692 **Conditional, astrocyte-specific $GABA_B$ receptor knockout mice (GB1-cKO mice).**
693 Functional $GABA_B$ receptor ablation was investigated in conditional, astrocyte-specific
694 $GABA_B$ receptor knockout mice (GB1-cKO), generated by crossbreeding *Gabbr*$1^{fl/fl}$
695 (RRID:MGI:3512742) (Haller et al., 2004) with GLAST-CreERT2 knockin mice
696 (RRID:MGI:3830051) (Mori et al., 2006). In some of the experiments, mice with
697 astrocytes-specific expression of the genetically encoded Ca^{2+} indicator GCaMP3 were
698 used. For that purpose R26-lsl-GCaMP3 mice (RRID:IMSR_JAX:014538) (Paukert et
699 al., 2014) were crossbred to GB1-cKO and control mice. The selective deletion of the
700 receptor subunit GABBR1 is sufficient to completely block functional $GABA_B$ receptor
701 activity (Bettler et al., 2004). To induce DNA recombination in GLAST-
702 CreERT2x$GABA_B^{fl/fl}$ or GLAST-CreERT2xR26-lsl-GCaMP3 mice (Paukert et al.,
703 2014), tamoxifen (10 mg/ml corn oil, Sigma, St. Louis, USA) was intraperitoneally
704 injected into 3-week-old mice on three consecutive days (100 mg/kg per body weight).
705 21 days after the first injection, mice were started to be analyzed. All mouse lines were
706 maintained in the C57BL/6N background.
707 **Immunohistochemistry.** The animals were anesthetized with Ketamine/Rompun (1.4
708 % ketamine, 0.2 xylazin, 0.9 % NaCl; 5 ml/kg per body weight) and intracardially
709 perfused with ice cold ACFS and subsequently with 4% paraformaldehyde (PFA) in 0.1
710 M phosphate buffer (pH 7.4). The brain was removed, dissected into the two
711 hemispheres, and post fixed for 4-6 hours in 4% PFA in 0.1 M phosphate buffer (pH
712 7.4) at 4 °C. The fixed brain tissue was cut in phosphate buffered saline (PBS) into
713 sagittal sections (50 -70 µm thickness) at a Leica VT1000S vibrato (Leica, Nussloch,
714 Germany). These sections were collected in 24-well tissue culture plates containing
715 PBS. Vibratome sections were incubated for one hour in blocking buffer (0.3% Triton

X-100, 5% horse serum in PBS) at RT (room temperature). The primary antibodies were diluted in the blocking solution and the sections were incubated overnight at 4°C. As marker for GABAergic interneurons mouse anti-GAD67 (RRID: AB_2278725; 1:500) was used. For astrocyte labeling the following antibodies were used: chicken anti-GFAP (RRID:AB_921444; 1:1000), and rabbit anti-GLAST (RRID:AB_304334; 1:250). $GABA_B$ receptors were stained with a guinea pig anti-GABABr1 (RRID:AB_1587048; 1:500). The slices were washed three times for ten min each in 1xPBS. The secondary antibody was diluted in the secondary antibody buffer (2% horse serum in PBS) and incubated for 2 h at room temperature. Secondary antibodies were donkey anti-mouse, anti-goat, and anti-rabbit (1:2000) conjugated with Alexa488, Alexa546, Alexa555, Alexa633, and purchased from Invitrogen (Thermo Fisher Scientific Inc). The sections were finally washed for 3 times with 1xPBS (10 min) and mounted in Aqua polymount (Polysciences). For astrocytic network labeling, after biocytin filling slices were fixed in 4% PFA in 0.1 PBS (pH 7.4) at 4°C. Biocytin was visualized with Alexa488-Streptavidin (RRID: AB_2315383; 1:500) applied in the staining protocol described above for 48 h.

Microscopic analysis and quantification. Confocal images were recorded by laser scanning microscopy (LSM 710, Zeiss**,** Carl Zeiss AG, Jena) using a 40x objective (Plan-Aprochomat 40x/1, 4 Oil DIC (UV) VIS-IR M 27). For excitation of fluorescent dyes, a Lasos Argon laser (454 nm to 514 nm) and a Helium-Neon laser (543 nm, 633 nm) were used. Z-stacks of images were taken at 0.5 mm intervals and processed with ImageJ using the JACoP v2.0 colocalization plugin(Cordelieres and Bolte, 2014). In brief, the deletion of *Gabbr1* was determined as a reduction of its immunolabel within the respective channel of the astroglial glutamate transporter GLAST. The

overlap coefficient and Mander's coefficient M2 were determined. Although both coefficients have their unique limitations, both indicated a significant and astrocyte-specific reduction of *Gabbr1* and were plotted in **Figure 6B** (9 sections from 2 GB1-cKO and 11 sections from 2 control mice; 2-sided; unpaired *t* test). The analysis of co-localization probably underestimates the *Gabbr1* removal, since the spatial resolution in single optical sections is less than the size of the fine astrocyte processes contacting presynaptic terminals that are *Gabbr1*-positive as well.

