Buried Treasure? Overlooked and Newly Discovered Evolutionary Contributions to Human Brain Diseases

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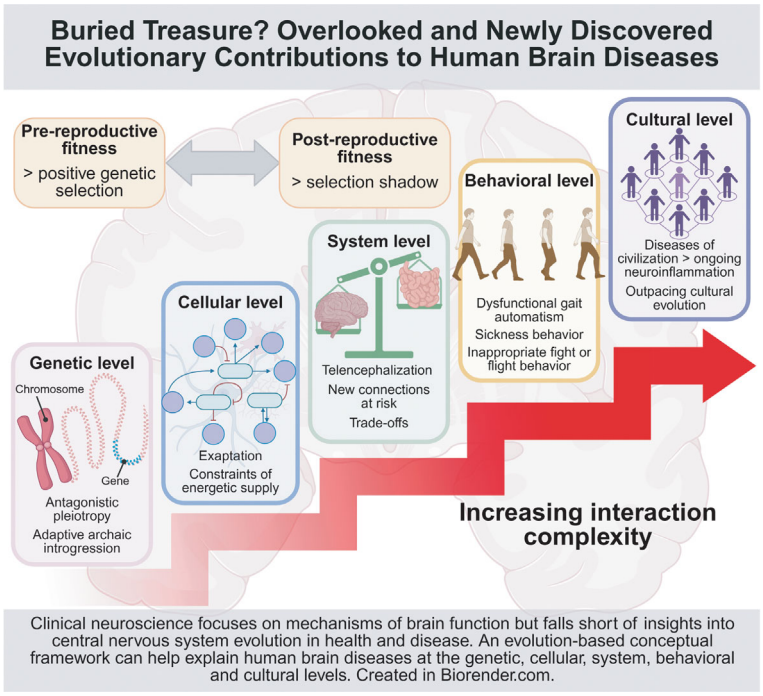

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Recapitulative schema of different exploratory levels of the evolutionary impact on human neurological diseases.

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Clinical neuroscience focuses on the mechanisms of brain function, but this approach falls short of insights into how the central nervous system (CNS) evolved, both in health and disease. Here, we discuss evolutionary concepts relevant to understanding human brain diseases, on the genetic, subcellular, cellular, connectomic, behavioral, and cultural levels. By revisiting common neurological diseases, we discuss evolved residues from our ancestors, mechanisms of exaptation, antagonistic pleiotropy, and human longevity with the consequent outpacing of biological evolution by cultural evolution. An evolution-based conceptual framework can propel transdisciplinary research targeting the constraints imposed by and compensatory adaptations involved in human-specific neurological diseases.

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Neurological research is increasingly successful in deciphering the pathophysiological cascades of neurological disorders. However, clinically useful concepts only deal with the "*proximate*" causes of brain diseases, which include (patho-)physiology as well as ontogeny of a given biological trait. "*Ultimate*" or evolutionary explanations, in addition, address the phylogeny or adaptive significance of relevant traits. The latter perspective is usually not considered in clinical contexts,[1] although natural selection imposed by evolution maximizes reproduction at the expense of health. For instance, as basal ganglia dysfunction, especially at the nigrostriatal level, mechanistically explains motor deficiencies in Parkinson's disease (PD) (proximate causation), the failure of conserved habitual patterns of behavior in this disease could reflect a trade-off or the limited ability of natural selection to optimize designs (ultimate level). Earlier considerations of the relevance of evolutionary theory for the understanding of neurological diseases have largely remained without any resonance,[2] and the study of neurological diseases lags behind evolutionary-informed research in psychiatry, although both disciplines overlap, to a certain degree, in dealing with dysfunction of the brain.[3,4] However, based on a book project and a conference on the evolutionary roots of human brain diseases, a group of experts from different disciplines compiled and synthesized the present article. The aim is to present salient clinical examples highlighting useful crosstalk between neurology and evolutionary biology as a way to improve understanding and treatment of neurological diseases. One other crucial reason to include an evolutionary perspective on neurological diseases is the fact that animal models of neurological diseases are imperfect, almost always only partially mimicking human diseases and usually requiring iatrogenic manipulations to create the model. Therefore, the question arises to what extent human neurological diseases are specifically or exclusively attributable to our species. When studying human-specific evolution, the group has reviewed both "paleontological" studies exploring changes along an evolutionary trajectory over time, as well as "neontological" studies comparing presently living species. Thus, the research includes studies on disease vulnerability in our closest extant relatives (ie, great apes and other nonhuman primates [NHPs]), as well as comparisons with our direct forebears, that is, ancestral humans.[5] Human brain diseases may, in part, result from a dysfunction of evolutionarily conserved mechanisms that were biologically helpful in ancestral environments, but have become maladaptive in modern environments.[5]

With these considerations in mind, we review selected neurological diseases from an evolutionary perspective. After discussing differences in human brain anatomy and physiology compared with NHPs, we will explore the evolutionary impact on neurological diseases at different "levels," starting with the genetic level, then discussing subcellular and cellular differences, connectomic

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and systemic considerations, and finally proposing behavioral and cultural aspects, as well as a consideration of cultural evolution. At each exploratory level, there is a potential for new insights and innovative research projects. Due to space constraints, this review is not exhaustive and will mainly focus on two highly influential evolutionary concepts highlighting the relevance of evolutionary theory for the understanding of neurological diseases. One is called "*mismatch*"; it explains why past adaptations to ancestral environments may no longer be biologically advantageous under modern environmental conditions, mainly excess caloric intake, sedentary lifestyles (ie, paucity of physical exercise), and novel sources of stress that were absent in our evolutionary past. The second concept is referred to "*antagonistic pleiotropy*." It explains why traits and genes that improve biological fitness when reproductive activity peaks (ie, early adulthood) can be detrimental to health later in life (senescence). These 2 areas are of special interest to neurology, which does not denigrate the relevance of other evolutionary constraints on biological fitness, such as *host-pathogen co-evolution, trade-offs* (a biological trait being under conflicting selection pressures), or the role of defense mechanisms such as pain and fever.[6] The latter evolutionary causes of disease vulnerability are spared, because the present article largely excludes communicative diseases from an evolutionary analysis. Currently used evolutionary concepts are presented separately in Box 1.

Differences in Specialization of Brain Anatomy

Whereas the basic *bauplan* of the brain is similar in all mammals, the brain of *Homo sapiens* (HS) diverges from the brain of NHPs and other mammals in a few, largely quantitative rather than qualitative, ways (Figure 1). At the macroscopic level, it is easy to determine the considerable enlargement of the human telencephalon as compared with other NHPs, including great apes, even when considering allometric measures (ie, brain size or weight relative

Box 1. Currently used evolutionary concepts, as applicable to human brain diseases.

Selected evolutionary concepts applicable to human brain diseases (adapted from Diederich et al, 2024).

Adaptive introgression

Advantageous archaic genetic variants adapted to local environments as a result of interbreeding between archaic hominins and HS.

Central pattern generator

Phylogenetically preserved cellular networks located in the medulla and the brainstem, allowing automatized complex behaviors (ambulation, mastication, feeding, etc.).

