

**Perineuronal net deglycosylation associates with tauopathy-induced gliosis and  
neurodegeneration**

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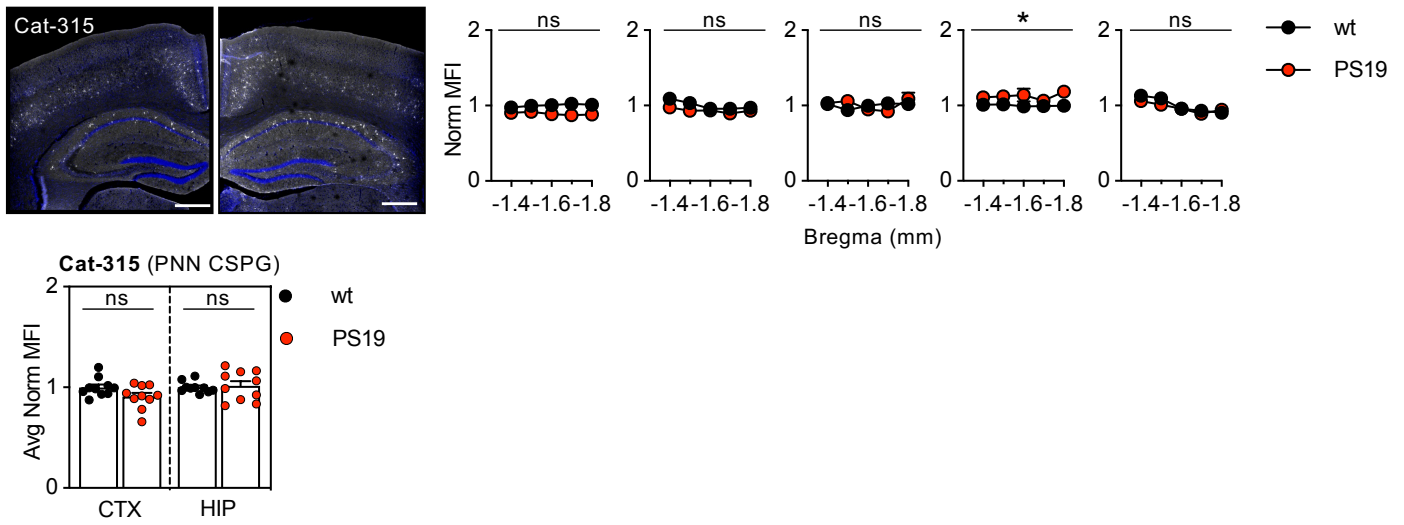
**Supplemental Table 6.** Whole Hippocampal %CS Isomers vs Histology in 9m-PS19 mice (Main Figure 4)

**Supplemental Table 7.** Hippocampal TUNEL assay (% area) in 9m-PS19 mice (Main Figure 5)

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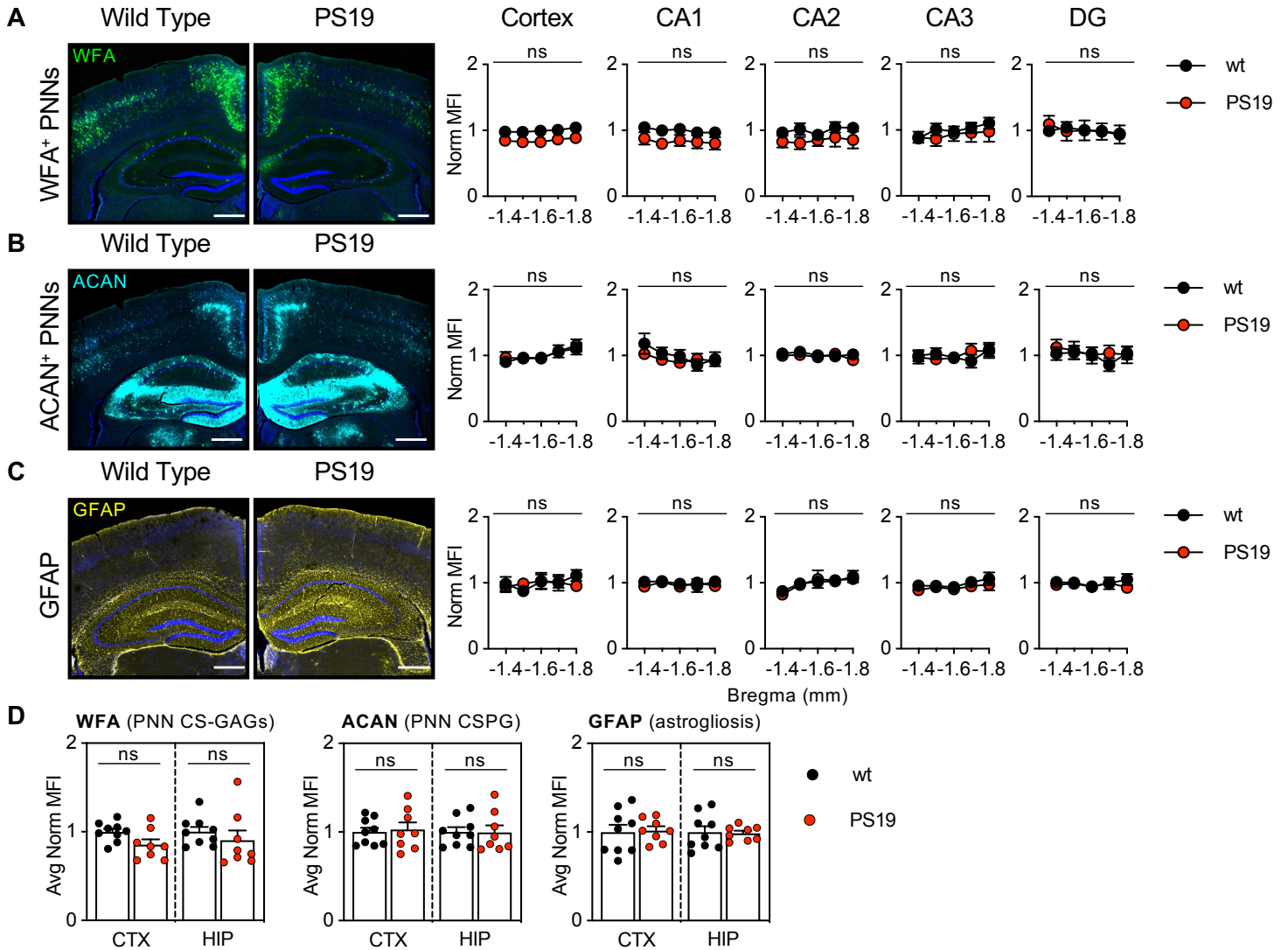
**Supplemental Table 9.** DG TUNEL Assay vs Whole Hippocampal CS Isomers in 9m-PS19 mice (Main Figure 5)