Quantitative real-time PCR (qRT-PCR). Levels of messenger RNA (mRNA) and genomic DNA were detected by reverse transcriptase PCR. Hippocampi of 7 GB1-cKO and 7 control mice (7 weeks old) were removed from the skull, homogenized (Precellys homogenizer, peqlab, Erlangen, Germany) and divided for RNA extraction with RNeasy mini kit (QIAGEN, Hilden, The Netherlands) as well as for DNA analysis RNA/DNA ALL Prep-Kit (QIAGEN, Hilden, The Netherlands). Successful gene recombination was determined by quantifying the loss of the loxP flanked gene region. Primers were located closely upstream and downstream of the 5' loxP site. Control and cKO were homozygously floxed for the *Gabbr1* locus ($Gabbr1^{fl/fl}$); controls were wild type for the GLAST locus ($GLAST^{+/+}$) and GB1-cKOs were heterozygous for the CreERT2 transgene in the GLAST locus ($GLAST^{CreERT2/+}$). Since only non-recombined alleles were amplified, reduction of the respective PCR signal indicated successful recombination. Values (ΔCT) of GB1-cKO animals were normalized to the mean ΔCT values of control animals.

For quantification of the PCR products, the fluorescent dye EvaGreen (Axon) was used. PCR runs were performed using the CFX96 Real-Time PCR Detection System (BioRad). All reactions were carried out in triplicates. Neuregulin 1 type III (NrgIII)

764 and β-actin were used as endogenous gene controls. Data normalization and analysis
765 were performed with the qbase+ real time PCR data analysis software (Biogazelle)
766 based on the ΔΔCT-method.
767 Primer sequences for CDNA analysis by qRT-PCR were as follows (in 5` to 3`
768 direction): ATPase forward GGA TCT GCT GGC CCC ATA C; ATPase reversed CTT
769 TCC AAC GCC AGC ACC T, b-Actin forward CTT CCT CCC TGG AGA AGA GC;
770 b-Actin reversed ATG CCA CAG GAT TCC ATA CC; *Gabbr1* forward CGA AGC
771 ATT TCC AAC ATG AC; *Gabbr1* reversed CAA GGC CCA GAT AGC ATC ATA.
772 Primer sequences for genomic DNA were as follows: NRGIII forward GTG TGC GGA
773 GAA GGA GAA AAC T; NRGIII reversed AGG CAC AGA GAG GAA TTC ATT
774 TCT TA; b-Actin forward CTG CTC TTT CCC AGA CGA GG; b-Actin reversed AAG
775 GCC ACT TAT CAC CAG CC; *Gabbr1* forward CAG TCG ACA AGC TTA GTG
776 GAT CC, *Gabbr1* reversed TCC TCG ACT GCA GAA TTC CTG.
777 ***In vivo* recordings.** GB1-cKO mice and wild-type littermates (12-16 weeks) were
778 placed in a stereotaxic frame under urethane anaesthesia (1.8 g/kg, intraperitoneal
779 injection), constantly monitored for body temperature and breathing rate, and kept warm
780 with a heating pad. Electrodes were placed stereotaxically according to the
781 atlas(Paxinos, 2012). Local field potentials (LFP) were recorded through stainless steel
782 macroelectrodes (1 MΩ) placed in the CA1 layer (AP, -2; L, 1.4; V, 1.1 mm from
783 Bregma) and amplified (Differential AC Amplifier Model 1700, A-M System),
784 bandpass filtered between 0.1 Hz and 500 kHz, and digitized at 100 kHz (PowerLab
785 4/25T and LabChart, ADInstruments) running in a PC for direct visualization and
786 storage. Then, two nichrome stimulating electrodes (Isolated Pulse Stimulator Model
787 2100, A-M Systems) were placed in the vibrissae. After stabilization and basal activity

recordings, an electrical stimulus (10 Hz, 10 s duration at 10 V) was applied to vibrissae. Three stimuli were applied with an interstimulus period of ≥ 5 minutes.

