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ORIGINAL INVESTIGATION

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Prior non-spatial pretraining eliminates sensorimotor disturbances and impairments in water maze learning caused by diazepam

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Abstract Diazepam has been reported to impair spatial learning in the water maze. This experiment reexamined this topic using control groups that had first been non-spatially pretrained to familiarize them with the general behavioral strategies required in the water maze task. Naive rats given diazepam (0.5, 3.0, 6.0 mg/kg, IP) displayed dose-related maze acquisition impairments and sensorimotor disturbances (swimming in the periphery of the pool, deflecting off or swimming over the hidden platform, jumping off the platform when placed there after a trial, ataxia on a narrow wooden beam). The sensorimotor disturbances interfered with the acquisition of information about the spatial location of the platform, occurred in the absence of impairments in a subsequent visible platform task or swim speed, and correlated strongly with measures of acquisition. In contrast, the non-spatially pretrained groups did not exhibit sensorimotor disturbances in the water maze and acquired the maze task as rapidly under diazepam as control rats. The non-spatially pretrained groups continued to display diazepam-induced sensorimotor disturbances (ataxia) in a novel beam walking task. CGS8216 (10.0 or 20.0 mg/kg), a benzodiazepine receptor antagonist, attenuated the effect of 3.0 or 6.0 mg/kg diazepam in naive rats, suggesting that the effects of diazepam were mediated by benzodiazepine receptors. Occupancy of benzodiazepine receptors by diazepam does not prevent robust spatial learning in the water maze.

Key words Spatial learning · Benzodiazepines · CGS8216 · Diazepam and sensorimotor disturbances · Benzodiazepines and sensorimotor disturbances

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Introduction

Benzodiazepine drugs have been reported to produce amnesia in humans (Lister 1985) and spatial learning deficits in the water maze task (McNaughton and Morris 1987; Arolfo and Brioni 1991; McNamara and Skelton 1992, 1993). This led to the hypothesis that benzodiazepines play a specific role in learning and memory (Arolfo and Brioni 1991; McNamara and Skelton 1992, 1993). However, benzodiazepines can have general disruptive effects on behavior, and it is possible that sensorimotor disturbances, as opposed to a specific effect on learning and memory, caused the poor learning scores in this task. The issue of general drug-induced sensorimotor disturbances is important. As learning is inferred from behavior, if drugs cause sensorimotor disturbances that affect behaviors required to perform the task, it would be difficult to conclude that the drugs interfered with learning or memory mechanisms. Recent work found that NMDA and muscarinic antagonists caused profound sensorimotor disturbances in addition to deficits in conventional measures of spatial learning (Saucier and Cain 1995, 1996; Beiko et al. 1996; Cain et al. 1996a,b). By their nature, these sensorimotor disturbances reduced the amount of information the rats obtained about the location of the hidden platform during spatial training by reducing contact with it. The sensorimotor disturbances correlated highly with conventional measures of maze acquisition, accounting for more than 98% of the variance in some cases. These findings agreed with the view that the impairments in naive rats trained under NMDA or muscarinic antagonists might be due to drug-induced sensorimotor disturbances, not learning impairments (Keith and Rudy 1990).

The additional finding that rats given NMDA or muscarinic antagonists performed as well as controls if they were first non-spatially pretrained (Saucier and Cain 1995; Beiko et al. 1996; Cain et al. 1996a,b; Saucier et al. 1996) was consistent with this suggestion. The non-spatial pretraining (NSP) familiarized the rats with the general behavioral requirements of the task by swim-

ming in the maze in the absence of distal cues (Morris 1989). The hidden platform was present in the pool, which allowed for "use of platform" learning, but was moved after every trial. In this way the rats learned to swim away from the wall of the maze and to climb onto the platform when it was encountered. NSP eliminated the drug-induced sensorimotor disturbances, allowing the rats to contact the platform frequently during training and thereby gain enough information about its location to learn its location. NSP separated the phase of training when the rats learned the general behavioral requirements of the task from the phase when they learned the spatial location of the hidden platform. This suggested the need for additional research on the involvement of benzodiazepines in the water maze task. Here we examined the effect of NSP in this task in rats given diazepam (DZP). We also used a detailed behavioral analysis (Whishaw and Tomie 1987; Whishaw 1989; Cain et al. 1996a,b; Saucier et al. 1996) to document any sensorimotor disturbances and more fully characterize the strategy used by the rats.

