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Behavioural Brain Research 3629 (2003) 1–10
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# Children with Fetal Alcohol Syndrome are impaired at place learning but not cued-navigation in a virtual Morris water task

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Received 14 October 2002; received in revised form 7 January 2003

Accepted 7 January 2003

**Abstract**

We employed a computerized (virtual) Morris water task (VMWT) to measure place learning and cued-navigation in eight adolescent males (9.5–16.5 years old) diagnosed with Fetal Alcohol Syndrome (FAS). Eight adolescent males matched for age and ethnicity with no history of prenatal alcohol exposure served as controls. Participants were trained to navigate to a hidden platform in a fixed location relative to a set of four conspicuous extramaze cues. After 20 hidden platform trials, a single no-platform probe trial was conducted, followed by 8 trials during which the platform was visible (cued-navigation). The FAS group traveled further than controls to navigate to the hidden platform during training. During the probe trial, controls navigated more directly to the platform region and persisted in searching where the platform had been more than the FAS group. Cued-navigation was comparable in both groups, suggesting that group differences in place learning were not attributable to visual-motor or motivational deficits in the FAS subjects. This pattern of impaired place learning and spared cued-navigation is similar to that reported in rats exposed to ethanol during periods of prenatal or early postnatal brain growth, as well as in animals with hippocampal damage.


*Keywords:* Place learning; Fetal Alcohol Syndrome; Virtual Morris water task; Spatial navigation; Hippocampus

## 1. Introduction

Fetal Alcohol Syndrome (FAS) is a set of profound and life-long morphological, neurological, behavioral, and cognitive consequences of exposure to high levels of ethanol in utero [6,14]. FAS is associated with a variety of behavioral abnormalities, including learning difficulties, attention, and mnemonic deficits. However, relatively little is known regarding the specific forms of learning and memory that are impaired following prenatal alcohol exposure. Further, there is no consensus regarding the neurobiological underpinnings of the cognitive abnormalities related to prenatal alcohol exposure. Given the broad spectrum of behaviors that are disrupted in children with FAS, there are likely to be widespread changes in brain, including changes in biochemistry, physiology, and neuroanatomy. An important challenge for FAS researchers concerns identifying patterns of impaired and spared cognitive abilities in tasks that have well-described neural substrates.

Some attention has been directed at understanding how alcohol-related learning and memory deficits may be related to alterations in hippocampal formation circuitry. Work with humans, nonhuman primates, and rodents indicate that selective lesions of the hippocampus are sufficient to produce severe impairments in certain forms of learning and memory [34]. Particularly, impaired is the ability to learn and remember spatial locations. For example, it is now well established that rodents with hippocampal lesions are impaired at place learning in the Morris water task (MWT) [27,35,39]. In this task, normal animals learn to swim directly to a hidden escape platform in a circular pool of opaque water from each of several release points. Subsequently, if the platform is removed during a probe trial, they persist in searching where the platform had previously been located [25,26]. In contrast, animals with hippocampal lesions take indirect, circuitous paths to the hidden platform throughout training and

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doi:10.1016/S0166-4328(03)00028-7

do not persist in searching at the platform location during a probe trial. Hippocampal-lesioned animals are, however, similar to normal animals in their ability to navigate directly to a visible platform (cued-navigation).

Several studies have reported impairments in rodent place learning in the MWT following long-term or acute exposure to ethanol during prenatal [8,37,45] or early postnatal [9,13,41] brain development. Cued-navigation in the MWT appears to be unaffected by prenatal exposure to ethanol [13]. Thus, a similar behavioral dissociation between cued-navigation and place learning exists in prenatal ethanol-exposed rats and animals with damage to hippocampal circuitry. Although exposure to ethanol during brain development may cause widespread changes throughout the brain, impairments in rodent place learning following prenatal alcohol exposure may be directly related to physiological and biochemical alterations in hippocampal circuitry. For example, prenatal exposure to moderate levels of ethanol alters markers of glutamatergic transmission in the hippocampus [30]. This disruption may underlie deficits in long-term potentiation (LTP) of hippocampal synapses in ethanol-exposed animals [5,36], which is critical for place learning in the MWT [28].

Relatively, little is known regarding how prenatal alcohol exposure affects the hippocampus and hippocampal-dependent behaviors in humans with FAS. One study has reported impaired memory for objects and their spatial locations in FAS ([42], but see [15]). These forms of memory are thought to be dependent upon hippocampal and parahippocampal circuitry, thus, these regions may not function properly in FAS. However, these behavioral impairments occur against a backdrop of deficits in a wide variety of neuropsychological tests. For example, Mattson and Roebuck [22] employed standardized tests of verbal and nonverbal memory and found nonverbal memory deficits in individuals exposed to high levels of ethanol prenatally. Thus, while it is difficult to determine whether there is a unique hippocampal locus for the aforementioned mnemonic deficits, this result suggests that hippocampal-dependent behaviors are impaired in FAS. Because alcohol-related structural changes in hippocampal tissue have not been observed in MR volumetric analyses [1], behavioral deficits in spatial learning and memory may reflect alterations in hippocampal neurochemistry and physiology, as well as functional alterations in other critical brain regions.

