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Degradation of Signal Timing in Cortical Areas V1 and V2 of Senescent Monkeys

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Senescence in monkeys results in a degradation of the functional properties of cortical cells as well as prolonged hyperactivity. We have now compared the spontaneous and visually evoked activity levels, as well as the visual response latencies of cells in cortical areas V1 and V2 of young and very old monkeys. We found that V1 cells within layer 4 exhibit normal latencies. In contrast, in other parts of V1 and throughout V2 hyperactivity in old monkeys is accompanied by dramatic delays in both the intracortical and intercortical transfer of information. Extrastriate cortex (area V2) is affected more severely than striate cortex (V1). Delayed information processing in cerebral cortex should contribute to the declines in cortical function that accompany old age.

Keywords: degradation, latency, senescent monkeys, visual information processing, visual cortex

Introduction

Visual information is processed sequentially by the mammalian brain. Processing begins in the retina with the different classes of retinal ganglion cells (Leventhal *et al.*, 1980), continues in the lateral geniculate nucleus of the thalamus with corresponding classes of relay cells, and then proceeds into layer 4 of striate visual cortex (area V1).

Cells in layer 4 project to other V1 cells, which then project to extrastriate cortical areas. There are over thirty extrastriate visual cortical areas in old world monkeys and man. These areas are at least partially segregated into parallel streams, termed dorsal (M) and ventral (P), which derive many differences in properties from the retinal ganglion cells initiating their afferent inputs. Cortical areas within both streams are organized hierarchically such that progressively more complex functions are carried out at progressively higher levels in the hierarchy (Van Essen *et al.*, 1992; Brewer *et al.*, 2002).

Visual function declines with age and changes in the function of visual cortex appear to mediate much of this decline (Spear *et al.*, 1994; Schmolesky *et al.*, 2000). Senescence in monkeys results in a degradation of the receptive field properties of cells in visual cortex as well as prolonged hyperactivity (Schmolesky *et al.*, 2000; Leventhal *et al.*, 2003). It has been suggested that hyperactivity of brain cells during senescence results in the degradation of excitatory transmission that accompanies a number of age-related brain diseases, including Alzheimer's disease (Olney *et al.*, 1998; Perutz and Windle, 2001; Butterfield and Pocernich, 2003; Francis, 2003).

We have now studied the effects of senescence on the activity levels of cortical cells as well as rate of information transfer within the visual cortex. To accomplish this, the visual response latencies and spontaneous and visually evoked responses of cells in cortical areas V1 and V2 of young and very old monkeys were compared. We employed the same techniques used previously to determine the visual latencies of cells in a variety of visual cortical areas of young monkeys (Schmolesky *et al.*, 1998).

Materials and Methods

Preparation

The activity of single units was recorded in visual cortical areas V1 and V2 of four young (5–9 years old and six old (28–32 year old) paralyzed, anesthetized macaque monkeys using standard surgical and single unit recording techniques consistent with Society for Neuroscience and NIH guidelines (Leventhal *et al.*, 1995). Anesthesia was first induced with Ketamine HCL and then was maintained via artificial ventilation with a mixture of nitrous oxide (75%) and oxygen (25%) containing halothane (0.25–1.0%, as needed). All pressure points and incisions were infiltrated with a long-acting anaesthetic (1% lidocaine–HCl). A solution of D-tubocurarine (0.4 mg/kg/h) and gallamine triethiodide (7 mg/kg/h) was infused intravenously to induce and maintain paralysis. Expired pCO_2 was maintained at ~4% and body temperature was maintained at 38°C. Heart rate, ECG and cortical electrical activity were monitored throughout the experiment to assess the level of anesthesia. Animals were studied for as long as stable, reliable recording was possible. Optics were routinely checked and deterioration was minimal in even the longest experiment. The proportion of cells meeting the data inclusion criteria did not appear to decrease over time. The order in which areas were studied was varied from animal to animal, thereby reducing the impact that this factor could have on any latency differences found.

