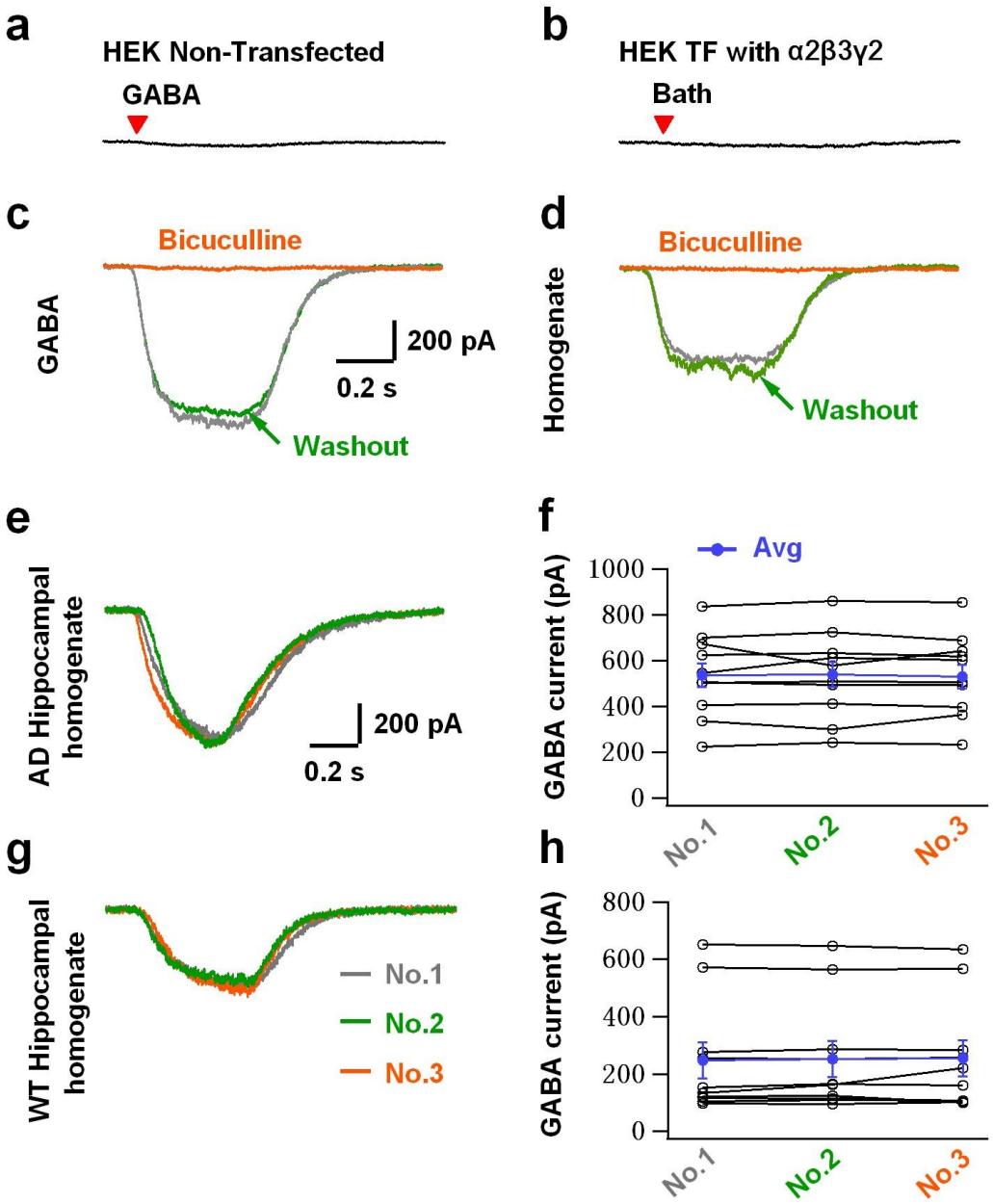
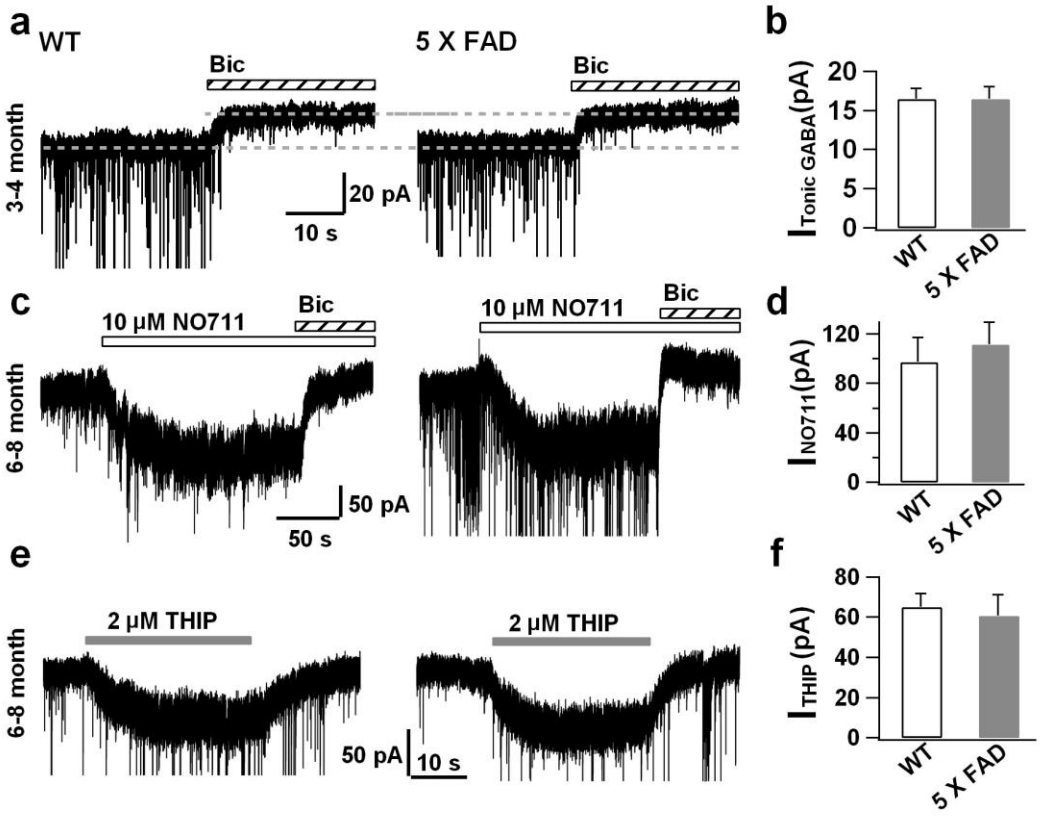