More research is needed to identify patterns of spared and impaired behaviors in FAS individuals using tasks comparable to those used in animal studies where there is more information regarding the impact of prenatal ethanol exposure on the underlying neural substrate(s) of learning. Recently, researchers have begun to study human place learning in a computerized (virtual) version of the MWT (VMWT) [3,10,11]. In the VMWT, participants view a computer-generated environment from a first-person perspective and navigate using a keyboard or joystick. Although there are obvious differences between real-world and virtual navigation, such as the lack of salient proprioceptive and vestibular signals in the latter, humans learn to take straight trajectories to the platform in the presence of conspicuous distal cues and show behavioral changes in relation to environmental manipulations involving distal cues similar to those described in rats [10,11]. Patients with hippocampal resections are impaired at place learning in the VMWT [2] and functional neuroimaging studies have reported hippocampal and parahippocampal activation during virtual navigation (see, e.g. [19]). Thus, it appears that virtual place learning requires and engages a similar neural substrate, including hippocampus and surrounding structures [2,19]. These similarities suggest that virtual navigation tasks like the VMWT may provide a useful methodology for investigating the neurobehavioral consequences of prenatal alcohol exposure. Because ethanol-exposed rats are impaired at place learning, but show no impairment in cued-navigation, we asked whether a similar behavioral dissociation would be observed in humans with FAS. To address this question, we used the VMWT to measure place learning and cued-navigation in adolescent males diagnosed with FAS and unexposed controls matched for age, sex, and handedness. Based upon the available behavioral data in ethanol-exposed animals, we hypothesized that prenatal exposure to alcohol would be associated with impaired place learning whereas cued-navigation would be spared. In addition to providing a control task for place learning in the VMWT, measuring cued-navigation is also important for ruling out visuo-perceptual, motor, motivational, and attentional deficits as potential explanations for place learning impairments.

## 2. Materials and methods

### 2.1. Participants

Eight males with a confirmed diagnosis of FAS were recruited to participate through the Genetics/Dysmorphology Clinic at the University of New Mexico Health Sciences Center and the Fetal Alcohol Syndrome Epidemiology Research Project at the University of New Mexico Center on Alcoholism, Substance Abuse, and Addictions (CASAA). All FAS participants met the following diagnostic criteria by one of two experienced pediatric dysmorphologists (Carol Clericuzio, M.D., or Luther Robinson, M.D.): (1) growth retardation, (2) facial dysmorphia, (3) neurodevelopmental problems as reported by caregivers, and (4) a confirmed diagnosis of substantial alcohol exposure during gestation. FAS participants ranged in age from 9.5 to 16.5 years ($M$ = 13.1 years). Previous reports have demonstrated that females within the age range used in this study are relatively poor at place learning in the VMWT compared to males in the same age range [3]. Thus, it is potentially difficult to detect place learning impairments in females with FAS. Therefore, we included only male participants in the present study. Seven FAS participants were right-handed and one was left-handed.

Four of the FAS participants were of Native American descent, three were Hispanic, and one was Caucasian. Eight male controls matched for age ($M = 13.2$ years), ethnicity, and handedness, and with no history of prenatal alcohol exposure were recruited from the same communities as the FAS participants. Control participants had no known neurodevelopmental disorder(s) and attended regular classes in school. Additional criteria sufficient for any participant to exclude from this study were: (1) moderate to severe mental retardation, (2) lack of fluency in English, (3) a history of head trauma with loss of consciousness, (4) previously diagnosed neurological illness, or (5) current treatment with antipsychotic medication. All participants and their legal guardians gave informed consent to participate in accordance with the guidelines for research with human participants at the University of New Mexico.

### 2.2. Materials and apparatus

The details of the VMWT employed in this study have been described in detail elsewhere [10,11], however, the basic features and procedures of the VMWT are repeated here. The environment consisted of a circular pool in the center of room with a square floor plan. Four conspicuous distal cues of equal size were placed around the distal room walls (see Fig. 1A). The cues were positioned such that one cue was on each of the four distal room walls and the platform could not be found by directly approaching a single cue from any

