dence based on animal studies favors the latter supposition. In deprived kittens, cortical columns do not seem to be "missing," and unusual cells are found which are not encountered in normal animals (*3*). Finally, experiments with kittens demonstrate that, during the sensitive period, single cortical neurons can selectively modify their responses after short periods of exposure to a particular stimulus (*18*).

If, in our astigmatic subjects, there were a recruitment of available cells to process detail of a given orientation, one might expect sensitivities greater than normal for that orientation. We find no evidence of such supersensitivity in our results. But normal human resolution approaches the limits imposed by the wave nature of light and the grain of the retina, and it therefore may be difficult or impossible to improve resolution by altering neural connections.

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References and Notes

1. T. N. Wiesel and D. H. Hubel, *J. Neurophysiol.* **26**, 1003 (1963).
2. ———, *ibid.*, p. 978; *ibid.* **28**, 1060 (1965); A. Globus and A. B. Scheibel, *Exp. Neurol.* **19**, 331 (1967); L. Ganz, M. Fitch, J. A. Satterberg, *ibid.* **22**, 614 (1968); E. Fifkova, *J. Neurobiol.* **1**, 285 (1970); H. B. Barlow and J. D. Pettigrew, *J. Physiol.* **218**, 98 (1971).
3. H. V. B. Hirsch and D. N. Spinelli, *Science* **168**, 869 (1970); *Exp. Brain Res.* **13**, 509 (1971); C. Blakemore and G. F. Cooper, *Nature* **228**, 477 (1970); C. Blakemore and D. E. Mitchell, *ibid.*, in press; J. D. Pettigrew, C. Olson, H. V. B. Hirsch, *Brain Res.*, in press.
4. R. Shlaer [*Science* **173**, 638 (1971)] found a definite shift in the distribution of disparities that were most effective in stimulating binocularly driven cortical neurons.
5. R. D. Freeman, D. E. Mitchell, M. Millodot, *Science* **175**, 1384 (1972).
6. A detailed account and additional data are given in D. E. Mitchell, R. D. Freeman, M. Millodot, G. Haegerstrom, *Vision Res.*, in press.
7. An interference fringe pattern is formed directly on the retina by imaging two coherent point sources, filtered from a laser beam, in the plane of the eye's pupil. For details, see F. W. Campbell, J. J. Kulikowski, J. Levinson, *J. Physiol.* **187**, 427 (1966); D. E. Mitchell, R. D. Freeman, G. Westheimer, *J. Opt. Soc. Amer.* **57**, 246 (1967); D. G. Green and M. M. Cohen, *Trans. Amer. Acad. Ophthalmol. Otolaryngol.* **75**, 629 (1971).
8. The grating was of high contrast, subtended 5° by 6° and had a spatial frequency of 6 cycles per degree and a luminance of 75 cd/m².
9. For each stimulus presentation of 20 seconds, 1000 data points were analyzed by a Digital Equipment Corporation PDP-8 computer to obtain a power spectrum. The standard error of the evoked potential measurements is less than 10 percent as determined by procedures outlined by J. S. Bendat and A. G. Piersol [*Random Data: Analysis and Measurement Procedures* (Interscience, New York, 1971)]. A detailed description of the data measurement and analytic procedures will be given elsewhere (L. N. Thibos, in preparation). Our techniques are similar to those described by D. Regan [*Evoked Potentials in Psychology, Sensory Physiology, and Clinical Medicine* (Chapman and Hall, London, 1972)] and N. W. Perry, D. G. Childers, J. C. Falgout [*Science* **177**, 813 (1972)].
10. A detailed description of the basic techniques can be found in F. W. Campbell and D. G. Green, *J. Physiol.* **181**, 576 (1965). The oscilloscope screen had an annular mask that limited the field to 2°. Contrast was 0.65 and screen luminance was 22 cd/m². Five or more determinations were made at each orientation. The standard error of the mean setting is of the order of 1.3 cycles per degree.
11. The normalized values in Fig. 2 are obtained by dividing each value by the maximum. For the evoked potential results, the maximum values, in microvolts (root-mean-square) from PT through AD are 3.14, 2.32, 3.75, and 2.27, respectively. The maximum visual resolution values, in cycles per degree, from PT through AD are 34, 29, 30, and 27.5, respectively.
12. Maffei and Campbell have found that over a wide range of contrast, the amplitude of the evoked potential is greater for vertical and horizontal than for oblique grating orientations [L. Maffei and F. W. Campbell, *Science* **167**, 386 (1970); F. W. Campbell and L. Maffei, *J. Physiol.* **207**, 635 (1970)].
13. M. Millodot and L. A. Riggs, *Arch. Ophthalmol.* **84**, 272 (1970); R. M. Harter and C. T. White, *Vision Res.* **8**, 701 (1968).
14. A likely location for these changes is at the level of cortical binocular cells or beyond [see (*12*)].
15. Evidently, a complex nervous system cannot develop to functional perfection solely through genetic control. There must be a period of plasticity during which the animal's experience helps to determine the connections of its neural network. Although not established in humans, a critical period of susceptibility to visual deprivation has been shown experimentally in cats and monkeys [D. H. Hubel and T. N. Wiesel, *J. Physiol.* **206**, 419 (1970); G. K. von Noorden, J. E. Dowling, D. C. Ferguson, *Arch. Ophthalmol.* **84**, 206 (1970)]. The case for astigmatically caused deprivation requires the condition to be present during the critical period. The available clinical evidence indicates that in cases of high astigmatism the condition is very likely to be present at birth and remain essentially unaltered into adulthood [S. Duke-Elder, *The Practice of Refraction* (Mosby, St. Louis, 1969), p. 94; M. Hirsch, in *Vision of Children*, M. Hirsch and R. Wick, Eds. (Chilton, Philadelphia, 1963), pp. 145–172; M. Hirsch, in preparation]. Our subjects who show vertical-horizontal orientation differences were optically uncorrected throughout childhood. It is not common to find individuals who have received ophthalmic lens corrections at a very early age. Two subjects we have examined so far, who were corrected at 2 and 3 years of age, respectively, showed no orientation effects in spite of considerable astigmatism.
16. It appears that the effects are permanent since they are present in individuals who have used optimal corrective lenses for a number of years.
17. C. T. Lombroso, F. H. Duffy, R. M. Robb, *Electroencephalogr. Clin. Neurophysiol.* **27**, 238 (1969).
18. J. D. Pettigrew and H. B. Barlow, in preparation.

