European Neurology

Clinical Neurology: Review Article

Eur Neurol
DOI: 10.1159/000541361

Received: April 25, 2024
Accepted: September 5, 2024
Published online: September 12, 2024

Brain Evolution in the Times of the Pandemic and Multimedia

Elisabete Castelon Konkiewitz[a] Edward B. Ziff[b]

[a]Faculdade de Ciências da Saúde (FCS), Universidade Federal da Grande Dourados (UFGD), Dourados, Brazil; [b]Department of Biochemistry and Molecular Pharmacology, New York University School of Medicine, New York, NY, USA

Keywords
Evolution · Brain · Internet · Pandemic · Epigenetics

Abstract
Background: In this paper, we argue that recent unprecedented social changes arising from social media and the internet represent powerful behavioral and environmental forces that are driving human evolutionary adaptive responses in a way that might reshape our brain and the way it perceives reality and interacts with it. These forces include decreases in physical activity, decreases in exposure to light, and face-to-face social interactions, as well as diminished predictability in biological rhythms (i.e., the sleep cycle is no longer dictated by natural light exposure and season). ***Summary:*** We discuss the roles of stress and of creativity and adaptability in *Homo sapiens* evolution and propose mechanisms for human adaptation to the new forces including epigenetic mechanisms, gene-culture coevolution, and novel mechanisms of evolution of the nervous system. ***Key Messages:*** We present the provocative idea that evolution under the strong selective pressures of today's society could ultimately enable *H. sapiens* to thrive despite social, physical, circadian, and cultural deprivation and possible neurological disease, and thus withstand the loss of factors that contribute to *H. sapiens* survival of today. The new *H. sapiens* would flourish under a lifestyle in which the current form would feel undervalued and replaceable.

Introduction

The role of social media in daily life has already given contemporary man an unprecedented profile in history, which the COVID-19 pandemic has radically accentuated [1, 2]. Social isolation has brought about adaptations, with the generalization of new forms of production, learning, communication, and leisure. The pandemic has made audiovisual and multimedia resources as fundamental to our survival as essentials like water, energy, and food supply services. Distance education, home office, videoconferences, and telemedicine are just a few examples of resources quickly incorporated into people's daily lives, which have redefined contact possibilities, information acquisition, subjective presentation, intimacy, group attachment, organization of work and rest, division of work and domestic tasks, and organizational hierarchies. Thus, even though the pandemic is over, its historical role as an accelerator of profound changes in the basic and structural elements of everyday life will have lasting consequences. These sociocultural reconfigurations imply new behavioral, cognitive, and affective demands, creating a new and very different environment from the one in which *H. sapiens* was selected.

For millennia, our species survived in small, predominantly rural societies, having in common the patriarchal family [3]. Functional rhythms (sleep, food,

karger@karger.com
www.karger.com/ene

Correspondence to:
Edward B. Ziff, edward.ziff@nyulangone.org

work, rest) were dictated by environmental circumstances, particularly by light (day and night) and seasons. Most of the tasks required physical work and movement. Social interactions involved face-to-face encounter between people, mostly within geographically defined surroundings, favoring a degree of isolation of social groups and the preservation of customs and traditions [4, 5].

Now, in the last 200 years, new examples of durable cultural and technological changes are appearing that are stable and could also guide *H. sapiens* evolution through gene-culture coevolution. These cultural and technological changes include the Industrial Revolution, the advent of electricity, growing urbanization and motorized means of locomotion, etc., which have emerged and have already brought major transformations in a short period. These recent changes are comparable in the magnitude of their impact to those of the Neolithic period, when stable settlement in villages, growing of crops, domestication of livestock, and the use of pottery and polished stone tools were established [6].

The challenges that have arisen in the past 20 years and particularly in the last 2 years of the pandemic transcend in speed and dimension previous developments in mankind's history. There is less face-to-face interaction, less exposure to light, less uniformity in sleep hours, less cohesion between geographically organized groups (school, church, neighborhood, city), and probably less cultural identification [5, 7]. Access to goods and the provision of services has expanded and has been diluted in a myriad of anonymous possibilities. The opportunities for spatial displacement (travel, change), but also for social interaction and affinity (belonging to a new political, religious, or sexual group), make the elements that determine the way of life and self-identity themselves transient and replaceable.

The brain of contemporary man is also continually flooded with information, which creates a need for a high capacity to filter, select, process, and synthesize multiple types of information [8–11]. While being suffocated by new cognitive challenges, contemporary man is deprived of stimuli that are biologically fundamental to his health and survival, such as movement, light, regularity of biological rhythms, and social contact. Environmental enrichment is well known to enhance neurophysiological plasticity, and to induce neurogenesis in hippocampus, a brain region fundamental to memory formation [12], and it can also enhance personal characteristics that distinguish one as an individual [13]. However, the new generations are developing within a state of need and deprivation. While from one perspective, we live in extremely enriched environments with a huge number of cognitive stimuli, at the same time, we lack beneficial physical and natural stimuli and social interactions.

Our Proposal

This essay examines, in light of the concepts of evolution, epigenetics, and neuroplasticity, the possible neurobiological repercussions of the current social transformation (Fig. 1). It is known that the brain is plastic and responds to the environment with neurochemical and structural changes. Changes also happen at the genetic level by mutational and epigenetic mechanisms [14]. Of particular relevance are the epigenetic mechanisms, which alter gene expression without altering protein-encoding DNA sequences. Although not yet fully evaluated for their role in human evolution [15], epigenetic mechanisms can be induced rapidly and are thought to link environmental stimuli to changes in gene expression that generate neuroplasticity [16, 17]. Thus, it is not unreasonable to suppose that the present social context is already promoting neurobiological evolutionary adaptations following on from the current modern man, *H. sapiens*, possibly conferring unprecedented skills, but also with possible shortcomings, weaknesses, and other difficulties that should now be considered and prevented.

Many speculations about the future of *H. sapiens* evolution are extrapolations of changes that are already in progress, such as changes in stature, brain volume, and skeletal frame [18, 19]. Our proposal is more radical and depends on new views of the mechanism of human evolution. Until recently, the modern synthesis [20] has been the widely accepted evolutionary theory and is a union of Darwinian species evolution with Mendelian gene inheritance. However, it is now evident that human evolution is much more complex and is also guided by non-Darwinian processes, including epigenetic [21] and social and abiotic and cultural mechanisms [22], greatly expanding the means by which human evolution may proceed.

We consider that adaptive human evolution will advance the human qualities of creativity and adaptability but may also have deleterious outcomes, such as increasing neurological disease. We cannot say accurately what will result except that given the discord between current pressures and those of the past, the human species will evolve and that its evolution may accelerate.

