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FUNCTIONAL DEGRADATION OF EXTRASTRIATE VISUAL CORTEX IN SENESCENT RHESUS MONKEYS

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Abstract—The receptive field properties of striate cortical (V1) cells degrade in senescent macaque monkeys. We have now carried out extracellular single unit studies of the receptive field properties of cells in extrastriate visual cortex (area V2) in very old rhesus (*Macaca mulatta*) monkeys. This study provides evidence that both the orientation and direction selectivities of V2 cells in old monkeys degrade significantly. Decreased selectivity is accompanied by increased visually driven and spontaneous responses. As a result, V2 cells in old animals exhibit markedly decreased signal-to-noise ratios. A significant degradation of neural function in extrastriate cortex may underlie the declines in higher order visual function that accompany normal aging.

Key words: aging, degradation, extrastriate cortex, rhesus monkeys, vision.

Visual abilities degrade during senescence. It has been reported that old humans exhibit deficits in visual function that include decreased acuity, contrast sensitivity, motion sensitivity, binocular summation (for review, see Spear, 1993) and slowed visual processing speed (Salthouse, 1993; Geldmacher and Riedel, 1999). Complex visual functions such as figure–ground segregation (Stanford and Pollack, 1984), three-dimensional representation (Norman et al., 2004) and perception of higher-order motion (Habak and Faubert, 2000) also degrade. The mechanisms underlying these age-related changes have just begun to be studied (Leventhal et al., 2003; Schmolesky et al., 2000; Wang et al., 2005).

Previous studies indicate that the retina and dorsal lateral geniculate nucleus (dLGN) of old monkeys are relatively normal (Ahmad and Spear, 1993; Spear, 1993; Spear et al., 1994; Kim et al., 1996; Schmolesky et al., 2000). It has been suggested that the declines in visual function that accompany old age result from a degradation of function in the visual cortex. Indeed, we have found that the function of cells in the primary visual cortex (V1) degrade in senescent monkeys and cats. Both the orientation and direction selectivity of V1 cells in old animals are decreased. These decreases are accompanied by increased visual responsiveness, increased spontaneous activity (baseline) and decreased signal to noise ratios (Schmolesky et al., 2000; Leventhal et al., 2003; Hua et al., 2006). In addition, the visual response latencies of V1 cells in old monkeys are greater in old than in young monkeys (Wang et al., 2005).

Primate cerebral cortex contains many extrastriate cortical areas outside of V1. These make important contributions to complex visual processing. We have found previously that the visual latency of cells in V2 increases with age. This increase is accompanied by increased peak response and baseline. The effects of age on the other properties of cells in extrastriate cortex are unknown. In the present experiment we have studied the orientation and direction selectivities of cells in area V2 in young adult and aged monkeys. The results provide evidence for a significant degradation of function in area V2 of very old monkeys.

EXPERIMENTAL PROCEDURES

Animals

All experimental protocols were consistent with the Society for Neuroscience and National Institute of Health guidelines for the humane use and care of animals. The minimum number of animals required for the study was used. Subjects for this study were two groups of rhesus monkeys (*Macaca mulatta*). Young adult monkeys (n=8, three male and five female) were 4–8 years old and weighed 3.2–6.8 kg. Old monkeys (n=3, two male and one female) were 30–32 years and weighed 4.5–8.2 kg. Monkeys were examined ophthalmoscopically and only monkeys having no optical or retinal problems that would impair visual function were studied. Retinal blood vessels, lens clarity and the maculae all were within normal limits.

Animal preparation and recording

Subjects were sedated with ketamine HCl (10–15 mg/kg, i.m., Ketalar, Parke-Davis, Morris Plains, NJ, USA) and then anesthetized with 3–5% halothane (Halocarton 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. All pressure points and incisions were infiltrated with a long-acting anesthetic (2% lidocaine HCl, Copley Pharmaceuticals, Canton, MA, USA). 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. Animals were

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Abbreviations: CO, cytochrome oxidase; DB, direction bias; OB, orientation bias.

