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Evolutionary Considerations on Aging and Alzheimer's Disease

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Abstract

Increasingly people are surviving into old age both in high and middle/low income countries. The increase in longevity is associated with increased levels of morbidity of both somatic and mental disorders during those added years. These pathologies prompt developing strategies for effective prediction, prevention and treatment of such disorders, among them the dementias such as Alzheimer's disease (AD).

Aging lies on a temporal continuum that starts at conception and ends at death. It refers to the aging processes occurring during an individual's lifetime. However, our understanding of aging remains limited. In the early stages of dementia, distinguishing normal from pathological aging remains complex. Medical research customarily investigates the immediate mechanisms or pathogenesis of "how" diseases come about and affect patients. Evolutionary perspectives consider the reasons "why" people may have become particularly vulnerable to different conditions.

Examining why people age is illuminating. Around the question whether aging is adaptive, we consider some evolutionary concepts useful around aging theories, among others antagonistic pleiotropy and life history theory and more recent concepts including evolvability and evolutionary developmental biology.

As AD seems to be specific to homo sapiens, its existence may in part be anchored in the adaptive changes that have occurred after the hominidae separated from the pongidae. Around the question why apparently non-adaptive conditions such as AD are so frequent, we consider, among other aspects, brain development including the related phenomena of altriciality and grandmothering, the evolution of ApoE and the genome lag hypothesis. We consider the idea that the neuropathological hallmarks of AD help mitigate neurodegeneration and cognitive decline rather than being its cause. Thus, an evolutionary look into AD may shed new light on the currently still sombre perspectives regarding disease-modifying treatments of AD and prove useful as a root cause analysis.

Keywords: Aging; Dementia; Alzheimer's disease; Etiology; Evolution; Ultimate causation

Introduction

Increasingly people are surviving into old age. This increase will continue over the coming decades with the old-old segments increasing more quickly relative to the young old [1,2]. This development is not limited to high income countries as it also occurs, with some time lag, in most middle and low income countries [3].

In most parts of the world, human longevity is now well in excess of that experienced by historical members of our species, even within recent times. This increase in longevity is associated with increased levels of morbidity of both somatic (e.g. cancer, vascular diseases) and mental disorders (e.g. dementia) during those added years. These pathologies have partly arisen as a result of more hygienic environments, better public health and improvements in medicine extending lives. Contemporary research programmes are aimed at developing strategies for effective prediction, prevention and treatment of such disorders. This particularly applies to the dementias such as Alzheimer's disease (AD) [4,5].

Aging lies on a temporal continuum that starts at conception and ends at death [6]. Aging refers to the aging processes occurring during an individual's lifetime. Aging is a different concept to life span, longevity or life expectancy. Life span refers to the maximum life span observed in a group. Longevity is the average life span expected under ideal conditions. Life expectancy is the average life span expected of a group at birth or any other given point in time after birth.

Despite this "grey tsunami", our understanding of senescence remains limited. In the early stages of dementia, distinguishing normal from pathological aging remains complex. As science progresses new treatments are developed for what may be considered to be abnormal or harmful processes, but the pathophysiological mechanisms targeted by such endeavours may only be compensatory, by-products or epiphenomenal [7,8]. An evolutionary perspective sheds new light on the origins of reasons for these phenomena.

Medical research customarily investigates the immediate mechanisms or pathogenesis of "how" diseases come about and affect patients. Evolutionary perspectives consider these too, but also examine reasons "why" people have become particularly vulnerable to different conditions. Evolution adds a deep historical "why" perspective as to the reasons why some diseases particularly occur in old age, providing root cause analysis to the problems of senescence [9,10].

Examining why people age is illuminating. Why is there a finite human lifespan at all? How has longevity evolved in *Homo sapiens*? Is aging adaptive? Why are apparently non-adaptive conditions such as the dementias so frequent? Scientists have developed hypotheses around the reasons for both the values and shortcomings for these phenomena. In this article, we discuss evolutionary ideas around aging and AD.

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Theories of Ageing - Is Aging Adaptive?

Aging lies on a temporal continuum that starts at conception and ends at death [6]. This article will now focus on aging, as distinct from longevity, life span or life expectancy.

Aging includes such phenomena as grey hair, wrinkles, arterial stiffness, osteoporosis, sarcopenia and relative immunodeficiency. Recognizing the differences between aging and disease is however complex [11]. Summarised potential differences maintaining that aging is not a disease because, unlike the changes that occur with any disease, age-related changes:

1. Occur in animals that reach a fixed size in adulthood,
2. Generally cross species barriers,
3. Occur after sexual maturation,
4. Can occur in animals removed from the wild and protected by humans, even if, for thousands or millions of years, that animal species has not been known to experience aging,
5. Increase vulnerability to death in every animal that ages, and
6. Occur in both animate and inanimate objects.

Therefore some clinical phenomena that doctors often consider as age-related disorders (e.g. many non-communicable diseases) may not be defined as diseases. Such diseases may be better defined in evolutionarily terms as a harmful dysfunction [12]. This is especially true if a process does not benefit an individual in a given set of circumstances even if such a process is physiological and not abnormal, unusual or pathological. Thus, distinctions as to what a disease is remain problematic, as there are normative social or subjective criteria as well as objective scientific criteria involved. The cursor on the spectrum between clearly normal aging and a clear disease state remains difficult to place.

A comprehensive theory of aging must then explain not only how but also why age-related changes (illnesses or not!) occur during a lifetime. More specifically, theories should explain why and when specific changes occur during life, and why natural selection has not averted their occurrence.

Aging is often regarded as cumulative, universal, progressive, intrinsic and deleterious [13]. However, this is not necessarily so as tremendous variation exists between species. *Hydra vulgaris* shows no evidence of aging and may be regarded as potentially immortal [14]. The naked mole rat, whose probability of death appears not to increase with age, is apparently hardly subject to diabetes, cancer, cardiovascular diseases and other senile ailments, but dies of extrinsic causes [15]. In other species, mortality even appears to decrease and fertility actually increases with age. This phenomenon, termed 'negative aging', exists in desert tortoises [16]. Yet other species age at a much slower rate than humans. Thus, some turtles have been claimed to live for hundreds of years and some whales up to 200.

