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# Progressive Age-Related Cognitive Decline in Tau Mice

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**Abstract**. Age-related cognitive decline and neurodegenerative diseases are a growing challenge for society. Accumulation of tau pathology has been proposed to partially contribute to these impairments. This study provides a behavioral characterization during aging of transgenic mice bearing tau mutations. THY-Tau22 mice were evaluated at ages wherein tau neuropathology in this transgenic mouse model is low (3-4 months), moderate (6-7 months), or extensive (>9 months). Spatial memory was found to be impaired only after 9 months of age in THY-Tau22 mice, whereas non-spatial memory was affected as early as 6 months, appearing to offer an opportunity for assessing potential therapeutic agents in attenuating or preventing tauopathies through modulation of tau kinetics.

Keywords: aging, learning, memory, tauopathy, transgenic model

## INTRODUCTION

Tauopathies, characterized by the dysfunction and aggregation of the microtubule-associated protein tau, represent some of the most devastating neurodegenerative disorders afflicting the elderly, including Alzheimer's disease (AD), progressive supranuclear palsy, corticobasal degeneration, Pick's disease, and frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) [1, 2].

Generation of transgenic mouse models expressing human tau in the brain has contributed to the understanding of the pathomechanistic role of tau in disease. In many models, however, the temporal pattern of cognitive decline has not been described [3]. This is of importance for pharmaceutical treatment, since knowing the phenotypes at each age is essential for setting up appropriate drug designs [4]. It is of particular concern to identify age-dependent phenotypes to relate behavioral anomalies to biologic markers appearing at different stages.

Even though tau pathology has been studied in AD and other tauopathies for many years, the direct significance of neurofibrillary tangle accumulation for neuronal and cognitive function is still unclear. Previously it was shown that animals with mutations in the amyloid-β protein precursor and presenilin display progressive, age-related behavioral impairments [5–7].

Because of these considerations, we evaluated several series of THY-Tau22 mice from 3 to 10 months of age. A cross-sectional design was used to avoid the possible influence of multiple testing on individual animals. THY-Tau22 mice overexpress mutated human tau, develop tau aggregates, coinciding with impaired hippocampus-dependent learning and memory, and attenuated late-phase long-term depression of synaptic transmission [8–10].

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Here we report that this animal model displays a wide spectrum of features characteristic to tauopathy and AD in an age-dependent manner: 3-4 month-old THY-Tau22 mice with early-stage tau pathology are unaffected behaviorally. Concurrent with the progressive tau pathology in the CA1, 6-7 month-old THY-Tau22 mice develop learning and memory deficits in behavioral tasks that are associated with hippocampal function, precisely the brain region affected by tau pathology.

## MATERIALS AND METHODS

### *Animals*

Heterozygous THY-Tau22 transgenic mice were compared with their wild-type (WT) littermates. Only males were used in these experiments. The tau mice overexpress mutated hTau under the control of a Thy1.2 promotor displaying tau pathology in the absence of any motor dysfunction [8]. The vector was injected into a C57BL6/CBA background and back-crossed to C57BL6. The progeny was genotyped using PCR on DNA isolated from tail biopsy. THY-Tau22 mice show no hearing loss or different sensitivity to thermal nociceptive stimulation up to 11 months [9, 10].

### *Experimental design*

Mice were divided into the following age groups, each consisting of 12 THY-Tau22 and 12 WT mice: 3-4 months, 6-7 months, and 9-10 months. Mice were tested cross-sectionally in the following experimental sequence: behavior, biochemistry, and histology. For each of the age groups, the complete sequence of behavioral tests required approximately 3 weeks and consisted of the following tasks in the sequence: classic Morris water maze test, probe test, social transmission of food preference, and contextual fear conditioning. All animals were kept in standard animal cages under conventional laboratory conditions (12 h/12 h light-dark cycle, 22°C), with *ad libitum* access to food and water (unless stated otherwise). Behavioral experiments were conducted during the light phase of their activity cycle.

### *Behavior*

#### *Morris water maze*

Spatial memory abilities were examined in the standard hidden-platform acquisition and retention version of the water maze [11]. A 150-cm circular pool was filled with water, opacified with non-toxic white paint, and kept at 26°C as previously described [12, 13]. A 15-cm round platform was hidden 1 cm beneath the surface of the water at a fixed position. Four positions around the edge of the tank were arbitrarily designated 1, 2, 3, and 4; thus dividing the tank into four quadrants (clockwise): target, adjacent 1, opposite, and adjacent 2. Each mouse was given four swimming trials per day (10 min intertrial interval) for five consecutive days. The start position (1, 2, 3, or 4) was pseudo-randomized across trials. Mice that failed to find the submerged platform within 2 min were guided to the platform, where they remained for 15 s before being returned to their cages. Escape latency (s), path length (cm), velocity (cm/s), and search patterns of the mice were tracked using the Ethovision video tracking system (Noldus Information Technology, Wageningen, The Netherlands).

