In vivo models to study the reward system and the body-brain circuit

Journal club

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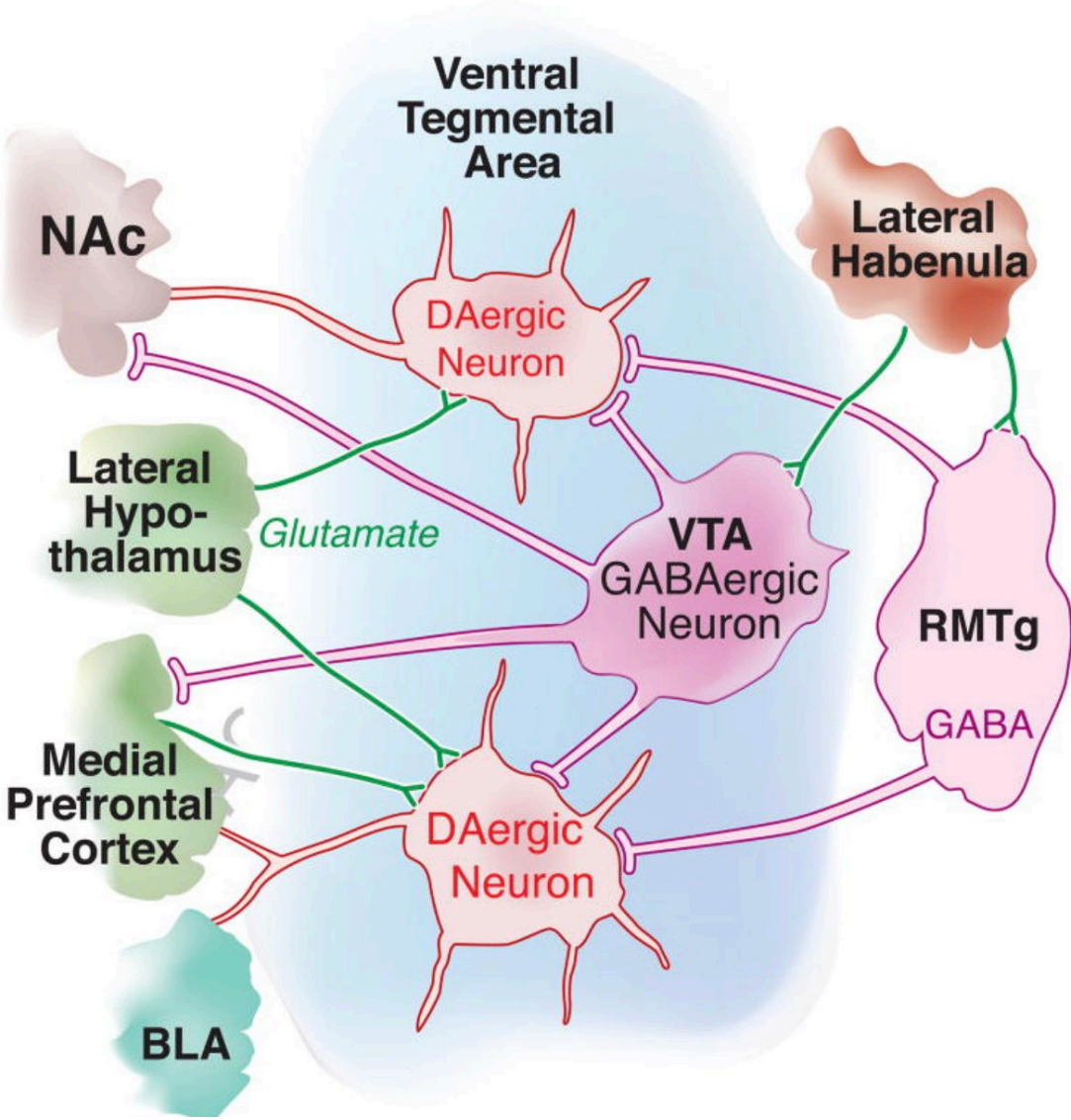
09.12.2025

The reward system

Rewards have several basic functions. A common view is that rewards induce subjective feelings of pleasure and contribute to positive emotions.

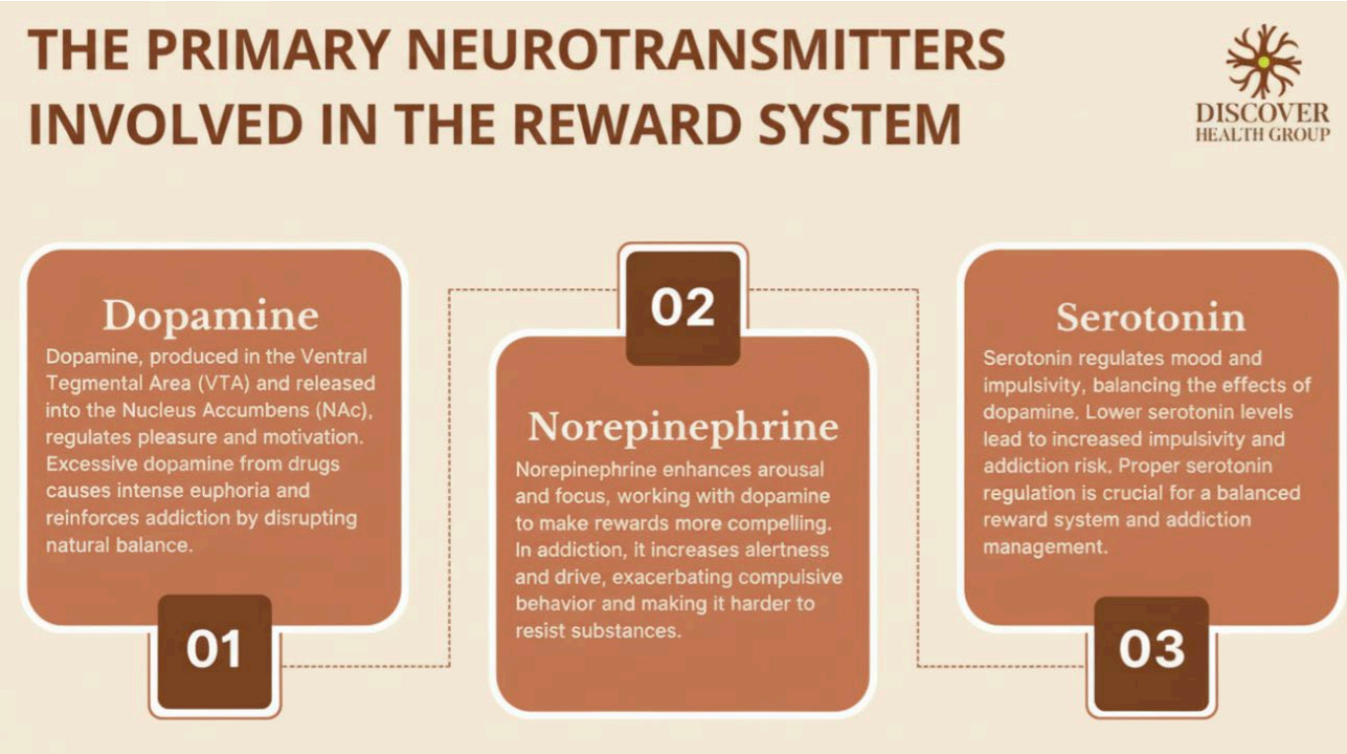
Unfortunately, this function can only be investigated with difficulty in experimental animals.

