Neuroscience and Biobehavioral Reviews

Functional neuroanatomy of allocentric remote spatial memory in rodents

--Manuscript Draft--

Manuscript Number:	NEUBIOREV-D-20-00666R3
Article Type:	IG005111:Review Article
Keywords:	Remote memory; retrieval; allocentric strategy; rodents; systemic consolidation
Corresponding Author:	Candela Zorzo SPAIN
First Author:	Candela Zorzo
Order of Authors:	Candela Zorzo
	Jorge L. Arias
	Marta Méndez
Abstract:	Successful spatial cognition involves learning, consolidation, storage, and later retrieval of a spatial memory trace. The functional contributions of specific brain areas and their interactions during retrieval of past spatial events are unclear. This systematic review collects studies about allocentric remote spatial retrieval assessed at least two weeks post-acquisition in rodents. Results including non-invasive interventions, brain lesion and inactivation experiments , pharmacological treatments, chemical agent administration, and genetic manipulations revealed that there is a normal forgetting when time-periods are close to or exceed one month. Moreover, changes in the morphology and functionality of neocortical areas, hippocampus, and other subcortical structures, such as the thalamus, have been extensively observed as a result of spatial memory retrieval. In conclusion, apart from an increasingly neocortical recruitment in remote spatial retrieval, the hippocampus seems to participate in the retrieval of fine spatial details. These results help to better understand the timing of memory maintenance and normal forgetting, outlining the underlying brain areas implicated.

The neurobiology behind remote spatial memory on the basis of experimental research

Highlights

1. Decline of rodent spatial memory is observed at longer retentions than a month.
2. Neocortex, and specially the prefrontal cortex, is critical to retrieve memories.
3. Hippocampus will be always necessary to retrieve spatial information.
4. Brain morphology and functionality can change due to retrieval of past events.

Abstract

Successful spatial cognition involves learning, consolidation, storage, and later retrieval of a spatial memory trace. The functional contributions of specific brain areas and their interactions during retrieval of past spatial events are unclear. This systematic review collects studies about allocentric remote spatial retrieval assessed at least two weeks post-acquisition in rodents. Results including non-invasive interventions, brain lesion and inactivation experiments, pharmacological treatments, chemical agent administration, and genetic manipulations revealed that there is a normal forgetting when time-periods are close to or exceed one month. Moreover, changes in the morphology and functionality of neocortical areas, hippocampus, and other subcortical structures, such as the thalamus, have been extensively observed as a result of spatial memory retrieval. In conclusion, apart from an increasingly neocortical recruitment in remote spatial retrieval, the hippocampus seems to participate in the retrieval of fine spatial details. These results help to better understand the timing of memory maintenance and normal forgetting, outlining the underlying brain areas implicated.

Keywords: Remote memory, retrieval, allocentric strategy, rodents, system consolidation.

Abbreviations: α-CaMKII, Ca2+/calmodulin-dependent kinase II-α; ACC, anterior cingulate cortex; AChE, acetylcholinesterase; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ANT, anterior thalamic nuclei; Ara-C, cytosine arabinoside; CCO, cytochrome c oxidase; cKO, conditional knock-out; CTCF, CCCTC-binding factor; DG, dentate gyrus; DLO, dorso-lateral orbital cortex; DNMT, DNA methyltransferase; EE, environmental enrichment; FrAs , frontal association; HC, hippocampus; HT, heterozygous; IEG, immediate early genes; IL, infralimbic cortex; ILN/LT, intralaminar nuclei/ lateral thalamic nuclei; Ins, insular area; KO, knock-out; L-

VGCCs, L-type voltage-gated calcium channels; L2/3, Layers 2/3; L4, layer 4; lENT, lateral entorhinal cortex; M1, primary motor cortex; M2, secondary motor cortex; MAM, methylazoxymethanol acetate; mENT, medial entorhinal cortex; MO, medial orbital; mPFC, medial prefrontal cortex; MS/Vddb, medial septum/vertical diagonal band of Broca; mtDNA, mitochondrial DNA; MTT, multiple trace theory; MWM, Morris water maze; NeuN, neuron-specific nuclear protein; NMB, nucleus basalis magnocellularis; NMDA, N-methyl-D-aspartate; PAR, parietal cortex; PL, prelimbic cortex; PKMζ, protein kinase M zeta; PND, postnatal day; pPtA, posterior parietal association cortex; pRe, perireuniens; PRh, perirhinal cortex; RA, retrograde amnesia; RAM, radial arm maze; Re, reuniens; ReRh, reuniens and rhomboid; Rh, rhomboid; RSP, retrosplenial cortex, S1, primary somatosensory cortex; S2, secondary somatosensory cortex; SCT, standard consolidation theory; STR, striatum; TGRA, temporary graded retrograde amnesia; V1, primary visual cortex; V2M, medial secondary visual cortex; V2L, lateral secondary visual cortex.

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AUTHORS: Candela Zorzo [1,2,*], Jorge L. Arias [1,2], Marta Méndez [1,2]

Candela Zorzo, Fellowship (MS) *.

[1] Laboratory of Neuroscience, Department of Psychology, University of Oviedo, Plaza Feijóo, s/n, E-33003, Oviedo, Spain;

[2] Instituto de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain.

Email: zorzocandela@uniovi.es

Jorge L. Arias, PhD.

[1] Laboratory of Neuroscience, Department of Psychology, University of Oviedo, Plaza Feijóo, s/n, E-33003, Oviedo, Spain;

[2] Instituto de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain.

Email: jarias@uniovi.es

Marta Méndez, PhD.

[1] Laboratory of Neuroscience, Department of Psychology, University of Oviedo, Plaza Feijóo, s/n, E-33003, Oviedo, Spain;

[2] Instituto de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain.

Email: mendezlmarta@uniovi.es

Declarations of interest: none

*** Correspondence**

Candela Zorzo, MS.

Laboratory of Neuroscience, Department of Psychology. University of Oviedo. Plaza Feijoo s/n. 33003 Oviedo, Spain. Institute of Neurosciences of the Principality of Asturias (INEUROPA).

zorzocandela@uniovi.es

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1. Introduction

1.1. Allocentric spatial navigation and brain structure and function

Spatial orientation is the ability to navigate the surrounding environment (Vorhees and Williams, 2014a). This navigation is supported by the allocentric strategy, also called place learning or cognitive mapping (O'Keefe and Nadel, 1978), which relies on the learning, memorization, and remembering of the location of certain geographical landmarks. In addition, a relationship between these landmarks needs to be established, making the environmental distal and visual cues the main elements of this framework (Epstein et al., 2017). This strategy is based on the integration and representation of multiple associations that are present in the environment (Epstein et al., 2017; Tolman, 1948) and is supported by a "cognitive map" that consists of the visual and mental images of the spatial representations (Tolman, 1948) needed to guide our behavior.

The allocentric strategy is supported by many structures of the limbic system, with the hippocampal formation at the core of it (Eichenbaum, 2017; Hunsaker and Kesner, 2018; O'Mara and Aggleton, 2019; Poulter et al., 2018; Rolls and Wirth, 2018). Aggleton and Brown initially proposed the extended network of the limbic memory system, which comprises, apart from the hippocampal formation, the fornix, the mamillary bodies and the anterior thalamic nuclei (Aggleton and Brown, 1999). Moreover, other brain areas have been included, such as the retrosplenial cortex (Todd et al., 2019), the medial prefrontal cortex, including the anterior cinculate (ACC), infralimbic (IL), and prelimbic (PL) cortices (Hunsaker and Kesner, 2018; Negrón-Oyarzo et al., 2018; Rinaldi et al., 2020), the perirhinal cortex (Ramos, 2017, 2013), the septum (Burjanadze et al., 2015; Smith and Pang, 2005) or the ventral striatum (Rinaldi et al., 2020). Furthermore, the limbic system interacts with other associative cortical areas, such as the posterior parietal cortex, an area implicated in the representation of the spatial features associated with spatial navigation (Kesner, 2009). The interactions among these mentioned brain regions are key for understanding spatial memory dynamics. Therefore, it is relevant to focus on larger brain networks rather

than on particular brain areas (Hunsaker and Kesner, 2018). To clarify, it should be noted that the hippocampal formation refers to the hippocampus (HC) (CA fields -also expressed as "hippocampus proper", dentate gyrus, and subiculum), the entorhinal cortex, the presubiculum, and the parasubiculum (O'Mara and Aggleton, 2019).

1.2. Timing of spatial memory maintenance

Once learning occurs, memories need to be consolidated in order to be recovered long after they are coded (Albo and Gräff, 2018). The process by which there is a reorganization of brain regions that support a certain memory trace in a time-dependent manner is known as systems consolidation and can take from days to months or even years. However, there is still an ongoing debate about the memory reorganization that leads to changes in the content of memory (Barry and Maguire, 2019; Hardt and Nadel, 2018; Sekeres et al., 2018; Winocur and Moscovitch, 2011).

The standard consolidation theory (SCT) considers that the memory trace is held in the HC at first to subsequently be consolidated in the neocortex. For this to happen, a hippocampal-cortical dialogue needs to be established. This dialogue relies on the passage of time and sets the HC as a temporary repository (Albo and Gräff, 2018). The successive reactivation of the hippocampal-cortical network triggers a strengthening of cortico-cortical interactions, which could ultimately lead memories to become independent from the HC (McClelland et al., 1995; Squire and Alvarez, 1995). By contrast, the multiple trace theory (MTT) argues that learning is encoded in distributed hippocampal-cortical networks and that the HC is always needed for successful retrieval, to re-experience details (Nadel and Moscovitch, 1997). This would mean that a failure or damage to the HC would lead to retrieval deficit, regardless of the memory's age (Martin et al., 2005; Teixeira et al., 2006).

According to the scientific literature, there is no clear and consensual distinction to determine exactly when a memory can be considered recent or remote, and both are part of what is considered long-term memories, as it encompasses those memories that last more than 24 hours (Dudai, 2004). Some authors

define recent long-term memories as those acquired previously in the timeframe of days or less, and remote long-term memories as those acquired in the timeframe of weeks or longer (Albo and Gräff, 2018; Asok et al., 2019). These assumptions are based on the gradually distributed recruitment of multiple brain regions over time (Barry et al., 2016; Frankland et al., 2006; Frankland and Bontempi, 2005), which have been linked to promote greater memory stability and enable the persistence of memory (Frankland et al., 2006; Tayler et al., 2013), suggesting a gradual strengthening of neocortical connections over time (Tonegawa et al., 2018). However, the time course of systems consolidation and the mechanisms that underlie remote memories are still being debated and not well understood. In terms of studies in rodents, Albo and Gräff (2018) defined remote memories as those lasting at least two weeks, in line with the results derived from Barry et al. (2016), which included as time-intervals to explore retrieval either one day, seven, 14 and 30 days, and suggested that systems consolidation of spatial memory takes at least two weeks (Barry et al., 2016). Even so, it is important to note that this distinction can be interpreted as somewhat arbitrary or lacking more scientific research.

In terms of allocentric spatial memories, there is relative consensus in terms of the brain networks implicated in spatial processing during learning-acquisition. Nevertheless, there is still a lack of clarity about the functional contributions of specific brain areas and connections implicated in retrieval. Several reviews have addressed the neurobiology of episodic memories (Bergstrom, 2016; Frankland et al., 2019; Joo et al., 2018; Lee et al., 2017; Moscovitch et al., 2016; Nader, 2015; Squire et al., 2015), and some of them specifically focus on spatial memory (Barry and Commins, 2011; Gøtzsche and Woldbye, 2016; Hunsaker and Kesner, 2018; Mitchell et al., 2018; Vorhees and Williams, 2014a). However, the reviews that distinctively focus on retrieval usually compile memory retention experiments without establishing a time-interval distinction, and they are not specific to spatial navigation, including different context-based behavioral paradigms (Frankland et al., 2019; Moscovitch et al., 2006, 2005; Winocur et al., 2013a).

Therefore, in this systematic review, we aimed to collect articles that examine allocentric remote spatial retrieval in rodents. In accordance with Albo and Gräff (2018), a time-interval of two weeks after learning-acquisition was considered for remote retrieval.

2. Methods

To examine the available literature of remote allocentric spatial memory in experimental studies (rodent: mice, rat), we performed this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009).

2.1. Search strategy

We conducted the search in the Pubmed and Scopus databases up to June 1, 2021. We did not perform any date publication restriction, including all articles published up to the mentioned date. The search keywords we applied and combined were: ("remote spatial memory"), ("remote spatial memory retrieval"), ("remote spatial memory recall"), and ("remote spatial retention"). We excluded article reviews by employing the NOT operator with the keyword ("review"). We maintained all mentioned search terms across each database.

2.2. Selection criteria

We limited the articles to the following inclusion criteria: (a) rodent subjects; (b) remote spatial memory assessed at least two weeks post-acquisition, based on (Albo and Gräff, 2018); (c) use of allocentric strategy to perform spatial tasks. We did not consider articles that omitted the inclusion criteria and/or met the following exclusion criteria: (a) experimental models designed to emulate specific pathologies; (b) types of manuscripts such as literature reviews, case reports, conference papers, correspondence, editorials, letters to the editor, editor's notes, other editorial materials, and commentaries; (c) non-navigational place-learning tests.

2.3. Screening for inclusion

We collated all references on Mendeley. First, we detected and deleted duplicate articles both automatically and manually. Second, we screened the title and abstract of the remaining articles, deleting the human studies. Third, we exhaustively analyzed the selected articles to exclude those that did not meet the selection criteria. If an article failed to meet the inclusion criteria at any point during the reviewing procedure, it was removed.

2.4. Description of the behavioral tasks

The articles included in this systematic review employed different behavioral tasks; the Morris Water Maze (MWM), the radial arm maze (RAM), the Barnes maze, the Double H-maze, and the Annular maze.

