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ORIGINAL INVESTIGATION

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Effect of ethanol on sustained attention in rats

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Abstract Acute exposure to ethanol produces deficits in sustained attention in humans, but these attentional deficits have not been modeled in animals. In this study, an operant task was used to investigate the effects of low and moderate doses of ethanol on sustained attention in rats. Performance on a two-choice reaction time task over a 1-h session was assessed immediately following administration of ethanol (0.0, 0.5, 0.75, 1.0 and 1.5 g/kg IP). Each rat was required to respond to a light stimulus of variable duration (20, 100, and 500 ms) occurring at one of two locations. Under control and saline conditions, increases in stimulus length systematically increased choice accuracy and decreased reaction time. Ethanol produced a dose-dependent decrease in choice accuracy that interacted with time, with an initial impairment that was stimulus length-dependent followed by a general vigilance decrement. The data demonstrate that ethanol impaired the ability of rats to direct and sustain attention to brief, infrequent stimuli, and provide a model for further investigations into the underlying neurobiological mechanisms for ethanol-induced attentional deficits.

Key words Ethanol · Rats · Attention · Vigilance · Reaction time

Introduction

Acute exposure to ethanol disrupts a variety of cognitive abilities in humans. Ethanol at low doses markedly impairs the ability to divide attention (Lamb and Robertson 1987; Moskowitz and Robinson 1987), and substantially affects the ability to sustain attention in continuous performance tasks (Linoilla et al. 1978; Koelega 1995). The impairments in sustained attention are typically measured as changes in accuracy or reaction time on tasks that require continuous psychomotor performance, or responses to brief, unpredictable stimuli. Such tasks create a high demand on attentional capacity and are consistently disrupted by low doses of ethanol in humans (Koelega 1995). Valid animal models of sustained attention, requiring sustained monitoring of specific locations to detect and respond to the occurrence of a brief stimulus, have recently been developed (Robbins et al. 1989; Bushnell et al. 1994; McGaughy and Sarter 1995). Performance in these tasks is impaired by a number of pharmacological treatments, including drugs active at benzodiazepine, dopamine and acetylcholine receptors (McGaughy and Sarter 1995; Muir et al. 1995). Whereas ethanol has been tested in rats on a number of reaction time tasks (Koob et al. 1988; Spirduso et al. 1989; Mayfield et al. 1992), the effects of ethanol on performance of an explicit sustained attention task in rats has not been tested to date.

The present study was designed to assess the effect of ethanol on performance of rats in a sustained attention task that required responses to brief, infrequent stimuli. The results demonstrate that ethanol disrupts sustained attention, and suggests that this model may reflect an attentional effect of ethanol similar to that observed in humans.

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Materials and methods

Twelve Long-Evans hooded rats, weighing 200 g at the start of training were housed in a standard vivarium with 12:12-h light:dark cycle, and had free access to food. The rats obtained water during operant performance and for 10 min in their home cage after daily testing. The operant chambers had a light 5 cm above each of two levers, with one lever and light on each side of the front panel, separated by 13 cm. Water reward (0.08 ml) was delivered to a centrally located cup on the floor near the back panel. The operant chamber was located within an outer sound-attenuating shell, and was connected via an interface to a computer that controlled and recorded all aspects of the task (Med Associates, Georgia, Vt., USA). After initial shaping to lever-press for water reward, rats were trained in a two-choice reaction time task. The task required that rats respond to the left or right light by pressing the left or right lever, respectively, in order to receive a water reward on an FR1 schedule. The duration of the light was varied

randomly between 20, 100 and 500 ms from trial to trial. Each stimulus length occurred with equal probability. Each session lasted 1 h and consisted of 150–180 trials. The intertrial interval was randomly determined (8–20 s), and began after the first lever press following light onset, or 3 s following light onset in the absence of a response. Criterion level performance was defined as three consecutive sessions with greater than 80% accuracy. All rats learned to perform the task within 40–60 sessions, with a mean (±SEM) trials to criteria of 54±6 sessions.

