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Review

Cognitive aging as an extension of brain development: A model linking learning, brain plasticity, and neurodegeneration

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Abstract

Differences in cognitive aging rates among mammals suggest that the pace of brain aging is genetically determined. In this work, we investigate the possibility that brain aging is an extension of brain development. It is possible that a subset of developmental mechanisms are extreme cases of antagonistic pleiotropy in that they are necessary for reaching adulthood and yet later cause age-related diseases. We derive a model linking development and brain aging in which childhood events essential for brain development later result in neurodegeneration. The hypothesis presented herein involves brain plasticity in which the same mechanisms that shape the adult phenotype continue at later ages contributing to cognitive dysfunction and eventually dementia. The same genetic program that decreases brain plasticity at early ages to focus our mind to the surrounding environment may continue in adulthood resulting in cognitive aging. Experimental implications for understanding neurodegeneration in this context are also discussed.

Keywords: Longevity; Mind; Neuroplasticity; Senescence; Synaptic plasticity

1. Introduction

Human aging is associated with a high prevalence of memory (Zec, 1995) and cognitive impairment (Craik and Salthouse, 1992; Brayne et al., 1995; Gallagher and Rapp, 1997; Stern and Carstensen, 2000). Due to the worldwide aging population, neurodegenerative illness and dementia represent growing public health problems. As the springboard to learning, thinking, emotions, and self-esteem, mental health is an important concern of aging adults. Studying the neurobiology of aging to delay and prevent mental illness must thus be a top priority for biomedical research.

Until recently, the prevailing theory was that aging and neurodegeneration derive from accumulated damage, such as oxidative damage or other by-products of cellular metabolism. Brain neurons were simply lost from birth onwards, resulting in age-related cognitive decline. In recent years, however, it has become apparent that, with the exception of specific pathologies, neurons remain relatively healthy during the lifespan (Morrison and Hof, 1997). In contrast, numerous biochemical and structural changes compromise neuron function, even without significant neuronal death (Teter and Finch, 2004). It now appears that synapse loss and dysfunction are determining processes in the destruction of cortical circuits (Masliah et al., 1993; Hof and Morrison, 2004; Verkhratsky et al., 2004). What changes with age is the wiring, the intricate network of connections between cells (Gopnik et al., 2000).

In parallel with the shift in our understanding of cognitive aging, a number of recent results suggest that aging in mammals may not be simply a result of accumulated damage (reviewed in de Magalhaes (2005) and de Magalhaes et al. (unpublished results)). One alternative hypothesis is that aging results from development, as proposed before (reviewed in Medvedev (1990) and Zwaan (2003)). This concept has been demonstrated in animals

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such as the salmon and even mammals (*Antechinus stuartii*), and so it is possible that some human age-related changes are indirect consequences of the developmental program. In this work, we investigate the possibility that brain aging is an extension of brain development. We propose a model linking brain development to aging in which processes essential for brain development, such as the need to decrease brain plasticity in early life, result in neurodegeneration.

2. Cognitive aging as a genetically determined process

2.1. Evolution shapes development for reproduction

Aging, as predicted by the evolutionary theory of aging, derives from the declining force of natural selection with age (Medawar, 1952; Hamilton, 1966; Rose, 1991). The emphasis of organisms is on reproduction, not post-reproductive survival. Evolution favors organisms that maximize cognitive function at reproductive age within the constraints of each species's nervous system (Sandberg, 2003). If reproduction shapes the genetic program responsible for what we are then subsequent events are irrelevant from an evolutionary perspective. There is little or no pressure to shape developmental processes in late life.

Antagonistic pleiotropy predicts the existence of genes beneficial early in life but harmful at later stages (Williams, 1957). If the developmental program merely exists to optimize fitness at a given time, i.e. the reproductive period, then the continuing actions of that same developmental program may be deleterious. The theoretical basis of our work is that a subset of developmental mechanisms may be extreme cases of antagonistic pleiotropy in that they are necessary for reaching adulthood and yet later cause age-related diseases. Therefore, the same developmental program that originates the adult phenotype may, in some cases, continue and be deleterious in adulthood.

2.2. Neurodegeneration is determined by the genetic program

The way brain aging occurs at such markedly different paces in different mammals, even in captivity, suggests that cognitive aging is not primarily a result of injury but is rather genetically determined, as hinted by others (Miller, 1999). One hypothesis then is that the variation in rates of age-related changes among mammals can be explained by linking the mechanisms of aging and development, as suggested before (reviewed in Medvedev (1990)). Herein, we focus on the possibility that such is the case for at least some aspects of normal brain aging.