Theories of aging are not necessarily mutually exclusive. Based on proximate causation, theories have been put forward to explain aging processes including free-radical damage, telomere attrition that may start very early in life [17], epigenetic changes and others [18,19]. Aging according to these theories seems a progressive "wear and tear" deterioration of physiological functions with increasing age. However, these wear and tear theories of aging, drawing analogies with mechanical objects like cars, are poor or incomplete models for aging [20]. Inanimate objects cannot repair themselves and inevitably move towards entropy and deteriorate. A living creature can repair itself theoretically indefinitely. Some species have moved towards astonishing capacities to repair tissue damage. Lizards and hydra vulgaris have remarkable powers of recuperation.

Such observations pose an evolutionary paradox when natural selection designs (Selects) organisms for optimal reproductive success (Darwinian fitness). Why then does evolution not prevent aging in the first place [21]? Several theories of aging based on evolutionary concepts have been put forward [22]. Some evolutionary approaches consider that aging may serve a primary useful biological function that aids survival, though usually through group selection, antithetical to Dawkins's selfish gene [23]. Williams [24] sidestepped this problem with his insight that a gene, which differentially affects survival and reproduction at a young age, might have a greater effect on the Darwinian fitness than does the same gene expressed later in life (or in a different environment).

Useful Evolutionary Concepts around Aging Theories

There are several important evolutionary concepts regarding aging theories we need to consider. Mutation Accumulation (MA) considers damage to the genome to occur through mutations or alleles that produce late-onset detrimental effects. Genes expressed only in later life, i.e., after a reproductive phase, can over evolutionary time give rise to substantial frequencies within populations. They may thereby contribute to the phenomenon of aging. However, MA as a theory is problematic as natural selection could easily have selected for more efficient repair mechanisms. Furthermore, MA requires a further explanation for how genes that minimally affect survival and reproduction in an ancestral environment have spread and become so frequent and detrimental [20]. MA theory therefore remains closely analogous to the wear and tear theories and, thus, proximate causation theories of aging.

Antagonistic pleiotropy (AP) is the phenomenon whereby genes change over time with respect to their fitness advantages [24]. This revolutionary concept extends Medawar's ideas that selection would be stronger on traits expressed at younger ages simply because a greater proportion of the population is alive to experience its effects [25,26]. Consider hypothetically a lethal or deleterious gene that is expressed only later in life. Many carriers will have passed on the gene before it kills them. The same gene would be quickly selected out if it killed individuals before they reproduced. However, a pleiotropic gene that gives a significant benefit early in life may still remain, even if it causes deleterious effects later when selection is weaker [24,27]. Certain mutations appear to be maladaptive and may have no benefits at all in any circumstances and not only result in dysfunctional behaviours but are eventually fatal. However, if the person survives long enough to reproduce the genes may be passed along to the next generation. Examples include Huntington's disease and, to some extent, AD or fronto-temporal dementia. However, may the genes responsible for these pathologies have some other early or heterozygous adaptive effect or function before pathology in an older person becomes evident? We shall come back to this when considering AD. Discussion of genetic "vulnerability" can be misleading if it fails to account for adaptive functions of the gene in other environments [27].

In a related process known as balancing selection, susceptibility alleles remain in the gene pool when they sometimes increase fitness, e.g. when the heterozygote has some reproductive advantage over the homozygote. Sickle cell disease is an example. However, aging is not

dependent on single genes so any balancing selection is likely to operate at the level of multiple genes. Besides balancing selection and AP, the reasons for some harmful genes remaining prevalent within the human genome may include: new mutations, founder effects or population bottlenecks, reproduction being prioritised at the expense of health, and artefacts of other processes called spandrels or exaptations.

Life history theory considers traits and events that affect the age schedule of fertility or of mortality [26,28,29]. It further includes the level of parental investment, senescence and death and considers the trade-offs resulting from different reproductive strategies [30] that depend on environmental and other factors. Thus, organisms with high mortality rates typically mature earlier than species with low mortality rates, and give birth to more offspring at a time [31-33]. Evolutionary plasticity of aging and longevity is an established experimental fact [22]. Banning reproduction before a certain age, as a mental experiment, would push up the mean longevity of a species [23]. Members of human families with long life spans delay age-related disease such as cancer, cardiovascular disease or diabetes by a decade compared to those without a history of longevity [34]. Thus, delaying the onset of age-related pathology and extending healthy life span may not just be theoretical [35]. Advocates of programmed senescence argue that single genes have been demonstrated to substantially extend life span [36,37]. The late 1990's genome analysis showed that genes favouring longevity were not random mutations. Rather, they had been around since our last common ancestors with creatures that diverged from our line billions of years ago, e.g. baker's yeast, worms, fruit flies that all share some of the aging genes.

Another genetic theory proposes a longevity timekeeper (cellular clock) which can delay the rate of accumulative damage during the post-maturational period of life [38]. However, repair mechanisms are often highly expensive and may not increase gene copies enough as the resources could be put into numerically more effective current reproduction and the ancestral body disposed of. This is the basis of the primary tenet of the disposable soma theory. It posits a selective advantage for any organisms that allocate most of their resources to development and reproduction but allocate only just enough to somatic maintenance to keep the organism in good condition for the required duration of life, i.e., long enough to rear their offspring when necessary.

These above theories remain contested [39] because - although useful and not mutually exclusive - they still need a larger unifying framework within evolutionary theory. However, they do demonstrate that aging processes can be side effects, bye-products or exaptations from other processes, which are adaptive though aging it, is not an adaptation.

More Recent Evolutionary Considerations

Evolutionary theories generally posit that reproductive success is the most important factor to increase the presence of genes in the next generation. However, genes can only out-compete other genes if they initially prepare the organism that carries them to be better adapted than others to the changing niche where the organism survives and reproduces. In rapidly changing environments the ability to select for variation and changes, i.e., adaptiveness, becomes crucial.

