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Zebrafish Model of Cognitive Dysfunction

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Abstract

Cognitive dysfunction is an impairment in one or more of the six cognitive domains (complex attention, executive function, learning and memory, language, perceptual motor and social cognition). The effect of pharmacological interventions can be studied using animal models of cognitive dysfunction, which are typically split into pharmacological, developmental and genetic models. Rodents are the most commonly used animal species for modelling cognitive dysfunction, although multiple models and test locations are often recommended to improve validity. Researchers thus unfortunately need to balance the validity of their experimental designs with financial, logistical and cost constraints. Zebrafish could be the answer to this conundrum as one of their many advantages over rodents is their high breeding rate which makes high-throughput screening more feasible and thus increases cost-effectiveness. The popularity of zebrafish has been increasing in recent times, as measured by the increasing number of zebrafish research publications. It is thus unsurprising that several zebrafish models of cognitive dysfunction have already been developed, together with zebrafish tests designed to measure zebrafish cognitive performance. Future research will undoubtedly lead to the development of new zebrafish models of cognitive dysfunction, as well as validate current ones to pave the way for widespread adoption.

Keywords: zebrafish, cognition, animal model, cognitive dysfunction, drug discovery

1. Introduction to cognitive dysfunction

Cognitive dysfunction is an impairment in one of the six cognitive domains as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). The six cognitive domains are complex attention, executive function, learning and memory, language, perceptual motor and social cognition [1]. Cognitive disorders are a category of mental health disorders and are officially termed 'neurocognitive disorders' by the DSM-5. There is a key difference between

cognitive impairment in neurocognitive disorders and in neurodevelopmental disorders; in that, the former is acquired, whereas the latter develops at birth or shortly thereafter. Neurocognitive disorders are broadly divided into mild neurocognitive disorders and major neurocognitive disorders, which are mostly made up of the dementias [1]. The difference between the two categories is innately arbitrary, as the diagnostic criteria rely on determining the degree of cognitive and functional impairment in the patient. The DSM-5 itself explicitly acknowledges that precise thresholds are difficult to determine because the cognitive and functional impairments associated with neurocognitive disorders exist in a spectrum. An impairment in one cognitive domain is sufficient for the diagnosis of a neurocognitive disorder, except in the case of Alzheimer's disease, whereby impairment of memory and one other domain is required [2]. Although Alzheimer's disease is typically responsible for the majority of neurocognitive disorders, among the medical conditions which can also affect mental functions are frontotemporal degeneration, Huntington's disease, Lewy body disease, traumatic brain injury, Parkinson's disease, prion disease and dementia/neurocognitive issues due to HIV infection [2, 3].

Treatments for cognitive dysfunction are broadly divided into psychopharmacological interventions and behaviour-based cognitive remediation, though both methods can be combined to supplement one another. Cognitive remediation focuses on teaching patients cognitive skills such as thinking and problem solving, which are typically taught in formal education or through real-world activities which the patient may not have had the opportunity to experience due to their condition [4]. In contrast, psychopharmacological interventions such as antipsychotics primarily aim to treat or manage the underlying cause of cognitive dysfunction but also improve cognition as they are usually capable of affecting a variety of central neuroreceptors [5]. Examples of antipsychotics which improve cognition include serotonin receptor antagonists such as clozapine [6] and α_2 -adrenoceptor antagonists such as iloperidone [7].

2. The animal model of cognitive dysfunction

While studies on behavioural-based cognitive remediation are perhaps best done in humans, the effect of pharmacological interventions can be studied using animal models of cognitive dysfunction. The following subsection aims to provide a brief overview of the six cognitive domains defined by the DSM-5 and the animal models which can be used to model a dysfunction in each domain. Animal models of cognitive dysfunction are typically split into three major categories, namely, the pharmacological, developmental and genetic models. Pharmacological models utilize treatments such as dopamine and serotonin agonists, to produce effects which mimic cognitive dysfunction. Developmental models induce cognitive dysfunction in young animals via brain lesions or by disrupting the normal maturation process by exposing the animals to certain compounds such as L-nitroarginine. Finally, genetic models produce animals with cognitive dysfunctions through either inbreeding or genetic modification [8].