Evolutionary mismatches

Conditions where a genotype formerly well-adapted to the environment becomes now maladapted to the present environment, possibly due to a change of this environment (migration, climate change, evolution of other species, etc.).

Exaptation

Concept explaining that an evolutionarily ancestral mechanism or pathway can adaptively change its function, mostly by exchanging the input and output targets.

A certain (genetic, connectomic, and behavioral) trait, once evolutionarily advantageous in ancestral environments, has become maladaptive upon environmental or cultural changes.

Mismatch

Evolutionary mismatch applies to biological situations where the previously fitness adaptive and advantageous genetics or neuronal pathways, or behavioral traits have become disadvantageous due to cultural or environmental changes.

Positive selection

Genetic selection, favouring the spread of beneficial alleles for survival and reproduction, a process that is much more infrequent than negative selection.

Selection shadow

"Blind spot" of selection due to ineffectiveness to eliminate deleterious mutations with deleterious expression in later life periods, as the selection pressures become ineffective, once the reproductive period has passed.

Trade-off

Observation that an evolutionarily beneficial change in one trait is associated with a detrimental change in another trait. When considering human brain evolution and the high energy expenditure of neurons, a trade-off between the size of the human brain (expansion) and the size of the human digestive tract (retraction) has been proposed. However, the trade-off concepts are often oversimplifying. For instance, shortening of the human digestive tract was also a consequence of the switch from a starch-rich vegetarian diet to a calorie-rich cooked protein diet.

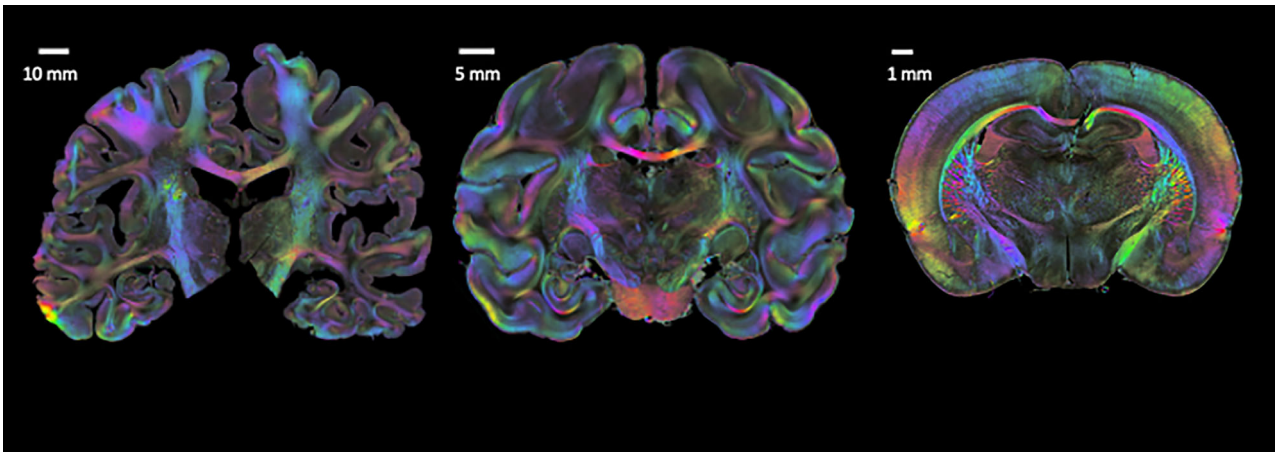

FIGURE 1: Comparison of the human, vervet, and rat brains (from left to right). The 3 species show both similarities in their bauplan, but also remarkable differences. For example, whereas the internal structure of the hippocampus seems to be quite similar, its localization in the brain differs significantly between the human and the vervet brain against the rat brain. The proportion of white matter is larger in the human brain than in the vervet brain than in the rat brain. Please note the different sizes of the scale bars.

to body size). Neurogenesis starts from basal progenitor cells, wandering out and differentiating in parallel radial trajectories. There is differential regulation of these highly conserved signaling pathways, assuring the complexity and diversity of neurons. In humans, the dynamic interplay of mechanical and molecular processes due to multiple genetic changes ensures both the size and the complexity of the isocortex. These processes are at risk for multiple neurodevelopmental vulnerabilities, each in itself and in combinations, and thus potential substrates for pathological processes.[7,8]

Whereas the brains of modern humans seem to be similar in volume to those of *H. Neanderthalensis*, a recent paper studying human transketolase-like 1 (TKTL1) concluded that modern humans have a larger neocortex than Neanderthals.[9] The expansion of volume is especially visible in the neocortex: prosimians have larger neocortices than rodents, whereas simians have larger neocortices than prosimians.[10] Interestingly, the human neocortex/rest of brain volume ratio differs only marginally from other simians. Within the neocortex, there are considerable differences between individual neocortical areas among non-primates, NHPs, and humans.[11]

The human prefrontal cortex shows considerable changes in connectivity and complexity in comparison with other primates.[12,13] Paleo-anthropological studies suggest that there is also considerable expansion of the posterior parietal cortex in modern humans compared with Neanderthals.[14,15] Numerically, human brains do not rank first in the absolute count of neurons, their brain-to-body mass ratio, the absolute cerebral cortex size, nor gyrification, but humans have the largest brain among primates when compared with the brains of nonhuman species.[16] The degree of folding increases with brain size across mammals and seems to be more influenced by non-genetic than genetic factors, whereas brain size is more strongly controlled by genetic factors.[17] Gyrification is changed in some mental and neurological disorders, for example, epilepsy, dementia, and attention deficit hyperactivity disorders (ADHDs), as discussed in Zilles et al.[17] In contrast, phylogenetic "reduction" of non-cortical parts of the brain, such as the magnocellular part of the red nucleus[18] or the oldest parts of the amygdala, including the central amygdaloid nucleus,[19] have been reported. Comparative anatomic studies of humans and NHPs reveal that the human locus coeruleus contains fewer neurons than predicted, according to the human neocortical volume.[20]

A closer look also reveals specific differences in microanatomy. For example, whereas there is a high degree of variance of cellular and fiber architectures in the human neocortical areas,[21] the between-subject variability in other primates and mammals seems to be substantially lower. The density of neurons per volume is lower in HS and reflective of the highly branched and elongated configuration of human neurons, and due to the fact that the ratio of astroglia to neurons has greatly decreased over evolutionary time. In addition, the synaptic density is particularly high in HS (up to 20,000 synapses per neuron), as well as the extensive arborization. Such architectural complexity is accompanied by slower maturation and delayed development in comparison with NHPs.