Six epochs (five second bins) during one minute in basal conditions were analysed. Also, the first 10 seconds, divided in 5 sec-bins, starting at the end of each stimulus were selected. Epoch was stored in a new file and converted to an adequate format to perform the spectral analyses (Clampfit 10.2, MDS Analytical Technologies). Spectral analyses for each bin were assessed by fast Fourier transformation through Hamming window with 50% overlap, obtaining the power density ($V^2 \bullet Hz^{-1}$) with a spectral resolution of 0.38 Hz, from 0.38 to 100.3 Hz. Since animals had different levels of baseline power density, the power values for each frequency were normalized as a percentage of the total power density recorded before computing group results. After normalization six epochs were averaged for basal and post-stimuli condition and compared between control littermate and GB1-cKO mice. We selected the following frequency bands: theta, 4–8 Hz; low gamma, 30–50 Hz and high gamma, 70-90 Hz.

For *phase-amplitude* coupling (PAC) analysis each 5-sec bin was converted to text format to perform the computation trough MATLAB (The MathWorks, Inc.). The process was performed by a custom-made script on MATLAB (https://github.com/abdel84/). Raw signal was decimated to a sample rate of 1 kHz, then an elliptical filter was applied to remove frequencies below 3Hz and two additional bandpass filters for both Theta (4-8 Hz) and Gamma (30-80 Hz) bands. The Theta phase and the Gamma amplitude, respectively, were extracted and computed to obtain their time series using the standard Hilbert transform as describer previously (Tort et al., 2010) and to obtain the Phase-Locking Value (PLV). This index represents the degree to which the Gamma amplitude is comodulated with the Theta phase and ranges

between 0 and 1, with higher values indicating stronger PAC interactions(Tort et al., 2010). To calculate the mean vector of PLV, circular statistics analysis was performed by using CircStat toolbox[19] and then normalized by Fisher's Z Transformation, to apply regular statistical analysis: $z' = 0.5\ [\ln(1+r) - \ln(1-r)]$.

Drugs and chemicals. *N*-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (AM251), (*S*)-(+)-α-Amino-4-carboxy-2-methylbenzeneacetic acid (LY-367385), 2-Methyl-6-(phenylethynyl)pyridine hydrochloride (MPEP), (2*S*)-3-[[(1*S*)-1-(3,4-Dichlorophenyl)ethyl]amino-2-hydroxypropyl](phenylmethyl)phosphinic acid hydrochloride (CGP55845), and (*R*)-Baclofen were purchased from Tocris (Bristol, UK). The Ca^{2+} indicator Fluo-4-AM was purchased from Life Technologies Ltd (Paisley, UK). Picrotoxin, atropine, thapsigargin, and 1,2-bis(2-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetate (BAPTA) were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Statistical analysis. The normality test was performed before applying statistical comparisons, which were made using non parametric Wilcoxon Rank-sum Test and parametric Student's *t* tests as deemed appropriate. Two-tailed, unpaired or paired *t* test was used for comparisons unless indicated. Data are expressed as mean ± standard error of the mean (SEM). When a statistical test was used, the precise two-sided *P* value and the test employed are reported in the text and/or figures legends. Statistical differences were established with $P < 0.05$ (*), $P < 0.01$ (**), and $P < 0.001$ (***, #). Blind experiments were not performed in the study but the same criteria were applied to all allocated groups for comparisons. Randomization was not employed. Sample size in whole-cell recording experiments was based on values previously found sufficient to detect significant changes in hippocampal synaptic strength in past studies from the lab.

For in vivo recordings an N of 3 repetitions of stimuli were applied, and independent recordings were summarized from 6 animals per condition, which provided sufficient statistical power while trying to minimize the number of animals sacrificed.

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AUTHOR CONTRIBUTIONS

G.P. and R.G. designed the study, performed experiments, and analyzed data. S.M., A.C., A.H-V., M.M-F., A.D. and M.F. performed slice experiments. J.B. and E.D.M. performed *in vivo* experiments and analyzed data. A.R. and D.M-V performed theta-gamma coupling index analysis. A.Agarwal and D.B. provided the astrocyte-GCaMP3 mouse line, and B.B. provided floxed GABBR1 mouse line. F.K. supervised the generation of astrocyte-specific GABBR1 knockout (and GCaMP3-expressing) mice and directed the molecular biological, immunohistochemical and confocal laser-

scanning microscopy analysis. L.S. crossbred the GABBR1 knockout (and GCaMP3-expressing) mice and performed the knockout analysis by molecular biology. L.S. and R.Q. performed immunohistochemistry and confocal laser-scanning microscopy. A.Araque designed the study and contributed to interpretation of the data. G.P. and A.Araque wrote the paper. All authors discussed the results and commented on the manuscript.

