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The effects of aging on the frequency of nerve fibers in rhesus monkey striate cortex☆

Kirsten Nielsen, Alan Peters*

Department of Anatomy and Neurobiology, Boston University School of Medicine, 715 Albany Street, Boston, MA 02118, USA

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Abstract

In the rhesus monkey primary visual cortex, there are bundles of vertically oriented myelinated axons, which mainly contain efferent fibers originating from pyramidal cells. At the level of layer 4Cβ, the bundles are regularly arranged and the nerve fibers in them are closely packed. In order to determine if a significant loss of intracortical nerve fibers occurs as the primate cerebral cortex ages, the frequency of vertically oriented myelinated fibers was examined at the level of layer 4Cβ in 1-μm-thick, tangential sections. The results show no statistically significant differences in the numbers of vertically oriented fibers beneath 1 mm^2 of cortical surface between young, middle-aged, and old monkeys, and electron microscopic examination reveals few signs of degenerating axons. There is, however, an age-related breakdown of the myelin in sheaths that surround some axons. Thus, the data indicate that there is not a loss of vertically oriented myelinated fibers from the cortical gray matter during aging, although their sheaths may be altered.

Keywords: Primate; Aging; Area 17; Myelinated axons; Visual cortex

1. Introduction

During normal aging, both humans [1,2] and monkeys [3,4,18,26] exhibit cognitive decline that is considered to reflect age-related cortical dysfunction. However, on the basis of recent studies, it has been concluded that this decline cannot be attributed to a significant age-related loss of neurons from the cerebral cortex [10,17,19,22,23,27]. Indeed, the cortical gray matter appears to be well preserved during normal aging, although there are changes in layer 1. Layer 1 becomes thinner with age, loses synapses, and shows a pronounced thickening of the glial-limiting membrane [21,22], and in area 46 the thinning of layer 1 correlates with both age and the cognitive decline exhibited by aging monkeys [29].

One entity throughout the brain that is severely affected by normal aging is myelin, and, in aged monkeys, many myelin sheaths in the cortex and in the white matter show signs of losing their integrity [21,24]. Age-related changes in myelin had been noted earlier, when it was found that, in human primary visual cortex, there is an age-related decrease in the intensity of staining of myelin in the line of Gennari [15], and a pallor in the staining of white matter in normally aged human brains [11]. More recently, it has been shown [8,24] that, in aging monkeys, the myelin sheaths of many nerve fibers show age-related alterations such as the formation of balloons and splits between lamellae. Interestingly, the percentage of nerve fiber profiles in the vertically oriented bundles in rhesus monkey visual cortex that show age-related alterations in their myelin sheaths correlates directly with the extent of cognitive impairment displayed by these monkeys [24]. It is suggested that this correlation is not specific to the visual system, but that it occurs because the breakdown in the integrity of the myelin is a general process that results in a slowing of the conduction rates along affected nerve fibers throughout the brain. The consequence would be to alter the timing in neuronal circuits, resulting in the impaired cognition displayed by aging primates [24]. This may contribute to the significant degradation of orientation and direction selectivity shown by neurons in the visual cortices of old rhesus monkeys [32],

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* Corresponding author. Tel.: +1-617-638-4235; fax: +1-617-638-4216.

E-mail address: apeters@bu.edu (A. Peters).

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although the authors of this study suggest that decrease selectivities and increased excitability of visual cortical neurons in old monkeys is likely to be due to degradation of cortical inhibition.

The volume of white matter in the cerebral hemispheres of both humans and monkeys is also reduced with age, by between 15 and 28% [1,9,20,31,33]. This has been demonstrated using magnetic resonance imaging scans of both human and monkey cerebral hemispheres, which show that as the volume of white matter decreases, the lateral ventricles increase in size, yet the volume of gray matter is unaltered [1,19,31]. The conclusion that there is a loss of white matter with age is supported by a recent study in which stereology was used to examine the white matter in the cerebral hemispheres of 10 human brains [33]. This study concluded that, compared to the brains of young subjects, those from elderly subjects show a 17% loss in the volume occupied by myelinated fibers and an overall 27% decrease in the total length of nerve fibers with age, most of the loss being of small-diameter fibers.