Materials and methods

Animals

Male Long-Evans hooded rats were tested during the light phase of a 12:12-h light:dark cycle at approximately the same time of day. Unless indicated otherwise all rats were experimentally naive but were handled until tame.

Water maze

The water maze was a white pool 1.5 m in diameter. The square (15×15 cm) hidden platform was 1 cm below the surface of the water, which was at 29°C and was made opaque by a layer of floating white polypropylene pellets. The visible platform protruded 2.5 cm above the surface of the water and was marked prominently by a 15-cm high plastic object. Trials were videotaped with a camera above the pool, and movements in the maze were tracked, digitized, stored on disk, and objectively analyzed (Poly-Track, San Diego Instruments).

Procedure

Some rats received NSP (Morris 1989) before being spatially trained. For NSP the hidden platform was moved to a new quadrant after every trial (4 days, three trials per day, 4-h intertrial interval, no drug). Black curtains around the pool eliminated distal cues. Rats swam until they found the hidden platform, or for 120 s. If they failed to find the platform they were placed on it by hand and remained there for 30 s. Search times were recorded.

Prior to spatial training a rat was placed into the pool at North and swam in the pool for 60 s with no platform to provide a baseline probe trial measure. For spatial training ten trials were given with the hidden platform in the Southeast quadrant. A trial was begun by placing a rat into the pool facing the wall at North, South, East, or West pseudorandomly. Swimming continued for 60 s or until the rat found and climbed onto the hidden platform. If still swimming at 60 s, it was placed on the platform for 15 s. A 60-s post-training probe trial then was given, followed by ten trials with the visible platform, which was moved pseudorandomly to a new position after every trial (rats introduced at North). No black curtains were used. A heat lamp maintained core temperature between trials.

Groups and drug treatment

The following groups received DZP (Roche) before spatial training: Naive DZP 0.5 (0.5 mg/kg IP, *n*=9); Naive DZP 3 (3.0 mg/kg, *n*=9); Naive DZP 6 (6.0 mg/kg, *n*=10). The following groups were first given NSP, followed 5 days later by spatial training under DZP: NSP DZP 3 (3.0 mg/kg, *n*=8); NSP DZP 6 (6.0 mg/kg, *n*=9). A pretrained DZP group was not tested with 0.5 mg/kg DZP because the Naive DZP .5 group was not impaired relative to controls (see Results). Coadministration of CGS8216, a specific benzodiazepine receptor antagonist, was used to evaluate the role of benzodiazepine receptors in the behavioral effects produced by DZP (McNamara and Skelton 1993). Groups were the DZP 3+CGS group (3.0 mg/kg DZP+10.0 mg/kg CGS8216; *n*=6), and the DZP 6+CGS group (6.0 mg/kg DZP+20 mg/kg CGS8216; *n*=7). The Vehicle Control group (*n*=8) received an equivalent volume of vehicle (1.0 mg/kg). All injections were at 30 min before the start of spatial training. A control group pretrained under vehicle, then spatially trained under vehicle, was not included because it was found that this group did not differ from naive controls (Saucier and Cain 1995). The Random Platform group (*n*=5) was trained on the hidden platform task only (no injection; hidden platform moved pseudorandomly after each trial) to provide data from a group with no consistent information about platform location. As there were no impairments in the visible platform task in any of the naive DZP groups (see Results), two additional groups were tested on this task to determine whether experience with the general task requirements gained during hidden platform training might have served as pretraining: Visible DZP 3 (3.0 mg/kg, *n*=6), Visible DZP 6 (6.0 mg/kg, *n*=6). These naive groups, lacking prior experience with the hidden platform task, might exhibit impairment in the first water maze task they excountered, the visible platform task. The time from drug injection to the start of training on the visible platform task was equivalent to the time from injection to visible task training in the naive DZP groups.

