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*Review Article*

# Human Neoteny Revisited: The Case of Synaptic Plasticity

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*ABSTRACT* The process of learning requires morphological changes in the neuronal connections and the formation of new synapses. Due to the importance of memory and learning in our species, it has been suggested that the synaptic plasticity in a number of association areas is higher in the human brain than in other primates. Cortical neurons in mammals are characterized by higher metabolism, activity, and synaptic plasticity during development and the juvenile stage than in the adult. In *Homo sapiens*, brain development is retarded compared with other primates, especially in some association areas. These areas are characterized by the presence of neurons, which remain structurally immature throughout their lifespans and show an increase in the expression of the genes, which deal with metabolism and the activity and synaptic plasticity in adulthood. The retention of juvenile features in some adult neurons in our species has occurred in areas, which are related to episodic memory, planning, and social navigation. The increase of the aerobic metabolism in these neurons may lead, however, to higher levels of oxidative stress, therefore, favoring the development of neurodegenerative diseases which are exclusive, or almost exclusive, to humans, such as Alzheimer's disease. Am. J. Hum. Biol. 23:729–739, 2011. 

## INTRODUCTION

Pedomorphic traits can be seen in the case of the phenomenon of progenesis, or the interruption of ontogeny due to premature sexual maturation or, more frequently, when the phenomenon of neoteny occurs as the result of prolonged or delayed development. The term neoteny was first used by Kollmann (1905) to describe the preservation of juvenile characteristics in adulthood (Gould, 1977). Neoteny may be an important factor in human evolution given that the retention of the fetal growth rate and the prolongation of the stages of development can lead to hypermorphosis and may have caused the increase in brain size that characterizes the evolution of the genus *Homo*. Bolk (1926) was the first to characterize *Homo sapiens* as a primate that managed to develop to sexual maturity despite permanently retaining numerous fetal or pedomorphic characteristics, among which he cited the flat face, the scarcity of body hair, the round head, the absence of the cranial superciliary arch, and sagittal crest, the increase in brain size and the prolonged period of growth and infant dependency. This view gained support of a number of paleoanthropologists, as in the case of Montagu (1962). This point of view was also strongly supported by Gould (1977) who proposed that neoteny could explain the evolution of *H. sapiens*, not only because of the retention of numerous pedomorphic characteristics but also because of the general temporal deceleration in our development that characterized our evolution. Retarded development may have caused the long childhood, late maturation, and large brain characteristic of *H. sapiens*. A longer period of fetal growth would result in the higher number of cortical neurons that characterize the human brain and would also increase neuronal complexity because it would allow for more complex dendritic and synaptic growth and more numerous connections between neurons (Parker and McKinney, 1999). Cognitive capacities seem to be related to cortical size and complexity, which in the case of a hyperdeveloped brain like that of humans, would give rise to more complex mental constructions, improving cognitive capacity (Gibson, 1990).

However, despite the similarity between young great apes and adult humans, a number of articles have suggested that Bolk's theses are unsustainable, because their authors did not consider the adaptive factors that could have influenced the retention of these juvenile traits. In contrast, the evolution of human traits seems to have occurred in a mosaic way, since the evolutionary direction of every trait is determined by natural selection, and the capacity for independent variation in each trait is enormous. Therefore, both "pedomorphic" and "peramorphic" processes seem to have been involved in human evolution (Leigh and Park, 1998; Leigh and Shea, 1996; McKinney and McNamara, 1991; Shea, 1989; Thompson et al., 2003). In contrast, the evolution of the human lineage seems to be characterized by a number of derived characters dealing with life-history, such as slow maturation, long-life spans and slow aging, postmenopausal longevity, and age of weaning (Hawkes, 2006; Robson and Wood, 2008). Among them, slow maturation appears as one of the derived features that could explain the apparent "neoteny" of some specific traits in the human lineage, particularly in the case of cerebral growth (Hawkes, 2006).

The rate and period of cerebral growth in mammals are related to the life history of each individual species. Among mammals, primates have the longest life histories: they mature more slowly and for prolonged periods, they have lower birth rates after long gestation periods, they

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tend to produce single offspring, and they have long-life expectancies as adults (Hawkes, 2006). There is great diversity in the cerebral growth patterns of the different species of primates. Variations in growth rate and the duration of cerebral growth lead to diversity in the size of the adult brain. The variations in brain size that occur during the postnatal period seem to be more related to cerebral growth rates than to time lapses in cerebral growth, which seem to play a secondary role (Leigh, 2004). The period of growth of the human brain, however, seems to be significantly longer than the period of growth of a chimpanzee's brain. The human brain reaches 95% of its adult size between 7 and 11 years of age and completes the final 5% of growth in a period of time nearly as long as that required for the initial 95%. Cerebral growth in *H. sapiens* occurs over approximately the first decade and a half of life after conception (Caviness et al., 1996). The brain of a chimpanzee reaches adult size at the age of 5 years (Bogin, 2006). The rate of brain growth in humans in the postnatal period is also much higher than the rate of cerebral growth in chimpanzees, at least in absolute terms (Leigh, 2004). A large brain is achieved either through the extension of the cerebral growth period or through an increased rate of cerebral growth, or both of these (Robson and Wood, 2008; Vinicius, 2005). In humans, both a prolonged growth period and an increased growth rate occur. The prolongation of the cerebral growth period and fetal growth rates during infancy and childhood explains the large brain size in *H. sapiens* (Bogin, 2006).

In humans, the period of fastest cerebral growth occurs during infancy and childhood. In the juvenile period, between 7 and 12 years old, cerebral growth and body growth slow down (Bogin, 2006). According to Bogin, this provides reproductive advantages for the mother. In childhood, the human brain is able to grow, in part, due to the slow rate of growth of the body. The low rate of body growth and small body size may alleviate competition with adults for food, which allows human infants to have a shorter suckling period. A short-suckling period means members of the group other than the mother can provide food and care for children. This allows mothers to shorten intervals between pregnancies, thereby increasing reproductive output and providing reproductive advantages for the mother and siblings of the child. A secondary benefit of reduced corporal growth would be an increase in the cerebral growth rate and brain size, which together with an extended period of development, would lead to increased cognitive capacity as well as an increased capacity for learning and social conduct among our predecessors (Bogin, 2006; Robson et al., 2006).

According to de Beer (1951), the deceleration of development, such as that seen in primates and especially in humans, had to be accompanied by the prolonged retention of tissues with preserve embryonic characteristics, which would be susceptible to modifications at relatively late ages. Jacobson (1977; cited in Gould) suggested that "neuronal neoteny had occurred in human beings. During ontogeny, individual neurons develop highly specific synaptic connections. In early stages, these connections are modifiable. This flexible period occurs at different times for different types of neurons." According to this opinion, "human development is so intensely delayed that even adults may retain sufficient flexibility to hold on to the adaptive animal state dependent on learning. During ontogeny, there is a progressive reduction in the capacity to form new neuronal connections and to modify existing connections. This reduction occurs at different times in different types of neurons. Those that are generated late in ontogeny and those that mature slowly could retain a higher degree of modifiability in the adult. A high degree of modifiability of neuronal connections in the adult would imply the continuation of development processes in later stages of the lifecycle." The higher capacity for modification of these neuronal connections might explain, in part, how the functional superiority of the human brain has been achieved without a comparable increase in the informational content of the genome of our species. Similar to King and Wilson, Jacobson believed that the decisive differences that distinguish us from the chimpanzee occurred due to genetic changes in few regulating systems (King and Wilson, 1975).

The development of the human brain does not stop when it reaches adult size. As will be described later, synaptic reorganization continues throughout development and cerebral myelinization continues into the third or fourth decade of life (Yakovlev and Lecours, 1967). The adult human brain uses between 20 and 25% of its metabolic energy at rest, while apes use between 11 and 13% and other mammals use between 2 and 8% (Bogin, 2006; Mink et al., 1981). The elevated metabolic cost of the human brain may be due solely to its large size, which involves having longer axons and a greater number of connections. However, as described in the following sections, there is evidence that in certain areas of the human cerebral cortex an increase in neuronal activity as well as increased synaptic activity and plasticity have occurred, which may partially explain the increase in cerebral metabolism in our species. As described below, increased-synaptic plasticity and elevated neuronal metabolism are characteristics of the brains of children and juveniles. So, in humans, certain cortical neurons may have retained juvenile characteristics into adulthood.

In mammals, most learning takes place at an early age. Learning requires modifications in the neuronal contacts, such as synaptic remodeling and the formation of new synapses, which seem to be more easily generated during infancy and childhood. Because *H. sapiens* depend on the transmission of culture through language, learning and memory have taken on greater importance in our species than in other mammals. Therefore, the possibility that the human neurons involved in learning retain juvenile characteristics in adulthood cannot be ignored.

