

# **Pain perception in animals and the underlying regulatory mechanism**

2024-04-30

- **Overview of pain perception in animals**

——涂 雯

- **Neuronal mechanisms of pain perception in animals**

——李小龙

- **Impact of pain perception on animal behavior**

——李 畅

# Overview of pain perception in animals

- How to evaluate the Nociception and its impact on different organisms?
- What is the cellular and molecular mechanism of pain and its significance for animals?
- What are the new pain treatment methods available?

TW

2024.04.30

## Pain perception



The toothache is not a disease actually, but it will torment you as long as it happens.



## Pain

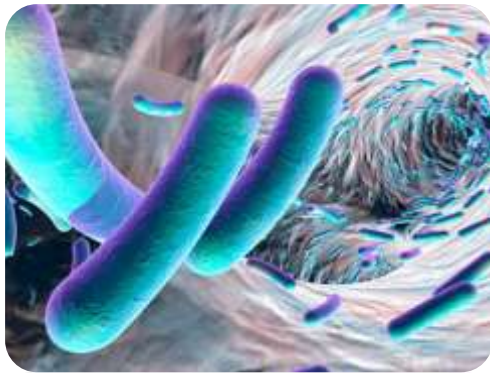
An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.

How to evaluate the Nociception and its impact on different organisms?

# Pain perception

## Nociception

- Unpleasant stimulation
  - chemical burning
  - sharp cutting
  - bruising pressure
- Physiological and behavioral responses



**Bacteria**



***Drosophila***



**Bumblebee**

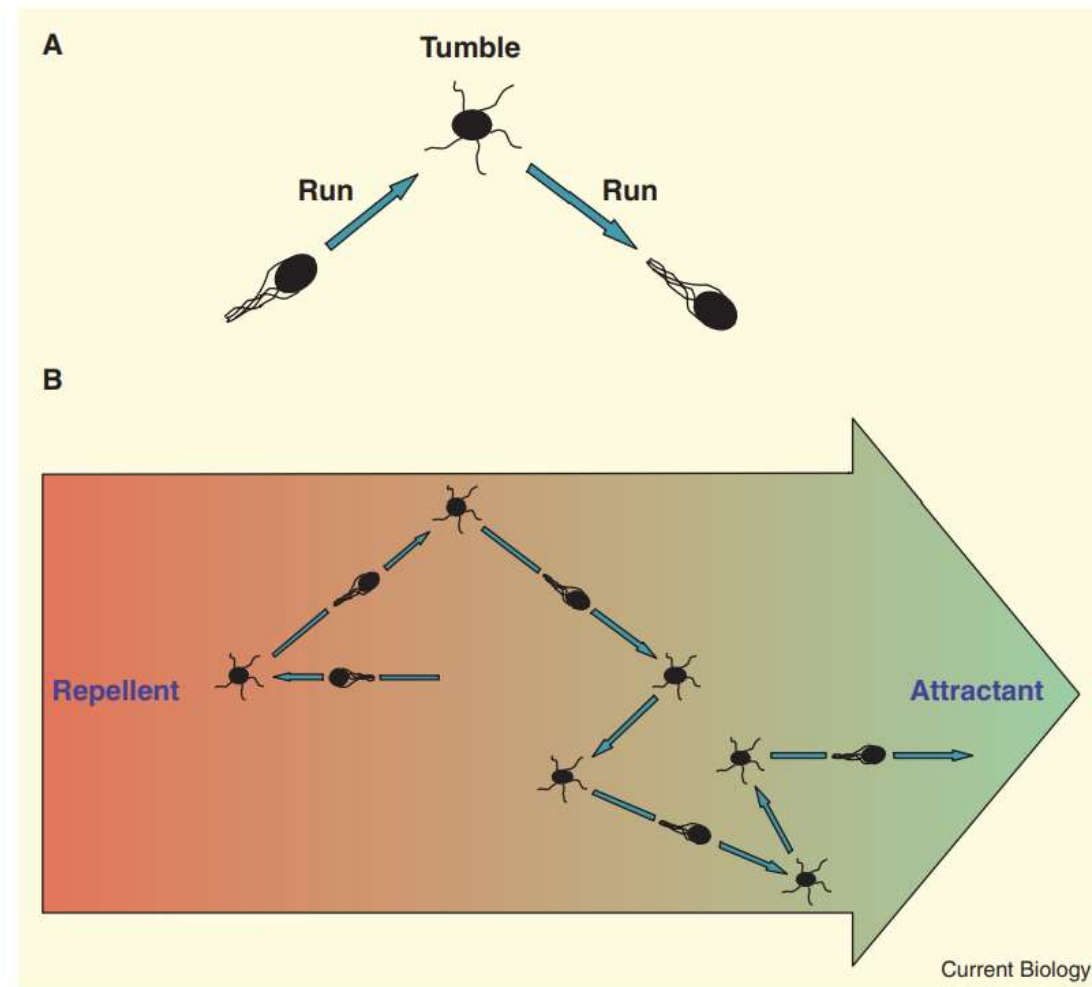


**Mice**

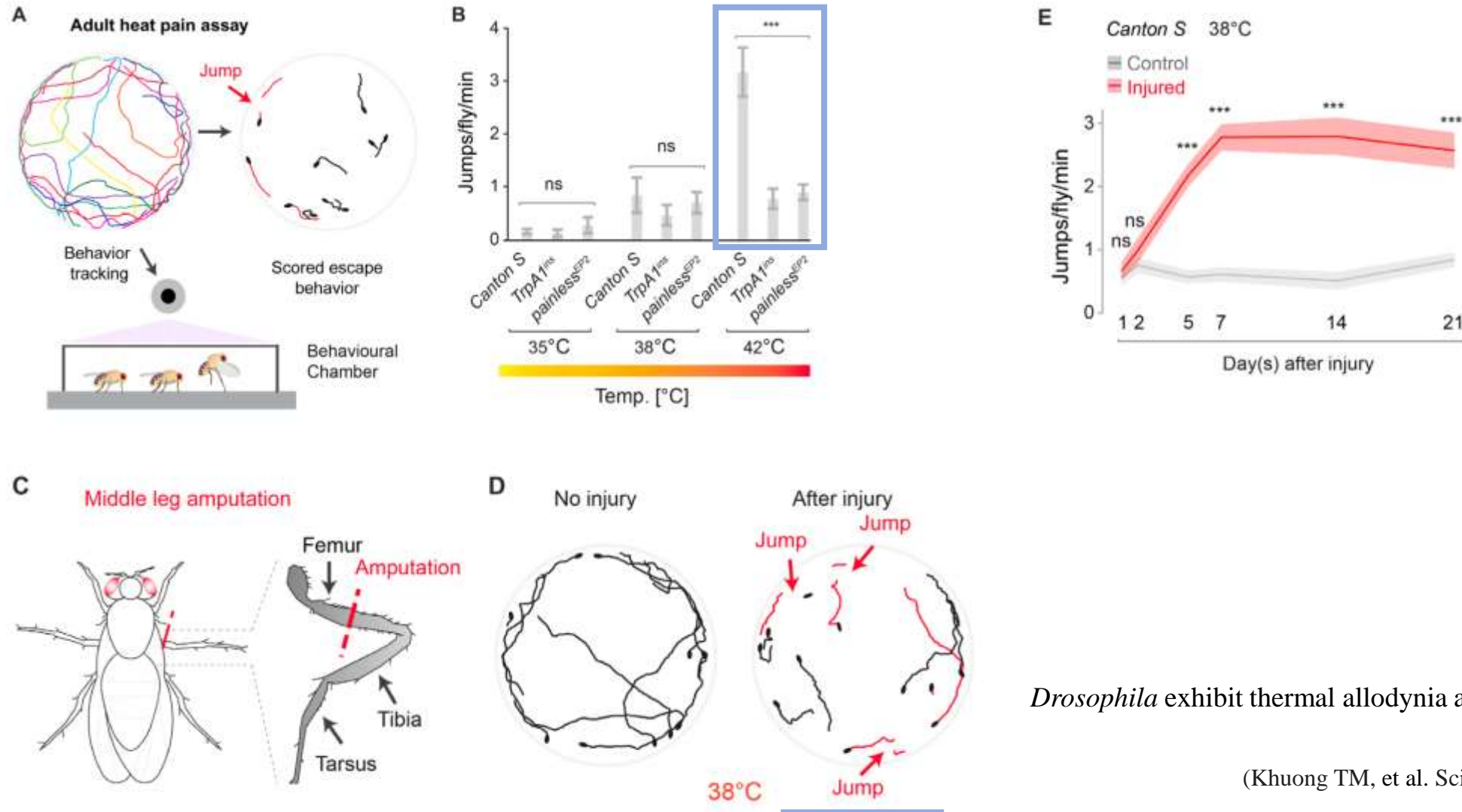
## Pain

- Actual or potential tissue damage
- An unpleasant sensory and emotional experience

# Bacterial chemotaxis



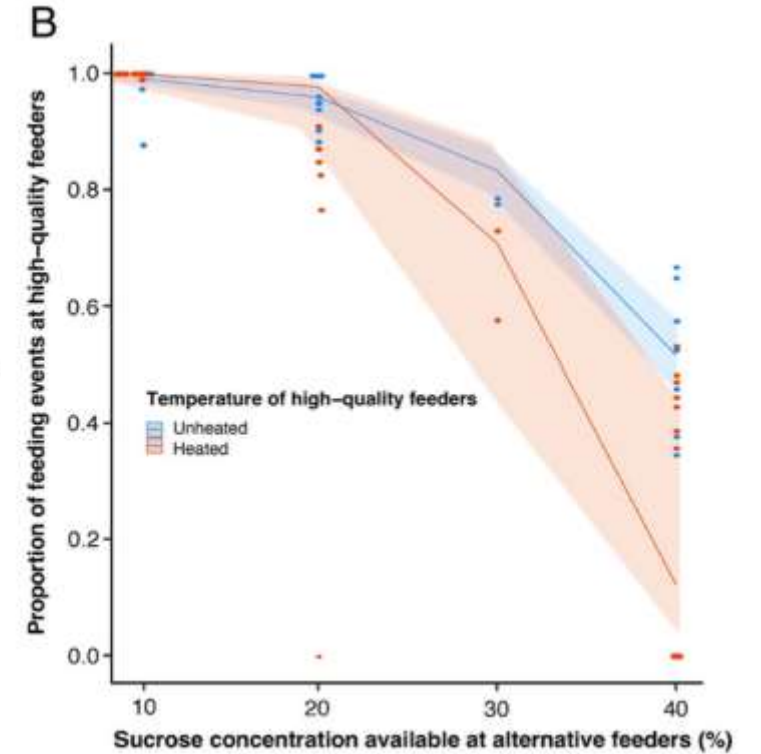
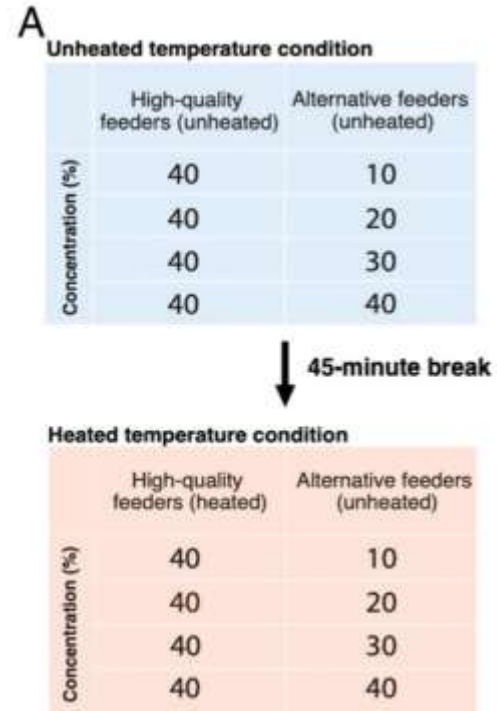
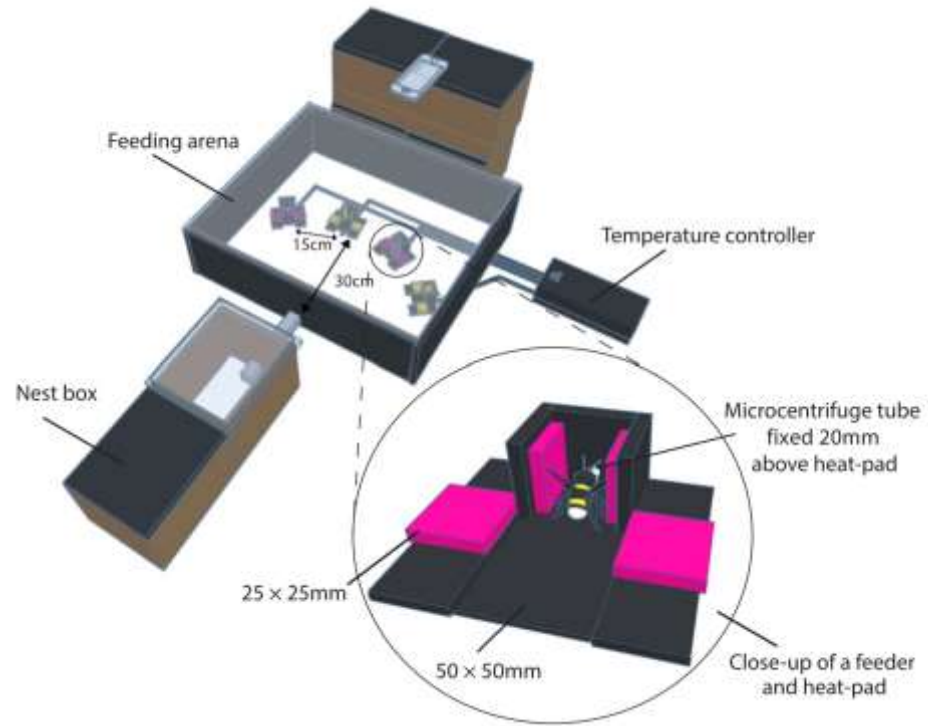
# *Drosophila* and chronic pain



*Drosophila* exhibit thermal allodynia after injury.

(Khuong TM, et al. Sci Adv. 2019)

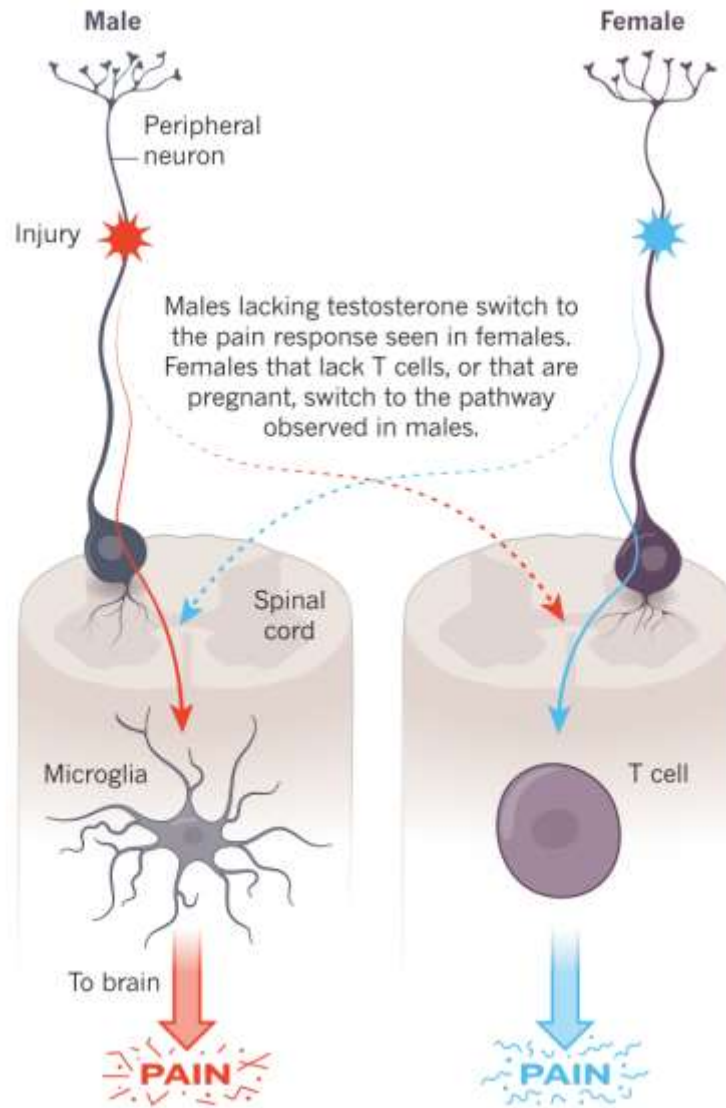
# Motivational trade-offs in bumblebees



Bees traded off their motivation to avoid noxious heat against their preference for high sucrose concentrations.



## Mice and two routes to pain



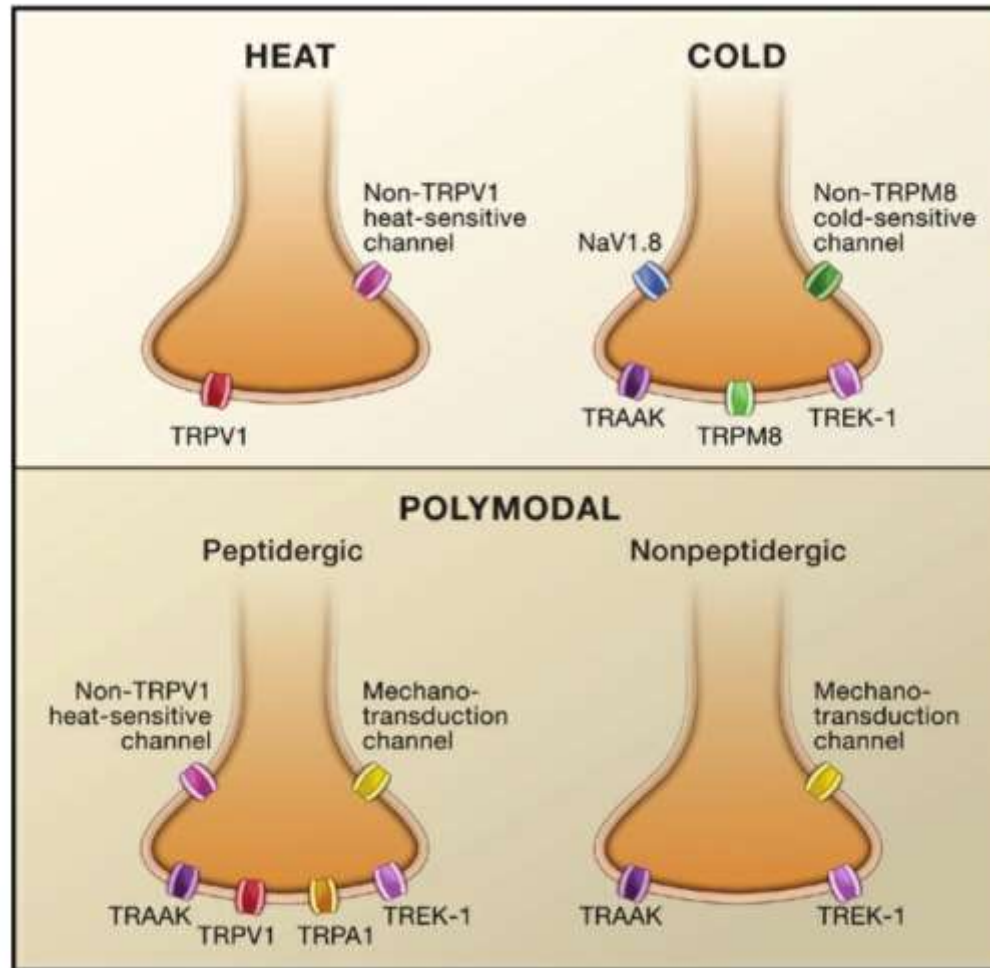
### Sexes don't feel pain the same way

In **male mice**, depends on immune cells in the spinal cord called microglia.

In **females**, it is T cells that seem to control pain.

What is the cellular and molecular mechanism of pain and its significance for organisms?

