Figure S1

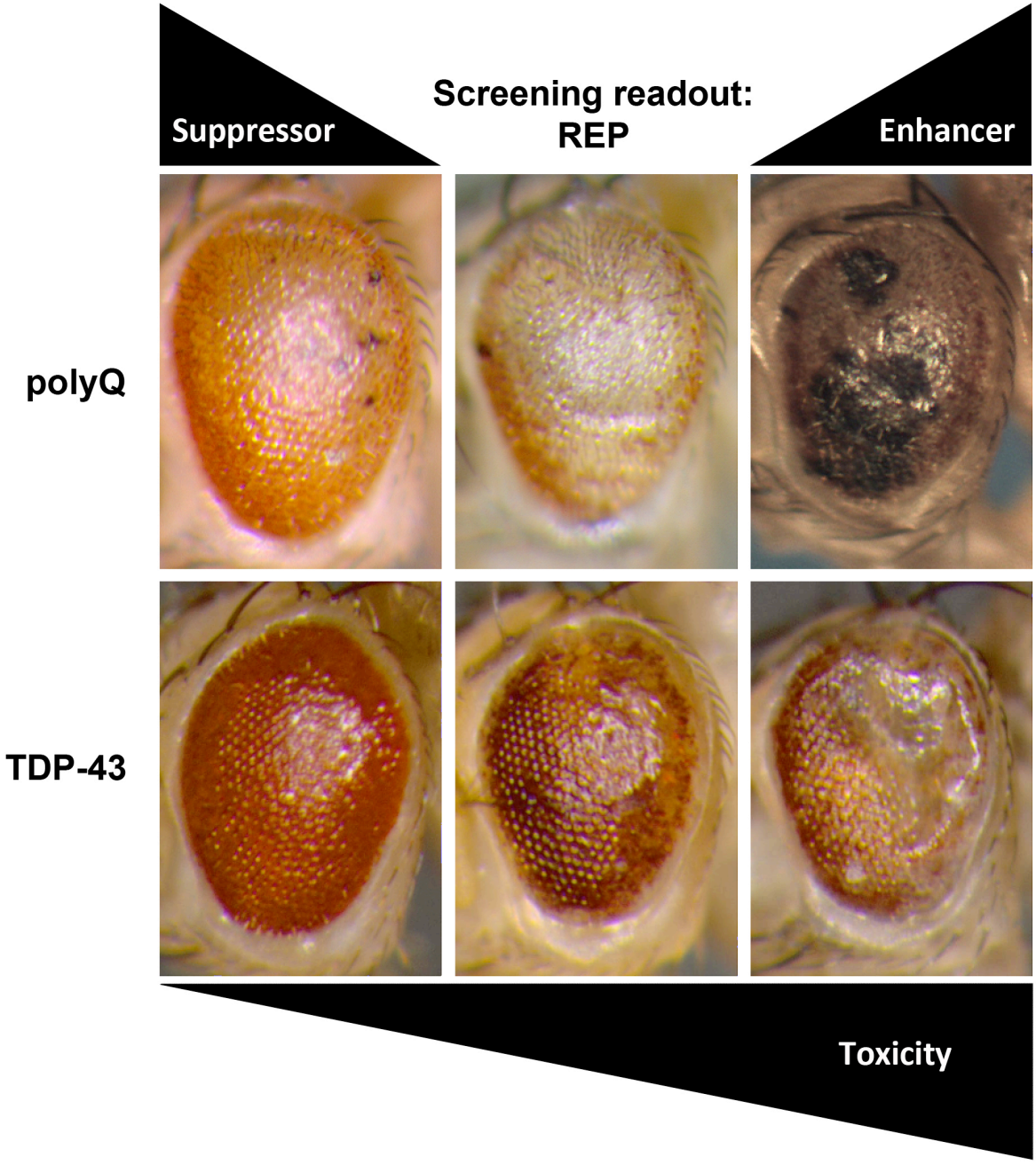

Figure S1: REPs induced by expression of polyQ and TDP-43 and their modification by enhancers and suppressors. All identified modifiers of the Tau[R406W]-induced REP were cross references with results from a previous screen set to identify modifiers of polyQ-induced toxicity. Modifiers with similar effects on Tau[R406W] and polyQ-induced REPs were further tested for modification of a REP induced by eye-specific expression of ALS-linked TDP-43. Interestingly, almost all tested (19 out of 20) modifiers also changed the REP induced by TDP-43 expression.