Selection might in some circumstances favour the evolution of death [40]. The reason is not the naive idea of making space for youth, but the increased capacity of a sufficient number of newly generated variants to allow for continuing evolution by natural selection. This refers to evolvability, which is high if a biological system has a high degree of heritable genetic variation on which natural selection can act. Evolvability is an adaptation to changing environments and requires the death of previous occupants of a niche. Genes and epigenetic mechanisms involved in aging relate to environmental stress, e.g. heat, exercise, caloric restriction. Some environmental conditions have a biphasic dose-response effect, called hormesis, i.e., low-dose stimulation and high-dose inhibition or toxicity. Thus, moderate stress may slow down aging [41]. According to many theories, aging is the passive consequence of external inescapable variables and, thus, pointless in the light of evolution. However, this point of view changes as soon as we consider evolvability represented by dynamic processes regulated by internal and external factors [42-44]. These theories begin to explore why creatures live and inevitably die, but they do not fully explain why we actually age at the organismic level. In particular, evolutionary theories need to resolve issues around the ranges of speed of aging in any given species. Why would it be adaptive for organisms to slowly decline when it might be more efficient to deteriorate quickly and die? Gene-environment interactions are pivotal mechanisms particularly important in humans. Genes of our species may have been favoured to promote survival in rapidly changing environments due to climatic fluctuations through the promotion of flexible behavioural patterns rather than fixed action patterns. Aging may not be an adaptive process in itself except as a feature of another truly adaptive process. As such, aging is a spandrel or exaptation. Evolutionary biology of aging seems to needs such explicit terms, rather than the term "adaptations", for features that arise as by-products whatever their subsequent exaptive utility may be.

Recognising that historical causes of biological features are different from their current utilities is of paramount importance. Worldwide numerous people die each day of age-related causes such as AD, cancer and cardiovascular disease. The incidence of all of these diseases increases rapidly with age. Cultural protection of the aged is one contemporary reason for this increase (hygiene, healthier lifestyle, medicine, etc.). However, a parsimonious evolutionary explanation for the existence of aging requires explanatory mechanism based on individual fitness and selection, generation after generation, if aging is more than the result of recent morality and cultural protection. Increased survival of the elderly may involve reciprocation of caring capacity. This may be a by-product of kin selection, parental investment and attachment and inherent in human altruism which leads humans to look after their kin and elderly family [45,46]. However, this comes at a cost and may conversely partly explain some instances of suicide [47] and elder abuse.

From the second half of the 20th century, a growing minority insisted on the relevance of ontogeny to evolutionary theory, laying the foundations for evolutionary developmental biology, also called evo-devo. This concept integrates embryological processes, developmental constraints, and evolution [48]. In brief, gene-environment interactions shape gene expression by epigenetic means, which fosters phenotypic variability. Evo-devo considers that aging and embryogenesis link together in several ways. Developmental genes may mediate the aging process. Conversely, aging-related genes might be involved in the early developmental period [49]. For instance, proto-oncogenes ensuring cellular proliferation in early life may prove lethal if reactivated later in life by carcinogens such as irradiation or smoking. Interestingly, older parental age influences negatively their progeny's lifespan [50].

These ideas are clearly reminiscent of antagonistic pleiotropy (cf. above). However, AP belongs to the reductionist gene-centred models of biology and evolution. Researchers remain divided over the need

for such a revision of evolutionary theory [51]. Defenders plead for an extended theory, which encompasses developmental processes, epigenetics, phenotypic plasticity and evolvability [52-54]. They argue for a multilevel selection theory, from genes to individuals, from groups to populations and to species, acknowledging not just one, but four systems of inheritance: genetic, epigenetic, behavioural and cultural. In complex ecosystems, selection acts upon many such components as well as on processes and propensities [53]. In human evolution, particularly considering medicine and psychiatry, this may need an evolutionary theory paradigm shift.

If we consider physiological aging from an evolutionary perspective, e.g. as an exaptation, it is quite natural to ask what evolutionary perspective may contribute to our understanding of processes usually considered pathological. Although we may not consider diseases of the elderly as adaptations, we may still ask whether some features linked to pathological aging may have had some evolutionary advantage for homo sapiens sapiens (HSS) during the environment of evolutionary adaptedness (EEA). This is a particularly interesting question to ask with regard to neurodegenerative disorders, first among them AD.

An Evolutionary Perspective Regarding AD

Much fundamental research in AD is carried out in mice. This is surprising as naturally occurring AD is extremely uncommon in mammals other than elderly humans. An old chimpanzee held in captivity is one of the exceedingly rarely documented cases in a non-human being of histologically typical AD as witnessed by the presence of both amyloid plaques and neurofibrillary tangles [55]. AD seems to be specific to HSS and its existence in humans and its absence in the primates most closely related to HSS requires an explanation. This explanation may at least in part be anchored in the adaptive changes that occurred either when the hominidae separated from the pongidae or during the hominidae evolution or, more likely, both. Before looking at these adaptations possibly relevant to AD, let us briefly consider AD.

Alzheimer's Disease (AD)

AD is a brain disorder with identifiable clinical features at least if it presents as a typical monopathology. The typical clinical AD syndrome is a cognitive disorder characterized by an initially insidious and consequently progressive decline that affects first memory, more specifically episodic memory, and later executive functions, language and visuospatial skills. However, executive problems may appear quite early in the course of AD and prospective memory deficits may be among the first to become clinically relevant. Several lines of evidence indicate that the primary progressive amnestic syndrome so characteristic of the initial stages of typical AD is the consequence of the neuropathological changes in the medial temporal structures, in particular the entorhinal cortex and the hippocampus. This sequence of cognitive deterioration reflects the progressive expansion of AD-type lesions in the brain starting in the mediotemporal brain regions and consequently invading the allocortex and isocortex [56]. Variations, however, occur mainly in late-onset forms and may be more pronounced than those suggested by early epidemiological studies [57]. Cognitive deficits progressively cause functional impairment that follows a typical pattern in pure cases, which allows for functional staging of disease progression [58]. Behavioural and psychological symptoms and signs are tremendously frequent in AD and paramount when carers help or treat patients with AD.

AD is a leading cause of morbidity in the elderly. Yet, its origin is unknown. Surely, a great deal of knowledge has been accumulated over the last three decades regarding the pathological cascades in the brain, but research makes it increasingly clear that the causes of AD will never be explained in a monocausal, mechanistic and linear way. Numerous risk factors have been described and, thus, a causal explanation of AD is more likely to stem from a dynamic life-long perspective in the context of increasing longevity pushed to its extreme in the human species with advanced age being the most important risk factor for sporadic AD. AD accounts for 60% to 70% of cases of dementia [59,60]. Most people who develop AD do so after the age of 65, but early-onset AD characterized by a strong genetic inheritance occasionally occurs. These rare genetically determined autosomal dominant young-onset cases related to APP, PS1 and PS2 mutations represent less than 1% of all cases and cannot operate as a thorough model for the much more frequent sporadic late-onset cases although associations with these genes increase the risk for sporadic AD. In short, there is currently no comprehensive etiological model of AD.