Brain aging is consistent across mammals despite vast differences in longevity (Finch, 1993; Small et al., 2004), which is in accordance with a linkage between the well-orchestrated developmental pathways and aging (Fig. 1).

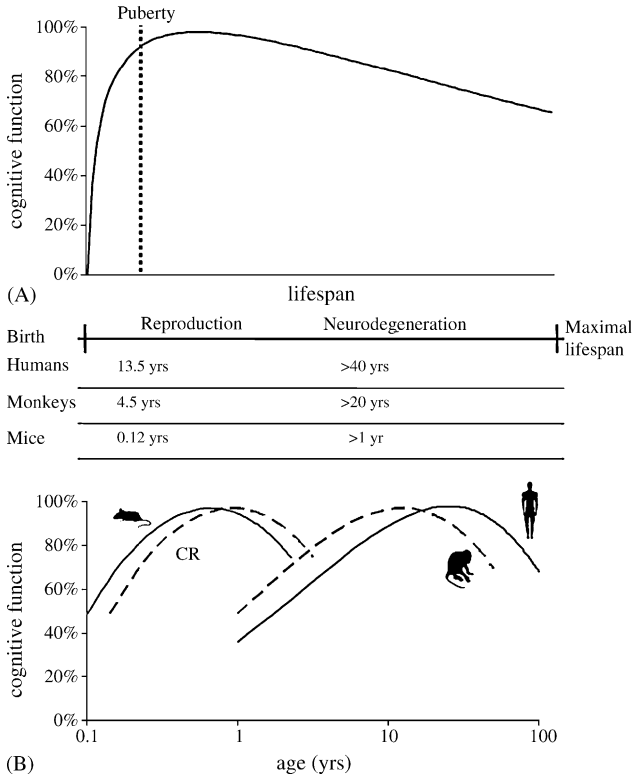

Fig. 1. Cognitive function across the lifespan. (A) Cognitive function must rapidly increase after birth and then peak at or shortly after reproductive fitness. Afterwards, cognitive function must remain stable until the offspring is independent. What happens at later ages is irrelevant from an evolutionary perspective and hence the decline in cognitive functions at old age is inevitable. These life history events such as reproduction and neurodegeneration are proportional among different mammals despite marked differences in lifespan. It is as if aging is the same process only timed at different rates (Miller, 1999). (B) According to our model, changing the onset and pace of brain development will affect cognitive aging. A slower development implies a slower aging process and vice versa. This can be observed by comparing the cognitive function of humans (straight black line) and rhesus monkeys (dotted black line) or mice (straight gray line) and caloric restricted mice (dotted gray line). Animals drawn using the fonts by Alan Carr.

Age-related neurodegeneration has been characterized in non-humans primates such as rhesus monkeys, baboons, chimpanzees, and macaques (Brayne et al., 1995; Erwin and Hof, 2002; Corr, 2004; Voytko and Tinkler, 2004). These changes appear to occur significantly faster than in humans. For example, the dendritic spine is the locus of long term synaptic plasticity associated with storage of memories in the brain (Ramon y Cajal, 1995), and a 40% decrease in denditric spine number has been observed in people over 50 years (Jacobs et al., 1997). Interestingly, a 50% decline in spine numbers has been reported in old (27–32 years) monkeys (Nimchinsky et al., 2002). Similar results have been observed for synapse numerical densities per unit volume in old (24–32 years) rhesus monkeys (Peters et al., 1998).

The developmental program can be defined as a genetically determined sequence of cellular and molecular events designed to produce a given adult phenotype. If a portion of this sequence of events that orchestrates

development also influences – even if "unintentionally" from an evolutionary perspective – age-related changes that would explain why remarkably similar species age at such different paces. One hypothesis then is that a slower development will result in slower age-related changes and vice versa (Fig. 1). Longer-lived species, such as humans, that develop slower and they take longer to reach their physical, reproductive, and intellectual peak would have their age-related changes delayed because of a mechanistic link between the timing of development and the pace of age-related changes.

