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Dendritic and spinal alterations of the spiny stellate cells of the human visual cortex during normal aging

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Abstract

The visual cortex undergoes age related changes that have been studied mainly in rats Maccaca Mulata, and human beings. Despite the fact that there is no extensive neuronal loss in aged brains, a lot of important pathological changes are found in the morphology of the neurons. The present study describes the morphological alterations of the spiny stel-late cells of the human primary visual cortex during normal aging, using Golgi method, Golgi-Nissl staining and Nissl staining. Two types of spiny stellate cells have been studied. the first one located at layer 4Cα and the second one located at layer 4Cβ. Even if some spiny stel-late cells retain high number of primary dendrites in the aged group there seems to be important spine loss, and extensive dendrite pathology. Age-related changes were more significant in spiny stellate cells of layer 4Cβ. Dendritic and spinal alterations described in the present study could explain the decline in visual functions during normal aging.

Key words: *visual cortex, aging, spiny stellate cells, Golgi method.*

Introduction

The geniculorecipient zones of layer 4 of the visual cortex – layers 4Cα and 4Cβ receive their afferent input from separate populations of geniculate neurons [7,19].

Axons from the parvocellular division of the lateral geniculate nucleus arbour in layer 4Cβ and 4A, while afferents to layer 4Cα originate in the magnocellular division. The magnocellular axons arborize farther than parvocellular and cover 6 times larger area [7].

The parvocellular pathway is related to wavelength specific responses, while the magnocellular pathway exhibits broad band responses to all visual wavelengths [45].

Visual functions are impaired during normal aging either through both normal deterioration of eye tissues and increased incidence of eye pathology, or due to pathology of the central visual mechanisms [19,25].

Aged humans demonstrate a decline in visual acuity, impairment of the binocular summation, changes

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in contrast sensitivity and wavelength sensitivity [15, 26,31,40,42,51]. Moreover, impairment of spatial frequency contrast sensitivity [33], hyper acuity [15], orientation discrimination and motion direction detection have been revealed [6,33,48]. Anatomical and morphological studies concluded that retinal abnormalities and changes of the subcortical areas do not explain the perceptual deficits [1,24,41] and recent neuroimaging studies suggest that age-related dedifferentiation may apply at the neural level [27,35]. Furthermore, Hua *et al.* (2006) described a significant functional degradation of the primary visual cortex from aged animals, which could be regarded as direct evidence for the loss of function in visual cortical cells [19].

A number of morphological changes have been described in the visual cortex during normal ageing. In layer 1 of rhesus monkeys, electron microscopy revealed fewer dendritic and spine profiles per unit area, thickening of the glial limiting membrane and a concomitant decrease in the numerical density of synapses with age [36]. Furthermore, an age-related breakdown of myelinated nerve fibres has been reported [38].

Xu *et al.* (2007) investigated possible age-related changes in the dendritic trees of the pyramidal cells of the rat visual cortex and revealed differences in dendritic branching and spinal density [53].

In our previous study, we demonstrated significant changes in the pyramidal and stellate cells of the human visual cortex in Alzheimer's disease [30].

In order to understand the responsible mechanisms for the age-related decline of the visual function we tried in the present study to find out if there are significant morphological alterations in dendritic arborisations and the dendritic spines of the spiny stellate cells of the human visual cortex during normal ageing.

Material and methods

In the present study we attempt to describe the morphological and morphometric alterations of the dendritic arborisation and the alterations of the dendritic spines of the spiny stellate cells of the visual cortex using the Golgi silver impregnation technique, Golgi-Nissl staining and Nissl staining.

The visual cortices of twenty male individuals who died accidentally have been used. All the brains had been examined using routine histopathology methods and no macroscopic or microscopic signs of pathology had been observed. The brains were divided in two groups, the first of them consisted of ten individuals aged 40-55 years and the second of the remaining ten individuals aged 75-86 years (Table I).

