

# Time-dependent changes in the pattern of activation of the noradrenergic Locus coeruleus after nerve injury in rats

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## INTRODUCTION

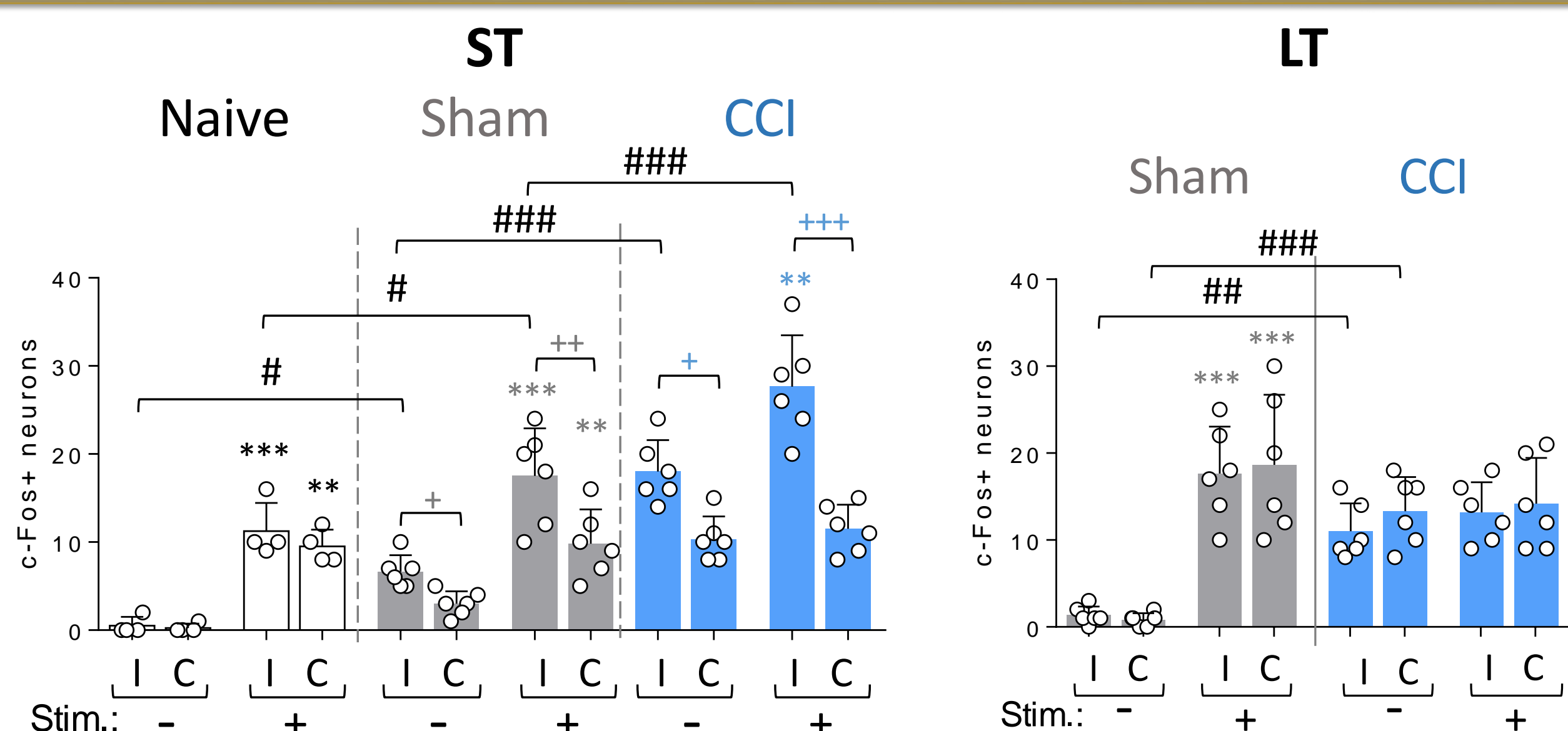
The noradrenergic-locus coeruleus (LC) is a key brain area related with pain plasticity. The mechanisms that underlie the changes produced in the transition from acute to chronic pain are still unknown. In order to advance in the mechanisms involved, LC activation and its projections have been explored, in addition to the ongoing pain study, which is very little studied at preclinical level in spite of its high clinical relevance.

