Neurobiology of Aging 76 (2019) 1–8

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Aging affects correlation within the V1 neuronal population in rhesus monkeys

Xuan Wang [a], Bing Zhang [a], Huan Wang [a], Jiachen Liu [a], Guangwei Xu [a,*], Yifeng Zhou [a,b,c,**]

[a] Hefei National Laboratory for Physical Sciences at Microscale, School of Life Science, University of Science and Technology of China, Hefei, Anhui, P.R.China
[b] State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Sciences, Beijing, P.R.China
[c] Neurodegenerative Disorder Research Center and Brain Bank, Material Science at Microscale National Laboratory, School of Life Sciences, Key Laboratory of Brain Function and Disease, Chinese Academy of Sciences, University of Science and Technology of China, Hefei, Anhui, P.R.China

ARTICLE INFO

Article history:
Received 11 May 2018
Received in revised form 29 November 2018
Accepted 29 November 2018
Available online 7 December 2018

Keywords:
Aging
Monkey
V1 area
Neuronal correlation
Inhibitory circuitry

ABSTRACT

Visual function declines with age. This deterioration results not only from changes in the optical system but also from the functional degradation of the central visual cortex. Although numerous studies have explored the mechanisms of age-related influences on vision, they have failed to acknowledge the significance of neuronal correlation in dysfunction of the visual cortex. Previous research has focused on the functional degradation of individual neurons, with age-induced changes in correlation between neurons still unknown. In the present study, using electrophysiological techniques, we investigated the age-related changes in neuronal correlation in the macaque V1 area and the underlying mechanisms of those changes. Our results showed that aging led to an increase in the correlation of neurons and changed the noise-signal correlation structure, which may impact population coding efficiency. Furthermore, we found that the age-induced decline in the inhibitory circuitry accounted for the alteration in neuronal correlation.

1. Introduction

Visual abilities in humans decline with age. Previous psychological studies have shown deficits in the visual functions of the elderly, and electrophysiological studies have provided a wide range of evidence for age-related neuronal changes within the visual cortex (Hua et al., 2006; Leventhal et al., 2003; Liang et al., 2010; Schmolesky et al., 2000; Wang et al., 2005, 2014; Yang et al., 2008, 2009a,b; Yu et al., 2005, 2006; Yuan et al., 2014; Zhang et al., 2008).

The receptive properties of neurons and interactions among neurons are key factors determining the functions of the visual cortex. During aging, the receptive properties of neurons decline markedly in the visual cortex, with the orientation and direction tuning abilities of visual neurons also weakened in aged animals (Schmolesky et al., 2000). In addition, the contrast sensitivity of aged visual neurons is inferior to that of young visual neurons (Yang et al., 2008). Other receptive properties also decline significantly with age (Wang et al., 2005; Yang et al., 2009a,b; Yu et al., 2005; Zhang et al., 2008). In the context of aging, however, no attempt has been made to explore the changes in neuronal correlation, a type of interactive relationship among neurons. Therefore, the relationship between the alteration of neuronal correlation and dysfunction of the visual cortex remains poorly understood.

Neuronal correlation includes noise correlation and signal correlation. With repeated presentations of identical stimuli, the responses of neurons from trial to trial can be extremely variable (Shadlen and Newsome, 1998; Tolhurst et al., 1983). This variability is often shared among neurons. The degree of shared trial-to-trial variability in neuronal populations is called noise correlation, whereas signal correlation refers to the correlation of the mean responses of the neuronal population to an ensemble of stimuli (Cohen and Kohn, 2011). Neuronal correlations have a strong impact on the accuracy of information processing (Abbott and Dayan, 1999; Averbeck et al., 2006; Shadlen and Newsome, 1998;

* Corresponding author at: Hefei National Laboratory for Physical Sciences at Microscale, School of Life Science, University of Science and Technology of China, Hefei, Anhui 230027, P.R.China. Tel./fax: +86-0551-63601436.
** Corresponding author at: Hefei National Laboratory for Physical Sciences at Microscale, School of Life Science, University of Science and Technology of China, Hefei, Anhui 230027, P.R. China, State Key Laboratory of Brain and Cognitive Science, Institute of Biophysics, Chinese Academy of Sciences, Beijing 100101, P. R. China, Neurodegenerative Disorder Research Center and Brain Bank, Material Science at Microscale National Laboratory, Key Laboratory of Brain Function and Disease, Hefei, Anhui 230027, P.R.China. Tel./fax: +86-0551-63601436.
E-mail addresses: weixu@mail.ustc.edu.cn (G. Xu), zhouy@ustc.edu.cn (Y. Zhou).

0197-4580/$ – see front matter © 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.neurobiolaging.2018.11.025

Zohary et al., 1994) and play a functional role in the processing of visual information (Graf et al., 2011; Smith and Kohn, 2008). Zohary et al. (1994) reported that the correlation of neuronal discharge can impact perceptual capacities. Consequently, determining how correlations are affected by aging is likely to be as important as understanding how aging affects the firing rates of individual neurons (Leventhal et al., 2003; Schmolesky et al., 2000).

We used extracellular multielectrode array recordings to examine changes in neuronal correlation in the V1 area between young and old rhesus monkeys. We found that aging increased noise correlation and disturbed the relationship between noise and signal correlation, which may be due to decay of the gamma-aminobutyric acid inhibitory system. These results should be helpful for understanding the decline in visual perception induced by aging, such as the speed of processing visual information, contrast sensitivity, and visual motion perception (Elliott et al., 1990; Norman et al., 2003, 2004; Owsley, 2011; Sloane et al., 1988; Snowden and Kavanagh, 2006).

2. Methods

2.1. Animal preparation and maintenance

Seven rhesus monkeys (*Macaca mulatta*; 5 males and 2 females) were classified into young (3 monkeys, 5–9 years old) and old groups (4 monkeys, 23–30 years old). All subjects were examined by ophthalmoscopy to confirm that their eyes were free of optical and retinal problems. All experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Institutional Animal Care and Use Committee of the University of Science and Technology of China.

Animal preparation was similar to that described in our previous study (Li et al., 2014). In brief, monkeys were first anesthetized with ketamine HCl (10 mg/kg, i.m.; Ben Venue Lab Inc, Bedford, OH, USA) and then maintained with isoflurane (3%–5%, in oxygen) during surgery. After tracheal and venous cannulation, the animals were placed on a stereotaxic apparatus. During the surgery and subsequent recordings, the ECG activity, respiratory rate, oxygen saturation (SpO_2), and expired CO_2 were monitored by the anesthetic gas module of the monitor (PM-7000, Mindray, Dartford, UK). When the level of expired CO_2 was close to 4.5% or 3.5%, tidal volume was decreased or increased, respectively, to ensure that the level of CO_2 was kept within 3.5%–4.5%. Rectal temperature was maintained at 37.5°C by an automated heating pad (Harvard Apparatus, Holliston, USA) during the experiment. After the animal's vital signs had stabilized, a small burr hole was drilled above the striate cortex (V1) and then protected with a solution of agar (4.5%, in saline) and petroleum jelly.

