CAPÍTULO 4

THE AGING BRAIN: A NEUROPSYCHOLOGICAL PERSPECTIVE ON COGNITIVE DECLINE
EL CEREBRO ENVEJECIDO: UNA PERSPECTIVA NEUROPSICOLÓGICA SOBRE EL DETERIORO COGNITIVO

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Abstract

Introduction: Aging represents a progressively increasing phenomenon that has collaterally increased the prevalence of neurodegenerative diseases. **Objective:** The present review has proposed to analyze, through the updated scientific bibliography, the main factors related to both normal and pathological aging around the world, systematizing the main findings as revealed from neuroscience. **Methods:** Systematic search of scientific literature published in the last decade from the Web of Science, Scopus, and PubMed. **Results:** The literature describes various highly reduced brain structures and functions in healthy older adults and those diagnosed with dementia; particularly prefrontal, parietal, temporo-hippocampal, dorsolateral regions, and cingulate cortex. In addition, patterns of white matter degradation, demyelination, and cholinergic, dopaminergic, and serotonergic conditions are reported. Neurobiological, genetic and environmental models coincide with the participation of specific markers such as amyloidal deposits, neurofibrillary tangles and microglial inflammation as gold standard elements in the diagnosis of normative aging and dementia related deterioration of the neuronal functions of the elderly, which in turn would respond to apoptotic predispositions and metabolic oxidation processes by free radicals. **Conclusions:** The scientific community sustains that the earlier an individual begins to promote prevention strategies in favor of cognitive reserve and neuroplasticity, the less likely they are to experience the patterns and consequences of cognitive impairment due to neurodegeneration. A high cognitive reserve therefore seems to act as a neuroprotective variable against the onset and development of disorders such as Alzheimer's.

Keywords: older adult, cognitive impairment, Alzheimer, brain systems, causal models, sociodemographic variables, dementia, cognitive reserve

Resumen

Introducción: El envejecimiento representa un fenómeno cada vez más prevalente que ha aumentado colateralmente la prevalencia de enfermedades neurodegenerativas. **Objetivo:** La presente revisión se propuso analizar, a través de la bibliografía científica actualizada, los principales factores relacionados tanto con el envejecimiento normal como patológico en todo el mundo, sistematizando los principales hallazgos revelados por la neurociencia. **Métodos:** Búsqueda sistemática de literatura científica publicada en la última década en las bases de Web of Science, Scopus and PubMed. **Resultados:** La literatura describe varias estructuras y funciones cerebrales altamente reducidas en adultos mayores saludables y aquellos diagnosticados con demencia; particularmente en regiones prefrontales, parietal, temporo-hipocampales, dorsolaterales y corteza cingulada. Además, se informan patrones de degradación de materia blanca, desmielinización y condiciones colinérgicas, dopaminérgicas y serotoninérgicas. Los modelos neurobiológicos, genéticos y ambientales coinciden con la participación de marcadores específicos como depósitos amiloides, ovillos neurofibrilares e inflamación microglial como elementos estándar en el diagnóstico del envejecimiento normativo y el deterioro relacionado con la demencia de las funciones neuronales de los ancianos, que a su vez responderían a predisposiciones apoptóticas y procesos de oxidación metabólica por radicales libres. **Conclusiones:** La comunidad científica sostiene que cuanto antes comience un individuo a promover estrategias de prevención a favor de la reserva cognitiva y la plasticidad neuronal, menos probabilidades tendrá de experimentar los patrones y consecuencias del deterioro cognitivo debido a la neurodegeneración. Una alta reserva cognitiva parece actuar como una variable neuroprotectora contra el inicio y desarrollo de trastornos como el Alzheimer.

Palabras clave: adulto mayor, deterioro cognitivo, Alzheimer, sistemas cerebrales, modelos causales, variables sociodemográficas, demencia, reserva cognitiva

1. INTRODUCTION

Aging represents a progressively increasing phenomenon around the world, which among developed countries, is reflected both in lower birth rates and longer life expectancy respectively. Likewise, aging can be significantly influenced by biological, social socioeconomic, cultural, and nutritional factors, among others, which can predict quality of life and vulnerability to neurodegenerative diseases during the senescence process (Aránguiz A., 2010; Rodríguez, 2011; Alvarado & Salazar, 2014).

