

University of Zurich[UZH]

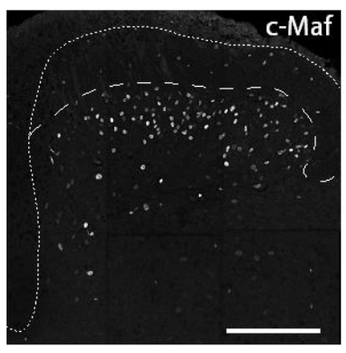
c-Maf expressing spinal interneurons are part of a dorsal horn circuit that integrates descending input from the cortex with peripheral sensory signals.

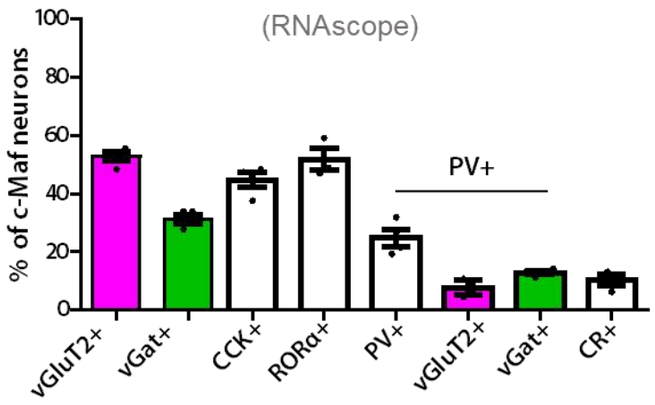
[1]N. Frezel, [1]E. Foster, [2]H. Wende, [3]P. Pelczar, [4]Michael Bösl,[1]L. Scheurer, [2]C.Birchmeier, [1,5,*]H.U. Zeilhofer, [1,*]H. Wildner

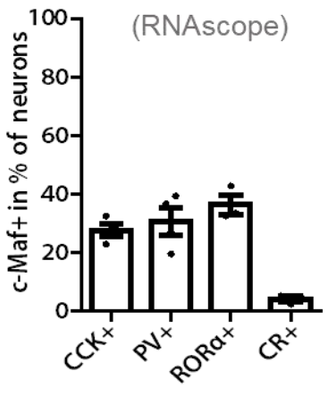
[1]Institute of Pharmacology and Toxicology, University of Zurich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland. [2]Max Delbrück Center, MDC, Berlin, Germany. [3]Universität Basel, Center for Transgenic Models (CTM), Basel, Switzerland. [4]University of Würzburg, Experimental Biomedicine, Würzburg, Germany. [5]Institute of Pharmaceutical Sciences, Swiss Federal Institute of Technology (ETH) Zürich, Switzerland

INTRODUCTION Interneurons in the deep dorsal horn (DH) of the spinal cord receive input mainly from non-nociceptive myelinated sensory fibers and are believed to be important for the processing of touch and proprioceptive input. There is also accumulating evidence that under certain pathogenic conditions such as neuropathy, deep dorsal horn excitatory interneurons gain access to pain processing circuits. However, detailed analysis of the effect these interneurons exert on pain signaling in naïve or neuropathic mice is lacking. Here we use the gene coding for the transcription factor c-Maf as a genetic marker to gain access to spinal interneurons in laminae III-IV. We used intersectional genetic targeting approaches to manipulate the activity of c-Maf interneuron populations and analyze their circuit integration.