During the recordings, anesthesia and paralysis were maintained by a continuous infusion of propofol (4 mg kg^{-1} $hour^{-1}$, i.v.), sufentanil (0.8 $\mu g \cdot kg^{-1} \cdot hour^{-1}$, i.v.), and gallamine triethiodide (7 mg kg^{-1} $hour^{-1}$, i.v.). Furthermore, anesthesia was supplemented with a mixture of N_2O (70%) and O_2 (30%). Atropine sulfate (1 mg, i.m.), dexamethasone (5 mg, i.m.), and penicillin (125 mg, i.m.) were administered every 12 hours throughout the experiment. Supplemental fluids (Ringer's solution and 5% dextrose, i.v.) were administered at 120 mL every 12 hours, adjusted based on urinary output.

Pupils were dilated with 0.25% tropicamide eye drops. Contact lenses were used to protect the corneas from desiccation; spectacle lenses and artificial pupils were used when needed. The optic disks were backprojected to a plotting screen using an ophthalmoscope and a corner cube prism. Experiments typically lasted 3–5 days. We checked the optical quality of the eyes frequently and cleaned the contact lenses as necessary during the experimental period.

2.2. Visual stimuli

All visual stimuli were displayed on a CRT monitor (640 × 480 pixels, 75 Hz, 45.2 cd/m^2 mean luminance; Sony G220, Japan) placed 114 cm from the animal. The program to generate the stimuli and perform online data analysis was written in MATLAB (MathWorks, USA) using the Psychophysics Toolbox (PTB-3) extensions (Brainard, 1997). Before each experiment, we checked or recalibrated the luminance nonlinearities of the CRT. We adopted drifting gratings as the visual stimuli. Each stimulation trial lasted 1 second. In the pattern for orientation selectivity, the Michelson contrast of the stimuli was set to 95%. The visual stimuli were presented 10 times (10 sweeps), with 12 different directions and a blank stimulus randomly interleaved in every sweep. The drifting grating (4 cycles per s) in each direction was presented for 1 second in every sweep. The blank stimuli consisted of the average brightness shown on a CRT monitor.

2.3. Data collection and analysis

Linear silicon electrodes were used (A1x32, electrode array width 100 μm; site area 177 μm^2; NeuroNexus, Ann Arbor, USA) in this study. All neuronal signals were passed through a front-end amplifier (cutoff frequency 10 kHz, 1000× Blackrock, Salt Lake City, USA) and digitized by a neural signal processing system (sampling frequency 30 kHz, 16 bits, Blackrock). Spikes were saved and detected using cluster analysis for offline data analysis (Offline Sorter v3.3.5, Plexon, USA). Based on the 2D or 3D features and spatial distribution, single units were isolated from the background noise by multiple algorithms.

2.4. Calculation of response variability and signal-to-noise ratio

In the visual system, the responses of neurons are extremely variable. The spike counts elicited by identical stimuli vary significantly from trial to trial. Spike count variability is often quantified by the ratio of variance to mean spike count, defined as the Fano factor (FF):

$$FF = \frac{\sigma^2}{R_{means}}$$

The signal-to-noise ratio (SNR) is an important parameter used to measure the signal extraction capacity and fidelity of an individual neuron. Here, SNR_σ was adopted and calculated as follows:

$$SNR_\sigma = \frac{R_{means}}{\sigma}$$

where σ is the standard deviation of the spike count and R_{means} is the mean response of neurons to each trial.

2.5. Measures of correlation

We characterized correlation using the spike count correlation, r_{sc}, that is, the Pearson correlation coefficient of the evoked spike counts of 2 cells to the repeated presentation of a particular stimulus. The variable r_{sc} was calculated as follows (Kohn and Smith, 2005):

$$r_{SC} = \frac{E(N_1 \cdot N_2) - E(N_1) \cdot E(N_2)}{\sigma_{N_1} \cdot \sigma_{N_2}}$$

where E is the expected value under the stimulus direction that can evoke the most neurons, σ is the SD of the responses, and N_1 and N_2 are the spike counts of cells 1 and 2, respectively. Before the noise correlation was calculated, the spike counts of neurons were normalized by subtracting the mean and dividing by the SD of the set of responses. Statistical evaluation was performed after converting r_{sc} to Z-scores using the Fisher transformation as follows:

$$z = \frac{1}{2}\ln\left(\frac{1+r_{SC}}{1-r_{SC}}\right)$$

Subsequently, we determined tuning similarity as the signal correlation r_{signal}, which was calculated as the Pearson correlation of the mean responses of cells to each tested direction (Ko et al., 2011). The value of r_{signal} is near 1 for neurons with similar orientation tuning and approaches -1 for neurons with opposite tuning.

To exclude interference from the differences in firing rates between a pair of neurons, we measured the difference (d) as follows:

$$d = \frac{|R_1 - R_2|}{(R_1 + R_2)}$$

where, R1 is neuron 1, R2 is neuron 2, and | | indicates absolute value.

2.6. Statistical analysis

When comparing the differences in average value between 2 groups, we used the paired *t*-test or Mann-Whitney test based on the sample distributions. We analyzed the correlation relationship between different parameters by Spearman correlation. We performed linear regression fitting on the data and compared the differences between the slopes of the lines by ANOVA interaction effect. All results in the present study were expressed as means ± SEM.

3. Results

We recorded a total of 492 cells in young monkeys and 344 cells in old monkeys. Neurons were recorded from the same cortical depths and with similar receptive field eccentricities (<8°) for each monkey.

3.1. Variability and SNR of individual neurons

We previously reported that the response variability in old monkeys is significantly higher than that in young monkeys (Yang et al., 2009a). Our current results further confirmed this finding. As shown in Fig. 1, the V1 cells exhibited a larger response variability and lower SNR in old monkeys than in young monkeys (Fano factor, 1.90 ± 0.05 for young group and 2.35 ± 0.04 for old group, $p = 0.0072$, Mann-Whitney test; SNR_σ, 2.35 ± 0.09 for young group and 2.16 ± 0.05 for old group, $p = 0.0356$, Mann-Whitney test).

3.2. Age-related effects on noise correlation and relationship between noise and signal correlation

Our main goal was to examine whether aging modifies neuronal correlations. We used the 32-channel linear electrode array to record the responses of neurons to visual stimuli with different directions and calculated the noise correlation of neurons not more than 2.6 mm apart. The distance between the neurons was estimated from the physical distance between the recording sites. In total, we analyzed 3920 and 4191 pairs in the young and old groups, respectively.

