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Research Article

THE POSSIBLE EXPERIMENTAL TOOLS USED TO ASSESS MEMORY FUNCTIONS IN THE ANIMAL MODELS OF ALZHEIMER'S DISEASE

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A R T I C L E I N F O

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A B S T R A C T

In Alzheimer's disease (AD) researches, animal models are an important resources for examine the efficacy of several drugs and its underlying mechanisms. Both transgenic and non transgenic (sporadic) animal models are enable to study different pathological features of the AD in vivo. Although there are several molecular and biochemical studies on the pathophysiology of AD, memory tests are a critical way for this disease. There are different behavioral tasks are used in several studies for assessing memory in animal models dependent on memory types. This paper review the main AD animal models and detail the commonly used behavioral tasks according memory types.

INTRODUCTION

Cognitive functions are a higher mental processes that lead to knowledge, involving all means of acquiring information (1). In humans, cognitive functions are often assessed through written or spoken language, while in animals such as rats and mice, learning and memory must be accessed through different types of behaviors tests (2).

Memory is ability of the brain to acquire, store, retain and retrieve information. Memory includes three basic processes of encoding (forming a memory code), storage (maintaining encoding information), and retrieval (recalling information). Memory can be classified according to several criteria; content (e.g. declarative/explicit and non-declarative/implicit memory), duration (e.g. short-term and long-term memory), nature (associative and non-associative memory), function (e.g. working and reference memory), or motivation (appetitive and aversive memory) (3). There are a wide variety of behavioral tasks are performed according to the types of memory (Fig.1).

Declarative or explicit memory

Declarative or explicit memory is a type of long-term memory, it is associated with consciousness and awareness. The hippocampus and temporal cortex have an essential roles in this type of memory. Explicit memory is a higher-level mental function with speech and language two main examples of cognitive function in human.

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This type of memory is for actual knowledge about the dates, people, things, and places.

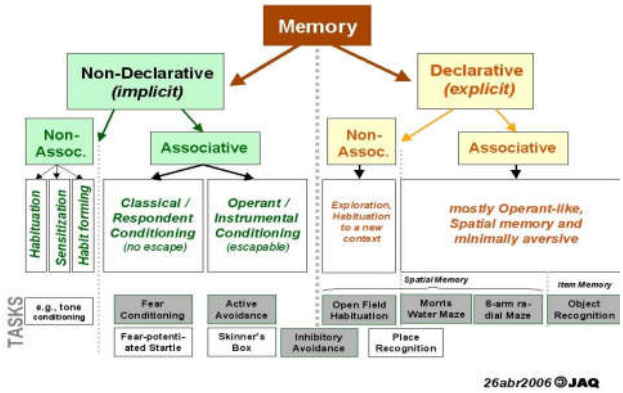

Figure 1 Memory types and some example of behavioral tests that have access to them. (3)

Non-declarative or implicit memory

Non-declarative or implicit memory dose not a associated with consciousness or awareness**.** With this type of memory, individual is able to utilize previous experiences to perform a current mission without awareness (4). Implicit memory is divided in to procedural memory and priming memory (5). Procedural memory, includes habits and motor skills such as riding a car and walking, that, once acquired, become automatic and unconscious (5). The processing of this type of memory is in the striatum. Priming memory, involves helping some person to recognize objects or words by previous exposure to them and it is processed in the neocortex (4).

Associative and non-associative memory

Associative learning involves classical and operant conditioning. In this type of memory an object is able to learn and remember the relationship between uncorrelated stimulus for example, recall the name of places or someone from a certain perfume (3).

There are two categories of non-associative memory; habituation and sensitization that depend on different reflex pathways. Habituation is a decline in response to a stimulus due to repeated exposure to these stimulus. For example, an animal will be excited when a strange sound or tone is played. However, if this tone is played repeatedly, the animal will ultimately no longer be excited by the tone. In sensitization, the object is response to lesser intensity stimuli after experiencing a noxious (intense) one (6).

