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Supplementary information

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This document includes:

Supplementary Notes.

Supplementary Note 1: Mapping a nociceptive hotspot in μ-opioidergic ACC neurons.

To identify pain-responsive neurons in the ACC, we used the TRAP2 activity-dependent transgenic mouse for nociceptive neural tagging (*pain*TRAP) [1,66]. Repeated noxious 55ºC stimuli to the hindpaw activated *Fos*-driven Cre recombination, permanently labeling nociceptive neurons with tdTomato throughout the nervous system (**Extended Data Fig. 1a–b**). Labeled *pain*TRAP+ neurons were distributed across the dorsal (Cg1) and ventral (Cg2) ACC but concentrated within a ~700-μm segment of the ACC (+1.69 to +0.97 mm AP; **Extended Data Fig. 1b-d**), anterior to known mid-cingulate circuits for reflexive pain responses [81,82]. Two weeks later, mice were re-exposed to the same noxious stimulus, and we immunostained for FOS protein (*pain*FOS) to assess reactivation of the *pain*TRAP+ neural population. Compared to no-stimulus controls (**Extended Data Fig. 1e-g**), *pain*TRAP mice showed a 2.3-fold increase in double-labeled painTRAP+/painFOS+ neurons (**Extended Data Fig. 1c,f**), indicating stable recruitment of a pain-reactive ACC neural ensemble.

Given the dense expression of mu-opioid receptors (MORs) in the ACC [83–86] and their known role in analgesia [28,87], we next asked whether pain-responsive neurons in this region express the MOR-encoding gene *Oprm1*. Using fluorescent *in situ* hybridization and HALO deep-learning histology quantification, we measured co-expression of *Oprm1* and noxious stimulus-induced *Fos* mRNA (*painFos*) in male and female mice with either uninjured or neuropathic pain conditions (**Extended Fig. 2**). On average, ~30% of *painFos*+ neurons expressed *Oprm1* in uninjured mice, increasing to ~50% during chronic neuropathic pain (**Extended Data Fig. 2c–d**), indicating enhanced recruitment of MOR-expressing ACC neurons in persistent pain states.

To further refine the identity and distribution of these opioidergic nociceptive neurons, we mapped *Oprm1* expression across ACC layers. Approximately 71% of *Oprm1*+ cells in Cg1 co-expressed the excitatory pyramidal neuron marker *Slc17a7* (VGLUT1; 9,488 of 13,047 cells) and were evenly distributed across cortical layers (**Extended Data Fig. 2b-d**). However, both the proportion of *Oprm1*+ cells and mRNA transcript density per cell increased down the layers in a graded manner, similar to quantifications in MOR-mCherry mice [88], but in contrast, we did not detect sex differences. Consistent with *pain*TRAP counts (**Extended Data Fig. 1**), *painFos* expression was highest in Cg1 Layer 2/3, where ~25% of *Oprm1*+ cells also expressed *painFos*, suggesting that specific subsets of excitatory MOR-expressing neurons in superficial *vs.* deep layers may be preferentially engaged by noxious events.

Supplementary Note 2: Molecular profiling of opioid and nociceptive ACC cell-types over the development of chronic pain.

To identify ACC cell types involved in acute *vs.* chronic neuropathic pain processing and opioid receptor-mediated analgesia, we performed single-nucleus RNA sequencing (snRNA-seq) from neurons within the nociceptive hotspot defined by *pain*TRAP (**Extended Data Fig. 3**). We collected bilateral ACC punches from mice at 3 days, 3 weeks, and 3 months after bilateral spared nerve injury (SNI [89]), along with uninjured controls (n = 4 mice per injury

condition/timepoint), for subsequent Differential Expressed Gene (DEG) analysis over the development of chronic pain [90]. To enrich for allodynia-relevant activity, we applied a light-touch (0.16 g) mechanical stimulus to the hypersensitive, injured paws 5 minutes before tissue collection to induce immediate early gene (IEG) mRNA expression (**Extended Data Fig. 3a**). We analyzed 104,302 single nuclei from the n = 16 mice and identified 23 distinct cell-type clusters (**Extended Data Fig. 3b**), including 14 glutamatergic, 3 GABAergic, and 6 non-neuronal populations (**Extended Data Fig. 3c,d**). Cluster distributions were consistent across all injury conditions (**Extended Data Fig. 3c,i**).

We next assessed the expression of opioid receptors (*Oprm1, Oprd1, Oprk1, Oprl1*) and their peptide ligands (*Penk, Pdyn, Pomc, Pnoc*; **Extended Data Fig. 3e**). In alignment with others [88] and our fluorescence *in situ* mapping (**Extended Data Fig. 2**), *Oprm1* showed a graded increase across glutamatergic neurons, from Layer 2/3 intratelencephalic (IT) types to Layer 6 corticothalamic (CT) types (**Fig. S3e, h**). In contrast with some reports [88,91,92], we observed limited expression in *Sst* or *Vip* GABAergic interneurons. To identify nociceptive cell types, we used two orthogonal IEG-based activity measures: a weighted activity score and Nebulosa density mapping across 25 IEGs (*pain*IEGs; **Extended Data Fig. 3f–g**). Only three cell types—L2/3 IT-3 (Cluster 3), L5 IT-1 (Cluster 6), and L6 CT-2 (Cluster 13)—showed consistent *pain*IEG activation across all three SNI timepoints – all of which expressed Oprm1 (**Extended Data Fig. 3h**).

To determine whether chronic pain alters ACC gene expression over time, we performed differential expression analysis across all 23 clusters using a pseudo-bulk edgeR approach (FDR < 0.05, $\log_2$FC > |0.25|). At 3 days post-SNI, we identified 3,583 DEGs, with 43, 208, and 184 DEGs for the *pain*IEG+ clusters, L2/3 IT-3, L5 IT-1 and LC CT-2, respectively (**Extended Data Fig. 3j**). Synaptic gene ontology (SynGO) analysis of these DEGs revealed changes in synaptic translation, vesicle cycling, and synapse organization (**Extended Data Fig. 3k**) [93]. Contrary to bulk-sequencing reports without cell-type resolution [94–96], few DEGs remained at 3 weeks (n = 635 total) and 3 months (n = 180 total) across all clusters (**Extended Data Fig. 3j**), making cluster-specific pathway analysis statistically infeasible. These findings suggest that despite persistent pain behaviors; ACC gene expression largely returns to a baseline state over time. This mirrors findings in peripheral dorsal root ganglia neurons, where transcriptional changes resolve by 2–8 weeks post-injury [97]. While some reports show decreased MOR expression in the mid-cingulate cortex with chronic pain [40,98], *Oprm1* expression in the anterior ACC remained stable across all conditions and cell types, with no change detected at any timepoint post-SNI—confirmed by both snRNA-seq and FISH in male and female mice (**Extended Data Fig. 2**) [99]. This stability supports the feasibility of targeting ACC MOR+ neurons for MOR promoter-based cell-type-specific therapies, independent of chronic pain-induced transcriptomic changes.

Supplementary Note 3: Necessity and sufficiency of ACC MORs for morphine analgesia.

Given prior evidence for the role of ACC MORs in mediating opioid pain relief [28], we next sought to test the necessity of ACC MORs expressed by ACC neurons to facilitate morphine analgesia on both the sensory-reflexive and affective-motivational components of pain behaviors [1] (**Extended Data Fig. 4a,b**). First, we knocked out *Oprm1* in ACC neurons by injecting AAV9-*hSyn*-eGFP-Cre into *Oprm1*$^{Flox/Flox}$ mice[100] (**Extended Data Fig. 4c,e**), leaving MORs intact elsewhere in the nervous system. qPCR confirmed >50% reduction in *Oprm1* (**Extended Data Fig. 4d**). Following a systemic dose of morphine (0.5 mg/kg, i.p. [28,29,101]) shown to selectively mediate affective analgesic responses without altering sensory thresholds, mice were tested on a battery of evoked-sensory stimuli tests to calculate changes in analgesia. Deletion of ACC MORs did not affect mechanical withdrawal thresholds, but significantly impaired morphine's effect to reduce affective-motivational behaviors (*e.g.,* paw licking, biting, guarding, and escape [66,100,102]; **Extended Data Fig. 4a**) in response to noxious 55ºC water and 6ºC acetone stimuli, relative to controls with intact MOR expression (**Extended Data Fig. 4f–g**). One week later, the same mice were tested on a 60-second exposure to an inescapable 50ºC hotplate. ACC MOR deletion blunted morphine-induced analgesia, as reflected in increased duration of licking and guarding behaviors (**Extended Data Fig. 4h**). In controls, morphine increased the latency between the initial reflexive paw withdrawal and the onset of paw licking behavior—from ~1 second to ~7.2 seconds. This dissociation between reflexive and affective responses was abolished in mice lacking ACC MORs (**Extended Data Fig. 4i**). Moreover, once bouts of affective-motivational behaviors began, ACC MOR-deleted mice spent more time engaged in licking (**Extended Data Fig. 4j**), indicating a loss of morphine suppression of aversive motivational drive.

To test sufficiency, we re-expressed human MOR (hMOR) in the ACC of global MOR knockout mice (MOR KO; *Oprm1*$^{Cre/Cre}$) [103] using a Cre-dependent AAV.DJ-*hSyn*-FLEx-mCherry-2A-hMOR [104] (**Extended Data Fig. 4k**). qPCR and mCherry fluorescence confirmed successful hMOR expression (**Extended Data Fig. 4l,m**). In MOR KO mice, morphine (0.5 mg/kg) had no effect on affective-motivational pain behaviors, but hMOR re-expression restored morphine analgesia in response to noxious 55ºC water and 6ºC acetone stimuli (**Extended Data Fig. 4n–o**). On the inescapable hotplate assay, morphine in hMOR-re-expressing mice increased the latency to initiate licking and reduced total engagement in affective-motivational behaviors (**Extended Data Fig. 4p**). This also restored the temporal dissociation between reflexive and affective responses (**Extended Data Fig. 4q–r**), mirroring the wild-type phenotype.

Supplementary Note 4: Chronic-pain reconfiguration of ACC ensemble coding and selective opioid rescue.

Spared-nerve injury (SNI) produces a broad degradation of information encoding in ACC ensembles. In the present data set (**Fig. 3 and Extended Data Fig. 11**), decoders trained on population activity in the dorsal ACC predict paw-licking with high fidelity in acute pain but perform markedly worse after SNI. A similar loss of fidelity has been reported for both noxious and innocuous tactile stimuli in a recent calcium-imaging study of the mouse ACC [105]; there, stimulus decoding accuracy declined in parallel with neuropathic allodynia (Acuña Fig. 3N,O). Furthermore, these authors report both hyperexcitability of ACC neurons (Acuña, Fig. 3E) and increased responsiveness of nociceptive stimulus-responsive neurons to touch (Acuña, Fig. 3L). They found that decoding impairments were rescued by the non-opioidergic analgesic gabapentin (Acuña, Fig. 4E,F).

In the current experiments, we did not find any significant change in population-level decoding of Lick following capsaicin (**Fig. 2e, Extended Data Fig. 8h**) or following morphine in either condition (**Extended Data Fig. 8h, Extended Data Fig. 11b, c**). However, we identified improvements of single cell selectivity (d') for lick among pLick neurons observed following morphine in both experiments (**Extended Data Fig. 8l, Extended Data Fig. 11i,j**), which suggest that a rescue of Lick-related information in particular morphine-responsive ensembles.

It is important to note that direct comparison of effects of the gabapentin results from Acuña et al.[105] and those of our morphine treatments are not possible between these two studies, as sensory and behavioral information may not be represented by the same ensembles in the same manner. Indeed, we observed contrasting adaptations in pLick neurons following chronic pain. Specifically, we did not see an increase in activity in pLick neurons in SNI mice compared to controls (**Fig. 3k,l**), and, furthermore, these neurons reduced their activity during licking. These differences suggest – though not definitively, due to our large experimental differences – that the hyper-excitable and -responsive sensory neurons identified by Acuña et al. are a distinct ensemble, adapted uniquely following chronic pain.