The reason for the white matter loss is not known, but it may be that the decrease reflects a loss of nerve fibers entering and leaving the cortex, and the goal of the present study is to determine whether there is a concomitant loss of efferent nerve fibers from the primate cerebral cortex with age. To carry out this determination, we have assessed the effects of age on the frequency of the vertically oriented nerve fibers in the primary visual cortex of the rhesus monkey. The primary visual cortex was chosen for study because there is already a good deal of information about the effects of normal aging on this cortex. For example, it has been previously shown that with age there is no significant loss of neurons from monkey primary visual cortex [10,27,35] and no significant alteration in the thickness of the cortex, or its volume [10,25], although there are changes in the integrity of the myelin sheaths of intracortical fibers [24].

The majority of the nerve fibers in primary visual cortex are contained in vertical bundles that are regularly spaced and make their appearance in layers 2/3 [28] (Fig. 1). Most of the nerve fibers within these vertical bundles are efferent fibers that originate from the pyramidal cells of layers 2 through 5 and the spiny stellate cells of layer 4B. At the level of layer 4Cβ (Fig. 1; dotted line), which is readily defined, the myelinated nerve fibers in the bundles are closely packed and the bundles contain the greatest numbers of myelinated nerve fibers. Thus, it is easy to reproducibly take horizontal sections at exactly the same depth from the visual cortices of different monkeys (see Fig. 2), to count the myelinated nerve fibers within a given area of a section, and so determine their frequency in monkeys of different ages. This makes it possible to ascertain whether there is a loss of the vertically oriented nerve fibers from primary visual cortex with age.

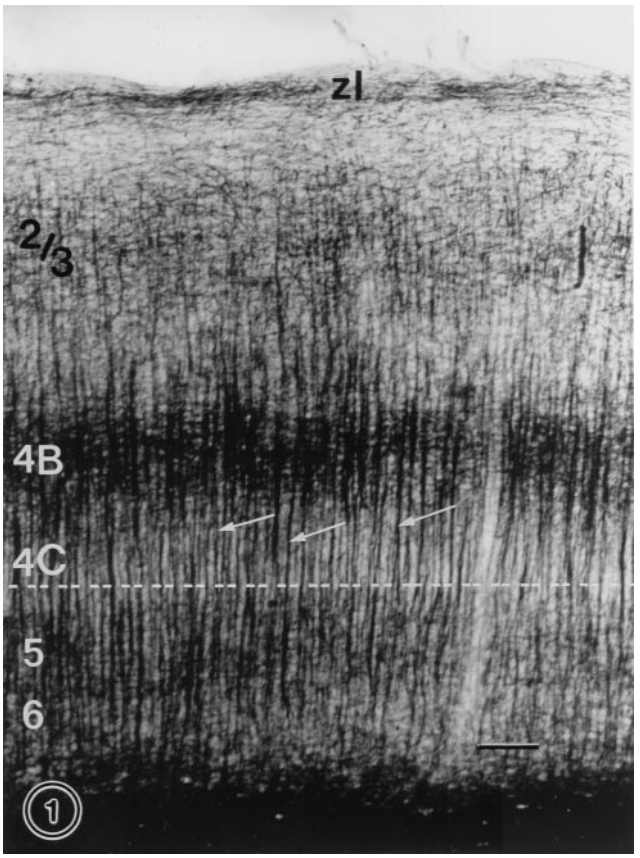

Fig. 1. A myelin-stained section through the depth of primary visual cortex of a 5-year-old rhesus monkey (AM 5). The cortical layers are indicated to the left. There are three horizontal plexuses of myelinated axons: the zonal layer at the level of layer 1 (zl), the stripe of Gennari located in layer 4B, and the inner band of Baillarger in layer 5. Additionally, there are prominent vertically oriented myelinated axons which appear in layer 2/3 and aggregate into bundles (arrows) as they descend through the cortex toward the white matter. Layer 4C lies deep to the stripe of Gennari and is subdivided into two layers, of which the innermost one is layer 4Cβ, indicated by the dotted line. It is in layer 4Cβ where most of the vertically oriented myelinated axons form discrete bundles (arrows). Scale bar = 100 μm.