Visual Stimulation

Flashing visual stimuli were generated on a Tektronix 608 display driven by a Picasso image synthesizer (Innisfree). The Picasso was controlled by a PC computer in conjunction with specially designed hardware and software (Cambridge Electronics Design, Ltd). Our system is able to randomly generate a broad spectrum of visual stimuli under computer control, collect the data and perform online statistical analyses. A perimeter apparatus was used to position an oscilloscope display at any point in the animal's visual field, maintaining a fixed distance between the display and the animal's retina.

For each cell, pre-testing was conducted using a hand-held opthalmoscope to determine the preferred stimulus configuration (spot or bar), orientation, size, phase and/or color. In cases where the preferred parameters were clear, the non-preferred parameters were not assessed quantitatively. For any parameter where pre-testing did not clearly demonstrate the preferred attribute (e.g. white, red or green) each parameter attribute was presented via computer and the determination of the optimal stimulus was deferred for offline analysis. In general, each cell provided quantitative latencies to at least two stimuli and some to as many as six.

Each computer-generated flashing stimulus was presented 50 times with an ON period of 0.5 s and an OFF period of 3 s. The stimulus that elicited the optimal response was determined and the latency of the response to that stimulus included in the data set. The optimal response was the one judged to be the greatest in magnitude (based on peak firing rate and ratio of peak to baseline) and lowest response variability (based

on percentage of trials that had a significant response and the variability of response latencies from trial to trial). For all 487 cells studied the optimal response was obtained while stimulating with a white (8.37 cd/m^2) or black (0.91 cd/m^2) spot or bar with a contrast of 80% [(8.37 – 0.91 cd/m^2)/(8.37 + 0.91 cd/m^2)]. The size of spots and bars/squares was varied to match RF size and optimize response.

Spike Train Analysis

Response strength, response variability, times of neuronal modulation were determined for each spike train using an adaptation of the Poisson spike train analysis originally described by Legendy and Salcman (1985) and modified by Hanes *et al.* (1995). Since a distribution of interspike intervals (ISIs) approximates a Poisson distribution (Rodieck *et al.*, 1962; Smith and Smith 1965), this method provides a good null hypothesis to detect changes in neuronal modulation (Legendy and Salcman, 1985). Our Poisson spike train analysis determines how improbable it is that the number of action potentials within a specific time interval is a chance occurrence and provides a great deal of information about temporal patterns of neuronal activity.

Effects of Anesthesia

It is a concern that differential effects of anesthesia upon cortical function in young and old monkeys could impact our results. This possibility has been tested by studying the properties of individual cells while systematically varying anesthesia and paralytic levels. We find that giving as much as four times the minimum level of general anesthesia or paralytic required to anesthetize or paralyze both old and young animals does not alter the degree of selectivity for orientation and direction V1 cells exhibit. Latency and spatial frequency sensitivity are also not changed in V1 by varying anesthesia or paralytic levels in young and old animals. The responsiveness of cells in both groups declines similarly when very high levels of anesthesia are employed. Thus, problems with anesthesia in old animals are not a concern.

Results

The visual response latencies of 352 cells in areas V1 and V2 of old (28- to 32-year-old) monkeys and 135 cells in areas V1 and V2 of young (5- to 9-year-old) monkeys were determined. Both *macaca mulatta* and *macaca fascicularis* were studied. The receptive fields of the cells studied ranged from 2 to 6° from the projection of the fovea. The results for the two groups did not differ. The onset of visually evoked activity was determined for each spike train using an adaptation of the Poisson spike train analysis. This analysis has been used previously in our laboratory to study the visual latencies of cells in a variety of cortical areas in macaque monkeys (Schmolesky *et al.*, 1998). Examples of the raster plots used to determine the visual onset response latencies of cells in areas V1 and V2 are shown in Figure 1.

Figure 1 illustrates the visual response latencies of typical cells recorded from areas V1 and V2 of young and old monkeys. Notice that the response profiles of cells in layer 4 do not differ in young (Fig. 1*A*,*B*) and old (Fig. 1*E*,*F*) animals. This was true in layer 4Calpha (Fig. 1*A*,*E*) as well as in layer 4Cbeta (Fig. 1*B*,*F*), indicating that layer 4 cells receiving inputs from both the magnocellular and the parvocellular layers of the lateral geniculate nucleus exhibited normal latencies. Outside of layer 4 the latencies of cells in area V1 are longer in old (Fig. 1*G*) than in young (Fig. 1*C*) monkeys. The difference in latency between cells in area V2 of old (Fig. 1*H*) and young (Fig. 1*D*) animals was even greater.