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ventilated, and anesthesia was maintained with a mixture of N_2O (70%), O_2 (30%) and halothane. Heart rate was monitored continuously to assess the level of anesthesia. The dose of halothane was increased if the heart rate changed in response to nociceptive stimulation (paw or tail pinch) and was decreased when the heart rate showed continuous slowing. The level of anesthesia was comparable in old and young animals. Expired CO_2 partial pressure was monitored and maintained at approximately 4%. Body temperature was maintained at 38 °C with a heating pad.

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. The normality of the optics and retinal vasculature was monitored throughout the experiment. No visible deterioration in optics occurred during the experimental period in both old and young animals. A small hole (with diameter of 3–5 mm) was positioned above the lunate sulcus. Extracellular action potentials of isolated V2 cells located on the posterior bank of lunate sulcus were recorded with glass or glass-coated tungsten microelectrodes. The two kinds of electrodes were used equally in young and old monkeys, and there were no obvious differences in their sampling properties. The electrode was advanced using a hydraulic microdrive (David Kopf Instruments, Tujunga, CA, USA). The direction of electrode penetrations was as parallel as possible to the border between areas V1 and V2 in order to minimize any bias resulting from non-random sampling from cytochrome stripes which run perpendicular to the V1/V2 border (Livingstone and Hubel, 1987; Wong-Riley, 1994).

Visual stimulation

When a single unit was isolated, the eye affiliation was determined and all stimuli were presented monocularly to the dominant eye. Each cell's receptive field was carefully plotted on a tangent screen by hand with the use of an ophthalmoscope. A Sony Multiscan 17se color monitor (85-Hz frame rate, Sony, Tokyo, Japan) was positioned at 171 cm in front of the animal's eye and centered on the receptive field of the cell.

The program to generate the stimulus was written in MATLAB (Math Works, Natick, MA, USA), using the extensions provided by the high-level Psychophysics Toolbox (Brainard, 1997) and low-level Video Toolbox (Pelli, 1997). To quantify the physiological orientation biases (OB) and direction biases (DB) of V2 cells, drifting bars were used, whose width, length and speed were optimal for the recorded cell. The orientation of each bar presented was orthogonal to its direction of motion. We used 10 presentations of moving bars at each of 24 randomly generated orientations or directions from 0° to 360° to compile the tuning curves for the cells studied. For most cells the luminance was 39 cd/m^2 for bar stimuli and 0.95 cd/m^2 for the background. In some cases, lower luminances were employed. No differences in the results were observed using high and moderate contrast stimuli.

Data collection and analysis

Signals from the microelectrode were amplified conventionally ($\times$1000) and filtered (300–3000 Hz, bandpass), then digitized (sampling frequency of 10,000 Hz) using an acquisition board (National Instruments, Austin, TX, USA) controlled by IGOR software (WaveMetrics, Portland, OR, USA). The original waves were stored in the computer for off-line analysis. The responses to moving bars defined as the maximal value (peak response) in the poststimulus time histogram (bin width of 10 ms). Before each drifting bar presentation, spontaneous (baseline) activities were obtained during a 0.5–0.7 s "blank stimulus" period. A cell's signal to noise ratio was defined as the ratio of the cell's response to the optimal stimulus and the cell's spontaneous activity. Signal to noise ratios were determined multiple times for each cell. They remained consistent from trial to trial.

Orientation and direction selectivity were calculated for each cell using the statistical methods described in detail elsewhere (Leventhal et al., 1995). Briefly, the responses of each cell to the different stimulus orientations and directions were stored as a series of vectors. The vectors were added and divided by the sum of the absolute values of the vectors. The angle of the resultant vector gave the preferred orientation and direction of the cell. The length of the resultant vector, termed the orientation bias (OB) or direction bias (DB), provided a quantitative measure of the orientation or direction sensitivity of the cell. Previous studies in our laboratory have indicated that a bias of 0.1 is significant at the $P<0.005$ level (Rayleigh test) and that OB of 0.1, 0.3 and 0.5 correspond to maximum to minimum response ratios of 1.5:1, 3.7:1 and 10.8:1, respectively (Leventhal et al., 1995).

Statistical comparisons between young and old monkey data were carried out using chi-square test, Mann-Whitney *U* test and Kruskal-Wallis test. The significance level was set at 0.05.

