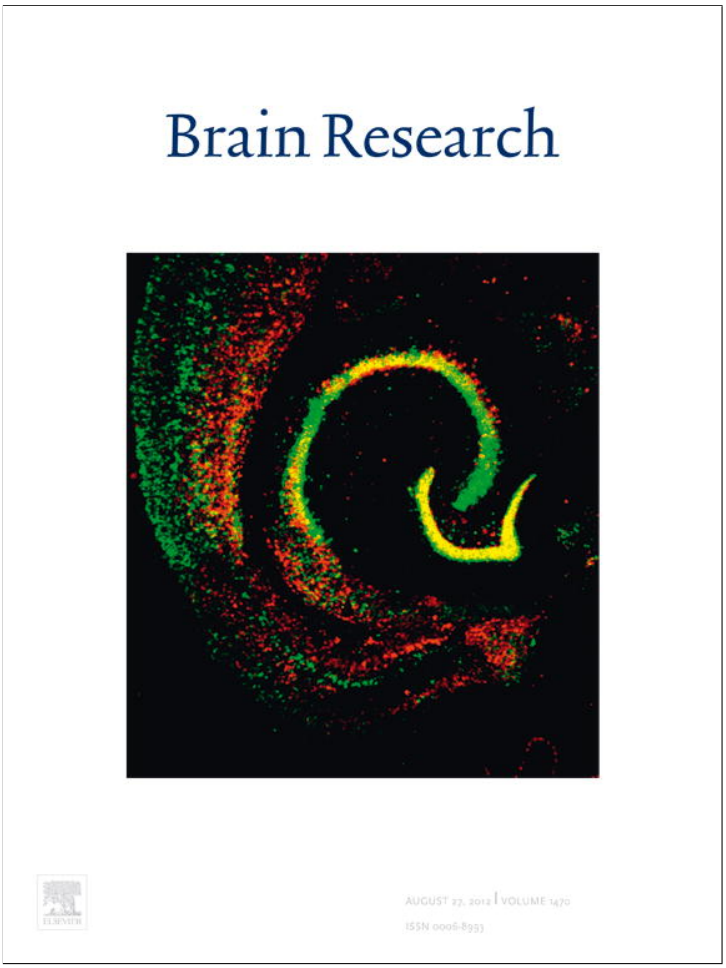

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Research Report

Selective effects of aging on simple and complex cells in primary visual cortex of rhesus monkeys

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ABSTRACT

The visual system is hierarchically organized between and within areas. Previous studies have found that aging affects different visual areas in a progressive manner, e.g. more degradation occurs in the primary visual cortex (V1) than in the dorsal lateral geniculate nucleus (dLGN), and more in the secondary visual (V2) and middle temporal (MT) visual areas than in V1. In view of these findings, we hypothesize that higher levels within the visual information hierarchy are affected more severely by aging. Hierarchies exist not only between visual areas but also within areas (e.g. V1, has a simple to complex cell hierarchy). We expected that a similar pattern of ageing effects should be found within a given visual area. To study this question, primary visual cortex is a good candidate because there is good evidence for the simple to complex cell hierarchy. In this paper, we applied single unit recording techniques to study the visual response properties of V1 simple and complex cells in young and old monkeys in vivo. We found that the orientation and direction selectivity of complex cells were significantly degraded in old monkeys, while those of simple cells were relatively spared from the effects of aging. These findings are consistent with the hypothesis that higher hierarchical levels in the visual system, both between and within areas, may be affected more severely by aging.

1. Introduction

The degradation of neuronal response properties which presumably underlies the decline in visual function accompanying normal aging has been investigated by using the single unit recording technique in a variety of visual areas (Liang et al., 2010; Schmolesky et al., 2000; Spear et al., 1994; Yang et al., 2008; Yu et al., 2006). The emergent picture suggests that the effect of aging could be differentiated at each processing stage and results in the progressive functional degradation along the hierarchy of

Abbreviations: ANOVA, analysis of variance; DB, direction selectivity; LGNs, lateral geniculate nucleus; MT, middle temporal area; OB, orientation bias; SE, standard errors of the mean; SD, standard deviation; RMR, relative modulation ratio; V1, primary visual cortex; V2, extrastriate cortex.

