Supporting Information

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SI Text

Genotypes.

Fig. 1. ctr: *elav-GAL4/+*. p53 null: $p53^{11\text{-}1B\text{-}1}$. tau: *elav-GAL4/+; UAS-tau*^{R406W}*/+*. tau + p53 null: *elav-GAL4/+;UAS-tau*^{R406W}, $p53^{11\text{-}1B\text{-}1}/p53^{11\text{-}1B\text{-}1}$.

Fig. 4. tau: *elav-GAL4/+;UAS-tau*^{R406W}*/+*. Clc-LOF: *elav-GAL4/+;* $Clc^{DG23206}$*/+* or *elav-GAL4/+; UAS-tau*^{R406W}*/*$Clc^{DG23206}$. Chc-1: (*elav-GAL4/*Chc^{1} or *elav-GAL4/*Chc^{1}*; UAS-tau*^{R406W}*/+*. Chc-4: *elav-GAL4/*Chc^{4} or *elav-GAL4/*Chc^{4}*; UAS-tau*^{R406W}*/+*. Rab26-OE: *elav-GAL4/+; UAS-Rab26/+* or *elav-GAL4/+; UAS-Rab26/+; UAS-tau*^{R406W}*/+*. UAS-Rab26-DN: *elav-GAL4/+; UAS-Rab26*^{T204N}*/+* or *elav-GAL4/+; UAS-tau*^{R406W}*/UAS-Rab26*^{T204N}. Rab26 RNAi: *elav-GAL4/+; UAS-Rab26 RNAi 43730/+* or *elav-GAL4/+; UAS-Rab26 RNAi 43730/+; UAS-tau*^{R406W}*/+*. Sytβ-LOF: *elav-GAL4/+;* $Sytβ^{DG10711}$*/+* or *elav-GAL4/+; UAS-tau*^{R406W}*/*$Sytβ^{DG10711}$. Sytβ RNAi: *elav-GAL4/+; UAS-Sytβ RNAi JF02593* or *elav-GAL4/+; UAS-tau*^{R406W}*/UAS-Sytβ RNAi JF02593*. Amph-LOF: *elav-GAL4/+;* $Amph^{EY9339}$*/+* or *elav-GAL4/+;* $Amph^{EY9339}$*/+; UAS-tau*^{R406W}*/+*. Amph RNAi: *elav-GAL4/+; UAS-Amph RNAi 7190/+* or *elav-GAL4/+; UAS-tau*^{R406W}*/UAS-Amph RNAi 7190*.

Fig. S1. ctr: *elav-GAL4/+*. tau: *elav-GAL4/+;UAS-tau*^{R406W}*/+*. tau + $p53^{11\text{-}1B\text{-}1}$: *elav-GAL4/+;UAS-tau*^{R406W}, $p53^{11\text{-}1B\text{-}1}/p53^{11\text{-}1B\text{-}1}$.

$p53^{5A\text{-}1\text{-}4}$: $p53^{5A\text{-}1\text{-}4}$. tau + $p53^{5A\text{-}1\text{-}4}$: *elav-GAL4/+; UAS-tau*^{R406W}, $p53^{5A\text{-}1\text{-}4}/p53^{5A\text{-}1\text{-}4}$.

Fig. S7. ctr – SCA3: *elav-GAL4/+*. ctr + SCA3: *elav-GAL4/+; UAS-ATXN3-Q78/+*. EGFP + SCA3: *elav-GAL4/+; UAS-EGFP/+; UAS-ATXN3-Q78/+*. Amph-LOF + SCA3: *elav-GAL4/+;* $Amph^{EY9339}$*/+; UAS-ATXN3-Q78/+*. Chc-LOF + SCA3: *elav-GAL4/*Chc^{1}*; UAS-ATXN3-Q78/+*. Clc-LOF + SCA3: *elav-GAL4/+; UAS-*$Clc^{DG23206}$*/UAS-ATXN3-Q78*. Sytβ RNAi + SCA3: *elav-GAL4/+; UAS-Sytβ RNAi JF02593/UAS-ATXN3-Q78*. Rab26-OE + SCA3: *elav-GAL4/+; UAS-Rab26/+; UAS-ATXN3-Q78/+*. Rab26-DN + SCA3: *elav-GAL4/+; UAS-ATXN3-Q78/UAS-Rab26*^{T204N}.

