SUPPLEMENTARY INFORMATION

Extended Materials and Methods

Immunohistochemistry

Mice were transcardially perfused with phosphate-buffered saline (PBS, pH 7.4, Gibco) followed by 4% formaldehyde in PBS, and brains were post-fixed overnight at 4°C. Free floating sections (30 µm) were cut using a vibratome (Leica VT100) and incubated with blocking solution (10% donkey serum in PBS with 0.3% Triton-X 100) for 1 h at room temperature, then incubated at room temperature over night with primary antibody diluted in blocking solution followed by staining with secondary antibodies after extensive washing in PBS. Sections were mounted on glass slides with Vectashield plus DAPI (Vector) and coverslipped.

Quantification

For quantification of recombination (n = 1 representative animals per time point) in S1, every PV+ cell was counted and scored for co-labeling with EYFP using ImageJ (4-11 sections / animal; 853-1760 PV+ cells scored per animal). For quantification of recombination in hippocampus (n = 1 representative animals per time point) every PV+ cell (729-981 cells / animal) in dentate gyrus, CA1, CA2 and CA3 was counted and scored for co-labeling with EYFP (10-12 sections / animal). For quantification of the number and distribution of PV+ cells in S1 in NR1f/f and PV-Cre/NR1f/f mice (n= 3 per genotype; every third 30 µm section was counted, 6 sections / animal) to include all six cortical layers, and every PV+ cell was counted in ImageJ and assigned to layers 2/3 or 4-

6 based on its position in relation to the layer 4 barrels. 1329-1571 cells per animals were counted.

Slice electrophysiology

For identification of the parvalbumin positive interneurons by the expression of the mCherry fluorescent protein during slice electrophysiology, PV-Cre mice were used as controls. Mice were anesthetized with an intraperitoneal injection of a mixture of ketamine (1.1 mg/kg) and xylazine (0.16 mg/kg) and AAV DIO ChR2-mCherry (*1*) was injected into hippocampus (1.8 mm posterior to bregma and 1.5 mm from the midline; n = 5 PV-Cre and 5 PV-Cre/NR1f/f mice, 5-7-week old. 7-10 days after viral transduction transverse hippocampal slices (400 μm thickness) were prepared in ice-cold dissection buffer (in mM: 238 sucrose, 2.5 KCl, 1 $CaCl_2$, 5 $MgCl_2$, 26 $NaHCO_3$, 1 NaH_2PO_4, 11 glucose, gassed with 5% CO_2/95% O_2, pH 7.4) as described (*2, 3*). Slices were incubated in an interface incubation chamber containing extracellular artificial cerebrospinal fluid (aCSF; in mM: 119 NaCl, 2.5 KCl, 2.5 $CaCl_2$, 1.3 $MgCl_2$, 26 $NaHCO_3$, 1 NaH_2PO_4, 11 glucose, gassed with 5% CO_2/95% O_2, pH 7.4) and allowed to recover for 30 min at 30°C, then maintained at room temperature (24-26°C) at least 30 min. Slices were then transferred to a submerged recording chamber, and continuously perfused with aCSF. The tungsten bipolar electrode (FHC) was placed in the stratum radiatum or oriens and the Schaffer collateral/commissural fibers were stimulated at 0.1 Hz. The patch recording pipettes (2-5 MΩ) for whole-cell recording were filled with internal solution containing (in mM): 115 cesium methanesulfonate, 20 CsCl, 10 HEPES, 2.5 $MgCl_2$, 4 adenosine triphosphate disodium salt, 0.4 guanosine triphosphate trisodium salt, 10

sodium phosphocreatine, and 0.6 EGTA, at pH 7.25 with CsOH. Picrotoxin (0.15 mM, Sigma) was dissolved in aCSF to block $GABA_A$ receptor-mediated synaptic transmission for whole-cell patch clamp recordings. All experiments were performed at room temperature 24-26 °C. All experiments and the analysis of data were performed in a blind manner. Recordings were performed using a MultiClamp 700B amplifier and Digidata 1440A, and data was acquired and analyzed using Clampex 10 and Clampfit 10 (Axon Instruments). Results are reported as mean ± SEM. Statistical significance was evaluated by Student-t test with statistical significance set at $P < 0.05$.