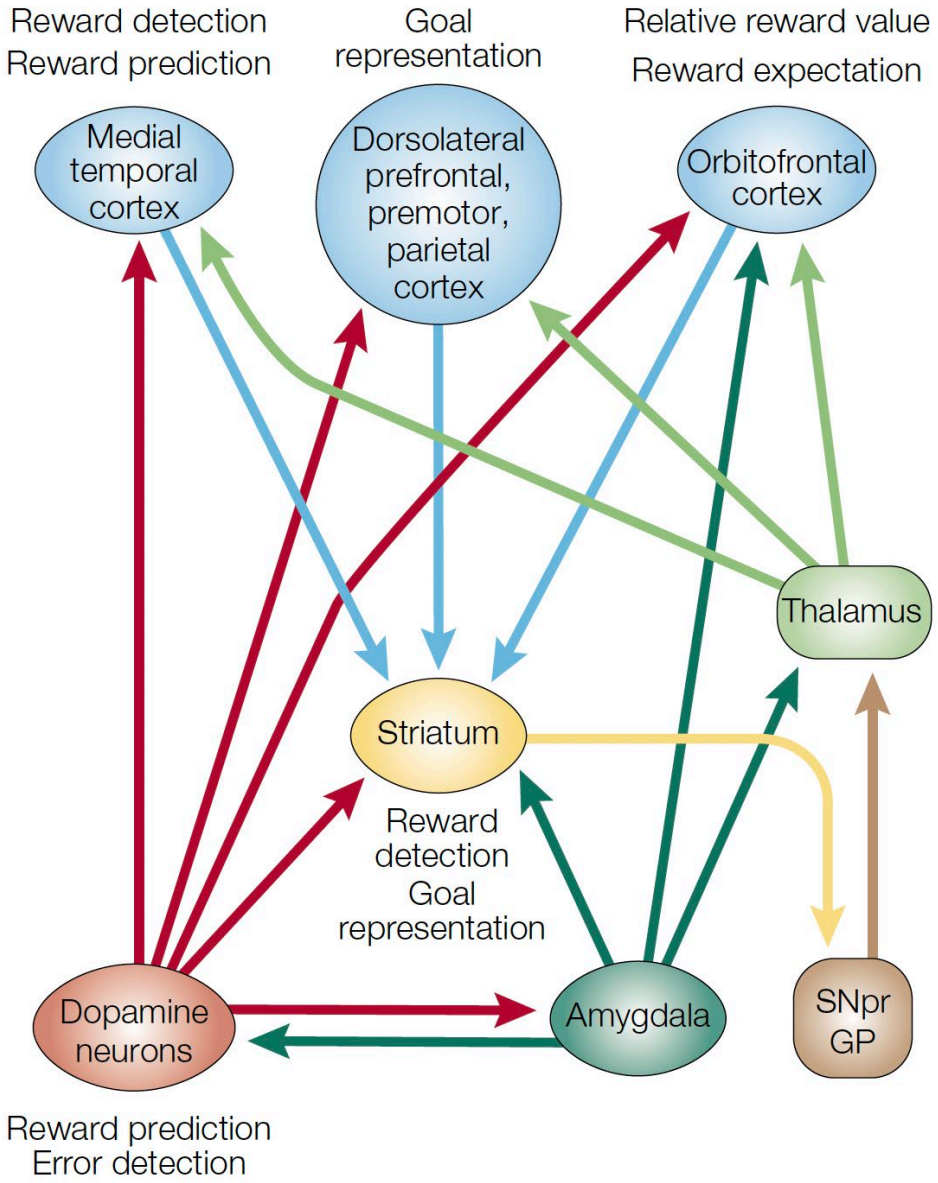
A prominent example are the dopamine neurons in the pars compacta of substantia nigra and the medially adjoining ventral tegmental area



