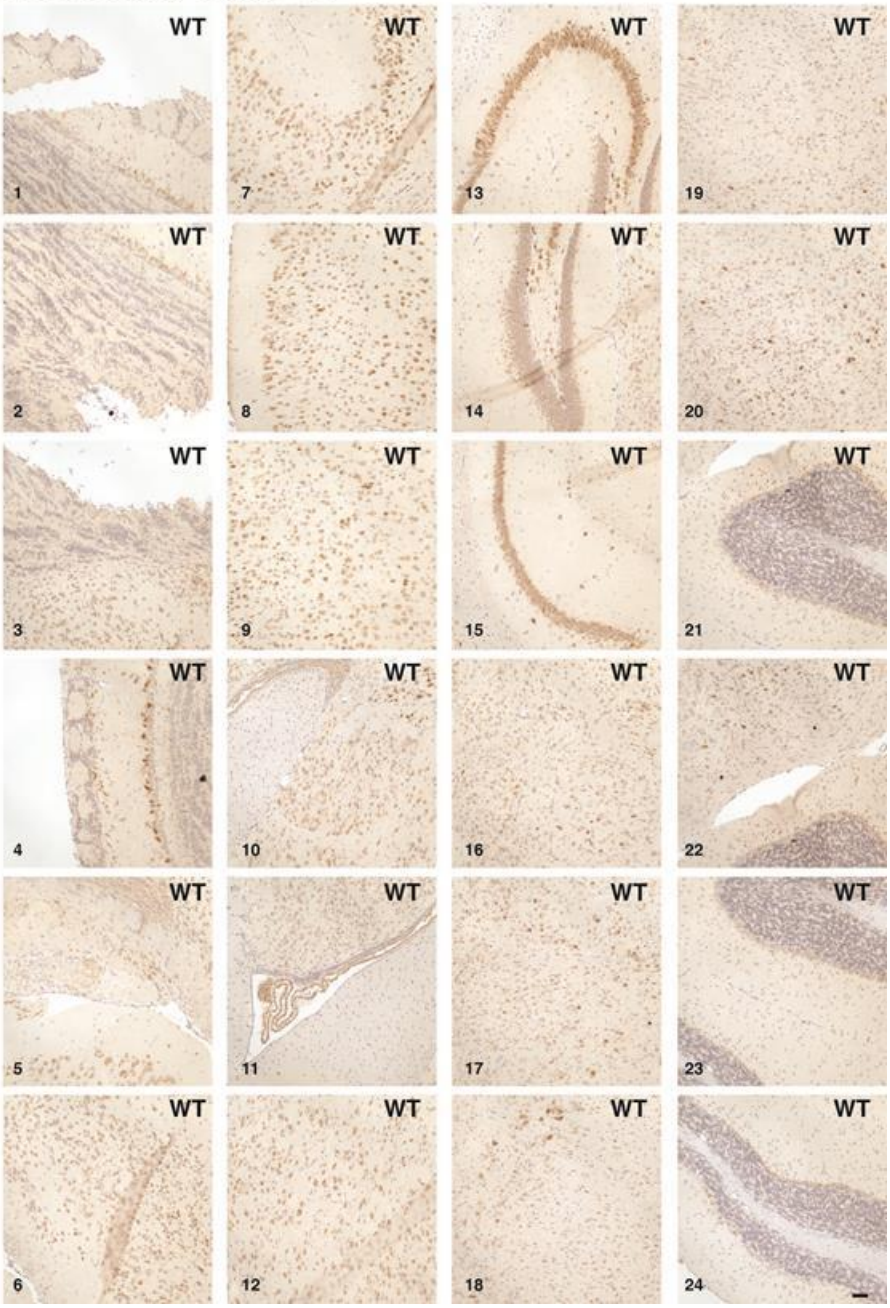
