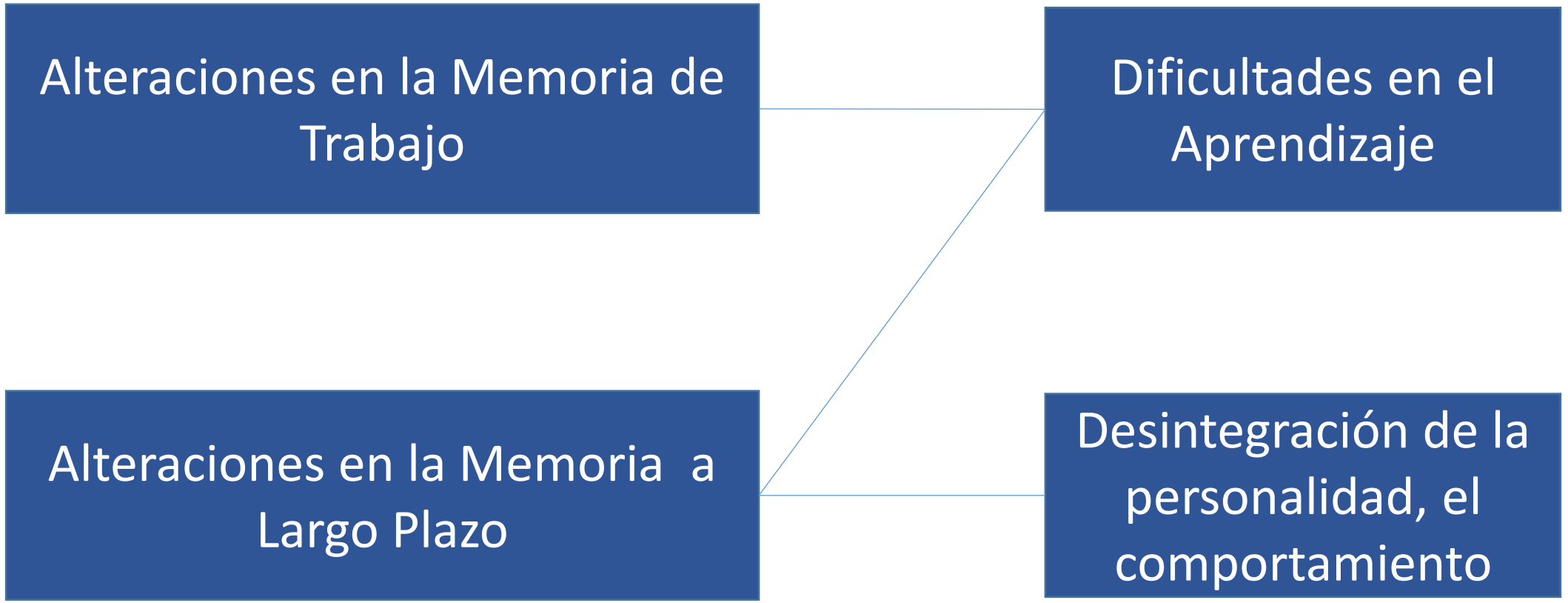


Paciente H.M.
(**Henry Gustav Molaison**)





Brenda Milner


Alteraciones en la Memoria de Trabajo
Alteraciones en la Memoria a Largo Plazo
Dificultades en el Aprendizaje
Desintegración de la personalidad, el comportamiento

La alteración de circuitos neurales, lesiones focales y alteraciones del neurodesarrollo pueden afectar considerablemente los procesos de aprendizaje y memoria

Neurodegeneration

OPEN ACCESS

REVIEW

Neuronal network disintegration: common pathways linking neurodegenerative diseases

Rebekah M Ahmed,[1,2] Emma M Devenney,[1,2] Muireann Irish,[2,3] Arne Ittner,[4] Sharon Naismith,[5] Lars M Ittner,[4] Jonathan D Rohrer,[6] Glenda M Halliday,[2] Andrew Eisen,[7] John R Hodges,[2] Matthew C Kiernan[1]