•10.1016/j.biopsych.2011.11.010

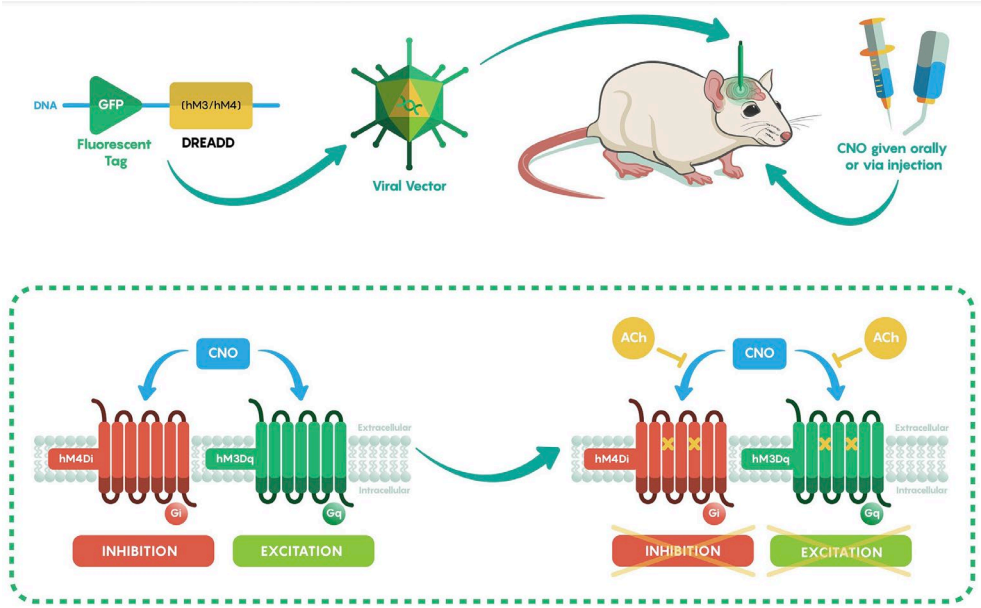
The regulation of the reward system





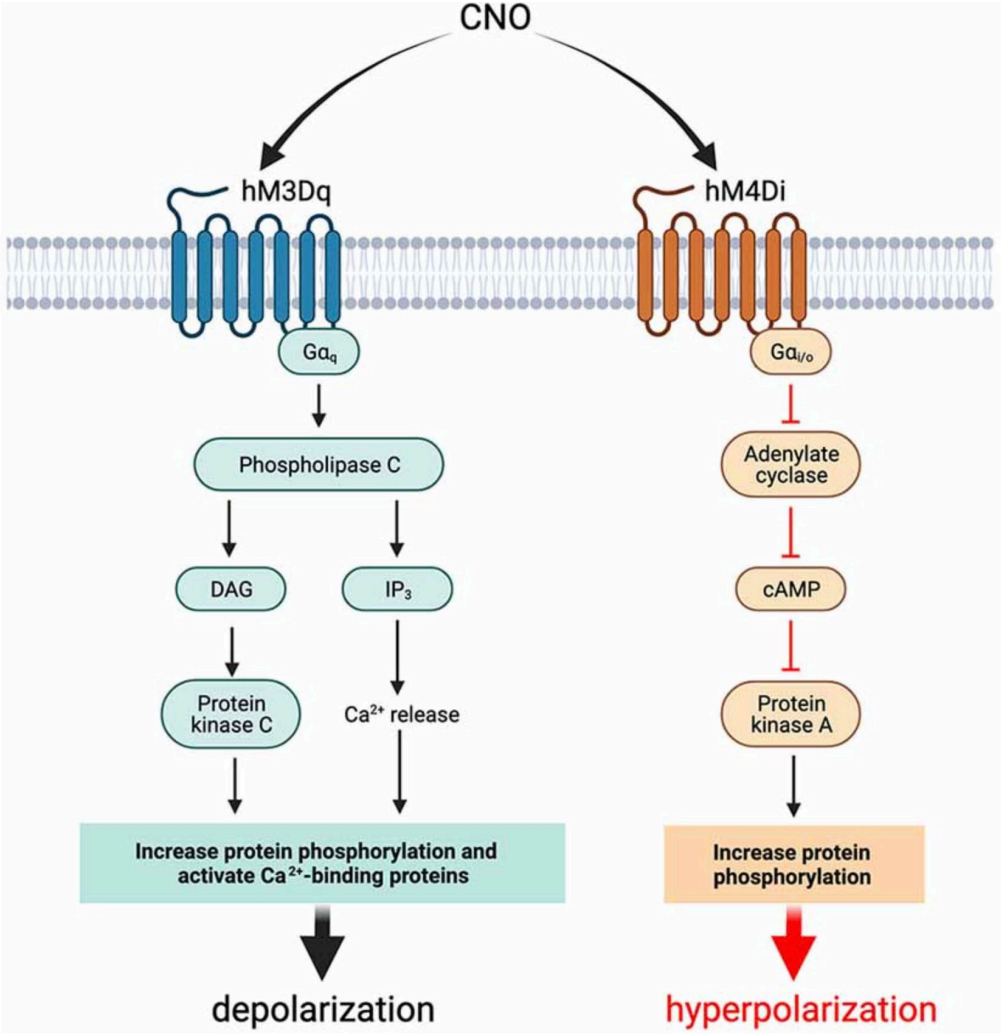
10.1016/j.biopsych.2011.11.010, Schultz et al 2000

The reward system on immunity: DREDD system



Designer Receptor Exclusively Activated by Designer Drugs (DREADDs) to specifically control reward system activity.

Muscarinic receptors responds only to a synthetic ligand: **CNO: clozapine-ligand**



