SUPPLEMENTAL FIGURES

Figure S1. Epileptiform Activity Emerges During Reduced Intensity of Gamma Activity in hAPPJ20 Mice. EEG recordings from the left and right parietal cortex were performed in freely moving NTG (n=5) and hAPPJ20 (n=11) mice. The intensity of gamma activity (20–80 Hz), frequency of epileptiform discharges (spikes) and exploratory activity were measured in 1-min intervals for 60 min. Numbers in or above bars represent mice.
(**A**) hAPPJ20 mice, but not NTG controls, displayed frequent spikes.
(**B**) Low and high gamma intensities were arbitrarily defined in each mouse as minutes with values below or above 50% of the total gamma intensity amplitude (left). Minutes of EEG recording with low intensity of gamma activity had higher spike rates than minutes with high intensity of gamma activity (right) in hAPPJ20 mice.
(**C**) Increased gamma activity during exploratory (Expl.) behavior (left) was associated with decreased epileptiform discharges (right) in hAPPJ20 mice. $^{**}p < 0.01$, $^{***}p < 0.001$ by two-sample unpaired (A) or paired (B, C) Student's t test. Values in bar graphs are mean ± SEM.

Figure S2. Spike Trains Recorded from GAD67^{eGFP} Interneurons in Layer II/III of the Parietal Cortex.
(**A**) Spike traces recorded from GFP-positive interneurons of GAD67^{eGFP} transgenic mice without (NTG/GAD67^{eGFP}; black) or with hAPP (hAPPJ20/GAD67^{eGFP}; red) expression evoked by 800-ms current of 300, 380, and 460 pA. All neurons recorded showed fast-spiking phenotypes. At threshold, these neurons displayed stuttering (above) or tonic (below) firing patterns in both genotypes.
(**B**) Current (I)-spike frequency curves for GAD67^{eGFP} interneurons in NTG/GAD67^{eGFP} (black; n= 14 cells) and hAPPJ20/GAD67^{eGFP} mice (red; n = 10 cells) were obtained using 800-ms current steps with increments of 20 pA. Values are mean ± SEM.
(**C**) Coefficient of variation of the interspike interval (CVISI) for spike trains recorded in (B) that displayed ≥ 3 spikes. Values are mean ± SEM.
(**D**–**F**) Effect of reducing the sodium conductance on firing properties in a single compartment model of a cortical fast-spiking interneuron. To simulate firing in fast-spiking interneuron, we used the model developed by Golomb et al. (2007). The model incorporates a voltage-gated Na+ current, a delayed rectifier K+ current, a D-type K+ current and a leak current (Golomb et al., 2007). The only parameter that was varied in this published model was θm, which controls the strength of the window Na+ current, and gd which specifies the maximal D-type K+ conductance. For these simulations, we set θm = -24 mV and gd = 1.8 mS/cm2, and tested the effects of reducing the maximal Na+ conductance (gNa) from a starting value of 112.5 mS/cm2. (**D**) Effect of reducing gNa on the shape of action potentials evoked by a step current of 6 μA/cm^2. (**E**) Effect of reducing gNa on the action potential amplitude, measured from the peak to the trough of the after-hyperpolarization, on absolute and relative amplitude. (**F**) Input-output curves, showing spike rates evoked by 800-ms current steps for three different values of gNa. More than a 65% reduction in gNa was required to induce a failure to maintain high frequency spike rates over this stimulus range.

Reference:
Golomb, D., Donner, K., Shacham, L., Shlosberg, D., Amitai, Y., and Hansel, D, (2007). Mechanisms of firing patterns in fast-spiking cortical interneurons. PLoS Comput Biol 3(8):e156

Figure S3. Nav1.1 Is Expressed by PV/GABAergic Interneurons In Vivo.
(**A**) Nav1.1 *in situ* hybridization was performed on floating coronal sections of brains from NTG mice. Nav1.1 mRNA was prominently expressed in the parietal cortex (PC; between arrowheads). Double *in situ* hybridization for Nav1.1 (black) and immunohistochemistry for PV

