RESEARCH PAPER

Animal Models of Cognitive Impairment: A Comprehensive Review of Recent Advances and Translational Challenges

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Abstract

Cognitive impairment is a common feature of several neurological and psychiatric disorders and represents a major challenge in both clinical management and therapeutic development. However, the translation of findings from preclinical animal models to clinical trials remains limited, owing to several factors, including incomplete or poorly designed models, inappropriate selection of animal species, insufficient biological variability, and limitations in construct, face, and predictive validity. Therefore, careful and systematic model design is essential to improve the translational relevance of preclinical research. Animal models of cognitive impairment remain indispensable for elucidating the underlying mechanisms of cognitive dysfunction and for the preclinical evaluation of potential therapeutic interventions. Over the past two decades, advances in genetic engineering, pharmacological approaches, and behavioural neuroscience have significantly expanded the diversity and sophistication of available models. These include models based on rodents, non-human primates, and, increasingly, non-mammalian organisms. Despite these advances, the translation of promising preclinical findings into clinical efficacy remains relatively low. This translational gap is frequently associated with limitations in the construct, face, and predictive validity of existing models, together with fundamental differences between animal and human brain architecture, neurobiology, and cognitive processes. Addressing these challenges through appropriate model selection, rigorous experimental design, and improved validation strategies is crucial for enhancing the predictive value of animal models and facilitating successful translation into clinical research. This review provides a brief recap of different types of animal models and cognitive impairment animal model.

Keywords: Cognitive impairment, animal models, Pharmacological models, Genetically Modified Models

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1. Introduction

Animal models of cognitive impairment are essential for investigating the neural mechanisms underlying learning, memory, and attention. Because these functions arise from complex interactions among multiple neural systems, they cannot be adequately examined using simple *in-vitro* models alone. Animal models also provide valuable platforms for evaluating potential therapeutic agents and assessing the neurocognitive toxicity of environmental contaminants and substances of abuse. Although monkeys, rats, and mice remain widely used, complementary nonmammalian models - including fish, flies, and flatworms - are increasingly being developed. These emerging models offer significant advantages for high-throughput screening and for identifying the molecular and neural mechanisms that regulate cognitive function.

Pharmacological models are widely used to study cognitive dysfunction and to understand the role of neurotransmitter–receptor systems in learning, memory, and attention. They are also important for evaluating cognition-enhancing drugs for conditions such as Alzheimer's disease, ADHD, Parkinson's disease, and schizophrenia. The acetylcholine system, involving muscarinic and nicotinic receptors, is strongly associated with cognition, while glutamate and NMDA receptors also play an important role. Substances such as ethanol can produce significant cognitive impairment [1].

Animal models are also valuable in studying neurobehavioral toxicity. Cognitive effects of toxicants such as lead, mercury, and PCBs have been demonstrated in animal studies. Similarly, MPTP, which affects midbrain dopamine neurons, has helped establish the role of dopamine in cognitive and neurological functions and contributed to the development of treatments for Parkinson's disease [2].

Mice are increasingly used to study the molecular basis of cognition and for developing

new drugs. Genetically modified and transgenic mice are particularly useful for studying Alzheimer's disease, aging-related cognitive decline, and the role of cholinergic receptors in learning and memory. Therefore, reliable and rapid cognitive testing methods are important.

Pharmacological, genetic, neurotoxic, aging, and traumatic brain injury models can reproduce selected features of cognitive impairment and are widely used in drug discovery and preclinical research. Genetically modified mice are particularly useful for studying neurodegenerative disorders such as Alzheimer's disease, while zebrafish provide a cost-effective complementary model for studying cognition and screening potential cognition-enhancing drugs [3].

Animal models can also reproduce specific types of cognitive impairment caused by aging and neurotrauma. Studies in aged animals, particularly monkeys, help identify age-related cognitive changes and develop new treatments. Similarly, neurotrauma models help researchers understand the mechanisms of cognitive impairment and evaluate potential therapies.

Non-mammalian models are increasingly used as complementary models to mammalian studies rather than as replacements. Mammals have greater similarity to human brain structure and function but are generally expensive and time-consuming. Non-mammalian models are cost-effective and suitable for high-throughput screening of toxicants and potential therapeutic drugs, although their similarity to human cognition is limited.

