available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Aging affects response variability of V1 and MT neurons in rhesus monkeys

Yun Yang[a], Zhen Liang[a], Guangxing Li[a], Yongchang Wang[a,b], Yifeng Zhou[a,c,*]

[a]Vision Research Laboratory, School of Life Science, University of Science and Technology of China, Hefei, Anhui 230027, PR China
[b]Department of Neurobiology and Anatomy, School of Medicine, University of Utah, Salt Lake City, UT 84132, USA
[c]State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Science, Beijing 100101, PR China

ARTICLE INFO

Article history:
Accepted 10 April 2009
Available online 17 April 2009

Keywords:
Aging
Macaque
Response variability
MT
V1

ABSTRACT

Visual function declines with age. Much of the decline may result from functional degradation in central visual areas. To investigate the physiological mechanisms underlying visual function declines during normal aging, we compared the response variability of cells in primary visual cortex (V1) and middle temporal visual area (MT) in young adult and very old macaque monkeys using single-neuron in vivo electrophysiology. We found that mean response and response variability in both V1 and MT of old monkeys are significantly higher than in young monkeys. And response-to-noise ratio in old monkeys is significantly lower than in young ones. The results are consistent with an age-related degradation of inhibitory intracortical circuits. The neural changes described here could contribute to declines in visual function during senescence.

1. Introduction

Human visual abilities decline with age. Psychological experiments have shown that aged humans exhibit decreased acuity, contrast sensitivity, binocular summation and symmetry perception (Faubert, 2002; Sekuler and Sekuler, 2000; Spear, 1993). Senescent humans are also less efficient at tasks requiring orientation discrimination and/or motion percept (Bennett et al., 2007; Betts et al., 2007; Norman et al., 2003; Snowden and Kavanagh, 2006). Ocular decline in the elderly alone cannot account for all of the changes that occur with normal aging (Ball and Sekuler, 1986; Bennett et al., 1999; Herbert et al., 2002; Sekuler et al., 2000). Therefore, impaired visual performance in aged human must be, at least in part, due to degeneration and/or dysfunction in central visual areas.

In order to relate single cortical cell properties to discrimination behavior one needs to know two factors: the difference in the response to each different stimulus (signal) and the variability of the single cell responses (noise). If aging affects either of the factors, it could affect the performance of sensory neurons in a way that might contribute to or account for the deficiency we observed in elderly humans.

The effects of aging on the first factor, the signal, have been examined in several studies that have measured how aging affects the mean rate of firing elicited by a variety of stimuli. It has been shown that aging increases responsiveness to optimal and non-optimal stimuli disproportionally and reduces stimulus selectivities of single neurons in visual cortical areas (Hua et al., 2006; Leventhal et al., 2003; Liang et al., 2008; Schmolesky et al., 2000; Yang et al., 2008b; Yu et al., 2006).

* *Corresponding author*. School of Life Science, University of Science and Technology of China, Hefei, Anhui 230027, PR China. Fax: +86 551 3607014.
E-mail address: zhouy@ustc.edu.cn (Y. Zhou).

0006-8993/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainres.2009.04.015

However, the effects of aging on the second aspect of neuronal responses, the noise, have so far not been examined. The responses of cortical sensory neurons are extremely variable, with the number of spikes elicited by identical stimuli varying significantly from trial to trial (Nover et al., 2005; Snowden et al., 1992; Tolhurst et al., 1981, 1983; Vogels et al., 1989). This variability is most often interpreted as 'noise' and could be detrimental to the sensory system (Carandini, 2004; Machens et al., 2003; Sadeghi et al., 2007; Shadlen and Newsome, 1995; Stein et al., 2005). Theoretical studies have suggested that a high level of noise would limit the performance of neural encoding (Roddey et al., 2000; Sadeghi et al., 2007). Therefore, it is possible that aging affects the response variability of cortical neurons and in turn disturbs visual information processing.

To address this, we used extracellular single-neuron recording techniques to examine the response variability of V1 and MT cells in old rhesus monkeys. The results provide evidence for a significant degradation of function in areas V1 and MT of old monkeys.

2. Results

Variability of visually evoked responses was measured in a total of 79 V1 cells (23 units from *young monkey* 1, 27 from *young monkey* 2, and 29 from *young monkey* 3) and 93 MT cells (26 units from *young monkey* 1, 35 from *young monkey* 2, and 32 from *young monkey* 3) from three young monkeys and 71 V1 cells (22 units from *old monkey* 1, 18 from *old monkey* 2, 17 from *old monkey* 3 and 14 from *old monkey* 4) and 102 MT cells (19 units from *old monkey* 1, 28 from *old monkey* 2, 29 from *old monkey* 3 and 26 from *old monkey* 4) from four old monkeys. The mean number of trials for young and old monkeys does not significantly differ for V1 ($p=0.674$) and MT populations ($p=0.334$). The effect of aging is affected by the eccentricity of the display and the foveal vision may be affected more than the peripheral vision (Atchley and Andersen, 1998). So, all V1 cells studied here had receptive fields between 2 and 5° from the fovea. All MT cells studied had receptive fields within 15° from projection of the fovea, and most were within 8°.

