ELSEVIER

NEUROBIOLOGY OF AGING

Neurobiology of Aging 20 (1999) 447–454

Commentary

Brains, maturation times, and parenting☆

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Finch and Sapolsky propose that the slow development of human infants and their consequent long period of dependency on their parents have favored the evolution of genes that retard brain senescence, specifically recently evolved variants of the apolipoprotein E gene. We examine here the probable reasons why human maturation is so slow, and the influence of this slow development on parental dependence and patterns of survival. Large brains are expensive in terms of energy, anatomic complexity, and the time required to reach particular stages of postnatal maturation. We hypothesize that the maturational time costs arise from the fact that the brain is unique among the organs of the body in requiring a great deal of interaction with the environment (learning experience) to achieve adult competence, and thus that the brain serves as a rate-limiting factor governing the maturation of the entire body. Although the brain achieves its adult size at an earlier age than the other organs of the body, it does not become structurally and functionally mature until some point after sexual maturity [30]. The classical studies of developmental myelination by Flechsig [14,15] indicate that the brain matures slowly in stepwise hierarchies proceeding, for example, from the thalamus to the primary cortical sensory areas to the higher cortical areas of the temporal, parietal, and frontal lobes. Quartz and Sejnowski [33] have proposed that the brain builds sequentially from one level to the next on the basis of experience, and thus larger brains may require more time to mature, in part because they have more levels.

We have examined the time costs associated with enlarged brains by analyzing the relationships between average brain size and the average times required to reach various stages of postnatal maturation, such as the eruption of various classes of teeth and reproductive maturity, in different primate species. Because both brain and developmental timing variables are related to body mass, we have first extracted the statistical effect of mass for each variable and then compared the residual values related to brain weight and maturation times (Fig. 1). The near identity of the five maturation timing relationships as a function of relative brain size illustrate the consistent, clock-like nature of these relationships (Fig. 2). It is remarkable that the times required to attain each of these maturational stages, which range from events occurring in infancy to the threshold of adulthood, are so similarly influenced by relative brain size. However, although the absolute times required by humans to reach any particular stage of maturation are longer than for any other primate, humans actually mature somewhat faster than would be expected for a primate of our brain size. We will return to this interesting point later in our discussion.

Is there a similar relationship between relative brain size and prenatal development time as measured by the length of gestation? This conjectural relationship has been proposed [38], and it has been widely assumed to be true. Fig. 3 plots relative brain size versus relative gestation time for primates, and it is evident that the relationships with both neonatal and adult brain size are very weak. A lack of relationship between gestation length and relative brain size has been previously noted for another group of large-brained mammals, the toothed whales [27]. We conclude that there is a major difference between prenatal and postnatal maturation time with respect to brain size. A possible explanation for the lack of correlations with gestation length is that the fetus is in a passive state relative to its environment while in the womb, whereas in postnatal development the young primate is actively probing its environment and constructing a neural representation of its world. The active acquisition of information by the brain may serve as the rate-governing factor for the maturation of the entire body.

We have extended the analysis of the relationship between brain weight and postnatal maturation times to the component structures of the brain based on the extensive volumetric data collected painstakingly by Heinz Stephan and his colleagues [6,7,16,17,43,44]. As would be expected, the relative sizes of many of the brain's component structures are related to a broad range of postnatal developmental timing measures (Fig. 4). There is also a strong tendency for

☆ This work was supported by NIH grants EY11759 and DA08944, the Howard Hughes Medical Foundation, and the Hixon Fund.