Detailed behavioral analysis

A detailed behavioral analysis was made from the Poly-Track digital files and video playback (Cain et al. 1996b). A computer-resident template divided the pool into three areas: the "periphery" (outer 52%), the circular innermost area (central 13%), and the "platform ring", containing all possible platform locations (middle 35%). Three acquisition measures were: 1) hidden and visible platform search time, 2) platform quadrant search time during the posttraining probe trial, and 3) percent of hidden platform training trials with direct or circle swims (Whishaw and Tomie 1987; Whishaw and Jarrard 1995). Circle swims were included because DZP, like antimuscarinic drugs, frequently caused curved swim paths (Whishaw and Jarrard 1995). Only efficient circle swims (path did not cross itself or exceed one 360° circle in the pool) were counted. Time spent swimming in the platform ring was measured and percent of swim time in the platform ring was calculated.

The following sensorimotor disturbances were measured during hidden platform training: 1) periphery swimming as a measure of thigmotaxis (Whishaw and Tomie 1987), 2) swimovers (swimming over and off the hidden platform; Morris 1989; Whishaw and Auer 1989), and 3) deflections (making contact with the platform, deflecting off it, and swimming away; Cain et al. 1996b).

Beam task

Naive and NSP groups given NMDA or muscarinic receptor antagonists exhibited equivalent ataxia on a beam task, and ataxia might be relevant to a rat's ability to mount the platform in this task (Cain et al. 1996b; Saucier et al. 1996). Therefore some rats walked on a narrow wooden beam (1.8 cm wide×86 cm long) as a measure of ataxia. Time to traverse the beam and falls off the beam onto soft padding were scored. A commonly used dose of DZP (3.0 mg/kg: McNamara and Whishaw 1990; Arolfo and

Brioni 1991; McNamara and Skelton 1991, 1992, 1993) was selected. Rats from the Naive DZP 3 (n=6), NSP DZP 3 (n=7), and Vehicle Control groups (n=6) were tested between 1 and 2 weeks after training in the water maze under the same drug treatment as in the water maze experiment.

Results

Water maze

Mean search time for the NSP groups to find the platform on the first and last days of NSP were: NSP DZP 3, 47.6 s and 19.3 s; NSP DZP 6, 55.6 s and 16.5 s. The NSP rats acquired strategies for swimming away from the wall and climbing onto the hidden platform as soon as it was encountered.

Hidden platform search time differed between groups [repeated measures ANOVA, $F(5,9)=8.0$, $P<0.0001$] and across trials [$F(9,378)=6.2$, $P<0.0001$], but there was no interaction ($P>0.05$; Fig. 1A). The Naive DZP 3 and Naive DZP 6 groups had longer search times than the NSP DZP 3, NSP DZP 6, and Vehicle Control groups (Newman-Keuls; $P<0.05$). Neither the NSP nor the Naive DZP 0.5 groups differed from the Vehicle Controls ($P>0.05$). The DZP 3+CGS and DZP 6+CGS groups did not differ from controls [main effect of group, $P>0.05$; main effect of trial, $F(9,162)=7.5$, $P<0.0001$; interaction, $P>0.05$; Fig. 2A]. The groups did not differ in visible platform search time ($P>0.05$; Fig. 1A).

Analyses were conducted on the other acquisition measures to evaluate whether: 1) there was a dose-dependent effect of DZP among the naive DZP and Vehicle Control groups, 2) the NSP DZP 3 or DZP 3+CGS groups differed from the Vehicle Controls, or 3) the NSP DZP 6 or DZP 6+CGS groups differed from the Vehicle Controls. Among the naive DZP and Vehicle Control groups there were significant main effects of group and significant dose-dependent effects for all measures [platform quadrant search time: one-way ANOVA, $F(3,32)=10.8$, $P<0.0001$, contrast t-test, $t(32)=5.7$, $P<0.0001$, Fig. 1B; percent direct and circle swims, $F(3,32)=3.2$, $P<0.003$, $t(32)=3.2$, $P<0.003$, Fig. 1C; percent of time in platform ring, $F(3,32)=12.6$, $P<0.0001$, $t(32)=6.0$, $P<0.0001$, Fig. 3B]. The Naive DZP 0.5, NSP DZP, and DZP+CGS groups did not differ from the Vehicle Controls on any measure (Newman-Keuls, $P>0.05$; Figs 1 and 3). Additional paired t-tests of the baseline and post-training probe trial data were conducted to determine whether the rats increased their search time in the platform quadrant after spatial training. All groups displayed increases from the baseline probe (range of group means: 10.5–15.5 s; none differed from chance, 15 s, $P>0.05$) to the post training probe trial (range of group means: 18.3–26.2 s; paired t-tests, range of ts: 3.2–4.8, range of Ps: <0.03–<0.002) except the Naive DZP 3 and Naive DZP 6 groups ($P>0.05$). In sum, the acquisition measures indicated that the Naive DZP 3 and Naive DZP 6 groups were impaired relative to the Vehicle Controls, while both NSP DZP groups, both DZP+CGS groups, and the Naive DZP 0.5 group acquired the task as effectively as the Vehicle Controls.

