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Review Article

The Convergence of Intelligence and Longevity

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Humans are the most intelligent mammals and the longest-lived. Intelligence and longevity are characteristics of our species, and they probably evolved together. They are also individual traits; individual differences in intelligence, health, and longevity are directly correlated. People who are cognitively well-endowed are more likely to possess a number of favorable physical attributes, including disease resistance and longevity.

The convergence of intelligence and longevity during evolution was inevitable. Something as extraordinary as the human brain can only have evolved in an organism whose physiological systems are highly reliable, efficient, and coherent. The human brain takes about 30 years to achieve maturity, although a case may be made for 50 or 60 years. A brain that requires such a long period of development needs a strong supporting cast in the soma.

The resilience and longevity of the brain are reflected by the same qualities in the soma, and several ideas have been put forth to explain the association. We propose that the genetic elements that engineered our efficient and durable brain have exercised similar effects on our somatic systems. Almost all of the genes that generate and maintain the human brain are also active in the periphery, endowing our tissues with the same efficiency and durability. The speed, flexibility, and efficiency of neural networks are homologous with similar attributes that govern the behavior of gene networks for intelligence and longevity.

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The Convergence of Intelligence & Longevity

Simply stated, we humans are the most intelligent of all the Earthly creatures, and we also happen to be the longest-living mammals. The two complex traits run together. Intelligence speaks to a flexible and efficient brain. It is directly correlated with good health and longevity, an efficient and resilient soma. The correlations are well known from studies of individuals. That they have been operative during the evolution of our species is equally true.

The Longest-Living Mammal*

We humans are the longest-living representatives of the mammalian class, violating several natural laws along the way. We enjoy – perhaps endure is a better word – decades of post-reproductive longevity. The why of it is a mystery. There is no advantage, from the Darwinian perspective, to living beyond the involution of one's generative apparatus. Nevertheless, everyone reading these words is likely to live well beyond their reproductive capacity, if they haven't already done so.

That we humans live a long time is beyond dispute. Life expectancy at birth has edged past 80 in most developed countries, and that includes at least 30 years of *post-reproductive* longevity. Universal longevity is a modern invention, but it proves that freed from the burdens of want, disease, and wanton killing, humans can live up to their genetic potential.

Longevity is the natural state of human beings. Paleoanthropologists assure us that life expectancy during prehistoric times was in the range of 20 to 30 years. By 1500 or 1600, when reliable data first became available, mortality levels were still very high, and life expectancy was 35–40 years. (Council et al., 2000) Thirty-five years is not very long by modern standards, but it affords sufficient time for propagation, and that, supposedly, is what counts to natural selection. Longevity, therefore, in historic terms, is life past 40. In prehistoric societies, very few people lived to that age. There has never been a Stone Age skeleton unearthed that

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was older than 54. The presumption is that ageing and post-reproductive longevity are *unnatural events*. On the other hand, we learn this from the 90th Psalm:

> The days of our years are threescore years and ten; and if by reason of strength they be fourscore years, yet is their strength labor and sorrow; for it is soon cut off, and we fly away.

There aren't reliable data on longevity prior to the Psalms, some of which were composed prior to the Exile (587 BC), but we do have data about the lives of famous men in ancient Greece, about Italian painters and poets during the Renaissance, and about English physicians in the Royal College from 1500 to 1840 AD. These data show that many individuals managed to live to three score and ten. Plato was about 76 when he died, Aristotle 62, and Socrates 70, although he might have lived longer if not for the hemlock. Hippocrates reportedly died in his mid-80s, and Sophocles died in his mid-90s. (Perls et al., 2002) The artist Titian lived to almost 90. Leonardo da Vinci († 67 years) drew several pictures of a 100-year-old man. Andrea della Robbia, a Florentine artist famous for his terra cottas, reportedly lived to age 90, and around the same time, Michelangelo lived to age 91. (Griffin, 2008) (Montagu, 1994) It may be true, therefore, that *life expectancy at birth* was about 35 years from Paleolithic times until about 1700 AD, but once a man reached maturity or a woman had safely birthed her last child, individuals could look forward to a life span that was almost as long as it is now.

Neo-anthropologists are men and women who study stone-age people living today. They report similar numbers based on direct observations. They have taken the trouble to visit tribes who survive without access to the benefits of modern medicine and hygiene. Having observed, at no small hazard, the !Kung San of the Kalahari Desert, the Aché of the Paraguayan forests, the Hadza in the Eastern Rift Valley of Tanzania, and, in the Amazon, the Piro, Machiguenga, Hiwi, and Yanomano, they consistently report that 30-40 percent of the tribeswomen survive well into their post-reproductive years. Many individuals reach age 60, and a few reach 70. (Finch, 1996:498) (Hill and Hurtado, 1991) Stone-age tribes have high rates of infant and maternal mortality, but once they pass those obstacles, they live as long as Greek philosophers.

It is true that some species live a long time, some even longer than we do. Certain deepwater fish, for example. The sturgeon may live to a hundred years or longer. Cod and lake trout are long-lived, too, and other animal centenarians include tortoises, parrots, and the Greenland shark. Also, there are long-lived plants, like Georges Balanchine's rubber tree, whose cuttings survive in the lofts and villas of all his favorite disciples. Civic boosters in Crystal Falls, Michigan, claim that the 'world's largest and oldest living organism' is the 'Humongous fungus' (*Armillaria solidipes*) which occupies 37 nearby acres and mostly lives underground. The HF sends up edible "honey mushrooms," which are said to be quite delicious. It is supposed to be 10,000 years old. Another Armillarium, in Oregon, covers no fewer than 2200 acres. God only knows how old it is, but it's still making a pest of itself. There is also a stand of aspen trees in south-central Utah that extends over 106 acres, with more than 40,000 individual trees, all of them clones arising out of a root structure that is at least 80,000 years old. Some say it is as old as a million. "Pando" it's called, and it's still sending up new stems.

Some coelenterates have extraordinary powers of regeneration and can reproduce by simply dividing in half; theoretically, they are immortal. There isn't much to a coelenterate, though, besides two layers of cells, one on the outside and one on the inside, and in between an amorphous mass of jelly. Some coelenterates are "true" jellyfish, and others are not-so-true. Should the immortal jellyfish have been the pinnacle of evolution? Or the fungus?

None of these estimable organisms, from fish to fungi, manage to evade an iron law of biology. They survive only as long as they retain their reproductive capacity. That humans survive well past the shriveling of their generative organs is attributable to their self-absorbed extravagance and better ignored. It's not the way organisms are supposed to be.

In Defiance of Natural Laws

Living for 30 or 40 years longer than our reproductive capacity is the way Nature made us. In that respect, humans are different from lake trout, cod, and sturgeon. Not only different, but unique. We defy the two principles that govern the life span of species, whether they are bristlecone pines that live five thousand years or mayflies that live for a day. One is the structural principle, that big organisms live longer than small ones. It makes sense, if only because it takes a while to get big. So, whales live a long time, and elephants may live as long as 80 years. Human beings, of course, are not quite so big, but we are exceptional. Humans live longer than whales and elephants, but our size is little different from sheep and pigs, who live about 25 years. Human longevity is four times that predicted from body mass. (Hulbert, 2010)

Second is the metabolic principle. (Finch, 1997) Animals choose to utilize their physiology extravagantly or even salaciously, resulting in a shortened life span; or they may prefer a frugal metabolism resulting in a prolonged life span. Centenarians, for example, tend to be subclinically hypothyroid; that means the thyroid gland is a bit sluggish, not dangerously so, but low enough to make their metabolism go slow. Their body temperatures are also lower than normal. They exemplify the rate of living theory, proposed in 1908 by a German biologist, Max Rubner, who was 77 when he died.

Rubner observed that animals with higher basal metabolic rates had shorter life spans. He suggested that the amount

of life an organism enjoyed was constrained by its physiology, like respiratory rate or heart rate, and that the number of breaths or heartbeats of every species is fixed.

