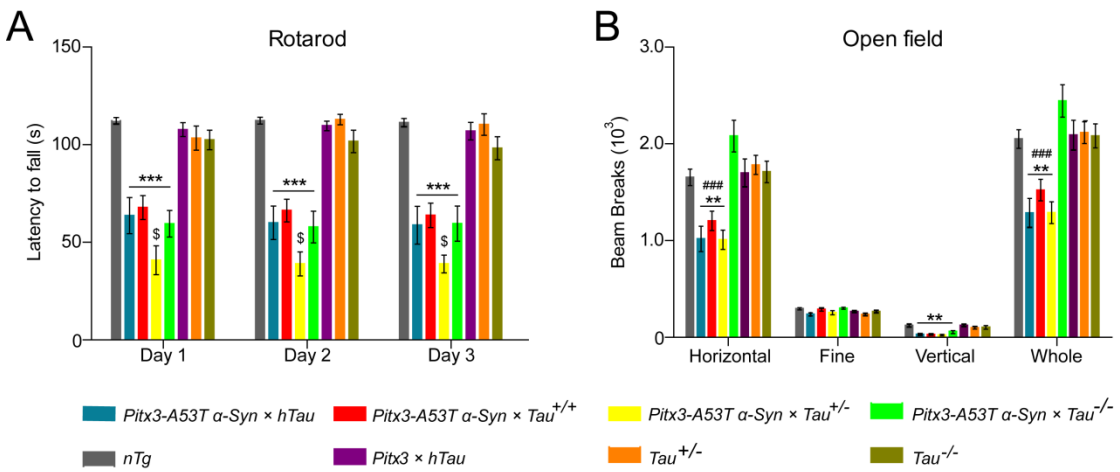

Figure. S1 Tau deficiency exacerbates the movement impairments in the α-syn *A53T* conditional transgenic mice. (A) The latency to fall was quantified by the rotarod test for 6-month-old mice. (B) The horizontal movement, fine movement, vertical movement and whole movement of all the mice were measured using the open-field test at 12-month-old. n ≥ 10 male mice per genotype per time point. Values are mean ± SEM. $^{**}P < 0.01$, $^{***}P < 0.001$ (versus age-matched *nTg*, *Pitx3* × *hTau*, *Tau*$^{+/-}$, *Tau*$^{-/-}$); $^{\$}P < 0.05$ (versus age-matched *Pitx3-A53T α-Syn* × *hTau*, *Pitx3-A53T α-Syn* × *Tau*$^{+/+}$ and *Pitx3-A53T α-Syn* × *Tau*$^{-/-}$); $^{\#\#\#}P < 0.001$ (versus age-matched *Pitx3-A53T α-Syn* × *Tau*$^{-/-}$).