Nevertheless, the results of Acuña et al.[105] contextualize the degradation of behavior-encoding we observe following the induction of SNI. First, these data suggest that chronic pain broadly and multimodally degrades information encoding in ACC ensembles. Second, these results suggest that this information degradation results from complementary processes in the ACC: excessive and insufficient recruitment of sensory- and behavior-responsive neurons, respectively. Third, these show that this neural sensory hypersensitivity and behavioral hyposensitivity are associated with behavioral sensory hypersensitivity (Acuña, Fig. S13D) and perseverative, spontaneous motivational-affective behaviors (Fig. 3m), respectively. Together, our two studies suggest that persistent pain diminishes the signal-to-noise ratio of ACC population codes across multiple behavioral and sensory domains.

Supplementary Note 5: Modeling higher-order cingulate processes for pain affective-motivational dimensions using LUPE AMPS.

Theories of ACC function center around highly specialized cognitive-affective functions— task engagement, motivation, error detection, attention allocation, value appraisal, and action selection. Value appraisal of sensory information may lead to the engagement of appropriate motor actions[13,106], which are critical in measured performance in cognitive tasks involving decision-making based on sensory-guided information[107]. During a painful experience, the "task" can be defined as sustained motivational recuperative behaviors, and the "decision" as the selection to engage in protective and/or escape behaviors[66]. We find that ACC nociception preferentially engages animals in affective-motivational pain attending and escape behaviors. This aligns with the ACC's established role in amplifying task-relevant signals[108], especially under conflicting conditions[109] —such as balancing pain, ongoing behaviors, and analgesic effects. In acute pain, this circuitry may facilitate adaptive responses by enhancing nociceptive signals that promote protective behaviors like licking or rearing. In chronic pain, where pain persists beyond tissue injury, this same circuitry may become maladaptive, sustaining heightened emotional and behavioral responses to ongoing pain. Specifically, in line with ethological theory, the detailed behavioral measurements and dynamic transitions quantified from our LUPE experiments indicate that these volitional behaviors are composed of observable, stereotyped behavioral motifs that construct larger behavior repertoires, relying on affective and motivation-based signaling in the ACC during pain experiences[110].

Developing precise, accurate, and reliable preclinical methods to capture behavioral biomarkers that reflect the complexity of pain is essential for identifying treatments that engage cognitive-emotional pain circuits. Traditional rodent measures—such as reflexive withdrawal thresholds—provide valuable information about stimulus detection but fail to capture the affective-evaluative dimensions of pain that shape motivational behavior. In this context, deep learning and machine vision have become powerful tools for automated, high-resolution behavioral analysis, enabling unbiased quantification of pain-related dynamics and responses to analgesics or neural interventions[111–113]. LUPE advances this field by combining expert-guided semi-supervised classification with unsupervised clustering to robustly identify a core set of interpretable, ethologically grounded behaviors. Unlike fully unsupervised methods such as MoSeq[114] — which rely on fine-scale pose dynamics to define micro-behaviors that may not map cleanly onto cognitive-affective states[112] — LUPE explicitly captures high-level, volitional behaviors like paw licking that are historically linked to pain. By modeling transitions between these behaviors as Markov processes and clustering them using a k-means framework, LUPE identifies latent behavioral states that encode injury and analgesia, including a reproducible pain-associated state (*Pain State-4*). From these latent dynamics, we derive the mouse *Affective-Motivational Pain Scale* (AMPS) — a continuous, data-driven metric that tracks affective-motivational aspects of pain and their relief with opioids. Together, these features make LUPE a significant leap forward in behavioral phenotyping for pain neuroscience. It not only enables standardized and high-throughput behavioral analysis but also provides a new lens for decoding internal pain states — advancing our ability to evaluate therapeutics that target the affective burden of pain.

Supplementary Note 6: Rethinking opioid pain relief.

Opioids have been used for millennia in medicinal cases to alleviate the unpleasantness of pain and make it "less bothersome"[1,115]. Today, many prescription analgesics for moderate-to-severe pain are opioid derivatives, including morphine, codeine, oxycodone, hydrocodone, fentanyl, tramadol, methadone, hydromorphone, buprenorphine, and tapentadol[5,116,117]. Despite their efficacy, these compounds carry fatal and addictive side effects, largely due to the widespread activation of opioid receptors in critical areas processing reward and respiration. This highlights the urgent need for novel, non-opioid therapies to address the Opioid Epidemic[118,119]. While there have been significant reductions in opioid prescribing over the past decade, few safer alternatives for pain management have emerged, leaving millions of chronic pain patients with limited treatment options. Over recent decades, analgesic drug development aimed at molecular targets in peripheral sensory afferent neurons or spinal neural circuits has seen both clinical trial failures[6] and recent successes[120]. These efforts are directed toward advancing non-opioid pain management. Different pain-relieving drugs do not equally

interfere with the same underlying mechanisms or parts of the nervous system that contribute to pain [121]—for example, non-steroidal anti-inflammatory drugs (NSAIDs) reduce cyclooxygenase production of prostaglandins, Nav1.7 and Nav1.8 sodium channel blockers reduce peripheral nociceptor transmissions to the spinal cord, or as we show here, morphine modulates cortical affective processes to reduce pain unpleasantness [5,26,100,115]. Thus, identifying neural mechanisms that mediate opioid effects on unpleasantness are a critical step for advancing therapeutic discovery efforts aimed at developing more targeted, effective, and safer treatments[1].

Supplementary Note 7: Translating MOR-promoter chemogenetics to the clinic.

The present study shows that selectively silencing μ-opioidergic ensembles in the ACC can relieve the affective burden of chronic pain without producing tolerance or reinforcement. A logical next goal is to adapt this strategy for human use by pairing a human MOR promoter (*hMORp*) with AAV delivery and non-invasive blood–brain-barrier opening via focused ultrasound (FUS-BBBO)[70,122–124].

We have previously demonstrated that *hMORp* restricts reporter expression almost exclusively to *OPRM1*+ pyramidal neurons in the macaque ACC after intraparenchymal AAV1 infusion, achieving >90 % cell-type specificity with minimal spread to neighboring cortices [2]. This primate validation suggests that promoter specificity, and therefore circuit selectivity, could be preserved in the human ACC, whose *OPRM1* regulatory sequence and laminar architecture are highly conserved.

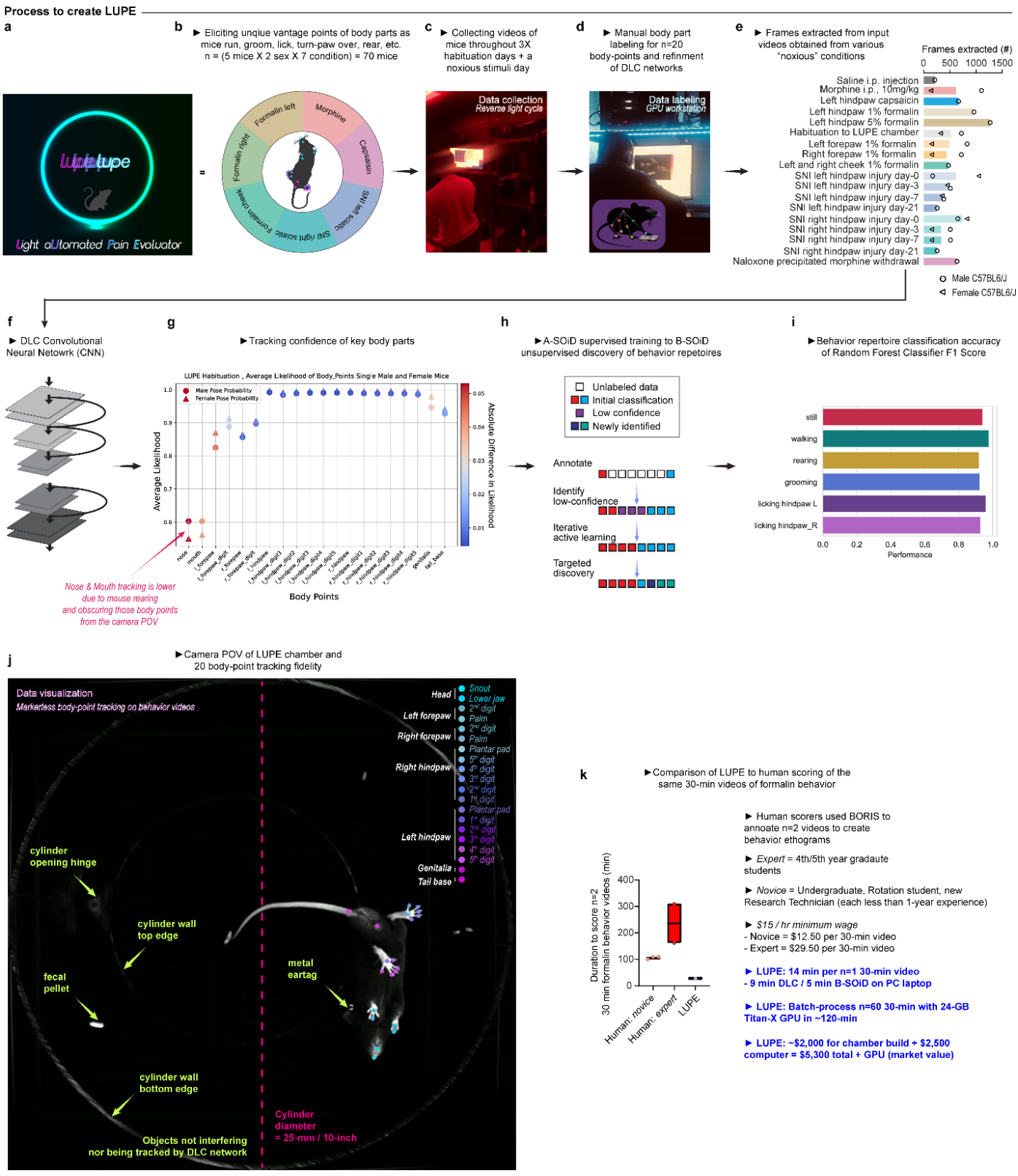
Direct stereotaxic AAV injection is already used clinically for movement disorders, yet it requires burr-hole drilling and needle tracks that carry hemorrhagic and infectious risks, especially if multiple cortical or subcortical pain hubs must be targeted. FUS-BBBO combines a systemically infused AAV with transient, MRI-guided ultrasound sonications to open the blood–brain barrier over millimeter-scale foci. The method has been applied in human patients[125,126] for antibody and chemotherapeutic delivery with an excellent safety record and no permanent tissue damage. In large-animal models, single FUS sessions enrich vector genomes 50- to 100-fold within the sonicated voxel while sparing the rest of the brain, making it an attractive, incision-free alternative for gene transfer to the ACC.

A chronic pain treatment could involve a one-time intravenous dose of an AAV-capsid optimized for human neurons carrying *hMORp*-hM4Di. FUS-BBBO would then concentrate the vector within the dorsal ACC bilaterally; expression stabilizes within weeks. Patients would thereafter self-administer an orally bioavailable DREADD agonist such as deschloroclozapine on an as-needed basis. Because the ligand is inert at endogenous receptors and active only at the engineered *hMORp*-DREADD ensemble, analgesia would be mediated by a single cortical node, circumventing the respiratory depression and reward pathway engagement that limit systemic opioids. Ligand dosing can be titrated, withheld, or re-initiated without loss of efficacy in pre-clinical models, offering a reversible and adjustable alternative to ablative surgery or continuous deep-brain stimulation.

Before human trials, several gaps must be addressed: (i) Dose optimization and biodistribution of systemic AAV under FUS-BBBO; (ii) Long-term safety of *hMORp*-driven DREADD expression, especially under repeated ligand exposure, including potential limitations such as deficits to decision-making and executive cognitive functions, analgesic tolerance and dependence, respiratory depression, motor impairment, and addiction-liability; and (iii) Ligand selection focusing on FDA-approved molecules with favorable pharmacokinetics and negligible off-target actions.

Combining promoter-level cell specificity with acoustic targeting offers a scalable path toward circuit-precise, addiction-sparing analgesia. As FUS-BBBO platforms mature and systemic AAV capsids advance in clinical pipelines, *hMORp*-based chemogenetics could be deployed as a single-session outpatient procedure that endows patients with on-demand control over their own cortical pain circuitry, thereby moving the field beyond broad opioids toward personalized, precision pain medicine.

