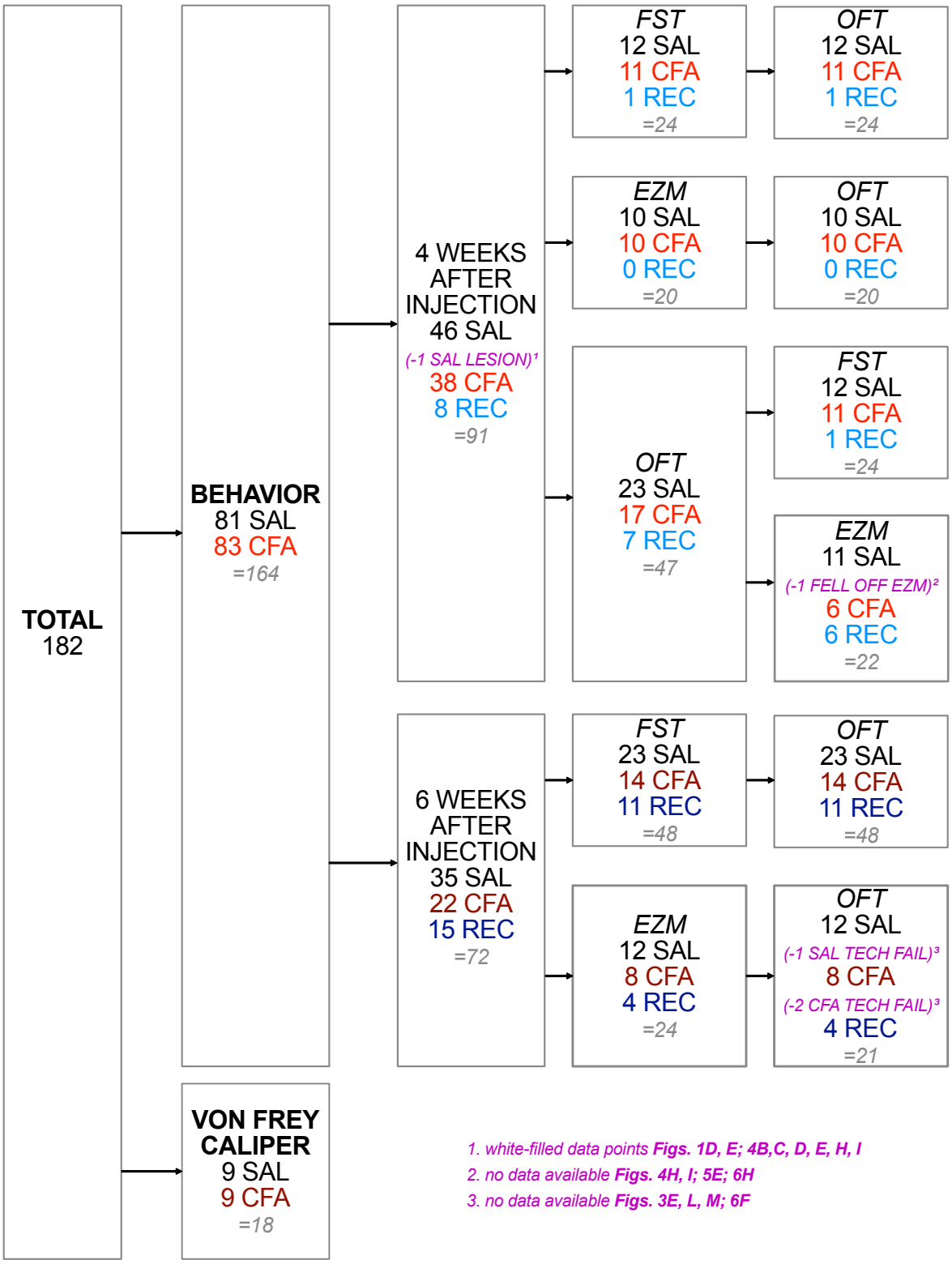


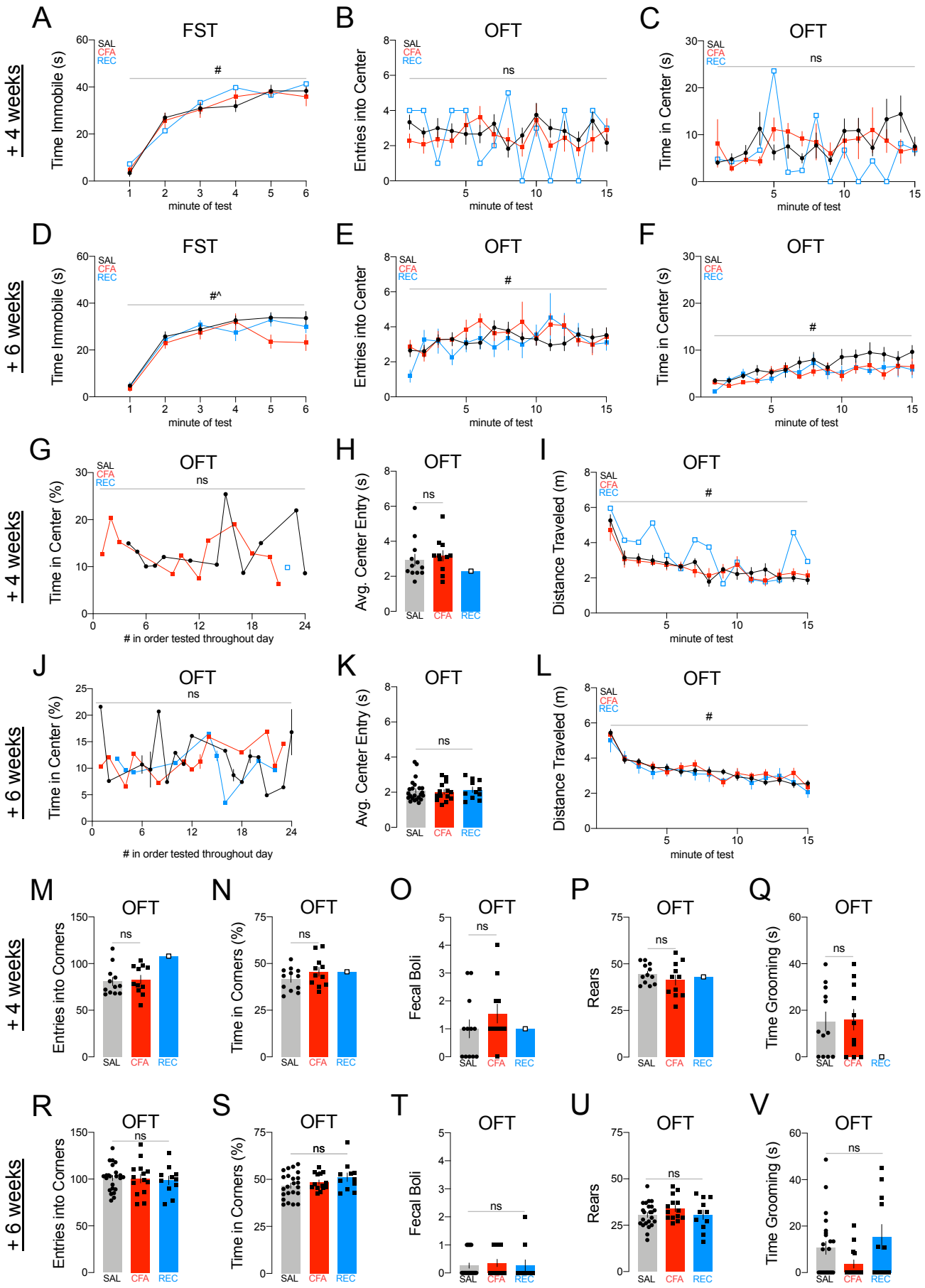
FIGURE S1. Flow-chart depicting animal usage and sample size per experiment. No mice were excluded from this study. One mouse with a probable paw lesion as evidence by an aberrant paw withdrawal latency in the Hargreaves assay is represented in white-filled data points in main **Figs. 1** and **4**; statistical analyses are provided in the results with and without its data. No EZM data are available for one mouse which fell off the maze, but its available Hargreaves and OFT data are included in **Fig. 4.** No OFT data is available for three mice for which videos were not recorded in a technical failure, but their available Hargreaves and EZM data are included in **Fig. 3**.