The MWM consists of a circular maze filled with water that is placed in a room with visual cues that allow the animal to orientate itself and to locate a platform that is hidden below the water's surface (Morris, 1984). The RAM is a maze with different arms in which animals can use external cues located in the room to find the food reward (Olton and Samuelson, 1976). To prevent animals from orienting themselves through the maze using internal cues, some investigators rotate it while maintaining the spatial location of the baited arms in relation to room cues (Ramos, 2009). As for the Barnes Maze, it is a dry land behavioral test that consists of a circular platform with spaced holes around the perimeter. One of these holes, the target hole, allows the animals to escape and can be found by using an allocentric strategy (Barnes, 1979). The double H-maze is a water-escape memory task that consists of three parallel run arms intersected by a perpendicular central arm, which makes it possible to hide an escape platform. In this case, the layout allows the researcher to guide the subjects along a specific path (Pol-Bodetto et al., 2011). Finally, the Annular maze is a circular corridor placed in the circular pool designed by Morris (Morris, 1984), in which subjects need to find an escape platform (Hollup et al., 2001).

3. Results

3.1. Study selection

Pubmed and Scopus yielded 270 and 184 articles, respectively. Thus, we identified a total of 397 potentially relevant articles, after discarding duplicates. Then, we screened papers for eligibility and removed 305 after reading the title and abstract. Carrying out an in-depth reading, we assessed 92 articles for full eligibility. Of these articles, 51 did not match the selection criteria and were excluded. Therefore, a total of 41 articles were selected for this systematic review. The systematic study selection can be viewed in the flow chart diagram shown in Figure 1 [Insert Figure 1 here].

3.2. Study characteristics

The 41 articles that were selected showed different methodological approaches to study remote spatial memory, so we divided them into five groups. There were a total of 18 non-invasive studies, six inactivation studies, nine lesion studies, four pharmacological treatment/chemical agent studies, and four genetic manipulation studies. We categorized them into different subsections with an associated table in which we reported a summary of the main results, outlining different pieces of information on account of each methodology.

3.3. Non-invasive studies

In this section, we included studies in which no manipulation had occurred and those that explored the role of other remote spatial retention factors, such as retraining, sequencing of different hippocampal-dependent memory tasks, cued context, or circadian rhythms. A total of 18 articles were collected attending to these specifications (to view a summary, see Table 1).

Remote spatial retrieval success was reported using the MWM and at time-intervals over two weeks from learning-acquisition. More specifically, the study of Barry et al. (2016) showed good behavioral performance at a time-interval of 14 and 30 days after memory acquisition, which was accompanied by higher neuronal activity in certain brain areas. When measuring Zif268 Immediate Early Genes (IEGs) via immunostaining, the 30-day retention group showed higher expression in the anterior cingulate cortex (ACC) and prelimbic cortex (PL) compared to a retention memory group assessed prior to two weeks

since learning-acquisition (Barry et al., 2016). Based on Albo and Gräff (2018), we categorized this last group as a recent memory group. In addition, infralimbic cortex (IL) Zif268 activity was higher both in 14-day and 30-day groups when compared to one or two recent memory groups, respectively. In terms of c-fos activity within the medial prefrontal cortex (mPFC), the PL area revealed higher activity in the 14-day and 30-day group compared to one recent memory group and cage controls, or two recent memory groups and cage control animals, respectively. Similar results were observed in the IL, with increased c-fos counts found in the 14-day and 30-day groups when compared to two different recent memory groups and cage controls. In terms of Arc expression, the ACC revealed enhanced activity in the 30-day group compared to a recent group and cage controls. Similar results were obtained in the PL, observing the same differences in the 14-day retention group as in the 30-day group. Finally, for the mPFC, there was an increase in the IL Arc expression in the 30-day retention group compared to one recent memory group and cage control animals (Barry et al., 2016). Therefore, successful spatial retrieval was identified for time-intervals of 15 and 30 days after memory acquisition, but not for higher time-intervals, such as 45 and 60 days. Retrieval was accompanied by higher ACC, PL, and IL cytochrome c oxidase (CCO) activity (an index of brain metabolic demands [Gonzalez-Lima and Cada, 1994]) across good performers, compared to those which failed to solve the task. A positive correlation was also found between the time spent in the reinforced quadrant and the CCO activity, regardless of the time from learning-acquisition (Zorzo et al., 2020). Similar behavioral responses were observed in the study of Bonaccorsi et al. (2013), which found good spatial retention with time-intervals of 20 and 30 days, but not when 50 days had elapsed. Moreover, the authors showed higher c-fos activity in the prefrontal cortex (ACC, IL) in the 30-day and 50-day group when compared to controls. A higher ACC activity in these groups was also observed when comparing them with groups that tested recent memories. In addition, the 30-day group showed an enhanced IL activity compared to recent memory groups (Bonaccorsi et al., 2013). Accordingly, a preserved MWM remote spatial memory with a delay-interval of one month was reported, revealing robust task-specific increases of Arc expression determined by *in situ* hybridization measurements of Arc mRNA expression. This was found in the PL and the regions anatomically close to the mPFC, such as the frontal association

(FrAs) and medial orbital (MO) area, the latter also being greater than in a recent memory group, in addition to the dorsolateral orbital cortex (DLO). Moreover, specific Arc activity increases were found in layers 2/3 (L2/3) and 4 (L4) within the PL (for more details see Gusev and Gubin, 2010a). By contrast, other authors found that a time-interval of 30 days from learning-acquisition can lead to an altered spatial memory retention when assessed in the MWM (Carr et al., 2016). Despite animals not achieving a successful retrieval, a higher ACC c-fos activity was still found when compared with a cage control and a recent-memory group, supporting the role of the mPFC during higher demanding cognitive processes (Carr et al., 2016). It is interesting to note that even though the ability to establish spatial relationships seems to emerge around postnatal day (PND) 18, remote spatial retention is not found at that age, but rats can display good retention at PND50, accompanied by higher ACC c-fos activity (Tzakis et al., 2020).

In terms of long-term retrieval, the key role of the mPFC and its anatomically nearby regions has been proven, with other cortical areas also showing important contributions. In terms of conserved retrieval in the MWM, higher c-fos counts were reported in the medial entorhinal cortex (mENT) in the 14-day group when compared to cage controls (Barry et al., 2016). A higher CCO activity in the 15-day and 30-day groups was also observed when compared to the groups that failed spatial retention, *i.e.*, 45-day and 60-day groups, showing a positive behavioral correlation (Zorzo et al., 2020). However, in the study of Bonaccorsi et al. (2013), higher lateral entorhinal cortex (lENT) recruitment was not observed. In the case of perirhinal cortices (PRh), both the 14-day and 30-day groups showed an enhancement of c-fos activity compared to one recent group and cage controls. In terms of Arc expression, 14-day and 30-day retention groups revealed higher activity in the PRh, in comparison with two recent groups and cage controls (Barry et al., 2016). As for brain oxidative metabolism, the same results as in ENT were shown in PRh (Zorzo et al., 2020). The retrosplenial (RSP) and parietal cortices (PAR) were also evaluated, and an enhancement of c-fos expression within the 30-day group in comparison to cage controls was revealed. Concerning PAR, c-fos counts exhibited higher activity in the 14-day group when compared to one recent group and cage control animals, and Arc expression reflected higher activity in the 14-day group in comparison to

two recent groups and cage controls, in addition to higher activity in the 30-day group when compared to one recent group and cage controls (Barry et al., 2016). However, another study found no differences in remote retention retrieval (Bonaccorsi et al., 2013). Furthermore, Arc mRNA expression revealed a robust implication of the primary and secondary somatosensory cortices (S1 and S2, respectively), the primary motor cortex (M1), RSP (for more details see Gusev & Gubin, 2010a), and lENT (Gusev et al., 2005; Gusev and Gubin, 2010a), in addition to a higher implication of the insular (Ins) area, after a preserved one-month retrieval, when compared to a recent group (Gusev and Gubin, 2010a). A different pattern of activity depending on cortical layers was also noted, showing more frequent increases in Arc mRNA fractions in L2/3 and L4 in PAR, visual primary (V1), visual medial secondary (V2M), and more detailed in visual lateral secondary (V2L), V2M, S1, M1 and secondary motor cortex (M2). This reveals a stereotypical laminar distribution (cortical laminar pattern similarity) (Gusev and Gubin, 2010a). In addition, a remote spatial retrieval, although preserved, was associated with fewer strengthened correlations when compared to a more recent one, determined by Arc mRNA expression (Gusev and Gubin, 2010b). It is interesting to note that higher c-fos activity was found in the V1 at different remote points, regardless of behavioral response (Bonaccorsi et al., 2013). In terms of brain metabolic demands, higher RSP, PAR, and M1 CCO activity was found in groups that had retained spatial information when compared to those with unsuccessful retrieval, showing a positive correlation between the rate of retrieval and CCO activity (Zorzo et al., 2020).

As could be expected, the HC is one of the key regions implicated in spatial memory retention. Consequently, IEG expression differences were found within the HC after remotely remembering a target location in the MWM. In particular, c-fos and Arc counts were higher in the CA3 subfield, with the 14-day remote retention group showing differences when compared to a recent memory group (Barry et al., 2016). It was also noted that, following a one-month MWM remote retention, the mRNA Arc expression was robust in the CA3, dentate gyrus (DG), and subiculum, whereas the CA1 and ventral HC suffered decay (Gusev et al., 2005). Higher DG and CA1 c-fos activity with time-intervals of 20, 30, and 50 days

were also reported, when compared to a cage control group, although it is important to note that the 50-day retention group did not succeed at retrieval (Bonaccorsi et al., 2013). When examining memory retention in other spatial tasks, such as in the Radial Arm Maze (RAM), higher c-fos activation was found in the CA3 and CA1 subfields of the HC after prolonged periods of time, such as 6 weeks, when compared with a recent-memory group. Moreover, authors found that the dorsal DG was activated by mere re-exposition to the previously known environment (Schlesiger et al., 2013). More detailed analyses focused on deciphering the cell types needed during remote spatial retrieval, assessed in the MWM 30 days post-learning-acquisition, pointed out that a specific recruitment of new neurons in the DG is needed for successful retention. These neurons become incorporated into complex hippocampal-cortical networks, suggesting that they need to be present at the moment of training for successful retrieval (Trouche et al., 2009). In addition, higher CCO activity was found across CA1, CA3, and DG in the 15-day and 30-day groups that successfully completed the MWM, compared to those that did not achieve the retention criteria. As in previously reported results, this shows a positive behavioral correlation (Zorzo et al., 2020).

Another subcortical region associated with remote retrieval that has gained attention is the thalamus, highlighting the role of the reuniens and rhomboid (ReRh) nuclei following 25 days of retention in the MWM, which leads to higher c-fos counts in the Reuniens (Re) and Rhomboid (Rh) regions in comparison to controls and a recent-memory group (Loureiro et al., 2012).

In terms of sex differences, male rats have been reported to outperform females in a 30-day spatial retention. Males showed higher retention scores when 30 days had elapsed. This was determined by more correct responses and fewer reference errors in the RAM task. The training effect was also present in both sexes, with male and female rats better retaining spatial information when using longer training protocols (Sebastian et al., 2013). This article also focused on assessing the impact of protein expression associated with long-term spatial memory. In particular, protein kinase M zeta (PKMζ) expression within the HC seems to be important in male remote retention, as males showed an enhancement of synaptic PKMζ expression, in addition to a positive correlation with retention scores. However, through the examination

of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluA2, synaptic GluA2 expression was shown to display a positive memory retention correlation regardless of sex (Sebastian et al., 2013). No sex differences in behavioral retrieval were revealed when using the MWM at several post-acquisition time-intervals, particularly, 15, 30, 45, and 60 days from learning-acquisition (Zorzo et al., 2020).

In terms of behavior, the sequencing of different hippocampal-dependent memory tests can also have an impact both on memory retrieval and brain activation. Studies suggest that performing the MWM followed by RAM, in comparison to only the MWM, leads to a similar MWM remote retention 31 days after the last training session. Thus, there is no different retrieval output due to more spatial training, nor are there any differences in ACC and CA1 activity due to training, assessed by c-fos activity (Wartman and Holahan, 2013). More detailed analyses have revealed that both types of training (combined and MWM only) lead to higher ACC apical branches than in controls, and that the rats that performed two different types of spatial training had a greater number of ACC basal branches, and CA1 apical and basal branches, in addition to an increased ACC and CA1 apical and ACC basal dendritic length, when compared to controls. In terms of spines, an enhancement of ACC and CA1 apical and basal total spines was revealed in the two hippocampal-dependent groups, in addition to higher CA1 apical spine density, when compared to controls (Wartman and Holahan, 2014). Furthermore, retrieval can also depend on the salience of the cues. In an impoverished context –limited to the room in which MWM remote spatial memory is evaluated–, there is a different behavioral output than in an enriched one. Thus, the difference between a cue-enriched versus a cue-impoverished context in spatial retention is reflected in outperformance of cue-enriched contexts, with a delay of 25 days, revealing a lower memory trace resistance as a result of context impoverishment (Lopez et al., 2008). Finally, retrieval can also depend on circadian rhythms, as better remote memory has been shown if training was performed during the dark-phase (Gritton et al., 2012).

It is important to note that, at a behavioral level, not all groups showed successful retention when time-intervals were longer (Carr et al., 2016; Ramos, 2009). However, the study of Carr et al. (2016) used a different MWM learning protocol than the groups that showed spatial retrieval success in the same time-interval. In particular, Carr et al. (2016) applied a massed learning protocol (12 trials in two days), contrary to the distributed training sessions of other studies, *i.e.*, four trials during five (Barry et al., 2016; Zorzo et al., 2020) or seven days (Bonaccorsi et al., 2013; Gusev et al., 2005; Gusev and Gubin, 2010a, 2010b), or five trials during five consecutive days (Wartman and Holahan, 2013). Regarding Ramos (2009), this study employed the RAM task to show that 18 days is an acceptable time-interval for successful spatial retrieval but that, after 30 days, retraining is needed. This differs from other RAM studies that have found a correct retrieval with equal or longer periods of time (Haijima and Ichitani, 2008; Schlesiger et al., 2013; Sebastian et al., 2013; Wartman et al., 2014; Wartman and Holahan, 2013). In this case, it seems that the differences cannot be explained by the learning protocol, as it is similar to the protocol of Haijima and Ichitani (2008), in which successful retrieval was found with a time-lapse of 35 days. Two hypotheses were formulated from these results: either the memory engram suffers a transformation from a detailed to a schematic one, or there is an original memory deficit. In order to shed light on these possibilities, the authors set up a training reminder, which turned out to be useful when applied before day 18, but not later. No significant differences emerged due to an overtraining protocol, suggesting that a loss of detailed information from the original learning and perhaps a partial contribution of the recall deficit hypothesis is happening (Ramos, 2009). The employment of the double-H maze test led to partially similar results, proving that memory is retained across 18 days (Pol-Bodetto et al., 2011).

