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AGING AFFECTS CONTRAST RESPONSE FUNCTIONS AND ADAPTATION OF MIDDLE TEMPORAL VISUAL AREA NEURONS IN RHESUS MONKEYS

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Abstract—In the present study we studied the effects of aging on the coding of contrast in area V1 (primary visual cortex) and MT (middle temporal visual area) of the macaque monkey using single-neuron *in vivo* electrophysiology. Our results show that both MT and V1 neurons in old monkeys are less sensitive to contrast than those in young monkeys. Generally, contrast sensitivity is affected by aging more severely in MT cells than in V1 cells. Specifically, MT cells were affected more severely than motion direction selective V1 cells. Particularly, we found that MT neurons in old monkeys exhibited enhanced maximum visual responses, higher levels of spontaneous activity and decreased signal-to-noise ratios. In addition, we also found age-related changes in neuronal adaptation to visual motion in MT. Compared with young animals, the contrast gain of MT neurons in old monkeys is less affected, but the response gain by adaptation of MT neurons is more affected. Our results suggest that there may be an anomalous visual processing in both the magnocellular and parvocellular pathways. The neural changes described here are consistent with an age-related degeneration of intracortical inhibition and could underlie some deficits in visual function during normal aging.

Key words: aging, contrast sensitivity, degeneration, middle temporal area, macaque.

A wealth of psychophysical evidence has shown that human visual abilities decline during normal aging (Stanford and Pollack, 1984; Kline, 1985; Spear, 1993; Wist et al., 2000; Norman et al., 2003; Snowden and Kavanagh, 2006). Much of the decline cannot be attributed to the optical changes of the eye or changes in the retina (Spear, 1993; Norman et al., 2003). In fact, over the last two decades, a lot of work has been done to investigate the location and mechanism of degradation in visual function during aging (Spear, 1993; Spear et al., 1994; Schmolesky et al., 2000; Leventhal et al., 2003; Yu et al., 2006). However, there has been little research on how aging affects coding of image contrast in central visual pathways.

Coding of contrast provides several advantages as a paradigm for studying the way in which information is encoded into the responses of visual neurons. The response of neurons in visual cortex could exhibit prominent contrast gain control which may be mediated by a divisive inhibitory mechanism (Ohzawa et al., 1982; Bonds, 1991; Heeger, 1992; Freeman et al., 2002; Priebe and Ferster, 2006). Moreover, variation of stimulus contrast can influence the tuning for other parameters, such as spatial frequency and speed (Sceniak et al., 2002; Alitto and Usrey, 2004; Betts et al., 2005; Pack et al., 2005; Krekelberg et al., 2006a; Livingstone and Conway, 2007). In the present work, we have examined how aging affects contrast response functions (CRF) of neurons in primary visual cortex (V1) and middle temporal visual area (MT), and have analyzed the difference of aging effect between them. We chose the two sites because they represent different levels within the hierarchy of visual processing.

Adaptation is a fundamental property of the visual brain. Although adaptation may produce some negative consequences, it allows cells to encode the visual information in a varying environment and to function over a limited range (Mather et al., 1998; Muller et al., 1999; Kohn and Movshon, 2004; Krekelberg et al., 2006b). It has been well established that visual motion processing of human is strongly affected by adaptation (Van Wezel and Britten, 2002; Krekelberg et al., 2006b). Previous studies in macaque MT indicate that adaptation may be involved with the opponent mechanisms that underlie direction and speed selectivity in MT (Krekelberg and Albright, 2005; Krekelberg et al., 2006b). To further examine the effects of aging on the properties of MT neurons, we also studied the age-related changes in neuronal adaptation to visual motion in MT. Our results provide evidence for significant degradation within visual processing pathways of old monkeys.

EXPERIMENTAL PROCEDURES

Animal preparation and electrophysiology

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

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Abbreviations: CRF, contrast response function; MT, middle temporal visual area; V1, primary visual cortex.

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23–31 years old and weighed 5.2–8.7 kg. According to a lifespan analysis of rhesus macaques housed at the Yerkes Primate Center, our 23 to 31-year-old monkeys can be considered old and monkeys of these ages correspond to 70 to 90-year-old humans, whereas the 5 to 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 the 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 seemed to be within normal limits. All experimental protocols were consistent with the Society for Neuroscience and National Institutes 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. All efforts were made to minimize the number of animals used and their suffering.

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. I.v. 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 triethiodide (7 mg/kg/h, Sigma) was infused i.v. 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 (durations for each monkey: 3 days for OM1, 3 days for OM2, 4 days for OM3, 4 days for OM4, 4 days for YM1, 5 days for YM2, 5 days for YM3). 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, CA, USA) 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 computer. Recordings were made in MT during the first 2 or 3 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 projection of the fovea, and most were within 15°.

To confirm the recording sites, small lesions were made at the end of each penetration by passing DC current through the tip of the electrode (2 μA for 5 s, negative). At the end of each experiment, the monkeys were deeply anesthetized and perfused through the heart with 700 ml of lactated Ringer's solution containing 0.1% heparin, followed by 1000 ml of 1% paraformaldehyde and 2.5% glutaraldehyde in 0.1 M phosphate buffer at pH 7.4, followed by 600 ml of lactated Ringer's solution containing 5% dextrose. Brains were removed and sections (40 μm) were stained for Nissl substance with Cresyl Violet or for myelin using the method of Gallyas (1979), the borders of MT were determined by its characteristic myelination (Van Essen et al., 1981). We also relied on the high proportion of directional cells with relatively small RFs to confirm that the recordings were made in MT. The locations of the electrode tracks in V1 were determined as described (Leventhal et al., 1995; Schmolesky et al., 1998).

