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Ginkgo biloba promotes short-term retention of spatial memory in rats

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Abstract

This study examines possible interactions between exposure to *Ginkgo biloba* extract and enriched environments on the acquisition and retention of spatial learning following massed and spaced trials. After 4 weeks of exposure to either ginkgo or vehicle, 8-week-old rats were tested using a Morris Water Maze in either massed or spaced trials. While ginkgo did not have an effect on maze acquisition or long-term retention, it did promote short-term retention of spatial memory. Following reversal training, ginkgo promoted short-term retention for two groups but impaired retention for a third. These results suggest that ginkgo has powerful effects on short-term retention that vary with training conditions.

Keywords: *Ginkgo biloba*; Water maze; Learning

1. Background

Herbal extracts from the Chinese "maiden hair tree" *Ginkgo biloba* have been used for medicinal purposes for thousands of years (Major, 1967). Recently, many have claimed that an extract prepared from the leaves enhances memory and concentration. However, there are relatively few controlled studies examining this claim, and the results reported are often contradictory (Wesnes et al., 2000; Solomon et al., 2002). Nevertheless, ginkgo is widely viewed as a memory-enhancing agent, and there are over 24 different brands of *G. biloba* extract sold in the United States (Itil et al., 1998) accounting for over US$240,000,000 sales in 1997.

Recent studies have provided conflicting evidence of the effects of *G. biloba* extracts at promoting learning and memory. Ginkgo extracts increase brain activity as measured by an increase in alpha, and decrease in delta and beta waves in young adult males with no cognitive deficits (Itil et al., 1996) and patients with Alzheimer's disease (Itil et al., 1998). Similarly, ginkgo promotes attention, concentration (cerebral insufficiency scale), and short-term memory (Wechsler Memory Scale) in elderly patients with cognitive impairments (Winther et al., 1998) but not in cognitively intact elderly subjects (standard neuropsychologic testing, including MMSE, Stroop Color and Word Test; Weschsler Memory Scale, Mix and Crews, 2000; Solomon et al., 2002). In younger subjects, ginkgo promotes attention measured by the Cognitive Drug Research computerized assessment battery (Kennedy et al., 2000) but does not enhance different aspects of learning and memory (Wechsler Memory Scale and Sternberg Memory Scanning Test, Moulton et al., 2001). Older subjects taking ginkgo experienced enhanced memory but not attention (Rigney et al., 1999; Wesnes et al., 2000).

A similar range of effects has been observed in rodents. High doses of ginkgo (100 mg/kg) promote acquisition and retention of appetitive operant conditioning in adult mice (100 mg/kg EGb 761, Winter, 1991), short-term (but not long-term) memory in passive avoidance tests in aged mice (100 mg/kg, Stoll et al., 1996), and lower doses promote spatial learning in aged rats (50 mg/kg EGb 761, Winter, 1998; 1 mg/kg Zingicomb, Topic et al., 2002b). Mice that had received *G. biloba* extract (Egb 761; 100 mg/kg) for 4 or 8 weeks quickened acquisition of appetitive operant conditioning (bar pressing for a food reward), fewer performance errors, and greater retention 10 weeks after termination of the conditioning (Winter, 1991). Rats that had received *G. biloba* extract (EGb 761; 50 mg/kg) 30 min before spatial

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learning testing (eight-arm radial arm maze) learned the maze faster and made fewer errors than animals that received the drug after testing (Winter, 1998). In a similar study, aged rats (22–24 months old) performed poorer in initial trials during water maze testing when compared with young (3-month-old) rats. *G. biloba* was provided in combination with *Zingiber officinale* (Zingicomb) for 9 days prior to conclusion of water maze testing. At an effective dose of 0.29 mg/kg ginkgo (1 mg/kg Zingicomb) but not 2.9 mg/kg ginkgo (10 mg/kg Zingicomb) improved escape latency times in the aged animals (Topic et al., 2002b). A similar effect of lower doses of ginkgo was reported in a one-trial step-through avoidance task. Rats received an acute dose of Zingicomb (0.5, 1, 10, or 100 mg/kg) 60 min prior to the acquisition trial, which was completed 24 h prior to a one-trial step-through inhibitory avoidance task. The results indicate that rats receiving 10 mg/kg Zingicomb (effective ginkgo dose of 2.9 mg/kg) performed better than animals receiving either higher or lower doses (Topic et al., 2002a).

