Translational Assays for Assessment of Cognition in Rodent Models of Alzheimer's Disease and Dementia.

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Abstract

Cognitive dysfunction appears as a core feature of dementia, which includes its most prevalent form, Alzheimer's disease (AD), as well as vascular dementia, frontotemporal dementia and other brain disorders. AD alone affects more than 45 million people worldwide, with growing prevalence in aging populations. There is no cure, and therapeutic options remain limited. Gene–edited and transgenic animal models, expressing disease-specific gene mutations, illuminate pathogenic mechanisms leading to cognitive decline in AD and other forms of dementia. To date, cognitive tests in AD mouse models have not been directly relevant to the clinical presentation of AD, providing challenges for translation of findings to the clinic. Touchscreen testing in mice has enabled the assessment of specific cognitive domains in mice that are directly relevant to impairments described in human AD patients. In this review we provide context for how cognitive decline is measured in the clinic, describe traditional methods for assessing cognition in mice and outline novel approaches, including the use of the touchscreen platform for cognitive testing. We highlight the limitations of traditional memory-testing paradigms in mice, particularly their capacity for direct translation into cognitive testing of patients. While it is not possible to expect direct translation in testing methodologies, we can aim to develop tests that engage similar neural substrates in both humans and mice. Ultimately, that would enable us to better predict efficacy across species and therefore improve the chances that a treatment that works in mice will also work in the clinic.

Measuring Cognitive Decline In Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive impairment and changes in behavior and personality. The disease continues to be a major public health issue owing to its increased prevalence, long duration, high cost of care and lack of disease-modifying drugs. In a subset of familial cases of AD, disease-causing mutations have been identified in genes encoding the amyloid precursor protein (APP; from which amyloid-β (Aβ) is derived by proteolytic cleavage), and presenilin-1 (PS1) or -2 (PS2) (Bettens et al. 2013). In addition, apolipoprotein E4 (ApoE4) and other genes have been identified that are associated with an increased risk of developing AD in the highly prevalent sporadic forms (Bettens et al. 2013). While the vast majority of AD cases are sporadic, and thus the underlying pathogenic mechanisms remaining largely unknown, Aβ and tau have been identified as key molecules that drive the pathology in both familial and sporadic forms of AD (Querfurth and LaFerla 2010). The identification of pathogenic mutations in familial AD has led to the generation of transgenic animal models with Aβ and/or tau pathologies that recapitulate important aspects of the human disease. These animal models have become major *in vivo* tools to investigate mechanisms leading to cognitive decline in AD and other forms of dementia (Webster et al. 2014) (A summary of five commonly used mouse models can be found in Table 1). While no animal model can recapitulate the entirety of AD in humans, the aim is to model cognitive impairments that appear as core clinical features of AD. With this in mind, we present an overview of neuropsychological assessments, outline the temporal progression of cognitive decline in the clinic and then discuss how behavioral tests in mice relate to the core features seen in human AD.

The first, and the most noticeable, impairments in patients are in episodic memory and semantic memory (Salmon and Bondi 2009; Weintraub et al. 2012). These are accompanied by impairments in executive function, attention (vigilance), visuospatial abilities, language and changes in mood (Foldi et al. 2002; Landes et al. 2001; Salmon and Bondi 2009; Weintraub et al. 2012). In the late stages of the disease, spatial memory, verbal recall and general cognition are also affected (Bondi et al. 2008). Cognitive impairment in AD is detected and diagnosed through a combination of patient history and an objective cognitive assessment. The Mini-Mental State Examination (MMSE) is one of the most commonly administered screening tools for cognitive impairment and has high sensitivity (69-90%) for dementia in clinical settings (Boustani et al. 2003). The MMSE screens domains of orientation to time and place, attention and memory, concentration, and language and praxis, however, it doesn't cover all domains relevant to all dementias (Cullen et al. 2007; Tangalos et al. 1996). Moreover, the MMSE has been criticized for bias towards education level, sex, language of administration, and ethnicity (Dai et al. 2013; Fratiglioni et al. 1993; Freidl et al. 1996; Jones and Gallo 2002; Marshall et al. 1997). Thus, the utility of MMSE as a diagnostic tool when used in isolation has been questioned and has led to calls for more research into other brief screening methods with improved sensitivity and specificity (Boustani et al. 2003; Shulman et al. 2006). Many mental state examinations have since been developed with additional advantages such as speed of administration, excellent test-retest reliability and higher sensitivity for assessing cognitive changes (Webster et al. 2014). It is common for memory testing to be performed if routine history and bedside mental state examination cannot provide a confident diagnosis. Both verbal and visual memory tests are used in the clinical setting, requiring patients to recall concepts or stimuli after a delay (Benton 1992; Wechsler 1997). Computerized cognitive tests are being increasingly used in attempts to reduce the cost of large-scale screening for age-related cognitive decline. Covering many cognitive domains, 17 test batteries for testing older adults were identified in a recent review article (Zygouris and Tsolaki 2015). These computerized batteries offer many advantages over traditional pen and paper assessments including: increased standardization of administration and stimulus presentation, accurate measures of response latencies, and