RESULTS

We recorded a total of 89 cells from V2 of three old and 183 cells from eight young monkeys. In most monkeys, the data were collected from three to five penetrations in each monkey. The recording depths and eccentricities (less than 8 degrees) of the cells studied were comparable in the young and old groups.

Orientation and direction selectivities

Our results provide evidence for reduced OB and DB of V2 cells in old monkeys (Table 1, Figs. 1 and 2). The percentage of V2 neurons showing significant OB ($\geq$0.1) was smaller for old animals (28%; 25 of 89) than for young controls (70%; 129 of 183; chi-square test, $P<0.001$). The cells that were strongly biased for orientation (OB $\geq$0.2) were affected by aging more severely. The percentage of

Table 1. Descriptive statistics of visual response properties of V2 cells between old and young monkey groups

Property	Young monkey cells (n=183)	Old monkey cells (n=89)	Mann-Whitney *U* test	Kruskal-Wallis test
Orientation bias	0.17±0.12	0.078±0.055	$P<0.001$	$P<0.001$
Direction bias	0.13±0.10	0.088±0.059	$P<0.001$	$P=0.001$
Peak responses (spikes/s)	73.6±45.2	156.5±78.3	$P<0.001$	$P<0.001$
Baseline (spikes/s)	12.1±8.51	33.6±16.3	$P<0.001$	$P<0.001$
S/N ratio	10.9±15.3	5.15±2.55	$P<0.001$	$P=0.001$

Two-group comparisons of OB, DB, peak responses, baseline, and signal to noise (S/N) ratio were carried out between groups of young and old monkeys using both Mann-Whitney *U* tests and Kruskal-Wallis tests. Data are presented as mean±SD.