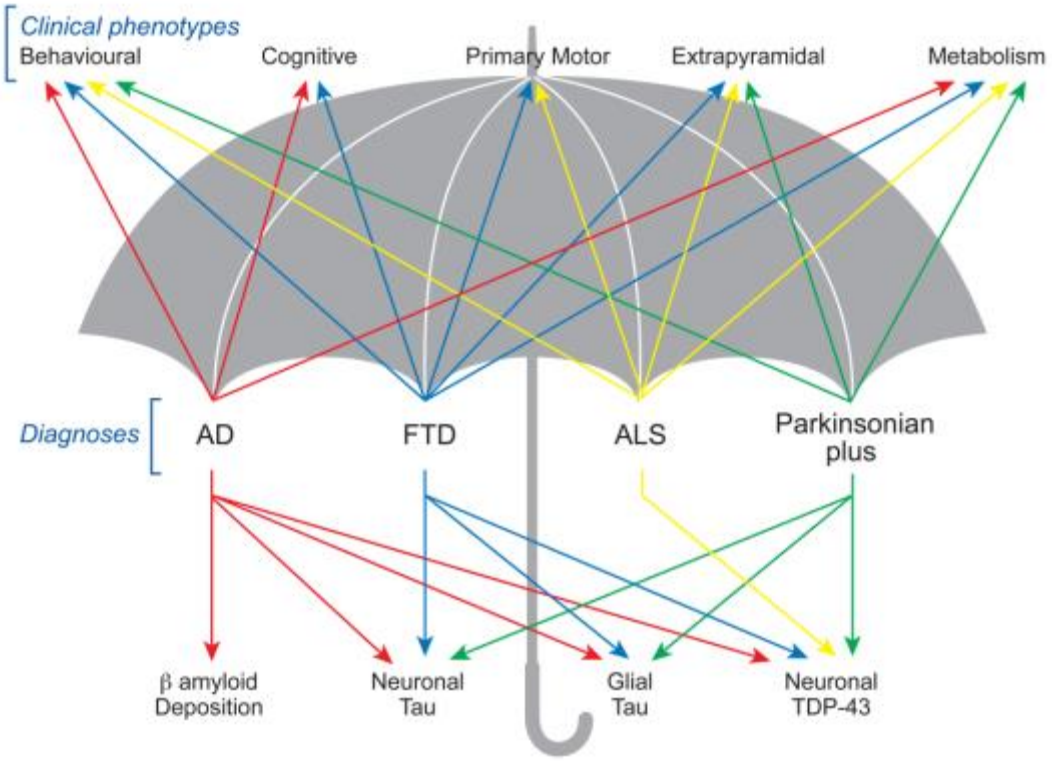
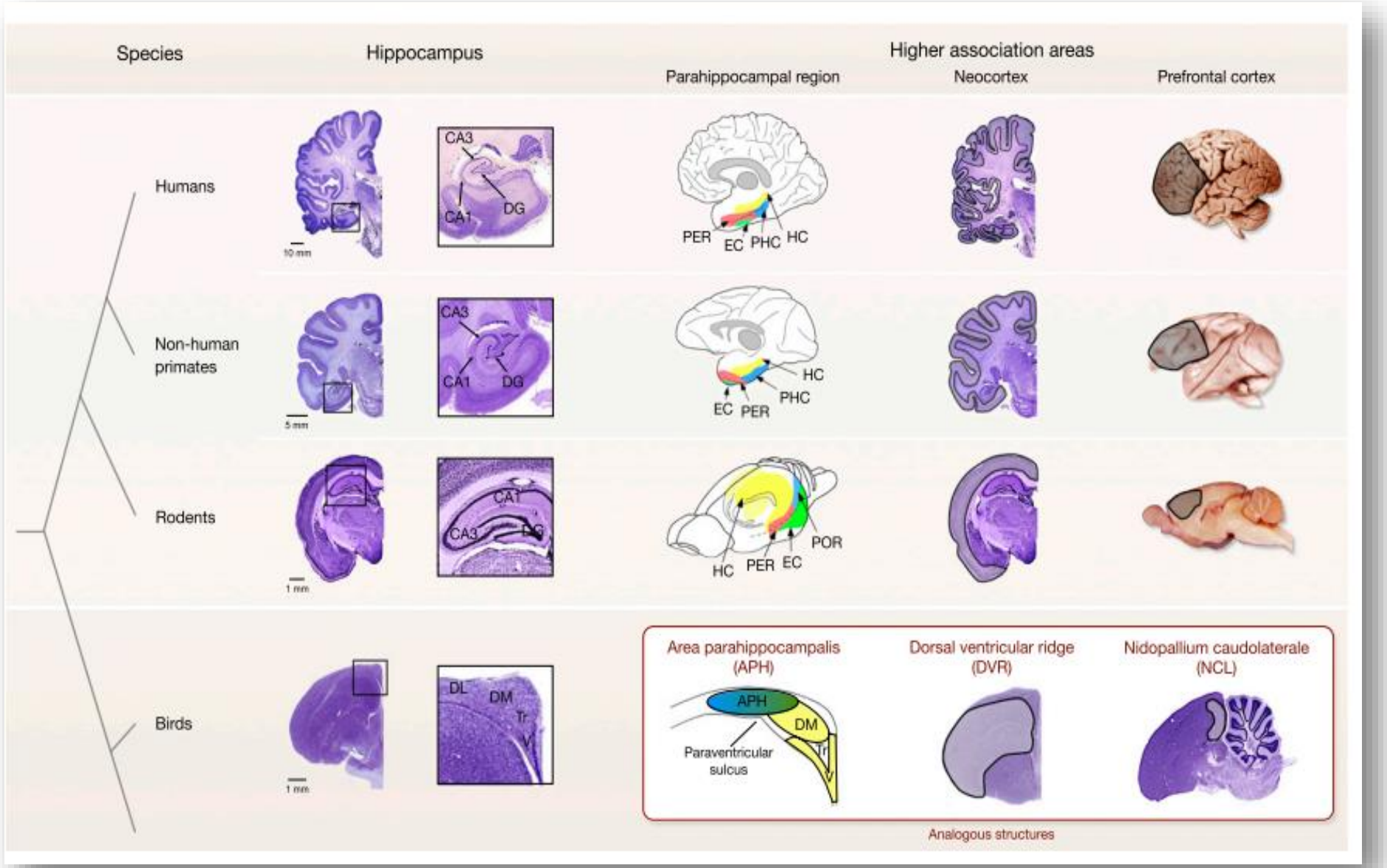
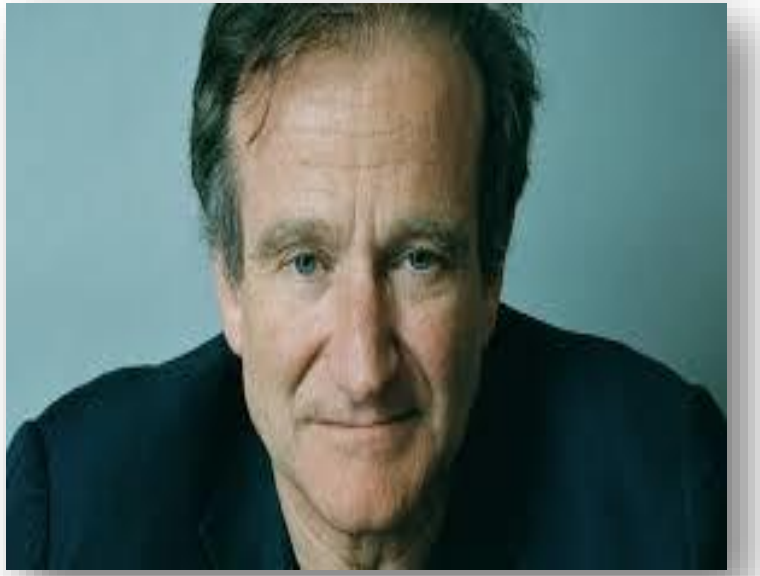


Figure 1 Clinical and pathological overlap in neurodegeneration: showing overlap at both a phenotypic and pathological level between multiple neurodegenerative conditions.



