1.84 times that in the bubbles. These were thus recognizable in bright field by the usual criterion of contrast reversal on passing from underfocus to overfocus.

Figure 1B is a high magnification image of part of a <110> grain taken with a 50-μm objective aperture, which allowed {111} and {200} reflections from both xenon and aluminum to contribute to the image. The film was tilted so that one-dimensional lattice fringes were formed. Aluminum {111} lattice fringes (0.234 nm), as well as parallel moiré fringes due to the mismatch between {111} aluminum and xenon planes, are visible. The high degree of crystalline perfection apparent in this figure is representative of that observed in many of the bubbles.

Figure 1C is an image from a <110> grain taken with a 20-μm objective aperture (indicated by the circle in Fig. 1A), which allowed only {111} and {200} xenon reflections to contribute to the image and excluded all beams diffracted from the aluminum matrix. Again, because of the tilt of the aluminum film about a <111> direction, systematic row diffraction conditions were operating, resulting in a one-dimensional lattice image from {111} planes within the xenon bubble. The faceted nature of the bubbles is evident in Fig. 1, B and C. Figure 1D is an image formed in the same manner as that in Fig. 1C of a bubble whose crystalline perfection is somewhat disturbed near the center.

An analysis of 130 bubbles exhibiting {111} xenon lattice fringes revealed that, in general, the bubbles were faceted but often irregular in shape, although a number of images were consistent with truncated octahedra. The largest bubble in this population was approximately 8 nm, and the smallest was about 2 nm. By approximating the bubble shapes with circles of equivalent projected area and using the resulting diameters as characteristic dimensions, we obtained a roughly symmetrical distribution of sizes ranging from 1.7 to 6.6 nm (mean, 3.5 nm; standard deviation, 1 nm).

The equilibrium pressure, P, required by a spherical bubble of diameter D to balance its surface free energy is given simply by $P = 4\gamma/D$, where γ is the surface tension. Taking γ for aluminum as 0.95 N m^{-1} and neglecting the (small) surface tension of xenon yielded (for spherical bubbles with the above size distribution) equilibrium pressures ranging from 6 to 22 kbar (mean, ~11 kbar). Taking the *fcc* lattice parameter for xenon as 0.604 nm and extrapolating the isotherms of Anderson and Swenson (*10*) to 300 K, we estimate a pressure of 7 kbar within the xenon bubbles; this indicates that they are close to or somewhat below equilibrium pressure. The absence of strain contrast around the bubbles, when viewed under bright-field diffraction contrast-imaging conditions, is a further indication that the bubble pressure differs by, at most, a few kilobars from equilibrium.

Use of the modified Simon equation (*11*) to estimate the melting temperature of macroscopic xenon with the same density as that in our precipitates yielded an expected melting temperature, T_m, of approximately 430 K. Thus for our room temperature observations, the xenon is at a temperature greater than $\frac{2}{3}T_m$ and may be expected to be sufficiently "hot" to anneal out crystalline imperfections. Indeed, we observed a rapid decrease in intensity in higher order xenon reflections, which is indicative of a large Debye-Waller factor at room temperature. Large mean square displacement of atoms from equilibrium positions may result in high defect mobilities and may account for the high degree of crystalline perfection in many bubbles.

We have demonstrated how ion implantation into a host metal matrix may be used to facilitate lattice imaging of an inert gas solid at high pressure. Indeed, if the imaged reflections represent larger spacings than those available within the host matrix, an objective aperture of suitable diameter may be chosen such that lattice information about the bubble alone is contained in the image (Fig. 1C). Information about the interface between the host lattice and bubble (Fig. 1B) and about crystalline defects within the bubbles themselves (Fig. 1D) is thus accessible. Such information cannot be obtained from electron diffraction patterns alone. For small bubbles, the thermodynamic properties may differ from bulk values because the high ratio of surface area to volume may yield behavior strongly dependent on surface or interface properties. For instance, it may be speculated that superheating may occur if the interfacial xenon atoms, in contact with the aluminum, have a larger effective Debye temperature than that of bulk xenon at these pressures.