Long-term and short- term memory

Declarative memory and many forms of non-declarative memory involves; long- term and short-term memory. In long-term memory, the information are storage for a long period of time, (e.g. for many years). This type of memory involves a process of persistent modification in the nerve fibers structure, size and number that called long term potentiation (7). However, the information in short-term memory are storage in a short period of time (e.g. mints to hours). Hippocampus has an essential role in the consolidation of short-memory into long-memory. Working memory is a model of short memory that remain the information available (for few seconds), while the object plans an activity based on it. This type of memory is dependent on the prefrontal cortex (8).

Cognitive functions including learning and memory are intensively assessed in many laboratories in order to study the alterations of these functions in pathological situations such as Alzheimer's, Parkinson's and schizophrenia diseases. Moreover, cognitive functions test is very useful to study different therapies and their effects on the behavior(9).

Rodents (rats and mice) are the most commonly animal models used in behavioral neuroscience research. They are well suited animal models, as they display a variety of cognitive functions with relevance to human disorder (9). Rodents perform well in several of the standard neuropharmacological tests, and their size makes it suitable to perform more invasive experiments (10).

Experimental models of Alzheimer's disease

Experimental animal models are critical to increasing our understanding of the pathophysiological mechanisms of the Alzheimer's disease which are essential to investigate treatment strategies that could improve the outcome of this disease. Transgenic mouse is the most commonly used animal model that overexpress specific human genes such as genes encoding APP, tau, presenilin (PS1 and PS2), and apolipoprotein E (ApoE) that associated with the familial form of Alzheimer's (13). In addition, some studies identified that endothelial nitric oxide synthase (eNOS) and alpha-macroglobulin mutant genes are highly susceptible to Alzheimer's disease (14).

Transgenic animal models of Alzheimer's disease

A number of gene targeting technologies are using to generate different transgenic mice models such as APP transgenic mice, double transgenic mice, triple transgenic mice and 5xFAD transgenic mice (11).

APP transgenic mice

APP transgenic mice is a widely used Alzheimer's disease transgenic animal models that used to express the transgene of the human amyloid precursor protein (12). In previous studies, APP transgenic mice exhibited only an accumulation of Aβ within the cells, but no plaque formation, suggesting that learning and memory impairment occur independently of senile plaques formation, but it occurs due to Aβ intracellular accumulation. The lack of neuritic beta-amyloid plaques in these mice models was expected be related to the low expression of the APP gene(13).

However, in other studies, a platelet-derived growth factor-β promoter (PDAPP), are using to increase the expression of human APP gene which resulting in wide-ranging extracellular Aβ deposits with the formation of senile plaques at 6-9 months of animal age(14).

In addition, other transgenic mice models such as APP23 and Tg2576 also demonstrated APP overproduction and senile plaques formation that associated with neuronal loss in the hippocampus. In Tg2576 mice, senile plaques develop at 8 months of mice age, whereas in APP23 mice senile plaques formation occur at 6 months of age (14).

The conjugation between Swedish double mutation mice (APP23 and Tg2576) and presenilin gene mutations leading to plaques formation in the olfactory bulb, thalamus, hypothalamus and neocortex at an earlier age. These animal models also exhibit progressive senile plaque formation, microglial activation and Aβ42 accumulation in the hippocampus which ultimately leading to behavioral deficits (13).

