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Assessment of spatial memory in mice

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Abstract

Improvements in health care have greatly increased life span in the United States. The focus is now shifting from physical well-being to improvement in mental well-being or maintenance of cognitive function in old age. It is known that elderly people suffer from cognitive impairment, even without neurodegeneration, as a part of 'normal aging'. This 'age-associated memory impairment' (AAMI), can have a devastating impact on the social and economic life of an individual as well as the society. Scientists have been experimenting to find methods to prevent the memory loss associated with aging. The major factor involved in these experiments is the use of animal models to assess hippocampal-based spatial memory. This review describes the different types of memory including hippocampal-based memory that is vulnerable to aging. A detailed overview of various behavioral paradigms used to assess spatial memory including the T-maze, radial maze, Morris water maze, Barnes maze and others is presented. The review also describes the molecular basis of memory in hippocampus called as 'long-term potentiation'. The advantages and limitations of the behavioral models in assessing memory and the link to the long-term potentiation are discussed. This review should assist investigators in choosing suitable methods to assess spatial memory in mice.

Keywords

Hippocampus; Spatial memory; Mazes; Long-term potentiation

Introduction

The average life expectancy in the United States has dramatically increased due to improved nutrition and health care measures (Harman 1999). The US Census Bureau projects that there will be 72 million people over the age of 65 by 2030 representing 20% of the total US population (Kinsella et al. 2001). This increase in life span reflects better health care, but at the same time it raises the concern about "health span". Furthermore, it should be emphasized that the quality of life is key not only in terms of physical well-being, but also in terms of mental well-being.

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Conflict of interest statement

The authors have no conflicts of interest.

It is well known that as individuals age physiological functions progressively decline and this decline is associated with slow adaptations in behavior, motivation, cognition, physical activity, body composition, energy expenditure and hormonal balance (Young 1997). However, one of the most significant problems people deal with, as they get older is a decrease in memory function. The very fact that elderly people are suffering from cognitive impairment as a result of “normal aging”, even in the absence of any overt neurodegenerative disease, makes it a very challenging problem.

Memory is one of the earliest cognitive functions to show decline during aging (Albert and Funkenstein 1992) and this decline has a devastating social and economic impact on individuals, families, the health care system, and society as a whole. The terminology used to define the decline in memory as we age (>50 years) is “age-associated memory impairment” (AAMI), when all other obvious causes of memory decline (for example—Alzheimer’s disease, cerebrovascular episodes, head injury, etc.) except normal aging, have been ruled out. It is surprising to note that the prevalence of AAMI is estimated to be 35–98% (Larrabee and Crook 1994). Apparently, AAMI seems to be a very prominent although not an inevitable consequence of normal aging in the population.

In this review, we will first describe different types of memory including hippocampal-based spatial memory, which is particularly vulnerable to the effects of aging. Secondly, various behavioral models used to determine hippocampal-based spatial memory in mice will be described. Lastly, an overview of the concept of long-term potentiation (LTP) as an important “experimental analog” for the molecular basis of memory will be provided.

What is learning and memory?

In one of the definitions proposed “Learning is referred to as a more or less permanent change in behavior that occurs as a result of practice,” (Kimble et al. 1961). According to Eric Kandel (Kandel et al. 2000; Yarasheski et al. 1995), learning and memory are thought to be a continuous process, and he stated that, “Learning is the process by which we acquire knowledge about the world and memory is the process by which that knowledge of the world is encoded, stored, and later retrieved.” Though used synonymously, learning is the process that modifies subsequent behavior while memory is the ability to remember past experiences. Cognition, on the other hand, is a broad term that applies to processes such as memory, association, language, attention, concept formation and problem solving (Coren et al. 1984).

Memory can be divided into short-term (working memory) and long-term memory. Short-term memory has a limited capacity and lasts only for a period of several seconds to a minute. In contrast, longterm memory can store larger quantities of information for potentially unlimited duration. Anderson (1976) divided long-term memory into declarative (explicit) or non-declarative (implicit) memory. Declarative memory answers the question “what”, and it includes knowledge of facts such as places, things and people, and the meaning of these facts. Declarative memory is further sub-divided into episodic memory, which is the personally experienced event specific to a particular context such as time and place; and semantic memory, which involves knowledge of these facts taken independent of

the context in which they were learned (Miller 1956; Tulving 1972; Fig. 1). The major brain structure involved in declarative memory is the hippocampus along with other medial temporal lobe structures (Squire and Zola 1996). Formation of a new declarative memory is a sequential process that includes acquiring new knowledge (encoding), retaining the information (storage), and bringing it back (retrieval). Furthermore, memories are continually being consolidated in the neocortex (Solms and Turnbull 2002). Non-declarative or implicit memory, on the other hand, answers the question “how”. It is the acquisition of motor skills and habits and is mediated by neostriatum and cerebellum (Bechara et al. 1995; Knowlton et al. 1996; Salmon and Butters 1995). In addition, the amygdala mediates emotional memory and has been shown to be involved in memory consolidation (Cahill et al. 1995).

Episodic memory, a type of declarative memory that depends on the ability to remember in a determined temporal and spatial context (Tulving 1972), is especially vulnerable to normal aging. Elderly people are more susceptible to forget the context related to an episodic event than the event per se (McIntyre and Craik 1987). It has been demonstrated that the elderly perform adequately in memory tasks that require less effort, as in implicit memory tasks that require them to repeat or recognize a stimulus (Craik and McDowd 1987; Light et al. 1992; Puckett and Stockburger 1988). But, their performance diminishes if they have to recollect or retrieve the information retained in their mind or carry out some actions without reminders (Dobbs and Rule 1989; Einstein et al. 1995; Schonfield and Robertson 1966).

Typically, spatial memory is conceptualized as a subtype of episodic memory because it stores information within the spatio-temporal frame (O’Keefe and Nadel 1978). Nadel and O’Keefe’s cognitive map theory suggested that spatial memory is dependent on the hippocampus. There were two lines of evidence suggesting that this was the case. The first was the most famous amnesic patient H. M. reported in late 1950s. This person had severe impairment in acquiring new memories after the medial temporal lobe was surgically removed (Scoville and Milner 1957). The other piece of evidence was the discovery of place cells. “Place cells are neurons that fire depending on animal’s place in the environment independent of any particular stimulus or ongoing behavior” (Eichenbaum 1996). Recently, the concept of cognitive mapping has been taken one step further to describe the role of the hippocampus in the construction of mental images (Bird and Burgess 2008).

During the past decades strong evidence has emerged showing that the hippocampus is critical to learning and memory as well as to age-related cognitive deficits (Corkin2002; Corkinetal. 1997; Gadian et al. 2000; Pigott and Milner 1993; Scoville and Milner 1957; Smith et al. 1999; Squire 1992; Stefanacci et al. 2000; Tulving and Markowitsch 1998; Vargha-Khadem et al. 1997). Studies of human subjects with hippocampal damage provide evidence that this brain region plays a critical role in spatial memory (Abrahams et al. 1997; Astur et al. 2002; Feigenbaum et al. 1996; Goldstein et al. 1989; Maguire et al. 1996; Rosenbaum et al. 2000; Teng and Squire 1999). Patients with bilateral medial temporal lobe damage exhibit severely impaired episodic memory, but have relatively preserved semantic memory (Bayley et al. 2008; Schmolck et al. 2002). They can perform well on a procedural skill and habit learning. Their vocabulary is normal as well as their knowledge of facts learned in the past. Functional imaging studies investigating the brain activity of people

during navigation in a virtual reality town have demonstrated high activity in the hippocampus (Bohbot et al. 2004; Maguire et al. 1998). Similarly, an interesting study in licensed London taxi drivers showed that extensive navigational experience is associated with greater hippocampal gray volume as compared to controls (Maguire et al. 2006). Also, studies of non-human subjects (including rats and monkeys) with hippocampal lesions or age-associated changes in hippocampus demonstrate impaired learning on spatial memory tasks (Bannerman etal. 1999; de Bruin etal. 2001; Gallagher and Rapp 1997; Jarrard 1993; Murray et al. 1998; Pouzet et al. 2002).

All of this evidence is further supported by the fact that the hippocampus (store house of declarative memory) is particularly vulnerable to the effect of aging (Mesulam 1999; Miller and O'Callaghan 2005). The hippocampus appears to be an early target of age-related structural and physiological changes (Hasan and Glees 1973) and damage to the hippocampus results in similar cognitive impairments as experienced by elderly people (Barnes 1979, 1988; Gallagher and Nicolle 1993; Geinisman et al. 1986). Considerable evidence supports that aged humans have trouble navigating or finding their way in a large environment and remembering spatial relationships among landmarks (Bruce and Herman 1983; Caplan and Lipman 1995; Cherry and Park 1989; Evans et al. 1984; Flicker et al. 1984; Kirasic 1991; Kirasic et al. 1992; Kirasic and Bernicki 1990; Lipman and Caplan 1992; Moffat et al. 2001; Naveh-Benjamin 1987; Ohta et al. 1981; Park et al. 1990; Perlmutter et al. 1981; Sharps and Gollin 1987; Thomas 1985; Uttl and Graf 1993; Weber et al. 1978; Wilkniss et al. 1997; Zelinski and Light 1988). In some studies, humans show a 30–80% drop in performance of spatial memory tasks with advancing age (Cherry and Park 1993; Evans et al. 1984; Kirasic and Bernicki 1990; Moffat et al. 2001; Moore et al. 1984; Sharps and Gollin 1987).

There are abundant human studies that have administered various supplements to improve cognitive function (Arwert et al. 2003; Chandra 2001; Duffy et al. 2008; Fintelmann and Gruenwald 2007; Frick et al. 2002; Grodstein et al. 2007; Jorissen et al. 2001; Kotani et al. 2006; Krikorian etal. 2010; Kritz-Silverstein etal. 2003; Thorp et al. 2009) but with less definitive measures in sight. "Nootropics" or "smart drugs" are said to improve mental function such as cognition and memory. There are myriad of supplements including− caffeine, *Ginkgo biloba, Bacopa monniera,* and drugs not limited to galantamine, memantine, donezepil, piracetam and rolipram (Bora et al. 2005; Brown et al. 2007; Capek and Guenther 2009; French et al. 2007; Gomer et al. 2007; Kennedy et al. 2007; Mecocci et al. 2009; Neyens et al. 1995; Rutten et al. 2008; Smith et al. 2003; Stough et al. 2008). Similarly, scientists are utilizing animals to understand the pathophysiology of brain aging to gain insight into the potential mechanism with the hope of finding ways to prevent or hopefully reverse memory loss (Barnes etal. 1996a,b; Blecharz-Klin et al. 2009; Costa et al. 2008; Dow-Edwards et al. 2008; Hebda-Bauer et al. 1999; Lei et al. 2003; Magnusson et al. 2007; Markowska et al. 1998; McDonald et al. 2005; Nishiyama et al. 1997; Wang et al. 2007; Yasui et al. 2002).

How to assess hippocampal-based spatial memory in mice?

In 1948, psychologist Edward Tolman was the first to study spatial behavior in rats. He put hungry rats at the entrance of a maze consisting of true paths and blind alleys and provided food at the end. Tolman observed that the error rate decreased with the number of trials (Tolman and Gleitman 1949). It was 3 decades later when the spatial reference memory system was proposed by Olton (Olton et al. 1979) to designate the type of memory process involved in obtaining spatial information over various trials. In contrast to spatial working memory, spatial reference memory has more capacity, lasts longer and resists interference (Olton et al. 1979).

Since the initial experiments by Tolman, evaluation of hippocampal-based spatial learning and memory has been assessed by numerous behavioral paradigms in rodents (D'Hooge and De Deyn 2001; Holcomb et al. 1998; Holmes et al. 2002; Koopmans et al. 2003; Kuc et al. 2006; Paul et al. 2009). Many of these behavioral memory paradigms are designed and established for rats. But, it is well known that mice are a valuable resource for researchers especially with the advancement of various genetic mouse models. In addition, mice are inherently different than rats in terms of physical and motivational factors when utilized in learning and memory tasks. For these reasons the behavioral tests used for rats cannot be directly used for mice (Paul et al. 2009). There is a critical need to design memory tasks specifically designed or adapted for mice. In this part of the review we will discuss various behavioral paradigms that can be used to assess hippocampal-based spatial memory in mice and include their advantages and disadvantages (Fig. 2).

T-maze

The T-maze is a simple behavioral paradigm used to assess spatial memory. It consists of a capital T-shape design with a stem length of 35 cm and an arm length of 28 cm for mice (rats: 50 cm and 40 cm, respectively). There is a single choice point with only two alternatives. In this test the animals are allowed to freely explore each arm of the device; then the number and order of visits to the arms are recorded. The principle of alternation is based on the fact that the animals prefer to visit the less recently visited arm, thus implicating that it will need to recall which was the last arm visited. These tests can be performed in two manners: 1) free tests or 2) forced tests. In the latter, one of the arms of the device is blocked in order to favor alternation behavior (Bats et al. 2001; Deacon and Rawlins 2006; Lalonde 2002).

Alternatively a positive reinforcer may be placed in one of the arms so as to reward alternation behavior. This appetitively motivated learning task is utilized in various studies (Fanelli et al. 1983; Schlesinger et al. 1986). Moreover, by increasing the interval between tests it is possible to conduct studies designed to evaluate spatial working memory in which a decrease in alternation behavior can be observed (Dember and Fowler 1959). In our studies, we utilized an appetitively motivated task using a previously described protocol (Bizon et al. 2007; Deacon and Rawlins 2006). Briefly, since the mice need to learn to locate the food reward, they were food deprived to 85% of ad libitum body weight and maintained at this weight throughout the experiment. Mice were habituated to the maze on day 1 and

arm preference was determined. The animals were trained against their preference in subsequent training trials (4 trials/day for 3 days) by baiting the other arm of the maze. Entries into the unbaited arm were scored as incorrect responses, and those into the baited arm were scored as correct responses. The time required to enter the baited arm and reach the target was recorded as latency. The T-maze was swabbed with 70% ethanol between animals to eliminate odors. In order to assess spatial memory mice are subjected to two probe trials (Days 5 and 12). During the probe trials, the maze was rotated 180°, but all cues, including the experimenter, remained stationary. Those mice entering the baited arm were designated as using a “place” strategy, which has been shown to involve the medial temporal lobe, including the hippocampus. Those mice entering the unbaited arm (i.e., making same body turn as used during training) were designated as using a “response” strategy that relies on caudate nucleus (Packard et al. 1989; Packard and McGaugh 1996). There are various protocols described that can be used in terms of number of trials, type of reward or methodology used (Barnes et al. 2004; Belzung et al. 2001; Crusio et al. 1990; Deacon 2006; Gerlai 1998; Lohninger et al. 2001; Wenk 2001). It has been shown that with aging associated loss of hippocampal function, aged animals use a response strategy more often as compared to adult animals who use place strategy more frequently (Barnes et al. 1980; Rapp et al. 1997).

In our lab, we have used a T-maze to study spatial memory in mice and found it to be useful to test Ames dwarf mice (Brown-Borg et al. 1996). In our experience the simplicity of the T-maze makes it one of the best paradigms to evaluate learning behavior in mice as compared to other complicated mazes (Sharma et al. 2010). We found that mice preferred a liquid reward (sweetened condensed milk) rather than normal chow or peanuts.

The T-maze has been used to evaluate spatial memory in mice in many studies and has been shown to be sensitive to the effects of drugs and toxins that enhance or impair spatial memory (Ferragud et al. 2010; Franowicz et al. 2002; Goulet et al. 2003; Incerti et al.; Ito and Canseliet 2010; Pierard etal. 2007; Pistell and Ingram 2010; Sanchez-Santed etal. 1997; Sanderson et al. 2009; White 1974). Recently, an aquatic version of the T-maze has been adapted and utilized (Del Arco et al. 2007; Locchi et al. 2007). One arm of the maze was painted black and the other arm white, with the correct arm leading to an escape ladder (Granholm et al. 2000). In another water escape motivated version, the mice are required to locate the hidden platform beneath the water in one of the arms thus utilizing natural tendency of mice to escape to a safer place (Belzung et al. 2001; Jaffard et al. 1991; Paylor et al. 1994). Another modification requires the animal to choose between a light and dark compartment in the T-maze (Raffalli-Sebille et al. 1990; Venault et al. 2006). Various studies have also used the T-maze to assess age-related cognitive decline (Caoetal. 2007; Heikkinenetal. 2004; von Bohlenund Halbach et al. 2006; Zhou et al. 2007).

The most important advantage of using a T-maze is that it is the simplest device to assess spatial working memory. The T-maze does not require automated video-recording systems (but does require constant observation by the experimenter) and also provides highly reproducible results. In contrast, the major disadvantage is that it has a single choice point with only two alternatives, which increases the possibilities of success (by default the probability of choosing the correct arm is 50%) or that the rodent may use a strategy other

than spatial to solve the maze. It can therefore be used to assess working memory but not reference memory. Depriving the animal of food can be a potential problem. Another disadvantage with using the T-maze is that it requires constant handling of animals, which may induce stress and affect the test result. But, habituating the animal and handling by the same experimenter reduce this stress. One of the modifications performed to avoid manipulation and stress is the addition of removable doors at the entrance of each arm so that the unselected arm can be blocked (Gerlai 1998; Spowart-Manning and van der Staay 2004). The Y-maze is similar to the T-maze, but has three 35 cm long identical arms. The only difference is that the arms require a gradual turn as compared to the sharp turns in the T-maze, which might decrease the learning time in the Y-maze.

Multiple T-maze

The Multiple T-maze as the name suggests are several T-mazes put together to form one maze. This maze consists of a wooden platform of 150 cm×130 cm×15 cm and a path width of 8 cm with seven different choice points (Lohninger et al. 2001; Pangratz-Fuehrer et al. 2005). In another study, the maze arms were 3 cm wide and 55 cm above the floor, with 12 choice points (Lewejohann et al. 2004). These mazes add complexity (more choices/alternatives) to the T-maze and are being utilized as spatial learning tasks. With this maze, mice have to learn a complex route, which is stable from trial to trial and, thus, requires spatial reference memory (Ingram 1988). Similar to the T-maze, memory retention is evaluated as the ability of food deprived mice to locate the hidden food with a decrease in latency and an increase in correct decisions (Pangratz-Fuehrer et al. 2005). Mice are placed in a start box in a black cylindrical chamber (Prior et al. 1997). After 10 s have elapsed, the chamber is lifted and the first trial is started. Mice are allowed to search for the reward and the trial is completed when mice reach the goal box, or if failed, after 5 min. After each trial the entire maze is cleaned with 1% incidin or 70% alcohol solution to avoid odor cues. Mice are trained with three such trials per day for 4 days. Trials are carried out using 20-min intervals. The following parameters are recorded on a computerized tracking system—correct or wrong decision, path length, speed and latency to reach the goal box. Probe trials can be conducted on days 5 and 12 for short-term and long-term retention memory with no training during the time period between Days 5 and 12.

