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REVIEW

Spatial memory tasks in rodents: what do they model?

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Abstract The analysis of spatial learning and memory in rodents is commonly used to investigate the mechanisms underlying certain forms of human cognition and to model their dysfunction in neuropsychiatric and neurodegenerative diseases. Proper interpretation of rodent behavior in terms of spatial memory and as a model of human cognitive functions is only possible if various navigation strategies and factors controlling the performance of the animal in a spatial task are taken into consideration. The aim of this review is to describe the experimental approaches that are being used for the study of spatial memory in rats and mice and the way that they can be interpreted in terms of general memory functions. After an introduction to the classification of memory into various categories and respective underlying neuroanatomical substrates, I explain the concept of spatial memory and its measurement in rats and mice by analysis of their navigation strategies. Subsequently, I describe the most common paradigms for spatial memory assessment with specific focus on methodological issues relevant for the correct interpretation of the results in terms of cognitive function. Finally, I present recent advances in the use of spatial memory tasks to investigate episodic-like memory in mice.

Keywords Declarative memory · Episodic memory · Procedural memory · Spatial memory · Working memory

Introduction: what is interesting about spatial memory?

The experimental analysis of cognitive functions occupies a central place in the neurosciences and experimental psychology. Complex forms of learning and memory are attracting more and more interest within the scientific community because of their importance in understanding human autobiographical knowledge and sense of self. Spatial memory is probably one of the most intensively investigated cognitive mechanisms in experimental psychology and neuroscience. Three major approaches in studying spatial learning and memory can be identified: cognitive psychology, cognitive neuroscience and molecular and cellular cognition. Cognitive psychologists aim to understand the way that spatial learning and memory are processed in the species of interest. Spatial memory has attracted the interest of cognitive neuroscientists since the discovery and description of place cells in the hippocampus. Indeed, the possibility of recording and measuring specific neuronal firing patterns in specific neuronal subtypes and brain regions provides an ideal experimental model for studying the cellular substrates underlying cognition and the neurophysiological mechanisms of mental processes. Based on human and animal data generated by cognitive psychologists and neuroscientists, molecular and cellular biologists mainly use spatial memory as a model for understanding the mechanisms underlying cognition. In this case, the primary animal models are rodents. In particular, the investigation of spatial memory in transgenic mice has become a common approach for investigating the molecular and cellular players involved in human autobiographical memory and its degeneration in dementia. For example, spatial memory abilities are commonly analyzed to validate transgenic mice thought to model age-related memory decline or neurodegenerative or psychiatric diseases known to affect declarative memory such as Alzheimer's and Parkinson's diseases, schizophrenia, autism and attention deficit and hyperactivity disorder (ADHD).

The focus of the present review is to describe the way in which spatial memory in rodents can be used as a model to investigate human memory and its decline in mental disorders. The proper interpretation of rodent behavior in tasks for determining spatial memory and its validation in terms of

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human cognitive functions is only possible if we know how spatial memory works in the species of interest. In the present review, I first give an overview of the various types of human cognitive functions and the manner in which they are affected in neuropsychiatric and neurodegenerative diseases. Next, I introduce the concept of spatial memory and describe the various navigation strategies that are considered to rely on the different forms of spatial memories. I then discuss the different forms of spatial memory that can be used as a model for more general cognitive functions such as working memory, procedural memory, or episodic memory that are impaired in human diseases. Finally, I describe the appropriate experimental conditions and parameters for the analysis of the various types of memories in rodents and mention some recent advances in the use of spatial memory tasks in mice.

Various forms of memory

Memory is the process by which experience-based information is encoded, stored and finally retrieved. The duration that a memory is stored, i.e., the time between memory acquisition and retrieval, is used to differentiate between short-term and long-term memories (Atkinson and Shiffrin 1968; Baddeley and Warrington 1970; Milner 1972). Short-term memory has a limited capacity (i.e., amount of information that can be stored and retrieved) and has a short-term temporal decay, usually defined between several seconds and one minute (Eysenck 1988). Often, short-term memory is confused with working memory, although the two concepts are generally believed to be distinct. Working memory is a term that was used by Miller (1956) to refer to memory while it is being used to plan and carry out behavior. Specifically, working memory is considered a cognitive process that includes attention, short-term memory and information processing (Baddeley 1992; Becker and Morris 1999). Information stored in short-term memory can be transferred into long-term memory by a process called consolidation (Dudai 2004; Wang and Morris 2010). Contrary to short-term memory, long-term memory can store unlimited amounts of information for potentially unlimited duration.

Memories are classified into various subtypes also depending on the type of information stored and cognitive processes underlying its encoding. Cognitive psychologists identify two major classes of long-term memory: declarative (or explicit) and non-declarative (or implicit) memory (Anderson 1976). Non-declarative memories, as indicated by the name, are unconsciously recalled without awareness of the experiences that have formed them. Non-declarative memories are, for instance, procedural memories required for the execution of integrated procedures involved in both cognitive and motor skills, e.g., for typing on the computer keyboard or riding a bicycle. In contrast, declarative memory is consciously activated and includes the knowledge or recollection of facts and the meaning of these facts. Declarative memory is further subdivided into semantic and episodic memories (Tulving 1972). Semantic memories store general factual knowledge independent of personal experience or recollection thereof, e.g., knowing that "Romeo and Juliet" is a tragedy written by William Shakespeare. In contrast, episodic memories are recollections of personal experiences, e.g., remembering when you went to the theater to see a performance of "Romeo and Juliet". The repeated encoding of self-experienced episodic memory has been postulated to lead to experience- and context-independent semantic memory (Squire 1992; Eichenbaum et al. 1999; Buzsáki and Moser 2013).