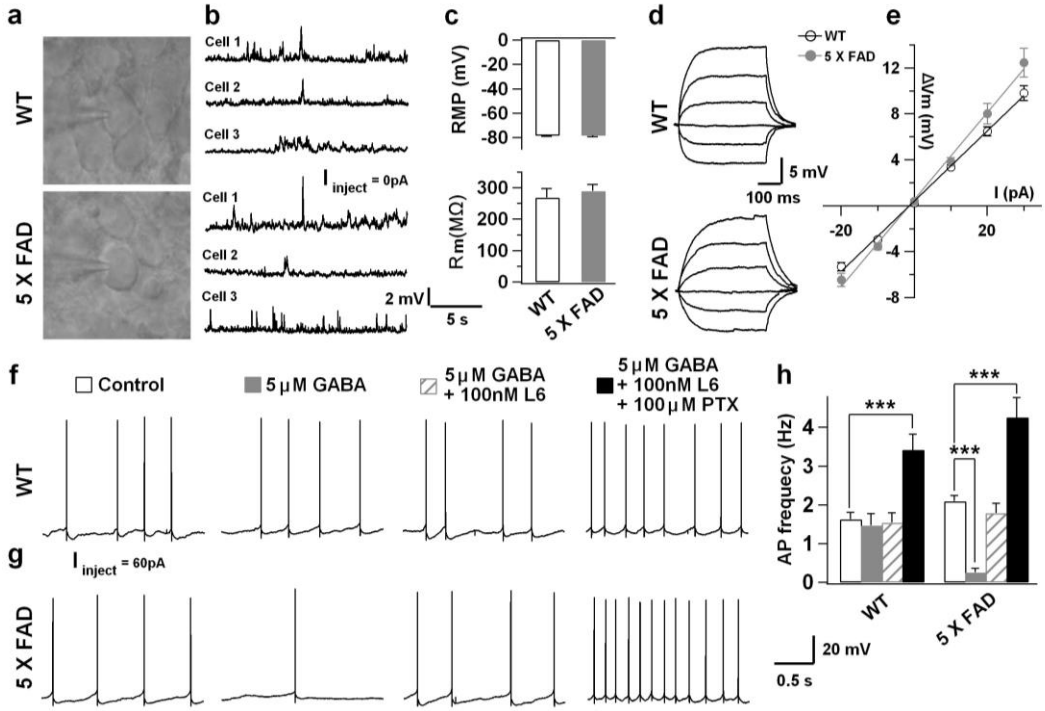
SUPPLEMENTARY FIGURES:



Supplementary Figure 1. Control experiments for brain homogenate puff assay. (**a**) Puffing GABA (10 μM) onto non-transfected HEK cells did not evoke any significant responses. (**b**) Puffing bath solution onto $GABA_A$-R-expressing HEK cells also not evoked any responses. (**c**) GABA (10 μM) evoked responses after puffing onto α2β3γ2-transfected HEK cells were completely blocked by bicuculline (50 μM). (**d**) Similarly, brain homogenate-evoked responses were also blocked by bicuculline. (**e, f**) Triple micropipettes filled with the same AD hippocampal homogenate solution evoked the same size of GABA responses. (**g, h**) Triple micropipettes filled with the same WT hippocampal homogenate solution also evoked the same size of GABA responses, although smaller than that evoked by AD hippocampal homogenate solution.



Supplementary Figure 2. Tonic GABA currents in dentate granule cells in both WT and 5xFAD mice. (**a**) Representative traces showing tonic currents revealed by application of $GABA_A$-R antagonist Bic (100 µM) in dentate granule cells in 3-4 months old WT (left) and 5xFAD animals (right). (**b**) Quantitative data analysis showed no significant difference between the tonic currents in young adult WT versus AD mice ($P > 0.9$). (**c**) Typical traces showing tonic currents induced by blockade of neuronal GABA transporter GAT1 with NO-711 in dentate granule cells (6-8 months old animals). Large mIPSCs were truncated to better illustrate the tonic current. (**d**) Quantified data showing no significant difference between the tonic currents induced by NO-711 in WT vs 5xFAD mice ($P > 0.4$). (**e**, **f**) No significant difference was found in THIP-induced tonic currents (mostly mediated by δ-$GABA_A$-Rs) in dentate granule cells between WT and 5xFAD animals (6-8 months old; $P > 0.7$). Data are presented as mean ± s.e.m.



Supplementary Figure 3. Abnormal tonic GABA current reduces neuronal excitability of dentate granule cells in 5xFAD animals. (**a**) DIC images of dentate granule cells in hippocampal slice recordings. (**b**) Spontaneous synaptic events detected in dentate granule cells under resting state. (**c**) No difference in resting membrane potential (top) or membrane resistance (bottom) of dentate granule cells between WT and 5xFAD animals. (**d, e**) Cell membrane input-output curves were tested by a series of current injections, showing similar properties between WT and 5xFAD dentate granule cells. (**f, g**) Representative traces showing action potential firing in one granule cell (**f**, WT; **g**, 5xFAD; current clamp, 60 pA injected current) under various conditions: control, 5 μM GABA, 5 μM GABA+100 nM L655708, and 5 μM GABA+100 nM L655708+100 μM picrotoxin (PTX). (**h**) Quantified data for action potential firing frequency in dentate granule cells after different treatments (n = 14 for each group). Data are presented as mean ± s.e.m., *** $P < 0.001$. Note that 5 μM GABA significantly inhibited action potential firing in 5xFAD granule cells, which were reversed by α5 subunit specific inverse agonist L655708, suggesting that α5-$GABA_A$-R-mediated tonic current plays an inhibitory role on neuronal excitability. As expected, blocking all GABA inhibition with 100 μM picrotoxin increased neuronal firing in both WT and 5xFAD granule cells.

Supplementary Table 1. Summary information on human hippocampal tissue.

Case number	PMI (hr)	Age at onset	Age at death	Race/Sex
AD PATIENTS				
OS03-163	4.5	< 52	55	W/F
E04-76	30.5	65	72	W/M
E05-04	4.5	52	64	W/F
E05-145	13	74	87	W/F
E06-155	6.5	56	67	W/M
E07-38	12	70	77	W/M
OS02-75	4.5		78	W/M
OS02-108	>12	76	88	W/F
OS03-298	22	84	93	W/F
CONTROL CASES				
OS01-127	22.5		34	W/F
OS02-35	6		75	W/F
OS03-390	7		74	W/F
E05-74	6		59	B/M
E06-113	4.5		20	B/F
E06-114	6.5		53	B/M
E04-32			70	W/M
E08-137	15.5		92	W/F
OS01-112	6		65	W/F