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Review

Paying more attention to attention: Towards more comprehensive cognitive translation using mouse models of Alzheimer's disease

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ABSTRACT

The cognitive phenotyping of mouse models of Alzheimer's disease (AD) currently focuses on impairments in learning and memory. However, AD is not simply a memory disorder, but other cognitive domains, and in particular attention, can also be impaired even at very early stages of the disease. In this review we argue for the benefits of including other constructs, and in particular attention, in preclinical studies to identify drug targets and disease mechanisms of AD in mouse models. First we give a brief account of the evidence for attentional deficits in AD; we then summarise methods to assess equivalent aspects of attention in mice, followed by a review of recent evidence for attentional impairments in widely used mouse models of AD. We conclude by suggesting that a multidimensional approach to cognitive assessment in preclinical models, in which a number of aspects of cognition are investigated while confounding factors are minimized, is becoming increasingly feasible and may contribute significantly towards the development of more targeted therapeutic interventions.

Contents

1. Background

Alzheimer's disease (AD) is a progressive, neurodegenerative disease characterised by a gradual but profound decline in cognitive abilities and the appearance of β-amyloid (Aβ) and tau aggregates (plaques and tangles) in the brain. Because the loss of memory is the most common symptom lamented by affected patients [2,43,105], the disease is often regarded simply as a memory disorder. In the majority of individuals with AD, however, multiple cognitive domains are compromised including attention and response control; indeed such impairments can occur early in the disease and precede language and spatial impairments [1,3,5,7,9,10,50,64,73,76,86,94,98,100]. Therefore, the current

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criteria for the diagnosis of probable AD stipulate deterioration of two or more areas of cognition (including memory), of sufficient magnitude to interfere with work or social function [65,103].

Since the mid 1990s, an increasing number of transgenic mouse models have been employed to address how gene mutations related to the familial form of AD may affect the functional integrity of the neuronal networks underlying cognition [36,111]. Mice overexpressing these human, pathogenic genes for amyloid precursor protein (APP), tau, and/or the presenilins progressively develop β-amyloid plaques and/or tangles of hyperphosphorylated tau in the hippocampus and cortex, the major neuropathological hallmarks of the disease [41]. The extent to which these mice truly develop a comprehensive AD typical phenotype is still a matter of debate [35,111], but many studies have used such animals successfully to demonstrate a direct role of Aβ or tau pathology in the development of learning and memory deficits. Moreover, these memory deficits have been remedied to some extent by a wide variety of treatments, including those aiming to reduce β-amyloid load [99]. On the face of it this seems an eminently sensible and highly promising approach. It is perhaps surprising, then, that the translation of findings from such studies into successful treatments for AD has yielded somewhat disappointing results: currently only four treatments – three cholinesterase inhibitors and one partial NMDA-receptor antagonist – have received approval for symptomatic treatment by health authorities. Although a number of reasons have been put forward for the discrepancies between animal model and human findings, one contributing factor might be the narrow focus of animal studies almost exclusively on memory, which represents only one facet – albeit an important one – of the profile of cognitive impairment in AD. For example, studies utilising automated cognitive test batteries have revealed that the cognitive enhancing effects of cholinesterase inhibitors in AD patients may largely be due to attention-enhancing effects, rather than direct actions on memory per se [93,94]. Similarly, memantine can positively affect attention in AD patients [38,87], although its action on glutamatergic receptors may favour direct effects on memory.

Conceivably, translation from mouse to clinic might be improved if we were to widen our scope in preclinical studies to include not only memory, but also other relevant constructs such as attention. An impediment to this approach, however, has been that tests of attention have not been widely available for mice. This situation, however, is changing. In this review, we summarise novel approaches to the assessment of attention and response control in mouse models of AD, and compare the findings from such tests with attentional deficits reported in human studies. We conclude that new attentional paradigms for mice may present a powerful addition to preclinical approaches to cognition in AD, and that a more comprehensive study of cognition in mouse models is now possible, and desirable.

2. Attentional deficits in AD

A detailed account of attentional deficits in AD can be found in excellent reviews elsewhere [5,77,80]. Here, we focus on studies using well-established tests of attention that have been shown to be sensitive to AD, and that have been adapted for studies with rodents.

