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Impaired Alternation Test Performance in Adult Rats Following Prenatal Alcohol Exposure

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ZIMMERBERG, B., S. MATTSON AND E. P. RILEY. *Impaired alternation test performance in adult rats following prenatal alcohol exposure.* PHARMACOL BIOCHEM BEHAV 32(1) 293–299, 1989.—The effects of prenatal exposure to ethanol on an alternation test were examined in adult Long Evans rats from three prenatal treatment groups: prenatal alcohol exposed (35% ethanol-derived calories, 35% EDC), nutritional control (0% ethanol-derived calories, 0% EDC) or standard control (lab chow, LC). Subjects were trained to alternate presses on levers to the left and right of a center food trough. Prenatal treatment did not affect the acquisition of this spatial alternation task. However, during the asymptotic performance phase of the task, subjects prenatally exposed to alcohol received fewer rewards and made more errors compared to the two control groups, which did not differ from each other. Even when test sessions were limited to 10 min, performance deficits in the 35% EDC group persisted. When visual cues were made available above the correct bar in a second experiment, performance deficits in alcohol-exposed subjects were no longer apparent. Marked sex differences were also noted in this task: males received more reinforcements, but also made more errors. Prenatal alcohol exposure may disrupt the normal development of behavioral laterality subserving position preferences, and this disruption may partly explain why performance of some spatial tasks is particularly sensitive to the effects of prenatal alcohol exposure.

Alcohol Cerebral laterality Alternation test Fetal Alcohol Syndrome

HYPERACTIVITY and learning impairments are now well-documented behavioral consequences of prenatal alcohol exposure both in humans and in animal models of fetal alcohol exposure (29,36). Similar types of behavioral dysfunctions have also been suggested to be associated with altered cerebral dominance (12, 13, 22) and nonstandard cerebral dominance has been related to a variety of types of early brain damage (22). It has been suggested that the slower growth of dominant structures may make them more vulnerable to prenatal insult (14). Thus, it is possible that alcohol may be disrupting the normal pattern of left-right hemispheric maturation in utero. One early sign of alcohol-induced altered lateralization may be that neonates born to heavily-drinking mothers make significantly more head turns to the left (26), while normal human neonates have a marked tendency to turn their heads to the right (37). Head position has been found to be correlated with later handedness (30), and children diagnosed as having Fetal Alcohol Syndrome have been noted to have a higher than expected incidence of left-handedness (Streissguth and Little; Tlucak and Ernhart; unpublished observations).

In animal models of behavioral laterality, consistent side (left-right) preferences have been detected in T-mazes, Dashiell mazes, open fields, two-lever operant chambers and rotometers (7–10, 16, 39). However, a small percentage (usually less than 10%) of rats lack a clear spatial bias on a variety of tasks (7, 9, 18, 39). Rats without side preferences, selected by T-maze or rotation tests, have difficulty learning left-right discrimination tests (18,40) and it has been suggested that performance of spatial tasks may require an optimal degree of intrinsic cerebral asymmetry (18). Recently, we reported that prenatal alcohol exposure reduces side preference behavior in both juvenile and adult rats (41,42). Alcohol-exposed offspring at both ages exhibited less side preference and switched more frequently between sides.

If prenatal alcohol exposure alters the standard pattern of hemispheric lateralization, then tasks requiring spatial discriminations should be particularly sensitive to alcohol's disruptive effects. Recently, three-week-old alcohol-exposed offspring were found to exhibit impaired performance in a Morris water task (4). There is also some indirect evidence that prenatal alcohol exposure may differentially impair performance on spatial tasks. For example, performance deficits were detected in a Y-maze, but not in a straight alley, in pups exposed to alcohol in utero (2). However, since the type of testing apparatus was confounded with differences in alcohol administration procedure and age of the subjects, this evidence is inconclusive. Similarly, when two- to seven-day-old rat pups prenatally exposed to alcohol had to choose between left and right to find their littermates, their performance was impaired. A week later, they performed as well as control pups in a more complex homing task that did not involve a left-right discrimination (11). Again, this experi-

ment involved an age as well as a task difference, so the question of a differential impairment of spatial discrimination was not directly addressed.