> The restless monkey breathes at the rate of 32 times a minute, in contrast to man's average 18 times. The elephant, tortoise, snake, and other animals noted for their longevity have a respiratory rate which is less than man's. The tortoise, for instance, who may attain the age of 300 years, breathes only 4 times per minute.[†]

The mouse, the human, and the elephant share the same metabolic processes; but compared to a mouse, the same processes take seven times longer in humans and 20 times longer in elephants. The speed of a species' metabolism, therefore, is a determinant of longevity. The larger the animal, the slower its metabolic rate. (Speakman, 2005)

The Etruscan shrew, for example, *Suncus etruscu*, is the smallest terrestrial mammal. In a single minute, he or she breathes about 800 times, and its heart can beat 1500 times. Shrews, however, live only 24 months, max. Elephants have a resting heart rate of 25-35 per minute and breathe 12-16 times. To support its cardiopulmonary athleticism, the tiny shrew must eat two to three times its body weight every day, and its diet is composed of highly nutritious worms, spiders, and slugs. Elephants eat several hundred pounds of low-calorie vegetation, which is only a fraction of their body weight, depending, of course, on how big the elephant is. The largest weigh seven tons, I'm told.

The mammals are distributed on a rate of living line. Blue whales are to the right of the elephants, and Etruscan shrews are at the very far left. We humans are a special case. Our maximum longevity exceeds that of elephants and blue whales, although our metabolism is faster. The two allometric equations below, from a research group at the University of Wollongong, show the relation between life span and the basal metabolic rate in a large number of mammals and birds. As we learned, there is a regular relation between body mass and longevity among mammals and birds. (Hulbert et al., 2007)

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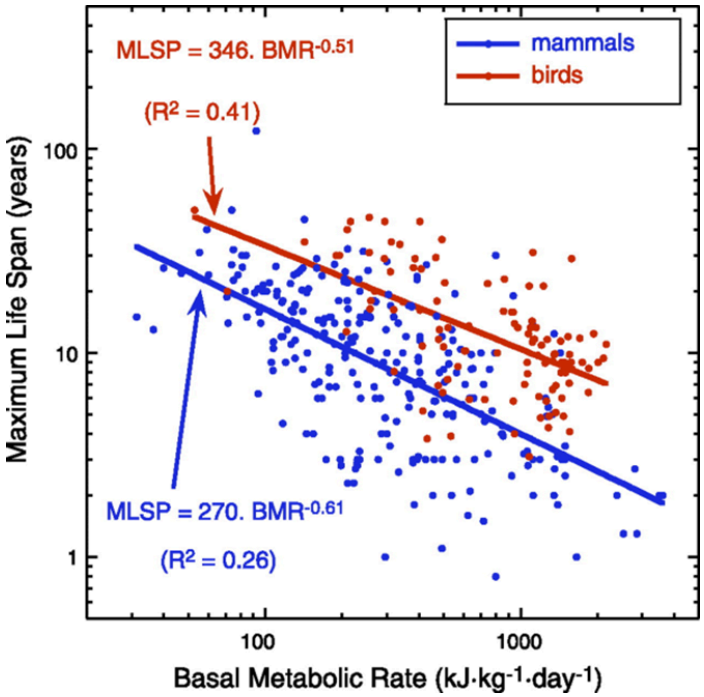

Birds of the same size and BMR are longer-lived than mammals, perhaps because they are less vulnerable to predators. In both birds and mammals, lifespan is inversely related to metabolic rate.

The rate-of-living theory has been bolstered by several studies that link a lower basal metabolic rate (evident from one's heartbeat) to increased life expectancy. *It would consequently appear that a number of physiological parameters are scaled such that the number of them in a lifetime is relatively constant.* (Lindstedt & Calder, 1981) Stated thus, the correlation between metabolic rate, energy expenditure, and lifespan has been elevated to the status of a biological law and ultimately a fixture in pop science. We are said to have a fixed number of heartbeats that we can use up rapidly or slowly, and once we reach that number, we die.[‡] (Speakman et al., 2002)

The exceptional longevity of humans defies the structural and metabolic principles, not to mention the iron law of natural selection. Maybe we're special.

The Primacy of Brain

The primacy of the brain with respect to longevity was first broached by George Sacher, who lived to age 63. Sacher was a mathematician and biologist who worked on the Manhattan Project and then at the Argonne National Laboratory. His first project was to study the biological effects of radiation, for example, its effects on DNA. This led him to the problem of DNA repair and thence to his life's work, the study of longevity. Since he was a mathematician, he approached the problem by means of allometric equations, formulae that described how body mass and the relative size of different organs differ among animals. He showed that the lifespan of different animals, including humans, was a function of brain weight divided by body weight. The formula he constructed predicted a maximal lifespan of humans of 90-100 years, which is just about right.[§] (Sacher, 1978)

Sacher's observations extended to brain growth during gestation. (Sacher & Staffeldt, 1974) Longer pregnancy in different species is a function of brain size. Fetal brain growth seems to be a priority in primates and especially in humans. The fetal brain in primates is twice the size of other mammals with similar body weights. In humans, a baby's brain is 10% of his body weight and consumes no less than 60% of her energy. The brain weight of an adult human is only 2% of body weight and consumes 20% of her energy. The human brain reaches adult size by age seven, well in advance of any other body system. In effect, brain development is a pacemaker for physical growth and maturation. (Martin, 2013)

What makes us different, and the reason why we live so long, is because we have a complex, efficient, and adaptable brain. The *primacy of brain* is how we evolved. Something as extraordinary as the human brain can only have evolved in an organism whose physiological systems are highly reliable, efficient, and coherent. The human brain takes

about 30 years to achieve maturity, although a case may be made for 50 or 60 years. A brain that requires such a long period of development needs a strong supporting cast in the soma. We live as long as we do because our brains are over-engineered.

To be precise: the resilience and longevity of the brain are reflected by the same qualities in the soma. The genetic elements that engineered our efficient and durable brain have exercised similar effects on all our other complex functional systems. As we shall see, almost all the genes that generate and maintain the human brain are also active in the periphery, endowing our tissues with the same efficiency and durability.

Intelligence as Fitness Indicator

In addition to longevity, the human species has four signal characteristics: social cooperation, neuromuscular coordination, speech and language, and abstract intelligence. They are interdependent, and one assumes they evolved together. They also appear to have developed over a comparatively short span of time, during what has been called our 'runaway' evolution. (Wills, 1993) The four characteristics are direct reflections of mental power; longevity is an indirect reflection. Nevertheless, the connection between longevity and intelligence, as we shall see, is no less fundamental. (H. S. Kaplan & Robson, 2002)

Surmises about hominid evolution are necessarily speculative, but the contention that mental powers and longevity co-evolved is defensible because when we study the lives of human beings, we find they co-occur. Our mental powers are strongly correlated with good health and longevity; the correlations are even stronger in modern societies where personal safety, adequate nutrition, comfortable housing, and good health care are equitably distributed.**

Intelligence is IQ, abstract intelligence, the ability to manipulate symbols in one's mind. It is only one mental power; the others are, if anything, more essential to life. The powers of the brain are also expressed in its governance of the 'autonomic' nervous system and all the physiological functions, the immune response and neuroendocrine function, sensory discrimination and neuromuscular coordination, sociality, and emotional regulation. Yet the relevant research on health and longevity has focused on one in particular, abstract intelligence. It's not because writers and scientists are biased in its favor as the most important human characteristic, although they might be, and it may be, too. The practical reason is that abstract intelligence is measurable and *mirabile dictu* expressible as a number, IQ.†† Two strong correlates of IQ are socio-economic status and years of education; they play an equivalent role in studies of health and longevity, and they, too, are also expressible as numbers. Nevertheless, the focus on IQ, SES, or education does not diminish the relevance of other mental powers. In fact, they are highly correlated with IQ. The several powers of the human brain run together. Thus, IQ is a surrogate for mental power in general. (Deary, 1994) (Deary et al., 2004) It reflects the integrity, coherence, and efficiency of the brain itself.

Intelligence is "the ability to understand complex ideas, to adapt effectively to the environment, to learn from experience, to engage in various forms of reasoning, to overcome obstacles by taking thought." (Neisser et al., 1996) "Intelligence is what an IQ test measures" (Boring, 1961), a cute saying that is misconstrued as beggaring the definition. In fact, the IQ test captures the convergence of all the cognitive powers in a 'positive manifold': the fact that all intelligence subtests, ranging from scholastic tests to tests of social intelligence, correlate positively. (Van der Maas et al., 2014) A century ago, Charles Spearman (†82) concluded that because performance on all mental tests was correlated, all mental abilities were derived from a single factor, *g*, the *general factor*. The modern notion of IQ, based on an individual's average performance on 10-12 cognitive tests, is the practical equivalent of *g*. However, the nature of the general factor itself remained elusive.

