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Structural changes that occur during normal aging of primate cerebral hemispheres

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Abstract

Human and non-human primates show cognitive decline during normal aging. Originally, the decline was attributed to a loss of cortical neurons, but recent studies have shown there is no significant cortical neuronal loss with age. Neurons acquire pigment, but the only other obvious changes are in layer 1 of neocortex. Layer 1 becomes thinner as apical tufts of pyramidal cells lose branches, as well as synapses, and at the same time the glial limiting membrane thickens. How dendrites and synapses in deep layers are affected by age is uncertain, but there are decreases in the levels of some neurotransmitters and receptors. Throughout the brain myelin sheaths show signs of breakdown. This may contribute to cognitive decline because it would cause a slowing of conduction along nerve fibers, disrupting the timing in neuronal circuits. Concomitantly, the myelin-forming oligodendrocytes develop swellings along their processes and gain dense inclusions. Microglial cells and astrocytes accumulate large amounts of phagocytosed material with age, although the origins of this material are not known.

Keywords: Normal aging; Cerebral cortex; Humans; Monkeys; Neurons; Neuroglia

1. Introduction

The preponderance of studies of the effects of age on the brain have been directed towards determining the underlying causes of Alzheimer's disease, because the devastating behavioral changes that occurs as a consequence of Alzheimer's disease severely affect not only the patient, but the lives of the immediate family. It is only in the past 25 years, or so, that much attention has been paid to the effects of normal aging on the brain. It is clear that normal aging brings about a progressive decline in several aspects of cognitive function, and although the effects are generally mild, in some individuals they can affect daily living. The changes that occur during normal aging are a decline in short-term memory; increase in forgetfulness; increase in the time it takes older individuals to learn new information; slowing in the speed of response; and decline in the facility to solve ongoing problems (executive function) [1]. As the proportion of senior citizens gradually increases, there is a need to understand the bases for these declines in cognitive function, because only then means can be found to decelerate the decline, thereby allowing more severely affected individuals to lead independent lives. Another reason to determine what changes occur as a consequence of normal aging is that any pathological changes that result in dementia are superimposed on the normal aging changes that have preceded them. Consequently, it is important to know what changes can be considered 'normal' and which ones are 'abnormal'.

One of the difficulties in studying the effects of normal aging on the brains of humans is that it is rare to have informative data on the cognitive status of an individual prior to death, and to know if the individual showed early signs of dementia. Even when such data are available, postmortem delays usually make it difficult to obtain brain tissue in a state of preservation optimal enough for detailed structural analyses. One solution to these problems is to find a model for normal human aging, and one of the best models is provided by the rhesus monkey (*Macaca mulatta*). Rhesus monkeys have a life span of about 30 years. They are sexually mature at 5 years of age and only 25% reach an age of 25 years [2], so that monkeys over 25 years of age can be considered old and the effects of age can be determined by comparing their brains with those of young monkeys.

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Furthermore, the effects of age on their cognitive status can be assessed using cognitive tasks that have been adapted from human psychological test batteries [3]. Such tests show that the primary age-related cognitive deficits exhibited by aging monkeys are similar to those that affect humans, namely, they show declines in short-term memory and executive system function [1,3]. Moreover, there are no indications that rhesus monkeys get Alzheimer's disease. Even in old age, none of their cortical neurons show neurofibrillary tangles. However, as in humans amyloid deposition is a feature of aging in the monkey brain, and the amyloid accumulates in the form of β-amyloid (Aβ), but antibodies specific for either the 40- or 42-amino acid carboxy terminal of Aβ reveals a preponderance of Aβ42 in the senile plaques of humans with Alzheimer's disease, whereas Aβ40 is more abundant in rhesus monkeys [4]. It is also interesting that the deposition of β-amyloid varies among species of primates. In rhesus monkeys the β-amyloid is primarily associated with plaques, whereas in squirrel monkeys the amyloid is primarily associated with blood vessels [4]. Although the plaques in rhesus monkeys have dystrophic neurites associated with them, the distribution and frequency of plaques relates only to increasing age, not to cognitive status [5].

