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The removal and addition of cues does not impair spatial retrieval and leads to a different metabolic activity of the limbic network in female rats

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ABSTRACT

The retrieval of spatial memories does not always occur in an environment with the same stimuli configuration where the memory was first formed. However, re-exposure to a partial portion of the previously encountered cues can elicit memory successfully. Navigation with contextual changes has received little attention, especially in females. Thus, we aimed to assess memory retrieval using the Morris Water Maze spatial reference protocol in female adult Wistar rats. Rats were trained with five allocentric cues, and retrieval was explored one week later either with the same cues, or with four removed, or with three added cues. We studied the underlying brain oxidative metabolism of the hippocampus, prefrontal, parietal, retrosplenial, entorhinal, and perirhinal cortices through cytochrome c oxidase (CCO) histochemistry. Neither cue removal nor cue addition impaired retrieval performance. Retrieval with a degraded subset of cues led to increased prefrontal, hippocampal, retrosplenial, parietal, and perirhinal CCO activity. Retrieval with extra cues led to an enhancement of CCO activity in the hippocampus and retrosplenial cortex. Different patterns of network intercorrelations were found. The cue-removal group presented a closed reciprocal network, while the group with extra cues had separate parallel networks. Both groups showed a simpler network than the group with no cue modifications. Future research is needed to delve into behavioral and brain-related functions of spatial memory processes under modified environmental conditions.

1. Introduction

Spatial orientation is a complex cognitive skill that allows us to remember landmark locations and integrate routes and is crucial for everyday functioning (Cimadevilla and Piccardi, 2020; Epstein et al., 2017). It is generally accepted that spatial navigation is based on a world-centered (allocentric) and/or a self-centered (egocentric) strategy (Colombo et al., 2017). The allocentric strategy—which is based on the "cognitive mapping hypothesis" and depends on the extended hippocampal system (Hunsaker and Kesner, 2018)— employs distal visual cues that are located in the environment to guide behavior effectively (Epstein et al., 2017; Poulter et al., 2018; Tolman, 1948).

Quite often, the retrieval of spatial memories does not occur in an environment with the same stimuli configuration where the memory was initially established. Thus, re-exposure can happen in the presence of some, but not all, the previously encountered cues (Jo et al., 2007; Jo and Choi, 2014; Mei et al., 2011).

The presence of some of the original stimuli is sufficient to activate the entire memory, revealing that from partial or degraded spatial cues, it is possible to achieve allocentric navigation (Jo et al., 2007; Jo and Choi, 2014; Mei et al., 2011; Nakazawa et al., 2002). Theoretical models have proposed that this ability can be reached through pattern completion, defined as the recovery of a past event by identifying a previous similar experience (Rolls, 2016). Pattern completion seems to rely on the hippocampus (HC) (Ngo et al., 2021; Rolls, 2016), and some of the studies focused on spatial memory from partial cues have identified behavioral impairments after CA3 lesioning (Jo et al., 2007; Nakazawa et al., 2002). The pivotal role of the prefrontal cortex (PFC) has been proposed under these circumstances (Jo et al., 2007; Jo and Choi, 2014). Conversely, when adding novel landmarks to the original cues, successful retrieval has been shown, even with infusions of NMDAR antagonists into the PFC (Jo and Choi, 2014). However, more recently, impaired retrieval with additional cues has been reported, and the retrieval deficit correlates with reduced limbic metabolic activity

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(Zorzo et al., 2021).

The above-mentioned studies were performed exclusively on male rats. We need to study the behavioral response and brain activity in female rats. Therefore, in the present study, we trained female rats on an allocentric spatial reference memory protocol in the Morris Water Maze (MWM) (Morris, 1984). Seven days later, we explored memory retrieval either with the same cues, or with four removed, or with three added cues. We assessed oxidative metabolism through cytochrome c oxidase (CCO) histochemistry to study brain-related function. CCO histochemistry indicates the activity of the terminal enzyme in the respiratory electron transport chain, reflecting energy consumption linked to the cognitive task (Méndez et al., 2021; Wong-Riley, 1989; Zorzo et al., 2021). Thus, we studied the CCO activity in the hippocampus and the prefrontal, retrosplenial, parietal, and rhinal cortices, which are also involved in allocentric spatial navigation and retrieval (Ekstrom et al., 2017; Hunsaker and Kesner, 2018; Wenjun et al., 2020; Zorzo et al., 2022). Some of them have been related to contextual changes (Jo et al., 2007; Jo and Choi, 2014).

2. Material and methods

2.1. Subjects

A total of 49 female adult Wistar rats (204.60 ± 4.11 g. at the beginning of the experiment) were used. All the animals were maintained at controlled room temperature (20 ± 2º C) and humidity (65–70%) under an artificial light-dark cycle of 12 h (on: 08:00–20:00; off: 20:00–08:00 h). The animals had access to food and tap water ad libitum. The procedures and manipulation of the animals used in this study followed the European Communities Council Directive 2010/63/UE and the Spanish legislation related to the protection of animals used for experimentation and other scientific purposes (RD 53/2013). The study was approved by the local committee for animal studies at Oviedo University.

2.2. Experimental procedure

All rats were handled daily for seven days prior to the beginning of the behavioral procedure. Behavioral tests were performed between 9:00 and 13:00 h. First, the rats were trained in an allocentric spatial reference memory task performed in the MWM. Training was conducted with five visual cues with different volumes and color patterns surrounding the pool. Seven days after the end of the last session, spatial retrieval was assessed under different conditions: maintenance of the five original cues (group 5CF, $n = 9$), maintenance of one original cue (group 1CF, $n = 10$), maintenance of the original five cues and addition of three extra cues (group 8CF, $n = 10$) (Fig. 1). For the 1CF group, the cue maintained during retrieval was always the same (i.e., the cue closest to the platform). Two more control groups were added: a swim-control group that swam in the pool for an equivalent average time as the experimental groups in the learning and retrieval phases, but without the platform or the visual cues (group SCF, $n = 10$), and a learning-control group that performed the spatial reference memory task with the five cues and was sacrificed seven days later without performing the retrieval task (group CF, $n = 10$). To avoid environmental cues in the SCF group, black curtains were placed around the maze.