## Acute Pain: Nociceptor Diversity



Activating the Nociceptor:

■ **Heat**

■ **Cold**

■ **Mechanical Stimuli**

➤ Candidate Mechanotransducers:

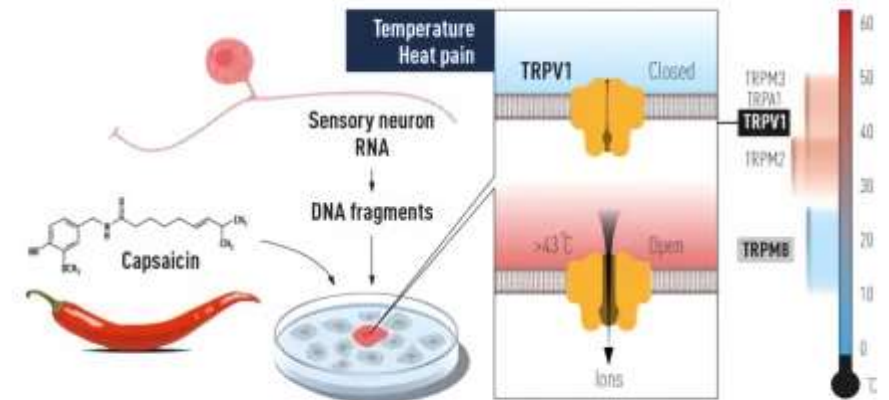
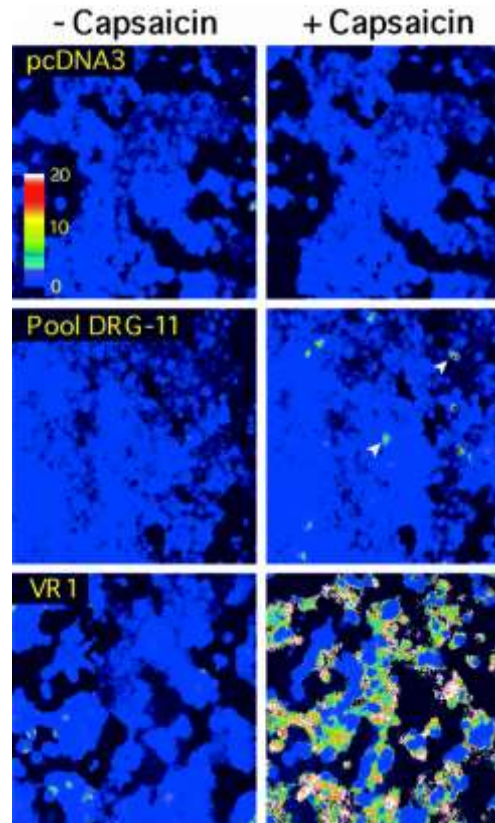
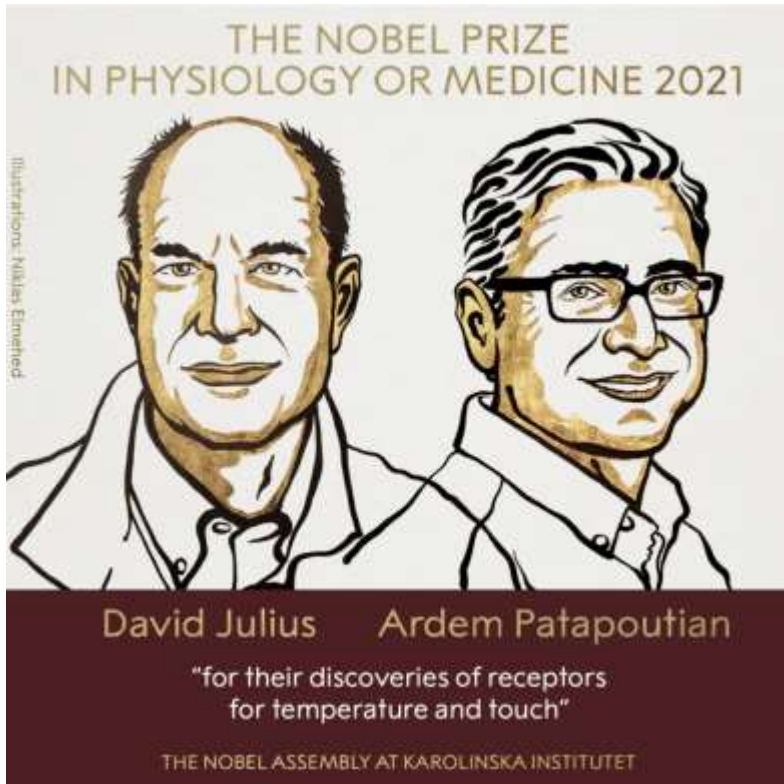
✓ DEG/ENaC Channels

✓ TRP Channels

✓ KCNK Channels

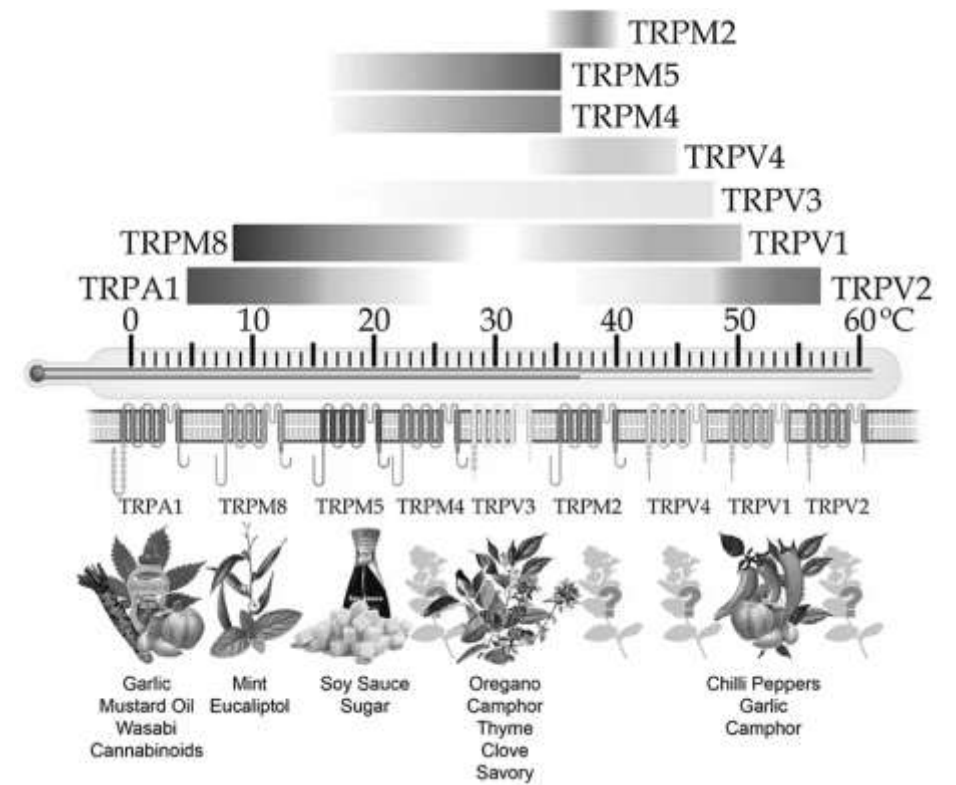
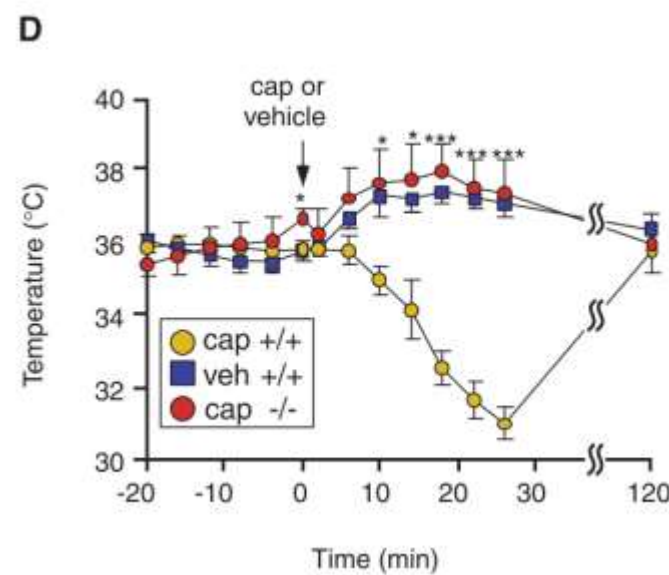
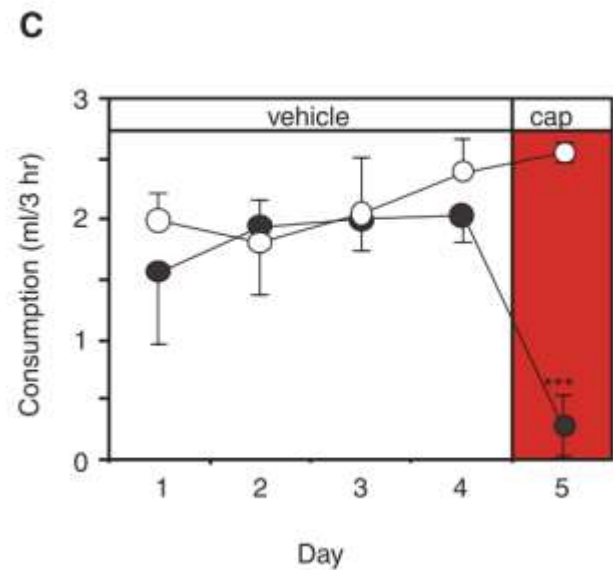
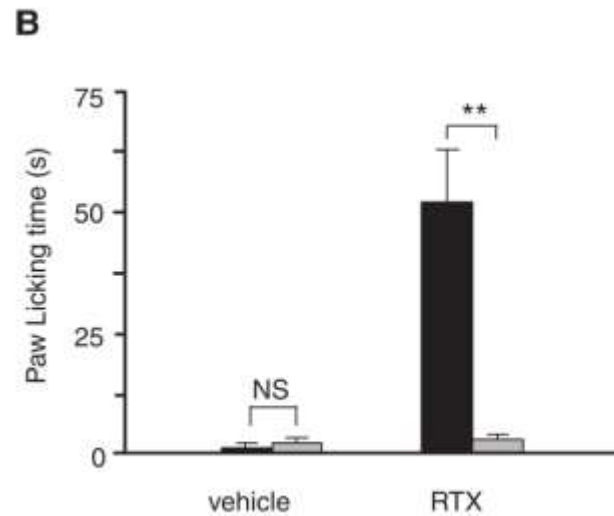
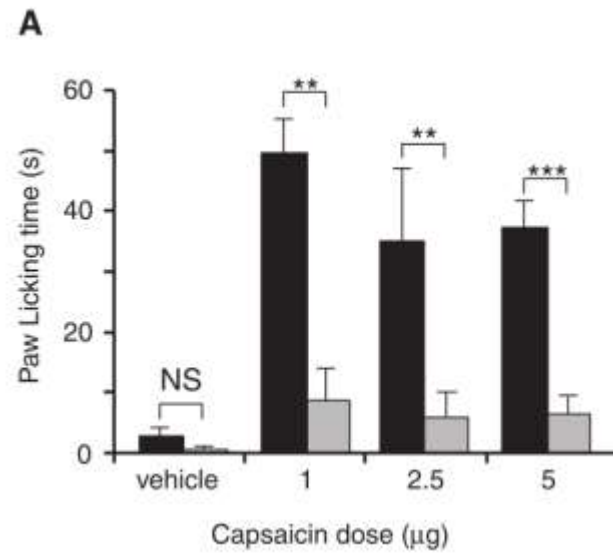
■ **Chemical**

# Discovery of capsaicin receptor TRPV1



(Caterina MJ, , et al. Nature. 1997 )

# Impaired behavioral and physiological responses to vanilloid compounds in mice lacking TRPV1



(Caterina MJ, et al. Science. 2000)

(Latorre R, et al. Q Rev Biophys. 2009)

# Nociceptive neurons and molecules in genetically tractable organisms

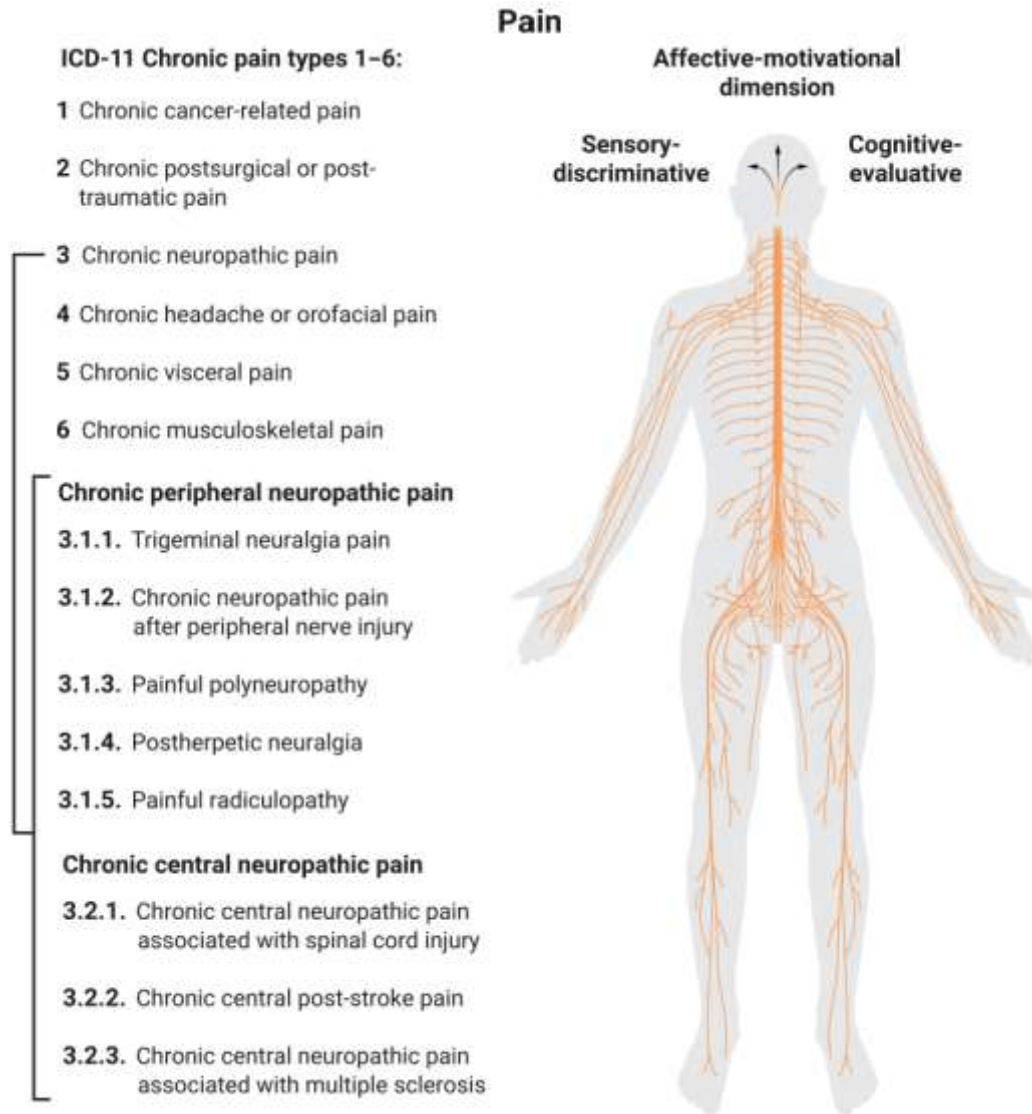
**Table 1. Nociceptive neurons and molecules in genetically tractable organisms.**

Nociception modality	Genetic models	Neuronal detectors <b>Mouse</b> , fly, worm	Candidate molecular sensors: worm	Candidate molecular sensors: fly	Candidate molecular sensors: mouse
<b>Noxious heat</b>	Mouse, fly, worm	<b>C-fiber, A-<math>\delta</math></b> , cIVda, <i>AWC</i> , <i>AFD</i>	?	Painless, dTRPA1, anoctamin	TRPV1–4, anoctamin, TREK-1
<b>Noxious mechanical</b>	Mouse, fly, worm	<b>C-fiber, A-<math>\delta</math></b> , cIVda, <i>PVD</i>	DEGT-1/MEC-10	PPK/BBA, Piezo	TRPA1, TRPV4, TREK-1 Possibly Piezo-1/-2, TMCs
<b>Noxious chemical</b>	Mouse, fly, worm	<b>C-fiber, A-<math>\delta</math></b> , GRN <sup>1</sup> , <i>PVD</i> , <i>ASH</i>	Odorant receptors, OSM-9	Painless, dTRPA1	TRPA1, TRPV1
<b>Noxious cold</b>	Mouse, fly, worm	<b>C-fiber</b> , cIIIda, <i>PVD</i>	TRPA1	TRPM, PKD2, NOMP-C	TRPM8/TRPA1

<sup>1</sup>GRN, gustatory receptor neuron.



# Peripheral divergence and central convergence in pain mechanisms

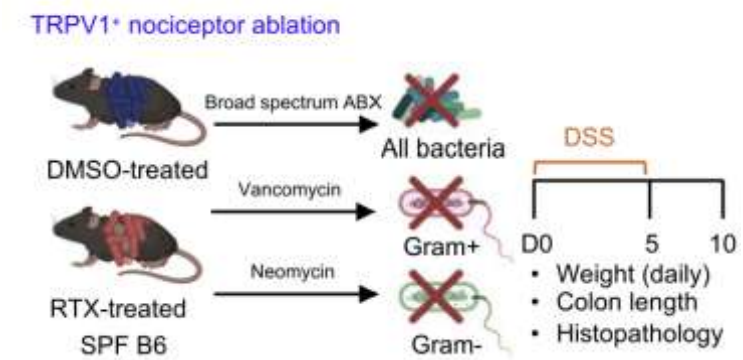


From the perspective of human health,  
the significance of pain:

- ◆ **Protective effect**
- ◆ **Disease signals**
- ◆ **Assist in diagnosis**
- ◆ **To avoid further damage**

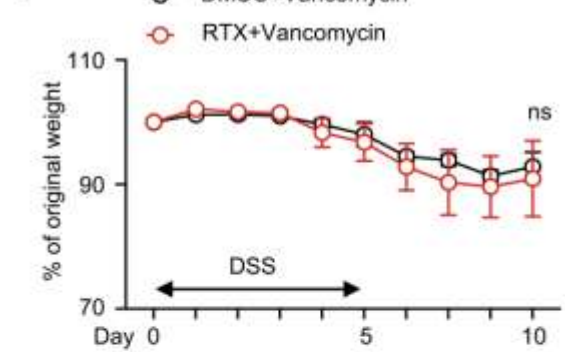
# Gut-innervating nociceptors regulate the intestinal microbiota to promote tissue protection

A

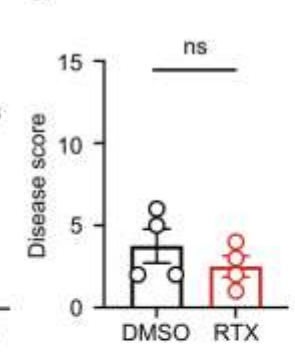


二甲基亚砷(DMSO)  
 树酯毒素(RTX)  
 葡聚糖硫酸钠(DSS)  
 万古霉素(vancomycin,优先清除革兰氏阳性菌)  
 新霉素(neomycin,优先清除革兰氏阴性菌)