Regiones cerebrales claves para la memoria episódica



Robin Williams
(1951 – 2014)

Ronald Reagan
(1911 – 2004)

Rosa Parks
(1913 – 2005)

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

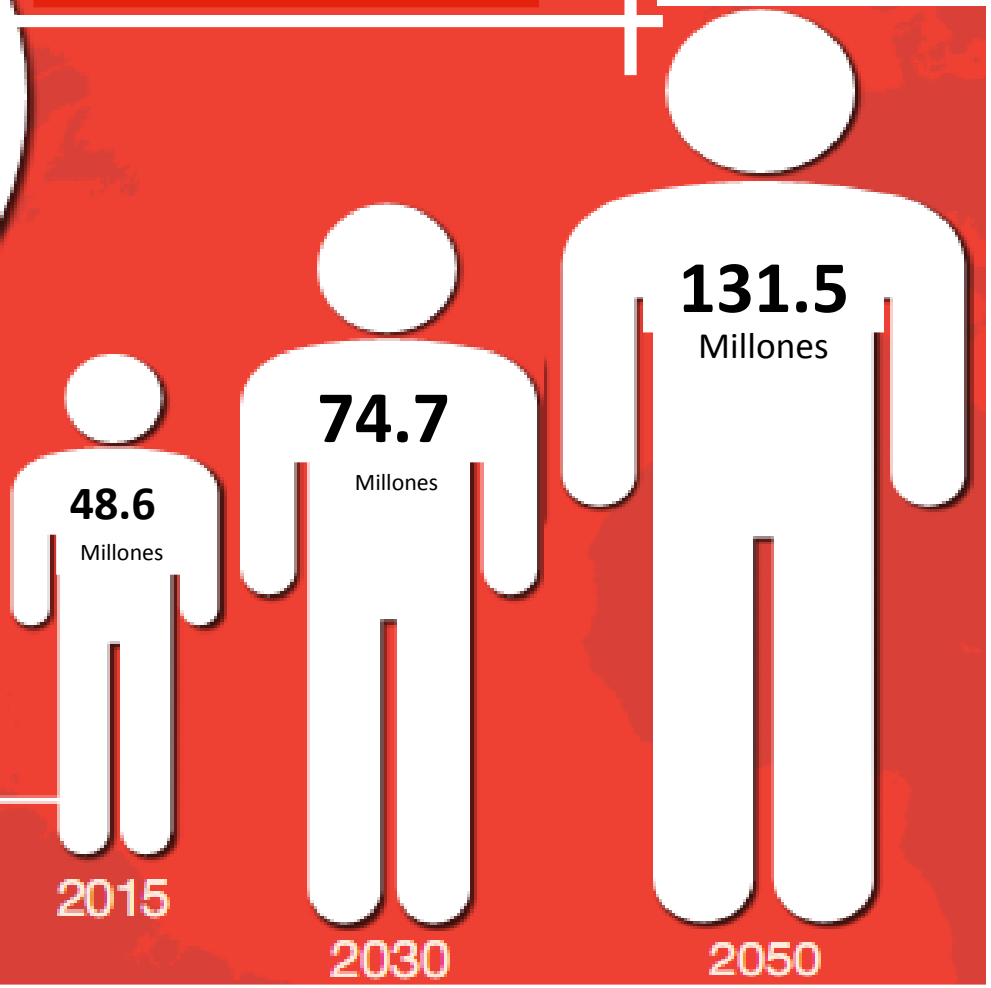
World Alzheimer Report 2015

46, 800, 000
Personas padecen demencia a nivel mundial

En **2015** se diagnosticaron **9.9** millones de nuevos casos

UN CASO CADA 3 SEGUNDOS

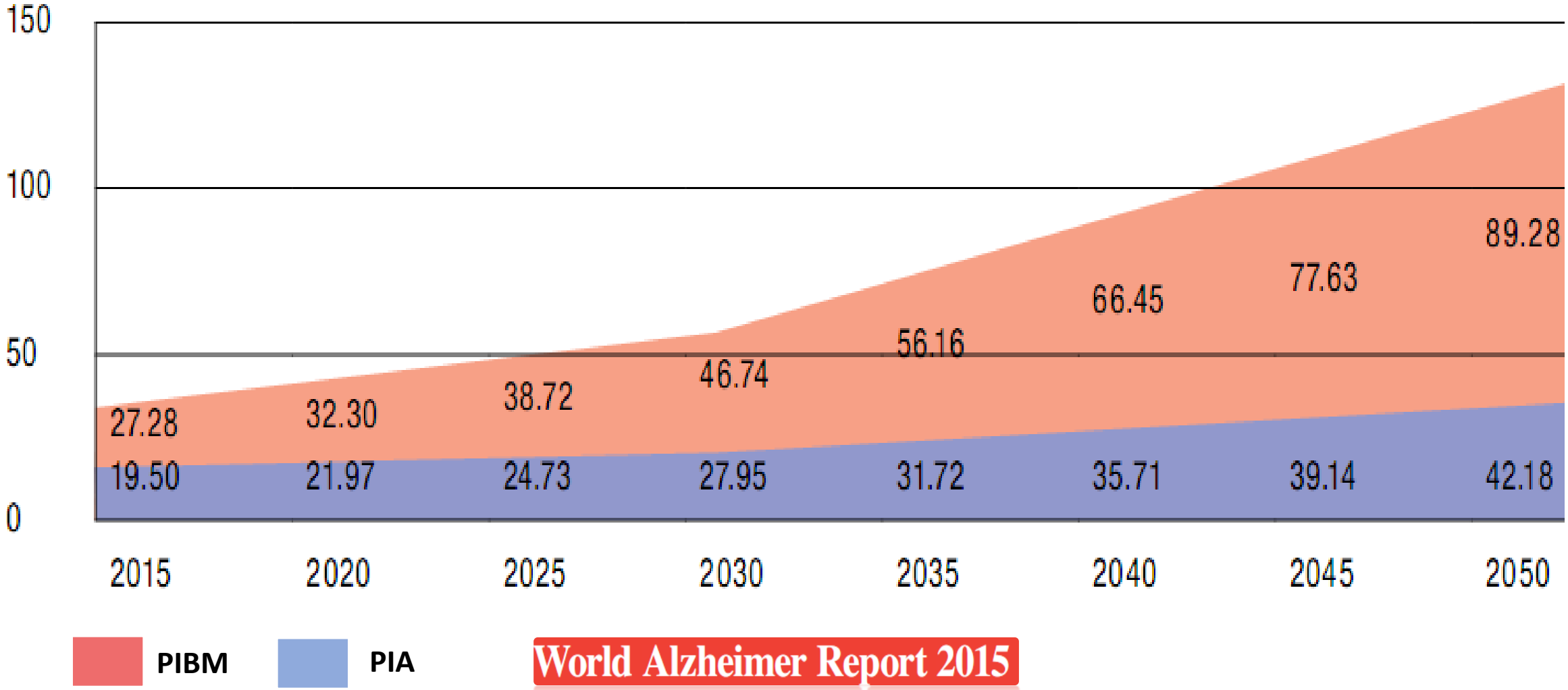
Este valor se duplica cada 20 años



Tendencias Actuales y Pronósticos a Largo Plazo

World Alzheimer Report 2015

CRECIMIENTO DEL NÚMERO DE PERSONAS CON DEMENCIA EN PAÍSES CON ALTOS INGRESOS (PIA) E INGRESOS BAJOS Y MEDIOS (PIBM)