2. Materials and methods

2.1. Animals

Pieces of primary visual cortex from 16 rhesus monkeys (*Macaca mulatta*), ranging in age from 5 to 33 years, were used for this study. Four of the monkeys were young (5–6 years), four were middle aged (9–12 years), and eight were old (25–33 years). The age and sex of each animal is given in Table 1, with the age rounded to the nearest year. Details of the perfusion protocol for fixing the brains are given in an earlier publication [22]. The perfusions were carried out in full accordance with the approved Institutional Animal Care and Use Committee regulations. In brief, the monkeys were pre-anesthetized with Ketamine, and a Ketamine/Rompun mixture was then administered i.v. to a state of areflexia. The monkeys were tracheally intubated, artificially respired

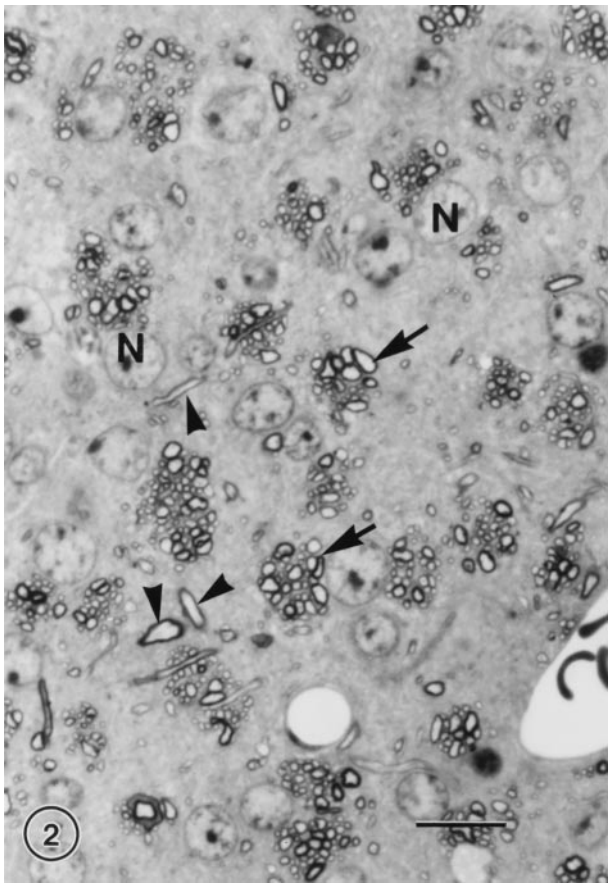

Fig. 2. A 1-μm-thick tangential section through layer 4Cβ at the level indicated by the dotted line in Fig. 1. The vertically oriented myelinated axon profiles are viewed in cross section and show that most of the fibers aggregate into discrete bundles (arrows). Nuclei of spiny stellate cells (N) are evident. The profiles of the longitudinally and obliquely oriented fibers indicated by the arrowheads were not included in the nerve fiber counts. Scale bar = 10 μm.

with CO_2/O_2, and transaortically perfused with a warm solution of 1% paraformaldehyde and 1.25% glutaraldehyde in 0.1 M cacodylate or phosphate buffer at pH 7.4. Following this primary fixation, one cerebral hemisphere was removed from each animal and fixed further by immersion in a cold solution of 2% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M cacodylate or phosphate buffer at pH 7.4. The tissue remained in this fixative for a minimum of 3–7 days.

2.2. Tissue preparation

Eight to ten pieces of primary visual cortex, cut into approximately 2-mm-thick blocks, were then removed from the opercular surface of the occipital lobe (area 17) about 3 mm caudal to the lunate sulcus, where the center of the visual field is represented. These blocks of tissue were osmicated, dehydrated in an ascending series of alcohols, and embedded in Araldite. Two of the embedded blocks of visual cortex were randomly chosen from each monkey.

Table 1
The age, sex, and frequency of myelinated axons for each monkey

Monkey code	Age (years)	Sex	Number of myelinated axons per mm^2
Young monkeys			
AM 05	5	M	97 840
AM 16	5	M	93 810
AM 10	6	M	107 700
AM 76	6	F	119 300
Group mean			104 700 (SD ± 11 370)
Middle aged monkeys			
AM 47	9	M	126 100
AM 53	10	M	127 800
AM 20	12	F	107 400
AM 42	12	M	108 700
Group mean			117 500 (SD ± 10 950)
Old monkeys			
AM 19	25	F	84 770
AM 12	27	F	120 800
AM 15	27	F	113 900
AM 27	28	M	104 800
AM 17	28	F	115 800
AM 26	29	F	110 400
AM 41	32	F	110 000
AM 65	33	F	116 600
Group mean			109 600 (SD ± 11 160)

Semi-thick sections (1 μm) were taken perpendicular to the pial surface, stained with toluidine blue, and used to determine the level of layer 4C. The blocks were then turned and sectioned in the tangential plane until layer 4Cβ had been reached. Semi-thick tangential sections were then taken at the level of layer 4Cβ for light microscopy (Fig. 2).