Fig. S8. ctr: *elav-GAL4/+*. p53 null: $p53^{11\text{-}1B\text{-}1}$. tau: *elav-GAL4/+; UAS-tau*^{R406W}*/+*. tau + p53 null: *elav-GAL4/+;UAS-tau*^{R406W}, $p53^{11\text{-}1B\text{-}1}/p53^{11\text{-}1B\text{-}1}$.

GFP-Atg8a: *elav-GAL4/+; UAS-GFP-Atg8a/+*. Tau + Atg8a: *elav-GAL4/+; UAS-tau*^{R406W}*/ UAS-GFP-Atg8a*. GFP-ref(2)P: *elav-GAL4/+; UAS-GFP-ref(2)P/+*. Tau + ref(2)P: *elav-GAL4/+; UAS-tau*^{R406W}*/UAS-GFP-ref(2)P*.

Primers.

ChIP primers for* Drosophila *p53 gene.

dp53 ChIP For 5′-CGCTTGTACTTGCATCATTCG-3′;

dp53 ChIP Rev 5′-GCGCCTTGGCTGGATAAAC-3′;

3′ UTR ChIP For 5′-GTGGCAGCCGGTCGAA-3′;

3′ UTR ChIP Rev 5′-CAGCCAAAGCGGATGCA-3′.

ChIP primers for* Drosophila *rpr gene.

rpr ChIP For 5′-CGGAAAACTGATATGGCGATAAG-3′;

rpr ChIP Rev 5′-CGGTCCCTCAGTCTCCAAGTC-3′.

***ChIP primers for validation of candidates in* Drosophila.**

Amph ChIP For 5′-ATGTTCAGCCACACAAGTACACGT-3′;

Amph ChIP Rev 5′-ATGTACATTAAAAACAAGGTTCCGC-3′;

Clc ChIP For 5′-TCTGCTGCCAGTGAAAAACG-3′;

Clc ChIP Rev 5′-CAAGTTCACCGTGGCATCAT-3′;

Chc #1 ChIP For 5′-AGAAAAGAGGCAGCATTATCATCA-3′;

Chc #1 ChIP Rev 5′-CGCAACTCAACATGGCTGACT-3′;

Chc #2 ChIP For 5′-GCTGGATTGTCCGAATTTGAC-3′;

Chc #2 ChIP Rev 5′-GCAGGAATGCGGCAGACT-3′;

Rab26 #1 ChIP For 5′-GGTGCAGAGTTACCGTGCTACA-3′;

Rab26 #1 ChIP Rev 5′-GGTGTGCGACACGGCTACTT-3′;

Rab26 #2 ChIP For 5′-CACGACGATGCTATCATGGC-3′;

Rab26 #2 ChIP Rev 5′-ACGATAGCCAGGATATCCGGT-3′;

Sytβ ChIP For 5′-CCTCGCTGGGCATGTGAT-3′;

Sytβ ChIP Rev 5′-CCTTTGTGCCAAATTTAATTGTCA-3′.

ChIP primers for human BIN1.

hBIN1 prom For 5′-AGGGAATGGCCTGTGTGAAC-3′;

hBIN1 prom Rev 5′-GAGAAATCGAGTCCCAGGAATG-3′;

hBIN1 intron1 For 5′-GCACCCGGTCAGTTGTCTATC-3′;

hBIN1 intron1 Rev 5′-GCAGCTGGCGTGATCCA-3′.

Solutions. RIPA buffer was composed of 10 mM Tris·Cl (pH 8.0), 1 mM EDTA, 0.5 mM EGTA, 1% Triton X-100, 0.1% sodium deoxycholate, 0.1% SDS, and 140 mM NaCl. NEEM buffer was made up of 10 mM Hepes pH 7.6, 1.5 mM $MgCl_2$, 0.1 mM EDTA, 10 mM KCl, and 300 mM sucrose. NEB buffer was made up of 0.32 M sucrose, 5 mM $CaCl_2$, 3 mM $Mg(Ac)_2$, 0.1 mM EDTA, and 10 mM Tris·HCl (pH 8).