ARRIVE GUIDELINE		FULFILLMENT
Study design	The groups being compared, including control groups	CFA (50 μL, Thermo Fisher), or sterile saline as a control, was injected into the plantar surface of the right hind-paw.
	The experimental unit (single animal, litter, cage)	Comparison of individual mice injected with saline or CFA was used to determine the behavioral alteration induced by inflammatory pain.
Sample size	Specify the exact number of experimental units allocated and total number in each experiment, and total number of animals used	A total of 182 male wild-type C57BL/6J mice (Jackson Laboratories). Please refer to **Fig**. **S1**.
	Explain how the sample size was decided, provide details of any a priori sample size calculation if done	Sample sizes were decided based on previous studies that reported *n*=10-12 as enough power to assess significance among experimental groups. *A priori* calculations of sample size with power analysis are recommended.
Inclusion & exclusion criteria	Describe any criteria used for including or excluding animals or experimental units during the experiment, and data points during the analysis. Specify if these criteria were established a priori. If no criteria were set state this explicitly.	No animals were excluded from analysis in this study. Please refer to "Post-hoc group assignment" in the Methods section for details.
	For each experimental group, report any not included in the analysis and explain why. If there were no exclusions, state so.	No animals were excluded from analysis in this study. Some data for four animals were unavailable due to technical errors. Please refer to **Fig**. **S1**.
	For each analysis, report the exact value of n in each experimental group	Please refer to **Figs**. **2B**, **2D**, **3B**, **3D**, **4B**, and **S1**.
Randomization	State whether randomization was used to allocate experimental units to control and treatment groups. If done, provide the method used to generate the randomization sequence.	A computerized shuffle algorithm of animals to randomly allocate treatment is recommended.
	Describe the strategy used to minimize potential confounders such as the order of treatments and measurements or animal location	Mice were tested in alternative saline – CFA order to avoid the confound of time of day or circadian rhythm effects across the duration of a testing day/session.
Blinding	Describe who was aware of the group allocation at the different stages of the experiment	CFA administration results in visually obvious paw edema while handling the animal, preventing a fully blinded experimental design. However, all data collection was video-recorded in black and white, and analysis was conducted with Any-Maze video tracking software and confirmed with triplicate, blinded, manual scoring after the conclusion of the Hargreaves assay.
Outcome measures	Clearly defined all outcome measures assessed	Please refer to "Apparatus" in the Methods section for details.
Statistical methods	Provide details of the statistical methods used for each analysis including software	Please refer to "Statistical analysis of behavioral data" in the Methods section for details.
	Describe any methods used to assess whether the data met the assumptions of the statistical approach and what was done if the assumptions were not met	Please refer to "Statistical analysis of behavioral data" in the Methods section for details.
Experimental animals	Provide species-appropriate details of species, strain and substrain, sex, age or stage, weight	Male wild-type C57BL/6J mice were 8 weeks of age at CFA injection.
	Provide further relevant information on the provenance of the animals, health status, genetic mod, genotype	Wild-type mice were purchased from Jackson Laboratories. No adverse health consequences were observed other than the induced hind-paw inflammation.
Experimental procedures	What was done, how it was done, what was used; When and how often; Where & acclimatization	Please refer to "CFA Administration," "Experimental Design," and "Apparatus" in the Methods section for details, as well as **Figs**. **2A**, **3A**, and **4A**.

	Why, rationale	Please refer to the Introduction section for details.
Results	Summary/descriptive stats for each experimental group with a measure of variability where applicable	Please refer to the Results section for details.
	If applicable effect size with a CI	Please refer to the Results section of **Fig. 7** for details.
Abstract	Research objective, animal species, strain and sex, key methods, principal findings, and study conclusions	Please refer to the abstract for this overview.
Background	Include sufficient scientific background to understand the rationale and context for the study and explain the experimental approach	Please refer to the Introduction section for details.
	Explain how the animal species and model used address the scientific objectives and where appropriate the relevance to human biology	Please refer to the Introduction and Discussion sections for details.
Objectives	Clearly describe the research question, research objectives and where appropriate specific hypotheses being tested	Please refer to the Introduction section for details.
Ethical statement	Provide the name of the ethical review committee or equivalent that has approved the use of animals in this study and any relevant license or protocol numbers if applicable	All procedures were approved by the Washington University Institutional Animal Care and Use Committee (IACUC) in accordance with the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals.
Housing and husbandry	Provide details of conditions and enrichment	Mice were housed in groups of 4 to 5, in standard cages with corn-cob bedding and nesting material, on a 12/12-hour dark/light cycle (lights on at 7:00 AM), and received food *ad libitum* throughout the experiment.
Animal care and monitoring	Describe any interventions or steps taken in the experimental protocols to reduce pain suffering and distress	Mice were anesthetized with 2% isoflurane and sedation was confirmed by the absence of a reflex during a toe pinch for CFA injection. All mice were confirmed to exhibit no ostensible stress response to handling or the environment (shaking, vocalizations, jumping) immediately prior to behavioral testing. Upon completion of the FST, mice are gently taken out of the water, dried with towels, and placed on a heating pad in a clean, bedding-free cage to dry and recover.
	Report any expected or unexpected adverse events	No adverse health consequences were observed other than the induced hind-paw inflammation.
	Describe the humane endpoints established, signs that were monitored	Twenty-four hours after the conclusion of the Hargreaves assay, mice were euthanized by rapid cervical dislocation.
Interpretation/implications	Interpret the results, taking into account the study objectives and hypotheses, current theory, and other relevant studies in the literature	Please refer to the Discussion section.
	Comment on limitations including potential sources of bias, limitations of the animal model, and imprecision	The current work is similarly limited to one species, one strain, one sex, and one model of inflammatory pain to permit the granularity of our analyses. Investigating the effect of inflammatory or neuropathic pain on rats, other strains or sub-strains of mice such as CD1 or C57BL/6N, and female rodents is just as critical to better understanding the intersection of pain and emotion, as the results here may not extrapolate to these other populations. Furthermore, the present study focuses only on three assays of exploratory behavior and stress coping strategy, as our group's previously published work addresses motivational,

		hedonistic, and appetitive behaviors elsewhere. Lastly, the meta-analysis of similar literature was conducted primarily to inform and guide the interpretation and discussion of our results. This meta-analysis is limited without a registered protocol, quality assessments of risks of bias, meta-regression or stratified meta-analysis, and analyses of publication bias.
Generalizability /translation	Comment on whether and how the findings of this study are likely to generalize to other species or experimental conditions including any relevance to human biology	Please refer to the Discussion section.
Data access	If and where study data are available	The supplemental file is also available open-source on Figshare (https://figshare.com/s/6bab90f9fb282e3f875f) and the Open Science Framework (https://osf.io/2wpjn/?view_only=5974c94d968d4e55bf6fce986992298e).
Declaration of interests	Declare any potential conflicts of interest including financial and none	The authors declare no conflict of interest or competing financial interests.
	List all funding sources	This work was supported by National Institute on Drug Abuse grants DA041781, DA042499, DA045463 to JAM.

Table S1. Guide to study's fulfillment of Animal Research: Reporting of *In Vivo* Experiments checklist recommendations.


+ 4 weeks
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CFA
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Time in Center (%)
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FIGURE S2. Multiple aspects of coping strategy in the FST and exploratory behavior in the OFT do not change at four or six weeks after the induction of inflammatory pain, regardless of time of day tested or across duration of test. (# effect of time; * effect of group; ^ interaction of time and group; ns not significant.)

A: Time spent immobile in seconds, per minute of the FST, changes from minute to minute but not between groups, four weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(3.986, 83.71)}$=63.51, p<0.0001; group $F_{(1, 21)}$=0.002739, p=0.9588; interaction $F_{(5, 105)}$=0.5232, p=0.7582; n=12 SAL, 11 CFA).

B: Entries into the center, per minute of the OFT, do not change from minute to minute and do not change between groups, four weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(7.654, 160.7)}$=1.137, p=0.3415; group $F_{(1, 21)}$=1.241, p=0.2778; interaction $F_{(14, 294)}$=0.7810, p=0.6897; n=11-12).

C: Time spent in the center, per minute of the OFT, does not change from minute to minute and does not change between groups, four weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(7.678, 161.2)}$=1.249, p=0.2757; group $F_{(1, 21)}$=0.06874, p=0.7957; interaction $F_{(14, 294)}$=1.172, p=0.2958; n=11-12).

D: Time spent immobile in seconds, per minute of the FST, changes from minute to minute and has a main effect of time x group, six weeks after saline or CFA injection regardless of thermal hyperalgesia status (2-way ANOVA for repeated measures: time $F_{(3.629, 163.3)}$=72.63, p<0.0001; group $F_{(2, 45)}$=1.777, p=0.1807; interaction $F_{(10, 225)}$=2.009, p=0.0035; n=23 SAL, n=14 CFA, n=11 REC). Interaction is not significant when when CFA and REC are pooled and compared to SAL ($F_{(5, 230)}$=1.660, p=0.1453).

E: Entries into the center, per minute of the OFT, change from minute to minute but not across group, six weeks after saline or CFA injection regardless of thermal hyperalgesia status (2-way ANOVA for repeated measures: time $F_{(8.632,388.4)}$=26.61, p<0.0001; group $F_{(2, 45)}$=0.2990, p=0.7430; interaction $F_{(28, 630)}$=0.7881, p=0.7751; n=11-23).

