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# Nicotine–alcohol interactions and attentional performance on an operant visual signal detection task in female rats

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**Abstract**

Nicotine and alcohol are very often co-used and co-abused. Thus, it is important to understand their interactions. In many ways, nicotine and alcohol have opposing effects. This can be clearly seen in terms of their effects on cognitive function. Nicotine effectively improves attention while alcohol impairs it. The current study was conducted to determine in a rat model the interaction of nicotine and alcohol on attention using an operant visual signal detection task. It is hypothesized that nicotine would reverse the alcohol-induced impairment in accuracy of performance in this task. Female Sprague–Dawley rats ($N=35$) were trained on a visual operant signal detection task for food reinforcement with 300 trials/session in three equal time blocks. The rats were divided into poor and good performers according to their predrug baseline performance accuracy. The first experiment examined the dose–effect function of alcohol (0, 0.375, and 0.75 g/kg ip) on this task. The lower alcohol dose significantly impaired percent correct rejection in the high-performing rats but not the low-performing rats. The higher alcohol dose significantly impaired percent hit performance during the first two thirds of the session in both high- and low-performing groups. The second experiment examined alcohol (0.75 g/kg ip) interactions with nicotine (0, 12.5, 25, and 50 μg/kg sc) on attentional performance. The 25 and 50 μg/kg nicotine doses caused a significant ($P<.05$) improvement in hit accuracy. Alcohol blocked this nicotine-induced improvement, even though at this later time it no longer had an effect of its own. In the high baseline group, the 25 μg/kg nicotine dose also caused a significant ($P<.025$) improvement in hit accuracy. As in Experiment 1, the high baseline group was not significantly impaired by 0.75 g/kg of alcohol. However, this alcohol dose did eliminate the nicotine-induced improvement. These results suggest that alcohol, when given alone, impairs sustained attention and blocks nicotine-induced attentional improvements even when it does not cause impairments on its own.


*Keywords:* Attention; Cognition; Nicotine; Ethanol

## 1. Introduction

Alcohol and nicotine are two of the most widely abused drugs in the world. They are quite often taken together (Hughes, 1995). Both alcohol and nicotine have effects on cognitive function. Although their interactive effects have not been fully characterized, it is clear that the interaction between these two psychoactive drugs is complex. Alcohol-induced attentional impairment may be reversed by nicotine, which by itself improves attention. On the other hand, alcohol may block the attentional improvement caused by nicotine.

Experimental evidence has demonstrated that both acute and chronic alcohol intake disrupts a variety of cognitive functions (Givens, 1995; Matthews et al., 1995; Moskowitz and DePry, 1967; Tracy et al., 1997; Tracy et al., 1999). It has been demonstrated that alcohol impairs the ability of rats to direct and sustained attention (Givens, 1997; Rohrbaugh et al., 1988). Alcohol also produces decrements in attention in humans. Human subjects intoxicated with alcohol have difficulty both in detecting the occurrence of brief infrequent stimuli and in sustaining detection performance over time (Koelega, 1995). On the other hand, mounting evidence suggests that nicotine can improve cognitive abilities in rodents and humans (for a review, see Rezvani and Levin, 2001). Also, it has been demonstrated that pretreatment with nicotine prevents, in a dose-dependent manner, (a) impaired air righting due to 2.0 g/kg alcohol and (b) impaired performance due to 2.0 g/kg alcohol. The same investigators

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have reported that alcohol-induced impairment of both reference and working memory in an eight-arm radial maze can be blocked by pretreating animals with nicotine (Tracy et al., 1999). Previously, we showed that alcohol blocked low-dose nicotine-induced memory improvement and precipitated memory impairment with high-dose nicotine treatment (Rezvani and Levin, 2002). Given the fact that drinking and smoking are very often conducted together, it is important to understand the interaction of alcohol and nicotine in relation to cognitive abilities. Understanding the interaction between these two drugs may be an important consideration for developing better treatment for nicotine and alcohol co-abuse.

Two major categories have been postulated for the concurrent use of alcohol and nicotine: (1) either drug may enhance the rewarding effects of the other drug or (2) either drug may decrease the aversive effects of the other. Collins et al. (1988) have proposed that alcohol and tobacco are used together because they have similar effects on brain nicotinic receptors. Furthermore, the same investigators suggest that nicotine does not facilitate drinking by reducing aversive effects of alcohol but by increasing the rewarding effects of ethanol. Recently, it was reported that systemic administration of alcohol or microinjection of nicotine into ventral tegmental area resulted in a dose-dependent increase in dopamine release in the nucleus accumbens in rats. Simultaneous administration of nicotine and alcohol resulted in an additive effect on dopamine release (Tizabi et al., 2002). The fact that both nicotine and alcohol consumption increase dopamine release in the nucleus accumbens supports Collins' speculation.