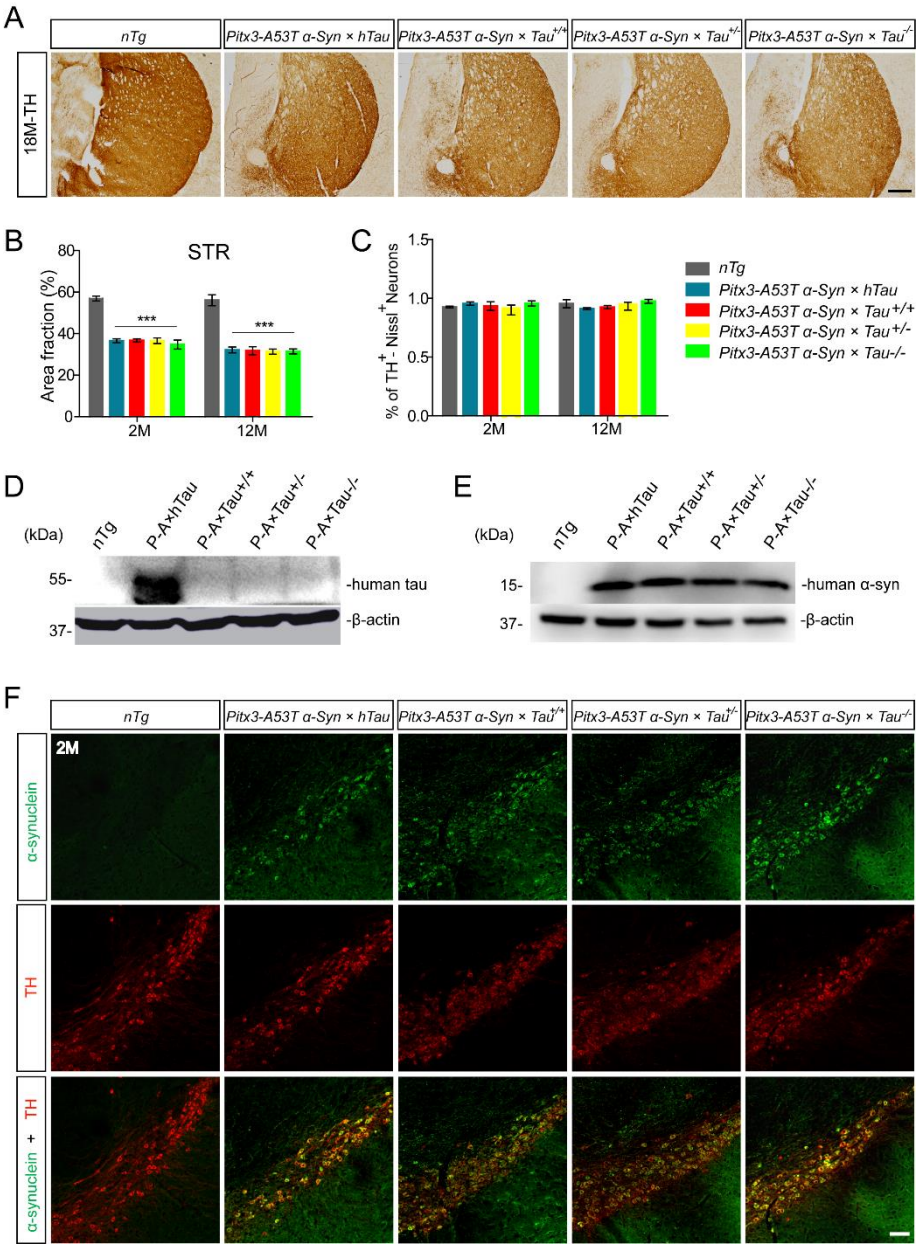

Figure. S2 The effects of tau on A53T α-syn-mediated mDANs degeneration and α-syn aggregation. (A) TH immunohistochemistry staining of the striatum coronal sections of mice. Scale bar: 100 μm. (B) The bar graph showed the areas of striatum in 2- and 12-month-old mice occupied by TH^+ fiber staining. (C) Percentage of TH and Nissl double-positive neurons to the total number of TH^+ cells in the SNC of the triple transgenic mice at 12- and 12-month-old. (D) Western blot showed the expression levels of human tau in midbrains of 2-month-old mice. (E) Western blot showed the expression levels of human α-syn in midbrains of 2-month-old mice. (F) Immunofluorescent images showed α-syn staining (green) in the mDANs (red) at SNC regions of 2-month-old mice. Scale bar: 100 μm. n = 5 per genotype per time

point. Values are mean ± SEM. $^{***}P < 0.001$ (Triple transgenic versus age-matched *nTg*).

