Prenatal Alcohol Exposure Causes Attention Deficits in Male Rats

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Children with fetal alcohol spectrum disorder (FASD) are often diagnosed with attention-deficit/hyperactivity disorder (ADHD). These children show increases in reaction time (RT) variability and false alarms on choice reaction time (CRT) tasks. In this study, adult rats prenatally exposed to ethanol were trained to perform a CRT task. An analysis of the distribution of RTs obtained from the CRT task found that rats with a history of prenatal ethanol exposure had more variable RT distributions, possibly because of lapses of attention. In addition, it was found that, similar to children with FASD, the ethanol-exposed rats had more false alarms. Thus, rats with prenatal ethanol exposure show attention deficits that are similar to those of children with FASD and ADHD.

Maternal ingestion of alcohol while pregnant has teratogenic effects on offspring, identified as fetal alcohol spectrum disorder (FASD; Jones & Smith, 1973; Jones, Smith, Ulleland, & Streissguth, 1973). In addition to impairments of learning and memory (Berman & Hannigan, 2000; Driscoll, Streissguth, & Riley, 1990), a number of studies have indicated that children with FASD have attention-deficit/hyperactivity disorder (ADHD)-like symptoms (Coles, Platzman, Lynch, & Freides, 2002; Coles et al., 1997; Leth-Steenesen, Elbaz, & Douglas, 2000; Hanson & Hiscock, 1990; O’Malley & Hanson, 2002; Seidel & Joschko, 1990; Streissguth, Barr, & Martin, 1984; Streissguth et al., 1986, 1994). Children with FASD are often diagnosed with ADHD (Coles et al., 1997; O’Malley & Hanson, 2002). Teachers and parents have reported behavioral similarities between children with FASD and ADHD, and such children have similar impairments on choice reaction time (CRT) and sustained attention tasks (Coles et al., 1997; Hanson & Hiscock, 1990; O’Malley & Hanson, 2002). Detailed analyses indicate that children with FASD and ADHD are impaired on CRT and continuous performance tasks (CPT; Rosvold et al., 1956). On sustained attention RT tasks, children with FASD perform similarly to children with ADHD, and both populations perform worse than healthy children on measures of attention that include variability of RTs and increased false alarms (Coles et al., 1997; Simmons, Wass, Thomas, & Riley, 2002). These data indicate that RT performance may be a good way to evaluate the performance of rats with prenatal ethanol exposure for ADHD-like symptoms.

Because attention deficits are frequently observed in children with FASD, it is of interest to develop an animal model that could be used to explore the neurobiological substrates of these impairments. There have been few previous studies of the effects of prenatal ethanol exposure on attention in rats. In the single previous study that we are aware of, Hayne, Hess, and Campbell (1992) examined the effects of prenatal ethanol exposure on elicitation and habituation of the heart rate orienting response. They found no effect of ethanol exposure on attention. These authors noted that much of the human research in this area has focused on tasks requiring sustained attention in which subjects were encouraged to respond quickly. They hypothesized the alcohol-exposed rats might show deficits if tested with an RT task that required sustained attention. Following this suggestion, the present study used a CRT task that requires sustained attention, in combination with a novel RT analysis, to detect lapses of attention in alcohol-exposed rats.

In a recent review of the variety of impairments observed in children with ADHD, Douglas (1999) suggested that inconsistent allocation of attention and effort underlies increases in RT variability shown by children with ADHD and that ADHD symptoms were more likely to be observed on tasks that (a) require consistent and sustained allocation of effort and attention, (b) have long preparatory intervals with low event rates, (c) are unpredictable, and (d) involve extraneous stimuli. RT variability has often been suggested to be an important indicator of attention (van der Meere, Gunning, & Stemerdink, 1996). Therefore, variability in RT distributions may be an important diagnostic indicator for ADHD.

The CRT task that we have developed for use with rats emphasizes each of the four qualities emphasized by Douglas (1999) that are likely to result in the detection of ADHD-like symptoms. Our CRT task requires the rat to wait for a variable preparatory interval before onset of the imperative stimulus. In order to maximize the sustained attention and effort requirements of the task, we increased the duration of the preparatory interval across training days. Changing the preparatory time requirement in this manner...
had the added effect of increasing the duration of preparatory intervals and decreasing the overall rate of reinforcement. We also manipulated the level of extraneous stimuli by training the rats on alternate days under salient and nonsalient conditions. Finally, as is introduced below, we were able to carry out a detailed analysis of the variability of the RTs.