A) C-Maf is expressed in a heterogeneous population of deep DH neurons

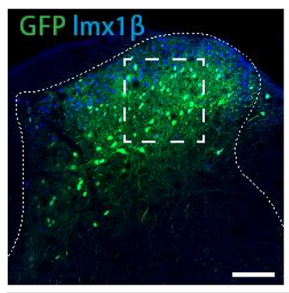


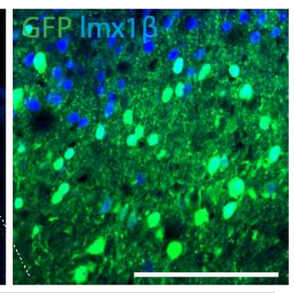


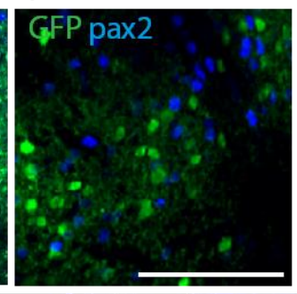


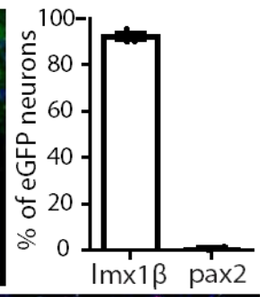
B) Targeting of c-Maf^{EX} neurons by intraspinal viral injection

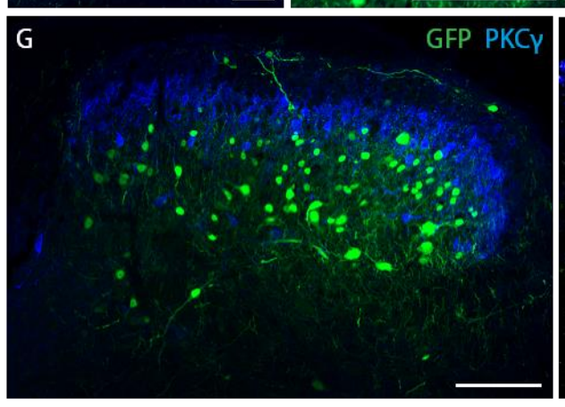
c-Maf^{Cre}; Imx1β^{Dre} mice

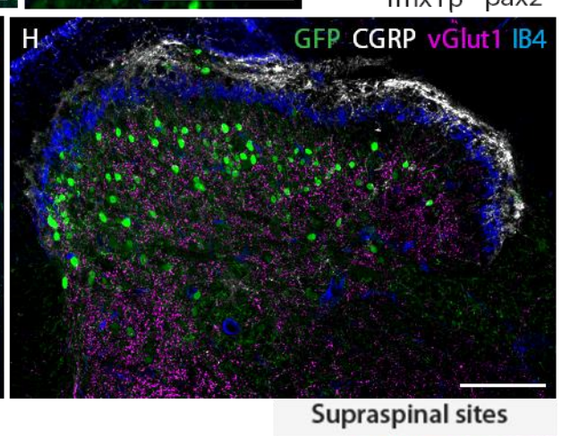






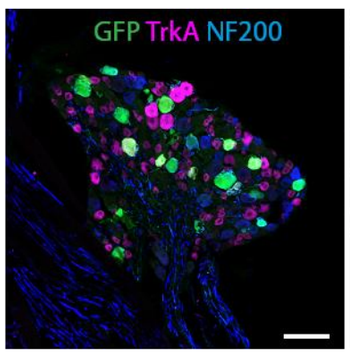


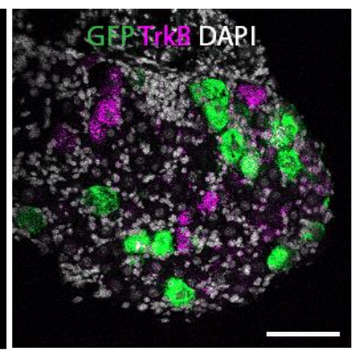


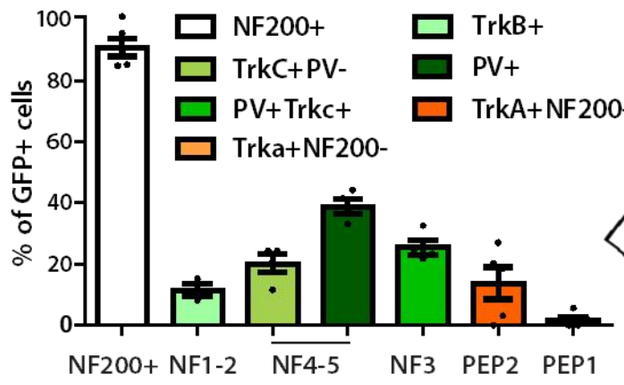


C) Circuit integration of c-Maf^{EX} neurons

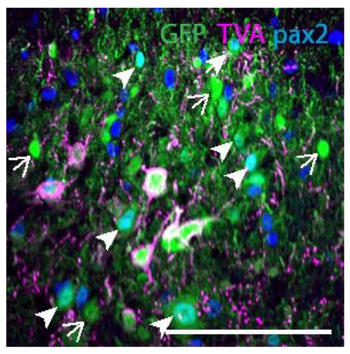
Dorsal root ganglia (IHC and RNAscope)