Considerable changes are also seen in the glial population in the human brain. Functional complexity of glial cells substantially increased from invertebrates to vertebrates, and, in mammals, there is high glial heterogeneity,

ranging from oligodendrocytes to astrocytes to microglial cells. Subpial intralaminar astrocytes are only found in NHPs and HS. Whereas the ratio of glial cells to neurons is reportedly higher in HS than in NHPs, new technics support that this ratio is 1:1 in the human brain.[22] Glial cells assure a wide range of homeostatic and defensive functions in the HS brain. Atrophy and loss of function, as well as reactive remodeling and astrogliosis can both accompany numerous human brain diseases.[23] A detailed description of the underlying dysfunctional cascades is beyond the topic of this review article. In short, however, "oligodendrocytes" are responsible for the myelination of neurons. From the clinical perspective, it remains unknown why multiple sclerosis, as a centrally demyelinating disease, naturally only affects humans. Complex interactions among environmental triggers, genetic susceptibility, and autoimmune dysregulation explain this vulnerability from a "proximate" perspective. It has been hypothesized that these processes may be facilitated by the considerable temporal extension of postnatal myelination, pruning, and brain maturation in humans, thereby possibly triggering immune-mediated demyelination in the third decade of human life.[24] The "astrocytes" are in charge of the astrocyte-neuron lactate shuttle (ANLS), providing the energy to the neurons in the form of L-lactate after aerobic glycolysis has first occurred in the glial cells.[25] Human cerebral energy consumption expressed as glucose utilization is estimated to be 450 µmol/min in humans in comparison to 30 to 60 µmol/min in NHPs.[26] This energy challenge is due to the considerably larger number of neurons in humans, and it is most prominent in the prefrontal cortex of the HS. It results in a 4-fold metabolic increase compared with NHP.[26]

Beyond its metabolic role, L-lactate can act as a neurotransmitter.[27] Thus, the exposure to L-lactate stimulates the expression of early genes such as *Arc* and *c-Fos.* They are activated upon long-term potentiation (LTP) induction, downstream of the activation of NMDA receptors. Moreover, LTP and synaptic plasticity can be modulated metabolically. Indeed, the blockage of L-lactate increases in astrocytes has been shown to block LTP, to impair memory, and to inhibit the turnover of dendritic spines.[28,29] Moreover, the overall improvements that L-lactate provides in terms of cognitive functions lead to the idea that L-lactate might also be beneficial for cell survival, hence delaying aging in general.[30] In summary, L-lactate formation favors neuroplasticity, and it is crucial for neuroprotection, the reason why physical exercise, inducing its production, may delay brain aging and neurodegeneration, and, in contrast, a sedentary lifestyle may be deleterious for the human brain.[31] Another source of L-lactate is glycogen, which is specifically accumulated in perisynaptic astrocytic processes in the brain and recruited following LTP.[29,32] The vital glycogen energy reservoir can build up during sleep, and its dysfunctional turnover is proposed as a mechanism linking sleep and mood disorders in HS.[33] For instance, sleep deprivation might result in reduced glycogen availability, which is known to impair glutamatergic synaptic transmission by slowing clearance of extracellular potassium and glutamate. This is a known cause of migraine and mood disorders in humans. Several studies sustain these pathomechanisms[34 for review], which are beyond the scope of this work.

At the nutritional level, feasible energy provision to the high demands of the HS brain cannot be expanded endlessly by increasing foraging time. Therefore, there may be a trade-off between human brain expansion and involution of the gastrointestinal tract (GIT) in HS, which only became possible by the ability to process protein-rich food (ie, cooking as a cultural evolution).[35,36] This also brings up the speculation that the resulting regression of the neuronal system at the GIT level has a higher susceptibility to disease initiation, which could explain, at least in part, the local triggering of synucleinopathies.

Exploring Evolutionary Impact at Various Levels

Genetic Level

Polygenic scores to predict the risks of neurological diseases bring up the issue of many competing evolutionary explanations behind, enhancing the complexity of any model building, possibly resolved in the future by artificial intelligence (AI) applications. Without being exhaustive, we propose several approaches on how to explore the evolutionarily driven genetic impact on neurological diseases.

Gene Expression is Different in Neurons. At the frontline concerning human neurological diseases, there are changes in terms of the regulation of gene expression. Differential gene upregulation in the human neocortex was already proposed in 1975 by King and Wilson in their pilote paper with the perfectly summarizing title "Humans and Chimpanzees: Their macromolecules are so alike that regulatory mutations may account for their biological differences."[37] By changes in the function of a single regulatory protein, there may be expression changes of many genes, and, in consequence, a different cellular molecular network alignment.[38–40] Although chimpanzees and humans share almost identical regulatory genes, current technology identifies about 100 species-specific genes in humans that are differently regulated. *FOS* and *JUN* gene activities between HS and NHPs function in highly separate patterns. Differential gene expression is also achieved by diffusible

molecular changes with an impact on many gene expressions (TRANS).[41] Specific to neurological considerations, neurons express more genes than non-neuronal cells, and changes in RNA splicing and processing are prominent features of oligodendrocytes and progenitor cells. Furthermore, a forward and backward interaction between genes and environment[42] applies in particular to the human neocortex, which is more susceptible to environmental influences than the neocortex of the NHP.

Antagonistic Pleiotropy. Whereas only a few neurological diseases are monogenetically inherited with high penetrance, most neurological diseases are genetically more complex, suggesting a combination of genes, each of which confers a limited risk for disease, with a larger impact of various (environmental) factors.[43] Often, antagonistic pleiotropy comes into play. This biological concept, first described in the context of research on aging, posits that a single gene can have multiple effects, some of which are beneficial while others are detrimental, depending on the context (Table 1). For instance, a gene may increase reproductive success early in life but contribute to ageing or disease later in life. Importantly, it also demonstrates that gene mutations associated with neurological diseases are not primarily defective mutations. Thus, by enhancing inflammatory responses, *APOE4*, first protects against infections, for instance, pediatric enteric infections, but later increases the vulnerability to aging and neurodegeneration.[44] Interestingly, although the reduction of parkin, which is a tumor suppressor, by somatic mutations of the *PRKN* gene may increase the risk for certain types of cancer,[45] it has also been reported that the loss of the function mutations that lead to Parkin deficiency could have a protective effect against the development of melanoma.[46] Thus, a positive selection in hunter-gatherer populations exposed to bright light can be hypothesized. In contrast, with increasing chances of human survival, the advantage of Parkin depletion was lost as inherited *PRKN* mutations increase the risk for neurodegeneration in the aged individuals. This disadvantage remains in the "evolutionary shadow," given that the typical age at onset of PD due to Parkin deficiency is in the fourth decade of life and hence past the peak human reproductive age. Therefore, there is no selection pressure against its propagation, and Parkin loss has turned from a pro-survival factor to a cause of age-associated neurodegeneration during evolution.[47] Although sometimes

TABLE 1. Examples of Antagonistic Pleiotropy of Selected Genes Related to Human Brain Diseases

Gene Specificities and Gene Mutations	Related Human Disease	Advantages in Former Hominins	Advantages in (Pre)Reproductive HS Phase
Apoϵ4	Alzheimer dementia	Protection against (enteric) infections	
DRD4 (7-repeat allele)	ADHD	Increased curiosity and novelty-seeking, and thus enhanced environmental exploration by hunter-gatherers	
HAR	Frontotemporal lobe degeneration		Acquisition of human unique cognitive, linguistic, and social abilities
Huntingtin	Huntington disease		Acceleration of early cerebral development by the increase of the CAG repeats up to 40
PARKIN	Parkinson's disease	Potential protection against cancer by somatic mutations	
Various gene mutations, including tag SNP (rs3135388[T]) for HLA-DRB1*15:01	Multiple sclerosis	Protection against various infections in the former steppe pastoralist population	

