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EFFECTS OF ETHANOL ON VISUAL UNIT ACTIVITY IN THE THALAMUS,(U)
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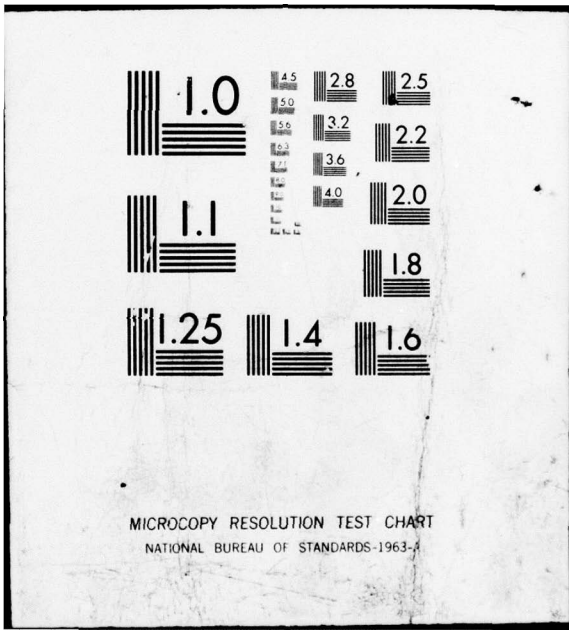
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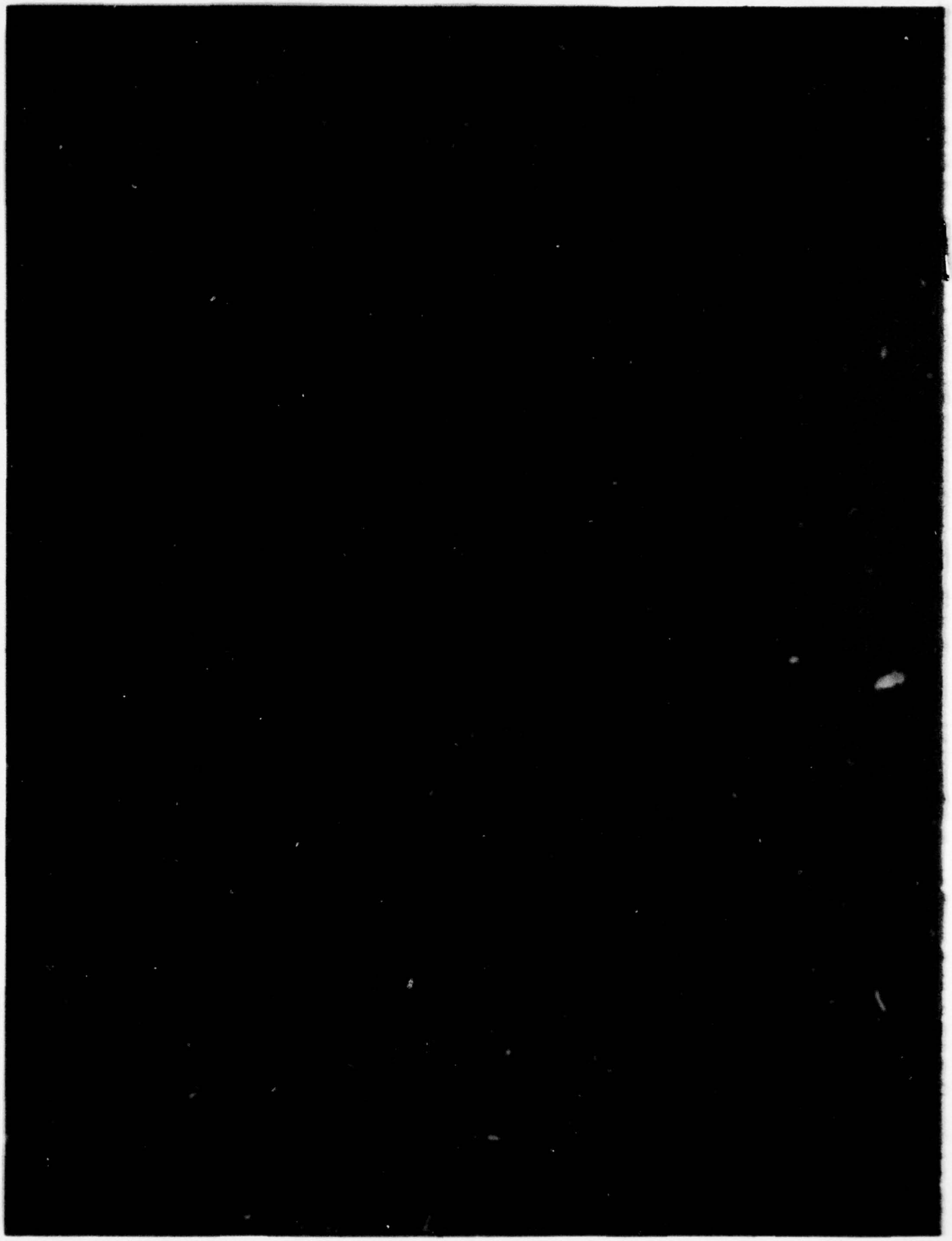