## ANATOMICAL AND FUNCTIONAL CHANGES DURING CEREBRAL DEVELOPMENT IN MAMMALS

In the brains of mammals, significant histological changes take place during the period of postnatal development. These changes are characterized by a transitory initial overproduction of synapses and neurotransmitters, followed by the gradual elimination of excess connections (Rakic et al., 1986). Synaptogenesis in the human cerebral cortex seems to be heterochronic, while synaptogenesis increases rapidly in the postnatal period in the primary auditory and visual cortex, in the prefrontal cortex synaptogenesis, and dendritic development occur at much slower pace. Therefore, in humans, cortical development occurs differently in different regions, including the timing of maximum growth and myelinization. However, in Rhesus macaques, the period of synaptogenesis is not only

much shorter than in humans but also occurs similarly in all cortical areas. In both species, postnatal synaptogenesis is followed by a plateau in childhood, in which, synaptic density is significantly higher than in adulthood (Huttenlocher and Dabholkar, 1997).

Changes in local metabolic rates of glucose (LCMR glc) during development have been documented in the brains of humans, macaques, rodents, cats, dogs, and sheep by means of 2-deoxy-2(18F)fluoro-D-glucose (FDG) and positron emission tomography (Chugani et al., 1987). In cats, a positive relationship has been found between LCMR glc and synaptogenesis, or the formation of new synapses, during postnatal development. A positive correlation has also been found between the metabolic maturation of several neuroanatomical regions and the emergence of conducts mediated by those specific regions (Jacobs et al., 1995). Cats have very low LCMR glc levels during the first 15 days after birth, after which, these levels begin to increase until reaching adult values at 60 days. Increases occur again at 90 and 120 days. LCMR glc levels reach their peak at 180 days and then begin to progressively decrease until they reach adult values (Chugani, 1999).

Changes in metabolic rates of glucose during brain development do not seem to be related to myelination. In macaques, all cerebral areas contain myelin at 3–6 months after birth, although myelination does not reach adult values until 3–5 years of age, which is not related to the metabolism of cerebral glucose. The histological evidence indicates that, in Rhesus monkeys neocortical synaptic density increases rapidly during the last 2 months of gestation, and reach levels 30–50% higher than adult levels at 2–4 months after birth. These levels are maintained until 3 years of age at which point they begin to gradually decrease throughout the remainder of the lifecycle, which in this species lasts a little more than 20 years (Boothe et al., 1979; Lidow et al., 1991; Rakic et al., 1986; Zecevic et al., 1989; Zecevic and Rakic, 1991).

Levels of local metabolism of glucose in the macaque are low at birth and progressively increase until the end of the second month after birth; they then remain stable between the ages of 2 and 6 months and subsequently begin to decline, reaching adult values at 3 years of age. Glucose metabolism reaches a plateau between 2 and 6 months, which seems to reflect the massive remodeling of dendrites that follow the overproduction of synapses. In this period, a higher level of metabolic, histological, and behavioral activity takes place in the developing macaque. Elevated values of LCMR glc seem to indicate periods of elevated neuroplasticity (Jacobs et al., 1995; Moore et al., 2000).

There relationship has been proved between synaptogenesis, dendritic reorganization, and LCMR glc in humans. In *H. sapiens*, local metabolism of glucose begins to increase at between 1 and 2 years of age, coinciding with the increase in synaptic density and the growth in dendritic length, which reach their maximum levels at between 8 and 10 years of age. In the human striate cortex, synaptic density reaches 60% higher than adult levels at between 8 months and 1 year of age, whereas in the frontal cortex, synaptic density reaches 50% higher than adult levels at between 1 and 2 years of age. After synaptic density reaches its peak, dendritic growth continues for several more years. Maximum dendritic length is reached in humans at between 8 and 10 years of age (Huttenlocher, 1979; Huttenlocher et al., 1982; Huttenlocher and de Courten, 1987; Jacobs and Scheibel, 1993; Mrzijak et al., 1990; Schade and van Groenigen, 1961). The plateau for cerebral glucose metabolism occurs in humans at between 4 and 9–10 years of age (Jacobs et al., 1995). Neuronal maturation, therefore, seems to take place more slowly in humans than in other mammals.

At birth, local rates of glucose use (LCMR glc) in humans are 30% lower than those of a normal young adult. In newborn humans, the highest metabolism rates of glucose are seen in the somatosensorial and somatomotor cortices, thalamus, brain stem, and cerebellar vermis. The rest of the cerebral cortex exhibits very low levels of glucose metabolism (Chugani, 1999). Between birth and 4 years of age, a pronounced increase in LCMR glc occurs in the human cerebral cortex, reaching levels twice as high as those of adults. These changes are only found in cortical areas and do not occur in the brain stem, thalamus, or basal ganglia. Between 4 and 9–10 years of age, the human cerebral cortex continues to register a LCMR glc that is twice as high as that of an adult. At about 9–10 years of age, cortical LCMR glc begins to decline reaching adult levels between 16 and 18 years of age (Chugani, 1998).

The maximum period of synaptogenesis seems to be much longer in humans than in other mammals and the human brain undergoes a prolonged period of development before reaching the adult state. In absolute terms, the period of maximum synaptogenesis seems to be much longer in humans than in the nonhuman primates studied to date, such as macaques. In macaques, the maximum LCMR glc value begins to decline long before puberty, while in humans this decrease begins shortly before the onset of puberty. On the other hand, the cerebral cortices of children are characterized by increased neuronal metabolism and synaptic activity and plasticity compared with those of adults.

The duration of the stages of brain cortical development can vary from individual to individual in the human species. Both the duration of the stages of development and the thickness that the cerebral cortex reaches, which reflects the density of neuronal extensions and synaptic connections, seem to a certain extent to be related to intelligence. Intelligence has also been associated with the capacity for neuroplasticity in the adult. In a group of subjects with an average intelligence quotient (IQ) (74–108, average 100), maximum frontal–cortical thickness was reached at 7 years of age, whereas in a group with a high IQ (121–149, average 128), maximum frontal–cortical thickness was reached at 11 years of age. Furthermore, individuals with high IQs have thicker frontal cortices, although in both groups that thickness subsequently decreases slightly (Shaw, 2007). The prolongation of cortical development and the continuity in the fetal rate of cerebral growing during the postnatal period would have given rise to a cortical hypermorphosis, which may be related to higher intelligence.

In the human brain, the fetal growth rate is retained, the stages of development prolonged, development delayed – and all of these are neotenic characteristics. Does the retention of juvenile characteristics into adulthood also occur in the neurons of certain human cortical areas? The characteristics of infant neurons in certain cortical areas in mammals, and especially in primates, consist of an elevated neuronal metabolism and elevated synaptic plasticity and activity. In the human being, some

of these childhood characteristics appear to have been retained in certain neurons even after development has stopped. Synaptic plasticity in adult stages has been linked to learning and memory. We briefly describe the existing relationships between the two-related processes.

## LEARNING, MEMORY, AND SYNAPTIC PLASTICITY

The study of different varieties of memory systems, from elemental forms of implicit memory in invertebrates and mammals to more complex forms of explicit memory based in the hippocampus, suggests that the key mechanism by which these different forms of memory are encoded, processed, and stored in the brain is modulated depending on the activity – both in terms of strength and structure – of specific synaptic connections. Short-term memory, which lasts only a few minutes, requires alterations in the effectiveness of pre-existing synaptic connections, which are the result of covalent modifications of also pre-existing proteins. On the other hand, long-term memory requires changes in genetic expression, which induce the synthesis of new proteins and the growth of new synaptic connections (Miniaci et al., 2008).

A large part of the new synaptic connections in adult mammals seem to be formed from dendritic spines. Dendritic spines are small protrusions that receive the majority of excitatory synapses. In laboratory cultures, the spines grow to form synapses in response to synaptic stimulation. During development, the spines exhibit structural plasticity depending on experience. In adults, new spines can appear in response to hormonal changes or sensory over-stimulation (Trachtenberg et al., 2002). Protein kinases like PKC and CaMKII play an important role in the formation of new dendritic spines (De Roo et al., 2008). In mice, 65% of new postsynaptic spines of the somatosensorial cortex are transitory during development and appear and disappear within a period of a few days. During development, therefore, a high degree of synaptic turnover takes place. Although in adult neurons the spines are still dynamic, the spine turnover rate is much lower and 73% of the spines are stable within a period of several weeks (Miniaci et al., 2008). Despite this stability, there is evidence that experience can change the cerebral structure of adult mammals. Exposing rodents to an enriching environment increases the complexity of the dendritic ramifications and the number of synapses. In primates (*Callithrix jacchus*), a 1-month stay in a complex environment increased the density of dendritic spines as well as the length and complexity of the dendrites in neurons of the hippocampus and prefrontal cortex. Levels of expression of several synaptic proteins in those areas also increased. All of the animals studied were sexually mature. These works indicate that the brains of rodents and primates maintain a certain degree of plasticity in adulthood, although not as high as that of developing brains. Therefore, it is clear that structural processes typically associated with cerebral development, like synaptogenesis, continue operating in the brains of adult mammals (Holtmaat et al., 2005; Kozorovitskiy et al., 2005).

