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Functional degradation of visual cortical cells in aged rats

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ABSTRACT

Functional degradation of mammalian visual cortex is associated with aging. It has been hypothesized that much of the decline might be mediated by a degradation of cortical inhibitory system during senescence. In the present work, we compared the properties of adaptation, onset latency and signal-to-noise ratio in primary visual cortex of young and old rats using extracellular single-unit techniques. The short-term synaptic plasticity of young and old rats was also studied using field potential recording techniques. We found significant increased adaptation, prolonged onset latency, lower signal-to-noise ratio and decreased short-term synaptic plasticity in aged rats. The results are in accordance with previously reported functional declines in old monkeys and old cats, indicating a universal mechanism of degradation in cortical function that accompanies old age in different mammalian species.

1. Introduction

Visual abilities decline during normal (non-pathological) aging. Psychophysical studies show that aged humans demonstrate declines in visual acuity, binocular summation, contrast sensitivity and wavelength sensitivity (Weale, 1975; Kline et al., 1983; Ross et al., 1985; Elliott et al., 1990; Schefrin et al., 1999; Nomura et al., 2003), spatial frequency contrast sensitivity (Owsley et al., 1981), temporal–frequency contrast sensitivity (Kline et al., 2001), hyperacuity (Elliott et al., 1990), orientation discrimination and motion direction detection (Owsley et al., 1981; Baracat and Marquie, 1992; Tran et al., 1998). However, a large body of evidence from anatomical and morphological studies of aged retina and subcortical areas provide little explanation for many of these perceptual deficits. Kim et al (1996) reported observing no significant differences between old and young rhesus monkey retina in the densities, total number or cell soma size of ganglion cells (Kim et al., 1996). Similar results are observed in the dorsal lateral geniculate nucleus (dLGN) of monkeys and rats (Satorre et al., 1985; Ahmad and Spear, 1993). In contrast to earlier findings regarding neuron loss, contemporary stereological studies indicate that neuronal death occurs in only a few areas of the old brain. In most regions, including the primary visual cortex, the number of neurons is stable during aging. Furthermore, neuronal morphological alterations in senescent human and nonhuman cortex are frequently reported (West, 1993; Peters et al., 1997; Uylings and de Brabander, 2002).

Schmolesky et al (2000) compared the stimulus selectivity of V1 cells in young and very old macaque monkeys and found a significant degradation of orientation and direction selectivity in aged animals. The decreased selectivity of cells in senescent monkeys was accompanied by a significant increase in spontaneous activity, resulting in a greatly reduced signal-to-noise ratio (Schmolesky et al., 2000). Interestingly,

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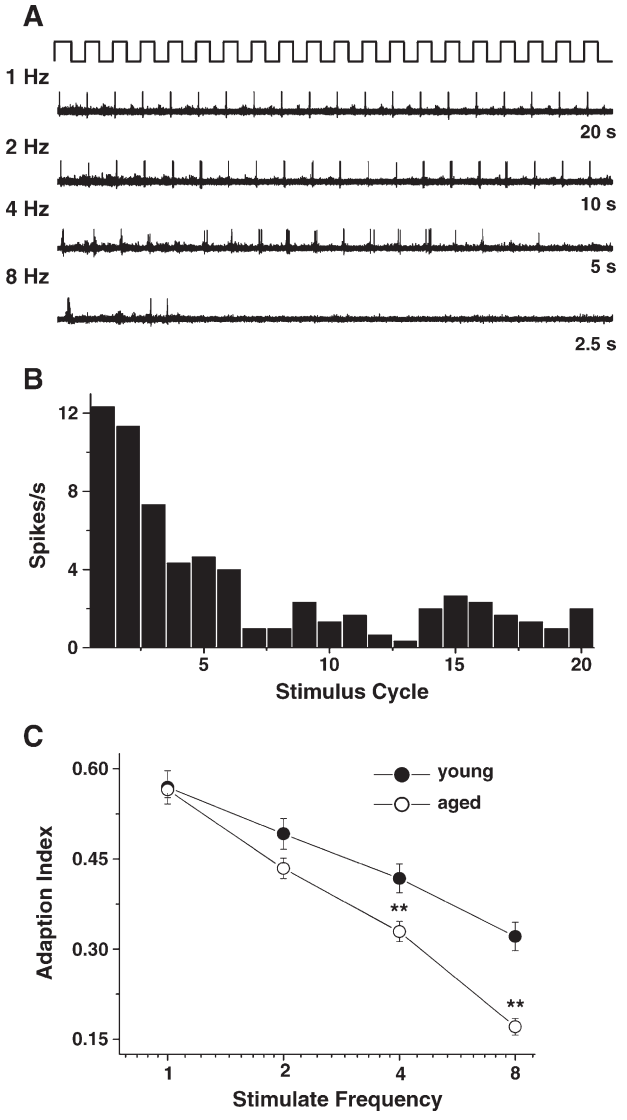