World Alzheimer Report 2015

LA DEMENCIA EN EL CARIBE

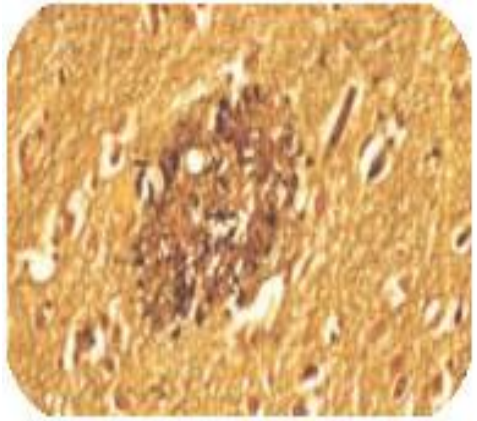
Las cifras se presentan en miles.

País	2010	2030	2050	Incremento (%)
Cuba	150	273	421	181
República Dominicana	54	125	241	346
Puerto Rico	48	79	109	127
Haití	22	42	86	291
Guadalupe	5	9	16	220
Guyana Francesa	1	2	5	400
Total	**280**	**530**	**878**	**449**

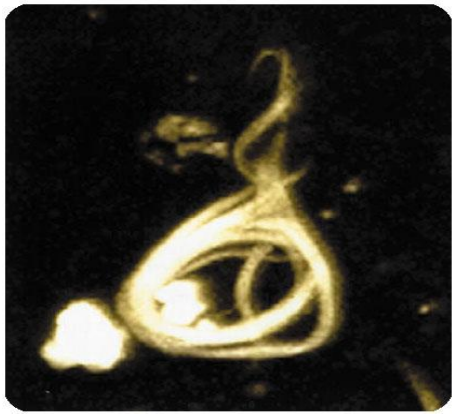
Informe ADI/Bupa: La demencia en América: El coste y la prevalencia del Alzheimer y otros tipos de demencia. Octubre 2013.

Plaquetas y Ovillos: Los marcadores de la EA

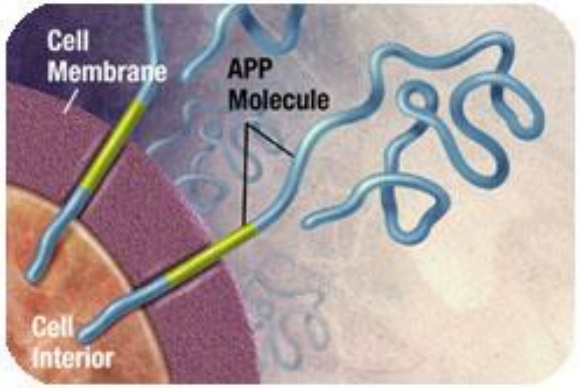
El cerebro de las personas con EA son abundantes en dos estructuras anormales:

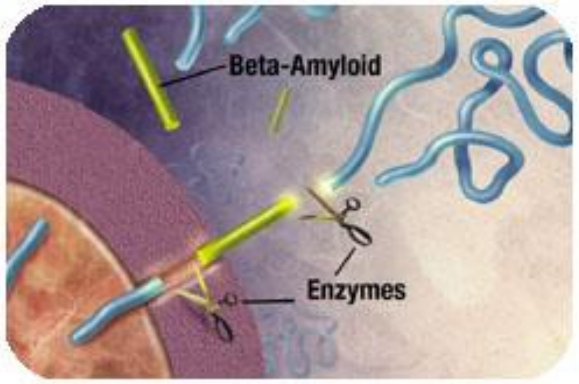


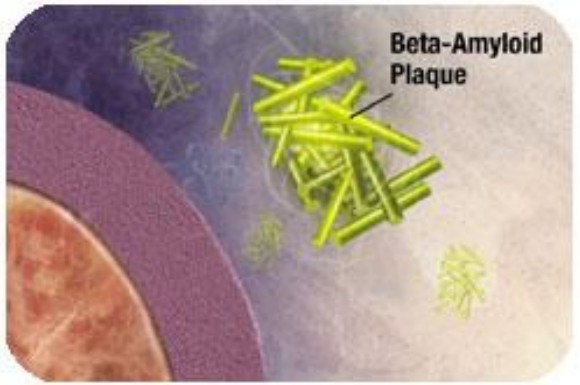
- Palquetas beta-amiloide (placas seniles): depocisiones densas de proteínas y material celular que se acumula fuera del axón celular.



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





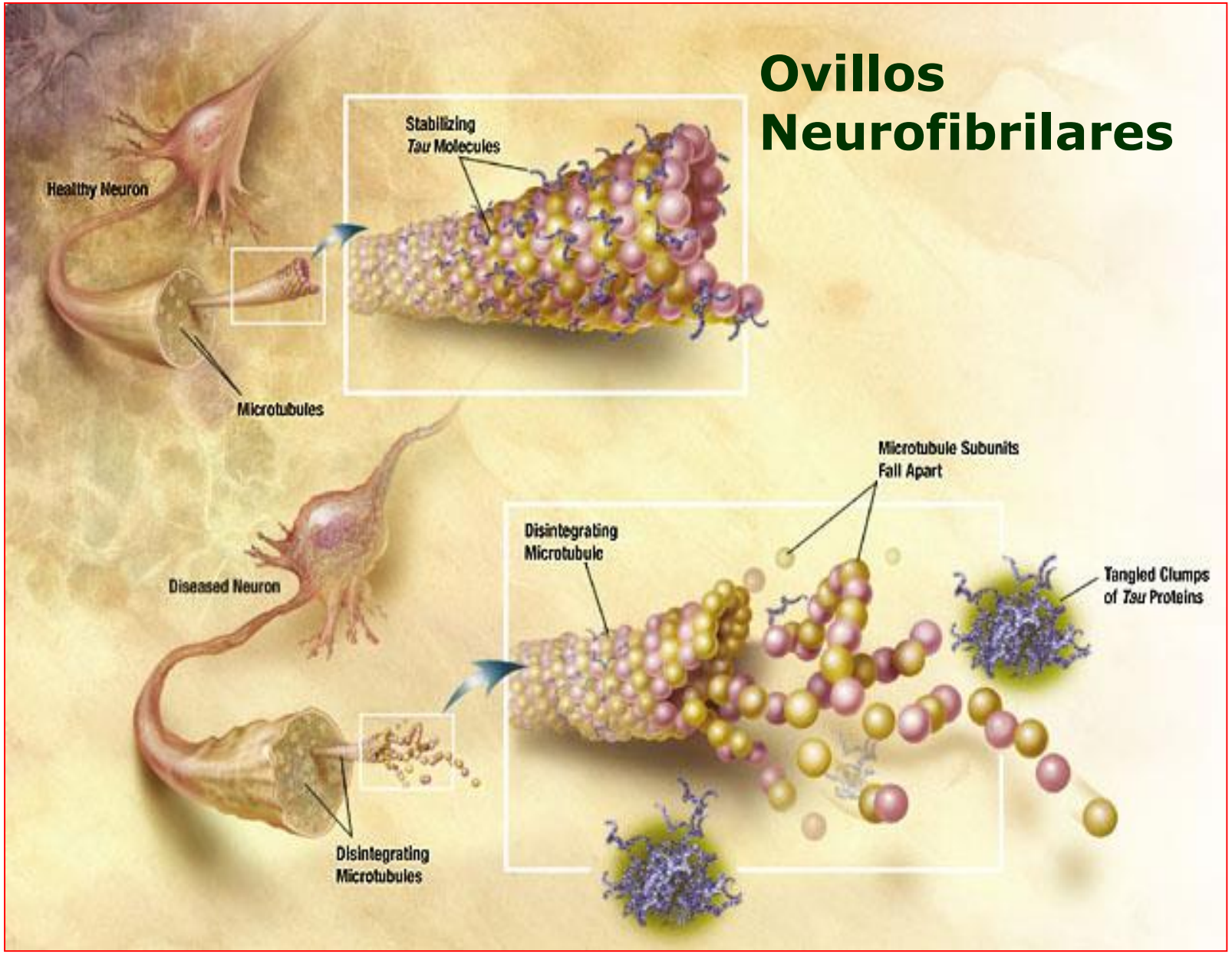


Placas beta-amiloides

La Proteína precursora de Amiloide (APP) es el precursor de las plaquetas beta-amiloides

1. APP se muestra como un filamento adherido a la membrana.
2. Las enzimas cortan el APP en fragmentos de proteínas, incluyendo el beta-amiloide.
3. Los fragmentos beta-amiloides se agrupan para formar las plaquetas.

