Feature Article

The Aging Brain: The Cognitive Reserve Hypothesis and Hominid Evolution

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ABSTRACT   Compared to other primates, humans live a long time and have large brains. Recent theories of the evolution of human life history stages (grandmother hypothesis, intergenerational transfer of information) lend credence to the notion that selection for increased life span and menopause has occurred in hominid evolution, despite the reduction in the force of natural selection operating on older, especially post-reproductive, individuals. Theories that posit the importance (in an inclusive fitness sense) of the survival of older individuals require them to maintain a reasonably high level of cognitive function (e.g., memory, communication). Patterns of brain aging and factors associated with healthy brain aging should be relevant to this issue. Recent neuroimaging research suggests that, in healthy aging, human brain volume (gray and white matter) is well-maintained until at least 60 years of age; cognitive function also shows only nonsignificant declines at this age. The maintenance of brain volume and cognitive performance is consistent with the idea of a significant post- or late-reproductive life history stage. A clinical model, "the cognitive reserve hypothesis," proposes that both increased brain volume and enhanced cognitive ability may contribute to healthy brain aging, reducing the likelihood of developing dementia. Selection for increased brain size and increased cognitive ability in hominid evolution may therefore have been important in selection for increased lifespan in the context of intergenerational social support networks. Am. J. Hum. Biol. 17:673–689, 2005.   © 2005 Wiley-Liss, Inc.

Analyses of the evolution of aging in general, and of human life history in particular, have become increasingly sophisticated over the past two decades (e.g., Finch and Kirkwood, 2000; Hawkes et al., 1997, 1998; Rose, 1991; Rose and Mueller, 1998). At the same time, advances in neuroimaging have made possible an increased understanding of volume and structure changes in the brain due to age in healthy, living individuals (e.g., Allen et al., 2005; Jernigan et al., 2001; Raz et al., 2004). In this paper, we attempt to reconcile patterns of brain aging derived from neuroimaging studies with the evolved life history stages of the latter half of the human life span. Furthermore, we suggest that a clinical model of successful brain aging, the "cognitive reserve hypothesis" (Stern, 2002), may have implications for understanding the evolution of the hominid brain, especially in the context of selection for increased longevity.

Two critical features distinguish modern humans from other primates: an extension of the lifespan and expansion of the brain. Human life expectancy in developed countries is >70 years, with individuals living >100 years not all that uncommon. Even in traditional hunter–gatherer populations, significant numbers of individuals survive past the age of 60 years. Blurton Jones et al. (2002; see also Hawkes, 2003) estimate that 45-year-old individuals in contemporary hunter–gatherer groups (Hadza, Ache,

!Kung) have a life expectancy of about 20 additional years, a figure that is not influenced by modern medical interventions. In contrast, our closet primate relatives, chimpanzees, typically live into their 40s in the wild and 50s in captivity, although the oldest recorded chimpanzee ("Cheeta" of Tarzan movie fame) has reached the age of 72 years (Roach, 2003).

Human brain size has undergone an even more dramatic change than lifespan over the course of hominid evolution: human brains are about 2.5 times larger than the brains of the great apes (Holloway, 1999). It has long been recognized that brain size, longevity, and energy metabolism are interrelated variables in mammals (see Hofman, 1983, and references therein). The existence of correlations among these variables does not provide any indication, however, of the selective forces that may have shaped their expression (Harvey and Clutton-Brock, 1985; Harvey et al., 1987). Humans are long-lived and large-brained. There can be little doubt that there has been selection for increased brain size—and increased intelligence or cognitive capabilities—in the genus *Homo*. But what is the relationship (if any) among increased longevity, brain aging patterns, and brain expansion in hominid evolution?

THE EVOLUTION OF LONGEVITY

As evolutionary theorists have long shown (Kirkwood, 2002; Medawar, 1952; Rose, 1991; Williams, 1957), selecting for longevity per se is difficult due to the basic fact that the force of natural selection declines throughout the reproductive lifespan. Environmental and stochastic factors are important in determining how long an individual lives (Finch and Kirkwood, 2000), which further reduces the opportunities for selection to act on longevity. Nonetheless, research on a wide variety of organisms has shown that there are genes that directly influence longevity (which should be thought of as "genes for survival" rather than "aging genes" [Kirkwood, 2002]) and that their expression has been shaped by natural selection. In contemporary populations, twin studies have shown that the heritability of lifespan in humans is in the range of 25–35% (Finch and Tanzi, 1997). While this is not a particularly high value (and one could predict that it would be somewhat lower in traditional settings), it does indicate

that genetic variability in longevity is present and potentially subject to selection.

Several theories have been suggested to explain the evolution of aging patterns (Kirkwood and Austad, 2000). The *mutation accumulation* theory follows directly from the fact that selection operates more strongly in the earlier rather than later part of the lifespan; the effects of aging are seen to result from the accumulation (in the absence of selection) of germ-line mutations that ultimately contribute to senescence. Williams' (1957) theory of *antagonistic pleiotropy* refined this notion. Williams suggested that there could be selection for certain genes based on their positive effects during the early, reproductive part of the lifespan, even if they had deleterious pleiotropic effects later in life. The accumulation of such late-acting deleterious genes would lead to senescence. Kirkwood's *disposable soma* theory (Kirkwood and Austad, 2000, and references therein) emphasizes the trade-off between energetic investment in reproduction versus somatic maintenance. Obviously, organisms must devote resources to somatic maintenance and repair, but ultimately, investment in reproduction relatively early in the lifespan will have greater fitness payoffs than maintaining an older body, especially as the chances of actually becoming old are so slim in most wild populations.

Taken together, these theories provide a substantial intellectual foundation for the idea that, in general, direct selection for longevity in animals is unlikely. However, the possibility remains that there may have been particular cases in which extraordinary circumstances—such as those that arose during human evolution—led to direct selection for increased lifespan.

The grandmothering hypothesis

Despite the fundamental barriers to direct selection for longevity or for features that are expressed late in the reproductive life or post-reproductively, many theorists have suggested that aspects of human aging may indeed represent adaptations that are expressed relatively late in life. Much of their attention has been focused on the evolution of menopause, the cessation of reproduction in women that appears to be quite different from late-life reductions in fertility observed in the vast majority of mammals (see Hawkes, 2003; Peccei, 2001, for review).

