

Spontaneous recovery of human spatial memory in a virtual water maze

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The occurrence of spontaneous recovery in human spatial memory was assessed using a virtual environment. In Experiment 1, spatial memory was established by training participants to locate a hidden platform in a virtual water maze using a set of four distal landmarks. In Experiment 2, after learning about the location of a hidden platform, the platform was placed in a new position within the virtual water maze in order to extinguish the original learning. An immediate test showed that participants searched for the platform at its most recent location. In contrast, on a delayed test (24 h), participants tended to seek the platform at the original location. These findings are consistent with the spontaneous recovery effect on spatial memory and are discussed in relation to the cognitive map theory and associative approach of spatial memory.

Spatial memory refers to the organisms' ability to store and retrieve knowledge about the characteristics of their environment (Postma, Jager, Kessels, Koppeschaar & van Honk, 2004). Similar to other types of memory, spatial memory implies acquisition, consolidation, and retrieval of spatial information, where the hippocampus plays a major role (Florian & Roulet, 2004; Moser & Moser, 1998). A well-known technique for

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experimental study of spatial memory is the water maze, in which a rat is placed in a circular pool and has to swim in order to locate a platform submerged just below the water surface. By learning the spatial relationship between the platform location and a set of distal landmarks in the environment, the animal acquires a preference for the platform-location area (Morris, 1981). Virtual versions of the water maze developed for use in human research have shown behavioral (Jacobs, Laurence & Thomas, 1997) and neurobiological (Goodrich-Hunsaker, Livingstone, Skelton & Hopkins, 2009) similarities between humans and rodents in spatial memory acquisition.

In the cognitive map theory (O'Keefe & Nadel, 1978), spatial memory is explained by the construction of a mental representation of the environment that includes all elements present in it. This representation is created from the activity of place cells located in the hippocampus (O'Keefe & Dostrovsky, 1971) and participation of associative learning processes is excluded. Alternatively, an associative approach of spatial memory assumes that in a goal location, associative processes operate. For the establishment of an association between a landmark in the environment and a goal, the former becomes a reliable predictor of the latter (Leising & Blaisdell, 2009). There is growing evidence for both approaches (c.f., Kelly & Gibson, 2007), but most are focused on the acquisition of spatial memory. In consequence other learning processes such as extinction or recovery of spatial memory have been investigated in a smaller extent.

Extinction refers to the suppression of a response when the reinforcer is omitted. This effect implies behavioral and neural changes (Myers & Davis, 2002) and it has been reported in a variety of learning tasks with human and non-human animals (Rescorla, 2001). Rather than forgetting the original memory, extinction involves the formation of a new, inhibitory type of memory (Konorsky, 1967; Pavlov, 1927; but see Delamater & Westbrook, 2014) and, like in other types, acquisition, consolidation, and retrieval are also required (Quirk & Muller, 2008). Under certain manipulations, such as interposing a retention interval (RI) between the extinction and test phases, extinguished responses are recovered (Bouton, 1993; Pavlov, 1927). This spontaneous recovery is one of the most robust effects reported in non-spatial learning tasks (Rescorla, 2004) and can be considered a failure of extinction retrieval, because good extinction retrieval produces low (or null) levels of response.

At a theoretical level, the study of the extinction and recovery of spatial memory allows to verify some predictions made by the cognitive map theory and the associative learning approaches. According to O'Keefe

and Nadel's theory (1978), a goal to be located serves as a reinforcer, and its location is integrated into the cognitive map as an additional site. During extinction, the goal is removed and a map update process erases the information about its location. This update process implies that extinction leads to the elimination of the memory about the location of a goal. Conversely, according to the associative approach, extinction does not erase the information of the goal position but it is only inhibited and, therefore, the possibility of recovering it persists. Hence, while both approaches can explain spatial memory extinction only the associative one predicts its spontaneous recovery. Understanding spatial memory extinction and its recovery has clinical implications too. Anxiety disorders are often treated with extinction-based exposure therapies (Barad, 2005; Rothbaum & Schwartz, 2002) and relapse can be partially explained by spontaneous recovery (Kehoe & Macrae, 1997). Spatial memory is considered as a component of declarative memory (Morellini, 2013; Nadel & Hardt, 2004; O'Keefe & Nadel, 1978) and declarative memory dysfunctions are linked to anxiety disorders (Bremner, Vermetten, Afzal & Vythilingam, 2004; Ehlers & Clark, 2000). Knowledge about extinction and recovery using models of spatial memory such as the water maze can contribute to enhance current therapeutic treatments.

Extinction of spatial memory in the water maze task requires the platform to be removed (simple extinction) or to be moved to a region in the opposite side of the pool (discrimination reversal learning). Both procedures suppress the preference for the original platform-location area (Lattal & Abel, 2001) but while there is an explicit non-reinforcement treatment on the simple extinction procedure, that does not occur in the discrimination reversal learning. Discrimination reversal learning has been considered a case of extinction which is expressed by a second acquisition learning that interferes with the previous one (Bouton, 1993; Bouton & Brooks, 1993).

Suppressing the preference for the platform-location area by means of a simple extinction or discrimination reversal learning procedures could be explained either by the cognitive map theory or by the associative approach, therefore it is not easy to infer the underlying psychological processes involved in such extinction treatments. Besides, evidence of spontaneous recovery for the first platform-location area preference is controversial due to the methodological differences in fundamental variables that influence the memory processes. Using rodents and the simple extinction procedure, imposing a 24 h RI before a final test did not produce spontaneous recovery (Méndez-Couz, Conejo, Vallejo & Arias, 2014) but with a 96 h RI it did occur (Prados, Manteiga & Sansa, 2003). The data suggest that spontaneous recovery could be a linear function of the RI. Nevertheless, spontaneous

recovery was reported using 24 h RI when four or eight but not 16 simple extinction trials were given (Rossato, Bevilaqua, Medina, Izquierdo & Cammarota, 2006). Hence, the RI-simple extinction trials interaction could be possible. Again, in experiments with rodents but using discrimination reversal learning instead, neither 24 h (Lattal, Mullen & Abel, 2003; Rossato et al., 2006) nor 120 h (Rossato et al., 2006) RI produced spontaneous recovery. Nevertheless, using 336 h RI generated a spontaneous recovery effect (Lattal et al., 2003). Data from human behavior studies are also controversial because after using the discrimination reversal learning procedure, in an immediate testing participants spent less time in the first platform-location area, while in a 24 h-delay test this time increased but not further than the chance level (Alvarado, Vila, Strempler-Rubio & López-Romero, 2011). This last result can be interpreted either as spontaneous recovery at the same level as chance or as a platform random-search strategy.