Ben-Shaanan et al, 2016

The reward system shows anti-tumor response *in vivo*

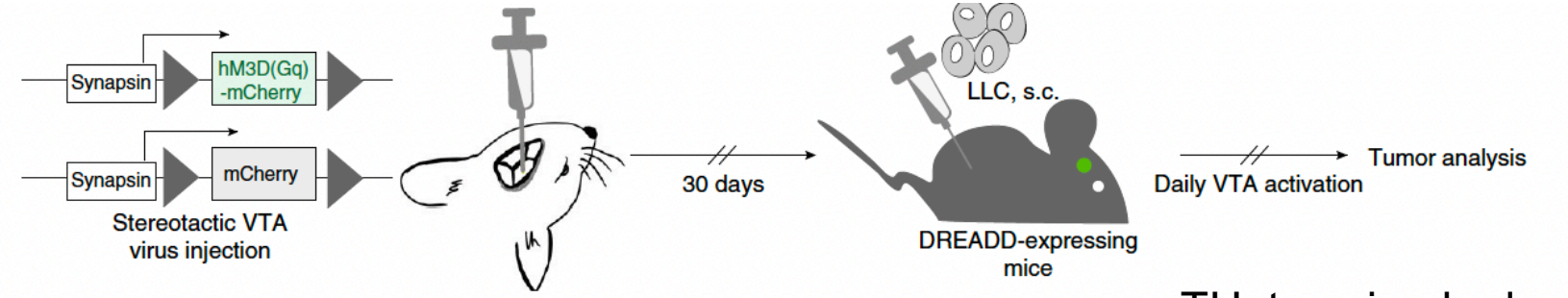
ARTICLE

DOI: 10.1038/s41467-018-05283-5 OPEN

Modulation of anti-tumor immunity by the brain's reward system

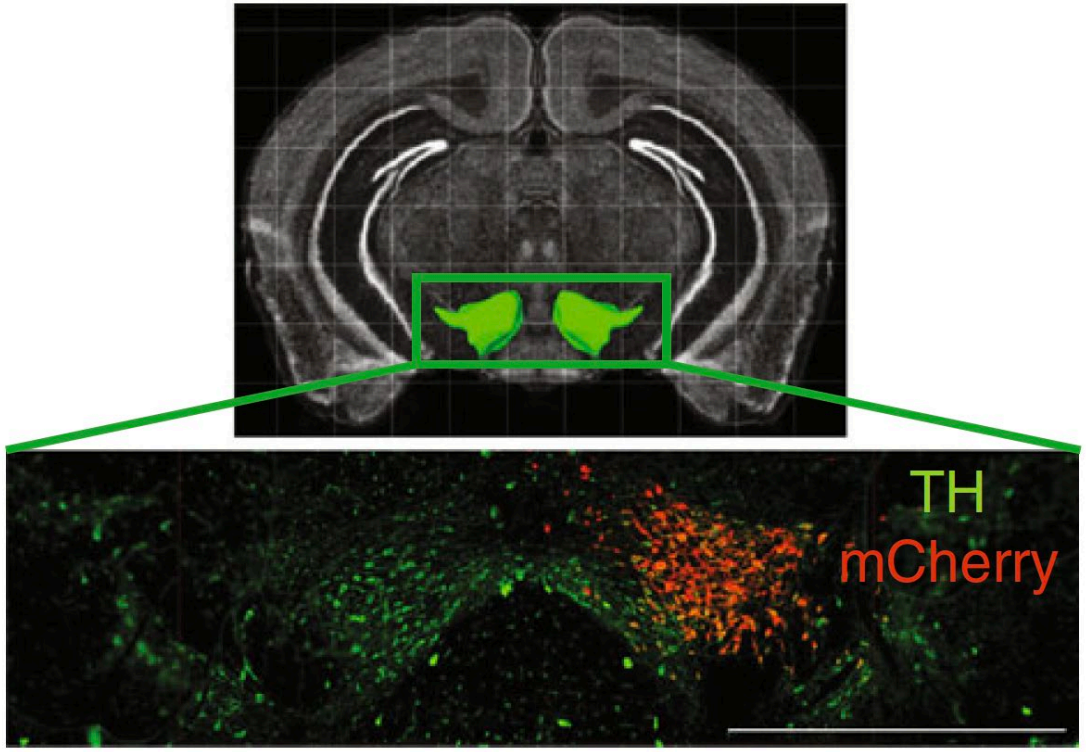
Tamar L Ben-Shaanan[1,2,3], Maya Schiller[1,2,3], Hilla Azulay-Debby[1,2,3], Ben Korin[1,2,3], Nadia Boshnak[1,2,3], Tamar Koren[1,2,3], Maria Krot[1,2,3], Jivan Shakya[1,4], Michal A. Rahat[1,4], Fahed Hakim[1,5,6] & Asya Rolls[1,2,3]

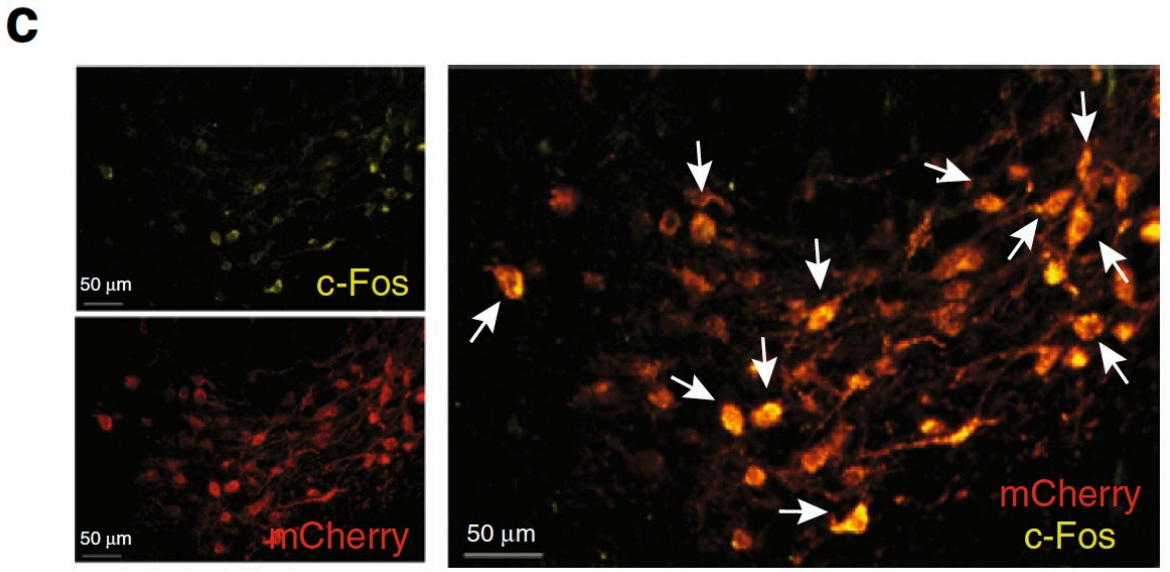
Functional expression of DREADD in the VTA



TH: tyrosine hydroxylase, marker for DAneurons
C-Fos: early activation marker

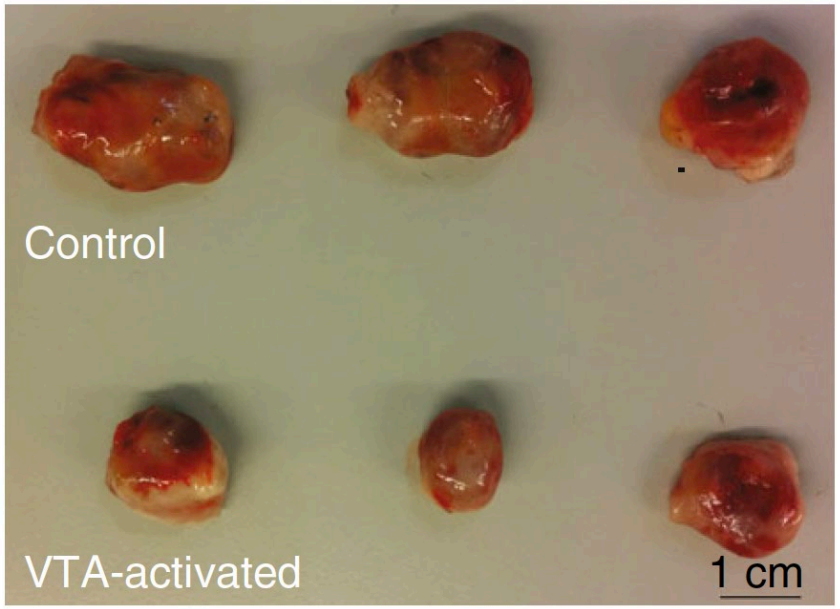
60.9% of the DREADD-expressing VTA neurons were c-Fos+

