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Longitudinal assessment of cognitive function in the APPswe/PS1dE9 mouse model of Alzheimer's-related beta-amyloidosis

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ABSTRACT

Preclinical models of Alzheimer's disease (AD)-related cognitive decline can be useful for developing therapeutics. The current study longitudinally assessed short-term memory, using a delayed matching-to-position (DMTP) task, and attention, using a 3-choice serial reaction time (3CSRT) task, from approximately 18 weeks of age through death or 72 weeks of age in APPswe/PS1dE9 mice, a widely used mouse model of AD-related amyloidosis. Both transgenic (Tg) and non-Tg mice exhibited improvements in DMTP accuracy over time. Breaks in testing reduced DMTP accuracy but accuracy values quickly recovered in both Tg and non-Tg mice. Both Tg and non-Tg mice exhibited high accuracy in the 3CSRT task with breaks in testing briefly reducing accuracy values equivalently in the 2 genotypes. The current results raise the possibility that deficits in Tg APPswe/PS1dE9 mice involve impairments in learning rather than declines in established performances. A better understanding of the factors that determine whether deficits develop will be useful for designing evaluations of potential pharmacotherapeutics and may reveal interventions for clinical application.

1. Introduction

Alzheimer's disease (AD) is a devastating progressive neurological disorder that leads to progressive cognitive impairment, substantially reduces the quality of life, and is a costly societal problem. The early symptoms of the disease involve difficulties remembering recent events (i.e., short-term memory) and problems in attention, which may contribute to problems with memory (Galvin et al., 2008; Gorus et al., 2006; Perry and Hodges, 1999; Perry et al., 2000; Pignatti et al., 2005) and eventually problems include difficulty speaking and thinking that progress to dementia (Petersen et al., 1999; Rebok et al., 1990). The direct care costs of AD and other dementias in 2022 were expected to reach $321 billion, which does not include the costs of informal caregiving (Alzheimer's Association, 2022).

Preclinical research using animal models of AD-associated neuropathology and related cognitive decline holds promise for the identification of potential therapeutics for AD-associated cognitive deficits. Typically, in preclinical studies using AD transgenic (Tg) mice, cognitive assessments involve the use of maze procedures that are conducted over a brief period of time in the life of an animal (e.g., Arendash et al., 2001; Blanchard et al., 2011; Chen et al., 2000; Dodart et al., 1999; Hsiao et al., 1996; Hulshof et al., 2022; Kim et al., 2012; King and Arendash, 2002; Kotilinek et al., 2002; Reiserer et al., 2007; Savonenko et al., 2005; Watanabe et al., 2009; Westerman et al., 2002). Fewer preclinical studies in AD Tg mice have used operant, food-reinforced procedures. There are at least 3 benefits of such tasks: (1) they are suitable for repeated within-subject testing that allows for multiple-dose screening of potential pharmacotherapeutics; (2) they allow within-session manipulation of variables

Abbreviations: 3CSRT, 3-choice serial reaction time; AD, Alzheimer's disease; APP, amyloid precursor protein; DMTP, delayed matching-to-position; ITI, intertrial interval; LH, limited hold; PS1, presenilin 1; PSI, pre-stimulus interval; Tg, transgenic; TO, timeout

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that affect performance (e.g., delay, stimulus duration, inter-trial interval durations) providing a more detailed characterization of the cognitive deficits profile and therefore a more detailed characterization of benefits of potential pharmacotherapeutics; and (3) data collection is automated and multiple animals can be tested simultaneously.

The current study used a longitudinal design to evaluate changes in cognitive function over time in a widely-used mouse model of amyloidosis, APPswe/PS1dE9 (APP/PS1 hereafter) mice, which reproduce important features of AD including elevated levels of amyloid-beta (Aβ) (particularly the more amyloidogenic β1-42 peptide), neuritic plaques, reductions in neurotransmitter markers, death of some neuronal populations, and age-related cognitive impairments (Borchelt et al., 1997; Jankowsky et al., 2004; Liu et al., 2008; Savonenko et al., 2005). We used an operant delayed matching-to-position (DMTP) task to assess short-term memory and an operant 3-choice serial reaction time (3CSRT) task (Tsutsui-Kimura et al., 2009), modeled after the popular 5CSRT task (Robbins, 2002), to assess attention. Both tasks are modeled on human tasks shown to be sensitive to mild cognitive impairment or AD-associated cognitive impairment (Fowler et al., 1997; Lee et al., 2003; Levinoff et al., 2005; Sahakian et al., 1988; Swainson et al., 2001; White and Ruske, 2002). Further, age- and delay-dependent deficits in accuracy in the DMTP procedure have been reported in another mouse model of amyloidosis (Woolley and Ballard, 2005), although in that study mice were only tested briefly every 2–4 months.

Based on the assumption that developing Aβ depositions would lead to declines in cognitive function like those observed in AD, we expected that accuracy in the DMTP and 3CSRT procedures would decline with age in the Tg mice and that declines in accuracy in the Tg mice would be greater under conditions previously shown to impact accuracy (e.g., delay in the DMTP task and stimulus duration in the 3CSRT). Finally, to address the possibility of repeated testing obscuring the development of cognitive deficits, we divided mice into 2 groups within each task—one group that underwent regular testing for the duration of the study (i.e., continuous testing groups) and a second group that alternated periods of testing and no testing (i.e., intermittent testing groups). We suspected that declines in accuracy might appear in Tg mice at younger ages in the intermittent testing groups compared to the continuous testing groups and/or that breaks in testing might exacerbate the development of deficits.

2. Method

2.1. Subjects

APP/PS1 Tg and non-Tg littermate mice were used. Initially, 2 male mice (stock 005864), hemizygous for the a transgene harboring the Swedish mutation associated with familial AD, that results in amyloid precursor protein (APPswe) and a transgene encoding the "DeltaE9" mutation of presenilin 1 (PSEN1dE9) and 4 female non-Tg mice (stock 005864) were purchased from The Jackson Laboratory (Bar Harbor, ME). Those mice were used to create the colony by breeding Tg males with non-Tg females. Tg and non-Tg males and females were used in the current experiments. Many more Tg mice were assigned to the study to address expected attrition (see Section 3.1). Mice were weaned at 23–31 days of age (mean: 27.5) and ear punched for tissue collection; mice were genotyped by an outside company (Transnetyx, Inc, Cordova, TN). Mice were singly housed throughout the experiment in polysulfone cages (Blue Line 1285L) with wood shaving bedding, a plastic nesting hut, and free access to tap water. Cages were maintained in ventilated racks (Blue Line) under a 12:12 light:dark cycle (lights on at 0800 hours).

Studies were conducted at Texas Tech University (TTU), in facilities accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International, and all procedures were approved by the TTU Institutional Animal Care and Use Committee and were conducted in accordance with the *Guide for the Care and Use of Laboratory Animals*.

2.2. Design of behavioral experiments

Mice were tested on a DMTP (N = 98) or a 3CSRT (N = 99) task. Within each task, mice were assigned to 1 of 2 testing groups—a continuous (DMTP-C, 3CSRT-C) or an intermittent (DMTP-I, 3CSRT-I) group (Fig. 1A). Mice in each continuous group were tested 5 days a week (Monday–Friday) without any scheduled breaks (some unscheduled breaks in testing occurred around holidays) whereas mice in each intermittent group were placed on scheduled breaks from 29–40 and 53–64 weeks of age. Testing sessions were conducted between 0900 and 1400 hours, Monday through Friday.

Following the behavioral testing protocol which ended at week 72 of life (see Sections 2.2.3 and 2.2.4), mice were exposed to 2 stressor tasks and subsequent behavioral assessments, data which will be described elsewhere.

2.2.1. Apparatus

Daily experimental sessions were conducted in operant conditioning chambers equipped with 20-mg food dispensers and either 2 retractable levers (8 chambers; DMTP task) or 3 nose poke response holes (8 chambers; 3CSRT task). For additional apparatus details, see Supplemental Material, Apparatus Details.

2.2.2. Food restriction procedure

Upon weaning, mice were given unlimited food access for at least 7 days, at which their "free-feeding" weight was calculated as the maximum weight observed during the unlimited food access period. Target weight was set at 85% of the calculated free-feeding weight. Each week, the target weight increased by 2% until the mice reached 20 weeks of age, whereafter, the target weight remained fixed. Mice were weighed daily and maintained at their target weight as follows: if mouse weight was less than or equal to target weight, mice were fed 2.5g + difference (target-current weight); if mouse weight was greater than the target weight, mice were fed 2.0 g of food. Food (Envigo 2020x, Teklad) was cut and weighed for each mouse daily. Mice were given 2 pellets (~4.4 g) each day on weekends.