## 9m-PS19 mice



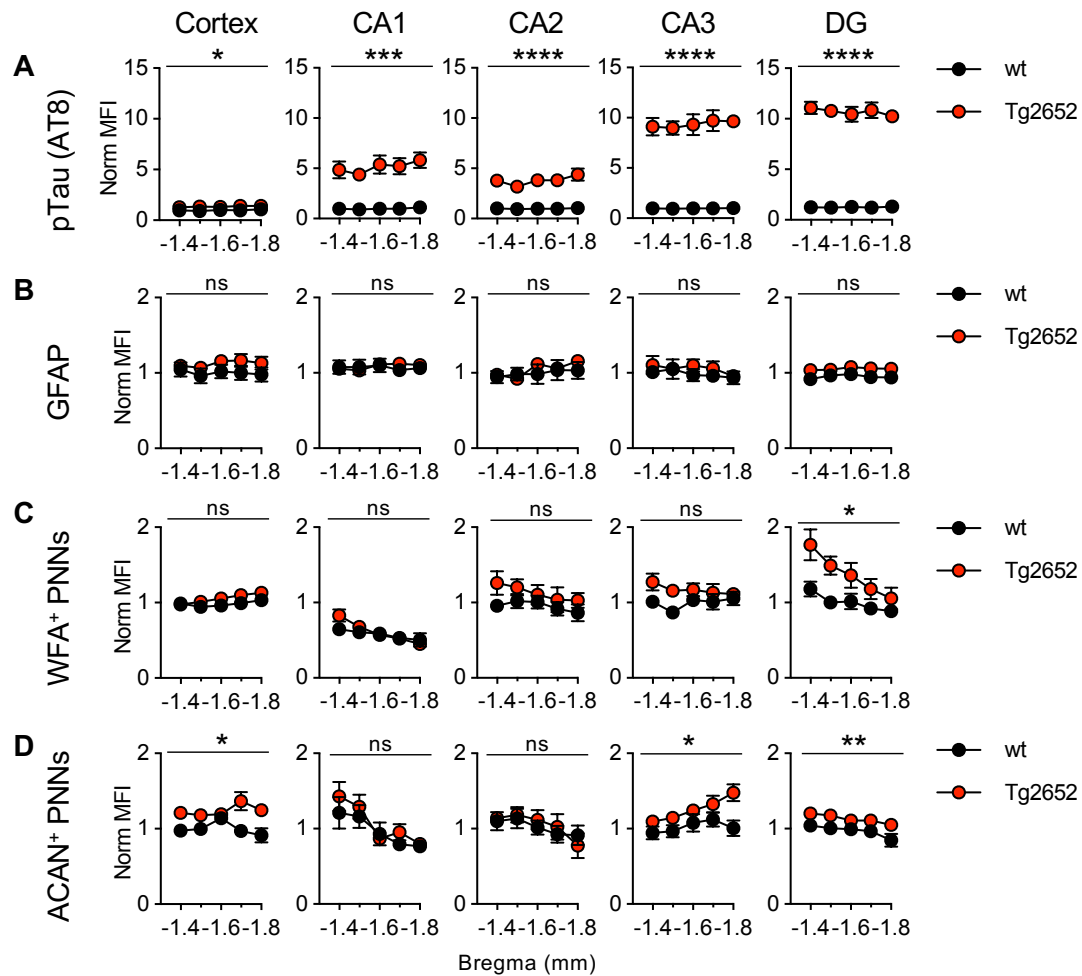
**Supplemental Figure 1. 9m-PS19 mice exhibit no change in aggrecan cleavage products (Main Figure 1 continued).** 5-region stereology analysis (Bregma -1.4 to -1.8 mm) of 9-month-old male and female PS19 mice show no changes in Cat-315 (ACAN cleavage, PNN CSPG) compared to age-matched, wt controls. Scale bar: 0.5 mm, representative images from male mice, dapi included in all images. Statistics reported in **Supplemental Table 1**.