F: Time spent in the center, per minute of the OFT, changes from minute to minute but not across group, six weeks after saline or CFA injection regardless of thermal hyperalgesia status (2-way ANOVA for repeated measures: time $F_{(9.207,414.3)}$=2.095, p=0.0278; group $F_{(2, 45)}$=0.7814, p=0.4639; interaction $F_{(28, 630)}$=1.030, p=0.4245; n=11-23).

G: Time spent in the center of the OFT does not change across time of day tested, using position in testing order as a proxy, four weeks after saline or CFA injection (SAL Pearson r^2=0.04554, p=0.5055, n=12; CFA Pearson r^2=0.1382, p=0.2603, n=11).

H: Average duration of visits to center is not different between saline and CFA mice, four weeks after injection (Mann-Whitney: U=50, p=0.3381, n=11-12).

I: Distance traveled, per minute of the OFT, changes from minute to minute but not between groups, four weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(6.855, 144)}$=12.37, p<0.0001; group $F_{(1, 21)}$=0.1229, p=0.7294; interaction $F_{(14, 294)}$=0.6419, p=0.8290; n=11-12).

J: Time spent in the center of the OFT does not change across time of day tested, using position in testing order as a proxy, six weeks after saline or CFA injection regardless of thermal hyperalgesia status (SAL Pearson r^2=0.08672, p=0.2512, n=23; CFA Pearson r^2=0.2769, p=0.0647, n=14; REC Pearson r^2=0.001613, p=0.9183, n=11).

K: Average duration of visits to center is not different between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (Kruskal-Wallis: KWstat=0.4318, p=0.8058, n=11-23).

L: Distance traveled, per minute of the OFT, changes from minute to minute but not across group, six weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(8.632, 388.4)}$=26.61, p<0.0001; group $F_{(2, 45)}$=0.2990, p=0.7430; interaction $F_{(28, 630)}$=0.7881, p=0.7751; n=11-23).

M: Entries into any of the four corners are not different between saline and CFA mice, four weeks after injection (Mann-Whitney: U=58, p=0.6393, n=11-12).

N: Time spent in any of the four corners is not different between saline and CFA mice, four weeks after injection (unpaired t-test: t_{21}=1.305, p=0.2059, n=11-12).

O: Number of fecal boli excreted during the OFT does not differ between saline and CFA mice, four weeks after injection (Mann-Whitney: U=45.50, p=0.1982, n=11-12).

P: Number of rearing events during the OFT does not differ between saline and CFA mice, four weeks after injection (unpaired t-test: t_{21}=1.070, p=0.2966, n=11-12).

Q: Time spent grooming during the OFT does not differ between saline and CFA mice, four weeks after injection (unpaired t-test: t_{21}=0.1347, p=0.8941, n=11-12).

R: Entries into any of the four corners are not different between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (ordinary one-way ANOVA: $F_{(2, 45)}$=0.1009, p=0.9042, n=11-23).

S: Time spent in any of the four corners is not different between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (ordinary one-way ANOVA: $F_{(2, 45)}$=1.187, p=0.1743, n=11-23).

T: Number of fecal boli excreted during the OFT does not differ between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (Kruskal-Wallis: KWstat=0.7073, p=0.7021, n=11-23).
U: Number of rearing events during the OFT does not differ between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (ordinary one-way ANOVA: $F_{(2, 45)}$=1.186, p=0.3149, n=11-23).
V: Time spent grooming during the OFT does not differ between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (Kruskal-Wallis: KWstat=3.837, p=0.1468, n=11-23).

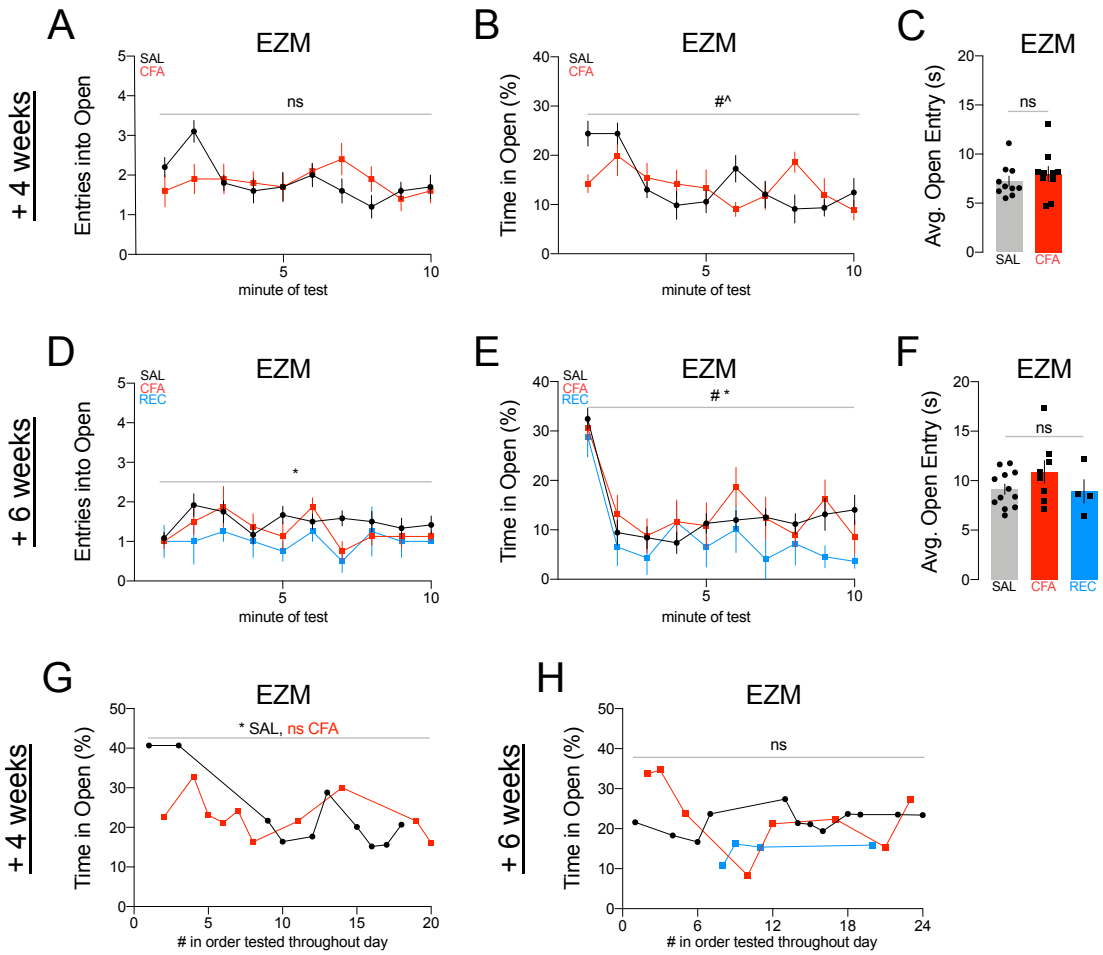


FIGURE S3. Multiple aspects of exploratory behavior in the EZM do not change four or six weeks after the induction of inflammatory pain, regardless of time of day tested or across duration of test. (# effect of time; * effect of group; ^ interaction of time and group; ns not significant.)

A: Entries into the open arms, per minute, do not change across time or between groups, four weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(5.615,101.1)}=1.955$, $p=0.0837$; group $F_{(1, 18)}=0.001137$, $p=0.9163$; interaction $F_{(9, 162)}=1.893$, $p=0.0563$; n=10 SAL, n=10 CFA).

B: Time spent in the open arms, per minute, changes from minute to minute and has a main effect of time x group, four weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(5.376,102.26)}=4.011$, $p=0.0018$; group $F_{(1, 19)}=0.2271$, $p=0.6391$; interaction $F_{(9, 171)}=2.550$, $p=0.0090$; n=10,10).

C: Average duration of visits to the open arms is not different between saline and CFA mice, four weeks after injection (unpaired t-test: $t_{18}=0.8353$, $p=0.4145$, n=10,10).