## MATERIALS AND METHODS

To evaluate the LC→spinal-cord (SC) and LC→anterior cingulate anterior (ACC) activation pathways, expression of cFos and cFos+FG (Fluoro-Gold) were explored in the LC of TH:Cre male Long-Evans rats submitted to chronic constriction injury (CCI) at 2 (short-term: ST) and 30 days (long-term: LT) after nerve injury with or without nociceptive stimulation. Ongoing pain was also evaluated at ST, MT (mid-term) and LT after modulation of LC and its projections to SC and ACC, using DREADD technology. The role of ACC was also explored.

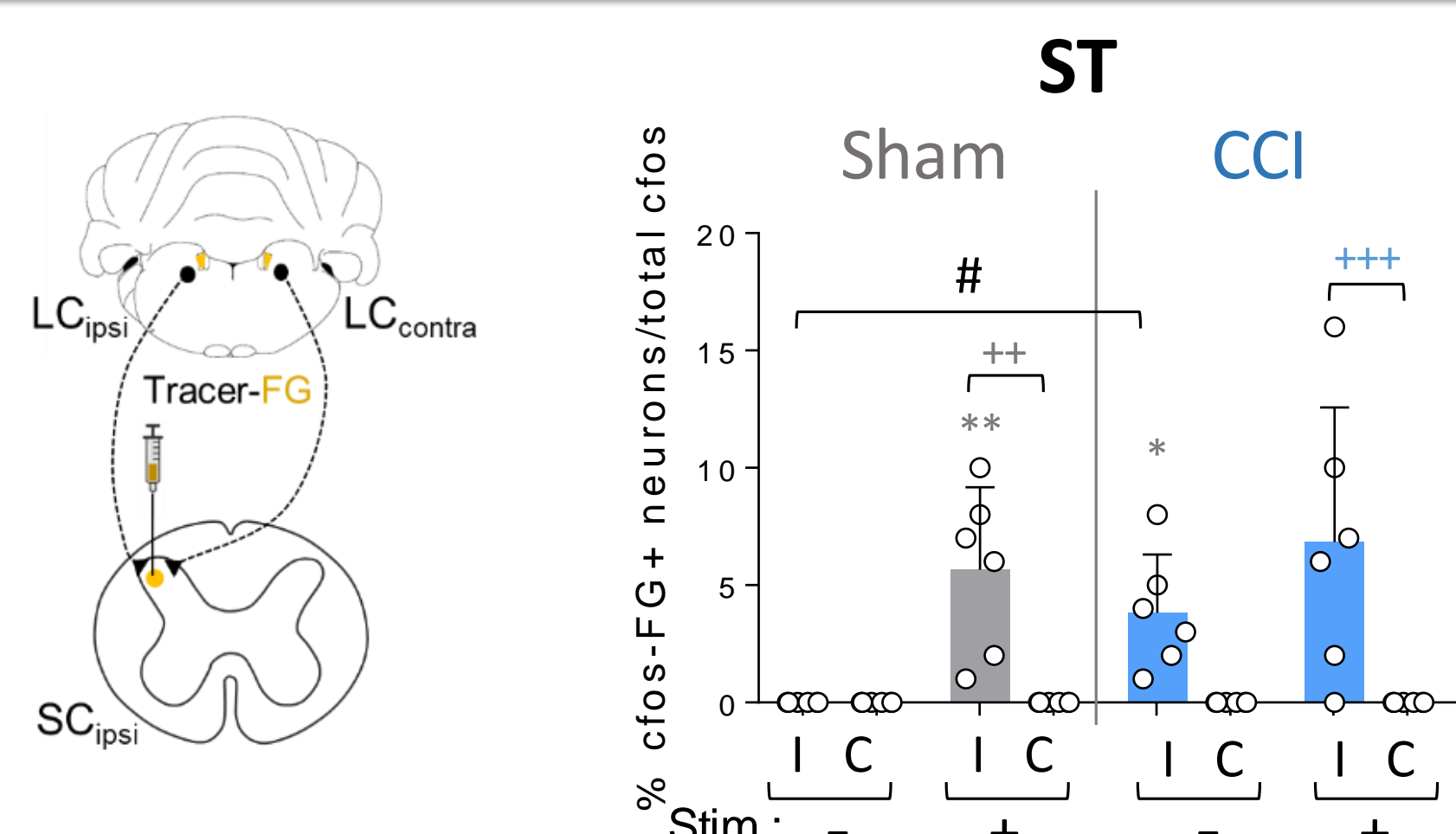
## RESULTS

### 1. Immunohistochemical study of LC activation

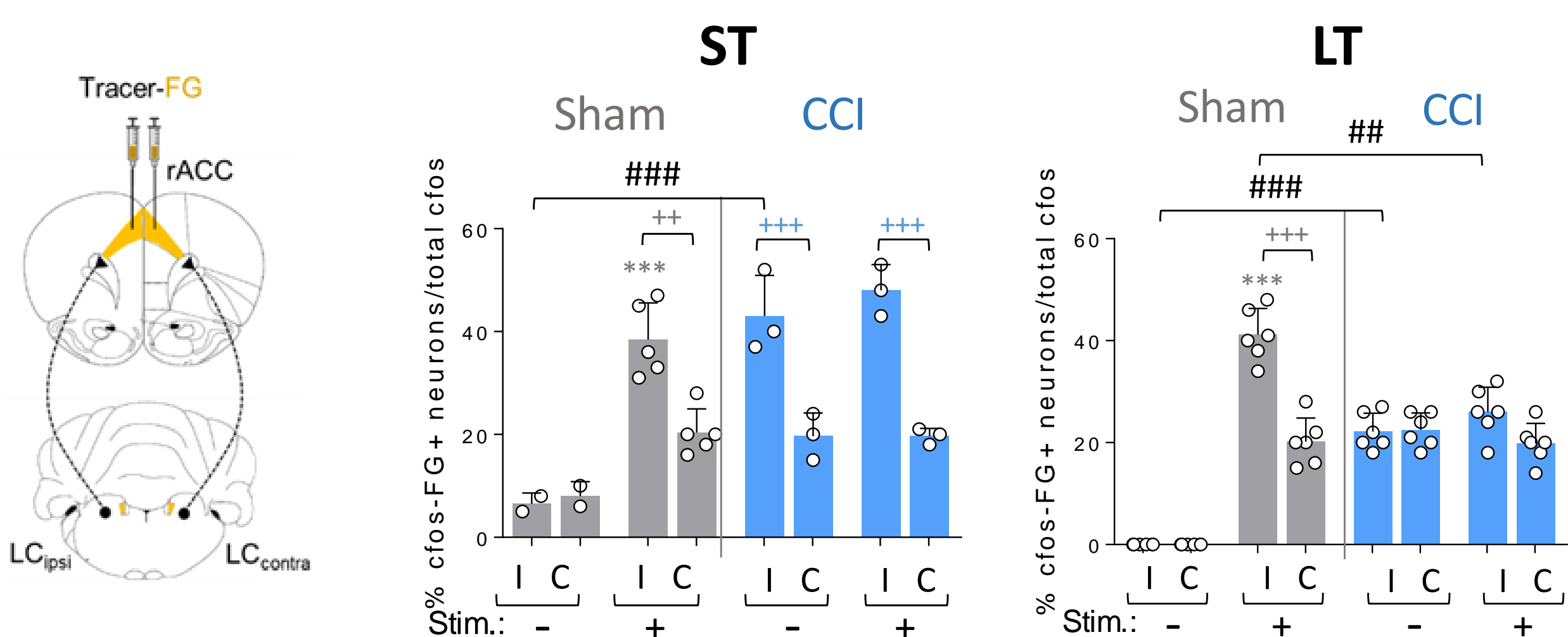


Higher and lateralized cFos expression in Sham-ST and CCI-ST compared with Naïve animals were found. Sham-LT behaved as Naïve and CCI-LT showed also higher levels of cFos but they were similar in both LCs. After nociceptive stimuli application, cFos increased in all groups excepting in CCI-LT animals.