Epidemiological data from the United Nations, indicate that in 2000, the percentage of adults over 65 years of age reached 6.9% of the population worldwide, predicting an exponential growth of up to 16.2% for the next decades (Cardona Arango & Pelaez, 2012; United Nations Population Division, 2012). That is, older adults will reach an approximate total of 6'304.070 individuals by 2045 (Reitz et al., 201; Borbón et al., 2014). This projection would respond to factors such as medical advances allowing life expectancy extension, although at the cost of both aging related physical and mental health problems.

This worldwide exponential life expectancy increase has led to a wide spectrum of research regarding neurobiological, genetic and environmental factors underlying aging related neuropathological processes such as Alzheimer's, Parkinson's or dementia (WHO, 2015; Gamba Rincón et al., 2017), whose impact over public health translates, among other things, into the high costs required for their treatments (Custodio et al., 2012).

In addition, it is worth to consider the blurred barrier between normative and pathological aging processes, both related to the decrease of cognitive

and physical functions (Jack et al., 2011; McKhann et al., 2011), which therefore, demand an objective close up to those neurocognitive components that, under normal aging conditions, remain relatively stable.

For example, Luo & Craik (2008), establish that cortical and subcortical regions associated to mnesic components such as semantic memory, tend to remain stable as long as older adults activate their memory capacities on a regular basis. However, such stability would be affected when trying to access information demanding greater degrees of information specificity.

Similarly, Custodio et al (2012), mention that procedural memory, responsible for allowing the execution of previously learned determined psychomotor actions (e.g. driving a vehicle), also tend to be maintained, although the ability of the older adult to learn to perform new actions or tasks, implies greater demands of cognitive effort and time.

Additionally, normal aging entails the gradual loss of other cognitive and psychomotor functions such as working memory, verbal and visuospatial learning, as well as processes such as sustained attention (Bäckman et al., 2005). Complementary, Merrill et al (2012), suggest that, on average, older adults would experience difficulties in remembering certain names (people, places or things), reflected in up to one standard deviation (1 SD) below the average obtained by young adults after standardized tests evaluations.

The relative decline accompanying normal aging, might also affect spatial abilities, with poor results both in spatial construction and learning tasks evaluated by the Wechsler test (Bäckman et al., 2005), likewise, executive functions reflect a slight affection during normal aging.

On the other hand, the progressive development of diagnosed neurodegenerative processes among older adults, also represents an alarming challenge for the affected population, the clinical community and society in general. In this line, contributions provided by neuroscience, psychiatry, geriatrics, genetics and psychology, during the last decades, have allowed us to better understand both normative and pathological aging processes.

In an attempt to answer the question about why the elderly brain becomes more vulnerable to functional decline and disease, theoretical models of particular interest have been proposed, considering apoptotic pre-programming, neuroplasticity, physical and intellectual exercise, and cognitive reserve. It has been established for example, that free radicals' production during metabolic-oxidative processes are particularly harmful, accelerating cell deterioration and turning individuals vulnerable to eventual dementia stages such as Alzheimer's disease (Drachman, 1997), therefore, the dietary assimilation of antioxidant components (Vitamin C and E) would have preventive effects over the Central Nervous System (CNS) by avoiding or regulating the free radicals' production (Schereder, 2010).

In addition, cognitive problems represent a predominant condition among the elderly, leading to serious biopsychosocial disabilities, strengthened by critical aging related experiences such as mourning, retirement, geriatric hospitalization and social isolation (Guerrón Camino, 2016). Likewise, it should be noted that, when accompanied by inactivity, aging might affect motor systems functionality, which consequently could accelerate the senescence process. Therefore, it has been suggested that by increasing physical activity levels and stimulating environment interaction, older

adults might experience positive effects on cognitive functions, reducing the risk of developing Alzheimer's disease (Rovio et al., 2005).

In addition, other sociodemographic variables such as educational level, gender, occupation or marital status, seem to exert a notorious influence on the elderly quality of life, cognitive decline vulnerability and neuronal degradation processes. Likewise, these approaches advocate for the optimal early adoption of preventive activities, such as physical and nutritional healthy habits and a proper stimulating and enriching environmental interaction (Scherder, 2010; Drachman, 1997).

