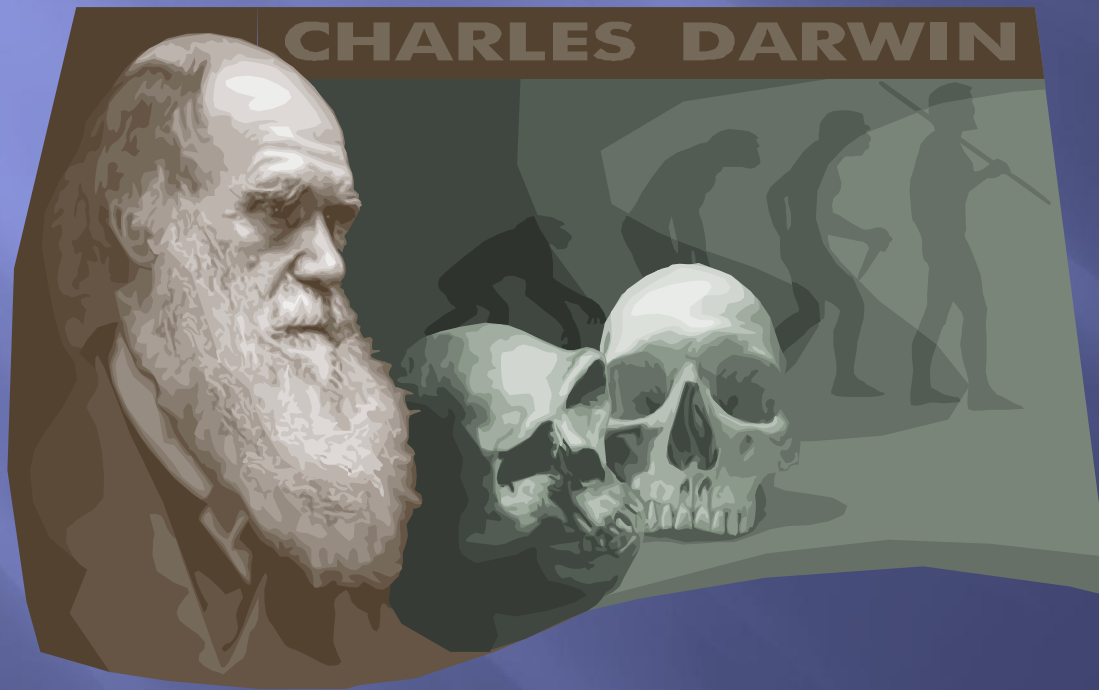


# Some evolutionarily informed explanations for aging and Alzheimer's 2018 Draft 10



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Acknowledgements

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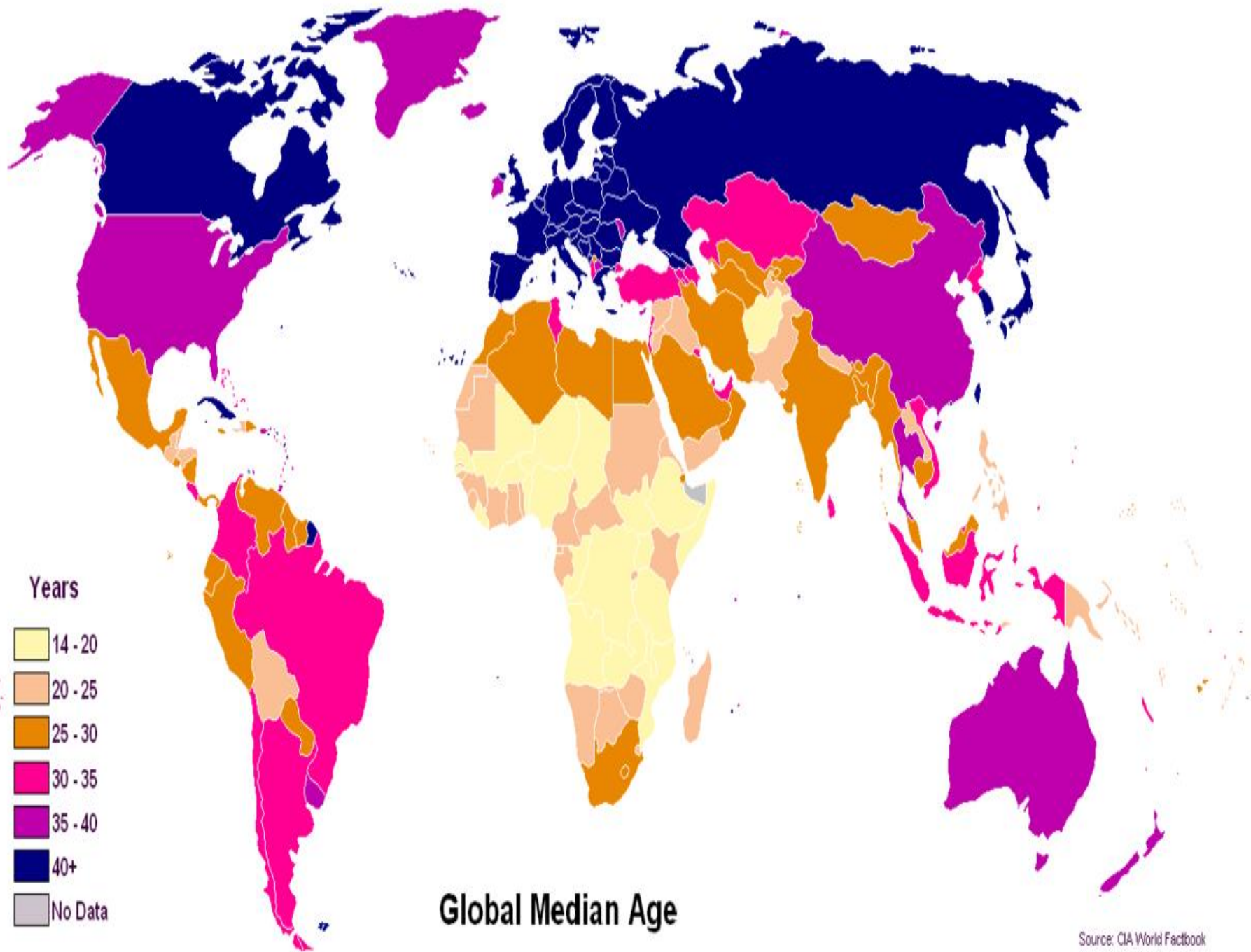
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# Some evolutionarily informed explanations for aging

- ▣ Increasingly people are surviving into old age both in high and middle/low income countries.
- ▣ This 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).
- ▣ **“Evolutionary Considerations on Aging and Alzheimer's Disease”** Gunten et al., J Alzheimers Dis Parkinsonism 2018, 8:1



Source: CIA World Factbook

# Aging is an Evolutionary Paradox

- ▣ 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..*

# Nothing in biology makes sense except in the light of evolution

Darwin transformed the way biological sciences are conceptualised and enabled asking new questions such as:-

What is the (adaptive) function of the human mind?

What problems did mind evolve to address?

How did nature select those processes/genes?

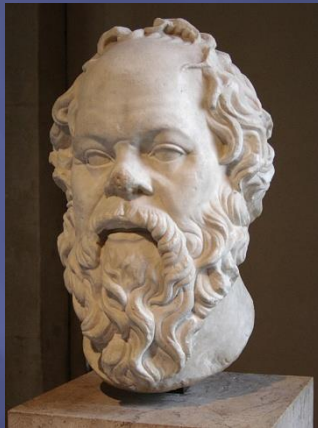
What is the history of those genes?

Why were/are they adaptive or now vulnerable?