The current study was conducted to determine the interactive effects of alcohol and nicotine on sustained attention using an operant visual signal detection task. This technique is useful in which both sensory function and attention can be simultaneously measured. (Bushnell et al., 1997; McGaughy et al., 1999; Rezvani et al., 2002; Rezvani and Levin, 2003). Nicotine-induced improvement and mecamylamine-induced impairment in this task have been recently reported (Rezvani et al., 2002). In the current study, we hypothesized that nicotine would reverse the alcohol-induced impairment in accuracy of performance in this task in rats.

## 2. Materials and methods

### 2.1. Animals

Adult female Sprague–Dawley rats ($N=35$) were used. Rats weighed $265 \pm 3$ (S.E.M.) g at the beginning of the experiment. Animals were housed in groups of three in plastic cages with wood shavings in a vivarium under controlled room temperature of $21 \pm 2$ °C, relative humidity at $50 \pm 10\%$, and reversed 12:12-h light–dark cycle (0700 a.m. to 1900 p.m. dark). The rats had ad libitum access to drinking water but were kept on a restricted feeding schedule to maintain their body weight at 80–85% of free feeding values. Animals were fed once a day after testing. All testing was performed between 09:00 a.m. and 17:00 p.m. These rats had been tested 12 days before starting these experiments for mecamylamine and nicotine response on the same task (Rezvani et al., 2002). The current experiment was initiated after the reestablishment of a stable baseline. Females are very understudied with regard to the psychopharmacology. Female rats were used to provide comparable data to our earlier work regarding drug effects on attentional performance and nicotine effects on memory. The drug doses were administered in a repeated measures counterbalanced design, which provided an index of drug effect averaged over any female cyclic variations.

The Duke University Institutional Animal Care and Use Committee approved the experimental protocols used in this study.

### 2.2. Experimental protocol

First, rats were trained to perform the visual signal detection task. This process took about 3 months. Then, to characterize the effects of alcohol on attentional performance in operant signal detection task and the interaction of alcohol with nicotine, two series of experiments were carried out. In Experiment 1, an alcohol dose–effect function was determined. In Experiment 2, interactions of a moderate dose of alcohol with nicotine were studied.

### 2.3. Experiment 1: Alcohol dose–effect function

To determine the effect of alcohol on this attentional task, rats were injected (intraperitoneally) with saline or one of the two doses of alcohol (0.375 or 0.75 g/kg) 10 min before the test. Then their performance was assessed in a 300-trial session. The interval between different doses was at least 2 days. All rats received all treatments following a counterbalanced design with random assignment.

### 2.4. Experiment 2: Nicotine interactions with alcohol

The same group of rats was injected with a combination of 0.75 g/kg alcohol and saline or a combination of 0.75 g/kg alcohol and one of the doses of nicotine (0, 12.5, 25, and 50 μg/kg) 10 min before the test. These doses of nicotine were chosen based on our recent work using the same task (Rezvani and Levin, 2003). Higher doses of nicotine have been shown to impair performance in this task (Rezvani et al., 2002). The interval between different experiments was at least 2 days. Alcohol was injected (intraperitoneally) first, and 1 min later nicotine was administered (subcutaneously). All rats received all treatments following a counterbalanced design with random assignment.

### 2.5. Drug preparation and dosing

Alcohol solution (16% v/v) was prepared fresh every day with saline and 200 proof alcohol for intraperitoneal administration. The pH of alcohol solution was 5.3. Nicotine ditartrate (Sigma, St. Louis, MO, USA) was dissolved in saline and injected subcutaneously in a volume of 1 ml/kg body weight. The nicotine doses are expressed as nicotine ditartrate salt. The pHs were 3.8–4.3 for the nicotine solutions.