The following experiments were designed to assess the effect of prenatal alcohol exposure on the acquisition and performance of a left-right alternation test in adult offspring. Subjects with known side preferences were tested to determine any relationship between altered behavioral laterality and deficits on a spatially-cued task.

GENERAL METHOD

Subjects

Offspring for testing were generated from Long Evans rats (Blue Spruce Farms, Altamont, NY). After acclimation to the laboratory, naive, nulliparous females were placed individually with a male in the late afternoon, and the bedding under their cages examined for the presence of a vaginal plug the next morning (Gestational Day 1). If a plug was detected, the female was weighed, individually housed in a standard plastic breeding cage, and assigned to one of the three treatment groups. Females in the Lab Chow (LC) control group had continuous access to standard lab chow and water throughout their pregnancies. Pregnant females in the other two groups were treated identically to LC females on Gestational Day (GD) 1 to 5. Starting on GD 6, pregnant females in the alcohol treatment condition were given a liquid diet consisting of ethanol, chocolate Sustacal (Mead Johnson), vitamins (Diet Fortification Mixture, ICN Nutritional Biochemicals, 0.3 g/100 ml), minerals (Salt XIV mixture, ICN Nutritional Biochemicals, 0.5 g/100 ml), and water. This diet provided 35% of the total caloric content as ethanol (35% ethanol-derived calories, 35% EDC). In the nutritional control group, pregnant females on GD 6 began receiving a similar liquid diet except that the ethanol was replaced isocalorically with sucrose (0% ethanol-derived calories, 0% EDC). Both diets provided 1.3 kcal/ml. A pair-feeding procedure was utilized to control for caloric intake. Each female in the 0% EDC group was yoked to one of the 35% EDC females and fed the amount consumed by that 35% EDC female, on a ml/kg body weight basis, for each specific day of pregnancy. Thus, each yoked pair received the same relative volume of diet (ml/kg) and hence the same number of calories on a body weight basis; the only difference being the presence or absence of alcohol.

On GD 20, the liquid diets were replaced by continuous access to lab chow and water and the breeding cages checked 3 times daily for births. Following parturition, pups were weighed, measured, and inspected for any obvious structural abnormalities. Litters were culled randomly to 10 offspring per litter (5 females and 5 males whenever possible). Litters were only handled at 5-day intervals to change the bedding. At 21 days of age, litters were weaned and weanlings were housed with a same sex littermate in the main colony.

The subjects for this experiment were all randomly selected from offspring whose side preference had previously been assessed (42). This side preference assessment included training the subjects to press a center level for food reward on a continuous reinforcement schedule for one week, free choice of left or right lever responding for a second week, and 2 days of extinction schedule. Subjects were not tested for at least two weeks before the start of this experiment, but were maintained at 85% of their original body weight.

Apparatus

Behavioral testing was conducted in 5 operant chambers (Coulbourn Instruments) encased in research chests. The chambers were first fitted with a center lever placed 15 cm above a recessed center food cup, and later with 2 levers 3.5 cm to the right or left of the food cup. The food cup was connected to a pellet dispenser which delivered 45 mg food pellets (Noyes). The side levers were each 2.5 cm from the floor and 1.5 cm from the side walls. A 28-V light was situated 3 cm above each lever. A 28-V houselight, centered above the food hopper, served as a cue for the start and end of the sessions. The boxes were interfaced with a microprocessor which recorded responses and controlled the delivery of reinforcements (Med Associates).

EXPERIMENT 1

Subjects

Male and female subjects from each of the three prenatal treatment groups (35% EDC, 0% EDC and LC) were tested (n's=6–7 per sex per prenatal treatment group). Each subject represented an independent litter. At the start of this experiment, the mean age was 168 days.