Choice accuracy, reaction time, intertrial interval (ITI) responses, and response omissions were recorded. Choice accuracy was the percentage of correct responses out of the total number of responses. Reaction time was defined as the time from stimulus onset to the first lever press within 3 s. Response omissions were the percentage of trials in which the rat failed to make a response within 3 s. Each session was divided into four 15-min time blocks for analysis of changes over time. After criterion performance was achieved, rats were tested with 10% ethanol (w/v in saline; 0.00, 0.50, 0.75, 1.00, or 1.50 g/kg IP) injected immediately before the start of a session. Each rat received each dose of ethanol, with the order counterbalanced across rats. The re-establishment of criterion performance was required before subsequent testing, which ensured a minimum of 3 days between successive injections. Rats continued to be trained every day between test days, but were not given any injection. Control data was obtained from the session that immediately preceded the session in which saline was injected. Accuracy and reaction time data were analyzed separately by analysis of variance for repeated measures along three within-subjects variables: signal length, dose of ethanol, and time block.

After the completion of behavioral testing, ethanol was injected on two additional occasions separated by 3 days in order to determine blood ethanol concentrations. Each rat was randomly assigned to receive two of the possible four doses. Rats were injected with 0.5, 0.75, 1.0 or 1.5 g/kg ethanol and 30 min later blood samples (20 µl) were collected from the lateral tail vein and diluted immediately in 180 µl ice-cold *tert*-butanol (0.2 µg/ml) as an internal standard. The samples were centrifuged (10 000 *g* for 10 min) and aliquots (10 l) of the supernatant were injected into a gas chromatograph that used flame-ionization detection. A glass column packed with 0.2% Carbowax was used to separate ethanol and *tert*-butanol.

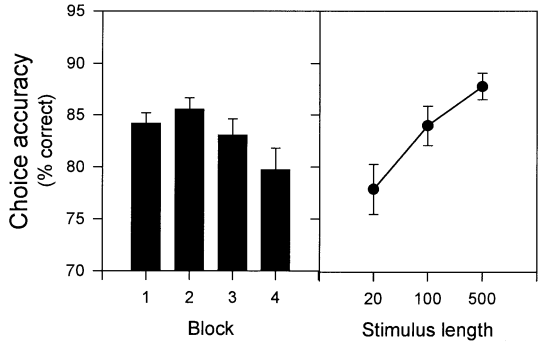

Fig. 1 Choice accuracy under control conditions in the two-choice reaction time task. Control data was taken from the session that preceded the session in which saline was injected. Both time block (*left panel*) and stimulus length (*right panel*) had significant effects on choice accuracy

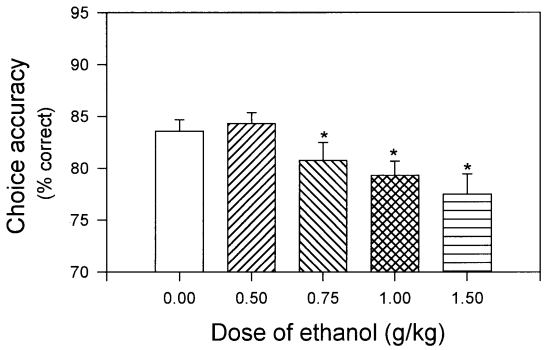

Fig. 2 The effect of ethanol on performance in the two-choice reaction time task. Choice accuracy decreased as the dose of ethanol increased. *P<0.05, when compared to saline (0.00 g/kg)

Results

Under control conditions, stimulus length and time block had significant effects on performance. The effect of stimulus length on choice accuracy ($F_{2,22}$=79.9, P<0.01) and reaction time ($F_{2,22}$=12.4, P<0.01) was such that the shorter the stimulus length, the lower the choice accuracy, and the slower the reaction time. Choice accuracy, but not reaction time, was also affected by time block (accuracy: $F_{3,33}$=5.6, P<0.01; reaction time: $F_{3,21}$=0.7, P>0.05), with accuracy decreasing in block 4 relative to blocks 1 or 2 (P<0.05; Fig. 1). Performance following saline was not different from that of control performance, and thus all subsequent analyses with ethanol were with respect to saline (i.e., 0.00 g/kg ethanol).

Choice accuracy was dose-dependently affected by ethanol ($F_{4,44}$=10.43, P<0.05; Fig. 2). Overall, the higher the dose of ethanol, the greater the effect on choice accuracy. Planned comparisons between saline and each of the doses of ethanol revealed that 0.75, 1.0 and 1.5 g/kg were each different from saline (Ps<0.05). Stimulus length had a robust effect on performance, significantly affecting choice accuracy ($F_{2,22}$=8.50, P<0.01). The shorter the stimulus, the lower the choice accuracy. Signal length did not interact with the effect of ethanol ($F_{8,88}$=1.3, P>0.05).