Fig. 1 – (A) An example showing the stimulus output digital analog converter (DAC) wave and a representative single unit recorded from a primary visual cortical neuron in aged rat responses to 1, 2, 4 and 8 Hz flash stimuli. On each frequency we record twenty stimulus cycles. (B) An example of PSTHs elicited from the visual response to flash stimuli at 2 Hz. Average spikes of the first and second evoked response could be seen as initial amplitude. Whereas average spikes of the fifteenth to twentieth evoked response could be seen as plateau amplitude. (C) The adaptation index (AI, average amplitude of the last five evoked response divided by average amplitude of the first and second evoked response) to flash stimuli at different frequencies (1, 2, 4 and 8 Hz). There was no significantly different of AI between young and old rats at 1 Hz and 2 Hz, but was significantly different at 4 Hz and 8 Hz. *t*-test $^{**}P<0.01$.

the same results were found in aging cats (Hua et al., 2006). Additionally, Mendelson and Wells (2002) observed declining temporal processing in the visual cortex of aged rats (Mendelson and Wells, 2002). Similarly, Wang et al (2005) found the degradation of signal timing in visual cortical areas of senescent monkeys (Wang et al., 2005). These results could be regarded as direct evidence for the loss of function in visual cortical cells of old animals.

In the present study, we used extracellular single-unit and field potential recording techniques to systematically examine age effects on the properties of cells in the primary visual cortex. Our studies aimed to test whether age-related changes in monkey and cat cortex can be generalized to other mammalian species and to explore the underlying mechanism of functional decline in visual cortex. We chose rats as subjects because rats can be a good model for more detailed future studies of age-related changes of synaptic mechanisms.

2. Results

We recorded a total of 97 neurons from young (51 cells) and aged (46 cells) rats. Our results showed significant decreases in signal-to-noise ratio, short-term depression and adaptation index to 4 and 8 Hz stimulus frequencies in aged rats compared with young rats. In addition, our data provided evidence that visual onset latency was significantly prolonged in aged rodents.

2.1. *Adaptation to flash stimuli*

We investigated the adaptation to flash stimuli in young and aged rats by using extracellular single unit recording techniques. Fig. 1A depicts a representative single unit recorded from an aged rat. Good consistency between flash stimuli and visual responses can be observed. We calculated the adaptation index of cortical cells in young and aged rats in response to flash stimuli delivered at 1, 2, 4 and 8 Hz (Experimental procedures; Fig. 1C). In the aged rats, the adaptation index is generally lower than that of young rats and significantly lower at 4 Hz (young: 0.42 ± 0.02; aged: 0.33 ± 0.02, $P<0.01$ *t*-test) and 8 Hz (young: 0.32 ± 0.02; aged: 0.17 ± 0.01; $P<0.0001$ *t*-test). Therefore, the response adaptation was greater in aged rats than that in young rats, especially at high temporal frequency.

Table 1 – Notes the difference of spontaneous rate, peak response, signal-to-noise ratio and latencies of neurons in primary visual cortex of young and old rats

	Spontaneous rate (Spikes/s) (mean ± SE)	Peak Response (Spikes/s) (mean ± SE)	Signal-to-noise ratio (mean ± SE)	Latency (ms) (mean ± SE)
Young ($n=51$)	1.55 ± 0.14	14.01 ± 1.20	11.22 ± 0.99	62.04 ± 2.66
Aged ($n=46$)	3.20 ± 0.43	14.48 ± 1.46	6.64 ± 0.67	100.33 ± 4.91
t-test, P	2.98E-4	0.80	2.74E-4	3.34E-10

Compared with neurons in young rats, the neurons in aged rats exhibited high spontaneous rates, prolonged stimulus response latencies and lower signal-to-noise ratio. However, the peak responses were not significantly different between young and aged rats.