2.2.3. DMTP task

2.2.3.1. DMTP training and standard sessions. Mice were trained to perform the DMTP task using food as a reinforcer over a series of training stages in which mice were initially trained to press either lever and subsequently to press a single extended lever, nose poke in the food cup to produce a presentation of both levers and then to press 1 of the 2 levers, with a press on the previously presented lever producing food delivery and a press on the other lever producing a 10-second timeout (TO) during which all lights were off and responses produced no scheduled consequences (see Table S1 and Supplemental Material, Supplemental Procedural Details). Following training, the final ("Standard") session settings were imposed (see Table S2 for details). During standard sessions, each trial began with the illumination of the house light and extension of 1 of the 2 levers, selected randomly without replacement (the Sample phase of the trial; Fig. 1B). A response on the extended lever within 20 seconds, the limited hold (LH), produced its retraction and initiated a delay (randomly selected without replacement from possible values of 0.1, 1, 2, 4, 8, 16, and 24 seconds; the Delay phase of the trial, Fig. 1B). The first nose poke response in the food hopper following completion of the delay produced extension of both levers (the Choice phase of the

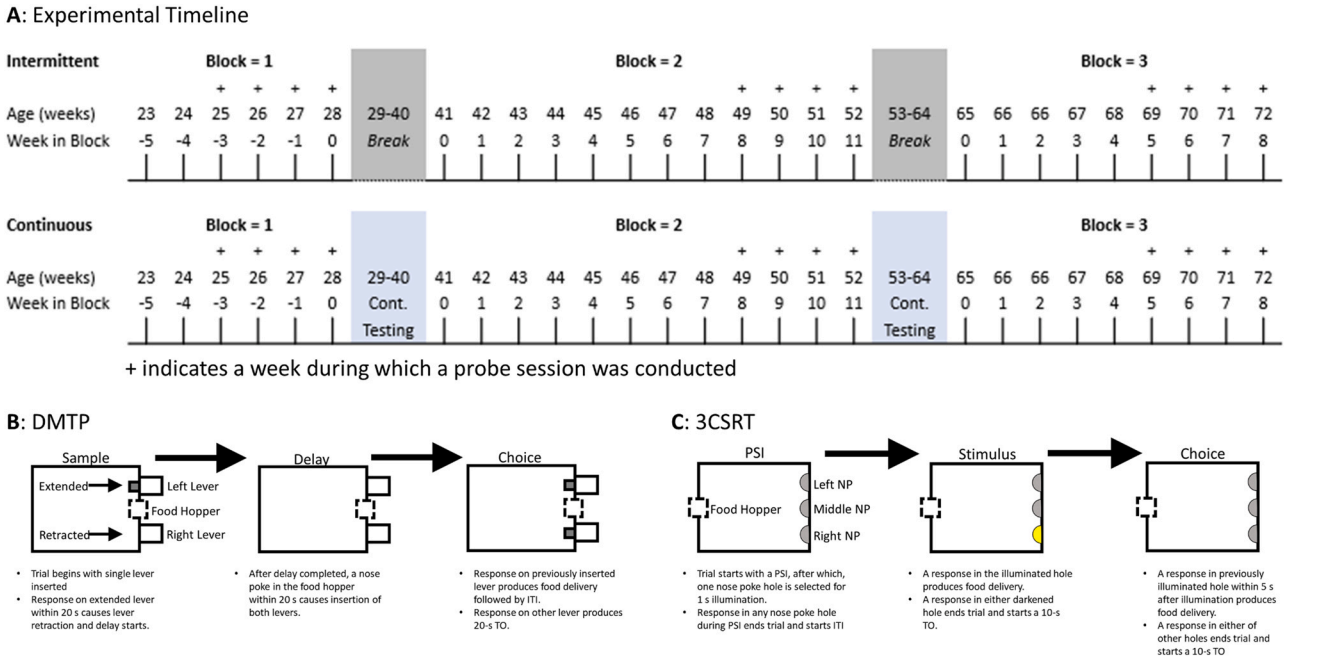

Fig. 1. (A) Experimental timeline of testing in the intermittent and continuous testing groups. (B) Diagram of trial structure in the delayed match-to-position (DMTP) procedure. (C) Diagram of trial structure in the 3-choice serial reaction time (3CSRT) procedure. ITI, intertrial interval; PSI, pre-stimulus interval; TO, timeout.

trial; Fig. 1B). A response on a lever within 20 seconds produced food delivery if it occurred on the previously presented lever or a 20-second TO if the response occurred on the other lever. Failure to respond during the Sample, Delay, or Choice phases within the 20-second LH, ended the trial and initiated a 10 second intertrial interval (ITI) during which all lights were off and responses produced no scheduled consequences, after which a new trial commenced. Sessions ended after 35 minutes or delivery of 60 reinforcers. Thus, in the DMTP task, food delivery depended on remembering which lever was presented prior to the variable delay (0.1–24 seconds) that separated the Sample and Choice phases, which allowed an assessment of how accuracy declined with delay.

2.2.3.2. DMTP probe sessions. Probe trials were conducted during the last 4 weeks of each testing block in the intermittent testing group and during the equivalent weeks in the continuous group (see Fig. 1A, weeks designated by asterisks). Four types of probe trials were conducted in the DMTP task (see Table S2): (1) a "Long Delays Probe" session during which the delays that intervened between sample and choice phases were longer (8, 16, 20, 24, 30, 36, and 40 seconds) than those utilized during the standard DMTP sessions; (2) a "Short ITI Probe" session during which the ITI that separated DMTP trials was 3 seconds instead of 10 seconds; (3) a probe session during which the fixed ratio (FR) response requirement on the sample lever was increased to 2 ("Sample FR 2 Probe"); and (4) a "Long ITI Probe" session during which the ITI that separated DMTP trials was 20 seconds instead of 10 seconds. The Long Delays Probe was conducted to determine if putatively more difficult trials would differentially impact performance accuracy across testing regimen groups or genotypes. The Short and Long ITI Probes were conducted to determine if ITI duration, previously shown to affect performance accuracy (Nelson and Wasserman, 1978; Roberts and Kraemer, 1982; Wixted, 1989), would differentially impact performance across groups or genotypes. The Sample FR 2 Probe was conducted to determine if increasing the FR on the sample stimulus, a manipulation previously shown to increase accuracy (White, 1985), would differentially impact performance across groups or genotypes. Other than the specified changes, the probe sessions retained the same session parameters as the standard sessions (see Table S2). The Long Delays Probe was implemented on each of the last 4 weeks for the first block of testing (Fig. 1A) whereas 1 of each of the 4 types of probe sessions was implemented on each of the last 4 weeks for the second and third blocks of testing (separate probe session type each week; Fig. 1A).

2.2.4. 3CSRT task

2.2.4.1. 3CSRT training and standard sessions. Mice were trained to perform the 3CSRT task over a series of training stages in which mice were initially trained to nose poke in any 1 of the 3 nose poke ports and subsequently to respond in only 1, illuminated nose poke port while illuminated or within a short period of time after its illumination (see Table S3 and Supplemental Material, Supplemental Procedural Details). Following training, the final ("Standard") session settings were imposed (see Table S4 for details). During standard 3CSRT sessions, each trial started with the illumination of the houselight for a 5-second pre-stimulus interval (PSI; Fig. 1C). A response in any hole during the PSI ended the trial and started a 5-second ITI during which time all lights were off and responses produced no scheduled consequences. If no nose poke response occurred during the PSI, one of the nose poke ports was randomly selected, without replacement, and illuminated for a maximum of 1 second (Stimulus, Fig. 1C). A nose poke in the illuminated hole while illuminated or within 5 seconds after its illumination ended produced food delivery followed by a 5-second ITI. A nose poke in one of the unilluminated holes during the same time period resulted in a 10-second TO during which all lights were off and responses produced no scheduled consequences. After TO completion, a new trial began. If no response occurred during the 1-second nose poke port illumination or within 5 seconds after its illumination, the 5-second ITI began, after which a new trial began. Sessions ended after 30 minutes or 100 reinforcer deliveries.

2.2.4.2. 3CSRT probe sessions. Probe trials were conducted during the last 4 weeks of each testing block in the intermittent testing group

and during the equivalent weeks in the continuous group (see Fig. 1A, weeks designated by asterisks). Two types of probe sessions were conducted in the 3CSRT task: (1) "Stimulus Duration Probe" sessions during which the duration of nose poke hole illumination was varied across trials (0.5, 1, 2, or 5 seconds in Stimulus Duration Probe A sessions or 0.25, 0.5, 0.75, 1 second in Stimulus Duration Probe B sessions) and (2) "Pre-Stimulus Interval Probe" sessions during which the interval between trial start and nose poke light onset varied across trials (1, 2, 4, or 5 seconds in Pre-Stimulus Interval Probe A sessions or 5, 8, 12, or 15 seconds in Pre-Stimulus Interval Probe B sessions). We evaluated the impact of stimulus duration variation because this has been shown to affect accuracy in a 5CSRT task and further, triple Tg (3xTgAD) mice exhibit lower accuracy at short durations but not at longer durations compared to wild-type mice (Romberg et al., 2011). We also evaluated the impact of varying the PSI because previous reports indicated that accuracy could be affected by variation in the interval preceding stimulus onset (Amitai and Markou, 2011; Dalley et al., 2007; Higgins and Breysse, 2008). The first type of Stimulus Duration Probe session (A) was implemented on each of the last 4 weeks for the first block of testing (Fig. 1A) whereas all 4 types of probe sessions were implemented on each of the last 4 weeks for the second and third blocks of testing (separate probe session each week; Fig. 1A). Other than the noted changes, task parameters during 3CSRT probe sessions were the same as during 3CSRT standard sessions (Table S4).

2.3. Analyses of Aβ accumulation

At week 77 (~530–550 days) of age, mice were euthanized via carbon dioxide inhalation followed immediately by cervical dislocation. After euthanasia, mice were dissected and brains were immediately removed, place on wet ice, and the right and left cortices and right and left hippocampi were separated and frozen. Samples were stored at −80 °C until analysis of Aβ 40 and 42. Brains were homogenized, and extracts were analyzed for human Aβ using a commercially available kit (KHB3481 and KHB2441; Biosource International/Invitrogen, Camarillo, CA) as described previously (Harris et al., 2022; Melnikova et al., 2016; Savonenko et al., 2005). Briefly, the right cortex and right hippocampus samples were weighed and homogenized in 8× mass of cold 5 M guanidine HCL or 50 mM Tris HCL with a hand-held motor (Fisher k749540-0000) and then mixed at room temperature for 3–4 hours. Samples were then placed back at −80 °C until dilution and assay. Brain homogenates were thawed and diluted 1:20 with reaction buffer (Dulbecco's phosphate buffered saline with 5% bovine serum albumin and 0.03% Tween-20) with 1 mM concentration of protease inhibitor (4-benzenesulfonyl fluoride hydrochloride; Calbiochem item 539131). The diluted brain samples were aliquoted and refrozen for analysis of Aβ. ELISA kits were used to determine the concentration of Aβ40 and Aβ42, expressed as μg/g of brain tissue. Samples for analysis of Aβ40 were assayed at a final dilution of 1:3000–1:5000 and samples for Aβ42 at a final dilution of 1:8000. A subset of non-Tg mouse brains was run at a dilution of 1:50. Each assay was run at a single dilution and the assay curve was treated with the same dilution of guanidine HCL, as per the manufacturer's instructions. Samples were all run in duplicate.