Procedure

Subjects were given 3 days of daily 30-min sessions during which only a center lever was available, and all responses were rewarded. This retraining was conducted to reverse any confounding effects of prior side preference assessment or extinction testing. During the next two weeks of testing, the operant boxes were modified so that two levers were now available, one to the right and one to the left of the center food trough. The cue lights above each lever were not illuminated. Subjects were then tested in 30-min sessions, five days a week, on an alternation test. This test required the subject to alternate left and right responses to receive reward. Each correct response was rewarded and recorded; the number of reinforcements was thus the same as the number of correct responses. Incorrect responses were recorded as errors. During the fourth week of testing, sessions were shortened to 10 min daily, and subjects tested for six days on the alternation test. The session length was changed because subjects were noted to be making about 50% of their total responses during the first ten minutes. Since 35% EDC subjects are known to have deficits in response inhibition (29), the results in the longer session may have been confounded by a differential effect of prenatal treatment on responding after satiety.

Data Analyses

Results were analyzed by repeated measures analysis of variance (ANOVA), with Huynh-Feldt corrections for interactions involving within-subject factors. Prenatal Treatment and Sex were between-subject factors and Day the within-subject factor. Scores were transformed when there were unequal variances across days (BMDP7D). Significant main effects were analyzed by multiple comparisons among means (Newman-Keul's test) and significant interactions between factors were analyzed by simple main effects followed by orthogonal contrasts.

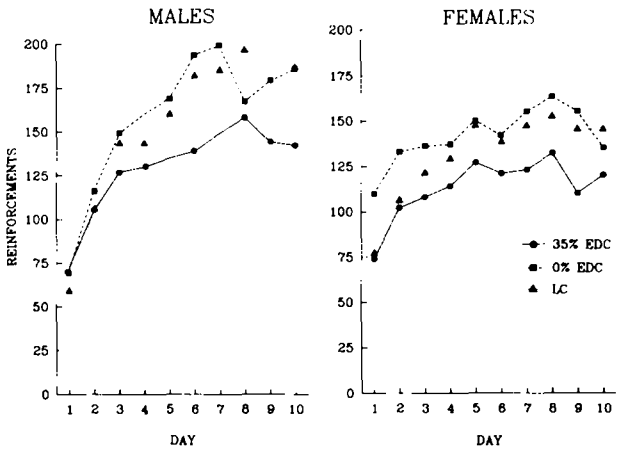

FIG. 1. Mean number of reinforcements obtained during each 30-min session for 10 days of responding on an alternation schedule for three prenatal treatment groups (35% EDC, 0% EDC and LC) for males (left panel) and females (right panel). Data points represent 6–7 subjects per treatment group.

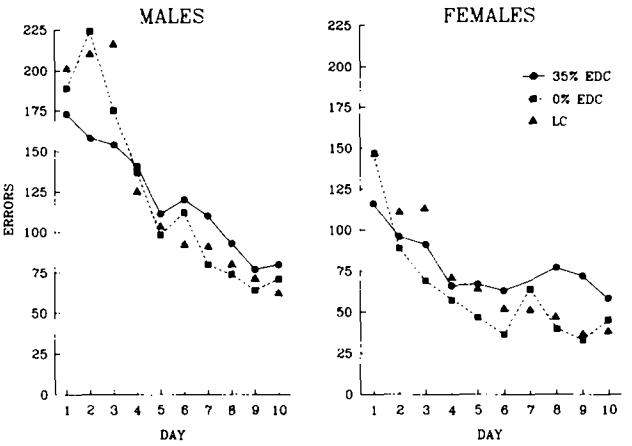

FIG. 2. Mean number of errors made during each 30-min session for 10 days of responding on an alternation schedule for three prenatal treatment groups (35% EDC, 0% EDC and LC) for males (left panel) and females (right panel). Data points represent 6–7 subjects per treatment group.