Important non-mammalian models include zebrafish, C. elegans, and Drosophila. Zebrafish are especially valuable because of the availability of extensive molecular and genetic information. Although no single animal model completely reproduces the complexity of human cognitive disorders, appropriate models provide valuable insights into disease mechanisms, therapeutic targets, drug efficacy, and safety. Therefore, the selection and validation of a suitable animal model are essential for obtaining reliable and translational results [4].

1. Classification of animal models

Animal models used in cognitive impairment research can be broadly classified according to the method used to produce cognitive dysfunction and the species employed **(Figure 1).**

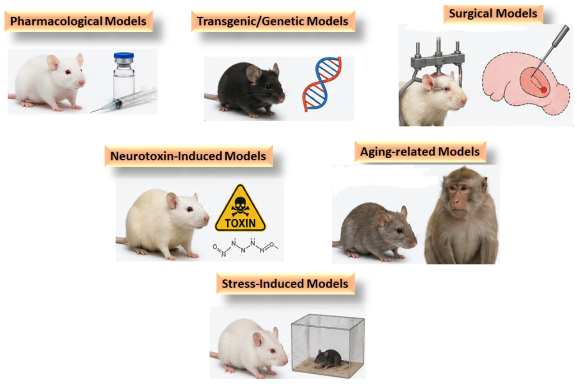

Figure 1. Different types of animal models

1.1. Pharmacological models

Cognitive impairment is induced using drugs or chemical agents that interfere with neurotransmitter systems. Various examples are Scopolamine-induced amnesia, Diazepam-induced cognitive impairment and NMDA receptor antagonists such as MK-80.

1.2. Transgenic animal models

Transgenic animal models provide valuable insights into biological processes and disease mechanisms. These genetically engineered animals contain foreign genetic material, known as a transgene, incorporated into their DNA. Such models are widely used to elucidate gene functions, investigate disease pathogenesis and progression, and evaluate potential therapeutic interventions. By enabling the study of complex biological processes in vivo, transgenic models serve as important tools in biomedical research [5,6]. Techniques to generate transgenic animals are shown in **Figure 2**.

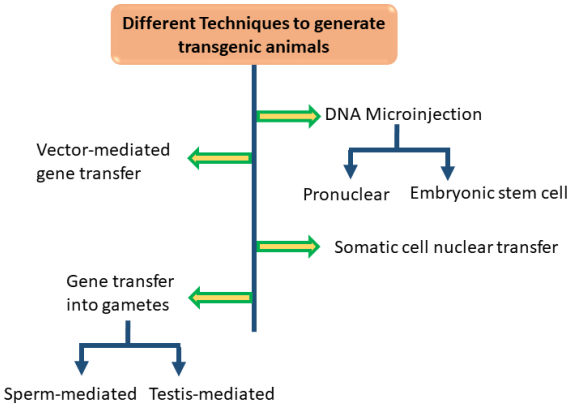

Figure 2: Techniques for transgenic animal generation

1.3. Surgical models

The use of animal models in surgical training is ethically complex, as it involves balancing the need for high-quality surgical models to prepare residents for real-world scenarios with the compassionate use of animals for training and research

[7]. Animal models are essential in surgical implant research, bridging *in-vitro* studies and human clinical trials. They help assess biocompatibility, safety, implant integration, tissue responses, and long-term effectiveness under controlled conditions. This is especially important in neurotechnology, where implant–nervous tissue interactions require careful evaluation [8, 9].

Animal models help evaluate implant–tissue interactions, including inflammation, fibrous capsule formation, tissue integration, and long-term stability. Rabbit models are commonly used because their bone structure and healing resemble humans [10]. Tests such as push-out and pull-out assays measure osseointegration. These models also assess implant function, complications, wear, and safety before human trials, and can mimic specific clinical conditions, especially in dental implant research [11].

1.4. Neurotoxin-induced animal models

Neurotoxin-induced animal models are widely used to study the pathogenesis of neurodegenerative diseases, particularly Parkinson's disease (PD). Neurotoxins such as MPTP, 6-OHDA, and rotenone can reproduce key features of PD, allowing researchers to investigate dopaminergic neuron loss, mitochondrial dysfunction, and neuroinflammation. These models are also valuable for identifying therapeutic targets and evaluating potential neuroprotective drugs.