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16. Abstract

The investigators studied the effects of ethanol on the spontaneous activity of single neurones in functionally differentiated subnuclei of a posterior thalamic visual projection area, nucleus rotundus, in the anesthetized pigeon. Low doses of ethanol, 0.05 - 0.10 ml/kg (producing blood levels of about 0.005 - 0.010%), inhibited activity in anterior rotundus but had complex excitatory-inhibitory effects on posterior rotundal cells. Nonvisual dorsal thalamic cells, and "lateral geniculate" neurones were inhibited by ethanol but threshold doses (0.25 - 0.40 ml/kg) were far higher than those for the rotundal cells (0.05 ml/kg). These differing dose-response curves for visual and nonvisual thalamic neurones suggest: (1) Low doses of ethanol may seriously impair peripheral visual functions; (ii) The behavioral effects of ethanol are highly dose-dependent; (iii) Effects of low doses of ethanol may not be extrapolated from high-dose effects since high-dose effects may "mask" effects dominant at low doses; (iv) The effects of a given dose of ethanol may vary widely and unpredictably among individuals. Thus, the notorious unpredictability of ethanol-induced changes in behavior or task performance may be the inevitable consequence of the reported differential dose-response effects on single neurones.

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I. Introduction.

Ethyl alcohol impairs driving or flying performance in part through an impairment in visual system function (9,10,19). The mechanisms of such ethanol-induced visual dysfunction are uncertain. Explanations include a slowing of information processing in the brain (10,17,25), impaired eye movement control (9,30,31), slowed target tracking (7), and impaired peripheral vision (18,32,34), among others (1,3,4). Indeed, there is some suggestion that visual functions need not be involved at all; that ethanol impairs "outputting," or the ability of the brain to output appropriate responses to a given stimulus configuration (28). The visual functions affected by ethanol, and, perhaps, even outputting, are largely mediated by retinal inputs to the superior colliculus (27) and the further collicular projections to the posterior thalamus (8,20) and beyond. Thus, it seemed likely that the behavioral effects of ethanol noted above could be explained, and further effects predicted, by a selective action of ethanol on visual neurones in the colliculo-cortical projection system. The present studies were undertaken to test this hypothesis. In such an investigation it is essential that drug effects be evaluated in terms of actions on sets of neurones of specified characteristics, since we have shown that drug effects may be limited to one small group of neurones, carrying specific messages, within a larger neuronal aggregate forming a visual relay nucleus (23). Our prior work has indicated that low doses of ethanol will inhibit spontaneous activity of directionally selective neurones in the nucleus rotundus of the pigeon (23). Rotundus is a visual relay nucleus in avian posterior thalamus. It receives information from the optic tectum-superior colliculus and relays it to telencephalon (24) and is thus at least functionally homologous to the lateralis posterior/pulvinar complex in mammals (8,20). In the present study we report differential effects of ethanol on functionally different neurone systems in rotundus and overlying dorsal thalamus, and suggest: (i) that such differential pharmacological specificity may be partly responsible for the varying behavioral effects produced by ethanol; (ii) that the effects of ethanol on posterior thalamic visual functions can explain most of the effects of ethanol on visual functions noted above; and (iii) that low doses of alcohol may be more toxic or dangerous than is generally recognized.