RESULTS

Maternal and Pup Data

The maternal and pup data are based on 34, 36 and 32 litters from the 35% EDC, 0% EDC and LC groups, respectively, from which the subjects were randomly selected. During pregnancy, the maternal percent weight gain was 29.46% for the 35% EDC dams, 30.05% for the 0% EDC dams, and 38.17% for the LC dams. Analysis of variance (ANOVA) revealed a significant effect of Prenatal Treatment, $F(2,96)=10.76$, $p<0.001$, and subsequent comparisons (Newman-Keul's tests) indicated that both the 35% EDC and the 0% EDC groups differed from the LC group (p's<0.01), but did not differ from each other. The mean daily alcohol consumption by the 35% EDC dams was 12.76 g/kg per day.

The litter mean birth weights for the 35% EDC litters were 5.27 g for the males and 4.73 g for the females; for the 0% EDC group they were 5.54 g for the males and 5.40 g for the females, and for the LC group they were 5.94 g for the males and 5.48 g for the females. An ANOVA of these weights indicated significant effects of Sex, $F(1,192)=10.79$, $p<0.01$, with males weighing more than females, and Prenatal Treatment, $F(2,192)=35.77$, $p<0.001$. Comparisons among means (Newman-Keul's tests) indicated that 35% EDC pups weighed less than the two control groups (p's<0.01), and that the 0% EDC pups weighed less than the LC pups ($p<0.05$).

At the time of testing, there were no longer any significant differences in body weight among the prenatal treatment groups; mean weights were 450.6 g for 35% EDC males, 288.0 g for 35% EDC females, 450.0 g for 0% EDC males, 284.3 g for 0% EDC females, 470.4 g for LC males and 282.2 g for LC females. The ANOVA indicated only a significant effect of Sex, $F(1,34)=268.22$, $p<0.001$.

Behavioral Results

During the first two weeks of daily 30-min tests, all prenatal treatment groups learned to alternate responses to receive food reward. There were two phases of this test: an initial acquisition phase and an asymptotic performance phase. Asymptotic performance was defined as no more than a 10% change in response rate from the previous day. Alcohol-exposed subjects, regardless of sex, initially appeared to be able to acquire this task as well as control subjects, but received fewer rewards and made more errors during the asymptotic performance phase.

Figure 1 shows the mean number of reinforcements (e.g., "correct" responses) obtained during the first 10 days of testing for males and females in the three prenatal treatment groups. There was a significant interaction between Prenatal Treatment and Day, $F(18,306)=1.77$, $p<0.05$. The 35% EDC group differed significantly from the control groups on Days 3 through 10 (p's<0.01), receiving fewer reinforcements on these days. The two control groups, in contrast, only differed on Days 1 and 2 (p's<0.01), with the 0% EDC group receiving more reinforcements on these days. There was also a significant interaction between Sex and Day, $F(9,306)=7.44$, $p<0.001$. Males received more reinforcements than females on Days 1, 3, 4, and 6 through 10 (p's<0.02). There was no Prenatal Treatment × Sex interaction.

Figure 2 shows the number of errors over 10 days of testing for males and females in the three prenatal treatment groups. It was necessary to perform a log transformation of these scores to stabilize the variance prior to the analysis. There was a significant interaction between Prenatal Treatment and Day, $F(18,306)=2.11$, $p<0.05$. Alcohol-exposed subjects made more errors on Days 6, 8, 9, and 10 compared to the two control groups (p's<0.02), which did not differ on any day. There was also a significant main effect of Sex, $F(1,34)=27.98$, $p<0.001$, with males making more errors than females. There were no Prenatal Treatment × Sex interactions.