In the science of psychometrics, *g* is a summary measure or index of the positive manifold. It represents the reciprocal positive interactions between abilities and processes that play key roles in cognitive development, like working memory, spatial ability, and language skills. (Van Der Maas et al., 2006) Spearman, however, identified it with 'mental energy', that is, "neural energy flowing through the brain and affecting all mental abilities." (Spearman, 1927) His idea was that *g* must have a biological basis, but if so, it has been difficult to come by. Recent studies, however, have indicated that structural correlates of intelligence are increased cortical volume, density, and connectivity. Its functional correlates are plasticity, efficiency, stability, and speed.

Cortical Structures

The first place to look for the biological basis of intelligence was brain structure, and indeed, there are individual differences that correlate with *g*. The brains of more intelligent humans tend to be larger; total brain volume accounts for about 16% of the variance in intelligence scores. (Thompson et al., 2002) (Haier et al., 2004) (Colom et al., 2006) However, there is no singular underlying neuroanatomical structure to general intelligence, and different brain 'designs' can generate equivalent intellectual performance. For example, the IQs of men and women are associated with activity in different brain regions; men are stronger in the frontal and parietal cortices, and women in the frontal regions and language areas. (Haier et al., 2005) Thus, women love to talk, and men hate to ask for directions.

More recent studies employ new imaging methods, such as functional MRI, positron emission tomography, magnetic resonance spectroscopy, diffusion tensor imaging, and

voxel-based morphometry. Thence, a consensus has arisen that individual differences in intelligence test scores are related to functional and structural variations in a distributed fronto-parietal network, including the dorsolateral prefrontal, anterior cingulate, and posterior parietal cortices, with regions in the temporal and occipital lobes and white matter, including the arcuate fasciculus. (Lee et al., 2006) (Jung & Haier, 2007) Thus, *g* is a distributed function, not confined to the cerebral cortex, but related to activity in many cortical and subcortical regions that are connected functionally. (Song et al., 2008)

White matter density in the parietal and prefrontal areas is found consistently to be correlated with *g*-loaded tests. (Haier et al., 2004) (Song et al., 2008) (Choi et al., 2008) The subcortical white matter is made up of axonal fiber tracts that are where neuronal connectivity and neural networks happen. The speed, flexibility, and efficiency of white matter tracts are expressed as 'integrity,' and it, too, is correlated with *g*. White matter integrity, however, is not particular to the frontal-parietal tracts. It is a characteristic of an intelligent brain and the basis for all its mental powers.

The neural efficiency hypothesis is that fast and efficient information processing among different brain areas is the foundation of higher cognitive abilities. Mental processing speed is a function of the white matter tracts; multiple sclerosis and cerebrovascular small vessel disease afflict the white matter, and slow mental processing can be demonstrated by neurocognitive tests. Tests of reaction time and inspection time are robustly associated with intelligence. (Grudnik & Kranzler, 2001) (Luciano et al., 2001) Crucially, the efficient qualities of white matter integrity are qualities shared by all the white matter tracts. The qualities that constitute integrity are correlated even among tracts that have nothing to do with higher cognitive function at all. They, too, are positively correlated with intelligence. (Chiang et al., 2009) (Penke et al., 2010)

The efficiency of neural communication has neuronal correlates in dendritic size and density. In brain areas that integrate different types of information, such as the frontal and temporal lobes, the pyramidal cells of intelligent people have larger dendrites – the long projections that are specialized to collect signals. Larger dendrites can transport information more quickly and sustain fast action potential kinetics during repeated firing. (Goriounova et al., 2018) Higher intelligence is also related to lower dendritic density and arborization; the neuronal circuitry associated with higher intelligence is organized in a sparse and efficient manner, fostering more directed information processing and less cortical noise during reasoning. (Genç et al., 2018)

Many years ago, Karl Lashley († 68) proposed that the biological basis of *g* resided in the *mass action* of functioning cortical tissue, and that the loss of intelligence, for example, following brain injury, was a function of decreased efficiency in cortical operations. (Lashley, 1949) Several observations in recent years support Lashley's definition of intelligence as a manifestation of brain efficiency. Intelligent individuals, despite their larger brains, tend to exhibit *less* brain metabolic activity during complex cognitive tasks. They display more focused cortical activation during cognitive performance, resulting in lower total brain activation than less intelligent individuals. (Neubauer et al., 2002) More direct connections between task-critical brain regions correspond to decreases in task-related neural activity and improvements in performance. (Rypma et al., 2006)

The easy communication among brain regions is illustrated by the resting state or default mode network of the brain (DMN). The DMN is a large region within the cerebral cortex, underlying brain regions that are 'goal-directed' or 'task-positive'; it includes the medial prefrontal cortex, the medial temporal lobe including the hippocampus, and parts of the cingulum and inferior parietal lobe. In normal individuals, the activity of the DMN is *negatively correlated* with that of task-positive regions. When the latter are active, the DMN is not, and vice versa. The transitions are rapid and continuous; cortical regions are constantly active as they interact, update, and re-configure the DMN. In intelligent individuals, the DMN configuration at rest tends to be closer to those of a wide variety of goal-directed networks, resulting in quicker and more efficient transitions. The implication is that intelligence is a function of modifying network connectivity efficiently when task demands change (Schultz & Cole, 2016); that human intellectual performance is related to how efficiently the brain integrates information among multiple brain regions. (Heuvel et al., 2009) (Li et al., 2009) (Ferguson et al., 2017)

A century ago, Spearman introduced the notion of 'mental energy' as the basis of *g*.[‡‡] He wasn't right, but he wasn't wrong either. If *g* is anything at all, it is likely the speed, flexibility, and efficiency with which mental energy (*qua* action potentials, information, 'brain fields') is transduced. It is ultimately the behavior of molecules and microstructures that enable the integrity of functional connectivity. Presumably, they serve a distributed fronto-parietal network in the service of abstract intelligence. But insofar as we have been able to determine, the qualities of integrity, speed, and efficiency are not exclusive to regions devoted to IQ, but are *general qualities possessed by many, if not all, regions of the brain*.

Correlates of IQ

If abstract intelligence is a function of neuronal connectivity and efficiency, it is unlikely that such qualities would not also characterize brain systems that regulate physiological functions, immune and neuroendocrine response, neuromuscular coordination, sociality, and emotional expression.

Thus, we know that IQ is directly correlated with physical attributes such as brain size, body symmetry, body mass

index, height, physical fitness, attractiveness, and fertility. It accounts for only a small part of the variance in any of these attributes, though, so if you happen to meet a tall, rich person with a big head, you can't assume that he or she is intelligent. (Van Court & Bean, 1985) (Furlow et al., 1997) (Prokosch et al., 2005) (Kanazawa & Reyniers, 2009) (Kanazawa, 2011) (Killgore & Schwab, 2012) (Keller et al., 2013) Physiological correlates of IQ include sensory discrimination (Deary, 1994) (Melnick et al., 2013), sleep efficiency (Fogel & Smith, 2011), blood levels of Insulin-like growth factor I (IGF-I) (Gunnell et al., 2005), heart rate variability (Thayer et al., 2009), and blood pressure (Waldstein et al., 2005) (Loucks et al., 2011) (Gale et al., 2012) (Rosenblad et al., 2012) (Wang et al., 2023).

Cognitive ability is related to neuromuscular skill. When British birth cohorts from 1958 and 1970 were followed up until they were in their early thirties, both good coordination and cognitive ability in childhood predicted less psychological distress in later life, better health, and less obesity. (Gale et al., 2009) In studies of schoolchildren, motor skill deficits occur at every level of cognitive ability, but they are much more common in children who are cognitively weak. (Planinsec & Pisot, 2006) (Piek et al., 2008) (Smits-Engelsman & Hill, 2012) Children who do better in school also happen to be more active and physically fitter. (Chandola et al., 2006) (Åberg et al., 2009) (Kwak et al., 2009) (London & Castrechini, 2011) (O'Callaghan et al., 2012) Even elite athletes, whom many consign to the category of dumb brutes, are more gifted than non-athletes in certain neurocognitive abilities. (Vestberg et al., 2012) (Jacobson & Matthaeus, 2014)

Such correlates are reflected in the association of lower intelligence with disease, especially cardiovascular disease (Batty et al., 2005) (Silventoinena et al., 2006) (Batty, Gale, et al., 2008) (Batty, Shipley, et al., 2008) (Pesta, 2022); but not cancer, where frequency varies. A positive association exists for cancers of the colon, prostate, breast, and skin melanoma, whereas an inverse association has been found for cancers of the lung, stomach, oropharynx, esophagus, and cervix uteri. (Hemminki & Li, 2003) (Vidarsdottir et al., 2008) Studies have associated IQ with unintentional injuries, suicidal behavior, and homicide risk. (Jokela et al., 2009)