Acquisition trials were further analyzed to identify differential search strategies [14–19]. Table 1 summarizes the eight different search strategies that were scored in these analyses. Such strategies ranged from proper spatial strategies to those that involved systematic scanning of the pool without actually relying on spatial information (non-spatial strategies), or those that merely consisted of repetitive loopings.

To evaluate retention memory, probe trials were presented 2 days after the last acquisition day. During these probe trials, the platform was removed, and the swimming path was recorded during 100 s. Time spent in each quadrant was measured. We also visualized these swimming paths using a custom-made MATLAB protocol. Briefly, swimming paths of individual mice were placed on top of each other to create heat plots for every group. Color intensities (from blue to red) indicated relative presence in specific areas of the pool.

#### *Social transmission of food preference task*

In this task, an animal is evaluated on its ability to learn about the safety of food from its conspecifics [20]. The select-reject decision process involves an evaluation of the sensory characteristics of the foodstuff, particularly its flavor. Two days prior to the experiment all mice were food deprived. On the third day, four 'demonstrator' mice were allowed to eat food containing a novel odor (paprika or celery) for 2 h. Immediately after, during a 2-h social encounter, demonstrators were able to exchange information about the food odor with the observer mice. The odor-reward pairing was equally counterbalanced among groups. Finally, 24 h after the interaction, the observers

Table 1
Summary of different search strategies mice can use to locate the hidden platform in the Morris water maze. These can be broadly classified as spatial, non-spatial or repetitive looping

| Main search strategy | Specific search strategy | Description search strategy |
|---|---|---|
| Spatial | Spatial direct | Mice swim to the platform in a straight line |
| | Spatial indirect | Mice swim to the platform with one small explorative loop |
| | Focal correct | Mice search for the platform in the correct quadrant |
| Non-spatial | Focal incorrect | Mice search for the platform in the wrong quadrant |
| | Scanning | Mice search for the platform in the center of the pool |
| | Random | Mice do not show preference to any part of the pool |
| Repetitive looping | Chaining | Mice search in the target annulus area |
| | Thigmotaxis | Mice display predontinant wall hugging behavior |

were given a preference test for the cued food odor versus another new food odor. Each observer was placed individually in a cage with two weighed cups of food containing the alternative scented foods, and allowed to eat for 2 h. The amount of grams eaten from both food cups was determined by weighing the remaining food.

*Contextual fear conditioning*

The test chamber ($26 \times 22 \times 18$ cm high) of the contextual fear conditioning experiment [21]. was made of clear Plexiglas, and the grid floor was used to deliver an electric shock using a constant current shocker (MED Associates Inc., St. Albans, Vermont, USA). The test chamber was placed inside a sound attenuated chamber. The experiment consisted of 3 days. On the first day, animals were placed in the testing chamber and were allowed to acclimate for 5 min. On the second day, animals were again placed in the testing chamber and after 2 min of exploration (baseline score), a buzzer was sounded for 30 s. This auditory stimulus, the conditional stimulus, was followed by a 2-s foot shock (0.3 mA), the unconditional stimulus. After the shock, mice were allowed to explore once more for 1 min before they received a second conditional-unconditional stimulus pairing. Finally, they were allowed to explore for another minute. Twenty-four h later, on the third and last day, the animals were placed in the same context for 5 min exploration (context score). After 90 min, the mouse was again placed in the test chamber. Environmental and contextual cues were changed: a white paper square insert was placed in the chamber to alter its color, and mint extract was used to alter the smell. After 3 min of free exploration (pre-conditional stimulus score), the auditory stimulus was delivered for 3 min (conditional stimulus score). Freezing behavior was recorded every 10 s.

*Biochemistry and histology*

After completion of the behavioral experiments, animals were killed and brains removed. Half of the brains were processed for biochemical studies, and the second half for histology. For biochemistry, hippocampi were dissected out using a coronal acrylic slicer (Delta Microscopies) at 4°C and stored at −80°C until use. Tissue was homogenized as described previously [8, 9]. For western blot analysis, samples were diluted in NuPage sample buffer (Invitrogen) and denaturated at 100°C for 5 min. Then, 15 μg of proteins were loaded on 4–12% NuPage Novex gels, and transferred to nitrocellulose or polyvinylidene fluoride membranes and incubated with appropriate antibodies. Signals were visualized by chemiluminescence (ECL; GE Healthcare). For histology, brains were fixed for 7 days in 4% paraformaldehyde, then incubated in 20% sucrose for 24 h and kept frozen until use. Free-floating coronal sections (40 μm) were obtained using a cryostat (Leica Microsystems). Sections of interest were used for free floating immunohistochemistry using tau antibodies as previously described [8, 9].