Therefore, the findings from the non-invasive studies show us that the prefrontal cortex is needed during the retrieval of older memories (Barry et al., 2016; Bonaccorsi et al., 2013; Gusev and Gubin, 2010a; Zorzo et al., 2020), as well as its adjacent areas such as the FrAs, the MO, and the DLO (Gusev and Gubin, 2010a), and its implication can be increased according to the age of the memory, reaching significance at some point between 14 and 30 days, and showing a gradual and linear increase (Barry et

al., 2016; Bonaccorsi et al., 2013). A small number of studies observed the recruitment of the entorhinal, perirhinal, retrosplenial, and parietal cortices as time goes by (Barry et al., 2016; Gusev et al., 2005; Gusev and Gubin, 2010a) or as a consequence of the rate of retrieval (Zorzo et al., 2020), in addition to the visual (Bonaccorsi et al., 2013; Gusev and Gubin, 2010a), motor (Gusev and Gubin, 2010a; Zorzo et al., 2020), and somatosensory cortices (Gusev and Gubin, 2010a). Others did not find a higher recruitment of entorhinal and parietal cortices (Bonaccorsi et al., 2013). In terms of the HC, non-invasive studies suggest that this structure may be essential to retrieve spatial details, as activity changes linked to successful retrieval have been reported at remote points (Barry et al., 2016; Gusev et al., 2005; Schlesiger et al., 2013; Trouche et al., 2009; Zorzo et al., 2020), with some articles showing fewer (Barry et al., 2016) or no differences (Bonaccorsi et al., 2013; Zorzo et al., 2020) with recent memory groups. Thalamic areas have also been studied (Loureiro et al., 2012). Taking into account the effect of manipulations at a behavioral level, performing a combination of different spatial tasks has been shown to have a minor impact on behavioral outcomes (Wartman and Holahan, 2013), but to lead to morphological hippocampal changes (Wartman and Holahan, 2014). If training occurs in a cue-enriched context, remote spatial retrieval is facilitated (Lopez et al., 2008), and training rats in the dark-phase has been reported to benefit further retrieval (Gritton et al., 2012).

In conclusion, studies that explore remote spatial retention without performing any invasive protocol offer an overview of the brain regions that are implicated in diverse memory processes. This section shows that most studies have been conducted with time-intervals of close to one month, showing conserved memory retention, and outlining that several regions are important to retrieve spatial information coded time ago.

3.4. Inactivation studies

In this section, we have considered the inactivation of brain regions, networks, or particular cell populations. Under these conditions, a total of six articles were collected (to view a summary, see Table 2).

The inactivation of the ACC prior to the retrieval probe with sodium channel blocker lidocaine administrations, assessed in the MWM, was found to disrupt one-month remote spatial memories. In addition, inactivation of the ACC with CNQX, an AMPA receptor antagonist, revealed similar behavioral effects as those found in lidocaine groups (Teixeira et al., 2006). To note, lidocaine suppresses the neuronal activity of both excitatory and inhibitory neurons, whereas CNQX only suppresses excitatory transmission, with this experiment revealing that both excitatory and inhibitory transmission are required in remote spatial recall.

Teixeira et al. (2006) also revealed that dorsal HC inactivation by lidocaine administrations before the remote retention test negatively affected one-month remote spatial memories in the MWM. However, it is noteworthy that this inactivation did not seem to differentiate between recent and remote spatial memory, as there were no behavioral differences between remote task performance and a recent memory group. This suggests that the HC contribution happens regardless of memory age (Teixeira et al., 2006). Other authors found similar results, reporting impairment in MWM 30-day spatial memories due to HC inactivation via lidocaine infusion prior to the retention probe. It was also noted that, when the drug was no longer active, the effect was reversed, at least in a recent memory group (Broadbent et al., 2006). Optogenetic inhibition studies have also been used to explore the role of certain projections in remote memory. In particular, Binder et al. (2019) carried out an optogenetic silencing of monosynaptic projections from the HC to the mPFC after learning-acquisition in the Barnes maze. The silencing took place during slow-wave sleep. The results showed that silencing these projections did not impair remote memory, assessed 16 days after learning-acquisition (Binder et al., 2019).

Another brain area used for targeted inactivation is the thalamus. Reversible inactivation of the Re and Rh thalamic nuclei, via lidocaine administrations prior to retrieval, does not show impaired retention when performed in the MWM with a retention interval of 25 days (Loureiro et al., 2012).

As mentioned in section 3.3., the sequencing of different hippocampal-dependent memory tasks can generate an impact on memory retrieval and its underlying brain regions. Training in the MWM followed

by training in another spatial task such as the RAM increased the processing demand on the HC when the ACC was inactivated by lidocaine –prior to the remote probe test–, causing a substantial deficit in remote probe performance 37 days post-learning-acquisition. It is noteworthy that, when training occurred only in the MWM, the ACC inactivation caused a subtle behavioral deficit. In addition, ACC inactivation resulted in higher CA1 c-fos positive cells after a delay of 37 days following spatial acquisition, both when the training was only in the MWM and when combined with RAM (Wartman et al., 2014).

One last approach to study the cell types needed for remote memory processing is to decrease specific cells. The use of methylazoxymethanol acetate (MAM), an antimitotic agent which reduces young granule neurons before spatial acquisition, has been found to lead to neurogenesis inhibition within the HC. It triggers a remote spatial MWM memory alteration, assessed 30 days after learning-acquisition. However, it is important to note that it is not a consequence of deficient training, as the animals showed conserved training despite the neurogenesis decrease (Goodman et al., 2010).

Thus, the results derived from this section reflect that the inactivation of the prefrontal cortex—particularly ACC—, leads to a memory failure in remote retrieval spatial (Teixeira et al., 2006; Wartman et al., 2014), regardless of whether both excitatory and inhibitory neurons are the target of inactivation, or only the excitatory ones (Teixeira et al., 2006). Concerning HC, Broadbent et al. (2006) and Teixeira et al. (2006) showed that the inactivation of excitatory and inhibitory transmission leads to a memory failure, not only post-learning, but also at remote points, and Goodman et al. (2010) outlined the role of the neurogenesis for remote retention. Hence, the prefrontal cortex, HC, and their interaction may be crucial. However, the silencing of monosynaptic projections from the HC to the mPFC just after learning does not cause deficits in remote retrieval but a negative effect when memory was evaluated earlier (5-days delay), revealing that the time-course of memory consolidation takes place over days to weeks (Binder et al., 2019). Finally, similarly to the previous section, thalamic inactivation was also studied, with no behavioral deficits found at remote points (Loureiro et al., 2012).

In conclusion, although more research is needed, we can claim that the inactivation studies support the main idea underlying non-invasive studies: to retrieve older spatial information, not only is the prefrontal cortex needed, but also the HC. Moreover, the thalamus seems to contribute during retrieval (based on non-invasive studies), but its participation may not be essential.

3.5.Lesion studies

In this section, a total of nine articles were collected (to view a summary, see Table 3).

Lesions to the mENT can also affect remote spatial memory retention, specifically when performed in the MWM and assessed one month after memory acquisition, showing that the mPFC is not the only indispensable cortical region for memory retrieval (Hales et al., 2018). This study revealed that an average extent lesion of 89.6% to the mENT triggers an important cell loss in adjacent cortical areas determined by neuron-specific nuclear protein (NeuN) histochemistry (Hales et al., 2018). Training with two-arm place discrimination in the RAM one month before RSP lesion also revealed severe memory retention impairments when tested one week after surgery (Haijima and Ichitani, 2008).

In terms of the HC, targeted lesions have been shown to trigger alterations in spatial memory retrieval across different behavioral tasks. Studies using the MWM reported that total and partial HC lesions can be detrimental to spatial memory retention when surgery took place 28 days (Winocur et al., 2013b) or 43-44 days after learning (Martin et al., 2005). The animals' retrieval was tested seven (Winocur et al., 2013b) or 12-13 (Martin et al., 2005) days after surgery, reaching a total time-interval since memory acquisition of 35 (Winocur et al., 2013b) or 56 days (Martin et al., 2005), which indicated a behavioral deficit both in totally- and partially-lesioned rats (Martin et al., 2005; Winocur et al., 2013b). When considering longer periods of time from learning-acquisition, an average HC lesion of 85.3% and 37.9% (limited to dorsal HC and performed 14 days prior to the retention probe test) led to a marked deficit in memory retention with intervals of 8 and 14 weeks. Similar results were observed when studying spatial retention in the annular maze, in which behavioral output worsened after 9 and 14 weeks (Clark et al., 2005a). It is interesting to note that the spatial retention impairments were not prevented by adding extra training.

Longer periods of MWM training (from post-weaning until reaching young adulthood) were shown to still lead to a spatial retrieval deficit in animals that displayed an average lesion of 82.8% when retrieval was tested 14 days after the last training session (Clark et al., 2005b). Moreover, similar results have been found when using the RAM, finding markedly impaired behavior after HC lesions one month after training (Haijima and Ichitani, 2008).

An additional brain region, apart from the cortices and the HC, that has been impaired via lesions to study remote memory is the thalamus. Lesions to the anterior (ATN) and lateral thalamic nuclei (including the intralaminar nuclei; ILN/LT) triggered impaired MWM memory retention 25 days post-acquisition. This suggests that it plays a role in remote memory, although it is important to point out that ANT lesions also caused impaired acquisition, suggesting that its correct functioning is not specific to retrieval (Lopez et al., 2009). These authors demonstrated that there is an altered cholinergic innervation of the ventral HC following ANT lesions, but not when the lesioned area is the ILN/LT, assessed by acetylcholinesterase (AChE) histochemistry (Lopez et al., 2009). Other thalamic nuclei lesions revealed similar results and, therefore, the percentage of animals that suffered a ReRh lesion and did not find the platform could not be attributed to chance. More specifically, they reflected an average of 74.0% with Re damage, with 29.7% to the left perireuniens (pRe), *i.e.*, a region that borders the Re, 35.5% to the right pRe, and 48.7% to the Rh. These lesions prevented increases of mushroom spines counted on apical and basal dendrites of CA1 and showed a reduced number of mushroom spines counted on apical and basal ACC dendrites, following 25 days post-acquisition in the MWM, determined by Golgi staining, in addition to reduced ACC and PL c-fos expression (Klein et al., 2019). Other authors revealed similar behavioral results. Disrupted retention was observed 25 days post-learning-acquisition in the MWM following ventral midline ReRh nuclei thalamic lesions, with animals subjected to excitotoxic fiber-sparing N-methyl-D-aspartate (NMDA) lesions (Loureiro et al., 2012).

The findings from lesion studies are focused on other cortical regions rather than the prefrontal cortex, such as mENT (Hales et al., 2018) —which take part in the hippocampal formation—, and the RSP

(Haijima and Ichitani, 2008), with both studies revealing an impaired spatial memory with delays closer to one month. Moreover, all the studies that addressed selectively lesioning the HC have found a deterioration in remote retrieval, including time-intervals closer to one month (Haijima & Ichitani, 2008; Winocur et al., 2013), but also with longer time-intervals (Clark et al., 2005a, 2005b; Martin et al., 2005), suggesting that HC lesions consistently lead to behavioral impairments, which cannot be prevented by extensive training lasting even from post-weaning to adulthood (Clark et al., 2005b). Again, thalamic nuclei have been investigated and have revealed impaired remote retention assessed with time-intervals closer to one month, although it is important to highlight that lesions were performed before training (Klein et al., 2019; Lopez et al., 2009; Loureiro et al., 2012). The remote retrieval deficit was noted by lesioning ANT (Lopez et al., 2009), ILN/LT (Lopez et al., 2009), and ReRh nuclei (Klein et al., 2019; Loureiro et al., 2012), with the ANT lesions also revealing a deficit during learning-acquisition (Lopez et al., 2009), while the ILN/LT and ReRh lesions specifically affect to retrieval (Klein et al., 2019; Loureiro et al., 2012).

To conclude, lesion studies add knowledge about the importance of the complete functionality of other cortical regions (mENT and RSP) aside from the prefrontal cortex, support the continuous implication of the HC, and, in line with previous sections, emphasize the importance of the thalamus.

3.6.Pharmacological/chemical agent studies

In this section, we also included chemical agents that can modify spatial memory, although they were not part of a specific pharmacological treatment. A total of four articles were included (to view a summary, see Table 4).

Clinical studies on cancer patients have cast doubts on the secondary effects associated with cognition of chemotherapeutic agents, such as cytosine arabinoside (Ara-C). Some of these studies found long-term spatial deficits when assessed 30 days after the last training session in the MWM. This behavioral impairment was accompanied by neuronal morphology alterations, such as a retraction observed in

pyramidal ACC apical dendrites, determined by Golgi staining. One article specifically reported a 15% reduction in dendritic length, 35% in spine density, and 36% in the number of branch points (Li et al., 2008). However, other authors have not been able to find MWM impaired remote spatial retention when assessed with the same time-interval of 30 days after memory acquisition (Fremouw et al., 2012), which leads to contrasting behavioral results. Both studies applied the Ara-C treatment for five consecutive days (Fremouw et al., 2012; Li et al., 2008).

One study looked at fluoxetine, a selective serotonin reuptake inhibitor commonly used for depressive disorder treatments. A harmful impact to the MWM remote retention was revealed following 17 days post-acquisition when animals were treated for four weeks. It is noteworthy that six weeks of fluoxetine cessation resulted in normalizing remote retention spatial behavior (Ampuero et al., 2013).

Remote memory has been reported to need DNA methyltransferase (DNMT) activity but there is a lack of information about the agents that can potentially affect it. Some research studies have addressed this issue, revealing that excessive formaldehyde can be linked to a reduced DNMT (determined by western blot) and, when performing bilateral HC formaldehyde administrations, it translates into MWM remote spatial retention impairment 30 days later (Tong et al., 2015).

The findings from this section help us to understand the potential side effects of certain treatments on remote retrieval, such as those reported by chemotherapy or fluoxetine treatment. However, as can be observed, research is still scarce.