Results from mouse models of aging support a link between cognitive aging and developmental pathways. Dwarf mice live longer than wild type counterparts and have a slower decline in cognitive ability (Kinney-Forshee et al., 2004). Intriguingly, not only are dwarf mice smaller but their puberty is delayed (Chandrashekar et al., 2004). On the other hand, growth hormone transgenic mice appear to age faster and reach puberty before controls. Interestingly, their cognitive peak occurs earlier, but their cognitive decline is faster (Bartke, 2003). Such findings are clearly in agreement with the idea that some developmental mechanisms are related to aging and, namely, brain aging. Similarly, caloric restriction (CR) delays aging, development, and cognitive decline (Fig. 1B).

As argued by others (Martin, 1978), the slow evolution of structural genes cannot account for differences in longevity among mammals. Recent evidence suggests that developmentally linked genes are responsible for differences in the nervous system of primates (Dorus et al., 2004). This is not surprising, of course, as evolution acts on developmentally related genes, not the basic biochemistry of life, but it can be applied to brain aging too. Our suggestion is that the basic, structural components of the nervous system are not a causal factor in brain aging as these are less likely to encode differences among similar species. Only components associated with the timing of neural development are expected to be associated with the regulation and timing of aging since these are expected to differ between primates. Of course, structural components may be disrupted with age, but as an effect, not cause of cognitive aging. Even among the genes regulating the timing of development, only a subset of these is expected to influence aging and identifying them will be a major challenge (see below).

3. A model linking brain development and neurodegeneration

Human cognitive function across the lifespan can be divided into three phases: (1) an abrupt increase in childhood; (2) a stabilization period during early adulthood; (3) cognitive decline (Fig. 1A). As mentioned above, the premise of this work is that events during brain development will later affect cognitive impairment. We focus particularly on brain plasticity, such as experience-dependent synaptic modifications that sculpt cortical circuits, which is crucial for brain development (Sandberg, 2003). Our proposal is that the age-related decrease in brain plasticity essential for development does not cease in adulthood. In other words, changes in brain plasticity that are crucial for young individuals to become adults continue beyond maturity to the point of causing age-related cognitive decline.

When we are born, the genetic program must optimize our mind to the environment. For instance, a baby can recognize subtle differences among sounds of all languages. This capacity is lost in the infant brain because to acquire a specific language the brain must develop a structure that emphasizes a given language and ignores the others (Gopnik et al., 2000). It is normal then that brain plasticity is greater at birth so we can adapt to a variety of situations (Fig. 2). For instance, even though a large number of synapses are created in infancy and early childhood, a large number of synapses are also destroyed in childhood (Huttenlocher, 1984; Huttenlocher and Dabholkar, 1997).

After puberty, the priority is no longer adaptation or intellectual developmental. The brain must be more stable because the emphasis has shifted to reproduction and childbearing (Fig. 2). Thus, synaptic plasticity, the activity-dependent modification of synapses, decreases with age (Gan et al., 2003), as does synaptic density (Huttenlocher and Dabholkar, 1997; Terry and Katzman, 2001; Huttenlocher, 2002; Brazel and Rao, 2004), so we focus on the surrounding environment. As understood by the pioneering

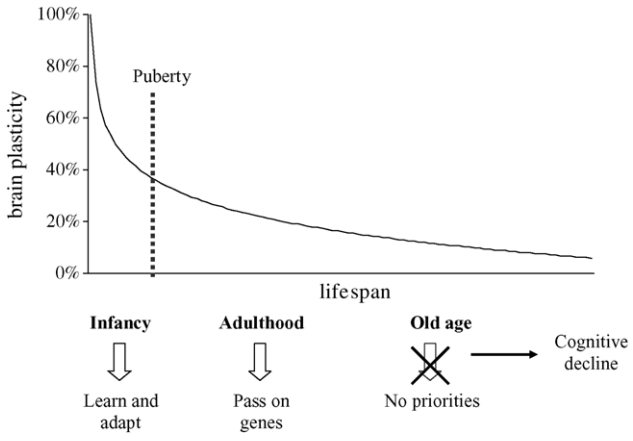

Fig. 2. Model representing the decline in brain plasticity across the lifespan. In infancy, the priority is to learn and adapt to the environment and so a greater brain plasticity is necessary. During adulthood, the priorities shift to reproduction and child rearing and so brain plasticity is lower than during infancy. At old ages, the force of natural selection has vanished and so from an evolutionary perspective there are no priorities like in infancy and adulthood. Since brain plasticity declined to yield the adult phenotype, it continues to decline at old age, contributing, unintentionally, to cognitive aging. The plot follows a logarithmic relation, which appears to be more in accordance with what we know about synaptogenesis and neuroanatomical models showing an exponential decline of NMDA receptors' levels with age (Sandberg, 2003). Whatever model is more accurate, it is clear that synaptic and brain plasticity decline with age, as supported by a large body of experimental evidence (Gopnik et al., 2000; Huttenlocher, 2002; Gan et al., 2003).

