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Alzheimer's disease: an evolutionary approach

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Summary - *Alzheimer's disease (AD) is a complex disease associated with advanced age whose causes are still not fully known. Approaching the disease from an evolutionary standpoint may help in understanding the root cause of human vulnerability to the disease. AD is very common in humans and extremely uncommon in other mammals, which suggests that the genetic changes underlying the alterations in cerebral structure or function that have taken place over the course of the evolution of the genus* Homo *have left specific neurons in the human brain particularly vulnerable to factors which trigger the disease. Most of the genes whose mutation leads to AD are involved in synaptic plasticity. Evidence has also been found relating AD to neuronal oxidative stress. Neurons in certain association areas of the human brain retain juvenile characteristics into adulthood, such as the increased expression of genes related to synaptic activity and plasticity, incomplete myelination and elevated aerobic metabolism, which can cause an increase in oxidative stress in these neurons. Oxidative stress can cause myelin breakdown and epigenetic changes in the promoter region of genes related to synaptic plasticity, reducing their expression. These changes may in some cases induce hyperphosphorylation of tau and β-amyloid deposits, which are characteristic of AD. The adaptation of humans to the cognitive niche probably required an increase in synaptic plasticity and activity and neuronal metabolism in neurons in areas related to certain cognitive functions such as autobiographical memory, social interaction and planning. The cost of these changes may have been the brain's increased vulnerability to factors which can trigger AD. This vulnerability may have resulted from the evolutionary legacies that have occurred over the course of the evolution of the human brain, making AD a possible example of antagonistic pleiotropy. The evolutionary approach allows apparently unrelated data from different disciplines to be combined in a manner that may lead to an improved understanding of complex diseases such as Alzheimer's.*

Keywords - *Epigenetics, Synaptic plasticity, Antagonistic pleiotropy, Brain's default mode network, Heterochrony, Reelin.*

Introduction

Along with molecular biology, evolutionary biology constitutes the foundation of modern biology. In contrast, the biomedical sciences, which study the biology and pathology of the species *Homo sapiens*, have shown little interest in this discipline. Fortunately, this situation is beginning to change, and over the last few decades the pool of publications attempting to relate human pathology to biological evolution has steadily increased (Eaton *et al.,* 1988 a, b; Nesse & Williams, 1994; Smith *et al.,* 1999; Stearns, 1999; Eaton *et al.,* 2002; Burns, 2007; Nesse, 2008; Brüne, 2008; Sanjuán, 2009; Gluckman *et al.,* 2009).

The relevance of evolutionary biology in the biomedical sciences lies primarily in the contributions that this discipline can provide in terms of research. Focusing on disease from an evolutionary standpoint can expand the horizons of biomedical research and lead to hypotheses that never would have been postulated had they been formulated from a traditional perspective (Nesse, 2008). The evolutionary approach to disease has already contributed interesting ideas, such as:

1) The concept of coevolution between microorganisms and hosts.
2) The selection of antibiotic-resistant strains.
3) The distinction between diseases and defence mechanisms, like fever, coughing and vomiting.
4) Design compromises, such as bipedalism, which promotes lumbar disc herniation.
5) The incompatibility between our genotype, which resulted from the slow adaption to the ancient environment in which our species evolved, and our current environment (genome lag).
6) Evolutionary legacies, which increase our reproductive capacity at the cost of increasing our vulnerability to certain diseases (Nesse & Williams, 1994).

Antagonistic pleiotropy is a phenomenon in which evolutionary changes favour survival and reproduction in youth but increase the possibility of developing certain diseases at a post-reproductive age. Examples of such evolutionary changes in youth and their subsequent risks in adulthood include oestrogens and breast cancer or testosterone and prostate cancer. In antagonistic pleiotropy, genes which are advantageous at a reproductive age can become harmful at a post-reproductive age, when they are no longer subject to the filter of natural selection.

The concepts of genome lag, evolutionary legacies that increase vulnerability to disease and antagonistic pleiotropy can be particularly useful in understanding complex diseases in which multiple genetic and environmental factors are involved and which are sometimes associated with advanced age and are predominantly or exclusively human, like Alzheimer's disease (AD), frontal dementia and schizophrenia (Bufill & Blesa, 2006). This article does not aim to describe the cause or causes that result in the onset of AD. Rather, it seeks to analyse the contributions of evolutionary biology which can provide an improved understanding of the pronounced vulnerability of the human species in relation to the not yet fully understood factors that lead to the development of Alzheimer's disease.

Alzheimer's disease

AD, the most common cause of dementia, is characterised by deposits of abnormal peptides in the brain. Neurofibrillary (NF) tangles made up of the aggregation of hyperphosphorylated tau protein are found in the interior of the neuron, where they form double-helicoidal filaments that distort the neuronal cytoskeleton. Neuritic plaques, on the other hand, are made up of the accumulation of beta amyloid peptides (Aβ), fragments of a transmembrane protein called amyloid precursor protein or APP, found in the extracellular space. These abnormal peptide deposits are also found in a relatively high percentage of the elderly who do not present signs of cognitive impairment, although in these cases the proportion of lesions tends to be lower than in patients with AD. Patients with AD also exhibit amyloid deposits in small cerebral blood vessels, inflammatory reactions in areas where abnormal peptides are deposited, loss of synapses and finally neuronal destruction.

AD usually appears after 65 years of age and its prevalence doubles every five years. In the over-85 population, the prevalence of AD in developed countries ranges from 20 to 40% (Mesulam, 2000).

The fact that AD has an elevated prevalence in the elderly does not mean that the disease is an inevitable characteristic of old age. In certain individuals the disease can manifest at an earlier age or with greater intensity due to genetic or environmental factors. A certain proportion of the elderly population does not present Aβ deposits or NF tangles, while others develop these lesions at relatively early

stages in their lives (Ohm *et al.,* 1995; Braak *et al.,* 1997). AD seems to be a disease associated with age, but not an inevitable concomitant of old age.

In a small percentage of cases, AD is the result of mutations in the genes *APP, PSEN1* and *PSEN2*, located in chromosomes 1, 14 and 21. These tend to be early-onset cases that are transmitted in an autosomal dominant manner. In most of the cases, however, AD seems to be caused by an interaction involving a variety of still poorly understood genetic and environmental factors, primarily including advanced age, a history of cranial trauma or cerebral vascular accidents, certain toxins, and being a carrier of the *ε4* allele of apolipoprotein E. The risk of developing AD is four times higher among heterozygous carriers and ten times higher for homozygous *ApoE4* carriers (Mayeux, 1998).

Some evidence points to a possible connection between inflammatory mechanisms and AD. There seems to be an activation of microglial cells in the brains of patients with AD, especially in the senile plaques. This has led some researchers to suggest a relationship between inflammatory processes that take place in the early phases of life or chronic inflammatory processes associated with age and the subsequent development of AD (Finch, 2005).

Recently, genome-wide association studies (GWAs) have revealed an association between AD and the *CLU* gene, which is located on chromosome 8 and encodes apolipoprotein J, variants of which reduce the risk of developing AD by 15%, and the *PICALM* and *CR1* genes, which are located on chromosomes 11 and 1 (Harold *et al.,* 2009; Lambert *et al.,* 2009), although the relationship between AD and these genes seems to be much less significant than the relationship between AD and *ApoE4*.

Alzheimer's disease and evolutionary biology

Several factors make AD especially suited to an evolutionary approach. Firstly, it is a very common disease with a substantial genetic component in which numerous genes seem to play a role and, with the exception of the rare case of autosomal dominant mutation, onset almost always occurs at an advanced age, suggesting that AD may be an example of antagonistic pleiotropy. Secondly, some studies suggest that the incidence of AD is significantly higher in developed countries than in traditional societies. If this is true, it would support the hypothesis that certain factors related to industrialised societies could favour the development of the disease, which would suggest that genome lag could play a role in AD. The term genome lag (Eaton *et al.,* 1988b) refers to the fact that the human genome, which determines our anatomy, physiology, impulses, emotions and cognitive capacity, developed slowly in the ancient environments in which our ancestors lived and which were radically different from our current environment. For the greatest part of our over two million years of existence, members of the genus *Homo* were foragers and hunter-gatherers. The human environment changed drastically about 10,000 years ago with the development of agriculture, and the rate of change has been multiplying exponentially since the industrial revolution 200 years ago. This has led to an increasingly greater imbalance between a genome adapted to an environment that no longer exists and a current environment that has nothing to do with the one in which our species evolved. This gap may contribute to the development of different physiological and emotional disorders (Eaton *et al.,* 1988a, b, 2002).

Thirdly, AD is very common in elderly humans and very uncommon in other mammals. Since the beginning of the 20th century numerous comparative anatomy studies have been conducted on the brains of different species of mammals in zoos and laboratories. These studies, which include detailed microscopic examinations, have detected only a single case of a non-human brain manifesting the criteria that define AD. A high percentage of non-human primates and some carnivores present Aβ deposits at an advanced age, but unlike humans, these animals present few neuritic plaques. Until very recently NF tangles had not been documented in any

other species. It seemed, therefore, that AD was specific to *Homo sapiens*, although some species of mammals, like non-human primates, may have developed an incomplete form of Alzheimer's (Cork *et al.,* 1988; Price 1993; Walker 1993; Gearing *et al.,* 1994, 1997; Poduri *et al.,* 1994; Erwin *et al.,* 2001; Head *et al.,* 2001).

A captive chimpanzee of advanced age and with high blood cholesterol levels was recently found to also have cerebral amyloid deposits and neuronal NF tangles, lesions practically identical to those found in human AD. This is the only recorded case of AD in animal species other than humans, although it should be noted that the disease occurred in the species evolutionarily closest to our own, whose brain structure and function in many respects is similar to that of humans (Rosen *et al.,* 2008).

AD seems to be extremely uncommon in other animals, whereas in humans it is extremely prevalent in old age. This suggests that the genetic changes which underlie alterations in cerebral structure and function that have taken place over the course of human evolution may significantly increase the susceptibility of our species to factors that lead to the development of AD (Bufill & Blesa, 2006).

