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The Importance of Distinguishing Allocentric and Egocentric Search Strategies in Rodent Hippocampal-Dependent Spatial Memory Paradigms: Getting More Out of Your Data

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Additional information is available at the end of the chapter

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Abstract

While the brain works as a dynamic network, with no brain region solely responsible for any particular function, it is generally accepted that the hippocampus plays a major role in memory. Spatial memory operates through the hippocampus with communication with the prefrontal and parietal cortices. This chapter will focus on two separate reference frames involved in spatial memory, egocentric and allocentric, and outline the differences of these reference frames and associated search strategies with relevance to behavioural neuroscience. The importance of dissociating these search strategies is put forward, and steps researchers can take to do so are suggested. Neurophysiological and clinical differences between these spatial reference frames are outlined to further support the view that distinguishing them would be beneficial.

Keywords: allocentric, egocentric, hippocampus, maze, navigation, networks, spatial memory

1. Introduction

Spatial memory is the cognitive process of noticing, encoding, and retrieving landmarks in the surrounding environment, to allow an organism to navigate and exist in the world. It is important for survival, by enabling searching and finding safety and food and being able to return to found places without issue. It is the domain of the hippocampus and medial temporal lobe,

with links to the retrosplenial cortex and parietal cortex [1]. Seminal studies in humans and animals have demonstrated the important role that the hippocampus plays in navigating the world around us [2, 3]. In humans, damage to the temporal lobe causes disturbances to spatial navigation [4], and similarly, humans employed in roles that require fantastic spatial navigation skills have enlargement of the hippocampus and its connections [5, 6]. In parallel, through multiple manipulations such as lesion, electrophysiological and optogenetic studies, the hippocampus has been shown to be equally important to animal spatial memory. Disruptions to hippocampal tissue or silencing of neurons in the hippocampus leads to spatial memory deficits [7, 8]. This parallel role of the hippocampus in both humans and animals allows research to be performed on these animals with the insights gained able to be extrapolated to humans.

2. Spatial memory in behavioural testing

Behaviourally characterising an animal model of disease often involves a battery of tests that investigate the animal's motivation, locomotor activity, startle reflex, anxiety, fear response, social behaviour, learning, memory and other emotional and cognitive traits. Dysfunctions in these behaviours are used to infer structural and functional changes in the brain, and the recovery of performance on these tests is used to evaluate the effectiveness of potential therapeutics. These inferences are only accurate with the use of appropriate tests with high specificity both for the behaviour in question and in terms of the specific brain regions recruited during test performance. Therefore, behavioural tests that are specific to one domain or behavioural tests that can correctly dissociate multiple domains should be used. Rodent spatial memory tests, often mazes, are commonly used in preclinical drug development and fundamental science experiments. The use of these behavioural tests dates back over a century, and a plethora of maze designs have been developed since then to probe different aspects of learning and memory [9]. Complex networks of brain regions and neuron populations are required to orientate and navigate using information such as environmental, vestibular and proprioceptive cues [10]. The current general consensus is that spatial memory encompasses two distinct but related reference frames, egocentric and allocentric. Here, we outline the differences between these reference frames and their relevance in behavioural neuroscience and discuss the merits of placing a stronger emphasis on distinguishing egocentric and allocentric search strategies in spatial memory tests.

3. What are allocentric and egocentric search strategies?

The egocentric reference frame is also referred to as a fixed, self-centred or first-person perspective. Egocentric navigation is based on direction (left-right) responses and actions independent of environmental cues. Directional decisions are made at single or sequential choice points; however, these locations are not used as cues and are therefore still egocentric in nature [11]. For example, memorising routes based on sequential turns would employ a mostly egocentric strategy (**Figure 1A**). Path integration, the summation of travelled vectors to deduce current position, is an example of an egocentric strategy that can navigate through

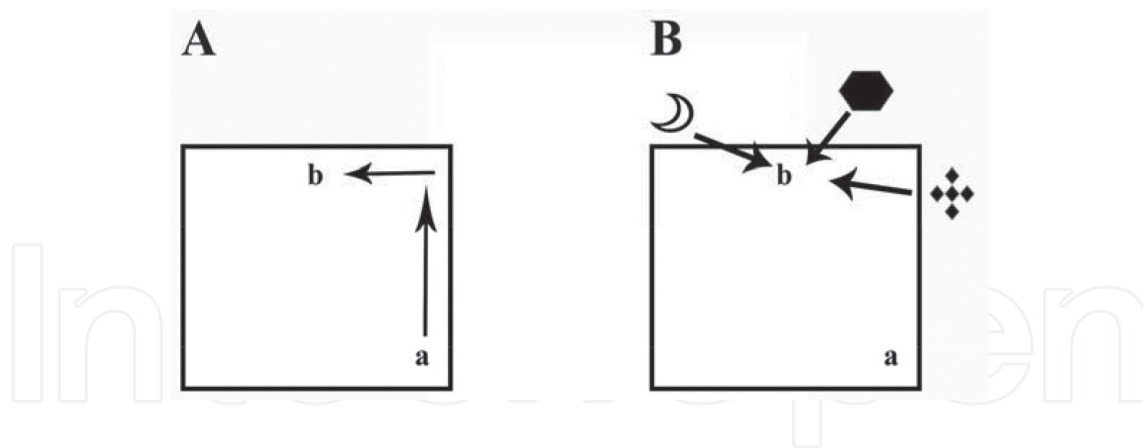


Figure 1. Schematic of egocentric (A) and allocentric (B) frames in a spatial memory task. Within each arena, (a) is the start position and (b) is the goal location. Egocentric strategies are referenced from self with set directions and distances to the goal (shown indirect here but may also be direct). Note that if the start position (Aa) is changed, the strategy would fail to reach the goal (Ab). Allocentric strategies relate the location of the goal to visual cues. Note that if the start position (Ba) is changed, the strategy would still successfully locate goal (Bb). If the visual cues are moved, the strategy would fail to reach the goal (Bb).

novel paths. The allocentric reference frame, on the other hand, can be thought of as a third-person perspective. Allocentric navigation utilises external cues or landmarks in relation to each other to navigate and is independent of self (**Figure 1B**). Utilising compass directions (north, south, east, west) is an example of allocentric reference frame use as these directions are relative to the Earth and do not change depending on the orientation of the navigator [12]. An advantage of allocentric navigation is the flexibility of being able to locate novel points from various start locations as long as the external cues remain the same. In situations where external cues are changing, minimal or absent, egocentric strategies become more salient [1].