### 2. Immunohistochemical study of LC → SC and LC → ACC activation



LC → SC projection evaluation showed cFos-positive cells in the LC<sub>ipsilateral</sub> in basal CCI-ST and after nociceptive stimuli in Sham-ST and CCI-ST. None LT-group (Sham-LT or CCI-LT) showed cFos-positive cells.



LC → ACC projection showed a higher ipsilateral activation in basal CCI-ST as well as in Sham-ST and CCI-ST after stimulated conditions. CCI-LT showed similar higher levels of cFos expression in both LCs in basal and stimulated conditions

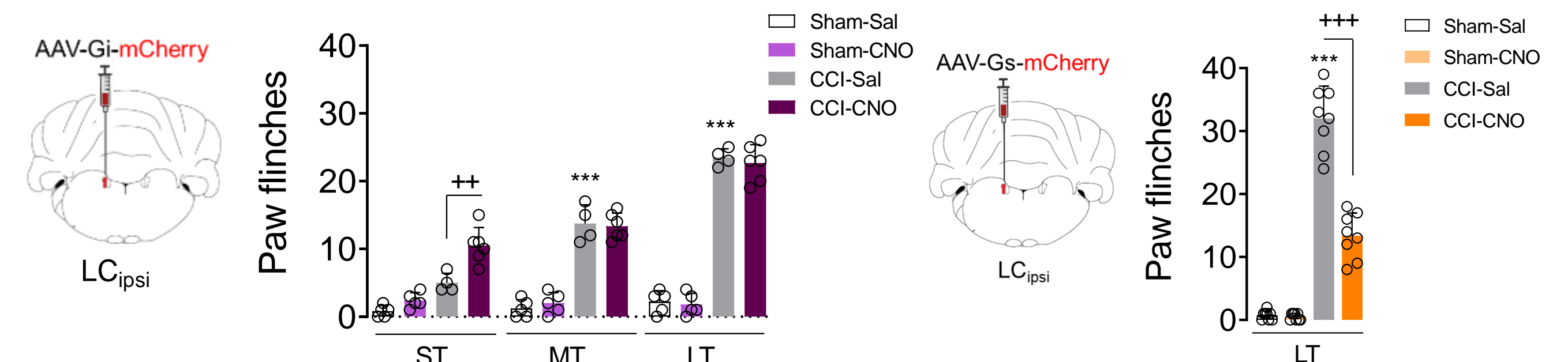
Stim.: - (non stimulated); Stim.: + (stimulated); I (ipsilateral-paw); C (contralateral-paw)

Three-way ANOVA + Tukey-posthoc: #vs Control (Naive vs Sham; Sham vs CCI); \*vs NoEst; +vs Ipsi-paw