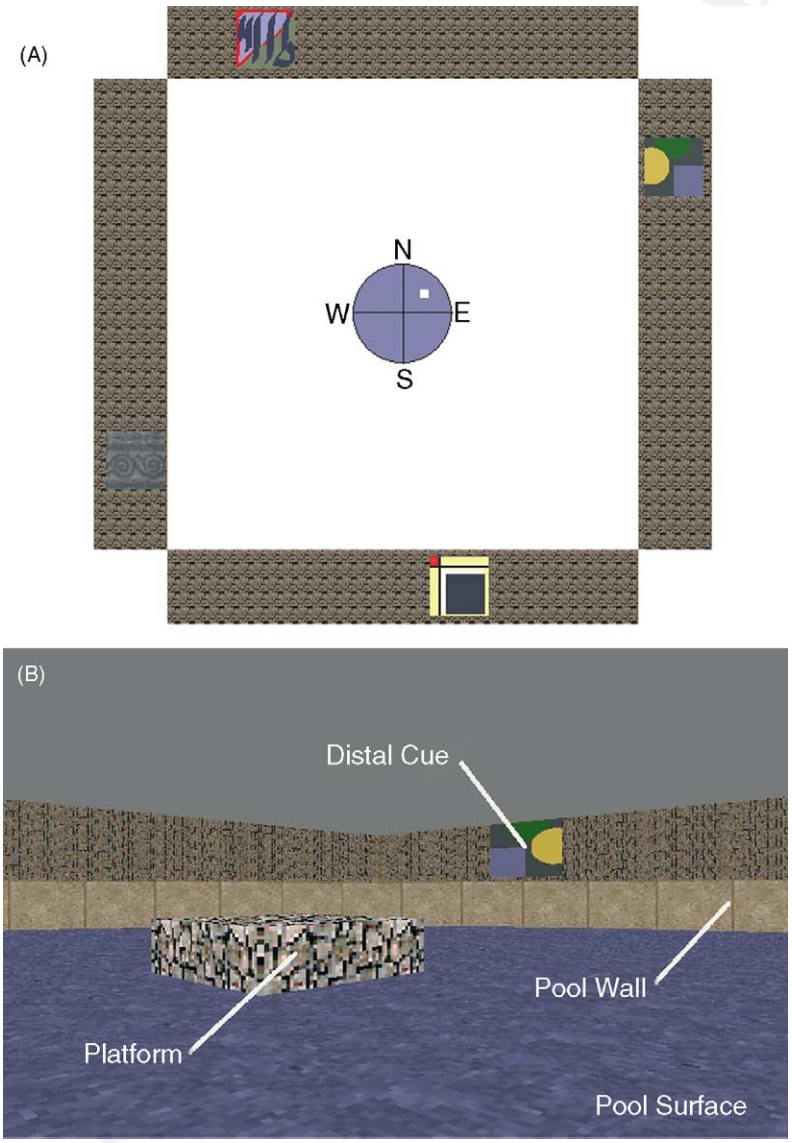


Fig. 1. (A) A scale layout of the virtual Morris water task environment. Distal walls and cues are laid flat. The circular pool was centered in the room and the platform (white square) was located in the NE quadrant of the pool. The four starting locations are labeled 'N', 'E', 'S', and 'W'. (B) A representative, first-person view from the center of the circular pool showing the pool surface, pool wall (enclosure), one distal cue, and visible platform. The labels are included for illustrative purposes and were not present during the experiment.

release point. The platform was positioned in the center of one quadrant (NE) and occupied approximately 2% of the pool area.

A first-person view of the virtual environment was displayed on a 14 in. PC laptop monitor with a 45° field of view (see Fig. 1B). The observer's position was always slightly above the surface of the water and forward movement was controlled by the UP arrow key on the keyboard. Rotation was controlled by the LEFT and RIGHT arrow keys. Backward navigation or up-down movement within the pool was not possible. A full, 360°, rotation in the absence of forward movement required approximately 2.5 s and a straight path from one side of the pool to the other took approximately 4 s to complete.

### 2.3. Design and procedure

The experiment was conducted in three phases that required a total of approximately 30 min to complete. During phase I, participants in each group completed five hidden platform training trial blocks, which consisted of four trials in each block. The starting location for each trial was selected pseudorandomly from one of four locations around the perimeter of the pool, and all four starting locations were used during each trial block. A total of 60 s was allotted to find that platform for each trial. If the allotted time elapsed, the platform was made visible and a tone was sounded to inform the participant that the platform was visible. Once the platform was located, participants remained on the platform for 5 s during which time they could rotate and view the environment, but could not leave the platform. The display was then removed and a 2-s intertrial interval followed. Path length to navigate to the platform was recorded for each trial as the ratio of total path length traveled to the diameter of the pool.

Phase II consisted of a single 45-s probe trial with the platform removed from the environment. The starting location for the probe trial was selected pseudorandomly from the two starting locations furthest from the platform location (i.e. the S and W starting points from Fig. 1A). Five dependent measures were recorded for the probe trial: (1) latency to enter the platform quadrant, (2) path length to enter the platform quadrant, (3) initial heading error (the angular deviation from a straight trajectory to the platform measured 1 s after movement was initiated), (4) percentage of time spent in the platform quadrant, and (5) percentage of the total probe trial path length spent in the platform quadrant (NE quadrant in Fig. 1A).

Phase III consisted of two visible platform trial blocks during which the platform was raised slightly above the surface of the water, as illustrated in Fig. 1B. Path length measurement and selection of starting locations were identical to the procedures of phase I.

