

Fig. S1. TDP Tg-low animals express low levels of TDP-43. Immunoblot comparing TDP-43 protein levels among non-transgenic (non-Tg), TDP Tg-low, a TDP-43 transgenic line with moderate overexpression (TDP Tg-OE1), and a TDP-43 transgenic line with high levels of overexpression (TDP Tg-OE2). The TDP-43 sequence in each strain was verified by sequencing to code for full-length wild-type TDP-43. The slightly lower molecular weight of TDP Tg-low may be due to a lack of post-translational modifications, particularly phosphorylated TDP-43, which are present in the higher copy TDP-43 strains.

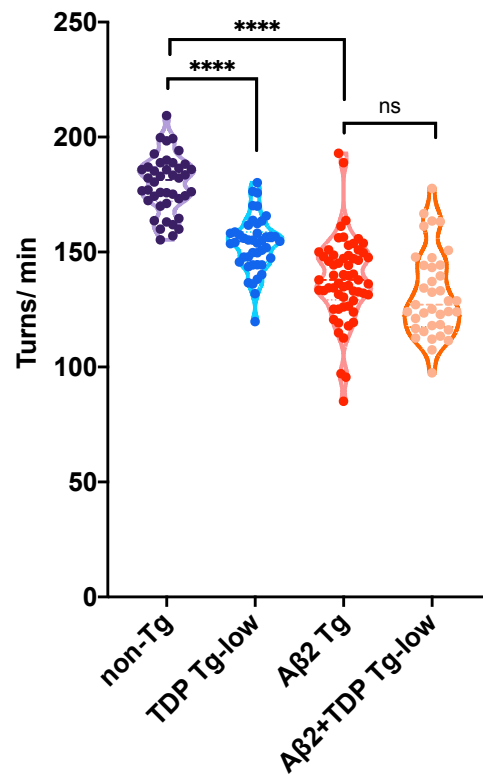


Fig. S2. tau+TDP Tg-low animals do not synergize with Aβ. Rates of thrashing in liquid were measured using unbiased computer-assisted tracking and analysis. The number of turns (thrashes) per second were recorded (turns/ sec). ns=not significant, **** $p < 0.0001$. N=128 (non-TG), 202 (TDP Tg-low), 140 (Aβ Tg), 97 (Aβ+TDP Tg-low), from 3 independent replicates. **** $p < 0.0001$, ns=not significant.

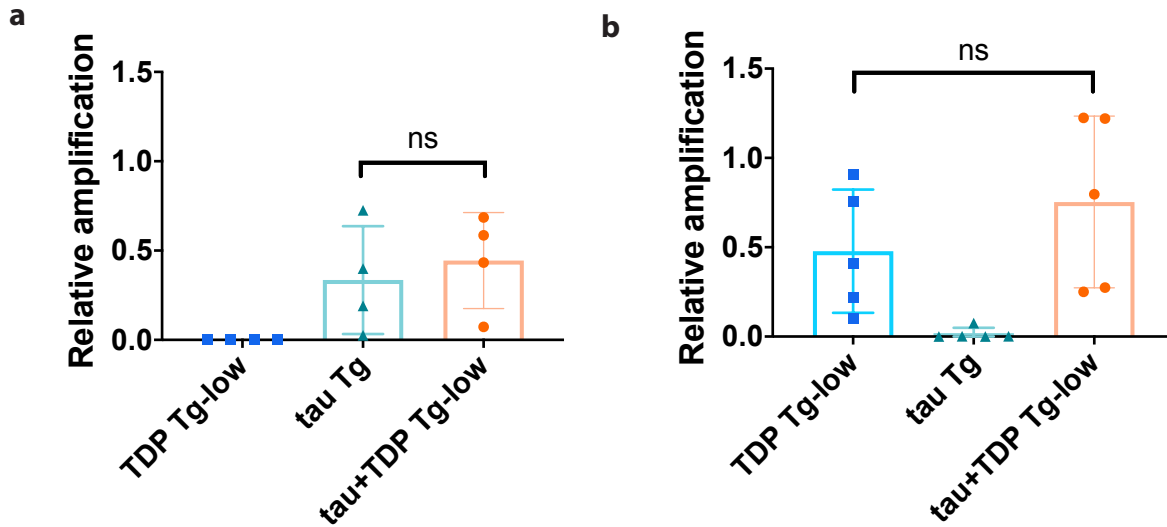


Fig. S3. mRNA expression of tau and TDP-43 transgenes are unchanged in tau +TDP-43 Tg-low. **a** Quantitative reverse-transcription PCR (qRT-PCR) testing expression of the tau transgene. tau signal is normalized to expression of an internal control gene, *rpl-32*, and plotted as arbitrary units. **b** qRT-PCR testing expression of the TDP-43 transgene. TDP-43 signal is normalized to expression of an internal control gene, *rpl-32*, and plotted as arbitrary units. ns=not significant.