efficiencies of staffing and cost (Wild et al. 2008; Zygouris and Tsolaki 2015). Their development has also been driven by the need to detect subtle changes in cognition for early detection and providing clear outcome measures for drug trials. One example is CANTAB (Cambridge Neuropsychological Test Automated Battery), in which two of the battery's tasks have been shown to be sensitive to early cognitive decline in patients (Blackwell et al. 2004). Another test battery developed for repeat testing, CogState, has sensitivity in tracking subtle changes in cognition (Collie et al. 2003; Falleti et al. 2006; Maruff et al. 2002). However, the breadth of tasks used and the variability in domains covered by computerised test batteries, makes it very hard to compare between studies and patients. Additionally, it is evident that some tasks are more sensitive to mild cognitive impairment (MCI) and AD deficits than others, but this has not been well investigated. Comparisons between new tools and the traditional supervised modes of cognitive assessment have been described, which highlight that the two testing formats deviate in their ability to predict the same mental constructs (Ruggeri et al. 2016).

Ideally, preclinical rodent cognitive testing would assess identical domains to those seen in the clinic. However, there is a lack of consensus in the clinic as to what test or battery provides the most accurate diagnosis, or ability to detect change in cognition overtime. While the 2011 guidelines for the diagnosis of dementia indicate which domains to test, no recommendations on what tasks clinicians and researchers should use to investigate these cognitive domains have been made (McKhann et al. 2011). As such, the wide varieties of batteries that are used make it extremely difficult to pick comparable tasks in preclinical animal models of dementia. Many cognitive domains impaired in AD have been extensively modeled in rodents (e.g. working memory, associative memory), while others have received less attention due to limitations in the available assessment methods (executive function, attention). For some cognitive domains, such as semantic memory, a proxy for the human domain is measured (e.g. reference memory). Other cognitive domains impaired in clinical AD, such as those involving specific aspects of language (i.e. verbal acuity tasks and verbal recall tasks), simply cannot be accurately modeled in rodents.

Not So A-Mazing Methods For Modeling Memory In Mice

Historically, maze-based tasks have been used to assess spatial and non-spatial working memory in mice. Working memory refers to the ability to temporarily hold information where it can be drawn upon to guide behavior. T- and Y-shaped mazes are often used to assess working memory and exploit the natural exploratory tendency of mice to alternate their choice of arms (Ashe and Zahs 2010; Webster et al. 2014). A more complex maze-type task used to assess spatial working memory in mice is the radial-arm maze (RAM). A mouse is placed in the central platform and allowed to explore the 6-8 reward-baited arms radiating outwards. Mice with intact working memory will remember which arms they have previously visited for the reward and will avoid re-entering a previously entered arm. Many deficits in working memory have been described in AD mouse models (Webster et al. 2014). The Morris water maze (MWM) is the most widely used task for testing spatial memory in rodents and many variations exist, testing working memory, reference memory and associative memory. The mouse is placed in a circular pool, filled with water, and their swim path is tracked (Morris et al. 1982). The mouse must use cues external to the pool to navigate to a submerged platform and typically escape times decrease with training. The MWM is the gold-standard test for assessing cognition in AD mouse models, yet the exact protocol used and the specific domain modeled are often overlooked in the reporting of impairments (Webster et al. 2014). The delayed matching-to-place (DMP) variant of the water maze requires rodents to learn to escape to a hidden platform that is typically moved to a new location each day and performance is followed across many days and weeks (da Silva et al. 2014). This task and the more complicated variation, the delay-non-matching to place task (DNMTP), both test working memory across a delay (da Silva et al. 2014). Varying the length of the delay can provide insight into how long mice can retain information in their working memory. Deficits

in DNMPT tasks have been found in AD mice (Balducci et al. 2010; Blanchard et al. 2011; Grootendorst et al. 2005), and have been shown to be hippocampal-dependent (Blanchard et al. 2011; Sloan et al. 2006). This task has utility for studies assessing potential therapeutic compounds as each animal can perform many trials per day and thus can serve as its own control.