2.1. Complex attention

The cognitive domain of complex attention consists of sustained attention, divided attention, selective attention and information processing speed [9]. As the aptly named attention deficit

hyperactivity disorder (ADHD) is likely to be the first disorder affecting this domain which comes to mind, it is hardly surprising that animal models of a dysfunction in complex attention are usually also animal models of ADHD. One such animal model of complex attention is spontaneously hypertensive rats which exhibit all the characteristic behaviours of ADHD, including impaired sustained attention [10]. Animal tests have also been developed to study sustained attention, such as the '5-choice serial reaction time task' as well as an operant task which requires rats to detect and discriminate between signals and non-signals [11]. The '5-choice serial reaction time task' can also be used as a measure of information processing speed [12].

2.2. Executive function

The cognitive domain of executive function consists of planning, decision-making, working memory, responding to feedback/error correction, overriding habits and mental flexibility [9]. Executive function is typically associated with the prefrontal cortex and is believed to be significantly more complex in primates as compared to rodents [12]. However, the use of rodent models of executive function should not be entirely discounted for the same reasons that they have become widely used today as animal models. These reasons include being a more cost effective and simpler system for study, but one that still possesses many of the complex characteristics which are of interest [13]. There is also evidence to believe that rats are also capable of executive functions such as decision-making and that homologous regions within the prefrontal cortex of primates and rats also have parallel cognitive functions [13]. Among the aspects of executive function which have been replicated using animal models is working memory, using tasks such as the spatial delayed response and spatial search tests. Decision-making has also been modelled using animals by utilising behavioural tasks (reversal learning, reinforcer devaluation and delay discounting), which require flexible adaptation in response to a changing environment [14]. As a decline in executive function is a characteristic of the ageing process, aged rats can also be used to simulate age-related cognitive decline [12].

2.3. Learning and memory

The cognitive domain of learning and memory consists of immediate memory and recent memory (including free recall, cued recall and recognition memory) [9]. Inbred 'senescence accelerated' mice display spontaneously occurring age-related learning and memory defects, as well as difficulty in acquiring new behaviours [15]. Animal models of Alzheimer's disease such as the PDAPP transgenic mice can also be used as models of learning and memory dysfunction as they display memory impairments in object recognition tasks and also have difficulty in learning tasks [16]. Other methods of producing animal models with impaired learning and memory include the genetic modification of genes such as the tuberous sclerosis genes [17] and causing brain injury to the animals in the form of mild trauma or concussions [18]. Several tests designed to assess animal learning and memory include the Morris water maze [19] and passive avoidance tasks which utilise apparatus such as the elevated T-maze [20].

2.4. Language

The cognitive domain of language consists of expressive language (including naming, fluency, grammar and syntax) and receptive language [9]. Currently, no animal model has been

produced which mimics an acquired language dysfunction in humans. However, a rodent model of developmental language disability has already been developed from an observation that humans with impaired language development also have difficulty in processing rapidly presented auditory information [21]. It is the authors' hope that animal models of language dysfunction will be developed in the future once it becomes possible to teach animals the languages used by humans or for humans to learn animal languages.

2.5. Perceptual motor

The perceptual motor cognitive domain consists of construction and visual perception [9]. No animal models specifically meant to replicate a perceptual motor dysfunction have been found in literature. This could possibly be because perceptual motor skills rely on integrating information from a variety of sensory inputs and are thus exceedingly challenging to replicate in animal studies. As the name suggests, perception is a major component of this domain but may be difficult to assess in animals. Perceptual motor skills may also involve fine motor tasks, which may be difficult to teach all but non-human primates [22].

2.6. Social cognition

The cognitive domain of social cognition consists of recognition of emotions, theory of mind and behavioural regulation [9]. Animal models of social cognition have been produced, such as the oxytocin receptor null mice model of autism which displays impaired social memory [23] said to be analogous to human social cognition deficits [24]. Valproic acid-exposed rodents have also been used to model the behavioural characteristics of autism spectrum disorder, including a dysfunction of social cognition, as they tend to avoid interacting socially [25]. Social cognition can also be assessed through rodent behaviour tests, the degree of social interaction and so forth, although there is debate on whether these measures actually assess social behaviour or social cognition. However, certain social constructs such as 'theory of mind' will require the use of non-human primates or possibly another animal species besides rodents [24].

