



Synaptic activity of specific central amygdala neurons is differentially affected by pain and sphingolipid receptor signaling

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Background

Chronic pain

- Chronic pain affects more than 50 million adults in the United States
- More than 50% of chronic pain patients experience a mental health disorder

The Central Amygdala (CeA)

- The CeA has overlapping function in chronic pain processing and mental health disorders and has been termed the “nociceptive amygdala”
- Neurons are almost exclusively GABAergic
- One of the major neuron subclasses identified primarily in the CeL express corticotropin releasing hormone (CeL^{CRH+})

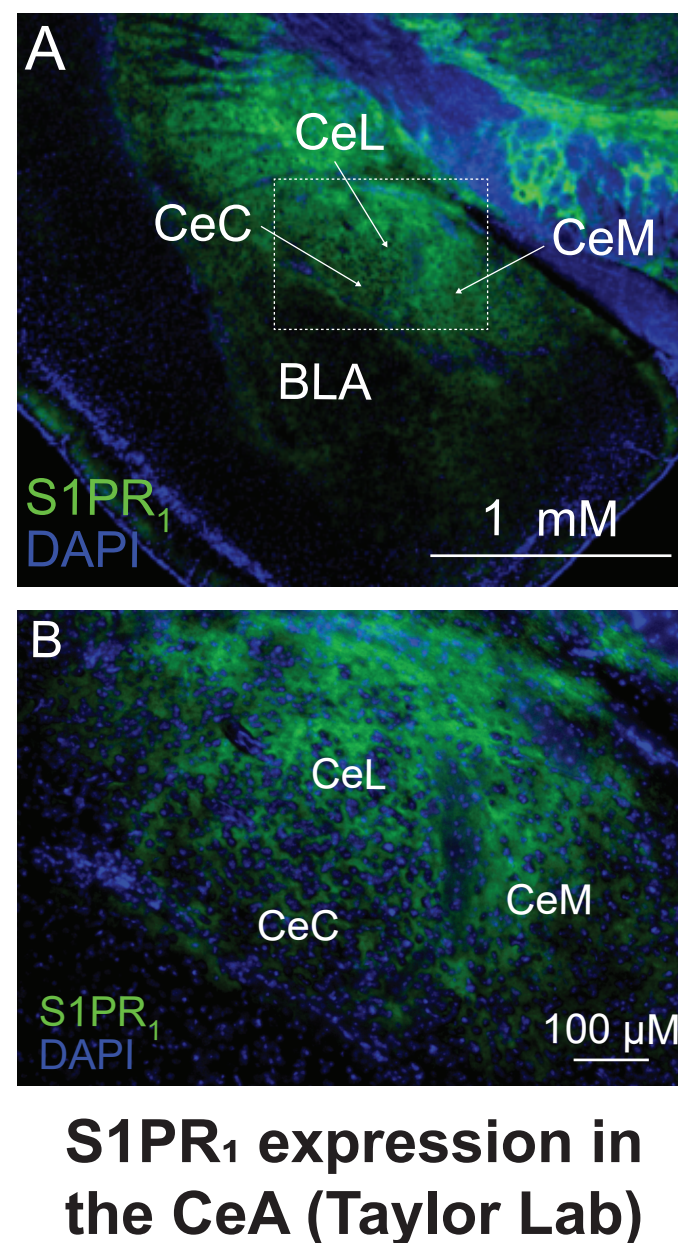
Corticotropin-Releasing Hormone (CRH) in the CeA

- CeL^{CRH+} neurons receive nociceptive inputs from the parabrachial nucleus (PBN) and send projections to the periaqueductal gray (PAG)
- CRH signaling in the PAG drives anxiogenic behaviors
- CeL^{CRH+} neurons are sensitized in acute, but not chronic, stage of neuropathic pain