Finally, the possibility cannot be ruled out that in their initial phases both Aβ deposits and NF tangles act as defences against factors such as oxidative stress and infection, and only when they are produced in excess or adopt certain structures do they take on neurotoxic properties and contribute to the development of AD (Smith *et al.,* 2000; Soscia *et al.,* 2010).

Approaching the subject of AD from an evolutionary perspective requires answers to the following questions.

1) What evolutionary legacies explain our susceptibility to AD? Could AD be related to the genetic changes underlying the alterations in cerebral structure and function that have taken place over of the course of the evolution of genus *Homo*?
2) Why do these genes related to AD still exist today? Could these genes be beneficial at a juvenile and reproductive age and potentially harmful at an advanced age (antagonistic pleiotropy)?
3) Do new environmental factors contribute to the development of AD? Could the phenomenon of genome lag play a role in the development of AD?
4) Do deposits of abnormal peptides represent the cause of AD, or are they only a product of it, or do they initially act as a defence against factors that can contribute to the development of the disease?

Although the causes of AD are not yet known, the evolutionary approach to the disease can provide insight into understanding why human beings have an elevated vulnerability to this disorder. The data currently available allow the following hypotheses to be posed:

1) Certain genetic changes which have led to structural and functional alterations in the brain which took place over the course of the evolution of the genus *Homo* have made us vulnerable to different factors which can lead to AD (evolutionary legacies).
2) These changes are essential for the human brain to function correctly in youth and adulthood but can become harmful at an advanced age under certain circumstances (antagonistic pleiotropy).

Evolutionary legacies

Structural changes

The size of the human brain has increased significantly over the course of human evolution: 3 million years ago it measured 450 cubic centimetres whereas in modern humans it measures 1,345 cubic centimetres. The human brain does not seem to have increased in size over the last 200,000 years.

In *Homo sapiens* changes have also taken place in cerebral organisation, such as an increase in the size of the neocortex at the expense of the temporal association, prefrontal and parietal areas; a prefrontal increase in white matter compared to grey matter, which indicates an increase in neuronal connections;

a considerable increase in connections between the prefrontal lobe and temporal and parietal association areas; and an increase in prefrontal area 10, which is related to planning behaviours and episodic memory (Rilling & Insel, 1999; Semendeferi *et al.,* 2001; Bruner 2003; Schoenemann *et al.,* 2005; Bruner & Holloway, 2010). As Bruner's work demonstrates, the brains of anatomically modern humans are characterised above all by an increase in the size of the parietal lobes. This increase in parietal volume seems to begin as far back as *Australopithecus*, prior to the increase in frontal volume. The parietal lobes are multimodal association areas that are involved in the integration of different sensory modalities, in spatial coordination, in attention and in the internal representation of reality. The fronto-parietal system is a complex network that is the foundation for higher human mental faculties such as the capacity to reason (Bruner, 2010).

Human pyramidal neurons in the association areas, particularly in the prefrontal area, have more dendritic spines and are more complex than pyramidal neurons in non-human primates (Elston *et al.,* 2001).

Changes in brain development

The human brain also develops much more slowly than the brains of non-human primates. The neocortex is myelinated in newborn macaques but not in humans, for whom myelination begins after birth. In macaques, neocortical myelination is complete at two years old, whereas in humans, myelination in the prefrontal areas continues well into the third decade of life (Parker & McKinney, 1999).

A neuron is only functionally mature after its axon is myelinated. The more evolutionarily recent association areas, such as the prefrontal and temporoparietal areas, are organised more simply than the primary areas. They are also the last to myelinate, and many of their neurons remain poorly myelinated throughout life (Braak *et al.,* 2000). These neurons, therefore, seem to retain juvenile characteristics into their adult lives.

The rate of growth of the human brain in the postnatal period is much higher than that of the great apes, such as chimpanzees (Leigh 2004). A human brain therefore not only undergoes a much longer growth period than other primates, but also has a much higher postnatal growth rate.

Changes in cerebral metabolic expenditure

Whereas at rest metabolic expenditure in humans does not differ from that of other mammals of our size, a much higher proportion of human metabolic energy is used by the brain than in other mammals, including non-human primates. The adult human brain uses between 20 and 25% of its metabolic energy at rest, while apes use between 11 and 13% and other mammals use between 2 and 8% (Mink *et al.,* 2007). The proportion of metabolic energy used by the brain is positively associated with diet quality. The fossil record indicates that at the time *Homo erectus* was evolving, around 1.8 million years ago, substantial changes took place both in diet and in brain size. These changes seem to be related to the transition to a hunter-gatherer economy and an increase in the consumption of meat, which improved the quality of the diet and allowed for the ingestion of large quantities of long-chain polyunsaturated fatty acids such as docosahexaenoic acid and arachidonic acid which, along with other factors, led to an increase in brain size (Leonard *et al.,* 2007). The increase in human brain size has been associated with a decrease in the length of the intestinal tract, an increase in body fat reserves and less muscle mass compared to other primates (Aiello & Wheeler, 1995; Leonard *et al.,* 2007).

Although the increase in the energetic expenditure of the human brain may be due solely to its large size, the length of its axons and its high number of synapses, recently discovered data that we will discuss in greater depth later, show that the neurons of certain cortical areas retain an elevated synaptic activity and a high metabolism into adulthood, which would contribute to the elevated expenditure of cerebral energy found in our species.

Changes in gene expression

A considerable portion of the genetic changes that took place over the course of the evolution

of the human brain seem to have occurred as the result of an increase in the expression or in the number of copies of certain genes and not through structural changes. The key phenotypic differences between the human brain and that of the chimpanzee may be the result of changes in the promoter and regulatory regions of various genes associated with neuronal activity. The general level of neuronal activity and the underlying metabolic processes related to it are markedly higher in the human cerebral cortex than in non-human primates. In the human cerebral cortex, studies have found the increased expression of genes that encode proteins related to synaptic plasticity, such as thrombospondins and *CaMK2*, as well as to synaptic transmission, axonal transport along microtubules, and lipid metabolism, which could play a role in neuronal membrane synthesis and turnover. This increased expression has also been documented in genes related to neuroprotection and the control of protein folding (chaperone proteins), which offer protection against the build-up and deposit of abnormal proteins. The most significant differences between humans and non-human primates in terms of genetic expression in the brain are found in the association cortex (Cáceres *et al.,* 2003, 2007).

Neuronal aerobic metabolism is markedly higher in humans than in other primates and it is higher in non-human primates than in other mammals. Although compared to other animals it is high in both humans and chimpanzees, neuronal metabolism is considerably higher in humans than in chimpanzees. Many of the genes involved in the mitochondrial electron transport chain (ETC) have seen not only an increase in expression but also positive selection for some of their variants, which may have contributed to an increase in the speed of electron transport and to a reduction in the production of free radicals, in other words, oxidative stress. Genes related to complex IV (cytochrome c oxidase) and genes that encode the proteins that transport electrons between complexes III and IV (CYCS) are among the ETC genes whose expression has increased in humans over the course of evolution (Uddin *et al.,* 2004).

A large part of the genes whose expression has increased in the human brain are related to synaptic plasticity and activity. Many of the changes in cerebral genetic expression which occurred over the course of human evolution, especially in the cortical association areas, seem to be adaptations for the purpose of maintaining high levels of neuronal activity over a long lifetime, especially increased synaptic activity and plasticity (Cáceres *et al.,* 2003, 2007).

Heterochrony and synaptic plasticity

A recent study compared the expression of 7,958 genes in the prefrontal cortex and caudate nucleus of humans, chimpanzees and macaques. In different regions of the prefrontal cortex of adult humans, a high percentage of genes were found to have levels of expression similar to those of a young chimpanzee. However, these changes in expression did not affect the entire transcriptome; rather most of the genes whose expression had increased in humans were related to cerebral growth and development, suggesting a mosaic evolution (Somel *et al.,* 2009).

Local cerebral glucose metabolic rates (LCMRglc) have been found to be considerably higher in childhood and development than in adulthood in several species of mammals studied (rats, cats, dogs and especially non-human primates). This also occurs in humans. A direct relationship has been found between LCMRglc and synaptogenesis, synaptic activity and dendritic reorganisation. The child's brain, therefore, is characterised by increased neuronal metabolism, synaptic plasticity and activity compared to the adult brain (Jacobs *et al.,* 1995; Chugani 1999).

In *Homo sapiens* an increase has not only taken place in the expression of genes related to neuroplasticity; the selection of alleles which improve the capacity for plasticity and synaptic repair also seems to have occurred. E apolipoproteins (ApoE) are involved in the transport and uptake of cholesterol and play a significant role in the phospholipid homeostasis of the neuronal membrane, taking part in the processes of repairing these membranes and therefore playing a role in synaptic plasticity as well as neuroprotection.

Humans are the only mammals that present a polymorphism for the gene that encodes ApoE, with three alleles: *ε2*, *ε3* and *ε4*. Numerous studies have confirmed that the presence of allele *ε4* is the most important risk factor for the development of AD after advanced age. However, the *ε4* allele is an ancestral variant that is very similar to what is found in non-human primates, and *ε3* and *ε2* are mutations produced from that allele whose expansion seems to have taken place within the last 200,000 years (Fullerton *et al.,* 2000). Allele *ε3* is the most widespread in all human populations, with frequencies at or above 60%. A considerable body of clinical and neuroradiological data, as well as data from neuronal cultures, suggest that carriers of alleles *ε3* and *ε2* possess an elevated capacity for synaptic plasticity and repair, which may indicate that their selection is at least partly due to neuroprotective action and increased neuroplasticity (Bufill & Carbonell, 2004, 2006). Other factors, like the adaptation to a diet rich in meat and animal fats may have also been involved in the selection of ε*3* (Finch & Stanford, 2004).

Both the morphology and the function of certain human neurons belonging to the cerebral association areas indicate that these areas may have retained juvenile characteristics into adulthood, such as incomplete myelination, increased synaptic activity and plasticity, and enhanced neuronal metabolism. Over time, this increase in metabolism can lead to enhanced oxidative stress which may accelerate neuronal aging. Over the course of the evolution of the human brain, an increase in the expression of neuroprotective genes and the mitochondrial electron transport chain may have occurred in response to selective pressures to prevent cellular damage as a consequence of oxidative stress (Bufill *et al.,* 2011). The increase in the expression of both these genes and their variants or alleles can vary from individual to individual, meaning that certain people may be better protected than others from factors capable of increasing oxidative stress.