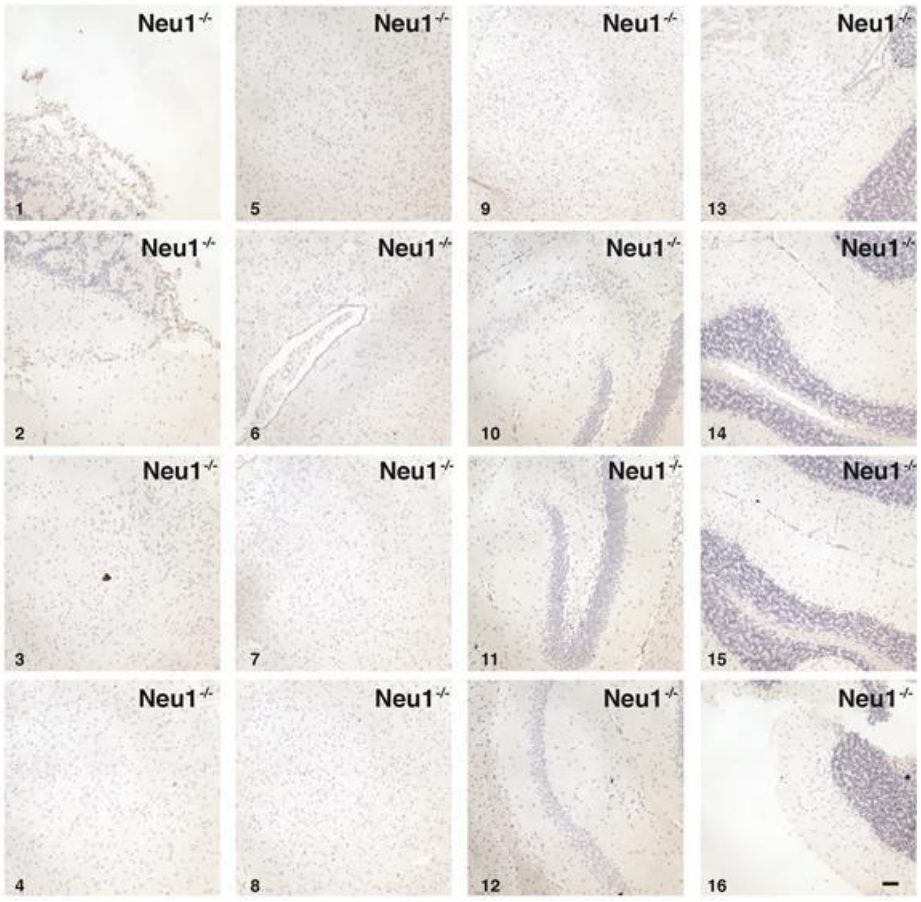
Supplementary Figure S1