neuroscientist Ramón y Cajal, the fixed neuronal population of the adult brain is necessary to maintain the functional stability of the adult brain circuitry (Ramon y Cajal, 1995), and recent results support the idea that brain plasticity is greater in childhood than in adulthood (Gopnik et al., 2000; Huttenlocher, 2002). A developmental loss of neural mechanisms for plasticity has been suggested (Huttenlocher, 2002).

Brain plasticity and neuromodulation continue to decrease even in aged individuals (Fig. 2). "You can't teach an old dog new tricks", or so the proverb goes and, in fact, a decline in learning rate has been observed in elderly people as well as in numerous animal models (Kausler, 1994). Brain plasticity in adulthood has also been shown to be decline (Huttenlocher, 2002; Gan et al., 2003). Therefore, our hypothesis is that, in later stages, this developmentally linked process continues – because there is no evolutionary pressure for it not to – and causes cognitive dysfunction. Our proposal is that the brain plasticity changes aimed at increasing the robustness of the human mind in childhood and adolescence later contribute to cognitive aging and eventually dementia.

4. Implications of our model in studying the genetics of cognitive aging

Aging is probably the second most complex biological phenomenon. Certainly, the most complex of biological phenomena is the human brain. Thus understanding brain aging is a Herculean task. How cortical circuits develop and senesce is beyond our current knowledge. Nonetheless, and based on our present understanding of brain development and aging, we wanted to offer some glimpses of possible mechanisms at work and how experimental approaches can be used to understand the linkage between brain development and cognitive aging.

4.1. Cellular and molecular mechanisms in brain aging

On one hand, age-related changes occur in neuronal and synaptic numbers that can be seen as extensions of development (Fig. 3A). During development, neurogenesis and synaptogenesis occur, but these processes fade away as we age (Katz and Shatz, 1996; Sandberg, 2003). Similarly, both neuronal death and synaptic pruning appear to occur in primate development (Fig. 3A). Synaptic density in the human brain reaches its peak in infancy followed by marked selective pruning until adulthood. Likewise, neuronal numbers appear to reach a prenatal peak followed by a steady decline (Gopnik et al., 2000; Huttenlocher, 2002). One hypothesis is that the steady, programmed, decline in synaptic and neuronal numbers is necessary for brain development – as suggested by others (Gopnik et al., 2000; Huttenlocher, 2002) – but later causes cognitive aging. Indeed, programmed cell death occurs in early childhood (Waters et al., 1994). Apoptotic pathways, such as BCL2,

