Behavioural Brain Research 203 (2009) 151–164

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Review

Spatial memory: Theoretical basis and comparative review on experimental methods in rodents

Carrillo-Mora Paul[a,*], Giordano Magda[b], Santamaría Abel[a]

[a] Laboratorio de Aminoácidos Excitadores, Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez, Mexico City 14269, Mexico
[b] Laboratorio de Plasticidad, Departmento de Neurobiología Conductual y Cognitiva, Instituto de Neurobiología, UNAM-Campus Juriquilla, Mexico

ARTICLE INFO

Article history:
Received 12 May 2009
Accepted 17 May 2009
Available online 23 May 2009

Keywords:
Spatial working memory
Spatial reference memory
Morris maze
Radial maze
Barnes maze

ABSTRACT

The assessment of learning and memory in animal models has been widely employed in scientific research for a long time. Among these models, those representing diseases with primary processes of affected memory – such as amnesia, dementia, brain aging, etc. – studies dealing with the toxic effects of specific drugs, and other exploring neurodevelopment, trauma, epilepsy and neuropsychiatric disorders, are often called on to employ these tools. There is a diversity of experimental methods assessing animal learning and memory skills. Overall, mazes are the devices mostly used today to test memory in rodents; there are several types of them, but their real usefulness, advantages and applications remain to be fully established and depend on the particular variant selected by the experimenter. The aims of the present article are first, to briefly review the accumulated knowledge in regard to spatial memory tasks; second, to bring the reader information on the different types of rodent mazes available to test spatial memory; and third, to elucidate the usefulness and limitations of each of these devices.

Contents

* Corresponding author at: Laboratorio de Aminoácidos Excitadores, Instituto Nacional de Neurología y Neurocirugía M.V.S., Insurgentes Sur No. 3877, México D.F. 14269, Mexico. Tel.: +5255 5606 3822x2013.
E-mail address: neuropolaco@yahoo.com.mx (C.-M. Paul).

0166-4328/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.bbr.2009.05.022

1. Memory

Memory is not a static, isolated or single brain function; memory can be best described as a complex network of different interrelated functions working together to manage information. For this reason, it would be more appropriate to define it in terms of a *memory system*. Thus, a memory system could be defined as a brain function whose purpose is to classify, encode, store and recover a wide diversity of information relevant for the subject. Interestingly, the taxonomy of these memory systems has evolved in parallel to our knowledge of the anatomical and physiological basis of memory [105]. Some of these classification systems are based only on clinical observations, while others combine experimental and neuropsychological evidence. In general terms, memory can be classified in two major groups: Declarative, referent to information that is conventionally transmitted or expressed; and procedural or non-declarative, representing the information about motor or perceptual skills that may not be orally transmitted [113,123,125] (Table 1). Another frequent distinction is made between short- and long-term memory. Spatial memory cannot be strictly assigned to one of these classification subsystems; it is, indeed, part of several of these categories (as we will discuss later), since it involves aspects of non-declarative memory (procedural), declarative (semantic and episodic memories), as well as of both short- and long-term memory [89].

1.1. Spatial memory

Spatial cognition is related to the answer for the general question "where?" and "where" can mean several different things for living organisms: "Where am I?", "Where does it hurt?", "Where are my limbs located?", "Where is my home?", "Where are my keys?", etc. Spatial cognition is obtained through exploratory behaviour, an instinctive and widely preserved behaviour in all animal species, including man. This type of behaviour can be considered an expression of natural curiosity or may represent the need to acquire information when subjects face a new environment, and new stimuli [14,120]. Thus, spatial memory can be defined as that brain function responsible for recognizing, codifying, storing and recovering spatial information about the arrangement of objects or specific routes [66]. Although spatial memory is present in most animal species [13], spatial memory representations may be quite different in humans and other animals. Since humans are able to use symbolic spatial representations – maps, diagrams, and oral or written information – direct experience is not a necessary requirement for spatial learning [85,127].

The concept of space has at least two dimensions, the personal-corporal space—which includes the location of corporal stimuli, the knowledge of the position of limbs, etc., and the external space. The information obtained from these sources is organized and used by two kinds of processes: egocentric and allocentric strategies [23,105].

1.1.1. Egocentric strategy

It is based on the information provided by bodily cues, and therefore it is independent of spatial cues. When using this strategy, the subject functions as its own central point of reference, and so, all other object positions are defined in direct relation to its position in space; i.e., when the traditional clockwise scheme is used to define spatial positions, or when the conventional directions (left, right, forward or backward) are employed [68,95].

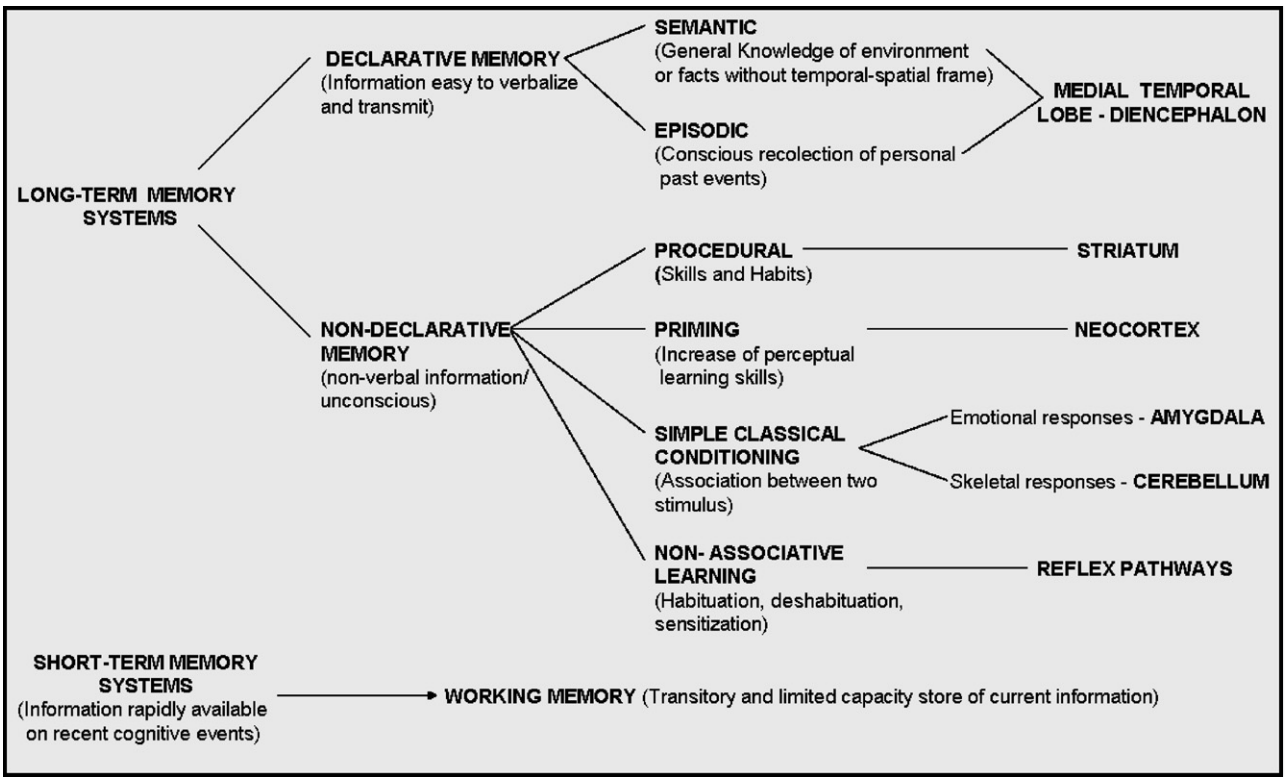
1.1.2. Allocentric strategy

It depends on spatial cues. When using this strategy the subject memorizes the target location in relation to the spatial position of the environmental reference landmarks [13], meaning that it is based on a spatial representation. The location of a particular target is established through a system of coordinates that are independent of the observer; this system often uses distant or closer points of reference; i.e., latitude and longitude used by humans to locate places in a map [68,95].

In humans, there is evidence supporting a difference between the memory process required for short routes or whole pathways (requiring sequential spatial processing) and the memory process required for spatial localization of objects. The latter can also be divided into an exact/metric object processing system, that endows every object with an exact system of coordinates; and the memory for relationships between objects and their characteristics (memory for visual recognition) [66]. Moreover, there is experimental evidence indicating a difference between a short-term processing of active memory (spatial working memory) and a long-term storage of spatial locations, also known as spatial reference memory [90]. The *spatial working memory* is a system that allows temporal storage of a limited amount of spatial information, and keeps it available for immediate access. Alternatively, this information may be used for other cognitive processes. Further evidence supports the dissociation between simple visual working memory (visual recall of objects, figures, etc., but not information about their spatial relationships) and spatial association memory. Interestingly, neuronal networks at cortical–occipital, parietal–dorsal, and frontal areas, have been involved in spatial working memory [3].

On the other hand, the *spatial reference memory* system was first proposed by Olton in 1979 [95] to designate the type of memory process involved in obtaining spatial information over various trials. In contrast to spatial working memory, spatial reference memory exhibits more capacity, duration and resistance to interference [99]. Typically, spatial memory is conceptualized as a subtype of episodic memory [95] because it stores information within a spatial–temporal frame. In this regard, some authors have suggested the need to distinguish between two main types of spatial memory: (1) the one consisting of a *detailed* perceptual–spatial representation of the experienced environments (clearly corresponding to episodic or autobiographic memory); (2) the one consisting of *schematic* topographic representations (corresponding to semantic memory) [89]. Thus, a *detailed* spatial memory map would contain vivid and integral information for routes or exits; it would include a wide variety of visual components: objects, colours, places, features and further relationships among them. Altogether, these components would allow the subject to recall and vividly re-experience the spatial scenario. In turn, the *schematic* representation memory would contain only the information needed to guide the animal through a given environment, with particular emphasis on those visual elements necessary for successful navigation [85,89]. However, it is important to note that, when using the nomenclature to denote either semantic or episodic memory to subdivide spatial memory, it becomes particularly difficult to apply these terms to non-human subjects because the definition of these terms implies qualities inherent to human subjects, for instance that information can be expressed orally, and conscious recollection of experience, among others. Therefore, it is not easy to know if rodents, for instance, are capable of using a "semantic" memory system, and it becomes more difficult if we define this specific memory only in terms of "general knowledge", or "general information" lacking a defined temporal–spatial frame. Similarly, episodic memory has been difficult to define and experimentally characterize in animals. Indeed, for some research groups, a mnemonic representation of a particular event, what has been called "time traveling" is only inherent to humans [124]. Recently, however, some researchers have been using behavioural paradigms that require the animals to recall and associate simultaneously visual, temporal and spatial information of a given event. The results of these experiments have been proposed as indirect evidence of a memory system

Table 1
Classification of memory systems (based on Squire [113], Tulving [123] and Tulving & Schacter [125]).



comparable to human episodic memory. Nonetheless, at this point, all these paradigms have explored only the components of short-term and working memories [35,36], emphasizing the need for more detailed studies.