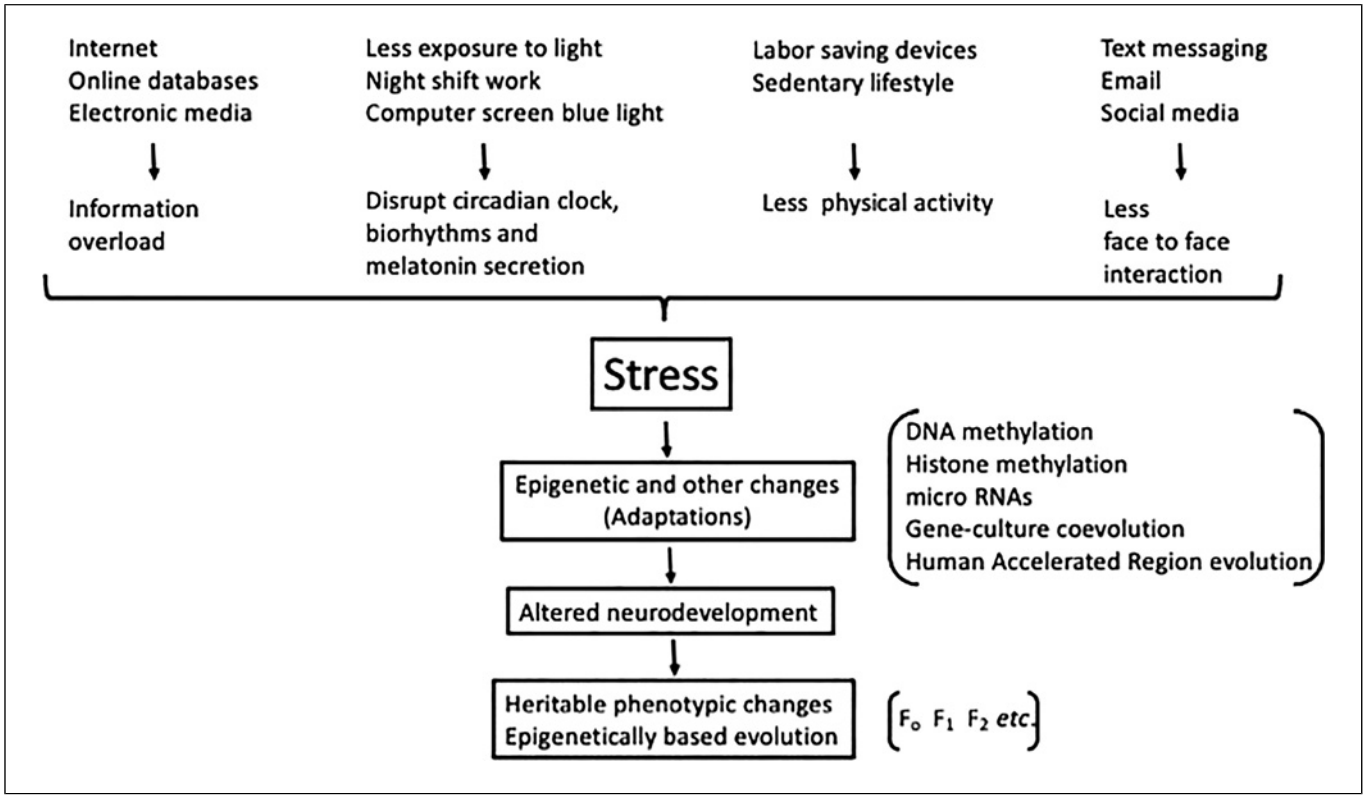

Fig. 1. Hypothetical pathway of adaptation to contemporary environmental challenges. Various contemporary forces (internet, less exposure to light, etc.) exert biological and social pressures (information overload, disrupted circadian clock, etc.) that have physiological consequences, collectively referred to as stress, that influence evolution by epigenetic and other mechanisms, resulting in altered neurodevelopment and heritable phenotypic change. See text.

Perspective on Concepts of Human Evolution and Genetics

Our understanding of how species evolve has changed dramatically since the time of Charles Darwin's natural selection theory. Darwin's theory holds that variants in the population arise at random and are subjected to selective pressures of the environment, which favor the variants that provide the best adaptation, thus promoting the appearance of new life forms. The laws of inheritance of Gregor Mendel placed Darwinian evolution into a functional perspective and stated that genes are unitary and come in pairs that are inherited, one from each parent. The modern synthesis is a fusion of these two processes in which evolution takes place through gradualism, a slow, sustained, and incremental process of selection that occurs gene by gene, and incorporates small, successive changes in phenotype [23]. Punctuated equilibrium is an alternative to gradualism proposed by and Gould and Eldredge [24]. In punctuated equilibrium, organisms evolve rapidly during periods of great selective pressure, which are followed by lengthy periods of evolutionary stasis (lack of change) [25]. Because random mutations that are the substrate for Darwinian selection are rare [26], evolution by this process alone will be slow [27].

Lamarck, Epigenetics, and Control of the Flow of Genetic Information

In the early 19th century, the French biologist, Jean-Baptiste Lamarck, proposed a mechanism for evolution quite different from Darwin's. Lamarck argued that organ development would be proportional to the extent of organ use. He further proposed that organ changes acquired during an individual's lifetime could be preserved by transmission to the offspring [28, 29]. In Lamarckian theory, phenotypic changes arise from the interaction of the individual with the environment, while with Darwinian theory, they arise from random mutations. Auguste Weismann, a main critic of Lamarck, stated what

became known as Weismann's dogma, that the genetic formation of gametes (the germ cells) is not influenced by somatic cells (cells of the body), and that the characteristics acquired by the soma of an individual cannot be transferred to the germ cells, the cells that will give rise to the next generation [30]. Long-term transmission of Lamarckian adaptations requires such transfer. Epigenetic mechanisms, which were unknown at that time, could however be a basis for Lamarckian inheritance.

Mechanisms of Epigenetic Control

Epigenetic changes – also called epigenetic marks – modify the utilization of genetic information rather than modifying the information itself, as would arise from Darwinian mutations of DNA nucleotide sequences. Rather than altering the structure of the protein that a gene encodes, epigenetic mechanisms change the levels or circumstances of gene and protein expression. Three distinct epigenetic mechanisms have been described.

DNA Methylation

DNA methylation modifies the chemical structure of particular bases in DNA. Most frequent is the conversion of cytosine to methyl-cytosine by the addition of a single-carbon methyl group to the base, cytosine. Methylation can alter the binding to DNA of proteins that regulate gene activity and thereby change gene expression, yet leave the protein-encoding information of the DNA intact [31].

Histone Modification

The second epigenetic mechanism is the methylation and acetylation of histones, which are the proteins that pack DNA into chromatin [32]. Methylation and acetylation regulate chromatin compaction and thereby alter the ability of the transcriptional machinery to access DNA, which can turn gene expression on and off [33], a form of epigenetic control.

Regulatory RNAs

With the third epigenetic mechanism, specialized RNAs turn off gene activity by inducing the degradation of specific messenger RNAs (mRNAs) [34]. In the degradation mechanism, a large RNA that does not code for protein (a long noncoding RNA) is transcribed and processed to yield a small RNA, called a micro-RNA, that associates by base pairing with one or more specific mRNAs [35]. Upon binding of the micro-RNA to a mRNA, the mRNA is degraded, which silences the gene. This mechanism is epigenetic because the expression of the gene is regulated while the base sequence of DNA is not modified.

These epigenetic modifications are, in particular instances, heritable [36]. When cells divide, the epigenetic marks may be maintained by reproducing the old methylation and acetylation patterns on the new DNA strands and histones. Micro-RNAs can partition between the daughter cells during cell division and thereby be inherited. Somatic cells can release micro-RNAs within small extracellular vesicles called exosomes that transport the micro-RNAs to other cells [37] including to the gametes (sperm or egg) [38]. Following fertilization, such micro-RNAs may be amplified in somatic cells of the developing embryo, thereby passing the epigenetic gene regulatory functions of the micro-RNAs to the offspring [39].