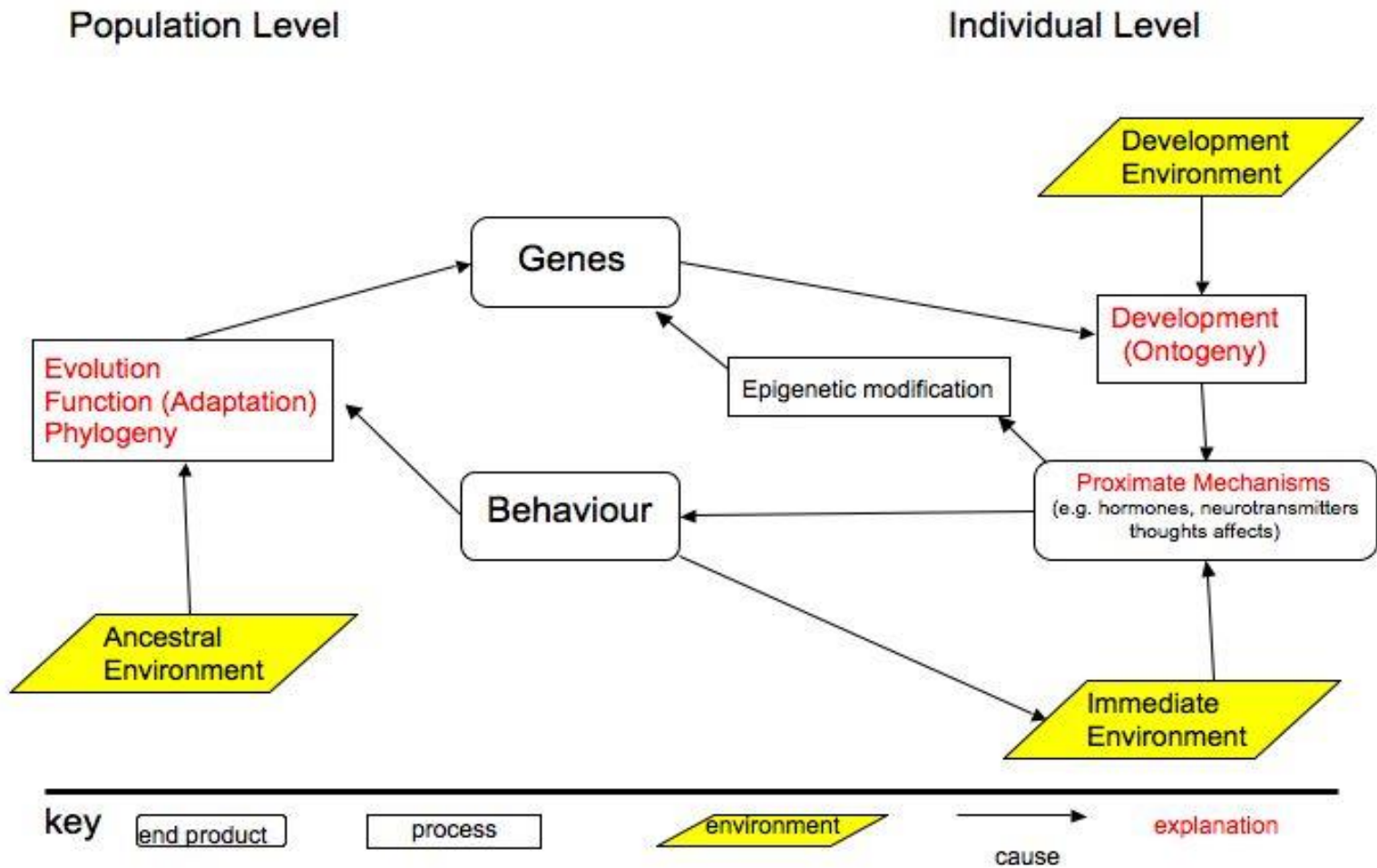
What relevance has this to aging and Alzheimer's disease?

# Socrates

- ▣ I will further Question
- ▣ the main evolutionary theories
- ▣ anthropological and
- ▣ biochemical aspects of aging and Alzheimer's
- ▣ and how they can be integrated



# Evolutionary theory ROOT-causes i.e. Ontogenetic and Phylogenetic causes



# Alzheimer's disease (AD)

- ▣ (AD) is a complex disease associated with advanced age whose causes are still not fully known.
- ▣ Approaching the disease from an evolutionary standpoint helps 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.