(brown) on 30-μm floating sections from NTG mice revealed that Nav1.1 is expressed by PV-positive GABAergic interneurons in different brain regions.
(**B**) Double fluorescence *in situ* hybridization for Nav1.6 (red) and immunohistochemistry for PV (green) were performed on 10-μm cryosections from NTG mice. Nav1.6 mRNA was expressed by glutamatergic and PV/GABAergic cells in the hippocampus but predominantly expressed by PV/GABAergic cells in the parietal cortex. Arrowheads in bottom panel (merged) indicate cells double-labeled for Nav1.6 and PV (yellow) or positive for Nav1.6 (red) or PV (green) only.
(**C**) Primary neocortical neurons were prepared from neonatal NTG mice, maintained in vitro for 2 weeks, and immunostained for GAD67 (red) and Nav1.1 (green; top panels) or Nav1.6 (green; bottom panels). Nuclei were counterstained with DAPI (blue). Nav1.1 was expressed exclusively by GABAergic cells (yellow arrowheads), whereas Nav1.6 was also expressed by non-GABAergic cells (white arrowheads).
(**D**) Western blots showing the levels of Nav1.1, Nav1.6, and interneuronal subpopulation markers in different brain regions of NTG mice. Consistent with our Nav1.1 and Nav1.6 *in situ* hybridization data, Nav1.1 was prominently expressed in the parietal cortex. CR, calretinin; CB, calbindin; DG, dentate gyrus; EC, entorhinal cortex; FC, frontal cortex; HIP, hippocampus; PC, parietal cortex. Scale bars: 1 mm (A, top left panels); 10 μm (A, top right and bottom panels); 50 μm (B).

Figure S4. Inhibition of VGSCs Reduces Gamma Activity and Enhances Hypersynchrony in hAPPJ20 Mice. EEG recordings from the left (L) and right (R) parietal cortex (PC) were performed in hAPPJ20 and NTG mice before and after i.p. injection of the VGSC blocker riluzole (20 mg/kg) or phenytoin (100 mg/kg).
(**A**) Riluzole reduced gamma activity and increased spike frequency independently of changes in exploratory behavior. Compared with baseline levels (dash lines), riluzole-treated hAPPJ20 mice with (light blue; inactive) or without (dark blue; active) reduced exploratory behavior (left) had similar levels of gamma activity (center) and spike frequency (right). Numbers in bars are mice.
(**B**) hAPPJ20 mice, but not NTG controls, displayed frequent epileptiform discharges at baseline. Phenytoin increased the frequency of the spikes in hAPPJ20 mice but not in NTG controls.
(**C**) Details of epileptiform discharges indicated in gray in (B).

Figure S5. Increasing Nav1.1 Levels Reduces Context-dependent Learning Deficits in hAPPJ20 mice. Activity of the indicated groups of mice in a novel open field during an initial two days of testing and during retesting in the same arena on days 7 and 23-24. Only mice with comparable levels of activity on trial 1 were included in this analysis (Figure 7C includes all mice tested). In all three test periods, bigenic mice habituated faster and more completely than hAPPJ20 mice. *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ by two-way repeated-measures ANOVA and Bonferroni test. Asterisks indicate differences between NTG and hAPPJ20 mice. No significant differences were detected between bigenic and NTG or Nav1.1 mice.

SUPLEMENTAL TABLE

Table S1. Spike Properties of Fast-spiking GABAergic Interneurons and Pyramidal Neurons in Layer II/III of the Parietal Cortex in GAD67^{eGFP} Mice with or without hAPP Expression.

Synaptic alterations in fast-spiking GABAergic cells of the parietal cortex in GAD67^{eGFP} transgenic mice without (NTG/GAD67^{eGFP}) or with hAPP (hAPPJ20/GAD67^{eGFP}) expression (top). Synaptic alterations in layer II/III pyramidal neurons (Pyr) of the parietal cortex in hAPPJ20 (hAPPJ20/Pyr) and NTG (NTG/Pyr) mice (bottom). AHP, afterphyperpolarization; Cm, membrane capacitance; Ri, input resistance; RMP, resting membrane potential. Values are mean ± SEM. *$p<0.05$ by Student's t test.