Learning induces the remodeling of neural circuits through de novo synaptogenesis or morphological changes that lead to increased synaptic connectivity and the appearance of new functional units such as dendritic spines, or the conversion of silent synapses into active synapses (Bruel-Jungerman et al., 2007). Neuronal changes induced by learning are similar to the neuronal growth and differentiation process in a broad segment of the animal kingdom. These changes reflect the fact that environmental stimuli take advantage of development processes that are latent or inhibited in differentiated neurons. The synaptic changes associated with learning and memory storage in the adult brain reuse important mechanisms for the formation and adjustment of synaptic connections during the development of the nervous system (Bailey and Kandel, 2008). Did an increase in synaptic plasticity occur in certain neurons during the evolution of the genus *Homo*, which did not take place in nonhuman primates?

## FUNCTIONAL AND STRUCTURAL NEURONAL CHANGES DURING THE EVOLUTION OF THE HUMAN BRAIN

The cerebral cortex contains many different types of neurons, including projection neurons with long axons and neurons with short axons, which contribute to the make-up of local circuits. Projection neurons only reach functional maturity after axon myelination (Braak and Braak, 1996; Braak et al., 2006). The primary areas were the starting points of neocortical evolution, and in many mammals, these make up most of the neocortex. The primary areas are those organized in the most complex manner, whereas first order or unimodal, association areas, and premotor areas are organized more simply, and polymodal association areas are organized yet more simply. As the distance from the primary areas and the proximity to the allocortex increases (hippocampus, olfactory bulb, etc.), the structural immaturity of the association areas also increases (Arendt et al., 1998; Braak and Braak, 1996; Braak et al., 2006).

Myelination begins in the prenatal period, progresses in a specific sequence and continues into adulthood. It begins in the primary areas of the neocortex, continues in the premotor cortex and first-order association areas and finally takes place in the prefrontal cortex and heteromodal-association areas. As the distance from the primary areas grows, the average content of myelin gradually decreases (Yakovlev and Lecours, 1967). The last areas to myelinate are those of the anterior mesocortex, which remain poorly myelinated in the adult human. The mesocortex is made up of the transition zones between the allocortex and the neocortex, which mature relatively late in primates and even more so in humans (Nieuwenhuys, 1999).

Cortical projection neurons with incompletely myelinated axons are chronically subject to a high-energetic turnover and, as a result, are more susceptible to the influence of oxidative stress (Braak et al., 2006). Therefore, there are relatively extensive areas of the human-cerebral cortex that remain structurally immature throughout our lifespan. During the evolution of primates, and especially of apes and humans, the size of these areas increased considerably (Braak et al. 2006).

Many studies conducted in recent years have shown that the adult-human cerebral cortex has undergone an increase in the expression of genes related to aerobic metabolism and synaptic plasticity and activity. Genetic variants that induce increased-synaptic plasticity in our species also seem to have been selected. Researchers have documented the positive selection and accelerated evolution of genes that intervene in the mitochondrial electron

transport chain in anthropoid primates and a higher expression of such genes in both chimpanzees and humans. The increase in the expression of genes related to aerobic metabolism is more pronounced in humans and is particularly clear in the anterior-cingulate cortex (Uddin et al., 2004). This suggests that the energetic-metabolic pathways that support neuronal function in adults were modified during the evolution of the common ancestors of chimpanzees and humans and that they underwent new modifications in our human ancestors. These modifications indicate an increased functional activity and neuronal metabolic demand in both species (Uddin et al., 2004, 2008).

The neurotransmitter serotonin (5 HT) plays an important role in memory, learning, and other cognitive functions. Cortical serotonergic innervation in primates seems to be more complex and regionally heterogeneous than in other mammals. Drugs that increase serotonergic activity improve memory, attention span, and processing speed in rodents and macaques. Dysfunctions in the serotonergic system contribute to the onset of depression, obsessive compulsive disorders, anxiety disorders, and impulse control disorders. To test whether humans have a unique pattern of serotonergic innervation in relation to other primates, areas 9 and 32 of the prefrontal cortex and area 4 of the primary motor cortex were examined in macaques, chimpanzees, and humans. Area 9 is essential for working memory, which is a critical component in the capacity for language, while area 32 has been associated with cognitive capacities such as the theory of the mind. An increase in serotonergic innervation in the infragranular layers of the prefrontal cortex occurred during the evolution of humans and chimpanzees. The axons of these serotonergic neurons exhibit a spiral morphology (coils), which has been related to increased plasticity, suggesting evolution toward increased cortical plasticity, learning, and behavioral flexibility in these species (Raghanti et al., 2008).

Comparing genetic expression in the cerebral cortex of humans, chimpanzees, and macaques through different independent techniques, changes in genetic expression in the human cortex were found to be attributable mainly to an increase in expression, and a large part of the genes that have increased their expression in humans are related to high levels of neuronal activity (Cáceres et al., 2003). General levels of neuronal activity and the metabolic processes related to it are unusually high in the adult human cerebral cortex compared with nonhuman primates. Increased expression has been documented in genes related to synaptic transmission such as *SYN47*; synaptic plasticity such as *CAMK2A*, which is involved in learning and memory; the release of synaptic vesicles such as *ATP2B1*; to axonal transport in microtubules like *KIF3A*; to energetic metabolism and lipid metabolism, and the synthesis and turnover of cellular membranes. An increase was also found in humans in the expression of genes related to cellular protection and to the encoding of chaperone proteins, which play a neuroprotective role in controlling protein folding. The elevated expression of genes related to energetic metabolism in the human-cerebral cortex indicates that the general level of physiological activity in the adult-cerebral cortex is higher in humans than in chimpanzees or macaques. Despite the elevated neuronal metabolic rate in humans, the extraordinary longevity of *H. sapiens* may have promoted the selection of neuronal adaptations that allow such cells to function for much longer than in other primates. Human beings have developed adaptations that allow them to maintain elevated levels of neuronal activity over a long-lifetime (Cáceres et al., 2003).

Several of the changes in genetic expression in the human-cerebral cortex are related to an increase in synaptic plasticity. Many of the genes involved in this are also involved in cerebral development. The growth and maintenance of neuronal extensions require the transport, by means of kinesins, of cytoskeleton and organelle proteins associated with the membrane (Morfini et al., 2001). Mitochondria are found between the organelles associated with the membrane, which are transported by kinesins. The proteins transported by the kinesins include neurexin and neuroligin, both involved in the formation of new synapses. Kinesins facilitate the communication between genes and synapses and the over-expression of one of them, *KIF17*, has been found to improve spatial and working memory in mice (Puthanveettil et al., 2008). The machinery needed for releasing and recycling has to be assembled in the presynaptic terminals, but the proteins involved in these processes are synthesized in the cellular body and transported by kinesins to the appropriate location. Levels of the expression of kinesins change during cerebral development in rodents and their peaks of expression correspond to periods of growth and the elongation of neurites in certain areas (Morfini et al., 2001; Puthanveettil et al., 2008). The increase in the expression of kinesin-encoding genes in humans is probably related in part to an increase in synaptic plasticity. The increase in the expression of genes that encode the proteins involved in the synthesis and turnover of neuronal membranes may also be related to synaptic repair and remodeling and the formation of new synapses.

Thrombospondins are glycoproteins of the extracellular matrix that play a role in cellular adhesion, neurite growth, and the formation of synapses. Analyses of the expression of thrombospondin-encoding genes in humans, chimpanzees, and macaques show that thrombospondin-encoding genes 2 and 4 have significantly increased their expression in the human brain. The expression of the gene for thrombospondin 2 has doubled and that of the gene for thrombospondin 4 has increased sixfold in humans compared with chimpanzees and macaques. Increases in the expression of thrombospondins have led to increased-synaptic plasticity in humans, inducing higher synapsis density, higher synaptic turnover, and higher rates of neuritic growth (Cáceres et al., 2007).