Recognition memory has been widely assessed in AD mouse models and impairments interpreted as modeling amnesia (Table 1). The novel object recognition test (NORT) consists of a training phase where the animals are presented with two similar objects, and following an interval, one of the objects is replaced with a novel object and investigation of the two is assessed (Dere et al. 2007; Giralt et al. 2011; Taglialatela et al. 2009). The NORT is extremely simplistic and an adaption has been recently developed task to more closely model episodic-like memory (Webster et al. 2014). In the What-Where-Which task (WWWhich) the animal must integrate the location of a particular object with specific contextual cues to form an episodic-like memory and several AD mouse models have been shown to have impairments (Davis et al. 2013a; Davis et al. 2013b). Associative memory is necessary for binding representations of two or more stimuli, a process key to episodic memory and deficits in both paradigms measuring this (fear conditioning and passive avoidance) have been reported in multiple AD mouse models (Webster et al. 2014).

Inference of genuine cognitive dysfunction in these tasks can be challenging as performance relies on many non-cognitive processes. For example, the water maze is confounded by motor impairments and ceiling effects (i.e. swimming velocity) that reduce its sensitivity in detecting improvements in cognition (Kapadia et al. 2016). This task also relies on stressful conditions to motivate performance, a factor known to negatively affect cognition (Joels and Baram 2009). Caution interpreting avoidance tasks (e.g. fear conditioning) is recommended as inability to enter/exit the chamber could be due to altered motor capabilities, reduced pain threshold, deficits in vision or sedation. Performance on one-trial tests like alternation in T-mazes do not allow sufficient time for habituation, rendering them sensitive to environmental factors, experimenter handling, anxiety, and novelty-induced hyperactivity (Hughes 1990). A comprehensive review of 49 studies testing performance of the Tg2576 mouse model (expressing the APP695 Swe mutation) of AD on 5 commonly used tasks assessing spatial memory found that significant variation between the tasks existed (Stewart et al. 2011). This review showed the likelihood of detecting impairment in the Tg2576 model was highest when the T-maze was used and lowest when using a dry version of the water maze (Barnes circular maze). Presumably if an AD mouse model shows working memory impairment, this phenotype should be detected across a number of tasks. Conflicting results in this field are common, with some investigators finding deficit at one age and others finding no change in the same strain-matched animal model (Puzzo et al. 2015). As such, the field is moving towards using translational cognitive tests, with robust and reproducible protocols, that are as close to clinical assessment methods as possible.

