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Supplemental information

Disrupted population coding

in the prefrontal cortex underlies pain aversion

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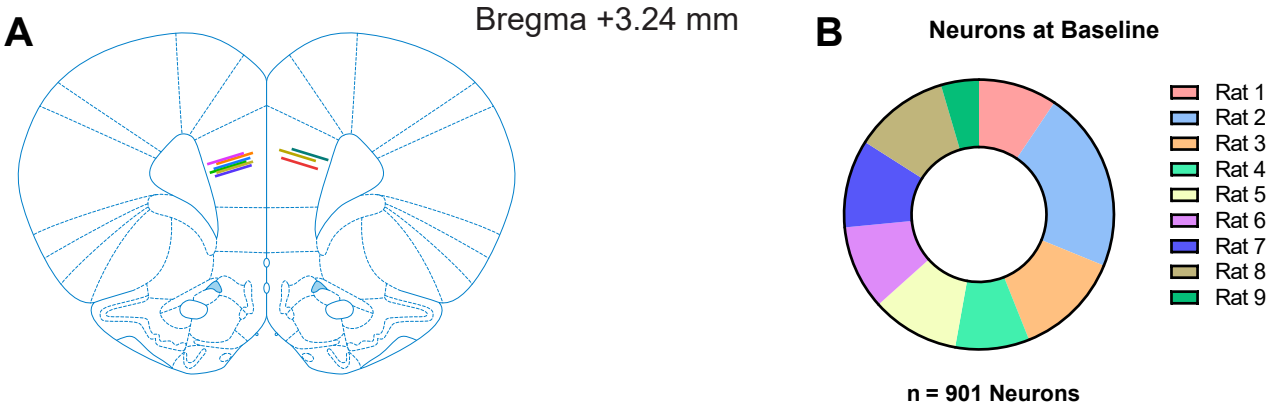
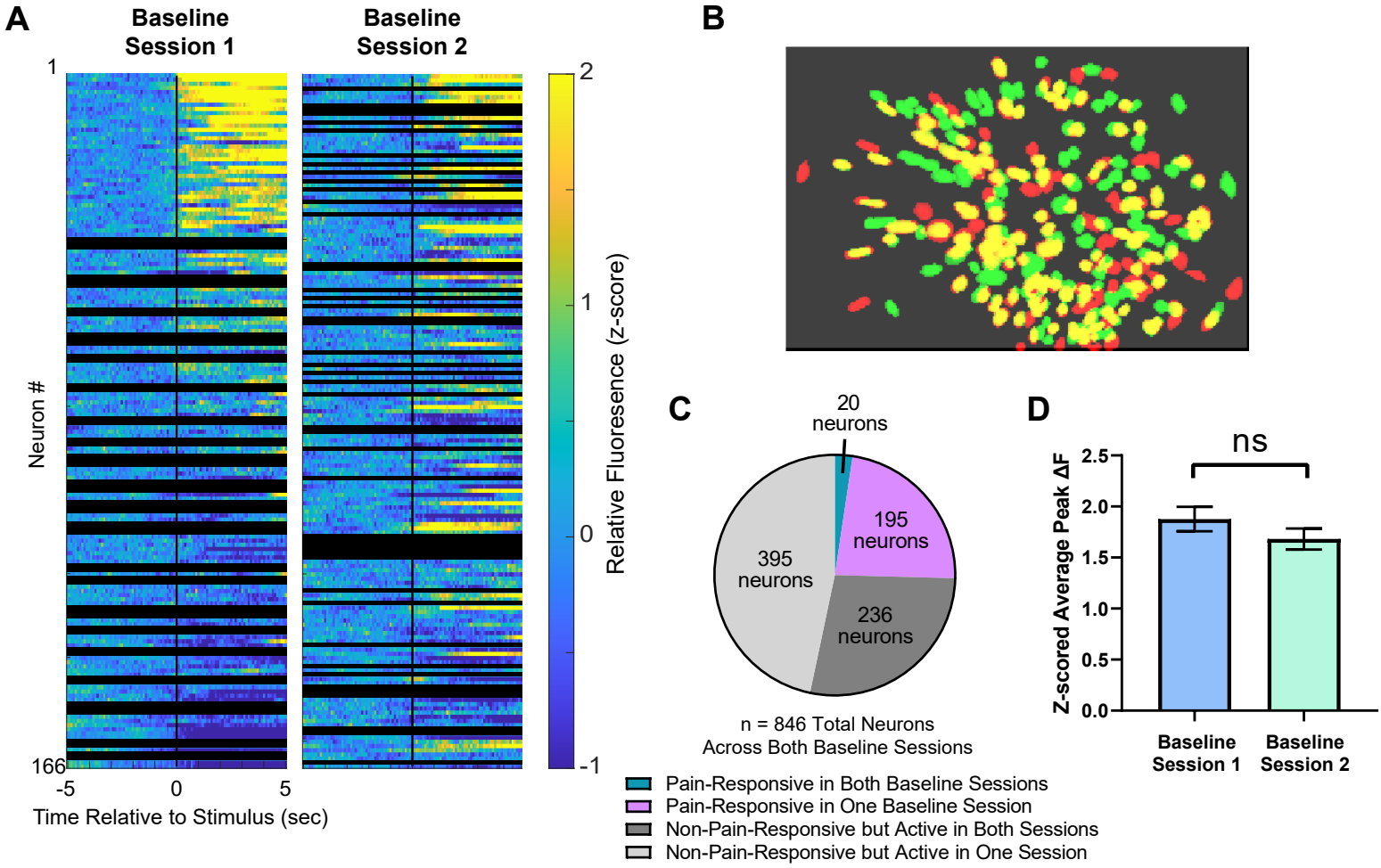
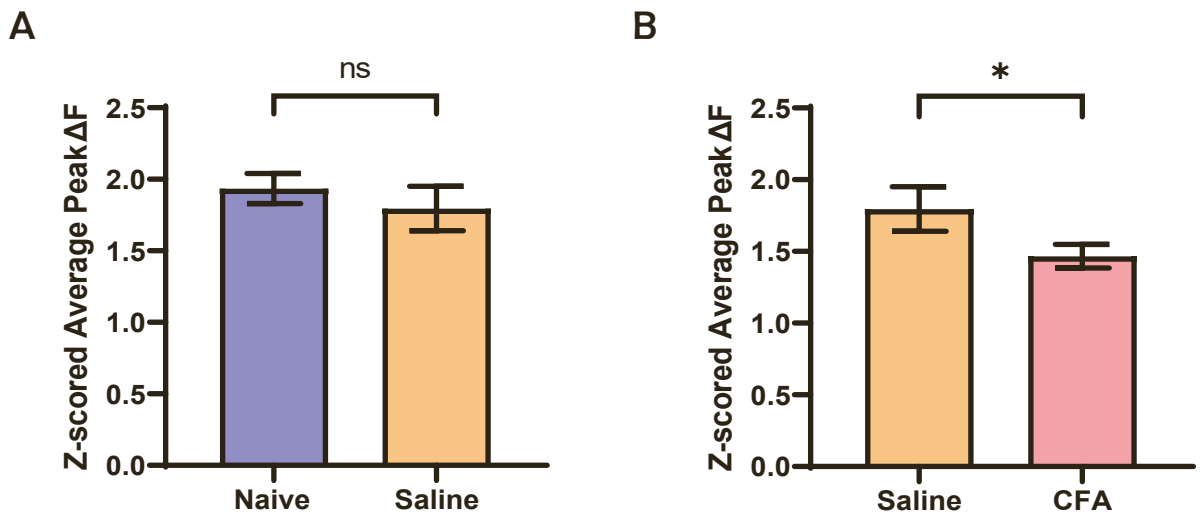


