



# Spatial locations gone awry: Object and spatial memory deficits in children with fetal alcohol syndrome

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**Abstract**—Hippocampus vulnerability following gestational alcohol exposure has been demonstrated neuroanatomically and behaviorally in animal models of fetal alcohol syndrome (FAS). There have been no similar demonstrations in humans. The Smith and Milner (1981) Memory for 16 Objects task has been used to explore the effects of right vs left temporal lobectomy with varying degrees of damage to the hippocampus. In the present experiment, this same task was administered to 15 children with FAS (mean age 10.03, S.D. = 2.33) and 15 control children (mean age 10.02, S.D. = 2.31). Similar to patients with right temporal lobectomies and a large excision to the hippocampus, children with FAS were able to perform immediate but not delayed object recall, had a general spatial memory deficit ( $P < 0.05$ ), and significantly distorted the spatial array ( $P < 0.05$ ). Although these results are consistent with an interpretation of hippocampal dysfunction, gestational alcohol exposure is known to result in a wide-ranging spectrum of neuropsychological deficits that vary in both extent and severity. Visuospatial deficits on the Beery test of Visuomotor Integration and Clock Drawing are suggestive of the other neural regions that may be involved in producing the behavioral deficits in children with FAS.

**Key Words:** fetal alcohol syndrome; spatial memory; hippocampus.

## Introduction

Animal models of fetal alcohol syndrome (FAS) have repeatedly demonstrated the vulnerability of the hippocampus both neuroanatomically [2, 8, 19, 24, 80-82] and behaviorally [14, 21, 24, 25, 63, 83]. Hippocampal integrity has not been tested directly in the human fetal alcohol syndrome. Physiological [57] and behavioral [53] studies in animals have established the predominant role of the hippocampus in spatial cognition, and particularly in "cognitive mapping" [58]. Studies of human hippocampal function are more tentative, focusing on memory in general [71] and spatial memory in particular [23, 60, 67, 68]. Behavioral evidence of hippocampal dysfunction in children with FAS has the potential to offer insight into the neural basis of the cognitive deficits demonstrated in this developmentally disabling condition.

Whether or not children with FAS have hippocampal dysfunction is of interest for several reasons. Primarily,

FAS is a developmental disorder and the study of these children could provide valuable information about human hippocampal function. Because the hippocampus is a structure vital to learning and memory, a better understanding of this area could lead to improved rehabilitative efforts of children with FAS and to new knowledge about the learning process in normal children. Since spatial learning and memory are the most thoroughly studied functions of the hippocampus in animals, it is appropriate to determine whether children with presumed hippocampal dysfunction demonstrate a parallel deficit. Children gestationally exposed to alcohol have been reported to have difficulty with the processing of spatial information [7, 74], but there has been no discussion of which neural systems might be responsible. A wealth of evidence points to the hippocampus in animal models.

In animal models, the number of neurons in the hippocampal CA1 region is decreased during neurogenesis following ethanol (EtOH) exposure. For example, Barnes and Walker [8] demonstrated that the CA1 pyramidal population in the dorsal hippocampus was reduced by 20% in a group of 60 day-old

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animals allowed free access to an ethanol-containing liquid diet during gestational days [10–21]. CA2-4 cells were not affected. When ethanol was administered from gestational day 12 through to postnatal day 7, Davies and Smith [19] also demonstrated changes in the CA1 pyramidal cell population: a 20% decrease in the basilar dendritic length and a 12.4% decrease in the cell bodies. Additionally after pregnant rats were exposed to 3 g/kg of ethanol two times a day throughout pregnancy, Abel *et al.* [2] showed a significant difference in CA1 pyramidal cells in control animals ( $68.9 \pm 4.7$  apical dendrites and  $67.02 \pm 2$  basilar dendrites) compared to the EtOH-exposed group ( $47.2 \pm 2.2$  and  $48.8 \pm 1.4$ , respectively). In a radial arm maze task, a decrease (16–20%) in the number of CA1 pyramidal cells was significantly correlated with working memory errors.

Other changes that have occurred are in hippocampal field CA4 and the dentate granule cells [80, 82]. As a final example, the mossy fiber projection from the dentate gyrus to Ammon's horn is also altered. Ethanol exposure during a period of time equivalent to the human first and second trimester resulted in an overabundance of infrapyramidal mossy fibers [81]. The alteration in the mossy fiber projection may affect the transfer of information from the entorhinal cortex into the hippocampus.

Given neuromorphological data confirming the deleterious effect of early postnatal exposure to alcohol, it is natural to hypothesize that hippocampally-associated behaviors will be affected in FAS. Although this hypothesis has not been specifically tested in a human population, a variety of studies with children [17, 74] and adults [28] provide hints that learning deficits in FAS may result *in part* from hippocampal dysfunction. Many more studies have examined this issue specifically in animal models.

Goodlett *et al.* [25] tested spatial navigation on the Morris water maze in rats exposed to alcohol during the third trimester equivalent. This task is known to be a robust indicator of hippocampal functional integrity [53]. Three groups of animals were tested: a binge-like or condensed alcohol exposure group, a uniform alcohol exposure group, and a control group. Although spatial navigation was affected in both alcohol-exposed groups, it was particularly affected in animals exposed to a large amount of alcohol at one time. Similar findings were reported by Blanchard *et al.* [14] and Gianoulakis [21]. Interestingly, when rats were required to alternate left and right responses to receive a reward (spatial alternation), the impairment demonstrated by the group of animals prenatally exposed to ethanol was alleviated by the introduction of a visual cue that signalled the correct response [83]. Thus it appears that although the learning of place, or spatial relationships, is affected, cue learning is unaffected in these animals. This differential effect on two forms of learning parallel what is seen after hippocampal lesions in rats and monkeys

[55]. Additionally, after delayed nonmatching-to-sample and Morris water maze testing, Kim and associates [33] have concluded that fetal ethanol exposure may affect spatial but not nonspatial learning/memory in the same rat.

The above studies leave little doubt of hippocampus vulnerability in animal models of FAS, but to be useful, research with animal models must be informative about their counterpart human condition. Unfortunately, the relationship of neurodevelopmental and learning and memory effects of prenatal ethanol exposure between rodents and humans is not well understood. Hippocampus pathology is one area in need of further research.

Streissguth and colleagues [73] tried to index hippocampal function in their neuropsychological test battery, but their tests (Memory for Designs, Children's Memory Test, digit span subtest of the Wechsler Intelligence Scale for Children, and the Seashore Rhythm Test) have no association with the hippocampus. Results from Memory for Faces, a test sometimes associated with right hippocampal damage in adults [50], were inconclusive due to administration problems. And last, in a subsequent abstract, Gray and Streissguth [28] describe Milner's [51] stepping-stone maze as "Milner's original test of hippocampal dysfunction" (p. 294). Milner [51], however, found the stepping-stone maze to be sensitive not only to bilateral hippocampal impairment, but also to lesions of the right temporal cortex, right parietal cortex, and frontal lobe.

In the experiment reported in this paper, the Memory for 16 Objects task [41, 68] was administered to control children and children with FAS. Although the immediate and delayed spatial recall component of this task have previously been demonstrated to be a sensitive indicator of right hippocampal damage, the object recall component is sensitive to lesions of the left temporal cortex as well [68]. On the basis of these results it can be predicted that if children with FAS have damage in the hippocampal formation and adjacent temporal neocortex, then they will perform more poorly on delayed object recall and immediate and delayed spatial recall tasks compared to control children. Additionally, since spatial memory deficits should not be exclusively associated with hippocampus damage, other visuospatial measures were also administered to assess the possible contribution of other brain structures in producing behavioral deficits in FAS.