Like memory, attention is not a unified concept, but comprises distinct cognitive subdomains thought to be subserved by multiple cortical and subcortical brain regions. Although opinions differ as to the appropriate classifications and terminology with which best to understand attention [34,47,66,82,83,85,101], there is broad agreement on a distinction between selective attention, divided attention and sustained attention (vigilance) [81,88].

2.1. Selective attention

Selective attention refers to the process of rapidly selecting more relevant stimuli from less relevant stimuli for further cognitive processing. Selection of visual items for higher level processing may be based on features such as spatial location, colour, orientation, shape, semantic categories or conjunctions of these [26]. In addition, selective attention may also involve inhibition of irrelevant stimuli [77]. Two main tasks have been used to assess aspects of selective attention in AD patients: variants of the Spatial Cueing Task, originally developed by Posner, are employed to assess spatial attention [84], and Visual Search tasks are used to study visual attention guided by shape and colour [73]. Both attention shifts and feature conjunction search have been shown to selectively activate the superior parietal cortex [27].

Studies of AD using these tests suggest that selective attention on the basis of simple visual features or locations appears largely preserved in mild AD [73], but profound and robust impairments occur when more than one feature of a compound stimulus or multiple modalities must be attended to, or when attention needs to be shifted from one location to another [11,19,37,39,76,77,80].

2.2. Divided attention

Divided attention refers to the ability to attend to more than one stimulus, modality or process at one time [80]. Apart from using complex selective attention paradigms that require the monitoring of multiple sensory modalities, divided attention is commonly assessed with dual-task paradigms. In such paradigms, a participant performs two tasks separately before performing the two tasks simultaneously, and reduced performance on the simultaneous task version is referred to as the dual-task decrement [4]. AD patients generally show stronger dual-task decrement than healthy, age matched controls [5], but it is a matter of debate whether these impairments might simply be due to increased task difficulty and cognitive load [80]. However, more recent studies suggest that AD-related deficits of dual-task performance might be the result of poor "executive control". Executive control is thought to require different types of attentional processing that optimise higher order cognitive capacities of selecting, scheduling and monitoring plans of action [5,7,45,90].

2.3. Sustained attention

Sustained attention (vigilance, a concept overlapping with that of "phasic alertness" [82]) may be defined as a state of continuous readiness to respond to unpredictable events [80,107]. It is usually measured by the speed and accuracy of detecting infrequent and/or unpredictable targets. Common sustained attention tasks are simple signal detection tests [1,5], or choice signal detection tasks that also involve focused and/or divided attention processes such as the Mackworth jump clock test [14,52,54] or the continuous performance task [8] and non-lexical tasks, such as 4- and 5-choice serial reaction time tasks [5,74,94]. Sustained attention is largely supported by a right-sided fronto-parietal network distinct from the posterior parietal system mediating aspects of selective attention [28,51,82]. In particular the right prefrontal cortex is found to be more active during vigilance tasks, when measured both by functional resonance imaging and positron emission tomography [55]. Cholinergic afferents from the basal forebrain to the prefrontal and parietal cortex are particularly important for sustaining attention [10,11,30,46,59,70].

Both parietal cortex and prefrontal cortex can be affected by AD-typical pathology [13,22], and cholinergic neurons are particularly vulnerable to AD-related degeneration [31,106]. Consistently, many studies have suggested that vigilance is reduced in AD

patients [1,3,5,12,53,64,74,94]. Moreover, Sahakian and colleagues showed that cholinergic enhancers commonly prescribed for AD patients are more effective on sustained attention than memory tasks [93,94]. Disagreement persists over the time course of impairments in sustained attention in AD. Although it was initially suggested that vigilance is affected only in the later phases of AD [53,74], more recent studies suggest that attentional impairments occur as early as memory impairments, and may therefore provide a valuable diagnostic tool for prodromal AD [3,12,14,50,64,94,100].

3. Measuring attention in mouse models

Although attentional impairments are clearly an important aspect of AD, they have rarely been considered when assessing cognition in mouse models of the disease. The neglect of attention in mouse models is partially due to the lack of suitable testing paradigms for the mouse that provide reliable, selective measures comparable to human test results.