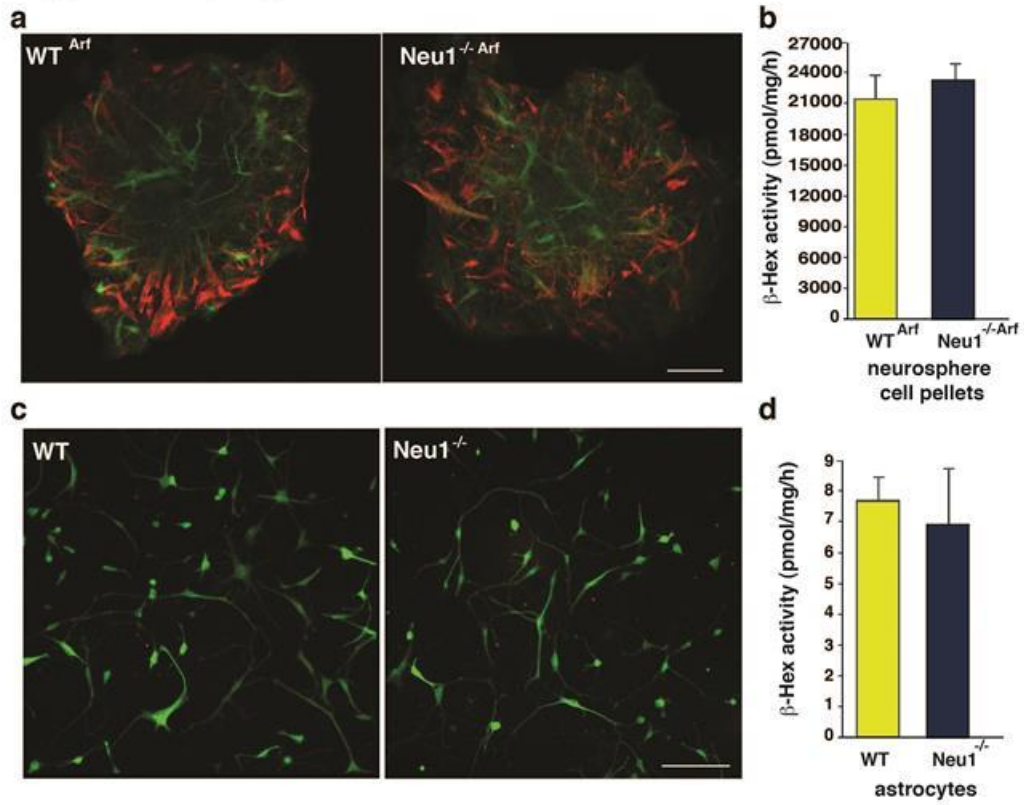


Supplementary Figure S1. Neu1 expression in the wild-type (WT) mouse brain. Representative images of WT brain sections stained with anti-Neu1 antibody. 1 to 24 from olfactory bulb to cerebellum. Mice used for histological analyses were 5 months of age. Scale bar 20μm.

Supplementary Figure S2

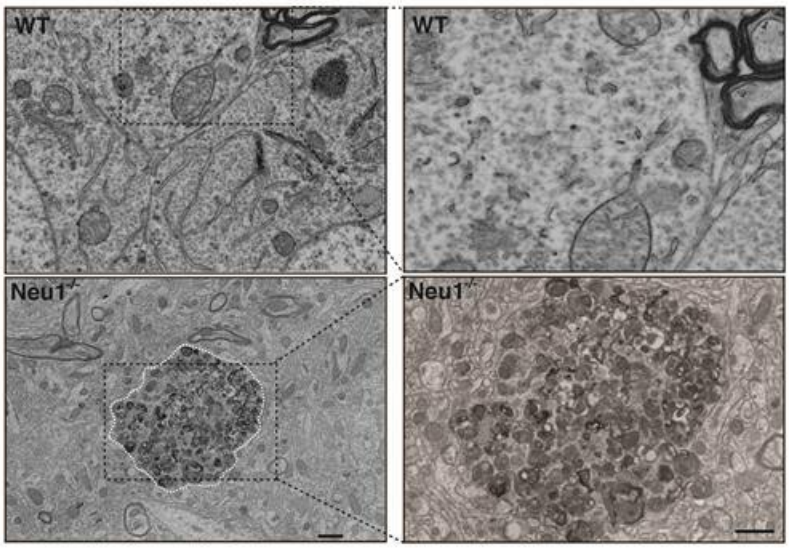


Supplementary Figure S2. Neu1 expression in the *Neu1*$^{-/-}$ mouse brain. *Neu1*$^{-/-}$ brain sections stained with anti-Neu1 antibody show no reactivity. 1 to 16 s from olfactory bulb to cerebellum. Mice used for histological analyses were 5 months of age. Scale bar 20μm.