Most of the regions of the genome that show an accelerated rate of substitutions in the human lineage, since the divergence from the common ancestor of humans and chimpanzees, are associated with genes related to transcriptional regulation and neuro-development. *HAR1* has undergone the most changes and is part of a gene expressed during human-cortical development. In the adult brain, *HAR1* is expressed in the frontal cortex, hippocampus, thalamus, and hypothalamus. *HAR1* seems to influence the expression of reelin, a protein of the extracellular matrix (Pollard et al., 2006).

Reelin plays a role in the cortical development of the fetus and, in adulthood, in synaptic plasticity. The increase in the expression of reelin was a key element, which gave rise to the increased cortical development that occurred during the evolution of mammals (Aboitiz et al., 2002; Bar et al., 2000). Whereas, the brains of most adult mammals

express reelin only in GABAergic interneurons, especially in the dendritic spines, in primates, it is also expressed in pyramidal neurons, and in humans, the expression of reelin has even been found in glial cells (Roberts et al., 2005). The distribution of reelin is much more widespread in the brains of adult primates than in any other mammal studied to date. All the data point to a relationship between reelin and the modulation of synaptic plasticity in the adult. This modulator role is remarkably distinct in the primate brain (Martinez-Cedeño et al., 2002). The expression of reelin seems to have increased in direct relation to cerebral complexity: the more complex the brain, the more cortical cerebral cells that contain reelin.

In humans, alleles have also been selected, which among other functions, seem to increase synaptic plasticity. These include allele $\epsilon^3$ of the apolipoprotein E, which interacts with reelin, modulating plasticity, and playing an important role in the formation of long-term memory (Bufill and Carbonell, 2006). The human variant of the gene *FoxP2* experienced positive selection during human evolution and all indications suggest that this is due to its capacity to improve linguistic ability. In transgenic mice, it has been shown that the human form of the gene *FoxP2* increases synaptic plasticity of the spiny neurons of the striate and dendritic connections in cortico-basal circuits (Enard et al., 2009). In reptiles, basal ganglia are associated with motor control. They regulate motor control in humans too, but they are also involved in cognitive capabilities, such as working memory, visual memory, and verbal memory. The human variant of *FoxP2*, which has been fixed in the last 200 kyrs, can increase synaptic plasticity and the connectivity of basal ganglia, which in turn, can increase cognitive flexibility, creating the potential for language and creativity. Synaptic plasticity is essential to the neuronal encoding and processing of information and allows the formation of new associations and patterns of behavior (Lieberman, 2009).

High degrees of synaptic plasticity and activity in the adult human brain seem to have been retained through an increase in the expression of certain genes, many of which are related to cerebral development and, to a lesser extent, through the positive selection of certain genetic variants. This increased genetic expression in humans that has not occurred equally in all areas of the brain: in the anterior cingulate cortex, there is a higher expression than in the visual or primary motor cortices, which exhibit very few differences between them, and in the cortical areas of association, this increased expression is higher than in the primary areas or in phylogenetically older structures, such as the caudate nucleus or the cerebellum (Khaitovich et al., 2004). Changes in genetic expression occur due to modifications in transcription-coding sequences, DNA methylation, replacements in nucleotides, insertions and deletions in promoter regions or other regulatory regions, genetic duplications, and the reorganization of chromosomes (Preuss et al., 2004).

Analyses were recently conducted on the levels of genetic expression of 7,958 genes in the brains of humans, chimpanzees, and macaques during the postnatal-development period. The study focused on maturation in the prefrontal cortex and caudate nucleus. The prefrontal cortex is the last region to mature during ontogeny, whereas, the caudate nucleus matures relatively early. It was found that in human beings, 2,979 genes are expressed differently between the two regions and that 58% of those matured more slowly in the prefrontal cortex than in the caudate nucleus. In different regions of the human prefrontal cortex, such as the superior and dorsolateral frontal gyrus, the number of neotenic genes, i.e., genes whose expression in humans correspond to that of young chimpanzees, was double that of neotenic genes in chimpanzees. Adult human beings were found to be similar to juvenile chimpanzees in terms of their cerebral genetic expression profiles. Neotenic changes only affected a limited group of genes expressed in the brain and not in the complete cerebral transcriptome, which suggests mosaic evolution and indicates that neotenic genes tend to be related to cerebral growth and development. Differences in the cerebral genetic expression between humans and chimpanzees are relatively small at birth, but subsequently increase. The tendency toward neoteny in humans is particularly prominent during the early phases of adolescence, a period of substantial cortical reorganization (Somel et al., 2009).

Brain-glucose metabolism is mainly used to supply energy by means of oxidative phosphorylation. When glucose metabolism exceeds that used in oxidative phosphorylation, in the presence of oxygen, aerobic glycolysis takes place. Aerobic glycolysis is involved in cell proliferation, and in the brain, it may be related to cell development in fetuses and newborns and to activity-dependent synaptic changes in adults. In synapses, aerobic glycolysis is associated with the flow of glutamate and Na+ to the astrocytes and with the regulation of the turnover of the AMPA receptor in the postsynaptic area of the dendritic spines by means of the Na+/K+-ATPase pump, as well as with the biosynthesis of proteins, lipids, and nucleic acids. Cerebral aerobic glycolysis represents 35% of the glucose used in the brains of newborns, while in adults, it represents 11% in sleeping subjects and 19% in awake individuals (Vaishnavi et al., 2010). As discussed in more detail below, recent findings show that certain association areas in the human brain retain elevated levels of aerobic glycolysis in adulthood, which suggests the possibility that elevated synaptic activity and plasticity persist in these areas in later stages of life (Buckner et al., 2008; Vaishnavi et al., 2010).

Aerobic glycolysis in the adult human brain, which seems to be related to an increase in synaptic activity and plasticity, is significantly elevated in certain areas of the cortex of association related to cognitive functions, which have undergone considerable modification during the evolution of the human species. A significant increase in aerobic glycolysis has been detected in the dorsolateral prefrontal cortex, which is associated with working memory, and in a group of areas that make up the brain's default-mode network, which display elevated activity when the individual is at rest and not engaged in any purposeful activity. These areas are the ventromedial prefrontal cortex, the dorsomedial prefrontal cortex, the posterior cingulate cortex, the inferior parietal lobe, the lateral temporal cortex, and the hippocampus and surrounding areas (Buckner et al., 2008; Vaishnavi et al., 2010). They include areas 9 and 32, which have undergone evolutionary changes in the serotoninergic innervations that very likely led to increased-synaptic plasticity (Raghanti et al., 2008) and prefrontal area 10, which in humans is relatively large compared with the homologous area in the great apes and has a higher number of connections with other areas of association (Semendeferi et al., 2001). An

increase in activity has also been detected in areas of the chimpanzee brain that would correspond to the brain's default network in humans, but whether an increase in aerobic glycolysis takes place in those areas is unknown (Rilling et al., 2007). Using functional connectivity analysis, homologous regions have also been discovered in the brain's default-mode network of the brain of the macaque, including the cingulate cortex, the inferior parietal lobe, the hippocampus and the parahippocampal region, the superior temporal gyrus, and the prefrontal cortex (Vincent et al., 2007). It is not known if the increase in synaptic activity and plasticity which occurs in the human brain's default network is a specialization of the brain of *H. sapiens* or if it also occurs in other primate species. Since human cerebral metabolism is far greater than in other primate species and the brain's default-mode network is located among the areas in which the greatest metabolism is observed, it seems likely that the increased-synaptic plasticity that occurs in this area would be greater in humans than in nonhuman primates, which would therefore, constitute human specialization. However, this hypothesis can only be confirmed by subsequent studies.

The increase in metabolism of the human brain may be partially explained by the increase in brain size and the consequent increase in the length of neuronal extensions. However, the fact that this increase is more pronounced in certain areas of the brain, regardless of the length of the neuronal extensions and the increase in the expression of genes related to synaptic activity and plasticity in certain areas of the human cerebral cortex, suggest that these areas have given rise to increased gene expression, which would have led to an elevated capacity for learning and memory in adulthood.

Neurons belonging to certain areas of the human cerebral cortex exhibit a higher metabolism and a higher degree of synaptic plasticity and activity in adulthood than the cortical neurons of other mammals, including nonhuman primates. So it appears that human neurons belonging to particular association areas retain juvenile characteristics throughout adulthood, which suggests that a neuronal neoteny has occurred in *H. sapiens*, which allows the human brain to function, to a certain degree, like a juvenile brain during adult life.