Visual stimulation

When a single unit was isolated according to principal component analysis (Lewicki, 1998), 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 inch 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 cell, we recorded a series of tuning curves to determine the optimal direction, spatial and temporal frequency, position, and size of a drifting sine wave grating. Stimuli of different contrasts with at least seven levels ranging between 0.038 and 1.0 were presented in a pseudo-random order. Two to five trials were made to obtain CRF of each neuron.

We also compared the effects of adaptation on the contrast-response functions of young and old MT neurons using drifting gratings of different contrasts in the preferred direction. The adaptation protocol we used is similar to that described by Kohn and

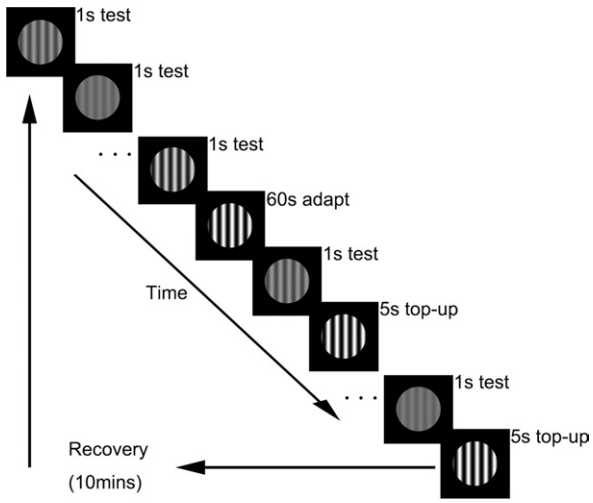

Fig. 1. Diagram of the adaptation protocol. Responses to sine-wave grating (1 s) of varying contrast drifting in the preferred direction were measured before and after adaptation to a full-contrast grating drifting in the same direction for 60 s; top-up gratings were presented preceding each test stimulus to maintain adaptation levels. Each trial was followed by 10 min of recovery. Three trials were recorded. Adapted with permission from Kohn and Movshon (2003).

Movshon (2003) (see Fig. 1). First, a trial consisting of test stimuli of drifting gratings with varying contrasts (1 s duration) was presented randomly as a control test, followed by a 60 s, full-contrast adapting grating drifting in the neuron's preferred direction. Then, a second sequence of test stimuli is presented. Top-up adaptation stimuli (5 s duration) were presented between each pair of post-adaptation test stimuli. We recorded three trials in each adaptation condition. The recovery time between each trial was 10 min.

Data collection and analysis

After the response of an isolated cell was amplified with a microelectrode amplifier (X1000′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. At the time of each presentation, we presented mean luminance on screen for 3 s, and then the stimulus appeared and started to move. After the completion of one trial (2 s), the stimulus was again held static on screen for 0.5 s. There were no blank interstimulus intervals. A baseline value was obtained during a time window of 0.5–1 s before each stimulus was presented. Spontaneous activity was defined by the mean of baseline values. All baseline values below 1 spike/s were set equal to 1 spike/s for signal noise ratio analyses (Schmolesky et al., 2000). A cell's signal to noise ratio was defined as the ratio of the cell's response to the optimal stimulus (contrast close to 1) and the cell's spontaneous activity (Schmolesky et al., 2000; Leventhal et al., 2003).

We fit the CRFs of our cells with using the following equation:

$$R = R_{\max} \times \left(\frac{C^n}{C^n + C_{50}^n} \right) + M$$

Where R is the neuronal response, C is the luminance contrast, R_{max} is the maximum attainable response, C_{50} is the half-saturation contrast, M represents the spontaneous activity, and n is the exponent that determines the steepness of the response function. This function has been shown to provide a good fit to CRFs from visual cortex in the cat and monkey cortex (Albrecht and Hamilton, 1982; Albrecht et al., 1984; Geisler and Albrecht, 1997; Tolhurst and Heeger, 1997). These fits described our data well, accounting for 95% and 87% of the variance on average respectively in young and old groups. In line with previous studies (Kohn and Movshon, 2003), we also found that adaptation rarely affected n in both young and old groups. So when we fit the control and adapted functions, we forced n to assume a single value optimized jointly for both conditions.

Unlike psychophysical experiments in which contrast sensitivity is defined as the reciprocal of the lowest detectable contrast, we have used C_{50} as an index of it (Sclar et al., 1990). The smaller values of C_{50}, the more contrast sensitive the neurons. The exponent (n) determines the steepness of the CRF, larger values being associated with steeper slopes, which help neurons sustain high sensitivity to local changes in contrast (Sclar et al., 1990). Furthermore, to quantify the effects of adaptation on the CRF, we defined the ratio of the R_{max} after adaptation (post-R_{max}) and the R_{max} before adaptation (pre-R_{max}) as a change in response gain (R_{max} (post/pre)), and the ratio of the C_{50} after adaptation (post-C_{50}) and the C_{50} before adaptation (pre-C_{50}) as a change in contrast gain (C_{50} (post/pre)) (Kohn and Movshon, 2003). The larger C_{50}(post/pre), the greater the change in contrast gain; the smaller R_{max}(post/pre), the greater the change in the response gain.