### 2.6. Visual signal detection task

The operant chambers 29 × 25 × 29 cm (HWD) were equipped with a signal light, a house light, two retractable levers (Coulbourn Instruments, Lehigh Valley, PA, USA), 13 cm apart, 2.5 cm above the floor of the chamber inserted horizontally 2.5 cm into the chamber, a food cup in the center of the front panel of the chamber, 2.2 cm above the floor, and a white noise amplifier (Med Associates, Georgia, VT, USA), mounted above the signal lever generating background white noise of about 65 dB. The signal or cue light was located above the food cup at the center of the front panel, 28 cm above the floor of the chamber. A signal consisted of 500 ms increase in the brightness of the signal light to levels of 0.027, 0.073, 0.148, 0.269, 0.466, 0.762, and 1.22 lx above a background illumination of 1.2 lx. Signals were generated using the Med Associates software running a Pentium computer processor using the Windows operating system.

Rats were trained to perform a visual signal detection task. The final task was conducted in daily 300 trial sessions divided into three equal 100 trial blocks (Fig. 1). Two trial types, ‘‘signal’’ and ‘‘blank,’’ were presented in equal number in each session in groups of four (two signal and two blank, in random order) at each signal intensity. Each signal trial included a presignal interval, the signal (cue light), and a postsignal interval. The presignal intervals were selected randomly from 12 different values ranging from 0.3 to 24.4 s. Following the signal, a postsignal interval of 2, 3 or 4 s (selected randomly) occurred. These temporal parameters yield a trial presentation rate of five trials/min. Blank trials were presented identically, except the intensity of the signal light did not change (Bushnell, 1998; Bushnell et al., 1997; Rezvani et al., 2002; Rezvani and Levin, 2003).

A trial began with both levers retracted from the chamber, then both levers were inserted into the chamber simultaneously at the end of the postsignal interval. Both levers were retracted simultaneously when one of them was pressed or if 5 s passed without a press. If the rat failed to press a lever, a response failure was recorded. Every correct response (i.e., a press on the signal lever in a signal trial or a press on the blank lever in a blank trial) was followed by the illumination of the food cup and delivery of one 20-mg food pellet. After each incorrect response (i.e., a press on the signal lever in a blank trial or a press on the blank lever in a signal trial), or response failure, the rat received a 2-s period of darkness (time out) with no pellet delivery. For half the rats, the left lever was defined as the signal lever and the right lever as the blank lever; the opposite assignment was made for the remaining rats.

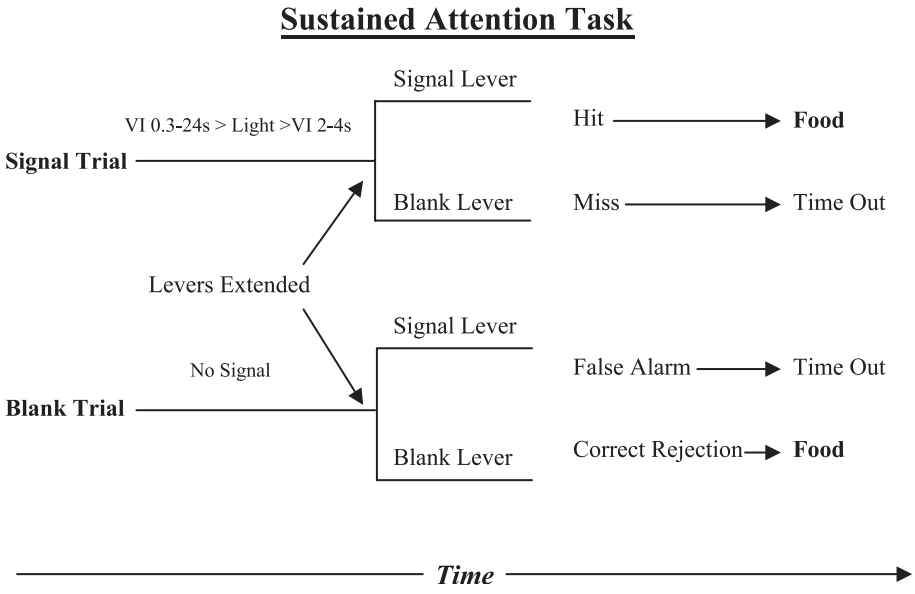


Fig. 1. Signal detection task sequence of trials. This task comprised two types of trials, signal and blank, which differed only in that a light signal was presented in each signal trial and omitted in blank trials. In each trial, the rat pressed either of two retractable levers to report that a light signal had or had not occurred in that trial. Four possible outcomes result in each trial: hit, miss, false alarm, and correct rejection. Hits and correct rejections were followed by delivery of food, misses, and false alarms by a 2-s ‘‘time out’’ period without delivery of food. VI stands for variable intervals for pre- and postsignal during the signal trial.