In 1948, Edward Tolman proposed for the first time that the process of solving mazes by animals under experimentation could not be explained merely by the systematic utilization of associations between external stimuli and behavioural responses [121]. This was suggested on the basis that, after a certain period of training, animals were capable to infer shortcuts, or even to establish true redundant strategies to solve the mazes. Therefore, Tolman concluded that these rodents were able to create real global representations of the external environment in order to locate the goal within the maze, a strategy that he named *cognitive maps* [121]. This hypothesis initially received limited support, due to the fact that there was not enough evidence to confirm it. The original description by O'Keefe and Dostrovsky [94], of "place cells" in the hippocampus provided immediate support to this hypothesis, thus reopening the concept of *cognitive maps*. These hippocampal "place cells" can be detected by means of extracellular *in vivo* recordings of the main neurons from CA1 and CA3 regions in a freely moving animal. In this regard, there is evidence correlating spatial location errors with alterations in the "in-place" discharge pattern of these neurons. In addition, further studies have demonstrated the relationship between these discharge patterns with the spatial conformation of environmental objects, or with the dimensions of the exploration field [40].

In general terms, the mesial area of the temporal lobe is needed for acquisition of spatial memory, either detailed or schematic. However, there is no agreement on the structures required for retention and recovery of these varieties of spatial information [90]. Neuropsychological evidence has demonstrated that temporal lobe lesions can produce what is typically known as *topographic disorientation*; this alteration is described as a limitation of a subject's ability to move in a given spatial frame due to an alteration in the capacity to perceive, in a precise manner, the spatial relationships and the distances between different points of reference [54,105]. Experimental evidence points to the hippocampus as the fundamental structure in charge of this task [93]; some clinical studies suggest that in humans the most relevant structure for this purpose is the right parahippocampal gyrus [92]. Moreover, most of the studies so far have demonstrated that lesions of the temporal lobe are responsible for alterations in allocentric orientation, while the egocentric orientation is preserved. On the other hand, disorientation and topographic amnesia have been documented after medial and posterior parietal lesions. In these patients the impairment in egocentric orientation seems to predominate [138].

It has been recently proposed that egocentric and allocentric strategies are indeed working in parallel, and that the prevalence of one over the other will depend on specific factors inherent to the spatial task at hand; i.e., the number of movements between presentation and retrieval, the number and size of objects to be remembered, the size and spatial structure of the environment, and the duration of the previous experience in the same environment [23].

2. Experimental evaluation of spatial memory in rodents

2.1. Mazes

Mazes are the experimental devices more often employed for global evaluation of spatial memory in rodents, although not the only ones used for this purpose. In general terms, in these devices the animals are food- or water-deprived since food and water are used as behavioural reinforcers. These devices have been employed since the beginning of the past century [133,137]. The first mazes used for evaluation of animal behaviour were, indeed, reduced adaptations of mazes built in the 17th century, such as the one at

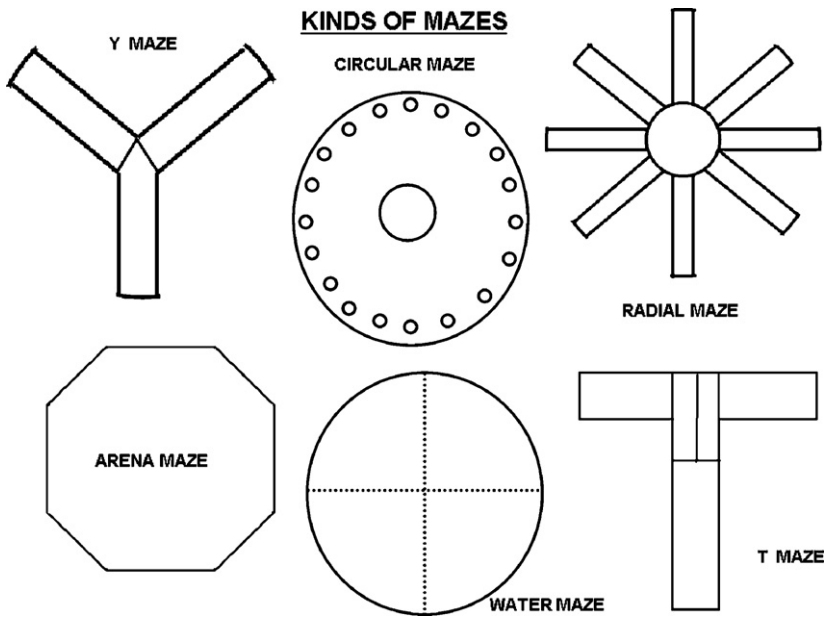


Fig. 1. Different types of mazes for the evaluation of spatial memory (based on Hodges [53]).

Hampton Court's, in the London area. Other mazes have been developed since then, either open with multiple route options (Barnes, Morris, Oasis, Circular, etc.), open with restricted options – such as radial mazes – [97], "T" or "Y" shapes, or with restricted but serial and complex options (serial "T" maze by Stone, Biel serial T water maze, Cincinnati maze, etc.) [134] (see Fig. 1).

The fundamental assumption for the use of these mazes is based on the behavioural principle that animals should learn and remember the location that provides them with safety, food, water or some other reward by means of visual–spatial signals. However, since what is being evaluated is a complex animal behaviour, it is impossible to exclude other processes, either cognitive (such as associative learning or conditioning, non-spatial short and long-term memory, temporal memory, conditional discrimination, anxiety, etc.) or non-cognitive (balance, propioception, stress, reflex activities, etc.) [11,30]. Therefore, several research groups have made adaptations to the mazes and evaluation protocols in order to accurately assess particular behavioural aspects using the same device (for instance spatial reference memory, and spatial working memory) [16,22,37,38]. Even those devices designed to evaluate only spatial memory have particular behavioural requirements, from spontaneous exploratory behaviour to complex action sequences. When training the animals to solve the maze, one may use positive reinforcers such as food, water, sweetened water, refuge or the opportunity to explore new objects; or negative reinforcers such as water immersion, intense light, wind, a loud noise, among others.

Although similar procedures are used in most mazes, it is a mistake to assume that all of them are exploring the same cognitive process. For instance, how much does visual–spatial information, other kinds of spatial information (like sounds or odors), or non-spatial information, is responsible for guiding behaviour? The answer varies depending on the device. There are a considerable number of variables that are not always under control or appropriately standardized to attain comparable results in different studies (see Table 2).

Despite the considerable diversity of mazes developed to evaluate spatial memory, those more commonly used are the Morris water maze, the radial maze designed by Olton and Samuelson, and the Barnes' circular maze [37,53]. In this review, we will focus our attention on the variants to these mazes, as well as their applications, advantages and limitations.

2.2. Spontaneous alternation behavioural tests

Traditionally, one of the simplest procedures to study spatial learning and memory has been the spontaneous alternation behaviour. This kind of behaviour is considered, in general terms, as a parameter of exploratory behaviour in novel environments. According to some reports, alternation behaviour has been described in rats since postnatal day 30, and is inversely correlated with age [72]. The test is performed in devices either in "T" or "Y" shapes, where the animals are allowed to freely explore each arm of the device; then, the number and order of visits to the arms is recorded (see Fig. 2). The principle of alternation is based on the fact that the animal under observation will prefer to visit the less recently visited arm, thus implicating that it will need to recall which was the last arm visited [120]. These tests can be performed in two manners: (1) free test; and (2) forced test. In the latter, one of the arms of the device is blocked in order to favour alternation behaviour [11,31,72]; alternatively a positive reinforcer may be placed inside of the arms so as to reward alternation behaviour. Moreover, by increasing the interval between tests it is possible to conduct studies designed to evaluate spatial working memory in which a decrease in alternation behaviour can be observed [34].

The original "T" or "Y" mazes required constant handling of the animals, inducing stressful responses in the animals (i.e., mice often display panic responses such as temporal paralysis) often affecting the results of the test. For this reason, an alternative device

Table 2
Variables influencing animal performance in different mazes.

Type of maze
Selected protocol
Species and animal strain
Animal gender
Nutritional status of the animals
Potential infections
Stress
Time and schedule of the study
Environmental cues
Animal age
Drugs used
Stimuli driving behaviour: appetitive vs. aversive

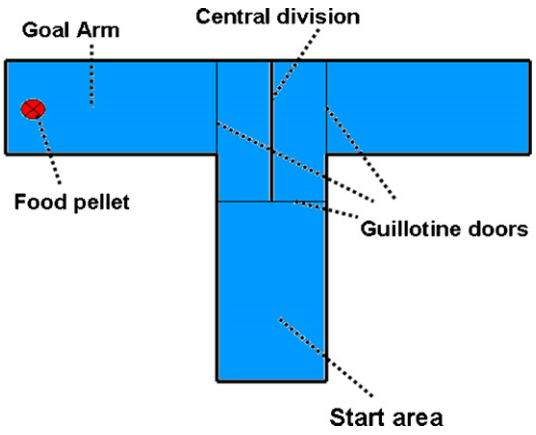


Fig. 2. Schematic representation of the "T" maze (based on Deacon and Rawlins [31]).

called "continuous alternation task" – in which removable doors are added to the entrance of each arm in order to block the access to the unselected arm – has been built. Through this simple modification excessive manipulation is avoided and stress is decreased [47,112]. More recently, aquatic versions of "T" mazes have been adapted (some of them containing a mechanism of continuous alternation) in order to induce more consistent behavioural responses in rodents [32,76].

On the other hand, elevated "T" mazes (50 cm above the ground) are often used as anxiety models to evaluate stress responses in rats and mice [122]. "T" mazes, and their variants "Y" mazes, present the advantage of being simple devices useful for the assessment of spatial working memory, and also providing highly reproducible results. As a bonus, they do not require automated video-recording systems. In contrast, their major disadvantage is restricting the selection options for the animal, thereby significantly increasing the possibilities of success and/or the use of alternative strategies for solving the maze, such as olfactory cues.

There are other more complex models of "T" mazes, these were developed by Stone in 1929 in order to evaluate age-related memory alterations in rodents. In these mazes, the animal continuously faces the option of choosing between two possible routes to reach an exit rewarded with food (see Fig. 3). Paradoxically, in his original work, Stone did not find any change in the rate of maximum learning in relation to age when using the device [115]. Later on, opposite findings were reported where significant alterations in performance in relation to age were found [48,132]. Presently, serial mazes are often employed in studies exploring aging processes, as well as in pharmacological, toxicological and neurodevelopmental models; however, their use is still moderate, and this is probably why their potential advantages are not well known [59,60].