A summary of the response latencies of cells in areas V1 and V2 of old and young monkeys is shown in Figure 2. Notice that the shortest latencies are represented in similar proportions in area V1. This reflects the fact that the latencies of layer 4 cells did not differ in V1 of old and young animals (Table 1). The latencies of V1 cells outside of layer 4, on the other hand, averaged 13 ms longer in old monkeys (Table 1). Cells throughout area V2 exhibited longer latencies in old animals (Fig. 2). The latencies of V2 cells were, on average, 32 ms longer in old monkeys (Table 1).

Cells in area V2 receive excitatory afferent inputs from cells in area V1. Thus, at the population level, V2 cells must have longer latencies than their afferent V1 cells. In order to approximate how long it takes information to travel from area V1 to area V2, we determined the difference between the latencies of V2 cells exhibiting relatively short latencies (30th percentile) (Fig. 2) and the latencies of V1 cells outside of layer 4 in both young and old animals. The mean difference in latency between these cells in young and old animals was 10 and 20 ms, respectively (Table 1). The increased difference in latency between V1 and V2 in old monkeys indicates that it takes longer for V2 cells to be activated by V1 cells in old animals.

Cells within areas V1 and V2 that receive excitatory inputs directly from the LGNd and V1, respectively, should have shorter latencies, overall, than higher order cells in these areas that receive their excitatory inputs solely from intracortical afferents. This is because additional synapses separate higher order cells from the retina. An age related delay in intracortical processing should, therefore, increase the range of latencies within an area. In order to determine if senescence increases the delay imposed by intracortical processing, the difference in latency between short and long latency cells within areas V1 and V2 was determined for both old and young monkeys. In area V1, non-layer 4 cells exhibiting short latencies (30th percentile) differed in latency from long latency cells (90th) percentile by 15 ms in young monkeys and 30 ms in old ones. In area V2, short (30th percentile) and long (90th percentile) latency cells exhibited latencies that were separated by 30 ms in young monkeys and 60 ms in old ones. The increased range of latencies in both areas V1 and V2 (Fig. 2) suggests that intracortical information processing takes longer in both areas V1 and V2 of old animals. The especially large increase in the range of latencies in old V2 suggests that V2 is affected more than area V1 ($P \ll 0.001$ in both cases).

Neuronal hyperactivity has been hypothesized to ultimately result in a degradation of excitatory transmission in a variety of brain diseases (Olney *et al.*, 1998; Perutz and Windle, 2001; Butterfield and Pocernich, 2003; Francis, 2003). Delayed information transfer in old monkey cortex is consistent with a degradation of excitatory transmission. We therefore related the spontaneous firing rates and peak visually evoked responses to the visual latencies of cells in area V1 and V2 in old and young monkeys.

Figure 3 shows that V1 and V2 cells in old monkeys exhibited longer latencies as well as much higher spontaneous and peak firing rates than did cells in young monkeys ($P \ll 0.001$in all cases; Table 1). The increase in spontaneous or maintained discharge rate was especially marked in both areas V1 and V2 (Table 1). This should have a profound impact since cortical neurons are firing continually at these very high maintained rates in old brains. It is noteworthy that, in both V1 and V2 of old monkeys, a few cells with the longest latencies (over 120 and 160 ms, respectively) exhibited lower peak responses and spontaneous firing rates, on average, than did the other old cells (Fig. 3). The visual responses of these cells were extremely variable, erratic and unselective indicating a serious breakdown of function.