The Stone T-maze is a modified version of 14-unit maze and water-based T-maze for testing hippocampal-dependent memory (Del Arco et al. 2007; Locchi etal. 2007). It is modified from a version previously used in rats (Ingram 1988). In this version mice need to wade through water following a correct sequence of left and right turns to reach a dark dry goal box (Pistell and Ingram 2010).

Various studies have used the Multiple T-maze for assessing spatial memory in mice (Kunesova et al. 2008; Patil et al. 2009; Zheng et al. 2009). The advantage of using the Multiple T-maze is that it utilizes a more complex choice system with multiple-choice points and therefore can be utilized to test both working and reference memories. The disadvantage is that it requires a computerized tracking system that may not be available to all researchers. Like the T-maze, food deprivation and handling of animals can be a potential problem.

Radial-arm maze

The radial maze was developed by Olton and Samuelson (1976). It consists of 8 or 12 arms, 5 cm wide and 35 cm long for mice (rats 10 and 50 cm respectively) with a central platform. A pellet of food is placed at the end of each arm. Based on a principle similar to the T-maze, an animal who has been food deprived is placed in the center and is allowed to collect food pellets from each arm (sampling without replacement). The optimal strategy for obtaining all the food in the least amount of time is to visit each arm only once during a trial. The number of visits to empty arms (unbaited arms) is calculated as errors made (Wenk 2004). This original version tested spatial working memory. Olton also developed a variant that allowed assessing reference memory in addition to working memory. To test both, only three or four arms are baited with a food reward (Olton et al. 1979). Re-entry into a previously baited (now empty) arm is defined as a “working memory” error. Entries into never-baited arms are counted as “spatial reference memory” errors. Further studies have confirmed that the animal uses spatial cues to recognize the arms previously visited (Mazmanian and Roberts 1983; Suzuki et al. 1980). In addition, mice with induced hippocampal lesions exhibited impaired memory in the radial-arm maze (Olton 1983; Olton et al. 1979; Olton and Papas 1979). Moreover, learning in a radial-arm maze is sensitive to the effects of aging and aged rats have been shown to need more trials to reach a required performance (Barnes et al. 1980; Davis et al. 1983; Wallace et al. 1980).

An aquatic version of radial maze has been developed in which the stimulus driving behavior is linked to aversive stimuli rather than to appetite. Animals locate an escape platform hidden in some quadrant of the maze (Hyde et al. 1998). A variation of the radial-arm maze task (standard 8-arm, four baited arm task and cued version task) has also been used to study strain specific abilities (Ammassari-Teule and De Marsanich 1996; Ammassari-Teule et al. 1993).

The advantage of the radial-arm maze is that the training protocol and data interpretation of the basic version are simple and various studies having used the 8-arm radial maze for evaluation of spatial working memory and for spatial reference memory (Belotti and Galey 1996; Dudchenko2004; Hodges 1996; Schmitt etal. 2003; Zhang etal. 2005) as well as the 12-arm radial maze (Demas et al. 1998). The other advantage is that this test induces only a moderate level of stress (Hodges 1996). The radial maze has also been used to study age-related cognitive decline in various mouse models (Bernstein etal. 1985; Krazem etal. 2003; Lebrun etal. 1990; Lohmannand Riepe 2007; Marighetto et al. 2000; Nogues et al. 1996; Takahashi et al. 2009; Touyarot et al. 2002; Touzani et al. 2003). It has been suggested that mice use several types of information for task performance and as they mature they turn more often to distal cues for orientation (Chapillon et al. 1995).

The limitation of the radial maze is that an animal can use a serial strategy going from one arm to another instead of using spatial cues. There is also a possibility that olfactory cues can be used to detect those arms already visited (Wasserman and Jensen 1969). Some research groups have used the aromatic saturation strategy allowing the animals to freely explore the maze before the test without any food pellets with the aim to saturate the maze with aromatic cues (Dudchenko 2004; Roullet et al. 1993). Other strategies involve cleaning

the device or/and rotating the arms while preserving the location of the food reward (Dudchenko 2004). One study failed to demonstrate learning in the radial maze (Mizumori et al. 1982) and some authors debate if the radial maze is actually measuring spatial memory (Dubreuil et al. 2003). However, the three or four arm-baited versions can be used to avoid this problem. Some studies indicate that radial devices are not sensitive enough to spot differences between animal strains or genders (Seymoure et al. 1996; van Haaren et al. 1990, 1987). But, various knockout mice have been successively trained on the radial maze (Dutar et al. 2002; Egashira et al. 2004; Mineur et al. 2002; Zlomuzica et al. 2009). Similarly, the radial maze has been used in both male and female mice to detect gender differences in learning behavior (LaBuda et al. 2002).

Morris water maze

The Morris water maze (Morris 1984) was invented by Richard G. M. Morris in 1981 as an alternative to the radial maze (Morris 1981). This device is one of the most widely used paradigms (D'Hooge and De Deyn 2001; Gallagher et al. 1993; Morris et al. 1982). It consists of a round pool filled with water made opaque using milk or white paint. The animal learns to locate the platform hidden under the water from four different starting points. Over a number of trials animals learn the location of the hidden platform based on distal cues and with time the latency to locate the platform decreases. The strength of learning is tested afterwards by a probe trial in which the hidden platform is removed and the amount of time spent in the former region of platform is measured (Morris 1981). In this maze, mice can use three different strategies (Brandeis et al. 1989) to locate the escape platform: a praxic strategy, when the animal learns the sequence of movements needed to reach the platform, a taxic strategy, when the animal uses cues or visual proximal guides to reach the platform, or a spatial strategy, when the animal reaches the target using information about the spatial location of the platform according to the spatial configuration of distal cues. The size of pool for mice can be 75–150 cm in diameter (rats 150–180 cm). The diameter may or may not affect the performance depending on the strain of animals used (Van Dam et al. 2006; van der Staay 2000).

Various parameters obtained with this maze include latency to find the platform, swim path length, swimming velocity, time spent in each quadrant, number of platform crossings, and percent of trials with failures (2 min without finding the platform). According to one study, the mean proximity to a former location of the platform is the most sensitive measure to assess in water maze performance (Maei et al. 2009). Other factors that may influence the performance of the mice on the Morris water maze include the number of trials per day, number of days of training, duration of each trial and the inter-trial interval (Zhou et al. 2009).

The Morris water maze permits the accurate and reproducible study of reference memory, spatial working memory and learning (D'Hooge and De Deyn 2001; Dudchenko 2004). The Morris water maze has been shown to be highly sensitive in the assessment of damage to the hippocampus (Bannerman et al. 1999; Morris et al. 1982; Sutherland et al. 1982). Furthermore, aged animals exhibit consistent impairment in learning the location of the escape platform (Foster et al. 1991; Gage et al. 1984; Gallagher et al. 1990). Recently, the

assessment of age-related decline in spatial memory in mice was conducted using the Morris water maze to better elucidate the mechanisms involved (Francia et al. 2006; Harburger et al. 2007; Pan et al. 2008; Pawlowski et al. 2009; Polydoro et al. 2009; Tong et al. 2007; von Bohlen und Halbach et al. 2006; Zhao et al. 2009). A longitudinal study in mice indicated that previous learning in the Morris water maze could prevent some age-related spatial learning deficits (Vicens et al. 2002).

Learning has been shown to be faster on the Morris water maze compared to other mazes possibly due to aversive stimuli, with acquisition in 5 days of training (Hodges 1996). This maze does not require previous preparation (water or food deprivation) thus limiting the number of days needed to proceed with experimentation. The biggest advantage is that the use of water in this maze eliminates the possibility that animals use aromatic cues to orient themselves in the escape search, one potential confounding factor that occurs in the dry-land mazes. The Morris water maze, although simple to build and adapt, requires video-recording systems and software for complete analysis of behavioral parameters, equipment that may not be readily available to all researchers.

However, this behavioral paradigm when directly adapted for mice, is associated with problems. It is important to take into account that cognitive performance may be affected by additional stress on experimental animals due to swimming (de Quervain et al. 1998; Holscher 1999). In particular, swimming in the Morris water maze is associated with neurochemical changes (Kirby et al. 1997) that may interfere with testing cognitive function (Patil et al. 2009). Most of the researchers believe that previous habituation is needed before the actual trials are conducted to decrease the stress level (Morris 1981) while some do not (Avila-Costa et al. 2006). Furthermore, the variation in using visual ‘extramaze’ cues like salient cues, diffuse cues and absence of cues can also affect the spatial performance (Champagne et al. 2002).

Barnes maze

To avoid the stress induced by swimming, Carol Barnes developed a dry-land maze (Barnes 1979). This paradigm consists of a circular platform at a height of 140 cm, with holes along the perimeter (12, 20 or 40 depending on the diameter). It is surrounded by black curtains with visual cues on them. During testing, animals receive reinforcement to escape from the open platform surface to a small, dark, recessed chamber located under one of the holes called the “target box”. The principle is similar to that of the standard, non-cued Morris water maze but less stressful in the assessment of spatial learning (Deacon et al. 2002; Harrison et al. 2009, 2006; Pompl et al. 1999). It was initially designed to assess spatial learning and memory in rats, but was later adapted for mice (Pompl et al. 1999). This device has been considered appropriate for mice because of their propensity to find and escape through small holes (Barnes et al. 1980; Pompl et al. 1999) and the natural preference of rodents for a dark environment (Bach et al. 1995).

The method used in our lab was adapted from a recently published protocol (Sunyer et al. 2007). In the pre-training trial, the mouse is placed in the middle of the maze under a dark colored box allowing the mice to be in random orientation before each trial (similar to the

different start quadrants in the Morris Water Maze). After 10 s have elapsed, the chamber is lifted, and the mouse is allowed to explore the maze for 5 min. Various types of aversive stimuli—sounds (78–108 dB) intense light, food, and air jets are often used to induce escape behavior (Ingram et al. 1994; Moscovitch et al. 2005). The following parameters are recorded (during acquisition and testing): errors, latency(s), and search strategy. Errors are defined as nose pokes and head deflections over any hole that does not have the target box. Latency is defined as the time it takes to locate the target box. Mice are trained for four trials per day for 4 days with an inter-trial interval of at least 15 min. After each trial the entire maze is cleaned with 70% alcohol. To further avoid odor cues, the maze can be rotated around its central axis. On days 5 and 12, a probe trial is conducted to evaluate short-term and long-term memory retention without any training between Days 5 and 12. Search strategies are determined by examining each trial and placing the mice into one of the three categories 1) Spatial−moving directly to the target hole or to an adjacent hole before visiting the target hole (≤3 errors); 2) Random—hole searches separated by crossing through the center of the maze or an unorganized search; or 3) Serial−the first visit to the target hole was preceded by a visit to adjacent holes in a serial manner, clockwise or counter clockwise in direction.

Aged animals are impaired in learning the location of the hidden escape tunnel, in retaining a memory of the location, and in learning a new location of the escape tunnel (Barnes 1979; Barnes and McNaughton 1985; Barnes et al. 1980). Results of another study revealed a similar pattern of learning using the Barnes maze in aged mice that was consistent with the idea that spatial learning is particularly vulnerable to effects of aging (Bach et al. 1999).

The main advantage of the Barnes maze is that being a dry-land maze, it does not induce stress as in the Morris water maze that involves swimming. In addition, like the Morris water maze, it allows evaluation of learning working memory and spatial reference memory (Sunyer et al. 2007). It is particularly suitable for mice since these animals exhibit a lower performance on the Morris water maze (Bach et al. 1995; Lukoyanov et al. 1999). Various studies in mice have successfully utilized the Barnes maze to assess spatial memory (Babovic et al. 2008; Bach et al. 1995; Barrett et al. 2010; Fabricius et al. 2008; Holmes et al. 2002; Inman-Wood et al. 2000; Koopmans et al. 2003; McAfoose et al. 2009; O'Leary and Brown 2009; Patil et al. 2009).

One disadvantage of the Barnes maze is that learning can be very slow or even absent in some cases. This can be explained by the lack of stressful stimuli, thereby producing more exploratory behavior than escape responses in animals that are not sufficiently motivated to escape (Sunyer et al. 2007). This can result in an increase in the number of errors due to further exploration of the maze although the mouse learned the association between the spatial cues and the escape location previously. Harrison et al. (2006) proposed a solution to this extra-exploratory behavior by calculating latency, path length and number of errors to the first encounter of the escape hole, called primary latency, primary path length and primary errors, respectively. Another disadvantage of the Barnes maze is that it can also stimulate non-spatial strategies like a serial strategy that can then affect performance. If the maze is not cleaned appropriately, the animals can use "aromatic cues" to solve the maze. One of the studies using multiple mazes to study spatial memory demonstrated that mice

committed considerably more errors than expected by random and this could be due exploratory behavior of mice and may not indicate impairment in spatial memory (Lewejohann et al. 2004).

Cheeseboard maze

An alternative maze developed to avoid problems associated with Morris water maze in mice is called as the Cheeseboard maze (Llano Lopez et al. 2010). This maze involves a task equivalent to the cognitive demands of the Morris water maze but is more suitable to murine species as it takes into account their ecological behavior (Kesner et al. 1989). The Cheeseboard maze, like the Morris water maze, uses a circular arena, in which a single target (reward or escape) can be positioned in various predefined positions, allowing assessment of reference and working memory. It consists of a wooden circular board (110 cm diameter) with 32 holes in a regular radial fashion similar to 8-arm radial maze. Some studies have adopted the original regular square design of Kesner (Pillay et al. 2008) while others have adopted a random pattern (Yoshida et al. 2001). Animals in this task also need to be food deprived and the reward used is freshly prepared diluted condensed milk. After the initial habituation, each trial requires the animal to locate the well containing the reward within 2 min. Two such trials are given per day for 5 days with an inter-trial interval of 1 min. During the probe trial the animals are allowed to search on the cheeseboard in the absence of reward, thus allowing the assessment of spatial strategy.

In this study, the investigators also showed that Cheeseboard maze had a higher effect size for the main effect of days in the acquisition of reference memory as compared to Morris water maze experiments. They showed that animals were able to reach a stable level of performance in 4 days of training that was highly comparable (correlation significant) to the same animals performance in the subsequent working memory experiments (Llano Lopez et al. 2010). Additional time was required in the Cheeseboard maze experiments for the introduction and acclimatization to the food deprivation schedule but overall the total time was far less than that reported for a dry-land maze like the radial-arm maze (Schmitt et al. 2003). In addition, the use of a dry environment effectively prevents floating thus overcoming one major problem of the water mazes. Further, unlike the Morris water maze or the Barnes maze, the Cheeseboard maze task does not rely on negative reinforcement. Although the Barnes maze has been reported to be less stressful than the Morris water maze in terms of hypothalamo-pituitary-adrenal responses (Harrison et al. 2009) the Cheeseboard maze should be even less stressful because it does not require the use of either high light intensity, loud noise or wind to reinforce the escape response as in the Barnes maze (Nithianantharajah and Murphy 2009). The Cheeseboard maze is typically performed under conditions of dim lighting, without aversive stimuli, and with extensive pre-training habituation on the apparatus and in the testing room.

One of the limitations of the Cheeseboard maze is that the spatial distribution of the food wells where a palatable reward can be hidden has not been clearly defined. It is obvious that the number of potential reward sites as well as their relative spatial distribution could affect task difficulty. Food deprivation and use of the same starting position can be an issue with the Cheeseboard maze. However, when the animals are first placed and covered by a box,

their head may not be in a specific direction when the box is lifted (random head direction). This can thus be comparable to different starting points used in Morris water maze.

Hole board discrimination test

The hole board apparatus consists of an open-field chamber with a 16-hole floor insert. This apparatus was originally used to look at exploratory behaviors (Belzung and Le Pape 1994; File 2001; Rogers et al. 1999). Hole board-learning paradigms were then used for rats by some researchers (Oades and Isaacson 1978; van der Staay et al. 1990a,b). It was later adapted to assess learning behavior in mice by retrieving a food pellet located in one hole out of four in a hole board task setup (Brosnan-Watters and Wozniak 1997; Brosnan-Watters et al. 1996). However, this task is not complex enough to assess reference and working memory. Recently, Kuc et al. (2006) have adapted this hole board-learning task for mice that allows for simultaneous assessment of spatial working and reference-memory performance. Across trials, animals have to remember the same four holes out of the 16 that are always baited.

Like other mazes, animals are food deprived and then habituated by allowing the mice to collect all the food pellets that were placed in every hole (one pellet per hole). For the learning trials the same four holes are baited with a food pellet during each trial. The software automatically ends a trial when all four pellets have been collected or after 3 min have elapsed. The start position of a mouse is randomly changed across trials. Mice readily acquire this task within 4 days when submitted to six trials per day or within 8 days when submitted to only four trials per day. The hole board floor insert is cleaned with alcohol to homogenize potential olfactory traces. In some experiments, reversal training is conducted under the same testing conditions as during acquisition training; however, the animals have to learn a different baited-hole configuration. The average number of errors per trial an animal made each day is used as a measure of cognitive performance. Errors consist of entering a hole that was never baited (reference-memory error), re-entering a hole (working-memory error) or missing a baited hole (error of omission). When appropriate, the task completion time and the number of head entries can also be analyzed.

In a similar test, another study used a four-hole board test to assess spatial delayed discrimination. This apparatus consists of a 4-hole board (30 cm×40 cm×30 cm) with spatial cues on it. Food deprived animals are placed on the center of the board and covered with a black cylinder for 30 s for initial random orientation. After the cylinder is removed, the mouse is allowed to explore and collect the reward. For measurement of retention, exploration frequency and time are recorded for each hole for 3 min with no food pellets in the apparatus (Galey and Jaffard 1992; Venault et al. 2006).