Mice and rats are commonly used, while other species, such as gerbils and non-human primates, may be selected for specific neurological conditions. Animal models provide an important advantage because in vitro, ex vivo, and in silico approaches cannot fully replicate the complex interactions between the brain and the whole body. Using both male and female animals also helps assess sex-related differences in disease progression and drug responses [12, 13].

Various neurodegeneration models [14]:

(a) Dopaminergic Neurodegeneration Models
Used mainly to study Parkinson's disease by inducing damage to dopaminergic neurons.

(b) Cholinergic Neurodegeneration Models
Used to study Alzheimer's disease and related cognitive disorders by causing dysfunction or loss of cholinergic neurons.

(c) Neuroinflammation-Induced Neurodegeneration Models
Used to investigate how chronic inflammation and activation of microglia contribute to neuronal damage and neurodegenerative diseases.

1.5. Aging-related animal models

Aging can be understood through multiple models, including biological, cellular, cognitive, and psychosocial frameworks, each highlighting different mechanisms and perspectives on the aging process. Aging related animal models are essential for understanding how aging contributes to neurodegeneration and for developing age-targeted strategies to prevent or slow down disease progression [15].

Aging is the major risk factor for the most degenerative disease such as Alzheimer, Parkinson, Huntington, and Amyotrophic lateral sclerosis. Aging related animal model mimic natural aging processes and are widely used to study age-associated changes in the brain, disease mechanism and to evaluate therapeutic intervention [16].

Most research on mechanisms of aging is being conducted in a very limited number of classical model species, i.e., laboratory mouse, rat, the common fruit fly (Drosophila melanogaster) and roundworm. **Table 1** Shows the different aging related animal models [17].

Table 1: Aging related animal models

Type of Model	Description / Examples	Key Features	Applications
Naturally Aged Animals	Animals allowed to age naturally. Examples: aged mice and rats.	Cognitive decline, reduced motor function, decreased synaptic plasticity and altered neurochemistry.	Study of normal brain aging and age-related changes.
Accelerated Aging Models	Genetic or environmental	Early memory deficits, oxidativ	Study of mechanisms of accelerate

	methods used to accelerate aging. Examples: SAMP8, SAMR1 mice	e stress and neuronal loss.	d aging and neurodegeneration.
Genetically Modified Models	Transgenic or knockout animals showing premature aging or age-related pathology. Examples: SOD1, Klotho knockout, APP/PS1 mice.	Neuronal dysfunction, protein accumulation and disease-related changes.	Study of interactions between aging and neurodegenerative diseases.
Environmental/Lifestyle-Based Models	Aging influenced by	Metabolic changes,	Study of modifiable factors
	factors such as high-fat diet, chronic stress, caloric restriction or lack of exercise.	inflammation and altered brain function.	affecting brain aging.

1.6. Stress-induced animal models

Stress-induced animal models are used to study the effects of chronic or acute stress on the brain and nervous system. They help investigate mechanisms involved in depression, anxiety, cognitive impairment, neuroinflammation, and neurodegeneration [18].

1.6.1. Chronic restrain stress (CRS)

CRS are used to evaluate the effect of psychological behavior such as depression, anxiety, cognitive impairment. Mice and rats are repeatedly restrained for a fixed period over several days or weeks [19].

1.6.2. Chronic unpredictable mild stress (CUMS)

Chronic Unpredictable Mild Stress animal model used to study the effects of long-term, mild, and unpredictable stress caused by depression and anxiety. Animals are exposed to different mild stress in an unpredictable manner for several weeks [20].

1.6.3. Chronic Social Defeat Stress (CSDS)

Social Defeat Stress animal models are used to identify the effects of repeated social stress on depression, anxiety, and neurological changes. In this model, animals are repeatedly exposed to an aggressive or dominant animal, producing social defeat. This mimics repeated social adversity and leads to measurable behavioral and neurobiological changes relevant to stress-related disorders [21].

1.6.4. Chronic Social Isolation (CSI)

Chronic Social Isolation animal model are used to evaluate the effects of prolonged lack of social interaction on behavior and brain function. Animals are housed individually for long time of period to induce anxiety, depressive, cognitive impairment, and neurobiological changes. Ex: Mice and rats.