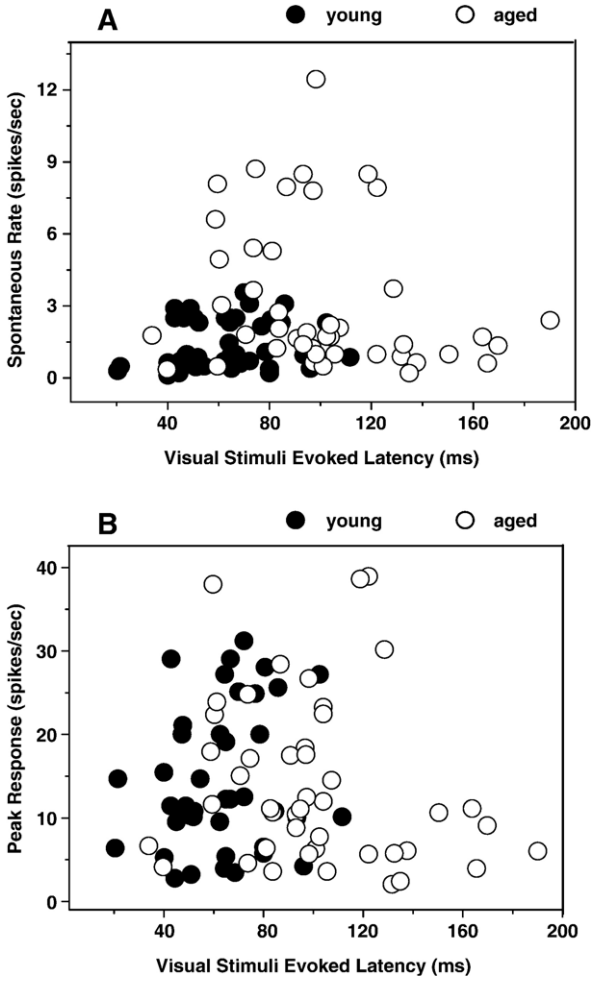

Fig. 2 – Scatter plot shows the significantly different of spontaneous rates and visual-evoked onset latency in primary visual cortical neurons between old and young rats. (A) Compared with neurons in young rats, neurons in old rats exhibit prolonged latencies as well as greatly increased spontaneous activity. (B) Although peak responses of neurons in old rats are a little higher than that in young rats, the difference was not significant. Response rates are in action potentials per second and latencies are in milliseconds.

2.2. *Spontaneous rate, peak response and signal-to-noise ratio*

Subsequently, we compared the spontaneous rate and peak response of neurons between the young and the old rats. The spontaneous rate was significantly higher in old rats (3.20±0.43 Spikes/s) compared to young ones (1.55±0.14 Spikes/s) ($P<0.01$ *t*-test). However, the peak response value showed no statistically significant increase for the old rats (14.48±1.46 Spikes/s) compared with the young rats (14.01±1.20 Spikes/s) ($P=0.80$ *t*-test). As a result, the signal-to-noise ratio of the neurons of young rats (11.22±0.99) is significantly higher than that of aged rats (6.64±0.67) ($P<0.01$ *t*-test). Table 1 shows that decreased signal-to-noise ratio is the result of increased spontaneous activity in aged rats. These results suggest that detection capability of visual cortical neurons declines with age.

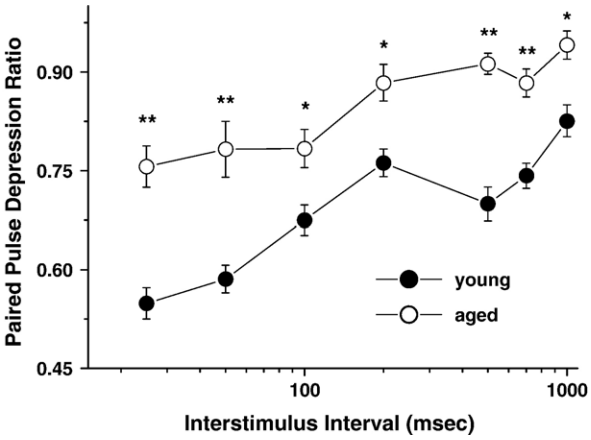

Fig. 3 – Paired-pulse depression at stimulus intervals of 25, 50, 100, 200, 500, 700 and 1000 ms in primary visual cortex of young ($n=6$) and aged rats ($n=5$) are significantly different. Averaged paired-pulse depression ratio increased significantly in aged animals. $^{*}P<0.05$, $^{**}P<0.01$; Mann–Whitney *U* test.