In this line, Benitez Perez (2017) and Creagh Peña M (2015), suggest that both life expectancy extension and neurodegenerative processes control, implies a scientific goal towards elderly global health, where good quality aging would imply developing and maintaining physical and neurocognitive activity patterns, strengthened by social support factors such as family, community and cultural constant interaction. Furthermore, these findings also allow us to project ourselves towards scenarios where aging can not only be experienced in a healthy way, but also, where this process can be potentially delayed

1.1 Sociodemographics, aging and cognitive decline

The previously described findings are complemented by the contributions of authors such as Gamba et al (2017), who through a non-experimental comparative analysis, evaluated the neuropsychological performance of a sample of 456 older adults divided into three groups (workers vs. retirees vs. institutionalized), through the application of the NEUROPSI (Ostrosky et al., 2007) and the Adapted Minimental-State Examination (Roselli et al., 2000), whose results showed that, compared to the internalized group,

working older adults and retirees, showed lower declines on recall memory, working memory, learning processes and executive functions; factors that, in contrast, reflected more impairment among the internalization group.

In addition, Mora et al (2012) and Abarca et al (2008), indicated that the "educational level factor" played a relevant modulating role, where institutionalized older adults (mostly non or partially educated subjects) show a less efficient development in neurocognitive tests, while maintaining less interaction with the outside both at the socio-family and affective levels, becoming seemingly more vulnerable to cognitive deterioration.

Likewise, Luna Soliz & Vargas Murga (2018), suggest that variables such as being 75 years old or older ($p < 0.001$), unemployment ($p = 0.026$), having less than 8 years of education ($p = 0.003$) and having experienced a depressive episode in the last year ($p < 0.001$), are factors associated with dementia related cognitive impairment. Meanwhile, Mias et al (2017), report that the female gender and low schooling, would significantly influence cognitive functionality at advanced ages.

A similar approach was reported by Sanchez Contreras et al (2010), who analyzed the relationship between cognitive impairment, educational level and occupation, in a sample of 155 older adults distributed among cognitively healthy individuals, patients with Alzheimer's Disease (AD), and patients with Mild Cognitive Impairment (MCI) respectively. The results indicated a significant difference ($p = 0.014$) between the AD and MCI groups, who performed mostly manual tasks throughout their lives, compared to the cognitively healthy subjects, whose occupational activities

were mostly related to intellectually and academically demanding jobs and/or professions.

These data suggest that occupational and educational variables might act as predisposing factors towards cognitive deterioration conditions when associated with limited intellectual effort activities, negatively affecting the subject's functional cognitive reserve once reached advanced ages. Additionally, Portillo (2015) indicates that MCI conditions seem mostly related to older adults with either no level of education, widowed and/or single.

Consistent with these findings, Scherder (2010) argues that the elderly brain tends to become more vulnerable to disease and degeneration in response to factors that are integrated into a cyclical model including both physical and mental inactivity, leading to changes at the sensory and central nervous systems respectively, both translating into neurodegeneration and dementia pathology. In addition, the author mentions risk factors such as apoptosis genetic predisposition and free radicals' metabolic production, both leading to neuronal death commonly found among overweight people, variables that might play an important role on aging cells degeneration processes underlying dementia related conditions.

In this sense, reaching older adulthood would imply facing progressive processes of both anatomical and physiological degeneration, making it quite challenging to maintain our regulatory systems at a 100% in order to ensure sufficient nutrients to properly sustain life (Whalley, 2015), although, evidence suggests that such processes could slow down by promoting mental function compensation throughout life, strengthening neuroplasticity and cognitive reserve through habits including nutrition

and daily neurocognitive exercise, among other protective variables such as social interaction and physical activity.

In addition to environmental and sociodemographic factors such as low schooling or scarcity of economic resources, a wide range of evidence also indicates that genetic variables (Apo E genotype) and neurobiological markers (amyloid plaques, neurofibrillary tangles, microglial inflammation), can play a preponderant role when it comes to cognitive impairment among the elderly (Scarmeas et al., 2003).

On the other hand, dementia conditions imply both neurodegradation processes and anatomical-physiological deterioration, factors overpassing those of normative aging, and that unfortunately represent a tangible threat in the global epidemiological context.

