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NAVIGATION IN THE MORRIS SWIM TASK AS A BASELINE FOR DRUG DISCRIMINATION: A DEMONSTRATION WITH MORPHINE

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A morphine versus saline discrimination was demonstrated using the Morris swim task as the behavioral baseline. The apparatus was a large circular pool filled with water made opaque by floating polypropylene pellets. Rats were placed in the tank in randomly selected locations (12 trials per session) and could escape by swimming to a platform submerged 2 cm below the surface. Morphine (5.6 mg/kg) or saline was injected prior to training sessions. The position of the platform in a given session depended on the drug condition, thus forming the basis for discriminative responding. Three of the 4 rats acquired the discrimination, as evidenced by direct swims to the condition-appropriate platform. Generalization probe sessions were conducted following acquisition. Probe sessions were preceded by injections of morphine (0, 1.0, 3.0, 5.6, or 10.0 mg/kg) and involved placing the rat in the pool for 1 min without a platform. Swim patterns revealed a gradient, with probe swimming more concentrated in the area of the morphine platform position after higher morphine doses. In addition, dose-dependent increases in the likelihood of swimming first to the morphine-associated platform location were obtained. These results illustrate the generality of drug discrimination across different behavioral procedures, and of particular interest with respect to spatial learning, demonstrate interoceptive stimulus control of navigation.

Key words: drug discrimination, Morris water maze, spatial learning, morphine, rat

Drug-discrimination procedures are among the most important and widely used preparations in behavioral pharmacology because of their value in classifying and characterizing drugs (see reviews by Riley, 1997; Stolerman, 1993; Young, 1991a). Contemporary applications of the procedure generally involve a conditional discrimination in which a specific response (say, pressing the left lever in a two-lever operant chamber) is reinforced after administration of a dose of a given drug. During another session, pressing the right lever is reinforced after a vehicle administration. With such training, lever pressing comes under the control of the drug in that left- or drug-lever responding is occasioned after drug, but not vehicle, administration, and right- or vehicle-lever responding is occasioned after vehicle, but not drug, administration. Further evidence of stimulus control comes from generalization tests in which drug doses higher or lower than that used in training are substituted for the training dose, and are associated with a dose-dependent gradient of drug-lever responding. Drugs of the same pharmacological class as the training drug also frequently occasion drug-lever responding, whereas drugs from different classes typically occasion vehicle-lever responding (Riley; Stolerman; Young).

The results of drug-discrimination studies have shown considerable generality across various methods. For example, similar drug-discrimination patterns have been obtained with a variety of different species and procedures. In addition to the lever-press arrangement with food reinforcement described above, drug discrimination has been established with other maintaining events (e.g., shock avoidance; Shannon & Holtzman, 1976) and with other apparatus (e.g., t maze; Overton, 1982). The present study sought to determine whether the generality of drug discrimination could be extended to an escape procedure involving spatial navigation: the Morris swim task (Morris, 1981).

The Morris swim task involves placing the

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rat in a large pool with a small escape platform slightly submerged beneath water made opaque so that the platform is not visible. Morris (1981) showed that rats rapidly learn to navigate directly to the platform from any release spot and, thus, the procedure has become a widely used tool in the study of spatial learning (Cain & Saucier, 1996; Gallistel, 1990). Accounts of spatial learning in the swim task differ, but most emphasize the control of navigation by stimuli located outside the pool (e.g., Morris). However, analysis of stimulus control in the swim task has been limited, and it remains difficult to specify with precision the nature of the stimuli that control navigation (Cain, Beiko, & Boon, 1997; Whishaw & Mittlelman, 1986).