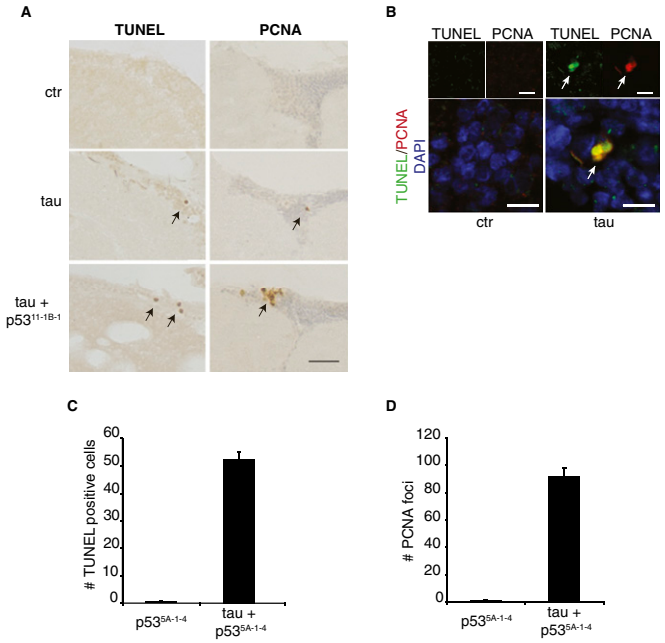

Fig. S1. p53 is neuroprotective in a *Drosophila* tauopathy model. (*A*) Loss of p53 ($p53^{11\text{-}1B\text{-}1}$) in the brain increases tau-induced cell death, as indicated by TUNEL staining (*Left*) and cell-cycle activation and as monitored with PCNA expression (*Right*), arrows. (Scale bar: 20 μm.) (*B*) Colabeling of PCNA, TUNEL-positive neurons in tau-transgenic flies, arrows. (Scale bars: 5 μm.) (*C*) Apoptosis, indicated by the number of TUNEL-positive neurons, increases in the brains of tau-transgenic, $p53^{5A\text{-}1\text{-}4}$ animals. (*D*) Cell-cycle reactivation, indicated by the number of PCNA-positive foci, increases in the brains of tau-transgenic, $p53^{5A\text{-}1\text{-}4}$ animals. Flies are 10-d-old ($n \geq 6$ per genotype). In the graph, values represent mean ± SEM. ctr, control: *elav-GAL4*/+.

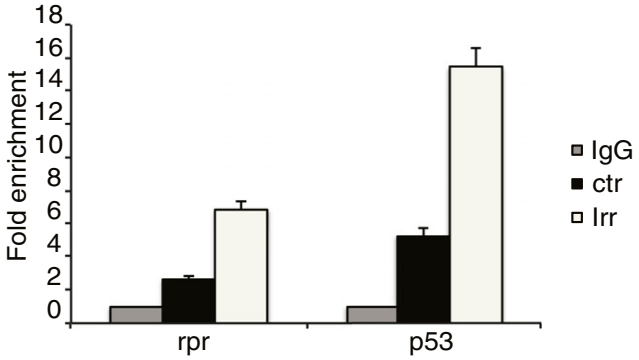

Fig. S2. p53 antibody specifically immunoprecipitates p53 protein. ChIP assay showing that p53 binds regulatory regions of the *p53* and *rpr* genes. Fold enrichment is expressed relative to IgG control. Values have been normalized to the total DNA and represent mean ± SEM. The graph is representative of one of three independent triplicate assays. Chromatin for IP was taken from untreated (ctr) or irradiated (Irr) w^{1118} embryos.