Ten-Minute Sessions

In the fourth week of testing, test sessions were shortened

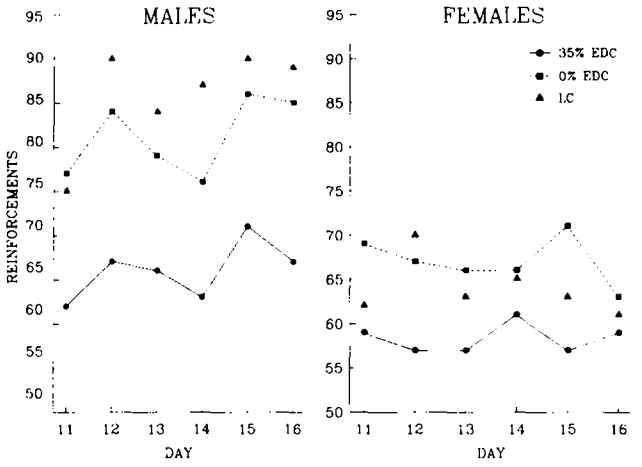

FIG. 3. Mean number of reinforcements obtained during each 10-min session for 6 days of responding on an alternation schedule for three prenatal treatment groups (35% EDC, 0% EDC and LC) for males (left panel) and females (right panel). Data points represent 6–7 subjects per treatment group.

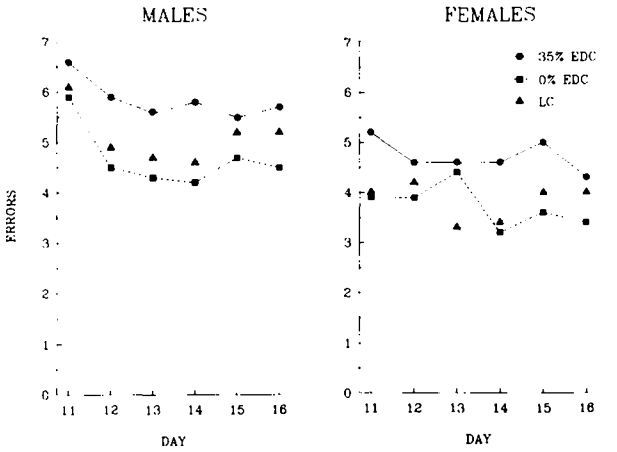

FIG. 4. Mean number of errors made during each 10-min session for 6 days of responding on an alternation schedule for three prenatal treatment groups (35% EDC, 0% EDC and LC) for males (left panel) and females (right panel). Data points represent 6–7 subjects per treatment group.

to ten minutes. This schedule change did not eliminate the main significant effects of prenatal treatment, although it did strengthen the suggestion seen in the second week that 35% EDC subjects were impaired during an asymptotic performance phase of this alternation test. As seen in Fig. 3, male and female 35% EDC subjects continued to obtain fewer reinforcements (e.g., "correct" responses) over the next six days of testing. Prenatal Treatment had a significant effect on the number of reinforcements, $F(2,34)=3.56$, $p<0.05$, with the 35% EDC group receiving fewer rewards than the two control groups (p's<0.05), which did not differ from each other. Males received more reinforcements than females, $F(1,34)=11.26$, $p<0.01$. There was no Prenatal Treatment × Sex interaction.

Prenatal treatment also significantly affected the number of errors in the 10-min test. Figure 4 shows the mean errors for males and females for the six days of 10-min sessions. Prenatal Treatment had a significant effect on the number of errors, $F(2,34)=4.82$, $p<0.05$, with the 35% EDC group making more errors than the control groups (p's<0.05), which did not differ from each other. There was a significant main effect of Sex, $F(1,34)=13.07$, $p=0.001$; males made more errors than females. Again, Prenatal Treatment did not interact with Sex.

Further analyses (Spearman rank-order correlations) were then performed to compare number of reinforcements and errors on the alternation test on Day 16 with the degree of side preference on the previous left-right lever choice. Results from Day 16 were used to reflect asymptotic performance levels. A side preference index of Left-Right/Total Responses was computed from the previous side preference assessment (42). Mean side preference indices (±SEM) were 0.55±0.11 for 35% EDC males, 0.63±0.12 for 35% EDC females, 0.88±0.03 for 0% EDC males, 0.90±0.03 for 0% EDC females, 0.88±0.07 for LC males, and 0.83±0.11 for LC females. Prenatal Treatment had a significant effect on side preference, $F(2,34)=8.94$, $p<0.01$, with 35% EDC subjects having significantly lower indices than control groups (p's<0.01), which did not differ from each other. Correlations were performed separately for each prenatal treatment condition since side preferences differed significantly among groups. Among the LC group, a significant positive association was detected between the number of reinforcements and side preference (rho$=+.698$, $p<0.01$). Conversely, there was also a significant negative association between the number of errors and side preference (rho$=-.534$, $p<0.05$). In the 0% EDC and 35% EDC groups, however, there were no associations between side preference and number of reinforcements or errors.