For example, some studies estimate that dementia affects near 50 million people worldwide, from which a 60% belong to low and middle income countries such as those of Latin America and the Caribbean, a number to be reflected in around 9.1 million people by 2040, equaling North America data" (Llibre and Gutiérrez, 2014).

As a matter of fact, neurodegenerative pathologies such as Alzheimer's Disease (AD) represent some of the conditions with the greatest impact on the quality of life of the elderly and their environment, thus promoting the neuroscientific interest for a better understanding of the mechanisms involved in progressive neuronal degeneration and its effects on the cognitive, emotional and psychosocial spectrum of the patient (Arriagada, 2016).

In this line, the WHO (2014) describes AD as the most common form of dementia, representing 75% of these pathologies worldwide. AD is conceived as a chronic and progressive cerebral syndrome that alters higher cortical functions such as decision-making, memory, thinking, orientation, comprehension, language, learning, self-care, etc., whose semiology affects both patients and caregivers.

In addition, the World Bank indicates that 58% of Alzheimer's patients do live in underdeveloped or developing countries, a percentage that might increase up to a 63% by 2030 and up to a 68% by 2050 respectively (Balbás Liaño, 2016).

Likewise, the United Nations has stated that mental and neurological disorders, including AD, represent an important cause of morbidity contributing to the global burden of non-communicable diseases, thus reflecting a clinical and scientific challenge for the 21st century (WHO, 2014).

The incidence of dementia increases with age; with 4 out of 1000 people between 60 and 64 years old being affected, while, in patients older than 90 years, the figure increases to 105 people per each thousand (INEC, 2017).

In Ecuador, approximately 941,000 people (7% of the total population) are older adults, and it is presumed that by the year 2050 there will be more than 3,000,000 older adults, reaching 18% of the total of its inhabitants and constituting itself as a highly vulnerable population to the development of degenerative pathologies such as AD (INEC, 2017).

Likewise, the TASE foundation (2017), indicates that there would be some 59.000 people with AD and other dementias in Ecuador, and for each of them, there would be at least seven affected family members, that is; 420.000 Ecuadorians would be directly linked to the disease and its consequences.

1.2 Some insights on the neurobiology of healthy and dementia affected aging

In an attempt to study the effects of aging on the functional integrity of the brain's anterior-posterior cognitive network associated with memory and planning, also known as the *Default Neural Network* or *The Default Network* (Buckner & Carroll, 2007), authors Andrews et al (2007), using Magnetic Resonance Imaging (MRI), analyzed a sample of 93 healthy subjects between 18 and 93 years of age. Results indicated that, contrary to the young subjects, the older adults showed significant declines ($p < 0.001$) at the integrative functionality and interconnectivity of the analyzed brain areas (medial prefrontal cortex, bilateral hippocampal and parahippocampal cortex, and bilateral parietal cortex), which were complemented by a significant disruption ($p < 0.05$) of connectivity at the dorsal attentional system level (intraparietal sulcus, medial temporal area, and inferior precentral sulcus).

Likewise, the older adults group showed noticeable levels of white matter degradation and poorer performance during semantic decision tasks *(Category Fluency Test-Animals, the Word Fluency Test, the Trailmaking Test B, and the Weschler Memory Scale- Revised (WMS-R) Andrews et al (2007).*

Complementary, understanding aging related cognitive decline processes has been complemented thanks to studies such as those by Plassman et al

(2007), indicating that up to 14% of people over 71 years of age report some type of dementia symptoms. Additionally, St. Jacques et al (2010) reported less connectivity between the amygdala and posterior brain regions among the elderly, which seems to suggest changes at the emotional stimuli processing (Dennis & Thomson, 2014).

In addition, Koch et al (2010), compared 21 older adults to 17 healthy young people, and found brain connectivity deficits among the first group at the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) respectively. Brain regions similarly characterized by decreased brain connectivity manifested by functional neuroimaging among healthy older adults have been reported at the frontal, temporal, limbic, and paralimbic levels, as well as at the subcortical level (see Achard & Bullmore, 2007).

Complementary, Whalley (2016) indicates that evidence provided by comparative postmortem studies between brain samples from young individuals and those belonging to older adults, reveals a marked between group difference, with more expanded grooves and narrower gyri among aged brains related to young brains, features associated with neuronal shrinkage on a larger scale due to degradation of gray matter. Likewise, ventricular cavities enlargement in elderly brains represents another reported characteristic.