It should be noted that this paradigm has been used to evaluate the behavioural effects of lesions of the hippocampus, thalamus, neocortical areas, and basal ganglia, and it has also demonstrated to be accurate for the valoration of the behavioural changes occurring after pharmacological manipulation with anticholinegic, dopaminergic and serotonergic drugs [11,72].

2.3. Radial maze

The radial maze is the prototype of a "multiple-solution problem" task. The radial maze was developed by Olton and Samuelson in 1976 [97], and was originally designed to evaluate spatial working memory in rats. The original device was conceived as eight linear routes or arms confluent in the center as the rays of a wheel (see Fig. 4). At the beginning of the paradigm known as win-shift, a pellet of food is placed at the end of each arm; thereafter, the animal

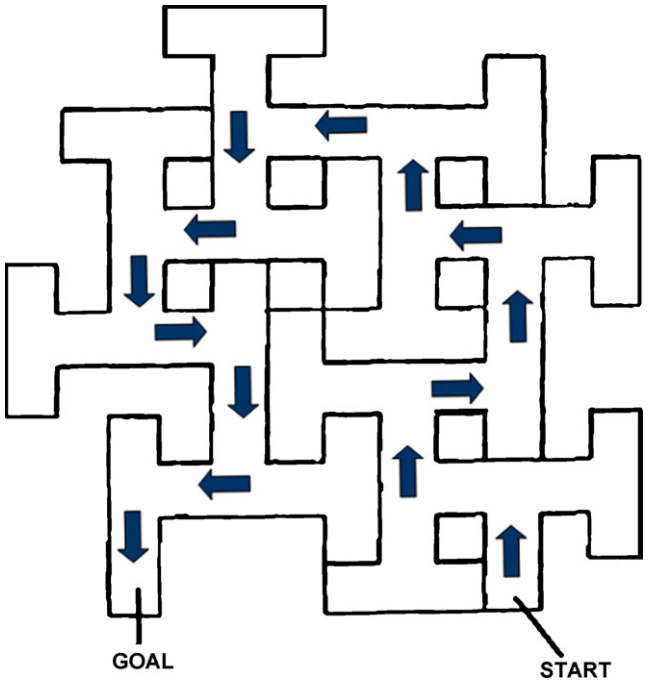


Fig. 3. General schematic representation of the complex maze, or serial in "T" maze (based on Ingram [60]).

subjected to food-deprivation is placed on the centre of the maze and allowed to choose freely those arms containing food until the eight pellets have been collected. The optimum strategy implies a minimum number of visits to empty arms, or visiting a given arm only once. The device does not require serial responses, algorithms or special cues for the rat to choose the right arms with pellets [97]. Under these conditions, rats have been found to perform the maze test efficiently, but immediately some limitations of the device were noticed, such as the fact that, given the reduced number of options or routes to choose, the performance was unconveniently optimal from the first trials. For this reason, nine arms were added to the device (total 17), a strategy that immediately produced an increase in the number of errors. A second modification consisted of simplifying the methods for spatial orientation inside the maze through the use of visual codes or cues to decrease the amount

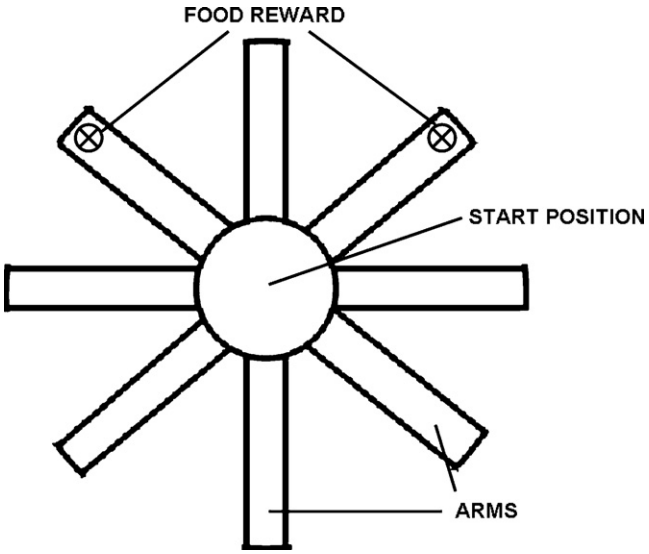


Fig. 4. Standard 8-arm radial maze.

of information needed to be retained in working memory [95,99]. Different versions of this maze have been adapted by using external visual cues or "spatial cues", where the location of the reward is matched to a particular external cue. These cues consist of different kind of objects (such as chairs, tables, drawings, etc.) or persons. Other versions – also known as non-spatial radial mazes – replace the use of external visual cues by internal cues (different aromatic signals for each arm, or tactile/visual cues). There are also aquatic versions of this maze; different strains of mice have been tested and have shown optimum learning and memory performances. This type of maze avoids the need for gating devices, besides decreasing significantly the use of olfactory cues [58].

Two types of memory are believed to participate in solving a radial maze: a retrospective memory that informs the animal about the arms that have already been visited, and a prospective memory that anticipates the action for the election of new options [120]. In their original description, Olton and Samuelson suggested that, for solving the maze, the animals build a mental "list" of places already visited in order to choose only the places that have not been visited yet [97]; however, shortly thereafter, experiments performed by Susuki and coworkers [117], in which the position of external visual cues was modified during the tests, showed that the performance of the animals was significantly affected, thus suggesting that the animal uses the information provided by the surrounding environment to recognize the arms previously visited. This was later confirmed by Mazmanian and Roberts through experiments in which the global vision of the environment was progressively reduced [81]; they observed an improvement in performance related to the increase in visibility. These findings contradicted the concept of the "mental list" proposed by Olton. In spite of this evidence, and based on a series of experiments, Brown [18] proposed that when approaching an arm's entrance ("microchoices"), and before choosing the correct arm ("macrochoices"), the animal can be considered to be making a decision independent of the global environment. This particular issue, whether the animal stores a global view of the environment or if it follows individual cues to solve this type of maze, is still a matter of debate today [120].

This maze has some important limitations that have resulted in modifications. These are:

(1) The animal in the maze can use an exploratory strategy without the need for spatial references. In other words, the animal may first visit the adjacent arms to those visited previously, and may continue doing so, either in a clockwise or anti-clockwise direction, thus increasing the probability of success. The use of this strategy can be reduced by adding mobile doors to the arms, thereby confining the animal inside an arm for a short time before it can choose the next option, thus preventing serial access to the arms [38,98]. Despite this modification, one must consider that the maze possesses pre-established and static routes (arms) through which the search for food will take place, therefore the animal does not need to remember a specific route in order to reach the target in the shortest time possible, as it occurs with the water maze. On the other hand, it has been proposed that the radial position of the arms in regular angles can favour the election of a given arm, thereby facilitating the use of motor strategies instead of cognitive strategies. For this reason, some research groups have used radial mazes with arms in irregular positions, forming different angles with the core of the device, which have decreased the precision in rodents' performance [49].
(2) Animals may use other strategies for finding food in addition to spatial orientation, and this may considerably affect the results. For instance, olfactory cues can be used to detect those arms already visited, thereby modifying the behaviour of the animals [136]. In order to solve this problem, some research groups have used the "aromatic saturation" strategy, allowing the animals to freely explore the maze before the test without any food pellets with the aim to saturate the maze with aromatic cues [107]. Other strategies involve cleaning the device or/and rotating the arms while preserving the location of the food reward [39].
(3) The influence of the learning processes is evident along the trials, since the number of successful attempts increases with time. Spatial working memory might then turn itself into spatial long-term memory. If the observer ignores this possibility, the results can be easily misinterpreted [98].
(4) In order to be trained on this spatial task, animals may be food or water deprived. Animals can be maintained at a certain body weight, to prevent them from reaching satiety. Alternatively, they can be deprived for a certain number of hours; it has been shown that the speed of learning might be related with the time of food-deprivation. In this case, if food-deprivation is not sufficient, then animals do not respond well, forcing the learning process to be delayed [53]. In this regard, some authors have reported that feeding animals prior to some specific challenging tasks – such as "delayed matching-to-position task" – increases the number of errors during the test. Briefly, the task consists of a first phase in which the subject is free to select among different arms until the baited arm is found. Shortly thereafter, the animal is placed in a neutral location for a variable interval of time (delay), to further be challenged to choose the position previously selected (match) [70].

Food or water-deprivation has to be planned according to the recommended limits for the species or strain chosen. In addition, at the end of the test, animals need some recovery time during which deprivation should be slowly reverted, depending on the duration of the study [56]. Similarly, some drugs (cholinergic blockers, amphetamines, etc.) may induce anorectic episodes, also affecting regular behaviour in the maze [12], and this should be taken into consideration when designing a protocol.

Aquatic of the radial maze have been developed, in which the stimulus driving behaviour is no longer linked to appetitive (food or water intake), but to aversive (water immersion) stimuli. In these devices, the animal must locate an escape platform hidden in some quadrant of the maze. The first versions required a complex automated-mechanical system [22], but recently the devices have been improved and simplified [57]. Moreover, some alternative radial mazes have been developed in which the aversive stimulus is represented by open space and high luminosity; their escape places are located at the end of some arms, eliminating in this manner the need for food-deprivation [102].
(5) Some studies indicate that radial devices are not sensitive enough to spot differences between animal strains or genders [110,130,131]; however, it is necessary to consider that one report suggested that, depending on the type of memory being studied and the protocol used, this device might be useful to detect differences, specially for rats [71].
(6) Studies comparing the radial and Morris mazes have shown that the number of trials required to achieve acceptable performance levels in some tasks – such as "spatial delayed match-to-position task" in the radial maze – are often twice as much as those required for the Morris maze, thus the acquisition process is slower [100]. These differences have been explained in part by the kind of stimuli used in each maze: appetitive in the radial maze vs. aversive in the aquatic maze. Important performance differences can be also observed during the test phase, and have been attributed to the fact that in contrast to the aquatic maze, animals in the radial maze may use a spontaneous alternation strategy. Moreover, in the radial maze, the performed task has often been shown to be more sensitive to

the deleterious effects of scopolamine suggesting a differential neurochemical substrate [100].

In general terms, the advantages that the various versions of the radial maze offer are:

- The training protocol and data interpretation of the basic version is simple.
- Radial mazes can be adapted to meet different experimental needs [2,18,22,38,39,49,53,58,71,80,96,97].
- The scientific literature validating and supporting its use in mice and rats is considerable, since it has been widely employed to test the effects of an important number of drugs, including anticholinegic agents, cannabinoids, dopaminergic agents, dopaminergic blockers, barbiturics, glutamatergic agonists, endogenous modulators (kynurenic acid), among others [2,12,18,22,24,38,57,58,64,71,94,97,102,107,110,114,130,131,136].
- These mazes can be used for the evaluation of spatial working memory and for spatial reference memory too [39,53].
- They have the advantage of generating only a moderate level of stress in the animals during testing [53].