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Retrograde State Dependent Learning

Abstract. *Sodium pentobarbital administered intravenously after acquisition in a one-trial passive avoidance task results in state dependent (drug dissociated) learning in male albino rats. Findings have methodological implications for drug-based research and theoretical implications for drug discrimination studies. Predictions based on a stimulus generalization hypothesis are not supported, whereas those based on an information storage hypothesis are supported.*

State dependent learning can be demonstrated with a variety of drugs in a wide range of tasks, including one-trial passive avoidance conditioning (*1*). The basic state dependent learning paradigm utilizes four groups: (i) group D-D is trained in a drugged state (D) and tested for retention in the same drugged state, (ii) group ND-ND is trained in a nondrugged state (ND) and tested for retention in a nondrugged state, (iii) group D-ND is trained in a drugged state and tested in a nondrugged state, and (iv) group ND-D is trained in a nondrugged state and tested in a drugged state. Groups D-D and ND-ND show transfer of training from acquisition to retention testing, whereas groups D-ND and ND-D do not. Transfer of training occurs only when the drug states are the same in acquisition and test.

Two hypotheses have been advanced to explain state dependent learning (*1*). (i) The stimulus hypothesis suggests that a drug affects perception of the stimulus complex during the acquisition of a task. Thus, if the drug state during

Table 1. Summary of group comparisons with the use of Scheffe's "S," indicating significant ($P < .05$) and nonsignificant (NS) differences; D, drugged state; ND, nondrugged state; and C, control.