Furthermore, aging related hippocampal volume reduction is equally visible, which explains typical memory difficulties markedly accentuated under AD diagnosis and other dementias. Nevertheless, it should be emphasized that these superficial comparisons may omit initial conditions of pathological neurodegeneration, such as those present in AD, whose biological markers, which include decreased brain volume, could appear even decades before the symptomatic manifestations.

Likewise, two important cerebral anatomical characteristics related to normative senescence are cortical thickness and specific brain structures/regions volume. MRI studies indicate that, compared to neurodegeneration affected brains, the elderly healthy brains show less volume reduction at the posterior prefrontal cortex, as well as in the temporal, occipital, and parietal lobes respectively (Whalley, 2016).

In this regard, frontal lobes deterioration through normal aging is reflected in prefrontal cortex decreased production of neurochemicals such as dopamine, norepinephrine and acetylcholine respectively, leading to degenerative changes at the basal forebrain (Zhang, 2004). In addition, gradual deficit of executive functions is identified after standardized evaluations by means of neurocognitive tests and brain neuroimaging techniques, reflecting white matter tracts alterations interconnecting frontal and prefrontal areas with other regions of the brain (Whaley, 2016).

These age-related white matter changes become evident with the appearance of hyper intensity marks after MRI analysis attributed to microvascular lesions potentially explained by blood vessels extra cranial conditions. Interestingly, such white matter hyperintensity marks in older adults seem correlated to an economically limited childhood, which points to a biological-environmental interaction where sociodemographic factors seem to significantly underlie age related cognitive function deterioration (Kalaria, 2009).

On the other hand, in the case of AD, last decades have strengthened the evidence regarding characteristic changes within the Central Nervous System (CNS) such as cortical atrophy patterns at the frontal, temporal, parietal, and occipital levels (Scherder, 2010; Regeur et al., 1994; Swaab et al., 1998). Likewise, findings from MRI neuroimaging have frequently

shown atrophy processes at the basal ganglia, the septum, and particularly the cerebral hippocampus (middle temporal lobe), a structure in charge of short-term memory processes, significantly affected during the course of the disease.

Similarly, evidence suggests that AD patients show notorious metabolic reduction parameters related to mitochondrial enzyme degeneration and adenosine triphosphate production (ATP), an essential cellular energy nucleotide (Sullivan & Brown, 2005). Moreover, this metabolic reduction seems common at the prefrontal and temporo-parietal cortex level among AD patients, playing a seemingly decisive role in both atrophy and neurocerebral dysfunction processes.

In addition, the cholinergic, glutamatergic, dopaminergic and serotonergic systems at the entorhinal cortex, hippocampus and amygdala, are severely affected in AD, particularly during its more advanced stages, thus affecting memory functions. Furthermore, such neurochemical conditions are also identified at the middle prefrontal and inferior parietal cortex respectively, whose functions are associated with attentional processes and graphomotor skills (Mesulam, 2004). It has been suggested that cholinergic decline might underlie the production of two key cognitive decline neuromarkers: amyloid plaques and neurofibrillary tangles (Scherder, 2010).

1.3 Plaques, Tangles and Microglia: Key biomarkers in aging and dementia.

At the microscopic level, aging brain biomarkers among both healthy and dementia affected elderly, have been widely documented. In this sense, not only smaller neurons with less elaborate dendritic connections have been

detected, particularly at the prefrontal cortex and basal ganglia (Whalley, 2016), but also, a notorious reduction in brain cell clusters accompanied by specific toxic protein formations, such as amyloid plaques and neurofibrillary tangles respectively.

Amyloid plaques are identifiable through brain staining processes at the interneuronal spaces and are formed by an excessive and toxicological accumulation of components such as the beta-amyloid protein (β-amyloid), associated with cholesterol transport and antimicrobial activity in addition to other elements such as zinc, immunoglobulins and E and J apolipoproteins. The presence of these plaques represents iconic neurobiological markers in the AD diagnostic process, however, their identification does not necessarily underlie dementia symptoms (Snowdon, 2001).