### 2.7. Behavioral measures and statistical analysis

Four possible outcomes (dependent variables) resulted in each trial: percent hit, percent correct rejection, response latency, and response omissions. The analysis of percent hit also included light stimulus intensity as a within-subject factor. The test session was divided into three blocks of 100 trials and measures of response accuracy were analyzed across blocks as a repeated measure. The Superanova/Statview computer program (SAS, Cary, NC) was used for the statistical analysis. Linear and quadratic trend analyses were used to determine the monotonic and inverted-U-shaped functions with increasing doses. Significant interactions were followed-up by tests of the simple main effects. The threshold for significance was $P < .05$.

To determine possible differential drug effects in rats with different levels of baseline performance, the rats were divided into high- and low-performing groups based upon each animal's accuracy during baseline tests prior to drug treatment. Accuracy was defined as the average value of the percent hit and percent correct rejection scores (see below). These two subgroups (high: $n = 18$; low: $n = 17$) were entered into analyses of the effects of the drugs as a between-group factor on measures of percent hit, percent correct rejection, response latency, and response omission. This type-grouping factor is recommended by Keppel (1973) because of fewer assumptions concerning the homogeneity of regression. This design has been used previously (Rezvani et al., 2002).

## 3. Results

### 3.1. Experiment 1: Alcohol dose–effect function

#### 3.1.1. Percent hit

As shown in Fig. 2, the higher dose of alcohol (0.75 g/kg) caused a significant decrease in percent hit relative to control during the first and second 20-min block of the session. By the last 20-min block, there was no apparent effect of alcohol on percent hit response. Alcohol at the lower dose of 0.375 g/kg did not exert a significant effect on percent hit. There were no significant differences between low-and high-performer groups for hit response.

#### 3.1.2. Percent correct rejection

Compared with saline, alcohol did not have a significant effect on correct rejection in the lower performing animals. In contrast, the higher performing animals showed a significant decrease in percent correct rejection with the lower alcohol dose of 0.375 g/kg ($P < .01$). The higher alcohol dose (0.75 g/kg) did not cause a significant effect on this measure (Fig. 3).

#### 3.1.3. Response latency

There was a very significant main effect of alcohol on hit response latency [$F(2,66) = 14.66$, $P < .0001$] reflecting an alcohol-induced slowing of response. Paired comparisons of the alcohol doses to control showed that the high (0.75 g/kg) alcohol dose significantly slowed response compared to control [$F(1,66) = 22.98$, $P < .0001$], whereas the 0.375 g/kg dose did not significantly affect latency. With vehicle

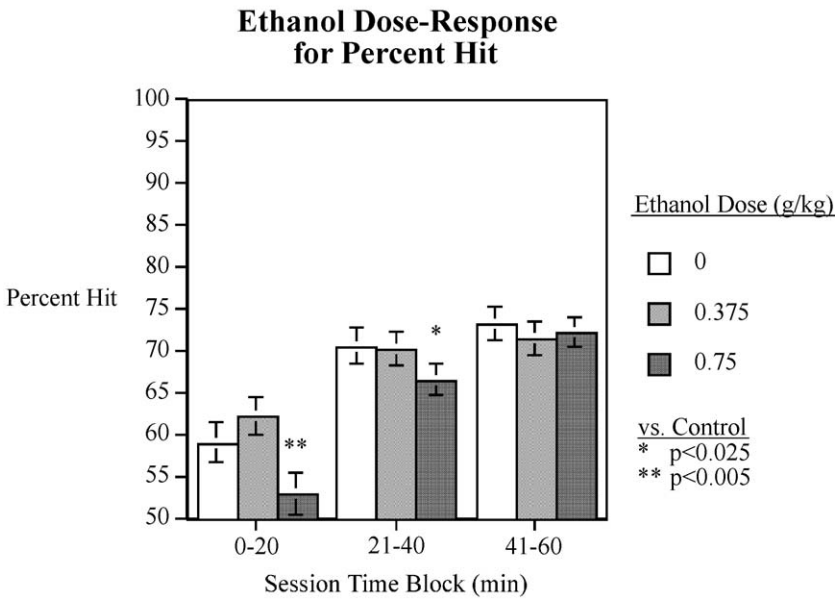


Fig. 2. Alcohol effect on percent hit during the different time blocks within the session (mean ± S.E.M.). Alcohol-induced impairments were seen with 0.75 g/kg ip in the first ($P < .005$) and second ($P < .025$), but not the third, session block.