2.4. Morris water maze

One of the methods most often used for the evaluation of spatial learning and memory, together with the radial maze, is the Morris water maze. This device was invented by Richard G.M. Morris in 1981 as an alternative for the radial maze. It was developed to evaluate the role of specific visual cues as proximal and distal references for spatial memory in rats [88].

3. Design and general procedure

This device consists of a round pool filled with opaque water. Opacity can be obtained with different substances: powder milk, white paint, titanium dioxide, among others. Inside the pool there is an escape platform slightly hidden (2–3 cm) below the water level (see Fig. 5). The protocol for the study of simple reference spatial memory includes dividing the pool into four equal quadrants (some include two extra concentric-radial divisions). Since water immersion represents an aversive stimulus training starts with a period of habituation during which the animals are immersed in the water and allowed to swim for a few minutes without a platform. It must be noted that not all researchers agree on the need for a habituation period [2]. Later on, a platform is placed in a fixed position in one of the sectors (quadrants) and the animals go through a period

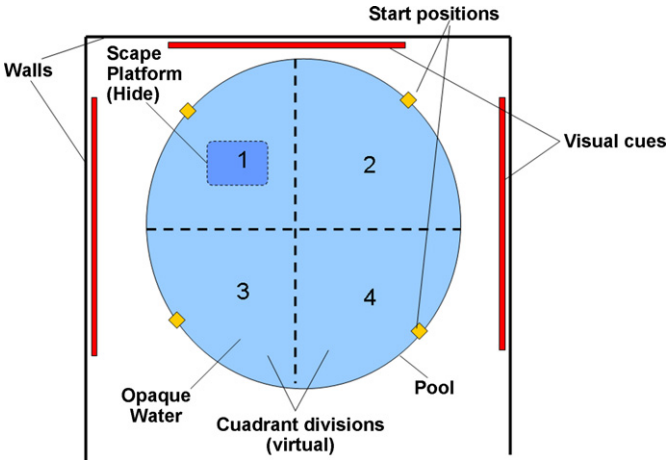


Fig. 5. Schematic representation of the Morris water maze.

of acquisition. During this period they are given a variable number of daily trials to find the platform. At the beginning of each trial animals are placed on different starting positions. The time it takes the animal to find the escape platform (latency) is recorded. The rat is allowed to stay on the platform for about 30–60 s to favour place learning. Trials can be video recorded, which is highly recommended, to document the trajectories that animals followed. After training, memory is evaluated in one additional trial [87], during this test trial, the platform may be removed, and visual cues can also be removed, to try and tease out which information is being used by the animal to find the platform.

In its original work, Morris demonstrated that rats do not require near visual cues to locate the hidden platform. The animals were able to find the platform merely on the basis of visual cues external to the device [88]. Shortly thereafter, the same author described adaptations for improving the maze, such as tracking devices and automated-electronic recording, besides changes in the protocol to evaluate short-term memory using "matching to sample" tests, and new techniques to evaluate non-spatial strategies through double escape platforms [84]. In this regard, Brandeis and coworkers [16], proposed that the animals can use three different strategies to locate the escape platform: (1) A praxic strategy, when the animal learns the sequence of movements needed to reach the platform; (2) A taxic strategy, when the animal uses cues or visual proximal guides to reach the platform; and (3) A spatial strategy, when the animal reaches the target using information about the spatial location of the platform according to the spatial configuration of distal visual cues.

Typically, the Morris water maze is considered a device that explores and stimulates the use of spatial strategies based on environmental visual cues (allocentric). However, it can also be adapted in order to explore strategies based on cues provided by the subject itself (egocentric). For this purpose, animals can be tested in darkness, the platform can be hidden, or the maze can be surrounded by a curtain so as to prevent the use of distal spatial cues [86]. It has been proposed that overtraining can induce the expression of egocentric strategies, but so far the results obtained are not conclusive [65].

On the other hand, some recent reports have suggested that rodents predominantly use a directional – more than spatial – strategy to solve a conventional Morris water maze, thereby limiting its consideration as the optimum paradigm for spatial navigation [50].

4. Methodological variables

There are multiple methodological variables that need to be considered when using the water maze, and it is now becoming clear how these variables affect the performance of the animals [39]. One variable is the dimensions of the pool, for rats the optimal diameter is between 1.30 and 2 m (according to the original description by Morris). For mice, diameters can oscillate between 75 and 150 cm. Changes in diameter have been found to affect performance in some studies [129], but not in others [128], this difference may be due to the particular mouse strain employed [128]. Another variable which has been widely discussed in the literature is the presence [88] or absence [2] of previous habituation to the maze. Some groups suggest that the stimulus triggering escape behaviour is water immersion, so they are against habituation. In contrast, those in favour mention that habituation decreases the stress levels in the animals, and stimulates exploratory behaviour [37].

Additional sources of variation are the number of starting positions and their position in the maze, their number may vary from four (strictly related with the four quadrants of the pool) to eight or more. With regard to measures of performance, latency to find the platform is the simplest and more often used measure; it is also possible to obtain other measures by using automated recording

devices, such as distance traveled, swimming velocity, time spent in each quadrant, the graphic representation of the trajectories, and others. In this regard, a recent study explored several criteria searching for the most sensitive measure of water maze test performance. The study included measures like the percent time in a virtual quadrant or zone, the mean proximity to a former location of the platform, and the number of platform crossings. The authors found that mean proximity to a former location of the platform is the most sensitive measure to assess water maze performance [78].

Other important variables include the number of trials per day, the number of days of training, the duration of each trial, as well as the time spent on the platform, these variables often vary from one study to the next. It has been recommended to use an average of 4–6 trials per day for 5–10 days, or until latencies to find the platform become homogeneous; every trial should last 60–180 s, considering 15–60 s on the platform. In this regard, in a series of studies using the Morris water maze, it was demonstrated that spatial retention lasted only 4 h when animals were trained for 10 trials in a single day. Retention capacity was significantly improved when training sessions were spaced by 5 min and 2 h intervals [15]. Interestingly, the same study showed that, when intervals were increased to 6 and 24 h, there was no further improvement in the retention capacity. Other important variables are the quality and quantity of the visual cues used. It is still unclear how many cues or which shape should be employed. Some reports suggest that simplifying visual cues (few in number and simple forms) improves spatial learning [73]. However, to our knowledge, there are no studies that have systematically studied the effect of quality and quantity of visual cues on spatial learning in the Morris water maze.

According to several studies, the precision exhibited by animals in finding the platform is directly related to spatial navigation abilities, suggesting that animals build cognitive maps with the help of distal visual cues [6]. In contrast, on the basis of some studies performed by Sutherland et al. [118], it has been proposed that the spatial navigation routes within the Morris water maze do not imply real "spatial mapping", but may rely on simpler strategies, such as an active re-orientation process based on "familiar" scenes more than specific visual cues [118]. This hypothesis is supported by studies using low levels of illumination during each phase of the task, that have shown that visual information is not needed at the beginning or at the end of the task (platform stay), but only during the search for the platform [1].

5. Factors influencing animal performance in the Morris water maze

It has been demonstrated that body weight, physical condition and age influence swimming velocity [37]. Several other studies have shown that male animals perform better when compared with females, a fact attributable not only to physical strength but to differences in spatial navigation abilities [16,111]. One study has shown that these differences disappear when animals are older than 6 months of age, suggesting that the differences reported for younger animals reflect differential maturation between genders [20]. Others have suggested that this difference between genders can disappear depending on the phase of the hormonal cycle during which females are tested. Indeed, they have proposed that low levels of estrogen significantly improve spatial performance, and when levels are high, spatial performance decreases [27]. Studies in males have shown circadian fluctuations on spatial performance that seem to be related to significant variations in blood testosterone levels [62,67]. In support of these observations, female subjects after testosterone administration have shown improvements in spatial skills [52]. Thus, gonadal hormones appear to affect spatial performance in the Morris water maze.

The Morris water maze has also allowed the identification of performance differences among species, strains or even transgenic animals, allowing a more detailed study of the factors influencing the learning processes, but making it harder to compare the results of different studies [75,76,140].

Some behavioural features are present more frequently in some species than in others; i.e. thigmotaxis (the tendency to swim in circles following the pool wall) is more frequent in mice than rats, and represents a source of errors in performance. In general the performance in this test is better for rats than mice, possibly due to the superior swimming skills of rats. Indeed, it has been found that, when comparing rats and mice in non-aquatic paradigms, there were no differences in spatial skills [139]. Performance differences can be also attributed to the differences in susceptibility to stress: mice have better performances in tests not involving aversive or stressing stimuli [44]. Although it is hard to make specific recommendations on the basis of these findings, some authors suggest the use of Long-Evans rats, and of the pigmented C57BL/6 mice because they show the best performances in the Morris water maze [74,126].

The age of the animals also plays an important role in this test. It is widely accepted that learning capacity declines with age, which is evidenced in the performance in this maze. With age, swimming skills, exploratory behaviour and locomotion decrease. These motor deficits have to be separated from the cognitive deficits that may be present in order to conclude that structural or functional changes occurring in the aged brain may contribute to the decrement of visual–spatial skills [46].

With regard to the role of stress in this water maze, this test involves an aversive stimulus that can affect the performance of the animals regardless of their cognitive skills. In the strain of hyperactive rats sensitive to stress (Wistar-Kyoto), learning in the Morris water maze is affected or even blocked [55]. Experimental evidence suggests that the autonomic and endocrine mechanisms underlying stressful conditions are responsible for the deleterious effects on learning-memory processes [110]. Thus, the researcher should consider using an additional learning task, or measuring corticosterone levels, to determine if the deficits observed in the Morris water maze, are indeed the result of alterations in learning and memory.

6. Disadvantages

(1) Possibly, one of the greatest disadvantages of this device is the use of an aversive behavioural stimulus (aquatic immersion), accounting for the negative effects of stress. It is, however, possible to decrease stress levels by previously exposing the animals to the testing environment (habituation). If, in addition, less sensitive animal strains are employed, the accuracy of the test will be assured. Nevertheless, stress should never be ignored, even if it is assumed that habituation will reduce it to manageable levels. Furthermore, since stress is one of the triggering factors for behaviour in this device, it should be considered that the use of GABA agonists (currently known to exert anxiolytic or depressive effects in the CNS) could considerably affect learning and memory of the animals [84]. Of further consideration is the issue that, when cognitive alterations are generated in the animals under observation, this fact will probably produce longer swimming periods accompanied by disorientation, which in turn will indubitably trigger considerable more stress, thus affecting the performance. In comparative terms, both radial and circular Barnes mazes generate low levels of stress during the progress of the test [83]; however, to our knowledge, there are no comparative studies in regard to this issue. Nonetheless, the three paradigms have shown to be sensitive to the deleterious effects of augmented corticosterone levels associated with stress [55,109].