EXTENDED EXPERIMENTAL PROCEDURES

Transgenic Mice

We studied heterozygous transgenic C57BL/6J mice expressing hAPP with the Swedish and Indiana FAD mutations and NTG littermate controls from line J20 (hAPPJ20 mice) (Mucke et al., 2000). For some experiments, hAPPJ20 mice were crossed with BAC transgenic C57BL/6J mice expressing eGFP directed by GAD67 regulatory sequences (Jackson Laboratory; strain: CB6-Tg(Gad1-EGFP)G42Zjh/J, line G42) (Chattopadhyaya et al., 2004) or BAC-Nav1.1 transgenic FVB/N mice from line 1 overexpressing wildtype murine Nav1.1 (Tang et al., 2009). In both crosses, we analyzed F1 offspring. Unless indicated otherwise, measurements were performed on sex-balanced groups at 4 to 7 months of age by investigators who were unaware of the genotype or treatment of the mice. For harvesting of brain tissue, mice were deeply anesthetized and flush-perfused transcardially with phosphate buffer. Hemibrains were drop-fixed in 4% phosphate-buffered paraformaldehyde or stored at –70°C. All experiments were approved by the Institutional Animal Care and Use Committee of the University of California, San Francisco.

Human Tissues

Inferior parietal cortex was dissected from frozen brains of 22 AD cases (age 78.4±10.8 years, mean±SD) and seven nondemented controls (age 83.5±15.3 years) from the Alzheimer's Disease Research Center, University of California, San Diego. AD was diagnosed according to the criteria of the Consortium to Establish a Registry for Alzheimer's Disease and the National Institute on Aging. Diagnoses were confirmed by the presence of amyloid plaques and neurofibrillary tangles in formalin-fixed tissue from the opposite hemibrain.

Immunohistochemistry

Tissue preparation and immunohistochemistry were performed as described (Palop et al., 2011a; Palop et al., 2011b). Primary antibodies used included rabbit anti-parvalbumin (1:5,000; Swant), rabbit anti-Nav1.1 (1:200; Alomone Labs), rabbit anti-Nav1.6 (1:1,000; Alomone Labs), and mouse anti-GAD67 (1,000; Chemicon). Primary antibodies were detected with biotinylated goat anti-rabbit (1:200; Vector Laboratories, Burlingame, CA) or with fluorescein-labeled donkey anti-rabbit (1:300, Jackson ImmunoResearch, West Grove, PA), Alexa 594 donkey anti-mouse (1:500; Invitrogen), or Alexa 488 donkey anti-rabbit (1:250; Invitrogen).

In Situ Hybridization

Tissue preparation and *in situ* hybridization were performed as described (Palop et al., 2011a; Palop et al., 2011b). Antisense and sense RNA probes were generated from linearized plasmids (NCBI#: BE944238 for Nav1.1 and AI839069 for Nav1.6) containing DNA sequences for Nav1.1 (327 base pairs) or Nav1.6 (289 base pairs) with T3 and T7 polymerase (Promega, Madison, WI) and premixed RNA-labeling nucleotides containing digoxigenin (Roche Molecular Biochemicals, Palo Alto, CA). For double fluorescence *in situ* hybridization plus immunohistochemistry, digoxigenin-labeled probes were detected with the HNPP fluorescent detection set (Roche), followed by standard fluorescence immunohistochemistry with polyclonal anti-PV (1:1000; Swant Swiss Abs) or anti-GFP (1:500; Molecular Probes) antibodies. Nav1.1- and PV-positive neurons (Figure 3; arrowheads) were quantified in two consecutive sections 100 μm apart from 4–7-month-old NTG (n=3), hAPPJ20 (n=4), and GAD67^{eGFP} (n=2) mice. Neurons with robust Nav1.1 or PV (Figure 3; arrowheads) expression were counted. In all, 551 neurons positive for PV and/or Nav1.1 were identified and analyzed. Because *Nav1.1* mRNA and PV expression did not show complete co-location, the proportion of PV-positive cells

expressing *Nav1.1* mRNA (PV+/*Nav1.1*+) and the relative *Nav1.1* mRNA signal intensity in PV cells were calculated for each genotype.