### 3m-PS19



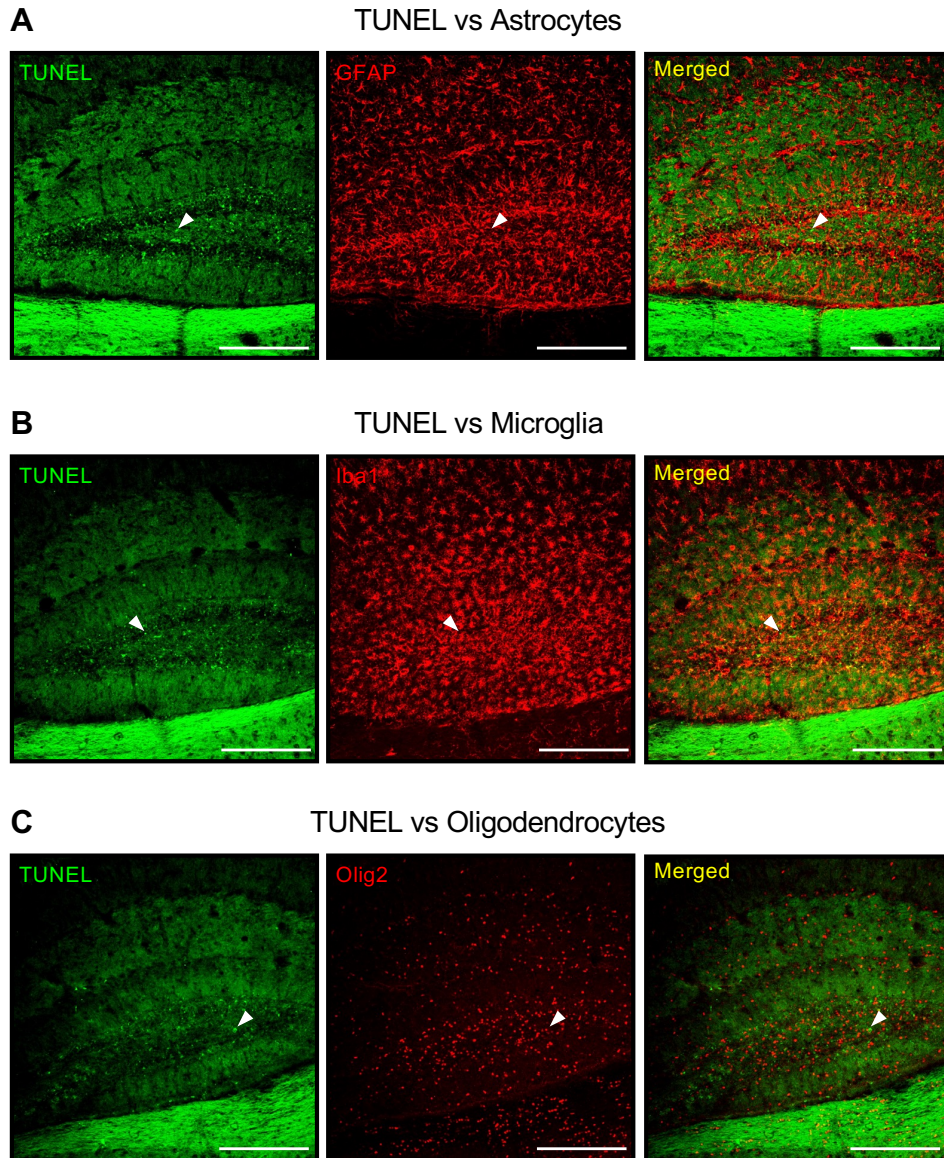
**Supplemental Figure 2. 3m-PS19 mice exhibit stable PNNs in the absence of gliosis (Main Figure 2 continued).** 5-region stereology analysis (Bregma -1.4 to -1.8 mm) of 3-month-old PS19 mice show no changes in **A**) WFA (PNN CS-GAGs), **B**) ACAN (PNN CSPG), or **C**) GFAP (astrogliosis) compared to age-matched, wt controls, averaged in **D**). Scale bar: 0.5 mm, representative images from male mice, dapi included in all images. Statistics reported in **Supplemental Table 2**.

### 4m-Tg2652



**Supplemental Figure 3. 4m-Tg2652 mice exhibit stable PNNs (Main Figure 3 continued).** 5-region stereology analysis (Bregma -1.4 to -1.8 mm) of 4-month-old Tg2652 mice exhibit robust accumulation of **A**) pTau (AT8) without **B**) gliosis (GFAP, astrogliosis) or loss of either **C**) WFA (PNN CS-GAGs) or **D**) ACAN (PNN CSPG). Statistics reported in **Supplemental Table 4**.

## 9m-PS19



**Supplemental Figure 4. 9m-PS19 mice exhibit minimal TUNEL colocalization with glia in the dentate gyrus.** TUNNEL staining in 9-month-old PS19 mice showed minimal colocalization with **A)** astrocytes, **B)** microglia, and **C)** oligodendrocytes within the hippocampal dentate gyrus. Scale bar: 0.25 mm, representative images from male mice, dapi not included.