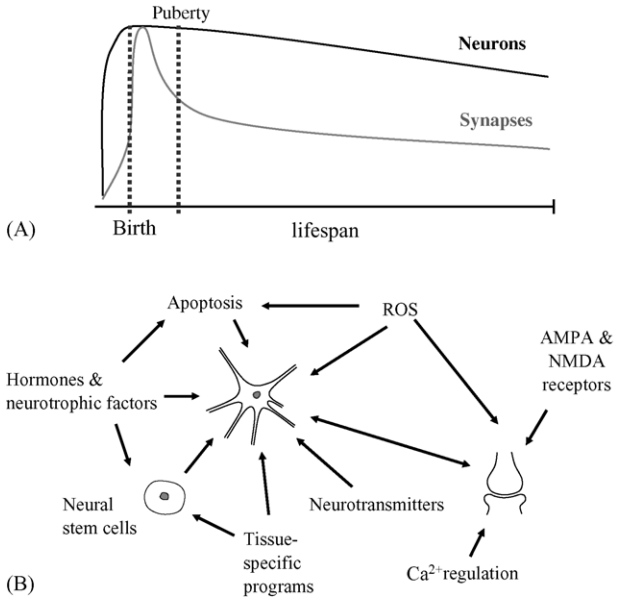

Fig. 3. Schematic representation of possible cellular and molecular factors involved in mammalian brain development and aging. (A) The number of neurons (black line) and synapses (gray line) during the lifespan. Neurons are expected to peak prior to birth and then decline in numbers throughout the lifespan. Synapses have been reported to peak during infancy and then gradually decline (Huttenlocher, 1979, 2002). (B) Different neurotrophic and neuroendocrine factors such as BDNF, NGF, and serotonin may mould cell populations during development and aging in the brain. These factors may also be involved in shaping the pace at which these events take place, but it is likely that tissue-level genetic programs also exist. For example, possible mechanisms affecting the number of synapses include synaptic pruning as well as a decrease in the expression of NMDA receptors. Apoptotic and oxidative pathways, such as BCL2, hydrogen peroxide, and superoxide likely play a role too. The interplay of these players remains, however, beyond current scientific knowledge.

could then to play a role in brain development – as supported by experimental evidence (Chan and Yew, 1998) – and later influence cognitive aging. In contrast to apoptosis, the decline in neural stem cells in the adult brain could account for the loss of plasticity and increase in robustness during adulthood while indirectly playing a role in cognitive aging at later ages (Brazel and Rao, 2004).

As mentioned above, however, the idea of dying neurons as a cause of cognitive aging now seems overly simplistic. In contrast, pathways that sculpt neuronal circuits during brain development also serve fundamental roles in regulating synaptic plasticity and cell survival in the adult brain. These pathways, which may differ between brain regions, involve neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) and neurotransmitters such as serotonin (Mattson et al., 2004). BDNF and serotonin, in particular, promote differentiation and survival (Gross et al., 2002), but their levels decrease with age, making them potential mechanisms in modulating brain development and aging (Fig. 3B). Moreover, in transgenic mice in which the postnatal rise of BDNF was accelerated, the maturation of GABAergic innervation and inhibition was accelerated. In accordance with our model, the age-

dependent decline of cortical long-term potentiation induced by white matter stimulation, a form of synaptic plasticity sensitive to cortical inhibition, occurred earlier. The transgenic mice also showed a precocious development of visual acuity and an earlier termination of the critical period for ocular dominance plasticity (Huang et al., 1999).

The link between neuroendocrine factors and aging has been well established (Kinney-Forshee et al., 2004; de Magalhaes, 2005) and indeed genes related to neuroendocrine functions are differently expressed with age in the human brain (Jiang et al., 2001; Lu et al., 2004). Sex hormones such as estrogen have been shown to increase synaptic plasticity (Woolley, 1998) and affect synaptic communications (McEwen, 2002). Growth hormone, which is important in development and has been related to cognitive aging (Kinney-Forshee et al., 2004), has been shown to induce NMDA receptors (see below) in an age-related fashion (Le Greves et al., 2002). Certainly, neuroendocrine factors are important in brain development and aging acting as signaling pathways for the normal ontogeny, which may be time-specific. Nonetheless, local-level programs and players are likely involved too (Fig. 3B).

One major player in synaptic plasticity and memory formation is the *N*-methyl-D-aspartate (NMDA) receptor family, whose levels – at least NR2B – decline with age in rats (Clayton et al., 2002), monkeys (Bai et al., 2004), and humans (Lu et al., 2004). For example, hippocampal degeneration in rats has been related to a downregulation of NR2B (Clayton et al., 2002) while in mice NR2B and NR1 levels decline and NR2A levels increase with age. Another family of receptors is the alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA) family, which is involved in synaptic plasticity. Interestingly, AMPA receptors are not expressed in early postnatal life, showing that they are developmentally triggered. AMPA receptors have also been related to neurodegenerative disorders and age-related memory decline (Franciosi, 2001). The main point of interest, however, is understanding the temporal regulation of these and other receptors (see below).

Numerous other mechanisms may play a role. Succinctly, Ca^{2+}-synaptic plasticity – which can be partly regulated by NMDA receptors – may be involved in age-related memory decline (Foster, 1999). Moreover, the neural cell adhesion molecule (NCAM) has been implicated in synaptic plasticity in development and aging (Ronn et al., 2000). Similarly, neuregulin 1 has been involved in development and apoptosis in the developing nervous system as well as neurodegeneration (Grinspan et al., 1996). In rats, synaptophysin, which is involved in synaptic plasticity, declines with age (Smith et al., 2000). All these players are potential topics of study under the model presented here not only in their functions but also in understanding how these genes are regulated during development. Of importance are the experimental approaches used to identify which factors regulate the developmental program and, indirectly, cognitive aging.

