Effects of chronic alcohol consumption on spatial reference and working memory tasks

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Abstract

The aim of this work was to determine the spatial memory impairments induced by chronic alcohol consumption in rats. The alcoholization process began on the 21st postnatal day and alcohol concentrations were gradually increased to reach a concentration of 20% that was maintained for 4 mon. Behavioral tests were performed in the Morris Water Maze (MWM). The first study assessed the effects of chronic alcohol intake on two reference memory tasks (a place learning with multiple trials and a new place learning carried out in the same experimental context). Alcohol-treated animals presented no overall impairment in their ability to process spatial information. Deficits were restricted to reduced behavioral flexibility in spatial strategies. The second study assessed working memory in two tasks in which information about platform location was only valid for one trial. In the first working memory task, the animals had to perform one trial per day and in the second task they were submitted to four trials per day. At the end of the second experiment, all animals were trained in a visual-cued task. In the second experiment, the most important deficits in alcohol-treated animals occur in spatial working memory tasks, and this impairment was independent of the intertrial interval used. In the second spatial working memory task, performance of the alcohol-treated animals in the earlier trials affected their performance in subsequent trials, suggesting that a process of proactive interference had taken place. The visual-cued task demonstrated that these behavioral impairments were produced without visuo-perceptual impairments. © 2000 Elsevier Science Inc. All rights reserved.

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1. Introduction

Chronic alcohol consumption has a detrimental effect on behavior and cognitive processes such as learning and memory (Beracochea et al., 1987; Beracochea et al., 1989; Beracochea et al., 1992; Beracochea & Jaffard, 1985; Melis et al., 1996; Walker & Hunter, 1978). Chronic alcohol treatments produce structural and functional alterations of the central nervous system (CNS), which can explain the behavioral impairments associated with chronic alcohol ingestion. More specifically, cell loss in specific cerebral structures (Riley & Walker, 1978; Belzunegui et al., 1995), reduced regional metabolic activity (Bontempi et al., 1996), a decreased cerebral cholinergic activity (Arendt et al., 1989; Beracochea et al., 1992; Melis et al., 1996), and other alcohol-induced changes have all been associated with learning and memory impairments. Recent studies suggest that some behavioral impairments associated with alcohol intake can be related to altered expression of GABA receptor subunits in specific brain regions (Charton et al., 1997; Mhatre et al., 1993; Mhatre & Ticku, 1992).

Since alcohol does not affect all memory processes in the same way it is useful to analyze the effects of alcohol on the individual memory processes involved. Different kinds of spatial memory can be studied in rats using the Morris water maze (MWM) (Frick et al., 1995). This task is based on the ability of rats to learn spatial locations using spatial cues (Cheng, 1986; Whishaw, 1998) and other strategies to formulate spatial representations of their environment. In this task, the rats use reference memory to learn a set of general rules which enable them to locate a hidden platform. The location of the platform and, therefore, the relationship between the platform and the spatial cues that the animal uses to locate it are constant throughout the experimental process. The MWM can also be used to study working memory, and in these tasks, a temporary association is made between the stimuli (Frick et al., 1995). The position of the escape platform in the MWM is changed from one trial to the next and the information available to the animal in each trial can not be used to locate the platform in subsequent trials.
These two kinds of memory can be differentially affected depending on the treatments, suggesting that they have different neuroanatomical and neurochemical substrates. Therefore, acquisition of a place learning with components of reference memory is affected by impaired hippocampal function (McNamara & Skelton, 1993) whereas impairments in working memory tasks are mainly associated with treatments that interfere with prefrontal medial cortex function (DeBruin et al., 1994; Granon et al., 1994; Granon & Poucet, 1995). Alcohol treatments also impair performance of memory tests. Chronic alcohol consumption has been associated with deficits in spatial working memory (Gibson, 1985; Givens & McMahon, 1997; Givens, 1996; White et al., 1997) although the results of the reference memory tests are not consistent (Steigarwald & Miller, 1997; Arendt et al., 1989; Matthews et al., 1996). These data suggest that chronic alcohol consumption could affect memory processes by altering the structure and/or function of specific brain regions such as the hippocampus and/or the prefrontal medial cortex.

