Research report

Apathy-like behaviour in tau mouse models of Alzheimer's disease and frontotemporal dementia

Lianne Robinson [a],[*],[1], Eline Dreesen [a],[1], Miguel Mondesir [a], Charles Harrington [a],[b], Claude Wischik [a],[b], Gernot Riedel [a]

[a] School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, Foresterhill AB25 2ZD, United Kingdom
[b] TauRx Therapeutics Ltd, 395 King Street, Aberdeen AB24 5RP, United Kingdom

A B S T R A C T

Apathy is the most common behavioural and psychological symptom in Alzheimer's disease (AD) and other neurodegenerative diseases including frontotemporal dementia (FTD) and Parkinson's disease (PD). In patients, apathy can include symptoms of loss of motivation, initiative, and interest, listlessness, and indifference, flattening of emotions, absence of drive and passion. Researchers have later refined this to a reduction in goal direct behaviours. In animals, specific symptoms of apathy-like behaviour have been modelled including goal directed or nest-building behaviour which are seen as indicative of proxies for motivation and daily activities. In the present study a nest-building protocol was established using four different inbred mouse strains (CD1, BALB/c, C57Bl/6J, C3H) before assessing AD and FTD tau transgenic mice of Line 1 (L1) and Line 66 (L66) in this paradigm. Female mice aged 5 – 6 months were assessed in the home cage over a period of 7 days with nest-building behaviour scored by three independent experimenters at intervals of 1-, 2- and 7-days post nestlet introduction. Inbred mouse strains displayed different levels of nesting behaviour. BALB/c mice were more proficient than CD1 and C3H mice, while all strains displayed similar nest-building behaviour by day 7. In the tau mouse models, L66 presented with impaired nesting compared to wild-type on days 1 and 2 (not day 7), whereas L1 performed like wild-type on all days. Anhedonia measured in a sucrose preference test was only observed in L66. Anhedonia and low nesting scores in L66 mice are indicative of apathy-like phenotypes. Differences evident between the L1 and L66 tau transgenic mouse models are likely due to the different human tau species expressed in these mice.

1. Introduction

Neuropsychiatric symptoms (NPS), previously referred to as behavioural and psychological symptoms, are very common in patients with dementia. Twelve different domains (delusions, hallucinations, agitation, depression, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, appetite and eating abnormalities) are assessed using the Neuropsychiatric Inventory (NPI) through a short questionnaire and outcomes are reliable and valid [1]. The most common NPS in Alzheimer's disease (AD) patients is apathy (65%), followed by hyperactivity (64%) and affective behaviours (59%), with psychosis being present in only 38% of cases. This is in accordance with a recent meta-analysis of 48 studies performed between 1990 and 2014 [2] which categorised the NPI for these

four syndromes. Alternative classifications also exist [3] yet apathy remained the most prevalent syndrome [4]. This observation even holds when other forms of dementia such as dementia with Lewy bodies, vascular dementia, behavioural variant of Fronto-Temporal Dementia (bvFTD), Parkinson's disease with dementia and primary progressive aphasia are included in the analysis [5–9], but appears to be dependent on disease severity and the history of treatment with cholinesterase inhibitors. To understand the neurobiology of these NPS and their influence on disease progression, they need to be explored in animal models of the different types of dementia. Webster and colleagues have previously described various AD models in terms of non-cognitive behavioural symptoms but failed to consider apathy [10].

Despite the absence of appropriate tests and definitions, apathy is increasingly diagnosed as a behavioural symptom in dementia [11,12].

In bvFTD patients with genetic predispositions, apathy was identified as an early marker for FTD onset and prognostic for clinical deterioration of cognitive function [13]. It is defined as a disorder of motivation and reward with a lack of tenacity for persistent goal-directed actions [14–17]. Back-translation to rodents and utilisation of goal-directed tasks has mapped the underlying brain regions and transmitter systems (reviewed in [18–22]). To date multiple behavioural assays have been implemented to assess apathy-like behaviour in AD mouse models including using actimetry to measure reductions in spontaneous activity [23,24] or the assessment of motivational deficits in the Hebb-Williams maze [25]. However, beta amyloid-based AD mouse models appear to lack generalised apathy measured as approach behaviour in a social context or free-roaming global activity in a home cage [26], whereas more specific tests such as nest building, and sucrose preference deficits have confirmed apathy in both AD and FTD mouse models. Cathomas and colleagues [27] described 5 subdomains of apathy observed in humans and explained that at least 3 of these subdomains, self-care, social interaction, and exploration, can be assessed in mouse models. More recently, studies of apathy-like behaviours in rodents have focused on modelling the activities of daily living (ADL) that are also impaired in AD and FTD patients. Impairments in rodent-typical behaviours indicative of ADLs including nest building, food burrowing and marble burying have been observed in 5 x FAD and PS1/PS2 DKO mice [28,29].

The nest-building task is a simple rodent test for self-care [30], in which a low score for the quality of the nest built by an animal is indicative of apathy-like behaviour. Reduced nest-building behaviour has been reported for PS1/PS2 DKO [29,31], 3xTgAD [32,33], TgCRND8 [34], APPswe/PS1 bigenic [35] and 5 x FAD [28] mouse models. All are transgenic, mutant amyloid-beta based models, or mixed amyloid and tau models as in the case of the 3xTgAD raising the question of whether transgenic tau and tau mutants alone also suffer from apathy-like symptoms. When compared with clinical symptoms in bvFTD, genetic models based on mutant tau such as V337M also present with apathy-like behaviour as observed in nest building tests [36,37].

As apathy-like behaviour in animals (as with humans) has various possible definitions it is important to measure performance in different behavioural assays in-order to confirm/indicate apathy-like behaviours as performance in an individual test alone may not be sufficient and open to various interpretations. A combination of different behavioural tests for the different aspects of apathy-like behaviour observed in mice is therefore warranted. In contrast to the natural species-specific behaviour assessed by nest-building performance, the sucrose preference test measures the reward aspect and provides a more direct measure for hedonic responses in rodents [38–41] with a decrease in sucrose intake typically interpreted as anhedonia. Here, anhedonia is defined as a diminished interest or reduced pleasure in activities and is a core symptom of depressive disorders (see DSM-5 [42]). From a motivational point of view, the sucrose preference test involves the two underlying aspects of 'wanting' (the motivational effort needed to obtain a reward) and 'liking' (the hedonic capacity and inability to experience pleasure: [43]. Therefore, deficits in sucrose preference can impinge of various behaviours including motivation, anhedonia, learning and stress [44].

Apathy and depression may co-occur and share overlapping symptoms including decreased interest or initiative and reduced motivation (see [45] for review). Although they have distinct neural brain circuits and neurobiological markers these can also overlap making diagnosis and treatment difficult [45]. Consequently, the sucrose preference test is frequently applied to reveal reduced motivation indicative of apathy-like behaviour in mouse models [46]. So far, AD/FTD models have confirmed reduced preference for sucrose [31,47–49] or no effect [50,51]. Therefore, differences obtained with the sucrose preference test would confirm an apathy-like phenotype established by nest building. While nesting behaviour is considered to be more goal directed and self-care related, sucrose preference may be more akin to the exploration sub-domain assessing impaired novelty seeking in humans [27].

These data provide strong evidence that tau mouse models of AD/

FTD can be used to mimic disease related NPS and in this study we have explored these behavioural phenotypes in two other tau transgenic lines. In the model organisms used here, L1 mouse model overexpresses the truncated core-tau aggregation domain of the AD paired helical filament (PHF; residues 296–390) and presents with a progressive histopathological spread of diffuse oligomeric tau deposits following a Braak-like AD spreading pattern [52]. This model exhibits spatial learning and memory impairments from 3 months onwards [52]. Line 66 (L66) mice overexpress full-length human tau carrying two pathogenic point mutations (P301S and G335D). Mice develop aggressive filamentous tau aggregates in the form of neurofibrillary tangles in the hippocampus and entorhinal cortex and display progressive motor phenotypes [52].

The objective of this research was to determine whether L1 and L66 mice show NPS and, more specifically, apathy-like behaviour. This was achieved by first establishing a nest-building protocol and comparing the activity of four standard mouse lines, and then testing the tau transgenic cohorts using this protocol.

