abnormalities in schizophrenia may also be linked to abnormal function in the reward substrate (*12*). If so, our data would suggest that it is a hyperactive dopaminergic reward substrate that typifies the schizophrenic patient and is returned to a normal range of function by neuroleptic treatment (*13*).

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References and Notes

1. M. E. Jarvik, in *The Pharmacological Basis of Therapeutics*, L. S. Goodman and A. Gilman, Eds. (Macmillan, Toronto, 1970), pp. 151–203; D. F. Klein and J. M. Davis, *Diagnosis and Drug Treatment of Psychiatric Disorders* (Williams & Wilkins, Baltimore, 1969), pp. 52–138.
2. R. A. Yokel and R. A. Wise, *Science* **187**, 547 (1975); *Psychopharmacologia* **48**, 311 (1976); G. Fouriezos and R. A. Wise, *Brain Res.* **103**, 377 (1976).
3. The rewarding quality of food is defined as the quality that causes trained animals to continue to perform their learned response and causes untrained animals to learn such responses. We take no position here on issues stemming from attempts to more precisely analyze reward phenomena; for present purposes our usage of "reward" subsumes all of the qualities variously designated as "reinforcement," "incentive," and "priming" in the specialist literature.
4. Neuroleptic drugs block or attenuate lever-pressing habits for a variety of rewards in animals (*2, 14, 15*). Since neuroleptics block central dopamine release and receptors (*16*), this has suggested the possibility that central dopaminergic systems play a critical role in mediation of reward phenomena (*2*). On the other hand, since neuroleptics cause parkinsonian side effects in man, and since Parkinson's disease involves a difficulty in initiation of voluntary movements, it has been suggested that neuroleptics attenuate lever-pressing habits because of some nonselective action on motor mechanisms (*14*).
5. The normally rewarded control group was treated in the same manner as the pimozide groups except that vehicle (tartaric acid) was injected instead of drug.
6. No statistically significant differences between groups were revealed by analysis of variance ($F_{3,26} = 0.26$, not significant).
7. Three-way analysis of variance (treatments by trials by subjects) revealed a significant treatment effect ($F_{3,28} = 12.1$, $P < .001$), a significant trial effect ($F_{3,84} = 49.1$, $P < .001$), and a significant treatment by trials interaction ($F_{9,84} = 5.9$, $P < .001$). The interaction reflected the fact that while there were no significant differences between groups on the first test trial, the nonreward group ($t_{14} = 4.32$, $P < .01$), the 1.0 mg/kg group ($t_{14} = 4.34$, $P < .01$), and the 0.5 mg/kg group ($t_{14} = 2.96$, $P < .01$) each differed from the control group by the fourth trial.
8. Data from Fig. 1E rule out two additional artifactual explanations of data from Fig. 1, B and C. First, repeated drug-food pairings might produce a conditioned taste aversion that accounts for progressively poorer performance with repeated testing in the pimozide groups. In Fig. 1E, however, the same day 4 performance under pimozide was produced in animals that had no prior drug-food pairings; a taste aversion hypothesis cannot account for these data. In a fatigue hypothesis, pimozide would cause abnormal susceptibility to fatigue, and the progressive decrease in responding within sessions would reflect fatigue and not extinction. This hypothesis cannot account for the day 4 performance of Fig. 1E, nor can a hypothesis that drug accumulation causes the performance deficit.