Heterochrony and brain's default mode network

Cerebral glucose metabolism is mainly used to supply energy by means of oxidative phosphorylation. When glucose metabolism exceeds that used in oxidative phosphorylation, in the presence of oxygen, aerobic glycolysis takes place. Aerobic glycolysis is involved in cellular proliferation, and in the brain it may be related to cell development in foetuses and to activity-dependent synaptic changes in adults. Cerebral aerobic glycolysis seems to play a critical role in biosynthesis and synaptic activity and plasticity. In humans, aerobic glycolysis represents 35% of the glucose used in the brain of a newborn and 19% of the glucose used in the brain of an alert adult (Vaishnavi *et al.,* 2010).

Certain association areas in the human brain retain elevated levels of aerobic glycolysis in adulthood, which suggests the possibility that elevated synaptic activity and plasticity persist in these areas in later stages of life (Buckner *et al.,* 2008; Vaishnavi *et al.,* 2010; Vlassenko *et al.,* 2010). Aerobic glycolysis in the adult human brain is significantly elevated in cortical areas related to cognitive functions which have undergone major modifications during the evolution of the human species, such as the dorsolateral prefrontal cortex, which is associated with working memory, and in a set of areas that make up the brain's default mode network, which display elevated activity when the individual is at rest and not engaged in any purposeful activity. These areas are the ventromedial prefrontal cortex, the dorsomedial prefrontal cortex, the posterior cingulate cortex, the inferior parietal lobe, the lateral temporal cortex and the hippocampus and adjacent areas (Buckner *et al.,* 2010; Vaishnavi *et al.,* 2010). An increase in resting activity has also been detected in areas of the chimpanzee brain that would correspond to the brain's default mode network in humans, but whether an increase in aerobic glycolysis takes place in those areas is unknown (Rilling *et al.,* 2007). The brain's default mode network has been related to the coordination of the activity among different brain regions and to autobiographical memory, planning and functions related to social interaction, such as the theory of mind and moral decision making (Buckner *et al.,* 2008; Vaishnavi *et al.,* 2010). This system allows humans, and perhaps to a

certain extent the great apes, to travel mentally in time, to project the ego into the personal past and future (Seeley *et al.,* 2007).

Could the functional and structural changes which took place over the course of the evolution of the human brain be related in some way to humans' increased vulnerability to certain neurodegenerative diseases, particularly Alzheimer's disease?

Evolutionary legacies and Alzheimer's disease

In and of themselves, neither brain size nor longevity can be the cause of human vulnerability to AD. Neither elephants nor cetaceans develop the lesions characteristic of AD, despite the fact that they live long lives and have large brains (Bartzokis, 2004).

Myelination, heterochrony and AD

The parietal lobe manifests a decrease in glucose metabolism in the very early phases of AD. The parietal lobe has undergone considerable expansion during the evolution of the human brain and it is 20 times larger than that of the macaque. The parietal lobe, along with certain areas of the prefrontal lobe, is one of the last areas of the human brain to myelinate and many of its neurons remain little myelinated for the entire lifespan, which may explain their vulnerability to factors capable of triggering AD (Jacobs *et al.,* 2012).

The human brain develops heterochronologically. The association areas myelinate much later than other areas and many of the neurons in these areas remain incompletely myelinated in adulthood. In other words, they permanently retain juvenile characteristics.

The lesions that are characteristic of AD initially appear in poorly myelinated neurons in limbic system areas related to memory and learning, such as the hippocampus and neighbouring areas, and the association cortex. Highly myelinated neurons in primary areas are only affected in the final phases of the disease, and to a much lesser degree. High levels of myelination increase the speed of nervous transmission and reduce the expenditure of neuronal energy, which is much more elevated in neurons with longer projections, multiple connections and poor myelination, present in large number in the association areas (Braak *et al.,* 2000). This increase in energy expenditure in these neurons may have an influence on humans' elevated susceptibility to developing AD.

The myelin in the central nervous system is comprised of oligodendrocytes, which are the brain cells most vulnerable to the various different factors related to AD, such as oxidative stress, chronic hypoperfusion, hypertension, traumas and toxins. Oligodendrocytes play a key role in maintaining functional synaptic plasticity, synaptogenesis and dendritic growth in adulthood, and therefore their destruction would negatively affect those functions (Bartzokis, 2004).

Oligodendrocytes contain high concentrations of iron, which is released upon their destruction. Some evidence has indicated that the soluble form of β-amyloid has a chelating effect on iron, but an excess of this metal can give rise to the oligomerisation of β-amyloid, which has a neurotoxic effect. The combination of an elevated lipid and iron content and elevated metabolic activity makes oligodendrocytes especially vulnerable to oxidative stress. The little myelinated neurons of certain association areas are the most vulnerable to this oxidative stress and are first to experience dysfunction and myelin breakdown (Bartzokis 2004; Bartzokis *et al.,* 2007).

The loss of neurotrophic factors secondary to oligodendrocyte destruction negatively affects the underlying neurons. The unique pattern of myelinisation that occurs in the human brain may contribute to the susceptibility of certain neurons to the factors capable of triggering the onset of AD (Bartzokis, 2004; Bartzokis *et al.,* 2007).

Heterochrony, synaptic activity and plasticity and AD

Children that carry ε*4* allele of ApoE have a thinner entorhinal cortex and parahippocampal region, which are related to memory and are also the areas of the brain in which the NF tangles characteristic of AD first appear (Shaw, 2007). The possibility cannot be ruled out that children

who are carriers of *ε4*, who consequentially have a reduced capacity for plasticity and synaptic repair, are predisposed to developing synaptic dysfunction relatively early in their lives.

Multiple bodies of evidence have shown that oxidative stress is not only always associated with Alzheimer's disease, but that it is one of the first events that occurs in the development of the disease (Shi *et al.,* 2007; Su *et al.,* 2008). The increase in aerobic metabolism in certain human neurons that retain juvenile characteristics into adulthood, such as incomplete myelination and elevated synaptic activity and plasticity, can make these neurons more likely to exhibit greater oxidative stress with age, and can make them more vulnerable to that stress. The distribution of the extracellular β-amyloid plaques found in subjects with AD coincides almost exactly with the brain's default mode network, which suggests that elevated synaptic activity and plasticity could predispose individuals to developing the deposits of abnormal peptides characteristic of AD. The presence or absence of these peptides, and their degree of accumulation if they are present, may be dependent on the metabolic efficiency of each individual, on the possession of certain neuroprotective gene variants and certain endogenous and exogenous factors, such as cerebral ischemia, cranial trauma, exposure to toxins, inflammation or infections, which vary from person to person (Buckner *et al.,* 2008; Vlassenko *et al.,* 2010).

The use of Pittsburgh compound-B positron emission tomography (PIB-PET) has revealed that β-amyloid deposits in the cerebral cortex are associated with a decrease in the functional connectivity of certain areas of the brain's default mode network. The regions in which a decrease in functional connectivity occurs in AD are the mid-temporal lobe, the posterior cingulate cortex, the ventromedial prefrontal cortex and the angular gyrus. In other areas, however, such as the dorsal prefrontal cortex, deposits of β-amyloid are related to increased functional connectivity. This increase in functional connectivity may be compensatory, due to aberrant hyperactivation, or both, or may occur because certain regions of the default mode network are more vulnerable than others to the neurotoxic action of β-amyloid deposits (Mormino *et al.,* 2011).

A recent study has shown that an excessive increase in synaptic activity in turn increases the production of β-amyloid in the cerebral interstitial fluid in transgenic mice, which tend to produce β-amyloid plaques as they age. The elevated synaptic activity and plasticity of the human brain's default mode network may therefore be the cause of most of the lesions characteristic of AD that appear in the areas of the brain that make up this system. In fact, carriers of the *ε4* allele of ApoE, who also carry a higher risk of developing AD, have been found to have a higher rate of activity in the brain's default mode network when at rest than non-carriers of that allele (Bero *et al.,* 2011; Walter & Jucker, 2011). As the abnormal peptide deposits characteristic of AD develop, synaptic plasticity and activity decreases in certain areas of the default mode network and compensatory hyperactivation occurs in others. The retention of juvenile characteristics such as increased synaptic plasticity and activity in certain neurons of the human brain may make them more vulnerable to the multiple factors that can trigger the onset of AD (Bufill *et al.,* 2011).

Epigenetic changes and AD

An analysis of the frontal cortex of a group of individuals between 26 and 106 years old showed a significant reduction in the expression of certain genes starting at 40 years of age, while the expression of other genes increased from that age onwards and many others were seemingly unaffected. Among the genes whose expression diminished significantly were those involved in synaptic plasticity and mitochondrial function, including *CaMK2a*, *Cdk5* and *p35*, as well as protein encoding genes involved in stabilising microtubules and in axonal transport, such as kinesins. The decreased expression of these genes was caused by epigenetic changes in the DNA of the promoter region of the gene, which exhibited increased vulnerability to oxidative stress. The degree of reduction in this genetic expression varied greatly from one individual to the next and does not seem to occur with age in chimpanzees and other

non-human primates. Other studies have shown that decreased genetic expression occurs primarily in the association areas and hardly ever in the primary areas, the cerebellum or other phylogenetically older cerebral areas. At the same time, the expression of neuroprotective genes increases with age, especially those with antioxidant activity (Bowling *et al.,* 1993; Lu *et al.,* 2004).

Epigenetic changes consist of potentially reversible biochemical modifications in DNA or histones – proteins that constitute the main component of the chromatin in chromosomes – which activate or deactivate the affected gene, or increase or decrease the expression of that gene. These epigenetic changes mainly affect the promoter region of the DNA. The methylation of the promoter zone of the DNA translates to the deactivation or decreased expression of the gene, whereas histone acetylation translates to the activation or increased expression of the gene. A multitude of factors such as hormones, drugs or environmental toxins can induce epigenetic changes (Gräff & Mansuy, 2008; Ptak & Petronis, 2008).