2. Materials and methods

2.1. Animals

All wild-type animals were bred in open housing and supplied by Charles River Laboratories (CRL; Margate; UK). They were group housed upon arrival in controlled conditions in open housing (Makrolon type III cages, corncob bedding, 2 cage changes per week, ambient temperature $21 \pm 1\,^\circ C$, relative humidity 50–65%, 17–20 air changes per hour) in the Medical Research Facility at the University of Aberdeen. Food (Special Diet Services, Witham, UK) and water was available ad libitum, and a circadian rhythm was maintained of 12 hr light/dark cycle (lights on at 7 am) with simulated sunrise and sunset (30 min). All mice were weighed three times weekly in the mornings (9–11 am) and all behavioural tests were performed during the light cycle. Sample sizes were based on power calculations and all experiments were performed blind, counterbalanced and in accordance with the European Communities Council Directive (63/2010/EU) and a project license with local ethical approval under the UK Animals (Scientific Procedures) Act (1986) and its Amended Regulations (2012), and following ARRIVE 2.0 guidelines [53].

In experiment 1, four different female inbred mouse strains were used: i) C57Bl/6J; ii) CD1; iii) C3H and iv) BALB/c. They were aged 5–6 months with N = 12 per strain.

In experiment 2, female homozygous transgenic L1, L66 and wild-type (NMRI) litters were generated as previously described [34]. They were bred and maintained in commercial isolators with positive pressure in small cohorts in shoebox cages on commercial diet and bedding at CRL. At about 4.5 months, randomly selected animals were delivered (by van) to the Medical Research Facility at the University of Aberdeen and maintained in groups of up to 10 animals in open-top Makrolon type III cages with free access to water and food (see above). L1 mice express truncated tau 296–390 fused with an N-terminal endoplasmic reticulum-directing signal sequence while L66 mice express full-length human tau40 (htau 40; 1–441 amino acids) carrying two mutations (P301S and G335D). Both transgene constructs were inserted under the murine Thy1 cassette, for neuronal expression. All mice were aged 5 – 6 months with L66 (N = 12), L1 (N = 11) and NMRI (N = 12) mice used in experiment 2. This was based on previously reported observations that sensorimotor impairments and cognitive phenotypes along with relevant tau pathology can be revealed in these mouse models at ~6 months of age [52]. Only female mice were utilised in both the nest-building task development and subsequent assessment of tau transgenic lines to ensure consistency with previous phenotypic observations in L1 and L66 mice [52]. Furthermore, other studies have reported that nesting behaviour in mice was not influenced by sex [54,55].

2.2. Behavioural testing

2.2.1. Nest building

Apathetic-like behaviour was measured using behavioural tests of nest building and sucrose preference. To assess nest building, animals were single housed in Makrolon Type III cages (Tecniplast, Milan, Italy) containing corn cob, saw dust bedding, a cardboard tube (DBM Scotland Ltd, UK) and 1 nestlet (50 mm x 50 mm square pressed cotton, DBM Scotland Ltd, UK) prior to the start of the dark cycle. Throughout the testing period, animals were given access to food and water ad libitum. The nest building ability of the mice was scored after a period of 16 h (Day 1), 48 hrs (Day 2) and 168 hrs (Day 7) following the introduction of the nestlet. The scoring of the nests was performed by three independent researchers two of whom were blind to the genotype and mouse strain. We applied the scoring system developed by Deacon [56] which employed a five-point scale (see Fig. 1A for representative images). Briefly, a score of 1 was assigned if the nestlet remained pre-dominantly untouched. If it was partially torn up a score of 2 was given and when the nestlet had been almost entirely shredded although there was no clear nest area a score of 3 was assigned. Only when the nestlet was entirely shredded and a nest area established was a score of either 4 (nest was flat) or 5 (perfect crater shaped nest with walls higher than the body height of the mouse) assigned. The score of the 3 researchers was averaged for each mouse and used for analysis. Additionally, inter-rater reliability between the different raters was calculated for each experiment using the formula:

IRR (inter-rater reliability %) = Total score agreements/(Total ratings*number of raters)*100.

2.2.2. Sucrose preference and spontaneous activity

For the sucrose preference test, animals were housed in activity cages (54 ×50 x 37 cm) (Ugo Basile, Italy). Each activity cage was surrounded by 2 pairs of infra-red (IR) photocell arrays (emitters and detectors) that recorded both horizontal (locomotion) and vertical (rearing) activity of the mice with the upper IR array being positioned ~6 cm above floor level. Movement is registered each time an animal crosses the IR sensors (1 cm distance between sensors) and is recorded via an electronic interface with a thermal printer and the PC based software Win-DAS (Ugo Basile, Gemonio, Italy). Each cage was filled with corn cob bedding and equipped with two water bottles and animals had access to food and water ad libitum throughout testing. Two days following nest building tests, the animals were individually housed in the activity cages and allowed three days of habituation to the cage. After this, one of the water bottles was exchanged for a bottle containing 1% sucrose solution and the weights of the two bottles recorded. The position of the sucrose bottle (left or right) was counterbalanced for animals/groups. After 24 hrs, both bottles were weighed, and the position of the sucrose bottle alternated to avoid any spatial preference. The weights of the two bottles were recorded again after a further 24 hrs and then animals were returned to their home cages. Water and sucrose consumption for each animal was averaged for a 48-hr period and sucrose preference determined as sucrose consumption divided by the total intake of sucrose and water multiplied by 100. In order to control for possible water/sucrose leakage small bags were attached to the bottle holders close to the spouts and used to collect any fluid. Spontaneous locomotor activity and rearing behaviour were also recorded and analysed for the initial 10 min of habituation to the activity cages.
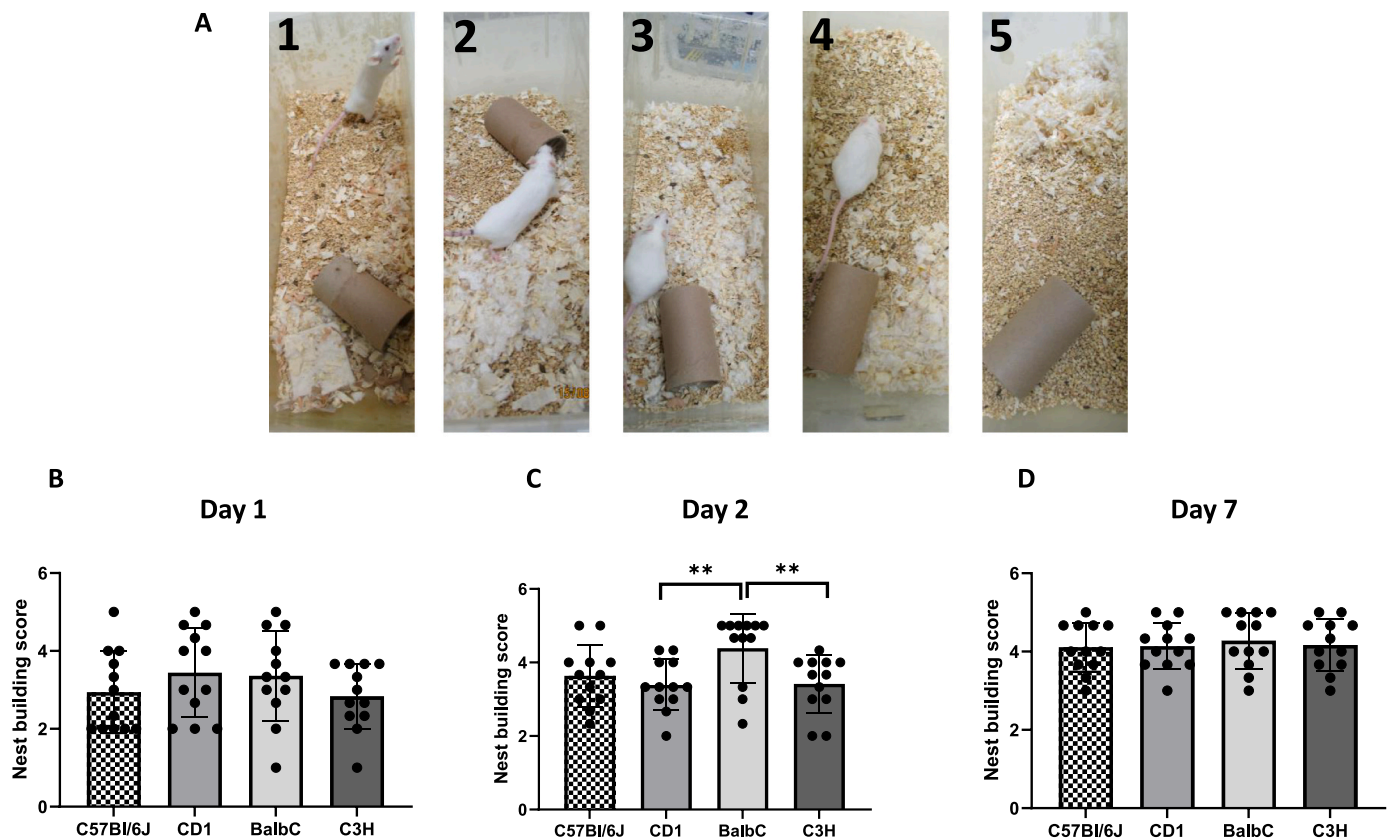

Fig. 1. Nest-building behaviour in four inbred mouse strains. (A) Representative photographs of nest building scoring protocol with a score of 1 – 5 given depending on extent of nestlet shredding and nest construction. A score of 1 indicates the absence of any nestlet shredding whilst 5 depicts a near perfect nest construction (see Methods for further details). (B) Nest-building behaviour on day 1 revealed similar nest building scores for all four mouse strains (C) BALB/c mice displayed a significant improvement in nesting behaviour compared to C3H and CD1 mice. (D) All strains presented with improved nest building performance by day 7 with no differences observed between strains. Bars indicate mean ± SD with scatter of individual data recorded for group members. Kruskal Wallis and Mann Whitney non-parametric tests were used to analyse strain differences across the three testing sessions and asterisks indicate significance of differences: **$p < 0.01$.