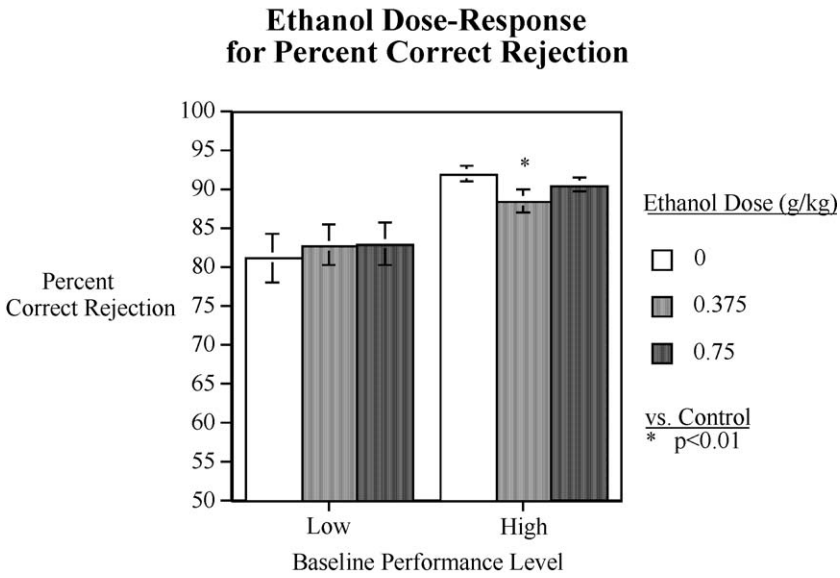


Fig. 3. Alcohol (0.375 g/kg ip) caused a significant ($P < .01$) impairment in percent correct rejection in the high but not the low baseline performers (mean ± S.E.M.).

injections, the rats averaged 631 ± 65 ms (mean ± S.E.M.); with 0.375 g/kg alcohol they averaged 638 ± 60 ms, and with 0.75 g/kg they averaged 790 ± 69 ms hit response latency.

*3.1.4. Response omissions*

Alcohol caused a significant [$F(2,70) = 5.81$, $P < .005$] increase in the number of response omissions. The higher 0.75 g/kg alcohol dose caused a significant ($P < .01$) increase in response omissions from 1.2 ± 0.7 omissions per session with vehicle to 9.0 ± 2.7 omissions per session with the higher alcohol dose. The lower alcohol dose did not cause a significant effect (2.2 ± 1.2 omissions per session).

*3.2. Experiment 2: Alcohol–nicotine interactions*

*3.2.1. Percent hit*

The alcohol main effect was significant [$F(1,31) = 7.43$, $P < .025$]. Alcohol reduced average percent hit from 63.2%

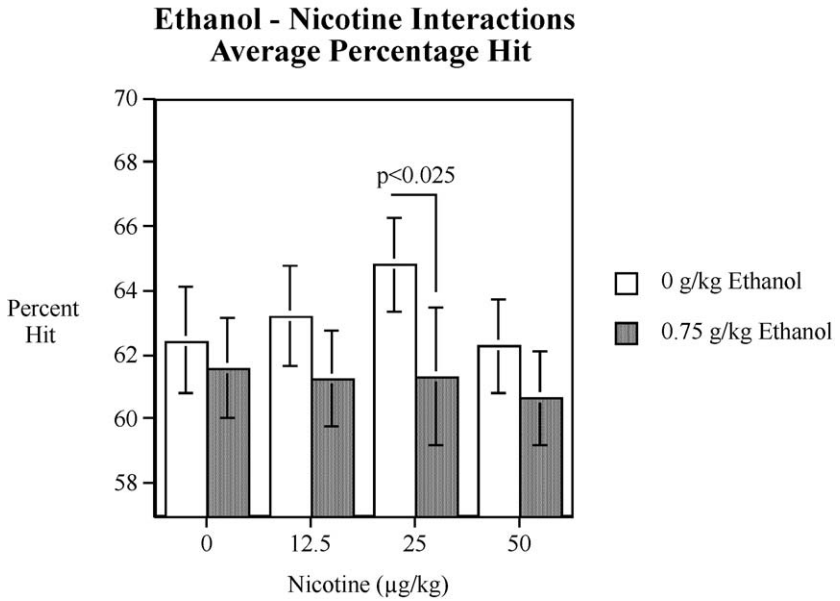


Fig. 4. Alcohol (0.75 g/kg ip) caused a significant ($P < .025$) impairment in percent hit when given with 25 μg/kg nicotine (mean ± S.E.M.).

to 61.3% (Fig. 4). The Alcohol × Block interaction was significant [$F(2,62)=3.74$, $P<.05$]. Similar to Experiment 1, alcohol reduced percent hit in the first 20-min block from 55.4% to 52.1% and in the second 20-min block from 65.9% to 63.7%, but not in the third 20-min block in which the rats had nearly the same percent hit without (68.2%) and with alcohol (68.0%).