# Ageing

- ▣ Aging lies on a temporal continuum that starts at conception and ends at death
- ▣ 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.

# Some evolutionarily informed potential explanations for aging

- Evolutionary perspectives consider the reasons “why” people may have become particularly vulnerable to different
- 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.

# Some evolutionarily informed explanations for aging

- 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
  - grandmothering,
  - the evolution of ApoE
  - the genome lag hypothesis.

# Six General evolutionary explanations for vulnerability to medical/psychiatric disorders

- ▣ 1. Mismatch between aspects of our bodies and novel environments
- ▣ 2. Constraints on what natural selection can do
- ▣ 3. Trade-offs that keep any trait from being truly perfect
- ▣ 4. Traits that increase reproduction at the cost of health
- ▣ 5. Protective defences such as anxiety and depression
- ▣ 6. Pathogens that evolve faster than we do.
- ▣ 7. Other concepts are necessary in addition

# Further key Concepts important in Ageing theories

1. Darwinian fitness
2. Dual inheritance theory
3. Antagonistic Pleiotropy
4. Kin Selection
5. Inclusive fitness
6. Life history theory
7. Parental investment
8. [https://www.rcpsych.ac.uk/pdf/Evolutionary\\_Psychiatry\\_GLOSSARY\\_2.pdf](https://www.rcpsych.ac.uk/pdf/Evolutionary_Psychiatry_GLOSSARY_2.pdf)



# Evolutionary criteria

- ▣ In biology, ultimate causation is unique to evolutionary science and, evolutionary formulations of psychiatric disorder are usually theories and hypotheses of ultimate causation.
- ▣ Then we must consider such theories at the level of the:-
  - ▣ gene
  - ▣ individual
  - ▣ family/kin
  - ▣ species/group

# Psychiatry

- ▣ Then the primary problem for evolutionary psychiatry becomes:-
- ▣ “How can disorders that are seemingly maladaptive and intuitively decrease fitness continue to be expressed and inherited?”.
- ▣ George Williams was the first to apply evolutionary theory to health in the context of senescence.

# Antagonistic pleiotropy

- ▣ An effect whereby genes that change in respect of their fitness advantages, over time.
- ▣ It is an important concept in the evolutionary theory for aging.





# 3 leading explanations for the apparent paradox

- ▣ Given that natural selection is so powerful at optimizing complex adaptations, why does it seem unable to eliminate genes (susceptibility alleles) that predispose to common, harmful, heritable mental disorders,?
- ▣ There are three leading explanations for this apparent paradox from evolutionary genetic theory:

## 3 leading explanations for the apparent paradox

1. Ancestral neutrality (susceptibility alleles were not harmful among ancestors),
2. Balancing selection (susceptibility alleles sometimes increased fitness), and
3. Polygenic mutation-selection balance (mental disorders reflect the inevitable mutational load on the thousands of genes underlying human behavior).

# Mutation-selection models

- ❑ Evolution also provides a new framework to guide psychiatric gene hunting
- ❑ Mutation-selection models suggest that susceptibility alleles with the largest effect sizes may also be the rarest, the most recent, and the most population specific – an insight with important implications for the methods most likely to locate mental disorder susceptibility alleles.
- ❑ Mutation-selection explanations further justify the search for less polygenic, and more genetically mappable, endophenotypes.

# Dual inheritance theory

- ▣ **Dual inheritance theory (DIT)**, also known as gene–culture coevolution or biocultural evolution was developed to explain how human attributes including behaviour, is a product of two different and interacting evolutionary processes: genetic and cultural evolution.
- ▣ In DIT, culture is defined as information and behaviour acquired through social learning.

# Dawkins' selfish genes

- ▣ A parsimonious evolutionary explanation for the existence of aging requires an explanation that is based on **individual fitness** and selection, not on group selection.
- ▣ The evolutionary biologists, J.B.S. Haldane, Peter B. Medawar and George C. Williams realized that aging does not evolve for the "good of the species".
- ▣ Instead, aging evolves because natural selection becomes inefficient at maintaining function (and fitness) at old age.

