Journal of Alzheimer's Disease 37 (2013) 109–125
DOI 10.3233/JAD-122296
IOS Press

Amyloid and Tau Neuropathology Differentially Affect Prefrontal Synaptic Plasticity and Cognitive Performance in Mouse Models of Alzheimer's Disease

Adrian C. Lo[a], Emilia Iscru[a,1], David Blum[b], Ina Tesseur[c,d], Zsuzsanna Callaerts-Vegh[a], Luc Buée[b], Bart De Strooper[c,d], Detlef Balschun[a] and Rudi D'Hooge[a,*]
[a]*Laboratory of Biological Psychology and Leuven Institute for Neuroscience & Disease (LIND), University of Leuven, Leuven, Belgium*
[b]*INSERM U837 Alzheimer and Tauopathies, & Université Lille Nord de France, Institute of Predictive Medicine and Therapeutic Research, France*
[c]*Center for Human Genetics and Leuven Institute for Neuroscience & Disease (LIND), University of Leuven, Leuven, Belgium*
[d]*VIB Center for the Biology of Disease, VIB-Leuven, Belgium*

Accepted 6 May 2013

Abstract. Alzheimer's disease (AD) is a consequence of degenerative brain pathology with amyloid plaque deposition and neurofibrillary tangle formation. These distinct aspects of AD neuropathology have been suggested to induce a cascade of pathological events ultimately leading to neurodegeneration as well as cognitive and behavioral decline. Amyloid and tau neuropathology is known to develop along distinct stages and affect parts of the brain differentially. In this study, we examined two mouse AD lines (AβPPPS1-21 and Tau22 mice), which mimic different partial aspects of AD pathology, at comparable stages of their pathology. Since prefrontal cortex (PFC) is one of the first regions to be affected in clinical AD, we compared long-term potentiation (LTP) of synaptic responses in medial PFC of AβPPPS1-21 and Tau22 mice. Frontal LTP was impaired in AβPPPS1-21 mice, but not in Tau22 mice. Consequently, we observed different behavioral defects between AβPPPS1-21 and Tau22 animals. Apart from spatial learning deficits, AβPPPS1-21 transgenic mice were impaired in fear learning, aversion learning, and extinction learning, whereas THY-Tau22 were impaired in appetitive responding. Discriminant function analysis identified critical behavioral variables that differentiated AβPPPS1-21 and THY-Tau22 mice from wild type littermates, and further confirmed that amyloid- versus tau-pathology differentially affects brain function.

Keywords: Alzheimer's disease, amyloid, cognition, prefrontal cortex, synaptic plasticity, tau

INTRODUCTION

Alzheimer's disease (AD) is characterized by two pathobiochemical events that are thought to affect synaptic function and ultimately result in neurodegeneration [1–3]. A first series of events involve amyloid-β (Aβ) peptides cleaved from the amyloid-β protein precursor (AβPP) that aggregate extracellularly into soluble oligomers and insoluble amyloid plaques [4]. Secondly, hyperphosphorylated tau proteins translocate to the somatodentritic region of the neuron and ultimately aggregate into intracellular neurofibrillary tangles (NFTs). Soluble forms of tau have been shown to severely compromise neural function [5].

[1]Present address: Laboratory of Synapse Biology, University of Leuven, Leuven, Belgium.

*Correspondence to: Dr. Rudi D'Hooge, Laboratory of Biological Psychology, Tiensestraat 102, B-3000, Leuven, Belgium. Tel.: +32 16326142; E-mail: rudi.dhooge@ppw.kuleuven.be.

ISSN 1387-2877/13/$27.50

Amyloid and tau neuropathology both develop along distinct stages, but appear to affect parts of the brain differentially [6]. Amyloid pathology initiates in neocortex and spreads to hippocampus and other brain regions [7], whereas tau pathology starts in the limbic system and spreads toward the neocortex [8]. Patients suffering from AD eventually show deficits in episodic memory [9], fear conditioning and flexibility [10], and various other cognitive functions [11]. However, clinical AD is heterogeneous both with respect to pathology and behavioral symptoms [12, 13], and it remains largely unknown whether Aβ- and tau-related pathology contribute to similar or different functional defects.

Amyloid- and tau-based mouse models, which mimic partial aspects of AD pathology and show neurocognitive deficits, are crucial to contemporary preclinical AD research [14–20]. In this study, we directly compared two distinctive transgenic mouse models that show either amyloid (AβPPPS1-21; [21]) or tau pathology (Tau22; [22, 23]) using a variety of AD-relevant behavioral protocols. The mice had been backcrossed to C57Bl/6J background, and experimental conditions were equated across groups (i.e., behavioral protocols and their timing, housing and handling conditions, gender, and age). Given the different pathogenetic trajectory of amyloid and tau pathology, we hypothesized that different cognitive functions might be compromised in these two mouse lines. In addition, we expected that cognitive functions that were compromised at the earliest stages would be most relevant to discriminate wild type from transgenic mice in each of these mouse models. We also wanted to determine whether amyloid and tau pathology affected different aspects of neocortical performance. Further, we investigated whether the putative behavioral differences between the two AD models would coincide with differences in prefrontal synaptic plasticity. Hippocampal plasticity has been tested in AD mouse models and related to spatial learning defects [20, 24–26], but prefrontal cortex (PFC) has been shown to play a central role in various aspects of rodent behavior as well [27, 28]. To investigate whether PFC might be differentially affected by amyloid or tau neuropathology, we compared recordings of synaptic plasticity in medial PFC between the two models.

MATERIAL AND METHODS

Transgenic mouse lines and genotyping

AβPPPS1-21 mice were provided by Dr. Mathias Jucker (Hertie Institute for Clinical Brain Research, Tübingen, Germany). Heterozygous AβPPPS1-21 were backcrossed to C57BL/6J mice (Elevage Janvier, Le-Genest-Saint-Isle, France) for >5 generations. AβPPPS1-21 transgenic mice co-expressed human amyloid-β protein precursor (AβPP) Swedish double mutation (KM670/671NL) and presenilin1 L166P mutation under the control of a Thy1 promoter [21]. Amyloid deposition started at the age of 2–3 months in frontal cortex, and subsequently in hippocampus. By the age of 7–8 months, the first signs of cognitive impairment arose [29] and amyloid deposition occurred in all brain regions, except cerebellum.

THY-Tau22 (Tau22) mice backcrossed for >5 generations into a C57BL/6J background were provided by Dr. Luc Buée (INSERM U837, Lille, France). These mice co-expressed the human tau mutations G272V and P301S within the tau repeat domains under the control of a Thy1 promoter [22]. At the age of 3 months, phosphorylated tau (AT8 staining) occurred in hippocampus and frontal cortex. Pathological tau (AT100 staining) was detected at the age of 6 months in hippocampus, amygdala, striatum, and olfactory bulb. At the age of 7–8 months, cognitive impairment was observed [20, 22, 30].

We bred four batches of mice (two of each line) and examined transgenic males (AβPPPS1-21 tg = 35; Tau22 tg = 30) and their wild type littermates (AβPPPS1-21 wt = 35; Tau22 wt = 28) at 9–10 months of age (i.e., when robust behavioral impairments were observed). All offspring were PCR genotyped using DNA isolated from tail biopsies as previously described [21, 22]. Different animals were used for *in vitro* electrophysiology and behavioral assessment. Table 1 indicated which batch of animals was used for which behavioral tasks with their respective sample sizes. All animals were kept at the Leuven animal facilities in standard animal cages under conventional laboratory conditions (12 h light/dark cycle, 22°C), with *ad libitum* access to food and water, unless stated otherwise. Experiments were conducted during the light phase of the activity cycle. All protocols were reviewed and approved by the animal experiments committee of the University of Leuven, according to European directives.

Extracellular recordings from medial PFC

Electrophysiological recordings were performed on coronal PFC slices, cut at 1.5–2.5 mm rostral from Bregma. Animals were killed by cervical dislocation and the whole brain was rapidly dissected into ice-cold preoxygenated artificial cerebrospinal fluid (ACSF)

Table 1
Overview of the mice used in the various behavioral tasks

Behavioral test	AβPPPS1-21	Tau22
Open field	Batch 1 & 2	Batch 3 & 4
Dark light box	Batch 1 & 2	Batch 3 & 4
Morris water maze	Batch 1 & 2	Batch 3 & 4
Social recognition	Batch 1	Batch 3
Passive avoidance	Batch 1	Batch 3
Scheduled appetitive conditioning	Batch 2	Batch 4
Conditioned taste aversion	Batch 2	Batch 4

AβPPPS1-21: Batch 1 (wt = 20; tg = 15); Batch 2 (wt = 15; tg = 15); Tau22: Batch 3 (wt = 15; tg = 15); Batch 4 (wt = 13; tg = 15).

consisting of (in mM) 124 NaCl, 4.9 KCl, 2.5 $CaCl_2$, 1.3 $MgSO_4$, 1.2 NaH_2PO_4, 25.6 $NaHCO_3$, 16.6 D-glucose, gassed with 95% O_2/5% CO_2, at pH 7.4. Usually, 2 slices (400 μm thick) were prepared per mouse using a lab-made tissue chopper, and incubated for 1 h at room temperature before being placed in a submerged-type four-chamber recording system (Campden Instruments LTD, Loughborough, Leics., UK), and maintained there at 32°C and a flow rate of 1.8 to 2 ml/min/chamber. In all experiments, custom-made monopolar tungsten electrodes were used for stimulation, ACSF-filled glass electrodes (5–7 MΩ resistance) for recording of field excitatory postsynaptic potentials (fEPSPs). The initial slope of the fEPSPs served as a measure of this potential. To assess basic properties of synaptic responses, I/O curves were established by stimulation with 30 to 90 μA constant currents. The stimulation strength was adjusted to evoke a fEPSP slope of 40% of the maximum and kept constant throughout the experiment. During baseline recording, 3 single stimuli (0.1 ms pulse width; 10 s interval) were measured every 5 min. Once a stable baseline was established, long-term potentiation (LTP) was induced by 4 episodes of high-frequency stimulation at 100 Hz for 1 s, with 5-min interval between consecutive episodes.

Immunohistochemistry on PFC sections

We examined PFC of 9–10 month old AβPPPS1-21 and Tau22 transgenic mice for amyloid deposits and phosphorylated tau, respectively. Fixed hemibrains were cut into 40 μm thick coronal sections. In AβPPPS1-21 PFC, coronal sections were stained with HRP-labeled 6E10 antibody to detect Aβ depositions specifically on free-floating sections. Tyramide-fluorescein (Perkin Elmer) was used to amplify antibody signals conform to manufacturer's instructions. Negative controls omitting primary antibody and controls for cross-reactivity of the tyramide label were included in all experiments. DAPI was used as a counter stain. In Tau22 PFC, phosphorylated tau (AT8; pSer202/205) was immunolabeled on 40 μm thick free-floating sections, as previously described [22] using AT8 antibody (Thermo Scientific; 1:200), and the reaction was visualized with diaminobenzidine.