AD Mouse line	Human mutations	Promoter	Age that deficit occurs				
			Working memory	Recognition memory	Attention	Executive function	Spatial Memory
Tg2576	APP695 Swe	Syrian Hamster PrP	↓ 3-5 m (Chapman et al. 1999; Hsiao et al. 1996; King and Arendash 2002; Lalonde et al. 2004; Ohno 2009)	↓ 12-14 m (Bardgett et al. 2011; Oules et al. 2012; Yassine et al. 2013)	N/A	↓ 6-12 m (Shirey et al. 2009; Zhou et al. 2007)	↓ 9-15 m (Bardgett et al. 2011; Hsiao et al. 1996; Oules et al. 2012)
			N/C 2-4, 9 m (Corcoran et al. 2002; Holcomb et al. 1999)			N/C 5.5-10 m (Dong et al. 2005; Guérin et al. 2009)	N/C 3-19 m (Holcomb et al. 1998; King and Arendash 2002; King et al. 1999; Zhou et al. 2007)
APP/PS1	APP695 Swe, PSEN1ΔE9	Mouse PrP	↓ 8 -10.5 m (Kim et al. 2015c; Sierksma et al. 2013)	↓ 5-8 m (Guo et al. 2015; Otalora et al. 2012; Petrov et al. 2015)	N/A	↓ 6-8 m (Cheng et al. 2013; Filali and Lalonde 2009; Filali et al. 2011; Hooijmans et al. 2009; Jankowsky et al. 2005; Stover and Brown 2012)	↓ 7-15 m (Cao et al. 2007; Guo et al. 2015; Hooijmans et al. 2009; Jiao et al. 2015; Tapia-Rojas et al. 2015)
			N/C (Cao et al. 2007; Lalonde et al. 2004; Pietropaolo et al. 2012; Reiserer et al. 2007a)				N/C 6-26 m (Jankowsky et al. 2005; Pietropaolo et al. 2008; Reiserer et al. 2007b; Stover and Brown 2012)
3xTg-AD	APP695 Swe, PSEN M146V, Tau 4R0N P301L	Mouse-Thy1	↓ 3-7 m (Carroll et al. 2007; Nelson et al. 2007; Rosario et al. 2006; Zhang et al. 2010)	↓ 4-9 m (Cantarella et al. 2015; Clinton et al. 2007; Zhang et al. 2010)	↓ 9 m (Cantarella et al. 2015; Clinton et al. 2007; Romberg et al. 2011; Zhang et al. 2010)	↓ 6 m (Filali 2012; Marchese et al. 2014; Stover et al. 2015)	↓ 2.5-9 m (Cantarella et al. 2015; Clinton et al. 2007; Marchese et al. 2014; Stover et al. 2015; Zhang et al. 2010)
			↑ 6.5 m (Stover et al. 2015)				

TgCRND8	APP695 Swe & Ind	Syrian Hamster PrP	↓ 3, 6, 9 m (Burgess et al. 2014; Hyde et al. 2005; Maliszewska-Cyna et al. 2016)	↓ 2-4 m (Francis et al. 2012; Görtz et al. 2008; Greco et al. 2010; Romberg et al. 2013b)	↓ 4-5 m (Romberg et al. 2013b)	↓ 4 m (Musilli et al. 2013)	↓ 2.5-9 m (Chishti et al. 2001; Görtz et al. 2008; Hyde et al. 2005)
						↑ 4-5 m (Romberg et al. 2013b)	N/C 1.5-4 m (Hyde et al. 2005; Musilli et al. 2013)
5xFAD	APP695 Swe, Lon & Flo, PSEN1 M146L & L286V	Mouse-Thy1	↓ 4-5 m (Francis et al. 2012; Görtz et al. 2008; Musilli et al. 2013)	↓ 4-8 m (Fratiglioni et al. 1993; Giannoni 2013; Tohda et al. 2012)	↓ 7 m (Masood 2015)	↓ 4-6 m (Baruch et al. 2015; Girard et al. 2013; Girard et al. 2014)	↓ 3.5-6.5 m (Baruch et al. 2015; Fragkouli et al. 2014; Ohno 2009; Yang et al.)

Table 1: Cognitive impairments in AD mouse models relative to wild-type controls. A variety of studies investigating the cognition of 5 common AD mouse lines referred to throughout this review. Working memory tasks refers to performance in T & Y mazes, recognition memory refers to performance in novel object recognition tests, attention refers to performance in 5 choice serial reaction time tasks, executive function refers to studies where animals underwent reversal of a previously learned task, and spatial memory was restricted to performance in Morris water maze and Barnes circular maze. ↑***= increased,*** ↓ ***= decreased, N/C = no change, N/A = not assessed, m = month***