DISCUSSION

There were two distinct phases in this testing procedure, an acquisition phase and an asymptotic performance phase. Prenatal alcohol exposure caused deficits in the asymptotic performance of a spatial alternation test in adult offspring but did not result in deficits in acquiring the spatial discrimination. Alcohol-exposed subjects may have had an initial advantage because, as seen in the previous side preference assessment (42), they already alternate more between levers when given a free left-right choice. Control subjects may have to overcome more of a position bias when learning this task. Continued testing, even in a shorter session, did not result in an eventual improvement by the 35% EDC subjects. Thus, alternation test deficits were probably not due to increased error responding in the later part of the longer sessions after the animals were sated.

The impairments detected on this test might reflect a nonspecific performance deficit in alcohol-exposed subjects. To determine if the impairments were specific to spatial behavior, a second experiment was conducted with the addition of visual cues.

EXPERIMENT 2

Subjects

The subjects for this experiment, as in the first experiment, were chosen from subjects previously assessed for

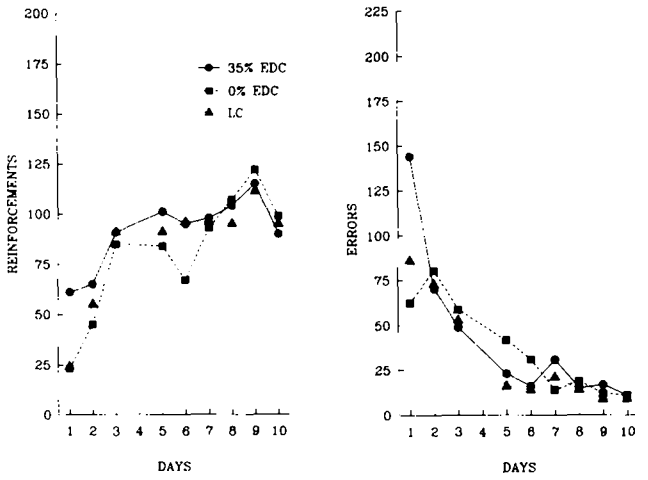

FIG. 5. Mean number of reinforcements (left panel) and total errors (right panel) during cued alternation test for females from three prenatal treatment groups: 35% EDC, 0% EDC and LC. Bars represent 10 days of daily 30-min sessions for 7–9 subjects per prenatal treatment group.

side preference in the two-lever paradigm (42). They represented independent litters from each of the three prenatal treatment groups (35% EDC, 0% EDC and LC). Since Prenatal Treatment and Sex did not interact in the analyses in Experiment 1, only female subjects were tested (n's=7–9 per prenatal treatment group). The mean age of the subjects when testing began was 145 days.

Procedure

The same paradigm was followed for this experiment as for the previous experiment, except that visual cues were now available above the correct lever. Thus, when reward was available on the right lever, the right light was on, and vice versa. Subjects were required to alternate between left and right levers on a continuous reinforcement schedule as in Experiment 1. Subjects were tested for daily 30-min sessions, five days per week, for two weeks. Although the subjects were tested on Day 4, due to a programming failure there were no data output that day.

RESULTS

Figure 5 shows the mean number of reinforcements and mean number of errors for the three prenatal treatment groups over the two weeks of cued alternation testing. There was no effect of prenatal treatment on the number of reinforcements obtained. There was a significant interaction between the Prenatal Treatment and Day, $F(16,168)=2.92$, $p<0.001$. The 35% EDC group made more errors on Day 1 compared to both control groups (p's<0.001). There were no other significant differences among any groups on any other day.

