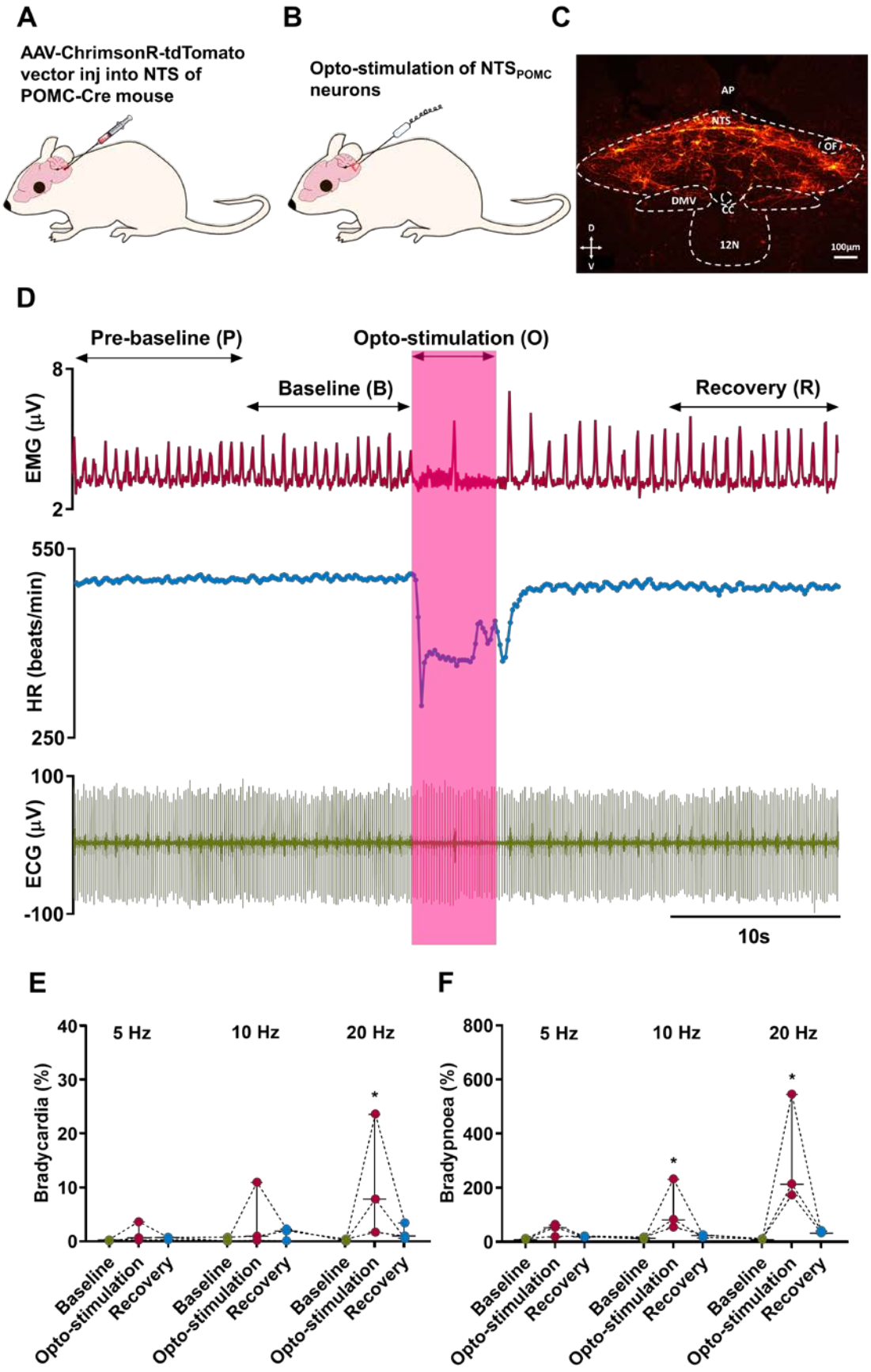