9. Running time data showed a significant trial effect ($F_{7,133} = 6.90$, $P < .001$) and a significant trial by treatment interaction ($F_{21,133} = 2.04$, $P < .001$). For the trial 8 data there were significant differences between control and nonreward scores ($t_{10} = 3.44$, $P < .01$), control and pimozide (1.0 mg/kg) scores ($t_{10} = 2.15$, $P < .01$) but not control and 0.5 mg/kg scores ($t_{10} = 1.29$, not significant). There was considerable variability in latency data, which showed no statistically reliable differences by our tests.
10. We have not seen similar effects of pimozide against opiate reward and thus do not suggest that all positive rewards or hedonic stimuli depend on the integrity of a dopaminergic substrate. Opiates may be unique in their independence of dopamine mechanisms or may represent a class of such rewards; however, further research may implicate brain dopamine in even opiate reward.
11. O. Sacks, *Awakenings* (Duckworth, London, 1973).
12. Several days of treatment with neuroleptic drugs are required before therapeutic effects are seen [P. Lerner, P. Nosé, E. K. Gordon, W. Lovenberg, *Science* **197**, 181 (1977)]. Similarly, in our paradigm pimozide did not reach maximum behavioral effectiveness until the fourth day of testing or later. If schizophrenia involves the abnormal function of a dopaminergic reward substrate, an unlearning process like that caused by repeated pimozide testing might account in part for the delayed onset of neuroleptic therapeutic effects.
13. This runs opposite to earlier speculations linking abnormal reward mechanisms to schizophrenia. Our view is that the reward system is hyperactive or hyperresponsive in schizophrenia, where the earlier view was that a (noradrenergic) reward system might be partially degenerated in schizophrenia [L. Stein and C. D. Wise, *Science* **171**, 1032 (1971)]. Either hyperactivity or hypoactivity of a central reward substrate could explain the observation that while schizophrenics appear to have a normal range of affective responses, these responses are typically inappropriate to the environmental situation [J. D. Page, *Psychopathology* (Aldine, New York, 1971), p. 191].
14. H. C. Fibiger, D. A. Carter, A. G. Phillips, *Psychopharmacologia* **47**, 21 (1976); S. Ahlenius and J. Engel, *Acta Pharmacol. Toxicol.* **40**, 115 (1977).
15. E. T. Rolls, B. J. Rolls, P. H. Kelly, S. G. Shaw, R. J. Wood, R. Dale, *Psychopharmacologia* **38**, 219 (1974).
16. Pimozide is a selective blocker of dopamine release [P. Seeman and T. Lee, *Science* **188**, 1217 (1975)] and of dopamine receptors [L. L. Iversen, *ibid.*, p. 1084; P. A. Janssen, S. Niemegeers, K. H. L. Shellekens, A. Dresse, F. M. Lenaerts, A. Pinchard, W. K. A. Shaper, J. M. Van Neuten, F. J. Verbruggen, *Arzneim. Forsch.* **18**, 261 (1968); N.-E. Andén and U. Strombom, *Psychopharmacologia* **38**, 91 (1974)]. While pimozide can block noradrenergic receptors as well [J. B. Blumberg, R. E. Taylor, F. Sulser, *J. Pharm. Pharmacol.* **27**, 125 (1975)], it does not do so at the low doses discussed here (P. Zarevics, E. Weidley, P. E. Setler, *Psychopharmacology*, in press).
17. Supported by the Non-Medical Use of Drugs Directorate and the National Research Council of Canada. We thank Janssen Pharmaceuticals for donating the pimozide; F. E. Bloom, S. L. Foote, and S. J. Henriksen for criticisms of the manuscript; and T. Gray for use of equipment.