ADHD = attention-deficit/hyperactivity disorder; Apoϵ4 = Apolipoprotein E4; CAG = cytosine- adenine- guanine; DRD 4 = dopamine D4 receptor; HAR = Human Accelerated Regions; HLA-DRB = human leukocyte antigen-D-related beta chain; SNP = single-nucleotide polymorphism.

contested, it has been proposed that the expression of the seven-repeat allele of the *DRD4* gene variant could be a genetic risk factor for ADHD. This allele seems to be associated with "novelty seeking," and thus may have been positively selected in hunter-gatherers, in which it seems more prevalent than in sedentary people living in similar environments. Concordantly, a large study on Native American populations in Amazonia and Patagonia found significant differences in allele distribution between recent past hunter-gatherer and agriculturalist populations, with a significant increase of the 7R allele among hunter-gatherers.[48] One of the presently highest genetic risk factors for multiple sclerosis, the tag SNP for *HLA-DRB1*15:01* was immunologically advantageous in human populations that were among the first to domesticate animals, and thus were exposed to new pathogens. The migration pattern of these early herders from the Pontic steppe to Western and Northern Europe some 5,000 years ago impressively matches present-day prevalence rates of multiple sclerosis in these European regions.[49] Finally, "new" human-specific genes, such as the *FOXP2* gene, positively impact language faculties but are also believed to increase the risk for autism.[50] Table 1 brings up other genes relevant for neurological diseases, but with properties of antagonistic pleiotropy. Of note, this overlapping principle in evolutionary genetics also applies to other genetic mechanisms, as described below.

Adaptive Archaic Introgression. In building up the present human genetic structure, there has been a considerable impact by other hominins: Neandertals, Denisovans, as well as unidentified "ghost" hominins.[51–53] Hybridization occurred between HS and these other hominins around 50.000 years ago. The genetic flow from Neanderthals may be particularly important, with an estimated 2% of Neanderthal genetic variants still found in HS.[51] "Archaic genetic variants" thus introgressed from Neanderthals and Denisovans were adaptive in ancestral environments but may exert detrimental effects in HS in modern conditions due to a mismatch between modern and ancient lifestyles. Adaptive archaic introgression (AAI) of genes has had a mostly favorable influence on immunity with protection against certain viral infections or zoonoses in environments that were novel to HS when migrating into Eurasia.[54] However, whereas genetic variants in former hominins may have been adapted to past environmental conditions, they may no longer be advantageous in present environments of HS (*evolutionary mismatch*). AAI shapes behavioral phenotypes that are not yet disease phenotypes and concerns, for instance, sleep quality or the length of a depressive episode.[55] One of the alleles of the DARS gene introgressed from Neanderthals is protective against white matter diseases. AAI from the Denisovan genome induces better adaptation to life at higher altitude, however, with the trade-off of higher blood viscosity.[55,56] Although, in general, Neanderthal alleles are downregulated in the brain, their enrichment increases reward seeking and impulsivity, thus potentially augmenting the risk of such behaviors to a neurologically pertinent level in modern society (ADHD, addiction, and impulse control disorder in Parkinsonian syndromes).[55,57]

Human Accelerated Regions. Whereas there is high genetic overlap between NHPs and HS, specific genetic sequences, the so-called Human Accelerated Regions (HARs) have been positively selected during human evolution as they enhance fitness by contributing to functional specialization through differential expression of gene regulation in neurons.[58,59] They are highly expressed in the HS-expanded frontotemporal brain regions. As enriched in postsynaptic structures and synaptic signaling, they here contribute to the HS-unique cognitive, linguistic, and social abilities.[60] On the downside, strong enrichment of HAR is seen in frontotemporal lobar degeneration,[61] and, although beyond the focus of this review, by their effects on neurodevelopment and on the risk for psychiatric disorders such as schizophrenia and autism.[62,63]

Short Tandem Repeats. Short tandem repeats (STRs) represent a frequently overlooked yet important component of the human genome. Repetitive sequences make up more than half of our DNA and play critical roles in gene expression and regulation. Polymorphic STRs can influence a broad range of biological processes, including epigenetic modifications, such as histone changes, DNA methylation, and alterations in genome architecture, all of which can affect the expression of both nearby and distant genes. Variations in intergenic and intragenic STRs have been shown to correlate with the expression of neighboring genes in a tissue-specific manner. Notably, expression-associated STRs are often enriched at transcription start sites and tend to colocalize with putative enhancers. The expansion of STRs in the human genome may have contributed to evolutionary fitness, yet their inherent instability presents a double-edged sword—potentially driving evolution and causing disease.

More than 70 neurological diseases are caused by unstable tandem repeats, with the most prominent being Huntington's disease [HD], Friedreich disease, fragile X syndrome, and cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS).[64] Higher cognitive performances and higher brain volumes have been reported in HD children with up to a CAG repeat number of 40 (highest general ability index),[65–67] with a

tipping point thereafter. It is imaginable that these genetic changes were advantageous to early HS, living as hunters-gatherers in a precarious environment and with a considerably shorter lifespan than present HS. More generally, longer repeats produce high-performing neuronal circuits by the generation of neurons with increased connectivity and function, thus contributing to evolutionary fitness, while later, these same repeats may accelerate neurodegeneration.[68] Thus, longer repeats are not per se subjected to natural selection and may escape selective constraints. Conversely, if these genetic variations alter brain function on which selection can operate, they will only be maintained in the gene pool when they favor favoring the reproductive fitness.[3] This can be argued to be the case in patients with HD.[65–67] However, at the somatic level of striatal projection neurons, ongoing CAG repeat expansion (genetic mosaicism) finally induces senescence of these neurons, thus "selecting them out."[69,70] Other neurological diseases due to unstable repeats are less well explored, among them Friedreich's ataxia and Fragile X disease. GAA trinucleotide repeats are present in both primates and HS. In orangutans, there is a maximum of 5 GAA repeats,[71] whereas in human Friedreich ataxia, there is homozygous GAA repeat expansion between 70 and 1000 triplets.[72] In subjects with a fragile X chromosome, the expansion of the unstable repeats occurs in successive generations. Premutation carriers, mostly male subjects at advanced age, develop the fragile X-associated tremor/ataxia syndrome that can also include neuropathy and mild dysexecutive symptoms.[73] Paradoxically, at a premutation range, there is a higher level of gene activity than in healthy controls, whereas it is substantially decreased in patients with CGG repeat expansions over 200. These examples pose the question of a tipping point in function, with the reversal of gene activity occurring at a certain number of CGG repeats. In the case of Friedreich's disease, the tipping point appears to relate to normality versus neurological disease, whereas, in Fragile X, there are 2 phenotypes, both with neurological disability but age-dependent in terms of disease onset.[74] In HD, a paradoxically higher cognitive performance was reported for young HD carriers has so far not yet been reported for any other unstable repeat disease.