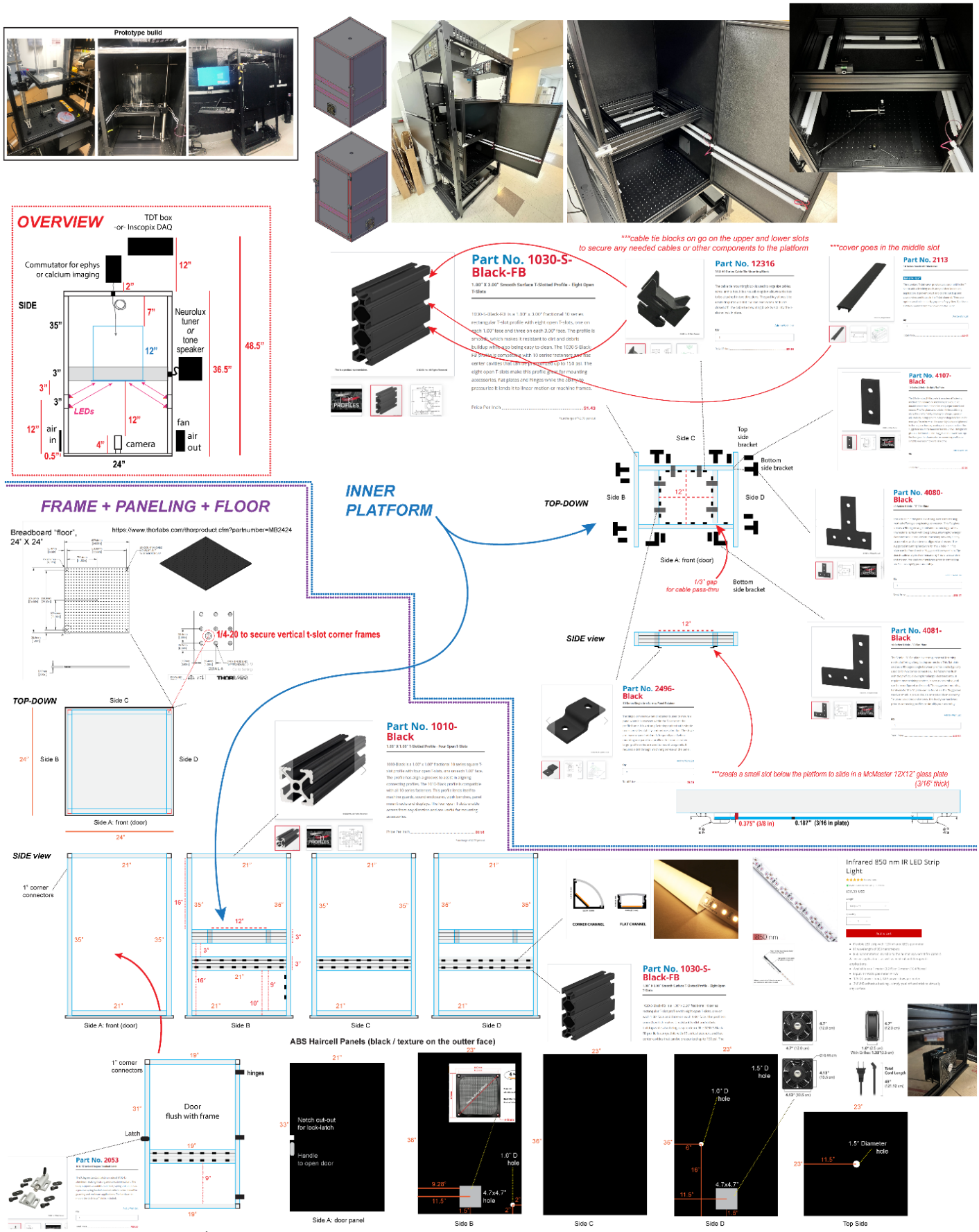
Supplementary Figures



Supplementary Fig. 1 | Process to create the LUPE analysis package.

(a) LUPE (**L**ight a**U**tomated **P**ain **E**valuator), a novel method for studying pain in mice in a controlled environment that allows for streamlined ethological behavior classification using open-source, machine learning algorithms for pose estimation and behavior classification. **(b)** Model training data includes video data from different pain and analgesia behavioral assays, capturing a range of behavior sequences with diverse pose dynamics. **(c)** Experimental assays were collected under reverse light cycles.

Video data was collected for three days when mice habituated to behavior room and LUPE chamber and on the fourth day when pain or analgesia assay was performed. **(d)** Input data for the LUPE-DLC network included manually extracted frames that were labeled with 20 body-points for each training iteration using a graphics processing unit (GPU). **(e)** Sum of frames labeled per experimental conditions per sex were manually selected based on sequences of behaviors where pose was not labeled confidently or correctly by the model. **(f)** This procedure of training evaluation, manual frame extraction and labeling, and retraining was iterative, taking advantage of DLC's convolutional neural network algorithm until pose-estimation performance was qualitatively and **(g)** quantitatively confident and accurate. The quantitative evaluation of the LUPE-DLC model was based on the computed mean average Euclidean error (MAE) between the manual labels and the ones predicted by DLC after each training iteration. The labeled test (DLC produced, unseen images) and training images were evaluated qualitatively to confirm model predictions aligned with required accuracy for pose assignment. **(h)**After developing the LUPE-DLC network, A-SOiD's active-learning algorithm translated the 2-dimensional pose of the 20 body-points into meaningful behavioral classification. **(i)** The A-SOiD active-learning training procedure was iterated 27 times until the model successfully classified six behavior motifs of interest at a high degree of confidence assessed by the random forest classifier F1 score. **(j)** Example image of the bottom-up camera perspective of the LUPE chamber details the maintained pose-estimation of the 20 body-points of interest while ignoring noise of the background in the image. **(k)** To compare the savings of time and money by utilizing LUPE networks, time to complete behavior classification for two 30-minute behavior assays was compared between LUPE, novice (n=3), and expert (n=2) human scorers. LUPE outcompeted human-scorers by requiring approximately 14 minutes to complete behavior classification of one 30-minute behavior recording.



Supplementary Fig. 2 | Process to create the LUPE chamber.

The standardized chamber consists of commercially available components, such as plastic sheeting, 80/20 t-slot frames and brackets, and infra-red 850-nm LED strips. The exact build

specifications, specifically the distance from the camera lens to the glass floor plate and location of the LEDs, provide a consistent video recording environment that can be easily replicated with and across labs. All dimensions and part numbers are listed in the figure layout. The ~ total time to build the LUPE chamber is 2.5 hours.

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Supplementary Statistics

Table S1

Row	Fig	Statistic-model	Variable	Degrees of freedom	Parameter	P-Value	n units	Multiple comparisons test	P-Values
1	1h, State 1	One-Way ANOVA	Injury conditions	(2, 57)	F = 8.19	0.0007	19-20 animals /group Uninjured/capsaicin: 10M/10F Formalin: 10M/9F	Uninjured vs. formalin	0.0039
								Uninjured vs. capsaicin	0.0017
								Formalin vs. capsaicin	0.96
2	1h, State 2	One-Way ANOVA	Injury conditions	(2, 57)	F = 0.75	0.48	19-20 animals /group (see row 1 for sex info)		

3	1h, State 3	One-Way ANOVA	Injury conditions	(2, 57)	F = 5.29	0.0078	19-20 animals /group (see row 1)	Uninjured vs. formalin	0.035
								Uninjured vs. capsaicin	0.010
								Formalin vs. capsaicin	0.89
4	1h, State 4	One-Way ANOVA	Injury conditions	(2, 57)	F = 16.53	<0.0001	19-20 animals /group (see row 1)	Uninjured vs. formalin	0.0001
								Uninjured vs. capsaicin	<0.0001
								Formalin vs. capsaicin	0.64
5	1h, State 5	One-Way ANOVA	Injury conditions	(2, 57)	F = 2.14	0.13	19-20 animals /group (see row 1)		
6	1h, State 6	One-Way ANOVA	Injury conditions	(2, 57)	F = 2.11	0.13	19-20 animals /group (see row 1)		
7	1k, PC1	One-Way ANOVA	Injury conditions	(2, 57)	F = 6.585	0.0027	19-20 animals /group (see row 1)	Uninjured vs. formalin	0.0095
								Uninjured vs. capsaicin	0.0058
								Formalin vs. capsaicin	0.9840
8	1k, PC2	One-Way ANOVA	Injury conditions	(2, 57)	F = 5.237	0.0082	19-20 animals /group (see row 1)	Uninjured vs. formalin	0.0610
								Uninjured vs. capsaicin	0.0080
								Formalin vs. capsaicin	0.7086
9	1l, Uninjured PC1	One-Way ANOVA	Morphine dose	(4,95)	F = 38.81	<0.0001	20 animals/dose; 10M/10F	0mg/kg vs. 0.5mg/kg	0.2176
								0mg/kg vs. 1.0mg/kg	0.0328
								0mg/kg vs. 5.0mg/kg	<0.0001
								0mg/kg vs. 10mg/kg	<0.0001
10	1l, Formalin PC1	One-Way ANOVA	Morphine dose	(4,94)	F = 11.38	<0.0001	19-20 animals /dose, 0, 1,10mg/kg: 10M/9F 0.5mg/kg: 9M/10F	0mg/kg vs. 0.5mg/kg	0.0074
								0mg/kg vs. 1.0mg/kg	0.1411
								0mg/kg vs. 5.0mg/kg	<0.0001

							5mg/kg: 10M/10F	0mg/kg vs. 10mg/kg	<0.0001
11	1l, Capsaicin PC1	One-Way ANOVA	Morphine dose	(4,94)	F = 13.98	<0.0001	19-20 animals /dose, 0,1,5,10mg/kg: 10M/10F 0.5mg/kg: 9M/10F	0mg/kg vs. 0.5mg/kg	0.0379
								0mg/kg vs. 1.0mg/kg	0.0083
								0mg/kg vs. 5.0mg/kg	<0.0001
								0mg/kg vs. 10mg/kg	<0.0001
12	1l, Uninjured PC2	One-Way ANOVA	Morphine dose	(4,95)	F = 21.74	<0.0001	20 animals/group; 10M/10F	0mg/kg vs. 0.5mg/kg	0.1170
								0mg/kg vs. 1.0mg/kg	0.0238
								0mg/kg vs. 5.0mg/kg	<0.0001
								0mg/kg vs. 10mg/kg	<0.0001
13	1l, Formalin PC2	One-Way ANOVA	Morphine dose	(4,94)	F = 7.507	<0.0001	19-20 animals/ group (see row 10)	0mg/kg vs. 0.5mg/kg	0.8454
								0mg/kg vs. 1.0mg/kg	0.7129
								0mg/kg vs. 5.0mg/kg	0.0397
								0mg/kg vs. 10mg/kg	0.0004
14	1l, Capsaicin PC2	One-Way ANOVA	Morphine dose	(4,94)	F = 15.89	<0.0001	19-20 animals per group (see row 11)	0mg/kg vs. 0.5mg/kg	0.0014
								0mg/kg vs. 1.0mg/kg	0.0007
								0mg/kg vs. 5.0mg/kg	<0.0001
								0mg/kg vs. 10mg/kg	<0.0001
15	2g	Two-Way ANOVA	Treatment	(1,4909)	0.052	0.82	Baseline: 1051; Mor: 1247; Cap: 1256; Mor + Cap: 1359 cells N=5 animals (all male)		
			Injury	(1,4909)	56.71	<0.0001			
			Interaction	(1,4909)	11.08	0.0009		Baseline: treatment	0.030
								Capsaicin: treatment	0.046
								No morphine: injury	<0.0001
								Morphine: injury	0.0043
16	2i	Two-Way ANOVA	Treatment	(1,908)	F = 6.25	0.0005	Cap: 229 Cap+Mor:227 cells N=5 animals (all male)		
			Behavior	(1,908)	F = 2.59	<0.0001			
			Interaction	(1,908)	F = 2.69	0.0004		Cap, States	0.96
								Cap+Mor, States	<0.0001
								Pain on, Treatment	<0.0001
								Pain off, Treatment	0.19
17	2j	Two-Way ANOVA	Treatment	(1,742)	F = 48.71	<0.0001	Cap: 196 Cap+Mor:186 cells N=5 animals (all male)		
			Behavior	(1,742)	F = 1.12	0.29			
			Interaction	(1,742)	F = 5.01	0.026		Cap, States	0.97
								Cap+Mor, States	0.021
								Pain on, Treatment	<0.0001
								Pain off, Treatment	0.0008

