ulus test thus offers more rapid assessment of a sensitivity decrement than commonly used tests of sustained attention do (*6, 20*) and allows effective separation of overall performance, sensitivity decrement over time, and shifts in response criterion. Signal detection measures can be derived either with the use of a confidence rating scale, as in this study, or from single response data (*5*). The test has detected deficits in overall sensitivity during sustained attention among children born to schizophrenic mothers and lower response criteria among hyperactive children (*4, 5*). Further application may help clarify which clinical groups have actual deficits in sustained attention, as evidenced by unusually sharp sensitivity decrements over time, rather than deficits in overall performance (*6*). Furthermore, certain clinical disorders may be characterized by altered response criteria rather than by sensitivity differences. These distinctions may provide theoretically more useful separations for clinical and psychopharmacological purposes than the more global findings of "attention deficits" characteristic of much work on sustained attention among clinical populations.

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8. $$P_c = \frac{1}{V_u + (U_u - U_d)} - \frac{1}{V_d} \text{ diopters}$$
where V and U refer to the image (screen-to-lens) and object (slide-to-lens) distances (in meters), respectively, and subscripts u and d refer to the undegraded (focused) and degraded (defocused) conditions, respectively. The values of P_c for the low, moderate, and high image degradation were 1.8, 2.0, and 2.1 diopters, respectively. The diopter correction values refer to the required change in the projector lens to focus the image. The required accommodation of the eye is determined by eye-to-screen distance, which was constant across conditions.
9. A stimulus observation interval of 1 second, corresponding to the interstimulus interval, was used. The choice of observation interval was validated through the use of reaction time data to plot functions of the response rate to targets versus time since target (latency), a method originally developed by J. P. Egan, G. Z. Greenberg, and A. I. Schulman [*J. Acoust. Soc. Am.* **33**, 993 (1961)] for tasks with undefined observation intervals. The response-rate–latency function peaked within 1 second and was subsequently flat and low for latencies greater than 1 second. This analysis indicated that a 1-second interval provided a clear cutoff between correct and incorrect responses (hits and false alarms) to targets.
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12. Chi square tests of goodness of fit of the individual ROC's showed that 75 of the 84 ROC's fitted (2 image degradation conditions by 3 blocks by 14 subjects) were well modeled by a straight line on normalized axes, the probabilities associated with the χ^2 values being sufficiently high to reject the hypothesis of nonlinearity ($\chi^2 < 3.823$, $P > .05$ for the 75 cases).
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14. The mean A_z values for the four sessions were as follows for the successive trial blocks. Session 1: .95, .94 and .87; session 2: .96, .93, and .92; session 3: .94, .93, and .93; and session 4: .97, .95, and .94.
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Altered Activity in the Hippocampus Is More Detrimental to Classical Conditioning Than Removing the Structure

Abstract. *Hippocampal ablation has no effect on the acquisition of the rabbit's classically conditioned nictitating membrane response. Systemic administration of scopolamine, which alters hippocampal neuronal activity, severely retards acquisition of the conditioned response in normal animals and those with cortical ablations. In animals with hippocampal ablations, however, scopolamine has no effect on conditioning. These findings suggest that altered neuronal activity in the hippocampus is more detrimental to conditioning than removing the structure.*

A number of laboratories have adopted the rabbit's classically conditioned nictitating membrane response (NMR) as a model system for studying neuronal substrates of associative learning in mammals (*1–3*). Research with this preparation has implicated the hippocampus in the acquisition of the conditioned NMR.

Berger and Thompson (*4*) reported increased neuronal activity in the hippocampus during NMR conditioning. Specifically, both single and multiple unit activity in the pyramidal cell layer of the hippocampus increased during the first few pairings of the conditioned stimulus (CS) and the unconditioned stimulus (US). This increased neuronal activity preceded the behavioral response by as much as 35 to 40 msec and formed a temporal model of the NMR. Other studies have demonstrated that this hippocampal neuronal response is a more general phenomenon that occurs to a variety of CS's (*5*) and US's (*2*) and in more than one species (*6*).

