**Supplementary Figure 1:** Chronic inflammatory pain induced by CFA has no effect on locomotion. 

**a,** The number of entries in open and closed arms in the elevated plus maze is not different in CFA mice compared to control mice (Ctl-Open, n=8 vs. CFA-Open, n=10; Ctl-Closed, n=8 vs. CFA-Closed, n=10; unpaired t-test). **b,** Locomotor activity measured in a circular corridor is not different in CFA mice (n=10) compared to control mice (n=10), unpaired t-test. All data are expressed as means ± SEM.
Supplementary Figure 2: Histologically verified cannula placements for experiments with injection of LSP4-2022 in the amygdala. For the verification of the cannulation site, animals were sacrificed by decapitation and brains post-fixed in 4% PFA-PBS for 3 days. Fixed brains were cut using a vibratome in 80 μm-thick serial coronal sections. Cannulation sites were then identified under a dissecting microscope and then reported manually according to the Franklin & Paxinos mouse atlas. a, Representative pictures of cannula placement visualised by a DAPI staining. Note that the cannula is placed in proximity of the intermediate capsule (A/P -1.34 mm, L ±2.9mm, DV -4.25mm), injectors are longer to also allow the access to vITC (DV -4.75mm). b, c, Bilateral placements of the tip of cannula are indicated. Colors indicate treatment group, see legend. Coronal planes containing the BLA and the CeA are shown. Anteroposterior coordinates from bregma are indicated. Panel b is related to Figure 2 and panel c to Supplementary Figure 4 experiments.
Supplementary Figure 3: Amygdala injection of mGlu4 ligands in CFA mice, effect on mechanical sensitivity, anxiety, locomotion and extinction recall. a, b, Mechanical sensitivity was assessed by innocuous (a) and intermediate (b) von Frey filament stimulation 10 days after injection (T0 vs Naïve, T20, T40 and T60 is compared for each group, Ctf-LSP4-2022, n=7; Ctf-vehicle, n=7; CFA-LSP4-2022, n=9; Cfa-vehicle, n=7, nonparametric Wilcoxon rank-sum test). c, The number of open or closed arms entries in the elevated plus maze was not different in the groups (Ctf-LSP4-2022-Open, n=7 vs. Ctf-vehicle-Open, n=10; CFA-LSP4-2022-Open, n=11 vs CFA-vehicle-Open, n=8; Ctf-LSP4-2022-Closed, n=7 vs. Ctf-vehicle-Closed, n=10; CFA-LSP4-2022-Closed, n=11 vs CFA-vehicle-Closed, n=8, unpaired t-test). b, Locomotor activity was not affected by amygdala injection of mGlu4 compounds. Colors indicate treatment group, see legend (Ctf-LSP4-2022, n=8, Ctf-optogluram, n=8 vs. Ctf-vehicle, n=9; CFA-LSP4-2022, n=8; CFA-optogluram, n=7 vs Cfa-vehicle, n=10, One-way ANOVA). c, Fear conditioning was not different in the groups prior to paw injection (Ctf-vehicle, n=19 vs CFA-vehicle, n=14, two-way ANOVA). During extinction learning, CFA-vehicle mice (n=14) showed enhanced CS-evoked freezing compared to Ctf-vehicle mice (n=19) (*p<0.05,**p<0.01, two-way ANOVA followed by a Bonferroni’s test). At extinction recall, amygdala injection with LSP4-2022 had no effect in CFA mice (CFA-LSP4-2022, n=6 vs CFA-vehicle, n=8) and in the control (Ctf-LSP4-2022, n=5 vs. Ctf-vehicle, n=14), two-way ANOVA. Data are presented as one block of 4 CSs. Empty symbols correspond to non-injected or vehicle injected mice and filled symbols to LSP4-2022 injected mice. All the results are expressed as means ± SEM, except in (a) and (b) expressed as median ± IQR.
Supplementary Figure 4: Selectivity of LSP4-2022 & Optogluram in vivo.