2. Effects of age on numbers of neurons in human cortex

Detailed reviews of the effects of normal aging of the population of cortical neurons have already been published [6–8] and so only a brief account will be presented here. With space limitations, not all of the articles dealing with aging in the primate cerebral hemispheres can be mentioned individually, but references to the original articles will be found in the reviews that are cited.

Among the first studies of the effects of age on neuronal numbers were those of Brody [9] who examined several cortical areas. He concluded that as many as 49% of cortical neurons are lost with age. These studies set the stage for the belief that there is a correlation between the loss of cortical neurons and cognitive decline. Further support for the conclusion that neurons are lost during normal aging came from a number of studies carried out during the 1970s and 1980s [6,8]. The first investigator who appeared to reach the opposite conclusion was Cragg [10].

Cragg's [10] conclusion that significant numbers of neurons are not lost during normal aging was subsequently supported by the results of Terry et al. [11], and by Haug and his co-workers [12] who carried out an extensive study involving 120 human brains. Haug suggested that the reported losses of cortical neurons could be attributed to the fact that when tissue is processed for microscopic examination the brains of older individuals shrink less than those of younger ones: the consequence is that neuronal densities are higher in sections from younger cortices than in sections from older cortices, thus giving the impression of neuronal loss with age.

Terry et al. [11] examined the brains of normal subjects between the ages of 24 and 100 years of age. Using an image analysis system, Terry et al. [11] concluded that with age neuronal density is not changed, and suggested that some of the earlier reports of large losses of neurons with age might have been due to the inclusion of individuals with early stages of Alzheimer's disease among the brains that were assumed to be normal. Terry et al. [11] also found there is a decrease in the sizes of some of the larger neurons coupled with an increase in the number of smaller neurons, and they took this to indicate that some of the larger neurons shrink with age. Schutz and Hunziker [13] have also concluded that neurons can shrink with age, but there appear to be no recent studies that address this issue.

More recent studies on the effects of normal aging on neuronal number have concurred that there is no significant loss of cortical neurons with age. For example, Leuba and Kraftsik [14] examined primary visual cortex and found that although its surface area can vary between 15 and 40 cm^2 among individual brains, there is no statistically significant loss of neurons with age. This variation in the size of area 17 serves to bring out the point that there may be large differences in the volumes of specific cortical areas in primates, so that unless sufficient numbers of specimens are compared to carry out a statistical analysis, it can be very difficult to be certain how total populations of neurons in specific cortical areas are affected by age.

In 1984 a stir was created among the anatomical community by Gundersen [15] who introduced new, originally 'unbiased', but now termed 'design-based', disector methods for counting neurons. The contention was that previous methods of counting neurons were inaccurate and that by using these new methods, accurate estimates of total neuronal numbers could be readily obtained [16]. Using these new stereological principles Pakkenberg and Gundersen [17] ascertained that in the entire cerebral hemisphere there is an overall loss of about 9.5% of cortical neurons with age. They found no change in the packing density of neurons, and ascribed the loss of neurons to a decrease in the total volume of gray matter. However, it should be pointed out that others, like O'Donnell et al. [18], have concluded that cortical gray matter volume does not decrease with age.

Recently, Gómez-Isla et al. [19,20] used the modern stereological methods to determine the effects of normal aging on the neurons in human entorhinal cortex and superior temporal sulcus. They found no age-related loss of neurons. In contrast, compared to young adults, in a group of Alzheimer (AD) brains both areas showed a neuronal loss that amounted to 48–53%. Similarly, Lueba and Kraftsik [21] estimated that compared to normal brains the primary visual cortex in AD brains can lose as many as 30% of its neurons. Obviously, there is a striking difference between

normal and AD brains in terms of the preservation of neuronal populations.

At present it is not clear if there is a loss of neurons from the hippocampus during normal aging. The role of the hippocampus in learning, and the fact that there is a massive loss of hippocampal neurons in A.D., has lead to extensive studies of the effects of normal aging on this structure. As with neocortex, early studies led to the conclusion that there is loss of neurons from hippocampus during normal aging, but more recent studies suggest that only some portions of hippocampus may be affected. For example, West [22] reported a loss of neurons from the hilus of the dentate gyrus, but not from other subfields. On the other hand, Simic et al. [23] have reported losses of neurons only from the CA1 subfield and subiculum. How to interpret such data is not clear, and no consensus appears to have been reached about the effect of normal aging on neurons in the hippocampal subdivisions.