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visual-information processing. For example, studies have provided evidence that the effects of aging on the dorsal lateral geniculate nucleus (dLGN) are minor (Spear et al., 1994), whereas those in the striate cortex (V1/primary visual cortex) are substantial (Schmolesky et al., 2000; Spear et al., 1994). Neurons in extrastriate cortex (V2) have been found to be affected more greatly by aging than V1 (Yu et al., 2006). Similarly, area MT shows more age-related functional changes than V1 (Liang et al., 2010; Yang et al., 2009). Considering these findings together, we hypothesize that higher hierarchical levels are affected more severely by aging.

In addition to the hierarchical organization of different visual cortical structures or areas, hierarchical processing appears to occur even within individual areas. In area MT, for instance, pattern cells, which respond best when the axis of motion of a moving plaid pattern coincides with the cell's preferred axis of motion for a moving grating, are thought to be formed from a selective summation of earlier-stage component cells. The latter respond best to a moving plaid pattern when the axis of motion of either one of the component gratings coincides with the cell's preferred motion axis for a single grating stimulus (Movshon et al., 1986; Rust et al., 2006). In V1, simple and complex cells are also thought to represent successive stages in an information-processing hierarchy, i.e. complex cell receptive fields appear to be formed by summation of responses from multiple simple cells having the same orientation selectivity but different phase relationships (Alonso and Martinez, 1998; Alonso, 2009; Crowder et al. 2007; Gilbert, 1977; Hubel and Wiesel, 1962; Hubel and Wiesel, 1968; Ibboston et al., 2005; Martinez and Alonso, 2001; Martinez et al., 2005; Skottun et al.,1991; van Kleef et al., 2010). Simple cells play a role in the early stages of information processing (e.g. simple cells are selective to the orientation of a line in a specific location), while complex cells, which integrate the information obtained from simple cells, have positional invariance (e.g. complex cells are selective to the orientation of a line regardless of its exact position within the receptive field). Cells in primary visual cortex were classified as "simple" or "complex" by an index, the relative modulation ratio (RMR), defined as the ratio of the first Fourier component to the mean component (FFT1/FFT0) of a neuron's spike response to an optimal drifting sinusoidal grating (Skottun et al., 1991). Experiments showed that neuronal RMR values are distributed bimodally (e.g., Alonso and Martinez, 1998; Alonso, 2009; Crowder et al. 2007; Ibboston et al., 2005; Martinez et al., 2005; Skottun et al.,1991). The idea of two discrete classes of "simple" and "complex" cells has been challenged by some recent intracellular recording work (Mata and Ringach, 2005; Mechler and Ringach, 2002; Priebe et al., 2004; Ringach, 2004). The RMR values calculated from membrane potential response appear to lie on a continuum rather than in discrete categories, suggesting that simple and complex cells may represent the extremes of the continuum. However, recent work has shown that the concept of distinct simple and complex categories of spiking responses can be consistent with the action of a threshold on membrane potential responses that lie on a continuum (Crowder et al., 2007). In any case, it is generally accepted that the spiking responses of early cortical cells constitute categorically different cell classes, which probably have different roles in visual processing.

In the present study we wanted to address the question of whether complex cells, which are located at a higher stage of the visual processing hierarchy, are more severely affected by aging than simple cells. To assess this hypothesis, we investigated the spiking responses of V1 simple and complex type cells to visual stimuli in anesthetized and paralyzed monkeys.

2. Results

We recorded a total of 91 cells from the primary visual cortex of four young monkeys (5–9 years of age) and 50 cells of three old monkeys (16–20 years old). Based on the RMR (see Methods) (Movshon and Tolhurst, 1975; Skottun et al., 1991), we found 24 simple and 67 complex cells in young monkeys (26% simple, 74% complex), while in old monkeys we found 17 simple cells and 33 complex cells (34% simple, 66% complex). In each monkey, the data were collected from three to five penetrations. The recording depths and eccentricities (ranging from 2° to 29°) of the cells studied were comparable in the young and the old groups.