1.6.5. Maternal Separation (MS)

Maternal Separation is an early-life stress animal model. MS model are used to identify how the separation of newborn from the mother affects the brain development, behavior, and stress responses in future life. Newborn are separated from their mother for a fixed period each day during early development [22].

1.6.6. Immobilization Stress (IS)

The effects of acute or repeated physical and psychological stress are studies by Immobilized Stress animal model. In this model animals are temporarily immobilized, which activates the stress-response system which. This model mainly used for study of stress mechanisms and evaluation of anti-stress, antidepressant and neuroprotective drugs [23].

2. Behavioral assessment methods for the evaluation of cognitive performance in animal models

Animals are unable to speak and they can't tell you whether they remember what just happened, or what they are experiencing at this moment. The most direct way to understand what they are thinking is to observe their behaviors. Behavioral assessment of cognitive function is widely used in experimental studies such as physiological mechanism research of related disease models and drug intervention evaluations.

The rodent behavioural assessment methods are the scientific approach used in rodent model to assess various motor, sensory cognitive functions and emotional behaviour to identify behavioural patterns of animal. These methods are essential for studying psychological, neurological models and neurotoxicity diseases. These models help to understand pathology behind psychological changes and serve as preclinical models for testing potential treatments. There are several behavioral assessment methods are available to assess rodent behavioural changes.

2.1. Open field habituation test (OFH)

Open field habituation test is use to assess spatial behavior of animal (mice and tars). Spatial behaviour involves aspects of habituation, exploratory behavior, locomotor activity, and anxiety-related responses that allow an animal to localize itself within an environment. In this test animal moves into an open environment until they will get comfortable in new environment. The animal is permitted to search the perimeter freely within a certain period of time. This can take as long as 2–10 min [24, 25].

2.2. Y-maze test

In Alzheimer's case animals and humans both have same symptoms of severe memory loss. The Y maze test are used to test the cognitive ability of mice/rats models of neurological diseases. This test is mainly used in the analysis of discriminative learning, working memory and reference memory of animals. It can be used to measure the rodent's willingness to explore new environments, which is usually preferred over returning to familiar spaces.

The Y maze consists of three identical arms, and there is a food supply device at the end of each arm (**Figure 3**). The size of arm is varying for both rat and mice. Measurement of spatial working memory of mice/rats can be evaluated by allowing mice to explore all three arms of the maze. Animal's spatial memory ability can be reflected according to the analysis of the animal's feeding strategy, which refers to the number of times, total time spent, correct times, wrong times, routes, and other parameters related to entering each arm. Compared with the eight-armed maze, the Y maze is simple and feasible to perform. The practicality of the Y maze has contributed to its prevalent use in the evaluation of learning and memory functions [26, 27].

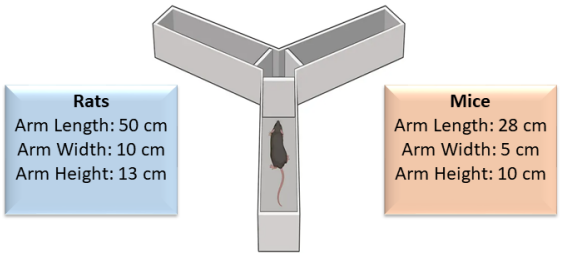

Figure 3: Y Maze Device

2.3. Passive avoidance test/ inhibitory avoidance test

The passive avoidance test used to evaluate long term learning and memory retention of mice and rats based on negative reinforcement. This test mainly used in CNS disorder such as neuroscience, psychopharmacology, toxicology, and cognitive research to evaluate the effects of drugs, brain lesions, toxins, or genetic modifications on aversive learning and memory retention.

In this test, animal is placed in a well-lit side of a two-compartment box and offered access through a narrow hole to a closed dark compartment (**Figure 4**). When the animal enters the dark side following its natural instinct, the opening is closed, and a mild foot shock is given. Thus, during this acquisition phase, the animal learns that the moving to the dark compartment has negative consequences. After the first acquisition, the animal is taken to its home cage and returned to the arena (test phase) after a delay, usually 24 h. During the test phase the animal is again placed in the white compartment and the passive avoidance response is evaluated. The latency to enter is taken as a measure of the memory

strength. Memory performance is positively correlated with the latency to escape from the white compartment; the better the recollection, the greater the latency [28, 29].