A significant negative correlation was observed between r_{sc} and distance in both groups (young: $r = -0.88$, $p < 0.0001$; old: $r = -0.81$, $p < 0.0001$, Spearman correlation) (Fig. 2A), as reported in previous studies on adult animals (Gu et al., 2011; Huang and Lisberger, 2009; Smith and Kohn, 2008). In the V1 area of both young (dashed line) and aged (solid line) macaques, the noise correlation decayed as the distance between neurons increased. Furthermore, we found that the negative correlation of the young group was more significant than that of the old group (slope: $k = -0.037 \pm 0.005$, old group; $k = -0.054 \pm 0.006$, young group; $p = 0.035$, ANOVA interaction effect).

Across all pairs in the young group, the average value of r_{sc} was 0.239 ± 0.004, similar to previous measurements in V1 (Gutnisky and Dragoi, 2008; Kohn and Smith, 2005; Rasch et al., 2011; Reich et al., 2001; Smith and Kohn, 2008). Nevertheless, there was a significant difference between the 2 groups, with the old group exhibiting an average r_{sc} value of 0.343 ± 0.005 (Fig. 2B). Across all distances, the average r_{sc} for each distance in the old group increased significantly compared to that in the young group. Thus, these results suggest that aging increased the noise correlation of the neuronal populations in the macaque V1 area.

The signal correlation between pairs of neurons (r_{signal}) was measured as the Pearson correlation coefficient of the mean responses across all stimulus directions (Vinje and Gallant, 2000). Results indicated that the mean r_{signal} was positive and stronger in the old group than that in the young group, both overall and at various distances (Figs. 3A and B).

It is well established that r_{sc} is related to r_{signal} (Cohen and Maunsell, 2009; Cohen and Newsome, 2008; Gutnisky and

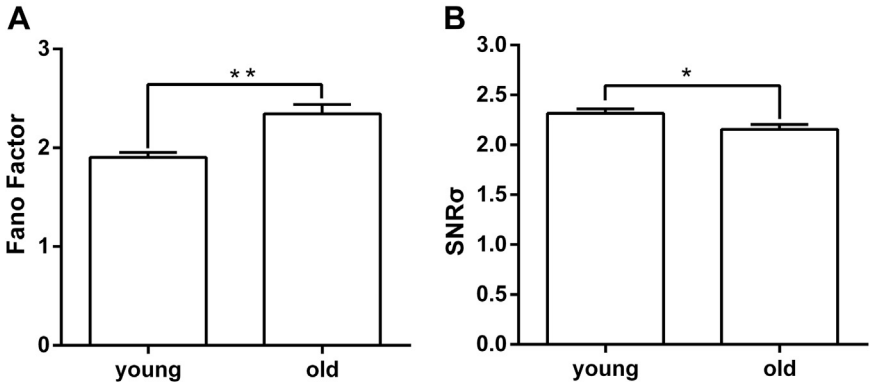

Fig. 1. Comparisons of the Fano factor and SNR_σ in V1 cells from young and old monkeys. (A) Fano factor of single units. (B) Signal-to-noise ratio of signal units. Mann-Whitney test was used. $^*p < 0.05$, $^{**}p < 0.01$. Data are means ± SEM. Abbreviation: SNR, signal-to-noise ratio.

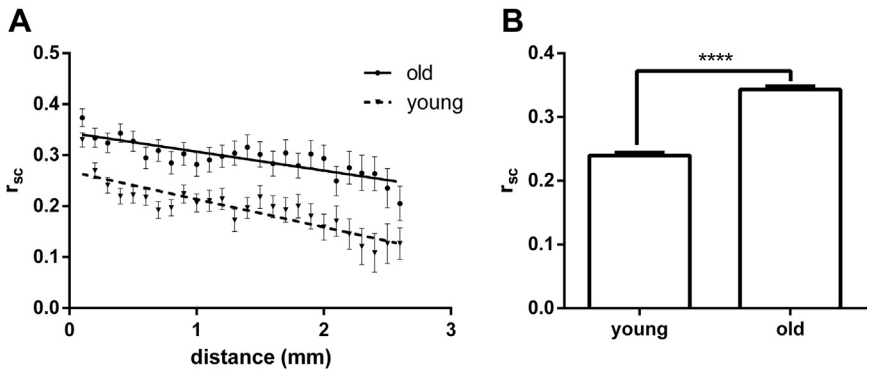

Fig. 2. Measurement of noise correlation. (A) Dependence of r_{sc} on distance in young and old groups. Distance bins started at 0.1 mm and extended to 2.6 mm in 0.1 mm increments. Average of all data was plotted at the center value of each bin. Error bars on this and all subsequent plots indicate mean ± SEM; young group: dot and solid line; old group: triangle and dashed line. Lines represent regression fits (ANOVA). (B) Average value of r_{sc}, which was significantly affected by aging ($p < 0.0001$, Mann-Whitney test). ****$p < 0.0001$.

Dragoi, 2008; Huang and Lisberger, 2009; Kohn and Smith, 2005; Smith and Kohn, 2008; Zohary et al., 1994); therefore, it is essential to evaluate whether aging alters this relationship. Fig. 3C shows the relationship between r_{sc} and r_{signal} in the 2 groups, quantified using general linear models with r_{signal} as a continuous variable and age group as a categorical factor. Analysis showed that there was a significant positive correlation between r_{sc} and r_{signal} in both the young and old groups (young: $r = 0.15$, $p < 0.0001$; old: $r = 0.37$, $p < 0.0001$, Spearman correlation).

Importantly, there was a significant difference in the slope of the relationship of r_{sc} and r_{signal} between the young and old groups (slope: $k = 0.097 \pm 0.010$, young group; $k = 0.289 \pm 0.011$, old group; $p < 0.0001$, ANOVA interaction effect), with stronger interaction between the 2 types of correlations detected in the old group. The accuracy of information processing strongly depends on population coding in the cortex (Abbott and Dayan, 1999; Averbeck et al., 2006; Shadlen and Newsome, 1998; Zohary et al., 1994). The quality of population coding is influenced by the tuning functions of individual neurons (Butts and Goldman, 2006) and the structure of neuronal correlations, which is, in turn, affected by both the relationship between r_{sc} and r_{signal} and the distribution of neuronal correlation (Cohen and Maunsell, 2009; Cohen and Newsome, 2008; Gutnisky and Dragoi, 2008; Smith and Kohn, 2008; Zohary et al., 1994). The change in the relationship between r_{sc} and r_{signal} implies that population coding may be disturbed (Gu et al., 2011).

3.3. Age-related effects on the basic properties of correlation

Over the past 2 decades, noise correlation has been reported in many cortical areas under a variety of behavioral and stimulus conditions. In those studies, noise correlation tended to be highest for nearby neurons (Lee et al., 1998; Smith and Kohn, 2008) and those with similar functional properties or tuning (Cohen and Maunsell, 2009; Ecker et al., 2010; Gutnisky and Dragoi, 2008; Huang and Lisberger, 2009; Kohn and Smith, 2005; Zohary et al., 1994). Many other factors can also systematically bias correlation estimates, such as response strength, time period for counting spikes, spike sorting, and fluctuations in internal states (Cohen and Kohn, 2011). In our experiment, the time period for counting spikes and method of spike sorting did not differ between the young and old groups. Hence, we were able to focus on the other factors participating in the age-related effects of noise correlation.