Statistical comparisons between young and old monkeys' data were carried out using *t*-test, two-way ANOVA test or Mann-Whitney *U* test.

RESULTS

We measured the CRF of 102 MT cells from four old monkeys (23–31 years old) and 93 MT cells from three young monkeys (5–9 years old) using extracellular single unit recording technique. In order to study the age-related changes in neuronal adaptation to visual motion, we also recorded the CRFs before and after adaptation to sinusoidal gratings drifting in the preferred direction (see Experimental Procedures). To evaluate the different effects of aging on V1 and MT, we recorded 79 young V1 cells and 71 old V1 cells in the same animals as above. The CRFs were fitted using the Naka-Rushton equation (see Experimental Procedures).

Contrast sensitivity

Our results indicate increased C_{50} of MT cells in old monkeys (Tables 1, 2, Fig. 2A and Fig. 3). The percentage of MT cells showing significant contrast sensitivity ($C_{50} \leq 0.20$) was smaller for old monkeys (40%, 41 of 102) than for young controls (99%, 92 of 93). The cells that were highly contrast sensitive ($C_{50} \leq 0.1$) were also affected greatly by aging. The percentage of such cells was much smaller in old monkeys (2%, 2 of 102) compared with young monkeys (34%, 32 of 93). It is obvious that MT cells in young monkeys have smaller C_{50} values (0.04∼0.23; median value: 0.11) than cells in old monkeys (0.07∼0.37; median value: 0.21; Mann-Whitney *U* test, $P<0.001$) (Table 2). We also analyzed the distribution of C_{50} of cells in old and young monkeys. Fig. 3A shows the percentage of cells having different C_{50} values. It is worth noting that the

Table 1. Descriptive statistics of visual response properties of MT for each monkey

Monkey	N	C_{50}	n	MR	BR	STN
OM1	19	0.243±0.043	2.38±0.912	127.6±28.7	29.55±9.09	5.93±3.52
OM2	28	0.217±0.028	2.52±0.456	130.8±34.9	27.86±7.48	6.01±4.46
OM3	29	0.221±0.034	2.444±0.657	114.5±27.6	25.70±8.90	5.52±2.18
OM4	26	0.211±0.031	2.51±0.818	119.8±32.4	26.77±5.22	4.67±2.21
YM1	26	0.103±0.024	2.84±0.73	83.35±23.98	8.00±5.01	14.13±8.63
YM2	35	0.121±0.035	2.91±0.95	81.32±20.24	7.81±4.69	16.71±18.63
YM3	32	0.114±0.037	3.07±1.18	76.51±16.89	10.46±6.79	11.83±17.71

Subjects were briefly named as OM1-4 (for old monkeys 1 to 4) and YM1-3 (for young monkeys 1 to 4). Other data columns represent the number of cells (*N*), the mean value (mean±standard deviation) of C_{50}, exponent (n), maximum response (MR), baseline response (BR) and signal-to-noise ratio (STN) for each monkey.

Table 2. Descriptive statistics of visual response properties of MT cells between young (YM) and old monkey (OM) groups

Properties	YM cells (n=93)	OM cells (n=102)	Mann-Whitney U-test
Maximum response (spikes/s)	69.9±20.7	127.5±31.9	$P<0.001$
Baseline (spikes/s)	9.6±5.7	27.9±8.4	$P<0.001$
Signal noise ratio	14.8±16.7	5.7±3.3	$P<0.001$
C_{50}	0.11±0.03	0.22±0.05	$P<0.001$
C_{50}(V1)	0.25±0.07	0.33±0.08	$P<0.001$
Exponent (n)	2.98±0.99	2.44±0.73	$P<0.01$

Two group comparisons of maximum response, baseline, C_{50}, exponent (n) and signal-to-noise ratio were performed between young and old monkeys using Mann-Whitney U test. Data are presented as mean±S.D. C_{50} values of V1 cells in both groups are also shown.

effects of aging seem to get stronger with the oldest animal (OM1 was 31 years old) (Table 1), although this effect does not reach significance compared with other old groups (P=0.32, Mann-Whitney U test).