Anesthetized electrophysiology

For all anesthetized electrophysiology PV-Cre mice were used as controls to enable expression of ChR2-mCherry in FS-PV+ interneurons in both genotypes. The scalp incision was sutured, and post-injection analgesics were given to aid recovery (0.1 mg/kg Buprenex).

Mice were anesthetized with isoflurane and held in place with a head post cemented to the skull. All incisions were infiltrated with lidocaine. A small craniotomy was made over barrel cortex approx 200 μm posterior to the virus injection site. Extracellular single-unit and local field potential recordings were made with tetrodes or stereotrodes. Stimulus control and data acquisition was performed using software custom written in LabView (National Instruments, Austin TX) and Matlab (The Mathworks, Natick MA) by Ulf Knoblich.

Light stimulation was generated by a 473 nm laser (Shanghai Dream Lasers, Shanghai, China) controlled by Grass stimulator (Grass Technologies, West Warwick,

RI) or computer. Light pulses were given via a 200 μm diameter, unjacketed optical fiber (Ocean Optics, Dunedin FL) positioned at the cortical surface. For experiments using the broad range of light stimulation frequencies (8, 16, 24, 32, 40, 48, 80, 100, and 200 Hz), we stimulated in bouts of 3 s of 1 ms pulses at 46 mW/mm^2 at each frequency in random order. For broadband light stimulation we gave 3 s bouts of 1 ms light pulses at frequencies randomly selected from an even distribution of 5-200 Hz.

Spike waveforms of RS and FS cells were characterized, as shown in the examples below. Units were hand-separated post-hoc using manual cluster-cutting software (SpikeSort3D, Neuralynx). Cross correlation analysis was used to confirm unit separation. Units that were not easily separable were discarded. Spike waveforms of RS and FS cells were characterized, as shown in the examples below, by measuring (1) the ratio between the amplitude of the initial peak (a) to the following trough (b) and (2) the duration of the spike at half height (c). Dotted line indicates mean baseline level in the absence of spikes.
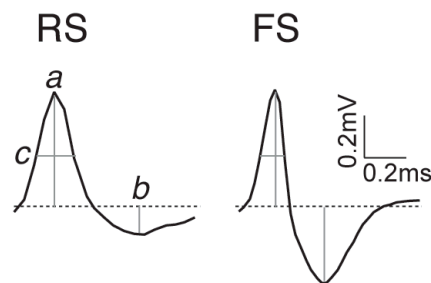
In PV-Cre mice, mean FS spike width was 163.1 ± 3.2 ms and peak:trough ratio was 1.3 ± 0.03 (n = 50). Mean RS spike width was 267.4 ± 6.4 ms and peak:trough ratio was

2.25 ± 0.06 (n = 18). In PV-Cre/NR1f/f mice, mean FS spike width was 172 ± 5.7 ms and peak:trough ratio was 1.4 ± 0.02 (n = 32). Mean RS spike width was 257 ± 9.7 ms and peak:trough ratio was 2.32 ± 0.08 (n = 16). In both PV-Cre and PV-Cre/NR1f/f mice, FS and RS cells were significantly different in both spike width ($P < 0.01$ in both sets of mice; Mann-Whitney test) and peak:trough ratio ($P < 0.01$ in both sets of mice).

To quantify the relative power (P_{rel}) within a specific frequency band (e.g., 36-44 Hz), we calculated the power within that band (P_{36-44}) divided by the total power from 1 to 100 Hz (P_{1-100}) as follows: $P_{rel} = P_{36-44}/P_{1-100}$. To quantify the changes in the power within a specific frequency band in response to optogenetic manipulation, we computed the relative power ratio (P_{ratio}) using the relative power in that band during light stimulation (Light) and without light stimulation (Baseline) as follows: $P_{ratio} = P_{rel\ Light}/P_{rel\ Baseline}$. If the relative power in a range did not change with light stimulation, the expected relative power ratio was 1.

