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Effects of age on latency and variability of visual response in monkeys

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Visual function declines during normal aging[1]. The neural mechanisms underlying age-related changes have just begun to be revealed. It has been demonstrated that retinal ganglion cells and cells in dorsal lateral geniculate nucleus (dLGN) in old monkeys are relatively normal[1,2]. However, age-related functional degradations have been found at cellular level in mammalian visual cortex[2−4]. Decreased orientation and direction selectivity of neurons in primary visual cortex (V1) have been reported in both aged monkeys[2,3] and cats[1)]. Similar degradation of stimulus selectivity also occurs in secondary visual cortex (V2) in old monkeys[2)]. In addition, we have reported prolonged response latency in both V1 and V2 of old primates[4].

Response latency of neuron can be affected by several factors, including conduction speed of the axons, synaptic integration, action potential initiation and the response variability. These factors may all contribute to delayed visual response in aged animals. For example, increased response variability will affect the temporal integration in synaptic transmission, resulting in prolonged response latency in the postsynaptic neurons. On the other hand, the evaluation of latency depends on the reproducibility of response. The more variable the spike train driven by external stimulus, the longer time will be needed to reach the peak in the post-stimulus time histogram (PSTH). Thus, a prolonged latency will be observed. In the present experiment, using monkeys in early stage of senescence as subjects, we studied the effects of age on response variability and its relationship with the prolonged latency, aiming to investigate possible neural mechanisms underlying the age-related alteration of response latency.

Subjects for this study were 3 young adult (5—6 years old) and 3 old (21—22 years old) male rhesus monkeys (*Macaca mullata*). All experimental protocols were consistent with the guidelines of the Society for Neuroscience and National Institute of Health. Monkeys were examined ophthalmoscopically to ensure that they had no optical or retinal problems that would impair visual function. Conventional acute extracellcular single unit recording technique was used to record the activity of V1 neurons of anaesthetized and paralyzed monkeys. The receptive field properties of neurons were analyzed as described previously[4,5]. Visual stimuli were presented on a tangent screen positioned 171 cm from the retina (3 cm corresponds to 1° of visual angle). The visual stimulus was a flashing square within receptive field with optimal size for each cell, which is commonly used in related studies. The luminance of the stimulus used was 12.3 cd/m^2 for white and 0.95 cd/m^2 for black. For each cell, we presented the identical visual stimulus for 50 times, with an ON period of 0.5 s and an OFF period of 3 s, and accumulated a PSTH that represents the probability of firing as a function of time. The neurons with low response variability fire at almost the same time in 50 presentations, resulting in a sharp rising branch in PSTH. In contrast, the neurons with high response variability will produce a peak with a relative flat rising branch. Then, the rising branch of the first peak in PSTH with an amplitude equal or larger than three times of spontaneous activity was fitted by a Gaussian curve ($y=y_0+A\exp(-((x-x_0)/\sigma)^2)$) whose half-width ($\sigma$) was taken as a measure of the trial-to-trial variability[6], and time offset (x_0) as the response latency (Peak latency).

We studied the visual responses of 90 V1 cells in young monkeys and 99 V1 cells in old monkeys. Fig. 1 represents four typical PSTHs. The cells recorded in aged animals showed significant prolonged response latencies and increasing response variabilities, compared with cells in young monkeys (Table 1, Fig. 2(a), (b)). The finding of prolonged latency in aged animals is consistent with our previous study[4]. However, the subjects we used in the present experiment were 21—22 years old monkeys, while the monkeys in our previous study[4] were 28—32 years old. Analysis based on the sex maturation and lifespan[7] revealed that the degree of senescence of 21—22 years old monkeys approximately equals 60—70 years old human beings, and 28—32 years old monkeys correspond to 80—90 years old human beings. The present results have demonstrated that the prolonged response latency occurs during the early stage of aging. It provided possible neural mechanisms underlying the delay in visual signal analysis and slowness of reaction time for visual stimulus in old people[1]. The average σ for young monkey cells was 2.82 ms. In comparison, V1 cells in aged monkeys showed significant increased value of σ (4.56 ms), suggesting higher variability of response. The increase in re

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2) Yu, S., Wang, Y., Li, X. et al., Functional degradation of extrastriate visual cortex in senescent monkeys. (Submitted)