3.7.Genetic manipulation studies

In this section, we did not include specific knock-out (KO) animals designed to emulate a certain pathology. Under these conditions, a total of four articles were included (to view a summary, see Table 5).

A deficiency of Cyp7b1, a gene that catalyzes the biosynthesis of neuroactive steroids, may be associated with impairments in spatial memory (Maehata et al., 2020). Particularly, it has been shown that Cyp7b1 KO mice exhibit remote spatial memory failure, with recent memory mostly conserved. In addition,

dendritic spine density was found to be reduced in the HC. This suggests that this structure is implicated in the long-term maintenance of spatial memory (Maehata et al., 2020).

Moreover, many studies have established that the CCCTC-binding factor (CTCF), an 11-zinc finger protein that protects genes from inappropriate chromatin interactions (Gaszner and Felsenfeld, 2006) and modulates epigenetic processes such as DNA methylation, is important for systems consolidation (Kim et al., 2018). The use of a CTCF conditional knock-out (cKO), in which there is a loss of CTCF in the forebrain excitatory neurons, revealed that a 27-day MWM memory triggers an impaired behavioral outcome. When deleting inhibitory neurons, similar but less strong behavioral impairments were found, probably because heterozygous (HT) CTCF deletion was performed instead of homozygous CTCF deletion, which is lethal. The study showed that despite the hippocampal CTCF deletion, there was no HC LTP disruption when recording the last four minutes (E-LTP) or the last eight minutes (L-LTP). However, cKO mice displayed an L-LTP disruption in the ACC but cortical LTP in HT CTCF mice was preserved. Additionally, a cortical altered gene expression in cKO CTCF mice was observed, assessed by RNA sequencing (Kim et al., 2018).

Other studies explored the role of mitochondrial DNA (mtDNA) in remote spatial memory. In particular, trans-mitochondrial mice have helped us understand that remote memories can be disrupted due to mitochondrial dysfunction induced by pathogenic mtDNAs. Thus, trans-mitochondrial mice, generated by the introduction of mitochondria carrying ΔmtDNA, and specifically those that contain more than an excess of 50% loads of ΔmtDNA, exhibited an impaired 36-day remote memory, assessed in the Barnes maze. In addition, mitochondrial respiration deficiencies and reduced Ca2+/calmodulin-dependent kinase II-α (α-CaMKII) in the visual cortex and DG were also found (Tanaka et al., 2008).

Finally, because gene expression is regulated, among others, by L-VGCCs calcium influx, a cKO mice model directed to L-type voltage-gated calcium channels (L-VGCCs) was generated. The employment of this model reported that CaV1.2cKO mice show impaired spatial memory retention with longer intervals of time since learning-acquisition in the MWM, while preserving previous learning (White et al., 2008).

To summarize, some authors have found the occurrence of neurosteroids in the HC (Maehata et al., 2020), CTCF-mediated gene regulation in cortical neurons (Kim et al., 2018), the necessity of unaltered calcium channels across the HC and cortex (White et al., 2008), and the importance of unaffected mitochondrial function (Tanaka et al., 2008). Therefore, results derived from genetic manipulation studies add information about the molecular mechanisms of systems consolidation, suggesting the importance of the HC and the cortex to achieve a successfully remote retrieval.

3.8.Details about behavioral procedures

The assessment of remote spatial memory retrieval and the previous spatial learning task was carried out using different behavioral tests. The MWM was employed in 34 studies, the RAM in six, the Barnes maze in two, and the Double H-maze and Annular maze each in one. All the procedures included were limited to evaluating memory under allocentric representations.

3.8.1. Morris Water Maze

Most articles included in this systematic review assessed remote spatial memory using the MWM task. The number of trials per day and training days were different according to learning protocols: one trial for 28 consecutive days (Gritton et al., 2012), two trials for 14 consecutive days (White et al., 2008), four trials for five (Barry et al., 2016; Kim et al., 2018; Maehata et al., 2020; Zorzo et al., 2020), six (Lopez et al., 2008; Loureiro et al., 2012), seven (Bonaccorsi et al., 2013; Gusev et al., 2005; Gusev and Gubin, 2010a, 2010b; Hales et al., 2018), eight (Klein et al., 2019; Lopez et al., 2009; Loureiro et al., 2012), or ten consecutive days (Broadbent et al., 2006), five trials for four (Ampuero et al., 2013), five (Wartman et al., 2014; Wartman and Holahan, 2014, 2013), or eight consecutive days (Winocur et al., 2013b), six trials for three (Teixeira et al., 2006) or seven consecutive days (Teixeira et al., 2006), eight trials for three (Tzakis et al., 2020), five (Fremouw et al., 2012), seven (Li et al., 2008), or 10 consecutive days (Clark et al., 2005a), 10 trials for four consecutive days (Martin et al., 2005), 12 trials for two (Carr et al., 2016) or five (Goodman et al., 2010) consecutive days, 20 trials spread across three consecutive days, and 24 trials

in one day (Trouche et al., 2009). One article even presented an extensive learning protocol, which consisted of eight trials for 49 days of training, in blocks of five consecutive training days per week (Clark et al., 2005b).

The study of spatial memory retrieval took place with post memory acquisition time-intervals of 14 (Barry et al., 2016; Gritton et al., 2012; Maehata et al., 2020), 15 (Zorzo et al., 2020), 17 (Ampuero et al., 2013), 20 (Bonaccorsi et al., 2013), 21 (Tzakis et al., 2020), 25 (Klein et al., 2019; Lopez et al., 2009, 2008; Loureiro et al., 2012), 27 (Kim et al., 2018), 30 (Barry et al., 2016; Bonaccorsi et al., 2013; Broadbent et al., 2006; Carr et al., 2016; Fremouw et al., 2012; Goodman et al., 2010; Gusev et al., 2005; Gusev and Gubin, 2010a, 2010b; Hales et al., 2018; Li et al., 2008; Teixeira et al., 2006; Tong et al., 2015; Trouche et al., 2009; White et al., 2008; Zorzo et al., 2020), 31 (Wartman and Holahan, 2013), 35 (Winocur et al., 2013b), 37 (Wartman et al., 2014; Wartman and Holahan, 2014), 45 (Zorzo et al., 2020), 50 (Bonaccorsi et al., 2013), and 56 days (Martin et al., 2005), and also eight (Clark et al., 2005a; Zorzo et al., 2020), 14 (Clark et al., 2005a), and 16 weeks (Clark et al., 2005b) following training.

3.8.2. Radial arm maze

In some of the articles included here, the RAM was used to examine remote spatial memory.

The learning protocols carried out were as follows: three trials across 10 consecutive days (Sebastian et al., 2013), five trials for four (Wartman et al., 2014; Wartman and Holahan, 2013), or 19 consecutive days (Schlesiger et al., 2013), six trials for 10 consecutive days (Sebastian et al., 2013), or eight (Ramos, 2009) or 12 trials (Haijima and Ichitani, 2008) per day until animals reached the learning criteria, defined as 11 correct trials in one session (Haijima and Ichitani, 2008) or 14 correct trials on two consecutive days (Ramos, 2009).

In terms of remote retention testing, the following trials were carried out: one single trial (Schlesiger et al., 2013), an average of three test trials (Sebastian et al., 2013), 12 trials (Haijima and Ichitani, 2008), or even the same procedure as training (Ramos, 2009). Different time intervals were used, such as 18 (Ramos,

2009) or 30 days (Ramos, 2009; Sebastian et al., 2013), and five (Haijima and Ichitani, 2008) or six weeks (Schlesiger et al., 2013). In terms of the studies of Wartman et al. (2014) and Wartman and Holahan (2013), it is important to note that they used the RAM in order to examine the potential impact that an additional spatial task could have on MWM retention.

3.8.3. Barnes Maze

Training was conducted for three trials during seven consecutive days (Tanaka et al., 2008) or four trials during four consecutive days (Binder et al., 2019), with 12 (Tanaka et al., 2008) or 20 holes (Binder et al., 2019).

In terms of remote retention testing, one single trial (Binder et al., 2019) or three probe trials (Tanaka et al., 2008) were carried out 16 (Binder et al., 2019) or 36 days later (days (Tanaka et al., 2008).

3.8.4. Double H-maze

The article included in this review that used the double H-maze did so by performing three trials for six consecutive days and assessing memory retention with 18-day intervals (Pol-Bodetto et al., 2011).

3.8.5. Annular maze

In the study of Clark et al. (2005a), animals were given eight trials during 10 consecutive days, and remote retention was assessed by a single probe test performed when nine weeks from learning-acquisition had elapsed.

3.8.6. Remote retention across mazes and rodent species

In order to delve into the potential maze-differences in remote retrieval, we considered articles that assessed retrieval in an interval of time close to one month (from 25 to 35 days). We selected this period of time to reduce variability, and we distinguished between mice and rats. Under these criteria, we found a total of 25 studies, of which 23 used the MWM (92%) (Barry et al., 2016; Bonaccorsi et al., 2013; Broadbent et al., 2006; Carr et al., 2016; Fremouw et al., 2012; Goodman et al., 2010; Gusev et al., 2005;

Gusev and Gubin, 2010b, 2010a; Haijima and Ichitani, 2008; Hales et al., 2018; Kim et al., 2018; Klein et al., 2019; Li et al., 2008; Lopez et al., 2009; Loureiro et al., 2012; Teixeira et al., 2006; Tong et al., 2015; Trouche et al., 2009; Wartman and Holahan, 2014; White et al., 2008; Zorzo et al., 2020), while two of them selected the RAM (8%) (Ramos, 2009; Sebastian et al., 2013). All of the studies showed good retrieval, except for two (Carr et al., 2016; Ramos, 2009), one for each behavioral task. Of all the studies, 18 were performed with rats (72%) (Barry et al., 2016; Broadbent et al., 2006; Carr et al., 2016; Gusev et al., 2005; Gusev and Gubin, 2010b, 2010a; Haijima and Ichitani, 2008; Hales et al., 2018; Klein et al., 2019; Li et al., 2008; Lopez et al., 2009; Loureiro et al., 2012; Ramos, 2009; Sebastian et al., 2013; Tong et al., 2015; Wartman and Holahan, 2014; Zorzo et al., 2020) and the remaining 7 with mice (28%) (Bonaccorsi et al., 2013; Fremouw et al., 2012; Goodman et al., 2010; Kim et al., 2018; Teixeira et al., 2006; Trouche et al., 2009; White et al., 2008). In terms of studies performed in rats, 16 out of the 18 (88.8%) showed a successful retrieval, except for Carr et al. (2016) and Ramos (2009), while 100% of the mice studies succeeded.

4. Discussion

In this systematic review, we aimed to examine the current available literature on remote spatial memory, considering three main aspects: the research had been performed in rats and mice; studies had evaluated spatial retrieval using an allocentric strategy; at least two weeks from learning-acquisition had elapsed to consider a memory remote.

We divided the manuscripts attending to the different methodologies that the researchers selected to examine spatial retrieval. Thus, we differentiated between studies that explored memory retrieval in healthy animals without any invasive intervention and those based on invasive manipulations. Concerning studies that applied some intervention, we distinguished between the inactivation of a target brain area or even functional networks or cell populations, studies that performed a lesion on an anatomically well-defined area of the brain, those that used pharmacological interventions or chemical agents, and finally, a section that addressed genetic manipulation studies. It is important to note that, when we refer to non-

invasive studies, we used this term only to discard the invasive ones, but we included non-invasive manipulations whose aim was to examine the interaction with remote spatial memory. As a consequence, the associated table that summarizes the main results of each article was slightly different across the mentioned sections. Due to the relative extent of behavioral tasks used to assess retrieval success or failure, we included another subsection aimed at depicting the foundations of the behavioral paradigms to offer more details about the training and retrieval procedures.

From the reviewed studies on remote spatial retrieval, it is possible to point out two main findings of the behavioral outcome and the brain areas that seem to sustain remote allocentric spatial memory (to view a summary, see Figure 2) [Insert Figure 2 here].

4.1. How long can an allocentric spatial memory last in rodents?

Non-invasive methods that accurately reflect animal behavior without invasive interventions showed that rodents have an intact spatial memory with time-intervals of 14 (Barry et al., 2016), 15 (Zorzo et al., 2020), 18 (Pol-Bodetto et al., 2011; Ramos, 2009), 20 (Bonaccorsi et al., 2013), 21 (Tzakis et al., 2020), 25 (Lopez et al., 2008; Loureiro et al., 2012), 30 (Barry et al., 2016; Bonaccorsi et al., 2013; Gusev et al., 2005; Gusev and Gubin, 2010a; Trouche et al., 2009; Zorzo et al., 2020), 31 (Wartman and Holahan, 2013), 37 (Wartman and Holahan, 2014), and 42 days (Schlesiger et al., 2013), showing a decay in spatial memory retention when a longer time had passed since learning-acquisition, such as 45 (Zorzo et al., 2020), 50 (Bonaccorsi et al., 2013), and 60 days (Zorzo et al., 2020). However, other authors found forgetting after 14 (Gritton et al., 2012) and 30 days (Carr et al., 2016; Ramos, 2009) but this was just in a minority of studies.

Data outcomes from control animals that took part in lesion or inactivation studies displayed similar results. These results revealed conserved memory retention with time-intervals of 16 (Binder et al., 2019), 25 (Klein et al., 2019; Lopez et al., 2009; Loureiro et al., 2012), 30 (Broadbent et al., 2006; Goodman et al., 2010; Hales et al., 2018; Teixeira et al., 2006), 35 (Haijima and Ichitani, 2008), and 37 days (Wartman

et al., 2014). Contrary to the studies of Bonaccorsi et al. (2013) and Zorzo et al. (2020), conserved memory in sham-lesion animals was also found with periods of time that exceeded 50 days (Clark et al., 2005a, 2005b; Martin et al., 2005). Interventions such as pharmacological treatments, chemical agent administrations, or genetic manipulations added comparable results about how long rodents can retain spatial information. Conserved spatial memory retention was found under standard conditions with a delay of 14 (Maehata et al., 2020), 17 (Ampuero et al., 2013), 27 (Kim et al., 2018), 30 (Fremouw et al., 2012; Li et al., 2008; Tong et al., 2015; White et al., 2008), and 36 days (Tanaka et al., 2008).