In order to increase motivation and attention to the behavioral task, participants earned points for finding the platform during phases I and III. The points were only treated as a running "score" (i.e. points were not valuable for other rewards). Cumulative point totals were displayed numerically and as a histogram at the top of the display. The number of points awarded on a given trial was inversely related to the latency to find the platform. Ten points were awarded if the latency exceeded 40 s, 20 points were awarded for latencies between 20 and 40 s, and 30 points were awarded for latencies under 20 s. Participants were instructed to attempt to earn as many points as possible by quickly navigating to the platform during each trial. All participants were informed that the platform would always be in the same location relative to the constellation of distal cues and that they would begin in several different locations.

Following phase III, participants were interviewed regarding the strategies they employed to solve the VMWT, whether they believed the platform was in a fixed location, and whether they believed there were multiple release points. They were also asked about their experience playing video games (hours per day and examples of favorite games) and to rate the difficulty of the task (1 = very easy, 10 = very difficult). All participants were tested individually and an experimenter (D.H. or P.K.) was in the same room with the participant throughout training.

## 3. Results

Separate univariate analyses of variance (ANOVAs) were conducted on each dependent measure for each experimental phase. History of prenatal alcohol exposure (FAS or control) served as a single between-subject factor. All reported effects are significant at $P \leq 0.05$ unless otherwise stated.

We obtained scores on a standard measure of nonverbal intelligence (Raven's matrices) for all participants in the present study, which were collected as part of a neuropsychological assessment for a separate study. The FAS group ($M = 84.0$, S.E.M. $= 5.0$) had significantly lower scores on Raven's matrices than the control group [$M = 109.88$, S.E.M. $= 4.05$, $F(1, 14) = 16.15$]. This measure, however, was not a significant covariate for any analysis reported later in which there was a group difference in place learning [all $F$ values $<1$, all $P$ values $>0.75$]. For this reason, nonverbal IQ was not included as a covariate in our analyses. However, we do report and interpret significant Pearson's correlations ($P < 0.05$) between Raven's matrices scores and the VMWT-dependent measures for all participants as well as within groups.

### 3.1. Phase I: place learning

"Swim" paths during the 20 place learning trials of phase I for a representative control and FAS participant are illustrated in Fig. 2. Seven of the eight control participants learned to take direct trajectories to the platform, usually within the first trial block. In contrast, only two FAS participants learned to navigate directly to the platform from each

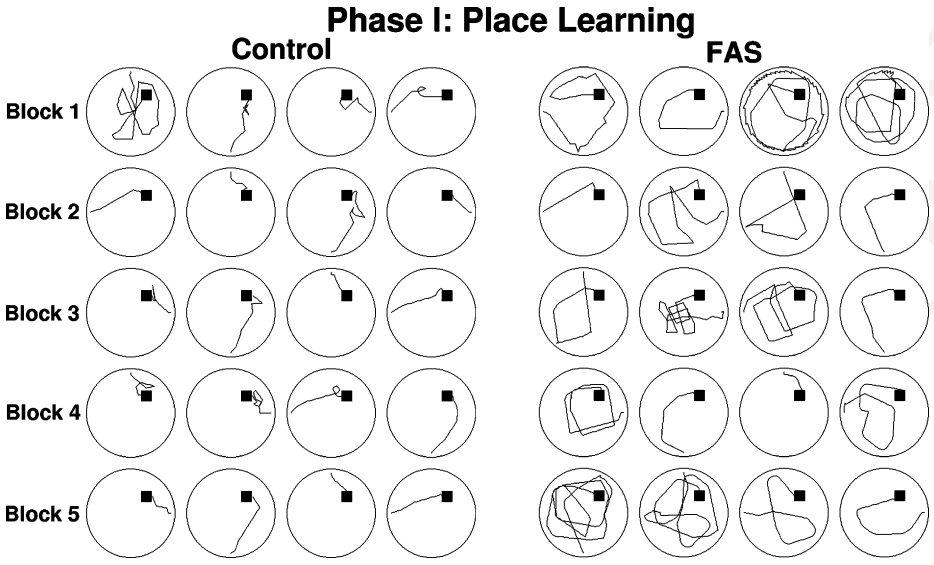


Fig. 2. Swim paths for each of the 20 hidden platform (place learning) trials for one FAS and one control participant who performed at the median level for their respective groups throughout hidden platform training. Paths for individual trials are ordered from left to right within each trial blocks.

of the four starting locations. The remaining FAS participants consistently took circuitous or random routes to the platform.

A summary of performance during the hidden platform and visible platform trial blocks is provided in Fig. 3. In order to reduce within-group variability for analysis, the mean path lengths to navigate to the platform were averaged for trial blocks 2–3 and trial blocks 4–5.

The control and FAS groups did not significantly differ in path length to navigate to the platform during trial block 1 [$F(1, 14) < 1$, $P = 0.79$]. The control group had significantly shorter path lengths to navigate to the platform than the FAS group during trial blocks 2 and 3 [$F(1, 14) = 4.83$].