Cellular and Subcellular Levels

Neurons vulnerable to damage and various neurodegenerative processes are elongated and have a dense arborization.[75] They are implicated in neuromodulatory control networks and reach vulnerable bioenergetic tipping points during the long human life. Mitochondrial energy mechanisms are very efficient by supplying 32 ATP molecules through oxidative phosphorylation, but also produce reactive oxygen species (ROS).[76] Diverse selection mechanisms at the organismal and cellular level normally assure mitochondrial homogeneity and preservation of mitochondrial efficiency.[77] However, together with maximal mitochondrial stress, ROS and related endogenous toxins build up during long human lives and trigger damage to mitochondrial DNA (mtDNA), especially in postmitotic somatic neurons.[78] Being tissue dependent, the resulting mitochondrial mutational load can thus be somatic or non-inherited. Due to heteroplasmy, this load varies from mitochondrion to mitochondrion and from cell to cell. The energy supply again shows characteristics of antagonistic pleiotropy. On one side, there is fitness-adapting mitochondrial upregulation at a young age; on the other side, mitochondrial upregulation in older age can have detrimental effects with a higher risk for senescence. Dying cells release mitochondrial fragments that can function as damage-associated molecular patterns (DAMPS).[79,80] As mtDNA is derived from bacteria (endosymbiotic theory), DAMPS may not be recognized as organism-inherent molecules and therefore trigger vigorous immune responses, potentially driving neuroinflammation and neurodegeneration.[78] The aging process also accelerates naturally occurring mtDNA mutations (heteroplasmy).[76] An efficient mitochondrial energy supply is most challenged at the synaptic level in HS, because there is a considerably higher number of synapses per neuron compared to NHPs. As succinctly formulated by Bolam and Pissadaki, HS are "living on the edge with too many mouths to feed."[81] This mechanism may, in part, explain the human-specific selective vulnerability of long, highly branched, unmyelinated dopaminergic neurons in the substantia nigra.[82]

In regard to neurotransmitter action, it is highly interesting to observe that these substances are evolutionarily older than the central nervous systems (CNS), brains, or neurons. In fact, many of them have acted as biomodulators in plants, where they served different biological purposes compared with animals.[83] As animals evolved, however, the binding sites of neurotransmitters in primitive nervous systems and brains have greatly diversified over time. In fact, the evolution of receptors is at least as important as the "co-optation" of biomodulators for neurotransmission. Receptors are located at various distances from the cell body, on axons and dendrites, and in differing patterns across brain regions and species.[84] The distribution of receptor types differs between species, even in unimodal sensory areas such as the visual cortex.[85] The regional variability of neurotransmitter receptors represents an extensive basis for modulating signal transmission and fine-tuning the activity of neurons, for example, via metabotropic receptors at apical dendrites of large pyramidal cells in cortical layer V that seem to play a role in

conscious experience.[86] As an example, in a study comparing 5-HT receptors between humans and NHPs, it has been shown that serotonin receptors have undergone both positive and negative (purifying) selection, even though a considerable number of 5-HT receptors have been evolutionarily highly conserved.[87] Serotonin has been involved in almost countless different functions. In higher mammals (including ourselves), serotonin has an impact on complex social behaviors, regulating social hierarchies, etc.[88] It is certainly beyond the scope of this article to review the multiple functions of all neurotransmitters and their evolutionary history.

Network and Whole Brain Level

At this level, we approach the evolutionary question of vulnerable human neurological pathways that can become dysfunctional. Numerous new optical and neuroimaging techniques have revolutionized the way human brain connections are visualized and studied.[89] Pathway comparisons in ancient hominins are not available, but connectomic comparisons between NHPs and HS reveal important differences between species. The so-called Default Mode Network (DMN) shows decreased activity during externally oriented tasks and increased activity during baseline and conditions with interoceptive-like features such as autobiographical, episodic, and semantic memory, future thinking, and mind-wandering. Whereas the human DMN includes areas of the prefrontal, inferior parietal, and temporal cortex, there are major differences in the connectivity profiles across species. Specifically, the connection of the medial prefrontal cortex and the posterior cingulate cortex seems to be unique in the human brain.[90] In terms of fiber architecture, considerable differences between species can be found in the proportion of white versus grey matter or the topography of brain areas, whereas others, for example, the laminar organization of the neocortex or the shape of the hippocampus seem to be more similar (see Figure 1). Such different connectivity profiles, both on a functional and a structural level, are presumably associated with the rapid development of cognitive performance.[90–92]

Due to the evolutionary expansion, there is an extension of downstream control in mammals compared with other vertebrates, with the potential to "overrun" action selection circuitries of the basal ganglia. While at risk for causing neurological deficits, this principle can also trigger compensation mechanisms.[93] In terms of connectivity, considerable differences between species can be found in the proportion of white versus grey matter, or on the topography of brain areas, or in the descending pathways controlling skilled hand movements, which have evolved rather late during evolution. Interestingly, there are considerable interspecies differences, even for the corticomotoneuronal connections within NHPs. These direct, long corticofugal pathways that originate in layer V of the motor cortex and include corticomotoneuronal connections, are particularly vulnerable to the degenerative process seen in amyotrophic lateral sclerosis (ALS) with the clinical phenotypes of the split hand or split foot syndrome.[94,95] Nevertheless, the relevance of these interspecies differences for function (and dysfunction) is not yet fully understood, and the question of whether "overrunning" is generalizable, or needs to be further proven by future research.[96]

In NHPs and especially in HS, there is a high level of development and specialization of the parietal lobe, including the precuneus. Studies comparing the endocast between modern humans and Neandertals have indicated that there is an increase in size and complexity of the parietal cortex.[15] The anatomy in this region is compacted, invoking spatial and metabolic constraints and subsequently an increased sensitivity to the damage of the accumulation of β-amyloid aggregates in this region.[3,97] Although recent evolutionary telencephalization may suggest newer connectomic modules with potentially pronounced axonal stretching, there is, in parallel, also remarkable conservation of "old tools," for instance, the modular organization of the basal ganglia. Its organization has been largely conserved for 500 million years, from lampreys to primates. However, the behavioral repertoire associated with basal ganglia connections has considerably expanded, becoming varied and versatile, especially in HS, where it includes parallel-processed and similarly organized pathways for motor, emotional, and cognitive functions.[98,99] In PD and other movement disorders, this principle of exaptation may increase the risk of overall neurological frailty that mechanistically involves synchronous dysfunction of several networks emanating from the primary altered brainstem-basal gangliar-thalamic cortical pathways, involving both motor and non-motor disease manifestations. This degenerative process is further facilitated by the exceptional longevity of modern HS.[100,101]

Behavioral Level

It is tempting to assume that any evolutionary impact at the neuro-behavioral level would be clinically evident and easy to identify. Beyond identification, however, mechanistic precision is more complicated because different pathophysiological disruptions can impact clinical manifestations in a similar way. Residual but now dysfunctional or demasked evolutionarily old behaviors or disinhibition of formerly useful but now obsolete behaviors, and disequilibrium of competitive behaviors can all lead to similar clinical outcomes and yet have different causations and

clinical significance. As in other situations, syndromes are often linked to a multifactorial background, characterized by complex interdependencies among environment, phenotype, and genotype. Some of the mechanisms, along with clinical correlates in neurological disorders, are outlined in Table 2, and selected syndromes and their clinical context are described later.