General mental ability tends to be lower in people with poor health and also in patients with mental disorders; in both instances, cognitive weakness is usually apparent well before the onset of illness. (Blackson, 1995) (Batty et al., 2005) Lower IQ scores are associated with an increased risk for schizophrenia, severe depression, and other psychoses. (Zammit et al., 2004) In a longitudinal study of 3,258 male veterans, lower cognitive ability at induction was associated with an increased risk of depression, anxiety, alcohol abuse, and PTSD, and often all four together. (Gale et al., 2008) In a follow-up study of more than a million Swedish conscripts, the risk of hospital admission rose with each point decrease in the nine-point IQ score. A standard deviation decrease in IQ led to a 60% greater likelihood of admission for schizophrenia, a 49% increase for other non-affective psychoses, 50% for mood disorders, 51% for neurotic disorders, 60% for adjustment disorders, 75% for personality disorders, 75% for alcohol-related disorders, and 85% for other substance abuse disorders. (Gale et al., 2010) The impact of severe mental illnesses like schizophreniform disorders on life expectancy is stronger than risk factors like smoking, diabetes, and obesity – as much as 15 years for men and 18 years for women. (C.-K. Chang et al., 2011)

Conversely, in children, higher intelligence is associated with better self-regulation. (Calero et al., 2007) Higher intelligence is also associated with personality traits such as openness to experience, introversion, and low neuroticism. Smarter people are more conscientious. They are even wiser, although they usually have to wait several decades to get that way. (Moutafi et al., 2003) (Chamorro-Premuzic & Furnham, 2004) (Luciano et al., 2004) (Koenen et al., 2009) (Grossmann et al., 2013) (Murray et al., 2014)

Alzheimer's disease (AD) is a prototype of aging-related degeneration and the prime example of the relation between the integrity of one's neural systems and longevity. People with more education are less likely to develop AD. When they do, the condition occurs later in life, and deterioration is very rapid. People with lower intellectual achievement are more likely to develop AD, the symptoms arise earlier, and the disease takes a long, painful course. The origins of this striking observation were epidemiological studies of dementia in Shanghai, France, Italy, Sweden, Finland, Israel, and New York City. Illiterate or poorly educated subjects are two to three times more likely to develop Alzheimer's than highly educated subjects. Higher occupational attainment has a similar, sanguine effect. Researchers have examined the obvious explanations and established that it's not a function of relative facility with psychological testing, nor is it mediated by lifestyle differences or the availability of medical care. (Schmand et al., 1997) (Fritsch et al., 2005) (Valenzuela & Sachdev, 2006) (McDowell et al., 2007) (Ngandu et al., 2007) (Allegri et al., 2010) (Sharp & Gatz, 2011) (A. R. Huang et al., 2018) (Nianogo et al., 2022)

People who are cognitively well-endowed to begin with are comparatively protected against ageing-related cognitive decline -- they have more 'cognitive reserve'. Normal ageing, it appears, is a different process for individuals who are well-educated and intellectually active compared to people who are neither. It's not my discovery, by any means. Education and mental ability are good-prognosis indicators in response to virtually every medical condition or procedure.

Accordingly, intelligence is related to longevity. Ian Deary, a psychologist at the University of Edinburgh, took advantage of Britain's early 20th century preoccupation with testing schoolchildren. He was able to trace the life courses of 2,230 residents of Aberdeen who had been tested at school in 1932,

when they were 11 years old. The survival curves from 1932 to 1997 are divergent. Comparing subjects who were 15 points apart in IQ at age 11, the likelihood of survival until 1997 for the lower group was only 79% that of the higher group; comparing groups who were 30 points apart, the survival rate of the lower group was 63% of the higher group. (Whalley & Deary, 2001) Deary's study took cognizance of many likely competing elements, like overcrowding during childhood, a measure of poverty, and even the Second World War, which accounted for the sharp drop in survival for men when they were in their twenties. Deary's findings have been replicated by at least nine studies, all of which reported that people with higher intelligence tend to live longer. The studies were conducted in Australia, America, and Europe, based on mental ability tests taken before adolescence. The follow-up periods were as long as 70 years. No studies, so far, have refuted the results. (Deary, 2010)

The Fundamental Connection Is in the Genome

One assumes that the fundamental connection among all the mental powers, and between brain and soma, is a function of the behavior of the human genome. The heritability of intelligence is 0.50 across all studies, but varies with age, with a heritability coefficient (h^2) of 40% in childhood and rising to 60% in early adulthood and 80% in later life. (Petrill, 2002)

As a rule, studies of the correlates of IQ control for the relevant environmental variables. When there have been opportunities to address the genetic contribution more directly, in a re-analysis of data from three twin registries in the USA, Sweden, and Denmark, all three samples individually and in the combined populations showed a clear genetic relationship between intelligence and lifespan. In the combined sample, the genetic contribution to the covariance was 95%; in the US study, 84%; in the Swedish study, 86%; and in the Danish study, 85%. (Arden et al., 2016)

The necessary question is: what is it about the genome that mediates the correlation? Intelligence and longevity are highly heritable. The evidence is overwhelming that there are genetic influences on individual differences in general cognitive abilities, and that the genetic influence is substantial; intelligence, *g*, has the highest adult heritability of any psychological trait. (Carroll, 1993) (Gray & Thompson, 2004) (Plomin, 2008) However, the genetic polymorphisms underlying normal-range intelligence differences remain elusive. (Deary et al., 2010)

Complex traits like intelligence are 'polygenic', arising from the activity of multiple genes (Gray & Thompson, 2004). Genome-wide association studies continue to identify more novel genomic loci and genes for intelligence (Sniekers et al., 2017), the most recent identifying 190 novel loci and 939 novel associated genes and replicating previous associations with 15 loci and 77 genes. (Savage et al., 2018) However, such studies have identified genes that explain only about 4% of the variance of intelligence in independent samples. (Plomin & von Stumm, 2018)

Quantitative genetic studies suggest that genes that mediate intelligence are also associated with personality traits such as openness, less risky behavior, self-efficacy, personality, well-being, with educational attainment, socioeconomic success, and longevity. (Krapohl et al., 2014) (Trampush et al., 2017) They also influence birth weight and length, brain structure, including head circumference in infancy, brain volume, neurogenesis, synaptogenesis, plasticity, and myelination; and in multiple brain regions, supporting the distributed nature of *g*. (Posthuma et al., 2002) (Thompson et al., 2002) (Pol et al., 2006) (Gray & Thompson, 2004) (Brans et al., 2010) (Sniekers et al., 2017) (Hill et al., 2019) (Coleman et al., 2019) However, and in accord with the previous section, we have also learned that genes associated with intelligence overlap with genes for non-cognitive functions; noncognitive and cognitive-performance genetics demonstrated associations of similar magnitude. (Demange et al., 2021)

Genes for intelligence are inversely related to certain metabolic disorders, BMI, obesity, waist-to-hip ratio, body mass index, and waist circumference, and also with neuropsychiatric disorders such as Alzheimer's disease, depression, 'neuroticism', and schizophrenia. (Savage et al., 2018) (Sniekers et al., 2017)

Reflecting the positive manifold, most genes found to be associated with a particular learning ability or disability (such as reading) will also be associated with other learning abilities and disabilities (such as mathematics). Moreover, some 'generalist genes' for learning abilities and disabilities are even more general in their effect, encompassing other cognitive abilities such as memory and spatial ability. Genetic correlations are consistently greater than 0.50 and often near 1.0 across different cognitive abilities. (Petrill, 2002) (Plomin et al., 2007) (Haworth et al., 2009)

Mental power is the efficacy and efficiency of the brain. It is expressed in multiple systems that operate more or less independently. However, the efficacy and efficiency of every system are correlated with those of all the others. The correlations are not very high, not high enough to be predictive in individual cases, but sufficient to influence the health and longevity of populations. Evolution, too, thrives on small associations; a very small difference in birth rate, for example, will spell success for one group and extinction for another. Physiological regulation, strength and neuromuscular coordination, social engagement, and emotional stability are all signs of a well-engineered brain, just as abstract intelligence is. The powers of various mental systems are inter-correlated and are all associated with good health and longevity. It may fly in the face of common experience. Common experience tells us that individuals are not uniform in their abilities. Some of us are good in A, B,

and C, and others in X, Y, and Z. But when large numbers of individuals are examined, doing very well in ABC suggests doing well in XYZ as well. In the numbers that count to evolution, most humans do OK in A through Z.