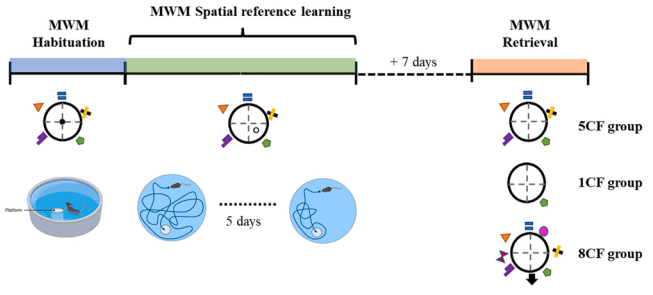

Fig. 1. Experimental design. All groups performed MWM habituation followed by five days of learning. Seven days later, spatial retrieval was tested under full (5CF), partial (1CF), and novel (8CF) cue availability.

2.3. Estrous cycle

Vaginal smears were taken by performing a direct cytology method for three consecutive days one week before the learning procedure to verify that the estrous cycle was not altered, and immediately after the sacrifice to determine the different stages during the retention probe. For this purpose, 1–2 mL of 0.9% Sodium Chloride (*Sigma-Aldrich, Spain*) was introduced into the rat's vagina with a plastic pipette to subsequently absorb the liquid (Cora et al., 2015). The vaginal secretion sample was mounted on a slide, and the cellular type, number, and disposition were observed with a light microscope (Leica DFC490, Germany) to determine the stage of the estrous cycle.

2.4. Behavioral procedure

2.4.1. Apparatus

The MWM was in the center of a 16 m^2 room illuminated by an indirect 4000 lx light. The pool was 150 cm in diameter and 40 cm high and was filled with tap water with a temperature of 22 ± 2 °C. Inside the MWM was a hidden escape platform 2 cm beneath the water's surface, 10 cm in diameter and 28 cm high. The pool was divided into four imaginary quadrants, three non-reinforced and one reinforced through the placement of the escape platform. To provide allocentric cues, the maze was surrounded by black panels located 30 cm away, on which the visual cues were placed. Cue selection and arrangement varied during the retrieval phase according to the experimental design. The animal's behavior was recorded *(*V88E, *Sony, Spain)* using a computerized video-tracking system (Ethovision XT 14.0, *Noldus Information Technologies, Wageningen, The Netherlands*).

2.4.2. Habituation

One day before conducting the spatial reference learning task, animals were habituated to the testing contingencies of the task. Thus, they were subjected to four trials in which they had to reach a visible platform that protruded from the water in the center of the pool. Rats were released from each quadrant facing the pool wall following a pseudo-randomized sequence. The SCF group swam in the maze for an equivalent average time as the experimental groups but without the platform or cues. Once the habituation session had ended, the animals were carefully dried and returned to their home cage.

2.4.3. Learning phase

Following habituation, the learning phase began, which lasted five days. Each day, the subjects performed six trials, with an inter-trial interval of 30 s. The first four trials were acquisition trials, in which rats had to reach the hidden platform located in the reinforced quadrant. Rats were released from each quadrant facing the pool wall following a pseudo-randomized sequence. Once the animal had found the platform, it remained in the reinforced place for 15 s. If the animal failed to reach the platform after 60 s, it was placed on it for 15 s. After completing the four daily training trials, a 60-s learning probe trial was carried out. For that purpose, the escape platform was removed, and the rat was introduced in the opposite quadrant to the platform's position in previous trials. Finally, rats received an additional trial with the platform in its usual position to avoid possible learning extinction. The SCF group swam in the maze for an equivalent average time, but without the platform or cues. Once the training session had ended, the animals were carefully dried and returned to their home cage.

2.4.4. Retrieval phase

Seven days after the last learning session, the 5CF, 1CF, and 8CF groups underwent a memory retrieval test with a single 60-s retrieval probe trial, under the different environmental conditions explained in Section 2.2. Experimental procedure. For this purpose, the platform was removed from the pool. The SCF group swam in the maze for 60 s but without cues. Once the retrieval session had ended, the animals were carefully dried and returned to their home cage until sacrifice.

2.5. Sacrifice and tissue processing

The 5CF, 1CF, 8CF, and SCF groups were decapitated 90 min after completing the retrieval probe test. Seven days after memory acquisition, the CF group was also decapitated without having performed the retrieval probe trial to establish control of spatial learning. Then, the encephalon was removed, frozen in N-methyl butane (*Sigma-Aldrich, Spain*), and stored at − 40 °C. 30 μm thick coronal sections were performed with a cryostat (*Leica CM1900, Germany*). The regions of interest and their distances in mm counted from bregma were: + 3.24 mm for the cingulate (CG), infralimbic (IL), and prelimbic cortex (PL); − 3.48 mm for the CA1 and CA3 subfields of the dorsal hippocampus, dentate gyrus (DG), granular retrosplenial (RSG), agranular retrosplenial (RSA), and parietal cortex (PAR); and − 4.68 mm for the entorhinal (ENT) and perirhinal (PHr) cortices, according to Paxinos and Watson's atlas (Paxinos and Watson, 2005) (Fig. 2).

2.6. Cytochrome c oxidase histochemistry

The procedure performed for tissue treatment was the previously described (Zorzo et al., 2019), based on the method of Gonzalez-Lima and Cada (1994). To control for possible staining variability, homogenized brain tissue standards were cut at different thicknesses (10, 30, 40, and 60 μm) and included in the different stainings. The sections and standards were fixed with a glutaraldehyde solution (*Merck, Spain*) at 0.5% (v / v) and sucrose (≥99.5% (GC)) at 10% (m / v) in phosphate buffer (0.1 M, pH 7.6) for 5 min. Then, they were immersed three consecutive times in a sucrose solution at 10% (m / v) in phosphate buffer (0.1 M, pH 7.6) for 5 min each bath. Then, they were introduced into a Tris buffer solution (*Sigma-Aldrich, Spain*) (0.05 M, pH 7.6), which contained 0.5% dimethylsulfoxide (*Fisher Scientific, Spain*), 10% sucrose (*Sigma-Aldrich, Spain*) (m / v) and cobalt chloride hexahydrate (*Sigma-Aldrich, Spain*) at 0.0275% (m / v) for 8 min. A last bath of phosphate buffer (0.1 M, 7.6 pH) was applied for 5 min. Subsequently, both the sections and the standards were incubated in the dark and at 37° C in a phosphate buffer solution (0.1 M, pH 7.6) containing cytochrome c (*Sigma-Aldrich, Spain*) at 0.0075% (m / v), catalase (*Alfa Aesar, Spain*) at 0.002% (m / v), sucrose at 5% (m / v), dimethylsulfoxide at 0.25% (v / v), and diaminobenzidine tetrachloride (*Sigma-Aldrich, Spain*) at 0.05% (m / v), for 1 h under slow stirring. This reaction was halted by fixing the tissue in phosphate buffer (0.1 M, 7.6 pH) with sucrose at 10% (w / v) and formaldehyde (*Fisher Scientific, Spain*) at 4% (v / v) at room temperature for 30 min. Finally, the sections and standards were dehydrated in increasing ethanol concentrations, rinsed with xylene, and then mounted with Entellan (*Merck, Spain*) and glass coverslips. The sections were labeled and stored until quantification.