## Method

### Subjects

The subjects were 30 native American school-aged children with a mean age of 10.026, S.D. = 2.28. With one exception, these children all attended school in one school district. Fifteen of the children (mean age = 10.03, S.D. = 2.33) had previously

been identified as FAS\* by a University of Arizona geneticist/dysmorphologist.† The control subjects (mean age 10.02, S.D.=2.31) were age- and gender-matched peers with no previous history of special education. All children participating in this study were recruited with the assistance of the district educational psychologist.

Twelve of the 30 children were younger and from a primary school (kindergarten through to third grade). Sixteen were older and from a middle school (fourth through to sixth grade). Two additional students were seventh graders. There were 11 males and four females total in each group. School records indicated that after psychoeducational testing some of the children with FAS had also been diagnosed by the school psychologist with attention deficit hyperactivity disorder ( $n=2$ ), mild retardation ( $n=5$ ), low average intelligence ( $n=2$ ), learning disability ( $n=4$ ), developmental reading disorder ( $n=1$ ), and average intelligence ( $n=2$ ).‡ Impressively, most ( $n=12$ ) of the students with FAS were being educated in the regular classroom for at least part of the school day and endeavoring to keep up with their classmates with age-appropriate social skills.

### Procedure

*Memory for 16 Objects: immediate memory.* Each student was brought to the testing room and seated at a table in a seat opposite to the experimenter. On the table was a wooden board that measured 60 cm × 60 cm. On top of this board was a piece of brown wrapping paper with similar dimensions. The piece of paper was marked with 16 dots in a specific configuration (see Fig. 3). These 16 dots comprised a spatial reference system that was used for all of the subjects. The configuration of objects, in contrast, was unique for each subject and determined by a random number generator. The objects were in place prior to the child entering the testing situation, and the child never saw 16 reference points.

The child's first task was to estimate the price of each object. The objects were toys or other objects that are familiar to

children: a pencil sharpener, paper clip, scissors, tape, toy police car, green block, toy teddy bear, small toothpaste tube, toy skateboard, battery, baby's bottle top, a spool of thread, screwdriver, lock, a whistle, and a plastic spoon. The experimenter directed the subject's attention to each object asking "How much do you think the ... costs?" This task was not a test of frontal lobe dysfunction as in the Smith and Milner [67, 68] study, but rather an effort to direct the child's attention to each object.

After the child estimated a price for each object, the experimenter asked the child to turn away from the test apparatus. After the child complied, the experimenter put all the objects from the board into a brown paper bag, and removed the brown wrapping paper that contained the spatial reference system. A plain piece of heavy brown paper was put in its place. The experimenter instructed the child to sit down once again. "Try to remember the objects that were here in front of you. I would like you to name as many as you can think of."

Each child performed object recall until reaching a point where he/she stated that no more could be remembered. Upon completion, the experimenter emptied the bag of objects to the side of the wooden board. "Here are all the objects that were in front of you. Now I want you to put them back to where they were." When the child was finished replacing the objects, the experimenter said, "Very nice. Now I would like you to take a second look at the way you have put the objects. Are there any objects you would like to change or rearrange?" After the subject had indicated that he or she was finished, the experimenter asked "Is this the way the objects looked before?" Upon acknowledgement, the child was returned to his/her classroom.

*Delayed memory.* Twenty-four hours later and without notice the child was brought back to the testing room and seated in the same chair in front of the wooden board. This time, however, there were no objects on the brown wrapping paper. The experimenter repeated the instructions for object and spatial recall as stated for the immediate recall condition.

*Scoring.* In object recall, the number of objects recalled by each subject was recorded. In spatial recall, the position of each object was marked and labeled. The distance (in cm) between the marked location and the original object location was measured.

*Visuospatial measures.* These included a face recognition task from the Kaufman Achievement Battery for Children (K-ABC), the Wechsler Intelligence Scale for Children (WISC) Mazes subtest, the Beery test of Visuomotor Integration (VMI), and a Draw-a-Clock test.

*The facial recognition test* is a part of the K-ABC. The test is relatively simple and designed for children of prekindergarten age. For the purposes of this research, the test was used as a screening tool to study whether children with FAS have difficulty with facial recognition. Each subject was required to view one or two faces. After 5 sec, this was taken away, and the child shown a picture with several faces. The child's task was to point to the original face in the group of faces. A total of 18 faces was presented to each subject: 12 single face presentations and three double face presentations.

*The Mazes test* of the WISC requires each subject to traverse from start to finish on a set of mazes that becomes progressively more difficult. Dependent upon the difficulty level of the maze, the subject is allowed from 2 to 5 errors. In addition, the maze must be solved within a certain time period.

*The Developmental Test of Visual-Motor Integration (VMI),* or the Beery test [10, 11], is a "copying test" designed primarily for preschool and elementary school age children. It provides age norms through 14 years of age. Twenty-four geometric designs are presented in a sequence that follows a developmental gradient of difficulty. The subject's task is to copy the

\*The application of the term "fetal alcohol syndrome" has undergone substantial revision. In 1989 [69], it was recommended that this group be divided into either "fetal alcohol syndrome" (FAS) or "fetal alcohol effects" (FAE). FAS meant that in addition to a child having a mother who admitted to drinking during pregnancy, the child demonstrated (1) dysmorphic facial features, (2) growth retardation, and (3) learning and/or behavioral difficulties. An FAE child, in contrast, demonstrated only two of these three defining characteristics. Unfortunately the term FAE has been applied in an indiscriminate manner to children whose mothers are suspected of drinking during pregnancy and it has been recently suggested that this term be abandoned [1, 32]. The present group of children have all be identified on the basis of maternal alcohol consumption during pregnancy and should not be considered a *bona fide* sample of FAS children.

†Recent attempts have been made to identify fetal alcohol syndrome children on several Native American reservations. Children previously receiving special education services are highly suspect and are likely to be the first individuals identified.

‡These additional diagnoses are not uncommon to FAS. The unfortunate stereotype of Native Americans as alcoholics, however, has alerted clinicians to identify more of these children as gestationally exposed to alcohol. In the unsuspected mainstream caucasian population, in contrast, labels such as "learning disability" and "educably mentally retarded" may be acting to mask prenatal alcohol exposure.

designs in a space that is equal to that of the original. The reproductions are scored as either "correct" or "incorrect".

**Clock drawing.** Each subject was asked to draw a large clock, and then to draw hands that pointed to the time twenty to four [70].

## Results

### Memory for 16 Objects

**Object recall.** Results were analyzed using a repeated measures ANOVA with factors of group and time of administration. There was no main effect for group [ $F(1, 28) = 1.93$ , n.s.] or for time [ $F(1, 28) = 3.33$ , n.s.]. A significant group  $\times$  time interaction [ $F(1, 28) = 7.12$ ,  $P < 0.05$ ] indicated a differential pattern of responding between the groups in the tasks of immediate and delayed object recall (Table 1).

The difference in the number of objects recalled in the immediate memory condition was not significant ( $T[28] = 0.31$ ). In the delay memory condition, the difference was significant at the  $P < 0.05$  level ( $P = 0.028$ ).

