THE UNIVERSITY OF UTAH

Scott Smith
Associate General Counsel

June 13, 2006

Dr. Marcelo E. Nasif
Mrs. Maria Nasif
[redacted]

Dear Dr. and Mrs. Nasif:

I am writing on behalf of the University of Utah ("University") in response to your letter of May 16, 2006, in which you requested information regarding "OIPM-0007." The University is governed by the Utah Government Records Access and Management Act ("GRAMA"), found at Utah Code Annotated Section 63-2-101 and related sections. GRAMA requires the University, in certain cases, to provide copies of records to individuals who request those records with reasonable specificity. Because your request does not ask for a particular record or set of records, but rather asks for general information, the University is under no obligation to respond and chooses not to respond to this particular request.

Thank you for your attention to this matter.

Sincerely,

Scott Smith

Dear Primate Freedom,

Can you please give specific record # to inquire about the status of this primate?

Thank You,

Maria Nasif

[redacted]

P.S. Your fax doesn't work! (Afterhours)

Office of General Counsel
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THE UNIVERSITY OF UTAH

Scott Smith
Associate General Counsel

August 2, 2006

Dr. Marcelo E. Nasif
Mrs. Maria Nasif
[redacted]

Dear Dr. and Mrs. Nasif:

I am writing in response to your letter dated July 4, 2006 in which you request "the following records of the female macaque '01PM-0007': Records of her daily care logs including her birth records, records of drugs administered, blood samples taken, when and if she was moved from one part of the laboratory to another and necropsy reports if she is no longer alive."

Attached is an article from *Science* magazine that details the drugs that would have been administered to this macaque. This article is the only record in our possession of which we are currently aware that is responsive to your request. If further records come to our attention, we will be sure to forward those to you as well. In addition, I will tell you that our best approximation is that this animal passed away in 2002.

Sincerely,

Scott Smith

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REPORTS

GABA and Its Agonists Improved Visual Cortical Function in Senescent Monkeys

Audie G. Leventhal,[1*] Yongchang Wang,[1] Mingliang Pu,[1] Yifeng Zhou,[2] Yuanye Ma[3]

Human cerebral cortical function degrades during old age. Much of this change may result from a degradation of intracortical inhibition during senescence. We used multibarreled microelectrodes to study the effects of electrophoretic application of γ-aminobutyric acid (GABA), the GABA type a (GABAa) receptor agonist muscimol, and the GABAa receptor antagonist bicuculline, respectively, on the properties of individual V1 cells in old monkeys. Bicuculline exerted a much weaker effect on neuronal responses in old than in young animals, confirming a degradation of GABA-mediated inhibition. On the other hand, the administration of GABA and muscimol resulted in improved visual function. Many treated cells in area V1 of old animals displayed responses typical of young cells. The present results have important implications for the treatment of the sensory, motor, and cognitive declines that accompany old age.

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Aging is known to adversely affect visual function in humans. Senescent humans exhibit decreased visual acuity, binocular summation, contrast sensitivity, motion sensitivity, and wavelength sensitivity. The elderly also respond much more slowly in visual tests and do not perform as well at shape discrimination tests as do the young and middle aged (*1–10*). It has been hypothesized that many of the foregoing declines during old age are due to degeneration and/or dysfunction in central visual areas (*10, 11*).

The receptive field properties of cells in the visual cortex (area V1) have been studied for over 40 years. The cells in area V1 are known to respond selectively to both the angular orientation and the direction of motion of lines, bars, and edges (*12*). The orientation- and direction-selective responses of V1 cells are thought to participate in the perception of form and motion.

We reported previously (*11*) that primate visual cortical function declines because V1 cells in old (26 to 30 years old) macaque monkeys exhibit decreased orientation and direction selectivity, accompanied by increased visual responsiveness, increased spontaneous activity, and a decreased ability to signal visual stimuli above background activity (signal-to-noise ratio). We have now studied the effects of electrophoretic application of the inhibitory transmitter γ-aminobutyric acid (GABA), the GABA type a (GABAa) agonist muscimol, and the GABAa antagonist bicuculline on the receptive field properties of individual V1 cells in old monkeys. We tested the hypothesis that the application of GABA and GABA agonists on individual V1 cells can improve visual function in old animals.

We studied a total of 242 neurons in six young monkeys (7 to 9 years old) and 257 neurons in seven old monkeys (26 to 32 years old) (fig. S1). Both *Macaca mulatta* (75% of cells) and *M. fascicularis* (25% of cells) were studied. The results for the two species did not differ and thus are combined in the figures. Some of the animals included in this study also provided data for a previous one (*11*).