After the semi-thick sections had been obtained, thin sections were taken from the cortices of four of the monkeys (AM 17, AM 41, AM 47, and AM 53) for electron microscopic evaluation. The thin sections were stained with uranyl acetate and lead citrate, and the morphology of the myelinated axons examined with a JEOL 100S electron microscope.

2.3. Determining the frequency of vertically oriented myelinated axons

From each block of visual cortex, well stained, semi-thick horizontal sections at the level of layer 4Cβ were selected, and three micrographs were taken at random of nonoverlapping fields. The micrographs were taken using a Zeiss ICM 405 light microscope with a ×40 immersion lens, and a 4 × 5-inch sheet film camera. Nomarski diffraction was used to enhance the contrast in the micrographs. Three micrographs were taken from each of two cortical blocks, resulting in a total of six micrographs from each monkey. The negatives were printed to a final magnification of ×2100, and a counting frame, which covered most of the micrograph and had an area of approximately 4.0×10^4 mm^2, was drawn on each micrograph. All transversely sectioned myelinated axon profiles within the frame were

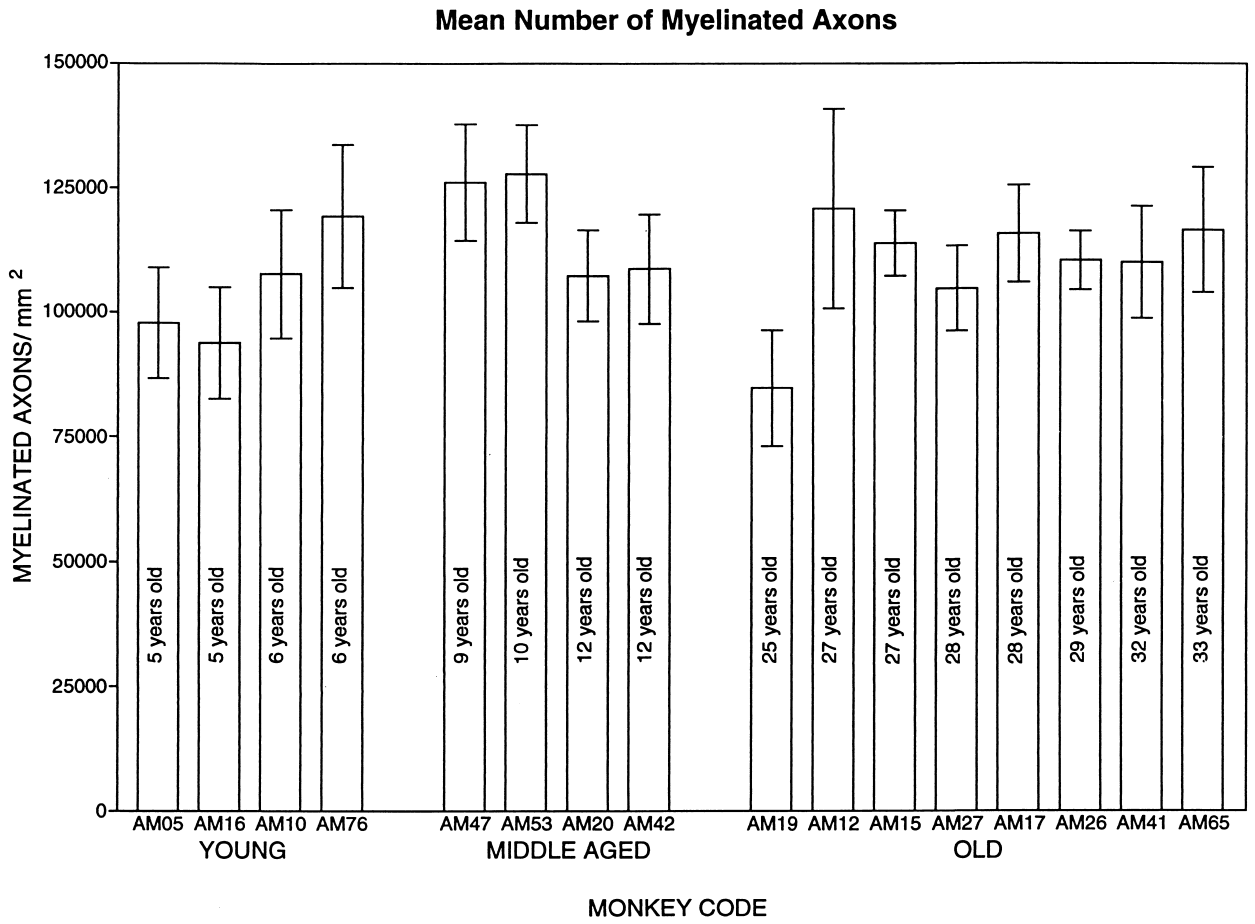

Fig. 3. A bar graph distribution of the mean number of vertically oriented myelinated axons per unit area for each monkey and the standard deviation. The animals are listed in chronological order from left to right, and grouped as young, middle-aged, and old.

counted, as well as those profiles that intersected the upper and right borders of the counting frame. As is usual in making such counts, axon profiles that intersected the other two borders of the counting frame were not included in the counts. Any nerve fiber profiles whose lengths were three times greater than their widths (see Fig. 