G.C. Williams (1957) originated the idea that menopause may not simply be a manifestation of normal mammalian aging but may instead represent an adaptation. He suggested that by ceasing reproduction years before the full effects of senescence take hold, women could enhance their fitness by devoting more energy to raising existing (and slowly maturing) children rather than producing additional ones.

More recently, there has been an emphasis on the possible inclusive fitness benefits of "grandmothering," whereby menopausal women assist their own daughters in the raising of their children (Hawkes, 2003). Hawkes presents the grandmothering hypothesis in the context of Kirkwood's disposable soma theory of aging. She points out that, although both chimpanzee and human females have declines in fertility late in life, human females are much more likely than chimpanzees to be in vigorous health with a relatively long life expectancy when they reach this stage. Such a pattern of investment in somatic maintenance over reproductive capacity could only have evolved if there was a concomitant payoff in increased (inclusive) fitness. Changes in diet that accompanied the origins of *Homo* could have placed juveniles in a position of requiring more assistance from adults to obtain food; under such a circumstance, not only maternal but grandmaternal investment in offspring could have been selected for (Hawkes, 2003). Studies of foraging and provisioning by postmenopausal Hadza women demonstrate that they can make a substantial contribution to the nutritional welfare of their grandchildren (Hawkes et al., 1997). The results of such investment would be a reduction in the age of weaning and shortening of birth-spacing intervals.

Demographic evidence for or against the grandmothering hypothesis comes from both paleontological and recent modern human populations. Paleodemographic studies tend to highlight the fact that older individuals are rare among the remains recovered from past hominid populations, and thus in general they do not provide support for the grandmother hypothesis or any other adaptive hypotheses for the extension of longevity. For example, Caspari and Lee (2004) show that there is only a gradual increase in the ratio of older-to-younger adult fossils recovered going from Australopithecines to early *Homo* to Neandertals, a finding that

provides only weak support for the grandmothering hypothesis. In contrast, the ratio of older-to-younger adults increases dramatically in early Upper Paleolithic (modern human) populations, an indication, Caspari and Lee suggest that if there is a grandmother effect, perhaps it emerges only in the wave of cultural and behavioral innovations associated with the emergence of modern people—innovations that may have helped older people live longer.

As Hawkes (2003) points out, paleodemographic reconstructions of past populations are problematic due to sampling bias, difficulties associated with determining the age of skeletal individuals, and other issues. More critically, the age structures of populations are influenced by a wide variety of factors and thus it would be virtually impossible to discern a specific effect of longevity on inclusive fitness based on paleodemographic data. A high representation of older individuals in a local sample does not have to be interpreted as support of the grandmother hypothesis (see Caspari and Lee, 2004), and a relatively low representation of them does not mean that there were not fitness benefits associated with increased longevity. Certainly, documenting the *existence* of such individuals in past populations is important.

More direct demographic evidence for the grandmother hypothesis comes from investigations of recent populations for which comprehensive data on longevity, survival, and fertility are available. Several of these studies find support for a positive effect of grandmothers on the fertility of their daughters and survival of their grandchildren. Using multi-generational records from the 18th and 19th centuries, Lahdenpera et al. (2004) showed that among "pre-modern" Finns and Canadians (from several fishing and agricultural communities), women with a longer post-reproductive lifespan had more grandchildren and thus increased fitness. Their daughters (and in some cases, sons) had children earlier and more often and were more successful in raising them. The grandmother effect waned as the daughters of grandmothers themselves became postreproductive, and mortality increased dramatically at this point. Mace (2000), using data collected in the mid-20th century in rural villages in Gambia, found that young women whose mothers were alive reproduced at an earlier age and that cumulative

survival rates of first-borns were higher for those children whose grandmothers were still alive. Limited support for the grand-mother hypothesis has also come from studies of vital records collected in Tokugawa, Japan (1671–1871) (Jamison et al., 2002).

The grandmothering hypothesis is important because it represents the best explanation currently available for direct selection of longevity in hominid evolution. The hypothesis is theoretically plausible, and empirical evidence in its support is being collected (see also Alvarez, 2000). Interestingly, very little has been said about the potential role of (older) fathers or grandfathers in the evolution of longevity. Age-specific fertility rates for males in many societies do not decline until well after the age of 50 (e.g., Mace, 2000); polygynous marriage systems may also allow long-lived males to have increased fertility (Josephson, 2002). Also, both older women and older men could play a role in the evolution of longevity if intergenerational information transfer about food procurement has been a critical factor in hominid evolution (Kaplan and Robson, 2002; see below).

BRAIN SIZE AND LONGEVITY

Despite the apparently fundamental constraints on direct selection for longevity in animals, the grandmother hypothesis and other theoretical models provide plausible explanations for how such selection could have occurred in hominid evolution. Let us now return to the issue of the evolution of brain size in the context of increasing longevity.

As mentioned above, longevity and brain size are strongly correlated across mammal species; the relationship between these two variables is also mediated by metabolic and reproductive rates (Hofman, 1983). Two kinds of explanations have been offered to explain why brain size and longevity should be correlated (Rose and Mueller, 1998). Physiological explanations posit that there is a direct cellular or biochemical relationship between increasing brain size and increasing longevity. Although several physiological explanations have been proposed, none are particularly clear on exactly how encephalization and longevity are directly linked.

Physiological models for the link between brain size and longevity are essentially constraint models, which do not require selec-

tion as a mechanism for evolution in either of these two variables (Rose, 1991). For example, changes in metabolic or reproductive rate could be the main cause of changes in brain size or longevity, since these are all correlated variables. In contrast, selectionist or ecological models suggest that changes due to natural selection in one of these two variables could have a selection effect on the other, but there would be no need for a direct physiological link between the two.