The effects of GABA, muscimol, and bicuculline on the responses of two typical cells in old monkeys and one in a young monkey are illustrated in Fig. 1. Before drug administration, cells in old animals responded equally well to all orientations and directions (Fig. 1, A and D). After GABA and muscimol administration, some of these cells responded strongly to a narrow range of preferred orientations and directions and exhibited nearly no response to the nonpreferred orientations and directions (Fig. 1, B and E). This differential effect on preferred and non-preferred orientations and directions suggests that the effect of GABA is not simply to nonselectively decrease the responses of the cell to all visual stimuli. Additionally, as illustrated in Fig. 1H, GABA administration did not affect the selectivity of most of the already strongly selective cells (Fig. 1G) in young animals.

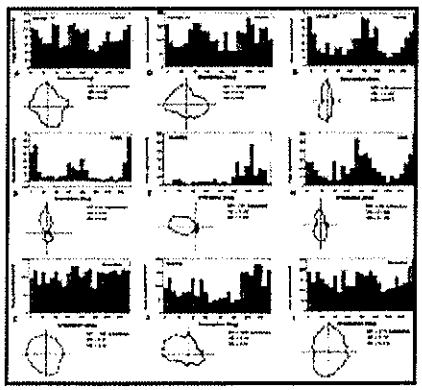

Fig. 1. Tuning curves and corresponding polar plots obtained for two representative cells in old monkeys (A to F) and one typical cell from a young monkey (G to I) that received treatment with GABA, muscimol, and bicuculline. The maximum (peak) responses (MR), orientation biases (OB), and direction biases (DB) are shown for each condition. A typical old cortical cell showing a lack of orientation and direction sensitivity is shown in (**A**). Three minutes after GABA application (**B**), this cell exhibited strong orientation and moderate direction selectivity. The cell's peak response decreased, as did its spontaneous activity. GABA application was then discontinued, and bicuculline

application was begun (**C**). Bicuculline reversed the effects of GABA. The responses of a second cell in visual cortex of an old monkey showing a degradation of orientation and direction selectivity are shown in (**D**). Three minutes after muscimol administration (**E**), this cell exhibited moderate orientation selectivity, very strong direction selectivity, a decreased peak response, and decreased spontaneous activity. Five minutes after the discontinuation of muscimol administration, the drug-induced improvement disappeared (**F**). A tuning curve typical of the majority of cells in young monkeys is shown in (**G**). The cell was selective, and its selectivity was not affected by the administration of GABA (**H**). On the other hand, application of bicuculline resulted in a more than 300% increase in peak response and greatly reduced orientation selectivity (**I**). [View Larger Version of this Image (46K GIF file)]

We also investigated the effects of the application of bicuculline on cells in young and old animals. In the old animals, bicuculline did not change stimulus selectivity to any great extent and resulted in a somewhat increased visual response (Fig. 1C). In contrast, as has been reported previously (*13, 14*), bicuculline greatly diminished selectivity in young animals and greatly increased the magnitude of the visual response (Fig. 1I).

The effects of GABA and muscimol administration on the orientation and direction selectivities of all V1 cells studied in old monkeys are summarized in Table 1. Both GABA and muscimol resulted in increases in the percentage of cells that exhibited significant orientation and direction selectivity. In fact, the percentages of orientation- and direction-selective cells approached those seen in normal animals after the application of GABA and muscimol. On average, however, the degree of selectivity of most cells in old monkeys after drug administration was still lower than that seen in young animals (Table 1, legend). Additionally, unlike in young animals in which bicuculline greatly diminishes selectivity (*13, 14*), bicuculline did not significantly affect the already low percentage of direction-selective cells in old animals. The number of orientation-selective cells was only reduced slightly (Table 1).

Table 1. Effects of drug application on the percentages of orientation- and direction-selective cells in area V1 of old monkeys. Old monkeys exhibit a reduction in orientation- and direction-selective cells as compared to young monkeys. Bicuculline results in a small decrease in the number of orientation-selective cells and no change in the number of direction-selective cells. In contrast, GABA and muscimol are capable of increasing the orientation- and direction-selective responses of cortical cells. Although many cells in old monkeys do become selective after drug application, most still do not exhibit the strong selectivities seen in young animals. In old animals, the mean orientation bias increased from 0.098 ± 0.031 to 0.148 ± 0.053 (mean ± SD), whereas the mean direction bias increased from 0.061 ± 0.022 to 0.114 ± 0.035 (mean ± SD) after GABA application. These values are lower than

the average biases seen in young animals. Our results for young animals indicate mean biases of 0.37 for orientation and 0.2 for direction (*11*).