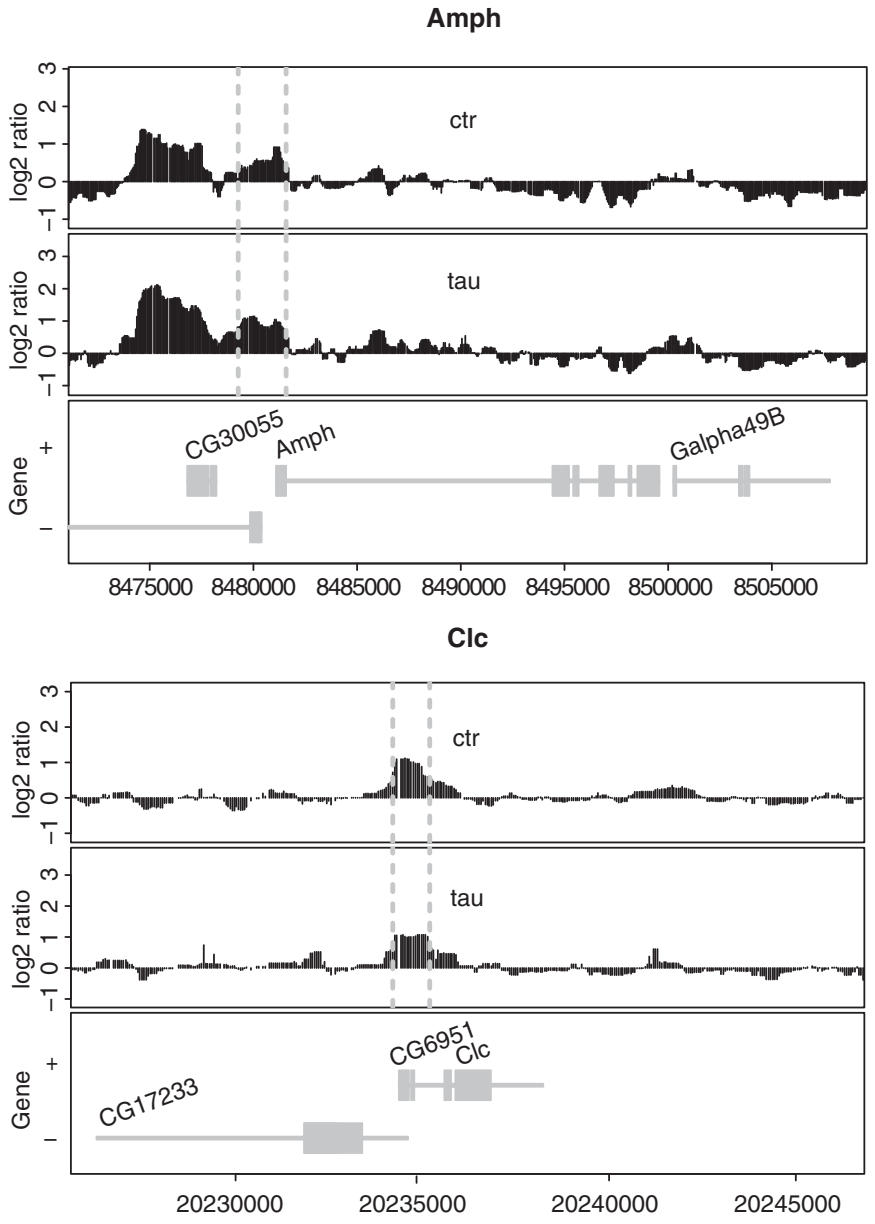

Fig. S3. (Continued)