18	2k	Two-tailed unpaired t-test	Treatment 0-1s	286	t = 1.90	0.058	Cap: 135 bouts; Cap+Mor: 153 bouts N=5 animals (all male)		
19	2k	Two-tailed unpaired t-test	Treatment 1-2s	286	t = 3.62	0.0003	Cap: 135 bouts; Cap+Mor: 153 bouts N=5 animals (all male)		
20	2l	Two-tailed unpaired t-test	Treatment 0-1s	454	t = 0.59	0.55	Cap: 229 cells; Cap+Mor: 227 cells N=5 animals (all male)		
21	2l	Two-tailed unpaired t-test	Treatment 1-2s	454	t = 0.68	0.50	Cap: 229 cells; Cap+Mor: 227 cells N=5 animals (all male)		
22	2m	Two-tailed unpaired t-test	Treatment 0-1s	386	t = 3.61	0.0003	Cap: 196 cells; Cap+Mor: 186 cells N=5 animals (all male)		
23	2m	Two-tailed unpaired t-test	Treatment 1-2s	386	t = 0.78	0.43	Cap: 196 cells; Cap+Mor: 186 cells N=5 animals (all male)		
24	2o	Two-sided Kolgomorov-Smirnov test	Treatment		KS statistic = 0.0906	1.11e-23	0mg/kg: 10010 lick frames, n=20 animals (10M/10F); 0.5mg/kg: 4810 lick frames, n=19 animals (9M/10F)		
Row	Fig	Statistical model	Variable	Degrees of freedom	Parameter	P-Value	n units	Multiple comparisons test (Tukey unless otherwise specified; excessive non-significant values excluded for space)	P-Value
25	3b	Two-Way RM ANOVA	Day	(4,64)	F = 4.65	<0.0001	9 animals/group (5F, 4M)		
			Injury	(1,16)	F = 28.76	0.0023			
			Interaction	(4,64)	F = 4.35	0.0036		-1: SNI vs. Uninjured	0.68
								+1: SNI vs. Uninjured	0.0003
								+7: SNI vs. Uninjured	0.011

								+14: SNI vs. Uninjured	<0.0001
								+21: SNI vs. Uninjured	0.0002
								SNI: -1 vs. +1	0.0003
								SNI: -1 vs. +7	0.0004
								SNI: -1 vs. +14	0.0001
								SNI: -1 vs. +21	0.0003
26	3d	Two-Way RM ANOVA	Day	(4,64)	F = 10.05	<0.0001	9 animals/ group (5F, 4M)		
			Injury	(1,16)	F = 80.47	<0.0001			
			Interaction	(4,64)	F = 8.71	<0.0001		-1: SNI vs. Uninjured	0.88
								+1: SNI vs. Uninjured	<0.0001
								+7: SNI vs. Uninjured	<0.0001
								+14: SNI vs. Uninjured	<0.0001
								+21: SNI vs. Uninjured	<0.0001
								SNI: -1 vs. +1	<0.0001
								SNI: -1 vs. +7	<0.0001
								SNI: -1 vs. +14	<0.0001
								SNI: -1 vs. +21	<0.0001
27	3e	Two-Way RM ANOVA	Day	(4,64)	F = 4.77	0.0020	9 animals/ group (5F, 4M)		
			Injury	(1,16)	F = 5.20	0.037			
			Interaction	(4,64)	F = 3.71	0.0089		-1: SNI vs. Uninjured	0.82
								+1: SNI vs. Uninjured	0.13
								+7: SNI vs. Uninjured	0.032
								+14: SNI vs. Uninjured	0.0073
								+21: SNI vs. Uninjured	0.0043
								SNI: -1 vs. +1	0.0228
								SNI: -1 vs. +7	0.0002
								SNI: -1 vs. +14	0.0001
								SNI: -1 vs. +21	0.0005
28	3f	Two-Way RM ANOVA	Injury	(1,16)	F = 9.00	0.0085	9 animals/ group (5F, 4M)	Uninjured: +21 vs. morphine	0.046
								SNI: +21 vs. morphine	0.020
			Treatment	(1,16)	F = 11.23	0.0041		+21: uninjured vs. SNI	0.0072
								Morphine: uninjured vs. SNI	0.0126
			Interaction	(1,16)	F = 0.08	0.78			
29	3g	Two-Way ANOVA	Day	(4,2581)	F = 7.16	0.0064	Uninjured -1 day: 91; 1 day: 145; 7 days: 288; 14 days:134; 21 days: 207 cells SNI -1 day: 112; 1 day: 372; 7 days: 387; 14 days: 418; 21 days: 437 cells		
			Injury	(1, 2581)	F = 7.45	<0.0001			
			Interaction	(4, 2581)	F = 8.82	<0.0001		+21: SNI vs. Uninjured	<0.0001
								Uninjured: -1 vs. +1	0.045
								Uninjured: +1 vs. +7	0.045
								Uninjured: +1 vs. +21	0.0073
								Uninjured: +14 vs. +21	0.0043
								SNI: -1 vs. +1	0.0007
								SNI: -1 vs. +7	0.019
								SNI: -1 vs. +14	0.0002
								SNI: -1 vs. +21	<0.0001
								SNI: +7 vs. +21	0.010
30	3h	Two-Way ANOVA	Day	(4,2560)	F = 2.94	0.019	Uninjured		
			Injury	(1, 2560)	F = 29.53	<0.0001			

			Interaction	(4, 2560)	F = 2.91	0.021	-1 day: 104; 1 day: 135; 7 days: 313; 14 days: 154; 21 days: 213 cells <u>SNI</u> -1 day: 133; 1 day: 341; 7 days: 417; 14 days: 378; 21 days: 382 cells	-1: SNI vs. Uninjured	0.92
								+1: SNI vs. Uninjured	0.027
								+7: SNI vs. Uninjured	0.015
								+14: SNI vs. Uninjured	0.0013
								+21: SNI vs. Uninjured	<0.0001
								SNI: -1 vs. +1	0.0028
								SNI: -1 vs. +21	0.0009
								SNI: +7 vs. +21	0.033
31	3i	Two-Way ANOVA	Injury	(1, 1041)	F = 39.22	<0.0001	<u>Uninjured</u> 21 days: 207 cells, Mor: 128 cells <u>SNI</u> 21 days: 437 cells, Mor: 273 cells		
			Treatment	(1, 1041)	F = 81.76	<0.0001			
			Interaction	(1, 1041)	F = 4.45	0.035		21 days: Injury	<0.0001
								Morphine: Injury	<0.0001
								Uninjured: Treatment	<0.0001
								SNI: Treatment	0.0003
32	3j	Two-Way ANOVA	Injury	(1, 1014)	F = 30.80	<0.0001	<u>Uninjured</u> 21 days: 207 cells, Mor: 128 cells <u>SNI</u> 21 days: 437 cells, Mor: 273 cells	21 days: Injury	<0.0001
								Morphine: Injury	0.0010
			Treatment	(1, 1014)	F = 33.83	<0.0001		Uninjured: Treatment	0.0029
								SNI: Treatment	<0.0001
			Interaction	(1, 1014)	F = 0.58	0.035			
33	3k	Two-Way ANOVA	Injury	(1, 1041)	F = 11.17	0.0007	<u>Uninjured</u> 21 days: 207 cells, Mor: 128 cells <u>SNI</u> 21 days: 437 cells, Mor: 273 cells	21 days: Injury	0.11
								Morphine: Injury	0.0028
			Treatment	(1, 1041)	F = 4.37	0.037		Uninjured: Treatment	0.66
								SNI: Treatment	0.0023
			Interaction	(1, 1041)	F = 1.86	0.17			
34	3l	Two-Way ANOVA	Injury	(1, 1014)	F = 0.48	0.49	<u>Uninjured</u> 21 days: 207 cells, Mor: 128 cells <u>SNI</u> 21 days: 437 cells, Mor: 273 cells		
			Treatment	(1, 1014)	F = 6.42	0.012		Uninjured: Treatment	0.069
								SNI: Treatment	0.076
			Interaction	(1, 1014)	F = 0.035	0.85			
35	3m, 21 days	Linear regression	Lick rate x Magnitude of lick responses	(1, 7)	B = -1.05 ± 0.22, R^2 = 0.76, F = 22.68	0.0021	9 animals (5F, 4M)	Bonferroni for 2 comparisons	0.0042

			Pain state occupancy x Magnitude of lick responses	(1,7)	B = -0.41 ± 0.16, R^2 = 0.48, F = 6.53	0.038			0.076
36	3m, Mor	Linear regression	Lick rate x Magnitude of lick responses	(1, 7)	B = -0.73 ± 0.29, R^2 = 0.48, F = 6.32	0.040	9 animals (5F, 4M)	Bonferroni for 2 comparisons	0.080
			Pain state occupancy x Magnitude of lick responses	(1,7)	B = -0.34 ± 0.11, R^2 = 0.55, F = 8.65	0.022			0.044
37	3m, Change from 21 days to Mor	Linear regression	Lick rate x Magnitude of lick responses	(1, 7)	B = -0.85 ± 0.30, R^2 = 0.54, F = 8.10	0.035	9 animals (5F, 4M)	Bonferroni for 2 comparisons	0.050
			Pain state occupancy x Magnitude of lick responses	(1,7)	B = -0.32 ± 0.092, R^2 = 0.63, F = 12.07	0.010			0.020
Row	Fig	Statistical model	Variable	Degrees of Freedom	Parameter	P-Value	N units	Multiple comparisons test	P-values
38	4e (also shown in S17c)	Two-Way ANOVA	Days	2, 141	F = 21.76	<0.0001	19-30 animals per group YFP: 10M/9F hm4: 15M/15F		
			Virus	1, 141	F = 18.80	<0.0001			
			Interaction	2, 141	F = 7.096	0.0012		Baseline YFP vs hm4	0.9987
								23 days YFP vs hm4	<0.0001
								29 days YFP vs hm4	0.0300
								YFP baseline vs 23 days	<0.0001
								YFP baseline vs 29 days	<0.0001
								YFP 23 vs 29 days	0.6104
								hm4 baseline vs 23 days	0.3312
								hm4 baseline vs 29 days	0.3247
								hm4 23 vs 29 days	>0.9999
39	4g, pain states	Two-Way ANOVA	Day	2, 141	F = 24.04	<0.0001	19-30 animals per group YFP: 10M/9F hm4: 15M/15F		
			Virus	1, 141	F = 21.44	<0.0001			
			Interaction	2, 141	F = 8.53	<0.0001		Baseline YFP vs hm4	0.69
								23 days YFP vs hm4	<0.0001
								29 days YFP vs hm4	<0.0001
								YFP baseline vs 23 days	<0.0001
								YFP baseline vs 29 days	<0.0001
								YFP 23 vs 29 days	0.37
								hm4 baseline vs 23 days	0.0050
								hm4 baseline vs 29 days	0.0440
								hm4 23 vs 29 days	0.72
40	4g, non pain states	Two-Way ANOVA	Day	2, 141	F = 42.52	0.0001			
			Virus	1, 141	F = 39.74	0.0001			
			Interaction	2, 141	F = 12.95	0.0001		Baseline YFP vs hm4	0.62