2; arrow heads) were excluded form the counts. The ratio of length to width of such fibers was determined using a ruler. Omitting such fibers from the counts ensured that horizontally oriented intracortical fibers and obliquely oriented afferent thalamic fibers were excluded. Thus, the frequency of vertically oriented myelinated axons beneath 1 mm^2 of cortical surface was determined for each micrograph. The mean and standard deviation of these counts for each monkey were then calculated.

2.4. Statistical analysis

Each animal was assigned to a group: young, middle-aged, or old (see Table 1). All of the data were entered into the GraphPad PRISM 2.0 computer program. A one-way analysis of variance (ANOVA) and regression analysis were performed.

3. Results

3.1. Frequency of myelinated axons

Tangential sections through layer 4Cβ were identified by the presence of densely packed, small spiny stellate cells and the aggregation of the vertically oriented myelinated axons into discrete, tightly packed bundles (Fig. 2). The mean and standard deviation of the frequency of vertically oriented myelinated axons beneath 1 mm^2 of cortical surface were determined for each monkey, and the results are given in Fig. 3. When the data for each group of monkeys are pooled, the mean number of myelinated axons per mm^2 for the young group is 104 700 (SD $\pm$ 11 370), for the middle-aged group is 117 500 (SD $\pm$ 10 950), and for the old group of monkeys is 109 600 (SD $\pm$ 11 160) (Table 1). When the mean values for each of the three groups are compared, utilizing a one-way ANOVA, no significant differences exist between the groups ($P = 0.29$), indicating that there is no significant loss or gain of vertically oriented myelinated axons with age. To confirm this observation, the mean number of myelinated axons per mm^2 for each mon-