	Old monkey				Young monkey control
	Control	GABA	Muscimol	Bicuculline	
Orientation selective	39%	81%	73%	22%	88%
Direction selective	23%	63%	68%	24%	69%

The effects of drug administration on the visually evoked response and spontaneous activity of V1 cells in old monkeys are summarized in Fig. 2, A and B, respectively. GABA and muscimol both decreased peak visual response and spontaneous activity (*t* test, $P < 0.01$ in each case). Muscimol was more potent than GABA, and its application resulted in responses that were within the normal range. Bicuculline had the opposite effect and resulted in increased visual and spontaneous responses (*t* test, $P < 0.001$ in both cases). In each case, 5 to 10 minutes after the cessation of drug administration, the cells reverted to the preapplication state.

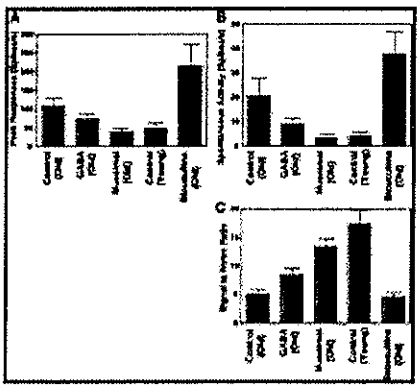

Fig. 2. The maximum visually evoked responses (**A**) and spontaneous activities (**B**) of V1 cortical cells in untreated old monkeys, untreated young monkeys, and old monkeys treated with GABA, muscimol, and bicuculline. Cortical cells in old monkeys exhibit abnormally high peak responses and spontaneous activities as compared to young monkeys. Bicuculline reduces GABA-mediated inhibition and increases peak responses and spontaneous activities. GABA and muscimol reduce the peak responses and spontaneous activities of cortical cells to levels close to those seen in young monkeys. Additionally, GABA and muscimol increased signal-to-noise ratios dramatically in old animals. Bicuculline did not improve signal-to-noise ratios in old animals (**C**). [View Larger Version of this Image (24K GIF file)]

Proper brain function requires that stimuli evoke reliable responses that are easily discernable from background activity. We reported previously (*11*) that the ratio of the visually evoked response to background activity was much lower in old than in young monkeys. Histograms showing effects of drug application on the ratio of the peak visually evoked response to the spontaneous discharge rate (referred to here as signal-to-noise ratio) of cortical cells are presented in Fig. 2C. Both GABA and

muscimol administration resulted in higher ratios (*t* test, $P < 0.01$ in both cases) and thus an improved ability to signal visual stimuli. On the other hand, bicuculline did not affect signal-to-noise ratios significantly in old animals because ratios were already low.

If GABA-mediated inhibition degrades during old age, then GABA and GABA agonists should be more effective in old than in young animals. Conversely, GABA antagonists should be more effective in young than in old monkeys. The results in Table 2 show that GABA and muscimol both result in larger percentage decreases in visually evoked and spontaneous activity in old than in young animals (*t* test, $P < 0.01$ in both cases). Bicuculline, on the other hand, resulted in larger percentage increases in visually evoked and spontaneous activity in young monkeys than in old ones (*t* test, $P < 0.01$). Taken together these results strongly suggest a decrease in the amount of GABA-mediated inhibition in cortex.

Table 2. Effects of drug application on responses of V1 cells. Changes in peak visually evoked response and spontaneous firing rate induced by GABA, muscimol, and bicuculline in young and old monkeys. GABA and muscimol resulted in larger percentage decreases in neuronal firing rates in old than in young monkeys. Bicuculline resulted in larger percentage increases in neuronal firing rates in young than in old monkeys.