2.7. Cytochrome c oxidase optical density quantification

The CCO histochemical staining intensity was quantified by optical densitometry using a computer-assisted image analysis workstation (*MCID, Interfocus Imaging Ltd., Linton, England*) consisting of a high-precision illuminator, a digital camera, and a computer with specific image analysis software. Measurements of standards in each of the incubation baths were taken. Brain target structures were measured in the right hemisphere, using four non-overlapping readings in each section across three consecutive sections. Consequently, a total of 12 measurements per area and subject were collected. The average optical density values were transformed into CCO activity units, determined by the enzymatic activity of the standards measured (Gonzalez-Lima and Cada, 1994).

2.8. Statistical analysis

We employed the SigmaStat 14 program (*Systat, Richmond, USA*) for data analysis. We used the Shapiro-Wilk test to evaluate the normality assumption and the Levene test to assess homoscedasticity for ANOVA analysis. When assumptions were violated ($P < .05$), we used nonparametric tests.

Regarding estrous cycle, a one-way ANOVA was used to determine whether the retention percentage during retrieval was related to the estrous cycle stages in the 5CF, 1CF, and 8CF groups. To determine a possible statistical relationship between the estrous cycle stages and the different female groups, we used Chi-square (χ^2) distribution.

As for the behavioral data, the time spent in the reinforced quadrant was compared to the time spent in the three non-reinforced quadrants for each group and day, using a one-way ANOVA or the Kruskal-Wallis one-way analysis of variance on ranks. To compare responses during retrieval, a two-way ANOVA was performed (Factor 1: group; Factor 2:

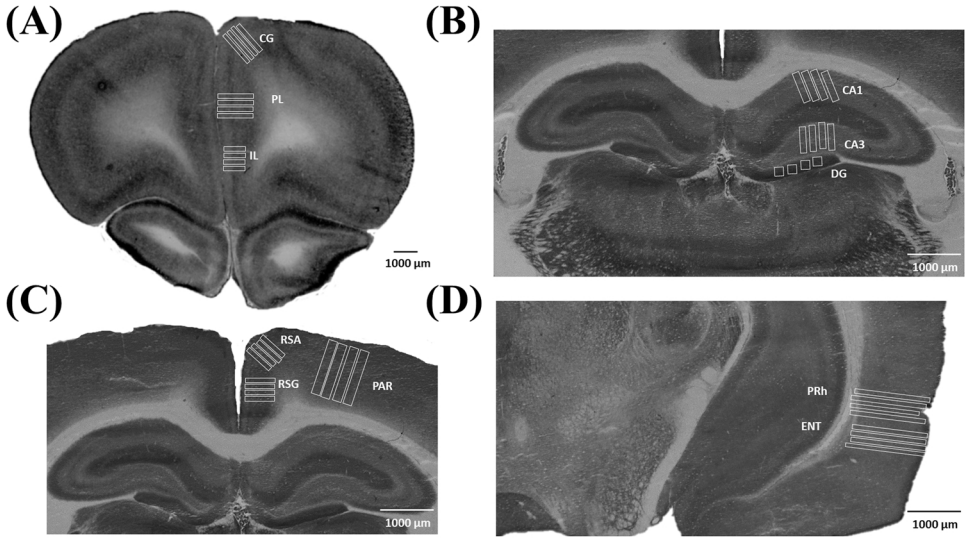

Fig. 2. Sampling frames of CCO histochemistry in brain coronal slices using a 30x magnification. (A) Cingulate, prelimbic and infralimbic cortex. (B) CA1, CA3, and dentate gyrus. (C) Granular and agranular retrosplenial and parietal cortex. (D) Perirhinal and entorhinal cortex. CG = Cingulate cortex, PL = Prelimbic cortex, IL = Infralimbic cortex, DG = Dentate Gyrus, RSG = Granular retrosplenial cortex, RSA = Agranular retrosplenial cortex, PAR = Parietal cortex, PRh = Perirhinal cortex, ENT = Entorhinal cortex.

quadrants). The escape latencies were analyzed independently by group, applying a repeated-measures ANOVA or its nonparametric equivalent, Friedman's repeated measures. Concerning CCO activity data, a one-way ANOVA or the Kruskal-Wallis one-way analysis of variance on ranks was performed in each brain region. The Holm-Sidak post-hoc method was applied with parametric tests and Dunn's method with nonparametric procedures.

The analysis of interregional correlations was performed by calculating Pearson product-moment correlations, using the "jacknife" procedure to avoid estimation bias, and noting the significant correlations (Sinharay, 2010).

Differences were considered statistically significant at the.05 level. Finally, for graphic representation, we employed the SigmaPlot 14 program (*Systat, Richmond, USA*). We present the data as mean ± standard error of mean (SEM).

3. Results

3.1. Estrous cycle

There was no statistically significant difference between the estrous phases in the retention percentage of experimental groups during retrieval ($H_3 = 5.026$, $P = .170$). Chi-square distribution revealed that the stages of the estrous cycle in the female groups included were not significantly related ($\chi^2_6 = 6.085$, $P = .414$).

