Aging-associated Changes in Human Brain

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Abstract. A wide variety of anatomic and histological alterations are common in brains of aged individuals. However, identification of intrinsic aging changes—as distinct from changes resulting from cumulative environmental insult—is problematic. Some degree of neuronal and volume loss would appear to be inevitable, but recent studies have suggested that the magnitudes of such changes are much less than previously thought, and studies of dendritic complexity in cognitively intact individuals suggest continuing neuronal plasticity into the eighth decade. A number of vascular changes become more frequent with age, many attributable to systemic conditions such as hypertension and atherosclerosis. Age-associated vascular changes not clearly linked to such conditions include hyaline arteriosclerotic changes with formation of arterial tortuosities in small intracranial vessels and the radiographic changes in deep cerebral white matter known as "leukoaraiosis." Aging is accompanied by increases in glial cell activation, in oxidative damage to proteins and lipids, in irreversible protein glycation, and in damage to DNA, and such changes may underlie in part the age-associated increasing incidence of "degenerative" conditions such as Alzheimer disease and Parkinson disease. A small number of histological changes appear to be universal in aged human brains. These include increasing numbers of corpora amylacea within astrocytic processes near blood-brain or cerebrospinal fluid-brain interfaces, accumulation of the "aging" pigment lipofuscin in all brain regions, and appearance of Alzheimer-type neurofibrillary tangles (but not necessarily amyloid plaques) in mesial temporal structures.

Key Words: Aging; Dendritic complexity; Glial changes; Lipofuscin; Neurofibrillary tangles; Neuronal loss.

INTRODUCTION

I can live with my arthritis,
My dentures fit me fine,
I can see with my bifocals,
But I sure do miss my mind.
—Anonymous

Aging, along with taxes, is one of the absolute certainties of life. Everyone knows what aging is, and can recognize it when they see it. It is thus truly amazing how little we understand about the process. Although many diseases become more likely as one ages—stroke, Alzheimer disease, Parkinson disease—it is not at all clear that any diseases are *inevitable* consequences of aging. Indeed, is difficult to provide even a noncontroversial, nontrivial definition of aging. A typical definition might be "a progressive, unfavorable loss of adaptation resulting in decreasing expectation of life with the passage of time." That is, the older you get, the closer you are to death.

Despite these caveats, there are criteria that may be applied to any anatomic or functional change that is to be regarded as a part of the normal aging process. Such changes must be (a) universal, i.e. found in any individual that lives sufficiently long; (b) intrinsic, i.e. not the consequence of any dietary or other environmental effect;

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and (c) progressive, as we understand aging to be a progressive phenomenon. To this list, some would add the criteria of deleterious, as we generally think of the changes of aging—in physical terms—as undesirable.

This review focuses on the anatomic changes that occur in the aging human brain. Our emphasis is on identifying universal, intrinsic, progressive changes, but reference is also made to aging-associated diseases, to the possible role of normal age-related changes in promoting such diseases, and (where possible) to the relationship of such changes to current biochemical theories of aging.

CHANGES IN BRAIN SIZE, NEURONAL NUMBER, AND DENDRITIC COMPLEXITY

The brain, or at least its neuronal component, is a postmitotic organ. As neurons may be lost, but not added, it is statistically inevitable that *average* neuronal number (and *average* brain weight) will decline with age. Among populations of neurologically normal individuals, average brain weight gradually declines after the age of 60, and average individuals typically show losses of about 2 to 3 grams (g)/year from normal adult average weights of 1400 g (for men) and 1250 g (for women). These decreases appear to be largely attributable to changes in the white matter and are most marked in the frontal lobes. A complicating factor in such determinations is the "secular effect," or the progressive trend toward increased mean body height and brain weight during the 20th century. As a consequence, lower brain weights in the elderly, compared with younger individuals dying at the same time, might be interpreted as the result of developmental or nutritional effects early in life rather than atrophic changes late in life.