Behavioral testing

Open field

Increased open field activity has been reported in several AD models [31–33]. To measure exploratory activity in the open field test, mice were dark-adapted for 30 min before being placed in the open field arena (50 × 50 cm²). After 1-min habituation, exploratory behavior was recorded for 10 min using *Ethovision* (Noldus, Wageningen, The Netherlands). Variables measured were path length and time spent in the open field center.

Dark light box

To test anxiety levels, dark-adapted mice were placed in an arena with a dark (20 × 26.5 cm²) and a light compartment (27 × 26.5 cm²). Light and camera were 64 cm underneath and 92 cm above the apparatus, respectively. Mice were placed in the middle of the dark compartment, and recording started after 5 s. Time spent in the light compartment was measured for 10 min (ANYMAZE, Illinois, US). The arenas were thoroughly cleaned with water after every session.

Morris water maze

Spatial learning capacity was tested in the standard hidden-platform acquisition and retention version of the Morris water maze [34, 35]. The maze consisted of a large circular pool (diameter 150 cm) filled with water (26°C) to a depth of 16 cm. Water was opacified with non-toxic white paint to prevent animals from seeing the platform. The circular platform (diameter 15 cm) was hidden 1 cm beneath water surface at a fixed position. The pool was situated at the center of a brightly lit room with various fixed cues (e.g., posters, computers, tables) and the experimenter always sat in the same place. Mice were trained for 14 days to find the hidden platform. There were four trials per training day; with a trial interval of 30 min. Mice were placed into the pool at one of four starting locations. When mice failed to find the platform within 2 min, they were guided to the platform and were to stay on it for 15 s, before being returned to their cages. Escape latency, distance moved, and velocity were recorded with *Ethovision* (Noldus, Wageningen, The Netherlands). Two days of rest after the 5th and

10th day of testing were followed by probe trial to evaluate spatial memory. During the probe trial, the platform was removed, and the swimming path was recorded during 100 s as well as time spent in each quadrant. After the second probe trial, acquisition trials continued for another four days, followed by a third probe trial 24 h later. Afterwards, the platform was removed and extinction was measured for three days. During extinction training, swimming paths were recorded for 100 s, four trials a day. Mice were released from four pseudorandomly chosen starting locations. Time spent in the target quadrant was measured.

Social recognition

Recognition memory has been reported to be impaired in AD [29, 36]. To measure social recognition memory, we used a large transparent Plexiglas box divided into three compartments by removable transparent Plexiglas walls with small square openings as described previously [37, 38]. Briefly, a holding cage was placed in the middle of the two outer compartments and the procedure consisted of three consecutive phases. In a first phase, mice were placed in the middle compartment for a 5 min acclimation (acclimation phase). In a second phase (sociability phase), an unfamiliar male mouse (S1) was introduced in a holding cage in one outer compartment, while the other holding cage remained empty. Exploratory behavior toward the S1 mouse and the empty holding cage was measured for 10 min. In the third phase (social novelty and recognition phase), another unfamiliar male mouse (S2) was introduced in the other compartment. During this last phase, exploratory behavior toward mice S1 and S2 was recorded for 10 min. Exploratory behavior was defined as sniffing time toward a holding cage (with or without mice in it). The location of the S1 and S2 mouse was counterbalanced across testing animals and the apparatus was cleaned thoroughly with water after each mouse.

Scheduled appetitive conditioning

In recent years, operant conditioning procedures have revealed interesting aspects of motivational and cognitive performance of AD mouse models [40–42]. Response-reinforcement association learning in continuous reinforcement procedure was previously shown to be intact in AβPP/PS1dE9 mice [39]. However, we still needed to examine how AβPPPS1-21 mice would respond to more demanding performance schedules. Appetitive learning was investigated in automated operant chambers according to published protocols [43]. The chambers were placed in ventilated, sound-isolated cubicles and equipped with a grid floor, a feeder, and nose poke operandum (Coulbourn Instruments, Allentown, US). Mice were kept on a food restriction schedule to keep their body weight at 80–90% of their free-feeding weight. They were trained in daily trials of 30 min during which they learned to use the nose poking device to obtain food pellets (Noyes precision pellets; Research Diets, New Brunswich, US). Mice received food pellets during all trials, but reinforcement schedules gradually increased in intensity. Rate of nose poking in each trial was recorded with Graphic State 3.0 software (Coulbourn Instruments, Allentown, US). Training started with continuous reinforcement trials (CRF, i.e., every nose poke was rewarded), followed by fixed ratio trials (FR5, i.e., every 5th nose poke was rewarded; FR10, i.e., every 10th nose poke was rewarded), variable ratio trials (VR10, i.e., on average every 10th nose poke was rewarded), and ended with variable interval trials (VI30, i.e., nose pokes were reinforced on average every 30 s).

Conditioned taste aversion

During the conditioned taste aversion protocol, the animal learned to discriminate between safe and non-safe food sources based on experience (e.g., malaise inducing effects). We used an aversive conditioning procedure involving gustatory stimuli [2]. Mice learn to associate a novel sweet taste (saccharine solution: conditioned stimuli, CS) with lithium-evoked malaise (unconditioned stimuli, US), and consequently avoid drinking the sweetened solution. Water-deprived mice were trained individually for 5 days to drink from modified 15 ml Falcon® tubes in two daily 30 min sessions (morning and afternoon). The amount of water consumed was determined by weighing the tubes before and after each drinking session. During the conditioning session, mice received saccharine solution (0.5% saccharine tap water), and were 15 min later injected with 6 mEq/kg LiCl i.p. and left in the testing cage for another 15 min for observation of signs of malaise (prone position for extended period of time). Thirty min after removal of the saccharine drinking tubes, the mice were returned to their home cages. Twenty-four hours after conditioning, mice were again placed in the test cage and presented with a choice of water and saccharine solution for 30 min. Based on the amount of water and saccharine consumed, an aversion index (AI) was calculated as AI = water intake/(water + saccharine solution intake) × 100. This AI reflects the strength of acquired taste aversion memory. AI >80% indicates strong aversion (water > saccharine), whereas AI

≤50% indicates weak aversion or preference for saccharine. To test for extinction of conditioned taste aversion, a choice of water and saccharine was presented for 12 consecutive morning sessions (in the afternoon, only water).

Passive avoidance

Fear conditioning was examined in a step-through box with a small illuminated compartment and a larger dark compartment with grid-floor as described previously [34]. The grid-floor was connected to a constant current shocker (MED Associates Inc., St. Albans, Vermont, US). Animals were adapted to the dark for 30 min, and then placed in the small illuminated compartment. After 5 s, the sliding door to the dark compartment was opened and entry latency was recorded. When the mouse entered the dark compartment with all four paws on the grid, the door was closed and a foot shock (0.3 mA, 2 s) was delivered. The retention test was 24 h later and the same procedure was maintained, with the exception of the electric shock delivery. Step-through latency was recorded with a cut-off of 300 s.

Statistics

All data are shown as means ± SEM. Differences between mean values were determined using 1-way or 2-way analysis of variance (ANOVA), or 2-way repeated measures (RM) ANOVA procedures with Tukey tests for *post hoc* comparison. We used *group* (AβPPPS1-21 wt, AβPPPS1-21 tg, Tau22 wt, and Tau22 tg) as between-subject variable and *day/phase* as within-subject variable. ANOVA on the probe trial results used factors *group* and *quadrant*. Because wild type mice from both models showed differences in some task aspects, we chose to consider them as two separate groups instead of pooling them. A stepwise discriminant function analysis (DFA) was used to examine for both mouse lines which variables contributed significantly to the differences between wild type and transgenic animals. Briefly, variables were included in the model one at the time, based on statistical criteria. In all statistical tests, differences of $p < 0.05$ were considered significant.

RESULTS

Medial PFC synaptic plasticity impaired in AβPPPS1-21 mice with amyloid deposits

In the first set of experiments, medial PFC field potentials were evoked in cortical brain slices from AβPPPS1-21 and Tau22 mice. Two-way RM ANOVA indicated that basic synaptic transmission was overall not impaired in PFC (Fig. 1A-B; $F_{3,15} = 2.51$, n.s.), similar to published observations in hippocampus [3–5]. After high-frequency stimulation, LTP was readily evoked in both models. The slope of fEPSPs among groups was different over time as 2-way RM ANOVA revealed significant interaction between *group* and *time* ($F_{93,806} = 1.48$, $p < 0.01$). *Post-hoc* comparisons indicated no significant changes over time in fEPSP slopes in AβPPPS1-21 wt, Tau22 wt, and Tau22 tg (it should be noted that variability and group sizes were different between the wild type groups). In AβPPPS1-21 tg, however, fEPSP slopes were significantly lower from 95 min post-induction onwards (Fig. 1C-D; $p < 0.01$). However, abundant 6E10 staining (for amyloid deposits) was found in PFC of AβPPPS1-21 mice (Fig. 1E-F) as well as increased levels of AT8 staining (for hyperphosphorylated tau) in Tau22 brains (Fig. 1G-H). The electrophysiology data suggest that PFC-sensitive tasks might be impaired in AβPPPS1-21 mice, but not in Tau22 mice. Therefore, we included PFC-dependent extinction sessions in Morris water maze and conditioned taste aversion.

Open field activity increased in AβPPPS1-21 mice

We used the open field test to measure general exploration and activity levels between the different groups. We measured a significant *group* effect for path length ($F_{3,119} = 6.75$, $p < 0.001$). *Post hoc* comparisons indicated significant longer path lengths in AβPPPS1-21 transgenic mice compared to wild type mice ($q = 3.80$, $p < 0.05$). Wild type mice and Tau22 transgenic mice were not different in path length (Table 2), nor were there differences in time spent in the center of the open field ($F_{3,119} = 1.61$, n.s.).

Anxiety-related behaviors reduced in Tau22 mice

Anxiety levels were measured with the dark light box. We measured a significant *group* effect for time spent in the light compartment ($F_{3,119} = 17.36$, $p < 0.001$). *Post-hoc* comparisons indicated longer presence in the light compartment in Tau22 transgenic mice compared to wild type mice ($q = 4.03$, $p < 0.05$), indicating an anxiolytic-like effect in Tau22 transgenic mice. Conversely, AβPPPS1-21 wild type and transgenic mice did not show differences in anxiety-related behavior. The number of compartment crossings was not significantly different among groups (Table 2; $F_{3,119} = 1.17$, n.s.).