The above-described forms of memories have been defined based primarily on studies in human patients with brain lesion. These studies are relevant not only for the definition of the different types of memories but also for identifying the neuroanatomical regions involved. Although the aim of the present paper does not include a discussion of the vast literature on human studies, the case of Henry Gustav Molaison (H.M.) should be mentioned as it was the most influential for the definition of cognitive theories (Scolville and Milner 1957). At the age of 27, H.M. underwent surgery to treat epilepsy during which large parts of both temporal lobes (including the hippocampus, para-hippocampal region and amygdala) were removed. As a consequence, H.M. displayed anterograde amnesia and temporally graded retrograde amnesia for declarative forms of memory. Interestingly, his working memory and procedural memory were not affected by the surgery. In the context of spatial learning and memory, although H.M. was heavily impaired in certain spatial memory tests, he was still capable of learning and memorizing the topographical layout of his residence and drawing a map of it. These observations were fundamental for the understanding the neuroanatomical substrates of specific cognitive processes (Corkin 2002).

Neuronal substrates of memory: "of mice and men"

How do these definitions of different types of memory apply to non-human animals and specifically to rats and mice, the most popular animal models used in cognitive neuroscience? Whereas rats and mice are accepted as possessing non-declarative memories, whether these species process and store complex information similar to human semantic and declarative memory is still under debate. In particular, episodic memory is considered to be an exclusively human cognitive function because its definition has been linked to autonoetic consciousness (Tulving 2002), a feature that can be demonstrated only in humans (Griffiths et al. 1999). For non-human animals, the definition of episodic-like memory has been proposed. The criterion for episodic-like memory is that a behavioral response should be based on "what" occurred "where" and "when" during a past experience (Clayton and Dickinson 1998).

Although classical paradigms to measure spatial memory cannot be strictly interpreted in terms of episodic-like memory, human and rodent spatial memory are generally accepted to show several similarities to semantic and episodic memory (O'Keefe and Nadel 1978; Cohen and Eichenbaum 1993; Burgess et al. 2002; Buzsáki and Moser 2013). As previously suggested by the studies of H.M., the major brain structure involved in the encoding, storage and retrieval of declarative memory is the entorhinal cortex–hippocampal system (Squire 1992; Squire and Zola 1996; Eichenbaum 2001; Gabrieli and Kao 2007; Hasselmo 2012). Furthermore, declarative memories are constantly consolidated in the neocortex (Wang and Morris 2010) and whether the hippocampus is involved in the retrieval of long-term memories that have previously been consolidated in the neocortex remains unclear (McClelland et al. 1995; Nadel and Moscovitch 1997; Manns et al. 2003). Studies in rats and mice have shown that memory consolidation involves a relatively simple cascade of molecular and cellular events that alter synaptic efficacy and the interaction between the hippocampus and cerebral cortex (McGaugh 2000; Dudai 2004). Human and animal studies have demonstrated that the same anatomical structures underlying declarative memory are also involved in spatial memory (D'Hooge and De Deyn 2001; Burgess et al. 2002; Stella et al. 2012). Numerous lines of evidence in humans and rodents indicate that non-declarative procedural memory is mediated by the neostriatum and cerebellum (Salmon and Butters 1995; Knowlton et al. 1996; Nagao and Kitazawa 2008) and, in the case of non-declarative emotional memory, by the amygdala (Bechara et al. 1995; Cahill et al. 1995; Adolphs et al. 2005). Thus, declarative and non-declarative memories seem to be processed by the same brain regions in humans, rats and mice. Is working memory also controlled by similar neuronal processes in rodents and humans? The observation that H.M. and other cases of patients with medial temporal lobe damage had intact working memory functions (Drachman and Arbit 1966; Baddeley and Warrington 1970; Milner 1972; Cave and Squire 1992) suggests that brain structures in the medial temporal lobes, including the hippocampus, are involved in long-term memory, whereas working memory is independent of these structures. Functional neuroimaging studies in humans indicate that the prefrontal cortex plays a major role in working memory function (Baddeley 1992; Paulesu et al. 1993; Smith and Jonides 1997; 1998). Recently, the perirhinal cortex and hippocampus have been proposed to be involved in some forms of human working memory related to visual perception (Ranganath et al. 2004; Graham et al. 2010). Whereas maintenance of visual information occurs in the inferior temporal cortex, the retrieval of goal-directed associative memory depends on top-down signals from the anterior prefrontal cortex (Ranganath et al. 2004). Moreover, spatial working memory tasks activate both the parietal cortex and the prefrontal cortex in humans (Cohen et al. 1997). Thus, working memory has been postulated to involve the interaction between many networks throughout the brain, among which the prefrontal cortex seems to be important for processing information (Rowe et al. 2000; Gazzaley et al. 2005). Studies in rats indicate that, similarly to humans, working memory and executive functions are controlled by the prefrontal cortex (for a review, see Kesner and Churchwell 2011). For instance, single-unit recordings in rats have revealed that neurons in the dorsolateral prefrontal cortex remain active during working memory storage/processing (Fuster et al. 1982). In conclusion, despite the limitations of modeling human cognition in animals, mice and rats are considered as a valid approach to investigate the mechanisms underlying the different forms of memory functions.

Memory disorders

Appropriate animal models for an analysis of memory function are particularly important for the study of the molecular causes of memory disorders in humans and for testing potential therapies. Memory disorders have a high impact on the quality of life of affected patients and their carers with high costs for society. Disturbances of memory functions are core pathology and associated features of several neurological diseases such as Alzheimer's disease, Parkinson's disease, schizophrenia, autism, ADHD, bipolar disorder and epilepsy (Huber and Paulson 1985; Förstl and Kurz 1999; Kenworthy et al. 2008; van Os and Kapur 2009; Pagonabarraga and Kulisevsky 2012; Stretton and Thompson 2012). Declarative and episodic memories are particularly susceptible to decline attributable to ageing (McIntyre and Craik 1987) or neurodegenerative disease. For instance, selective impairment of episodic memory is a preclinical marker for the future development of Alzheimer's disease (Almkvist and Winblad 1999). Deficits in semantic and episodic memory are observed in other neurodegenerative diseases such as Parkinson's disease (Elgh et al. 2009) and psychiatric diseases such as schizophrenia (Boyer et al. 2007). Consistent with its role in declarative memory, the hippocampus is particularly vulnerable to the effect of aging (Miller and O'Callaghan 2005) and Alzheimer's disease (Morris and Baddeley 1988; Drago et al. 2011). In addition to episodic memory, another cognitive function that is often affected in neuropsychiatric and neurodegenerative disorders is working memory. Deficits in working memory and executive function controlled by the prefrontal cortex are hallmark symptoms of schizophrenia (Goldman-Rakic 1994) and ADHD (Barkley 1997). In the case of ADHD, hypoactivity of the mesocortical dopaminergic system is suggested to be responsible for the cognitive symptoms (Liston et al. 2011), whereas dysfunction of the prefrontal cortex of schizophrenic patients is associated with impairments of several neurotransmitter systems, such as dopamine,