Although these findings suggest that the hippocampus is part of a neural system involved in acquisition of the classically conditioned response (CR), its precise role remains unclear since hippocampal ablations do not affect the acquisition of the conditioned NMR (*7–9*).

Although removal of the hippocampus does not disrupt NMR conditioning, manipulations that alter neuronal activity in the hippocampus do disrupt it. Manipulations that block hippocampal theta, such as systemic scopolamine administration (*10*), microinjections of scopolamine into the medial septum (*11*), and medial septal lesions (*12*) all retard acquisition of the NMR. These results are consistent with data showing a strong relationship between the occurrence of hippocampal theta and the acquisition of the conditioned NMR (*12*). Manipulations that produce hippocampal seizures, such as hippocampal stimulation after conditioning trials (*3*) and local penicillin injections (*2*), also retard NMR acquisition. In each instance, the appearance of the first CR's are greatly retarded, but once they occur, conditioning proceeds at a normal rate and becomes asymptotic. That removal of the hippocampus does not affect NMR conditioning while alteration of hippocampal activity se-

verely retards its acquisition suggests that altered neuronal activity in the hippocampus may be more detrimental to classical conditioning than removal of the structure (*12, 13*).

Systemic administration of scopolamine in the rabbit both alters hippocampal neuronal activity by eliminating hippocampal theta (*14*) and retards acquisition of the conditioned NMR (*10*). This manipulation thus provides a useful tool for examining the relationship between altered neuronal activity in the hippocampus and retarded acquisition of the conditioned NMR. If the retardation of conditioning after scopolamine administration is due to the altered neuronal activity in the hippocampus, conditioning should not be retarded in scopolamine-treated rabbits with hippocampal ablations. We now report such an effect.

The animals were 30 experimentally naïve male and female New Zealand albino rabbits. The animals were initially subdivided into three surgical conditions: hippocampal ablations, ablations of the overlying cortex, or controls. Animals to be given ablations were treated with chlorpromazine and anesthetized by sodium pentobarbital injection in the marginal ear vein. All lesions were produced by aspiration (*8, 9*).

After a 2-week recovery period, half the animals in each surgical condition were randomly assigned to either a scopolamine [1.5 mg per kilogram of body weight, dissolved in saline (2 mg/ml) (*15*)] or a saline group. Thus the final design consisted of six groups with three surgical conditions (hippocampal, cortical, normal) crossed with two drug treatments (scopolamine and saline).

All animals received daily subcutaneous injections of the appropriate drug 45 minutes before being tested. Testing took place in an NMR conditioning apparatus (*8, 9*). Animals were placed in conditioning chambers and presented with 100 CS-US (a 6-V light and a 2-mA shock to the eye) pairings per day for 10 days. Conditioning was measured by (i) total number of CR's out of the 1000 possible and (ii) number of trials required to reach a criterion of five consecutive CR's. For all trials, the CS had a duration of 500 msec with the US overlapping the last 50 msec. The intertrial interval was a constant 30 seconds.

Table 1. Mean number of trials to reach a criterion of five consecutive CR's and mean total CR's.

Group	Trials to criterion	Mean total CR's
Hippocampal-scopolamine	165.4	658.4
Hippocampal-saline	182.4	760.8
Cortical-scopolamine	503.8	449.2
Cortical-saline	194.2	722.4
Normal-scopolamine	560.6	392.0
Normal-saline	203.0	732.6

After 10 days of training, all animals underwent sensitivity tests to determine if either the drug or the lesions had altered the animals' sensitivity to the light or shock (*16*). At the conclusion of testing, all animals with lesions were killed and their brains examined histologically (*17*).

Whereas control and cortical animals given scopolamine acquired the conditioned NMR more slowly than saline controls, rabbits with hippocampal ablations showed no retardation of conditioning due to drug treatment (Fig. 1). This is demonstrated in an analysis of the mean number of trials required to reach five consecutive CR's (Table 1) which revealed a significant interaction of drug and lesion [$F(2, 24) = 6.40$, $P < .01$]. Planned comparisons showed that whereas cortical and normal animals given scopolamine conditioned more slowly than saline controls [532.2 versus 198.6 trials to five consecutive CR's, $t(18) = 6.30$, $P < .001$], hippocampal animals given scopolamine or saline conditioned at about the same rate [165.4 versus 182.4 trials, $t(8) < 1$, $P > .05$]. Analysis of the mean total number of CR's (Table 1) produced the same results. Analysis of the data from CS and US sensitivity tests did not reveal any significant differences between the groups.