Samples of the primary visual cortex (calcarine sulcus) were excised and immersed in a fixing solution

Table I. Subject summary

Younger				Older			
Gender	Age	Cause of death	Brain weights	Gender	Age	Cause of death	Brain weights
M	40	Car accident	1320	M	70	Acute heart infarction	1125
M	42	Car accident	1288	M	72	Pulmonary embolism	1098
M	47	Acute heart infarction	1352	M	75	Acute heart infarction	1234
M	44	Pulmonary embolism	1297	M	78	Car accident	1185
M	52	Car accident	1365	M	86	Acute heart infarction	1200
M	55	Acute heart infarction	1289	M	81	Pulmonary embolism	1156
M	48	Acute heart infarction	1302	M	82	Acute heart infarction	1180
M	43	Car accident	1340	M	80	Acute heart infarction	1207
M	50	Acute heart infarction	1301	M	79	Acute heart infarction	1190
M	54	Car accident	1378	M	83	Acute heart infarction	1125
Mean	47.5		1323.2		78.6		1170

of 10% formaldehyde at room temperature where they remained for 25 days. Then, they were immersed in a dilution of potassium dichromate (7 g of potassium dichromate and 1 ml of formaldehyde 37% in 300 ml of tap water) at room temperature. They remained in that solution for seven days and then they were immediately immersed in an aqueous solution of 1.5% Silver Nitrate for seven more days at a temperature of 18°C in the photoprotected environment. After the fixation, the specimens were embedded in low melting point paraffin and cut in a slicing microtome at thick sections at the range of 100 μm. Some of the sections were post-stained with 10% methylene blue for Golgi-Nissl staining and after a rapid differentiation they were covered with entellan.

Neurons examined consequently for quantitative alterations met the criteria set forth by Jacobs *et al.* (1997) [22] that request uniform staining of neuronal processes, absence of precipitated debris, good contrast between cells and background, and relatively uniform tissue thickness.

For each one of the 20 brains, 20 spiny stellate cells from the fourth layer were selected.

For each of the selected cells we captured videos using an Amscope 10Mpx microscope camera. The videos analyzed in image sequences of 200 serial digital images in Image J application and imported into Neuromantic application as stacks and used for three dimensional neuronal reconstructions.

Particles that were analyzed included: the total dendritic length, total number of dendritic segments and bifurcations, length and number of dendritic segments per dendritic order, as well as the daughter branching ratio and dendritic tree asymmetry. Furthermore, the tracings were analyzed quantitatively using the Image J program according to Sholl's method of concentric circles [46]. Concentric cycles were drawn, at intervals of 15-μm centred on the cell bodies, and dendritic intersections within each cycle were counted.

For the estimation of qualitative and quantitative changes of the dendrites magnifications 400× have been used.

Spine counts were carried out on the dendrites of layer 4 spiny stellate cells, on the basis of 300 photomicrographs. Visible spines were counted on three segments of the dendritic field. The first segment, 20-30 μm in length, was located on the primary dendrite, the second segment, 20-30 μm in length, was located on the secondary branch and the third one, 40-50 μm, was located along the tertiary or quaternary dendritic branch. For every one of the segments described above, 20 serial digital pictures have been taken and used in the Neuromantic application for the three dimensional representation of the segments including the dendritic spines.

Adjacent samples of the visual cortex have been used for Nissl staining for the definition of laminar borders and estimation of the depth of selected neurons in the visual cortex. Laminar nomenclature criteria were taken from several publications which describe the cytoarchitecture of striatal cortex layers [3,7,15,28, 39,48], while laminar widths were estimated on 50 digital pictures using Image J application.

All the specimens were studied in an Axiostar Plus Zeiss photomicroscope, digital photographs were taken with an Amscope microscope camera and for the statistical analysis the Student's test was performed. Significance is taken as $p < 0.05$.

Results

Although macroscopic signs of pathology were not detected on the older brains, they exhibited a 10% loss of weight (Table I, $p < 0.001$).

