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Functional degradation of visual cortical cells in old cats

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Abstract

Visual function declines with age. Using extracellular single-unit in vivo recordings, we compared the function of primary visual cortical (area 17) cells in young and old paralyzed, anesthetized cats. The results reveal that cortical neurons in old cats exhibit higher visually evoked responses, higher spontaneous activities, lower signal-to-noise ratios, and weaker orientation and direction selectivity than do cells in young adult cats. These findings are consistent with previously reported age related declines in cortical function in senescent macaque monkeys. Thus, similar declines in cortical function accompany old age in different mammalian species with well developed cortices.

Keywords: Old cat; Visual cortical cells; Functional declines; Orientation selectivity; Direction selectivity; Signal-to-noise ratio

1. Introduction

Studies of visual perception show that human visual function declines with age. Senescent humans show decreased visual acuity, binocular summation, contrast sensitivity and wavelength sensitivity [14,16,27,29,39,41,42,52,55,71] as well as poor or slowed performance at tasks requiring orientation discrimination and/or motion direction detection [3,40,64,65,73]. Age related changes in the retina [48,63,66] and subcortical visual pathways [61] cannot explain the foregoing declines.

Schmolesky et al. [57] compared the responses of cells in primary visual cortex (VI) of young adult macaque monkeys with those of very old macaque monkeys. That study provided the first evidence for a significant degradation of orientation and direction selectivity in senescent animals. Their results also indicated that the decreased stimulus selectivity of cells in old monkeys was accompanied by increased responsiveness to all orientations and directions as well as an increase in spontaneous activity. The ability of old neurons to differentiate signals from noise was also reduced.

To date there have been no studies of age related declines in visual cortical function in higher mammalian species other than the monkey. We, thus, have for the first time, used extracellular single-unit recording techniques to examine orientation and direction sensitivity as well as visual responsiveness of VI cells in old and young adult cats. Our aim was to test whether age related changes in monkey cortex can be generalized to other species with well developed visual systems. We chose cats as subjects because cats have a well developed visual system and thus are used widely in studies of visual cortex.

2. Methods

2.1. Subjects

Subjects for this study were four young, sexually mature cats (1–3 years old) and four old cats (12 years old). Several lines of evidences indicate that a cat about 12 months old can be considered sexually mature and functional aging of the brain takes place in cats of 10 years or older [6,7,22,32].

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All cats were examined ophthalmoscopically before the experiment to confirm that they had no optical or retinal problems that would impair visual function. All experiments were done strictly in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Preparation for extracellular recording

The preparation for extracellular single-unit recording was carried out as previously described [58]. Briefly, cats were lightly anesthetized with ketamine HC1 (20 mg/kg). Lidocaine (1%) was applied to all incisions of surgical entry. After the intravenous and tracheal cannulae were inserted, cats were placed in a stereotaxic apparatus. Pupils were maximally dilated with atropine (1%), and appropriate contact lenses were used to protect the corneas. Neosynephrine (5%) was administered to retract the nictitating membranes.

A mixture of urethane (20 mg/h/kg body weight) and gallamine triethiodide (10 mg/h/kg body weight) was infused intravenously to maintain anesthesia and paralysis. Expired pCO_2 was maintained at approximately 4%. Heart rate (about 180–220 pulses/min) and EEG was monitored throughout the experiment to assess the level of anesthesia. A small hole was drilled in the skull 4 mm posterior to the ear bars and 2 mm lateral to the midline. A glass-coated tungsten microelectrode (with an impedance of 3–5 MΩ) was positioned and advanced using a hydraulic micromanipulator (NARISHIGE, Japan). The small hole was filled with a 4% solution of agar in saline and sealed with wax. After the preparation was complete, the optic discs of the two eyes were reflected on a tangent screen positioned 114 cm from the retina and the central areas for both eyes were located. Spectacle lens were used as needed.

At the end of the experiment, the cat was deeply anesthetized and perfused through the heart. Blocks of tissue containing area 17 (striate cortex) were removed, post-fixed overnight in cold 4% paraformaldehyde in PBS and then embedded with wax for later morphological studies.