*Statistics*

The behavioral performance of THY-Tau22 transgenic mice and non-transgenic WTs was initially evaluated for the three behavioral time points separately. This allowed determination of whether progressive behavioral impairment was shown by transgenic mice—namely, that transgenic mice differed from WTs at the later, but not the earlier time points. All behavioral comparisons were done by means of analysis of variance (ANOVA). As a second determination of whether progressive behavioral changes had occurred in transgenic mice between the three time points, performance of transgenic mice tested at the earlier time point was compared directly to that of transgenic mice tested at the later time point. Similar comparisons were also performed between both age groups of non-transgenic animals to determine the presence of any normal age-related behavioral changes. Data were analyzed using SPSS Statistics

19.0 (SPSS Inc). All group differences were deemed significant at $p < 0.05$.

## RESULTS

### *Behavior*

The hippocampus is a brain region critical for learning and memory [22–28]. THY-Tau22 mice and WTs (at 3-4, 6-7, and 9-10 months; $n = 12$ per group) were subjected to the Morris water maze, a routinely used task to assess hippocampal function in mice. The mice received four training trials per day for five consecutive days and their time to find the platform, the distance traveled and the swimming speed were recorded and analyzed using RM-Anova (day × genotype × age). At 3-4 months of age, both groups showed good performance during the acquisition of the platform position ($p > 0.05$; Fig. 1A). Also, 6-7 month THY-Tau22 mice were indistinguishable from their age-controlled WTs ($p > 0.05$; Fig. 1B). At 9-10 months, the WTs quickly learned to find the platform, whereas the THY-Tau22 mice did not ($F_{1,88} = 187.54$; $p < 0.001$; Fig. 1C). Bonferroni's *post hoc* analysis revealed that from day 3 onwards, the 9-10-month-old THY-Tau22 performed significantly worse (longer path lengths and longer escape latency) than their age-matched control WTs. This was also reflected in the probe trial where 9-10 months WT mice preferentially spent more time in the former target quadrant compared to THY-Tau22 mice ($F_{1,22} = 31.21$, $p < 0.001$). At the younger ages (3-4 and 6-7 months), both groups spent most of their time searching in the target quadrant and thus were indistinguishable from each other (both $p > 0.05$; Fig. 1D, 1E). Also, swim speed in the water maze, as an index of motor performance, was analyzed. Velocity did not differ between groups at any of the ages, nor did mice show any changes in swim speed over time (all $p > 0.05$).

During acquisition training, different search strategies can be used and we categorized the different acquisition trials to one of the three main categories including spatial, non-spatial, and peripheral looping. RM-Anova (day × genotype × age) revealed a significant change in spatial strategy choice ($F_{8,260} = 8.022$; $p < 0.001$). Both 3-4 (Fig. 2B–E) and 6-7 (Fig. 2C–F) months old WT and THY-Tau22 mice progressively used more spatial strategies, whereas the 9-10 (Fig. 2D–G) months old THY-Tau22 group did not, in contrast to their age-matched WT littermates ($F_{2,65} = 89.949$), $p < 0.001$). 9-10 month old THY-Tau22 mice appeared to be using more peripheral looping. Indeed, when comparing the heat plots of the probe, we observed that young and aged WT mice mostly searched the area close to the designated platform position. In contrast, 9-10 month old THY-Tau22 mice seemed to be circling rather more aimlessly (Fig. 2 inserts).

Subsequently, mice were subjected to a non-spatial learning and memory test, the social transmission of food preference test. While WTs had a significant preference for the scented foods their respective demonstrators ate at all ages tested ($t_{11} = 4.51$, $p < 0.01$ for 3-4 months; $t_{11} = 4.75$, $p < 0.01$ for 6-7 months; and $t_{11} = 4.05$, $p <= 0.01$ for 9-10 months respectively; Fig. 3A–C), THY-Tau22 mice showed only a clear preference for the cued food at 3-4 months ($t_{11} = 3.58$, $p < 0.01$; Fig. 3A), that decreased at 6-7 months ($t_{11} = 2.22$, $p < 0.05$; Fig. 3B), and totally vanished at 9-10 months ($p > 0.05$; Fig. 3C). Direct comparisons between WT and THY-Tau22 mice at all three ages revealed no significant differences (all $p > 0.05$).

Finally, mice underwent contextual fear conditioning. At 3-4 (Fig. 3D) and 6-7 (Fig. 3E) months, both groups show equal freezing responses in all phases (all $p > 0.05$; Fig. 3D and E). At 9-10 months, THY-Tau22 animals showed less conditioned freezing responses than WTs during the context trial ($F_{1,22} = 8.059$, $p < 0.01$; Fig. 3F). Both groups displayed similar freezing responses in the following pre-conditional and conditional stimulus trials (all $p > 0.05$).