A variety of maze techniques have been used to examine spatial learning and memory in rats. Currently, the primary maze designs used in learning and memory studies are the radial arm maze (Olton, 1978) and the water maze (Morris, 1984). The traditional radial arm maze consists of a central start location with choice arms with a food reward at the end radiating out from the center. Most mazes have a symmetrical design so that upon returning to the central location from a choice arm, the rat is presented with the same type of choices. The radial arm maze can be used to test a variety of memory tests including short-term working memory and long-term reference memory by examining the number, sequence of arms, and the total length of time necessary to complete the task. However, this task relies on animals being motivated to receive a food reward for performance. The water maze consists of a large circular pool of water with escape platforms placed at specific locations. The presence or absence, location, and visibility of the escape platform can be changed to examine short-term memory retention, transfer, and visual discrimination through the collection of latency to complete the task, distance traveled, swim speed, and time spent in distinct regions of the maze. The use of this swimming task minimizes the motivational problems associated with appetitive tasks but is complicated if animals have motor impairments.

Acquisition of spatial learning skills in rats can be affected by a variety of factors. Normal subjects can demonstrate increased spatial learning skills following housing in enriched environments (Passineua et al., 2001; Paylor et al., 1992). In enriched environments, animals are housed in a continually novel environment produced through biweekly changes of structural and moveable objects or "toys" in the cage. Animals in environmentally enriched housing conditions for 1 year demonstrated better spatial learning abilities in the Morris Water Maze (Pham et al., 1999; Park et al., 1992). Animals raised in environmentally enriched housing appear to process contextual information faster than animals housed in environmentally impoverished housing (Woodcock and Richardson, 2000).

The timing of testing and training trials in the spatial tasks also appears to have an effect on learning ability. Spaced trials, in which testing occurs over consecutive days, appears to benefit young (Kraemer and Randall, 1995) and adult rats more (Goodrick, 1973) compared to massed trials. Similarly, short-term memory (1 day after cessation of training) is enhanced after massed trials, in which acquisition occurs within a single day rather than over consecutive days. However, long-term memory retention (14 days after the cessation of training) is significantly impaired in rats trained in massed trials (Spreng et al., 2002).

This study examined the relationship between a purported memory enhancer (*G. biloba* extract), enriched environments, and testing schedule on acquisition, short-term, and long-term retention of spatial learning in the Morris Water Maze. Based on previous studies that indicate a greater effect of ginkgo in human subjects with cognitive impairments (Winther et al., 1998) and aged rats (Winter, 1991; Winter, 1998; Topic et al., 2002b), we predict a greater effect of ginkgo in promoting spatial learning under adverse conditions, such as impoverished environmental conditions and massed trials.

2. Methods

2.1. Subjects

This study examined behavior in 40 young (4 week old; 51–75 g) male Sprague–Dawley rats (Charles River). Animals were maintained in groups of five within $72 \times 30 \times 45$-cm glass enclosures. The animals were randomly assigned to either impoverished ($n = 20$) or enriched housing conditions ($n = 20$). Animals in both housing conditions were allowed ad libitum access to food and water, and bedding was changed twice weekly. In the enriched housing conditions, a novel environment was obtained by the addition of large structural and smaller movable objects that were changed twice weekly. Enrichment items consisted of a variety of items: raised platforms with interchangeable ladders or ramps, plastic bowls (21 cm diameter), and white PVC or black plastic drainage tubes (30 cm long and 10 cm diameter). Smaller moveable objects included balls of steel wool; wooden sticks; bird toys, such as "Olympic rings" and mirrors; and ferret toys, such as small brightly colored plastic balls with and without bells. Animals were maintained in the respective housing conditions for 4 weeks prior to and throughout the behavioral testing phases. All procedures followed a protocol approved by the local Institutional Animal Care and Use Committee in accordance with institutional and federal guidelines.