The 0.75 g/kg dose of alcohol significantly ($P<.025$) impaired percent hit accuracy when given together with the 25 μg/kg dose of nicotine. The alcohol-induced impairment was from a higher baseline performance than was seen with control injections (Fig. 4). Nicotine did not significantly increase percent hit performance averaged over all the signal intensities, but at dose of 25 μg/kg it did significantly improve performance in the middle signal intensities of 0.269–0.762 lx. The interaction of Alcohol × Nicotine × All Signal Intensities [$F(6,192)=1.62$, $P=.05$] was followed-up by tests of the simple main effects at each signal intensity of nicotine on percent hit and the modification of nicotine effects with alcohol coadministration. Nicotine caused significant improvements in hit accuracy at the middle signal intensities ($P<.025$ for 12.5 μg/kg nicotine and $P<.05$ for 25 μg/kg nicotine). Alcohol coadministration significantly reversed both of these effects ($P<.0005$ for 12.5 μg/kg nicotine and $P<.001$ for 25 μg/kg nicotine).

### 3.2.2. Percent correct rejection

Nicotine, when given alone, significantly improved percent correct rejection from 84.8 ± 1.6% with saline to 86.9 ± 1.2% with 12.5 μg/kg nicotine ($P<.025$) and 86.9 ± 1.5 with 50 μg/kg of nicotine ($P<.05$). With a nicotine dose of 25 μg/kg, the rats also showed a comparable rise in percent correct rejection with an average of 86.7 ± 1.4%, but this fell just short of being statistically significantly different than control ($P<.06$). Interestingly, the 0.75 g/kg alcohol dose caused a statistically significant ($P<.01$) increase in percent correct rejection. The combination of alcohol with nicotine did not significantly modify the nicotine-induced improvement in percent correct rejection (Fig. 5).

Table 1
Alcohol and nicotine effects on response latency (milliseconds)

| Nicotine (μg/kg sc) | Alcohol (g/kg ip) | |
|---|---|---|
| | 0 | 0.75 |
| 0 | 644 ± 65 | 708 ± 67 |
| 12.5 | 633 ± 59 | 727 ± 82 |
| 25 | 626 ± 60 | 693 ± 69 |
| 50 | 687 ± 76 | 749 ± 85 |

### 3.2.3. Response latency

The main effect of alcohol on response latency was significant [$F(1,33)=9.81$, $P<.005$] reflecting the increase in latency caused by alcohol. There was no significant effect of nicotine or Alcohol × Nicotine interaction on response latency (Table 1).

### 3.2.4. Response omissions

There were significant main effects of nicotine [$F(3,99)=3.43$, $P<.05$] and alcohol [$F(1,33)=6.45$, $P<.025$]. As shown in Fig. 6, alcohol significantly increased response omissions relative to control ($P<.05$).