Awake electrophysiology

After implantation of electrodes, animals were allowed to recover for 4-5 days before recording. Recording sessions took place in an empty box (L30 cm x W19 cm x H13 cm). Electrophysiological signals were filtered between 0.1 and 9000 Hz and were digitized at a rate of 30 kHz using a Neuralynx data acquisition system (Neuralynx, Inc., Bozeman, MT). All analysis was performed offline in Matlab. Signals were downsampled to 947 Hz. Multi-taper spectral methods were used for all analyses in the frequency domain. Gamma events were found by filtering data between 30 and 50 Hz (126th order FIR filter) and taking the Hilbert transform to compute the envelope. A 1 s moving average

window was applied to the envelope, and a gamma epoch was said to occur when the envelope remained above the mean for a predetermined amount of time. The data from two animals (one of each genotype) were contaminated with 60-Hz noise, presumably due to improper grounding. These animals were excluded from the analysis.

Mouse behavior

Open field analysis

Activity in a novel open field (42W cm x 42D cm x 30.5H cm) was measured with a VersaMax Animal Activity Monitoring System (AccuScan Instruments). Each monitor consisted of sets of 16 light beams arrays in the horizontal X and Y axes, spaced 1.0" apart. One mouse was placed in each monitor and during 60 min the hardware detected beams broken by the animal, with the software (VersaMax, AccuScan Instruments) determining the location and activity of the animal. For the pharmacological treatment, one set of mice was first monitored in the open field for 30 min. Directly thereafter MK-801 (M107; Sigma) (0.2 or 0.3 mg/kg) was injected intraperitoneally and the mice were monitored for additionally 60 min, in the same boxes as before. Behavioral parameters analyzed included horizontal activity, total distance (cm), number of movements, movement time (sec), resting time (sec), vertical activity, number of vertical movements, vertical time (sec), stereotype counts, number of stereotypy, stereotype time (sec), margin distance (cm), margin time (sec), center distance (cm), center time (sec), rearing activity, number of rearing movements, and rearing time (sec), according to the manufacturer's definitions.

Acoustic startle and prepulse inhibition

The startle chamber (inner dimensions: 27W cm x 27H cm x 16D cm) consists of a speaker mounted on the top and a piezoelectric sensing platform on the floor. The animals were first habituated to the experimental equipment for two days, with each mice being placed in a startle chamber and exposed to 65 dB ambient noise for 5 min. Day three, the PPI testing day, each animal was exposed to 65 dB ambient noise for 5 min followed by the testing session. The PPI paradigm consisted of trials with presentation of a startle stimulus (120 dB, 40 ms) alone and trials where a prepulse of different intensities (70, 75, 80, 85 or 90 dB; 20 ms) preceded the startle stimulus by 100 ms. Trials were presented in blocks, with each block consisting of one startle stimulus alone trial, each of the prepulse-pulse stimulus trials, and a no stimulus trial, in a fixed pseudo randomized order. A total of six blocks were presented in a session and corresponding responses were averaged for each mouse and trial separately. The maximum response in Newton (N) within 65 ms post-stimulus was utilized as the startle amplitude. The acoustic startle response (ASR) was calculated as the mean startle amplitude of the pulse-alone trials. The percent PPI was calculated using the following equation: [100-(mean Prepulse response/mean ASR) x 100)]. The acoustic startle threshold was assessed in the same apparatus by determining the startle response to increasing sound intensities (70, 75, 80, 85, 90, 95, 100, 105, 110, 115 and 120 dB) presented in six blocks in fixed pseudo-randomized order.