2.4. Data analysis

For the survival analysis, a Cox proportional hazards regression on the age of death of each mouse was conducted using the "survival" package (Therneau, 2022) in the free open-source statistical language *R* (R Core Team, 2018). The age of death was coded as "Censored" if the mouse was euthanized.

Mixed effects logistic regression, conducted using the glmer command in the lme4 library (Bates et al., 2015) of *R*, was used to assess effects on accuracy in the DMTP and 3CSRT tasks, similar to that described previously (Bailey et al., 2018; Wileyto et al., 2004; Young, 2018). Because aggregating binomial outcomes risks misidentification of interactions (Dixon, 2008) and fails to retain information regarding differential sample size (due to attrition) as well as differential variability (due to individual differences or experimental control), we chose to retain the choice data in its binomial form. The repeated measures binomial outcome data collected in the DMTP and 3CSRT procedures necessitated the use of mixed effects logistic regression (for additional details, see Supplemental Material, Statistical Analyses). It is important to note that a logistic regression analyzes the relation between the log odds of an outcome (i.e., the log-transformed ratio of the probability of an outcome occurring to the probability of the outcome not occurring, which is unbounded, unlike percent correct and thus not subject to the same artifacts) and 1 or more predictors. Thus, the regression coefficients returned by the analysis indicate the change in log odds of a correct response for each unit change in the predictor (for a comparison of decreases in proportion correct, odds correct, and log odds correct, see Fig. S1A–C).

Aβ levels in the brain were analyzed using a linear mixed effects model generated using the lmerTest package in R (Kuznetsova et al., 2017), which provides *p*-values for linear mixed effects models. Aβ levels in the brain were analyzed using the sex of the mouse, brain region (cortex or hippocampus), and type of Aβ (Aβ40 or Aβ42) and all possible interactions as predictors with random effects specification for the within-subject variables of brain region and type of Aβ.

3. Results

3.1. Survival

Tg mice exhibited lower survival rates than non-Tg littermates (Fig. 2A and B). By 72 weeks of age, only 35% (24/69) female Tg and 56% (25/45) male Tg mice remained alive. Female and male non-Tg mice exhibited similar rates of survival with 77% (27/35) of female and 76% (29/38) of male non-Tg mice alive at 72 weeks of age. Cox proportional hazards regression supported the conclusion that Tg mice die earlier than non-Tg mice (Hazard Ratio [HR] = 3.74, $z = 3.62$, $p = 0.0003$), but not that Sex (HR = 0.95, $z = -0.12$, $p = 0.907$) or the interaction of Sex and Genotype (HR = 0.57, $z = -1.03$, $p = 0.301$) increased risk of dying (see Table 1 for the number of mice that contributed data to each block of testing).

3.2. DMTP standard

In our primary analysis, we did not include Sex as a predictor because of the high rates of attrition obtained in the Tg mice and we wanted to maximize the sample sizes of Tg mice at later ages. Subsequent analyses investigated the role of Sex (see Section 3.2.4). At short delays, mice performed with high accuracy throughout the study (Fig. 3). As delay increased, accuracy (i.e., log odds of a correct response; "odds correct" for brevity) decreased (Table 2, model term 6; Fig. 3; also see Fig. S2 for probability of a correct response) reaching chance levels (i.e., log odds of 0, denoted by a horizontal dotted line in Fig. 3) by 24-second delay.

3.2.1. Breaks in testing temporarily reduced accuracy

The effect of breaks in testing on DMTP performance accuracy was investigated by posthoc comparisons of statistically significant interactions involving the Group variable (see Table 2). Of the 16 interactions involving the Group variable, 10 met criterion for statistical significance (Table 2, model terms 7, 8, 10, 13, 19, 21, 24, 27, 29, and 30). We focused on the highest-level interactions because

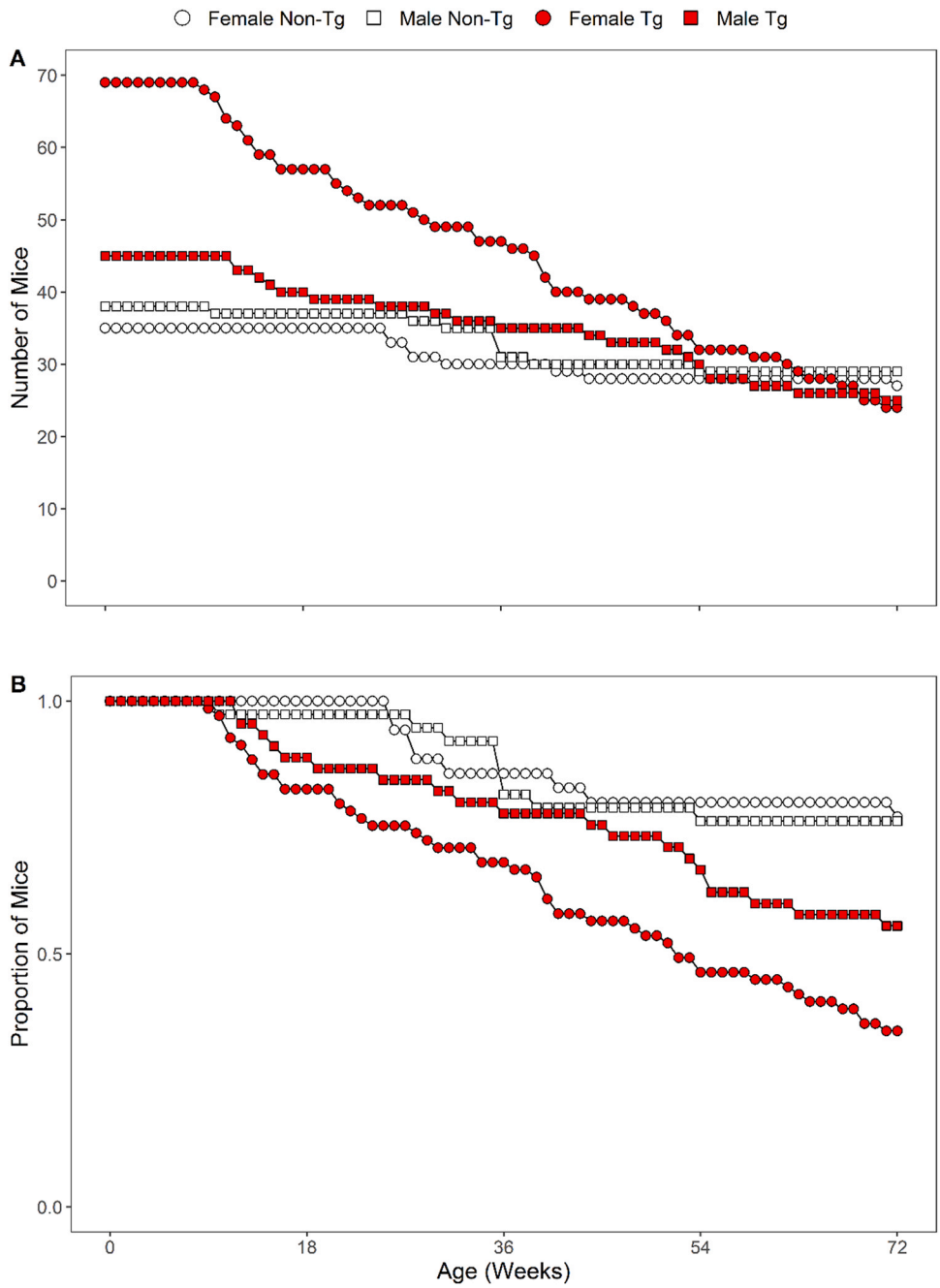

Fig. 2. Shorter lifespan in transgenic mice. Survival analysis for female and male non-transgenic (Non-Tg) and transgenic (Tg) APPswe/PS1dE9 mice for (A) the absolute number of mice enrolled in the study and (B) the number of mice as a proportion of those initially assigned to the experiment. Note. Cox proportional hazards regression indicated a higher risk of dying in transgenic mice (hazard ratio [HR] = 3.74, $p = 0.0003$) but that risk of dying was not significantly different based on Sex (HR = 0.95, $p = 0.907$) or the interaction of Sex and Genotype (HR = 0.57, $p = 0.301$).

the lower-level interactions are subsumed within the higher-level interactions. We explored the interaction between Group, Genotype, Block, and Week (Table 2, model term 27) for Group differences by comparing the coefficient of Week between the 2 Groups for each combination of Genotype and Block and found that for non-Tg mice the coefficient of Week was greater in DMTP-C compared to DMTP-I mice during Block 1 and greater in DMTP-I compared to DMTP-C mice during Blocks 2 and 3 (Table S5, model term 27), due to the post-break declines, which were followed by improvements across weeks in the DMTP-I mice (Fig. 3). Further, in Tg mice, the coefficient of Week was greater in DMTP-C compared to DMTP-I mice during Block 1 and greater in DMTP-I compared to DMTP-C mice during Blocks 2 and 3 (Table S5, model term 27), again driven by post-break declines that preceded improvements across weeks (Fig. 3; also see Fig. S3).