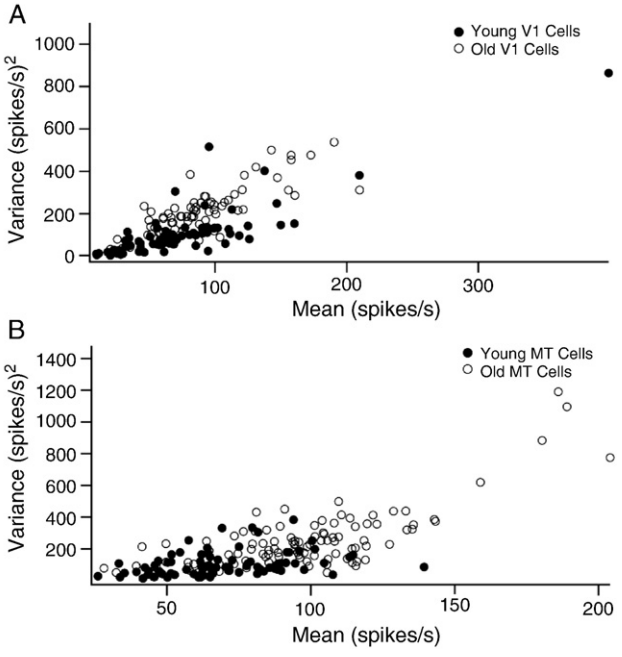

Fig. 1 – Scatter plot showing response variance against mean response of cells in cortical areas V1 (A) and MT (B) of young and old monkeys. Compared with cells in young monkeys, cells in old monkeys exhibit a larger response variance as well as an increased mean response ($p<0.001$ in both cases, Mann–Whitney test).

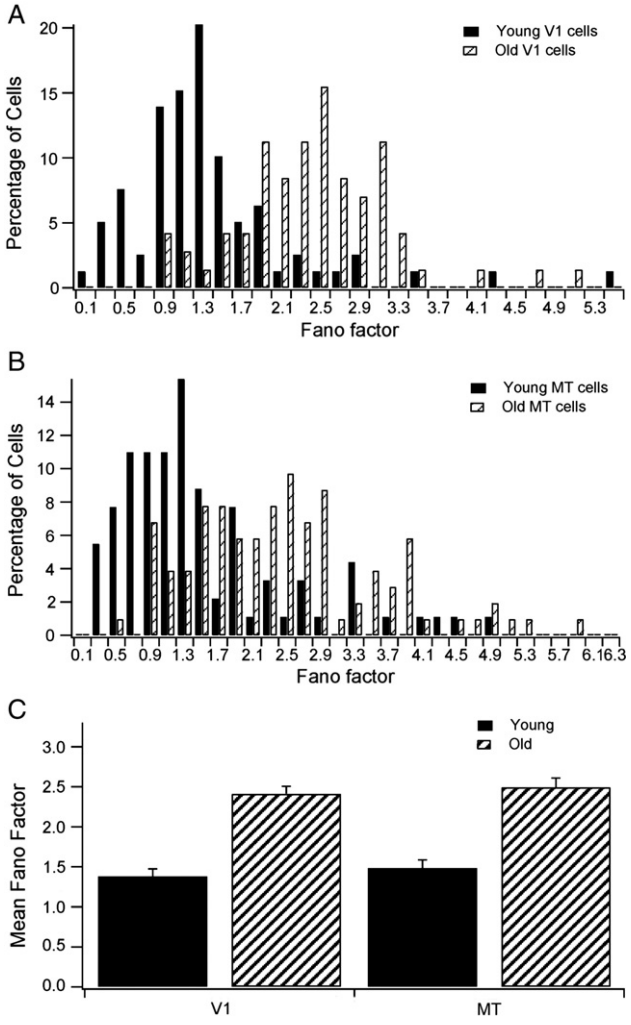

Fig. 2 – Variability of spike count for young and old populations. (A–B) Distribution of Fano factor (FF) of V1 and MT neurons for young and old monkeys is shown. (C) Mean FF of responses in old monkeys is significantly higher than in young monkeys for V1 ($p<0.001$, Mann–Whitney test) and MT ($p<0.001$) areas. Error bars represent SEM.