Basis for Evolution of *H. sapiens* and Disappearance of *Homo neanderthalensis*

How did today's *H. sapiens* evolve? The evolution of *H. sapiens* can be traced to the divergence of the Hominin family (the family to which humans belong) from the great ape family, between 9.3 and 6.5 million years ago [40]. Within the Hominin family is the genus *Homo* and within *Homo*, the species, *H. sapiens*. *Homo* consists of numerous other species besides *H. sapiens*, as many as 15, with *H. sapiens* being the only one that is not extinct [41]. *Homo habilis* (handyman) was the earliest known species of *Homo* and gave rise about 1.9 million years ago to *Homo erectus* (standing man) [42]. Yet other species of *Homo* evolved before *H. sapiens*, which was first observed about 300,000 years ago.

Insights into the basis for *H. sapiens* survival and domination of the natural world, while all other *Homo* species perished, come from a comparison of *H. sapiens* evolution with the evolution of *H. neanderthalensis*, more commonly called Neanderthal man. These two hominids are thought to have evolved from a common ancestor more than 500,000 years ago, and the two species lived apart, with *H. sapiens* localized to Africa, while Neanderthal lived in Europe and Western Asia [43]. The anthropological record suggests that by 40,000 years ago, modern man was flourishing but Neanderthal had become extinct.

Neanderthal and *H. sapiens* coexisted for nearly 400,000 years in Europe and Asia [44]. As discussed by Zwir et al. [45], Neanderthal was a capable toolmaker and was superior in hunting large animals, while *H. sapiens* lived in larger social groups, carried out trade and

commerce with others who were not their kin, and developed figurative art. *H. sapiens* advanced socially, evolved more varied diets, began to accumulate cultural knowledge and standardized technology, expressed themselves artistically, and had longer lifespans. *H. sapiens* with these advanced capabilities appeared first in Africa and spread throughout the continent. By 100,000 years ago, *H. sapiens* had evolved at the cognitive and social levels and in their adaptability to a challenging environment [45]. Adaptability enabled *H. sapiens* to migrate as the climate changed, so it could flourish in new locations. By 50,000 years ago, through a combination of social and neurobiological advances, they displayed creative imagination similar to that of modern humans.

Insight into Human Evolution from Genome Comparisons

Comparison of the genome of *H. sapiens* with the genomes of Neanderthal and chimpanzee, the two hominids closest to modern man [45] have provided insight into the genetic basis for the flourishing of *H. sapiens*. First, by correlating single-nucleotide polymorphisms in the genome sequences of over 4,000 Germans, Finns, and Koreans with their psychological profiles, researchers at Washington University in St. Louis identified networks of genes that were linked to specific aspects of human personality: emotional reactivity, self-control, and self-awareness. Notably, over one-third of the genes in these networks were absent in the genomes of Neanderthal and chimpanzees. Many corresponded to long noncoding RNAs, and many fell in gene clusters that were expressed in relevant brain regions. Overall, the study suggested that modern humans evolved a capacity for flexible thinking that provided *H. sapiens* with novel creativity and social awareness. Indeed, one of the most unique qualities of humankind is the capacity for learning and adaptation. We are able to survive in the desert but also in the forest. Our brain not only has circuits for innate behavior, but is built in a way so that it can contain many networks with multimodal functions, ones that can work in different ways [46, 47].

Recent Evolution of *H. Sapiens*

H. sapiens continues to evolve, and human genome mutations have been identified that arose during what is regarded as recent evolutionary time, within the past 10,000 years, and that adapted humans to local environments. These include a mutation that confers the ability to metabolize lactose as an adult [48], which is discussed below, plus other recent mutations that confer resistance to pathogenic environments such as posed by malarial parasites and trypanosomes, and other mutations for high-altitude survival in oxygen-deficient regions, and yet others for resistance to arsenic found in ground water. Of note are mutations in genes that determine skin color and that adapt the individual to high UV light levels (darker skin) versus the ability to produce vitamin D (lighter skin) [49].

These examples support continued evolution of *H. sapiens*, however with a time scale of thousands of years, which corresponds more closely to classical Darwinian evolution, rather than the rapid evolution we propose. Is there an example of rapid human evolution driven by the environment that could support our proposal for evolution driven by contemporary social forces?

A Role for Epigenetics in Rapid Evolution: The Hunger Winter

A striking example of epigenetic control by the environment, in which stress, nutrition, and mother's health together epigenetically influenced offspring, arose during the winter of 1944–1945, when a great famine struck parts of the Netherlands that were under German occupation [50, 51]. Although after the end of the war the food supply was restored, it soon became clear that children born to malnourished mothers continued to feel the effects of famine and suffered completely unexpected impacts. As these children grew into adulthood, the "children of the Hunger Winter" were plagued by brain dysfunctions, including cognitive impairment, antisocial behavior, depression, and schizophrenia, as well as by heart disease and obesity [52, 53]. It seemed that the stress of prenatal nutrient scarcity had caused profound and lasting changes in the growth and functioning of the brain, even when food intake had returned to normal.

Maternal nutrition has profound effects on fetal development [54], and it can be speculated that during intrauterine development, epigenetic adaptation mechanisms that control gene expression were triggered in the brains of the unborn Dutch children because developmental mechanisms had predicted a future environment of scarcity based on the scarcity of nutrition during the famine. This, however, turned out to be a biological error since actually the food supply returned to normal, but nevertheless, gene expression did not revert to the original.

In search of an explanation, researchers at the University of Leiden examined the DNA of the Hunger Winter children and found that prenatal food scarcity caused the promotor of the gene encoding the receptor

for glucocorticoids (GCs) to be methylated, which silenced the gene and shut down expression of the GC receptor protein [55]. GCs are stress hormones that adapt bodily functions to contend with stressful situations. Levels of GCs are governed by a feedback pathway in which GCs repress their own expression by a mechanism dependent on GC binding to the glucocorticoid receptor (GR) [56]. In the absence of normal GR expression, as was the case for the Hunger Winter offspring, the body cannot limit the levels of GCs in the bloodstream. The resulting high GC levels alter embryonic development of the brain and other somatic tissues, leading to higher risk for heart disease, obesity, and schizophrenia in the adult. Below, we discuss the transgenerational transmission of such effects [57].

The modern-day pandemic is a counterpart of the Hunger Winter and a source of stress because of the threat of dying, the threat of losing loved ones, the threats of the social system breaking down (financial chaos, health care chaos), and confinement (loss of social activities, routine, breakdown of social networks, and daily encounters), which cause anxiety and depression. Thus, the fate of the Hunger Winter children may have relevance for today.

The concept of epigenetic reprogramming, as occurred with the Hunger Winter children, suggests a new relationship between environment, mother, and fetus, in which the mother reprograms the development of her descendants by epigenetic mechanisms to prepare the offspring for coming environments. The existence of such pathways provides a mechanistic basis for regulating the human phenotype in response to today's social forces.

The Contemporary Forces That May Drive Evolution

What exactly are the new forces in contemporary society that we propose will redirect human evolution and are responses to these forces under gene control that could be reprogrammed? We suggest three such forces.