gamma aminobutyric acid and glutamate (Barch and Ceaser 2012). Thus, different diseases affect different forms of memory. This means that the use of animal models for specific memory disorders requires the use of behavioral paradigms and analyses that allow the discrimination between different cognitive functions. To this end, several tasks involving spatial learning and memory have been established to model specific types of memory (e.g., working memory, long-term memory, procedural memory, episodic-like memory).

Various forms of spatial memory and navigation strategies

As mentioned above, the study of spatial memory is a classic experimental approach to investigate various forms of memory in rodents. The term spatial memory refers to memories that store information regarding the location of physical objects in space, in other words, the spatial properties of the environment. Obviously, spatial memory is extremely important for the fitness of an animal, because it allows the location of a nest or shelter and relevant resources such as food, water, or sexual partners to be remembered. A typical behavioral response that relies on spatial memory is navigation, which is the ability to travel from one place to another. This means that navigation is the observable and measurable behavior that is used by behavioral biologists to obtain insight into spatial memory. Indeed, the major challenge of studying behavior in animals is the interpretation of a behavioral response in terms of a specific function. In fact, behavior is nothing more than the expression of a muscular contraction (or lack thereof) in response to a stimulus. Thus, behavioral biologists do not analyze "memory" or "anxiety" but simply motor re-actions.

Navigation from one location to another can be achieved by using several distinct strategies that rely on two major groups of cues: idiothetic (interoceptive, internal) and allothetic (exteroceptive, external) cues. Idiothetic cues are generated by self-movement (proprioceptive and vestibular cues, sensory flow, or efferent copies of movement commands) and navigation based on these cues is called idiothetic navigation. One kind of idiothetic navigation is dead reckoning (also called path integration in non-human animals) in which the distances and turns of the animal are memorized while moving so that the shortest route back to a starting position is computed by adding the vectors for each part of the journey (O'Keefe and Nadel 1978; McNaughton et al. 1996, 2006; Thompson and Varela 2001). In contrast, allothetic navigation relies on a representation of the environment based on visual, auditory, olfactory, or tactile cues present in the environment. Although both idiothetic and allothetic strategies are accepted to work together to guide proper spatial behavior (O'Keefe and Nadel 1978; McNaughton et al. 1996), allothetic navigation is the one that has attracted most interest by the scientific community. In particular, allothetic navigation plays a central role in most theories related to spatial memory as a model for human declarative memory. This is probably also the reason that the term spatial memory is mainly used in cognitive psychology and neuroscience in the context of memories that provide a spatial representation of several items in the environment. This type of memory was first postulated in the place learning theory of Tolman (1948) who suggested that animals learn and memorize the spatial layout of an environment and the position of specific targets or objects within that environment and in relation to each other. The concept of place learning was then extended by O'Keefe and Nadel (1978) in their cognitive map theory that designates the hippocampus as being the location in which spatial information is stored and flexibly used for navigation. The idea that the hippocampus is required for the acquisition and storage of declarative memory and spatial memory was initially suggested by observations in human subjects who had lesions in the hippocampus or temporal lobes and who suffered from antograde amnesia for declarative memories and spatial memories (Scolville and Milner 1957). The other relevant piece of evidence was the description of place cells in the rat hippocampus, namely neurons that show high rates of firing whenever an animal enters a specific location in the environment independent of any particular stimulus or ongoing behavior. The discovery of place cells strongly supported the theory of a cognitive map based on the flexible use of distal landmarks. The theory also postulated that spatial memory is a subtype of episodic memory that stores information within the spatio-temporal frame (O'Keefe and Nadel 1978). This theory was further extended by Cohen and Eichenbaum (1993) who created the definition "relational memories" as a higher category of memories that included episodic and spatial memory (Eichenbaum et al. 1999).

Importantly, theories concerning spatial learning and memory rely on two assumptions. First, a central issue of the place learning theory is the flexible use of distal landmarks so that a cognitive map can be used to guide navigation even in situations in which previously available paths to a goal are blocked and novel routes are computed (Tolman et al. 1946). Second, the cognitive map should rely on the position of additional landmarks relative to each other. This means that allothetic cues should not be used based on a stimulus–response rule but on the ensemble of external cues. These constrictions complicate the interpretation of animal data, because the mere fact that external cues are provided does not imply a control on which information the animals use to navigate and the manner in which they compute the trajectory to reach a specific goal in a maze. For instance, procedural or stimulus–response processes such as circling or vector heading can support a good performance in the water maze task (Wolfer and Lipp 2000). In the case of circling, animals learn that the platform is located at a certain distance from the wall and keep swimming in circle within the annulus containing the platform. In the

case of vector heading, animals learn that the platform is placed somewhere along the vector pointing to a single landmark. In both cases, animals do not require a cognitive map to find the target; specifically, they do not need to know the configuration of multiple allothetic cues and the exact position of the platform. Thus, the evaluation of the performance of an animal in a spatial task should focus on the navigation strategy used and not only rely on whether the animal successfully solves the task (for a review, see Wolfer and Lipp 2000). For this reason, the analysis of searching strategies by means of a transfer trial (also called "probe trial") is considered the most reliable way to analyze spatial learning and memory in the water maze task (Hodges 1996) and public domain software is available to facilitate a thorough analysis of searching strategies (see Wolfer et al. 2001).

