Supplementary Figure S1

a

Aβ immunostaining (6 months)

$APP^{sw/0}\ Pdgfr\beta^{+/+}$ $APP^{sw/0}\ Pdgfr\beta^{+/-}$
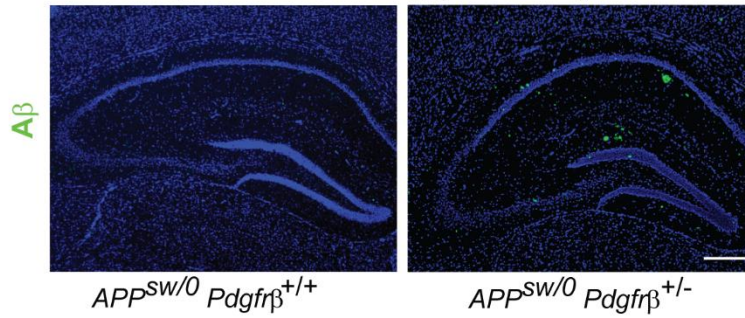
b

Thioflavine-S staining (6 months)

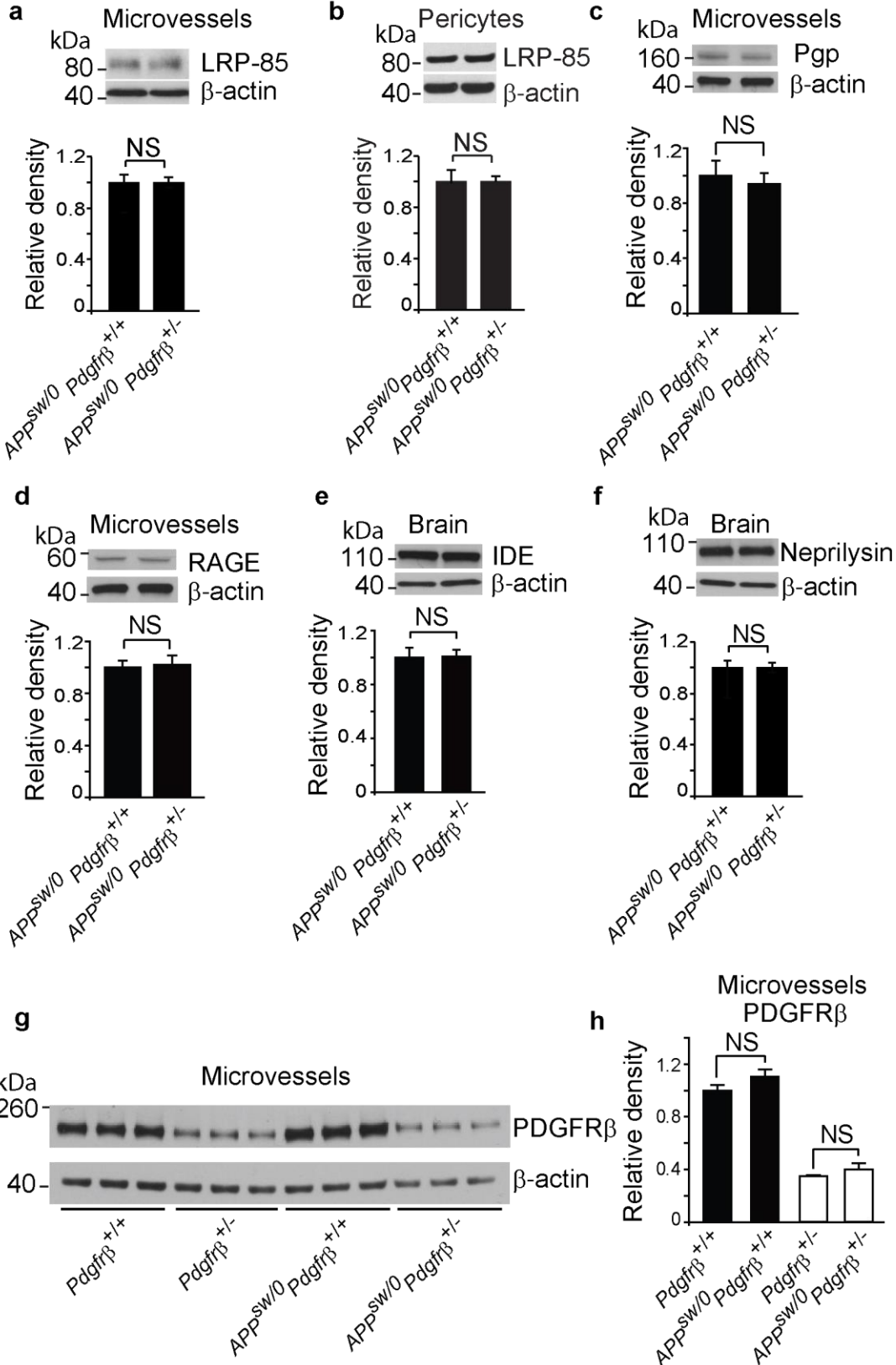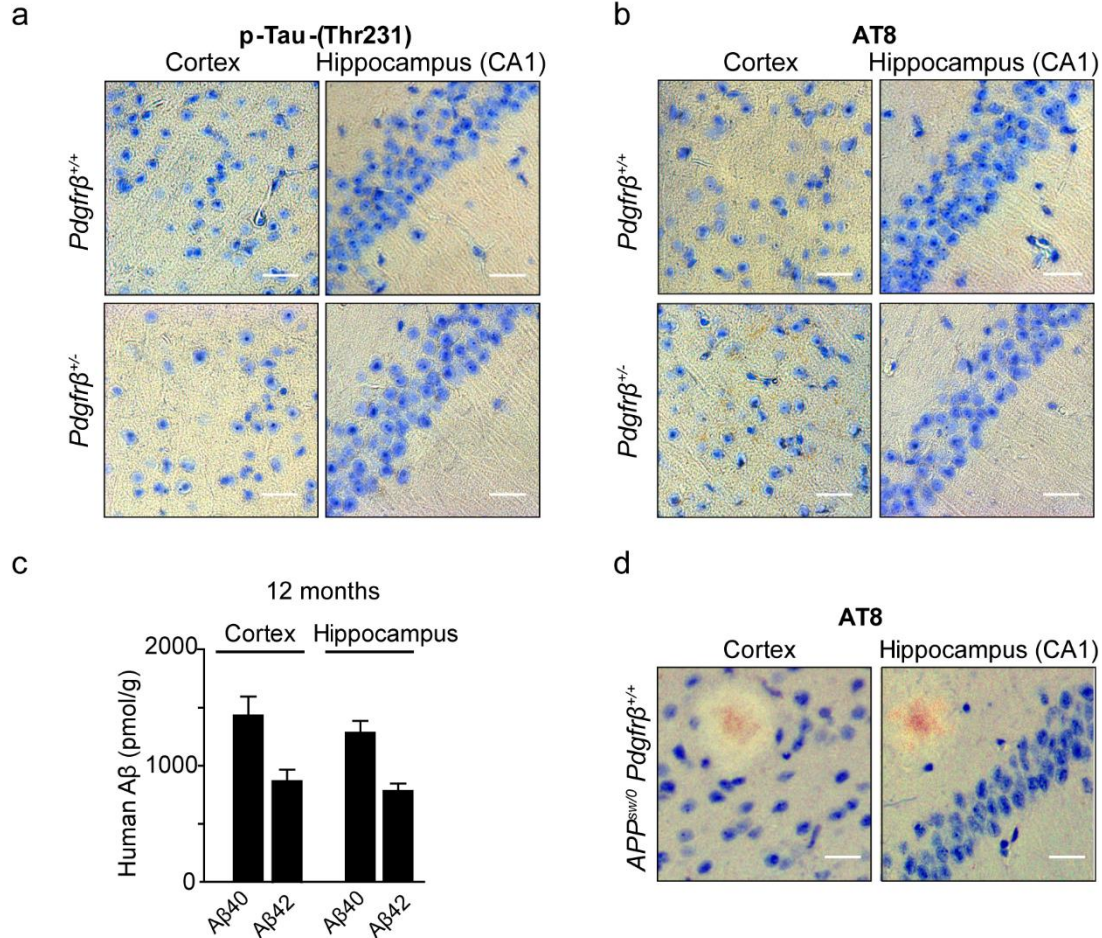$APP^{sw/0}\ Pdgfr\beta^{+/+}$ $APP^{sw/0}\ Pdgfr\beta^{+/-}$
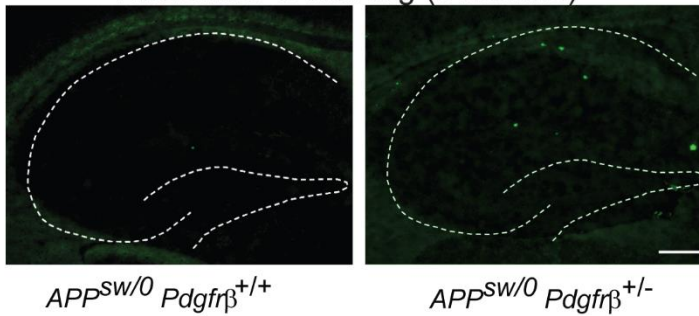
Supplementary Figure S1. Aβ pathology in pericyte-deficient $APP^{sw/0}\ Pdgfr\beta^{+/-}$ mice. a-b, Representative cortex and hippocampus sections stained for Aβ (**a**) and thioflavin S (**b**) in 6-month old $APP^{sw/0}$; $Pdgfr\beta^{+/+}$ and $APP^{sw/0}$; $Pdgfr\beta^{+/-}$ mice. Images are representative findings from 6 mice per group. Scale bar, 100 µm.
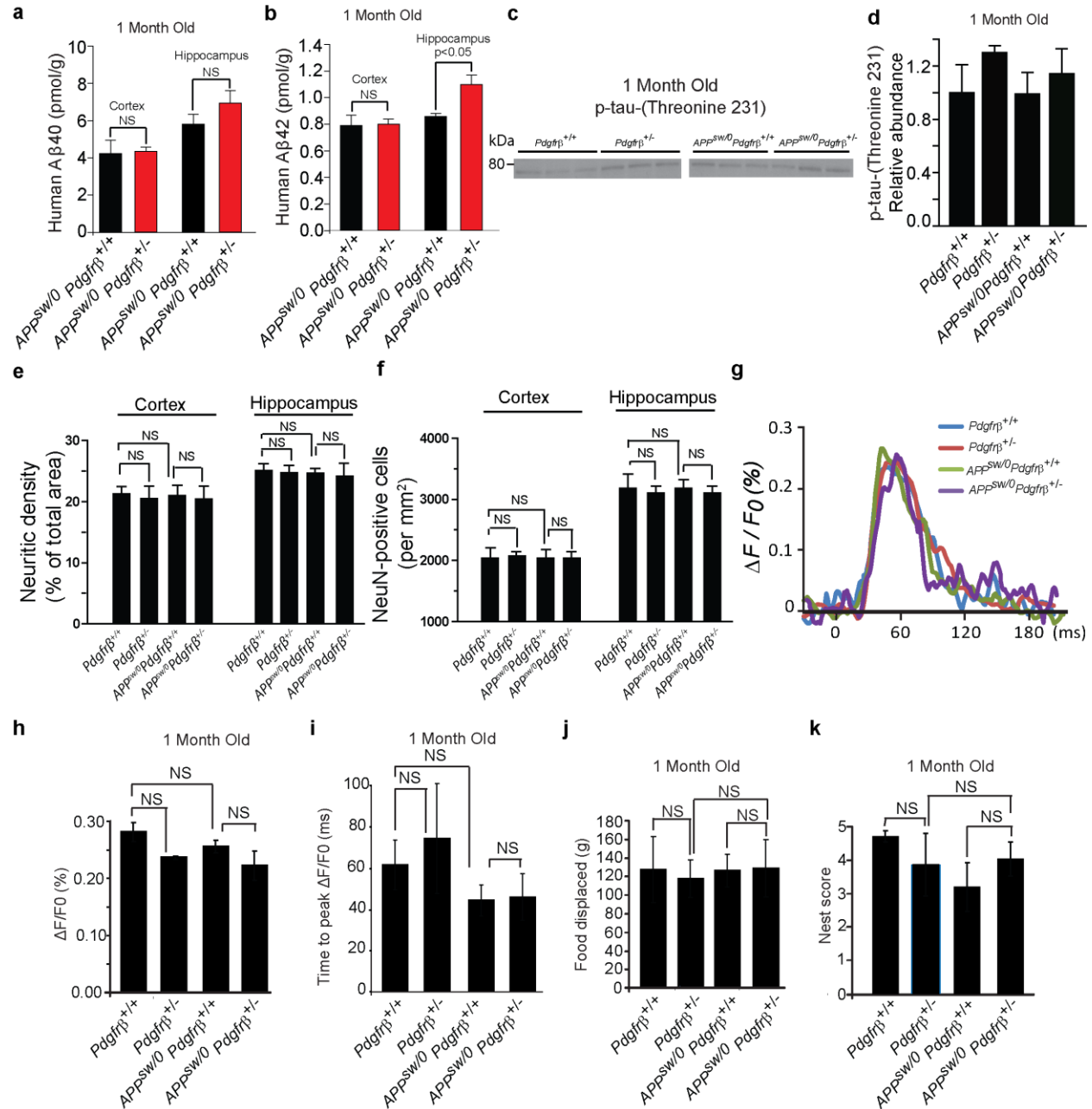
Supplementary Figure S2