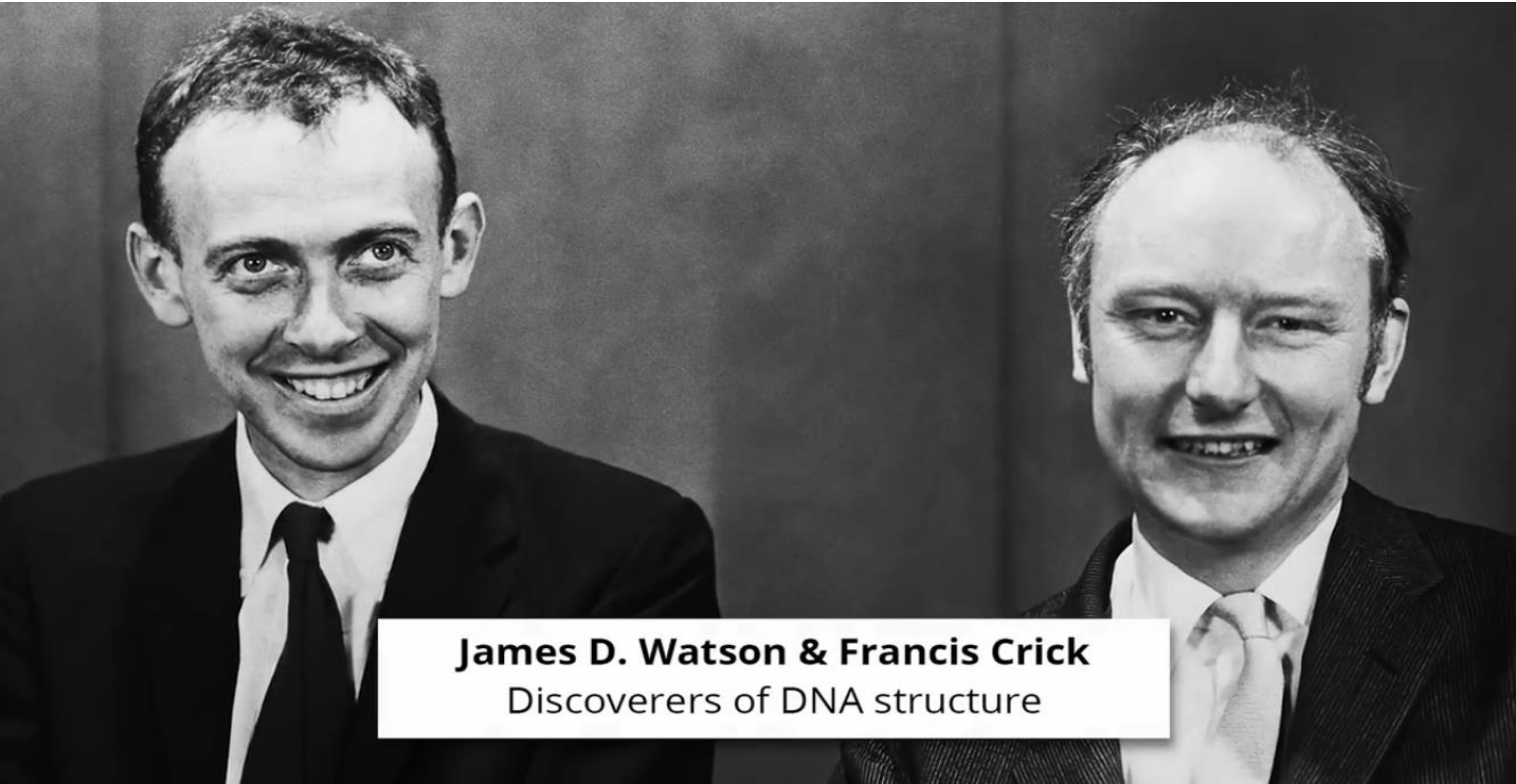
Este mecanismo es extra-celular…



- Las neuronas tienen una estructura que le da soporte que se denominan microtúbulos.
- Una proteína denominada tau estabiliza los microtúbulos.
- En la EA la tau cambia y los microtúbulos colapsan y forman los ovillos.

COGNICION
INICIATIVA CUBANA EN SALUD COGNITIVA

Genes y Demencia


James D. Watson & Francis Crick
Discoverers of DNA structure

Current Opinion in Biotechnology 1994, 5:663–667

APOE is a major susceptibility gene for Alzheimer's disease

Allen D Roses and Ann M Saunders

Duke University Medical Center, Durham, USA

The initial report on *APOE* as a susceptibility gene for late-onset Alzheimer's disease was presented a little more than two years ago. During the past year, several significant events have given added impetus to research into Alzheimer's. The association of increased allele frequency of *APOE4* with Alzheimer's disease has been reproduced in several dozen laboratories around the world. The protective effect of the *APOE2* allele has been reported and also rapidly verified. No evidence exists to support the notion of linkage disequilibrium with any nearby locus on chromosome 19. The neuropathological demonstration of apolipoprotein E (apoE) within neuronal cytoplasm in a location suitable for proposed interaction with microtubule-associated protein tau and MAP2c has introduced a new view of neuronal neurobiology. As apoE is not known to be expressed in neurons, its relationship with cellular receptors, such as the low-density lipoprotein related receptor, and the mechanism of intracellular trafficking are now important research problems. The role of apoE as a metabolic co-factor in neuronal metabolism presents new possibilities for neuronal mechanisms of

Current Opinion in Biotechnology 1994, 5:663–667

APOE is a major susceptibility gene for Alzheimer's disease

Inheritance of one or two *APOE4* alleles increases the risk of Alzheimer's disease by about threefold for each *APOE4* allele dose

"Heredar uno o dos alelos del APOE 4 incrementa el riesgo de Enfermedad de Alzheimer alrededor de tres veces…"

disease was presented a little more than two years ago. During the past

microtubule-associated protein tau and MAP2c has introduced a new view of neuronal neurobiology. As apoE is not known to be expressed in neurons, its relationship with cellular receptors, such as the low-density lipoprotein related receptor, and the mechanism of intracellular trafficking are now important research problems. The role of apoE as a metabolic co-factor in neuronal metabolism presents new possibilities for neuronal mechanisms of

Am. J. Hum. Genet. 45:586–591, 1989

Genetic Studies of Human Apolipoproteins. X. The Effect of the Apolipoprotein E Polymorphism on Quantitative Levels of Lipoproteins in Nigerian Blacks

To date, Nigerian blacks have the highest observed frequency of the *APO E*4* allele in world populations

Summary

Hum
focus
black
teins
are .
low-
terol and low-density lipoprotein cholesterol by 9.19 mg/dl and 11.11 mg/dl, respectively. The average ex-
cesses of the *APO E*4* allele are to increase total cholesterol and low-density lipoprotein cholesterol by

"Hasta la fecha, los nigerianos tienen la frecuencia observada más alta del alelo APOE 4 en la población mundial..."