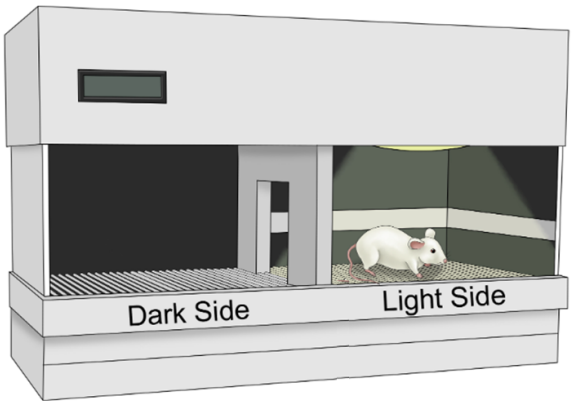

Figure 4: Passive avoidance test device

2.4. Step-down inhibitory avoidance test

In Step-Down Avoidance Test assesses the single-trial inhibitory learning of animal. The step-down apparatus made up of an acrylic chamber with a removable electrified grid floor, with an elevated vibrating platform in the center. The grid floor made up of stainless steel with 0.3 cm diameter and the direct current electric shocks are delivered to the grid floor by an isolated stimulator [30].

An animal place in elevated platform and receiving mild foot shock upon stepping down; during retention testing, the latency to step down serves as a readout of aversive memory consolidation. Conduct Vision automates precise measurement of step-down latency and freezing duration, eliminating observer bias. This test mainly used for evaluating cholinergic, GABAergic, and glutamatergic modulation of memory.

2.5. Active avoidance test

In the active avoidance test, rats learn to escape an aversive stimulus by moving to an adjacent compartment when a light/tone conditioned stimulus is presented. Although sensorimotor abilities may influence performance, older rats show a slower increase in avoidance responses than younger rats. This poorer performance is mainly attributed to reduced acquisition and retention of learned experiences, rather than decreased pain sensitivity, movement, attention, arousal, or habituation [31].

2.6. 8-arms radial maze test

The 8-arms radial maze is used to assess spatial learning and working memory in rodents. The animal must remember which of the eight arms it has already visited and avoid revisiting them. Errors in arm selection indicate impaired memory or learning. The test is widely used to study aging, Alzheimer's disease, neuroinflammation, and myelin-related changes, with automated tracking providing accurate and objective behavioral data [32].

2.7. Morris water maze test

The Morris water maze is a widely used for assessing spatial learning and memory in rodents. Richard Morris was developed Morris water maze test in 1981 to assesses how animals learn and remember the location of a hidden escape platform within a circular pool of water. This behavioral task uses a rodent's natural dislike to water, motivating it to find a way out [33].

2.8. Radial arm water maze

The Radial Arm Water Maze is a behavioral test used to assess spatial learning and memory in rodents by combining the aversive motivation of the Morris Water Maze with the spatial complexity of a radial arm maze [34].

3. Conclusion and future perspectives

Cognitive impairment is common in a variety of neurological and psychiatric conditions, including stroke, traumatic brain injury, schizophrenia, Alzheimer's, and Parkinson's disease. Animal models of cognitive function are used in the identification and evaluation of specific compounds for their pharmacological efficacy. Based on animal models of cognition also helpful in prediction of specific conditions for which compounds would be most useful. These model also estimate the therapeutic index of medicine. Cognitive functions measure by Open field habituation test, Y-maze test, Passive avoidance test, Active avoidance test, 8-arms radial maze test, Morris water maze test and Radial arm water maze.

In recent years, with the development and progress of different kinds of animal models of cognitive impairment have been discovered. Meanwhile, these animal models also have made a great contribution in pharmacological research field, which is essential for the development of new drugs and pre-clinical trials. However, animal modeling also faces a series of challenges and difficulties, mainly due to the low success rate and instability of modeling. Due to the experimental conditions in different laboratories are different, the same animal model may not be replicated between different laboratories. In addition, because psychological is different from other pathogenic factors, it is quite difficult to make strict quantification. On the other hand, even some of the behavioral indicators to evaluate the animal models sometimes are controversial. Therefore, more precise and improved stress animal models and detective methods are also needed in the near future. This review

will helpful to the researcher to select best animal model to evaluate the efficacy of medicine.

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