Supplementary Figure 1. Location of GRIN lens implants in the PL-PFC and summary statistics on number of recorded neurons in each animal. Related to Figure 1.

(A) Schematic of GRIN lens implants in the PL-PFC. (B) Number of neurons recorded for each rat (n = 901 neurons).

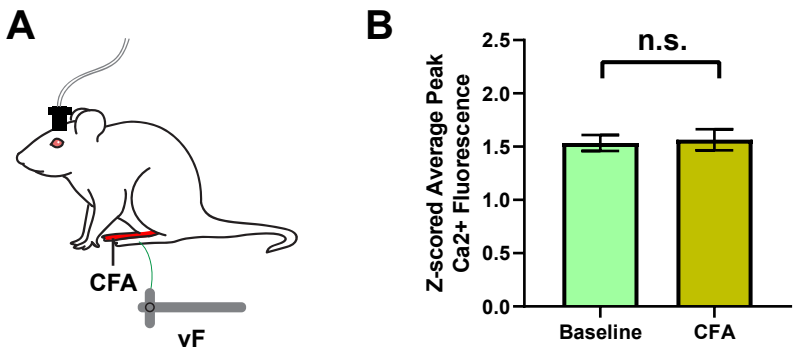


Supplementary Figure 2. Neuronal response in the PL-PFC across sessions. Related to Figure 1.
(A) All neurons (n = 166) that were active across sessions recorded on different days. Neurons were identified as active when they have exhibited a change in fluorescence during any time across the recorded session. Black sections indicate sessions in which no associated active neuron was found for that session. (B) Contours matched across two different recording sessions at baseline conditions. Red indicates one session recorded during baseline conditions whereas green indicates another session recorded during baseline conditions. Yellow indicates the overlap of neurons between the two sessions and are matched across the sessions. (C) The proportion of neurons that were pain-responsive in both baseline recording sessions (3 days apart) was small. (D) There is no significant difference between mean peak ΔF in PL-PFC neurons across recording sessions. 1st baseline session n = 525 neurons; 2nd baseline session n = 577 neurons; p = 0.2144, unpaired Student's *t* test. Data represented as mean ± SEM.



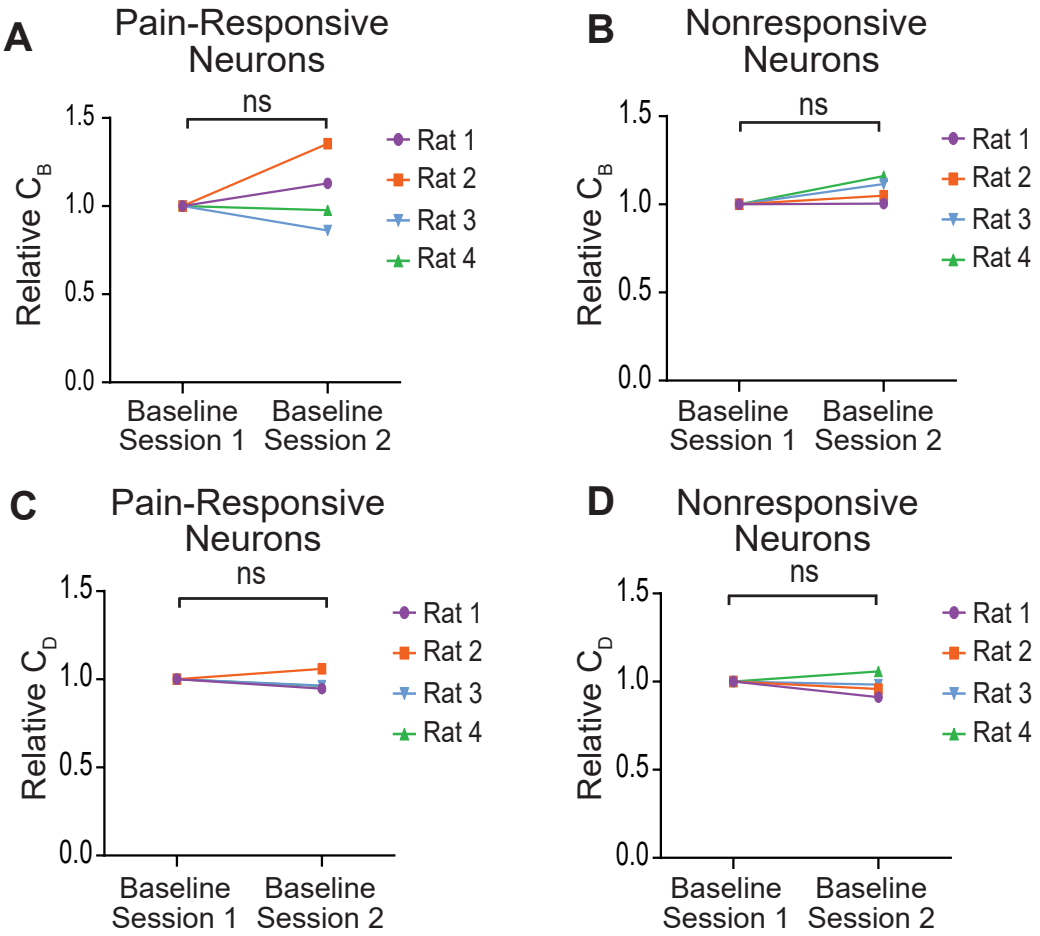
Supplementary Figure 3. CFA-treated rats demonstrate a decrease in the prefrontal nociceptive response compared to saline-treated rats. Related to Figure 1.