Nonetheless, Keith and Galizio (1997) brought navigation itself under stimulus control. They demonstrated conditional control of navigation by visual stimuli in the swim task by training rats in two physically separate pools: one painted black and the other painted white. A multiple-component repeated-acquisition procedure was used in which the hidden platform was always in a fixed location in one pool (performance component) and varied from session to session in the other (acquisition component). After 10 to 20 training sessions, rats showed evidence of conditional control. In the performance-component pool, rats swam rapidly and directly to the platform. In the acquisition-component pool, latencies were long and swim paths erratic on the first trial of a session, but after just one or two trials, rapid direct swims to the new platform position were observed. These results showed conditional control of navigation by visual stimuli, and it seemed plausible to try to adapt the procedure to drug discrimination. Indeed, the rapid learning seen in the swim task suggests the prediction that drug discrimination might be readily acquired with this procedure. Consider that Riley (1997) has shown that drug-discrimination training can be accelerated using the conditioned taste aversion procedure, which, like spatial navigation, is characterized by rapid learning. On the other hand, the evolutionary history that shaped spatial learning may suggest a different prediction. Some classic treatments view spatial learning as involving a preparedness to develop a ''map'' that permits landmarks in the environment to exert rapid stimulus control (e.g., Gallistel, 1990; O'Keefe & Nadel, 1978). From this standpoint, learning relations between interoceptive cues and spatial locations might be seen as contraprepared, and thus, difficult or impossible to learn. The present study examined the possibility of establishing interoceptive control over navigation by training rats to swim to a hidden platform that was located in one position on sessions following injections of 5.6 mg/kg morphine and in another location following saline injections.

METHOD

Subjects

Four albino Holtzman Sprague-Dawley rats, 120 days old at the onset of testing, served as subjects. Their coats were marked with harmless black ink to enhance video tracking.

Apparatus

The apparatus was a circular white pool (1.5 m diameter, 30.5 cm deep). The pool was filled to a level of 23 cm with water, and a layer of polypropylene pellets floated on the surface of the water to prevent rats from seeing the submerged escape platform (see Cain et al., 1997). A small white platform (10 cm diameter, 20 cm high) was submerged 2 cm below the surface of the water in a location determined by experimental condition (see below). The water temperature was maintained at approximately 30 °C. The swimming pool was illuminated using indirect halogen lighting (500 W) reflected off the white painted ceiling. Black-and-white vinyl shower curtains, marked with large distinctive patterns, completely enclosed the water tank in a circular fashion (see Figure 1).

A closed circuit camera centered over the tank was aimed directly downward, capturing the entire surface of the water. The video signal was transduced by an interface made to track a contrasting object (a rat) in the visual field of the camera. Software (San Diego Instruments) permitted the evaluation of several dependent measures including latency to reach the platform, path length, initial heading, and overall swim speed.

Procedure

Pretraining. During two preliminary sessions, rats were trained to swim to a fixed lo-

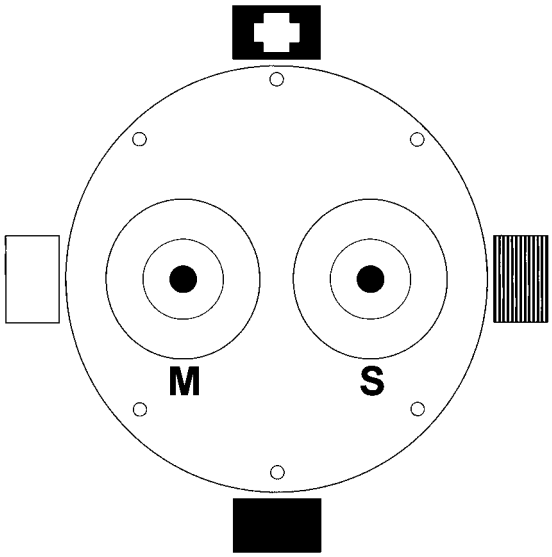

Fig. 1. The pool (1.5 m diameter; not drawn to scale) is depicted. Within the pool, small gray circles indicate drop-off points, and larger dark circles the location of the platforms (M = morphine; S = saline). Surrounding the platforms are two rings generated by the data analysis software (not visible to the rats). The inner ring (20 cm diameter) was used to determine criterion responding in training, and the outer ring (45 cm diameter) was used to determine dwell time during probe trials. Outside this graphic representation of the apparatus, the visual patterns displayed on a curtain that encircled the apparatus are represented by squares that indicate the pattern displayed on the entire quadrant of the curtain (north: large white cross on black; east: vertical stripes; south: solid black; west: solid white).

cation in the pool. This phase of training involved placing the rat in the water until it reached the platform or until 1 min elapsed. At the onset of each trial, the rat was placed in the tank, facing the outside, at any of six release locations (see Figure 1). After reaching the platform, rats were permitted to remain on it for 15 s, and then were removed from the pool area for a 2-min intertrial interval. If the rat failed to reach the platform within 1 min, it was placed on the platform by the experimenter. Twelve trials were conducted in each session, with each release location used twice per session. Sessions were conducted 5 days per week. Release locations were randomly determined, with the constraints that no more than three northerly or three southerly release points were used consecutively, and the same release point was not used twice in a row. The location of the platform was fixed during any given session, and although no injections were given during the two pretraining sessions, the location of the platform was the same as that later used for the saline condition.