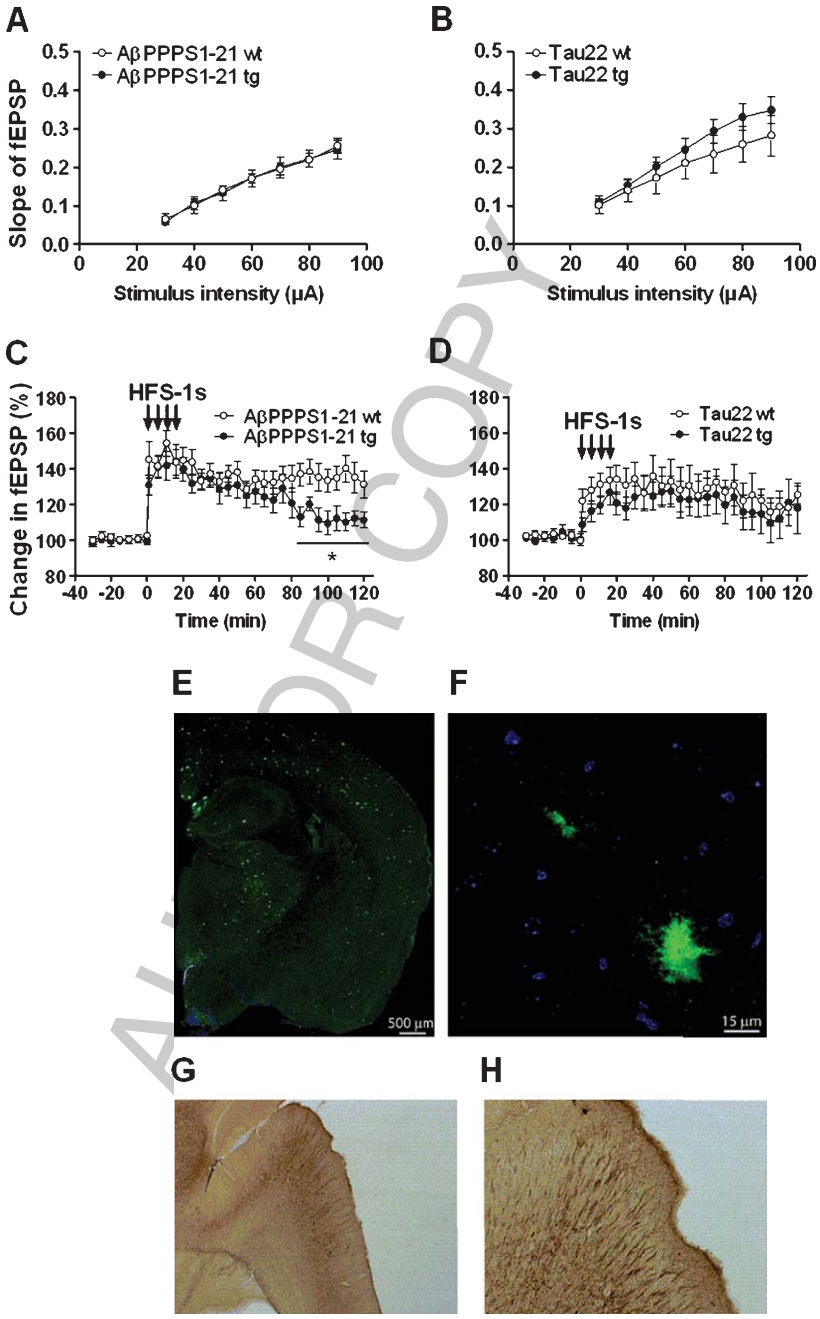

Fig. 1. Extracellular electrophysiological recordings on medial PFC slices from transgenic and wild type mice. (A-B) Input-output curves are not different between transgenic and wild type mice of either model. (C) Prefrontal LTP declined during the last 30 min in AβPPPS1-21 transgenic mice ($n = 7$) compared to wild type mice ($n = 10$). (D) Prefrontal LTP in Tau22 mice ($n = 8$) similar to wild type littermates ($n = 5$). fEPSPs are expressed as means ± SEM. Asterisks indicate difference in fEPSPs between high-frequency stimulation and subsequent time points, $^*p < 0.05$ (Tukey pairwise). (E) Representative photomicrograph of a coronal hemi-brain section from a 10 month-old AβPPPS1-21 mouse stained for Aβ deposits. (F) Higher magnification of an Aβ deposit in PFC. (G) AT8-stained representative photomicrograph of a coronal PFC section of a 10 month-old Tau22 mouse with. (H) Higher magnification of AT8-positive staining of hyperphosphorylated tau in PFC.

Table 2
Overview of open field and dark light box parameters

Behavioral test	AβPPPS1-21		Tau22		F-value
	wt ($n=35$)	tg ($n=30$)	wt ($n=28$)	tg ($n=30$)	
Open field					
Distance moved (cm)	4907 ± 185	5579 ± 237	4705 ± 142	4453 ± 147	6.75^{***}
Time in center (s)	109 ± 7	91 ± 6	102 ± 4	102 ± 5	1.61
Dark light box					
Time in light (%)	35.4 ± 1.4	39 ± 1.9	43.6 ± 1.8	50.2 ± 1.4	17.36^{***}
Crossings (n)	47 ± 3	45 ± 3	40 ± 2	44 ± 2	1.17

AβPPPS1-21 and Tau22 mice both display impaired spatial learning and memory

Mice were trained for 14 days to find the hidden platform in a large circular pool filled with opacified water. Probe trials were interspersed on day 6, 11, and 15 to evaluate spatial memory. RM ANOVA of the acquisition phase for factor *day* and *group* indicated that all animals learned to locate the hidden platform ($F_{13,1547} = 123.77$, $p < 0.001$), but that some groups were less accurate (factor *group* $F_{3,119} = 9.48$, $p < 0.001$; Fig. 2A-B). *Post-hoc* comparisons indicated significant longer escape latencies in AβPPPS1-21 transgenic ($p < 0.05$) and Tau22 transgenic mice ($p < 0.001$) compared to their respective control littermates. Tau22 transgenic mice were already significantly slower than their wild type littermates on day 1. We separately analyzed the escape latency of each trial on day 1 (Fig. 1A-B inserts). We found significant *group* ($F_{3,120} = 3.85$, $p < 0.05$), *trial* ($F_{3,360} = 46.95$, $p < 0.001$), and *group by trial* effects ($F_{9,360} = 1.96$, $p < 0.05$). The occurrence of non-cognitive defects that could have interfered with performance could be excluded as all groups had similar escape latencies on the first trial and only differed on the fourth trial (Tau22 wt versus Tau22 tg: $q = 4.34$, $p < 0.05$). Moreover, swimming velocity was not different between groups (data not shown).

During the second probe trial, a significant *group by quadrant* effect was detected on time spent in quadrants ($F_{9,476} = 10.44$, $p < 0.001$). Wild type mice from both models displayed a robust preference for the target quadrant during the second probe trial in contrast to AβPPPS1-21 and Tau22 transgenic mice (Fig. 2C-D). After additional training, a significant *group by quadrant* effect was found during the third probe trial ($F_{9,476} = 7.96$, $p < 0.001$), and *post-hoc* comparisons indicated that wild type and transgenic mice from both AD models developed a preference for the target quadrant ($p < 0.001$). However, wild type mice of both the AβPPPS1-21 ($p < 0.001$) and Tau22 lines ($p < 0.001$) had a stronger target quadrant preference than their transgenic littermates (Fig. 2E-F).

AβPPPS1-21 mice fail to display extinction of spatial preference

Following spatial acquisition learning in the Morris water maze, the platform was removed and extinction of spatial preference was assessed for three days. Extinction learning is predominantly PFC dependent [27, 44]. Two-way RM ANOVA showed significant effects of *group* ($F_{3,119} = 8.69$, $p < 0.001$), *day* ($F_{2,238} = 42.03$, $p < 0.001$), and *group by day* ($F_{6,238} = 2.811$, $p < 0.05$) on time spent in target quadrant. Interestingly, AβPPPS1-21 and Tau22 transgenic mice showed a different extinction curve. *Post-hoc* comparisons indicated no significant change in target quadrant preference for AβPPPS1-21 transgenic mice between day 1 and 3 (day 1 versus day 3: $q = 2.03$, n.s.), whereas all other groups displayed a significant decrease in target quadrant preference after 3 days of extinction (day 1 versus day 3: wild type mice from AβPPPS1-21 model: $q = 9.78$, $p < 0.001$; wild type mice from Tau22 model: $q = 8.13$, $p < 0.001$; Tau22 transgenic mice: $q = 6.19$, $p < 0.001$).

AβPPPS1-21 and Tau22 mice both display impaired (social) recognition memory

The sociability and preference for social novelty protocol assesses exploratory behavior towards novel conspecifics as well as recognition memory. During the sociability phase, no significant effect of *group* ($F_{3,61} = 1.99$, n.s.) was measured in either model. Both wild type and transgenic mice of the two models showed normal social exploratory behavior, and spent more time exploring the S1 mouse than the empty cage ($F_{1,61} = 103{,}10$, $p < 0.001$; Fig. 3A-B).

In the social novelty and recognition phase, preference for social novelty or social recognition was measured by introducing another stranger mouse.