The amyloid hypothesis as a causal model of AD, was initially proposed by John Hardy and David Allsop in 1991, who proposed that the pathological sequence of those who suffer from this neurodegenerative disease, responds to a progressive and toxicological accumulation of interneuron protein deposits, whose effect might explain the gradual and exponential degradation of neuronal structures and their synaptic functions, thus resulting in neuronal death and deterioration of the of the brain functional faculties. The scientific evidence that supports this argument has been strengthened by genetic studies, and longitudinal analysis of clinical and cognitive biomarkers (Dang et al., 2018).

Amyloid proteins are located in different areas of the human body, which seem to be related to specific pathologies, however, genetic studies, human autopsies, and brain neuroimaging in AD patients suggest that the accumulation of this protein might drive the development of the

progressive neurodegeneration of this disease, also causing significant psychological deterioration in those who suffer from it, as well as among their caregivers (Ashton et al., 2018; van der Kant et al., 2019).

Nevertheless, the delay regarding clinical manifestation and pathophysiological onset of many affected patients, make it difficult to accurately determine the regions of appearance of the amyloid deposit, therefore, it is considered that the aberrant accumulation of this protein in the brain seems the main event activating the disease cascade (Mormino and Papp, 2018).

Age is naturally among the main risk factors associated with the amyloid deposit pattern, since the average profile of AD patients over 65 years of age is significantly associated with the incidence of positive Positron Emission Tomography (PET)-amyloid responses. Interestingly, regardless of an individual's cognitive state, it has been estimated that 5% of healthy people between 50 and 60 years of age respectively, are amyloid-positive. Likewise, it has been determined that more than 50% of older adults over 80 years of age might be amyloid-positive, so that age reflects a pivotal demographic risk factor for dementia related conditions such as AD (Arbizu et al., 2015).

On the other hand, neurofibrillary tangles consist of an abnormal set of intertwined small protein fibrils within neurons, particularly present under AD diagnosis. These components are formed by intracellular microtubules of TAU protein hyperphosphorylation, a pathological aggregate with often insoluble characteristics (Von Bernhardi et al., 2010). It is worth mentioning that, like senile plaques, these abnormal deposits would also be present among healthy older adults, although at

considerably lower levels and with a distribution mostly located at the cortical level (Hof, & Morrison, 2004; Price et al., 2009).

In complement, elderly associated memory deficits and neurodegenerative diseases are notoriously related to hippocampal synaptic abnormalities. In this sense, the Tau protein promotes axonal filaments assembly through an intraneuronal pathway structure, thus preserving neuronal health through toxic proteins purification, therefore, its dysfunction leads to synaptic alteration and microtubules degradation among various nerve cells (Naseri et al., 2019).

Both types of biomarkers (amyloid plaques and neurofibrillary tangles), represent *gold standard* dementia diagnosis elements, so their identification through neuroimaging techniques such as PET or Magnetic Resonance Imaging (MRI), help clinical prevention processes and treatment of such pathologies, particularly in early stages.

In addition, an alternative model that might explain neuronal degradation and death during senescence, particularly under neurodegenerative conditions such as AD, has also been considered. This model suggests that microglial inflammation activate autoimmune mechanisms with eventual neurotoxic consequences, that is, the protein deposits in AD patients are recognized by microglial receptors (responsible for phagocytosis and neuronal immunology processes), and as a result, triggering an innate immune response, characterized by the release of various inflammatory chemical mediators at a neuronal level, thus contributing to the disease progression and neuronal death (Krauthausen et al., 2014; Regen et al., 2017).

Subsequently, microglial inflammation might accelerate the elderly brain's higher cognitive function deterioration, affecting learning and memory processes, effects then extrapolated to adaptive behavior (Sarlus & Heneka, 2017). Genetic studies support that microglia remain inactive while in absence of strange stimuli, however, it is capable of scanning nearby brain regions by monitoring the entire brain parenchyma. In this sense, when an acute inflammatory brain lesion is detected, a microglial protection response is activated in order to compensate for the damage. However, if the inflammatory condition is chronic, and the stimulus persists significantly, the brain immune process becomes detrimental, therefore contributing to neuronal loss (Calsolaro & Edison, 2016).