To analyze the relationship between response strength and noise correlation, we measured the geometric mean responses of neuron pairs (Cohen and Kohn, 2011). In our study, r_{sc} depended on the response strength of each neuron in the pair (Fig. 4A) and their geometric mean response (Fig. 4B), which is consistent with previous studies (Cohen and Maunsell, 2009; de la Rocha et al., 2007; Ecker et al., 2010; Mitchell et al., 2009). The value of r_{sc} increased with the increase in firing rate in both the young and old groups. Previous studies have shown that aging increases the firing rate of individual neurons in many cortical areas (Hua et al., 2006; Leventhal et al., 2003; Schmolesky et al., 2000; Yuan et al., 2014; Zhang et al., 2008). Therefore, the increase in noise correlation could be attributed to the age-related increase in the response strength of neuron pairs. However, we wanted to know whether the change in r_{sc} was entirely from the increase in response strength. Therefore, we studied the effect of aging on the relationship between r_{sc} and response strength. Results showed that the r_{sc} of the

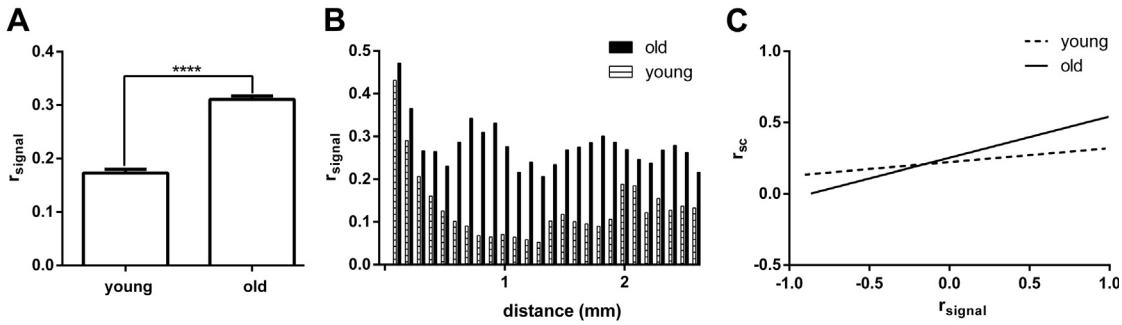

Fig. 3. Aging affected the relationship between noise and signal correlation. Mean values of r_{signal} were stronger in the old group than in the young group, both overall (A) and at various distances (B). (C) r_{sc} was correlated with r_{signal} in both the young and old groups. Data points of each pairs are not shown in this scatter plot. Lines represent regression fits. Solid line: old group; dashed line: young group. ****$p < 0.0001$.

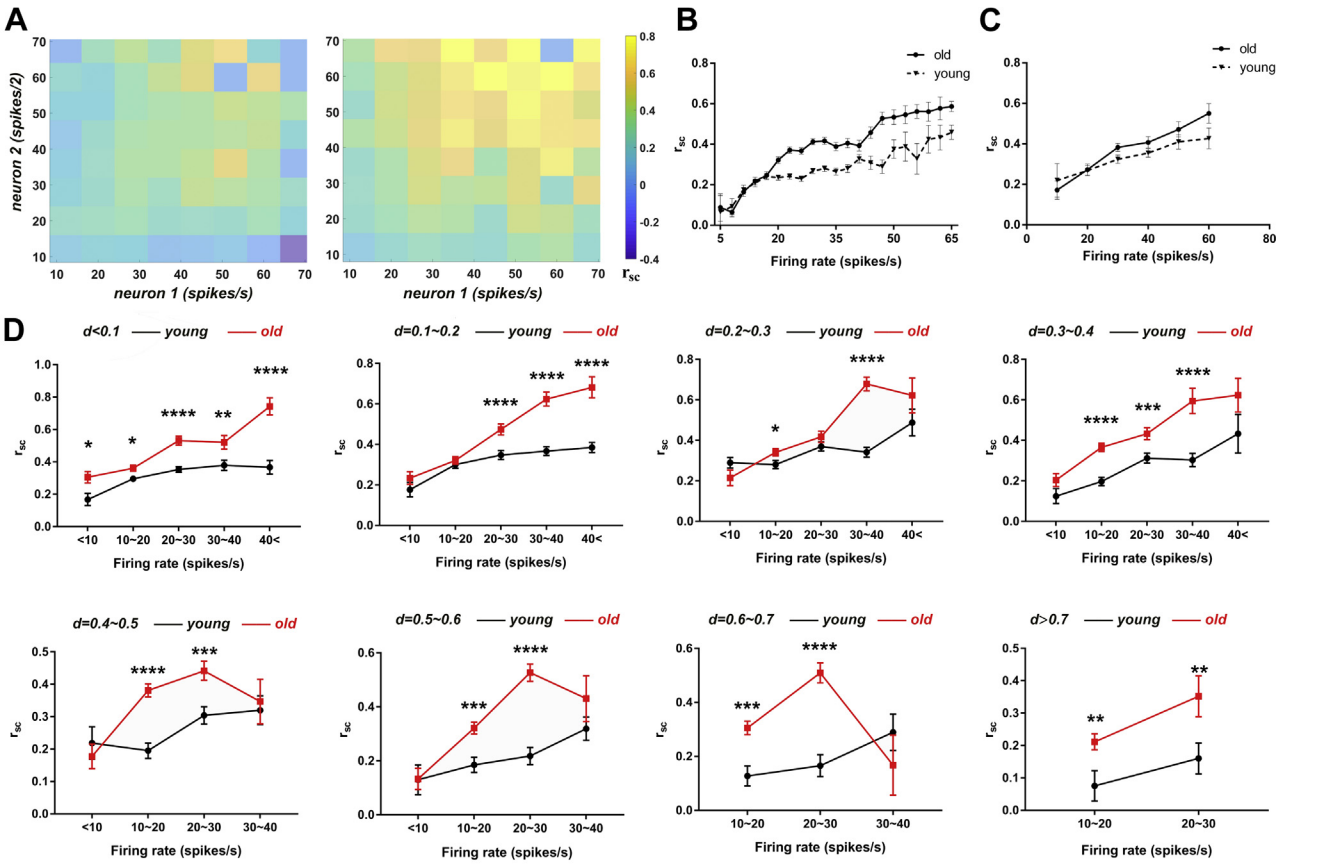

Fig. 4. r_{sc} depended on response strength. (A) r_{sc} increased with the firing rate of each 2 neurons. The right graph indicates old group, whereas the left graph indicates the young group. (B) Value of r_{sc} increased with the geometric mean firing rate in young and old groups. (C) Value of r_{sc} from pairs within a 0.2-mm distance in young and old groups. (D) Comparison of r_{sc} between old and young groups at different d levels and firing rates. $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; $^{****}p < 0.0001$. Young group: dot and solid line; old group: triangle and dashed line.