2.7. An overview of the current animal models for modelling cognitive dysfunction

Even from the brief overview above, it is clear that animals have been an invaluable tool for modelling dysfunctions in four of the six cognitive domains, though modelling a dysfunction in the language and perceptual motor cognitive domains is currently proving to be a challenge. Rodents are by far the most commonly used animal species for modelling cognitive dysfunction, though other species such as non-human primates, felines and canines have been used as well [26]. Whilst there is great discord on the validity of rodent models in comparison to the more complex non-human primate models, rodents are preferred by the vast majority of laboratories worldwide due to economical, logistical and ethical constraints regarding the use of non-human primates [26]. However, rodent models have been criticised for lacking in predictability when translating results into human clinical trials [27, 28]. One possible way of improving the predictability of rodent models is to use more than one model and to replicate the study at different locations [27]. While such an experimental design may improve the validity of rodent models of cognitive dysfunction, the financial costs will undoubtedly rise in

tandem with the number of models and test locations used, in addition to increasing logistical and spatial requirements. Thus, researchers will unfortunately need to balance the validity of their experimental designs with financial, logistical and cost constraints.

3. Zebrafish as an emerging animal model of cognitive dysfunction

The solution to the problem of validity versus practicality could be as simple as replacing rodents with another animal species such as zebrafish (*Danio rerio*), which are becoming increasingly popular [29] (Figure 1) due to their high breeding rate, which in turn makes high-throughput screening feasible. This is because the oviparous zebrafish breed continuously throughout the year and have relatively short generation times of between 3 and 5 months [30]. Zebrafish offspring also quickly mature ex utero, gaining vision and the ability to swim freely as well as feed, all within 72 hours. Larval zebrafish in their early life can survive in just 50 µl of solution, enabling the use of microtitre plates for high-throughput screening to discover compounds with a certain desired effect. In addition to being relatively small, zebrafish larvae are also translucent, and thus in vivo imaging techniques such as fluorescent reporters may be used to monitor the progression of diseases at the cellular and subcellular levels [31]. Dissolving the compounds to be tested directly in the tank water is also an option with zebrafish, eliminating the necessity of performing invasive procedures such as injections. Zebrafish are thought to absorb substances dissolved in the tank water through the gastrointestinal tract and also via the transdermal route in the case of immature zebrafish. These routes of absorption are possible