Less Physical Activity

Exercise has a well-known capacity to augment lifespan and cardiovascular health [58], and greater personal physical activity is thought to have provided *H. sapiens* a greater lifespan than its evolutionary precursors or modern-day primates. Using estimations of step counts per day (walking) as a measure of physical activity, and taking present-day hunter-gatherers to represent the lifestyle of early *H. sapiens*, it was found that early humans walked each day about three times as far as the great apes and the evolutionary ancestors of *H. sapiens* [59]. Selection for walking long distances and other forms of increased physical activity may account for the longer *H. sapiens* lifespan. However, in recent years, physical activity has decreased greatly because the modern lifestyle expressly reduces the physical effort required for daily life, leading to what has been called the "physical activity transition" [60]. This transition to lower activity may reduce longevity and create an evolutionary mismatch [59], which could eventually select for individuals whose longevity is not linked to physical exercise. Physical exercise regulates all forms of epigenetic marks (DNA methylation, histone acetylation and methylation, microRNA production) and thereby alters processes related to aging, muscle regeneration, cognition, obesity, and neurological disease [61]. Thus, a decrease in physical activity may influence many bodily processes including brain function through epigenetic mechanisms in a way that is potentially heritable.

Less Exposure to Light

Our ability to function day-to-day depends on circadian biorhythms, which are established by exposure to circadian light-dark cycles [62]. Because our metabolic needs vary periodically during the 24-h cycle, our functions related to nutrition display circadian control, which suggests that maintenance of metabolic and cardiac health requires adherence to the 24-h cycle. Significantly, disruption of the 24-h cycle by environmental factors such as night shift work [63], which requires observing work hours out of synchrony with the normal workday [64], jetlag, and restriction of sleep can cause cardiometabolic disorders, including elevated blood glucose levels and hypertension and increased risk of cancer and neuropsychiatric disorders [63, 65]. Other recent developments including our ability to communicate freely across the globe, to access information at all hours and to work outside the context of the usual workplace through use of the internet and home offices, compound this problem.

Technology can also disrupt circadian rhythms. Blue light is the spectral component of light that synchronizes body processes by suppressing the production of the sleep-inducing natural product, melatonin, during daytime [66]. Melatonin is normally produced as dusk approaches and natural light diminishes, whereupon melatonin promotes 24-h circadian synchrony and entry into the sleep state. Repeated blue light exposure, out of synchrony with the normal 24-h cycle, such as before bedtime (called artificial light at night), can suppress melatonin expression, disrupt circadian rhythms, and

impair sleep and cognitive functions [66]. Electronic media, such as computers, smartphones, tablets, etc., emit high levels of blue light and can reset circadian rhythms and also disrupt the biological clock [67]. For example, exposure to a white backlit tablet computer screen reduces melatonin production and disrupts the sleep-wake cycle and the predictability of the biological rhythms [66].

Less Face-to-Face Social Interaction and Changes in Social Roles

Humans are a highly prosocial species [68], and social isolation has strong effects on brain function [69]. The internet and social media have been particularly disruptive. Gen Z'ers (those born between mid to late 1990s and the early 2010s) report high levels of anxiety, depression, and distress resulting from excessive use of the internet and social media and are undergoing a mental health crisis [70]. Younger groups in affluent and privileged societies have a high rate of internet addiction, and during the pandemic, Gen Z'ers, who since childhood have used the internet, spent up to 10 h per day on social media, approximately twice as much as prior to the pandemic. Fifty percentage of this use is passive, such as scrolling through screens, which is particularly injurious to affective well-being and is correlated with impairment of feelings about self and with a decrease in overall satisfaction with life [71].

The New Course of Human Evolution

Could epigenetic mechanisms, which can act rapidly and respond to the environment and influence development, have effects that are inherited and play a role in *H. sapiens* evolution? Indeed, epigenetic changes can be inherited by two general types of mechanisms, as illustrated by rodent models. The first is intergenerational transmission, which is a form of inheritance in which a trait in a parent affects that trait in the offspring [72], such that transmission is, at a minimum, from parent to child. An example arises when a female pup (F_1 generation) is exposed to aggressive behavior or neglect by the mother (F_0) [73]. This maternal behavior induces an epigenetic change in somatic cells of the female pup (F_1), presumably in the brain, that leads it to also act aggressively when it reaches motherhood and to fail to groom or care for her own pups (F_2). Thus, aggressive behavior of the F_0 mother causes an epigenetic change in the F_1 generation pups, which causes them, upon maturation and motherhood, to repeat the mother's behavior and to fail to groom their own offspring (F_2). In this case, the epigenetic change is transmitted by a mother to her pups by means of an epigenetically determined behavior, failure to groom pups, a process that can act upon each generation. In this way, epigenetic mechanisms can be mediators of intergenerational effects of early life adversity [74].

With the second mode of transmission, transgenerational transmission, epigenetic markers are transmitted to multiple generations, independent of a requirement for a behavioral influence at each generation. This may take place when the environment induces an epigenetic change in somatic cells of a parent (F_0), that is, the expression of a particular micro-RNA, and the micro-RNA is transmitted by an exosome-mediated pathway, as discussed above, from the somatic cell to the germ cells of that individual, which makes possible transmission of the micro-RNA to the offspring (F_1). By repetition of this mechanism, the epigenetic mark and the consequences of its expression may be transmitted to future generations (F_2, F_3, etc.) in as much as it is passed through the germ line. In this case, there is no requirement for each generation to be exposed to the environmental factor [75].

Evidence is accumulating for epigenetic transmission of effects of stress that arises from human, traumatic historical events, including the holocaust, slavery, ethnic cleansing, and other instances in which human populations are subjected to oppression [76]. These examples of transmission of the effects of stress may have their basis in deregulation of GR expression, similar to what took place with the Hunger Winter children [77]. It is not fully established whether transmission of epigenetic effects of historical trauma takes place by intergenerational or transgenerational mechanisms.

Gene-Culture Coevolution and Niche Construction Theory

Could culturally based environmental pressures be a selective force in evolution? Although cultural factors are not traditionally thought to govern genetic evolution, our proposal requires that culture plays such a role. Gene-culture coevolutionary theory [78] and niche construction theory (NCT) [79] provide theoretical frameworks for this aspect of our proposal.

Gene-culture coevolution [80] posits that gene mutation can alter culture, and stable aspects of culture can contribute to a selective evolutionary environment that determines which genotypes survive and reproduce. An example of such a cultural factor is the practice of deforestation of land in Western Africa for use in farming, which causes the formation of pools of rainwater where mosquitoes can breed. The mosquitoes transmit malaria; however, the sickle cell mutation in the hemoglobin gene

in the hemizygous state protects against malaria. Therefore, deforestation, a cultural feature that leads to the breeding of mosquitoes, also leads to selection for the sickling mutation, an evolutionary change [81].

Another precedent for culture-based genetic evolution is the aforementioned selection for lactase gene mutation in dairy farming communities. Lactase is an enzyme that is required for metabolism of lactose, the major sugar in milk. In most mammals, lactase expression declines after infancy, making milk unsuitable as an adult nutritional source. However, in a proportion of humans, most frequently in persons of northern European descent, expression of lactase continues into adulthood, making milk suitable as a source of adult nutrition [48]. Mutations that maintain the activity of the lactase gene promoter in adulthood were strongly selected about 6000 years ago during the Neolithic period in European populations that domesticated cattle. Domestication of cattle created an environmental basis for selection for the lactase mutation, because in the context of cattle domestication, which is a feature of culture, the mutation made dairy products a new source of nutrition [48], an example of gene-culture coevolution.