Navigating environments outside of experimental settings requires the use of both allocentric and egocentric reference frames, with relative saliencies falling within a spectrum [1]. Experiments in controlled settings with specifically designed spatial memory tasks aim to dissociate these reference frames; however, it is argued that complete dissociation is not achieved [1]. Nevertheless, the employment of more precise tasks as well as the use of more rigorous analytical techniques allows greater dissociation and investigation into navigational strategy preference and specific dysfunctions in reference frames. Nonspatial strategies such as random or serial searches can often be successful in that they result in lower latencies to a goal. These, however, are not indicative of spatial memory, and measures should be put in place to detect such strategy use. The following section provides an overview of the various spatial memory tasks currently used in behavioural neuroscience and their ability to effectively probe egocentric and allocentric search strategies.

4. Spatial memory and navigation paradigms

There are a large variety of behavioural tests for both rodents and humans that provide a measure of spatial memory and navigation [9, 13, 14]. Generally, rodent spatial memory tests

utilise maze apparatus that have a goal area that the animals must find, learn and remember. These goals can be positive reinforcements such as food rewards, escapes from negative stimuli such as water or bright light or a result of instinctive behaviour such as exploratory drive. Human spatial memory testing, on the other hand, is mostly conducted on virtual reality setups that create controlled three-dimensional environments with goals usually being explained to the subject by the researcher. More recently, steps have been taken to combine aspects from both animal and human tests to increase the similarity and therefore translatability of these tests. Virtual reality versions of rodent tests have been developed for humans [15], and virtual reality and touchscreen setups for rodents that were developed from human equivalents have also become popular [16, 17]. Distinguishing allocentric and egocentric reference frames and search strategies used in spatial memory tasks for rodents differs depending on the type of test. Some tasks are designed to encourage employment of a single strategy, and so performance on that task is reflective of the saliency of that particular reference frame. Other tasks can be completed with a combination of allocentric and egocentric strategies, and subsequent analysis or probe tests are needed to infer deficits or preferences in these reference frames. Consideration of what types of spatial navigation are being tested, and extra steps to dissociate these strategies are often overlooked, despite the relative ease of implementing such measures. Below we discuss popular maze apparatus used to investigate spatial memory and various tests, controls and analyses that can help distinguish egocentric and allocentric navigation.

Spatial memory can be investigated through a variety of tests on mazes such as the Y-maze, cheeseboard maze, Morris water maze, Star maze, Barnes maze, radial arm maze and T-maze. These mazes encompass investigation of a range of spatial memory, including long-term, short-term and working memory, as well as cognitive flexibility. Tests that probe allocentric reference frames include the use of static visual cues which the rodent can use to develop a cognitive map. Efforts are made to minimise proximal cues and create open, unobstructed spaces to avoid non-allocentric strategies. The opposite is true for egocentric tasks where visual cues are minimised or made irrelevant (incorrect or random). The most accurate way of testing for egocentric strategies is to perform a test in the dark, which ensures removal of visual distal cues that could be used for allocentric strategies [18]. Many apparatus that are used to investigate egocentric navigation restrict movements to narrow channels or arms to create distinct choice points where egocentric strategies are encouraged [19].

Constructed in the shape of a capitalised 'T', the **T-maze (Figure 2A)** is a simple apparatus used to probe working and short-term spatial memory. Due to the shape of the maze, only two options, a 90-degree left or right turns, are available to the rodent when leaving the start arm. The T-maze can be unbaited, baited or use negative stimuli to drive exploration of the maze [20]. Generally, one of the arms is correct (unexplored, food/water rewarded, containing escape platform) and is learnt in the presence of intact memory. Internal and external visual cues can be used to probe navigational strategy [21]. Briefly, animals can be trained with the presence of extra-maze visual cues and an intra-maze visual cue. Reaching the goal arm can be achieved by either remembering to turn in the correct direction, move towards or avoid the intra-maze cue or move to the correct area in relation to the static external cues. Following successful acquisition of the task, animals can be tested on probe trials which involve systematically switching the cues or correct turn direction so that they are now incorrect. Indeed,

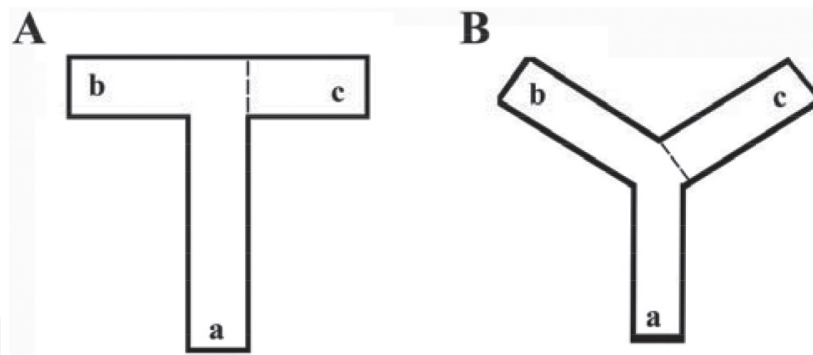


Figure 2. Schematic of a T-maze and Y-maze. (A) is the start location and the (B) and (C) arms are the choice arms. One choice arm (C shown here) may be physically blocked during the first phase of unbaited tests to create a novelty seeking drive to that arm when made accessible in the second phase.

rats were shown to have an overall preference for a direction-based strategy on the T-maze, suggesting that this apparatus encourages egocentric navigation [21]. Using similar visual cue manipulations on the T-maze, transgenic mice expressing an Alzheimer's disease-related mutation were shown to have specific allocentric place learning deficits in the absence of a general disruption in learning and memory, highlighting the importance of including these probe tests when possible [22].