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PII: S0197-4580(99)00076-7

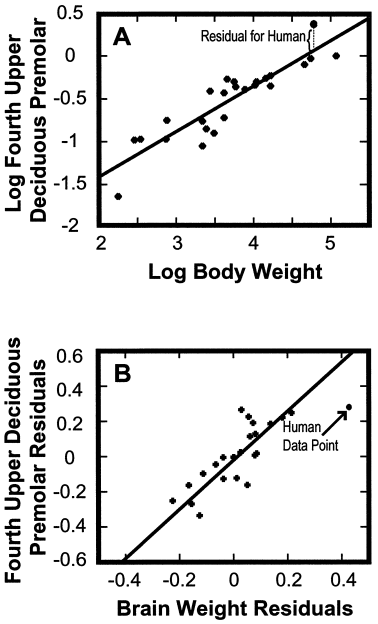


Fig. 1. The method of residual analysis. (a) For each species for which data was available, the log-transformed mean age of the fourth deciduous upper premolar (dpu4) eruption was plotted versus the log-transformed mean body weight. This is usually the last deciduous tooth to erupt. The least-squares regression line was calculated: for each species, the vertical distance between the species' data point and the regression line is the residual, represents the part of the dependent variable not predicted by the independent variable, and is uncorrelated with the independent variable [19]. The tooth eruption data were taken from reference 40; the brain and body weight data were kindly provided by Professor Robert Martin. (b) For each combination of brain structure and maturation time, maturation time residuals were plotted against brain structure weight residuals. Major-axis regression [41] was used to construct a regression line.

different brain structures to fall in the same rank order with respect to the amount of correlation with each of the measures of maturation time (Table 1). Structures such as the

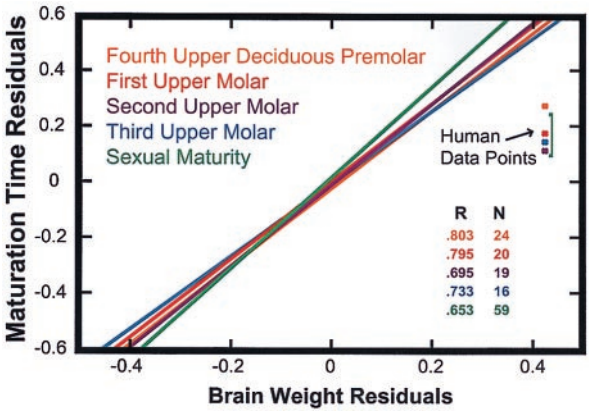


Fig. 2. Maturation time residuals versus brain weight residuals. Human data points are marked separately, and a range of human ages at female sexual maturity [high value 17, from Finland in the 1800s [13]; low value 12.1, from parts of the contemporary U.S. population [20]] is shown. The tooth eruption data were taken from reference 40; the brain and body weight data were kindly provided by Professor Robert Martin; the sexual maturity data was taken from ref. 37.

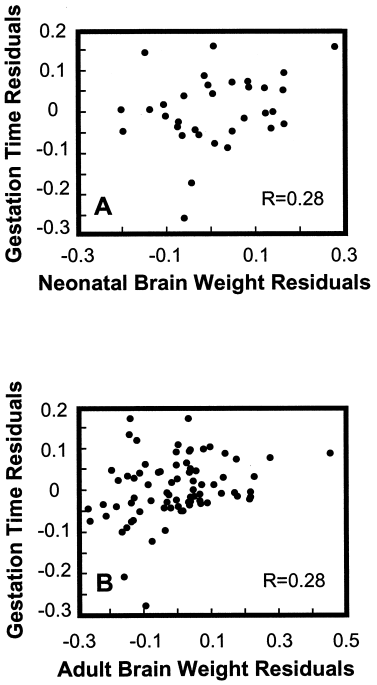


Fig. 3. Gestation time residuals versus brain weight residuals: the data for this analysis were kindly provided by Professor Robert Martin. (a) Gestation time residuals versus neonatal brain weight residuals. Residuals were calculated with respect to neonatal body weight. (b) Gestation time residuals versus adult brain weight residuals. Residuals were calculated with respect to adult body weight.

hypothalamus, which directly participates in the regulation of maturation, the neocortex, which is very sensitive to the experience of the organism, and the thalamus, which controls much of the input and output of the neocortex, are highly correlated with maturation times. These structures are also well correlated with maximum life span [3]. By contrast, olfactory structures tend to be negatively correlated with measures of maturation time.