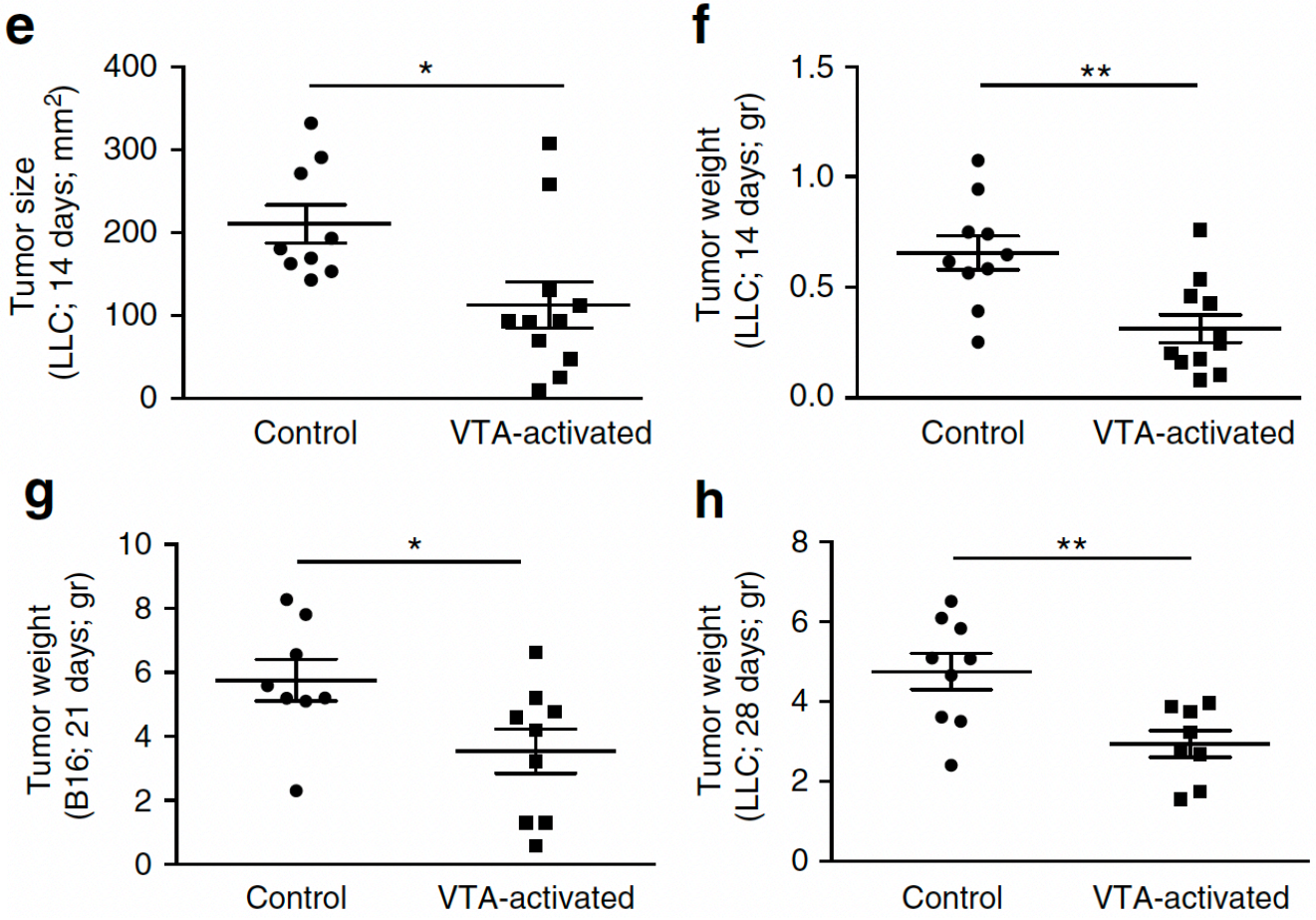




VTA activation attenuates tumor growth

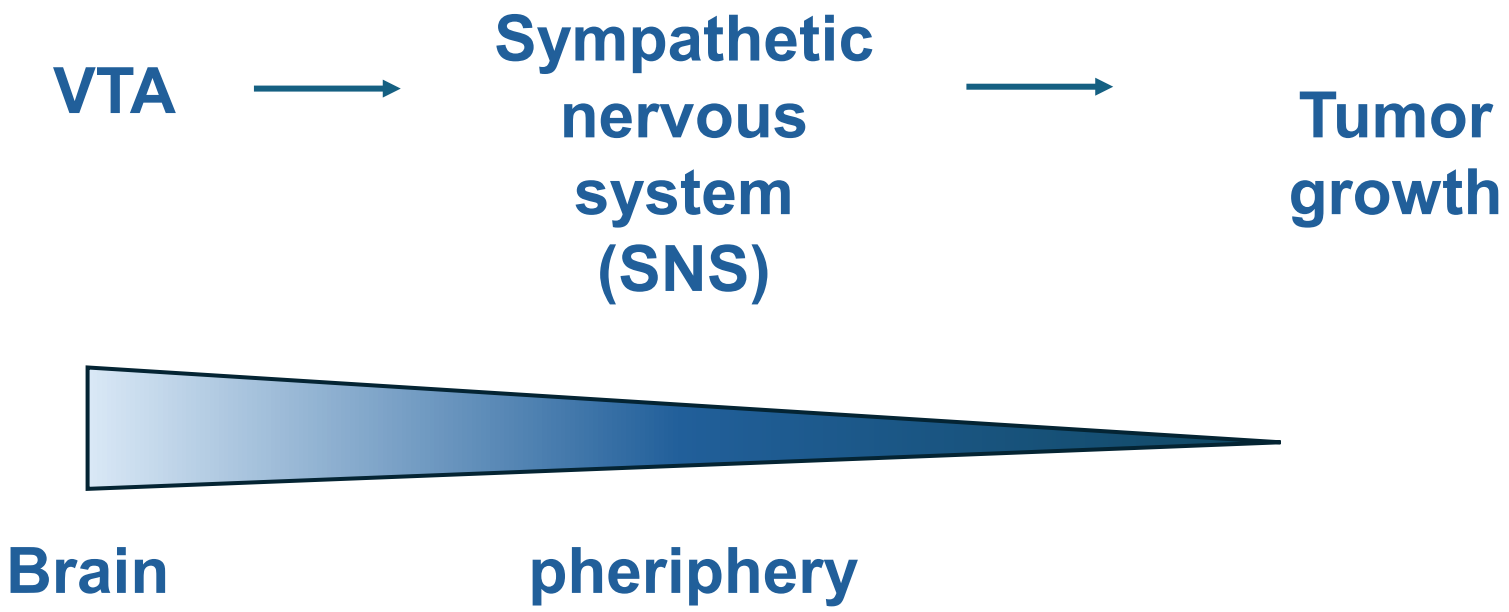
To measure the effect of VTA activation on tumor growth the authors used LLC (Lewis lung carcinoma) and B16 melanoma