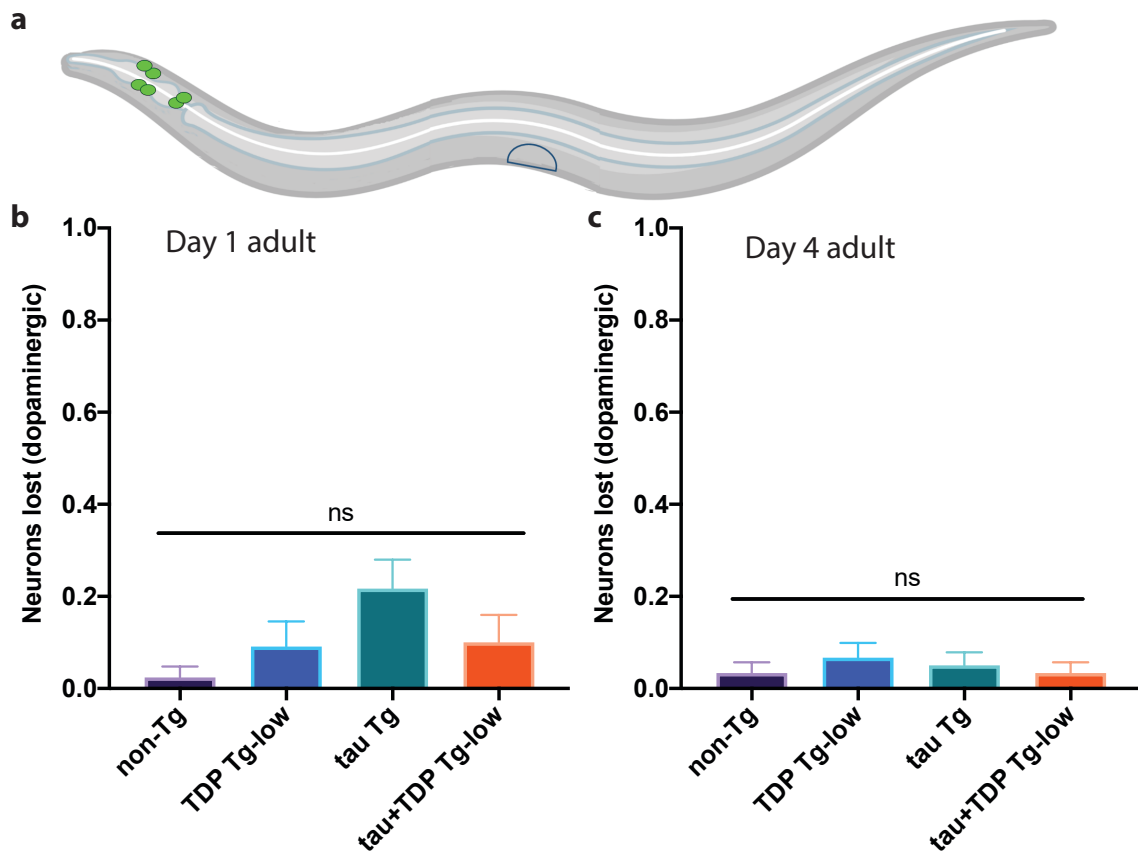


Fig. S4. Co-expression of tau and TDP-43 does not impact dopaminergic neurons. **a-c** Assessment of dopaminergic neurons in tau+TDP Tg-low animals. **a** Depiction of neurons scored (green). **b** Quantification of neurons lost in developmentally synchronized day 1 adult (**b**) and day 4 adult (**c**) *C. elegans*. ns = not significant. N>45 for all strains and timepoints scored, from at least 3 independent replicates.