a. Mechanical allodynia induced by CFA injection was abolished in WT mice treated with LSP4-2022 (n=8), but not in mGlu4 KO mice (n=11) as assessed by innocuous, intermediate and noxious von Frey filament stimulation. b. Mechanical allodynia induced by CFA injection was abolished in WT mice treated with optogluram (n=6) but not in mGlu4 KO mice (n=10) as assessed by von Frey filament stimulation. Data were analyzed using the nonparametric Wilcoxon signed-rank test, followed by the Holm’s method for multiple testing correction (T0 vs Naive, T20, T40 and T60 is compared for each group, *p<0.05, for WT mice and #p<0.05, ##p<0.01 for KO mice). All data are expressed as medians ± IQR.
Supplementary Figure 5: *Light microscopy characterization of mGlu₄ localization in the mouse amygdala.* **a,** Enlarged view of the mGlu₄ labeling around the mITCv cluster in wild type and in mGlu₄ KO mice. No positive immunosignal was detected in mGlu₄ KO mice. Scale bar: 30 µm. **b, c,** Co-staining of mGlu₄ (in red) with synaptic markers (in green): in panel (b) VGLUT1 and in panel (c) VGLUT 3. No colocalisations were observed in areas surrounding the mITCv. Scale bars: 10 µm.
Supplementary Figure 6: Neuronal activation of ITCs in chronic pain mice is rescued by intraperitoneal injection of LSP4-2022 (10mg/kg). a, Diagram showing localization of ITCs (intercalated cell clusters) in the amygdala. CeA, central amygdala; LA, lateral amygdala; IITC, lateral ITC; mITCd, medial dorsal ITC; mITCv, medial ventral ITC. b, Images showing immunoreactivity for Zif 268 in mITCv from mice of different groups as indicated. Scale bars: 30µm. c, d, e, Quantification of Zif 268 positive cells (expressed as % of the number of DAPI positive cells) in the ITCs indicates that LSP4-2022 treatment rescued neuronal activation of ITCs in CFA mice. Panel c, Pooled data from IITC, mITCd and mITCv, Ctrl-LSP4-2022, n=5 vs. Ctrl-vehicle, n=5; CFA-LSP4-2022, n=5 vs CFA-vehicle, n=5, unpaired t-test. Panel d, Data from mITCd only, CFA-LSP4-2022, n=4 vs. Ctrl-vehicle, n=4; CFA-LSP4-2022, n=5 vs CFA-vehicle, n=4, unpaired t-test. Panel e, Data from mITCv only is quantified, CFA-LSP4-2022, n=5 vs. Ctrl-vehicle, n=4; CFA-LSP4-2022, n=5 vs CFA-vehicle, n=5, **p<0.01,***p<0.001, unpaired t-test.
**Supplementary Figure 7: Selectivity and light-controlled anti-allodynic effect of optogluram.**

**a, b,** Optogluram was tested at high concentration (30 μM) for its ability to either potentiate or inhibit the activation of the mGlu receptors induced by the addition of an agonist at the EC20 (**a**) (mGlu1,5 with Quisqualate at 20 nM and 1 nM; mGlu2 with LY354740 at 1 nM; mGlu3 with LY354740 at 1 nM; mGlu4,6,7,8 with L-AP4 at 3 nM, 100 nM, 10 μM and 10 nM respectively) or the EC80 (**b**) (mGlu1,5 with Quis at 2 μM and 100 nM; mGlu2 with LY354740 at 100 nM; mGlu3 with LY354740 at 100 nM; mGlu4,6,7,8 with L-AP4 at 300 nM, 10 μM, 1 mM and 1 μM respectively) in the dark (green bars) and under violet light (violet bars). At 30 μM, optogluram potentiated the activation of mGlu4 and mGlu6, and to a lesser extent of mGlu8 at both light conditions, while not significantly potentiating or inhibiting other subtypes. Note that, no differences over mGlu4 activation were obtained between the dark and violet light conditions due to saturation of optogluram effect at the high concentrations used. Data show normalized receptor activation or inhibition for >3 independent experiments, done in triplicate, and are represented as means ± s.e.m. **c, d,** Mechanical sensitivity assessed by the innocuous (**c**) and intermediate (**d**) von Frey filament is restored in CFA mice treated with optogluram. This analgesic effect is abolished when optogluram is inactivated by violet light (385nm, violet rectangle) and recovered when optogluram is reactivated by green light (505nm, green rectangle). Data are expressed as medians ± IQR and analyzed using the nonparametric Wilcoxon signed-rank test, followed by the Holm’s method for multiple testing correction (T0 vs Naïve, T20, T25, T30, T35, T40 and T45 is compared for each group, CFA-vehicle, n=9 and CFA-optogluram, n=8 *p<0.05. **e,** Anxiety-like behavior assessed in the EPM revealed the anxiolytic property of optogluram (30μM). Open arm exploration is increased with optogluram, strongly reduced by violet light and increased again by green light (CFA-optogluram, n=7 vs. CFA-vehicle, n=7; *p<0.05, **p<0.01, unpaired t-test). **f,** Depressive-like behavior assessed in the splash test revealed the antidepressant property of optogluram (30μM). Time of grooming is increased with optogluram, strongly reduced by violet light and increased again by green light (CFA-optogluram, n=10 vs. CFA-vehicle, n=10; ***p<0.001, unpaired t-test). All data are expressed as means ± SEM except in (**c**) and (**d**) expressed as medians ± IQR.
Supplementary Figure 8: Histologically verified cannula placements for optopharmacological experiments (related to Figure 3). For the verification of the cannulation site, animals were sacrificed by decapitation and brains post-fixed in 4% PFA-PBS for 3 days. Fixed brains were cut using a vibratome in 80 μm-thick serial coronal sections. Cannulation sites were then identified under a dissecting microscope and then reported manually according to the Franklin & Paxinos mouse atlas. As can be seen, the cannula were placed in proximity of the intermediate capsule (A/P -1.34 mm, L ±2.9mm, DV -4.65mm). Bilateral placements of the tip of hybrid cannula are indicated. Colors indicate treatment group, see legend. Coronal planes containing the BLA and the CeA are shown. Anteroposterior coordinates from bregma are indicated.