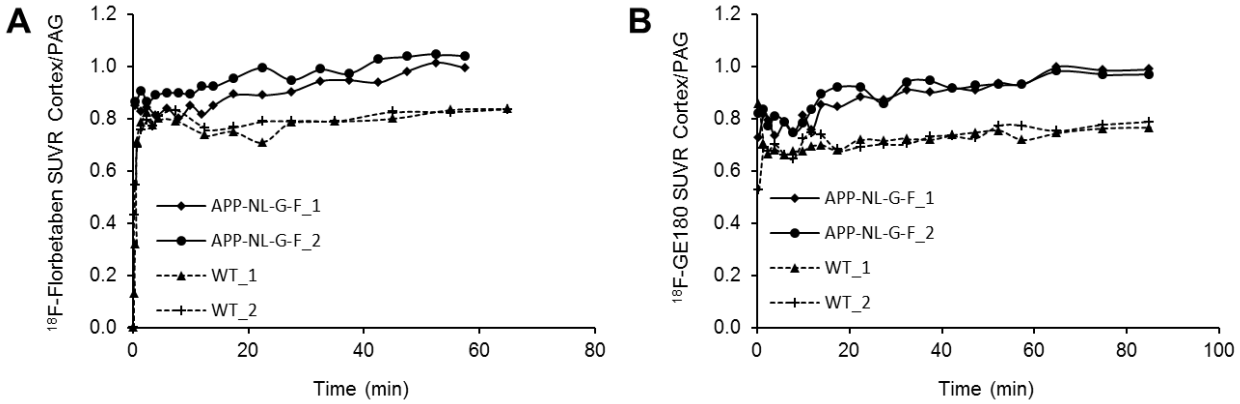
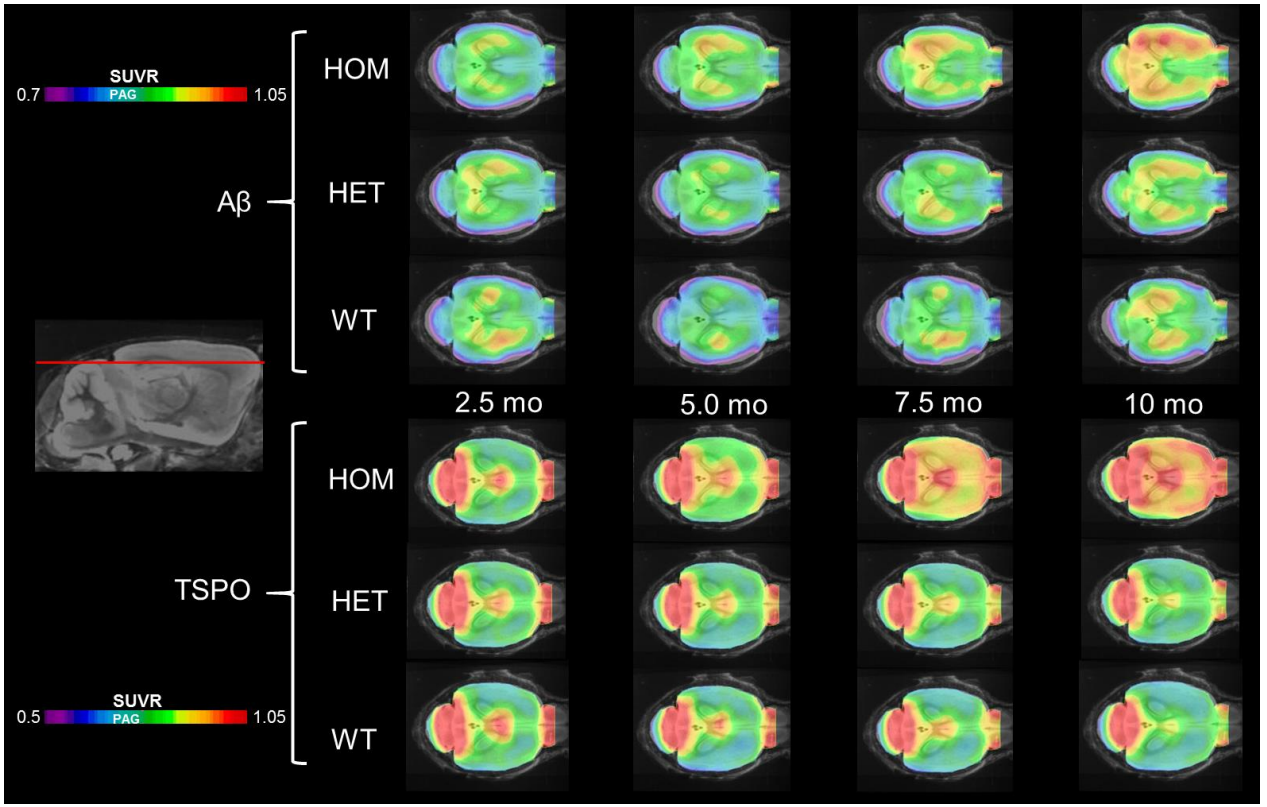