### *Biochemistry and histology*

Histological and biochemical analyses were performed on brain tissue from THY-Tau22 mice and WT littermates that had been used in the behavioral experiments. Immunoblot and immunohistochemical analysis of tau phosphorylation at Ser396 and Thr181 show hyperphosphorylation of tau in the hippocampi of THY-Tau22 mice detectable from 3 months and increasing with age (Fig. 4). Also, the levels of total tau protein increase slightly with age in THY-Tau22 mice ($n = 3$/age group per genotype).

## DISCUSSION

Prior studies involving behavioral endpoints in mutant tau transgenic mice have revealed cognitive impairments in some tasks [29–43]. Here, a cross-sectional design was used to avoid the possible influence of multiple testing on individual mice. The aim of the present study was to determine possible

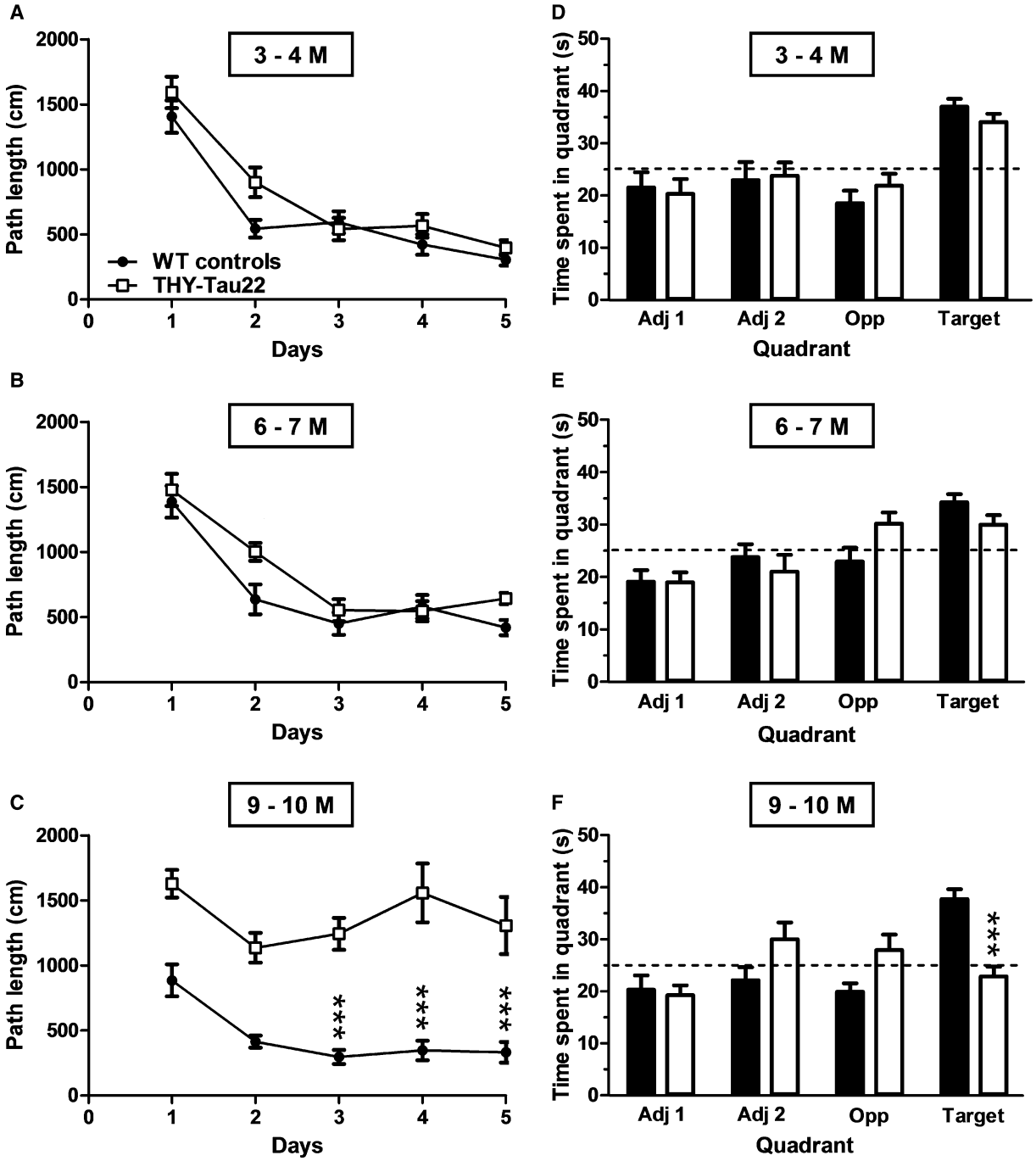


Fig. 1. Spatial memory impairment appears at 9 months of age in THY-Tau22 mice. WT mice (dark symbols) and THY-Tau22 mice (white symbols) were tested at different ages with the MWM. At 3-4 months of age, both groups showed good performance during the acquisition of the task (A) and memory retention (D). WT and THY-Tau22 mice at 6-7 months of age continued to show good performance during learning (B) and retention (E). At 9 to 10 months of age, WT mice learned the platform location, whereas THY-Tau22 mice showed impairment in the learning curve during acquisition (C). THY-Tau22 mice of 9-10 months of age spent an almost equal amount of time in each quadrant during the probe trial, whereas WT mice preferentially spent more time in the quadrant where the platform was previously located (F). Values are expressed as means ± SEM; asterisks indicate significant difference between THY-Tau22 and WT control values (***$p < 0.001$; **$p < 0.01$; *$p < 0.05$).