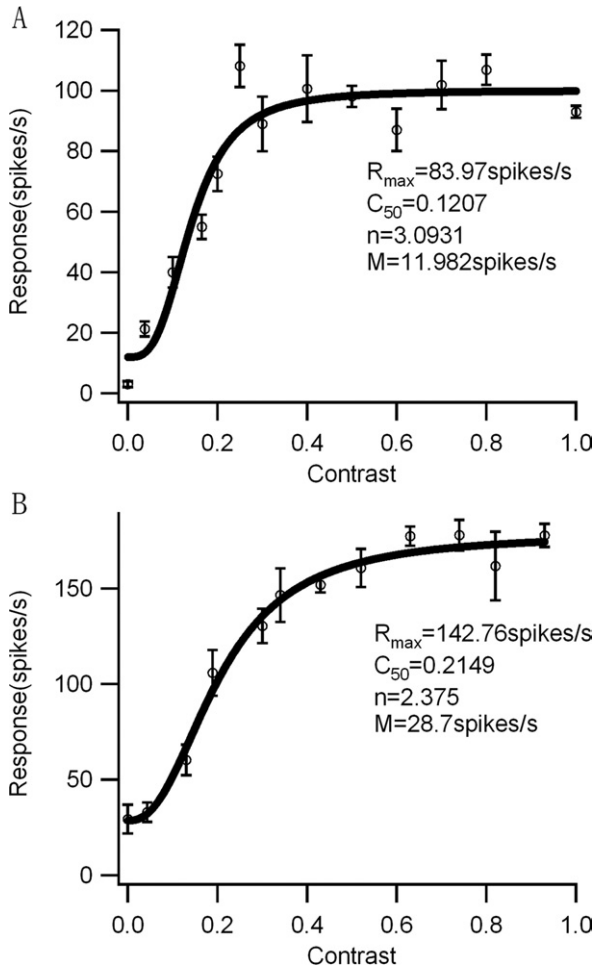

Fig. 2. Curve-fits for CRF obtained from a typical young monkey MT cell (A) and a typical old monkey MT cell (B). Responses are to drifting sine-wave gratings of randomly varied contrast from 0.038–1 at 12 levels. Compared with young MT cells, old MT cells saturate at higher contrast. This is accompanied by increased baseline and maximum response. Each point represents the response for the stimulus of the indicated contrast. The results of fittings are shown. Old MT cells show elevated maximum visual response (R_{max}), spontaneous activity (M) and half-saturation contrast (C_{50}) but reduced slope of CRF (n). Error bars indicate S.E.M.

We also compared the values of C_{50} from MT and V1 neurons' CRF. A summary of the C_{50} of cells in areas V1

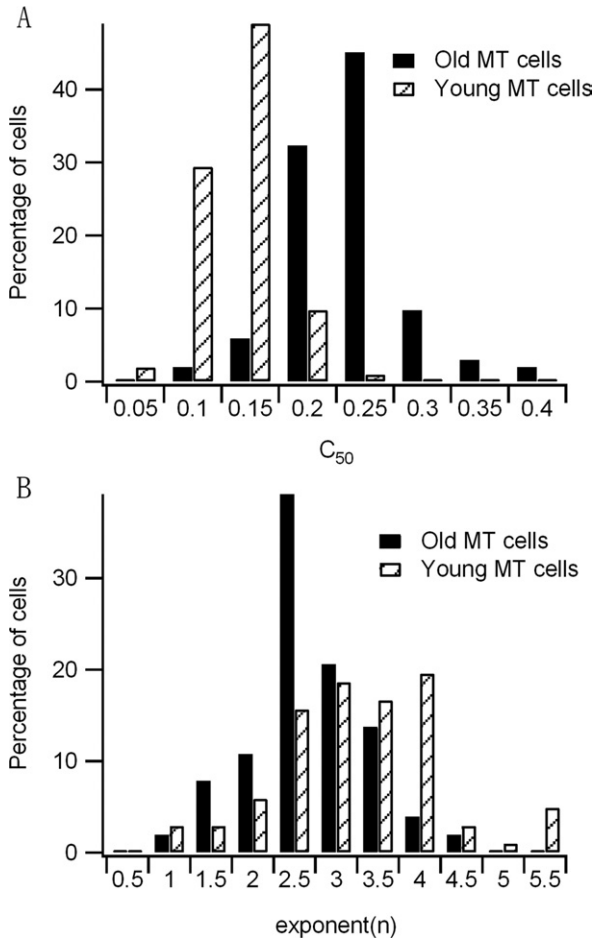

Fig. 3. Percentage of MT cells with different C_{50} and exponent (n) values for young and old monkeys. The total number of neurons is 93 for young monkeys and 102 for old monkeys. Compared with young monkeys, old monkey MT cells show significantly increased C_{50} ($P<0.001$) and reduced exponent (n) ($P<0.001$). (A) Percentage of cells with different C_{50} values. Most cells (60%, 61 of 102; OM1, N=12; OM2, N=17; OM3, N=20; OM4, N=13) in old monkeys have values of C_{50} larger than 0.20, whereas most cells (99%; 92 of 93) in young monkeys have values of C_{50} less than 0.20. It is notable that, of 61 cells ($C_{50}>0.2$), 42 cells have values of n less than 2.5. (B) Percentage of cells with different exponent (n) values. Most cells in young monkeys (71%; 65 of 93) have values of n larger than 2.5, whereas most cells (59%; 61 of 102) in old monkeys have values of n lower than 2.5.