Developing AD is linked to a combination of factors, some of which can be partly controlled (e.g. lifestyle and environmental factors), but others cannot (e.g. age and genes) [61]. 50-70% of the risk may be genetic and non-modifiable with many genes usually involved. The best-known genetic risk factor is the presence of the ApoE4 allele. Apolipoproteins are lipid-binding molecules and play an important role in lipid metabolism. The ApoE4 allele increases the risk of the disease in homozygotes but also in heterozygotes and between 40 and 80% of people with AD possess at least one ApoE4 allele. Eliminating the ApoE4 allele would yield an estimated 7% reduction in AD incidence [62]. As for many human diseases, environmental effects and genetic modifiers result in incomplete penetrance. For example, certain Nigerian populations do not show, among other differences, the relationship between level of ApoE4 and incidence and age of onset for AD seen in other human populations [63]. ApoE4 is the ancestral form of the gene, and ApoE3 arose later with a single cytosine to thymidine substitution at position 112 after the human lineage diverged from that of chimpanzees and bonobos. Another such mutation at position 158 in the ApoE 3 allele later gave rise to the ApoE 2 form of the gene [64]. The more recent ApoE alleles might have other neurological benefits besides AD protection, including fewer tangles and plaques in young adults and after head trauma or a decreased risk of cellular death as compared to ApoE4 [65].

ApoE4 is most likely not the only genetic risk factor and genome-wide association studies have found other genes that affect the risk, but to a much lower extent than ApoE4. Indeed, as age is the greatest risk factor for AD the number of genes influencing the risk for AD may be significantly larger. Further risk factors, many of them modifiable, include a history of head injuries, depression, vascular factors and others [5]. About 35% of dementia is attributable to a combination of the following nine risk factors: education to a maximum of age 11-12 years, midlife hypertension, midlife obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, and social isolation [61]. Each of them has its own multiple risk factors in terms of both genetic make-up and potentially modifiable environment. As AD seems to be specific to HSS the aetiopathogeny of AD may be in part anchored in the adaptive changes that occurred during the hominidae evolution.

Brain Development in HSS, Brain Size, Evolution of ApoE and Synaptic Activity

The alignable sequences within genomes of humans and chimpanzees differ by perhaps 35 million single-nucleotide substitutions, i.e., about 5 per year, on average, across the species since HSS divergence

from a common ancestor. Additionally, the complete genomes also differ by deletions, insertions and duplications. Depending on what aspects are considered, the overall difference between the chimp and human genome may be around 5% [66,67]. Since mutation rate is relatively constant, roughly one-half of these changes occurred in the human lineage. This genetic difference seems small when compared to phenotypic differences between the two species. Major phenotypic differences include increased brain size, gracious bipedalism, elaborated language, abstract thinking and metacognition, fine hand manipulation and tool-use, major altriciality and the capacity to deliberately change their habitats. Also HSS is now the only living representative of its species [68] of which the most distinctive feature is brain development. There are also phenotypic differences in other features such as growing older far past reproductive age [64,69,70], the relationship between longevity and fertility [30,31] [32,39,50,71-73], grand-mothering [23,74-80], altriciality and neoteny as well as investment in off-spring [81,82] and kin selection as a form of inclusive fitness [45,46] are related to increased brain size, longevity and, ultimately, aging and AD. These changes allowed for the development of higher mental capacities giving our ancestors a selective advantage within the EEA [83].

Perhaps, the selective pressures that led to the enormous increase in the weight of the human brain led, in turn, to the species-specific behavioural and psychological attributes as well as disease vulnerabilities of HSS [84].

The increase of brain size alone is insufficient to explain the difference between species, including human and non-human primates. Indeed, there have been larger brains on earth both currently (elephants and whales) or in past hominids (H neanderthalensis). The increase of the associative neocortex appears more decisively relevant than the absolute brain size. Far more developed in HSS than in any other mammal species, the parietal, frontal and medio-temporal structures sustain the more complex mental functions and learning that allow for flexible adaptation of behaviours. These features propel humans out of the realm of functioning only aware of the present, or immediacy, into that of an extended and historic time-space. This generates an awareness and ability to plan or account for a before and an after. Through ontogenesis, these neocortical associative areas are the last to myelinate and to acquire functional maturity; this bears witness to the necessity of continuous brain-environment interactions that shape our individualities. Their development is heterochronic with regard to other brain areas that develop earlier and require less – though still much - training for adequate functioning (bipedalism, fine hand movements, etc.). Temporally fine-tuned changes in gene regulation are critical to the heterochronous patterns of neurodevelopment within the human brain [85].

Heterochronic development of the associative neocortex closely relates to the human phenomenon of mothering and grand mothering as training through environmental and social exposure needs perhaps two decades to reach maturation [76]. This maturation parallels the progressive myelination of higher associative areas, in particular the frontal lobes over a similar time frame. Apolipoproteins and their evolution (cf. also later) may have played some role here as protective ApoE alleles may have been selected for grand mothering [86]. The ApoE4 allele is associated with a younger age of menopause [87] though some controversy persists. If true, the ApoE3 or ApoE2 alleles would provide an obvious procreative advantage. The ApoE2 allele later evolved from the ApoE3 form and may have spread, relative to the other alleles by any combination of the above hypotheses including neuroprotective function, cardiovascular effects, or random genetic drift [7]. ApoE3 and ApoE2 may not have been selected to decrease aging, but possibly to increase longevity in the context of a species in need of long postpartum care of its off-spring. Many other similar phenomena are likely to have occurred over evolutionary times of human evolution.