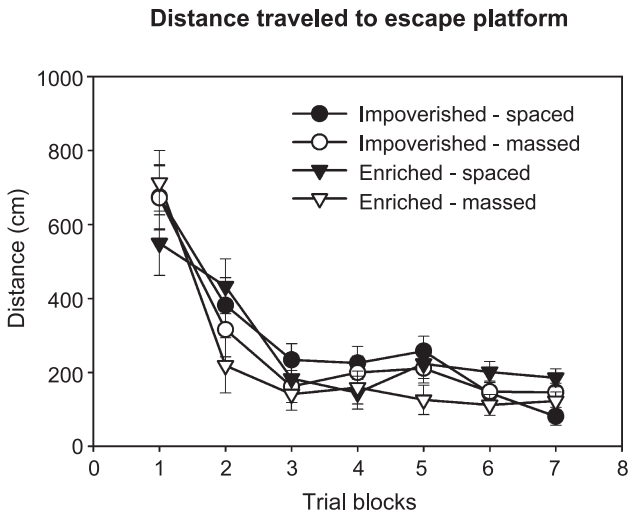

Fig. 1. Distance traveled by rats to reach the submerged platform during acquisition for each of the four groups.

2.2. Drug

A commercially available form of ginkgo extract was obtained at a local health food store (General Nutrition Centers). The extract contained 24% ginkgo Flavonglycosides along with 7.5% Stevia Extract (GNC product number 887224; Herbal Plus Standardized *G. biloba*. Half of the animals in each housing condition ($n=10$ enriched environment, $n=10$ impoverished environment) received daily oral doses of 10 mg *G. biloba* extract per kilogram body weight mixed in 10% sucrose water. While many previous studies had focused on the effects of relatively high doses of *G. biloba* on learning and memory, recent reports (Topic et al., 2002a; Topic et al., 2002b) and preliminary data in the laboratory indicate the efficacy of lower doses. Control animals ($n=10$ enriched environment, $n=10$ impoverished environment) received an equivalent volume of 10% sucrose solution. To provide a consistent dosage to the animals, a gavage needle was used to deliver the solution into the mouth (cheek pouch) with no complications. Drug administration occurred daily for 28 days prior to and throughout the behavioral testing phases. On testing days, drug administration occurred prior to behavioral testing.

2.3. Behavioral testing

Testing in the Morris Water Maze (Morris, 1984) began following 4 weeks of exposure to the housing and drug conditions. Half of the animals (now 8 weeks old) in each environmental condition ($n=5$) were trained in massed trials (all 21 acquisition trials occurring in a single day) or spaced trials (3 trials per day for 7 days) in a design modeled after Spreng et al. (2002). Rats were run in blocks of five animals so that the intertrial interval was approximately 10 min. For massed trials, the time between blocks was approximately 1 h. In spaced trials, the time between blocks was approximately 23 h. During acquisition trials, the animals were released from predetermined start locations and swam through the maze to find the hidden escape platform. The platform remained in a fixed location throughout all acquisition trials. The latency to find the hidden escape platform and the distance traveled to the escape platform were observed. At the end of the acquisition phase, the escape platform was removed, and animals received a 60-s probe trial to examine short-term retention (5 min after last acquisition trial) or long-term retention (14 days after last short-term retention trial). During probe trials, the percentage of time spent in a zone three times the diameter of the hidden platform (representing 7.1% of the area of the maze) was examined consistent with the method of Spreng et al. (2002).

After the long-term retention testing, the ability of rats to relearn the task was tested using a series of reversal trials followed by a single probe trial. Immediately following the 14-day probe trials, animals underwent four reversal trials in which the hidden escape platform was located in the quadrant opposite to the location used during initial acquisition. Within 5 min of the last reversal trial, short-term retention was examined using a 60-s probe in which the hidden platform was removed from the water maze.