Another factor to consider in this task is the large age range, 9.2 years, of the 30 subjects enrolled in this study. Although a significant correlation between age and the immediate object recall task ( $r = 0.48$ ,  $P < 0.01$ ), and between age and the delayed object recall task ( $r = 0.56$ ,  $P < 0.01$ ) resulted, there was no interaction effect between age and group [ $F(1, 26) = 0.23$ , n.s.] in the immediate object recall task [ $F(1, 26) = 0.01$ , n.s.] indicating that age facilitated the performance of both groups equally (Fig. 1).

**Spatial recall.** The spatial task was also analyzed in a repeated measures ANOVA. There was a main effect of

both group [ $F(1, 28) = 4.93$ ,  $P < 0.05$ ] and time [ $F(1, 28) = 25.81$ ,  $P < 0.001$ ]. The lack of an interaction effect indicated that both groups responded similarly at both time period (Table 1).

In addition, in both groups, the standard deviation was larger in the delay task. The difference between the standard deviation in the immediate and delayed spatial recall tasks, however, was not significant as determined by the Hartley F-Max test [22]. The difference in the standard deviations between the two groups is significant in both immediate location recall [ $F(14, 14) = 3.01$ ,  $P < 0.05$ ] and in delayed location recall [ $F(14, 14) = 3.11$ ,  $P < 0.05$ ]. Figure 2 illustrates the object-location layouts produced by some control children and some children with FAS.

Mean spatial displacement in the group with FAS ranged from 5.75 to 21.59 cm in the immediate recall condition and 5.67 to 26.75 cm in the delayed object recall condition. Corresponding values in the control group were 4.38–12.31 cm (immediate) and 5.06–15.56 cm (delayed). Thus, because the range and therefore the standard deviation is large in this task, it would be unwise to attribute a blanket "spatial memory deficit" to all children with FAS. Also, in a rank order correlation analysis, no relationship was found between the number of objects recalled in the object memory task and the extent of displacement in the spatial location recall task.

There was no significant correlation with age in either the immediate spatial recall task ( $r = -0.15$ ) or in the delayed spatial recall task ( $r = -0.12$ , n.s.).

**Spatial distortion.** Although spatial displacement scores were informative with regard to whether or not subjects were able to remember the position of an object, this measure does not show how the subjects perceived

Table 1. Means and standard deviations in Memory for 16 Objects

	Object		Spatial		Distortion	
	Control	FAS	Control	FAS	Control	FAS
Immediate	7.27 $\pm$ 1.67	7.07 $\pm$ 1.91	7.74 $\pm$ 2.36	9.80 $\pm$ 4.10	2.07 $\pm$ 1.03	3.47 $\pm$ 2.20
Delay	8.33 $\pm$ 1.59	6.87 $\pm$ 1.88	9.54 $\pm$ 3.23	13.57 $\pm$ 5.70	2.47 $\pm$ 1.30	3.87 $\pm$ 2.20

Note: Object denotes number of objects recalled, spatial denotes centimeter displacement, and displacement is the mean number of shared locations between objects.

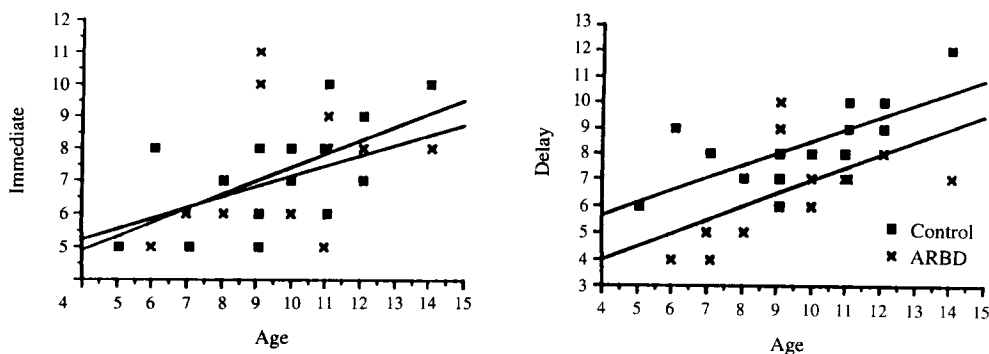


Fig. 1. Age change in the number of objects recalled.

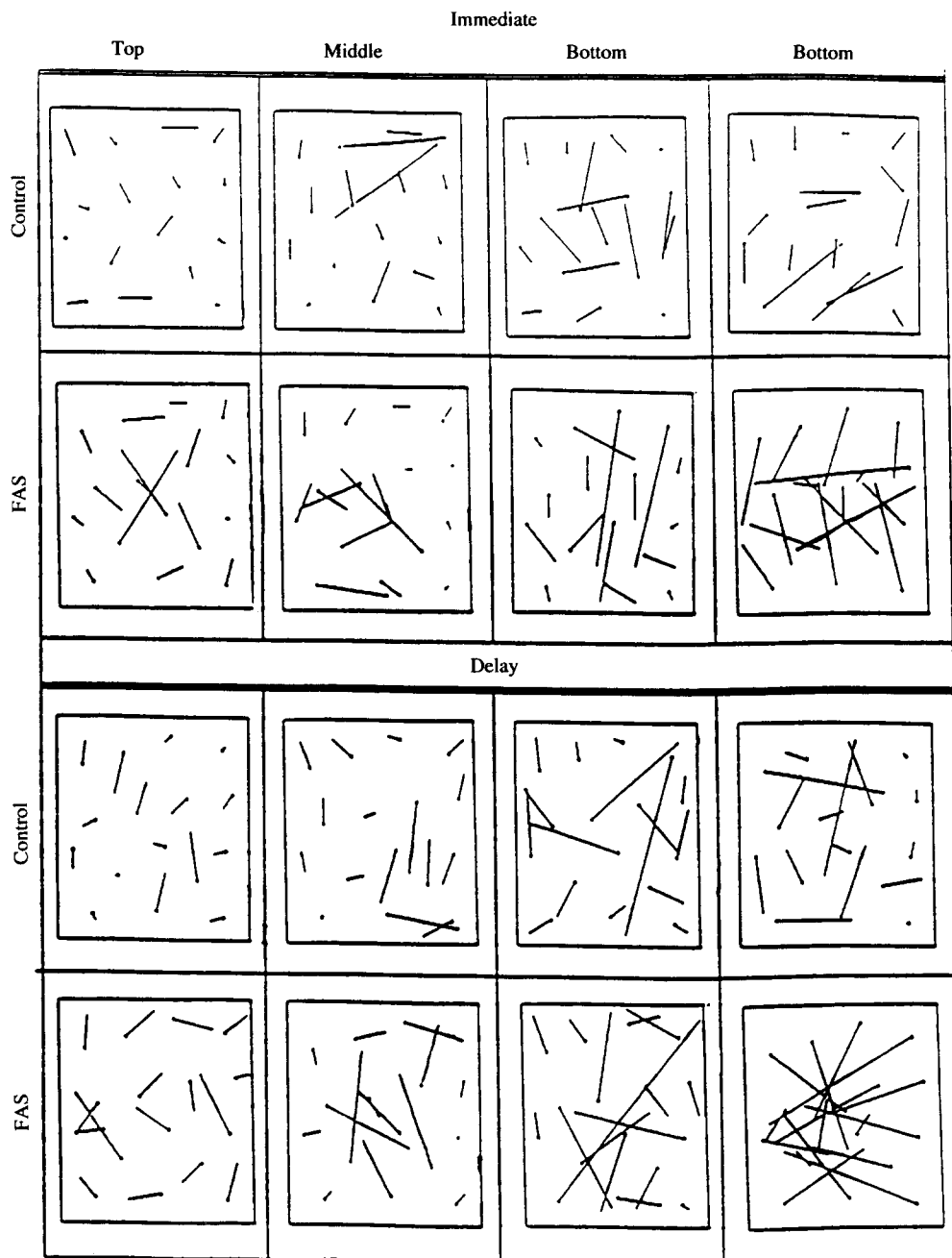


Fig. 2. Object-location reproductions in control children and children with FAS. TOP=a top performer. MIDDLE=a middle performer. BOTTOM=a bottom performer. The filled in circles represent the original object location, and a line is extended to the student-defined location.