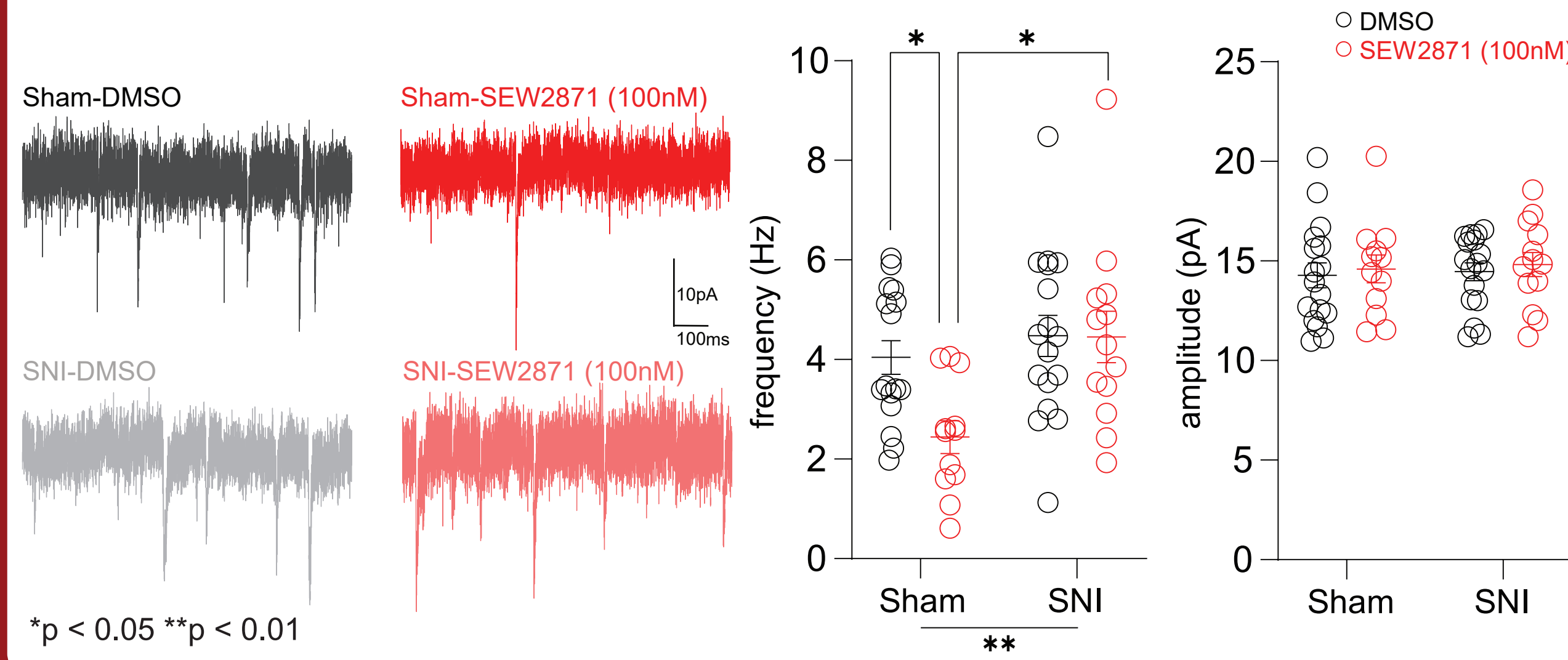
Sphingosine-1-Phosphate (S1P)

- S1P is a bioactive sphingolipid that interacts with five G protein-coupled S1P receptor subtypes (S1PR₁₋₅)
- S1PR_s are strongly expressed in the CeA
- S1P signaling is reported to have differential effects on the pain experience based on experimental location within the central nervous system