Generally, HS interact with their environment through both goal-directed and habitual behaviors in a similar way to that seen in other animals. HS excel in flexible, goal-directed behaviors that are sensitive to the expected outcome. However, these behaviors are also slow, conscious, and effortful, requiring constant dialogue between the orbitofrontal cortex and the dorsomedial striatum and a high level of dendritic spine plasticity.[102] In contrast, the evolutionarily older habitual behaviors are fast, largely unconscious, and effortless, automatized, and rigid, without modulation by any anticipated outcome.[103] Their execution heavily relies on the dorsolateral striatum with dopaminergic input from the substantia nigra. These striatal hubs are at risk of dysfunction in neurological diseases, such as Parkinsonian syndromes, with the consequence that habitual behaviors may not be easily accessed anymore.

Cultural Level

Selection forces have considerably changed since humans developed the social cultural niche. Novel vascular and metabolic syndromes are caused by mismatch, inducing again, new selection forces (Figure 2). The transition from a hunter-gatherer way of life to agriculture and sedentary lifestyles has brought about an enormous number of new challenges to human health. Whereas the domestication of crops and animals surely helped provide the required amount of calories for more people than ever before, these

TABLE 2. Examples of Evolutionary Impact at the Behavioral Level of Neurological Diseases

Behavior	Evolutionary Meaning	Neurological Disease With Dysfunction	Clinical Symptoms
• Dysfunctional evolutionarily old behaviors			
Blindsight	Apprehension of danger in the peripheral visual field and immediate reaction	Parkinson's disease	Loss or dysfunction of blindsight features
Gait automatization	Gait facilitation as habitual behavior	Parkinson's disease	Loss of gait automatization: gait initiation is difficult; the necessity of *conscious* gait control
Arm swinging synchronized with gait	As a remnant of quadrupedalism, facilitation of gait and balance	Parkinson's disease Medication-induced Parkinsonism	Asymmetry or loss of arm swing; block walking
• Demasking or disinhibition of formerly useful behaviors			
Violent nocturnal gesticulations in REM sleep	Nocturnal entrainment of a fight and flight reaction; previously adaptive	REM sleep behavior disorder	Violent gesticulations concordant with aggressive dream content; non-violent daily-life gestures also possible
• Disequilibrium of various behaviors			
Emotional fine tuning	Refinement of interindividual communication	Frontotemporal lobe degeneration; Parkinson's disease	Deterioration of emotional interactions (from "poker face" to inappropriate anger outbursts)
• Behaviors with novel meaning			
Sickness behavior	Evolutionary old adaptive behavior in case of injury or infection	Various neurodegenerative diseases	Social withdrawal, lack of initiative or "élan vital", apathy, depression

REM = rapid eye movement.

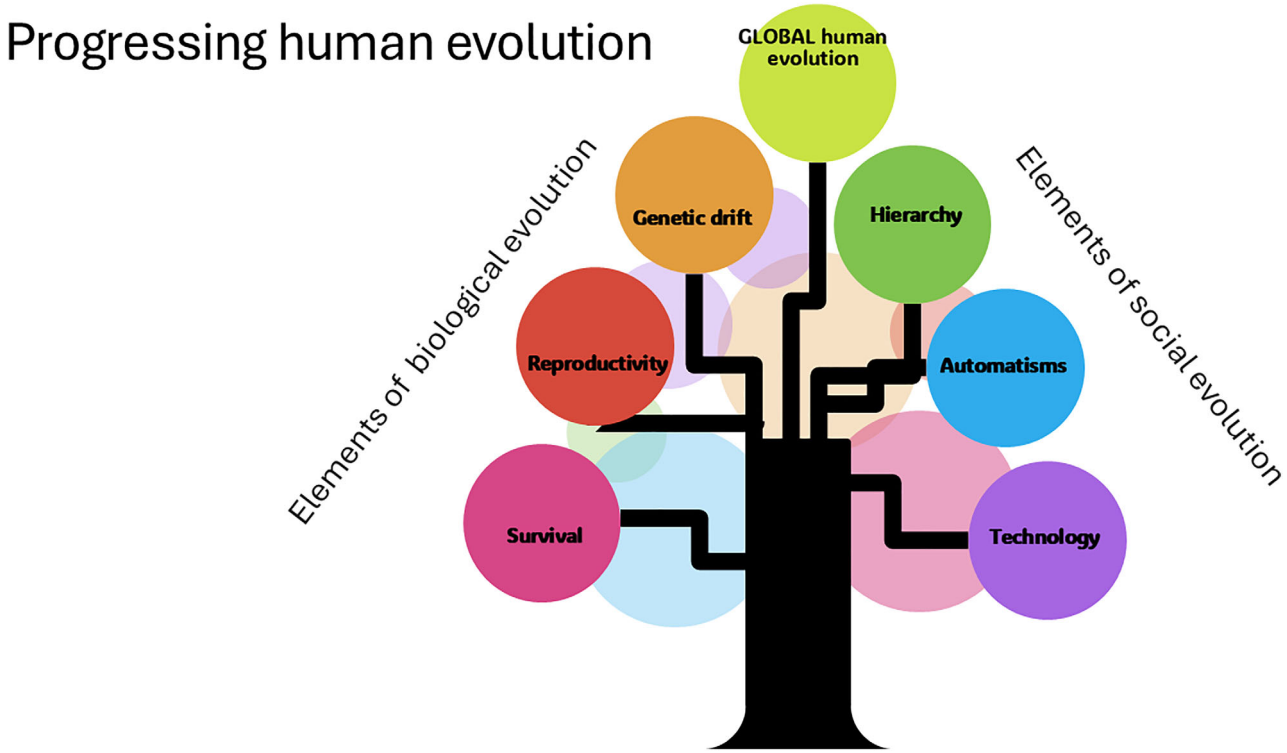

FIGURE 2: Tree symbolizing factors contributing to the global human evolution. The left-sided branches indicate various factors of the biological evolution, and the right-sided branches indicate various factors of the sociocultural evolution.

developments came at a cost to human health. Increasing amounts of carbohydrates, for example, promoted the emergence of dental caries. In addition, it changed the microbiota in the human gut dramatically. By and large, the diversity of the gut microbiota has grossly decreased following the transition from hunter-gatherer nutrition to agriculture. Compared to the microbiota in great apes, Neanderthals, and hunter-gatherers, our present diet has caused an impoverishment of the diversity of gut microbiota. Furthermore, the domestication of animals and the increased physical proximity to domesticated animals have produced an incredible number of new pathogens that "spilled over" to our species. Indeed, tuberculosis and many other pathogenic agents spread among members of our species because of the domestication of animals. Our Western lifestyles of the last 150 years or so have been associated with dramatically improved hygiene, which has come at a cost, however. The lack of exposure to immunologically relevant "old friends," such as helminths during childhood, is a classic example of evolutionary mismatch. As exposure to certain pathogens has been prevented by hygienic measures, the maturing immune system fails to mature in adaptive ways, such that it may attack one's own body tissue. This is probably the main cause of new epidemics of autoimmune diseases. In addition, some bacteria, such as *Helicobacter pylori* (*H. pylori*), can promote stomach cancer, if not properly treated. *H. pylori*, however, is not a threat to human health when exposure to certain helminths has taken place before. Together, novel environments may support the initiation and persistence of a low-grade chronic inflammasome,[104] an established risk factor for neurodegeneration,[105,106] diabetes, and cardiovascular disease.[107] It remains open to speculation, if these changes facilitate the initiation and propagation of hyperphosphorylated, aggregated tau, and a-synuclein in the enteric nervous system with secondary spreading to the CNS.[108]