2.3. Statistical analysis

All data are expressed as mean ± Standard Deviation (SD). Data from the nest-building tests were analysed using non-parametric tests including Kruskal Wallis and Friedman tests followed by post-hoc and planned comparisons with Mann-Whitney or Wilcoxon tests. Two-way Analysis of Variance (ANOVA) followed by multiple comparison t-tests or one-way ANOVA with appropriate post-hoc t-tests were used for the purpose of sucrose preference and activity analysis. To determine sucrose preference compared to a level of chance, a one-sample t-test was performed with the chance level set at 50%. All statistical analyses were conducted using GraphPad Prism (version 9; GraphPad Software Inc., USA) with a 95% confidence level assumed and alpha set to 5%. Only statistical significances are mentioned in text.

3. Results

3.1. Experiment 1- Nest building as an assessment of apathy in mice

The effectiveness of the nest-building protocol was confirmed using four different inbred strains of mice with the results depicted in Fig. 1B – 1D. Inter-rater reliability (IRR) between the three independent raters for this experiment was 52.78% with IRR between rater pairs ranging from 59.03% to 77.78%. Analysis of nesting behaviour of the different mouse strains across all testing sessions revealed an overall difference in performance (Kruskal-Wallis: $p < 0.0001$). A more in-depth post-hoc analysis confirmed that all strains increased their nest building scores across testing sessions (Wilcoxon matched pairs tests: C57Bl/6 J (Day 1 – Day 2 $p = 0.0039$; Day 1 – Day 7 $p = 0.001$); CD1 (Day 2 – Day 7 $p = 0.0078$); C3H (Day 1 – Day 2 $p = 0.0469$; Day 1 – Day 7 $p = 0.0039$) and BALB/c (Day 1 – Day 2 $p = 0.0078$). A Kruskal-Wallis analysis comparing individual sessions between strains yielded no difference between strains on day 1 (Fig. 1B) or day 7 (Fig. 1D), but a significant difference was evident on day 2 ($p = 0.0265$) (Fig. 1C). Mann-Whitney tests further confirmed that this was mainly due to BALB/c subjects which built near complete nests by day 2, while C3H ($p = 0.0068$) and CD1 ($p = 0.0058$) mice needed longer to achieve high nest-building scores. This finding suggests that different mouse strains may require longer to build nests and that the multiple testing session protocol used in this present study enables identification of these timing differences.

3.2. Experiment 2 – Differential observation of apathy-like behaviour in AD and FTD mouse models

The assessment of nest-building performance in L66 and L1 transgenic mice is summarised in Fig. 2. Inter rater reliability was confirmed as 50.96% and ranged from 54.81% to 83.65% for individual rater pairings. A main effect of genotype was confirmed for scores on days 1 (Figs. 2A) and 2 (Fig. 2B) (Kruskal Wallis: $p = 0.0082$ and $p = 0.0044$) but not day 7 (Fig. 2C), suggesting that a ceiling had been attained. No difference was evident between WT and L1, but L66 presented with lower scores on days 1 and 2. This was confirmed by planned comparison of WT and L66 on both days 1 and 2 (Mann-Whitney tests: day 1 $p = 0.0028$ and day 2 $p = 0.0014$) suggesting a globally lowered propensity for nest building in this bvFTD mouse strain. Findings therefore confirm that L66 mice display lower nest-building performances when faced with a novel environment. This may be interpreted as apathy-like behaviour.

Furthermore, a difference in performance was observed across the tests (Kruskal-Wallis test: ($p < 0.0001$)); all lines increased the quality of their nests over the 7-day observation period. Increases in nest-building scores over days were confirmed for NMRI wild-type mice. This was due mainly to a significant increase from day 2 to day 7 ($p = 0.016$). Similar increases in nesting were revealed in L1 and L66 mice (Friedman tests: L1: $p = 0.0372$; L66: $p = 0.0008$) with Wilcoxon matched pairs tests confirming significant increases in nestbuilding scores from day 1 and 2 to day 7 (all p values <0.05).

We next sought to confirm these conclusions using an anhedonia test of sucrose preference. We reasoned that L66 mice would consume less sucrose containing fluid (Fig. 3A-H). Calculation of the sucrose preference for all three lines yielded a main effect of genotype (one-way ANOVA (F(2,32) = 10.41; $p = 0.0003$) and while L1 mice expressed similar scores to WT subjects, L66 mice were greatly reduced in sucrose preference (compared with WT: $p = 0.0023$; L1: $p = 0.0007$). L66 mice remained at chance (dashed line, Fig. 3A and E) level of 50% indicating the lack of any preference. By contrast a significant preference for the sucrose was evident for both L1 and WT mice ($p = 0.0007$ and $p = 0.002$ respectively). Similar statistical results were obtained for sucrose consumption (Fig. 3B and F) and water intake (Fig. 3C and G). Both proxies confirmed the genotype differences, with L66 drinking less sucrose ($p = 0.005$) and more water ($p = 0.0033$) than WT mice. L1 mice did not differ from WT controls although they displayed an overall tendency to decreased total fluid intake ($p < 0.05$) (Fig. 3D and H). Analysis of performance across the two days of testing confirmed no difference across days. Overall, there was a clear phenotype in anhedonia for L66
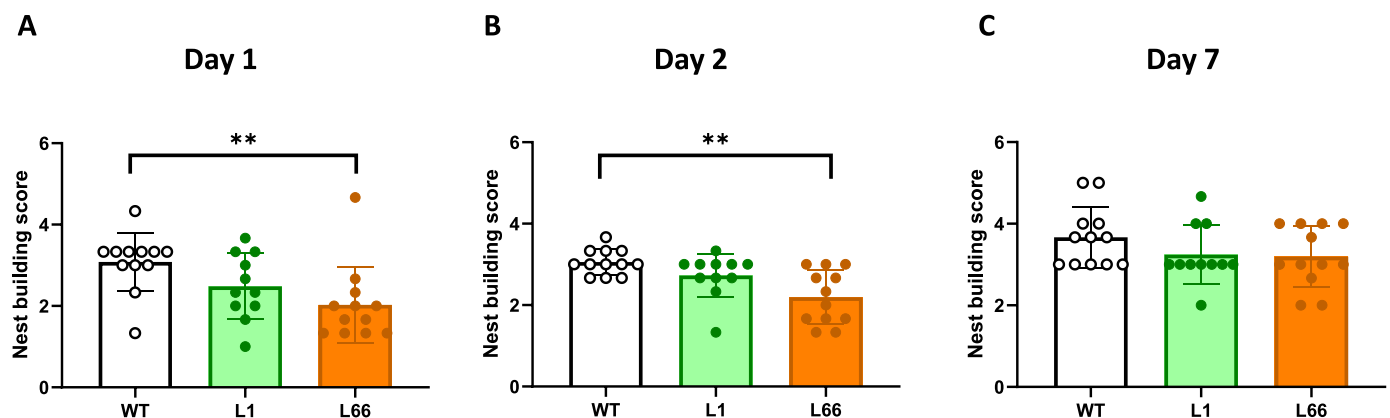