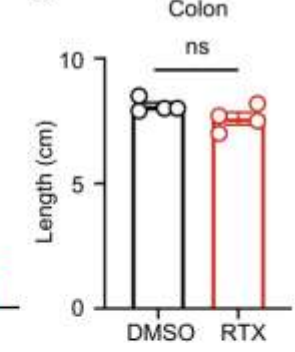
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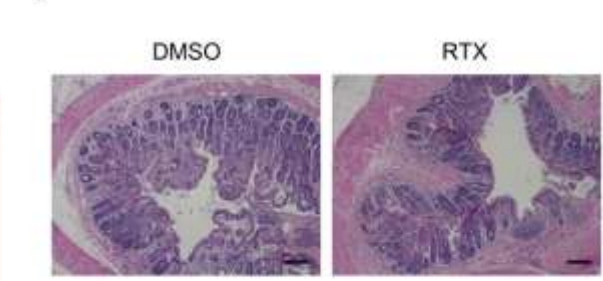
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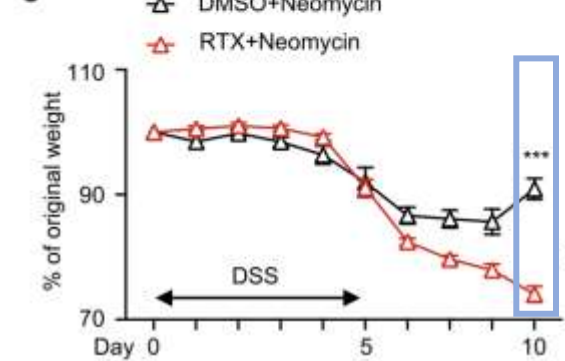
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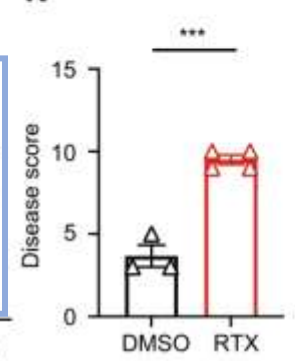
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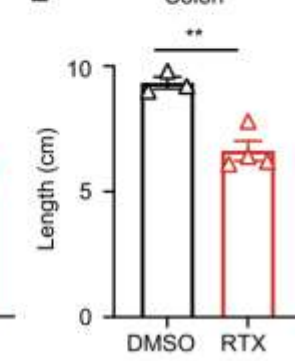
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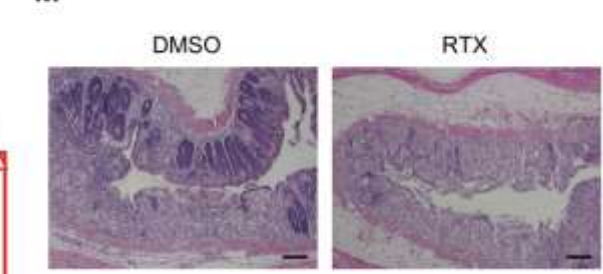
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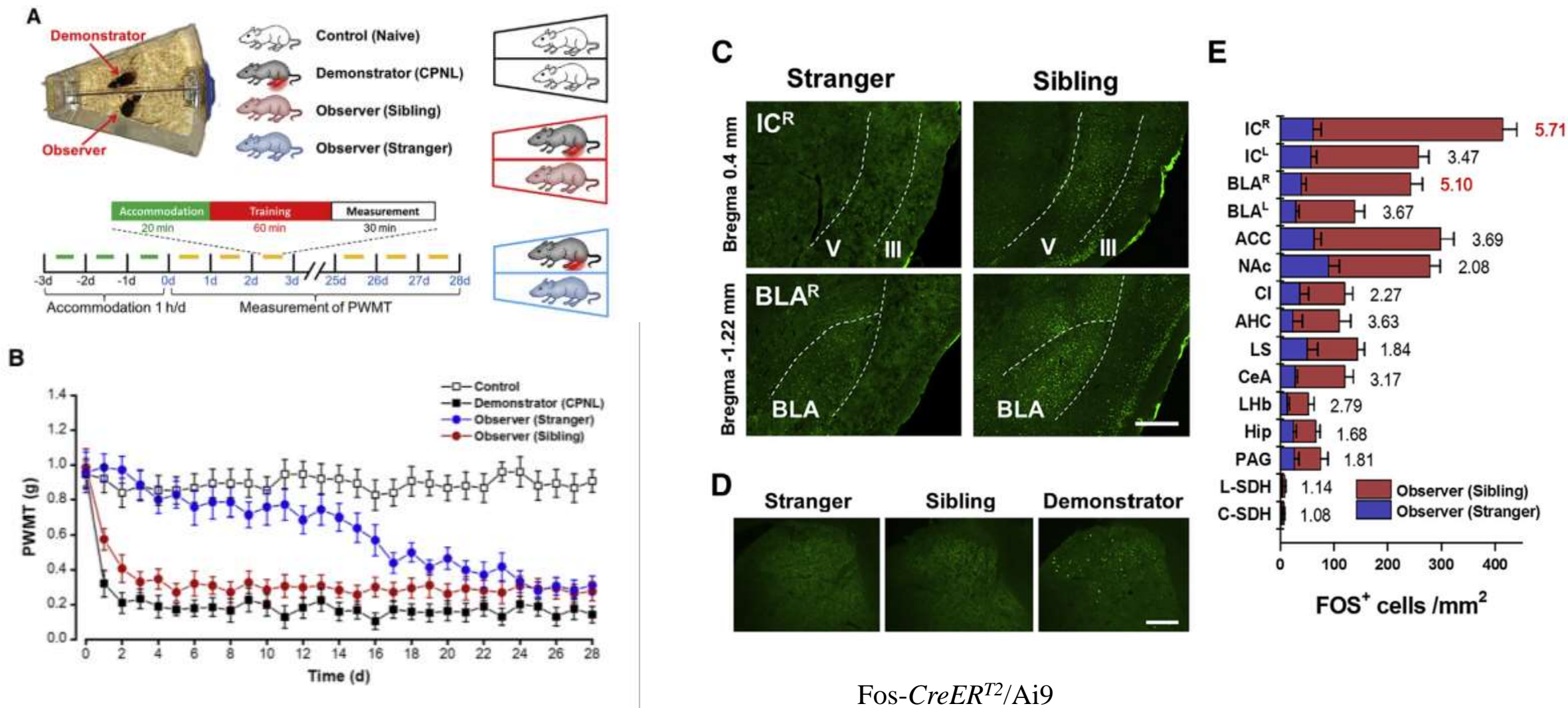


M





# Glutamatergic synapses from the insular cortex to the basolateral amygdala encode observational pain



右侧岛叶（IC）和右侧杏仁核基底外侧部（BLA）

(Zhang MM, et al. Neuron. 2022)

# Summary

## 1. Evaluate the nociception of organisms

Bacterial chemotaxis, migration towards attractants and away from repellents.

Drosophila and chronic pain, exhibit thermal allodynia after injury.

Bumblebee, motivational trade-offs.

Mice, two routes to pain

## 2. Cellular and molecular mechanism of pain and its significance for organisms

**Act pain and chronic pain**

**TRPV1**

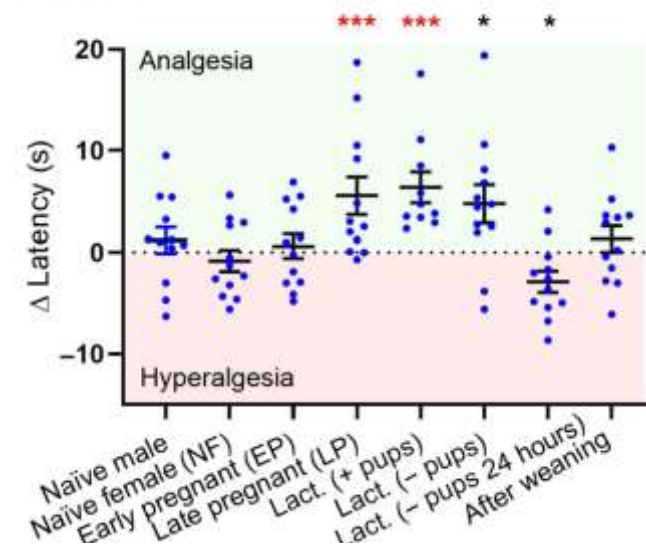
**IBDs**, interact with microorganisms to promote the intestinal microenvironment

**Chronic pain empathy**, from the insular cortex to the basal lateral amygdala

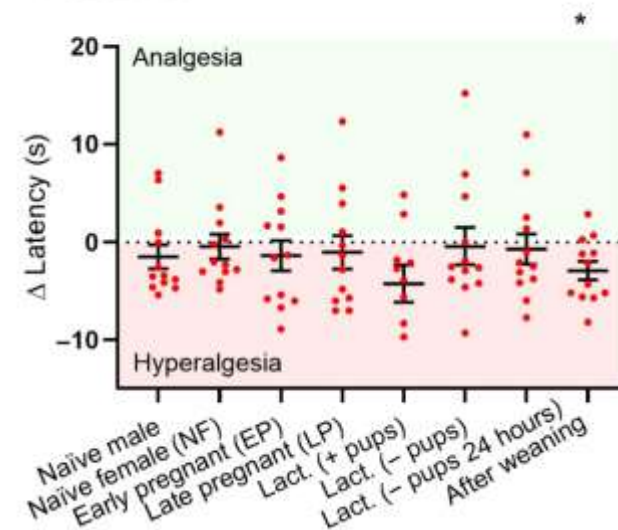
# Diversity in animal pain relief



**C Male  $\Delta$**



**D Female  $\Delta$**



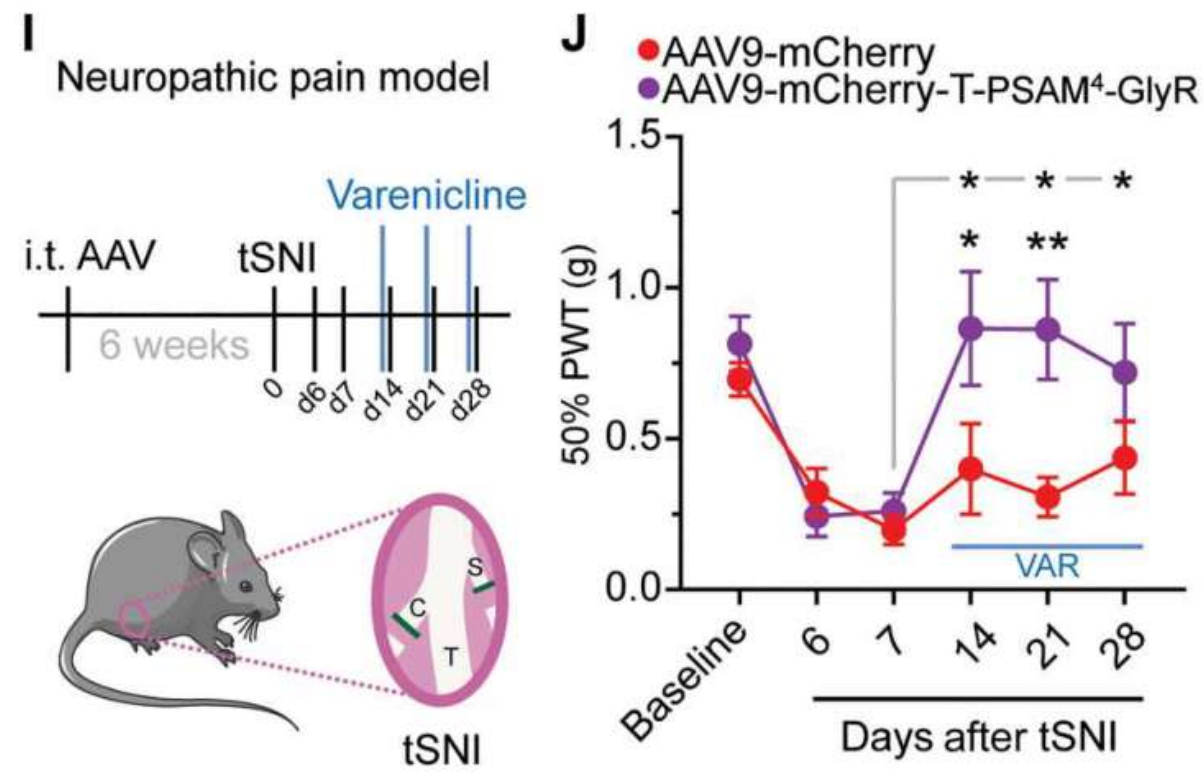
What are the new pain treatment methods available?

# Treatment for pain



- <https://www.msdmanuals.cn/home/brain-spinal-cord-and-nerve-disorders/pain/overview-of-pain>
- <https://www.mayoclinic.org/zh-hans/chronic-pain-medication-decisions/art-20360371>

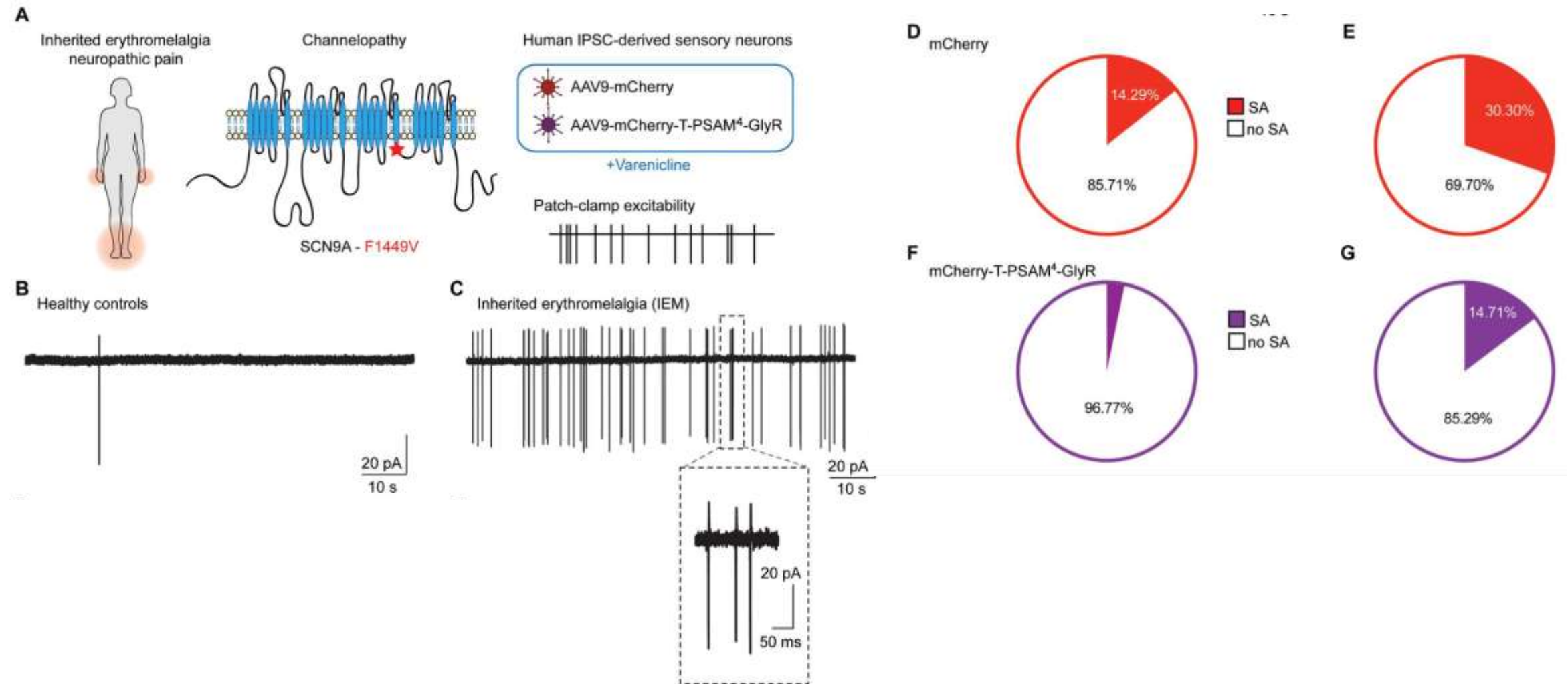
# PSAM<sup>4</sup>-GlyR-mediated silencing of inflammatory joint and neuropathic pain



胫骨保留神经损伤 (tSNI) 模型



# Silencing of SA in a human neuropathic pain model



## **Take home message**

1. Model animals are commonly used as chronic pain models and appropriate choices are made through motivational trade-offs, while there are gender differences in pain pathways.
2. TRPV1 interacts with microorganisms, promotes the gut microenvironment. The chronic pain empathy from the insular cortex to the basal amygdala also reveals the importance of pain.
3. A humanized chemogenetic system inhibits murine pain-related behavior and hyperactivity in human sensory neurons.



# **Neuronal mechanisms of pain perception in animals**

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## Different pain



屁股坐榴莲



# Question

1. How is pain transmitted to the brain?
2. How is pain transmitted in the brain?
3. What is the loop between emotions or cognition and pain?

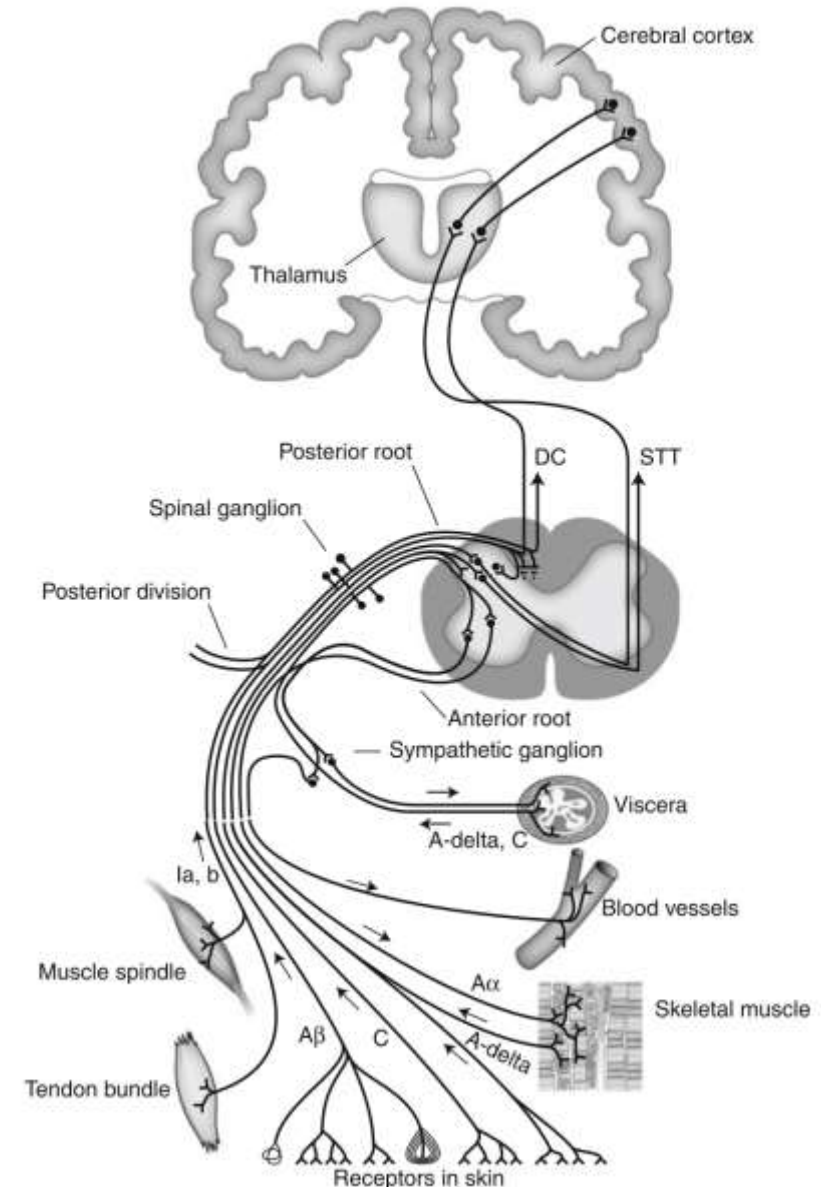
How is pain transmitted to the brain?

# Pain pathways

The pain pathway can be envisioned as a three-neuron pathway that transmits noxious stimuli from the periphery of the cerebral cortex.