ApoE3 and ApoE2 polymorphisms are likely to have emerged at some point in human evolution that was accompanied by a rapid increase in brain size and the development of new neuronal connectomes sustaining complex mental functions. This may have happened when homo ergaster appeared on the world stage around 1.5 mya ago [64]. Together with the limbic mediotemporal structures, the higher functioning associative neocortex is among the first to degenerate in AD and FTD. These structures correspond to a large network, called sometimes the brain's default mode network that refers to the observation that its metabolic activity remains high at rest [88]. However, the evolutionary development of the human brain away from the non-human primate brains is far more complex and deserves being looked into according to a variety of neuronal systems of which 16 have been tentatively identified that may be linked to different neurodegenerative disorders [89].

Indeed, simple monocausal explanations may hide the truth. Thus, why has the APOE4 allele not been eliminated from the gene pool altogether, in favour of ApoE2 and ApoE3 as they appear to be more adaptive? We may still be in the process of selecting out APOE4 [7,90], but there may be potential counterbalancing benefits of the ApoE4 isoform. These could include possible protection against liver damage in patients with the hepatitis C virus, a decreased chance of spontaneous abortion in foetuses, reduced cardiovascular response to mental stress and the association of ApoE4 homozygosity with type-III hyperlipoproteinemia [7].

Synaptic activity and synaptogenesis are high in the developing brain and a large part of the genes whose expression has increased in the human brain as compared to non-human primate brains relate to synaptic plasticity and activity predominant in neocortical association areas [91] that are particularly vulnerable do AD. This is in line with the disconnection hypothesis of AD neuropathology [57] according to which AD symptomatology relates to the disconnection between brain areas secondary to the degeneration of specific neurons. AD lesions start mainly in the more poorly myelinated neurons in the limbic system related to memory and learning and in the associative cortex [92]. Ontogenetically, a significant reduction of the expression of genes involved in synaptic plasticity occurs starting at 40 years, which is unlike what occurs with other categories of genes that remain up-regulated with age and seem less vulnerable to oxidative stress. Genes expressing mitochondrial function evolve in parallel to that of genes involved in synaptic plasticity. This may not surprise as high synaptogenesis is likely to need both appropriate neuronal constituents and high levels of energy. Highly complex mechanisms underly synaptogenesis and neurogenesis. As an example, reelin, an extracellular matrix protein modulates synaptogenesis together with ApoE. Counteracting synaptic dysfunction induced by β-amyloid, it can nevertheless be fragmented by oxidative stress and finally contribute to amyloid deposits [92].

The heritability of a person's general cognitive ability sometimes referred to as Spearman's g increases with age suggesting that the relative effect of the environment on g as a measure of brain plasticity decreases with age [93]. What this means is unclear, but it is compatible with the idea that those with higher brain plasticity during their younger years of life survive longer relative to those with lower plasticity. As ApoE4 is phylogenetically the oldest ApoE isoform, it is of interest to

note that ApoE4 carriers have on average, lower levels of intellectual functioning [94]. Women's more extensive involvement in education may have contributed to their increased life expectancy relative to men. Interestingly, telomere length was 5-6% shorter in male babies and infants whose mothers had not graduated from high school [95]. Older people with high cognitive and brain plasticity may have had better adaptive capacities and survival chances and, thus, helped HSS spread around the world and develop farming, tools and civilisation.

The cognitive changes observed in normal aging reveal that crystallised functions are better preserved than fluid components of cognition [96]. The needs of an elderly person meant to transmit their knowledge to those of the younger generation may predict this differential pattern. A similar dissociation as to cognitive aging has been found for verbal versus performance IQ with the latter one declining early and fast relative to verbal IQ that increases up to older age before it declines again in the more advanced stages of old age. Clearly, cognitive capacities have been selected just like any other human feature [97]. "Wisdom" in the aging femina/HSS may therefore have been naturally (socially) selected. This is inconsistent with the idea that there is no evolutionary pressure in the post-reproductive period. Developmental psychologists who consider human development to last past the reproductive period over the whole lifespan corroborate this positive view of aging [98]. This pressure may be transposed on the next generation with those having wise grandparents having better chances to reproduce in a complex societal context. This is a further aspect sustaining an extended grandmother hypothesis, at times called the library hypothesis [76].

Socio-emotional regulation improves with age which is associated with increased investment in emotionally meaningful others, notably kin [99]. Similarly, personality traits are paramount for social interactions. Although they seem relatively stable and we know little about personality changes in later life, some changes at the population level seem to occur [100]. People increase in measures of social dominance (a facet of extraversion) in young adulthood, conscientiousness, and emotional stability. However, people go on increasing on measures of agreeableness and conscientiousness into older age. Emotional stability increases during the 60s and then remains stable or decreases slightly. Openness increases up to the 50s and then decreases [100]. Thus, we hypothesize that this pattern of personality traits across a population of elderly people may favour competent transmission of knowledge from one generation to the next and contribute substantially to conflict resolution in kinship groups. Consciousness rather that naive optimism may positively influence life span as a result of a healthier life style [101]. Exploring the influence of personality traits on cognitive decline and the occurrence of behavioural and psychological symptoms and signs in dementia is a new research field [102]. An evolutionary perspective may well benefit this endeavour. If it is correct that people with high brain or cognitive plasticity have better adaptive capacities, and thus increased survival and reproductive chances, perhaps high behavioural and personality repertoires and plasticity act as a buffer against environmental variation. At that, a highly interesting side track of this train of thought is its implication that increased adaptability, once it has come into existence, may potentially slow evolutionary processes [93]. Thus, although evolutionary pressures on HSS obviously persist these pressures may have been reduced by domestication, modern medicine and other cultural reasons that drove up the longevity of the human species.

Brain Metabolism, Oxidative Stress

The energy consumption at rest by the human brain relative to body weight is far higher in humans than in any other species including great apes. It uses about 20% of the whole energy consumption at rest, which is about twice that of apes and three to 10 times higher than in other mammals [85,92]. The general level of neuronal activity is far higher in humans and this may be explained in part by the observation that many neurons in phylogenetically younger areas retain "juvenile" characteristics into adulthood (incomplete myelination, increased synaptic activity and plasticity, and hence enhanced neuronal metabolism) [92].

High metabolism is likely to be a prerequisite for high synaptogenesis and synaptic activity. High glucose metabolic rates have been found in young animals, but in no adult animal species is the oxygen requirement as high as in the human species. Oxidative phosphorylation is more efficient in producing energy but aerobic glycolysis contributes essential molecules to the growth of the brain. Thus, aerobic glycolysis is critical during development, and oxidative phosphorylation is highest during adulthood [85]. Oxidative phosphorylation within the primate lineage, with concomitant genetic changes, becomes enhanced with closer phylogenetic proximity to humans. Time-regulated gene expression affecting metabolic pathways is critical to the heterochronous patterns of neurodevelopment in the human brain [85].