Supplemental Table 1: Histological Changes in 9m-PS19 (Main Figure 1)							
2-way ANOVA / Mixed-effects p-value F (DFn, DFd)	AT8 (pTau)	GFAP (astrogliosis)	WFA (PNN CS-GAGs)	ACAN (PNN CSPG)	Cat-315 (PNN CSPG)	T-test p-value (t, df) <b>Normality?</b> Yes/No (wt, PS19)	Iba1 (microgliosis)
<b>Cortex</b>	<b>&lt;0.0001*</b> F (1, 18) = 26.0	<b>0.005*</b> F (1, 18) = 10.1	0.21 F (1, 18) = 1.7	0.72 F (1, 18) = 0.1	0.06 F (1, 18) = 3.9	<b>Cortex</b>	0.13 (n/a) No (<0.1, <0.1)
<b>CA1</b>	<b>&lt;0.0001*</b> F (1, 18) = 105.6	<b>0.005*</b> F (1, 18) = 10.4	<b>&lt;0.0001*</b> F (1, 18) = 156.7	0.08 F (1, 18) = 3.4	0.17 F (1, 18) = 2.1	<b>CA1</b>	<b>0.0002*</b> (n/a) No (<0.1, 0.6)
<b>CA2</b>	<b>&lt;0.0001*</b> F (1, 18) = 179.8	<b>0.0002*</b> F (1, 18) = 20.8	<b>&lt;0.0001*</b> F (1, 18) = 51.9	0.54 F (1, 18) = 0.4	0.92 F (1, 18) = < 0.1	<b>CA2</b>	<b>&lt;0.0001*</b> (5.3, 18) Yes (0.6, 0.7)
<b>CA3</b>	<b>&lt;0.0001*</b> F (1, 18) = 140.3	<b>&lt;0.0001*</b> F (1, 18) = 33.3	<b>&lt;0.0001*</b> F (1, 18) = 80.1	0.99 F (1, 18) = < 0.1	<b>&lt;0.05*</b> F (1, 18) = 4.6	<b>CA3</b>	<b>&lt;0.0001*</b> (6.5, 18) Yes (0.1, 0.7)
<b>DG</b>	<b>&lt;0.0001*</b> F (1, 18) = 91.5	<b>&lt;0.0001*</b> F (1, 18) = 26.6	<b>&lt;0.0001*</b> F (1, 18) = 26.5	0.47 F (1, 18) = 0.5	0.67 F (1, 18) = 0.2	<b>DG</b>	<b>&lt;0.0001*</b> (n/a) No (<0.1, 0.7)
<b>Average t-tests</b>							
<b>Cortex Avg</b> (t, df) <b>Normality?</b> (wt, PS19)	<b>&lt;0.0001*</b> (5.1, 18) Yes (1.0, 0.3)	<b>0.005*</b> (3.2, 18) Yes (0.2, 0.4)	0.17 (n/a) No (<0.1, 0.2)	0.67 (0.4, 18) Yes (0.1, 0.3)	0.07 (2.0, 18) Yes (0.3, 0.3)	<b>Cortex Avg</b> (t, df) <b>Normality?</b> (wt, PS19)	0.13 (n/a) No (<0.1, <0.1)
<b>Hippocampus Avg</b> (t, df) <b>Normality?</b> (wt, PS19)	<b>&lt;0.0001*</b> (11.9, 18) Yes (0.7, 0.8)	<b>0.0001*</b> (4.9, 18) Yes (0.6, 1.0)	<b>&lt;0.0001*</b> (7.3, 18) Yes (0.8, 0.9)	0.74 (n/a) No (<0.1, 0.2)	0.75 (0.3, 18) Yes (0.1, 0.4)	<b>Hippo Avg</b> (t, df) <b>Normality?</b> (wt, PS19)	<b>&lt;0.0001*</b> (n/a) No (<0.1, 0.4)
<p><b>Statistics for 9m-PS19 mice:</b> n=10 wild type (5M/5F) and n=10 PS19 (5M/5F), 2-way ANOVA or mixed effects, matched regions for AT8, GFAP, WFA, ACAN, and Cat-315 stereology (p-value and F (DFn, DFd) shown). Averaged comparisons were performed on the averaged values for AT8, GFAP, WFA, ACAN, Cat-315 (Bregma -1.4 to -1.8 mm) and Iba1 (-1.6 and -1.7 mm) (p-values, t value (t), and degrees of freedom (df) shown). 2-way ANOVA and mixed effects data were not assessed for normality, t-test data were assessed for normality using Shapiro-Wilk test (outcome and p-values shown); normal (Gaussian) distributed data were analyzed using parametric t-test (two-tailed) and data that did not show normality were analyzed using non-parametric Mann Whitney test (two-tailed).</p>							