These limitations may be overcome by determinations of ratios between intracranial volume and brain volume,

or by assessments of sulcal widening and ventricular enlargement (reflecting cerebral atrophy) in the elderly. The average ratio of brain volume to skull volume remains constant at 95% up to the age of 60 years, after which there is a progressive decline to about 80% in nonarians. This progressive decline shows some scatter, however, suggesting that some or all of the decline may be attributed to genetic variation or environmental factors. Sulcal widening and ventricular enlargement also occur with aging. The average volume of the lateral and third ventricles, for instance, increases from 15 ml in teenagers to 55 ml for those over 60 years of age. Quantitative analyses of cerebral structures have indicated a progressive reduction in hemispheric volume after the age of 20, which is greater in men (3.5% per decade) than in women (2% per decade). The initial loss is largely cortical, followed by greater declines in the volume of subcortical white matter. These relative changes have been interpreted as reflecting a loss of interneurons, with implications for age-associated cognitive changes.

Imaging studies have been used to assess age-associated changes in brain volume in vivo. These have shown age-associated declines in cerebral volume and increases in ventricular volume, similar to those found in autopsy series. There is, however, considerable variation, and many elderly individuals do not show detectable volume changes.

Assessment of age-associated neuronal loss is complicated by difficulties inherent in estimating total or regional cortical volume changes, by variations in cortical architectonics and consequent sampling errors, by interindividual variations in patterns of loss across brain region, and by artefactual cortical and neuronal cellular volume changes associated with brain fixation. Early studies of age-associated changes in the cerebral cortex yielded an estimated neuronal loss of 15 to 35%, and subsequent computerized image analysis techniques suggested losses as high as 50% among large neurons. Some of these latter changes, however, appear to be attributable to changes in neuronal cell size rather than neuronal cell number. There are significant age-associated decreases in neuronal cell size, especially among large neurons, and consideration of these changes has led to much more modest estimates of age-associated cerebral cortical neuronal loss (1).

Some of the difficulties inherent in estimating total cerebral cortical neuronal number are avoided by analyzing smaller structures such as the hippocampus. Even here, however, there is difference of opinion regarding the amount of neuronal loss and the relative loss in different sectors. For the basal nucleus of Meynert, the main source of cholinergic innervation for the cerebral cortex, both steady declines and unchanging neuronal counts (2) have been reported. For the cerebellum, there appears to be a considerable age-associated decrease in average number of

Purkinje cells, although some elderly individuals show no age-associated loss (3). In the hypothalamus there are age-associated alterations in the sizes of certain neurons and organelles (4) and in diurnal and annual patterns of neuronal vasopressin expression (5). Within the calcarine cortex, there is a reported gradual age-associated decline in the density of intracortical myelinated fibers (6), but this is not seen in the parahippocampal gyrus (7).

Neurons are complex structures, and age-associated changes in dendritic complexity and synaptic number have also been investigated. Regressive changes have been reported for the dendritic trees in frontal and temporal cortex and in the limbic system of aging individuals. These changes commence with loss of dendritic spines, are followed by changes in the size and shape of horizontal branches, and culminate in loss of basilar dendrites or branches of the apical shaft (8). Age-associated decreases in numbers of synapses have been reported for frontal (but not temporal) cerebral cortex (9). In contrast, Buell & Coleman (10) have shown continuing dendritic growth and increasing dendritic complexity for parahippocampal pyramidal cells of cognitively normal individuals well into the eighth (but not tenth [11]) decade of life. These latter studies employed the Golgi-Cox technique for staining of dendritic trees, which is less prone to artefact than the rapid Golgi method employed by others. These results suggest that "normal" aging, at least into the eighth decade, is characterized by preservation of neuronal plasticity, and that age-associated declines in neuronal dendritic complexity are pathological.