In summary, the data from studies of the effects of normal aging on the human cerebral cortex suggest that while there might be some small overall loss of neurons from neocortex, it is nowhere near as massive as earlier studies indicated. Further, some neocortical areas appear to lose no neurons.

3. Effects of age on the numbers of neurons in monkey cerebral cortex

As in studies of human cortex, the early studies of non-human primate cortex by Brizzee and his colleagues [24], begun in the 1970s, led them to conclude that cortical neurons are lost with age. They examined the effects of aging on sensorimotor, frontal cortices, and the CA1 zone of hippocampus. However, all subsequent studies on monkey cortex found no neuronal loss. The subsequent studies were begun by Vincent et al. [25] who examined primary visual cortex and concluded that there is no neuronal loss with age. Later studies of visual cortex have examined the neurons in the cytochrome oxidase blobs [26], and the large Meynert cells [27,28], and determined that there is no loss of neurons from these subpopulations. Other cortical areas that have been examined are motor cortex [29], area 46 of prefrontal cortex [30], and entorhinal cortex [31], and again the investigators report that neurons are not lost with age. It has also been found that there is no age-related loss of neurons from the hippocampus of rhesus monkeys [32,33]. The overall conclusion from these studies is that, as in humans, loss of cortical neurons is not the basis for normal, age-related, cognitive decline in monkeys.

4. Effects of age on cortical neurons

With age, most cortical neurons gain some lipofuscin granules, or age pigment, in their cytoplasm, but the amount is variable. In general, the inhibitory non-pyramidal cells seem to acquire more lipofuscin than the excitatory pyramidal neurons. Also, large neurons have more lipofuscin than smaller ones, but this is not a rule, so that among the larger cortical neurons, the Meynert cells of visual cortex [27] come to contain little age pigment, while the Betz cells of motor cortex can become so full of pigment that their nuclei are displaced to one side of the cell body [29]. But otherwise the cell bodies of cortical neurons seem to be slightly affected by age.

It is unclear how age affects the dendrites of most neurons. In one of the more recent studies, Jacobs et al. [34] examined the basal dendrites in prefrontal area 10 and in visual area 18 of the human brain using Golgi impregnated material. They concluded that with age there is a decrease in total dendritic length and a substantial decrease in dendritic spine numbers, amounting to about 50%. However, after about 50 years of age the dendritic measures remained relatively stable. Similar results have been obtained in studies of the monkey brain. However, it is never certain that Golgi impregnation fills all of the branches of dendrites to their tips, and a much better approach would be to examine intracellularly filled neurons.

Dendrites that are severely affected by age are ones in the apical tufts of pyramidal cells. These dendrites populate layer 1, where they receive input from a variety of sources. In studies comparing layer 1 of both area 46 of prefrontal cortex [35] and primary visual cortex [36] in young (5–12 years old) and old (>24 years of age) monkeys, it became apparent that apical dendrites in layer 1 show signs of degeneration, and branches are lost (Fig. 1). The result is that layer 1 becomes thinner with age. The loss of the dendrites is accompanied by a loss of dendritic spines and about 50% of the synapses. In both areas the thinning of layer 1 correlates with age, but only in area 46 do the thinning of layer 1 and the loss of synapses, both correlate with and the cognitive status of the monkeys. This difference might be due to the fact that prefrontal cortex has a greater role in cognition than primary visual cortex.

5. Age related changes in synapses

Most of the studies on the effects of age on synapses in primates have been carried out on human material, and the data are inconclusive. Cragg [10] found no significant decline in the density of synapses from human frontal cortex with age. Hutterlocher [37] obtained a similar result for synapses in layer III of middle frontal gyrus, and later Hutterlocher and de Courten [38] ascertained that in temporal lobe and in primary visual cortex the number of synapses remains relatively unchanged until about 70 years of age. In contrast Gibson [39] reported a 20% loss of synapses from frontal cortex, but no loss from temporal cortex, and in a light microscopic study of frontal cortex using antibodies to synaptophysin, Masliah et al. [40] also