Discrimination training. General procedures were as described above, but after pretraining rats received intraperitoneal injections of 5.6 mg/kg morphine or saline 15 min prior to each training session. On sessions that followed saline injections, the platform was always placed in the east quadrant, 33 cm towards the center of the tank. After morphine injections, the platform was located in the west quadrant, again 33 cm towards the center of the tank (see Figure 1). For analysis purposes, a correct (condition-appropriate) response was defined by two criteria. The first criterion was that the rat swim to the correct platform without breaking the plane of a circle (20 cm diameter) centered on the condition-inappropriate platform (see Figure 1). The second criterion for a condition-appropriate response was that the latency to reach the escape platform was less than or equal to 10 s. Training criteria required that 90% or better condition-appropriate responding be achieved across at least eight of ten sessions and also that in eight of those ten sessions the first trial was correct. When these criteria were met, probe testing sessions replaced the regular training session on two of the five weekly sessions.

Generalization probes. As with training sessions, probe sessions were preceded by injections, but to assess generalization, the range of doses included 1.0, 3.0, and 10.0 mg/kg morphine in addition to 5.6 mg/kg and saline. The rat was placed in the pool 15 min after injection on probe sessions, but no platform was present. The swim path was observed for 60 s in the absence of the platform, and the session was then terminated. For purposes of generalization data analysis, the rat's swim path during the 60 s was divided into time spent within a circle (45 cm diameter) around the saline platform location (saline dwell time), a circle (45 cm diameter) around the morphine platform (morphine dwell time), and time spent outside both circles. Each probe performance was also analyzed with a variation of the criteria used to determine correct responding in baseline (i.e., if the swim path intercepted the position of the morphine platform first, it was characterized