**Supplemental Table 2: Histological Changes in 3m-PS19 (Supplemental Figure 2)**

<b>2-way ANOVA / Mixed-effects p-value F (DFn, DFd)</b>	<b>WFA (PNN CS-GAGs)</b>	<b>ACAN (PNN CSPG)</b>	<b>GFAP (astrogliosis)</b>
<b>Cortex</b>	0.05 F (1, 15) = 4.5	0.81 F (1, 15) = <0.1	0.96 F (1, 15) = <0.1
<b>CA1</b>	0.09 F (1, 15) = 3.3	0.60 F (1, 15) = 0.3	0.78 F (1, 15) = 0.1
<b>CA2</b>	0.24 F (1, 15) = 1.5	0.60 F (1, 15) = 0.3	0.81 F (1, 15) = 0.1
<b>CA3</b>	0.60 F (1, 15) = 0.3	0.97 F (1, 15) = <0.1	0.52 F (1, 15) = 0.4
<b>DG</b>	0.97 F (1, 15) = <0.1	0.71 F (1, 15) = 0.1	0.80 F (1, 15) = 1.1
<b>Average t-tests</b>			
<b>Cortex Avg (t, df) Normality? (wt, PS19)</b>	0.05 (2.1, 15) Yes (1.0, 0.3)	0.76 (0.3, 15) Yes (0.2, 0.7)	0.87 (0.2, 15) Yes (0.4, 0.6)
<b>Hippocampus Avg (t, df) Normality? (wt, PS19)</b>	0.14 (n/a) No (0.3, <0.1)	0.97 (<0.1, 15) Yes (0.3, 0.1)	0.85 (0.2, 15) Yes (0.3, 0.6)

**Statistics for 3m-PS19 mice:** n=9 wild type (6M/3F) and n=8 PS19 (3M/5F) age-matched mice, 2-way anova or mixed effects, matched regions for WFA, ACAN, and GFAP stereology (p-value and F (DFn, DFd) shown). Averaged comparisons were performed on the averaged values for WFA, ACAN, GFAP (Bregma -1.4 to -1.8 mm) (p-value, t value (t), and degrees of freedom (df) shown). 2-way ANOVA and mixed effects data were not assessed for normality, t-test data were assessed for normality using Shapiro-Wilk test (outcome and p-values shown); normal (Gaussian) distributed data were analyzed using parametric t-test (two-tailed) and data that did not show normality were analyzed using non-parametric Mann Whitney test (two-tailed).



**Supplemental Table 3: Histological Changes in 6m-PS19 (Main Figure 2)**

<b>2-way ANOVA / Mixed-effects</b> p-value F (DFn, DFd)	<b>AT8</b> (pTau)	<b>GFAP</b> (astrogliosis)	<b>WFA</b> (PNN CS-GAGs)	<b>ACAN</b> (PNN CSPG)	<b>T-test</b> p-value (t, df) <b>Normality?</b> Yes/No (wt, PS19)	<b>Iba1</b> (microgliosis)
<b>Cortex</b>	0.10 F (1,16) = 3.0	0.74 F (1, 16) = 0.1	0.05 F (1, 16) = 4.6	0.24 F (1, 16) = 1.5	<b>Cortex</b>	0.76 (0.3, 15) Yes (0.1, 0.2)
<b>CA1</b>	0.39 F (1,16) = 0.8	0.71 F (1, 16) = 0.1	0.21 F (1, 16) = 1.7	0.18 F (1, 16) = 1.9	<b>CA1</b>	0.96 (<0.1, 16) Yes (0.8, 0.1)
<b>CA2</b>	0.63 F (1,16) = 0.2	0.80 F (1, 16) = 0.1	0.13 F (1, 16) = 2.5	0.24 F (1, 16) = 1.5	<b>CA2</b>	0.70 (0.4, 16) Yes (0.1, 0.1)
<b>CA3</b>	<b>0.003*</b> F (1,16) = 12.0	0.57 F (1, 16) = 0.3	0.09 F (1, 16) = 3.3	0.05 F (1, 16) = 4.3	<b>CA3</b>	0.94 (0.1, 16) Yes (0.3, 0.3)
<b>DG</b>	0.10 F (1,16) = 3.0	0.42 F (1, 16) = 0.7	0.08 F (1, 16) = 3.6	0.12 F (1, 16) = 2.7	<b>DG</b>	0.47 (0.7, 16) Yes (0.5, 0.2)
<b>Average t-tests</b>						
<b>Cortex Avg</b> p-value (t, df) <b>Normality?</b> Yes/No (wt, PS19)	0.10 (1.7, 16) Yes, (0.3, 0.5)	0.74 (0.3, 16) Yes, (0.5, 0.2)	0.05 (2.1, 16) Yes, (1.0, 0.3)	0.24 (1.2, 16) Yes, (0.8, 0.2)	<b>Cortex Avg</b> p-value (t, df) <b>Normality?</b> Yes/No (wt, PS19)	0.76 (0.3, 15) Yes, (0.1, 0.2)
<b>Hippocampus Avg</b> p-value (t, df) <b>Normality?</b> Yes/No (wt, PS19)	0.19 (1.4, 16) Yes, (0.8, 0.6)	0.72 (0.4, 16) Yes, (0.7, 0.1)	<b>0.04*</b> (n/a) No, (0.5, <0.1)	0.05 (n/a) No, (0.3, <0.1)	<b>Hippocampus Avg</b> p-value (t, df) <b>Normality?</b> Yes/No (wt, PS19)	0.77 (0.3, 16) Yes, (0.2, 0.1)