2.3. Visual stimulation

Visual stimulus patterns were drifting sinusoidal gratings shown on a CRT monitor (1024 × 768, 85 Hz), placed 57 cm away from animal's eyes. The program to generate the stimulus was written in MATLAB, using the extensions provided by the high-level Psychophysics Toolbox [8] and low-level Video Toolbox [44]. When a single unit was isolated, the cell's receptive field was carefully mapped by consecutively presenting a series of computer-generated light spots on the CRT. We selected optimal stimulus size, temporal and spatial frequency for each cell. Each stimulus was presented monocularly to the dominant eye. Then, a set of sinusoidal gratings with optimal stimulus parameters, moving in 24 different directions (0–360° scale with an increment of 15°) was used to compile the orientation and direction tuning curves. The orientation of each drifting stimulus was orthogonal to its direction of motion. Before each stimulus presentation, 5 s spontaneous activities were obtained while mean luminance was shown on the display. The duration of each stimulus presentation was less than 5 s with a 5 min interval between stimuli for functional recovery. The contrast for each stimulus was set at 80%. The mean luminance of the display was 19 cd/m^2, and the environment luminance on the cornea was 0.1 lx.

2.4. Data collection and analysis

After the signal was amplified with a microelectrode amplifier (NIHON KOHDEN, Japan) and differential amplifier (FHC, USA), action potentials were fed into a window discriminator with audio monitor. The original voltage traces were digitized using an acquisition board (National Instruments, USA) controlled by IGOR software (WaveMetrics, USA). The original data (Fig. 1A) were saved for later analysis.

The post-stimulus time histograms (PSTHs) of response were obtained for further analysis (Fig. 1B). The responses of a cell to the sinusoidal gratings were fast Fourier transformed and defined as the amplitude of the fundamental Fourier com-

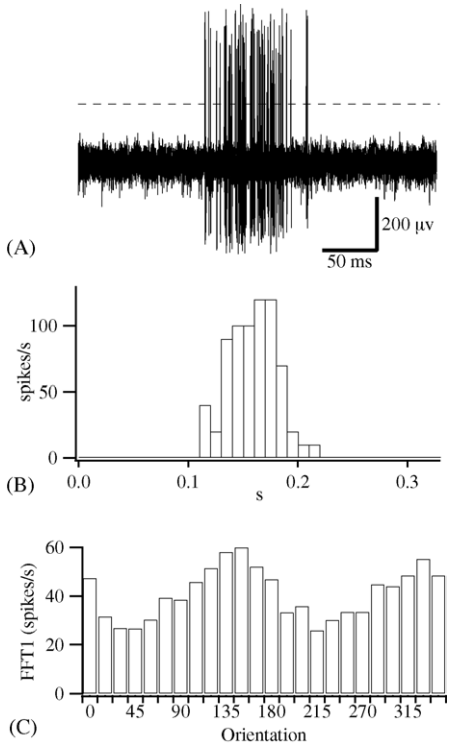

Fig. 1. An example showing the visual responses of an area 17 neuron in an old cat and analysis of the responses. (A) Each cycle of the neuron's original response was superimposed in one stimulus period (0.333 s). A spike above the broken horizontal line is counted as an action potential. (B) The PSTH derived from (A) for further analysis. Bin width was 10 ms. (C) The neuron's orientation tuning curve. The curve was established on a 360-degree scale with an increment of 15°. The orientation of the drifting gratings were orthogonal to its moving direction. The responses were defined as the fundamental Fourier components (FFT1). The FFT1 at each stimulus direction was computed from the PSTH such as the one shown in (B).