## CONCLUSION

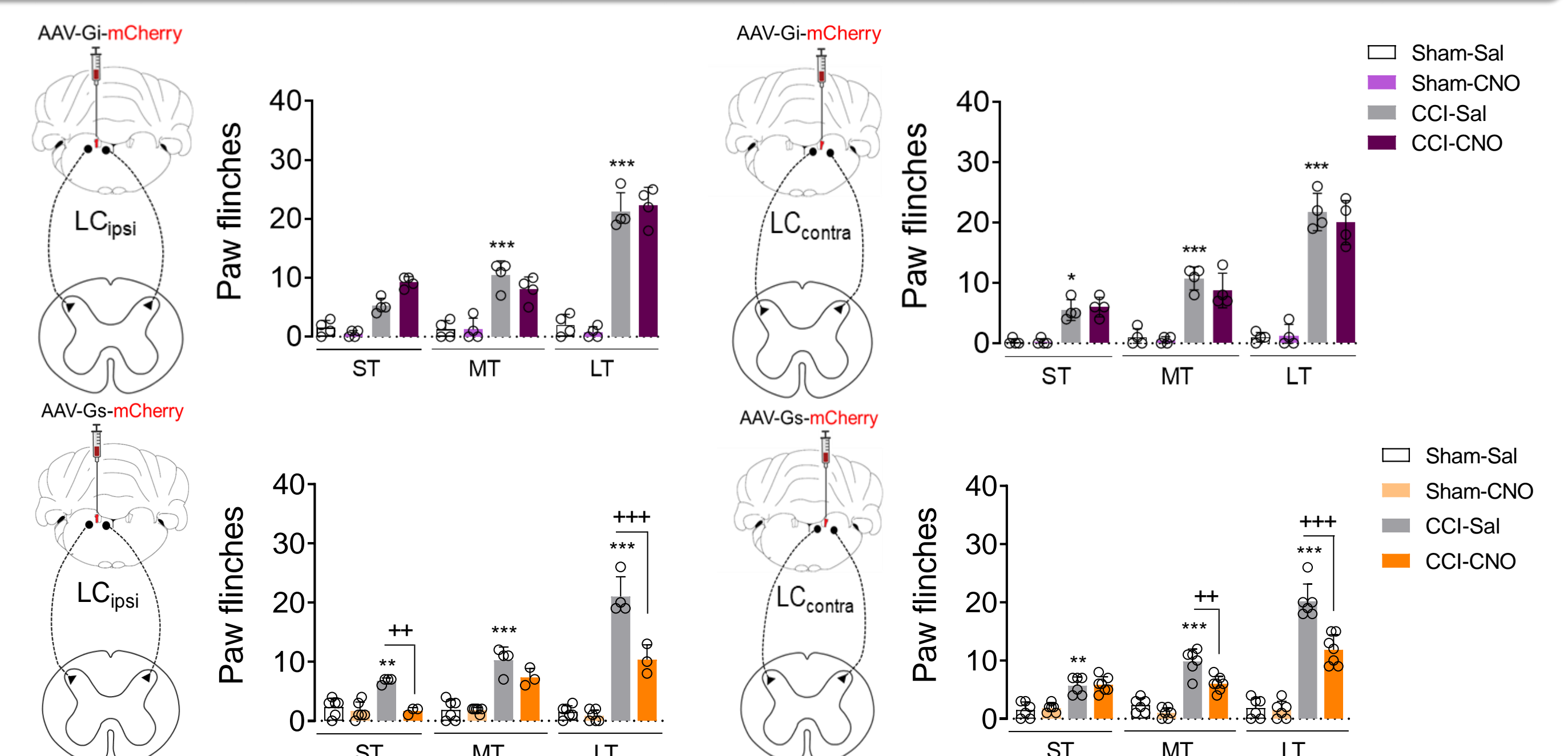
The pattern of LC activation changes along neuropathy. Specific LC modules promote analgesia but also nociception.