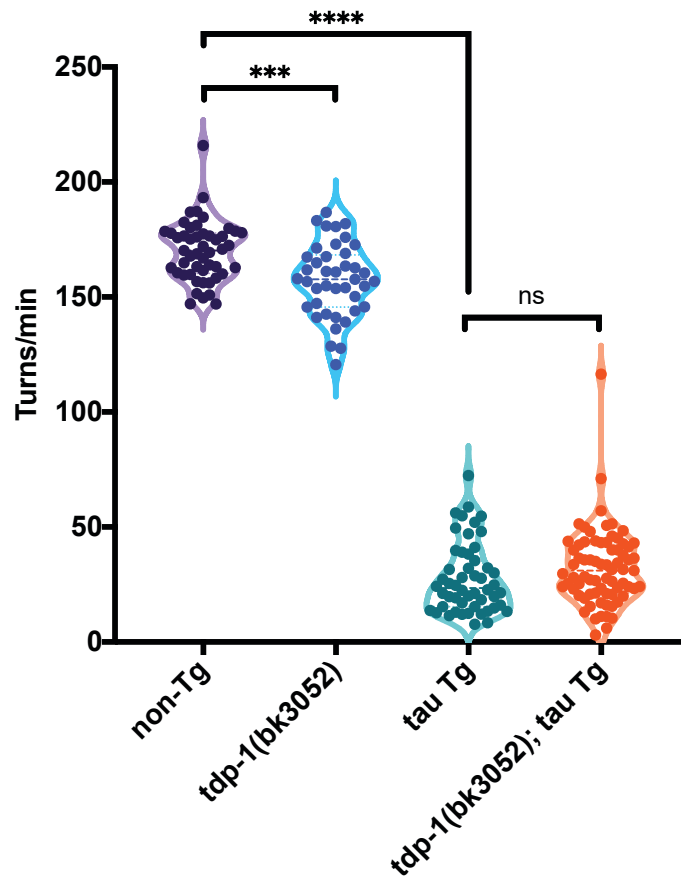
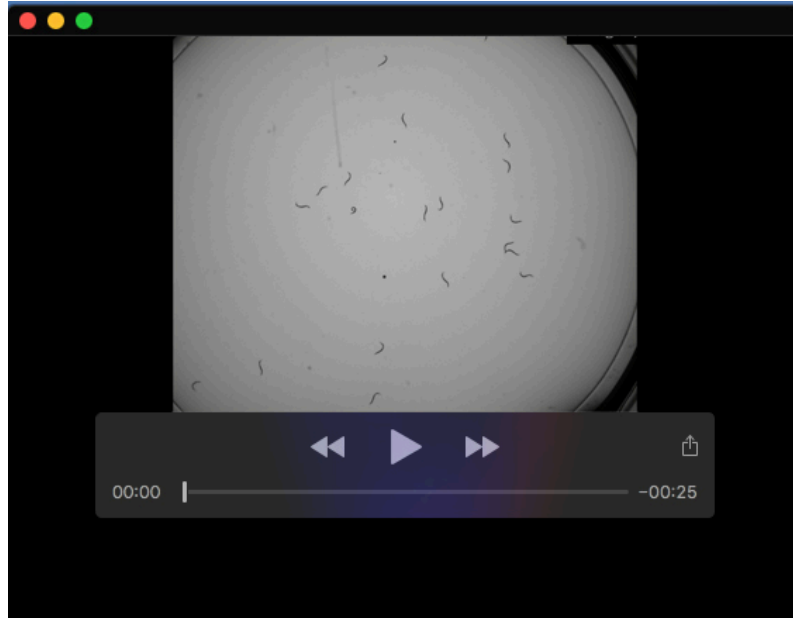