(2) Immersion itself may produce some complications for the animals under experimentation if the water of the device is not maintained in optimum conditions (temperature, translucency, etc.). Respiratory, ophthalmic and other infections often appear if the maze is not properly maintained [37].
(3) In addition, animals can use one of the three distinct strategies mentioned above (or their combinations) to escape in the Morris water maze. Consequently, an alteration in performance during the test can indicate a defect in some of the mentioned strategies. In this case, the use of an alternative method to establish which of these strategies is altered should be considered [37].
(4) Some studies have demonstrated that animals most often use a directional strategy, running up from the start position (egocentric). Real spatial navigation (allocentric) can be verified only when during the test phase the spatial stimuli are removed [50].
(5) Although the device is simple to build and adapt, it requires video-recording systems and software for the complete analysis of behavioural parameters, and sometimes this equipment is not easy to acquire for all research groups.

7. Advantages

(1) Learning is faster in this device than in other mazes (radial maze, circular maze) possibly due to the aversive stimulation. In addition, each trial takes only 60–120 s, and accurate curves of acquisition can be obtained in 5 days of training [53].
(2) It permits the accurate and reproducible study of reference memory, spatial working memory and learning [37,39].
(3) It does not require previous preparation (water or food-deprivation), thus limiting the number of days needed to proceed with experimentation.
(4) Eliminates the possibility that animals use "aromatic cues" to orient themselves in the escape search, as it occurs in the "dry" devices (circular and radial maze).
(5) It is supported by a considerable number of reports in the literature validating its use in different animal models of neurocognitive disorders, such as cerebrovascular disease [103,106,142], encephalic trauma [141], alterations of brain development [28], metabolic alterations [135], Alzheimer's disease [45,82], and others [77]. In addition, it has been used with transgenic mice, although caution should be used when interpreting the results in these animals since the genetic manipulation may affect both cognitive and non-cognitive components [139].

7.1. Barnes circular maze

The circular maze was created by Carol Barnes to evaluate spatial learning in a "dry" or non-aquatic device in rats [8]. In this device, the animals are placed on an elevated, open, circular platform. The animal is exposed to intense light, or to a loud noise. In response to this intense stimulation the animal searches for shelter and enters one or more of the 18 holes around the platform (see Fig. 6).

The size and characteristics of the device are as follows: a 92 cm diameter platform—of a variety of colours depending on the animal strain studied (white, grey or black); the platform contains 18–20 holes, each 5 cm in diameter, equally distributed around the platform and separated by 7.5 cm; the device stands 105 cm above the floor. In one or more holes there are escape boxes communicated with the platform through transparent plastic tunnels arranged in such a way that they cannot be seen from the platform. Similar to the Morris water maze the simultaneous use of a video-monitoring system is recommended to obtain automated behavioural recordings.

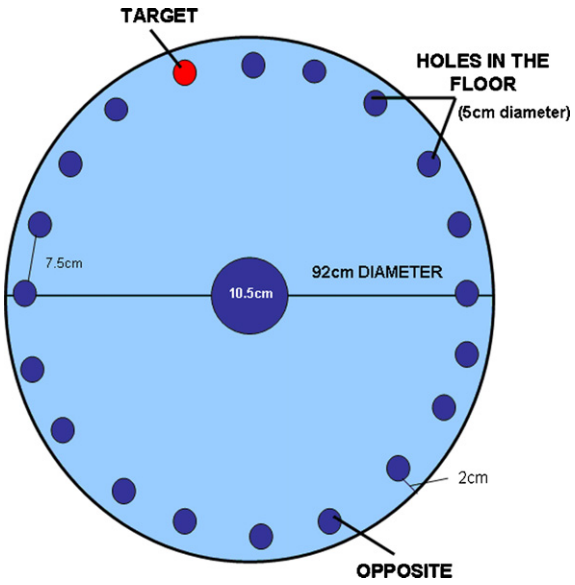


Fig. 6. Schematic representation of the Barnes circular maze (based on Sunyer et al. [116]).

8. General protocol

It is suggested that each trial last 3 min per animal, with an inter-trial interval of 15 min, with four trials per day during the acquisition phase. The first phase, or habituation, consists of placing the animal on the center of the platform and then, turning on the source of noise or other aversive stimulus. Then the animal is gently taken to the escape hole; once in the escape chamber, all stressful stimuli are turned off, and the animal is kept inside for two additional minutes. Before acquisition, it is suggested that the platform be cleaned to eliminate aromatic traces. Also, the platform should be periodically rotated, keeping the location of the escape routes constant. During acquisition, animals are placed on the center of the platform and the stressors are activated for 3 min, the latency to find the escape hole, as well as the number of errors (visits to wrong holes) are recorded. If the animal does not reach the escape hole within 3 min, the experimenter places it at the entrance of the escape hole for 1 min, and then it takes it back to its home-cage. This protocol continues until the number of daily-programmed trials has been completed. The day of testing may start 24 h after the last day of acquisition, or 12 days later, depending on the type of memory being explored [116].

Although the device was originally designed to be used with rats, soon it experienced modifications in order to be used with mice as well. Indeed, the device has been considered appropriate for this species because of its ability to find and escape through small holes [9,102]. In order to be used with mice, the device needed some modifications such as reductions in the size of the platform (69 cm), the number of holes (16) and their diameter (4.45 cm), as well as the addition of a 15 cm tall circular wall by the platform perimeter. The performance of the animals can be improved by adding visual cues, either internal (at perimetral wall) or external (somewhere around the device; i.e., curtains or walls) [103] (see Fig. 7). Various types of aversive stimuli to induce escape behaviour have been used. Among them, sounds (78–108 dB), intense light, food, and air jets are often used [56,90]. Additional modifications for its use with mice have included the relocation of the escape holes (12) at the level of the perimetral wall. In a study specifically dedicated to testing the accuracy of this modification, four different mice strains were analyzed. The authors found that C57BL mice exhibited the best performance of all; in light of these results, this modification has been adopted for studies with this strain [69].

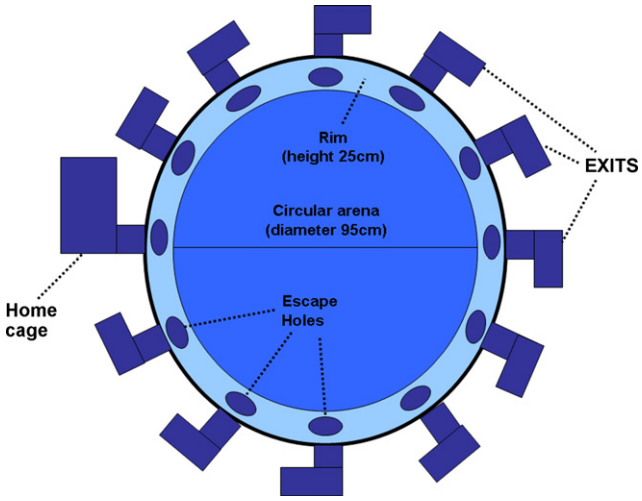


Fig. 7. Schematic representation of the circular (Barnes) maze device adapted for mice (Based on Koopmans et al., [69]).

Some authors still discuss the real usefulness of this device to evaluate spatial strategies in animals. In a comparative study carried out by Brown and Terrinoni [19], the circular maze was tested with three variants: the original version of Barnes, a version by Pompl and coworkers [103], and a new one with divisions between each escape hole [19]. The authors found that mice had a tendency for using serial instead of spatial strategies, for solving the maze, which increased with the addition of the perimetric wall, thus favouring thigmotaxis in the animals.

9. Disadvantages

(1) The most important disadvantage of this device discussed in literature is that learning can be very slow or even absent in some cases, and this has been explained by the lack of stressful stimuli, thereby producing more exploratory behaviour than escape responses as the animals are not sufficiently motivated to escape [116]. In this regard, it has been reported that some animals can reach the entrance of the escape hole, but do not enter, in these cases it is suggested that the latency to reach the entrance should be recorded as a goal response (primary latency) [51].
(2) The device can also stimulate non-spatial strategies—serial strategies or even thigmotaxis affecting performance. If the maze is not cleaned appropriately, the animals can use "aromatic cues" to solve the maze.

10. Advantages

(1) The most important advantage of this device is that it does not induce stress, since the aversive stimuli employed here are much less aggressive than those used in other devices [116].
(2) Similar to the previously described mazes, this one allows the evaluation of learning, working memory and spatial reference memory [116].
(3) The majority of the studies employing the Barnes maze indicate that it is useful for the study of learning and memory in rats and mice. Particularly, it is suitable for mice since these animals exhibit a lower performance in the Morris water maze [4,77].
(4) There is enough evidence supporting the value of the circular maze in different experimental models of CNS disorders, such as brain trauma [43], aging [79], Alzheimer's disease [103], toxic lesions [104], neuropsychiatric alterations [101] and stress [30,91]. In addition, it has been shown to be useful in the evaluation of some drugs with quite different pharmacological actions, such as acetyl-L-carnitine [10] and cocaine [61], or even for experiments testing specific diet regimes, such as those enriched with *n*-3 fatty acids [42].

10.1. Other devices

Besides the devices already described (which typically are focused on spatial navigation through specific environments), other devices have been designed as alternatives to evaluate spatial learning that do not necessarily require this navigation behaviour (i.e., operant conditioning chambers). Also, some other devices, not conventionally considered as specific for the evaluation of spatial skills, have been adapted for this purpose (passive and active avoidance). Regarding the first type, there are some automated operant conditioning chambers, in which the animal needs to choose a response or decide between different levers by activating some detection mechanism with its nose, such as orifices in the wall of the operant chamber [33], or a screen sensitive to touch [119]. This behaviour is reinforced by rewards consisting of food or water.

In the device designed by Delcasso et al., the selection of points present in the walls of the chamber is required [33]. These points form transversal, horizontal or crossed lines, and water is obtained as a reward from a dispenser located at the base of the device. In this device, rapid acquisition of the task has been reported, even with a single trial. Accordingly, retention is optimal within 5 min to 24 h intervals. Interestingly, the same study [33] showed that the administration of scopolamine altered (as it did in other devices) the performance of this spatial task, although it did not affect visual recognition tasks that took place in the same chamber. On the basis of these results the authors suggested that scopolamine is unable to modify attention, alertness or general visual processing, but it can, indeed, affect spatial memory processes. This chamber thereby can be comparatively as useful as others to evaluate spatial memory. These findings support the hypothesis that the muscarinic/cholinergic system is relevant for maintaining spatial working memory, which is in agreement with similar propositions by other authors [80]. Thus, in this device, spatial skills are required for associative learning, however the type of information the animal needs to resort to in order to solve the task is different from that found in the spatial navigation devices (mazes). In the latter, the subject receives continuous visual cues while at different points in the maze. In contrast, in the operant chamber, the selection of the spatial target is followed by reinforcement with water that is obtained from a distinct spatial location, making the association between response and reward, more difficult.