The **Y-maze** (Figure 2B) works much in the same way as a T-maze; however, the apparatus is designed in a Y shape with three equal arms at 120 degrees from each other. Unbaited tests are popular on this apparatus, relying on the animal's innate preference to explore previously unexplored areas. Short-term memory can be tested by blocking access to one of the arms in the first phase of the test and observing the time spent in that arm in the second phase where all three arms can be accessed. There is a variable delay between phases to control short-term memory load of the task. This novel arm preference task is a test for allocentric spatial memory as rodents use both intra- and extra-maze cues to remember the location of the novel arm. Working memory can also be tested by allowing the animal to freely explore all three arms and observing if they chose to enter the arm most recently explored or they alternate and enter the more novel arm—this is called spontaneous alternation. Spontaneous alternation can also be investigated on the T-maze; however, because the arms of the Y-maze are equal (and can each become new start arms), alternation can be continuously measured without constant investigator interaction. Modifying the protocol to include baited arms and including or removing the use of proximal and distal cues allows for the investigation of allocentric and egocentric strategies [23–25].

The **Biel water maze** was developed by William Biel [26] and is constructed of multiple T-mazes that interconnect to create a labyrinth in which rodents must navigate from the 'Start' to 'Goal' to escape the maze. The maze is run in visible light, and no explicit distal cues are provided; in addition, the maze is covered by a large container to minimise access to both distal and proximal cues. Parameters that are used to measure egocentric navigation include errors across trials and escape latency. However, this maze had limitations in design and level of difficulty, most importantly that it was run in visible light which could provide distal or proximal cues from the box overhead [19]. The **Cincinnati water maze (CWM)** is an extension of the Biel water maze. It is a complex labyrinth water maze consisting of nine interconnecting

T-mazes (**Figure 3**). An experimental rodent must get from position A to position B and is motivated by its survival instinct to leave the water. It is designed to employ egocentric search strategies based on the physical dimensions and design of the maze that creates nine choice points (rather than six in the Biel water maze) at intersections where rodents are required to make a left or right turn. The CWM is constructed using an acrylic material so that the walls are smooth, and no proximal cues are available. The width of the channels ensures the rodent cannot climb the walls of the maze, and running the test in the dark under infrared light can act as a double insurance against the use of visual cues [19]. Generally, the number of errors, number of start return and latency to escape are the main parameters reported for this maze.

The radial arm maze (RAM) consists of a central circular area from which multiple arms radiate outwards. Rodent spatial memory is measured by the ability to remember the location of baited arms through the use of salient cues around the maze room (allocentric) [27] or an egocentric-focused paradigm that employs forced arm entry. An example of an egocentric paradigm using the RAM follows. In this instance the maze has automated doors that open and close to allow entry for the animal. The animal starts in one arm, and once the experiment starts, two adjacent arms to the start arm are opened to construct a Y shape. There will be a food reward at the end of one arm, determined for each mouse to be either left or right. The maze arm entered by the animal becomes the new start arm, which the animal is restricted to during an intertrial interval. Following an intertrial interval, two arms adjacent to the new start arm are opened, with the direction of arm (left or right) being correct with a food reward. The experiment continues in this fashion and requires the animal to navigate the maze in reference to its own position [28]. By limiting access to only three arms (in addition to the original start arm) at a time, this insures against a non-egocentric strategy to be used by the

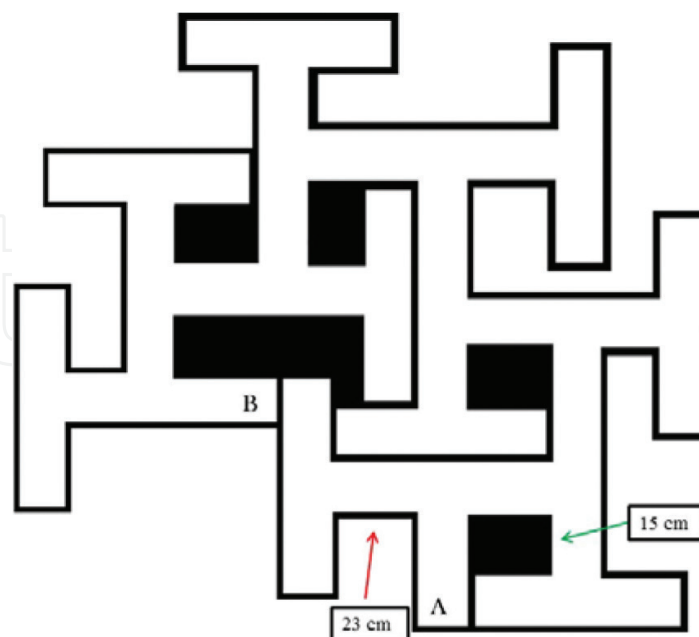


Figure 3. The Cincinnati water maze (CWM), original image from Vorhees and Williams [19], is a labyrinth-like maze that is performed in the dark. The forced left or right choice in addition to the lack of visual cues promotes egocentric strategies. (A) Is the start location and (B) is the escape platform.

animal. For example, if all arms of the RAM were available, the animal could use the serial strategy of entering each arm sequentially in order to find the food reward. For the RAM, measurements such as number of errors and rank of the first error [27] are reported to indicate memory performance. While the RAM can be used to investigate both egocentric and allocentric search strategies, the armless Morris water maze became the standard for allocentric testing [13], with the open opaque water acting as a mask for both choice points to learn a set sequence, and olfaction. In contrast to the armed designs of egocentric tests, mazes that target allocentric spatial strategies are designed to be open and free from intra-maze objects/edges that may act as choice points [13].