the spatial layout as a whole. Thus, a spatial distortion variable was used to assess whether or not the children with FAS remembered place, even when they could not remember the object-place association. Distortion was scored as follows. The subjects' placement of the 16 objects was examined and compared to the experimenter-determined spatial reference positions. Specifically, each object was assigned to a location based upon distance. The location that was the shortest distance from the object determined the object-location assignment. In several cases, more than one object was assigned to a single location. This left several locations unclaimed by objects, indicating, perhaps, that these locations were

not represented in visual memory. This possibility was analyzed with a repeated measures ANOVA.

When the number of unclaimed locations was analyzed, there was a significant group effect [ $F(1, 28)=6.03, P<0.05$ ], but no effect of time [ $F(1, 28)=1.79, n.s.$ ] and no interaction [ $F(1, 28)=0.00, n.s.$ ]. Means and standard deviations are presented in Table 1. As with the displacement measure, the distortion variable indicates that spatial memory is more severely affected in some individuals with FAS than others.

The difference in the standard deviations between the groups was again significant in both the immediate

location recall condition [ $F(14, 14) = 4.54, P < 0.01$ ] and in the delayed location recall condition [ $F(14, 14) = 2.85, P < 0.05$ ], indicating more variability around the mean in the group with FAS than in the control group.

In sum, distortion scores indicate that both groups demonstrate uniform forgetting from the immediate memory condition to the delay memory condition. Thus, although location perception remains stable, the significant group effect indicates that the spatial gestalt is less accurate in the group with FAS. It appears that the spatial memory deficit on this task applies not only to the matching of objects to their locations, but also to location in general. Some examples of location distortion are shown in Fig. 4. Compare these to the spatial reference shown in Fig. 3.

### Visuospatial measures

**Facial recognition.** Out of 18 possible correct, the control group had a mean score of  $14.53 \pm 2.13$ , and the group with FAS had  $13.80 \pm 2.04$ . In a multiple regression analysis, there was a significant correlation of facial recognition with age ( $r = 0.55, P < 0.01$ ), but not with group [ $F(1, 26) = 0.34$ ].

**Mazes.** The mean score was  $10.93 \pm 3.87$  in the control group and  $9.13 \pm 2.59$  in the group with FAS. In a multiple regression analysis, although no main effect of age [ $F(1, 25) = 0.27$ ] resulted, there was a significant interaction [ $F(1, 25) = 8.91, P < 0.01$ ]. The starting value or intercept also differed between the groups [ $F(2, 25) = 6.17, P < 0.01$ ] (see Fig. 5).

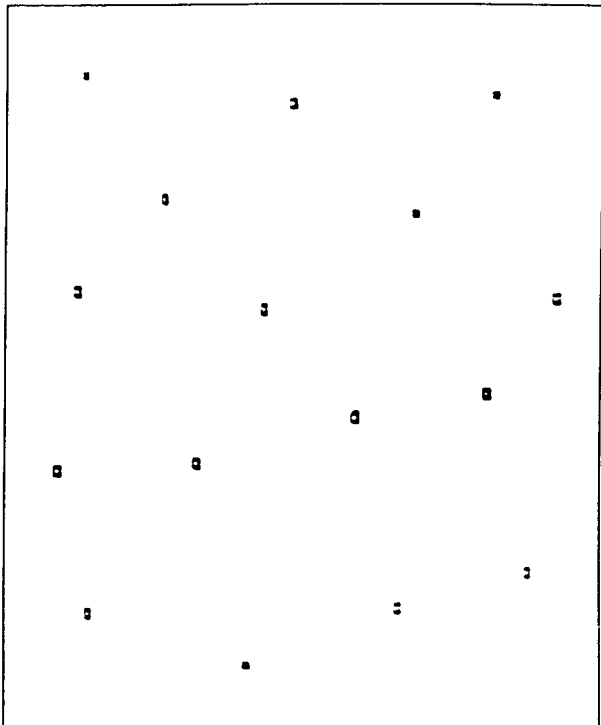


Fig. 3. Spatial reference system in the 16-object spatial localization task.

**The visual motor test of integration.** A substantial difference was observed between the control group and the group with FAS [ $F(1, 28) = 13.15, P < 0.001$ ] on the VMI in a one-way ANOVA. The mean score of the control group was  $8.47 \pm 2.80$ , and the mean score of the group with FAS was  $5.13 \pm 2.20$ . VMI performance was not significantly correlated with age ( $r = -0.12$ ).

Although the VMI can be discontinued after three consecutive failures, many students opt to complete the test. A significant group effect [ $F(1, 28) = 8.34, P < 0.01$ ] in a one-way ANOVA indicated that the children with FAS made fewer attempts ( $19.93 \pm 4.13$ ) than the control group children ( $23.27 \pm 1.71$ ). A multiple regression analysis additionally indicated a significant group  $\times$  age interaction [ $F(1, 26) = 5.77, P < 0.05$ ] and a differing intercept between the groups [ $F(1, 26) = 10.47, P < 0.001$ ] (Fig. 6).

Correct or incorrect scores on the VMI are not informative about the quality of a reproduction, thus a more thorough analysis of the individual drawings became necessary. Upon close examination, two difficulties became particularly evident: corner difficulties and distortions. These difficulties were evaluated and quantified.

Corner difficulties included rounded corners, open corners, and dog ears (see Fig. 7). In the group with FAS, each child had an average of  $3.12 \pm 1.82$  designs with a corner difficulty. This number was  $1.30 \pm 1.32$  in the control group. The difference was significant [ $F(1, 28) = 9.79, P < 0.01$ ]. The older control group had  $1.27 \pm 1.38$  corner difficulties and the older group with FAS had  $3.45 \pm 1.41$  corner difficulties. This difference was significant [ $F(1, 16) = 10.95, P < 0.01$ ]. The younger control group had  $1.35 \pm 1.36$  corner difficulties and the group with FAS had  $2.62 \pm 2.37$ . This difference was not significant, perhaps due to the fact that the younger group with FAS reproduced only more simple figures since they reproduced fewer figures.

The appearance of "dog ears" (Fig. 7d-f) was the most remarkable corner difficulty. A dog ear occurs when a child begins to draw a corner at an incorrect angle, and then attempts to correct the angle. As a consequence, an extra line and an extra angle are introduced to the form. A reproduction that contains a dog ear is considered immature [10, 11]. In total, the control group produced  $0.42 \pm 0.69$  dog ears and the group with FAS produced  $1.35 \pm 1.70$ . The fact that this difference shows only a trend toward significance [ $F(1, 28) = 3.80, P = 0.06$ ] is most likely due to the fact that the younger group with FAS produced zero dogeared figures. Again, this is probably due to their low number of total stimulus forms reproduced. In contrast, the majority of dog-eared figures were produced by the subjects in the middle school, in the older children. The older control subjects produced  $0.48 \pm 0.81$  dog ears while the older group with FAS produced  $2.25 \pm 1.67$ , a significant difference [ $F(1, 16) = 8.24, P < 0.02$ ].