A   **Day 1**   **B**   **Day 2**   **C**   **Day 7**

Fig. 2. Nest-building performance of L1 and L66 mouse models of AD and bvFTD. (A) L66 mice presented with a significantly reduced nest building score compared to WT control animals on day 1; (B) L66 mice continued to display a significantly lower nest building score compared to WT animals on day 2. (C) No significant difference in nest building scores were evident on day 7 when all genotypes displayed a progressive improvement in nest building across days. Bars indicate mean ± SD with scatter of individual data recorded for group members. Kruskal Wallis and Mann Whitney non-parametric tests confirmed statistical differences between strains across the three sessions. Asterisks indicate significance of differences; **$p < 0.01$.
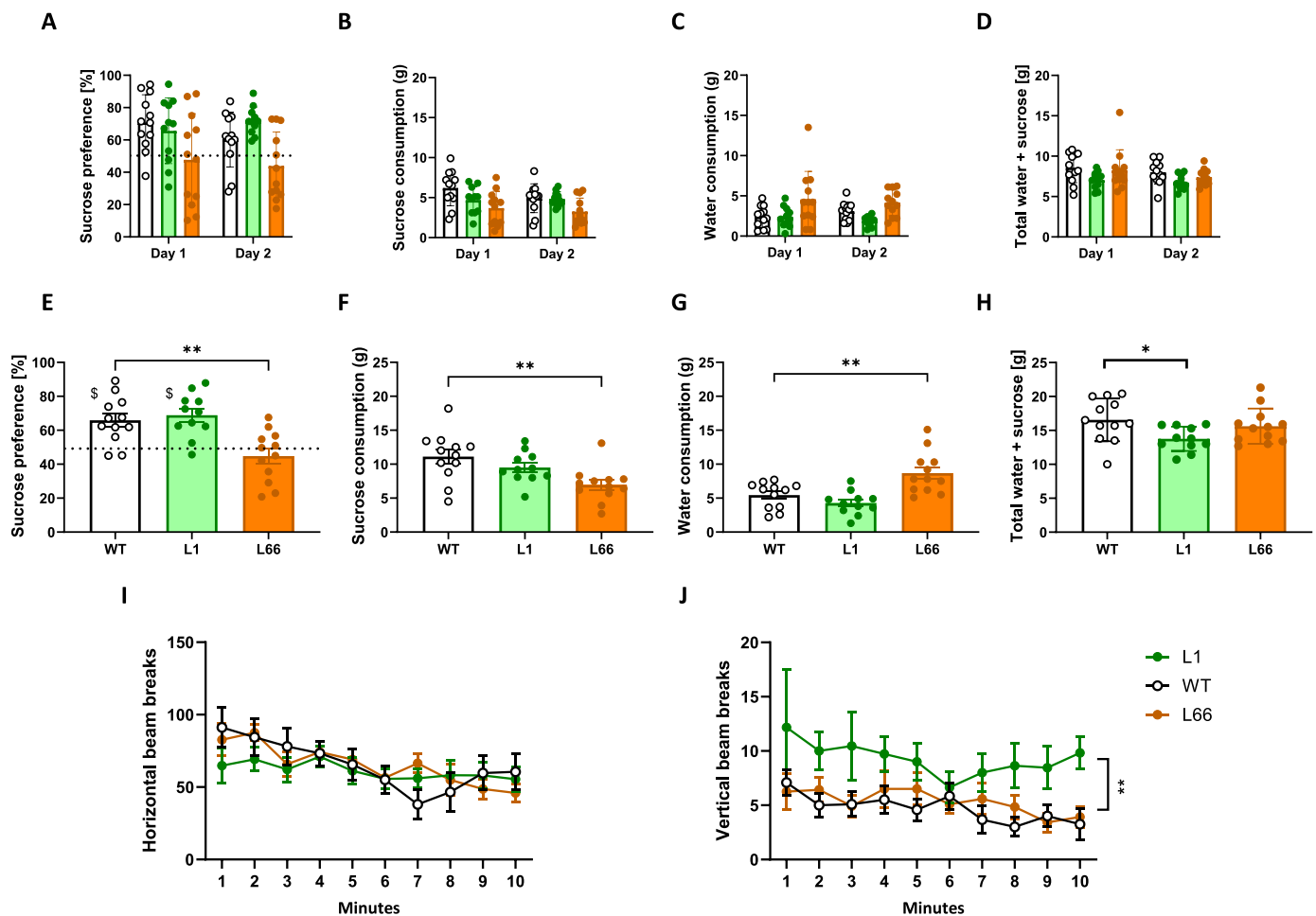
Fig. 3.. Sucrose preference and spontaneous activity in L1 and L66 mice. (A) Comparison between genotypes across days shows a decreased preference for sucrose in L66 animals compared to WT and L1 mice. (B) L66 mice consumed less sucrose solution across the two days of testing and displayed increased water intake (C). (D) L1 mice presented with a tendency for decreased total fluid intake across both days. No significant differences in performance between the two days were observed for any of the parameters. (E) Analysis of overall performance from the two days (average) revealed that L66 mice displayed a significant decrease in preference for sucrose compared to WT and L1 mice and one sample t-tests confirmed that the performance of L66 mice was not significantly different from chance level (50%- see dashed line); (F) L66 consumed significantly less sucrose solution than WT controls and instead consumed increased amounts of water compared to both WT and L1 mice (G). (H) The total fluid intake of L1 mice was significantly decreased compared to WT. Spontaneous activity measured via horizontal (I) and vertical (J) infra-red beam crossings in the activity cages showed no differences in locomotor activity for genotypes. All mice presented with a similar gradual reduction in horizontal activity levels across the 10-minute habituation period. However, L1 mice displayed increased levels of rearing compared to both L66 and WT mice, indicated by a significant increase in vertical beam crossings. Two or one-way ANOVAs followed by appropriate post-hoc t-tests were used to confirm statistical significances between genotypes. Values are expressed as mean ± SD and individual data points of each subject. Asterisks indicate significance of differences; * $p < 0.05$; **$p < 0.01$.

mice adding substance to our interpretation that L66, but not L1 mice, may exhibit increased apathy-like behaviour.

While recording sucrose and water intake, we also monitored vertical and horizontal activity of the mice through two lines of infra-red beams. These data are shown in Fig. 3I and J. Horizontal beam crossings did not differ between genotypes (Fig. 3I) but there was a main effect of time (F(9, 288) = 5.874; $p = 0.0002$) with no interaction between terms. These results confirm similar ambulatory responses of all genotypes which habituate over the 10-minute observation period. By contrast a significant difference between genotypes was observed for vertical IR beam crossings (Fig. 3J (F (2320) = 20.84; $p < 0.0001$), but no time effect or interaction. A planned comparison between individual groups confirmed that rearings were heightened in L1 (F (1,21) = 10.5; $p = 0.0039$), but not L66 mice. The absence of any activity-related anomaly in L66 therefore confirms that the deficits observed in nest building and sucrose preference tests are not due to activity-related deficiencies in these mice.

4. Discussion

4.1. Nest building differs between mouse strains

The main neuropsychiatric symptom that is present in all patients suffering from any type of dementia is apathy [5,6]. It is also one of the main inducers of caregiver stress and subsequent institutionalisation of patients [57,58]. The translation of an interview-based assessment in humans to behavioural assessments in mice might not seem very intuitive and appropriate, but the finding that the self-care subdomain of apathy observed in the clinic can be translated to rodents and assessed via care for their nest and nest building has enabled a measure of apathy-like behaviour in mice [27]. Initially we assessed the effectiveness of the nest-building protocol as a measure of apathy-like behaviour in mice. Using four different inbred strains of mice we established a nest-building protocol with which to assess nesting of mice for up to 7 days. All four strains displayed a progressive increase in nest building over testing sessions. Yet BALB/c mice accomplished this faster than

other strains, especially CD1 and C3H lines. These data validated our protocol for drug and genotype comparisons. Interestingly, all strains (including NMRI WT mice of experiment 2) had the same level of nest building during the first 24 h, suggesting no deficits in any of these 'WT' lines. However, the progress and efficiency in nest building differed and was only revealed through multiple testing times confirming previous work that C3H and CD1 mice are poorer nest builders than BALB/c mice [59,60].

4.2. Differential expression of apathy-like behaviour in bvFTD and AD mouse models

The sucrose/saccharin preference test has previously been utilised to assess anhedonia and depressive-like symptoms. However, the link between the dopaminergic system being involved in preference for sweet solutions [61,62], nest building behaviour [63] and apathy-like symptoms of goal-directed behaviour and hypophagia [64,65] along with its key involvement in the pathology of apathy [66–69] supports the test as a possible measure of apathetic like behaviour in the present and previous studies testing transgenic models of neurodegeneration [48].

Assessment of nest-building behaviour and sucrose preference in L1 and L66 tau transgenic mouse models of AD and bvFTD, respectively, confirmed that L66 mice exhibited reduced nest building and anhedonia, which could be interpreted as apathy-like behaviour. These mice genetically and pathologically seem to mimic elements of human FTD. The difference to L1, which also overexpresses human tau (albeit a different fragment) and shows no deficits in nest building or sucrose preference indicates that the psychotic anomaly of L66 is dependent on the tau species expressed.