Evidence supporting these proposals on factors underlying cognitive impairment and dementia conditions such as AD, are presented by Long and Holtzman (2019) (see Table 1), comparatively systematizing the main characteristics of both the amyloid deposit model and the microglial inflammation model respectively

Table 1.

Comparative synthesis of the amyloidal model vs. the microglial model of Alzheimer's disease

Amyloid Deposit Model	Microglial Inflammation Model
The amyloid hypothesis is supported by genetic findings pointing to a pathological predisposition underlying duplication of the β-Amyloid (Aβ) protein locus precursor.	Microglial inflammation model has experienced a growth reinforcing the understanding of pathogenesis, the essential event is represented by the immune microglial toxicological response that would lead to neuronal degeneration.

The amyloid deposit model continues to be one of the main standards in explaining the origin of age-related neurofunctional deterioration, mainly Alzheimer's Disease. Longitudinal and biomarker studies estimate that the accumulation of neuritic plaques within the human brain is complementary to the dissemination of Tau protein in correlation to the involved regional structures.	Clinical-neuropathological correlational analyzes have demonstrated the stereotyped propagation of inflammatory mechanisms on brain structures affecting the connection of neuroanatomical networks.
In general terms, Aβ precedes both normative and pathological cognitive impairment symptoms, becoming a gold standard biomarker for AD diagnosis.	Longitudinal and cross-sectional PET imaging findings indicate that, unlike the amyloid deposition model, microglial inflammation appears to be significantly correlated with the progression of cognitive impairment
Brain plaque accumulation model has provided the greatest scientific contribution to elderly cognitive decline explanation. However, a large number of plaque mutations still represents a limitation regarding unknown functions, as in the case of the amyloid precursor protein (APP).	One of the main limitations of the microglial inflammation model is related to the difficulty in analyzing whether the propagation is either harmful or protective. Some authors suggest that, at different stages of the disease, effects might change from protective triggering within the context of amyloid deposition into harmful activation during microglial inflammation.
Amyloid-based treatment has turned out to be ineffective when it comes to	Although anti-inflammatory trials with rodent models have attempted to

long term positive changes in the course of symptomatic spread, leading to treatment limitations focusing on pre-clinical strategies instead of intervention therapies.	reduce symptoms with mixed results, therapeutic strategies in human patients continue to focus mostly on Tau expression reduction (Alzheimer, Parkinson, Huntington).

Note. Main contributions and limitations of the amyloid deposit model vs. the microglial inflammation model (Long and Holtzman, 2019).

Regarding microglial inflammation, a preventive anti-inflammatory, although not necessarily exclusive treatment, has been suggested, which in clinical practice, would imply a substantial economic loss for both pharmaceutical industry and the standardized treatment for neurodegenerative diseases such as Alzheimer's. In any case, evidence indicate that, up to now, prevention habits such as continuous cognitive training, social interaction and physical activity, seem to be not only crucial protective factors, but also the most recommendable strategies promoting neuronal reserve and neuroplasticity (Bermejo et al., 2016).

1.4 Telomeres and Chromosomes

Located at the chromosome edges, telomeres constitute non-coding nucleic acid sequences that play a protective and stabilizing role for DNA, preventing apoptosis (Pemberthy López et al., 2015). It is during the embryonic stage that the "telomerase" enzyme replicates the telomeric sequences, preventing their shortening and wear, however, this enzyme is inactivated shortly before birth, although the spermatogonia associated with Follicle Stimulating Hormone (FSH) keep on producing it (Aranda Anzaldo & Dent M 2017). Nevertheless, mitosis DNA replication degrade telomeric sequences, progressively shortening both their size and that of the chromosomes, a process that, over time, leads to the eventual cellular

deterioration typical of aging (Haidong Zhu et al. al., 2011; Nilsson et al., 2013; Zhang et al., 2014).

Interestingly, organisms such as planarian *(Phylum Platyhelminthes)* also produce telomerase, which in this species, allows individuals to regenerate muscles, skin, the digestive system and even the brain, slowing down the aging process (Noreña et al., 2015). In compliment, gene therapy studies using viruses whose genes have been replaced by telomerase enzyme (rAAV vector) to later be injected into the genome of adult mice, have shown that, in contrast to control individuals (uninoculated rodents), experimental mice age more slowly, prolonging their life expectancy by up to 24%, in addition to presenting improvements in memory and muscle coordination (Gonzales-Suarez et al., 2001; Bernardes de Jesus B et al., 2012; Mendelsohn & Larrick, 2012; Almudena Villa and Martínez Juanes, 2014).