The Barnes maze is based upon the preference for dark, enclosed spaces by rodents. It is an open circular maze with holes around the perimeter (**Figure 4**). Underneath one of these holes is the 'target box' goal, which provides a small enclosed space for the rodent. During testing the maze is flooded with bright lights, sounds and/or air jets to provide motivation to find the goal. Distal cues are provided around the room to help the rodent navigate. Number of errors, escape latency and search strategies are commonly reported as a measure of spatial memory performance [20]. Visual cue manipulations on the Barnes maze show that distal cues are more salient than proximal cues, with animals trained without distal cues (with a marker at the goal location) showing decreased performance [29]. Thus this task tends to encourage allocentric strategies.

The Morris water maze (MWM) has been an integral part of neuroscience research as a gold standard when testing spatial memory in rodents since its introduction (Morris et al. [38]). The MWM utilises a large, circular pool with opaque water and a hidden escape platform (**Figure 5A**). Multiple distal cues are placed around the maze to aid the rodent to reach the

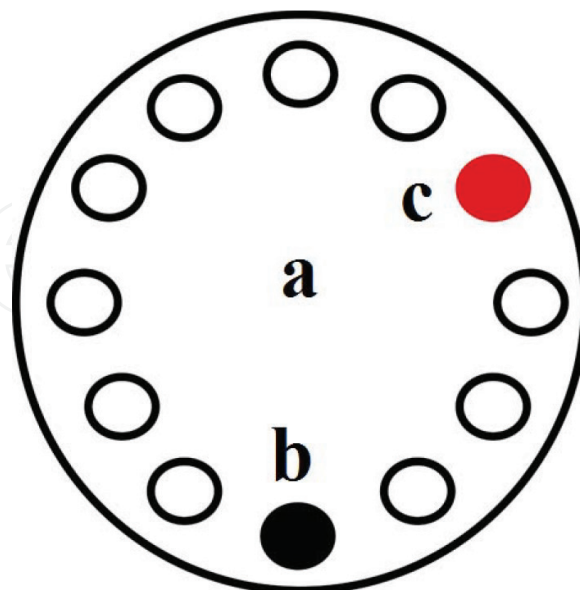


Figure 4. Schematic of the Barnes maze. Animals start in the Centre of the maze (A) and must find and remember the location of the hidden escape box (B). After acquisition, the correct location can be changed (C) to investigate cognitive flexibility.

hidden platform they use to escape. Most protocols are performed over multiple days, with multiple trials per day, and while the hidden platform position remains the same, starting position for the research animal is often changed to minimise egocentric strategies. However, if the start location is kept consistent, and the test is performed in the dark without external cues, rodents can complete the MWM using an egocentric strategy [30]. After training, the escape platform is removed, and reference memory is tested. Animals are expected to spend an increased amount of time in the quadrant where the goal previously was. The location of the goal can also be changed to investigate reversal learning and cognitive flexibility. The main motivation for the rodent to navigate the maze is to escape the water. The main advantage of the MWM when testing allocentric search strategies is the removal of intra-maze visual and olfactory cues with the use of opaque water. Indeed, the masking of any available olfactory cues is imperative due to the rodents' powerful sense of smell and the use of olfaction in their navigation [31]. However, the water in the MWM can also be a disadvantage, especially when working with mice because they are not natural swimmers in the wild and become stressed in the water [32].

The cheeseboard maze (CBM) (Figure 5B) is a dry version of the MWM and is similarly a long-term spatial memory test as well as a measure of cognitive flexibility. The CBM is a uniform circular arena with wells that can be baited. The wells radiate in lines evenly from the centre of the board. Spatial cues are placed around the CBM. Rodents are food deprived for the duration of the experiment to provide motivation to find the food reward. The location of the baited well is different for each animal and is kept constant across trials and days for each individual mouse. Animals should learn to use the spatial cues placed around the maze to find the baited well from the start area in the centre to receive the reward and are expected to use allocentric search strategies. Following acquisition of the goal location, the location of the food reward is changed, and the animal then must adopt a new learning strategy (reversal). This is a measure of cognitive flexibility and is testing the ability of the animal to ignore the initial position of the reward and learn the new location of the second reward. Compared to the MWM which relies on survival motivation, the CBM relies on hunger drive. Both tasks involve distal cues to guide the mouse to its goal, be it the platform of the MWM or the food reward of the CBM. These different motivations could influence the cognitive processing of

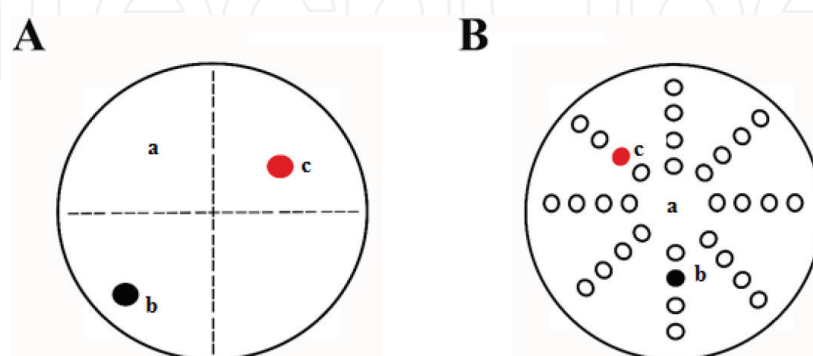


Figure 5. The Morris water maze (A) and the dry cheeseboard maze (B). (a) is the start location, (b) is the goal location, and (c) is a new goal location used to investigate cognitive flexibility. Both apparatus are circular, open-arena mazes that can contain goal locations in a range of xy coordinates.

