

# Review: Neuropathology and behavioural features of transgenic murine models of Alzheimer's disease

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## Neuropathology and behavioural features of transgenic murine models of Alzheimer's disease

Our understanding of the underlying biology of Alzheimer's disease (AD) has been steadily progressing; however, this is yet to translate into a successful treatment in humans. The use of transgenic mouse models has helped to develop our understanding of AD, not only in terms of disease pathology, but also with the associated cognitive impairments typical of AD. Plaques and neurofibrillary tangles are often among the last pathological changes in AD mouse models, after neuronal loss and gliosis. There is a general consensus that successful treatments need to be applied before the onset of these pathologies and associated cognitive symptoms. This

review discusses the different types of AD mouse models in terms of the temporal progression of the disease, how well they replicate the pathological changes seen in human AD and their cognitive defects. We provide a critical assessment of the behavioural tests used with AD mice to assess cognitive changes and decline, and discuss how successfully they correlate with cognitive impairments in humans with AD. This information is an important tool for AD researchers when deciding on appropriate mouse models, and when selecting measures to assess behavioural and cognitive change.

Keywords: Alzheimer's disease, amyloid, behavioural tests, cognitive decline, mouse models, tau

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## Introduction

Dementia is a term used to describe a syndrome, caused by various diseases of the brain, characterized by significant decline in multiple cognitive areas including memory, language, social cognition, executive and perceptual functions. The most recent Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-V) introduces the term 'Major Neurocognitive Disorders', with some changes in criteria compared to DSM-IV [1], including more specific details on the degree of impairment observed in the aforementioned cognitive domains, and the inability to explain such impairments

by any other means [2]. Population-based studies show that Alzheimer's disease (AD), dementia with Lewy bodies and vascular dementia are the most common pathological substrates for dementia [3–6]. AD is the most common type of dementia and is associated with a decline in cognitive abilities, such as memory and visuo-spatial skills. Early-onset familial AD accounts for <1% of AD diagnoses, and typically occurs before the age of 65 years [7]. Late-onset AD most often occurs over the age of 65 years and is much more common.

Murine models of AD recapitulate aspects of the disease, often through gene mutations associated with familial AD, and can powerfully elucidate critical aspects of pathogenesis. Although this type of AD is less common, the pathological phenotypes are similar to sporadic AD. Extracellular beta amyloid plaques, intracellular hyperphosphorylated tau, synaptic and

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neuronal loss and neuroinflammation, are all associated with the disease [8]. The amyloid cascade hypothesis [9,10] proposed that amyloid (A $\beta$ ) plaque deposition is key to the pathogenesis of AD, with tau pathology, inflammation and subsequent cell damage as contributing factors. Neuronal and neurotransmitter changes follow A $\beta$  deposition, leading eventually to cell death. Cognitive decline may be a result of neuronal dysfunction from toxic soluble A $\beta$  [11], or inhibited synapse remodelling linked to A $\beta$  oligomers [12]. Therapeutic trials have targeted the clearance of A $\beta$ , with some success in both murine models [13,14] and in humans [15,16]. However, immunotherapy targeting A $\beta$  has not yet translated into improved cognitive functioning [17–19]. A greater understanding of the role of A $\beta$  molecular forms, their temporal role in AD development and their interaction with other pathogenic factors is required.

Oxidative stress is a key factor in AD, whereby the balance between oxidants and antioxidants is disrupted, leading to an excess of oxidants [20,21]. Several mechanisms may contribute towards oxidative stress, including dysfunction of mitochondria [22,23], accumulation of A $\beta$  [22,24] and hyperphosphorylated tau [25,26] and neuroinflammation [27,28]. Biomarkers of oxidative stress in AD have been identified; however, a relatively recent systematic review by Chang *et al.* [29] concluded that although serum markers of lipid peroxidation are elevated in AD, there is insufficient evidence to justify the use of biomarkers as predictors of AD severity or outcome.

Recent studies have investigated the interacting and modifying factors of the defining pathological features of AD; Jonsson *et al.* [30] reported that a coding mutation (A673T) in the amyloid precursor protein (APP) gene has a protective effect against AD and cognitive decline. Genome-wide association studies have reported AD genetic risk factors, with Chapuis *et al.* [31] recently identifying a gene (FERMT2) that has a role in regulating APP metabolism and A $\beta$  production. Researchers are yet to fully explore the interacting and modifying factors of AD pathogenesis using AD mouse models in great detail.

The current review will discuss how well, and in what aspects, murine models of AD recapitulate the physiological, neuropathological and cognitive changes associated with human AD. A complete critical analysis of all AD models and their phenotypes is beyond the scope of this

review, so the particular focus will be on commonly used amyloid-based transgenes (overexpressors of APP and/or its processing enzymes), wild-type human tau or mutant microtubule associated protein tau (*MAPT*) expressors, and selected combined and triple transgenes.

## Murine models of AD

AD pathology primarily consists of amyloid plaques and neurofibrillary tangles (NFT). Other pathological features of AD include neuronal and synaptic loss, dystrophic neurites, reactive astrocytes, activated microglia and BBB dysfunction [32].