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Alzheimer's disease: the cholesterol connection

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A hallmark of all forms of Alzheimer's disease (AD) is an abnormal accumulation of the β-amyloid protein (Aβ) in specific brain regions. Both the generation and clearance of Aβ are regulated by cholesterol. Elevated cholesterol levels increase Aβ in cellular and most animals models of AD, and drugs that inhibit cholesterol synthesis lower Aβ in these models. Recent studies show that not only the total amount, but also the distribution of cholesterol within neurons, impacts Aβ biogenesis. The identification of a variant of the apolipoprotein E (*APOE*) gene as a major genetic risk factor for AD is also consistent with a role for cholesterol in the pathogenesis of AD. Clinical trials have recently been initiated to test whether lowering plasma and/or neuronal cholesterol levels is a viable strategy for treating and preventing AD. In this review, we describe recent findings concerning the molecular mechanisms underlying the cholesterol–AD connection.

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Alzheimer's disease: the cholesterol connection

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"APOE es una de las mayores apolipoproteías en el plasma y el principal transportador de colesterol en el cerebro…"

Am. J. Hum. Genet. 45:586–591, 1989

Genetic Studies of Human Apolipoproteins. X. The Effect of the Apolipoprotein E Polymorphism on Quantitative Levels of Lipoproteins in Nigerian Blacks

*"Hasta la fecha, los nigerianos tienen la frecuencia observada más alta del alelo APOE 4 en la población mundial, pero sus ajustes medios de en el nivel de colesterol se encuentra entre los **más bajos** entre los estudios que relacional el colesterol y el APOE…esto podría ser a causa de su **dieta** baja en grasa animal"*

are .027, .677, and .296. The effect of APO E polymorphism is significant only on total cholesterol and low-density lipoprotein cholesterol. The average excesses of the *APO E*2* allele are to lower total cholesterol and low-density lipoprotein cholesterol by 9.19 mg/dl and 11.11 mg/dl, respectively. The average excesses of the *APO E*4* allele are to increase total cholesterol and low-density lipoprotein cholesterol by

Neuroepidemiology 1998;17:14–20

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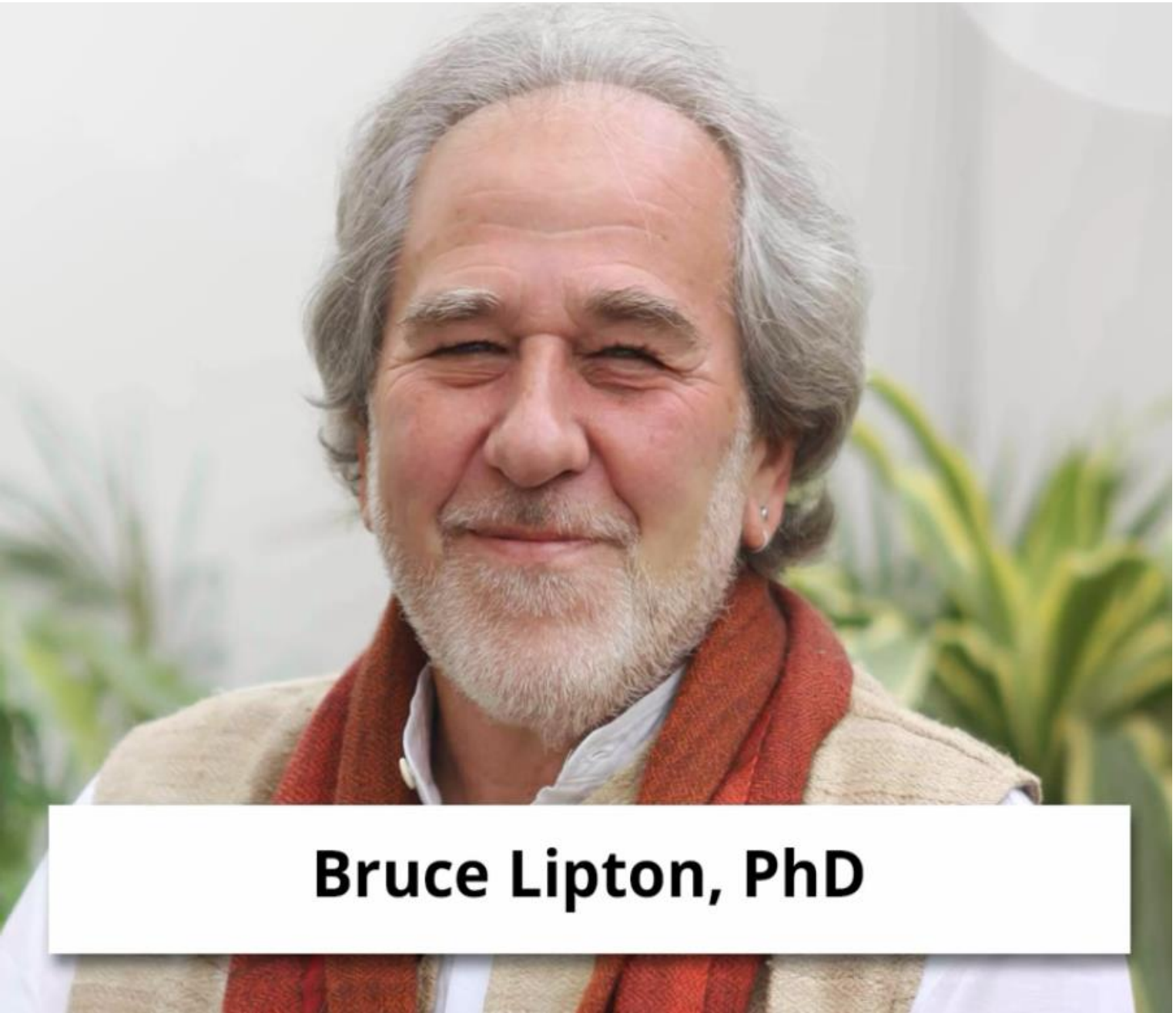
"En Nigeria, donde la frecuencia del APOE 4 es alta, pero los niveles de colesterol son bajos, la Enfermedad de Alzheimer suele ser rara. Sin embargo, los afroamericanos tienen una alta prevalencia de Alzheimer tanto como los demás nortemaericanos. La asociación entre el genotipo APOE y el colesterol parece ser un resultado del estilo de vida occidental…."