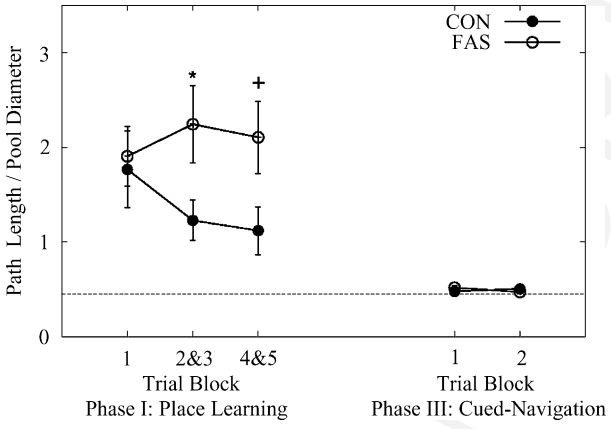


Fig. 3. Mean path length (±S.E.M.) for each group to navigate to the platform during hidden platform (place learning) and visible platform (cued-navigation) training. The no-platform probe trial was conducted between hidden and visible platform training. The '∗' indicates a statistically significant group difference at $P = 0.05$, '+' indicates a $P$ value of 0.051. The dashed line indicates the lowest possible path length value.

A similar group difference was apparent for trial blocks 4 and 5, however, this difference only approached statistical significance [$F(1, 14) = 4.57$, $P = 0.051$]. Despite the qualitative difference in place learning described earlier and the apparent quantitative differences between the FAS and control groups during trial blocks 2–3 and 4–5, a repeated measures ANOVA failed to detect a significant interaction between trial block and group [$F(2, 28) = 1.77$, $P = 0.189$]. Main effects for trial block and group were also not detected by ANOVA (both $P$'s $> 0.07$).

The control group earned 16% more points than the FAS group during hidden platform training (data not shown), however, this difference failed to reach significance [$F(1, 14) = 2.93$, $P = 0.11$]. The FAS and control groups did not significantly differ in latency to initiate forward movement [$F(1, 14) = 1.18$, $P = 0.29$] or rate of forward movement during hidden platform training [$F(1, 14) < 1$, $P = 0.56$]. Collectively, the latter three results suggest that there were minimal or no group differences in attention to or motivation to perform the behavioral task during phase I.

No significant Pearson's correlations between Raven's matrices scores and the path length measures during phase I were obtained for the combined FAS and control groups. Within the FAS group, however, there were significant correlations for path length during trial blocks 2–3 ($r = 0.749$) and trial blocks 4–5 ($r = 0.812$). These correlations indicate that higher nonverbal intelligence scores in the FAS group predicted longer path lengths during the latter hidden platform training blocks during phase I. The fact that higher nonverbal intelligence was associated with poorer place learning suggests that place learning deficits in the VMWT are not simply related to a more general, nonspecific intellectual impact of prenatal alcohol exposure.

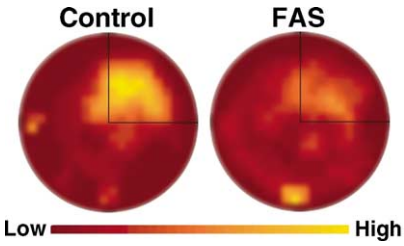


Fig. 4. Dwell time for each group during the no-platform probe trial. Yellow indicates regions where a relatively high amount of time was spent, whereas red indicates regions where a relatively low amount of time was spent. The platform quadrant is demarcated by the black lines.

### 3.2. Phase II: probe trial

During the no-platform probe trial, controls spent a majority of time searching in the quadrant of the virtual pool where the platform had been during the 20 hidden platform trials of phase I. Fig. 4 is a pseudocolor diagram portraying the composite dwell time for all control and FAS participants during the probe trial. Areas in yellow depict regions occupied for a relatively high percentage of the time, whereas areas in red were occupied a relatively low percentage of the time. As can be seen in Fig. 4, the FAS group spent less time in the platform quadrant and more time in the other regions of the pool. Although the FAS group appears to spend more time at the start point, this was the result of two FAS participants who initiated movement and subsequently stopped near the starting location. The FAS and control groups did not significantly differ in latency to initiate forward movement [$F(1, 14) < 1$, $P = 0.85$] or in rate of movement during the probe trial [$F(1, 14) < 1$, $P = 0.51$].

There were significant differences between the FAS and control groups for four of the five dependent measures (see Fig. 5). Although the FAS group took nearly three times longer to enter the platform quadrant than controls, this difference was not significant [$F(1, 14) = 2.91$, $P = 0.11$] due to the high variability in the FAS group on this measure (Fig. 5A). However, path length to enter the platform quadrant was significantly higher in the FAS group compared to controls [$F(1, 14) = 8.40$] (Fig. 5B). Most striking was the difference in initial heading error [$F(1, 14) = 14.23$]. One second after forward movement was initiated, controls were on average, 4° away from a straight trajectory to the center of the platform (Fig. 5C). In contrast, the FAS group deviated from a perfect trajectory by 45°, the equivalent of an entire field of view as illustrated in Fig. 1B. Collectively, the group differences on these measures indicate that the control group navigated to the platform region more directly than the FAS group.