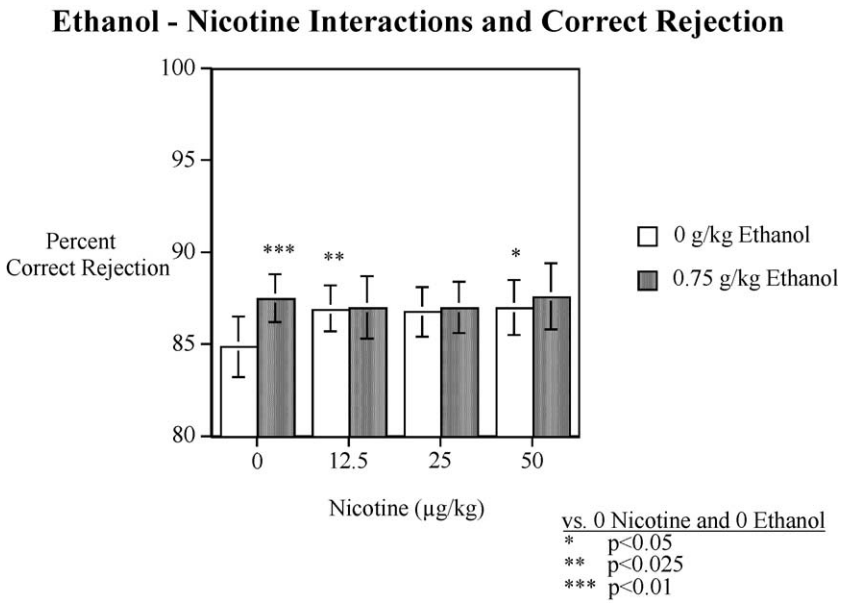


Fig. 5. Percent correct rejection for alcohol interaction with nicotine (mean ± S.E.M.). The combination of alcohol with nicotine did not significantly modify the nicotine-induced improvement in percent correct rejection.

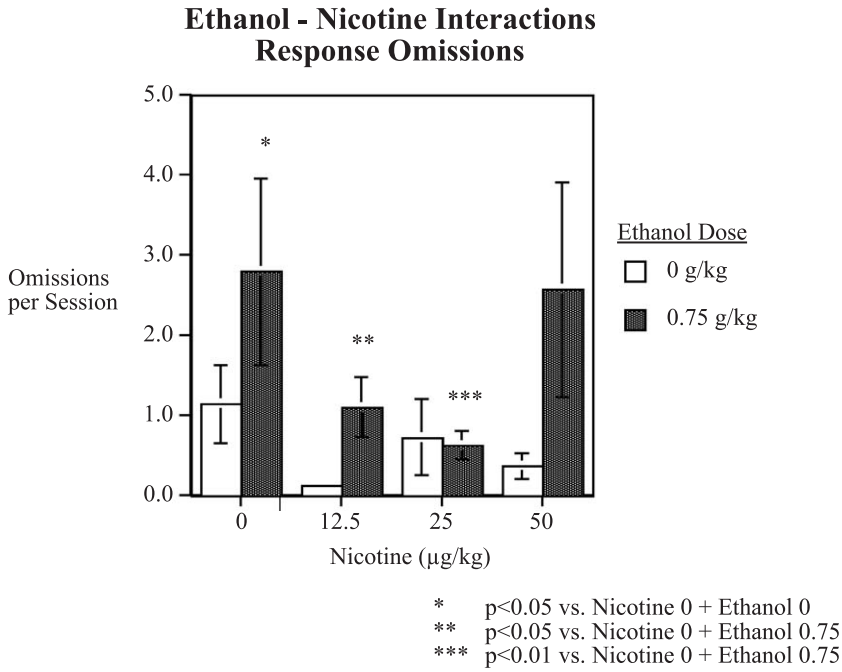


Fig. 6. Response omissions for alcohol interaction with nicotine (mean ± S.E.M.). The combination of alcohol with nicotine significantly decreased the alcohol-induced increase in response omissions.

The low 12.5 μg/kg ($P < .05$) and middle 25 μg/kg ($P < .01$) doses of nicotine significantly attenuated this effect, but the higher 50 μg/kg nicotine dose did not.

## 4. Discussion

The present study demonstrated that alcohol significantly impaired sustained attention of female rats in a visual signal detection task. The alcohol-induced attentional impairment diminished over the course of a 1-h test session. In contrast, nicotine improved sustained attention in the same task. When alcohol and nicotine were coadministered, alcohol blocked the nicotine-induced attentional improvement, even during the later part of the session when alcohol by itself did not have a significant effect on attentional function.

The present data failed to support our initial hypothesis that nicotine would reverse the alcohol-induced impairment in attention. On the contrary, it was shown that alcohol diminished the nicotine-induced attentional improvement. These results do not explain the cooccurrence of alcohol and nicotine use. One may argue that the nicotine doses selected for these experiments were not high enough to counteract the impairing effects of alcohol. This relatively low dose range of nicotine was selected based on our previous findings. The higher nicotine doses have been shown to impair performance in this task (Rezvani et al., 2002). The interactions of alcohol and nicotine might be different in humans since the psychological (or sensory) aspect of smoking plays a major role in positive effects of nicotine intake through smoking. Another possibility is that the interactions of alcohol and nicotine might be different for the reinforcing effects of these drugs and the effects of these drugs on sustained attention, as measured in the current study.