Differences in the magnitude of the coefficient of delay between Groups depended on the values of Genotype and Week (Table 2, model term 29). We explored the interaction by comparing the coefficient of Delay between the 2 Groups for each combination of Genotype and Week (24 comparisons). Of the 24 comparisons, 14 met the criteria for statistical significance (see Table S5, model term 29) and indicated that in non-Tg mice, the magnitude of the coefficient of delay in DMTP-C mice exceeded that magnitude in DMTP-I mice during Weeks 0–3 and similarly, in Tg mice, the magnitude of

Table 1
Number of mice contributing data in each block of testing by procedure, group, sex, and genotype

Genotype	Sex	Block 1	Block 2	Block 3
DMTP-C				
Non-transgenic	Female	7	7	7
Non-transgenic	Male	11	8	8
Transgenic	Female	11	9	8
Transgenic	Male	10	10	7
DMTP-I				
Non-transgenic	Female	8	8	8
Non-transgenic	Male	10	7	7
Transgenic	Female	12	11	8
Transgenic	Male	9	7	6
3CSRT-C				
Non-transgenic	Female	7	6	6
Non-transgenic	Male	7	7	7
Transgenic	Female	13	11	7
Transgenic	Male	10	10	8
3CSRT-I				
Non-transgenic	Female	7	7	7
Non-transgenic	Male	7	7	5
Transgenic	Female	8	7	4
Transgenic	Male	8	8	5

Key: 3CSRT, 3-choice serial reaction time; DMTP, delayed matching-to-position.

the coefficient of delay in DMTP-C mice exceeded the magnitude in DMTP-I mice during Weeks 0–9.

Finally, the statistically significant interaction between Group, Block, Week, and Delay (Table 2, model term 30) indicated that the effect of delay on accuracy depended on the values of Group, Block, and Week. We conducted posthoc comparisons of the coefficient of Delay between the DMTP-C and DMTP-I groups for each combination of the values of Block and Week. Of the 26 comparisons (see Table S5, model term 30), 17 met the criteria for statistical significance and indicated that the magnitude of the coefficient of Delay was greater: (1) in DMTP-I compared to DMTP-C mice during Weeks −5 and −4 of Block 1, indicating an initial difference between the groups that dissipated by the completion of the first block; (2) in DMTP-C mice during Weeks 0–8 of Block 2, reflecting the break-induced declines in accuracy in DMTP-I mice (Fig. 3, Block = 2); (3) in DMTP-C mice during Weeks 0–4 of Block 3, reflecting break-induced declines in accuracy in DMTP-I mice (Fig. 3, Block = 3); and (4) in DMTP-I mice during Week 7 of Block 3, indicating a steeper decline in accuracy as delay increased in the DMTP-I mice (Fig. 3, Block = 3, Week 7 panel, compared dashed and solid lines).

3.2.2. *Transgenic mice performed as well or better than non-Tg mice*

We had expected that Tg mice would exhibit delay-, age-, and possibly testing regimen-dependent declines in DMTP accuracy, but Tg mice performed as well as or better than the non-Tg mice. Overall, there was no main effect of Genotype on odds correct (Table 2, model term 3). There were 6 interactions involving Genotype that met the criterion for statistical significance (Table 2, model terms 7, 20, 21, 25, 27, and 29). We explored the 2 highest-level interactions (Table 2, model terms 27 and 29) because the other interactions were subsumed within these higher-level interactions.

We explored the interaction of Group, Genotype, Week, and Delay by comparing the coefficient of Delay between the 2 Genotypes for each combination of Group and Week. The coefficient of Week was significantly greater in Tg mice than non-Tg mice during Block 1 in DMTP-C mice (Table S6, model term 27) only,

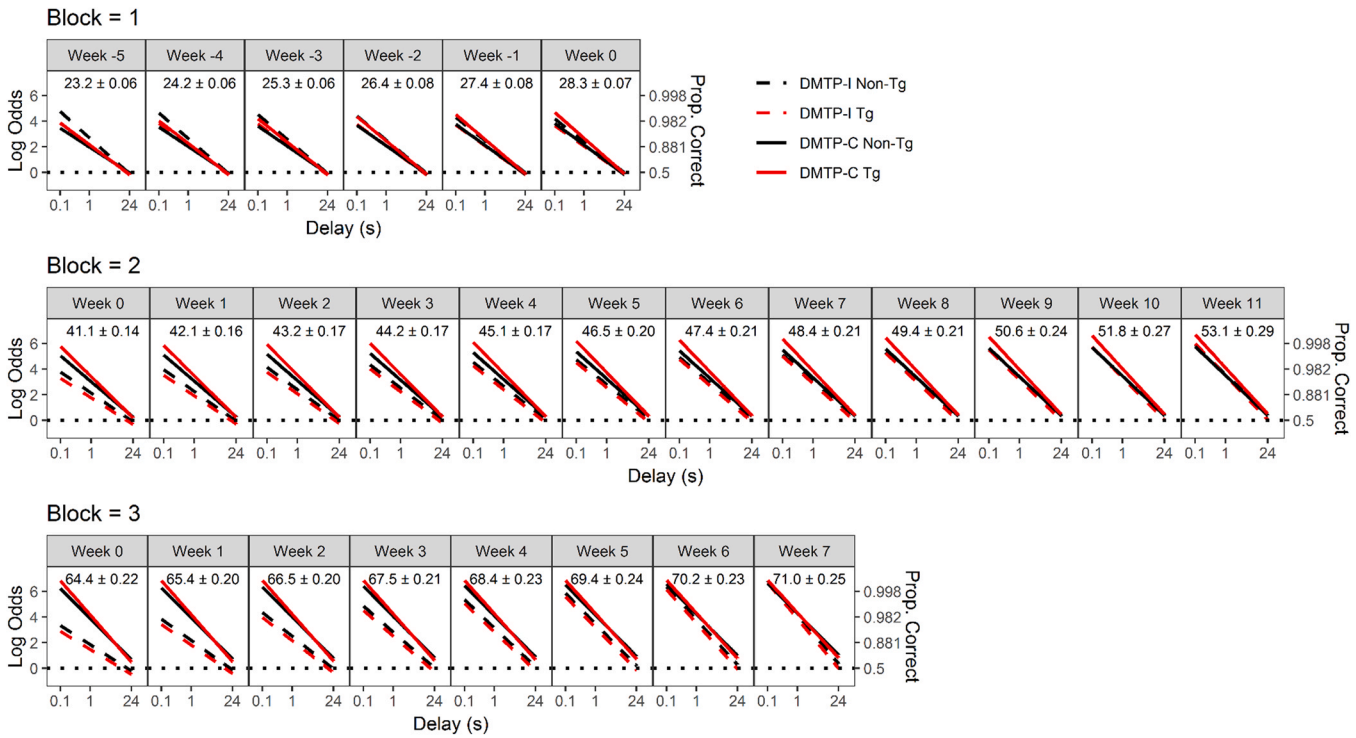

Fig. 3. Odds of a correct response versus delay over time in the study during DMTP standard sessions. Model-estimated log odds of a correct response in the DMTP procedure as a function of the delay for the last 5 weeks (Week −5 to Week 0) of the initial block of testing ("Block = 1," top row), the next block of testing ("Block = 2," middle row), and the last block of testing ("Block = 3," bottom row) for non-transgenic (Non-Tg) and transgenic (Tg) mice in the continuous (DMTP-C) and intermittent (DMTP-I) groups. Model-estimated log odds of a correct response was calculated using the emmeans package based on the logistic regression model fitted with the glmer package. Text annotations at the top of each graph indicate the mean age of the mice in weeks ± 1 standard error of the mean (SEM). Horizontal dotted line indicates chance performance. Abbreviation: DMTP, delayed matching-to-position.

Table 2
Model term number, predictor, coefficient estimates (Estimate) of the predictor, standard errors (SE) of the estimates, and resulting *z*-statistic (*z*) and associated *p*-values (*p*) from the multilevel logistic regression analysis of standard DMTP sessions

Model term	Predictor	Estimate	SE	*z*	*p*
1	(Intercept)	1.899	0.065	29.28	< 0.001
2	Group [DMTP-C]	0.403	0.065	6.21	< 0.001
3	Genotype [Non-Tg]	−0.002	0.065	−0.03	0.975
4	Block	0.396	0.040	9.99	< 0.001
5	Week	0.076	0.006	13.56	< 0.001
6	Delay	−2.007	0.041	−49.12	< 0.001
7	Group [DMTP-C]*Genotype [Non-Tg]	−0.143	0.065	−2.20	0.028
8	Group [DMTP-C]*Block	0.261	0.040	6.58	< 0.001
9	Genotype [Non-Tg]*Block	0.069	0.040	1.73	0.084
10	Group [DMTP-C]*Week	−0.034	0.006	−6.14	< 0.001
11	Genotype [Non-Tg]*Week	−0.007	0.006	−1.26	0.207
12	Block*Week	0.067	0.003	22.34	< 0.001
13	Group [DMTP-C]*Delay	−0.232	0.041	−5.68	< 0.001
14	Genotype [Non-Tg]*Delay	0.073	0.041	1.78	0.075
15	Block*Delay	−0.218	0.017	−12.47	< 0.001
16	Week*Delay	−0.049	0.003	−17.17	< 0.001
17	Group [DMTP-C]*Genotype [Non-Tg]*Block	0.048	0.040	1.21	0.227
18	Group [DMTP-C]*Genotype [Non-Tg]*Week	−0.001	0.006	−0.24	0.813
19	Group [DMTP-C]*Block*Week	−0.067	0.003	−22.19	< 0.001
20	Genotype [Non-Tg]*Block*Week	0.012	0.003	3.92	< 0.001
21	Group [DMTP-C]*Genotype [Non-Tg]*Delay	0.095	0.041	2.32	0.021
22	Group [DMTP-C]*Block*Delay	−0.027	0.017	−1.57	0.116
23	Genotype [Non-Tg]*Block*Delay	−0.008	0.017	−0.48	0.631
24	Group [DMTP-C]*Week*Delay	0.026	0.003	9.01	< 0.001
25	Genotype [Non-Tg]*Week*Delay	0.008	0.003	2.62	0.009
26	Block*Week*Delay	−0.041	0.004	−9.46	< 0.001
27	Group [DMTP-C]*Genotype [Non-Tg]*Block*Week	0.009	0.003	2.88	0.004
28	Group [DMTP-C]*Genotype [Non-Tg]*Block*Delay	−0.018	0.017	−1.04	0.300
29	Group [DMTP-C]*Genotype [Non-Tg]*Week*Delay	−0.007	0.003	−2.50	0.013
30	Group [DMTP-C]*Block*Week*Delay	0.072	0.004	16.45	< 0.001
31	Genotype [Non-Tg]*Block*Week*Delay	−0.007	0.004	−1.59	0.111
32	Group [DMTP-C]*Genotype [Non-Tg]*Block*Week*Delay	−0.004	0.004	−0.83	0.408