Fig. 1 shows that V1 and MT cells in old monkeys exhibited a larger response variance as well as a higher mean response than did cells in young monkeys ($p<0.001$ in both cases, Mann–Whitney test). In studies of the visual system, spike count variability is often quantified by the ratio of the variance to mean spike count, defined as the Fano factor (FF) (Kara et al., 2000). So, in the present study, we compared the values

of FFs of V1 and MT neurons in young and old monkeys. We pooled the data from all recordings to calculate the mean FFs for V1 and MT populations in young and old monkeys. No significant difference was found in the FF distribution of neurons between individuals of the same age group for both V1 and MT areas. The results are shown in Figs. 2A–C. The variability in old monkeys is significantly higher than in young monkeys both for V1 (mean FF=2.41 versus 1.38, $p<0.001$, Mann–Whitney test) and MT populations (mean FF=2.51 versus 1.47, $p<0.001$). It is worth noting that there is not any significance in the difference between the data from V1 and MT in young monkeys, which has been observed in previous studies and suggests that response variability may arise from mechanisms inherent in the cell itself (Shadlen and Newsome, 1998; Snowden et al., 1992).

The ability of one neuron to discriminate changes around a given stimulus can be estimated by a response-to-noise ratio (defined by the mean divided by the standard deviation (SD)) that relates the slope of the tuning curve to the SD of the responses (Butts and Goldman, 2006; McAdams and Maunsell, 1999). Because aging causes a significant increase in SD and response rate (Figs. 3A, B), it is natural to speculate how aging affects response-to-noise ratios in both V1 and MT. To address this, we also compared response-to-noise ratios for V1 and MT populations in young and old monkeys when the stimulus was set optimal. The results are shown in Figs. 3C, D. Response-to-noise ratio in old monkeys is significantly lower than in young monkeys for both V1 (mean response-to-noise ratio=6.33 versus 7.84, $p=0.001$, Mann–Whitney test, $p<0.001$) and MT (mean response-to-noise ratio=6.63 versus 7.91, $p<0.001$) populations.

3. Discussion

In the present study, we examined how aging affects the trial-by-trial variability of visually evoked responses across macaque V1 and MT and found that, for both V1 and MT populations, spike count variability in old monkeys is significantly higher than in young monkeys. Further, response-to-noise ratio in old animals is significantly lower than in young ones.

In our previous studies, we have measured spontaneous activity as noise and found increased spontaneous activity in old animals (Hua et al., 2006; Leventhal et al., 2003; Liang et al., 2008; Schmolesky et al., 2000; Wang et al., 2005; Yang et al., 2008a,b; Yu et al., 2006). Generally, spontaneous activity is a reasonable "noise" (Goldberg et al., 2004) and may reflect an intrinsic dynamical behavior of neural circuits (Anderson et al., 2000; Cossart et al., 2003; Kenet et al., 2003; Shu et al., 2003). However, spontaneous activity of neurons is mostly the activity that is measured when there is no external stimulus, and therefore usually no task is involved. Response variability is thought to be noise which comes from keeping the external