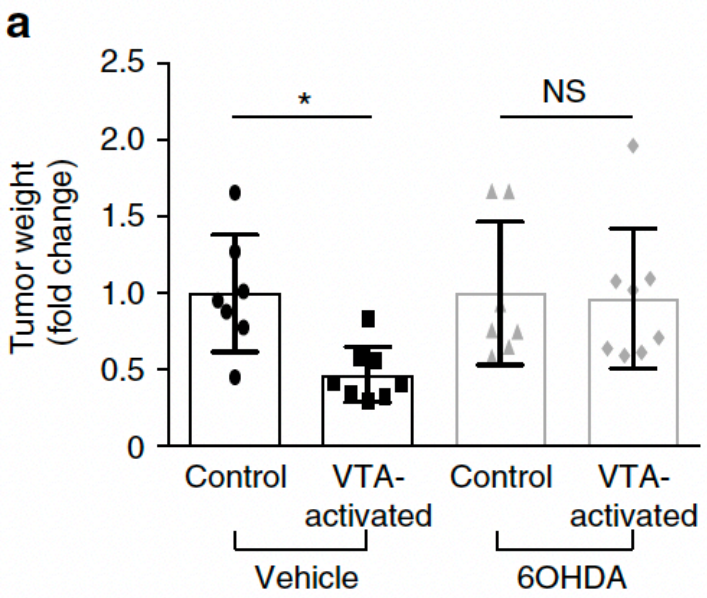
➢ This effect is unlikely to be direct since dopamine do not cross the BBB