Mutations in three genes have been identified as causing autosomal dominant AD [APP, presenilins (*PSEN1* and *PSEN2*)] through altering A $\beta$  production, and share similar pathological features to sporadic AD [33]. These gene mutations have therefore been the focus of many AD mouse models. Transgenic animals based on amyloid production typically express high levels of A $\beta$  peptide usually through altering the processing of APP [34]. Altered APP processing is usually achieved through introduction of human APP (hAPP), or a *PSEN* gene mutation, which affects  $\gamma$ -secretase enzyme activity, and subsequently alters the cleavage of APP to A $\beta$ 1-42 [35,36]. Cleavage of APP occurs by both  $\beta$ -secretase enzyme [also known as  $\beta$ -site amyloid-cleaving enzyme 1 (BACE1)] at the N-terminus of the A $\beta$  peptide, and the  $\gamma$ -secretase enzyme (A $\beta$  C-terminus) activity [36], resulting in a 42 amino acid peptide. This peptide makes up the extracellular fibrillar A $\beta$  which forms the senile, compact plaques with dense cores. The ratio between A $\beta$ 40 and A $\beta$ 42, rather than just overall A $\beta$  expression, is thought to be a significant factor in determining plaque load and toxicity [34].  $\alpha$ -secretase activity is involved in cleavage of APP to A $\beta$  fragments between residues 16 and 17 of the A $\beta$  peptide, resulting in a truncated A $\beta$ 17-40 or A $\beta$ 17-42 fragment. *PSEN* genes also have several other functions in addition to cleavage of  $\gamma$ -secretase, and there is current debate over whether they may be altered by gene mutations leading to AD [37], rather than, or in addition to, changes to the A $\beta$ 40/A $\beta$ 42 ratio [38].

Single mutations in the *PSEN1* or *PSEN2* genes cause APP processing by  $\gamma$ -secretase activity to shift towards the more toxic A $\beta$  1-42 rather than A $\beta$  1-40 [39], although these mice do not develop plaques unless crossed with APP overexpressor lines [40].

*PSEN1* and *PSEN2* gene mutations are functionally similar, although *PSEN1* is more severe [41].

Neurofibrillary tangles are also a significant hallmark of AD, and are composed of hyperphosphorylated forms of tau protein [35]. There are no known *MAPT* gene mutations associated with sporadic AD, but they do occur in fronto-temporal dementia (FTLD-tau) and Parkinson's disease, linked to chromosome 17 (FTDP-17; [42]). Tau protein binds microtubules stabilizing them in the axons, but in some disease states hyperphosphorylated tau dissociates from the microtubules and forms prefibrillar oligomeric and fibrillary aggregates such as NFTs and paired helical filaments ([43]). A $\beta$  oligomers have been reported to contribute to tau oligomerization [44]. Improved animal models are essential for further understanding the relationship between amyloid and tau pathology. Transgenic mice that recapitulate the NFT therefore express either wild-type human tau or mutant *MAPT* [35]. A number of double-transgenic mice models go one step further and attempt to model the functional interaction between APP and mutant *MAPT* expression, to more closely mimic the overall pathology seen in AD, with triple transgenes also including a *PSEN1* gene mutation.

AD mouse models that exhibit one or more of the main features of the disease also exhibit additional neuropathological changes associated with the disease, such as changes to cells within the neurovascular unit [45]. For example astrocytes, which are typically involved in cerebral homeostasis, become activated in AD [46] and co-localize with amyloid plaques [47]. Early astrocyte damage and dysfunction have been linked to AD pathogenesis [48–50]. Microglia are immune cells that also become activated and co-localize with amyloid plaques [51,52]. Some AD mouse models associated with altered A $\beta$  production are known to develop cerebral amyloid angiopathy (CAA) whereby amyloid deposition builds up on arterial walls. It is a pathological feature of AD that can also be found in the elderly without AD, and can be associated with cerebral haemorrhage [53]. Mouse models that exhibit CAA (such as TgAPP23 and TgCRND8) are useful for assessing small vessel disease and cerebral haemorrhage in relation to AD, but interpreting causal links between pathological and behavioural phenotypes can be difficult, as symptoms may be due to cerebral abnormalities [11].