The device designed by Talpos et al. is based on the same principle of operant conditioning, it incorporates a touch-sensitive screen, which is divided into 12 target windows (options), and reinforcement consists of food pellets. In preliminary tests animals have been shown to learn quickly, and the test has been shown to have a high sensitivity for hippocampal lesions [119].

Other behavioural paradigms requiring the use of spatial information are passive and active avoidance tasks (PA and AA, respectively). The PA test consists on a box divided into two equal compartments separated by a guillotine-style door; one of the compartments is illuminated and the other remains in darkness. The illuminated side contains a metallic grid through which electric current can be applied. First, the subject is placed in the illuminated compartment with the door closed, and few minutes later, the gate is opened, allowing the animal to enter the dark compartment; just after it enters, the door is closed again and an electric discharge current is applied. During the retention phase (after different intervals, depending on the study), the subject is placed in the illuminated side, the door is opened and the time that the animal takes to enter the dark compartment is recorded [63].

For the AA task, the device is similar to the one described above, but the main difference is that the communication between compartments remains open all the time, so the animal is free to avoid or escape the noxious stimulus. In addition, both compartments are illuminated and intermittent lights and/or sounds are emitted just before the electric current is applied. For this task, the latency between the sound/light or the electric stimulus and the animal's entrance to the next compartment is recorded (avoidance or escape) [29].

Both tasks are widely employed for the evaluation of learning deficits produced by lesions, drugs or behavioural manipulations. Both are based on the associative learning between a noxious stimulus (the electrical discharge) and a specific behaviour (the entrance to the next compartment) [7]. In the case of PA, latency will depend on how well the animal remembers not to enter the dark compartment. In contrast in the case of AA, the animal is warned through a conditioning stimulus to avoid or escape the noxious stimulation. In other words, in PA the animal should avoid a behavioural response in order to remain safe, while in AA the subject must generate a behavioural response (avoidance or escape) in order to be safe.

Both avoidance tasks require limited spatial skills, since the compartment that needs to be avoided is visible to the animal all the time from any angle, and does not require distal visual cues to be located [26]. Regardless of whether some groups might consider avoidance tasks as unsuitable for the evaluation of spatial memory, some adaptations may turn these tests into good approaches for this purpose [25]. In this regard, some devices have been developed in which food-deprived animals are placed on a circular area containing food pellets on the ground; then, subjects are trained to navigate and collect food, but always avoiding the "punishment area" where they can receive an electric shock of low intensity. This "punishment area" can be identified by means of internal and external visual cues [21]. These passive and active avoidance adaptations have been used to evaluate spatial navigation skills, as well as long-term spatial memory. The studies performed thus far have found that animals show rapid acquisition of the task, and that these tasks can be useful to evidence gender differences in performance. This device has also been highly recommended as an alternative for behavioural evaluation of mice, a species with better performance in "dry" devices [25].

Finally, the visual recognition tasks have also been used for the evaluation of working memory. This paradigm was first described by Ennaceur and Delacour and has faced multiple changes since then [41]. It has been shown to be useful for assessment of learning and memory in different animal species. The device is based on the natural exploratory behaviour inherent to rodents and other animals when they are placed in front of novel stimuli. Indeed, this is one of its advantages, as it does not require food or water-deprivation (nor aversive stimuli) to generate a behavioural response. In addition, it is a two-phase task one is acquisition and the other is the test itself, and these two phases are separated by variable intervals, thus allowing the analysis of different components of the learning process: acquisition, consolidation, and retention. However, one of the main problems that this device presents is the difficulty to define what "exploratory behaviour" exactly means. New computer software has been designed in order to facilitate and standardize the criteria for recognition of small new objects [108]. It is believed that spatial skills are necessary for this task since the animal recognizes as "new" the object exhibiting different topographic characteristics, however, the spatial relations between the object and the context becomes irrelevant as there is no need for distant visual cues in order to locate the object. In several experiments, this task has been shown to be sensitive to hippocampal lesions that also hinder spatial memory [17]. In this regard, other reports have suggested that perirhinal and insular cortex are necessary for the consolidation of the characteristics of "familiar" objects, whereas the hippocampus is needed for the association of the object with its spatial context [5]. More work on this area is needed to determine what this test is really evaluating.

11. Concluding remarks

Spatial memory evolved in different species possibly because it provides information on spatial locations, objects configuration and specific routes relevant for the preservation and survival of the species. By means of this memory system, animals can locate food sources while preventing risky situations on the basis of previous experiences. Spatial memory recruits different neuronal mechanisms (conscious and unconscious, short- and long-term memory, etc.) to achieve its goal. In this review we have dealt with the evaluation of spatial memory in laboratory animals (particularly in rodents) as has been done for more than 100 years. The method more often used is the behavioural analysis through the use of mazes. Among the most accepted and better-known mazes are the Morris water maze, the radial maze and the Barnes circular maze. In parallel, there are also a considerable number of variants for each of them, exhibiting various adaptations depending on the particular experimental protocol used. The variety of devices and experimental protocols make it difficult to compare the results obtained across studies, taking into account this caveat, a summary of the advantages and disadvantages of each task will be attempted. Based on the information reviewed herein, it can be said that the radial maze appears to be an adequate device for the study of spatial working memory (or spontaneous alternation) in rodents, since it possesses the advantage of being simple in design, easy to use, the acquisition process is rapid and reproducible, and it does not induce high levels of stress in animals. Moreover, factors that may affect the results can be easily controlled, for instance eliminating aromatic cues, using doors at the entrance of the arms, increasing the number of arms, and even changing an appetitive stimulus for an aversive one, such as water immersion. In addition there are some commercial automatic devices available that facilitate training and testing.

In regard to the study of spatial reference memory, the most recommended device is the Morris water maze, useful for studying spatial strategies based on distal visual cues (allocentric). It can be modified to explore non-spatial strategies (egocentric). In this device, learning is fast and consistent, there is not a pre-established route for animals, and so the possibilities of navigation are infinite. Given its characteristics, its use for experiments with mice is limited (particularly for those strains showing high reactivity to stress).

The Barnes circular maze and passive or active avoidance tasks are better for experiments using mice given the tendency of these animals to escape through small holes, and their better performance in devices that do not require swimming.

It is important to consider the limitations of each device when designing an experiment. For instance, the radial maze limits the search options while favouring serial strategies, and so learning can be delayed; the water maze uses a strong aversive stimulus – water immersion – that can modify the animal performance; in contrast, the circular maze results less stimulating for some animals, sometimes producing a delayed learning or even the failure to acquire the escape behaviour. Therefore, it is expected that new devices for the behavioural evaluation of spatial memory will be developed over the next several years.

Final recommendations when choosing a maze are: (1) consider the specific experimental paradigm to be explored (learning or memory, or both, short or long-term memories, mouse or rats subjects, etc.), and (2) the knowledge and experience that your group has on a specific device. Once the decision has been made, the limitations and advantages of the selected device should be considered in order to obtain as much information as possible, while controlling for non-specific effects.