NCT is a particular formulation of gene-culture coevolution in which the organism guides its own evolution by establishing aspects of culture or the physical environment that provide evolutionary selection and genetic evolution [82]. NCT provides a basis for our proposal that aspects of the modern culture, such as excess use of the internet, can provide selective pressures for *H. sapiens* evolution.

More generally, evolutionary theorists Eva Jablonka and Marion Lamb have proposed broad interactions between social and cultural factors and epigenetic mechanisms, with each modifying the other. Social factors such as sexual behavior, exercise, social stress, consumption of alcohol, smoking, lack of physical activity, and performing shift work activate epigenetic pathways that change gene expression [22, 83].

Stress, Allostasis, and Mechanisms of Evolution Driven by the New Environmental Forces

We propose a role for stress in ongoing human evolution because the new environmental factors that we cite disrupt the norms of society and dislocate individuals from their daily routines and social interactions. We are creating urbane cultures where a person has a weaker connection to family members and neighborhood. People spend more hours alone. We are less supported by strong and lasting attachments – romantic attachments, but also time spent with parents and friends. In past generations, family groups kept together for decades, such as when living on the same farm, a practice that has waned.

Stress has an impact on physiological processes in the human body, and the researcher of environmental stress, the late Bruce McEwen, described mechanisms, called allostatic mechanisms, that maintain these physiological processes at their optimal, functional set points. When metabolic or other forces shift the processes away from their set points, allostatic mechanisms restore the processes to the set points to maintain the activities of interlocking metabolic and neuroendocrine system pathways within a functional range, a process described as "achieving stability through change" [84].

Significantly, allostatic return to a set point creates an expense to the body, such as an energy deficit or an activation of the immune system, a deficit that is called "allostatic load" [85]. Severe adverse conditions of stress, such as sleep deprivation, can cause allostatic overload that disrupts metabolic and neuroendocrine functions and can increase metabolic syndrome, including type II diabetes [86], a situation reminiscent of the plight of the Hunger Winter children. Similarly, when societal processes are displaced from their set points, social allostasis can restore the set point, but with a social expense and the induction of social allostatic load [87]. Social allostatic load may be induced by income-based challenges leading to food scarcity, poverty, and ultimately violence and social exclusion. We suggest that social allostatic load may also be induced by the societal changes we have described and be a basis for human evolution.

The body's response to stress involves the autonomic nervous system and the hypothalamic pituitary adrenal axis. The first releases catecholamines (adrenalin) to prepare for fight or flight, and the second releases GCs (cortisol), which provides a long-term response to distress. These neuro-modulators regulate brain regions associated with emotional reactivity, such as the amygdala, and others associated with executive function, such as the prefrontal cortex. Blair and Ku [88] argue that stress, if long-lasting, could alter the sensitivity of these brain systems to GCs and catecholamines, as seen in the Hunger Winter children, and the altered sensitivity could represent a human evolutionary change.

A Mutational Basis for the Proposed Rapid Brain Evolution

We have discussed how *H. sapiens* survival has been promoted by evolutionary increases in human adaptability and ingenuity, which suggests that were brain evolution to continue through similar changes, the evolution could help us to contend with the new challenges. However, enhancement of complex brain functions, such as cognitive processes, may encounter evolutionary barriers because

they require changes in subtle aspects of brain development or function, and these may only be achieved through mutation of multiple genes with interrelated functions [89]. One mechanism for overcoming this barrier relies on the presence, in the general population, of a pool of alleles of genes that encode brain-related functions, with each gene being represented by several alleles [90]. Reassortment of allelic variants of multiple genes for brain functions could take place in a small number of generations and could provide phenotypic variation that speeds human brain evolution. A newly discovered class of regulatory DNA sequences called human-accelerated regions (HARs) offers a mechanism for this reassortment and selection [91]. HARs are DNA sequences approximately 200–300 nucleotides long that have evolved rapidly in humans [91–93]. Many HARs are enhancers [92], regulatory elements that bind transcription factors that control gene activity, and a high proportion of them regulates genes for brain development or function [94–96]. HAR sequence differences appear to cause subtle changes in expression of genes under control of the HAR [97], and thus, HAR structural variability may create multiple alleles for a particular gene, with each allele displaying a somewhat different pattern of expression. Reassortment of such alleles of genes for brain function would provide a rich supply of new brain phenotypes that would be subject to selection, thereby speeding human brain evolution [94].

Conclusions

Social and technological changes that disrupt an individual's medical, psychological, and environmental norms are likely to exert strong selective pressures that ultimately alter human behavior in a heritable way. Because environmental adversity, social stress, and traumatic experiences are recognized to induce such heritable changes [98], they could well provide a basis for adaptive evolution.

What period of time would the proposed evolution require and which genes would be involved? The epigenetic effects of the Hunger Winter took place in one generation, and a variety of mechanisms could provide phenotypic diversity within in a small number of generations [99]. Genes that control metabolic pathways that modify the response to stress or to allostatic overload or that decrease the dependence of cardiovascular health on physical exercise may evolve. Indeed, genes that respond to exercise and resistance training have been identified [100]. Other changes may uncouple individuals from circadian rhythms, enhance information processing by the brain, or decrease dependence of emotional reward on social interactions. However, nonadaptive epigenetic modifications could also arise and increase rates of neurological disease. A computational analysis indicated that the rate of evolution of genes for polygenic diseases exceeds the rate for monogenic disorders, which exceeds the rate for housekeeping genes [101].

We may expect that behavioral changes propagated by cultural institutions, like social media, will have a very strong influence on the *H. sapiens* phenotype. However, these changes will not bring our society to an end, and we will not perish because of lack of sunlight or exercise or face-to-face contact. It is our behavior that will change, and we will evolve other needs and even other abilities. Also, the outcome will not only be negative. We may gain new creativity and adaptability, in a manner paralleling the early *H. sapiens*. Also, we do not suggest that changes will take place in a catastrophic way, and our suggestions have no moral or ethical sense. We only make the observation that these changes in relationships can take place by a form of gene-culture coevolution more rapidly than we can account for by classical evolutionary mechanisms and that the changes can accelerate because of today's social pressures.

We suggest, in a provocative way, that this process could affect speciation within the genus, *Homo*, which would, of course, require a very lengthy period of time. It is more probable that *H. sapiens* will adapt rather than evolving into an altogether new species. We cannot judge the course of such evolution; however, we suggest that present-day social change is providing new bases for selection, and in the face of such strong, selective pressures, evolution may proceed rapidly. Close observation of our society and future research may reveal the possible gains and possible losses in this process.

Conflict of Interest Statement

The authors declare that they have no competing interests.

Funding Sources

The authors declare that neither author has received funding for this project or for any related project.

Author Contributions

E.C.K. proposed the subject of the review, and both E.C.K. and E.B.Z. wrote the manuscript.