Oxidative stress can also induce epigenetic changes by means of hypermethylation of the promoter region of certain genes, including various genes related to synaptic plasticity (Bowling *et al.,* 1993: Lu *et al.,* 2004). Hypermethylated genes seem to be more susceptible to the toxic action caused by the β-amyloid peptide, which would further increase oxidative damage to DNA (Zawia *et al.,* 2009). Oxidative stress can also, by means of epigenetic changes, activate certain gene pathways, such as those related to inflammation, which are hyperactive in AD (Shi & Gibson, 2007).

Several studies conducted over the last decade have found a reduction in histone acetylation in animal models which present neurodegeneration with diminished cognitive capacity. A relationship has recently been found between histone deacetylase 2 (HDAC2), an enzyme that reduces histone acetylation, and the cognitive deficiencies manifested in mice that overexpress the p25 protein, which leads to the production of β-amyloid and hyperphosphorylation of tau. HDAC2 was especially elevated in the neurons of the hippocampus of these mice and caused the compaction of chromatin, which particularly affects different genes related to synaptic plasticity, producing a reduction in their expression. Reducing HDAC2 levels promoted histone acetylation and increased the expression of mRNA in the genes related to neuroplasticity. The reduction of HDAC2 also improved the cognitive capacity of the mice with neurodegeneration (Gráff *et al.,* 2012).

In vitro studies have exposed neurons of the hippocampus to stimuli associated with AD, such as hydrogen peroxide and β-amyloid oligomers. Both treatments resulted in an increase in HDAC2 with a reduced expression of genes related to synaptic plasticity (Gräff *et al.,* 2012).

A significant increase in HDAC2 has been found in brain samples from patients who have had AD, especially in the hippocampus and entorhinal cortex (Gräff *et al.,* 2012). The findings of these studies show that epigenetic changes induced by HDAC2 which block the expression of different genes related to neuroplasticity can contribute to the development of AD, that these epigenetic changes may be triggered by oxidative stress or β-amyloid, and that, in animal models, the memory disorders associated with these epigenetic changes may be reversible through the inhibition of HDAC2.

Several genes associated with AD encode proteins involved in synaptic plasticity, including the genes that encode the amyloid precursor protein or APP, presenilins 1 and 2 and E apolipoproteins. AD may be a syndrome that is the product of the dysfunction of multiple proteins whose expression increased as the brains of our human ancestors evolved. This would have made them more vulnerable to oxidative stress and probably to other factors as well, such as infections, traumas or toxins. A significant proportion of these proteins would be related to synaptic plasticity. Each individual's metabolic efficacy – in which genes involved in the mitochondrial electron transport chain play an important role – and the environmental factors with which each individual comes into contact throughout his

or her life would determine whether the characteristic deposits of abnormal peptides associated with AD appeared or not, and to what extent.

Reelin signalling pathway and AD

Among the proteins associated with neuroplasticity that may be related to AD, proteins involved in the reelin signalling pathway are of special interest. Reelin is a large extracellular matrix protein that shares the same membrane receptors as E apolipoproteins, with which it very likely interacts. ApoE genes may modulate the action of reelin and *ε3* and ε*2* and do so more effectively than *ε4*. Reelin and ApoE modulate synaptic plasticity in the adult brain, inducing changes in the neuronal cytoskeleton by means of the phosphorylation of proteins like Dab1, CdK5 and p35, genes whose expression frequently diminishes with increased age (Fig. 1).

Reelin is expressed in Cajal-Retzius neurons during cerebral development before birth and regulates neuronal migration and positioning during this stage of the life cycle. In the adult brain, reelin expression remains in the GABAergic neurons and is involved in functions such as neuroplasticity and synaptogenesis. Increased synthesis of reelin may have contributed to the expansion of the neocortex which occurred during the evolution of mammals. In primate brains this has led to a greater expression of reelin than in other mammals. Humans as well as non-human primates, unlike carnivores and rodents, also express reelin in the pyramidal neurons of the hippocampus and neocortex, as well as in GABAergic neurons. The expression of reelin seems to have increased in direct relation to the increase in cerebral complexity (Bar *et al.,* 2000; Martinez-Cedeño *et al.,* 2002).

Reelin modulates the activity of NMDA receptors related to learning, improves the activity of these receptors and helps to control synaptic function (Chen *et al.,* 2005; Herz & Chen, 2006). Reelin can also counteract synaptic dysfunction induced by the β-amyloid peptide, which suppresses the long-term potentiation and activity of NMDA receptors. When β-amyloid deposits reach the elevated levels seen in AD, reelin loses its capacity to counteract the functional suppression of synaptic activity (Durakoglugil *et al.,* 2009).

Mutant mice with a defective reelin encoding gene, in addition to presenting anomalies in neuronal positioning, present hyperphosphorylation of the tau protein, which is a precursor to the formation of NF tangles in humans. Oxidative stress induces in vitro fragmentation of the p35 protein, which is part of the reelin signalling pathway, resulting in the p25 fragment which induces prolonged activation of the Cdk5 protein and hyperphosphorylation of tau. Decreased activity or dysfunction of presenilins reduces the presence of the CaMK2 protein in synapses, which also causes dysfunctions in the reelin signalling pathway, such as the fragmentation of p35, the formation of p25 and hyperphosphorylation of tau. By interacting with the immature form of APP, p25 may also contribute to an increase in amyloid deposits (Patrick *et al.,* 1999, Saura *et al.,* 2004).

The human reelin gene includes the repetition of GGC tandem triplets in the non-encoding region of 5'UTR. The number of these triplets varies between 4 and 13. The alleles with the most GGC triplets have a lower expression of reelin, so the possibility cannot be ruled out that carriers of these alleles might experience a greater decrease in the expression of reelin if they have undergone epigenetic changes induced by oxidative stress or other factors (Persico *et al.,* 2006).

Depletion of reelin is detectable long before the onset of β-amyloid pathology in the murine hippocampus and in a pre-clinical AD stage in the human frontal cortex. This suggests the possible causative role of reelin decline in the precipitation of AD (Herring *et al.,* 2012).

The dysfunction and changes in the expression of the genes that encode the proteins that participate in the reelin signalling pathway, which are involved in synaptic plasticity, could contribute to the accumulation of the deposits of abnormal peptides characteristic of AD. It seems highly unlikely, however, that dysfunction of this pathway would be the only cause of these lesions, although all the data suggest that the dysfunction

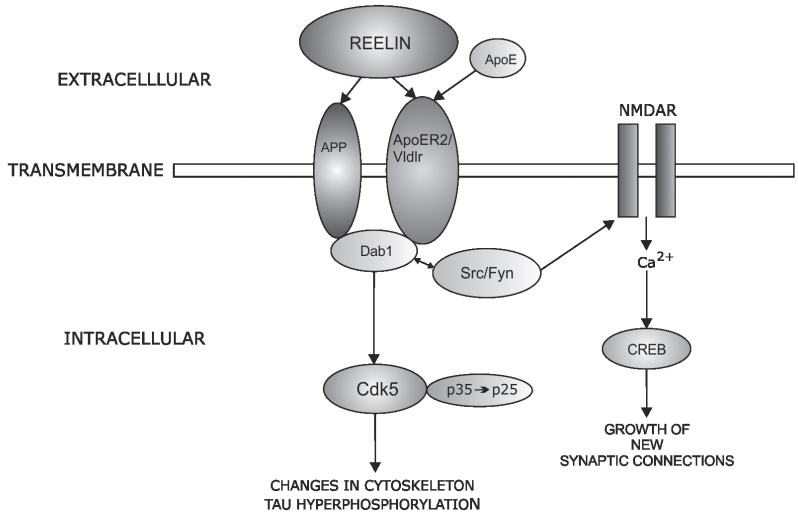

Fig. 1 - The reelin signaling pathway. The increase in synaptic plasticity requires coupling Reelin receptor and Dab1-Src/Fyn complex to the NMDA receptor. These induces increase of input of Calcium through NMDA receptors which increases the phosphorylation of CREB and influences learning and memory. Prolongued activation of Cdk5 by oxidative stress induces TAU hiperphosphorilation.

of several proteins related to synaptic plasticity is associated with the onset of AD.

Over the course of the evolution of the human brain, some juvenile characteristics have been retained into adulthood (such as increased aerobic metabolism, synaptic activity and plasticity and incomplete myelination) in certain neurons in areas involved with complex cognitive functions, like autobiographical memory, long-term planning, moral decision-making and social interaction. The cost of these evolutionary legacies may be increased oxidative stress, which could result in damage to the oligodendrocytes and myelin breakdown in poorly myelinated neurons and foster epigenetic changes in the promoter regions of certain genes, increasing the expression of some, such as genes related to inflammation, while diminishing the expression of others, such as those related to synaptic plasticity, some of which have seen increased expression over the course of the evolution of our species. In the long run these changes in genetic expression could lead – depending on the metabolic efficacy of each individual – to the deposit of abnormal peptides characteristic of AD. This, together with the increase in longevity, which began in the Upper Palaeolithic and has risen extraordinarily over the last century, would make the brain of *Homo sapiens* especially vulnerable to developing AD in old age (Fig. 2).

Antagonistic pleiotropy

The brain of any animal is, like its anatomy and physiology, a reflection of the ancestral surroundings in which its predecessors lived. The ecological and social conditions the animal was exposed to contributed to the selection of genes that favour survival and reproduction in those surroundings.

