Figure EV1. Genotype confirmation of ECrTgTau(-Mapt\textsuperscript{0/0}) mice by qPCR.

qPCR using RNA extracted from fresh frozen brain tissue of 18-month-old tau knockout mice (Mapt\textsuperscript{0/0}), ECrTgTau, and ECrTgTau crossed to Mapt\textsuperscript{0/0} mice (ECrTgTau-Mapt\textsuperscript{0/0}, n = 4 mice/group) was transcribed into cDNA using primers recognizing human tau transgene (P301L tau, top) or genomic mouse tau (MapT, bottom). GAPDH mRNA was co-transcribed as amplification control. ECrTgTau-Mapt\textsuperscript{0/0} and ECrTgTau mice showed human tau expression, and Mapt\textsuperscript{0/0} and ECrTgTau-Mapt\textsuperscript{0/0} mice lacked mouse tau expression.
A Immuno-FISH of huTau mRNA and protein in ECrTgTau mice

B Tau in hippocampal extracts

**Figure EV2.** DG neurons do not express but have human tau in ECrTgTau(-Mapt<sup>−/−</sup>) mice.

A Representative images of the fluorescence in situ hybridization of transgenic human tau mRNA combined with immunofluorescence labeling of human tau protein (Tau<sub>13</sub> antibody) shows human tau protein (green) in neuronal cell bodies in the EC and the DG (white arrowheads), but human tau mRNA only in EC neurons both in ECrTgTau(-Mapt<sup>−/−</sup>) and ECrTgTau mice. n = 3 sections/mouse and 3 mice/group. Scale bars, 50 μm.

B Human tau (huTau, Tau<sub>13</sub> antibody) and total tau (hu+moTau, DAKO antibody) levels in hippocampal extracts from 18-month-old mice are similar in ECrTgTau and ECrTgTau-Mapt<sup>−/−</sup> mice. Mean ± SEM, n = 3 mice/group, two-tailed Student's t-test. ns, non-significant.

Source data are available online for this figure.
Figure EV3. Propagation of full-length tau to neurons not glia in the DG of ECrTgTau(-Mapt0/0) mice.

A Horizontal ECrTgTau-Mapt0/0 brain section co-immunolabeled with Tau13 (mouse antibody recognizing the N-terminal end of human not mouse tau; epitope: aa20–35, red) and DAKO (polyclonal rabbit antibody recognizing the C-terminal half of all mouse and human tau; epitope: multiple sites in aa243–441; green). Human tau in cell bodies in both EC and DG neurons (white arrowheads) was recognized by both antibodies against the N-terminus and the C-terminal half, suggesting the trans-synaptic propagation of full-length tau. Scale bars, 50 μm.

B, C Co-immunostaining of human tau with GAD67 and Parvalbumin suggest the propagation of tau to a few GABAergic interneurons (white arrowheads) in the DG of ECrTgTau-Mapt0/0 (B) and ECrTgTau (C) mice. Astrocytes (GFAP) and microglia (Iba1) did not have human tau in either mouse line. n = 4 sections/mouse, 3 mice/group. Scale bars, 50 μm.
Figure EV4. Increased phospho-tau and axonal changes in ECrTgTau mice.
A Stereological counting of DAPI nuclei in EC layer II/III suggested no obvious neuronal loss in ECrTgTau(-Mapt0/0) mice at 18 months of age.
B Western blotting for pre-synaptic marker synapsin-1 (Syn-1) showed similar levels, indicating no major synapse loss in ECrTgTau(-Mapt0/0) mice at 18 months of age.

Data information: Mean ± SEM, n = 4 sections/mouse, 3 mice/group, one-way ANOVA with Bonferroni correction. ns, not significant.
Source data are available online for this figure.

Figure EV5. Reduced neurodegeneration in 12-month-old rTg4510-Mapt0/0 mice.
A Whole brain weights of 12-month-old animals show severe brain matter loss in rTg4510 compared to WT mice (weight loss > 23%), which was partially rescued in rTg4510-Mapt0/0 mice.
B Cortical thickness, measured from CTX surface to corpus callosum, decreased in rTg4510 mice at 12 months by ~50% compared to WT, and rTg4510-Mapt0/0 showed CTX thinning of ~30% at 12 months.
C The number of cortical neurons (NeuN+ cells) in 12-month-old rTg4510 mice was significantly reduced (~63% of WT). The number of neurons in rTg4510-Mapt0/0 slightly decreased to ~88% of Mapt0/0 mice (ns).

Data information: Mean ± SEM, n = 3 mice/group, one-way ANOVA with Bonferroni for multiple comparison. ns, not significant.

Figure EV6. Elevated ER stress in the presence of mouse tau in rTg4510 mice.
Western blot analysis of extracts from 9-month-old mice revealed equally high ubiquitin levels in rTg4510 and rTg4510-Mapt0/0 mice compared to controls; P301Tau aggregates appear to expose a similar challenge to the proteasome both in the presence and in the absence of mouse tau. Levels of the endoplasmatic reticulum (ER) stress marker CHOP seemed elevated only in rTg4510 mice, suggesting less ER stress and subsequent trigger of apoptotic pathways in the absence of mouse tau. Mean ± SEM, n = 3 mice/group, one-way ANOVA with Bonferroni. ns, not significant.
Source data are available online for this figure.
Figure EV7. Lack of mouse tau largely delays onset of NFT-induced neurodegeneration.

A, B Average ratios of (A) tangle number:neuron loss (=tangles/([number of neurons in WT or MapT\textsuperscript{0/0} controls] - [number neurons in rTg4510 or rTg4510-MapT\textsuperscript{0/0}]) and (B) average rations of tangle number:cortex thinning (=tangles/[CTX thickness of WT or MapT\textsuperscript{0/0} controls] - [CTX thickness of rTg4510 or rTg4510-MapT\textsuperscript{0/0}]) at 9 and 12 months of age highlight the improved neuronal survival at given tangle load in rTg4510-MapT\textsuperscript{0/0} mice. Comparing the effect of NFTs on neuronal loss (A) and cortex thinning (B) between 9- and 12-month-old animals discovers a delayed onset of pathological changes—in the context of tangles—in tau-null animals. n = 3 mice/group.

C Representative images of an immuno-FISH for human tau protein (TauY9 antibody, pink) and human tau mRNA (green) on brain sections of 9-month-old rTg4510(-MapT\textsuperscript{0/0}) mice. Human tau transgene expression appears diminished in the outer CTX layers in rTg4510 but not rTg4510-MapT\textsuperscript{0/0} animals (low magnification images). In rTg4510-MapT\textsuperscript{0/0} animals, more EC neurons still express human tau mRNA while having human tau protein accumulated in the somata (white arrowheads) compared to rTg4510 mice; the neurotoxicity caused by P301Ltau expression, missorting into the soma, and aggregation seems to be reduced in the absence of mouse tau. n = 4 sections/mouse, 2 mice/group. Scale bars, 100 μm.

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