The mechanism of VTA on tumor growth

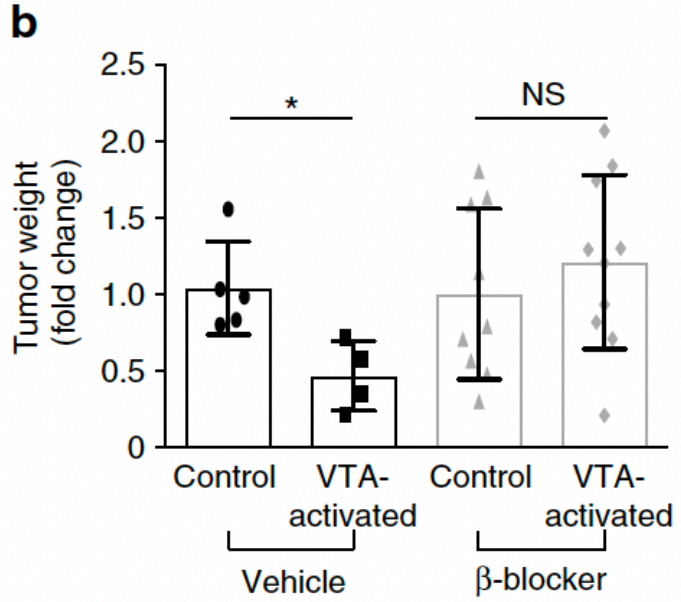


SNS mediates the effect of VTA on tumor

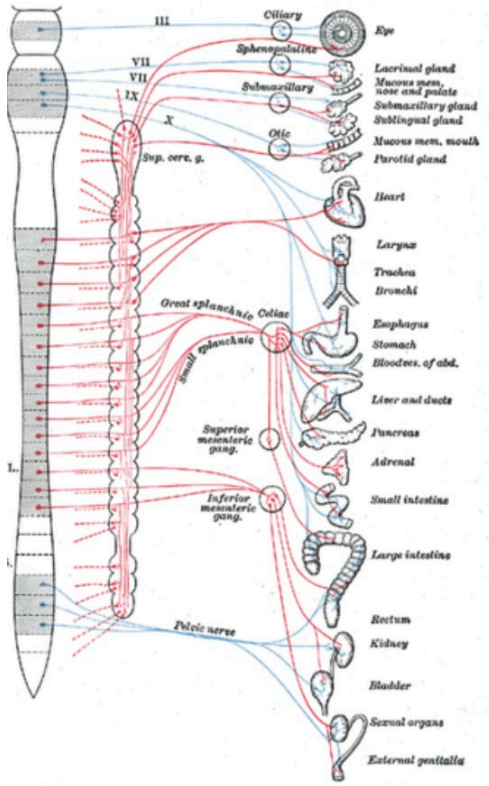
6OHDA blocks peripheral SNS

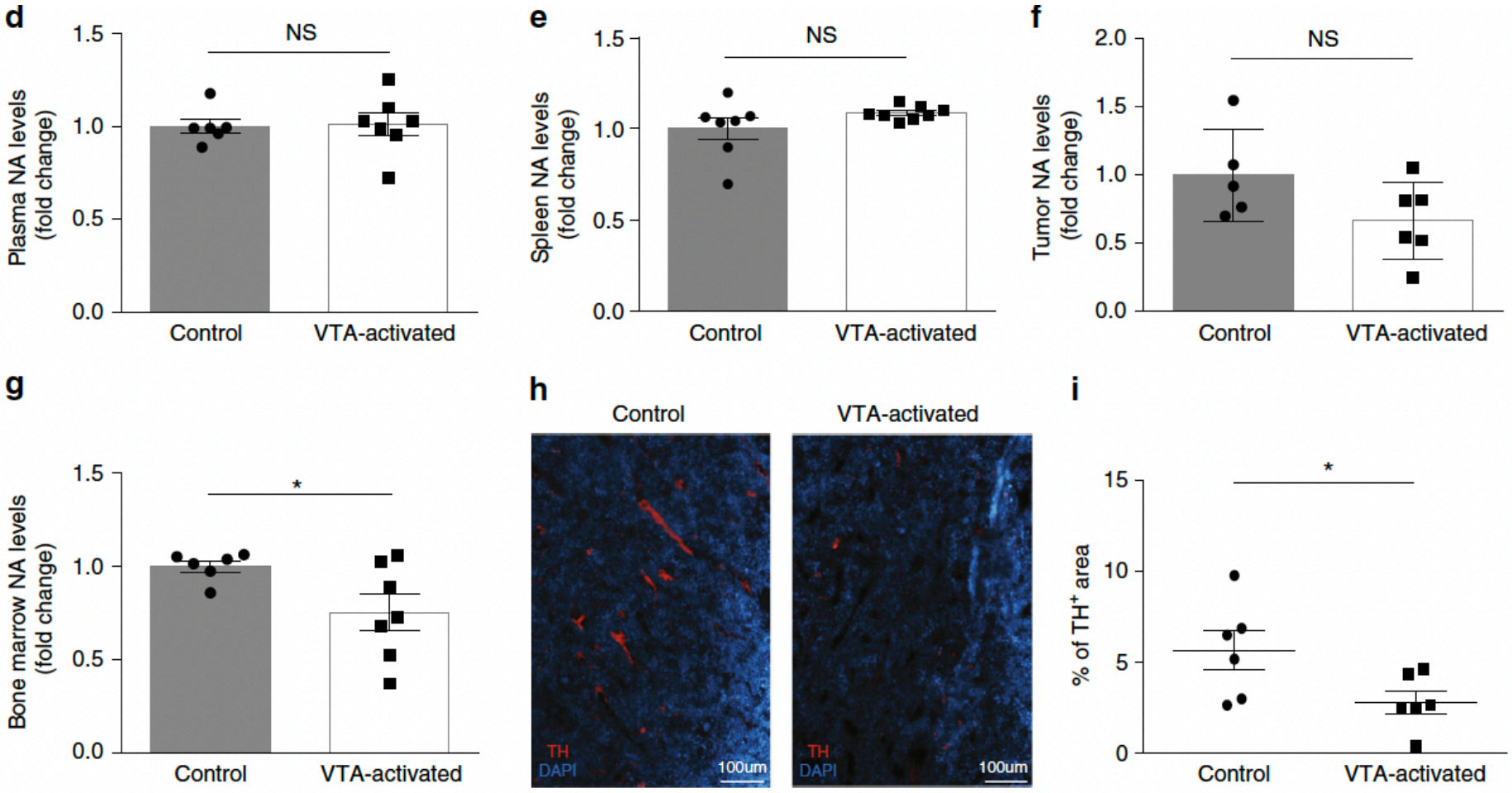


NADOLOL block beta-adrenergic receptor



SNS mediates a reduction in the NA levels in the bone marrow



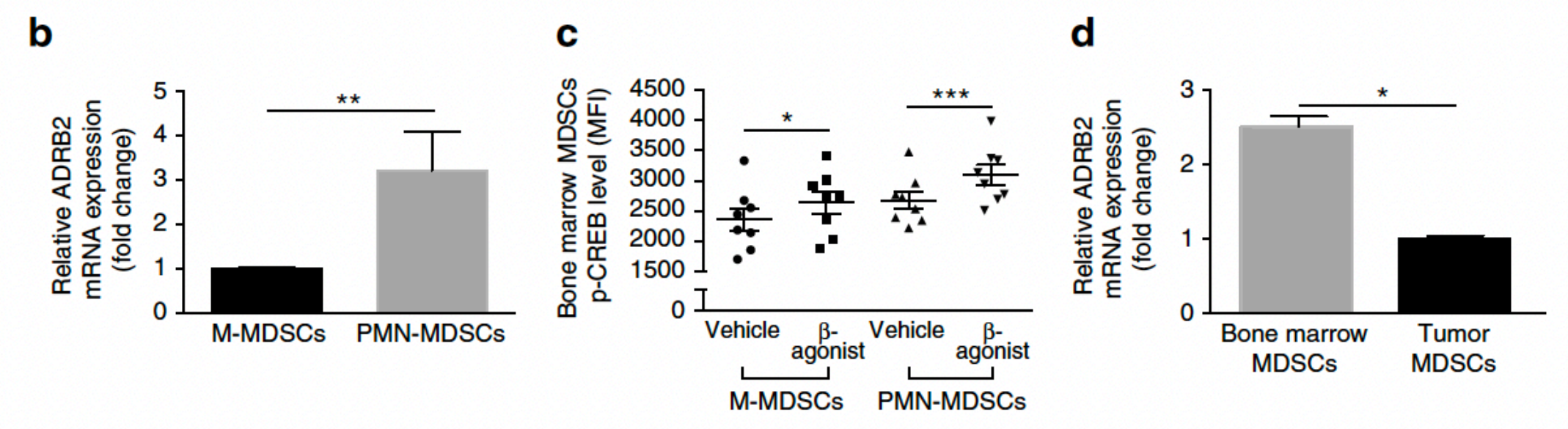


- TH: responsible NA synthesis and expressed by sympathetic fibers in the periphery