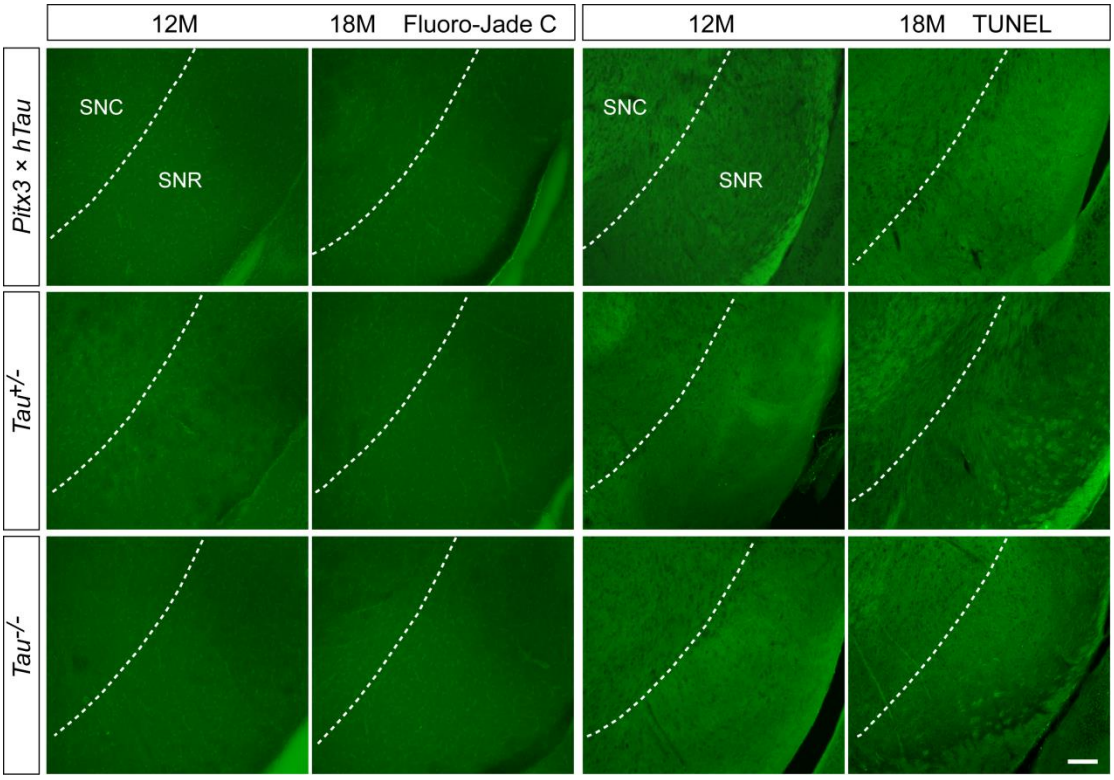

Figure. S3 No obvious Fluoro-Jade C^{+} and TUNEL^{+} cells were found in the SNR of *Pitx3* × *hTau*, *Tau*$^{+/-}$ and *Tau*$^{-/-}$ mice at 12- and 18-month-old. Representative coronal sections of midbrain had been shown with white dotted lines demarcating the boundary between SNC and SNR. The ventrolateral area was considered as SNR. Scale bar: 100 μm.

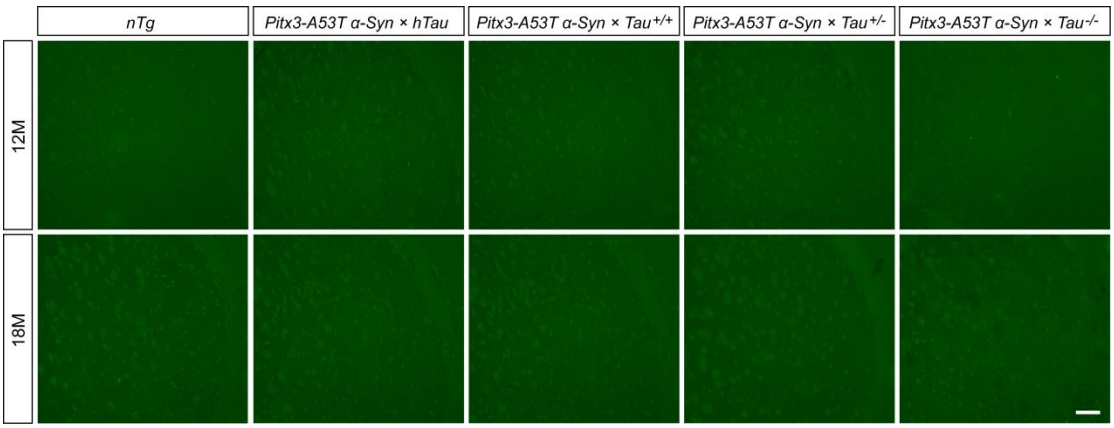

Figure. S4 No obvious Fluoro-Jade C^{+} cells were found in the striatum of triple transgenic mice. Scale bar: 100 μm.