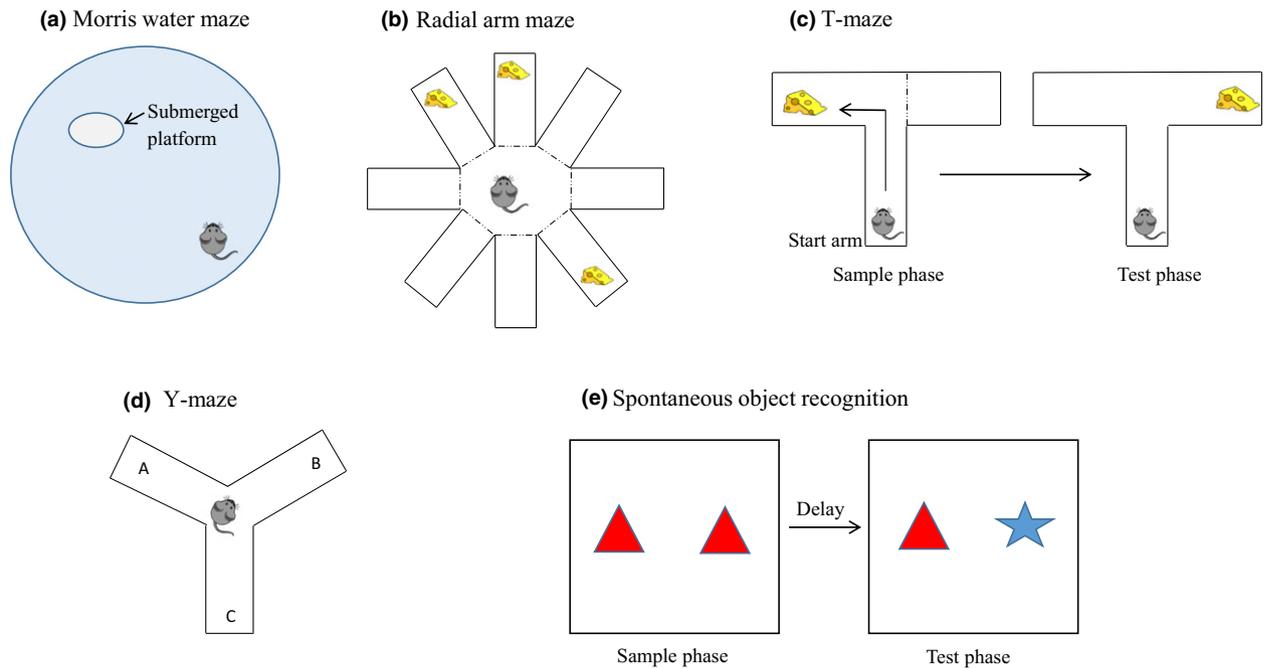
## Testing cognition in animals

The hippocampal formation is one of the earliest brain regions to be affected by AD, with impairments in working memory and declarative memory among the first symptoms to be reported by AD patients [54]. Tests of visuo-spatial processing are useful measures of cognitive impairment in the disease, however, by the point in which patients undergo neuropsychological assessment, neuropathology may have been present for years without notable symptomatology [55].

Hippocampal-dependent tasks measure early cognitive changes in mouse models of neurodegenerative diseases and so will be the sole focus of the review, with a comprehensive overview of these and other tasks being reported elsewhere [56,57]. Tasks used in mouse models of AD include the Morris water maze [58,59], the radial arm maze (RAM) [60], the T-maze/Y-maze [61] and the spontaneous object recognition (SOR) task [62].

The Morris water maze is a test of hippocampal-dependent spatial memory whereby rodents typically have to locate a submerged platform using external visual cues (Figure 1). Escape latency and/or search path are used as measures of learning acquisition, in which good spatial learning is reflected by a decrease in escape latency and/or the search path used to locate the platform. Hippocampal-dependent spatial working memory has been measured using a number of paradigms, particularly the RAM, which involves baiting the arms of the maze with food that does not get replenished. Efficient searching through reduced entries to previously visited arms suggests that the animal remembers where it has previously visited. Alternation tasks using the T-maze or the Y-maze utilize the animal's natural exploratory behaviour to measure the animal's tendency to enter the less recently visited arm (s). These spatial alternation tasks require minimal training in contrast to the RAM.

The SOR task relies on rodent's innate preference for novelty, as they demonstrate recognition for a familiar object through preferential exploration of a novel object. The SOR task is not typically hippocampal-dependent, unless the time delay between the sample and test phases is increased from minutes to hours [63]. Rodent behavioural tasks are thought to rely on the same neural mechanisms as in humans, so they can provide a reliable measure of cognitive function in animal models of neurodegeneration that closely



**Figure 1.** Test apparatus for a series of rodent cognitive tasks. (a) The Morris water maze. Animals are required to locate a submerged (hidden) platform. Escape latency and/or search path are used as measures of spatial memory. Memory impairment is demonstrated through no decrease in escape latency. (b) Radial arm maze. The animal begins in the centre of the maze, with each arm baited with food. The animal can explore these arms and consume the food reward, but the food is not replenished. Spatial working memory is assessed through the number of times unbaited arms are re-entered. Memory impairment is demonstrated when unbaited arms are repeatedly visited. The dashed lines represent the line to be crossed for an arm entry to be counted. (c) T-maze alternation task. During a sample phase, the animal begins in the start arm and is forced to enter either the right or left arm (in this example, the left), receiving a food reward. For the test phase, the animal again begins in the start arm, but has the choice between previously entered arm and the novel arm. The animal receives a food reward for entering the arm not previously visited during the sample phase. Memory impairment is demonstrated if the animal fails to alternate between the arms from sample to test phase. The dashed line represents the door blocking entry to the right arm during the sample phase. (d) Y-maze alternation task. The animal begins in the centre of the maze in this continuous version of the alternation task. For a period of time (e.g. 10 min) the animal can freely explore the three arms of the maze (labelled here as 'A', 'B' and 'C'). Memory impairment is demonstrated if the animal fails to display a tendency to alternate between the less visited arms. (e) Spontaneous object recognition. Animals can freely explore two copies of an object in an open field in a sample phase. Following a delay (of minutes or hours), the animal is returned to the open field and exposed to a copy of the sample object and a novel object in the test phase. Recognition of the familiar object is shown through greater exploration of the novel object over the familiar object. Memory impairment is demonstrated through equal exploration of both objects at test.

reflects the cognitive decline seen in human neurological disease.

they reflect human AD in terms of pathology and cognitive changes.

### How well do models of AD recapitulate physiological, neuropathological and behavioural changes associated with the disease?

Specific mouse models, categorized as those that over-express A $\beta$ , those with mutations affecting secretase processing of APP and those with NFT pathology (through introducing human wild-type tau or mutant *MAPT*), will now be discussed, considering how well

### Altering A $\beta$ through APP processing

Human APP mutations mainly occur at one or both of the two cleavage sites that result in A $\beta$  production. For example,  $\gamma$ -secretase cleavage site mutations, such as V717I and V717F, alter the ratio between A $\beta$ 40 and A $\beta$ 42 production to favour the more toxic A $\beta$ 42 [34], but many express the K670N/M671L Swedish double mutation at the  $\beta$ -secretase cleavage site which results in increased BACE cleavage and production of A $\beta$ 40

and A $\beta$ 42. Others combine both the Swedish mutation with a  $\gamma$ -secretase cleavage site mutation [38].