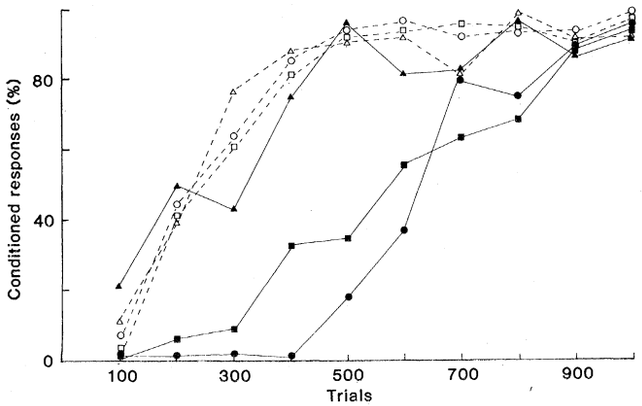

Fig. 1. Mean percentage of CR's over the 10 days of training for animals in each of the six experimental conditions. Filled symbols indicate treatment with scopolamine, and open symbols, with saline. Symbols indicating surgical condition: triangles, hippocampal ablation; squares, cortical ablation; and circles, normal control.

The data are consistent with results of earlier studies indicating that (i) dorsal hippocampal ablation does not affect acquisition of the conditioned NMR and (ii) systemic administration of scopolamine retards acquisition of the CR. The major new finding is that systemic scopolamine, which alters hippocampal neuronal activity and retards NMR conditioning in normal rabbits, does not affect conditioning in rabbits with hippocampal ablations. These results suggest that certain patterns of neuronal activity in the hippocampus are more detrimental to conditioning than ablating the structure (*18*). This interpretation may be helpful in explaining the paradox between data indicating clear changes in hippocampal neuronal activity during conditioning and those indicating no effect of hippocampal lesions on acquisition of the conditioned NMR. Although the hippocampus is apparently not essential for acquisition of the conditioned NMR, it can play a modulatory role.

An understanding of how the hippocampus interacts with brainstem (*19*) and cerebellar (*20*) structures that seem essential to acquisition of the CR should provide a better understanding of the role of the hippocampus in conditioning.

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Alcohol-Induced Spasms of Cerebral Blood Vessels: Relation to Cerebrovascular Accidents and Sudden Death

Abstract. *Ethyl alcohol produced graded contractile responses in rat cerebral arterioles and venules in vivo and in isolated canine basilar and middle cerebral arteries at a concentration range (10 to 500 milligrams per deciliter) which parallels that needed for its graded effects of euphoria, mental haziness, muscular incoordination, stupor, and coma in humans. Two specific calcium antagonists, nimodipine and verapamil, prevented or reversed the alcohol-induced cerebrovasospasm and thus may prove valuable in treating the hypertension and stroke observed in heavy users of alcohol.*

Ethyl alcohol contributes to numerous deaths and is a leading cause of fatal vehicular accidents, particularly among the young (*1*). Ongoing clinical studies in the United States and Scandinavia indicate a higher than normal incidence of hemorrhagic stroke and aneurysmal subarachnoid hemorrhage among heavy users of alcohol; such episodes may occur within 24 hours of a drinking binge (*2–5*). Several investigators have suggested that excessive alcohol consumption predisposes humans to stroke and sudden death (*2–4, 6, 7*).

Epidemiological and clinical evidence indicates that alcoholics in the later stages have a high incidence of hypertensive vascular disease (*7, 8*). However, it is difficult to associate the development of hypertension with the incidence of stroke and aneurysmal subarachnoid hemorrhage in "binge drinkers" (*2–6*). Moreover, it is not known why hypertension develops in alcoholics.

Chronic abuse of alcohol also produces atrophy of cortical, subcortical, and cerebral areas in the brain, brain damage, blackouts, functional neuronal deficits, psychoses, and hallucinations (*9, 10*). These changes in alcoholics, like the hypertension, have not been adequately explained.