Time on task was also an important factor in performance. Choice accuracy was significantly affected by time block ($F_{3,33}$=14.0, P<0.01), and this block effect interacted with the effect of ethanol ($F_{12,132}$=2.8, P<0.05). The three-way interaction between stimulus length, block and ethanol was not significant (P>0.1). A separate analysis of variance at each block was performed and revealed that there were two separable effects of ethanol in the task: an early effect in the first block, and a later effect in the third and fourth blocks. There were significant effects of ethanol in block 1 ($F_{4,44}$=8.3, P<0.01), block 3 ($F_{4,44}$=4.4, P<0.01), and block 4 ($F_{4,44}$=7.3, P<0.01), but not in block 2 ($F_{4,44}$=0.2, P>0.05). Planned comparisons between saline and each dose of ethanol revealed that the 1.0 and 1.5 g/kg doses decreased accuracy in block 1, that the 1.5 g/kg dose decreased accuracy in block 3, and that all but the 0.5 g/kg dose decreased accuracy in block 4. Figure 3 shows the dose-response relation between ethanol and choice accuracy in the first and fourth blocks. The lack of effect in block 2 followed by a progressively worse impairment of

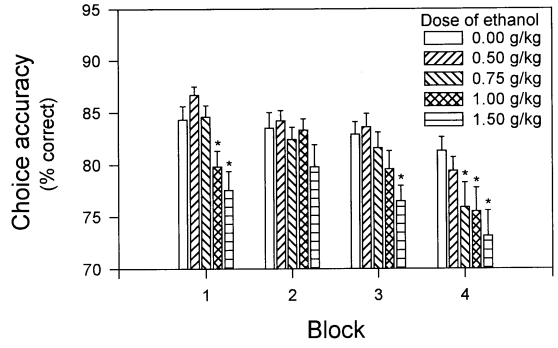

Fig. 3 The effect of ethanol on choice accuracy as a function of time block. Each block represents a period of 15 min. Ethanol reduced choice accuracy in the first (1.0 and 1.5 g/kg), third (1.5 g/kg), and fourth (0.75, 1.0 and 1.5 g/kg) blocks. *P<0.05, when compared to saline within the same time block

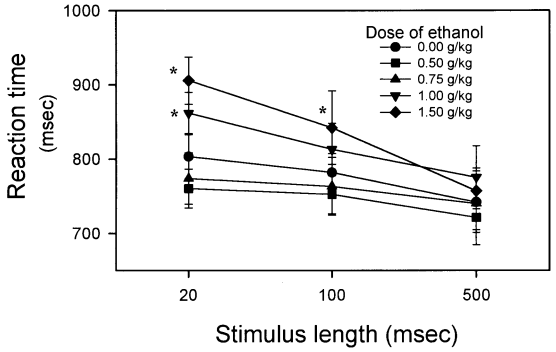

Fig. 5 The effect of ethanol on reaction time as a function of stimulus length. Reaction time deceased as stimulus length increased, and was bi-directionally affected by ethanol, with a decrease at the 0.5 g/kg dose, and an increase at the 1.0 and 1.5 g/kg doses. Ethanol and stimulus length interacted, with the 20-ms stimulus being the most affected by ethanol. *P<0.05, when compared to saline within the same signal length

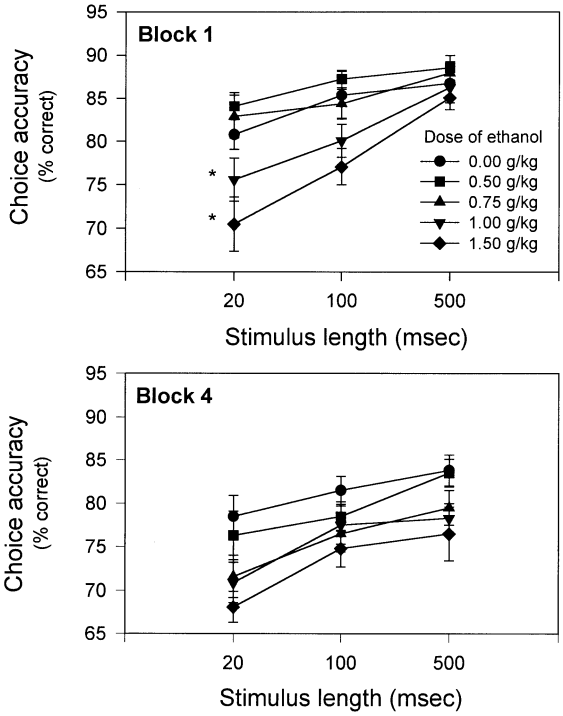

Fig. 4 The effect of ethanol on choice accuracy as a function of stimulus length in blocks 1 and 4. Only in block 1 was there an interaction between ethanol and stimulus length, with the 1.0 and 1.5 g/kg doses of ethanol producing a decrease in accuracy specifically to the 20-ms stimulus. *P<0.05, when compared to saline within the same block and signal length

choice accuracy in blocks 3 and 4 suggests that ethanol produces a decrement in vigilance.