References

1 Hajek A, König H-H. Social isolation and loneliness of older adults in times of the COVID-19 pandemic: can use of online social media sites and video chats assist in mitigating social isolation and loneliness? Gerontology. 2021;67(1):121–4. https://doi.org/10.1159/000512793
2 Hamilton JL, Nesi J, Choukas-Bradley S. Reexamining social media and socioemotional well-being among adolescents through the lens of the COVID-19 pandemic: a theoretical review and directions for future research. Perspect Psychol Sci. 2022;17(3):662–79. https://doi.org/10.1177/17456916211014189
3 Boyd R, Richerson PJ. Large-scale cooperation in small-scale foraging societies. Evol Anthropol. 2022;31(4):175–98. https://doi.org/10.1002/evan.21944
4 Shultz S, Opie C, Atkinson QD. Stepwise evolution of stable sociality in primates. Nature. 2011;479(7372):219–22. https://doi.org/10.1038/nature10601
5 Wolfers LN, Utz S. Social media use, stress, and coping. Curr Opin Psychol. 2022;45:101305. https://doi.org/10.1016/j.copsyc.2022.101305
6 Çilingiroğlu C. The concept of "Neolithic package": considering its meaning and applicability. Doc Praehist. 2005;32:1–13. https://doi.org/10.4312/dp.32.1
7 Chen W, Lee K-H. Sharing, liking, commenting, and distressed? The pathway between Facebook interaction and psychological distress. Cyberpsychol Behav Soc Netw. 2013;16(10):728–34. https://doi.org/10.1089/cyber.2012.0272
8 Klingberg T. The overflowing brain: information overload and the limits of working memory. Oxford, USA: Oxford University Press; 2008.
9 Broad KD, Rocha-Ferreira E, Hristova M. Placental, matrilineal, and epigenetic mechanisms promoting environmentally adaptive development of the mammalian brain. Neural Plast. 2016;2016:6827135. https://doi.org/10.1155/2016/6827135
10 Steele RG, Hall JA, Christofferson JL. Conceptualizing digital stress in adolescents and young adults: toward the development of an empirically based model. Clin Child Fam Psychol Rev. 2020;23(1):15–26. https://doi.org/10.1007/s10567-019-00300-5
11 Arnold M, Goldschmitt M, Rigotti T. Dealing with information overload: a comprehensive review. Front Psychol. 2023;14:1122200. https://doi.org/10.3389/fpsyg.2023.1122200
12 Ohline SM, Abraham WC. Environmental enrichment effects on synaptic and cellular physiology of hippocampal neurons. Neuropharmacology. 2019;145(Pt A):3–12. https://doi.org/10.1016/j.neuropharm.2018.04.007
13 Kempermann G. Environmental enrichment, new neurons and the neurobiology of individuality. Nat Rev Neurosci. 2019;20(4):235–45. https://doi.org/10.1038/s41583-019-0120-x
14 Berger SL, Kouzarides T, Shiekhattar R, Shilatifard A. An operational definition of epigenetics. Genes Dev. 2009;23(7):781–3. https://doi.org/10.1101/gad.1787609
15 Burggren W. Epigenetic inheritance and its role in evolutionary biology: Re-evaluation and new perspectives. Biology. 2016;5(2):24. https://doi.org/10.3390/biology5020024
16 Levenson JM, Sweatt JD. Epigenetic mechanisms in memory formation. Nat Rev Neurosci. 2005;6(2):108–18. https://doi.org/10.1038/nrn1604
17 Shang A, Bieszczad KM. Epigenetic mechanisms regulate cue memory underlying discriminative behavior. Neurosci Biobehav Rev. 2022;141:104811. https://doi.org/10.1016/j.neubiorev.2022.104811
18 Ruff CB, Trinkaus E, Holliday TW. Body mass and encephalization in Pleistocene Homo. Nature. 1997;387(6629):173–6. https://doi.org/10.1038/387173a0
19 Stibel JM. Decreases in brain size and encephalization in anatomically modern humans. Brain Behav Evol. 2021;96(2):64–77. https://doi.org/10.1159/000519504
20 Huxley A. Evolution: the modern synthesis. London: Unwin; 1942.
21 Mathov Y, Batyrev D, Meshorer E, Carmel L. Harnessing epigenetics to study human evolution. Curr Opin Genet Dev. 2020;62:23–9. https://doi.org/10.1016/j.gde.2020.05.023
22 Jablonka E, Lamb MJ. Evolution in four dimensions: genetic, epigenetic, behavioral, and symbolic variation in the history of life. Revised ed. Cambridge, Massachusetts: The MIT Press; 2014.
23 Saunders P. Random variations, gradualism and the role of natural selection. Theor Biol Forum. 2021;114(2):27–39. https://doi.org/10.19272/202111402003
24 Gould SJ, Eldredge N. Punctuated equilibrium comes of age. Nature. 1993;366(6452):223–7. https://doi.org/10.1038/366223a0
25 Pagel M, O'Donovan C, Meade A. General statistical model shows that macroevolutionary patterns and processes are consistent with Darwinian gradualism. Nat Commun. 2022;13(1):1113. https://doi.org/10.1038/s41467-022-28595-z
26 Orr HA. The population genetics of beneficial mutations. Philos Trans R Soc Lond B Biol Sci. 2010;365(1544):1195–201. https://doi.org/10.1098/rstb.2009.0282
27 Scally A, Durbin R. Revising the human mutation rate: implications for understanding human evolution. Nat Rev Genet. 2012;13(10):745–53. https://doi.org/10.1038/nrg3295
28 Burkhardt RW Jr. Lamarck, evolution, and the inheritance of acquired characters. Genetics. 2013;194(4):793–805. https://doi.org/10.1534/genetics.113.151852
29 Skinner MK, Nilsson EE. Role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology: unified evolution theory. Environ Epigenet. 2021;7(1):dvab012. https://doi.org/10.1093/eep/dvab012
30 Bline AP, Le Goff A, Allard P. What is lost in the Weismann barrier? J Dev Biol. 2020;8(4):35. https://doi.org/10.3390/jdb8040035
31 Mattei AL, Bailly N, Meissner A. DNA methylation: a historical perspective. Trends Genet. 2022;38(7):676–707. https://doi.org/10.1016/j.tig.2022.03.010
32 Zhang Y, Sun Z, Jia J, Du T, Zhang N, Tang Y, et al. Overview of histone modification. Adv Exp Med Biol. 2021;1283:1–16. https://doi.org/10.1007/978-981-15-8104-5_1
33 Francis NJ, Kingston RE, Woodcock CL. Chromatin compaction by a polycomb group protein complex. Science. 2004;306(5701):1574–7. https://doi.org/10.1126/science.1100576
34 Statello L, Guo C-J, Chen L-L, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cel Biol. 2021;22(2):96–118. https://doi.org/10.1038/s41580-020-00315-9
35 Filipowicz W, Bhattacharyya SN, Sonenberg N. Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? Nat Rev Genet. 2008;9(2):102–14. https://doi.org/10.1038/nrg2290
36 Bošković A, Rando OJ. Transgenerational epigenetic inheritance. Annu Rev Genet. 2018;52:21–41. https://doi.org/10.1146/annurev-genet-120417-031404
37 Valadi H, Ekström K, Bossios A, Sjöstrand M, Lee JJ, Lötvall JO. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cel Biol. 2007;9(6):654–9. https://doi.org/10.1038/ncb1596
38 Reilly JN, McLaughlin EA, Stanger SJ, Anderson AL, Hutcheon K, Church K, et al. Characterisation of mouse epididymosomes reveals a complex profile of microRNAs and a potential mechanism for modification of the sperm epigenome. Sci Rep. 2016;6:31794. https://doi.org/10.1038/srep31794
39 Sharma U. Paternal contributions to offspring health: role of sperm small RNAs in intergenerational transmission of epigenetic information. Front Cel Dev Biol. 2019;7:215. https://doi.org/10.3389/fcell.2019.00215
40 Almécija S, Hammond AS, Thompson NE, Pugh KD, Moyà-Solà S, Alba DM. Fossil apes and human evolution. Science. 2021;372(6542):eabb4363. https://doi.org/10.1126/science.abb4363