Translational Touchscreen Tasks For Assessing Cognition In Mice

Touchscreens can be used to administer cognitive tests to rodents that are analogous to those used in clinical assessments such as the CANTAB. In Bussey-Saksida touchscreens, animals learn to discriminate between two visual stimuli projected onto a touch-sensitive computer screen and are rewarded for correct responses (Bussey et al. 2012). This method is non-aversive, relies on reward to motivate animals and once basic learning has been acquired, tasks can then be scaled in complexity to mimic human cognitive tests. Performance is assessed over numerous trials, conferring much higher sensitivity and enabling the detection of enhancements as well as impairments (Burrows and Hannan 2016). Pre-training allows for ample habituation, reducing potential for anxiety and novelty-induced hyperactivity to impact on performance. Mice are consistently trained in the same chamber and, when they complete the task of interest, can be assessed on a number of other tasks to ascertain their full cognitive phenotype. Furthermore, cognitive batteries of touchscreen tasks can be used to study aspects of cognition not previously testable in rodents such as attention, executive function and behavioral inhibition (Fig. 1). While some tasks are uniquely used in rodents (e.g. 5-choice serial reaction task), some are direct analogues of clinical tests and their use will provide insight into the neural mechanisms underlying specific facets of cognition. Demonstrating this approach, a group utilizing touchscreens recently identified the same cognitive deficits in patients and mice containing the same mutation (Nithianantharajah et al. 2015).

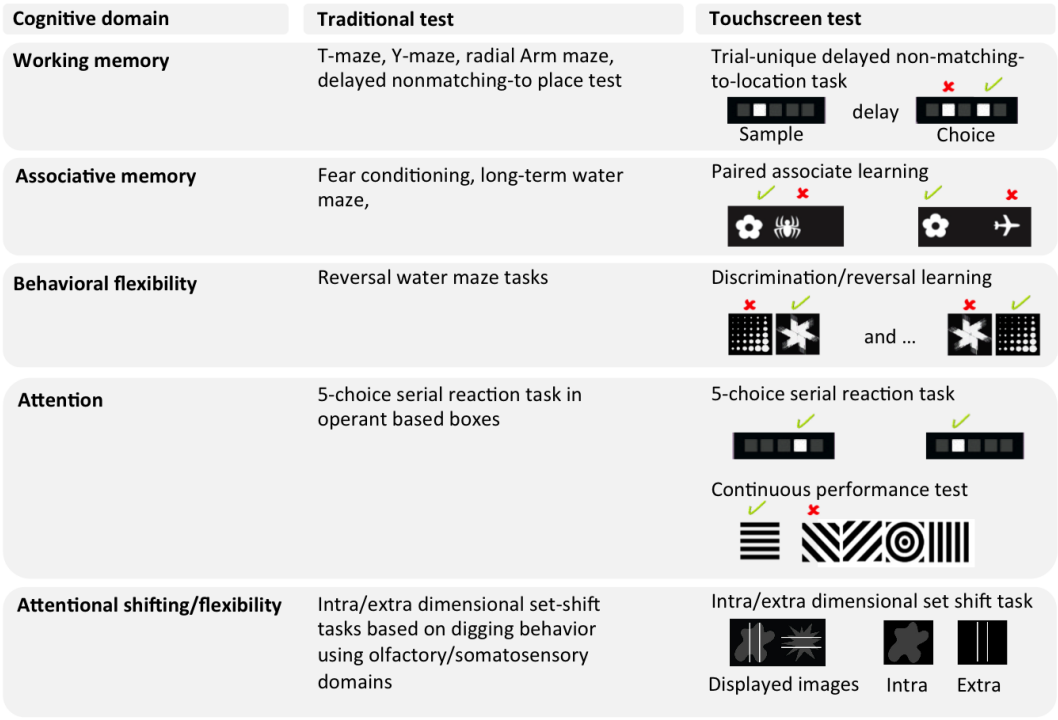

Fig 1: Rodent traditional and translational touchscreen tasks for assessing cognitive domains relevant to Alzheimer's disease.

An example of a task that is directly translated from the clinic is the paired-associate learning (PAL), a part of the Cambridge Neuropsychological Test Automated Battery (CANTAB) and shown to be sensitive to early cognitive decline in patients with Alzheimer's disease (Blackwell et al. 2004). PAL is an associative learning task, which requires correct recall of contextual information regarding certain events (Bartko et al. 2011; Bussey et al. 2012; Kim et al. 2015b; Talpos et al. 2009). Rodents learn the association between an image (e.g. image A, B and C) and its respective correct location (e.g. location 1, 2, 3) on the computer screen. While AD mouse models have yet to be assessed on PAL performance, much work has been done to uncover the neural substrates underlying accurate performance. PAL has been shown