old group was greater than that of the young group under the same response strength conditions (Figs. 4A and B). However, in addition to the geometric mean response, r_{sc} is also related to the firing rate of the neuron with weaker response strength in a pair of neurons (Cohen and Kohn, 2011). Therefore, considerable differences (d) in firing rates between a pair of neurons will lead to a weak noise correlation. To exclude the impact of d, we compared r_{sc} between the old and young groups at different d levels and firing rates. Results showed that the old group had a stronger noise correlation than the young group at all d levels and all firing rates (Fig. 4D). This phenomenon was ubiquitous regardless of the magnitude of response strength. However, the age-related increase in the firing rate was not the only factor influencing the increase in noise correlation. The abovementioned results were calculated across all pairs of neurons, regardless of distance. To eliminate the impact of distance, we reanalyzed the data from pairs within a distance of 200 μm (young: 623 pairs; old: 603 pairs). As shown in Fig. 4C, the results were similar to those in Fig. 4B. In addition to the increase in the firing rate induced by aging, other factors were involved in the increase in r_{sc}, including the decline in inhibitory circuits, as described below.

3.4. Age-related effects of the inhibitory system on noise correlation

Our previous studies suggested that degradation of inhibitory intracortical circuits occurs in the process of aging and affects the functions of individual neurons, such as spatial and temporal frequency response properties, orientation and direction selectivity, and contrast sensitivity (Hua et al., 2006; Leventhal et al., 2003; Schmolesky et al., 2000; Wang et al., 2005; Yang et al., 2008; Yu et al., 2006). Degradation of inhibitory systems can affect the signal processing of neuronal populations. Middleton et al. (2012) reported that inhibitory circuitry maintains the low correlation among excitatory neurons; specifically, neuronal correlation is modulated by stimuli through feedforward inhibitory circuitry. Hence, we investigated how aging affected the inhibitory circuitry and modified noise correlation.

First, based on spike waveform features, we divided the V1 neurons of each age group into fast spiking (FS) and regular spiking (RS) neurons (Figs. 5A and B). In the primary sensory cortex, RS neurons are presumed to be excitatory neurons and FS neurons are presumed to be inhibitory neurons, both of which form functional networks that process sensory stimulus information (Bruno and Simons, 2002). We found a significant difference in the proportion of FS neurons between the young and old groups (young: 20% [75/376]; old: 13% [36/267]). The proportion of FS neurons in the young group is consistent with that reported in previous study (Nowak et al., 2008), whereas the proportion declined in the old group.

The spontaneous and stimulus-evoked activities of the neurons were also affected by aging. Results showed that the FS neurons exhibited an obvious decrease in spontaneous activity and peak-evoked firing rates in the old group (spontaneous: $p < 0.0001$; evoked: $p = 0.03$, Mann-Whitney test) (Figs. 5C and D). These findings imply that aging may decrease the proportion and activity of inhibitory interneurons and weaken the ability of the inhibitory system.