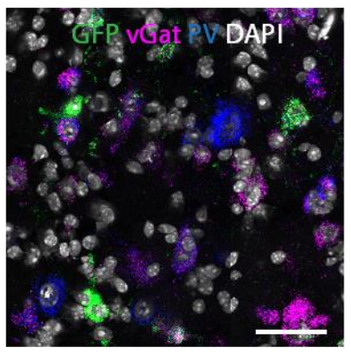


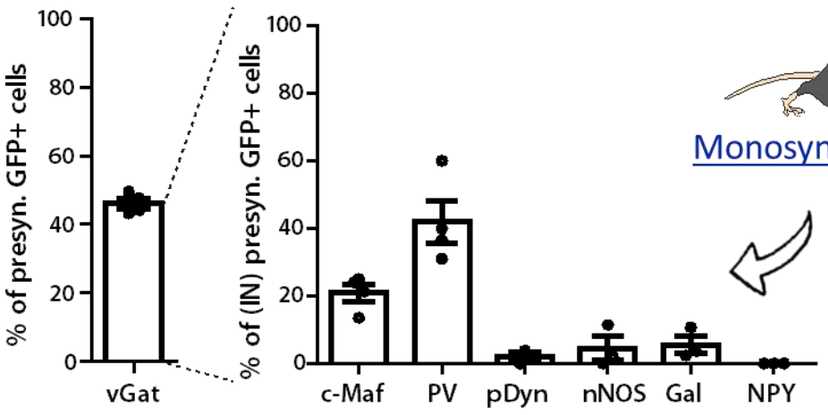


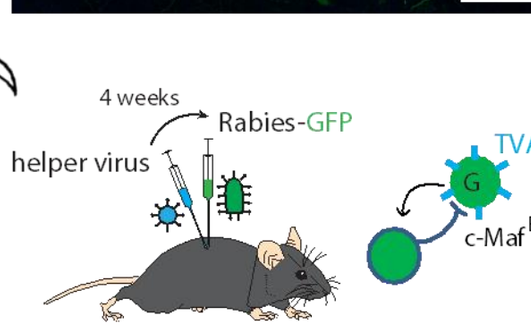


Spinal cord (IHC and RNAscope)



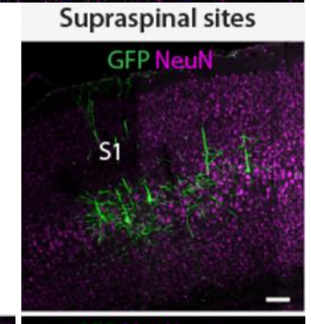


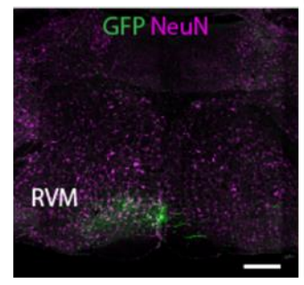


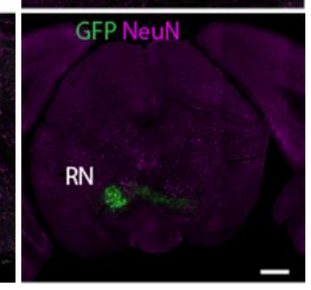


Monosynaptic retrograde tracing (rabies virus)