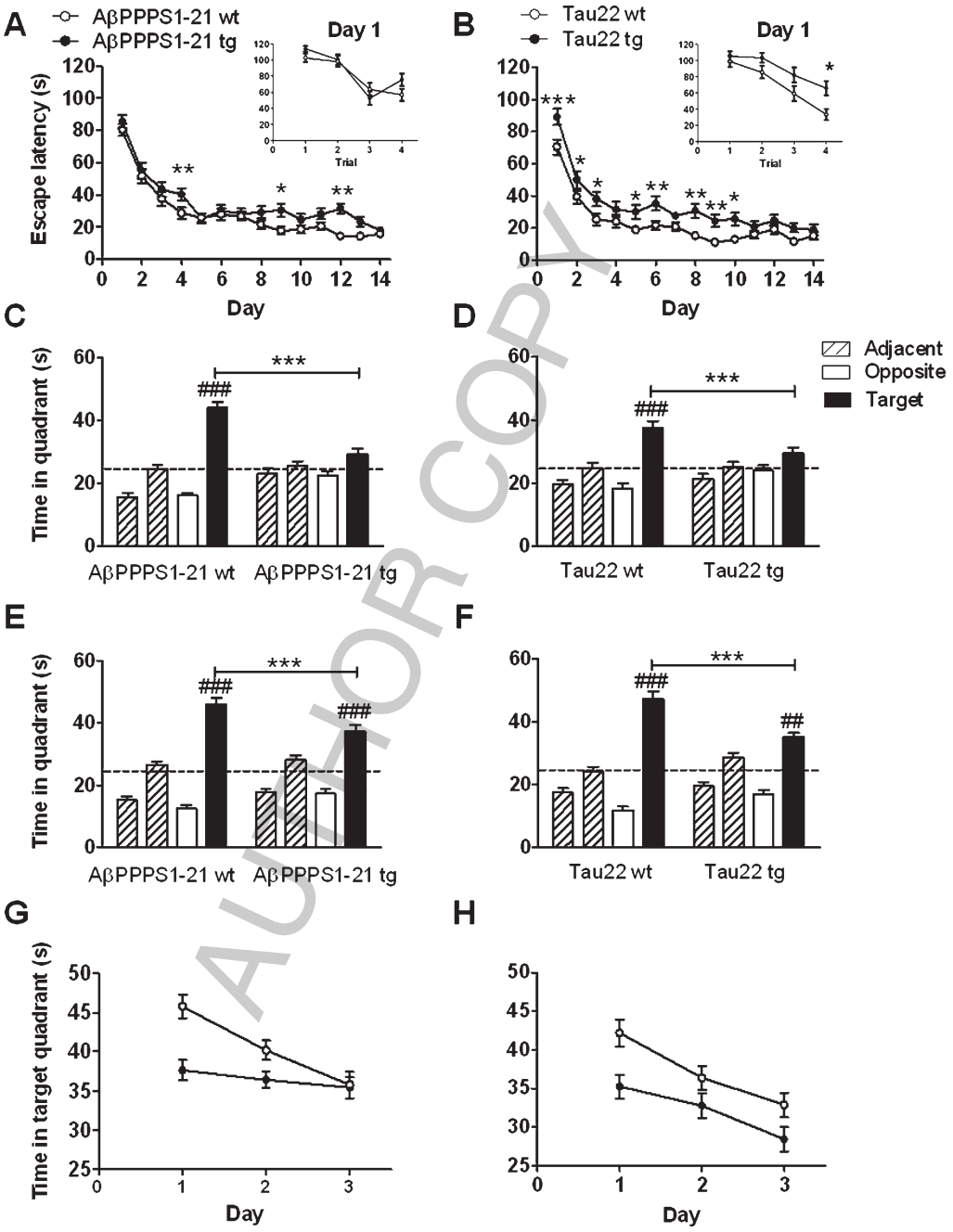

Fig. 2. Morris water maze performance in AβPPPS1-21 (wt = 35, tg = 30) (A, C, E, G) and Tau22 mice (wt = 28, tg = 30) (B, D, F, H). During 14 days of acquisition (A-B), mice were given a probe trial after day 5, 10 (C-D) and 14 (E-F). On the first probe trial, no significant target quadrant preference was obvious in all groups (data not shown). After significant target preference (black bars) in both wild type and transgenic mice, three days of extinction sessions were performed (G-H). Escape latencies and time spent in quadrant are expressed as means ± SEM. Asterisks indicate difference in escape latency between wild type and transgenic mice with $*p<0.05$, $**p<0.01$, $***p<0.001$, (Tukey pairwise); target quadrant versus other quadrants with $\#\#p<0.01$, $\#\#\#p<0.001$ (Tukey pairwise).

Using exploration time as dependent variable, two-way ANOVA indicated a significant *stranger mouse* ($F_{1,122} = 17.18$; $p<0.001$) and *group by stranger mouse* effect ($F_{3,122} = 6.61$; $p<0.001$). Wild type littermates showed more exploration toward S2 ($p<0.001$), whereas both AβPPPS1-21 and Tau22 transgenic mice were indifferent in exploring the stranger mice (Fig. 3C-D).

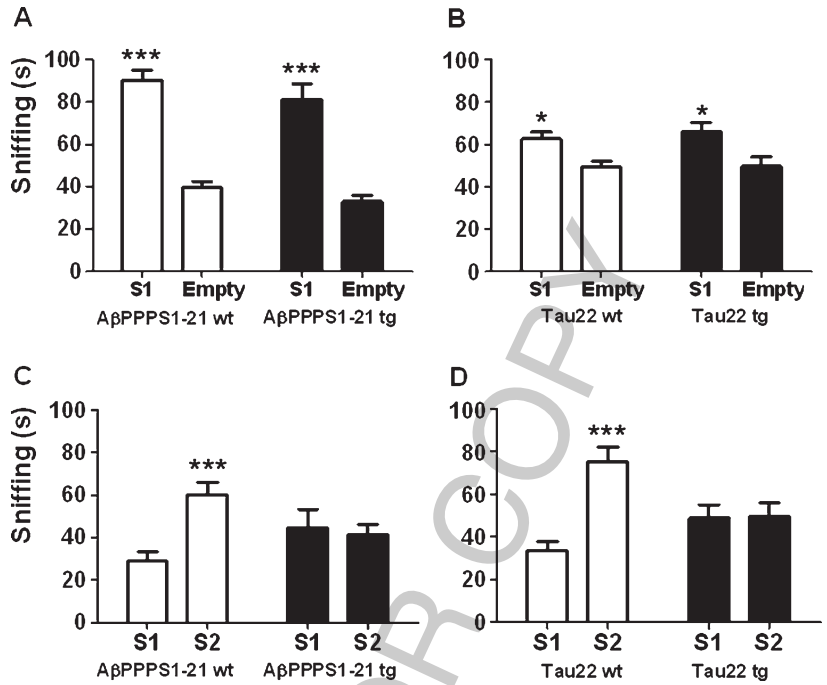

Fig. 3. Social recognition memory during social novelty and recognition phase in AβPPPS1-21 (wt = 20, tg = 15) (A-C) and Tau22 mice (wt = 15, tg = 15) (B-D). (A-B) In both models, all mice showed significant preference for S1 compared to an empty compartment. (C-D) In both models, wild type mice (white bars) showed a significant interest in the novel stranger mouse (S2), while transgenic mice (black bars) spent equal time exploring both mice. Also, the exploration time for the novel mouse was significantly different between genotypes. Exploration time (sniffing) is expressed as means ± SEM. Asterisks indicate significantly more exploration compared to the other compartment with $*p < 0.05$, $***p < 0.001$ (Tukey pairwise).

Appetitive responding reduced in Tau22 mice

In an appetitive conditioning protocol, food-deprived mice learned to obtain food pellets by activating a nose poke device. Using reward schedules with increasing intensity, we evaluated appetitive operant conditioning in the AβPPPS1-21 and Tau22 model. Using nose poke numbers as dependent variable, 2-way RM ANOVA indicated a significant effect of *protocol* ($F_{5,260} = 283.11$; $p < 0.001$) and *group by protocol* effect ($F_{15,260} = 2.50$, $p < 0.01$) (Fig. 3A-B). *Post-hoc* comparisons indicate less nose pokes in Tau22 mice compared to wild type littermates during the last protocol (VI30) ($q = 4.32$, $p < 0.05$). This protocol is considered the most demanding. AβPPPS1-21 transgenic mice and their wild type littermates were similar across all reward schedules ($q = 0.59$, n.s.).

Conditioned taste aversion impaired in AβPPPS1-21 mice

AβPPPS1-21 and Tau22 mice had no difficulty in learning to drink from modified water tubes. No differences were measured in total water intake between transgenic and their wild type littermates (AβPPPS1-21 wild type versus transgenic mice: $q = 2.27$, n.s.; Tau22 wild type versus transgenic mice: $q = 2.45$, n.s.), even though we detected a significant *group* effect in water intake ($F_{3,54} = 8.41$, $p < 0.001$), which *post-hoc* comparisons showed to be related to a generally higher water intake in Tau22 compared to AβPPPS1-21 mice (water intake in ml, AβPPPS1-21 wild type mice: 1.18 ± 0.08; AβPPPS1-21 transgenic mice: 1.03 ± 0.06; Tau22 wild type mice: 1.50 ± 0.06; Tau22 transgenic mice: 1.33 ± 0.06). On the conditioning day, no differences were measured in saccharine intake ($F_{3,54} = 2.04$, n.s.; saccharine intake in ml, AβPPPS1-21 wild type mice: 1.48 ± 0.09; AβPPPS1-21 transgenic mice: 1.52 ± 0.11; Tau22 wild type mice: 1.73 ± 0.09; Tau22 transgenic mice: 1.70 ± 0.06). Twenty-four h later (and after lithium injection), we observed a significant *group* effect on saccharine intake ($F_{3,54} = 3.29$, $p < 0.05$) (Fig. 4A-B). Overall, mice drank less than before the lithium injection. In AβPPPS1-21 tg mice, however, this was still significantly more than in AβPPPS1-21 wt ($q = 5.188$, $p < 0.01$). This also resulted in a significant *group* effect on the aversion index ($F_{3,54} = 19.90$, $p < 0.001$).

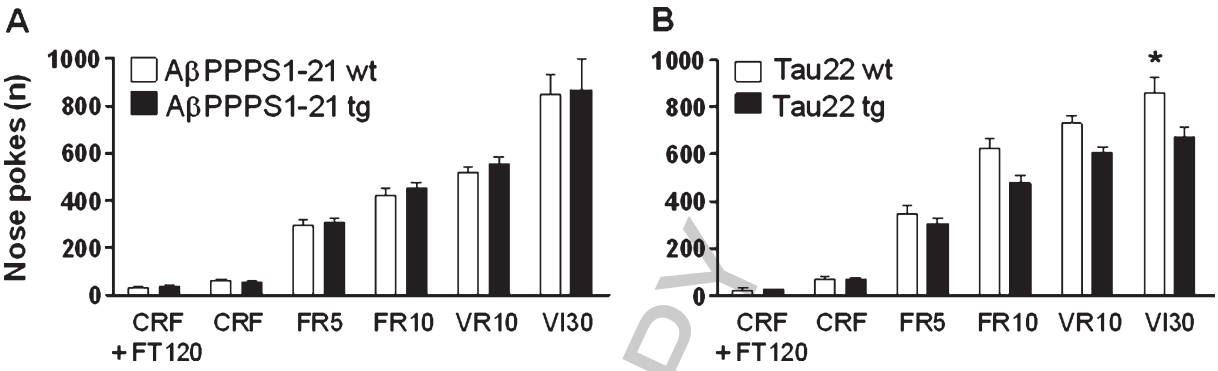

Fig. 4. Appetitive responding in AβPPPS1-21 and Tau22 mice. (A) Response acquisition in AβPPPS1-21 showed no difference between wild type ($n = 15$) (white bars) and transgenic mice ($n = 15$) (black bars). (B) In Tau22 mice, transgenic mice ($n = 15$) (black bars) show difficulty in learning more complex protocols compared to wild type mice ($n = 13$) (white bars). Nose pokes are expressed as means ± SEM. Difference in nose poke rates with $*p < 0.05$ (Tukey pairwise).