Laminar values are consistent with those of previous cytoarchitectonic findings for primary visual cortex [15]. In Nissl preparations, area 17 is characterized by well-developed granular layers. The internal granular layer is divided by a zone deficient in cells, which corresponds to Gennari's line. The internal granular layer is subdivided in layers 4A, 4B and 4C. Layers 4A and 4C contain very small granule cells.

Two main types of spiny stellate cells have been detected in layer 4. The first type of cells is located in the part of the visual cortex, which refers to sublayer 4Cα in Nissl preparations, neurons have a medium-sized polyhedric cell soma and 4-5 primary dendrites covered by spines, ramifying to secondary and tertiary dendritic branches and extending radially away from the soma to the upper parts of layer 4 (Fig. 1A). Even if a dendrite rises by chance, it never reaches as far as the surface of the cortex, like those of the pyramidal cells, and never climbs out of the lower layers.

The second type of spiny stellate cells is located in the part of layer 4 which refers to sublayer 4Cβ, neurons have quite larger cell soma and 3-4 primary dendrites which ramify to more secondary and tertiary branches, bearing fewer spines than the first and extending radially in a smaller distance than the first (Fig. 1B).

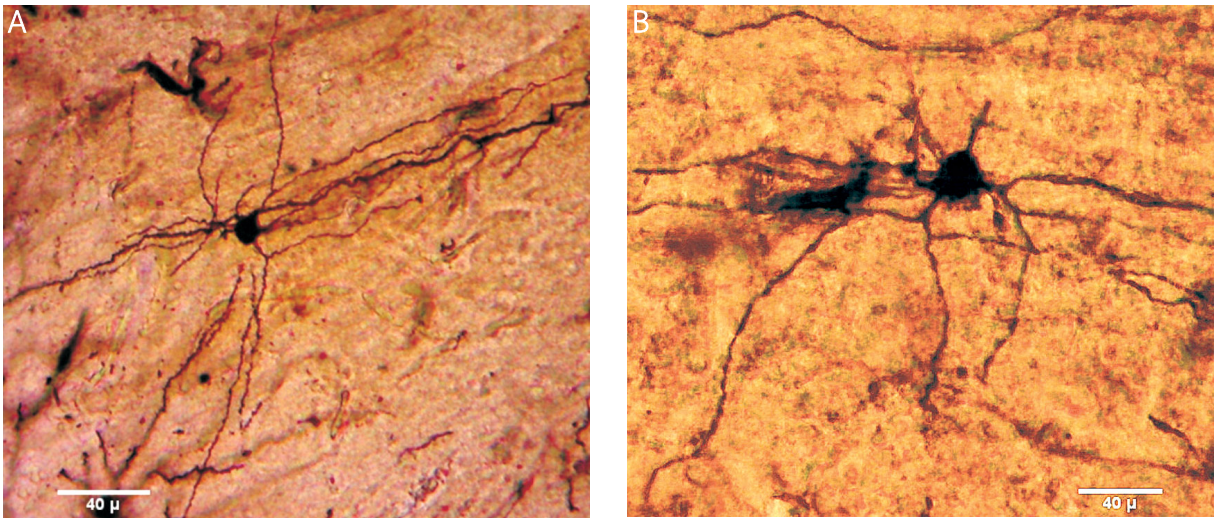

Fig. 1. A) Type 1. **B**) type 2 stellate cell from the human visual cortex from the older brains. Golgi method.

The dendrites of the first type of cells seem to give synapses with the basal dendrites of the layer 4B pyramidal cells and the horizontal dendritic branches of the pyramidal cells of layers 5 and 6. The dendrites of the second type form synapses with the horizontal dendritic branches of the pyramidal cells of infragranular layers.

Stellate cells demonstrate a significant loss of the total number of dendrites in normal aging (Fig. 2A, $p < 0.009$). Total dendritic length (Fig. 2B, $p < 0.012$), as well as the number of terminal branches, the number of bifurcations and the number of branches per order were severely decreased (Fig. 2A, $p < 0.02$).

The average branching order (Fig. 2C, $p < 0.05$) and the daughter ratio were significantly decreased in the older group, while tree asymmetry did not exhibit a significant difference between the two groups (Fig. 2F, Fig. 3A, $p < 0.04$).