Quantitative measurements of trial latency, distance traveled, and time in zones were recorded and evaluated using the Noldus Ethovision Behavioral Analysis System. All data were analyzed statistically using the General Linear Model module of SPSS for Windows 11.0. When appropriate, Tukey Post Hoc Tests were conducted. All data are expressed as mean + S.E.M.

Table 1
Time spent in the training location in the short-term (Column A) and long-term test (Column B) following acquisition training and short-term (Column C) after reversal training. All results are mean + S.E.M.

				(A) Short-term test following acquisition	(B) Long-term test following acquisition	(C) Short-term test following reversal
Spaced trials	Impoverished	Sugar	$n=5$	27.1 ± 7.3	17.2 ± 3.1	14.7 ± 4.4
	environment	Ginkgo	$n=5$	31.4 ± 7.3	16.3 ± 3.1	33.1 ± 4.4
	Enriched environment	Sugar	$n=5$	44.1 ± 7.3	13.8 ± 3.1	28.8 ± 4.4
		Ginkgo	$n=5$	31.3 ± 7.3	19.1 ± 3.1	26.3 ± 4.4
Massed trials	Impoverished	Sugar	$n=5$	39.8 ± 7.3	2.5 ± 3.1	23.2 ± 4.2
	environment	Ginkgo	$n=5$	54.9 ± 7.3	10.4 ± 3.1	10.0 ± 4.2
	Enriched environment	Sugar	$n=5$	23.3 ± 7.3	5.1 ± 3.1	6.8 ± 4.2
		Ginkgo	$n=5$	52.1 ± 7.3	5.1 ± 3.1	27.7 ± 4.2

3. Results

3.1. Acquisition of spatial learning

Results of the initial acquisition training are depicted in Fig. 1. To analyze the initial acquisition of spatial memory, we ran separate four-way repeated measure ANOVAs using the distance traveled to the escape platform and the latency of trial as dependent measures. Training protocol (spaced vs. massed), environment (impoverished vs. enriched), and drug (ginkgo vs. sugar) served as between-subject factors, and trial blocks represented the within-subject factor. There was no four-way interaction, but there was a significant three-way interaction of trial block, environment, and training [$F(6,192)=3.14$, $P<.01$]. Individual two-way ANOVAs were conducted comparing the effects of environment and training within each trial block. There were no significant two-way interactions or main effects of environment or training on any trial block. Thus, there were no effects of ginkgo on acquisition and no significant group differences at the end of training.

3.2. Short-term retention

To examine short-term retention, a probe trial was completed within 5 min of the last acquisition trial. The amount of time spent exploring a region immediately surrounding the platform location (7.1% of the total maze area) was recorded and converted into a percentage of the time spent in the entire maze. The results are depicted in Column A of Table 1 and in Fig. 2—the horizontal line represents the amount of time that would have been spent in the platform location by chance alone (7.1%).

The percentage of time spent exploring the platform region was analyzed using a three-way ANOVA (drug—sugar vs. ginkgo; environment—impoverished vs. enriched; training—spaced vs. massed trials). While there was no three-way interaction, there was a significant two-way interaction involving drug and training [$F(1,32)=6.438$, $P=.016$; eta$^2=.167$]. Planned contrasts between drug groups were conducted using independent sample t tests. For the massed-trained animals, the group exposed to ginkgo spent more time in the training zone than animals exposed to sugar ($t=3.119$; $df=18$; $P=.006$). There was no difference between the drug groups in the spaced condition.

3.3. Long-term retention

Long-term retention was examined in a probe trial completed 14 days after the last acquisition trial. Results are depicted in Column B of Table 1 and in Fig. 3. Once again, a three-way ANOVA (Drug × Environment × Train-Training) was conducted on the percentage of time spent exploring the platform location. There were no three-way or two-way interactions. However, there was a main effect of