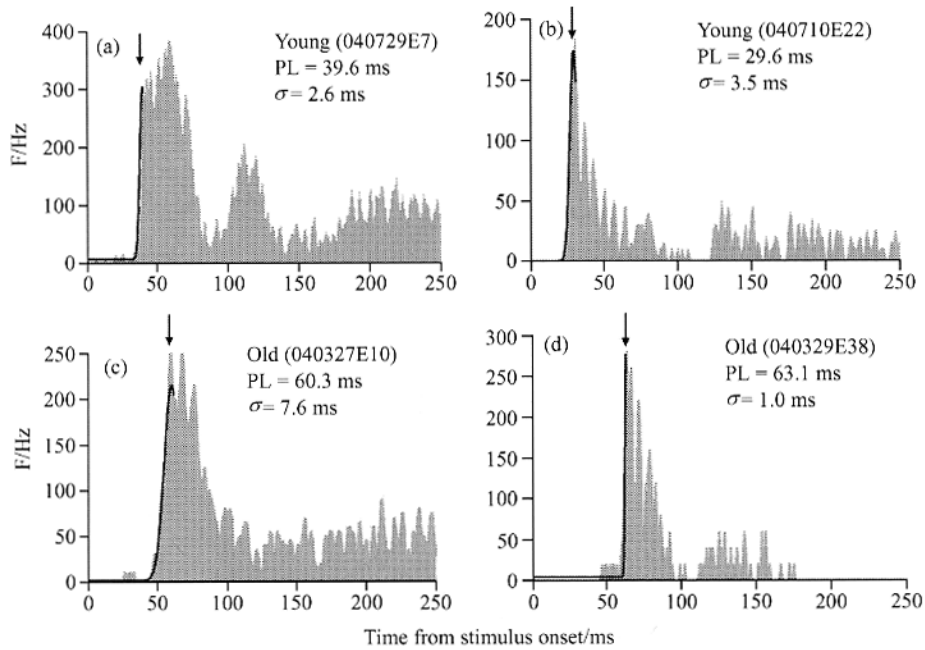

Fig. 1. Four typical PSTHs obtained from young and old monkeys. Black lines represent the raising branch of the Gaussian curve used to fit the peak in PSTH, and the half-width (σ) of this Gaussian curve was used as a measure of response variability. Arrows indicate the peak latency (PL).

Table 1 Latency and $\acute{o}$ for cells in young and old monkeys, data represented as mean ± SD

	Young	Old	P (Mann-Whitney U test)	P (F test)
Peak latency/ms	42.4 ± 8.4	61.5 ± 26.5	<0.01	<0.001
σ/ms	2.82 ± 2.12	4.56 ± 4.19	<0.01	<0.001

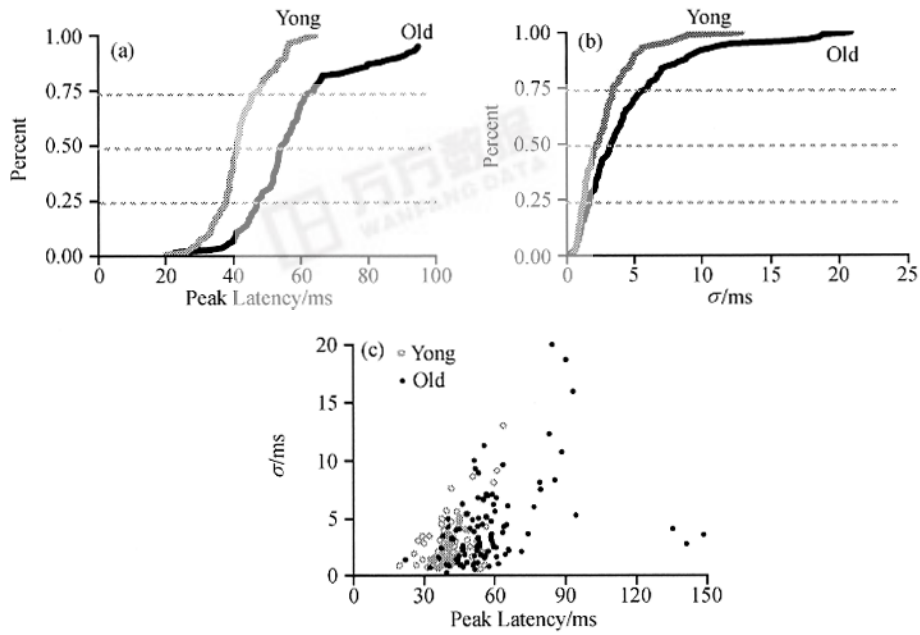

Fig. 2. The percentage of cells with any given latency and σ value are shown in cumulative distribution plots ((a) and (b)). The data from each cells are shown in scatterplots for young and old monkeys (c), indicating correlation between the latency and σ.

sponse variability will affect the information transmission and processing[8,9]. In addition, the diversity of both latency and value of σ in old monkey cells was significantly higher than in young monkey cells (Table 1, Fig. 2(c)). The increased diversity of latency and σ may adversely affect the synchronization of neural network, which is important for brain function[10]. Thus, the current results provided new clues of mechanisms underlying age-related functional decline of visual system. Previous studies have reported that aging affects many aspects of normal physiological process, including the expression of receptor[11], synaptic structure[12] and balance between excitatory and inhibitory neural transmission[3]. All of these changes may affect response variability, but the detailed mechanisms await further investigation.

We also studied the relationship between increased variability and prolonged latency of visual response. Our results demonstrated that response variability was correlated with response latency (Fig. 2(c). Correlation coefficient r=0.48, p<0.01 for young monkey cells; r=0.51, p<0.01 for aged monkey cells.). In cells with prolonged latency (>average latency of young monkey cells +1.5 SD) in aged monkeys, 43% (21/49) showed higher response variability (> average ó of young monkey cells + 1.5 SD), suggesting that the increased variability might be a factor causing the delayed response of cortical cells in aged monkeys. On the other hand, the results indicated that other mechanisms in addition to the response variability may also be involved in the prolongation of response latency in aged animals (Fig. 1(d)). For example, the decrease in conduction speed of axons in aging[13] may be another reason for the prolonged latency. All of these implied that the alteration of response latency in aged animal may be a result of several factors working together.

In summary, our results provided the first evidence that both prolonged latency and increased response variability occur in the early stage of senescence. The degradation of the two response properties may play an important role in age-related functional degeneration of visual system. In addition, the prolonged latency is correlated with increased response variability, suggesting that the variability is one of the factors that cause the alteration of response latency in aging.

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