Either brain size or longevity can be seen as the driving force in ecological models linking the evolution of the two variables. Selection for increased brain size—and presumably increased intelligence—should lead to decreases in mortality, as increased intelligence would confer on the organism an enhanced ability to cope with variable environmental conditions (Charlesworth, 1980). Prolonged survival would increase the force of natural selection at later stages in the lifespan and increase the potential for longevity selection. Human technological abilities, a product of increased brain size, may provide the greatest buffer against environmental conditions and thus potentially provide an even more conducive context for longevity selection (Rose and Mueller, 1998).

This situation can be looked at from the opposite perspective: that selection for longevity could in turn lead to selection for increased brain size. Allman et al. (1993a) point out that the longer an animal lives, the more likely it is to encounter severe environmental crises. Since one presumed function of increased brain size is an enhanced ability to store information about resources in the environment (Harvey et al., 1980), longer-lived species should select for increased brain size to sustain individuals through the environmental crises they will face over a long lifespan. This view is easily reconciled with the longevity-first view discussed in the previous paragraph. Taken together, these two hypotheses highlight the fundamentally interactive relationship between brain size and longevity when examined from an ecological perspective.

Brain Size and Longevity in Primates

As discussed above, the correlation between brain size and longevity across a wide range of mammal species is well-established. Allman and colleagues (1993a, 1993b, 1998, 1999)

have examined in detail brain and life history correlates within the Primate order. Using brain size and lifespan residuals (to control for body weight), they found that there is a high correlation between the two variables in haplorhine primates, and when taken on their own, in humans and the great apes (Allman et al., 1993a). In other words, although humans are exceptional within primates for brain size and lifespan length, they are not exceptional in the quantitative relationship between the two. This indicates that one may expect that the same ecological and/or physiological factors that keep the two variables correlated in primate (especially great ape) evolution in general, will also have been important in hominid evolution in particular.

Allman and colleagues (1998, 1999) also looked at the relationship between lifespan and parenting within primates. Larger brain size requires longer periods of development (longer lifespan), and Allman et al. (1998) predicted that the sex that invested most in the raising of offspring should live longer. Looking at a wide range of primates, they found that females, which in the majority of primate species is the sex that cares most intensely for offspring, live significantly longer than males (this discrepancy could be due to several factors, including greater metabolic demands in larger-bodied males or injuries suffered in male competition). In primate species where males made a significant contribution to the care and raising of offspring (such as the siamang), there was no difference between the sexes. Human males do not live as long as human females, although the discrepancy is not as great as in other ape species (Allman et al., 1999). Demographic and epidemiological data show that there are two age-specific peaks for the female survival advantage over males. One occurs around the age of 25 years, when women are (traditionally) entering the age of greatest responsibility for childcare and men are engaged in the most high-risk, competitive behavior. The second peak occurs later, around the age of ~50 years, the age at which women commonly become grandmothers (again, in traditional settings).

Information Transfer and the Coevolution of Brain and Longevity

Allman and colleagues (1999, 2002) have proposed a scenario for the evolution of longevity and large brain size in humans in the context of the development of the extended family. As mentioned above, Allman et al. "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" (1999, p 452). They argue that an extended family was initially required to raise slow-developing, large-brained infants and children, who are incapable of adequately foraging for food on their own (Kaplan et al., 2000).

The "economy" of the extended family is one in which food and information about food can be passed from parents *and* grandparents to younger members of the family. Longevity would be particularly advantageous as a means of retaining information about how to respond to food-scarcity events that occur only rarely (intervals of decades) (Allman et al., 1999). Allman et al. (2002) further speculate that these information-storage-and-transfer capabilities were a direct outcome of changes (unique to humans and great apes) in Brodmann's area 10 (frontal pole) and the anterior cingulate cortex, regions of the brain which govern our ability to retrieve memories about past events and to formulate adaptive responses to adverse circumstances.

Allman's scenario is in broad agreement with the coevolutionary model of brain size and longevity proposed by Kaplan and his colleagues (Kaplan et al., 2000; Kaplan and Robson, 2002). The model of Kaplan et al. is based in part on a comparative analysis of age-specific net food production (measured in calories) between chimpanzees and human hunter-gatherers. By the age of 5 years, chimpanzees reach a break-even point between food production and consumption; their net food production reaches a (relatively low) peak in young adulthood and then remains relatively flat over the course of their lifespan. In contrast, until about the age of 15 years, young humans run a large net food production deficit. At this age, productivity increases sharply, however, becoming a net positive (i.e., they produce more than they consume) by around age 20, and continuing to rise through adulthood, until a peak is reached at around age 45 years. Although a decline in productivity starts at this age, net positive food production is still observed at 60 years of age.

Kaplan and colleagues point out that chimpanzees depend almost entirely on food products that can be directly gathered by hand, with relatively small contributions from food that must be extracted (e.g., termites) or hunted. In contrast, human hunter–gatherers are primarily dependent on extracted (e.g., tubers or nuts) or hunted foods. Extracting or hunting food requires more learning than simply gathering food. "Human hunting is the most skill-intensive foraging activity and differs qualitatively from hunting by other animals...Human hunters use a wealth of information to make context-specific specific decisions during both search and encounter phases of hunting." (Kaplan and Robson, 2002, p 10225). The later stages of hominid evolution have been characterized by the development of large package food procurement techniques that require intensive learning to do at all and experience to do well (Kaplan et al., 2000). The evolution of large brain size and increased longevity followed the hominid entry into this niche.

The Kaplan and Allman models both highlight the importance of intergenerational transfer of information about food procurement in the context of the coevolution of large brain size and longevity. Kaplan and his colleagues place a greater emphasis on the specific importance of hunting and learning to hunt in their model, while Allman and colleagues stress the importance of episodic memory in learning complex skills and locating scarce food resources. Although the grandmothering hypothesis can be held to be in opposition to these viewpoints—especially regarding the issue of the relative importance of hunting (Kaplan et al., 2000)—it is not mutually exclusive with the notion that intergenerational sharing of food and information provides an adaptive context for the evolution of large brain size and extended lifespan.

APOLIPOPROTEIN E POLYMORPHISMS

Theoretical work by Caleb Finch and his colleagues (Finch and Sapolsky, 1999; Finch and Stanford 2004) has drawn attention to the lipid transport protein apolipoprotein (apo) E as a potential genetic link between the evolution of larger brain size and increased longevity in humans and their ancestors. ApoE plays an important role in the intracellular transport and metabolism of triglycerides and cholesterol (Mahley and Rall, 2000). In addition, apoE, which is produced in the liver and the brain, has several neurobiological functions, including axon regeneration and remyelinization.