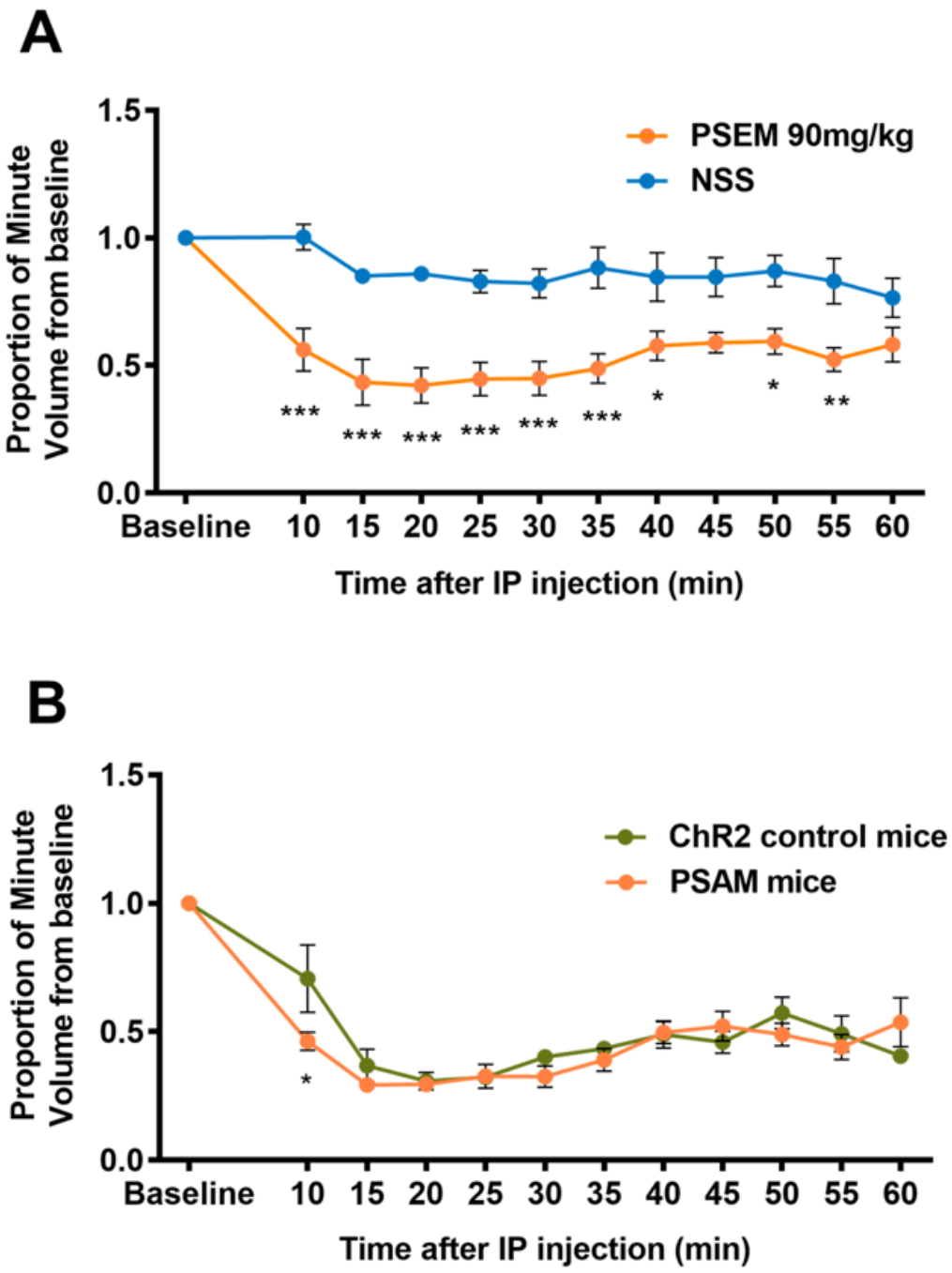
Supplemental Figure 1.