		Control	GABA	Muscimol	Bicuculline
Old monkeys	Peak response	100%	-28.8%	-61.1%	+40.4%
	Spontaneous rate	100%	-57.6%	-83.4%	+88.4%
Young monkeys	Peak response	100%	-20.1%	-28.7%	+214.2%
	Spontaneous rate	100%	-11.2%	-9.1%	+416%

The results of this study show that the administration of GABA and muscimol results in improved orientation and direction selectivity, accompanied by decreased visual responsiveness, decreased spontaneous activity, and an increased ability to signal visual stimuli. Some cells in V1 of old animals displayed responses typical of cells in young animals after drug application. A restoration of function was evident as soon as 2 minutes after drug delivery. Five to 10 minutes after discontinuation of drug administration, neuronal function reverted to preapplication levels. Application of bicuculline resulted in much smaller changes in the properties of old V1 cells than in the properties of young ones. It should be mentioned that the iontophoretic application of noradrenaline is reported to improve the signal-to-noise ratio of cells in cat visual cortex (*15*) and primate motor cortex (*16*). Whether age affects noradrenaline levels in primate cortex is not known.

The foregoing results are consistent with the hypothesis that reductions in GABA-mediated intracortical inhibition contribute to the degradation of cortical function that accompanies old age. Our finding that GABA agonists exert a weaker effect on cortical cells in young monkeys than in old ones further supports this idea. The finding that bicuculline is more effective in young than old monkeys is also compatible with this suggestion.

A decrease in intracortical inhibition could result from diminished release of

transmitter, diminished production of transmitter, a degradation of transmitter receptors, membrane changes, etc. Although our findings cannot pinpoint the changes in old monkeys, the present findings show that simply adding GABA and GABA agonists does facilitate visual function in old animals. Thus, it is tempting to speculate that normal aging results in a decreased ability to produce GABA in cerebral cortex. It is noteworthy that an age-related degradation of GABA-mediated inhibition has also been reported in the inferior colliculus. The effects of age on the inferior colliculus include reductions in the number of GABA-immunoreactive neurons, the concentration of GABA, GABA release, and GABA receptor binding (*17*, *18*). Similar studies in primate cortex need to be carried out.

Some V1 cells in old animals exhibited responses typical of cells in young ones after the application of GABA and GABA agonists. However, most cells exhibited only partial recovery as a result of drug administration. Thus, factors other than a degradation of GABA-mediated inhibition may also be involved. Because GABA-mediated inhibition is prevalent throughout the neocortex (*19*, *20*), it is likely that changes similar to those seen in V1 will exist in many cortical areas in old animals. Thus, the improvement in function of V1 cells after the application of GABA and its agonists has important implications for the treatment of the sensory, motor, and cognitive declines that accompany old age.

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Supporting Online Material

www.sciencemag.org/cgi/content/full/300/5620/812/DC1

Materials and Methods

Fig. S1

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(2003).
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Materials and Methods

Preparation The procedures for this study were also used for our previous study of senescent monkey cortex *(S1)*. Briefly, subjects for this study were young adults (7 to 9 year old) and very old (26 to 32 year old) *Macaca mulatta* and *Macaca fascicularis* (Fig. S1). Only 25% of rhesus macaques reach the age of 25 and only 6% reach the age of 30 or older *(S2)*. Thus, our 26-32 year old monkeys can be considered old. The 7-9 year old monkeys are at an age that is considered sexually mature *(S3)*. All animals were examined ophthalmoscopically and had no apparent optical or retinal problems that would impair visual function. The retinal blood vessels, lens clarity and the maculae all appeared to be within normal limits. V1 cells studied had receptive fields between 2 and 5 degrees from the fovea. Monkeys were prepared for electrophysiological recording using standard techniques consistent with Society for Neuroscience and National Institute of Health and University of Utah Institutional Animal Care and Use Committee guidlines.

Monkeys were first sedated with Ketamine HCl and then anesthetized with halothane (5%) in a 70:30 mixture of NO_2:O_2. Intravenous and tracheal cannulae were inserted and animals were placed in a stereotaxic apparatus. All pressure points and incisions were infiltrated with a long-acting anaesthetic (1% lidocaine HCl). A solution of d-tubocurarine (0.4mg/kg/hr) and gallamine triethiodide (7 mg/kg/hr) was infused intravenously to induce and maintain paralysis. Animals were ventilated and anesthesia was maintained with a mixture of nitrous oxide (75%) and oxygen (25%) and halothane (0.25-1.0%) as needed. Expired pCO_2 was maintained at approximately 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.