1. Primary afferent neuron in spinal ganglion.
2. Second-order neuron in dorsal horn.
3. Third-order neuron in thalamic nuclei

A $\alpha$ :传递肌肉运动的信号  
A $\beta$ :传递非疼痛性的触觉信息，如触摸、压力和振动等。

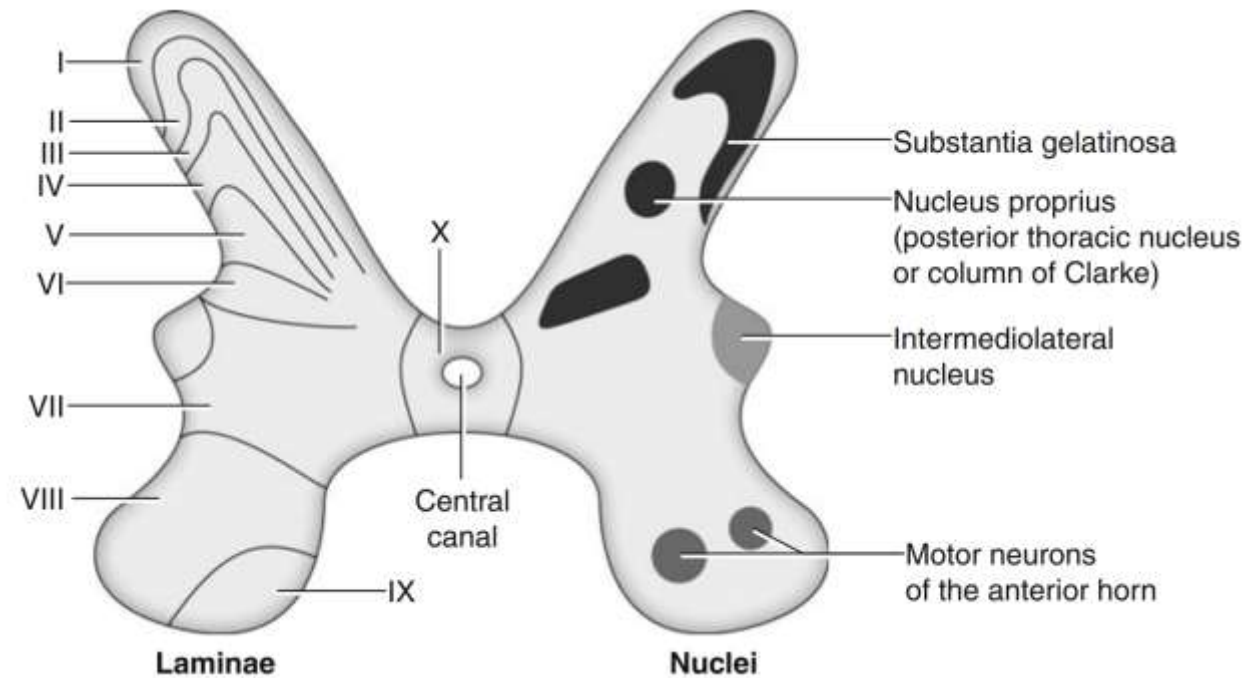
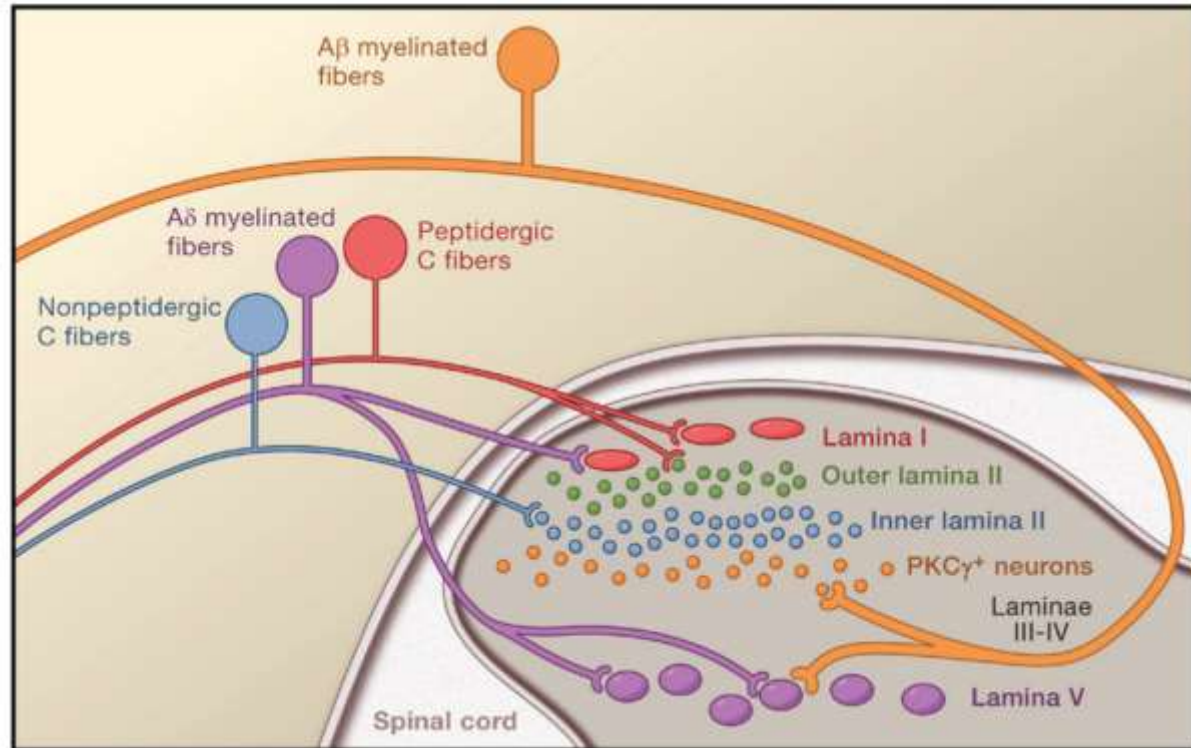


# Nociceptors

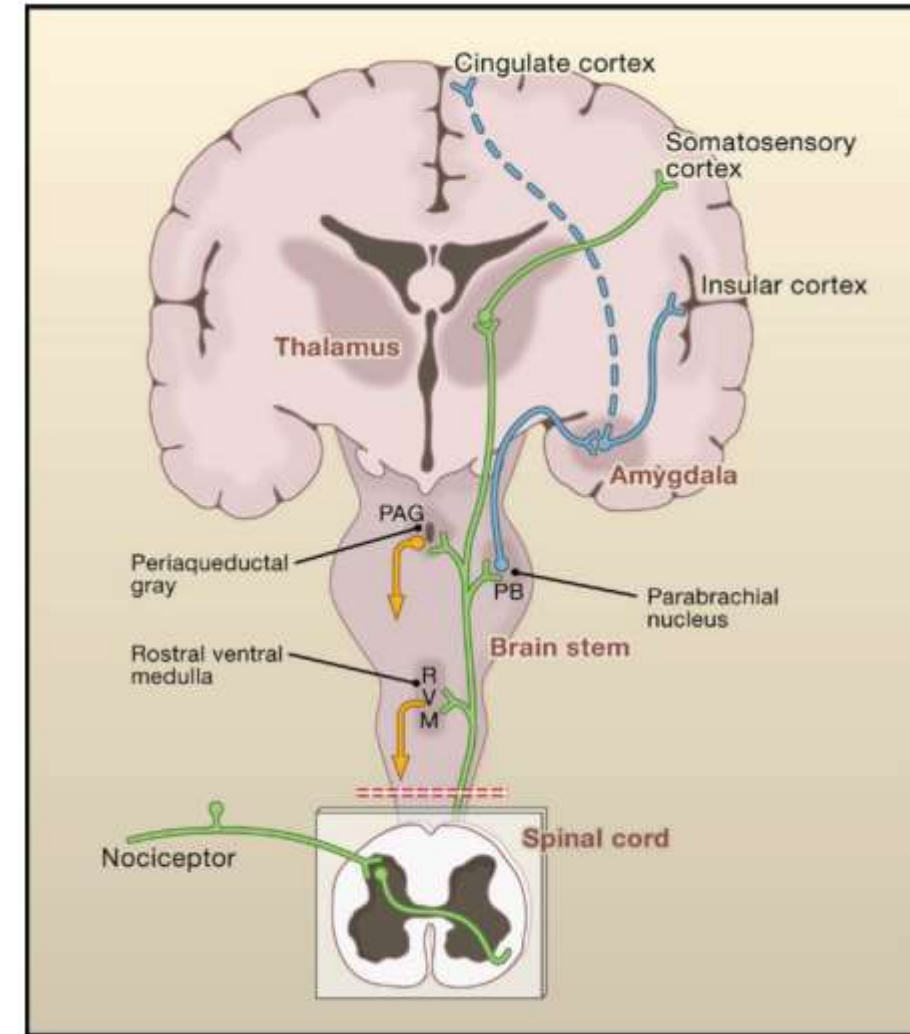
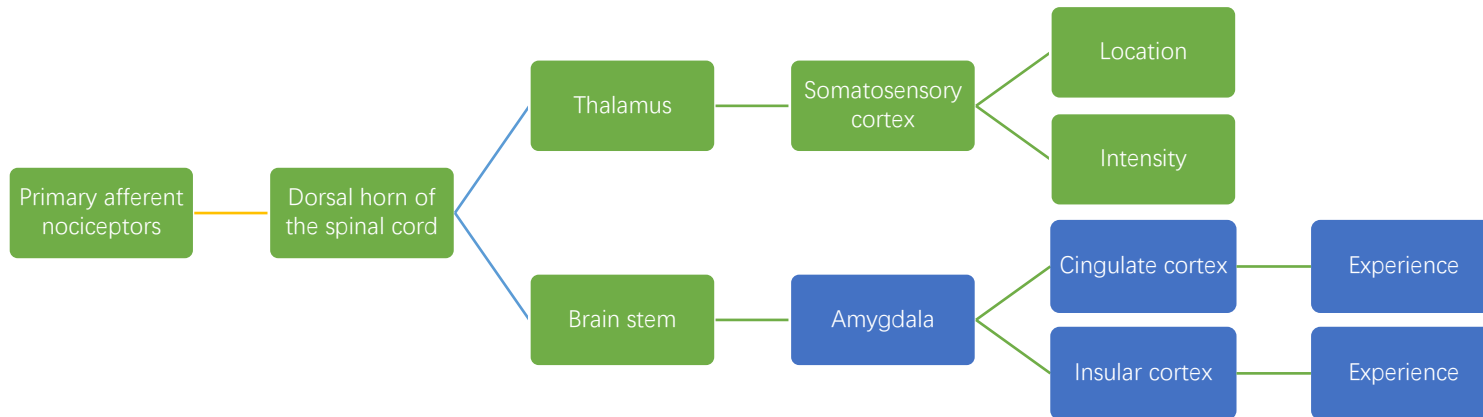
The nociceptors have two types of axons : unmyelinated (A- $\delta$  fibers) or myelinated(C fibers )

	A- $\delta$ fibers	C fibers
Level	primary afferent fibers	primary afferent fibers
Size	small in diameter	large in diameter
Conduction	slow and unmyelinated	fast and myelinated
Condition	multitude of noxious stimuli such as chemical, thermal, and mechanical	mechanical stimuli over a specific intensity
Example	aching, diffuse, dull, or burning quality of pain	a sharp, localized, and pricking quality of pain

# Nociceptors to the dorsal horn



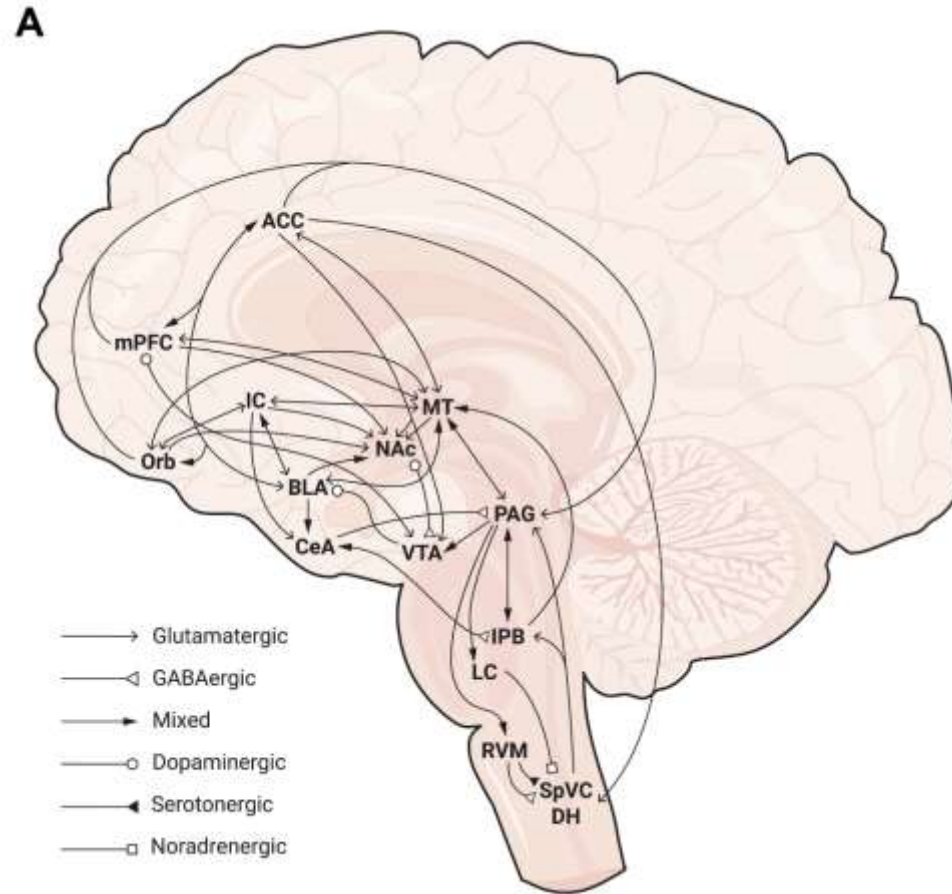
# Nociceptors to the dorsal horn to brain





How is pain transmitted in the brain?

# Pain circuits in the brain





**Richard Palmiter 理查德·帕尔米特**

**Professor of Biochemistry**

**生物化学教授**

Investigator, HHMI 霍华德休斯医学研究所 (HHMI) 研究员

PhD 1968 Stanford University

1968年 斯坦福大学博士

AB 1964 Duke University

AB 1964 杜克大学

Off.: J661 | Ph.: 206.543.6064 | Fax: 206.685.1792

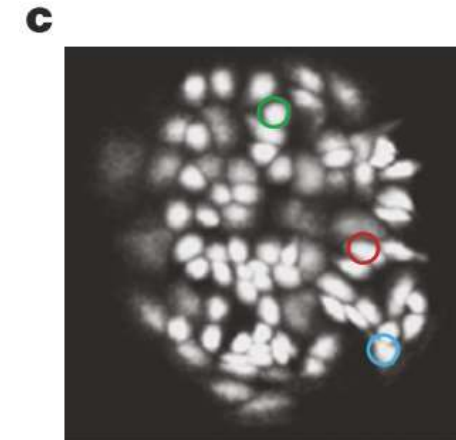
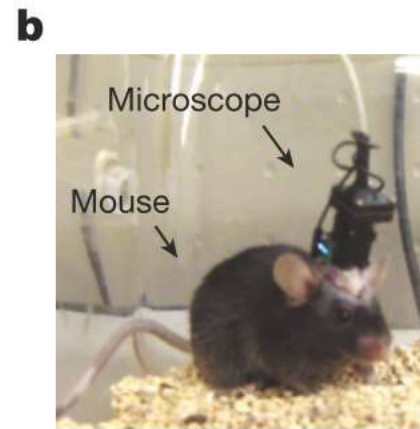
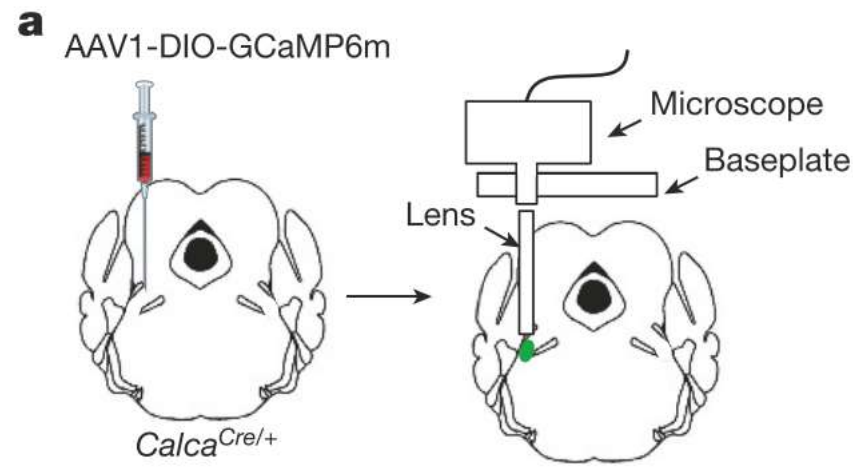
[HHMI Website](#)

Our laboratory uses mouse genetic models and viral gene transfer to dissect neural circuits involved in innate behaviors.

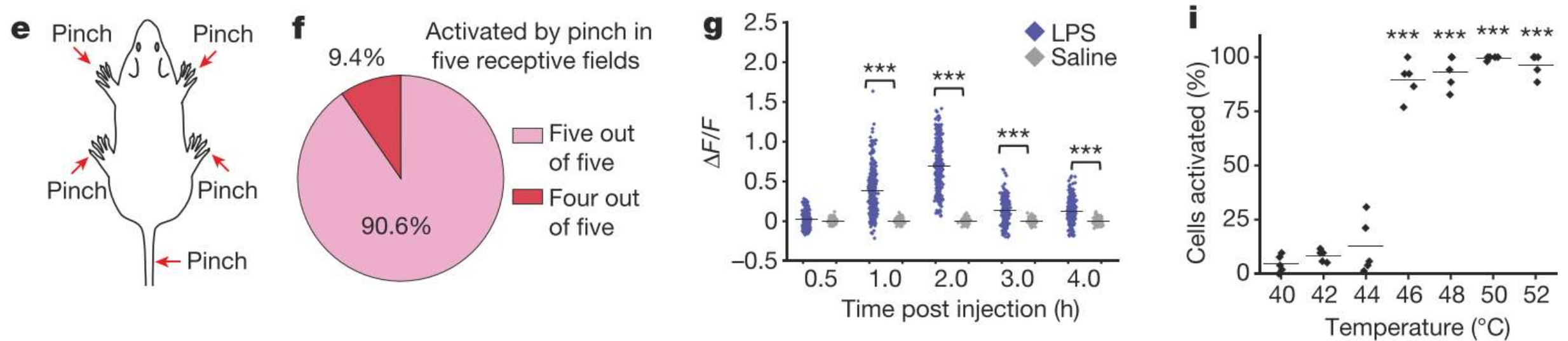
- 1988 Elected to National Academy of Sciences  
1988年 当选为美国国家科学院院士
- 1988 Elected to American Academy of Arts and Sciences  
1988年 当选为美国艺术与科学院院士
- 1987 Elected Fellow of American Association for the Advancement of Science  
1987年 当选为美国科学促进会院士

## Encoding of danger by parabrachial CGRP neurons

Carlos A. Campos<sup>1</sup>, Anna J. Bowen<sup>1</sup>, Carolyn W. Roman<sup>1</sup> & Richard D. Palmiter<sup>1</sup>



# CGRP<sup>PBN</sup> neurons are activated by painful stimuli





## Investigator, McGovern Institute

Professor, Brain and Cognitive Sciences

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Fan Wang is uncovering the neural circuit mechanisms that govern sensory perception, pain, and behavior.

[LAB WEBSITE](#)

Office:  
617-258-6415

Address:  
46-4165A

Email:  
[fan\\_wang@mit.edu](mailto:fan_wang@mit.edu)

[Publications](#)

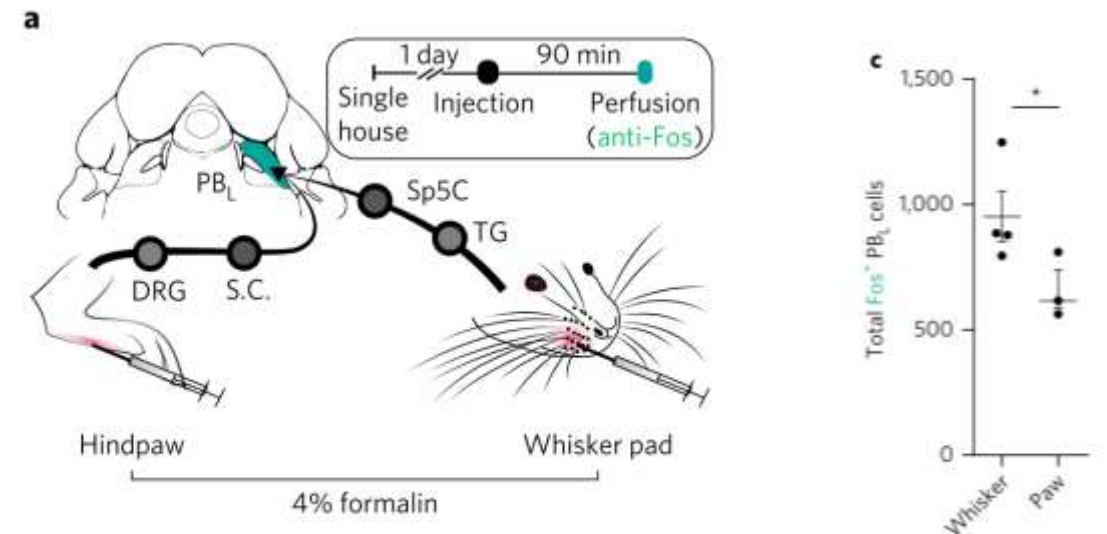


# A craniofacial-specific monosynaptic circuit enables heightened affective pain

Erica Rodriguez<sup>1</sup>, Katsuyasu Sakurai<sup>1</sup>, Jennie Xu<sup>1</sup>, Yong Chen<sup>2</sup>, Koji Toda<sup>3</sup>, Shengli Zhao<sup>1</sup>, Bao-Xia Han<sup>1</sup>, David Ryu<sup>1</sup>, Henry Yin<sup>3</sup>, Wolfgang Liedtke<sup>2</sup> and Fan Wang<sup>1\*</sup>

三叉神经节 (TG): 头部和面部区域的有害刺激  
中枢神经系统神经节 (DRG): 颅外区域的有害刺激

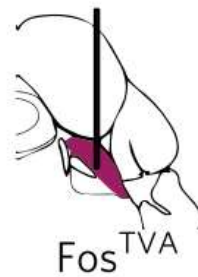
面部疼痛和身体疼痛哪个更疼?