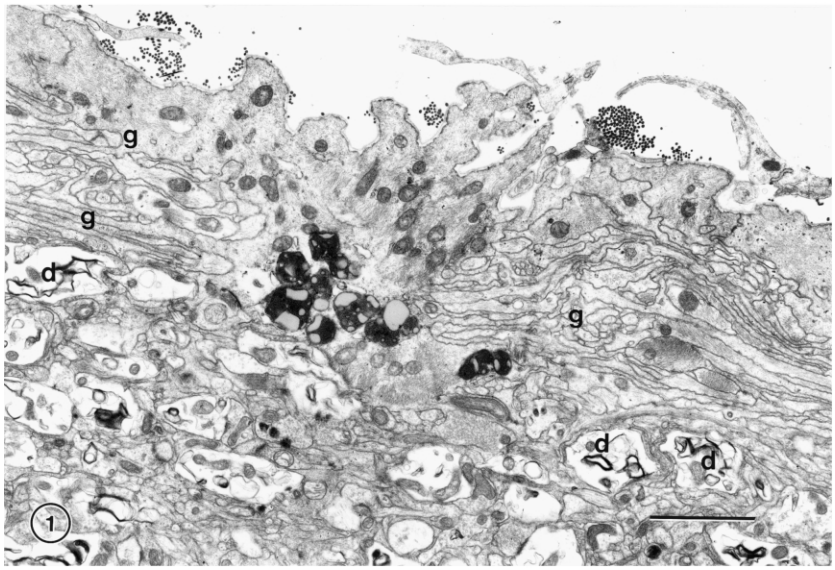

Fig. 1. Electron micrograph showing the outer surface of the cerebral cortex of area 17 in a 25 year old monkey. The glial limiting membrane (g), which is formed by the processes of astrocytes, is considerably thickened in old monkeys. In the upper part of layer 1 many of the dendritic profiles (d) are swollen and have membranous inclusions, indicating that they are degenerating. Scale bar = 2 μm.

found an average of 20% fewer axon terminals in old as compared to young brains.

Even fewer studies have been carried out in macaques. Uemura [41] reported a loss of synapses from prefrontal cortex, and suggested that the age-related loss of about 20% paralleled a loss of dendritic spines. Since most of the synapses in cerebral cortex involve dendritic spines this is a reasonable assumption, and there is a similar correlation between spine and synapse loss in layer 1 of area 46 [35] and area 17 [36]. But the impressive loss of some 50% of synapses from layer 1 seems to be unique to that layer, and it might be confined to neocortex, because Tigges et al. [42] found no change in the number of synapses in the outer third of the dentate gyrus. The only change in dentate gyrus was a 3% decrease in the number of synapses involving dendritic shafts. In addition, Tigges et al. [43] found no change with age in the numbers of symmetric synapses on the perikarya of Betz cells in motor cortex, and similarly Zecevic et al. [44] has reported that the frequency of synapses in the neuropil of motor cortex does not alter.

More studies are required, but on the basis of the existing data, it would seem that apart from layer 1 of neocortex there might be only a slight loss of synapses from cortex with age. However, this does not agree with the data suggesting that some 50% of dendritic spines are lost from the human cortex, since dendritic spines are the main recipients of the input to pyramidal cells, which account for some 80% of neurons in cerebral cortex.

Although there may not be profound changes in the frequency of synapses in the cortex, there are changes in neurotransmitter levels with age, especially of neurotransmitters which arise from subcortical nuclei that lose neurons with age [45]. Thus, there is a marked loss of dopamine from the aged cerebral cortex of the monkey and it is well known that depletion of dopamine from cortex affects the working memory performance of monkeys [46]. In addition there are significant reductions in the levels of acetylcholine, norepinephrine, and serotonin, although the losses do not occur uniformly throughout the cortex [46–48]. On the other hand, the levels of glutamate, which is the primary neurotransmitter in cortex, appear not to be affected by age.