3.1. Tests of selective attention for mice

Classic tests of selective visuospatial attention such as the Spatial Cueing Task are not particularly suitable for rats or mice because the assessment of covert orienting processes requires the animal to fixate a point in space. Although rat operant versions of such tests have been developed and have provided valuable data [15,20,21,92,104], caution is required when attributing impairments on these tasks solely to covert shifts of attention, as changes in reaction time may simply reflect alterations in response preparation after a cue (e.g. overt orienting).

However, the recent development of automated cognitive testing methods for mice [16–18,44,67,88,102] may soon open up promising opportunities to assess selective attention in AD mouse models. In particular, the touchscreen-operated cognitive test method (Fig. 1a) [16,17], which allows the presentation of complex stimulus material to mice, may provide an opportunity to develop, for example, mouse analogues of the Visual Search paradigm widely used to assess attention shifts and divided attention in AD [39,80]. Furthermore, some aspects of selective and divided attention may already be measured using variants of the mouse 5-choice serial reaction time task described in the next section [6,23,88].

3.2. Tests of sustained attention for mice

A sustained attention task extensively used in rats and mice is the 5-choice serial reaction time task (5-CSRTT) [68,88]. Conventionally run in an operant box with nine nose-poke holes (5 of which are used for the task), animals are trained to respond with a nose-poke to brief flashes of light pseudorandomly displayed in one of five spatial locations. Nose-poke responses to the correct hole are rewarded by the presentation of a food reward in a magazine at the rear of the chamber. Subsequent test sessions consist of daily sessions with high event rates, where either the stimulus duration and/or the interval between stimuli are manipulated to increase attentional demand.

Performance is measured by the spatial and temporal accuracy of responding to stimuli during the course of a session: standard vigilance measures include errors of commission (i.e. responding to a different hole than the one where the light appeared), errors of omission (i.e. failure to respond within a 5-s time window after a stimulus), and reaction times. In addition, other measures of the task, such as premature and perseverative responses, can assess aspects of response control involved in executive functioning [23,88]. Furthermore, the standard 5-CSRTT paradigm can be modified to include tests of the ability of rats to ignore brief bursts of white noise while detecting the visual target, thus introducing aspects of selective attention [6,88].

More recently, the 5-CSRTT has been adapted for use with mice [32,44,48,78,79], and for use in more flexible, touchscreen-based operant chambers that allow easier manipulations of task conditions (Fig. 1a,b) [16,91]. In the latter version of the task, the 5 response holes of the classic task version are replaced by stimuli briefly displayed in one of 5 locations on the touchscreen (Fig. 1b). Procedurally very similar to touchscreen-operated human cognitive test batteries (Fig. 1a), the mouse responds to the stimuli by directly touching the screen with a nose poke. In addition to reducing task acquisition times – mice can be trained to stable baseline performance with 2 s stimulus duration within 3–4 weeks compared to 5–6 weeks in the standard operant version – the flexibility of the touchscreen technology increases the possibilities for targetting other aspects of attention, e.g. by introducing distinct non-signal visual stimuli in order to more closely match the demands of the human CPT (see below). Moreover, measures of attention can be compared with measures of other cognitive abilities such as memory, obtained from procedurally similar tasks in the same testing environment [16]. The 5-CSRTT has now been adapted for use in a touchscreen apparatus [91; see below], which could allow development of a version more similar to the human CPT. Furthermore, other developments of this task are also possible, for example, the inclusion of variable intertrial intervals (ITIs) to increase the demand on vigilance.

In its basic form, the 5-CSRTT essentially measures the ability of the rodent to sustain spatial attention divided among a number of locations over a large number of trials and therefore has obvious analogies with Leonard's 5-CSRTT much used in human experimental psychology (Fig. 1c) [108], and to some extent, to the classic Continuous Performance Test (CPT) of sustained attention by Mirsky and Rosvold [8]. However, CPT tasks usually contain signal and non-signal events, providing the measures of hits/misses (signal) and correct rejections/false alarms (non-signal). While incorrect responses (commission errors) on the 5-CSRTT are regarded as analogues to CPT false alarm rates and omission errors may be interpreted as misses [46,88], the 5-CSRTT does not include non-signal events and therefore falls short of providing analogous measures for correct rejections. Therefore, although tremendously useful for dissociating the neural mechanisms underlying sustained attention processes in health and disease, the 5-CSRTT has been criticised for its limited cross-species translatability [110]. In particular, rodent 5-CSRTT data do not match classic measures of signal detection theory, the standard method used to interpret human vigilance data.