In evaluating the results described above, there are four aspects that have to be taken into account. First, the number of acquisition and extinction trials were different in each study, and in some of them the extinction phase was carried in a single session (Prados et al., 2003; Rossato et al., 2006; Alvarado et al., 2001) while for others it was carried in multiple sessions (Lattal et al., 2003; Méndez-Couz et al., 2014). So, the learning degree should have been different at the moment of the spontaneous recovery assessment. Second, several studies reported that the simple extinction produced immobility in the course of the extinction trials (Schulz, Buddenberg & Huston, 2007; Schulz, Houston, Buddenberg & Topic, 2007; Schulz, Topic, De Souza Silva & Huston, 2004) and it has been pointed out that this sit-and-wait strategy may hinder the study of the spontaneous recovery (Lattal et al., 2003). Third, measurement of the platform preference area as a spontaneous recovery index is common for all those studies, but this variable has been regarded ambiguous because a shorter time spent at the platform-location area could reflect poor spatial learning, as well as a high degree of accuracy about the platform-location which may motivate animals to seek in another place if not located at the expected position (Hardt, Hupbach & Nadel, 2009). Finally, when extinction is delivered using the discrimination reversal learning, measurement of spatial preference is not the best way to evaluate what the animal has learned during the discrimination or reversal phase (Lattal, Honarvar & Abel, 2004). Therefore, using this variable may be difficult to distinguish between spontaneous recovery and extinction retrieval (e.g., Alvarado et al., 2011).

For spatial memory studies in the water maze task, platform preference area is a preference-related parameter but another useful kind of parameters are the motor-skill related, and both of them have been considered necessary to analyze the effects of spatial memory extinction (c.f., Vargas-López, Lamprea & Múnera, 2011). One of these parameters is the first quadrant choice of the animals in the maze. This variable has been demonstrated useful in rodent water maze studies (Whishaw & Tomie, 1997) and it may be more sensitive than platform preference area for revealing spontaneous recovery of spatial memory.

The aim of this study, therefore, was to verify the occurrence of spontaneous recovery of human spatial memory using a discrimination reversal learning in a virtual water maze task, assessing both preference for platform position-area and the choice of the first quadrant of the maze. The expression of spontaneous recovery for the original platform position would provide evidence for the associative processes in the extinction of spatial memory, while its absence would favor the cognitive map theory perspective.

EXPERIMENT 1

There are two categories for spatial information, egocentric or *landmark-based behavior* and allocentric or *place learning*; true spatial memory has been assumed place learning dependent (Nadel & Hardt, 2004; O'Keefe & Nadel, 1978; Potegal, 1972). A good demonstration of true spatial memory is the Morris's (1981) study (c.f., Sutherland & Dick, 1984), who trained rats to locate a hidden platform in a water maze using distal landmarks. To assess the occurrence of spontaneous recovery of spatial memory, first we have to make sure of establishing it in its true form (i.e., based on place learning). Thus, Experiment 1 is a systematic replication of Morris' Experiment 1 (1981). In addition to the use of human participants and a virtual version of the water maze, another difference with respect to Morris' work (1981) is that in our study a set of only four distal landmarks was used to mark the location of the platform. This difference in the number of landmarks reduces the probability that a single landmark perceived from an egocentric perspective could provide information about the specific location of the platform (c.f., Redhead & Hamilton, 2007).

METHOD

Participants. The participants were 26 male and 22 female undergraduate students ($M_{\text{age}} = 21.8$, $SD_{\text{age}} = 1.33$). All were volunteers recruited by verbal request. They had no previous experience in these or other experiments that employ a virtual water maze, and were divided into 4 groups as follows: The Cue + Place and Place groups each contained 7 men and 5 women, while the Cue and Place + Random groups each consisted of 6 men and 6 women. Before the experiment started, participants signed an informed consent form.

Materials and apparatus. The experiment was conducted in a 3 x 2.5 m room with a chair and a desk on which a 14-inch IBM compatible PC was placed. Once seated, the participant's view was straight at the PC monitor at an average distance of 50 cm. The virtual water maze was designed using the Maze Suite software v.2.3.0.1 (Ayaz et al., 2011). It consisted of a square pool showing –from a first-person perspective– a blue-colored floor in which participants “swam”, bordered by a black margin. The walls and ceiling surrounding the maze were white. An invisible line divided the maze into four quadrants. A landmark was suspended in the center of each quadrant (W = sofa; X = table; Y = chair; Z = door). The platform was a square that occupied approximately 1.10% of the total area of the maze. When presented, it was visible above floor level and colored red (see Figure 1).

Movement in the maze was controlled by the arrow keys on the PC keyboard: the up (↑) and down (↓) arrows allowed subjects to scroll forward and backward, respectively, while the left (←) and right (→) keys rotated the axis of participants towards the left and right, respectively, but with no accompanying movement (Hardt et al., 2009). Full rotation without movement took approximately 4 s, while crossing the maze from corner to corner required about 9 s.

Design and procedure. Four groups of participants were trained to locate a platform in the maze and then exposed to a test without the platform. The groups were: (a) Cue + Place, a visible platform remained fixed between a pair of distal landmarks (e.g., WY); (b) Place, similar to (a) but the platform was hidden; (c) Cue, the platform was visible, but changed position semi-randomly in each trial, being placed between a pair of distal landmarks (e.g., XZ) with the restriction that it could not appear twice

consecutively in the same point; and, (d) Place + Random, similar to the Cue group but the platform remained hidden.

The experiment consisted of one session that lasted approximately 15 min. Participation was individual. The researcher led each participant into the experimental room and after providing the necessary instructions printed in Spanish on a sheet of paper and answering any questions, he left the room.