Supplemental Figure 1. Cardiorespiratory effect of opto-stimulation of NTS_{POMC} neurons in vivo. A. Injection of AAV-ChrimsonR-tdTomato into the NTS. **B.** opto-stimulation of NTS_{POMC} neurons in urethane anaesthetised $NTS_{POMC(Chrim)}$ mice. **C.** Histological section of medulla showing the transduced NTS_{POMC} neurons expressing tdTomato and location of optic fibre. **D.** Representative traces of ECG and EMG showing the bradycardia and bradypnoea evoked by opto-stimulation (20ms × 20Hz for 5s, red bar, periods for calculation of normalised HR and respiratory changes marked). **E.** Significant bradycardia (%) is seen only with opto-stimulation at 20Hz (vs baseline). **F.** Bradypnoea (%) is seen with opto-stimulation at 10Hz and 20Hz (vs baseline).

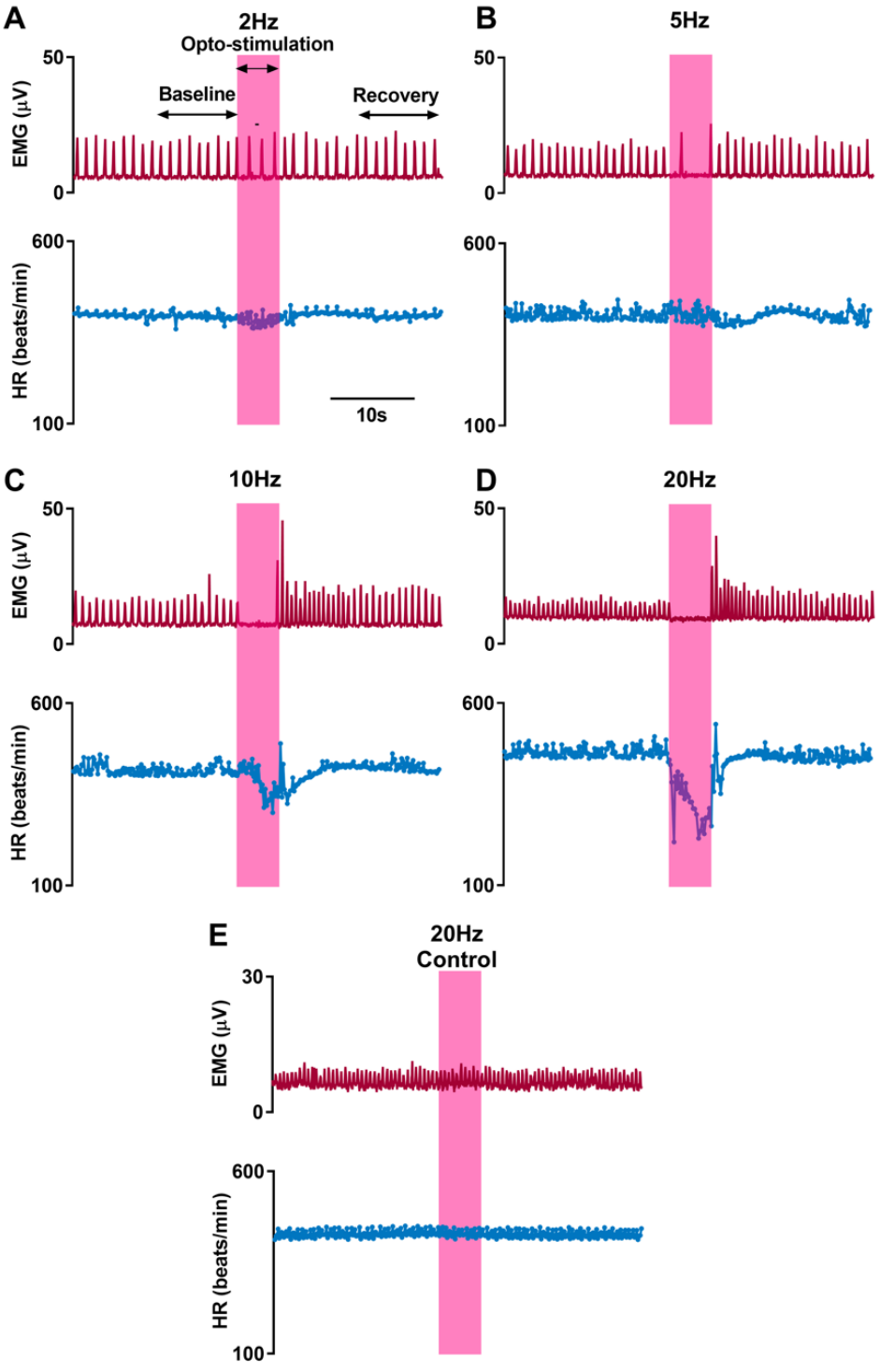
Data are presented as median, min to max. Data were analysed by Friedman test followed by Dunn's multiple comparison test, n=3, *$p<0.05$.