An operant vigilance task for rodents providing measures of signal rejection was developed by McGaughy and Sarter [62]. In this task rats are required to attend to a single location to detect whether or not a cue stimulus was presented. Two response levers are presented after each trial, and the animal is required to press one lever if the stimulus was perceived, and the other lever if it deems that no stimulus was presented. Similar to human vigilance tasks such as the CPT, the task measures Hits, Misses, Correct Rejections and False Alarms and is therefore amenable to signal detection analysis. However, because the stimulus is only ever presented in one location, the task does not include a choice component enhancing attentional demand. Although not as extensively used as the 5-CSRTT, the contribution of neurotransmitter systems, in particular the cholinergic system, to the different measures of the tasks has been well characterised in rats [61,95], making the paradigm particularly suitable for preclinical AD studies [69]. Specifically, 192 IgG-saporin lesions of the basal forebrain lead to an increase in correct signal detection errors, while the number of correct rejections remained unchanged [60,63]. Recently, the task has been successfully adapted for use with mice, and although no transgenic mice

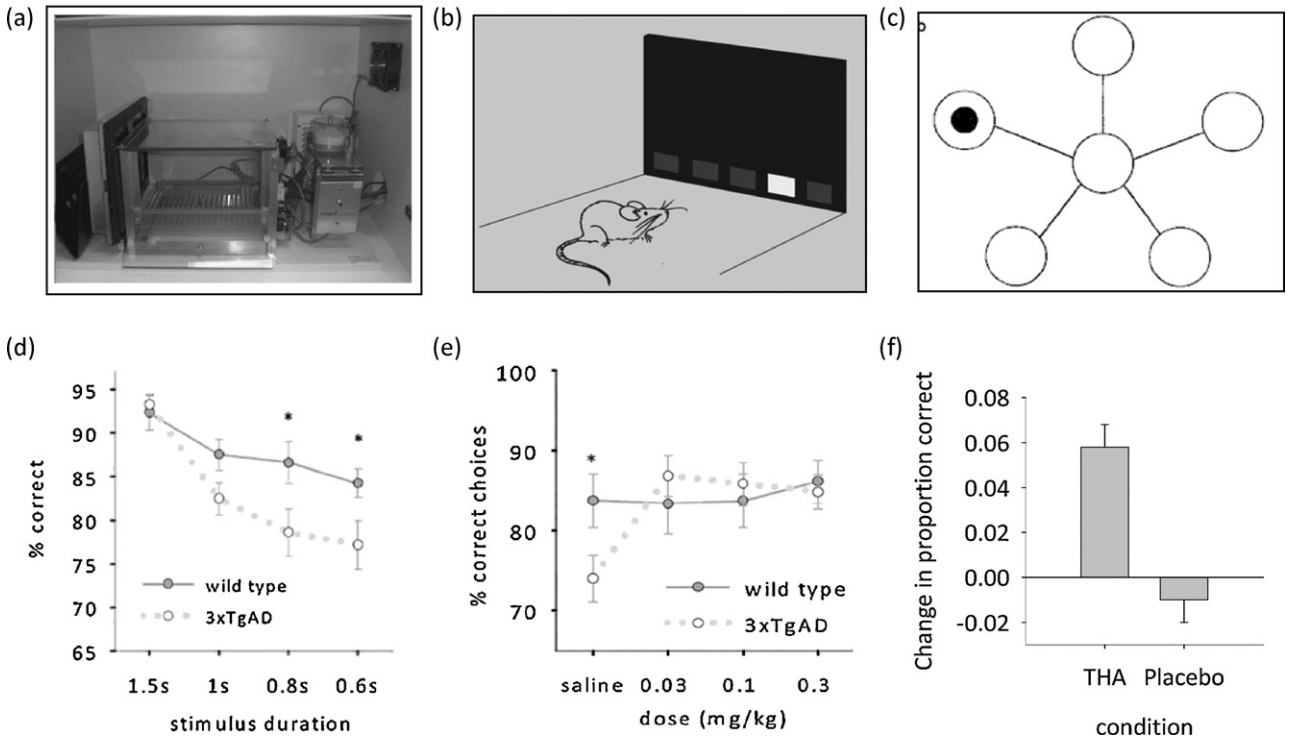

Fig. 1. Measuring sustained attention in patients and mouse models of AD. (a) Touchscreen-operant cognitive testing chamber for mice. (b) 5-CSRTT for animals: the animal has to respond to a brief flash of light in one of 5 response windows with a nose poke to that window. (c) 5-CSRTT for patients: the subject has to respond to a brief flash of light in one of 5 locations with a touch to that location (figure taken from [91]). (d) Response accuracies (% correct responses of total responses) of 3xTgAD mouse model of AD and wild type controls. (e) The anticholinesterase donepezil rescues the sustained attention deficit in 3xTgAD mice (performance at 0.8 s stimulus duration, reproduced from [81]). (f) A similar attenuation of response accuracy deficits is seen after administration of the anticholinesterase tetrahydroaminoacridine (THA) in AD patients (reproduced from [94]).

have been tested to date, it may prove very valuable for assessing sustained attention in mouse models of disease [56,102].

Finally, Young and colleagues have recently developed a vigilance task for mice that combines the choice reaction time aspects of the 5-CSRTT and includes non-signal events, thus providing multiple manipulations of attentional load [110]. The task is run in a 9-hole box and includes Go (83% of trials, light in one of 5 locations) as well as No/Go trials (17% of trials, all 5 locations lit). Although another very promising approach for studying vigilance in transgenic mice, further validation studies are needed to test the practicality and selectivity of the task.