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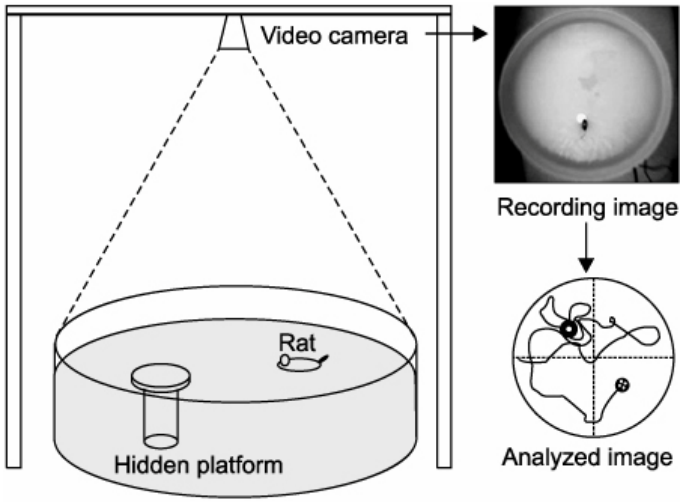

Figure 2 Morris water maze task consists of hidden platform, circular water pool and video camera that records animals movement in water pool (17).

Advantages and disadvantages

Morris water maze is easily used task as the rodents learn readily and quickly comparing with other maze tasks (3). However, in this task, it is difficult to distinguish between spatial learning and motor skill impairments. In addition, working memory is not possible to assessed by this task independently (7).

T-maze

In several animal studies, T-maze task has been used to assess the spatial working memory and the effects of drugs that impair or enhance spatial memory in rodents (18). In addition, different studies have used this task to evaluate age-related cognitive function defects.

The T-maze apparatus is shaped like a letter T, consist of tow arms, right and left arms (Fig.3). The rodent placed at the base of this apparatus. A reward i.e food placed in one arm. The animal walks forward and chooses between tow arms of the maze to collect a reward (19).

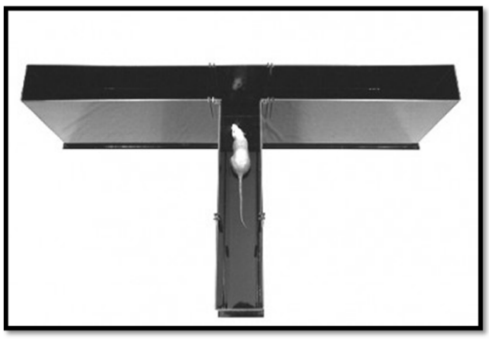

Fig 3 T -maze test

Natural alternation: The natural alternation can be assessed by running an animal in this maze repeatedly (many times) without reward to explore the maze and alternate between right and left arms (18).

Learning and memory test: In training session, a reward is placed in one arm, then a hungry animal run through the maze to collect a reward. In test session, the reward is removed from the arm and the animal must learn to choose an arm that presented reward in previous session, indicating that animal remembers the arm that it visited before(19) (20).

Advantages and disadvantages

The major advantages of the T-maze is including; the simplicity of the apparatus to evaluate spatial working memory and it does not need video-recording systems because it depend on the experimenter observation. However, in this task, it is difficult to assess reference memory because in the T-maze device there are only two options, that can increases the ability of animal to solve the maze. In addition, the T-maze test needs continuous handling of rodents, that may lead to stress which can affect the task result. But, handling the animal by the same experimenter decrease this stress (20).

Y-maze

The Y-maze apparatus is shaped like a letter Y, it consist of three identical arms (Fig 4). It is similar to the T-maze, but it consist of three identical arms with gradual turns that reduce the time of learning as compared to the T-maze which described by sharp turns.

Fig 4 Y-maze apparatus

Radial arms maze

The 8-radial arm-maze task has been used widely in assessing spatial learning, working and reference memory. This task requires the rodent to use the spatial cognition to learn the position of a reward (21).

The apparatus consists of a circular central platform surrounded by eight equally spaced arms. Visual cues are placed around the experimental room to discriminate the site of the arms. During training, food cups (rewards) are placed at the arms end to encourage animal exploration. In the test session, working memory is tested when the animal enter each arm for one time (Fig.4) (3).

The re-entry of animal into the arms is resulting in a working memory error, while reference memory errors are assessed when the rodent entering never baited arms (22).