							19-30 animals per group YFP: 10M/9F hm4: 15M/15F	23 days YFP vs hm4	<0.0001
								29 days YFP vs hm4	<0.0001
								YFP baseline vs 23 days	<0.0001
								YFP baseline vs 29 days	<0.0001
								YFP 23 vs 29 days	0.38
								hm4 baseline vs 23 days	0.0044
								hm4 baseline vs 29 days	0.050
								hm4 23 vs 29 days	0.67
41	4h (also shown in 4l)	Two-way ANOVA ,	Day	2, 94	F = 4.41	0.0147	19-30 animals per group YFP: 10M/9F hm4: 15M/15F		
			Virus	1, 47	F = 12.27	0.0010			
			Interaction	2, 94	F = 8.68	0.0003		Baseline YFP vs hm4	0.4096
								23 days YFP vs hm4	0.0009
								29 days YFP vs hm4	<0.0001
								YFP baseline vs 23 days	0.0004
								YFP baseline vs 29 days	0.0014
								YFP 23 vs 29 days	0.9432
								hm4 baseline vs 23 days	0.9743
								hm4 baseline vs 29 days	0.2068
								hm4 23 vs 29 days	0.2992
42	4j	Two-tailed unpaired t-tests	Virus	10	T ratio = 5.00	see multiple comparisons column for p-values due to space restraint	6 animals per group (3M/3F)	mMORp-hm4 vs mMORp-yfp mORB	0.00054
					2.15			PL	0.057
					2.54			IL	0.030
					5.76			ACC	0.00018
					3.87			CLA	0.0031
					2.55			AIC	0.029
					2.95			NAc	0.015
					4.47			RSP	0.0012
					2.69			lHAB	0.023
					4.19			CL	0.0019
					3.69			PVT	0.0042
					5.77			ZI	0.00018
					1.43			PIC	0.18
					2.71			BLA	0.022
					2.47			CeA	0.033
					8.10			dPAG	0.00001
					0.40			vlPAG	0.70
					0.45			DRN	0.66
					1.67			PBN	0.13
43	4k, Von Frey	One-way ANOVA	Virus/Treatment	6, 89	F = 3.255	P=0.0061	11-30 animals per group Uninjured Morphine:11 animals (6M/5F) mMORp-YFP: 15	mMORp-yfp vs mMORp-hm4	0.9777
								mMORp-yfp vs con/fon-hm4	0.8872
								mMORp-yfp vs morphine	>0.9999
								mMORp-yfp vs SNI + mMORp-hm4	0.5027
								mMORp-yfp vs SNI + mMORp-yfp	0.6494
								mMORp-yfp vs SNI + morphine	0.6228

							animals; 10M/5F mMORp-hm4: 15 animals; 10M/5F Con/fon-hm4: 15 animals; 8M/7F Neuropathic Morphine: 10 animals; 5M/5F mMORp-YFP: 19 animals; 10M/9F mMORP-hm4: 30 animals; 15M/15F	mMORp-hm4 + con/fon-hm4	0.9998
								mMORp-hm4 vs morphine	0.9835
								mMORp-hm4 vs SNI + mMORp-hm4	0.0887
								mMORp-hm4 vs SNI + mMORp-yfp	0.2029
								mMORp-hm4 vs SNI + morphine	0.1868
								Con/fon-hm4 vs. morphine	0.9153
								Con/fon-hm4 vs SNI + mMORp-hm4	0.0328
								Con/fon-hm4 vs SNI + mMORp-yfp	0.1010
								Con/fon-hm4 vs SNI + morphine	0.0917
								Morphine vs SNI + mMORp-hm4	0.6279
								Morphine vs SNI + mMORp-yfp	0.7286
								Morphine vs SNI + morphine	0.7054
								SNI + mMORp-hm4 vs SNI + mMORp-yfp	>0.9999
								SNI + mMORp-hm4 vs SNI + morphine	>0.9999
								SNI + mMORp-yfp vs SNI + morphine	>0.9999
44	4k, acetone	One-way ANOVA	Virus/Treatment	6, 89	F = 19.46	P<0.0001	See row 6	mMORp-yfp vs mMORp-hm4	<0.0001
								mMORp-yfp vs con/fon-hm4	<0.0001
								mMORp-yfp vs morphine	<0.0001
								mMORp-yfp vs SNI + mMORp-hm4	<0.0001
								mMORp-yfp vs SNI + mMORp-yfp	>0.9999
								mMORp-yfp vs SNI + morphine	0.7974
								mMORp-hm4 + con/fon-hm4	0.9992
								mMORp-hm4 vs morphine	0.8794
								mMORp-hm4 vs SNI + mMORp-hm4	0.8605
								mMORp-hm4 vs SNI + mMORp-yfp	<0.0001
								mMORp-hm4 vs SNI + morphine	0.0002
								Con/fon-hm4 vs. morphine	0.6460
								Con/fon-hm4 vs SNI + mMORp-hm4	0.9859
								Con/fon-hm4 vs SNI + mMORp-yfp	<0.0001
								Con/fon-hm4 vs SNI + morphine	0.0011
								Morphine vs SNI + mMORp-hm4	0.1846
								Morphine vs SNI + mMORp-yfp	<0.0001
								Morphine vs SNI + morphine	<0.0001

								SNI + mMORp-hm4 vs SNI + mMORp-yfp	<0.0001
								SNI + mMORp-hm4 vs SNI + morphine	0.0055
								SNI + mMORp-yfp vs SNI + morphine	0.8578
45	4k, 55-degree water	One-way ANOVA	Virus	6, 89	F = 13.57	<0.0001	See row 6	mMORp-yfp vs mMORp-hm4	<0.0001
								mMORp-yfp vs con/fon-hm4	<0.0001
								mMORp-yfp vs morphine	<0.0001
								mMORp-yfp vs SNI + mMORp-hm4	<0.0001
								mMORp-yfp vs SNI + mMORp-yfp	>0.9999
								mMORp-yfp vs SNI + morphine	0.1921
								mMORp-hm4 + con/fon-hm4	0.9920
								mMORp-hm4 vs morphine	0.9912
								mMORp-hm4 vs SNI + mMORp-hm4	0.7194
								mMORp-hm4 vs SNI + mMORp-yfp	<0.0001
								mMORp-hm4 vs SNI + morphine	0.0170
								Con/fon-hm4 vs. morphine	>0.9999
								Con/fon-hm4 vs SNI + mMORp-hm4	0.9855
								Con/fon-hm4 vs SNI + mMORp-yfp	<0.0001
								Con/fon-hm4 vs SNI + morphine	0.0938
								Morphine vs SNI + mMORp-hm4	0.9951
								Morphine vs SNI + mMORp-yfp	0.0002
								Morphine vs SNI + morphine	0.1637
								SNI + mMORp-hm4 vs SNI + mMORp-yfp	0.0002
								SNI + mMORp-hm4 vs SNI + morphine	0.2941
								SNI + mMORp-yfp vs SNI + morphine	0.3416
46	4l	One-way ANOVA	Treatment	4, 95	F = 21.74	<0.0001	20 animals per group (10M/10F)	0mg/kg vs. 0.5mg/kg	0.2212
47	4l	One-way ANOVA	Treatment	1, 16	F = 9.003	0.0085	9 animals per group (5M/4F)	SNI no treatment vs morphine	0.0204
Row	Fig	Statistical model	Variable	Degrees of Freedom	Parameter	P-Value	N units	Multiple comparisons test	P-values
48	Ext. Data 1h, entire ACC	Two-tailed t-test	Stimulus	2	T= 3.304	0.0807	2 animals/ group Hot water TRAP: 1M/1F Home cage TRAP: 2F		

49	Ext. Data 1h, peak range	Two-tailed t-test	Stimulus	2	T = 4.837	0.0402	2 animals/ group Hot water TRAP: 1M/1F Home cage TRAP: 2F		
50	Ext. Data 4d	Unpaired t-test	Virus (cre-GFP vs GFP)	4	T = 2.978	0.0408	3 animals/group		
51	Ext. Data 4f, von Frey	Two-way RM ANOVA	Treatment (before/after morphine)	1,23	F = 0.7618	0.3918	11 GFP (6M/5F), 14 cre-GFP (9M/5F)		
			Virus	1,23	F = 0.0002	0.9886			
			Interaction	1,23	F = 0.5584	0.4625			
52	Ext. Data 4f, hot water	Two-way RM ANOVA	Treatment (before/after morphine)	1,23	F = 11.32	0.0027	11 GFP (6M/5F), 14 cre-GFP (9M/5F)		
			Virus	1,23	F = 0.1637	0.6895			
			Interaction	1,23	F = 8.729	0.0071		Baseline vs morphine GFP	0.0006
								Baseline vs morphine cre-GFP	>0.9999
53	Ext. Data 4f, acetone	Two-way RM ANOVA	Treatment (before/after morphine)	1,23	F = 14.05	0.001	11 GFP (6M/5F), 14 cre-GFP (9M/5F)		
			Virus	1,23	F = 0.0461	0.0461			
			Interaction	1,23	F = 18.15	0.0003		Baseline vs morphine GFP	<0.0001
								Baseline vs morphine cre-GFP	>0.9999
54	Ext. Data 4g								
	von Frey	Mann-Whitney test	Virus (Cre vs. GFP)		U = 56	0.2086	11 GFP (6M/5F), 14 cre-GFP (9M/5F)		
	hot water	Mann-Whitney test	Virus (Cre vs. GFP)		U = 28	0.0061			
	acetone	Mann-Whitney test	Virus (Cre vs. GFP)		U = 14	0.0002			
55	Ext. Data 4h	Unpaired t-test	Virus (Cre vs. GFP)		T = 1.1772 (latency), T = 1.351 (total)	0.0897 (latency), 0.6175 (total)			
56	Ext. Data 4i	Unpaired t-test	Virus (Cre vs. GFP)		T = 3.601	0.0015			
57	Ext. Data 4j	Unpaired t-test	Virus (Cre vs. GFP)		T = 2.718	0.0123			
58	Ext. Data 4l	Unpaired t-test	Virus (YFP vs hMOR)		T = 7.692	0.0006	4 YFP, 3 hMOR		
59	Ext. Data 4n von Frey	Two-way RM ANOVA	Treatment (before/after morphine)	1,24	F = 0.2633	0.6125	10 YFP, 16 hMOR	Baseline - morphine vs YFP	>0.9999
			Virus	1,24	F = 0.2633	0.7760		Baseline - morphine vs hMOR	0.9418
			Interaction	1,24	F = 0.1564	0.6960			
60	Ext. Data 4n, hot water	Two-way RM ANOVA	Treatment (before/after morphine)	1,24	F = 4.323	0.0485	10 YFP, 16 hMOR	Baseline - morphine vs YFP	0.501

			Virus	1,24	F = 5.579	0.0266		Baseline - morphine vs hMOR	0.0001
			Interaction	1,24	F = 15.29	0.0007			
61	Ext. Data 4n, acetone	Two-way RM ANOVA	Treatment (before/after morphine)	1,24	F = 13.35	0.0154	10 YFP, 16 hMOR	Baseline - morphine vs YFP	>0.9999
			Virus	1,24	F = 1.351	0.2564		Baseline - morphine vs hMOR	<0.0001
			Interaction	1,24	F = 6.801	0.0154			
62	Ext. Data 4o								
	von Frey	Mann-Whitney test			U = 75.5	0.8134	10 YFP, 16 hMOR-YFP		
	hot water	Mann-Whitney test			U = 1	<0.0001			
	acetone	Mann-Whitney test			U = 3	<0.0001			
63	S4p						10 YFP, 16 hMOR-YFP		
	Latency to withdraw	Mann-Whitney test			U = 77	0.8971			
	Latency to attend	Mann-Whitney test			U = 23	0.0018			
	Total withdrawals	Mann-Whitney test			U = 63	0.3806			
	Total attending	Mann-Whitney test			U = 10	<0.0001			
64	Ext. Data 4q	Mann-Whitney test			U = 19.5	0.0007			
65	Ext. Data 4r	Mann-Whitney test			U = 32	0.0103			
66	Ext. Data 5c, left	Permutation test	Real vs. shuffled			<0.0001	19-20 animals /group 10M/10F capsaicin 10M/9F formalin 10M/10F SNI 100 shuffles/animal		
67	Ext. Data 7c, right	Permutation test	Real vs. shuffled			<0.0001	19-20 animals/ group (see row 15), 100 shuffles/animal		
68	Ext. Data 5d	Permutation test	Real vs. shuffled			<0.0001	20 animals (10M/10F)/ dose, 100 shuffles/animal		
69	Ext. Data 5e	Permutation test	Real vs. shuffled			<0.0001	19-20 animals /dose (see row 11) 100 shuffles/animal		
70	Ext. Data 5f	Permutation test	Real vs. shuffled			<0.0001	19-20 animals /group (see row 10) for sex info		