Leth-Steensen and coworkers (2000) have pointed out that differences between children with ADHD and healthy children on RT tasks are largely due to an abnormally large number of slow responses. These slow responses cause the RT distributions of children with ADHD to have greater positive skew than the RT distributions of age-matched controls. These authors proposed that this skew is an important empirical marker that reflects the presence of periodic lapses of attention in the responding of children with ADHD. Furthermore, they suggested that these lapses of attention can be differentiated from the ability to respond quickly. These authors argued that the peak (modal point) of the distribution of RTs is the same for children with ADHD and healthy control children, indicating that, in general, ADHD children can respond just as fast as healthy controls. However, the RT distributions of ADHD children are skewed to the right because of the more frequent occurrence of lapses of attention, which result in long RTs. These authors fitted a complex ex-Gaussian distributional model to the RT distributions of children with ADHD and healthy control children. An ex-Gaussian analysis provides independent measures of the peak and tail of the RT distribution (see the Dependent Variables section for a more detailed explanation of the ex-Gaussian analysis). This analysis indicated that the peak of the distribution was similar for ADHD and control groups but that the tail of distribution was longer for the ADHD group.

One of the most prominent aspects of ADHD is the occurrence of lapses of attention. In the present study, we used a CRT task to investigate whether rats with prenatal ethanol exposure show impairments in sustained attention similar to those observed in children with ADHD and FASD. We characterized the RT distributions using both the deviation from the mode approach and the ex-Gaussian approach used by Leth-Steensen and coworkers (2000), and compared the results from both approaches to show that they measure parallel aspects of RT distributions. Our goal was to establish a suitable animal model that allows study of the etiology of attention impairments in children with FASD.

Method

Subjects

Thirty male Sprague–Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN), weighing between 250 and 350 g at the beginning of training, were used. Fifteen of the 30 rats had prenatal ethanol exposure (see below). The rats were housed 2 per cage, and lights were on in the colony room from 7 a.m. to 7 p.m. Food was available ad libitum, and rats had 20 min access to water following the testing session. The subjects were tested 5 days a week and had full access to water on the following days. One week prior to behavioral training, the rats were placed on water restriction. Subjects used in this study were maintained in accordance with U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals (National Institutes of Health, 2002), as amended August, 2002. All experimental protocols were approved by the Institutional Animal Care and Use Committee of the University at Buffalo, The State University of New York.

Prenatal Ethanol Exposure

Timed pregnant Sprague–Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) were purchased and delivered on Gestation Day (GD) 6. To mimic the binge-drinking behavior that produces high blood ethanol concentrations in humans at risk for fetal alcohol syndrome–fetal alcohol exposure, we administered ethanol to the rats via intragastric intubation from GD 8 through GD 20. Rats were treated with a daily dose of 0 or 6 g/kg ethanol (20% [wt/vol] in 0.9% saline), except during weekends. Treatment was carried out by two intubations at 0 or 3 g/kg (5–6 hr apart; between 10 a.m. and 5 p.m.) during weekdays. A single daily dose of 0 or 4 g/kg ethanol was given during weekends. The 0 g/kg control group received the same volume of sucrose solution (30% [wt/vol] in 0.9% saline) to substitute isocalorically for ethanol. The blood ethanol concentration measured 1.5 hr after the second daily dose of ethanol was between 281 and 341 mg/dl (measured in an additional 3 pregnant rats) on GD 20. To control for the possible effect of under nutrition, we pair-fed rats in the control and ethanol-treated groups. The averaged litter sizes were 13.6 ± 0.5 (n = 5) and 341 mg/dl (measured in an additional 3 pregnant rats) on GD 20. To control for the possible effect of under nutrition, we pair-fed rats in the control and ethanol-treated groups. The averaged litter sizes were 13.6 ± 0.5 (n = 5) and 16.6 ± 0.7 (n = 5) for the control and ethanol-treated groups, respectively. There was no difference in the litter sizes between the control and ethanol-treated groups: independent t test, t(8) = 0.22, p > .05. Averaged pup weights also did not differ between these two groups: independent t test, t(135) = 0.77, p = .44. The averaged pup weights in the control and ethanol-treated groups were 6.02 ± 0.06 (n = 68) and 5.93 ± 0.08 g, respectively.

Rearing and Cross-Fostering

In the past, ethanol-treated dams have been observed to display a certain degree of negligence toward pups in the current laboratory setting. Therefore, a cross-fostering procedure was used. On Postnatal Day 1, pups were individually weighed and examined for gross physical abnormalities, and the litters were culled randomly so that there were not more than 10 male pups in each litter. The litters were then transferred to surrogate dams, which did not receive any treatment and had delivered 2 days earlier. The
litters from control dams were switched among control dams in order to control for possible effects of switching dams. Litters were weaned on Postnatal Day 21, and 3 male littermates from 10 litters—5 control litters and 5 ethanol-treated litters—were used in this experiment. The unit of analysis was the litter, thus the average of the rats from a single litter was used as a single data point.