An advantage of this learning paradigm over other paradigms (i.e. the radial-arm maze and water maze) is that it is fully automated (infrared beams are used to track activity on the floor and nose pokes into the holes). Another distinct feature of hole board discrimination is that four different hole board chambers can be simultaneously used and several animals can be tested at the same time making it useful for high throughput testing. Moreover, this learning task appears to be sensitive to drug and experimental manipulations (van der Staay

and Bouger 2005). One of the limitations, like the T-maze and the radial maze, is that the animals are food deprived which can induce stress and affect learning behavior.

Object localization

Object localization is a reference memory task dependent on cognitive mapping of environmental stimuli (Chapillon and Roullet 1997; Thinus-Blanc and Ingle 1985). It consists of a grey circular open field (diameter: 40 cm, wall height: 30 cm) made of polyvinyl chloride, with a floor covered by a sheet of white paper that is replaced after every trial. Spatial cues in the form of a black and white-striped cardboard pattern can be placed on the walls. Three identical round metal objects (diameter: 2 cm, height: 3 cm) are displayed in a V-shaped configuration in the open field. The mice are placed in center and are allowed to explore the maze during the habituation phase. After the habituation, during the learning phase, mice are placed in the center. The number of times the animals lean against the objects and the number of object sniffing episodes are recorded during four daily sessions lasting 15 min/day for three days. During the probe trial, the position of all three objects is changed to a different configuration. The animals are thus required to detect the novelty in a spatial context. Between each trial the objects are washed with water, and then dried in order to minimize olfactory cues. In another version, only two identical objects are used. For the learning phase, the two objects are kept side by side while during the probe trial the objects are kept diagonally opposite to each other (Wang et al. 2009). In another study, six different objects were used during the learning phase while the next few sessions used five objects followed by a session where one of the five objects was replaced by a new object (Lee et al. 2005).

The advantage of this behavioral paradigm is that it is simple and easy to design. It is not as stressful to mice as a dry-land maze and does not require food deprivation. However, in one study, the authors concluded that only object sniffing episodes could be considered as spatial tasks. Since object exploration as determined by the number of leanings, is not susceptible to intersession habituation, learning could not be measured (Belzung et al. 2001). Furthermore, this simple task to detect spatial novelty is not useful to assess spatial reference memory.

Complex alley maze

The complex alley maze was first described by McGaugh (1961). In this behavioral paradigm, mice have to learn a complex route through a maze leading to their home cage. The maze is comprised of a standard cage (37×21 ×15 cm), two tunnels and a larger central cage (56 × 32 ×18 cm). The cages are divided into several fields by Plexiglas walls with holes leading to adjacent fields. The animal is placed in the start box, which is the larger central cage. The mice have to learn the route through the tunnels leading to the home cage and avoid the dead ends. At the goal, the observer opens the door and allows the animal to enter the home cage as a reward. A trial is completed after mice reach the goal or after 20 min. The route is stable from trial to trial and thus requires spatial reference memory (Lewejohann et al. 2004). Observations are conducted using digital imaging techniques with automated animal tracking software. The number of errors (an error is counted for each time the mouse enters the first field of a path leading in the wrong direction), the number of total

field entries and time used are calculated. After the acquisition of learning, long-term reference memory can be assessed after a delay of a few days.

The advantages of this maze include that it is dry, it involves the natural tendency of mice to go through tunnels and it does not need food deprivation as a motivator. As the route is stable from trial to trial, it is a good measure of reference memory. However, in the same study, one particular strain of mutant mice was not inclined to explore and thus remained in the start box for the 20-min trial (Lewejohann et al. 2004). Another limitation is that it needs a video tracking system that can add to research expenses.

Repeated acquisition and performance chamber

Most of the mazes utilized for evaluation of learning and memory measure the performance of a learned behavior. Thus these behavioral paradigms are not useful to assess the time course of the effects of experimental manipulations. A multiple schedule of repeated acquisition and performance was thus developed to assess learning vs rote performance within-behavioral test session and within-subject utilizing an apparatus modified from the rat (Furuya et al. 1988).

The repeated acquisition and performance chamber consists of a start box and a goal chamber separated by five compartments with one-way doors to prevent animals from returning to previous compartments. Following habituation, the animals are water deprived and then are allowed to explore for 20 min. In the repeated acquisition component, mice are required to learn a new sequence of door openings in each session. During the performance component, with an audio signal to discriminate it from repeated acquisition, the sequence of doors leading to the goal chamber containing saccharin is constant across sessions (Brooks et al. 2000). Latency to reach the goal box and sequence of door errors are recorded during the 10-min performance session.

Initially it takes considerable time to train the animals but there are several advantages. Repeated measures can be studied in same subject over long periods of time and each animal can be used as its own control (Thompson 1973; Wenger et al. 2004). This allows for comparison of the rate of learning at multiple levels of difficulty within the same test session. This paradigm has also been shown to be sensitive to hippocampal lesions resulting in longer latencies and increased errors in learning as well as it is useful to detect strain differences in spatial learning (Brooks et al. 2000).

Operant delayed response paradigms

Dunnettand colleagues (Dunnett 1985; Dunnett et al. 1988,1990; Dunnett and Martel 1990) developed a lever-pressing Delayed Matching (Nonmatching) to Position protocol for spatial working memory in rats by modifying a delayed conditional discrimination task (Herremans et al. 1994; Wallace et al. 1980). Recently, Goto et al. (2010) adapted the Delayed Matching to Position task for mice lever pressing using operant-conditioning chamber. The typical apparatus consists of a box with retractable levers. However, other response alternatives (e.g. illuminated response holes for nose-poke) have also been used (Delcasso et al. 2007; Wenger et al. 2004). The chamber is kept in a sound attenuating box in a test room. On pressing the

correct lever, a dispenser delivers a food pellet as a reinforcer. In a typical Delayed Matching (Nonmatching) to Position task, the trial starts by the presentation of either a left or right front lever (sample) and the animal is required to press the lever. When the ratio requirement for presses to the lever is met, a delay interval is started. This is followed by the presentation of a choice of left or right front levers. In a matching condition, the choice of the same front lever as the sample is reinforced, whereas the other is not. In the non-matching version the animal is reinforced for pressing the lever that has not been presented before. The proportions of correct choices show a delay-dependent decrement. A higher ratio of response requirement to the sample resulted in increased accuracy, but the duration of inter-trial interval had no effect (Goto et al. 2010).

Delayed Matching to Position tasks use operant-conditioning chambers and have been a powerful means by which to study animal working memory (Brown and Wong 2007; D'Amato 1973; White 1985). Although the lever-pressing Delayed Matching to Position and other versions of delayed lever-pressing paradigms (Heise 1984; Heise etal. 1976; Pontecorvo 1983) are fundamentally similar to maze paradigms as a means of testing spatial working memory, lever-pressing procedures have numerous analytic advantages over maze procedures. Operant memory tests allow precise control of trial timing, retention and interval duration. The protocol can be arranged to include several trials per session. One potential problem with this paradigm is the possibility that animals may orient themselves to the correct lever during the delay and wait for the lever to be presented (Fletcher and Davis 1965). Another problem is that the stimulus to be remembered is not clearly defined (Pontecorvo 1983).

Summary of behavioral paradigms to assess learning and memory

Serial mazes are often employed in studies exploring aging processes, as well as in pharmacological, toxicological and neuro-developmental models, however, their use is still moderate, and this is probably why their potential advantages are not well known (Ingram 1988; Ingram et al. 1994) (Table 1). These behavioral tasks have provided many insights into the neurobiological mechanisms and the neuroanatomical substrates of learning and memory in rodents and are now commonly used to assess the effects of novel and potential therapies.

Maze-based tests are rather inexpensive, require minimal technological sophistication and are rapidly acquired. However, they are space-consuming and labor intensive without the video tracking system. In addition, mice may use non-spatial strategies to solve the maze defeating the very purpose of the task thus; careful study designs are needed to avoid such learning patterns.

In order to be trained to properly use these spatial tasks, animals may be food or water deprived. Animals can be maintained at a certain body weight, to prevent them from reaching satiety. Alternatively, they can be deprived for a certain number of hours; it has been shown that the speed of learning might be related to the time of food deprivation. If food deprivation is not sufficient, the learning process can be delayed. Similarly, food deprivation in the Multiple T-maze is considered to be more stressful than the Barnes maze (Inman-Wood et al. 2000). In addition, this task requires a significant motor component, a

potential confound for studies involving mice that have motor or muscle dysfunction resulting from age or genetic manipulation.

It has been demonstrated that stress-related or anxiety-related behavior of two strains could result in differences between performance on water mazes and land mazes (Ennaceur et al. 2006; Kinsey et al. 2007). The stress produced by motivators and the physical fatigue produced by swimming exercise has an effect on the performance of mice (Mizunoya etal. 2004). Swimming in water mazes is considered an additional stress on experimental animals and therefore may have profound effects on cognitive performance (de Quervain et al. 1998; Holscher 1999). Mice differ from rats and thus need special consideration (Whishaw and Tomie 1996). Unlike rats, mice are not natural swimmers. The surface to mass ratio is also higher for mice than rats, leading to more rapid and substantial chilling when exposed to cool water (Gordon 2007). In addition to the stress induced by swimming, mice can adopt non-spatial strategies like thigmotaxis (wall hugging) that can alter the test results (Lipp and Wolfer 1998; Whishaw and Tomie 1996). Mice are also not fond of swimming and have often been reported to resort to passive floating in the Morris water maze (Nakazawa et al. 2003; Westerman et al. 2002). Mice perform better in tests not involving aversive or stressful stimuli (Francis et al. 1995) and they are comparable to rats in non-aquatic paradigms (Whishaw and Tomie 1996).

Another important variable to be considered is the gender of the animals (Frick et al. 2002; Harburger et al. 2008). Estrogen has been shown to affect memory in mice throughout a lifespan (Gresack et al. 2007). In addition, it has been demonstrated that an age-related decrease in spatial memory begins at an earlier age in female mice than in male mice and may be related to the cessation of estrous cycling (Frick et al. 2000). In a metanalysis, gender differences in mice were discussed in terms of spatial memory and showed that there is a small female advantage in the water maze and a small male advantage in the radial maze (Jonasson 2005).

The Morris water maze is simple and learning is rapid as compared to other behavioral paradigms such as the radial-arm maze (Becker et al. 1980). Studies comparing the radial and Morris mazes have shown that the number of trials required to achieve acceptable performance levels on some tasks in the radial maze is often two times that required for the Morris water maze, thus the acquisition process is slower (Ormerod and Beninger 2002). These differences are attributed to the fact that in contrast to the aquatic maze, animals in the radial maze may use a spontaneous alternation strategy. In comparative terms, both radial and circular Barnes mazes generate low levels of stress during the progress of the test (McLay et al. 1998) but these and the Morris water maze are sensitive to the deleterious effects of augmented corticosterone levels associated with stress (Holscher 1999; Sandi 1998; Wenk 2004).

The age of the animals also plays an important role in these tests. It is widely accepted that learning capacity declines with age, and this can be observed in the performance on these mazes. With age, swimming exploratory behavior and locomotor behavior decrease. These motor deficits have to be separated from the cognitive deficits that may be present in order to conclude that structural or functional changes occurring in the aged brain are contributing to

the decrement of visual-spatial skills (Geinisman et al. 1995). It is therefore extremely important to select a test of spatial memory that induces minimum stress in old animals such as those that do not involve food restriction. In addition, it is important to take into account treatment-induced changes in sensori-motor function and motivational levels that can indirectly influence learning and memory.

A recent study proposed that at least two mouse strains and at least a land and a water maze paradigm should be applied when reliable data needs to be generated. This statement may be particularly relevant when drugs are studied for the improvement of learning and memory (Patil et al. 2009). The T-maze was used in one study, followed one week later by the Morris water maze (Bizon et al. 2007), while in another study, the Multiple T-maze was used with other measures of spatial memory like the Y-maze (Kunesova et al. 2008) or the Morris water maze (Weitzdoerfer et al. 2004). The inclusion of multiple paradigms, such as the parallel examination of appetitive and aversive conditioning in the same animals, can yield a more comprehensive and accurate characterization of the phenotypic profile of genetically modified mice (Yee et al. 2004).

Considerable evidence shows that the most useful approach is to use a set of tests rather than using single “hallmark” tests for evaluation of spatial memory. The findings from only one test can be misleading but comparing the results from different tests, one can obtain convincing results (Lewejohann et al. 2004).

What is the neurochemical basis of memory?

Synaptic plasticity, the changes in the structure or biochemistry of synapses that alter their post-synaptic effects, is considered to be the cellular mechanism underlying learning and memory. In late 1940, psychologist Donald Hebb hypothesized that permanent memory traces could be laid down by the sustained activation of neural networks (Hebb 1949). Bliss and coworkers, thirty years later, observed a long-lasting increase of synaptic strength in the rabbit dentate gyrus in response to high-frequency stimulation (Bliss and Gardner-Medwin 1973; Bliss and Lomo 1973). This synaptic enhancement eventually became known as long-term potentiation and is most extensively studied in the hippocampus (Douglas and Goddard 1975). Long-term potentiation displays many of the characteristics thought to be required for the molecular mechanism of memory formation (deToledo-Morrell et al. 1988; Gallagher and Nicolle 1993; Landfield and Lynch 1977; Moore et al. 1993; Shankar et al. 1998; Ward et al. 1999a,b).

Long-term potentiation (LTP) is extensively studied in thinly cut hippocampal slices that are kept alive in a bath of artificial cerebrospinal fluid. A brief, high-frequency train of action potentials in any one of the three major anatomical pathways within the hippocampus (the perforant pathway, the mossy fiber pathway or the Schaffer collateral pathway) produces long-term potentiation (Bliss and Collingridge 1993). The Schaffer collateral pathway lies between the presynaptic CA3 neurons and the CA1 postsynaptic target cells and is the best studied synaptic pathway in the hippocampus. Hippocampal lesions in this pathway disrupt long-term potentiation and lead to memory deficits.

Long-term potentiation, like the memory storage in intact animals, occurs in two phases: the early phase of LTP (usually described < 1 h after stimulation) that does not require protein synthesis and gene transcription; and the late phase of LTP (usually described >3 h after stimulation) that involves protein synthesis and gene transcription (Abel et al. 1997; Bliss and Collingridge 1993). Age-related deficits have been reported in the late phase of LTP (Eckles-Smith et al. 2000; Lanahan et al. 1997; Moore et al. 1993). Barnes showed that after multiple daily LTP induction sessions, LTP decayed more quickly in aged rats as compared to adult rats (Barnes 1979).

A great deal of evidence indicates that the N-methyl D-aspartate (NMDA) receptor is critical for most forms of LTP (Collingridge et al. 1983; Errington et al. 1987; Morris etal. 1990a,b; Shankar etal. 1998). Activation of NMDA receptors leads to calcium influx into the cell. When calcium enters the post-synaptic cell it activates protein kinases such as calcium/calmodulin protein kinase II (Malenka et al. 1989; Malinow et al. 1989). Calcium/calmodulin protein kinase then activates the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, which increases conductance to sodium and potassium followed by increased responsiveness to glutamate (Lynch 2004). Calcium influx also leads to activation of adenyl cyclase, which in turn activates ATP to cAMP. This then activates protein kinase C leading to the phosphorylation of cAMP responsive transcription factor (CREB), protein synthesis and structural changes (Eichenbaum and Cohen 2001).

N-methyl D-aspartate (NMDA) receptor activation also plays an important role in the acquisition of spatial memory (Morris et al. 1986; Tsien et al. 1996). Pharmacological blockade of NMDA receptors or deletion of the NMDA receptor 1 (NR1) subunit of the NMDA receptor leads to a substantial impairment of spatial memory reference tasks (Danysz et al. 1995; Morris et al. 1990a,b; Tsien et al. 1996). Similarly, NR1 knockout mice show impairment of LTP (Nakazawa et al. 2003). In addition, it is important to note that with aging there is decrease in the expression of certain subunits of the NMDA receptor and their function in the hippocampus (Barnes et al. 1997; Clayton et al. 2002; Eckles-Smith et al. 2000; Magnusson 2001; Magnusson et al. 2006; Sonntag et al. 2000).

In 1990, an NMDA-receptor-independent form of LTP was discovered in CA1 pyramidal cells (Grover and Teyler 1990). When NMDA receptors are blocked, this form of LTP can be induced if very high-intensity stimuli (in terms of frequency, duration or current amplitude) are applied. This form of synaptic plasticity appears to be mediated by calcium influx through voltage-dependent, L-type calcium channels (vdcc) and has been called vdccLTP (Aniksztejn and Ben-Ari 1991; Cavus and Teyler 1996; Coussens and Teyler 1996a,b; Grover and Teyler 1990; Johnston et al. 1992; Morgan et al. 2001; Morgan and Teyler 2001a,b; Teyler et al. 1994). Like nmdaLTP, vdccLTP appears to be synapse-specific, that is, only the synapses active during vdccLTP induction are strengthened (Grover and Teyler 1992). Unlike nmdaLTP, which requires serine-threonine kinases (Lovingeretal. 1987; Malenka et al. 1989; Malinow et al. 1989), vdcc LTP appears to require tyrosine kinase (Cavus and Teyler 1996).

Previous studies of LTP in aged animals (using high-intensity stimulus parameters) observed no LTP-induction deficits (Barnes et al. 1996a,b; Chang et al. 1991). However, one study

observed that vdccLTP if measured in isolation, was increased in magnitude in aged animals (Shankar et al. 1998). In the light of this new evidence, the authors suggested that the expected decrease in nmdaLTP in aged animals was probably offset by the increased vdccLTP. When lower intensity stimuli were used or vdcc LTP was blocked, the nmdaLTP deficits were unmasked (Boric et al. 2008; Deupree et al. 1993; Moore et al. 1993; Rosenzweig et al. 1997).