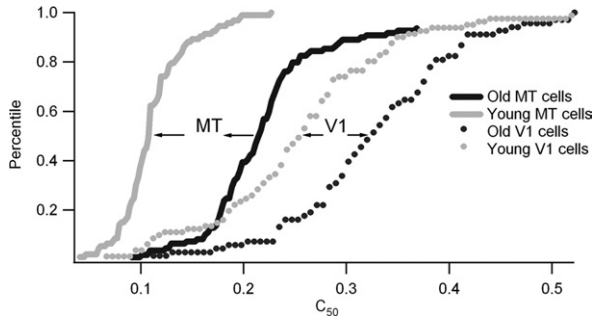

Fig. 4. Percentage of cells with any given C_{50} in area V1 and MT is shown in cumulative distribution plots, where solid and gray lines (or dots) represent the combined data of old and young monkeys, respectively. Using two-way ANOVA with age and brain areas as factors, we found a significant effect of brain area ($P<0.001$) and age ($P<0.001$) as well as an interaction of age and brain area ($P<0.01$). In addition, the difference in C_{50} between young and old cells in MT is greater than in V1 ($P<0.001$). This indicates aging generally affects MT more than V1.

and MT is shown in Fig. 4 and Table 2. The average C_{50} within area V1 is also higher in old (0.11∼0.54; median value: 0.32) than in young monkeys (0.07∼0.45; median value: 0.25) (Fig. 4). The mean difference in C_{50} between young and old animals in areas V1 and MT was 0.08 and 0.11 respectively. We applied a two-way ANOVA to the C_{50} values with age and brain area as group factors. The test result revealed a significant effect of age ($P<0.001$) and brain area ($P<0.001$) on C_{50}. This indicates that V1 cells in old monkeys are also less contrast sensitive than those in young monkeys. More importantly, the interaction of age and brain area ($P<0.001$) demonstrated that the decline of MT cells was significantly more severe than that of V1 cells. Notice that the values of C_{50} in V1 are statistically higher than in MT in both young and old groups. This suggests that MT neurons have higher contrast sensitivity than V1 neurons, which is consistent with previous studies (Sclar et al., 1990).

Because only direction selective neurons in V1 are the ones that project to MT (Movshon and Newsome, 1984; Hawken et al., 1988), we selected direction sensitive neurons from V1 population. In our studies, neurons exhibiting a direction bias of 0.1 or greater will be considered to be direction sensitive (Leventhal et al., 1995). The average C_{50} of these direction sensitive V1 neurons is higher in old (24 of 71, mean value: 0.243) than in young monkeys (45 of 79, mean value: 0.18, $P<0.001$). The interaction of age and brain area revealed that MT cells were affected more severely than direction sensitive V1 cells ($P<0.05$, two-way ANOVA). This indicates that problems may occur within the V1–MT pathway. We also found that the average C_{50} of these non-direction sensitive V1 neurons is higher in old (47 of 71, mean value: 0.39) than in young monkeys (34 of 79, mean value: 0.34, $P<0.001$).

The slope of CRFs

The exponent n characterizes the steepness of the CRF, larger values being associated with steeper slopes. Steeper slopes may help neurons maintain high contrast sensitivity (Sclar et al., 1990). In addition, the steep slopes of contrast-response function could potentially serve to enhance stimulus selectivity (for direction, orientation, spatial frequency, etc.) of cortical neurons (Albrecht and Geisler, 1991; Heeger, 1992; Albrecht et al., 2002). We have also analyzed the values of n in young and old groups. Our results show that the percentage of MT cells showing steep slopes ($n\geq2.5$) was smaller for old monkeys (40%, 41 of 102) than for young monkeys (70%, 65 of 93). The percentage of cells having different n values is shown in Fig. 3B. CRFs of MT neurons in old monkeys exhibited slopes that were less steep than those in young monkeys (Table 1, 2).

Maximum visual and spontaneous activity

In order to further investigate the relationship between the decreases in contrast sensitivity and age-related changes in neuronal activity, we analyzed the maximum attainable and baseline responses of all recorded MT cells. Similar with previous findings (Schmolesky et al., 2000; Leventhal et al., 2003; Wang et al., 2005, 2006; Yu et al., 2006), we found that old monkeys' MT cells showed increased maximum attainable and baseline responses (110.8 spikes/s, 21.1 spikes/s, median values, respectively) compared with young monkeys' MT cells (73.6 spikes/s, 7.72 spikes/s, median values, respectively) (Tables 1, 2, and Fig. 5A–B). It seems that baseline activity was affected more severely by aging than was the maximum attainable response. More than 50% of cells in old monkeys showed baseline activity greater than 20 spikes/s. In contrast, 90% of cells in young monkeys exhibited baseline activity less than 20 spikes/s. Overall, old monkey cells increased their baseline activities by 200%. As a result, signal-to-noise ratios of old monkey neurons are significantly lower than those of young monkey neurons (median value: 5.0 in aged group, 9.8 in young group) (Tables 1, 2, Fig. 5C). This indicates a degraded ability of aged cells to convey signals from a noisy background.