							100 shuffles/animal		
71	Ext. Data 5g	Permutation test	Real vs. shuffled			<0.0001	19 animals/group, 10M/9F, 100 shuffles/animal		
72	Ext. Data 5h	Permutation test	Real vs. shuffled			<0.0001	30 animals /group, 15M/15F, 100 shuffles/animal		
73	Ext. Data 5j	One-Way RM ANOVA	States	(5, 342)	F = 91.15	<0.0001	58 animals (30M/28F)	Uninjured vs. 1% formalin	
74	Ext. Data 5k	One-Way RM ANOVA	States	(5, 342)	F = 41.98	<0.0001	58 animals (30M/28F)	Uninjured vs. 5% formalin	
75	Ext. Data 6d, phase 1	One-Way ANOVA	Injury conditions	(3, 65)	F = 43.31	<0.0001	10-20 animals /group Uninjured/capsaicin: 10M/10F 1% formalin: 10M/9F 5% formalin: 5M/5F	Uninjured vs. 5% formalin	<0.0001
								Capsaicin vs. 5% formalin	<0.0001
								1% formalin vs. 5% formalin	<0.0001
76	Ext. Data 6d, phase 2	One-Way ANOVA	Injury conditions	(3, 65)	F = 19.27	<0.0001	19-20 animals /group (see row 24)	Uninjured vs. capsaicin	<0.0001
								Uninjured vs. 1% formalin	<0.0001
								Uninjured vs. 5% formalin	<0.0001
77	Ext. Data 6d, total	One-Way ANOVA	Injury conditions	(3, 65)	F = 26.27	<0.0001	19-20 animals /group (see row 24)	Capsaicin vs. 1% formalin	0.0028
								Capsaicin vs. 5% formalin	<0.0001
								1% formalin vs. 5% formalin	<0.0001
								0 vs. 0.5 mg/kg	0.60
								0 vs. 1.0 mg/kg	<0.0001
								0 vs. 5.0 mg/kg	<0.0001
78	Ext. Data 6e, Walk, uninjured, p1	One-Way ANOVA	Morphine dose	(4,95)	F = 33.99	<0.0001	19-20 animals /group No injury (all doses): 10M/10F 1% Formalin:	0 vs. 10.0 mg/kg	0.13
								0 vs. 0.5 mg/kg	0.27
								0 vs. 1.0 mg/kg	0.0002
								0 vs. 5.0 mg/kg	<0.0001

							0-0.5mg/kg: 10M/9F 1-10mg/kg: 10M/10F		
79	Ext. Data 6e, Walk, formalin, p1	One-Way ANOVA	Morphine dose	(4, 93)	F = 108.1	<0.0001	19-20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.0045
								0 vs. 0.5 mg/kg	0.0043
								0 vs. 1.0 mg/kg	<0.0001
								0 vs. 5.0 mg/kg	<0.0001
80	Ext. Data 6e, Walk, uninjured, p2	One-Way ANOVA	Morphine dose	(4,95)	F = 33.99	<0.0001	20 animals /group 10M/10F	0 vs. 10.0 mg/kg	0.23
								0 vs. 0.5 mg/kg	0.16
								0 vs. 1.0 mg/kg	0.0008
								0 vs. 5.0 mg/kg	<0.0001
81	Ext. Data 6e, Walk, formalin, p2	One-Way ANOVA	Morphine dose	(4,93)	F = 33.99	<0.0001	19 -20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.30
									0.90
									<0.0001
									<0.0001
82	Ext. Data 6e, Lick, no injury	One-Way ANOVA	Morphine dose	(4,95)	F = 0.20	0.94	20 animals /group 10M/10F		
								0 vs. 0.5 mg/kg	
								0 vs. 1.0 mg/kg	
								0 vs. 5.0 mg/kg	
83	Ext. Data 6e, Lick, formalin, p1	One-Way ANOVA	Morphine dose	(4, 93)	F = 8.38	<0.0001	19-20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.0003
									0.24
									0.012
									<0.0001
84	Ext. Data 6e, Lick, uninjured, p1	One-Way ANOVA	Morphine dose	(4,95)	F = 0.073	0.99	20 animals /group 10M/10F		
								0 vs. 0.5 mg/kg	
								0 vs. 1.0 mg/kg	
85	S8e, Lick, formalin, p1	One-Way ANOVA	Morphine dose	(4, 93)	F = 2.08	0.090	19 -20 animals /group (see row 27)	0 vs. 5.0 mg/kg	
86	Ext. Data 6f, Capsaicin Walk	One-Way ANOVA	Morphine dose	(4, 94)	F = 66.52	<0.0001	19-20 animals /group 0,1-10 mg/kg: 10M/10F 0.5 mg/kg: 9M/10F	0 vs. 10.0 mg/kg	0.013
								0 vs. 0.5 mg/kg	0.023
								0 vs. 1.0 mg/kg	<0.0001
								0 vs. 5.0 mg/kg	<0.0001
87	Ext. Data 6f, Capsaicin Lick	One-Way ANOVA	Morphine dose	(4, 94)	F = 8.21	<0.0001	19-20 animals /group (see row 35)	0 vs. 10.0 mg/kg	0.0083
								0 vs. 0.5 mg/kg	0.11
								0 vs. 1.0 mg/kg	0.0092

								0 vs. 5.0 mg/kg	<0.0001
88	Ext. Data 6g, State1, uninjured	One-Way ANOVA	Morphine dose	(4, 95)	F = 40.91	<0.0001	20 animals/ dose; 10M/10F	0 vs. 10.0 mg/kg	0.32
								0 vs. 0.5 mg/kg	0.050
								0 vs. 1.0 mg/kg	<0.0001
								0 vs. 5.0 mg/kg	<0.0001
89	Ext. Data 6g, State1, formalin	One-Way ANOVA	Morphine dose	(4, 94)	F = 20.92	<0.0001	19-20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.0002
								0 vs. 0.5 mg/kg	0.020
								0 vs. 1.0 mg/kg	<0.0001
								0 vs. 5.0 mg/kg	<0.0001
90	Ext. Data 6g, State1, capsaicin	One-Way ANOVA	Morphine dose	(4, 94)	F = 14.57	<0.0001	19-20 animals /group (see row 35)	0 vs. 10.0 mg/kg	0.068
								0 vs. 0.5 mg/kg	0.017
								0 vs. 1.0 mg/kg	<0.0001
								0 vs. 5.0 mg/kg	<0.0001
91	Ext. Data 6g, State2, uninjured	One-Way ANOVA	Morphine dose	(4, 95)	F = 29.76	<0.0001	19-20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.12
								0 vs. 0.5 mg/kg	0.020
								0 vs. 1.0 mg/kg	<0.0001
								0 vs. 5.0 mg/kg	<0.0001
92	Ext. Data 6g, State2, formalin	One-Way ANOVA	Morphine dose	(4, 94)	F = 13.55	<0.0001	19-20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.083
								0 vs. 0.5 mg/kg	0.11
								0 vs. 1.0 mg/kg	<0.0001
								0 vs. 5.0 mg/kg	<0.0001
93	Ext. Data 6g, State2, capsaicin	One-Way ANOVA	Morphine dose	(4, 94)	F = 14.57	<0.0001	19-20 animals /group (see row 35)	0 vs. 10.0 mg/kg	0.0088
								0 vs. 0.5 mg/kg	0.0021
								0 vs. 1.0 mg/kg	<0.0001
								0 vs. 5.0 mg/kg	<0.0001
94	Ext. Data 6g, State3, uninjured	One-Way ANOVA	Morphine dose	(4, 95)	F = 18.22	<0.0001	20 animals/ dose; 10M/10F	0 vs. 10.0 mg/kg	0.99
								0 vs. 0.5 mg/kg	0.99
								0 vs. 1.0 mg/kg	0.0074
								0 vs. 5.0 mg/kg	<0.0001
95	Ext. Data 6g, State3, formalin	One-Way ANOVA	Morphine dose	(4, 94)	F = 12.08	<0.0001	19-20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.99
								0 vs. 0.5 mg/kg	0.95
								0 vs. 1.0 mg/kg	0.0033
								0 vs. 5.0 mg/kg	<0.0001
96	Ext. Data 6g, State3, capsaicin	One-Way ANOVA	Morphine dose	(4, 94)	F = 18.22	<0.0001	19-20 animals /group (see row 35)	0 vs. 10.0 mg/kg	0.79
									0.79
								0 vs. 0.5 mg/kg	0.12
								0 vs. 1.0 mg/kg	<0.0001

97	Ext. Data 6g, State4, uninjured	One-Way ANOVA	Morphine dose	(4, 95)	F = 0.98	0.42	20 animals/ dose; 10M/10F	0 vs. 5.0 mg/kg	
98	Ext. Data 6g, State4, formalin	One-Way ANOVA	Morphine dose	(4, 94)	F = 9.30	<0.0001	19-20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.15
								0 vs. 0.5 mg/kg	.99
								0 vs. 1.0 mg/kg	0.10
								0 vs. 5.0 mg/kg	0.0019
99	Ext. Data 6g, State4, capsaicin	One-Way ANOVA	Morphine dose	(4, 94)	F = 14.46	<0.0001	19-20 animals /group (see row 35)	0 vs. 10.0 mg/kg	0.0065
								0 vs. 0.5 mg/kg	0.011
								0 vs. 1.0 mg/kg	0.0004
								0 vs. 5.0 mg/kg	<0.0001
100	Ext. Data 6g, State5, uninjured	One-Way ANOVA	Morphine dose	(4, 95)	F = 3.11	0.019	20 animals/ dose; 10M/10F	0 vs. 10.0 mg/kg	0.015
								0 vs. 0.5 mg/kg	0.14
								0 vs. 1.0 mg/kg	0.017
								0 vs. 5.0 mg/kg	0.62
101	Ext. Data 6g, State5, formalin	One-Way ANOVA	Morphine dose	(4, 94)	F = 9.28	<0.0001	19-20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.99
								0 vs. 0.5 mg/kg	0.99
								0 vs. 1.0 mg/kg	0.99
								0 vs. 5.0 mg/kg	<0.0001
102	Ext. Data 6g, State5, capsaicin	One-Way ANOVA	Morphine dose	(4, 94)	F = 6.47	0.0001	19-20 animals /group (see row 35)	0 vs. 10.0 mg/kg	0.99
								0 vs. 0.5 mg/kg	0.99
								0 vs. 1.0 mg/kg	0.92
								0 vs. 5.0 mg/kg	0.0003
103	Ext. Data 6g, State6, uninjured	One-Way ANOVA	Morphine dose	(4, 95)	F = 0.98	0.42	20 animals/ dose; 10M/10F	0 vs. 10.0 mg/kg	.99
								0 vs. 0.5 mg/kg	.99
								0 vs. 1.0 mg/kg	.048
								0 vs. 5.0 mg/kg	0.84
104	Ext. Data 6g, State6, formalin	One-Way ANOVA	Morphine dose	(4, 94)	F = 2.51	0.046	19-20 animals /group (see row 27)	0 vs. 10.0 mg/kg	0.065
								0 vs. 0.5 mg/kg	.41
								0 vs. 1.0 mg/kg	0.0012
								0 vs. 5.0 mg/kg	0.0038
105	Ext. Data 6g, State6, capsaicin	One-Way ANOVA	Morphine dose	(4, 94)	F = 5.02	0.0010	19-20 animals /group (see row 35)	0 vs. 10.0 mg/kg	0.0065
									0.011
									0.0004
									<0.0001
106	Ext. Data 7c, simulation	Kolgomorov-Smirnov test	Still sim v real		KS = 0.032	4e-73	6.2e5 still, 6.4e5 walk, 5.7e5 rear, 6.4e5		
			Walk sim v real		KS = 0.062	0			

			Rear sim v real		KS = 0.032	4e-36	groom, 5.4e5 lick		
			Groom sim v real		KS = 0.068	4e-309			
			Lick sim v real		KS = 0.17	0.			
107	Ext. Data 7c, capsaicin	Kolgomorov-Smirnov test	Still vs. lick		KS =0.147	0	46417 still, 39337 walk, 14367 rear, 33874 groom, 9234 lick		
			Walk vs. lick		KS = 0.347	0			
			Rear vs. lick		KS = 0.294	0			
			Groom vs. lick		KS =0.147	0			
108	Ext. Data 7c, formalin	Kolgomorov-Smirnov test	Still vs. lick		KS =0.391	0	25578 still, 27654 walk, 21927 rear, 23872 groom, 7448 lick		
			Walk vs. lick		KS = 0.448	0			
			Rear vs. lick		KS = 0.431	0			
			Groom vs. lick		KS =0.221	0			
109	Ext. Data 7c, SNI	Kolgomorov-Smirnov test	Still vs. lick		KS =0.303	0	110670 still, 107461 walk, 37053 rear, 79202 groom, 14501 lick		
			Walk vs. lick		KS = 0.314	0			
			Rear vs. lick		KS = 0.328	0			
			Groom vs. lick		KS =0.165	0			
110	Ext. Data 7f	Kolgomorov-Smirnov test	S1 vs. S2		KS = 0	1	3 in state 1, 2 in state 2, 6553 in state 3, 25327 in state 4, 887 in state 5, 1199 in state 6		
			S1 vs. S3		KS = 0.999	0.0013			
			S1 vs. S4		KS = 0.999	0.0013			
			S1 vs. S5		KS = 0.993	0.0015			
			S1 vs. S6		KS = 0.997	0.0014			
			S2 vs. S3		KS = 0.999	0.0112			
			S2 vs. S4		KS = 0.999	0.0112			
			S2 vs. S5		KS = 0.993	0.0120			
			S2 vs. S6		KS = 0.997	0.0115			
			S3 vs. S4		KS = 0.108	0			
			S3 vs. S5		KS = 0.423	0			
			S3 vs. S6		KS = 0.167	0			
			S4 vs. S5		KS = 0.458	0			
			S4 vs. S6		KS = 0.081	0			
			S5 vs. S6		KS = 0.489	0			
111	Ext. Data 8d, Still	Multiple paired t-tests	Real vs. Shuffled	4	t = 5.12	0.0065	5 animals (all male)	Baseline (FDR p<0.01)	q = 0.0066
					t = 16.0	<0.0001		Cap (FDR p<0.01)	q = <0.0001
					t = 16.55	<0.0001		Mor (FDR p<0.01)	q = <0.0001
					t = 10.42	0.0005		Mor + Cap (FDR p<0.01)	q = 0.0007