Overall, these results reflect that rodents can maintain memory for spatial locations up to or close to one month, and it becomes difficult with higher time-intervals. This supports the idea that the passage of time can result in a fragile memory state leading to a loss of precision or decay of memory representations. Thus, memories can fade, impoverish, and become schematic over time (Barry and Maguire, 2019). In this line, it may be interesting to allude to the transformation theory: a memory engram suffers a transformation when going from a detailed to a schematic one (Winocur et al., 2010; Winocur and Moscovitch, 2011). It can be hypothesized that, as the consolidation process progresses, spatial detailed memories can be transformed to more generic ones, containing a coarse representation of the environment (Ramos, 2009), and these schematized memories, lacking contextual details, may not be enough to successfully retrieve a remote spatial memory. Moreover, it has been proposed that, over time, firstly, specific stimulus attributes are forgotten, which leads to memory generalization, and later, memory will be no longer accessible by retrieval cues (Ko and Frankland, 2021).

Apart from the course of time, it is suggested that one of the underlying causes of the decline in memory retrieval may a consequence of fewer training sessions. However, the studies of Bonaccorsi et al. (2013) and Zorzo et al. (2020), which used the same protocol in the 15-day (Zorzo et al., 2020), 20-day (Bonaccorsi et al., 2013), and 30-day group (Bonaccorsi et al., 2013; Zorzo et al., 2020), suggests that the behavioral failure was not a consequence of the training itself but rather of the moment at which the retrieval was assessed. Moreover, we suggest that the existence of fewer studies with time-intervals

exceeding one month reflects the researcher's rejection to use these time-periods because of memory weakening (if the aim is to study the neurobiology of remote memories, this time frame would not be adequate). In this scenario, it is relevant to highlight that the limited duration of the spatial memory may be due, at least in part, to its valence. As far as we know, it is more common to observe successful retrieval with time-lapses that exceed one month in other hippocampal-based tasks that are context-specific, such as fear conditioning (Cox et al., 2013; Do-monte et al., 2015; Gale et al., 2004; Izquierdo et al., 2002; Quinn et al., 2008; Ritov and Richter-Levin, 2017), reaching retention even seven (Quinn et al., 2008) or 16 months after memory formation (Gale et al., 2004). Thus, the differences with spatial memory are possibly due to the nature of learning. Fear conditioning gives rise to a strong emotional aversive response (Bocchio et al., 2016; Sah et al., 2020), whereas most navigation tasks are based on negative reinforcements that provoke an escape response. Therefore, it might be easier to remember a potential threat linked to adaptation and survival processes.

4.2. Methodological differences can explain remote spatial retrieval discrepancies across studies

Some authors observed conserved memory widely exceeding one month (Clark et al., 2005a, 2005b; Martin et al., 2005). In this context, it is possible to observe a relationship between successful remote recall and the number of trials carried out during the acquisition phase. Specifically, remembering the location of a platform 56 days after learning is possible due to a training of 40 total trials over four days (Martin et al., 2005), while an even longer memory, such as the one that is derived from the study by Clark et al. (2005b), it is feasible thanks to a very extensive training, from 392 trials over 49 days. Thus, when normal forgetting of a spatial memory is due to an excessive time-interval, extra training can be beneficial.

On the other hand, a small number of studies found forgetting with periods of time inferior or equal to one month (Carr et al., 2016; Gritton et al., 2012; Ramos, 2009). Under these circumstances, the training, and trial distribution across days may be an important variable. Although subjecting the animals to several

total trials comparable to the majority of the MWM studies, Carr et al. (2016) employed a massed protocol of 12 trials a day for two days, and Gritton et al. (2012) employed one trial a day during 28 consecutive days. We cannot state that all rodents submitted to the mentioned protocols would show a memory deficit, as other authors have shown a good MWM performance despite using 24 trials in one day (Trouche et al., 2009), or two trials during 14 consecutive days (White et al., 2008), but taking into account that most of the studies employed distributed learning, a relationship could exist. In the case of Ramos (2009), whose study was done in the RAM, we believe that the forgetting cannot be explained by training, as successful retrieval with lower intervals of time using the same acquisition protocol was observed. More research is needed to delve into the behavioral response of this spatial task, which is underrepresented. In addition, the forgetting that Gritton et al. (2012) and Ramos (2009) observed can be reversed under different conditions. In this regard, Gritton et al. (2012) observed that if the learning occurs during the light-phase, there is no retrieval, and that retention scores are rescued if acquisition is carried out during the dark phase. The study of Ramos (2009), which aimed to clarify whether a spatial memory trace had lost detail, and was consequently transformed into a more schematic memory, used a reminder treatment that enabled animals to explore the maze freely one day before the retention probe test, but without the reward in the target arm. Results indicated that the reminding had to be done before day 18 post-acquisition, suggesting that as time goes by, the original detailed memory can be progressively transformed into a schematic one, which leads to a difficult recovery (Ramos, 2009). Moreover, the development of rodents needs to be taken into account, due to an early cognitive development triggering failure in spatial location retrieval at remote points, shown in preadolescent rats (Tzakis et al., 2020).

4.3. Impact of different navigational tasks on remote spatial retrieval

In the results section, we made a distinction between the different behavioral procedures used across various mazes, including the MWM, RAM, Barnes maze, Double H-maze, and Annular maze. In terms of the potential differences because of using distinct memory procedures or mazes, particularly with time-intervals from 25 to 35 days, it is not possible to draw any statistical conclusion, given that most of the

researchers employed the MWM, which prevents us from being able to compare samples. This leads to an underrepresentation of other spatial memory behavioral mazes. The predominant use of the MWM can be explained by the multiple advantages it presents, such as the minimal training it requires to establish a consolidated spatial memory, the absence of food deprivation, or the facility to create spatial paradigms based on the allocentric strategy without the presence of proximal cues, which is easier to ensure using circular pools (Vorhees and Williams, 2014b). Even so, it could be interesting to compare spatial retrieval across different behavioral tasks to understand if it is possible to establish transferability between them.

4.4. Cross-species comparison on remote spatial retrieval

Traditionally, the rat has been most used to study spatial learning and memory processes, whereas the mouse is predominantly used for genetic studies (Hok et al., 2016). This difference is also reflected in spatial retrieval studies, as most of them have been performed in rats. In terms of differences between species, our descriptive analysis suggests there may not be a wide distinction in terms of retrieving spatial information in time-intervals close to one month. Considering data from non-invasive treatments or controls from the invasive ones, most rats succeeded at retrieval and so did all mice. However, as far as we know, behavior and brain activity differences exist between species, for example, disparities in the stability of spatial representations (for a review, see Hok et al., 2016), thus, the scientific community could benefit from deeper analysis.

4.5. Sex differences in remote spatial retrieval

There is a relative consensus about sex differences in spatial learning and spatial memory, with various studies indicating that males outperform females. However, most of the research in the field is limited to the beginning of the training (Anderson et al., 2013; Woolley et al., 2010), and studies aimed to decipher sex differences on remote retrieval are still scarce. Sebastian et al. (2013) showed that the outperformance of males is also present during the recovery of a 30-day spatial memory, while Zorzo et al. (2020) did not observe any sex differences. Interestingly, the study of Sebastian et al. (2013) showed differential

molecular mechanisms at the moment of retrieval, such as an enhancement of synaptic PKMζ in males and higher synaptic GluA2 expression in both sexes, leading to sexually dimorphic expression (Sebastian et al., 2013). Considering that the male and female brain functioning in spatial cognition seems to be different (Méndez-López et al., 2009; Sneider et al., 2011) and due to the lack of a more profound understanding of the female brain functioning on long-lasting spatial memories, we emphasize that research is needed. Furthermore, only four of the articles collected were conducted on females. Thus, it is important to highlight this underrepresentation and the need to explore potential sex differences across long-term spatial memories (Beery and Zucker, 2011; Will et al., 2017).

4.6. Brain areas implicated in remote spatial retrieval

In terms of the neuroanatomy of spatial memory retrieval, several brain regions have been reported to play a key role in remembering allocentric spatial information coded a long time ago. In particular, they refer to the prefrontal (Barry et al., 2016; Binder et al., 2019; Bonaccorsi et al., 2013; Carr et al., 2016; Gusev and Gubin, 2010a; Kim et al., 2018; Li et al., 2008; Teixeira et al., 2006; Tzakis et al., 2020; Wartman and Holahan, 2013, 2014; Zorzo et al., 2020), insular (Gusev and Gubin, 2010a), orbital (Gusev and Gubin, 2010a), frontal association (Gusev and Gubin, 2010a), perirhinal (Barry et al., 2016; Zorzo et al., 2020), entorhinal (Barry et al., 2016; Gusev et al., 2005; Gusev and Gubin, 2010a; Hales et al., 2018; Zorzo et al., 2020), parietal (Barry et al., 2016; Gusev and Gubin, 2010a; Zorzo et al., 2020), retrosplenial (Barry et al., 2016; Gusev and Gubin, 2010a; Haijima and Ichitani, 2008; Zorzo et al., 2020), motor (Gusev and Gubin, 2010a; Zorzo et al., 2020), somatosensory (Gusev and Gubin, 2010a), and visual cortices (Gusev and Gubin, 2010a; Tanaka et al., 2008). Furthermore, a great extent of studies suggests that the HC is a key brain area for remote spatial retrieval (Barry et al., 2016; Binder et al., 2019; Broadbent et al., 2006; Clark et al., 2005b, 2005a; Goodman et al., 2010; Gusev et al., 2005; Haijima and Ichitani, 2008; Maehata et al., 2020; Martin et al., 2005; Schlesiger et al., 2013; Tanaka et al., 2008; Teixeira et al., 2006; Trouche et al., 2009; Wartman et al., 2014; Wartman and Holahan, 2013; Zorzo et al., 2020), in addition to other

subcortical structures such as the thalamus, in which authors often address the differential nuclei, that is, Re, Rh, ANT and ILN/NT (Klein et al., 2019; Lopez et al., 2009; Loureiro et al., 2012).

Non-invasive studies offer a wide overview of the enrolment of several areas during remote retrieval, including those that conform the limbic system and the extended network, in addition to other associative and primary cortices. As far as we know, the previously mentioned areas play a role during spatial processing in the learning phase (Hunsaker and Kesner, 2018), and their later contribution (during retrieval) reflects that re-exposure to the spatial contingences can reactivate the neuronal ensembles activated during codification (Tayler et al., 2013). However, some of the studies that include different time-intervals and study neuronal activity reflect that the brain engagement may change over time, suggesting increasing participation of the mPFC and other neocortical and parahippocampal areas (Barry et al., 2016; Bonaccorsi et al., 2013), supporting both system consolidation main theories (discussed below). Interestingly, some of these articles reflected that the activity of the HC was similar across retention intervals, which showed retrieval success, proposing its relevance across spatial retrieval, regardless of how much time has elapsed (Barry et al., 2016; Bonaccorsi et al., 2013; Zorzo et al., 2020). Thus, according to the main results in the field, it is possible to suggest that brain morphology and functionality may change as time goes by, and also in response to retrieval. Nevertheless, the main question to be answered, which is still being debated, is how all these brain areas contribute to remote spatial retrieval. Higher activity has been found in all the previously mentioned structures (see section 3.3.), suggesting its functional implication, and some of the studies have found a co-activation, determined by higher IEG expression, in the HC and other cortical regions (Barry et al., 2016; Bonaccorsi et al., 2013; Carr et al., 2016; Wartman and Holahan, 2013). However, are all the mentioned areas essential to retrieve spatial information that has been coded some time ago? Do they show a distinct contribution? To address this issue, the most valuable information comes from lesion and inactivation studies.

Inactivation and lesion studies support the main findings derived from non-invasive studies: not only cortical regions are required to retrieve allocentric spatial information coded some time ago, but also the

HC. In terms of cortical regions, disturbances across the prefrontal cortex (Teixeira et al., 2006; Wartman et al., 2014), RSP (Haijima and Ichitani, 2008), and mENT (Hales et al., 2018) trigger a remote retrieval deficit, suggesting that these structures are essential at remote points. Nonetheless, the majority of the research is in the HC (Binder et al., 2019; Broadbent et al., 2006; Clark et al., 2005a, 2005b; Goodman et al., 2010; Haijima and Ichitani, 2008; Martin et al., 2005; Teixeira et al., 2006; Winocur et al., 2013), and all the studies included in this review have found that the HC is mandatory for successful retrieval. The hippocampal formation is the main area that supports the allocentric strategy (Eichenbaum, 2017; Hunsaker and Kesner, 2018; O'Mara and Aggleton, 2019; Poulter et al., 2018; Rolls and Wirth, 2018), and is responsible for processing fine details (Sekeres et al., 2018). Thus, it may be important to access spatial details to remember a specific location that is based on cognitive mapping (Tolman, 1948; Winocur et al., 2013b).

Additionally, a distinction has been revealed between the areas that make up the HC. CA1 and CA3 specifically recover remote spatial memories, whereas the DG codes the general configuration of the environment, not being specific to the task (Schlesiger et al., 2013). Interestingly, the retrieval of a spatial task has been reported to need the recruitment of adult-generated neurons within the HC to become functionally integrated into complex hippocampal-neocortical networks (Goodman et al., 2010; Trouche et al., 2009). This suggests that neurogenesis is not only important during the learning *per se* but is also vital in post-acquisition stages such as memory consolidation (Goodman et al., 2010). Moreover, dendritic spine density was found to be reduced in the HC, which suggests that this structure is implicated in the long-term maintenance of spatial memory (Maehata et al., 2020). Recently, Ko and Frankland (2021) proposed that hippocampal neurogenesis represents one process that rewires hippocampal circuitry and leads to hippocampal engrams modification. Specifically, it has been suggested that, at intermediate stages, neurogenesis causes the forgetting of specific stimuli, which can result in memory generalization due to less precise information, and then, the neurogenesis-mediated rewiring of hippocampal engram

circuitry translates into natural forgetting, showing that the neurogenesis process is one of the mechanisms underlying system consolidation (Ko and Frankland, 2021).