It has also been shown that LTP induction is due to NMDA receptor activation while LTP maintenance involves modification of AMPA receptors. The ampakines, positive modulators of AMPA receptors, have been shown to be cognitive enhancers (Ingvar et al. 1997) indicating that up-regulation of AMPA receptor-mediated synaptic responses facilitate LTP formation. Another neurotransmitter Gamma Amino butyric acid (GABA) has been shown to be involved in learning and memory. The benzodiazepine potentiates the effect of GABA and produces impairment of learning and memory while reverse agonists and antagonists of benzodiazepine receptors has been shown to enhance memory (Lister 1985; McGaugh 1989). Similarly, noradrenaline, serotonin and histamine are also shown to be possibly involved in learning and memory processes (D'Hooge and De Deyn 2001). Acetylcholine and its interaction with other neurotransmitters and neuromodulators—including norepinephrine, dopamine, serotonin, GABA, opioid peptides, galanin, substance P and angiotensin II are also involved in modulation of learning and memory processes (Decker and McGaugh 1991).

The strong link between spatial memory and synaptic plasticity has been extensively reviewed (Martin et al. 2000). Furthermore, there has been experimental proof that learning induces LTP-like processes in the hippocampus (Foster et al. 2000; Foster et al. 1996; Power et al. 1997). Like the performance on the mazes, LTP is a feature of the hippocampus and is influenced by stress (Shors et al. 1990; Shors and Thompson 1992). A study found that stress impairs both spatial memory and LTP suggesting that a common mechanism is shared by the two assessment parameters (Baker and Kim 2002). Moreover, it has been demonstrated that animals with more durable LTP in a given age group tended to show the best spatial learning, providing support to the hypothesis that LTP at hippocampal synapses and spatial learning may depend on similar mechanistic processes (Barnes 2003).

Though a great deal is understood about spatial memory from research over the past few decades, there are still several unanswered questions. Experimental paradigms of memory are very important in the elucidation of the pathophysiology of age-associated memory impairment as they can be utilized to study memory-enhancing drugs. Spatial memory problems such as the inability to find your way back home or forgetting where you left your car keys, can be devastating in old age. In conclusion, to better understand the age-related impairment of hippocampal-based spatial memory and to tease apart the mechanisms, it is important to select a set of appropriate behavioral paradigms. In addition, to generate meaningful data and convincing interpretation of these results, additional experimental studies using long-term potentiation are equally important. It is anticipated that such studies will make it possible to develop therapeutic treatments to prevent or alleviate memory decline in normal aging and provide a greater quality of life to those getting older.

References

Abel T, Nguyen PV, Barad M, Deuel TA, Kandel ER, Bourtchouladze R. Genetic demonstration of a role for PKA in the late phase of LTP and in hippocampus-based long-term memory. Cell 88 (5), 615–626,1997. [PubMed: 9054501]

Abrahams S, Pickering A, Polkey CE, Morris RG. Spatial memory deficits in patients with unilateral damage to the right hippocampal formation. Neuropsychologia 35 (1), 11–24,1997. [PubMed: 8981373]

Albert MS, Funkenstein HH. The effects of age: normal variation and its relation to disease In: Asbury AK, McDondald WI, McKhann GM (Eds.), Diseases of the Nervous System: Clinical Neurobiology. Saunders, Philadelphia, pp. 598–611,1992.

Ammassari-Teule M, De Marsanich B. Spatial and visual discrimination learning in CD1 mice: partial analogy between the effect of lesions to the hippocampus and the amygdala. Physiology & Behavior 60 (1), 265–271,1996. [PubMed: 8804674]

Ammassari-Teule M, Hoffmann HJ, Rossi-Arnaud C. Learning in inbred mice: strain-specific abilities across three radial maze problems. Behavioral Genetics 23 (4), 405–412,1993.

Anderson JR. Learning and Retention Language, Memory and Thought. Lawrence Erlbaum Associates Inc, NewJersey 378–437,1976.

Aniksztejn L, Ben-Ari Y. Novel form of long-term potentiation produced by a K+ channel blocker in the hippocampus. Nature 349 (6304), 67–69, 1991. [PubMed: 1845914]

Arwert LI, Deijen JB, Drent ML. Effects of an oral mixture containing glycine, glutamine and niacin on memory, GH and IGF-I secretion in middle-aged and elderly subjects. Nutritional Neuroscience 6 (5), 269–275, 2003. [PubMed: 14609312]

Astur RS, Taylor LB, Mamelak AN, Philpott L, Sutherland RJ. Humans with hippocampus damage display severe spatial memory impairments in a virtual Morris water task. Behavioral Brain Research 132 (1), 77–84, 2002.

Avila-Costa MR, Fortoul TI, Nino-Cabrera G, Colin-Barenque L, Bizarro-Nevares P, Gutierrez-Valdez AL, Ordonez-Librado JL, Rodriguez-Lara V, Mussali-Galante P, Diaz-Bech P, Anaya-Martinez V. Hippocampal cell alterations induced by the inhalation of vanadium pentoxide (V(2)O(5)) promote memory deterioration. Neurotoxicology 27 (6), 1007–1012, 2006. [PubMed: 16684564]

Babovic D, O'Tuathaigh CM, O'Connor AM, O'Sullivan GJ, Tighe O, Croke DT, Karayiorgou M, Gogos JA, Cotter D, Waddington JL. Phenotypic characterization of cognition and social behavior in mice with heterozygous versus homozygous deletion of catechol-O-methyltransferase. Neuroscience 155 (4), 1021–1029, 2008. [PubMed: 18674597]

Bach ME, Hawkins RD, Osman M, Kandel ER, Mayford M. Impairment of spatial but not contextual memory in CaMKII mutant mice with a selective loss of hippocampal LTP in the range of the theta frequency. Cell 81 (6), 905–915,1995. [PubMed: 7781067]

Bach ME, Barad M, Son H, Zhuo M, Lu Yf, Shih R, Mansuy I, Hawkins RD, Kandel ER. Age-related defects in spatial memory are correlated with defects in the late phase of hippocampal long-term potentiation in vitro and are attenuated by drugs that enhance the cAMP signaling pathway. Proceedings of the National Academy of Sciences of the United States of America 96 (9), 5280–5285,1999. [PubMed: 10220457]

Baker KB, Kim JJ. Effects of stress and hippocampal NMDA receptor antagonism on recognition memory in rats. Learning & Memory 9 (2), 58–65, 2002. [PubMed: 11992016]

Bannerman DM, Yee Bk, Good MA, Heupel MJ, Iversen SD, Rawlins JN. Double dissociation of function within the hippocampus: a comparison of dorsal, ventral, and complete hippocampal cytotoxic lesions. Behavioral Neuroscience 113 (6), 1170–1188,1999. [PubMed: 10636297]

Barnes CA. Memory deficits associated with senescence: a neurophysiological and behavioral study in the rat. Journal of Comparative Physiology & Psychology 93(1), 74–104,1979.

Barnes CA. Aging and the physiology of spatial memory. Neurobiology of Aging 9 (5–6), 563–568,1988. [PubMed: 3062467]

Barnes CA. Long-term potentiation and the ageing brain. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 358 (1432), 765–772, 2003.

Barnes CA, McNaughton BL. An age comparison of the rates of acquisition and forgetting of spatial information in relation to long-term enhancement of hippocampal synapses. Behavioral Neuroscience 99 (6), 1040–1048,1985. [PubMed: 3843538]

Barnes CA, Nadel L, Honig WK. Spatial memory deficit in senescent rats. Canadian Journal of Psychology 34 (1), 29–39,1980. [PubMed: 7388694]

Barnes CA, Danysz W, Parsons CG. Effects of the uncompetitive NMDA receptor antagonist memantine on hippocampal long-term potentiation, short-term exploratory modulation and spatial memory in awake, freely moving rats. The European Journal of Neuroscience 8 (3), 565–571,1996a. [PubMed: 8963448]

Barnes CA, Rao G, McNaughton BL. Functional integrity of NMDA-dependent LTP induction mechanisms across the lifespan of F-344 rats. Learning & Memory 3 (2–3), 124–137, 1996b. [PubMed: 10456083]

Barnes CA, Rao G, Shen J. Age-related decrease in the N-methyl-D-aspartateR-mediated excitatory postsynaptic potential in hippocampal region CA1. Neurobiology of Aging 18 (4), 445–452,1997. [PubMed: 9330977]

Barnes P, Hale G, Good M. Intramaze and extramaze cue processing in adult APPSWE Tg2576 transgenic mice. Behavioral Neuroscience 118 (6), 1184–1195, 2004. [PubMed: 15598128]

Barrett GL, Reid CA, Tsafoulis C, Zhu W, Williams DA, Paolini AG, Trieu J, Murphy M. Enhanced spatial memory and hippocampal long-term potentiation in p75 neurotrophin receptor knockout mice. Hippocampus 20 (1), 145–152, 2010. [PubMed: 19360854]

Bats S, Thoumas JL, Lordi B, Tonon MC, Lalonde R, Caston J. The effects of a mild stressor on spontaneous alternation in mice. Behavioral Brain Research 118 (1), 11–15, 2001.

Bayley PJ, O'Reilly RC, Curran T, Squire LR. New semantic learning in patients with large medial temporal lobe lesions. Hippocampus 18 (6), 575–583, 2008. [PubMed: 18306299]

Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. Science 269 (5227), 1115–1118,1995. [PubMed: 7652558]

Becker JT, Walker JA, Olton DS. Neuroanatomical bases of spatial memory. Brain Research 200 (2), 307–320,1980. [PubMed: 7417818]

Belotti M, Galey D. Consequences of selective blockade of septal noradrenergic afferents on anxiety and spatial working memory performance in mice. Pharmacology, Biochemistry and Behavior 53 (3), 541–547,1996.

Belzung C, Le Pape G. Comparison of different behavioral test situations used in psychopharmacology for measurement of anxiety. Physiology & Behavior 56 (3), 623–628,1994. [PubMed: 7972418]

Belzung C, Chapillon P, Lalonde R. The effects of the lurcher mutation on object localization, T-maze discrimination, and radial arm maze tasks. Behavioral Genetics 31 (2), 151–155, 2001.

Bernstein D, Olton DS, Ingram DK, Waller SB, Reynolds MA, London ED. Radial maze performance in young and aged mice: neurochemical correlates. Pharmacology, Biochemistry and Behavior 22 (2), 301–307,1985.

Bird CM, Burgess N. The hippocampus and memory: insights from spatial processing. Nature Reviews. Neuroscience 9 (3), 182–194, 2008. [PubMed: 18270514]

Bizon J, Prescott S, Nicolle MM. Intact spatial learning in adult Tg2576 mice. Neurobiology of Aging 28 (3), 440–446, 2007. [PubMed: 16504344]

Blecharz-Klin K, Piechal A,Joniec I, Pyrzanowska J, Widy-Tyszkiewicz E. Pharmacological and biochemical effects of Ginkgo biloba extract on learning, memory consolidation and motor activity in old rats. Acta Neurobiologiae Experimentalis (Wars) 69 (2), 217–231,2009.

Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. Nature 361 (6407), 31–39, 1993. [PubMed: 8421494]

Bliss TV, Gardner-Medwin AR. Long-lasting potentiation of synaptic transmission in the dentate area of the unanaestetized rabbit following stimulation of the perforant path. The Journal of Physiology 232 (2), 357–374,1973. [PubMed: 4727085]

Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. TheJournal of Physiology 232 (2), 331–356,1973. [PubMed: 4727084]

Bohbot VD, Iaria G, Petrides M. Hippocampal function and spatial memory: evidence from functional neuroimaging in healthy participants and performance of patients with medial temporal lobe resections. Neuropsychology 18 (3), 418–425, 2004. [PubMed: 15291720]

Bora E, Veznedaroglu B, Kayahan B. The effect of galantamine added to clozapine on cognition of five patients with schizophrenia. Clinical Neuropharmacology 28 (3), 139–141, 2005. [PubMed: 15965314]

Boric K, Munoz P, Gallagher M, Kirkwood A. Potential adaptive function for altered long-term potentiation mechanisms in aging hippocampus. The Journal of Neuroscience 28 (32), 8034–8039, 2008. [PubMed: 18685028]

Brandeis R, Brandys Y, Yehuda S. The use of the Morris Water Maze in the study of memory and learning. The International Journal of Neuroscience 48 (1−2), 29–69, 1989. [PubMed: 2684886]

Brooks AI, Cory-Slechta DA, Murg SL, Federoff HJ. Repeated acquisition and performance chamber for mice: a paradigm for assessment of spatial learning and memory. Neurobiology of Learning and Memory 74 (3), 241–258, 2000. [PubMed: 11031130]

Brosnan-Watters G, Wozniak DF. A rotating holeboard procedure for testing drug effects on spatial learning and memory in mice. Brain Research. Brain Research Protocols 1 (4), 331–338,1997. [PubMed: 9384812]

Brosnan-Watters G, Wozniak DF, Nardi A, OlneyJW. Acute behavioral effects of MK-801 in the mouse. Pharmacology, Biochemistry and Behavior 53 (3), 701–711,1996.

Brown RE, Wong AA. The influence of visual ability on learning and memory performance in 13 strains of mice. Learning & Memory 14 (3), 134–144, 2007. [PubMed: 17351136]

Brown ES, Frol AB, Khan DA, Larkin GL, Bret ME. Impact of levetiracetam on mood and cognition during prednisone therapy. European Psychiatry 22 (7), 448–452, 2007. [PubMed: 17766093]

Brown-Borg HM, Borg KE, Meliska CJ, Bartke A. Dwarf mice and the ageing process. Nature 384 (6604), 33,1996.

Bruce PR, Herman JF. Spatial knowledge of young and elderly adults: scene recognition fromfamiliar and novel perspectives. Experimental Aging Research 9 (3), 169–173, 1983. [PubMed: 6641777]

Cahill L, Babinsky R, Markowitsch HJ, McGaugh JL. The amygdala and emotional memory. Nature 377 (6547), 295–296,1995. [PubMed: 7566084]

Cao X, Cui Z, Feng R, Tang YP, Qin Z, Mei B, Tsien JZ. Maintenance of superior learning and memory function in NR2B transgenic mice during ageing. The European Journal of Neuroscience 25 (6), 1815–1822, 2007. [PubMed: 17432968]

Capek S, Guenther RK. Caffeine's effects on true and false memory. Psychological Reports 104 (3), 787–795, 2009. [PubMed: 19708406]

Caplan LJ, Lipman PD. Age and gender differences in the effectiveness of map-like learning aids in memory for routes. The Journals of Gerontology. Series B: Psychological Sciences and Social Sciences 50 (3), P126–133,1995. [PubMed: 7767690]

Cavus I, Teyler T. Two forms of long-term potentiation in area CA1 activate different signal transduction cascades. Journal of Neurophysiology 76 (5), 3038–3047,1996. [PubMed: 8930253]

Champagne D, Dupuy JB, Rochford J, Poirier J. Apolipoprotein E knockout mice display procedural deficits in the Morris water maze: analysis of learning strategies in three versions of the task. Neuroscience 114 (3), 641–654, 2002. [PubMed: 12220566]

Chandra RK. Effect of vitamin and trace-element supplementation on cognitive function in elderly subjects. Nutrition 17 (9), 709–712, 2001. [PubMed: 11527656]

Chang PL, Isaacs KR, Greenough WT. Synapse formation occurs in association with the induction of long-term potentiation in two-year-old rat hippocampus in vitro. Neurobiology of Aging 12 (5), 517–522,1991. [PubMed: 1770987]

Chapillon P, Roullet P. Habituation and memorization of spatial objects' configurations in mice fromweaningto adulthood. Behavioral Proceedings 39 (3), 249–256,1997.

Chapillon P, Roullet P, Lassalle JM. Ontogeny of orientation and spatial learning on the radial maze in mice. Developmental Psychobiology 28 (8), 429–442,1995. [PubMed: 8582531]

Cherry KE, Park DC. Age-related differences in three-dimensional spatial memory. Journal of Gerontology 44 (1),P16–22,1989. [PubMed: 2910992]

Cherry KE, Park DC. Individual difference and contextual variables influence spatial memory in younger and older adults. Psychology and Aging 8 (4), 517–526,1993. [PubMed: 8292280]

Clayton DA, Mesches MH, Alvarez E, Bickford PC, Browning MD. A hippocampal NR2B deficit can mimic age-related changes in long-term potentiation and spatial learning in the Fischer 344 rat. The Journal of Neuroscience 22 (9), 3628–3637, 2002. [PubMed: 11978838]

Collingridge GL, Kehl SJ, McLennan H. Excitatory amino acids in synaptic transmission in the Schaffer collateral-commissural pathway of the rat hippocampus. The Journal of Physiology 334, 33–46,1983. [PubMed: 6306230]

Coren S, Porac C, Ward Lm. Sensation and Perception. Academic Press, Orlando, 1984.

Corkin S What's new with the amnesic patient H.M.? Nature Reviews. Neuroscience 3 (2), 153–160, 2002. [PubMed: 11836523]

Corkin S, Amaral DG, Gonzalez RG, Johnson KA, Hyman BT. H. M'.s medial temporal lobe lesion: findings from magnetic resonance imaging. The Journal of Neuroscience 17 (10), 3964–3979,1997. [PubMed: 9133414]

Costa MS, Botton PH, Mioranzza S, Souza DO, Porciuncula LO. Caffeine prevents age-associated recognition memory decline and changes brain-derived neurotrophic factor and tyrosine kinase receptor (TrkB) content in mice. Neuroscience 153 (4), 1071–1078, 2008. [PubMed: 18436387]

Coussens CM, Teyler TJ. Long-term potentiation induces synaptic plasticity at nontetanized adjacent synapses. Learning & Memory 3 (2–3), 106–114,1996a. [PubMed: 10456081]

Coussens CM, Teyler TJ. Protein kinase and phosphatase activity regulate the form of synaptic plasticity expressed. Synapse 24 (2), 97–103,1996b. [PubMed: 8890451]

Craik FIM, McDowd JM. Age differences in recall and recognition. Journal of Experimental Psychology and Learning 13,474–479,1987.

Crusio WE, Bertholet JY, Schwegler H. No correlations between spatial and non-spatial reference memory in a T-maze task and hippocampal mossy fibre distribution in the mouse. Behavioral Brain Research 41 (3), 251–259, 1990.

D'Amato MR. Delayed matching and short-term memory in monkeys. Psychology Learning & Motivation 7, 227–269,1973.

Danysz W, Zajaczkowski W, Parsons CG. Modulation of learning processes by ionotropic glutamate receptor ligands. Behavioral Pharmacology 6 (5 And 6), 455–474,1995.