**Apparatus**

Sixteen locally constructed experimental chambers were used. These chambers are described in detail by Richards, Mitchell, de Wit, and Seiden (1997). The chambers had stainless steel grid floors, aluminum front and back walls, Plexiglas sides and Plexiglas tops. The test panel had two water dispensers located on either side of a centrally located snout-poke hole. Stimulus lights were mounted above the two water dispensers and the center snout-poke hole. A Sonalert tone generator (Newark Inone, Chicago, IL) with a frequency of 4500 Hz was mounted above the left stimulus light. The water dispenser and stimulus lights were arranged so that they were level with the rat’s eyes when the rat’s snout interrupted an infrared beam in the center snout-poke hole. Snout poking and head entries into the water dispensers were monitored with infrared detectors. Water reinforcement was delivered to the left and right water feeders by syringe pumps (PHM-100; MED Associates, East Fairfield, VT). The experimental contingencies were programmed with the MED-PC programming language.

**Procedure**

The rats were trained to hold their snout in the center snout hole until either the left or right stimulus light was turned on. The amount of time required for the rat to hold its snout in the center snout-poke hole before the onset of the imperative stimulus (left or right stimulus lights) was called the hold time. As described below, the hold time was determined individually for each rat. After the presentation of the imperative stimulus, a head-entry response into the water dispenser associated with the stimulus light was reinforced (50 μl of 3% [wt/vol] sucrose water) if the rat’s RT was shorter than a criterion RT. If the rat’s RT was longer than the criterion RT, it did not receive a water reward. Once the hold time criterion was reached and the imperative stimulus was presented, the rat had 2 s to respond to the imperative stimulus or the trial ended (the imperative stimulus was turned off) and the response was counted as an omission.

The purpose of using a criterion RT was to selectively reinforce fast responses. The criterion RT for reinforcement was adjusted for each individual rat according to the following rules. For every two correct responses made under the criterion time limit, the time limit was reduced. For every incorrect or slow response, the limit was increased. The schedule of decrement—increment (in seconds) was 27.00, 10.00, 5.00, 2.50, 1.00, 0.89, 0.79, 0.71, 0.63, 0.56, 0.50, 0.45, 0.40, 0.35, 0.32, 0.28, 0.25, 0.22, 0.20, 0.18, 0.16, 0.14, 0.13, 0.12, 0.11, and 0.01. At the start of the session, the criterion RT was set at 0.71 s. Adjusting the criterion RT in this manner resulted in each rat receiving reinforcement on approximately three out of four responses when the correct side was chosen. Because of the adjusting nature of the procedure, the actual rate of reinforcement was the same for fast and slow rats.

The rats were tested on alternating days in either a salient condition with the houselight off, which made it easier for the rats to detect the stimulus lights, or a nonsalient condition (houselight on). Training occurred 5 days a week. Within a 2-week period, each rat received 5 days testing in the salient condition and 5 days testing in the nonsalient condition.

As was mentioned above, the onset of the imperative stimulus was contingent on the rats holding their snouts in the center snout-poke hole for a variable hold time period. An average hold time was specified for each individual rat at the start of each test session, and the criterion hold time varied around the specified average from trial to trial during the session hold time. Thus, from the animal’s perspective, the hold time was unpredictable. The hold time was cumulative; for example, if the hold time was 4 s, the rat could meet this requirement by holding its snout in the hole for 2 s on the two different occasions. The average hold time was adjusted for each test session depending on performance during the previous test session performance. If the rat completed 100 trials during the previous test session, the average hold time was increased by 0.5 s; if less than 100 trials were completed on the previous test session, the average hold time was decreased by 1.0 s.

Each test session was terminated after 30 min or 100 trials, whichever came first. The Sonalert tone generator was turned on at the beginning of each test session and remained on to indicate that the box was active. Termination of the session was indicated by offset of the tone.

Preliminary training consisted of five sessions in which the chamber was dark (salient condition), during which an autoshaping procedure was in place. In the autoshaping procedure, rats were required to make a center snout poke into the center hole to turn both the left and right stimulus lights on. Once the side stimulus lights were turned on, a response to either the left or right alternatives was rewarded. Two consecutive choices to the same side initiated a forced trial to the opposite side. If the rat did not respond to the center snout-poke hole within 2 min, the center light would flash for 30 s, and the left and right stimulus lights would turn on. A response to either side was then reinforced. After 2 weeks on the autoshaping procedure, the rats were switched to the RT task described above. Rats were trained on the RT task with a 0.1-s center hold time until they reliably completed 100 trials within 30 min, and had at least 90% correct choices.