2.3. *Onset latency to flash stimuli*

We compared the onset latencies which response to the onset of a single flashing pulse between the cells of young and aged rats. As Table 1 and Figs. 2A, B show, visual onset latency was significantly prolonged in the aged group (100.33±4.91 ms) compared to the young rats (62.04±2.66 ms) ($P<0.01$ *t*-test).

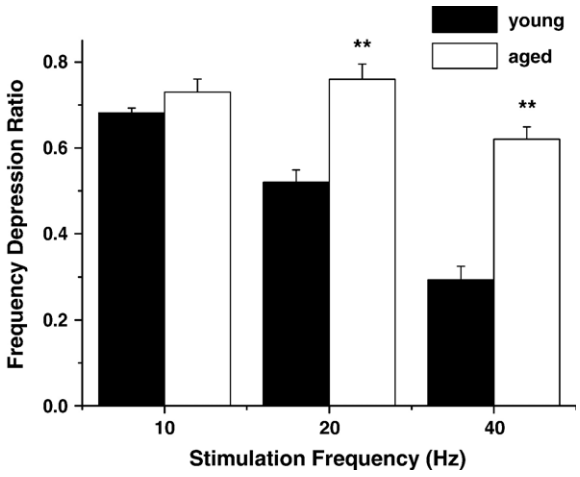

Fig. 4 – The difference of frequency depression of primary visual cortex at stimulus frequencies 20 and 40 Hz in young ($n=6$) and aged rats ($n=5$) is shown. Averaged relative amplitude of field potentials increased significantly in aged group during 20 and 40 Hz frequency stimuli. $^{**}P<0.01$; Mann–Whitney *U* test.

2.4. *Short-term synaptic plasticity*

Short-term synaptic plasticity, one type of activity-dependent synaptic plasticity, provides an automatic, dynamic gain-control mechanism (Abbott et al., 1997) and affects some of the specific temporal-filtering properties of the visual cortex (Chance et al., 1998). To assess age-related variability in short-term plasticity, we investigated the synaptic plasticity of young and aged rats by using paired-pulse stimulus and frequency stimulus (see Experimentalprocedures).

In general, shorter paired-pulse stimulus interval induces stronger depression (Jia et al., 2004). We detected a weak depression of the second field potential at interstimulus intervals of up to 1000 ms in all groups. Our results indicate a significant decrease in paired-pulse depression (PPD) at all stimulus intervals in aged rats, compared to young rats (Fig. 3).

To investigate the short-term plasticity induced by the steady-state behavior of synaptic transmission, we used the pulses stimulation of 10, 20 and 40 Hz. The result presented compares the frequency-dependent depression ratios in young and aged rats (Fig. 4). The frequency-dependent depression decreased significantly in aged rats compared with the ratios in young rats tested at frequencies of 20 Hz and 40 Hz ($P<0.01$).

3. Discussion

We found that neurons located in the visual cortex of aged rats show significantly increased adaptation to flash stimuli, decreased signal-to-noise ratio and prolonged onset latency compared with those in young rats. The enhanced adaptation in aged rats suggests that neurons easily "fatigue" in older brains compared to younger brains. The decreased signal-to-noise ratio in aged rats indicates a decreased ability to extract a sensory signal from the noisy background. This is likely the underlying mechanism of reduced sensitivity in old animals. Prolonged onset latency implies the degradation of the information processing rate within visual cortex, contributing to the signal processing decline observed during aging.