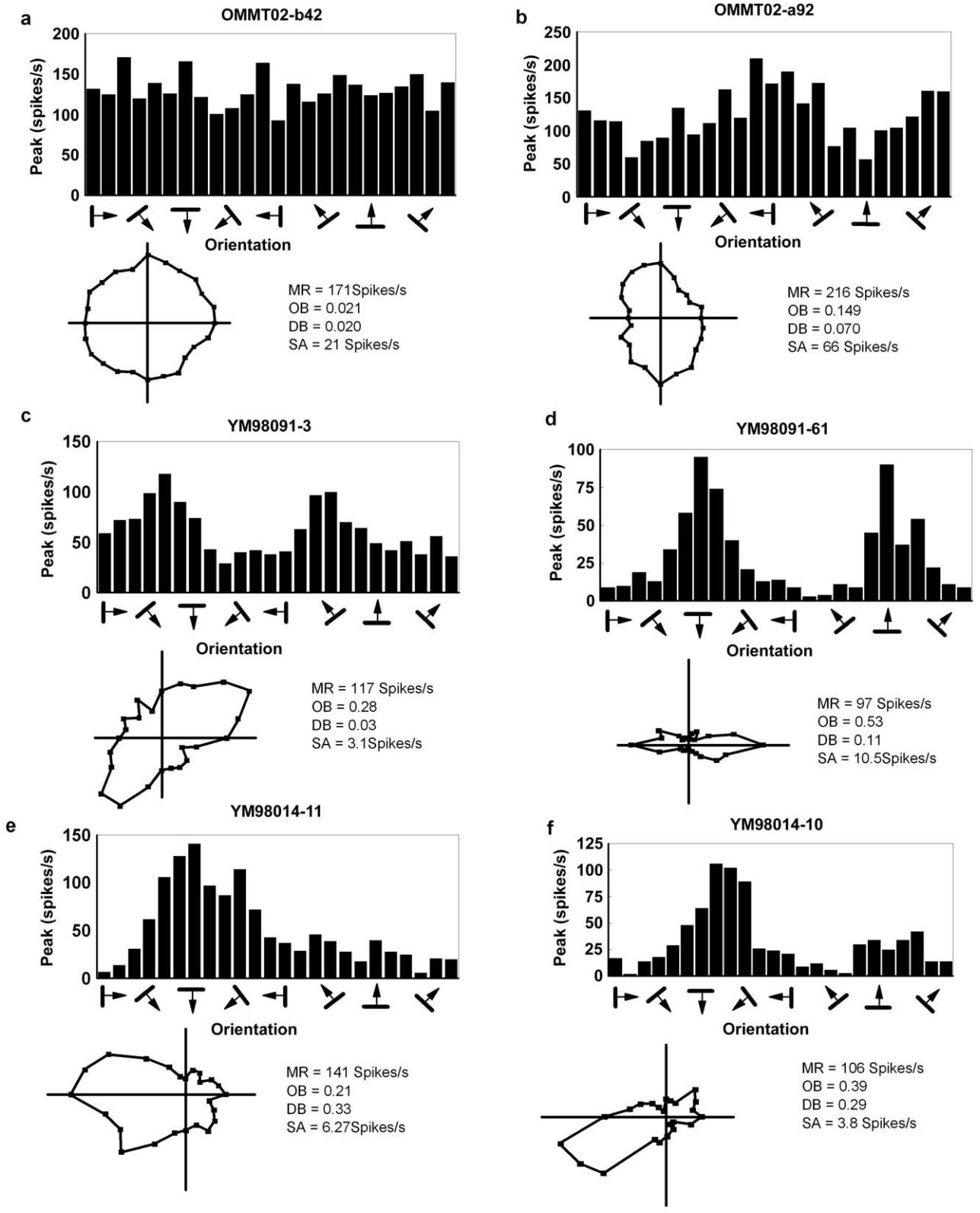

Fig. 1. Tuning curves and corresponding polar plots obtained from two old monkey V2 cells (a, b) and four young V2 cells (c–f). Responses were to drifting luminance bars of systematically varied orientation and direction. The orientation of the drifting bars is orthogonal to the directions indicated. Each point in the polar plots represents the response for the stimulus moving in the indicated direction. The maximum response (MR), spontaneous activity (SA), OB and DB are shown. Cells in V2 of old monkeys exhibit reduced OB and DB.