Post-hoc comparisons indicated a significant difference between AβPPPS1-21 wild type and AβPPPS1-21 transgenic mice ($q = 6.12$, $p < 0.01$) (Fig. 4C). AI was not different between Tau22 wild type and Tau22 transgenic mice (Fig. 4D).

AβPPPS1-21 mice fail to display extinction of conditioned taste aversion

For CTA extinction, saccharine and water were presented simultaneously over 12 consecutive days. Results were grouped in extinction blocks (1 block = 3 days). 2-way RM ANOVA indicated a significant *group* ($F_{3,54} = 17.54$, $p < 0.001$) and *group by block* ($F_{12,206} = 2.31$, $p < 0.01$) effect for AI. *Post-hoc* comparisons indicated a significant AI drop in AβPPPS1-21 wt and Tau22 wt at block 5 compared to AI during the initial test (AβPPPS-21 wt: $q = 5.14$, $p < 0.01$; Tau22 wt: $q = 5.01$, $p < 0.01$). In AβPPPS1-21 tg, no changes in AI were observed across consecutive extinction blocks. In Tau22 tg, AI was significantly lower from block 4 onwards compared to AI during the initial test ($q = 5.58$, $p < 0.001$) (Fig. 5E-F).

AβPPPS1-21 mice display impaired passive avoidance

Wild type and transgenic mice from both models displayed similar motivation to enter the dark compartment during training ($F_{3,60} = 0.81$, n.s.; Fig. 5). During 24 h memory retention test, a significant increase in step-through latency indicated robust contextual memory acquisition. Using RM ANOVA, we observed a significant effect on step-through latency on *group* ($F_{3,120} = 3.13$, $p < 0.05$), *phase* ($F_{1,120} = 53.99$, $p < 0.001$), and *group by phase* interaction ($F_{3,120} = 3.21$, $p < 0.05$). AβPPPS1-21 wild type mice displayed stronger contextual memory retention (step-through latency training versus retention: $q = 6.709$, $p < 0.001$), while AβPPPS1-21 transgenic mice did not (Fig. 6A). In contrast, Tau22 wild type and transgenic mice acquired strong contextual memory (step-through latency training versus retention: Tau22 wild type: $q = 7.50$, $p < 0.001$; Tau22 transgenic: $q = 5.81$, $p < 0.001$) (Fig. 6B). Furthermore, during retention phase, step-through latency in AβPPPS1-21 wild type mice was significant different from AβPPPS1-21 transgenic mice ($q = 4.06$, $p < 0.05$).

Discriminative behavioral variables differ between AβPPPS1-21 and Tau22 mice

Variables used for discriminative functional analysis (DFA) are summarized in Tables 3 and 4. DFA identifies the variables which maximally contribute to differences between genotypes. The direct entry method included all variables and could discriminate wild type and transgenic mice from both AD models. In the stepwise forward model, the variables that significantly discriminated the genotypes in the two different models were incorporated. In the AβPPPS1-21 model, three variables were identified as sufficient to discriminate the genotypes (Table 4). In both batch 1 and 2, time spent in the target quadrant (Morris water maze) was consistently found to be the strongest variable to discriminate AβPPPS1-21 wild type from transgenic mice (Wilks' Lambda method; group 1: $F_{1,33} = 11.87$, $p < 0.01$; group 2: $F_{1,28} = 25.16$, $p < 0.001$).

In the Tau22 model, three variables were incorporated in the stepwise forward DFA model: time spent

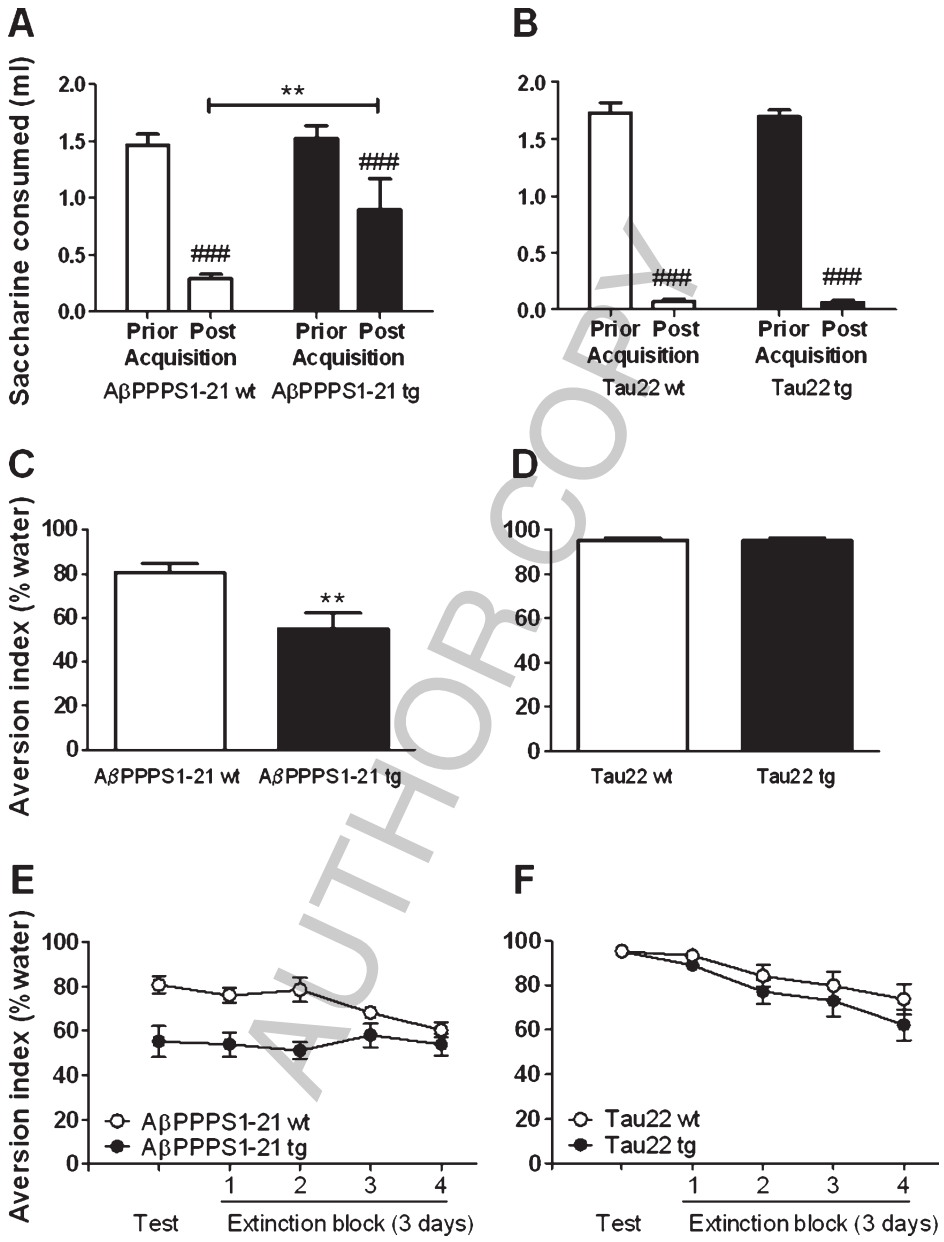

Fig. 5. Conditioned taste aversion in AβPPPS1-21 and Tau22 mice. (A-B) Saccharine intake prior to lithium injection was similar among all groups. After lithium injection, all mice drank less saccharine, but AβPPPS1-21 tg continued drinking more saccharine than wild type mice. Saccharine consumption are expressed as means ± SEM. ###$p < 0.001$, difference in saccharine consumption compared to prior acquisition. **$p < 0.01$, difference between groups. (C) Conditioned taste aversion in AβPPPS1-21 showed a significant difference in saccharine intake between wild type ($n = 15$) and transgenic mice ($n = 15$), indicating an impaired memory in the latter group. (D) In Tau22 mice, both wild type ($n = 13$) and transgenic mice ($n = 15$) showed similar aversion for saccharine. Additionally, we tested fear extinction for 12 consecutive sessions (1 extinction block = 3 days). AβPPPS1-21 wild type, Tau22 wild type and Tau22 transgenic mice show no deficit in extinction learning. AβPPPS1-21 transgenic mice do not display extinction learning over time. Aversion indexes are expressed as means ± SEM. **$p < 0.01$, difference in aversion index (1-way ANOVA). (E) After the initial dual presentation, extinction was performed and AβPPPS1-21 transgenic mice failed to show extinction learning. (F) Tau22 transgenic mice were similar to wild type mice and displayed extinction learning.

exploring S2 (SPSN), VR10 protocol in the scheduled appetitive conditioning task and time spent in the light compartment. Here, the strongest variables to discriminate Tau22 wild type from transgenic mice were the VR10 response rates in the scheduled appetitive conditioning task for batch 3 ($F_{1,26} = 13.78$, $p = 0.001$),

Table 3
The variables used for DFA analysis

Behavioral task	Variables	Abbreviation
Open field	Path length	OF-Path
	Time in center	OF-Center
Dark light box	Time in light compartment (%) Crossings	DLB-Light DLB-N
Morris water maze	Escape latency day 1 versus 4	MWM-esc1vs4
	Escape latency day 4 versus 10	MWM-esc4vs10
	Time in target quadrant during probe 2	MWM-P2
	Slope during extinction learning	MWM-Ext
SPSN	Percentage time exploring stranger 2 mouse	SPSN-Ratio
Passive avoidance	X-fold increased step-through latency	PA-xfold
Conditioned taste aversion	Aversion index	CTA-AI
	Slope during extinction learning	CTA-ext
Scheduled appetitive conditioning	Nose pokes during FR10	SAC-FR10
	Nose pokes during VR10	SAC-VR10
	Nose pokes during VI30	SAC-VI30

Table 4
Summary of the DFA outcome. AβPPPS1-21 wild type and transgenic mice as well as Tau22 wild type and transgenic mice can be discriminated on various variables

Included variables	Model	Batch	Direct entry method	Stepwise-forward method	
				Significance	Variables retained
All variables	AβPPPS1-21	1	$p = 0.065$	$p < 0.01$	MWM-P2 SPSN-Ratio
		2	$p < 0.05$	$p < 0.001$	MWM-P2 CTA-AI
	THY-Tau22	3	$p < 0.01$	$p < 0.01$	SPSN-Ratio DLB-Entries
		4	$p < 0.01$	$p < 0.001$	SCH-VR10 DLB-Light

and time spent exploring S2 (SPSN) in batch 4 ($F_{1,27} = 11.06$, $p < 0.01$). In summary, it appears that spatial learning and conditioned taste aversion distinguish AβPPPS1-21 mice from their normal littermates, whereas dark-light box performance and scheduled appetitive conditioning are decisive for Tau22 mice. Social recognition memory discriminates AβPPPS1-21 as well as Tau22 mice.