112	Ext. Data 8d, Walk	Multiple paired t-tests	Real vs. Shuffled	4	t = 7.04	0.0022	5 animals (all male)	Baseline (FDR p<0.01)	q = 0.0022
					t = 14.73	0.0001		Cap (FDR p<0.01)	q = 0.0003
					t = 7.72	0.0015		Mor (FDR p<0.01)	q = 0.0021
					t = 14.09	0.0002		Mor + Cap (FDR p<0.01)	q = 0.0003
113	Ext. Data 8d, Rear	Multiple paired t-tests	Real vs. Shuffled	4	t = 6.72	0.0026	5 animals (all male)	Baseline (FDR p<0.01)	q = 0.0026
					t = 8.75	0.0009		Cap (FDR p<0.01)	q = 0.0019
					t = 7.11	0.0021		Mor (FDR p<0.01)	q = 0.0026
					t = 13.79	0.0002		Mor + Cap (FDR p<0.01)	q = 0.0007
114	Ext. Data 8d, Groom	Multiple paired t-tests	Real vs. Shuffled	4	t = 11.71	0.0003	5 animals (all male)	Baseline (FDR p<0.01)	q = 0.0004
					t = 12.98	0.0002		Cap (FDR p<0.01)	q = 0.0004
					t = 10.95	0.0004		Mor (FDR p<0.01)	q = 0.0004
					t = 12.52	0.0002		Mor + Cap (FDR p<0.01)	q = 0.0004
115	Ext. Data 8d, Lick	Multiple paired t-tests	Real vs. Shuffled	3	t = 11.48	0.0015	5 animals (all male)	Cap (FDR p<0.01)	q = 0.0029
					t = 6.22	0.0084		Mor + Cap (FDR p<0.01)	q = 0.0085
116	Ext. Data 8g	Permutation tests	Real vs. Shuffled	1000	Morphine, Grooming, M3	0.064			
					All other tests displayed in figure	0			
117	Ext. Data 8j	Permutation tests	Real vs. Shuffled	1000	All tests displayed in figure	0			
118	Ext. Data 8l, positive *p*Lick	Two-Way ANOVA	Treatment	(1, 1816)	F = 4.39	0.037	Cap: 229 cells; Cap+Mor: 227 cells N= 5 animals (all male)	Still	0.58
								Walk	0.46
								Rear	0.031
								Groom	0.46
			Behavior	(3, 1816)	F = 28.0	<0.0001			
			Interaction	(3, 1816)	F = 0.56	0.94			
119	Ext. Data 8l, negative *p*Lick	Two-Way ANOVA	Treatment	(1, 1484)	F = 11.45	0.0007	Cap: 196 cells; Cap+Mor: 186 cells N= 5 animals (all male)	Still	0.41
								Walk	0.16
								Rear	0.032
								Groom	0.017
			Behavior	(3, 1484)	F = 16.62	<0.0001			
			Interaction	(3, 1484)	F = 0.51	0.69			
120	Ext. Data 9f	Permutation tests	Real vs. shuffled		SNI1, pin prick	0.21	1000		
					SNI1, hot water	0.08			
					SNI2, light touch	007			
					SNI2, water	0.01			
					SNI2, acetone	0.08			
					SNI3, light touch	0.02			
					SNI4, acetone	0.01			
					SNI5, pin prick	0.02			
					SNI5, acetone	0.04			
					SNI5, water	0.02			
					SNI7, acetone	0.03			
					SNI8, light touch	0.01			
					SNI9, light touch	0.01			
					SNI9, water	0.04			

					Ctrl1, pin prick	0.03			
					Ctrl2, light touch	0.01			
					Ctrl2, hot water	0.03			
					Ctrl2, pin prick	0.02			
					Ctrl2, hot water	0.01			
					Ctrl3, water	0.02			
					Ctrl3, acetone	0.02			
					Ctrl4, water	0.02			
					Ctrl4, pin prick	0.03			
					Ctrl4, acetone	0.32			
					Ctrl5, light touch	0.06			
					Ctrl5, acetone	0.02			
					Ctrl5, hot water	0.01			
					Ctrl7, water	0.01			
					Ctrl7, pin prick	0.01			
					All other tests	0			
121	Ext. Data 11b, left	Mixed effects RM model	Day	(4,41)	F = 0.3615	0.83	9 animals/ group (5F, 4M)		
			Injury	(1, 16)	F = 5.05	0.039			
			Interaction	(4, 41)	F = 3.97	0.0082		-1: SNI vs. Uninjured	0.066
								+1: SNI vs. Uninjured	0.041
								+7: SNI vs. Uninjured	0.042
								+14: SNI vs. Uninjured	0.0068
								+21: SNI vs. Uninjured	0.10
								SNI: -1 vs. +1	0.022
								SNI: -1 vs. +7	0.053
								SNI: -1 vs. +14	0.0056
122	Ext. Data 11b, right	Mixed effects RM model	Day	(1,10)	F = 0.12	0.73	9 animals/ group (5F, 4M)		
			Injury	(1,13)	F = 5.15	0.041		+21: SNI vs. Uninjured	0.20
								Mor: SNI vs. Uninjured	0.048
			Interaction	(1,10)	F = 0.47	0.51			
123	Ext. Data 11c, SNI	Mixed effects RM model	Day	(5,76)	4.62	0.001	9/animals/group (5F, 4M)		
			Injury	(1,16)	208.2	<0.0001			
			Interaction	(5,76)	4.05	0.0026			
124	Ext. Data 11c, Ctrl	Mixed effects RM model	Day	(1,10)	1.45	0.22	9/animals/group (5F, 4M)		
			Injury	(5,76)	770.4	<0.0001			
			Interaction	(1,16)	1.03	0.41			
125	Ext. Data 11f, left	Mixed effects RM model	Day	(5,76)	F = 0.30	0.87	9 animals/ group (5F, 4M)		
			Injury	(1,16)	F = 2.71	0.12			
			Interaction	(4,36)	F = 2.42	0.067			
126	Ext. Data 11f, right	Mixed effects RM model	Day	(1,9)	F = 0.76	0.41	9 animals/ group (5F, 4M)		
			Injury	(1,13)	F = 6.95	0.021		+21: SNI vs. uninjured	0.11

								Mor: : SNI vs. uninjured	0.0047
			Interaction	(1,9)	F = 4.11	0.073			
127	Ext. Data 11g, SNI	Mixed effects RM model	Day	5, 81	F = 3.859	0.0035	9/animals/group (5F, 4M)		
			Real vs Shuffle	1, 16	F = 208.7	<0.0001			
128	Ext. Data 11g, Ctrl	Mixed effects RM model	Day	5, 81	F = 1.444	0.22	9/animals/group (5F, 4M)		
			Real vs Shuffle	1, 16	F = 774.7	<0.0001			
129	Ext. Data 11i, left	Two-Way ANOVA	Injury	(1, 2581)	F = 10.74	0.0011	Uninjured -1 day: 91; 1 day: 145; 7 days: 288; 14 days:134; 21 days: 207 cells SNI -1 day: 112; 1 day: 372; 7 days: 387; 14 days: 418; 21 days: 437 cells		
			Treatment	(4, 2581)	F = 6.57	<0.0001			
			Interaction	(4, 2581)	F = 3.80	0.0044		-1: SNI vs. Uninjured	0.93
								+1: SNI vs. Uninjured	0.56
								+7: SNI vs. Uninjured	0.0034
								+14: SNI vs. Uninjured	0.11
								+21: SNI vs. Uninjured	<0.0001
								SNI: -1 vs. +1	0.070
								SNI: -1 vs. +7	0.43
								SNI: -1 vs. +14	0.0074
								SNI: -1 vs. +21	0.012
								Uninjured: +1 vs. +7	0.0016
								Uninjured: +1 vs. +21	0.0015
130	Ext. Data 11i, right	Two-Way ANOVA	Injury	(1, 1041)	F = 50.21	<0.0001	Uninjured 21 days: 207 cells, Mor: 128 cells SNI 21 days: 437 cells, Mor: 273 cells		
			Treatment	(4, 1041)	F = 19.51	<0.0001			
			Interaction	(4, 1041)	F = 3.92	0.048		21 days: Injury	<0.0001
								Mor: Injury	<0.0001
								Uninjured: Treatment	<0.0001
								SNI: Treatment	0.032
131	Ext. Data 11j, left	Two-Way ANOVA	Injury	(1, 2560)	F = 25.98	<0.0001	Uninjured -1 day: 104; 1 day: 135; 7 days: 313; 14 days: 154; 21 days: 213 cells SNI -1 day: 133; 1 day: 341; 7 days: 417; 14 days: 378; 21 days: 382 cells		
			Day	(4, 2560)	F = 7.32	<0.0001			
			Interaction	(4, 2560)	F = 4.00	0.0031		-1: SNI vs. Uninjured	0.10
								+1: SNI vs. Uninjured	0.0005
								+7: SNI vs. Uninjured	<0.0001
								+14: SNI vs. Uninjured	0.0010
								+21: SNI vs. Uninjured	<0.0001
								SNI: -1 vs. +1	<0.0001
								SNI: -1 vs. +7	0.0001
								SNI: -1 vs. +14	<0.0001
								SNI: -1 vs. +21	<0.0001
132	Ext. Data 11j, right	Two-Way ANOVA	Injury	(1, 1014)	F = 9.99	0.0016	Uninjured 21 days: 207 cells,	21 days: Injury	0.0001
								Mor: Injury	0.37