Throughout the probe trial, controls spent a greater percentage of time [$F(1, 14) = 6.86$] and path length [$F(1, 14) = 9.71$] searching in the platform quadrant than the FAS group (Fig. 5D and E). The group differences on these two measures indicate that controls searched more persistently in the platform quadrant than the FAS group, which is consistent with an interpretation of impaired place learning in FAS.

Significant Pearson's correlations were detected between Raven's matrices scores and the percent time spent in the platform quadrant ($r = 0.515$) and latency to enter the platform quadrant ($r = -0.596$). Correlations computed for the individual groups revealed that controls with higher nonverbal intelligence scores spent a greater percentage of time searching in the platform quadrant during the probe trial ($r = 0.842$), however, a nonsignificant negative correlation was observed for the FAS group ($r = -0.647$). A significant positive correlation was also observed between Raven's matrices scores and the percent path length controls spent in the platform quadrant ($r = 0.853$). Significant correla-

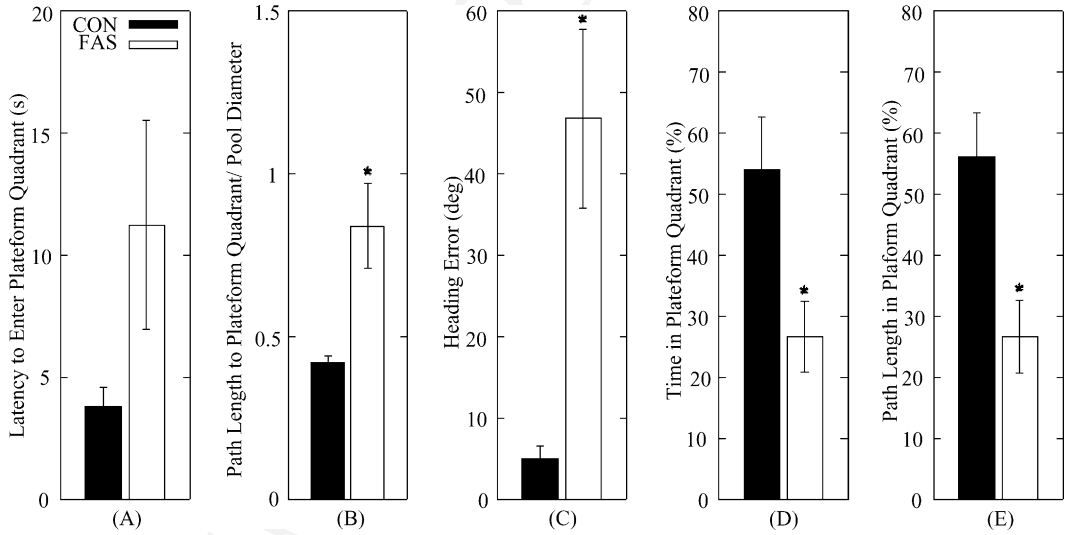


Fig. 5. Group means for each of the five no-platform probe trial-dependent measures. (A) Latency to enter the platform quadrant, (B) path length to enter the platform quadrant, (C) initial heading error, (D) percent time in the platform quadrant, and (E) percent path length in the platform quadrant. The '∗' indicates a statistically significant group difference at $P = 0.05$. Error bars are ±S.E.M.

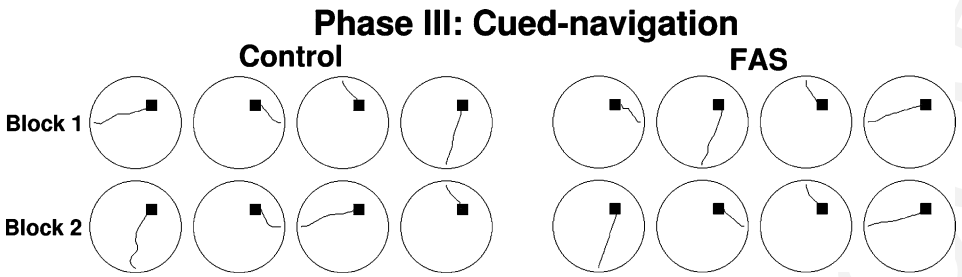


Fig. 6. Swim paths for each of the eight visible platform (cued-navigation) trial for the FAS and control participants from Fig. 2. Paths for individual trials are ordered from left to right within each trial blocks.

tions for latency to enter the platform quadrant were not detected within the individual groups, however, controls with higher nonverbal intelligence scores entered the platform more quickly ($r = -0.676$) whereas higher nonverbal intelligence scores were associated with longer latencies in the FAS group ($r = 0.423$). Significant correlations were not detected between Raven's matrices scores and the remaining dependent measures both for the combined and individual group analyses. As with the correlations reported for the phase I-dependent measures, the results of these analyses suggest that the place learning deficits in the FAS group are not simply related to the general intellectual impact of prenatal alcohol exposure.