The distributions of RMR of neurons in the young and old groups were shown in Fig. 1. There was a bimodal distribution of the RMR in both aged and young groups. Statistical analyses indicated no significant difference between these two distributions (Kolmogorov–Smirnov or K–S test, $p=0.22$) and that the proportion of complex cells showing lower RMR (<1) in old monkeys was consistent with that in young monkeys ($p=0.34$), suggesting similar proportions of simple and complex cells in both groups.

Fig. 2 illustrates responses to visual stimuli of simple and complex cells recorded from young and old monkeys. Orientation bias (OB) and direction bias (DB) are used to measure the degree of tuning of cells to orientation or to the direction of motion of visual stimuli. Using these indices, the values of selectivity range from 0 to 1, with 0 indicating the cell is completely insensitive to orientation (direction) and 1 corresponds to response at only one orientation (direction). Orientation and direction selectivity (OB and DB, respectively) were

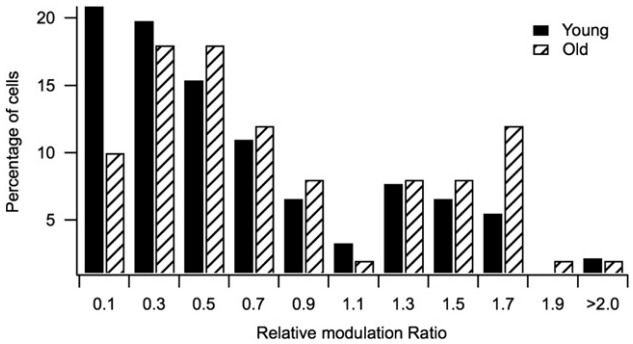

Fig. 1 – Distribution of RMR for V1 neurons in young and old monkeys. The distribution of RMR of neurons between the two age groups is similar (K–S test, $p=0.22$). The proportion of simple cells (having RMR >1) in old monkeys is consistent with that in young monkeys (K–S test, $p=0.34$).