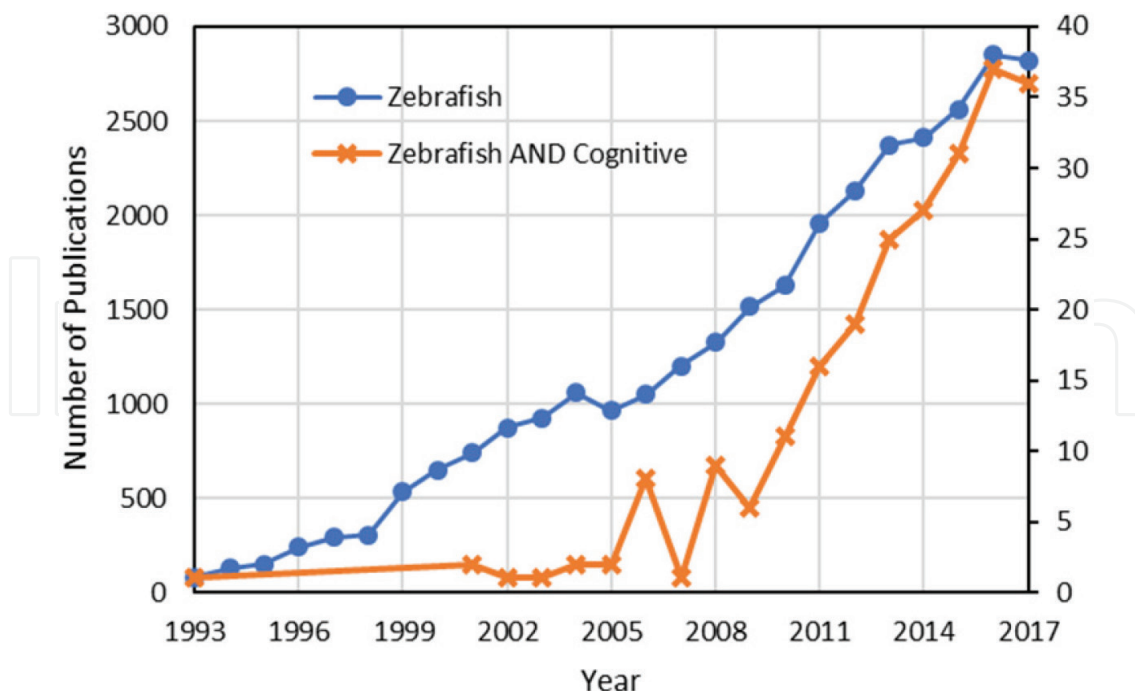


Figure 1. Publications with the keyword 'Zebrafish' versus publications with the keywords 'Zebrafish AND Cognitive', as indexed by PubMed from the year 1993 (first appearance of articles with the keywords 'Zebrafish AND Cognitive') to 2017.

in immature zebrafish as they start swallowing from their third day of life and do not develop scales until they are several weeks old. Despite zebrafish being fish and hence more removed from humans in an evolutionary sense as compared to mammalian rodents, their genes are nonetheless around 75% homologous to human genes. This makes identifying the human orthologues present in zebrafish relatively simple as both human and zebrafish genomes have already been fully sequenced. Additionally, constructs of RNA, protein or DNA can be injected into embryos at an early stage of development to modify their gene and hence protein expression. Morpholinos are modified oligonucleotides which may be inserted into zebrafish embryos via an injection to decrease the expression of selected genes. This method enables as many as 500 knockout zebrafish embryos to be swiftly and effortlessly produced over a period of several hours [32, 33]. The blood-brain barrier in zebrafish is also tight junction based and highly permeable to macromolecules, meaning that zebrafish will be extremely responsive to test compounds [34]. Anatomy wise, zebrafish brains also have similarities to human brains in that both possess defined forebrain, midbrain and hindbrain. Both humans and zebrafish also have a diencephalon, telencephalon and cerebellum, as well as peripheral nervous system with motor, sensory and autonomic components [35]. Zebrafish also exhibit 'higher' behaviours and show integrated neural functions such as memory, conditioned responses and social behaviour [35]. All these aspects make zebrafish an attractive animal model for research into cognitive dysfunction due to their cost-effectiveness, scalability and similarity to humans as compared to several other animal models (**Table 1**). In addition, pharmacologic, developmental and genetic animal models of cognitive dysfunction can be easily produced using zebrafish and on a much larger scale as compared to rodents due to their higher breeding rate. The 'higher' behaviours and cognitive ability exhibited by zebrafish will also enable the use of cognitive and behaviour tests to assess cognitive dysfunction, much like those used for rodent models.

3.1. The progress towards developing a zebrafish model of cognitive dysfunction

While the concept of using zebrafish as an animal model may be relatively new as compared to other more established animal models such as rodents, zebrafish models of cognitive dysfunction and zebrafish cognitive tests have already been developed. While rodent pharmacologic and developmental models of cognitive dysfunction have parallels in zebrafish, no genetic models have been developed thus far. Zebrafish have also been found to display an age-related decline in cognitive dysfunction [36], similar to that found in other animal models such as rodents. Unfortunately, most zebrafish cognitive dysfunction models excluding those which involve unconditioned or reflexive behaviours may need to be carried out in adults as the neural system of zebrafish is still immature at the larval stage [37].

3.1.1. Complex attention

In the case of the cognitive domain of complex attention, there is no attention task for zebrafish which is widely accepted, and thus validated zebrafish behaviour tasks for measuring learning are used to infer attention [38]. However, the march of progress is relentless, and tasks have already been developed to test complex attention, such as the 'virtual object recognition test' [39] and the '3-choice serial reaction time task' [40] for adult zebrafish. It is

Animal model	Canines/felines	Non-human primates	Rodents	Zebrafish
Upkeep cost per animal	\$\$\$	\$\$\$\$	\$\$	\$
Space required	●●●○	●●●●	●●○○	●○○○
Breeding rate	●●○○	●○○○	●●●○	●●●●
Feasibility of high-throughput screening	●○○	●○○	●●○	●●●
Anatomical similarity to humans	●●○	●●●	●●○	●○○
Genetic similarity to humans	●●○	●●●	●○○	●○○

The '\$' symbols represent the relative upkeep cost for the four animal models, with a greater number of '\$' symbols signifying a greater cost. The number of shaded circles as compared to unshaded circles serves as a relative comparison for the different attributes between the four animal models, with the superlative having all circles shaded.