Since cerebral hypoxia may play a role in the psychotomimetic actions of hallucinogens (*11*) and since alcoholics exhibit alterations in regional cerebral blood flow (*12*), we wondered whether alcohol can exert direct actions on cerebral blood vessels. We report that alcohol can produce vasospasm in intact cerebral arterioles and venules and in isolated cerebral arteries at concentrations that induce intoxicating, psychotomimetic, or lethal effects in humans. The contractile effects of alcohol on cerebral blood vessels can be abrogated by use of calcium antagonists (nimodipine or verapamil).

For the in vivo studies, the diameters of pial arterioles and venules in male Wistar rats (*13*) were measured quantitatively with an image-splitting television microscope recording system (*14*). Responsiveness of selected arterioles (17 to 58 μm) and venules (22 to 55 μm) was tested before and after administration of alcohol topically, intra-arterially, intraperitoneally, or intravenously.

For the in vitro studies, helical strips 10 to 15 mm long by 1.5 to 2.0 mm wide were cut from segments of canine middle cerebral and basilar arteries, suspended isometrically under 1 g of tension, and incubated in chambers containing normal Krebs-Ringer bicarbonate solution (37°C) through which a mixture of 95 percent O_2 and 5 percent CO_2 was bubbled (*15*). Graded concentrations of alcohol were then added to the bathing solution. Contractional force was measured with Grass FT-03 force-displacement transducers and recorded on a Grass model 7 polygraph.

Perivascular, intracarotid, or systemic administration of graded doses of ethanol resulted in rapid and graded constriction of all cortical arterioles examined (Fig. 1 and Table 1). Local administration of alcohol at concentrations between 10 and 50 mg/dl produced threshold constriction of the arterioles. Such effects, and those produced by concentrations of alcohol up to approximately 200 mg/dl, gradually disappeared within 5 to 40 minutes, depending on the dose. Doses of alcohol that resulted in perivascular or blood concentrations greater than 300 mg/dl usually resulted in arteriolar spasms that were irreversible and often followed by rupture within 5 to 10 minutes, leading to focal hemorrhages. Perivascular or intracarotid administration of 0.01 to 1 percent ethanol produced a concentration-related vasoconstriction of cortical venules, with an 8 to 60 percent reduction in vessel diameter (N = 8 animals); doses of ethanol above 0.3 percent often resulted in irreversible spasm and rupture. Blood flow in cortical microvessels was curtailed markedly.

Table 1. Alcohol-induced vasoconstriction of rat cortical arterioles in vivo. Alcohol was administered to the surface of the brain in 0.1-ml volumes or intraperitoneally in doses of 0.5, 1.0, 2.0, or 4.0 g/kg. Observations were made 30 to 60 minutes after systemic (intraperitoneal) administration of alcohol. All experimental values are significantly different from the corresponding control values ($P < .001$, paired t-test). Values are means ± standard errors for eight rats per group.

Route of administration and dose	Arteriolar diameter (μm)		Reduction (%)
	Before alcohol	After alcohol	
Perivascular			
Cerebrospinal fluid (0.1 ml)	27.4 ± 0.57	27.5 ± 0.56	0
10 mg/dl	27.5 ± 0.56	24.0 ± 0.50	12.7
25 mg/dl	27.4 ± 0.52	22.5 ± 0.42	17.8
100 mg/dl	27.3 ± 0.53	21.7 ± 0.38	20.5
250 mg/dl	27.3 ± 0.53	20.8 ± 0.35	23.8
1000 mg/dl	27.5 ± 0.56	20.2 ± 0.34	26.5
Systemic			
Saline	38.2 ± 0.72	38.4 ± 0.73	0
0.5 g/kg	38.0 ± 0.72	34.2 ± 0.66	10
1.0 g/kg	38.4 ± 0.74	30.4 ± 0.58	20.8
2.0 g/kg	38.2 ± 0.72	26.2 ± 0.46	31.4
4.0 g/kg	38.0 ± 0.71	24.6 ± 0.42	35.2