ponent (FFT1) of the PSTH integrated over a time equaling the stimulus modulation period. The FFT1 value of each stimulus direction was used to draw the orientation tuning curve (Fig. 1C). The method for calculation of orientation bias and direction bias has been described elsewhere [31,57]. Briefly, the responses of each cell to the different stimulus orientations or directions were stored as a series of vectors. The vectors were added and divided by the sum of the absolute values of the vectors. The angle of the resultant vector gave the preferred orientation or direction of the cell. The length of the resultant vector, termed the orientation or direction bias (OB or DB), provided a quantitative measure of the orientation or direction sensitivity of the cell. A cell with bias ≥ 0.1 was considered significantly biased for orientation or direction. A cell with bias ≥ 0.2 was considered strongly biased for orientation or direction. A cell's signal-to-noise ratio (STN) was defined as the ratio between the cell's visually evoked response to the optimal stimulus and the cell's spontaneous response [13]. To avoid data skewing or overestimation, all spontaneous activities below 1 spike per second were set equal to 1 spike per second for signal-to-noise analysis. The spontaneous activity was subtracted from stimulus evoked response before OB, DB and STN analyses.

Statistical comparisons between young and old cat data were carried out using *t*-tests.

All mean values were in format of mean ± standard deviation.

2.5. Effects of anesthesia

It is a concern that differential effects of anesthesia upon cortical function in young and old cats could impact our results. We have examined this possibility here and previously in monkeys [30,57]. We have, in both old and young animals, recorded the properties of individual cells while systematically varying anesthetic and paralytic levels. We found that giving as much as four times the minimum level of general anesthesia or paralysis required to anesthetize or paralyze both old and young animals does not alter the degree of selectivity for orientation and direction VI cells exhibit. Greatly increased anesthesia decreased neuronal responsiveness in both groups similarly. In addition, a greater sensitivity of old animal to anesthesia is hard to reconcile with our findings that old cells exhibit higher spontaneous and higher visually evoked firing rates than do young cells. Thus, we conclude that problems with anesthesia in old animals are not a concern.

3. Results

We studied a total of 158 neurons in four young adult cats and 160 neurons in four old cats. Neurons recorded from each group of cats were at the same range of depth from the surface of brain to avoid laminar bias. Cells studied had receptive fields within 8 degrees from the central area. No significant difference was found in the eccentricity distribution of neurons between the young and old groups ($p = 0.44$, *t*-tests). The proportions of simple and complex cells studied were similar in the two groups (57 simple cells, 103 complex cells in the old group, and 68 simple cells, 90 complex cells in the young group). Since simple and complex cells exhibited similar age-related changes, data from the two types of cells were combined. For convenience, subjects studied were briefly named as OC1-4 (for old cat one to four) and YC1-4 (for young cat one to four) (Table 1).

3.1. Orientation and direction selectivity

The percentage of area 17 neurons showing significant orientation bias (OB ≥ 0.1) was smaller in old cats (72.5%, 116 of 160) than that in young cats (98.1%, 155 of 158). Similarly, the percentage of cells that were strongly biased for orientation (defines cells that exhibit OB ≥ 0.2) was lower in old cats (30.6%, 49 of 160) than that in young cats (84.8%, 134 of 158).

Fig. 2A shows the percentile of cells having different OB values. It is clear that cells in old cats (dots) are less biased than those in young cats (open circles). Mean OB showed significant interanimal variability between OC3 and any of other old cats ($p < 0.05$) but not across young ones ($p > 0.05$, Table 1). Nevertheless, the mean orientation bias for each individual old cat was significantly less than that for any individual young cat ($p < 0.01$). An additional analysis