Although Peters et al (1997) showed no indication of declines in thickness, volume, or number of neurons in aged striate cortex of monkey (Peters et al., 1997), the morphological plasticity of synapses appears to be seriously impaired, including the number, size and surface contact area of the synaptic junctions in aged rodent and human brains (Bertoni-Freddari et al., 1988). The density of synapses in primary visual cortex is also decreased in aged rats (Connor et al., 1981). This decrease in the number of synaptic junctions might be the basis of the increased adaptation in aged rats, especially at frequencies over 4 Hz.

In addition, morphological results indicate a small decline in the white matter volume of aged human brains (Pakkenberg and Gundersen, 1997). There were also reported large losses of axonal myelin sheath in different layers of primary visual cortex of old monkeys (Peters et al., 2000; Peters et al., 2001; Peters, 2002). These results suggest that neural cells, the myelinating oligondendroglia in particular, might be vulnerable to age-related changes. Moreover, recent work suggests that changes in dendritic tree morphology and density of synapses could possibly explain the reduced stimulus selectivity, and that lowered conductance of axons might result from alterations of their myelin sheaths (Peters, 2002; Duan et al., 2003). This may be the underlying mechanism accounting for the prolonged onset latencies we observed in this study. Furthermore, the prolonged visual onset latencies might be necessary to compensate for decreased levels of transmitter release.

In agreement with findings in senescent monkeys (Schmolesky et al., 2000; Wang et al., 2005), we found significantly increased spontaneous activity in aged rats. The declining function of cortical inhibitory systems could explain the increased spontaneous activity we observed. Consistent with our previous work in old cats, the signal-to-noise ratio – which relates to the detection capability of sensory neurons – is significantly decreased with aging (Hua et al., 2006). Schmolesky et al (2000) suggested that the decrease of GABAergic inhibition system in old monkey cortex could account for many of the functional declines they observed. Leventhal et al (2003) showed that GABA and agonists of $GABA_A$ receptors significantly improve the function of V1 neurons in old macaque monkeys. Moreover, a number of other studies also support the conclusion that there is a weakness of GABAergic inhibition in the cortex of old animals (Post-Munson et al., 1994; Dustman et al., 1996). Therefore, reduced GABAergic inhibition in old animals might be a reasonable explanation for the decline of cortical functions during aging. Controversially, Mendelson reported no significant difference in average onset latency and spontaneous activity of the cells in young and old rats' visual cortex (Mendelson and Wells, 2002). Our previous work in the cat suggests that urethane anesthesia has a considerably mild effect on neuronal response properties (Hua et al., 2006). In contrast to urethane few studies have investigated the effects of Equithesan on neuronal response properties. The discrepancies between our results and Mendelson's may be due to differences in the visual stimulation parameters and/or the use of different anesthetics (Mendelson's rats were anaesthetized with Equithesan whereas ours were anaesthetized with urethane).

Previous work suggests that presynaptic Ca^{2+}-dependent neurotransmitter depletion and postsynaptic GABAergic inhibition may be crucial for short-term synaptic depression in the geniculo-cortical pathway (Jia et al., 2004). If there were a reduction of synaptic junctions and a subsequent impairment in inhibitory system function in aging, then the short-term synaptic plasticity should also be impaired. Our findings demonstrate significantly decreased paired-pulse depression and frequency depression at 20 and 40 Hz of geniculo-cortical pathway in aged rats. Hence, the impairment of short-term synaptic plasticity in aged rats might also be induced by the degradation of GABAergic system. This result is consistent with the hypothesis that reductions in GABA-mediated cortical inhibition contribute to the degradation of cortical function that accompanies old age (Leventhal et al., 2003).

Several possibilities accounting for the functional degradation of neurons in visual cortex exist. First, there were other inhibitory pathways, such as the serotonergic, cholinergic, dopaminergic and noradrenergic system might be involved (Scarpace and Abrass, 1988; Waterhouse et al., 1990; Amenta et al., 1991; Bigham and Lidow, 1995). Second, a reduction in GABAergic inhibition could result from either a decreased

expression of GABA receptors or from a reduced release of GABA transmitter 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 $GABA_A$ receptors ($\alpha 1$, $\gamma 2$ and $\beta 2/3$) remained almost unchanged but the corresponding mRNAs exhibited significant age dependent decreases (Gutierrez et al., 1997). Finally, an age-related change in interactions between intracortical excitation and inhibition systems can not be ruled out (Cepeda et al., 1996; Matsuyama et al., 1997). Further studies are necessary to elucidate these mechanisms.