Tests and protocols for spatial memory in rats and mice

The type of memory tested depends on the protocol and experimental conditions used. In the following paragraphs, I give an overview of the most common tests for spatial learning and memory in rodents, with a particular focus on the way that the different forms of memory can be assessed depending on the layout of the maze and protocols used. Moreover, I will describe those factors that might influence the performance of the animals independently of their cognitive abilities, e.g., hyperactivity, novelty-induced behavior, anxiety and stress (Morellini and Schachner 2006; Morellini et al. 2010). Indeed, mice show a high interindividual variability in coping strategies that impact on their performance in several behavioral tests (Benus et al. 1989; Jakovcevski et al. 2008, 2011). Because the use of an active or passive coping strategy is often affected in knockout and mutant mice (Brandewiede et al. 2005; Morellini and Schachner 2006), the coping strategy should be analyzed and taken into account when evaluating the cognitive abilities of mice. For instance, poor performance in a hippocampus-dependent test of a mouse model for ageing-induced dementia has been shown not to be caused by memory impairments but by the inability of the mice to use a passive coping strategy (Brandewiede et al. 2005).

Four principal paradigms are typically used to measure spatial working memory and spatial reference memory in rodents: the radial arm maze, the T or Y maze, the spatial version of spontaneous object recognition and the water maze tests. With the exception of the T and Y mazes, which are almost exclusively used to measure working memory, the other tests can be used to assess the different forms of memory depending on the conditions and protocol used.

Radial arm maze The radial arm maze is one of the most common paradigms for spatial working memory and spatial reference memory and was originally designed for rats (Olton and Samuelson 1976). The classic maze consists in eight equidistantly spaced arms radiating from a small circular central platform. The number of arms can be changed depending on the protocol and aims of the study (Olton et al. 1977; Lenck-Santini et al. 2001; Cole and Chappell-Stephenson 2003). At the end of each arm, a reward (usually food) is located that is not visible from the central platform. The maze is typically placed in a room surrounded by distal cues. The idea behind the task is that food-deprived animals (maintained at 85%–90% of body weight under *ad libitum* feeding conditions) use the distal cues to identify the arm that must be visited in order to receive the reward. One session starts by placing an animal in the center of the maze until it has collected all the rewards present in the maze. Further sessions can be perfomed over several days. The index of memory is the number of errors, namely the number of entries made into arms that do not contain the reward. Two protocols can be applied. One protocol requires that all arms are baited and the perfect performance is made by an animal that, within a session, visits each arm only once; thus, each entry in one arm is rewarded. Any re-entry into a previously visited arm (that no longer contains the reward) is not rewarded and considered an error. Animals are trained over several sessions and days until their performance (i.e., number of errors) reaches an asymptotic level. Because animals must remember which arms have been visited within one session, this protocol can only assess spatial working memory and not reference memory. A problem related to this protocol is that a perfect performance can be achieved by using a serial strategy, namely by making successive choices into adjacent arms; this strategy would not rely on spatial memory based on allothetic cues but either on idiothetic navigation or procedural responses.

To test reference spatial memory, a protocol is used in which only a subset of arms (e.g., four of eight) is baited. Because the baited arms are always the same throughout the training over several sessions and days, entries into unbaited arms that never contained the reward are defined as errors and used as an index of reference spatial memory. This protocol has the advantage of also allowing the evaluation of working memory by counting the entries in a previously visited arm. Thus, entries into an arm more than once and entries into non-baited arms count as working memory errors and reference memory errors, respectively. Indeed, the opportunity to simultaneously test both spatial reference memory and spatial working memory is considered a typical advantage of this paradigm compared with other tests (Hodges 1996).

Spontaneous alternation and win-shift tests in T and Y mazes T and Y mazes are almost exclusively used to measure working memory in rats and mice (Hughes 2004). The T maze is used in spontaneous alternation and win-shift tests, whereas the Y maze is almost exclusively used in the spontaneous

alternation test. The mazes are composed of three arms connected to form a T (with one central arm and two opposite arms) or a Y with an angle of 120° between two adjacent arms. In the case of the Y maze, the three arms have the same size, whereas in the case of the T maze, the central arm can be shorter or longer than the two opposite arms that have the same size. The spontaneous alternation test relies on the tendency of rats and mice to explore unfamiliar stimuli. Under this assumption, we expect that, given the choice to enter two arms, animals will enter the less recently visited one. Originally, the spontaneous alternation test was designed with the T maze. In the T maze, animals are placed at the dead-end of the central arm and can freely enter either the left or the right arm. Once the animal enters one of the two opposite arms, the animal is removed and placed once again at the starting position at the end of the central arm from whence it can start the next trial during which working memory is tested. Based on the principle that animals would spontaneously visit unfamiliar places, they are expected to alternate, i.e., enter the arm that was not visited in the previous trial. Because functional working memory is required to remember the arm that was last visited and thereby to alternate, an alternation is considered a correct choice, whereas a re-entry into a previously visited arm is counted as an error. Each animal undergoes several trials and the percentage of alternations among all trials is calculated. Because animals have a binary choice, values that are not higher than the chance level of 50% are interpreted as an indication of impaired working memory.