The aim of this study was to assess the effects of chronic alcohol treatment in spatial reference and working memory. Spatial reference memory was assessed in two different tasks. In the first task (place learning), we studied the effect of chronic alcohol intake on the long-term retention of spatial information. Spatial cues and the location that the animals were required to remember remained constant throughout the training sessions. This constant relationship is characteristic of reference memory tasks since the rats must learn general rules (i.e., they locate a platform of constant position). In a new place learning in the same stimular context, conclusions can then be drawn about the beneficial effect of the first place learning and the flexibility of their spatial strategies and also about the possible effect of alcohol on these cognitive-behavioral processes.

Spatial working memory was also assessed in two different tasks after chronic alcohol intake. During the working memory task (place learning with one trial), two different intertrial intervals were used to determine the effect of alcohol when the delay period between the acquisition trial and retention trial was increased. The aim of the second working memory task, that consisted of four daily trials, was to determine whether alcohol induces memory impairments when proactive interference is increased (influence of current trial N-1, on current trial N). Proactive interference increases with decreasing intertrial interval (ITI) (Dunnet & Martel, 1990). Therefore, with a short ITI (30 s) the presence of proactive interference should be clearly visible. In both tasks the information available to the animals was only valid for one trial and could not be used for subsequent trials.

Since alcohol could also affect visuoperceptive or motivational components a visual-cued task was used to rule out or confirm the affect of alcohol on these processes. The visual-cued task also provides information on the behavioral flexibility of the animals i.e. the ability of these to change from a spatial to a non-spatial strategy (DeBruin et al., 1994).

2. Methods

2.1. Subjects

Twenty-six male Wistar rats (central vivarium of the University of Oviedo) were used. The animals were randomly assigned to one of the two following groups: alcoholic group (n = 13) and control group (n = 13). Rats were housed individually in a temperature-controlled colony (21 ± 2 °C) on a constant light-dark cycle (08:00–20:00). All control rats were given free access to food and water. The rats in the alcoholic group were given free access to food but their ingestion of drink followed a protocol of gradually increasing alcohol consumption.

2.2. Alcohol treatment

The alcohol treatment was carried out over a period of 5 months and 27 days. Intake of alcohol was increased gradually from an initial concentration of 2% ethanol that was doubled each week during the first month to reach a concentration of 20%, which was then maintained for the following 4 months. This final ethanol concentration was also maintained for the 27 days of the experimental behavior studies. After recording the behavioral observations, all the animals (alcohol-treated and control animals) were deeply anaesthetized with ethyllic ether and vascularly perfused with 10% formaldehyde in phosphate buffer (pH 7.4). Before starting the vascular perfusion, 3 ml of blood were extracted to determine serum alcohol levels of the alcohol-treated animals. The samples were sent to a commercial laboratory (Echevarne Laboratory, Spain) for analysis of blood alcohol concentrations by gas chromatography.

2.3. Apparatus

The apparatus consisted of a circular pool with the following dimensions: diameter, 150 cm; walls, 43 cm high. The pool was filled with water (21 +/− 2°C) and was made opaque with nontoxic white paint. The goal platform (11 cm diameter) could be placed anywhere in the pool at a distance of 30 cm from the pool edge. The platform was submerged to a depth of 2 cm beneath the surface of the water. The pool was divided into four imaginary quadrants (A, B, C, and D) and the platform was placed in the center of the quadrant. The pool was placed in an experimental room furnished with several extra-maze cues and remained immobile in the room throughout the entire experimental period. An automatic video system (Ethovision, Noldus) was used to record the animals’ movements in the pool.

2.4. Behavioral procedures

The day before the place learning the animals were released into the circular pool without the goal platform for a 60 s period of free exploration. From the following day on-
wards the animals were submitted to the following training protocol:

1. Place learning with multiple trials (days 1–4). Place learning consisted of training the rats to escape from the water using a hidden platform. The experimenter remained near the computerized recording system for the duration of the trial except for when introducing the animal into or removing it from the pool. The platform was placed in the center of quadrant B where it remained throughout the experiment. The rats were introduced into the pool from one of the four release positions (at the edge of quadrant A, B, C, or D). The rat left the pool at the center of the edge of one of the pool quadrants (the exit quadrant differed pseudorandomly between the trials). Each animal was submitted to four daily trials over a period of four days. At the start of each trial the animal was placed in the center of the edge of one of the quadrants. The trial finished when the animal found the platform. When the rat did not find the platform within 60 s the experimenter placed it on the platform where it remained for 15 s. After this period the rat was returned to its cage for 30 s after which it was introduced into the pool again. This process was repeated until the animal had completed all the trials.