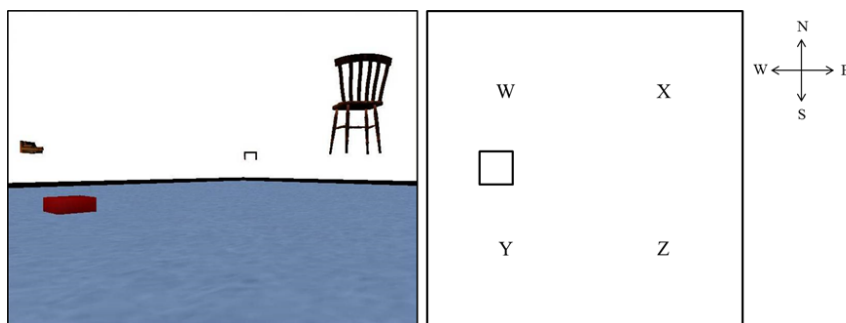


Figure 1. Left. Participant's view of the virtual water maze. Right. Schematic representation of the virtual water maze, the four landmarks, W, X, Y and Z, and the platform (empty square).

The experiment was conducted in four phases: Practice, Pre-training, Acquisition and Test. Each phase or trial began when the subject pressed the *Enter* key on the computer keyboard. During the Practice phase, participants received the following instructions:

Suppose you have been swimming in a pool for a long time and now you are tired and just about to drown. The only way to survive is to find a platform in the pool. In order to survive you have to find the platform. Before initiating your searching you have to learn how to swim. Now, you will practice your swimming. Find the navigation (arrows) keys and press “↑” to swim ahead, “←” to swim left, “→” to swim right, y “↓” to swim backward. Let's verify if you have understood the instructions.

Then participants could freely navigate through the maze in order to become familiar with the virtual environment and to learn how to move through it. This phase consisted of a single trial that began in the center of the maze facing north. There was no platform or landmarks. This phase

lasted 30 s. Pre-training phase consisted of two trials that began in the southwest corner of the maze facing east. A visible platform was placed in the center of the maze and the participant had to contact it in order to continue to another trial or the next phase, respectively. Instructions for this phase were as follows:

You already know how to swim and now you will learn to go to a platform. In the next screen press the navigation keys in order to swim to the platform located in the center of the pool until you reach it. If you do it, the following written message will appear on the screen "*You survived, you found the platform* [positive feedback]". Let's verify if you have understood the instructions.

And finally, for the Acquisition phase, instructions were:

Now the platform will be hidden underwater. Although you can't see it, be sure that it will always be at the same place. You have to swim to find it before you drown. Heed to the landmarks at the top of the pool because it will help you to find the platform. If you find it, the following written message will appear on the screen: "*You survived, you found the platform*". But if time is over and you could not find it you'll see the message "*You drowned. Try again* [negative feedback]". You have to locate the platform as many times as you are asked to. Sometimes the platform will be deeper than normal but you have to continue searching. The study finishes when you see the message "*Thanks for your participation, you have finished*" on the screen.

Acquisition consisted of 8 trials, each with a maximum duration of 60 s. Every trial began in one of the corners of the maze with the participant's view facing towards the external walls; the same corner was never presented twice consecutively. Subjects had to locate the platform. If they did so within 60 s, then positive feedback was provided. In contrast, if after 60 s the subject failed to locate the platform, negative feedback was delivered. In the Cue + Place and Place groups, the pair of landmarks that pointed to the location of the platform was counterbalanced so that each pair was reinforced for one fourth of the participants. Finally, the Test phase consisted of a single trial lasting 60 s with no platform, but with the landmarks present. Participants began this trial at the center of the maze facing the opposite quadrant in relation to the position where the platform was placed during the Acquisition phase. Thus, it involved a new starting point. Once the test was completed, the experiment ended.

Data analysis. Statistical analyses were performed using SPSS v. 17 and a result was considered significant at $p < .05$. During training, latency to locate the platform and the probability of initial choice of reinforced quadrant was analyzed in blocks of two trials. For the Test, the first quadrant choice and the time spent in each quadrant of the maze was analyzed. For the quantification of this last variable and for all groups, the A+ quadrant was considered as the reinforced quadrant, while the B-, C-, and D- quadrants were considered as the unreinforced quadrants (see Figure 2b). For the quadrant choice, an area surrounding the location of the platform in quadrant A+ was bounded and the same was done for the remaining quadrants. Thus, the first area in which the participant entered was recorded as the quadrant chosen. This area was twice the size of the platform.

RESULTS AND DISCUSSION

Figure 2a shows the latency to locate the platform and demonstrates that the highest efficacy in task completion occurred in the groups for which the platform was visible (Cue and Cue + Place). When the platform was hidden participants needed more time to locate it (Place and Place + Random groups). During most of the training phase, the highest latency to locate the platform occurred in the group Place + Random. A 2 x 2 x (4) ANOVA with the factors of location (mobile vs. fixed), view of the platform (visible vs. hidden), and blocks of trials (1-4), revealed a main effect ($p < .01$) for each one: location $F(1, 92) = 7.78$ ($\eta_p^2 = .07$); view $F(1, 92) = 71.11$ ($\eta_p^2 = .43$); and blocks of trials $F(3, 276) = 18.05$ ($\eta_p^2 = .16$). Interactions of Location x View, $F(1, 92) = 6.85$, $p = .01$, $\eta_p^2 = .06$, and Blocks of trials x View, $F(3, 276) = 5.35$, $p < .01$, $\eta_p^2 = .05$, were also found. For the Location x View interaction two 2 x (4) ANOVA were conducted. The first one analyzed performance differences between groups with fixed and mobile platform groups (Place and Cue + Place vs. Place + Random and Cue respectively) and it revealed a main effect for location, $F(1, 94) = 4.30$, $p < .05$, $\eta_p^2 = .04$, and blocks of trials, $F(3, 282) = 17.19$, $p < .01$, $\eta_p^2 = .15$, factors. The second 2 x (4) ANOVA analyzed performance differences for the hidden and visible platform groups (Place and Place + Random vs. Cue and Cue + Place respectively). This analysis detected a main effect for view, $F(1, 94) = 62.68$, $p < .01$, $\eta_p^2 = .40$, and blocks of trials, $F(3, 282) = 17.79$, $p < .01$, $\eta_p^2 = .15$. Two 2 x (4) ANOVA were conducted for the Blocks of trials x View interaction. The first one compared the blocks of trials between visible platform groups. It revealed only block of trials differences, $F(3, 138) = 6.92$, $p < .01$, $\eta_p^2 = .13$, and post

hoc comparisons (HSD) showed differences between the Block 1 and Block 4 ($p < .05$). The second 2 x (4) ANOVA compared the blocks of trials between hidden platform groups and it revealed between-group differences, $F(1, 46) = 7.87, p < .01, \eta^2_p = .14$, and on blocks of trials, $F(3, 138) = 12.66, p < .01, \eta^2_p = .21$, with Block 1 different from Block 4 (HSD, $p < .05$).