# Parental investment:

- ▣ **The** investment that parents make in an offspring which increases that offspring's chances of surviving.
- ▣ By definition, such investment imposes a cost to the parents as measured by their ability to invest in other offspring, current and future.
- ▣ Components of fitness include the wellbeing of existing offspring, parents' future reproduction, and inclusive fitness through aid to kin.

# Do we age to make way for others?

- ❑ August Weissmann suggested– that selection might favour the evolution of a death mechanism that ensures species survival by making space for more youthful, reproductively prolific individuals
- ❑ But this explanation turns out to be wrong.
- ❑ Since the cost of death to individuals likely exceeds the benefit to the group or species, and because long-lived individuals leave more offspring than short-lived individuals (given equivalent reproductive output), selection would not favour such a death mechanism.

## Part 2 Life expectancy

- ▣ It is theoretically not impossible, in an open thermodynamic system, for a living organism to have the full capacity to repair all of its tissues and thus to live forever.
- ▣ The trade-off is that those repair mechanisms are expensive and the resources could alternatively be put into current reproduction.
- ▣ Natural selection shapes lifespan as a life history trait to maximize reproduction not health or happiness
- ▣ The genes that cause senescence must persist for some reasons



# Life expectancy

- ▣ First, some genes are never exposed to selection, because they have no deleterious effects during the lifetimes of animals in the wild.
- ▣ Other forces kill all individuals before the effects of such aging genes have any effect.
- ▣ There is no selection against these aging genes unless, a species passes several generations in a benign environment (domestication), such as a zoo or laboratory, where long-living individuals can have a reproductive advantage.

# Life expectancy

- ▣ A second reason is genes that cause senescence persist because they may offer benefits early in life that are greater than their costs later in life.
- ▣ Such pleiotropic effects can increase the frequency of a gene even if it causes substantial detrimental effects on life span in the wild.

# Life expectancy

- ▣ *Remember* Natural selection benefits genes, not individuals (Dawkins' selfish gene concept!)
- ▣ Natural selection delivers, over generations, organisms that maximize their reproductive success (In this case when young and of reproductive age), even at the expense of individual happiness, health and longevity.
- ▣ **Psychiatrists treat people not genes!!**

# Life expectancy

- ▣ Why and when did people start living for longer?
- ▣ Did the arrival of the grand parenting generation and the ability to live longer facilitating this , give our ancestors a selective advantage?
- ▣ Living to an older age has profound effects on the population sizes, social interactions.
- ▣ The genetics of early modern human groups may explain why they were more successful than other archaic humans such as the Neanderthals.

# Obstetric dilemma

- ❑ In anatomically modern humans, infants are essentially immature at birth. This reflects an evolutionary compromise between the size of the infant's brain (and head) and the diameter of its mother's birth canal (An evolutionary constraint and Trade-off”).
- ❑ In contrast to non-human primates the human brain continues to grow after birth at the same pace for more than a year.
- ❑ Brain maturation (synaptic pruning and myelination) and developing adult social competence is extended well into the third decade of life requiring extended periods of parental care.

# Menopause

- ▣ Menopause can be considered as a problem for the point of view of reproduction and the selfish genes/Darwinian fitness of the individual
- ▣ Most animals do not show any cessation of reproduction with age, and the very existence of menopause in humans may be a life history trait that maximizes fitness, **perhaps by ensuring care for existing children instead of risking more reproduction.**

# Menopause and ApoE3

- ▣ In line with this speculation, women who have at least one ApoE4 allele (E4/E4 or E4/E3) reach menopause earlier than women with other ApoE genotypes.
- ▣ Finally, the ApoE genotype seems to play a role in the variation of life expectancy in European populations, but such an effect seems to disappear in the oldest old (over 100 years of age), perhaps by escaping the forces of selection.
- ▣ These findings therefore support the assumption of a putative fitness advantage of non-ApoE4 genotypes over ApoE4 homo- or heterozygosity.