Table 1. A comparison of the current animal models of cognitive dysfunction.

interesting to note that both zebrafish tasks are adapted from the tasks used in rodents, which bode well for the prospects of both tests being widely accepted in the future for the testing of complex attention in zebrafish.

3.1.2. Executive function

For the cognitive domain of executive function, reversal learning tasks have been used to demonstrate the behavioural flexibility of adult zebrafish, which is associated with executive function [37]. However, it should be noted that executive function also includes aspects of working memory and feedback/error correction [9]. Thus, zebrafish models meant to assess the cognitive domains of complex attention as well as learning and memory could also be used to assess executive function, depending on the working definition regarding the scope which executive function covers.

3.1.3. Learning and memory

For the learning and memory cognitive domain, the behaviour tasks which are used to assess this cognitive domain include the condition place preference, predator avoidance, T-maze, plus maze, three-compartment zebrafish maze and the three-choice discrimination tests [38] for adult zebrafish. The pharmacological method of inducing cognitive dysfunction has also been used to produce adult zebrafish which have deficits in learning and memory, by treating them with compounds such as antiepileptic drugs [41] or scopolamine [42]. Larval zebrafish may also be used to model nonassociative learning as they display short- and long-term habituation to visual and acoustic stimuli, which leads to the suppression of characteristic manoeuvre responses to these stimuli [43].

3.1.4. Language

In the case of the language cognitive domain, zebrafish models of dysfunction in this domain are also currently absent from literature, possibly due to the reasons previously discussed.

3.1.5. *Perceptual motor*

In the case of the perceptual motor cognitive domain, zebrafish models of dysfunction in this domain are also currently absent from literature, possibly due to the reasons previously discussed.

3.1.6. *Social cognition*

Lastly, the cognitive domain of social cognition is measured in adult zebrafish by exploiting its natural shoaling behaviour. The shoaling may be achieved using live zebrafish or by presenting computer-generated images of zebrafish and quantifying the resulting shoaling behaviour using parameters such as the distance between the test zebrafish and the other shoaling members [44]. Pharmacological methods of inducing social cognition dysfunction include treatment with dizocilpine [45]. Ethanol can also be used as a developmental model of social cognition dysfunction, as zebrafish embryos exposed to ethanol develop social cognition dysfunction in adulthood [46].

3.2. An overview of several cognitive dysfunction tests developed for zebrafish

3.2.1. *Three-choice discrimination*

3.2.1.1. *Purpose*

- Evaluates all five of Bushnell's five categories of attention (orienting, expectancy, stimulus differentiation, sustained attention and parallel processing) in an animal, when modified to include additional stimuli as potential distractions [38, 47].
- Requires zebrafish to be able to orient themselves as well as being able to anticipate the result of an action.

3.2.1.2. *Procedure*

- A zebrafish is trained to swim from a start chamber into one of three chambers using food as a reinforcement.
- The correct chamber which contains food is illuminated with white light, whereas the empty incorrect chambers are left dark.

3.2.1.3. *Critical assessment*

- The zebrafish must overcome its preference for dark places in order to select the correct chamber, and this demonstrates that the zebrafish is learning rather than acting solely on instinct.
- The addition of a third chamber is an improvement over the T-maze as it reduces the chance level from 50 to 33%.

3.2.2. *Three-choice serial reaction time*

3.2.2.1. *Purpose*

- Evaluates the ability of a zebrafish to learn a complex behavioural task [40, 48].
- Demonstrates the capacity of zebrafish for learning and memory.

3.2.2.2. *Procedure*

- A zebrafish is first trained to approach the response aperture of a tank when it is lit by a stimulus light, using food as a reinforcement.
- The trained zebrafish is then placed in a tank with three response apertures and given a brief period to nose poke the lit aperture to receive reinforcement in the form of food.