The time spent in each quadrant is shown in Figure 2b. The group Place showed a preference (> 15 s) for quadrant A+, which was confirmed by conducting a one-tailed one-sample t -test, $t(11) = 3.35, p < .01, d = 2.02$. For each group, a one-way ANOVA was conducted to determine differences in permanence among quadrants, but this was true only for the Place group, $F(3, 44) = 14.43, p < .01, \eta^2_p = .49$, where quadrant A+ was different from the other groups (HSD, $p < .01$).

The probability of initial choice for A+ quadrant for all groups in both block of trials and testing are shown in Figure 2c and 2d respectively. To quantify this variable, a value of 1 was assigned to the selected quadrant, and a value of 0 for the quadrants which were not chosen by the participant. Next, the average number of participants who chose a specific quadrant was calculated. For block of trials a repeated measures ANOVA was conducted revealing between-group differences, $F(2, 69) = 8.08, p < .01, \eta^2_p = .19$. By conducting several one-tailed one-sample t -tests, it was confirmed that this variable did not exceed chance level on Block 1 in either group but it did on Block 4 only for group Place, $t(23) = 4.23, p < .01, d = 1.76$. Finally, for testing, a one-tailed one-sample t -test revealed that the group Place chose quadrant A+ above the chance level (.25), $t(11) = 3.83, p < .01, d = 2.30$, but this did not occur with any other quadrant, or in any other group ($p > .05$).

This experiment shows that in Place group there was a reliable consistency between the latency to locate the platform and the probability of initial choice of the reinforced quadrant. In addition, during the test this group showed both preference and initial choice for quadrant A+. For all the other groups, this was not true. Therefore, it could be said that a spatial memory for the hidden platform-location was formed only in the Place group. In contrast, there is a possibility that both Cue and Cue + Place groups have employed a landmark-based behavior strategy to solve the maze. It may have facilitated the performance in the maze task but may have prevented the formation of a spatial memory (c.f., O'Keefe & Nadel, 1978). However, further evidence is required to confirm this.

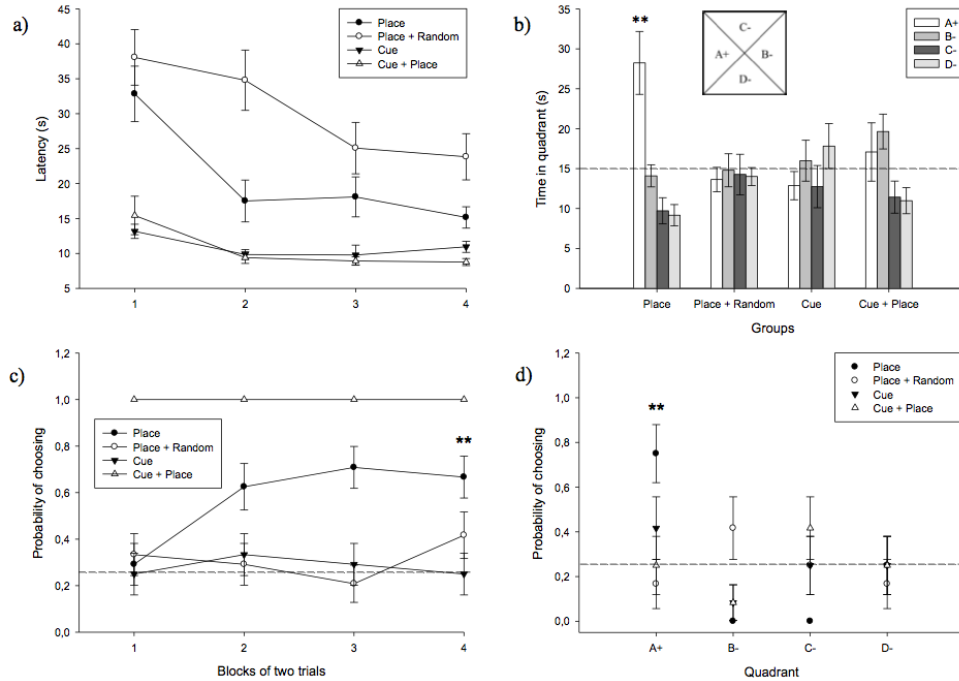


Figure 2. a) Mean escape latencies during acquisition training for the Place group (solid circle), the Place + Random group (empty circle), the Cue group (solid triangle), and the Cue + Place group (empty triangle). b) Mean time spent in the reinforced quadrant (A+), the opposite quadrant (B-), and the adjacent quadrants (C- and D-) during the test trial. c) Probability of choosing a quadrant. d) First quadrant chosen during the test trial. Error bars denote standard errors of the mean; the dotted line shows the chance level. ** indicates $p < .01$

The data show that humans are able to learn the location of a hidden platform in a virtual water maze task using a few distal landmarks available as long as they maintain a constant spatial relationship. This result is consistent with findings from other studies with rats and humans in traditional or virtual mazes, respectively, but with more distal landmarks available during training (Morris, 1981, Jacobs et al., 1997). These data also show the consistency among latency for reach and preference behavior of the reinforced quadrant during the Training and Test phases in humans (c.f., Whishaw & Tomie, 1997).

Experiment 1 represents a systematic replication of the study reported by Morris (1981, Experiment 1), but using human subjects, and of the partial human replication conducted by Jacobs and cols. (Jacobs et al., 1997). In all three experiments, the results obtained for the Place group are equivalent: Decreased latency to locate the platform, and acquisition of a preference for the appropriate quadrant. Also, the Cue and Place + Random groups had not been previously conducted with humans, but results are similar to those obtained with rats (Morris, 1981). The first group quickly located the platform, while the latter did so at a slower rate, though none acquired a preference for any quadrant of the maze or showed a choice directed towards a particular quadrant at the beginning of the Test. The performance of the Cue group showed that variables such as the appropriate shift in the virtual environment, motivation to complete the experimental task, or the provision of positive feedback on their performance, are not sufficient for the acquisition of spatial memory. The performance of the Place + Random group confirmed that participants are able to learn how to use distal landmarks to locate the platform, even when the current location of the platform could not be inferred by just paying attention to those landmarks.