Neuronal adaptation to visual motion

To assess age-related changes of neuronal adaptation to visual motion in MT, we compared the CRFs of MT neurons for young (YM1, $N=9$; YM2, $N=18$; YM3, $N=14$) and old monkeys (OM1, $N=5$; OM2, $N=11$; OM3, $N=8$; OM4, $N=9$) before and after adaptation to sinusoidal gratings drifting in the preferred direction. An example of the effect of adaptation on the CRF of an old MT neuron is shown in Fig. 6A. Adaptation caused a substantial change both in response gain and in contrast gain. Here, we define R_{max} (post/pre) as the ratio of R_{max} post- and pre- adaptation to calculate the change in response gain, and C_{50} (post/pre) as the ratio of C_{50} post- and pre-adaptation to calculate the changes in contrast gain. The distributions of various R_{max} (post/pre) and C_{50} (post/pre) for cells in young and old animals are shown in Fig. 6B and 6C. Cells in old monkeys exhibited smaller R_{max}(post/pre) (0.72±0.13) than did cells in young monkeys (0.82±0.12; t-test, $P<0.05$), which means that the response gain of cells in old animals is affected more by adaptation. However, the comparison of

C_{50}(post/pre) for young monkey cells (3.05±0.98) versus old cells (2.36±1.19) showed adaptation affects old MT neurons' contrast gain in a relatively narrow operating range compared with cells in young monkeys (*t*-test,

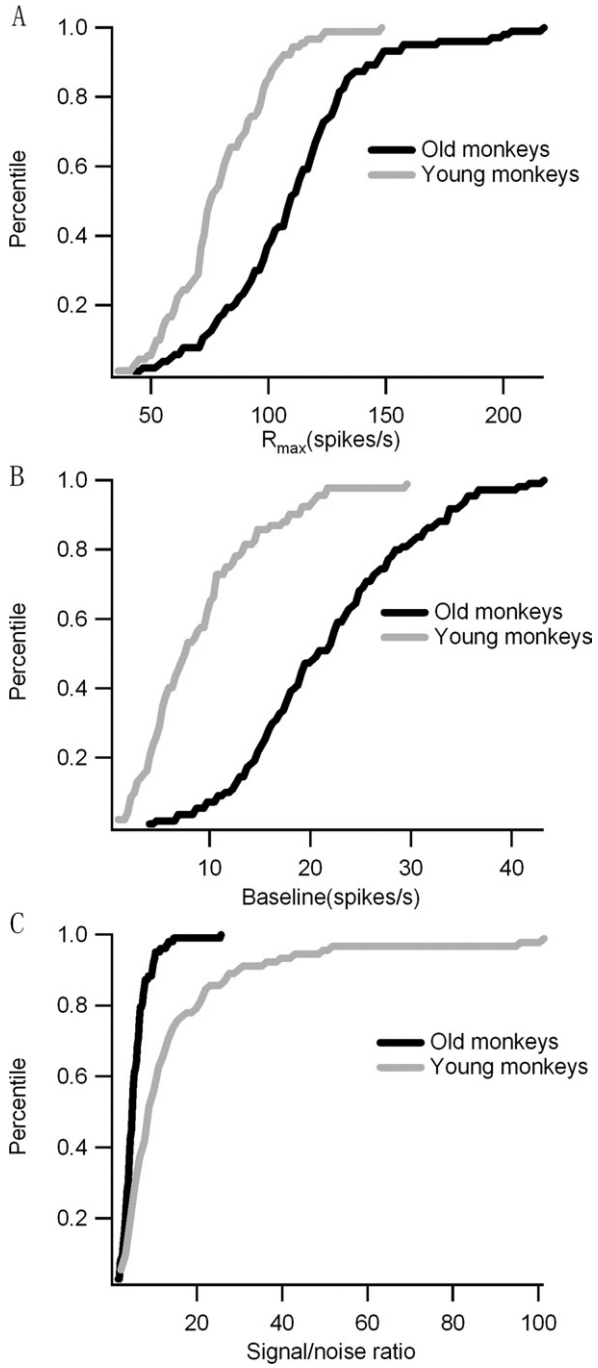

Fig. 5. Maximum response, baseline and signal to baseline ratio in young and old monkey's MT cells. The percentage of young (n=93) and old (n=102) monkey cells with any given maximum response (A), baseline (B) and signal to noise ratio (C) is shown in cumulative distribution plots, where solid black and gray lines represent the data of old and young monkeys, respectively. Old monkey cells show increased peak and baseline responses but decreased signal to noise ratios compared with young monkey MT cells.