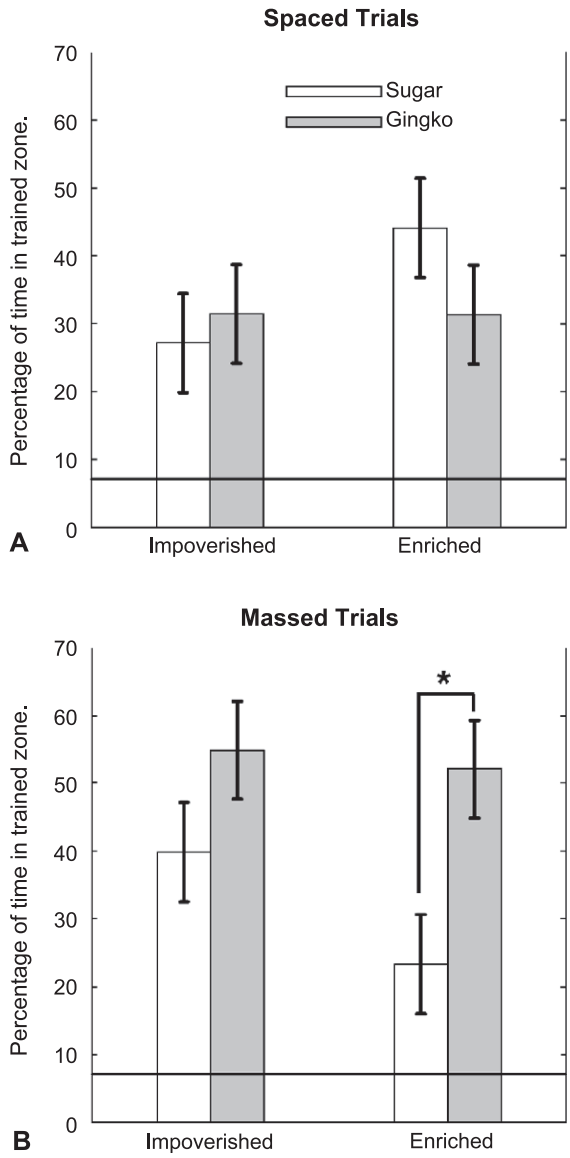

Fig. 2. Time spent in the training location in the short-term test as a percentage of total time spent in the water maze for each of the groups. The horizontal line represents the amount of time that would have been spent in the training location by chance (7.1%). All results are mean + S.E.M. Single asterisks (*) indicate significant differences between ginkgo- and sugar-treated animals based on independent group t tests with $P<.05$.

training schedule as animals that were trained in spaced trials spent more time in the training location than animals trained in massed trials [$F(1,32)=24.243$; $P<.001$; eta$^2=.431$]. Exposure to ginkgo extract had no effect on the long-term retention of the hidden platform location as tested in the 14-day probe trial.

3.4. Short-term retention following reversal trials

After animals had completed four-reversal trials in which the platform was placed in a location opposite from the original training position, a short-term probe trial was completed. Because animals that underwent spaced train-