The Cue + Place group in our study showed a level of chance performance without consistency in the initial choice of a quadrant during Test. This finding is significant because it indicates that participants did not learn the location of the platform from the distal landmarks; they based their search on the same visible platform instead. This result is opposite to that obtained with rats (Morris, 1981) and humans (Jacobs et al., 1997), and suggests differential control of different landmarks present in the virtual water maze on the behavior of the participants in this group.

EXPERIMENT 2

Spontaneous recovery for the preference of first reinforced quadrant was demonstrated by Lattal and cols. (Lattal et al., 2003). Nevertheless, some other studies have failed to obtain the same result by using either discrimination reversal learning (Rossato et al., 2006) or simple extinction (Méndez-Couz et al., 2014; Rossato et al., 2006). However, it is possible that some methodological aspects of all those studies could influence the obtained results. There is evidence that simple extinction produces immobility (e.g., Schulz et. al, 2007) so this effect should hinder to detect the spontaneous recovery of spatial memory. Moreover, some authors have considered that preference for the platform-location area is not an adequate

variable to measure the spatial memory (e.g., Hardt et al., 2009), furthermore when a discrimination reversal learning procedure is employed (Lattal et al., 2004). Therefore, the aim of Experiment 2 was to verify if measuring a motor-skill related parameter facilitates the detection of the spontaneous recovery of a spatial memory in humans trained in a virtual water maze task using a discrimination reversal learning procedure. Spontaneous recovery was assessed using two different measurements during the test phase: a) reinforced quadrant preference; and, b) the first quadrant chosen.

METHOD

Participants. The participants were 20 undergraduate students ($M_{\text{age}} = 20.2$, $SD_{\text{age}} = 1.67$), divided into 2 groups: Group Control and Group Recovery, each integrated by 7 men and 3 women. Recruitment of participants and other details were identical to those mentioned in Experiment 1.

Materials and apparatus. Both the experimental and virtual environments were the same as in Experiment 1.

Design and procedure. Two groups of participants were trained in the virtual water maze task to locate a hidden platform before completing a test with the platform removed. For half of the subjects in each group during the Discrimination phase the platform was placed between the WY landmarks, while for the Reversal phase it was located between the XZ landmarks in the opposite quadrant of the maze. For the remaining half of each group these conditions were inverted. A test was conducted either at the end of training (Group Control), or the following day (Group Recovery). The starting point for the Test phase was counterbalanced so that half of the participants in each group began at the center of the north wall, and the other half at the center of the south wall (i.e., on the half-way of the two trained locations), both with a view towards the outside of the maze. This involved a new starting point and encouraged subjects to make a choice regarding the pair of landmarks that had pointed out the location of the hidden platform (WY or XZ) during training. The remaining details of the procedure were identical to those of Experiment 1.

Data analysis. Data analyses were similar to those described for Experiment 1, but with certain exceptions. During Test, only the time spent

in the reinforced quadrant during Discrimination (A+), and the reinforced quadrant during Reversal (B+) phases were recorded. In the analysis of the quadrant to which participants swam first, it was only considered to calculate the chance level of the A+, B+, C- quadrants, because quadrant D was the starting point.

RESULTS AND DISCUSSION

The latencies to locate the platform for both groups in each phase of training are shown in Figure 3a. For each phase, a 2 x (4) ANOVA was conducted with the factors group (Control vs. Recovery), and blocks of trials (1-4). It revealed a main effect ($p < .01$) for the factor blocks of trials as follows: Discrimination, $F(3, 114) = 29.91$, $\eta_p^2 = .44$, and Reversal, $F(3, 114) = 28.16$, $\eta_p^2 = .42$. Multiple post hoc comparisons (HSD) of both groups revealed a difference in the latency to locate the platform for each phase of training between the Block 1 and Block 4 trials ($p < .01$), with lower latency in Block 4. The probability of initial choice for A+ quadrant for both groups in each phase of training was also analyzed by a 2 x (4) ANOVA with the same factors as before and it revealed a main effect ($p < .01$) only for the factor blocks of trials, Discrimination, $F(3, 114) = 11.52$, $\eta_p^2 = .23$, and Reversal, $F(3, 114) = 20.66$, $\eta_p^2 = .35$. Multiple post hoc comparisons (HSD) for both groups revealed a difference in this variable between the Block 1 and Block 4 trials ($p < .01$), with higher probability for discrimination and lower probability for reversal Block 4. Due to the absence of between-group differences on Block of trials, we integrated the data for each phase and then the probability for quadrant B+ as a first choice was calculated (Figure 3b). One-tailed one-sample t -test revealed a probability above the chance level (.25) to choose A+ quadrant during last discrimination block of trials, $t(39) = 8.58$ ($d = 2.74$), while the probability of choosing the same quadrant during the last block of trials of the Reversal phase was below chance level, $t(39) = 5.73$ ($d = 1.83$), $p < .01$ in both cases.

Permanence in quadrants A+ and B+ for each group is shown in Figure 3c. A 2 groups (Control vs. Recovery) x 2 quadrants (A+ vs. B+) ANOVA revealed a main effect for quadrant factor, $F(1, 36) = 5.49$, and a Group x Quadrant interaction, $F(1, 36) = 5.50$, with a $\eta_p^2 = .13$ and $p < .05$, for both of them. The Group x Quadrant interaction was analyzed by conducting two one-way ANOVA in order to detect within-group differences in the time spent in both reinforced quadrants. The results showed that the Control group spent less time in A+ than B+ quadrant, $F(1, 18) = 7.49$, $\eta_p^2 = .29$, $p = .01$. The time spent in any quadrant for both groups was not longer than the chance level (15 s), as confirmed by applying a one-