### 3. LC involvement in ongoing pain

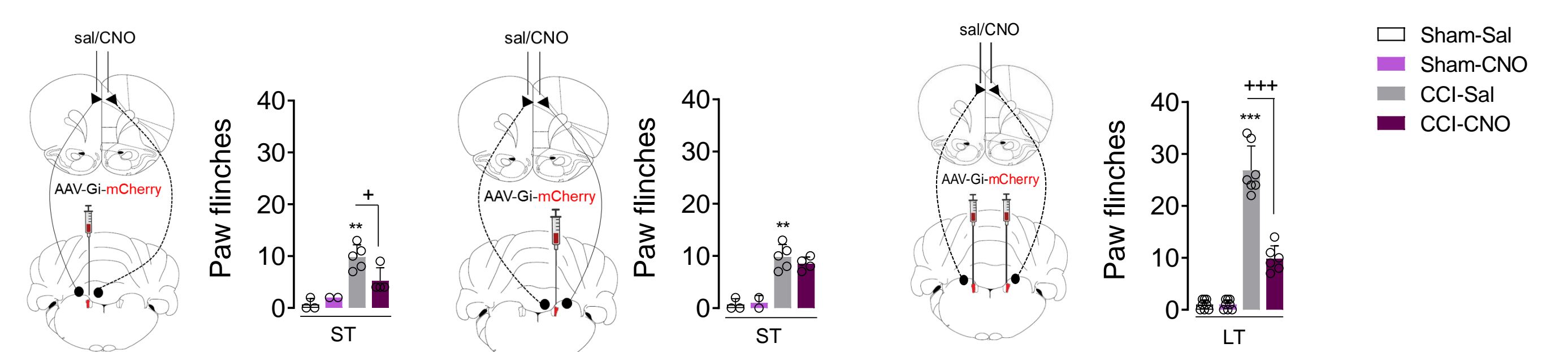


Global blockade of the LC<sub>ipsilateral</sub> system, but not LC<sub>contralateral</sub>, increased spontaneous pain in CCI-ST animals while the activation relieved it at LT.

### 4. Role of LC → SC and LC → ACC in ongoing pain

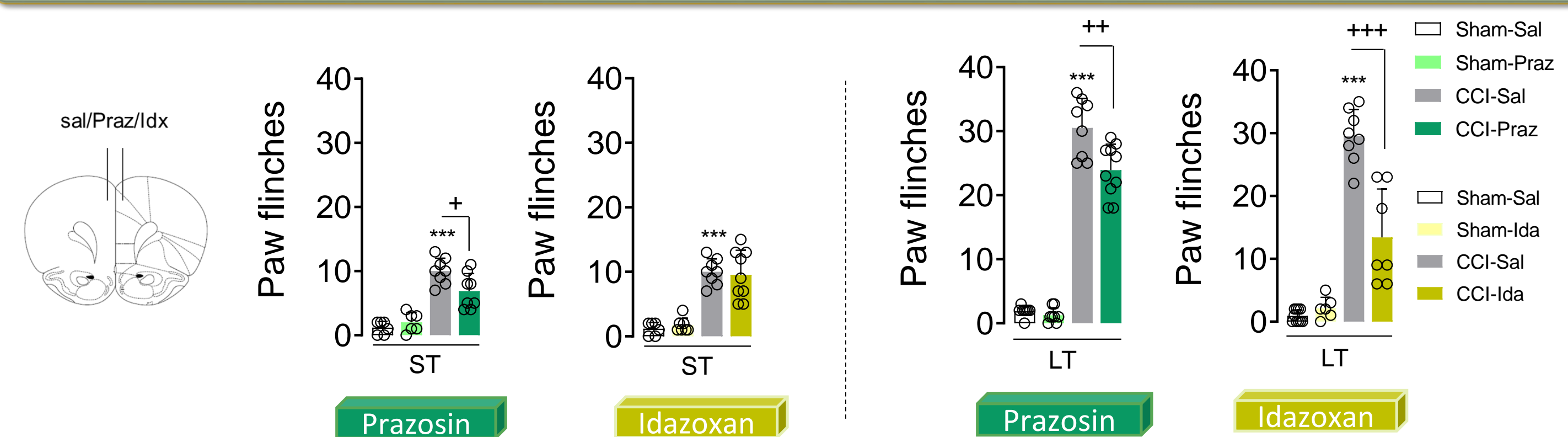


Chemogenetic blockade of the LC<sub>ipsilateral</sub>→SC, but not LC<sub>contralateral</sub>→SC, projection increased spontaneous pain at ST and decreased when both LC<sub>ipsilateral</sub> and LC<sub>contralateral</sub> are activated



Chemogenetic inactivation of LC<sub>ipsilateral</sub>→ACC at ST, but not LC<sub>contralateral</sub>, reduced spontaneous pain. Blockade of bilateral LC→ACC pathway at LT also decrease it.

### 5. Role of ACC alpha-adrenoceptors in ongoing pain



Intra-rACC administration of alpha1-adrenoreceptors antagonist (Prazosin) reduced ongoing pain at ST and LT, while the alpha2-adrenoreceptors antagonist (Idazoxan) only did it at LT

Two-way ANOVA or Two-way repeated measures ANOVA + Tukey-posthoc: \*vs Sham-sal; +CCI-sal

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