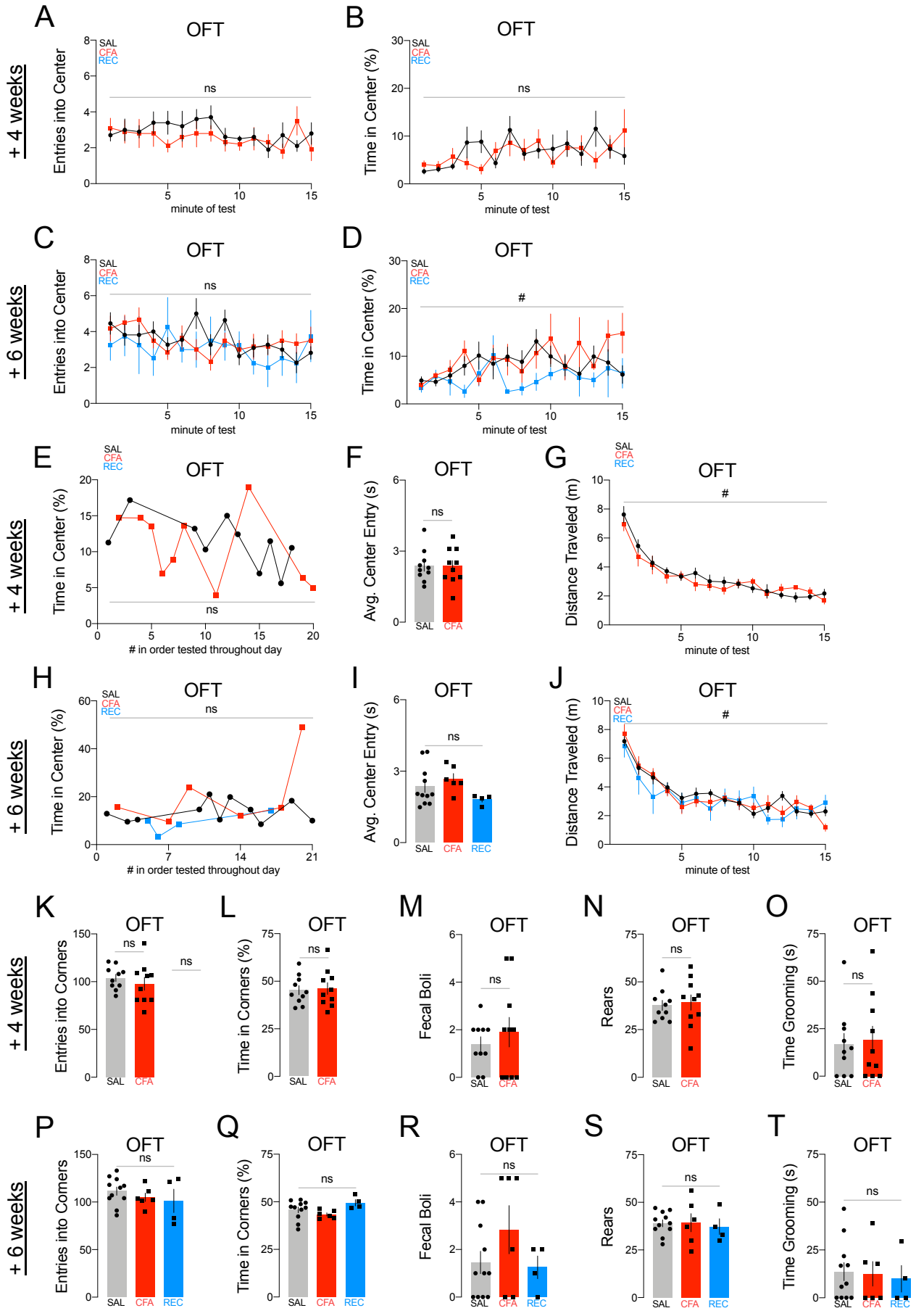
D: Entries into the open arms, per minute, do not change from minute to minute but do change across group, six weeks after injection (2-way ANOVA for repeated measures: time $F_{(5.831, 122.5)}=1.534$, $p=0.1745$; group $F_{(2, 21)}=3.536$, $p=0.0475$; interaction $F_{(18, 189)}=0.7006$, $p=0.8081$; n=12 SAL, n=8 CFA, n=4 REC). When CFA and REC are pooled and compared to SAL, there is still a main effect of group (group $F_{(1, 22)}=4.794$, $p=0.0395$, n=12,12).

E: Time spent in the open arms, per minute, changes from minute to minute and across group without a main effect of time x group, six weeks after saline or CFA injection regardless of thermal hyperalgesia status (2-way ANOVA for repeated measures: time $F_{(6.735, 141.4)}=11.65$, $p<0.0001$; group $F_{(2, 21)}=3.504$, $p=0.0486$; interaction $F_{(18, 189)}=0.6769$, $p=0.8314$; n=4-12). When CFA and REC are pooled and compared to SAL, only main effect of time is significant (time $F_{(6.569, 144.5)}=14.40$, $p<0.0001$; n=10-12).

F: Average duration of visits to the open arms is not different between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (ordinary one-way ANOVA $F_{(2, 21)}=1.441$, $p=0.2592$; n=4-12).

G: Time spent in the open arms change across time of day tested for saline-injected mice, four weeks after injection (SAL Pearson $r^2=0.6807$, $p=0.0033$, n=10; CFA Pearson $r^2=0.1032$, $p=0.3653$, n=10).

H: Time spent in the open arms does not change across time of day tested, using position in testing order as a proxy, six weeks after saline or CFA injection regardless of thermal hyperalgesia status (SAL Pearson r^2=0.1917, p=0.1546, n=12; CFA Pearson r^2=0.1801, p=0.2947, n=8; REC Pearson r^2=0.2302, p=0.5202, n=4).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ns
#
Entries into Center
Time in Center (%)
minute of test
in order tested throughout day
Avg. Center Entry (s)
Distance Traveled (m)
Entries into Corners
Time in Corners (%)
Fecal Boli
Rears
Time Grooming (s)

FIGURE S4. Multiple aspects of exploratory behavior in the OFT, conducted 48 hours after the EZM, do not change four or six weeks after the induction of inflammatory pain, regardless of time of day tested or across duration of test. (# effect of time; * effect of group; ^ interaction of time and group; ns not significant.)

A: Entries into the center, per minute of the OFT, do not change from minute to minute and do not change between groups, four weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(7.306, 131.5)}$=0.9160, p=0.4992; group $F_{(1, 18)}$=0.7102, p=0.4014; interaction $F_{(14, 252)}$=0.8367, p=0.6288; n=10 SAL, n=10 CFA).

B: Time spent in the center, per minute of the OFT, does not change from minute to minute and does not change between groups, four weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(6.887, 124.0)}$=1.573, p=0.1505; group $F_{(1, 18)}$=0.1394, p=0.7133; interaction $F_{(14, 252)}$=1.258, p=0.2342; n=10,10).

C: Entries into the center, per minute of the OFT, do not change from minute to minute and do not change across group, six weeks after saline or CFA injection regardless of thermal hyperalgesia status (2-way ANOVA for repeated measures: time $F_{(7.422, 133.6)}$=1.313, p=0.2462; group $F_{(2, 18)}$=0.5896, p=0.5649; interaction $F_{(28, 252)}$=0.8537, p=0.6819; n=11 SAL, n=6 CFA, n=4 REC).

D: Time spent in the center, per minute of the OFT, changes from minute to minute but not across group, six weeks after saline or CFA injection regardless of thermal hyperalgesia status (2-way ANOVA for repeated measures: time $F_{(6.810, 122.6)}$=1.220, p=0.2974; group $F_{(2, 18)}$=2.509, p=0.1094; interaction $F_{(28, 252)}$=0.8744, p=0.6522; n=4-11).

E: Time spent in the center of the OFT does not change across time of day tested, using position in testing order as a proxy, four weeks after saline or CFA injection (SAL Pearson r^2=0.3167, p=0.0903, n=10; CFA Pearson r^2=0.1514, p=0.3006, n=9).

F: Average duration of visits to center is not different between saline and CFA mice, four weeks after injection (unpaired t-test: t_{18}=0.03074, p=0.9758, n=10,10).

G: Distance traveled, per minute of the OFT, changes from minute to minute but not between groups, four weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(6.235,113.8)}$=32.54, p<0.0001; group $F_{(1, 18)}$=0.3149, p=0.5816; interaction $F_{(14, 252)}$=0.9072, p=0.5516; n=10,10).

H: Time spent in the center of the OFT does not change across time of day tested, using position in testing order as a proxy, six weeks after saline or CFA injection regardless of thermal hyperalgesia status (SAL Pearson r^2=0.02985, p=0.6115, n=11; CFA Pearson r^2=0.2988, p=0.2617, n=6; REC Pearson r^2=0.5527, p=0.2566, n=4).

I: Average duration of visits to center is not different between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (Kruskal-Wallis: KWstat=4.436, p=0.1071, n=4-11).

J: Distance traveled, per minute of the OFT, changes from minute to minute but not across group, six weeks after saline or CFA injection (2-way ANOVA for repeated measures: time $F_{(5.075, 91.34)}$=29.34, p<0.0001; group $F_{(2, 18)}$=0.2805, p=0.7587; interaction $F_{(28, 252)}$=1.398, p=0.0942; n=4-11).

K: Entries into any of the four corners are not different between saline and CFA mice, four weeks after injection (unpaired t-test: t_{18}=0.8015, p=0.4333, n=10,10).