A behavioral paradigm that relies on novelty seeking has been argued as being extremely sensitive to changes in anxiety and stress caused by the constant handling of the animals (Griffiths and Whalsten 1974; Gerlai 2001). For this reason, the continuous spontaneous alternation test in the Y maze was proposed as an alternative paradigm in which animals freely move without being handled between trials. In the case of the spontaneous alternation test in the Y maze, animals are placed in the center of the maze and left to move until they perform a fixed number of transitions between arms. The parameters used to calculate working memory is the ratio (or percentage) of alterations among the total number of transitions. As for the T maze, an alternation is defined as occurring when an animal enters the arm that was not visited in the previous transition. For instance, if we name the three arms A, B and C, an animal making a transition between arm A and B would be carrying out an alternation if it then entered arm C, whereas an entry into A is considered as an error. A limitation of the Y maze is that the inter-trial interval cannot be controlled, as animals freely decide when to make a transition. Because working memory depends on the duration for which a memory is stored (in this case, the time interval between two consecutive transitions), performance (i.e., number of alternations) can be affected by the velocity by which animals complete the given number of transitions within one session. For this reason, the average time required to perform one transition is calculated (by dividing the time to complete one session by the number of total transitions) to control this confounding factor (Morellini and Schachner 2006; Morellini et al. 2010). Contrary to the Y maze, the inter-trial interval in the T maze test is defined by the experimenter by controlling the time between the end of one trial and the start of the next trial at which time-point the animals are placed once again in the starting arm. In this way, working memory can be challenged by increasing the inter-trial intervals (e.g., 5, 15, 30, or 60 s). To combine the advantages of the spontaneous alternation in the T maze (i.e., the control of the inter-trial interval) and Y maze (i.e., no handling and thereby reduced stress for the animals), a modified T maze test for the mouse that allows continuous spontaneous alternation has been proposed (Gerlai 1998). In this case, sliding doors are placed at the entrance of the opposing arms and proximal to the dead-end of the central arm. A session is started by placing a mouse at the dead-end of the central arm with the door closed. After 5 s, the door is opened and the mouse is allowed freely to enter one of the two opposing arms. Once the mouse has entered one arm, access to the opposite one is occluded by the sliding door and the mouse can only return into the dead-end of the central arm in which it is confined for a given period before starting the next trial. With this protocol, mice are not handled between trials but the inter-trial interval is defined by the duration that mice are confined at the starting position in the central arm between trials (Morellini et al. 2010).

A general limitation of the spontaneous alternation test is that the performance is not only affected by working memory function but also by novelty seeking and the exploratory behavior of the animals. Although these behavioral confounders can be analyzed in specific paradigms, such as the open field, elevated plus maze, "new cage new object" tests (Brandewiede et al. 2005; Morellini and Schachner 2006), task-specific effects cannot be excluded. This problem can be solved by using the win-shift paradigm. The wins-shift test is a delayed-no-match-to-sample test in which animals, given the choice between two stimuli, must avoid the most recently experienced stimulus. In the T maze, mice must follow a win-shift criterion ("if you win, then shift") in order to get a reward (usually food) that is located in one dispenser at the end of the arm opposite to the arm in which it was previously found. In principle, the test runs similarly to the spontaneous alternation in the T maze, with the only difference being that an alternation is rewarded by food placed in dispensers at the end of the left and right arms. One limitation of the win-shift paradigm is that the performance is influenced by the motivation to obtain the food reward, so that animals are generally food-deprived to a level maintaining 80%-90% of their body weight under *ad libitum* feeding. Moreover, factors such as handling and stress might also influence the alternation rate. With the aim of controlling these confounds, we have established a free-choice win-shift

test for mice in which animals can freely emerge from their home cage, enter the central arm of a T-maze and perform a whole session with a given number of trials without being handled (Morellini et al. 2010). The test starts by opening a door connecting the home cage to the end of the central arm, so that a mouse can freely enter the central arm and explore one of the opposing arms. As the mouse enters, for example, the left arm, the door at the right arm is closed, so that the mouse can only return into the central arm and finally into its home cage. In the first trial of each session, the dispensers in both arms are baited. After the mouse has entered one arm, eaten the food reward and returned to its home cage, it is confined there by keeping the door closed for a fixed time (i.e., 15, 30, or 60 s depending on the demands of the task). The second trial is started by opening the door once again. During trials, 2–14 mice must find the food reward following the win-shift rule, namely the reward is only in the dispenser in the arm opposite to the one in which the mouse has previously found it. In addition to the number of correct choices, emergence latency (time required to enter into the T-maze with four paws from the moment when the door is opened), latency to eat the reward (time required to eat the food pellet after the mouse has entered the T-maze) and duration of each trial (measured from the moment that a mouse has entered the central arm to the moment that it returns into the home cage) are recorded. These additional parameters are used as an index of anxiety and motivation (Morellini et al. 2010).

Both spontaneous alternation and win-shift tests have been shown to be sensitive to altered function of the hippocampus (Roberts et al. 1962; Deacon et al. 2002) and are commonly used to assess working memory impairments in mouse models for several neuropsychiatric and neurodegenerative disorders, such as schizophrenia, Alzheimer's disease and ADHD. The idea that (spontaneous or rewarded) alternation in the T and Y mazes is indicative of the working memory function was suggested by Olton et al. (1977) and is based on the hypothesis that animals must remember the latest arm that they have visited, avoiding interference between spatial information from different successive trials within a session. Indeed, the ability to store and manipulate multiple items within a short time period is typical of human working memory (Baddeley 1992). On the other hand, several studies have shown that alternation is normal in rats in which the prefrontal cortex has been lesioned (Aggleton et al. 1995; Deacon et al. 2003), in contradiction to the idea that this brain region has a pivotal role in human working memory (Paulesu et al. 1993; Smith and Jonides 1997; 1998). In this context, Sanderson and Bannerman (2012) have suggested that alternation is supported by short-term memory rather than working memory. Based on their studies on mice deficient for the AMPA receptor subunit GluA1, Sanderson and Bannerman (2012) propose that habituation supports spontaneous alternation in mice. Habituation is a form of adaptive behavior and non-associative learning that indicates a decrease in response to a stimulus after repeated presentations (Thopmson and Spencer 1966). In the context of the T and Y mazes, the stimulus is one arm and the response is its exploration (i.e., visiting the arm). Sanderson and Bannerman (2012) assume that the tendency to explore the last-visited arm declines because of habituation, thus leading to an alternation (i.e., entering the less familiar arm). Therefore, under this hypothesis, no maintenance and manipulation of information is required for the alternation behavior suggesting that spontaneous alternation and win-shift tests cannot be used to measure working memory function as defined for humans.