3.2. Behavioral results

Time spent by the 5CF group in each pool's quadrant revealed differences between quadrants from the second day (D1: $H_{(3)}$= 7,383, P=.061; D2: $F_{(3, 29)}$= 16.476, P<.001; D3: $F_{(3, 32)}$= 16.138, P<.001; D4: $F_{(3, 32)}$= 24.753, P<.001; D5: $H_{(3)}$= 21.072, P<.001). Post-hoc analysis showed differences between quadrant D and the rest of the quadrants

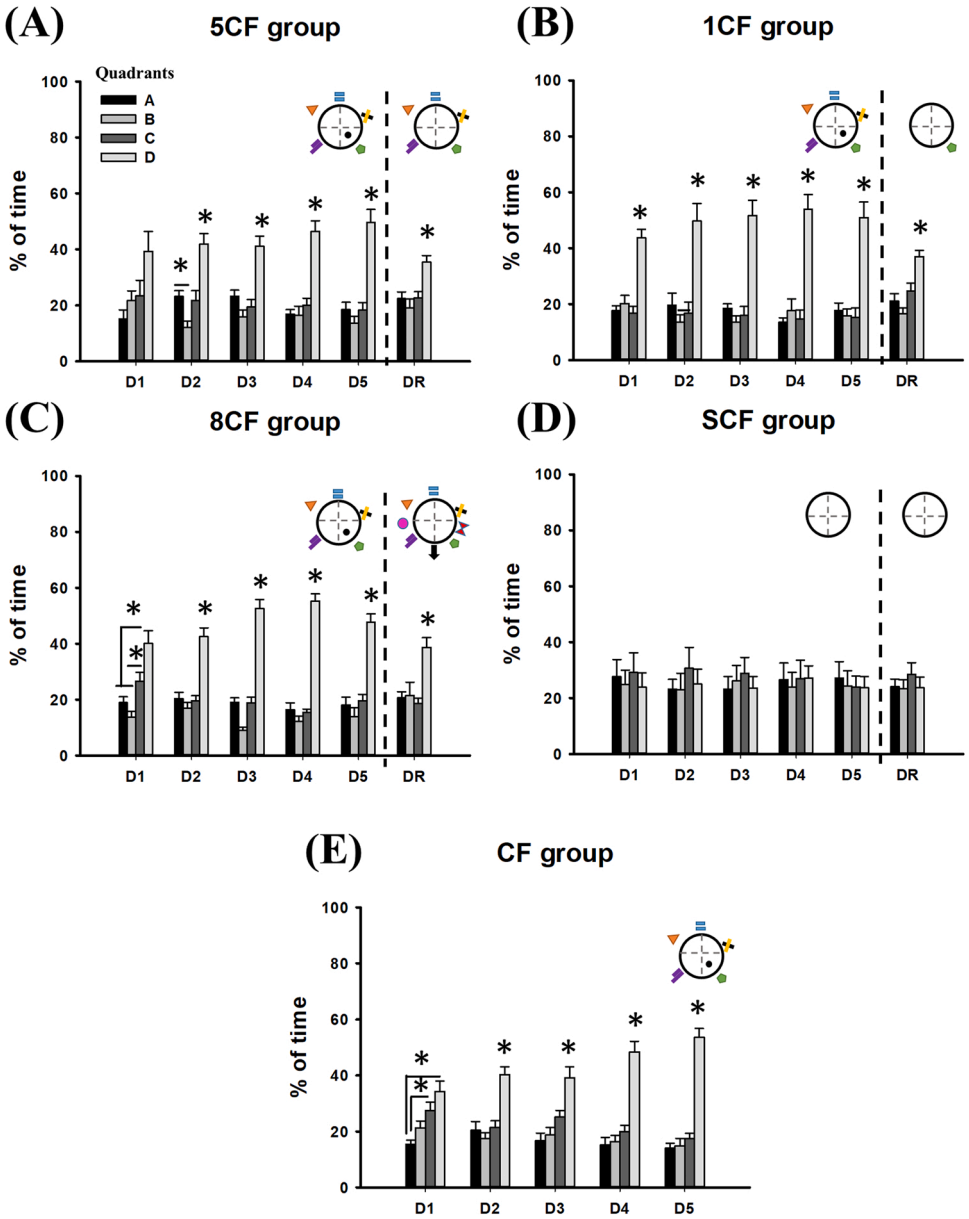

Fig. 3. Time spent in reinforced and non-reinforced quadrants during the learning and retrieval probe tests in the MWM. The x-axis shows the days. (A) 5CF group. (B) 1CF group. (C) 8CF group. (D) SCF group. (E) CF group. DR = Day of Retrieval. Differences were considered statistically significant if * $P \leq .05$. Data are expressed as mean ± SEM.

from the second day ($P<.05$), in addition to differences between quadrants A and B ($P=.041$) on day two. In the retrieval probe test, the 5CF group showed differences between quadrants ($F_{(3,\ 32)}= 7{,}840$, $P=.002$), with the Holm-Sidak method revealing more time spent in the reinforced quadrant than in the non-reinforced quadrants ($P<.05$) (Fig. 3A). The 1CF group showed successful learning from the first day (D1: $H(3) = 21.733$, $P<.001$; D2: $F(3, 36) = 13.846$, $P<.001$; D3: $H(3) = 22.257$, $P<.001$; D4: $F(3, 36)= 25.830$, $P<.001$; D5: $F(3, 36) = 21.839$, $P<.001$). In the retrieval probe test, the 1CF group showed differences between quadrants ($F(3, 36) = 12.714$, $P<.001$). The Holm-Sidak method revealed more time spent in the reinforced quadrant than in the non-reinforced quadrants during learning and retrieval ($P<.05$) (Fig. 3B). The 8CF group also displayed differences between quadrants (D1: $F_{(3,\ 36)}= 20.419$, $P<.001$; D2: $F_{(3,\ 36)}= 25.000$, $P<.001$; D3: $F_{(3,\ 36)}= 79.411$, $P<.001$; D4: $H_{(3)}= 85.064$, $P<.001$; D5: $H_{(3)}= 30.466$, $P<.001$). In the retrieval probe test, the 8CF group showed differences between quadrants ($H(3) = 14.652$, $P<.001$). Post-hoc analysis revealed differences between quadrants D withA and B ($P<.05$), in addition to differences between quadrants B and C ($P<.05$) on day one, and differences between quadrant D and the non-reinforced quadrants during the remaining learning and retrieval probe tests ($P<.05$) (Fig. 3C). In the SCF group, there were no differences between quadrants across all the matched-training days (D1: $H_{(3)}=.504$, $P=.918$; D2: $H_{(3)}=.978$, $P=.807$; D3: $H_{(3)}=.635$, $P=.888$; D4: $H_{(3)}=.166$, $P=.983$; D5: $F(3, 36)=.107$, $P=.956$), or during the retrieval probe test ($F(3, 36) =.477$, $P=.700$) (Fig. 3D). Finally, the CF group achieved the learning criteria from day one (D1: $H(3) = 18.699$, $P<.001$; D2: $H(3) = 19.655$, $P<.001$; D3: $F(3, 36) = 11.543$, $P<.001$; D4: $F(3, 36) = 31.819$, $P<.001$; D5: $F(3, 36) = 60.871$, $P<.001$). Post-hoc analysis showed the differences between quadrant D and the rest of the quadrants from the second day of the test ($P<.05$), as well as differences between quadrants A and C ($P<.05$) and between quadrants A and D ($P<.05$) on the first day of the task (Fig. 3E).