ACCUMULATION OF PIGMENTS

Lipofuscin is a complex, poorly soluble, intracellular pigment that accumulates progressively within secondary lysosomes in neurons and other post-mitotic cells. Because of its insolubility, lipofuscin is difficult to characterize biochemically, but it is known to contain polymerized residues of peroxidized lipids and proteins. In experimental animals, dietary supplementation with the anti-oxidant vitamin β-tocopherol results in decreased lipofuscin accumulation in brain (12). Lipofuscin serves no known function, and is viewed as a by-product of normal, age-related "wear and tear" associated with cellular function.

Lipofuscin is evident in inferior olivary neurons in infancy, appears in spinal cord neurons in childhood, and accumulates progressively with age in neurons throughout the CNS. Lipofuscin is particularly prominent in neurons of the cranial and spinal motor nuclei, the red nucleus, portions of the thalamus, the globus pallidus, the inferior olivary nuclei, and the dentate nucleus of the cerebellum. In the cerebral cortex, lipofuscin accumulation is most marked in large neurons of the precentral gyrus, and aged cerebral cortical pyramidal cells develop lipofuscin-containing proximal axonal swellings (13).

The Purkinje cells of the cerebellum appear to remain relatively free of lipofuscin accumulation. In rats, lipofuscin first appears in neurons at about 8 weeks of age and subsequently increases linearly with age. Caloric restriction is a proven method for prolonging lifespan in experimental animals, and aged, caloric-restricted mice show less intraneuronal lipofuscin accumulation than do control animals of equivalent age (14).

In addition to lipofuscin, there is accumulation of other intracellular pigments with aging. Neuromelanin, a by-product of catecholamine synthesis, accumulates in "pigmented" brainstem nuclei (substantia nigra, locus coeruleus, and the dorsal motor nucleus of the vagus nerve) until approximately 60 years of age, after which there is a decline. A peroxidase-positive granule, distinct from lipofuscin, accumulates with age in glial cells of estrogen-sensitive hypothalamic regions. The appearance of these granules is accelerated by estrogen, and coincides with the appearance of 27-, 72-, and 90-kDa heat-shock proteins (15).

ALZHEIMER-TYPE CHANGES

Alzheimer disease is characterized pathologically by the appearance of extracellular amyloid deposits with and without neuritic elements, and by intraneuronal changes, including neurofibrillary tangles, granulovacuolar degeneration, and Hirano bodies. All of these changes also occur, albeit to lesser degree, in the brains of elderly, cognitively intact individuals.

Some degree of neurofibrillary tangle formation is found in mesial temporal structures (amygdala, hippocampus, and adjacent cortical areas, but not the neocortex) in virtually all elderly individuals (16). In contrast, deposition of amyloid and formation of neuritic amyloid plaques is seen only in some cognitively intact, elderly individuals, and is generally more frequent in neocortical areas (16, 17). Occasional apparently normal elderly individuals may show impressive degrees of amyloid deposition in the absence of abnormal neuritic elements. Dickson et al (18) used the presence or absence of such diffuse neocortical amyloid deposits to distinguish "normal" and "pathological" aging, although the two groups were not clinically different in their study. Others have found that such diffuse amyloid deposition correlates with mild cognitive impairment (19), and is not found in carefully studied, cognitively normal elderly individuals (17). This is consistent with studies showing increasing *prevalence*, but not increasing *density*, of amyloid plaques with increasing age (20), a finding which suggests that either (a) amyloid deposition is not progressive in normal aging, or (b) increased density of amyloid deposits gives rise to cognitive impairment and thus removes one from the category of "normal." This latter interpretation would suggest that amyloid deposition is not a normal component of the aging process, but represents early (pre-clinical) Alzheimer disease (19).

Granulovacuolar degeneration and Hirano bodies are additional microscopic features of Alzheimer disease and some other diseases. In Alzheimer disease and in "normal" aging, granulovacuolar changes are found almost exclusively in the pyramidal cells of the hippocampus, predominantly in the CA1 field. The prevalence of granulovacuolar changes in nondemented elderly populations increases with age after the sixth decade, reaching 75% by the ninth decade. Hirano bodies are occasionally seen in young adults, but become increasingly common with advancing age.