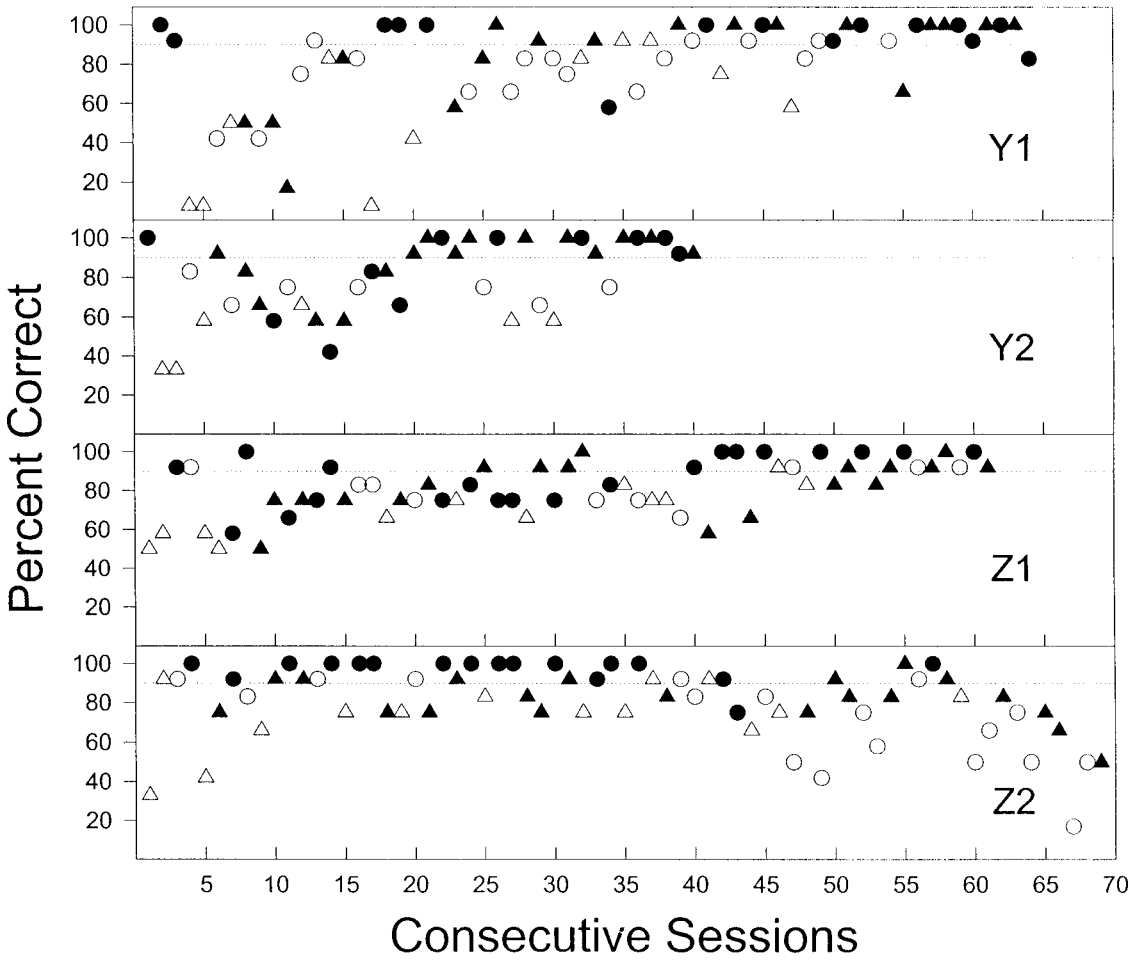

Fig. 2. Acquisition of the morphine discrimination for each rat. Percentage of correct trials per session are indicated by either circles (saline training sessions) or triangles (morphine training sessions). Filled symbols indicate that performance on the first trial of that session was correct, and open symbols indicate incorrect initial trials. The dotted line represents the criterion cut-off for 10 of 12 correct responses.

as a morphine response; a swim path that intercepted the saline platform position first was classified as a saline response).

Even after the probe sessions had begun, training sessions were conducted on three of the five weekly sessions, and probe sessions were conducted only when the criteria for maintenance of discrimination were met. For a probe test to be conducted, responses on 4 of the last 5 training days had to be 90% condition appropriate. Furthermore, on the session immediately preceding the planned probe session, the first response had to be correct, with at least 90% condition-appropriate responding. Each dose was tested three times. The order of doses during generalization probes was determined randomly, with the constraint that the end of each cycle of determinations (one exposure to each dose including a saline injection) was completed before beginning the next cycle.

RESULTS

Acquisition of discrimination. Extensive training was required to establish the morphine–saline discrimination. In fact, only 3 of the 4 rats met acquisition criteria. Figure 2 shows the acquisition data for each rat with percentage of correct swims per session plotted on the vertical axis (recall that a correct swim was defined as one in which the rat reached

the platform in less than 10 s without entering the 20-cm circle that defined the condition-inappropriate zone). For 3 of the rats (Rats Y1, Y2, and Z1) accuracy increased across sessions. Rat Y1 met the acquisition criteria in 64 sessions, Y2 required 42 sessions, and Z1 required 49 sessions. Although Rat Z2 showed improvement across sessions, its performance never reached criterion levels, and it was dropped from the study after 70 sessions.

Generalization tests. The left panels of Figure 3 show percentage of morphine responding (morphine area dwell time divided by morphine plus saline area dwell times multiplied by 100%) averaged across the three determinations and plotted as a function of morphine dose. Thus, scores higher than 50% on this measure reflect more time spent swimming in the morphine area relative to time spent in the saline area (with 100% indicating that the animal failed to enter the saline area during the probe session). The generalization gradients showed a dose-dependent increase in morphine responding for all 3 rats. Rat Y1's average morphine area responding was approximately 50% after saline injections as well as after 1.0 mg/kg of morphine, with gradual increases in morphine dwell time at the higher doses. Steeper gradients were obtained from Rats Y2 and Z1. Rat Y2 (middle left panel) spent relatively little time in the morphine area after saline and 1.0 mg/kg injections, but relatively more time there at all higher doses. Similar results were apparent for Rat Z1 (bottom left panel). The absolute dwell-time data presented in Table 1 show that the percentages shown in Figure 3 reflected dose-related increases in time spent in the morphine area and decreases in time spent in the saline area. For example, rats spent from 4.2 to 8.5 s in the morphine area after saline and 11.5 to 15.1 s after 5.6 mg/kg morphine. In summary, all 3 rats provided evidence of generalization gradients along the dimension of morphine dose.