The two-way ANOVA analysis showed an interaction effect between groups and quadrants ($F_{(9,\ 140)}= 2.788$; $P = .005$). Post-hoc analysis revealed differences in the target quadrant, where the 5CF, 1CF, and 8CF groups displayed higher permanence than the controls ($P < .05$), but no differences were observed between them or between the non-reinforced quadrants ($P < .05$).

As for latencies, the 5CF group showed significant differences across days ($F_{4,\ 32}= 4.845$, P=.004), specifically between days four ($P=.010$) and five ($P=.020$), in comparison with day one (Fig. 4A). The 1CF group revealed significant differences ($X^2_4= 14.814$, $P<.001$), observing a reduction in latencies on the fourth ($P =.016$) and fifth ($P=.020$) days of the task compared to the first day (Fig. 4B). The 8CF group showed significant differences ($F_{4,\ 36}= 4.260$, $P=.006$) between day two compared to the fourth day of the task ($P=.002$) (Fig. 4C). Finally, the CF group showed differences throughout the days ($F_{4,\ 36}= 12.419$, $P<.001$), with a reduction on the fourth ($P<.001$) and fifth ($P<.001$) days of the task compared to the first day, as well as on the fourth (P=.002) and fifth (P=.021) days of the task, compared to the second day, and on the fourth ($P=.002$) and fifth ($P=.025$) day compared to the third day (Fig. 4D). Latencies for the SCF group (not shown) represent an average of the 5CF, 1CF, and 8CF time to reach the platform.

3.3. CCO activity results

Analysis of CCO activity showed differences between the groups across all the brain areas measured (CG: $H_{(4)}= 22.852$, $P < .001$; PL: $H_{(4)}= 28.431$, $P < .001$; IL: $H_{(4)}= 26.567$, < 0.001; CA1: $H_{(4)}= 28.912$, $P < .001$; CA3: $H_{(4)}= 28.690$, $P < .001$; DG: $H_{(4)}= 16.827$, $P = .002$; RSG: $H_{(4)}= 22.690$, $P < .001$; RSA: $H_{(4)}= 26.175$, $P < .001$; PAR: $H_{(4)}= 25.781$, $P < .001$; PRh: $H_{(4)}= 25.254$, $P < .001$; ENT: $H_{(3)}= 22.279$, $P < .001$). Dunn's method revealed that the 5CF group showed higher CCO activity than the SCF and CF groups across CG, PL, IL, CA1, CA3, DG, RSG, RSA, PAR, PRh, and ENT ($P < .05$). The 1CF group showed higher metabolic activity than the SCF and CF groups across CG, PL, IL, CA1, CA3, RSA and PAR ($P < .05$), and higher CCO activity in PRh compared to the SCF group ($P < .05$). The 8CF group showed higher CCO activity than the SCF and CF groups across CA1 and

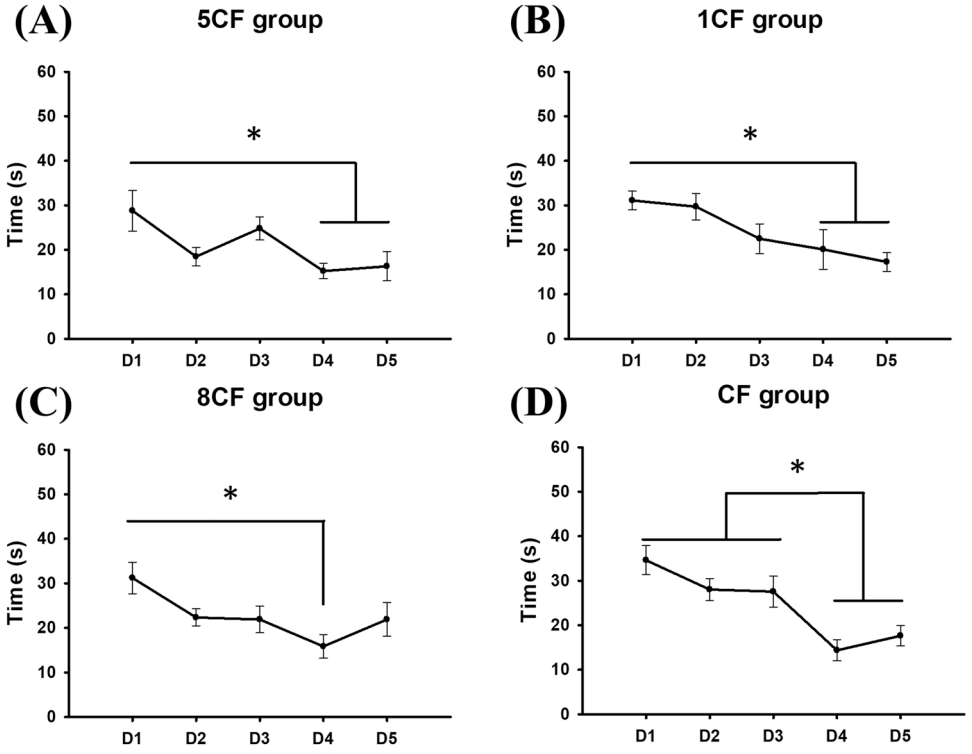

Fig. 4. Latencies to reach the platform during the MWM learning. The x-axis shows the days. (A) 5CF group. (B) 1CF group. (C) 8CF group (D) CF group. DR = Day of Retrieval. Differences were considered statistically significant if * $P \leq .05$. Data are expressed as mean ± SEM.

RSG ($P < .05$). Finally, there were differences between the 5CF and 1CF groups in DG ($P < .05$), or between the 5CF and 8CF groups in ENT ($P < .05$) (Fig. 5).

3.4. CCO interregional correlations

Significant interregional correlations of CCO activity are shown in Table 1 for the 5CF group, in Table 2 for the 1CF group, in Table 3 for the 8CF group, in Table 4 for the SCF group, and in Table 5 for the CF group. Schematic graphic representations are shown in Fig. 6.