Spatial version of spontaneous object recognition test The spatial version of the spontaneous object recognition test is based on the same assumption as the spontaneous alternation test, namely that rodents have an intrinsic tendency to investigate new stimuli. In other words, the test is a sort of delayed-no-match-to-place paradigm. Contrary to the spontaneous alternation test, this paradigm is mainly used as a model for spatial reference memory and not for spatial working memory. During a sample trial, animals are exposed to an arena in which two identical objects are located (some experimenters use more than two objects). A test trial is performed after a certain time interval (usually 10–60 min and 24 h to assess short-term memory and long-term memory, respectively). During the response trial, animals are re-exposed to the arena in which one of the objects is placed in a new position within the maze. If proper spatial information is provided (e.g., landmarks around the maze or the maze is asymmetrically shaped), animals are expected to spend more time investigating the displaced object than the non-displaced object. Similarly to the spontaneous alternation test, the performance in this paradigm is affected by changes in novelty seeking, exploratory behavior and anxiety. On the other hand, the spontaneous object recognition test has the advantage that these confounds can be controlled by measuring the absolute time spent investigating the objects in the sample and response trials. Another advantage of this task is that a non-spatial version can be performed to test whether an impaired performance is caused exclusively by the spatial component of the paradigm. Namely, the non-spatial version is achieved by substituting one of the two objects with a new unfamiliar one that is placed at the same position that the replaced object had in the sample trial. Because different objects might trigger different exploratory behavior because of their intrinsic properties (muster, shape, size), the two types of objects used as "new" and "old" during the sample and test trials have to be counterbalanced within the experimental groups.

Water maze test The water maze is the most popular task with which to analyze spatial learning and memory in mice and rats. The water maze (often called the Morris water maze) was

first established for the rat by Morris (1981). Performance in the water maze has been shown to be extremely sensitive to several experimental manipulations affecting hippocampal function (Morris et al. 1982; Bannerman et al. 1999). In this paradigm, animals are placed in a large circular maze (usually with a diameter of 1.5–2 m) filled with water made opaque by using milk or white paint. In order to escape the water and to return to the home cage, animals must learn, by using allothetic cues, the location of an invisible platform slightly submerged beneath the water surface. Contrary to the radial arm, T and Y mazes, animals are not restrained in alleys but can freely move within an open circular arena. Because the size of the escape platform is much smaller than the size of the arena (usually 10–15 cm in diameter), the chances of finding the platform by randomly swimming throughout the arena are low. Such a random searching strategy would lead to long escape latencies (i.e., time required to find the platform within one learning trial) because of longer swimming paths. On the contrary, an animal that can exactly locate the platform must use a spatial strategy and find the platform within a few seconds by swimming the shortest stretch between the starting position and the platform. Thus, learning and memory abilities of the animals are evaluated by measuring the escape latency, which is expected to decrease to an asymptotic level over successive training trials. Because the escape latency is influenced by swimming velocity or floating events, the distance swum in order to find the platform is considered a better parameter for learning than escape latency.

Whereas the principles behind the water maze test are simple, several different protocols and modifications to the paradigm have been established and validated in mice and rats in order to investigate specific cognitive functions. Here, I will give an overview of the most common protocols and conditions, while I refer to other reviews for an extended description of the water maze test (D'Hooge and De Deyn 2001; Dudchenko 2004; Van Dam et al. 2006). Two classic protocols are used: the so-called spatial version of the water maze in which the platform is hidden and should be located based on extra-maze landmarks and the non-spatial version in which the platform is made visible by placing a visible cue onto it. In the case of the spatial version, the animals are assumed to locate the platform by relating its position to those of the distal cues surrounding the pool. As discussed above, the ability to relate separate cues to each other has been postulated to characterize general cognitive functions necessary to create not only a cognitive map but also semantic and episodic memories (O'Keefe and Nadel 1978; Cohen and Eichenbaum 1993; Burgess et al. 2002; Buzsáki and Moser 2013). Moreover, the cognitive map theory and relational theory require that landmarks are used in a flexible way (O'Keefe and Nadel 1978; Cohen and Eichenbaum 1993). To be sure that this is the case in the spatial version of the water maze test, the starting position along the wall of the pool is randomly changed between trials. Indeed, if the animals are always started from the same position, they might find the platform by using idiothetic navigation, e.g., by swimming for a certain time at a certain angle from the starting position. Contrary to the spatial version, the non-spatial version of the water maze (also called the "visible platform") can be solved by a simple stimulus–response in which the visible cue on the platform is the stimulus and the swimming towards it is the response. Commonly, the non-spatial version is performed after the spatial version to test whether a poor performance is attributable to spatial memory deficits or is caused by alterations in other functions that can impact on the performance in both the spatial and non-spatial versions of the water maze test (e.g., motivation, stress-response, or sensory-motor function and coordination).

Although the distance swum to find the platform during the training trials can be a good indicator of learning and memory abilities, only a thorough analysis of the swimming paths is considered to allow a proper interpretation of spatial memory function. Indeed, animals might successfully find the platform by using searching strategies that are not based on the knowledge of the precise platform position, such as circling (swimming in a circle within the annulus containing the platform by using the wall of the maze as reference) or vector heading (swimming along a vector between two landmarks). For instance, hippocampus-lesioned rats and mice have been shown to find the hidden platform successfully by using strategies other than place learning (Morris et al. 1990; Whishaw et al. 1995; Lipp and Wolfer 1998; D'Hooge and De Deyn 2001). Whereas escape latency can be easily measured, the analysis of the searching strategy can be performed only by means of an automated tracking system. One parameter that can be analyzed during the training trials is "mean minimal distance to the platform" (Maei et al. 2009). Low values of this parameter mean that the animal swims in the proximity of the platform, thus suggesting that the animal can precisely localize the platform. The transfer trial (also called "probe trial") is surely the most accurate and commonly used method to evaluate not only searching strategies but also spatial reference memory. The transfer trial is performed by removing the platform and letting the animal swim for a fixed time (usually 60 or 90 s). In this way, all animals spend the same amount of time searching for the platform and their navigation strategy can be evaluated. By analyzing the swimming path and occupancy of the different zones of the arena, a precise determination of the animal's search at the platform position or its use of alternative strategies such as circling and vector heading can be made (Wolfer and Lipp 2000; Wolfer et al. 2001; Evers et al. 2002; Law et al. 2003).