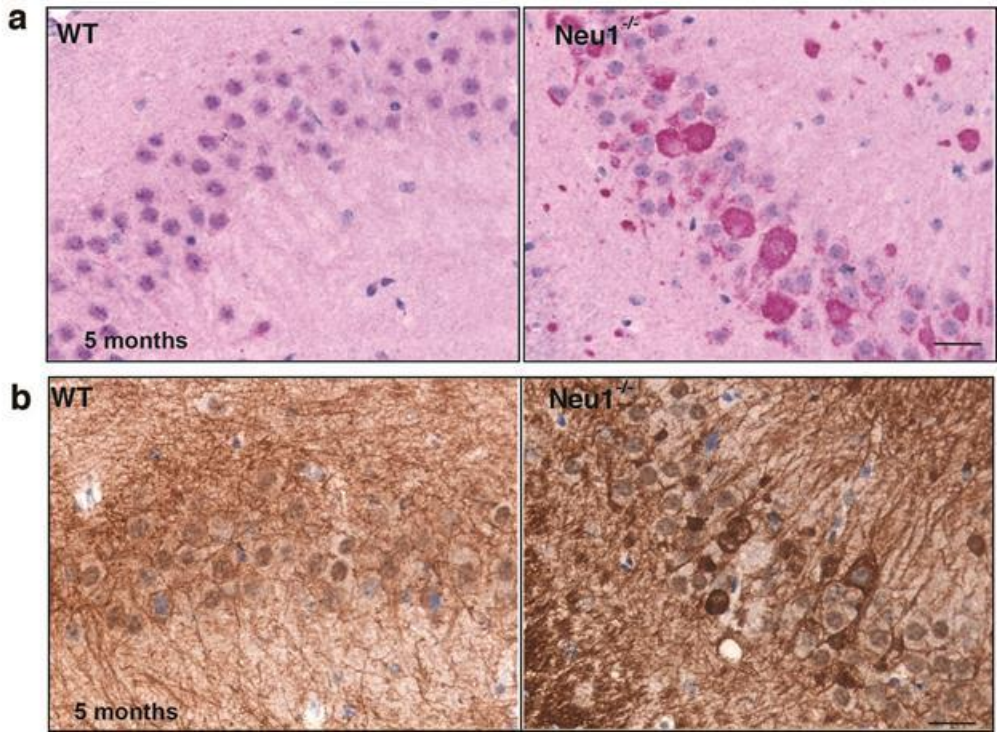
Supplementary Figure S3. Extent of Lysosomal exocytosis in *Neu1*$^{-/-}$ neural cells. **a,** Neurospheres were stained with markers of astrocytes (GFAP, red) and neurons (β-III tubulin, green). **b,** Similar amount of lysosomal exocytosis in *Neu1*$^{-/-}$ astrocytes and in WT astrocytes. Lysosomal exocytosis was measured as β-hex enzyme activity in the culture medium of primary astrocytes. **c**, Representative picture of WT^{Arf} and *Neu1*$^{-/-/Arf}$ hippocampal neurons stained with β-III tubulin (green) and GFAP (red). **d**, Similar extent of lysosomal exocytosis in *Neu1*$^{-/-}$ and in WT neurospheres cell pellets. Scale bar 100μm. Data are represented as mean ± SD (error bars) of 3 independent experiments.

Supplementary Figure S4



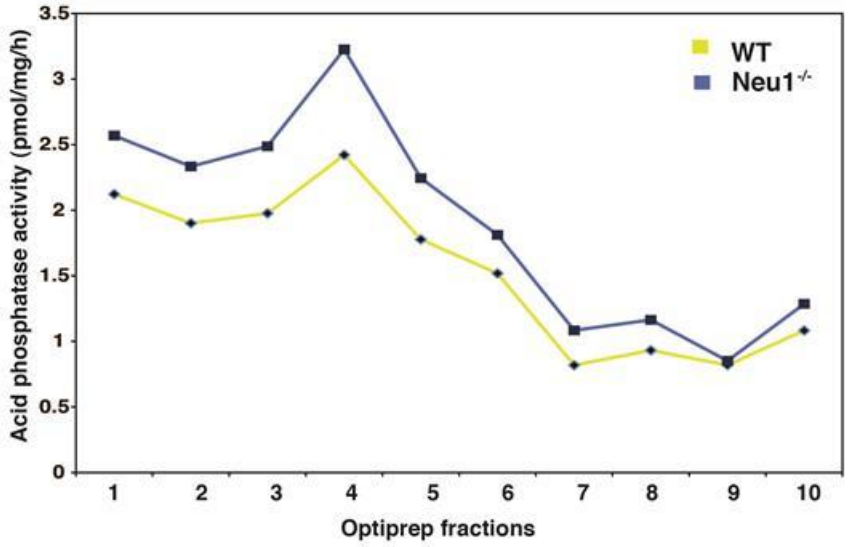
Supplementary Figure S4. Dystrophic neurites in *Neu1*$^{-/-}$ brains. Representative electron microscopic images of WT and *Neu1*$^{-/-}$ hippocampal specimens shows the presence of dystrophic neurites in the *Neu1*$^{-/-}$ hippocampal area. Right panels represent higher magnification of left panels. Mice used for these analyses were 5 months of age. Scale bar 500nm.