			Treatment	(1, 1014)	F = 4.78	0.029	Mor: 128 cells SNI 21 days: 437 cells, Mor: 273 cells	Uninjured: Treatment	0.81
								SNI: Treatment	0.0009
			Interaction	(4, 1014)	F = 3.22	0.073			
133	Ext. Data 11k, left	Mixed effects RM model	Day	(4, 52)	0.29	0.89	9 animals/ group (5F, 4M)		
			Injury	(1, 52)	2.37	0.13			
			Interaction	(4, 52)	0,29	0.88			
134	Ext. Data 11k, right	Mixed effects RM model	Treatment	(1, 10)	16.28	0.0024	9 animals/ group (5F, 4M)	Uninjured: +21 vs. mor	0.0047
								SNI: +21 vs. mor	0.090
			Injury	(1, 13)	3.57	0.082			
			Interaction	(1, 10)	3.33	0.098			
135	Ext. Data 11l, left	Mixed effects RM model	Day	(4, 36)	1.83	0.15	9 animals/ group (5F, 4M)		
			Injury	(1, 36)	0.61	0.45			
			Interaction	(4, 36)	0.66	0.63			
136	Ext. Data 11l, right	Mixed effects RM model	Treatment	(1, 9)	5.34	0.046	9 animals/ group (5F, 4M)	Uninjured: +21 vs. mor	0.16
								SNI: +21 vs. mor	0.43
			Injury	(1, 13)	0.013	0.91			
			Interaction	(1, 9)	0.86	0.46			
137	Ext. Data 13a, Von Frey	Two-way ANOVA	Time	2, 42	F = 0.7207	0.4007	15 animals per group mMORp-yfp and hm4: 10M/5F con/fon-hm4: 8M/7F		
			Virus	1, 42	F = 0.4099	0.6663			
			Interaction	2, 42	F = 0.4725	0.6267			
138	Ext. Data 13a, acetone	Two-way ANOVA	Time	2, 42	F = 44.52	<0.0001	15 animals per group (see row 11)		
			Virus	1, 42	F = 15.29	<0.0001			
			Interaction	2, 42	F = 10.16	0.0003		Baseline mMORp-yfp vs. mMORp-hm4-mCherry	0.6556
								Baseline mMORp-yfp vs con/fon-hm4	0.2608
								Baseline mMORp-hm4 vs con/fon-hm4	0.7643
								DCZ mMORp-yfp vs mMORp-hm4	<0.0001
								DCZ mMORp-yfp vs con/fon-hm4	<0.0001
								DCZ mMORp-hm4 vs con/fon-hm4	0.9907
								Baseline vs DCZ mMORp-YFP	0.8497
								Baseline vs DCZ mMORp-hm4	<0.0001
								Baseline vs DCZ con/fon-hm4	<0.0001
139	Ext. Data 13a, 55-	Two-way ANOVA	Time	2, 42	F = 58.91	<0.0001	15 animals per group		
			Virus	1, 42	F = 9.995	0.0003			

	degree water		Interaction	2, 42	F = 17.95	<0.0001	(see row 11)	Baseline mMORp-yfp vs. mMORp-hm4-mCherry	>0.999
								Baseline mMORp-yfp vs con/fon-hm4	>0.999
								Baseline mMORp-hm4 vs con/fon-hm4	>0.999
								DCZ mMORp-yfp vs mMORp-hm4	<0.0001
								DCZ mMORp-yfp vs con/fon-hm4	<0.0001
								DCZ mMORp-hm4 vs con/fon-hm4	>0.999
								Baseline vs DCZ mMORp-YFP	0.6787
								Baseline vs DCZ mMORp-hm4	<0.0001
								Baseline vs DCZ con/fon-hm4	<0.0001
140	Ext. Data 13b, latency to withdraw	One-way ANOVA	Virus	2,42	F = 18.47	<0.0001	15 animals per group (see row 11)	mMORp-yfp vs. mMORp-hm4	<0.0001
								mMORp-yfp vs. con/fon-hm4	0.3843
								mMORp-hm4 vs. con/fon-hm4	0.0002
141	Ext. Data 13b, Total withdrawals	One-way ANOVA	Virus	2,42	F = 14.38	<0.0001	15 animals per group (see row 11)	mMORp-yfp vs. mMORp-hm4	<0.0001
								mMORp-yfp vs. con/fon-hm4	0.3586
								mMORp-hm4 vs. con/fon-hm4	0.0013
142	Ext. Data 13b, latency to attend	One-way ANOVA	Virus	2,42	F = 25.60	<0.0001	15 animals per group (see row 11)	mMORp-yfp vs. mMORp-hm4	<0.0001
								mMORp-yfp vs. con/fon-hm4	<0.0001
								mMORp-hm4 vs. con/fon-hm4	0.7708
143	Ext. Data 13b, duration of attending	One-way ANOVA	Virus	2,42	F = 90.87	<0.0001	15 animals per group (see row 11)	mMORp-yfp vs. mMORp-hm4	<0.0001
								mMORp-yfp vs. con/fon-hm4	<0.0001
								mMORp-hm4 vs. con/fon-hm4	0.0050
144	Ext. Data 13c	One-way ANOVA	Virus	2,42	F = 15.38	<0.0001	15 animals per group (see row 11)	mMORp-yfp vs. mMORp-hm4	0.0021
								mMORp-yfp vs. con/fon-hm4	<0.0001
								mMORp-hm4 vs. con/fon-hm4	0.1778
145	Ext. Data 13d, withdrawal threshold	One-way ANOVA	Virus	2,42	F = 19.67	<0.0001	15 animals per group (see row 11)	mMORp-yfp vs. mMORp-hm4	<0.0001
								mMORp-yfp vs. con/fon-hm4	0.0245
								mMORp-hm4 vs. con/fon-hm4	0.0029
146	Ext. Data 14b, Von Frey	Two-way ANOVA	Time	8, 224	F = 74.17	<0.0001	mMORp-YFP: 19 animals; 10M/9F	mMORp-yfp baseline vs 21 days	<0.0001

							mMORP-hm4: 30 animals; 15M/15F	mMORp-hm4 baseline vs 21 days	<0.0001
			Virus	1, 28	F = 0.519	0.4772			
			Interaction	8, 224	F = 0.2193	0.9866			
147	Ext. Data 14b, acetone	Two-way ANOVA	Time	8, 224	F = 5.851	<0.0001	mMORp-YFP: 19 animals; 10M/9F mMORP-hm4: 30 animals; 15M/15F		
			Virus	1, 28	F = 110.5	<0.0001			
			Interaction	8, 224	F = 5.443	<0.0001		Baseline mMORp-hm4 vs mMORp-yfp	0.9960
								SNI 21 mMORp-hm4 vs mMORp-yfp	0.4866
								SNI 21 + DCZ mMORp-hm4 vs mMORp-yfp	<0.0001
								SNI 24 mMORp-hm4 vs mMORp-yfp	0.0196
								SNI 24 + DCZ mMORp-hm4 vs mMORp-yfp	<0.0001
								SNI 26 mMORp-hm4 vs mMORp-yfp	0.0017
								SNI 26 + DCZ mMORp-hm4 vs mMORp-yfp	<0.0001
								SNI 28 mMORp-hm4 vs mMORp-yfp	<0.0001
								SNI 28 + DCZ mMORp-hm4 vs mMORp-yfp	<0.0001
								mMORp-hm4 baseline vs SNI 21	<0.0001
								mMORp-hm4 SNI 21 vs 24	0.5452
								mMORp-hm4 SNI 21 vs 26	0.0846
								mMORp-hm4 SNI 21 vs 28	<0.0001
								mMORp-yfp baseline vs SNI 21	0.0019
								mMORp-yfp SNI 21 vs 24	>0.9999
								mMORp-yfp SNI 21 vs 26	>0.9999
								mMORp-yfp SNI 21 vs 28	0.9937
148	Ext. Data 14b,	Two-way ANOVA	Time	8, 224	F = 8.048	<0.0001	mMORp-YFP: 19		
			Virus	1, 28	F = 62.95	<0.0001			

	55-degree water		Interaction	8, 224	F = 7.006	<0.0001	animals; 10M/9F mMORP-hm4: 30 animals; 15M/15F	Baseline mMORp-hm4 vs mMORp-yfp	0.1858
								SNI 21 mMORp-hm4 vs mMORp-yfp	0.2800
								SNI 21 + DCZ mMORp-hm4 vs mMORp-yfp	<0.0001
								SNI 24 mMORp-hm4 vs mMORp-yfp	0.8396
								SNI 24 + DCZ mMORp-hm4 vs mMORp-yfp	<0.0001
								SNI 26 mMORp-hm4 vs mMORp-yfp	<0.0001
								SNI 26 + DCZ mMORp-hm4 vs mMORp-yfp	0.0017
								SNI 28 mMORp-hm4 vs mMORp-yfp	<0.0001
								SNI 28 + DCZ mMORp-hm4 vs mMORp-yfp	<0.0001
								mMORp-hm4 baseline vs SNI 21	0.0310
								mMORp-hm4 SNI 21 vs 24	0.9416
								mMORp-hm4 SNI 21 vs 26	<0.0001
								mMORp-hm4 SNI 21 vs 28	<0.0001
								mMORp-yfp baseline vs SNI 21	0.4656
								mMORp-yfp SNI 21 vs 24	0.7740
								mMORp-yfp SNI 21 vs 26	>0.9999
								mMORp-yfp SNI 21 vs 28	0.9126
149	Ext. Data 14c, lick left	Two-way ANOVA	Time	2, 141	F = 21.76	<0.0001	mMORp-YFP: 19 animals; 10M/9F mMORP-hm4: 30 animals; 15M/15F		
			Virus	1, 141	F = 18.8	<0.0001			
			Interaction	2, 141	F = 7.096	0.0012		Pre-SNI mMORp-hm4 vs mMORp-yfp	0.9987
								SNI 23D mMORp-hm4 vs mMORp-yfp	<0.0001
								SNI 29D mMORp-hm4 vs mMORp-yfp	0.0300
								mMORp-hm4 pre-SNI vs 23D	0.3312
								mMORp-hm4 pre-SNI vs 29D	0.3247
								mMORp-yfp pre-SNI vs 23D	<0.0001
								mMORp-yfp pre-SNI vs 29D	<0.0001
150	Ext. Data 14c, groom	Two-way ANOVA	Time	2, 141	F = 0.061	0.9410	mMORp-YFP: 19 animals; 10M/9F		
			Virus	1, 141	F = 0.0055	0.9408			
			Interaction	2, 141	F = 1.01	0.3668			

							mMORP-hm4: 30 animals; 15M/15F		
151	Ext. Data 14c, rear	Two-way ANOVA	Time	2, 141	F = 50.23	<0.0001	mMORp-YFP: 19 animals; 10M/9F mMORP-hm4: 30 animals; 15M/15F	mMORp-hm4 pre-SNI vs 23D	<0.0001
								mMORp-hm4 pre-SNI vs 29D	<0.0001
								mMORp-yfp pre-SNI vs 23D	<0.0001
								mMORp-yfp pre-SNI vs 29D	<0.0001
			Virus	1, 141	F = 11.23	0.001		Pre-SNI mMORp-hm4 vs mMORp-yfp	0.9446
								SNI 23D mMORp-hm4 vs mMORp-yfp	0.2042
								SNI 29D mMORp-hm4 vs mMORp-yfp	0.1024
			Interaction	2, 141	F = 0.8195	0.4428			
152	Ext. Data 14c, walk	Two-way ANOVA	Time	2, 141	F = 18.64	<0.0001	mMORp-YFP: 19 animals; 10M/9F mMORP-hm4: 30 animals; 15M/15F	mMORp-hm4 pre-SNI vs 23D	0.0002
								mMORp-hm4 pre-SNI vs 29D	<0.0001
								mMORp-yfp pre-SNI vs 23D	0.0088
								mMORp-yfp pre-SNI vs 29D	0.1160
			Virus	1, 141	F = 0.1458	0.7031			
			Interaction	2, 141	F = 0.6917	0.5024			
153	Ext. Data 14c, still	Two-way ANOVA	Time	2, 141	F = 3.910	0.0223	mMORp-YFP: 19 animals; 10M/9F mMORP-hm4: 30 animals; 15M/15F	mMORp-hm4 pre-SNI vs 23D	0.2827
								mMORp-hm4 pre-SNI vs 29D	0.0841
								mMORp-yfp pre-SNI vs 23D	0.7618
								mMORp-yfp pre-SNI vs 29D	0.9111
			Virus	1, 141	F = 0.6160	0.4339			
			Interaction	2, 141	F = 0.4031	0.6690			
154	Ext. Data 14d, PC1	Two-way RM ANOVA	Day	2, 94	31.81	<0.0001	mMORp-YFP: 19 animals; 10M/9F mMORP-hm4: 30 animals; 15M/15F	Baseline vs. 21 days + DCZ	<0.0001
								Baseline vs. 28 days + DCZ	<0.0001
								21 days + DCZ vs. 28 days + DCZ	0.85
			Virus	1, 47	2.71	0.11			
			Interaction	2, 94	2.64	0.076			
155	Ext. Data 14d, PC2	See statistics for Figure 4H							
156	Ext. Data 15e, left panel	Two-way ANOVA	Time	8, 192	F = 0.1334	0.9977	12-14 animals/ group Uninjured: 6M/6F Injured: 7M/7F		
			Virus	1, 24	F = 8.830	0.0066		Pre-test neuropathic MORp-iC++ vs uninjured MORp-iC++	>0.9999
								Session 1 neuropathic vs uninjured	0.1943
								Session 2 neuropathic vs uninjured	0.1788
								Session 3 neuropathic vs uninjured	0.3385

								Session 4 neuropathic vs uninjured	0.0019
								Session 5 neuropathic vs uninjured	0.0063
								Session 6 neuropathic vs uninjured	0.0005
								Session 7 neuropathic vs uninjured	0.0917
								Post-test neuropathic vs uninjured	0.0396
			Interaction	8, 192	F = 1.605	0.1256			
157	Ext. Data 15e, right panel	Unpaired t-test	Virus	24	t = 2.098	0.0466	12-14 animals/ group Uninjured: 6M/6F Injured: 7M/7F		