A significant decrease in the number of intersections in the distal circles has been revealed by Sholl analysis (Fig. 3B-C, $p < 0.035$).

Spinal density

The total number of dendritic spines of the spiny stellate neurons was also substantially lower in the older group (Fig. 3D, Fig. 4A-B, $p < 0.05$).

Age-related differences between stellate cells subtypes

Spiny stellate cells located in layer 4Cβ seem to be severely affected by age. Even if the loss of terminal branches per neurons and daughter ratio were not significantly different between the two types of stellate cells, a statistically significant difference in the loss of the total dendritic length, number of branches per neuron, in the average branching order and in spinal density has been revealed (Fig. 3E, $p < 0.05$).

Discussion

There is converging evidence that age-related cognitive deficits may be not due to severe neuronal loss, but rather could be related to regional specific morphological alterations of cortical neurons. Duan *et al.* (2003) have shown a significant decrease in the dendritic arborisation and spinal density of the pyramidal neurons in human and non-human cerebral cortex during normal aging [14]. Golgi and electron microscopy studies have reported a significant decrease in the total number of dendritic spines on the dendritic tufts of the pyramidal cells in the prefrontal cortex in old primates in comparison to young ones [11].

Age-related changes that occur in the visual cortex are very similar to those that were previously encountered in other cortical areas [37]. Peters *et al.* (1998) described a decrease in the frequency of synapses with age and a thinning of layer 1 in area 17, while studies in electron microscopy revealed an increase in the frequency of intermediate filaments in the perikarya and processes of the astrocytes throughout layer 1 and an increase in the frequency of phagocytosed material in the astrocytes [39].