Supplementary Figure S2. Expression of different Aβ clearance receptors and enzymes and PDGFRβ in pericyte-deficient $APP^{sw/0}Pdgfr\beta^{+/-}$ mice. a-b, Relative abundance of LRP1 compared to β-actin determined by immunoblotting of brain microvessels (**a**) and isolated pericytes (**b**) from 9 month old $APP^{sw/0}\ Pdgfr\beta^{+/+}$ and $APP^{sw/0}; Pdgfr\beta^{+/-}$ littermates. **c-d**, Relative abundance of P-glycoprotein (Pgp) (**c**) and receptor for advanced end glycation end products (RAGE) (**d**) compared to β-actin determined by immunoblotting of brain microvessels from 9 month old $APP^{sw/0}\ Pdgfr\beta^{+/+}$ and $APP^{sw/0}; Pdgfr\beta^{+/-}$ littermates. **e-f**, Relative abundance of insulin-degrading enzyme (IDE) (**d**) and neprilysin (NEP) (**e**) compared to β-actin determined by immunoblotting in forebrain homogenates from 9 month old $APP^{sw/0}; Pdgfr\beta^{+/+}$ and $APP^{sw/0}; Pdgfr\beta^{+/-}$ littermates. In **a-f**, mean $\pm$ s.e.m., n=4 mice per group. NS, non-significant by Student's t-test. **g-h**, Relative abundance of PDGFRβ compared to β-actin in brain microvessels derived from 9 month old $Pdgfr\beta^{+/+}, Pdgfr\beta^{+/-}, APP^{sw/0}; Pdgfr\beta^{+/+}$ and $APP^{sw/0}; Pdgfr\beta^{+/-}$ littermates. In **h**, mean $\pm$ s.e.m., n=3 mice per group. NS, non-significant by ANOVA followed by Tukey's posthoc tests.