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α_2-Adrenergic Mechanisms in Prefrontal Cortex Associated with Cognitive Decline in Aged Nonhuman Primates

Abstract. *This study provides evidence that the α_2-adrenergic receptor agonist clonidine ameliorates the cognitive deficits exhibited by aged nonhuman primates through drug actions at α_2 receptors. Furthermore, pharmacological profiles in animals with lesions restricted to the dorsolateral prefrontal cortex indicate that this area may be the site of action for some of clonidine's beneficial effects. These results demonstrate that α-adrenergic systems contribute to cognitive function and suggest a new strategy for treating memory disorders in aged humans.*

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Most research on age-related cognitive disorders has emphasized the loss of cholinergic neuronal function (*1*), thus focusing studies of possible pharmacological "replacement therapy" on cholinergic drugs. However, studies of Alzheimer's patients and aged nonhuman primates have found little therapeutic value for indirectly acting cholinergic agonists, and directly acting agonists have had reliable, but limited, beneficial effects (*2*). This may be attributed in part to the complexity of degenerative processes in the aging brain, which include not only loss of cholinergic neurons but deterioration of other neurotransmitter

systems, including those that involve the catecholamines. Levels of dopamine and norepinephrine (NE) are reduced in the brains of aged rodents (*3*), monkeys (*4*), and humans (*5*), and NE loss is further exaggerated in Alzheimer's disease (*6*). Catecholamine loss in the aged nonhuman primate is particularly pronounced in the prefrontal and anterior temporal cortices (*4*) and in the catecholaminergic neurons of the brainstem that project to the cortex (*7*). The prefrontal and temporal cortices also contain amyloid plaques that stain for the catecholamine-synthesizing enzyme tyrosine hydroxylase (*8*).

If loss of catecholamines contributes to age-related cognitive decline, then pharmacological treatments that facilitate their transmission may ameliorate the cognitive deficits. This hypothesis was investigated by examining the effects of catecholaminergic agonists on cognitive performance in five female rhesus monkeys ranging from 17 to over 30 years of age. The animals were trained on a delayed-response task that is sensitive to aging (*9*). In this task, the animal views one of two food wells being baited, the wells are covered with identical cardboard plaques, and an opaque screen is lowered for a prescribed delay period. At the end of this time the screen is raised and the animal is allowed to select a well. In order to observe the effects of each drug dose on mnemonic capacity during a single session, the delays used were varied between 0 seconds and the temporal interval previously determined to yield chance performance (the range of delays used for each animal appears in Fig. 1). Within this range, five different delay lengths were selected and quasi-randomly distributed over the 30 trials that made up a daily test session. Each monkey was tested twice a week, once with a single dose of drug and once with a placebo treatment according to quasi-random assignment (*10*).