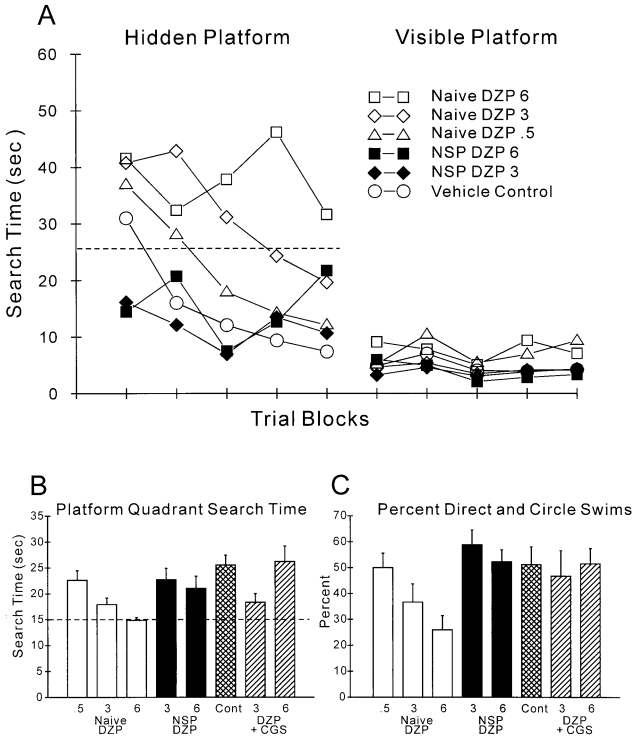

Fig. 1A–C Water maze acquisition. **A** Hidden and visible platform search time for the naive and NSP DZP groups plotted as trial blocks (two trials/block). The performance of the Random Platform Control group is indicated by the *horizontal dashed line* in the hidden platform graph. **B** Hidden platform quadrant search time during the post-training probe trial. **C** Percent direct and circle swims during hidden platform training trials. In all graphs the values represent group means. *CGS* CGS8216; *DZP* diazepam; *NSP* non-spatial pretraining

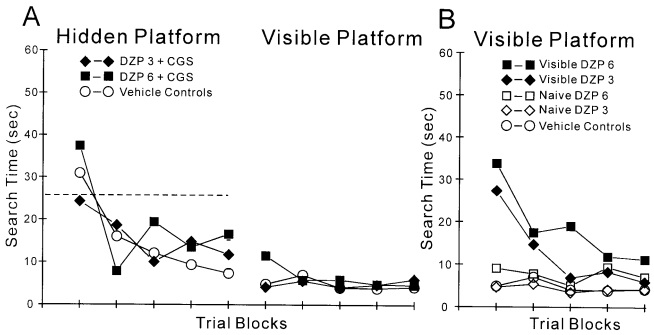

Fig. 2A, B Water maze aquisition. **A** Hidden and visible platform task search time for the DZP+CGS groups plotted as trial blocks (two trials/block). The performance of the Random Platform Control group is indicated by the *horizontal dashed line* in the hidden platform graph. **B** Visible platform search time for the visible DZP groups plotted as trial blocks (two trials/block). Data from Fig. 1A for the Naive DZP 3 and Naive DZP 6 groups are included for comparison