Furthermore, non-invasive, lesion, and inactivation studies have outlined the role of the thalamus, one of the main areas that make up the extended network of the limbic memory system (Aggleton and Brown, 1999). The midline thalamus is highly and bidirectionally connected to the HC and mPFC and is widely linked to episodic memory (Leszczyński and Staudigl, 2016; Quet et al., 2020). In addition, the anterior thalamus has been proposed to act as a hub that modulates the hippocampal-memory system and the frontoparietal networks implicated in attention, being a key structure to achieve an efficient allocation of attention to memory representations (Leszczyński and Staudigl, 2016), and which is consequently implicated in the time-dependent reorganization of spatial memories (Klein et al., 2019; Lopez et al., 2009; Loureiro et al., 2012). It is not surprising that creating a lesion in certain thalamic nuclei, such as the ReRh, causes a spatial deficit retrieval. This behavioral impairment has been accompanied by a reduction of mushroom spines within the HC and mPFC, in addition to lower c-fos activity in the mPFC. These results suggest that ReRh neurons may regulate hippocampal connectivity and spinogenesis within the ACC (Klein et al., 2019). Similarly, Loureiro et al. (2012) observed a ReRh activation in the retrieval task when adding the implication of the ventral midline thalamus in the maintenance of long-lasting memories. Although reversible inactivation caused a retrieval deficit, they also observed an impaired remote memory when excitotoxic lesions were targeted at ReRh. Authors have observed that the thalamic nuclei may participate in spatial consolidation over time, maybe because of a functional interconnection with other brain areas, such as the HC and/or mPFC, although it may not be essential for recovering *per se* (Loureiro et al., 2012). The INT thalamic nuclei have also been revealed to contribute to remote spatial memory (Lopez et al., 2009). Altogether, these results highlight the importance of the hippocampal-cortical dialogue to remember a spatial memory, with the thalamus standing out as a hub for regulating these interactions (Loureiro et al., 2012). However, thalamic lesion studies performed the surgery before learning-acquisition. Therefore, they are not specific to systems consolidation. Nevertheless, they still add

valuable information about the specific role of this structure in remote retrieval, as rats display normal acquisition rates, and normal recent memory retention following ventral midline (Klein et al., 2019; Loureiro et al., 2012) and lateral lesions (Loureiro et al., 2012), but not when lesioning the anterior nuclei (Loureiro et al., 2012).

The findings from genetic manipulation studies provide useful information about the molecular mechanisms required to maintain memories (for review see. Asok et al., 2019), supporting the relevance of both the cortex and HC. For example, Maehata et al. (2020) revealed that, during remote retrieval, the occurrence of 7a-hydroxylated neurosteroids is needed, and consequently, KO models present an impaired remote memory, in addition to altered spine density within the HC. Also, some molecular deficiencies, such as a depletion of L-VGCCs both in HC and cortex are strongly associated with spatial memory retention (White et al., 2008), and a depletion of excitatory neurons in the HC induces ACC abnormalities (Kim et al., 2018).

Finally, the evaluation of the impact of certain pharmacological treatments adds essential knowledge linked to clinical purposes. As a consequence, it becomes important to take into consideration the potential transient side effect that the fluoxetine could cause in remembering remote memories (Ampuero et al., 2013), as well as that endogenous formaldehyde is associated with an impairment in remote memory retention and DNMT, which is also found in an autopsied HC from Alzheimer's disease subjects (Tong et al., 2015). Finally, in light of the current studies, it is not possible to reach a conclusion about the impact of Ara-C in remote memories, as one study detected a damaging effect in rats (Li et al., 2008), but it was not found in mice (Fremouw et al., 2012). It is important to note that, although a similar methodology was used, they employed a different dosage (400mg/kg body in rats and 275 mg/kg in rodents). Although most of these studies only reflect the relationship between drugs and the behavioral response, some of them also add valuable information about brain activity. For example, Li et al. (2008) observed retraction of ACC apical dendrites, but not on CA1, revealing prefrontal cellular morphometric alterations in response to impaired remote retention.

4.7. Allocentric remote spatial retrieval and systems consolidation theories

The notion that the extra-hippocampal structures are increasingly crucial over time, and that this occurs due to interactions between the HC and the cortical modules is shared by the two main theories of systems consolidation, that is, the SCT and the MTT. Nevertheless, the SCT and the MTT differ in terms of the HC recruitment over time. The SCT states that memory will be completely independent of the HC once the process of systems consolidation is completed, and as a consequence, a hippocampal lesion would not affect remote retrieval (McClelland et al., 1995; Squire and Alvarez, 1995). The MTT, based on patients who did not show a temporary graded retrograde amnesia (TGRA) but a non-grade one, argues that this structure is always needed for successful retrieval, no matter how old the memories are (Nadel and Moscovitch, 1997; Winocur and Moscovitch, 2011). Moreover, the MTT proposes that the activation of a memory implies re-experiencing the original episode and it generates a hippocampal reactivation. Consequently, each time an episodic memory is reactivated, it is subsequently re-encoded, and this leads to multiple memory traces located in hippocampal-cortical neuronal assemblages (Albo and Gräff, 2018). Experimental results that reveal that the hippocampal formation is always needed during retrieval help to better understand non-graded retrograde amnesia (RA) patients, while they fail to solve the TGRA, characterized by severe loss of memory from shortly before the damage, but preserved older events (Winocur et al., 2013a). However, it is important to consider the nature of the episodic memory to better understand the differences found between non-graded RA and TGRA: whereas non-graded RA is linked to contextually rich memories, TGRA is associated with semantic or schematic memories (Winocur and Moscovitch, 2011). In this scenario, the study of Winocur et al. (2013b) deserves greater attention. They showed that rats with hippocampal lesions displayed a failed retrieval of spatial memory tasks after one month, but a conserved fear conditioning response, with the same time-interval. As both tasks are hippocampal-dependent, but they differ in the detailed information required to show a retrieval response, these results suggest that spatial retrieval needs detailed spatial information to be remembered, whereas this does not necessarily happen in the case of fear conditioning, given that the response can be elicited by

nonspecific, schematic information (Winocur et al., 2013b). The results derived from this review, which explored the role of HC support that remote retrieval in the context of allocentric spatial navigation requires to precisely remember the spatial features dependent on the HC (cue location and the spatial association between them), support the MTT theory. Moreover, as ENT conforms the hippocampal formation, its lesioning could be interpreted in the same way, considering that this structure exerts major projections to HC (Hales et al., 2018).

Even though the HC is needed to reach successful retrieval during spatial navigation, there may be a change within the hippocampal-cortex mnemonic function (Gusev et al., 2005; Gusev and Gubin, 2010a, 2010b), and critical debate has highlighted another flawed point of the SCT. This point refers to the assumption that memory consolidated within extra-hippocampal structures is a reproduction of the previously learned hippocampal memory, although, as we know from experimental research, as time goes by, memories can lose their context-specificity, becoming more generalized and losing precision over time (Sekeres et al., 2018; Winocur et al., 2010; Winocur and Moscovitch, 2011). Therefore, the SCT and MTT also differ in the nature of the memory that is consolidated in the extra-hippocampal areas (Barry and Maguire, 2019; Winocur and Moscovitch, 2011). The SCT suggests that memories become consolidated in their original form in the cortical areas, whereas the MTT argues this premise, and states that the neocortex is required for abstract, schematic representation (Moscovitch et al., 2016; Winocur and Moscovitch, 2011). The transformation hypothesis proposed one decade ago develops the idea beyond the MTT: memories are transformed into schema in the cortex, without replacing the detailed hippocampal memory, and both of them can co-exist and interact depending on the environmental demands (Winocur et al., 2010; Winocur and Moscovitch, 2011). This theory also proposes a functional differentiation across the long hippocampal axis, where the posterior HC supports fine details of memories, the anterior is associated with gist or global context, and the prefrontal cortex is responsible for memory schemas (Sekeres et al., 2018). Thus, in terms of cortical recruitment, here, we can outline the increasing engagement of the mPFC, as well as the other neocortical and parahippocampal areas, suggesting that

spatial memories are reorganized in a time-dependent manner, with the mPFC, mENT, and RSP cortex being critical for processing remote spatial memories (Haijima and Ichitani, 2008; Hales et al., 2018; Teixeira et al., 2006). Both SCT and MTT theories suggest that, as memories progressively mature, the connections between different cortical modules are strengthened, and the integrating role is assumed by the prefrontal cortex (Frankland and Bontempi, 2005). Additionally, the RSP functioning on remote retrieval might be associated not only with its role in information storage and long-term spatial representation but also considering that it exerts afferent and efferent connections with the parahippocampal-hippocampal memory network (Hunsaker and Kesner, 2018; Kesner, 2013; Todd and Bucci, 2015).

In terms of the HC-cortical dialogue, supported by all system-consolidation theories (although with discrepancies about content), inactivation and lesion studies help to better understand its time-course. Inactivation studies aim to silence the HC just before the retrieval test and outline its importance at the specific moment at which retrieval is assessed. Lesion studies need to leave an interval of time between surgery and the evaluation of the retrieval. As a consequence, they could be disrupting the hippocampal-cortical dialogue prior to retrieval testing. Total and partial hippocampal lesions occurring with periods of time that oscillate between one month and 114 days post-learning (Clark et al., 2005a; 2005b; Haijima and Ichitani, 2008; Martin et al., 2005; Winocur et al., 2013b) have been shown to lead to equal memory decline. This supports the idea that the HC is always needed during the retrieval of a spatial task, regardless of memory age. However, if we hypothesize that spatial memories are consolidated over time in cortical areas and are independent of the HC, the dialogue should occur after the mentioned time-intervals. It is the only way to explain how hippocampal damage triggers an impaired remote memory. If this is the case, there should be a later moment at which a hippocampal lesion does not affect retrieval, in order to support the SCT. We believe this hypothesis is not very plausible, due to modifications in cortical areas found earlier, suggesting that the hippocampal-neocortical dialogue occurs before. Research has shown that spatial retrieval in the MWM, alone or in combination with another spatial-dependent memory task

performed before the water maze retention probe test, leads to recruitment of both mPFC and HC areas (Wartman and Holahan, 2013) and that when inactivating a prefrontal area, there is a subtle behavioral deficit that is accompanied by higher HC activity (Wartman et al., 2014). A greater dendritic complexity within the HC and mPFC was also found, suggesting synaptic and systems consolidation processes (Wartman et al., 2014). All these studies were performed with time-lapses close to one month. Similarly, the study of Barry et al. (2016) revealed hippocampal activation in addition to other cortical areas, such as the mPFC, PAR, PRh, and mENT, arguing the continuous role of the hippocampal formation in the retrieval of a spatial memory, particularly when there is a detailed spatial representation. Furthermore, Teixeira et al. (2006) did not find a recent memory impairment after an ACC inactivation, and some non-invasive studies observed a gradual and linear increase of the prefrontal cortex activity (Barry et al., 2016; Bonaccorsi et al., 2013), which suggests that the hippocampal-cortex dialogue is not established immediately, but takes time to occur, in accordance with both the SCT and the MTT theories (Nadel and Moscovitch, 1997; Squire and Alvarez, 1995). In particular, an interval of time between two weeks and one month has been proposed in which memories are set within extra-hippocampal structures, giving rise to a gradually distributed brain network implicated in spatial retrieval (Barry et al., 2016). To specifically address this question, Binder et al. (2019) silenced the monosynaptic projections from HC to mPFC after learning-acquisition and revealed conserved retention following 16 days post-learning-acquisition. However, it is important to outline that the silencing was done before day five post-acquisition, and not at remote points. It was also limited to the projection of the ventral and intermediate HC to mPFC, not including the dorsal projections, which could explain their results (Binder et al., 2019). We believe these types of studies add the most valuable information about systems consolidation, as the brain is explored at a network level, which can help to better understand the functioning of larger neural networks (Hunsaker and Kesner, 2018).

Taken together, evidence in rodents shows that, apart from the increasingly key role of the neocortex and parahippocampal cortices in allocentric remote retrieval, HC recruitment may be critical, regardless of

memory age, which supports the MTT and transformation hypothesis instead of the SCT. It is proposed that to succeed at remote retrieval tasks, it is essential to attend to fine spatial details. These findings are important to better understand results derived from non-graded RA patients, because of delving into the temporal features of amnesia.

5. Limitations

The articles collected in this systematic review feature a wide range of methodologies that can affect the results. Some articles revealed differences not only with controls, but with recent memory groups, leading to a great variability of research aims. Moreover, we have considered as remote those memories lasting at least two weeks. However, the definition of recent and remote memories requires further research, as we still need to better understand the time-course of systems consolidation. Finally, there is a need to include females in remote spatial memory approaches to equally represent both sexes.

6. Conclusions

Considering most of the behavioral results on remote spatial retrieval explored in non-invasive interventions, lesion and inactivation studies, pharmacological treatments, chemical agent administrations, or genetic manipulations, it is difficult to retrieve spatial information in rodents, including rats and mice, when the time-periods exceed one month or are close to this timeframe. This does not seem to be a consequence of fewer training sessions, but rather has to do with the time elapsed. However, spatial memory normal forgetting can be reversed via extensive training protocols. In terms of the brain areas underlying successful remote allocentric spatial memories, the critical role of cortical areas has been uncovered, in particular the participation of the mPFC, RSP, or PRh, in addition to other associative and primary cortices that participate during spatial navigation. Moreover, the thalamus remains important, and the implication of the hippocampal formation—including both HC and ENT—may be essential, supporting the MTT theory and transformation hypothesis instead of the SCT model. This suggests that remote retrieval during spatial navigation needs to recover spatial details to successfully perform the task,

adding information about the temporal features of normal forgetting. Finally, it is suggested that the brain morphology and functionality, both at a molecular or systems level, can change over time and because of remembering past spatial events.

Financial Support

Fundación Española para la Ciencia y la Tecnología (FECYT) AYUD/2021/51378, Ministerios de Ciencia e Innovación PID2020-117259RB-I00 and Programa "Severo Ochoa" de Ayudas Predoctorales de la Consejería de Cultura y Deporte del Principado de Asturias (PA-18-PF-BP17-011) to C.Z.

Acknowledgments

We thank AINDACE Foundation (Ayuda a la Investigación del Daño y Enfermedades Cerebrales).

Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

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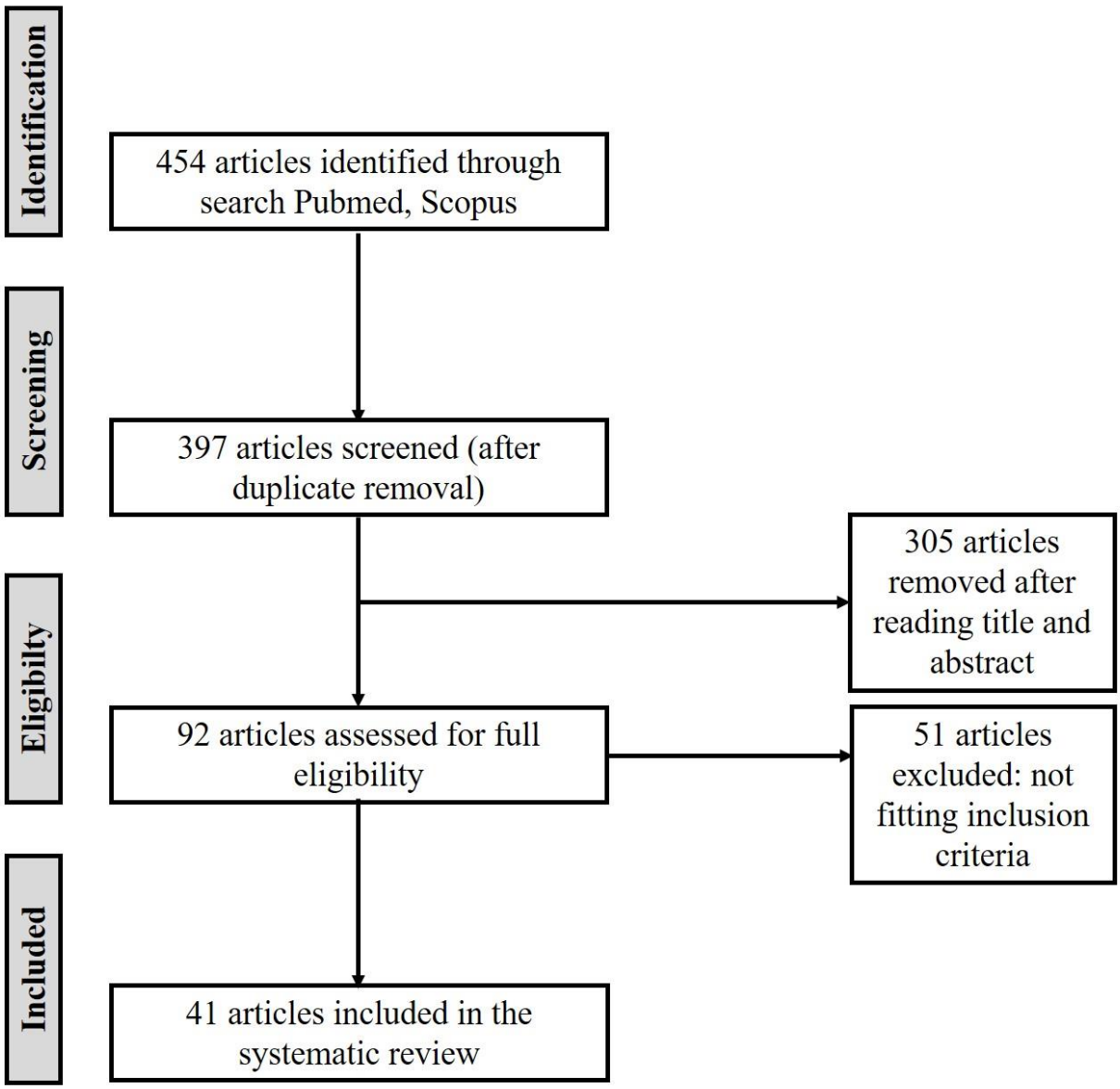


Figure 1. Literature Flow diagram of the selection process in the different phases of the systematic review.

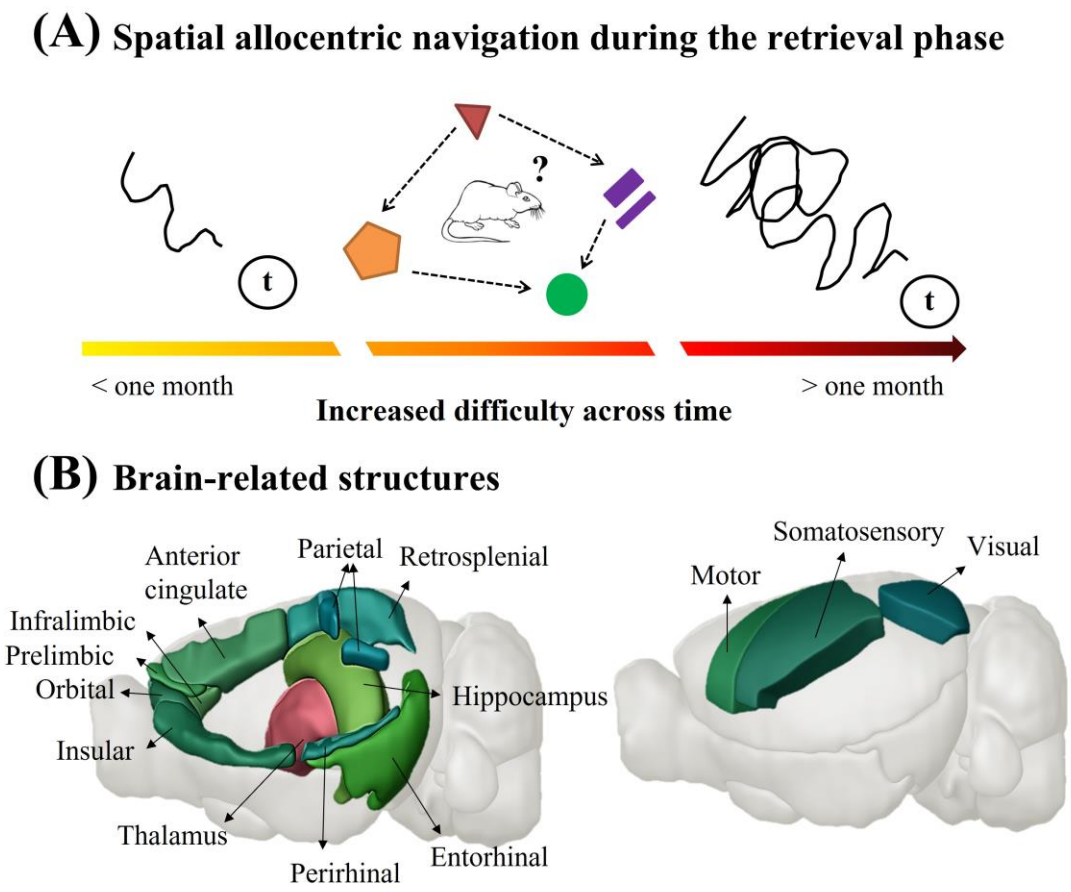
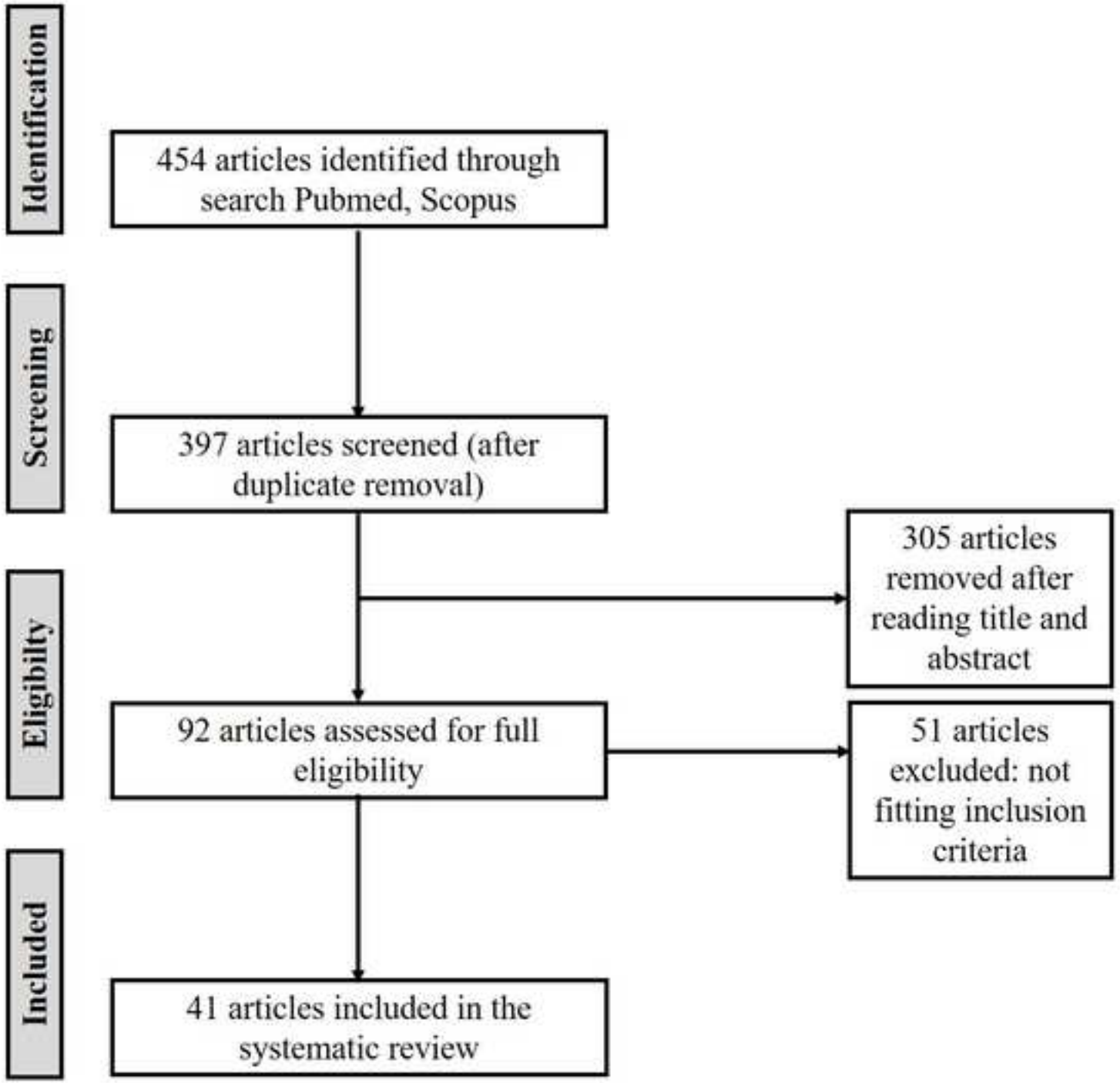


Figure 2. (A) Schematic illustration of the spatial allocentric navigation during the retrieval phase. t represents target location. (B) Schematic illustration of the brain areas involved during the retrieval of spatial memories.