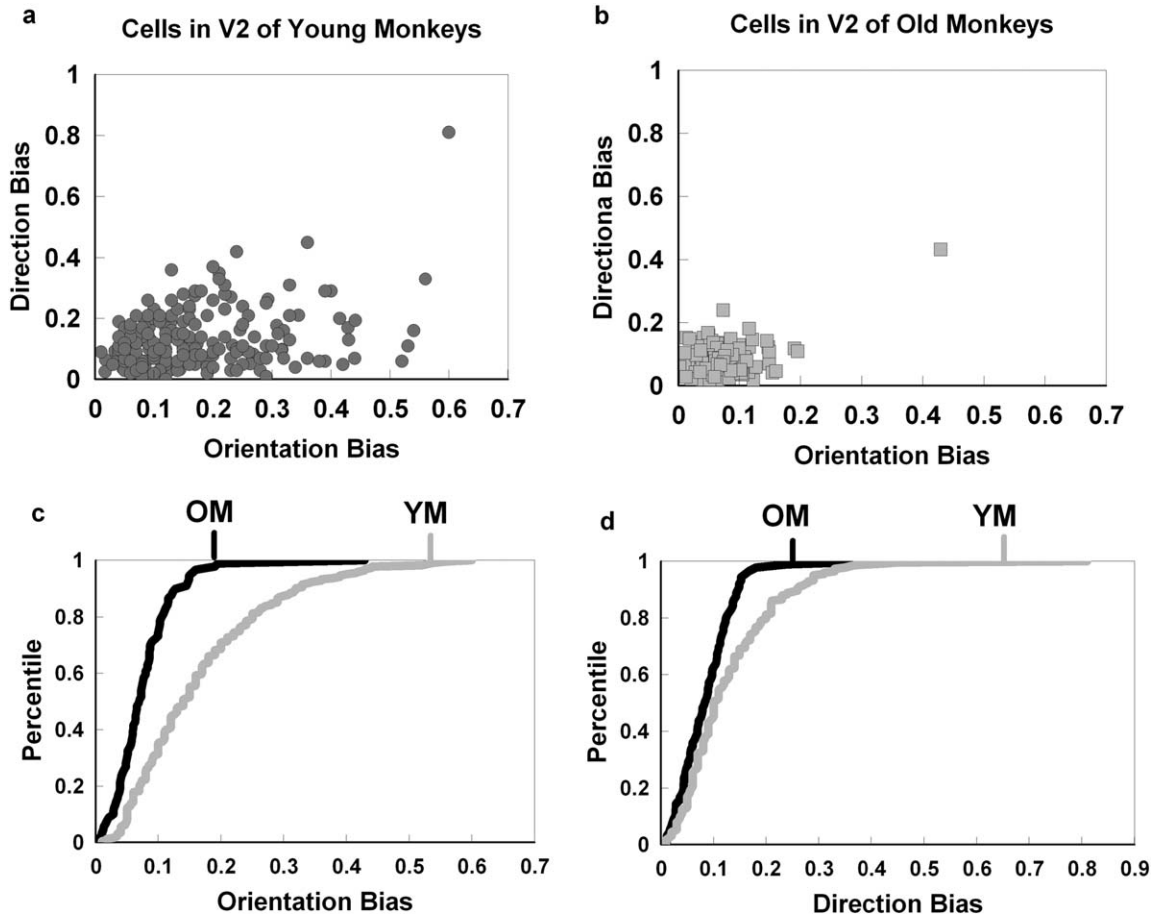

Fig. 2. OB and DB in young and old monkey V2 cells. The data from V2 cells in young (n=183) and old monkeys (n=89) are shown in scatterplots (a, b). The percentage of cells with any given OB or DB value is shown in cumulative distribution plots (c, d) where solid black and gray lines represent the data of old and young monkeys, respectively. Old monkey cells show reduced OB and DB relative to young monkey cells.

such cells was decreased the most in old animals (1.1%; one of 89) compared with young controls (35%; 64 of 183; chi-square test, $P<0.001$). We also analyzed the overall degrees of the OB of cells in old and young animals. V2 cells in old monkeys exhibited significantly lower OB when compared with cells in young monkeys.

As with OB, the percentage of cells showing significant DB in old monkeys (38%; 34 of 89) was lower than in young monkeys (54%; 99 of 183; chi-square test, $P=0.014$). The percentage of cells showing strong direction selectivity (DB $\geq$0.2) in old monkeys (2.2%; 2 of 89) was also lower than in young monkeys (21%; 39 of 183; chi-square test, $P<0.001$). Overall, cells in old animals exhibited decreased DB compared with young animals.

Consistent with previous studies (Zeki, 1978; Burkhalter and Van Essen, 1986; Peterhans and von der Heydt, 1993; Levitt et al., 1994; Gegenfurtner et al., 1996), we found that, in V2 of young monkeys, the percentage of neurons that showed a significant DB (54%, 99 of 183) was smaller than the percentage of orientation selective cells (70%,129 of 183; chi-square test, $P=0.001$). In contrast, in old monkeys we did not observe more orientation selective cells (28%, 25 of 89) than direction selective ones (38%, 34 of 89; chi-square test, $P=0.15$). This suggests a severe affect of age upon orientation selectivity in V2. In fact, the percentage of V2 cells showing significant DB was decreased by 30% (from 54% to 38%) in old monkeys, while the percentage for orientation selective cells was decreased by 60% (from 70% to 28%). The relatively greater effects of age upon orientation selectivity in V2 have not been reported for V1. In V1 (Schmolesky et al., 2000; Leventhal et al., 2003; Hua et al., 2006) orientation and direction selectivities were reduced similarly by age.

Spontaneous and visually evoked responses

In order to investigate the relationship between the decrease in stimulus selectivity and age-related change in neuronal responsiveness, we analyzed the baseline and visually evoked (peak) responses of all recorded V2 cells. In line with our previous findings (Leventhal et al., 1995; Schmolesky et al., 2000; Wang et at, 2005; Hua et al., 2006), we found that old monkey cells showed significantly increased baseline and peak responses compared with young monkey cells (Table 1, Fig. 3a and b). Baseline activity was affected more severely than peak response. Eighty percent of cells in young monkeys showed baseline activities less than 20 spikes/s. In contrast, 80% of cells in