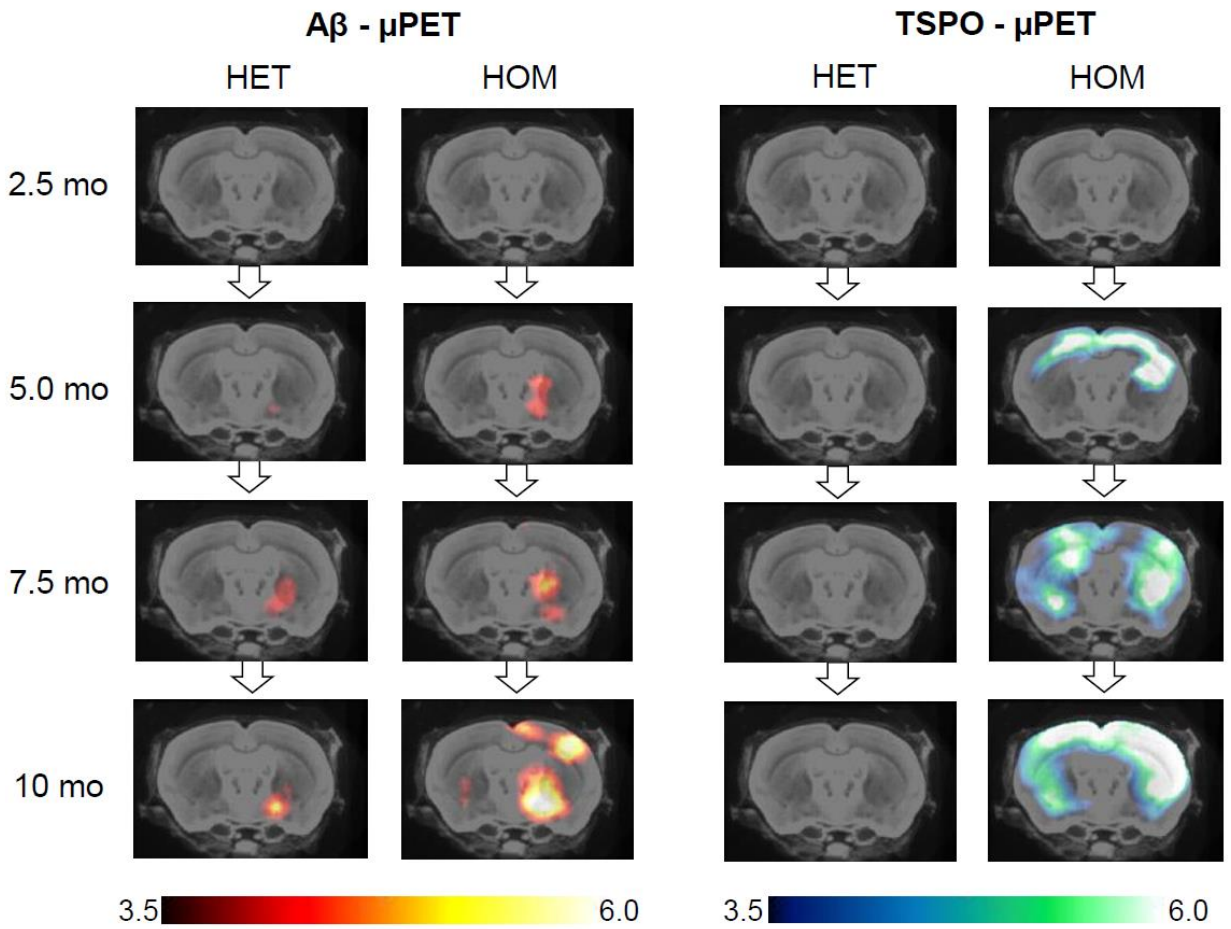