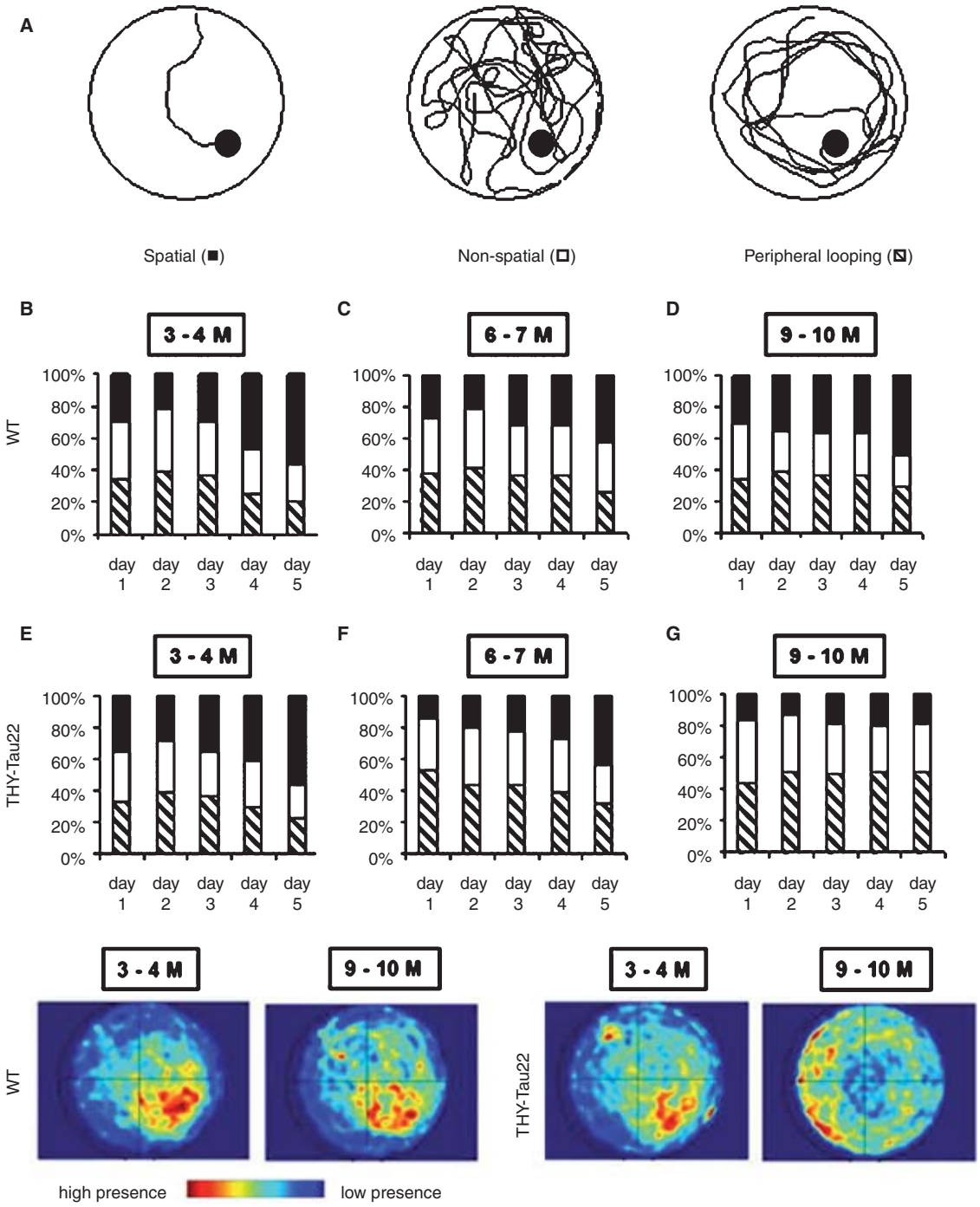


Fig. 2. MWM search strategy. Path length traces were placed in three categories according to their strategy in locating the hidden platform. Representative traces are shown for spatial, non-spatial, and peripheral looping strategies (A). See detailed definitions in text. Percentage of trials using a given strategy plotted as a function of genotype and day of platform training. At 3-4 and 6-7 months of age, peripheral looping strategy use and non-spatial strategy use decreased, where spatial strategy use increased in WT (B-C) and tau mice (E-F). At 9-10 months, peripheral looping and non-spatial strategy use dropped in WT, coinciding with an augmentation in spatial strategy use (D). However in the aged THY-Tau22 mice this was not the case indicating that the THY-Tau22 mice from this age group failed in learning the position of the platform (G). Values are expressed as means. Heatplots of the probe trials (without platform) after 5 consecutive days of acquisition illustrate clear target preference in 3-4 and 6-7 (data not depicted) and 9-10 months old WT mice. 3-4 and 6-7 months (data not depicted) old THY-Tau22 mice also show target preference, but this disappears at 9-10 months.