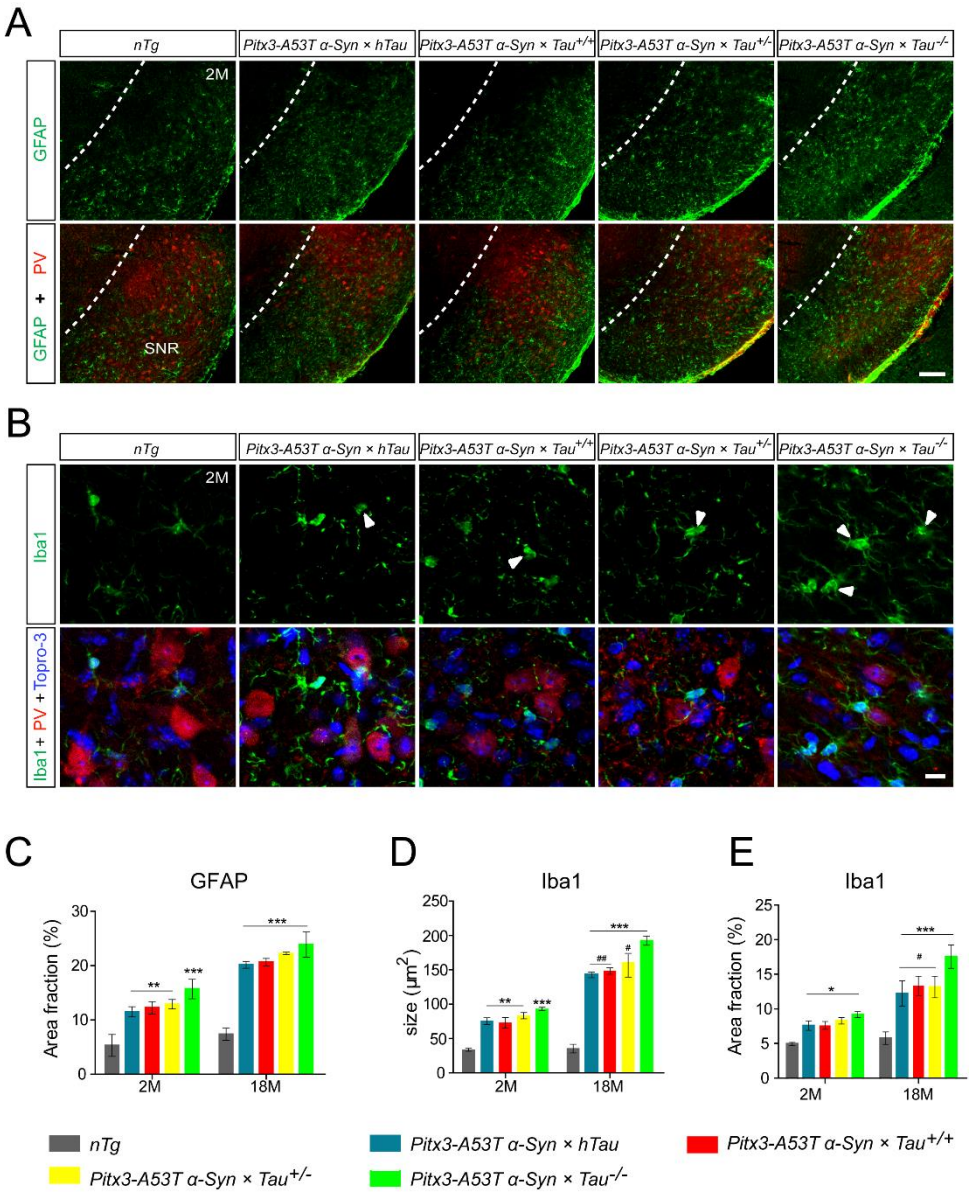

Figure. S5 Significant increases in astrocytosis and microgliosis were observed in the SNR of triple transgenic mice. (A) GFAP (green) and PV (red) costaining in the SNR of 2-month-old mice. Scale bar: 100 μm. (B) Iba1 (green), PV (red) and Topro-3 (blue) costaining in the SNR of 2-month-old mice. The arrowheads pointed to the activated microglia. Scale bar: 10 μm. (C) The bar graph showed the areas of SNR in 2- and 18-month-old mice occupied by GFAP staining. (D) The bar graph showed the sizes of Iba1-positive cells in the SNR. (E) The bar graph showed the area fraction of Iba1-positive cells in the SNR. n = 5 per genotype per time point. Values are mean ± SEM. $^{**}P < 0.01$, $^{***}P < 0.001$ (versus age-matched *nTg*); $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ (versus

age-matched *Pitx3-A53T α-Syn* × *Tau*$^{-/-}$).