The block-specific effects of ethanol were also analyzed by stimulus length. In block 1, choice accuracy was affected by stimulus length ($F_{2,22}$=15.0, P<0.05), and this stimulus length effect interacted with dose ($F_{8,88}$=2.6, P<0.05), although the effect of dose and stimulus length did not interact in blocks 3 and 4 (Ps>0.05; Fig. 4). To further isolate the variables responsible for the block 1 interaction, a separate one-way analysis was performed on each stimulus length, and it was found that only the two shortest stimuli yielded an effect of ethanol (20 ms: $F_{4,44}$=8.7, P<0.01; 100 ms: $F_{4,44}$=4.5, P<0.01; 500 ms: $F_{4,44}$=0.7, P>0.05). Pairwise comparisons further revealed that choice accuracy was decreased at both the 1.0 and 1.5 g/kg doses for the 20-ms stimulus (Ps<0.05; Fig. 4).

Ethanol produced a dose-dependent effect on reaction time ($F_{4,44}$=3.00, P<0.05; Fig. 5). Ethanol increased reaction time following the 1.5 g/kg and 1.0 g/kg doses (Ps<0.05), and decreased reaction time following the 0.50 g/kg dose (P<0.05). The effect of ethanol on reaction time interacted with stimulus length ($F_{2,22}$=3.00, P<0.05), but did not interact with block (P>0.05). Post-hoc analysis revealed that the increase in reaction time following 1.0 g/kg occurred at the 20-ms stimulus length, and following 1.5 g/kg occurred at both the 20-ms and 100-ms stimulus length.

Ethanol did not affect intertrial interval responses or the total number of trials completed, but did produce an increase in response omissions ($F_{4,44}$=15.4, P<0.01), due only to an effect at the largest dose (1.5 g/kg; P<0.05; Table 1). The 1.5 g/kg dose increased response omissions to 22.0% of total trials from 9.4% of trials for saline, although most of these omissions occurred in the last time block. The percentage of omissions in block 4 are given in Table 1, and only the 1.5 g/kg dose had a significantly higher percentage in the final block (T_{11}=3.0, P<0.05). The number of trials completed over the 1-h session was nearly identical for each of the ethanol doses: 162±4 for saline, 161±3 for 0.25 g/kg, 164±3 for 0.5 g/kg, 164±3 for 0.75 g/kg, 162±3 for 1.0 g/kg and 167±4 for 1.5 g/kg.

To test for the possibility that tolerance may have developed to the effects of ethanol because of the repeated measures design, the order in which doses were given was analyzed, and was not found significantly to influ-

Table 1 Intertrial interval (*ITI*) responses, response omissions, and blood ethanol concentration (*BEC*) as a function of dose of ethanol given intraperitoneal and expressed as grams of ethanol per kilogram body weight (g/kg). BEC was determined from blood taken 30 min after ethanol administration and is expressed in mg%. *n*=12 for behavioral measures and *n*=6 for BEC

Dose (g/kg)	ITI responses	Response omissions	% Block 4 omissions	BEC (mg%)	BEC (range)
0.00	108±18	15.2±1.2	32±5		
0.50	118±21	11.4±1.5	29±7	46.7±2.2	35–51
0.75	135±27	15.4±2.0	26±9	71.8±4.6	48–89
1.00	103±24	20.5±1.6	34±6	88.9±7.5	65–116
1.50	146±10	36.8±2.1*	46±7*	128.4±9.8	97–154

* $P<0.05$,when compare to saline (0.0 g/kg)

ence ethanol-induced changes in either choice accuracy or reaction time (*P*s>0.05). Each of the doses of ethanol resulted in blood ethanol concentrations that were significantly different from one another, and that were in the range of expected values (Table 1).