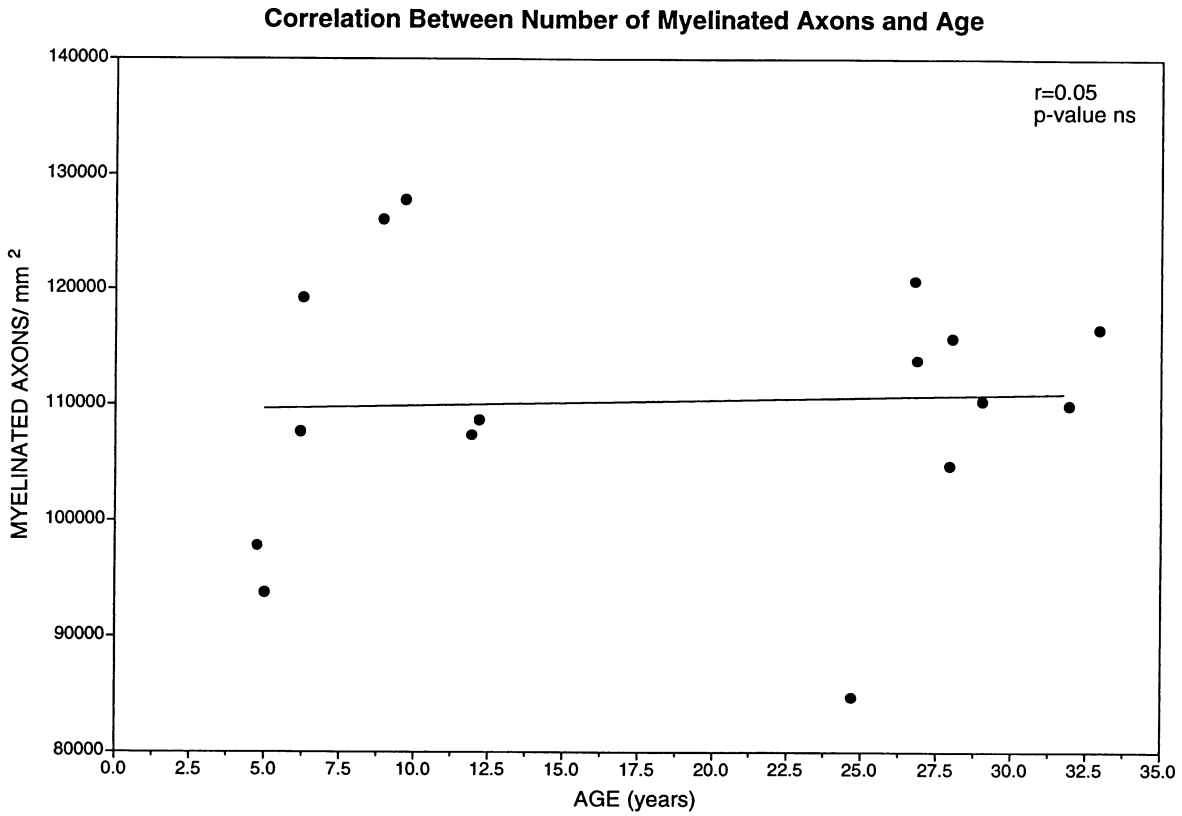

Fig. 4. A plot of the number of vertically oriented myelinated axons per unit area versus age. There is no statistically significant correlation between the two measures.

key was plotted against age, and there is no statistically significant correlation (Fig. 4).

The monkeys were then grouped by gender to determine whether the frequency of axons differed among males versus females, bearing in mind that both the young and middle-aged groups of monkeys contain only one female, and the old group of monkeys contains only one male. The mean for the male group ($n = 7$, ages 2–28 years) was 109 500 (SD $\pm$ 13 030) and for female group of monkeys ($n = 9$, ages 6–33 years) was 111 000 (SD $\pm$ 10 780). When the two means were compared using a two-tailed student's *t*-test, there was no statistically significant difference ($P = 0.81$). In addition, neither the male nor the female group demonstrated a correlation between the mean number of myelinated axons per mm^2 and age.

Together, these data suggest that the frequency of vertically oriented myelinated axons is the same in males and in females and that significant numbers of these nerve fibers are not lost with age.

3.2. Electron microscopic examination

Normally, the cytoplasm of axons with myelin sheaths contain mitochondria, microtubules, and neurofilaments, and the myelin sheaths are compact with little cytoplasm between the lamellae, except at the paranodes. The myelinated nerve fibers examined in thin sections taken from two middle-aged monkeys (AM 47, AM 53) had this appearance. In the cortices of the two old monkeys examined by electron microscopy (AM 17 and AM 41), the majority of axons were unaltered by age, but the myelin sheaths of some of the nerve fibers exhibited age-related changes such as ballooning of the myelin or splits in their myelin sheaths that contained dark cytoplasm. Examples of normal axons surrounded by altered myelin sheaths are shown in Fig. 5, which is from the cortex of a 32-year-old monkey (AM 41). In some cases (A_1), the sheaths have split, and, in other cases (A_2), the sheaths balloon out at one side. The micrograph in Fig. 5 is unusual in that it also shows axons that appear to be degenerating. Thus, one axon (A_3) has a dark cytoplasm, while adjacent sheaths (A_4) appear to have lost their axons and surround debris. However, such images are unusual and, despite an intense search, very few nerve fibers that could be construed to be degenerating were encountered in the thin sections from the older monkeys.