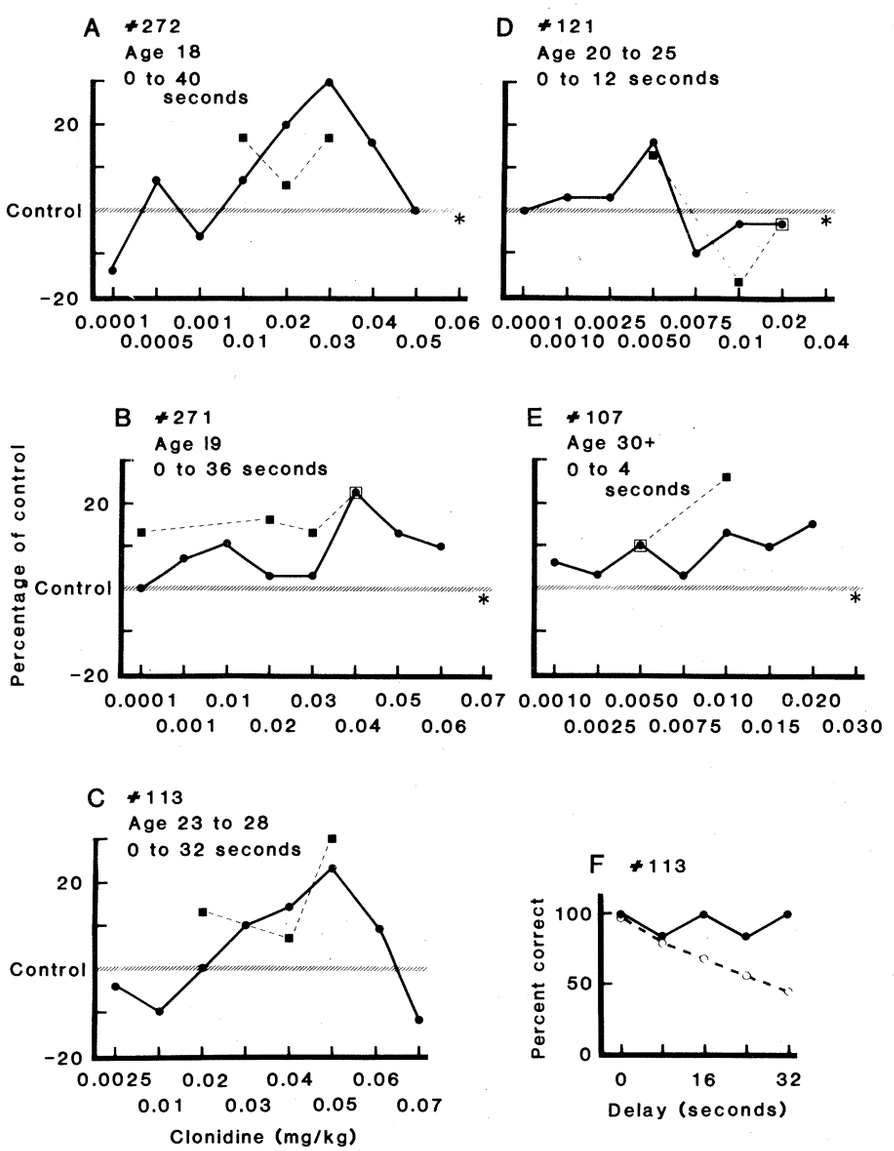

Fig. 1. (A to E) Individual clonidine dose-response curves for the five aged rhesus monkeys tested on the delayed-response task. The range of delays used for each animal is indicated; the data presented are collapsed across all delays. Performance on clonidine is calculated as the percentage of change from the performance on matched placebo (saline). Four of the five aged monkeys exhibited near-perfect performance (approximately 30 percent) after receiving the most effective dose of clonidine. (■) Replications of selected doses; in some cases the animal was too sedated to test (*). (F) Representative delay/response function for one aged animal. Performance on saline is indicated by the open circles; the animal performed well at short delays and more poorly as the delay lengthened. (●) Performance on clonidine (0.05 mg/kg); the improvement was most marked at the longer delays.

The aged animals performed consistently over the 18 months of the study. Their performance with the placebo was 64 ± 6 percent (mean ± standard error) correct over 32 sessions, with errors occurring primarily at the longer delays (Fig. 1F). As might be expected, there was an inverse relation between the age of the animal and the length of the delays at which they could perform correctly, with the youngest monkeys performing better at the longest delays (Fig. 1).

A variety of drugs that affect catecholamine transmission were tested (*11*). One of these, the α_2-receptor agonist clonidine, improved delayed-response performance in each of the five aged monkeys; at the most effective clonidine dose, four of the five animals were able to achieve near perfect performance [test for trend showed significant quadratic but not linear components: linear, $F(1, 24) = 0.07$, not significant; quadratic, $F(1, 24) = 7.23$, $P < 0.05$; analysis of variance (1-ANOVA-R) on middle dose range, main effect of clonidine dose, $F(3, 12) = 4.01$, $P < 0.05$; most effective dose of clonidine versus matched placebo control, $t_{dep} = 9.75$, $P < 0.001$] (Fig. 1). Marked improvements with clonidine were found with the oldest monkey (30+ years), which performed 93 percent correctly after receiving 0.01 mg/kg (Fig. 1E). As expected, since saline-treated animals made most of their errors after long delays, clonidine's beneficial effects were most apparent at these longer intervals (Fig. 1F).

At the highest doses, the aged animals were impeded by clonidine's sedative effects. However, every animal appeared to develop tolerance to this side effect. In some animals, tolerance to the sedative effects was necessary before the beneficial effects of the drug could be observed (*12*). This was true of the one monkey (121) who was not consistently improved by isolated injections of the

drug (Fig. 1D). However, the repeated administration of 0.02 mg of clonidine per kilogram to this animal resulted in a reliable improvement in delayed-response performance (first injection, −3 percent compared to saline; fifth injection, 17 percent compared to saline). The finding that clonidine's sedative effects can mask its beneficial actions may be important to consider in human clinical trials, which usually entail only single injections.