Davis HP, Idowu A, Gibson GE. Improvement of 8-arm maze performance in aged Fischer 344 rats with 3, 4-diaminopyridine. Experimental Aging Research 9 (3), 211–214, 1983. [PubMed: 6641784]

de Bruin JP, Moita MP, de Brabander HM, Joosten RN. Place and response learning of rats in a Morris water maze: differential effects of fimbria fornix and medial prefrontal cortex lesions. Neurobiology of Learning and Memory 75 (2), 164–178, 2001. [PubMed: 11222058]

de Quervain DJ, Roozendaal B, McGaugh JL. Stress and glucocorticoids impair retrieval of long-term spatial memory. Nature 394 (6695), 787–790,1998. [PubMed: 9723618]

Deacon RM. Appetitive position discrimination in the T-maze. Nature Protocols 1 (1), 13–15, 2006. [PubMed: 17406206]

Deacon RM, Rawlins JN. T-maze alternation in the rodent. Nature Protocols 1(1), 7–12, 2006. [PubMed: 17406205]

Deacon RM, Bannerman DM, Kirby BP, Croucher A, Rawlins JN. Effects of cytotoxic hippocampal lesions in mice on a cognitive test battery. Behavioral Brain Research 133 (1), 57–68, 2002.

Decker MW, McGaugh JL. The role of interactions between the cholinergic system and other neuromodulatory systems in learning and memory. Synapse 7 (2), 151–168, 1991. [PubMed: 1672782]

Del Arco A, Segovia G, Garrido P, de Blas M, Mora F. Stress, prefrontal cortex and environmental enrichment: studies on dopamine and acetylcholine release and working memory performance in rats. Behavioral Brain Research 176 (2), 267–273, 2007.

Delcasso S, Jeantet Y, Cho YH. A new test for long-term spatial memory using an operant chamber in mice. Behavioral Brain Research 178 (2), 200–207, 2007.

Demas GE, Nelson RJ, Krueger BK, Yarowsky PJ. Impaired spatial working and reference memory in segmental trisomy (Ts65Dn) mice. Behavioral Brain Research 90 (2), 199–201,1998.

Dember WN, Fowler H. Spontaneous alteration after free and forced trials. Canadian Journal of Psychology 13,151–154,1959. [PubMed: 13815794]

deToledo-Morrell L, Geinisman Y, Morrell F. Age-dependent alterations in hippocampal synaptic plasticity: relation to memory disorders. Neurobiology of Aging 9 (5–6), 581–590,1988. [PubMed: 3062469]

Deupree DL, Bradley J, Turner DA. Age-related alterations in potentiation in the CA1 region in F344 rats. Neurobiology of Aging 14 (3), 249–258,1993. [PubMed: 8321393]

D'Hooge R, De Deyn PP. Applications of the Morris water maze in the study of learning and memory. Brain Research. Brain Research Reviews 36 (1), 60–90, 2001. [PubMed: 11516773]

Dobbs AR, Rule BG. Adult age differences in working memory. Psychology and Aging 4 (4), 500–503,1989. [PubMed: 2619956]

Douglas RM, Goddard GV. Long-term potentiation of the perforant path-granule cell synapse in the rat hippocampus. Brain Research 86 (2), 205–215,1975. [PubMed: 163667]

Dow-Edwards DL, Weedon JC, Hellmann E. Methylphenidate improves performance on the radial arm maze in periadolescent rats. Neurotoxicology and Teratology 30 (5), 419–427, 2008. [PubMed: 18538539]

Dubreuil D, Tixier C, Dutrieux G, Edeline JM. Does the radial arm maze necessarily test spatial memory? Neurobiology of Learning and Memory 79 (1), 109–117, 2003. [PubMed: 12482685]

Dudchenko PA. An overview of the tasks used to test working memory in rodents. Neuroscience and Biobehavioral Reviews 28 (7), 699–709, 2004. [PubMed: 15555679]

Duffy KB, Spangler EL, Devan BD, Guo Z, Bowker JL, Janas AM, Hagepanos A, Minor RK, DeCabo R, Mouton PR, Shukitt-Hale B, Joseph JA, Ingram DK. A blueberry-enriched diet provides cellular protection against oxidative stress and reduces a kainate-induced learning impairment in rats. Neurobiology of Aging 29 (11), 1680–1689, 2008. [PubMed: 17524525]

Dunnett SB. Comparative effects of cholinergic drugs and lesions of nucleus basalis or fimbria-fornix on delayed matching in rats. Psychopharmacology (Berlin) 87 (3), 357–363,1985. [PubMed: 3936093]

Dunnett SB, Martel FL. Proactive interference effects on short-term memory in rats: I. Basic parameters and drug effects. Behavioral Neuroscience 104 (5), 655–665,1990. [PubMed: 2244974]

Dunnett SB, Evenden JL, Iversen SD. Delay-dependent short-term memory deficits in aged rats. Psychopharmacology (Berlin) 96 (2), 174–180,1988. [PubMed: 3148143]

Dunnett SB, Martel FL, Iversen SD. Proactive interference effects on short-term memory in rats: II. Effects in young and aged rats. Behavioral Neuroscience 104 (5), 666–670,1990. [PubMed: 2244975]

Dutar P, Vaillend C, Viollet C, Billard JM, Potier B, Carlo AS, Ungerer A, Epelbaum J. Spatial learning and synaptic hippocampal plasticity in type 2 somatostatin receptor knock-out mice. Neuroscience 112 (2), 455–466, 2002. [PubMed: 12044463]

Eckles-Smith K, Clayton D, Bickford P, Browning MD. Caloric restriction prevents age-related deficits in LTP and in NMDA receptor expression. Brain Research. Molecular Brain Research 78 (1–2), 154–162, 2000. [PubMed: 10891595]

Egashira N, Tanoue A, Higashihara F, Mishima K, Fukue Y, Takano Y, Tsujimoto G, Iwasaki K, Fujiwara M. V1a receptor knockout mice exhibit impairment of spatial memory in an eight-arm radial maze. Neuroscience Letters 356 (3), 195–198,2004. [PubMed: 15036628]

Eichenbaum H Is the rodent hippocampus just for 'place'? Current Opinions Neurobiology 6 (2), 187–195,1996.

Eichenbaum H, Cohen NJ. From Conditioning to Conscious Recollection: Memory Systems of the Brain. Oxford University Press, New York, 2001.

Einstein GO, McDaniel MA, Richardson SL, Guynn MJ, Cunfer AR. Aging and prospective memory: examining the influences of self-initiated retrieval processes. Journal of Experimental Psychology. Learning, Memory, and Cognition 21 (4), 996–1007, 1995.

Ennaceur A, Michalikova S, van Rensburg R, Chazot PL. Models of anxiety: responses of mice to novelty and open spaces in a 3D maze. Behavioral Brain Research 174(1), 9–38, 2006.

Errington ML, Lynch MA, Bliss TV. Long-term potentiation in the dentate gyrus: induction and increased glutamate release are blocked by D(−)aminophosphonovalerate. Neuroscience 20(1), 279–284,1987. [PubMed: 2882444]

Evans GW, Brennan PL, Skorpanich MA, Held D. Cognitive mapping and elderly adults: verbal and location memory for urban landmarks. Journal of Gerontology 39 (4), 452–457,1984. [PubMed: 6736581]

Fabricius K, Wortwein G, Pakkenberg B. The impact of maternal separation on adult mouse behaviour and on the total neuron number in the mouse hippocampus. Brain Structure & Function 212 (5), 403–416, 2008. [PubMed: 18200448]

Fanelli RJ, Burright RG, Donovick PJ. A multivariate approach to the analysis of genetic and septal lesion effects on maze performance in mice. Behavioral Neuroscience 97 (3), 354–369,1983. [PubMed: 6871027]

Feigenbaum JD, Polkey CE, Morris RG. Deficits in spatial working memory after unilateral temporal lobectomy in man. Neuropsychologia 34 (3), 163–176,1996. [PubMed: 8868274]

Ferragud A, Haro A, Sylvain A, Velazquez-Sanchez C, Hernandez-Rabaza V, Canales JJ. Enhanced habit-based learning and decreased neurogenesis in the adult hippocampus in a murine model of chronic social stress. Behavioral Brain Research 210 (1), 134–139, 2010.

File SE. Factors controlling measures of anxiety and responses to novelty in the mouse. Behavioral Brain Research 125 (1–2), 151–157, 2001.

Fintelmann V, Gruenwald J. Efficacy and tolerability of a Rhodiola rosea extract in adults with physical and cognitive deficiencies. Advances in Therapeutics 24 (4), 929–939, 2007.

Fletcher HJ, Davis JK. Evidence supporting an intratrial interpretation of delayed response performance of monkeys. Perceptual and Motor Skills 21 (3), 735–742, 1965. [PubMed: 4955182]

Flicker C, Bartus RT, Crook TH, Ferris SH. Effects of aging and dementia upon recent visuospatial memory. Neurobiology of Aging 5 (4), 275–283,1984. [PubMed: 6531065]

Foster TC, Barnes CA, Rao G, McNaughton BL. Increase in perforant path quantal size in aged F-344 rats. Neurobiology of Aging 12 (5), 441–448, 1991. [PubMed: 1770978]

Foster TC, Gagne J, Massicotte G. Mechanism of altered synaptic strength due to experience: relation to long-term potentiation. Brain Research 736 (1–2),243–250, 1996. [PubMed: 8930330]

Foster TC, Fugger HN, Cunningham SG. Receptor blockade reveals a correspondence between hippocampal-dependent behavior and experience-dependent synaptic enhancement. Brain Research 871 (1), 39–43, 2000. [PubMed: 10882780]

Francia N, Cirulli F, Chiarotti F, Antonelli A, Aloe L, Alleva E. Spatial memory deficits in middle-aged mice correlate with lower exploratory activity and a subordinate status: role of hippocampal neurotrophins. The European Journal of Neuroscience 23 (3), 711–728, 2006. [PubMed: 16487153]

Francis DD, Zaharia MD, Shanks N, Anisman H. Stress-induced disturbances in Morris water-maze performance: interstrain variability. Physiology & Behavior 58 (1), 57–65, 1995. [PubMed: 7667428]

Franowicz JS, Kessler LE, Borja CM, Kobilka BK, Limbird LE, Arnsten AF. Mutation of the alpha2A-adrenoceptor impairs working memory performance and annuls cognitive enhancement by guanfacine. The Journal of Neuroscience 22(19), 8771–8777, 2002. [PubMed: 12351753]

French KL, Bimonte-Nelson HA, Granholm AC. Galantamine effects on memory, spatial cue utilization, and neurotrophic factors in aged female rats. Cell Transplantation 16 (3), 197–205, 2007. [PubMed: 17503733]

Frick KM, Burlingame LA, Arters JA, Berger-Sweeney J. Reference memory, anxiety and estrous cyclicity in C57BL/6NIA mice are affected by age and sex. Neuroscience 95 (1), 293–307, 2000. [PubMed: 10619486]

Frick KM, Fernandez SM, Bulinski SC. Estrogen replacement improves spatial reference memory and increases hippocampal synaptophysin in aged female mice. Neuroscience 115 (2), 547–558, 2002. [PubMed: 12421621]

Furuya Y, Yamamoto T, Yatsugi S, Ueki S. A new method for studying working memory by using the three-panel runway apparatus in rats. Japanese Journal of Pharmacology 46 (2), 183–188,1988. [PubMed: 3379828]

Gadian DG, Aicardi J, Watkins KE, Porter DA, Mishkin M, Vargha-Khadem F. Developmental amnesia associated with early hypoxic-ischaemic injury. Brain 123 (Pt 3), 499–507, 2000. [PubMed: 10686173]

Gage FH, Dunnett SB, Bjorklund A. Spatial learning and motor deficits in aged rats. Neurobiology of Aging 5 (1), 43–48,1984. [PubMed: 6738785]

Galey D, Jaffard R. Post-training medial septal stimulation improves spatial information processing in BALB/c mice. Neuroscience Letters 143 (1–2), 87–90,1992. [PubMed: 1436684]

Gallagher M, Nicolle MM. Animal models of normal aging: relationship between cognitive decline and markers in hippocampal circuitry. Behavioral Brain Research 57 (2), 155–162,1993.

Gallagher M, Rapp PR. The use of animal models to study the effects of aging on cognition. Annual Reviews Psychology 48, 339–370,1997.

Gallagher M, Burwell RD, Kodsi MH, McKinney M, Southerland S, Vella-Rountree L, Lewis MH. Markers for biogenic amines in the aged rat brain: relationship to decline in spatial learning ability. Neurobiology of Aging 11 (5), 507–514,1990. [PubMed: 2234281]

Gallagher M, Burwell R, Burchinal M. Severity of spatial learning impairment in aging: development of a learning index for performance in the Morris water maze. Behavioral Neuroscience 107 (4), 618–626,1993. [PubMed: 8397866]

Geinisman Y, de Toledo-Morrell L, Morrell F. Loss of perforated synapses in the dentate gyrus: morphological substrate of memory deficit in aged rats. Proceedings of the National Academy of Sciences of the United States of America 83(9),3027–3031,1986. [PubMed: 3458260]

Geinisman Y, Detoledo-Morrell L, Morrell F, Heller RE. Hippocampal markers of age-related memory dysfunction: behavioral, electrophysiological and morphological perspectives. Progress in Neurobiology 45 (3), 223–252,1995. [PubMed: 7777673]

Gerlai R A new continuous alternation task in T-maze detects hippocampal dysfunction in mice. A strain comparison and lesion study. Behavioral Brain Research 95 (1), 91–101,1998.

Goldstein LH, Canavan AG, Polkey CE. Cognitive mapping after unilateral temporal lobectomy. Neuropsychologia 27 (2), 167–177,1989. [PubMed: 2927627]

Gomer B, Wagner K, Frings L, Saar J, Carius A, Harle M, Steinhoff BJ, Schulze-Bonhage A. The influence of antiepileptic drugs on cognition: a comparison of levetiracetam with topiramate. Epilepsy & Behavior 10 (3), 486–94,2007. [PubMed: 17409025]

Gordon CJ. Thermophysiological responses to hyperthermic drugs: extrapolating from rodent to human. Progress in Brain Research 162, 63–79, 2007. [PubMed: 17645915]

Goto K, Kurashima R, Watanabe S. Delayed matching-to-position performance in C57BL/6N mice. Behavioral Processes, 2010.

Goulet S, Dore FY, Mirault ME. Neurobehavioral changes in mice chronically exposed to methylmercury during fetal and early postnatal development. Neurotoxicology and Teratology 25 (3), 335–347, 2003. [PubMed: 12757830]

Granholm AC, Sanders LA, Crnic LS. Loss of cholinergic phenotype in basal forebrain coincides with cognitive decline in a mouse model of Down's syndrome. Experimental Neurology 161 (2), 647–663, 2000. [PubMed: 10686084]

Gresack JE, Kerr KM, Frick KM. Life-long environmental enrichment differentially affects the mnemonic response to estrogen in young, middle-aged, and aged female mice. Neurobiology of Learning and Memory 88 (4), 393–408, 2007. [PubMed: 17869132]

Grodstein F, Kang JH, Glynn RJ, Cook NR, Gaziano JM. A randomized trial of beta carotene supplementation and cognitive function in men: the Physicians' Health Study II. Archives of Internal Medicine 167 (20), 2184–2190, 2007. [PubMed: 17998490]

Grover LM, Teyler TJ. Two components of long-term potentiation induced by different patterns of afferent activation. Nature 347 (6292), 477–479,1990. [PubMed: 1977084]

Grover LM, Teyler TJ. N-methyl-D-aspartate receptor-independent long-term potentiation in area CA1 of rat hippocampus: input-specific induction and preclusion in a non-tetanized pathway. Neuroscience 49 (1), 7–11,1992. [PubMed: 1357588]

Harburger LL, Lambert TJ, Frick KM. Age-dependent effects of environmental enrichment on spatial reference memory in male mice. Behavioral Brain Research 185 (1), 43–48, 2007.

Harburger LL, Pechenino AS, Saadi A, Frick KM. Post-training progesterone dose-dependently enhances object, but not spatial, memory consolidation. Behavioral Brain Research 194 (2), 174–180, 2008.

Harman D Free radical theory of aging: increasing the average life expectancy at birth and the maximum life span. Journal of Anti-Aging Medicine 2 (3), 199–208, 1999.

Harrison FE, Reiserer RS, Tomarken AJ, McDonald MP. Spatial and nonspatial escape strategies in the Barnes maze. Learning & Memory 13 (6), 809–819, 2006. [PubMed: 17101874]

Harrison FE, Hosseini AH, McDonald MP. Endogenous anxiety and stress responses in water maze and Barnes maze spatial memory tasks. Behavioral Brain Research 198 (1), 247–251, 2009.

Hasan M, Glees P. Ultrastructural age changes in hippocampal neurons, synapses and neuroglia. Experimental Gerontology 8 (2), 75–83, 1973. [PubMed: 4696517]

Hebb DO. The Organization of Behavior. Wiley, New York, 1949.

Hebda-Bauer EK, Morano MI, Therrien B. Aging and corticosterone injections affect spatial learning in Fischer-344 X Brown norway rats. Brain Research 827 (1–2), 93–103,1999. [PubMed: 10320697]

Heikkinen T, Puolivali J, Tanila H. Effects of long-term ovariectomy and estrogen treatment on maze learning in aged mice. Experimental Gerontology 39 (9), 1277–1283, 2004. [PubMed: 15489050]

Heise GA. Behavioral methods for measuring effects of drugs on learning and memory in animals. Medical Research Reviews 4 (4), 535–558,1984.

Heise GA, Conner R, Martin RA. Effects of scopolamine on variable intertrial interval spatial alternation and memory in the rat. Psychopharmacology (Berlin) 49 (2), 131–137, 1976. [PubMed: 825899]

Herremans AH, Hijzen TH, Slangen JL. Validity of a delayed conditional discrimination task as a model for working memory in the rat. Physiology & Behavior 56 (5), 869–875,1994. [PubMed: 7824586]

Hodges H Maze procedures: the radial-arm and water maze compared. Brain Research Cognitive Brain Res 3 (3–4), 167–181, 1996.