Once the animal was placed on life support, care was taken to adjust the level of anesthesia so that vital signs were comparable in old and young animals. A cylindrical chamber or small burr hole was positioned above striate cortex (V1), filled with a 4% solution of agar in saline and sealed with wax. The eyes were protected from desiccation with contact lenses. Spectacle lenses and artificial pupils were used when needed to focus the eyes on a tangent screen positioned 228 cm from the retina. The locations of the optic discs and foveae were determined repeatedly during the course of each recording session. Care was taken to monitor the normality of the optics and retinal vasculature in old and young animals. No visible deterioration in optics occurred during the experimental period (2-5 days). Action potentials of isolated cortical cells were recorded extracellularly with microelectrodes having impedances of 3-5 MΩ. The electrode was advanced using a hydraulic microdrive.

Visual Stimulation Visual stimuli were generated on a Tektronix 608 display in conjunction with a Picasso image synthesizer and texture/motion generator. The Picasso and texture/motion generator are controlled by computer using a specially designed hardware and software package. The center of the display screen was 171 cm from the animal's retina. Stimuli were presented monocularly to the dominant eye. The physiological orientation biases (OB) and direction biases (DB) of cortical cells were studied quantitatively. The orientation of each drifting stimulus presented was orthogonal to its direction of motion (the orientation is 90° less than the direction). Five to 20 presentations of moving bars, spots or sinusoidal gratings at each of 24 to 36 randomly generated orientations or directions from 0° to 360° were used to compile the tuning curves for the cells studied. The responses of the cells were studied at a variety of

spatial frequencies (c/d, cycles per degree) when gratings were employed. The size and temporal frequency/velocity of the drifting stimulus used was the optimal for the cell. The luminance of the stimuli employed was 8.37 cd/m^2 for white spots and bars and 0.91 cd/m^2 for black spots and bars. The contrast for bar and spot stimuli was defined as the ratio of the luminance of the spot or bar to its background. The contrast for sinusoidal gratings was defined as the ratio of the luminance of the center of the light and dark cycles of the gratings. In both cases, the contrast was kept at 80% [(8.37-0.91 cd/m^2)/(8.37+0.91 cd/m^2)].

Analysis of Orientation and Direction Selectivities The responses of the cells to the drifting visual stimuli presented were stored in the computer for later analysis. The responses to the sinusoidal gratings were fast Fourier transformed (FFT) and defined as the peak to peak value of the fundamental Fourier component (F1) of the poststimulus time histogram integrated over a time equaling the stimulus modulation period (FFT1 spikes/sec). For stimuli other than gratings the responses were defined as the peak response (Hz) of the poststimulus time histogram. At the time of each drifting bar presentation baseline values were obtained during a 0.5 – 0.7 second "blank stimulus" period.

Orientation and direction selectivity were calculated using the statistical methods described in detail previously *(S1)*. Briefly, the responses of each cell to the different stimulus orientations and directions were stored as a series of vectors. The vectors were added and divided by the sum of the absolute values of the vectors. The angle of the resultant vector gave the preferred orientation and direction of the cell. The length of the resultant vector, termed the orientation or direction bias, provided a quantitative measure

of the orientation or direction sensitivity of the cell. Previous studies in our laboratory have indicated that a bias of 0.1 is significant at the $p < 0.005$ level (Raleigh test) and that orientation biases of 0.1, 0.3, and 0.5 correspond to maximum to minimum response ratios of 1.5:1, 3.7:1, and 10.8:1, respectively *(S4)*.

Drug application GABA agonists and antagonist were delivered through multibarreled microelectrodes. Three barrels held various drugs, one barrel was filled with 4M NaCl in order to record the action potentials of the cells and another was filled with vehicle solution (pH at 4.5) for current balancing. Drugs were dissolved in saline at 4 mM to 50 mM, pH at 3.5 to 5.0. Administration of one drug at a time is accomplished by passing 20 – 30 nA through the appreciate barrel. Holding current (15 – 20 nA) were applied through other barrels simultaneously in order to prevent leakage of the other drugs.

Statistical Analysis Whenever possible, statistical comparisons between young and old monkey data were carried out in two ways. The first approach compared the entire data set of each old monkey to that of each young monkey using one-way ANOVAs, t-tests, Kruskal-Wallis one-way ANOVAs and/or Mann-Whitney rank sum tests, as appropriate. The second approach reduced the data set of each monkey to the average score, and compared young monkeys versus old monkeys using these single data points (t-test or Mann-Whitney rank sum test). The results of these two approaches were virtually identical in all cases. Only t-test values are given in the text.