Supplemental Figure 2



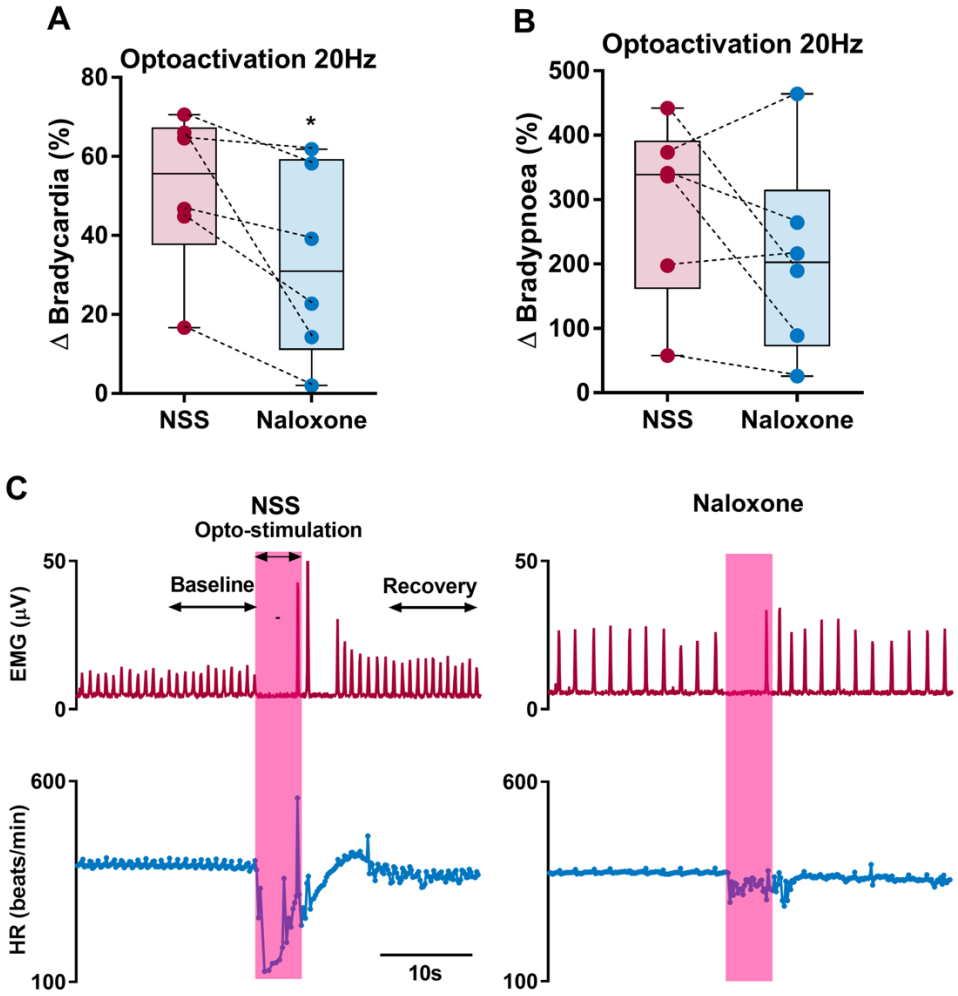
Supplemental Figure 2. A. Activation of POMC neurons with PSEM^{89s} (90mg/kg) produces a long-lasting respiratory depression (compared to saline control) in PSAM mice (n=8/group, RM 2-way ANOVA with Bonferroni post hoc). B) Subsequent control experiments also showed that PSEM^{89s} produced an equivalent degree of respiratory depression in control mice (injected with AAV-DIO-ChR2, n=4) and in naïve littermates (n=4, data not shown). Plethysmography with normalised minute volume (referenced to baseline period) (* P<0.05, ** P<0.01, *** P<0.001)

Supplemental Figure 3.