In most species, the genes that have been selected are those that promote adaptation to the surrounding environment. Some species, however, are able to modify their surroundings, creating a new ecological niche to which they can adapt. By developing technology, language and symbolic culture, and by increasing social complexity, our human ancestors developed a cognitive niche, which probably led to the selection of genes

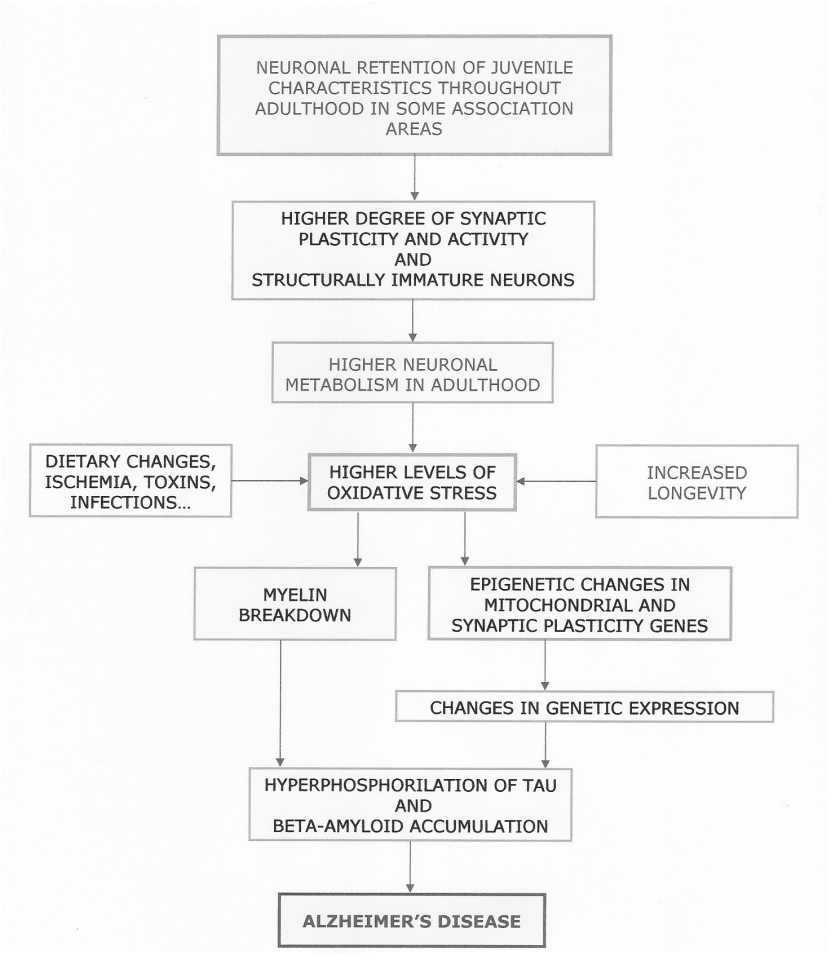

Fig. 2 - Evolutionary legacies and Alzheimer's disease.

that contributed to augmenting certain cognitive capacities (Barrett *et al.,* 2007). These include genes related to language, memory and learning, many of which are involved in synaptic plasticity and activity. In preliterate societies the storage and transmission of ideas and knowledge depended solely on individual cerebral capacity, which makes the existence of intense pressure for the selection of genes related to learning, long-term memory and the transmission of information by means of language highly likely (Bufill & Carbonell, 2004). The human variant of the gene *FoxP2*, for example, which is related to language, increases synaptic plasticity and connectivity, which in turn increases cognitive flexibility and the processing and coding of information – functions of great importance to human survival, which depends so heavily on language, learning and the accumulation of knowledge (Lieberman, 2009).

Adaptation to the cognitive niche demanded increased cerebral activity, without which the cognitive traits that characterise us as humans would never have developed. This may have led to the retention of juvenile characteristics in certain neurons into adulthood, which allowed high levels of activity and synaptic plasticity

to be maintained over a lifetime, at the price of increased aerobic metabolism and oxidative stress with age (Bufill *et al.,* 2011).

The promoter region of some genes, like those related to synaptic plasticity and mitochondrial function (several of which have increased their activity over the course of the evolution of human brain), seem to be extremely vulnerable to oxidative stress and to other factors such as toxins and ischemia, which would diminish their expression by means of epigenetic changes. The decrease in the expression of some of these genes such as reelin (*reln*), *CaMK2*, presenilins and others could lead to the abnormal peptide deposits that are characteristic of AD. In our species, the elevated activity of these genes is essential for the brain to function correctly, and the effects of their dysfunction do not appear until post-reproductive age, at which time the education of grandchildren would be complete, so no selection against them would have occurred. Genes that are useful in youth and middle age, given their vulnerability, can in certain cases become harmful in old age. Therefore, AD may be an example of antagonistic pleiotropy and the price humans pay for longevity and advanced cognitive capacities.

Gene selection that contributes to prolonged longevity seems to have occurred in intelligent social animals like elephants, some cetaceans, non-human primates and especially in *Homo sapiens*, given the importance of preserving knowledge and skills and transmitting these to children over an extended period of time. This may explain the selection of neuroprotective genes in humans. Depending on the presence of alleles in these genes, some people would be more protected than others from potentially harmful factors associated with age.

Genome lag

Although AD has been found in people of advanced age in all of the societies studied to date, the prevalence of AD seems to be considerably lower in traditional agricultural societies like those found in rural India than in developed societies. A study conducted by the same team of epidemiologists in Nigeria and the United States found that among people older than 65 of Yoruba ethnicity in Nigeria the prevalence of AD was 1.15%, whereas among African Americans of the same age prevalence was 6.7% (Hendrie *et al.,* 2001). In rural areas of Latin America, AD is only one-fourth as prevalent as it is in Western countries, although in cities like Havana and Sao Paulo the prevalence of the disease is similar to that in the West (Qiu *et al.,* 2009).

Cardiovascular diseases

The increase in the prevalence of AD among the elderly in developed societies could be largely due to cardiovascular diseases from dietary changes and because of ever increasing sedentism in these societies. Hypertension, diabetes, hypercholesterolemia and obesity rates are significantly higher among inhabitants of industrialised countries than among traditional agriculturalists or hunter-gatherers. An alteration in cerebral circulation may contribute to increased deposits of β-amyloid, accelerating the progression of AD. Ischemic lesions in white brain matter may also aggravate or accelerate the onset and progression of the disease (Stewart 1998).

Dietary changes

The incidence and prevalence of AD has risen significantly in Rumania since the fall of the communist regime in 1989. The only factor significantly associated with this increase is the change in eating habits, which went from a light diet composed of industrially unprocessed foods to an abundant diet made up of industrially processed foods containing numerous additives and rich in saturated fatty acids (Cornutiu, 2011).

The change from a predominantly vegetarian diet to an omnivorous diet rich in animal fats which began some 2.5 million years ago could have had a significant effect on the evolution of the brain of our human ancestors, leading to an increase in the size of the encephalon. There may also be a relationship between the consumption of meat and AD.

The study of Sr/Ca ratios in fossil bones indicates that hominids already had a considerable proportion of meat in their diet 1,800,000 years ago. So the human organism has had sufficient time to adapt to a carnivorous diet. The meat of wild animals, however, is extremely lean, with only 1 or 2% fat, and it is very rich in polyunsaturated fatty acids. The development of agriculture gave rise to significant changes in diet, changes which became even more pronounced after the industrial revolution. Domesticated animals not only have a greater proportion of fat than wild animals, but these fats also have a very different composition. Levels of polyunsaturated fatty acids, omega 6 and omega 3 are higher in wild animals than in domesticated animals, in which monounsaturated fatty acids predominate. In wild animals, omega 3 accounts for between 8 and 9% of total fatty acids, and the proportion of omega 6 to omega 3 is 3 to 1. This proportion is 12 to 1 in domestic animals (Mann, 2000).

Sixty percent of the structural material of the brain is made up of lipids. The large size of the human brain and its high degree of interconnectivity require long-chain polyunsaturated fatty acids that can only be obtained through diet. Alpha-linolenic acid (ALN, 18: 3ω3) and linoleic acid (AL, 18: 2ω6) are the primary precursors for polyunsaturated fatty acids in the neuronal membrane. In the central nervous system they produce docosahexaenoic acid (ADH, 22: 6ω3) and arachidonic acid (AA, 20: 4ω6) as end products (Broadhurst *et al.,* 2002).

Neuronal signalling systems need these long-chain polyunsaturated fatty acids to function correctly. Changes in the balance between omega 6 and omega 3 can affect the fluidity of cellular membranes. ADH deficiency has been linked to attention disorders and hyperactivity and to a less positive clinical outlook in cases of depression and schizophrenia. In rats given diets rich in omega 3, an increase was found in the expression of protein-coding genes involved in synaptic plasticity, energy metabolism and the metabolism of proteins related to the cytoskeleton, many of which present alterations in subjects with AD (Broadhurst *et al.,* 2002; Horrocks *et al.,* 2004).

ADH stimulates the growth of neuronal extensions and helps to increase synaptic function. In transgenic mice a diet rich in omega 3 produces a 40 to 50% reduction in β-amyloid deposits in the hippocampus and parietal cortex. Oxidative stress induces lipid peroxidation and the loss of polyunsaturated fatty acids in the neuronal membrane. ADH has antioxidant activity and may protect against AD, helping to restore the integrity of the cellular membrane. Dietary changes that have occurred in developed countries can lead to alterations in the composition and metabolism of cerebral lipids, making them more vulnerable to oxidative stress, which through changes in the expression of certain genes, could lead to the abnormal peptide deposits characteristic of AD (Farooqui *et al.,* 1998; Kitajka *et al.,* 2004).

However, a study conducted in Canada found no relationship between AD or dementia and omega-3 fatty acids and ADH in erythrocyte membranes (Kröger *et al.,* 2009). On the other hand, the higher prevalence of dementia among Australian aborigines than in the general Australian population (Smith *et al.,* 2008) brings the hypothesis that a Western lifestyle favours the onset of AD into question.

Exposure to toxins

The inhabitants of developed societies are also exposed to certain toxins, which may also play a role in AD. A recent study has shown that having been subjected to general anaesthesia could triple the risk of developing AD (Bufill *et al.,* 2009). Pathological conditions that require surgery with general anaesthesia may confuse the issue somewhat, but some studies show that some anaesthetics may increase the oligomerisation and neurotoxicity of peptides related to AD, such as the β-amyloid peptide (Eckenhoff *et al.,* 2004). Hypothermia induced by anaesthesia can also lead to the hyperphosphorylation of tau (Planel *et al.,* 2007). Reversible hyperphosphorylation of tau has been documented in certain mammals during hibernation, a period characterised by a significant and prolonged reduction in body temperature.

Several factors related to changes in lifestyle in developed societies, like sedentism, a hypercaloric diet, contact with certain toxins and, above all, vascular factors, may increase the risk of AD. These factors are new to the environment; they are new developments which our human ancestors did not have to adapt to.

The data currently available are, however, contradictory, and for now there is not enough information to state with any certainty that genome lag is the cause of AD. The increase in vascular risk factors that has taken place in Western societies might accelerate or aggravate the disease, but more comparative studies between traditional and developed societies must be conducted before any definitive conclusions can be drawn.