3.2.2.3. *Critical assessment*

- The correlation with the rodent equivalent from which this test is derived from is unclear due to anatomical differences between the two species.
- It is also unclear if the stimulus light is visible from all areas of the test tank and thus a failure of the zebrafish to see the stimulus light could be incorrectly perceived as a deficit in learning and memory.
- The amount of time that the zebrafish is given to eat the food reinforcement should also be carefully chosen to allow sufficient time for the zebrafish to finish the food.

3.2.3. *Three-compartment zebrafish maze*

3.2.3.1. *Purpose*

- Evaluates spatial discrimination learning in zebrafish and also demonstrates avoidance discrimination learning in zebrafish [38, 49].

3.2.3.2. *Procedure*

- A zebrafish is first placed in the middle of a three-chambered tank, with partitions at either end of the central chamber.
- After a minute, the partitions are lifted, and the zebrafish is allowed to swim into either the left or right chambers.
- If the zebrafish swims into the chamber designated as the 'wrong' side, the partition is pushed until it is within 1 cm from the end of the tank, in order to confine the zebrafish and 'punish' it.
- After 10 seconds, the zebrafish is allowed to return to the central chamber, and the protocol can be repeated as needed.

3.2.3.3. *Critical assessment*

- Zebrafish can reliably learn and remember the response contingencies when this behavioural task is repeated multiple times.

3.2.4. *Plus maze*

3.2.4.1. *Purpose*

- Evaluates a zebrafish's ability to learn and remember the association between a single visual cue and a food reward (simple associative learning), as well as the location of the food reward (spatial learning) [38, 50].

3.2.4.2. *Procedure*

- The plus maze is placed on a rotating circular platform, and a zebrafish is first transferred into the middle of the plus maze (four-armed radial maze), which is bounded by start box to prevent the zebrafish from entering the arms before the start of the experiment.
- The zebrafish then undergoes habituation (food provided in all arms) and shaping trials (food provided only in certain arms next to a visual cue, such as a red plastic card).
- The final training step involves the use of paired and unpaired groups whereby the food is provided together with or independently of the visual cue.
- Zebrafish learning can then be tested by providing only the visual cue with the food being inaccessible (associative learning) or by providing the food in a fixed location relative to external visual cues such as room equipment, without any visual cues in the maze itself (spatial learning).
- Parameters such as the time spent in the target arm and the number of entries into the target arm versus other arms are quantified to assess zebrafish learning and memory.

3.2.4.3. *Critical assessment*

- The four distinct spatial locations provided by the plus maze is again an improvement over the T-maze.
- The plus maze provides stimuli in a predictable way and is thus unsuitable for measuring sustained attention.
- It is also possible that the spatial learning task is accomplished by the zebrafish via non-spatial strategies such as by remembering a single salient cue next to the target location.

3.2.5. *Reversal of learning*

3.2.5.1. *Purpose*

- Evaluates the ability of a zebrafish to adapt or shift their response strategy when presented with changing environmental contingencies [37].

3.2.5.2. Procedure

- Commonly involves first training a zebrafish to discriminate between two stimuli such as different coloured lights and only reinforcing responses to one stimulus.
- Once the zebrafish reaches a certain response criterion, the contingency is reversed so that the other stimulus is reinforced and the previously 'correct' stimulus is not.
- Subsequent extensions to this test include changing the colour of the stimuli (intra-dimensional shift) or adding a third dimension such as shape, before the reversal (extradimensional shift).

3.2.5.3. Critical assessment

- Zebrafish follow a similar pattern of improvement as mammals when subjected to multiple reversals and interdimensional shifts as they require increasingly fewer trials to reach the response criterion.

3.2.6. Shoaling behaviour

3.2.6.1. Purpose

- Evaluates shoaling behaviour in zebrafish, which is one aspect of zebrafish social behaviour [44].

3.2.6.2. Procedure

- A group of around ten zebrafish are first habituated together in the experimental tank on several occasions before use.
- Each of the habituated zebrafish can then be placed individually in an experimental tank without any stimuli, in order to measure their baseline behaviour.
- Shoaling behaviour can subsequently be induced using methods such as:
 - Placing live stimulus fish inside/outside the experimental tank.
 - Displaying animated zebrafish images.
- Shoaling behaviour is recorded and subsequently quantified by video tracking software to determine behaviour parameters such as distance to the stimulus, distance to the bottom of the tank and angular velocity.