Whatever it is that endows an organism with this degree of integrity is expressed in other complex functional systems as well, particularly in the *soma*. That this must be true is evidenced by numerous observations of positive associations between intelligence and health and longevity, resistance to cognitive decline with ageing, and even morphological attributes, like height and body symmetry. (Miller, 2000) For this reason, it has been proposed that intelligence is a "general fitness factor"; in evolutionary terms, a behavioral representation of the fitness of the organism to survive and to thrive. (Harrington, 1997)

Genes for Longevity

Longevity is an inherited trait; about 50% of the variation in human lifespan may be explained by genetic differences (h^2 = 0.50). Longevity and healthy ageing cluster in families. The heritability of achieving age 70 free of heart attack, coronary surgery, stroke, diabetes, or prostate cancer is at least 50%. The offspring of centenarians are a remarkably healthy and long-lived lot themselves. Male and female siblings of US centenarians were 17- and 8 times more likely, respectively, to reach the age of 100.[§§] The offspring of centenarian parents are also less prone to ageing-related diseases. The heritability of living to at least 100 has been estimated at 33% in women and 48% in men. (vB Hjelmborg et al., 2006) (Adams et al., 2008) (Nebel et al., 2011) (Beekman et al., 2013) (Brooks-Wilson, 2013) (Dutta et al., 2014) (Govindaraju et al., 2015)

The heritability of longevity is roughly the same as that of intelligence, and the present state of understanding is similar for both. There must be genes for longevity, just as there are for intelligence and every other human trait. There are doubtless many genes that mediate longevity, and long-lived individuals must have a lot of them, or at least the right ones. However, only a couple have been identified thus far.

The Pleiotropic *APOE* Gene

ApoE is one reason why longevity and intelligence are correlated. The favorable alleles are protective of the brain and soma. They also appear to support brain development.

The *ApoE* gene is one of only two genes that have consistently been associated with longevity. (Corder et al., 1993) (Beekman et al., 2013) (Sebastiani et al., 2019) *ApoE* is most familiar for its association with Alzheimer's disease. The gene has three alleles, *ε2*, *ε3*, and *ε4*. About 15% of people have one or two ε4 alleles, but 60–80% of AD patients have at least one *ApoE4* allele. (Y. Huang & Mahley, 2014)

The *ε2* allele, on the other hand, is protective against Alzheimer's disease, and *ε3* is neutral. The *ε2* allele also confers longevity, and ε4 is associated with a shorter lifespan even in individuals who don't develop Alzheimer's disease. The *ε4* allele is hardly ever found in people who live past 90. (Deelen *et al.*, 2011) (Beekman et al., 2013) (Garatachea et al., 2015)

Apolipoprotein E (apoE) is a plasma protein that plays an important role in lipid and lipoprotein metabolism. Its cardinal function is to transport lipids among various cells and tissues of the body. It is a key regulator of plasma lipid levels and participates in the homeostatic control of plasma and tissue lipid content. (Mahley, 1988) (Y. Huang & Mahley, 2014)

The *ApoE* gene encodes the brain's primary cholesterol transporter, apolipoprotein E, which arises primarily from hepatic synthesis. The second most common site of synthesis is the brain. (Elshourbagy et al., 1985) In the brain, it is normally produced by glial cells and by neurons in response to stress or damage. It thus contributes to neuronal maintenance and repair. (Y. Huang & Mahley, 2014) Oxidative stress and mitochondrial function are affected in an *ApoE* isoform-dependent manner. ApoE is an endogenous immunomodulatory agent that affects both the innate and the adaptive immune responses. Several stress response pathways implicated in the aging process appear to be influenced by the *ApoE* genotype. (Vitek et al., 2009) (Dose et al., 2016)

For a long time, it was customary to designate *ε3* as the parent allele from which the other two evolved because ε3 is the most common allele in humans.(Poduri et al., 1994) As it happens, non-human primates have the *ApoE* gene, but the only allele they have is *ε4*. *ε4* is the parent gene, therefore, and hominids were beneficiaries of mutations that generated *ε2* and *ε3* alleles.

ApoE2 and apoE4 differ from apoE3 by single amino acid substitutions, but small differences spell large differences in protein configuration. ApoE4 is more susceptible to proteolytic cleavage than apoE3; fragments of apoE4 are potentially neurotoxic. (Brecht et al., 2004) (Harris et al., 2003) (Y. Huang et al., 2001). They also target the mitochondria of neurons, leading to mitochondrial dysfunction. (S. Chang et al., 2005).

ApoE is involved in maintaining and regulating synaptic activity and strength. ApoE3 and apoE4 have markedly different effects on neurite extension. The former stimulates neurite extension, while *ε4* has the opposite effect. It disrupts microtubule formation, synaptogenesis, and hippocampal neurogenesis. (Nathan et al., 1995) (Levi & Michaelson, 2007) (Y. Huang & Mahley, 2014)

ApoE status influences metabolism to support neuronal integrity and survival; not only are *ε4* carriers more prone to Alzheimer's disease, but they also have more difficulty recovering from brain injury. The new, beneficial alleles have more general effects. *ε2* and *ε3* carriers are less prone to

premature atherosclerosis and coronary heart disease. (Wilson et al., 1996) In the brain and soma, *ApoE* regulates the metabolism of cholesterol, with $\varepsilon 2$ supporting 'good' HDL cholesterol and $\varepsilon 4$ supporting 'bad' LDL cholesterol. (Davignon et al., 1988) It gave hominids more functional integrity and resilience not only in their brains but also in their cardiovascular system.

There is also evidence that points to *ApoE* effects on brain development. Structural brain differences in $\varepsilon 4$ carriers may appear in infancy, including lower hippocampal, frontal, and temporal lobe volumes, as well as gray and white matter. (Dean et al., 2014) (Knickmeyer et al., 2014) A recent large cross-sectional imaging and neuropsychological study of 1187 children and youth, aged 3 to 20 years, suggested a number of differences in brain volume, fractional anisotropy, or thinning by *APOE* genotypes as well as cognitive ability performance. (L. Chang et al., 2016) Smaller hippocampal volumes among $\varepsilon 4/\varepsilon 4$ individuals were associated with poorer performance on attention and working memory tasks. (L. Chang et al., 2016) In a longitudinal twin study with serial assessments at ages 7, 12, and 16, ApoE4 was associated with lower Verbal, Performance, and Full Scale IQ scores during childhood and adolescence. Full Scale IQ was lower by 1.91 points per $\varepsilon 4$ allele. (Reynolds et al., 2019)

ApoE illustrates how a single gene can influence the development and resilience of the brain and soma over a lifetime. Like other genes that mediate intelligence, its beneficent alleles support synaptic plasticity and neuronal connectivity. It also confers disease resistance. As it happens, centenarians have the same number of disease-risk genes as everyone else, but they don't tend to develop ageing-related diseases until their nineties. They appear to have greater numbers of genes that are protective against disease, among them ApoE2 and ApoE3. (Perls et al., 2002)

Gene Networks of Infinite Variety

Before the genome was sequenced, it was thought that humans must have at least 100,000 genes. Then we learned we have barely a fifth of that number – fewer genes than a tomato. That's what is to be found if one just counts protein-coding genes on DNA. With advances in molecular profiling, however, we have been able to map the expression of genes in cells, tissues, and organs by measuring gene products. Since active genes produce RNA and proteins, tissue differences in gene activity can be probed by characterizing the RNA and proteins they contain – collectively known as the 'transcriptome'.

We have more effective genes than tomatoes do because transcriptase is able to pick and choose data from multiple sites on DNA to generate messenger RNA. Thus, when we aver that complex traits such as intelligence and longevity are 'polygenic,' what we mean is that the proteins and RNAs that underlie such traits are the products of gene networks, cleverly identified by transcriptase in ways we are far from understanding. Thus, information can be transcribed from most of both strands of DNA. The genomic architecture is not co-linear, nor does it obey the rule of 'one gene, one protein.' It is interleaved and modular. Genomic sequences are multifunctional, used for multiple independently regulated transcripts and regulatory regions. (Kapranov et al., 2007)

Multiple genes form networks with all the accoutrements of graph theory, like small world properties, hubs and edges, clustering coefficients, etc. For any particular trait, there may be one or a few 'core genes,' and they are hubs of the network. The total number of genes in the network – 'peripheral genes' -- may outnumber core genes by 100:1 or more. The sum of small effects across peripheral genes can far exceed the genetic contribution of variants directly affecting the core genes themselves. (Boyle et al., 2017) (Aravind et al., 2009) (Nowick & Stubbs, 2010)

Intelligence and longevity may be considered 'complex traits,' but that is an understatement. After all, they speak to nothing less than the robust good health of the brain and soma, than which nothing is more essential. In fact, intelligence and longevity reflect the contributions of multiple complex traits, all emerging from extensive gene networks, with their several core genes and multiple peripheral genes; the latter are likely constituents of other gene networks, which are highly interconnected.