**Statistics for 6m-PS19 mice:** aged-matched n=8 wild type (4M/4F) and n=10 PS19 (5M/5F), 2-way anova or mixed effects, matched regions for WFA, ACAN, GFAP, and AT8 stereology analyses (p-value and F (DFn, DFd) shown). Iba1 # in cortex were assessed for all 4M/4F WT but only 5M/4F PS19 due to cortex region missing from brain tissue slices of one of the female PS19 mice. Averaged comparisons were performed on the averaged values for WFA, ACAN, GFAP, AT8 (Bregma -1.4 to -1.8 mm) and Iba1 (-1.6 and -1.7 mm) (p-value, t value (t), and degrees of freedom (df) shown). 2-way ANOVA and mixed effects data were not assessed for normality, t-test data were assessed for normality using Shapiro-Wilk test (outcome and p-values shown); normal (Gaussian) distributed data were analyzed using parametric t-test (two-tailed) and data that did not show normality were analyzed using non-parametric Mann Whitney test (two-tailed).

<b>Supplemental Table 4: Histological Changes in 4m-Tg2652 (Main Figure 3)</b>				
<b>2-way ANOVA / Mixed-effects p-value F (DFn, DFd)</b>	<b>AT8 (pTau)</b>	<b>GFAP (astrogliosis)</b>	<b>WFA (PNN CS- GAGs)</b>	<b>ACAN (PNN CSPG)</b>
<b>Cortex</b>	<b>0.01*</b> F (1, 12) = 8.9	0.25 F (1, 13) = 1.4	0.20 F (1, 13) = 1.8	<b>0.01*</b> F (1, 13) = 8.8
<b>CA1</b>	<b>0.0002*</b> F (1, 12) = 29.6	0.84 F (1, 13) = < 0.1	0.63 F (1, 13) = 0.2	0.48 F (1, 13) = 0.5
<b>CA2</b>	<b>&lt;0.0001*</b> F (1, 12) = 34.2	0.65 F (1, 13) = 0.2	0.18 F (1, 13) = 2.1	0.73 F (1, 13) = 0.1
<b>CA3</b>	<b>&lt;0.0001*</b> F (1, 12) = 112.1	0.52 F (1, 13) = 0.4	0.07 F (1, 13) = 4.0	<b>0.01*</b> F (1, 13) = 8.6
<b>DG</b>	<b>&lt;0.0001*</b> F (1, 12) = 257.4	0.13 F (1, 13) = 2.6	<b>0.03*</b> F (1, 13) = 5.9	<b>0.003*</b> F (1, 13) = 13.6
<b>Average t-tests</b>				
<b>Cortex Avg</b> p-value (t, df) <b>Normality?</b> Yes/No (wt, Tg2652)	<b>0.0006*</b> (n/a) No, (0.2, <0.1)	0.26 (1.2, 13) Yes (0.7, 0.6)	0.19 (1.4, 13) Yes (0.9, 0.9)	<b>0.01*</b> (n/a) No (0.1, <0.1)
<b>Hippocampus Avg</b> p-value (t, df) <b>Normality?</b> Yes/No (wt, Tg2652)	<b>&lt;0.0001*</b> (10.2, 12) Yes (0.2, 0.1)	0.50 (0.7, 13) Yes (0.1, 0.2)	<b>0.04*</b> (2.3, 13) Yes (0.6, 0.6)	<b>&lt;0.05*</b> (2.2, 13) Yes (0.1, 0.8)
<b>Statistics for 4m-Tg2652 cohort:</b> n=8 wild type (4M/4F) and n=7 Tg2652 (3M/4F) age-matched mice, 2-way anova or mixed effects, matched regions AT8, GFAP, WFA, ACAN stereology (p-value and F (DFn, DFd) shown). AT8 was assessed for all 3M/4F Tg2652 but only 3M/4F WT due to technical error during the staining process for one of the male wt mice. Averaged comparisons were performed on the averaged values (Bregma -1.4 to -1.8 mm) (p-value, t value (t), and degrees of freedom (df) shown). 2-way ANOVA and mixed effects data were not assessed for normality, t-test data were assessed for normality using Shapiro-Wilk test (outcome and p-values shown); normal (Gaussian) distributed data were analyzed using parametric t-test (two-tailed) and data that did not show normality were analyzed using non-parametric Mann Whitney test (two-tailed).				