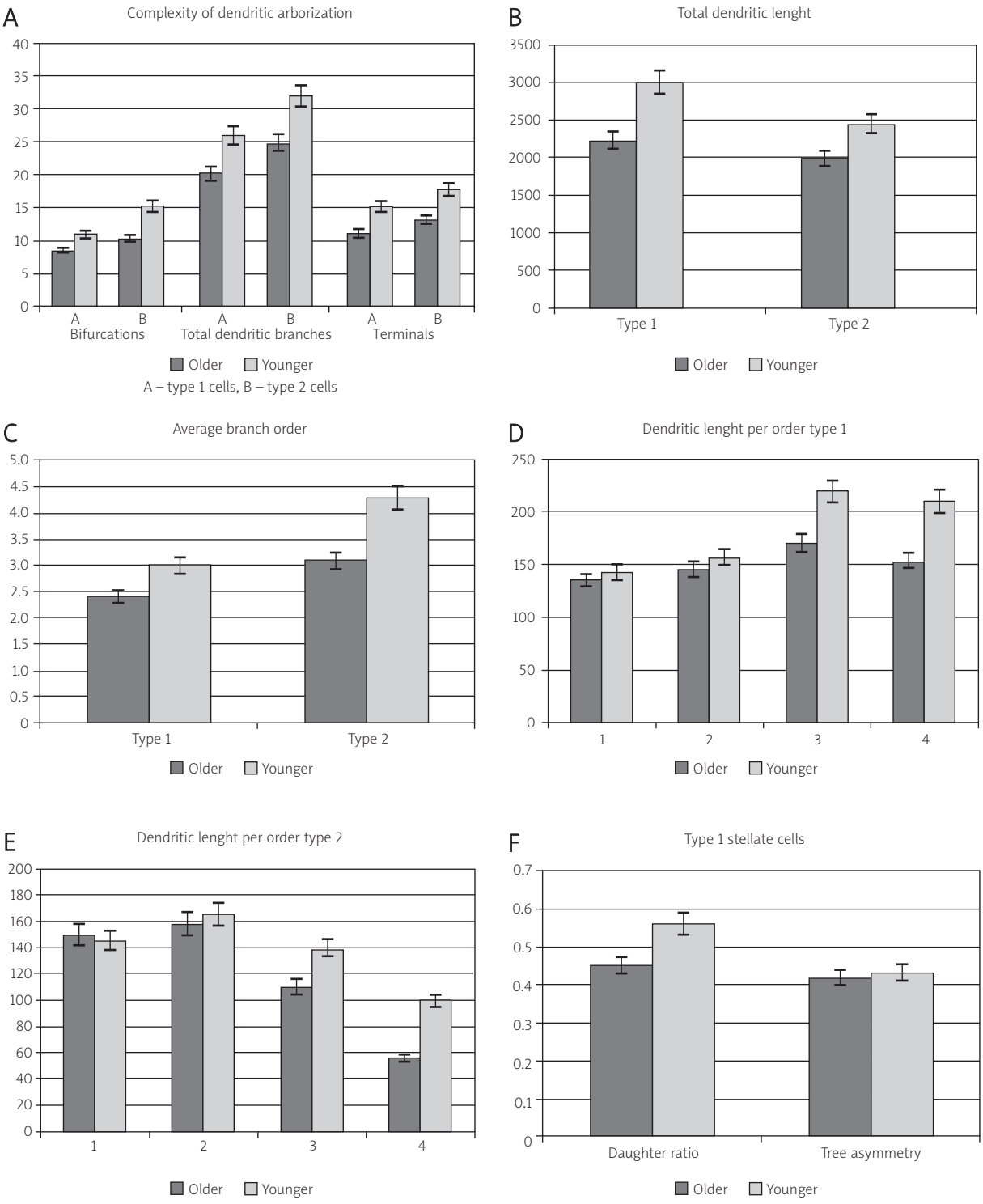

Fig. 2. A) Complexity of dendritic arborisations. **B)** Total dendritic length. **C)** Average branching order. **D)** Dendritic length per order in type 1. **E)** Dendritic length per order in type 2. **F)** Daughter ratio and tree asymmetry of the stellate cells from the visual cortex in normal controls and older brains. (Error bars indicate standard deviation, $p < 0.05$).