4. Sustained attention in mouse models of AD

The recent advancement of mouse attention tasks has yielded some insights into the degree of attentional impairments in mouse models of AD. In addition to their native mouse genes, such animals typically overexpress one or several human gene mutations linked to rare, inherited, early onset forms of the disease: patients carrying single mutated alleles for β-amyloid precursor protein (APP) or presenilin 1 develop AD-typical cognitive deficits and neuropathological hallmarks (β-amyloid plaques and tau tangles) as early as in their mid-thirties [42,99]. Other disease-relevant transgenic mouse lines carry mutations in the human tau gene, which, although not directly linked to inherited forms of AD, can cause some cases of frontotemporal lobe dementia [33]. Most transgenic mice overexpressing these altered human genes progressively develop β-amyloid deposits (in case of APP or PS1 transgenic animals) or tau tangles (Tau transgenic mice) as well as age-dependent learning and memory deficits, thus mimicking important aspects of the disease [41]. One of the most comprehensive mouse models of AD-typical pathology to date is the 3xTgAD mouse line harbouring human APP_{swe}, $PS1_{M146V}$ and Tau_{P301L} transgenes [75]. Unlike most other AD mouse models, 3xTgAD mice show profound rises in β-amyloid levels, which affect prefrontal cortex and hippocampus at around 6–8 months, *and* hyperphosphorylated tau tangles (12–18 months).

Using the touchscreen version of the 5-CSRTT, we have recently demonstrated that 3xTgAD mice express sustained attention deficits [91]. Under conditions of low attentional demand, performance of male, 12 month old 3xTgAD mice was undistinguishable from wild-type controls. However, under conditions of high attentional demand (shorter stimulus durations), 3xTgAD mice made more commission errors, i.e. they selectively increased responding to incorrect locations (Fig. 1d). Importantly, the reduction in response accuracies was not accompanied by changes in omission errors, response latencies or magazine latencies. Since 3xTgAD mice initially responded as accurately as wild type mice, but subsequently failed to sustain their attention over the duration of the task, the impairment may be regarded as a vigilance deficit. Finally, it was found that all of these attentional impairments in the 3xTgAD mice could be completely reversed by the administration of the AD drug donepezil (Aricept, approved by the United States Food and Drug Association and the UK's Medicines Control Agency in 1996/1997), a cholinesterase inhibitor increasing the availability of acetylcholine at the synapse (Fig. 1e).