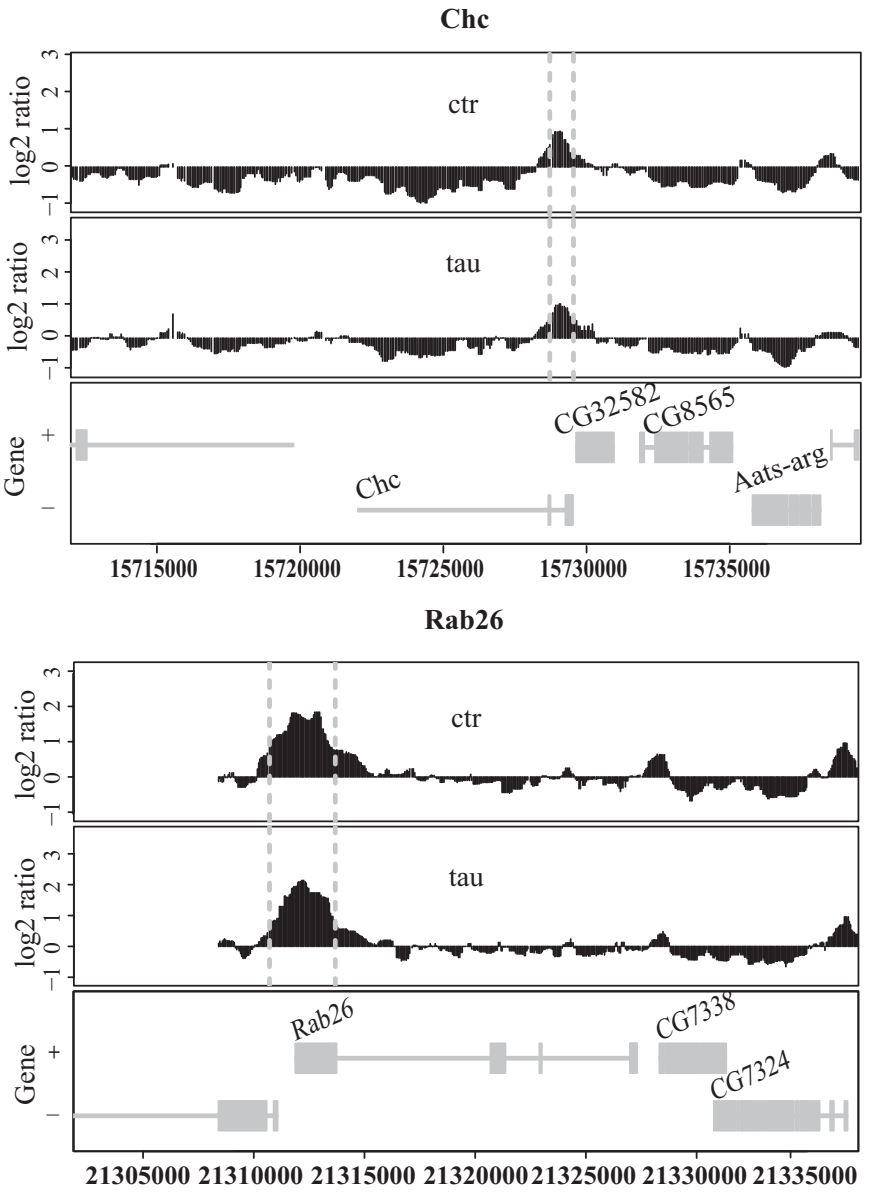

Fig. S3. (Continued)

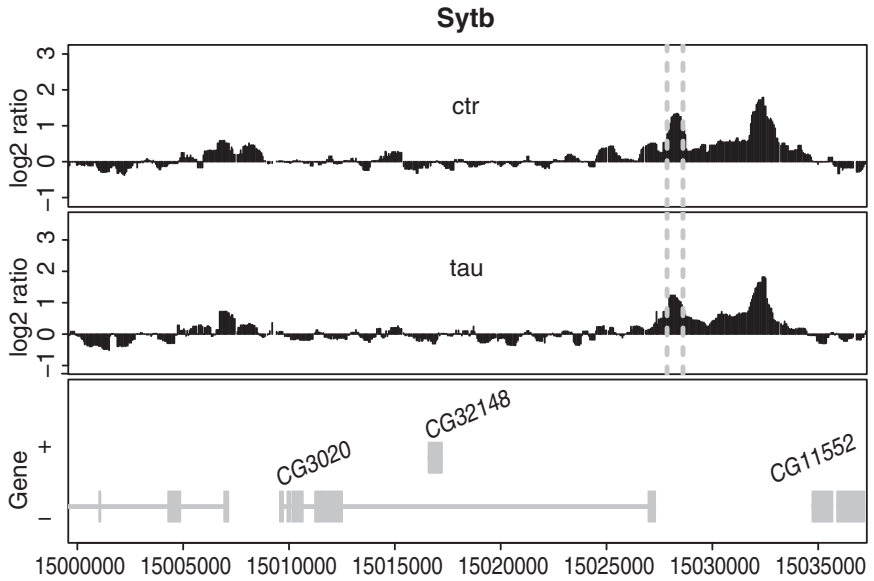

Fig. S3. Representative high-resolution ChIP-chip analysis of p53 binding to the promoter regions of the *Amph*, *Clc*, *Chc*, *Rab26*, and *Sytß* genes. The log2 ratio fluorescence values for control flies (*Top*) and tau flies (*Middle*) chromatin hybridization is shown for a region of 30 kb. Gene positions in the genome (*Bottom*) are represented with rectangles (exons), connected by lines (introns). ctr, control: *elav-GAL4*/+.