# PB<sub>L</sub>-nociceptive neurons project axons to multiple emotion- and instinct-related centers in the brain

**a**  
1<sup>st</sup> stimulation

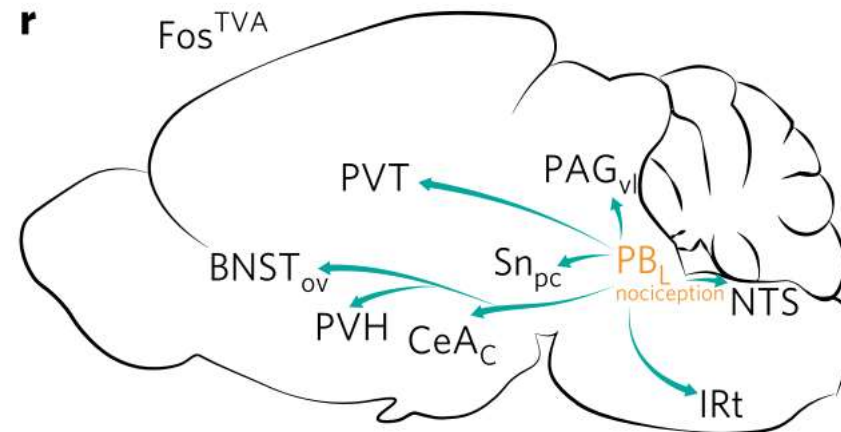
CANE-Cre;  
AAV-flex-GFP



>10 days

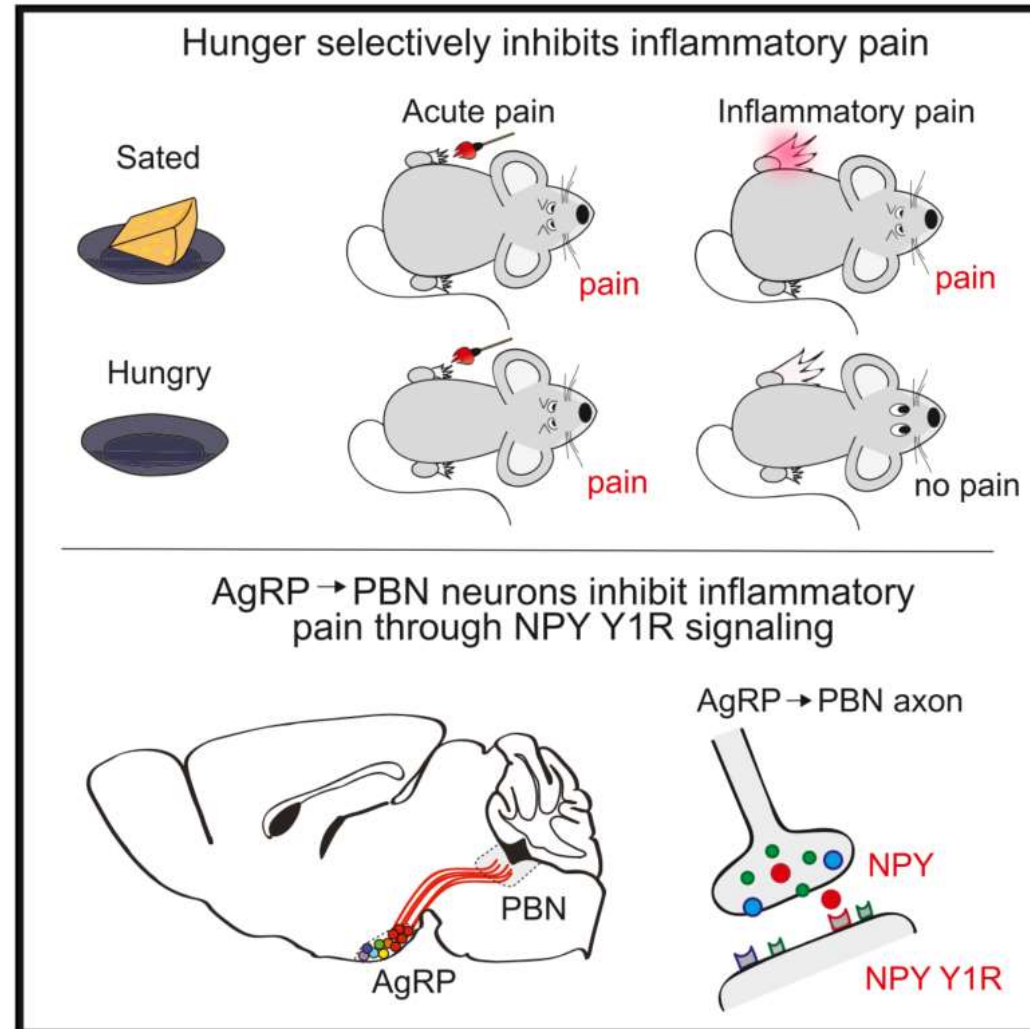
2<sup>nd</sup> stimulation

Perfusion  
Anti-Fos



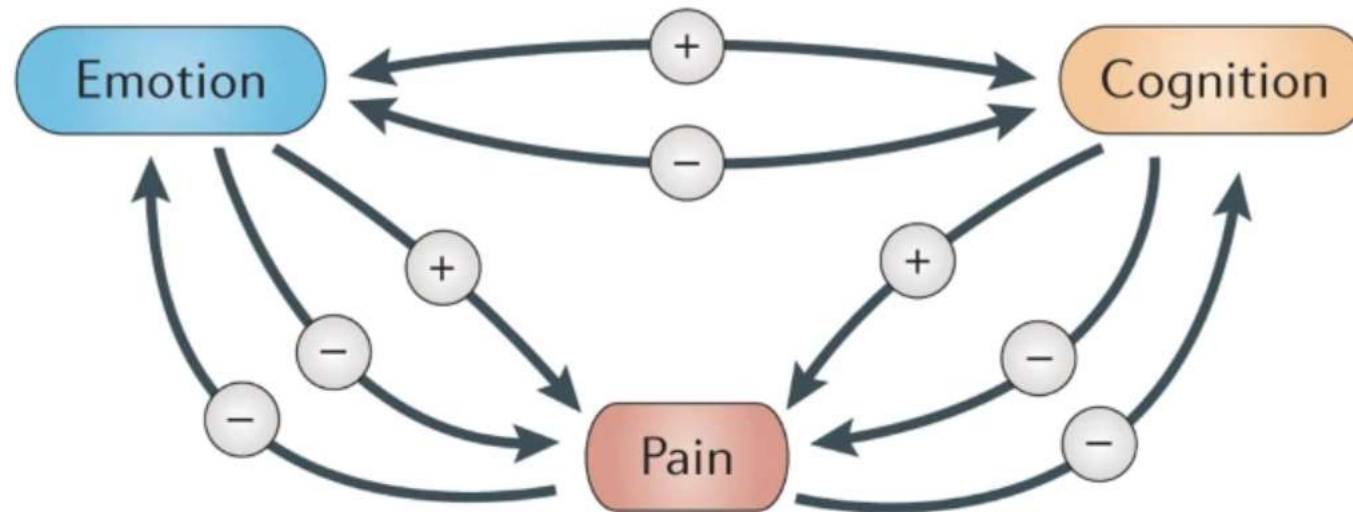


# A Neural Circuit for the Suppression of Pain by a Competing Need State

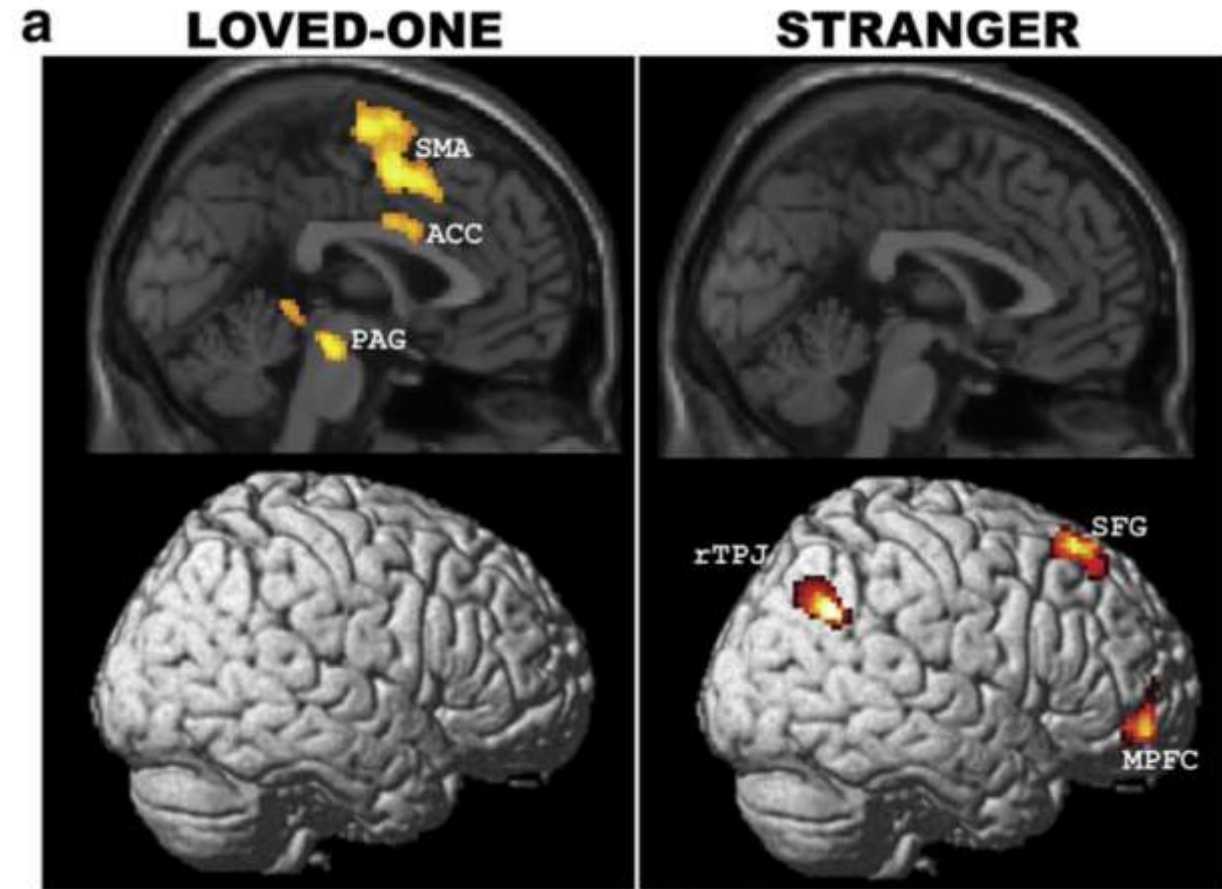
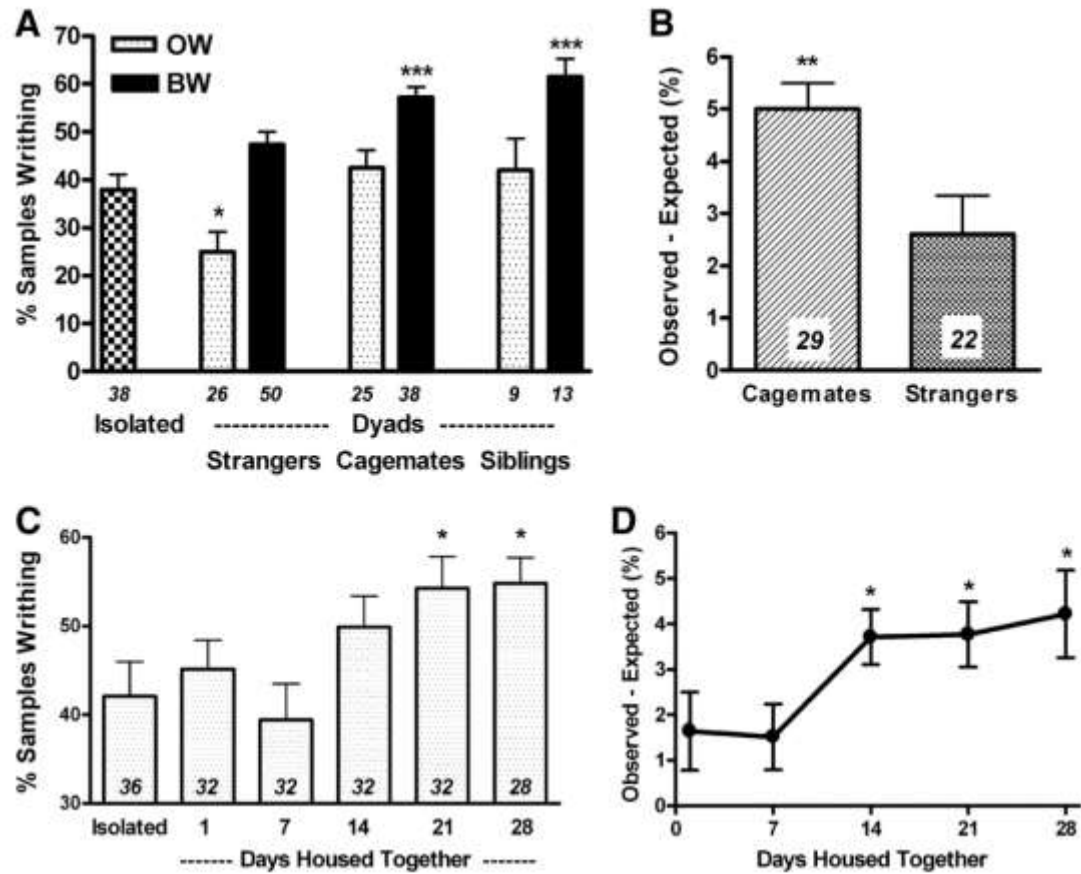


What is the loop between emotions or cognition and pain?

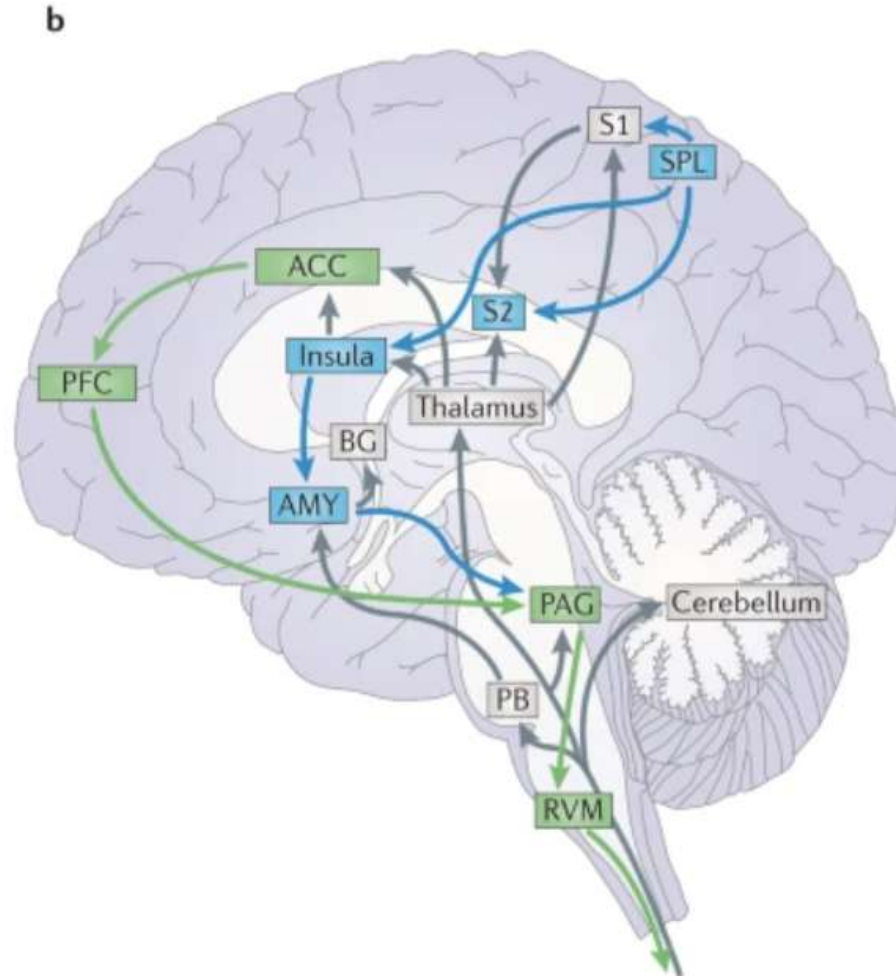
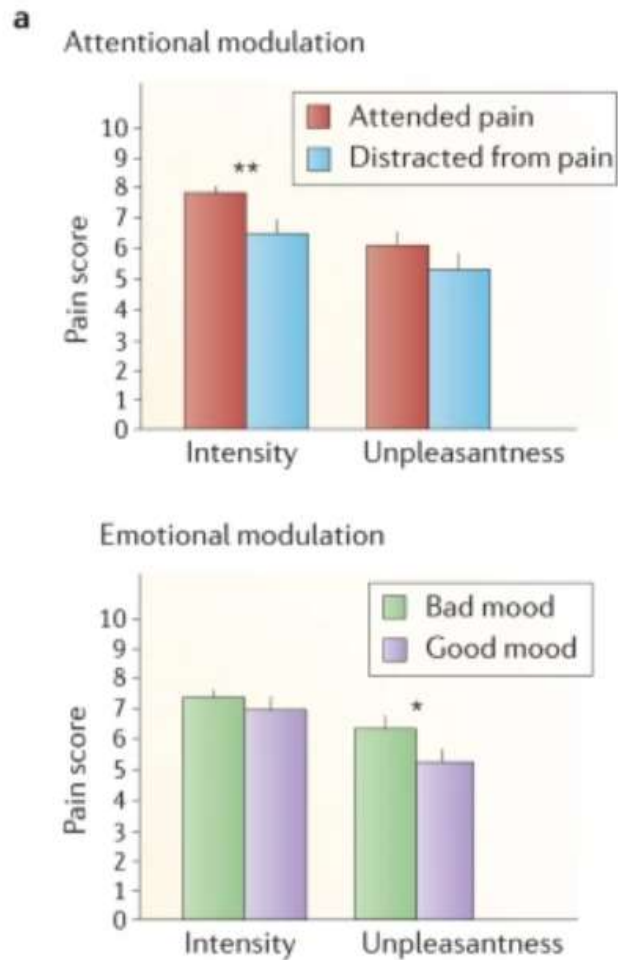
## Feedback loops between pain, emotions and cognition



# Emotional contagion in pain



# Attentional and emotional factors modulate pain perception via different pathways



## Take home message

- The pain pathway can be envisioned as a three-neuron pathway that transmits noxious stimuli from the periphery to the cerebral cortex
- Pain can be transmitted to various parts of the brain via PB neuron
- Pain, attention, and emotion can influence each other through different pathways

# **Impact of pain perception on animal behavior**

- What are the behavioral methods of pain in various model animals?
- What are the types of behaviors caused by pain?
- What is the relationship between chronic pain and learning and memory behavior?