DISCUSSION

In this experiment, visual cues were available above the correct lever. The addition of the cue light eliminated the performance deficit detected in Experiment 1 during the asymptotic phase of testing. These results suggest that subjects exposed to alcohol prenatally may have had difficulty performing the first alternation test when they were more dependent on spatial (left-right of center) information. The 35% EDC group made more errors on Day 1 on this test compared to controls. However, this result does not necessarily indicate an effect on learning per se. The 35% EDC subjects also received more reinforcements on Day 1, and their total response rate was greater than controls. Since these 35% EDC subjects had tended to over-respond on an extinction schedule after CRF training compared to control offspring (42), the increased errors on Day 1 more likely reflected a protracted effect of the previous experiment that was not seen in Experiment 1 because the extinction schedule was conducted in the presence of the same cue lights.

GENERAL DISCUSSION

Adult rats exposed to alcohol in utero were found to make more errors and receive fewer reinforcements compared to offspring from pair-fed or standard control dams during the asymptotic performance phase of an operant alternation task. Alcohol-induced deficits were still present when the test session was shortened to exclude confounding effects of responding after satiation. These performance deficits might be differentially related to the use of spatial cues, because the addition of a cue light over the correct bar enabled alcohol-exposed offspring to perform as well as control offspring during the asymptotic phase. Alternatively, alcohol-exposed offspring might require more cues regardless of modality (e.g., kinesthetic or visual) than do control offspring to perform at the same level.

The apparent amelioration provided by the visual cue suggests that alcohol-exposed offspring may have difficulty relying only on spatial or kinesthetic cues and may need more salient visual information to perform a left-right discrimination. Supporting evidence for this hypothesis is the recent report (5) that additional visual cues in a Morris water task will ameliorate performance deficits in three-week-old rats prenatally exposed to alcohol. Thus, although alcohol-exposed subjects can learn this alternation task, they never achieve the same optimal level of performance as control groups, who may use a combination of spatial and visual strategies and can therefore "out-perform" alcohol-exposed offspring.

These results extend earlier studies showing that prenatal alcohol exposure reduces the number of reinforcements obtained on some appetitively-motivated operant conditioning tasks. Adult male offspring exposed to alcohol during gestation and while nursing received fewer reinforcements on both a continuous reinforcement (CRF) schedule and a fixed-ratio (FR-10) schedule, but not on a schedule that alternated FR-10 on the left and right bars (FR-10-10) (27). The authors do not report how many sessions were run on this alternating schedule; it may be that all subjects were still learning this task, and deficits would have been seen in the alcohol-exposed offspring after the subjects reached an asymptotic performance level. This laboratory has reported that alcohol-exposed offspring (35% EDC) received fewer reinforcements on FR schedules ranging from FR-2 to FR-33, but not on a CRF schedule (33). In agreement with the earlier study (33), the number of reinforcements obtained on the one-bar retraining CRF schedule in the present investigation did not differ among prenatal treatment groups, nor did the number of reinforcements differ in these subjects in their initial CRF training (42). Martin *et al.* (27) used a different alcohol administration paradigm (alcohol as the sole

source of fluid intake plus dietary injections) that differed from the one used in the present study, and they extended the alcohol regimen for lactation. These procedural differences make it difficult to directly compare their results to our studies using liquid diet administration only during gestation.

Another interesting finding in this study was the marked sex difference. Males obtained more reinforcements than females, regardless of prenatal treatment. Typically, males are reported to perform better than females on tasks requiring spatial discriminations (19). It might appear from these results that males performed better on this alternation test because they received more reinforcements. However, males also made more errors, and when ratios of responses per reinforcement were calculated, there was no longer any difference between males and females. At least for this alternation test, it appears that males and females had comparable performance levels, and that males only appeared to perform better because they responded more.