II. Methods.

Urethane-anesthetized white carneau pigeons were used, since pigeons are a useful and inexpensive model system for ethanol intoxication (11,23,33). The dose of urethane used was usually 1.8 gm/kg, which was sufficient to block eye movements for the 8- to 12-hour duration of the experiments. The birds were clamped in a special stereotactic apparatus built to permit virtually unobstructed access to the visual field of the left eye of the animal. Head and electrode alignments were such that the Karten and Hodos atlas (13)

coordinates could be used. Extracellular unit recordings were made by using micropipettes filled with a 4:1 mixture of NaCL and KCl; the tip was broken back to give electrode resistances of the order of 1 megohm. Higher impedance (10-megohm) electrodes were often necessary for single unit isolation in the small-celled posterior area of n. rotundus. Amplifying and display procedures were conventional, using Neurolog modules, and the integrated spontaneous rates were written out on a Grass Polygraph. In the usual experiment, the micropipette was inserted into the thalamus of the pigeon until an appropriately responding, spontaneously active single unit was isolated. Three types of neurones were used: (i) nonvisual units from the dorsal thalamus overlying nucleus rotundus; (ii) nonselective units from posterior rotundus (2) (these units responded to any stimulus configuration that moved); and (iii) directionally selective, anterior rotundal neurones which also preferred small target sizes (5^{o} arc). During the recording period the animal was undisturbed, in an isolation chamber with its right eye closed and its left eye viewing a screen whose luminance was 2.0 footcandles. Qualitative response categorization was achieved by aural evaluation of unit responses to manually moved dark cardboard targets positioned against the tangent screen. Dilute ethanol was administered intravenously, or intramuscularly, after a 45-min control recording. Doses are given as milliliters of 95 percent ethanol per kilogram of body weight. Only those units were used which could be followed for at least 1 hour post-treatment and which gave no signs of damage discharge or sudden spike configuration changes during the recording period.

III. Results.

We recorded from a total of 36 neurones.

Twenty anterior rotundal neurones were studied. Ethanol always produced an inhibition of spontaneous activity in these units. Threshold dose was 0.05 ml/kg. Doses of 0.20 ml/kg or higher completely blocked spontaneous activity, though activity evoked by moving stimuli was not completely blocked. Indeed, periodic testing with moving stimuli was the only way of determining that the unit had not been killed by the ethanol or otherwise "lost." Doses around 0.10 ml/kg induced a 50- to 80-percent drop in spontaneous rate, with a mild depression of the evoked activity examined (Fig. 1). Duration of action of ethanol at 0.10 ml/kg was 60 to 120 minutes. Duration of effect of higher doses of ethanol could not be determined, since the units usually could not be "held" (recorded from) for more than 3 hours post-ethanol, and recovery from inhibition did not occur within this time.

Ethanol effects on the 10 posterior rotundal units studied were complex. A dose of 0.10 ml/kg produced, in the six units tested, a 30- to 50-percent inhibition of spontaneous rate beginning 2 to 5 minutes after injection and lasting for 2 to 10 minutes. This was followed by an increase in rate to 1.5 to 3.0 times mean control levels. The increase lasted 60 to 120 minutes (Fig. 1). Again, the duration of effect was difficult to assess,

since the posterior rotundal units could not be "held" for as long a time as the anterior cells. Activity evoked by moving stimuli was also enhanced during the period of increased spontaneous activity. In three and four additional units, respectively, doses of 0.05 ml/kg and 0.10 ml/kg produced increases in spontaneous rate of 40 percent and 60 percent. However, these units could only be "held" for 20 to 30 minutes post-ethanol. In four units, a dose of 0.20 ml/kg induced an 80-percent reduction in spontaneous activity, and similarly depressed evoked responses over the 80- to 120-minute periods that post-drug recording could be taken.