(A) Saline injection into the hindpaw does not alter mean peak ΔF recorded from PL-PFC pyramidal neurons, in response to pin prick. Naive condition: n = 901 neurons; saline treatment: n = 417 neurons; p = 0.4554, unpaired Student's *t* test. (B) 2 days after treatment, CFA-treated rats (n = 713 neurons) showed a decline in nociceptive response compared with saline-treated rats (n = 417 neurons); p = 0.0413, unpaired Student's *t* test. Data represented as mean ± SEM.



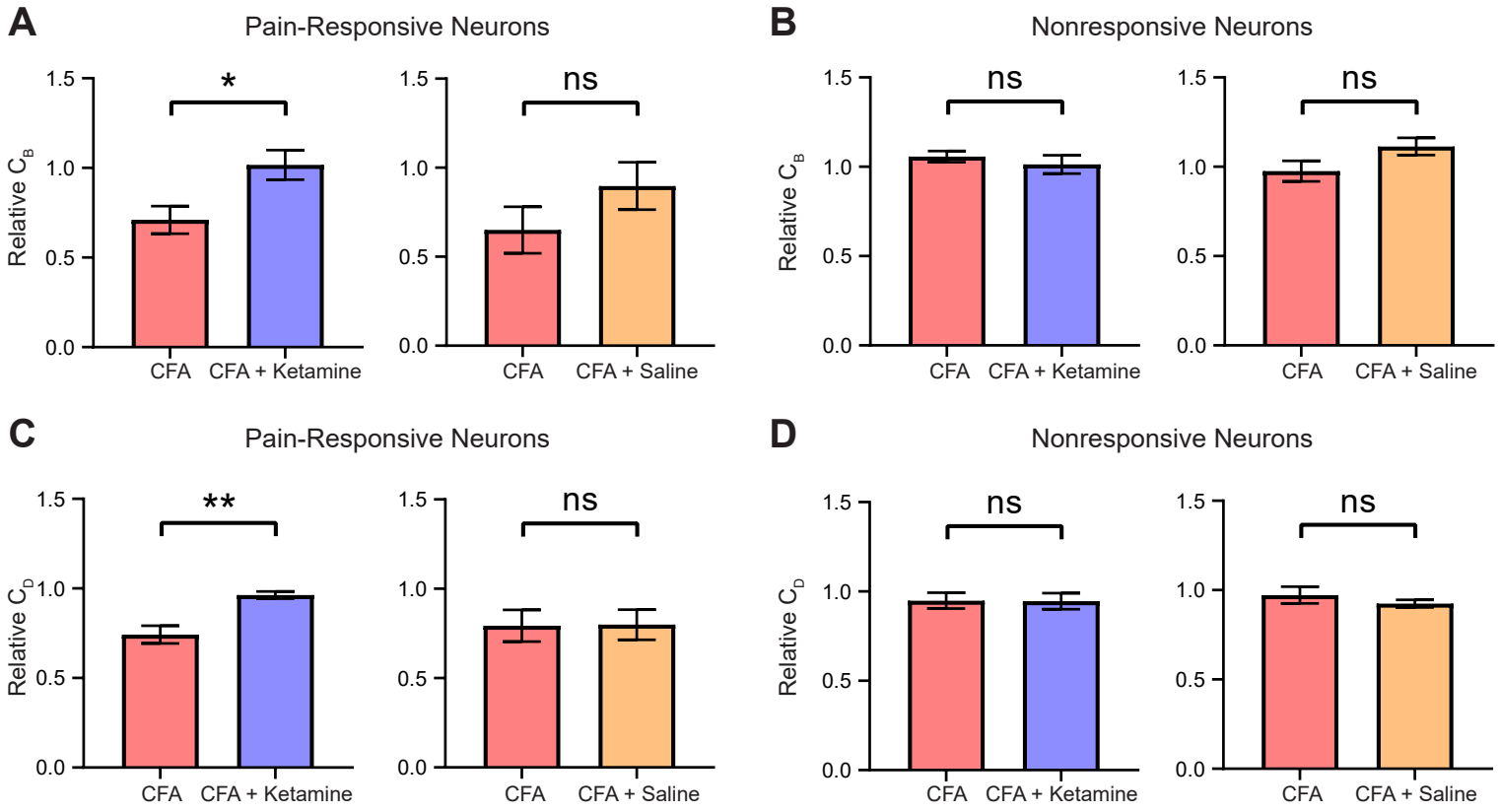
Supplementary Figure 4. Inflammatory pain does not affect the PL-PFC response to acute non-noxious stimuli. Related to Figure 1.