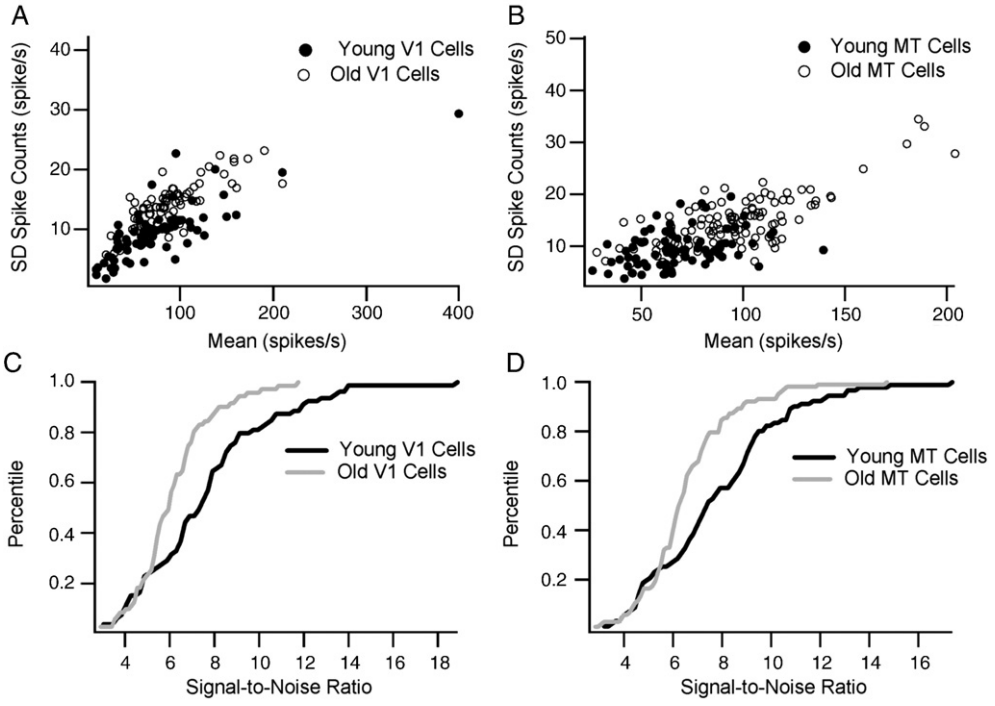

Fig. 3 – (A, B) Scatter plot showing standard variance (SD) against mean response of cells in cortical areas V1 and MT of young and old monkeys. Compared with cells in young monkeys, cells in old monkeys exhibit a larger SD as well as an increased mean response ($p<0.001$ in both cases, Mann–Whitney test). (C, D) Response-to-noise ratios of V1 and MT populations in young and old monkeys are plotted. This is a cumulative plot, showing the proportion of cells achieving a given response-to-noise ratio value, where solid gray and black lines represent the combined data of old and young monkeys. Old monkey cells showed decreased signal-to-noise ratios compared with young monkey cells for both V1 and MT ($p<0.001$ in both cases, Mann–Whitney test).

stimulus the same on multiple trials and may reflect inputs with reliable signals about differences. Mounting experimental evidence has demonstrated that spontaneous activity may have a significant effect on neuronal responses (Arieli et al., 1996; Azouz and Gray, 1999; Lampl et al., 1999; Pare et al., 1998) and spontaneous cortical states before the presentation of a stimulus have an impact on the cortical information processing at the time the stimulus is presented (Kenet et al., 2003; Ringach, 2003; Tsodyks et al., 1999). Thus, spontaneous activity and "noise" we defined in the present study are actually coupled.

Together with average firing rate, response variability allows tuning curves to be interpreted in terms of which stimuli would lead to most informative responses and is thought to play an important role in determining the encoding properties of sensory neurons (Butts and Goldman, 2006). It seems that high response variability would affect stimulus encoding and increase estimated discrimination thresholds from population responses (McAdams and Maunsell, 1999; Nover et al., 2005; Snowden et al., 1992). Previous studies have also indicated that high response variability would disrupt fine discrimination of sensory neurons (Butts and Goldman, 2006). The literature on aging has indicated that age-related deterioration in cognition function may be due to higher levels of neural noise and a fall in response-to-noise ratios (Bennett et al., 2007; Welford, 1984). Because V1 and MT are important sites which are thought to be intimately involved in the perception of orientation and motion (Born and Bradley, 2005; Hubel and Wiesel, 1968; Maunsell et al., 1990; Newsome et al., 1989; Vogels and Orban, 1991), abnormal response variability at the sites may contribute to these perceptual declines. Our results suggest that excessive response variability indeed does occur in V1 and MT of old monkeys.

So far the origin of response variability in the visual cortex remains unknown and it has generated explanations ranging from shorter refractory periods of cortical neurons (Kara et al., 2000) to a nonlinear transformation between inputs and firing rate of the neurons (Carandini, 2004). In vitro experiments suggest that the large variability does not have its origin in the neurons themselves, but is a property of intact cortical circuits (Holt et al., 1996). It is tempting to speculate that the increased response variability we observed may reflect the degeneration of cortical circuits through neuron death and/or synapse loss in old brains. It has been reported that the number of cortical neurons is minimally changed in aged macaque monkeys and humans (Morrison and Hof, 1997, 2007; Peters et al., 1998). Thus, changes in axonal morphology as well as changes in dendritic morphology are likely to be a significant contributor to age-associated extravagant irregularity we observed in the present study, which has been indicated in previous studies (Geinisman et al., 1995; Masliah et al., 1993).

The recurrent excitatory and inhibitory connections between and within layers of the cerebral cortex are fundamental to the operation of local cortical circuits (Douglas and Martin, 2004; Markram et al., 2004). It has been reported that the level of response variability may result from the balance of excitation and inhibition in the output layer (Shadlen and Newsome, 1998; Stein et al., 2005; Vreeswijk and Sompolinsky, 1997). Excitation needs to be balanced with inhibition to maintain a proper dynamic range of response. It seems that the results reported here may reflect the degree of imbalance between excitation and inhibition. In fact, many previous studies have suggested a degradation of inhibitory intracortical circuits in old human and non-human primate cortex (Bennett et al., 2007; Betts et al., 2005, 2007; Leventhal et al., 2003; Schmolesky et al., 2000; Wang et al., 2005; Yu et al., 2006). Studies of human visual cortex have shown that L-glutamic acid decarboxylase (GAD), an enzyme needed to synthesize the inhibiting transmitter GABA, is reduced during aging (McGeer and McGeer, 1976). Therefore, we assume that a degradation of GABA system in V1 and MT may be a major reason for both increased response variability and decreased response-to-noise ratio in old monkeys.