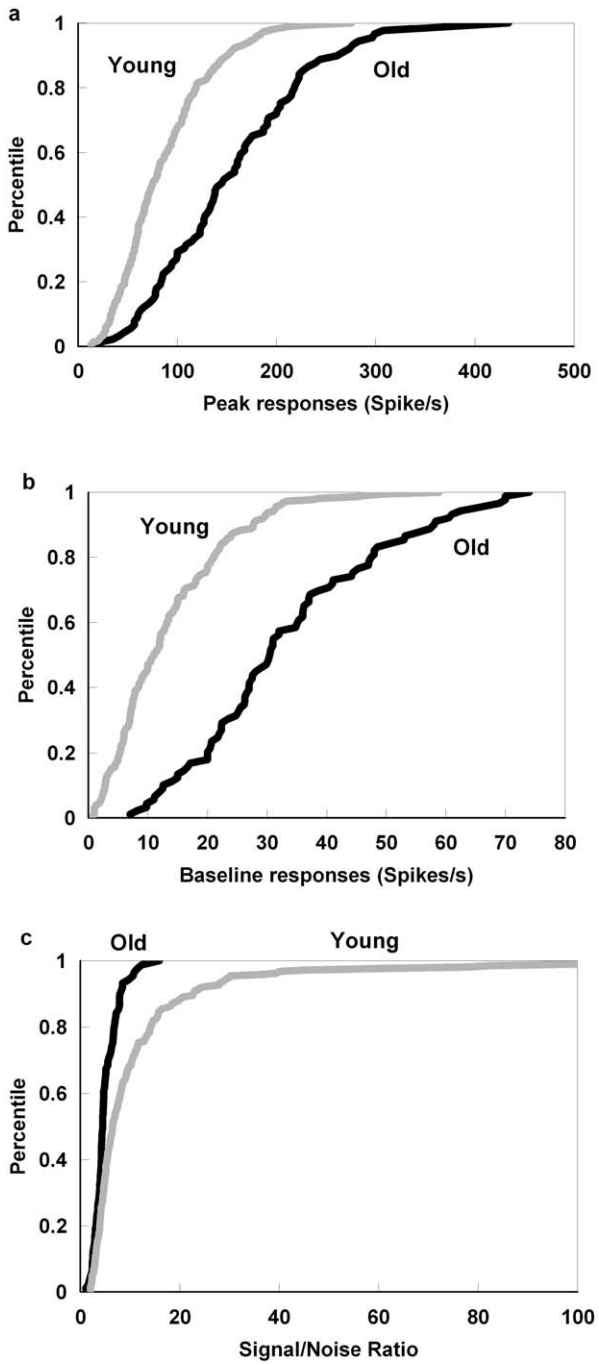

Fig. 3. Visually driven response, spontaneous activity and signal to noise ratio in young and old monkey V2 cells. The percentage of young (n=183) and old (n=89) monkey cells with any given peak response(a), baseline response(b) or signal to noise ratio(c) is shown in cumulative distribution plots, where 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 ratio compared with young monkey cells.

old monkeys exhibited baseline activities greater than 20 spikes/s. Overall, old monkey cells increased their baseline activities 200%. The peak responses of old cells increased by 100%. As a result of the relatively greater increase in baseline activity, signal to noise ratios decreased dramatically in old animals (Table 1, Fig. 3c).

DISCUSSION

In the present experiment we examined the effects of age upon the response properties of V2 cells in monkeys. V2 cells in old animals exhibit decreased orientation and direction selectivity, increased visually driven and spontaneous activities and decreased signal to noise ratios.

A number of factors that might complicate our results deserve careful consideration. First, possible differential effect of anesthesia upon cortical function in young and old animals is a concern. However, in the present study we paid special attention to maintain comparable levels of anesthesia in old and young animals. Previously, we have recorded the properties of individual cells while systematically varying anesthetic and paralytic levels. We found that giving as much as three times the minimum level of general anesthesia or paralysis to both old and young animals does not alter the degree of V1 or V2 cells' selectivity for orientation and direction. Greatly increased anesthesia decreased neuronal responsiveness in both groups similarly (Wang et al., 2005; Hua et al., 2006). In addition, it has been reported that the sensitivity to anesthesia increases during aging in both humans (Schwartz et al., 1989) and animals (Hoffman et al., 1985; Magnusson et al., 2000). If problems related to anesthesia affected our results significantly, then we would expect to find the lower spontaneous and evoked activities in old monkeys. This is not the case. In fact, visually evoked responses are greater in old, anesthetized animals.