4. Discussion

This study investigated the retrieval (one-week delay) of an allocentric spatial memory and the underlying oxidative metabolism of hippocampal and cortical brain areas in female adult rats. Neither removal nor addition of extra-maze cues from the original learning phase disrupted retrieval performance. Whereas retrieval with a degraded subset of cues resulted in increased prefrontal, hippocampal, retrosplenial, parietal, and perirhinal CCO activity, adding novel cues led to an increment of CCO activity restricted to the hippocampus and retrosplenial cortex. Furthermore, different networks of intercorrelations were found: the cue-removal group showed a closed reciprocal network, and the group with extra cues, separate parallel networks. Both groups revealed a less complex network of intercorrelations between the learning and retrieval phases than the group with no cue modifications.

Males and females are known to behave differently in spatial navigation procedures, with evidence from human (Castillo et al., 2021; Fernandez-Baizan et al., 2019; León et al., 2016; Sneider et al., 2015; Yu et al., 2021) and animal studies (Mifflin et al., 2021; Qi et al., 2016; Safari et al., 2021; Simpson and Kelly, 2012; Yagi et al., 2017). Some authors attribute better male performance to task difficulty (Chamizo et al., 2020), different swimming patterns (Devan et al., 2016), motivation to complete the task (Mifflin et al., 2021), or different spatial strategies, suggesting that males tend to use geometric information whereas females rely more on landmarks during navigation (Aguilar-Latorre et al., 2022; Andersen et al., 2012; Chamizo et al., 2016). Nevertheless, although there are studies including females, most of the research in spatial learning and memory processes using the MWM has been performed only in males, leading to an under-representation of female behavioral and brain-related responses. From our point of view, it is crucial to incorporate research on females, particularly in cognitive processes such as spatial cognition that seem to differ between sexes.

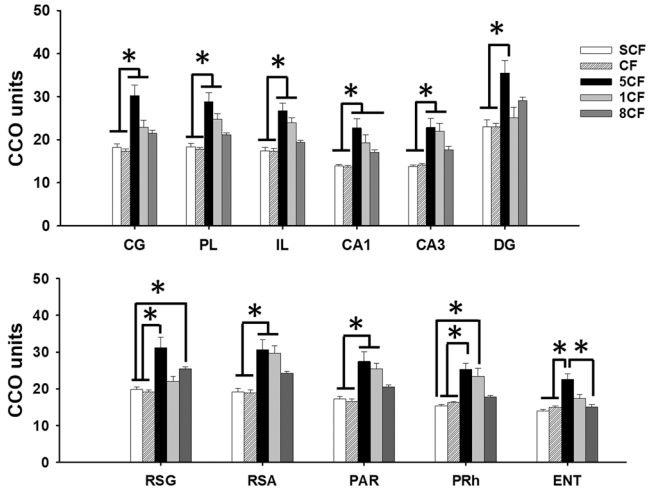

Fig. 5. CCO values (mean ± SEM) in 5CF, 1CF, 8CF, SCF, and CF groups. CG = Cingulate cortex, PL = Prelimbic cortex, IL = Infralimbic cortex, DG = Dentate Gyrus, RSG = Granular retrosplenial cortex, RSA = Agranular retrosplenial cortex, PAR = Parietal cortex, PRh = Perirhinal cortex, ENT = Entorhinal cortex. Differences were considered statistically significant if * $P \leq .05$. Data are expressed as mean ± SEM.

In terms of allocentric spatial retrieval with cue-availability modifications, there is no evidence in female rats. Under partial-cue conditions, we have previously shown that male rats show a conserved one-week memory retrieval (Zorzo et al., 2021), in line with prior studies with a few hours of delay (Jo et al., 2007; Jo and Choi, 2014). Now, using a comparable study design and methodologies, we have found an adequate response in females, as the 1CF group achieved a good performance as of day one of the learning phase, in addition to a reduction in escape latencies. The group also displayed successful retrieval after allocentric information was reduced. This successful performance may have been achieved through pattern completion (Gold and Kesner, 2005; Kesner et al., 2016), a cognitive process defined as the ability to recover an entire memory from its fragments (Gold and Kesner, 2005; Kesner et al., 2016), which is indispensable for processing information (Hunsaker and Kesner, 2013). Pattern completion can be studied by manipulating the availability of extra-maze cues of the environment. It should be taken into account that an elevated reduction of the original cues requires increased reliance on pattern completion (Paleja and Spaniol, 2013). Therefore, it seems that a less informative MWM environment does not affect female performance, similar to previous studies that reported males' successful retrieval under partial-cue conditions (Jo et al., 2007; Jo and Choi, 2014; Zorzo et al., 2021). Nevertheless, it is important to consider one potential limitation of the present study, as all the animals from the 1CF group followed the same pattern configuration during retrieval: the only cue maintained was located closest to the platform, which can be thought to provoke a less-demanding cognitive mapping. It could be argued that the animals are employing a guide strategy to solve the task, where the availability of a single landmark can represent a beacon. In an attempt to avoid this issue, we separated the cues from the pool to prevent proximal cues and to favor allocentric, distal extra-maze cues. In this sense, we note that all the groups (5CF, 1CF, 8CF, CF) performed the training with the same cue configuration and they showed similar latencies and permanence. In the case of retrieval, we found that the three experimental groups displayed similar permanence in the correct quadrant, and all of them spent more time than the swim-controls. Therefore, at a behavioral level, we observed no differences in the cognitive demand in response to distal cues. Moreover, it is generally accepted that when rats are trained with multiple cues in the MWM, they identify the location of the platform by learning the configuration of the cues rather than each landmark individually (Harvey et al., 2009). More research is needed to delve into these mechanisms in female rats.

As for novel cues, we also found a good outcome in the 8CF group, revealing that adding three landmarks to the original cues did not disrupt female spatial retrieval with a one-week delay. We note that learning was adequate, as the probe test and escape latencies show. To our knowledge, there are no female studies with these characteristics. The few available studies show opposite results in males: Jo and Choi (2014) revealed conserved memory retention with a two-hour delay, whereas our previous study in males with the same study design and methodologies showed a failed one-week spatial retention (Zorzo et al., 2021). Therefore, a longer time interval in which retrieval is assessed could generate a more complex procedure that could benefit female performance. Taking into account that women tend to encode and recall detailed information, whereas men usually code and recall gist information, Herrera et al. (2019) propose that females' cognitive processing may allow them to better identify changes in the environment, which could occur when adding extra cues in the retrieval phase with a one-week delay.

In the MWM, some studies have shown that females tend to swim for a longer time than their male counterparts in the periphery of the pool (Devan et al., 2016), although other studies do not find statistical differences in healthy rodents (Macúchová et al., 2017; Méndez-López

Table 1
5CF group's significant interregional correlations of CCO activity.