ApoE is a polymorphic protein that exists in three different isoforms (apoE2, apoE3, and apoE4), which are produced by three different alleles at a single locus (Mahley and Rall, 2000). They differ from one another only by single amino-acid substitutions. The different alleles confer different levels of susceptibility to both cardiovascular and neurological diseases. A gene-dosage effect has been shown for apoE4 indicating that it is a major risk factor for the development of Alzheimer disease (Corder et al., 1993); in addition, it is associated with slower recovery from head trauma and stroke and unfavorable course in multiple sclerosis (Enzinger et al., 2004; Mahley and Rall, 2000). ApoE4 is also associated with higher levels of increased total and LDL cholesterol, and consequently, with increased risk of heart disease (Davignon et al., 1988).

The other two apoE isoforms present a somewhat different clinical picture. ApoE2 homozygosity is a prerequisite for developing the genetic disorder type III hyperlipoproteinemia, which is associated with an increased risk of heart disease. However, only 10% of apoE2 homozygotes actually develop this condition, and in general the apoE2 allele is associated with a decreased risk (compared to apoE4) of both atherosclerosis and neurological disease. The situation is similar for apoE3, which may be considered "protective" against the development of heart disease and dementia. ApoE3 is the most common form found in human populations with allele frequencies ranging from 50% to 90%, apoE4 is next most common, with frequencies of 5–35%, and apoE2 is least common, with frequencies of 1–15% (Fullerton et al., 2000; Mahley and Rall, 2000).

ApoE Evolution and Longevity

Finch and Sapolsky's (1999) detailed hypothesis about the evolution apoE polymorphisms gives this protein a central role in the evolution of brain size and longevity. Rather than limiting their discussion to humans, Finch and Sapolsky place the apoE polymorphism in a broader zoological perspective. They point out that normal brain

aging in a variety of long-lived primate and mammal species is typically accompanied by Alzheimer-like histopathological changes in the brain, which in turn lead to the development of specific types of memory impairment. Of potential relevance to this, phylogenetic analyses indicate that the primitive and most widely distributed isoform of apoE is apoE4. So, in essence, the wide distribution of apoE2 and apoE3 (especially) in modern human populations suggests that these "new" versions of apoE have been selected for. Because the debilitating effects of apoE4 come relatively late in life, this would also suggest that the effects of selection may have been manifest through fitness benefits accruing to older individuals.

Finch and Sapolsky propose several selective scenarios for apoE3. Most critically, they place the allele in the context of the grandmothering hypothesis. Since apoE3 appears to be associated in older age with both increased cardiovascular health and resistance to neurological disease and injury, the allele could have been selected for in a matrilocal social organization in which grandmothers contributed to the maintenance of their grandchildren. As they state (p 420): "In view of the positive effects of apoE3 on cardiovascular health in human populations, the evolution of apoE3 would have thus favored grandmothering in early humans. The transfer of ecologically important information by grandmothers or other elders would also require intact memory. We suggest that one or more new apoE alleles were established prior to grandmothering, or may have been a direct factor in this new social function."

In addition to grandmothering, hunting may have also played a role in the evolution of apoE3; Finch and Stanford (2004) suggest that it is one of several potential candidate alleles in humans that may be associated with the adoption of a meat-based diet. The extension of the lifespan in hominid evolution probably coincided with an increase in big-game hunting. Compared to chimpanzees, who obtain most of their calories from nonmeat sources, the human diet is relatively high in fat and cholesterol. Elevated blood cholesterol level is associated with the development of heart disease, and diets high in animal fat may also be associated with increased rates of Alzheimer's disease. Finch and Stanford argue that in the context of increased longevity, which would give the opportunity for the expressions of chronic diseases associated with high meat consumption, apoE3 would be selected for. Of course, this scenario presupposes that people actually did live longer and that older individuals made important contributions to the fitness of younger, transgenerational kin.

Finch and Sapolsky's hypothesis has been endorsed by proponents of both the intergenerational information transfer/hunting model (Kaplan and Robson, 2002) and the grandmothering hypothesis (Hawkes, 2003) as a possible genetic mechanism underlying the evolution of human longevity. Koochmeshgi et al. (2004) recently reported that apoE4 carriers had an earlier age of menopause than possessors of other apoE isoforms; they found that the age at which half of the apoE4 carriers had undergone menopause was over a year earlier than for apoE2/3 carriers. Koochmeshgi et al. interpreted this as evidence against the grandmothering/apoE3 hypothesis, based on the logic that delaying menopause would be counter to the expectations of that model. On the contrary, such a finding supports some of Finch and Sapolsky's (1999) speculations on the possible direct role of apoE3 on slowing down the developmental schedule.

Fullerton et al. (2000) have provided a comprehensive analysis of haplotype diversity associated with the major apoE isoforms. They date the most recent common ancestor of all apoE variants to 311,000 years ago, and the origins of apoE2/3 diversity to about 200,000 years ago. Fullerton et al. suggest that the variability in the apoE system does not indicate a long-term balanced polymorphism, although they do find evidence that the relatively recent and rapid spread of apoE3 may indicate an adaptive role for that protein. They do not endorse the Finch and Sapolsky hypothesis, however, rejecting it on the basis of the orthodox genetic argument that late-in-life phenotypic expressions of a gene should have little influence on fitness. Fullerton et al. point to the role of apoE in lipid absorption, neural growth, and immune function as being a more likely source of a selective advantage expressed during the reproductive lifespan. Other investigators look at the geographic population distribution of apoE alleles and suggest that infectious disease may be the causative agent shaping the evolution of this polymorphism (Mahley and Rall, 2000); apoE3

is most common in more densely populated agricultural groups, while apoE2 and apoE4 have highest frequencies in culturally and geographically isolated populations. Support for an infectious disease model comes from a study that shows that apoE4 in combination with exposure to herpes simplex virus type I increases the risk of developing Alzheimer disease (Itzhaki et al., 2004). However, carrying this same allele protects against severe liver damage caused by hepatitis C (Wozniak et al., 2002), which may indicate that apoE4 may be selected for in some environments despite its late-in-life detrimental effects.