Genomic sequence	gene
caca**CAAA**cactcg**ac**at**g**ctcacaagagcgcgc	Amph
tgccccatcctttgt**C**AT**G**cc**C**TT**G**atcagt**caagt**caa	Chc
ccgagtcgatctggt**C**A**TG**tccgtctgtccgtat	
tagtccacaaggtca**C**A**TG**tcct	Rab26
ctccc**CTTGcc**tc**gaccagt**cat	
ctacgatgaagtgga**C**A**TG**cacccagccccgtcc	
atggggctgtaatca**C**A**TG**ccca	Sytb
gcaa**CAAG**ttgcga**aa**aa**g**cttt	

Fig. S4. Genomic sequences of p53-responsive elements identified in synaptic gene promoters. Bold and uppercase characters indicate potential p53 consensus.

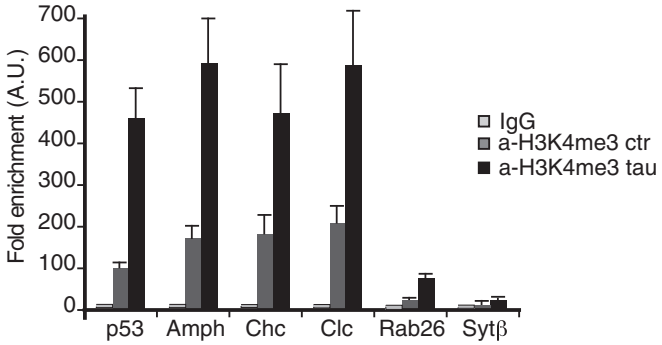

Fig. S5. ChIP assay for H3K4me3 histone modification showing that the selected synaptic genes are actively transcribed. Fold enrichment is expressed relative to negative control (IgG). Values have been normalized to the total DNA and represent mean ± SEM. The graph is representative of one of the three independent triplicate assays. Flies are 10-d-old.

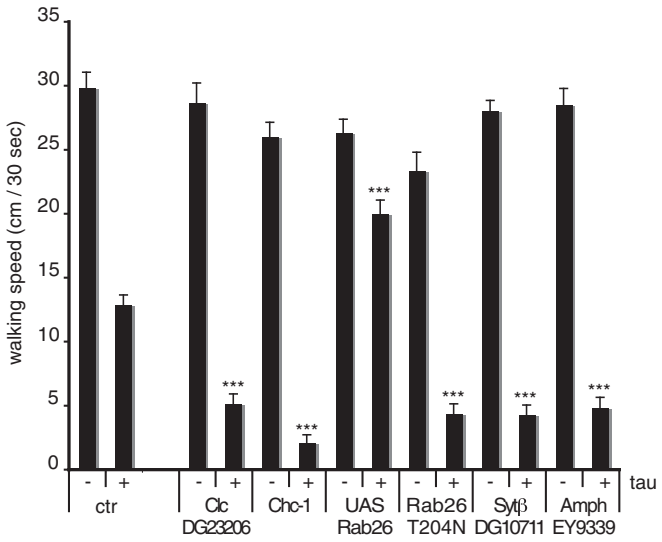

Fig. S6. Altering the function of synaptic genes in tau-transgenic animals modifies locomotion, measured as walking speed. Flies are 2-d-old (n = 18 flies per genotype). In the graph, values represent mean ± SEM. Asterisks indicate significant differences compared with tau-transgenic flies by ANOVA with Student–Newman–Keuls post hoc test for multiple comparisons. ***$P < 0.001$. ctr, control: *elav-GAL4*/+.

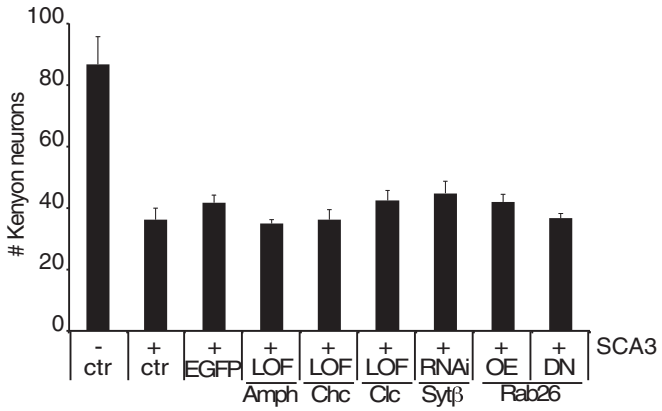

Fig. S7. Synaptic function modifiers do not alter neuronal toxicity of mutant ataxin 3. The number of Kenyon neurons per 250 μm^2 was counted. Flies are 10-d-old (n = 6 flies per genotype). In the graph, values represent mean ± SEM. ctr, control: *elav-GAL4*/+; SCA3, mutant ataxin 3: *UAS-ATXN3-Q78*.