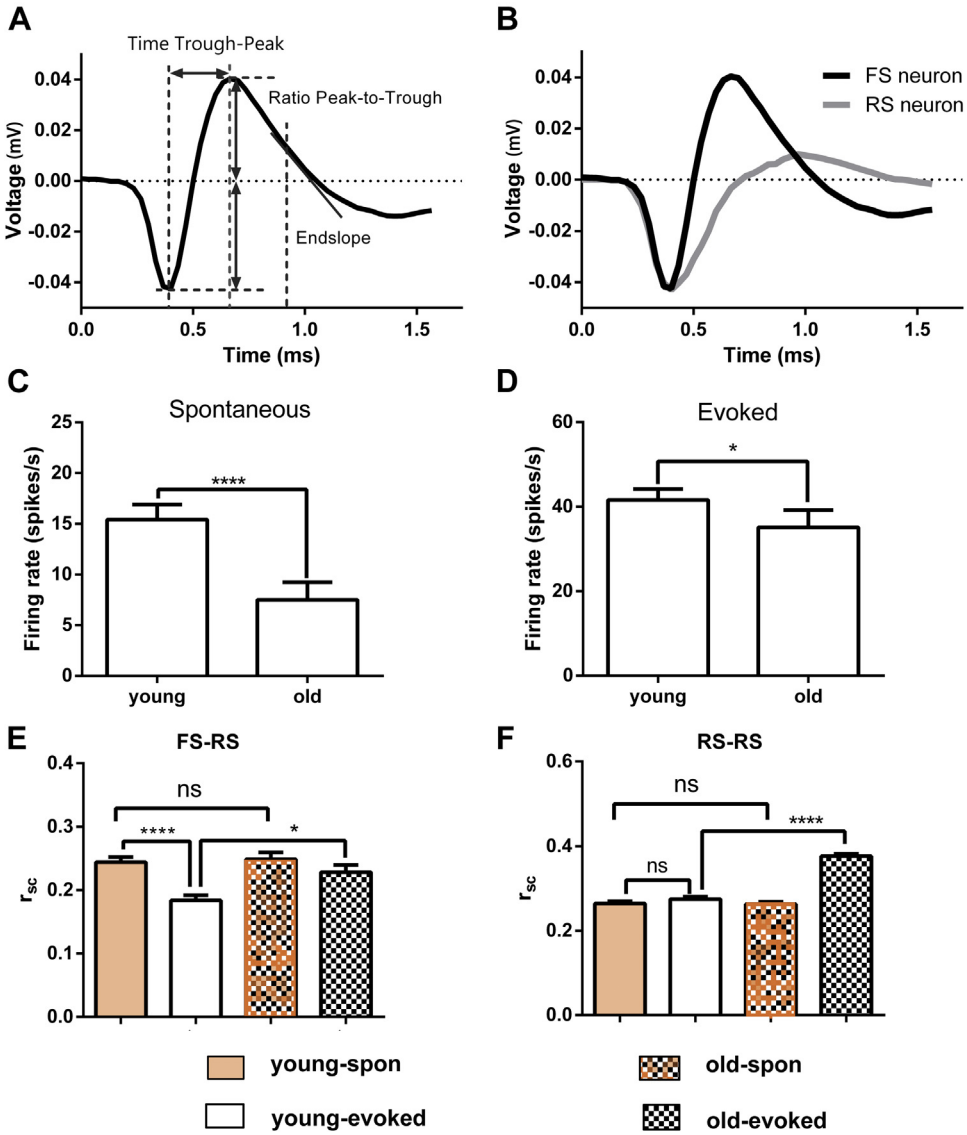

Fig. 5. Aging affected the inhibitory circuitry and decreased the decorrelation effects in V1. (A) Representative spike wave of a V1 neuron. Time trough peak is the duration between spike trough and peak; ratio peak-to-trough is the peak/trough amplitude ratio; end slope is the slope of the waveform at 0.5 ms after the trough. (B) Representative FS and RS neurons, which are separated by their spike wave characteristics. FS neurons had a shorter trough-peak duration (<0.45 ms), larger peak-to-trough ratio (>0.8), and negative end slope (end slope <0). (C and D) Aging decreased the activity of FS neurons for both spontaneous activity and peak-evoked firing rates ($p < 0.0001$ and $p < 0.05$, Mann-Whitney test). (E) Alteration in correlation of FS-RS activity. Young-spon and young-evoked are the correlation coefficients of FS-RS spontaneous and stimulus-evoked activity in the young group, respectively; old-spon and old-evoked are the correlation coefficients of FS-RS spontaneous and stimulus-evoked activity in the old group, respectively. (F) Alteration in correlation of RS-RS activity. Young-spon and young-evoked are the correlation coefficients of RS-RS spontaneous and stimulus-evoked activity in the young group, respectively; old-spon and old-evoked are the correlation coefficients of RS-RS spontaneous and stimulus-evoked activity in the old group, respectively. $^{*}p < 0.05$, $^{****}p < 0.0001$. Abbreviations: FS, fast spiking; RS, regular spiking; ns, no significant difference.

To reveal how functional coupling modulates network response, we divided pairs of neurons in each age group into 3 categories (RS-RS, FS-RS, and FS-FS). There were 2539 RS-RS pairs, 1219 FS-RS pairs, and 162 FS-FS pairs in the young group, and 3275 RS-RS pairs, 837 FS-RS pairs, and 79 FS-FS pairs in the old group. In the young group, the average correlation coefficients of RS-RS and FS-RS under spontaneous activity were 0.264 ± 0.005 and 0.244 ± 0.008, respectively. The presentation of a visual stimulus significantly reduced the average correlation coefficient of the FS-RS pairs to 0.184 ± 0.008 ($p < 0.0001$, paired *t*-test); there was no significant difference between the correlation coefficients of the RS-RS pairs under spontaneous and evoked activity, with the latter being 0.275 ± 0.005 ($p = 0.06$, paired *t*-test) (Figs. 5E and F, blank column). These results are consistent with a previous study in the rat whisker barrel cortex (Middleton et al., 2012), which indicates that, although stimulus presentation reduced FS-RS correlation, RS-RS correlation was uniformly low for both spontaneous and stimulus-evoked activities in our study.

However, the stimulus-induced decorrelation of FS-RS activity was weakened in the old group. For FS-RS pairs, the average correlation coefficient of spontaneous activity was similar to that in the young group (young: $r_{sc} = 0.244 \pm 0.008$; old: $r_{sc} = 0.249 \pm 0.011$, $p = 0.68$, Mann-Whitney test) and the average correlation coefficient of stimulus-evoked activity was higher than that of the young group (young: $r_{sc} = 0.184 \pm 0.008$; old: $r_{sc} = 0.228 \pm 0.011$, $p = 0.027$, Mann-Whitney test) (Fig. 5E). Furthermore, aging did not impact the average correlation coefficient of RS-RS spontaneous activity (young: $r_{sc} = 0.264 \pm 0.005$; old: $r_{sc} = 0.263 \pm 0.005$, $p = 0.71$, Mann-Whitney test), but increased the average correlation coefficient of stimulus-evoked activity (young: $r_{sc} =$

0.275 ± 0.005; old: $r_{sc} = 0.376 \pm 0.006$, $p < 0.0001$, Mann-Whitney test) (Fig. 5F). Thus, we concluded that the influence of aging on the decorrelation of inhibitory populations contributed to the increase in the correlation of excitatory populations during stimulus presentation.

4. Discussion

Using a multichannel system and extracellular recordings, we ascertained for the first time that aging influences the correlation of neuronal populations in the macaque V1. First, we found that aging affected the correlation between pairs of neurons; for example, the noise correlation increased, signal correlation became more positive, and the slope of the relationship between r_{sc} and r_{signal} increased. Therefore, the population coding efficiency may also be altered. Second, we found that neuronal correlation was influenced partly by the increased firing rate of neurons. The change in the inhibitory circuit also contributed to the alteration of neuronal correlation. Our results showed that aging reduced the proportion and intensity of the response by the inhibitory neurons, thereby affecting the inhibitory system and resulting in increased correlations between neurons (Fig. 6).

Over the past 2 decades, noise correlation has been measured in many cortical areas under a wide variety of behavioral and stimulus conditions. In those studies, most neurons were located in the primary sensory cortex (Ecker et al., 2010; Gutnisky and Dragoi, 2008; Kohn and Smith, 2005; Rasch et al., 2011; Reich et al., 2001; Smith and Kohn, 2008). In the present study, the average noise correlation in the V1 of the young group was similar to that reported in previous studies, which ranged from 0.1 to 0.2 (Gutnisky and Dragoi, 2008; Kohn and Smith, 2005; Rasch et al., 2011; Reich et al., 2001; Smith and Kohn, 2008).

We found that in each group (young vs. old), noise correlation depended on distance, with nearby neurons tending to have stronger correlations than distant pairs, which was likely because nearby neurons received more common inputs than those farther apart. Previous studies have shown that r_{sc} decays slowly with distance (Lee et al., 1998; Smith and Kohn, 2008). We found that the rate of decay was significantly slower in the old group than that in the young group, which implied that the size of the correlated neuronal pool may be affected by aging.

Several earlier experimental studies have shown that declines in noise correlation contribute to the enhancement of coding. For example, the decline of neuronal correlation is accompanied by an increase in information coding during attention (Cohen and Maunsell, 2009), adaptation (Gutnisky and Dragoi, 2008), and perceptual learning (Gu et al., 2011).

It is generally believed that positive noise correlations in neuron populations with similar tuning may harm the SNR of the population coding (Bair et al., 2001; Zohary et al., 1994). Although Gu et al. (2011) illustrated that population coding efficiency is a function of the slope and intercept of the r_{noise} and r_{signal} relationship, they also concluded that efficiency is very sensitive to changes in the slope but not the intercept, with a higher slope indicating lower population coding efficiency. In the present study, we found that aging affected both the distribution of r_{signal} and the relationship between r_{sc} and r_{signal} in V1, suggesting that aging might impede population coding and information processing.

In general, there is a positive correlation between r_{sc} and firing rates (Cohen and Kohn, 2011). The correlations among neurons that fire few spikes are weaker than the correlations among neurons that respond more strongly. In our previous studies, we measured the average firing rates of neurons in the visual cortex of monkeys and found that firing rates increased in old animals (Leventhal et al., 2003; Schmolesky et al., 2000; Wang et al., 2005; Yu et al., 2006). Therefore, the age-related increase in noise correlation could be partly attributable to the increased firing rates of neurons in the elderly.