Table 5
Summary of the results

Process	AβPPPS1-21	THY-Tau22
Spatial learning	Impaired	Impaired
Recognition memory	Impaired	Impaired
Passive avoidance	Impaired	Not impaired
Appetitive conditioning	Not impaired	Impaired
Hippocampus-independent fear conditioning	Impaired	Not impaired
Spatial extinction learning	Impaired	Not impaired
Non-spatial extinction learning	Impaired	Not impaired
Medial PFC LTP	Impaired	Not impaired

DISCUSSION

In the current report, we directly compared two murine AD models in a variety of cognitive protocols, and observed behavioral changes that might relate to neuropathological differences between the two models. It has been reported that neuropathology starts in both models around 2–3 months of age [21, 22], whereas behavioral deficits emerge around 8–9 months [20, 45]. Notably, the AβPPPS1-21 model mainly shows amyloid-related features, whereas the Tau22 model exclusively displays tau pathology. We should note that, although some hyperphosphorylated tau (visualized with AT8 staining) was seen in AβPPPS1-21 brains, no NFTs were detected in these mice [21].

Results of the present functional comparison have been summarized in Table 5. Defects in spatial learning, social recognition memory, and conditioned taste aversion were prominent in AβPPPS1-21 mice, whereas impaired dark-light box performance, social recognition memory, and scheduled appetitive conditioning were typical for Tau22 mice. Only AβPPPS1-21 mice displayed defects in extinction protocols. Interestingly, synaptic plasticity was impaired

in medial PFC of AβPPPS1-21 mice, but not in Tau22 mice, which could at least partly explain the behavioral differences between these mouse lines.

In the open field test, AβPPPS1-21 transgenic mice were more active compared to wild type littermates. In reports using the same mouse model, open field activity measures were unchanged in AβPPPS1-21 transgenic mice [21, 46]. However, published reports on open field performance in AD mouse models are inconsistent as hyperactivity was found in Tg2576 and AβPP/PS1-A246E mice [31, 32], whereas AβPP/PS1dE9 mice displayed no changes [47]. Sample size in some reports were lower and/or variability in the transgenic group was larger than observed by us [21, 46]. The reason for this inconsistency remains unclear, but inter-laboratory differences might play some role as open field performance was shown to be highly susceptible to this [48]. In our study, increased motor activity was confined to this specific task and not observed in other behavioral tasks. Conversely, reduced anxiety-related behavior, which Tau22 mice displayed in the dark-light box [20, 22], was not observed in the open field. However, it should be noted that open field activity might be less reliable to measure anxiety [34, 43], compared to other anxiety-related tasks [49].

Impaired hippocampus-dependent spatial learning and recognition memory has previously been described in the mouse models examined here [20, 29]. Such defects in spatial learning and memory have been found in other AD mouse models as well [18, 19, 50, 51], and are thought to relate to some of the learning and memory defects in AD patients [9, 11, 36, 52]. We consistently found impairments in spatial learning and novelty seeking behavior in both AD models. Notably, we observed reduced efficacy in finding the hidden platform as well as absence of novelty preference. Since both models show prominent pathology in hippocampus [21, 22, 30], these impairments indicate that both amyloid- or tau-related pathology affect hippocampal function. Conversely, changes in social novelty seeking behavior might have been related to factors other than hippocampus-dependent memory. For example, olfactory deficits have been described both in AβPP- and tau-based mouse models and AD patients [53–55], and could have affected discrimination between novel and familiar mice in the present study. Also, increased aggression has been reported in AβPP- and tau-based models [56–58], which could have influenced social responses in the male mice used in the present studies. Interestingly, both AβPPPS1-21 and Tau22 mice were eventually able to remember the location of the hidden platform after prolonged training, and indeed learning deficits could also be overcome by prolonged training in other hippocampus-impaired rodents [59, 60].

Passive avoidance and taste aversion learning were impaired in AβPPPS1-21, but not in Tau22 mice, which is consistent with previous reports [61, 62]. It is also consistent with impaired passive avoidance in other AβPP-based models, but relative sparing in tau models [63–66]. In both transgenic models, amygdala [21, 22] was severely affected, and avoidance learning as well as conditioned taste aversion depend on a fear circuit that prominently includes amygdala [61, 62, 67–72]. One might argue that shorter step-through latencies in passive avoidance in AβPPPS1-21 mice could be partially explained by non-cognitive aspects such as impaired sensory abilities. However, in an independent cohort of AβPPPS1-21 mice, we found no differences in pain sensitivity in the hot plate test (unpublished data).

Hippocampal LTP was impaired in AβPPPS1-21, but not in Tau22 mice [20, 22, 25]. Presently, we found that PFC synaptic plasticity was impaired in AβPPPS1-21 (see [73]), but not in Tau22 mice. Amyloid deposition was very prominent in PFC of AβPPPS1-21 mice [21], whereas in Tau22 PFC, only AT8-positive hyperphosphorylated tau was found, but no other phosphorylated tau species, nor NFTs [21]. Other authors have reported rather severe defects in hippocampal LTP in AβPPPS1-21 mice [25], which are difficult to compare quantitatively to our measurements given the differences between brain regions and electrophysiological protocols. We induced LTP by more physiological theta burst stimulation [74, 75], which might have responded differently to pathology than more intense induction protocols.

Medial PFC, which is part of a functional network that includes hippocampus and amygdala [76–79], has been implicated in extinction of learned behaviors [27, 44, 78, 80, 81]. We therefore implemented extinction sessions after water maze and taste aversion learning. We observed that AβPPPS1-21 mice continued to search the target quadrant during the water maze extinction trials, and failed to show extinction of conditioned taste aversion. Tau22 mice displayed normal extinction in our study, whereas another tau model, Tau P301L, displayed facilitated extinction of conditioned taste aversion [62]. It should also be noted that other AβPP-based models did display normal extinction performance in some protocols [82–85], but these findings were difficult to relate to the present observations. For example, AβPP(swe,arc) mice persisted to visit an initially rewarded corner in an automated IntelliCage®,

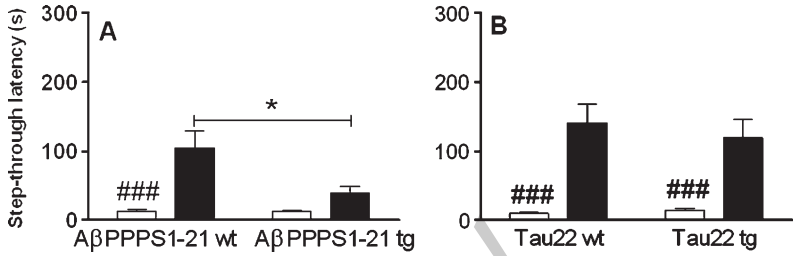

Fig. 6. Passive avoidance in AβPPPS1-21 and Tau22 mice. (A) AβPPPS1-21 transgenic mice ($n = 15$) in the passive avoidance task were unable to remember the aversive shock they received 24 h ago, compared to wild type mice ($n = 20$). (B) In Tau22 mice, both wild type ($n = 15$) and transgenic mice ($n = 15$) developed an aversion for the dark compartment. Step-through latencies are expressed as means ± SEM. Differences in step-through latency between groups with $*p < 0.05$; $###p < 0.001$, acquisition (white bars) and retention time (black bars) within group (Tukey pairwise).

but the authors were cautious in interpreting this as an extinction defect [86]. Bonardi et al. [85] found a lack of fear-associated extinction learning in 4 month old AβPP/PS1dE9 mice, but were unable to replicate this finding in other behavioral set ups.

In recent years, several laboratories have introduced instrumental conditioning tasks in the cognitive assessment of rodent models of human brain disease [40–42]. During such tasks, animals are trained on increasingly demanding response-reinforcement relationships. AβPPPS1-21 mice were similar to wild types in scheduled appetitive conditioning, whereas Tau22 transgenic mice lagged behind on the more demanding schedules. In another study, AβPP/PS1dE9 transgenic mice also failed to show any impairment on a continuous reinforcement schedule [39]. Operant responding was shown to involve both hippocampus [87] as well as striatum [88]. Although tau pathology was not observed in striatum of Tau22 transgenic mice [22], defects in this task suggest that appetitive motivational aspects might be impaired in Tau22 mice [56, 89].

Amyloid and tau pathology have been shown to develop along different stages. We therefore hypothesized that characteristic dysfunctions might differentiate between the different mouse models. For example, hippocampus-dependent tasks might be most characteristically impaired in Tau22 mice. Discriminant functional analysis was used to identify the behavioral variables that were most useful to discriminate between the different mouse lines. Although some apparently characteristic changes were unable to discriminate decisively between the two mouse lines (e.g., extinction defects), this analysis further confirmed that amyloid- versus tau-related pathology does result in different dysfunctional profiles. Hippocampus- or amygdala-dependent variables apparently contributed most to separate AβPPPS1-21 mice from wild types, whereas anxiety-related and hippocampal parameters discriminated Tau22 from wild type mice. We should be cautious, however, that any behavioral difference could also be due to changes (in gene expression) unrelated to amyloid or tau pathology.

In conclusion, we examined two pathophysiologically distinct mouse AD models [21, 22], and found different profiles of functional impairments between them. These findings confirm earlier suggestions of different memory impairments between AβPP- and tau-based mouse models. Furthermore, medial PFC plasticity was impaired in AβPPPS1-21, but not in Tau22 mice (possibly relating to the observed differences in extinction learning). The deficits in AβPPPS1-21 mice suggested that amyloid-related pathology might be more pervasive and/or widespread than tau pathology.

Acknowledgments

This work was financially supported by 7FP grant MEMOSAD (LB, BDS and RDH). ACL, ZCV, DB and RDH are supported by the federal science fund FWO-Vlaanderen (grant number G.0327.08) and a grant of the University research Council (GOA/12/008). DB and LB are also supported by INSERM, CNRS, DN2M, FEDER, France Alzheimer, IMPRT, University of Lille 2, Lille Regional Hospital (CHRU), Région Nord/Pas-de-Calais, LECMA, MEDIALZ and ANR (AMYTOXTAU, ADONTAGE and ADORATAU grants), and the LABEX (excellence laboratory program invest for the future) DISTALZ (Development of Innovative Strategies for the Transdisciplinary approach to ALZheimer's disease). We furthermore thank Véronique Hendrickx and Leen Van Aerschot for technical assistance.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1779).

REFERENCES

[1] Mandelkow EM, Mandelkow E (1998) Tau in Alzheimer's disease. *Trends Cell Biol* **8**, 425-427.

[2] Selkoe DJ (2002) Alzheimer's disease is a synaptic failure. *Science* **298**, 789-791.