EVOLUTION AND HEALTHY BRAIN AGING

One of the most important insights provided by Finch and Sapolsky is that if longevity in humans is an adaptation (via whatever mechanism), then the health of older individuals becomes an important selective factor. This is especially true of behavioral health, as the ability to transfer information or operate within a complex social kin network requires reasonably intact cognitive abilities. It is interesting to note that compared to other systems of the body, nerve transmission rates decline relatively slowly (Schulz and Salthouse, 1999); in addition, norms for standard neurocognitive tests do not generally have to be age-corrected until age 60 and above, although there may be modest declines in performance across the adult lifespan (Petersen, 2003). In the absence of pathology, significant global cognitive decline should not be considered to be a normal aspect of aging (Lindeboom and Weinstein, 2004). If there has been selection for longevity, it is reasonable to speculate that intact mental function until relatively old age is a direct or indirect outcome of this selective process.

The Aging Brain

As the body progresses through adulthood and old age, the brain undergoes several changes (Raz, 1999, 2001; Uylings et al., 2000). There is an overall loss of volume, which can be quite pronounced when comparing a healthy younger adult with a very old adult (Figure 1). The sulci widen as a result of the loss of brain tissue in the gyri. The changes in the gross anatomy are presumably a result of changes in the microstructure of the brain: loss of neurons or reduction in neuron size, loss of synapses, pruning of dendritic trees, and so on. In Alzheimer disease and other dementias, the accumulation of histopathologies ultimately results in a gross loss of brain tissue—in some regions—which exceeds that which is seen in healthy aging. Virtually all brain regions and structures lose volume with age, although recent neuroimaging research has shown that the loss of tissue can occur at quite different rates (Allen et al., 2005; Good et al., 2001; Jernigan et al., 2001; Raz et al., 2004; Sowell et al., 2003; Walhovd et al., 2005). As we will see below, in the context of understanding healthy brain aging, even global changes in brain tissue volumes with age may provide important insights into the relationship between increased longevity and the maintenance of behavioral health.

Brain tissue is divided into gray matter (primarily neuron cell bodies and dendrites) and white matter (myelinated axons and supporting cells). Most of the gray matter can be found on the outer surface on the brain, in a folded sheet about 4 mm thick, which is known as the cortex. Other functional concentrations of neurons known as nuclei are found below the surface of the brain. The white matter contains the myelinated axons that serve to connect neurons in different regions (including cortical areas and nuclei), both inter- and intrahemispherically. White matter volume is influenced by several factors, including the size of axons, the relative complexity of axonal branching, and the extent of myelinization, in addition to the distribution of nonaxonal elements (such as glial cells).

Changes in gray and white matter volume with age do not occur at the same rate. Earlier studies based on preserved brains indicated that the gray matter/white ratio declines at first through the first part of adulthood but then rises starting around the age of 50 years (Miller et al., 1980). Gray matter appears to decline linearly with age across the entire lifespan, resulting in an ultimate loss of about 10% of the neurons of the neocortex (Pakkenberg and Gundersen, 1997). Pakkenberg and Gundersen characterize this amount of cell less to be a "relatively small number," which seems a reasonable assessment. In addition, neuronal processes are surprisingly well preserved in some brain regions, even into very old age (Uylings et al., 2000). Although
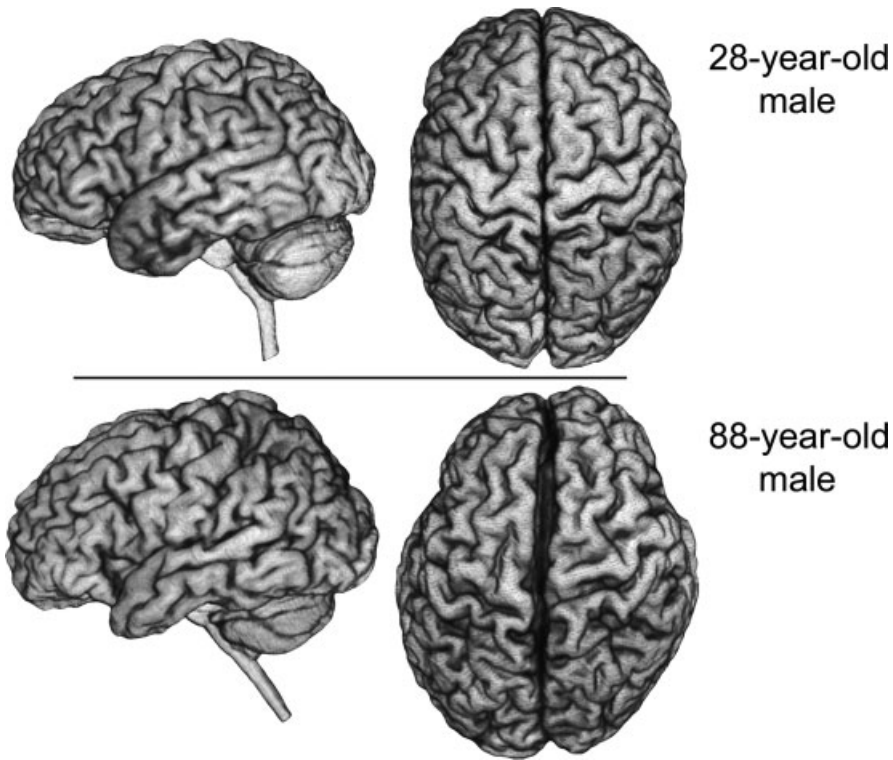
Fig. 1. High-resolution 3-D MRI reconstructions (side and top views) of a healthy young adult male (28 years) and an older healthy male (88 years).

synapses are lost throughout the adult lifetime of an individual (starting in the 20s), the rate of loss, in the absence of disease, is slow enough that even at the age of 100 years, most people will preserve enough intracerebral connectivity to avoid clinical dementia (Terry and Katzman, 2001).