4. Discussion

This study demonstrates that there is no significant loss of the well-defined vertically oriented myelinated nerve fibers from beneath a mm^2 of the primary visual cortex with

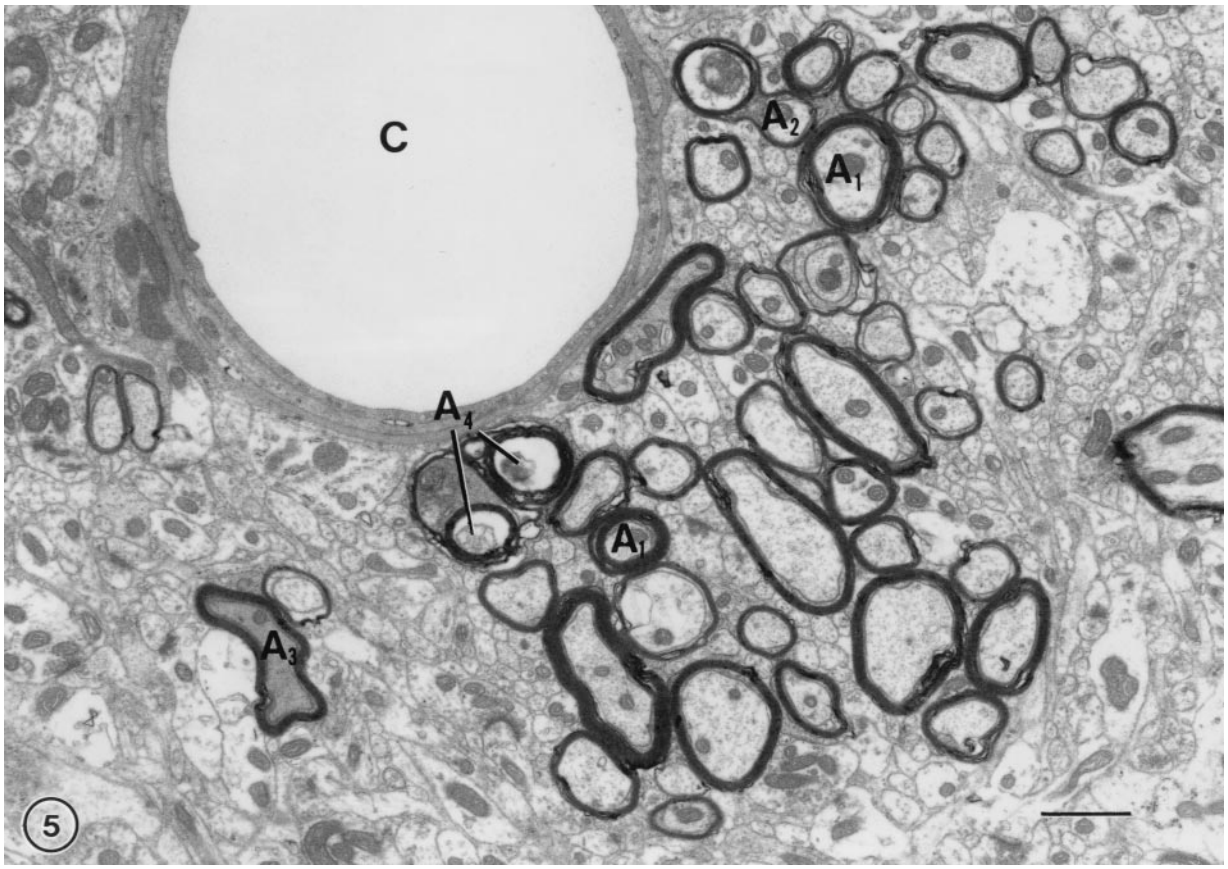

Fig. 5. An electron micrograph of a tangential section through layer 4Cβ of a 32-year-old monkey (AM 41), to show a bundle of vertically oriented myelinated axons adjacent to a capillary (C). In old monkeys, it is common to encounter axons that have either splits in the lamellae of their sheaths (A_1), or ballooned sheaths (A_2), but it is rare to encounter fibers with altered axons like the ones shown here. One fiber has an axon (A_3) with dark cytoplasm that is generally regarded as being a typical sign of degeneration, while in other fibers the axon appears to be shriveled (A_4). Scale bar = 1 μm

age. Since an unbiased stereological method was not used, the analysis has some limitations. But these limitations are probably of no great concern, because there is also evidence that no significant numbers of neurons, including ones that give rise to these fibers, are lost from the monkey primary visual cortex with age. Indeed, the cell bodies of cortical neurons in old monkeys show no signs of degeneration [35] and primary visual cortex does not lose volume as it ages [10,25]. There is also evidence that significant numbers of neurons are not lost from either the specific populations of large neurons in layer 4B and Meynert cells [10,27] or the neurons in the cytochrome oxidase blobs [12]. Indeed, the general consensus seems to be that with age, there is no significant loss of neurons from any part of the cerebral cortex of primates [17,23,34]. However, the approach used here considers the effects of aging on only a subpopulation of nerve fibers in visual cortex. It does not address the issue of whether other subpopulations of nerve fibers, such as the thalamic afferents, are affected by age, nor does it address the issue of whether the frequency of nerve fibers in other cortical areas are similarly unaffected.