**Supplemental Table 5: Whole Hippocampal %CS Isomers (Main Figure 4)**

	<b>Wild Type</b> Mean ± SEM	<b>Tauopathy model</b> Mean ± SEM	<b>p-value</b> (t, df)	<b>Normality?</b> Yes/No (wt, pTau)
<b>T-tests</b>				
	<b>9m-PS19 mice</b>			
<b>0S-CS</b>	5.4 ± 0.1	5.3 ± 0.2	0.67 (0.4, 17)	Yes (0.6, 0.1)
<b>4S-CS</b>	88.9 ± 0.2	89.1 ± 0.2	0.54 (0.6, 17)	Yes (0.5, 0.2)
<b>6S-CS</b>	3.6 ± 0.1*	3.4 ± 0.1*	<b>0.02*</b> (2.6, 17)	Yes (0.1, 0.2)
<b>2S6S-CS</b>	1.0 ± <0.1*	1.1 ± <0.1*	<b>0.02*</b> (2.6, 17)	Yes (0.6, 0.5)
<b>4S6S-CS</b>	1.0 ± <0.1	1.0 ± <0.1	0.34 (1.0, 17)	Yes (0.8, 0.1)
<b>Avg #S per CS isomer</b>	0.97 ± <0.01	0.97 ± <0.01	0.19 (1.4, 17)	Yes (0.6, 0.1)
<b>T-tests</b>				
	<b>6m-PS19 mice</b>			
<b>0S-CS</b>	5.4 ± 0.2	5.0 ± 0.2	0.23 (1.2, 16)	Yes (0.1, 0.4)
<b>4S-CS</b>	85.0 ± 0.3	85.6 ± 0.4	0.27 (1.1, 16)	Yes (0.5, 0.7)
<b>6S-CS</b>	7.0 ± 0.1	6.7 ± 0.2	0.26 (1.2, 16)	Yes (0.4, 0.5)
<b>2S6S-CS</b>	2.2 ± 0.1	2.2 ± 0.1	0.84 (0.2, 16)	Yes (0.5, 0.6)
<b>4S6S-CS</b>	0.5 ± <0.1	0.5 ± <0.1	0.98 (<0.1, 16)	Yes (0.8, 0.7)
<b>Avg #S per CS isomer</b>	0.97 ± <0.01	0.98 ± <0.01	0.36 (n/a)	No (<0.1, 0.5)
<b>T-tests</b>				
	<b>4m-Tg2652 mice</b>			
<b>0S-CS</b>	9.6 ± 0.2	10.0 ± 0.1	0.10 (1.8, 13)	Yes (0.9, 0.7)
<b>4S-CS</b>	78.9 ± 0.3	78.6 ± 0.2	0.53 (0.6, 13)	Yes (0.5, 0.8)
<b>6S-CS</b>	9.1 ± 0.1	9.0 ± 0.1	0.53 (0.6, 13)	Yes (0.8, 0.5)
<b>2S6S-CS</b>	2.0 ± 0.1	2.0 ± 0.1	0.81 (0.2, 13)	Yes (0.2, 0.2)
<b>4S6S-CS</b>	0.4 ± <0.1	0.4 ± <0.1	0.26 (1.2, 13)	Yes (0.7, 0.9)
<b>Avg #S per CS isomer</b>	0.93 ± <0.01	0.92 ± <0.01	0.07 (2.0, 13)	Yes (0.7, 0.5)

**Statistics:** 9m-PS19 mice cohort included n=10 wild type (5M/5F) and n=10 PS19 (5M/5F) age-matched mice, 6m-PS19 mouse cohort included n=8 wild type (4M/4F) and n=10 PS19 (5M/5F) age-matched mice, 4m-Tg2652 mouse cohort included n=8 wild type (4M/4F) and n=7 Tg2652 (3M/4F) age-matched mice used in the histology analyses. Only 9 wild type mice were not included in the 9m-PS19 CS-GAG analysis because a female wt sample was contaminated during processing. Averaged comparisons were performed between wild type and tauopathy mouse model (p-values, t value (t), and degrees of freedom (df) shown). T-test data were assessed for normality using Shapiro-Wilk test (outcome and p-values shown); normal (Gaussian) distributed data were analyzed using parametric t-test (two-tailed) and data that did not show normality were analyzed using non-parametric Mann Whitney test (two-tailed).

**Supplemental Table 6: Whole Hippocampal %CS Isomers vs Histology in 9m-PS19 mice (Main Figure 4)**

	<b>WFA</b> (PNN CS-GAGs)	<b>ACAN</b> (PNN CSPG)	<b>Cat-315</b> (PNN CSPG)	<b>AT8</b> (pTau)	<b>GFAP</b> (astrogliosis)	<b>Iba1</b> (microgliosis)
<b>0S-CS</b>	R <sup>2</sup> =0.01, p=0.67	R <sup>2</sup> =0.16, p=0.09	R <sup>2</sup> =0.02, p=0.61	R <sup>2</sup> =0.05, p=0.37	R <sup>2</sup> =0.12, p=0.14	R <sup>2</sup> <0.01, p=0.82
<b>4S-CS</b>	R <sup>2</sup> =0.01, p=0.70	R <sup>2</sup> =0.19, p=0.06	R <sup>2</sup> <0.01, p=0.74	R <sup>2</sup> =0.06, p=0.32	R <sup>2</sup> =0.11, p=0.16	R <sup>2</sup> =0.01, p=0.65
<b>6S-CS</b>	<b>R<sup>2</sup>=0.33, p=0.01*</b>	R <sup>2</sup> <0.01, p=0.98	R <sup>2</sup> <0.01, p=0.89	<b>R<sup>2</sup>=0.31, p=0.01*</b>	<b>R<sup>2</sup>=0.28, p=0.02*</b>	<b>R<sup>2</sup>=0.30, p=0.02*</b>
<b>2S6S-CS</b>	<b>R<sup>2</sup>=0.45, p=0.002*</b>	R <sup>2</sup> <0.01, p=0.86	R <sup>2</sup> =0.11, p=0.18	<b>R<sup>2</sup>=0.32, p=0.01*</b>	<b>R<sup>2</sup>=0.36, p=0.007*</b>	<b>R<sup>2</sup>=0.36, p=0.006*</b>
<b>4S6S-CS</b>	R <sup>2</sup> =0.20, p=0.05	<b>R<sup>2</sup>=0.38, p=0.005*</b>	R <sup>2</sup> =0.03, p=0.50	R <sup>2</sup> =0.05, p=0.37	R <sup>2</sup> =0.02, p=0.52	R <sup>2</sup> =0.03, p=0.47