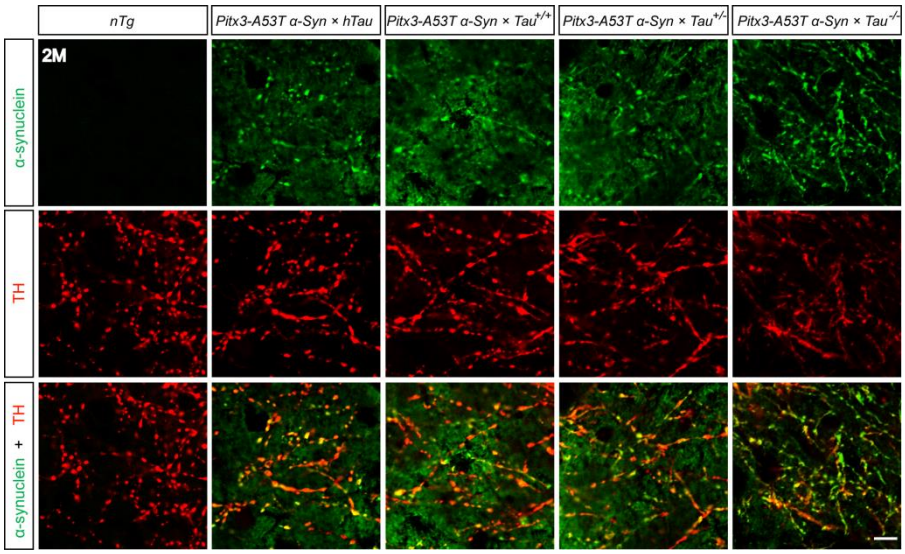

Figure. S6 α-syn was expressed in the TH^{+} axon terminals in SNR of triple transgenic mice at 2-month-old.

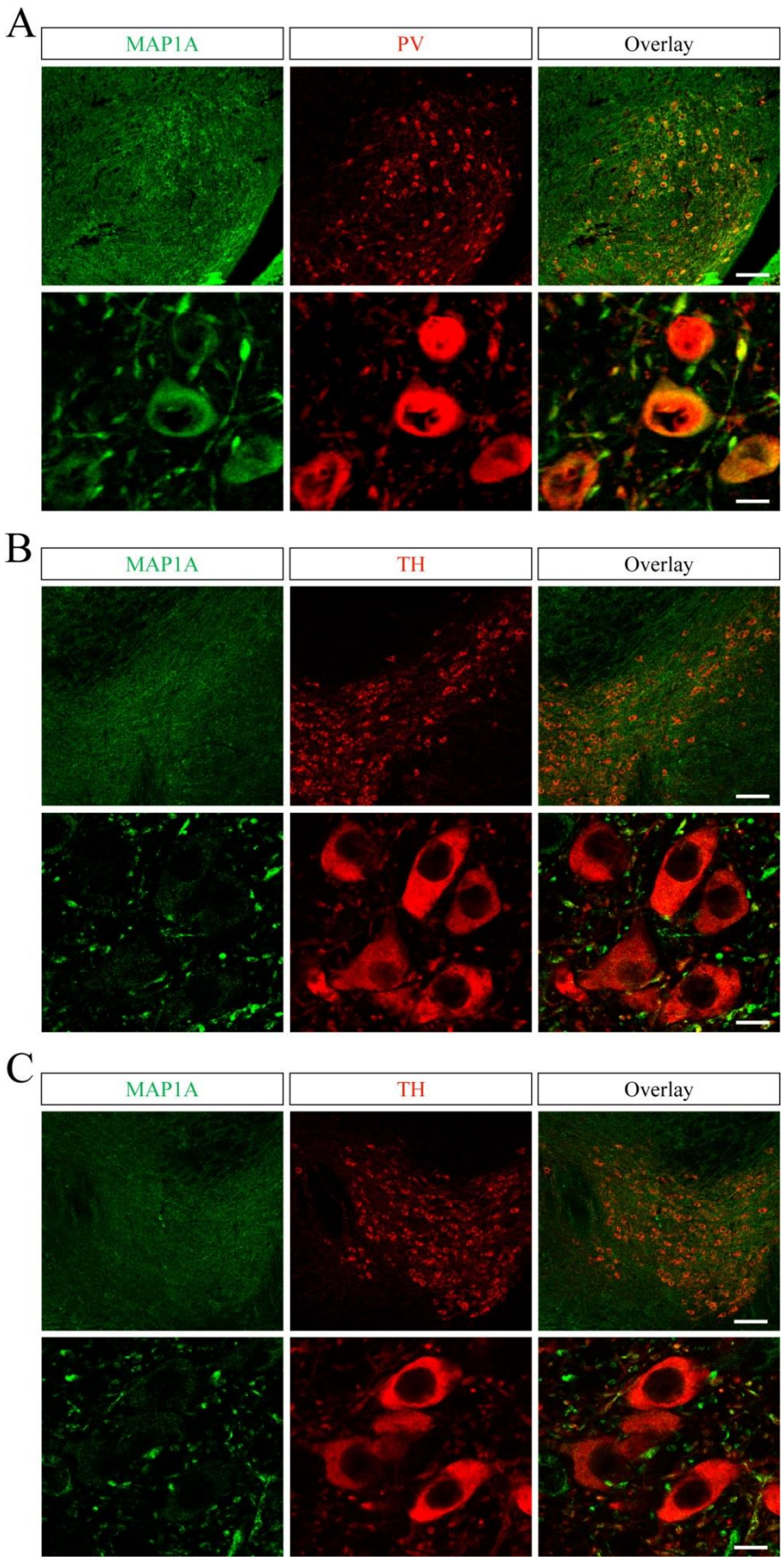

Figure. S7 MAP1A was prominently expressed in the PV^{+} neurons of the SNR, while