Improvements in cognitive performance by clonidine appear to result from actions at α-adrenergic receptors, as they were blocked by the α-adrenergic receptor antagonist yohimbine in a dose-dependent manner [1-ANOVA-R on the effects of low and high doses of yohimbine on clonidine performance: main effect of yohimbine dose, $F(1, 4) = 26.7$, $P < 0.01$; most effective dose of yohimbine, $t_{dep} = 8.38$, $P < 0.01$)] (Fig. 2A). Furthermore, administration of yohimbine alone actually exaggerated the cognitive deficits [1-ANOVA-R on the effects of low and high doses of yohimbine compared to matched placebo control: main effect of yohimbine dose, $F(1, 3) = 32.4$, $P < 0.05$; most effective dose of yohimbine versus saline, $t_{dep} = 6.09$, $P < 0.01$)] (Fig. 2B). The performance of the oldest animal was worsened by the lowest dose of yohimbine tested (0.1 mg/kg), while the younger monkeys needed increasingly higher doses (0.5 to 1.5 mg/kg) to show marked impairments (Fig. 2B) (*13*). Impairments were not seen with the β-receptor antagonist propranolol (*14*), suggesting that it is the α-adrenergic rather than the β-adrenergic system that is linked to delayed response deficits with age.

To specify the type of α receptor involved, three aged monkeys were treated with the selective α_1 antagonist prazosin (0.01 to 1.0 mg/kg), either alone or in combination with clonidine (0.02 mg/kg). In contrast to the results with yohimbine, even the highest dose of prazosin had little effect on delayed performance [the most effective dose altered performance 5.7 ± 4.0 percent compared to matched placebo control, $t_{dep} = 1.43$, not significant]; nor was prazosin capable of reversing clonidine's beneficial effects [the most effective dose of prazosin (1.0 mg/kg) altered performance on clonidine by 2.3 ± 3.2 percent, $t_{dep} = 0.56$, not significant). Thus it appears that clonidine's ability to improve spatial working memory results primarily from actions at α_2 receptors.

To examine the specificity of clonidine's effects on cognitive function, the aged monkeys were trained on a visual pattern discrimination task that does not rely on working memory. In this task, the animals must learn to discriminate between two simple geometric patterns, the reward always being associated with one of the two. The oldest animals performed poorly on this task; however, they were not improved by doses of clonidine that facilitated their delayed-response performance (59 ± 3 percent correct for saline, 55 ± 3 percent for clonidine). Conversely, the two youngest monkeys performed well on the visual discrimination task and were not impeded by doses of yohimbine that reduced delayed-response performance to chance levels of responding (100 ± 0 percent for both saline and yohimbine). The absence of effects of clonidine and yohimbine on the visual discrimination task indicates that these agents are not affecting delayed-response performance through a general alteration of motivation, anxiety, alertness, or blood pressure—nonspecific consequences that would be expected to affect performance on both types of tasks. Consonant with this interpretation are the findings that neither the hypotensive agent propranolol nor the sedative diazepam altered the delayed-response performance of the aged monkeys (*14, 15*). Rather, clonidine and yohimbine may have direct effects on cognitive function, particularly those mnemonic functions utilized in the performance of the delayed-response task.

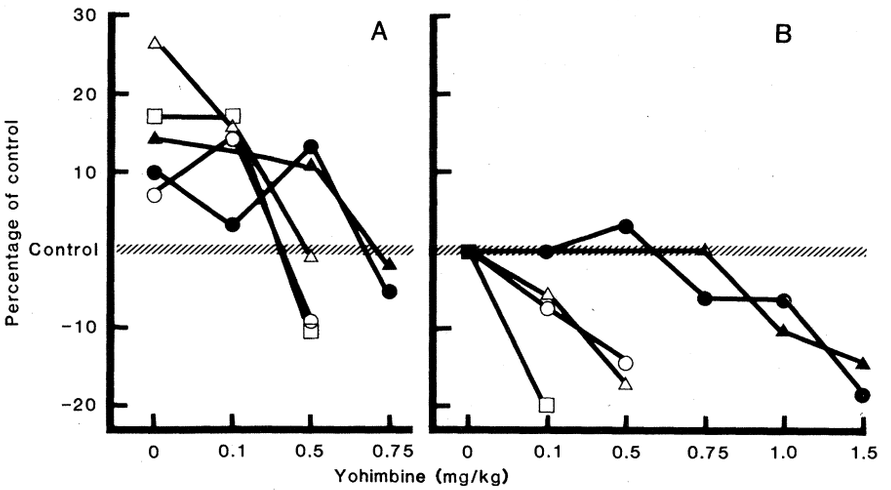

Fig. 2. (A) Ability of increasing doses of yohimbine to block the response to clonidine (0.02 mg/kg). Data represent the percentage of change from the performance on saline, collapsed across all delays. Data are presented for each aged monkey: 272 (●), 271 (○), 113 (△), 121 (▲), and 107 (□). (B) Yohimbine administered by itself impaired performance below the control level to chance levels (approximately −15 percent). The oldest monkey (107) was impaired by the lowest dose of yohimbine (0.1 mg/kg), while the youngest monkey (272) was impaired by the highest dose (1.5 mg/kg).