Omission trials were excluded from analysis. The fixed effects portion of the model included estimates for the predictors of Group (effect-coded: DMTP-C = 1, DMTP-I = −1), Genotype (effect-coded: non-transgenic = 1, transgenic = −1), Block (1–3; continuous and centered), Week in Block (−5 to 0 in Block 1, 0–11 in Block 2, and 0–7 in Block 3; continuous and centered), and log-transformed Delay values ("Delay" 0.1, 1, 2, 4, 8, 16, and 24; continuous and centered) and all possible interactions of the 5 predictors. The random effects portion of the model included estimates of Block, Week, and Delay for each Subject, without interactions.
Key: DMTP, delayed matching-to-position; non-Tg, non-transgenic; Tg, transgenic.

indicating that Tg mice improved at a greater rate during the last 6 weeks of Block 1. Next, we explored the interaction of Group, Genotype, Week, and Delay by comparing the coefficient of Delay between Genotypes for each combination of Group and Week. The magnitude of the coefficient of Delay was greater in Tg compared to non-Tg mice across all weeks in the DMTP-C group (Table S6, model term 29). Inspection of Fig. 3 indicates that this resulted from higher accuracy in Tg mice at short delays that decreased more steeply as delay increased (compare red solid lines, which start at higher values, to black solid lines in Fig. 3; also see Fig. S3). In DMTP-I mice, the magnitude of the coefficient of Delay did not differ significantly between Genotypes (Table S6, model term 29).

3.2.3. Secondary analyses of transgenic mice

Because of the high proportion of Tg mice that did not survive for the full duration of the study, we considered the possibility that those mice that died early were the most likely to exhibit deficits. We conducted a secondary analysis using only Tg mice that died before completing the study (for details see Supplemental Material, Secondary Analyses) and found no evidence of age-related decline in that sub-group of mice (see Table S7 and Fig. S5). We also conducted an analysis of DMTP results using only Tg mice that completed the study and therefore had documented Aβ deposition in the brain (for details see Supplemental Material, Secondary Analyses) and found no evidence of age-related decline in that sub-group of Tg mice (see Table S8 and Fig. S6).

3.2.4. Secondary analysis using Sex as a predictor

Although our primary analyses did not distinguish between male and female mice to maximize our sample sizes, we conducted secondary analyses using Sex as a predictor to assess whether the decline was evident in female Tg mice because female APP/PS1 Tg mice exhibit greater brain Aβ deposition than male Tg mice (Wang et al., 2003). According to multilevel logistic regression analysis (Table S9), female mice performed at lower accuracy, on average, than males. Post-hoc comparisons between males and females (Table S10) and between genotypes (Table S11) for statistically significant interactions involving both Sex and Genotype indicated that lower accuracy in females was not restricted to Tg females and that within female mice, non-Tg mice performed at lower accuracy than Tg mice, results consistent with the main analysis indicating that Tg mice, on the whole, did not exhibit declines in performance relative to non-Tg mice.

3.3. DMTP probe sessions

Analysis of the results from the DMTP probe sessions yielded weak evidence of differential sensitivity to the probe session manipulations produced by Genotype differences (Table 3; Fig. 4A–D; see Supplemental Material, Supplemental Results for detailed results and Fig. S4 for the probability of correct response). Post-hoc comparisons of statistically significant interactions involving Genotype, did not reveal any differences between Genotypes during the Long Delays (Fig. 4A) or Short ITI (Fig. 4B) probe sessions. During the Sample FR 2 Probe sessions (Fig. 4C), the coefficient of Delay was

Table 3
Model term number, predictor, coefficient estimates (Estimate) of the predictor, standard errors (SE) of the estimates, and resulting *z*-statistic (*z*) and *p*-values (*p*) from the multilevel logistic regression analysis of DMTP probe sessions

Model term	Predictor	Estimate	SE	*z*	*p*
Long Delays Probe					
1	(Intercept)	0.243	0.027	8.84	< 0.001
2	Group [DMTP-C]	0.029	0.027	1.06	0.292
3	Genotype [Non-Tg]	0.008	0.027	0.28	0.780
4	Block	0.115	0.033	3.52	< 0.001
5	Delay	−0.893	0.080	−11.12	< 0.001
6	Group [DMTP-C]*Genotype [Non-Tg]	−0.055	0.027	−2.02	0.043
7	Group [DMTP-C]*Block	0.110	0.033	3.35	< 0.001
8	Genotype [Non-Tg]*Block	0.011	0.033	0.35	0.727
9	Group [DMTP-C]*Delay	0.027	0.080	0.33	0.739
10	Genotype [Non-Tg]*Delay	−0.041	0.080	−0.51	0.609
11	Block*Delay	−0.258	0.108	−2.38	0.017
12	Group [DMTP-C]*Genotype [Non-Tg]*Block	−0.041	0.033	−1.25	0.213
13	Group [DMTP-C]*Genotype [Non-Tg]*Delay	0.097	0.080	1.21	0.227
14	Group [DMTP-C]*Block*Delay	−0.280	0.108	−2.59	0.010
15	Genotype [Non-Tg]*Block*Delay	0.010	0.108	0.10	0.925
16	Group [DMTP-C]*Genotype [Non-Tg]*Block*Delay	−0.092	0.108	−0.85	0.397
Short ITI Probe					
1	(Intercept)	2.285	0.093	24.68	< 0.001
2	Group [DMTP-C]	0.350	0.093	3.78	< 0.001
3	Genotype [Non-Tg]	0.025	0.093	0.27	0.786
4	Block	0.090	0.130	0.69	0.488
5	Delay	−2.211	0.109	−20.30	< 0.001
6	Group [DMTP-C]*Genotype [Non-Tg]	0.065	0.093	0.70	0.482
7	Group [DMTP-C]*Block	−0.106	0.130	−0.82	0.415
8	Genotype [Non-Tg]*Block	−0.098	0.130	−0.75	0.452
9	Group [DMTP-C]*Delay	−0.239	0.109	−2.19	0.028
10	Genotype [Non-Tg]*Delay	−0.033	0.109	−0.30	0.763
11	Block*Delay	0.062	0.174	0.35	0.723
12	Group [DMTP-C]*Genotype [Non-Tg]*Block	0.107	0.130	0.82	0.410
13	Group [DMTP-C]*Genotype [Non-Tg]*Delay	−0.217	0.109	−2.00	0.046
14	Group [DMTP-C]*Block*Delay	0.614	0.174	3.53	< 0.001
15	Genotype [Non-Tg]*Block*Delay	0.028	0.174	0.16	0.874
16	Group [DMTP-C]*Genotype [Non-Tg]*Block*Delay	−0.211	0.174	−1.21	0.226
Sample FR 2 Probe					
1	(Intercept)	2.599	0.112	23.20	< 0.001
2	Group [DMTP-C]	0.229	0.112	2.04	0.041
3	Genotype [Non-Tg]	−0.099	0.112	−0.88	0.379
4	Block	0.151	0.176	0.86	0.390
5	Delay	−2.490	0.114	−21.81	< 0.001
6	Group [DMTP-C]*Genotype [Non-Tg]	−0.184	0.112	−1.64	0.100
7	Group [DMTP-C]*Block	0.050	0.176	0.29	0.775
8	Genotype [Non-Tg]*Block	−0.127	0.176	−0.72	0.470
9	Group [DMTP-C]*Delay	0.072	0.114	0.63	0.531
10	Genotype [Non-Tg]*Delay	0.111	0.114	0.97	0.331
11	Block*Delay	0.004	0.203	0.02	0.986
12	Group [DMTP-C]*Genotype [Non-Tg]*Block	0.372	0.176	2.11	0.035
13	Group [DMTP-C]*Genotype [Non-Tg]*Delay	0.094	0.114	0.83	0.408
14	Group [DMTP-C]*Block*Delay	0.370	0.203	1.82	0.069
15	Genotype [Non-Tg]*Block*Delay	0.172	0.203	0.85	0.398
16	Group [DMTP-C]*Genotype [Non-Tg]*Block*Delay	−0.573	0.203	−2.82	0.005
Long ITI Probe					
1	(Intercept)	2.383	0.122	19.49	< 0.001
2	Group [DMTP-C]	0.090	0.122	0.74	0.459
3	Genotype [Non-Tg]	0.006	0.122	0.05	0.961
4	Block	0.565	0.161	3.52	< 0.001
5	Delay	−2.222	0.141	−15.77	< 0.001
6	Group [DMTP-C]*Genotype [Non-Tg]	−0.046	0.122	−0.38	0.705
7	Group [DMTP-C]*Block	−0.192	0.161	−1.20	0.231
8	Genotype [Non-Tg]*Block	0.127	0.161	0.79	0.428
9	Group [DMTP-C]*Delay	0.059	0.141	0.42	0.677
10	Genotype [Non-Tg]*Delay	0.056	0.141	0.40	0.691
11	Block*Delay	−0.201	0.226	−0.89	0.374
12	Group [DMTP-C]*Genotype [Non-Tg]*Block	0.378	0.161	2.36	0.019
13	Group [DMTP-C]*Genotype [Non-Tg]*Delay	−0.103	0.141	−0.73	0.466

(*continued on next page*)

Table 3 (*continued*)

Model term	Predictor	Estimate	SE	*z*	*p*
14	Group [DMTP-C]*Block*Delay	0.459	0.226	2.04	0.042
15	Genotype [Non-Tg]*Block*Delay	−0.038	0.226	−0.17	0.866
16	Group [DMTP-C]*Genotype [Non-Tg]*Block*Delay	−0.266	0.226	−1.18	0.240

The fixed effects portion of the model included estimates for the predictors Group (effect-coded: DMTP-C = 1, DMTP-I = −1), Genotype (effect-coded: non-transgenic = 1, transgenic = −1), Block (0–2; continuous and centered), and log-transformed Delay values ("Delay" 8, 16, 20, 24, 30, 36, and 40 seconds for the delay probe and 0.1, 1, 2, 4, 8, 16, and 24 seconds for the sample FR and ITI probes; continuous and centered) and all possible interactions of the 4 predictors. The random effects portion of the model included estimates of Block and Delay for each Subject, without interactions.
Key: ITI, intertrial interval; non-Tg, non-transgenic.

larger in Tg mice than non-Tg mice in the DMTP-I group during Block 3 (−3.69 vs. −2.17, $p = 0.026$), a result driven by higher accuracy in the DMTP-I Tg mice at short delays during Block 3 (Fig. 4C, compared dashed red to dashed black lines). Finally, during the Long ITI Probe sessions (Fig. 4D), the coefficient of Block was higher in DMTP-C non-Tg mice than in Tg mice (0.88 vs. −0.13, $p = 0.011$), indicating improvement from Blocks 2–3 in the DMTP-C non-Tg, but not Tg mice.