At some point, our ancestors began eating more meat than earlier primates [103]. Interestingly, with the increase of brain size in Homo erectus a change in diet took place with an increase of meat intake and, thus, long-chained polyunsaturated fatty acids necessary for brain development [92]. Selection for more effective extraction of vital nutrients from food may also have allowed increasing success in parenting and added to the development of larger and more social brains. However, at the same time as improved nutrition allowed for a longer life span in socially and physically protected environments, it also led to the preservation of or selection of genes that now give rise to vulnerability to diseases of old age. Dietary habits of many HSS living in sedentary mode in modern affluent societies favour cognitive decline. Specific diets such as the Mediterranean-Dietary Approach to Systolic Hypertension Diet Intervention for Neurodegenerative Delay (MIND) may slow age-related cognitive decline [104]. As primates and the gut macrobiota have co-evolved over aeons the new research development relating the gut micorbiota to physiological and pathological aging may not surprise. Microbiome changes occur over the life span with some variants being associated with longevity although this evidence may only be correlative [105]. However, the study of the microbiota-gut-brain axis is under way and microbiome changes may represent a significant risk factor for Parkinson's disease; α-synucleine aggregates are found in the myenteric and submucosal plexus before the appear in the brain [105]. Amyoloid and lipopolysaccharide production by intestinal bacteria may favour pro-inflammatory pathways and contribute to the pathogenesis of AD [106]. Diseases like AD have a cost to kin. These effects on kin may also set a constraint in the capacity of human brains to increase further by means of those related evolutionary processes.

Phylogenetically, the development of high brain activity absorbing 20% of the energy input to satisfy the needs of an organ weighing perhaps 2% of the whole body can only take place if the trade-off is positive gene propagation. The spread of HSS across the planet bears witness to this occurrence. However, if sustained over longer periods of time such high metabolic rates may lead to enhanced oxidative stress known to accelerate neuronal aging, a theory underlying much of the research efforts currently deployed in AD. Oxidative stress has many effects on the cellular metabolism. One of them is the induction of lipid peroxidation leading to loss of polyunsaturated fatty acids in

the neuronal membrane [92], equalling to some extent dietary changes of modern HSS. Genes playing a central role in synaptic plasticity, vesicular transport and mitochondrial function are less expressed with age with markedly increased DNA damage in the promoters of genes. DNA damage may reduce the expression of selectively vulnerable genes involved in learning, memory and neuronal survival, initiating a programme of brain aging that starts early in adult life [93]. If high metabolism leads to enhanced oxidative stress, it is easy to predict that high metabolic brain rate must favour the development of anti-oxidative metabolic pathways. Indeed, induction of antioxidant and DNA repair genes is part of the stress response [93]. Lymphoblastoid cell lines derived from centenarians had significantly higher activity of the poly-ADP-ribose-polymerase, a DNA repair protein, than cell lines from younger individuals [107]. If these observations are true, we navigate here in the realm of genetic and epigenetic co-evolution that teleonomically optimizes adaptation.

Pygmies have about 53% of ApoE3, which is much lower than in average Caucasian populations where about three quarters have ApoE3 [64]. Short stature with small bodies needs less food supplies, which is an advantage in a habitat where food is scarce. However, it also reduces the quantity of free radicals, one of the more important proximate factors involved in explaining aging. Thus, in the context of the pygmies' living conditions, selection for ApoE3 may have been less important than in populations with larger body sizes. Furthermore, only weak evidence for selection on genes associated with height variation was found in pygmy and negrito populations, leading to the conclusion that classical explanations for the pygmies' short stature such as locomotion in closed forests and thermoregulation that imply direct selection for short stature may be insufficient explanations. Pygmies in different continents face high loads of infectious diseases and thus have very high mortality rates [108]. These findings suggest that the short stature of different pygmies in West and East Africa and Papua New Guinea might have evolved as a by-product of selection for fast-life histories in these populations [108]. Short stature is considered the result of a life history trade-off between the fertility benefits of larger body size against the costs of late growth cessation, under circumstances of significant young and adult mortality.

Genome Lag Hypothesis

The genome lag hypothesis posits in general terms that some of the modern human health problems arise due to the environmental changes alienating us (Mismatch hypotheses) from our EEA as hunter-gatherers. In other words, humans are less adapted to the modern environment than they were to the ancestral one. Such mismatches may be the physical or psychosocial environment. Indeed, life-style has changed in many ways since the agricultural revolution. Some consider the agricultural revolution as one of the major human historical catastrophes as it has driven humankind in a feed-forward spiral deleterious to not only humans but also the entire planet [68]. Adverse changes that have resulted include, among the more important ones, many aspects related to territoriality and diet.

Whether or not dementia is really less frequent in rural than urban environments as reported earlier is uncertain as methodological issues related to illiteracy may have previously biased the results. However, some life-style issues are modifiable and can influence the occurrence of dementia. Although age, the most important risk factor for neurodegeneration, is inescapable, other factors including affective or vascular disorders have the potential to be positively influenced. Low levels of education, midlife hypertension and obesity, hearing loss, late-life depression, diabetes, physical inactivity, smoking, and social isolation are risk factors for dementia [61]. Next to these factors, a new possible culprit identified recently would definitely be related to human-induced environmental changes, i.e., traffic-related air pollution correlated with dementia incidence in Northern Sweden [109]. The relationship between AD and millions of toxins is unclear, but we are only just entering the era of ecotoxicity that is likely to bring about new and perhaps ever more disturbing insights.