Group	D-D	ND-ND	D-ND	ND-D	C	D-D and ND-ND	D-ND and ND-D	D-ND and ND-D and C
D-D	—	NS	.05	.05	.05	—	.05	.05
ND-ND		—	.05	.05	.05	—	.05	.05
D-ND			—	NS	NS	.05	—	—
ND-D				—	NS	.05	—	—
C					—	.05	.05	—
D-D and ND-ND						—	.05	.05

testing for retention differs from that during acquisition, perception of the stimulus complex will also differ, and a performance decrement can be expected. It is assumed that state dependent learning is a special case of stimulus generalization. (ii) The storage hypothesis suggests that for transfer of training from acquisition to retention test to be possible, information storage following acquisition trials and information retrieval during retention trials must occur under equivalent central nervous system (CNS) "states." The hypothesis dictates that the CNS state effective during information storage must be redintegrated for retrieval of that information.

In studies demonstrating state dependent learning, the drug was given prior to acquisition trials; therefore, the effect of the drug on the stimulus sampling interval during the trials was indistinguishable from the effect on the information storage interval after the trials. In our study the drug was administered intravenously, immediately after the acquisition trial. Thus, the drug effect on the CNS can be presumed to be present during "memory consolidation," or the information storage interval (*2*), and not present during the stimulus sampling interval. In retention tests, we administered the drug just prior to testing.

The stimulus hypothesis suggests that because no animal was in a drugged state during stimulus sampling in acquisition training, transfer would be shown only by those animals not in a drugged state during retention testing (groups ND-ND and D-ND). The storage hypothesis predicts that transfer will be shown by those animals whose drug state in retention testing is the same as the drug state effective during information storage in acquisition (groups D-D and ND-ND).

We found that drug administration after acquisition resulted in transfer only in animals of groups D-D and ND-ND and not in animals of groups D-ND and ND-D, which did not differ significantly from operated, no-treatment controls. Thus, the ability of an organism to perform this task requires that he be tested in the same drug state under which information storage occurred.

Our design parallels that used by others examining disruption of memory consolidation or retrograde amnesia following postacquisition administration of anesthetic. Pearlman *et al.* (*2*) demonstrated that retrograde amnesia

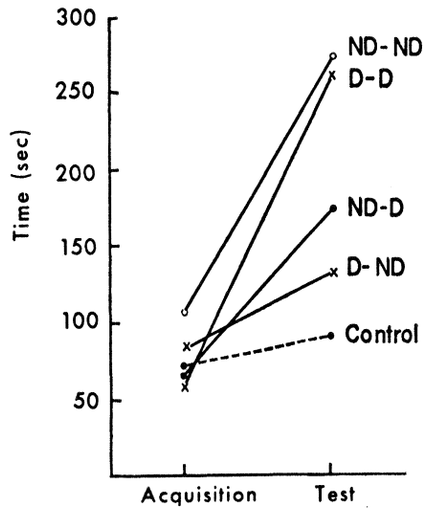

Fig. 1. Change in response latency by group (D-D, ND-ND, D-ND, ND-D, and control). Values are means for ten animals.

could be produced by administration of sodium pentobarbital after a training trial. Experimental procedures that give a drug before or after behavioral training may be affected by state dependent learning, as our experiment with sodium pentobarbital shows. Thus a demonstration of retention, or lack of retention, of a learned response must include a control for state dependent learning.

We implanted jugular catheters (*3*) to ensure rapid onset of drug effect in 50 naive, adult, male, albino rats (Holtzman) weighing from 250 to 300 g. Ten rats were assigned to each of four experimental groups and a control group.

For training the rats, we used a passive avoidance box consisting of two chambers with grid floors. A small (18 by 30 by 45 cm) white start chamber illuminated by a 25-watt frosted bulb was separated by an opaque sliding door from a large (41 by 30 by 45 cm) black chamber illuminated by a 25-watt red bulb.

In the acquisition trial, the animal was placed in the start compartment. After 180 seconds the door to the larger, dimmer compartment was opened and the step-through latency was recorded. Immediately after the animal entered the dimmer compartment, the door between the compartments was closed and a footshock (85 volts, 1.5-ma intensity, 2-second duration) was delivered to the animal. After the termination of footshock, the animal was removed from the passive avoidance apparatus, injected on an adjoining table, and returned to his home cage. The intravenous injections were given within 11 to 13 seconds of the termination of footshock and resulted in an almost immediate mild ataxia but never resulted in unconsciousness. Observable drug effects last about 30 minutes.