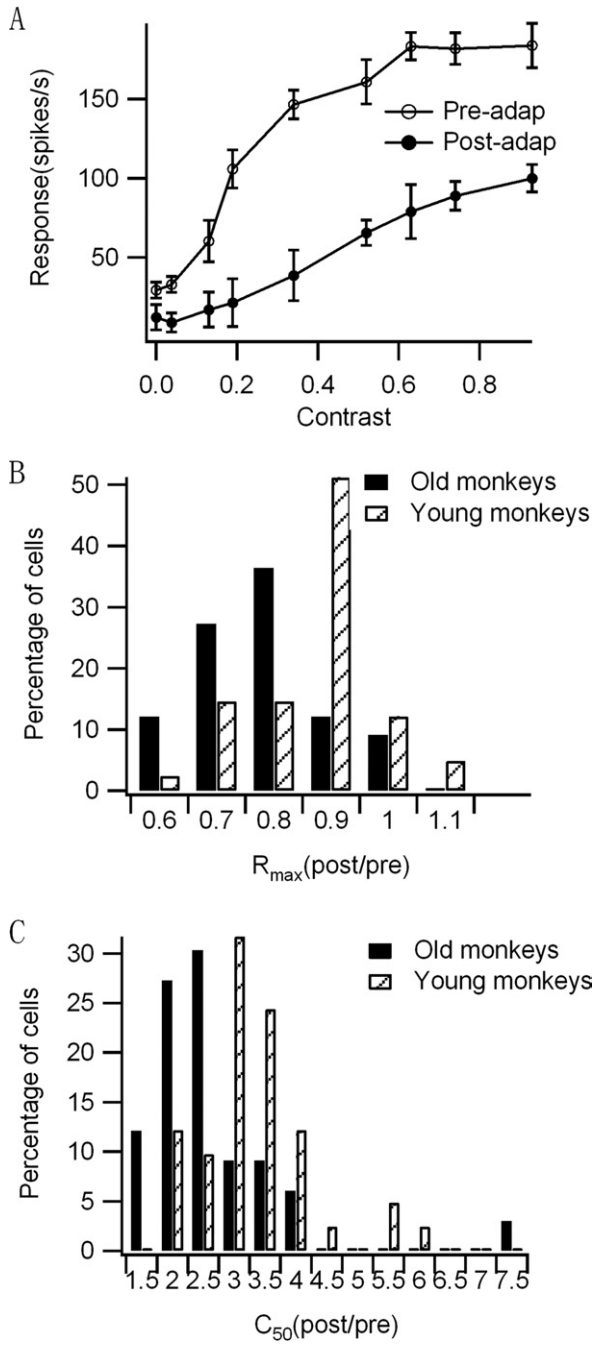

Fig. 6. (A) Adaptation effects in an example old MT neuron are shown. CRFs before (open symbols, thin line) and after (filled symbols, thick line) adaptation were measured. Adaptation reduces maximum fire rating of the cell and causes a change in contrast gain (R_{max}(post/pre)=0.63, C_{50}(post/pre)=2.23). Error bars indicate S.E.M. (B, C) Percentage of cells with different R_{max}(post/pre) (B) and C_{50}(post/pre) (C) values (see Experimental Procedures) for young and old monkeys. The total numbers of neurons are 41 for young monkeys and 33 for old monkeys. Compared with young monkeys (0.82±0.12), old monkey MT cells show reduced R_{max}(post/pre) (0.72±0.13; P<0.05). This indicates that after adaptation old cells exhibited a greater change in response gain. Compared with young monkeys (3.05±0.98), old monkey MT cells show reduced C_{50}(post/pre) (2.36±1.19; P<0.01). This indicates that after adaptation old cells exhibit less change in contrast gain.

$P<0.01$). It is worth noting that our results in young groups are somewhat different from Kohn and Movshon's (2003) results. In their studies, R_{max}(post/pre) have a mean value of 0.78 and C_{50}(post/pre) have a mean value of 3.28. These differences could be attributable to adaptation protocol. They used a 40 s adapting stimulus, while we used a 60 s adapting stimulus.

DISCUSSION

In the present experiment, we examined the effects of aging on the contrast sensitivity of macaque V1 and MT cells. Both MT and V1 neurons in old monkeys are less sensitive to contrast than those in young ones. Contrast sensitivity is affected by aging more severely in MT cells than in V1 cells. Specifically, MT cells were affected more severely than direction selective V1 cells. In addition, just like V1, MT neurons in old monkeys exhibited increased maximum and spontaneous responses, and decreased signal-to-noise ratios. We also found, after adaptation, old cells exhibited a narrower operating range in contrast gain than did young cells, accompanied by deterioration in response gain.

The interpretation of our results is complicated by a number of factors. First, we must carefully take into account the possibility of differential effects of anesthesia upon neuronal activity in young and old monkeys. In our previous studies, we have examined this possibility by recording the properties of individual cells while systematically varying anesthetic and paralytic levels. We found that greatly increasing anesthesia decreased neuronal responsiveness in young and old groups similarly (Wang et al., 2005). In fact, we paid special attention to maintain comparable levels of anesthesia in old and young monkeys. We found that, giving as much as four times the minimum level of general anesthesia or paralytic required to anesthetize or paralyze both old and young animals does not change the degree of contrast sensitivity significantly that V1 and MT cells exhibit, when we systematically varied anesthesia and paralytic levels. It has been reported that sensitivity to anesthesia increases during aging in both humans (Schwartz et al., 1989) and animals (Hoffman et al., 1985; Magnusson et al., 2000). However, we found that old cells exhibited higher maximum and spontaneous activities than did young cells. Thus, we conclude that problems with anesthesia are not a concern.

It has been reported that age-related contrast-sensitivity deficit is not due to senile miosis (Sloane et al., 1988; Elliott et al., 1990), and this deterioration may reflect a cortical mechanism (Crassini et al., 1988; Pardhan et al., 1996; Bennett et al., 1999). Previous studies of single-cell responses in the aged macaque visual system have suggested that receptive field properties including contrast sensitivity in the magnocellular and parvocellular LGNd laminae, even the geniculorecipient cells of V1, are relatively unaffected by aging (Spear et al., 1994; Schmolesky et al., 2000). However, we have demonstrated that the function of V1 or V2 cells declines during aging (Schmolesky et al., 2000; Leventhal et al., 2003; Wang et al., 2005; Yu et al., 2006). M (for magno-) pathway is often thought to be highly involved in the perception of motion and provides predominant input to MT (Newsome et al., 1989; Maunsell et al., 1990). So, it seems that degradation within early visual cortex of M-pathway would be a possible candidate to explain the changes observed in MT among aged monkeys. In addition, contrast normalization is locally mediated by GABAergic mechanism in MT itself (Thiele et al., 2004). Our results also revealed that contrast sensitivity of MT neurons in old monkeys decreases even more than the direction selective V1 neurons that are thought to project to MT. Together with the results from V1 in old monkeys, we assume that both magnocellular and parvocellular pathways may be affected by aging, consistent with previous studies (Spear, 1993; Habak and Faubert, 2000; Faubert, 2002; Snowden and Kavanagh, 2006).