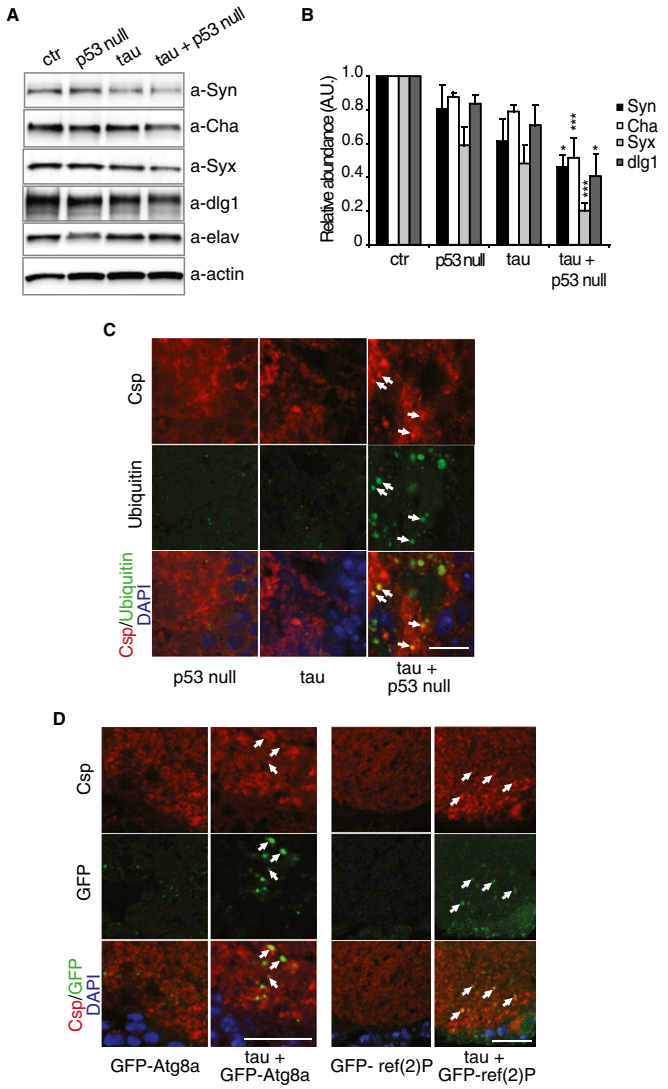

Fig. S8. Synaptic abnormalities in tau-transgenic animals. (*A*) There is a significant reduction in the expression of synaptic markers in the brains of tau-transgenic, p53-null flies. (*B*) Quantification of the protein expression reduction relative to control. In the graph, values represent mean ± SEM of at least three Western blots per antibody. Asterisks indicate significant differences compared with control flies by ANOVA with Bonferroni post hoc test for multiple comparisons. $*P < 0.05$; $***P < 0.001$. ctr, control: *elav-GAL4*/+. (*C*) Ubiquitin accumulates at synapses when tau is expressed in the absence of p53. (*D*) Autophagy markers accumulate at synapses in tau-transgenic flies. Flies are 10-d-old. (Scale bars: 10 μm.) Syn, Synapsin; Cha, Choline acetyltransferase; Syx, syntaxin; dlg1, discs large 1; Elav, embryonic lethal abnormal vision; Csp, Cysteine string protein; Atg8a, Autophagy-specific gene 8a, detected with a transgenic reporter (*UAS-GFP-Atg8a*) and anti-GFP immunofluorescence; ref(2)P, refractory to sigma P, also known as p62 and SQSTM1, detected with a transgenic reporter (*UAS-GFP-ref(2)P*) and anti-GFP immunofluorescence.

Dataset S1. List of genes bound by p53 in tau-transgenic flies throughout the whole *Drosophila* genome

Dataset S1

Dataset S2. Gene Ontology analysis of the genes bound by p53 in tau-transgenic flies. To reduce the redundancy in gene set annotation, we used functional annotation clustering, which groups similar annotations together

Dataset S2

Dataset S3. Detailed list of the synaptic-transmission–related terms

Dataset S3