References

[1] Arolfo MP, Nerad F, Schenk F, Bures J. Absence of snapshot memory of the target view interferes with place navigation learning by rats in the water maze. Behav Neurosci 1994;108:308–16.
[2] Avila-Costa MR, Fortoul-van Der Goes TI, Niño-Cabrera G, Colin-Barenque L, Bizarro-Nevares P, Gutierrez-Valdez AL, et al. Hipocampal cell alterations induced by inhalation of vanadium pentoxide (V_2O_2) promote memory deterioration. Neurotoxicology 2006;27:1007–12.
[3] Awh E, Jonides J. Overlapping mechanisms of attention and spatial working memory. Trends Cog Sci 2001;5:119–26.
[4] Bach ME, Hawkins RD, Osman M, Kandel ER, Mayford M. Impairment of spatial but not contextual memory in CaMKII mutant mice with a selective loss of hippocampal LTP in the range of the theta frequency. Cell 1995;81:905–15.
[5] Balderas I, Rodriguez-Ortiz CJ, Salgado-Tonda P, Chavez-Hurtado J, McGaugh JL, Bermudez-Rattoni F. The consolidation of object and context recognition memory involves different regions of the temporal lobe. Learn Mem 2008;15:618–24.
[6] Baldi E, Efoudebe M, Lorenzini CA, Bucherelli C. Spatial navigation in the Morris water maze: working and long lasting reference memories. Neurosci Lett 2005;378:176–80.
[7] Bammer G. Pharmachological investigations of neurotransmitter involvement in passive avoidance responding: a review and some new results. Neurosci Biobehav Rev 1982;6:247–96.
[8] Barnes C. Memory deficit associated with senescence: a neurophysiological and behavioral study in the rat. J Comp Physiol Psychol 1979;93:74–104.
[9] Barnes C, Nadel L, Honig WK. Spatial memory deficit in senescent rats. Can J Psychol 1980;34:29–39.
[10] Barnes CA, Markowska AL, Ingram DK, Kametani H, Spangler EL, Lemken VJ, et al. Acetyl-l-carnitine 2: effects of learning and memory performance of aged rats in simple and complex mazes. Neurobiol Aging 1990;11:499–506.
[11] Bats S, Thoumas JL, Lordi B, Tonon MC, Lalonde R, Caston J. The effects of a mild stressor on spontaneous alternation in mice. Behav Brain Res 2001;118:11–5.
[12] Beatty W, Bierley R. Scopolamine degrades spatial working memory but spares spatial reference memory: dissimilarity of anticholinergic effect and restriction of distal visual cues. Pharmacol Biochem Behav 1985;23:1–6.
[13] Benhamou S, Poucet B. A comparative analysis of spatial memory processes. Behav Process 1996;35:113–26.
[14] Berlyne DE. Novelty and curiosity as determinants of exploratory behavior. Br J Psychol 1950;41:68–80.
[15] Bolding K, Rudy JW. Place learning in the Morris water task. Making the memory stick. Learn Mem 2006;13:278–86.
[16] Brandeis R, Brandys Y, Yehuda S. The use of the Morris water maze in the study of memory and learning. Int J Neurosci 1989;48:29–69.
[17] Broadbent NJ, Squire LR, Clark RE. Spatial memory, recognition memory and hippocampus. Proc Natl Acad Sci 2004;101:14515–20.
[18] Brown MF. Does a cognitive map guide choices in tha radial-arm maze? J Exp Psychol Anim Behav Process 1992;18:56–66.
[19] Brown MF, Terrinoni M. Control of choice by the spatial configuration of goals. J Exp Psychol Anim Behav Process 1996;22:438–46.
[20] Bucci DJ, Chiba AA, Gallagher M. Spatial learning in male and female Long-Evans rats. Behav Neurosci 1995;109:180–3.
[21] Bures J, Fenton AA, Kaminsky Y, Wesierska M, Zahalka A. Rodent navigation after dissociation of the allocentric and idiothetic representations of space. Neuropharmacology 1998;37:689–99.
[22] Buresova O, Bures J, Oitzl MS, Zahalka A. Radial maze in the water tank. An aversively motivated spatial working memory task. Physiol Behav 1985;34:1003–5.
[23] Burgess N. Spatial memory: how egocentric and allocentric combine. Trends Cog Sci 2006;10:551–7.
[24] Chess AC, Simoni MK, Alling TE, Bucci DJ. Elevations of endogenous kynurenic acid produces spatial working memory deficits. Schizo Bull 2007;33:797–804.
[25] Cimadevilla JM, Fenton A, Bures J. Continuous place avoidance task reveals differences in spatial navigation in male and female rats. Behav Brain Res 2000;107:161–9.
[26] Cimadevilla JM, Kaminsky Y, Fenton A, Bures J. Passive and active place avoidance as a tool for spatial memory research in rats. J Neurosci Methods 2000;102:155–64.
[27] Coluccia E, Louse G. Gender differences in spatial orientation: a review. J Environ Psychol 2004;24:329–40.
[28] Czurko A, Czeh B, Seress L, Nadel L, Bures J. Severe spatial navigation deficits in the Morris water maze after single high dose of neonatal X-ray irradiation in the rat. Proc Natl Acad Sci 1997;94:2766–71.
[29] Das A, Dikshit M, Singh HK, Nath C. Evaluation of effect of scopolamine on stages of active avoidance learning in rats. Ind J Pharmachol 2003;35:47–50.
[30] Dawood MY, Lumley LA, Robison CL, Saviolakis GA, Meyerhoff JL. Accelerated Barnes maze test in mice for assessment of stress effects on memory. Ann N Y Acad Sci 2004;1032:304–7.
[31] Deacon RM, Rawlins NP. T-maze alternation in the rodent. Nat Protoc 2006;1:7–12.
[32] Del Arco A, Segovia G, Garrido P, de Blas M, Mora F. Stress, prefrontal cortex and environmental enrichment: studies on dopamine and acetylcholine release and working memory performance in rats. Behav Brain Res 2007;176:267–73.
[33] Delcasso S, Jeantet Y, Cho YH. A new test for long-term spatial memory using an operant chamber in mice. Behav Brain Res 2007;178:200–7.
[34] Dember WN, Fowler H. Spontaneous alternation after free and forced trials. Can J Psychol 1959 l;13:151–4.
[35] Dere E, Huston JP, De Souza-Silva MA. Integrated memory for objects, place and temporal order: evidence for episodic-like memory in mice. Neurobiol Learn Mem 2005;84:214–21.
[36] Dere E, Kart-Teke E, Huston JP, De Souza-Silva MA. The case for episodic memory in animals. Neurosci Biobehav Rev 2006;30:1206–24.
[37] D'Hooge R, De Deyn P. Aplications of the Morris water maze in the study of learning and memory. Brain Res Rev 2001;36:60–90.
[38] Dubreuil D, Tixer C, Dutrieux G, Edeline JM. Does the radial arm maze necessarily test spatial memory? Neurobiol Learn Mem 2003;79:109–17.
[39] Dudchenko PA. An overview of the task used to test working memory in rodents. Neurosci Biobehav Rev 2004;28:699–709.
[40] Eichenbaum H, Dudchenko P, Wood E, Shapiro M, Tanila H. The hippocampus, memory, and place cells: is it spatial memory or a memory space? Neuron 1999;23:209–26.
[41] Ennaceur A, Delacour J. A new one-trial test for neurobiological studies of memory in rats. 1. Behavioral data. Behav Brain Res 1988;31:47–59.
[42] Fedorova I, Hussein N, Di Martino C, Muriguchi T, Hoshiba J, Majchrzak S, et al. An n-3 fatty acids deficient diet affects mouse spatial learning in the Barnes circular maze. Prost Leuko Essen Fatty Acids 2007;77:277–9.
[43] Fox GB, Fan L, LeVasseur RA, Faden AI. Effect of traumatic brain injury on mouse spatial and non-spatial learning in the Barnes circular maze. J Neurotrauma 1998;15:1037–46.
[44] Francis DD, Zaharia MD, Shanks H, Anisman H. Stress induced disturbances in Morris water-maze performance inter-strain variability. Physiol Behav 1995;58:57–65.
[45] Frautschy SA, Yang F, Calderon L, Cole GM. Rodent models of Alzheimer's disease: rat Aβ infusion approaches to amyloid deposits. Neurobiol Aging 1996;17:311–21.
[46] Geinisman Y, DeToledo-Morrell L, Morrell F, Heller RE. Hippocampal markers of aged-related memory dysfunction: behavioral, electrophysiological and morphological perspectives. Prog Neurobiol 1995;45:223–52.
[47] Gerlai R. A new continuous alternation task in the T maze detects hippocampal dysfunction in mice. A strain comparison and lesion study. Behav Brain Res 1998;95:91–101.
[48] Goodrick CL. Learning by mature-young and aged Wistar rats as a function of test complexity. J Gerontol 1972;27:353–7.
[49] Grobety MC, Schenk F. The influence of spatial irregularity upon radial maze performance in the rat. Learn Behav 1992;20:393–400.
[50] Hamilton DA, Aker sKG, Johnson TE, Rice JP, Candelaria FT, Weisend MP, et al. The relative influence of place and direction in the Morris water task. J Exp Psychol 2008;34:31–53.
[51] Harrison FE, Reiserer RS, Tomarken AJ, McDonald MP. Spatial and non spatial escape strategies in the Barnes maze. Learn Mem 2006;13:809–19.
[52] Healy SD, Braham SR, Braithwaite VA. Spatial working memory in rats: no differences between the sexes. Proc Roy Soc B 1999;266:2303–8.
[53] Hodges H. Maze procedures: the radial-arm and water maze compared. Cog Brain Res 1996;3:167–81.
[54] Holdstock JS, Mayes AR, Cezayirli E, Isaac CL, Aggleton JP, Roberts N. A comparison of egocentric and allocentric spatial memory in a patient with selective hipocampal damage. Neuropsychologia 2000;38:410–25.
[55] Holscher C. Stress impairs performance in spatial water maze learning task. Behav Brain Res 1999;100:225–35.
[56] Hong SM, Lui Z, Fan Y, Neumann M, Won SJ, Lac D, et al. Reduced hippocampal neurogenesis and skill reaching performance in adult Emx1 mutant mice. Exp Neurol 2007;206:24–32.
[57] Hyde LA, Hopligth BJ, Denenberg VH. Water version of the radial-arm maze: learning in three inbred strains of mice. Brain Res 1998;785:236–44.
[58] Hyde LA, Sherman G, Denenberg VH. Non-spatial water radial arm maze learning in mice. Brain Res 2000;863:151–9.
[59] Ingram DK, Sprangler EL, Iijima S, Ikari H, Kuo H, Greig NH, et al. Rodent models of memory dysfunction in Alzheimer's disease and normal aging: moving beyond the cholinergic hypothesis. Life Sci 1994;55:2037–49.
[60] Ingram DK. Complex maze learning in rodents as a model of aged related memory impairment. Neurobiol Aging 1988;9:475–85.
[61] Inman-Wood SL, Williams MT, Morford LL, Vorhees CV. Effects of prenatal cocaine on Morris and Barnes maze tests of spatial learning and memory in the offspring of C57BL/6J mice. Neurotoxicol Teratol 2000;22:547–57.
[62] James TW, Kimura D. Sex differences in remembring the locations of objects in an array: location-shifts versus location-exchanges. Evol Hum Behav 1997;18:155–63.
[63] Jarvik ME, Kopp A. An improved one-trial passive avoidance learning situation. Psychol Rep 1967;21:221–4.
[64] Jonasson Z. Meta-analysis of sex differences in rodent models of learning and memory: a review of behavioral and biological data. Neurosci Biobehav Rev 2005;28:811–25.
[65] Kealy J, Diviney M, Kehoe E, McGonagle V, OïShea A, Harvey D, et al. The effects of overtraining in the Morris water maze on allocentric and egocentric learning strategies in rats. Behav Brain Res 2008;192:259–63.
[66] Kessels RPC, de Haan EHF, Kappelle LJ, Postma A. Varieties of human spatial memory: a meta-analysis on the effects of hippocampal lesions. Brain Res Rev 2001;35:295–303.
[67] Kimura D, Hampson E. Cognitive pattern in men and women is influenced by fluctuations in sex hormones. Curr Dir Psychol Sci 1994;3:57–61.