L: Time spent in any of the four corners is not different between saline and CFA mice, four weeks after injection (unpaired t-test: t_{18}=0.2235, p=0.8256, n=10,10).

M: Number of fecal boli excreted during the OFT does not differ between saline and CFA mice, four weeks after injection (unpaired t-test: t_{18}=0.7209, p=0.4803, n=10,10).

N: Number of rearing events during the OFT does not differ between saline and CFA mice, four weeks after injection (unpaired t-test: t_{18}=0.3106, p=0.7597, n=10,10).

O: Time spent grooming during the OFT does not differ between saline and CFA mice, four weeks after injection (Mann-Whitney: U=49.50, p=0.9885, n=10,10).

P: Entries into any of the four corners are not different between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (Brown-Forsythe ANOVA: $F_{(2,5.5)}$=0.5386, p=0.6115, n=4-11).

Q: Time spent in any of the four corners is not different between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (ordinary one-way ANOVA: $F_{(2,18)}$=2.611, p=0.1010, n=4-11).

R: Number of fecal boli excreted during the OFT does not differ between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (Kruskal-Wallis: KWstat=1.541, p=0.4806, n=4-11).

S: Number of rearing events during the OFT does not differ between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (ordinary one-way ANOVA: $F_{(2, 18)}$=0.08389, p=0.9199, n=4-11).

T: Time spent grooming during the OFT does not differ between saline and CFA mice regardless of thermal hyperalgesia status, six weeks after injection (Kruskal-Wallis: KWstat=0.1536, p=0.9291, n=4-11).

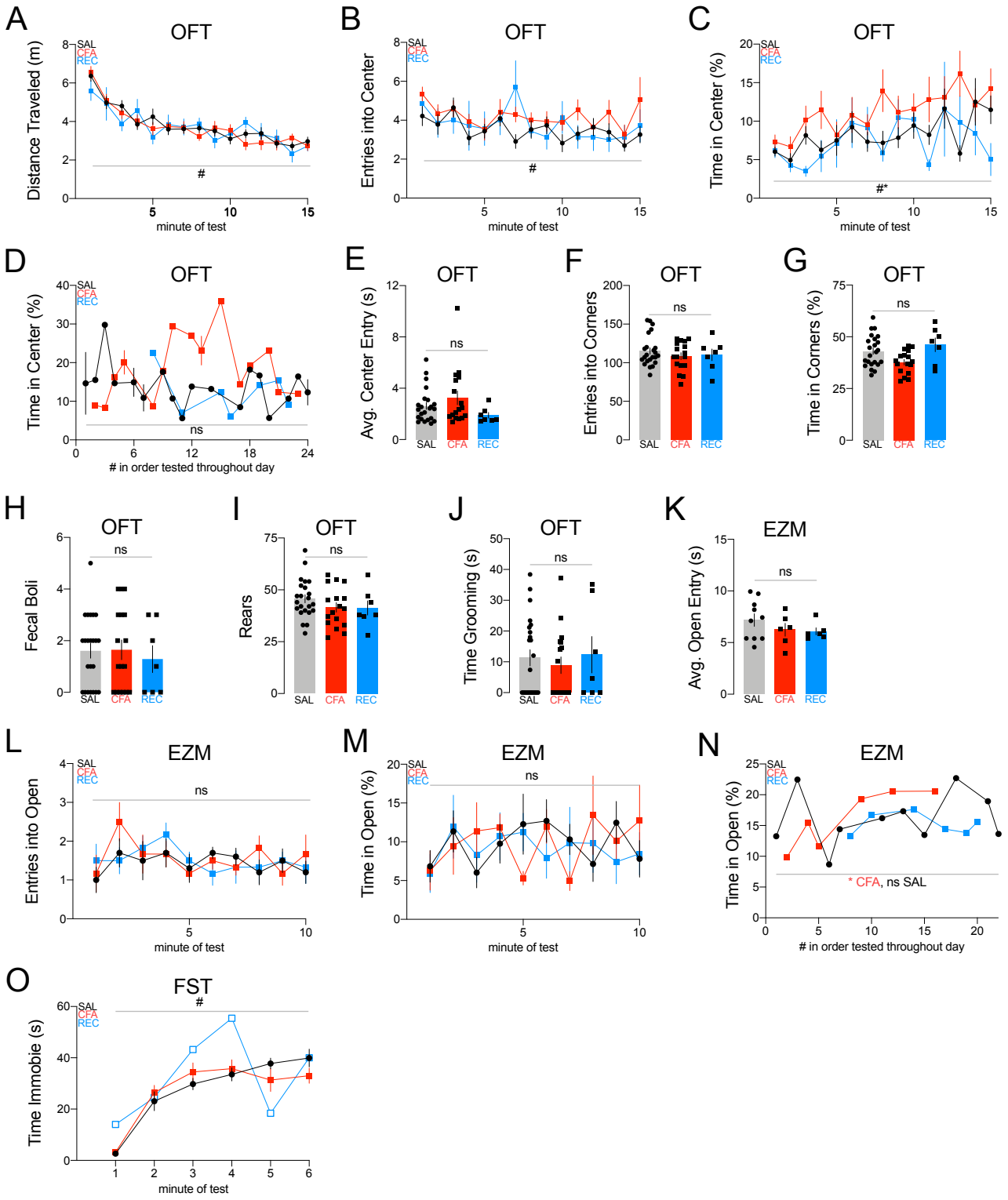

FIGURE S5. Multiple aspects of coping strategy in the FST, exploratory behavior in the EZM, and exploratory behavior in the OFT do not change four weeks after the induction of inflammatory pain, *when the OFT is conducted 48 hours before either the FST or EZM.* (# effect of time; * effect of group; ^ interaction of time and group; ns not significant.)

A: Distance traveled, per minute of the OFT, changes from minute to minute but not across groups (2-way ANOVA for repeated measures: time $F_{(8.889,391.1)}=22.04$, $p<0.0001$; group $F_{(2, 44)}=0.09102$, $p=0.9312$; interaction $F_{(28, 616)}=1.071$, $p=0.3684$; n=23 SAL, n=17 CFA, n=7).

B: Entries into the center, per minute of the OFT, change from minute to minute and but do not change among groups (2-way ANOVA for repeated measures: time $F_{(9.504,418.2)}=1.881$, $p=0.0494$; group $F_{(2, 44)}=2.764$, $p=0.0740$; interaction $F_{(28, 616)}=0.8333$, $p=0.7138$; n=7-23).

C: Time spent in the center, per minute of the OFT, change from minute to minute and across groups, but without a main effect of time x group (2-way ANOVA for repeated measures: time $F_{(8.389,369.1)}=2.192$, $p=0.0251$; group $F_{(2, 44)}=3.745$, $p=0.0315$; interaction $F_{(28, 616)}=1.012$, $p=0.4498$; n=7-23).
D: Time spent in the center of the OFT does not change across time of day tested, using position in testing order as a proxy (SAL Pearson $r^2=0.1108$, $p=0.1772$, n=23; CFA Pearson $r^2=0.04335$, $p=0.4565$, n=17; REC Pearson $r^2=0.09160$, $p=0.5094$, n=7).
E: Average duration of visits to center is not different between saline and CFA mice regardless of thermal hyperalgesia status (Kruskal-Wallis: KWstat=3.698, p=0.1574, n=7-23).
F: Entries into any of the four corners are not different between saline and CFA mice regardless of thermal hyperalgesia status (Kruskal-Wallis: KWstat=0.2280, p=0.8920, n=7-23).
G: Time spent in any of the four corners is different between SAL- and CFA-injecting mice continuing to experience thermal hyperalgesia, but not between SAL-injected mice and all CFA-injected mice regardless of thermal hyperalgesia status (ordinary one-way ANOVA $F_{(2, 44)}=4.528$, $p=0.0163$; Dunnett's multiple comparisons SAL vs. CFA $p=0.0417$; n=7-23; SAL vs. CFA+REC unpaired t-test: $t_{45}=1.332$, $p=0.1896$, n=23,24).
H: Number of fecal boli excreted during the OFT does not differ between saline and CFA mice regardless of thermal hyperalgesia status (Kruskal-Wallis: KWstat=0.2813, p=0.8688, n=7-23).
I: Number of rearing events during the OFT does not differ between saline and CFA mice regardless of thermal hyperalgesia status (ordinary one-way ANOVA: $F_{(2, 44)}=0.1.187$, $p=0.3146$, n=7-23).
J: Time spent grooming during the OFT does not differ between saline and CFA mice regardless of thermal hyperalgesia status (Kruskal-Wallis: KWstat=0.5008, p=0.7785, n=7-23).
K: Average duration of visits to the open arms is not different between saline and CFA mice regardless of thermal hyperalgesia (Kruskal-Wallis: KWstat=0.8601, p=0.6695, n=10 SAL, n=6 CFA, n=6 REC).
L: Entries into the open arms, per minute, do not change from minute to minute and do not change across group (2-way ANOVA for repeated measures: time $F_{(5.539,\ 105.2)}=1.209$, $p=0.3089$; group $F_{(2,\ 19)}=0.1825$, $p=0.8346$; interaction $F_{(18,\ 171)}=0.6430$, $p=0.8615$; n=6-10).
M: Time spent in the open arms, per minute, does not change from minute to minute and does not change across groups (2-way ANOVA for repeated measures: time $F_{(6.063,\ 115.2)}=0.6485$, $p=0.6928$; group $F_{(2,\ 19)}=0.1182$, $p=0.8892$; interaction $F_{(18,\ 171)}=0.7607$, $p=0.7435$; n=6-10).
N: Time spent in the open arms changes across time of day tested, using position in testing order as a proxy, for CFA mice continuing to exhibit thermal hyperalgesia (SAL Pearson $r^2=0.04388$, $p=0.5613$, n=10; CFA Pearson $r^2=0.7827$, $p=0.0192$, n=6; REC $r^2=0.002279$, $p=0.9284$, n=6). This correlation does not persist when CFA and REC mice are pooled, i.e. all mice injected with CFA regardless of thermal hyperalgesia status (Pearson $r^2=0.1573$, $p=0.2018$, n=12).
O: Time spent immobile in seconds, per minute of the FST, changes from minute to minute but not between groups (2-way ANOVA for repeated measures: time $F_{(3.984,\ 83.66)}=56.40$, $p<0.0001$; group $F_{(1,\ 21)}=0.02175$, $p=0.8842$; interaction $F_{(5,\ 105)}=2.189$, $p=0.0609$; n=12 SAL, 11 CFA).