A major indirect cost of large brain size in primates

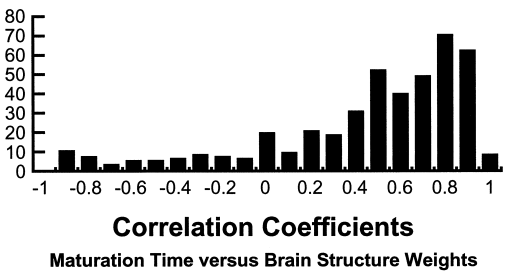


Fig. 4. Histogram of the correlation coefficients for 429 comparisons of brain structure weight or volume residuals and maturation time residuals. The 39 brain structures used are listed in Table 1; the 11 maturation time measures used are age at upper and lower last deciduous premolar eruption, upper and lower first through third molar eruption, female age at sexual maturity, female age at first reproduction, and maximum lifespan. Correlation coefficients were plotted (rather than their squared values) to display the negative relationships between olfactory structures and maturation time.

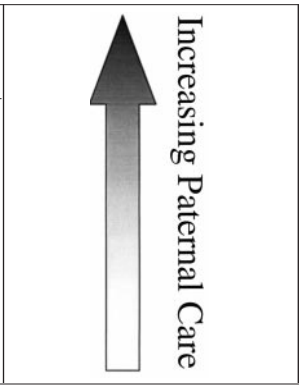
Table 1
Relationship between timing variable residuals and brain structure residuals[a]

Age at fourth upper deciduous premolar eruption		Age at third upper molar eruption		Age at sexual maturity	
Thalamus	**0.973**	**Ventral pons**	**0.956**	**Neocortical gray matter**	**0.787**
Subthalamus	**0.968**	**Neocortex as a whole**	**0.949**	**Lateral geniculate nucleus**	**0.747**
Neocortex as a whole	**0.916**	**Neocortical gray matter**	**0.937**	**Primary visual cortex, gray**	**0.724**
Hypothalamus	**0.911**	**Neocortical white matter**	**0.926**	**Neocortical white matter**	**0.718**
Striatum	**0.902**	**Telencephalon**	**0.924**	**Neocortex as a whole**	**0.682**
Ventral pons	**0.893**	**Hypothalamus**	**0.917**	**Telencephalon**	**0.674**
Telencephalon	**0.889**	**Subthalamus**	**0.907**	**Hypothalamus**	**0.665**
Amygdala, magnocellular part of basal nucleus	**0.877**	**Thalamus**	**0.888**	**Amygdala, magnocellular part of basal nucleus**	**0.654**
Diencephalon	**0.877**	**Striatum**	**0.876**	**Brain as a whole**	**0.653**
Neocortical white matter	**0.875**	**Amygdala, magnocellular part of basal nucleus**	**0.848**	**Mesencephalon**	**0.652**
Cerebellar nuclei, total	**0.867**	**Diencephalon**	**0.834**	**Diencephalon**	**0.638**
Neocortical gray matter	**0.864**	**Primary visual cortex, gray**	**0.812**	**Striatum**	**0.605**
Amygdala, corticobasolateral	**0.824**	**Lateral geniculate nucleus**	**0.812**	**Cerebellum**	**0.604**
Primary visual cortex, gray	**0.82**	**Cerebellum**	**0.809**	**Cerebellar nuclei, total**	**0.604**
Cerebellum	**0.806**	**Cerebellar nuclei, total**	**0.801**	**Thalamus**	**0.59**
Lateral geniculate nucleus	**0.806**	**Anterior commissure**	**0.799**	**Amygdala, corticobasolateral**	**0.58**
Brain as a whole	**0.803**	**Amygdala, corticobasolateral**	**0.761**	**Amygdala**	**0.544**
Mesencephalon	**0.802**	**Brain as a whole**	**0.733**	**Ventral pons**	**0.541**
Amygdala	**0.762**	**Medulla**	**0.712**	**Subthalamus**	**0.537**
Anterior commissure	**0.743**	Mesencephalon	0.69	**Medulla**	**0.522**
Medulla	**0.734**	Amygdala	0.689	**Anterior commissure**	**0.517**
Vestibular complex, total	**0.679**	Septum	0.573	**Vestibular complex, total**	**0.486**
Septum	0.55	Amygdala, centromedial	0.518	Septum	0.359
Trigeminal complex	0.55	Vestibular complex, total	0.497	Amygdala, centromedial	0.343
Amygdala, centromedial	0.491	Trigeminal complex	0.435	Substantia innominata	0.34
Pallidum	0.46	Lateral olfactory tract	0.404	Schizocortex	0.242
Substantia innominata	0.378	Pallidum	0.362	Paleocortex	0.222
Schizocortex	0.375	Accessory olfactory bulb	0.355	Pallidum	0.199
Hippocampus	0.335	Paleocortex	0.284	Trigeminal complex	0.161
Accessory olfactory bulb	0.3	Schizocortex	0.265	Lateral olfactory tract	0.003
Medial habenular nucleus	0.286	Substantia Innominata	0.202	Hippocampus	−0.015
Lateral olfactory tract	−0.013	Hippocampus	0.047	Accessory olfactory bulb	−0.076
Paleocortex	−0.035	Medial habenular nucleus	−0.04	Medial habenular nucleus	−0.161
Olfactory tubercule	−0.092	Olfactory tubercule	−0.055	Pre-piriform cortex	−0.201
Pre-piriform cortex	−0.242	Pre-piriform cortex	−0.152	Pre-piriform cortex	−0.218
Septum, triangular nucleus	−0.563	Retrobulbar cortex	−0.463	**Septum, triangular nucleus**	**−0.444**
Retrobulbar cortex	−0.59	**Septum, triangular nucleus**	**−0.761**	**Total olfactory bulb**	**−0.486**
Total olfactory bulb	**−0.888**	**Total olfactory bulb**	**−0.916**	**Main olfactory bulb**	**−0.494**
Main olfactory bulb	**−0.889**	**Main olfactory bulb**	**−0.92**	Retrobulbar cortex	−0.518