Fig 4 8-radial arm-maze apparatus

Advantages and disadvantages

Radial arm-maze task is used to assess different types of memory; working memory, reference (long-term) memory and motor (egocentric) memory (21). In addition, in this task, the observer can distinguishes between spatial learning and motor impairment (e.g. if the animal has motor impairment it can still choose the target arm). However, this task is an appetitive task, that may cause a problem in some conditions (e.g. in old rodents which require full food supplies). Training the rodents mostly takes more time than Morris water maze (3).

Novel Object recognition task

Object recognition is the process by which an animal is aware that an object has been previously experienced (3). Novel object recognition task is classified as declarative, associative item memory (3). It is performed by placed the animal in any simple box. A typical box has a 50cm high, made of plastic or wood with a frontal transparent wall. In this experiment, a rodent is trained to recognize particular object, this object is made of metal or plastic in order to easy cleaning between different sessions (2). The procedure of this task consists of; habituation phase, familiarisation phase, and test phase. Before the testing phase, all rodents have at least two training or exploration sessions for contextual habituation and familiarisation with a number of novel objects inside the box (2). During the test phase, tow objects are placed in the animal box, one familiar (identical to the explored object) and the other, a novel (unexplored object) (23). A normal rodent should spend less time investigating the familiar object relative to the novel one. The results of the novel object recognition test are influenced by both cortical and hippocampal lesions

(2) (Fig 5).

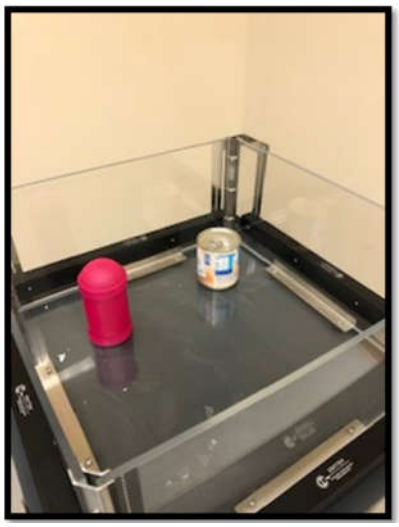

Fig 5 Novel object recognition test using tracking system connected with camera

Advantages and disadvantages

Novel object recognition it is not a complex task because it requires no reward or external motivation, but a little training for familiarization and habituation is required (3). Object recognition task is very useful to assess short-term memory and long-term memory. Despite the object recognition task has been used widely in assessing the different types of memory, it also has limitations. The level of exploration during habituation and familiarisation phase sometimes can be inconsistent. The exploration level can increase by the using of large open-field area or mild food deprivation (2).

Fear conditioning

Fear conditioning task is classified as non-declarative (implicit), associative memory (3). This task is commonly used to study hippocampus and amygdale dependent memory functions (24). It is a learning paradigm in which the rodent is learned to associate a certain cue or context with an aversive stimulus (e.g. mild electrical shock, or air puff). In this task, when the rodent is subsequently exposed to the context associated with the aversive stimulus such as electrical shock, it will display a freezing behavior. Freezing is a specific response to fear, in freezing response the animal is crouched without any visible movement of the body, except for respiration (25).

This behavior can be disappeared by repetitive exposure to the context in the absence of aversive stimulus. Freezing is used as an indicator of hippocampus and amygdale memory function (3). Decreased freezing during the extinction test is used to evaluate efficacy of the cerebral cortex to inhibits amygdala activity (24).

Advantages

One of the most important advantages of fear conditioning task is that it is form of passive learning (without active effort) which can be used in several strains of rodents, even when more obvious motor disorders are problematic in other learning tasks (26). In addition, This task requires less elaborate apparatus and it requires much less time for training and test session comparing with other learning and memory tests (25)

Active avoidance or Shuttle Avoidance

According to the memory types, the active avoidance task is classified as implicit (non-declarative), associative memory. This task is an operant conditioning, for example the rodent should learn the relationship between conditioned stimulus (light) and unconditional stimulus (shock) in order to predict shock with light and avoid it by escaping to the other side (3). The shuttle box apparatus consist of a rectangular box divided at the center by a sliding door. This box is lighted by overhead lights and has a grid floor to produce a footshock (Fig.6) (27).

