Supplementary-Fig. 1. Selective BACE1 labeling at swollen/sprouting axonal terminals/ processes and in rosette-like dystrophic axonal neurites in aged 3xTg-AD mice (all images were from a 24 month-old animal). Panels (A-C) show BACE1 labeled axonal profiles in the hippocampal formation. Labeled swollen terminals/processes (as indicated by arrows) are

common in the stratum oriens, but also visible in the strata radiatum and pyramidale. Panel (D) shows many swollen processes located between the striatum and overlying parietal cortex (also see similar profiles labeled by Aβ antibody 4G8 in S-Fig. 3B, C). In double immunofluorescence, BACE1 labeling may colocalize with synaptophysin (SYN, E-G), growth associated protein 43 (GAP-43, H-J) and APP stained with the monoclonal antibody 22C11 (K-M) in the subiculum. Panels (N-Q) show an example that the BACE1 antibody does not visualize any perisomatic or discretely-distributed swollen axonal terminals in the cortex and hippocampus in a 22 month-old non-transgenic mouse. Colocalization of BACE1 and synaptophysin is otherwise clearly seen in the mossy fiber terminals (mf). Scale bar = 500 μm in (A); equal to 100 μm for (N-P) and 50 μm for remaining panels.

Supplementary-Fig. 2. Swollen axonal terminals in the hippocampus co-localizing with markers of excitatory and inhibitory neurons. Panels (A) show colocalization of 3D6 and neurogranin labeling at swollen axonal processes and around small neuritic plaques in hippocampal stratum oriens (green arrows). Note neurogranin labeling of the pyramidal neuronal somata. Panels (D-F) demonstrate that 3D6 labeled perisomatic puncta colocalize with GABA transporter 1 around CA1 pyramidal neuronal somata. Scale bar = 100 μm in (A) applying to other panels.

Supplementary-Fig. 3. Visualization of axon terminal labeling by 4G8 and E50 in sections using a strong formic acid pretreatment. Panels (A-G) are low and high power views of 4G8 labeling from a 20 month-old 3xTg-AD mouse. Note the swollen axonal processes between the striatum and cortical white matter (B, C), and the labeled puncta aligning along the apical dendrite of some hippocampal pyramidal neurons (G). Panels (H-P) show perisomatic puncta, swollen axons

and extracellular plaques visualized by E50 in a 2 month-old (H-J) and a 20 month-old (K-P) transgenics. Note again the perisomatic granular labeling apposing to hippocampal and cortical pyramidal neuronal somata and apical dendrites (N-P). Scale bar = 500 μm in (A), applying to (H and K); equivalent to 250 μm for (B); 100 μm for (E-G, I, J, L, M) and 67 μm for (D, N-P).

Supplementary-Fig. 4. Characterization of axon terminal labeling using antibodies targeting the Aβ C-terminal (Ter40 and Ter42), and APP C- (CT15) and N- (22C11) terminals. Panels (A-D) compare labeling patterns of 6E10 (A, B), Ter40 (C) and Ter42 (D) between mirror sections from a 14 month-old 3xTg-AD mouse processed without formic acid pretreatment. Ter40 and Ter42 show little labeling in neuronal somata, but do label extracellular plaques around the subiculum (fat green arrows). Panels (E-J) are double immunofluorescent labelings for 6E10 vs Ter40 (E-G) and Ter42 (H-J4) in sections (12 μm) treated with 90% formic acid for 20 minutes. Again, Ter40 and Ter42 do not exhibit intrasomal and terminal-like labeling (arrows in enlargements of the framed areas). Panels (K-N) show labeling of CT15 in the hippocampal formation and cortex in a 20 month-old 3xTg-AD mouse. Labeling is seen inside pyramidal neuronal somata (K, L). Swollen axonal processes (K) and perisomatic puncta (M, arrows) are also visualized. Panels (O-R) show 22C11 labeling inside pyramidal neuronal somata and in plaque-associated dystrophic neurites (fat arrows). Some small swollen axons are labeled as well, but no perisomatic punctuate structures are visible around pyramidal neuronal somata. A large amount of axon terminals in the stratum lacunosum-moleculare are labeled by 22C11 (R). Scale bar = 500 μm in (A); equivalent to 250 μm for (B-D); 100 μm for (E-I, J3, J4, K, O-R); and 50 μm for (J1, J2, L-N).