## POSSIBLE SELECTIVE PRESSURES RESPONSIBLE FOR NEURONAL NEOTENY

The human adaptation to the "cognitive niche" (Barret et al., 2007; Tooby and De Vore, 1987) may have been one of the selective pressures that led to neuronal neoteny. The language and symbolic culture characteristic of *H. sapiens* imply the dependence on learning and memory throughout our lives. This, in turn, requires an increase in synaptic plasticity, which may have given rise to a strong-selective pressure that favored both an increase in genetic expression and the selection of alleles capable of improving that plasticity (Bufill and Carbonell, 2006). The gene–culture coevolution may have played an important role in human cerebral evolution (Lumsden and Wilson, 1981, 1983). Neuronal neoteny may have resulted from that gene–culture coevolution.

Neuronal neoteny in *H. sapiens* is still an exaggeration of tendencies already observed in nonhuman primates and especially in the great apes. Nonhuman primates had to adapt to an arboreal environment and a relatively complex social life, which fostered an improved ability to store and process information. This brought with it a larger brain and higher intelligence, which resulted in decreased fatalities at the hands of predators, a longer period of development, and a longer lifespan – tendencies that are accentuated in the great apes, which have larger brains and live longer lives than monkeys, and especially in *H. sapiens* due to the cognitively demanding niche to which our species had to adapt (Kaplan and Robson, 2002). Neuronal neoteny contributes to increasing information storage and processing capacities throughout life, which is why it was selected during primate evolution and, to a much greater extent, during the evolution of the genus *Homo*.

In *H. sapiens*, adults of a relatively advanced age whose memories functioned as living repositories of information may have been useful for the successful adaptation to the increasing-cultural complexity that took place during the Paleolithic, and especially after the Upper Paleolithic. Through a feedback process, growing cultural complexity would have increased the chance for survival of individuals of a relatively advanced age, who were responsible for the transmission of information from generation to generation (Caspari and Lee, 2004; Rosenberg, 2004). The simultaneous increase in intelligence and longevity were a possible consequence of the adaptation of *H. sapiens* to the "cognitive niche," which required the prolongation of the period of development and the preservation of juvenile characteristics in adulthood in certain neurons belonging to the cortical areas that evolved most during human evolution: the areas of association.

The recent finding of an increase in aerobic glycolysis and, therefore, in synaptic activity and plasticity in the dorsolateral prefrontal cortex and in the brain's default network, however, suggests that other selective pressures may have also influenced the retention of juvenile neuronal characteristics in the human species. The dorsolateral prefrontal cortex is related to working memory, whereas the brain's default network is related to autobiographical memory, planning, and functions related to social interaction and navigation, such as the theory of the mind and moral decision-making (Buckner et al., 2008; Vaishnavi et al., 2010). It is therefore possible that the increase in working memory, social complexity, and the need to plan future behavior had as much or more influence on the development of neuronal neoteny as did culture.

## NEURONAL NEOTENY AND BRAIN VULNERABILITY

The increase in the aerobic metabolism occurring in human neurons that retain certain juvenile characteristics in adulthood, such as incomplete myelination or elevated synaptic activity and plasticity, can make these neurons more likely to exhibit greater oxidative stress with age, and can make them more vulnerable to that stress. This may contribute to the development of exclusively or predominantly human neurodegenerative diseases such as Alzheimer's or frontal dementia. Actually, the distribution of the β-amyloid brain plaques is almost coincident with the brain's default network. This strongly suggests that the elevated-synaptic plasticity and activity enhances the development of the abnormal peptide deposits, which are characteristic of Alzheimer's disease, each case being

dependent on inter-individual metabolic efficiency (Buckner et al., 2008; Vlassenko et al., 2010).

After the age of 40, a considerable reduction in the cortical expression of certain genes takes place in humans, especially in those related to synaptic plasticity, vesicular transport, and mitochondrial function (Lu et al., 2004). In other words, relatively reduced expression occurs in genes related to learning and memory, whose activity increased during human cerebral evolution. Meanwhile, other genes, in general, those with neuroprotective functions, increase their expression with age. There is a great inter-individual variability in this decrease in genetic expression. The decrease in expression occurs, most of all, in the cortical areas of association and hardly ever in the primary areas, the cerebellum, or other phylogenetically older cerebral areas. It also seems that the decrease in expression of these genes does not occur in chimpanzees or in other nonhuman primates. Given that the decrease in genetic expression occurs in the cortical areas with the highest metabolism, and that oxidative stress has been shown to cause selective damage in the promoter region of these genes in neuronal cultures, oxidative stress brought on by an elevated metabolism is very likely the cause of the decrease in the expression of the genes related to learning and memory that human beings undergo as they age (Lu et al., 2004; Fraser et al., 2005). Alzheimer's disease is practically exclusively human, with the only exception being a case detected in a domestic chimpanzee of advanced age (Rosen et al., 2008), although nonhuman primates and some carnivores have been found to exhibit cerebral lesions in old age that may prove to be a form of incomplete Alzheimer's (Cork et al., 1988; Erwin et al., 2001; Gearing et al., 1994, 1997; Head et al., 2001; Poduri et al., 1994; Price, 1993; Walker, 1993).

Multiple lines of evidence have shown that oxidative stress is not only always associated with Alzheimer's disease but also it is one of the first events that occurs in the onset of the disease (Shi and Gibson, 2007; Su et al., 2008). In fact, the lesions common to the disease initially appear in the incompletely myelinated neurons of the limbic system, which are related to memory and learning, and of the cortex of association and only in the last phases of the disease are the highly myelinated neurons of the primary areas affected and, even then, they are affected to a much-lesser extent. These incompletely myelinated neurons exhibit a high metabolism and an increased tendency toward oxidative stress with age (Braak and Braak, 1996; Braak et al., 2006). Oxidative stress seems to be capable of inducing hypermethylation in the promoter region of different genes, including those related to synaptic plasticity. Many of the genes associated with Alzheimer's disease are involved in such plasticity (Forero et al., 2006) and many studies have suggested that the decrease in the expression of genes related to neuroplasticity may induce the hyperphosphorylation of tau and the β-amyloid deposits characteristic of the disease (Patrick et al., 1999; Saura et al., 2004). Hypermethylated genes seem to be more susceptible to the toxic action of the peptide β-amyloid (Zawia et al., 2009), which may create a feedback mechanism that would accelerate the deposit of abnormal peptides common to Alzheimer's disease.

A recent study suggests that an excessive increase in synaptic activity may be one of the most important factors in the regulation of the production and secretion of β-amyloid in the interstitial fluid of the brain (Bero et al., 2011). In the study, the whiskers of transgenic mice which produce β-amyloid plaques with age and whose barrel cortex had been previously studied were unilaterally hyperstimulated. The results suggest that factors that elevate endogenous neuronal activity during prolonged periods accelerate the deposit of β-amyloid. At rest, the brain's default-mode network in human carriers of the allele ApoE ϵ4—who are at greater risk of developing Alzheimer's—has been shown to be more active compared with noncarriers of the allele. The elevated-synaptic activity and plasticity of the brain's default-mode network in humans may make this system more prone to the development of the lesions commonly associated with Alzheimer's disease (Bero et al., 2011; Walker and Jucker, 2011). Neuronal neoteny may have given rise to an increase in oxidative stress, which, in some individuals, has led to the deposit of the abnormal peptides characteristic of Alzheimer's disease. The great apes are long-living animals that, although to a lesser degree than humans, also have increased neuronal metabolism, which is why they too may occasionally develop the disease.

Frontal dementia, another exclusively human disease, is associated in its initial phases with the severe, selective affectation of the spindle or von Economo neurons of the anterior-cingulate cortex and the frontoinsular cortex, another important node in the default network. These cells are exclusive to human beings, chimpanzees, bonobos, gorillas, and orang-utans, although similar neurons have been found in some cetaceans and in elephants. They probably play a role in social and emotional conduct. Von Economo cells in *H. sapiens* are larger and more numerous than in the great apes. In humans, these cells are not detected until after birth, they mature slowly and late and do not reach adult values until 4 years of age (Seeley et al., 2006). The delayed development of these neurons and of the anterior-cingulate cortex (one of the areas of the brain that in humans has a higher metabolism and therefore is more susceptible to oxidative stress), suggests that neuronal neoteny may be the cause of humans' unique propensity for developing frontal dementia.