to be sensitive to hippocampal damage (Talpos et al. 2009), and involve cholinergic (Bartko et al. 2011) and glutamatergic (Talpos et al. 2009) systems. A variation of this task has shown more specifically, that dysfunction of the dorsal hippocampus affects the performance of the task, not its acquisition (Kim et al. 2015b). In humans (Eichenbaum 2000; Owen et al. 1995; Simons and Spiers 2003) as well as in rodents (Bussey et al. 2001; Gaffan and Parker 1996) the concurrent activation of the hippocampus and prefrontal cortex is involved in encoding and retrieval of object-in-place associative memory. It is thought that the hippocampus contributes to the location component, while the perirhinal cortex contributes to the object information. Understanding how familial AD mutations impact on these brain areas to impair associative memory in mice will provide an understanding of the temporal and spatial degeneration of the brain in AD models, and whether that pattern is analogous to that seen in human patients.

The trial unique delayed-nonmatching-to-location (TUNL) task assesses spatial working memory, and is akin to the more commonly used DNMPT (Kim et al. 2015b; McAllister et al. 2013; Oomen et al. 2013; Talpos et al. 2010). In the TUNL task, an animal nose-pokes a stimulus (white square) displayed on one side of the screen (left or right) and after a delay is shown two stimuli on both sides. The animal is rewarded for choosing the stimulus that appears on the opposite side from the one it first selected. Spatial separation between the two stimuli and the delay between the two presentations can be changed in different stages of the experiment. Compared to the DNMPT, the TUNL task uses multiple locations for the two stimuli across trials, with pairs of location being repeated much less often, making it very close to being 'trial-unique'. This feature also circumvents the possibility of using a mediating strategy as in the DNMPT, making it impossible to predict the correct location, because it uses an array of possible spatial locations (Chudasama and Muir 1997; Herremans et al. 1996). This also allows detection of memory for location, as well as pattern separation of spatial information, both of which involve the hippocampus (Aggleton et al. 1992; Deadwyler et al. 1996; Gilbert et al. 1998; Hampson and Deadwyler 1996; Leutgeb et al. 2007). Indeed, it has been shown that distance between locations in such tasks influences the magnitude of impairments in rats with hippocampal lesions (Kesner et al. 2004). This task was first developed using rats (Talpos et al. 2010), and subsequently modified for use in mice (Kim et al. 2015b), both studies demonstrating that this task is highly sensitive to hippocampal dysfunction. Moreover, this task could also successfully detect dysfunction of the prefrontal cortex in mice (McAllister et al. 2013). Indeed, the TUNL task holds potential utility in detecting the role of hippocampus and its connections with the prefrontal cortex in AD. Like PAL, the TUNL task is yet to be used to assess memory in AD mice models.

Attention is an over-arching cognitive domain, encompassing a variety of subtypes including sustained attention (vigilance), orientation and novelty seeking, spatial attention, selective attention and divided attention. These subtypes have been reported as impaired early in AD (Foldi et al. 2002; Perry et al. 2000). The 5-Choice Serial Reaction Time Task (5-CSRTT) is a rodent behavioral task developed for modeling attention in mice (Robbins 2002). The task assesses the ability of an animal to pay attention and respond to a brief stimulus in one of 5 distinct spatial locations. Mice complete many trials each day and the attention demands placed on the animal can be manipulated by the addition of a distracter (e.g. playing a tone before stimulus presentation), varying the delay before stimulus presentation, or by decreasing the stimuli brightness or length. Sustained attention is assessed by examining the animal's response accuracy, the number of trials they fail to respond to (omissions) and response reaction time. Two AD mouse models have been assessed on the 5-CSRTT using rodent touchscreens; 9-month-old 3xTg-AD mice and 4-5 month old TgCRND8 mice (Romberg et al. 2013a; Romberg et al. 2013c; Romberg et al. 2011). 3xTg-AD mice have 1 APP mutation (KM670/671NL), a PS1 mutation (M146LV) and a Tau mutation (*MAPT* P130L), and develop cognitive deficits at a slow to medium pace (Oddo et al. 2003). Conversely, TgCRND8 have two APP mutations (KM670/671NL + V717F) under a prion promoter, causing this model to progress at an accelerated pace (Chishti et al. 2001). Both of

these mice show deficits in attention when required to pay attention to a brief stimulus (0.6 or 0.8s long), but remain unimpaired with longer stimuli (1 or 1.5s) (Romberg et al. 2013c; Romberg et al. 2011). In the 3xTg-AD mice, this seems to be a function of reduced vigilance, meaning they cannot maintain attention as time progresses. This phenomenon is analogous to what is seen human AD patients (Foldi et al. 2002).