The right panels of Figure 3 show the morphine area dwell times for each individual probe session. In the first cycle, as morphine dose was increased, the relative time spent in the morphine area increased in all 3 rats. Rats Y2 and Z1 each responded approximately 30% to 35% less in the morphine area at saline and 1.0 mg/kg than at the higher doses of morphine during the first cycle of testing. The gradient obtained from Rat Y1 was a somewhat different shape. The gradient was flat up through 3.0 mg/kg, with higher levels of morphine responding occurring at the training dose and above. In general, gradients obtained during the second cycle of determinations were similar in form to those obtained in the first. One notable exception was for Rat Y1, whose gradient was flat until the highest morphine dose was tested. The third cycle of doses for Rats Y1 and Y2 (right panels) resulted in gradients that were less clearly under morphine stimulus control. Although the peak of Rat Y1's gradient was at 5.6 mg/kg, morphine responding was roughly equivalent after saline and 10 mg/kg. Rat Y2 showed twin peaks at 3.0 and 10.0 mg/kg, but responding at 5.6 and 1.0 mg/kg and saline was equivalent. However, stimulus control remained sharp for Rat Z1, which showed continued high levels of morphine responding for the three highest doses tested. In summary, there was some evidence of a flattening of generalization gradients by the third cycle of determinations for 2 rats (Y1 and Y2).

The dwell-time measures presented in Figure 3 reflect the swimming patterns of subjects for the full 60-s probe. Such extended exposure to extinction conditions might have interfered with stimulus control, particularly late in the probe trial. An alternative measure that is less influenced by extinction conditions is the initial platform area choice on each probe trial. Using the criteria that were operative in determining correct responding in training (Figure 1), each probe trial was analyzed in terms of which area was first entered. Figure 4 shows the percentage of initial swims to the morphine area. All 3 rats swam to the saline area first during each saline test session and to the morphine area first on all three 10 mg/kg test sessions. Responding to intermediate doses revealed a fairly steep gradient, indicating that stimulus control in the initial portion of the probes remained fairly strong throughout the three cycles of probe determinations.

Table 2 shows swimming speeds as function of morphine dose, and the absence of reliable effects indicates that the gradients observed in Figures 3 and 4 were obtained at doses that did not produce impairments in overall swimming performance.