At this point in training, the average center hold time and minimum RT criteria were adjusted as indicated above. In addition, training conditions were alternated between salient and nonsalient every day. The rats were trained for 10 weeks under these conditions. Two prenatal ethanol-treated rats were removed from the study because they were unable to learn the task.

**Dependent Variables**

The last 2 weeks of the 10-week training period were used for data analysis. This period included 5 salient and 5 nonsalient test days. For all measures except hold time and number trials completed, the data for salient and nonsalient days were analyzed separately. RT was the elapsed time from onset of the stimulus light above the left or right water dispenser to insertion of the snout into the indicated water dispenser.

False alarms were defined as the rat pulling its snout out of the center hole before the stimulus light came on and inserting its head into one of the two water dispensers. Because there were more opportunities for false alarms to occur with longer hold times, the number of false alarms was computed as a rate measure by dividing the number of false alarms for each trial by the required hold time for that trial. Because the false alarm data were strongly skewed to the right and not normally distributed, a log₁₀ transform was performed on this measure in order to normalize it for statistical analysis. Omissions were defined as trials in which 2 s elapsed without a response after the presentation of the imperative stimulus. The percent of correct choice responses was also examined. The average hold time and number of trials completed were calculated for salient and nonsalient conditions combined, as the adjustment of hold time was contingent on the number of trials completed on both salient and nonsalient test days. The mean and standard deviation for each rat over the 5 salient and 5 nonsalient sessions were determined for each of the measures described above.

The shape of the salient and nonsalient RT distributions was characterized by two different methods. In the first method, the mode was computed by grouping the RTs into 50-ms bins and computing a running frequency for bins: 0–50 ms, 50–60 ms, 60–70 ms, and so on. The midpoint of the 50-ms bin with the highest frequency of RTs provided the estimate of the mode. In order to measure the direction and degree to which the distributions were skewed, we computed the DevMode (deviation from the mode)
measure by subtracting the modal RT from the mean RT. The second method was to determine the best fitting ex-Gaussian distribution for each animal by using a curve fitting program, RTSYS version 1.0 (Heathcote, 1996). This program provided the maximum likelihood estimators for mu (mean of the Gaussian component), sigma (the standard deviation of the Gaussian component, and tau (the mean of the exponential tail of the distribution). The program also provided chi-square values that indicated the reliability of the fit of ex-Gaussian to the obtained RT data.

Data Analysis

Data for each condition (nonsalient and salient) were averaged for each rat over a period of 10 days. This resulted in a maximum of 500 RTs for both the nonsalient and salient conditions for each rat. The unit of measure for analysis was the litter, thus the average of the rats from a single litter was used as a single data point. This resulted in an n of 5 for each group. Each dependent variable was analyzed by means of a two-way within- and between-subjects analysis of variance. The within-subject factor was stimulus salience, and the between-subjects factor was prenatal exposure to ethanol. If there was a significant effect of prenatal exposure to ethanol, or an interaction between prenatal exposure to ethanol and saliency, an independent samples t test was done separately on the salient and nonsalient conditions, respectively. All four plots indicate differences in the shapes of the distributions between the salient and nonsalient conditions. There was a significant effect of stimulus saliency, an interaction between prenatal exposure to ethanol and saliency, and the reaction time distribution of the prenatal ethanol-exposed litter had a longer tail than that of the control litter.

Results

The RT distributions for two litters, one with prenatal ethanol treatment and a control litter with a similar modal RT, are shown in the top row of Figure 1. This figure indicates clear qualitative differences in the shapes of the distribution between the litters given prenatal ethanol exposure and control litters. The RT distributions of the litters that received prenatal ethanol treatment are more variable and have longer tails. There are also clear qualitative differences in the shape of the distributions between the salient and nonsalient conditions. The RT distributions of both litters with prenatal ethanol treatment and control litters were slower and more variable in the nonsalient condition. The differences in the RT distributions that were due to prenatal exposure to ethanol and the salient–nonsalient conditions are quantitatively characterized below.

Mean RT

There was no significant effect of prenatal ethanol treatment on mean RT. There was a significant effect of stimulus saliency, \( F(1, 8) = 43.25, p < .001 \), with the nonsalient condition slower than the salient condition. There was no interaction between prenatal ethanol treatment and stimulus saliency (see Table 1).

Standard Deviations

The standard deviation of the prenatal ethanol-treated group was significantly greater than that of the control group, indicating more variable RTs in the prenatal ethanol exposure group, \( F(1, 8) = 11.99, p < .01 \). Follow-up independent samples t tests showed that there was an effect of prenatal ethanol treatment in both the nonsalient, \( t(8) = 2.72, p < .05 \), and salient, \( t(8) = 3.12, p < .05 \), conditions. There was a significant effect of stimulus saliency, \( F(1, 8) = 19.01, p < .01 \), with the nonsalient condition more variable than the salient condition. There was no interaction between prenatal ethanol treatment and stimulus saliency (see Table 1).