3.2.6.3. Critical assessment

- Zebrafish are diurnal like humans and thus have good vision, which helps the face validity of this test.
- Electronic devices meant for humans can also be used for this zebrafish test, which increases cost-effectiveness.

- It is not known if virtual fish are truly equivalent to live fish in inducing zebrafish social behaviour as virtual fish do not interact with the experiment fish.
- Other social behaviours such as aggression and reproduction have not been studied using this model.

3.2.7. *T-maze*

3.2.7.1. *Purpose*

- Evaluates a zebrafish's ability associate visual stimuli with a food reward (similar to the plus maze) [51].

3.2.7.2. *Procedure*

- Similar to the plus maze, but the T-maze only possesses two arms rather than four arms.
- Different coloured or patterned sleeves could be fitted to the arms or goal boxes instead of lights.

3.2.7.3. *Critical assessment*

- Similar to the plus maze, although the T-maze only contains two chambers and thus fewer distinct spatial locations.

3.2.8. *Virtual object recognition*

3.2.8.1. *Purpose*

- Evaluates an animal's attention when presented with novel stimuli [39].
- Zebrafish can identify shape information independently of motion information.

3.2.8.2. *Procedure*

- A zebrafish is placed in a transparent tank, and two displays are used to display either static or dynamic identical images on both ends of the tank.
- After a 10-minute familiarisation trial, the zebrafish is returned to the home tank and later subjected to a novel shape recognition trial (one familiar image, one novel image).
- Recognition time (seconds) is measured when the zebrafish approaches the display area and orients its head towards the display.

3.2.8.3. *Critical assessment*

- Testing sequence is fairly rapid, and no animal training is required, other than the initial exposure session.

3.2.9. Zebrafish larvae visual/acoustic stimuli habituation

3.2.9.1. Purpose

- Evaluates zebrafish larvae nonassociative learning as the test requires a degree of memory storage and retrieval [43].
- Zebrafish larvae show long-term habituation to visual stimuli and short-term habituation to acoustic stimuli, as demonstrated by a decline in the rate of characteristic movements in response to repeated exposure to visual or acoustic stimuli.

3.2.9.2. Procedure

- Visual stimulation is provided by first equilibrating a zebrafish larva to a uniformly lit testing chamber and then abruptly extinguishing the light, which triggers a unique turning behaviour termed the O-bend:
 - The training procedure is then repeated at desired intervals in either a massed or spaced fashion, before returning the zebrafish to a holding tank.
 - The visual stimulation can then be repeated after a desired amount of time to determine how much of the habituation training remains.
- Acoustic stimulation is provided by exposing a zebrafish larva to a series of acoustic stimuli with varying intensities and intervals between each stimulus, to trigger a characteristic kinematic startle response termed 'short-latency C-start':
 - After a short resting period of several minutes, the protocol is repeated to determine the degree of habituation.

3.2.9.3. Critical assessment

- Being able to use larval zebrafish allows for high-throughput screening methods.
- The characteristic responses are relatively simple and may not be suitable for testing higher cognitive functions.
- Memory retention time also appears to be relatively short, ranging from minutes in short-term habituation to hours in long-term habituation. Thus, zebrafish larvae may not be suitable for testing learning and memory over longer periods of time.

4. Conclusions and future directions

In conclusion, zebrafish have the potential to replace rodents as the most widely used model of cognitive dysfunction, mainly due to their higher cost-effectiveness, and may have already begun doing so as several zebrafish models of cognitive dysfunction have already been developed. Future areas of research into the zebrafish model of cognitive dysfunction could focus on producing new models of cognitive dysfunction to complement the existing models,

as well as to expand the scope of research into cognitive dysfunction that is possible using zebrafish. Already existing models should also be further examined to validate them in hopes that in the near future, certain tasks will become widely accepted tests of cognitive dysfunction in zebrafish. Another potential area of research is the development and characterisation of mutant zebrafish strains to produce genetic models of cognitive dysfunction in zebrafish.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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