- El paradigma tradicional plantea la idea de que la biología es controlada por la actividad de los genes.

- Brude Lipton, desarrolló un grupo de experimentos y demostró que la actividad de los genes no es solo activada o inhibida por sus información intrínseca , sino además por la información del ambiente

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

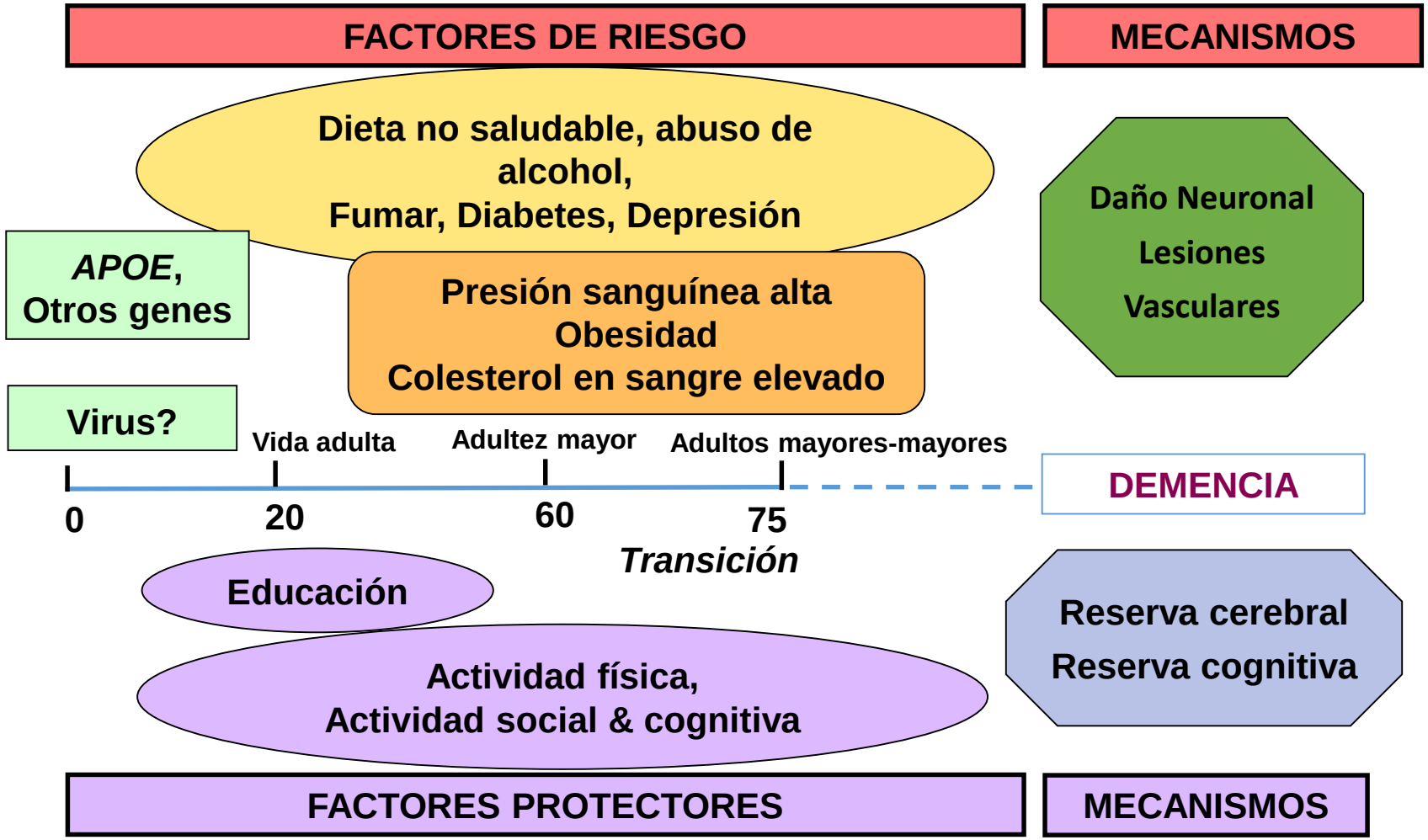
more than eightfold greater than that of the 2013 GWAS by accumulating the genetic data of ~635,000 individuals. This vast increase in number enabled the identification of nine novel AD risk loci, increasing the current total

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)

Neuropsicología y Envejecimiento: Una breve introducción

RANY™ HEALTH

Encuentro III

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