[a] Correlations with a p value of less than 0.05 are in boldface.

Table 2
Male survival and male care

Primate	Male/female survival ratio	Male care
Titi monkey	1.208	Carries infant from shortly after birth [23,35]
Owl monkey	1.151	Carries infant from shortly after birth [35,48]
Siamang	1.093	Carries infant in second year [12]
Goeldi's monkey	1.027	Both parents carry infant [25]
Human (Sweden 1780–1991)	0.924–0.951	Supports economically, some care
Gorilla	0.889	Protects, plays with offspring [45]
Gibbon	0.834	Pair-living, but little direct role [12]
Orangutan	0.831	None [36]
Spider monkey	0.786	Rare or negligible [34,46]
Chimpanzee (21)	0.667	Rare or negligible [18,29]



arises from the long period during which offspring require some degree of parental support and care [1]. In most anthropoid primates (monkeys, apes, humans) large-brained offspring are typically single births [37], which is due to the large energy costs of rearing these offspring. The parents must live long enough past sexual maturity to sustain the serial production and maintenance of a sufficient number of offspring to replace themselves, while allowing for the early death or infertility of offspring. Therefore, we hypothesized that in large-brained species having single births, the sex that bears the greater burden in the care of offspring will tend to live longer [4]. Natural selection will tend to favor genes that enhance survival in adults in the sex that provides the most care for offspring. If the caretaking parent dies, the offspring will probably die as well, but if the noncaretaking parent dies, this event will have little impact on the offspring's chances of survival. The death of a noncaretaking parent might even enhance the survival of its offspring by removing a competitor for scarce food resources.