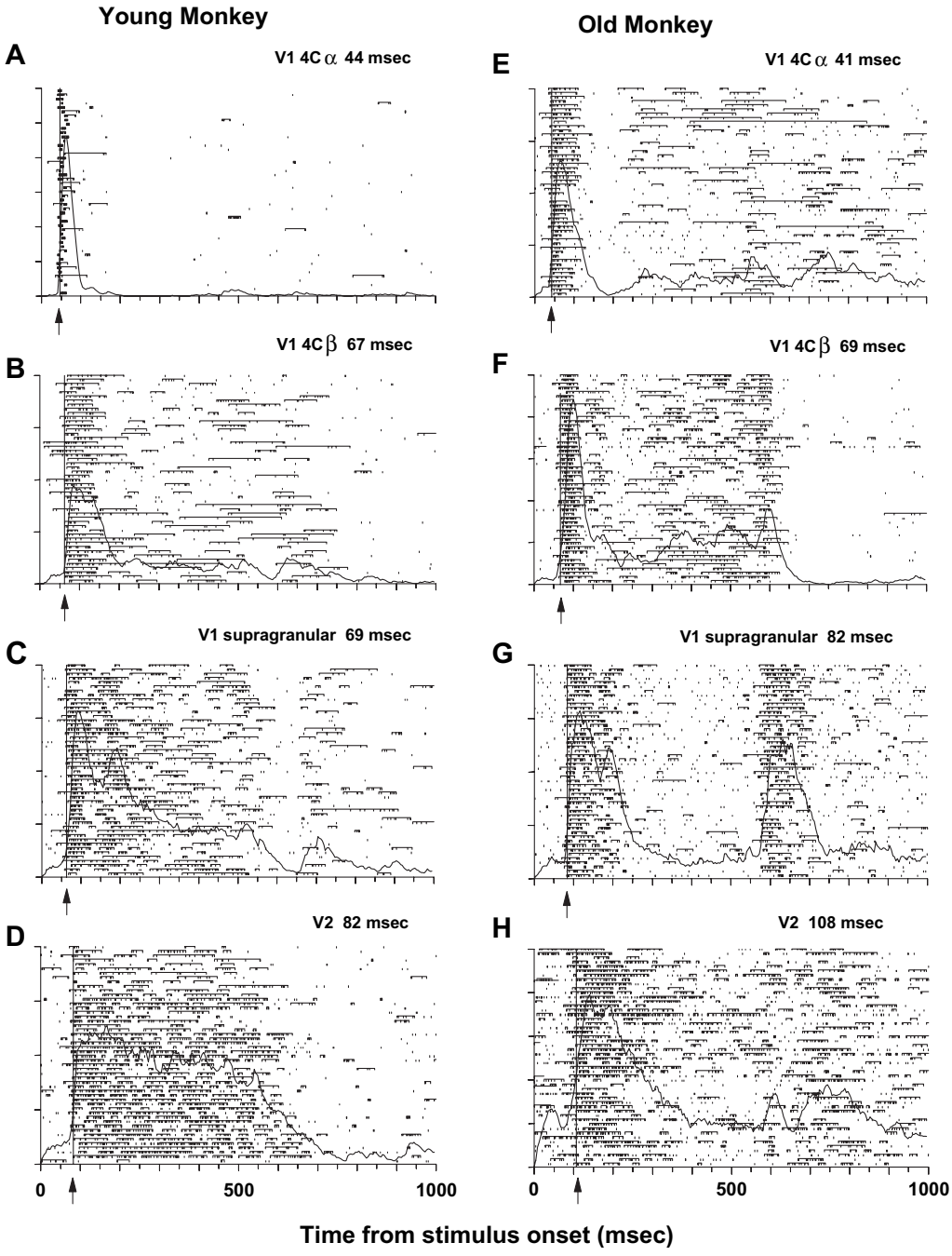

Figure 1. Visually evoked onset response latencies of cells in areas V1 and V2 of old and young monkeys in response to flashing, non-drifting stimuli. Fifty stimulus presentations were employed for both old and young monkeys in all cases. Notice that the latencies of cells in layer 4 do not differ in young (*A*, *B*) and old (*E*, *F*) animals. This was true in layer 4Calpha (*A*, *E*) as well as in layer 4Cbeta (*B*, *F*), indicating that layer 4 cells receiving inputs from both the magnocellular and the parvocellular layers of the lateral geniculate nucleus exhibited normal latencies. Spontaneous activity was, however, higher for old layer 4 cells (see also Schmolesky *et al.*, 2000). Outside of layer 4 the latencies of cells in area V1 are longer in old (*G*) than in young (*C*) monkeys. The difference in latency between cells in area V2 of old (*H*) and young (*D*) animals was even greater.