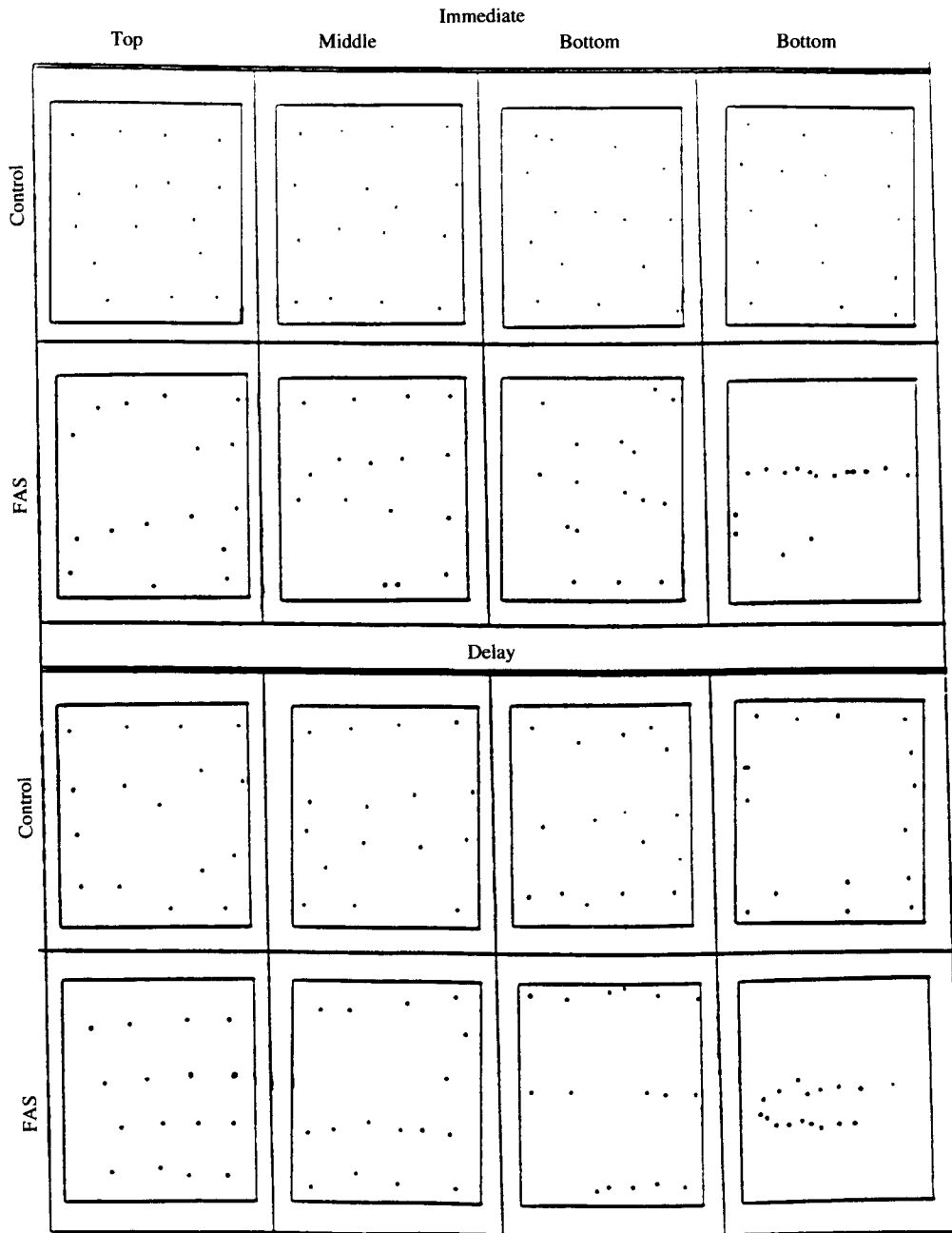


Fig. 4. Some examples of location distortion in control children and children with FAS.

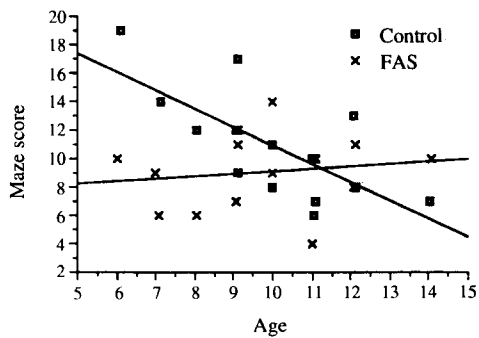


Fig. 5. Age change in the standard scores of the Mazes task.

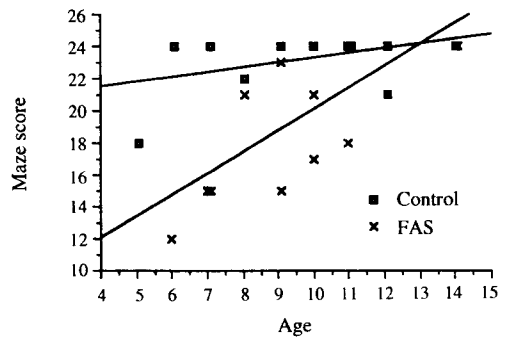


Fig. 6. Age change in the number of attempted figures on the VMI.