Supplementary Figure S5



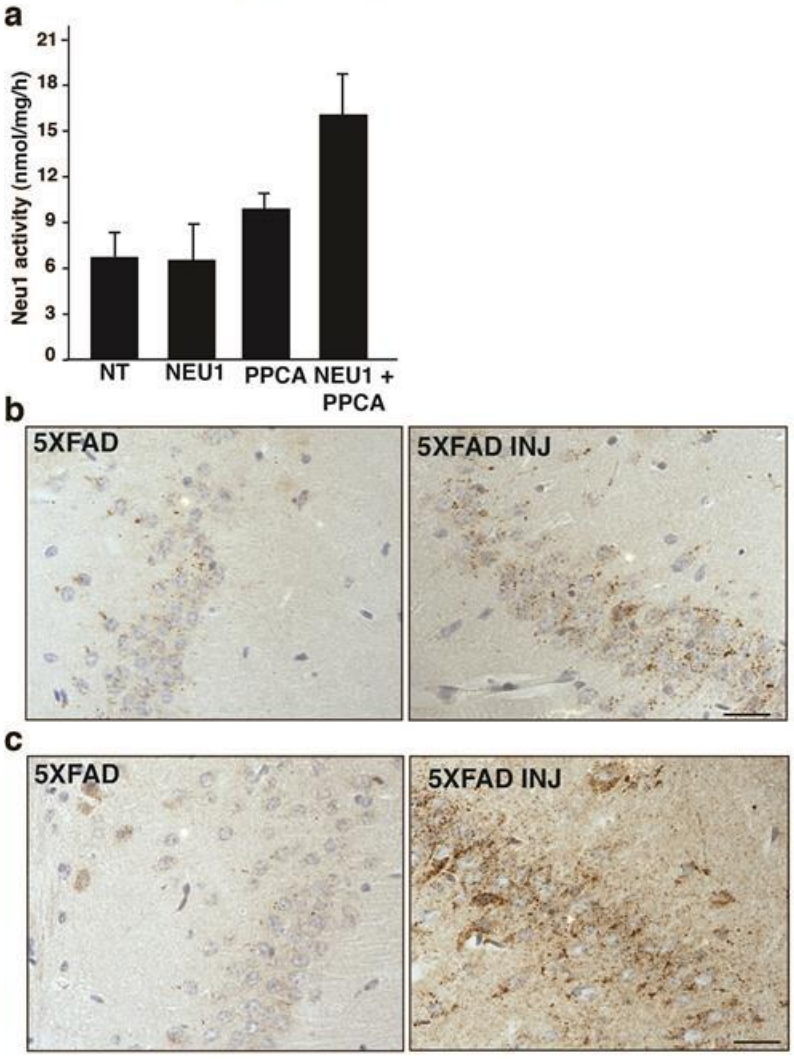
Supplementary Figure S5. Loss of Neu1 results extensive cytoskeletal remodelling and impaired intracellular trafficking. a, b Build-up of APP in older *Neu1*$^{-/-}$ brains was paralleled by the accumulation of ubiquitin (pink) and neurofilaments (brown) respectively. Mice used for these analyses were 5 months of age. Scale bar 20μm.

Supplementary Figure S6



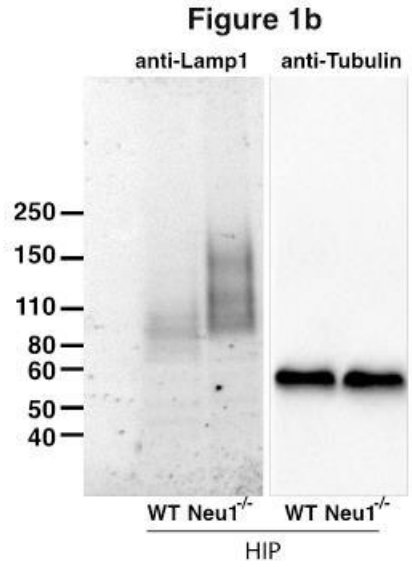
Supplementary Figure S6. Acid phosphatase activity in lysosomal fractions. WT and *Neu1*$^{-/-}$ lysosomal fractions obtained after an Optiprep density gradient were assayed for acid phosphatase activity. Mice used for these analyses were 5 months of age.