## PDAPP

The first transgenic mouse model to develop robust amyloid plaque deposition was generated by Games *et al.* [64], and contained hAPP with mutations associated with familial, early-onset AD (FAD V717F Indiana) using C57Bl/6, DDA/2J and Swiss-Webster mouse strains (Table 1). The PDAPP (platelet-derived growth factor promoter amyloid precursor protein) mice exhibit amyloid deposition from 6 to 9 months of age, with further pathologies characteristic of AD such as dystrophic neurites (immunoreactive against phosphorylated tau; [65]), the co-localization of activated astrocytes and microglia with plaques and a decrease in synaptic density [64]. There is no development of NFTs or neuronal loss up to at least 18 months of age [66].

There is an age-related memory impairment in the SOR task, with all PDAPP mice initially performing as well as controls in discriminating between novel and familiar objects at 3 months of age, but by 6 months onwards, the homozygous PDAPP mice fail to successfully discriminate between objects. When tested in the RAM, only homozygous PDAPP mice show significant

reference memory impairments through entering incorrect unbaited arms more often than controls, but PDAPP mice show working memory impairments through revisiting previously baited arms more often than controls [35]. Chen *et al.* [67] reported spatial memory impairments in the Morris water maze with 3-month-old PDAPP mice impaired at learning the first platform location. Dodart *et al.* [68] reported sensorimotor impairments in PDAPP mice from 3 months of age, as they failed to habituate to an open field typically exhibited through a decrease in locomotor activity levels over time.

The reported cognitive and behavioural impairments all precede the onset of disease pathology in PDAPP mice, which suggests there is early dysfunction to mechanisms linked to these impairments, and may contribute to the plaque and cellular pathology which is typical of AD.

## Tg2576

Tg2576 mice were developed by Hsiao *et al.* [69], overexpressing the Swedish APP mutation (K670N/M671L) on a C57Bl/6  $\times$  SJL background [35]. These mice show an increase in A $\beta$  levels at 6 months, and plaque deposition between 9 and 12 months of age across the cortex and hippocampus [70]. These mice recapitulate

**Table 1.** Timeline of onset of amyloid pathology and cognitive test impairments in transgenic mouse models of AD

| Transgenic mouse model | Mutation  | Amyloid deposition (months) | SOR (months)        | Water maze (months) | T-maze (months) | Y-maze (months) |
|------------------------|---|-----------------------------|---------------------|---------------------|-----------------|-----------------|
| PDAPP                  | APP (Indiana V717F)                                 | 6–9                         | 6                   | 3                   |                 |                 |
| Tg2576                 | APP (Swedish K670N-M671L)                           | 9–12                        | 12–15               | 6                   | 10              | 10              |
| TgAPP23                | APP (Swedish K670N-M671L)                           | 6–12                        | 3–4                 | 3                   |                 |                 |
| TgCRND8                | APP (Swedish K670N-M671L and Indiana V717F)         | 3–5                         | 3–5                 | 3                   |                 |                 |
| J20                    | APP (Swedish K670N-M671L and Indiana V717F)         | 5–7                         | 4                   | 6–9                 |                 |                 |
| APP + PSEN1            | APP (Swedish K670N-M671L), PSEN1 M146L              | 6–8                         |                     | 15–17               |                 | 3               |
| TAPP                   | APP (Swedish K670N-M671L), MAPT P301L               | 6                           |                     | 7–8                 |                 |                 |
| Tg2576n/VLW tau        | APP (Swedish K670N-M671L), G272V, MAPT P301L, R406W | 9                           |                     | 16                  |                 |                 |
| 3xTgAD                 | APP (Swedish K670N-M671L), MAPT P301L, PSEN1 M146V  | 5                           | Intact at 11 months |                     | 6–9             |                 |

AD, Alzheimer's disease; SOR, spontaneous object recognition; APP, amyloid precursor protein; PDAPP, platelet-derived growth factor promoter amyloid precursor protein; PSEN1, presenilin; MAPT, microtubule associated protein tau; TAPP, tau amyloid precursor protein.

many of the neuropathological features of AD, including astrogliosis [71], microgliosis [72] and dystrophic neurites [71]. Similar to the PDAPP mice, there is no observed neuronal loss; however, there is also no significant decrease in synaptic density [73,74]. A $\beta$  increases may be linked to synaptic dysfunction, if not necessarily synapse loss [73,75].

Tg2576 mice show repetitive exploration behaviours from 10 months of age in the spontaneous Y-maze alteration task [69], and from 10 months onwards in the T-maze alternation task [75]. Tg2576 mice exhibit soluble A $\beta$  before 6 months of age, but do not develop progressive spatial acquisition and memory performance impairments until 6 months onwards [76]. In the SOR task, Tg2576 mice fail to discriminate between novel and familiar objects after a 24 h delay compared to controls at 12–15 months of age [77]. Tg2576 mice exhibited greater exploration in an open field [75] and an increased interest in exploring the central areas [78]. Tg2576 mice have also been reported to show increased aggression towards cage mates [79].

Cognitive impairments in the Tg2576 mice occur much later than the PDAPP mice, which may be related to the significant decrease in synaptic density observed in the PDAPP mice. Similar to the PDAPP mice, the cognitive and behavioural impairments in the Tg2576 mice either precede or coincide with the A $\beta$  pathology, again suggesting there is early dysfunction occurring prior to plaque deposition and glial response.