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Physiological Basis of Anisometropic Amblyopia

Abstract. *In the visual cortex of kittens that have received their only visual experience while wearing a high-power lens before one eye, most neurons are dominated by input from the normal eye. Moreover, contrast sensitivity and resolving power are lower for stimulation through the originally defocused eye, mimicking psychophysical results from human anisometropic amblyopes.*

Anisometropic amblyopia is a developmental disorder of vision: babies with uncorrected differences in refractive power in the two eyes are often left later in life with defective vision in one eye, which cannot then be rectified optically and which is not caused by any obvious retinal or ocular pathology (*1*).

Brief occlusion of one eye (*2, 3*) even with a translucent diffuser (*4*) causes neurons in the visual cortex of kittens or monkeys (which normally often receive input from both eyes) to become almost totally dominated by the nondeprived eye. Such developmental changes in the ocular dominance of cortical cells are restricted to a postnatal sensitive period (*5*); this phenomenon therefore provides an animal model for the profound amblyopia that occurs if one eye is totally occluded within the first few years of a baby's life (*6*).

It is tempting to think that anisometropic amblyopia is essentially similar in its causes to the amblyopia caused by occlusion. Because the two eyes are not normally capable of adopting different accommodative states, it is assumed that an anisometropic baby sets its accommodative effort to bring images to a sharp focus in one eye, leaving the other retinal image inevitably and habitually blurred. The constant defocus (*7*) in one eye will reduce the contrast (*8*) of its image, especially for high spatial frequencies (*9*); neurons in the visual pathway (particularly those with very small receptive fields of higher resolving power, near the visual axis) should thus be deprived of adequate stimulation through that eye, as suggested by Ikeda and Wright (*10*). We have recorded from cells in the visual cortex of kittens reared with artificial anisometropia and have found changes in ocular dominance and in the spatial resolution of neurons which are similar to certain characteristics of human amblyopia.

Five kittens were reared in a totally dark room except for exposure in a well-lit environment for an hour or two each day, when each animal wore a pair of goggles (*4*) containing a high-power negative spherical lens [−8 diopters for three animals, −12 for the other two (*11–13*)] in front of one eye. Retinoscopic examination showed that the accommodative state of the animals was appropriate for the eye with no lens in front of it and did not differ between the two eyes. The kittens soon grew accustomed to the goggles and would run, jump, and play with each other with no evidence of discomfort. They each received a total of

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between 43 and 80 hours of visual experience and, at the age of 9 to 17 weeks, were prepared for electrophysiological recording (*14*).

They were anesthetized by artificial ventilation with about 80 percent N_2O and paralyzed by intravenous infusion of Flaxedil. The electrocardiogram, electroencephalogram, and end-expiratory CO_2 were constantly monitored. Some animals were prepared under aseptic conditions and were ventilated through an endotracheal intubation, so that they could be revived and recorded from several times. Special attention was paid to the optical condition of the eyes. We fitted contact lenses with 3-mm artificial pupils and used additional spectacle lenses to correct the refractive state as judged by ophthalmoscopy and by optimizing the spatial resolution of individual neurons (*15*). The projections of the central areas, plotted with a reversible ophthalmoscope, were only slightly divergent under paralysis, just as in normal cats, which suggested that the animals had not developed severe strabismus [which might itself have produced changes in ocular dominance (*3, 9, 16*) and in the resolution (*10*) of visual neurons].

The recording sessions were arranged according to a schedule in which the kittens were identified only by code numbers and the experimenters knew neither which eye had been defocused nor the power of the lens. In addition, the series included three control animals, in which both eyes had been identically defocused, and five completely normal kittens.

In the anisometropic animals, 228 cells were recorded, all in or near the area centralis projection area of the primary visual cortex, as confirmed by subsequent histological examination (*14*). Almost all were orientation selective (*13*). After each unit's receptive field had been plotted on a tangent screen (separately through the two eyes in the case of binocularly driven cells) responses were analyzed quantitatively. Moving gratings were generated on a large oscilloscope (28 by 25 cm) by a computer (PDP-11/10) according to a raster-scan technique (*17*). The screen, whose mean luminance was 250 cd/m^2, was placed 114 or 57 cm from the cat's eyes, depending on the spatial resolving power of the cell. The orientation of the stripes was set to the optimum for the receptive field, which was positioned in the center of the screen; the better direction of motion was chosen, and the temporal frequency of the drift (the number of cycles of the grating passing across the receptive field per second) was optimized. The computer gave four presentations each of 14 different spatial frequencies of the grating, in one-third octave steps, in a randomized, interleaved series. For each presentation the experimenter adjusted the contrast of the grating through a logarithmic potentiometer and pressed a button when he judged by ear that the cell was just responding with either a modulated firing pattern, in time with the bars of the grating, or with an unmodulated increase in activity (*18, 19*). The computer registered the contrast threshold determined in this way and printed out all the settings at each frequency.

In this way we were able to construct for each cell, through each eye, a contrast sensitivity function—a graph of the reciprocal of threshold contrast against the spatial frequency of the grating. These functions (Fig. 1) usually have a clear optimum spatial frequency, with attenuation in sensitivity on both the low-frequency side (fitted by a smooth curve) and on the high side [fitted by an exponential function (*20*)]. For the 67 cells that we have studied in normal kittens, the optimum spatial frequency of each binocular neuron is usually much the same in the two eyes, and the contrast sensitivity functions are remarkably similar in shape.