tailed one-sample t -test ($p > .05$). However, for the Control group the time spent in quadrant A+ was shorter than that predicted by chance, $t(9) = 2.84$ ($d = 1.89$), $p < .01$. Finally, Figure 3d shows the first quadrant chosen on the tests. Applying the aforementioned t -test confirmed that the Control group selected quadrant B+, $t(9) = 5.7$, $p < .01$, $d = 3.8$, while Recovery group chose quadrant A+, $t(9) = 2.42$, $p = .01$, $d = 1.61$, at the beginning of the Test above the chance level (.33). All other choices remained at chance level ($p > .05$). A two-group ANOVA (Control vs. Recovery) \times 2 reinforced quadrants (A+ vs. B+) revealed an interaction of Group \times Reinforced quadrant, $F(1, 36) = 21.60$, $p < .01$, $\eta_p^2 = .37$, which was then analyzed by a two-factor ANOVA conducted to compare the groups in terms of the first quadrant chosen. This analysis revealed a significantly higher initial choice of quadrant A+ for Recovery group with respect to the choice made for that quadrant by Control group, $F(1, 18) = 10.80$, $p < .01$, $\eta_p^2 = .37$. The inverse pattern occurred for quadrant B+ which was significantly chosen more often by the Control group than by the Recovery group, $F(1, 18) = 10.80$, $p < .01$, $\eta_p^2 = .37$.

For both groups, the decrease in the latency to locate the hidden platform as well as the increase in the probability for initially swimming to A+ quadrant during Discrimination phase are consistent with results of the Place group in Experiment 1. Such data pattern indicates the acquisition of a spatial memory. During the Reversal phase, this early spatial memory was extinguished and a new spatial memory was formed allowing participants to locate the platform in its current position. Evidence of this is the decrease in latency to find the new platform position as well as the increase in the probability to choose the quadrant in which it was contained (B+), along with the reduction in the probability to choose the previously reinforced quadrant (A+).

For the spatial preference test, there is no evidence of spontaneous recovery of the preference for the first reinforced quadrant (A+). This result is opposite to those obtained with rodents exposed to discrimination reversal learning (Lattal et al., 2003) or simple extinction (Prados et al., 2003). Nevertheless, a quadrant choice test revealed that on an immediate Test, the Control group initially chose the last reinforced quadrant (B+) while on a delayed Test, the Recovery group initially chose the first reinforced quadrant (A+). The behavior of the Control group indicates an extinction retrieval of spatial memory whereas behavior of the Recovery group indicates a spontaneous recovery of spatial memory.

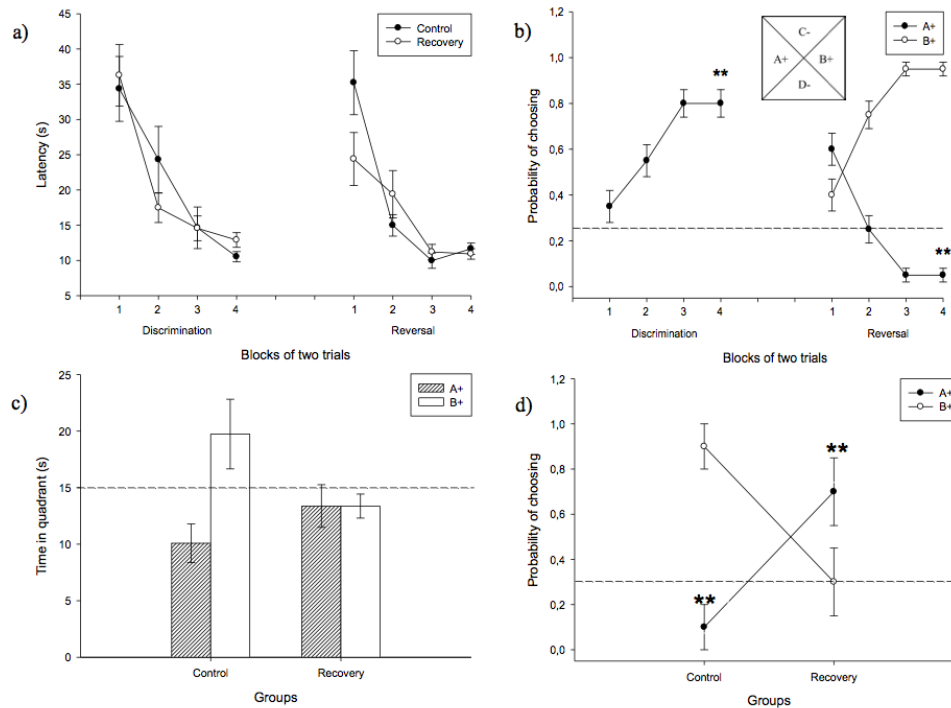


Figure 3. a) Mean escape latencies during acquisition training for Control group (solid circle) and Recovery group (empty circle). b) Probability of choosing a quadrant during the Discrimination (A+) and Reversal (B+) phases. c) Mean time spent in the reinforced quadrant A+ y B+. d) First quadrant chosen during the test trial. Errors bars denote standard errors of the mean; the dotted line shows the chance level. ** indicates $p < .01$

GENERAL DISCUSSION

Experiment 1 demonstrated that participants are able to acquire a spatial memory based on place learning when a set of distal landmarks maintains a constant spatial relation with a hidden platform in a virtual water maze. This is a typical result for human spatial memory research (e.g., Jacobs et al., 1997). However, this experiment also demonstrated that by using a conspicuous landmark to mark the hidden platform position, learning to distal landmarks was impaired. The theoretical implications of a result like this have been analyzed in a growing number of empirical studies

(e.g., Chamizo, Aznar-Casanova & Artigas, 2003) and reviews (e.g., Leising & Blaisdell, 2009) which try to identify the psychological mechanisms underlying spatial memory.

In Experiment 2, an originally spatial memory was extinguished by using discrimination reversal learning. It produced the acquisition of a second spatial memory while suppressing the behavior indexes of a previous spatial memory (Lattal & Abel, 2001; Lattal et al., 2004). During an immediate test, extinction retrieval for the first spatial memory was observed. Nonetheless in a delayed test a spontaneous recovery of the same memory was detected. This result is consistent with other demonstrations of spontaneous recovery of spatial memory obtained with discrimination reversal learning (Lattal et al., 2003) or simple extinction (Prados et al., 2003) with rodents.