Supplementary Figure S7

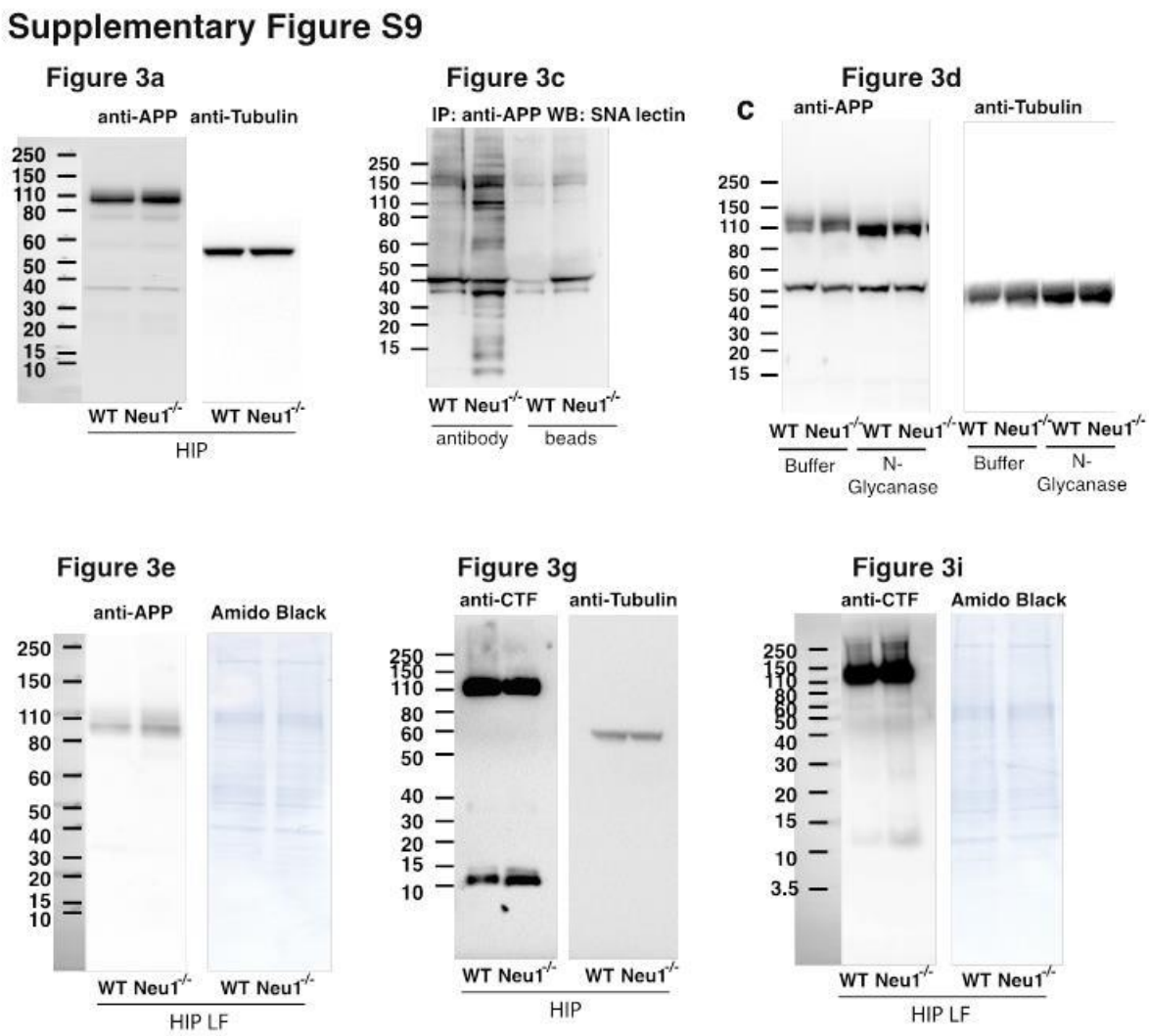


Supplementary Figure S7. Upregulation of NEU1 and PPCA in 5XFAD mice injected with an adeno-associated virus containing human *NEU1* and *PPCA* (5XFAD INJ). a, Neuro2a cells were transduced with adeno-associated virus containing human *NEU1*, *PPCA* (protective protein cathepsin A), or both. The highest Neu1 activity was achieved in the presence of both transgenes. Data are represented as mean ± SD (error bars) of 3 independent experiments. **b and c**, 5XFAD mice were