Mode

There was no significant effect of prenatal exposure to ethanol on modal RT. There was a significant effect of stimulus saliency, \( F(1, 8) = 21.73, p < .01, \) with the nonsalient condition slower than the salient condition. There was no interaction between prenatal exposure to ethanol and stimulus saliency (see Table 1).

DevMode

The DevMode of the prenatal ethanol-exposed group were significantly greater than that of the control group, indicating that the RTs for the prenatal ethanol-exposed group were skewed further to the right than the RTs for the control group, \( F(1, 8) = 8.26, p < .05 \). Follow-up independent samples t tests showed that the effect of prenatal exposure to ethanol was significant under both the salient and nonsalient conditions. There was a significant effect of stimulus saliency, \( F(1, 8) = 32.79, p < .001 \), with the DevMode being larger in the nonsalient condition. There was no interaction between prenatal exposure to ethanol and stimulus saliency (see Table 1).

Ex-Gaussian Fits

The bottom row of Figure 1 shows the best fitting ex-Gaussian distributions for the two litters shown in the top row of Figure 1.
As was the case for the obtained RT distribution in the top row, the bottom row of this figure indicates that there are clear qualitative differences in the shapes of the best fitting ex-Gaussian distributions of the litters given prenatal ethanol treatment and control litters. The ethanol-treated litters have lower peaks and longer tails. There are also clear qualitative differences between the salient and nonsalient conditions. However, the ex-Gaussian was found to be a poor fit to many of the distributions obtained with litters in this study; a poor fit was characterized by a significant chi-square value, indicating that the estimated ex-Gaussian distribution was significantly different from the obtained distribution. For the prenatal ethanol-treated litters, significant chi-square values were obtained for three of five litters in the salient condition and all five litters in the nonsalient condition. For the control litters, significant chi-square values were obtained for all five litters in the salient condition and all five litters in the nonsalient condition. Previous studies have used the data from subjects with obtained distributions that were significantly different from the ex-Gaussian distribution, with the assumption that although ex-Gaussian analysis did not effectively fit the data, it still provided an important indicator of distribution shape (Leth-Steensen et al., 2000). In the present study, we were interested in comparing our mode and DevMode measures to those obtained from the ex-Gaussian analysis. Elimination of the data from litters that poorly fit the ex-Gaussian distribution would have made this comparison difficult to interpret given the small number of remaining litters, so we also included all of the litters in the analysis.

**Mu**

There was no significant effect of prenatal ethanol treatment on mu. There was a significant effect of stimulus saliency, $F(1, 8) = 114.32, p < .001$, with the nonsalient condition resulting in larger mu values. There was no interaction between prenatal ethanol treatment and stimulus saliency (see Table 1).

**Sigma**

There was no significant effect of prenatal ethanol treatment on sigma. There was a significant effect of stimulus saliency, $F(1, 8) = 27.44, p < .001$, with the value of sigma being larger in the nonsalient condition. There was no interaction between prenatal ethanol treatment and stimulus saliency (see Table 1).

**Tau**

The estimated value of tau was greater for the prenatal ethanol-treated group than the control group, $F(1, 8) = 7.29, p < .05$. Follow-up $t$ tests showed that there was an effect of prenatal ethanol treatment in both the nonsalient and salient conditions. There was a significant effect of stimulus saliency, $F(1, 8) = 41.63, p < .001$, with the nonsalient condition estimate of tau being larger than the salient condition estimate of tau. There was no interaction between prenatal ethanol treatment and stimulus saliency (see Table 1).

**False Alarms**

The prenatal ethanol-treated litters had significantly more false alarms than the control group under both the salient and nonsalient conditions, $F(1, 8) = 8.69, p < .05$. Follow-up $t$ tests showed that there was an effect of prenatal ethanol treatment in both the nonsalient and salient conditions, with the ethanol-treated group having a higher rate of false alarms than controls in both conditions. There was also a significant effect of stimulus saliency, $F(1, 8) = 41.03, p < .001$, with the nonsalient condition having a higher rate of false alarms than the salient condition. There was no interaction between prenatal ethanol treatment and stimulus saliency (see Table 1).