To induce the drugged state, we injected sodium pentobarbital (12.5 mg/kg) into the jugular catheter. Animals in the nondrugged condition received an equivalent volume of normal saline. All injections were pushed through the catheter by 0.15 ml of saline.

We administered the retention test 24 hours after the acquisition trial. The drugged or nondrugged states were induced 25 to 30 seconds prior to testing in the same manner as at acquisition. The retention test was identical to the acquisition trial, except no footshock was given and any step-through latency of more than 300 seconds terminated the trial.

All combinations of drugged and nondrugged, acquisition, and test yielded the four experimental groups. To establish a standard for comparison, an operated, nontreatment control group received neither injection nor footshock in acquisition or test trials.

The group means for acquisition and retention test latencies are shown in Fig. 1. A one-way analysis of variance performed on the step-through latency data for the four groups plus the control indicated a significant treatment effect ($F_{4, 45} = 10.1214$; $P < .001$). There were no significant differences among groups for acquisition latencies. A post hoc analysis with the use of Scheffe's "S" (*4*) identified the components that contributed to the significant treatment effect (Table 1). Both group D-D and group ND-ND had significantly longer test latencies than the control group ($P < .05$), indicating they had learned the passive avoidance response. Neither group D-ND nor group ND-D was significantly different from the control group. For these two groups, acquisition training was not transferred to the retention test trial. However, state dependent learning is not an all-or-none phenomenon. Clearly groups D-ND and ND-D show some retention. If groups D-ND and ND-D are pooled, the combined group does differ from the control group. However, the no-state change groups (D-D and ND-ND) showed greater transfer than the state change groups (D-ND and ND-D) when contrasted either individually or in groups.

In a comparison of groups D-D and

ND-ND against groups D-ND and ND-D and the control, a significant difference ($P < .05$) indicates greater transfer for the groups that did not have a state change (D-D and ND-ND).

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References and Notes

1. D. A. Overton, in *Psychopharmacology: A Review of Progress 1957–1967*, D. H. Efron, Ed. (Public Health Service Publ. No. 1836, U.S. Department of Health, Education, and Welfare, Washington, D.C., 1968), pp. 918–930; H. Oishi, S. Iwahara, K. M. Yang, A. Yogi, *Psychopharmacologia* **23**, 373 (1972).
2. C. A. Pearlman, Jr., S. K. Sharpless, M. E. Jarvik, *J. Comp. Physiol. Psychol.* **54**, 109 (1961).
3. Each animal was anesthetized intraperitoneally with sodium pentobarbital (Nembutal) (30 mg/kg). An incision about 3 cm long, 1 cm from midline, was made in the neck and the underlying tissue layers were teased apart to expose the jugular vein. A heparin-filled (outside diameter, 1.27 mm) polyethylene catheter (Intramedic) was inserted caudally into the jugular vein for approximately 2 cm and secured with sutures around the vein and catheter. The free end of the catheter was then run subcutaneously to the occiput and attached to a 20-gauge hypodermic needle. The corked needle hub was fixed to the skull with dental acrylic anchored to 0.80 stainless steel screws. The catheter was flushed daily with 0.10 ml of a 1000-unit solution of sodium heparin (Liquamin). Four days were allowed for postoperative recovery before training began.
4. R. E. Kirk, *Experimental Design: Procedures for the Behavioral Sciences* (Brooks/Cole, Belmont, Calif., 1968).
5. Supported in part by the Space Sciences Research Center, University of Missouri.

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Behavioral Maintenance of High Concentrations of Blood Ethanol and Physical Dependence in the Rat

Falk *et al.* (*1*) clearly state the criteria for an animal model for alcoholism, claim that their technique satisfies all the criteria, and then describe an experiment which fails to meet them. The criteria, as stated by Falk *et al.* (*1*), are:

> . . . (i) animals should orally ingest ethanol solutions excessively and chronically in a pattern that increases the concentration of blood ethanol analogous to that in the alcoholic; (ii) unequivocal physical dependence on ethanol must be demonstrated; (iii) food and ethanol should be available from sources physically separate so that the factors determining ethanol intake are not inextricably bound to those primarily concerned with meeting nutritional requirements; (iv) the experimental arrangement should retain an elective aspect to the ethanol ingestion by not programming extrinsic reinforcing events (for example, shock avoidance, food pellet delivery) contingent upon drinking ethanol.