However, we found that the correlations were uniformly stronger in older animals than in young animals within each firing rate stratum, which suggests that another factor may be involved in altering the correlations. We found that changes in inhibitory circuitry may play an important role in the alteration of neuronal correlations. Our results exhibited a significant decrease in the proportion of FS neurons in the old group. In general, FS neurons are considered parvalbumin-positive inhibitory interneurons (PV^+).

In addition to the change in proportion, we also found that the activity of FS neurons declined in the old group. Using direct optogenetics, PV^+ neuronal activity has been shown to be negatively correlated with cortical response (Atallah et al., 2012; Lee et al., 2012). Therefore, the upregulation in the cortical response of old animals, as shown in many previous studies (Leventhal et al., 2003; Schmolesky et al., 2000; Wang et al., 2005), could be attributed to the weakened responses of inhibitory interneurons, especially PV^+ neurons.

With visual stimuli, the firing of RS neurons usually becomes stronger. It is a biological and experimental phenomenon that stronger firing can evoke greater correlation between neuronal pairs (Cohen and Kohn, 2011). As a result, RS-RS firing should be more correlated than the spontaneous state. However, we did not find an increase in noise correlation of RS-RS firing in young monkeys (Fig. 5F), which could be attributed to the decorrelation of inhibitory neurons (Middleton et al., 2012). The decline in the proportion and activity of FS neurons implied a weakening of the

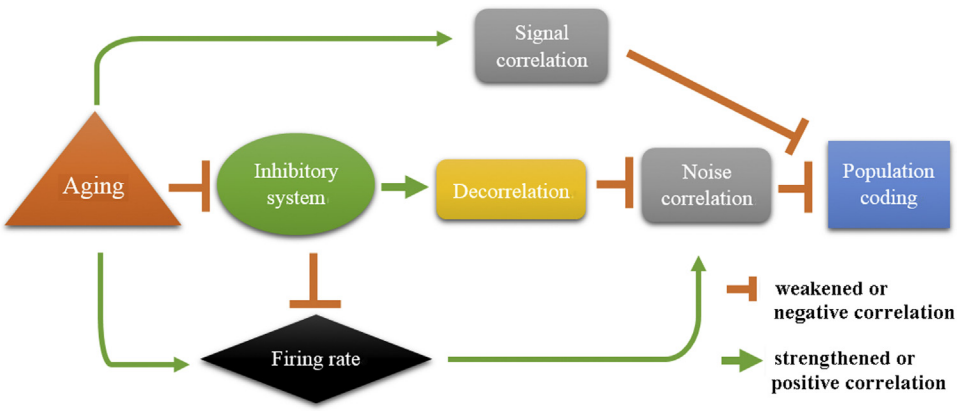

Fig. 6. Participation of the inhibitory system in the alteration of neuronal correlation induced by aging.

feedforward inhibitory circuitry during aging. Indeed, analysis of FS-RS correlation supported this speculation. The decorrelation regulated by inhibitory neurons maintained low correlation among the excitatory neurons. This decline in decorrelation led to the change in neuronal correlation. In addition to decorrelation, the increase in firing rate of pyramidal neurons induced by the decline in the inhibitory system also had an important impact on the change in RS-RS noise correlation.

The structure of neuronal correlation is vital for population coding (Abbott and Dayan, 1999; Averbeck et al., 2006; Shadlen and Newsome, 1998; Zohary et al., 1994). However, the changes in neuronal correlation during aging remain an underexplored field. Our results demonstrated for the first time that aging increased the noise and signal correlation of neural activity in the primate V1, thus providing a new explanation for visual cortex dysfunction in the elderly. Furthermore, we found that both the proportion and firing rates of FS neurons in old monkeys were decreased compared to those in young monkeys. Accordingly, decorrelation by inhibitory neurons was impaired significantly. These results suggest that decay of the gamma-aminobutyric acid inhibitory system plays a key role in the alteration of the neuronal correlation structure during aging and may lead to deficits in coding visual information by neuronal populations.

Acknowledgements

The authors thank Dr. Shan Yu for assistance with article modification. This work was supported by the National Natural Science Foundation of China (NSFC 31230032, NSFC 91749102 to YZ, NSFC 31571074, and NSFC 21876041).

Disclosure statement

The authors have no actual or potential conflicts of interest.