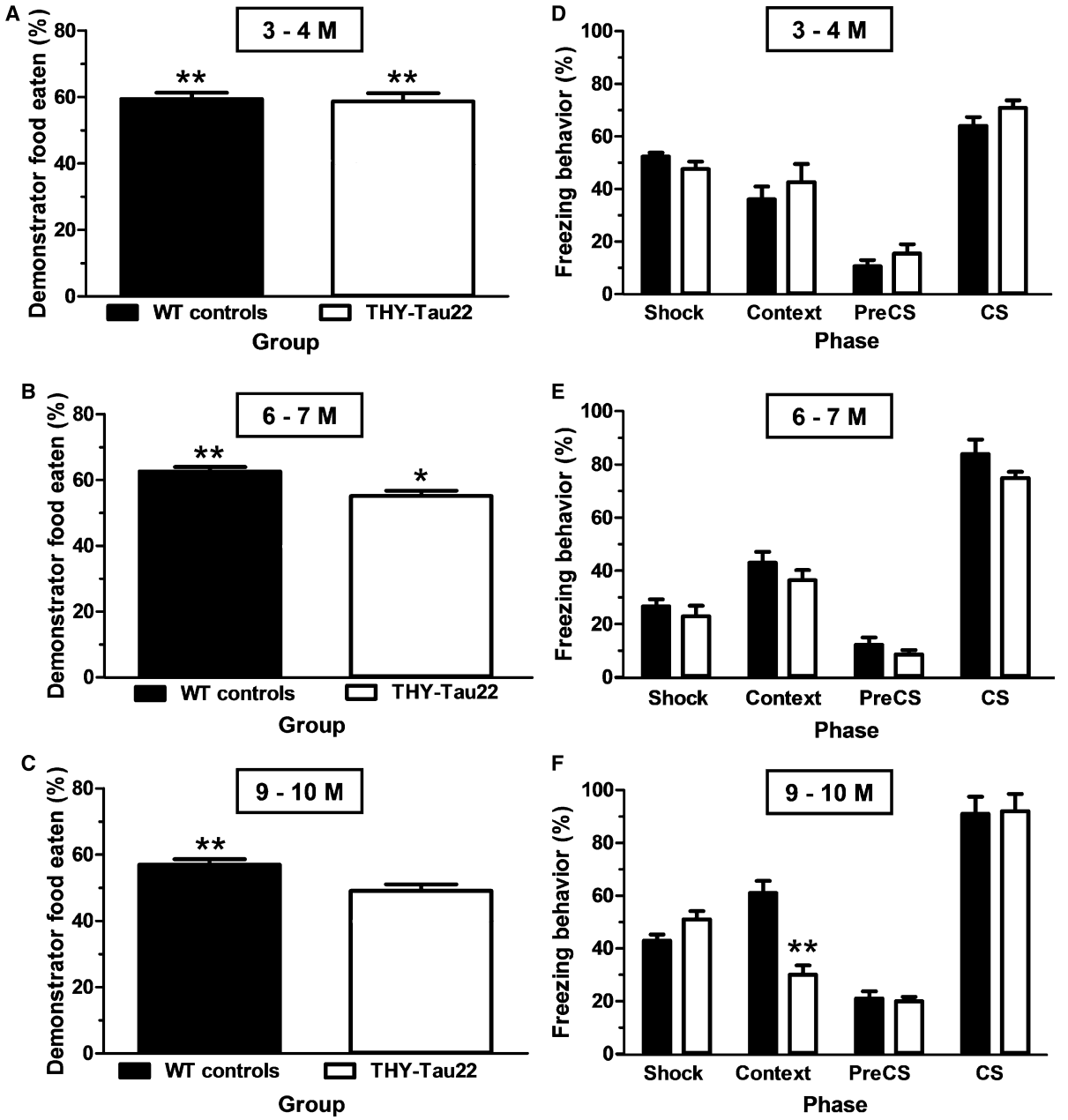


Fig. 3. Non-spatial memory impairment occurs as early as 6 months of age in THY-Tau22 mice. Social transmission of food preference. Amount of food eaten in a 2 h interval over the 24 h choice test. While WTs had a significant preference for the scented foods their respective demonstrators ate all ages tested (A–C), THY-Tau22 mice showed only a clear preference for the cued food at 3-4 months (A), that decreased at 6-7 months (B), and totally vanished at 9-10 months (C). Contextual fear conditioning. At 3-4 (D) and 6-7 (E) months, both groups show equal freezing responses in all phases. At 9-10 months, THY-Tau22 animals showed less conditioned freezing responses than WTs during the context trial (F). Both genotypes displayed similar freezing responses in the following pre-conditional and conditional stimulus trials. Asterisks indicate significant difference between the two genotypes or significant preference for the cued food in the social transmission of food preference task (***$p < 0.001$; **$p < 0.01$; *$p < 0.05$).