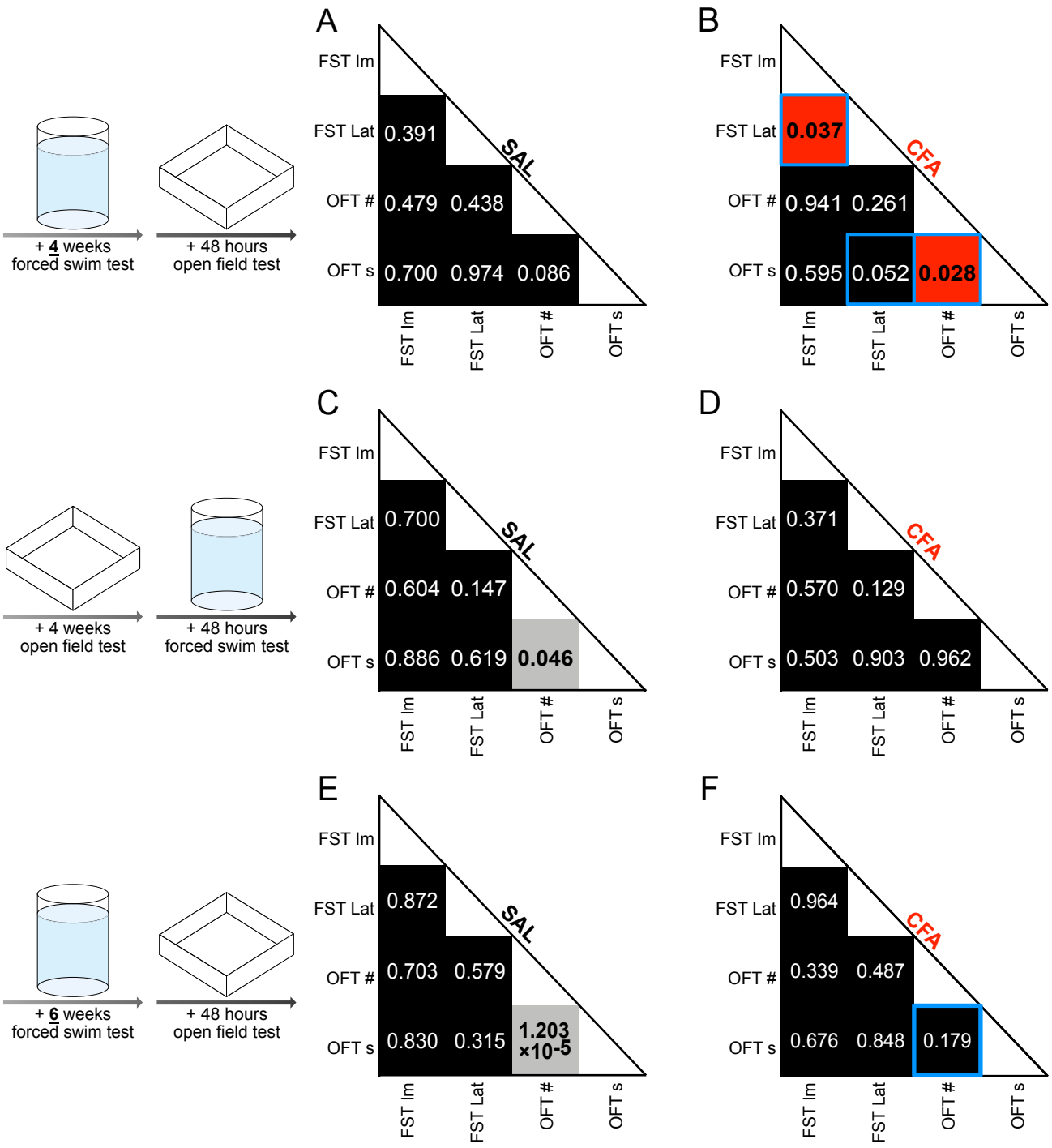

FIGURE S6. Measures of exploratory behavior in the OFT do not consistently or reliably correlate with measures of coping strategy in the FST, four or six weeks after the induction of inflammatory pain. **A**. In saline-injected mice tested first in the FST and later in the OFT, there are no significant correlations among time spent immobile in the FST, latency to immobility in the FST, entries into the center of the OFT, and time spent in the center of the OFT (n=12).
B. In CFA-injected mice tested first in the FST and later in the OFT, latency to immobility in the FST correlated with time spent immobile in the FST (Spearman r=0.645), and time spent in the center of the OFT correlated to entries into the center of the OFT (Spearman r=0.671, n=11). When CFA and REC were grouped back together, the significance of both correlations persisted; and latency to immobility in the FST was also significantly associated with time spent in the center of the OFT (Spearman r=-0.587, n=12).
C. In saline-injected mice tested first in the OFT and later in the FST, only time spent in the center of the OFT correlated to entries into the center of the OFT (Spearman r=0.594, n=12).
D. In CFA-injected mice tested first in the OFT and later in the FST, no measures correlated to each other (n=11).

E. In saline-injected mice tested first in the FST six weeks after injection, followed by the OFT, only time spent in and entries into the center significantly correlated (Spearman r=0.779, n=23).
F. In CFA-injected mice tested first in the FST six weeks after injection, followed by the OFT, no measures correlated (n=14). When CFA and REC were grouped back together, time spent in and entries into the center of the OFT were significantly correlated (Pearson r=0.546, n=25).