Other, perhaps more specific, age-related alterations also affect neurotransmitter receptors. For example, Gazzaley et al. [49] have shown that in the dentate gyrus of aging monkeys there is a decrease in the level of *N*-methyl-D-aspartate (NMDA) glutamate receptors in the distal dendrites of granule cells, which receive the perforant path input from entorhinal cortex. This reduction in NMDA receptor level occurs despite no evident loss of dendrites or of synapses from the molecular layer of dentate gyrus [42] and the authors suggest that this loss of receptors may contribute the age-related memory loss associated with aging. Similar specific age-related alterations in neurotransmitter receptor levels are also shown in the study of Rosene and Nicholson [50]. They examined the levels of seven receptors in the hippocampus, amygdala, entorhinal cortex and temporal lobe cortices of rhesus monkeys. They found significant reductions in the levels of M1 cholinergic receptor levels in hippocampus and amygdala, but a much smaller loss from temporal lobe cortices, while M2 cholinergic receptor levels showed significant reductions in all of the structures examined. In contrast, $GABA_A$ receptors were not significantly altered by age in any of the structures, although the benzodiazepine (BZD) binding sites, which are modulatory sites on the $GABA_A$ receptor complexes, showed increased binding in the old monkeys. And in agreement with the results of Gazzaley et al. [49], for the excitatory amino acid systems Rosene and Nicholson

[50] found significant reductions in the level of NMDA and kianate receptors in the hippocampus and in temporal lobe cortices. At present, the exact meaning of these age-related receptor levels is not clear.

6. Age changes in axons and myelin sheaths in cortex

There are no indications that there is a massive loss of nerve fibers from the cortex during normal aging, but the only definitive studies have been made on monkey cortex. Lintl and Braak [51] reported that there is reduction in the myelin staining of nerve fibers in the line of Gennari in aged human visual cortex, but in studies of aged monkey cerebral cortex few nerve fibers with degenerating axons have been seen [52,53], and examination of the frequency of nerve fibers in the vertical bundles in monkey primary visual cortex revealed that significant numbers of these nerve fibers are not lost with age [53]. However, myelin sheaths of nerve fibers are affected [52,54]. As observed in electron microscopic preparations, the age-related alterations in sheath structure are of two basic types (Fig. 2). The most common alteration is one in which there is local splitting of the sheath at the major dense line to accommodate electron dense cytoplasm that must be derived from the myelin-forming oligodendrocyte. Another common alteration is the formation of fluid-filled blebs, or balloons, that can be as large of 10 μm in diameter. These myelin balloons are produced by splitting of the intra-period line, and in longitudinal sections of nerve fibers several blebs and dense inclusions can be seen along the same internode of a nerve fiber. It is suggested that such alterations in myelin are signs of myelin breakdown, or degeneration.

Two other types of alterations suggest that the production of myelin is continuing during aging. Thus, with age there is an increase in the frequency of nerve fibers that have redundant myelin. In this situation the axon is located to one side of an oversized sheath (Fig. 2). The other alteration is an increase in the frequency of thick sheaths, some of which split circumferentially, so that one set of inner compact lamellae are separated by a split from an outer set. In a study of the effects of age on the thickness of myelin sheaths in monkey visual cortex [55], it was found that sheaths of nerve fibers become thicker with age and that unusually thick sheaths, with more than ten lamellae, become increasingly common in old monkeys. It is these thick sheaths that split. It seems then that the production of myelin is continuing with age, even as degeneration of myelin is occurring.

The frequency of occurrence of altered in myelin sheaths of old monkeys significantly correlates with both age and the cognitive status of the monkeys, and we have hypothesized [52,54] that this correlation occurs because the conduction velocities along the affected nerve fibers are reduced by damage to the myelin sheaths. This would lead to a breakdown in the normal timing sequences within neuronal circuits and so affect the normal functioning of the cortex.

7. Nerve fibers in white matter

Although not many nerve fibers appear to be lost from cortex, the story for white matter is different. Kemper [56] described a reduction in the staining intensity of white matter with age, and axial MRI scans from both humans