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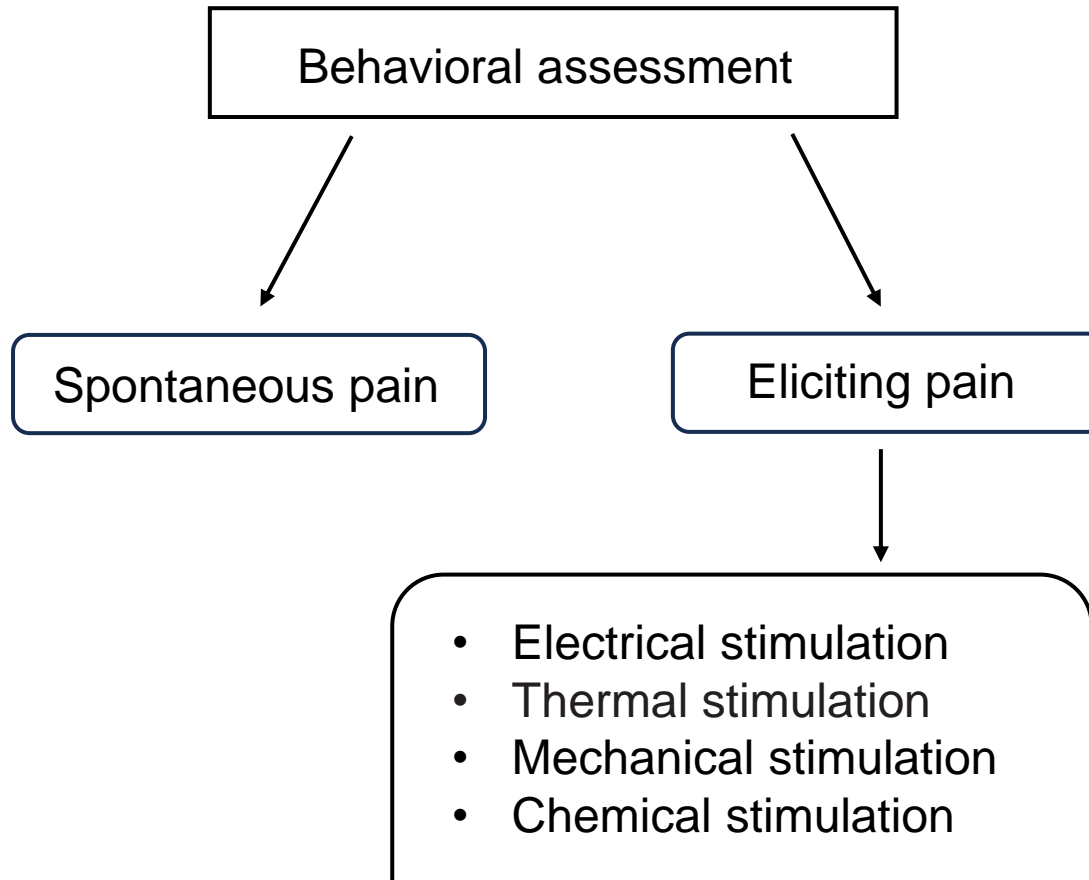


What are the behavioral methods of pain in various model animals?

## Model animals commonly used in pain research



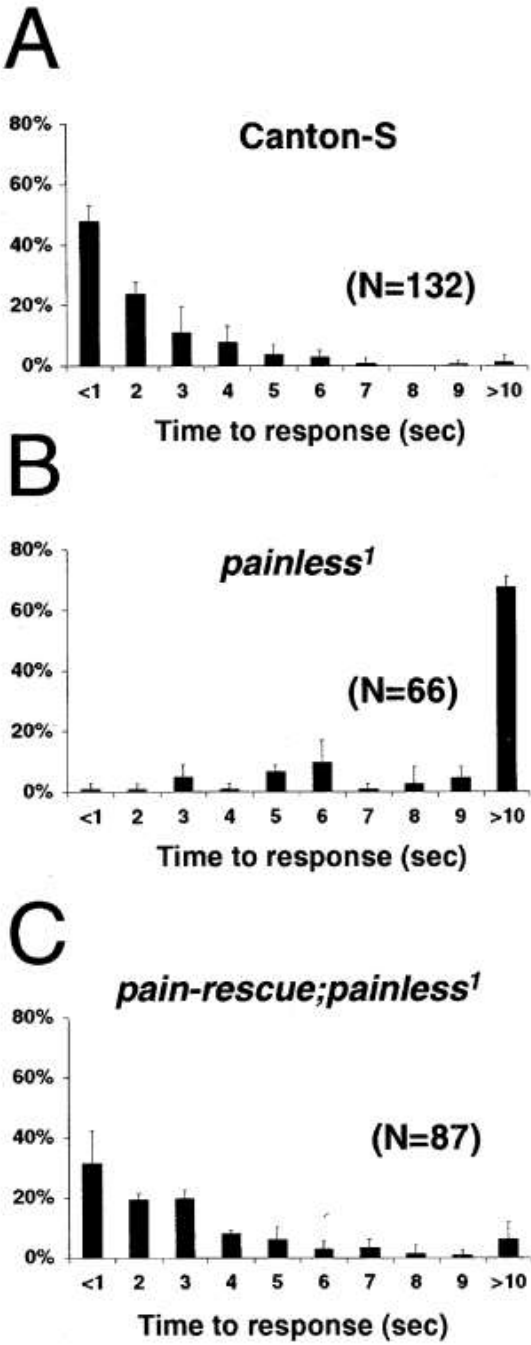
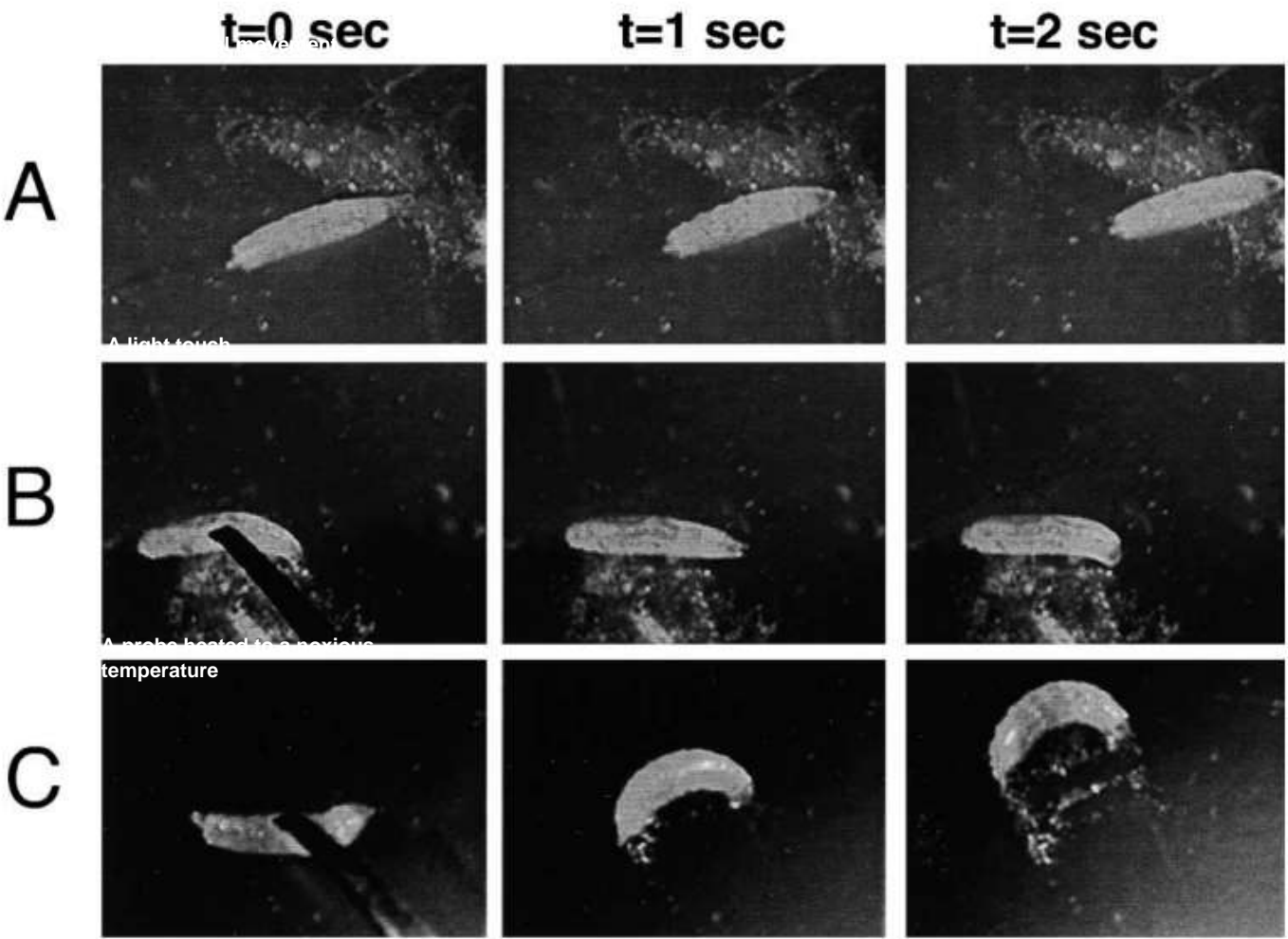
# Characteristics of behavioral detection methods in pain research



## Behavioral models of nociception

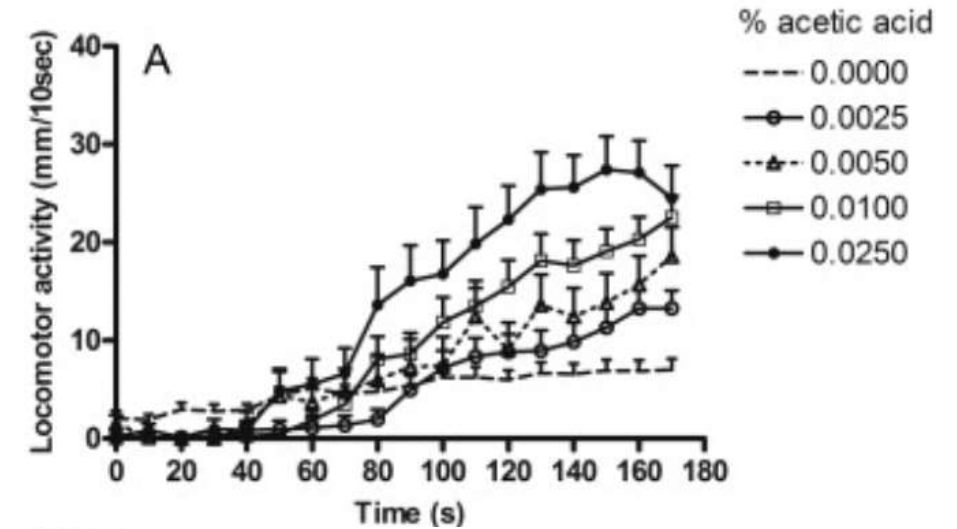
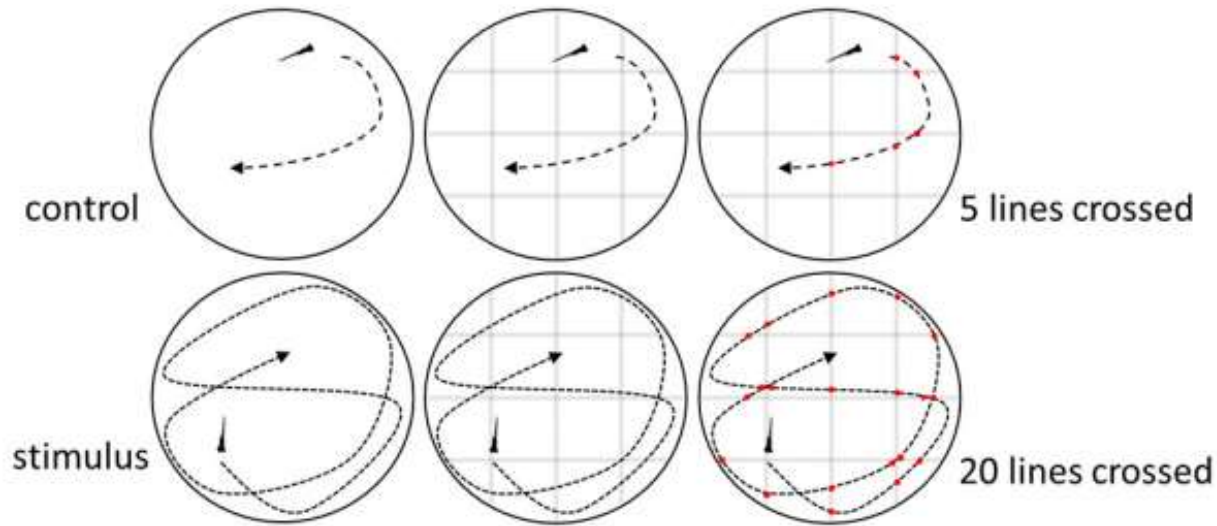
- Specificity
  - Input specificity
  - Output specificity
- Sensitivity
  - Response sensitivity
  - Pharmacological manipulations sensitivity
- Validity
- Reliability
- Reproducibility

Painless is required for both thermal and mechanical nociception

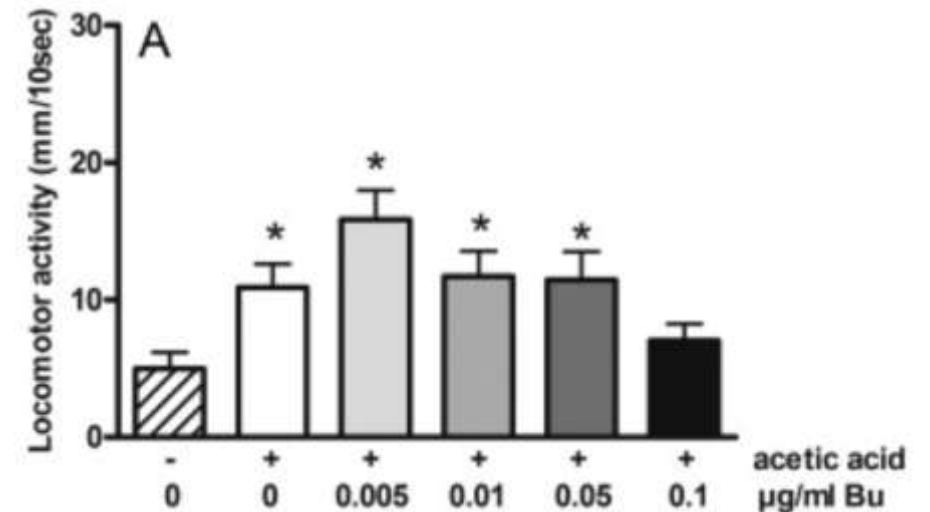
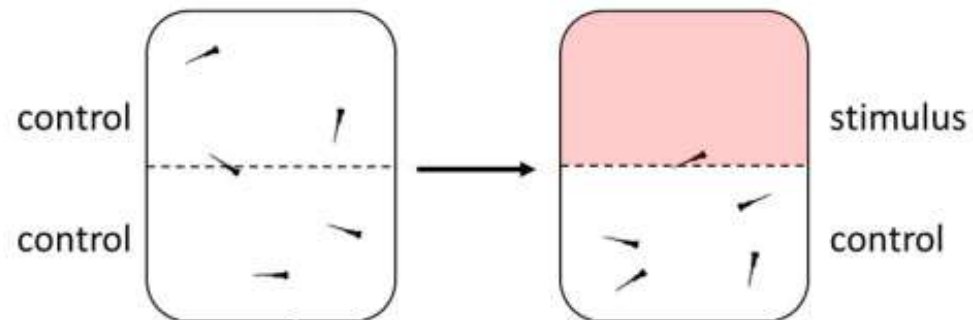


Zebrafish are often used in pain studies to test the effectiveness of analgesics

### A Locomotion assay



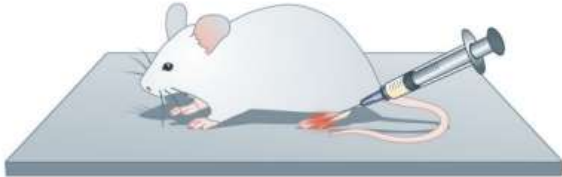
### B Place preference test



# Rodents are the most commonly used animal models for pain research

## a Types of pain measurement

### Chemical



### Cold



### Electrical



### Heat



### Mechanical



### Spontaneous



## Jeffrey S. Mogil

### Professor

Canada Research Chair in Genetics of Pain Tier I  
E. P. Taylor Chair in Pain Studies

Stewart Biological Sciences Bldg.  
Room N7/42, 398-6085  
jeff at psych.mcgill.ca  
<http://paingeneticslab.ca>

### Research Areas

Behavioral Neuroscience

- The genetics of pain
- Sex differences in pain biology
- The development of animal models and measures of pain
- Interactions between social behaviour and pain
- The identification of laboratory environmental factors affecting pain