Discussion

This study provides the first evidence that the rate of information processing within visual cortex degrades during senescence. We have shown that the visual response latencies of cells in layer 4 of area V1 are normal. Outside of layer 4, cells in area V1 display abnormally long latencies. Latencies are also longer in area V2 of old monkeys and information takes longer to travel from area V1 to area V2 in old animals. The range of latencies observed in area V1 and, especially in area V2, is greater in old than in young monkeys, indicating that intracortical information processing slows during old age.

Our analyses have dealt with latency differences among populations of cells in areas V1 and V2 of old and young monkeys. Overall, the difference in latency between cells in areas V1 and V2 is greater in old animals, suggesting delayed intercortical signal transfer. Age also results in a greater range of latencies within both areas V1 and V2, suggesting delayed intracortical processing. The present data are not sufficient to

determine exactly how much latency increases with age for cells having various types of afferent inputs. Visual latency is undoubtedly determined by a variety of excitatory and inhibitory mechanisms. We do not know the source of all of the inputs of the individual cells we studied. The mechanisms mediating age related changes that result in the increased latencies we observe remain to be determined.

It is also noteworthy that our measure of latency determines when the cell's first responses reach statistical significance above background activity. We have reported both previously (Schmolesky *et al*., 2000) and here that spontaneous activity is higher and signal to noise ratios are lower in old than in young monkeys. This could contribute to the longer latencies in old animals since a stronger visual response may be needed to reach significance above background in old than in young animals.

A decrease in axonal conduction velocity and/or delayed synaptic transmission could also contribute to the age related latency increase in old monkeys. In fact, it has been reported that there is a degradation of myelinated fibers in area V1 and prefrontal cortex that correlates with behavioral deficits in old monkeys (Peters *et al*, 2001a,b; Peters, 2002; Peters and Sethares, 2002). Moreover, recent work indicates that the dendrites and synapses, as well as the dendritic spines of V1 cells and corticocortical projection cells, degrade in old monkeys (Peters, 2002; Duan *et al*., 2003).

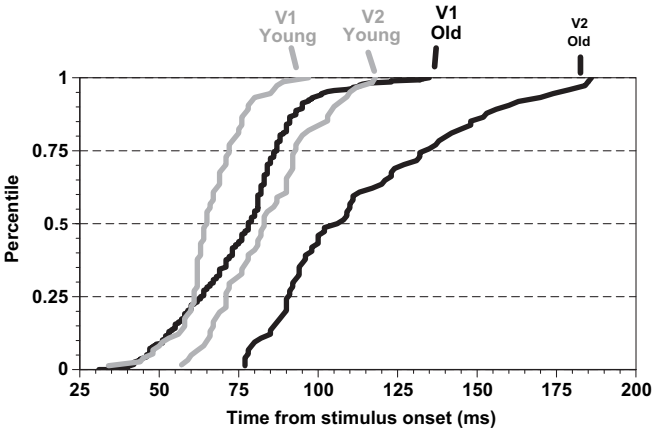

Figure 2. The percentage of cells with any given onset latency in areas V1 and V2 are shown in cumulative distribution plots, where solid gray and black lines represent the combined data of young and old monkeys, respectively. The difference in latency between cells in areas V1 andV2 is greater in old animals indicating that signal transfer between these areas takes longer in old monkeys. Also, the range of latencies within both areas V1 and V2 is significantly greater in old than in young monkeys. Thus, intracortical signal transfer takes longer in both areas V1 and V2 of old monkeys and area V2 is affected more than area V1.