behavioral impairments in THY-Tau22 transgenic mice compared to their WT littermates in tests of cognitive function. The age groups examined were 3-4 months, when tau tangles first appear in the transgenic animals, and 6-7 and 8-9 months to correspond to a period when tangle load increases dramatically. The

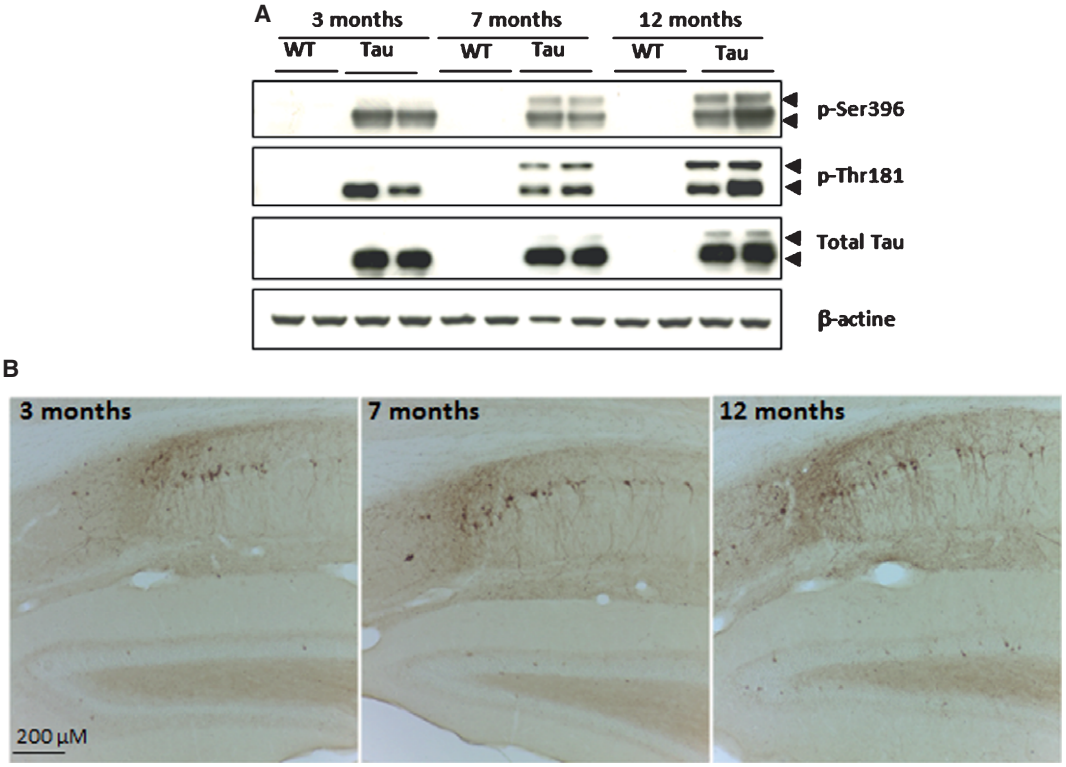


Fig. 4. Increase of hippocampal tau hyperphosphorylation in THY-Tau22 mice. Immunoblot analysis of progressive tau hyperphosphorylation at Ser396 and Thr181 in the hippocampus of THY-Tau22 mice aged 3, 7, and 12 months (A). Immunohistochemical analysis of the progressive abnormal tau phosphorylation at Ser422 in the CA1 area of the hippocampus at the same ages (B).

results presented here indicated progressive cognitive impairment in hTau transgenic mice for spatial and non-spatial learning and memory tasks.