4.2. Gene expression changes with age

The model presented herein is in line with the recent data regarding genes differently expressed with age in the human (Lu et al., 2004) and mouse brain (Verbitsky et al., 2004), and in the human hippocampus (Blalock et al., 2003). Briefly, genes involved in synaptic transmission are downregulated with age, such as GABA A receptors, the aforementioned NMDA receptors, serotonin receptors, and genes involved in calcium homeostasis (Lu et al., 2004). Myelination and lipid metabolism genes are upregulated with age, which can be seen as an extension of events present at early stages of development: axons of the major neural pathways in the human brain continue to develop throughout childhood and adolescence (Paus et al., 1999). In the hippocampus, genes downregulated with age include synaptic and neurite plasticity genes while genes upregulated include myelin-related proteins (Blalock et al., 2003). Lastly, in mice, aging leads to a downregulation of genes involved in neural plasticity and of developmentally regulated genes (Lee et al., 2000).

In line with the delay of cognitive aging in CR mice, CR in rodents attenuates the BDNF decline with age (Lee et al., 2002). Moreover, CR attenuates the age-related decline in neurotransmitters during aging as well as some neuronal receptors (Finch, 1993), and induces the expression of genes involved in brain plasticity (Mattson et al., 2002). In fact, CR induces the expression of developmentally regulated genes in the mouse brain when compared to age-matched controls, including HOX family genes (Lee et al., 2000). The next step is linking these players, such as neurotransmitters, neurotrophic factors, and hormones, to the developmental program in order to understand the complex transcriptional control involved.

4.2.1. Reactive oxygen species in brain plasticity

One class of genes shown to be differently expressed during brain aging are those related to oxidative stress with reactive oxygen species (ROS), which have been linked to brain aging (Lee et al., 2000; Jiang et al., 2001; Blalock et al., 2003; Lu et al., 2004; Verbitsky et al., 2004). Although ROS may be a source of damage, recent results suggest that ROS act as signaling molecules in development and later in neurodegeneration (reviewed in Maher and Schubert (2000), Serrano and Klann (2004) and de Magalhaes (2005)). If ROS act as signaling molecules for growth and development, then it is normal for faster-growing mammals to have higher levels of oxidative stress (Rollo, 2002). For example, the accelerated pace of development in rodents may be the reason why these feature higher levels of oxidative damage. Interestingly, not only are ROS involved in a number of signaling processes, including developmental pathways, but some ROS can also modulate synaptic plasticity (reviewed in Serrano and Klann (2004)). Therefore, it is possible that ROS play a role in developmental mechanisms that later influence aging.

Although the exact mechanisms are still unknown, it appears that ROS influence synaptic plasticity in an age-

specific fashion (reviewed in Serrano and Klann (2004)). Some ROS – superoxide and hydrogen peroxide in particular (Kamsler and Segal, 2004) – appear to be necessary for synaptic plasticity during development. Our interpretation is that while some ROS are involved in synaptic plasticity during development, with age, however, the way ROS modulate synaptic plasticity is changed. Considerable evidence exists that ROS generation increases with age and oxidative stress is associated with learning impairments (reviewed in Serrano and Klann (2004)). Yet our proposal is that this increase in ROS with age is a consequence of the lack of responsiveness in the brain to ROS. ROS may then indirectly cause damage and so a feedback loop is formed between ROS trying to stimulate synaptic plasticity and oxidative stress. Therefore, our argument is that ROS do not trigger cognitive aging, but rather are under control by developmental mechanisms and thus form part of its signaling cascade. Like many other factors, ROS are deregulated with age due to the actions of the developmental program and thus cause damage. Clearly, the role of ROS, not just as sources of damage, but also as signaling molecules during brain development merits further attention when studying cognitive aging.

4.3. Experimental implications

One aim of this work is that future studies on normal aging focus on interpreting results with a different perspective by linking aging to development rather than seeing normal cognitive aging as merely a result of damage. If our model is correct, even if not entirely accurate – which is likely given how much there is to learn about the human brain – then studying the interplay of genetic factors responsible for development that shape the adult phenotype will have profound implications for aging research. Certainly, not all developmental mechanisms in the brain are linked to aging, and identifying those that are will be a complex, problematic task.