### 3.3. Phase III: cued-navigation

Fig. 6 illustrates swim paths for each of the eight visible platform trials for the two participants represented in Fig. 2. In contrast to the group differences observed in place learning, all control and FAS participants navigated directly to the visible platform throughout the eight trials of phase III. A significant main effect of group was not detected during phase III [$F < 1$]. Specifically, no significant group differences in path length to navigate to the platform were observed for trial block 1 [$F(1, 14) = 1.27$, $P = 0.28$] or trial block 2 of phase III [$F(1, 14) = 1$, $P = 0.47$] (see Fig. 3). A repeated measures ANOVA failed to detect a significant trial block main effect or an interaction (both $P$'s $> 0.18$). The FAS and control groups earned a comparable amount of points during phase III, with the FAS group only earning 1% fewer points than controls [$F(1, 14) = 1$, $P = 0.33$]. Collectively, the results obtained during phase III indicate that FAS individuals are not significantly impaired at cued-navigation. No significant correlations were detected between Raven's matrices scores and the two path length measures obtained during the phase III visible platform trial blocks. This was true for each group as well as for both groups combined.

### 3.4. Post-experiment interview

Only seven of the eight pairs of participants completed the post-experiment interview, thus, data for seven participants in each group are reported in this paragraph. All 14 participants reported playing video games regularly and were able to provide several examples of the video games they played frequently. On average, FAS and control participants reported playing video games 1.27 h/day (S.E.M. = 0.94) and 0.72 h/day (S.E.M. = 0.69), respectively. This difference was not significant [$F(1, 14) = 1.41$, $P = 0.25$] and given the direction of the difference, a discrepancy in video game-playing experience is not likely to account for impaired place learning in FAS. Six of the seven participants in each group correctly reported that multiple starting points were used. A different distal cue was visible from each of the four starting locations, thus, it appears that both groups attended to the distal cues and recognized the relationship between the starting location and the local view from that location. All participants reported that they attempted to navigate based upon the distal cues. However, five of the seven FAS participants reported that the platform routinely changed locations during phase I, despite explicit instructions that the platform was in a fixed location relative to the constellation of distal cues. In contrast, only one control subject reported that the platform moved during phase I, and this participant did not learn to place navigate. Five of the seven FAS participants reported taking circuitous or random paths to the platform as the primary strategy they employed, whereas six of the seven control participants reported navigating directly to the platform relative to the distal cues. Although there were group differences in place learning, both groups rated the phase I hidden platform training trials as relatively easy (FAS: $M = 3.14$, control: $M = 3.29$), based on a 10-point scale.

## 4. Discussion

Consistent with reports of impaired place learning in rats exposed to ethanol during early brain development, we observed place learning deficits in a VMWT in humans with FAS. Compared to normal controls, individuals with FAS consistently took longer paths to navigate to a hidden platform relative to conspicuous distal cues during training (Figs. 2 and 3). During a no-platform probe trial, FAS-related deficits were observed in initial approach to the platform region (Fig. 5A–C) and persistence in searching

where the platform had been located during training (Figs. 4 and 5D and E). In contrast, FAS individuals and controls were comparable in their ability to navigate to a visible platform (Figs. 3 and 6), indicating that cued-navigation is not impaired in FAS. Both groups were also comparable in latency to initiate navigation for each trial and navigated at a comparable speed throughout the experiment. These similarities collectively suggest that both groups were engaged in performing the task and rule out group differences in visual acuity, motor control, motivation, and attention to the behavioral task as alternative explanations for impaired place learning in the FAS group.

The present study joins the report of Uecker and Nadel [42] in suggesting that impairments in hippocampal-dependent learning are important consequences of prenatal exposure to alcohol in humans. The observed pattern of impaired place learning and spared cued-navigation in FAS is similar to the behavioral dissociation observed in rats with hippocampal damage [38], and in animals exposed to ethanol during early brain development [13]. Place learning in the VMWT appears to involve a similar set of psychological processes to those involved in rodent place learning in the MWT (see, e.g. [8]), and to engage and require hippocampal circuitry [2,19]. Thus, a common neural consequence may underlie the place learning deficits observed in rats and humans exposed to ethanol during early brain development. Place learning impairments in the MWT have been linked to ethanol-related alterations in hippocampal biochemistry and physiology, as well as decreases in the number of hippocampal neurons, decreases in dendritic spine density on hippocampal pyramidal cells [5], and alterations in the organization of hippocampal neurons [43]. Gross changes in hippocampal volume have not been observed in rats exposed to alcohol prenatally, nor have such changes observed in humans exposed to alcohol prenatally ([1], but see [4,29]). It is possible that changes in hippocampal physiology, biochemistry, and/or neuronal morphology may underlie the FAS-related impairment in place learning reported here.