Holcomb L, Gordon MN, McGowan E, Yu X, Benkovic S, Jantzen P, Wright K, Saad I, Mueller R, Morgan D, Sanders S, Zehr C, O'Campo K, Hardy J, Prada CM, Eckman C, Younkin S, Hsiao K, Duff K. Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. Nature Medicine 4(1), 97–100,1998.

Holmes A, Wrenn CC, Harris AP, Thayer KE, Crawley JN. Behavioral profiles of inbred strains on novel olfactory, spatial and emotional tests for reference memory in mice. Genes, Brain, and Behavior 1 (1), 55–69, 2002.

Holscher C Stress impairs performance in spatial water maze learning tasks. Behavioral Brain Research 100 (1–2), 225–235, 1999.

Hyde LA, Hoplight BJ, Denenberg VH. Water version of the radial-arm maze: learning in three inbred strains of mice. Brain Research 785 (2), 236–244,1998. [PubMed: 9518631]

Incerti M, Vink J, Roberson R, Wood L, Abebe D, Spong CY. Reversal of alcohol-induced learning deficits in the young adultin a model of fetal alcohol syndrome. Obstetrics & Gynecology 115(2 Pt 1), 350–356. [PubMed: 20093910]

Ingram DK. Complex maze learning in rodents as a model of age-related memory impairment. Neurobiology of Aging 9 (5–6), 475–485,1988. [PubMed: 3062459]

Ingram DK, Spangler EL, Iijima S, Ikari H, Kuo H, Greig NH, London ED. Rodent models of memory dysfunction in Alzheimer's disease and normal aging: moving beyond the cholinergic hypothesis. Life Sciences 55 (25–26), 2037–2049,1994. [PubMed: 7997063]

Ingvar M, Ambros-Ingerson J, Davis M, Granger R, Kessler M, Rogers GA, Schehr RS, Lynch G. Enhancement by an ampakine of memory encoding in humans. Experimental Neurology 146 (2), 553–559,1997. [PubMed: 9270067]

Inman-Wood SL, Williams MT, Morford LL, Vorhees CV. Effects of prenatal cocaine on Morris and Barnes maze tests of spatial learning and memory in the offspring of C57BL/6J mice. Neurotoxicology and Teratology 22 (4), 547–557, 2000. [PubMed: 10974593]

Ito R, Canseliet M. Amphetamine exposure selectively enhances hippocampus-dependent spatial learning and attenuates amygdala-dependent cue learning. Neuropsychopharmacology 35 (7), 1440–1452, 2010. [PubMed: 20200510]

Jaffard R, Mocaer E, Poignant JC, Micheau J, Marighetto A, Meunier M, Beracochea D. Effects of tianeptine on spontaneous alternation, simple and concurrent spatial discrimination learning and on alcohol-induced alternation deficits in mice. Behavioral Pharmacology 2 (1), 37–46,1991.

Jarrard LE. On the role of the hippocampus in learning and memory in the rat. Behavioral and Neural Biology 60 (1), 9–26,1993. [PubMed: 8216164]

Johnston D, Williams S, Jaffe D, Gray R. NMDA-receptor-independent long-term potentiation. Annual Review of Physiology 54,489–505,1992.

Jonasson Z Meta-analysis of sex differences in rodent models of learning and memory: a review of behavioral and biological data. Neuroscience and Biobehavioral Reviews 28 (8), 811–825, 2005. [PubMed: 15642623]

Jorissen BL, Brouns F, Van Boxtel MP, Ponds RW, Verhey FR, Jolles J, Riedel WJ. The influence of soy-derived phosphatidylserine on cognition in age-associated memory impairment. Nutritional Neuroscience 4 (2), 121–134, 2001. [PubMed: 11842880]

Kandel E, Schwartz J, Jessel TM. The Principles of Neural Science, 4 ed. McGraw-Hill Companies, New York, 2000.

Kennedy DO, Jackson PA, Haskell CF, Scholey AB. Modulation of cognitive performance following single doses of 120 mg *Ginkgo biloba* extract administered to healthy young volunteers. Human Psychopharmacology 22 (8), 559–566, 2007. [PubMed: 17902186]

Kesner RP, Farnsworth G, DiMattia BV. Double dissociation of egocentric and allocentric space following medial prefrontal and parietal cortex lesions in the rat. Behavioral Neuroscience 103 (5), 956–961,1989. [PubMed: 2803562]

Kimble GA, Hilgard ER, Marquis DG. The definition of learning (chapter 1) In: Kimble GA (Ed.), Hilgard and Marquis' Conditioning and Learning. Appleton-Century-Crofts, New York, pp. 1–3, 1961.

Kinsella K, Velkoff V, Bureau UC. An Aging World: 2001. U.S. Government Printing Office, Washington DC, 2001.

Kinsey SG, Bailey MT, Sheridan JF, Padgett DA, Avitsur R. Repeated social defeat causes increased anxiety-like behavior and alters splenocyte function in C57BL/6 and CD-1 mice. Brain, Behavior, and Immunity 21 (4), 458–466, 2007.

Kirasic KC. Spatial cognition and behavior in young and elderly adults: implications for learning new environments. Psychology and Aging 6(1), 10–18,1991. [PubMed: 2029357]

Kirasic KC, Bernicki MR. Acquisition of spatial knowledge under conditions of temporospatial discontinuity in young and elderly adults. Psychological Research 52 (1), 76–79, 1990. [PubMed: 2377727]

Kirasic KC, Allen GL, Haggerty D. Age-related differences in adults' macrospatial cognitive processes. Experimental Aging Research 18 (1–2), 33–39, 1992. [PubMed: 1446693]

Kirby LG, Chou-Green JM, Davis K, Lucki I. The effects of different stressors on extracellular 5-hydroxytryptamine and 5-hydroxyindoleacetic acid. Brain Research 760 (1–2), 218–230, 1997. [PubMed: 9237538]

Knowlton BJ, Mangels JA, Squire LR. A neostriatal habit learning system in humans. Science 273 (5280), 1399–1402, 1996. [PubMed: 8703077]

Koopmans G, Blokland A, van Nieuwenhuijzen P, Prickaerts J. Assessment of spatial learning abilities of mice in a new circular maze. Physiology & Behavior 79 (4–5), 683–693, 2003. [PubMed: 12954410]

Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, Sakakibara M, Yoshimoto T, Guo J, Yamashima T. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neuroscience Research 56 (2), 159–164, 2006. [PubMed: 16905216]

Krazem A, Marighetto A, Higueret P, Jaffard R. Age-dependent effects of moderate chronic ethanol administration on different forms of memory expression in mice. Behavior Brain Research 147 (1–2), 17–29, 2003.

Krikorian R, Nash TA, Shidler MD, Shukitt-Hale B, Joseph JA. Concord grape juice supplementation improves memory function in older adults with mild cognitive impairment. British Journal of Nutrition 103(5), 730–734, 2010. [PubMed: 20028599]

Kritz-Silverstein D, Von Muhlen D, Barrett-Connor E, Bressel MA. Isoflavones and cognitive function in older women: the SOy and Postmenopausal Health In Aging (SOPHIA) Study. Menopause 10 (3), 196–202, 2003. [PubMed: 12792289]

Kuc KA, Gregersen BM, Gannon KS, Dodart JC. Holeboard discrimination learning in mice. Genes, Brain, and Behavior 5 (4), 355–363, 2006.

Kunesova G, Hlavacek J, Patocka J, Evangelou A, Zikos C, Benaki D, Paravatou-Petsotas M, Pelecanou M, Livaniou E, Slaninova J. The multiple T-maze in vivo testing of the neuroprotective effect of humanin analogues. Peptides 29 (11), 1982–1987, 2008. [PubMed: 18647630]

LaBuda CJ, Mellgren RL, Hale RL. Sex differences in the acquisition of a radial maze task in the CD-1 mouse. Physiology & Behavior 76 (2), 213–217, 2002. [PubMed: 12044593]

Lalonde R The neurobiological basis of spontaneous alternation. Neuroscience & Biobehavior Reviews 26 (1), 91–104, 2002.

Lanahan A, Lyford G, Stevenson GS, Worley PF, Barnes CA. Selective alteration of longterm potentiation-induced transcriptional response in hippocampus of aged, memory-impaired rats. The Journal of Neuroscience 17 (8), 2876–2885,1997. [PubMed: 9092609]

Landfield PW, Lynch G. Impaired monosynaptic potentiation in in vitro hippocampal slices from aged, memory-deficient rats. Journal of Gerontology 32 (5), 523–533, 1977. [PubMed: 196001]

Larrabee GJ, Crook TH III. Estimated prevalence of age-associated memory impairment derived from standardized tests of memory function. International Psychogeriatrics 6 (1), 95–104,1994. [PubMed: 8054499]

Lebrun C, Durkin TP, Marighetto A, Jaffard R. A comparison of the working memory performances of young and aged mice combined with parallel measures of testing and drug-induced activations of septo-hippocampal and nbm-cortical cholinergic neurones. Neurobiology of Aging 11 (5), 515–521,1990. [PubMed: 2234282]

Lee I, Hunsaker MR, Kesner RP. The role of hippocampal subregions in detecting spatial novelty. Behavioral Neuroscience 119 (1), 145–153, 2005. [PubMed: 15727520]

Lei H, Wang B, Li WP, Yang Y, Zhou AW, Chen MZ. Anti-aging effect of astragalosides and its mechanism of action. Acta Pharmacolica Sinica 24 (3), 230–234, 2003.

Lewejohann L, Skryabin BV, Sachser N, Prehn C, Heiduschka P, Thanos S, Jordan U, Dell'Omo G, Vyssotski AL, Pleskacheva MG, Lipp HP, Tiedge H, Brosius J, Prior H. Role of a neuronal small non-messenger RNA: behavioural alterations in BC1 RNA-deleted mice. Behavioral Brain Research 154 (1), 273–289, 2004.

Light LL, LaVoie D, Valencia-Laver D, Owens SA, Mead G. Direct and indirect measures of memory for modality in young and older adults. Journal of Experimental Psychology. Learning, Memory, and Cognition 18 (6), 1284–1297, 1992.

Lipman PD, Caplan LJ. Adult age differences in memory for routes: effects of instruction and spatial diagram. Psychology and Aging 7 (3), 435–442, 1992. [PubMed: 1388865]

Lipp HP, Wolfer DP. Genetically modified mice and cognition. Current Opinions in Neurobiology 8 (2), 272–280, 1998.

Lister RG. The amnesic action of benzodiazepines in man. Neuroscience and Biobehavioral Reviews 9 (1), 87–94,1985. [PubMed: 2858084]

Llano Lopez L, Hauser J, Feldon J, Gargiulo PA, Yee BK. Evaluating spatial memory function in mice: a within-subjects comparison between the water maze test and its adaptation to dry land. Behavioral Brain Research 209 (1), 85–92, 2010.

Locchi F, Dall'Olio R, Gandolfi O, Rimondini R. Water T-maze, an improved method to assess spatial working memory in rats: Pharmacological validation. Neuroscience Letters 422 (3), 213–216, 2007. [PubMed: 17629404]

Lohmann P, Riepe MW. Neurotoxic effects of repetitive inhibition of oxidative phosphorylation in young adults surfacing with deficits of spatial learning in old age. The Journals of Gerontology. Series A: Biological Sciences and Medical Sciences 62 (12), 1352–1356, 2007.

Lohninger S, Strasser A, Bubna-Littitz H. The effect of L-carnitine on T-maze learning ability in aged rats. Archives of Gerontology and Geriatrics 32 (3), 245–253,2001. [PubMed: 11395170]

Lovinger DM, Wong KL, Murakami K, Routtenberg A. Protein kinase C inhibitors eliminate hippocampal long-term potentiation. Brain Research 436 (1),177–183,1987. [PubMed: 2825923]

Lukoyanov NV, Madeira MD, Paula-Barbosa MM. Behavioral and neuroanatomical consequences of chronic ethanol intake and withdrawal. Physiology & Behavior 66 (2), 337–346,1999. [PubMed: 10336163]

Lynch MA. Long-term potentiation and memory. Physiological Reviews 84 (1), 87–136, 2004. [PubMed: 14715912]

Maei HR, Zaslavsky K, Wang AH, Yiu AP, Teixeira CM, Josselyn SA, Frankland PW. Development and validation of a sensitive entropy-based measure for the water maze. Frontiers in Integrative Neurosciences 3, 33, 2009.

Magnusson KR. Influence of diet restriction on NMDA receptor subunits and learning during aging. Neurobiology of Aging 22 (4), 613–627, 2001. [PubMed: 11445262]

Magnusson KR, Kresge D, Supon J. Differential effects of aging on NMDA receptors in the intermediate versus the dorsal hippocampus. Neurobiology of Aging 27 (2), 324–333, 2006. [PubMed: 16399215]

Magnusson KR, Scruggs B, Zhao X, Hammersmark R. Age-related declines in a two-day reference memory task are associated with changes in NMDA receptor subunits in mice. BMC Neurosciences 8, 43, 2007.

Maguire EA, Burke T, Phillips J, Staunton H. Topographical disorientation following unilateral temporal lobe lesions in humans. Neuropsychologia 34 (10), 993–1001, 1996. [PubMed: 8843066]

Maguire EA, Burgess N, Donnett JG, Frackowiak RS, Frith CD, O'Keefe J. Knowing where and getting there: a human navigation network. Science 280 (5365), 921–924, 1998. [PubMed: 9572740]

Maguire EA, Woollett K, Spiers HJ. London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. Hippocampus 16 (12), 1091–1101, 2006. [PubMed: 17024677]

Malenka RC, Kauer JA, Perkel DJ, Mauk MD, Kelly PT, Nicoll RA, Waxham MN. An essential role for postsynaptic calmodulin and protein kinase activity in long-term potentiation. Nature 340 (6234), 554–557, 1989. [PubMed: 2549423]

Malinow R, Schulman H, Tsien RW. Inhibition of postsynaptic PKC or CaMKII blocks induction but not expression of LTP. Science 245 (4920), 862–866,1989. [PubMed: 2549638]

Marighetto A, Touzani K, Etchamendy N, Torrea CC, De Nanteuil G, Guez D, Jaffard R, Morain P. Further evidence for a dissociation between different forms of mnemonic expressions in a mouse model of age-related cognitive decline: effects of tacrine and S 17092, a novel prolyl endopeptidase inhibitor. Learning & Memory 7 (3), 159–169, 2000. [PubMed: 10837505]

Markowska AL, Mooney M, Sonntag WE. Insulin-like growth factor-1 ameliorates age-related behavioral deficits. Neuroscience 87 (3), 559–569, 1998. [PubMed: 9758223]

Martin SJ, Grimwood PD, Morris RG. Synaptic plasticity and memory: an evaluation of the hypothesis. Annual Reviews of Neuroscience 23, 649–711, 2000.

Mazmanian DS, Roberts WA. Spatial memory in rats under restricted viewing conditions. Learning Motives 14,123–139,1983.

McAfoose J, Koerner H, Baune BT. The effects of TNF deficiency on age-related cognitive performance. Psychoneuroendocrinology 34 (4), 615–619, 2009. [PubMed: 19028017]

McDonald SR, Sohal RS, Forster MJ. Concurrent administration of coenzyme Q10 and alpha-tocopherol improves learning in aged mice. Free Radicals in Biology & Medicine 38 (6), 729–736, 2005.

McGaugh JL. Facilitative and disruptive effects of strychnine sulphate on maze learning. Psychological Reports 8, 99–104,1961.

McGaugh JL. Involvement of hormonal and neuromodulatory systems in the regulation of memory storage. Annual Review of Neuroscience 12, 255–287,1989.

McIntyre JS, Craik FI. Age differences in memory for item and source information. Canadian Journal of Psychology 41 (2), 175–192,1987. [PubMed: 3502895]

McLay RN, Freeman SM, Zadina JE. Chronic corticosterone impairs memory performance in the Barnes maze. Physiology & Behavior 63 (5), 933–937,1998. [PubMed: 9618019]

Mecocci P, Bladstrom A, Stender K. Effects of memantine on cognition in patients with moderate to severe Alzheimer's disease: post-hoc analyses of ADAS-cog and SIB total and single-item scores from six randomized, double-blind, placebo-controlled studies. International Journal of Geriatric Psychiatry 24 (5), 532–538, 2009. [PubMed: 19274640]

Mesulam MM. Neuroplasticity failure in Alzheimer's disease: bridging the gap between plaques and tangles. Neuron 24 (3), 521–529, 1999. [PubMed: 10595506]

Miller GA. The magical number seven plus or minus two: some limits on our capacity for processing information. Psychology Review 63 (2), 81–97,1956.

Miller DB, O'Callaghan JP. Aging, stress and the hippocampus. Ageing Research Reviews 4 (2), 123–140, 2005. [PubMed: 15964248]

Mineur YS, Sluyter F, de Wit S, Oostra BA, Crusio WE. Behavioral and neuroanatomical characterization of the Fmr1 knockout mouse. Hippocampus 12 (1),39–46,2002. [PubMed: 11918286]

Mizumori SJ, Rosenzweig MR, Kermisch MG. Failure of mice to demonstrate spatial memory in the radial maze. Behavioral and Neural Biology 35 (1), 33–45,1982. [PubMed: 7126097]

Mizunoya W, Oyaizu S, Hirayama A, Fushiki T. Effects of physical fatigue in mice on learning performance in a water maze. Bioscience, Biotechnology, and Biochemistry 68 (4), 827–834, 2004.

Moffat SD, Zonderman AB, Resnick SM. Age differences in spatial memory in a virtual environment navigation task. Neurobiololgy of Aging 22 (5), 787–796, 2001.

Moore TE, Richards B, Hood J. Aging and the coding of spatial information. Journals of Gerontology 39 (2), 210–212,1984. [PubMed: 6699378]

Moore CI, Browning MD, Rose GM. Hippocampal plasticity induced by primed burst, but not long-term potentiation, stimulation is impaired in area CA1 of aged Fischer 344 rats. Hippocampus 3 (1), 57–66,1993. [PubMed: 8364683]

Morgan SL, Teyler TJ. Electrical stimuli patterned after the theta-rhythm induce multiple forms of LTP. Journals of Neurophysiology 86 (3), 1289–1296, 2001a.