CHANGES IN NEUROTRANSMITTERS

The prominent involvement of *cholinergic* systems in Alzheimer disease has prompted studies of changes in the neurotransmitter system associated with aging. Brain choline acetyltransferase levels and muscarinic binding decrease with increasing age (21), as do indices of cholinergic innervation in the caudate nucleus (22). *Dopaminergic* systems have also received particular attention because of their age-associated deterioration in Parkinson disease. There are age-associated declines in levels of striatal dopamine uptake sites (23), dopamine transporters (24), and dopamine levels (25). *Serotonergic* systems show age-associated declines in levels of cortical serotonin binding sites (22), *adrenergic* systems show age-associated decreases in cerebral cortical α_2- (26) and β_1- (27) (but not total β- [26]) adrenoreceptors, and *GABAergic* innervation of the cortex appears to decline with age (22). Tissue levels of glutamate and aspartate vary considerably among discrete areas of human brain, and brains from aged individuals show a number of alterations in these distributions (28).

VASCULAR CHANGES

Arteriosclerotic and atherosclerotic vascular changes become increasingly prevalent throughout the body as well as in the brain with advancing age. Small atheroma, usually without significant lumenal compromise, may be found in major intracranial vessels at the base of the brain in elderly individuals, but these deposits rarely affect vessels less than 2 mm in diameter in normotensive individuals. In contrast, hyaline arteriosclerotic changes occur in small intracranial vessels (< 1 mm diameter) of elderly individuals. The intima is thickened by a concentric increase in connective tissue and there is fibrous replacement of vascular wall smooth muscle. The vessels become thickened and more rigid, as well as elongated and tortuous. These arterial tortuosities are found predominantly at gray-white interfaces of the insular region and adjacent areas. They increase in number with advancing age and are not related to systemic hypertension (29).

A second type of blood vessel-associated change is expansion of perivascular spaces with the formation of *lacunae*. In contrast to arterial tortuosities, these small (3–20 mm diameter) lesions are most common and most pronounced in individuals with hypertension, but they do also occur in normotensive individuals (30). They are found predominantly in cerebral white matter and subcortical basal ganglia. They increase in frequency in the fifth and sixth decades, but thereafter become less common. Suggested pathogenic mechanisms include arterial pulsations and vascular lipohyalinosis, and, for larger lesions, either atheroma or emboli. Some authors have found correlations between multiple lacunae and intellectual impairment (31), but these lesions may only be markers for more widespread pathological changes in the white matter.

The advent of computed tomography, and especially magnetic resonance imaging, has revealed previously unrecognized changes in the deep cerebral white matter of many elderly individuals. These symmetrical, paraventricular areas of radiolucency (on computed tomography) or increased signal intensity (on T2-weighted magnetic resonance imaging) become more prevalent with advancing age (32). These changes were initially interpreted as white matter infarcts (Binswanger's disease), but are now known by the more noncommittal term *leukoaraiosis*. Some of these patients are demented, but many show no intellectual deficits (33). Patients with leukoaraiosis are more likely to have had strokes in the past (34), and are more likely to have strokes in the future (35), suggesting an association with vascular disease. Correlative studies have found a variety of histological alterations corresponding to these radiological abnormalities. These range from mild changes such as myelin pallor, focal ependymal loss, and dilated perivascular spaces to more severe abnormalities such as lacunar infarctions, extensive arteriosclerosis, and diffuse white matter necrosis (36). Venous collagenosis (37) and increased astrocyte water content (38) have also been suggested as pathologic substrates underlying the observed imaging abnormalities.