Deposits of abnormal peptides in AD: cause, result or defence?

Because AD is always associated with β-amyloid deposits and the formation of NF tangles, and because these seem to have neurotoxic properties, the general opinion of most researchers is that these abnormal peptides are responsible for causing the disease. However, a relatively high percentage of elderly people develop β-amyloid deposits without ever developing the consequential cognitive deterioration. Furthermore, drugs that reduce the production of β-amyloid, prevent its aggregation or promote its clearance have not been found to be effective in phase 3 of the studies carried out to date (Sperling *et al.,* 2011; Salomone *et al.,* 2012).

Just because certain symptoms or lesions are associated with a disease does not necessarily mean that they cause it. Coughs are usually associated with respiratory infections, and vomiting with digestive disorders. However, not only are these symptoms not the causes of these diseases, they are actually acting as defences by helping to eliminate excess bronchial secretions or toxic substances in the digestive tract (Nesse & Williams, 1994).

A growing body of evidence has shown that oxidative stress constitutes one of the earliest manifestations of AD and, as described previously, this oxidative stress can contribute to the development of β-amyloid deposits as well as the hyperphosphorylation of tau, which precedes the formation of NF tangles. The possibility cannot be ruled out that β-amyloid deposits and NF tangles initially serve to protect against oxidative stress, and only if they are produced in excess or under certain circumstances – like in the presence of certain metals, or when amyloid deposits adopt a fibrillar structure – do they take on neurotoxic properties (Smith *et al.,* 2000). β-amyloid also seems to have a chelating effect on the iron released during the destruction of the oligodendrocytes that make up myelin (Bartzokis, 2004; Bartzokis *et al.,* 2007).

The results of a recent study show that β-amyloid peptide has antimicrobial properties and that the absence of this peptide can lead to increased vulnerability to infection. Although the immune system has limited access to the central nervous system, it seems this could combat invading pathogens by means of different antimicrobial peptides, including the β-amyloid peptide. An abnormal accumulation of this peptide could be caused by persistent subacute infections in the central nervous system, by transitory infections capable of triggering self-perpetuating immune responses, by inappropriate inflammatory responses or by an excess of non-infectious prior factors, like traumas, ischemia, toxins or anaesthetics. In any case, the generation of the β-amyloid peptide may have an adaptive function in its initial phases (Soscia *et al.,* 2010).

Conclusions

Alzheimer's disease is extremely common in humans of advanced age and extremely rare in other animal species.

AD seems to depend, therefore, on derived traits specific to *Homo sapiens*. This disease has a considerable genetic component, which suggests that certain genetic changes underlying functional and/or structural changes that took place over the course of the evolution of the brain of

the genus *Homo* have significantly increased the vulnerability of our species to the factors associated with AD.

Data obtained to date show that the majority of genes associated with AD are involved in synaptic plasticity. There is also a great deal of evidence pointing to a relationship between neuronal oxidative stress and AD.

In the adult human association cortex an increase has been detected in the expression of genes directly or indirectly related to synaptic plasticity, compared to non-human primates. Juvenile mammals have significantly higher levels of synaptic plasticity and activity than adults. Although in humans levels of synaptic activity and plasticity are also much higher in childhood, our species continues to maintain high levels of synaptic plasticity and activity throughout adulthood, especially in certain cortical areas such as the brain's default mode network. The incomplete myelination of certain neurons belonging to the association areas of the human brain has also been observed. These neurons are the first and most severely affected by AD.

The price we have paid for increased synaptic activity and plasticity in these neurons is increased aerobic metabolism, which together with prolonged longevity, may cause greater neuronal oxidative stress, which in turn may cause myelin breakdown and epigenetic changes in the promoter region of genes related to synaptic activity and plasticity and mitochondrial function. This may have led to the human brain being more susceptible to developing certain neurodegenerative diseases like AD than the brains of other mammals.

There may well be factors other than oxidative stress associated with elevated synaptic plasticity and activity that increase the vulnerability of certain neurons to AD. Knowing these factors could open up new lines of research that would help in better understanding the disease.

Changes in genetic expression that have taken place in the brain during the evolution of our species are essential components to correct cerebral functioning in human beings. However, these changes can become harmful in old age under certain circumstances, increasing oxidative stress and reducing the expression of certain genes that are essential for correct neuronal function. AD can therefore be considered an example of antagonistic pleiotropy.

Finally, recent data suggest that both hyperphosphorylation of tau as well as β-amyloid deposits may initially have an adaptive function, providing protection from oxidative stress and infection. Only under certain circumstances, like in the presence of some metals, the adoption of certain structural forms or the excessive production of these peptides, would these neurotoxic properties develop, affecting neurons with elevated synaptic plasticity and metabolism with greater intensity. An improved understanding of this issue could have considerable therapeutic implications.

Some of the conclusions drawn in this article may be partly hypothetical, but they are based on proven facts and are experimentally verifiable. They suggest lines of research to be pursued, among them the study of epigenetic changes induced by oxidative stress and other factors such as toxins and infections in genes related to synaptic plasticity or the mitochondrial electron transport chain; the study of the relationship between the polymorphisms of these genes and AD; and longitudinal neuroimaging studies of cerebral regions that present increased neuroplasticity like the brain's default mode network, which may allow AD to be diagnosed in its initial phases.

One promising line of research derived from these conclusions is the search for treatments capable of reverting epigenetic changes that take place in the promoter regions of the genes related to synaptic plasticity under the influence of oxidative stress or other factors.

Some of these hypotheses could never have been posed without an evolutionary perspective, which allows connections to be drawn between apparently unrelated data from neurology, comparative anatomy, genetics, epidemiology, biological anthropology, primatology and other disciplines, like the comparison of human and non-human primate cerebral genomics. Only through interdisciplinary studies will the causes

of complex diseases like AD be discovered. Evolutionary biology, thanks to its holistic vision and its capacity to integrate, may prove to be a very useful tool in the biomedical sciences.

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Info on the web

www.alzforum.org
Information for researchers, physicians and the general public, with news, articles and advances in research on Alzheimer's disease.

www.nlm.nih.gov/medlineplus/alzheimersdisease.html
News and advances in the research and statistics on Alzheimer's disease.

www.rcgd.isr.umich.edu/ehap
Evolution and adaptation program Michigan University, with news about Darwinian medicine.

http://evmedreview.com
On-line publication news and abstracts on medicine and evolution

http://groups.google.com/group/brainevolution
The European Network for Brain Evolution Research.

www.ucm.es/info/neurosci
Cognitive Neuroscience and Evolution unity, Instituto Carlos III, Madrid, Spain.

References

Aiello L.C. & Wheeler P. 1995. The expensive-tissue hypothesis: the brain and the digestive system in human and primate evolution. *Curr. Anthropol.,* 36: 199-221.

Bar I., Lambert de Rouvroit C. & Goffinet A. 2000. The evolution of cortical development: an hypothesis based on the role of the reelin signaling pathway. *Trends Neurosci.,* 23: 633-638.

Barrett H.C., Cosmides L. & Tooby J. 2007. The hominid entry into the cognitive niche. In S.W. Gangestad & J.A. Simpson (eds): *The evolution of mind,* pp. 241-248. The Guilford Press, New York.

Bartzokis G. 2004. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiol. Aging,* 25: 5-18.

Bartzokis G., Po H.L. & Mintz J. 2007. Human brain myelination and amyloid beta deposition in Alzheimer's disease. *Alzheimers Dem.,* 3: 122-125.

Bero A.W., Yan P., Roh J.H., Cirrito J.R., Stewart F.R., Raichle M.E., Lee J.M. & Holtzman D.M. 2011. Neuronal activity regulates the regional vulnerability to amyloid-β deposition. *Nature Neurosci.,* 14:750-756.

Bowling A., Mutisya E., Walker L., Price D., Cork L. & Beal M. 1993. Age-dependent impairment of mitochondrial function in primate brain. *J. Neurochem.,* 60: 1964-1967.

Braak H. & Braak E. 1997. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol. Aging*, 18: 351-357.

Braak H., Tredici K.D., Schultz C. & Braak E. 2000. Vulnerability of select neuronal types to Alzheimer's disease. *Ann. N. Y. Acad. Sci.,* 924: 53-61.

Broadhurst C., Wang Y., Crawford M., Cunnane S., Parkington J. & Schmidt W. 2002. Brain-specific lipids from marine, lacustrine, or terrestrial food resources: potential impact on early African *Homo sapiens. Comp. Biochem. Physiol. B Biochem. Mol. Biol.,* 131: 653-673.

Bruner E. 2003. Fossil traces of the human thought: paleoneurology and the evolution of the genus *Homo. J. Anthropol. Sci.,* 81: 29-56.

Bruner E. 2004. Geometric morphometrics and paleoneurology: brain shape evolution in the genus Homo. *J. Hum. Evol*., 47: 279-303.

Bruner E. & Holloway R.L. 2010. A bivariate approach to the widening of the frontal lobes in the genus Homo. *J. Hum. Evol.,* 58: 138-146.

Brüne M. 2008. *Textbook of Evolutionary Psychiatry. The origins of psychopathology.* Oxford University Press, Oxford.

Buckner RL., Andrews-Hanna J.R. & Schacter DL. 2008. The Brain's Default Network. Anatomy, function and relevance for disease. *Ann. N. Y. Acad. Sci.,* 1124: 1-38.

Bufill E. & Carbonell E. 2004. Conducta simbólica y neuroplasticidad: ¿un ejemplo de coevolución gen-cultura? *Rev. Neurol.,* 39: 48-55.

Bufill E. & Carbonell E. 2006. Apolipoprotein E polymorphism and neuronal plasticity. *Am. J. Hum. Biol.,* 18: 556-558.

Bufill E. & Blesa R. 2006. Enfermedad de Alzheimer y evolución cerebral: ¿es la enfermedad de Alzheimer un ejemplo de pleiotropía antagónica? *Rev. Neurol.,* 42: 25-33.