Evidence demonstrates that the virtual water maze task is a hippocampal-dependent spatial memory task (Goodrich-Hunsaker et al., 2009). The presence of place cells on human hippocampus was also confirmed by Ekstrom et al. (2003). Hence, results for Experiment 1 and specifically those of the Place group can be explained by the construction of a cognitive map (O'Keefe and Nadel, 1978). In contrast, the results of the Cue + Place group are more difficult to explain from this perspective, since they contradict the idea that a cognitive map integrates all the elements present in the environment. Other studies have reported that eliminating an environmental cue such as a visible platform (Jacobs et al., 1997) or even a subset of distal landmarks (Nadel et al., 1998) do not impair the ability to find the platform position in a virtual water maze task. A possible explanation for these contradictory results is to suppose that the number of landmarks in the environment determines the construction of a cognitive map that allows to solve the water maze task. In our study a set of only four distal landmarks was used to locate the hidden platform whereas in the Jacobs and cols. (Jacobs et al., 1997) and Nadel and cols. (Nadel et al., 1998) studies, a larger set was employed. However, even by using this argument, it is hard to explain why in our study the Place group was able to construct a cognitive map while the Cue + Place group was not able to do so.

An alternative explanation could be to assume associative processes in the performance of Place and Cue + Place groups. For the Place group it is possible to argue that the contiguity and contingency (Rescorla, 1988) between the location of the platform and a specific pair of landmarks allowed the establishment of an association between these elements. That association resulted in excitatory conditioning in which the conditioned

response (CR) was the approach to the reinforced quadrant. The initial election and subsequent reinforced quadrant preference during the Test may be indicators of the intensity of CR. For the Cue + Place group, one possibility is that its performance reflects an overshadowing effect (Pavlov, 1927). It is possible to assume that the visible platform was a conspicuous visual cue (i.e., a beacon) placed directly above the platform location, which could have also been defined in relation to other distal landmarks (c.f., Chamizo et al., 2003; Redhead & Hamilton, 2007; Redhead, Hamilton, Parker, Chan & Allison, 2013). Both beacon and distal landmarks were contingent to the platform location but there was a higher contiguity between that and the beacon. Hence, the beacon salience could have been greater than the distal landmark salience (c.f., Chamizo et al., 2003). Following this reasoning, it is possible to assume that distal landmarks and the visible platform could be perceived as a compound conditioned stimulus (CS) in which the visible platform was the most prominent component, thus achieving better control over seeking behavior in participants. In the absence of the visible platform during the Test, participants' performance remained at the chance level. This was not true in the Place group, where the distal landmarks efficiently controlled participants' behavior. In support of this interpretation, there is evidence from humans that a visible platform can overshadow distal landmarks in a virtual water maze task (Chamizo et al., 2003). However, in that study, the decrease of generalization (Pearce, 1987) which might result from performing the test without one of the elements present during training (i.e., the visible platform) was controlled. Since the aim of this study was not to demonstrate overshadowing in spatial memory, appropriate control groups were not included. Hence a decrease of generalization cannot be ruled out in terms of explaining the data from the Cue + Place group. Despite that fact, it is true that the cognitive map theory cannot predict neither overshadowing nor decrease of generalization. According to this theory there are two independent systems to manage spatial information, a landmark-based behavior system based on the striatum functioning and a place learning system based on the hippocampus functioning (c.f., Packard & McGaugh, 1996). The landmark-based behavior system operates when a proximal landmark indicates the location of a goal while the place learning system operates when distal landmarks are placed. In some cases when proximal and distal landmarks are simultaneously present in the environment, both systems could operate without interfering each other (O'Keefe & Nadel, 1978). Nevertheless, the data of Cue + Place group does not support this claim. An associative approach could explain the behavior of the Cue and Place + Random groups as well. In both cases, the platform location was frequently changed so that

each pair of landmarks pointed out the absence of the goal rather than its presence. It is possible that each pair of landmarks developed inhibitory conditioned properties to some extent (c.f., Rescorla, 1968), which was reflected during testing as analogous to a random search for the platform. However, this interpretation requires further independent evidence.

In Experiment 2 using discrimination reversal learning, the reversal phase produced the reduction near to zero on the probability for choosing the reinforced quadrant during the discrimination phase. This is consistent with an extinction effect. As stated before both the cognitive map theory and the associative approach can explain spatial extinction, but the recovery effect detected during the delayed test could help to clarify this issue. Any post-extinction recovery effect is inconsistent with the cognitive map theory since it does not consider a change in the current, or extinguished, spatial memory by merely allowing the time to pass (O'Keefe & Nadel, 1978). It is the same for some other related spatial memory hippocampus-based theories. There is evidence that the location of a goal can be represented at the neural level through specialized cells called goal-related cells, located in the prefrontal cortex (Poucet et al., 2004). It has been assumed that during the spatial memory acquisition, the synapses between place cells and goal-related cells are strengthened (Burgess, Jackson, Hartley & O'Keefe, 2000); while during the reversal phase of the discrimination reversal learning, the same connections are weakened (Foster, Morris & Dayan, 2000). Still, these theories do not predict spatial memory recovery.

The recovery effect after the discrimination reversal learning has been interpreted as a case of spontaneous recovery (Lattal et al., 2003) which implies the participation of associative processes during spatial extinction. However, Rossato and cols. (Rossato et al., 2006) have suggested that recovery by means of such procedure is a reconsolidation effect rather than spontaneous recovery. The reconsolidation hypothesis pointed out that each time a consolidated memory is reactivated it must undergo a new consolidation processes to be maintained (Alberini, 2005). To solve this controversy, there are some aspects that have to be taken into account. First, reconsolidation processes operate upon a previously acquired memory to enhance it while an extinction procedure produces the acquisition of a new memory. Second, both types of processes are contingent on unreinforced trials but the amount of trials that each one requires to commence is different. Some studies have shown that a single unreinforced trial after spatial memory acquisition triggers the reconsolidation processes (Przybylski & Sara, 1997; Suzuki et al., 2004; but see Lattal et al., 2004). However, there is also evidence that by increasing the number of unreinforced trials an extinction effect is produced (Suzuki et al., 2004; see

also Merlo, Milton, Goozée, Theobald & Everitt, 2014). Finally, particular and mutually exclusive molecular mechanisms responsible for each one of those processes have been identified (Merlo et al., 2014). Hence, it is possible that both Lattal's and Rossato's claims are correct. Rossato and cols. (Rossato et al., 2006) position is based on the finding that intra-hippocampal infusion of the protein synthesis inhibitor anisomycin (ANI) after a single session of discrimination reversal learning impairs the retention of the original and reversed spatial preferences. On the other hand, Lattal and cols. position is based on the finding that subcutaneous administration of ANI before (Lattal & Abel, 2001) or after (Lattal et al., 2004) a discrimination reversal learning, distributed on several sessions, do not impair extinction acquisition. Moreover, these authors employed four times more unreinforced trials than the former, so it is very likely that their results reflect extinction rather than other processes. Since Lattal and cols. (Lattal et al., 2003) employed a similar discrimination reversal learning procedure which was used to produce extinction of spatial memory (Lattal & Abel, 2001; Lattal et al., 2004), the recovery effect reported by them could have been spontaneous recovery rather than a reconsolidation effect.