Table 1
Descriptive statistics of response properties for each cat

Cat	*N*	OB	DB	AR	OR	BR	STN
0C1	38	0.18 ± 0.08	0.15 ± 0.09	20.0 ± 7.1	47.2 ± 20.9	9.6 ± 4.4	5.3 ± 1.9
OC2	70	0.17 ± 0.11	0.12 ± 0.08	29.4 ± 16.4	58.0 ± 25.5	12.4 ± 5.9	6.0 ± 6.0
OC3	30	0.13 ± 0.07	0.14 ± 0.08	27.6 ± 8.3	56.9 ± 16.1	12.2 ± 6.4	6.5 ± 5.5
OC4	22	0.18 ± 0.12	0.13 ± 0.07	24.9 ± 7.3	56.5 ± 11.5	13.6 ± 6.4	6.4 ± 7.5
YC1	23	0.33 ± 0.20	0.27 ± 0.14	10.4 ± 6.4	31.4 ± 20.5	2.4 ± 2.3	23.3 ± 23.0
YC2	68	0.36 ± 0.13	0.24 ± 0.15	15.7 ± 6.8	46.7 ± 19.0	2.0 ± 1.3	30.2 ± 17.5
YC3	16	0.29 ± 0.13	0.27 ± 0.13	15.4 ± 8.7	43.6 ± 20.2	2.2 ± 1.4	30.6 ± 25.9
YC4	51	0.34 ± 0.14	0.20 ± 0.10	16.6 ± 6.2	44.9 ± 27.2	2.1 ± 1.2	28.0 ± 20.8

Subjects were briefly named as OC1-4 (for old cat one to four) and YC1-4 (for young cat one to four). Other data columns represent the number of cells (*N*), the mean value (mean ± standard deviation) of orientation bias (OB), direction bias (DB), average response across all orientations (AR), response to optimal orientation (OR), baseline response (BR) and signal-to-noise ratio (STN) for each cat.

compared the average OBs for young cats (0.34 ± 0.14) with old cats (0.16 ± 0.09) and showed a significant age related difference ($p < 0.000001$).

The percentage of cells showing significant direction bias (DB ≥ 0.1) in old cats (61.3%, 98 of 160) was less than in young cats (87.3%, 138 of 158). The percentage of cells showing strong direction selectivity (DB ≥ 0.2) in old cats (20.6%, 33 of 160) was also less than in young cats (51.9%, 82 of 158). The percentile of cells having different DB values clearly reflects this difference (Fig. 2B). The mean DB values showed significant interanimal variability between YC4 and any of other young cats ($p < 0.05$) but not among old cats ($p > 0.05$, Table 1). However, the mean DB of each individual old cat was significantly less than that of any individual young cat ($p < 0.05$). A comparison of averaged DB values for young cats (0.23 ± 0.13.) versus old cats (0.13 ± 0.08) also showed a significant age related difference ($p < 0.00001$).

3.2. Visually evoked activity

In order to determine whether the decreased selectivity of cells in old cats resulted from an increased responsiveness to non-optimal orientations and directions or from a reduced responsiveness to the optimal orientations and directions, or both, we compared the average response (AR) across all orientations of area 17 neurons in young and old cats. It is obvious that cells in young cats showed a smaller range of AR values than did cells in old cats (Fig. 3A). Most cells (76.6%) in young cats had AR values within 20 spikes/s. Cells in old cats showed a wide range of ARs, and most of them (67.5%) had AR values larger than 20 spikes/s. The mean ARs showed significant interanimal variability not only for old cats ($p < 0.05$) but also for young cats ($p < 0.05$, Table 1). However, the mean AR value for each individual old cat was significantly larger than for any individual young cat ($p < 0.02$). An additional comparison of averaged ARs for old cats (26.2 ± 12.7 spikes/s) versus young cats (15.2 ± 7.9 spikes/s) showed a significant aging difference ($p < 0.00001$).

We also compared the response of area 17 cells to their optimal stimulus (with optimal size, temporal and spatial frequency, orientation and moving direction) in young and old cats. For convenience, we call it optimal response (OR). Cells in old and young cats had similar range of OR values. However, more than half of the cells (58.2%) in young cats had OR values less than 44 spikes/s, while most of the cells (68.1%) in old cats had OR values equal to or higher than 44 spikes/s (Fig. 3B). *T*-tests indicated that the averaged OR value for the old cat population (55.1 ± 21.6 spikes/s) was significantly larger than that for young cat population (43.6 ± 22.7 spikes/s) ($p < 0.00001$). Therefore, area 17 cells in old cats show increased responsiveness to both optimal and non-optimal stimuli.