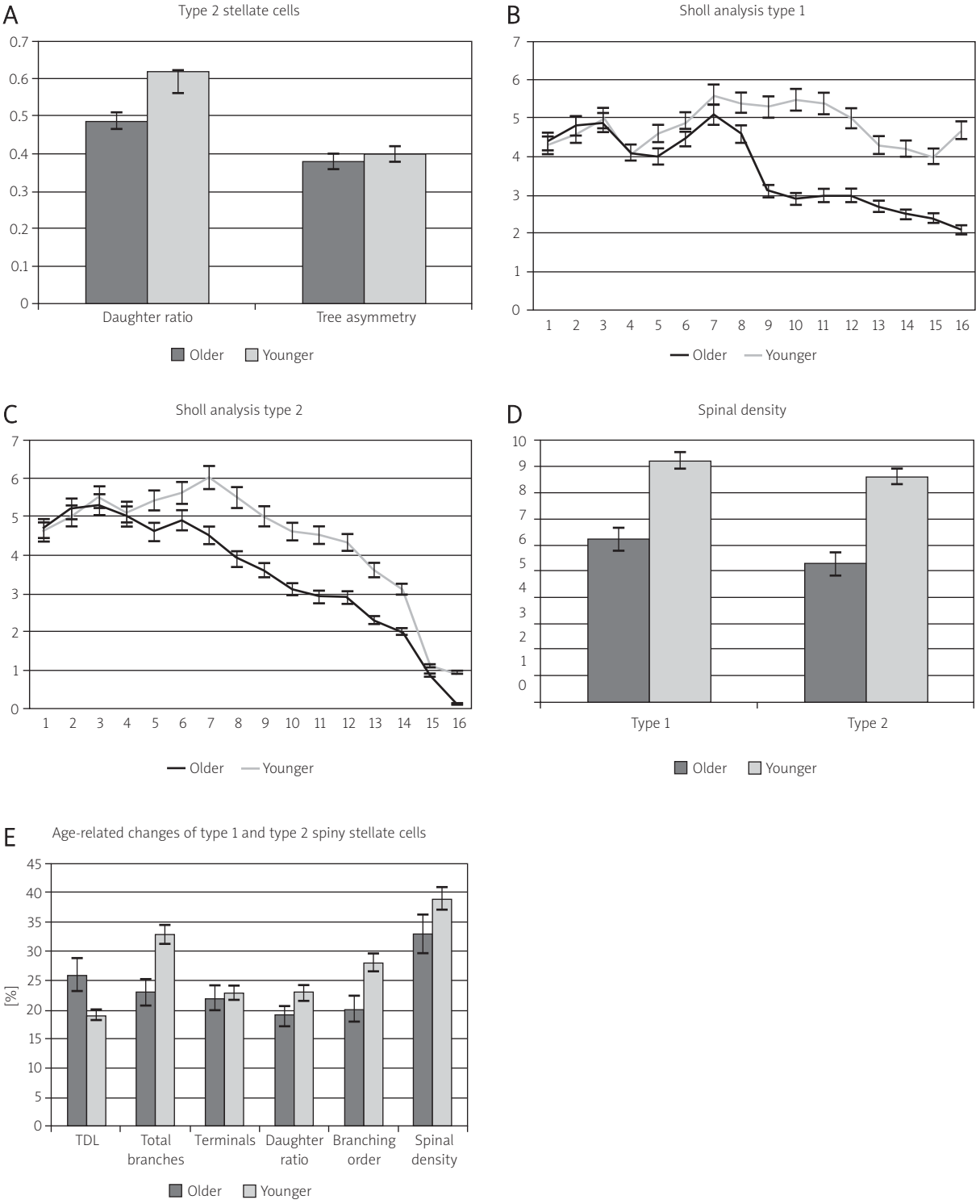

Fig. 3. A) Daughter ratio and tree asymmetry. **B)** Sholl analysis in type 1. **C)** Sholl analysis in type 2. **D)** Spinal density of the stellate cells from the visual cortex in normal controls and older brains. **E)** Cell-specific alterations during ageing. (Error bars indicate standard deviation, $p < 0.05$).

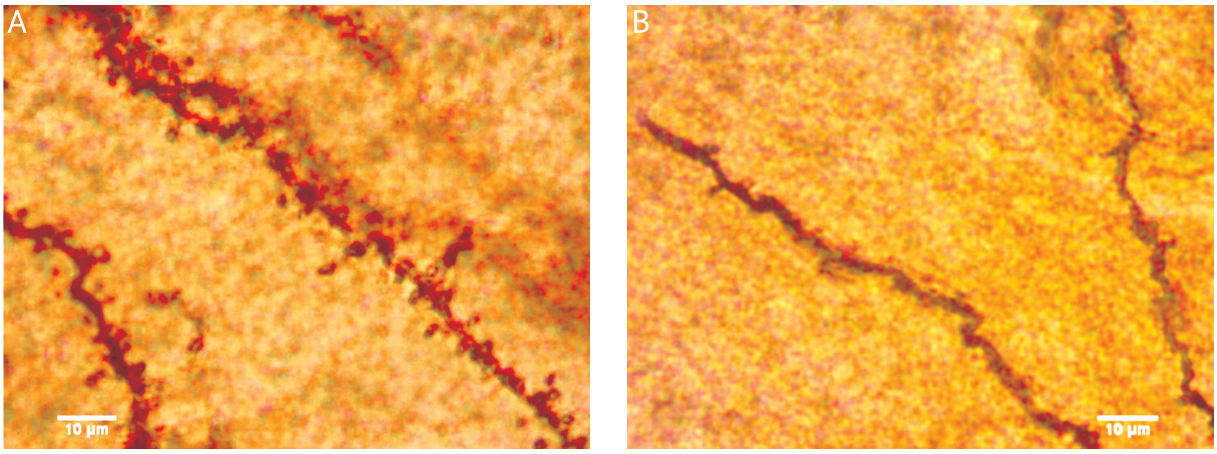

Fig. 4. A) Dendritic segment from type 1 stellate cells from a normal control brain and. **B**) Dendritic segment from type 1 stellate cells from an older brain.