CHANGES IN GLIA

Both astrocytes and microglia become more prominent in aging human brain. There is an age-associated increase in the numbers of cerebral cortical astrocytes immunoreactive for glial fibrillary acidic protein that becomes evident in the eighth decade (39). Activated astrocytes elaborate a neurotrophic cytokine, S100β, that has been implicated in the development of neuritic plaques in Alzheimer disease (40). With normal aging there are increased numbers of S100β-immunoreactive astrocytes in human cerebral cortex, a change that is accompanied by increased cerebral cortical tissue levels of S100β protein and S100β mRNA (41).

Microglia also show age-associated changes in human brain. Activated microglia, expressing the immunomodulatory cytokine interleukin-1, are significantly increased in number in brains of nondemented individuals over the age of 60, and this age-associated increase is accompanied by changes in microglial morphology (42). The numbers of enlarged and phagocytic microglial forms increase with age, while no significant increase is seen in the number of nonenlarged, nonactivated forms. Concomitant with these changes in microglial number and morphology there are significant age-associated increases in tissue levels of interleukin-1 mRNA (42). As microglial overexpression of interleukin-1 has been implicated in the pathogenesis of Alzheimer disease (43), these age-associated increases may contribute to the increasing incidence of Alzheimer disease with advancing age.

MISCELLANEOUS MICROSCOPIC CHANGES

Corpora amylacea are round, basophilic, PAS-positive structures, 5 to 20 μm in diameter, that lie within astrocytic processes in subependymal and subpial areas, especially in the globus pallidus, hippocampus, and posterior columns of the spinal cord. They are unusual in the first decade of life but are universal by the age of 40. Although they are essentially identical to the "polyglucosan bodies" and "Lafora bodies" associated with the diseases of the same names, their significance in normal aging remains obscure.

Ubiquitin-immunoreactive granular structures are found in limbic areas in middle age, and they increase in number and regional distribution with aging (18, 44, 45). They appear to derive from degenerating terminal axons, and actually *decrease* in frequency in advanced stages of Alzheimer disease and of dementia with Lewy bodies (45). Ubiquitin-immunoreactive *axonal spheroids* appear in brainstem structures in the second decade, and increase in number with advancing age (44).

Marinesco bodies are eosinophilic, ubiquitin-immunoreactive (44), intranuclear paranucleolar inclusions found in pigmented neurons, particularly in the substantia nigra. They can be found in most individuals beyond their second decade, and increase in numbers with advancing age. Unlike many of the microscopic changes associated with aging, Marinesco bodies are not associated with any known disease, and their significance remains obscure.

Granular glycogen bodies are intracytoplasmic inclusions found within cell processes in the cerebral cortex and underlying white matter of individuals older than 60 years. They are 5 to 50 μm in diameter and consist almost exclusively of densely packed α- or β-glycogen granules (46).

MOLECULAR ALTERATIONS WITH AGING

Oxidative damage, induced by free radicals, has long been thought to be an important component of the aging

process. Oxidized protein levels increase exponentially with age in human cerebral cortex (47), and lipofuscin, the most prominent age-associated morphological alteration, is thought to represent a cumulative by-product of oxidative damage to cell constituents. In experimental animals, chronic treatment with anti-free radical agents not only slows (or even reverses) the accumulation of oxidized proteins, but also restores short-term memory indices to those of young animals (48).

Accumulation of DNA damage is another mechanism thought to be fundamental in the aging process. Aging experimental animals show steady increases in both single- and double-strand genomic DNA breaks, and such damage is markedly higher in the cerebral cortex than in other regions (49). In human brain there are age-associated increases in oxidative damage to DNA, which are more marked for mitochondrial than for nuclear DNA (50). Mitochondrial DNA diversity, arising from acquired mutations, increases with age in the human brain (51).