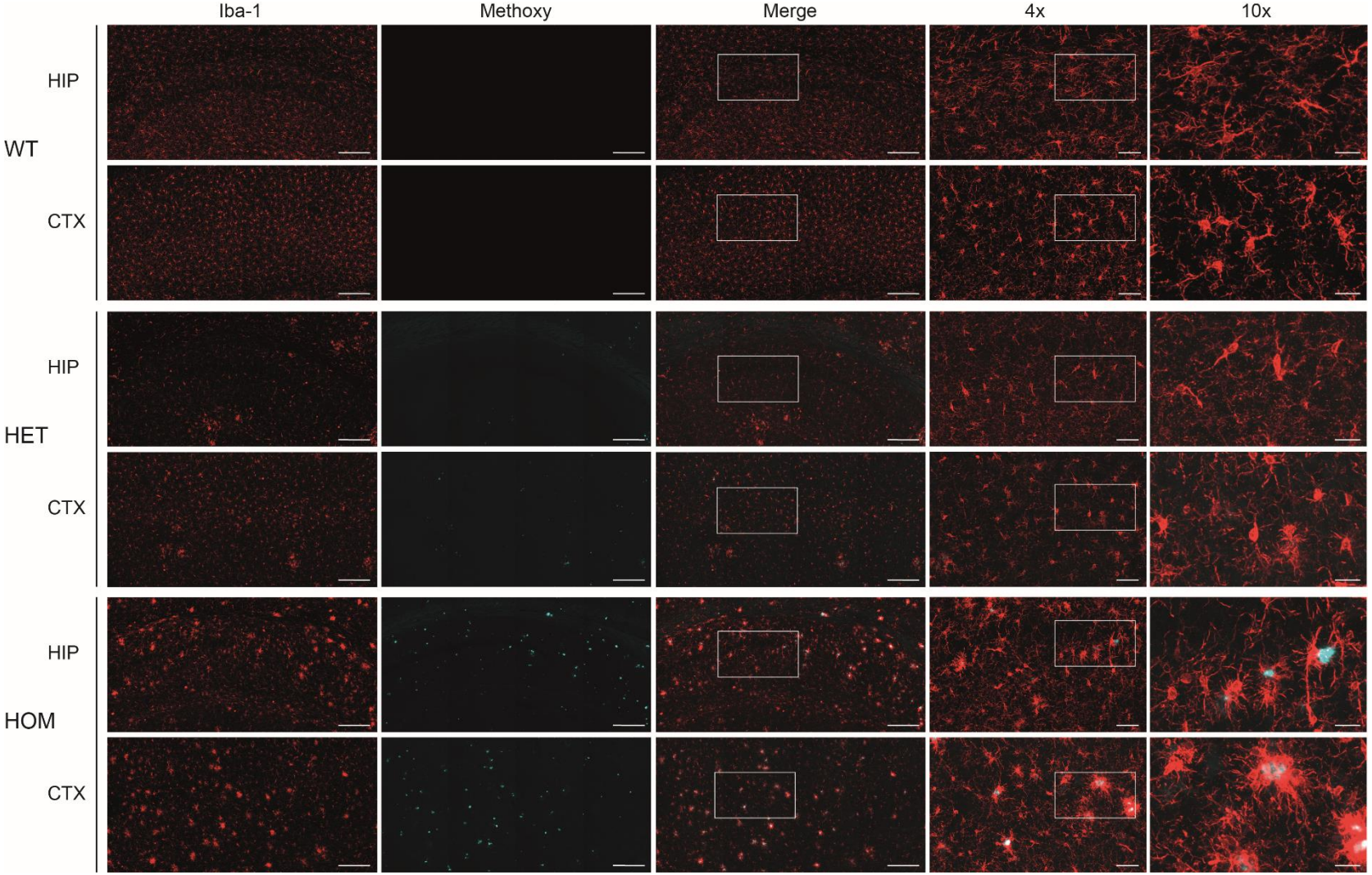
Supplemental Figure 1: Dynamic PET imaging of *App*$^{NL-G-F}$ mice with ^{18}F-florbetaben (**A**; 0-60 min p.i.) and ^{18}F-GE-180 (**B**; 0-90 min p.i.). Time-activity-curves show ratios of the cortical target region divided by the periaqueductal grey (PAG) for two *App*$^{NL-G-F}$ mice and two historic wild-type (WT) mice.