In summary, our results, together with those of previous studies, suggest that the functional declines in aged animals are likely the result of several factors, such as the impairment of inhibitory GABAergic system, the decrease of effective synaptic junctions and the loss of myelin sheaths of axons in visual system. These functional declines with aging are generalized in mammals. The underlying mechanism of the effect of aging on the visual cortex is quite complex, and much remains to be investigated.

4. Experimental procedure

4.1. *Subjects*

Six male 3- to 4-month-old and five male 23- to 25-month-old Long–Evans rats were used. All rats were given food and water *ad libitum*. According to previous research (Mendelson and Wells, 2002), our 23- to 25-month-old rats could be considered as aged whereas the 3- to 4-month-old rats as young. All rats were obtained from the Laboratory Animal Center, University of Science and Technology of China. All animal treatments were strictly in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Animals' eyes were checked regularly with an ophthalmoscope to ensure that they were free of cataracts. Only those animals with clear optics were used in the study.

4.2. *Preparation for recording*

Rats were anaesthetized with urethane (20%, 1.2 g/kg, i.p.) and then mounted in a stereotaxic apparatus. A craniotomy was performed over the visual cortex (approximately 7.0–8.0 mm posterior to bregma, 3.0–4.0 mm lateral to the midline for primary visual cortex and 3.0–4.0 mm posterior to bregma, 3.0–4.0 mm lateral to the midline for LGN). Dura mater was dissected away and the cortex was bathed with silicone oil to prevent from drying out and to reduce pulsations. Glycerine was administered periodically to prevent the cornea from drying out. Body temperature was maintained at 37.0±0.2 °C by temperature controller.

4.3. *Data collection and analysis*

4.3.1. *Extracellular single-unit recording, data collection and analysis*

Flash stimuli were used to investigate the adaptation of the cells in visual cortex. The stimulus was presented by a light-emitting diode (LED) located 1in front of the eye. Twenty stimuli delivered at frequencies of 1, 2,4 and 8 Hz were used for our adaptation studies because cells of aged rats display a critical flicker frequency (CFF) threshold about 7 Hz (Mendelson and Wells, 2002). Extracellular action potentials of neurons were recorded with glass electrodes filled with NaCl (2 M), having impedances of 4.0–5.0 MΩ.

Poststimulus time histograms (PSTHs) were constructed as the average number of evoked spikes following stimulus presentation. The evoked spikes of every stimulus in twenty stimuli were counted. The adaptation index (AI) on different frequencies was measured as the ratio of the average of the last five evoked response spikes in the plateau (spontaneous activity not subtracted) to the average of the first and second evoked response spikes.

The signal-to-noise ratio was defined as the ratio between the cell's visually evoked response and the cell's spontaneous response (Schmolesky et al., 2000). Visually evoked activity and spontaneous firing rate were quantified as follows: the spontaneous firing rate was calculated for 20 s before flashing stimulus while the environment luminance on the cornea was 0.05 lx. The evoked responses were measured as the average of the first five stimulus-evoked spikes to the neuron's optimal response frequency.

Finally, visual stimuli-evoked onset latency responses were determined. Onset latency response is defined as the first response that was twice the mean spontaneous rate and which occurred immediately after the onset of a single flashing pulse (Mendelson and Wells, 2002). Neuronal activity was collected using the IGOR programming environment (Wavemetrics, Lake Oswego, OR). Evoked action potentials were digitized (National Instruments) by routines written in the IGOR programming environment (Wavemetrics, Lake Oswego, OR) and stored in a computer for off-line analysis.

4.3.2. *Field potential recording, data collection and analysis*

Paired-pulse depression (PPD) was investigated by stimulating the LGN using two electrical pulses separated by interstimulus intervals ranging from 25 to 1000 ms (25, 50, 100, 200, 500, 700 and 1000 ms). Intervals between pairs of stimuli were at least 30 s. Optimal stimulus intensity was determined by running a full input–output series at the beginning of recording, and a stimulation intensity yielding 50–60% of maximum was selected for the experiment. The PPD ratio was measured as the size of the second postsynaptic potential (PSP) amplitude relative to the first PSP amplitude with paired-pulse stimulation (Jia et al., 2004). Saline filled, glass recording electrodes (2–3 MΩ impedance) were used to record neuronal activity.