Figure S2

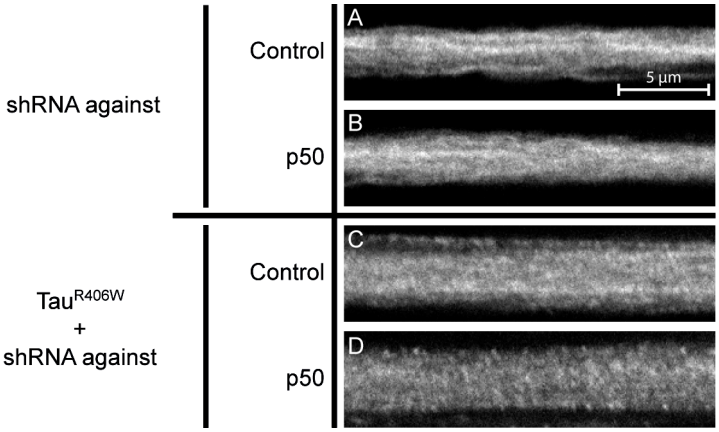

Figure S2: Tubulin network in axons of larval segmental nerves. To compare microtubule network integrity, segmental nerves with pan-neuronal expression (*elav*-Gal4) of the depicted constructs were analyzed by staining against Tubulin. **(A)** Segmental nerves of larvae expressing a control shRNA. Knockdown of p50 found to be an enhancer in the screen, coding for a member of the Dynein/Dynactin complex **(B)**, expression of Tau[R406W] **(C)**, nor the combination of Tau and shRNA **(D)** in segmental nerve neurons lead to evident changes in microtubule network integrity. Magnification is depicted in A (bar = 5 µm).