In a series of studies, Cain and his colleagues (for a review, see Cain 1998) pointed out the importance of dissociating the spatial information from other types of information that animals must learn in order to perform well in the water maze.

Indeed, in addition to learning the location of the platform by using allothetic cues, animals must learn to inhibit thigmotaxis (rats and mice instinctively search for an escape at the walls and not in the middle of the pool), to associate the platform with escape from the water and to learn simultaneously to coordinate motor responses related to swimming with the detection of visible cues (Morris 1989; Whishaw 1989; Bannerman et al. 1995). Experimental manipulations that might affect some of these behavioral responses will impair the performance independently of spatial memory function. In other words, if these factors are not controlled, a poor performance in the water maze might be erroneously interpreted in terms of impaired spatial memory. For this reason, the suggestion has been made that animals should be first pretrained in order to learn that they must search for a platform on which they can climb and remain until they are returned to their home cage (Morris 1981; Cain 1998). In order to avoid proactive interference between pretraining and the training in the spatial version of the water maze, the pretraining should ideally occur under darkness in a small maze in which the platform can be found within a few seconds of random swimming (Fellini et al. 2006; Fellini and Morellini 2011; Morellini et al. 2010).

The water maze is commonly used to measure spatial reference memory, namely mice are trained with the hidden platform in a fixed position over several trials and days and then the spatial reference memory is tested in a transfer trial performed at a certain time interval since the last training trial, typically 1 or 24 h to test short-term or long-term memory, respectively. On the other hand, new protocols have been designed to test working memory and episodic-like memory by using the water maze test. Steele and Morris (1999) have developed the delayed-matching-to-place (DMP) test in which the hidden platform moves location between training days. During each training day, animals undergo additional trials (usually four) with a short inter-trial-interval so that an increased performance within 1 day can only be explained in terms of enhanced working memory. Indeed, although reference memory can support the performance by providing a cognitive map of the landmarks, the location of the platform should be newly learned every day and the spatial information should be maintained and processed within a short-time interval. Because temporal and spatial components should be processed in order to find the platform successfully, this test has been suggested also to model episodic-like memory function (Morris 2001). The performance in the DMP test is extremely poor in rats with a lesioned hippocampus or hippocampal microinfusion of the N-methyl-D-aspartate receptor antagonist AP-5 (Steele and Morris 1999). Being to some extent similar to the DMP test, the trial-to-criterion protocol was designed to measure the ability of mice to learn new platform locations in the water maze quickly (Chen et al. 2000). In this protocol, animals are trained until they reach a performance that can be obtained only by knowing the location of the platform. Usually, this criterion corresponds to an average escape latency of 15 s over three consecutive trials (Chen et al. 2000; Morellini et al. 2010). When animals have reached the criterion, the platform is moved to a new position during the training session on the following day. Animals are then trained until they reach the criterion for a certain number of platform positions (usually 4 or 5). The parameter analyzed is the number of trials required to reach the criterion for each platform position. Alternatively, animals are trained for a certain number of days and the number of new platform positions that have been learned within this period is quantified. The trial-to-criterion protocol has been shown to be sensitive to detect cognitive impairment in transgenic mice modeling Alzheimer disease (Chen et al. 2000) and enhanced reversal-learning and working memory abilities in knockout mice with enhanced inhibition in the dentate gyrus (Morellini et al. 2010).

What spatial information do rats and mice use to navigate?

The popularity of spatial learning tasks derives from the idea that they require the flexible use of spatial relationships between multiple landmarks. The cognitive processing of the relational properties of various items is supposed to be controlled by the hippocampus and is considered characteristic not only of spatial memories but also of cognitive functions controlled by the hippocampus, such as episodic memory (Eichenbaum et al. 1996; Dusek and Eichenbaum 1997). For this reason, spatial learning tasks for rodents have been designed such that animals must rely on distal landmarks to find a goal within a maze, e.g., a hidden platform in a water maze. Contrary to distal cues (i.e., landmarks outside the maze with which the animal cannot interact), proximal cues (i.e., items within the maze or at the boundary of the maze) have been considered to support stimulus–response strategies that therefore would deviate from the theory of a cognitive map. This is the reason that most of the currently used spatial tasks are designed to reduce the presence of proximal cues. However, as thoroughly and clearly reviewed by Knierim and Hamilton (2011), several lines of evidence indicate that the general idea that navigation and spatial memories are predominantly supported by distal landmarks should be reconsidered. Whereas no doubt exists that distal cues are used during navigation, proximal cues such maze boundaries appear to be the most relevant allothetic cues used by animals, humans included, to navigate in space (Knierim and Hamilton 2011). Whereas the popularity of the water maze also derives from the fact that it does not provide intramaze cues, the water maze like any other maze has boundaries that can be used as proximal cues.

As has been shown, place learning can, indeed, occur in rats even in the absence of landmarks and might be based only on geometric information provided by the boundaries of the environment (Cheng 1986; Ramos 2000). We have demonstrated that mice also process geometry to navigate (Law et al. 2003; Fellini et al. 2006; Fellini and Morellini 2011). Place learning in the water maze task is facilitated when the maze is located in a room with a strengthened asymmetric shape (Law et al. 2003) and mice extrapolate the geometric information relative to the boundaries of a maze and use it to navigate even in the presence of a prominent cue behind the target (Fellini et al. 2006), suggesting that geometry represents relevant information for proper spatial learning in mice. We performed a water maze test in which we could precisely control those cues that the mice were using to locate the hidden platform (Fellini and Morellini 2011). Mice were trained to navigate in a circular water maze by means of four landmarks distributed either symmetrically (symmetry group) or asymmetrically (asymmetry group) around the maze. Thus, mice could locate a hidden platform by either differentiating the landmarks based on their intrinsic features (symmetry group) or in addition by geometric information, i.e., based on the relative distances between landmarks (asymmetry group). In order to be sure that the mice had to rely only on the landmarks to find the platform, the landmarks and the platform were pseudo-randomly rotated by 90° clockwise or counter-clockwise between trials. Data indicated that place learning occurred only in the asymmetry group, supporting the idea that mice navigate by using the relational properties between distal landmarks and that geometric information is required for proper allothetic navigation in this species. Whereas the investigation of the spatial information and navigation strategy that are used by rodents and humans is a matter of interest for comparative cognitive psychologists, the understanding of these phenomena is of great importance for every scientist aiming at the use of proper experimental conditions to study spatial memory in rats and mice.