Trains of fifteen stimuli delivered at 10, 20 and 40 Hz were used to study the short-term synaptic plasticity. Intervals between trains of stimuli were at least 60 seconds. The depression evoked by a train of pulses is called frequency-dependent depression. The frequency-dependent depression ratio was expressed as the averaged amplitude of the last three PSP relative to the amplitude of first one.

Data are presented as means±standard error of means (SEM). Statistical significance was estimated by *t*-test and Mann–Whitney *U* test analysis.

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REFERENCES

Abbott, L.F., Varela, J.A., Sen, K., Nelson, S.B., 1997. Synaptic depression and cortical gain control. Science 275, 220–224.

Ahmad, A., Spear, P.D., 1993. Effects of aging on the size, density, and number of rhesus monkey lateral geniculate neurons. J. Comp. Neurol. 334, 631–643.

Amenta, F., Zaccheo, D., Collier, W.L., 1991. Neurotransmitters, neuroreceptors and aging. Mech. Ageing Dev. 61, 249–273.

Baracat, B., Marquie, J.C., 1992. Age differences in sensitivity, response bias, and reaction time on a visual discrimination task. Exp. Aging Res. 18, 59–66.

Bertoni-Freddari, C., Meier-Ruge, W., Ulrich, J., 1988. Quantitative morphology of synaptic plasticity in the aging brain. Scanning Microsc. 2, 1027–1034.

Bigham, M.H., Lidow, M.S., 1995. Adrenergic and serotonergic receptors in aged monkey neocortex. Neurobiol. Aging 16, 91–104.

Cepeda, C., Li, Z., Levine, M.S., 1996. Aging reduces neostriatal responsiveness to N-methyl-D-aspartate and dopamine: an in vitro electrophysiological study. Neuroscience 73, 733–750.

Chance, F.S., Nelson, S.B., Abbott, L.F., 1998. Synaptic depression and the temporal response characteristics of V1 cells. J. Neurosci. 18, 4785–4799.

Connor, J.R., Diamond, M.C., Connor, J.A., Johnson, R.E., 1981. A Golgi study of dendritic morphology in the occipital cortex of socially reared aged rats. Exp. Neurol. 73, 525–533.

Duan, H., Wearne, S.L., Rocher, A.B., Macedo, A., Morrison, J.H., Hof, P.R., 2003. Age-related dendritic and spine changes in corticocortically projecting neurons in macaque monkeys. Cereb. Cortex 13, 950–961.

Dustman, R.E., Emmerson, R.Y., Shearer, D.E., 1996. Life span changes in electrophysiological measures of inhibition. Brain Cogn. 30, 109–126.

Elliott, D., Whitaker, D., MacVeigh, D., 1990. Neural contribution to spatiotemporal contrast sensitivity decline in healthy ageing eyes. Vision Res. 30, 541–547.

Gutierrez, A., Khan, Z.U., Miralles, C.P., Mehta, A.K., Ruano, D., Araujo, F., Vitorica, J., De Blas, A.L., 1997. GABAA receptor subunit expression changes in the rat cerebellum and cerebral cortex during aging. Brain Res. Mol. Brain Res. 45, 59–70.

Hua, T., Li, X., He, L., Zhou, Y., Wang, Y., Leventhal, A.G., 2006. Functional degradation of visual cortical cells in old cats. Neurobiol. Aging 27, 155–162.

Jia, F., Xie, X., Zhou, Y., 2004. Short-term depression of synaptic transmission from rat lateral geniculate nucleus to primary visual cortex in vivo. Brain Res. 1002, 158–161.

Kim, C.B., Tom, B.W., Spear, P.D., 1996. Effects of aging on the densities, numbers, and sizes of retinal ganglion cells in rhesus monkey. Neurobiol. Aging 17, 431–438.

Kline, D.W., Schieber, F., Abusamra, L.C., Coyne, A.C., 1983. Age, the eye, and the visual channels: contrast sensitivity and response speed. J. Gerontol. 38, 211–216.