References

Abbott, L.F., Dayan, P., 1999. The effect of correlated variability on the accuracy of a population code. Neural. Comput. 11, 91–101.
Atallah, B.V., Bruns, W., Carandini, M., Scanziani, M., 2012. Parvalbumin-expressing interneurons linearly transform cortical responses to visual stimuli. Neuron 73, 159–170.
Averbeck, B.B., Latham, P.E., Pouget, A., 2006. Neural correlations, population coding and computation. Nat. Rev. Neurosci. 7, 358–366.
Bair, W., Zohary, E., Newsome, W.T., 2001. Correlated firing in macaque visual area MT: time scales and relationship to behavior. J. Neurosci. 21, 1676–1697.
Brainard, D.H., 1997. The Psychophysics Toolbox. Spat. Vis. 10, 433–436.
Bruno, R.M., Simons, D.J., 2002. Feedforward mechanisms of excitatory and inhibitory cortical receptive fields. J. Neurosci. 22, 10966–10975.
Butts, D.A., Goldman, M.S., 2006. Tuning curves, neuronal variability, and sensory coding. PLoS Biol 4, 639–646, e92.
Cohen, M.R., Kohn, A., 2011. Measuring and interpreting neuronal correlations. Nat. Neurosci. 14, 811–819.
Cohen, M.R., Maunsell, J.H., 2009. Attention improves performance primarily by reducing interneuronal correlations. Nat. Neurosci. 12, 1594–1600.
Cohen, M.R., Newsome, W.T., 2008. Context-dependent changes in functional circuitry in visual area MT. Neuron 60, 162–173.
de la Rocha, J., Doiron, B., Shea-Brown, E., Josic, K., Reyes, A., 2007. Correlation between neural spike trains increases with firing rate. Nature 448, 802–806.
Ecker, A.S., Berens, P., Keliris, G.A., Bethge, M., Logothetis, N.K., Tolias, A.S., 2010. Decorrelated neuronal firing in cortical microcircuits. Science 327, 584–587.
Elliott, D., Whitaker, D., MacVeigh, D., 1990. Neural contribution to spatiotemporal contrast sensitivity decline in healthy ageing eyes. Vis. Res. 30, 541–547.
Graf, A.B., Kohn, A., Jazayeri, M., Movshon, J.A., 2011. Decoding the activity of neuronal populations in macaque primary visual cortex. Nat. Neurosci. 14, 239–245.
Gu, Y., Liu, S., Fetsch, C.R., Yang, Y., Fok, S., Sunkara, A., DeAngelis, G.C., Angelaki, D.E., 2011. Perceptual learning reduces interneuronal correlations in macaque visual cortex. Neuron 71, 750–761.
Gutnisky, D.A., Dragoi, V., 2008. Adaptive coding of visual information in neural populations. Nature 452, 220–224.
Hua, T., Li, X., He, L., Zhou, Y., Wang, Y., Leventhal, A.G., 2006. Functional degradation of visual cortical cells in old cats. Neurobiol. Aging 27, 155–162.
Huang, X., Lisberger, S.G., 2009. Noise correlations in cortical area MT and their potential impact on trial-by-trial variation in the direction and speed of smooth-pursuit eye movements. J. Neurophysiol. 101, 3012–3030.
Ko, H., Hofer, S.B., Pichler, B., Buchanan, K.A., Sjöström, P.J., Mrsic-Flogel, T.D., 2011. Functional specificity of local synaptic connections in neocortical networks. Nature 473, 87.
Kohn, A., Smith, M.A., 2005. Stimulus dependence of neuronal correlation in primary visual cortex of the macaque. J. Neurosci. 25, 3661–3673.
Lee, D., Port, N.L., Kruse, W., Georgopoulos, A.P., 1998. Variability and correlated noise in the discharge of neurons in motor and parietal areas of the primate cortex. J. Neurosci. 18, 1161–1170.
Lee, S.H., Kwan, A.C., Zhang, S., Phoumthipphavong, V., Flannery, J.G., Masmanidis, S.C., Taniguchi, H., Huang, Z.J., Zhang, F., Boyden, E.S., Deisseroth, K., Dan, Y., 2012. Activation of specific interneurons improves V1 feature selectivity and visual perception. Nature 488, 379–383.
Leventhal, A.G., Wang, Y., Pu, M., Zhou, Y., Ma, Y., 2003. GABA and its agonists improved visual cortical function in senescent monkeys. Science 300, 812–815.
Li, G., Yao, Z., Wang, Z., Yuan, N., Talebi, V., Tan, J., Wang, Y., Zhou, Y., Baker Jr., C.L., 2014. Form-cue invariant second-order neuronal responses to contrast modulation in primate area V2. J. Neurosci. 34, 12081–12092.
Liang, Z., Yang, Y., Li, G., Zhang, J., Wang, Y., Zhou, Y., Leventhal, A.G., 2010. Aging affects the direction selectivity of MT cells in rhesus monkeys. Neurobiol. Aging 31, 863–873.
Middleton, J.W., Omar, C., Doiron, B., Simons, D.J., 2012. Neural correlation is stimulus modulated by feedforward inhibitory circuitry. J. Neurosci. 32, 506–518.
Mitchell, J.F., Sundberg, K.A., Reynolds, J.H., 2009. Spatial attention decorrelates intrinsic activity fluctuations in macaque area V4. Neuron 63, 879–888.
Norman, J.F., Payton, S.M., Long, J.R., Hawkes, L.M., 2004. Aging and the perception of biological motion. Psychol. Aging 19, 219.
Norman, J.F., Ross, H.E., Hawkes, L.M., Long, J.R., 2003. Aging and the perception of speed. Perception 32, 85–96.
Nowak, L.G., Sanchez-Vives, M.V., McCormick, D.A., 2008. Lack of orientation and direction selectivity in a subgroup of fast-spiking inhibitory interneurons: cellular and synaptic mechanisms and comparison with other electrophysiological cell types. Cereb. Cortex 18, 1058–1078.
Owsley, C., 2011. Aging and vision. Vis. Res. 51, 1610–1622.
Rasch, M.J., Schuch, K., Logothetis, N.K., Maass, W., 2011. Statistical comparison of spike responses to natural stimuli in monkey area V1 with simulated responses of a detailed laminar network model for a patch of V1. J. Neurophysiol. 105, 757–778.
Reich, D.S., Mechler, F., Victor, J.D., 2001. Independent and redundant information in nearby cortical neurons. Science 294, 2566–2568.
Schmolesky, M.T., Wang, Y., Pu, M., Leventhal, A.G., 2000. Degradation of stimulus selectivity of visual cortical cells in senescent rhesus monkeys. Nat. Neurosci. 3, 384–390.
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.
Sloane, M.E., Owsley, C., Alvarez, S.L., 1988. Aging, senile miosis and spatial contrast sensitivity at low luminance. Vis. Res. 28, 1235–1246.
Smith, M.A., Kohn, A., 2008. Spatial and temporal scales of neuronal correlation in primary visual cortex. J. Neurosci. 28, 12591–12603.
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.
Tolhurst, D.J., Movshon, J.A., Dean, A.F., 1983. The statistical reliability of signals in single neurons in cat and monkey visual cortex. Vis. Res. 23, 775–785.
Vinje, W.E., Gallant, J.L., 2000. Sparse coding and decorrelation in primary visual cortex during natural vision. Science 287, 1273–1276.
Wang, Y., Zhou, Y., Ma, Y., Leventhal, A.G., 2005. Degradation of signal timing in cortical areas V1 and V2 of senescent monkeys. Cereb. Cortex 15, 403–408.
Wang, Z., Yao, Z., Yuan, N., Liang, Z., Li, G., Zhou, Y., 2014. Declined contrast sensitivity of neurons along the visual pathway in aging cats. Front. Aging Neurosci. 6, 163.
Yang, Y., Liang, Z., Li, G., Wang, Y., Zhou, Y., 2009a. Aging affects response variability of V1 and MT neurons in rhesus monkeys. Brain Res. 1274, 21–27.
Yang, Y., Liang, Z., Li, G., Wang, Y., Zhou, Y., Leventhal, A.G., 2008. Aging affects contrast response functions and adaptation of middle temporal visual area neurons in rhesus monkeys. Neuroscience 156, 748–757.
Yang, Y., Zhang, J., Liang, Z., Li, G., Wang, Y., Ma, Y., Zhou, Y., Leventhal, A.G., 2009b. Aging affects the neural representation of speed in Macaque area MT. Cereb. Cortex 19, 1957–1967.
Yu, S., Wang, X., Fu, Y., Zhang, J., Ma, Y., Wang, Y., Zhou, Y., 2005. Effects of age on latency and variability of visual response in monkeys. Chin. Sci. Bull. 50, 1163–1165.
Yu, S., Wang, Y., Li, X., Zhou, Y., Leventhal, A.G., 2006. Functional degradation of extrastriate visual cortex in senescent rhesus monkeys. Neuroscience 140, 1023–1029.
Yuan, N., Liang, Z., Yang, Y., Li, G., Zhou, Y., 2014. Changes of spatial and temporal frequency tuning properties of neurons in the middle temporal area of aged rhesus monkeys. Eur. J. Neurosci. 40, 2652–2661.
Zhang, J., Wang, X., Wang, Y., Fu, Y., Liang, Z., Ma, Y., Leventhal, A.G., 2008. Spatial and temporal sensitivity degradation of primary visual cortical cells in senescent rhesus monkeys. Eur. J. Neurosci. 28, 201–207.
Zohary, E., Shadlen, M.N., Newsome, W.T., 1994. Correlated neuronal discharge rate and its implications for psychophysical performance. Nature 370, 140–143.