A human version of the 5-CSRTT does exist, however the mouse and human versions are not directly comparable, and caution should be used when drawing translational conclusions from rodent 5-CSRTT studies (Wilkinson 1963; Young et al. 2009). The Continuous Performance Test (CPT) of sustained attention (Beck et al. 1956) is analogous to the 5-CSRTT and a mouse version of the CPT has been recently developed (Kim et al. 2015a). In this task, mice are required to respond to signal and non-signal stimuli across numerous trials, and scores of hits, misses, rejections, and false alarms are recorded. The requirement to rapidly discriminate between target and non-target stimuli, adds a layer of complexity that has been shown to be important in observing decreased vigilance (Parasuraman 1979).

Executive dysfunction, while not the focus of diagnosis of AD, is impaired early in the disease (Baudic et al. 2006; Perry et al. 2000). Executive function is an overarching term for many distinct functions, and specifically impaired in AD is the ability to set-shift, self-monitor and solve difficult problems (Baudic et al. 2006; Lange et al. 1995). Cognitive flexibility and response inhibition are the most commonly modeled aspects of executive function in mice. Response inhibition can be assessed with the 5-CSRTT using measures of impulsivity (premature responses) and failure to disengage from previous response (perseveration) (Chudasama 2011). When assessed on 5-CSRTT, the 3xTg-AD mouse model showed a tendency to perseverate after a correct response, indicating these mice may be more compulsive than their wild-type counterparts (Romberg et al. 2011). The TgCRND8 mice did not show this deficit, and it is possible that the additional tau mutation in the 3xTg-AD mice may be responsible for the perseverative responses (Romberg et al. 2013c). Impairments in cognitive flexibility are often measured by assessing reversal learning, where the stimulus-reward is switched and the animal is required to inhibit its response to the previously learned stimuli and learn the new one. Many different AD mouse models have shown impairment in reversal learning (Cheng et al. 2014; Filali et al. 2012; Papadopoulos et al. 2013; Webster et al. 2014), however these tasks are simplistic and equivalent tasks are not routinely used in the clinic.

Set-shifting tasks, like the Wisconsin Card-Sorting Task are the gold standard for assessing executive function in humans (Nelson 1976). They evaluate the ease with which a person can discard a previously formed rule to ascertain the new, correct rule. Rodent set-shifting tasks take advantage of natural digging behavior, and involve training the animal to dig in 2 containers for a food reward. Containers can be discriminated from each other by odor, texture of medium, and/or texture of the container, allowing the experimenter to modify which dimension signifies the correct container and test the animal's ability to shift between stimuli dimensions to successfully retrieve the food reward (Bissonette and Powell 2012). Tg2576 mice have been assessed on the digging set-shifting task and were reported to show an impairment in reversal compared to wild-type mice (Zhou et al. 2007). A key component of set-shifting is that the extra-dimensional shift (shifting between odor to texture vs. different odors) takes longer to learn. In this particular study, the extra-dimensional shift did not confer increased difficulty for wild-type animals, indicating that the task was not optimally designed to assess set-shifting. This is not an uncommon issue for set-shifting tasks in rodents, as stimulus bias, lengthy training and low sample sizes (only one mouse can be run at a time, and the experimenter must be present at all times) make optimization and interpretation of this task difficult (Brigman et al. 2005; Garner et al. 2006). Touchscreen variations of the set-shifting task allow animals to be tested simultaneously, cutting down on experimenter time, increasing sample size as well as allowing counter-balancing and removing time-of-day effects within groups (Brigman et al. 2005). They also allow the use of the same types of

stimuli (objects and locations on a computer screen), and the same types of responses (screen touches) as the human set-shifting tasks. A number of groups have developed set-shifting touchscreen tasks, similar to the intra- extra- dimensional (IED) set-shifting task featured in the CANTAB battery (Brigman et al. 2005; Dickson et al. 2014). These tasks reported issues of stimulus bias and in the difficulty of the shift between dimensions, so further development is required to optimize this task before extensive characterisation of set-shifting in rodent models can occur.