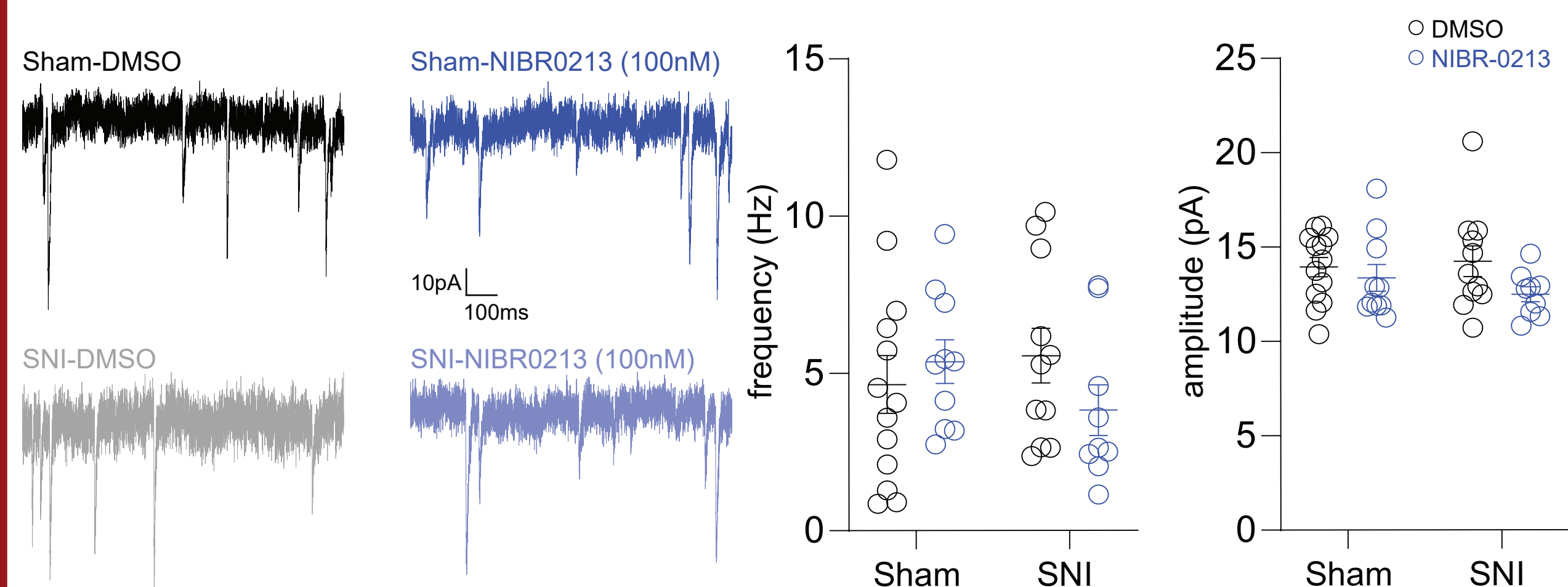
Goal: Dissect the S1PR₁ signaling pathway in the CeL using an S1PR₁ agonist (SEW2871) and antagonist (NIBR-0213) and to determine its effects on synaptic transmission in a model of neuropathic pain.