2. Transfer task (day 5). After the animal had completed the four day place learning task, on the fifth day it was placed in the pool for 30 s without the goal platform and the time it spent in each quadrant was recorded (transfer test). The transfer test is used to determine the degree of learning the animals have acquired with respect to the position of the platform in the pool.

3. New place learning (days 6–9). In this experiment the position of the escape platform in the pool was changed. This was placed in the opposite quadrant to that used in the initial place learning (quadrant A) and the position of departure of the animal from the pool varied pseudorandomly between the quadrants and trials, as in the initial place learning. The duration of the entire task was four days with four trials per day. The interval between the four daily trials of 5 min. The position of the platform in the pool is changed pseudorandomly between the four possible positions of the platform in the pool (quadrant A, B, C, and D). In the retention trial, the position of the platform and, therefore, the exit were constant. The intertrial interval; i.e., the interval between acquisition and retention trials, was 30 s plus the 15 s the animals remained on the platform (reinforcement time). There was an interval between the four daily trials of 5 min. If the animals did not locate the escape platform within 60 s, the experimenter placed them on it.

4. Transfer test (day 10). The procedure followed was the same as that described for the initial place learning.

5. Working memory task (single-trial place learning (days 11–20). The animals were submitted to two trials, one acquisition and one retention trial, per day. In the acquisition trial, the animal had to find a submerged platform in order to escape from the water. If the animal did not find the platform in 60 s, the experimenter placed the animal on the platform, where it remained for 15 s before being placed in its cage for 30 s on days 1, 3, 5, and 7, and for 5 min on days 2, 4, 6, and 8. After this interval, the animal was again introduced into the circular pool for the retention trial. The goal quadrant; i.e., the quadrant containing the escape platform, remained constant on the same day for the acquisition and retention trials but varied pseudorandomly over the eight days of the experiment.

6. Working memory task: four-trial place learning (days 21–26). This task was carried out over six days with four trials per day. Each trial consisted of an acquisition trial and a retention trial. The position of the platform and, hence, the exit during the acquisition trials varied pseudorandomly between the four possible positions of the platform in the pool (quadrant A, B, C, and D). In the retention trial, the position of the platform and, therefore, the exit were constant. The intertrial interval; i.e., the interval between acquisition and retention trials, was 30 s plus the 15 s the animals remained on the platform (reinforcement time). There was an interval between the four daily trials of 5 min. If the animals did not locate the escape platform within 60 s, the experimenter placed them on it.

7. Visual-cued task (day 27). In this task the animal departs from a specific location (quadrant A) and locates a green colored escape platform (11 cm in diameter) which juts out 2 cm above the surface of the water. The position of the platform in the pool is changed pseudorandomly in the different trials. The visual task is carried out over two days, with two sessions per day and four trials per session. The intertrial interval was 15 s, and the reinforcement time on the platform was 30 s.

2.5. Statistics

The distances swam by the animals and the escape latencies were taken as the dependent variables. Results were analyzed by ANOVA for repeated measures. When necessary, simple effects and post hoc comparisons (HSD) were calculated. The Student’s t test was used for the comparison of mean pairs when the variances were homogenous and in cases of normality.

3. Results

3.1. Body weight and ethanol blood levels

Body weights of control animals (473 ± 35.05) and alcohol-treated animals (463 ± 25.35) were not significantly different at the end of the experimental behavior studies (p > 0.05). Serum levels of ethanol were 0.46225 ± 0.165 g/L (mean ± SEM).

3.2. Place learning with multiples trials

Statistical analysis of the escape latencies revealed that alcohol did not affect place learning in the MWM (no significant differences were detected between the groups). In
both groups, escape latencies decreased with training [control group: \(F(3, 72) = 21.54; p < 0.000\); alcohol-treated group: \(F(3, 72) = 16.31; p < 0.000\)] (Fig. 1A). On the other hand, with regards the distances swam in the maze, animals in the control group swam a greater distance than animals in the alcohol-treated group [\(F(3, 72) = 5.21.54; p < 0.000\); alcohol-treated group: \(F(3, 72) = 16.31; p < 0.000\)].