stereotactically injected with an admixture of AAVPPCA and AAVNEU1 and the levels of expression of NEU1 and PPCA were measured 4 weeks later. 5XFAD INJ mice expressed a higher level of NEU1 (b) and PPCA (c) than did 5XFAD animals injected only with carrier solution as demonstrated by immunohistochemistry analyses using anti-NEU1 and anti-PPCA antibodies. Scale bar 20μm.

Supplementary Figure S8

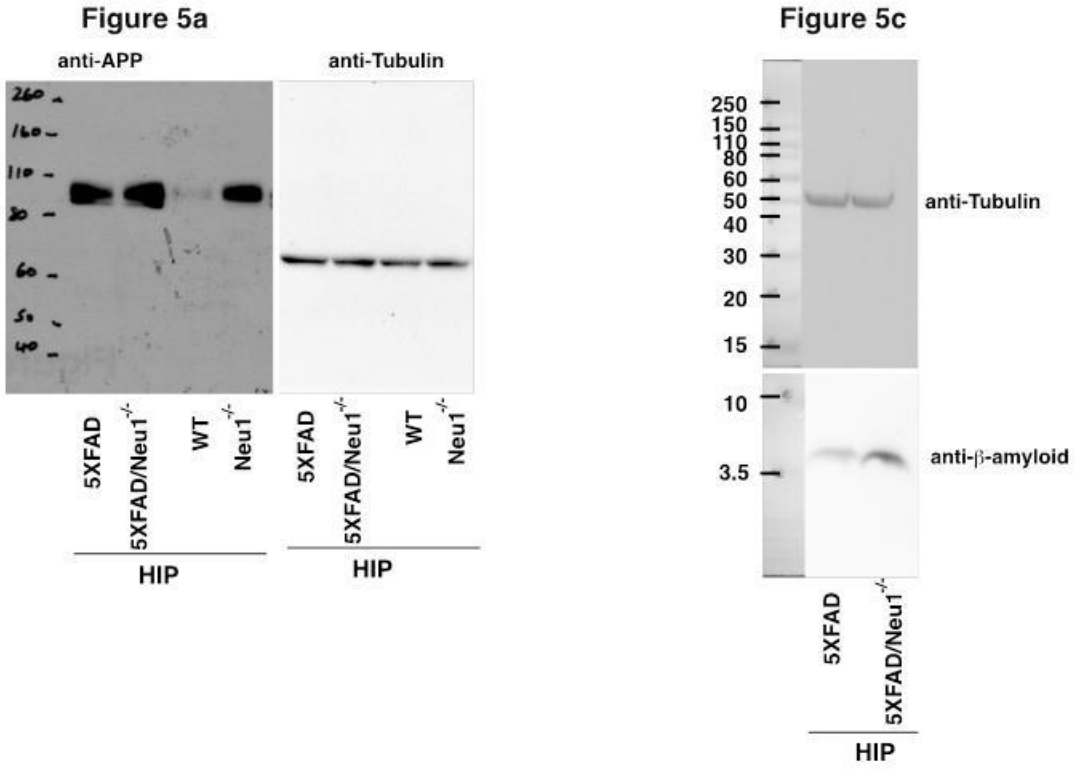


Supplementary Figure S8. Whole unaltered Western blots from Figure 1. Labelling is consistent with Figure 1.