Although these findings seem encouraging and reflect new challenges for the scientific community in the context of their potential application in humans, authors indicate that rAAV vectors might experience limited integration with the human genome with potential carcinogenic effects, thus, more evidence is required (Almudena Villa and Martínez Juanes, 2014).

2. CONCLUSIONS

2.1 Mental Stimulation, Cognitive Reserve and Active Aging

The above described evidence invites us to reflect on a better understanding of cognitive deterioration processes during both normative and pathological aging; these, so far, unavoidable phenomena translated

into brain functional decline at a higher or lower level, finds an intrinsic association with neurobiological, genetic and environmental factors. In this sense, predisposition to the development of dementia-type conditions such as Alzheimer's disease would be mediated by elements that, once integrated, seem to play a decisive role in establishing diagnosis and treatment plans.

Additionally, the general consensus points to the need to establish cognitive deterioration prevention processes in order to either avoid or reduce the possibilities of its activation and its pathological effects. In practice, it certainly seems more feasible to prevent Alzheimer's than to cure it, and therefore, to direct clinical-therapeutic strategies towards neurocognitive exercise, the promotion of healthy habits such as physical activity, adequate nutrition restricting or preventing free radicals' production on a large scale, as well as interaction with culturally and intellectually enriching environments.

The scientific community also sustains that the earlier an individual begins to promote prevention strategies in favor of cognitive reserve and neuroplasticity, the lower the chances of experiencing the patterns and consequences of cognitive impairment due to neurodegeneration. A high cognitive reserve therefore, seems to act as a neuroprotective variable against the onset and development of disorders such as Alzheimer's. In this regard, education, physical exercise, work occupation, bilingualism, positive social relationships, intellectual stimulation and creativity, seem to play a relevant role preventing such conditions (Redolat Iborra, 2012).

Likewise, a proactive lifestyle might be the best way to prevent age-associated cognitive decline, as the aging brain can activate its neuroplasticity and counteract the negative consequences of decline,

putting into motion compensatory and adaptive capacities through cognitive reserve (Grady, 2012).

The concept of cognitive reserve finds association with that of neuroplasticity, suggesting that every time we learn something new, we create new synaptic connections and neural networks, empowering the brain to restructure and recover processes. This adaptive potential of the nervous system allows the brain to potentially recuperate from disorders or injuries, and thus, reducing the effects of structural alterations produced by pathologies such as Alzheimer's and other conditions such as multiple sclerosis, Parkinson's, dyslexia, insomnia, etc. (Jones et al., 2006; Kraft, 2012).

As mentioned before, the interaction with enriched and stimulating environments could activate learning drive changes and adaptations in pre-existing neural connections, promoting neuroplasticity. In the daily context, authors such as Stern (2012) recommend promoting activities related to a lower number of ß-amyloid deposits in advanced ages, which are systematized below:

- ~ Reading and writing (literature, magazines, newspapers, e-mails, etc…)
- ~ Board games: Cards, crossword puzzles, chess, puzzles, word search.
- ~ Jenga, graphic mazes, math problems, training cards
- ~ Musical learning
- ~ Bilingualism/polylingualism
- ~ Plastic arts (Painting, drawing, sculpture)

- ~ Sleep hygiene: Delta waves (< 2Hz) activate glial cells that purify the cerebrospinal fluid, eliminating the metabolic waste accumulated during daytime synapses (sleep deprivation increases the accumulation of Beta-amyloids
- ~ Reduction/elimination of alcohol and tobacco consumption

Finally, the promotion of activities related to art, culture and science strengthen the benefits of neuroplasticity and cognitive reserve, factors that, as has been reviewed, are key in the prevention of neurodegenerative pathologies (Palmiero et al., 2020; Simonton, 2012; McFadden & Basting, 2010). It is therefore recommended to visit museums, concerts (classical music, jazz, opera), planetariums, cinema, etc. Activities that, in addition to promoting mental health and cognitive reserve, dignify human beings, enriching their quality of life and, by extension, their cultural environment.

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