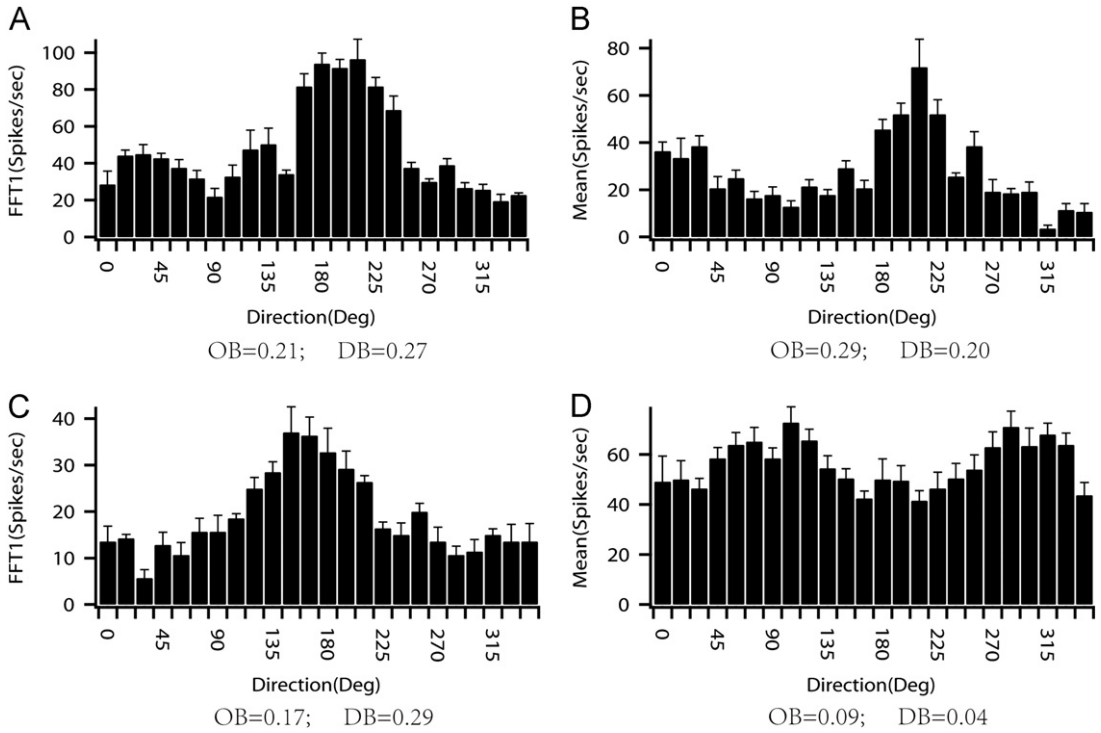

Fig. 2 – Tuning curves of grating responses as functions of orientation and direction of motion, for single neurons in young and old monkeys. The response for each direction is presented as the mean ± SE. The tuning curves of simple cells show similar profiles in young (A) and old monkeys (C). In contrast, the tuning curves of complex cells in old monkeys (D) have broader tuning (less selectivity) than those in young monkeys (B).

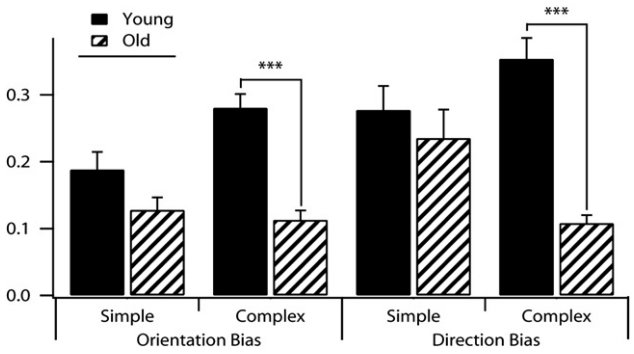

Fig. 3 – Effects of aging on indices of orientation selectivity and direction selectivity of simple and complex cells in area V1. Complex cells show significant age-related changes in orientation and direction selectivity, whereas simple cells show slight but non-significant decreases in old monkeys.

degraded in old monkeys. However, the shapes of the tuning curves of simple cells showed similar profiles in both young (Fig. 2A) and old monkeys (Fig. 2C). In contrast, the tuning curves of complex cells in old monkeys (Fig. 2D) exhibited less selectivity than those in young monkeys (Fig. 2B).

A summary of the response of simple and complex cells in young and old monkeys to sinusoidal gratings is shown in Fig. 3 and Table 1. All data in the figures and text are expressed as mean ± SD. A two-way ANOVA (age X cell type) showed a significant effect of age on OB ($F1,137=17.69$, $p<0.001$) and DB ($F1,137=11.26$, $p<0.001$), with no effect of the cell type on these response properties ($F1,137=1.31$, $p=0.25$; and $F1,137=1.01$, $p=0.32$, respectively). More importantly, the interaction between age and cell type showed that the declines in the OB ($F1,137=5.43$, $p<0.05$) and DB ($F1,137=8.79$, $p<0.01$) in complex cells were significantly greater than those in simple cells. To further examine this result, *t*-test was applied to the dataset. The OB and DB of complex cells showed a significant decrease in old monkeys (0.108 ± 0.014 and 0.106 ± 0.008, respectively) compared with those in young monkeys (0.280 ± 0.021 and 0.354 ± 0.031, respectively; *t*-test, both $p<0.001$). In contrast, the differences in the OB and DB of simple cells between the young (0.189 ± 0.027 and 0.278 ± 0.036, respectively) and old (0.139 ± 0.018 and 0.261 ± 0.045, respectively) monkeys were not significant (t-test, both $p>0.05$). Thus response selectivity exhibited more vulnerability to aging in complex cells than in simple cells.