Previous studies have found that response variability is much lower in alert animals than in anesthetized animals (Gur et al., 1997; Gur and Snodderly, 2006). It is a concern that differential effects of anesthesia upon cortical function in young and old monkeys could impact our results. So, using the anesthetized preparation for studying response variability may not be a good choice. However, it is hard to train old animals to perform visual tasks under the present experimental conditions. The shortage could be explained by (1) degraded rewarding system of old monkeys and (2) relatively poor learning ability. In fact, in the present study we paid special attention to maintain comparable levels of anesthesia in young and old monkeys (Wang et al., 2005, 2008a,b). Previous studies have shown that heart rate, expired pCO_2 and ECG are good indicators of anesthetic depth (McKelvey and Hollingshead 2000; Villeneuve and Casanova 2003). These indicators were monitored throughout the experiment to assess the level of anesthesia. We have also recorded the response of individual cells while systematically varying anesthetic and paralytic levels. We have just found that changing the levels of anesthesia similarly affects the responsiveness of V1 and MT cells in both young and old groups. Problems with anesthesia in old animals have been minimized as possible.

To conclude, the results of the present study provide evidence that response variability in both macaque V1 and MT is significantly affected by aging. The results may reflect some degree of imbalance between excitation and inhibition within old brains and contribute to perceptual declines in visual tasks in old primates. Further studies of the affects of age upon higher visual cortex will help clarify the neural mechanisms underlying the deficits in higher order visual function that accompany normal aging.

4. Experimental procedures

4.1. *Animal preparation and electrophysiology*

All experimental followed protocols were consistent with the Society for Neuroscience and National Institute of Health guidelines for the humane use and care of animals. The experiments described here were approved by the University of Utah Institutional Animal Care and Use Committee.

Subjects for this study were two groups of rhesus monkeys (*Macaca mulatta*). Young adult monkeys ($n=3$, male) were 5–9 years old and weighed 3.6–6.2 kg. Old monkeys ($n=4$, male)

were 23–31 years old and weighed 5.2–8.7 kg. According to a life-span analysis of rhesus macaques housed at the Yerkes Primate Center, our 23–31 year old monkeys can be considered old and monkeys of these ages correspond to 70–90 year old humans, whereas the 5–9 year old monkeys are at an age that is considered sexually mature (Tigges et al., 1988). Cycloplegic retinoscopy was performed for each monkey according to a similar analysis by Fernandes et al. (2003) before the experiment. Monkeys were well examined ophthalmoscopically and had no apparent optical or retinal problems that would impair visual function. Retinal blood vessels, lens clarity and the maculae all appeared to be within normal limits.

The techniques used in our laboratory have been reported in detail elsewhere (Leventhal et al., 1995, 2003; Schmolesky et al., 2000). Subjects were sedated with ketamine HCl (10 mg/kg, i.m., Ketalar, Parke-Davis, Morris Plains, NJ, USA) and then anesthetized with halothane (5%, Halocarbon Laboratories, River Edge, NJ, USA) in a 70:30 mixture of N_2O:O_2. Intravenous and tracheal cannulae were inserted. Animals were placed in a stereotaxic apparatus, and all pressure points and incisions were infiltrated with lidocaine HCl (2%). A mixture of D-tubocurarine (0.4 mg/kg/h, Sigma, St. Louis, MO, USA) and gallamine trithiodide (7 mg/kg/h, Sigma) was infused intravenously to induce and maintain paralysis. Monkeys were ventilated, and anesthesia was maintained with a mixture of N_2O (70%) and O_2 (30%) and halothane (0.25–1.0%) as needed. Expired pCO_2 was maintained at approximately 4%. Body temperature was maintained at 38 °C with a heating pad. Heart rate, ECG and cortical electrical activity were monitored throughout the experiment to assess the level of anesthesia. Animals were studied for as long as stable, reliable recording was possible (3–5 days). The locations of the optic discs and foveae were determined repeatedly during the course of each recording period. We routinely monitored the normality of the optics and retinal vasculature in old and young animals. No visible deterioration in optics occurred during the experimental period. The proportion of cells meeting the data inclusion criteria did not appear to decrease over time.