Basic sensory functions as well as higher cognitive ones degrade during senescence. However, higher cognitive functions are much more susceptible to the effects of age than are basic sensory ones. For example, it is a common observation that during extreme old age a person may be capable of seeing his relatives but may not be able to recognize them. Higher order visual recognition tasks such as face and object recognition are, in fact, delayed during senescence (Nakamura *et al*., 2001; Leonards *et al*., 2002). Consistent with this, we find that very old monkeys perform poorly compared with young ones in complex shape discrimination tasks (Y.Y. Ma, Y.C. Wang, Y.F. Zhou and A.G. Leventhal, in preparation). Our results provide a possible neural basis for this phenomenon.

It is likely that the visual pathways up to and including area V1 provide a neural substrate for our ability to detect shapes. Face and object recognition, however, have been hypothesized to be mediated by much higher cortical areas such as V4 and inferotemporal cortex (Reilly, 2001; Girard *et al*., 2002). Neurons in these areas normally exhibit long latencies because they occupy high levels of the cortical hierarchy (Nowak and Bullier, 1998; Schmolesky *et al*., 1998).

The present results indicate that the rate of information processing is normal up to and including layer 4 of area V1 in old monkeys. It has been reported previously that the properties and latencies of cells in the dorsal lateral geniculate nucleus of old monkeys are relatively normal (Spear *et al*., 1994). Thus, the ability of old animals to detect visual stimuli should be relatively normal.

On the other hand, our results show that both intracortical information processing and the intercortical transfer of information slow during senescence. The effects of age are greater in extrastriate cortex (V2) than striate cortex (V1). The implication of these findings is that areas such as V4 and inferotemporal cortex that depend heavily upon inputs from other cortical areas should be profoundly affected by old age (Peters, 2002; Duan *et al*., 2003). The inputs to these areas should not only be delayed significantly, but should also be desynchronized. Higher order cortical areas receive afferent inputs directly from lower order ones such as area V1, as well as indirectly from afferent pathways that include multiple cortical areas and, thus, multiple synapses. For this reason, different delays will be imposed upon different afferent inputs to higher order areas. It has been suggested that synchronization based upon latency contributes strongly to organizing the neural responses encoding different objects (Gawne *et al*., 1996).

Table 1
Discharge rates of cells recorded in V1 and V2 of old and young monkeys

	Visual area	Young	Old	*t*-value	Significance
Latency (ms)	V1 (layer 4)	53.3 ± 7.4 (n = 18)	52.7 ± 7.4 (n = 71)	0.49	$P > 0.10$
	V1 (outside layer 4)	70.1 ± 8.1 (n = 56)	83.6 ± 12.9 (n = 207)	9.14E-13	$P \ll 0.001$
	V2	82.2 ± 21.1 (n = 61)	114.4 ± 24.2 (n = 74)	8.77E-6	$P \ll 0.001$
Peak response (spikes/s)	V1	102.2 ± 54.7 (n = 74)	140.1 ± 69.2 (n = 278)	1.81E-06	$P \ll 0.001$
	V2	82.7 ± 35.8 (n = 61)	135.8 ± 57.4 (n = 74)	4.13E-09	$P \ll 0.001$
Spontaneous activity (spikes/s)	V1	10.4 ± 8.5 (n = 74)	25.3 ± 18.1 (n = 278)	1.93E-20	$P \ll 0.001$
	V2	17.4 ± 9.2 (n = 61)	36.6 ± 20.8 (n = 74)	6.20E-10	$P \ll 0.001$

Note that the latencies of layer 4 cells did not differ in V1 of old and young animals. The latencies of V1 cells outside of layer 4, on the other hand, averaged 13 ms longer in old monkeys. Cells throughout area V2 exhibited longer latencies in old animals. The latencies of V2 cells were, on average, 32 ms longer in old monkeys. Old cells also exhibited much higher spontaneous and peak activities than young cells in both areas V1 and V2. The differences in spontaneous discharge rates were especially pronounced indicating that neurons in old cerebral cortex are continually firing at abnormally high rates.