the rodents. MWM has been criticised as unduly stressful [13], with the research animal having to employ avoidance learning. The CBM, while food deprivation may provide a similar stress [13], involves positive reinforcement through the food reward. There are some arguments that positive reinforcement may not be sufficient enough [13] to encourage the research animals to learn, in comparison to a test such as MWM where negative consequences must be avoided. It may be that each test provides a different angle to the study of cognition. Panicked stress may be detrimental to effective learning or a stronger drive compared to food deprivation. The main advantage of the MWM in terms of teasing out allocentric and egocentric strategies is that it is a cleaner allocentric maze. In the MWM, the use of opaque water that the rodents must swim through minimises the availability of choice points and olfactory cues. In comparison, the CBM is a maze that requires rodents to not only navigate using the distal cues but also around the wells. Hence, rodents may incorporate these wells into their navigation strategy—something that cannot be done in the MWM. This could provide an opportunity for the rodents to employ non-allocentric strategies, such as the serial strategy. This issue of detecting said egocentric versus allocentric search strategies is further discussed in the following section.

The Star maze (Figure 6), designed by Rondi-Reig et al. [33], is a purpose-built water maze that allows for the distinction of allocentric and egocentric search strategies. It is a circular water maze consisting of five water channels that form a central pentagon, and five water channels radiate out from this pentagon. The walls of the maze have a uniform colour, and the water is made opaque. The goal of the maze is to find the hidden platform in order to escape. Extra-maze cues on the walls are made available when analysing allocentric navigation. The setup of this maze allows for multiple protocols to test allocentric or egocentric navigation.

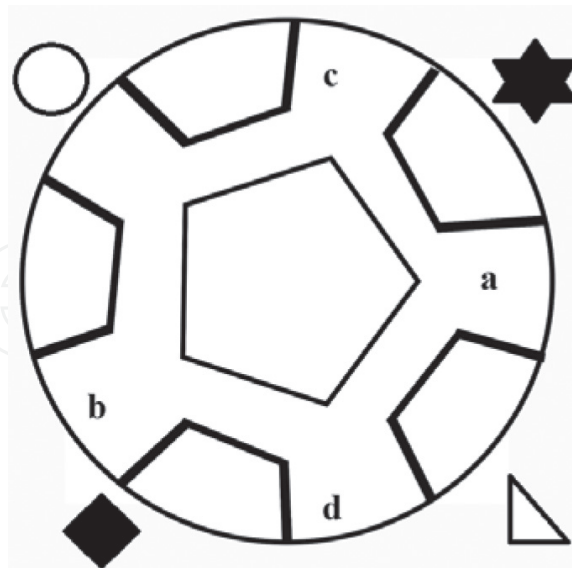


Figure 6. The Star maze, adapted from Rondi-Reig et al. [33], which is a water maze that allows for the investigation of spontaneous search strategy used by rodents. The design of the Star maze is such that either egocentric route learning or allocentric navigation can be analysed. For example, animals are trained from start position (a) to goal (b) until a threshold performance is reached. The start position is then moved to (c). An egocentric strategy would lead the animals to (d), whereas an allocentric strategy would continue to navigate to (b).

The first protocol, 'the multiple strategies version', is set up to investigate spontaneous navigation strategy that is employed by the rodent. The second protocol investigates egocentric navigation by setting up the maze so that a sequence of direction movements sends the rodent to the escape platform. The final protocol requires rodents to use the spatial cues provided in order to escape from randomly assigned start points [33]. This maze is a great setup as it allows the elucidation of individual search strategies, and given that it is a water maze, it controls for equal motivation and opportunity [13].

5. Analysing search strategies to compare the use of egocentric or allocentric search strategies

Spatial memory proficiency is commonly measured through a range of parameters in the above-mentioned mazes including latency, distance and time spent in target quadrants. However, evidence suggests that these analyses are not providing sophisticated enough insights into cognition and behaviour [34]. The Current trend is a deeper analysis of spatial navigation in order to produce more efficient research and more efficient use of research animals [34], moving beyond the well-known parameters of latency and distance. Research is now interested in the search strategy employed by research subjects and animals (**Figure 7**). Search strategy analysis can observe the complexity and dynamic nature of cognition employed in spatial memory mazes. For example, while different genotypes may have no significant differences in the typical parameters of latency, distance or target quadrant, a difference in approach to goal could exist and demonstrate changed cognition as a result of genotype. This may be more reflective of the innate differences that can exist in individual cognition despite similar anatomy. Of particular interest is the path trace analysis of allocentric tests in open field-type mazes, where movement is not restricted by walls (such as the MWM, CBM or Barnes maze). Although the absence of choice points aims to encourage allocentric strategies in these mazes, evidence suggests egocentric strategies can still be used; view-matching on distal cues can lead to egocentric cue guidance (e.g. face the star and then turn left) [35], which can successfully complete the task. Non-allocentric strategies such as serial strategies (visit all locations) and chaining (knowing distance from the edge of the maze) can also be successful strategies that also cannot be seen using traditional metrics (see **Figure 7**). These search strategies can be manually assigned through blinded categorisation or be analysed using automated algorithms. While historically latency and distance have been used as measures of cognitive disturbance in the MWM, time spent in the target quadrant on the probe day and search strategy are adjunct parameters that can provide a deeper analysis. Indeed, Rogers et al. [34] elegantly put forth how imperative investigating search strategy and setting up a high-powered experiment can be. Their study demonstrated not only the importance of high saliency cues but also the depth and breadth of information available through the analysis of search strategy.