3.4. 3CSRT standard

Overall, odds correct was high in all groups and did not vary substantially across blocks (Fig. 5A, Table 4, model terms 1 and 4; also see Fig. S7 for the probability of correct response).

3.4.1. Breaks in testing temporarily reduced accuracy

As in the DMTP task, odds correct were on average higher in the continuous (3CSRT-C) group than the intermittent (3CSRT-I) group (Fig. 5A; Table 4, model term 2), primarily due to the decreases in odds correct that initially occurred after each break in the 3CSRT-I group (Fig. 5A, compare dashed lines to solid lines in Blocks 2 and 3). Of the interaction terms involving the Group variable (Table 4, model terms 6, 7, 9, 12, 13, 14, and 16), 4 met the criteria for statistical significance (Table 4, model terms 7, 9, 14, and 16). We explored the 4-way interaction of Group, Genotype, Block, and Week (Table 4, model term 16) because the other interactions were subsumed within it and found that the coefficient of Week was greater in the 3CSRT-I group during Blocks 2 and 3 for non-Tg and Tg mice (Table S12), with those differences driven by the post-break decreases in odds correct in the 3CSRT-I group (Fig. 5A).

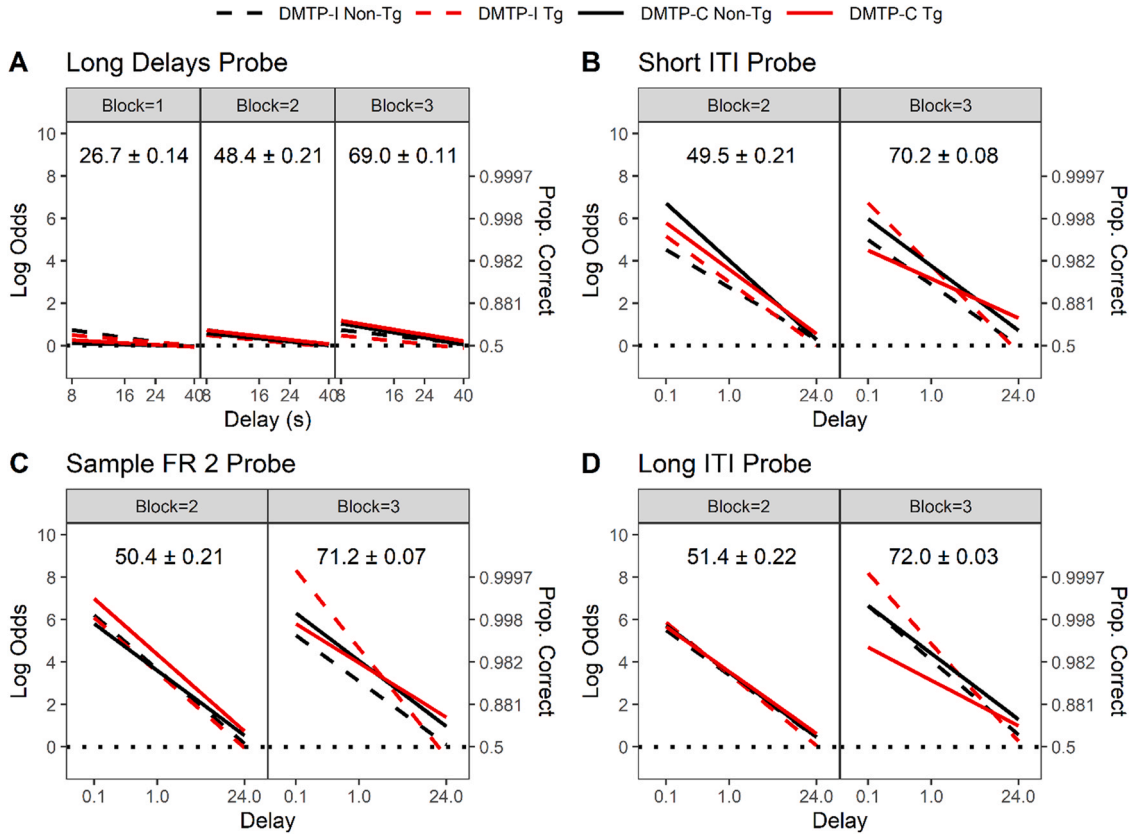

Fig. 4. Odds correct versus delay functions from DMTP probe sessions. Model-estimated log odds of a correct response in the DMTP procedure for non-transgenic (Non-Tg) and transgenic (Tg) mice in the continuous (DMTP-C) and intermittent (DMTP-I) groups are shown during the 4 types of probe sessions: (A) DMTP probe sessions with longer delays (8–40 seconds), (B) DMTP probe sessions with a short ITI (3 seconds), (C) DMTP probe sessions with an increased sample FR (2), and (D) DMTP probe sessions with a long ITI (20 seconds). Other details as in Fig. 3. Note. X-axis scale is different in A than in B–D graphs. Abbreviations: DMTP, delayed matching-to-position; ITI, intertrial interval; FR, fixed ratio; Tg, transgenic.

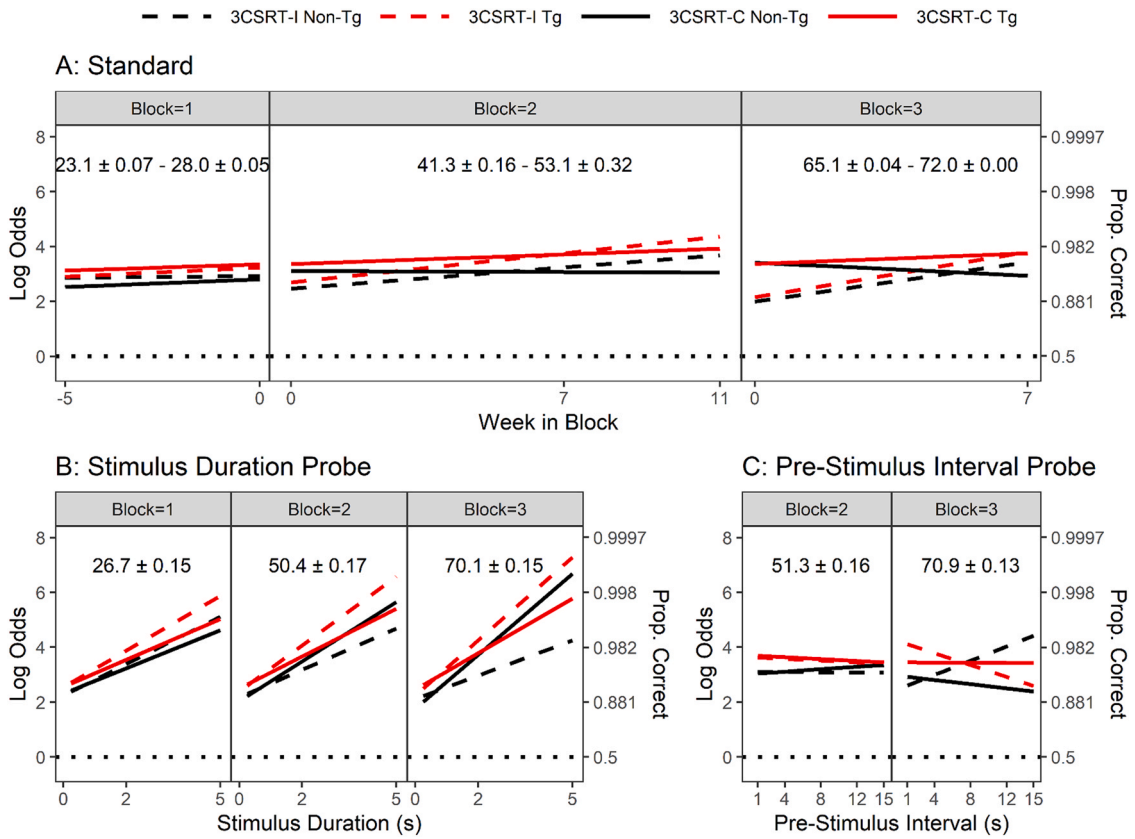

Fig. 5. Odds of a correct response in the 3CSRT task over time in standard sessions and during probe sessions. Model-estimated log odds of a correct response during the 3CSRT procedure for non-transgenic (Non-Tg) and transgenic (Tg) mice in the continuous (3CSRT-C) and intermittent (3CSRT-I) groups during (A) Standard 3CSRT sessions, (B) 3CSRT probe sessions during which the duration of the light on was varied, and (C) 3CSRT probe sessions during which the pre-stimulus interval at the start of each trial was varied. Text annotations within A graphs indicate average start age ± 1 SEM and average end age ± 1 SEM. Text annotations with B and C graphs indicate average age ± 1 SEM. Other details as in Fig. 3. Abbreviation: 3CSRT, 3-choice serial reaction time.