Schizophrenia is another disease that is apparently unique to humans, with onset generally occurring in late adolescence. One of the more noteworthy negative symptoms of the illness is the loss of neotenic psychological characteristics such as curiosity and the ability to learn in adulthood. Patients exhibit apathy, a lack of curiosity and motivation, a lack of behavioral flexibility, and a significant decrease in learning ability (Bemporad, 1991). Many studies have found a decrease in the expression of reelin, a protein related to synaptic plasticity, in the hippocampus and prefrontal and temporal cortices of schizophrenic patients (Eastwood and Harrison, 2006). The brain's default-mode network has also been found to have abnormal activation and connectivity in schizophrenic patients (Garrrity et al., 2007; Harrison et al., 2007). The default-mode network of these patients seems to be hyperactive in certain areas, such as the posterior-cingulate cortex, and hypoactive in others, such as the prefrontal cortex, the anterior-cingulate cortex, and the parahippocampal region. This results in changes in the connectivity of this system with other cerebral networks and alterations in the communication of the default mode with other areas of the brain. The dysfunction of the default mode may also cause hyperactivity in other areas of the brain, which could interfere with normal thought processes, leading to the

delirium, hallucinations, and attention deficits that characterize the illness (Garrity et al., 2007).

Some primarily or exclusively human neurodegenerative diseases or neurodevelopment disorders may be, in part, the result of the retention of juvenile characteristics in adulthood in certain neurons associated with learning, memory, and other complex cognitive functions.

## CONCLUDING REMARKS

The adult human cerebral cortex has undergone an increase in the expression of genes related to aerobic metabolism and synaptic plasticity and activity compared with those of nonhuman primates. This increased expression has been mainly caused by changes in the promoter region of these genes, many of which are involved in cerebral development. Alleles capable of inducing increased neuroplasticity have also been selected in humans and the cortical expression of neuroprotectors has also increased. The comparison of cortical genetic expression between humans and chimpanzees shows that adult humans are similar to juvenile chimpanzees in terms of their cerebral genetic expression. Changes in genetic expression are especially clear in the prefrontal and temporoparietal areas of association and in the anterior-cingulate cortex. Human beings have developed adaptations that allow them to maintain elevated levels of synaptic plasticity and activity over a long-lifetime. Certain human neurons belonging to the areas of association or related to memory, planning future actions, and social interactions retain juvenile characteristics throughout adulthood, which suggests that in *H. sapiens* a neuronal neoteny has occurred. In other words, pedomorphic characteristics have been retained. Many different factors could have acted as selective pressures leading to neuronal neoteny. Because of the adaptation of humans to our cognitive niche and the importance of language and symbolic culture, the gene–culture coevolution may have played a role both in the delay of development and in the retention of juvenile neuronal characteristics in adulthood. Social complexity could have been another significant selective pressure.

In mammals, most learning takes place during the development stage. Learning requires morphological changes in neuronal connections or synapses—changes which include everything from remodeling to the formation of new synapses. The potential for these changes to occur is known as synaptic plasticity. These processes also take place in adult mammals, albeit to a much lesser degree. The genus *Homo* evolved in a demanding cognitive niche and *H. sapiens* depends on the transmission of culture through language, which made the human brain into a living repository of knowledge during most of our evolution. Due to the importance that learning and memory have taken on in human beings, some authors have suggested the possibility that certain neurons or cerebral areas retain juvenile characteristics, which would permit increased-synaptic plasticity and activity in adulthood. Moreover, an increase in the social complexity and the need for an extended planning and working memory may have played a more relevant role than pure cultural factors in this increase of synaptic plasticity.

The increased-synaptic plasticity might explain, in part, how the functional superiority of the human brain has been achieved without a comparable increase in the informational content of the genome of our species. In all mammal species studied, cortical neurons exhibit elevated synaptogenesis, synaptic activity, and dendritic reorganization during development, as well as an elevated metabolism. The cerebral cortices of children are characterized by increased neuronal metabolism and synaptic activity and plasticity compared with those of adults. The peak period of synaptogenesis seems to be much longer in humans than in other mammals. The deceleration of cerebral development has also occurred in nonhuman primates, especially in the great apes, but this characteristic is accentuated in *H. sapiens*. Certain areas of the human brain such as the areas of association, which have undergone a considerable increase in size during the evolution of primates and especially of humans, are structurally immature in adulthood and their neurons are incompletely myelinated. The neurons in these areas, therefore, retain pedomorphic characteristics in adulthood.

The increase in aerobic metabolism that took place in the human beings become older and may contribute to the development of exclusively or primarily human neurodegenerative and neurodevelopmental diseases such as Alzheimer's, frontal dementia, and schizophrenia, which may be the price our species pays for our elevated cognitive capacity, our longevity, and our advanced-social intelligence.

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## LITERATURE CITED

Aboitiz F, Montiel J, Lopez J. 2002. An hypothesis on the early evolution of the development of the isocortex. Brain Res Bull 57:481–483.

Arendt T, Brückner MK, Gertz HJ, Marcova L. 1998. Cortical distribution of neurofibrillary tangles in Alzheimer's disease matches the pattern of neurons that retain their capacity of plastic remodeling in the adult brain. Neuroscience 83:991–1002.

Bailey CH, Kandel ER. 2008. Synaptic remodeling, synaptic growth and the storage of long-term memory in *Aplysia*. Prog Brain Res 169:179–198.

Bar I, Lambert de Rouvroit C, Goffinet A. 2000. The evolution of cortical development: an hypothesis based on the role of the reelin signaling pathway. Trends Neurosci 23:633–638.

Barrett HC, Cosmides L, Tooby J. 2007. The hominid entry into the Cognitive Niche. In: Gangestad SW, Simpson JA, editors. The evolution of mind. New York: The Guilford Press. p 241–248.

Bemporad JR. 1991. Dementia praecox as a failure of neoteny. Theor Med 12:45–51.

Bero AW, Yan P, Roh JH, Cirrito JR, Stewart FR, Raichle ME, Lee JM, Holtzman DM. 2011. Neuronal activity regulates the regional vulnerability to amyloid-β deposition. Nat Neurosci 14:750–756.

Bogin B. 2006. Modern human life history: the evolution of human childhood and fertility. In: Paine RR, Hawkes K, editors. The evolution of human life history. Santa Fe, New Mexico: School of American Research Press. p 197–230.

Bolk L. 1926. Das problem der menschwerdung. Jena: Gustav Fisher.

Boothe RG, Greenhough WT, Lund JS, Wrege K. 1979. A quantitative investigation of spine and dendritic development of neurons in visual cortex (area 17) of *Macaca nemestrina* monkeys. J Comp Neurol 186:473–490.

Braak H, Braak E. 1996. Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. Acta Neuropathol 92:197–201.

Braak H, Rüb U, Schultz C, Del Tredici K. 2006. Vulnerability of cortical neurons to Alzheimer's and Parkinson's diseases. J Alzheimers Dis 9:35–44.

Bruel-Jungerman E, Davis S, Laroche S. 2007. Brain plasticity mechanisms and memory: a party of four. Neuroscientist 13:492–505.

Buckner RL, Andrews-Hanna JR, Schacter DL. 2008. The Brain's Default Network. Anatomy, function and relevance to disease. Ann N Y Acad Sci 1124:1–38.

Bufill E, Carbonell E. 2006. Apolipoprotein E polymorphism and neuronal plasticity. Am J Hum Biol 18:556–558.

Cáceres M, Lachuer J, Zapala MA, Redmond JC, Kudo L, Geshwind D, Lockhart DJ, Preuss TM, Barlow C. 2003. Elevated gene expression levels distinguish human from non-human primate brains. Proc Natl Acad Sci USA 100:13030–13035.

Cáceres M, Suwyn C, Maddox M, Thomas JW, Preuss TM. 2007. Increased cortical expression of two synaptogenic thrombospondins in human brain evolution. Cereb Cortex 17:2312–2321.

Caspari R, Lee SH. 2004. Older age becomes common late in human evolution. Proc Natl Acad Sci USA 101:10895–10900.

Caviness VS, Kennedy DN, Richelme C, Rademacher J, Filipeck PA. 1996. The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. Cereb Cortex 6:726–736.

Chugani HT, Phelps ME, Mazziotta JC. 1987. Positron emission tomography study of human brain functional development. Ann Neurol 22:487–497.

Chugani HT. 1998. A critical period of brain development: studies of cerebral glucose utilization with PET. Prev Med 27:184–188.

Chugani HT. 1999. Metabolic imaging: a window on brain development and plasticity. Neuroscientist 5:29–40.

Cork L, Powers R, Selkoe D, Davies P, Geyer J, Price D. 1988. Neurofibrillary tangles and senile plaques in aged bears. J Neuropathol Exp Neurol 47:629–641.

de Beer G. 1951. Embryos and ancestors. New York: Oxford University Press.

De Roo M, Klauser P, Mendez Garcia P, Poglia L, Muller D. 2008. Spine dynamics and synapse remodeling during LTP and memory processes. Prog Brain Res 169:199–207.

Eastwood SL, Harrison PJ. 2006. Cellular basis of reduced cortical reelin expression in schizophrenia. Am J Psychiatry 163:540–542.