[68] Klatzky RL. Allocentric and egocentric spatial representations: definitions, distinctions, and interconnections. In: Freksa C, Habel C, Wender KF, editors. Spatial cognition—an interdisciplinary approach to representation and processing of spatial knowledge. Berlin: Springer-Verlag; 1998. p. 1–17.
[69] Koopmans G, Blokland A, Nieuwenhuijzen PV, Prickaerts J. Assesment of spatial learning abilities of mice in a circular maze. Physiol Behav 2003;79:683–93.
[70] Kyrkby DL, Jones DNC, Higgins GA. Influence of prefeeding and scopolamine upon performance in a delayed matching-to-position task. Behav Brain Res 1995;67:221–7.
[71] LaBuda CJ, Mellgren RL, Hale RL. Sex differences in the acquisition of a radial maze task in the CD-1 mouse. Physiol Behav 2002;76:213–7.
[72] Lalonde R. The neurobiological basis of spontaneous alternation. Brain Res Rev 2002;26:91–104.
[73] Lamberty Y, Gower AJ. Simplifying environmental cues in a Morris-type water maze improves place learning in old NMRI mice. Behav Neural Biol 1991;54:89–100.
[74] Lindner MD, Schallert A. Aging and atropine effects on spatial navigation in the Morris water task. Behav Neurosci 1988;102:621–34.
[75] Lipp HP, Wolfer DP. Genetically modified mice and cognition. Curr Op Neurobiol 1998;8:272–80.
[76] Locchi F, Dall'Ollio R, Gandolfi O, Rimondini R. Water T-maze, an improved method to assess spatial working memory in rats: pharmacological validation. Neurosci Lett 2007;422:213–6.
[77] Lukoyanov NV, Madeira MD, Paula-Barbosa MM. Behavioral and neuroanatomical consequences of chronic ethanol intake and withdrawal. Physiol Behav 1999;66:337–46.
[78] Maei HR, Zaslavsky K, Teixeira CM, Frankland PW. What is the most sensitive measure of water maze probe test performance? Front Integr Neurosci 2009;3:1–9.
[79] Markowska AL, Spangler EL, Ingram DK. Behavioral assessment of the senescence-accelerated mouse (SAM P8 and R1). Physiol Behav 1998;64:15–26.
[80] Maviel T, Durkin TP. Role of central cholinergic receptor sub-types in spatial working memory: a five-arm maze task in mice provides evidence for a functional role of nicotinic receptors in mediating trace access processes. Neuroscience 2003;120:1049–59.
[81] Mazmanian DS, Roberts WA. Spatial memory in rats under restricted viewing conditions. Learn Motiv 1983;14:123–39.
[82] McDonald MP, Overmier JB. Present imperfect: a critical review of animal models of the mnemonic impairments in Alzheimer's disease. Neurosci Biobehav Rev 1998;22:99–120.
[83] Mclay RN, Freeman SM, Zadina JE. Chronic corticosterone impairs memory performance in the Barnes maze. Physiol Behav 1998;63:933–7.
[84] McNamara RK, dePape GE, Skelton RW. Differential effects of benzodiacepine receptor agonist on hipocampal long term potentiation and spatial learning in the Morris water maze. Brain Res 1993;626:63–70.
[85] Moffat SD, Hampson E, Hatzipantelis M. Navigation in virtual maze: sex differences and correlation with psychometric measures of spatial ability in humans. Evol Hum Behav 1998;19:73–87.
[86] Moghaddam M, Bures J. Contribution of egocentric spatial memory to place navigations of rats in the Morris water maze. Behav Brain Res 1996;78:121–9.
[87] Morris RGM. Developments of a water maze procedure for studying spatial learning in the rat. J Neurosci Methods 1984;11:47–60.
[88] Morris RGM. Spatial localization does not require the presence of local cues. Learn Motiv 1981;12:239–60.
[89] Moscovitch M, Nadel L, Winocur G, Gilboa A, Rosenbaum RS. The cognitive neuroscience of remote episodic, semantic and spatial memory. Curr Opin Neurobiol 2006;16:179–90.
[90] Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C, et al. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J Anat 2005;207:35–66.
[91] Mueller BR, Bale TL. Early prenatal stress impact on coping strategies and learning performance is sex dependent. Physiol Behav 2007;91:55–65.
[92] Nyffeler T, Gutbrod K, Pflugshaupt T, vonWartburg R, Hess CW, Müri RM. Allocentric and egocentric spatial impairments in a case of topographical disorientation. Cortex 2005;41:133–43.
[93] O'Keefe J. An allocentric spatial model for the hippocampal cognitive map. Hippocampus 1991;1:230–5.
[94] OïKeefe J, Dostrovsky J. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res 1971;34:171–5.
[95] O'Keefe J, Nadel L. The hippocampus as a cognitive map. Oxford: Clarendon Press; 1978.
[96] Olton DS. The radial arm maze as a tool in behavioural phamachology. Physiol Behav 1985;40:793–7.
[97] Olton DS, Samuelson RJ. Remembrance of place passed. Spatial memory in rats. J Exp Psychol: Anim Behav Process 1976;2:97–116.
[98] Olton DS, Collison C, Werz M. Spatial memory and radial arm maze performance of rats. Learn Motiv 1977;8:289–314.
[99] Olton DS, Becker JT, Handelmann GE. Hippocampus space and memory. Behav Brain Sci 1979;2:313–65.
[100] Ormerod BK, Beinnger RJ. Water maze versus radial maze: differential performance of rats in spatial delayed match-to-position task and responde to scopolamine. Behav Brain Res 2002;128:139–52.
[101] O'Tuathaigh CM, Babovic D, OïSullivan GJ, Clifford JJ, Tighe O, Croke DT, et al. Phenotypic characterization of spatial cognition and social behavior in mice with "knockout" of the schizophrenia risk gene neuregulin 1. Neuroscience 2007;147:18–27.
[102] Paganelli RA, Benetolli A, Miltus-Lima KC, Cestari-Junior LA, Favero-Filho, Milani H. A novel version of the 8-arm radial maze: effects of cerebral ischemia on learning and memory. J Neurosci Methods 2004;132:9–18.
[103] Pompl PN, Mullan MJ, Bjugstad K, Arendash GW. Adaptation of the circular plataform spatial memory task for mice: use in detecting cognitive impairment in the AAP_{sw} transgenic mouse model for Alzheimer disease. J Neurosci Methods 1999;87:87–95.
[104] Raber J, Rola R, LeFevour A, Morhardt D, Curley J, Mitzumatsu S, et al. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. Radiat Res 2004;162:39–47.
[105] Rains DG. Sistemas de memoria. In: Rains DG, editor. Principios de neuropsicología humana. 1st ed. México: Mc Graw Hill; 2004. p. 241–86.
[106] Rogers DC, Hunter AJ. Phototrombotic lesions of the rat cortex impair acquisition of the water maze. Pharmacol Biochem Behav 1997;56:747–54.
[107] Roullet P, Lassalle J, Jegat R. A study of behavioral and sensorial bases of radial maze learning in maze. Behav Neural Biol 1993;59:173–9.
[108] Rutten K, Reneerkens OAH, Hamers H, Sik A, McGregor IS, Prickaerts J, et al. Automated scoring of novel object recognition in rats. J Neurosci Methods 2008;171:72–7.
[109] Sandi C. The role and mechanisms of action of glucocorticoid involvement in memory storage. Neural Plast 1998;6:41–52.
[110] Seymoure P, Hui-Dou H, Juraska JM. Sex differences in radial arm maze performance: Influence of rearing environment and room cues. Psychobiology 1996;24:33–7.
[111] Sherry DGH, Hampson E. Evolution and the hormonal control of sexually dimorphic spatial abilities in humans. Trends Cog Sci 1997;1:50–6.
[112] Spowart-Manning L, van der Staay FJ. The T-maze continuous alternation task for assessing the effects of putative cognition enhancers in the mouse. Behav Brain Res 2004;151:37–46.
[113] Squire LR. Mechanisms of memory. Science 1986;232:1612–9.
[114] Steckler T, Drinkenburg WH, Sahgal A, Aggleton JP. Recognition memory in rats. I. Concepts and classification. Prog Neurobiol 1998;54:289–311.
[115] Stone C. The age factor in animal learning. I. Rats in the problem box and the maze. Gen Psychol Monogr 1929;5:1–30.
[116] Sunyer B, Patil S, Hoger H, Lubec G. Barnes maze, a useful task to assess spatial reference memory in the mice. Nat Protoc 2007;390:10–38.
[117] Susuki S, Augerinos G, Black AH. Stimulus control of spatial behavior on the eight-arm maze in rats. Learn Motiv 1980;11:1–18.
[118] Sutherland RJ, Chew GL, Baker JC, Linggard RC. Some limitations on the use of distal cues in place navigation by rats. Psychobiology 1987;15:48–57.
[119] Talpos JC, Dias R, Bussey TJ, Saksida LM. Hippocampal lesions in rats impair learning and memory for locations on a touch-sensitive computer screen: The "ASAT" task. Behav Brain Res 2008;192:216–25.
[120] Thinus-Blanc C. Exploration and spatial knowledge. In: Animal Spatial Cognition. Behavioral and Neural Approaches. 1st ed. Singapore: Word Scientific; 1996. p. 1–42.
[121] Tolman EC. Cognitive maps in rats and men. Psychol Rev 1948;55:189–208.
[122] Torrejais JC, Rosa CC, Boerngen-Lacerda R, Andreatini R. The elevated T-maze as a measure of two types of defensive reactions: a factor analysis. Brain Res Bull 2008;76:376–9.
[123] Tulving E. How many memory systems are there? Am Psychol 1985;40: 385–98.
[124] Tulving E, Markowitsch HJ. Episodic and declarative memory: role of the hippocampus. Hippocampus 1998;8:198–204.
[125] Tulving E, Schacter DL. Priming and human memory systems. Science 1990;247:301–6.
[126] Upchurch M, Wehner JM. Differences between inbred strains of mice in Morris water maze performance. Behav Gen 1988;18:55–68.
[127] Uttal DH. Seeing the big picture: map use and the development of spatial cognition. Dev Sci 2000;3:247–86.
[128] Van Dam D, Lenders G, De Deyn PP. Effect of Morris water maze diameter on visual-spatial learning in different mouse strains. Neurobiol Learn Mem 2006;85:164–72.
[129] van der Staay FJ. Effects of the size of the Morris water tank on spatial discrimination learning in the CFW1 mouse. Physiol Behav 2000;68: 599–602.
[130] van Haaren F, van Hest A, Heinsbroek RP. Behavioral differences between male and female rats: effects of gonadal hormones on learning and memory. Neurosci Biobehav Rev 1990;14:23–33.
[131] van Haaren F, Wouters M, van de Poll N. Absence of behavioural differences between male and female rats in different radial arm maze procedures. Physiol Behav 1987;39:409–12.
[132] Verzar-McDougall EJ. Studies in learning and memory in ageing rats. Gerontologia 1957;1:65–85.
[133] Vincent SB. The white rat and the maze problem. J Anim Behav 1915;5:1–24.
[134] Vorhees CV. Maze learning in rats: a comparison of performance in two water mazes in progeny prenatally exposed to different doses of phenytoin. Neurotoxicol Teratol 1987;9:235–41.
[135] Vorhees CV, Acuff-Smith KD, Weisenburger WP, Minck DR, Berry HK. Branched chain amino acids improve radial arm maze and water maze forced choice learning in rat offspring exposed in utero to hyperphenylalaninemia. Neurotoxicol Teratol 1992;14:35–41.
[136] Wasserman EA, Jensen DD. Olfactory stimuli and the "pseudo-extinction" effect. Science 1969;166:1307–9.

[137] Watson JB. Kinaesthetic and organic sensation: their role in interactions of the white rat to the maze. Psychol Rev Monogr 1907;Suppl. 8(33):1–100.
[138] Weniger G, Ruhleder M, Wolf S, Lange C, Irle E. Egocentric memory impaired and allocentric memory intact as assessed by virtual reality in subjects with unilateral parietal cortex lesions. Neuropsychologia 2009;47: 59–69.
[139] Whishaw IQ, Tomie JA. Of mice and mazes: similarities between mice and rats on dry land but not water maze. Physiol Behav 1996;60:1191–7.
[140] Wolfer DP, Stagljar-Bozicevic M, Errington ML, Lipp HP. Spatial memory and learning in transgenic mice: fact or artifact? News Physiol Sci 1998;13:118–23.
[141] Yamaki T, Murakami N, Iwamoto Y, Sakakibara T, Kobori N, Ueda S, et al. Cognitive dysfunction and histological findings in rats with chronic stage contusions and diffuse axonal injury. Brain Res Protocol 1998;3:100–6.
[142] Yonemori F, Yamada H, Yamaguchi A, Uemura A, Tamura A. Spatial memory disturbance after focal cerebral ischemia in rats. J Cereb Blood Flow Metab 1996;16:973–80.