Discussion

Control performance in the two-choice reaction time task was sensitive to parametric manipulations of stimulus length and exhibited a decrement in accuracy over time. The most difficult stimulus condition, the 20-ms light, substantially lowered accuracy and concurrently increased reaction time. These features suggest that the task provides a useful measure of attentional processes, in that the rat is required to direct and maintain attention in order to detect the brief, unpredictable stimuli. A similar, albeit more elaborate, five-choice serial reaction time task has been used extensively to investigate the role of the basal forebrain cholinergic system in attentional function in rats (see Robbins et al. 1989).

Ethanol dose-dependently impaired performance on the two-choice reaction time task. In terms of percentage change, the decrease in accuracy is small, suggesting that ethanol does not produce a complete disruption of overall performance but rather has a subtle, yet consistent, effect on attentional processing. Upon closer inspection, ethanol produced two specific effects on choice accuracy. First, ethanol impaired choice accuracy in block 1, and this impairment occurred specifically to the shortest stimulus, that is, the stimulus that required the greatest level of attention to accurately process. Thus, ethanol appears to have impaired the ability of rats to direct attention to the stimulus. Second, ethanol impaired the rat's ability to maintain continuous performance over an extended period of time, as indicated by an ethanol-induced decrement in choice accuracy during the final time block.

The stimulus length-dependence of the initial ethanol-induced impairment in choice accuracy suggests an acute effect of ethanol on directed attention. The fact that performance at the 500-ms stimulus was unaffected by ethanol indicates that ethanol did not impair the ability of rats to detect and respond to the stimuli. The preferential effect of ethanol at the shortest stimulus length is consistent with the hypothesis that the level of stimulus processing intensity was reduced by ethanol. There was no increase in first block response omissions following ethanol, providing evidence that the rats continued to detect and respond to the 20-ms stimulus, but failed to respond appropriately. Thus, following the 1.0 and 1.5 g/kg doses of ethanol, the rats do not to have a deficit in sensory (e.g., an increased perceptual threshold) or motor processes, but simply fail to adequately attend to the stimulus location.

A second aspect of the attentional deficit that emerged following ethanol was a loss of accuracy over time, i.e., a vigilance decrement. The 1.5 g/kg dose of ethanol decreased accuracy in block 3, and all but the lowest dose decreased accuracy in block 4, yet ethanol had no effect on accuracy in block 2. An increasing impairment by ethanol as time on task increased was not observed in reaction time data. This pattern of results – a decrease in accuracy over time with no effect on reaction time – has been observed in humans that are performing a visual sustained attention task following consumption of ethanol (Rohrbaugh et al. 1988). In that study, subjects were required to detect and respond to degraded target stimuli (40-ms duration) that were presented at a rate of one stimulus per second. The resultant decrement in accuracy over time was potentiated by ethanol, and after testing a variety of peripheral sensorimotor functions, the authors determined that the vigilance decrement induced by ethanol was not due to peripheral mechanisms, but rather was due to centrally mediated processing. In the present experiment, the fact that the vigilance decrements were not specific to the shortest stimuli, and occurred over a relatively long period of time, further dissociates the vigilance effects from the directed attention effects observed in the first block. With the exception of the 1.5 g/kg dose, response omissions didn't increase in block 4 following ethanol, and thus, rats continue to detect and respond to the stimuli, but progressively fail to indicate accurately the location of the stimulus. The lack of stimulus-length dependence for the ethanol effects in block 4 appears to run counter to a strict sustained attention interpretation, and suggests that, as the task proceeds, ethanol may increasingly impair other processes that influence performance, like response selection.

Ethanol, at the 1.0 and 1.5 g/kg doses, increased reaction times specifically to the shorter stimuli, an effect that provides additional support for the conclusion that moderate doses of ethanol disrupt directed attention. Although studies in humans have reported ethanol-induced increases in reaction time under conditions of high attentional demand (see Maylor et al. 1992; Koelega 1995), such effects have not been investigated in animal studies designed to determine the neural mechanisms of sustained attention. The two-choice task used in the present experiment places fewer demands on attention than a five-choice reaction time task, in which evidence for a

speed-accuracy trade-off has been observed (Robbins et al. 1989). Thus, with only two stimulus locations and a single response rule, rats may have been able to adopt a speed-accuracy trade-off strategy in which they slowed responding to the briefest stimuli in order to maintain accuracy. Under more demanding conditions, the limits of such a strategy may be exceeded, and an ethanol challenge would then produce a generalized effects on reaction time, combined with progressive loss of accuracy for the briefest stimuli. The current task encourages such a speed-accuracy trade-off strategy by allowing up to 3 s for a behavioral response.