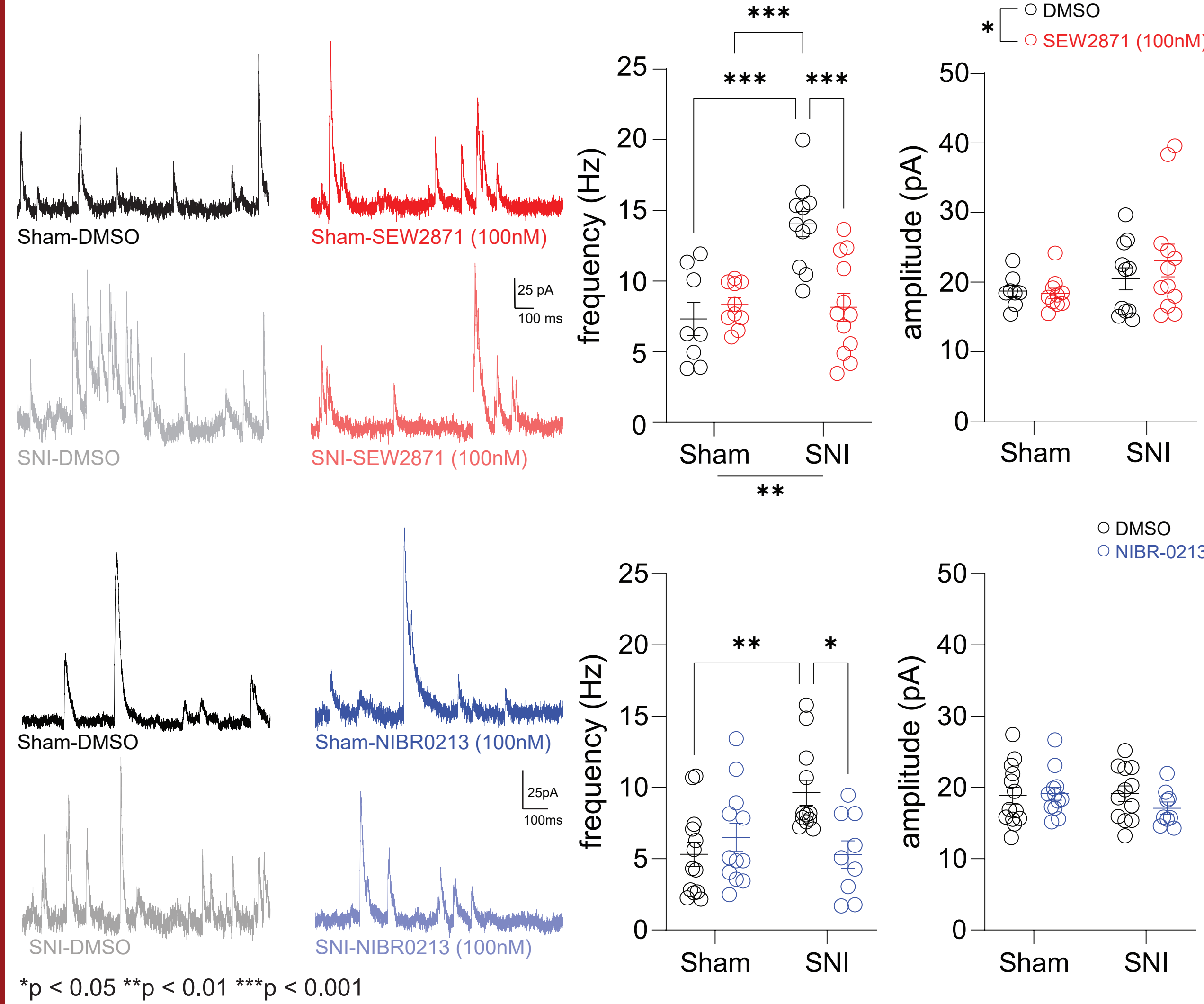
SEW2871 decreases frequency of sEPSCs onto CeL^{CRH+} neurons from sham, but not SNI mice.