Fig.6 The Active Avoidance apparatus (shuttle box), divided in to two chambers

On habituation day an animal is placed in shuttle box for about 10 minutes to explore the learning environment and to become familiarized with it (3).

Bothe test and training session have similar protocol. In this task, a rodent is placed in one chamber of the shuttle box for 50 second to one minute. After one minute the conditioned stimulus (light), is turned off in the chamber in which the animal is in, after that light is turn on and an unconditioned stimulus (0.5 mA shock for 5 second) is delivered (27).

Both light and shock are terminated at the same time. During intertrial intervals, rodent is move freely between box chambers. Intertrial intervals are important ensure that the only association is occur between the conditioned and unconditional stimulus without other predictive stimulus. The next session usually starts in the chamber where the animal was placed at the end of the intertrial intervals (3)(28).

If the animal cross to the other chamber during conditioned stimulus (light), the Active Avoidance is recorded by the automated shuttle box. However, failure to respond is recorded, when the mouse fails to escape to the other chamber during the trial session. The animal must receives a lot of training session in order to improve the performance. The major disadvantage of this task includes the animal stress (28).

Inhibitory or Passive avoidance

Passive avoidance is an aversive conditioning task depend on emotional associative learning, in which the animal learns to associate a specific context (i.e dark area or stepping from high platform) with the occurrence of aversive stimuli (electrical shock) (29)(3). Inhibitory avoidance behavior of animals is defined as the inhibition of the natural preference of animal for the dark environment after exposure to an electrical shock (inescapable shock) (Fig.7). Thus, this paradigm combines fear conditioning with the avoidance of entering a certain aversive (i.e dark area) (30).

Fig 7 Passive avoidance (step-trough avoidance)

Passive avoidance task is similar to active avoidance paradigm, but in the passive avoidance task there in no conditioned stimulus such as light (30).

There are two different forms of the passive avoidance task, step-down and step-through passive avoidance.(3)

In the step-down test, the animal is placed on a high platform in which the rodent can step down onto the (shock grid) floor. In this task, the rodent will be subjected to the unconditional stimulus (foot shock) when it stepping, that will leading to avoidance to step down in next session (30). Step-down passive avoidance paradigm is more sensitive to the lesion-induced or drug-induced changes in the locomotor activity compared to step-through passive avoidance paradigm (31).

The step-trough, is as an emotional memory test, combining an instrumental response with fear conditioning. In this task, the animal placed in specific test box that divided in to two chambers, one dark and one bright, and theses tow chambers are separated by a sliding door (Fig.6). At first, the animal is placed in the bright chamber. When an animal entering the dark chamber it will be subjected to 0.2-0.4 mA foot shock, that will learn an animal to associate the dark area with the aversive stimulus (shock)(24). Failure to respond is recorded, when the mouse move to the dark (unsafe) area. The major advantage of this test includes the simplicity in that safe (bright) and unsafe (dark) chamber are clearly defined for rodent. Thus, an animal not required a lot of training session (29).

CONCLUSION

Animal behavioral tasks have become an important tools in many areas of neuroscience research and are beneficial for studying the i) pathophysiological mechanisms of different neurological disorders such as Alzheimer's, Parkinson's and schizophrenia disease, ii) the functional alterations that caused by chemical treatment or genetic mutation, and iii) the effects of novel therapies on the behavior of disease models.

These tasks are useful in the Alzheimer's disease field, as a clinical manifestation of this disease is learning and memory loss. Despite cognitive function tests of animal models has a certain limitations and cannot measure some cognitive functions that are related to humans, each of these animal behavioral tasks can provide essential information on the efficacy of targets.

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