Kline, D.W., Culham, J.C., Bartel, P., Lynk, L., 2001. Aging effects on Vernier hyperacuity: a function of oscillation rate but not target contrast. Optom. Vis. Sci. 78, 676–682.

Leventhal, A.G., Wang, Y., Pu, M., Zhou, Y., Ma, Y., 2003. GABA and its agonists improved visual cortical function in senescent monkeys. Science 300, 812–815.

Matsuyama, S., Nei, K., Tanaka, C., 1997. Regulation of GABA release via NMDA and 5-HT1A receptors in guinea pig dentate gyrus. Brain Res. 761, 105–112.

Mendelson, J.R., Wells, E.F., 2002. Age-related changes in the visual cortex. Vision Res. 42, 695–703.

Nomura, H., Ando, F., Niino, N., Shimokata, H., Miyake, Y., 2003. Age-related change in contrast sensitivity among Japanese adults. Jpn. J. Ophthalmol. 47, 299–303.

Owsley, C., Sekuler, R., Boldt, C., 1981. Aging and low-contrast vision: face perception. Investig. Ophthalmol. Vis. Sci. 21, 362–365.

Pakkenberg, B., Gundersen, H.J., 1997. Neocortical neuron number in humans: effect of sex and age. J. Comp. Neurol. 384, 312–320.

Peters, A., 2002. The effects of normal aging on myelin and nerve fibers: a review. J. Neurocytol. 31, 581–593.

Peters, A., Nigro, N.J., McNally, K.J., 1997. A further evaluation of the effect of age on striate cortex of the rhesus monkey. Neurobiol. Aging 18, 29–36.

Peters, A., Moss, M.B., Sethares, C., 2000. Effects of aging on myelinated nerve fibers in monkey primary visual cortex. J. Comp. Neurol. 419, 364–376.

Peters, A., Sethares, C., Killiany, R.J., 2001. Effects of age on the thickness of myelin sheaths in monkey primary visual cortex. J. Comp. Neurol. 435, 241–248.

Post-Munson, D.J., Lum-Ragan, J.T., Mahle, C.D., Gribkoff, V.K., 1994. Reduced bicuculline response and GABAA agonist binding in aged rat hippocampus. Neurobiol. Aging 15, 629–633.

Ross, J.E., Clarke, D.D., Bron, A.J., 1985. Effect of age on contrast sensitivity function: uniocular and binocular findings. Br. J. Ophthalmol. 69, 51–56.

Satorre, J., Cano, J., Reinoso-Suarez, F., 1985. Stability of the neuronal population of the dorsal lateral geniculate nucleus (LGNd) of aged rats. Brain Res. 339, 375–377.

Scarpace, P.J., Abrass, I.B., 1988. Alpha- and beta-adrenergic receptor function in the brain during senescence. Neurobiol. Aging 9, 53–58.

Schefrin, B.E., Tregear, S.J., Harvey Jr., L.O., Werner, J.S., 1999. Senescent changes in scotopic contrast sensitivity. Vision Res. 39, 3728–3736.

Schmolesky, M.T., Wang, Y., Pu, M., Leventhal, A.G., 2000. Degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys. Nat. Neurosci. 3, 384–390.

Tran, D.B., Silverman, S.E., Zimmerman, K., Feldon, S.E., 1998. Age-related deterioration of motion perception and detection. Graefes Arch. Clin. Exp. Ophthalmol. 236, 269–273.

Uylings, H.B., de Brabander, J.M., 2002. Neuronal changes in normal human aging and Alzheimer's disease. Brain Cogn. 49, 268–276.

Wang, Y., Zhou, Y., Ma, Y., Leventhal, A.G., 2005. Degradation of signal timing in cortical areas V1 and V2 of senescent monkeys. Cereb. Cortex 15, 403–408.

Waterhouse, B.D., Azizi, S.A., Burne, R.A., Woodward, D.J., 1990. Modulation of rat cortical area 17 neuronal responses to moving visual stimuli during norepinephrine and serotonin microiontophoresis. Brain Res. 514, 276–292.

Weale, R.A., 1975. Senile changes in visual acuity. Trans. Ophthalmol. Soc. U.K. 95, 36–38.

West, M.J., 1993. Regionally specific loss of neurons in the aging human hippocampus. Neurobiol. Aging 14, 287–293.