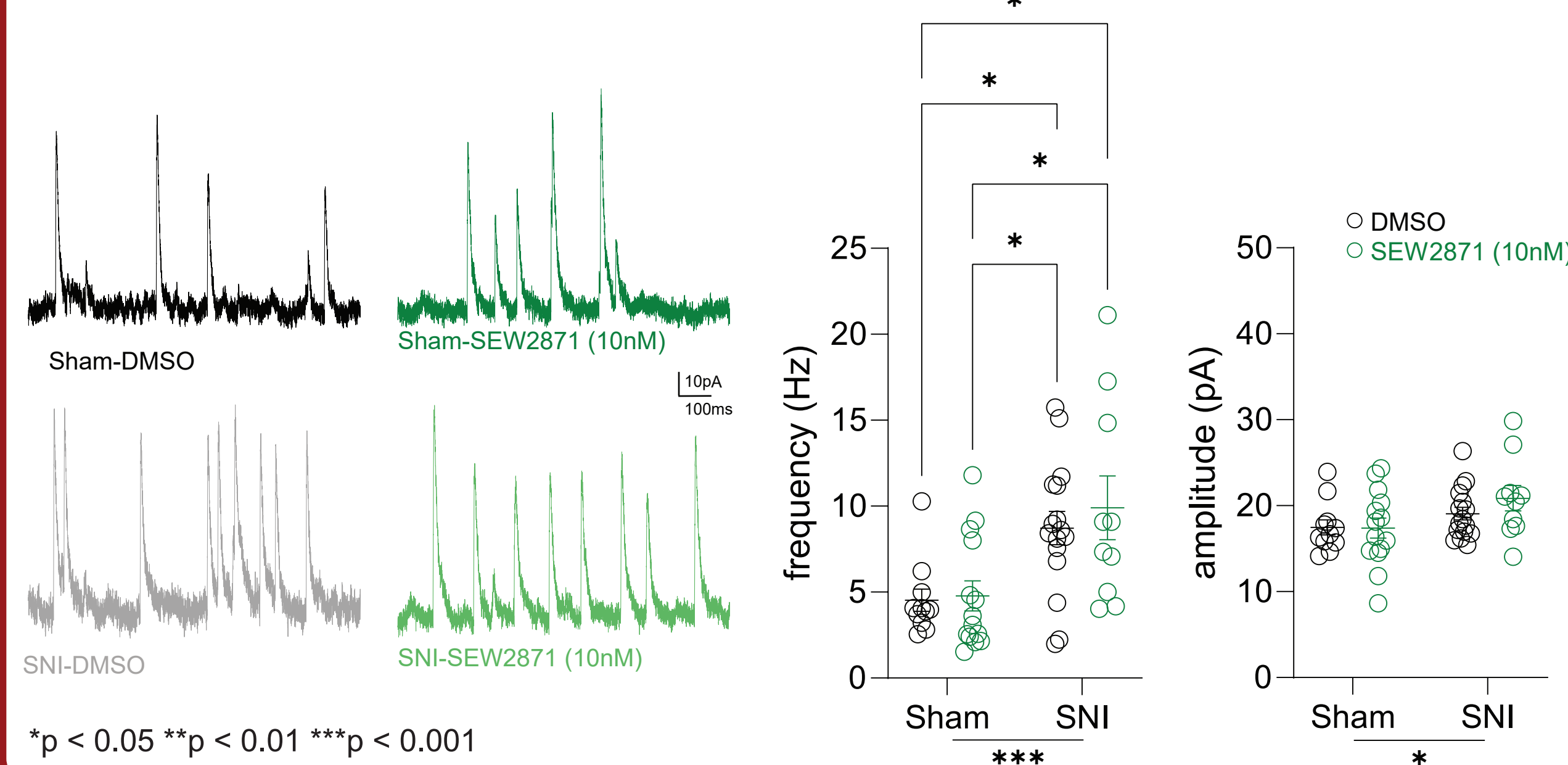
NIBR-0213, has no effect on sEPSCs onto CeL^{CRH+} neurons from either sham or SNI mice.



SNI increases frequency of sIPSCs onto CeL^{CRH+} neurons, and SEW2871 and NIBR-0213 decrease the frequency in SNI, but not sham mice.



sIPSCs onto CeL^{CRH+} neurons are unaffected by a lower concentration of SEW2871.



Conclusions and Discussion

- S1PR₁ agonist, SEW2871 **decreases** excitatory input onto CeL^{CRH+} neurons only in **uninjured** mice.
- S1PR₁ antagonist, NIBR-0213 has no effect on excitatory input onto CeL^{CRH+} neurons, suggesting receptor internalization during SNI.
- SNI **increases** inhibitory input onto CeL^{CRH+} neurons.
- Both S1PR₁ agonism and antagonism **attenuate** SNI-increased inhibitory input onto CeL^{CRH+} neurons, possibly through different mechanisms.
- Lower concentration of SEW2871 does not affect inhibitory input onto, CeL^{CRH+} neurons, suggesting this drug could be acting through internalization.