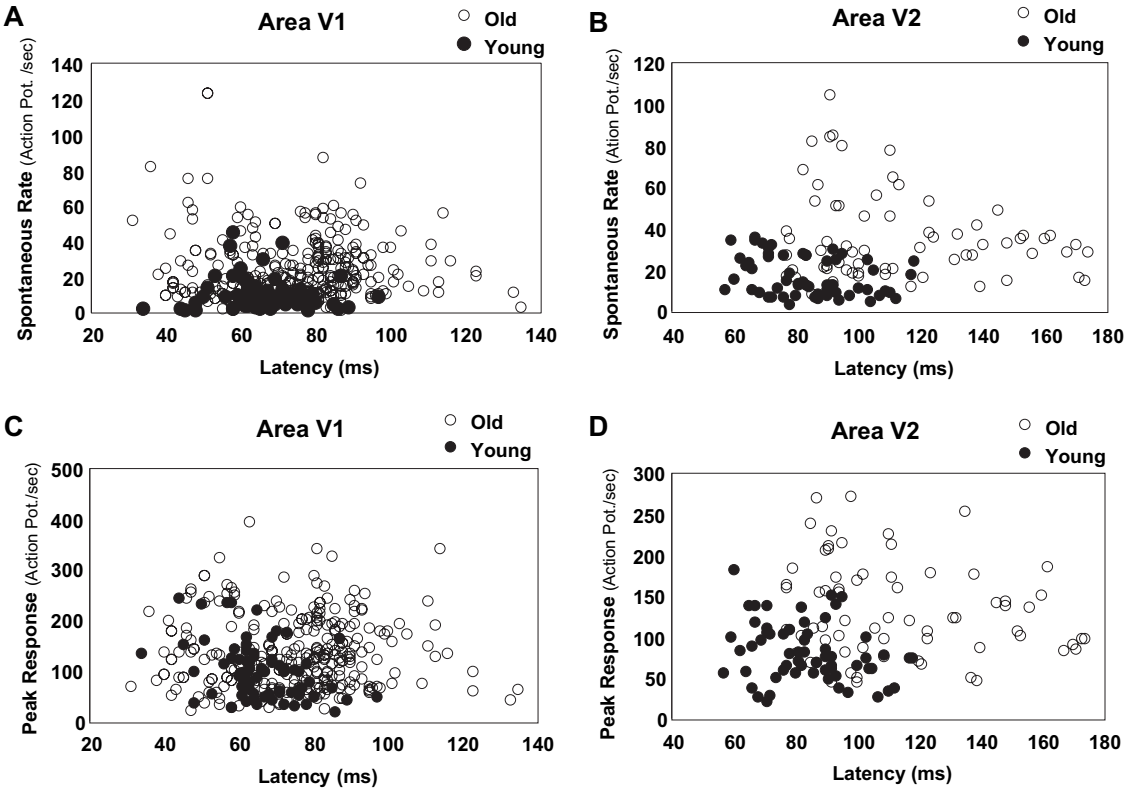

Figure 3. Scatter plot showing the spontaneous activities (*A*, *B*) and peak visually evoked responses (*C*, *D*) of cells in cortical areas V1 (*A*, *C*) and V2 (*B*, *D*) of old and young monkeys. Compared with cells in young monkeys, cells in old monkeys exhibit very long latencies as well as greatly increased spontaneous and peak responses. Response rates are in action potentials per second and latencies are in milliseconds.

Excitotoxic hyperactivity has been hypothesized to ultimately result in failure of excitatory transmission in Alzheimer's, Huntington's, epilepsy, and other brain diseases (Olney *et al.*, 1998; Perutz and Windle, 2001; Butterfield and Pocernich, 2003; Francis, 2003). The old cells studied here exhibited abnormally high visually evoked and spontaneous activities. The increased latencies we observed may reflect early failure of excitatory transmission induced by hyperactivity of cortical cells. Changes in axonal morphology as well as changes in dendritic morphology that have been reported in old monkeys could both reflect excitotoxic activity. We suggested previously that GABAergic inhibition degrades during old age in monkeys. GABA agonists reduce hyperactivity in old monkeys and improve brain function (Leventhal *et al.*, 2003). Old monkeys exhibit behavioral deficits similar to humans in the early stages of senescence. Thus, it is tempting to speculate that restoring GABAergic inhibition to appropriate levels or in some other way reducing hyperactivity during the earliest stages of senescence will limit the declines in brain function that accompany old age.

Notes

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