Enard W, Gehre S, Hammerschmidt K, Hölter SM, Blass T, Somel M, Brückner MK, Schereiweis C, Winter C, Sohr R, Becker L, Wiebe V, Nickel B, Giger T, Müller U, Groszer M, Adler T, Aguilar A, Bolle I, Calzada-Wack J, Dalke C, Erhardt N, Favor J, Fuchs H, Gailus-Durner V, Hans W, Hölzwimmer G, Javaheri A, Kalaydjiev S, Kallnick M, Kling E, Kunder S, Mobbrugger I, Naton B, Racz I, Rathkolb B, Rozman J, Schrewe A, Busch DH, Graw J, Ivandic B, Klingenspor M, Klopstock T, Ollert M, Quintanilla-Martinez L, Schulz H, Wolf E, Wurst W, Zimmer A, Fisher SE, Morgenstern R, Arendt T, Hrabé de Angelis M, Fisher J, Schwarz J, Pääbo S. 2009. A humanized version of FoxP2 affects corticobasal ganglia circuits in mice. Cell 137:961–971.

Erwin J, Nimchinsky E, Gannon P, Perl D, Hof P. 2001. The study of brain aging in great apes. In: Hof P, Mobbs C, editors. Functional neurobiology of aging. San Diego: Academic Press. p 447–455.

Fraser HB, Khaitovich P, Plotkin JB, Pääbo S, Eisen MB. 2005. Aging and gene expression in the primate brain. PLoS Biol 3:1653–1661.

Forero DA, Casadesus G, Perry G, Arboleda H. 2006. Synaptic dysfunction and oxidative stress in Alzheimer's disease: emerging mechanisms. J Cell Mol Med 10:796–805.

Garrity AG, Pearlson GD, McKiernan K, Lloyd D, Kiehl KA, Calhoun VD. 2007. Aberrant "default mode" functional connectivity in schizophrenia. Am J Psychiatry 164:450–457.

Gearing M, Rebeck G, Hyman B, Tigges J, Mirra S. 1994. Neuropathology and apolipoprotein E profile of aged chimpanzees: implications for Alzheimer disease. Proc Natl Acad Sci USA 91:9382–9386.

Gearing M, Tigges J, Mori H, Mirra S. 1997. β-Amyloid (Aβ) deposition in the brains of aged orangutans. Neurobiol Aging 18:139–146.

Gibson KR. 1990. New perspectives on instincts and intelligence: brain size and the emergence of hierarchical mental construction skills. In: Parker ST, Gibson KR, editors. "Language" and intelligence in monkeys and apes. New York: Cambridge University Press. p 97–128.

Gould SJ. 1977. Ontogeny and phylogeny. Cambridge, MA: The Belknap Press of Harvard University Press.

Harrison BJ, Yücel M, Pujol J, Pantelis C. 2007. Task-induced deactivation of midline cortical regions in schizophrenia assessed with fMRI. Schizophr Res 91:82–86.

Hawkes K. 2006. Slow life histories and human evolution. In: Paine RR, Hawkes K, editors. The evolution of human life history. Santa Fe, NM: School of American Research Press. p 95–126.

Head E, Milgram N, Cotman C. 2001. Neurobiology models of aging in the dog and other vertebrate species. In: Hof P, Mobbs C, editors. Functional neurobiology of aging. San Diego: Academic Press. p 457–468.

Holtmaat AJGD, Trachtenberg JT, Wilbrecht L, Sheperd GM, Zhang X, Knott GW, Svoboda K. 2005. Transient and persistent dendritic spines in the neocortex in vivo. Neuron 45:279–291.

Huttenlocher PR. 1979. Synaptic density in human frontal cortex. Developmental changes and effects of aging. Brain Res 163:195–205.

Huttenlocher PR, de Courten C, Garey LJ, Van der Loos H. 1982. Synaptogenesis in human visual cortex: evidence for synapse elimination during normal development. Neurosci Lett 33:247–252.

Huttenlocher PR, de Courten C. 1987. The development of synapses in the striate cortex of man. Hum Neurobiol 6:1–9.

Huttenlocher PR, Dabholkar AS. 1997. Regional differences in synaptogenesis in human cerebral cortex. J Comp Neurol 387:167–178.

Jacobs B, Scheibel AB. 1993. A quantitative dendritic analysis of Wernicke's area in humans. I. Lifespan changes. J Comp Neurol 327:83–96.

Jacobs B, Chugani HT, Allada V, Chen S, Phelps ME, Pollack DB, Raleigh MJ. 1995. Developmental changes in brain metabolism in sedated rhesus macaques and vervet monkeys revealed by positron emission tomography. Cereb Cortex 3:222–233.

Jacobson M. 1977. Development of specific neuronal connections. In: Gould SJ, editor. Ontogeny and phylogeny. Cambridge, MA: The Belknap Press of Harvard University Press. p 401.

Kaplan HS, Robson AJ. 2002. The emergence of humans: the coevolution of intelligence and longevity with intergenerational transfers. Proc Natl Acad Sci USA 99:10221–10226.

Khaitovich P, Muetzel B, She X, Lachmann M, Hellmann I, Dietzsch J, Stiegele S, Do HH, Weiss G, Enard W, Heissig F, Arendt T, Nieselt-Struwe K, Eichler EE, Pääbo S. 2004. Regional patterns of gene expression in human and chimpanzee brains. Genome Res 14:1462–1473.

King MC, Wilson AC. 1975. Evolution at two levels in humans and chimpanzees. Science 188:107–116.

Kollman J. 1905. Neue gedanken über das alter problem von der abstammung des menschen. Corresp.-Bl. Deutsch Ges Anthrop Ethnol Urges 36:9–20.

Kozorovitskiy Y, Gross CG, Kopil C, Battaglia L, McBreen M, Stranahan AM, Gould E. 2005. Experience induces structural and biochemical changes in the adult primate brain. Proc Natl Acad Sci USA 102:17478–17482.

Leigh SR. 2004. Brain growth, life history and cognition in primate and human evolution. Am J Primatol 62:139–164.

Leigh SR, Park PB. 1998. Evolution of human growth prolongation. Am J Phys Anthropol 107:331–350.

Leigh SR, Shea BT. 1996. Ontogeny of body size variation in African apes. Am J Phys Anthropol 99:43–65.

Lidow MS, Goldman-Rakic PS, Rakic P. 1991. Synchronized overproduction of neurotransmitter receptors in diverse regions of the primate cerebral cortex. Proc Natl Acad Sci USA 88:10218–10221.

Lieberman P. 2009. FOXP2 and human cognition. Cell 137:800–802.

Lu T, Pan Y, Kao SY, Li C, Koshane I, Chan J, Yankner BA. 2004. Gene regulation and DNA damage in the ageing human brain. Nature 429:883–891.

Lumsden CJ, Wilson EO. 1981. Genes, mind and culture. The coevolutionary process. Cambridge, MA: Harvard University Press.

Lumsden CJ, Wilson EO. 1983. Promethean fire: reflections on the origin of mind. Cambridge, MA: Harvard University Press.

Martinez-Cedeño V, Galazo MJ, Cavada C, Clascá F. 2002. Reelin immunoreactivity in the adult primate brain: intracellular localization in projecting and local circuit neurons of the cerebral cortex, hippocampus and subcortical regions. Cereb Cortex 12:1298–1311.

McKinney ML, McNamara KJ. 1991. Heterochrony: the evolution of ontogeny. New York: Plenum Press.

Miniacci MC, Kim JH, Puthanveettil SV, Si K, Zhu H, Kandel ER, Bailey CH. 2008. Sustained CPEB-dependent local protein synthesis is required to stabilize synaptic growth for persistence of long-term facilitation in *Aplysia*. Neuron 59:1024–1036.

Mink JW, Blumenschine RJ, Adams DB. 1981. Ratio of central nervous system to body metabolism in vertebrates: its constancy and functional basis. Am J Physiol 241:R203–R212.

Montagu MFA. 1962. Time, morphology and neoteny in the evolution of man. In: Montagu MFA, editor. Culture and the evolution of man. New York: Oxford University Press. p 324–342.

Moore AH, Hovda DA, Cherry SR, Villablanca JP, Pollack DB, Phelps ME. 2000. Dynamic changes in cerebral glucose metabolism in conscious infant monkeys during the first year of life as measured by positron emission tomography. Dev Brain Res 120:141–150.

Morfini G, Szebenyi G, Richards B, Brady ST. 2001. Regulation of kinesin: implications for neuronal development. Dev Neurosci 23:364–376.