Xu *et al.* (2007), using the Golgi method, revealed differences in dendritic branching and spinal density in rats during ageing [53].

In the present study a poverty of secondary and tertiary dendritic branches, loss of terminal branches of the spiny stellate cells and significant decrease in dendritic spines have been observed. Both types of stellate cells from the younger group exhibit more complex dendritic fields, however no significant difference in the number of primary dendrites has been observed.

Although the mechanisms underlying the dendritic and spinal changes in normal ageing are not yet clearly understood, they might be related to subjacent vascular, biochemical and molecular alterations.

Ageing brain undergoes chemical changes consisting of marked alteration of neurotransmitters and their receptors [21,23,32,49], as well as genetic changes consisting of down-regulation of specific genes, such as genes expressing Calcium channels subunits, GABA receptor subunits and genes involved in synaptic plasticity, in DNA repair mechanisms and in antioxidant defence [2].

In previous studies we have shown a correlation between morphological and spinal alterations of neurons and oxidative damage in degenerative diseases [4,5]. This could hold true for normal ageing too, while in the ageing brain there is a decline in the normal antioxidant defence mechanisms, which increase the vulnerability of the brain to the deleterious effects of oxidative damage [8].

Several studies have found increased levels of 8-hydroxy-2-deoxyguanosine, a biomarker of oxidative mitochondrial DNA damage in the aged brain [8,12] and oxidative-induced mutations in mtDNA accumulates with age in post mitotic tissues, such as the brain [18,47].

Sholl analysis showed a severe decrease in the number of intersections in the distal circles in aged individuals and loss of distal dendritic branches which are the more plastic components of the dendritic arborisation [52]. This finding could be related to the reduction of the expression of the MAP2 protein that has been detected in the aging cerebral cortex as well as to impairment of neuroplasticity [10]. Furthermore, recent research has identified brain-derived neurotrophic factor (BDNF) and serotonin (5-hydroxytryptamine, 5-HT) as two prominent signals that act in concert to regulate aspects of neural plasticity in multiple brain regions and that they play a role in ageing and age-related neurodegenerative disorders [29].

Spinal density was significantly lower in the group of aged individuals. Spinal loss might be consistent with mitochondrial abnormalities as a result of oxidative damage, to the dysfunction of protein synthesis molecular mechanisms [47], to receptor and neurotransmitter abnormalities, as well as to neuroplasticity impairment in the ageing brain.

The deterioration of eye tissues and increased incidence of eye pathology which usually take place during normal aging could also influence the spinal density and dendritic tree morphology in older patients [28].

Cell-specific alterations

Spiny stellate cells of the human visual cortex exhibited age-related alterations, which were more prominent on the cells located at layer 4Cβ.

Stellate cells from layer 4Cα receive projections from the M layers of the lateral geniculate bodies and project heavily to 4B [7,20], while the spiny stellate cells from layer 4Cβ receive inputs from the P layer of the lateral geniculate bodies and provide a dense innervation of layers 4A, 4B, 3B, 5 and 6 [10,54].

The M pathway is considered insensitive to colour when the luminance is balanced, has higher contrast sensitivity and responds to lower spatial frequencies. The P pathway is colour sensitive, has lower contrast sensitivity and is responsive to higher spatial frequencies and lower temporal frequencies [13,17,43,44].

Although both types of stellate cells are affected by age, the fact that neurons from 4Cβ layer are mainly affected might be related to fine vision impairment and functional degradation of the colour and fine vision during normal ageing [34].

Conclusion

The restriction of the dendritic arborisation and the severe loss of dendritic spines revealed in the present study in the neurons of the primary visual cortex of normal aging individuals lead to the loss of synapses, derange the functional communication between the visual cortex and other cortical or subcortical areas and could explain the central visual impairment observed by previous studies in normal ageing. Furthermore, different functional and anatomical domains of the central visual system are affected at different levels of severity during normal ageing.

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