(A) Schematic of CFA model. (B) There is no significant difference between mean peak ΔF in PL-PFC neurons in response to a von Frey filament (vF) at baseline or CFA treatment. Baseline n = 901 neurons; CFA n = 713 neurons; p = 0.7992, unpaired Student's *t* test. Data represented as mean ± SEM.



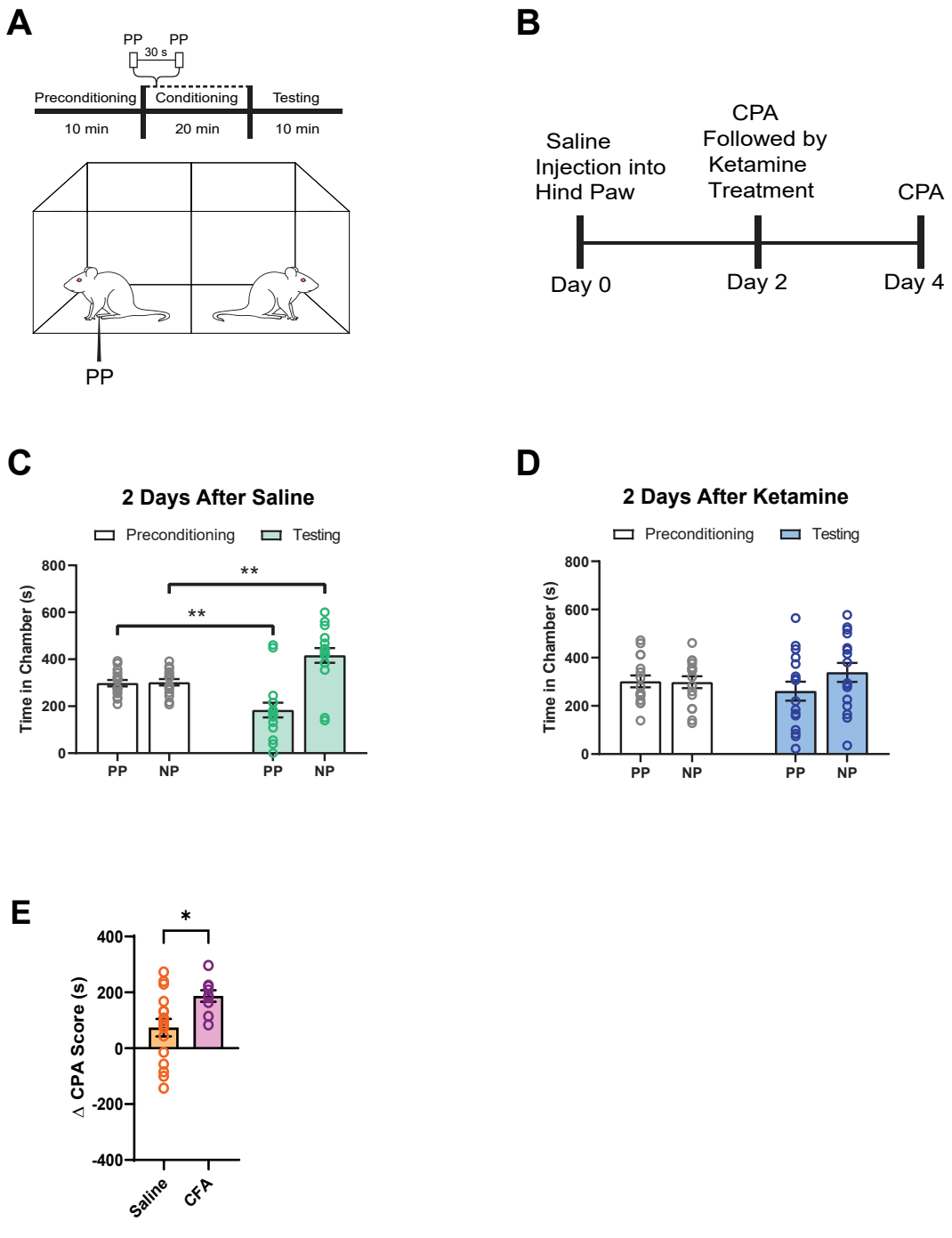
Supplementary Figure 5. Betweenness centrality and degree centrality remain constant in the baseline condition. Related to Figure 4.