Another question asked by this study was whether there would be a relationship between these subjects' degree of side preference and their performance on the alternation test. In the previous experiment (42), the subjects in the present study were tested on a left-right lever choice, and alcohol-exposed offspring demonstrated less side preference than either pair-fed or standard lab chow control offspring. Indeed, performance on the noncued alternation test was significantly related to side preference in LC control subjects: the greater the side preference, the greater the number of reinforcements and the fewer the number of errors. These results parallel previous findings that side preference positively correlates with number of reinforcements on several schedules of reinforcement (16,17). Side preference has been proposed to have an adaptive significance related to the way that the organism can most effectively cope with or strategically explore its environment (17). If prenatal alcohol exposure disrupts this internal spatial reference, then other strategies (e.g., visual information) may be necessary to perform left-right discrimination as effectively as nonexposed subjects.

In contrast to the LC controls, when side preference was compared to alternation test performance in the two liquid diet groups (the 35% EDC and 0% EDC groups) there was no significant association. Thus, strength of side preference behavior did not predict the degree of impairment on the alternation task for either of these two groups. One difficulty in interpreting these results for the undernourished groups is that there was very little variability in side preference in the 0% EDC group compared to the 35% EDC group; this may have precluded the possibility of finding a significant correlation due to a limited sampling distribution. However, there was enough variability in side preference among the 35% EDC subjects to conclude that clearly in this prenatal treatment condition there was no relationship between side preference and alternation test performance.

Undernutrition during gestation (common to both the 0% EDC and 35% EDC groups) may itself alter the development of cerebral dominance. When tested at one month of age, the 0% EDC group exhibited less side preference than the LC controls, although more than the 35% EDC group (41). Prenatal stress (artificial rearing) in the first week of life has been demonstrated to alter cerebral lateralization as seen in asymmetrical eye-opening (35). However, when tested as adults, undernourished control subjects (0% EDC) no longer differed in side preference behavior from LC control subjects (42), nor did they differ in their performance of the present alternation task. Undernourished control subjects may have experienced a developmental delay in side preference behavior, or, alternatively, they developed some compensatory mechanisms that restored normal side preference behavior. Perhaps these mechanisms were not available to alcohol-exposed subjects, who continued to exhibit less behavioral laterality as adults as well as poorer left-right discrimination performance. Since alcohol damage in utero probably affects several neuronal systems, further investigation is necessary to explore the relationship, if any, between altered behavioral laterality and other behavioral dysfunctions following prenatal alcohol exposure.

Two neuronal systems appear to be involved in both side preference behavior and alternation test performance: frontal cortex and hippocampus. For example, unilateral lesions of either of these two areas increase ipsilateral arm choice in a T-maze (20). Unilateral frontal cortex lesions also decrease contralateral turns in a Y-maze (8). Neuronal alterations have been reported in both cortex and hippocampus after prenatal alcohol exposure (3, 23, 34, 38). Selective damage to the hippocampus or the frontal cortex have both been associated with deficits in performance on alternation tests [e.g., (21, 24, 25, 28, 32)]. In addition, asymptotic performance on an operant alternation task was found to be selectively impaired by the administration of anticholinergic agents (15); acetylcholine is a major neurotransmitter in both frontal cortex and hippocampus. It would not be surprising if cholinergic systems underlie the behavioral deficits described here, since there are many behavioral similarities between animals exposed to alcohol prenatally and animals given anticholinergic drugs (29).

In summary, the results of this experiment and the preceding studies (41,42) suggest that the normal expression of side preference is altered in adult rats exposed to alcohol in utero, and that they may be less able to use spatial information in the performance of a spatial discrimination task. The optimal performance of the alcohol-exposed subjects is therefore compromised. However, we cannot yet determine the extent to which altered behavioral laterality contributes to deficits in performance on spatial tasks. Further studies on the relationship between alcohol-induced disruption of cerebral asymmetry and differential use of learning strategies may guide educational methods for children known to have been exposed to alcohol in utero.

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