Figure1



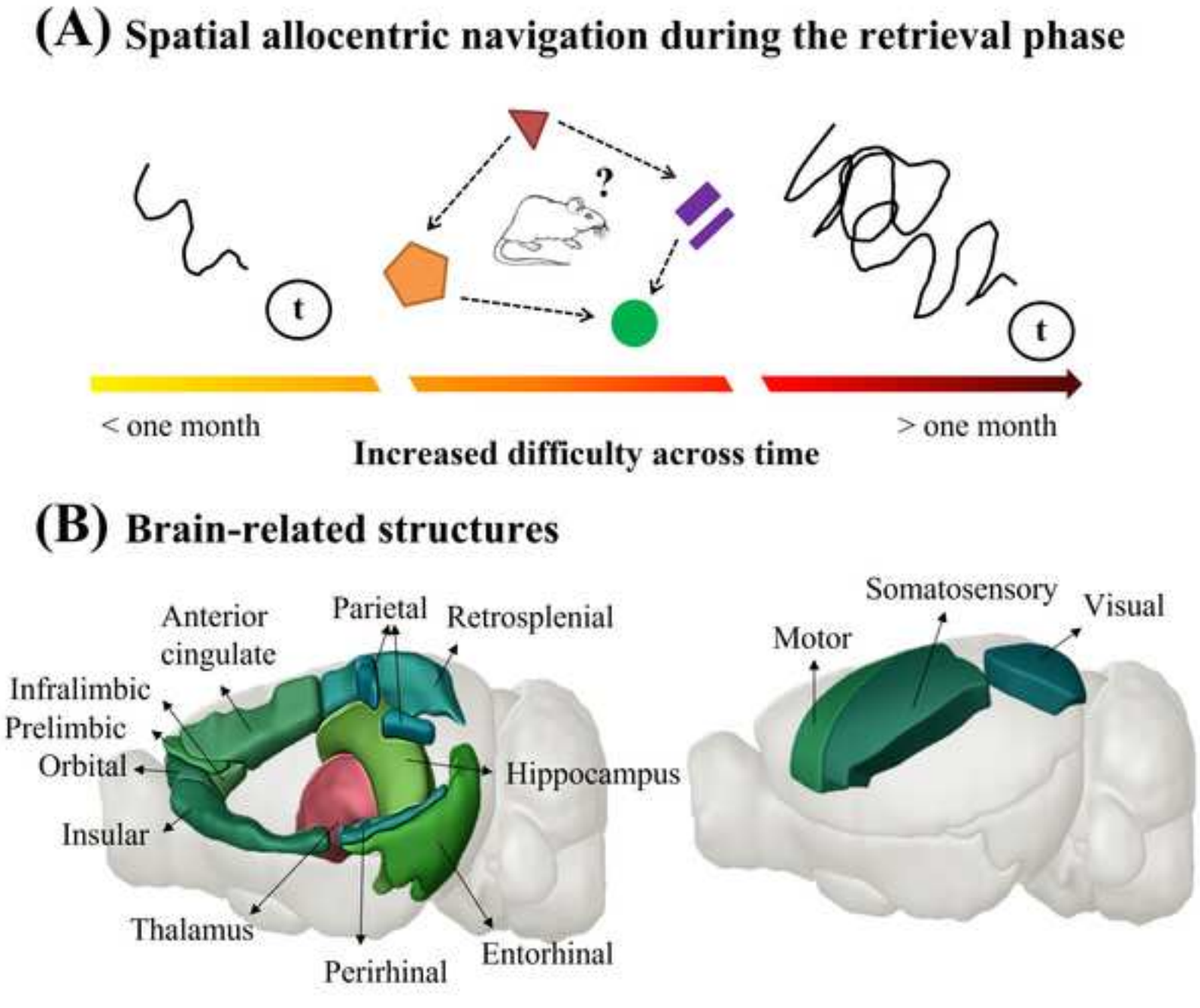


Table 1. Non-invasive studies

Reference Author, Year	Animal/ Strain/ Sex	Age/ Weight	Behavioral task	Remoteness	Brief behavioral results	Brain analysis	Brief brain results
Barry et al., 2016	Rat/ Wistar/ Male	- / 200-300 g.	MWM	14 days / 30 days	Conserved memory retention (14 and 30 days)	Zif268, c-Fos and Arc immunohistochemistry	The 14-day group displayed higher IL Zif268 expression compared to a recent group, higher PL, IL, PRh, and PAR c-Fos expression compared to a recent and cage control group, higher mENT c-Fos expression compared to a cage control group, higher CA3 c-Fos expression compared to a recent group, and higher ACC, PL, IL, PRh and PAR Arc expression compared to a recent and cage control group. The 30-day group showed higher ACC, PL, and IL Zif268 expression compared to a recent group, higher PL, IL, and PRh c-Fos expression compared to a recent and cage control group, higher CA3 c-Fos expression compared to a recent group, higher RSP and PAR c-Fos expression compared to a cage control group, and higher PL, PRh, and PAR Arc expression compared to a recent and cage control group.
Bonaccorsi et al., 2013	Mice/ C57BL/6/ Male	4 weeks / -	MWM	20, 30, 50 days	Conserved memory retention (20 and 30 days), impaired memory retention (50 days)	C-Fos immunohistochemistry	The 30-day and 50-day groups showed higher c-fos activity in the ACC and IL, compared to a cage control group and to recent groups in the case of ACC, whereas the difference in IL was restricted to the 30-day group with recent groups. The 20-day, 30-day, and 50-day groups showed higher c-fos activity in the V1, DG, and CA1, compared to a cage control group.
Carr et al., 2016	Rat/ Long-Evans/ Male	12 weeks / -	MWM	30 days	Impaired memory retention	c-Fos immunohistochemistry	The 30-day group showed higher ACC c-Fos expression compared to a cage control and a recent group, and higher CA1 activity compared to the cage controls.

Gritton et al., 2012	Rat/ Sprague-Dawley/ Male	- / 350 g.	MWM	14 days	Conserved memory retention when learning occurred during the dark phase, but impaired learning when it took place during the light-phase	-	-
Gusev et al., 2005	Rat/ Wistar/ Male	8 weeks / -	MWM	30 days	Conserved memory retention	Arc mRNA expression by *in situ* hybridization and Reverse transcriptase-polymerase chain reaction (RT-PCR)	Higher lENT, CA3, DG, and subiculum Arc mRNA expression and lower CA1 and ventral HC Arc mRNA expression in the 30-day group.
Gusev and Gubin, 2010a	Rat/ Wistar/ Male	8 weeks / -	MWM	30 days	Conserved memory retention	Arc mRNA expression by *in situ* hybridization and RT-PCR	The 30-day group showed task-specific Arc mRNA expression in PL, FrAs, MO, DLO, lENT, S1, S2, M1, RSP, and Ins Arc mRNA expression. The 30-day group displayed a different pattern of activity depending on cortical layers, showing higher expression in PAR, V1, V2M, V2L, S1, M1, M2 L2/3, and L4.
Gusev and Gubin, 2010b	Rat/ Wistar/ Male	8 weeks / -	MWM	30 days	Conserved memory retention	Arc mRNA expression by *in situ* hybridization and RT-PCR	The 30-day group showed fewer strengthened correlations in comparison to a recent memory group
Lopez et al., 2008	Rat/Long-Evans/ Male	- / 250-300 g.	MWM	25 days	Better retention in a cue-enriched group in comparison with a cue-impoverished one	-	-
Loureiro et al., 2012	Rat/Long-Evans/ Male	12 weeks/ 250-300 g.	MWM	25 days	Conserved memory retention	c-Fos immunohistochemistry	Higher Re and Rh c-Fos expression.

Pol-Bodetto et al., 2011	Rat/Long-Evans/ Male	- / 240-268 g	Double H-maze	18 days	Conserved memory retention	-	-
Ramos, 2009	Rat/ Wistar/ Male	- / 270-310 g.	RAM	18 days, 30 days	Conserved memory retention (18 days, 30 days with retraining) Impaired memory retention (30 days and 30 days with overtraining)	-	-
Schlesiger et al., 2013	Rat/ Long Evans/ Male	- / 250–290 g.	RAM	42 days	Conserved memory retention	c-Fos immunohistochemistry	The remote memory group showed higher CA1 and CA3 c-Fos expression. There is an increase in DG c-Fos expression after re-exposure to a known environment.
Sebastian et al., 2013	Rat/ Sprague-Dawley/ Male and Female	8 weeks/ -	RAM	30 days	Males outperform females trained during 6 days, and both sexes reveal a positive training effect	Western Blot	Enhancement of synaptic PKMζ in males and higher synaptic GluA2 expression in both sexes.
Trouche et al., 2009	Mice/C57 BL/6J/ Male	11 weeks / -	MWM	30 days	Conserved memory retention	c-Fos, BrdU, NeuN, Zif268 immunohistochemistry	New neurons in the DG are incorporated into complex hippocampal-cortical networks
Tzakis et al., 2020	Rat/ Long-Evans/ Male	18, 20, 22, 24 and 50 days/ -	MWM	21 days	Conserved memory retention when animals were 50 days old.	c-Fos immunohistochemistry	Higher ACC c-Fos activity when compared to an age-matched and recent memory group.

Wartman and Holahan, 2013	Rat/ Long-Evans/ Male	- / 190-250 g.	MWM and RAM	31 days	MWM followed by RAM, in comparison to only MWM performance, leads to a similarly MWM remote retention	c-Fos immunohistochemistry	Similar levels of ACC and CA1 c-Fos expression in both groups
Wartman and Holahan, 2014	Rat/ Long-Evans/ Male	- / 190-250 g.	MWM	37 days	MWM followed by RAM, in comparison to only MWM performance, leads to a similarly MWM remote retention	Golgi-Cox staining	Both groups showed more ACC apical branches, ACC and CA1 apical and basal total spines, and higher CA1 apical spine density, compared to controls. The MWM+RAM group revealed more ACC basal branches, CA1 apical and basal branches, an increased ACC and CA1 apical, and ACC basal dendritic length compared to controls.
Zorzo et al., 2020	Rat/ Wistar/ Male and Female	12-15 weeks/ 211-272	MWM	15, 30, 45, 60 days	Conserved memory retention (15 and 30 days) Impaired memory retention (45 and 60 days)	CCO histochemistry	Higher ACC, PL, IL, CA1, CA3, DG, RSP, ENT, PRh, PAR, and M1 CCO activity in the successful retrieval groups in comparison with the impaired memory groups.

In the Age/Weight column, when the authors expressed age in months, we changed it to weeks. There is only one exception in the study of Tzakis et al., 2020, expressed in days. In the Remoteness column, when the authors expressed it in weeks or months, we changed it to days.

Table 2. Inactivation studies

Reference Author, Year	Animal/ Strain/ Sex	Age/ Weight	Behavioral task	Remoteness	Brain inactivation (agent)	Brief behavioral results	Brain analysis	Brief brain results
Binder et al., 2019	Mice/ C57BL/6 mice/ Male	10-11 weeks / -	Barnes Maze	16 days	Projections from HC to mPFC (Optogenetic)	Conserved memory retention	-	-
Broadbent et al., 2006	Rat/ Long-Evans/ Male	- / 300-350 g	MWM	30 days	HC (lidocaine)	Impaired memory retention	-	-
Goodman et al., 2010	Mice/ C57BL/6 mice/ Male	9 weeks / -	MWM	30 days	Young granule neurons in the HC (MAM)	Impaired memory retention	BrdU, NeuN immunohistochemistry	Neurogenesis is inhibited
Loureiro et al., 2012	Rat/Long-Evans/ Male	12 weeks/ 250-300 g.	MWM	25 days	ReRh (lidocaine)	Conserved memory retention	-	-
Teixeira et al., 2006	Mice/ cross C57BL/6 NTacfBr and 129Svev/ Male	- / -	MWM	30 days	ACC (lidocaine, QNQX) HC (lidocaine)	Impaired memory retention	-	-
Wartman et al., 2014	Rat/ Long-Evans/ Male	- / 190-250 g.	MWM, MWM, and RAM	37 days	ACC (lidocaine)	Subtle memory retention deficit when training was performed in the MWM.	c- Fos immunohistochemistry in CA1	Higher ACC c-Fos expression in both training groups.

													Substantial memory retention deficits when training was performed in the MWM followed by RAM

In the Age/Weight column, when the authors expressed age in months, we changed it to weeks. In the Remoteness column, when authors expressed it in weeks or months, we changed it to days.

Table 3. Lesion studies

Reference Author, Year	Animal/ Strain/ Sex	Age/ Weight	Behavioral task	Remoteness	Brain lesion	Brief behavioral results	Brain analysis	Brief brain results
Clark et al., 2005a	Rat/ Long-Evans/ Male	- / 300-350 g.	MWM Annular Water Maze	56 days 63 days 98 days	HC	Impaired memory retention (56 and 98 days) in the MWM. Worse memory retention (63 days) in the Annular Water Maze	-	-
Clark et al., 2005b	Rat/ Long-Evans/ Male	12 weeks/ 300-320 g.	MWM	114 days	HC	Impaired memory retention although longer periods of training were performed	-	-
Haijima and Ichitani, 2008	Rat/ Wistar-Imamichi/ Male	12- 16 weeks / mean 318 g	RAM	35 days	HC RSP	Impaired memory retention with RSP and HC lesions	-	-
Hales et al., 2018	Rat/ Long-Evans/ Male	- / 300-400 g.	MWM	30 days	mENT	Impaired memory retention	NeuN immunohistochemistry	Lower NeuN expression in cortical areas adjacent to the mENT.
Klein et al., 2019	Rat/Lon-Evans/ Male	12 weeks/ 250-280 g.	MWM	25 days	ReRh	Impaired memory retention	Golgi staining c-Fos immunohistochemistry	ReRh lesion prevents increases of mushroom spines in the CA1 and ACC. Lower ACC and PL c-Fos expression

Lopez et al., 2009	Rat/ Long-Evans/ Male	12 weeks / -	MWM	25 days	ANT ILN/NT	Impaired memory retention	AChE histochemistry	Altered cholinergic innervation of ventral HC following an ANT lesion
Loureiro et al., 2012	Rat/Long-Evans/ Male	12 weeks/ 250-300 g.	MWM	25 days	Excitotoxic fiber-sparing NMDA in ReRh	Impaired memory retention	-	-
Martin et al., 2005	Rat/ Lister-hooded/ Male	- / -	MWM	56 days	HC	Impaired memory retention	-	-
Winocur et al., 2013	Rat/Long-Evans/ Male	5 months	MWM	28 days	HC	Impaired memory retention	-	-

In the Age/Weight column, when the authors expressed age in months, we changed it to weeks. In the Remoteness column, when authors expressed it in weeks or months, we changed it to days.

Table 4. Pharmacological treatment/chemical agent studies

Reference Author, Year	Animal/ Strain/ Sex	Age/ Weight	Behavioral task	Remoteness	Pharmacological treatment/ chemical agent	Brief behavioral results	Brain analysis	Brief brain results
Ampuero et al., 2013	Rat / Sprague-Dawley/ Male	- / 250-300 g	MWM	17 days	Fluoxetine	Impaired memory retention. It was reversed after 6 weeks of cessation.	-	-
Fremouw et al., 2012	Mice/ C57BL/ 6J/ Male	8 weeks / -	MWM	30 days	Ara-C	Conserved memory retention	-	-
Li et al., 2008	Rat / Sprague-Dawley/ Male	-/ 200-250 g	MWM	30 days	Ara-C	Impaired memory retention	Golgi staining	Altered ACC apical dendrites
Tong et al., 2015	Rat / Sprague-Dawley/ Male	- / 200-250 g	MWM	30 days	Formaldehyde	Impaired memory retention	Western Blot in HC	Excessive formaldehyde leads to reduced DNMT

In the Age/Weight column, when the authors expressed age in months, we changed it to weeks. In the Remoteness column, when authors expressed it in weeks or months, we changed it to days.

Table 5. Genetic manipulation studies

Reference Author, Year	Animal/ Strain/ Sex	Age/ Weight	Behavioral task	Remoteness	KO significance	Brief behavioral results	Brain analysis	Brief brain results
Maehata et al., 2020	Mice/ Cyp7b1 KO/ Male	11-18 weeks/ -	MWM	14 days	Deletion of exon 6 of the Cyp7b1 gene eliminates CYP7B1 protein and its enzyme activity completely	Impaired memory retention	Golgi staining	Spine density reduction in the HC
Kim et al., 2018	Mice/ CTCF cKO or HT CTCF/ Male and Female	12-15 weeks/ -	MWM	27 days	Loss of excitatory neurons (CTCF cKO)/ loss of inhibitory neurons (CTCF HT) in the HC	Impaired memory retention in CTCF cKO and weaker behavioral impairments in CTCF HT	Electrophysiology recordings RNA sequencing	L-LTP disruption in ACC and altered cortical gene expression in CTCF cKO
Tanaka et al., 2008	Mice/ ΔmtDNA in mito- mice/ Male	- /-	Barnes Maze	36 days	Excess of 50% loads of ΔmtDNA,	Impaired memory retention	Complex IV (COX) activity and Western blot	Mitochondrial respiration deficiencies and reduced α-CaMKII in visual cortex and DG.
White et al., 2008	Mice/ CaV1.2c KO/ Male and Female	Male/ female	MWM	30 days	L-type voltage-gated calcium channels failure	Impaired memory retention	-	-

In the Age/Weight column, when the authors expressed age in months, we changed it to weeks. In the Remoteness column, when the authors expressed it in weeks or months, we changed it to days.