Although clonidine acts at sites throughout the nervous system, some of the drug effects observed in this study may be localized in the brain region that has been linked most strongly to the performance of the delayed-response task, the prefrontal cortex surrounding the principal sulcus. Like aged monkeys (*16*), young monkeys with surgical ablations (*17*) or toxin-induced catecholamine depletions (*18*) of the principal sulcal region are unable to perform delayed-response tasks but can do visual discrimination tasks. The pattern of clonidine's effects in young monkeys with lesions of this cortical region suggests that clonidine can improve performance based on working memory through actions at postsynaptic α_2 receptors in the principal sulcal region. Such a hypothesis predicts that the more extensive the destruction of NE terminals in the principal sulcal cortex, the greater the proliferation of postsynaptic α_2 receptors in this region and the smaller the clonidine dose needed to improve mnemonic performance. This pattern of results was found in young adult monkeys in which the principal sulcal region was depleted selectively of catecholamines by the neurotoxin 6-hydroxydopamine (6-OHDA) (Fig. 3). The monkeys with the largest NE loss in the principal sulcal cortex were helped by low doses of clonidine (25 ± 3 percent improvement at 0.01 mg/kg); the animals with smaller NE depletions were improved greatly by higher doses (33 ± 9 percent at 0.04 mg/kg) and unoperated controls were unaffected by the drug (only 9 ± 6 percent at the most effective dose) (*19*).

The results of the depletion studies are consonant with clonidine acting at supersensitive, postsynaptic α_2 receptors in

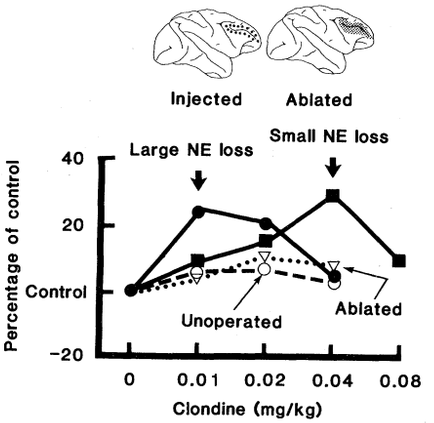

Fig. 3. Effects of clonidine on spatial memory in young monkeys with bilaterial lesions (*18*) of the principal sulcal cortex and in unoperated controls. Two groups of monkeys received injections of 6-OHDA into the principal sulcal cortex (inset). One group was treated with the NE uptake blocker desmethylimipramine (DMI) before surgery. The group that did not receive DMI (n = 2) (●) had the largest NE depletion (above 80 percent) and was improved by the smallest dose of clonidine; while the DMI-treated group (n = 3) (■) had a smaller NE loss (below 80 percent) and was improved by a higher dose of clonidine. Unoperated monkeys (n = 3) (○) were not significantly improved by clonidine. In contrast to the 6-OHDA–injected animals, three monkeys with ablations of the same cortical region (△) were not improved by clonidine compared to matched placebo controls. One of these animals had received a bilateral resection restricted to the banks and depths of the principal sulcus (inset), while the lesion in the other two monkeys included additional cortex on the dorsolateral convexity, extending posteriorly to the arcuate sulcus and medially to the longitudinal fissure (*21*).