Morgan SL, Teyler TJ. Epileptic-like activity induces multiple forms of plasticity in hippocampal area CA1. Brain Research 917 (1), 90–96, 2001b. [PubMed: 11602232]

Morgan SL, Coussens CM, Teyler TJ. Depotentiation of vdccLTP requires NMDAR activation. Neurobiology of Learning and Memory 76 (3), 229–238, 2001. [PubMed: 11726234]

Morris RGM. Spatial localization does not depend on the presence of local cues. Learning and Motivation 12, 239–260,1981.

Morris R Developments of a water-maze procedure for studying spatial learning in the rat. Journal of Neuroscience Methods 11 (1), 47–60,1984. [PubMed: 6471907]

Morris RG, Garrud P, Rawlins JN, O'Keefe J. Place navigation impaired in rats with hippocampal lesions. Nature 297 (5868), 681–683,1982. [PubMed: 7088155]

Morris RG, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an N-methyl-D-aspartate receptor antagonist, AP5. Nature 319 (6056), 774–776, 1986. [PubMed: 2869411]

Morris RG, Davis S, Butcher SP. Hippocampal synaptic plasticity and NMDA receptors: a role in information storage? Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 329 (1253), 187–204,1990a.

Morris RG, Schenk F, Tweedie F, Jarrard LE. Ibotenate lesions of hippocampus and/or subiculum: dissociating components of allocentric spatial learning. The European Journal ofNeuroscience 2 (12), 1016–1028,1990b.

Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C, McAndrews MP, Levine B, Black S, Winocur G, Nadel L. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. Journal of Anatomy 207 (1), 35–66, 2005. [PubMed: 16011544]

Murray EA, Baxter MG, Gaffan D. Monkeys with rhinal cortex damage or neurotoxic hippocampal lesions are impaired on spatial scene learning and object reversals. Behavioral Neuroscience 112 (6), 1291–1303, 1998. [PubMed: 9926813]

Nakazawa K, Sun LD, Quirk MC, Rondi-Reig L, Wilson MA, Tonegawa S. Hippocampal CA3 NMDA receptors are crucial for memory acquisition of one-time experience. Neuron 38 (2), 305–315, 2003. [PubMed: 12718863]

Naveh-Benjamin M Coding of spatial location information: an automatic process? Journal of Experimental Psychology. Learning, Memory, and Cognition 13 (4), 595–605, 1987.

Neyens LG, Alpherts WC, Aldenkamp AP. Cognitive effects of a new pyrrolidine derivative (levetiracetam) in patients with epilepsy. Progress in Neuropsychopharmacology & Biological Psychiatry 19 (3), 411–419,1995.

Nishiyama N, Moriguchi T, Saito H. Beneficial effects of aged garlic extract on learning and memory impairment in the senescence-accelerated mouse. Experimental Gerontology 32 (1–2), 149–160, 1997. [PubMed: 9088912]

Nithianantharajah J, Murphy M. Experience on the Barnes spatial maze influences PKCgamma levels in the hippocampus. The International Journal of Neuroscience 119 (7), 1014–1030, 2009. [PubMed: 19466636]

Nogues X, Jaffard R, Micheau J. Investigations on the role of hippocampal protein kinase C on memory processes: pharmacological approach. Behavioral Brain Research 75 (1–2), 139–146, 1996.

Oades RD, Isaacson RL. The development of food search behavior by rats: the effects of hippocampal damage and haloperidol. Behavioral Biology 24 (3), 327–337,1978. [PubMed: 743067]

Ohta RJ, Walsh DA, Krauss IK. Spatial perspective-taking ability in young and elderly adults. Experimental Aging Research 7 (1), 45–63, 1981. [PubMed: 7238550]

O'Keefe J, Nadel L. The Hippocampus as a Cognitive Map. Clarendon Press, Oxford, 1978.

O'Leary TP, Brown RE. Visuo-spatial learning and memory deficits on the Barnes maze in the 16-month-old APPswe/PS1dE9 mouse model of Alzheimer's disease. Behavioral Brain Research 201 (1), 120–127, 2009.

Olton DS. The use of animal models to evaluate the effects of neurotoxins on cognitive processes. Neurobehavioral Toxicology and Teratology 5 (6), 635–640, 1983. [PubMed: 6669182]

Olton DS, Papas BC. Spatial memory and hippocampal function. Neuropsychologia 17 (6), 669–682,1979. [PubMed: 522981]

Olton DS, Samuelson RJ. Remembrance of places passed: Spatial memory in rats. Journal of Experimental Psychology: Animal Behavior Proceedings 2, 97–116,1976.

Olton DS, Becker JT, Handelmann GE. Hippocampus, space and memory. Behavioral Brain Science 2, 313–365,1979.

Ormerod BK, Beninger RJ. Water maze versus radial maze: differential performance of rats in a spatial delayed match-to-position task and response to scopolamine. Behavioral Brain Research 128 (2), 139–152, 2002.

Packard MG, McGaugh JL. Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. Neurobiology of Learning and Memory 65 (1), 65–72,1996. [PubMed: 8673408]

Packard MG, Hirsh R, White NM. Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. The Journal of Neuroscience 9 (5), 1465–1472,1989. [PubMed: 2723738]

Pan D, Sciascia A II, Vorhees CV, Williams MT. Progression of multiple behavioral deficits with various ages of onset in a murine model of Hurler syndrome. Brain Research 1188, 241–253, 2008. [PubMed: 18022143]

Pangratz-Fuehrer S, Bubna-Littitz H, Propst F, Reitsamer H. Mice deficient in microtubule-associated protein MAP1B show a distinct behavioral phenotype and altered retina function. Behavioral Brain Research 164 (2), 188–196, 2005.

Park DC, Cherry KE, Smith AD, Lafronza VN. Effects of distinctive context on memory for objects and their locations in young and elderly adults. Psychology and Aging 5 (2), 250–255,1990. [PubMed: 2378690]

Patil SS, Sunyer B, Hoger H, Lubec G. Evaluation of spatial memory of C57BL/6J and CD1 mice in the Barnes maze, the Multiple T-maze and in the Morris water maze. Behavioral Brain Research 198 (1), 58–68, 2009.

Paul CM, Magda G, Abel S. Spatial memory: theoretical basis and comparative review on experimental methods in rodents. Behavioral Brain Research 203 (2), 151–164, 2009.

Pawlowski TL, Bellush LL, Wright AW, Walker JP, Colvin RA, Huentelman MJ. Hippocampal gene expression changes during age-related cognitive decline. Brain Research 1256,101–110, 2009. [PubMed: 19133237]

Paylor R, Johnson RS, Papaioannou V, Spiegelman BM, Wehner JM. Behavioral assessment of c-fos mutant mice. Brain Research 651 (1–2), 275–282,1994. [PubMed: 7922576]

Perlmutter M, Metzger R, Nezworski T, Miller K. Spatial and temporal memory in 20 to 60 year olds. Journal of Gerontology 36 (1), 59–65,1981. [PubMed: 7451838]

Pierard C, Liscia P, Philippin JN, Mons N, Lafon T, Chauveau F, Van Beers P, Drouet I, Serra A, Jouanin JC, Beracochea D. Modafinil restores memory performance and neural activity impaired by sleep deprivation in mice. Pharmacology, Biochemistry and Behavior 88 (1), 55–63, 2007.

Pigott S, Milner B. Memory for different aspects of complex visual scenes after unilateral temporal- or frontal-lobe resection. Neuropsychologia 31 (1), 1–15,1993. [PubMed: 8437678]

Pillay NS, Kellaway LA, Kotwal GJ. Early detection of memory deficits and memory improvement with vaccinia virus complement control protein in an Alzheimer's disease model. Behavioral Brain Research 192 (2), 173–177, 2008.

Pistell PJ, Ingram DK. Development of a water-escape motivated version of the Stone T-maze for mice. Neuroscience 166 (1), 61–72, 2010. [PubMed: 20026250]

Polydoro M, Acker CM, Duff K, Castillo PE, Davies P. Age-dependent impairment of cognitive and synaptic function in the htau mouse model of tau pathology. The Journal of Neuroscience 29 (34), 10741–10749, 2009. [PubMed: 19710325]

Pompl PN, Mullan MJ, Bjugstad K, Arendash GW. Adaptation of the circular platform spatial memory task for mice: use in detecting cognitive impairment in the APP (SW) transgenic mouse model for Alzheimer's disease. Journal of Neuroscience Methods 87 (1), 87–95,1999. [PubMed: 10065997]

Pontecorvo MJ. Effects of proactive interference on rat's continuous nonmatching to sample performance. Animal Learning & Behavior 11, 356–366,1983.

Pouzet B, Zhang WN, Feldon J, Rawlins JN. Hippocampal lesioned rats are able to learn a spatial position using non-spatial strategies. Behavioral Brain Research 133 (2), 279–291,2002.

Power JM, Thompson LT, Moyer JR Jr, Disterhoft JF. Enhanced synaptic transmission in CA1 hippocampus after eyeblink conditioning. Journal of Neurophysiology 78 (2), 1184–1187,1997. [PubMed: 9307149]

Prior H, Schwegler H, Ducker G. Dissociation of spatial reference memory, spatial working memory, and hippocampal mossy fiber distribution in two rat strains differing in emotionality. Behavioral Brain Research 87 (2), 183–194,1997.

Puckett JM, Stockburger DW. Absence of age-related proneness to short-term retroactive interference in the absence of rehearsal. Psychology and Aging 3 (4), 342–347, 1988. [PubMed: 3268278]

Raffalli-Sebille MJ, Chapouthier G, Venault P, Dodd RH. Methyl beta-carboline-3-carboxylate enhances performance in a multiple-trial learning task in mice. Pharmacology, Biochemistry and Behavior 35 (2), 281–284, 1990.

Rapp PR, Kansky MT, Roberts JA. Impaired spatial information processing in aged monkeys with preserved recognition memory. NeuroReport 8 (8), 1923–1928, 1997. [PubMed: 9223078]

Rogers DC, Jones DN, Nelson PR, Jones CM, Quilter CA, Robinson TL, Hagan JJ. Use of SHIRPA and discriminant analysis to characterise marked differences in the behavioural phenotype of six inbred mouse strains. Behavioral Brain Research 105 (2), 207–217,1999.

Rosenbaum RS, Priselac S, Kohler S, Black SE, Gao F, Nadel L, Moscovitch M. Remote spatial memory in an amnesic person with extensive bilateral hippocampal lesions. Nature Neuroscience 3 (10), 1044–1048, 2000. [PubMed: 11017178]

Rosenzweig ES, Rao G, McNaughton BL, Barnes CA. Role oftemporal summation in age-related long-term potentiation-induction deficits. Hippocampus 7 (5), 549–558, 1997. [PubMed: 9347351]

Roullet P, Lassalle JM, Jegat R. A study of behavioral and sensorial bases of radial maze learning in mice. Behavioral and Neural Biology 59 (3), 173–179,1993. [PubMed: 8503822]

Rutten K, Basile JL, Prickaerts J, Blokland A, Vivian JA. Selective PDE inhibitors rolipram and sildenafil improve object retrieval performance in adult cynomolgus macaques. Psychopharmacology (Berlin) 196 (4), 643–648, 2008. [PubMed: 18034336]

Salmon DP, Butters N. Neurobiology of skill and habit learning. Current Opinions in Neurobiology 5 (2), 184–190,1995.

Sanchez-Santed F, de Bruin JP, Heinsbroek RP, Verwer RW. Spatial delayed alternation of rats in a T-maze: effects of neurotoxic lesions of the medial prefrontal cortex and of T-maze rotations. Behavioral Brain Research 84 (1–2), 73–79,1997.

Sanderson DJ, Cunningham C, Deacon RM, Bannerman DM, Perry VH, Rawlins JN. A double dissociation between the effects of sub-pyrogenic systemic inflammation and hippocampal lesions on learning. Behavioral Brain Research 201 (1), 103–111,2009.

Sandi C The role and mechanisms of action of glucocorticoid involvement in memory storage. Neural Plasticity 6 (3), 41–52,1998. [PubMed: 9920681]

Schlesinger K, Pelleymounter MA, van de Kamp J, Bader DL, Stewart JM, Chase TN. Substance P facilitation of memory: effects in an appetitively motivated learning task. Behavior Neural Biology 45 (2), 230–239, 1986.

Schmitt WB, Deacon RM, Seeburg PH, Rawlins JN, Bannerman DM. A within-subjects, within-task demonstration of intact spatial reference memory and impaired spatial working memory in glutamate receptor-A-deficient mice. The Journal of Neuroscience 23 (9), 3953–3959, 2003.

Schmolck H, Kensinger EA, Corkin S, Squire LR. Semantic knowledge in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. Hippocampus 12 (4), 520–533, 2002. [PubMed: 12201637]

Schonfield D, Robertson BA. Memory storage and aging. Canadian Journal of Psychology 20 (2), 228–236, 1966. [PubMed: 5942327]

Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery and Psychiatry 20 (1), 11–21, 1957.

Seymoure P, Dou H, Juraska JM. Sex differences in radial maze performance: influence of rearing environment and room cues. Psychobiology 24, 33–37,1996.

Shankar S, Teyler TJ, Robbins N. Aging differentially alters forms of long-term potentiation in rat hippocampal area CA1. Journal of Neurophysiology 79 (1), 334–341,1998. [PubMed: 9425202]

Sharma S, Haselton J, Rakoczy S, Branshaw S, Brown-Borg HM. Spatial memory is enhanced in long-living Ames dwarf mice and maintained following kainic acid induced neurodegeneration. Mechanisms of Ageing and Development 131 (6), 422–435, 2010. [PubMed: 20561541]

Sharps MJ, Gollin ES. Memory for object locations in young and elderly adults. Journal of Gerontology 42 (3), 336–341,1987. [PubMed: 3571872]

Shors TJ, Thompson RF. Acute stress impairs (or induces) synaptic long-term potentiation (LTP) but does not affect paired-pulse facilitation in the stratum radiatum of rat hippocampus. Synapse 11 (3), 262–265,1992. [PubMed: 1321993]

Shors TJ, Foy MR, Levine S, Thompson RF. Unpredictable and uncontrollable stress impairs neuronal plasticity in the rat hippocampus. Brain Research Bulletin 24 (5), 663–667,1990. [PubMed: 2192774]

Smith TD, Calhoun ME, Rapp PR. Circuit and morphological specificity of synaptic change in the aged hippocampal formation. Neurobiology of Aging 20 (3), 357–358 359–360, discussion, 1999. [PubMed: 10588586]

Smith A, Brice C, Nash J, Rich N, Nutt DJ. Caffeine and central noradrenaline: effects on mood, cognitive performance, eye movements and cardiovascular function. Journal of Psychopharmacology 17 (3), 283–292, 2003. [PubMed: 14513920]

Solms M, Turnbull O. Memory and Phantasy The Brain and the Inner World: An Introduction to the Neuroscience of Subjective Experience. Other Press LLc 139–180, 2002.

Sonntag WE, Bennett SA, Khan AS, Thornton PL, Xu X, Ingram RL, Brunso-Bechtold JK. Age and insulin-like growth factor-1 modulate N-methyl-D-aspartate receptor subtype expression in rats. Brain Research Bulletin 51 (4), 331–338, 2000. [PubMed: 10704784]

Spowart-Manning L, van der Staay FJ. The T-maze continuous alternation task for assessing the effects of putative cognition enhancers in the mouse. Behavioral Brain Research 151 (1–2), 37–46, 2004.

Squire LR. Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans. Psychology Reviews 99 (2), 195–231,1992.

Squire LR, Zola SM. Structure and function of declarative and nondeclarative memory systems. Proceedings of the National Academy of Sciences of the United States of America 93 (24), 13515–13522,1996. [PubMed: 8942965]

Stefanacci L, Buffalo EA, Schmolck H, Squire LR. Profound amnesia after damage to the medial temporal lobe: a neuroanatomical and neuropsychological profile of patient E. P. Journal of Neuroscience 20 (18), 7024–7036, 2000. [PubMed: 10995848]

Stough C, Downey LA, Lloyd J, Silber B, Redman S, Hutchison C, Wesnes K, Nathan PJ. Examining the nootropic effects of a special extract of Bacopa monniera on human cognitive functioning: 90 day double-blind placebo-controlled randomized trial. Phytotherapy Research 22 (12), 1629–1634, 2008. [PubMed: 18683852]

Sunyer B, Patil S, Hoger H, Lubec GBarnes maze, a useful task to assess spatial reference memory in mice. Nature Protocols 198, 58–68, 2007.

Sutherland RJ, Kolb B, Whishaw IQ. Spatial mapping: definitive disruption by hippocampal or medial frontal cortical damage in the rat. Neuroscience Letters 31 (3), 271–276, 1982. [PubMed: 7133562]

Suzuki S, Augerinos G, Black AH. Stimulus-control of spatial behavior on the eight-arm maze in rats. Learning and Motivation 11,1–18,1980.

Takahashi E, Niimi K, Itakura C. Enhanced CaMKII activity and spatial cognitive function in SAMP6 mice. Behavioral Neuroscience 123 (3), 527–532, 2009. [PubMed: 19485558]

Teng E, Squire LR. Memory for places learned long ago is intact after hippocampal damage. Nature 400 (6745), 675–677,1999. [PubMed: 10458163]

Teyler TJ, Cavus I, Coussens C, DiScenna P, Grover L, Lee YP, Little Z. Multideterminant role of calcium in hippocampal synaptic plasticity. Hippocampus 4 (6), 623–634,1994. [PubMed: 7704107]

Thinus-Blanc C, Ingle D. Spatial behavior in the gebril. Journal of Comparative Psychology 99, 311–315,1985.

Thomas JL. Visual memory: adult age differences in map recall and learning strategies. Experimental Aging Research 11 (2), 93–97,1985. [PubMed: 4092723]

Thompson DM. Repeated acquisition as a behavioral base line for studying drug effects. The Journal of Pharmacology and Experimental Therapeutics 184 (2), 506–514,1973. [PubMed: 4688186]

Thorp AA, Sinn N, Buckley JD, Coates AM, Howe PR. Soya isoflavone supplementation enhances spatial working memory in men. The British Journal of Nutrition 102 (9), 1348–1354, 2009. [PubMed: 19480732]

Tolman EC, Gleitman H. Studies in spatial learning; place and response learning under different degrees of motivation. Journal of Experimental Psychology 39 (5), 653–659,1949. [PubMed: 15391108]

Tong H, Chen GH, Liu RY, Zhou JN. Age-related learning and memory impairments in adult-onset hypothyroidism in Kunming mice. Physiology & Behavior 91 (2–3), 290–298, 2007. [PubMed: 17449072]

Touyarot K, Poussard S, Cortes-Torrea C, Cottin P, Micheau J. Effect of chronic inhibition of calpains in the hippocampus on spatial discrimination learning and protein kinase C. Behavioral Brain Research 136 (2), 439–448, 2002.