We also examined age-related changes in the proportion of biased cells that had a bias index larger than 0.1. V1 cells were classified as "unbiased" (bias index < 0.1) or "biased" (bias index ≥ 0.1). By using contingency tables and chi-square tests for statistical evaluation, the age-related changes were examined in terms of the proportions of the two types of cells (Table 2). The percentages of unbiased and biased complex cells were significantly different between the two groups (chi-square, $p<0.001$), with a decreased proportion of the latter in old monkeys. Nevertheless, this was not the case for simple cells (chi-square, $p>0.05$). These findings further supported the idea that complex cells were more vulnerable to aging than simple cells.

Table 1 – Descriptive statistics of visual response properties of simple and complex cells in old and young monkey groups.

Cell types	Young monkeys	Old monkeys	Test	p value
OB (simple cells)	0.189 ± 0.027	0.139 ± 0.018	t-test	$p = 0.14$
OB (complex cells)	0.280 ± 0.021	0.108 ± 0.014	t-test	$p \ll 0.001$
DB (simple cells)	0.278 ± 0.036	0.261 ± 0.045	t-test	$p = 0.79$
DB (complex cells)	0.354 ± 0.031	0.106 ± 0.008	t-test	$p \ll 0.001$

By using independent samples t-test, comparisons of OB and DB are conducted between young and old monkey groups. Data are presented as mean $\pm$ SD. Cell types are noted in brackets.

Table 2 – Descriptive statistics of proportions of cells between young and old groups.

Cell types	Age group	Non-biased (%)	Biased (%)	p value
OB (complex)	Young	14 (20.90)	53 (79.10)	$x = 9.7$, $df = 1$, $p < 0.01$
	Old	17 (51.52)	16 (48.48)	
DB (complex)	Young	13 (19.40)	54 (80.60)	$x = 14.8$, $df = 1$, $p < 0.001$
	Old	19 (57.58)	14 (42.42)	
OB (simple)	Young	8 (33.33)	16 (66.67)	$x = 0.07$, $df = 1$, $p = 0.79$
	Old	5 (29.41)	12 (70.59)	
DB (simple)	Young	5 (20.83)	19 (79.17)	$x = 0.04$, $df = 1$, $p = 0.84$
	Old	4 (23.53)	13 (76.47)	

By using contingency tables, the age-related changes were examined in proportions of non-biased (bias index < 0.1) and biased cells (bias index ≥ 0.1). The proportions of biased complex cells decreased in old monkeys. In contrast, no age-related changes are found in simple cells.

3. Discussion

Our results provide the first evidence for selective effects of aging on simple and complex cells in the primary visual cortex. We have shown that the OB and DB selectivity indices of simple cells were about the same in V1 of young and old monkeys. However, the selectivity of complex cells showed significant age-related changes. These different degradations of stimulus selectivity in V1 simple and complex cells are consistent with a selective effect of aging on different stages of hierarchical processing in the visual pathway.

As proposed by a number of studies (Alonso and Martinez, 1998; Alonso, 2009; Hubel and Wiesel, 1962; Martinez and Alonso, 2001), the visual information-processing path of the primary visual cortex involves simple cells at an early level, whose responses are then integrated by complex cells. Previous studies found that age-related visual aberration begins with the primary visual cortex (Hua et al., 2006; Schmolesky et al., 2000). To thoroughly understand the effects of aging on the primary visual cortex, knowing which level first shows a significant degradation is necessary. Recently, Wang et al. (2005) measured the levels of spontaneous and visually evoked activity, and the visual-response latencies of cells in areas V1 and V2 of young and very old monkeys. Their results showed that V1 cells within layer IV showed about the same latencies in young and old animals, whereas this was not the case for the cells in other parts of V1 and throughout V2. Because simple cells mainly lie within the range of thalamic afferents, which are convergent in layer IV of the striate cortex, and complex cells exist in the range of simple-cell axons that are convergent in the superficial layers (Hubel and Wiesel, 1962), this finding is consistent with different effects of aging on the simple and complex cells. In the present study, we have carefully examined the effects of aging on the orientation and direction selectivity of simple and complex cells. In accordance with the results of the study by Wang et al. (2005), we have found that the stimulus selectivities of simple cells were relatively similar in young and old animals; however, complex cells were significantly affected by age.