[3] Walsh DM, Selkoe DJ (2004) Deciphering the molecular basis of memory failure in Alzheimer's disease. *Neuron* **44**, 181-193.

[4] Haass C (2004) Take five–BACE and the gamma-secretase quartet conduct Alzheimer's amyloid beta-peptide generation. *EMBO J* **23**, 483-488.

[5] Buee L, Bussiere T, Buee-Scherrer V, Delacourte A, Hof PR (2000) Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res Brain Res Rev* **33**, 95-130.

[6] Jucker M, Walker LC (2011) Pathogenic protein seeding in Alzheimer disease and other neurodegenerative disorders. *Ann Neurol* **70**, 532-540.

[7] Thal DR, Rub U, Orantes M, Braak H (2002) Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* **58**, 1791-1800.

[8] Braak H, Braak E (1991) Demonstration of amyloid deposits and neurofibrillary changes in whole brain sections. *Brain Pathol* **1**, 213-216.

[9] Backman L (1998) The link between knowledge and remembering in Alzheimer's disease. *Scand J Psychol* **39**, 131-139.

[10] Hoefer M, Allison SC, Schauer GF, Neuhaus JM, Hall J, Dang JN, Weiner MW, Miller BL, Rosen HJ (2008) Fear conditioning in frontotemporal lobar degeneration and Alzheimer's disease. *Brain* **131**, 1646-1657.

[11] Hailstone JC, Ridgway GR, Bartlett JW, Goll JC, Buckley AH, Crutch SJ, Warren JD (2011) Voice processing in dementia: A neuropsychological and neuroanatomical analysis. *Brain* **134**, 2535-2547.

[12] Van der Vlies AE, Verwey NA, Bouwman FH, Blankenstein MA, Klein M, Scheltens P, Van der Flier WM (2009) CSF biomarkers in relationship to cognitive profiles in Alzheimer disease. *Neurology* **72**, 1056-1061.

[13] Koric L, Felician O, Guedj E, Hubert AM, Mancini J, Boucraut J, Ceccaldi M (2010) Could clinical profile influence CSF biomarkers in early-onset Alzheimer disease? *Alzheimer Dis Assoc Disord* **24**, 278-283.

[14] Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G (1996) Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. *Science* **274**, 99-102.

[15] Gotz J, Chen F, Barmettler R, Nitsch RM (2001) Tau filament formation in transgenic mice expressing P301L tau. *J Biol Chem* **276**, 529-534.

[16] Rockenstein E, Mallory M, Mante M, Sisk A, Masliaha E (2001) Early formation of mature amyloid-beta protein deposits in a mutant APP transgenic model depends on levels of Abeta(1-42). *J Neurosci Res* **66**, 573-582.

[17] King DL, Arendash GW (2002) Behavioral characterization of the Tg2576 transgenic model of Alzheimer's disease through 19 months. *Physiol Behav* **75**, 627-642.

[18] Brody DL, Holtzman DM (2006) Morris water maze search strategy analysis in PDAPP mice before and after experimental traumatic brain injury. *Exp Neurol* **197**, 330-340.

[19] Pennanen L, Wolfer DP, Nitsch RM, Gotz J (2006) Impaired spatial reference memory and increased exploratory behavior in P301L tau transgenic mice. *Genes Brain Behav* **5**, 369-379.

[20] Van der Jeugd A, Ahmed T, Burnouf S, Belarbi K, Hamdame M, Grosjean ME, Humez S, Balschun D, Blum D, Buee L, D'Hooge R (2011) Hippocampal tauopathy in tau transgenic mice coincides with impaired hippocampus-dependent learning and memory, and attenuated late-phase long-term depression of synaptic transmission. *Neurobiol Learn Mem* **95**, 296-304.

[21] Radde R, Bolmont T, Kaeser SA, Coomaraswamy J, Lindau D, Stoltze L, Calhoun ME, Jaggi F, Wolburg H, Gengler S, Haass C, Ghetti B, Czech C, Holscher C, Mathews PM, Jucker M (2006) Abeta42-driven cerebral amyloidosis in transgenic mice reveals early and robust pathology. *EMBO Rep* **7**, 940-946.

[22] Schindowski K, Bretteville A, Leroy K, Begard S, Brion JP, Hamdane M, Buee L (2006) Alzheimer's disease-like tau neuropathology leads to memory deficits and loss of functional synapses in a novel mutated tau transgenic mouse without any motor deficits. *Am J Pathol* **169**, 599-616.

[23] Schindowski K, Belarbi K, Bretteville A, Ando K, Buee L (2008) Neurogenesis and cell cycle-reactivated neuronal death during pathogenic tau aggregation. *Genes Brain Behav* **7**(Suppl 1), 92-100.

[24] Walsh DM, Klyubin I, Fadeeva JV, Cullen WK, Anwyl R, Wolfe MS, Rowan MJ, Selkoe DJ (2002) Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation *in vivo*. *Nature* **416**, 535-539.

[25] Gengler S, Hamilton A, Holscher C (2010) Synaptic plasticity in the hippocampus of a APP/PS1 mouse model of Alzheimer's disease is impaired in old but not young mice. *PLoS One* **5**, e9764.

[26] Sydow A, Van der Jeugd A, Zheng F, Ahmed T, Balschun D, Petrova O, Drexler D, Zhou LP, Rune G, Mandelkow E, D'Hooge R, Alzheimer C, Mandelkow EM (2011) Tau-induced defects in synaptic plasticity, learning, and memory are reversible in transgenic mice after switching off the toxic tau mutant. *J Neurosci* **31**, 2511-2525.

[27] Milad MR, Quirk GJ (2002) Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature* **420**, 70-74.

[28] Brigman JL, Rothblat LA (2008) Stimulus specific deficit on visual reversal learning after lesions of medial prefrontal cortex in the mouse. *Behav Brain Res* **187**, 405-410.

[29] Scholtzova H, Wadghiri YZ, Douadi M, Sigurdsson EM, Li YS, Quartermain D, Banerjee P, Wisniewski T (2008) Memantine leads to behavioral improvement and amyloid reduction in Alzheimer's-disease-model transgenic mice shown as by micromagnetic resonance imaging. *J Neurosci Res* **86**, 2784-2791.

[30] Burnouf S, Martire A, Derisbourg M, Laurent C, Belarbi K, Leboucher A, Fernandez-Gomez FJ, Troquier L, Eddarkaoui S, Grosjean ME, Demeyer D, Muhr-Tailleux A, Buisson A, Sergeant N, Hamdane M, Humez S, Popoli P, Buee L, Blum D (2013) NMDA receptor dysfunction contributes to impaired brain-derived neurotrophic factor-induced facilitation of hippocampal synaptic transmission in a tau transgenic model. *Aging Cell* **12**, 11-23.

[31] Filali M, Lalonde R, Rivest S (2011) Anomalies in social behaviors and exploratory activities in an APPswe/PS1 mouse model of Alzheimer's disease. *Physiol Behav* **104**, 880-885.

[32] Deacon RM, Koros E, Bornemann KD, Rawlins JN (2009) Aged Tg2576 mice are impaired on social memory and open field habituation tests. *Behav Brain Res* **197**, 466-468.

[33] Sanchez PE, Zhu L, Verret L, Vossel K a, Orr AG, Cirrito JR, Devidze N, Ho K, Yu G-Q, Palop JJ, Mucke L (2012) Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer's disease model. *Proc Natl Acad Sci U S A* **109**, E2895-903.

[34] Goddyn H, Leo S, Meert T, D'Hooge R (2006) Differences in behavioural test battery performance between mice with hippocampal and cerebellar lesions. *Behav Brain Res* **173**, 138-147.

[35] Lo AC, Callaerts-Vegh Z, Nunes AF, Rodrigues CM, D'Hooge R (2013) Tauroursodeoxycholic acid (TUDCA) supplementation prevents cognitive impairment and amyloid deposition in APP/PS1 mice. *Neurobiol Dis* **50**, 21-29.

[36] Cheng PJ, Pai MC (2010) Dissociation between recognition of familiar scenes and of faces in patients with very mild Alzheimer disease: An event-related potential study. *Clin Neurophysiol* **121**, 1519-1525.

[37] Naert A, Callaerts-Vegh Z, D'Hooge R (2011) Nocturnal hyperactivity, increased social novelty preference and delayed extinction of fear responses in post-weaning socially isolated mice. *Brain Res Bull* **85**, 354-362.

[38] Nadler JJ, Moy SS, Dold G, Trang D, Simmons N, Perez A, Young NB, Barbaro RP, Piven J, Magnuson TR, Crawley JN (2004) Automated apparatus for quantitation of social approach behaviors in mice. *Genes Brain Behav* **3**, 303-314.

[39] Reiserer RS, Harrison FE, Syverud DC, McDonald MP (2007) Impaired spatial learning in the APPSwe+PSEN1DeltaE9 bigenic mouse model of Alzheimer's disease. *Genes Brain Behav* **6**, 54-65.

[40] Adriani W, Ognibene E, Heuland E, Ghirardi O, Caprioli A, Laviola G (2006) Motor impulsivity in APP-SWE mice: A model of Alzheimer's disease. *Behav Pharmacol* **17**, 525-533.

[41] Blackshear AL, Xu W, Anderson M, Xu F, Previti ML, Van Nostrand WE, Robinson JK (2011) A novel operant testing regimen for multi-construct cognitive characterization of a murine model of Alzheimer's amyloid-related behavioral impairment. *Neurobiol Learn Mem* **96**, 443-451.

[42] Lagadec S, Rotureau L, Hemar A, Macrez N, Delcasso S, Jeantet Y, Cho YH (2010) Early temporal short-term memory deficits in double transgenic APP/PS1 mice. *Neurobiol Aging* **33**, 203 e1-11.

[43] Callaerts-Vegh Z, Beckers T, Ball SM, Baeyens F, Callaerts PF, Cryan JF, Molnar E, D'Hooge R (2006) Concomitant deficits in working memory and fear extinction are functionally dissociated from reduced anxiety in metabotropic glutamate receptor 7-deficient mice. *J Neurosci* **26**, 6573-6582.

[44] Quirk GJ, Garcia R, Gonzalez-Lima F (2006) Prefrontal mechanisms in extinction of conditioned fear. *Biol Psychiatry* **60**, 337-343.

[45] Belarbi K, Burnouf S, Fernandez-Gomez F-J, Laurent C, Lestavel S, Figeac M, Sultan A, Troquier L, Leboucher A, Caillierez R, Grosjean M-E, Demeyer D, Obriot H, Brion I, Barbot B, Galas M-C, Staels B, Humez S, Sergeant N, Schraen-Maschke S, Muhr-Tailleux A, Hamdane M, Buée L, Blum D (2011) Beneficial effects of exercise in a transgenic mouse model of Alzheimer's disease-like Tau pathology. *Neurobiol Dis* **43**, 486-494.