The authors declare no competing financial interests.

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FIGURE LEGENDS

Figure 1. Changes on interneuron firing activity inhibit or potentiate transmitter release at single CA3-CA1 synapses. (A) *Left*, image of paired recorded GABAergic interneuron (IN; red) and CA1 pyramidal neuron (green). *Right*, scheme depicting paired recordings from interneuron and pyramidal neurons, and Schaffer collateral (SC) stimulating electrode. Scale bar, 25 mm. **(B)** Responses evoked by minimal stimulation showing regular EPSC amplitudes and transmission failures (15 consecutive stimuli; top), and averaged EPSCs (50 consecutive stimuli; bottom) before and after pairing SC stimuli with single (red) or bursts (blue) of interneuron APs. **(C-D)** Synaptic efficacy (i.e., mean amplitude of responses including successes and failures); success rate (percentage of effective EPSCs from the total number of stimuli); and synaptic potency (i.e., mean EPSC amplitude excluding failures) (bin width, 33 s) before and after pairing SC stimuli with single (**C**, red; $n = 10$) or bursts (**D**, blue; $n = 33$) of interneuron APs. Horizontal bars indicate the time of pairing. **(E)** Relative changes of synaptic parameters from basal (black) elicited by pairing SC stimuli with single (red) or bursts of interneuron APs (blue), in control ($n = 10$ and 33, for red and blue, respectively), picrotoxin (PTX; $n = 6$ and 7, for red and blue, respectively), and CGP55845 ($n = 5$ and 9, for red and blue, respectively). **(F)** Paired pulse ratio (PPR). **(G)** Success rate from synapses shown in **D**, and averaged values (black) in control and after IN burst stimulation (n = 33). The IN-mediated effects were independent on their initial values. **(H)** Relative potentiation of synaptic efficacy *vs.* interneuron firing activity ($n \geq 4$ for each data point; Hill equation fitting, $R^2 = 0.9955$). *$P < 0.05$, **$P < 0.01$, #$P < 0.001$; paired *t* test. See also Figure 1-figure supplement 1,2. Error bars indicate SEM, as in all other figures.

Figure 2. Interneuron activity regulates transmitter release at the same synapses depending on the firing rate. (A) Synaptic efficacy, success rate and synaptic potency before and after pairing SC stimuli with single (red) or bursts (blue) of interneuron APs (n = 6). Horizontal bars indicate the time of pairing. **(B)** Raw values of synaptic parameters plotted for both IN-stimulation conditions: control (black), IN single AP (red), and IN burst (blue) stimulation (n = 6). Note that the IN-mediated effects were independent on the initial values of synaptic parameters. **(C)** Relative changes of synaptic parameters from basal (black) elicited by pairing SC stimuli with single (red) or bursts of interneuron APs (blue) (n = 6). Synaptic efficacy: P = 0.008 (red), P < 0.001 (blue). Synaptic potency: P = 0.355 (red), P = 0.407 (blue). Success rate: P < 0.001 (red), P < 0.001 (blue); paired t test. **P < 0.01, #P < 0.001; paired t test.

Figure 3. Interneuron-induced synaptic potentiation requires astrocyte Ca^{2+} elevations. (A) Image of recorded interneuron (yellow) and SR101-labelled astrocytes (red) in CA1 region. Scale bar, 40 μm. **(B)** *Left*, astrocyte Ca^{2+} transient probability over time (zero time corresponds to interneuron depolarization) in resting conditions (white), and after evoking single (red) or bursts (blue) of interneuron APs, and somatic Ca^{2+} signals from four representative astrocytes in the field of view to single APs (red) and burst of interneuron APs (blue). Red and blue bars denote interneuron stimulation. *Right,* average values for those conditions. Single APs (red; P = 0.92; paired t test), burst of interneuron APs (blue; P = 0.007; 58 astrocytes, 9 slices). **(C)** Ca^{2+} transient probability index after bursts of interneuron APs in control (58 astrocytes, 9 slices; P <0.001; Wilcoxon rank-sum test), CGP55845 (91 astrocytes, 10 slices; P = 0.824; Wilcoxon rank-sum test), thapsigargin (41 astrocytes, 5 slices; P = 0.37; Wilcoxon rank-sum test), BAPTA-loaded astrocytes (41 astrocytes, 9 slices; P = 0.2622;