The adoption of an allocentric search strategy is completely dependent on the quality of landmarks available [34]. This adds another consideration to the design of experiments for researchers; the setup of the maze must be carefully considered. Additionally, Rogers et al.

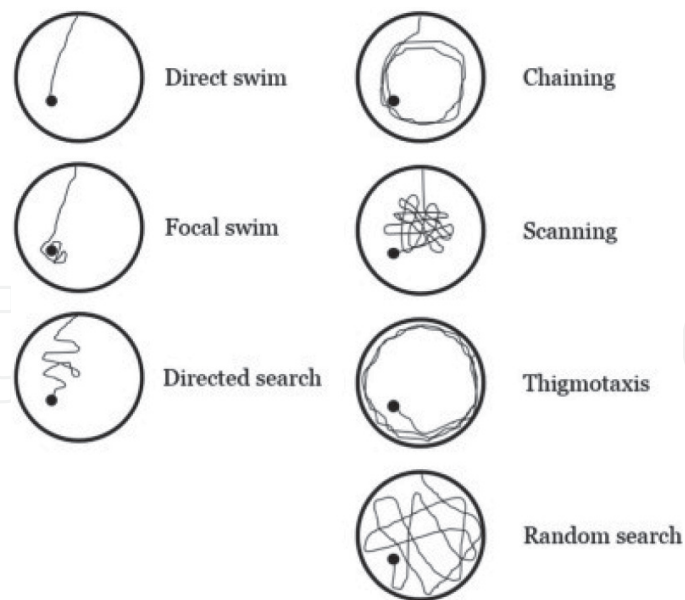


Figure 7. Selection of search strategies employed by rodents on the Morris water maze, adapted from Rogers et al. [34].

[34] demonstrated that the latency and path length parameters do not provide differentiation between the different search strategies and in fact do not provide a reliable analysis of spatial memory formation. From this arises the argument that not only does investigating search strategy allow for the elucidation of egocentric versus allocentric search strategies but that the saliency of distal cues allows the research animal to employ these strategies in the first place. It is important to note that more thorough methods for evaluating MWM performance have been suggested for a long time. The proximity measure, introduced in 1993, measures distance to the goal at a frequency of 10 Hz to get an average proximity throughout the trial. This measure was seen to be more sensitive than latency to the goal and was able to pick up subtle and otherwise masked effects [36]. Unfortunately, this measure is still currently under-reported and highlights the need to actively encourage extended analysis beyond latency, distance and time.

Building upon this, the study by Suzuki and Imayoshi [37] deftly investigated and presented a novel method of analysing navigation in the Barnes maze. The authors titled this 'network analysis method', which allowed for the visualisation of a rodent's exploratory patterns. The method involves several algorithms which initially determine the search strategy employed by a rodent (spatial, serial or random). Following this analysis, Suzuki and Imayoshi [37] were interested in determining if particular networks were associated with particular search strategies. A local network is the exploratory behaviour pattern of one mouse of one experimental group. Once local networks are established for all mice of an experimental group, a global network can be created from this data and demonstrates the exploratory behaviour of the whole experimental group. For this study, Suzuki and Imayoshi [37] focused on eight different exploratory behaviours that formed dynamic nodes. Following algorithmic analysis, links between the different nodes (i.e. exploratory behaviours) were established. The authors observed that as spatial learning is established across the experimental days, the global network is simplified,

and nodes surrounding the target area are stronger than indirect nodes with indirect links. Most importantly, as highlighted by Suzuki and Imayoshi [37], although significant differences in cognitions were subtle, these spatial navigation behaviours were able to be recognised and quantitatively analysed using the 'network analysis method'. The capacity to apply quantitative statistics to patterns of behaviour provides a fantastic opportunity to apply strong, scientific investigation into higher cognitive processing. This is a strong example of utilising search strategy analysis in order to identify the more dynamic substrates of the cognitive underpinnings of navigation. The successful identification of strengthened spatial memory by Suzuki and Imayoshi [37] using the 'network analysis method' demonstrates the brevity of utilising similar approaches when investigating spatial memory.

6. Neurophysiology of allocentric and egocentric strategies

Studies investigating the neurological correlates of egocentric and allocentric navigation have utilised lesion, electrophysiological and optogenetic techniques to better understand the distinct mechanisms underlying them. In many experimental and clinical settings, specific deficits in one reference frame but not the other are observed, further indicating separate mechanisms.

6.1. Lesion studies for identification of allocentric and egocentric brain networks

A number of studies have investigated the cognitive consequences of lesioning the hippocampus using spatial memory tests such as the MWM. The overwhelming consensus is that allocentric learning is impaired after hippocampal lesioning. One of the first studies to demonstrate this was by Morris et al. [38] in rats. They demonstrated that lesioning the hippocampus of rats resulted in an inability to navigate the MWM. This is supported by numerous other studies [7, 39, 40], which all found significant deficits in traditional spatial memory measurements such as time to platform, distance to platform and time spent in target quadrant (probe trial). Other lesion studies indicate the perirhinal cortex, entorhinal cortex and parietal cortices to be involved in allocentric search navigation [41–43]. Maze apparatus that can be utilised to test egocentric search strategies include RAM [44], Cincinnati water maze and Star maze [33]. While allocentric search strategies appear to be dependent majorly upon the temporal lobe components, egocentric navigation appears to have a broader network. A study using the RAM observed deficits in egocentric navigation after lesioning medial agranular cortices [44]. Comparatively, a fascinating study by Wolff et al. [45] demonstrated that region-specific lesions of the thalamus impaired egocentric and allocentric navigation independently. They postulated that lateral thalamic lesions interrupt communication between the striatum and frontal cortex, by destruction of the intralaminar nuclei. This interrupted pathway manifested as deficits in egocentric navigation. Indeed, studies have indicated that the dorsal striatum and head direction cells are involved in egocentric navigation [18]. The cerebellar-dentate nucleus has also been implicated in egocentric processes [46], demonstrating the complexity of the networks involved in these search strategies. While we have so far attempted to separate these two navigation strategies, they are not mutually exclusive. A fantastic review by