Both groups trained only on the visible platform task had longer search times than the Vehicle Controls [repeated measures ANOVA, $F(2,9)=7.0$, $P<0.006$; Visible DZP 3 and Visible DZP 6 versus Vehicle Controls,

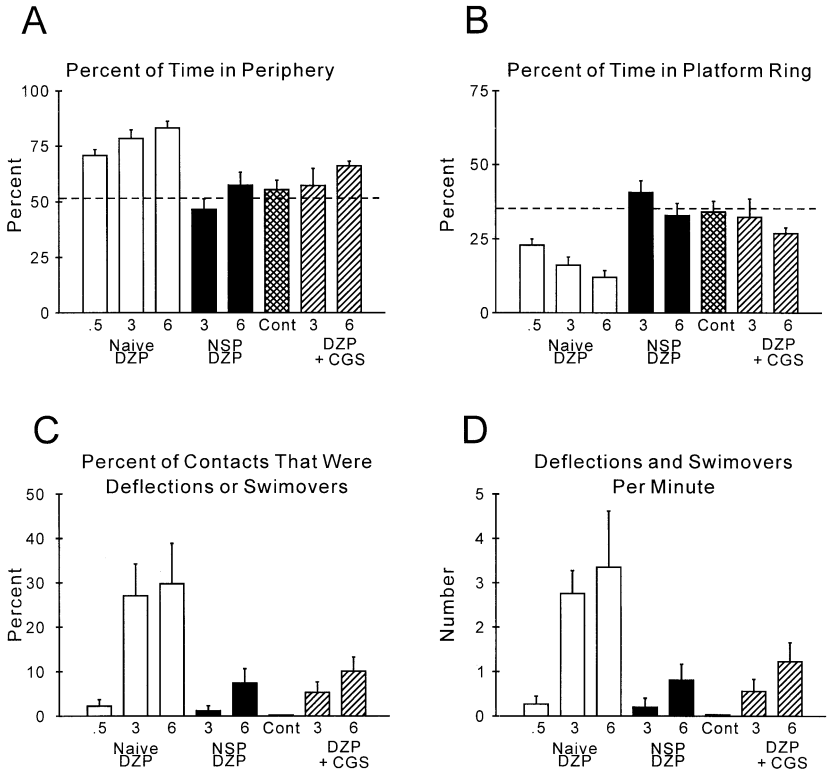

Fig. 3A–D Detailed behavioral analysis of hidden platform training. **A** Percent of time spent swimming in the periphery of the maze. The area of the periphery as a percentage of the whole maze area (52%) is indicated by the *dashed horizontal line*. **B** Percent of time spent swimming in the platform ring. The area of the platform ring as a percentage of the whole maze area (35%) is indicated by the *dashed horizontal line*. **C** Percent of all contacts with the platform that were either deflections or swimovers. **D** Number of deflections and swimovers per minute of swim time in the platform ring

$P<0.05$; Fig. 2B]. Thus, DZP impaired performance on this task if the rats were trained on it first, but the same treatment did not impair rats trained on the hidden platform task before the visible platform task.

Sensorimotor disturbances

Among the naive DZP and Vehicle Control groups there were significant group main effects and significant dose-dependent effects for all sensorimotor disturbance measures [percent of time in periphery: $F(3,32)=12.1$, $P<0.0001$; $t(32)=5.8$, $P<0.0001$; Fig. 3A; percent of contacts that were deflections or swimovers, $F(3,32)=6.4$, $P<0.002$; $t(32)=4.2$, $P<0.0001$; Fig. 3C; deflections and swimovers per minute, $F(3,32)=5.1$, $P<0.006$; $t(32)=3.8$, $P<0.0006$; Fig. 3D]. The Naive DZP 0.5 group did not differ from the Vehicle Controls on any measure ($P>0.05$). None of the NSP DZP or the DZP+CGS groups differed from the Vehicle Controls on percent of time in the periphery ($P>0.05$), and the NSP DZP and DZP 3+CGS groups did not differ from the Vehicle Controls on deflections and swimovers per minute ($P>0.05$). The DZP+CGS groups had a larger percent of contacts that were deflections or swimovers than the Vehicle Controls [3.0 mg/kg dose: $F(2,19)=3.9$, $P<0.04$; DZP 3+CGS versus Vehicle Controls, $P<0.05$; 6.0 mg/kg dose: $F(2,21)=3.8$, $P<0.05$; DZP 6+CGS versus Vehicle Controls, $P<0.05$]. The DZP 6+CGS group had more deflections and swimovers per minute than the Vehicle Controls [$F(2,21)=3.8$, $P<0.04$; DZP 6+CGS versus Vehicle Controls, $P<0.05$]. In sum, the Naive DZP 3 and Naive DZP 6 groups exhibited sensorimotor disturbances relative to the Vehicle Controls, but the Naive DZP 0.5 and NSP groups did not differ from the Vehicle Controls. The DZP+CGS groups had slightly but significantly more deflections and swimovers than the Vehicle Controls.