Consider two general kinds of gene networks. Some are hard-wired, or 'canalized'. That's why humans are born with two legs, not one or three, one heart, one head, etc. The essential features of our anatomy arise from canalized gene networks.

The genes that account for complex traits like longevity and intelligence are not canalized. They arise from flexible gene networks that vary from one individual to the next. The expression of a gene network is governed by transcription factors, which don't necessarily operate autonomously but are influenced by the environment of the cell. The products of such diverse networks – proteins, phenotypes, individuals -- are almost infinitely variable.

The evolution of complex human traits such as intelligence, personality, and longevity reflects the complexity and flexibility of gene networks. Evolutionary pressures, whether by natural selection or social preference, find complex traits more amenable to change, usually, but not always, in the direction of improvement. Mutable and flexible gene networks are the bass of the runaway evolution of the hominid lineage. (Gualtieri, 2021)

The Fox Genes

The FOX family of genes is a good example of how a dynamic genome influences the ongoing evolution of intelligence and longevity. *FOXO3A* is one member of the venerable *FOX* family of genes, and biogerontologists like it a lot because it is an evolutionary descendant of *DAF*, a gene

with mutations that increase the lifespan of a roundworm, *Caenorhabditis elegans*. That worm is the size of a twist of lint, and there are probably a gazillion of them in your compost pile right now; like fruit flies, they are cheap and easy to grow. That matters a lot to biologists, a frugal lot in the best of times. Also, *C elegans* is the simplest animal with a nervous system. The worms ordinarily live for 12-18 days, so one doesn't have to wait very long to find out if one's mutant specimens are long-lived or not.

The founding member of the *FOX* family is the 'forkhead gene' that was discovered in fruit flies (Drosophila) in 1987. (Weigel et al., 1989) A mutation in the gene gave the flies a little thingie on their heads that looks like a fork if one has a good imagination. Fruit flies and roundworms have only a single *FOX* gene, but mammals have several. *FOX* is so-named for 'forkhead box', a family of proteins that have a typical sequence of 80-100 amino acids, i.e., the 'box'.

The *FOX* genes generate DNA-binding proteins, transcription factors that direct the expression of other genes. Transcription factors turn genes on or off in a graded way, controlling their activity as if they were a volume control knob. Their role is to make sure that genes are expressed in the right cell at the right time and in the right amount throughout the life of the cell and the organism.

There are more than a hundred genes in the *FOX* family, and they all do interesting things, stimulating the genes that stimulate growth and development, metabolism, and, BTW, longevity. For example, *FOXO*. We humans have four of them, especially *FOXO3A*. Small differences in that gene are linked to longevity, first noted in a study of Japanese-Americans and then replicated in other ethnic groups. (Flachsbart et al., 2009) (Ziv & Hu, 2011). The G allele of *FOXO3A* is the one you want to have, all things being equal. It trebles your chances of living a hundred years. In Willcox's study of Japanese-Americans, the beneficent allele was most often found in the oldest subjects. Although they were eleven years older than the control group, they were less prone to heart disease, stroke, and cancer, were healthier, and had less difficulty walking. Although they were older, their cognitive functions were as sound as the younger controls'. (Willcox et al., 2008)

FOXO (Forkhead box O) transcription factors are important determinants in ageing and longevity. FOXO proteins are a subfamily of transcription factors that act as key regulators of longevity downstream of insulin and insulin-like growth factor signaling.

Invertebrate genomes have one *FOXO* gene, while mammals have four *FOXO* genes: *FOXO1, FOXO3, FOXO4,* and *FOXO6*. In mammals, this subfamily is involved in a wide range of crucial cellular processes that regulate stress resistance, metabolism, cell cycle arrest, and apoptosis. (Martins et al., 2016) FoxOs are master regulators that translate environmental stimuli arising from insulin, growth factors, nutrients, and oxidative stress into specific gene expression programs. Effective control of *FoxO3* in response to environmental stimuli is likely critical to prevent ageing and age-related diseases, including cardiovascular disease, type 2 diabetes, cancer, and neurodegenerative diseases. (Morris et al., 2015) (Maiese et al., 2007) (Hwang et al., 2018)

Another study of the *FOXO3* gene began as a genome-wide search for the genetic basis of intelligence. The authors of a recent study took advantage of 13 prior studies that had generated genome-wide association data on 78,308 unrelated individuals and also intelligence tests. They identified no fewer than 47 genes that were associated with high intelligence. The strongest association was a variant of *FOXO3*. They also examined a number of other traits that happened to have been collected in the original studies. There were positive associations of *FOXO3* with educational attainment, smoking cessation, intracranial volume, head circumference in infancy, and height. It was inversely associated with Alzheimer's disease, depression, schizophrenia, neuroticism, waist-to-hip ratio, body mass index, and waist circumference. (Sniekers et al., 2017)

Among other things, *FOXO3* (and related) proteins influence the expression of several mitochondrial DNA genes and are essential to mitochondrial energy regulation, control of oxidative stress, and inducement of apoptosis in damaged cells. (Geary, 2018)

One More *FOX*

FOX genes do interesting things, but more interesting is how they do it. For example, the *FOXP2* gene is the only gene found, to date, that governs the development of speech and language. Like most other genes and all the other *FOXO*'s, it has many roles; the gene is expressed in the lung, intestines, and cardiovascular system. (Shu et al., 2001) Its role in language, however, is striking. The discovery began with a remarkable family in the UK, the KEs; of 37 family members over four generations, 16 had severe articulation deficits (verbal dyspraxia). The problem the KEs have is mastering the coordinated movement sequences that underlie fluent speech, and a mutation in *FOXP2* is responsible. (Vargha-Khadem et al., 1998) (Lai et al., 2001)

Despite its connection to speech, *FOXP2* is not uniquely human. Songbirds have the gene, and if it is deleted in chicks, they never learn to sing and seem to stutter. (Haesler et al., 2007) It's not an experiment one wants to come home and tell one's little daughter about, but it proves something. Mice and chimpanzees have *FOXP2*, too, and Neanderthals had it as well. It beggars the onetime belief that *FOXP2* was the 'language gene' and uniquely human. It is simply a gene that participates in the neuromotor control of speech.

The exquisite control of many small muscles in the larynx and pharynx that make speech possible occurred when humans changed *FOXP2* ever so slightly, but just enough to change two amino acids in the FOXP2 protein. We're not sure when they did it, but the best guess is after *H Sapiens* evolved and before they migrated out of Africa. (Enard et al.,

2002) The mutation allowed our ancestors to speak clearly. How it does that stimulated a group of investigators at UCLA to compare human *FOXP2* to the less potent version carried by chimpanzees. To that end, they prepared two sets of cultured neurons. Both sets started even; they both had their *FOXP2* genes deleted. To one culture, they inserted the human gene, to the other, the chimp gene.

What happened was amazing. The human gene differs from the chimp gene by two amino acids out of 715. Yet the proteins expressed, transcription factors, had markedly different effects. Both chimp and human proteins stimulated 32 other genes and inhibited 25. However, human FOXP2 stimulated the expression of 61 additional genes and suppressed the expression of 55. *FOXP2* is 99.7% similar in humans and chimps, but those two amino acids on the human protein affect the behavior of no fewer than 116 additional genes. (Konopka et al., 2009) The sum of small effects by peripheral genes can exceed the genetic contribution of variants directly affecting the core genes themselves. Further, the networks are highly interconnected. (Aravind et al., 2009) (Nowick & Stubbs, 2010) (Boyle et al., 2017)

The *FOX* family illustrates, among other things, how humans contrived to dilate upon their paltry number of genes; they increased the size and complexity of gene networks. Proteins expressed by *FOX* genes are transcription factors that influence the behavior of many other genes. It's not only that the *FOX* genes are themselves pleiotropic. They change the behavior of other genes that also have pleiotropic effects. The organismal variety that is possible, for example, when one gene affects 173 others, is staggering to consider. Now consider that FOX genes aren't the only ones that express transcription factors; there are about 2,000 genes in human DNA that do so. All those genes stimulate other genes, some of which express transcription factors, too. At every point in a cascade, the opportunities for individual differences multiply exponentially. That's probably why, although as a species we are smart, social, healthy, well-coordinated, and talkative, not all of us are all of those things.