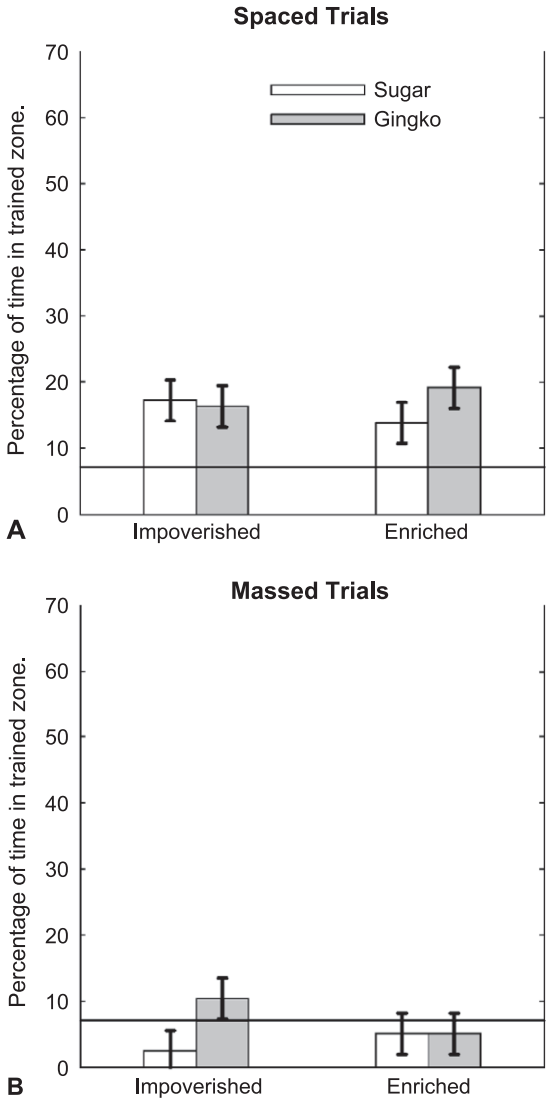

Fig. 3. Time spent in the training location in the long-term test as a percentage of total time spent in the water maze for each of the groups. The horizontal line represents the amount of time that would have been spent in the training location by chance (7.1%). All results are mean + S.E.M.

ing during initial acquisition spent more time in the platform location during the long-term retention test, it was necessary to analyze the results of the massed and spaced groups separately for the reversal phase of the study. Results for the two groups are depicted in Column C of Table 1 and in Fig. 4. Performance in the probe trial for each group was analyzed using a two-way ANOVA (Drug × Environment).

For the spaced training group, there was a significant drug-by-environment interaction [$F(1,16) = 6.331$; $P = .022$; $eta^2 = .284$]. Independent sample t tests indicated that there was no difference between drug groups for animals housed in enriched conditions. However, animals exposed to ginkgo in impoverished conditions spent more time in the new location than animals exposed to sugar water ($t = 4.572$, $df = 8$, $P < .005$).

In animals that had been previously tested in massed trials, the results were more complex. Once again, there was a significant drug-by-environment interaction [$F(1,16) = 14.899$; $P = .0013$; $eta^2 = .482$]. In animals housed in enriched environments, exposure to ginkgo resulted in increased time spent in the platform location during the probe trial ($t = 2.742$, $df = 8$, $P = .025$). However, for animals in the impoverished housing conditions, exposure to ginkgo decreased the time spent in the platform location ($t = 3.577$, $df = 8$, $P = .007$).