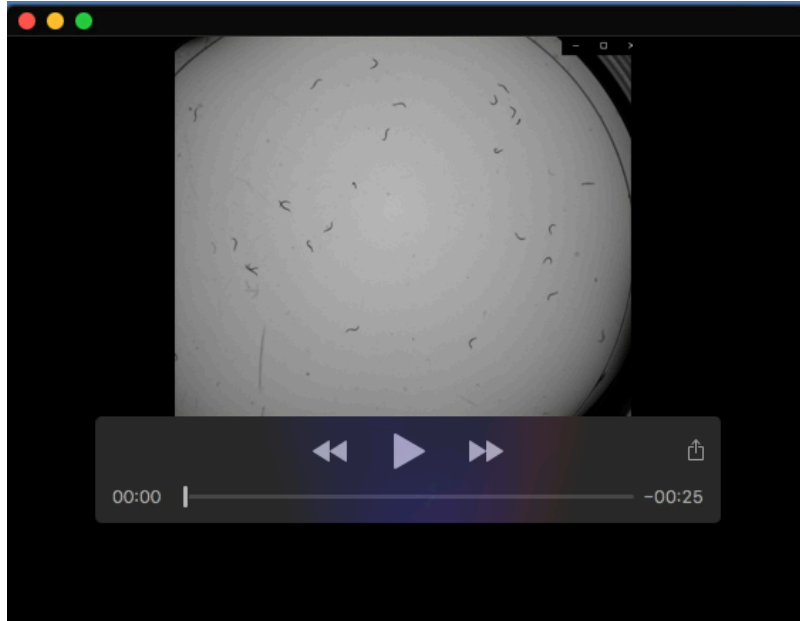
Fig. S5. Loss of the *C. elegans* homolog of TDP-43, *tdp-1*, does not alter tau-driven motility dysfunction. Rates of thrashing were measured using unbiased computer-assisted tracking and analysis. The number of turns (thrashes) per minute were recorded (turns/ min). ns=not significant, *** $P < 0.001$, **** $p < 0.0001$. N=49 (non-TG), 41 (*tdp-1(bk3052)*), 52 (tau Tg), 73 (*tdp-1(bk3052); tau Tg*), from 3 independent replicates.

Table S1. Strains used in this study.

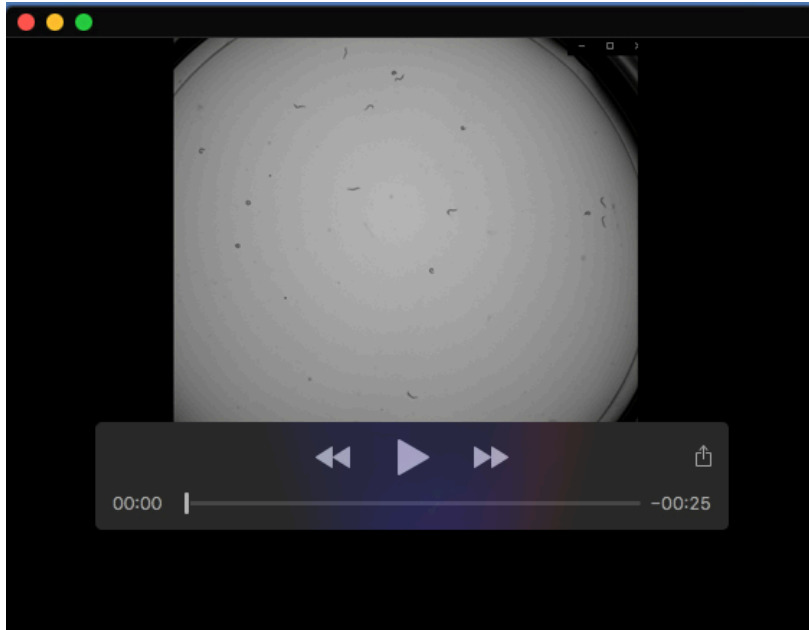
Abbreviation	Strain name	Genotype	Transgene
non-Tg	N2	wild-type	
tau Tg	CK1441	<i>bkIs1441[Paex-3::Tau WT(4R1N)+Pmyo-2::dsRED]</i>	human tau
A β Tg	GRU102	<i>gnals2[Pmyo-2::YFP+Punc-119::Abeta1-42]</i>	human A β
A β Tg 2	CL2355	<i>dvIs50[pCL45(snb-1::Abeta1-42::3'UTR(long) + mlt-2::GFP]</i>	human A β
polyQ Tg	CK241	<i>bkIs241[pF25B5.3::Q86-YFP]</i>	86 repeats of glutamine
TDP Tg-low	CK1943	<i>[Psnb-1::hTDP-43 WT::K4aptazyme::unc-54 3'UTR+Pmyo-3::mCherry]</i>	human TDP-43
tau+TDP Tg-low	NLS19	<i>bkIs1441[Paex-3::Tau WT(4R1N)+Pmyo-2::dsRED]; bkIs1943[Psnb-1::hTDP-43 WT::K4aptazyme::unc-54 3'UTR+Pmyo-3::mCherry]</i>	human tau and TDP-43
<i>sut-2(-); tau+TDP Tg-low</i>	NLS23	<i>sut-2(bk3011); bkIs1441[Paex-3::Tau WT(4R1N)+Pmyo-2::dsRED]; bkIs1943[Psnb-1::hTDP-43 WT::K4aptazyme::unc-54 3'UTR+Pmyo-3::mCherry]</i>	human tau and TDP-43
<i>sut-2(-); TDP Tg-low</i>	NLS24	<i>sut-2(bk3011); bkIs1943[Psnb-1::hTDP-43 WT::K4aptazyme::unc-54 3'UTR+Pmyo-3::mCherry]</i>	human TDP-43
<i>sut-2(-); tau Tg</i>	NLS25	<i>sut-2(bk3011); bkIs1441[Paex-3::Tau WT(4R1N)+Pmyo-2::dsRED]</i>	human tau
	EG1285	<i>oxIs12[Punc-47::GFP + lin-15(+)]</i>	GABAergic neuron GFP
	JPS617	<i>Ptph-1::GFP</i>	serotonergic neuron GFP
	WG1	<i>Pdat-1::GFP</i>	dopaminergic neuron GFP
	OH10972	<i>Peat-4::GFP</i>	glutamatergic neuron GFP
	LX929	<i>Punc-17::GFP</i>	cholinergic neuron GFP
	CK3052	<i>tdp-1(bk3052)</i>	