Swim speed

Swim speed obtained from the Poly-Trak analyses of the posttraining probe trial indicated that the Naive DZP 3 and Naive DZP 6 groups swam slightly faster than the Naive DZP 0.5 and Vehicle Control groups, which did not differ [Naive DZP 3, 12.2 ±0.4 distance units/s; Naive DZP 6, 12.3±0.7; Naive DZP 0.5, 10.5±0.4; Vehicle Control, 10.4 ±0.3; $F(3,32)=4.7$, $P<0.008$; Naive DZP 3 and Naive DZP 6 versus Vehicle Control and Naive DZP 0.5, $P<0.05$]. The NSP DZP 3 and DZP 3+CGS groups did not differ from the Vehicle Controls or each other (NSP DZP 3, 11.0±0.4; DZP 3+CGS, 10.9±0.9; $P>0.05$). The NSP DZP 6 group swam faster than the DZP 6+CGS and Vehicle Control groups, which did not differ [NSP DZP 6, 12.0 ±0.4; DZP 6+CGS, 10.7±0.5; $F(2,21)=4.5$, $P<0.03$; NSP DZP 6 versus DZP 6+CGS and Vehicle Controls, $P<0.05$].

General observations

The naive DZP rats did not behave adaptively when they encountered the hidden platform (e.g., deflections and

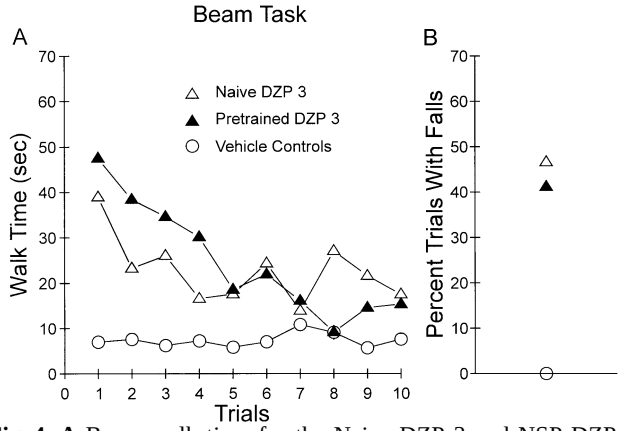

Fig. 4 **A** Beam walk time for the Naive DZP 3 and NSP DZP 3 groups. **B** Percent of beam walk trials on which a fall off the beam occurred. For key see **A**

swimovers). Also, when placed on the hidden platform after a trial without finding it, the following percentages of rats quickly walked or jumped off and continued swimming on training trials one to nine: Naive DZP 0.5, 22.2%; Naive DZP 3, 55.6%; Naive DZP 6, 80%; Vehicle Controls, 0%; NSP DZP 3, 0%; NSP DZP 6, 11.1%. The Naive DZP 3 and Naive DZP 6 rats swam slowly around the pool near the periphery and exhibited little search behavior in the pool (e.g., pauses, tight turns, orienting movements, head elevations; Whishaw and Tomie 1987). The overall impression was of debilitation in the Naive DZP 3 and Naive DZP 6 rats' ability to swim and behave adaptively in the pool.