### TgAPP23

TgAPP23 AD mice were generated using the Swedish double mutation (K670N/M671L) altering the  $\beta$ -secretase cleavage site, and the London (V717I) mutation altering the  $\gamma$ -secretase cleavage site, on a C57Bl/6  $\times$  DBA/2 background [80]. These mice overexpress hAPP across the hippocampus and cortex and are notable for their cerebrovascular phenotype [81]. Amyloid deposition is present from 6 months of age and substantial by 12 months, particularly in cerebral vessels which progressively decreases cerebral blood flow and alters vessel morphology [82,83]. TgAPP23 mice also display reactive gliosis and astrogliosis, dystrophic neurites, and synaptic loss [81], as well as a degree of neuronal loss in older TgAPP23 mice [84].

TgAPP23 mice show spatial impairments in water maze latencies and path lengths from 3 months of age

prior to substantial plaque deposition [85]. In the SOR task, TgAPP23 mice fail to discriminate between novel and familiar objects after a 24 h delay at 3–4 months of age [86]. Both SOR and water maze task impairments occur from around 3 months of age, therefore, preceding amyloid deposition. This is similar to the PDAPP and Tg2576 mice, though with slightly different ages of onset.

TgAPP23 mice exhibit a cerebrovascular phenotype making them a useful model for AD with CAA, but it is unclear how much of the neuropathology and cognitive profiles can be attributed to the hAPP mutation or the cerebrovascular changes [11].

TgAPP23 mice exhibit a decrease in exploratory behaviour in the open field, at 6–8 weeks, 3 and 6 months of age, while also showing significant impairments relative to control animals on the rotarod at 3 and 6 months [85]. TgAPP23 mice have also been reported to show increased aggression from 6 months of age, after the onset of both amyloid plaques and other discussed behavioural impairments [87].

### TgCRND8

TgCRND8 mice were developed on a C57Bl/6  $\times$  C3H background and contained both the APP Swedish double mutation (K670N-M671L) and the V717F Indiana mutation [35]. These mice present with A $\beta$  deposition at 3 months of age, with dense core plaques present by 5 months in the cortex and hippocampus [88,89], spreading to the cerebellum and brainstem by 8–9 months of age [11], which is associated with increased inflammatory response [90]. In addition, astrocytic gliosis and microglial activation in regions around plaques have been reported [89].

Chishti *et al.* [89] reported that these mice have significant acquisition impairments in hidden platform testing at 11 weeks, with longer swim paths and search latencies compared to controls. In addition, TgCRND8 mice show spatial reference memory impairments at 6–8 months of age, but were able to overcome this impairment when the hidden platform was visibly cued [91].

At 3–5 months of age, TgCRND8 mice fail to discriminate between novel and familiar objects on the SOR task with a 1 h delay [92], and in the Y-maze task, TgCRND8 mice perform comparably to controls up to around 11 months of age, demonstrating intact short-term spatial memory capacity [93]. Overall, and

similar to the previously discussed AD models, any significant cognitive impairments reported in the TgCRND8 mice coincide with amyloid deposition, occurring at an early age of around 3 months. However, the A $\beta$  pathology does occur at a younger age compared to the previous models, so the timeline from when the cognitive impairments are observed, to when amyloid deposition occurs, is much shorter, almost occurring simultaneously.

## J20

The J20 transgenic mouse features a high level of A $\beta$ 1-42 overexpression resulting from the introduction of both the Swedish (K670N and M671L) and Indiana (V717I) hAPP mutations in a C57Bl/6  $\times$  DBA2J background. Diffuse amyloid deposits appear from 5 to 7 months of age in the hippocampus and the neocortex, with larger neuritic plaques appearing after 9 months of age (Figure 2). J20 mice also exhibit a decrease in synaptophysin immunoreactivity indicating changes in synaptic function [11]. J20 mice are also a useful epilepsy model, due to abnormal neural hyperexcitability [94], and cerebrovascular function and neurovascular coupling in relation to neurodegeneration [95,96].

On the SOR task, J20 mice successfully discriminate between novel and familiar objects after a 1 h delay up to 15–16 months of age [97], but are unable to recognize familiar objects after a 4 h delay at 6–8 months of

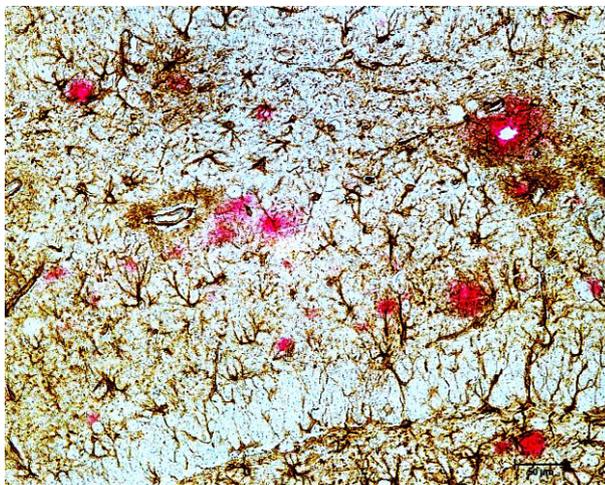
age [98]. When the delay is extended to 24 h, J20 mice are impaired from as early as 4 months old [99]. Overall, these findings suggest that J20 AD mice are able to successfully recognize a previously encountered object following a delay of up to 1 h, but not after a delay of over 4 h.

Palop *et al.* [100] reported that J20 mice aged 6–9 months of age are impaired in water maze hidden platform location as well as spatial location retention in probe trials. An alternative measure of spatial memory that relies on the animal's natural exploratory behaviour is the object-location (OL) task (a spatial variant of the SOR paradigm). AD mice with APP mutations show impairments on the OL from around 5 months of age [101]. Unlike the previously discussed AD models, the age of onset for spatial memory impairments in the water maze is not as early. Spatial memory impairments in the OL task are observed at a slightly younger age, so it can be concluded that, overall, impairments observed on both recognition and spatial memory appear to coincide closely with the deposition on amyloid in the hippocampus and cortex, from around 4 months onwards.