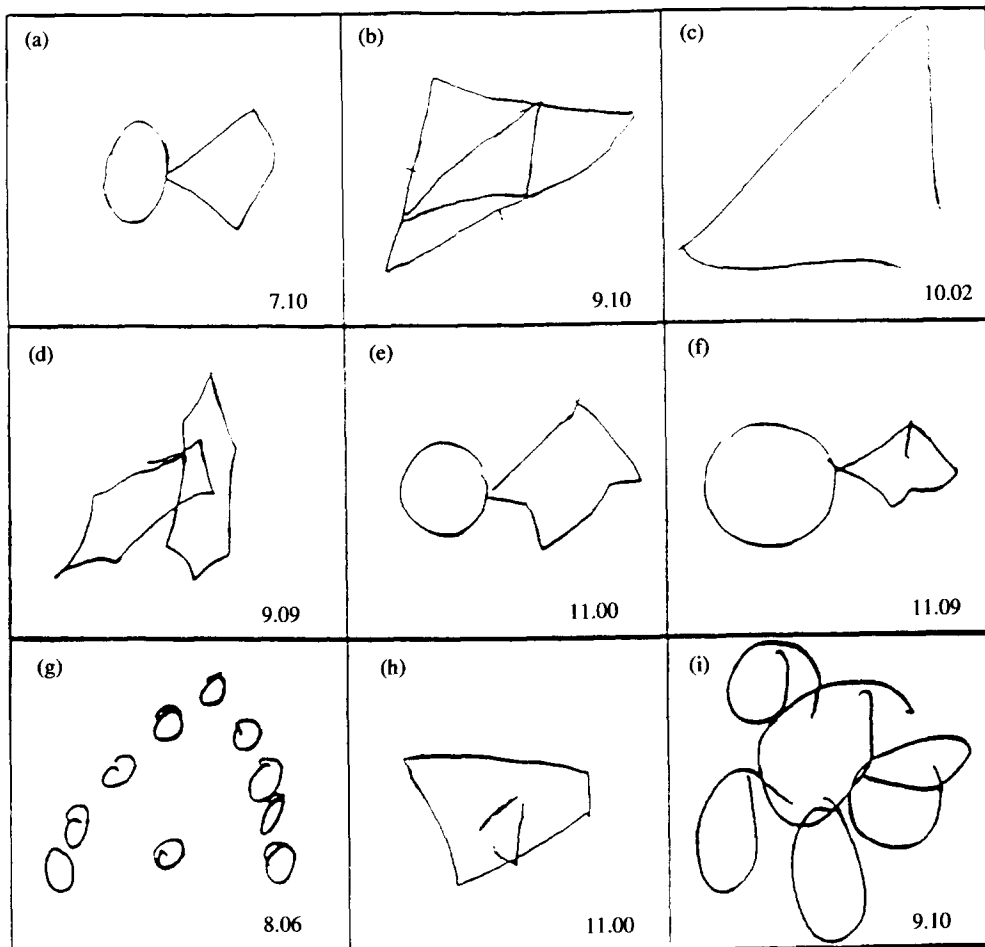


Fig. 7. Examples of corners difficulties (a–c; a = rounded corner, b = corner misalignment, and c = open corner), dog ears (d–f) and distortions (g–h) produced on the VMI by children with ARBD. Subject age is listed in the lower right corner of each box. The copy figures of a, e, and f was a diamond that touched a circle at its outer center perimeter. Figure (c) and (h) was a small isocetes triangle confined within a large isocetes triangle. The smaller triangle is supposed to touch the midpoints of the lines of the larger triangle. Figure (g) was originally a triangle formed from six circles. Figure (i) was originally three interlocking circles.

Distortions (Fig. 7h–i) were also apparent in many of the figures that were examined. A figure was scored as “distorted” if its original shape was difficult to discern. Each member of the group with FAS had an average of  $1.93 \pm 2.23$  figures containing a distortion. This number in the control group was  $0.60 \pm 2.23$  figures containing a distortion. This number in the control group was  $0.60 \pm 0.89$ . The difference between the groups was significant [ $F(1, 28) = 4.61, P < 0.05$ ]. The number of distortions in the younger group with FAS ( $2.76 \pm 2.21$ ) when compared to the control group ( $0.61 \pm 1.08$ ) showed a trend toward significance [ $F(1, 10) = 4.58, P < 0.06$ ]. There was not a significant difference between the older group with FAS ( $1.37 \pm 2.19$ ) and the older control group ( $0.59 \pm 0.80$ ).

*Clock drawing.* Clock drawing was scored on a number of dimensions: hand position (no correct hands, one correct hand, two correct hands, and before–after confusion), number position (numbers crowded to one side) (always the right), correctly placed numbers, and aborted attempts), and readability of numbers (for example, backwards letters). Before–after

confusion occurred when the minute hand was after the hour, rather than before. The low number and age range of subjects preclude substantial analyses of the above factors. Because hand position can be considered to reflect a knowledge of time, and because backwards numbers occurred predominantly only in the younger subjects, a chi-square analysis was performed for the “correctly placed numbers” variable only (see Fig. 8).

Although 11 control group members and only six experimental group members demonstrated a correct placement of numbers, this effect reached significance only when the drawings of the older group were compared ( $\chi^2 [1] = 4, P < 0.05$ ). Specifically, eight of the older control children ( $n = 9$ ) correctly placed the numbers on the clock, but only four of the older children with FAS ( $n = 9$ ) were successful.

## Discussion

The results of the Memory for 16 Objects task indicate that children with FAS are able to remember

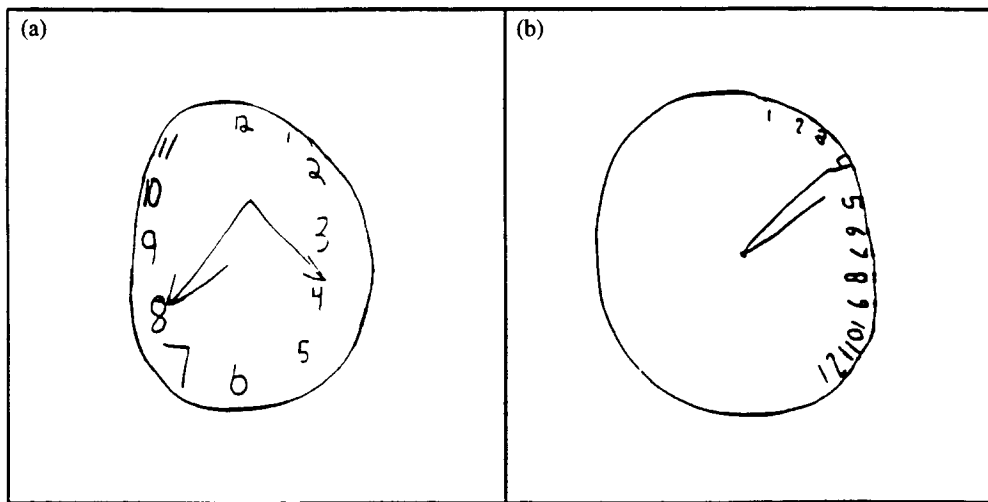


Fig. 8. (a) A correctly numbered clock. (b) An incorrectly numbered clock.

a similar number of objects as control subjects, albeit in the immediate object recall task only. In delayed object recall, the children with FAS recall fewer objects than in the immediate memory condition, whereas the control children are able to remember more. In addition, children with FAS are deficient in reproducing a spatial arrangement. Further evidence for deficits in processing and reproducing spatial information in FAS is gained after an examination of the performance of these children on the VMI and clock drawing. Whereas the results from the Memory for 16 Object task might bias one toward an interpretation of hippocampal dysfunction in children with FAS, the performance on the visuospatial measures calls for a consideration of such other structures as the parietal lobe, the frontal lobe, the cerebellum, or the basal ganglia. In the discussion that follows, the emphasis will be placed upon performance of the Memory for 16 Objects task first and then upon the visuospatial measures.

#### *Memory for 16 Objects*

*Object recall.* The children with FAS performed almost identically to patients that had undergone right temporal lobectomy with large lesions to the hippocampus in Smith and Milner's [68] study. In that study, as in ours, there were no differences between any of the groups in the immediate object recall condition. In delayed object recall, in contrast, children with FAS, patients with a right temporal lobectomy and extensive hippocampal excision, and two left temporal lobectomy subgroups (small hippocampal excision and large hippocampal excision) all performed poorly. That control children in our task recalled more objects during delayed recall replicates the performance of control and right temporal

lobectomy patients with little or no hippocampal damage in Smith and Milner's [68] study.

The finding that children with FAS perform more poorly on delayed object recall when compared with control children indicates dysfunction in participant neural structures. Smith and Milner's [68] study supported hippocampus involvement [see also 84], but recent research with primates that utilizes the delayed nonmatching-to-sample paradigm indicates extrahippocampal damage to the perirhinal, entorhinal cortex, or parahippocampal gyrus is primarily responsible for deficits in this task [47, 75]. Functional neuroimaging studies, in addition, demand consideration of the prefrontal cortex [76]. Additionally, and perhaps more importantly, gestational alcohol exposure can have a wide range of neural effects—not only on single brain structures, but also on neural networks of information processing. Normally cooperative brain functions are probably awry in FAS individuals.