**Omissions**

The mean ($\pm$ SEM) of the omissions for the prenatal ethanol-treated group on salient and nonsalient days were 16.40 ($\pm$ 3.33) and 35.53 ($\pm$ 7.25), respectively. The mean ($\pm$ SEM) of the omissions for the control group were 16.40 ($\pm$ 3.33) and 28 ($\pm$ 2), respectively. There was no significant effect of prenatal ethanol treatment on omitted trials. The rats made significantly more omissions in the nonsalient condition compared with the salient condition, $F(1, 8) = 15.49, p < .01$. There was no inter-

### Table 1

<table>
<thead>
<tr>
<th>Variable and group</th>
<th>Condition</th>
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<tr>
<td></td>
<td>Salient</td>
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<td>Mean response time (ms)</td>
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<tr>
<td>Mean standard deviation (ms)</td>
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<tr>
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<td>False alarms</td>
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<tr>
<td>Control</td>
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</table>

*Note. DevMode = deviation from the mode.
* $p < .05$, ethanol-treated group significantly different from corresponding control group.
† $p < .05$, significant effect of stimulus salience.
action between saliency and prenatal ethanol treatment on the number of omissions (see Table 1).

**Percent Correct**

The mean (± SEM) percent correct responses for the prenatal ethanol-treated group on salient and nonsalient days were 98.9 (± 0.14) and 96.76 (± 0.97), respectively. The mean (± SEM) percent correct responses for the control group on salient and nonsalient days were 99.39 (± 0.22) and 98.54 (± 0.26), respectively. There was no significant effect of prenatal ethanol treatment on percent correct. The rats made significantly more correct responses in the salient condition compared with the nonsalient condition, F(1, 8) = 13.13, p < .01. There was no interaction between saliency and prenatal ethanol treatment on the number of omissions (see Table 1).

**Hold Time and Trials Completed**

There was no significant effect of prenatal treatment on the average hold time, t(8) = -2.04, p = .076. The mean (± SEM) hold times for the ethanol-exposed and controls were 2.31 (± 4.23) s and 3.71 (± 0.64) s, respectively. As would be expected because the hold time criteria were adjusted so that each rat completed 100 trials, there was no effect of prenatal ethanol treatment on the number of trials completed. The mean (± SEM) number of trials completed for the ethanol-exposed and control groups were 91.37 (± 1.57) and 93.77 (± 1.17), respectively.

**Discussion**

The results indicate that prenatal ethanol-exposed adult rats have a variety of impairments in attention that are similar to impairments observed in children with FASD and ADHD. First, rats with prenatal exposure to ethanol had more variable RTs and tended to have slower mean RTs (although this latter difference did not reach statistical significance). These results are similar to what has been found in children with FASD and ADHD tested with CRT and CPT tasks. Children with FASD and/or ADHD have significant differences in RT variability (Coles et al., 2002; Misky, Pascualvaca, Duncan, & French, 1999; Seidel & Joschk, 1990). Slower mean RTs are sometimes (Seidel & Joschk, 1990; Streissguth et al., 1986, 1994), but not always (Coles et al., 1997; Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998), found in children ADHD and FASD. Second, rats with prenatal exposure to ethanol had significantly more false alarm responses. Children with FASD and ADHD also show more false alarms when tested on sustained attention tasks (Coles et al., 1997; Nelson & Hiscock, 1990).

One problem, which may affect the interpretation of the results, is the lack of an unhandled control group in order to ensure that the sucrose control offspring were behaving normally and that the alcohol-exposed offspring were impaired. It is possible that the impairments reported in the prenatal alcohol offspring are actually conservative because the sucrose control offspring were exhibiting some degree of impairment caused by handling stress. Conversely, it is possible that handling causes consequences in the offspring that are reversed in the prenatal alcohol offspring. Without an unhandled control group, it is not possible to determine whether either of these possibilities occurred. However, the present results clearly indicate that the ethanol-exposed adult rats tested in this study were impaired relative to sucrose control rats. Future studies are needed to examine the results obtained using handled ethanol-exposed and sucrose control groups and an unhandled control group.

**Increased Variability of RTs**

It has been suggested that children with ADHD are generally capable of responding as fast as healthy children but that they have more frequent lapses of attention that result in more frequent long RTs (Douglas, 1999; Leth-Steensen et al., 2000). These authors reported that the modal points of RT distributions generated by children with ADHD were not different from those of controls, indicating that they generally respond just as fast as healthy control children. However, the tails of the RT distributions in children with ADHD were more skewed to the right, as a result of more frequent lapses of attention. These lapses were reflected in longer mean RTs and greater variability as indicated by larger standard deviations. However increases in the mean and standard deviation of RTs do not necessarily indicate lapses of attention. For example, an overall slowing of RTs may also produce increases in mean and standard deviation. In order to demonstrate lapses in attention, the actual shape of the RT distribution needs to be quantitatively characterized to show that the mode of the distribution is relatively unchanged, whereas the length of the tail is increased. As was described in the introduction, Douglas (1999) and Leth-Steensen et al. (2000) used an ex-Gaussian analysis to quantitatively characterize the RT distributions of children with ADHD. In the present study, we quantitatively characterized the shape of the distributions in two ways. First, we used the same ex-Gaussian analysis that Leth-Steensen et al. (2000) used, and then we used a simpler DevMode analysis that we had previously developed (Sabol et al., 2003) to quantitatively describe the shape of the RT distribution.