(A) Relative C_B of pain responsive neurons remained relatively unchanged on two different days in the baseline condition. n = 4; p = 0.4774, unpaired Student's *t* test. (B) Relative C_B of nonresponsive neurons remained relatively unchanged on two different days in the baseline condition. n = 4; p = 0.0538, unpaired Student's *t* test. (C) Relative C_D of pain responsive neurons remained relatively unchanged on two different days in the baseline condition. n = 4; p = 0.5388, unpaired Student's *t* test. (D) Relative C_D of nonresponsive neurons remained relatively unchanged on two different days in the baseline condition. n = 4; p = 0.4969, unpaired Student's *t* test. Data represented as mean ± SEM.

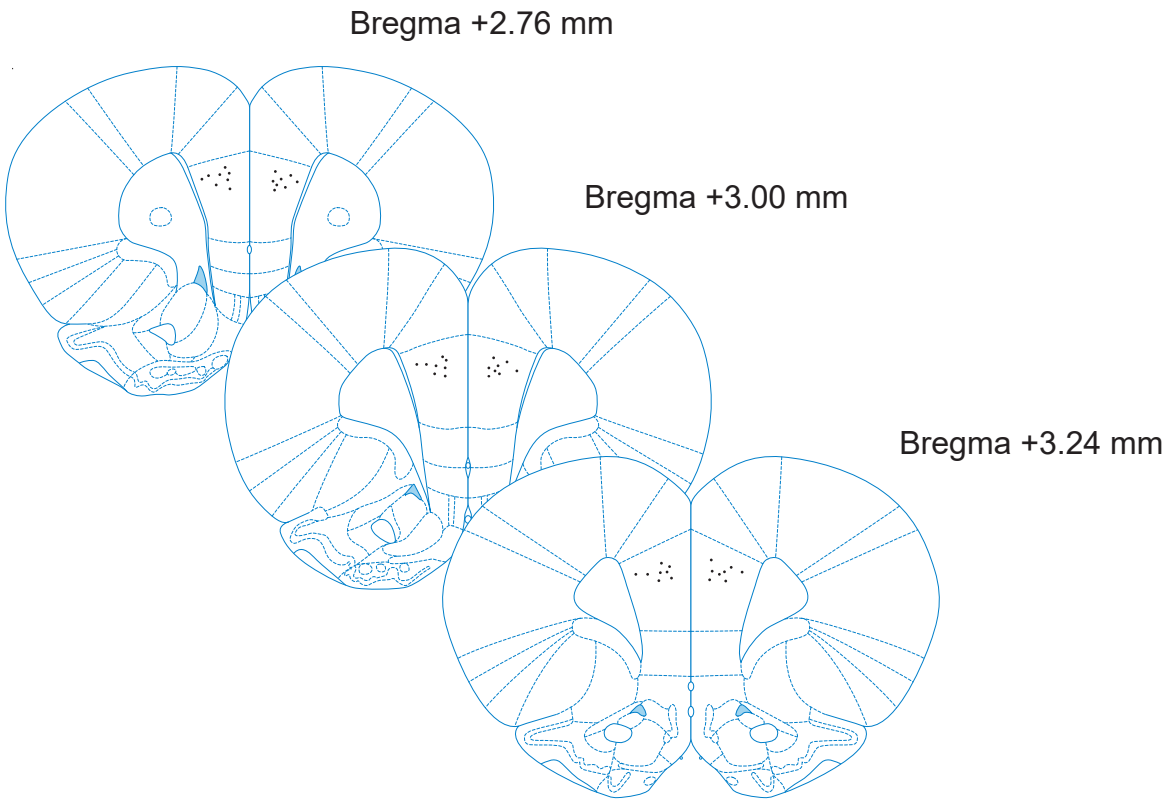


Supplementary Figure 6. Ketamine restores relative betweenness centrality and degree of pain responsive neurons. Related to Figure 4.

(A) Relative C_B, normalized with respect to the baseline condition. The bar graph on the left compares the change in relative C_B of pain-responsive neurons from the inflammatory pain state to the inflammatory pain condition two days after ketamine treatment. n = 4; p = 0.0350, unpaired Student's *t* test. The bar graph on the right compares the change in relative C_B of pain-responsiveneurons from the inflammatory pain state to the inflammatory pain condition two days after saline (control) treatment. n = 4; p = 0.2555, unpaired Student's *t* test. (B) Relative C_B, normalized with respect to the baseline condition. The bar graph on the left compares the change in relative C_B of nonresponsive neurons from the inflammatory pain state to the inflammatory pain condition two days after ketamine treatment. n = 4; p = 0.4975, unpaired Student's *t* test. The bar graph on the right compares the change in relative C_B of nonresponsive neurons from the inflammatory pain state to the inflammatory pain condition two days after saline treatment. n = 4; p = 0.1404, unpaired Student's *t* test. (C) Relative C_D, normalized with respect to the baseline condition. The bar graph on the