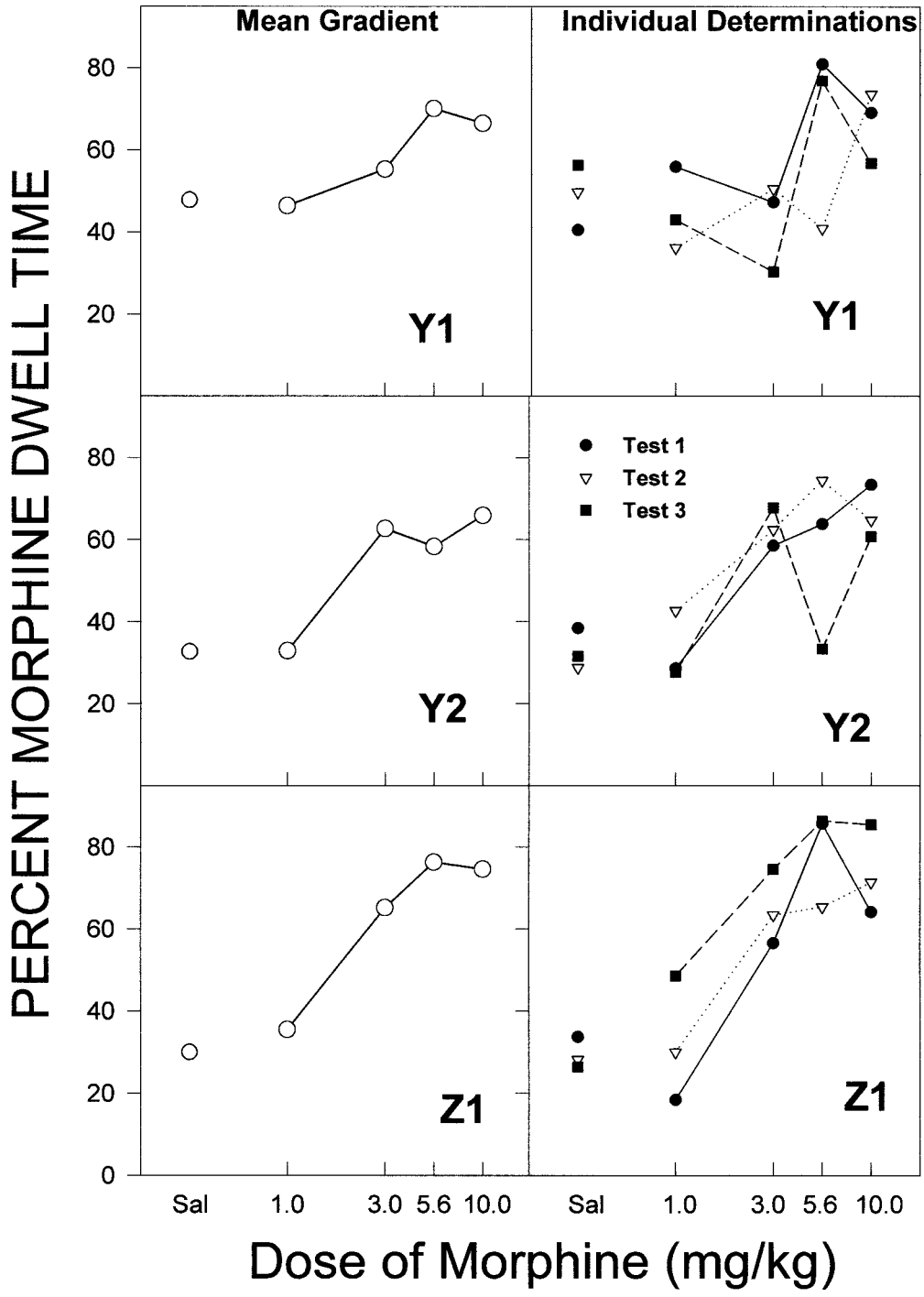

Fig. 3. Left panels show mean percentage of morphine dwell time (number of seconds spent in morphine target area divided by number of seconds spent in saline plus morphine target areas multiplied by 100%) during probe sessions as a function of morphine dose for the 3 rats tested. Right panels show percentage of morphine dwell time during individual probe sessions (Test 1 = black circles; Test 2 = white triangles; Test 3 = black squares) for each rat.

Table 1

Mean absolute dwell time (s) and standard deviation (in parentheses) in saline and morphine areas as a function of morphine dose during generalization probe tests.

Probe dose	Rat Y1		Rat Y2		Rat Z1	
	Saline	Morphine	Saline	Morphine	Saline	Morphine
Saline	9.3 (1.8)	8.5 (0.3)	10.5 (1.4)	5.1 (0.6)	9.8 (1.0)	4.2 (0.8)
1.0	8.2 (0.7)	7.1 (1.5)	9.7 (1.7)	4.6 (0.5)	9.8 (0.5)	5.4 (2.4)
3.0	8.0 (1.5)	9.9 (0.9)	7.5 (0.3)	12.6 (0.2)	6.4 (0.8)	12.0 (1.3)
5.6	4.9 (0.9)	11.5 (3.7)	8.1 (1.9)	11.3 (2.7)	4.7 (1.2)	15.1 (1.4)
10.0	5.3 (1.0)	10.5 (1.7)	7.4 (1.8)	14.3 (2.1)	4.6 (0.9)	13.5 (2.4)