Apathy-like behaviour observed in L66 mice in this present study is consistent with observations from other mouse models of bvFTD [36,48, 49,55,70,71]. What these models all have in common are the expression of mutant forms of tau akin to human genetic variants found in FTD, such as htau P301S/P301L/V337M. In addition, tau-related deficits in nest building and sucrose preference have also been reported in 3xTgAD mice [33,72] which could be ameliorated by lowering of the tau pathology but not of the levels of beta amyloid [33].

Therefore, the differences observed between the L1 and other tau mouse models for apathy-like behaviour is most likely accounted for by differences of expression of genetic forms of human tau with the models above all being reminiscent of our L66 model containing FTD-like mutations. Since no tau mutations have been associated with AD, L1 is a unique AD-like model with no apathy phenotype.

Differences in the experimental setup and sex of the mice could account for the different apathy-like behavioural phenotypes observed between the L66 and L1 mouse models in the current study and previous studies. Some groups have reported differences in nest-building behaviour depending on nesting material used, with significant impairments observed in the nesting behaviour of 3xTgAD mice when a paper towel was used as opposed to a cotton nestlet [32] whereas others have determined similar nesting scores independent of material used [33]. Sex differences in nest-building behaviour have also been reported for 3xTgAD; 5xFAD and > 9-month-old P301S mice [28,32,55]. By contrast, others have reported similar deficits in nesting behaviour irrespective of sex [54,55]. Furthermore, studies of apathy-like and motivational behaviours in 3xTgAD and 5xFAD mouse models using different behavioural tasks have reported increased motivational deficits and apathy-like phenotypes in female mice [24,25,73]. This is particularly relevant as only females were used in the current study. The age of animals at time of testing is unlikely to have been a factor as previous studies have used FTD and AD mouse models of a similar age (~6 months) or older (up to 24 months).

4.3. Apathy-like behaviour is not affected by motoric abnormalities of the mice

We have previously reported that L66 mice struggle with motor impairments [52] which can affect their performance in several behavioural tests including the rotarod, balance beam and normal gait using the Catwalk. Motor deficits are common amongst bvFTD models that display deficits in nest building and apathy-like phenotypes [49,55, 70,71,74]. Interestingly, in the current study the L66 mice showed no differences in spontaneous activity and therefore the impairments observed in nest building behaviour and the sucrose preference are unlikely to be a result of aberrant motoric abnormalities in these mice. Furthermore, the absence of a locomotor impairment with L66 mice in the current study suggests that the motor phenotype previously reported with this mouse model could be specific to sensorimotor impairments that primarily affect motor coordination, motor learning and gait [52].

By contrast, hyperactivity was observed in L1 mice. This was specific for vertical beam breaks and L1 mice therefore presented with increased rearings, but not ambulatory activity. Increased rearing behaviour of L1 mice could indicate a more inquisitive nature and increased exploration of the environment. This would be consistent with studies proposing that reduced rearing behaviour is indicative of apathy-like behaviour [24]. The hyperactivity phenotype of L1 is consistent with previous activity measures of this line in the water maze [52] and Barnes maze (unpublished results). Furthermore, heightened levels of activity are a common finding in tau transgenic mice [75–77] and it is also the second most common NPS in AD patients [2,5,6]. Observations of hyperactivity in other transgenic mouse models of AD are however somewhat inconsistent and dependent on experimental settings. Heightened activity seems more likely in the home-cage or a familiar environment (See Kosel [26] for review) than in novel surroundings. The altered activity observed in L1 mice may explain the somewhat reduced fluid intake, but it had no bearing on their sucrose preference.

5. Conclusions

Apathy like behaviour in mice can be assessed using the nest building and sucrose preference tests. We have first implemented a nest-building assay that allows continuous following of the progress of nesting behaviour as an indicator of apathy. It secondly enabled testing of tau transgenic lines akin to AD and FTD with strong phenotypes limited to the FTD/L66 model.

CRediT authorship contribution statement

Lianne Robinson: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Supervision; **Eline Dreesen:** Conceptualization, Methodology, Investigation, Formal analysis, Visualization, Writing – original draft; **Miguel Mondesir:** Investigation; **Charles Harrington:** Funding acquisition, Project administration Writing – review & editing; **Claude Wischik:** Funding acquisition, Project administration; **Gernot Riedel:** Conceptualization, Project administration, Supervision, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

Acknowledgements

(grant PAR1577).

References

[1] J.L. Cummings, The Neuropsychiatric Inventory: assessing psychopathology in dementia patients, Neurology 48 (5 SUPPL. 6) (1997), https://doi.org/10.1212/wnl.48.5_suppl_6.10s.

[2] Q.F. Zhao, L. Tan, H.F. Wang, T. Jiang, M.S. Tan, L. Tan, W. Xu, J.Q. Li, J. Wang, T. J. Lai, J.T. Yu, The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis, J. Affect. Disord. 190 (2016) 264–271, https://doi.org/10.1016/j.jad.2015.09.069.

[3] Y.E. Geda, L.S. Schneider, L.N. Gitlin, D.S. Miller, G.S. Smith, J. Bell, J. Evans, M. Lee, A. Porsteinsson, K.L. Lanctôt, P.B. Rosenberg, D.L. Sultzer, P.T. Francis, H. Brodaty, P.P. Padala, C.U. Onyike, L.A. Ortiz, S. Ancoli-Israel, D.L. Bliwise, J. L. Martin, M.V. Vitiello, K. Yaffe, P.C. Zee, N. Herrmann, R.A. Sweet, C. Ballard, N. A. Khin, C. Cara Alfaro, P.S. Murray, S. Schultz, C.G. Lyketsos, Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future, Alzheimer's Dement. 5 (2013) 602–608, https://doi.org/10.1016/j.jalz.2012.12.001.

[4] K.L. Lanctôt, J. Amatniek, S. Ancoli-Israel, S.E. Arnold, C. Ballard, J. Cohen-Mansfield, Z. Ismail, C. Lyketsos, D.S. Miller, E. Musiek, R.S. Osorio, P. B. Rosenberg, A. Satlin, D. Steffens, P. Tariot, L.J. Bain, M.C. Carrillo, J.A. Hendrix, H. Jurgens, B. Boot, Neuropsychiatric signs and symptoms of Alzheimer's disease: new treatment paradigms, Alzheimer's Dement.: Transl. Res. Clin. Interv. 3 (3) (2017) 440–449, https://doi.org/10.1016/j.trci.2017.07.001.

[5] P. Aalten, F.R.J. Verhey, M. Boziki, R. Bullock, E.J. Byrne, V. Camus, M. Caputo, D. Collins, P.P. De Deyn, K. Elina, G. Frisoni, N. Girtler, C. Holmes, C. Hurt, A. Marriott, P. Mecocci, F. Nobili, P.J. Ousset, E. Reynish, E. Salmon, M. Tsolaki, B. Vellas, P.H. Robert, Neuropsychiatric syndromes in dementia: results from the European Alzheimer disease consortium: part I, Dement. Geriatr. Cogn. Disord. 24 (6) (2007) 457–463, https://doi.org/10.1159/000110738.

[6] P. Aalten, F.R.J. Verhey, M. Boziki, A. Brugnolo, R. Bullock, E.J. Byrne, V. Camus, M. Caputo, D. Collins, P.P. De Deyn, K. Elina, G. Frisoni, C. Holmes, C. Hurt, A. Marriott, P. Mecocci, F. Nobili, P.J. Ousset, E. Reynish, E. Salmon, M. Tsolaki, B. Vellas, P.H. Robert, Consistency of neuropsychiatric syndromes across dementias: results from the European Alzheimer disease consortium – part II, Dement. Geriatr. Cogn. Disord. 25 (1) (2007) 1–8, https://doi.org/10.1159/000111082.

[7] G.C. Léger, S.J. Banks, Neuropsychiatric symptom profile differs based on pathology in patients with clinically diagnosed behavioral variant frontotemporal dementia, Dement. Geriatr. Cogn. Disord. 37 (1–2) (2014) 104–112, https://doi.org/10.1159/000354368.

[8] J.L. Mathias, K. Morphett, Neurobehavioral differences between Alzheimer's disease and frontotemporal dementia: a meta-analysis, J. Clin. Exp. Neuropsychol. 32 (7) (2010) 682–698, https://doi.org/10.1080/13803390903427414.