After the animal was placed on life support, the level of anesthesia was adjusted so that all vital signs were comparable in young and old animals. The eyes were protected from desiccation with contact lenses. Spectacle lenses and artificial pupils were used when needed. The locations of the optic discs and foveae were determined repeatedly during the course of each recording session. Electrode penetrations were advanced using a hydraulic microdrive (David Kopf Instruments, Tujunga, California) at an angle of 20° from horizontal. MT area is located through a craniotomy centered 16 mm lateral to the midline and 4 mm posterior to the lunate sulcus. For each recording, the size of the stimulus was determined to approximate the size of the classical receptive field by hand-mapping. Action potentials of isolated MT and V1 units were recorded using glass or glass-coated tungsten microelectrodes with impedances of 1–3 MΩ. The signals were then amplified and converted to standard pulses that were collected by a computer. Recordings were made in MT during the first two or three days for each monkey, and then in V1. The data were collected from three or four penetrations in each monkey. All cells studied had receptive fields within 25° from the projection of the fovea, and most were within 15°.

4.2. *Visual stimulation*

When a single unit was isolated according to principal component analysis, the eye affiliation was determined and all stimuli were presented monocularly to the dominant eye. All visual stimuli were displayed at a resolution of 1024×768 pixels and frame rate of 100 Hz on a 17 in. Sony Multiscan G220 monitor (Sony Corporation, Tokyo, Japan). The center of the video monitor was placed 57 cm from the animals' eyes. The program to generate the stimulus was written in MATLAB, using the extensions provided by the high-level Psychophysics Toolbox (Brainard, 1997) and low-level Video Toolbox (Pelli, 1997). The mean luminance of the display was 38.7 cd/m^2, and stimulus contrast was defined as the difference between the maximum and minimum luminance divided by their sum. All cells were driven by luminance modulated sine-wave grating moving steadily across the receptive field. For each neuron, we chose the dominant eye and covered the other with an opaque occluder. Then we recorded a series of tuning curves to determine the optimal orientation (for V1 cells), direction, spatial and temporal frequency, position, and size of a drifting sine-wave grating. The contrast of each stimulus was close to 100%. We measured neuronal responses during the presentation of the optimal stimulus for 2 s. Optimal stimulus here means the drifting sine-wave grating when its orientation (for V1 cells), direction, spatial and temporal frequency, position, and size were all set optimal. We collected 6–12 repetitions for each neuron and calculated the average numbers of spikes, standard deviation (SD) and variance.

4.3. *Data collection and analysis*

After the response of an isolated cell was amplified with a microelectrode amplifier (×1000, DAGAN 2400A, Dagan Corporation, Minneapolis, MN, USA), the amplified response was fed into an oscilloscope, an audio monitor, and was digitized using an acquisition board (National Instruments, USA) controlled by IGOR software (WaveMetrics, USA). The responses of the cells to the drifting stimuli were stored in the computer for offline analysis.

Statistical comparisons between young and old monkeys' data were carried out using Mann–Whitney *U* test.

Acknowledgments

This work was supported by grants from the Natural Science Foundation of China (30520120072, Y.Z.), NIH/NIA R01 AG 17922 (A.G.L.), and National Basic Research Program of China (2005CB522800).

REFERENCES

Anderson, J., et al., 2000. Stimulus dependence of two-state fluctuations of membrane potential in cat visual cortex. Nat. Neurosci. 3, 617–621.

Arieli, A., et al., 1996. Dynamics of ongoing activity: explanation of the large variability in evoked cortical responses. Science 273, 1868–1871.