DISCUSSION

One major question posed in this study was whether a morphine versus saline discrimination could be learned using the Morris swim task. With 3 of the 4 rats tested, the results were affirmative. Although there was some evidence of acquisition with the 4th rat, it failed to meet the discrimination criteria after 70 sessions. For the 3 rats that met the discrimination criterion, acquisition was not particularly rapid, with a range of 42 to 64 sessions to criterion required. In fact, these rates of acquisition were similar to those observed with rats in other studies using two-choice operant procedures with morphine. For example, Young, Masaki, and Geula (1992) trained 17 rats in a saline versus 5.6 mg/kg morphine discrimination using a fixed-ratio schedule of lever pressing with food reinforcement, and found that the mean number of sessions to acquisition criterion was 54. In a t-maze study, Overton (1982) found that a saline versus 4.0 mg/kg morphine discrimination required more than 31 sessions, and several rats were dropped from the study after failing to meet acquisition criteria in fewer than 60 sessions. Thus, acquisition of stimulus control of navigation in the swim task by morphine appears to be comparable to that seen in more standard drug-discrimination procedures.

A second concern of the present study was whether swimming patterns trained in the presence of 5.6 mg/kg morphine would generalize to other morphine doses. Generalization gradients were obtained using two different dependent measures, and both revealed dose-dependent increasing functions that were similar to gradients obtained with morphine using more traditional two-choice procedures (e.g., Shannon & Holtzman, 1976, 1979; Young et al., 1992). The gradients based on percentage of morphine-area dwell time across sessions (Figure 3) ranged from approximately 30% at saline and low doses of morphine to 75% for 5.6 and 10 mg/kg. The shapes of these gradients varied somewhat within rats, but for 2 rats (Y2 and Z1), gradients were sigmoidal with low and roughly equivalent morphine dwell time after saline and 1.0 mg/kg and high and roughly equivalent morphine dwell time at all other doses. The gradient for Y1 was flatter, but stimulus control was still revealed by the higher values at 5.6 and 10 mg/kg.

The differences in gradient shape revealed by the two indexes of generalization used in the present study (dwell time and percentage of initial swims) are reminiscent of the controversy involving appropriate measurement procedures in drug discrimination, and the resulting conceptualization of the nature of stimulus control by drugs (see Colpaert, 1991; Stolerman, 1991; Young, 1991b). The initial-swim gradients (Figure 4) tended to resemble those obtained from previous studies employing nominal response-selection measures (e.g., Colpaert, 1977); that is, these gradients tended to be relatively steep. On the other hand, dwell-time gradients (Figure 3) tended to resemble those using graded measures (e.g., D'Mello & Stolerman, 1978). It is important to note that these graded functions were not simply the result of averaging across subjects or averaging across dose determinations within subjects (see Figure 3). Thus, it is possible that the present procedure may offer a general method by which graded drug-discrimination functions may be obtained within subjects (see also McMillan & Hardwick, 2000; Snodgrass & McMillan, 1996).