# Grandmothers

- ▣ From a purely genetic and survival point of view, after parents, grandparents are the people most closely related to their grandchildren.
- ▣ Therefore in humans, [probabilistically] the most likely, in biological terms, to help ensure their grandchildren's continued existence.
- ▣ Grandmothers for example had an important role in foraging for food and teaching skills so that children were healthier and the group( kin) as a whole could flourish.



# Grandparents2

- Although the first modern people evolved at least 100,000 years ago in Africa, grandparents were a rarity for much of prehistory.
- Most of our prehistoric ancestors died before the age of 30 as a result of disease, famine, injury or childbirth.
- But 30,000 years ago the number of adults seeing their 30th birthday soared.
- Around the same time our hunter-gatherer ancestors went through a major change in complex behaviour.
- Artwork became more sophisticated, tools became more complex and food production shot up.



# Grandparents

- ❑ Fossil experts say the number of grandparents shot up dramatically 30,000 years ago as people started to live longer.
- ❑ With older people able to look after children, pass on knowledge and skills such as locating safe water and food sources and tool-making as well as sharing in food gathering, our ancestors were able to spread around the world and develop farming, tools and civilisation.

- ▣ 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.

# Part 3

## Alzheimer's disease

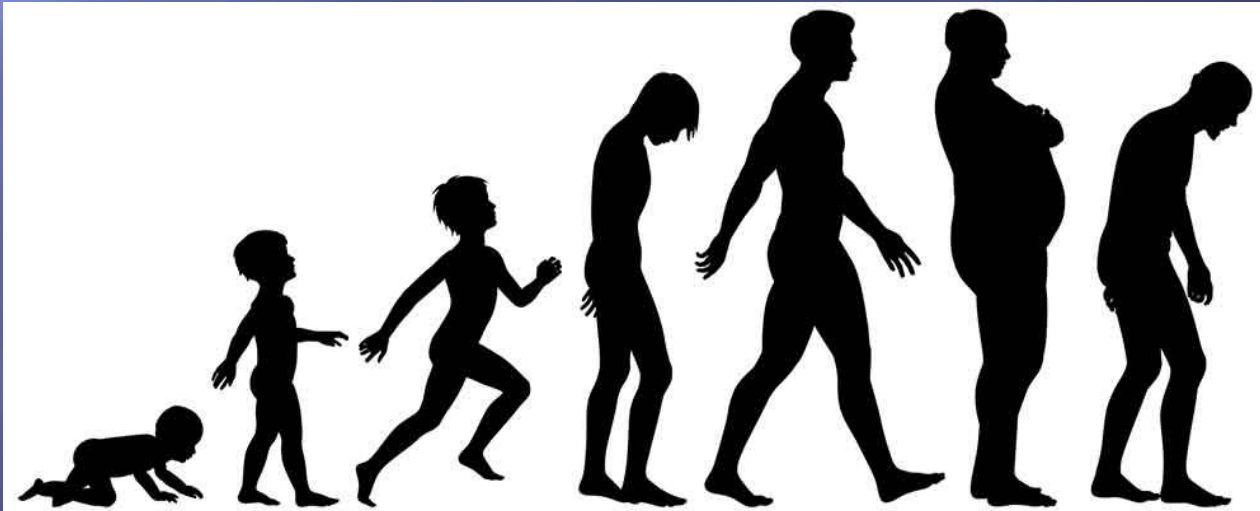


# Alzheimer's disease

- ▣ In 2010, there were between 21 and 35 million people worldwide with AD.
- ▣ It most often begins in people over 65 years of age, although 4% to 5% of cases are early-onset Alzheimer's which begin before this.
- ▣ It affects about 6% of people 65 years and older.

# Alzheimer's disease

- ▣ Viewing AD from an evolutionary perspective prompts a rethinking of the way we describe the relationship between the clinical dementia and the neuropathology by which we define the disease.
- ▣ By integrating the fields of phylogeny, life history theory, genetics, biochemistry, and evolutionary medicine, a unified theory of AD can be developed.