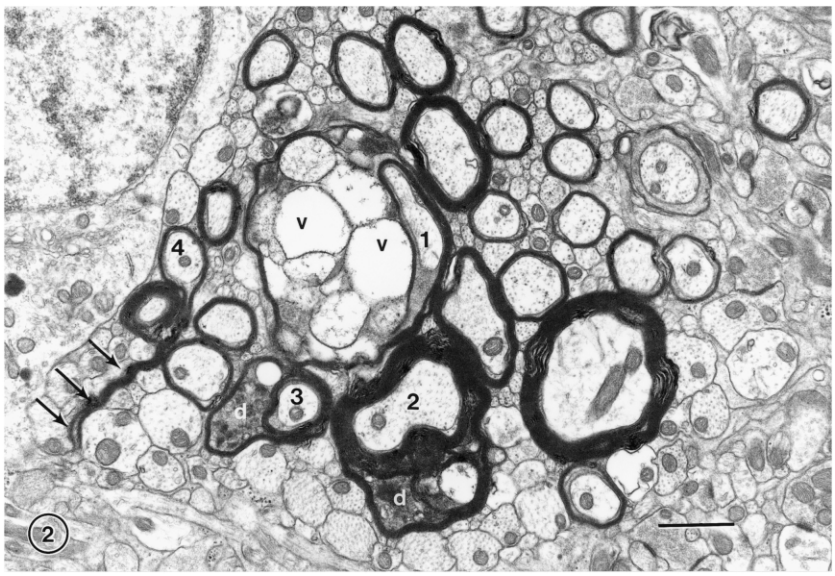

Fig. 2. Electron micrograph of a transversely sectioned bundle of nerve fibers in area 17 of a 27 year old monkey. One of the nerve fibers (1) has a sheath that has split to accommodate a swelling containing fluid-filled vesicles (v). Two other nerve fibers (2 and 3) have sheaths that have split to accommodate dense cytoplasm (d). Also note the nerve fiber (4) with a sheath of redundant myelin (arrows). Scale bar = 1 μm.

[57] and monkeys [58] show that significant amounts of white matter are lost. This results in an increase in the sizes of the ventricles, and in gyral atrophy, causing sulci to become wider. Using stereology Pakkenberg and Gundersen [59] have also recorded a loss of white matter from the aging human brain, and Tang et al. [60] have found old human brains have 15% less white matter than young ones, and they lose 27% of the total length of nerve fibers from white matter. At present the origins of the lost nerve fibers are unknown.

8. Age changes in neuroglial cells

By looking at the neuroglial cells in histological sections of cerebral cortices it is not too difficult to decide whether the sections are from young or old primates. With age all three types of neuroglia, the oligodendroglia, the astrocytes and the microglia come to contain inclusions, as do pericytes. And interestingly, in electron microscopic preparations the appearance of the inclusions is characteristic of the neuroglial cell type [8,61]. In case of the astrocytes (Fig. 3) and microglia the inclusions appear to be derived from phagocytosed material. The sources of the debris in the inclusions are not known, although myelin figures have been identified in the cytoplasm of some astrocytes in the brains of aged monkeys.

There is uncertainty about whether cortical neuroglial cells increase in number with age. In the human cortex Haug et al. [62] found no significant increase in the numbers of neuroglial cells, and in their examination of visual cortex, Leuba and Garey [63] came to the same conclusion. However, Hansen et al. [64] examined the midfrontal region of the human brain using antibodies to glial fibrillary acidic protein and concluded that the numbers of fibrous astrocytes increase significantly with age. But it might be that astrocytes were merely becoming more visible as amount of fibrous protein in their cytoplasm increased, making these cells more obvious. In rhesus monkey visual cortex Peters et al. [61] examined visual cortex and found the population of astrocytes not to increase. However, there was an increase in numbers of microglial cells and three out of the five old monkeys showed increases in oligodendrocytes.

In examining monkey cortex it is usually found that astrocytes undergo hypertrophy with aging, and as in human brain, there is an increased content of filaments in their cytoplasm. This is especially true of astrocytes in white matter [65], and it also occurs in layer 1 of cerebral cortex. Although there is no increase in the number of astrocytes in layer 1 with age (unpublished data), the age-related thinning of the layer, and the loss of dendrites and synapses [35,36], leads to astrocytosis in the neuropil. There is also a remarkable increase in the thickness of the glial limiting membrane (Fig. 1). This membrane is formed from the processes of astrocytes, and in young monkeys it is usually one or two processes thick, whereas in old monkeys it becomes much thicker. This may be interpreted as scarring in response to loss of components from the underlying neuropil.