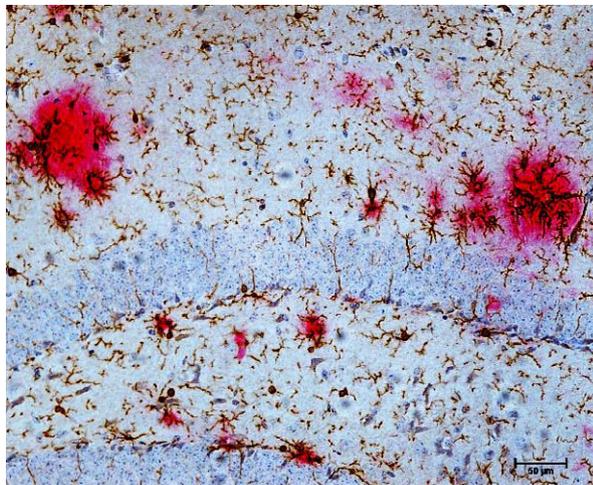
## Secretases

Specific mutations in the *PSEN* genes (*PSEN1* and *PSEN2*; [102,103] result in changes in  $\gamma$ -secretase activity leading to preferential processing of A $\beta$ 1-42

(A) GFAP and A $\beta$  dual label



(B) Iba1 and A $\beta$  dual label



**Figure 2.** Glial pathology associated with A $\beta$  plaques in the hippocampus of a 12-month-old hAPP-J20 mouse. A $\beta$  plaques (6E10, red) are associated with (A) reactive astrocytes (GFAP, brown) and (B) microglia (Iba-1, brown). Scale bar represents 50  $\mu$ m. Images are contrast enhanced.

fragments. Most *PSEN* gene mouse models are derived from *PSEN1* mutations.

### APP + PSEN1

Holcomb *et al.* [40] crossed the *PSEN1* transgene (M146L) with hAPP Tg2576 mice, and at 4–5 months of age APP + *PSEN1* mice had detectable insoluble A $\beta$ . At 6–8 months of age, APP + *PSEN1* mice show elevated levels of A $\beta$  compared to single transgenic Tg2576 littermates [40]. Spatial memory impairments appear as early as 12–14 weeks of age, with APP + *PSEN1* mice showing a significant reduction in the number of alternations on the Y-maze spatial task [104]. Arendash *et al.* [105] further supported these findings, reporting that APP + *PSEN1* mice showed a significant reduction in the number of alternations in the Y-maze task at 5–7 months of age, but also showed impairments in acquisition of spatial locations in the water maze at 15–17 months of age.

15–17-month-old APP + *PSEN1* mice exhibited sensorimotor deficits through a significant impairment on a balance beam test, and increased activity in the open field [105]. A more recent study by Wang *et al.* [106] measured sensorimotor gating in the APP + *PSEN1* mice at 3, 7 and 22 months of age, using the prepulse inhibition (PPI) of the startle response (attenuated startle response from a preceding stimulus). PPI was found to be lower in 7- and 22-month-old APP + *PSEN1* mice compared to age-matched controls, with the 7-month-old APP + *PSEN1* mice also exhibiting memory impairments in the water maze task and increased A $\beta$  plaque deposition compared to 3-month-old APP + *PSEN1* mice.

Correlating the onset of A $\beta$  pathology and impairments in spatial memory in the water maze suggest that these phenotypes are linked, with onset occurring around 6–7 months of age. However, spatial memory performance in the Y-maze reveals impairments from as early as 3 months of age, highlighting how task-specific demands can vary in sensitivity.

### BACE1 KO $\times$ APP

Luo *et al.* [107] developed the BACE1 knock out on a hAPP Tg2576 background. BACE1<sup>-/-</sup>Tg2576<sup>+</sup> phenotypically should be 'normal', in that they show no significant disease-associated pathology. These mice do not develop plaques or produce soluble A $\beta$  peptides [108]. In

the Y-maze alternation task, BACE1<sup>-/-</sup> Tg2576<sup>+</sup> mice at 4–6 months of age performed as well as wild-type controls and significantly better than Tg2576 mice who exhibit brain amyloid A $\beta$  (but not plaque deposition) at this age. These results suggest that BACE1 deficiency in a hAPP transgenic mouse model results in improved performance on the Y-maze alternation task, which may be linked to reduced A $\beta$  levels.

### Tau and triple transgenes

Most transgenic mouse models used to investigate tau and the formation of NFTs involve either introducing a gene for human wild-type tau, or mutant *MAPT* [35]. It is important to note that single transgenic mice with FTD-associated tau (e.g. the JNPL3 line expressing the P301L FTD-associated tau mutation) are better understood as models of FTD, rather than AD [38]. A number of studies have also modelled tau propagation through transgenic lines that overexpress P301L restricted to regions such as the entorhinal cortex where neurons are first affected by NFTs [109], or through injecting tau preformed fibrils into specific brain regions of PS19 transgenic mice overexpressing human P301S mutant tau, for example [110].