Impaired place learning in rodents and FAS individuals may also reflect functional alterations in other brain regions. Place learning in the rat is associated with a distributed set of neural circuitry, including the caudate-putamen [44], parietal cortex [17,18], cingulate cortex [40], and frontal cortex [18]. Interestingly, alterations in the caudate [1,20,21] and parietal cortex [1,32,33] have been reported in humans exposed to alcohol prenatally. Relatively, little is known regarding the entire set of neural circuitry involved in human place learning. However, if the neural substrate of place learning is similar in rodents and humans, then changes in these areas, as well as in the hippocampus, either individually or in combination, may have contributed to the FAS-related place learning impairments reported here. Skelton et al. [31] have reported impaired virtual place learning in patients with traumatic brain injury, suggesting that virtual place learning in humans may be sensitive to diffuse, nonspecific brain damage. The severe place learning impairments observed in hippocampal resection patients, however, are not observed in some patient populations, including individuals with high-functioning autism [16] and patients with tumors that do not encroach upon hippocampal circuitry [2]. Thus, any neural insult is not sufficient to cause severe place learning deficits in humans. However, given the alcohol-related changes in areas that are possibly involved in human place learning, a firm conclusion that alterations within hippocampal circuitry are responsible for impaired place learning in FAS cannot be drawn. It should also be noted, however, that striatal damage in rats also disrupts cued-navigation [7,23]. Thus, the lack of cued-navigation deficits in the FAS group suggests that the behavioral impact of alcohol-related alterations in the striatum may not have been detected in the present study. Nonetheless, the present results are only consistent with the hypothesis that hippocampal-dependent learning is impaired in FAS. One approach to further the hypothesis that alcohol-related changes in hippocampal circuitry underlies in impaired place learning in FAS involves combining behavioral tasks like the VMWT with functional neuroimaging measures of brain activity in FAS subject and normal controls. This approach is currently underway in our laboratory.

In addition to the impairments in place learning reported here, individuals prenatally exposed to ethanol are also impaired in standard, so-called “desktop”, tests of spatial learning [13,22]. Thus, it could be argued that the present findings reflect a more general deficit in spatial cognition than could be accurately measured by other behavioral measures. However, place learning in the VMWT [12] and spatial learning in other virtual navigation tasks [24] do not appear to tap the same psychological process measures by standard psychometric tests of spatial and learning and cognition or standard measures of verbal and nonverbal intelligence. In the present study, nonverbal IQ was not a significant predictor of all measures of place learning in the VMWT. In some cases, higher nonverbal intelligence scores were associated with poorer place learning in the FAS group. Thus, the place learning deficits reported here do not appear to reflect a general decline in intellectual abilities in the FAS group. Measuring behavior in FAS with standardized tests is certainly more likely to provide ecologically valid assessments of learning and memory deficits as they relate to school performance. We suggest that one important, potentially unique benefit of measuring learning in tasks like the VMWT, however, is its methodological and behavioral similarity to a model learning task used in animal studies, where much more is known regarding the underlying neurobiological consequences of prenatal ethanol exposure.

A systematic exploration of FAS-related patterns of impaired and spared performance in versions of model tasks used in nonhuman animals may greatly improve our understanding of the biological bases of the behavioral and cognitive abnormalities in FAS. To our knowledge, this is the first demonstration of a behavioral dissociation in humans with FAS that makes close contact with the nonhuman an-

imal literature on learning and memory following prenatal ethanol exposure. The clear behavioral dissociation between place learning and cued-navigation in the VMWT suggests that this methodology may also prove useful in developing a more complete neuropsychological profile of FAS, as well as less severe cases of prenatal alcohol exposure. Presently, we are investigating place learning and cued-navigation in individuals exposed to alcohol without a diagnosis of full-blown FAS to determine if exposure to low or moderate levels of alcohol is also associated with impaired place navigation. Future studies should also explore whether the effects reported here varies with age, sex, and ethnicity, as the generality of our findings and conclusions is limited to adolescent males who were of Native American or Hispanic ancestry. It is particularly important, however, to note that alcohol-related impairments in virtual place learning may be difficult to detect in females with FAS due to the relatively poor place learning observed in normal females within the age range studied here [12]. Thus, future studies could improve upon the methodology of the present study by including a broader range of hippocampal-dependent tasks that are not sexually dimorphic.

## Acknowledgements

This research was supported by the Mental Illness and Neuroscience Discovery (MIND) Institute Grant C2180 to D.D.S. Portions of the data reported here were presented at the 25th Annual Meeting of the Research Society on Alcoholism in San Francisco, CA, June 2002. The authors wish to thank Carol Clericuzio, Luther Robinson, Julia Powers, Jorge Ganem, and Paula Wilborne for their assistance with participant recruitment and data collection.

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