*Statistics: 9m-PS19 mouse cohort included n=10 wild type (5M/5F) and n=10 PS19 (5M/5F) age-matched mice used in the histology analyses. Only 9 wild type mice were not included in the 9m-PS19 CS-GAG analysis because a female wt sample was contaminated during processing. Linear regression of CS isomers to WFA, ACAN, Cat-315, AT8, and GFAP averaged normalized hippocampal MFI or averaged Iba1 counts per tissue mm<sup>2</sup>. Data used in linear regression analyses were not tested for normality.*

<b>Supplemental Table 7: Hippocampal TUNEL assay (% area) in 9m-PS19 mice (Main Figure 5)</b>				
	<b>Wild Type</b> Mean ± SEM	<b>9m-PS19 mice</b> Mean ± SEM	<b>p-value</b> (t, df)	<b>Normality?</b> Yes/no (wt, PS19)
<b>CA1</b>	1.00 ± 0.13	0.92 ± 0.14	0.53 (n/a)	No (0.5, <0.1)
<b>CA2</b>	1.00 ± 0.19	0.93 ± 0.17	0.79 (0.3, 18)	Yes (0.2, 0.2)
<b>CA3</b>	1.00 ± 0.11	0.86 ± 0.06	0.28 (1.1, 18)	Yes (0.5, 0.8)
<b>DG</b>	<b>1.00 ± 0.11*</b>	<b>1.80 ± 0.30*</b>	<b>0.02*</b> (2.5, 18)	Yes (0.2, 0.2)

**Statistics for 9m-PS19 mice:** aged-matched n=10 WT (5M/5F) and n=10 PS19 (5M/5F); averaged TUNEL % area quantified from the average of 2 dorsal hippocampal sections, t-test between wild type and PS19 mice (p-values, t value (t), and degrees of freedom (df) shown). T-test data were assessed for normality using Shapiro-Wilk test (outcome and p-values shown); normal (Gaussian) distributed data were analyzed using parametric t-test (two-tailed) and data that did not show normality were analyzed using non-parametric Mann Whitney test (two-tailed).

<b>Supplemental Table 8: Hippocampal TUNEL Assay vs Histology in 9m-PS19 mice (Main Figure 5)</b>				
	<b>WFA</b> (PNN CS-GAGs)	<b>AT8</b> (pTau)	<b>GFAP</b> (astrogliosis)	<b>Iba1</b> (microgliosis)
<b>CA1</b>	R <sup>2</sup> =0.01, p=0.66	R <sup>2</sup> =0.02, p=0.58	R <sup>2</sup> =0.07, p=0.27	R <sup>2</sup> =0.09, p=0.15
<b>CA2</b>	R <sup>2</sup> =0.02, p=0.54	R <sup>2</sup> <0.01, p=0.85	R <sup>2</sup> =0.08, p=0.23	R <sup>2</sup> =0.05, p=0.32
<b>CA3</b>	R <sup>2</sup> =0.07, p=0.25	R <sup>2</sup> =0.04, p=0.38	R <sup>2</sup> <0.01, p=0.95	R <sup>2</sup> <0.01, p=0.77
<b>DG</b>	R <sup>2</sup> =0.08, p=0.23	<b>R<sup>2</sup>=0.51, p=0.0004*</b>	<b>R<sup>2</sup>=0.68, p&lt;0.0001*</b>	<b>R<sup>2</sup>=0.62, p&lt;0.0001*</b>

**Statistics for 9m-PS19 mice:** aged-matched n=10 WT (5M/5F) and n=10 PS19 (5M/5F); linear regression against WFA, AT8, and GFAP used averaged stereology MFI histology, and linear regression against Iba1 used averaged Iba1 counts per tissue mm<sup>2</sup>. Data used in linear regression analyses were not tested for normality.

<b>Supplemental Table 9: DG TUNEL Assay vs Whole Hippocampal CS Isomers in 9m-PS19 mice (Main Figure 5)</b>	
<b>CS Isomer</b>	<b>Linear Regression</b>
<b>0S-CS</b>	R <sup>2</sup> =0.15, p=0.11
<b>4S-CS</b>	R <sup>2</sup> =0.16, p=0.09
<b>6S-CS</b>	<b>R<sup>2</sup>=0.26, p=0.03*</b>
<b>2S6S-CS</b>	<b>R<sup>2</sup>=0.33, p=0.01*</b>
<b>4S6S-CS</b>	R <sup>2</sup> =0.05, p=0.38
<b>Avg #S per CS/DS isomer</b>	<b>R<sup>2</sup>=0.22, p=0.04*</b>

**Statistics for 9m-PS19 mice:** aged-matched n=10 wt (5M/5F) and n=10 PS19 (5M/5F) used in the histology analyses. Only 9 wild type mice were not included in the 9m-PS19 CS-GAG analysis because a female wt sample was contaminated during processing. Linear regression of whole hippocampal %CS isomer to the averaged dentate gyrus TUNEL % area. Data used in linear regression analyses were not tested for normality.