New perspectives: episodic-like memory in rats and mice

The suggestion has been made that autobiographical memories, such as declarative memory and, in particular episodic memory, cannot be applied to non-human animals (Griffiths et al. 1999; Tulving 2002). Indeed, we cannot prove, in animals, whether they actively (consciously) remember a fact (declarative memory) or just have a knowledge (non-declarative knowledge). Nevertheless, several experimental designs have been established to study forms of memory in rodents and these might model human declarative and episodic memory, with a major role being played by tasks assessing spatial learning and memory. For non-human animals, the definition of episodic-like memory has been proposed. The criterion for episodic-like memory is that a behavioral response should be based on "what" occurred "where" and "when" during a past experience (Clayton and Dickinson 1998; see also above). What–where–when memory as a form of episodic-like memory was first proposed in an elegant study on Western scrub jays (Clayton and Dickinson 1998) and later in rats (Zhou and Crystal 2009). Although the computational, cellular and neuroanatomical processes underlying spatial memory are often assumed also to control episodic memory (Buzsáki and Moser 2013), none of the traditional tests used in mice and rats assess episodic-like memory (Morris 2001). Indeed, memory paradigms designed for the rat and mouse are concerned with the question of "what" and eventually "where" an event was experienced. In order to model human episodic memory, protocols have been designed that require mice also to use temporal cues for the localization of a target during a spatial learning task, such as in the DMP in the radial maze (Staddon 1984) and water maze (Steele and Morris 1999) tests, and in the novelty preference paradigm designed by Dere et al. (2005). Notwithstanding these efforts to model human episodic memory in mice, whether these paradigms fulfil the criteria for episodic-like memory is questionable, because they require either several trials and sessions or spatial preference results from familiarity or the time component can be solved based on the calculation of "how long ago" and not "when" a certain event took place (Clayton et al. 2003). Whereas Zhou and Crystal (2009) have shown, by means of a relatively complex experimental design, that rats possess episodic-like memory, the mouse has surprisingly been commonly used as model for human episodic memory but with no evidence that this species processes episodic-like memories. Recently, we have investigated whether and how mice compute complex ""what-where-when" information, providing the first experimental evidence that mice have episodic-like memories (Meier et al. 2010; Fellini and Morellini 2013). With this aim, we established an ecologically relevant paradigm for spontaneous learning and memory and showed that mice modulate their behavior based on the what-where-when components of past unique episodes, specifically on previous encounters of conspecifics at a defined location and at a specific time of the day. In this paradigm, male mice freely move within an arena in which female mice are confined at a determined location during a 20-min experience trial. When re-exposed to the arena in the absence of the females, male mice preferentially stay at the previous location of the females and perform intense urine marking, a behavior typically expressed in the presence of female mice. Thus, mice acquire the information of what (i.e., the female) was where (i.e., at a specific corner in the arena) during a unique experience. Moreover, we have shown that mice can distinguish at which time of the day they have encountered, in the same location of the arena, either a female mouse or a dominant male, demonstrating that they flexibly process "what-where-when" information, in agreement with the

definition of episodic-like memory for non-human animals. Finally, the expression of mRNA for the immediate early gene arc/arg3.1 is specifically induced in the hippocampus of mice undergoing the experience trial and the preference of the female location during the recall trial is blocked by stereotactic injection of the protein synthesis inhibitor anisomycin into the hippocampus, suggesting that the hippocampus is required for memory consolidation in this paradigm (Fellini and Morellini 2013). Thus, our observations that mice spontaneously generate "what-where-when" representations of single events encourage the use of spatial memory in this species for the investigation of neuronal and cellular processes underlying episodic memory in humans and its degeneration in neurological and neuropsychiatric disorders. The strength of this new behavioral paradigm for referencing spatial memory and episodic-like memory lies in the straightforward interpretation of the results that is possible thanks to the behavioral paradigm and analysis being designed by taking into consideration the biology of the mouse. Moreover, learning in this test occurs spontaneously (i.e., in the absence of punishments or rewards) within one trial and under the absence of anxiogenic or stressful stimuli, making this paradigm a valuable alternative to the commonly used tests for cognition in rodents and, in particular, in transgenic mice (Meier et al. 2010).

Concluding remarks

Learning and memory are analyzed by exposing animals to a behavioral paradigm and by observing how well they recall the task-specific contingencies. Several limitations have however to be kept in mind when assessing learning and memory functions in animals. First, the information that an animal learns and memorizes cannot be precisely assessed but only extrapolated from the animal's performance, which might also be affected by other functions not related to cognitive abilities, such as sensory-motor function, anxiety, novelty seeking, or activity of the stress response. Second, multiple sensory modalities guide animal behavior and several types of information can be used to solve a learning and memory task. For these reasons, an understanding of which cognitive processes are used in a specific task is relevant for interpreting the neuroanatomical structures underlying learning, memory consolidation and retrieval. Thanks to decades of studies investigating rodent navigation strategies and spatial memory, we are in a position to control most of the confounding factors that influence the performance of mice and rats in paradigms for spatial learning and memory. Nevertheless, we still need a better comprehension of the manner in which mice and rats use spatial information and navigate if we are to design experimental paradigms and behavioral analyses that enable a good evaluation of spatial working memory and spatial reference memory functions in rodents as a model of complex human cognitive abilities.

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