Bufill E., Bartes A., Moral A., Casadevall T., Codinachs M., Zapater E., Rovira J.C., Roura P., Oliva R. & Blesa R. 2009. Factores genéticos y ambientales que pueden influir en la forma senil de la enfermedad de Alzheimer: estudio de casos y controles anidado. *Neurología,* 24: 108-12.

Bufill E., Agustí J. & Blesa R. 2011. Human neoteny revisited: The case of synaptic plasticity. *Am. J. Hum. Biol.,* 23: 729-739.

Burns J. 2007. *The descent of madness. Evolutionary origins of psychosis and the social brain.* Routledge, London and New York.

Cáceres M., Lachuer J., Zapala M.A., Redmond J.C., Kudo L., Geshwind D.H., Lockhart D.J., Preuss T.M. & Barlow C. 2003. Elevated gene expression levels distinguish human from non-human primate brains. *Proc. Natl. Acad. Sci. U.S.A.,* 100: 13030-13035.

Cáceres M., Suwyn C., Maddox M., Thomas J.W. & Preuss T.M. 2007. Increased cortical expression of two synaptogenic thrombospondins in human brain evolution. *Cereb. Cortex,* 17: 2312-2321.

Chen Y., Beffert U., Ertunc M., Tang T.S., Kavalali E.T., Bezprozvanny I. & Herz J. 2005. Reelin modulates NMDA receptor activity in cortical neurons. *J. Neurosci.,* 25: 8209-8216.

Chugani H.T. 1999. Metabolic imaging: A window on brain development and plasticity. *Neuroscientist,* 5: 29-40.

Cork L., Powers R., Selkoe D., Davies P., Geyer J. & Price D. 1988. Neurofibrillary tangles and senile plaques in aged bears. *J. Neuropathol. Exp. Neurol.,* 47: 629-641.

Cornutiu G. 2011. The incidence and prevalence of Alzheimer's disease. *Neurodegenerative Dis.,* 8: 9-14.

Durakoglugil M.S., Chen Y., White C.L., Kavalali E.T. & Herz J. 2009. Reelin signaling antagonizes beta-amyloid at the synapse. *Proc. Natl. Acad. Sci. U.S.A.,* 106: 15938-15943.

Eaton S., Konner M. & Shostak M. 1988a. Stone agers in the fast lane: chronic degenerative diseases in evolutionary perspective. *Am. J. Med.,* 84: 739-749.

Eaton S., Shostak M. & Konner M. 1988b. *The Paleolithic prescription: a program of diet, exercise and a design for living.* Harper and Row, New York.

Eaton S., Strassman B., Nesse R., Neel J., Ewald P., Williams G., Weder A., Eaton S. 3rd, Lindeberg S., Konner M., Mysterud Y. & Cordain L. 2002. Evolutionary health promotion. *Prev. Med.,* 34: 109-118.

Eckenhoff R.G., Johansson J.S., Wei H., Carnini A., Kang B., Wei W., Pidikiti R., Keller J.M. & Eckenhoff M.F. 2004. Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity. *Anesthesiology,* 101: 703-709.

Elston G., Benavides R. & De Felipe J. 2001. The pyramidal cell in cognition: a comparative study in human and monkey. *J. Neurosci.,* 21: 163.

Erwin J., Nimchinsky E., Gannon P., Perl D. & Hof P. 2001. The study of brain aging in great apes. In P. Hof & C. Mobbs (eds): *Functional neurobiology of aging,* pp: 447-455. Academic Press, San Diego.

Farooqui A.A. & Horrocks L.A. 1998. Lipid peroxides in the free radical pathophysiology of brain diseases. *Cell. Mol. Neurobiol,.* 18: 599-608.

Finch C.E. & Stanford C.B. 2004. Meat-adaptive genes and the evolution of slower aging in humans. *Q. Rev. Biol.,* 79: 3-50.

Finch C.E. 2005. Developmental origins of aging in brain and blood vessels: an overview. *Neurobiol. Aging,* 26: 281-291.

Fullerton S.M., Clark A., Weiss K.M., Nickerson D.A., Taylor S.L., Stengârd J.H., Salomaa V., Vartiainen E., Perola M., Boerwinkle E. & Sing C.F. 2000. Apolipoprotein E variation at the sequence haplotype level: implications for the origin and maintenance of a major human polymorphism. *Am. J. Hum. Genet.*, 67: 881-900.

Gearing M., Rebeck G., Hyman B., Tigges J. & Mirra S. 1994. Neuropathology and apolipoprotein E profile of aged chimpanzees: implications for Alzheimer disease. *Proc. Natl. Acad. Sci. U.S.A.,* 91: 9382-9386.

Gearing M., Tigges J., Mori H. & Mirra S. 1997. β-Amyloid (Aβ) deposition in the brains of aged orangutans. *Neurobiol. Aging,* 18: 139-146.

Gluckman P., Beedle A. & Hanson M. 2009. *Principles of evolutionary medicine.* Oxford University Press, Oxford.

Gräff J. & Mansuy I. 2008. Epigenetic codes in cognition and behaviour. *Behav. Brain. Res.,* 192: 70-87.

Gräff J., Rei D., Guan J.S., Wang W.Y., Seo J., Hennig K.M., Nieland T.J.F., Fass D.M., Kao P.F., Kahn M., Su S.C., Samiei A., Joseph N., Haggarty S.J., Delalle I. & Tsai L.H. 2012. An epigenetic blockade of cognitive functions in the neurodegenerating brain. *Nature,* 483: 222-226.

Harold D., Abraham R., Hollingworth P., Sims R., Gerrish A., Hamshere M.L., Pahwa J.S., Moskvina V., Dowzell K., Williams A., Jones N., Thomas C., Stretton A., Morgan A.R., Lovestone S., Powell J., Proitsi P., Lupton M.K., Brayne C., Rubinstzein D.C., Gill M., Lawlor B., Lynch A., Morgan K., Brown K.S., Passmore P.A., Craig D., McGuinness B., Todd S., Holmes C., Mann D., Smith A.D., Love S., Kehoe P.G., Hardy J., Mead S., Fox N., Rossor M., Collinge J., Maier W., Jessen F., Schürmann B., van den Bussche H., Heuser I., Kornhuber J., Wiltfang J., Dichgans M., Frölich L., Hampel H., Hüll M., Rujescu D., Goate A.M., Kauwe J.S., Cruchaga C., Nowotny P., Morris J.C., Mayo K., Sleegers K., Bettens K., Engelborghs S., De Deyn P.P., Van Broeckhoven C., Livingston G., Bass N.J., Gurling H., McQuillin A., Gwilliam R., Deloukas P., Al-Chalabi A., Shaw C.E., Tsolaki M., Singleton A.B., Guerreiro R., Mühleisen T.W., Nöthen M.M., Moebus S., Jöckel K.H., Klopp N., Wichmann H.E., Carrasquillo M.M., Pankratz V.S., Younkin S.G., Holmans P.A., O'Donovan M., Owen M.J. & Williams J. 2009. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat. Genet.,* 41: 1088-1093.

Head E., Milgram N. & Cotman C. 2001. Neurobiology models of aging in the dog and other vertebrate species. In P. Hof & C. Mobbs (eds): *Functional neurobiology of aging,* pp: 457-468. Academic Press, San Diego.

Hendrie H.C., Ogunniyi A., Hall K.S., Baiyewu O., Unverzagt F.W., Gureje O., Gao S., Evans R.M., Ogunseyinde A.O., Adeyinka A.O., Musik B. & Hui S.L. 2001. Incidence of dementia and Alzheimer disease in 2 communities: Yoruba residing in Ibadan, Nigeria, and African Americans residing in Indianapolis, Indiana. *JAMA,* 285: 739-747.

Herring A., Donath A., Steiner K.M., Widera M.P., Hamzehian S., Kanakis D., Kölble K., El Ali A., Hermann D.M., Paulus W. & Keyvani K. 2012. Reelin depletion is an early phenomenon of Alzheimer's pathology. *J. Alzheimers Dis.*, 30: 963-979.

Herz J. & Chen Y. 2006. Reelin, lipoprotein receptors and synaptic plasticity. *Nature Rev. Neurosci.,* 7: 850-859.

Horrocks L.A., Farooqui A.A. 2004. Docosahexaenoic acid in the diet: its importance in maintenance and restoration of neural membrane function. *Prostaglandins Leukot Essent Fatty Acids,* 70: 361-72.

Jacobs B., Chugani H.T., Allada V., Chen S., Phelps M.E., Pollack D.B. & Raleigh M.J. 1995. Developmental changes in brain metabolism in sedated Rhesus macaques and

vervet monkeys revealed by Positron Emission Tomography. *Cerebral Cortex,* 3: 222-233.

Jacobs H.I., Van Boxtel M.P., Jolles J., Verhey F.R.J. & Uylings H.B. 2012. Parietal cortex matters in Alzheimer's disease: An overview of structural, functional and metabolic findings. *Neurosci. Biovehav. Rev.,* 36: 297-309.

Kitajka K., Sinclair A.J., Weisinger R.S., Weisinger H.S., Mathai M., Jayasooriya A.P., Halver J.E. & Puskás L.G. 2004. Effects of dietary omega-3 polyunsaturated fatty acids on brain gene expression. 2004. *Proc. Natl. Acad. Sci. U.S.A.,* 101: 10931-10936.

Kröger E., Verreault R., Carmichael P.H., Lindsay J., Julien P., Dewailly E., Ayotte P. & Laurin D. 2009. Omega-3 fatty acids and risk of dementia: the Canadian Study of Health and Aging. *Am. J. Clin. Nutr.,* 90: 184-192.

Lambert J.C., Heath S., Even G., Campion D., Sleegers K., Hiltunen M., Combarros O., Zelenika D., Bullido M.J., Tavernier B., Letenneur L., Bettens K., Berr C., Pasquier F., Fiévet N., Barberger-Gateau P., Engelbourghs S., De Deyn P., Mateo I., Franck A., Helisalmi S., Porcellini E., Hanon O, European Alzheimer's Disease Initiative Investigators, de Pancorbo M.M., Lendon C., Dufoil C., Jaillard C., Leveillard T., Alvarez V., Bosco P., Mancuso M., Panza F., Nacmias B., Bossù P., Piccardi P., Annoni G., Seripa D., Galimberti D., Hannequin D., Licastro F., Soininen H., Ritchie K., Blanché H., Dartigues J.F., Tzourio C., Gut I., Van Broeckhoven C., Alpérovitch A., Lathrop M. & Amouyel P. 2009. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat. Genet.,* 41: 1094-1099.