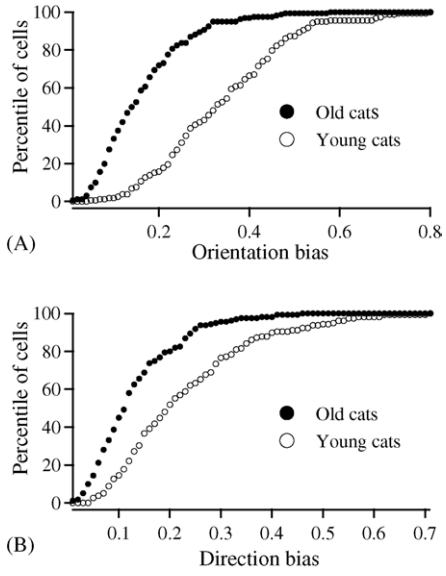

Fig. 2. Percentile of cells showing different orientation bias (OB) (A) and direction bias (DB) (B) values for old and young cats. The total number of neurons was 160 for old cats and 158 for young adult cats. A percentile at an OB or DB value at horizontal axis means the percentage of cells whose OBs or DBs are lower than the value. Old cats showed significantly decreased OB and DB values compared with young cats ($p < 0.000001$; $p < 0.00001$).

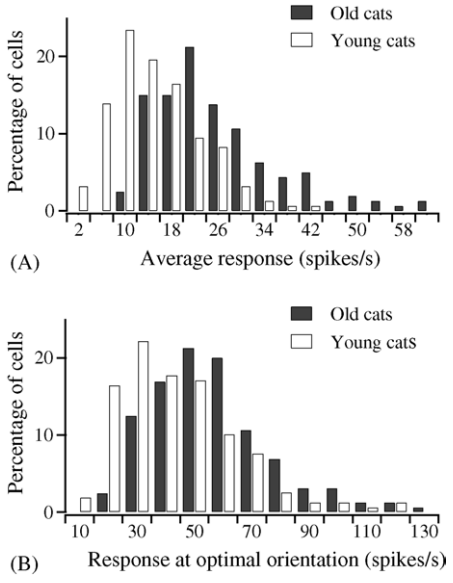

Fig. 3. Percentage of cells with different average response (AR) and optimal response (OR) values for old and young adult cats. The total number of neurons was 160 for old cats and 158 for young adult cats. Old cats showed a significantly increased AR and OR compared with young adult cats ($p < 0.00001$; $p < 0.0001$). (A) Percentage of cells with different AR values. Most cells (76.6%) in young cats had AR value less than 20 spikes/s, whereas most cells (67.5%) in old cats had AR value equal to or larger than 20 spikes/s. (B) Percentage of cells with different OR values. Most cells (68.1%) in old cats had OR value equal to or higher than 44 spikes/s, whereas more than half of the cells (58.2%) in young cats had OR value less than 44 spikes/s.

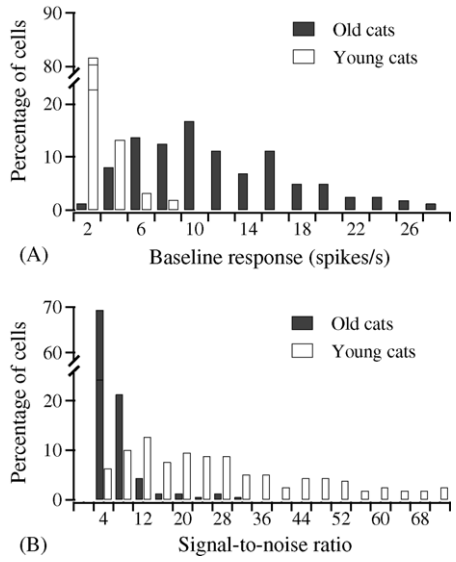

Fig. 4. Percentage of cells with different baseline response (BR) and signal-to-noise (STN) values for old and young adult cats. The total number of neurons in old and young cats was 160 and 158, respectively. Old cats showed significantly increased BR and significantly decreased STN compared with young adult cats ($p < 0.0000001$; $p < 0.000001$). (A) Percentage of cells with different BR values. Cells in young cats showed a significantly narrow range of BR values with the peak around 2 spikes/s, whereas cells in old cats had a broader range with the peak near 10 spikes/s. B, Percentage of cells with different STN values. Cells in old cats showed significantly narrower range of STN values with most cells (90.6%) having STN values less than 10. Cells in young cats showed a much larger range of STN values with most cells (70.9%) having STN values higher than 14.