Western Blot Analysis

Microdissections and western blot analysis were performed as described (Palop et al., 2005). Primary antibodies included rabbit anti-Nav1.1 (1:1,000; Alomone labs; amino acid residues (aa), 465–481, TASEHSREPSAAGRLSD), rabbit anti-Nav1.2 (1:2,000; Alomone labs; aa 467–485, ASAESRDFSGAGGIGVFSE), rabbit anti-Nav1.3 (1:200; Alomone Labs; aa 511–524, HLEGNHRADGDRFP), rabbit anti-Nav1.6 (1:5,000; Alomone Labs; aa 1042–1061, CIANHTGVDIHRNGDFQKNG), rabbit anti-GAD67 (1:1,000; Millipore), rabbit anti-calretinin (1:5,000; Swant), rabbit anti-parvalbumin (1:10,000; Swant), rabbit anti-calbindin (1:15,000; Swant), mouse anti-reelin (1:1,000; Millipore), and mouse anti-α-tubulin (1:1,000,000; Sigma). Primary antibodies were detected with horseradish peroxidase–conjugated secondary anti-mouse IgG antibody (1:10,000; Calbiochem) or HRP-conjugated goat anti-rabbit IgG (1:5,000; Calbiochem). Bands were visualized by ECL and quantitated densitometrically with ImageQuant software (Molecular Dynamics, Sunnyvale, CA). α-tubulin (α-Tub) served as a loading control.

Slice Electrophysiology for hAPPJ20 x GAD67^{eGFP}-BAC Mice

Mice were anesthetized with halothane and decapitated, according to a protocol approved by the UCLA Chancellor's Animal Research Committee. Brains were removed and placed in ice-cold cutting solution, containing (in mM): N-methyl d-glucamine (135), KCl (1), $CaCl_2$ (0.5), $MgCl_2$ (1.5), KH_2PO_4 (1.2), choline bicarbonate (20), D-glucose (10), with pH adjusted to 7.4 with HCl (giving a final [Cl^-] of ~145 mM). Coronal slices of the parietal cortex, 350 µm thick, were cut with a Microm HM 650 V vibratome (Thermo Scientific). Slices were maintained at room temperature in an interface chamber between humidified carbogen gas (95% O_2/5% CO_2) and artificial cerebrospinal fluid (aCSF), containing (in mM): NaCl (126), KCl (2.5), $CaCl_2$ (2), $MgCl_2$ (2), NaH_2PO_4 (1.25), $NaHCO_3$ (26), and D-glucose (10), pH 7.3–7.4 when bubbled with carbogen gas. Cortical slices were transferred to a submerged chamber and superfused at 5–8 ml/min with CSF at 32–34^{o}C. Neurons were visualized by IR-DIC videomicroscopy (Olympus, Melville, NY; BX51WI, 40x water-immersion objective). For whole-cell voltage-clamp recordings from pyramidal neurons, patch pipettes were filled with an internal solution containing (in mM): cesium-methylsulfonate (140), HEPES (10), EGTA (0.2), NaCl (5), MgATP (2), and NaGTP (0.2), and signals were acquired with an Axopatch 200A amplifier (Molecular Devices, Sunnyvale, CA). Series resistance and whole-cell capacitance were estimated and compensated to 70–80% (lag 7 µs). sIPSCs were recorded at the reversal potential of ionotropic glutamate receptors (0 mV); sEPSCs were recorded at the reversal potential of $GABA_A$ receptors (-65 mV); mIPSCs and mEPSCs were recorded in the presence of 0.5 µM tetrodotoxin and 50 µM $CdCl_2$. For whole-cell current-clamp recordings from GAD67^{eGFP} interneurons, patch pipettes were filled with an internal solution containing (in mM): K-gluconate (135), HEPES (10), EGTA (0.1), KCl (5), $MgCl_2$ (2), Na-ATP (4), and Na-GTP (0.3), and signals were acquired with an Axoclamp 2A amplifier (Molecular Devices). Recordings were discontinued if series resistance increased by >25%.