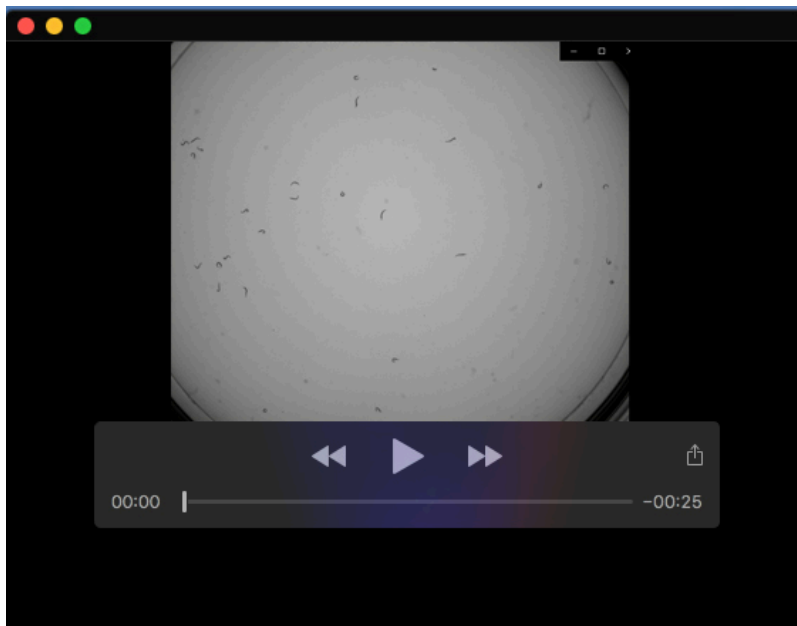
Movie 1. Non-Tg animals have normal swimming in liquid.



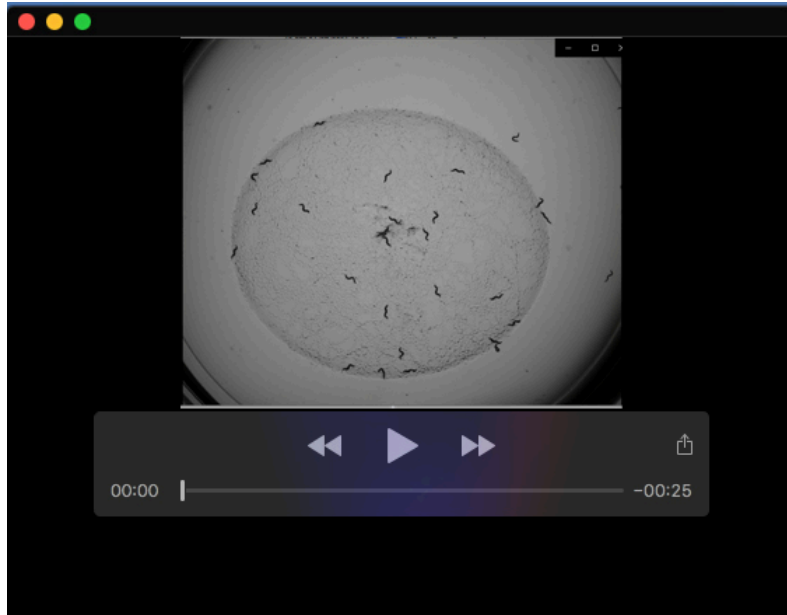
Movie 2. TDP Tg-low animals have decreased rates of swimming in liquid.