We tested this hypothesis by constructing survival tables for male and female anthropoid primates and comparing these data with the sexual division of care for offspring (Table 2). In chimpanzees, gorillas, orangutans, and gibbons, females provide most or all of the care of offspring, and in each case females live significantly longer than males [4,21]. Social organization, diet, and ecology vary greatly among these species, but they all share female care and a female survival advantage. By contrast, male siamangs take over the role of carrying infants during the second year of life and are the only male apes to carry infants on a regular basis [12]. Siamang males have a slight survival advantage over females in contrast to the strong female survival advantage in all of the other apes. In humans, there is a female survival advantage in all but two of the 141 World Health Organization countries, and the average male lifespan among reporting countries is about 94% of average female lifespan [47]. The human female survival advantage is also evident in the earliest demographic data from Sweden in 1780 and is present in adults in the Ache, a well studied modern hunter-gather population [22,24]. However, the human female survival advantage is smaller in percentage terms than that found in chimpanzees, orangutans, gibbons, or gorillas. This smaller female advantage is probably due to the larger role of human males in parenting. The most striking patterns of differential survival, however, come from the New World monkeys. In spider monkeys, females provide most of the care of offspring, and males live only about 79% as long as females; in owl and titi monkeys, males provide most of the care of offspring [48] and outlive females by 15 to 20%. These results indicate that parental caretaking roles have a profound influence on survival, and are consistent with the hypothesis of Finch and Sapolsky.

The differential mortality between caretakers and noncaretakers comes in part from the former being risk-averse and the later being risk-seeking [1]. Risk-seekers constantly probe their world, seeking out new opportunities and detecting hazards in the constantly changing environment. Through their probing, they generate new information that they communicate to close kin, thus enhancing their kin's survival and the propagation of their shared genes. Caretakers tend to avoid risk because they risk not only themselves but also their offspring. This may be a conscious decision or the result of genetically determined instincts that would be favored by natural selection because they would lead to more surviving offspring. A second major factor may be a differential vulnerability to the damaging effects of stress. Natural selection would also favor the evolution of genes in caretakers that would protect them against the damage induced by the stress of parental care.

In humans, the female survival advantage begins shortly after conception and continues throughout life. The largest female age-specific mortality rate advantage occurs around age 25. In the United States, as well as many other countries including Canada, Japan, Switzerland and Sweden, there is a second smaller peak or shoulder in the male to female death ratios later in life (Fig. 5a). Although smaller, these two peaks are consistently present in the Swedish data extending back to 1780 [24]. They are also present at about the same stages in the life cycles of chimpanzees [21] and gorillas [4]. The peak in early adulthood corresponds to the