For analysis of intrinsic properties of neurons recorded in current-clamp mode, input resistance was estimated at the resting membrane potential in response to 500-ms hyperpolarizing current steps of 20–40 pA. The membrane time constant and capacitance were estimated by fitting single exponentials to initial phases of these voltage responses. For analysis of action potential properties, neurons were recorded at resting or at -70 mV membrane potentials and depolarized with 800-ms current steps in 20-pA increments.

Voltage- and current-clamp recordings were analyzed in Igor Pro (Wavemetrics, Lake Oswego, OR) with custom-written procedures. For detection of synaptic events in voltage-clamp recordings, the signal was low-pass filtered at 500 Hz. Events were initially detected as

deflections exceeding 5–7 pA above a running 2-ms baseline mean; subsequently, events less than 5 SD above the baseline noise were rejected. To avoid multiple detections of large events, the event-detection algorithm recommenced after the peak of each detected event. Event detection was checked visually. To compare event amplitudes and interevent intervals, 500 consecutive events were sampled from each recording, starting at a random time point. These sampled events were used to both calculate the median values for each recording and to generate cumulative probability histograms for each genotype. Differences in the cumulative probability histograms were measured with the Kolmogorov–Smirnov statistic; statistical significance was evaluated by bootstrapping with blocks of 500 consecutive events from the pooled data set with 1000 repeats.

Slice Electrophysiology for hAPPJ20 x Nav1.1-BAC Mice

Mice were anesthetized with Avertin (tribromoethanol, 250 mg/kg) and decapitated, according to a protocol approved by the Institutional Animal Care and Use Committee at the University of California, San Francisco. Coronal sections 300 µm thick containing parietal cortex were prepared from 2.5–4-month-old mice. Slices were prepared on a Leica VT1000S vibratome in an ice-cold sucrose cutting solution (in mM): 79 NaCl, 23 $NaHCO_3$, 68 sucrose, 12 glucose, 2.3 KCl, 1.1 NaH_2PO_4, 6 $MgCl_2$, and 0.5 $CaCl_2$. Slices were transferred to a chamber filled with warmed carbogenated ACSF containing (in mM): 125 NaCl, 26 $NaHCO_3$, 2.5 KCl, 1 $MgCl_2$, 2 $CaCl_2$, 1.25 NaH_2PO_4, and 12.5 glucose and were incubated at 31–33ºC for 30 minutes and allowed to recover at room temperature for 30 minutes before recording.

For whole-cell voltage-clamp recordings from pyramidal neurons, patch pipettes were filled with an internal solution containing (in mM): 120 $CsMeSo_3$, 0.5 EGTA, 10 BAPTA, 10 Hepes, 2 Mg-ATP, 0.3 Na-GTP, 5 QX-314, pH 7.25. All recordings were performed at 31–33ºC in ACSF. sIPSCs were recorded at the reversal potential of ionotropic glutamate receptors (0 mV). Data were collected with a MultiClamp 700B amplifier (Molecular Devices) and ITC-18 A/D board (HEKA) using Igor Pro software (Wavemetrics) and custom acquisition routines (mafPC, courtesy of M.A. Xu-Friedman). For detection of synaptic events in voltage-clamp recordings, the signal was low-pass filtered at 500 Hz. Events were detected as deflections >5 pA above baseline. Event detection was checked visually. To compare event amplitudes and interevent intervals, 1000 consecutive events were sampled from each recording. Voltage clamp recordings were filtered at 2 kHz and digitized at 10 kHz. Electrodes were made from borosilicate glass (pipette resistance, 2–4 MΩ). During recordings, R_{series} was monitored and recordings were terminated if R_{series} changed by >30% or R_{series} exceeded 25 MΩ. R_{series} compensation was applied.