Recent in vivo neuroimaging studies of brain aging confirm that the gray matter declines linearly with age, while the white matter has a more curvilinear pattern of change (see references above). White matter volume actually increases through adulthood, peaking at 40–50 years of age; after this point, the white matter volume enters a period of accelerating decline, which becomes pronounced after the age of 60 (Figure 2). It is important to note, however, that a 60-year-old person probably has about the same amount of white matter as he or she had at 20 years of age, coupled with only a relatively modest reduction in gray matter. By the age of 80, however, white matter volume will have declined by more than 20% compared to its volume in younger adulthood (Allen et al., 2005).

Brain Aging and Life History

Total brain volume appears to be reasonably well-preserved even as people enter the seventh decade of life, and in the absence of disease or illness, cognitive function is also generally maintained until this age. Chimpanzees have a similar pattern of moderate total brain-size decline with age (Herndon et al., 1999). However, an important difference between humans and chimpanzees—indeed, between humans and all other primates—is the high metabolic cost of maintaining the human brain (Leonard and Robertson, 1994; Leonard et al., 2003). Although the overall energetic demands of the human body are as predicted for a primate our size, the brain accounts for 20–25% of the resting energy demands of our body, compared to 8–10% in other primates.
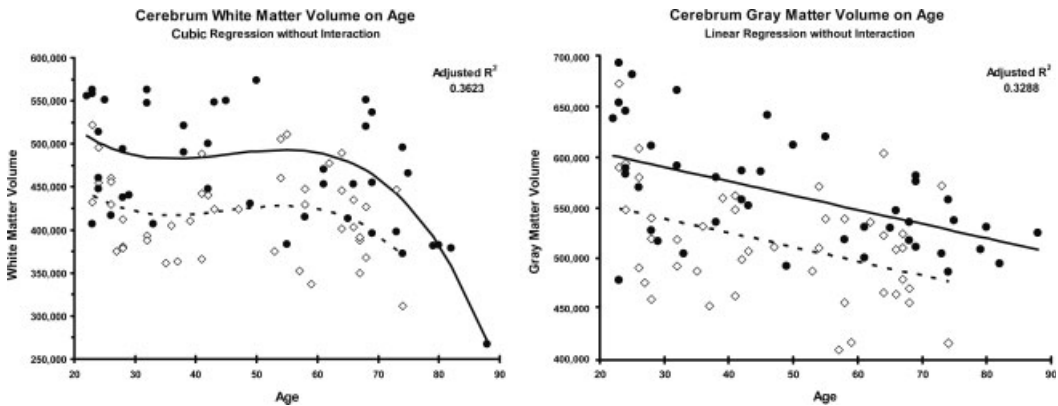
Fig. 2.   Best-fitting regression lines for cerebral white and gray matter volume versus age. Note that white matter volume peaks relatively late in life before declining precipitously starting at about 65 years. Eighty-seven total subjects (43 men and 44 women) are included in the analysis; solid line is the male regression line, dashed is the female regression line. Other than scaling differences, there was no significant difference in the age profiles between males and females (see Allen et al., 2005, for more details).

The energy demands of increasing human brain size has broad implications for the evolution of the human diet, body composition, and social networks (Leonard et al., 2003). In terms of maintaining brain size and function in older age, even if chimpanzees and humans demonstrate similar volumetric patterns of brain aging, from an energetic standpoint, these may be qualitatively different phenomena. Compared to other primates, in humans the balance between somatic maintenance and reproductive capacity (Kirkwood and Austad, 2000) is much more strongly influenced by the energetic demands of the brain. For human females, selection for increased longevity (whatever the exact mechanism) and large brain size could have provided a unique context for the evolution of menopause: the high energy demands of the brain could have made it much more difficult for an aging woman to provide sufficient care (including nutritional energy) to a child born late in her life. Such a supposition is speculative, of course, but it highlights the complex potential interactions among these evolutionarily critical variables.

Global patterns of gray matter change with age appear to follow a relatively straightforward path across the adult life span. The relatively constant linear declines in total gray matter volume, cortical neuron number (Pakkenberg and Gundersen, 1997), and synaptic density (Terry and Katzman, 2001) cut across the various stages and land-

marks of human aging. In contrast, white matter volume changes across the adult life span are more variable. White matter volume peaks at an age that coincides approximately with the age of menopause, and it begins its precipitous decline after the age of 60 years, coinciding with the increase in mortality associated with older age. It is interesting to note that one cortical (gray matter) structure with an aging profile similar to white matter is the hippocampus (Allen et al., 2005; Raz et al., 2004), which is essential for the storage and retrieval of information. Within the great apes, chimpanzees have a relatively larger hippocampus compared to gorillas and orangutans, which may reflect the more frugivorous and even carnivorous chimpanzee diet (Sherwood et al., 2004).

Although conditions such as Alzheimer disease have focused attention on cortical pathologies in brain aging, Pakkenberg and Gundersen (1997) speculate that given the relatively modest decline in neuron numbers in old age, changes in white matter may be most responsible for cognitive changes associated with normal aging (see also Guttmann et al., 1998). Only some of the loss of white matter in the aging brain can be attributed to Wallerian degeneration of axons following neuron cell death, and there may be a loss of myelin around axons without cell death (Pakkenberg and Gundersen, 1997). The development of white matter abnormalities

visible on MRI (e.g., they are commonly found in the white matter surrounding the ventricles) is correlated with poorer performance on several tests of cognition, including global cognitive function, processing speed, immediate and delayed memory, and executive function, while general intelligence and fine motor skills are not affected (Gunning-Dixon and Raz, 2000). These changes occur in the context of normal, healthy aging, although they are more common in people with a history of transient ischemia attack (TIA) and hypertension.

The slow increase in white matter volume over the first half of adulthood occurs at the same time as there is a slight decrease in gray matter volume, thus the white matter volume increases despite the fact that there should be some loss of myelinated fibers due to the loss of cortical neurons. This could indicate that as learning occurs during adulthood (including the acquisition of motor skills and the formation of new memories) there is an elaboration of existing neural pathways, resulting in an increase in (or maintenance of) the amount of myelinated fibers. Such a "constructivist" view of adult neural development is controversial but not without empirical support (Quartz and Sejnowski, 1997). The accelerating decrease in white matter volume starting around the age of 60 years may signal a decline in the body's maintenance of this metabolically expensive tissue.