Some premorbid personality traits or disorders may be more common among AD patients than controls suggesting that they could be risk factors for AD [110]. Psychological distress or proneness to psychological distress may be associated with a higher risk of AD [111]. Those with the highest life-long distress-proneness (90th percentile) had twice the risk of developing AD than those who were lowest in distress proneness (10th percentile). Distress-proneness may well be a cofactor leading to dementia in AD [112]. Neuroticism, depression and anxiety traits may exacerbate the state of cognitive impairment and hippocampal vulnerability to AD [113]. An obvious candidate mechanism is the well-known toxic effect of glucocorticoids on hippocampal neurons [114]. Distress-prone people are also vulnerable to depression, which in turn is associated with hypercortisolemia. Patients with AD show sizable increases in neuroticism scores and regardless of whether elevated neuroticism scores are an independent antecedent of AD or one of its early signs, distress-proneness predicts an increased risk of clinical AD in an elderly population [115]. These findings may be compatible with a genome-lag hypothesis insofar as coping with acute stress has been positively selected for while chronic stress may be more characteristic of modern human life than of our ancestors' who evolved in our EEA although this conjecture is highly speculative.

There is currently an epidemic of the metabolic syndrome as a disorder of affluence. Sedentary behaviour and dietary change are the usual direct culprits, which link to neurodegenerative dementia. Thus, premorbid physical under-activity was more common among AD patients than matched controls and the studies relating vascular risk factors to both vascular and neurodegenerative dementia are now legion [61,116].

These changes, of course, did not occur over evolutionary timescales. What actually occurred over evolutionary time spans was the adaptation to a physically active life and a diet much richer in meat and long-chained poly-unsaturated fatty acids than that of the other great apes. This may have been the prerequisite for the potential for development of the human brain needing a tremendously high baseline metabolism relative to the rest of the bodily tissues.

This development towards high brain metabolism and synaptogenesis should be accompanied by evolutionary adaptations to the new diet and to oxidative stress. One case in point is, again, the ApoE system (cf. above). ApoE3 and ApoE2 have a higher affinity to high-density lipoproteins (HDL) while ApoE4 preferentially binds to low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL). ApoE4 is the phylogenetically oldest of the three isoforms. The emergence of ApoE3 and, then, ApoE2 polymorphisms in humans may have occurred by sporadic mutation of the ApoE4 allele at some point of human evolutionary history [7] when our ancestors began eating more meat than earlier primates used to eat [103]. Dietary shift meant higher cholesterol intake, allowing the ApoE3 allele with its lowered risk of atherosclerotic vascular disease to confer a survival advantage to meat-eaters [7]. The spread of the ApoE3 allele would have conferred little advantage before the increase in brain size. Indeed, ApoE3 may also slow down aging-related neuronal demyelination. The ApoE2 increase, coupled with its inability to bind to LDL, may act to

increase amyloid-beta clearance [117]. Trials with a protein derived from Klotho, an anti-aging gene named after the Greek goddess who spins the thread of life acting against oxidative stress, may be a further interesting development in Alzheimer treatment trials [118].

Some theories of infection-induced neurodegeneration exist not only for prion diseases but also for AD and seem to have regained interest within the scientific community [119]. The race between microorganisms and their hosts' immune system has always been an on-going struggle and motor for evolution. Whether host-infectious particle interactions set off adverse immunological responses in neurodegeneration is uncertain, but putative treatment options currently being studied for AD include immunological types aimed at cleaning up amyloid deposits. Interestingly, the aforementioned ApoE4 may have been continuously selected given its possible protective effects against some viral infections [120] despite its less favourable action on lipids compared to ApoE2/3. This may have been a further reason on top of the free-radical hypothesis why pygmies have a lower ApoE3 frequency than Caucasians (cf. above).

Evolutionary Considerations

A major hurdle for any putative evolutionary psychiatry model is how to reconcile disorders like AD - that have a genetic component, but are seemingly maladaptive and intuitively decrease fitness - continue to be expressed and inherited. The usual tentative hypothesis is that there must be a 'trade-off', i.e., some other selective advantages or benefits outweighing risk and leading to enhanced reproductive success even at the expense of worse long-term health. Therefore we must ask "Do people with AD later in life have advantages earlier in life [20]?"

Currently, the only major unequivocal risk gene for sporadic AD is ApoE. ApoE4 has classically been seen as injurious, ApoE2 as protective and ApoE3 as neutral. As mentioned, protective ApoE alleles may have been selected for through the advantages conveyed by the human phenomenon of grand mothering. Although motherly care is the norm in all mammal species, grand mothering in nonhuman primates is almost entirely unheard [76]. This fits with the observation that dementia in nonhuman primates occurs shortly after reproductive senescence, whereas dementia in humans tends to occur around 20 years after menopause, allowing more time for post-reproductive females to contribute to the care of their grandchildren .

Much of the recent and current drug therapy research for AD targets the processes of Aβ production, oligomerization, aggregation and clearance, processes seen as abnormal and ultimately leading to the clinical picture of AD. Accordingly, Aβ lesions should be prevented from forming (e.g. with β- or γ-secretase inhibitors) or removed if present (e.g. with anti-Aβ immunotherapies). Despite almost three decades of research and several hundred clinical drug trials later, uncertainties about the extent, mechanisms, and clinical relevance of Aβ in AD remain [121]. It has been hypothesised that AD pathology in its prodromal stages, seen within the evolutionary time frame, may be a form of down-regulation to conserve resources in food-scarce environments [122] with brain areas involved in acquiring new information being dispensable once an animal has acquired the skills it needs to survive. Domesticated HSS has extended the life span far beyond what it was in the EEA. This theory views AD from a physiological paradigm point of view and suggests that AD pathology may not be causal, as implied by the traditional view of AD pathophysiology, but epiphenomenal and indicate rather than cause neurodegeneration. The observation that the correlation between plaque load and clinical features of AD appears limited, especially in the oldest patients may sustain this view[57,110].

Aβ-plaques may have preceded the more effective immune system, a hypothesis in line with the observation that Aβ has potent antimicrobial activity and may decrease deleterious excitatory neurotransmission [7]. The cleavage of APP by β- and γ-secretases forms Aβ that may have a concentration-dependent action on neuroplasticity through synaptic pruning. Similar considerations can be made regarding neurofibrillary degeneration as sequestration and aggregation of oligomerized PHF-τ into NFT may be protective. Thus, AP effects related to the role of Aβ and PHF-τ in synaptic pruning may be at the origin of AD when humans reach advanced age [7]. Another line of research has shown that β-amyloid may protect against oxidative stress and have chelating properties that neutralize iron released through the destruction of oligodendrocytes [92]. More generally, if β-amyloid is not the motor of neurodegeneration and possibly a bodily defence mechanism we may more easily understand why research following the β-amyloid hypothesis has produced no break-through in AD treatment and again led to a new failure with solenazumab [123].