41 Wood B, Collard M. The human genus. Science. 1999;284(5411):65–71. https://doi.org/10.1126/science.284.5411.65
42 Wood B. Human evolution. Bioessays. 1996;18(12):945–54. https://doi.org/10.1002/bies.950181204
43 Nielsen R, Akey JM, Jakobsson M, Pritchard JK, Tishkoff S, Willerslev E. Tracing the peopling of the world through genomics. Nature. 2017;541(7637):302–10. https://doi.org/10.1038/nature21347
44 Herrera KJ, Somarelli JA, Lowery RK, Herrera RJ. To what extent did Neanderthals and modern humans interact? Biol Rev Camb Philos Soc. 2009;84(2):245–57. https://doi.org/10.1111/j.1469-185x.2008.00071.x
45 Zwir I, Del-Val C, Hintsanen M, Cloninger KM, Romero-Zaliz R, Mesa A, et al. Evolution of genetic networks for human creativity. Mol Psychiatry. 2022;27(1):354–76. https://doi.org/10.1038/s41380-021-01097-y
46 Sporns O. The complex brain: connectivity, dynamics, information. Trends Cogn Sci. 2022;26(12):1066–7. https://doi.org/10.1016/j.tics.2022.08.002
47 Thiebaut de Schotten M, Forkel SJ. The emergent properties of the connected brain. Science. 2022;378(6619):505–10. https://doi.org/10.1126/science.abq2591
48 Gerbault P, Liebert A, Itan Y, Powell A, Currat M, Burger J, et al. Evolution of lactase persistence: an example of human niche construction. Philos Trans R Soc Lond B Biol Sci. 2011;366(1566):863–77. https://doi.org/10.1098/rstb.2010.0268
49 Fan S, Hansen MEB, Lo Y, Tishkoff SA. Going global by adapting local: a review of recent human adaptation. Science. 2016;354(6308):54–9. https://doi.org/10.1126/science.aaf5098
50 Lumey LH, Ravelli ACJ, Wiessing LG, Koppe JG, Treffers PE, Stein ZA. The Dutch famine birth cohort study: design, validation of exposure, and selected characteristics of subjects after 43 years follow-up. Paediatr Perinat Epidemiol. 1993;7(4):354–67. https://doi.org/10.1111/j.1365-3016.1993.tb00415.x
51 Rosenfield I, Ziff EB. Epigenetics: the evolution revolution. New York Review of Books; 2018.
52 Painter RC, Roseboom TJ, Bleker OP. Prenatal exposure to the Dutch famine and disease in later life: an overview. Reprod Toxicol. 2005;20(3):345–52. https://doi.org/10.1016/j.reprotox.2005.04.005
53 Roseboom TJ, Painter RC, van Abeelen AFM, Veenendaal MVE, de Rooij SR. Hungry in the womb: what are the consequences? Lessons from the Dutch famine. Maturitas. 2011;70(2):141–5. https://doi.org/10.1016/j.maturitas.2011.06.017
54 Wang J, Wu Z, Li D, Li N, Dindot SV, Satterfield MC, et al. Nutrition, epigenetics, and metabolic syndrome. Antioxid Redox Signal. 2012;17(2):282–301. https://doi.org/10.1089/ars.2011.4381
55 Tobi EW, Goeman JJ, Monajemi R, Gu H, Putter H, Zhang Y, et al. DNA methylation signatures link prenatal famine exposure to growth and metabolism. Nat Commun. 2014;5:5592. https://doi.org/10.1038/ncomms6592
56 Timmermans S, Souffriau J, Libert C. A general introduction to glucocorticoid biology. Front Immunol. 2019;10:1545. https://doi.org/10.3389/fimmu.2019.01545
57 Stenz L, Schechter DS, Serpa SR, Paoloni-Giacobino A. Intergenerational transmission of DNA methylation signatures associated with early life stress. Curr Genomics. 2018;19(8):665–75. https://doi.org/10.2174/1389202919666171229145656
58 Pinckard K, Baskin KK, Stanford KI. Effects of exercise to improve cardiovascular health. Front Cardiovasc Med. 2019;6:69. https://doi.org/10.3389/fcvm.2019.00069
59 Raichlen DA, Lieberman DE. The evolution of human step counts and its association with the risk of chronic disease. Curr Biol. 2022;32(21):R1206–R1214. https://doi.org/10.1016/j.cub.2022.09.030
60 Katzmarzyk PT, Mason C. The physical activity transition. J Phys Act Health. 2009;6(3):269–80. https://doi.org/10.1123/jpah.6.3.269
61 Fernandes J, Arida RM, Gomez-Pinilla F. Physical exercise as an epigenetic modulator of brain plasticity and cognition. Neurosci Biobehav Rev. 2017;80:443–56. https://doi.org/10.1016/j.neubiorev.2017.06.012
62 Patke A, Young MW, Axelrod S. Molecular mechanisms and physiological importance of circadian rhythms. Nat Rev Mol Cel Biol. 2020;21(2):67–84. https://doi.org/10.1038/s41580-019-0179-2
63 Boivin DB, Boudreau P. Impacts of shift work on sleep and circadian rhythms. Pathol Biol. 2014;62(5):292–301. https://doi.org/10.1016/j.patbio.2014.08.001
64 Burgard SA, Lin KY. Bad jobs, bad health? How work and working conditions contribute to health disparities. Am Behav Sci. 2013;57(8):1105–27. https://doi.org/10.1177/0002764213487347
65 Duez H, Staels B. Nuclear receptors linking circadian rhythms and cardiometabolic control. Arterioscler Thromb Vasc Biol. 2010;30(8):1529–34. https://doi.org/10.1161/ATVBAHA.110.209098
66 Wahl S, Engelhardt M, Schaupp P, Lappe C, Ivanov IV. The inner clock-blue light sets the human rhythm. J Biophotonics. 2019;12(12):e201900102. https://doi.org/10.1002/jbio.201900102
67 Touitou Y, Touitou D, Reinberg A. Disruption of adolescents' circadian clock: the vicious circle of media use, exposure to light at night, sleep loss and risk behaviors. J Physiol Paris. 2016;110(4 Pt B):467–79. https://doi.org/10.1016/j.jphysparis.2017.05.001
68 Silk JB, House BR. Evolutionary foundations of human prosocial sentiments. Proc Natl Acad Sci USA. 2011;108(Suppl 2):10910–7. https://doi.org/10.1073/pnas.1100305108
69 House JS, Landis KR, Umberson D. Social relationships and health. Science. 1988;241(4865):540–5. https://doi.org/10.1126/science.3399889
70 Office of the Surgeon General (OSG). Social media and youth mental health. The U.S. surgeon general's advisory [Internet]. Washington (DC): US Department of Health and Human Services; 2023.
71 Verduyn P, Lee DS, Park J, Shablack H, Orvell A, Bayer J, et al. Passive Facebook usage undermines affective well-being: experimental and longitudinal evidence. J Exp Psychol Gen. 2015;144(2):480–8. https://doi.org/10.1037/xge0000057
72 Branje S, Geeraerts S, de Zeeuw EL, Oerlemans AM, Koopman-Verhoeff ME, Schulz S, et al. Intergenerational transmission: theoretical and methodological issues and an introduction to four Dutch cohorts. Dev Cogn Neurosci. 2020;45:100835. https://doi.org/10.1016/j.dcn.2020.100835
73 Jawaid A, Roszkowski M, Mansuy IM. Transgenerational epigenetics of traumatic stress. Prog Mol Biol Transl Sci. 2018;158:273–98. https://doi.org/10.1016/bs.pmbts.2018.03.003
74 Burenkova OV, Grigorenko EL. The role of epigenetic mechanisms in the long-term effects of early-life adversity and mother-infant relationship on physiology and behavior of offspring in laboratory rats and mice. Dev Psychobiol. 2024;66(3):e22479. https://doi.org/10.1002/dev.22479
75 Liberman N, Wang SY, Greer EL. Transgenerational epigenetic inheritance: from phenomena to molecular mechanisms. Curr Opin Neurobiol. 2019;59:189–206. https://doi.org/10.1016/j.conb.2019.09.012
76 Bowers ME, Yehuda R. Intergenerational transmission of stress in humans. Neuropsychopharmacology. 2016;41(1):232–44. https://doi.org/10.1038/npp.2015.247
77 Yehuda R, Lehrner A. Intergenerational transmission of trauma effects: putative role of epigenetic mechanisms. World Psychiatr. 2018;17(3):243–57. https://doi.org/10.1002/wps.20568
78 Waring TM, Wood ZT. Long-term gene-culture coevolution and the human evolutionary transition. Proc Biol Sci. 2021;288(1952):20210538. https://doi.org/10.1098/rspb.2021.0538
79 Laland K, Matthews B, Feldman MW. An introduction to niche construction theory. Evol Ecol. 2016;30:191–202. https://doi.org/10.1007/s10682-016-9821-z
80 Creanza N, Feldman MW. Worldwide genetic and cultural change in human evolution. Curr Opin Genet Dev. 2016;41:85–92. https://doi.org/10.1016/j.gde.2016.08.006