Table 4
Model term number, predictor, coefficient estimates (Estimate) of the predictor, standard errors of the estimates, and resulting *z*-statistic and *p*-values from the multilevel logistic regression analysis of 3CSRT standard sessions

Model term	Predictor	Coefficient	SE	*z*	*p*
1	Intercept	3.141	0.057	55.43	< 0.001
2	Group [3CSRT-C]	0.162	0.057	2.86	0.004
3	Genotype [Non-Tg]	−0.194	0.057	−3.43	< 0.001
4	Block	−0.084	0.058	−1.44	0.151
5	Week	0.077	0.010	7.62	< 0.001
6	Group [3CSRT-C]*Genotype [Non-Tg]	−0.017	0.057	−0.31	0.758
7	Group [3CSRT-C]*Block	0.150	0.058	2.57	0.010
8	Genotype [Non-Tg]*Block	0.048	0.058	0.83	0.406
9	Group [3CSRT-C]*Week	−0.054	0.010	−5.38	< 0.001
10	Genotype [Non-Tg]*Week	−0.024	0.010	−2.40	0.017
11	Block*Week	0.030	0.002	13.77	< 0.001
12	Group [3CSRT-C]*Genotype [Non-Tg]*Block	−0.003	0.058	−0.05	0.961
13	Group [3CSRT-C]*Genotype [Non-Tg]*Week	−0.004	0.010	−0.40	0.688
14	Group [3CSRT-C]*Block*Week	−0.059	0.002	−27.05	< 0.001
15	Genotype [Non-Tg]*Block*Week	−0.014	0.002	−6.50	< 0.001
16	Group [3CSRT-C]*Genotype [Non-Tg]*Block*Week	−0.019	0.002	−8.86	< 0.001

The fixed effects portion of the model included estimates for the predictors of Group (effect-coded: 3CSRT-C = 1, 3CSRT-I = −1), Genotype (effect-coded: non-transgenic = 1, transgenic = −1), Block (1–3; continuous and centered), and Week in Block ("Week" −5 to 0 in Block 1, 0–11 in Block 2, and 0–7 in Block 3; continuous and centered) and all possible interactions of the 4 predictors. The random effects portion of the model included estimates of Block and Week for each Subject, without interactions.
Key: 3CSRT, 3-choice serial reaction time; non-Tg, non-transgenic.

Table 5
Model term number, predictor, coefficient estimates (Estimate) of the predictor, standard errors of the estimates, and resulting *z*-statistic and *p*-values from the multilevel logistic regression analysis of 3CSRT probe sessions

Model Term	Predictor	Coefficient	SE	*z*	*p*
Stimulus Duration Probe					
1	Intercept	3.591	0.119	30.05	< 0.001
2	Group [3CSRT-C]	−0.025	0.119	−0.21	0.833
3	Genotype [Non-Tg]	−0.267	0.119	−2.23	0.026
4	Block	0.087	0.072	1.21	0.227
5	Stimulus Duration	0.660	0.083	7.97	< 0.001
6	Group [3CSRT-C]*Genotype [Non-Tg]	0.176	0.119	1.47	0.141
7	Group [3CSRT-C]*Block	−0.009	0.083	−0.11	0.914
8	Genotype [Non-Tg]*Block	−0.048	0.083	−0.58	0.562
9	Group [3CSRT-C]*Stimulus Duration	0.097	0.072	1.35	0.177
10	Genotype [Non-Tg]*Stimulus Duration	−0.068	0.072	−0.95	0.341
11	Block*Stimulus Duration	0.110	0.019	5.67	< 0.001
12	Group [3CSRT-C]*Genotype [Non-Tg]*Block	0.119	0.083	1.44	0.150
13	Group [3CSRT-C]*Genotype [Non-Tg]*Stimulus Duration	0.130	0.072	1.82	0.068
14	Group [3CSRT-C]*Block*Stimulus Duration	0.063	0.019	3.22	0.001
15	Genotype [Non-Tg]*Block*Stimulus Duration	−0.017	0.019	−0.89	0.371
16	Group [3CSRT-C]*Genotype [Non-Tg]*Block*Stimulus Duration	0.105	0.019	5.42	< 0.001
Pre-Stimulus Interval Probe					
1	Intercept	3.348	0.097	34.46	< 0.001
2	Group [3CSRT-C]	0.032	0.097	0.33	0.743
3	Genotype [Non-Tg]	−0.228	0.097	−2.35	0.019
4	Block	−0.101	0.160	−0.63	0.528
5	Pre-Stimulus Interval	−0.003	0.024	−0.13	0.896
6	Group [3CSRT-C]*Genotype [Non-Tg]	0.002	0.097	0.03	0.980
7	Group [3CSRT-C]*Block	0.006	0.024	0.23	0.815
8	Genotype [Non-Tg]*Block	0.013	0.024	0.56	0.577
9	Group [3CSRT-C]*Pre-Stimulus Interval	−0.193	0.160	−1.20	0.229
10	Genotype [Non-Tg]*Pre-Stimulus Interval	−0.031	0.160	−0.19	0.846
11	Block*Pre-Stimulus Interval	−0.002	0.014	−0.11	0.915
12	Group [3CSRT-C]*Genotype [Non-Tg]*Block	0.006	0.024	0.26	0.796
13	Group [3CSRT-C]*Genotype [Non-Tg]*Pre-Stimulus Interval	−0.094	0.160	−0.59	0.555
14	Group [3CSRT-C]*Block*Pre-Stimulus Interval	−0.021	0.014	−1.46	0.144
15	Genotype [Non-Tg]*Block*Pre-Stimulus Interval	0.037	0.014	2.58	0.010
16	Group [3CSRT-C]*Genotype [Non-Tg]*Block*Pre-Stimulus Interval	−0.075	0.014	−5.24	< 0.001

Other details as in Table 4.
Key: 3CSRT, 3-choice serial reaction time; non-Tg, non-transgenic.

3.4.2. Tg mice performed better than non-Tg mice

We expected that Tg mice would exhibit declines in odds correct in the 3CSRT task as their ability to attend to the stimulus in the task degraded with advancing neuropathology. However, as in the DMTP task, there was little evidence for age-related declines in odds of a correct response or for a differential impact of breaks in testing in the Tg mice compared to the non-Tg mice. In fact, Tg mice performed at slightly higher odds correct, on average, compared to non-Tg mice (Table 4, model term 3; Fig. 5A).

Of the interactions involving Genotype (Table 4, model terms 6, 8, 10, 12, 13, 15, and 16), 3 met the criteria for statistical significance (Table 4, model terms 10, 15, and 16). We explored the 4-way interaction between Genotype, Group, Block, and Week (Table 4, model term 16; terms 10 and 15 subsumed within term 16) and found that during Blocks 2 and 3, Tg mice in the 3CSRT-C group exhibited greater improvements in odds correct across Weeks than did non-Tg mice (Table S13).

3.4.3. Secondary analysis using Sex as a predictor

As with the DMTP analysis, we conducted a secondary analysis of 3CSRT performance using Sex as a predictor to identify whether declines in performance were present in female Tg mice. A multilevel logistic regression analysis indicated that female mice performed the 3CSRT at lower accuracy than male mice (Table S14, model term 4). We conducted posthoc comparisons of female versus male (Table S15) and non-Tg versus Tg (Table S16) mice for any statistically significant interactions involving both Sex and Genotype. Although female Tg mice performed at lower accuracy, overall, compared to male Tg mice in the 3CSRT-C group, the same was not true in the 3CSRT-I group (Table S15, model term 17). Further, the difference between female and male Tg mice in the 3CSRT-C group stemmed from a difference in the last block of testing in which male Tg mice showed a greater rate of improvement across weeks than female Tg mice (Table S15, model term 32). Comparisons of Non-Tg and Tg female mice indicated that where differences occurred, Non-Tg female mice performed worse than Tg female mice (Table S16, model term 17), demonstrating that like the results for Tg mice overall, Tg female mice did not exhibit declines in performance relative to Non-Tg female mice.

3.5. 3CSRT probe sessions

During the Stimulus Duration Probe sessions, increases in Stimulus Duration increased accuracy (Fig. 5B; Table 5, Stimulus Duration Probe, model term 5). Tg mice performed, on average, at higher accuracy than the non-Tg mice (Table 5, Stimulus Duration Probe, model term 3) and the effect of increasing Stimulus Duration on increasing accuracy was greater in Tg mice than non-Tg mice in the 3CSRT-I group (1.01 vs. 0.43, $p = 0.02$), indicating larger improvements in accuracy in Tg mice for each 1-second increase in stimulus duration (Fig. 5B, compare red and black dashed lines).