Overall: Distinct CeL^{CRH+} synapses are differentially affected by both neuropathic pain and S1PR₁ signaling and can possibly be targeted for the treatment of the affective component of pain.

Future Directions

- Continue to elucidate the mechanisms by which S1PR₁ agonism and antagonism achieve the same effect on inhibitory input onto CeL^{CRH+} neurons.
- Determine from where the connections to these neurons are coming (PBN, local, etc.)
- Dissect the process of receptor internalization at synapses during SNI.
- Determine where S1PR_s are located and if their concentration changes during SNI.

References

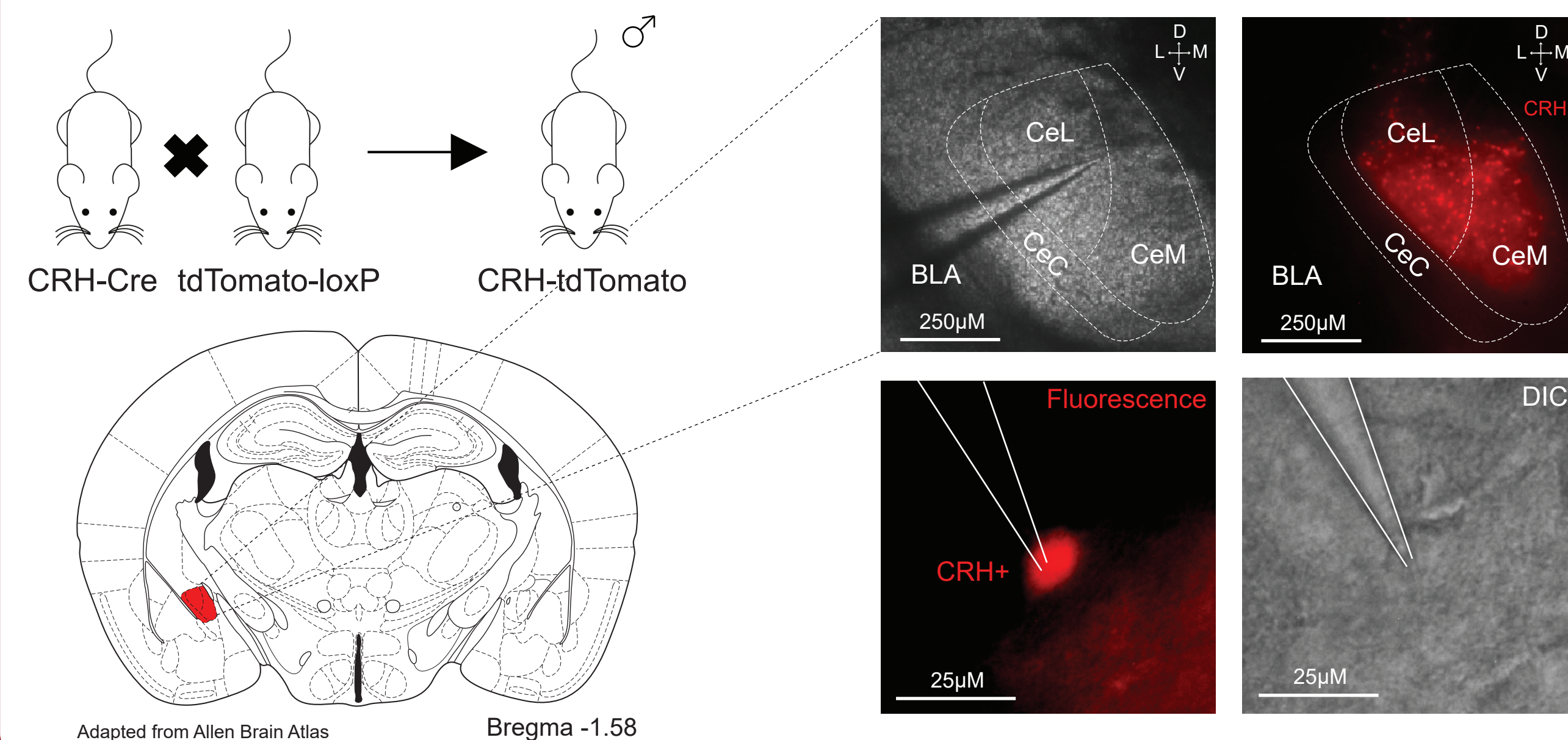
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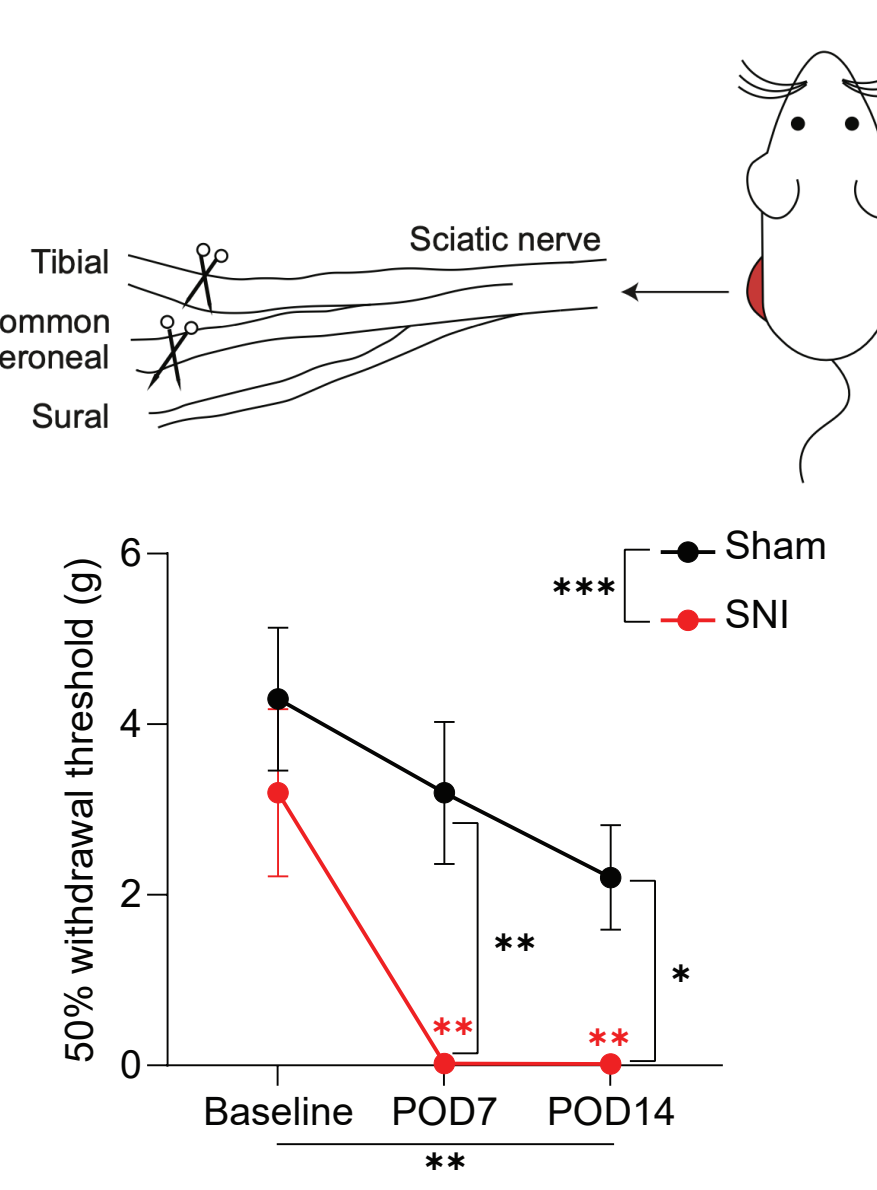
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Methods

Identifying CRH+ CeA Neurons



Spared Nerve Injury (SNI) Model of Neuropathic Pain



Electrophysiology