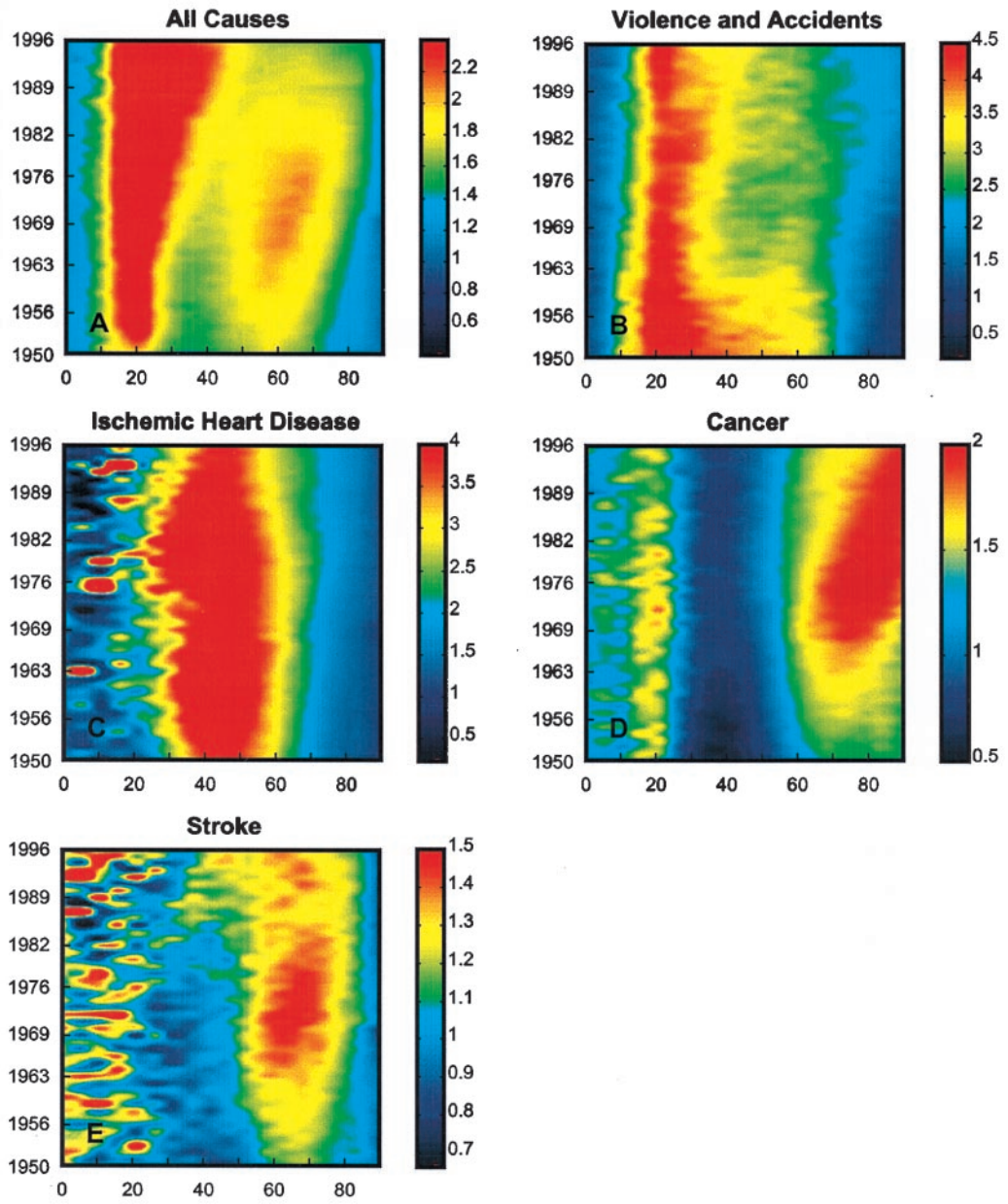


Fig. 5. Male-to-female age-specific mortality ratios, United States, 1950–1996. The horizontal axis represents age in years, the vertical axis represents calendar year, and the color plotted is the ratio of the male age-specific mortality rate from the named cause to the female age-specific mortality rate for the same age, year, and cause. Higher age-specific mortality ratios, represented by colors closer to red, indicate ages, years, and causes where the male risk of death exceeds the female risk of death. Raw data was provided by the World Health Organization (http://www.who.int/whosis/mort/download.htm); data analysis was conducted by the authors using Matlab and Perl. (a) Male-to-female age-specific mortality ratios for all mortality. (b) Male-to-female age-specific mortality ratios for mortality from murder, suicide, and accidents (ICD 7 categories A138–A150, ICD 8 categories A138–A150, ICD 9 categories B47–B56). (c) Male-to-female age-specific mortality ratios for mortality from ischemic heart disease (ICD 7 category A081, ICD 8 category A083, ICD 9 category B27). The inconsistent pattern in early ages is due to the low incidence of heart disease in young people. Although the death rate from ischemic heart disease dropped 60% between 1950 and 1996 [11], the male-female mortality differential remained remarkably constant over the same time period. (d) Male-to-female age-specific mortality ratios for mortality from cancer (ICD 7 categories A044–A060, ICD 8 categories A045–A061, ICD 9 categories B08–B17). There is a small but fairly consistent elevation of cancer death rates in males around age 20, which also contributes to the excess mortality in young-adult males. Between ages 35 and 45, there is a consistent elevation of female cancer death rates. (e) Male-to-female age-specific mortality ratios for mortality from stroke (ICD 7 category A070, ICD 8 category A085, ICD 9 category B29). The inconsistent pattern in early ages is due to the low incidence of stroke in young people.

period of greatest responsibility for childcare in women and greatest risk-seeking by men [1]. The second peak appears at about the time women commonly become grandmothers and is related to a higher risk of heart disease, stroke, and cancer in men. We believe that these two peaks represent two sets of underlying mechanisms, the first of which

mainly acts on young adults and the second on older individuals. The first peak is largely due to differences between males and females in risk-taking behavior, which causes higher death rates from accidents and violence in young males (Fig. 5b). The second peak may result from increased male vulnerability to pathological conditions that develop without overt symptoms over a long period of time, such as oxidative damage, hypertension, and vascular diseases, which may be related to the cumulative effects of stress. Figs. 5c, d, and e illustrate how the increased male-to-female mortality ratios for heart disease, cancer, and stroke come in waves that peak at successively later stages in life. Sapolsky [39] has shown in vervet monkeys, a species in which females are mainly responsible for the care of offspring, that male monkeys are highly vulnerable to stress-induced hippocampal neuron loss, whereas females are not. The hippocampal neurons serve to down-regulate the production of corticosteroids; their loss removes the inhibitory feedback on the stress response with widespread pathological results.

