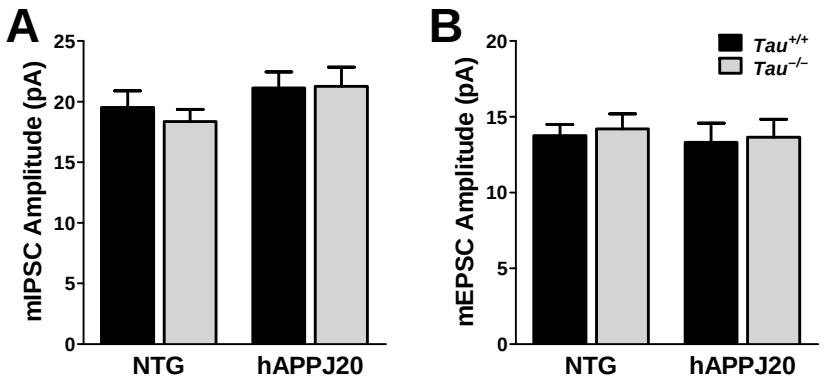
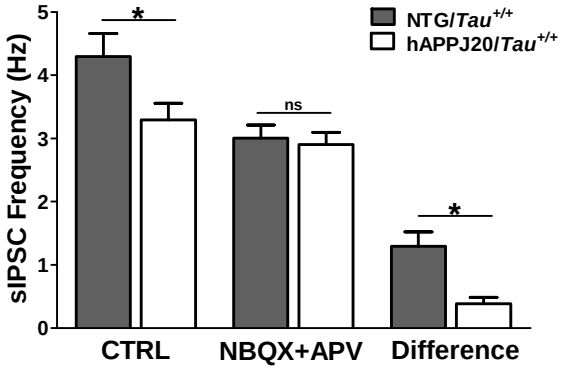
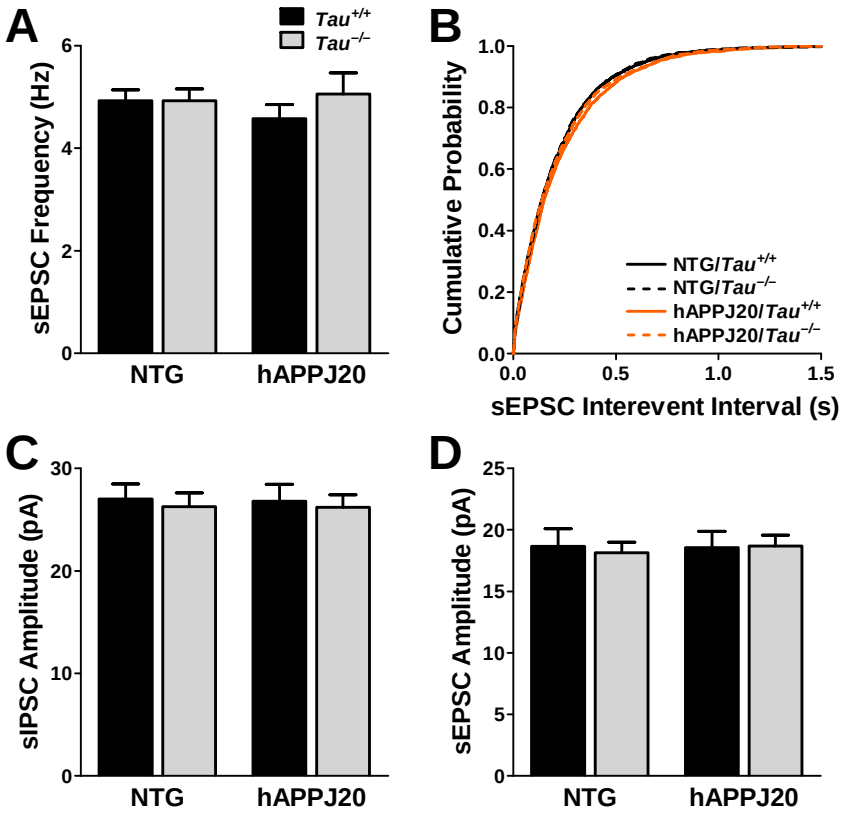


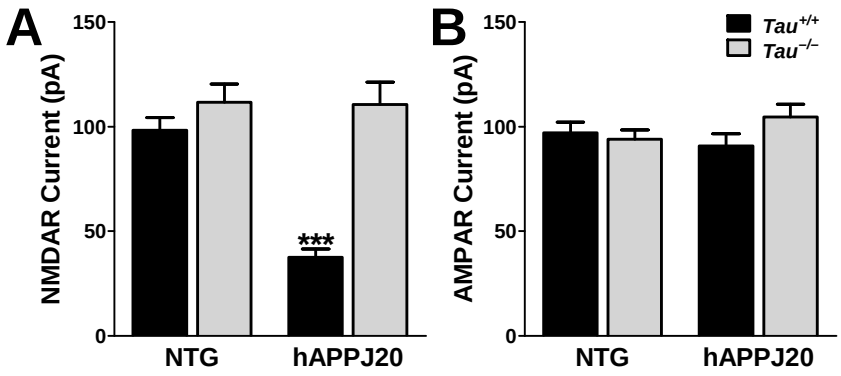

**Supplemental Figure 1.** No differences in miniature postsynaptic potential amplitudes in dentate granule cells across genotypes. Whole-cell recordings were made from acute hippocampal slices. The amplitude of miniature IPSCs (***A***) and mEPSCs (***B***) was unaffected by hAPP/Aβ expression and tau reduction ($n$ = 2000–2400 events from 10–12 cells, 200 events from each, in four mice per genotype).