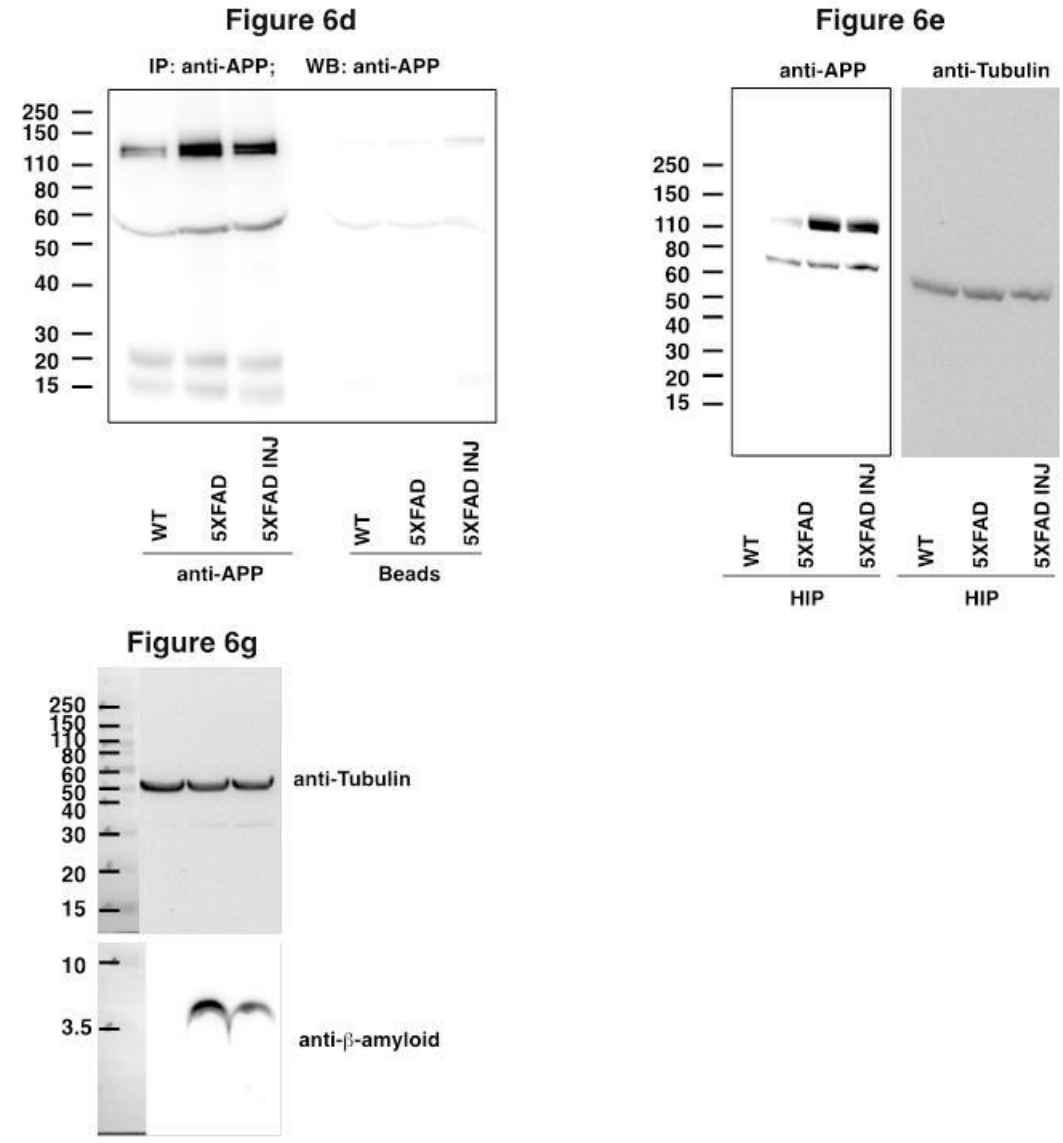
Supplementary Figure S9. Whole unaltered Western blots from Figure 3. Labelling is consistent with Figure 3.

Supplementary Figure S10



Supplementary Figure S10. Whole unaltered Western blots from Figure 5. Labelling is consistent with Figure 5.

Supplementary Figure S11



Supplementary Figure S11. Whole unaltered Western blots from Figure 6. Labelling is consistent with Figure 6