For this study, we used 8 trials in each phase (i.e., discrimination and reversal), so an extinction effect could be expected due to our procedure. This claim is based on evidence that 10 unreinforced trials after 12 acquisition trials in the water maze task are enough to produce extinction (Suzuki et al., 2004). Additionally, by using the same number of discrimination and reversal trials in the water maze, extinction of the preference for the first platform-position area was produced (Lattal & Abel, 2001; Lattal et al., 2003). Hence, it is expected that the recovery effect reported here consists in a spontaneous recovery of spatial memory.

The spontaneous recovery effect on a discrimination reversal learning procedure can be explained by the interference theory (Bouton, 1993; Bouton & Brooks, 1993). For this theory a CS representation is constructed during the discrimination and the reversal phase but whilst the former is associated with the presence of an unconditioned stimulus (US) (i.e., CS-US excitatory association), the latter is associated with the absence of such US (i.e., CS-US inhibitory association). At the end of the reversal phase the same CS has two mutually exclusive associations with the US. Bouton (1993) proposes that the second learning context codification helps an animal to eliminate this ambiguity, suggesting that even while the animal is in the second learning context, the CS-US inhibitory association remains active. Performing a test in a different context enables activation of the first excitatory CS-US association, which will result in the expression of the originally-acquired CR. In the case of spontaneous recovery, interference

theory assumes that time is functionally equivalent to a physical change of context. Thus, major delays in testing are accompanied by a larger contextual change relative to the present context during the reversal and, therefore, the probability of recovering the originally-acquired CR will be higher. Consistent with Bouton's theory, in Experiment 2 we may assume that during the Discrimination phase an association between a specific pair of landmarks (CS) and the location of the platform (US) was established. This resulted in the establishment of an approach response (CR) to the quadrant where the platform was located. During the Reversal phase, those same landmarks established an association that interfered with the approach response to the quadrant where the platform was originally located (i.e., CS-US inhibitory association). The delayed testing trial for the Recovery group involved a change of context relative to the context present during the reversal procedure, which favored the expression of the CR by re-activating the first excitatory CS-US association.

It is important to point out that the spontaneous recovery effect reported here is based on the choice quadrant test but not on the preference test. The latter test revealed neither recovery effect nor preference for any quadrant in the virtual water maze task. This is consistent with the claim about this type of test which says that it is not adequate to assess the spatial memory on discrimination reversal learning (Lattal et al., 2004). In this procedure, the Reversal phase is useful for retrieving a second acquisition that led the original memory to be extinguished. However, it is possible that persistence in the seeking behavior was also extinguished. After the Discrimination phase of training (i.e., during the initial trials of the reversal phase) persistence at the site originally reinforced had no programmed consequences. Instead, exploring the environment was reinforced by the location of the platform at a new site. During the Test performed after two different training phases (i.e., Discrimination and Reversal), participants may have a greater willingness to explore the maze while seeking the platform, and this tendency to explore may interfere with the persistence required to reveal a preference for a certain quadrant of the water maze, leading to performance as predicted by chance. Furthermore, there is evidence that the time spent in the platform-position area (i.e., reinforced quadrant) is not a very sensitive measure to assess spatial memory in the water maze task (Maei, Zaslavsky, Teixeira & Frankland, 2009).

Additionally, the conditions under which the preference test is conducted in the water maze discrimination reversal learning could be another confounding factor that interferes with revealing any behavioral effects produced by the acquisition of the spatial memory. Due to the fact that during the test trial, all trained landmarks are simultaneously present,

the specific response directed to either stimulus may affect the general pattern of response (c.f., Bouton & Brooks, 1993). For such reason, it is indispensable to further investigate the necessary and sufficient conditions to detect the effects of extinction and recovery of spatial memory in a reliable fashion.

In conclusion, the results of these two experiments suggest the participation of associative processes in human spatial memory. Experiment 1 demonstrated that the acquisition of spatial memory might be explained in terms of contiguity and contingency between a landmark and a goal that establishes an excitatory association whose CR is to approach the goal. Experiment 2 showed that presenting the landmark without the accompanying goal resulted in the extinction of the CR, but that a 24 h RI caused its spontaneous recovery. This last effect is similar to that reported on other discrimination reversal learning preparations (e.g., Bouton & Brooks, 1993) and suggests the participation of the associative processes on extinction of human spatial memory. Our data can neither exclude nor minimize the role of the hippocampus or the place cells on acquisition of spatial memory. In contrast, they indicate that the mechanisms originally proposed by O'Keefe and Nadel (1978) are insufficient to explain it, which therefore requires to add new mechanisms to elucidate the retention and retrieval of spatial memory after extinction.

RESUMEN

Recuperación espontánea de la memoria espacial en humanos en un laberinto virtual de agua. Se investigó la ocurrencia de recuperación espontánea de la memoria espacial en humanos expuestos a un entorno virtual. En el Experimento 1 la memoria espacial fue establecida por entrenar a los participantes a localizar una plataforma oculta en un laberinto virtual de agua empleando un conjunto de cuatro claves distales. En el Experimento 2, tras el aprendizaje sobre la localización de la plataforma, ésta se ocultó en un sitio novedoso dentro del laberinto virtual de agua a fin de extinguir el aprendizaje original. Una prueba inmediata mostró que los participantes buscaron la plataforma en su más reciente ubicación. En cambio, en una prueba demorada (24 h), los participantes tendieron a buscar la plataforma en el sitio en el que originalmente se colocó. Estos resultados son consistentes con un efecto de recuperación espontánea de la memoria espacial y son discutidos en relación a la teoría del mapa cognitivo y a la aproximación asociativa de la memoria espacial.

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