Although the average dwell-time gradients

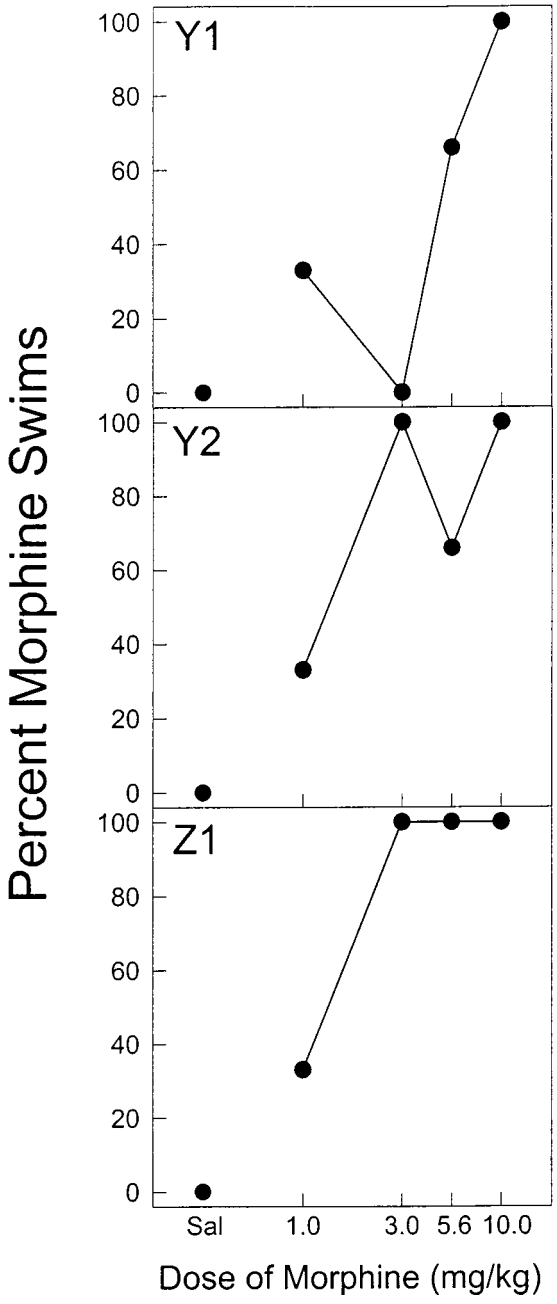

Fig. 4. Percentage of probe trials on which the initial swim response was to the morphine target area as a function of morphine dose in each rat tested.

generally were representative of individual sessions during the first two cycles, some flattening of these gradients was apparent by the third test cycle in 2 of the 3 rats. Observation revealed that, by the third cycle, Rats Y1 and Y2 appeared to develop a response pattern on probe trials that was characterized by swimming to the condition-appropriate platform area, and in the absence of the platform, then swimming about the periphery of the tank (thigmotaxis). Thus, the extinction conditions prevailing during probe trials may have been discriminated from training trials. Interestingly, data from recent studies suggest that stimulus control obtained in traditional discrete-response procedures is relatively unaffected by repeated exposure to extinction (Ator, 1990; Zarcone & Ator, 2000). For example, when food reinforcement no longer followed lever presses, Zarcone and Ator found that response rates declined, but that degree of stimulus control based on a lorazepam training stimulus remained high. Note, however, that in the present procedure the rat must continue to swim throughout the extinction probe trial, even if stimulus control declines. Thus, although a graded function can be obtained in individuals with the dwell-time measure, the initial-swim gradients may provide a closer counterpart to traditional discrete-response procedures.

Table 2

Mean swimming speeds (cm/s) and standard deviations (in parentheses) as a function of morphine dose during generalization probe tests.

Probe dose	Rat Y1	Rat Y2	Rat Z1
Saline	32.4 (1.3)	29.9 (0.3)	29.7 (4.4)
1.0	30.9 (1.3)	28.8 (1.3)	30.2 (7.3)
3.0	36.0 (1.8)	28.2 (1.5)	24.3 (1.1)
5.6	33.3 (0.7)	28.1 (3.3)	28.1 (8.5)
10.0	34.9 (1.3)	27.2 (0.4)	24.5 (2.8)

The relatively slow acquisition observed in the present study, along with the logistical problems posed by the swim task, may limit its utility as a tool to study drug discrimination. Variations on the present procedure (e.g., shorter probe sessions to reduce exposure to extinction conditions), however, might improve on the present results. In any case, the present results do provide a demonstration of the control of spatial navigation by interoceptive stimuli. The relatively prolonged acquisition might be related to the complexity of the discrimination. Consider that although navigation in the Morris swim task is generally understood to be controlled

by configurations of extrapool stimuli (e.g., Morris, 1981; Sutherland & Rudy, 1989), it is difficult to specify the precise contingencies that control the performance. For example, the spatial relation between the platform and extrapool cues depends upon the position of the rat in the pool at any point in time. With the procedure used in the present study, an additional level of complexity is added in which the significance of the extrapool configuration to navigation is under the contextual control of an interoceptive stimulus. Stimulus control of this nature may be required to explain some examples of navigation in the natural environment. For example, the seasonal control of direction of bird migration is, in part, under the influence of different hormonal states (Berthold, 1993). These and the present results indicate that theories of spatial learning that have emphasized cognitive maps of distal stimuli will have to account for contextual control by interoceptive stimuli as well (Gallistel, 1990; O'Keefe & Nadel, 1978). The techniques developed in the present study might be further developed to provide a laboratory analysis of such processes.

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