3.3. Spontaneous activity and signal-to-noise ratio

The baseline response (BR) of neurons was also compared in young and old animals. Fig. 4A shows that cells in young cats exhibit a significantly narrower range of BR values (1–8.9 spikes/s) than do cells in old cats (1.5–28.7 spikes/s). The mean BR showed significant interanimal variability between OC1 and any of other old cats ($p < 0.05$) but not across young cats ($p > 0.1$, Table 1). However, the mean BR for each individual old cat was significantly greater than for any individual young cat ($p < 0.00001$). An additional comparison of the average BRs of old cats (11.9 ± 5.8 spikes/s) versus young cats (2.1 ± 1.5 spikes/s) also showed a significant age related difference ($p < 0.0000001$).

Fig. 4B presents the distribution of various signal-to-noise ratios (STN = OR/BR) for cells in young and old cats. There is no doubt that cells in old cats showed a reduced range of STNs with most cells (90.6%) having STNs less than 10. Cells in young cats showed a much larger range of STNs and most cells (70.9%) had STNs higher than 14. The mean STN showed no significant interanimal variability in both old and young cats ($p > 0.05$, Table 1). The mean STN for each individual old cat was significantly lower than the mean for any individual young cat ($p < 0.003$). An additional comparison of the averaged STN for young cats (28.5 ± 20.3) versus old cats (6.0 ± 5.4) showed a significant age related difference ($p < 0.000001$).

4. Discussion

This study provides the first evidence for an age-related decline in visual cortical cell function in aged cats. Area 17 cells of old cats showed significantly decreased orientation and direction selectivity accompanied by increased spontaneous and visually driven activities. The decreased signal-to-noise ratio in old cats indicates a degraded ability of 'aged' cells to retrieve signals from noisy backgrounds. These results are in accordance with previous findings in senescent macaque monkeys [57].

4.1. Age related changes in the function of area 17 neurons

Area 17 neurons in aged cats showed a significant reduction in stimulus selectivity. This reduction was not the same for different groups of cells. Cells with OB ≥ 0.1 in old cats decreased by 25.6% compared to young cats, whereas cells with OB ≥ 0.2 decreased by 54.2%. Similarly, cells with DB ≥ 0.1 in old cats decreased by 26%, and cells with DB ≥ 0.2 decreased by 31.2%. That is to say, area 17 cells that were strongly biased for orientation and direction were more affected by age.

The age related reduction in orientation and direction selectivity in cat cortex was accompanied by an increased responsiveness to all visual stimuli. The average response across all orientations for the old cat population increased by 72.3% compared with the young, whereas the response to optimal stimuli increased by only 26.3%. Thus, the increased responsiveness to non-optimal orientations and directions appears to be an important mechanism mediating the reduction in stimulus selectivity in old cats. Finally, spontaneous activity in old cat cortex increased by 464% compared to young cats. This increase was much higher than the increase in peak response. As a result, the ratio of peak response to spontaneous activity (signal-to-noise ratio) in old cats was much lower than in young ones. The decrease in signal-to-noise ratio in old cats, thus, appears to mainly reflect the very large increase in spontaneous activity.

4.2. Mechanistic considerations

Psychological studies showed that the aged human, when compared with the young, exhibited decreased performance at tasks based on orientation or pattern perception [4,11,17,25] and declined motion direction identification [19,56,67,73]. Similar function impairment was also reported in the nonhuman subjects of old monkeys [2,28,50,69]. All these indicated that senescent subjects did present lower orientation and direction sensitivity than young counterparts. The decreased stimulus selectivity of VI neurons concurred

in old cats and aged macaque monkeys [57] provided direct evidences that functional changes of cortical neurons might underlie various visual perception degradation during aging. To uncover the mechanisms mediating these functional changes is thus of great importance to visual aging problems.