[46] Govindarajan N, Rao P, Burkhardt S, Sananbenesi F, Schluter OM, Bradke F, Lu J, Fischer A (2012) Reducing HDAC6 ameliorates cognitive deficits in a mouse model for Alzheimer's disease. *EMBO Mol Med* **5**, 52-63.

[47] Lalonde R, Kim HD, Fukuchi K (2004) Exploratory activity, anxiety, and motor coordination in bigenic APPswe+PS1/DeltaE9 mice. *Neurosci Lett* **369**, 156-161.

[48] Crabbe JC, Wahlsten D, Dudek BC (1999) Genetics of mouse behavior: Interactions with laboratory environment. *Science* **284**, 1670-1672.

[49] Van Gaalen MM, Steckler T (2000) Behavioural analysis of four mouse strains in an anxiety test battery. *Behav Brain Res* **115**, 95-106.

[50] Chen G, Chen KS, Knox J, Inglis J, Bernard A, Martin SJ, Justice A, McConlogue L, Games D, Freedman SB, Morris RG (2000) A learning deficit related to age and beta-amyloid plaques in a mouse model of Alzheimer's disease. *Nature* **408**, 975-979.

[51] Polydoro M, Acker CM, Duff K, Castillo PE, Davies P (2009) Age-dependent impairment of cognitive and synaptic function in the htau mouse model of tau pathology. *J Neurosci* **29**, 10741-10749.

[52] Weintraub S, Wicklund AH, Salmon DP (2012) The neuropsychological profile of Alzheimer disease. *Cold Spring Harb Perspect Med* **2**, a006171.

[53] Flunkert S, Hierzer M, Loffler T, Rabl R, Neddens J, Duller S, Schofield EL, Ward MA, Posch M, Jungwirth H, Windisch M, Hutter-Paier B (2013) Elevated levels of soluble total and hyperphosphorylated tau result in early behavioral deficits and distinct changes in brain pathology in a new tau transgenic mouse model. *Neurodegener Dis* **11**, 194-205.

[54] Wesson DW, Levy E, Nixon RA, Wilson DA (2010) Olfactory dysfunction correlates with amyloid-beta burden in an Alzheimer's disease mouse model. *J Neurosci* **30**, 505-514.

[55] Bolander A, Kieser D, Voss C, Bauer S, Schon C, Burgold S, Bittner T, Holzer J, Heyny-von Haussen R, Mall G, Goetschy V, Czech C, Knust H, Berger R, Herms J, Hilger I, Schmidt B (2012) Bis(arylvinyl)pyrazines, -pyrimidines, and -pyridazines as imaging agents for tau fibrils and beta-amyloid plaques in Alzheimer's disease models. *J Med Chem* **55**, 9170-9180.

[56] Van der Jeugd A, Blum D, Raison S, Eddarkaoui S, Buee L, D'Hooge R (2013) Observations in THY-Tau22 mice that resemble behavioral and psychological signs and symptoms of dementia. *Behav Brain Res* **242C**, 34-39.

[57] Vloeberghs E, Van Dam D, Coen K, Staufenbiel M, De Deyn PP (2006) Aggressive male APP23 mice modeling behavioral alterations in dementia. *Behav Neurosci* **120**, 1380-1383.

[58] Alexander G, Hanna A, Serna V, Younkin L, Younkin S, Janus C (2011) Increased aggression in males in transgenic Tg2576 mouse model of Alzheimer's disease. *Behav Brain Res* **216**, 77-83.

[59] McDonald RJ, Hong NS (2000) Rats with hippocampal damage are impaired on place learning in the water task when overtrained under constrained conditions. *Hippocampus* **10**, 153-161.

[60] Zhang M, Storm DR, Wang H (2011) Bidirectional synaptic plasticity and spatial memory flexibility require Ca2+-stimulated adenylyl cyclases. *J Neurosci* **31**, 10174-10183.

[61] Pistell PJ, Zhu M, Ingram DK (2008) Acquisition of conditioned taste aversion is impaired in the amyloid precursor protein/presenilin 1 mouse model of Alzheimer's disease. *Neuroscience* **152**, 594-600.

[62] Pennanen L, Welzl H, D'Adamo P, Nitsch RM, Gotz J (2004) Accelerated extinction of conditioned taste aversion in P301L tau transgenic mice. *Neurobiol Dis* **15**, 500-509.

[63] King DL, Arendash GW, Crawford F, Sterk T, Menendez J, Mullan MJ (1999) Progressive and gender-dependent cognitive impairment in the APP(SW) transgenic mouse model for Alzheimer's disease. *Behav Brain Res* **103**, 145-162.

[64] Taniguchi T, Doe N, Matsuyama S, Kitamura Y, Mori H, Saito N, Tanaka C (2005) Transgenic mice expressing mutant (N279K) human tau show mutation dependent cognitive deficits without neurofibrillary tangle formation. *FEBS Lett* **579**, 5704-5712.

[65] Deacon RM, Cholerton LL, Talbot K, Nair-Roberts RG, Sanderson DJ, Romberg C, Koros E, Bornemann KD, Rawlins JN (2008) Age-dependent and -independent behavioral deficits in Tg2576 mice. *Behav Brain Res* **189**, 126-138.

[66] Shiryaev N, Jouroukhin Y, Gozes I (2010) 3R tau expression modifies behavior in transgenic mice. *J Neurosci Res* **88**, 2727-2735.

[67] Welzl H, D'Adamo P, Lipp HP (2001) Conditioned taste aversion as a learning and memory paradigm. *Behav Brain Res* **125**, 205-213.

[68] Janus C, Welzl H, Hanna A, Lovasic L, Lane N, St George-Hyslop P, Westaway D (2004) Impaired conditioned taste aversion learning in APP transgenic mice. *Neurobiol Aging* **25**, 1213-1219.

[69] Yamamoto T (2007) Brain regions responsible for the expression of conditioned taste aversion in rats. *Chem Senses* **32**, 105-109.

[70] Herry C, Ciocchi S, Senn V, Demmou L, Muller C, Luthi A (2008) Switching on and off fear by distinct neuronal circuits. *Nature* **454**, 600-606.

[71] Hanna A, Horne P, Yager D, Eckman C, Eckman E, Janus C (2009) Amyloid beta and impairment in multiple memory systems in older transgenic APP TgCRND8 mice. *Genes Brain Behav* **8**, 676-684.

[72] Bienvenu TC, Busti D, Magill PJ, Ferraguti F, Capogna M (2012) Cell-type-specific recruitment of amygdala interneurons to hippocampal theta rhythm and noxious stimuli *in vivo*. *Neuron* **74**, 1059-1074.

[73] Battaglia F, Wang HY, Ghilardi MF, Gashi E, Quartarone A, Friedman E, Nixon RA (2007) Cortical plasticity in Alzheimer's disease in humans and rodents. *Biol Psychiatry* **62**, 1405-1412.

[74] Denayer E, Ahmed T, Brems H, Van Woerden G, Borgesius NZ, Callaerts-Vegh Z, Yoshimura A, Hartmann D, Elgersma Y, D'Hooge R, Legius E, Balschun D (2008) Spred1 is required for synaptic plasticity and hippocampus-dependent learning. *J Neurosci* **28**, 14443-14449.

[75] Larson J, Wong D, Lynch G (1986) Patterned stimulation at the theta frequency is optimal for the induction of hippocampal long-term potentiation. *Brain Res* **368**, 347-350.

[76] Jay TM, Witter MP (1991) Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. *J Comp Neurol* **313**, 574-586.

[77] McDonald AJ (1991) Organization of amygdaloid projections to the prefrontal cortex and associated striatum in the rat. *Neuroscience* **44**, 1-14.

[78] Milad MR, Vidal-Gonzalez I, Quirk GJ (2004) Electrical stimulation of medial prefrontal cortex reduces conditioned fear in a temporally specific manner. *Behav Neurosci* **118**, 389-394.

[79] Vertes RP (2004) Differential projections of the infralimbic and prelimbic cortex in the rat. *Synapse* **51**, 32-58.

[80] Myers KM, Davis M (2007) Mechanisms of fear extinction. *Mol Psychiatry* **12**, 120-150.

[81] Lebron K, Milad MR, Quirk GJ (2004) Delayed recall of fear extinction in rats with lesions of ventral medial prefrontal cortex. *Learn Mem* **11**, 544-548.

[82] Pardon MC, Sarmad S, Rattray I, Bates TE, Scullion GA, Marsden CA, Barrett DA, Lowe J, Kendall DA (2009) Repeated novel cage exposure-induced improvement of early Alzheimer's-like cognitive and amyloid changes in TASTPM mice is unrelated to changes in brain endocannabinoids levels. *Neurobiol Aging* **30**, 1099-1113.

[83] Rattray I, Scullion GA, Soulby A, Kendall DA, Pardon MC (2009) The occurrence of a deficit in contextual fear extinction in adult amyloid-over-expressing TASTPM mice is independent of the strength of conditioning but can be prevented by mild novel cage stress. *Behav Brain Res* **200**, 83-90.

[84] Codita A, Gumucio A, Lannfelt L, Gellerfors P, Winblad B, Mohammed AH, Nilsson LN (2010) Impaired behavior of female tg-ArcSwe APP mice in the IntelliCage: A longitudinal study. *Behav Brain Res* **215**, 83-94.

[85] Bonardi C, De Pulford F, Jennings D, Pardon MC (2011) A detailed analysis of the early context extinction deficits seen in APPswe/PS1dE9 female mice and their relevance to preclinical Alzheimer's disease. *Behav Brain Res* **222**, 89-97.

[86] Galsworthy MJ, Amrein I, Kuptsov PA, Poletaeva II, Zinn P, Rau A, Vyssotski A, Lipp HP (2005) A comparison of wild-caught wood mice and bank voles in the Intellicage: Assessing exploration, daily activity patterns and place learning paradigms. *Behav Brain Res* **157**, 211-217.

[87] Rapanelli M, Frick LR, Zanutto BS (2009) Differential gene expression in the rat hippocampus during learning of an operant conditioning task. *Neuroscience* **163**, 1031-1038.

[88] Featherstone RE, McDonald RJ (2004) Dorsal striatum and stimulus-response learning: Lesions of the dorsolateral, but not dorsomedial, striatum impair acquisition of a stimulus-response-based instrumental discrimination task, while sparing conditioned place preference learning. *Neuroscience* **124**, 23-31.

[89] Niv Y (2007) Cost, benefit, tonic, phasic: What do response rates tell us about dopamine and motivation? *Ann N Y Acad Sci* **1104**, 357-376.