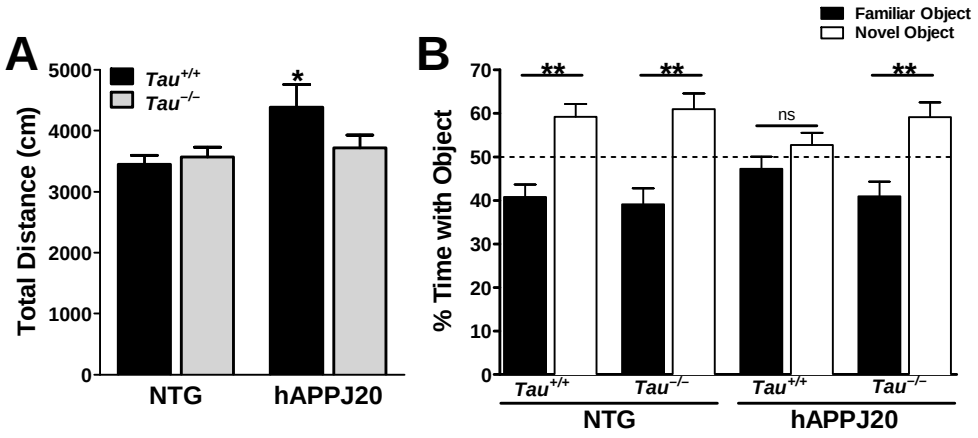

**Supplemental Figure 2**. Reduced excitatory drive onto inhibitory interneurons in hAPPJ20 mice. Whole-cell recordings were made from acute hippocampal slices. In the absence of pharmacological blockers, the frequency of sIPSCs onto granule cells was reduced in hAPPJ20/*Tau*$^{+/+}$ cells (CTRL, see also Fig. 9). To determine whether this effect was caused by reduced excitatory drive onto inhibitory interneurons, we blocked excitatory inputs with the AMPA receptor blocker 2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo[f]quinoxaline-2,3-dione (NBQX) and the NMDA receptor blocker (2R)-amino-5-phosphonovaleric acid (APV). In the presence of NBQX+APV, sIPSC frequency did not differ in NTG and hAPPJ20 mice. The difference between sIPSC frequencies recorded under control and NBQX+APV conditions (Difference) reflects the sIPSC component caused by excitatory inputs to inhibitory interneurons and was reduced in hAPPJ20 mice. (* $p < 0.05$ by ANOVA; $n = 10$ cells from three mice per genotype)




**Supplemental Figure 3.** No differences in sEPSC frequency, sEPSC amplitude, or sIPSC amplitude in dentate granule cells across genotypes. Whole-cell recordings were made from acute hippocampal slices. The frequency (***A,B***) and amplitude (***D***) of sEPSCs and the amplitude of sIPSCs (***C***) were unaffected by hAPP/Aβ expression and tau reduction ($n$ = 2800–3000 events from 14–15 cells, 200 events from each, in four mice per genotype).




**Supplemental Figure 4**. Tau reduction prevents NMDA receptor dysfunction in dentate granule cells of hAPPJ20 mice. Whole-cell recordings were made from acute hippocampal slices in the presence of picrotoxin. ***A***, NMDA receptor (NMDAR)–mediated currents were isolated as described in Methods. Evoked NMDAR currents were decreased in hAPPJ20/*Tau*$^{+/+}$ mice but not in hAPPJ20/*Tau*$^{-/-}$ mice (hAPP x tau interaction, $p < 0.0005$ by two-way ANOVA; *** $p <$ 0.001 vs all other groups by *post hoc* test; $n$ = 15–18 cells from four mice per genotype). ***B***, AMPA receptor (AMPAR)–mediated currents were isolated as described in Methods. There were no differences between genotypes.




**Supplemental Figure 5**. An independent line of *Tau*-deficient mice is also protected against hAPP/Aβ-induced behavioral deficits. Mice with a GFP knock-in allele replacing the *MAPT* locus (Tucker et al., 2001) were crossed with hAPPJ20 mice. ***A***, Elevated plus maze. Tau reduction prevented the hyperactivity typically seen in hAPP/$Tau^{+/+}$ mice ($p < 0.05$ by ANOVA; * $p < 0.05$ by *post hoc* test; $n = 10$ mice per genotype; age 4.5–7.5 months). ***B***, Novel object recognition test. hAPPJ20/$Tau^{+/+}$ mice showed no memory of the familiar object. This deficit was also blocked by tau reduction (** $p < 0.01$ between familiar and novel object; $n = 10$ mice per genotype; age 4.5–7.5 months).