It has been reported that the number of cortical neurons in macaque monkeys and humans is largely preserved during aging (Morrison and Hof, 1997, 2007; Peters et al., 1998). Specifically, studies in the superior temporal sulcus (STS), on the posterior bank of which MT is located, have failed to detect an age-related loss in humans and macaques (Duan et al., 2003; Morrison and Hof, 2007) but observed statistically significant age-related decreases in spine numbers and density of both apical and basal dendritic arbors (Duan et al., 2003; Morrison and Hof, 2007). Thus, age-related pre- and post-synaptic changes might occur.

Previous studies have suggested that efficacy of cortical inhibitory functions declines with age (Hasher and Zacks, 1988; Schmolesky et al., 2000; Leventhal et al., 2003; Butler and Zacks, 2006; Bennett et al., 2007). Our findings that MT cells in old monkeys showed increased spontaneous, visually driven activity and decreased signal-to-noise ratios may be particularly consistent with the hypothesis. Indeed, application of GABAa receptor antagonists in MT did result in increased stimulus-driven and spontaneous activity (Thiele et al., 2004). Studies of human visual cortex showed that L-glutamic acid decarboxylase (GAD), an enzyme needed to synthesize the inhibitory transmitter GABA, is reduced during aging (McGeer and McGeer, 1976). We hypothesize that age may negatively affect GABAergic connections in the macaque MT and thereby lead to increased spontaneous activity and decreased signal-to-noise ratios.

Our analysis of CRFs of V1 and MT neurons in young and old monkeys shows that old neurons exhibit less contrast sensitivity than do young neurons. Contrast normalization is thought to be mediated by intracortical suppression (Movshon et al., 1978; DeBruyn and Bonds, 1986; Heeger, 1992; Carandini et al., 1997; Britten and Heuer, 1999). Previous studies have showed that dopaminergic drugs improve human visual contrast sensitivity (Domenici et al., 1985). So, we hypothesize that the age differences in contrast normalization observed in the current studies are linked to a degradation of inhibitory intracortical circuits in old brain—GABAergic, cholinergic, dopaminergic or otherwise—that may have inhibitory effects in visual cortex. In fact, the hypothesis has been postulated in previous stud-

ies (Amenta et al., 1991; Bigham and Lidow, 1995; Schmolesky et al., 2000; Leventhal et al., 2003). We also observed that old MT neurons exhibited values of exponent (n) lower than that of young neurons. In addition to contrast sensitivity, another benefit of high exponents is to enhance stimulus selectivity for higher level neurons (Albrecht and Geisler, 1991; Heeger, 1992; Albrecht et al., 2002). The lower exponents of old MT neurons might contribute to their decreased stimulus selectivity, which is consistent with our previous work in V1 and V2 of old monkeys (Schmolesky et al., 2000; Leventhal et al., 2003; Yu et al., 2006).

Our data also demonstrate that, after adaptation, MT neurons in old monkeys displayed a greater reduction in response gain and a narrower operating range in contrast gain than MT neurons in young monkeys. The former result suggests that neurons easily 'fatigue' in old brains compared with young animals. The narrower operating range in contrast gain may reflect a decreased ability of cells to encode large fluctuations in stimulus strength (Ohzawa et al., 1985; Kohn and Movshon, 2003). More than one mechanism seems to contribute to this phenomenon. Differences in pre-CRF (C_{50}, baseline and maximum visual responses) between young and old groups may play a role. It has been concluded that pharmacological agents that block or activate inhibition fail to exert any modification on the strength of adaptation in V1 (DeBruyn and Bonds, 1986; Vidyasagar, 1990; McLean and Palmer, 1996). Thus, the adaptation results we observed are hard to explain by degradation of inhibitory intracortical circuits. Recent studies suggest that preferred adaptation is accompanied by a reduced excitability of MT neurons (Kohn and Movshon, 2003). The differences in adaptation between old and young neurons may be related to the different overall activity levels in young and old brains. Moreover, excitotoxic hyperactivity in old brain has been implicated in the degradation of brain function during senescence (Doble, 1999). In addition, a decline of adaptation effects inherited from an earlier cortical area may also provide a candidate, though we did not test the effect of aging on adaptation in earlier cortical areas.

CONCLUSION

In summary, the results of the present study demonstrate that coding of contrast in both area V1 and MT of monkeys is affected by aging, and MT is affected more severely by aging than V1. These findings may be related to an age-related degeneration of intracortical inhibition and indicate that some losses within the M-pathway seem to occur with age. Further studies of the effects of age upon extrastriate cortex are still needed to clarify the neural mechanisms underlying the deficits in visual motion function due to aging.

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