In summary, patterns of normal brain aging—in the absence of disease—indicate that it is a structure whose structural and functional integrity is reasonably well-maintained until at least 60 years of age. In the context of the evolution of human life history stages, there are at least two ways to interpret this finding. Human brain aging patterns, especially those observable for the white matter, may have been shaped in response to selection for increased longevity. Alternatively, the aging brain may be viewed as having posed no constraint on the selection for increased longevity, although brain aging patterns themselves may not have been shaped by natural selection. The apoE model intersects these two possibilities in that it posits that there has been selection for an allele that reduces the likelihood of developing clinical dementia, which would then allow "normal" patterns of brain aging to be expressed in the context of selection for increased longevity.

THE COGNITIVE RESERVE HYPOTHESIS

A common clinical belief about Alzheimer disease is that people who are better educated or more intelligent cope better with the onset of dementia (i.e., are longer able to maintain a normal life) compared to people who are less educated or less intelligent. Paradoxically, once full-blown clinical dementia has developed, the more educated/intelligent patient often succumbs to the disease more quickly (Stern et al., 1995). One possible explanation for this pattern is that such patients have maintained cognitive function despite the accumulation of Alzheimer pathologies; when they finally reach the point of clinical dementia, they are actually in a more advanced stage of the disease, hence their relatively rapid subsequent decline.

These clinical observations have received a measured level of support from epidemiological, pathological, and neuroimaging research conducted over the past 15 years. This research has formed the basis of the cognitive or cerebral reserve hypothesis (Stern, 2002). The reserve concept actually has two distinct, but not necessarily mutually exclusive, manifestations, which Stern (2002) refers to as *passive* and *active* models of reserve. The passive model suggests that simply having more cerebral tissue (i.e., larger brain size) is a protective factor against developing dementia. Individuals with larger brain size may cope longer with pathological changes in the brain due to the fact that they can absorb a greater amount of brain injury before reaching the threshold of functional impairment, hence the basis of their cerebral reserve. The active model of reserve focuses on the association between higher intelligence or higher educational attainment and the delay in dementia onset. Individuals with higher intelligence or greater educational attainment may have more extensive and efficient neural networks, which may help them cope with pathological changes in the brain by allowing them to compensate for these changes by making use of alternative networks; such individuals have more redundant networks that they can recruit to maintain normal cognitive function. It might be possible to accumulate more active reserve through the course of a cognitively enriched lifetime. Again, the passive (hardware) and active (software) models are not mutually exclusive; after all, neuroimaging

studies have shown that brain volume and performance on IQ tests are moderately but significantly correlated (see Macintosh, 1998).

Evidence for the passive (hardware) model of reserve was first obtained in a study by Katzman et al. (1988) in which postmortem brain examinations were performed on a series of 137 patients from a single nursing facility. Katzman et al. identified 10 patients who exhibited a high level of cognitive performance, as high as many patients who had no histological evidence of brain disease, yet these patients demonstrated pathological changes associated with mild Alzheimer's disease. Compared to controls, these 10 patients had significantly larger brains and higher neuron numbers. Katzman et al. interpreted these results in terms of a cognitive reserve, which allowed these patients to stave off the cognitive effects of Alzheimer disease despite the fact that they had evident Alzheimer pathology.

Since Katzman et al. (1988) published their findings, evidence for and against the passive model of cerebral reserve has appeared (in support—Mori et al., 1997; Schofield et al., 1995, 1997; Wolf et al., 2004a, 2004b; against—Edland et al., 2002; Graves et al., 1996; Staff et al., 2004). The different studies are somewhat difficult to compare with one another given different criteria for subject selection and assessment, and different brain measures (although many make use of total intracranial volume as a proxy for premorbid brain size). It is important to note that it has never been shown that *smaller* brain volume is in any way protective of developing Alzheimer disease. In keeping with the passive reserve model, smaller brain size (intracranial volume) was shown by Wolf et al. (2004b) to be a risk factor for developing mild cognitive impairment and dementia: in a study that included 96 consecutive referrals to a memory clinic and 85 healthy controls, subjects in the lowest quartile for intracranial volume had an odds ratio of 2.8 as compared to the other three quartiles to be cognitively impaired or demented. Researchers have also shown that larger premorbid brains size may decrease vulnerability to the long-term effects of traumatic brain injury (Kesler et al., 2003) and to chronic cognitive deficits associated with crack cocaine and crack cocaine/alcohol addiction (Di Sclafani et al., 1998).

The active (software) model of cognitive reserve has been tested in several epidemiological studies looking at the relationship between education/occupational status and the development of Alzheimer disease and other dementias. As might be expected given the large number of potentially confounding variables, some studies show positive results (e.g., Callahan et al., 1996; Katzman, 1993; Staff et al., 2004; Zhang et al., 1990) while others do not (Beard et al., 1992; Ott et al., 1999); some only show a relationship between education and the development of dementias other than Alzheimer (e.g., Cobb et al., 1995; Del Ser et al., 1999; Fratiglioni et al., 1991). No study has shown that having less education or lower occupational status has a protective effect against developing dementia. Evidence from neurophysiological studies also lend support to the active model of reserve. Compared to less-educated patients, more highly educated patients show a greater degree of disruption of cerebral metabolism and blood flow for a given level of dementia (Alexander et al., 1997; Stern et al., 1992); this indicates that the Alzheimer pathology is relatively more advanced in these well-educated patients but that they cope with these changes, presumably by recruiting alternative neural networks. Higher premorbid intellectual function has also been shown to be associated with retaining intellectual function in chronic epilepsy (Jokeit and Ebner, 2002).

The cognitive reserve hypothesis, in both its passive and active forms, is an intriguing concept that has received empirical support from a number of diverse studies. Although focused originally on Alzheimer disease, it may be that cognitive reserve is better thought of as a more general model to explain interindividual variation in the response to brain injury and pathology (Stern, 2002). With advancing age, the brain becomes increasingly vulnerable to insult and injury from a number of sources. In the past, individuals who possessed greater cognitive reserve—derived from gross brain size, life experience, or both—may have been more likely to reach a vigorous and healthy old age.