[9] K.G. Yiannopoulou, J.D. Papatriantafyllou, A. Ghika, N. Tsinia, E. Lykou, E. Hatziantoniou, D. Agiomyrgiannakis, A. Kyrozis, S.G. Papageorgiou, Defining Neuropsychiatric inventory scale differences across frontotemporal dementia syndromes, Psychogeriatrics 19 (1) (2019) 32–37, https://doi.org/10.1111/psyg.12358.

[10] S.J. Webster, A.D. Bachstetter, P.T. Nelson, F.A. Schmitt, L.J. Van Eldik, Using mice to model Alzheimer's dementia: an overview of the clinical disease and the preclinical behavioral changes in 10 mouse models, References 214, Front. Genet. 5 (APR) (2014) 1–23, https://doi.org/10.3389/fgene.2014.00088.

[11] P. Robert, C.U. Onyike, A.F. Leentjens, K. Dujardin, P. Aalten, S. Starkstein, F. R. Verhey, J. Yessavage, J.P. Clement, D. Drapier, F. Bayle, M. Benoit, P. Boyer, P. M. Lorca, F. Thibaut, S. Gauthier, G. Grossberg, B. Vellas, J. Byrne, Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders, Eur. Psychiatry 24 (2) (2009) 98–104, https://doi.org/10.1016/j.eurpsy.2008.09.001.

[12] G.K. Wilcock, S. Gauthier, G.B. Frisoni, J. Jia, J.H. Hardlund, H.J. Moebius, P. Bentham, K.A. Kook, B.O. Schelter, D.J. Wischik, C.S. Davis, R.T. Staff, V. Vuksanovic, T. Ahearn, L. Bracoud, K. Shamsi, K. Marek, J. Seibyl, G. Riedel, J. M.D. Storey, C.R. Harrington, C.M. Wischik, Potential of low dose Leuco-Methylthioninium Bis(Hydromethanesulphonate) (LMTM) monotherapy for treatment of mild Alzheimer's disease: cohort analysis as modified primary outcome in a phase III clinical trial, J. Alzheimer's Dis. 61 (1) (2018) 435–457, https://doi.org/10.3233/JAD-170560.

[13] M. Malpetti, P.S. Jones, K.A. Tsvetanov, T. Rittman, J.C. van Swieten, B. Borroni, R. Sanchez-Valle, F. Moreno, R. Laforce, C. Graff, M. Synofzik, D. Galimberti, M. Masellis, M.C. Tartaglia, E. Finger, R. Vandenberghe, A. de Mendonça, F. Tagliavini, I. Santana, S. Ducharme, C.R. Butler, A. Gerhard, J. Levin, A. Danek, M. Otto, G.B. Frisoni, R. Ghidoni, S. Sorbi, C. Heller, E.G. Todd, M. Bocchetta, D. M. Cash, R.S. Convery, G. Peakman, K.M. Moore, J.D. Rohrer, R.A. Kievit, J. B. Rowe, Genetic FTD Initiative (GENFI). Apathy in presymptomatic genetic frontotemporal dementia predicts cognitive decline and is driven by structural brain changes, Alzheimers Dement 17 (6) (2020) 969–983, https://doi.org/10.1002/alz.12252.

[14] R.S. Marin, Differential diagnosis and classification of apathy, Am. J. Psychiatry 147 (1) (1990) 22–30, https://doi.org/10.1176/ajp.147.1.22.

[15] R.S. Marin, Apathy: a neuropsychiatric syndrome, J. Neuropsychiatry Clin. Neurosci. 3 (1991) 243–254, https://doi.org/10.1176/jnp.3.3.243.

[16] P. Robert, K.L. Lanctôt, L. Agüera-Ortiz, P. Aalten, F. Bremond, M. Defrancesco, C. Hanon, R. David, B. Dubois, K. Dujardin, M. Husain, A. König, R. Levy, V. Mantua, D. Meulien, D. Miller, H.J. Moebius, J. Rasmussen, G. Robert,

M. Ruthirakuhan, F. Stella, J. Yesavage, R. Zeghari, V. Manera, Is it time to revise the diagnostic criteria for apathy in brain disorders? The 2018 international consensus group, Eur. Psychiatry 54 (2018) 71–76, https://doi.org/10.1016/j.eurpsy.2018.07.008.

[17] D.S. Miller, P. Robert, L. Ereshefsky, L. Adler, D. Bateman, J. Cummings, S. T. DeKosky, C.E. Fischer, M. Husain, Z. Ismail, J. Jaeger, A.J. Lerner, A. Li, C. G. Lyketsos, V. Manera, J. Mintzer, H.J. Moebius, M. Mortby, D. Meulien, S. Pollentier, A. Porsteinsson, J. Rasmussen, P.B. Rosenberg, M.T. Ruthirakuhan, M. Sano, S.C. Zucchero, K.L. Lanctôt, Diagnostic criteria for apathy in neurocognitive disorders, Alzheimers Dement 17 (12) (2021) 1892–1904, https://doi.org/10.1002/alz.12358.

[18] I.T. Kurniawan, M. Guitart-Masip, R.J. Dolan, Dopamine and effort-based decision making, Front. Neurosci. 5 (2011) 81, https://doi.org/10.3389/fnins.2011.00081.

[19] J.D. Salamone, I. Koychev, M. Correa, P. McGuire, Neurobiological basis of motivational deficits in psychopathology, Eur. Neuropsychopharmacol. 25 (8) (2015) 1225–1238, https://doi.org/10.1016/j.euroneuro.2014.08.014.

[20] J.D. Salamone, S.E. Yohn, L. López-Cruz, N. San Miguel, M. Correa, Activational and effort-related aspects of motivation: neural mechanisms and implications for psychopathology, Brain 139 (Pt 5) (2016) 1325–1347, https://doi.org/10.1093/brain/aww050.

[21] J.D. Salamone, M. Correa, S. Ferrigno, J.H. Yang, R.A. Rotolo, R.E. Presby, The psychopharmacology of effort-related decision making: dopamine adenosine and insights into the neurochemistry of motivation, Pharmacol. Rev. 70 (4) (2018) 747–762, https://doi.org/10.1124/pr.117.015107.

[22] J.D. Salamone, M. Correa, J.H. Yang, R. Rotolo, R. Presby, Dopamine, effort-based choice, and behavioral economics: basic and translational research, Front. Behav. Neurosci. 12 (2018) 52, https://doi.org/10.3389/fnbeh.2018.00052.

[23] R. Pardossi-Piquard, I. Lauritzen, C. Bauer, G. Sacco, P. Robert, F. Checler, Influence of genetic background on apathy-like behavior in triple transgenic AD mice, Curr. Alzheimer Res. 13 (8) (2016) 942–949, https://doi.org/10.2174/1567205013666160404120106.

[24] A. Bourgeois, I. Lauritzen, T. Lorivel, C. Bauer, F. Checler, R. Pardossi-Piquard, Intraneuronal accumulation of C99 contributes to synaptic alterations, apathy-like behavior, and spatial learning deficits in 3×TgAD and 2×TgAD mice, Neurobiol. Aging 71 (2018) 21–31, https://doi.org/10.1016/j.neurobiolaging.2018.06.038.

[25] E. Fertan, A.A. Wong, N.A. Vienneau, R.E. Brown, Age and sex differences in motivation and spatial working memory in 3xTg-AD mice in the Hebb-Williams maze, Behav. Brain Res. 370 (2019), 111937, https://doi.org/10.1016/j.bbr.2019.111937.

[26] F. Kosel, J.M.S. Pelley, T.B. Franklin, Behavioural and psychological symptoms of dementia in mouse models of Alzheimer's disease-related pathology, Neurosci. Biobehav Rev. 112 (2020) 634–647, https://doi.org/10.1016/j.neubiorev.2020.02.012.

[27] F. Cathomas, M.N. Hartmann, E. Seifritz, C.R. Pryce, S. Kaiser, The translational study of apathy—An ecological approach, Front. Behav. Neurosci. 9 (September) (2015) 1–7, https://doi.org/10.3389/fnbeh.2015.00241.

[28] R. Keszycki, G. Rodriguez, J.T. Dunn, A. Locci, H. Orellana, I. Haupfear, S. Dominguez, D.W. Fisher, H. Dong, Characterization of apathy-like behaviors in the 5xFAD mouse model of Alzheimer's disease, Neurobiol. Aging 126 (2023) 113–122, https://doi.org/10.1016/j.neurobiolaging.2023.02.012. PMID: 36989547; PMCID: PMC10106415.

[29] Si Y., Guo C., Xiao F., Mei B., Meng B. (2021) Noncognitive species-typical and home-cage behavioral alterations in conditional presenilin 1/presenilin 2 double knockout mice. Behav Brain Res. Feb 10; 418:113652. Doi: 10.1016/j.bbr.2021.113652. PMID: 34758364.