Another concern is that our recording sites did not sample different cytochrome oxidase (CO) compartments in old and young animals equally. In fact, some researchers believe that the function of cells within different CO stripes of V2 varies while others suggest that CO stripes of V2 are not functionally organized at all (Gegenfurtner et al., 1996; Ts'o et al., 2001). In this study we chose to make recordings at random positions across V2 in both young and old monkeys. In both groups we found that the percentage of selective cells did not differ across penetrations. Thus, we believe that the influence of sampling bias should be minor.

In previous studies (Schmolesky et al., 2000; Leventhal et al., 2003; Wang et al., 2005; Hua et al., 2006), we demonstrated that the function of V1 declines during aging. Thus, it is not surprising that we observed effects of age in V2. This area receives direct inputs from V1. One purpose of the present study was to investigate whether aging effects are compensated for (for example, see Adams, 1987; Wong et al., 2000) or accentuated by higher order areas.

In this study, we found that orientation selectivity is affected more severely than direction selectivity in V2. In contrast, in V1 of the same old animals, orientation and direction selectivities decline by similar degrees. Therefore, the severe effects of age upon orientation selectivity in old monkey V2 cells cannot be due solely to changes in

V1. A degradation of the connections between V1 and V2 or a degradation of V2 itself must occur. Consistent with previous studies (Schmolesky et al., 2000; Leventhal et al., 2003; Wang et al., 2005; Hua et al., 2006), our results show that V2 cells in old monkeys exhibit increases in both visually driven and spontaneous responses. This suggests that degradation of inhibitory intracortical circuits may occur. Studies of human visual cortex show that L-glutamic acid decarboxylase (GAD), an enzyme needed to synthesize the inhibiting transmitter GABA, is reduced during aging (McGeer and McGeer, 1976). We have reported previously that GABA and its agonists improve cortical function in V1 of old monkeys (Leventhal et al., 2003). Recent psychophysical work in human also suggests decreased inhibitory function in the old human visual system (Betts et al., 2005). It is known that GABAergic interneurons are widely distributed in V2 (Kritzer et al., 1992). Thus, decreased GABAergic inhibition may underlie the changes reported here.

V2 is the largest extrastriate visual area in the macaque (Sincich et al., 2003). V1 and V2 show similarities in selectivity for such stimulus features as orientation and direction. The age-related decline of stimulus selectivity in V2 cells combined the similar results obtained in V1 (Schmolesky et al., 2000; Leventhal et al., 2003, Hua, et al., 2006) may provide an explanation for the deficits in orientation and shape discrimination (Weston, 1948; Ordy and Brizzee, 1979; Owsley et al., 1981; Kline and Schieber, 1985; Owsley and Sloane, 1987) and motion perception (Kline and Schieber, 1985; Tran et al., 1998) observed in aged people. Moreover, previous research has demonstrated that V2 plays a very important role in higher order visual processing. For example, V2 cells encode border-ownership (Zhou et al., 2000; Rossi et al., 2001) and relative disparity (Bakin et al., 2000; von der Heydt et al., 2000; Thomas et al., 2002) which are important for figure–ground segregation. Also, cells in V2 are more capable of representing three-dimensional objects (Bakin et al., 2000; Lee, 2003) and higher-order stimuli (Baker, 1999; Roe, 2004) than area V1 cells. After V2 lesions, the ability to discriminate complex shapes is severely disrupted while the ability to discriminate simple stimuli is intact (Merigan et al., 1993). The observed functional degradation of V2 cells in old monkeys may mediate age-related deficits in higher visual functions, such as the decreased ability to segregate figure from ground (Stanford and Pollack, 1984), 3-D (Norman et al., 2004) and second order motion (Habak and Faubert, 2000) representation.

CONCLUSION

In summary, the results of the present study provide evidence that the properties of cells in extrastriate cortex (V2) degrade in senescent animals. This functional degeneration does not simply reflect a degradation of inputs from V1. Further studies of the affects of age upon extrastriate cortex will help clarify the neural mechanisms underlying the deficits in higher order visual function that accompany normal aging.

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