	PL	IL	CA1	CA3	DG	RSG	RSA	PAR	PRh	ENT
CG	***r*=.983** *P*<.001	***r*=.930** *P*<.001	***r*=.815** *P*=.013	-	***r*=.854** *P*=.006	***r*=.874** *P*=.004	***r*=.898** *P*=.002	***r*=.832** *P*=.010	***r*=.883** *P*=.001	***r*=.878** *P*=.001
PL		***r*=.920** *P*<.001	-	-	-	***r*=.874** *P*=.004	***r*=.898** *P*=.002	-	***r*=.883** *P*=.001	***r*=.878** *P*=.001
IL			***r*=.889** *P*=.003	***r*=.778** *P*=.002	***r*=.817** *P*=.013	***r*=.922** *P*=.001	***r*=.940** *P*<.001	***r*=.957** *P*<.001	***r*=.838** *P*=.004	-
CA1				***r*=.978** *P*<.001	***r*=.975** *P*<.001	***r*=.985** *P*<.001	***r*=.963** *P*<.001	***r*=.969** *P*<.001	***r*=.885** *P*=.001	-
CA3					***r*=.919** *P*=.001	***r*=.948** *P*<.001	***r*=.917** *P*=.001	***r*=.921** *P*=.001	***r*=.883** *P*=.003	-
DG						***r*=.975** *P*<.001	***r*=.983** *P*<.001	-	***r*=.805** *P*=.015	-
RSG							***r*=.979** *P*<.001	***r*=.967** *P*<.001	***r*=.873** *P*=.004	-
RSA								***r*=.981** *P*<.001	***r*=.860** *P*=.006	-
PAR									-	-
PRh										-

Table 2
1CF group's significant interregional correlations of CCO activity.

	PL	IL	CA1	CA3	DG	RSG	RSA	PAR	PRh	ENT
CG	-	-	-	-	-	-	-	-	-	-
PL		-	-	-	-	-	-	-	-	-
IL			-	-	-	-	-	-	-	-
CA1				-	-	-	***r*=.704** *P*=.023	-	-	-
CA3					***r*=-.71** *P*=.021	-	***r*=.894** *P*<.001	***r*=.820** *P*=.003	***r*=.755** *P*=.011	-
DG						***r*=.890** *P*<.001	-	-	-	-
RSG							-	-	-	-
RSA								***r*=.914** *P*<.001	***r*=.865** *P*=.001	-
PAR									***r*=.816** *P*=.004	-
PRh										-

Table 3
8CF group's significant interregional correlations of CCO activity.

	PL	IL	CA1	CA3	DG	RSG	RSA	PAR	PRh	ENT
CG	-	-	-	-	-	-	-	-	-	-
PL		***r*=.745** *P*=.013	-	-	-	-	-	-	-	-
IL			-	-	-	-	-	-	-	-
CA1				***r*=.805** *P*=.004	-	-	-	***r*=.884** *P*<.001	-	***r*=.963** *P*<.001
CA3					-	-	-	***r*=.885** *P*<.001	-	-
DG						-	-	-	-	-
RSG							***r*=.823** *P*=.001	-	-	-
RSA								-	-	-
PAR									-	-
PRh										-

Table 4
SCF group's significant interregional correlations of CCO activity.

	PL	IL	CA1	CA3	DG	RSG	RSA	PAR	PRh	ENT
CG	***r*=.789** *P*=.011	-	-	-	-	-	-	-	-	-
PL		-	-	-	-	-	-	-	-	-
IL			-	-	-	-	-	-	-	-
CA1				-	-	-	-	-	-	-
CA3					-	-	-	-	-	-
DG						-	-	-	-	-
RSG							-	-	-	-
RSA								-	-	-
PAR									-	-
PRh										-

et al., 2009), suggesting that habituation trials—similar to those performed in our study— trigger comparable male-female thigmotaxis (Méndez-López et al., 2009). This swim pattern is usually associated with anxiety, but not necessarily with longer trainings such as those used in MWM. Thigmotaxis is also proposed as a reflection of increased exploration (Devan et al., 2016), which could lead to greater approach to distal cues. This, in turn, could facilitate the discrimination of novel visual cues. Indeed, previous studies have found that females have a

Table 5
CF group's significant interregional correlations of CCO activity.

	PL	IL	CA1	CA3	DG	RSG	RSA	PAR	PRh	ENT
CG	-	-	-	-	-	-	-	-	-	-
PL		-	-	-	-	-	-	-	-	-
IL			-	-	-	-	-	-	-	-
CA1				***r*=.705** *P*=.002	-	-	-	-	-	-
CA3					-	-	-	-	-	-
DG						-	-	-	-	-
RSG							***r*=.820***P*=.003	-	-	-
RSA								-	-	-
PAR									-	-
PRh										-

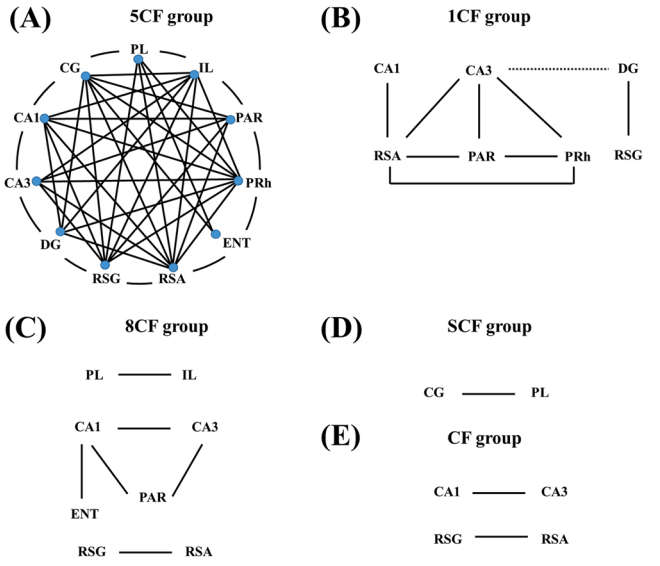

Fig. 6. Schematic diagram of the significant interregional correlations of CCO activity in (A) 5CF, (B) 1CF, (C) 8CF, (D) SCF, and (E) CF groups. Solid and dotted lines represent, respectively, positive and negative Pearson correlations.

greater tendency to revisit previous locations and show less diffusion of navigation, pointing to a different, more cautious exploratory behavior (Gagnon et al., 2018, 2016), which could partially explain our results. Moreover, a study that explored discrimination of local and distal cue changes revealed that females showed high levels of rearing and locomotion (Seib et al., 2018). Considering that the procedure presented herein requires detailed representations because the animals must adequately discriminate between original and novel landmarks, female rats can be assumed to perform this correctly.