Mrzijak L, Uylings HBM, van Eden CG, Judas M. 1990. Neuronal development in human prenatal and postnatal stages. Prog Brain Res 85:185–222.

Nieuwenhuys R. 1999. Structure and organization of fiber systems. In: Ten Donkelaar HJ, Nicholson C, Nieuwenhuys R, editors. The central nervous system of vertebrates, Vol. 1. Berlin: Springer. p 113–157.

Parker ST, McKinney ML. 1999. Origins of intelligence: the evolution of cognitive development in monkeys, apes and humans. Baltimore and London: The John Hopkins University Press.
Patrick GN, Zuckerberg L, Nikolic M, de la Monte S, Dikkes P, Tsai LH. 1999. Conversion of p35 to p25 deregulates Cdk5 activity and promotes neurodegeneration. Nature 402:615–622.
Poduri A, Gearing M, Rebeck G, Mirra S, Tigges J, Hyman B. 1994. Apolipoprotein E4 and beta-amyloid in senile plaques and cerebral blood vessels of aged *Rhesus* monkeys. Am J Pathol 144:1183–1187.
Pollard KS, Salama SR, Lambert N, Lambot MA, Coppens S, Pedersen JS, Katzman S, King B, Onodera C, Siepel A, Kern AD, Dehay C, Igel H, Ares M, Vanderhaeghen P, Haussler D. 2006. An RNA gene expressed during cortical development evolved rapidly in humans. Nature 443:167–172.
Preuss TM, Cáceres M, Oldham MC, Geshwind DH. 2004. Human brain evolution: insights from microarrays. Nature 5:850–860.
Price D. 1993. Overview of neuropathology in aged monkeys. Neurobiol Aging 14:685–686.
Puthanveettil SV, Monje FJ, Miniaci MC, Choi YB, Karl KA, Khandros E, Gawinowicz MA, Sheetz MP, Kandel ER. 2008. A new component in synaptic plasticity: upregulation of kinesin in the neurons of the gill-withdrawal reflex. Cell 135:960–973.
Raghanti MA, Stimson CD, Marcinkiewicz JL, Erwin JM, Hof PR, Sherwood CC. 2008. Differences in cortical serotonergic innervation among humans, chimpanzees and macaque monkeys: a comparative study. Cereb Cortex 18:584–597.
Rakic P, Bourgeois JP, Eckenhoff MF, Zecevic N, Goldman-Rakic PS. 1986. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science 232:232–235.
Rilling JK, Barks SK, Parr LA, Preuss TM, Faber TL, Pagnoni G, Bremner JD, Votaw JR. 2007. A comparison of resting-state brain activity in humans and chimpanzees. Proc Natl Acad Sci USA 104:17146–17151.
Roberts RC, Xu L, Roche JK, Kirkpatrick B. 2005. Ultrastructural Localization of Reelin in the Cortex in Post-Mortem Human Brain. J Comp Neurol 482:294–308.
Robson SL, van Schaik CP, Hawkes K. 2006. The derived features of human life history. In: Paine RR, Hawkes K, editors. The evolution of human life history. Santa Fe, NM: School of American Research Press. p 17–44.
Robson SL, Wood B. 2008. Hominin life history: reconstruction and evolution. J Anat 212:394–425.
Rosenberg K. 2004. Living longer: information revolution, population expansion and modern human origins. Proc Natl Acad Sci USA 101:10847–10848.
Rosen R, Farberg AS, Gearing M, Dooyema J, Long PM, Anderson DC, Davis-Turak J, Coppola G, Geshwind DH, Paré JF, Duong TK, Hopkins WD, Preuss TM, Walker LC. 2008. Tauopathy with paired helical filaments in an aged chimpanzee. J Comp Neurol 509:259–270.
Saura CA, Choi SY, Beglopoulos V, Malkani S, Zhang D, Shankaranarayana Rao BS, Chattarji S, Kelleher RJ, Kandel ER, Duff K, Kirkwood A, Shen J. 2004. Loss of presenilin function causes impairments of memory and synaptic plasticity followed by age-dependent neurodegeneration. Neuron 42:23–36.
Schade JP, van Groenigen WB. 1961. Structural organization of the human cerebral cortex. 1. Maturation of the middle frontal girus. Acta Anat 47:74–111.
Seeley WW, Carlin DA, Allman JM, Macedo MN, Bush C, Miller BL, DeArmond SJ. 2006. Early frontotemporal dementia targets neurons unique to apes and humans. Ann Neurol 60:660–667.
Semendeferi K, Armstrong E, Schleicher A, Zilles K, Van Hoesen GW. 2001. Prefrontal cortex in humans and apes: a comparative study of area 10. Am J Phys Anthropol 114:224–241.
Shaw P. 2007. Intelligence and the developing human brain. BioEssays 29:962–973.
Shea BT. 1989. Heterochrony in human evolution: the case of neoteny reconsidered. Yearb Phys Anthropol 32:69–101.
Shi Q, Gibson GE. 2007. Oxidative stress and transcriptional regulation in Alzheimer disease. Alzheimer Dis Assoc Disord 21:276–291.
Somel M, Franz H, Yan Z, Lorenc A, Guo S, Giger T, Kelso J, Nickel B, Dannemann M, Bahn S, Webster MJ, Weickert CS, Lachmann M, Pääbo S, Khaitovich P. 2009. Transcriptional neoteny in the human brain. Proc Natl Acad Sci USA 106:5743–5748.
Su B, Wang X, Nunomura A, Moreira PI, Lee H, Perry G, Smith MA, Zhu X. 2008. Oxidative stress signaling in Alzheimer's disease. Curr Alzheimer Res 5:525–532.
Thompson JL, Krovitz GE, Nelson AJ, editors. 2003. Patterns of growth and development in the genus Homo. Cambridge studies in biological and evolutionary anthropology, Vol. 37. Cambridge: Cambridge University Press.
Tooby J, De Vore I. 1987. The reconstruction of hominid evolution through strategic modeling. In: Kinzey WG, editor. The evolution of human behavior: primate models. New York: SUNY Press. p 183–237.
Trachtenberg JT, Chen BE, Knott GW, Feng G, Sanes JR, Welker E, Svoboda K. 2002. Long-term *in-vivo* imaging of experience-dependent synaptic plasticity in adult cortex. Nature 420:788–794.
Uddin M, Wildman DE, Liu G, Xu W, Johnson RM, Hof PR, Kapatos G, Grossman LI, Goodman M. 2004. Sister grouping of chimpanzees and humans as revealed by genome-wide phylogenetic analysis of brain gene expression profiles. Proc Natl Acad Sci USA 101:2957–2962.
Uddin M, Goodman M, Erez O, Romero R, Liu G, Islam M, Opazo JC, Sherwood CC, Grossman LI, Wildman DE. 2008. Distinct genomic signatures of adaptation in pre- and postnatal environments during human evolution. Proc Natl Acad Sci USA 105:3215–3220.
Vaishnavi SN, Vlassenko AG, Rundle M, Snyder MA, Mintun MA, Raichle ME. 2010. Regional aerobic glycolysis in the human brain. Proc Natl Acad Sci USA 107:17757–17762.
Vincent JL, Patel GH, Fox MD, Snyder AZ, Baker JT, van Essen LH, Zempel JM, Snyder LH, Corbetta M, Raichle ME. 2007. Intrinsic functional architecture in the anaesthetized monkey brain. Nature 447:83–86.
Vinicius L. 2005. Human encephalization and developmental timing. J Hum Evol 49:762–776.
Vlassenko AG, Vaishnavi SN, Couture L, Sacco D, Shannon BJ, Mach RH, Morris JC, Raichle ME, Mintun MA. 2010. Spatial correlation between brain aerobic glycolysis and amyloid β (Aβ) deposition. Proc Natl Acad Sci USA 107:17763–17767.
Walker L. 1993. Comparative neuropathology of aged nonhuman primates. Neurobiol Aging 14:667.
Walker L, Jucker M. 2011. Amyloid by default. Nat Neurosci 14:669–670.
Yakovlev PI, Lecours AR. 1967. The myelogenetic cycles of regional maturation of the brain. In: Minkowski A, editor. Regional development in early life. Oxford: Blackwell, p 3–70.
Zawia NH, Lahiri DK, Cardozo-Pelaez F. 2009. Epigenetics, oxidative stress and Alzheimer disease. Free Radic Biol Med 46:1241–1249.
Zecevic N, Bourgeois JP, Rakic P. 1989. Changes in synaptic density in motor cortex of Rhesus monkeys during fetal and postnatal life. Dev Brain Res 50:11–32.
Zecevic N, Rakic P. 1991. Synaptogenesis in monkey somatosensory cortex. Cereb Cortex 1:510–523.