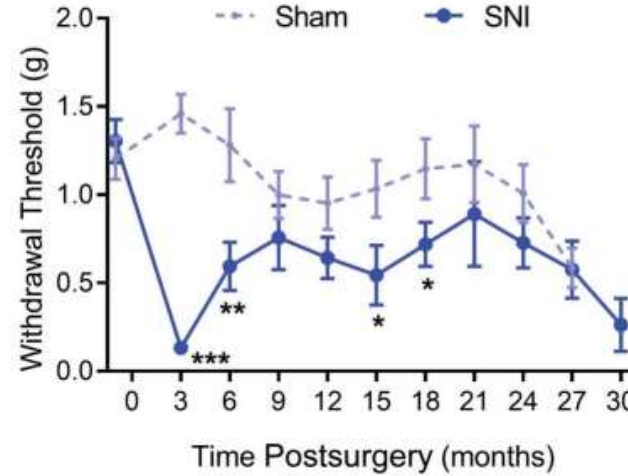


# The von Frey test

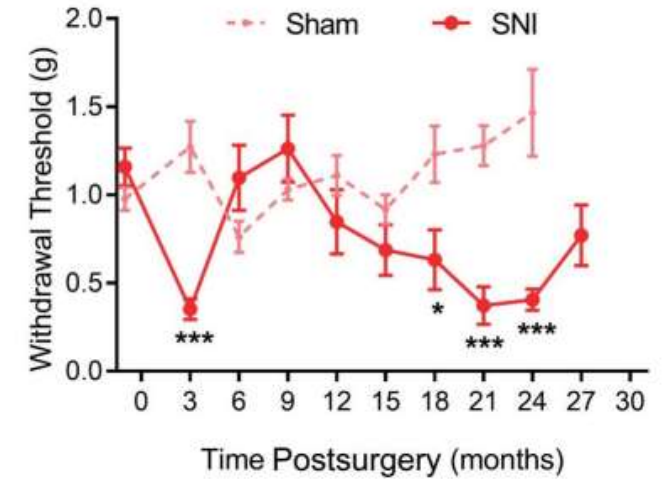
## Mechanical



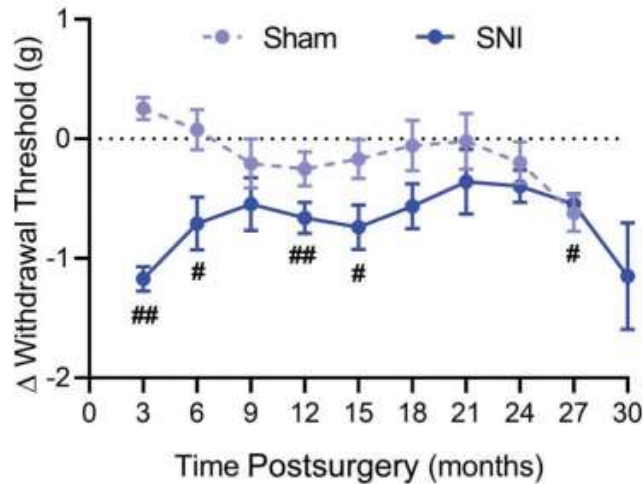
### A. Males



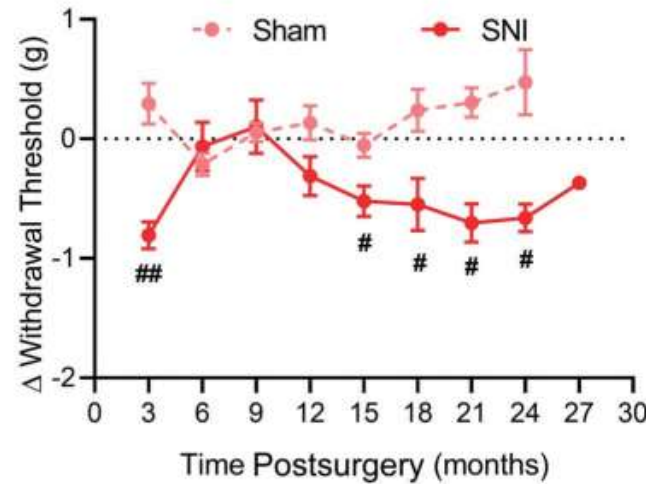
### B. Females



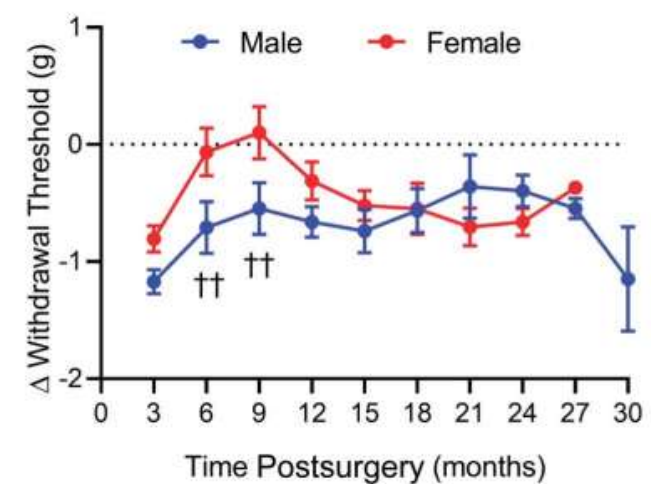
### C. Δ - Males



### D. Δ - Females



### E. SNI Only



Less Pain



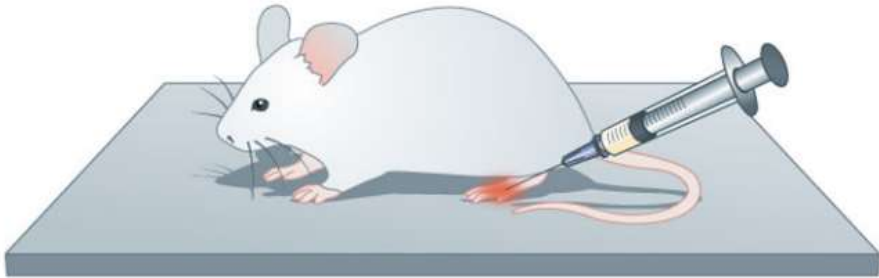
More Pain

SNI: Spared Nerve Injury

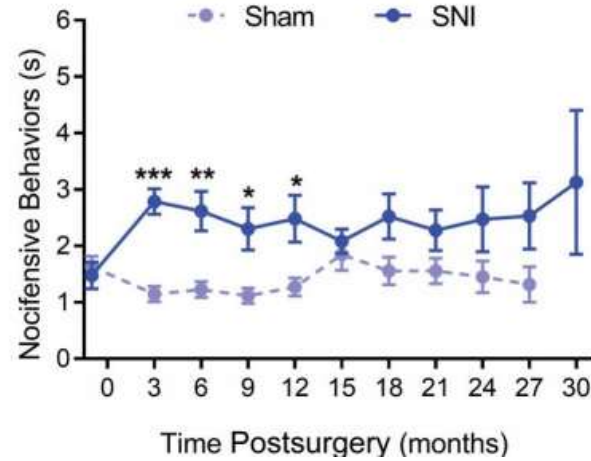


# The acetone drop test

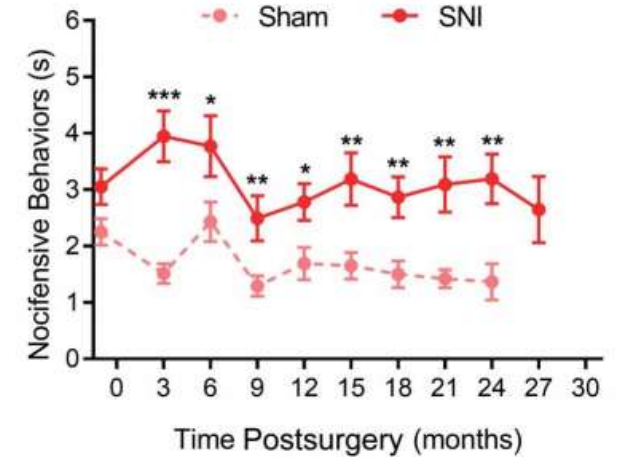
## Chemical



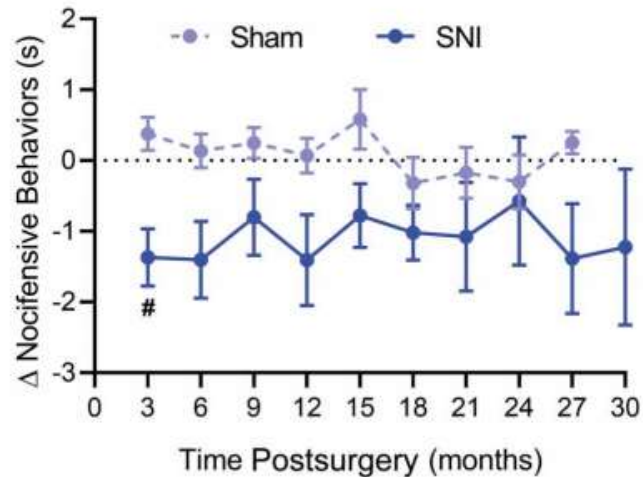
A. Males



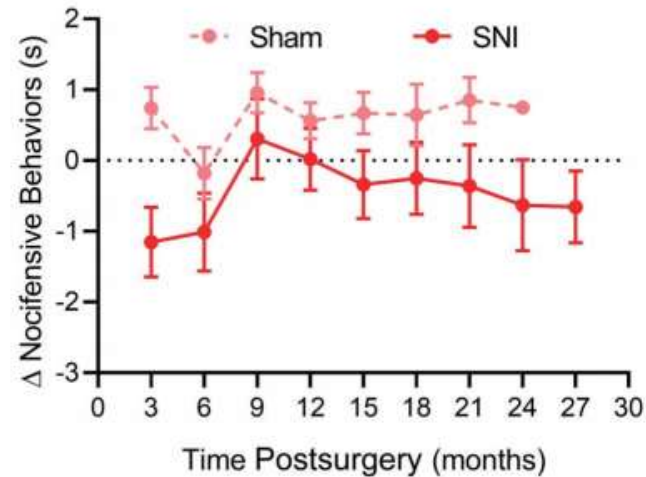
B. Females



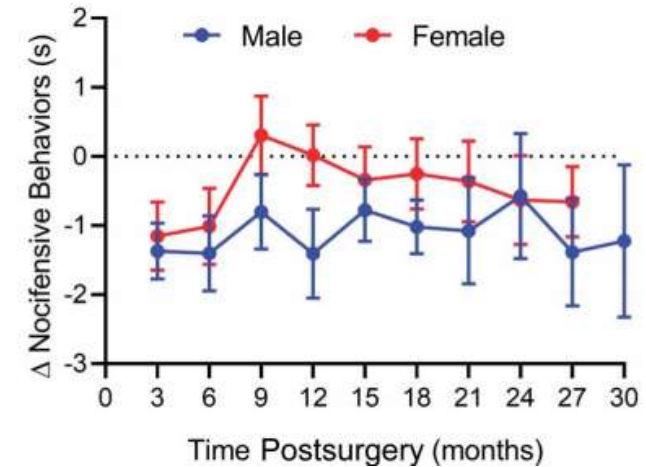
C. Δ - Males



D. Δ - Females



E. SNI Only



SNI: Spared Nerve Injury

What are the types of behaviors caused by pain?

# Noxious stimuli evoke exteroceptive and interoceptive perceptions and associated behaviors

Neuron

CellPress

Perspective

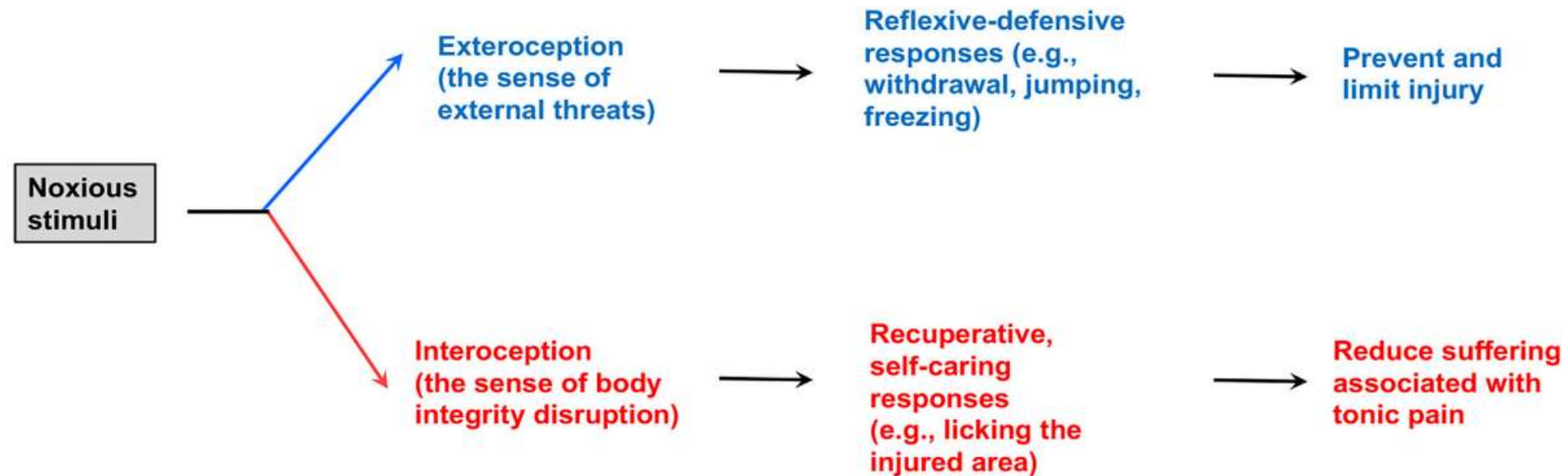
## A functional subdivision within the somatosensory system and its implications for pain research

Qiufu Ma<sup>1,\*</sup>

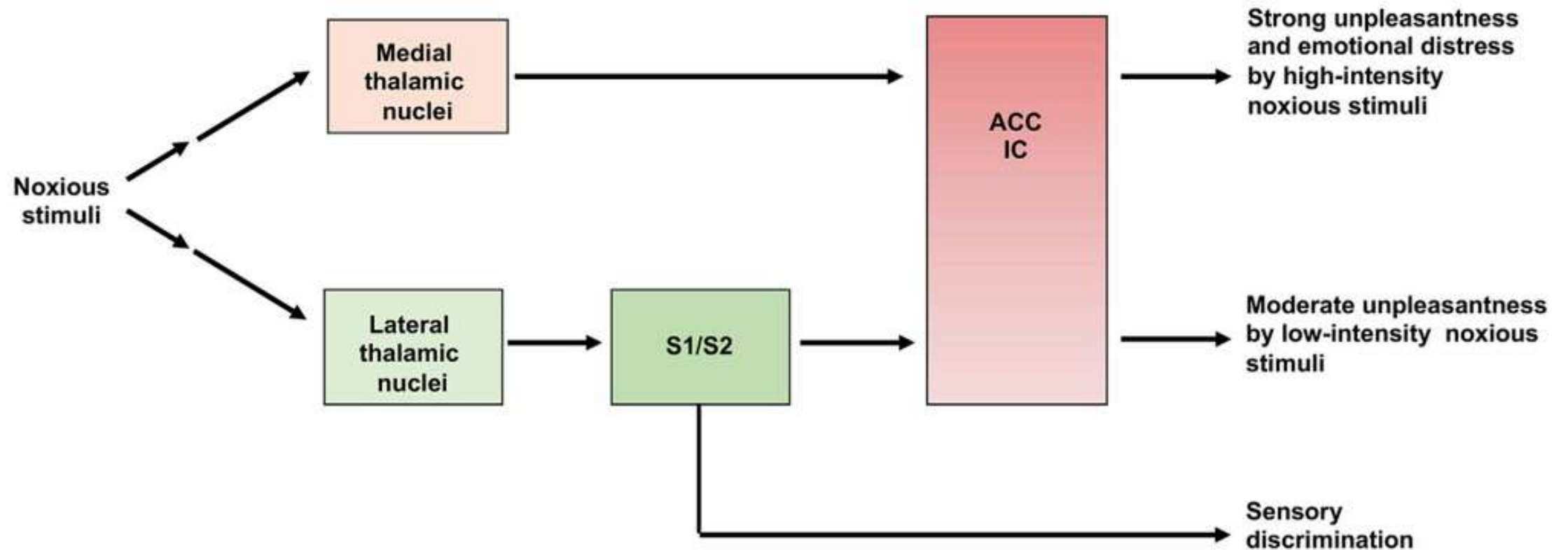
<sup>1</sup>Dana-Farber Cancer Institute and Department of Neurobiology, Harvard Medical School, Boston, MA 02115, USA

\*Correspondence: [qiufu\\_ma@dfci.harvard.edu](mailto:qiufu_ma@dfci.harvard.edu)

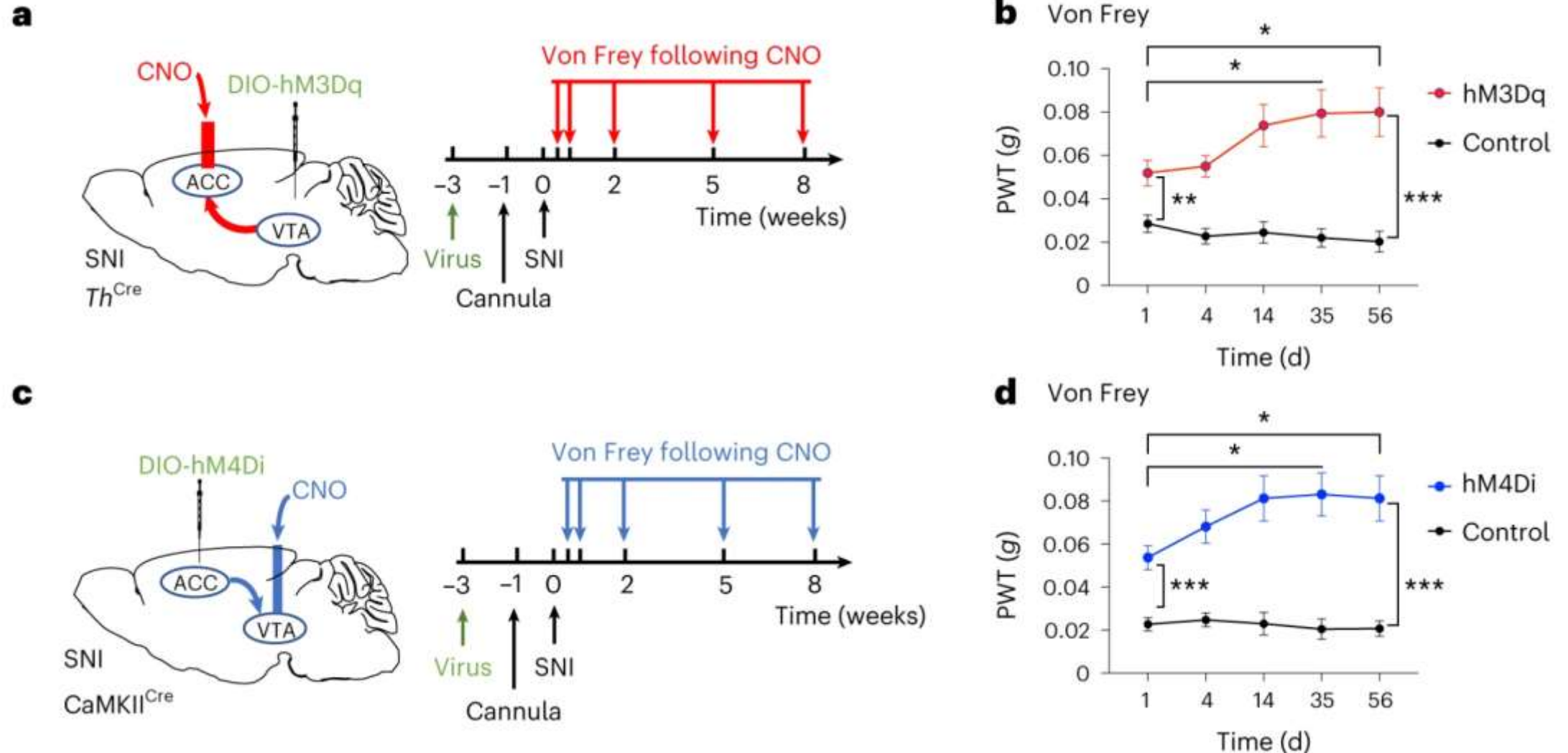
<https://doi.org/10.1016/j.neuron.2021.12.015>



Human studies reveal the segregation and convergence of the lateral versus medial thalamic pathways