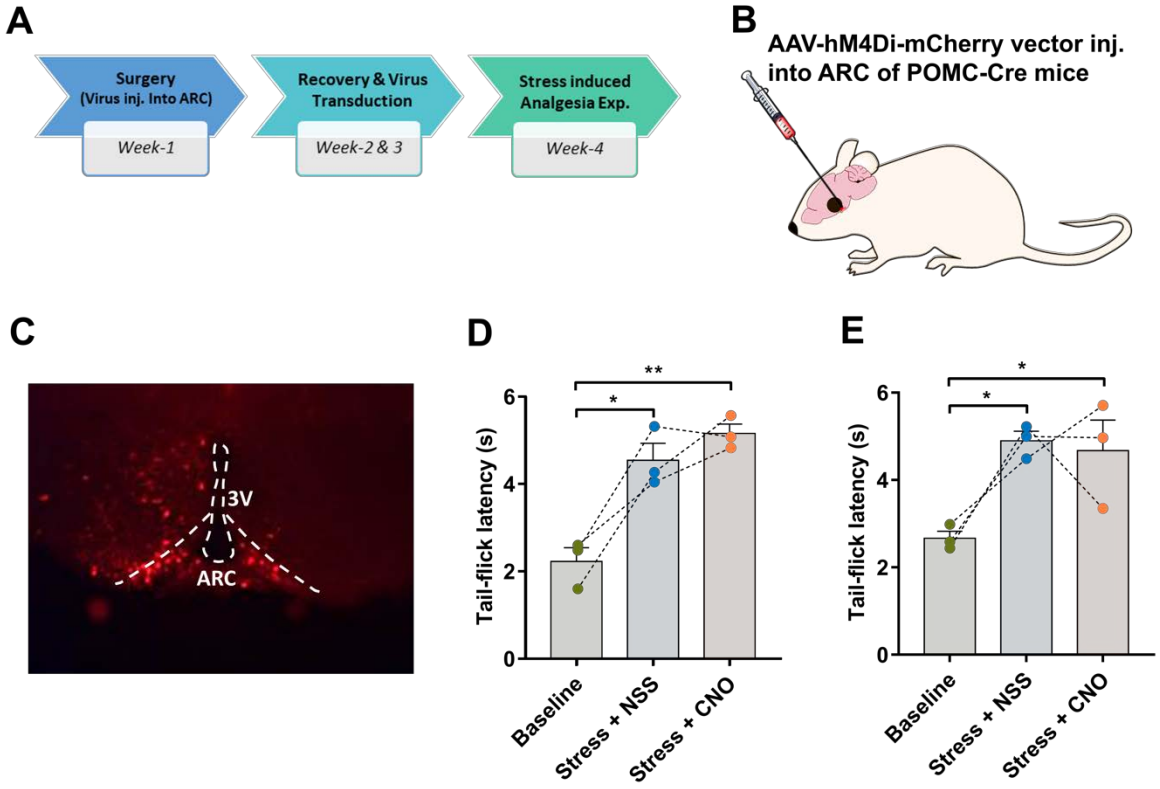
Supplemental Figure 3. Representative traces of heart rate and intercostal muscle EMG at different stimulation frequencies. Heart rate (lower panel) and EMG (upper panel, represents respiration) at **A.** 2Hz. **B.** 5Hz **C.** 10Hz and **D.** 20Hz in optic fibre implanted anaesthetised $NTS_{POMC(Chrim)}$ mice. A transient bradycardia and bradypnoea (increase in inter-breath interval) was seen during opto-stimulation. **E.** Heart rate and EMG in control vector injected mouse (implanted $NTS_{POMC(Dq)}$) following opto-stimulation at 20Hz.

Supplemental Figure 4.



Supplemental Figure 4. Effect of opioid antagonist naloxone on bradycardia and bradypnoea induced by opto-stimulation of NTS$_{POMC}$ neurons at 20Hz in NTS$_{POMC(Chrim)}$ mice. A. Δ Bradycardia was significantly lower 30 min after naloxone treatment (1 mg/kg, i.p) compared to the NSS (0.9% normal saline) treatment. **B.** Δ Bradypnoea was non-significant between naloxone and NSS treatment. **C.** Representative traces of heart rate and respiration shows naloxone vs NSS effect on opto-stimulation induced bradycardia and bradypnoea. Data are presented as median, min to max. Data were analysed by Wilcoxon matched-pairs signed rank test. n=6; *p<0.05.