During the Pre-Stimulus Interval Probe sessions, increases in interval duration were not systematically associated with changes in accuracy (Fig. 5C, Table 5, Pre-Stimulus Interval Probe, model term 5). Although overall, increases in Pre-Stimulus Interval did not systematically affect accuracy, posthoc comparisons indicated that during Block 3, the coefficient of Pre-Stimulus Interval was greater in 3CSRT-I non-Tg compared to 3CSRT-I Tg mice (0.13 vs. −0.11,

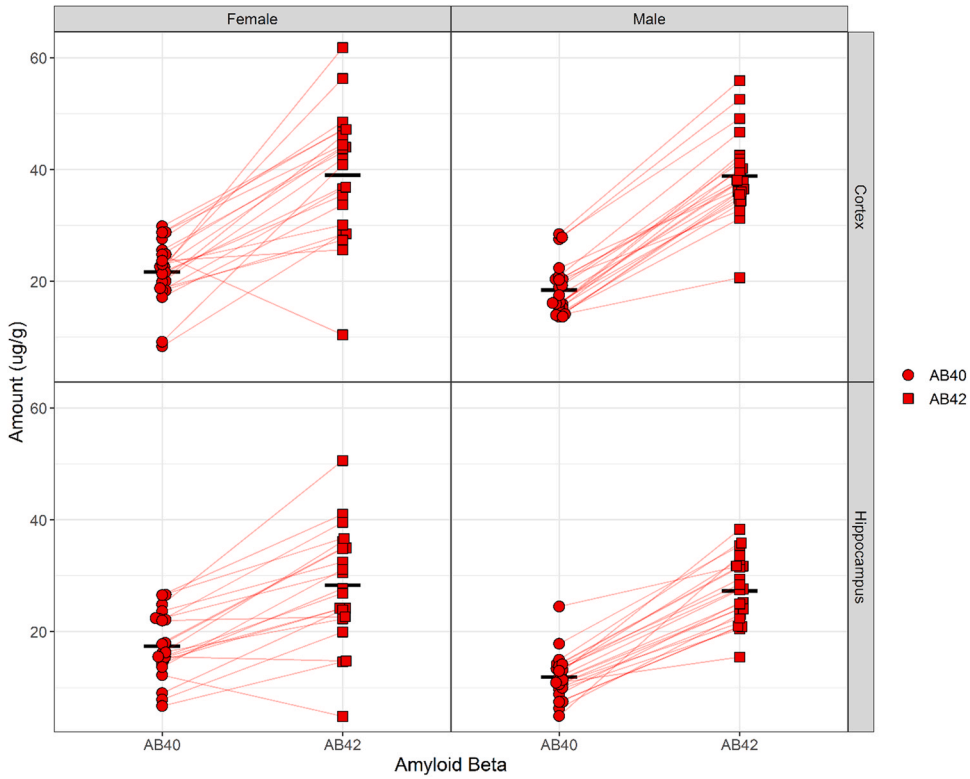

Fig. 6. Brain beta amyloid levels (μg/g) in transgenic APPswe/PS1dE9 mice at the end of the study.

$p = 0.004$), indicating improvements in accuracy with interval duration in the 3CSRT-I non-Tg, but not Tg mice (Fig. 5C, compare black and red dashed lines in Block = 3 panel).

3.6. Tg mice exhibit Aβ in brain

Female and male Tg mice both exhibited Aβ in the cortex and hippocampus with higher levels of Aβ42 than 40 (Fig. 6). Female mice had higher Aβ on average than male mice ($t[52.223] = -2.14$, $p = 0.04$), there was greater Aβ42 compared to Aβ40 ($t[61.504] = 10.75$, $p < 0.0001$), and there was more Aβ in the cortex than hippocampus ($t[71.386] = -3.25$, $p = 0.002$). Finally, there was an interaction between the type of Aβ and brain region and posthoc comparisons indicated higher Aβ42 than Aβ40 in each brain region and greater Aβ of each type in the cortex compared to Aβ of each type in the hippocampus, respectively (all $p < 0.0001$).

4. Discussion

The current study longitudinally evaluated the performance of APP/PS1 Tg and non-Tg mice in a DMTP and 3CSRT task to determine whether longitudinal testing with these tasks is suitable for evaluating potential therapeutic interventions for age-related cognitive declines in Tg mice. We expected that Tg mice would develop age-dependent, task parameter-dependent (e.g., delay-dependent in the DMTP), and possibly testing regimen (intermittent vs. continuous)-dependent deficits in performance. In contrast, accuracy in Tg mice improved over the course of the study in the continuous testing group performing the DMTP task and was higher, on average in Tg than non-Tg mice performing the 3CSRT task. Further, although declines in accuracy were observed in the intermittent groups in both tasks following breaks in testing, the declines were equivalent in Tg and non-Tg mice and accuracy quickly recovered. Similarly, during the DMTP and 3CSRT probe sessions, Tg mice performed as well or better than non-Tg mice.

Many studies have reported cognitive deficits in APP/PS1 Tg mice in other tasks, such as the Morris water maze as early as 6 month of age (e.g., Cao et al., 2007; Guo et al., 2015; Hooijmans et al., 2009; Jankowsky et al., 2005). Such results were interpreted as Aβ-induced cognitive impairment, a conclusion supported by the finding that different anti-amyloid approaches ameliorate or reduce deficit development (Janus et al., 2000; Laird et al., 2005; Morgan et al., 2000; for a discussion of anti-Aβ approaches see Savonenko et al., 2012). The lack of Tg deficits in this study raises the question of what aspects of the tasks and protocols might account for the lack of sensitivity of performance in these tasks to Aβ pathology.

Two possible explanations for the absence of deficits in Tg mice in the current study that we considered are the use of food restriction (see Van Cauwenberghe et al., 2016) and the likely lower stress entailed in our food reinforcement-based procedures as compared to water escape-based procedures. Neither explanation appears likely because deficits have been reported in food-restricted APP/PS1 Tg mice using food reinforcement (Lagadec et al., 2012; Montgomery et al., 2011) and in a different mouse model of amyloidosis also using food reinforcement in food-restricted mice (Woolley and Ballard, 2005).

A third possible explanation for the absence of Tg deficits and the observed improvements over time in the current study is the amount of exposure to the behavioral task. Regular exposure to behavioral testing might reduce or eliminate deficits by serving as enrichment, which has been reported to reduce Morris Water Maze (MWM) deficits, despite increasing Aβ levels (Jankowsky et al., 2005) or by simply maximizing accuracy via frequent practice (i.e., “practice effects” may have counteracted the development of deficits). Consistent with this suggestion is that Tg deficits were reported in DMTP accuracy using another mouse model of amyloidosis in which mice experienced limited (approximately 6 days) testing every 2–4 months (Woolley and

Ballard, 2005). Further, a recent study using frequent, longitudinal, testing of a paired associates learning and trial unique non-match to location task in APP/PS1 mice also found no declines in Tg performance over time and in fact, accuracy in the paired associates learning task improved equivalently over time in Tg and non-Tg through 1 year of age (Shepherd et al., 2021). Further, Shepherd et al. reported that prior touchscreen testing prevented subsequent deficits in MWM and increased markers of neurogenesis. Notably, even limited prior task exposure has recently been reported to prevent subsequent deficit development in an MWM task in APP/PS1 Tg mice (Lonnemann et al., 2023). Combined, these studies suggest that repeated testing may prevent deficit development, raising the possibility that APP/PS1 Tg mice exhibit deficits in the ability to learn new behaviors rather than in the ability to perform existing behaviors. It may be that APP/PS1 Tg mice are able to benefit from repeated testing because they exhibit modest, rather than extensive neurodegeneration (Jackson et al., 2016), which may be countered by the neurogenesis effects reported by Shepherd et al., and that mouse models with more extensive neurodegeneration would be more likely to exhibit longitudinal declines in performance in established performance. Such effects could explain the disconnection between Aβ levels and cognitive function reported previously (Jankowsky et al., 2005), suggesting that environmental factors can produce beneficial changes in the brain independent of Aβ levels, a result that could also have overcome potentially detrimental effects of social isolation/individual housing on cognitive function (Cao et al., 2018; Wang et al., 2018).

Interestingly, in contrast to the suggestion that repeated testing may alleviate deficits in APP/PS1 Tg mice, it appears that AD patients exhibit declines in cognitive function despite repeated cognitive assessments (Wilson et al., 2012) and clinical studies suggest that reduced practice effects are predictive of dementia risk (Jutten et al., 2020). In fact, in patients with mild cognitive impairment (MCI), the absence of practice effects predicts a transition to AD diagnosis (De Simone et al., 2021). Similarly, patients with MCI and cerebrospinal fluid markers indicative of AD performing a delayed matching-to-sample task did not show improvements 6 and 12 months after initial baseline testing (Cacciamani et al., 2018). It should be noted that the number of repeated exposures in the current study and other non-human animal studies cited above is typically much larger than the number of repeated exposures in clinical studies with MCI and AD patients (although see Lonnemann et al., 2023 for a recent demonstration of how limited prior task exposure can reduce deficit development) so that may explain the difference in when repeated testing prevents or does not prevent the development of deficits. Alternatively, it may be that the nature of the cognitive impairments in APP/PS1 mice is qualitatively different than that seen in patients with MCI and AD.

5. Conclusion

In summary, the current longitudinal study of cognitive function in APP/PS1 mice found little evidence for age-related declines in short-term memory (DMTP) or attention (3CSRT) in non-Tg or Tg mice, despite the buildup of Aβ in the brains of the Tg mice. Consideration of the literature on cognitive deficits in APP/PS1 mice suggests that the absence of deficits in the current study is not attributable to an absence of stress or to the use of food restriction. Whether and at what level of intensity repeated testing attenuates deficit development might be interesting for future investigations to understand the mechanisms of potential beneficial effects of repeated testing. Finally, the absence of deficits in APP/PS1 Tg mice in the current study indicates that the combination of procedures and testing regimens studied here cannot, unfortunately, be utilized in APP/PS1 mice to evaluate potential therapeutic interventions for cognitive decline.

CRediT authorship contribution statement

Paul L. Soto: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Funding acquisition. **Michael E. Young**: Formal analysis, Writing – review & editing, Visualization. **Giuliana M. DiMarco**: Investigation, Writing – review & editing. **Brianna George**: Investigation, Writing – review & editing. **Alena V. Savonenko**: Methodology, Formal analysis, Writing – review & editing, Visualization, Funding acquisition. **Breanna N. Harris**: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Funding acquisition.

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Verification

We have not submitted this manuscript to another journal, all authors have approved the manuscript, and if accepted, it will not be published elsewhere in the same form, in English or any other language, including electronically without the written consent of the copyright holder.

Disclosure statement

The authors declare no conflict of interest. Dr Alena Savonenko was employed at Johns Hopkins University while this work was being prepared. The opinions expressed in this article are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neurobiolaging.2023.03.010.

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