# Alzheimer's disease

About 35% of dementia is attributable to a combination of the following nine risk factors:

1. education to a maximum of age 11-12 years,
  2. midlife hypertension,
  3. midlife obesity,
  4. hearing loss,
  5. late-life depression,
  6. diabetes,
  7. physical inactivity,
  8. smoking, and
  9. social isolation
- ▣ Each of them has its own multiple risk factors in terms of both genetic make-up and potentially modifiable environment.

# Alzheimer's disease

- ▣ 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.
- ▣ As age is the greatest risk factor for AD the number of genes influencing the risk for AD may be significantly larger.



# Alzheimer's disease

- ❑ Developing AD is linked to a combination of factors, some can be partly controlled (e.g. lifestyle and environmental factors), but others cannot (e.g. age and genes) .
- ❑ 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.
- ❑ The ApoE4 allele increases the risk of the disease in homozygotes but also in heterozygotes
- ❑ 40 to 80% of people with AD possess at least one ApoE4 allele.
- ❑ Eliminating the ApoE4 allele would yield an estimated 7% reduction in AD incidence .

# Alzheimer's disease

- ▣ As for many human diseases, environmental effects and genetic modifiers result in incomplete penetrance.
- ▣ 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
- ▣ 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

- ▣ 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.

## - *Alzheimer's disease 2*

- ❑ 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.

# Where does menopause feature?

- ❑ It suggests that the increasing duration of dependence of infants on their mothers (and their mother's survival) created a selection pressure of expanding the human life span.
- ❑ It is then reasonable to assume that it became advantageous for early humans to survive sufficiently long enough beyond ceasing reproduction to raise offspring born shortly before menopause.
- ❑ A life history of a female who gave birth at age 40 and died before her offspring was socially mature (some 20 years later) would certainly not have been favoured by natural selection.
- ❑ Modern homo sapiens women have by far the longest post-reproductive lifespan of all primates.
- ❑ Experiencing and living beyond menopause is rare in non-human primates, but in humans there is perhaps 20 to 30 years to come after ovulation has terminated .

# Where do Grandparents feature in AD

- ❑ In addition to experiencing longer life spans mothers (and their offspring) benefited from additional help from their own mothers— i.e. grandmothering evolved.
- ❑ Among primates, grandmothering is unique to humans.
- ❑ In hunter-gatherer societies grandmothers contribute a substantial proportion of calories to the diet of their grandchildren.
- ❑ In addition, human grand-mothers help pass on social skills to subsequent generations another fitness advantage of postponing senescence.
- ❑ The emergence of ApoE3 and ApoE2 polymorphisms in humans may have occurred by sporadic mutation at some point of human evolutionary history, which were favoured by selection in order to delay senescence, thereby selecting against an early onset of AD-like pathology.

# ApoE variants

- ❑ The differential binding potential of ApoE variants to cholesterol fractions may therefore be an adaptive response to both changing diet in early humans, and the need of postponing senescence to advantage of grandparenting
- ❑ Captive chimpanzees, are extremely susceptible to developing hypercholesterolaemia and atherosclerotic plaques when fed a diet rich in protein and fat.
- ❑ An increasing meat intake of human ancestors that was probably advantageous in terms of protein supply for growing big brains would predict, in reverse, a shorter life span, given the atherogenic effect and high load of infectious particles of (raw) meat.

# Conclusions on Aging

- ❑ 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 the story





# So why do the alleles that predispose to Ageing and Alzheimer's disease still exist?

- ▣ We don't yet know 100%, but
- ▣ mismatch,
- ▣ constraints ,
- ▣ traits that increase reproduction at the cost of health ,
- ▣ Antagonistic pleiotropy
- ▣ life history,
- ▣ kin selection,
- ▣ mutation-selection,
- ▣ time lags, and
- ▣ balancing selection probably all play roles in different domains to different degrees.

# Conclusion

- ❑ 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.

# Summary

- ▣ Appreciating the ultimate causation of a given biological phenomenon will not automatically lead to dramatic changes in treatment.
- ▣ It can contribute to conceptual changes which should have an impact on future directions of research.
- ▣ Though explanations are ultimately grounded in biological evolution, environment, culture, and context are not considered any less important.

**THE END**