Beam task

The Naive DZP 3 and NSP DZP 3 groups had longer walk times than the Vehicle Control group, but did not differ between themselves [$F(2,9)=7.5$, $P<0.004$; Naive DZP 3 and NSPDZP 3 groups versus Vehicle Control group, $P<0.05$; Fig. 4A]. Falls off the beam exhibited a similar pattern [$F(2,19)=7.1$, $P<0.005$; Naive DZP 3 and NSP DZP 3 groups versus Vehicle Control group, $P<0.05$; Fig. 4B]. Thus both DZP groups were ataxic and performed poorly.

Correlations

Further examination of relations between acquisition measures and other behavioral measures was done using Pearson product-moment correlations (Table 1). All of the correlations were significant and some were large, accounting for more than 80% of the variance. Some confirmed the validity of the measures, e.g., a large positive correlation between summed platform search time and percent of time swum in the periphery and large negative correlations between summed platform search time and platform quadrant search time or percent direct or circle swims. The correlations also revealed a consistent association between incidence of sensorimotor disturbance and poor maze acquisition scores, e.g., a positive correlation between percent of contacts that were deflections or swimovers and hidden platform search time, and a negative correlation between percent of contacts that were deflections or swimovers and platform quadrant search time. Similar correlations were obtained with ataxia measured with the beam task. This suggests that the sensorimotor disturbances were not specific to the maze task.

Discussion

DZP caused both sensorimotor disturbances and water maze acquisition deficits in naive rats, but caused neither sensorimotor disturbances nor acquisition deficits in

Table 1 Correlations between behavioral measures. The values under *r* represent the product-moment correlation coefficient that resulted when measure 1 was correlated with measure 2. The water maze measures were from the hidden platform version of the task. The groups used for correlations involving only water maze measures were the naive diazepam groups and the Vehicle Controls. The groups used for correlations involving water maze measures and summed beam traverse time were the Naive DZP 3 and Vehicle Control groups

Measure 1	Measure 2	*r*	*P*
Summed platform search time	Platform quadrant search time	–0.49	<0.002
	% direct or circle swims	–0.90	<0.0001
	% of time in periphery	0.81	<0.0001
	% of contacts that were deflections or swimovers	0.77	<0.0001
	Summed beam traverse time	0.83	<0.0001
Platform quadrant search time	% of time in periphery	–0.53	<0.001
	% of contacts that were deflections or swimovers	–0.54	<0.001
	Summed beam traverse time	–0.66	<0.01
% Direct or circle swims	% of time in periphery	–0.67	<0.0001
	% of contacts that were deflections or swimovers	–0.66	<0.0001
	Summed beam traverse time	–0.60	<0.02
% Of time in periphery	% of contacts that were deflections or swimovers	0.57	<0.0001
	Summed beam traverse time	0.78	<0.001
% Of contracts that were deflections or swimovers	Summed beam traverse time	0.86	<0.0001

NSP rats. This is similar to findings obtained with various NMDA and muscarinic antagonists (Saucier and Cain 1995, 1996; Beiko et al. 1996; Cain et al. 1996a,b). The simplest interpretation of these findings is that DZP caused sensorimotor disturbances, which in turn caused the acquisition impairments. There is no evidence of a specific impairment in water maze learning or memory by DZP.

DZP caused ataxia in both naive and NSP rats on the beam task. This was expected because none of the rats had had prior experience with this task. The ataxia indicated that the drug-induced sensorimotor disturbances were not specific to the water maze task and that such sensorimotor disturbances can be seen easily with DZP in novel test situations.

Apart from deflections and swimovers, the DZP+CGS groups did not differ from the Vehicle Controls on any measure. The incidence of deflections and swimovers exceeded that of controls in most cases, but was closer to control values than to the respective naive DZP groups, a finding consistent with the control-level measures of task acquisition in these groups. This suggests that the effects of DZP were mediated by an action on benzodiazepine receptors.