Wilcoxon rank-sum test), and Ip3r2$^{-/-}$ mice (112 astrocytes, 14 slices; P= 0.4319; Wilcoxon rank-sum test). **(D)** *Left*, merge DIC and fluorescence image of CA1 pyramidal layer and stratum radiatum (s.r.) showing the location of the biocytin-filled astrocyte network (green). *Right*, maximal projection confocal image of the astrocytic syncytium revealed by biocytin-loading via whole-cell astrocyte recording, showing the distribution of biocytin-coupled astrocytes. Scale bars, 50 μm. *Bottom*, synaptic responses evoked by minimal stimulation (15 consecutive stimuli; light traces), and averaged EPSCs (50 consecutive stimuli; dark traces) before and after interneuron AP bursts in BAPTA-loaded astrocytes (blue). **(E)** Synaptic responses evoked by minimal stimulation (15 consecutive stimuli; light traces), and averaged EPSCs (50 consecutive stimuli; dark traces) before and after interneuron AP bursts in control (black) and Ip3r2$^{-/-}$ mice (red). **(F)** Relative changes of synaptic parameters induced by bursts of interneuron APs (filled bars), in control (n = 6; $P < 0.001$; paired t test), thapsigargin (n = 9), BAPTA-loaded astrocytes (n = 11), and Ip3r2$^{-/-}$ mice (n = 8). See also Figure 3-figure supplement 1. **$P < 0.01$, ***$P < 0.001$; paired t test.

Figure 4. Interneuron-induced synaptic potentiation requires astrocytic $GABA_B$ receptor and presynaptic mGluR activation. (A) Synaptic responses evoked by minimal stimulation (15 consecutive stimuli; top) and averaged EPSCs (bottom) before and after evoking bursts of interneuron APs in presence of AM251 (orange), MPEP+LY367385 (magenta), and AP5 (Blue). **(B)** Relative changes of synaptic parameters induced by bursts of interneuron APs before (open bars) and after (filled bars) receptor antagonist application ($n \geq 5$ neurons for each bar). *$P < 0.05$; paired t test. **(C)** Astrocyte Ca^{2+} transient probability index after evoking bursts of interneuron APs, before (open bars) and after (filled bars) receptor antagonist application ($n \geq 5$

slices for each bar). **(D)** Scheme of the proposed mechanisms for $GABA_A$ mediated synaptic inhibition and $GABA_B$-mGluR group I induced synaptic potentiation, respectively.

Figure 5. Effects of dynamic interplay between interneuron and astrocyte activity on excitatory synaptic transmission. (A) *Left*, averaged relative success rate of up-EPSCs and down-EPSCs over time evoked by an stimulation paradigm (*inset*) consisting of SC stimuli at 6 Hz and bursts of interneuron APs elicited by 90 depolarizing pulses (166 ms delivered at 3 Hz for 30 s), in control (black; n = 13), picrotoxin (PTX, red; n = 11), CGP55845 (blue; n = 11), and MPEP+LY (magenta; n= 8). Note that SC stimuli were phase-locked at the interneuron depolarization (up-EPSC) or resting level (down-EPSC). Each point represents the simple moving average of 15 consecutive EPSCs (note the corresponding initial gap at interneuron stimulation). Horizontal bars indicate the time of pairing. *Right*, expanded view of gray-shaded areas. **(B)** Relative changes of synaptic parameters relative to basal of up-EPSCs (closed bars) and down-EPSCs (open bars) in control and after receptor antagonist application (PTX + CGP55845; n = 9). See also Figure 5-figure supplement 1,2. *$P < 0.05$, **$P < 0.01$, #$P < 0.001$; paired *t* test.

Figure 6. $GABA_B$ receptor knockout in astroglial cells (GB1-cKO mice) impairs interneuron-mediated synaptic potentiation. (**A**) Confocal laser-scanning micrographs of hippocampal sections from wild-type (top row) and GB1-cKO (GLAST-CreERT2xGABBR1$^{fl/fl}$; bottom row) wildtype mice immunostained for the glial fibrillary acidic protein GFAP, astroglial glutamate transporter GLAST, and the $GABA_B$ receptor GABBR1. Please note the white arrow heads in wild-type that point towards co-localization of the $GABA_B$ receptor on astroglial GFAP-positive structures.