One Size Does Not Fit All

When assessing cognition in AD mouse models it is common practice to select one task, at one time point and scrutinize one outcome measure. There are many issues with this approach. Current methods lack standardization and produce variable results across laboratories. Often, a task is used to assess 'cognition' or 'memory' without consideration regarding the specific cognitive domains relevant to dementia. Some approaches are more affected by environmental variables due to the short time frame of testing (some are one-trial). The short nature of these tests also reduces sensitivity and the ability to detect subtle cognitive changes. Re-testing is not possible with most maze-based tasks, so tracking cognitive changes and therefore decline is thus limited with traditional methods. Given the requirement to develop therapies for early-stage disease to mitigate or slow cognitive decline, using blunt tools to detect severe impairments is far from ideal. Furthermore, without methods to track changes in cognition in animal models, therapeutics that have potential to slow cognitive decline, rather than completely reverse it, cannot be tested. Additional challenges arise from the many non-cognitive behaviors displayed by AD mouse models that can mask or produce phenotypes in behavioral tasks that look like impairments in cognition. Hyperactivity (Gil-Bea et al. 2007; Walker et al. 2011), altered anxiety levels (both high and low, (Lalonde et al. 2003; Puolivali et al. 2002; Reiserer et al. 2007a)) and changes in circadian rhythm (Musiek et al. 2015; Song et al. 2015) could all significantly confound performance in cognitive tasks. Furthermore, excessive aggression (Alexander et al. 2011; Pugh et al. 2007; Vloeberghs et al. 2006) and impairments in social interaction (Pietropaolo et al. 2012) in AD mutant mice can alter group housing dynamics or lead to single housing of animals. These housing conditions are difficult to keep consistent among a large group of animals and can disproportionately affect a subset of animals. Finally, impaired vision has been reported in a number of mouse models due to Aβ-induced retinal deterioration and mutation-background strain interactions (Wolf et al. 2016).

Despite these challenges, high quality behavioral data can be produced with careful experimental design, control of extraneous environmental factors, backcrossing transgenic models onto robust background strains and transparent reporting practices (Burrows and Hannan 2013). Furthermore, conducting a battery of tests to detect consistent phenotype will lead to more robust findings. While touchscreen testing mitigates many of the confounding effects of non-cognitive behaviors due to extensive habituation in the same chamber, the lengthy testing makes assessing acquisition of some tasks in accelerated transgenic models difficult. However, the sensitivity to subtle cognitive changes, the ability to re-run probe tests to measure changes in cognition and the similarity to clinical tests makes this platform very well suited as a tool for screening preclinical animal models of AD and dementia.

Lessons Learnt From Both Sides Of The Theapuetic Pipeline

Computerized testing remains a relatively recent development in neuropsychology and comprehensive evaluation of the reliability and validity of these tests is needed. No review has yet proposed one test as definitely better or more suitable (Zygouris and Tsolaki 2015). It may be impossible to select a test that is suitable for dementia, as there are many different types and with the shift towards early screening and diagnosis, it may be that a test to identify mild cognitive impairment (MCI) becomes the priority. This complicates the clinical scene further. While MCI may precede onset of dementia, many people with MCI do not go on to develop dementia, with MCI having little predictive ability for later diagnosis. The shift

towards early screening and diagnosis has led to an accompanying shift in the way computerized testing is being implemented in health care. Recently, models have been proposed that describe best practice for integrating these tests into neuropsychological assessments (Ruggeri et al. 2016). These models suggest the use of a brief computerized screening test if signs of possible impairment are identified and then, if required, a lengthier test to provide a more comprehensive profile. Recommendations for repeated testing at regular intervals to assess patients' progress and response to treatment have also been made. New information from the clinic, updated approaches in animal models, and information flow in both directions in the therapeutic pipeline, may optimize translational potential.

Traditional preclinical testing paradigms could account for many of the failures of interventions that are successful in an animal model but not in the human population (Burrows and Hannan 2013; Franco and Cedazo-Minguez 2014). Using tasks in mice that are analogous to clinical assessments may improve the direct translation into cognitive testing of patients as well as facilitating the development of novel therapeutic approaches for AD. Furthermore, the combined use of invasive manipulations and non-invasive imaging with this sophisticated behavioral analysis can give us a powerful approach for understanding mechanisms of cognitive decline in brain diseases.

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