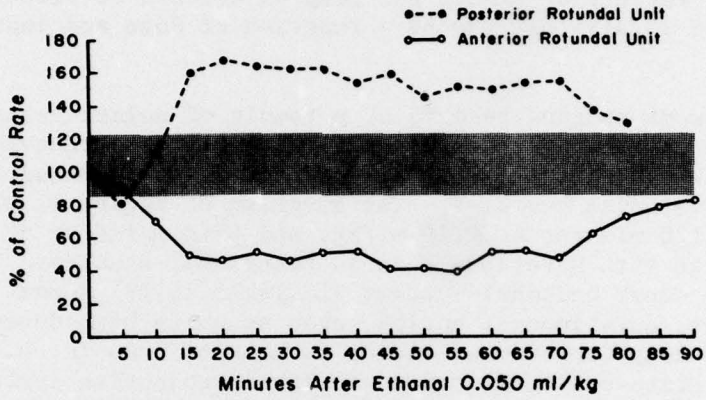

Figure 1.

Ethanol effects were also determined in six nonvisual units in the thalamus dorsal to posterior rotundus. Inhibition of spontaneous activity was seen in all, but the dose required was high; 50 percent inhibition required doses of 0.40 ml/kg or more.

Increasing levels of urethane anesthesia, to 2.3-2.5 gm/kg, had no observable effects in five each anterior and posterior rotundal neurones studied in an earlier series of control experiments, though the probability of finding spontaneously active neurones does increase with increasing depth of anesthesia (at least up to 2.4 gm/kg).

IV. Discussion.

Ethanol doses equal to or greater than 0.20 ml/kg virtually cut off spontaneous neuronal activity and inhibit visually evoked unit responses in the nucleus rotundus. Thus, these doses of ethanol severely inhibit the functions of colliculo-telencephalic visual projection system, just as would an anatomical lesion of n. rotundus. In fact, the behavioral consequences of such a lesion have recently been studied in monkeys (5). The

animals were trained on a task involving orientation to a novel stimulus and then lesions were made in the pulvinar which, as mentioned above, is, in part, a functional homolog of n. rotundus. The lesioned monkeys showed marked abnormalities of visual fixation including an abnormal prolongation of visual fixations on any one aspect of the stimulus array. This lesion-induced visual dysfunction is strikingly similar to some of those following administration of ethanol to human volunteers in doses equal to or greater than 0.20 ml/kg (19). Thus, at least some of the visual impairment produced by ethanol may be attributed to its effects on information transfer in the colliculo-cortical visual projection system. Since the collicular system mediates an impressive array of visual functions (27), ethanol may be expected to have a variety of subtle and complex effects on visual functions (7,9,10,17,18,25,28,30,31) that may be a function of dose and individual (see below).

These effects of ethanol seem to be a result of selective action on visual neurones since the threshold doses for inhibition of nonvisual dorsal thalamic cells were substantially higher than the doses required for full inhibition of the rotundal neurones. The duration of action of ethanol was quite long, 60 to 120 minutes at 0.10 ml/kg, and this duration of action is roughly in agreement with durations seen in behavioral studies. Studies of ethanol effects on other neuronal systems (12,14,15,16,29) report relatively brief, or transient, durations of action, even at quite high doses. The low threshold dose and long duration of action of ethanol seen in this study suggest that the retino-colliculo-cortical visual projection system is a primary locus (16) for ethanol action. Thus, in this instance at least, the effects of ethanol do not seem to be due to a generalized inhibition of brain function (7,10,17), but result from actions on specific, functionally defined target cells (14,15,16). Under the conditions of our experiment the spontaneous discharge rate of rotundal cells is largely determined by mean retinal illumination (21). Since ethanol can affect both retinal (3,33) and collicular (9) functions, it is not now possible to further define the locus of ethanol action in this system. Ethanol actions on brainstem activating systems could also be involved (12). Such activity is not likely to be a major factor, however, since electrical stimulation of these systems doesn't have an appreciable effect on mean rate of rotundal firing (21), nor does wide variation in depth of anesthesia.