the TH^+ neurons in the SNC and VTA expressed MAP1A at a low level. (A) MAP1A (green) and PV (red) costaining in the SNR of 2-month-old *nTg* mice. (B) Expression of MAP1A (green) and TH (red) in the SNC of 2-month-old *nTg* mice. (C) Expression of MAP1A (green) and TH (red) in the VTA of 2-month-old *nTg* mice. n = 5 per genotype per time point. Scale bars: low-magnification images, 100 μm; high-magnification images, 10 μm.

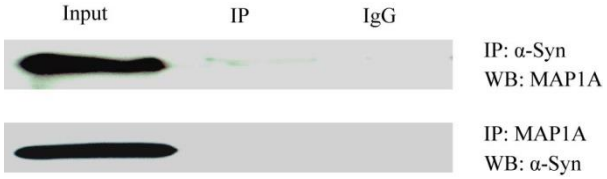

Figure. S8 There was no direct interaction between α-syn and MAP1A. Representative immunoblotting showed the absence of α-syn or MAP1A positive bands in MAP1A- or α-syn-immunoprecipitated protein fractions from the midbrain homogenates of 2-month-old *Pitx3-A53T α-Syn* × $Tau^{+/+}$ mice, respectively. Mouse or rabbit IgG were used as negative controls (n= 3 per genotype per time point).

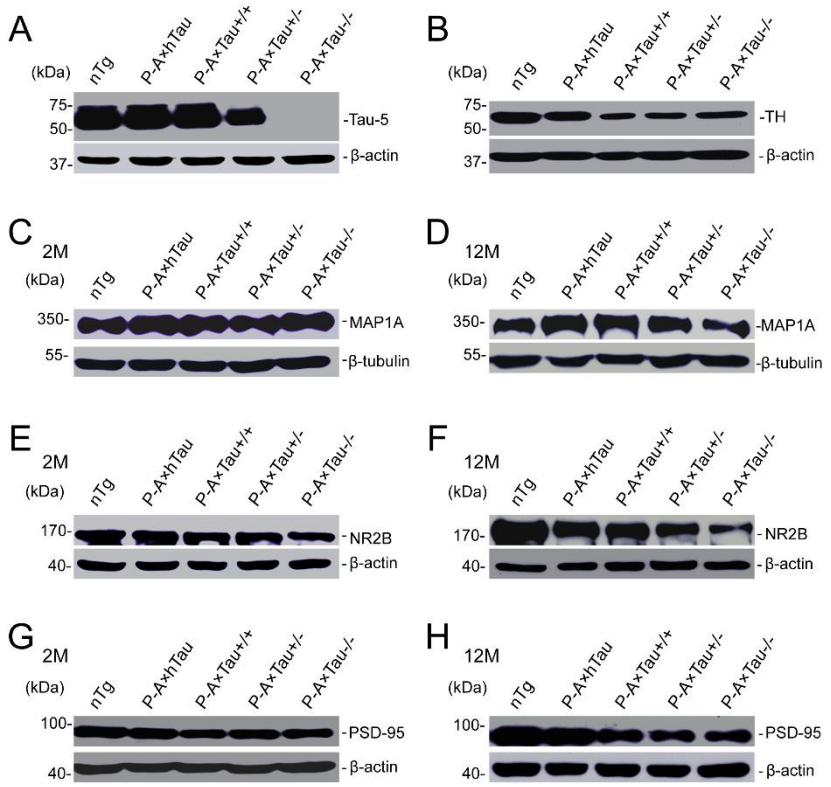

Figure. S9 The supplemental samples of western blotting. (A) and (B) Supplemental samples of Fig.2 E. (C) Supplemental sample of Fig.5 A. (D) Supplemental sample of Fig.5 B. (E) Supplemental sample of Fig.6 E. (F) Supplemental sample of Fig.6 F. (G) Supplemental sample of Fig.6 H. (H) Supplemental sample of Fig.6 I.