Our results have implications for the relation between functional degradation of different hierarchical levels in the visual pathway and the effects of aging. Generally, neurons receive visual information from lower levels, synthesize or integrate the information, and send it to higher levels. Subtle age-related changes in lower (earlier) processing levels, which may be difficult to experimentally detect, can be "inherited" by neurons at higher (later) processing levels. As a result, neurons at a higher processing level may show significant effects of aging due to cumulative effects from earlier stages. This may be the explanation underlying our findings that complex cells are significantly affected by aging, whereas simple cells are not. Based on this concept, we could expect that higher levels in the hierarchy than the complex-cell system should show similar, or even more severe, functional degradation in old animals. Indeed, previous studies have indicated that the effects of aging on the dLGN are minor, whereas those in the striate cortex, the subsequent processing area, are substantial (Schmolesky et al., 2000; Spear et al., 1994). Also studies on monkeys (Liang et al., 2010; Yang et al., 2008; Yang et al., 2009; Yu et al., 2006) have found that neurons in V2 and MT show more severe age-related degradation than those in V1. At the intracortical level, Liang et al. (2010) have found that older monkeys have a reduced percentage of pattern-cells relative to the proportion of component cells; the latter are lower in the hierarchy than the former. Overall, the hierarchical-aggravation hypothesis

that the aging effect is aggravated level-by-level in the hierarchy is supported by these results.

The hierarchical-aggravation hypothesis is also consistent with human psychophysical findings. Based on a series of studies of the effects of aging on perceptual processing and working-memory capacity for visual stimuli, Faubert (2002) concluded that a number of perceptual abilities diminish with age and that the extent of these deficits depends on the complexity of the neural circuitry required for processing in a given task. An example is related to the perception of first- and second-order stimuli. First-order stimuli are defined by modulations of luminance, e.g. sinewave gratings, and require only a single stage of linear filtering to explain their selective processing. Second-order stimuli are defined by changes in features, such as contrast or texture (Lu and Sperling, 2001), and their processing minimally requires a two-stage processing mechanism, i.e. an early filter selective for the texture features, and a late-stage filter selective for the modulation (Baker, 1999; Chubb and Sperling, 1989; Lu and Sperling, 2001; Wilson et al., 1992). Emerging evidence has suggested that the contrast sensitivity for first- and second-order stimuli are influenced differently by normal aging. The latter shows a significant decline much earlier (Tang and Zhou, 2009) during senescence and is more greatly affected by aging (Habak and Faubert, 2000) than the former. All these findings are consistent with the hierarchical-aggravation hypothesis proposed here. In most cases, more complex neuronal circuitry is required for information processing at higher levels and, therefore, these regions are more susceptible to age-related changes than those involved in more basic information processing.

In conclusion, we have found significant age-related changes in the complex cells but not in the simple cells of V1 in 16- to 20-year-old monkeys. We have therefore proposed a hierarchical-aggravation hypothesis based on this finding. We suggest that this hypothesis is consistent with previous findings in electrophysiology and human psychophysics.

4. Experimental procedures

4.1. Animals

The experiments were conducted on four young adult (4–6 years old) monkeys and three old (16–20 years old) male rhesus monkeys (Macaca mulatta). According to a life-span analysis of rhesus macaques by Tigges et al. (1988), the young monkeys in our study are sexually mature and the old monkeys studied are comparable to 60-year-old humans. All the monkeys were examined professionally by two ophthalmologists before the experiment to ascertain that they had no optical problem or obvious retinal problem that would impair visual function. All animal treatments were conducted strictly in accordance with the guidelines of the Society for Neuroscience and the National Institutes of Health. The experiments described here were approved by the University of Utah Institutional Animal Care and Use Committee.

4.2. Preparation for extracellular recording

The techniques used in our laboratory have been reported in detail elsewhere (Schmolesky et al., 2000). Briefly, monkeys were sedated with ketamine-HCl (10 mg/kg) and then anesthetized with halothane (5%) in a 75:25 mixture of NO_2:O_2. Intravenous and tracheal cannulae were next 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) and gallamine trithiodide (7 mg/kg/h) was infused intravenously to induce and maintain paralysis. The monkeys were ventilated, and anesthesia was maintained with a mixture of NO_2 (75%) and O_2 (25%), with the addition of halothane (0.25–1.0%). The expired CO_2 was maintained at approximately 4%, and the body temperature was maintained at 38 °C. The electrocardiograms and cortical electrical activity were monitored throughout the experiments to assess the level of anesthesia. We adjusted the level of anesthesia so that all the vital signs were comparable in young and old animals.