To obtain an estimate of the absolute spatial resolving power of each cell (Fig. 1), the function fitted to the high-frequency portion of the sensitivity curve was extrapolated to the cutoff spatial frequency, at which gratings of the highest possible contrast, 1.0, should cause a threshold response. The cutoff frequency determined in this manner varied from cell to cell even when their receptive fields were centered on the same point in the visual field. However, as in the lateral geniculate nucleus (*10*), resolution tended to be inversely related to eccentricity in the visual field, some cells with receptive fields close to the area centralis having cutoffs as high as 5 to 6 cycles per degree of visual angle, which is close to most estimates of the behavioral acuity of the cat (*12*).

In all the artificially anisometropic animals, the proportion of binocularly driven cells was reduced, and a majority of units (57 percent) were monocularly driven by the eye that had had normal visual experience. However, the remaining 43 percent of cells were responsive through the defocused eye, and 13 percent were monocularly driven by it. Therefore, although ocular dominance shifted toward the normal eye, the changes were not as complete as after monocular occlusion (*2–5*). When we considered the contrast sensitivity and resolution of neurons for stimulation through each eye, however, the results were clear: (i) All cells with the highest

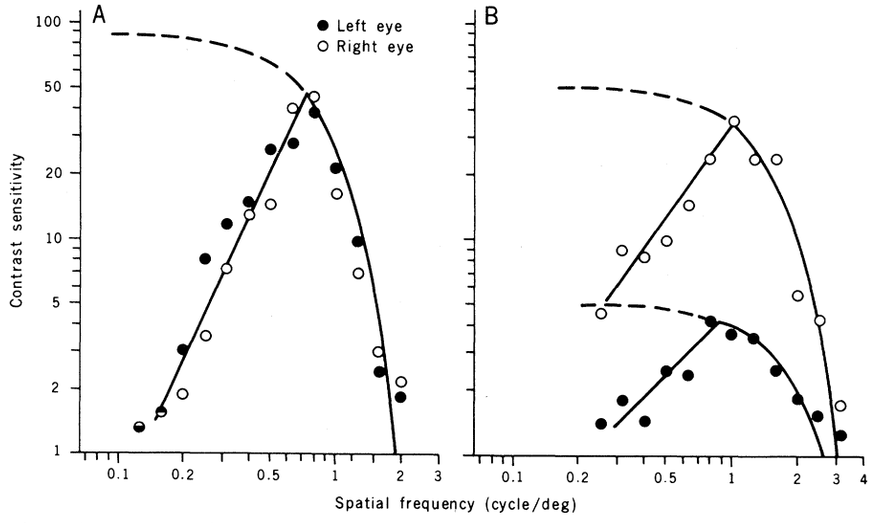

Fig. 1. Contrast sensitivity functions for two cortical units from normal kittens. The ordinate is the reciprocal of the threshold contrast of a grating, which gave a just-detectable response from the neuron as it drifted across the receptive field. (A) Unit K504/L16 was equally responsive through the two eyes, and the two contrast sensitivity curves were virtually identical. The points on the high-spatial-frequency side have been fitted by an exponential function (*19*), which is extrapolated backward as an interrupted line and extrapolated downward to meet the abscissa at the cutoff spatial frequency (about 2 cycle/deg). The points on the low-frequency side were fitted by eye with a smooth curve, usually a straight line, to define the optimum spatial frequency where this curve met the exponential function. (B) Unit K474/L3 was dominated by the right eye, and contrast sensitivity was greater through the right eye than through the left. However, the curves were similar in overall shape and position on the abscissa. (Even at the lowest spatial frequency used there were still about three full cycles of the grating present on the screen with a 57-cm viewing distance.)