The ex-Gaussian and the DevMode analysis identified similar differences in the shape of RT distributions between rats with and without prenatal ethanol exposure. In the ex-Gaussian analysis, mu indicates the location of the mean of the Gaussian component of the distribution, which is thought to reflect response speed on trials when the subject is attending. Similarly, in the DevMode, the modal RT is used to indicate the response speed on trials when the subject is attending. As is shown in Table 2, there was a strong correlation between these two measures (0.83), indicating that both measures provided parallel estimates of response speed although the mu values were smaller than the mode values (see Table 1). Although prenatal ethanol exposure had no effect on mode or mu,

<table>
<thead>
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<td><strong>Correlations Between Ex-Gaussian Analysis and Deviation</strong></td>
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<td>Mean response time (ms)</td>
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** p < .01.
these two measures were significantly larger in the nonsalient condition compared with the salient conditions in both control and prenatal ethanol-exposed rats, indicating that decreasing stimulus saliency resulted in slowed response times.

The ex-Gaussian analysis measured the tail of the distribution with tau (estimated mean of the exponential component of the distribution), whereas the deviation from the mode approach used the average DevMode to measure the tail of the distribution. As is shown in Table 2, there was a strong correlation between tau and DevMode (0.97), indicating that both measures provided parallel estimates of the size of the tail, although the absolute tau values were larger than the DevMode values (see Table 1). Both prenatal ethanol exposure and decreasing stimulus saliency significantly increased the values of tau and DevMode.

Sigma is an estimate of the standard deviation of the Gaussian component of the ex-Gaussian distribution. Table 2 shows that sigma was moderately correlated with the mean and mode measures but was not correlated with the two measures of variability (standard deviation and DevMode).

There is no analog for this measure in the deviation from the mode analysis. Sigma was not altered by prenatal ethanol exposure but was increased when stimulus saliency was decreased.

The high correlations between the mode and mu, as well as between DevMode and tau (see Table 2) indicate that the ex-Gaussian and DevMode approaches were measuring similar characteristics of the RT distribution. However, the DevMode approach has several advantages over ex-Gaussian approach. First, the ex-Gaussian approach requires using a complex curve-fitting procedure to fit the data to a theoretical distribution, which in the present study was found to provide poor fits to the distributions of many of the subjects. Second, the interpretation of the ex-Gaussian analysis is difficult because it is questionable whether the processes underlying the obtained RT distribution actually involved Gaussian or exponential distributions. In contrast, the DevMode approach involves simple computations and makes no assumptions about the shape of the distribution. The interpretation of the DevMode approach is straightforward: The mode indicates the location of the most frequently occurring RT, and the DevMode measure indicates the size and direction of the tail of the distribution.

Taken together, the results from the ex-Gaussian and DevMode analyses all indicate that prenatal ethanol exposure increased variability of the RT distributions. Although the mean and standard deviation were shown to be sensitive to the effects of prenatal ethanol treatment and saliency, the ex-Gaussian and DevMode approaches provide more information about the nature of the observed differences. These measures indicated that ethanol-exposed rats were in general able to react as quickly as the control rats (mu and mode), but that the distributions of ethanol-exposed rats were skewed to the right (tau and DevMode), perhaps as a result of more frequent lapses of attention.

**Impairments of Sustained Effortful Attention and Response Inhibition**

In the present study, by adjusting each rat’s preparatory hold time across sessions, we were able to maximize the amount of time the each rat was required to sustain attention and still complete the 100-trial session. In general, children with ADHD are more impaired on tasks that have low event or reinforcement rates and that require sustained effortful attention (Douglas, 1999; Sergeant, Osterlaan, & van der Meere, 1999). It is likely that the adjusting hold time requirement contributed to the impairments observed in fetal ethanol-treated rats. In addition to increased RT variability indicating lapses of attention, rats with prenatal exposure to ethanol also had more false alarms than control rats. A false alarm was defined as the rat pulling its snout out of the center hole and inserting its head in one of the two feeders in absence of the imperative stimulus. In these highly motivated water deprived rats, early responses may reflect poor response inhibition. High rates of false alarms on CRT tasks are also observed in children with FASD and ADHD. In addition, behavioral inhibition impairments have been reported in children with ADHD on go/no-go tasks, particularly when there are long intervals between each trial (van der Meere, Steiner, & Gunning, 1995; van der Meere, Vreeling, & Sergeant, 1992).