Atchley, P., Andersen, G.J., 1998. The effect of age, retinal eccentricity, and speed on the detection of optic flow components. Psychol. Aging 13, 297–308.
Azouz, R., Gray, C.M., 1999. Cellular mechanisms contributing to response variability of cortical neurons in vivo. J. Neurosci. 19, 2209–2223.
Ball, K., Sekuler, R., 1986. Improving visual perception in older observers. J. Gerontol. 41, 176–182.
Bennett, P.J., et al., 1999. Effects of aging on calculation efficiency and equivalent noise. J. Opt. Soc. Am. A, Opt. Image Sci. Vis. 16, 654–668.
Bennett, P.J., et al., 2007. The effects of aging on motion detection and direction identification. Vis. Res. 47, 799–809.
Betts, L.R., et al., 2005. Aging reduces center-surround antagonism in visual motion processing. Neuron 45, 361–366.
Betts, L.R., et al., 2007. The effects of aging on orientation discrimination. Vis. Res. 47, 1769–1780.
Born, R.T., Bradley, D.C., 2005. Structure and function of visual area MT. Annu. Rev. Neurosci. 28, 157–189.
Brainard, D.H., 1997. The Psychophysics Toolbox. Spat. Vis. 10, 433–436.
Butts, D.A., Goldman, M.S., 2006. Tuning curves, neuronal variability, and sensory coding. PLoS Biol. 4, e92.
Carandini, M., 2004. Amplification of trial-to-trial response variability by neurons in visual cortex. PLoS Biol. 2, E264.
Cossart, R., et al., 2003. Attractor dynamics of network UP states in the neocortex. Nature 423, 283–288.
Douglas, R.J., Martin, K.A., 2004. Neuronal circuits of the neocortex. Annu. Rev. Neurosci. 27, 419–451.
Faubert, J., 2002. Visual perception and aging. Can. J. Exp. Psychol. 56, 164–176.
Fernandes, A., et al., 2003. Ocular measurements throughout the adult life span of rhesus monkeys. Invest. Ophthalmol. Vis. Sci. 44, 2373–2380.
Geinisman, Y., et al., 1995. Hippocampal markers of age-related memory dysfunction: behavioral, electrophysiological and morphological perspectives. Prog. Neurobiol. 45, 223–252.
Goldberg, J.A., et al., 2004. Patterns of ongoing activity and the functional architecture of the primary visual cortex. Neuron 42, 489–500.
Gur, M., Snodderly, D.M., 2006. High response reliability of neurons in primary visual cortex (V1) of alert, trained monkeys. Cereb. Cortex 16, 888–895.
Gur, M., et al., 1997. Response variability of neurons in primary visual cortex (V1) of alert monkeys. J. Neurosci. 17, 2914–2920.
Herbert, A.M., et al., 2002. Aging and bilateral symmetry detection. J. Gerontol. B Psychol. Sci. Soc. Sci. 57, P241–P245.
Holt, G.R., et al., 1996. Comparison of discharge variability in vitro and in vivo in cat visual cortex neurons. J. Neurophysiol. 75, 1806–1814.
Hua, T.M., et al., 2006. Functional degradation of visual cortical cells in old cats. Neurobiol. Aging 27, 155–162.
Hubel, D.H., Wiesel, T.N., 1968. Receptive fields and functional architecture of monkey striate cortex. J. Physiol. 195, 215–243.
Kara, P., et al., 2000. Low response variability in simultaneously recorded retinal, thalamic, and cortical neurons. Neuron 27, 635–646.
Kenet, T., et al., 2003. Spontaneously emerging cortical representations of visual attributes. Nature 425, 954–956.
Lampl, I., et al., 1999. Synchronous membrane potential fluctuations in neurons of the cat visual cortex. Neuron 22, 361–374.
Leventhal, A.G., et al., 1995. Concomitant sensitivity to orientation, direction, and color of cells in layers 2, 3, and 4 of monkey striate cortex. J. Neurosci. 15, 1808–1818.
Leventhal, A.G., et al., 2003. GABA and its agonists improved visual cortical function in senescent monkeys. Science 300, 812–815.
Liang, Z., et al., 2008. Aging affects the direction selectivity of MT cells in rhesus monkeys. Neurobiol. Aging, doi:10.1016/j.neurobiolaging.2008.06.013.
Machens, C.K., et al., 2003. Single auditory neurons rapidly discriminate conspecific communication signals. Nat. Neurosci. 6, 341–342.
Markram, H., et al., 2004. Interneurons of the neocortical inhibitory system. Nat. Rev. Neurosci. 5, 793–807.
Masliah, E., et al., 1993. Quantitative synaptic alterations in the human neocortex during normal aging. Neurology 43, 192–197.
Maunsell, J.H., et al., 1990. Magnocellular and parvocellular contributions to responses in the middle temporal visual area (MT) of the macaque monkey. J. Neurosci. 10, 3323–3334.
McAdams, C.J., Maunsell, J.H.R., 1999. Effects of attention on the reliability of individual neurons in monkey visual cortex. Neuron 23, 765–773.
McGeer, E., McGeer, P., 1976. In: Terry, R.D., Gershon, S. (Eds.), Neurobiol. Aging, pp. 389–403.
McKelvey, D., Hollingshead, J.W., 2000. Small Animal Anesthesia and Analgesia. 2nd ed. Mosby, Toronto.
Morrison, J.H., Hof, P.R., 1997. Life and death of neurons in the aging brain. Science 278, 412–419.
Morrison, J.H., Hof, P.R., 2007. Life and death of neurons in the aging cerebral cortex. Int. Rev. Neurobiol. 81, 41–57.
Newsome, W.T., et al., 1989. Neuronal correlates of a perceptual decision. Nature 341, 52–54.
Norman, J.F., et al., 2003. Aging and the perception of speed. Perception 32, 85–96.
Nover, H., et al., 2005. A logarithmic, scale-invariant representation of speed in macaque middle temporal area accounts for speed discrimination performance. J. Neurosci. 25, 10049–10060.
Pare, D., et al., 1998. Impact of spontaneous synaptic activity on the resting properties of cat neocortical pyramidal neurons in vivo. J. Neurophysiol. 79, 1450–1460.
Pelli, D.G., 1997. The VideoToolbox software for visual psychophysics: transforming numbers into movies. Spat. Vis. 10, 437–442.
Peters, A., et al., 1998. Feature article: are neurons lost from the primate cerebral cortex during normal aging? Cereb. Cortex 8, 295–300.
Ringach, D.L., 2003. Neuroscience — states of mind. Nature 425, 912–913.
Roddey, J.C., et al., 2000. Assessing the performance of neural encoding models in the presence of noise. J. Comput. Neurosci. 8, 95–112.
Sadeghi, S.G., et al., 2007. Neural variability, detection thresholds, and information transmission in the vestibular system. J. Neurosci. 27, 771–781.
Schmolesky, M.T., et al., 2000. Degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys. Nat. Neurosci. 3, 384–390.
Sekuler, A.B., et al., 2000. Effects of aging on the useful field of view. Exp. Aging Res. 26, 103–120.
Sekuler, R., Sekuler, A.B., 2000. Age-related changes, optical factors, and neural processes. Encyclopedia Psychol. 8, 180–183.
Shadlen, M.N., Newsome, W.T., 1995. Is there a signal in the noise? Curr. Opin. Neurobiol. 5, 248–250.
Shadlen, M.N., Newsome, W.T., 1998. The variable discharge of cortical neurons: implications for connectivity, computation, and information coding. J. Neurosci. 18, 3870–3896.
Shu, Y., et al., 2003. Barrages of synaptic activity control the gain and sensitivity of cortical neurons. J. Neurosci. 23, 10388–10401.
Snowden, R.J., Kavanagh, E., 2006. Motion perception in the ageing visual system: minimum motion, motion coherence, and speed discrimination thresholds. Perception 35, 9–24.
Snowden, R.J., et al., 1992. The response of neurons in areas V1 and MT of the alert rhesus monkey to moving random dot patterns. Exp. Brain Res. 88, 389–400.
Spear, P.D., 1993. Neural bases of visual deficits during aging. Vis. Res. 33, 2589–2609.