Ongoing Evolution

Evolution has shaped the genetic constitution of humans over 2 million years under a broad range of environmental conditions and is exclusively based on and heavily biased to the effectiveness of reproduction and the maintenance of fitness in the pre-reproductive life. Humans were close to extinction several times in our evolutionary history, and thus went through genetic bottlenecks, which produced large phenotypic effects via genetic drift. Genetic changes continue to occur at a relatively slow rate, in stark contrast with much more rapid environmental changes as adaptations to sedentism, and changes in nutrition and lifestyle.[109,110] This dichotomy of slow biological and rapid cultural evolution also includes adaptations

to animal-borne pathogens (mainly because of the domestication of animals), novel foods, and climate change. For example, the positive selection of rs10166942[T] allele in local populations living in hotter climates induces the reduced expression of the cold sensor TRPM8 and, at the same time, protects against migraine occurrence.[111]

Clinical Examples Integrating Multiple Evolutionary Levels

Rapid Eye Movement Sleep Behavior Disorder

Rapid eye movement (REM) sleep behavior disorder (RBD) can precede the core motor syndrome of PD by years to decades, but it frequently also persists later on. There are several theories explaining this puzzling observation, among them, an ascending progression of the degenerative process.[112] At the evolutionary network level, the primarily evolved nuclei, among them the nucleus (sub)coeruleus, the nucleus ruber, and the superior colliculi, have undergone partial regression in HS, when compared with other NHPs.[18,20] At the evolutionarily behavioral level, immediate fight and flight reactions to a life-threatening danger are anchored in these nuclei, as well as in spinal cord central pattern generators.[113] Across vertebrae as diverse as lampreys and mammals, these evolutionarily conserved structures have been involved in aggressive and defensive behaviors, providing rapid responses to danger. Similarly, although not uncontested, repetitive threat simulation by mental rehearsal, as reported in normal REM sleep,[114,115] has been proposed to be crucial for survival in an evolutionary perspective.[114] As a further step, disease-related dysfunction of the mentioned brainstem structures even triggers inappropriate and potentially dangerous motor rehearsal in RBD, in analogy to behaviors observed after experimental sectioning of these areas in cats.[116–118] It is assumed that the vigor and speed of these movements, in contrast to bradykinetic movements of a patient with PD during daytime,[119] is assured by a hyperdirect pathway from the motor cortex to these nuclei, thus "overrunning" the action selection circuits of the basal ganglia.[120,121] The preferential disease involvement of these brainstem nuclei remains largely unexplained. But it can be speculated that nocturnal entrainment of defense mechanisms may have been a life-protecting adaptive behavior in hunter-gatherers, whereas it is no longer advantageous in HS living in environments without predators.

Parkinson's Disease

PD offers a particularly salient example for evolutionary discussions, and although the questions outnumber the answers, each is addressable with hypothesis testing. Indeed, it can be viewed as an outcome involving multiple evolutionary levels of dysfunction, primarily anchored in the mismatch between the massively evolved neocortex with demanding energy requirements and the ancient brainstem cells, nuclei, and networks that have not evolved in concert. For instance, the number of synapses formed by one reaching out dopaminergic neuron in the ventral striatum is 10-fold higher than in rodents. It is also 2 orders of magnitude higher than the synapses of other human neurons. However, in contrast, proportionally, the striatal volume has increased 10-fold relative to the absolute number of neurons. The total axonal length of an individual dopaminergic neuron has been estimated to be 4.5 m.[81] Beyond the most susceptible substantia nigra, disease involvement is seen in the locus coeruleus, the raphe nuclei, the pedunculopontine nucleus, etc.[119,120] Whereas in most patients with PD, there is no known genetic cause, 2 rather rare forms of PD due to mutations of the genes *LRRK2* and *PARKIN* seem to reflect antagonistic pleiotropy. That is, these genes are involved in superior immune function early in life, while triggering neuroinflammation later in life, which may cause neurodegeneration. Strictly speaking, however, these genetic variants are not fixed at the species level (which renders the expression "antagonistic pleiotropy" somewhat imprecise. It may also be accurate to describe these genetic effects as an example of *mutation-selection balance*, where a genetic variant that exerts deleterious effects after the reproductive lifespan is maintained due to its beneficial effects early in life, thus potentially slowing the process of purifying selection.

At the behavioral evolutionary level, automatized "bipedalism," a late evolutionary acquisition as being less energy-consumptive than quadrupedalism, is deficient in advanced stages of PD, and the patients have to walk consciously, effortfully, and laboriously. Gait facilitation of bipedalism by accompanying arm swinging becomes asymmetric or disappears. "Blindsight" is an evolutionarily anchored sensory automatism, and it assures the immediate approximative location of potentially threatening objects or living beings without any conscious appreciation. The underlying complex mechanisms implicate intact dialogue between subconscious visual pathways involving the superior colliculi (SC), the amygdala, and the basal ganglia. Blindsight is dysfunctional in PD, causing poor immediate visual appreciation of a moving object, hypometric saccades, and, as a reaction, blunted motor and emotional reactions.[122] The dysfunction of the system may also lead to false alarms in the form of minor hallucinations (the fleeing passage or sensation of the presence of a person or animal in the peripheral visual field) in the earliest non-medicated stages of PD.[123] "Defective light entrainment" is another Parkinsonian syndrome due

to involvement of an evolutionarily ancient system. The melanopsin-containing retinal ganglion cells (MGCs) are a light-sensitive system, well developed in nonmammalian vertebrates. In humans, MGC represents only 0.3% to 0.8% of the retinal ganglion cells.[124,125] When deficient, as seen in advanced PD, there is dysregulation of various circadian rhythms leading to inversion of the sleep–wake cycle.[126] Exaptation and realignment of networks have been offered as hypothetical explanations for this remarkable and multidimensional non-motor involvement of deficits in PD (cognitive, behavioral, autonomic, and sleep) that accompany the archetypal motor symptoms.[127]