The cognitive processes that underlie the acquisition and use of spatial information to solve a Morris water maze task are manifested by the implementation of spatial strategies such as "swimming directly to it" or "searching in the right quadrant for the platform" [14, 15, 18, 44, 45]. The use of such spatial strategies in WT mice was demonstrated to be lacking in some AβPP-transgenic mouse lines that often employ non-spatial strategies [16]. In the present study, 9-10 month old THY-Tau22 mice made little use of spatial strategies, and rather depended on alternative search strategies such as chaining and repetitive looping, strategies that do not require a spatial recall but use circular swimming to eventually bump into the platform. Analogous effects of tauopathy on spatial learning were observed for other AD mouse models [42, 46–48].

It was recently shown that AβPP/PS1 mutant mice harboring amyloid plaques in the brain displayed lower levels of social interaction [49]. These mice were less willing to engage in social interaction than their control WTs, avoiding an unfamiliar stimulus mouse. In the present study, we investigated olfactory memory in mice using the social transmission of food preference task. This phenomenon is understood to depend on the ability of the observer subject to detect olfactory cues on the breath of the demonstrator [20, 50]. Mutations that affect hippocampal function in mice have been shown to impair performance on this task [51, 52]. We were able to show that while WTs had a significant preference for the scented foods their respective demonstrators ate at all ages tested, tau transgenic mice developed olfactory memory deficits at 6-7 months.

Cognition requires changes in synaptic plasticity, mediated by cytoarchitectural changes [53]. Because neurofibrillary pathology predominates in the hippocampus, memory was evaluated using the hippocampus-dependent Morris water maze and passive avoidance tests [54, 55]. Plasticity in the hippocampal region (where our THY-Tau22 mice show pronounced pathology) is important for contextual learning, in accordance with the impairments seen in 9-10 month old THY-Tau22 mice in this classical form of Pavlovian conditioning. 9-10 month old THY-Tau22

mice failed to remember the stimulus in the passive avoidance test 24 h after an electric shock, consistent with results in other mouse lines expressing human tau [42, 56], and in some amyloid-β-based mouse lines [18, 57, 58].

Hippocampal synaptic short and long-term plasticity deficits in amyloid and tau mutated mouse models are well-documented [6, 10, 59–69]. Spatial learning defects result from defective hippocampal synaptic plasticity, and long-term potentiation (LTP)-like mechanisms subserve cognition [70]. The miss-sorting of tau from axons to dendrites could influence mRNA transport required for synaptic plasticity and tau protein is required for amyloid-β-induced impairment of hippocampal LTP [71–73]. Genetic perturbations of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionatereceptors (AMPARs) are widely used to dissect molecular mechanisms of sensory coding, learning, and memory. AMPAR modification can be obtained by depletion of the GluR-B subunit or expression of unedited GluR-B, both leading to increased $Ca^{2+}$ permeability of AMPARs. Mice with this functional AMPAR switch, specifically in forebrain, showed impaired olfactory memory. Moreover, GluR-B depletion in forebrain strongly correlated with decreased olfactory memory in hippocampus and cortex [74]. We have recently observed a lack of brain-derived neurotrophic factor, a factor that plays a critical role in hippocampus-dependent synaptic plasticity and memory, -induced synaptic enhancement in 7 month old THY-Tau22 mice, that was however unrelated to changes in AMPAR-dependent basal synaptic transmission [75].

We found spatial memory to be impaired only after 9 months of age in hTau mice, whereas non-spatial memory was affected as early as 6 months. This could be related to the nature of the learning. The learning in the water maze is clearly spatial, and also the context phase of the fear conditioning task is. In contrast, in social transmission of food learning the learning is mainly olfactory. Olfactory disorders are noted in a majority of neurodegenerative diseases [76, 77], but they are often misjudged and are rarely rated in the clinical setting. Another factor may well be task difficulty. For example, fear conditioning and food preference learning are easy in the sense that marked learning takes place in few trials. It may be that there are different thresholds of impairment of brain function for measureable performance deficit as cognitive ability declines with age, such that impairment is first detected only on difficult tasks and only later on easier tasks. Whatever the reason for the pattern of deficits turns out to be our results are similar to those seen in demented itself in that patients are first impaired only on difficult tasks, but are later also impaired on easier tasks [78].

Altogether, as previously described, and further confirmed in the present study, hTau mice develop age-dependent and progressive tau pathology. Behavioral tests assessing learning and memory showed that young THY-Tau22 mice, with early stages of tau pathology, did not present cognitive deficits. As tau accumulation progresses to a moderate stage of tau pathology, cognitive function also declines. Our results indicate that tauopathy in the THY-Tau22 mouse model coincides with distinct deficits in spatial and non-spatial hippocampus-dependent tasks in an age-dependent manner, in the absence of motor deficits, offering opportunities for assessing potential therapeutic agents in attenuating or preventing tauopathies through modulation of tau kinetics.

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Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1824).

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