The *APO* and *FOX* families are examples of how genetic pleiotropy underlies the common health of brain and soma. They are both ancient genes that have been modified during the course of evolution. Natural selection liked the genes because they had positive effects on development. It turned out that they had additional effects that contributed to our physiological reserve. (Luo et al., 1986) (Hannenhalli & Kaestner, 2009)

Gene Distribution

Genes may behave differently in brain and soma. They probably express themselves in different ways, and the proteins they generate must differ slightly in their structure and function. During evolution, the genome has deployed gene networks of ever-increasing size and complexity, with new RNAs and proteins to meet new requirements. The quality that new genes and proteins confer on the brain is reflected in other parts and in the soma. If one has the optimal genes in the brain, then other parts will enjoy the same benefit.

Half of our genes are said to be directed to brain structure and development, but few, if any, of those genes are exclusively devoted to the brain. They also express proteins that are active in other parts of the body. The functions of those genes and proteins are different in different parts, of course, but their activities are homologous. For example, brain and testis.

One of the events to which our genome had to adapt was the robust growth of the brain and an even more impressive increase in its powers, all within a comparatively short span of time. Yet, an evolving brain needed a soma that could support its metabolic needs and accommodate all of the mischief it wanted to get into, like moving out of the warm climate of the African bush to less temperate corners of the world, not to mention social cooperation, language, fine motor coordination, and abstract intelligence. It also needed a generative apparatus that would guarantee that improvements in the brain were transmitted to succeeding generations. Consider a squirrel born with a mutant gene that lent him the skills to surmount the best-protected bird feeder. Said squirrel is an advantage to his fellows because he can spill birdseed all over the patio; what greater advantage he would be to the race of squirrels if he could immortalize his skill with intelligent spermatozoa. My wife said that something like that has already happened in our backyard, but I think she was only joking.

I wondered if she had been reading the Protein Atlas again. The Atlas identified 419 genes that are especially active in both the brain and soma. The testis shares no fewer than 45 of those genes; a connection that exceeds, by far, that of any other organ. No fewer than 45 of the genes that the brain relies upon most for its structure and organization also contribute to the behavior of one's testes. (Karlsson et al., 2021)

What they both do, brain and testis, aside from causing undue remorse, is to generate enormous numbers of proteins and other molecules quickly, efficiently, and preferably with a low error rate. To those common ends, they rely on many of the same genes and proteins. They both do so in a protected environment. The testes, like the brain, are immunologically privileged sites. The same proteins that constitute the 'blood-brain barrier' to protect the brain from undesirable molecules also form a 'blood-testicular barrier' to protect the family jewels. (Holash et al., 1993) (Filippini et al., 2001) It doesn't stop there. Spermatozoa have protein receptors on their cell surface that are identical to those in the brain – neuronal receptors, you could say. Further, the quality of one's sperm, their numbers and concentration, and even the motility of the

little buggers is positively correlated with superior intelligence. (Meizel, 2004)

The brain is continually manufacturing proteins and other molecules. It is constantly building and unbuilding connections among its neurons and glial cells, and it does so even as we sleep. It generates a regular energy supply to feed its ever-active neural oscillations. Such activity is reflected in the testis, which is continually manufacturing new spermatozoa, and do they ever need energy, those neurons with little tails, able to surmount the most formidable obstacles and get us into almost as much trouble as our brain cells do.

The evolutionary collaboration between the brain and testis is shared by another reproductive organ, the placenta. The brain + placenta genes, like brain + testis genes, are pleiotropic (affecting several traits in parallel). They are all old genes that we share with chimps and, for all I know, daffodils, but evolution has taught them new tricks. Thus, a gene that was originally devoted to the testis or placenta found a role in brain development and function, or maybe it was the other way around. As the brain became more powerful, the improvements were deployed to the generative organs so they could be passed along to the next generation.

> Speciation always seems to recruit the same genes for the functions in question in the brain, testis, and placenta. The development of a new characteristic during speciation has to be intimately correlated with reproductive isolation to not become diluted at once. Therefore, the same genes responsible for enhanced brain function are also functional in the testis. (Wilda et al., 2000)

At the level of genes and the origination of proteins, therefore, the brain and testis have a lot in common, and we can generalize the principle to all the soma. The same genes and proteins in the brain operate similarly in the brain and soma. The efficiency of genes and proteins in the brain is reflected in all the other parts of the body. Since most genes are pleiotropic, most mutations are likely to have pleiotropic effects in disrupting several traits in parallel. Such pleiotropic mutations could produce positive genetic correlations in the functional efficiencies of different organ systems, yielding positive phenotypic correlations in different components of fitness, such as intelligence and fertility. (Pierce et al., 2009)

A Dynamic and Mutable Genome

It is futile to look for a longevity gene, or genes for intelligence, social cooperation, language, or neuromuscular control. The exceptional attributes of human beings don't arise from one gene, or from several. They are more likely generated by gene networks of inordinate complexity, and there are many different ways gene networks are assembled in different individuals. There is probably more than one gene network that gives rise to longevity, just as there must be for all the exceptional human attributes.

Not all the details of the theory have been worked out, but it accords with this simple observation. We are a longevous species and an intelligent one. We are all social, most of us, anyway, and we can move our fingers well enough to send a text. When we aren't talking, we may not be listening, but at least we're thinking about the next thing we want to say. How we get the way we are – well, each of us gets there in his or her particular way. Our gene networks can't be so different.

The human genome is uniquely dynamic and mutable. Techniques for higher-resolution genomewide analysis highlight the irregular and unpredictable behavior of the genome, endowed as it is with a high degree of variability. It has served the hominid lineage for better and worse. Genomic variability accounts for no small proportion of the missing heritability of complex diseases. (Hindorff et al., 2009) It has also presided over the runaway evolution of our lineage over the past two million years, and especially the past hundred thousand. The complex and adaptable human brain reflects a genome that is uniquely mutable and responsive to challenging environments. (Gualtieri, 2021)

Although single-nucleotide polymorphisms (SNPs) are the most abundant form of DNA variation in the human genome (Hinds, 2005), new technologies have shown that individual variation is also the consequence of structural variants involving larger segments of DNA (Goldstein, 2009) (Stranger et al., 2007) (Beckmann et al., 2007) (Schork et al., 2009). Two randomly selected human genomes differ by 0.1% when only SNPs are measured, but when structural variants are also measured, they differ by at least 1%. (The International HapMap Consortium, 2003) (Buchanan & Scherer, 2008)

The relevant principle is evolvability, a species trait that describes the capacity to generate heritable variations. (Kirschner & Gerhart, 1998) The essence of evolvability is inter-generational and intra-individual variability. Phenotypic variation drives natural selection, but variation ultimately derives from the variability of individual genotypes; evolvability describes a genome that can generate a spectrum of phenotypes ranging from major evolutionary innovations to small changes between generations. (Feder, 2007) (Draghi & Wagner, 2009)

Collectively, these findings illustrate how changes in gene regulation mediated by rapid evolution of non-coding regions contribute to phenotypic differences between humans and non-human primates despite the high degree of similarities and high levels of constraint in protein-coding sequences. (Won et al., 2019)

We hominids wouldn't have gotten nearly as far if our genes and proteins weren't as flexible as they are. We'd be back among the chimpanzees and bonobos, with whom we share 99% of our genes, or perhaps the daffodils, who have 34% of

our genes. There may be people who prefer a bonobonic lifestyle, but hardly anyone I know would prefer to be a daffodil.

Fate Rules Even You and I, Too, if That Also Makes You Feel Better — Zeus, in Ovid, Bk IX:418-438.

Just because you're tall and have a big head doesn't mean you're going to live a long time. The Fates rule all of us. You may be smart, but none of the correlations and associations described herein are anything near predictive. But, as I said, evolution thrives on small associations. Thus, our species has come to be intelligent and long-lived. We may even be growing more so. Meanwhile, we individuals have to endure the fateful problem of randomness. Biomolecules are pretty smart; they can do things we can't imagine how they do, but they make mistakes almost as often as we human beings do. One amino acid in the wrong place, and there you are, like Aristotle, dead at 62.