Males are more vulnerable to stroke than females. This may be a consequence of lower levels of low density lipoprotein in females. In addition, estrogen may reduce the risk of atherosclerosis through direct action on the cells of the arterial wall [8]. For all of the top 13 causes of death in the United States, the male death rate is higher than the female death rate [5]. Alzheimer's disease is the 14th leading cause of death in the United States; however, the death rate from Alzheimer's disease is the same for males and females [5]. The equivalence in the death rate for males and females due to Alzheimer's disease may result from the more vulnerable males having died from other causes at an earlier age. This elimination of vulnerable males may also be responsible for the equalization of the risk of stroke death after age 80 (Fig. 5e).

We believe that the main function of the brain is to protect against environmental variability through the use of memory and cognitive strategies that will enable individuals to find the resources necessary to survive during periods of scarcity [1,2]. The longer the lifespan, the greater the probability of encountering severe environmental variation that would disrupt the supply of food and other resources; therefore, larger brains are adaptively linked to longer lifespans among species.

A vivid example of the role of long-term memory in coping with an environmental crisis was recounted by the anthropologist Joseph Birdsell for a group of Australian Aborigines [9]: "About 1943 at the end of a long continued local drought of unusual severity in Nangatara tribal territory, Paralji, even then an old man, undertook to save his local group. From an area north of salt Lake Tobin the little group began to work their way across their own tribal territory, traversing at least 25 waters to finally reach the refuge waterhole Karbarki lying in the northwest corner of their tribal domain. Paralji previously had only visited Karbarki once in his life when his guardian took him on a journey as a part of his initiation into manhood more than half a century earlier. So that even this portion of the journey involved leading his band through much country with which he was not familiar. In time local food supplies began to fail at Karbarki so Paralji, then leaving some of his horde members behind, but accompanied by several younger men with their wives and families, left this waterhole and proceeded west into unknown districts. He was guided chiefly by remembrance of lines of place names mentioned in Nangatara ceremonial song cycles. These are sung at totemic ceremonies, and they detail the wanderings of ancestral beings. The minimal length of this hegira was 600 kilometers, of which some 350 kilometers traversed country known to Paralji only through tradition. The trip involved successfully locating 50 to 60 waterholes, and covered 5 to 7 months' period of time." The survival of this group of close kin depended on the elderly individual's long-term memory. Before there were written records and the only stores of environmental information were based on memory and oral traditions, the capacity for long-term memory in elderly individuals probably enhanced the survival of our ancestors countless times. Communication of this information even to nonkin could enhance the survival of one's descendants if these nonkin were the caretakers of one's children or grandchildren. For example, if during a period of scarcity remembered information concerning alternative resources led to the survival of the mother of one's grandchildren, it would enhance the propagation of one's genes.

The evolutionary model for the emergence of the apolipoprotein E2 and E3 genes, proposed by Finch and Sapolsky, is further supported by recent findings indicating that these alleles are found in elderly nondemented individuals with faster reaction times, as well as superior long and short term memory performance relative to nondemented E4 homozygotes [41]. The E2 genotype is also associated with increased survival in the elderly [41]. Throughout most of humanity's existence, the absence of maps and written records, and thus the necessary reliance on memory, would have favored the E2 and E3 genotypes even though the protective benefits from these genes might not have emerged until the individuals carrying them were postreproductive. This mechanism explains how a trait that manifests itself only late in life could be selected for. An analogous hypothesis has been advanced to explain the evolution of menopause in women [31].