81 O'Brien MJ, Bentley RA. Genes, culture, and the human niche: an overview. Evol Anthropol. 2021;30(1):40–9. https://doi.org/10.1002/evan.21865
82 Laland K, Odling-Smee J, Endler J. Niche construction, sources of selection and trait coevolution. Interf Focus. 2017;7(5): 20160147. https://doi.org/10.1098/rsfs.2016.0147
83 Alegría-Torres JA, Baccarelli A, Bollati V. Epigenetics and lifestyle. Epigenomics. 2011; 3(3):267–77. https://doi.org/10.2217/epi.11.22
84 Duckworth D. Handbook of life stress, cognition and health. In: Fisher S, Reason J, editors. Chichester: J. Wiley Ltd.; 1988.
85 McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. Horm Behav. 2003;43(1):2–15. https://doi.org/10.1016/s0018-506x(02)00024-7
86 McEwen BS, Karatsoreos IN. Sleep deprivation and circadian disruption: stress, allostasis, and allostatic load. Sleep Med Clin. 2015;10(1):1–10. https://doi.org/10.1016/j.jsmc.2014.11.007
87 Saxbe DE, Beckes L, Stoycos SA, Coan JA. Social allostasis and social allostatic load: a new model for research in social dynamics, stress, and health. Perspect Psychol Sci. 2020;15(2):469–82. https://doi.org/10.1177/1745691619876528
88 Blair C, Ku S. A hierarchical integrated model of self-regulation. Front Psychol. 2022;13:725828. https://doi.org/10.3389/fpsyg.2022.725828
89 Fagny M, Austerlitz F. Polygenic adaptation: integrating population genetics and gene regulatory networks. Trends Genet. 2021; 37(7):631–8. https://doi.org/10.1016/j.tig.2021.03.005
90 Levchenko A, Kanapin A, Samsonova A, Gainetdinov RR. Human accelerated regions and other human-specific sequence variations in the context of evolution and their relevance for brain development. Genome Biol Evol. 2018;10(1):166–88. https://doi.org/10.1093/gbe/evx240
91 Pollard KS, Salama SR, King B, Kern AD, Dreszer T, Katzman S, et al. Forces shaping the fastest evolving regions in the human genome. PLoS Genet. 2006;2(10):e168. https://doi.org/10.1371/journal.pgen.0020168
92 Capra JA, Erwin GD, McKinsey G, Rubenstein JLR, Pollard KS. Many human accelerated regions are developmental enhancers. Philos Trans R Soc Lond B Biol Sci. 2013;368(1632):20130025. https://doi.org/10.1098/rstb.2013.0025
93 Whalen S, Pollard KS. Enhancer function and evolutionary roles of human accelerated regions. Annu Rev Genet. 2022;56:423–39. https://doi.org/10.1146/annurev-genet-071819-103933
94 Won H, Huang J, Opland CK, Hartl CL, Geschwind DH. Human evolved regulatory elements modulate genes involved in cortical expansion and neurodevelopmental disease susceptibility. Nat Commun. 2019; 10(1):2396. https://doi.org/10.1038/s41467-019-10248-3
95 Girskis KM, Stergachis AB, DeGennaro EM, Doan RN, Qian X, Johnson MB, et al. Rewiring of human neurodevelopmental gene regulatory programs by human accelerated regions. Neuron. 2021;109(20):3239–51.e7. https://doi.org/10.1016/j.neuron.2021.08.005
96 Guardiola-Ripoll M, Fatjo-Vilas M. A systematic review of the human accelerated regions in schizophrenia and related disorders: where the evolutionary and neurodevelopmental hypotheses converge. Int J Mol Sci. 2023;24(4):3597. https://doi.org/10.3390/ijms24043597
97 Khatoon H, Raza RZ, Saleem S, Batool F, Arshad S, Abrar M, et al. Evolutionary relevance of single nucleotide variants within the forebrain exclusive human accelerated enhancer regions. BMC Mol Cel Biol. 2023;24(1):13. https://doi.org/10.1186/s12860-023-00474-5
98 Roth TL. Epigenetic mechanisms in the development of behavior: advances, challenges, and future promises of a new field. Dev Psychopathol. 2013;25(4 Pt 2):1279–91. https://doi.org/10.1017/S0954579413000618
99 Xavier MJ, Roman SD, Aitken RJ, Nixon B. Transgenerational inheritance: how impacts to the epigenetic and genetic information of parents affect offspring health. Hum Reprod Update. 2019;25(5):519–41. https://doi.org/10.1093/humupd/dmz017
100 Coffey VG, Hawley JA. The molecular bases of training adaptation. Sports Med. 2007;37(9): 737–63. https://doi.org/10.2165/00007256-200737090-00001
101 Podder S, Ghosh TC. Exploring the differences in evolutionary rates between monogenic and polygenic disease genes in human. Mol Biol Evol. 2010;27(4): 934–41. https://doi.org/10.1093/molbev/msp297