left compares the change in relative C_D of pain-responsive neurons from the inflammatory pain state to the inflammatory pain condition two days after saline treatment. n = 4; p = 0.9615, unpaired Student's *t* test. (D) Relative C_D, normalized with respect to the baseline condition. The bar graph on the left compares the change in relative C_D of nonresponsive neurons from the inflammatory pain state to the inflammatory pain condition two days after ketamine treatment. n = 4; p = 0.9659, unpaired Student's *t* test. The bar graph on the right compares the change in relative C_D of nonresponsive neurons from the inflammatory pain state to the inflammatory pain condition two days after saline treatment. n = 4; p = 0.4057, unpaired Student's *t* test. Data represented as mean ± SEM.



Supplementary Figure 7. Ketamine reduces the aversive effects of acute pain. Related to Figure 5.
(A) Schematic of conditioned place aversion (CPA) assay. During the conditioning phase, one of the chambers was paired with the acute noxious stimulus (PP), whereas the opposite chamber was not paired with a noxious stimulus (NP). Saline (as a control for CFA) was injected into the paws of rats. (B) Time course for CPA tests in saline-treated rats with ketamine treatment. (C) 2 days after saline injection, rats displayed avoidance of the chamber paired with the acute noxious stimulus (PP). n = 16; p = 0.0019, paired Student's *t* test. (D) A single dose of ketamine inhibited the aversive response to acute noxious stimuli in saline-treated rats. n = 16; p = 0.2558, paired Student's *t* test. (E) CFA-treated rats (n = 9) showed a greater decrease in the aversive response to acute noxious stimuli after ketamine treatment than saline-treated rats (n = 16). Δ CPA Score indicates the difference in CPA scores before and after ketamine treatment. p = 0.0193, unpaired Student's *t* test. Data represented as mean ± SEM.



Supplementary Figure 8. Intracranial injections are located in the PL-PFC. Related to Figure 7.
Schematic of intracranial injection locations in the PL-PFC.