Stein, R.B., et al., 2005. Neuronal variability: noise or part of the signal? Nat. Rev. Neurosci. 6, 389–397.
Tigges, J.G., et al., 1988. Survival rate and life span of rhesus monkeys at the Yerkes Regional Primate Research Center. Am. J. Primatol. 15, 263–273.
Tolhurst, D.J., et al., 1983. The statistical reliability of signals in single neurons in cat and monkey visual cortex. Vis. Res. 23, 775–785.
Tolhurst, D.J., et al., 1981. The dependence of response amplitude and variance of cat visual cortical neurones on stimulus contrast. Exp. Brain Res. 41, 414–419.
Tsodyks, M., et al., 1999. Linking spontaneous activity of single cortical neurons and the underlying functional architecture. Science 286, 1943–1946.
Villeneuve, M.Y., Casanova, C., 2003. On the use of isoflurane versus halothane in the study of visual response properties of single cells in the primary visual cortex. J. Neurosci. Methods 129, 19–31.
Vogels, R., Orban, G.A., 1991. Quantitative study of striate single unit responses in monkeys performing an orientation discrimination task. Exp. Brain Res. 84, 1–11.
Vogels, R., et al., 1989. The response variability of striate cortical neurons in the behaving monkey. Exp. Brain Res. 77, 432–436.
Vreeswijk, C.v., Sompolinsky, H., 1997. Irregular firing in cortical circuits with inhibition/excitation balance. In: Bower, J. (Ed.), Computational Neuroscience Trends in Research, pp. 209–213.
Wang, Y., et al., 2005. Degradation of signal timing in cortical areas V1 and V2 of senescent monkeys. Cereb. Cortex 15, 403–408.
Welford, A.T., 1984. Between bodily changes and performance: some possible reasons for slowing with age. Exp. Aging Res. 10, 73–88.
Yang, Y., et al., 2008a. Aging affects contrast response functions and adaptation of middle temporal visual area neurons in rhesus monkeys. Neuroscience 156, 748–757.
Yang, Y., et al., 2008b. Aging Affects the Neural Representation of Speed in Macaque Area MT. Cereb. Cortex, doi:10.1093/cercor/bhn221.
Yu, S., et al., 2006. Functional degradation of extrastriate visual cortex in senescent rhesus monkeys. Neuroscience 140, 1023–1029.