Supplementary Figure S3

Supplementary Figure S3. Absence of p-tau in *Pdgfrβ+/-* mice and *APPsw/0 Pdgfrβ+/+* mice. a-b, Representative cortex and hippocampus sections stained with antibodies against p-tau (Thr231) (**a**) and p-tau (Ser202/Thr205, AT8) (**b**) from 9 month old *Pdgfrβ+/+* and *Pdgfrβ+/-* mice. Scale bar, 25 μm. **c**, Human Aβ40 and Aβ42 levels in the cortex and hippocampus in 12 month old *APPsw/0; Pdgfrβ+/* mice. Mean ± s.e.m., n=6 mice per group. **d**, Representative cortex and hippocampus sections stained against p-tau (Ser202/Thr205, AT8) in 12 month old *APPsw/0; Pdgfrβ+/+* mouse. Scale bar, 25 μm. In **a**, **b** and **d**, images are representative findings from 6 mice per group.

Supplementary Figure S4

Supplementary Figure S4. Absence of structural and molecular pathology in young pericyte-deficient $APP^{sw/0}$ mice. a-b, Human Aβ40 and Aβ42 levels in the cortex and hippocampus of 1 month old $APP^{sw/0}$; $Pdgfr\beta^{+/+}$ and $APP^{sw/0}$; $Pdgfr\beta^{+/-}$ mice. **c-d,** p-tau (Thr231) western blot in forebrain homogenates (**c**) and quantification of p-tau levels relative to total tau (**d**) in 1-2 month old $Pdgfr\beta^{+/+}$, $Pdgfr\beta^{+/-}$, $APP^{sw/0}$; $Pdgfr\beta^{+/+}$ and $APP^{sw/0}$; $Pdgfr\beta^{+/-}$ mice. **e-f,** Quantification of SMI311-positive neurofilaments (**e**) and NeuN-positive neurons (**f**) in the cortex of 9 month old $Pdgfr\beta^{+/+}$, $Pdgfr\beta^{+/-}$, $APP^{sw/0}$; $Pdgfr\beta^{+/+}$ and $APP^{sw/0}$; $Pdgfr\beta^{+/-}$ mice. **g-i,** Representative time-lapse-imaging profile analysis of VSD signal response (**g**), peak amplitude

(**h**) and time-to-peak (**i**) in fluorescent VSD signal in the hind-limb somatosensory cortex after stimulation in 1-2 month old $Pdgfr\beta^{+/+}$, $Pdgfr\beta^{+/-}$, $APP^{sw/0}$; $Pdgfr\beta^{+/+}$ and $APP^{sw/0}$; $Pdgfr\beta^{+/-}$ mice. **j-l**, Burrowing (**j**), nest construction (**k**) and novel object location (**l**) in 1-2 month old $Pdgfr\beta^{+/+}$, $Pdgfr\beta^{+/-}$, $APP^{sw/0}$; $Pdgfr\beta^{+/+}$ and $APP^{sw/0}$; $Pdgfr\beta^{+/-}$ mice. In **a**, **b**, **e**, **f**, **h** and **i**, and in **j** and **k**, mean $\pm$ s.e.m., n=5 mice per group. In **d**, mean $\pm$ s.e.m., n=3 mice per group. NS, non-significant by ANOVA followed by Tukey's posthoc tests.

Supplementary Figure S5. Full scans of western blots.

Figure 4f APP

Figure 9a IgG

Supplementary Figure S.2a LRP-85

Supplementary Figure S.2b LRP85

Supplementary Figure S.2c Pgp

Supplementary Figure S.2d RAGE

Supplementary Figure S.2e IDE

Supplementary Figure S.2f Neprilysin

Supplementary Figure S.2g PDGFRβ

Supplementary Figure S.4c p-tau