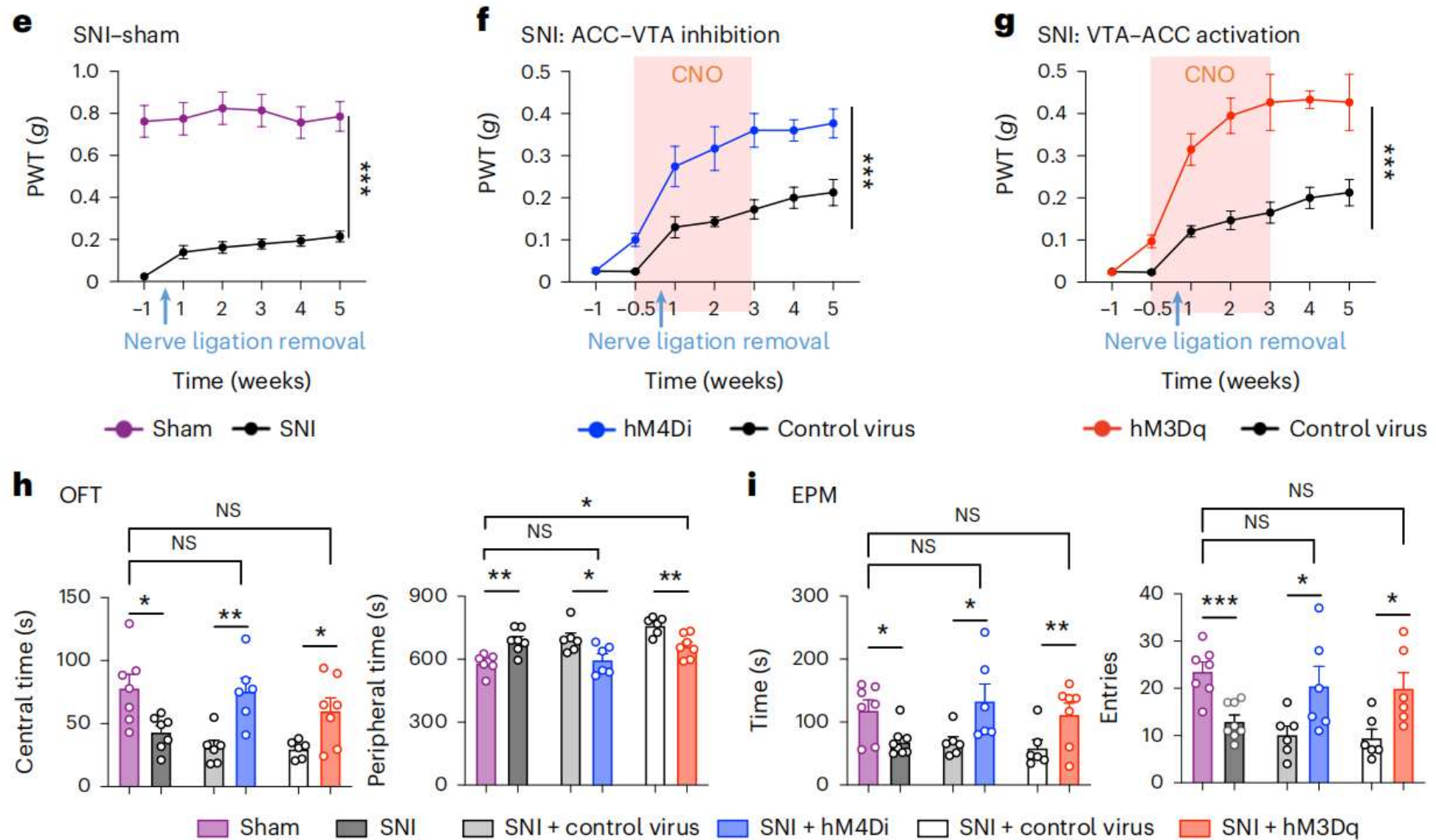


# Targeting ACC-VTA-ACC in-loop intersections relieves persistent pain



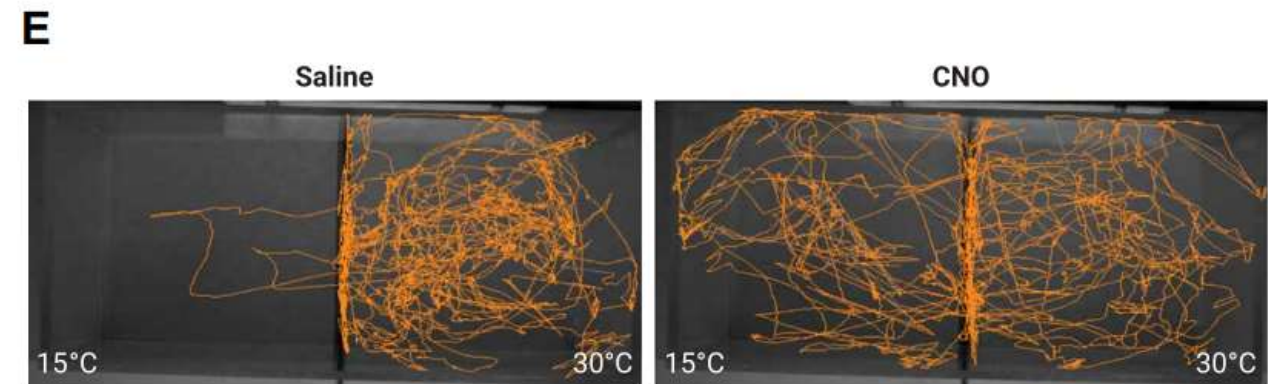
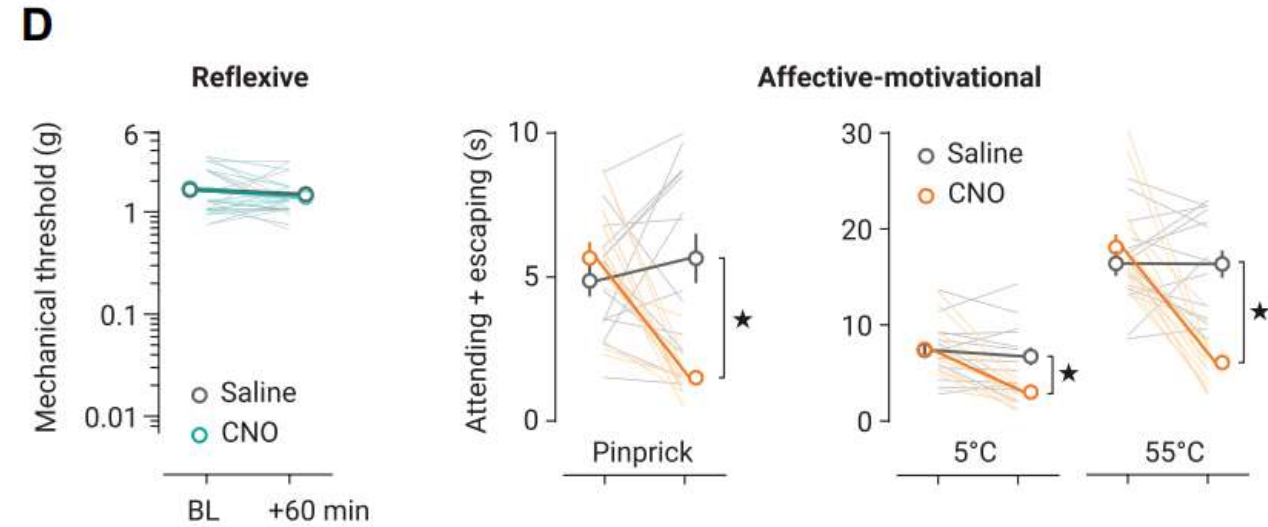
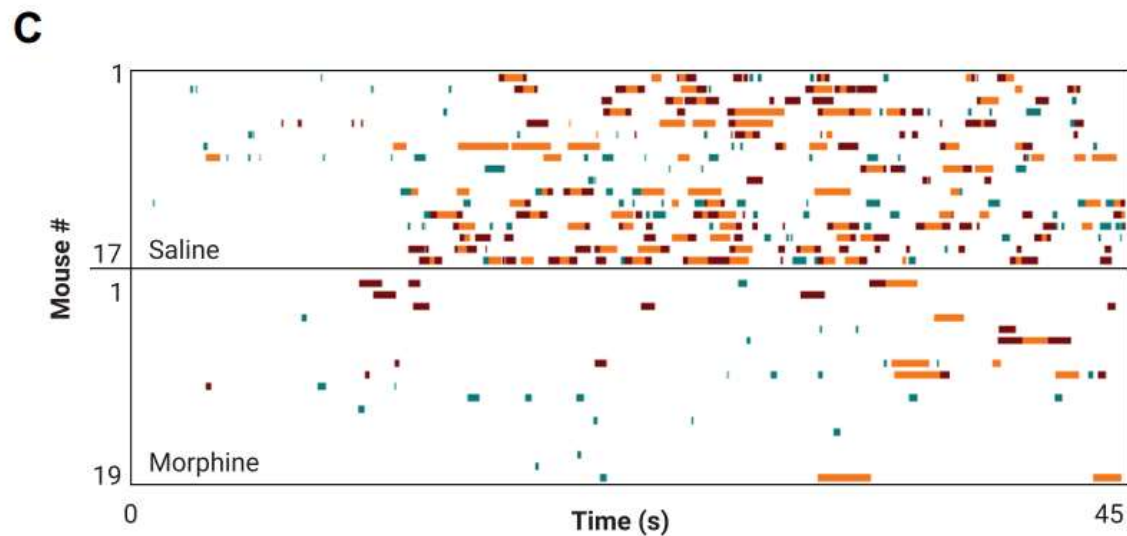
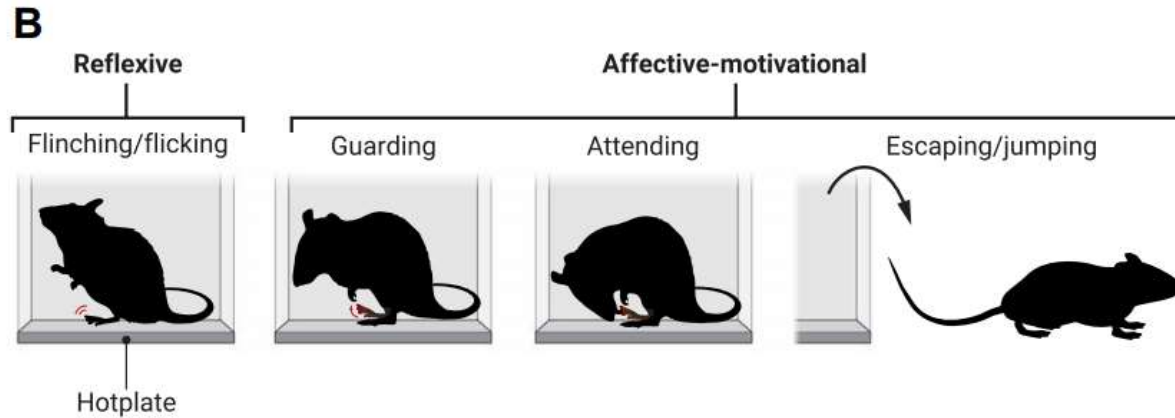


# Targeting ACC-VTA-ACC in-loop intersections relieves persistent pain



# An amygdala neural ensemble that encodes the unpleasantness of pain

Method: inhibition of nociceptive BLA neurons with hM4Di after injection of CNO

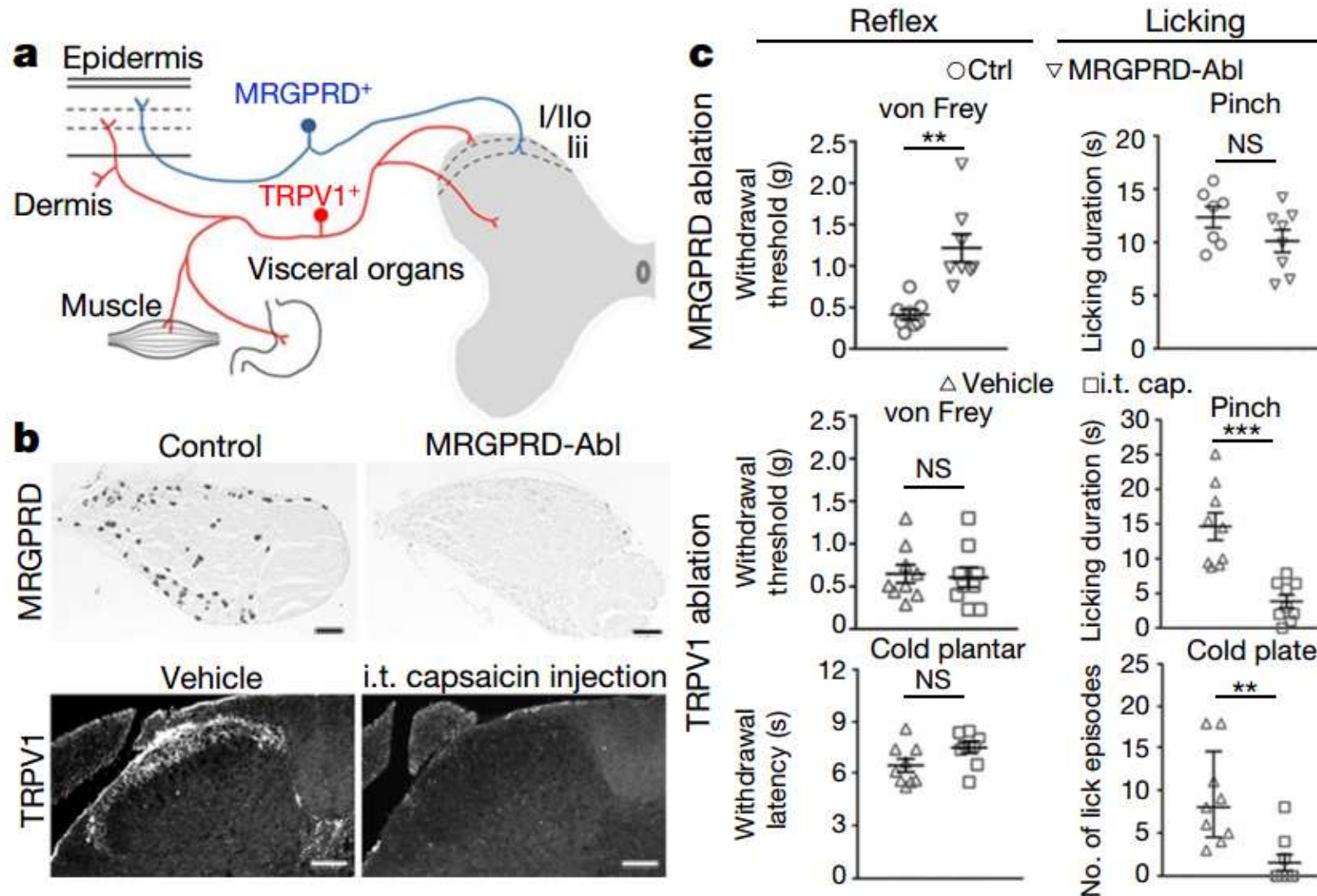


Mercer Lindsay, Nicole et al. Science translational medicine vol. 13,619 (2021): eabj7360.

Corder, Gregory et al. Science (New York, N.Y.) vol. 363,6424 (2019): 276-281.



TRPV1+, but not MRGPRD+ neurons are required for noxious stimuli-evoked licking



What is the relationship between chronic pain and learning and memory behavior?

好了伤疤就能忘了痛吗？



# Chronic pain interacts with learning and memory function

**Table 2.** Performance on the cognitive tasks, by study group\*

	Fibromyalgia patients (n = 23)	Age-matched controls (n = 23)	Older controls (n = 22)
Information-processing speed	139.45 ± 29.55	139.23 ± 29.55	118.50 ± 19.15
Working memory	22.22 ± 7.85	26.30 ± 1.67	22.09 ± 6.27
Free recall	23.56 ± 7.80	27.83 ± 6.43	23.91 ± 6.77
Recognition memory	2.53 ± 1.19	2.95 ± 1.07	2.80 ± 1.19
Verbal fluency	49.78 ± 11.63	56.08 ± 15.65	49.43 ± 13.74
Verbal knowledge	43.17 ± 7.62	51.26 ± 6.01	50.56 ± 7.93

\* Values are the mean ± SD.

Interestingly, in the case of chronic pain, in two patients, **amnesia** appeared to essentially be a miracle cure for their pain [62]. Before their amnesia, both had been on high levels of opioids alongside having tried other methods of pain relief, both pharmacological and behavioral. The first patient was hospitalized for her pain for a year. During this time, she was witnessed to have at least five seizures and, after one episode, she could not remember anything about her period of hospitalization but had normal long-term memories and cognitive functioning. To test her cognitive functioning, she was weaned off her opioid medication. To the physicians' surprise, she showed minimal withdrawal and substantially reduced pain. Pain was still substantially reduced 6 months on.

The second patient had a history of low back pain and sciatica [62]. Seemingly everything had been tried to ameliorate his pain, from nerve injections, steroids, implantation of an intrathecal morphine pump, psychotherapy, and drugs usually used for neuropathic pain, such as gabapentin and antidepressants. A period of time after a motorcycle accident, the man suffered severe amnesia despite his brain MRI scan apparently being normal. Again, for cognitive testing, the opioid dosages were significantly reduced, and he did not complain of further pain. Over the next 2 years, he started to regain some memories and have mild back and leg pain, but did not request further opioid treatment.

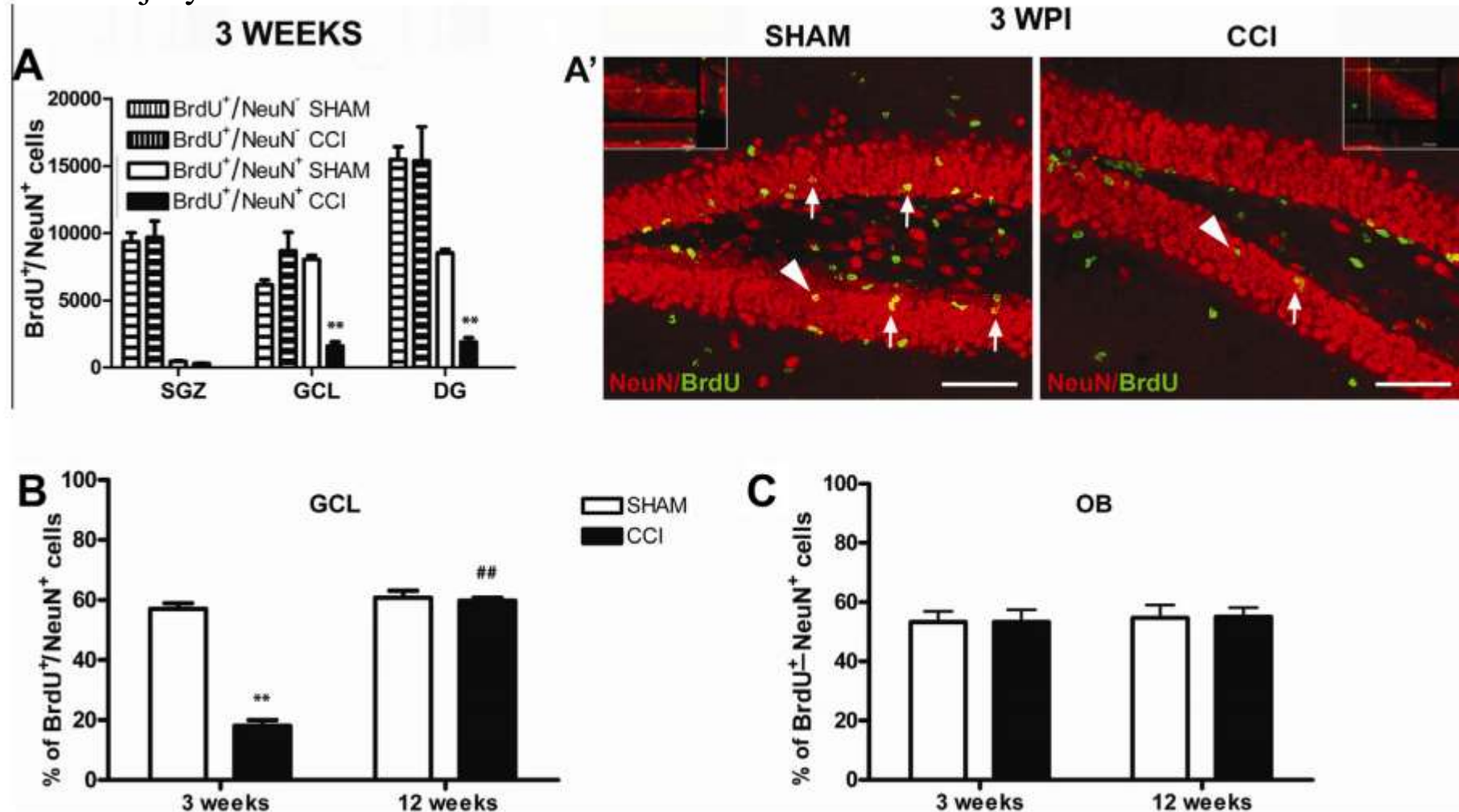
Park, D C et al. Arthritis and rheumatism vol. 44,9 (2001): 2125-33.

Phelps, Caroline E et al. Trends in cognitive sciences vol. 25,5 (2021): 365-376.

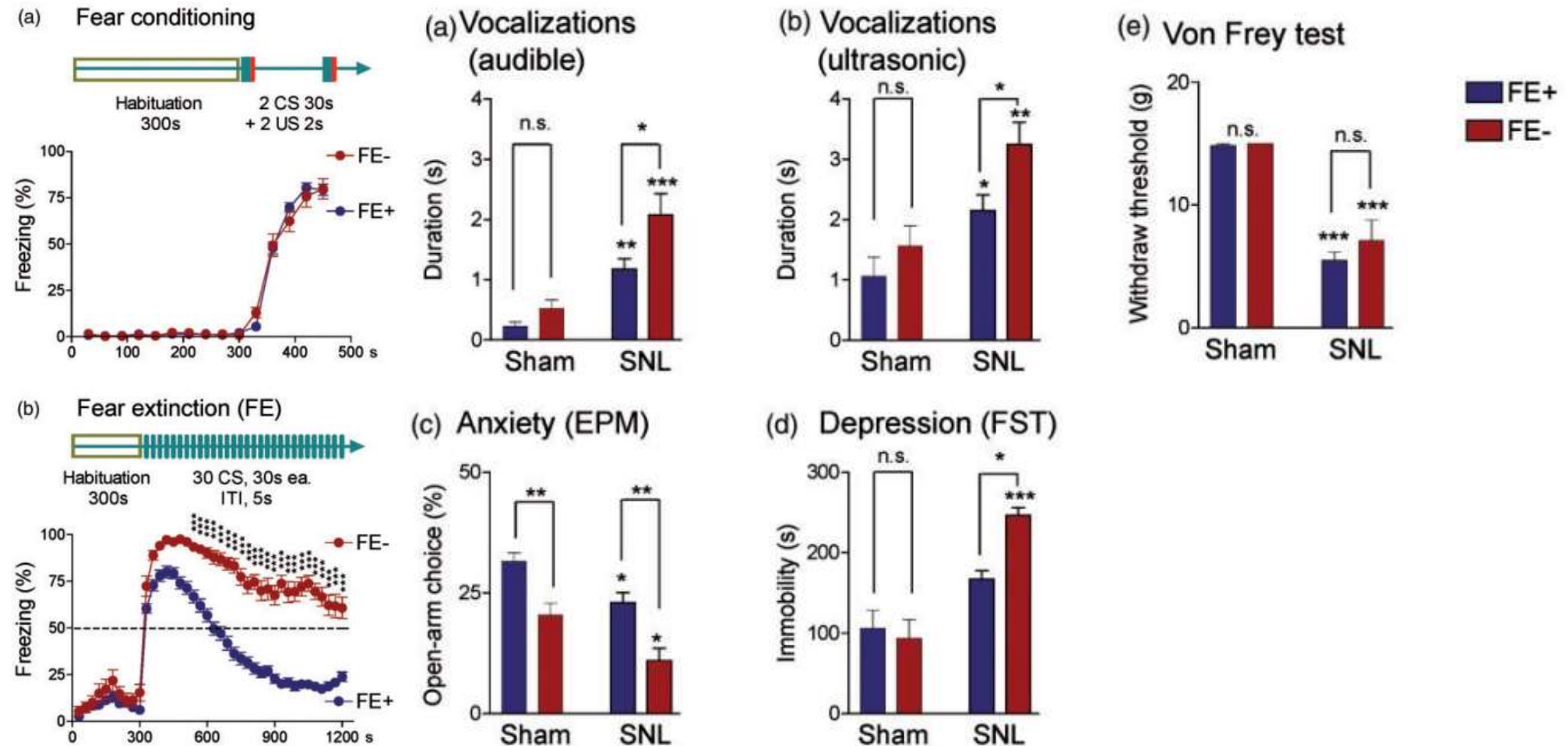


# CCI-induced neuropathic decreased neurogenesis, neuroplasticity and myelin remodeling in the hippocampus

CCI: Chronic constriction injury



# A positive correlation between extinction learning ability and neuropathic pain control



# Take home message

- Animal behavioral models are widely used in pain perception research
- The functional subdivision of the nociceptive somatosensory system into two branches.
  - The exteroceptive branch
  - The interoceptive
- Chronic pain is a persistence of the memory of pain and/or the inability to extinguish the memory of pain evoked by an initial inciting injury.



Thanks!