Ekstrom, Arnold and Iaria [1] goes into detail on theories that describe transitions between allocentric and egocentric strategies, as well as the overlap between them.

6.2. Electrophysiological studies for identification of allocentric and egocentric brain networks

There has been extensive research into the neural correlates of spatial memory and navigation. In the seminal book, *The Hippocampus as a Cognitive Map* [47, 48], O'Keefe and Nadel put forward evidence for a cognitive map of space in the hippocampus. A neural model for a spatial map was proposed, built by specialised populations of cells in the hippocampal formation that fire with direct relation to place (place cells). The flow of spatial information in this model begins with sensory and contextual stimuli from the neocortex moving through the entorhinal cortex where egocentric information is encoded. The signal then moves to the fascia dentata of the hippocampus where it is thought that this mix of information is organised and sent to the CA3 and CA1 field of the hippocampus. It is here that the construction of the spatial map is thought to be accommodated with place and misplace cell systems. This model paved the way for future research and identification of other specialised cell types such as head direction cells located between the entorhinal cortex and CA1 in the postsubiculum [49], boundary cells in the subiculum [50], grid cells in the entorhinal cortex [51] and speed cells in the medial entorhinal cortex [52]. Edvard and May-Britt Moser (grid cells), along with John O'Keefe (place cells), were awarded the Nobel prize in Physiology or Medicine in 2014 for their work in investigating these cells underlying the spatial representations of space in the brain. Grid cells, similar to place cells, fire in response to changing position in an environment [51]. These cells differ, however, in their response to a change in environment [53]. When exposed to a new environment, grid cells maintain their representation of space and can therefore represent universal metrics such as distance and direction. These properties suggest that grid cells are involved in path integration [54], a navigational method that integrates movement, direction and speed to compute location. Importantly, path integration primarily relies on an egocentric reference frame because the abovementioned movement, direction and speed are all relative to self [12]. On the other hand, place cells undergo remapping and adopt new, unrelated representations when exposed to novel environments. The resulting allocentric map includes locations predominantly independent of the path taken to get there [55].

Mechanistic differences between egocentric and allocentric reference frames are also observed in electrophysiological recordings. Theta oscillations, or the theta rhythm, are low-frequency (~7–9 Hz) local field potential oscillations that function as a temporal frame in which neurons fire action potentials [56]. Both place and grid cells demonstrate theta phase precession effects to differing levels during navigation. That is, as an animal travels closer to the peak firing field of a certain place or grid cell, that cell will fire earlier in the theta phase [57]. This adds an additional layer of encoded information that contributes to navigation. Furthermore, oscillatory activity has been shown to facilitate the coherency between brain regions involved in egocentric and allocentric navigation [58]. Specifically, low-gamma oscillations (25–50 Hz) between the CA1 and CA3 and high-gamma oscillations (65–140 Hz) between the CA1 and

entorhinal cortex. Indeed, these oscillatory frequency ranges in the CA1 are associated with changes in egocentric and allocentric behaviour [59].

6.3. Optogenetic studies for identification of allocentric and egocentric brain networks

Optogenetics is an outstanding technique to elucidate the functional relevance of particular neuron populations in specific brain regions and areas. A study by Andrews-Zwilling et al. [60] optogenetically inhibited hilar GABAergic neurons which led to a spatial memory retrieval impairment in the MWM. This study used the parameters escape latency and percentage time spent in target quadrant. However, there was no reported analysis of search strategy. As outlined by Rogers et al. [34], search strategy analysis is imperative to confirm spatial memory learning. For this study, it would be interesting to know the strategies employed by the mice and compare to controls, to see exactly how the optogenetic inhibition is affecting navigation. By knowing the effects upon search strategy, it provides further depth and breadth to understanding the cognitive processes occurring. Yamamoto et al. [8] further confirm a role for the hippocampus in spatial memory with their optogenetic inhibition of medial entorhinal cortex layer III (MEC) inputs to the CA1 of the hippocampus. This was demonstrated using the delayed nonmatch-to-place T-maze task, a working memory task that is based upon egocentric navigation, that is, it is based upon the successful alternation of turning left or right at a junction [61]. Building upon this, the study by Perusini et al. [62] demonstrated that optogenetically stimulating the dentate gyrus in aged mice improved memory retrieval in the contextual fear conditioning paradigm. This has great implications for the current problem of the world's extended life span and associated neurodegenerative diseases such as dementias. The hippocampus is a hub for memory and is linked to multiple networks, as demonstrated especially by Ito et al. [63]. Optogenetic inhibition of cells in the nucleus reuniens of the thalamus resulted in reduced trajectory-dependent firing of the CA1 region of the hippocampus. Projections from the medial prefrontal cortex to the nucleus reuniens which end in the CA1 hippocampus region are imperative to goal-directed map representation.