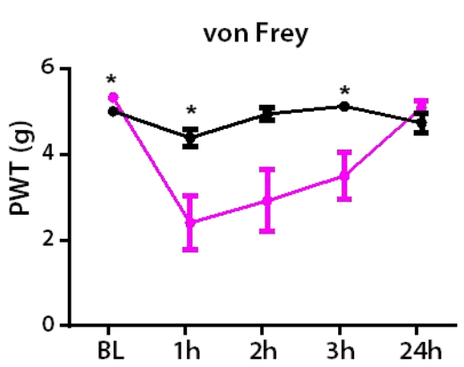
Supraspinal sites

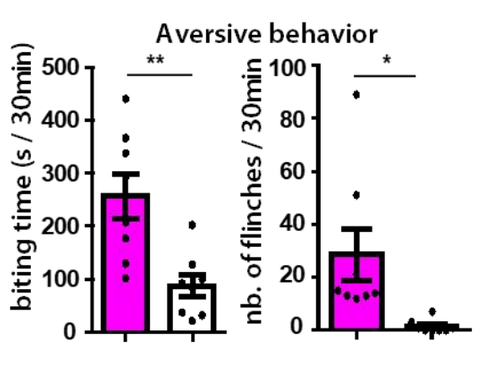


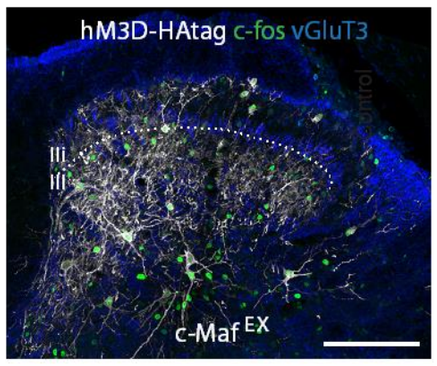


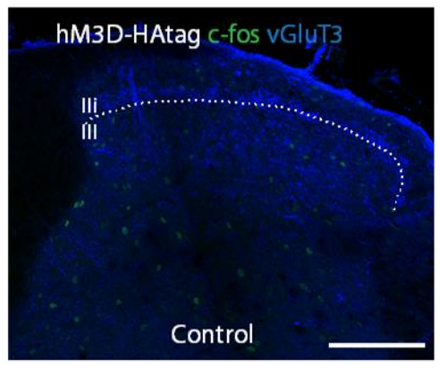


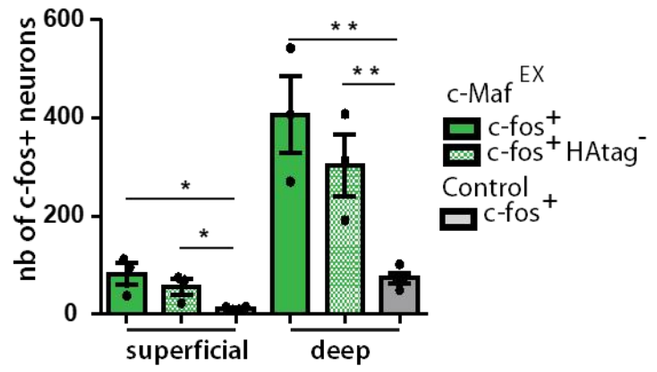
D) hM3Dq-mediated activation of c-Maf^{EX} neurons