Cognitive Reserve and Hominid Evolution

It should be apparent that many of the selective advantages attributed to apoE2/3 in the context of increased hominid longevity could also result from increasing cognitive reserve. Over the past two million years of hominid evolution, brain size expanded

3-fold, thus increasing the potential for the development of passive cognitive reserve. At the same time, the elaboration of technological and social intelligence, in the context of more extensive and elaborate cultural environments, undoubtedly led to an enrichment of the cognitive lives of individual hominids. Such cognitive enrichment could form the basis of increased active cognitive reserve. Of course, cognitive reserve only reflects a potential capacity to resist brain injury and disease, since its main advantages would emerge later in the lifespan of an individual.

No one would argue that the evolution of larger brain size in hominids is the result of selection acting to increase cognitive reserve in order to enhance health and survival in old age; other factors were undoubtedly more important in the direct selection for increased brain size (Lock and Peters, 1999). However, if selective conditions favored increased longevity and the survival of cognitively vital and intact older individuals, then enhanced cognitive reserve could have been one among many factors that contributed to selection for increased brain size and/or intelligence. Rose and Mueller's (1998) concept of the "pleiotropic echo" may be relevant here. The pleiotropic antagonism theory of aging focuses on the negative, late-acting effects of alleles that may be selected for given their capacity to enhance fitness earlier in the life span; senescence results from the phenotypic expression of alleles that occur after natural selection is (effectively) no longer operating on the organism. The pleiotropic echo concept recognizes that late-acting effects of an allele may be positive as well as negative. The positive effects of cerebral reserve in old age would then be a pleiotropic echo of selection for large brain size/increased cognitive capacity during the peak reproductive years.

The notion that cognitive reserve could have been a factor in selection for increase hominid lifespan is not mutually exclusive with the apoE2/3 selection hypothesis. The timeframes would be somewhat different, since apoE variability is only about 300,000 years old while hominid brain expansion began some 2 million years ago. The two factors could interact, attenuating the selective forces for each of them (assuming the apoE system does not play a large role in the genetics of brain size or cognition). For example, the effects of apoE4 could be mod-erated by other factors, such as whole or regional brain volume (Hashimoto et al., 2001), which could serve to lessen selection against that allele.

In summary, the implications of the cognitive reserve model in the context of the evolution of human longevity are as follows: (1) Relatively greater passive or active cognitive reserve increases the likelihood of healthy brain aging and intact cognitive function in old age, which would enhance the inclusive fitness of older individuals in a social system that relies on intergenerational provisioning and/or transfer of information about food sources; (2) selection for cognitive reserve in aging would be a secondary factor in the selection for increased brain size in hominids, but could contribute to a positive feedback loop between the evolution of larger brain size and increased longevity; and (3) cognitive reserve would moderate selection against apoE4 and selection for apoE2/3, which could be one factor in the continued maintenance of the apoE polymorphism.

CONCLUSION

Following Hawkes (2003), Allman et al. (2002), Kaplan and Robson (2002), and Finch and Sapolsky (1999), we have attempted to reconcile human brain aging patterns with our current understanding of the evolution of human life history stages (Figure 3). Both gray and white matter patterns of healthy brain aging are consistent with the notion that human cognitive function is reasonably well-maintained until at least 60 years of age (in the absence of pathology). Whether this pattern has been designed by natural selection or is a phylogenetic artifact of being a long-lived mammal and primate cannot be determined from human brain aging data alone. However, these data are consistent with models of human life history that indicate that older individuals may enhance their reproductive fitness by contributing to the survival of younger, intergenerational kin. The white matter data are particularly interesting in this regard, in that it appears to peak in volume at about the time of menopause, and does not undergo a significant decline until after the age of 60 years.

It is quite clear that aging and cognition are complex, multi-factorial phenomena, and that it is nearly impossible to neatly summarize or even anticipate all of the potential

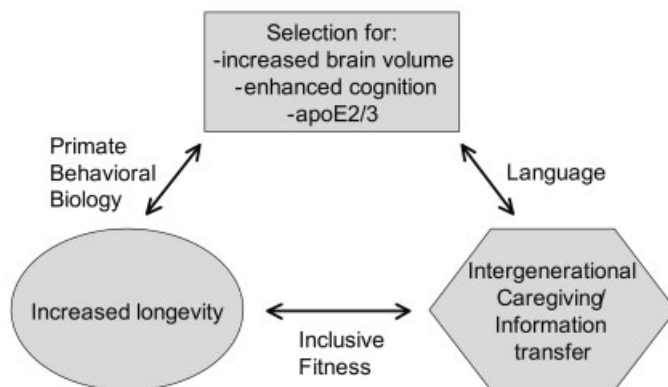## Interrelated Factors in the Evolution of Hominid Brain Size and Longevity

Fig. 3. Schematic illustration of the model for the coevolution of brain aging patterns, life history stages, and large brain size presented in this paper.

issues that could be relevant to their evolution. Our goal here has been to introduce two additional factors—brain aging patterns and the cognitive reserve hypothesis—to the ongoing discussion of this topic. We believe that an additional topic that should also be introduced to the discussion is the role of language. The evolution of the intergenerational transfer of information would be dependent on language capacity, and indeed could be a specific factor underlying selection for language abilities. The ability to identify and maintain intergenerational kin networks in the context of large social groups might also have been dependent on the development of symbolic language (Deacon, 1997). We do not want to go into these issues in detail here, but it seems to us that language may be a critical coevolutionary factor in this framework.

Evolutionary theory predicts that selection for longevity is very unlikely; the null hypothesis is that post-reproductive life history stages should be minimally subject to natural selection. Nonetheless, while it is not possible to reject the null hypothesis at this point, there is a reasonable amount of evidence to suggest that some form of longevity selection may have occurred during hominid evolution. Given the positive correlation between longevity and brain size observed in mammals (including primates), and the various models of the evolution

human life history stages that require the survival of cognitively intact older individuals, understanding the natural history of human brain aging could provide important insights into the resolution of this issue.

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