Does the experiment satisfy their criterion? The authors state that the rats (initially weighing just over 300 g) were reduced to 80 percent of their weight "by limiting food rations." They were then trained to obtain food, but their total intake of food was limited to maintain the rats' weight at 80 percent. "When the animals began drinking alcohol, additional food supplements were omitted for the remainder of the experiment, as the animal weights were increasing" (*1*). Thus, the animals were chronically and severely hungry, and alcohol intake was producing weight gain. I therefore conclude that factors determining alcohol intake were, in fact, inextricably bound to those concerned with meeting nutritional requirements. No controls are presented that show that the alcohol drinking observed in the experiment is attributable to schedule-induced polydipsia, rather than to simple malnutrition.

The study also fails to meet the first criterion. There is no demonstration that there was a chronic elevation of alcohol consumption analogous to that of the alcoholic. No tests were run to determine preference for alcohol after the conclusion of the experiment. The rats had no fluid available except for the alcohol solution while eating during the period of the experiment, and no tests made afterward are reported. In fact, it has been shown by Senter and Sinclair (*2*) that alcohol preference is not altered by alcohol overdrinking induced by schedule-induced polydipsia. Senter and Sinclair therefore conclude "that excessive drinking of alcohol associated with such treatment is not analogous to alcoholic habituation." This point is linked to the fourth criterion that the "experimental arrangement should retain an elective aspect to the ethanol ingestion." At no time were the rats offered an alternative source of fluid or of deficient calories. The rats had to drink alcohol to remain alive. Falk *et al.* may argue that schedule-induced polydipsia is not due to extrinsic reinforcing effects. This may be true when the rat drinks water beyond its physiological requirement, but it cannot be taken as a demonstrated fact because the causes of normal schedule-induced polydipsia are obscure and remain, as Falk *et al.* state, "the subject of further research and theoretical speculation." While the questions concerning normal schedule-induced polydipsia remain open, extreme reinforcing effects are produced when alcohol is introduced into the situation. To a chronically hungry rat, the drinking of an alcohol solution in the low concentrations used by Falk *et al.* is extremely likely to function as an "extrinsic reinforcing event."

Concerning the second criterion, Falk *et al.* state that they have demonstrated "physical dependence on ethanol in the rat as indicated by withdrawal convulsions." What Falk *et al.* actually present is some poorly controlled and unsystematic evidence concerning audiogenic seizures in rats subjected to the experimental conditions. It is unwarranted to equate audiogenic seizures with withdrawal convulsions caused by alcohol withdrawal. A propensity to audiogenic seizures can be produced by disease or nutritional deficiency (*3*). It seems likely that various types of nutritive deficiency were present in the rats, as a large part of their caloric requirement was satisfied by alcohol. A susceptibility to audiogenic seizures in this case can therefore hardly be viewed as unequivocal evidence for physical dependence on ethanol. A human alcoholic prefers to drink large amounts of alcohol when other nutritional substances are available. Falk *et al.* have demonstrated no change in preference for alcohol, but only an enhanced intake possibly created by hunger and other undetermined factors operating in schedule-induced polydipsia. There are also further cogent criticisms that have already been made of other studies utilizing schedule-induced polydipsia made by Myers and Veale (*4*) in their review. These criticisms, which are unnecessary to repeat here, apply to Falk *et al.*'s study with equal force.

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References

1. J. L. Falk, H. H. Samson, G. Winger, *Science* **177**, 811 (1972).
2. R. J. Senter and J. D. Sinclair, *Psychonom. Sci.* **9**, 291 (1967).
3. F. W. Finger, *Psychol. Bull.* **44**, 201 (1947).
4. R. D. Myers and W. L. Veale, in *The Biology of Alcoholism*, B. Kissin and H. Begleiter, Eds. (Plenum Press, New York, 1972), vol. 2, pp. 131–138.

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