Our finding that NSP rats can learn the location of the hidden platform under DZP as readily as controls is similar to findings of Zanotti et al. (1994) but unlike those of McNamara and Whishaw (1990). Zanotti found that DZP did not affect reversal learning in the water maze in rats first spatially trained with no drug. They also found that rats familiar with the task requirements by swimming in the pool without a hidden platform acquired the task normally under DZP. We obtained similar findings when room cues were occluded by black curtains during NSP. This suggests that swimming in the pool and climbing onto the hidden platform are sufficient to protect against the effects of DZP in this task. Whishaw (1989) emphasized the importance of "(behavioral) experience with the actual procedures required to solve a place problem" for the NSP effect, and we and others found that there is little benefit of NSP unless the NSP behaviors are similar or identical to those required in the actual task (Caldji and Vanderwolf 1996; Saucier et al. 1996). McNamara and Whishaw found a small but reliable deficit in platform search time in rats first allowed to swim in the pool with a new platform position each day, then spatially trained under DZP. However, only search time data were reported and it is not known whether the rats showed evidence of spatial learning by probe trial or swim trajectory measures. Also, a core temperature ≤30°C is associated with impairment in this task (Vanderwolf 1991), and the use of 18°C water by McNamara and Whishaw, in contrast to 26°C or 29°C water by Zanotti and ourselves, could have contributed to the different findings.

We have documented sensorimotor disturbances in the pool in naive rats given 3.0 or 6.0 mg/kg DZP, and on the beam task in both naive and NSP rats given 3.0 mg/kg DZP. The sensorimotor disturbances had the effect of reducing contact with and information about the spatial location of the platform. From the point of view of issues raised in the Introduction the sensorimotor disturbances seem important for judging whether DZP acts specifically on learning and memory mechanisms. Zanotti, using doses of 2.5 and 5.0 mg/kg, suggested that anxiolytic properties, rather than any direct action of DZP on learning and memory, produced water maze deficits in naive rats. Our data are consistent with the suggestion that DZP did not act directly on learning and memory mechanisms. However, they suggest the more parsimonious explanation that the deficits resulted from the sensorimotor disturbances that DZP caused. This conclusion is similar to one from similar experiments with NMDA and muscarinic antagonists (Saucier and Cain 1995; Beiko et al. 1996; Cain et al. 1996a,b; Saucier et al. 1996).

This is the first water maze study to find sensorimotor disturbances in the *absence* of impairments in the visible platform task or slowing of swim speed. It is also the first to find impairments due to DZP in a visible platform task in rats naive to all water maze testing. In conventional water maze training, hidden platform training might serve as pretraining for a subsequent visible platform task. Swim speed and visible platform ability do not necessarily reveal drug-induced sensorimotor disturbances in every case. In light of the limitations of these conventional water maze controls, both a detailed behavioral analysis of behavior and NSP control groups would seem to be essential in water maze work of this kind.

NSP nearly eliminated sensorimotor disturbances in the drugged groups. Powerful pretraining effects of this kind are not new. Herz (1959) and Steinberg et al. (1961) found that experience with task conditions eliminated the effects of scopolamine or a combination of amphetamine and barbiturate, and DeVietti et al. (1985) found that prior experience with the apparatus (a narrow alley with one end closed off) eliminated the behavioral "trapping" effect that resulted from scopolamine. Whishaw (1989) found that training in one water maze allowed rats to learn the location of a platform under muscarinic antagonism in a second water maze almost as well as controls. Morris (1989), whose NSP method was used here, found that NSP reduced NMDA antagonist-induced sensorimotor disturbances and improved water maze performance. Appropriate behavioral experience can facilitate later performance under drug in a variety of tasks, allowing excellent performance with drug treatments that cause severe impairments in naive rats. NSP allows for the learning of "use of platform" (Morris 1989) and other general behavioral strategies that are important for successful performance of the task under drugs. This allows rats to behave adaptively in the task and to acquire spatial information under a variety of drugs. Thus performance on the task depends on a complex interaction between what the animal knows about the task at the start of training, and drug action in the brain.

In sum, doses of DZP that produced marked sensorimotor disturbances and acquisition impairments in naive rats did not produce these in NSP rats. The sensorimotor

disturbances occurred in the absence of impairments in visible platform performance or a decrease in swim speed and correlated strongly with measures of maze acquisition. Occupancy of benzodiazepine receptors by DZP does not prevent robust spatial learning in the water maze. A fuller discussion of issues relating to spatial learning and drugs can be found in Cain and Saucier (1996).

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