As mentioned above, genes differently expressed with age may provide clues about the underlying mechanisms. For instance, as mentioned earlier, a number of synaptic transmission genes are downregulated with age but it is unclear why. According to our model, one possibility is that gene expression studies in adulthood alone are unable to uncover the underlying causal mechanisms. Maybe mechanisms responsible for altering cortical circuits in development are unchanged in adulthood and thus cannot be detected by gene expression studies in adulthood alone. Therefore, whole lifespan studies may provide clues about which genes trigger those changes. The majority of gene expression studies in the aging brain have so far focused on adulthood (Lee et al., 2000; Jiang et al., 2001; Blalock et al., 2003; Lu et al., 2004; Verbitsky et al., 2004). We argue that to understand brain aging it is necessary to study the lifespan as a whole – at least postnatal lifespan – and not merely its last segment. Gene expression studies, as well as epigenetic and physiological studies, over the entire lifespan and not just in adulthood may be necessary to understand the causes of brain aging.

Linking aging and development implies we cannot perturb aging without perturbing development. Experiments aiming to manipulate aging would ideally preserve normal ontogeny and only target developmental mechanisms after maturity. This has been done in CR, but it is also necessary while studying aging through genetic manipulations in animal models, such as rodents, and entails difficulties. Since genes involved in aging may be crucial at early stages of development, their manipulation through, for instance, gene knock-out might not be possible. In some cases, RNA technology may be employed in adulthood to block the activity of genes crucial in development. Another idea would be to use conditional expression to overexpress developmentally linked genes that are underexpressed with age (Lee et al., 2000). For example, forkehead family genes have been shown to be underexpressed in the aging human brain (Lu et al., 2004).

Other potential targets of genetic interventions include neuroserpin, a factor that promotes neural plasticity, and HOX family genes, whose expression in enhanced by CR (Lee et al., 2000). Interestingly, there is evidence that neuroserpin underwent positive selection during primate evolution (Dorus et al., 2004), making it a promising target for manipulations in model organisms. Similarly, BDNF is overexpressed when rodents are subjected to CR and may have undergone positive selection. Other genes that may have undergone positive selection in primates and appear to be downregulated with age include GDNF (Lee et al., 2000) and GAP43 (Blalock et al., 2003), despite some contrasting results for GAP43 (Lu et al., 2004). Finally, other promising targets could include NCAM and neuregulin 1. Lastly, CASP3 and CASP9 have also been shown to have undergone positive selection (Dorus et al., 2004), and caspases shown to play a role in modulating synaptic plasticity (Chan and Mattson, 1999).

5. Concluding remarks

There are caveats to this work. We barely account for prenatal development or the way different brain areas may change with age at different paces. Although plasticity occurs over an individual's lifetime, different types of plasticity dominate certain periods of one's life and are less prevalent on other periods. Not all cognitive and memory functions decline with age and different functions change at different paces with age (Craik and Salthouse, 1992; Kausler, 1994; Gopnik et al., 2000). Besides, we chose not to include neurodegenerative pathologies since diseases such as Alzheimer's, Parkinson's, and Creutzfeldt-Jacobs's – or even earlier-onset neurological pathologies such as Tay-Sachs, Rett, and Down's syndrome – may not to be part of normal brain aging. Lastly, different mechanisms can be in

place to regulate brain plasticity in different species just like different developmental mechanisms exist. While we focus mostly on mammals, alternative mechanisms are likely to occur in other vertebrate lineages. For example, extensive neurogenesis has been reported to occur in reptiles (Font et al., 2001) and birds (Nottebohm, 1989). It would be impossible to model the extraordinarily complex human mind. Rather, the aim of this work is to present one particular hypothesis by which neurodegeneration is linked to a subset of developmental mechanisms.

Overall, the model presented herein is that normal cognitive aging is a continuation of the genetic program that orchestrates the plasticity changes in early life. Differences in the rates of cognitive aging among mammals can then be linked to differences in the pace of developmental schedules. Our model applies conceptual, even abstract theories to real mechanisms in the context of brain aging: the mechanisms shaping learning at early ages later contribute to neurodegeneration. We link a number of mechanisms, including ROS and neuroendocrine signals, to development and aging in an orchestrated fashion in which fast development leads to fast aging and vice versa. Hopefully, this way of interpreting normal brain aging can foster new approaches for how to research and intervene in a crucial field such as cognitive aging.

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