Huntington's Disease

The clinical development of HD illustrates how evolutionary analyses of dysfunction may explain some heretofore age-specific dichotomies in this disease. At the genetic level, some findings suggest antagonistic pleiotropy. Specifically, greater numbers of CAG repeats increase pre-reproductive fitness. Indeed, the higher the number of repeats, the higher the general intelligence of children and adolescents of both sexes, and the thicker the cerebral cortex in female children.[128,129] Even when the CAG repeat is such that it leads to a mutated Huntington protein, these seemingly advantageous changes persist.[129] However, these findings still need to be confirmed by other research groups. Beyond cognition, the structural changes are linked to transitorily better motor and behavioral scores, decades before the disease manifests.[67] Although the topic has been discussed for decades, it is still unclear whether higher numbers of CAG repeats actually translate into higher biological (ie, reproductive) fitness in HD. Regardless, early developmental advantages due to better neuronal function and more efficient connectivity turn into a mid - and late-life disadvantages, as is evident in the motor, behavioral, and cognitive manifestations of typical HD, such that, beyond premature aging, there are now also rapidly progressing energetic deficits at the subcellular level.[68]

Alzheimer's Disease

At first look, Alzheimer's disease (AD) appears to be a distinctly human disease, although Alzheimer-like clinical and pathological signs have also been observed in some NHP[130] and dolphins. They share with humans a long post-reproductive life span.[131] At the animal model level, pathomechanisms of AD can be modeled in the rodent brain. *APOE4* assures protection against enteric infections in early life,[132] as higher amounts of β-amyloid activate immune responses to fight such infections.[133] In homozygote constellations, however, it is the most robust genetic risk factor for AD. It even triggers cognitive decline in Caucasians already at middle age,[134] although, paradoxically, there may be protection against attentional deficits in Afro-American women.[135] Extension of this concept is expressed in the antimicrobial protection hypothesis, postulating that β-amyloid deposits are due to the early innate immune response to both real, or erroneously perceived, immune challenges. β-amyloid may entrap infectious pathogens, and amyloid fibrillization may drive neuroinflammation, thus clearing pathogen deposits.[136] Because of this inflammatory role, the ancestral *APOE4* allele may have remained more prevalent in foraging cultures and in intertropical regions.[137] In contrast, in northern regions with reduced infectious risks, *APOE2* and *APOE3* variants might have been associated with a reproductive advantage due to a decrease in inflammation and an increase in longevity. This scenario of a new, secondary "trade-off" remains nonetheless speculative, because latitudinal trends are generally due to an admixture of multiple factors, including thermal regulation, rainfall, and light incidence, so leaving explanations relying on single effects as likely overly simplistic. Another hypothesis emphasizes the concept of mismatched environments, meaning that factors enhancing the risk for AD today, such as low exposure to infections, missing estrogenic neuroprotection, sedentarism, and malnutrition, may be more prevalent in present societies than in ancient cultures.[138]

At the supracellular and connectomic levels, the pivotal role of the entorhinal cortex for initiation and propagation of the AD process is well established.[139] However, the highly developed parietal lobe in HS also shows an increased vulnerability to neurodegeneration, probably because of its enhanced energy demands and vascularization.[14,97] Within the parietal lobe, the expansion of the precuneus is seen as a specific feature of HS, as not seen in chimpanzees. Its dysfunction in AD leads to visuospatial deficits, a prominent sign of AD.[140] Finally, neurodegeneration is triggered by neuroinflammation, formerly advantageous in injured hunter-gatherers as the so-called sickness behavior. As an evolutionary remnant, clinically expressed by social withdrawal, loss of interests, apathy, and depression, sickness behavior sheds new light on the observation that such behavior often precedes or accompanies neurodegenerative syndromes (Alzheimer's dementia, Lewy body dementia, frontotemporal lobar degeneration, etc.).[104]

Concluding Remarks on Changes and Pitfalls of Evolutionary Concepts

With an evolutionary perspective, clinical phenomenology can be reviewed afresh. Although our emphasis has been on diseases classified as neurological, our overall interest

extends to brain disorders, including psychiatric disorders. As this is beyond the scope of this presentation, we concur that strong evolutionary arguments can be posited for schizophrenia, bipolar disease, and other primary psychiatric conditions with parallel involvement of genetic, cellular, network, behavioral, and societal evolutionary levels. Mild depression with its cortege of immunological and metabolic changes saves energy and protects the organism, whereas anxiety stands as a defense mechanism against potential threats or adversaries. Non-disease phenotypes can be accepted within a wider spectrum of human normality. Under specific conditions, such phenotypes fill in "social niches," and may remain useful, although those actually thriving in a modern society may be very few.

However, such inclusive concepts – often prompted from outside the medical community – remain risky, especially when applied to neurological diseases, as they may prevent the individual patient from acquiring adequate medical recognition and help. In promoting the margins of normality, funding agencies may turn away from prioritizing research in these areas, whereas most subjects still suffer. In terms of environmental pollution or deprivation, misreading reversible or treatable disorders that could be overlooked because of newly embraced naturalistic inclusion is a further peril.

As authors, we consider that "evolutionary thinking" at different exploratory levels (see Figure 2) offers a unique opportunity simultaneously to seek broader and more specific insights into the pathogenesis and pathophysiology of human brain diseases. At a practical level, we encourage colleagues and patients to consider not only the usual "proximate" causes of a disease, but also its "ultimate" evolutionarily driven contribution.[1] Comparative behavioral neurology can elucidate how there is persistence of certain behavioral patterns in humans. The reality of a "price paid" for our cortical expansion in the context of a brainstem and spinal cord with less development allows both doctor and patient to consider both disease and adaptation in a new context. As directive, personalized medicine develops further, the ability to focus on "weak links" with new gene therapies or small cell-specific molecules may be feasible. Already, new tools from evolutionary science are being directly applied. For instance, comparative genetic analyses in bones of hominin predecessors have allowed new insights into innate immunity, and thus a better understanding of neuroinflammation and human susceptibility to certain zoonoses. Similarly, endocast research sheds immediate new light on preferential brain lobe development and provides estimates for the risk for specific regional neurodegeneration. In parallel, comparative connectomic research with NHP ("our cousins") may be instrumental in identifying disease-specific pathways in humans. The concept of antagonistic pleiotropy, presently applicable to several neurological diseases such as HD and AD, reveals that genetic mutations driving neurodegenerative processes at advanced age can actually be advantageous at an early reproductive age in terms of immunity or brain development. It is imaginable that this has to be extended to other diseases as well, and it also suggests a potentially smooth transition between so-called neurodevelopmental and so-called neurodegenerative diseases.[141–143] In clinical practice, our own experience with patients confirms a positive therapeutic interpretation of reconsidering disease within an evolutionary concept. For many patient discussions, however, "Evolution" translates widely into "Survival of the Fittest." This message falls short of the potential of an evolutionary perspective on the deep origins of neurological diseases and the positive therapeutic role an adaptationist view may convey in treating neurological disability.

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Potential Conflicts of Interest

All authors certify that they have nothing to report.

Authors Contributions

N.J.D., M.B., K.A., and C.G.G. contributed to the conception and design of the study; N.J.D., M.B., J.S.A., N.B., E.B., J.C., C.C., O.D., A.G., G.K., P.J., R.L., G.L., P.M., M.J.R., K.S.R., R.S., A.S., T.U., K.A., and C.G.G. contributed to the acquisition and analysis of data; N.J.D., M.B., E.B., C.C., A.G., P.J., K.S.R., A.S., K.A., and C.G.G. contributed to drafting the text or preparing the figures.

Data Availability

Not applicable.

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