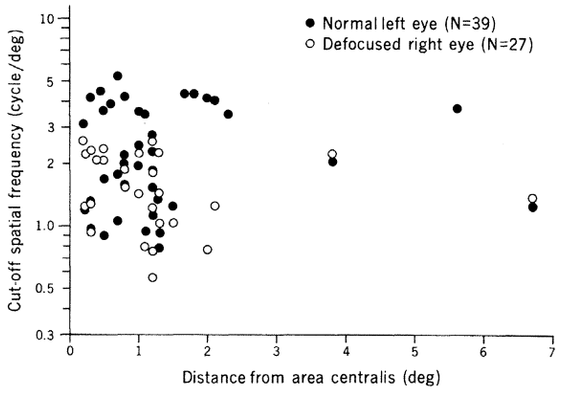

Fig. 2 (left). Cutoff spatial frequency plotted against the distance of the center of the receptive field from the area centralis for cat K521. The right eye had worn a −12-diopter lens during development.

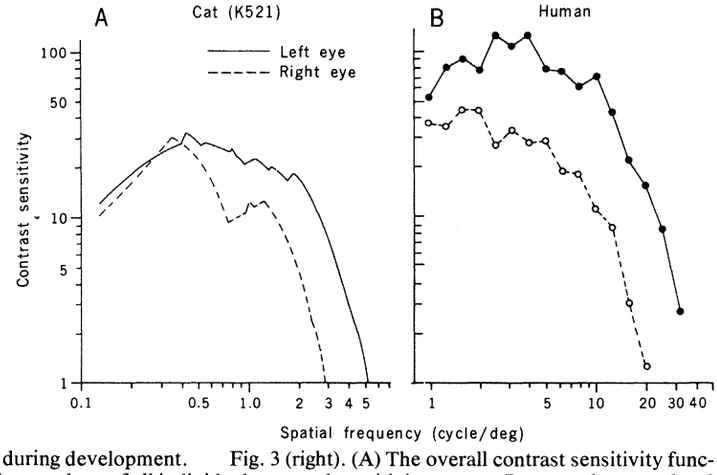

Fig. 3 (right). (A) The overall contrast sensitivity function of the sample of cells from cat K521 determined by drawing the envelope of all individual neuronal sensitivity curves. Because the exact level of sensitivity estimated for each cell depended on the criteria used by the experimenters to judge the threshold response (*18*), these curves cannot be taken as absolute determinations of neuronal sensitivity, but can legitimately be used to compare sensitivity in the two eyes. (B) Psychophysically determined contrast sensitivity functions for each eye of an anisometropic subject (*22*). The right eye was amblyopic and was more hypermetropic than the left. Data points for spatial frequencies below 10 cycle/deg were obtained with a viewing distance of 4.65 m, the remainder at 9.1 m. The average standard error of each point (mean of four judgments) was about 0.05 log unit.

cutoff spatial frequencies were monocularly driven by the normal eye. (ii) Cells monocularly driven by the defocused eye tended to have low cutoff spatial frequencies and low contrast sensitivity, though the shapes of the sensitivity curves were normal. (iii) The small proportion of binocular units also had low preferred spatial frequencies and the cutoff in the defocused eye tended to be lower than that in the normal eye (*21*).

Figure 2 illustrates the representative results for one animal, reared with a −12-diopter lens in front of the right eye. Results for the left eye are indistinguishable from those for normal cats but the highest cutoffs in the right eye are about an octave lower than those in the left.

The overall difference in contrast sensitivity in the two eyes can be conveniently summarized (Fig. 3A). We superimposed the sensitivity curves for all the neurons, fitted as in Fig. 1, and drew, for each eye, the envelope of the highest contrast sensitivity among all the curves, over the complete frequency range. The resulting functions thus display the maximum sensitivity achieved by the entire population of cells recorded in this animal, over the whole spectrum of spatial frequency. Behavioral capacity is presumably limited by the performance of the most sensitive cells in the visual system, so Fig. 3A might indicate the visual ability of this cat, or at least the difference in performance of the two eyes. Contrast sensitivity is lower in the originally defocused eye over much of the frequency range, but this effect is particularly exaggerated at high spatial frequencies. Essentially similar results were obtained from all five animals, and the effects were somewhat stronger after 12 diopters of defocus than after 8 diopters.