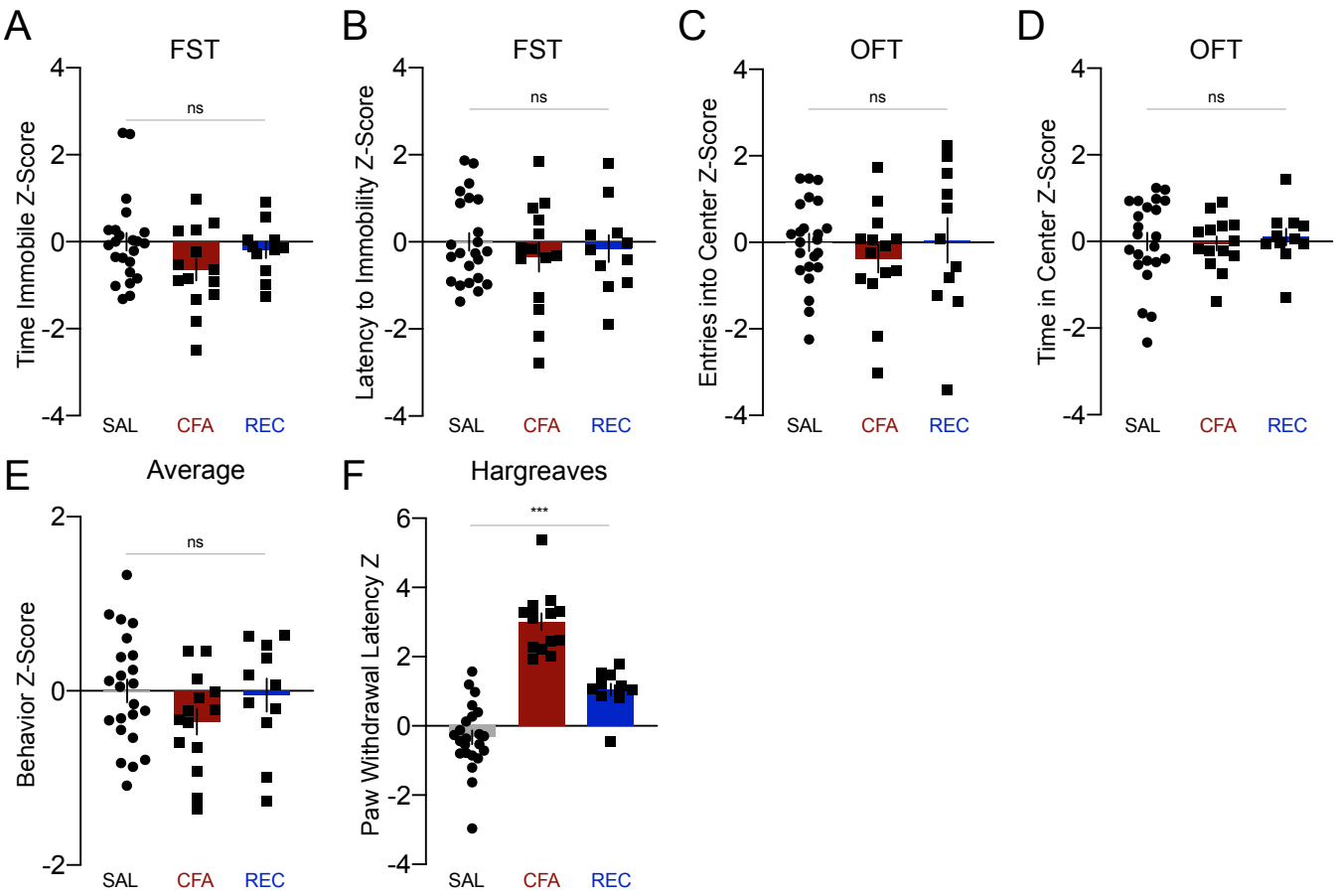

FIGURE S7. Individual z-scores for mice injected with saline or CFA and tested in the FST and OFT 6 weeks later.
A: Z-score representation of time spent immobile in the FST by mice injected with CFA and sustaining thermal hyperalgesia for six weeks (n=14), compared with mice injected with CFA which recovered (n=11), and with mice injected with saline (n=23) (Kruskal-Wallis: KWstat=2.826, p=0.2434).
B: Z-score representation of latency to immobility in the FST by mice injected with CFA and sustaining thermal hyperalgesia for six weeks (n=14), compared with mice injected with CFA which recovered (n=11), and with mice injected with saline (n=23) (ordinary one-way ANOVA $F_{(2, 45)}$=0.4699, p=0.6281).
C: Z-score representation of entries into the center of the OFT by mice injected with CFA and sustaining thermal hyperalgesia for six weeks (n=14), compared with mice injected with CFA which recovered (n=11), and with mice injected with saline (n=23) (ordinary one-way ANOVA $F_{(2, 45)}$=0.5017, p=0.6088).
D: Z-score representation of time spent in the center of the OFT by mice injected with CFA and sustaining thermal hyperalgesia for six weeks (n=14), compared with mice injected with CFA which recovered (n=11), and with mice injected with saline (n=23) (ordinary one-way ANOVA $F_{(2, 45)}$=0.1063, p=0.8994).
E: Average of z-scores, from four measurements: time immobile, latency to immobility, entries into center, time in center (ordinary one-way ANOVA $F_{(2, 45)}$=1.542, p=0.2251, n=11-23).
F: Z-score representation of paw withdrawal thresholds in the Hargreaves assay for thermal hyperalgesia by mice injected with CFA and sustaining thermal hyperalgesia for six weeks (n=14), compared with mice injected with CFA which recovered (n=11), and with mice injected with saline (n=23) (Kruskal-Wallis: KWstat=35.53, p<0.0001).

DATABASE Results on 04/07/20	Search String
Ovid Medline 305	exp "Freunds Adjuvant"/ or (Freund* adj2 adjuvant).mp. or freund adjuvans.mp. OR (CFA adj3 inject*).mp. AND (Exp Anxiety/ OR Exp depression/ OR Exp mood disorders/ OR Exp emotions/ OR emotion*.mp. OR "negative affect".mp. OR anxiety*.mp. OR anxiogenic.mp. OR anxiolytic.mp. OR depression.mp. OR depressive.mp. OR "pro-depressant".mp. OR depressogenic.mp. OR antidepressant.mp. OR "exploratory behavior".mp. OR "elevated plus maze".mp. OR "elevated zero maze".mp. OR "elevated 0-maze".mp. OR "forced swim".mp. OR affective.mp. OR ((cage OR test*) adj3 (behavior* OR behaviour*)).mp.) AND (Exp rodentia/ OR rodent*.mp. OR rats.mp. OR rat.mp. OR mice.mp. OR mouse.mp. OR murid*.mp. OR murine.mp. OR murinae.mp. OR maze*.mp. OR paw*.mp.)
Embase 408	('freund adjuvant'/exp OR ((freund* NEAR/2 adjuvant):ti,ab,kw,de) OR 'freund adjuvans':ti,ab,kw,de OR ((cfa NEAR/3 (inflammation OR inject*)):ti,ab,kw,de)) AND ('anxiety'/exp OR 'depression'/exp OR 'mood disorder'/exp OR 'emotion'/exp OR 'elevated plus maze test'/exp OR emotion*:ti,ab,kw,de OR 'negative affect':ti,ab,kw,de OR anxiety*:ti,ab,kw,de OR anxiogenic:ti,ab,kw,de OR anxiolytic:ti,ab,kw,de OR depression:ti,ab,kw,de OR depressive:ti,ab,kw,de OR 'pro-depressant':ti,ab,kw,de OR depressogenic:ti,ab,kw,de OR antidepressant:ti,ab,kw,de OR 'exploratory behavior':ti,ab,kw,de OR 'elevated plus maze':ti,ab,kw,de OR 'elevated zero maze':ti,ab,kw,de OR 'elevated 0-maze':ti,ab,kw,de OR 'forced swim':ti,ab,kw,de OR affective:ti,ab,kw,de OR (((cage OR test*) NEAR/3 (behavior* OR behaviour*)):ti,ab,kw,de)) AND ('rodent'/exp OR rodent*:ti,ab,kw,de OR rats:ti,ab,kw,de OR rat:ti,ab,kw,de OR mice:ti,ab,kw,de OR mouse:ti,ab,kw,de OR murid*:ti,ab,kw,de OR murine:ti,ab,kw,de OR murinae:ti,ab,kw,de OR maze*:ti,ab,kw,de OR paw*:ti,ab,kw,de)
Web of Science 275 results	1. TS=((Freund* near/2 adjuvant) or 'freund adjuvans' OR (CFA near/3 (inflammation OR inject*))) **2.** TS=(emotion* OR 'negative affect' OR anxiety* OR anxiogenic OR anxiolytic OR depression OR depressive OR 'pro-depressant' OR depressogenic OR antidepressant OR 'exploratory behavior' OR 'elevated plus maze' OR 'elevated zero maze' OR 'elevated 0-maze' OR 'forced swim' OR affective OR ((cage OR test*) near/3 (behavior* OR behaviour*))) **3.** TS=(rodent* OR rats OR rat OR mice OR mouse OR murid* OR murine OR murinae OR maze* OR paw*) 4. 1 AND 2 AND 3
Scopus 405	(TITLE-ABS-KEY ((Freund* w/2 adjuvant) or "freund adjuvans" OR (CFA w/3 (inflammation OR inject*)))) AND (TITLE-ABS-KEY (emotion* OR "negative affect" OR anxiety* OR anxiogenic OR anxiolytic OR depression OR depressive OR "pro-depressant" OR depressogenic OR antidepressant OR "exploratory behavior" OR "elevated plus maze" OR "elevated zero maze" OR "elevated 0-maze" OR "forced swim" OR affective OR ((cage OR test*) w/3 (behavior* OR behaviour*)))) AND (TITLE-ABS-KEY (rodent* OR rats OR rat OR mice OR mouse OR murid* OR murine OR murinae OR maze* OR paw*))
PubMed My NCBI 2 between 04/07/20 and 07/27/20	("elevated zero maze" OR "elevated plus maze" OR "open field test" OR "forced swim") AND ("complete Freund's adjuvant" OR "Freund's complete adjuvant")
INCLUSION CRITERIA	controlled studies with separate treatment (CFA) and control (saline-injected) groups, adult male C57BL/6 mice, unilateral, single injection, elevated zero or plus maze, open field test (for exploration, not locomotion), forced swim test
EXCLUSION CRITERIA	no saline-injected control group, other animals, neonates, juveniles, rats, other strains, constriction injury, sciatic nerve injury, spinal nerve ligation, formalin or carrageenan injection, injections into knee or face, experimental autoimmune encephalomyelitis

TABLE S2. Medical librarian-designed search string across four different databases on 04/07/20, additional PubMed Alerts thereafter, and inclusion and exclusion criteria used for meta-analysis screening and selection.