### TAPP

Lewis *et al.* [111] crossed the hAPP Tg2576 mouse line with the JNPL3 mouse line expressing the most common FTD-associated human tau mutation (P301L), forming the TAPP (tau amyloid precursor protein) bigenic line. The TAPP mice develop A $\beta$  plaque deposition comparable to Tg2576 mice and as early as 6 months of age [111], but the NFT pathology is more severe than JNPL3 mice, suggesting that the APP pathology may contribute towards exacerbating tangle formation [111]. Cognitive performance is not widely reported in this model, but they do have various motor disturbances [111]. Yuzwa *et al.* [112] recently reported TAPP mice were impaired on the water maze task at 7–8 months of age, which is at a slightly later age of onset to A $\beta$  deposition and in contrast to previously discussed AD models.

### Tg2576/VLW tau

Amyloid overexpressing Tg2576 mice were crossed with VLW mice with mutant 4R *MAPT* [113] containing a

triple mutation (G272V, P301L, R406W) on a C57Bl/6 × CBA background. These mice exhibit widespread A $\beta$  accumulation initially at 9 months of age, with widespread deposition, and neuronal loss in the entorhinal cortex and CA1 region of the hippocampus from 16 months of age [113]. Spatial memory tested in the Morris water maze reveals longer escape latencies compared to wild-type controls initially at 9 months of age, but predominantly from 16 months of age [113]. The spatial memory impairments in the water maze are first observed at a comparable age of onset relative to A $\beta$  deposition, but this is still at a later age of onset compared to previously discussed AD models.

### 3xTgAD

The 3xTgAD mouse line was developed by Oddo *et al.* [114], who generated a triple transgenic model by coinjecting two transgenes containing APP (Swedish) and *MAPT* P301L FTDP-17 mutations into embryonic cells from PS1M146V knock-in mice. 3xTgAD mice exhibit increased levels of A $\beta$ 1-40 and A $\beta$ 1-42, and NFTs. Amyloid plaques are present as early as 3 months of age, with NFTs appearing much later at 12 months of age in the hippocampus and cortex [114]. These mice also have altered synaptic function which progresses with age [114], and spatial memory impairments on the water maze from 6 months of age [115]. Davis *et al.* [116] reported intact recognition memory at 11 months of age, despite the presence of intracellular A $\beta$  from 5 months. In addition, 3xTgAD mice showed impairments on the T-maze task (being unable to successfully distinguish between novel and familiar arms), and the radial arm water maze from between 6 and 9 months of age [117]. Overall, A $\beta$  deposition occurs early in 3xTgAD mice prior to any significant cognitive impairments, which are reported from around 6 months of age. This is in contrast to the previously discussed AD models. NFTs also develop later, at around 12 months of age. Though 3xTgAD mice present with the two main features of AD, these findings suggest poor correlation between behavioural impairments and disease pathology, perhaps because A $\beta$  and tau develop independently of one another.

### Translation into therapeutic developments

There are currently only a select number of drugs available to treat AD, focusing on alleviating

symptoms, with no new drugs being approved since 2003. No drug has yet been identified to significantly alter the course of the disease, and translate successfully into clinical applications. This may be due to significant differences between rodent models and humans in terms of how they metabolise the drugs, how the drugs act upon certain mechanisms, and fundamental differences in neural circuitry between species [118].

Immunotherapy has been investigated preclinically in AD mouse models as a potential therapeutic strategy through preventing A $\beta$  aggregation. For example, administration of the monoclonal antibody bapineuzumab in PDAPP resulted in a reduction in both soluble and insoluble levels of A $\beta$  [119]. Immunotherapies targeting amyloid plaques have progressed to clinical trials, showing some promising reductions in rate of cognitive decline [120], and levels of A $\beta$  and tau following neuropathological investigations [18], but no trials have shown results that are both significantly efficacious and nonharmful. For example, a recent meta-analysis highlighted the lack of clinical efficacy of bapineuzumab [121] which failed Phase III trials, alongside similar monoclonal antibody solanezumab [122].

BACE1 is another therapeutic target, with administration of TAK-070 (a nonpeptidic BACE1 inhibitor) to Tg2576 mice resulting in a reduction in both soluble and insoluble A $\beta$ , and a reduction in cognitive impairments [123]. However, promising BACE1 inhibitor verubecestat has recently failed in clinical trial, although a trial with patients at an earlier stage of the disease continues [124]. Hung and Fu [125] have recently published a comprehensive review of AD drugs in clinical trials up to June 2017, including the therapeutic targets, trial status and clinical outcomes.

Stem cells have been investigated as a potential therapeutic strategy for AD. Administration of haplotype-matched murine neuronal stem cells to aged 3xTgAD mice reduced cognitive impairments, but had no significant effect on A $\beta$  or tau pathology [126].

There have also been recent advances in the use of optogenetics, a technique which modulates neuronal activity, as a therapeutic approach for neurodegenerative diseases, including AD [127]. However, this research is currently in the very early stages of research.

In summary, a number of therapeutic strategies have been developed in AD mouse models and have shown

promising results in terms of reducing A $\beta$  or tau, for example, showing that these models are good for recapitulating disease pathology. However, none of these strategies have yet successfully translated to clinical outcomes in AD patients, so there is a need for more advanced animal models that better model disease complexity.

## Discussion

No one model provides an ideal and complete characterization of AD as observed in humans, however, different models are useful for answering questions about specific aspects of the disease.

Within each type of AD model there are variations in terms of the onset of pathological features and cognitive decline, of which some can be accounted for by background strains as well as differing baseline abilities in terms of learning, memory and locomotion [39]. Even with AD models of the same genetic background, many cognitive tests are sensitive to small variations in task protocol, which can yield contrasting results [128]. Rodents are nocturnal and do not primarily rely on vision, but olfaction, which raises issues around their abilities to perform in tasks such as the Morris water maze [129]. Mice, in particular, are known to perform poorly in the water maze compared to rats, due to tendencies to swim nearer to the wall (a classic hallmark of anxiety; [130] and to be more buoyant [131]. The age of the animals is also a determining factor in water maze performance [132], which may be related to an age-related decline in motor abilities.