Moreover, distances swam by both groups of animals significantly decreased with training [control group: \(F(3, 72) = 35.16; p < 0.000\); alcohol-treated group: \(F(3, 72) = 6.63; p < 0.000\)] (Fig. 1B).

In relation to the transfer of this task, animals in both groups remained for a similar total period of time in the four quadrants of the MWM. Also, animals from both groups spent longer in the quadrant which had contained the escape platform during the initial place learning than in the remaining quadrants [control group: \(F(3, 72) = 15.80; p < 0.000\); alcohol-treated group: \(F(3, 72) = 17.54; p < 0.000\)] (Fig. 1C). There were also significant differences between the distances swam in the MWM by the animals in the two groups [\(F(1, 24) = 61.54; p < 0.000\)]. Moreover, animals from both groups swam a greater distance in the quadrant with the escape platform [control group: \(F(3, 72) = 13.20; p < 0.000\); alcohol-treated group: \(F(3, 72) = 4.65; p < 0.000\)] (Fig. 1D).

### 3.3. New place learning

The escape latencies of this new place learning reflect a difference in the performance of this task by control and alcohol-treated animals [\(F(1, 24) = 8.003; p < 0.01\)]. However, these differences were only observed on day 2 [\(F(1, 24) = 5.39; p < 0.05\)]. Also, escape latencies decreased with training control group: \(F(3, 72) = 7.37; p < 0.05\); alcohol-treated group: \(F(3, 72) = 9.54; p < 0.05\)] indicating that animals from both groups had learnt the new location of the escape platform (Fig. 2A).

The results of the transfer test corroborate that a new place learning has taken place in both groups. Firstly, all animals spent a different length of time [control group: \(F(3, 72) = 36.6; p < 0.05\); alcohol-treated group: \(F(3, 72) = 28.63; p < 0.05\)] (Fig. 2C) and swam different distances [control group: \(F(3, 72) = 60.95; p < 0.000\); alcohol-treated group: \(F(3, 72) = 10.98; p < 0.000\)] in each pool quadrant (Fig. 2D).

Analysis of the group effect did not detect any difference in the time spent by the animals from the two groups in each quadrant, although animals from the alcohol-treated group swam a shorter distance in the pool than animals from the control group [\(F(1, 24) = 76.37; p < 0.000\)].
3.4. Working memory task: single-trial place learning

In the acquisition trial, escape latencies \( t = (-4.13129), df = 24; p < 0.001 \) (Fig. 3A) and the distances swam in the pool \( t = (-2.47), df = 24; p < 0.05 \) (Fig. 3B) were significantly different in alcohol-treated compared to control animals. Moreover, in the retention trial the performance of alcohol-treated animals in the spatial working memory task was worse than that of control animals. There was a clear difference between the groups in both the escape latencies \( F(1, 24) = 27.85; p < 0.001 \) and the distances swam \( F(1, 24) = 11.16; p < 0.001 \) (Fig. 4C, 4D). Moreover, these differences between the groups in the escape latencies \( F(1, 24) = 6.9; p < 0.01 \), in the analysis of the simple effects in both groups this was found to be not significant.

3.5. Working memory task: four-trial place learning

In the acquisition trial, there were significant differences between the escape latencies of both groups \( F(1, 24) = 107.96; p < 0.05 \) although there were no significant differences between the trials. Nevertheless, the simple effect analysis revealed significant differences between trials in the alcoholic group \( F(3, 72) = 7.71; p < 0.05 \), specifically, between trials 1 and 4 and between trials 2 and 4 \( p < 0.05 \) (Fig. 5A). The distances swam by both groups were significantly different \( F(1, 24) = 102.91; p < 0.000 \) although differences between the trials were only found in the alcoholic group \( F(3, 72) = 3.39; p < 0.05 \), and more specifically between trials 1 and 4 \( p < 0.05 \) (Fig. 5B).