An alternative approach that places greater emphasis on reaction time performance has been successfully applied to the study of ethanol. Spirduso and colleagues (1987, 1989; Mayfield et al. 1994) have developed a reaction time task in which rats are trained to use their forepaws to hold down a lever until a stimulus that signals a subsequent footshock occurs. In order to avoid shock, rats learn to release the lever within 200 ms of stimulus onset. By putting a premium on speeded responses, the effects of ethanol on simple reaction time can be assessed. These studies have revealed some of the critical variables that contribute to performance of speeded reaction time tasks in the rat, such as age, intoxicated practice, tolerance, and blood ethanol concentration. The lack of order effects in the current studies is interesting in light of the findings that tolerance to ethanol-induced impairments in successful avoidances developed with intoxicated practice (Mayfield et al. 1994). The absence of tolerance in the current experiment may reflect the use of low doses of ethanol and infrequent injections.

At the 0.5 g/kg dose, ethanol decreased reaction time, but this effect was not specific to a particular stimulus length, and thus may reflect a general acceleration of responding at low doses. Systemic administration of the benzodiazepine receptor agonist chlordiazepoxide also produced a decrease in reaction time with no overall effect on accuracy in a similar two-choice reaction time task (Moore et al. 1992). The low dose effect may represent a form of behavioral disinhibition. Given the similarities between ethanol and benzodiazepines (e.g., the two drugs produce cross-tolerance; Criswell and Breese 1989), similar actions of the two drugs on performance in sustained attention tasks might be expected at all doses (see Koelega 1989, 1995). Interestingly, the effects of ethanol on reaction time did not interact with time block, suggesting that ethanol's effects on reaction time cut across the entire task, and consequently may not have significantly contributed to the vigilance decrement. The interpretation of the absence of a time-dependent change in reaction time is complicated by the potential development of acute tolerance and changes in blood ethanol concentration (BEC), both of which may influence reaction time (Spirduso 1989). Additional experiments in which ethanol is administered at different time points relative to behavioral testing are required to determined the relationship between changes in BEC, behavioral tolerance, and reaction time.

Because testing began immediately following injection of ethanol, the behavioral changes that occurred in block 1 reflect performance deficits during the ascending limb of the BEC curve, i.e., the first 15 min post-injection. Given that the effects of ethanol in block 4 are distinct from the initial effects, it appears that the cognitive/behavioral processes that are affected may differ as a function of the ascending and descending limbs of the BEC curve, with early impairments occurring due to deficits in stimulus-length dependent performance, or directed attention, while the later impairments are due to loss of accuracy over time, i.e., a vigilance decrement. The fact that the ethanol-induced impairment in accuracy is no longer present in the second block suggests the development of acute tolerance, although an improvement in block 2 is also observed in control data. The dissociation of early and late components may also relate to the general biphasic properties of ethanol's behavioral effects, but as with the reaction time data, any firm conclusions concerning the time-dependence of the accuracy effects await further studies in which the time of ethanol administration and behavioral testing are systematically varied.

It is not likely that motivational factors account for the overall pattern of results. Reaction time at the longest stimulus length (500 ms) was not affected by ethanol under any condition, suggesting that following ethanol, rats continue to detect, process, and respond appropriately to task stimuli. Intertrial interval responses, and the number of trials completed, were likewise not affected by ethanol. Conversely, response omissions increased following the 1.5 g/kg dose of ethanol, suggesting that this dose may have produced some sedative effects, specifically in block 4, in addition to impairing attentional performance. If sedation was the only explanation for the increase in response omissions, then ITI responses should have decreased. However, ITI responses were not suppressed following the 1.5 g/kg dose, and if anything were increased, suggesting that there is a shift in the temporal distribution of responses with increased response rates during the ITI period coupled with decreased responses following the stimulus.

Investigations into the neural basis of ethanol′s cognitive effects requires the development of good animal models. Now that valid animal models of attention have been developed (e.g., Bushnell et al. 1994; McGaughy and Sarter 1995), rigorous behavioral neuroscientific investigations can begin to dissect the neuronal mechanisms underlying ethanol-induced impairments in attention. Such an analysis applied to working memory has begun to yield reliable neural correlates in the septohippocampal system (Givens 1995, 1996). Preliminary results from our current investigations (Hutchinson et al. 1995) indicate that the effects of ethanol on attention may be mediated, in part, by interactions with circuits of the prefrontal cortex.

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