Touzani K, Marighetto A, Jaffard R. Fos imaging reveals ageing-related changes in hippocampal response to radial maze discrimination testing in mice. The European Journal of Neuroscience 17 (3), 628–640, 2003. [PubMed: 12581181]

Tsien JZ, Huerta PT, Tonegawa S. The essential role of hippocampal CA1 NMDA receptor-dependent synaptic plasticity in spatial memory. Cell 87 (7), 1327–1338, 1996. [PubMed: 8980238]

Tulving E. Episodic and semantic memory In: Tulving E, Donaldson W (Eds.), Organization of Memory. Academic Press, New York, pp. 381–403,1972.

Tulving E, Markowitsch HJ. Episodic and declarative memory: role of the hippocampus. Hippocampus 8 (3), 198–204,1998. [PubMed: 9662134]

Uttl B, Graf P. Episodic spatial memory in adulthood. Psychology and Aging 8 (2), 257–273,1993. [PubMed: 8323729]

Van Dam D, Lenders G, De Deyn PP. Effect of Morris water maze diameter on visual-spatial learning in different mouse strains. Neurobiology of Learning and Memory 85 (2), 164–172, 2006. [PubMed: 16290194]

van der Staay FJ. Effects of the size of the morris water tank on spatial discrimination learning in the CFW1 mouse. Physiology & Behavior 68 (4), 599–602, 2000. [PubMed: 10713304]

van der Staay FJ, Bouger PC. Effects of the cholinesterase inhibitors donepezil and metrifonate on scopolamine-induced impairments in the spatial cone field orientation task in rats. Behavioral Brain Research 156 (1), 1–10, 2005. [PubMed: 15862622]

van der Staay FJ, Krechting B, Blokland A, Raaijmakers W. The cone field: a spatial discrimination task for the automatic and simultaneous assessment of working and reference memory in rats. Journal of Neuroscience Methods 31 (1), 13–22,1990a. [PubMed: 2308378]

van der Staay FJ, van Nies J, Raaijmakers W. The effects of aging in rats on working and reference memory performance in a spatial holeboard discrimination task. Behavioral and Neural Biology 53 (3), 356–370,1990b. [PubMed: 2350322]

van Haaren F, Wouters M, van de Poll NE. Absence of behavioral differences between male and female rats in different radial-maze procedures. Physiology & Behavior 39 (3), 409–412,1987. [PubMed: 3575484]

van Haaren F, van Hest A, Heinsbroek RP. Behavioral differences between male and female rats: effects of gonadal hormones on learning and memory. Neuroscience and Biobehavioral Review 14 (1), 23–33,1990.

Vargha-Khadem F, Gadian DG, Watkins KE, Connelly A, Van Paesschen W, Mishkin M. Differential effects of early hippocampal pathology on episodic and semantic memory. Science 277 (5324), 376–380,1997. [PubMed: 9219696]

Venault P, Beracochea D, Valleau M, Joubert C, Chapouthier G. Mouse lines selected for difference in sensitivity to beta-CCM also differ in memory processes. Behavioral Brain Research 173 (2), 282–287, 2006.

Vicens P, Redolat R, Carrasco MC. Effects of early spatial training on water maze performance: a longitudinal study in mice. Experimental Gerontology 37 (4), 575–581,2002. [PubMed: 11830361]

von Bohlen und Halbach O, Zacher C, Gass P, Unsicker K. Age-related alterations in hippocampal spines and deficiencies in spatial memory in mice. Journal of Neuroscience Research 83 (4), 525–531, 2006. [PubMed: 16447268]

Wallace JE, Krauter EE, Campbell BA. Animal models of declining memory in the aged: short-term and spatial memory in the aged rat. Journal of Gerontology 35 (3), 355–363, 1980. [PubMed: 7410786]

Wang R, Tang Y, Feng B, Ye C, Fang L, Zhang L, Li L. Changes in hippocampal synapses and learning-memory abilities in age-increasing rats and effects of tetrahy-droxystilbene glucoside in aged rats. Neuroscience 149 (4), 739–746, 2007. [PubMed: 17935895]

Wang W, Li S, Dong HP, Lv S, Tang YY. Differential impairment of spatial and nonspatial cognition in a mouse model of brain aging. Life Sciences 85 (3–4), 127–135, 2009. [PubMed: 19450612]

Ward MT, Oler JA, Markus EJ. Hippocampal dysfunction during aging I: deficits in memory consolidation. Neurobiology of Aging 20 (4), 363–372,1999a. [PubMed: 10604429]

Ward MT, Stoelzel CR, Markus EJ. Hippocampal dysfunction during aging II: deficits on the radial-arm maze. Neurobiology of Aging 20 (4), 373–380,1999b. [PubMed: 10604430]

Wasserman EA, Jensen DD. Olfactory stimuli and the “pseudo-extinction” effect. Science 166 (910), 1307–1309,1969. [PubMed: 5350332]

Weber RJ, Brown LT, Weldon JK. Cognitive maps of environmental knowledge and preference in nursing home patients. Experimental Aging Research 4 (3), 157–174, 1978. [PubMed: 679967]

Weitzdoerfer R, Hoeger H, Engidawork E, Engelmann M, Singewald N, Lubec G, Lubec B. Neuronal nitric oxide synthase knock-out mice show impaired cognitive performance. Nitric Oxide 10 (3), 130–140, 2004. [PubMed: 15158692]

Wenger GR, Schmidt C, Davisson MT. Operant conditioning in the Ts65Dn mouse: learning. Behavioral Genetics 34 (1), 105–119, 2004.

Wenk GL. Assessment of spatial memory using the T maze. Current Protocols in Neuroscience Chapter 8, Unit 8 5B, 2001.

Wenk GL. Assessment of spatial memory using the radial arm maze and Morris water maze. Current Protocols in Neuroscience Chapter 8, Unit 8 5A, 2004.

Westerman MA, Cooper-Blacketer D, Mariash A, Kotilinek L, Kawarabayashi T, Younkin LH, Carlson GA, Younkin SG, Ashe KH. The relationship between Abeta and memory in the Tg2576 mouse model of Alzheimer's disease. The Journal of Neuroscience 22 (5), 1858–1867, 2002. [PubMed: 11880515]

Whishaw IQ, Tomie J. Of mice and mazes: similarities between mice and rats on dry land but not water mazes. Physiology & Behavior 60 (5), 1191–1197,1996. [PubMed: 8916170]

White SR. Atropine, scopolamine and hippocampal lesion effects on alternation performance of rats. Pharmacology, Biochemistry and Behavior 2 (3), 297–307, 1974.

White KG. Characteristics of forgetting functions in delayed matching to sample. Journal of Experimental Analytical Behavior 44 (1), 15–34,1985.

Wilkniss SM, Jones MG, Korol DL, Gold PE, Manning CA. Age-related differences in an ecologically based study of route learning. Psychology and Aging 12 (2), 372–375, 1997. [PubMed: 9189997]

Yarasheski KE, Zachwieja JJ, Campbell JA, Bier DM. Effect of growth hormone and resistance exercise on muscle growth and strength in older men. The American Journal of Physiology 268 (2 Pt 1), E268–276,1995. [PubMed: 7864103]

Yasui F, Matsugo S, Ishibashi M, Kajita T, Ezashi Y, Oomura Y, Kojo S, Sasaki K. Effects of chronic acetyl-L-carnitine treatment on brain lipid hydroperoxide level and passive avoidance learning in senescence-accelerated mice. Neuroscience Letters 334 (3), 177–180, 2002. [PubMed: 12453624]

Yee BK, Hauser J, Dolgov VV, Keist R, Mohler H, Rudolph U, Feldon J. GABA receptors containing the alpha5 subunit mediate the trace effect in aversive and appetitive conditioning and extinction of conditioned fear. The European Journal of Neuroscience 20 (7), 1928–1936, 2004. [PubMed: 15380015]

Yoshida M, Goto K, Watanabe S. Task-dependent strain difference of spatial learning in C57BL/6N and BALB/c mice. Physiology & Behavior 73 (1–2), 37–42, 2001. [PubMed: 11399292]

Young A. Ageing and physiological functions. Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences 352 (1363), 1837–1843,1997. [PubMed: 9460068]

Zelinski EM, Light LL. Young and older adults' use of context in spatial memory. Psychology and Aging 3 (1), 99–101,1988. [PubMed: 3268248]

Zhang JX, Chen XQ, Du JZ, Chen QM, Zhu CY. Neonatal exposure to intermittent hypoxia enhances mice performance in water maze and 8-arm radial maze tasks. Journal of Neurobiology 65 (1), 72–84, 2005. [PubMed: 16010673]

Zhao X, Rosenke R, Kronemann D, Brim B, Das SR, Dunah AW, Magnusson KR. The effects of aging on N-methyl-D-aspartate receptor subunits in the synaptic membrane and relationships to long-term spatial memory. Neuroscience 162 (4), 933–945, 2009. [PubMed: 19446010]

Zheng JF, Patil SS, Chen WQ, An W, He JQ, Hoger H, Lubec G. Hippocampal protein levels related to spatial memory are different in the Barnes maze and in the multiple T-maze. Journal of Proteome Research 8 (10), 4479–4486, 2009. [PubMed: 19650667]

Zhou X, Qyang Y, Kelsoe JR, Masliah E, Geyer MA. Impaired postnatal development of hippocampal dentate gyrus in Sp4 null mutant mice. Genes, Brain, and Behavior 6 (3), 269–276, 2007.

Zhou SJ, Zhu ME, Shu D, Du XP, Song XH, Wang XT, Zheng RY, Cai XH, Chen JF, He JC. Preferential enhancement of working memory in mice lacking adenosine A(2A) receptors. Brain Research 1303, 74–83, 2009. [PubMed: 19785999]

Zlomuzica A, Ruocco LA, Sadile AG, Huston JP, Dere E. Histamine H1 receptor knockout mice exhibit impaired spatial memory in the eight-arm radial maze. British Journal of Pharmacology 157 (1), 86–91, 2009. [PubMed: 19413573]

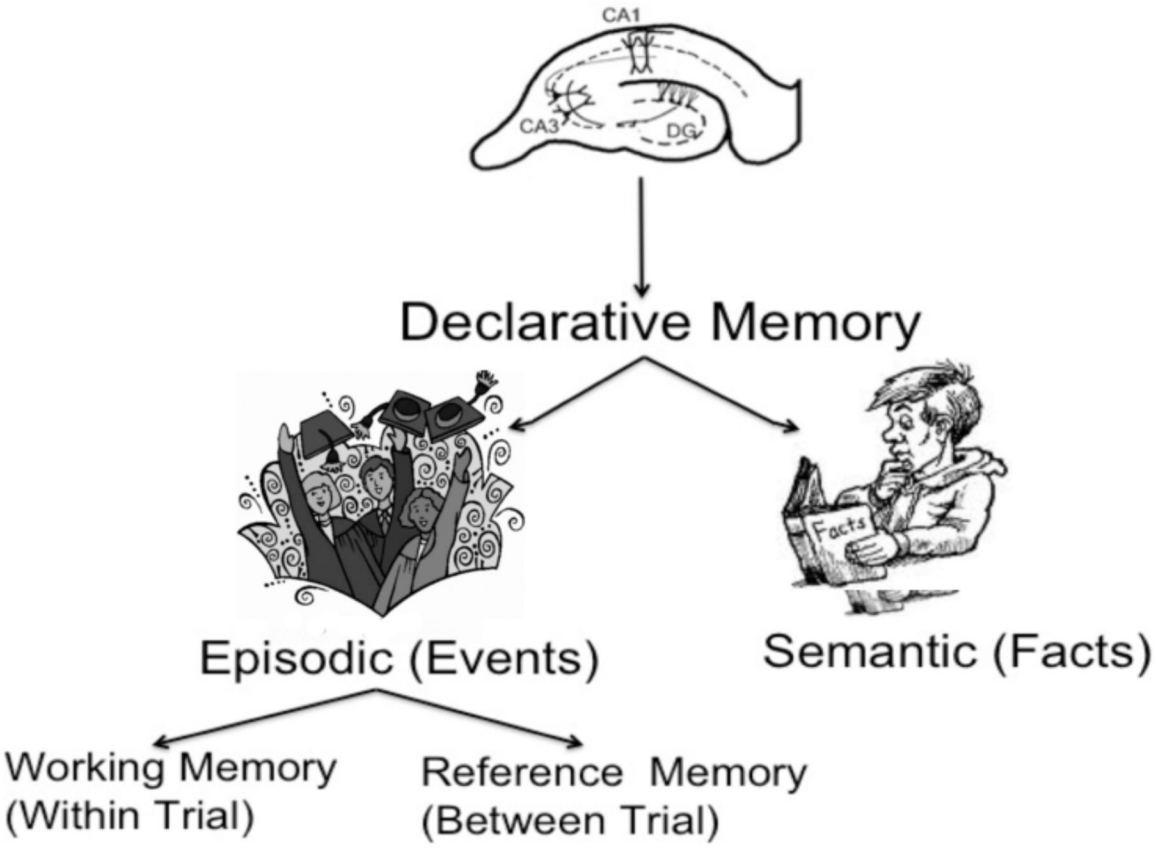

Fig. 1.
Classification of declarative memory (explicit memory).

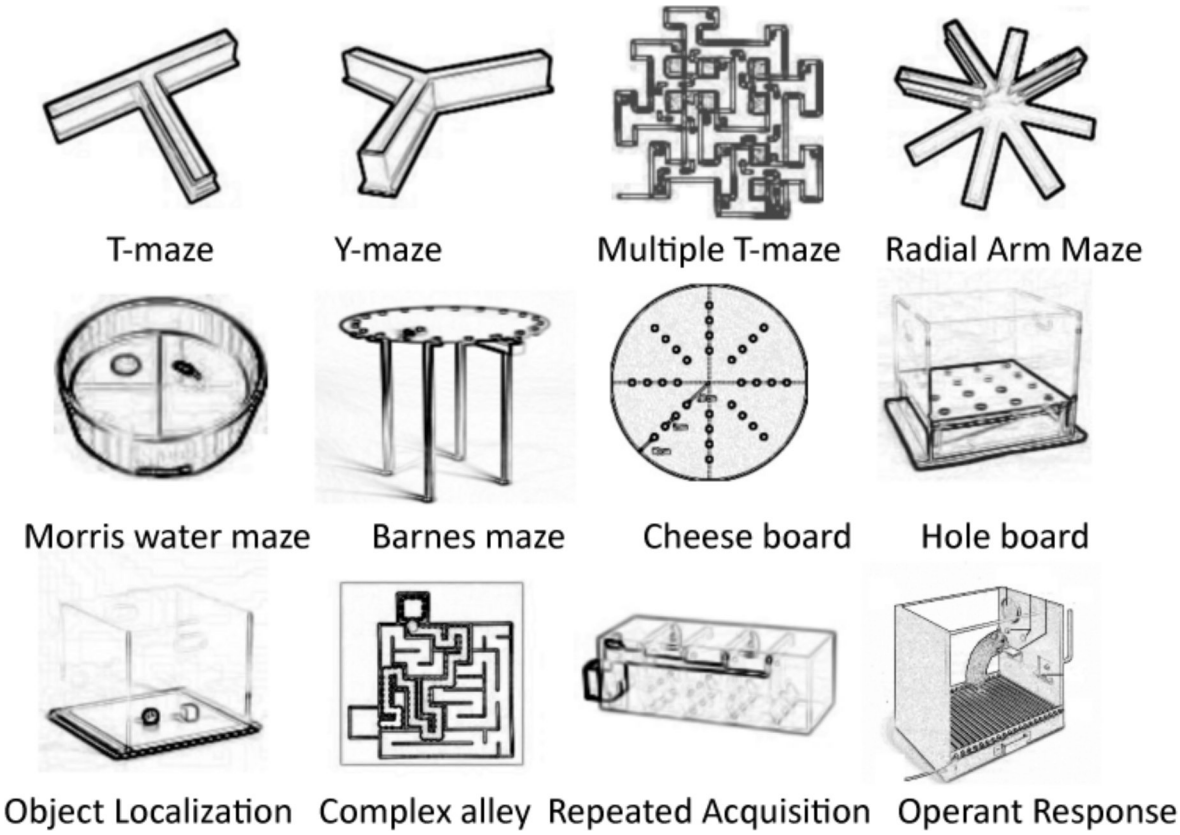

Fig. 2.
Different types of mazes.

Table 1:

Characteristics of different behavioral paradigms to assess spatial memory.

Behavioral Paradigm	Working/Reference Memory	Video Tracking System	Labor intensive	Use of aversive stimuli	Food/Water Deprivation	Advantages	Limitations
T-maze/ Y-maze	Working	Not Required	No	No	Yes	Very simple	Requires constant handling
Multiple T-maze	Working/ Reference	Required	No	No	Yes	Complex with multiple choice points	Requires constant handling
Radial Maze	Working/ Reference	Required	No	No	Yes	Moderate level of stress	Possible use of non-spatial strategy
Morris Water Maze	Working/ Reference	Required	Yes	Yes	No	Fast Learning	Stressful
Barnes Maze	Working/ Reference	Required	Yes	Mild	No	Non stressful, use natural motivation	Slow or absent learning
Cheese Board	Working/ Reference	Required	Yes	No	Yes	Non stressful	Spatial distribution not clear
Hole board	Working/ Reference	Required	Yes	No	Yes	Fully automated	Depends on exploratory behavior
Object Localization	Working	Required	No	No	No	Simple and easy to design	Depends on exploratory behavior
Complex Alley Maze	Working	Required	Yes	No	No	Use natural motivation	Depends on exploratory behavior
Repeated Acquisition & Performance	Working/ Reference	Required	No	No	Yes	Long term and within subject comparison	Time consuming
Operant Delayed response	Working	Required	No	Sometimes	Yes	Precise control of timing	Response may be predictable