**Impairments in Learning and Memory**

Up to this point, we have emphasized the similarity of the impairments observed in rats with prenatal exposure to ethanol to those of children with ADHD; however, Coles et al. (1997) have reported significant differences in neurocognitive and behavioral characteristics between children with ADHD and FASD. They found that in ADHD, children exhibited greater deficits on tests of attention. In addition, children with FASD often (but not always) have learning and memory impairments that are not typically found in children with ADHD. Children with FASD often have lower IQs than healthy children, whereas ADHD children do not (Jones et al., 1973). Specifically, children with FASD often have deficits in short-term, spatial, and verbal memory (Hamilton, Kodituwakku, Sutherland, & Savage, 2003; Olson et al., 1998; Uecker & Nadel, 1996, 1998); reversal learning (Kodituwakku, May, Clericiuzio, & Weers, 2001); habituation (Streissguth, Barr, & Martin, 1983; Streissguth et al., 1984); and executive function (Kodituwakku, Kalberg, & May, 2001; Olson et al., 1998). Similarly, animals with prenatal exposure to ethanol also display learning and memory deficits in spatial and reversal learning (Berman & Hannigan, 2000; Blanchard, Riley, & Hannigan, 1987; Gabriel, Johnston, & Weinberg, 2002; Westergren, Rydenhag, Bassen, Archer, & Conradi, 1996; Zimmerberg, Mattison, & Riley, 1989), passive avoidance (Abel, 1979; Clausing, Ferguson, Holson, Allen, & Paule, 1995; Lochry & Riley, 1980), and delay-dependent memory tasks (Nagahara & Handa, 1997). Because the impairment in learning and memory may impact the attention process, rats exposed to prenatal ethanol may be a poor model of ADHD because of learning impairments that are not observed in children with ADHD. Nonetheless, a quantitative analysis of RTs in rats as described in the present study appears to be a suitable behavioral model for the study of specific impairments in attention, such as the lapses of attention and problems in sustained attention often found in children with FASD and ADHD. In addition, rats exposed to ethanol prenatally appear to be an excellent model for the study of attention problems in children with FASD because they have both ADHD-like symptoms and learning and memory impairments similar to those found in children with FASD.
Despite of the aforementioned differences, attention problems in FASD and ADHD may have a common underlying neural basis. Abnormalities in the mesolimbic dopamine system have been proposed to be the underlying neural mechanism for ADHD (Davids, Zhang, Tarazi, & Baldessarini, 2003). Research has shown that prenatal ethanol-exposed animals have abnormalities in the function of the mesolimbic dopamine system. For example, prenatal exposure to ethanol causes persistent reduction in the activity of dopaminergic neurons in the ventral tegmental area (Xu & Shen, 2001). Others have reported that prenatal exposure to ethanol causes reductions in the number of dopamine receptors in the frontal cortex and striatum and a decrease in dopamine uptake sites (Druse, Tajuddin, Kuo, & Connerty, 1990; Lucchi, Covelli, Petkov, Spano, & Trabucchi, 1983; Lucchi, Covelli, Sspano, & Trabucchi, 1984; Nio, Kogure, Yae, & Onodera, 1991; Randall & Hannigan, 1999). In addition, the attention problems of children with FASD and ADHD are ameliorated by stimulants (Morrow, Hannigan, & Kapatos, 1999; Xu & Shen, 2001). Abnormalities in the function of the mesolimbic dopamine system in rats described in the present study may be useful to study the etiology and effective pharmacological treatment of ADHD symptoms in children with FASD or those with ADHD children.

In summary, we have developed a behavioral test procedure that identifies ADHD-like symptoms in rats with prenatal exposure to ethanol. First, we determined that the RT distributions of prenatal ethanol-exposed rats were more skewed to the right than control rats but that the modal RT of the distribution was unchanged. Similar changes in the shape of RT distributions have been observed in children with ADHD. The extended tail of RT distributions generated by these children and by prenatal ethanol-exposed rats in this study is thought to reflect more frequent long RTs that result from lapses of attention. Second, we determined that prenatal ethanol-exposed rats had more false alarm responses than controls. Children with FASD and ADHD also have more false alarms on CPT and CRT tasks. The increase in the number of false alarms may reflect poor behavioral inhibition. Results from previous studies suggest that these ADHD-like symptoms in prenatal ethanol-exposed rats may also be mediated by common neural substrates that underlie attention problems in humans with ADHD. Of particular interest is the dopaminergic system, which is found to be impaired in rats prenatally exposed to ethanol (Shen, Hannigan, & Kapatos, 1999; Xu & Shen, 2001). Abnormalities in the dopaminergic system are also thought to contribute to ADHD symptoms in humans. Therefore, the behavioral assay system in rats described in the present study may be useful to study the etiology and effective pharmacological treatment of ADHD symptoms in children with FASD.

References


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