The findings of this study supplement data generated in a recent study [24] that determined the percentage of nerve fiber profiles in the myelinated vertical bundles in layer 4C of monkey primary visual cortex with axons showing signs of degeneration. The frequency of occurrence of profiles that had lysosomes, large vacuoles, or a darkening of the axoplasm is between 0 and 0.6%, and there is no correlation between the frequency of degenerating fibers and age. The electron microscopic examination in the present study also reveals the presence of few degenerating axons. Together, these data suggest that if any nerve fibers are lost with age, the loss is not significant and only a few degenerating axons are present at any one time.

As far as nerve fibers are concerned, it seems to be the myelin sheaths that are most affected by age, since, as pointed out, in old monkeys some of the sheaths show signs of ballooning [8], splitting of the myelin lamellae, the formation of redundant myelin so that the sheath is too large for the enclosed axon, and the appearance of double sheaths in which one sheath is surrounded by another [24]. Since there is no evidence that there is a loss of a significant number of intracortical nerve fibers with age, the structural changes in the sheaths may be the basis for the decrease in myelin staining noted in the line of Gennari of aging humans [15], even though the authors attributed the decrease in staining intensity to a loss of nerve fibers. The age-related myelin changes may also explain the pallor of myelin stain-

ing in the white matter of human cerebral hemispheres [11], although it is also possible that age-related changes in the composition of myelin could alter its staining properties. However, as pointed out earlier, there is evidence from both stereological analyses [20,33] and from brain scans [1,31] that there is a decrease in white matter volume in the cerebral hemispheres of primates, which occurs in conjunction with a loss of nerve fibers in the white matter [33] during normal aging.

These data leave us with an interesting conundrum. If the white matter is largely composed of fibers originating from cortical neurons, then why is it that there is a loss of nerve fibers from the white matter of the cerebral hemispheres and yet there is no indication that significant numbers of intracortical efferent fibers are lost? If the age-related loss of 15–28% of the white matter [1,9,20,31,33] were due to fiber loss resulting from neuronal degeneration, then the number of neurons in the cortex should be reduced by a similar percentage. Yet, recent studies agree that the age-related loss of cortical neurons is not significant in primates [17, 23], and moreover, as our results have shown, there is no significant loss of myelinated nerve fibers from the efferent intracortical bundles.

One possible mechanism by which white matter fibers might be lost in the absence of neuronal or intracortical fiber degeneration is through the presence of sustaining collaterals. This phenomenon was first observed after experimental lesions of the cerebral and cerebellar cortices [6]. When such collaterals are present, a long branch of an axon may be cut and its degeneration will proceed in a centripetal direction to the site of the last collateral bifurcation, where it will stop. The extensive collateral branches proximal to the interrupted segment sustain the neuron and prevent degeneration.

The vertically oriented axons of the pyramidal cells of layers 2–5 in monkey primary visual cortex do exhibit extensive collateral projections before their axons enter the white matter [5,7,13,14,16,30]. For example, the pyramidal cells in the upper cortical layers give off extensive collaterals that contribute to the inner band of Baillarger of layer 5, while the neurons of layer 4A and 5 have extensive collaterals that contribute to the line of Gennari, at the level of layer 4B. Layer 5 pyramidal cells also have axon collaterals that branch within layer 5. Thus, an axon might degenerate once it has left the cortex and entered the white matter, with the main axon in the cortex being sustained by its extensive collateral branches. Such a pattern of degeneration would produce the decrease in white matter volume shown to occur with age.

In summary, this study demonstrates that the frequency of vertically oriented nerve fibers beneath a unit area of rhesus primary visual cortex is not significantly altered by gender or age. However, there is an age-related alteration in the integrity of myelin sheaths of these intracortical nerve fibers. Sustaining collaterals may be responsible for the preservation of those parts of the nerve fibers within the gray matter, while the projection branches of these same cortical efferent fibers may be lost from the white matter.

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