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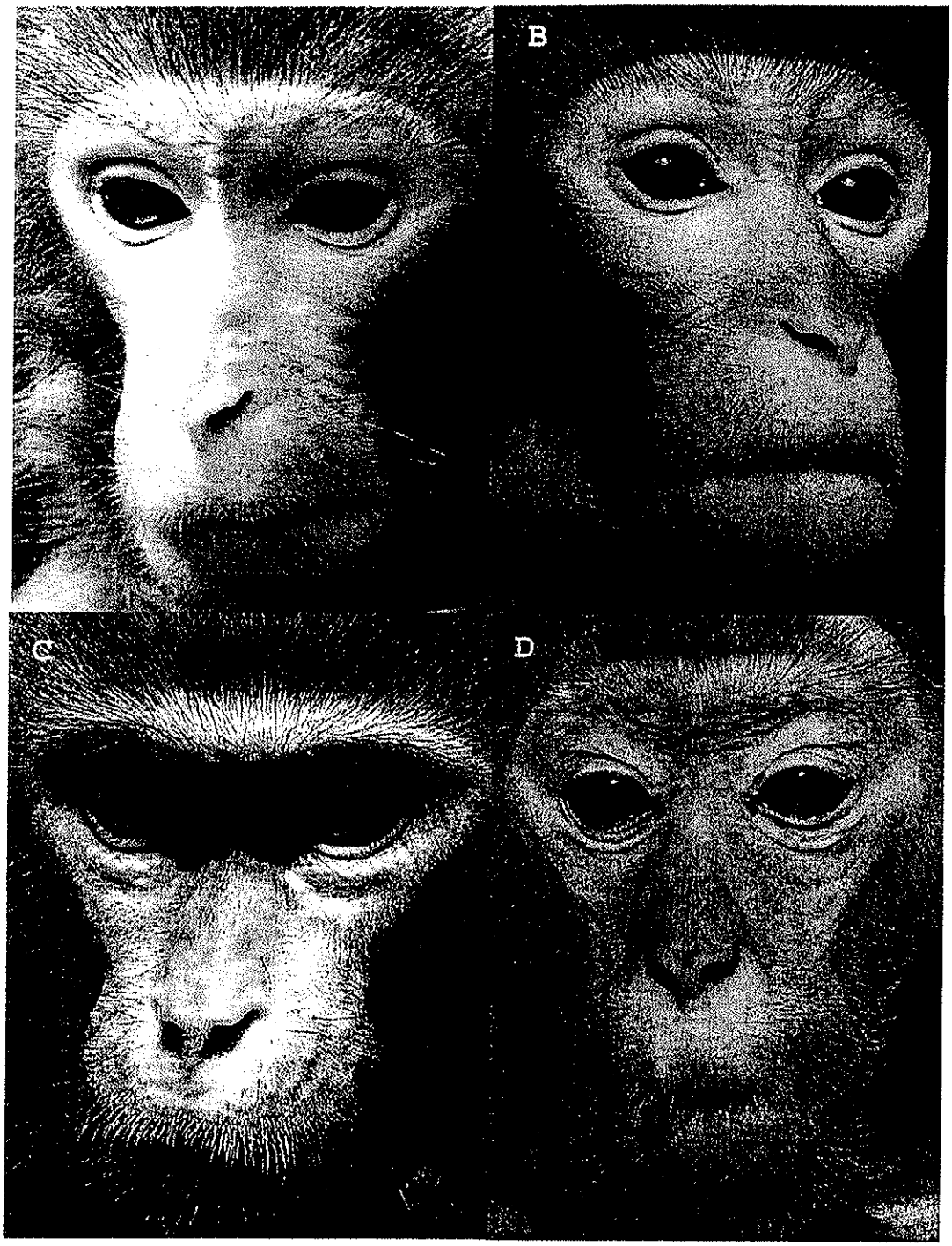
Fig. S1

Photographs of four year old (A), seven year old (B), 14 year old (C) and 26 year old (D) Rhesus monkeys (*macaca malatta*). Monkeys of these ages correspond to 12, 21, 38 and 78year old humans, respectively. Pictures are of animals located in the primate facility in Kunming, Yunnan Province, PRC. In the wild rhesus monkeys rarely if ever live more than 18-20 years. Very old (26-32years)monkeys exhibit cognitive declines similar to those seen in very old humans . Eectrophysiological studies provide evidence for a degradation in the properties of in cells in cerebral cortex that can account for some of the cognitive declines seen in senescent monkeys and humans. The application of the inhibitory neurotransmitter GABA and its agonists can improve the function of cortical cells in very old monkeys.


B
C
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