In Experiment 1, a dose of 0.75 g/kg alcohol impaired sustained attention of female rats in a visual signal detection task causing a significant reduction in percent hit response. This reduction in percent hit was most pronounced during the first 20 min of the session. The alcohol-induced deficit was still significant during the second 20 min, although the magnitude of the deficit was diminished. By the last 20-min block of the session, no alcohol-related deficit was detected. The fact that alcohol-induced impairment in accuracy is diminished in block 2 and is absent in block 3 of the session may suggest the development of acute tolerance to the effect of alcohol. Similar findings have been reported by Givens (1997) using a two-choice reaction time task. It is possible that because testing began shortly after injection of alcohol, the marked impairment in choice accuracy seen in first 20 min of the session (i.e., block 1) reflects performance deficits during the ascending limb of the blood alcohol concentration curve.

Similar to these findings, other investigators have shown that alcohol can disrupt a variety of cognitive functions including attention (Givens, 1997; Lamb and Robertson, 1987). Using a two-choice reaction time task, it has been shown that alcohol at doses of 0.75 g/kg and higher impairs ability of rats to direct and sustain attention to brief infrequent stimuli (Givens, 1997).

The alcohol effect on percent correct rejection was different from that of alcohol on percent hit. Neither dose

of alcohol showed a significant effect on percent correct rejection in low-performing group, but the lower dose of alcohol significantly decreased percent correct rejection in high-performing group. This may suggest that the high baseline accuracy group was more sensitive to the impairing effect of alcohol on this task.

Alcohol significantly impaired sustained attention by reducing percent hit accuracy when given together with the 25 μg/kg dose of nicotine. The alcohol-induced impairment was from a higher baseline performance than was seen with control injections (Fig. 4). In essence, alcohol blocked the significant improvement caused by 25 μg/kg with percent hit in the middle signal intensities.

Nicotine, at doses 12.5 and 50 μg/kg, when given alone, significantly improved attention by increasing percent correct rejection. Interestingly, alcohol at 0.75 g/kg dose also caused a statistically significant increase in percent correct rejection in the nicotine–alcohol interaction study. This was unexpected since the same alcohol dose in the first alcohol dose–effect study did not cause such an effect. It may be the case that the intermittent nicotine doses given in the second study had some carryover influence on alcohol reactivity. Unlike with percent hit, the direct combination of alcohol with nicotine did not diminish the nicotine-induced improvement in percent correct rejection. Nicotine may have enhanced performance in this task by interacting with the presynaptic nicotinic acetylcholine receptors to facilitate the release of neurotransmitters such as acetylcholine, serotonin, GABA, norepinephrine, dopamine, and glutamate (Wonnacott, 1997).

Previously, we showed that systemic administration of alcohol blocked nicotine-induced memory improvement and precipitated memory impairment when it was combined with a relatively high dose of nicotine (Rezvani and Levin, 2002). Other investigators have shown that treatment with nicotinic receptor agonists or cholinesterase inhibitors reverses alcohol-induced learning deficit (Beracochea et al., 1986; Hodges et al., 1991). It also has been shown that nicotine enhances latent inhibition and ameliorated alcohol-induced deficit in latent inhibition in mice (Gould et al., 2001). These findings along with ours suggest a functional interaction between alcohol and nicotinic systems in the brain. This interaction does not appear to be of a pharmacokinetic nature since previous works have demonstrated that neither drug influences the elimination rate of the other (Collins et al., 1988). Thus, it can be speculated that the interaction between alcohol and nicotine is of pharmacodynamic rather than pharmacokinetic origin. Indeed, both drugs have been shown to up-regulate the nicotinic receptors in the brain and modulate the release of several neurotransmitters, such as dopamine, serotonin, GABA, and glutamate, believed to be involved in cognition (Aistrup et al., 1999; Cardoso et al., 1999; DiChiara and Imperato, 1985; Museo and Wise, 1990).

In summary, these data show that alcohol, when given alone, impairs sustained attention and effectively reverses the selected components of nicotine-induced attentional improvement (i.e., percent hit). Interestingly, other components of nicotine-induced attentional improvement (i.e., percent correct rejection) are not affected by the same alcohol dose. Although significant, these effects are small. Female rats were tested in this study. It is possible that male rats may respond differently. With more specific nicotinic ligand and wider range of alcohol and nicotine dose function, further studies are warranted to further elucidate mechanism of nicotine–alcohol interactions.

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