[30] R. Deacon, Assessing burrowing, nest construction, and hoarding in mice, J. Vis. Exp. 59 (2012) 1–10, https://doi.org/10.3791/260.

[31] L. Yan, L. Li, W. Han, B. Pan, X. Xue, B. Mei, Age-related neuropsychiatric symptoms in presenilins conditional double knockout mice, Brain Res. Bull. 97 (2013) 104–111, https://doi.org/10.1016/j.brainresbull.2013.06.002.

[32] V. Torres-Lista, L. Giménez-Llort, Impairment of nesting behaviour in 3xTg-AD mice, Behav. Brain Res. 247 (2013) 153–157, https://doi.org/10.1016/j.bbr.2013.03.021.

[33] A. Van Der Jeugd, A. Parra-Damas, R. Baeta-Corral, C.M. Soto-Faguás, T. Ahmed, F. M. Laferla, L. Giménez-Llort, R. D'Hooge, C.A. Saura, Reversal of memory and neuropsychiatric symptoms and reduced tau pathology by selenium in 3xTg-AD mice, Sci. Rep. 8 (1) (2018) 1–12, https://doi.org/10.1038/s41598-018-24741-0.

[34] J.M. Walker, D. Klakotskaia, D. Ajit, G.A. Weisman, W.G. Wood, G.Y. Sun, P. Serfozo, A. Simonyi, T.R. Schachtman, Beneficial effects of dietary EGCG and voluntary exercise on behavior in an Alzheimer's disease mouse model, J. Alzheimer's Dis. 44 (2) (2015) 561–572, https://doi.org/10.3233/JAD-140981.

[35] M. Filali, R. Lalonde, Age-related cognitive decline and nesting behavior in an APPswe/PS1 bigenic model of Alzheimer's disease, Brain Res. 1292 (2009) 93–99, https://doi.org/10.1016/j.brainres.2009.07.066.

[36] B.A. Warmus, D.R. Sekar, E. McCutchen, G.D. Schellenberg, R.C. Roberts, L. L. McMahon, E.D. Roberson, Tau-mediated NMDA receptor impairment underlies dysfunction of a selectively vulnerable network in a mouse model of frontotemporal dementia, J. Neurosci. 34 (49) (2014) 16482–16495, https://doi.org/10.1523/JNEUROSCI.3418-14.2014.

[37] R.M. Ahmed, M. Irish, J. van Eersel, A. Ittner, Y.D. Ke, A. Volkerling, J. van der Hoven, K. Tanaka, T. Karl, M. Kassiou, J.J. Kril, O. Piguet, J.J. Götz, M.C. Kiernan, G. M. Halliday, J.R. Hodges, L.M. Ittner, Mouse models of frontotemporal dementia: a comparison of phenotypes with clinical symptomatology, Neurosci. Biobehav. Rev. 74 (2017) 126–138, https://doi.org/10.1016/j.neubiorev.2017.01.004.

[38] P. Willner, R. Muscat, M. Papp, Chronic mild stress-induced anhedonia: a realistic animal model of depression, Neurosci. Biobehav. Rev. 16 (4) (1992) 525–534, https://doi.org/10.1016/s0149-7634(05)80194-0.

[39] S. Scheggi, M.G. De Montis, C. Gambarana, Making sense of rodent models of anhedonia, 1049-0, Int. J. Neuropsychopharmacol. 21 (11) (2018), https://doi.org/10.1093/ijnp/pyy083.

[40] D.A. Pizzagalli, Depression stress and anhedonia: toward a synthesis and integrated model, Annu. Rev. Clin. Psychol. 10 (2014) 393–423, https://doi.org/10.1146/annurev-clinpsy-050212-185606. PMID: 24471371; PMCID: PMC3972338.

[41] M.Y. Liu, C.Y. Yin, L.J. Zhu, X.H. Zhu, C. Xu, C.X. Luo, H. Chen, D.Y. Zhu, Q. G. Zhou, Sucrose preference test for measurement of stress-induced anhedonia in mice, Nat. Protoc. Jul. 13 (7) (2018) 1686–1698, https://doi.org/10.1038/s41596-018-0011-z.

[42] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 5th ed.,, American Psychiatric Association,, 2013.

[43] J.P.H. Verharen, J.W. de Jong, Y. Zhu, S. Lammel, A computational analysis of mouse behavior in the sucrose preference test, Apr 27, Nat. Commun. 14 (1) (2023) 2419, https://doi.org/10.1038/s41467-023-38028-0. PMID: 37105954; PMCID: PMC4100068..

[44] K.C. Berridge, T.E. Robinson, J.W. Aldridge, Dissecting components of reward: 'liking', 'wanting', and learning (Feb), Curr. Opin. Pharmacol. 9 (1) (2009) 65–73, https://doi.org/10.1016/j.coph.2008.12.014.

[45] K.L. Lanctôt, Z. Ismail, K.K. Bawa, J.L. Cummings, M. Husain, M.E. Mortby, P. Robert, Distinguishing apathy from depression: a review differentiating the behavioral neuroanatomic and treatment-related aspects of apathy from depression in neurocognitive disorders (Feb), Int. J. Geriatr. Psychiatry 38 (2) (2023), e5882, https://doi.org/10.1002/gps.5882.

[46] A. Matynia, C.H. Ng, W. Dansithong, A. Chiang, A.J. Silva, S. Reddy, Muscleblind1, but not Dmpk or Six5, contributes to a complex phenotype of muscular and motivational deficits in mouse models of myotonic dystrophy, Mar 25, PLoS One 5 (3) (2010), e9857, https://doi.org/10.1371/journal.pone.0009857. PMID: 20360842; PMCID: PMC2845609..

[47] A. Romano, L. Pace, B. Tempesta, A.M. Lavecchia, T. Macheda, G. Bedse, A. Petrella, C. Cifani, G. Serviddio, G. Vendemiale, S. Gaetani, T. Cassano, Depressive-like behavior is paired to monoaminergic alteration in a murine model of Alzheimer's disease, pyu020, Int. J. Neuropsychopharmacol. 18 (4) (2014), https://doi.org/10.1093/ijnp/pyu020.

[48] D.J. Koss, L. Robinson, B.D. Drever, K. Plucińska, S. Stoppelkamp, P. Veselcic, G. Riedel, B. Platt, Mutant tau knock-in mice display frontotemporal dementia relevant behaviour and histopathology, Neurobiol. Dis. 91 (2016) 105–123, https://doi.org/10.1016/j.nbd.2016.03.002.

[49] A. Van der Jeugd, D. Blum, S. Raison, S. Eddarkaoui, L. Buée, R. D'Hooge, Observations in THY-tau22 mice that resemble behavioral and psychological signs and symptoms of dementia, Behav. Brain Res. 242 (2013) 34–39, https://doi.org/10.1016/j.bbr.2012.12.008.

[50] E. Vloeberghs, D. Van Dam, F. Franck, M. Staufenbiel, P.P. De Deyn, Mood and male sexual behaviour in the APP23 model of Alzheimer's disease, Behav. Brain Res. 180 (2) (2007) 146–151, https://doi.org/10.1016/j.bbr.2007.03.002. Mar 12.

[51] A. Pfeffer, T. Munder, S. Schreyer, C. Klein, J. Rasińska, Y. Winter, B. Steiner, Behavioral and psychological symptoms of dementia (BPSD) and impaired cognition reflect unsuccessful neuronal compensation in the pre-plaque stage and serve as early markers for Alzheimer's disease in the APP23 mouse model, Behav. Brain Res. 347 (2018) 300–313, https://doi.org/10.1016/j.bbr.2018.03.030.

[52] V. Melis, C. Zabke, K. Stamer, M. Magbagbeolu, K. Schwab, P. Marschall, R.W. Veh, S. Bachmann, S. Deiana, P.H. Moreau, K. Davidson, K.A. Harrington, J.E. Rickard, D. Horsley, R. Garman, M. Mazurkiewicz, G. Niewiadomska, C.M. Wischik, C. R. Harrington, G. Riedel, F. Theuring, Different pathways of molecular pathophysiology underlie cognitive and motor tauopathy phenotypes in transgenic models for Alzheimer's disease and frontotemporal lobar degeneration, Cell. Mol. Life Sci. 72 (11) (2015) 2199–2222, https://doi.org/10.1007/s00018-014-1804-z.