If it turns out that there is some validity in the above conceptualisations, then an alternative theoretical framework can be considered in which the neuropathological hallmarks help mitigate neurodegeneration and cognitive decline. More generally, neuronal self-defence as compensatory mechanisms against neurodegenerative disorders, both AD and others, is more and more considered a promising research route [124]. This framework prompts rethinking the current approach to disease-modifying treatments for AD and prudence may be advised in attacking these lesions directly [7].

However, the discussion above and the case of ApoE4 is an example of how a phylogenetic understanding of AD and other neurodegenerative disorders may develop. It is but an example and by no means fully explanatory per se. However, it illustrates that the precursor of ApoE4 in our ancestors became a risk factor for dementia only after lifestyle changed and longevity advantageous for altriciality reasons in HSS increased and favoured alternative alleles to provide adaptive and ultimately reproductive benefits to their carriers.

Conclusion

The current worldwide aging epidemic has prompted much interest and research on aging and diseases associated with aging. The usual standard approach is that of a mechanistic understanding of aging and disease focusing only on proximate causes of such processes. As a complement to this "how perspective" of aging and disease we have considered a "why perspective" of aging that illuminates life histories, why particular diseases occur in old age and why they occur at all [27]. Using Tinbergen's [9] method of integrating the fields of phylogeny and ontology, a more unified theory of AD or other neurodegenerative disorders can ultimately develop. Obviously, we are still far from this integration. However, the case of ApoE4 is an example of how a phylogenetic understanding of AD and other neurodegenerative disorders may develop. It illustrates that genetic adaptations in our ancestors have become risk factors for dementia once lifestyle changed.

The standard ontogenetic approaches, both genetic and epigenetic, can now be extended towards a complementary phylogenetic view of aging and age-related diseases utilising current evolutionary theories but they are nevertheless likely to require significant revision [51,52]. Evolutionary models may thus prove useful as a root cause analysis for each of the problems studied. Phenomena such as altriciality, menopause and grand mothering as examples of inclusive fitness, as well as age-related mental flexibility are closely related. Theories only considering aging as being the result of disease, decay and loss, miss

half of the story and they conflate as well as muddle the different concepts of life span, longevity and aging. We have therefore considered the processes from a Darwinian perspective suggesting that both the long post-reproductive period of life and grand mothering as unique phenomena encountered almost exclusively in HSS are evolutionary adaptations to the necessity of the extreme altriciality of our species. Longevity is correlated with aging, but aging itself, particularly beyond these reproductively necessary adaptations, is not the primary goal or adaptation.

Extrinsic mortality is unavoidable and the force of natural selection in humans weeding out pathological genes clearly declines with age. A hypothetical non-senescent, age-structured population will eventually and forcefully evolve a senescent life history whenever some mutations result in some degree of age-specificity in their effects on fitness. Genes that favour aging may then persist because they offer benefits early in life that are greater than their costs later in life. The increase of life span is then a balance between selective factors that extend the reproductive period and components of aging or intrinsic mortality that shorten it. These theories lie somehow between proximate and ultimate causation models as they go some way to explain why genes remain in the gene pool and how they nevertheless cause aging.

However ultimately we have to realise that natural selection delivers, over generations, organisms that maximize their reproductive success within the EEA of a given species even at the expense of the health of the very organisms that carry them. The ultimate causes of aging then become more recognisable and are a) the necessity to adapt to a changing environment (lock) that can only be achieved by producing new off-spring with new genetic and epigenetic constellations with a better fit to the environment (key) and b) the consequences that investing in repair mechanisms beyond reproductive trade-off is an evolutionary disadvantage. This is why eternal life purely through genetic-based evolution is impossible.

Reconsidering the complex interplays and predictors of behavioural and psychological changes occurring in old age, in particular in the realm of neurodegenerative disorders [102] may be worthwhile and correspond to another domain likely to benefit from an evolutionary analysis. Furthermore, there is some preliminary evidence that aging in HSS is not (exclusively) a declining process, specifically for functions that have been heavily selected for during the EEA. Some intrinsic aspects of aging may be adaptive and positively be selected for, while others serve the death mechanism necessary for resource limited populations to adapt to changing environmental conditions. Moreover, we are still evolving and selection has been acting to counter-act the deleterious effects of aging as the case of ApoE phylogeny may illustrate.

We have tried to look into the deeper phylogenetic causes of AD. Although any final phylogenetic understanding of AD is currently not within reach, AD is unlikely to be an adaptation. Evolution does not select for illness per se. However, an evolutionary look into AD pathology may shed new light on the currently still sombre perspectives regarding disease-modifying treatments of AD.

Overall, it is our impression that evolutionary theories and ultimate causation research is progressing regarding longevity (not discussed in this article) in HSS, in its infancy as to aging and only just about to start for age-related diseases such as AD. Without an evolutionary perspective though, it is impossible to understand appropriately the reasons regarding the origins and the ubiquity of these mental disorders. Without an evolutionary perspective, we believe it is hard to ask the right questions about the functional significance of many important even crucial aspects of human biological existence, both adaptive and maladaptive. Discovering mechanistically how the abnormal brain gives rise to the abnormal mind in order to make sense of mental illness, as posed by some [125-132], may not be sufficient methodological questioning.

Ultimately, much of the aging research agenda will require considerably closer integration with other areas of evolutionary science than has been achieved to date. Evolutionary psychiatry also must acquire a better integration with various branches of neuroscience and aging research. Logically it is imperative to investigate ultimate as well as proximate explanations in parallel. This stance provides the psychiatrist or neuroscientist with a more comprehensive understanding of the patient as well as a greater understanding of why alleles exist in the frequencies they do and can cause problems in some environments more so than in others. This will be aided by the understanding of human development, ecology, variation, and life history. Evolutionary psychiatry can then alter the emphasis from biochemical genetic reductionism and essentialist dichotomous classifications of health and illness to a more nuanced perspective of complexity, individual life history, life's vicissitudes in general and our species' million-year narrative. Ultimately, prediction, prevention and treatments will have to reflect the reasons why these problems have arisen at all and continue to do so.

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