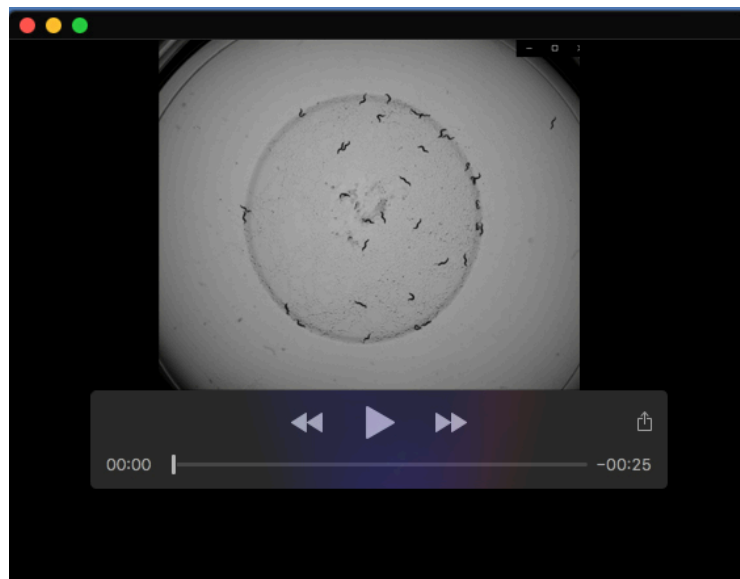
Movie 3. tau Tg animals have significantly impaired swimming in liquid.



Movie 4. tau+TDP Tg-low animals are unable to swim in liquid.



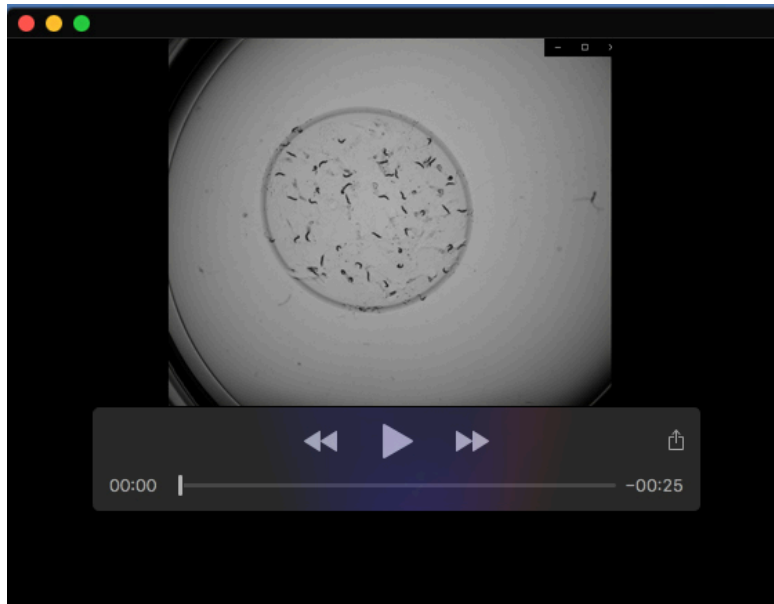
Movie 5. Non-Tg animals have normal motility on a solid surface.



Movie 6. TDP Tg-low animals have slower motility on a solid surface.



Movie 7. tau Tg animals have impaired motility on a solid surface.



Movie 8. tau+TDP Tg-low animals have significantly impaired motility on a solid surface.