In the retention trial, there was a significant difference between the escape latencies of the two groups \( F(1, 24) = 9.79; p < 0.005 \). However, no differences in this variable

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Fig. 2. New place learning: Animals from the control group and the alcohol-treated group acquired a new place learning in the same stimular context. The escape latencies and the distances swam decreased with training (A and B, respectively). However, control animals learnt the new position of the platform more rapidly than the alcohol-treated animals. Nevertheless, there were no differences between the distances swam by the two groups. The transfer test shows that all the animals spent more time (C) and swam further (D) in the quadrant in which the escape platform had been situated during the training session. Moreover, there was no difference between the two groups in the time spent in each quadrant, although the distances swam by the animals from both groups were different. (*differences between quadrants).
were recorded between the four sessions. Nevertheless, analysis of the simple effects revealed differences between the trials in the alcoholic group \( F(3, 72) = 4.29; p < 0.05 \), which were detected in the following pairs of trials: between trials 1 and 3, and between trials 2 and trials 3 and 4 \( (p < 0.05) \) Fig. 5C). On the other hand, there were no significant differences in the distances swam by the animals in the pool between the groups or between the trials (Fig. 5D).

Analysis of mean values of latencies and distances of the four sessions for acquisition and retention trials revealed significantly different escape latencies between control and alcohol-treated groups in both types of trials \( F(1, 24) = 64.64; p < 0.000 \). More specifically, the control group took less time to locate the platform than the alcohol-treated group \( (p < 0.05) \) (Fig. 6A). Also, the distances swam by both groups was significantly different in the acquisition trial \( F(1, 24) = \)

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**Fig. 3.** Acquisition trial. Working memory task: single-trial place learning. This figure shows the differences between the control and the alcohol-treated group in the acquisition trial. Significant differences in the escape latencies (A) and the distances swam (B) in the pool were found between the two groups of animals.

**Fig. 4.** Retention trial. Working memory task: single-trial place learning. The results of the retention trial show a poorer performance of alcohol-treated animals compared to normal animals in the working memory task that were reflected by differences in escape latencies (A and B) and in the distances swam (C and D). These differences were observed with both the delays imposed (30 s and 5 min).
39,37; \( p < 0.000 \) and the alcohol-treated group swam significantly further than the control group \( (p < 0.05) \) (Fig. 6B).

3.6. Visual-cued task

Statistical analysis of our results showed that animals from both groups were able to learn a location using visual cues. In both groups, escape latencies [control group: \( F(3, 72) = 11.56; p < 0.05 \); alcoholic group: \( F(3, 72) = 15.156; p < 0.05 \) (Fig. 7A) and the distances swam [control group: \( F(3, 72) = 20.87; p < 0.05 \); alcoholic group: \( F(3, 72) = 7.564; p < 0.05 \) (Fig. 7B) were shown to decrease with training. Nevertheless, in the group comparisons there was no difference between the escape latencies of the two groups (Fig. 6A) although animals in the control group swam a significantly greater distance in the maze than animals in the alcohol-treated group \( [F(1, 24) = 90.10; p < 0.000] \) (Fig. 6B).

4. Discussion

Our results demonstrate that both chronically alcohol-treated animals and control animals were capable of acquiring a place learning with multiple trials (Fig. 1A,B). The transfer task also showed that animals from both groups spent longer and swam a greater distance in the quadrant in which the escape platform had been located during the acquisition of a place learning (Figs. 1C,D). These results suggest that chronic alcohol consumption does not affect place learning. This, however, contrasts with previous findings of other authors (Arendt et al., 1989) who described impaired reference memory in a spatial task (radial arm maze) after chronic alcohol consumption following a similar protocol to that used in our study (18 weeks of alcohol ingestion at 20%). However, ours (Fig. 1) and other results (Homewood et al., 1991; Steigardl & Miller, 1997; Pereira et al., 1998) indicate that, in general, alcohol does not affect the processing of spatial information.