T-maze test

A modified T-maze, the discrete paired-trial variable-delay alternation task, was used (*4*). In brief, during the adaptation procedure animals were handled and exposed to the T-maze for 5 days (*4*). Thereafter a training period followed, with 3 days of ten forced-alternation runs - in the first run one goal arm was closed off and the other arm was kept open and contained a reward. In the following forced run the animals had access only to the opposite arm they had visited previously with a reward. The reward consisted of 70 μl of a 50/50 condensed milk/water drop and both arms had reward containers throughout the trials to avoid visual cues of the reward. The animals were placed in a holding cage between runs. Next, the discrete paired-trial delayed alternation training began. Each discrete trial consisted of a forced run and a choice run. In the forced run one goal arm was closed off and the other arm was kept open and contained a reward. After consuming the reward and spending a retention interval in the holding cage, the animals were placed back in the maze for the choice run. In the choice run the animals had access to both arms but only the opposite arm to the one entered in the previous forced run contained a reward. After an intertrial period of 45 s the animals were placed back in the maze for the next forced run. A different, randomly chosen pattern of forced runs was used every day (e.g. L-L-R-L-L-R-R-L-R-R) to avoid learning of any trial sequence. Animals were trained at a 5 s retention interval for 10 days or until successfully performing seven out of ten trials for 3 days in a row. Thereafter followed the working memory test for 3 consecutive days, using the same intratrial interval during 10 trials for each mouse per day, and repeated for 3 different intratrial intervals (i.e. 1 s, 20 s, 40 s).

Contextual and cued fear conditioning

Context-dependent fear conditioning: Foot chock (2 s; 0.7 mA constant current). Presence of freezing, defined as a lack of movement except for heartbeat and respiration associated with a crouching posture, was scored every 10 s by two observers to a total of 18 observations (10 s x 18 = 180 s = 3 min). The number of observations indicating freezing obtained as a mean from both observers was expressed as a percentage of the total number of observations.

Tone-dependent (cued) fear conditioning: Auditory cue (20 kHz, 75 dB sound pressure level (SPL)) coterminated with a foot shock (2 s, 0.8 mA constant current). When the animals were returned to the changed chamber after 24h, the animals were allowed to explore for 3 min where after they were exposed to a 3 min tone (10 kHz, 75 dB SPL). During the tone, freezing was scored every 10 s as described for the context-dependent fear conditioning.

Water Maze

The spatial reference task was a water maze task performed in a circular tank (diameter 1.8 m) filled with opaque water (24 ^{o}C). A fixed platform (10 cm diameter) was hidden below the water's surface in the centre of the target quadrant. The behavior of the mice was recorded using video camera and subsequently analyzed by software (TSE-Systems). Mice were placed into the maze from three fixed random points during training sessions. Mice were allowed to search for the platform for 60 s. Mice that did not find the platform within 60 s were gently guided to it and allowed to remain on the platform for 10 s. Two training trials were given every day with an intertrial interval of 5 min. During the probe

trial, the platform was removed and the mice were allowed to search for the platform for 60 s. Reversal training started the day after the probe trial, with the fixed platform moved to the quadrant opposite of the target quadrant in the initial training sessions. The same training procedure was conducted for the new platform location followed by a probe trial for the new target quadrant.

Modeling

Models used to simulate baseline activity (Supplementary Figure 3a and b) contained 20 excitatory and 10 inhibitory cells, modeled as simplified "theta" neurons, with individual cells implemented as in (*5*). Connectivity in this network is all to all. Synaptic weights, in the same notation as in (*5*), are g_{ie}=0.01, g_{ei}=0.025, g_{ee}=0.0175. All cells receive background noise an independent poisson train of excitatory input at an average rate of 100 Hz. In the same notation as the previous work, parameter b, which controls excitability such that a more negative value indicates less excitability, is set at -0.01 for all cells for control model cells (Supplementary Figure 3a, black trace), at -0.03 in inhibitory and -0.01 in excitatory cells for the PV-Cre/NR1f/f model cells (Supplementary Figure 3a and b, red traces), and at -0.03 in inhibitory and -0.02 in excitatory cells to model MK-801 application (Supplementary Figure 3b, orange trace). Signal processing is performed on the modeled LFP signal, which is the average of all EPSPs onto excitatory cells. The modeled LFP signal for each 500 ms trial was processed with a single 500 ms window using the Welch method and smoothed with an averaging window of 16 Hz.

The model used to simulate changes in spike time latency (Supplementary Figure 3c)

contained 10 "theta" neurons, with no reciprocal coupling, and light activation was simulated as 200 ms of 40 Hz excitatory synaptic drive via an EPSP with weight g_di=0.35. For the control case, parameter b is chosen uniformly between -0.03 and 0. For the PV-Cre/NR1f/f case, which is less excitable, parameter b is chosen uniformly between -0.1 and -0.07 in all of the cells.

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