Supplemental Figure 5.



Supplemental Figure 5. Effect of chemogenetic inhibition of ARC_{POMC} neurons on nociception and stress-induced analgesia. A. Timeline for ARC_{POMC} inhibitory chemogenetic experiment **B.** Schematic diagram shows injection of AAV2 hM4Di-mcherry into the ARC of POMC-Cre mice. **C.** Representative histological section of hypothalamus shows ARC_{POMC} neurons expressing mCherry in $ARC_{POMC(Gi)}$ mice. CNO failed to alter the stress induced analgesia in either **D.** $ARC_{POMC(Gi)}$ or **E.** control $ARC_{POMC(Chrim)}$ mice.

Data are presented as mean ± SE.*p<0.05, **p<0.01.

Supplemental Table 1. Details of vectors and procedures by group.

Experiment	Figure	Mice (n=)	Surgical procedure	Vector injected	Electrophysiology/Behavioural Assays
Acute medullary slice electrophysiology	Fig. 1 (A-C)	10	NTS viral vector injection	AAV-ChrimsonR-tdTomato	Slice electrophysiology
Acute optogenetic activation of NTS_{POMC} neurons	Suppl. Fig. 1 (A-F)	3	NTS viral vector injection	AAV-ChrimsonR-tdTomato	ECG/EMG
Chronic implanted optogenetic activation of NTS_{POMC} neurons	Fig. 2 (A-E, G, I-J), Fig. 3 (A, B, D, F-H), Suppl. Fig. 4 (A-B)	6	NTS Viral vector injection & optic fibre implantation	AAV-ChrimsonR-tdTomato	ECG/EMG, Hargreaves test, Tail-flick test, Conditioned place preference
	Fig. 2 (F, H), Fig. 3 (C, E)	6	NTS Viral vector injection & optic fibre implantation	AAV-hM3Dq-mcherry	ECG/EMG, Hargreaves test, Tail-flick test
Chemogenetic activation of NTS_{POMC} neurons	Fig. 4 (A-C, D, F), Fig. 5 (A-F)	6	NTS viral vector injection	AAV-hM3Dq-mcherry	Hargreaves test, Tail-flick test, Conditioned place preference, Open field test (n=5), Plethysmography (n=5)
	Fig. 4 (E, G), Fig. 5 (D-E), Fig 6 (E, G, I)	6	NTS viral vector injection	AAV-ChrimsonR-tdTomato	Hargreaves test, Tail-flick test, Open field test (n=4), Stress induced analgesia (n=4)
Chemogenetic activation of NTS_{POMC} neurons vs acute carrageenan induced inflammatory pain	Fig. 4 (H, J)	5	NTS viral vector injection	AAV-hM3Dq-mcherry	Von Frey test
Chemogenetic activation of NTS_{POMC} neurons vs chronic neuropathic pain	Fig. 4 (I, K, L)	6	NTS viral vector injection, Tibial Nerve Transection (TNT)	AAV-hM3Dq-mcherry	Von Frey test, Acetone test
Chemogenetic inhibition of NTS_{POMC} neurons	Fig. 6 (A-D, F, H)	8	NTS viral vector injection	AAV2 hM4Di-mcherry	Hargreaves test (n=6), Tail-flick test (n=6), Stress induced analgesia
Chemogenetic activation of POMC neurons with $PSEM^{89s}$	Suppl. Fig. 2 (A)	8	NTS viral vector injection	AAV-hSyn-FLEX-PSAM-$5HT_3$	Plethysmography
	Suppl. Fig. 2 (B)	4	NTS viral vector injection	AAV-EF1α-DIO-ChR2-mCherry	Plethysmography
Chemogenetic inhibition of ARC_{POMC} neurons	Suppl. Fig. 5 (A-D)	3	ARC viral vector injection	AAV2 hM4Di-mcherry	Stress induced analgesia
	Suppl. Fig. 5 (E)	3	ARC viral vector injection	AAV-ChrimsonR-tdTomato	Stress induced analgesia