the principal sulcal cortex. This idea was tested further by examining whether clonidine would remain effective in young adult animals in which the postsynaptic α_2-receptor population in the principal sulcal region had been removed surgically. The dorsolateral prefrontal cortex surrounding the principal sulcus was bilaterally ablated in three monkeys (see legend to Fig. 3) (*10, 20*). After recovering from surgery, the animals were administered clonidine (0.01 to 0.04 mg/kg) or a placebo and tested on delayed alternation, a variation of the spatial delayed-response task (*18*). In contrast to the results with aged monkeys, clonidine failed to improve the performance of these animals (10 ± 2 percent improvement for the most effective dose of clonidine, compared to 0 ± 9 percent for the matched placebo control, t_{dep} = 1.53). These results indicate that at least some of clonidine's actions require the presence of receptors in the principal sulcal region. Indeed, recent receptor localization studies in primate cortex show dense clonidine binding in specific layers of the principal sulcal cortex (*21*), and the prefrontal cortex is reported to contain the highest concentration of postsynaptic α_2 receptors in the rodent brain (*22*). Clonidine may act on these receptors in aged monkeys, improving delayed-response performance through a direct facilitation of the mnemonic and information-processing functions of the prefrontal cortex that are so vulnerable to deterioration with age.

These findings with clonidine are especially noteworthy given the scarcity of substances that have beneficial effects in aged human and nonhuman primates. α-Adrenergic drugs have been found to improve the mnemonic performance of aged rodents as well (*23*). These results suggest new possibilities for treatment of age-related cognitive disorders in humans. It has been reported that clonidine can benefit patients with Korsakoff's syndrome, a disease in which memory impairments are also accompanied by indices of NE loss (*24*). Adrenergic agonists might similarly be helpful for patients with Alzheimer's disease. Although previous research has focused on the loss of cholinergic cells in these patients (*25*), it is now apparent that extensive deterioration may also occur in the locus coeruleus (*26*), particularly in the anterior portion innervated by the prefrontal cortex (*27*), and, as might be predicted, NE levels are significantly reduced in the prefrontal and temporal cortices as well (*6, 28*). However, adrenergic receptors are not lost in this disease (*29*), and it is plausible that agonists could act directly on those receptors to provide effective replacement therapy. Adrenergic agents thus may provide an important complement to existing strategies for the treatment of this complex, degenerative disorder.

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10. Doses were chosen quasi-randomly. The experimenter testing the animal was unaware of the treatment conditions.
11. The drugs tested were clonidine (0.0001 to 0.07 mg/kg, courtesy of Boehringer-Ingelheim); levodopa and carbidopa (10 to 50 mg/kg and 5 to 20 mg/kg, courtesy of Merck Sharp & Dohme); apomorphine (0.001 to 0.06 mg/kg, courtesy of Merck Sharp & Dohme); propranolol (0.01 to 1.0 mg/kg, courtesy of Ayerst); diazepam (0.5 mg/kg, courtesy of Hoffmann–La Roche); yohimbine (0.1 to 0.5 mg/kg, Sigma); and prazosin (0.01 to 1.0 mg/kg, courtesy of Pfizer). Clonidine, propranolol, yohimbine, and low doses of prazosin were injected intramuscularly 15 minutes before testing; L-dopa, carbidopa, diazepam, and high doses of prazosin were mixed into banana and fed 90 minutes (L-dopa) or 30 minutes before testing.
12. Clonidine's sedative effects may account for the negative findings with this drug observed previously [R. T. Bartus, C. Flicker, R. L. Dean, in *Assessment in Geriatric Psychopharmacology*, T. Crook, S. Ferris, R. Bartus, Eds. (Powley, New Canaan, Conn., 1983), p. 263]. These authors also reported negative findings with L-dopa and apomorphine. However, as neither doses nor data were reported, it is difficult to make comparisons with the present study.
13. Since yohimbine increases the firing rate of locus coeruleus cells through actions at α_2 autoreceptors [S. J. Grant, Y. H. Huang, D. E. Redmond, *Life Sci.* **27**, 2231 (1980)] and blocks postsynaptic α_2 receptors, it is possible that higher yohimbine doses were needed in the younger monkeys to counteract the effects of increased NE release from more intact NE neurons.
14. At the most effective dose, propranolol (1.0 mg/kg) altered delayed performance by only 1 ± 4 percent compared to control performance on matched placebo in three monkeys.
15. Diazepam (0.5 mg/kg) had little effect on performance (0 ± 7 percent compared to control performance on matched placebo in two monkeys).
16. The similarity in the pattern of cognitive deficits between aged monkeys and monkeys with frontal lesions suggested to R. T. Bartus [in *Aging*, vol. 10, *Sensory Systems and Communications in the Elderly*, J. M. Ordy and K. Brizzee, Eds. (Raven, New York, 1979), p. 85] that frontal dysfunction may underlie many age-related cognitive impairments.
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