Advanced glycation end products—tissue and cell surface proteins modified nonenzymatically and irreversibly by glucose—accumulate with aging in human brain (52). Proteins so modified are strongly resistant to proteolytic processes and promote protein crosslinking. In the periphery, these end products can be removed by macrophages through a high-affinity receptor (53). Microglia may perform a similar function in the brain, and activation of microglia by glycated proteins may promote age-associated microglial changes.

RACE AND SEX DIFFERENCES IN BRAIN AGING

The effect of race on age-associated changes in brain has not received a great amount of attention. The age-associated appearance of Alzheimer-type neuropathological changes in nondemented populations is reported to be similar in American Caucasians and East African blacks (54), but less frequent in Hong Kong Chinese (55). Arterial tortuosities reportedly show no race specificity in American populations (29), and a magnetic resonance imaging study found similar degrees of age-associated ventricular enlargement and sulcal widening in "healthier" American black and nonblack individuals (56). In contrast, leukoaraiosis is reported to be more pronounced among elderly black individuals (56). In a recent review, Gorelick (57) concluded that age-associated intracranial atherosclerosis or intraparenchymal arterial sclerosis is more common and severe among Japanese, Chinese, and American blacks; and that extracranial (i.e. carotid) atherosclerosis is more common and more severe in whites.

Differences in brain aging in men and women have been reported. As noted above, autopsy series have found greater rates of age-associated cerebral atrophy in men than in women. Imaging studies have also suggested that elderly men show greater ventricular enlargement and sulcal widening than elderly women (56), although most of these sex-based differences disappear after correction for differences in total intracranial volume (58). Hippocampal atrophy, again assessed radiologically, is reportedly more common in "normal" elderly men (59), but these changes are accompanied by subtle reductions in delayed verbal recall performance, suggesting that they are pathological. Intracranial atherosclerosis is more marked in young adult men, but increases more rapidly in women after the sixth decade with the result that these changes are more severe in women by the ninth decade (reviewed by Gorelick [57]). Sex-specific, age-associated changes have been reported for the hypothalamic suprachiasmatic nucleus, with a decrease in total cell number in women but a decrease in vasoactive intestinal polypeptide-expressing neurons in men (60). Radiographically identified "leukoaraiosis" is reportedly more pronounced in elderly women than in elderly men (56), but sex has no effect on age-associated arterial tortuosities (29).

THE AGE-MATCHED CONTROL BRAIN

The various changes associated with aging of the human brain must be addressed when selecting "normal" control brains for tissue-based investigations of neurological disorders in elderly populations. Some age-associated changes are clearly pathological (e.g. cerebral cortical infarcts), while others are clearly not (e.g. corpora amylacea). Other changes are virtually universal in their prevalence, and must thus considered "normal" in some qualitative sense, but become readily recognizable as pathological when they exceed some quantitative threshold (e.g. neurofibrillary tangles). Still other changes are so common that rigorous exclusionary criteria may leave one with no control brains to study. As a practical matter, disease-free, cognitively intact, elderly individuals, dying suddenly and arriving at postmortem examination with minimal delay, with only minimal and inevitable gross and histological changes in their brains, are quite rare, and some selection criteria must be established that yields an acceptable number of specimens while excluding conditions or changes that would compromise investigational results. The selection process depends, of course, in part on the nature of the study and the question(s) to be addressed. Hypotheses originating from tissue-based findings—a study seeking to identify correlates of "normal" vs "pathological" aging (18), for instance—might require strict neuropathological exclusionary criteria for "normal" brains. In contrast, hypotheses originating from clinical findings—a study seeking to correlate cognitive changes with histological changes, for instance—might be fatally flawed if the very presence of such histological changes were an exclusionary criteria for identifying a group of "normal" controls. Situations presenting questions with less obvious "correct" answers are

also common, such as the degree of Alzheimer-type neuropathological change that might be acceptable in a study of dementia associated with schizophrenia. Successful pathological or clinico-pathological investigations are dependent upon careful consideration of such factors at the inception of the investigation as well as on a thorough neuropathological characterization of the collected brains.

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