Mendelson and Wells [36] observed temporal processing declines in the visual cortex of aged rats. They suggested that this could be related to reduced number of neurons in dendritic tree structures, decreased density of synapses, and loss of white matter as well as alterations in the myelin sheaths of axons in the visual cortex. Although there were once reports about neuron loss, contemporary stereological studies indicated that neuronal death occurred in only a few areas of the old brain and that in most regions, including the primary visual cortex, the number of neurons was stable during aging [23,24,45,46,47,51,62,68,72]. Neuronal morphological alterations have also been reported frequently in senescent human and nonhuman cortex [33,38,43,74]. Among these alterations, age related changes in dendrites are of particular interest since dendrites are the targets of the majority of synapses. For example, decrease of dendritic branches and spines of neurons in the aged rat neocortex would result in a significant loss of synaptic substrate, which, in turn, could influence how synaptic inputs were integrated [74]. Thus, age-related shifts in dendritic structures could also affect a neuron's physiological response properties. However, available literatures dealing with age associated changes of dendritic structures are inconsistent with each other. How dendrites change seemed to be brain region-, layer-, or species-dependent [9,18,21,38,43,74]. So, neuronal morphological changes are hard to explain the reduced stimulus selectivity and increased responsiveness that VI neurons exhibited in old cats and monkeys.

Schmolesky et al. [57] suggested that aging results in a decrease in GABAergic inhibition in old monkey cortex and that reduced inhibition could account for many of the function declines they observed. Leventhal et al. [30] showed that GABA and agonists of GABAa receptors significantly improve the function of VI neurons in old macaque monkeys. It was also reported that GABAa antagonists exerted a stronger effect in young than in old monkey cortex. A number of other studies also indicate that there is a weakness of GABAergic inhibition in the cortex of old animals [12,49]. Further, Sillito [59,60] and Eysel et al. [15] found that the orientation biases of neurons in young cat visual cortex could be significantly reduced by administration of bicuculline (a specific antagonist of GABAa receptor), indicating that blockade of GABAergic inhibition does lead to decreased orientation selectivity. Finally, Hu et al. [26] reported that bicuculline affected the direction sensitivity of neurons in the dorsal lateral geniculate nucleus of cats. Therefore, reduced GABAergic inhibition in old animals might be a reasonable explanation for the decline of cortical functions during aging. Nevertheless, some studies showed that other transmitter systems, such as serotonergic, dopaminergic and noradrenergic systems, might also affect cortical functions. First, the application of norepinephrine was reported to lead to an improvement in orientation, direction and velocity selectivity in cat visual cortex, as well as increased visual responses [35,37]. This result is, however, controversial [13,53,70]. Second, a layer and area dependent decline in adrenergic and serotonergic receptors has been observed in aged monkey neocortex [1,5,54]. Finally, age-related changes in the interactions between intracortical excitatory and inhibitory systems might also be considered [10,34]. Additional studies of cerebral cortical function in aged members of a variety of mammalian species are needed to clarify the mechanisms mediating the universal degradation of brain function that accompanies old age.

In summary, our results together with those of previous studies suggest that the age related changes we report here can be generalized to the visual cortex of a variety of higher mammals having well developed visual systems. Decreased GABAergic inhibition in old animals may be one of the important mechanisms underlying the decline of cortical function during aging. A reduction in GABAnergic inhibition could result from either a decreased expression of GAB A receptors or from a lowered synthesis of G ABA transmitters in the cortex, or both. However, little has been done on this work so far. An observation in the old rat cerebral cortex showed that the protein expression of the main subunits of GABAa receptors (α_1, γ_2 and $\beta_{2/3}$) remained almost unchanged but the corresponding mRNAs exhibited significant age dependent changes [20]. Supports from any other approaches are necessary to elucidate this mechanism.

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