*Spatial recall.* The role of the hippocampus in the processing of spatial information is well explored in rats. Smith and Milner's [68] study provides support for a similar role in the human right hippocampus. The poor performance of children with FAS on spatial localization is therefore suggestive of right hippocampus involvement. Children with FAS perform at a level that is significantly worse than control children when required to return objects to their original location. The lack of an interaction effect indicates that the deficit is similar at both the immediate and delayed time intervals. Patients with right temporal lobectomies and extensive lesions to the hippocampus perform in a very similar manner.

Timing of gestational alcohol exposure is typically an issue. The amount of alcohol the fetus is exposed to and the time period of exposure will influence the central nervous system and behavioral enactment of teratogenicity. Children exposed to alcohol *in utero* at different

gestational ages are likely to manifest different behavioral and cognitive effects. For example, the spatial localization performance variability in the group with FAS may be due to the variability of the alcohol exposure itself. Specifically, in the spatial memory task, the standard deviation differed significantly between the control group and the group with FAS in both the immediate and delayed recall conditions. A larger standard deviation in the group with FAS might be expected due to the fact that gestational alcohol exposure results in nonuniform effects. To further illustrate this point, West and associates [77] have recently reported a deficit in a spatial conditional alternation task in Sprague–Dawley rats exposed to alcohol in a short binge-like manner on postnatal day 6 but not on postnatal days 4 or 8. This finding emphasizes that the behavioral deficits produced by fetal alcohol exposure are dependent upon the timing of alcohol exposure during brain development. Unfortunately, the time periods most sensitive to alcohol toxicity in human development are unknown. In contrast, Goodlett and Peterson [26] have shown that rat pups given alcohol demonstrated a spatial memory deficit only if they were given alcohol on all days of the brain growth spurt, postnatal days 4–9, but not on only two consecutive days. This finding emphasizes the impact of multiple-binge exposures, especially during the brain growth spurt. However, it is important to note that the constricting effect of alcohol on the blood vessels of the umbilical cord [5, 6, 54] combined with the sensitivity of the hippocampus to hypoxia [20, 62] could mean that the hippocampus is sensitive to alcohol exposure most of the time.

Children with FAS not only failed to replace objects to their original locations, they also substantially distorted the overall spatial arrangement of the objects (see Figs 3 and 4). This effect was similar in both the immediate and delayed recall conditions. It indicated that memory for the spatial organization of the original stimulus array was severely disrupted, and perhaps encoded only superficially. These results indicate that children with FAS do not adequately form internal representations of spatial relations in the environment, suggesting a disruption in the formation of cognitive maps [58].

### Summary: Memory for 16 Objects

In sum, the results of the present experiment indicate that children with FAS may indeed have at least right hippocampal injury. This result is consistent with that predicted by animal models of FAS. Behavioral characteristics of left hippocampal injury remain to be demonstrated. At this time, no gross evidence of anatomic abnormalities in the hippocampus of low-functioning FAS individuals have been found with magnetic resonance imaging (MRI; [44, 45]). However,

few children have been studied and structural or functional abnormalities may still exist at the microscopic level. In high-functioning children with FAS, brain abnormalities are entirely absent on MRI scans [35, 36]. The results of the Memory for 16 Objects task suggest at least two directions for future research: (1) continued examination of hippocampus-mediated behaviors in children with FAS, and (2) further characterization of the deficient spatial behaviors in these children in order to define the responsible underlying neural circuitry. FAS is a complex multisymptom (neuro)developmental condition characterized by a great deal of variation between individuals. As such, it is unlikely that dysfunction in one cognitive, neuropsychological, or neurobiological system will explain all of the evidence. The performance of these children on the visuospatial measures is illustrative of this point.

### Visuospatial measures

*Facial recognition.* There was no difference between the groups on facial recognition. The significant correlation with age suggests that the ability to recognize faces develops with age: older children are better at facial recognition than younger children. This test indicates that children with FAS do not have difficulty with facial recognition. However, in light of the fact that facial recognition has previously been shown to be related to spatial memory difficulties [39], a more complex test of facial recognition might illuminate which aspects of facial recognition and memory are spared, vs which aspects, if any, are dysfunctional.

*Mazes.* Although children with FAS perform at a level that is significantly lower than control children on the Mazes task, a spatial task that requires planning, this effect appears to be due primarily to the performance of the younger subjects. The standard scores of the control subjects on this task decrease with increasing age. In contrast, the scores of the group with FAS remain stable. This pattern of results indicates that although this task may be too easy for the younger control subjects, it presents a similar challenge to subjects with FAS at all ages. The fact that children with alcohol-related birth defects had an overall lower mean than control children indicates an inability to plan a route through a maze. Executive functioning of the frontal lobe may be compromised.

*The VMI and clock drawing.* The VMI and clock drawing are simple yet informative measures that provide data permitting specific neuropsychological hypotheses to be developed and explored.

“Constructive activity is one of the most important forms of visual thinking.” ([40], p. 95). The reproductions from the VMI are striking illustrations of a disability in children with FAS. Corner difficulties and distortions are most apparent. Factors such as degree of corner angle, complexity and/or size of figure, and

number of corners to replicate likely play a role in determining whether or not a figure can be accurately reproduced.

In addition, the results of clock drawing indicate that individuals with FAS have difficulty reproducing an object with spatial dimensions. All of these subjects could maintain the clockwise orientation of the numbers, begin the numbers of the clock in the vicinity of the correct starting point, and with the exception of two subjects with aborted attempts, number their clocks from one to 12. These observations indicate that children with FAS are knowledgeable about the essential features of the object that is to be replicated. A lack of regard for the spacing of the numbers, however, could indicate either little advance planning or a missing representation in visual memory. Thus, although the children "remember" what a clock looks like, they are either (1) unable to organize this memory into an accurate reproduction, or (2) deficient in the ability to note spatial relationships.

*The role of the parietal cortex.* A drawing disability on a copying test such as the VMI can be regarded as a constructional apraxia, "an impairment in the reproduction or construction of designs and/or shapes due to an inadequate perceptual analysis of the visual model or an inability to translate the perception into an appropriate motor action" [12] ([13], p. 111). Similarly, clock drawing also indexes constructional apraxia. Parietal lobe damage is classically associated with this disability [18]. The right parietal cortex is implicated more often than the left parietal cortex, but the right-left asymmetry is not striking [79]. In fact, the left hemisphere has also been implicated in drawing deficits [34].

A problem in attributing responsibility for the constructional deficit in FAS to the parietal cortex is the relative lack of neuroanatomical evidence implicating this structure's involvement. Recently, Knight and colleagues [35, 36] demonstrated abnormal activity in both the left and right parietal lobes using magnetoencephalographic (MEG) imaging. At present, however, functional correlates of this neuroimaging technique are not known. In contrast, Mooney *et al.* [52] demonstrated that even though the volume of the neocortex was significantly reduced after alcohol exposure in rats during the third trimester equivalent, there were no effects in the parietal cortex.

Neuropsychological tests in this subject population have not previously been focused on the parietal cortex. Evidence for constructional apraxia, however, necessitates further examination of the role of this structure in FAS.