Microglial cells are phagocytes and they become activated during aging. Using specific antibodies, Sloane et al. [66] found the activation to be more obvious in white matter than in gray matter. Presumably this increased activation correlates with the fact that with increasing age it becomes more common to see microglial cells with large amounts of phagocytosed material in their cytoplasm. But again, the origin of this material is unknown, although it

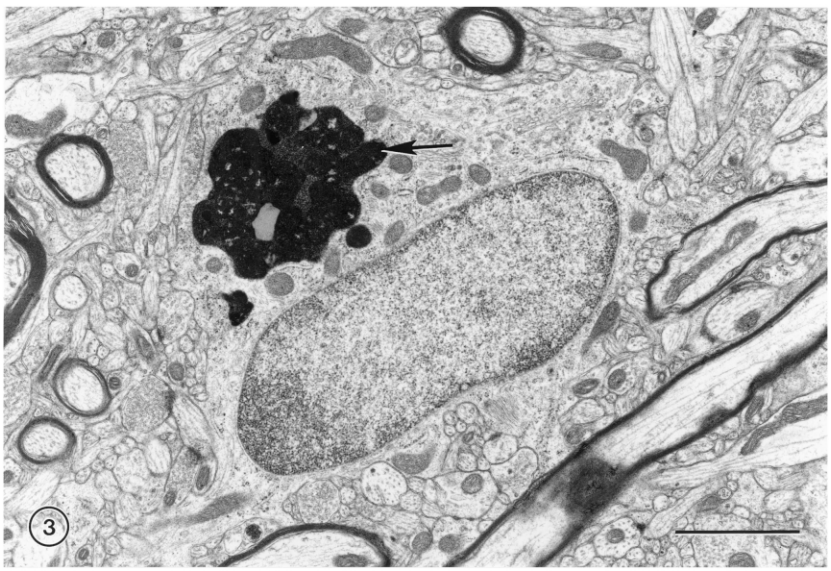

Fig. 3. Electron micrograph of an astrocyte from area 46 of prefrontal cortex in a 25 year old monkey. As is common in old monkeys the astrocyte contains a large, dense, phagocytic inclusion (arrow). Scale bar = 2 μm.

might be suspected that in white matter it correlates with the loss of some nerve fibers [60].

Oligodendrocytes form the myelin sheaths in the central nervous system, and with age some oligodendrocytes develop bulbous swellings along their processes [67]. These swelling contain inclusions. The origin of the material in the inclusions is not yet known, although the formation of the inclusions might correlate with the breakdown of myelin sheaths belonging to those oligodendrocytes. In addition it is common in old monkeys to find oligodendrocytes in pairs, groups and rows, which suggests that they, or their precursors, might be undergoing division with age.

9. Conclusions

Our knowledge about what structural changes occur during the normal aging of the primate cerebral cortex, and how these changes correlate with cognitive decline, is fragmentary. To date only a few cortical areas have been examined, but it is generally accepted that cognitive decline is not due to loss of significant numbers of neurons. For the deeper layers of the cortex the available data also suggest that aging has little effect on dendrites, but it is not clear if significant numbers of synapses are lost. Even if there are no great alterations in synaptic numbers, reductions do occur in the levels of some neurotransmitters and their receptors. Only in layer 1 there are profound structural changes with age. In layer 1 the apical dendritic tufts of pyramidal cells receive a variety of inputs, and as the powerful effects of some or all of these inputs are reduced, the normal functioning of the pyramidal cells must be compromised. There is also a considerable thickening of the glial limiting membrane associated with the layer 1 changes. However, it must be presumed that age changes, as yet unrecognized, are taking place throughout the cortex, because many microglial cells and astrocytes, as well as pericytes, come to contain large amounts of phagocytosed material, whose origins are not yet known.

Another obvious change that occurs with age is a breakdown of myelin sheaths. Concomitantly oligodendrocytes come to contain inclusions and some of them may be dividing. The alterations in myelin are ubiquitous and it is suggested that one underlying cause of cognitive decline might be that breakdown of myelin affects the timing in neuronal circuits, which in turn could affect memory.

Obviously, our understanding of normal aging is still superficial, and more in-depth, correlative studies need to be carried out before we have a comprehensive enough picture to fully understand what brings about the cognitive decline associated with normal aging, and what means might be devised to alleviate severe cognitive decline.

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