Leigh S.R. 2004. Brain growth, life history and cognition in primate and human evolution. *Am. J. Primatol.,* 62: 139-164.

Leonard W.R., Snodgrass J.J. & Robertson M.L. 2007. Effects of brain evolution on human nutrition and metabolism. *Ann. Rev. Nutr.,* 27: 311-327.

Lieberman P. 2009. FOXP2 and human cognition. *Cell,* 137: 800-802.

Lu T., Pan Y., Kao S.Y., Li C., Kohane Y., Chan J. & Yankner B.A. 2004. Gene regulation and DNA damage in the ageing human brain. *Nature,* 429: 883-891.

Martinez-Cedeño V., Galazo M.J., Cavada C. & Clascá F. 2002. Reelin immunoreactivity in the adult primate brain: intracellular localization in projecting and local circuit neurons of the cerebral cortex, hippocampus and subcortical regions. *Cerebral Cortex,* 12: 1298-1311.

Mayeux R. 1998. Gene-environment interaction in late-onset Alzheimer's disease: the role of apolipoprotein E4. *Alzheimer Dis. Assoc. Disord.,* 12: S510-515.

Mesulam M. 2000. *Principles of behavioral and cognitive neurology.* Oxford University Press, New York.

Mink J.W., Blumenschine R.J. & Adams D.B. 1981. Ratio of central nervous system to body metabolism in vertebrates: Its constancy and functional basis. *Am. J. Physiol.,* 241: R203-R212.

Mormino E.C., Smiljic A., Hayenga A.O., Onami S.H., Greicius M.D., Rabinovici M.J., Baker S.L., Yen I.V., Madison C.M., Miller B.L. & Jagust W.J. 2011. Relationships between Beta-Amyloid and Functional Connectivity in Different Components of the Default Mode Network in Aging. *Cerebral Cortex,* 21: 2399-2407.

Nesse R. & Williams G. 1994. *Why we get sick.* Vintage Books- Random House, New York.

Nesse R. 2008. The importance of evolution for medicine. In Trevathan W., Smith E. & McKenna J. (eds): *Evolutionary medicine and health,* pp. 416-431. Oxford University Press, New York.

Ohm T., Müller H., Braak H. & Bohl J. 1995. Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. *Neuroscience,* 64: 209-217.

Parker S.T. & McKinney M.L. 1999. *Origins of intelligence. The evolution of cognitive development in monkeys, apes and humans.* The John Hopkins University Press, Baltimore and London.

Patrick G.N., Zukerberg L., Nicolic M., de la Monte S., Dikkes P. & Tsai L.H. 1999.

Conversion of p35 to p25 deregulates Cdk5 activity and promotes neurodegeneration. *Nature,* 402: 615-22.

Persico A.M., Levitt P. & Pimenta A.F. 2006. Polymorphic GGC repeat differentially regulates human reelin expression levels. *J. Neural. Transm.,* 113: 1373-1382.

Planel E., Richter K.E., Nolan C.E., Finley J.E., Liu L., Wen Y., Krishnamurthy P., Herman M., Wang L., Schachter J.B., Nelson R.B., Lau L.F. & Duff K.E. 2007. Anesthesia leads to tau hyperphosphorilation through inhibition of phosphatase activity by hypothermia. *J. Neurosci.,* 27: 3090-3097.

Poduri A., Gearing M., Rebeck G., Mirra S., Tigges J. & Hyman B. 1994. Apolipoprotein E4 and beta-amyloid in senile plaques and cerebral blood vessels of aged *Rhesus* monkeys. *Am. J. Pathol.,* 144: 1183-1187.

Price D. 1993. Overview of neuropathology in aged monkeys. *Neurobiol. Aging,* 14: 685-686.

Ptak C. & Petronis A. 2008. Epigenetics and complex diseases: From etiology to new therapeutics. *Ann. Rev. Pharmacol. Toxicol.,* 48: 257- 76.

Qiu C., Kivipelto M. & von Strauss E. 2009. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues Clin. Neurosci.,* 11: 111-128.

Rilling J. & Insel T. 1999. The primate neocortex in comparative perspective using magnetic resonance imaging. *J. Hum. Evol.,* 37: 191-223.

Rilling J.K., Barks S.K., Parr L.A., Preuss T.M., Faber T.L., Pagnoni G., Bremner J.D. & Votaw J.R. 2007. A comparison of resting-state brain activity in humans and chimpanzees. *Proc. Natl. Acad. Sci. U.S.A.,* 104: 17146-17151.

Rosen R.F., Farberg A.S., Gearing M., Dooyema J., Long P.M., Anderson D.C., Davis-Turak J., Coppola G., Geshwind D.H., Paré J.F., Duong T.Q., Hopkins W.D., Preuss T.M. & Walker LC. 2008. Tauopathy with paired helical filaments in an aged chimpanzee. *J. Comp. Neurol.,* 509: 259- 270.

Salomone S., Caraci F., Leggio G.M., Fedotova J. & Drago F. 2012. New pharmacological strategies for treatment of Alzheimer's disease: focus on disease modifying drugs. *Br. J. Clin. Pharmacol,.* 73: 504-517.

Sanjuan J. 2009. *La teoría de la evolución en la medicina.* Editorial Médica Panamericana, Madrid.

Saura C., Choi S., Beglopoulos V., Malkani S., Zhang D., Shankaranarayana Rao B.S., Chattarji S., Kelleher R.J.3rd, Kandel E.R., Duff K. Kirkwood, A. & Shen J. 2004. Loss of presenilin function causes impairments of memory and synaptic plasticity followed by age-dependent neurodegeneration. *Neuron,* 42: 23-36.

Schoenemann P., Sheehan M. & Glotzer L. 2005. Prefrontal white matter volume is disproportionately larger in humans than in other primates. *Nat. Neurosci*., 8: 242-252.

Seeley W.W., Allman J.M., Carlin D.A., Crawford R.K., Macedo M.N., Greicius M.D., DeArmond S.J. & Miller B.L. 2007. Divergent social functioning in behavioral variant frontotemporal dementia and Alzheimer disease: reciprocal networks and neuronal evolution. *Alzheimer Dis. Assoc Disord.,* 21: S50-S57.

Shaw P. 2007. Intelligence and the developing human brain. *BioEssays,* 29: 962-973.

Shi Q. & Gibson G.E. 2007. Oxidative stress and transcriptional regulation in Alzheimer disease. *Alzheimer Dis. Assoc. Disord*., 21: 276-291.

Smith E., McKenna J. & Trevathan W. 1999. *Evolutionary Medicine.* Oxford University Press, New York.

Smith M.A., Joseph J.A. & Perry G. 2000. Arson: Tracking the culprit in Alzheimer's disease. *Ann. N. Y. Acad. Sci.,* 294: 35-38.

Smith K., Flicker L., Lautenschlager N.T., Almeida O.P., Atkinson D., Dwyer A. & LoGiudice D. 2008. High prevalence of dementia and cognitive impairment in Indigenous Australians. *Neurology,* 71: 1470-1473.

Somel M., Franz H., Yan Z., Lorenc A., Guo S., Giger T., Kelso J., Nickel B., Dannemann N., Bahn S., Webster M.J., Weickert C.S., Lechmann M., Pääbo S. & Khaitovich P. 2009. Transcriptional neoteny in the human brain. *Proc. Natl. Acad. Sci. U.S.A.,* 106: 5743-5748.

Soscia S.J., Kirby J.E., Washicosky K.J., Tucker S.M., Ingelsson M., Hyman B., Burton M.A.,

Goldstein L.E., Duong S., Tanzi R.E. & Moir R.E. 2010. The Alzheimer's disease-associated amyloid β-protein is an antimicrobial peptide. *PLoSOne,* 5: e9505.

Sperling R.A., Jack C.R. jr, Black S.E., Frosh M.P., Greenberg S.M., Hyman B.T., Scheltens P., Carrillo M.C., Thies W., Bednar M.M., Black R.S., Brashear H.R., Grundman M., Siemers E.R., Feldman H.H. & Schindler R.J. 2011. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement.,* 7: 367-385.

Stearns S. 1999. *Evolution in health and disease.* Oxford University Press, New York.

Stewart R. 1998. Cardiovascular factors in Alzheimer's disease. *J. Neurol. Neurosurg. Psychiatry,* 65: 143-147.

Su B., Wang X., Nunomura A., Moreira P.I., Lee H., Perry G., Smith M.A. & Zhu X. 2008. Oxidative stress signaling in Alzheimer's disease. *Curr. Alzheimer Res.,* 5: 525-532.

Uddin M., Wildman D.E., Liu G., Xu W., Johnson R.M., Hof P.R., Kapatos G., Grossman L.I. & Goodman M. 2004. Sister grouping of chimpanzees and humans as revealed by genome-wide phylogenetic analysis of brain gene expression profiles. *Proc. Natl. Acad. Sci. U.S.A.,* 101: 2957-2962.

Vaishnavi S.N., Vlassenko A.G., Rundle M., Snyder M.A., Mintun M.A. & Raichle M.E. 2010. Regional aerobic glycolysis in the human brain. *Proc. Natl. Acad. Sci. U.S.A.,* 107: 17757-17762.

Vlassenko A.G., Vaishnavi S.N., Couture L., Sacco D., Shannon B.J., Mach R.H., Morris J.C., Raichle M.E. & Mintun M.A. 2010. Spatial correlation between brain aerobic glycolisis and amyloid β (Aβ) deposition. *Proc. Natl. Acad. Sci. U.S.A.,* 107: 17763-17767.

Walker L. 1993. Comparative neuropathology of aged nonhuman primates. *Neurobiol. Aging,* 14: 667.

Walker L. & Jucker M. 2011. Amyloid by default. *Nature Neurosci.,* 14: 669-670.

Zawia N.H., Lahiri D.K. & Cardozo-Pelaez F. 2009. Epigenetics, oxidative stress and Alzheimer disease. *Free Radic. Biol. Med.,* 46: 1241-1249.

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