The second reference memory task (reversal task) showed that chronic alcohol consumption affected a new learning in the same experimental context as before but with the escape platform in a different location. More specifically, in the reversal task the alcohol-treated group required a greater number of trials before the escape latencies stabilized and a learning could be considered to have taken place (Fig. 2A). These results suggest that alcohol affects behavioral flexibility since the animals treated chronically with alcohol required a greater number of trials before they could correctly perform the reversal task. These data could imply...
that more perseverations took place in the group of alcohol-treated animals (searching for the platform in the quadrant in which it was located during the initial place learning). However, this impairment of behavioral flexibility was transient since alcohol-treated animals were also as capable of acquiring this new learning as control animals although they did so at a later stage (days 3 and 4 of the reversal task). Moreover, the transfer task also shows that both groups acquired a new place learning since all animals spent a longer time and swam a greater distance in the quadrant in which the platform was located during the reversal task. Devenport et al. (1989) also reported a reduced flexibility of the animals to adapt to changing environmental conditions. Similarly, in research by Gál & Bárdos (1994), there was no overall affectation of the processing of spatial information either. The behavioral impairment found in these tasks appears to be limited to a deficit in spatial behavioral flexibility and could be due to the fact that alcohol-treated animals are more resistant to the extinction of the previous learning and, therefore, take longer to learn a new spatial learning with the same contextual cues. From the results of the two spatial reference memory tasks, it is not possible to deduce that alcohol has a general effect on spatial learning since no deficits in the acquisition of place learnings were observed.

On the other hand, working memory processes are altered by chronic alcohol consumption. In the acquisition trial, alcohol-treated animals spent longer and swam a greater distance before locating the escape platform in the pool when the location of the platform was unknown in spite of being familiar with the environment (Fig. 3). During the acquisition trial, the rats had to explore the environment in order to locate a submerged platform which could have been situated in one of several possible locations. Animals are considered to present a spatial deficit when they present impaired ability to use spatial strategies required to explore a known environment in which there is a reward (the escape platform). Our findings could correspond to a spatial impairment which is only evident when the demands of the task vary in the different trials, although this can not be considered to be a general spatial impairment.

In our work, in the alcohol-treated animals we detected different deficits in the retention trial to those observed in the acquisition trial. During the retention trial, the animals have to relocate a platform that they have already found in a
previous trial and must retain in their working memory the previous location of the platform. In the retention trial the alcohol-treated animals took longer to locate the platform and swam a greater distance in the pool (Fig. 4). Therefore, in this trial the animals can no longer be considered to present impaired exploratory ability but rather an impaired ability to retain the location of the escape platform in the previous trial in their working memory. Moreover, these deficits in the alcohol-treated animals are independent of the temporal demands imposed in the task (Fig. 4); i.e., the degree of memory loss does not increase with increasing intervals between the trials (30 s and 5 min). This finding suggests that in this single trial task the effect of alcohol is not dependent on the interval between the trials, in contrast with the findings of Beracochea et al. (1992). Other authors recorded impairments in working memory in experiments in a radial maze (Arendt et al., 1988; Arendt et al., 1989; Homewood et al., 1991). However, Homewood et al. (1991) increased the temporal demands but did not observe an increased impairment in performance of the task.

In the working memory task with four daily trials, a deficit was observed in the performance of the alcohol-treated animals in both the acquisition (Fig. 5A,B) and the retention trials (Fig. 5C,D). This working memory task is more complex than the single daily trial task since it involves a sequential process rather than the isolated procedure involved in the single trial working memory task. As the experiment progresses, there is an increased probability that the earlier trials influence the following trials producing a phenomenon of proactive interference. Control animals correctly performed this task and no proactive interference took place. However, proactive interference did occur with the alcohol-treated animals in both the acquisition and the retention trials. In this task, in the acquisition trial alcohol-treated animals took longer to find the platform and also swam a greater distance suggesting that these animals were unable to locate the escape platform as rapidly as control animals. Moreover, in the later trials the distances swam by the animals and the escape latencies increased suggesting that the information available in previous trials has a detrimental effect on the animals’ performance. As in the place learning with a single trial, in the four trial place learning the spatial deficit shown by the alcohol-treated group could reflect an impaired spatial exploratory accuracy of these animals. This impairment becomes increasingly evident in the later trials in which the animals find it increasingly difficult to locate the escape platform due to proactive interference of spatial information in the performance of the task. Proactive interference also appears to occur between the retention trials and the working memory deficits become more evident in the later compared to the earlier trials. Our results are in accordance with those reported by Beracochea et al. (1987) and Tako et al. (1991) in chronically alcohol-treated rats (48 weeks). These authors observed severe deficits in the performance of a sequential alternation task. These memory deficits, as in our study, were only observed in the later trials suggesting that alcohol increases the vulnerability to proactive interference. The results of acquisition and retention trials averaged across the four sessions showed that the control group developed more efficient spatial strategies to search for the goal platform (Fig. 6). As occurred in the proactive interference study, here too differences were more pronounced in the acquisition trial compared to the retention trial. Possibly, this greater effect in the acquisition trial is due to more proactive interference compared to the retention trial (Fig. 5). These results yet again suggest the presence of a spatial working memory deficit in alcohol-treated animals, deduced from the differences existing between the acquisition and retention trials (Fig. 6A). Moreover, in the acquisition trial, employment of spatial strategies is impaired when the platform position is varied, and this deficit increases with the increase in proactive interference (Figs. 5, 6).

