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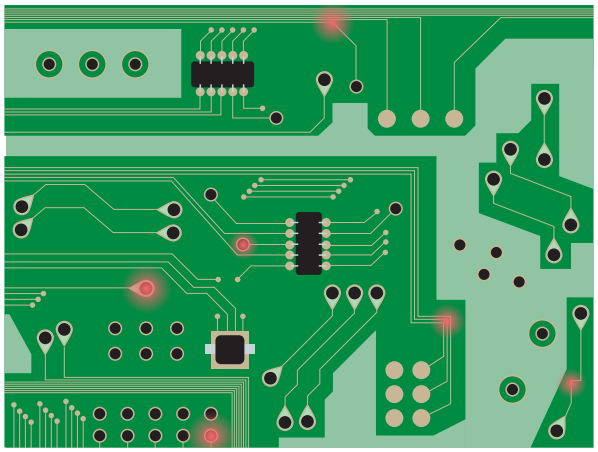
PAIN

A painful loss of inhibition

> 1 month after SNI, the calcium activity of S1 SOM$^+$ cells in injured mice was approximately half that of SOM$^+$ neurons in sham controls

Sensory aspects of pain are encoded in the somatosensory cortex (S1). In chronic neuropathic pain, S1 neuronal circuits reorganize and become hyperactive, but how different cortical cell types contribute to this hyperactivity is not clear. Now, Guang Yang and colleagues report that, in mice with chronic neuropathic pain, the inhibition of layer 5 (L5) pyramidal cells by somatostatin-expressing (SOM$^+$) interneurons in S1 is markedly reduced.

The authors used a model of neuropathic pain called spared nerve injury (SNI), in which two of three branches of the sciatic nerve are ligated, leaving the sural nerve intact. Starting from 2 days after SNI, the injured mice exhibited chronic mechanical allodynia — a symptom of neuropathic pain — as characterized by heightened sensitivity to mechanical stimulation of the hindpaw.



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To investigate SNI-induced changes in cortical activity, the authors used two-photon imaging of L5 pyramidal cells expressing a genetically encoded calcium indicator in the region of S1 corresponding to the injured hindlimb. Strikingly, 1 month after SNI, calcium activity in the somata of these neurons during rest was threefold greater than in controls and correlated with the severity of mechanical allodynia. Silencing the sciatic nerve with a sodium channel blocker did not inhibit L5 pyramidal cell calcium activity in SNI mice (but did in sham controls), indicating that this SNI-induced cortical hyperexcitability does not originate from peripheral sensory inputs.

Further imaging of the spines, apical dendritic tufts and dendritic branches of L5 pyramidal cells revealed that calcium activity was increased in all of these cell compartments in SNI mice and was dependent on increased synchronized synaptic inputs from L1. The axons of SOM$^+$ interneurons in S1 project to L1, so the authors imaged the calcium activity of these cells. Strikingly, 1 month after SNI, the calcium activity of S1 SOM$^+$ cells in injured mice was approximately half that of SOM$^+$ neurons in sham controls.

SOM$^+$ and parvalbumin-expressing (PV$^+$) interneurons generally inhibit pyramidal cells, and are themselves inhibited by vasoactive intestinal peptide-expressing (VIP$^+$) interneurons. At 1 month after SNI, PV$^+$ and VIP$^+$ interneurons in S1 showed considerably decreased and increased activity, respectively, compared with controls. Thus, SNI induces changes in SOM$^+$, PV$^+$ and VIP$^+$ interneuron activity that together may all contribute to pyramidal cell hyperactivity.

Last, the authors examined the effects of chemogenetically rescuing the activity of SOM$^+$ cells after SNI. Acute activation of SOM$^+$ cells reduced S1 L5 pyramidal cell calcium activity in SNI mice and considerably alleviated mechanical allodynia. Importantly, continuous chemogenetic activation of SOM$^+$ interneurons for the first week after SNI prevented the hyperexcitability of S1 L5 pyramidal neurons and protected against the onset of mechanical allodynia, as tested 1–3 weeks later.

Together, these results imply that SNI-induced cortical hyperexcitability is associated with a decrease in inhibition from S1 SOM$^+$ interneurons and suggest that targeting SOM$^+$ neurons after injury could help protect against the development of chronic pain.

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