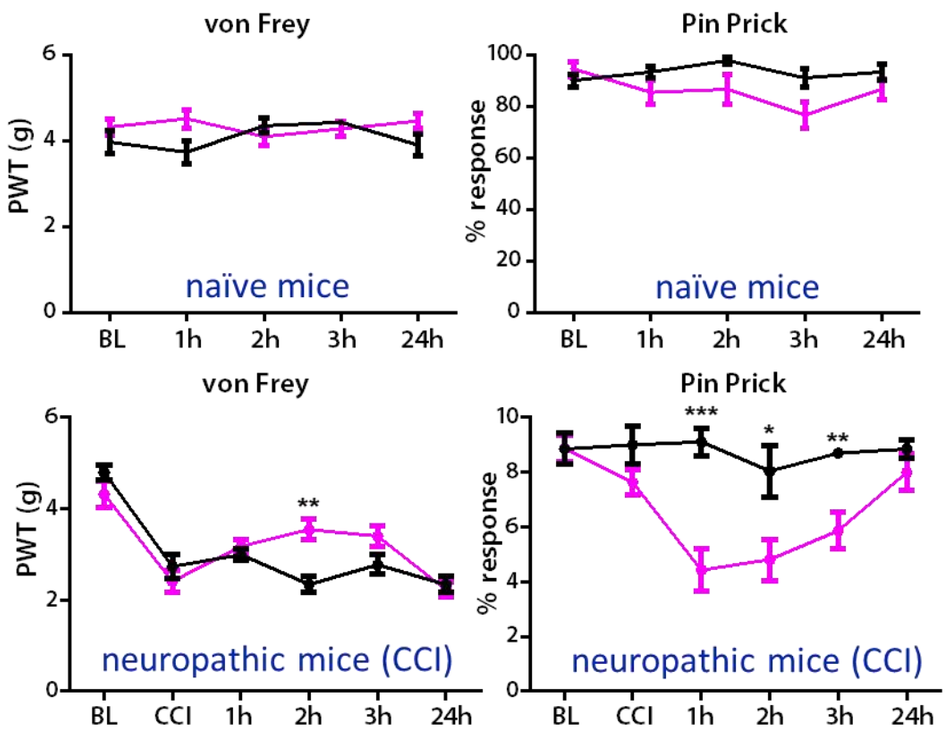




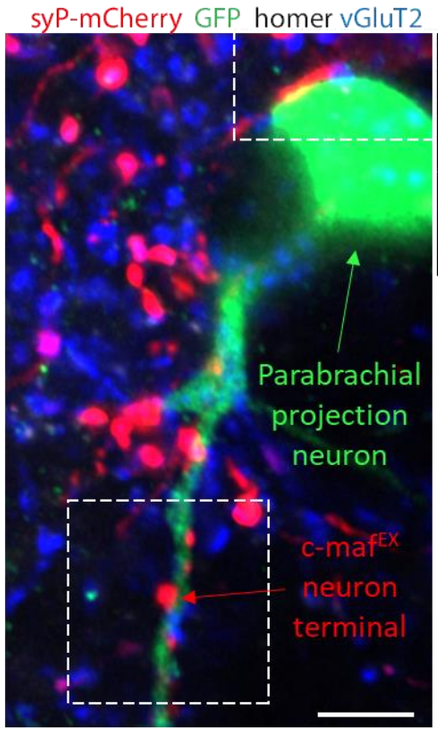


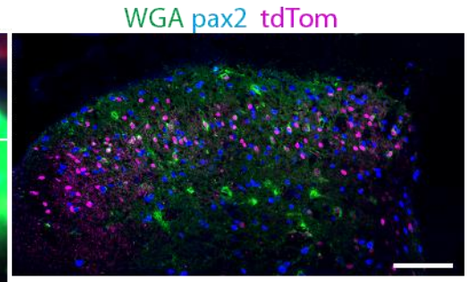


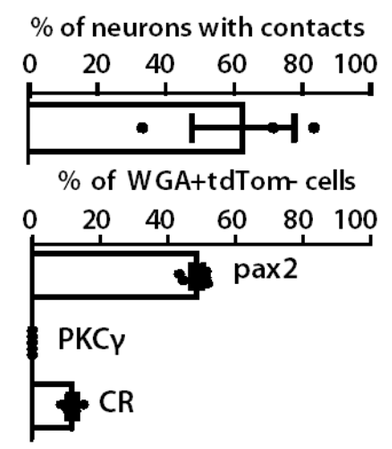
E) hM4Di-mediated silencing of c-Maf^{EX} neurons



F) c-Maf^{EX} neurons output: anterograde tracing







CONCLUSION

We have identified a population of deep dorsal horn interneurons that integrates descending inputs from the cortex with peripheral sensory signals to modulate the perception of sensory stimuli. Excitatory c-Maf neurons appear to be part of an altered circuit that detects noxious touch in neuropathic mice.