A 4-mm craniotomy was centered over the midline and 4 mm posterior to the ear bars, filled with 4% agar in saline, and sealed with petroleum jelly. The eyes were protected from desiccation with contact lenses. We recorded extracellular action potentials with glass-coated tungsten or glass microelectrodes (1–3 MΩ). V1 cells were studied at eccentricities ranging from 2° to 40°; however, most of the cells studied were between 3° and 15°. The electrode was advanced using a hydraulic microdrive (David Kopf Instruments, Tojunga, California).

4.3. Visual stimulation

We displayed all visual stimuli at a resolution of 1024×768 pixels and a frame rate of 100 Hz on a Sony Multiscan G220 monitor. The monitor was placed 57 cm from the animals' eyes, where it subtended a visual angle of $32 \times 24°$. The visual stimulus patterns composed drifting sinusoidal gratings in a circular aperture. The program to generate the stimuli was written in MATLAB®, using the extensions provided by the high-level Psychophysics Toolbox (Brainard, 1997; Pelli, 1997) and low-level Video Toolbox (Pelli, 1997). The mean luminance of the display was 37.8 cd/m^2 (candela per square meter). We presented the stimuli to the dominant eye. The starting phase was set to zero for all stimuli. The duration of two neighboring stimuli were equal (typically, 3 s). When a single unit was isolated, the cell's receptive field was carefully mapped by consecutively presenting a series of computer-generated sinusoidal grating patches, with the preferred direction determined by listening to the audio monitor. Then, we determined the optimal spatial and temporal frequency, size, and direction. After these initial characterizations of each cell, we randomly presented drifting sinusoidal gratings with 24 directions of motion. The contrast of each stimulus was 100%.

4.4. Data collection and analysis

After the response of an isolated cell was amplified with a microelectrode amplifier (DAGAN, USA), it was displayed on an oscilloscope, fed into an audio monitor, and digitized

using an acquisition board (National Instruments, USA) controlled by IGOR software (WaveMetrics, USA). The cells' grating responses were stored on hard disk for later analyses. At the time of each presentation, the spontaneous values were obtained during a 0.5–1 "second stationary sinewave grating" period. Spontaneous values below 1 spike/s were set to 1 spike/s for analyses of the signal–noise ratio (Schmolesky et al., 2000).

Indexes of orientation and direction selectivity were calculated for each cell using statistical methods described in detail elsewhere (Leventhal et al., 1995). Briefly, the responses of each cell to the different grating drift directions were represented as a series of vectors, and their vector-sum was then divided by the sums 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 vectors, termed the OB and DB, provided quantitative measures of the cell's orientation and direction selectivity

$$OB = \left| \frac{\sum_k R_k e^{j2\theta_k}}{\sum_k R_k} \right|$$

$$DB = \left| \frac{\sum_k R_k e^{j\theta_k}}{\sum_k R_k} \right|$$

where R_k is the mean spike rate in response to a drifting grating with direction θ_k (in radians). For *OB*, the responses were averaged for the two directions of motion at each orientation. The *OB* and *DB* indices are quite robust to noise in the data, and provide bounded ranges from 0 to 1, with 0 indicating complete isotropy (lack of tuning) to orientation (direction), and one corresponding to response at only one orientation (direction), i.e. perfect tuning.

Cells were classified as simple or complex based on the widely used criterion of RMR, defined as the ratio of the first Fourier component to the mean component (FFT1/FFT0) of a neuron's response to optimal-drifting sinusoidal gratings, after subtraction of the spontaneous response. The cell is classified as a simple cell when the ratio is above one and as a complex cell when the ratio is less than one (Skottun et al., 1991).

Acknowledgments

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