Perhaps the deficits described in the working memory tasks could be associated with the delayed performance of alcohol-treated animals in the reversal task, due to a primary disruption of working memory processes. In fact, some authors suggest that the most important effect of ethanol is its role in working memory processes and that it has little effect on information storage and retrieval processes (Givens & McMahon, 1997; Givens, 1996). Alcohol-treated animals presented a severe impairment in the working memory tasks in which the location of the escape platform only remained constant for one acquisition trial and one retention trial. However, in the reversal task, there was only an initial temporary effect and the animals rapidly learnt the new location of the platform. Perhaps this greater resistance to extinction in the alcohol-treated group is due to an initial deficit in working memory which results in an inability of these animals to retain new associations between the spatial cues which indicate the new location of the escape platform. This difficulty in retaining information in the working memory could be due to the interference of the associations between the previously learned spatial cues in the establishment of new spatial associations in a new place learning. In the reversal task, since the new associations between allocentric cues only have to be established once only a slight temporary deficit is observed. However, when these associations must be established for each trial the more pronounced deficits which we observed in the working memory tasks (one daily trial and four daily trials) are produced. Therefore, impaired behavioral flexibility could possibly be reinterpreted as deficits in spatial working memory in which the ability of alcohol-treated animals to establish associations between allocentric components of their environment with an escape platform of variable location is detrimentally affected. In other words, this would bring about a reduced flexibility of animals which would find it more difficult to react to changing environmental conditions (Devenport et al., 1989).

The results of the visual cued task show that the animals can use visual cues to learn locations (Fig. 6). Therefore, since the animals in the alcohol-treated group can correctly perform this task, they do not present either visuoperceptive
or motivational deficits. In addition, the correct performance of the animals in this group demonstrates that they are capable of changing from a spatial to a nonspatial strategy with the same speed and efficacy as control animals. Therefore, behavioral flexibility is not affected when the tasks require a change in orientation strategy (i.e., spatial orientation using other contextual cues). These results suggest that chronic alcoholization can perhaps be benefited by behavioral tasks based on the employment of visual-cued tasks when they present deficits in processing spatial information since, as we have pointed out, chronic alcohol ingestion does not affect the performance of tasks based on the orientation of subjects using visual cues.

On the other hand, alcohol can induce alterations in hippocampal function, which could, at least in part, explain the deficit we found here. Animals with hippocampal lesions have been reported to present impaired acquisition of a new place learning in the same stimular context (Brandeis et al., 1989) and in the performance of working memory tasks (Aggleton et al., 1992; Nagahara et al., 1995). Behavioral deficits result from alcohol-induced disruption of the normal functioning of this cerebral region. Nevertheless, alcohol can not be considered to mimic the detrimental effects of hippocampal lesions (Morris et al., 1990; Sutherland & Rodríguez, 1989) since we did not observe any impairment in the animals’ acquisition of a place learning. On the other hand, deficits in behavioral flexibility have also been found in animals with lesions of the medial prefrontal cortex consisting of a temporary deficit in the reversal task (DeBruin et al., 1994), similar to our findings. Nevertheless, DeBruin et al. (1994) suggest that prefrontal lesions affect behavioral flexibility when the animals must change from a spatial strategy (place learning) to a nonspatial strategy (visual-cued task), an effect that is not produced by alcohol. Similarly, many authors have reported the importance of the medial prefrontal cortex in rodents in working memory tasks (Granon & Poucet, 1995; Granon et al., 1994) and functional changes in the medial prefrontal cortex induced by alcohol consumption (Porrino et al., 1998a; Porrino et al., 1998b). It is, therefore, possible that the transient impairment we found is due to an altered function of the hippocampal formation and/or of the medial prefrontal cortex.

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