Supplemental Figure 2. Mean parametric SUVR images in axial planes of the Aβ tracer ^{18}F-FBB and the TSPO tracer ^{18}F-GE-180 at different ages of HOM and HET *App*$^{NL-G-F}$ and pooled WT mice projected on MRI mouse atlas.



Supplemental Figure 3: Voxel-wise group comparisons of Aβ and TSPO radiotracer uptake of homozygous (HOM) and heterozygous (HET) *App*$^{NL-G-F}$ mice versus age-matched WT mice at different ages. Two-sample t-test, $p<0.001$ uncorrected for multiple comparisons, $k>20$ voxels, projected upon an MRI mouse atlas (coronal slices).



Supplemental Figure 4. Representative immunohistochemical (Iba-1) images of microglial activation and histochemical images showing and fibrillar Aβ (Methoxy-X04), as well as merged images in cortical (CTX) and hippocampal (HIP) target regions for wild-type (WT) and heterozygous (HET) and homozygous (HOM) *App*$^{NL\text{-}G\text{-}F}$ mice. Scale bars represent 200 µm (columns 1-3), 50 µm (column 4) and 20 µm (column 5).

Supplemental Table 1: Overview of multimodal terminal readouts

Group	Biochemistry			Histochemistry				Behavior
(Age=10mo)	Aβ40 (µg/g)	Aβ42 (µg/g)	sTrem2 (ng/g)	Methoxy-X04 CTX (%)	Methoxy-X04 HIP (%)	Iba1 CTX (%)	Iba1 HIP (%)	Latency to platform (s)
App^{NL-G-F} (homozygous)	0.3±0.1*** n=8	96.9±23.7*** n=8	39.5±4.7*** n=8	1.3±0.3** n=4	1.4±0.1*** n=5	8.5±2.2* n=5	10.0±2.0*** n=5	29.4±16.8* n=11
App^{NL-G-F} (heterozygous)	<0.1 n=14	17.6±4.6 n=14	11.7±2.3 n=14	0.4±0.3 n=5	0.1±0.1 n=5	5.1±1.3 n=5	3.3±1.1 n=5	20.1±11.7 n=14
C57BL/6 (wild-type)	<0.1 n=4	0.3±0.2 n=3	9.5±1.7 n=4	not detected	not detected	4.3±0.9 n=4	2.4±0.8 n=4	14.3±4.7 n=3

Aβ and sTrem2 levels are given as ng per g of wet brain tissue. P-values for two-sided t-test in the comparison of homozygous *App*$^{NL-G-F}$ versus wild-type are given by: *p<0.05; **p<0.01; ***p<0.001; two-tails. Methoxy-X04 staining of homozygous *App*$^{NL-G-F}$ was tested against heterozygous *App*$^{NL-G-F}$ due to no detectable Aβ plaques in wild-type. Histology quantification: 3-dimensional 16-bit data stacks of 8192x4096x32 pixels of confocal microscope images were acquired for the whole cortex as well as hippocampus at a lateral resolution of 0.2 µm/pixel and an axial resolution of 1.0 µm/pixel. To quantify Iba1-positive microglia burden as well as plaque-load we used autothresholding in ImageJ. For staining of fibrillar plaques we acquired 3-dimensional 16-bit data stacks of 2048x2048x120 pixels from five different positions in the frontal cortex as well as hippocampus at a lateral resolution of 0.17 µm/pixel and an axial resolution of 0.4 µm/pixel. For plaque quantitation, we utilized custom-written Matlab software (MathWorks, Natick, USA).

Supplemental Table 2: Comparison between mouse models

Mouse model	Onset of congophilic Amyloidosis (months)	Age range of PET imaging (months)	Reference tissue	Amyloid µPET (Cortical Increase)	TSPO µPET (Cortical Increase)	Correlation sTrem2 - Amyloid-µPET (terminal)	Correlation sTrem2 - TSPO-µPET (terminal)	Correlation Water maze - Amyloid-µPET (terminal)	Correlation Water maze - TSPO-µPET (terminal)
App^{NL-G-F}	2.0	2.5-10.0	PAG	9.1%	19.8%	-	++ (pos.)	-	+ (pos.)
PS2APP (*16*)	5.0	5.0-16.0	WM	19.8%	20.2%	+++ (pos.)	+++ (pos.)	-	++ (neg.)
APP-SL70 (*26*)	5.0	5.5-12.5 (average)	WM	18.3%	17.6%	n.a.	n.a.	n.a.	n.a.

Overview of findings in homozygous *App*$^{NL-G-F}$ mice compared to other AD model mouse strains investigated with comparable µPET modalities. For comparing the correlations, we indicate significant R/r_S by + (0.2-0.5), ++ (0.5-0.8), +++ (0.8-1.0). n.a. = not assessed