Figure S3

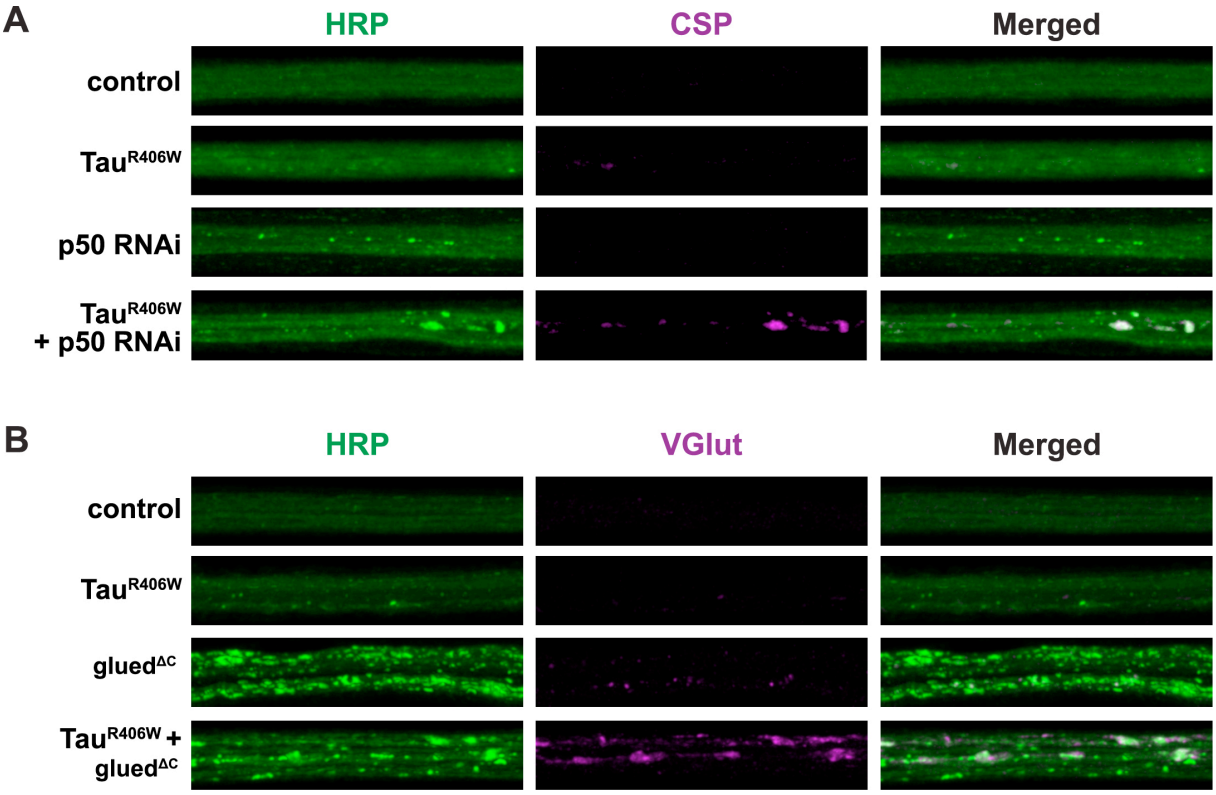

Figure S3: Effect of impaired retrograde transport and Tau[R406W] expression on neuronal integrity. Segmental nerves of Drosophila larvae expressing indicated transgenes under control of the pan neural driver (elav-Gal4, 29°C) were stained with HRP to visualize neuronal membranes (green, left panel). Transported cargo proteins CSP (A) or VGlut (B) are shown in the middle panel (magenta). An merged is shown on the right. While very few HRP punctae were observed in larvae expressing Tau[R406W], or p50 RNAi alone (A); the expression of Glued-DN led to a dramatically increase of HRP punctae (B). Irrespective of the nature of transported cargo proteins (magenta), significant accumulation of (A) Cysteine string protein (CSP) or (B) Vesicular glutamate transporter (VGlut) was only observed upon concomitant Tau[R406W] expression and impairment of retrograde transport.

Figure S4

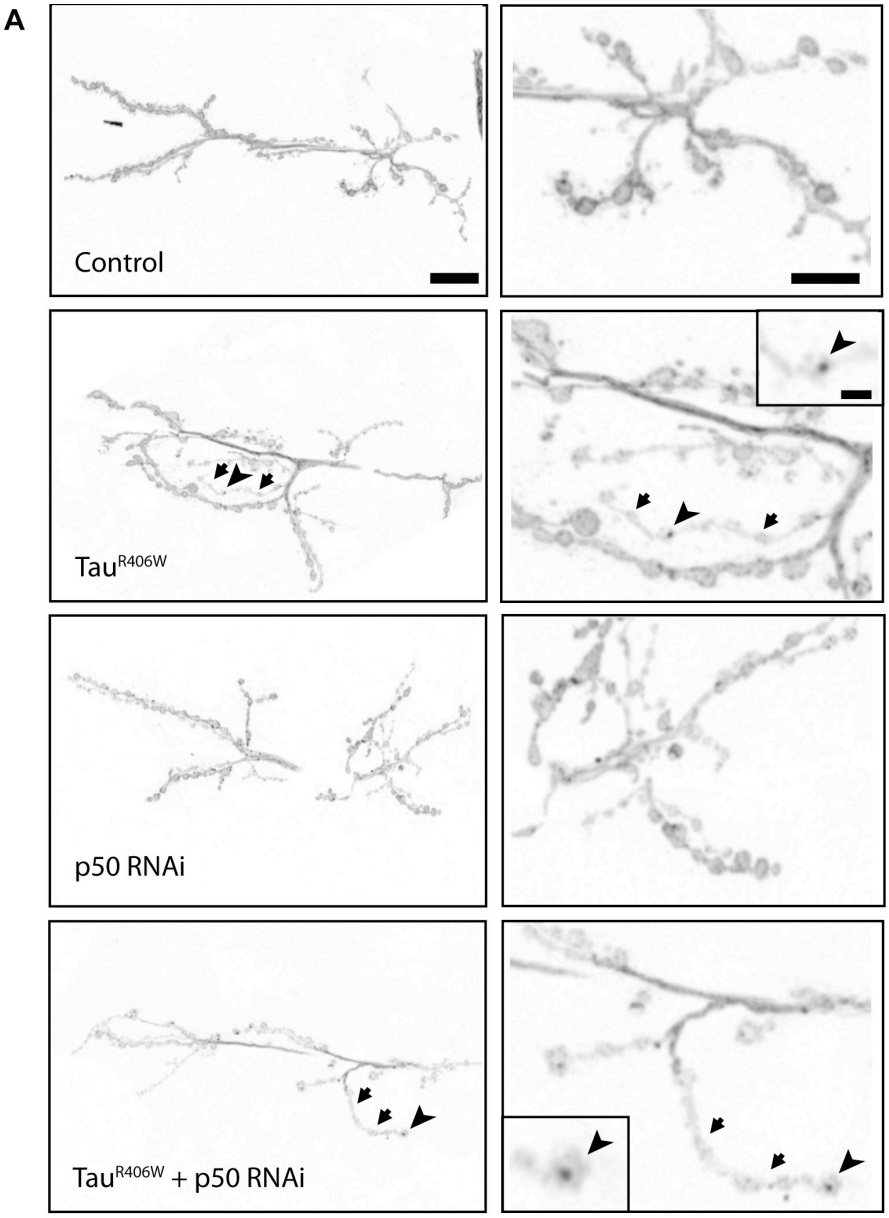
A
Control
Tau^{R406W}
p50 RNAi
Tau^{R406W} + p50 RNAi
B
illness scores
3
2
1
0
**
control
Tau^{R406W}
p50 RNAi
Tau^{R406W} + p50 RNAi