*The role of the frontal lobe.* There are several neural systems involved in constructional apraxia and the parietal cortex cannot be held uniquely responsible. A copying task is neuropsychologically complex, and many processing steps are involved. For example, since visual input must be converted into a plan of action, the pathologic disability may lie at the level of

visual or visuospatial perception and analysis, or because a motor response is required, the disability may be at the level of visual motor integration, motor skills, and monitoring responses [79]. The exact mechanisms underlying constructional apraxia are poorly understood. In addition, clock drawing requires abilities that extend beyond constructional skill [78].

In contrast to the perceptual processing deficit that follows a parietal lobe lesion, a "planning" disorder is thought to account for the drawing deficits of frontal lobe patients [29]. Pillon [61] suggests that visuoconstructive deficits due to parieto-occipital lesions of the right or left hemisphere and characterized by a loss of spatial organization can be compensated for by the presence of visual cues. Drawing disabilities in patients with frontal lesions, in contrast, are due to a loss of programming and the regulation of sequential behavior [40].

Interestingly, among the cortical areas most profoundly affected by gestational alcohol exposure in animals is area 6 [49], the premotor area, which sends projections to the motor cortex [37]. It is this area that appears necessary for the building of new motor programs [64]. In addition, Handmaker and colleagues [30] have provided evidence that high functioning children with FAS have difficulties with goal formulation, planning, and carrying out goal-directed behaviors, behaviors attributed to intact frontal lobe function. These deficits might be globally applied to social situations, academic work situations, and interpersonal efficiency in day-to-day chores. Strategies correcting for planning deficits could be amenable to remedial educational efforts. Careful research designs even without regard to neuropsychological variables could make an important contribution to treatment approaches designed for these children.

*The role of the cerebellum.* The cerebellum, as the hippocampus, has been demonstrated to be a sensitive target of gestational alcohol exposure neuroanatomically [59] and behaviorally [27, 48] in animal models, as well as behaviorally in humans [38, 42]. Its role in producing constructional apraxia must also be considered.

Associated motor and visual information are essential to performance of tasks like the VMI and clock drawing. Motor and parietal cortex communicate with the cerebellum by way of the pontine nuclei and mossy fibers. Mossy fibers, by their synapse onto granule cells, are thought to communicate *contextual* information about movement to the Purkinje cells (P-cells) of the cerebellum which then issues a motor command [4, 43].

Inputs from the motor cortex and the parietal cortex also enter the cerebellum through the inferior olive. Climbing fibers originate from the inferior olivary nuclei, and appear to respond to integrated information that is the product of higher brain

centers. Marr [43] thought that the 1:1 contact between climbing fiber and P-cell communicated a single elemental movement that was converted by the CNS into an instruction for a precise movement. Elemental movements are then smoothed into more concise movements in response to the contextual demands of the environment.

The theories of Marr [43] and Albus [4] can be used to begin to understand how the cerebellum integrates visual and motor information. For example, Albus [4] envisioned the cerebellum as generating a form of conditioned reflex. The unconditioned stimulus, elemental information about the motor requirements of the task is delivered by the climbing fibers. The conditioned stimulus is context information (position, velocity, and tension information of the muscles, tendons, and joints) delivered by the mossy fibers. The conditioned and unconditioned response is the behaviour. The role of the cerebellar P-cell is to learn the context of the movement so that it can perform automatically, procedurally, and thoughtlessly. After the P-cell has learned about the context, activity in the olivary nucleus should become unnecessary (see [4, 9, 31, 43, 66, 72] for further explanation and examples). Thus movement, in this drawing, becomes an automatic or conditioned response to contextual stimuli.

Empirical data suggest the contribution of specific cerebellar neuron-types to motor-behavioral deficits. For example, in animal models of FAS, a reduced number of granule cells and P-cells have been observed in the cerebellum after gestational alcohol exposure [15, 16]. If generalized to humans, then children with FAS could be deficient not only in the learning of fine motor sequences (P-cell), but could also be missing important contextual information (granule cells via the mossy fibers). In addition, Napper and West [56] have demonstrated a significant decrease in the number of inferior olivary neurons in rats exposed to alcohol during the third trimester equivalent. Thus, precise movements of exactly the kind required in drawing tasks may be compromised. Considered together, the nature of the deficit in FAS may be a difficulty in learning fine sequential movements that are best predicted within a unique movement context. Gross movements, in contrast, may be relatively unimpaired. Only further work will allow an elaboration of these hypotheses.

*The role of the corpus callosum.* Corpus callosum abnormalities have been demonstrated in MRI studies of children with FAS [44]. If the corpus callosum is abnormal in children with FAS, then one could expect degraded information transmission across the hemispheres of the brain. Callosum section itself has been shown to result in an impairment in (1) orientation toward a target, and (2) formation and maintenance of a spatial representation of a target [3]. The contribution of the corpus callosum to constructional apraxia in high functioning children with FAS can be further assessed

with instruments such as the tachistoscope or evoked potentials.

### **Additional hypotheses**

#### *The limbic system and the basal ganglia*

Clock drawing is often used to screen for dementia patients [46, 78]. Patients with Alzheimer's dementia (DAT) have difficulty recalling and reproducing on command the elements of a clock. They can, however, copy a clock without any evidence of graphic, motor, or even visuo-perceptual deficits. Patients with Huntington's disease (HD), in contrast, demonstrate planning deficits in the spatial layout of numbers [65]. Visuo-motor problems were not so apparent in the clock drawing task as in the VMI. Evidence of impaired visual organizational processes were apparent in both tasks. Thus, the tendency of the children in the present study to have either wide gaps between the numbers or to write all of the numbers on the right side of the clock might be attributed to their inability to plan or sequence their motor responses. The evidence for spatial neglect is negligible.

Patients with DAT have dementia associated with the limbic-cortical regions, in contrast, the dementia of patients with HD is associated with the basal ganglia and corticostriatal dysfunction. That children with FAS perform similarly to patients with HD is consistent with the finding of basal ganglia dysplasia in an MRI study of children with FAS [44, 45]. These findings, however, do not agree with findings of neuron loss in the limbic structures of animal models of FAS. Thus, although the clock drawing task might be regarded as a potentially informative test, the results of the present task should be regarded as neuropsychologically inconclusive and merely speculative. Further tests are needed to evaluate limbic-cortical vs basal ganglia and cortical striatal dysfunction in these individuals.

### **Summary: visuospatial measures**

The results of both the VMI and the clock drawing task indicate that individuals with gestational alcohol exposure demonstrate a form of constructional apraxia. However, the neuroanatomical locus of this disability remains speculative. A single region may be responsible, but it is more likely that interacting factors contribute both to the inability to copy a drawing and to reproduce from memory a common object. Currently, neuropsychological hypotheses regarding gestationally-produced alcohol disabilities are few and at best superficial. Further and more comprehensive evaluation of constructional apraxia should be performed. Ideally, the results of these tests could be used to further explore brain dysfunction in children with FAS.

## Overall conclusions

The neuroanatomical bases of fetal alcohol syndrome have been extensively explored in animal models. Neuropsychological testing has been performed in fetal alcohol syndrome children, but to date we have little understanding of the specific neurological sequelae. The present study has demonstrated that in addition to an inability to remember items after a delay, children with FAS have difficulty appreciating spatial relationships. Although it would be consistent with animal models to conclude that hippocampally-mediated behaviors are adversely effected after gestational alcohol exposure, performance deficits on other nonhippocampal spatial behaviors are suggestive of alternative neuropsychological explanations. Experiments that further characterize the behavioral changes in FAS, and thereby illuminate the status of underlying brain systems should ultimately help to shape more effective rehabilitative efforts.

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