In contrast, such locations of co-localization are largely missing in the GB1-cKO mice. Scale bars, 30 μm; inset, 15 μm. (**B**) *Top left*, qRT-PCR of hippocampal genomic DNA reveals a reduction of the *Gabbr1*$^{fl/fl}$ alleles by 28.5% (P = 0.003; unpaired t test), representing the percentage of astrocytes in the hippocampus. *Top right*, quantification of *Gabbr1* mRNA levels by qRT-PCR does not show a reduction of the *Gabbr1* message (P = 0.25; unpaired t test), as expected by the high levels of neuronal versus glial expression. Quantification of the immunolabels for *Glast* and *Gabbr1* were determined by the ImageJ plugin JACoP v.2 by calculating the overlap (P < 0.001; unpaired t test; *bottom left*) and Mander's M2 coefficients (P < 0.001; unpaired t test; *bottom right*), both indicate a significant reduction of astroglial *Gabbr1* expression (9 sections from 2 GB1-cKO and 11 sections from 2 control mice). **(C)** Confocal image from CA1 region of GB1-cKO mice showing the endogenous expression of GCaMP3 in astrocytes lacking *Gabbr1* (in green). Scale bar, 60 μm. (**D**) Intracellular Ca^{2+} signals induced by local agonist application of ATP (blue) and baclofen (green) from four representative astrocytes in wild-type and GB1-cKO mice, and astrocyte Ca^{2+} transient probability over time induced by agonist stimulation or after evoking bursts of interneuron APs (white). Arrow, green and blue squares denote ATP, baclofen, or interneuron stimulation. Scale bar, 100%, 15 s. (**E**) Ca^{2+} transient probability index after astrocyte stimulation in wild-type (n = 35 astrocytes from 7 slices; P < 0.001; Wilcoxon rank-sum test) and GB1-cKO mice. GB1-cKO astrocytes failed to increase intracellular Ca^{2+} in response to baclofen (n = 88 astrocytes from 8 slices; P = 0.12; Wilcoxon rank-sum test), and IN stimulation (n = 71 astrocytes from 8 slices; P = 0.14; Wilcoxon rank-sum test), but were activated by ATP (n = 82 astrocytes from 8 slices; P < 0.001; Wilcoxon rank-sum test). (**F**) Baclofen-evoked currents in CA1 pyramidal

neurons from wild-type and GB1-cKO mice before and after CGP55845 application (Wild-type: from 13.73 ± 2.12 to 2.09 ± 1.22 pA, before and after CGP55845; n = 7; paired *t* test; $P < 0.001$; GB1-cKO: 10.76 ± 1.0 to 2.85 ± 0.89 pA; before and after CGP55845; n = 8; $P < 0.001$). (**G**) Synaptic responses evoked by minimal stimulation (15 consecutive stimuli; gray traces), and averaged EPSCs (50 consecutive stimuli; black traces) before and after evoking bursts of interneuron APs in wild-type and GB1-cKO mice. (**H**) Relative changes of synaptic parameters from basal (black bars) induced by bursts of interneuron APs (white bars; n = 5; $P < 0.001$; paired *t* test), and after CGP55845 application (n = 3; $P = 0.38$; paired *t* test) in wild-type and GB1-cKO mice (n = 4; $P = 0.38$; paired *t* test). $^{**}P < 0.01$; # $P < 0.001$.

Figure 7. Astrocyte $GABA_B$ receptors participate in hippocampal theta and gamma oscillations *in vivo*. (A) Schematic illustration of the hippocampal recording configuration and whisker stimulation in anesthetized mice. (**B**) Representative LFP recordings and corresponding analysis of theta-phase and gamma-amplitude relation for control littermate (left) and GB1-cKO (right) mice. The raw signals (black) were high-pass filtered (1st row; grey and red, respectively) and then computed to extract the theta phase (2nd row) and gamma envelope (3rd row; grey and red, respectively) for control and GB1-cKO mice. (**C**) Normalized LFP power spectrum analysis for theta (4-8 Hz) and gamma frequencies (30-50 Hz, low gamma; 70-90 Hz, high gamma) in control littermate ($n = 6$) and GB1-cKO mice ($n = 6$) after whisker stimulation. *Inset,* Relative power changes for GB1-cKO and control littermate mice (theta band, $P = 0.007$; unpaired *t* test; low gamma, $P = 0.042$; Wilcoxon rank-sum test; and high gamma oscillations, $P = 0.738$; Wilcoxon rank-sum test). (**D**) Gamma-amplitude modulation by theta-phase for wild-type (left) and GB1-cKO mice (right), before (control) and after