A number of investigators have recently reported that human amblyopes suffer a similar reduction in contrast sensitivity as determined psychophysically (*22*). We have confirmed these findings in two anisometropic amblyopes, using the same television display and computer-controlled procedure as in our physiological experiments. The observer, with each eye covered in turn, fixated a point on the screen and set his contrast threshold for each stationary vertical grating presented by the computer. Figure 3B plots the results as the familiar psychophysical contrast sensitivity function (*17*) for one subject, who had a 3.25-diopter difference in spherical refractive error between the two eyes (*23*). Despite his wearing the optimal spectacle correction during the experiment, his contrast sensitivity was consistently lower in his right eye than in his left, the difference being greater at higher spatial frequencies.

The similarity between physiological (Fig. 3A) and psychophysical (Fig. 3B) results suggests that changes at or before the level of the visual cortex account at least in part for the loss of visual acuity in human anisometropic amblyopia. Ikeda and Tremain (*24*) have recently demonstrated a similar reduction of cutoff spatial frequency in the lateral geniculate nucleus after rearing cats with accommodation and pupillary constriction paralyzed by instillation of atropine. This suggests that the effects we have seen in the cortex reflect deficits earlier in the pathway: indeed there is recent evidence for a retinal defect in anisometropic amblyopes (*25*). But a reduction in contrast sensitivity restricted to one meridian can occur in humans who have suffered a meridional astigmatic defocus when young (*26*); such orientationally selective effects may occur at a cortical level. Thus, the neuronal defect responsible for anisometropic amblyopia might also be partly cortical.

The development of an animal model for the common human disorder of amblyopia offers hope for the design of more effective methods of treatment or prevention.

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References and Notes

1. S. Duke-Elder and K. Wybar, *System of Ophthalmology*, vol. 6, *Ocular Motility and Strabismus* (Kimpton, London, 1973), pp. 295-297.
2. T. N. Wiesel and D. H. Hubel, *J. Neurophysiol.* **26**, 1003 (1963); *ibid.* **28**, 1029 (1965); C. R. Olson and R. D. Freeman, *ibid.* **38**, 26 (1975); J. A. Movshon and M. R. Dürsteler, *ibid.* **40**, 1255 (1977); M. L. J. Crawford, R. Blake, S. J. Cool, G. K. von Noorden, *Brain Res.* **84**, 150 (1975); P. B. Schechter and E. H. Murphy, *ibid.* **109**, 165 (1976); C. K. Peck and C. Blakemore, *Exp. Brain Res.* **22**, 57 (1975).
3. F. H. Baker, P. Grigg, G. K. von Noorden, *Brain Res.* **66**, 185 (1974).
4. C. Blakemore, *J. Physiol. (London)* **261**, 423 (1976).
5. D. H. Hubel and T. N. Wiesel, *ibid.* **206**, 419 (1970).
6. G. K. von Noorden and A. E. Maumenee, *Am. J. Ophthalmol.* **65**, 220 (1965); S. Awaya, Y. Miyake, Y. Imaizumi, Y. Shiose, T. Kanda, K. Komuro, *Jpn. J. Ophthalmol.* **17**, 69 (1973).
7. H. H. Hopkins, *Proc. Phys. Soc. London* **79**, 889 (1962); G. Westheimer, *Vision Res.* **4**, 39 (1964).
8. Contrast is defined as $(L_{max} - L_{min})/(L_{max} +$