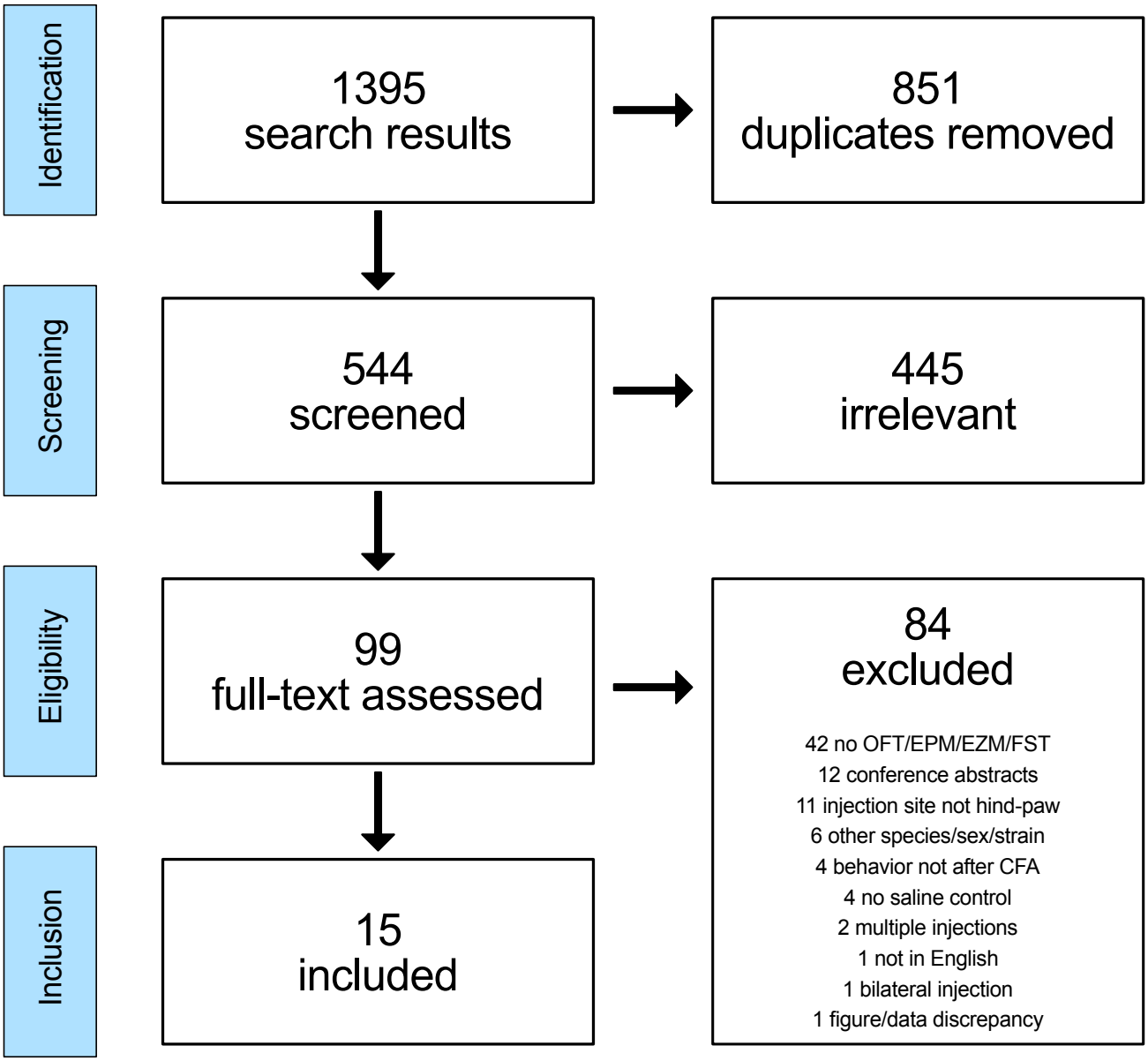

FIGURE S8. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for search, screening, selection, exclusion, and inclusion.

Forced Swim Test Meta-Analysis Extended Data									
Time Post-Injection	Hedges g	First Author	Last Author	Year	Journal	Avg. Age (Weeks)	Side Injected	Strain	Housing
1 week	-1.28	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	G
2 weeks	1.85	Laumet	Kavelaars	2020	Neurobiology of Pain	10.5	L	C57BL/6	?
3 weeks	-0.30	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	L	C57BL/6N	G
3 weeks	-0.04	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	G
3 weeks	0.01	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6J	G

TABLE S3. Age, side injected, sub-strain, and housing condition of each cohort and study included in the FST meta-analysis.

Elevated Plus Maze Meta-Analysis Extended Data										
Time Post-Injection	Hedges g	First Author	Last Author	Year	Journal	Avg. Age (Weeks)	Side Injected	Strain	Housing	Lighting
1 day	-0.66	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	G	230/160
1 day	-0.10	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	I	230/160
1 week	-1.70	Yue	Liu	2018	Brain Research Bulletin	7	R	C57BL/6	G	?
1 week	-0.22	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	L	C57BL/6N	G	230/160
1 week	-0.06	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	G	230/160
1 week	0.40	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6J	G	230/160
2 weeks	-2.69	Zheng	Yi	2017	Journal of Neuroscience	6.5	L	C57BL/6	G	5
2 weeks	-1.65	Tian	Tian	2017	Metabolic Brain Disease	9	L	C57BL/6	G	?
2 weeks	-1.47	Guan	Zhao	2020	Molecular Pain	7	R	C57BL/6J	G	?
2 weeks	-1.44	Sun	Yang	2020	Neurotoxicity Research	7	L	C57BL/6	G	?
2 weeks	-0.73	Luo	Yang	2020	Molecular Brain	7	L	C57BL/6	G	?
2 weeks	0.49	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	G	230/160
2 weeks	0.51	Liu	Zhang	2015	Physiology & Behavior	8	?	C57BL/6J	G	15/5
3 weeks	-2.60	Wang	Zhao	2015	Molecular Pain	8	L	C57BL/6	G	?
3 weeks	-1.58	Guo	Liu	2016	Nutritional Neuroscience	9	L	C57BL/6	G	?
3 weeks	-0.87	Sun	Wu	2016	International Immunopharmacology	7	L	C57BL/6	G	?
4 weeks	-1.84	Narita	Suzuki	2006	Neuropsychopharmacology	?	R	C57BL/6J	I	100

TABLE S4. Age, side injected, sub-strain, lighting, and housing condition of each cohort and study included in the EPM meta-analysis.

Open Field Test Meta-Analysis Extended Data										
Time Post-Injection	Hedges g	First Author	Last Author	Year	Journal	Avg. Age (Weeks)	Side Injected	Strain	Housing	Lighting
2 days	-0.080	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	G	290
2 days	-0.039	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	I	290
1 week	-1.843	Yue	Liu	2018	Brain Research Bulletin	7	R	C57BL/6	G	?
1 week	-0.411	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	L	C57BL/6N	G	290
1 week	0.183	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6J	G	290
1 week	0.332	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	G	290
2 weeks	-3.706	Guo	Wu	2018	Cerebral Cortex	10	R	C57BL/6	G	?
2 weeks	-2.195	Zheng	Yi	2017	Journal of Neuroscience	6.5	L	C57BL/6	?	60
2 weeks	-2.009	Sun	Yang	2020	Neurotoxicity Research	7	L	C57BL/6	?	?
2 weeks	-1.565	Guan	Zhao	2020	Molecular Pain	7	R	C57BL/6J	G	?
2 weeks	-1.278	Tian	Tian	2017	Metabolic Brain Disease	9	L	C57BL/6	G	dim
2 weeks	-0.728	Liu	Zhang	2015	Physiology & Behavior	8	?	C57BL/6J	G	15
2 weeks	-0.725	Luo	Yang	2020	Molecular Brain	7	L	C57BL/6	G	dim
2 weeks	1.170	Pitzer	Tappe-Theodor	2018	European Journal of Pain	10	R	C57BL/6N	G	290
3 weeks	-2.316	Guo	Liu	2016	Nutritional Neuroscience	9	L	C57BL/6	G	dim
3 weeks	-1.766	Wang	Zhao	2015	Molecular Pain	8	L	C57BL/6	G	?
3 weeks	-1.310	Sun	Wu	2016	International Immunopharmacology	7	L	C57BL/6	G	dim

TABLE S5. Age, side injected, sub-strain, lighting, and housing condition of each cohort and study included in the OFT meta-analysis.