Now let us return to the apparently anomalous human data points in Fig. 2. If humans were typical primates, we would expect from the regression that humans would become sexually mature at about age 44, but this is obviously much later than the age of sexual maturity in any human population (see Fig. 2, green regression). In the Ache [22], the average age of female sexual maturity is 15; in contemporary urban populations throughout the world, it is considerably earlier [13,19]. There is strong evidence that the age of sexual maturity is dependent on nutritional status and is

regulated through receptors in the hypothalamus to the hormone leptin secreted by fat cells [1]. Similarly, the eruption of the third molars, the "wisdom teeth," is another measure of reaching adulthood. We would expect from this regression that humans would reach this measure of adulthood at 38 years, when in fact the average age for the eruption of wisdom teeth in humans is only 20.5 [see Fig. 2, blue regression and [40]]. The eruption times of the last deciduous teeth and of the first and second molars are similarly accelerated relative to what would be expected from our brain weight. By contrast maximum human lifespan is well predicted by relative brain size [2]; thus the acceleration applies only to the pre-adult period of life.

If the brain is the pacemaker for postnatal development, humans have accelerated maturation relative to what would be expected for a primate of our brain size. We believe that this acceleration of the human maturation schedule relative to brain size was the product of the invention of the human network of kinship relationships, the extended family [1]. In great apes, mothers are dependent on their own resources to support their slowly developing offspring. Until fairly recently, human mothers typically have had the support of a mate and a whole network of relatives, an extended family including siblings, parents, aunts, uncles, grandparents, and cousins. Her mate and relatives served to buffer her from some of the crises that might overwhelm a youthful, inexperienced mother on her own. Thus human females were able to reproduce at a much earlier age than would be possible without the family support structure. Human families share both food and information, and this sharing process may accelerate the maturation of both body and brain [1]. For example, dendritic growth is experience dependent [33] and the human family may provide a richer environment favoring a more rapid maturation of brain circuitry [1]. Language probably first emerged within the context of these kinship networks as a means for sharing gossip and environmental information [1]. The emergence of language made it possible to communicate about places and events that were distant in space or time, as was the case for geographical information in the ceremonial songs that guided Paralji to waterholes he had never seen that led to the survival of his kin. Thus, the invention of the extended family kinship network enabled humans to evolve larger brains and escape the constraints imposed by extremely slow maturation.

We believe that the bulk of the comparative primate data strongly supports the hypothesis of Finch and Sapolsky; however, there is a finding that seems to be inconsistent with the idea that humans evolved protections against Alzheimer's disease. There exists a population of morphologically unique neurons, the spindle cells in layer 5 of anterior cingulate cortex, that are present in only humans, bonobos, chimpanzees, gorillas, and orangutans [28]. The concentration of the spindle cells declines in apes with taxonomic distance from humans. The spindle cells could not be detected in careful examinations of 23 other species of primates or in 30 nonprimate species, and thus seem to be unique to humans and the great apes and to be a fairly recently evolved trait. The size of the spindle cell bodies is strongly correlated ($r = 0.99$) with relative brain size in these primates. The sizes of neighboring cell types are not correlated with relative brain size. Their location in layer 5 indicates that they are the output from anterior cingulate cortex to other parts of the brain. The anterior cingulate is implicated in clinical and brain imaging studies in self-awareness [32], the subjective affective state [5,10], the capacity to interpret social situations [32], and the capacity to concentrate on the relevant information when conflicting cues are present [10,32]. The spindle cells are particularly vulnerable to degeneration in Alzheimer's disease relative to other types of cortical neurons [28]. Thus this recently evolved neuronal population appears to be more rather than less susceptible to this disease.

Understanding the web of relationships between the evolution of large brain size, the lengthening period of postnatal maturation, and the differential roles of caretakers and risk-seekers contributes to a new understanding of the patterns of vulnerability to many human afflictions and especially to the dementing illnesses of old age.

Acknowledgments

We thank Jukka Jernwald for calling our attention to the linkage between the timing of dental maturation and brain size. The data used as the basis for the analysis presented in Figure 5 was provided by the World Health Organization; all analyses were performed by the authors, and the World Health Organization does not necessarily endorse our conclusions.

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