[53] N. Percie du Sert, A. Ahluwalia, S. Alam, M.T. Avey, M. Baker, W.J. Browne, A. Clark, I.C. Cuthill, U. Dirnagl, M. Emerson, P. Garner, S.T. Holgate, D. W. Howells, N.A. Karp, S.E. Lazic, K. Lidster, C.J. MacCallum, M. Macleod, E. J. Pearl, O.H. Petersen, F. Rawle, P. Reynolds, K. Rooney, E.S. Sena, S. D. Silberberg, T. Steckler, H. Wurbel, Reporting animal research: explanation and elaboration for the ARRIVE guidelines 2.0, PLoS Biol. 18 (7) (2020), e3000411 https://doi.org/10.1371/journal.pbio.3000411.

[54] J.M. Walker, S. Dixit, A.C. Saulsberry, J.M. May, F.E. Harrison, Reversal of high fat diet-induced obesity improves glucose tolerance inflammatory response β-amyloid accumulation and cognitive decline in the APP/PSEN1 mouse model of Alzheimer's disease, Neurobiol. Dis. 100 (2017) 87–98, https://doi.org/10.1016/j.nbd.2017.01.004.

[55] Y. Sun, Y. Guo, X. Feng, M. Jia, N. Ai, Y. Dong, Y. Zheng, L. Fu, B. Yu, H. Zhang, J. Wu, X. Yu, H. Wu, W. Kong, The behavioural and neuropathologic sexual dimorphism and absence of MIP-3α in tau P301S mouse model of Alzheimer's disease, J. Neuroinflamm. 17 (1) (2020) 72, https://doi.org/10.1186/s12974-020-01749-w.

[56] R.M.J. Deacon, Assessing nest building in mice, Nat. Protoc. 1 (2006) 1117–1119.

[57] M.E. De Vugt, S.R. Riedijk, P. Aalten, A. Tibben, J.C. van Swieten, F.R. Verhey, Impact of behavioural problems on spousal caregivers: a comparison between Alzheimer's disease and frontotemporal dementia, Dement Geriatr. Cogn. Disord. 22 (1) (2006) 35–41, https://doi.org/10.1159/000093102.

[58] I. Leroi, V. Harbishettar, M. Andrews, K. McDonald, E.J. Byrne, A. Burns, Carer burden in apathy and impulse control disorders in Parkinson's disease, Int. J. Geriatr. Psychiatry 27 (2) (2012) 160–166, https://doi.org/10.1002/gps.2704.

[59] M.L. Rock, A.Z. Karas, K.B. Rodriguez, M.S. Gallo, K. Pritchett-Corning, R.H. Karas, M. Aronovitz, B.N. Gaskill, The time-to-integrate-to-nest test as an indicator of wellbeing in laboratory mice, J. Am. Assoc. Lab Anim. Sci. 53 (1) (2014) 24–28.

[60] B.N. Gaskill, K.R. Pritchett-Corning, C.J. Gordon, E.A. Pajor, J.R. Lucas, J.K. Davis, J.P. Garner, Energy reallocation to breeding performance through improved nest building in laboratory mice, PLoS ONE 8 (9) (2013), e74153, https://doi.org/10.1371/journal.pone.0074153.

[61] J.C. Brenes, J. Fornaguera, Effects of environmental enrichment and social isolation on sucrose consumption and preference: associations with depressive-like behavior and ventral striatum dopamine, Neurosci. Lett. 436 (2) (2008) 278–282, https://doi.org/10.1016/j.neulet.2008.03.045.

[62] E. Malatynska, H.W.M. Steinbusch, O. Redkozubova, A. Bolkunov, A. Kubatiev, N. B. Yeritsyan, J. Vignisse, S. Bachurin, T. Strekalova, Anhedonic- like traits and lack of affective deficits in 18-month-old C57BL/6 mice: implications for modeling elderly depression, Exp. Gerontol. 47 (2012) 552–564, https://doi.org/10.1016/j.exger.2012.04.010.

[63] M.S. Szczypka, K. Kwok, M.D. Brot, B.T. Marck, A.M. Matsumoto, B.A. Donahue, et al., Dopamine production in the caudate putamen restores feeding in dopamine-deficient mice, Neuron 30 (2001) 819–828, https://doi.org/10.1016/s0896-6273(01)00319-1.

[64] Y.B. Kim, M. Matthews, B. Moghaddam, Putative γ-aminobutyric acid neurons in the ventral tegmental area have a similar pattern of plasticity as dopamine neurons during appetitive and aversive learning, Eur. J. Neurosci. 32 (9) (2010) 1564–1572, https://doi.org/10.1111/j.1460-9568.2010.07371.x.

[65] I. Tsutsui-Kimura, H. Takiue, K. Yoshida, M. Xu, R. Yano, H. Ohta, H. Nishida, Y. Bouchekioua, H. Okano, M. Uchigashima, M. Watanabe, N. Takata, M.R. Drew, H. Sano, M. Mimura, K.F. Tanaka, Dysfunction of ventrolateral striatal dopamine receptor type 2-expressing medium spiny neurons impairs instrumental motivation, Nat. Commun. 8 (2017) 14304, https://doi.org/10.1038/ncomms14304.

[66] A. Baumann, C.G. Moreira, M.M. Morawska, S. Masneuf, C.R. Baumann, D. Noain, Preliminary evidence of apathetic-like behavior in aged vesicular monoamine transporter 2 deficient mice, Front. Hum. Neurosci. 10 (NOV2016) (2016) 1–10, https://doi.org/10.3389/fnhum.2016.00587.

[67] L.B. Zahodne, M. Marsiske, M.S. Okun, R.L. Rodriguez, I. Malaty, D. Bowers, Mood, and motor trajectories in Parkinson's disease: multivariate latent growth curve modelling, Neuropsychology 26 (1) (2012) 71–80, https://doi.org/10.1037/a0025119.

[68] K.F. Pedersen, G. Alves, D. Aarsland, J.P. Larsen, Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study, J. Neurol. Neurosurg. Psychiatry 80 (2009) 1279–1282, https://doi.org/10.1136/jnnp.2008.170043.

[69] K.F. Pedersen, J.P. Larsen, G. Alves, D. Aarsland, Prevalence and clinical correlates of apathy in Parkinson's disease: a community-based study, Park. Relat. Disord. 15 (2009) 295–299, https://doi.org/10.1016/j.parkreldis.2008.07.006.

[70] H. Koivisto, E. Ytebrouck, S. Carmans, R. Naderi, P.O. Miettinen, B. Roucourt, H. Tanila, Progressive age-dependent motor impairment in human tau P301S overexpressing mice, Behav. Brain Res. 376 (2019), 112158, https://doi.org/10.1016/j.bbr.2019.112158.

[71] K.M. Craven, W.R. Kochen, C.M. Hernandez, J.M. Flinn, Zinc Exacerbates tau Pathology in a tau Mouse Model, J. Alzheimers Dis. 64 (2) (2018) 617–630, https://doi.org/10.3233/JAD-180151.

[72] D. Lambracht-Washington, M. Fu, L.S. Hynan, R.N. Rosenberg, Changes in the brain transcriptome after DNA Aβ42 trimer immunization in a 3xTg-AD mouse model, Neurobiol. Dis. 148 (2021), 105221, https://doi.org/10.1016/j.nbd.2020.105221.

[73] E. Gür, E. Fertan, F. Kosel, A.A. Wong, F. Balcı, R.E. Brown, Sex differences in the timing behavior performance of 3xTg-AD and wild-type mice in the peak interval procedure, Behav. Brain Res. 360 (2019) 235–243, https://doi.org/10.1016/j.bbr.2018.11.047.

[74] P. Jul, C. Volbracht, I.E. de Jong, L. Helboe, A.B. Elvang, J.T. Pedersen, Hyperactivity with agitative-like behavior in a mouse tauopathy model, J. Alzheimers Dis. 49 (2016) 783–795.

[75] L. Pennanen, D.P. Wolfer, R.M. Nitsch, J. Götz, Impaired spatial reference memory and increased exploratory behavior in P301L tau transgenic mice, Genes Brain Behav. 5 (5) (2006) 369–379, https://doi.org/10.1111/j.1601-183X.2005.00165.x.

[76] M.L. Scattoni, L. Gasparini, E. Alleva, M. Goedert, G. Calamandrei, M.G. Spillantini, Early behavioural markers of disease in P301S tau transgenic mice, Behav. Brain Res. 208 (1) (2010) 250–257, https://doi.org/10.1016/j.bbr.2009.12.002.

[77] K. Tanemura, M. Murayama, T. Akagi, T. Hashikawa, T. Tominaga, M. Ichikawa, H. Yamaguchi, A. Takashima, Neurodegeneration with tau accumulation in a transgenic mouse expressing V337M human tau, J. Neurosci. 22 (1) (2002) 133–141, https://doi.org/10.1523/JNEUROSCI.22-01-00133.2002. PMID: 11756496; PMCID: PMC6757582.