The effects of low doses of alcohol, from the 0.05-ml/kg threshold through 0.15 ml/kg were more complex than the purely inhibitory sequelae of doses greater than 0.15 ml/kg. Cells in anterior rotundus preferentially respond to such abstract characteristics of moving stimuli as size, direction of movement, velocity, figure-ground contrast, etc. (22). These neurones are inhibited by ethanol at all doses. Spontaneous rate is more sensitive to the drug than is evoked activity in the sense that an ethanol dose of, say, 0.10 ml/kg may almost completely block spontaneous firing of a cell while its response to a moving target does not change qualitatively and is only moderately inhibited quantitatively (23). This suggests that ethanol

may differentially affect functionally different inputs to the rotundal cell (2) and also that spontaneous firing and stimulus-evoked firing of sensory projection cells may carry different kinds of information. The cells in posterior rotundus are simpler in response than the anterior rotundal units. They respond to any retinal image movement. Response amplitude is largely independent of stimulus size, shape, direction of movement, etc., although, within limits, increasing velocity of movement does increase frequency of cell discharge. Ethanol (0.05-0.15 ml/kg) increases the mean firing rate of these cells. The vigor of the stimulus-evoked response tends to follow spontaneous rate changes. In brief, ethanol inhibits anterior rotundal units, and it stimulates the posterior rotundal cells at low dose levels.

A number of interesting conclusions derive from this differential action. For example, there is some disagreement about effects of alcohol on peripheral vision (18,32,34) and other perceptual functions (1,4,7). This variability in the results of alcohol studies may well be, in part at least, an unavoidable consequence of the way in which alcohol works in the brain. Visual information is carried to many different areas of cortex over a number of anatomically distinct pathways. Each cortical area responds to different, though overlapping, sets of pattern abstractions from the retinal image. Perception of an object, such as this paper, can be thought of as resulting from parallel processing of some subset of the set of available abstractions (6). Both the set of abstractions and the ways in which they are combined for perception seem to be learned, at least in part (6). The present evidence suggests that each functionally defined subset of visual neurones is differentially affected by alcohol in a dose-dependent way. Thus, the information fed into the "parallel processor" will be distorted by ethanol or will be erroneous in some ways. The extent to which the resultant processor error can affect a visual function will depend on the number of ethanol-sensitive abstraction subsets used in that particular visual integration. The number and kind of subsets used for any visual perception are functions of the entire stimulus configuration and the mental set of the subject (26). These inevitably will differ considerably among individuals. It follows that results from studies on the effects of alcohol on visual perception must depend on the dose of alcohol used, the minutiae of stimulus configuration and presentation, and the developmental backgrounds of the subject population. Since no experiments can be identical in those ways, the results of experiments on ethanol ingestion must, as suggested above, differ--and this is an unavoidable consequence of the way ethanol acts in the brain.

The dose-response characteristics of the neurones in anterior and posterior rotundus and in "dorsal thalamus" differ rather considerably. This suggests, as indicated above, that the effects of alcohol on any given behavior are dose-dependent. Therefore, behavioral changes produced by high doses of alcohol cannot, with any confidence, be extrapolated to lower doses. After all, behaviors mediated by dorsal thalamus will not be affected

by doses of ethanol sufficient to induce complete inhibition of anterior rotundal neurones though, at high doses, the thalamic effects could appear to be the dominant determinant of behavior changes.

Ethanol ingestion has been implicated as a factor in many aircraft and automobile accidents. One response to this has been attempts to delineate "safe" levels of blood alcohol--levels which presumably will not increase the probability of having an accident. Now, in the present study, 0.20 ml/kg of ethanol will effectively cut off rotundal functions, and similar doses will affect visual performance in such a way as to increase the probability of an automobile or aircraft accident (9,10,19). However, threshold doses of ethanol in our experiments were 0.05 ml/kg. This is really a very small dose of ethanol, giving blood levels of about 0.005%, the equivalent very roughly, of 0.3-0.4 ounces of whiskey in a 70-kg person but still sufficient to distort visual integrative functions. Thus, it seems to this author that current ideas and regulations concerning "safe" blood ethanol levels for operators of aircraft and automobiles may have to be reviewed.

V. Summary.

We have shown in this study that alcohol exerts differential effects on discrete portions of the brain centers involved in the transfer of visual information to interpretative cortical areas. Inasmuch as the relative contribution of information arriving over each of these pathways to the decision-making process and subsequent behavior is affected by learning and experience, we may have explained in part why activity patterns resulting from visual stimuli are affected in an unpredictable manner by low doses of alcohol. The data also suggest that ethanol may impair visual functions at doses substantially below levels currently believed "safe."

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