The Fates are not at issue here, at least right now, because we are talking in the most general terms, where biology behaves as if it really does have laws. Our premise is that intelligence, the exemplar of all mental powers, is correlated with longevity. It is a sound premise but calls for explication. The explanations I have given here are neither original nor complete.

First, for example, a common-sense explanation: humans live a long time because we have a complex, efficient, and adaptable brain. Nature wouldn't have needed such a brain if its bearers lived only a short time. And it takes a long time to generate such a brain. It's a paraphrase of George Sacher, but it was amplified by Hillard Kaplan, an anthropologist who lived among the hunter-gatherer Machiguenga, Yaminahua, and Piro Indians in Peru and the Ache Foragers in Paraguay during the 1980s.

> Our proposal is that the shift to calorie-dense, large-package, skill-intensive food resources is responsible for the unique evolutionary trajectory of the genus Homo. The key element in our theory is that this shift produced co-evolutionary selection pressures, which, in turn, operated to produce the extreme intelligence, long developmental period, three-generational system of resource flows, and exceptionally long adult life characteristic of our species. (H. Kaplan et al., 2000)

And this: something as extraordinary as the human brain can only have evolved in an organism whose physiological systems are highly reliable, efficient, and coherent. The principles of organization that have endowed us with brains that work well must also be represented in the other functional systems. From Sacher himself:

> The selective process acts on mechanisms for increasing the stability of the organism at all levels, from the molecular to the systemic. (Sacher, 1982)

And this: such a brain regulates our physiology with a fine touch. It protects us from dangerous environments and endows us with vast powers over our destiny. It invented machines and harnessed electricity. It invented vaccines and antibiotics. Its capacities are far in excess of what any successful organism could possibly need. We live as long as we do because our brains are over-engineered, and so are our other parts.

> More complex animals might be engineered so well that they can outlast Nature's expectations as long as the opportunity arises. An appropriate analogy is a planetary space probe like the Pioneer mission to Mars. The Pioneer's engineers worked through all the problems and built in all the safeguards needed to be sure that the Pioneer probe would reach Mars and complete its mission. But the Pioneer space probe was still functioning as it left the Solar System. Space probes, like jetliners, are engineered to guarantee fail-safe completion of the mission; the quality of their engineering endows them with residual life after they have completed their mission. (Wachter, 1997)

Finally: Something as extraordinary as the human brain can only have evolved in the context of functional systems that have achieved a high degree of integrity, coherence, and energetic efficiency.

> The so-called "system integrity" hypothesis... posits that higher intelligence may be a marker for a general latent trait of a well-functioning body. That is, higher intelligence might be one aspect of a body that is generally "well-wired", and that responds more efficiently to environmental challenges or "allostatic load". (Gale et al., 2009) System integrity is also akin to the idea of a general fitness, '*f*', factor.(Deary, 2012)

We have already used the term 'integrity' with regard to the speed, flexibility, and efficiency of white matter tracts, which are correlated with *g*, characteristic of an intelligent brain and the basis for all its mental powers. We went on to suggest an explanation that may or may not be original:

> The genetic elements that engineered our efficient and durable brain have exercised similar effects on all our other complex functional systems. As we shall see, almost all of the genes that generate and maintain the human brain are also active in the periphery,

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> endowing our tissues with the same efficiency and durability.

Having given a few examples, we alluded to data that indicate that intelligence and longevity are derived from gene networks of inordinate complexity. The behavior of those networks is the crux of our argument:

> The genomic architecture is not co-linear, but interleaved and modular. Genomic sequences are multifunctional, used for multiple independently regulated transcripts and regulatory regions. Multiple functional elements can overlap in the same genomic space... (However) an interleaved genomic organization poses important mechanistic challenges for the cell. One involves the steric issues that stem from using the same DNA molecules for multiple functions. The overlap of functionally important sequence motifs must be resolved in time and space for this organization to work properly. (Kapranov et al., 2007)

One assumes that gene networks must also be characterized by speed, flexibility, and efficiency. As it happens, 'integrity' has also been applied to the genome, where it refers to the stability of DNA strands and the accuracy of the transcription process. Many of the same proteins that participate in DNA stability during replication and in the face of damage also preside over signal transduction in the cytosol, transcription control, and gene expression. The proteins form networks that link metabolism and ageing as tightly in humans as they are in model organisms such as *C. elegans*. (Müller et al., 2004) (R.M. Verstraeten et al., 2007) (Feeney et al., 2010) (Ide et al., 2010)

Our surmise is not that intelligence and longevity are isomorphic, but that they are homologous. The convergence of intelligence and longevity is a function of the integrity of neural networks and gene networks. They employ the same proteins in similar ways.

The primacy of the brain is captured in the arithmetic of our DNA: half of the protein-coding genes are occupied with brain development and function. Few, if any, of them, however, are exclusively occupied with the central nervous system. They also govern the development, regulation, maintenance, and cohesion of all our complex functional systems. It is possible that more genes will be discovered that participate in human intelligence, disease resistance, and longevity, and more of the variance in those attributes will thus be explained. The real challenge, however, as Kapranov suggests, is not the names of the genes or where they reside, but how they interact to form networks that are fast, flexible, and efficient, how they develop, and how errors are minimized.

The evolution of complex human traits such as intelligence, personality, and longevity reflects the complexity and flexibility of gene networks. Evolutionary pressures, whether by natural selection or social preference, find complex traits more amenable to change, usually, but not always, in the direction of improvement. But the Fates, as always, have the last say. Mutable and flexible gene networks are the bass of the runaway evolution of the hominid lineage. They have also been the source of many fell diseases that compromise intelligence, health, longevity, and our well-being. (Gualtieri, 2021)

Footnotes

* Humans may not be the longest-lived mammals. Some scientists believe that bowhead whales (*Balaena mysticetus*) live longer; more than a century and possibly as long as 211 years. The evidence for bowhead longevity, however, is indirect, if not speculative; for example, changes in the chemistry of the lens of their eyes, which is not quite as accurate as counting tree rings, and also happens to be temperature-sensitive.(George et al., 1999) Bowheads live in a really cold part of the world. Also, two bowheads were harvested recently by Eskimo hunters and were found to contain harpoon fragments dating from the 1880s. (J. C. "Craig" George & Bockstoce, 2008) I'm not sure that proves anything. Maybe someone in 1950 was using a really old harpoon. Baleen whales as a group are not long-lived compared to toothed whales, and solitary whales don't live as long as ones who are social. This is an important point. If intelligence and longevity were related, and if there were a longer-lived mammal than we, then there might also be a smarter mammal. Maybe there is, but I don't think it's the bowhead whale.

† Paramahamsa Yogananda, Autobiography of a Yogi.

‡ The number is 955,787,040. You need to keep track.

§ For the record: Maximum life span = (10.83)x(brain weight)$^{0.636}$ x (body weight)$^{)-0.225}$.

** Not to suggest they couldn't be *more* equitably distributed.

†† Abstract intelligence is reducible to a single number, IQ. To some, that is a dubious trick. Nevertheless, the reduction is done on the basis of sound mathematics, and IQ has been around a long time. Since 1912, in fact, when the only other numbers clinicians could call upon were body temperature, heart rate, blood pressure, blood counts, and urinalysis. (Berger, 1999)

‡‡ When asked what *g* is, Spearman replied, One has to distinguish between the meanings of terms and the facts about things. g means a particular quantity derived from statistical operations. Under certain conditions, the score of a person on a mental test can be divided into two factors, one of which is always the same in all tests, whereas the other varies from one test to another; the former is called the general factor or *g*, while the other is called the specific

factor. This then is what the *g* term means, a score-factor and nothing more. But this meaning is sufficient to render the term well defined so that the underlying thing is susceptible to scientific investigation; we can proceed to find out facts about this score-factor, or *g* factor. . . On weighing the evidence, many of us used to say that this *g* appears to measure some form of mental energy. But in the first place, such a suggestion is apt to invite needless controversy. This can be avoided by saying more cautiously that *g* behaves as if it measured an energy. In the second place, however, there seems to be good reason for changing the concept of energy to that of "power" (which, of course, is energy or work divided by time). In this way, one can talk about mind power in much the same manner as about horsepower. (Deary et al., 2008) (pp. 156 –157).

[§§] Males are less longevous than females. For a male to live a long time, he has to be more generously endowed with genes for longevity.

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