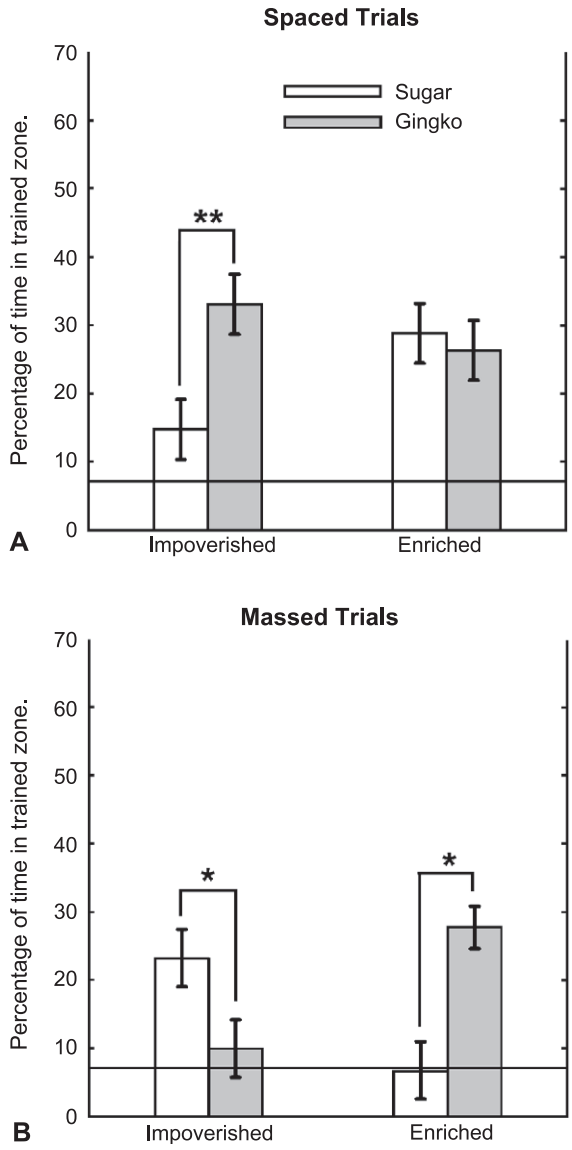

Fig. 4. Time spent in the training location in the short-term test as a percentage of total time spent in the water maze for each of the groups. The horizontal line represents the amount of time that would have been spent in the training location by chance (7.1%). All results are mean + S.E.M. Single asterisks (*) indicate significant differences between ginkgo- and sugar-treated animals based on independent group t tests with $P < .05$. Double asterisks (**) indicate $P < .01$.

4. Discussion

This experiment was designed to test whether *G. biloba* promotes spatial memory in rats. Although ginkgo had no effects on the initial acquisition of a spatial learning task, it did produce enhanced performance compared to placebo during short-term memory testing for animals trained with massed trials. Previous evidence indicates that ginkgo may have a greater cognitive effect in impaired individuals (Itil et al., 1998; Winther et al., 1998) than in cognitively intact subjects (Mix and Crews, 2000; Solomon et al., 2002). Because impoverished environments have been shown to impair spatial learning in rats (Passineua et al., 2001; Paylor et al., 1992; Park et al., 1992; Pham et al., 1999; Kraemer and Randall, 1995, Goodrick, 1973), we hypothesized that ginkgo would have greater effects in rats given massed training (analogous to cognitively impaired human subjects). The results of the short-term probe trials were consistent with that expectation.

Although, ginkgo promoted performance during the short-term memory test, there was no evidence for a drug effect during the 14-day probe trials. As shown in Fig. 3, none of the massed-trained animals performed at better-than-chance levels during this test. This indicates that levels of training provided in this study were not adequate to produce any retention of learning over the 2-week interval. Thus, any potential effects of ginkgo may have been masked by inadequate training or a too-lengthy retention interval.

Results of the probe test following reversal learning were more complex. As shown in Fig. 4, ginkgo enhanced performance in spaced-trained animals that had been housed in impoverished environments and in massed-trained animals housed in enriched environments. Ginkgo produced similar levels of performance in the spaced–enriched group, but the high level of performance by the placebo group produced a possible ceiling effect preventing the effects of ginkgo from being detected. Results from the massed–impoverished groups were more difficult to interpret; for these animals, ginkgo produced worse performance than placebo. Performance on reversal training depends in part on how strongly the competing memories of initial training are reactivated during retraining and testing. Thus, the conflicting results obtained here could indicate a complex interaction between the effects of ginkgo on the retention of two distinct and competing memory traces.

It is important to note that some of the negative findings in this study could be attributed to the small sample size employed (5 animals per group). For the interactions and main effects examined in the ANOVAs, we had moderate power (63%) to detect a large effect size (f=.40), but low power (30%) to detect medium effect sizes (f=.25; see Cohen, 1988). Thus, it is possible that more subtle effects of ginkgo on memory could have been missed by the current analyses. On the other hand, the present study used sample sizes equivalent to other published studies on rat spatial memory in the water maze (e.g., Spreng et al., 2002). Such studies routinely document group differences in performance; we therefore expected that a putative memory enhancement substance such as ginkgo should have been capable of producing detectable performance changes under similar conditions.

The results reported here are consistent with the existing literature, which documents mixed effects of ginkgo on memory. Some studies indicate dramatic promotion of memory (Wesnes et al., 2000; Topic et al., 2002b), while others indicate no change as a result of ginkgo exposure (Solomon et al., 2002). The overall results of this study clearly indicate that ginkgo has powerful effects on short-term retention of spatial information in rats. Following original spatial learning, ginkgo enhanced retention in massed-trained animals but not in animals given spaced training. Following reversal training, ginkgo enhanced memory performance for two of the groups but reduced performance in a third. This may indicate that the effects of ginkgo on cognition may be dependent upon the category of memory being examined or on the conditions of original learning.

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