As mentioned above, decreased response accuracies and higher vigilance decrements are also characteristic of AD patients on similar tasks [1,3,5,12,53,64,74,93,94]. Moreover, both the response accuracy impairment of 3xTgAD mice and the sustained attention

deficit of early AD patients can be ameliorated by cholinesterase inhibitors (Fig. 1e,f), which enhance the availability of acetylcholine at the synapse [91,93,94]. Thus, sustained attention deficits in 3xTgAD mice and AD patients share important characteristics and similarities.

Although 3xTgAD mouse is a comprehensive model of AD, expressing most of the classical pathological hallmarks of the disease [75], the presence of three major AD-related mutations makes it more difficult to attribute cognitive deficits to specific physiological abnormalities. Therefore, it is important to establish whether similar vigilance impairments can be found in other mouse models expressing either PS1/APP or tau transgenes only. Whereas our own results suggest that 4 month old tgCRND8 mice heterozygous for APP with the Swedish mutation express similar sustained attention deficits (Romberg et al., unpublished data), Lambourne et al. [48] found no deficit in response accuracies in transgenic mice expressing the human FTDP-17 tauV337M mutation on the classic 5-CSRTT in the 5-hole box. Although not a direct model of AD, but rather engineered to model frontotemporal dementia, the dissociations obtained with FTDP-17 tau_{V337M} and 3xTgAD mice on nearly identical tasks might suggest that intraneuronal β-amyloid accumulation and/or cholinergic receptor depletion, rather than tau aggregates, may be responsible for the sustained attention deficits. However, Lambourne and colleagues [48] presented only the mean response accuracies for each session, and thus it is conceivable that a vigilance decrement may have occurred within sessions. Further studies with different transgenic mouse lines may be necessary to resolve these issues. Another important factor that remains to be addressed is the time course of sustained attention deficits in transgenic mice, particularly in relation to age of onset of memory impairments.

5. Mouse models of AD also express alterations in response inhibition

In addition to the aspects of sustained attention discussed above, the 5-CSRTT also provides measures of response inhibition [6,23,88]. Response inhibition is required for the appropriate executive control of actions, a construct related to inhibitory aspects of selective and divided attention, as well as working memory [5,23,45,80,88,90]. Although a comprehensive discussion of executive functioning in patients and AD models is beyond the scope of this review, it is worth noting that both 3xTgAD mice and FTDP-17 tauV337M mice have shown abnormalities in response inhibition, which were independent of attentional demand: 3xTgAD mice made more perseverative errors, whereas FTDP-17 tauV337M mice showed increased premature responding [48,91].

Given the well-documented role of the prefrontal cortex in modulating executive function [23,24,29,30,90], the increase of perseverative/premature responding in 3xTgAD and FTDP-17 tauV337M mice may be interpreted as evidence for compromised prefrontal cortex circuitry. However, further experiments are needed to identify the precise neural and physiological causes of these impairments in AD mouse models. Understanding the causes of altered response control in such animals may provide a valuable contribution to the debate over whether executive functioning is selectively affected in AD patients, or compromised due to more general cognitive slowing and/or episodic memory deficits [5,7,9,25,80].

6. Conclusions

Studies of cognition in mouse models of AD are almost always really studies of memory. However, AD is not just a memory disorder, but one that affects many other aspects of cognitive function, and in particular attention. Here, we have summarized evidence that impairments in sustained attention and response inhibition similar to those seen in AD can be studied – and rescued – in mouse models of AD.

Indeed, there are practical advantages to studying attention in addition to memory in such models. Attention is, of course, important for successful memory function [71,72,96], so that in at least some cases tests of memory may be confounded by changes in attention. However, the converse is not necessarily true: at least some tests of attention, such as the 5-choice serial reaction time task, are not easily confounded by memory demands. Finally, although there is no question that the study of memory in mouse models of AD can benefit from the vast database relevant to the neural basis of memory in rodents [57,58,109], the literature on the neural substrates of attention in rodents is now itself extensive [23,40,49,68,88,92,96,97]. Thus there is little now to hold us back from embracing attention as an attractive target for preclinical AD research. Indeed, with the current trend towards testing humans and animals on a wide range of cognitive phenotypes using a single testing methodology [16,89], studies of cognition in disease in both humans and animal models may shift away from a predominantly unidimensional approach, to considerations of cognitive *profiles*, with a view to developing more targeted therapeutic interventions.

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