L_{min}), where L_{max} and L_{min} are the maximum and minimum intensities in the grating.
9. Spatial frequency is the number of cycles (dark plus light bar) of the grating per degree of angle subtended at the eye.
10. H. Ikeda and M. J. Wright, *Exp. Brain Res.* **25**, 63 (1976).
11. These dioptric disparities are much larger than those usually found in anisometropic humans. However, the smaller size of the kitten's eye, and the fact that the normal acuity of the cat (*12*) may not be as close to being limited by optical factors as that of man (*13*), made it advisable to produce gross degrees of anisometropia in order to defocus one eye sufficiently.
12. K. U. Smith [*J. Genet. Psychol.* **49**, 297 (1936)], D. W. Muir and D. E. Mitchell [*Science* **180**, 420 (1973)], and R. Blake, S. J. Cool, and M. L. J. Crawford [*Vision Res.* **14**, 1211 (1974)] all reported the cat's acuity to be about 5 cycle/deg. S. Bisti and L. Maffei [*J. Physiol. (London)* **241**, 201 (1974)], S. G. Jacobson, K. B. J. Franklin, and W. I. McDonald [*Vision Res.* **16**, 1141 (1976)], and D. E. Mitchell, F. Griffin, and B. Timney [*Perception* **6**, 181 (1977)] have recently found somewhat higher values.
13. D. H. Hubel and T. N. Wiesel, *J. Physiol. (London)* **160**, 106 (1962); *J. Neurophysiol.* **28**, 229 (1965).
14. C. Blakemore and R. C. Van Sluyters, *J. Physiol. (London)* **248**, 663 (1975).
15. H. Ikeda and M. J. Wright, *Vision Res.* **12**, 1465 (1972).
16. D. H. Hubel and T. N. Wiesel, *J. Neurophysiol.* **28**, 1041 (1965); U. Yinon, E. Auerbach, M. Blank, J. Friesenhausen, *Vision Res.* **15**, 1251 (1975); U. Yinon, *Exp. Brain Res.* **26**, 151 (1976).
17. O. H. Schade, *J. Opt. Soc. Am.* **46**, 721 (1956); F. W. Campbell and D. G. Green, *J. Physiol. (London)* **181**, 576 (1965).
18. C. Enroth-Cugell and J. G. Robson, *J. Physiol. (London)* **187**, 517 (1966); F. W. Campbell, G. F. Cooper, C. Enroth-Cugell, *ibid.* **203**, 223 (1969); H. Ikeda and M. J. Wright, *Exp. Brain Res.* **22**, 363 (1975).
19. F. W. Campbell, G. F. Cooper, C. Enroth-Cugell, *J. Physiol. (London)* **187**, 517 (1966).
20. The function used was $S = C\,e^{-\alpha^2 f^2}$, where S = contrast sensitivity, f = spatial frequency, and C and α are, respectively, sensitivity and space constants (which determine the position of the curve on the ordinate and abscissa). Campbell, Cooper, and Enroth-Cugell (*19*) found this function to fit similar results from cortical cells.
21. We found that for receptive field positions more than about 5° from the area centralis, where the average resolution of neurons is slightly lower than in the center, cells were more commonly binocularly driven. However, this result is not simple to interpret since monocular units are also more common for the central visual field in normal cats [K. Albus, *Brain Res.* **89**, 341 (1975)].
22. R. J. Gstalder and D. G. Green, *J. Pediatr. Ophthalmol.* **8**, 251 (1971); D. M. Levi and R. S. Harwerth, *Invest. Ophthalmol.* **16**, 90 (1977); R. F. Hess and E. R. Howell, *Vision Res.* **17**, 1049 (1977); J. Sjöstrand, *J. Metab. Ophthalmol.*, in press.
23. The subject, who was 39 years old, had no detectable strabismus. His spectacle correction was: left eye +0.75 D Sph ○ −1.25 D Cyl axis 170; right eye (amblyopic) +4.00 D Sph ○ −1.75 D Cyl axis 130. Snellen acuity through his corrected right eye was 6/60 (20/200). His anisometropia was not discovered until he was 7 years old, after which he wore spectacles. Despite intermittent patching of the left eye between the ages of 7 to 11 years, his acuity maintained no improvement.
24. H. Ikeda and K. E. Tremain, *J. Metab. Ophthalmol.*, in press.
25. R. S. Harwerth and D. M. Levi, *Vision Res.* **17**, 585 (1977).
26. D. E. Mitchell and F. Wilkinson, *J. Physiol. (London)* **243**, 739 (1974); R. D. Freeman, *Invest. Ophthalmol.* **14**, 78 (1975).
27. H.M.E. was supported by a fellowship from Columbia University College of Physicians and Surgeons and C.B. holds a Locke research fellowship from the Royal Society. Sponsored by grant G972/463/B from the Medical Research Council, London. We thank Dr. V. Emerson for help in some experiments and R. Cummings, P. Taylor, J. Eldridge, and B. Rhodes for technical assistance.
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Chronically Decerebrate Rats Demonstrate Satiation But Not Bait Shyness