No AD mouse model exhibits the full range of pathological phenotypes, making it difficult to correlate cognitive decline and pathological changes. Only a small number of AD models exhibit neuronal loss [39], with it being rarely reported in APP models, such as PDAPP and Tg2576 [67, 72], but more often reported in APP models combined with *PSEN1* gene mutations [133]. A $\beta$  impairs synaptic function, which is likely to be a major contributor to the cognitive impairments reported [36]. Studies have described a loss in synaptophysin-immunoreactivity around compact plaques in both PDAPP and Tg2576 mice, indicating changes to synapse function relating to A $\beta$  [72]. Soluble A $\beta$  may contribute towards cognitive impairments, which would account for why they are observed prior to compact plaque deposits [77]. Pathological and behavioural

features need consideration when selecting an AD model to test a specific hypothesis, and will depend on the precise mechanisms being investigated.

It is not clear how accurately the time course of amyloid plaque deposition and cognitive decline reflects human AD. Behavioural impairments are often reported prior to plaque deposition across AD mouse models, but it is likely that A $\beta$  pathology is present prior to the onset of cognitive impairments in humans [134]. It may, however, be likely that subtle changes in cognition occur prior to patients reporting the first notable changes with their physician.

Transgenic mice expressing both amyloid and tau pathology (e.g. TAPP and 3xTgAD) may seem like the ideal models to study human AD as they more closely reflect the disease. Although these mice present with the two main features of AD, these pathologies are reported as developing independently [38], and so do not fully mimic the disease progression seen in humans.

A number of emerging hypotheses linking other health conditions to dementia and AD present an opportunity for AD models to be utilized as models for other diseases. For example, recent studies suggest that A $\beta$  may play a role in promoting cerebrovascular atherosclerosis [135], which would make an APP mouse model suitable for studying this relationship and a number of other cerebrovascular and neurodegenerative diseases, particularly as such conditions rarely present independently in humans.

Two genetic variations which are important risk factors for sporadic AD are the allelic variations of apolipoprotein (APOE), and the R47H allele of the triggering receptor expressed on myeloid cells 2 (TREM2; [136]). APOE colocalizes with A $\beta$  and microglia. Mice that are haploinsufficient for human APOE show a significant decrease in plaque deposition in APP/*PSEN1* (L166P) and J20 mice [137,138], and APOE-knockout mice have been reported to clear A $\beta$  faster than control mice [139]. Disrupting the interaction between APOE and A $\beta$  may be a viable potential therapeutic approach to reduce A $\beta$  deposition.

There are conflicting reports regarding the effect of TREM2 on overall A $\beta$  plaque deposition which has been characterized in the APP/*PSEN1* and 5xFAD mouse models [140,141]. Ulrich *et al.* [142] reported that TREM2 haploinsufficient APP/*PSEN1* mice of 3 and 7 months of age showed no significant A $\beta$

deposition in the cortex. Further research supports these findings with Jay *et al.* [143] reporting that 4-month-old TREM2<sup>-/-</sup> APP/PSEN1 mice showed no significant cortical A $\beta$  deposition, and a decrease in hippocampal A $\beta$  deposition compared to TREM2<sup>+/+</sup> APP/PSEN1 mice (26). In comparison, Wang *et al.* [144] reported that 8-month-old TREM2<sup>-/-</sup> 5xFAD mice exhibited an increase in hippocampal A $\beta$  deposition, with no significant effect on cortical A $\beta$ . Further work is needed to elucidate the roles of APOE and TREM2 gene variations in AD, and refining animal models will be key to progressing how the function of these genes relate to certain pathological features of AD.

Touchscreen technology [145] could present as a way of standardizing and improving rodent cognitive and behavioural tests. A range of computer-automated cognitive tasks have been developed for rodents which are designed to mimic the neuropsychological tasks used with humans, improving their translational capability. Such tasks are carried out in the same apparatus with the same type of stimuli, improving the ability to compare performance across tasks. Romberg *et al.* [146] reported that TgCRND8 mice showed no impairment on a visual discrimination test, but were impaired on a test of object recognition, even with a short delay of 1 min. It is possible that the touchscreen version of the object recognition task is more difficult than the standard version, potentially due to rodents naturally being more dependent on olfaction than visual acuity, but the technology remains promising.

There have been varying results regarding the effect of sexual differences on AD mouse model phenotypes, but it is necessary to understand how such differences may contribute to making one sex more vulnerable or protected from disease. Research suggests that female AD mice have an increased vulnerability to AD phenotypes, but Dubal *et al.* [147] propose this may be more closely related to a greater beneficial effect of male hormones, and a more deleterious effect of female hormones in the brain of AD mouse models.

Developments in genome editing technology known as CRISPR/Cas9 allows for mice to be genetically engineered much more efficiently [148], as multiple gene variations can be introduced simultaneously. This technology is particularly significant for developing mouse models of late-onset AD, which is likely to involve multiple gene variations. Improved predictive models should lead to better translation between preclinical

and clinical studies, particularly for the more common late-onset AD.

## Conclusion

Mouse models of AD continue to be a central component in furthering our understanding of the disease and identifying new therapeutic targets for existing and novel compounds. It is important, however, to treat AD models as a reductionist tool for understanding the pathogenesis of AD, and research should be guided by human studies to look for the causal relationships human work cannot often provide.

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## Conflict of interest

The authors declare no conflict of interest.

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