EEG Recordings

Mice were implanted for video EEG monitoring after anesthesia with intraperitoneal Avertin (tribromoethanol, 250 mg/kg). Teflon-coated silver wire electrodes (0.125-mm diameter) soldered to a multichannel electrical connector were implanted into the subdural space over the left frontal cortex (1 mm lateral and anterior to the bregma) and the left and right parietal cortex (2 mm lateral and posterior to the bregma). The left frontal cortex electrode was used as a reference. All EEG recordings were carried out at least 10 days after surgery on freely moving mice in a recording chamber of 225 cm^2. Mice were fully habituated to the EEG setting for 24 hours before the experiments were conducted. EEG activity was recorded with the Harmonie software (version 5.0b, Stellate, Canada) for 3 h before and 24 h after phenytoin or riluzole injection. The number of sharp-wave discharges were automatically detected by the Gotman spike detectors (Harmonie, Stellate) with a threshold of 6x (sharp-waves larger than 6 times the mean EEG amplitude) and manually verified to exclude artifacts. For spectral analysis of EEG recordings, segments of 60 minutes of unfiltered EEG recordings (sampling rate 200 s^{-1}) from freely moving animals were analyzed using a custom-written procedure running under IGOR

Pro v6.12A (Lake Oswego, OR). Nonconvulsive seizures were observed in ~10% of hAPPJ20 mice during the ~24h of EEG recordings. None of the EEG recording segments used for gamma or spike analyses contained seizure activity.

For spectral analysis of EEGs, a series of Gabor FFT windows shifting with 64 points across the entire data segment were used, and the magnitude of the spectrum was obtained as the square root of the sum of the squared real part and the squared imaginary part. Thus, the magnitude of the spectrum is a real quantity and represents the total signal amplitude in each frequency bin (0.25 Hz bins) independent of phase. The gamma frequency band (gamma activity) represents the average of the spectral values in the 20–80 Hz range (Barth and Mody, 2011). The gamma activity values for each 0.32 s epoch were further averaged over 60 s of EEG recording. Low, intermediate and high intensity of gamma activities were defined as minutes with values <30%, 30–60%, >60% of the total amplitude of the gamma activity.

Drug Treatments

For acute treatment during EEG recordings (Figures 4A, B and S4), riluzole was dissolved at 2 mg/ml in 50% polyethylene glycol 400 in distilled water and injected IP at 20 mg/kg. Phenytoin was dissolved at 10 mg/ml in phosphate-buffered saline and injected IP at 100 mg/kg. For chronic treatment during behavioral testing (Figures 4D–F), phenytoin was dissolved every day in the drinking water at 0.15–0.75 mg/ml to reach final doses of 25, 50, 70, and 85 mg/kg/day.

Morris Water Maze

The water maze pool (122 cm diameter) contained opaque water with a 14-cm^2 platform submerged 2 cm below the surface. For spatial training sessions, mice were trained to locate the hidden platform over 5 consecutive days (two sessions of two trials per day, 4 h apart). The platform location was constant in hidden platform sessions and entry points were changed semirandomly between trials. Four hours after the last training session, the platform was removed and a 60-sec probe trial was performed. Cued training sessions with a black and white striped mast mounted above the platform were performed two days later. Mice were trained to locate the visible platform over two sessions of two trials each, where the platform location was changed for each session. Performance was monitored with an EthoVision video tracking system (Noldus Information Technology).

Open Field Behavior

Exploratory locomotor activity was measured in an open field (automated Flex-Field/Open Field Photobeam Activity System; San Diego Instruments). Mice were placed in one of four identical clear plastic chambers (40 x 40 x 30 cm) for 5 min (Figure 7) or 15 min (Figure 4), with two 16 x 16 photobeam arrays to detect horizontal and vertical movements. Total movements in the open field were reported. Each mouse was always retested in the same chamber. The apparatus was cleaned with 70% ethanol between trials.

Statistical analysis

Statistical analyses were performed with SPSS 10.0, STATA 11.2, or Prism 5.0. Experimenters were blinded with respect to genotype and treatment of mice and to diagnosis of human cases. Unless indicated otherwise, differences between two means were assessed by unpaired, two-tailed Student's *t* test and differences among multiple means by one-way ANOVA and Tukey-Kramer *post hoc* or contrast tests. Learning curves in the Morris water maze and in the open field were analyzed by two-way repeated-measures ANOVA and Bonferroni posttest. Before and after treatment effects were assessed by paired two-tailed Student's t test. Null hypotheses were rejected at the 0.05 level.

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