Figure S4: Effect of Tau[R406W] and concomitant silencing of Dynein/Dynactin complex on larval NMJ. (A) Representative images of a neuromuscular junction innervating muscle 6/7 in segment A2. Transgenes that were expressed under the control of the pan-neural driver (*elav-Gal4*, 29 °C) are indicated in the figure. HRP was used to visualize neuronal membranes. The NMJ of control larvae is uniformly stained. Larvae pan-neuronally expressing Tau[R406W] and *p50*-RNAi along with Tau[R406W] appear to have stretches of boutons with weak staining (arrowheads). The NMJs of *elav>Tau[R406W]* and *elav>Tau[R406W]* + *p50*-RNAi expressing larvae are characterized by the presence of bright spots of HRP staining appearing in boutons (arrows) unlike those in control larvae. Larvae pan-neuronally expressing p50-RNAi alone produce uniform HRP staining similar to control animals and fewer bright HRP spots. Scale bars represent 20 μm in the left panel, 10 μm in the left panel and 5 μm in the magnified images on the left. **(B)** Statistical analysis of membrane inhomogeneity revealed a small, but significant increase in *elav>Tau[R406W]* + *p50*-RNAi larvae compared to control larvae but not compared to *elav>Tau[R406W]* larvae.

Table S1: Unspecific modifiers of Tau[R406W]-induced REP

Name/CG	Effect on Tau	Effect on polyQ	Effect on TDP-43	Molecular/Biological function
Aats-his CG6335	L	L	E	Histidyl-tRNA synthetase
Rab30 CG9100	L	L	N.A.	GTPase, involved in protein transport
MED14 CG12031	L	L	E	RNA polymerase II transcription cofactor
Prp8 CG8877	E	L	SL	Pre-mRNA-processing/splicing factor
Nelf-E CG5994	E	L	E	Negative regulation of transcription from RNA polymerase II promoter during mitosis
RpS10a CG12275	E	L	E	Structural constituent of ribosome
- CG11985	L	L	E	Splicing factor 3B subunit
Prosbeta2 CG3329	L	L	SL	Catalytic constituent of the proteasome (beta-subunit), protein degradation
Rpn9 CG10230	E	L	E	Proteasome component, protein degradation
bic CG3644	L	L	E	RNA binding, intracellular mRNA localization
- CG6364	E	L	E	Uridine kinase activity, might be involved phagocytosis, engulfment.
- CG6873	E	E	SL	Actin binding/polymerization, involved in neurogenesis
Nrx-IV CG6827	E	L	L	Transmembrane receptor activity, involved in cell-cell interactions
CycJ CG10308	E	E	E	Cyclin-dependent protein kinase regulator, involved in cell cycle regulation
- CG8086	E	L	E	Unknown mol. function, might be involved in neurogenesis
bru CG2478	E	L	E	Unknown mol. function, involved in cytokinsesis
- CG8108	L	L	L	Suggested as zinc ion binding, biological function unknown
Ard1 CG11989	L	L	L	Peptide alpha-N-acetyltransferase activity, involved in oogenesis and neurogenesis

Smg5 CG8954	E	E	L	Unknown molecular function, involved in nonsense-mediated mRNA decay.
l(3)neo38 CG6930	L	E	-	zinc ion binding/regulation of chromatin silencing
Tcp-1η CG8351	L	L	N.A.	ATPase/cytoplasmic microtubule organization;
- CG12050	L	L	SL	unknown
MRG15 CG6363	S	S	N.A.	Chromatin silencing
Hop CG2720	S	S	N.A.	Heat shock chaperonin-binding

Table lists gene name (if applicable) and gene ID of all candidates identified to have a similar effect on polyQ-, TDP-43- and Tau-induced REPs. Mode of modification is indicated: enhancement (E), suppression (S), lethal (L) or semi-lethal (SL); not analyzed (N.A.). A brief summary of the molecular and biological functions assigned to the identified gene products is listed.