The studies examined above indicate that some regional differentiation exists between the individual networks involved in allocentric and egocentric navigation. Taken together, it would appear that the hippocampus and surrounding areas are strongly involved in spatial memory and in particular the allocentric search and egocentric navigation strategies. Understanding the effects upon spatial memory and navigation is enhanced by analysing the search strategies employed by research animals. Disruptions to normal functioning could result in compensatory mechanisms that disguise impairments to spatial memory, if the appropriate analyses are not performed. Future studies should use techniques such as optogenetics to specifically investigate cell populations in the hippocampus and associated areas and their role in spatial memory and allocentric and egocentric navigation strategies using specifically designed mazes such as the Star maze. It is widely accepted that the hippocampus has a role in spatial memory, but we are now starting to understand how disrupting spatial memory alters navigational pathways.

7. Search strategies and their relevance to ageing and disease

Further incentive to differentiate egocentric and allocentric navigation in spatial memory tests arises from evidence in studies of human ageing and disease showing that deficits are observed in specific search strategies. Studies in real-world environments such as supermarkets [64] and roads [65] confirm the anecdotally long-held belief that spatial memory performance worsens with normal ageing. Elderly humans also perform worse in virtual reality versions of mazes designed to investigate spatial memory [66] accompanied by changes in electrophysiological event-related potentials [67]. Allocentric navigation seems to be affected more so than egocentric navigation [25, 67], and specific deficits arising only when switching to an allocentric from an egocentric strategy have also been observed [68]. These behavioural changes may be a result of age-related changes in the hippocampus including decreased synapse function and long-term potentiation [69]. Declines in other domains such as working memory and sensory perception most likely also contribute to the decreased spatial memory performance seen in ageing; however, the vulnerability of allocentric over egocentric strategies prompts the need for further investigation into the mechanism behind this deficit. Interestingly, allocentric-specific deficits also seem to manifest in the young (6–7 years old) as well as the elderly [70], suggesting the deficit may be related to cognitive load.

Alongside ageing is an increase in risk for neurodegenerative disorders such as Alzheimer's disease (AD) and associated decline in memory. Topographical disorientation is an early symptom of AD that involves the inability to orientate in the environment and often leads to patients being prone to getting lost. A systematic review of egocentric and allocentric spatial ability in AD by Serino and colleagues [71] observed an allocentric deficit in both mild cognitive impairment and AD. Furthermore, a later study by Allison and colleagues showed allocentric-specific deficits can also be seen in asymptomatic preclinical AD, suggesting allocentric spatial memory tasks may be useful in the early diagnosis of AD [72]. Similar allocentric-specific deficits are also observed in neurodevelopmental disorders such as attention deficit hyperactivity disorder [73]. Although the ability to learn locations from allocentric representations has been shown to be decreased in patients with autism spectrum disorder (ASD) as well [74], there is sparse literature and agreement on this topic [75]. Cognitive symptoms are an untreated aspect of schizophrenia, and allocentric-specific deficits have been observed [76].

Many spatial memory deficits in cognitive decline and disease seem to preferentially affect the allocentric reference frame and navigational strategy. Constructing an allocentric cognitive map of an environment would allow navigation from any start point to a goal location compared to an egocentric sequence, which would only be viable from a single start point to reach a goal. Intuitively, allocentric search strategies are more complex than egocentric strategies and therefore may experience loss of function before the onset of more severe deficits that then go on to affect the egocentric reference frame. In a similar vein, there is also evidence to suggest that perhaps the allocentric reference frame is a culmination of many egocentric frames, meaning egocentric frames are likely to exist without allocentric frames but not vice versa [77]. This could explain the disproportionate dysfunction in allocentric abilities and the relative persistence of

egocentric ones. Another possibility is that specific navigational deficits are a reflection of inaccurate (unconscious) selection of the search strategy most suited for the task at hand [78].

8. Why is the distinction important?

Animal models allow the investigation of specific forms of memory and dysfunctional neuro-components, as a way to parallel human illness. Since humans and animals have analogous brain regions with similar functions, it is helpful to the expansion of biological knowledge to investigate possible disruptions in order to understand the fundamental neuroscience.

Distinguishing egocentric and allocentric search strategies in spatial memory tests is important because:

1. Accuracy and integrity of experimental results would be stronger. Due to the fact that one strategy may be preferentially affected over the other, not considering the distinction has a similar effect to not measuring the effect of an unknown variable. Results may become skewed, diluted or even completely masked.
2. There is a potential to discover novel therapeutic targets. Coupling behavioural data with known physiological and molecular pathways underlying these search strategies could elucidate specific deficits in disease.
3. They can function as more precise outcome variables that can potentially be utilised in early diagnosis of cognitive impairments. Detection of subtle deficits may also be improved.
4. Understanding the inner workings of our brains will be advanced.

9. Conclusions

Reviewed here is evidence supporting the distinction of egocentric and allocentric reference frames in spatial memory. These reference frames and their respective search strategies are closely related and are often used in combination when navigating. We argue that because these reference frames involve different mechanisms and they are differentially affected by experimental manipulations and disease, they should be appropriately dissociated when investigated. Rodent mazes such as the Star maze have been developed to tackle this issue by directly probing egocentric and allocentric strategies. Other, more widely used mazes such as the Y-maze and RAM are able to probe these strategies with slightly modified protocols. Open arena apparatus such as the MWM, CBM and Barnes maze can provide different insights on spatial memory performance, but an often overlooked and informative parameter is the qualitative measurement of path traces and investigation of search strategies. Not only has the investigation of search strategy been shown to be required to confirm the creation of an allocentric map, it provides a depth and breadth to understanding the cognitive processes occurring post-experimental intervention or modification. We strongly encourage and recommend the adoption of search strategy analysis and comparison between experimental groups, in order to gain the most from your data.

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