The aim of this study is to consider the under-represented sex (Beery and Zucker, 2011) to include knowledge about female neurobiological functioning, which may be differential (Spets et al., 2021; Yagi and Galea, 2019). Therefore, we studied the female brain oxidative metabolism under full (5CF), partial (1CF), and novel (8CF) cue availability during MWM retrieval through CCO activity. We included two control groups. The swim-control group (SCF) was formed to isolate the motor activity inherent to the task, in addition to other variables such as contact with the water and the researcher. The learning-control group (CF) did not perform the spatial retrieval task but was trained in the pool with the five cues.

Brain metabolic results showed an enhancement in the CCO activity in the 5CF group compared to both controls in all the included limbic areas, revealing the role of cortex and HC during spatial retrieval (Barry et al., 2016; Zorzo et al., 2022). As expected, the group with intact cue availability displayed an interrelated and complex brain network organization, as previously reported (Banqueri et al., 2018). Thus, retrieval with identical cues engages the prefrontal, parietal, retrosplenial, perirhinal, and entorhinal cortex, as well as the hippocampus (Barry et al., 2016; Bonaccorsi et al., 2013; Gusev and Gubin, 2010). The interactions between all these structures are essential for spatial processing (Hunsaker and Kesner, 2018). Notably, the SCF group only showed a significant correlation between the CG and PL, and the CF group across the CA1 and CA3, and retrosplenial subdivisions. Both control groups showed equivalent CCO activity across all the areas measured.

However, under partial-cue availability (1CF group), there is an increased CCO activity compared to both control groups in CG, PL, IL, CA1, CA3, RSA, and PAR, as well as increased 1CF CCO activity compared to the SCF group in PRh. The pattern completion process may rely on the hippocampal system, specifically through recurrent excitatory connections among CA3 cells (Gold and Kesner, 2005) and their projections to CA1 and ENT (Poli et al., 2018). Accordingly, a CA3 N-methyl-D-aspartate (NMDA) receptor gene ablation under partial-cue conditions leads to a specific disruption of spatial memory, in addition to decreased CA1 activity (Nakazawa et al., 2002). Moreover, the functional role of the PFC has been highlighted, as its lesioning triggers memory deficits (Jo et al., 2007; Jo and Choi, 2014), with NMDA receptors showing a pivotal role (Jo and Choi, 2014). Interestingly, remembering contextual details from a single retrieval cue leads to increased PFC activity in rodents (Jo et al., 2007) and humans (Dobbins et al., 2002). It is proposed that both hippocampus and PFC can interact in memory retrieval after reducing allocentric cues (Jo et al., 2007). Our results add to the evidence about the recruitment of HC and PFC in females, in addition to RSA—which is densely connected to visual areas and plays a key role in spatial discrimination (Hindley et al., 2014; Wang et al., 2012). Our results also show the contribution of PAR and PRh, both implicated in navigation (Hunsaker and Kesner, 2018; Ramos, 2013; Whitlock, 2017), with the latter showing spatial retrieval deficits when lesioned (Ramos, 2008). Furthermore, correlational analysis revealed a closed reciprocal network that engages some of the cortical areas studied (RSG, RSA, PAR, PRh) and the HC. CA3 is positively connected with RSA, PAR, and PRh and inversely connected with DG, the main area involved in pattern separation, which is needed for coding (Hunsaker and Kesner, 2013; Rolls, 2016).

Regarding the 8CF group, there is an increment of CA1 and RSG CCO activity compared to both control groups. Thus, we suggest the participation of HC and the retrosplenial cortex in the successful recognition of spatial changes. Modifications in the spatial environment have been shown to trigger re-exploration, and this behavior is accompanied by changes in CA1 place cell firing (Lenck-Santini et al., 2005). Hippocampal recordings show that CA1 activity reflects discrimination between novel and familiar environments (Allegra et al., 2020). The retrosplenial cortex is a key structure in the incorporation of new spatial information with multiple connections to the HC and related cortices (Kesner, 2013, 1998). Furthermore, the 8CF group shows three different parallel networks, one more complex, including hippocampal and related cortices, and two separate prefrontal and retrosplenial networks. The more complex network engages the CA1, CA3, ENT, and PAR. The first three are critical structures that conform the trisynaptic circuit and are essential when processing novel information (Amaral and Witter,

1989; Poulter et al., 2018). The PAR cooperates with the HC during spatial navigation processing (Hunsaker and Kesner, 2018; Kesner, 2009).

Finally, sex hormones are known to be involved in hippocampus-dependent cognition, where their impact may be influenced by training and type of task (Duarte-Guterman et al., 2015). One limitation of this work is that we did not study the phase of the estrous cycle during spatial learning, altestroushough we verified that the rats exhibited a normal estrous cycle before initiating the learning task. We explored the estrous cycle during retrieval and did not observe differences in the percentage of retrievals between estrous cycle phases or associations between cycle phases and the 1CF, 5CF, and 8CF groups. We suggest that the estrous cycle does not interfere with retrieval in the present study, similar to that of Farhadinasab et al. (2009), which showed no differences between proestrus and estrous phases in spatial retrieval.

5. Conclusions

To summarize, there is a variable contribution of CCO activity in response to changes in the environmental configuration when evaluating a one-week spatial memory in female rats that achieve successful spatial retrieval. A higher and interrelated involvement of the limbic system is required when cues are not modified. Most brain areas are also involved under partial-cue conditions, and adding novel cues leads to CCO enhancement in the HC and RSG. Future research is needed to examine the brain basis responsible for processing distal environmental changes, both in males and females.

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CRediT authorship contribution statement

Candela Zorzo: Investigation, Formal analysis, Writing – original draft, Visualization. **Jorge L. Arias:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Resources, Funding acquisition. **Marta Méndez:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of interest

All the authors declare that there are no actual or potential conflicts of interest, including any financial, personal, or other relationships with other people or organizations that could inappropriately influence this work. The work described has not been submitted for publication elsewhere, in its entirety or in part, and all the authors listed have approved the enclosed manuscript.

Data Availability

Data will be made available on request.

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