Abstract. *Taste substances applied to the oral cavity result in either ingestion or rejection, each with a characteristic muscular response pattern. These responses are the same in decerebrate and intact rats; the caudal brainstem appears to be the neural substrate of ingestion and rejection responses. The experiment determined whether decerebrates can alter these discriminative responses as a function of food deprivation or toxicosis. Food-deprived decerebrate rats, like intact ones, ingested a taste substance they had rejected when sated. However, these same decerebrates, in contrast to controls, neither rejected nor decreased ingestive reactions to a novel taste after that taste had been repeatedly paired with lithium chloride–induced illness. Although the forebrain may be important for integrating ingestion, some aspects of this control seem to be represented in caudal brain areas.*

Although many complex reflex sequences exist within the spinal cord and caudal brainstem (*1*), the integration and control of these sequences required for normal behavior has usually been attributed to higher levels of the brain. Bard (*2*) concluded that structures caudal to the hypothalamus are incapable of altering consummatory responses as a function of visceral or humoral variables. Bard's version of Jacksonian neurology provides the basis for most current interpretations of the effects of hypothalamic and other limbic system lesions and electrical stimulation on attack, copulation, grooming, thermoregulation, and food and water intake (*3, 4*).

Neural models for maintaining energy balance have hypothesized hypothalamic mechanisms for controlling both the initiation and cessation of feeding behavior (*3*). The metabolic monitors necessary to effect this control were also presumed to be located within the hypothalamus. Recently, the hegemony of the hypothalamus has been effectively challenged by experiments demonstrating the importance of systems outside the hypothalamus, and even outside the brain, in controlling feeding behavior (*5*). Nevertheless, the predominant assumption remains that the forebrain controls ingestive behavior even if some of the requisite information comes from the periphery.

In contrast, Garcia has suggested that the peculiar associability of gustatory and visceral stimuli evidenced in bait shyness (*6*) may reflect the intimate relationship of gustatory and visceral afferents within the nucleus of the solitary tract (*7*). Therefore, one might predict that a decerebrate animal could alter its ingestive behavior as a consequence of illness, but not of repletion. We have found just the opposite. The chronically

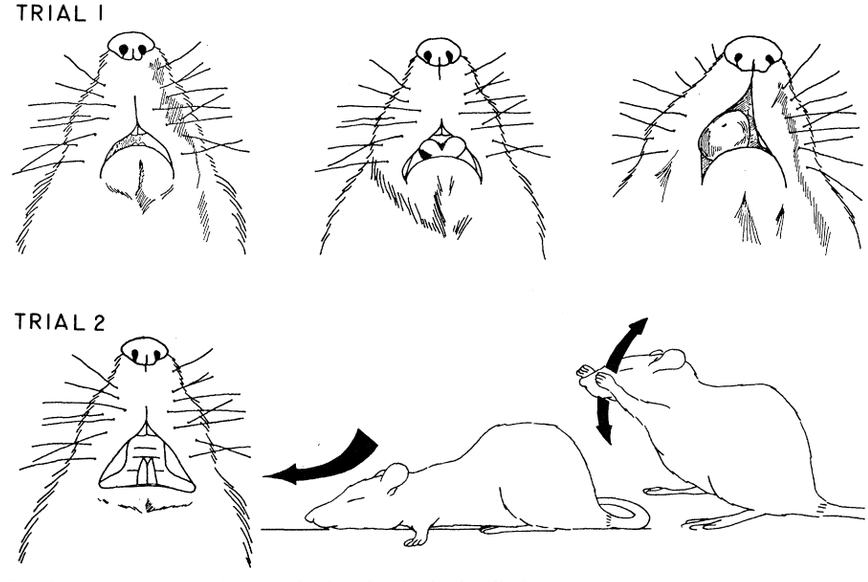

Fig. 1. Taste reactivity for unpaired and paired stimuli. Sucrose, NaCl, and HCl stimuli when presented intraorally in 50-μl presentations elicit an ingestion sequence composed of rhythmical movements of mandible and tongue and lateral tongue flicks (trial 1). After a single pairing of the taste stimulus with LiCl injection, the taste elicits a replica of the rejection response to quinine. This rejection response is composed of gaping, chin rubbing, and paw shakes (trial 2).

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