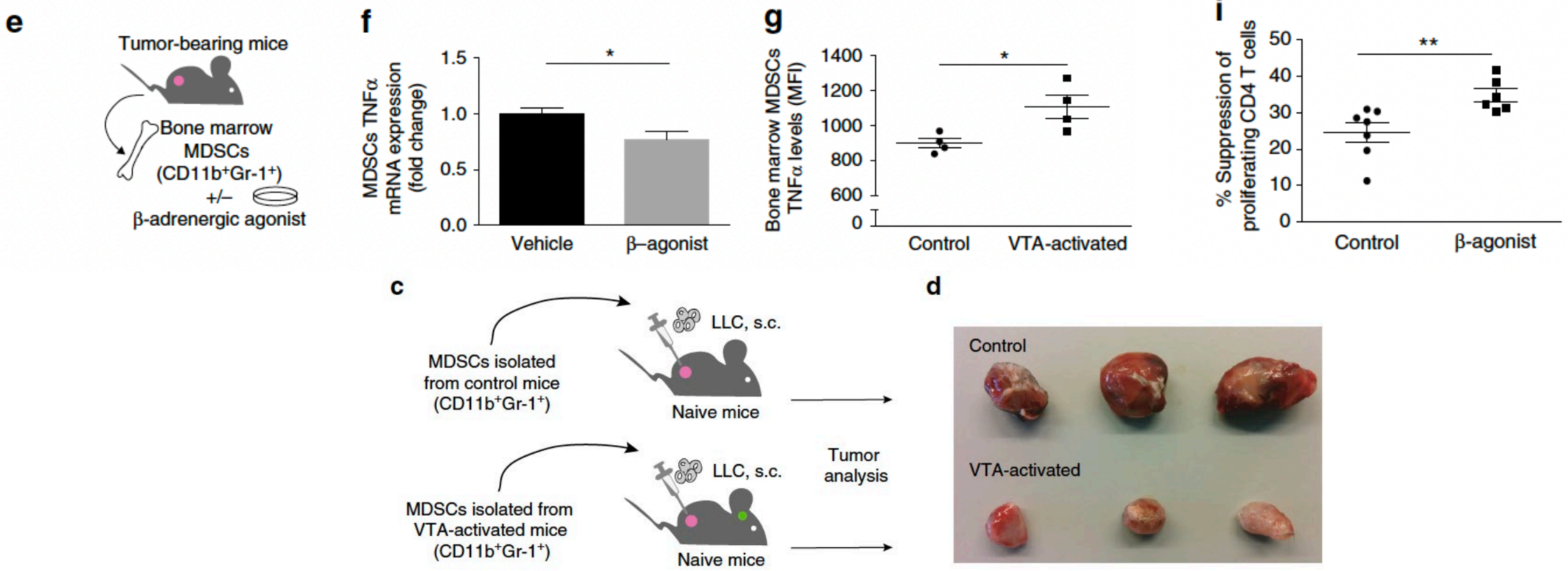
Which cells mediate the anti-tumor response?

Myeloid-derived suppressor cells (MDSCs) support tumor growth

Are the MDSCs affected by changes in NA levels?



NA inactivates MDSCs which prevent CD4 T cell proliferation



- MDSCs VTA-activated are sufficient to reduce tumor growth

Summary

- The authors identified a link between the reward system and tumor growth
- The effect it is indirect and it is activated through the SNS
- Specifically, the β-adrenergic receptors on MDSC increases the immunosuppressive effect by reducing CD4-T cell proliferation

The regulation we just described is apparently unidirectional, meaning from the brain to the periphery.

How can we study the consequences of a peripheral effect on the CNS?

The body-brain axis reguates inflammatory responses *in vivo*

Article

A body–brain circuit that regulates body inflammatory responses

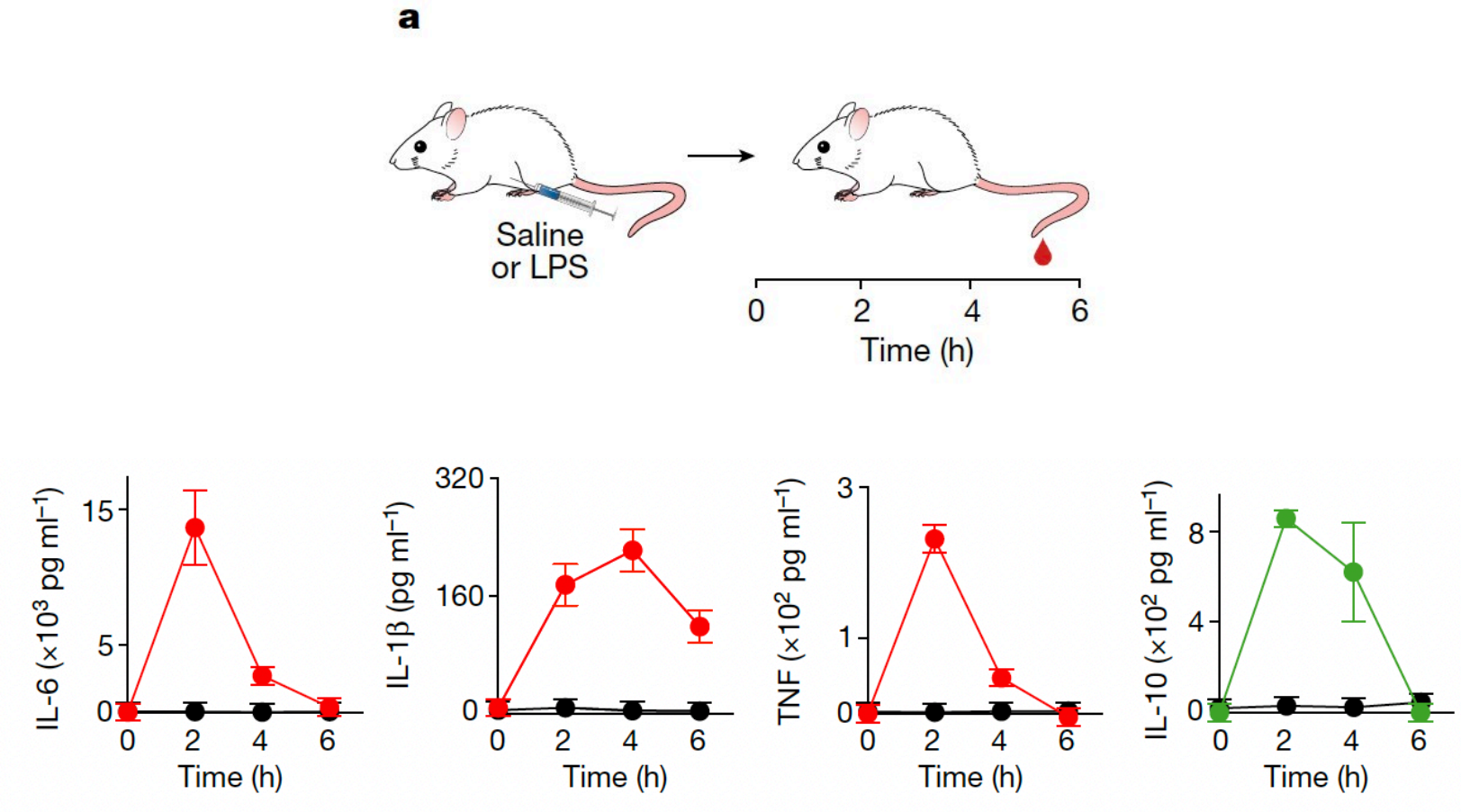
https://doi.org/10.1038/s41586-024-07469-y

Received: 14 June 2023

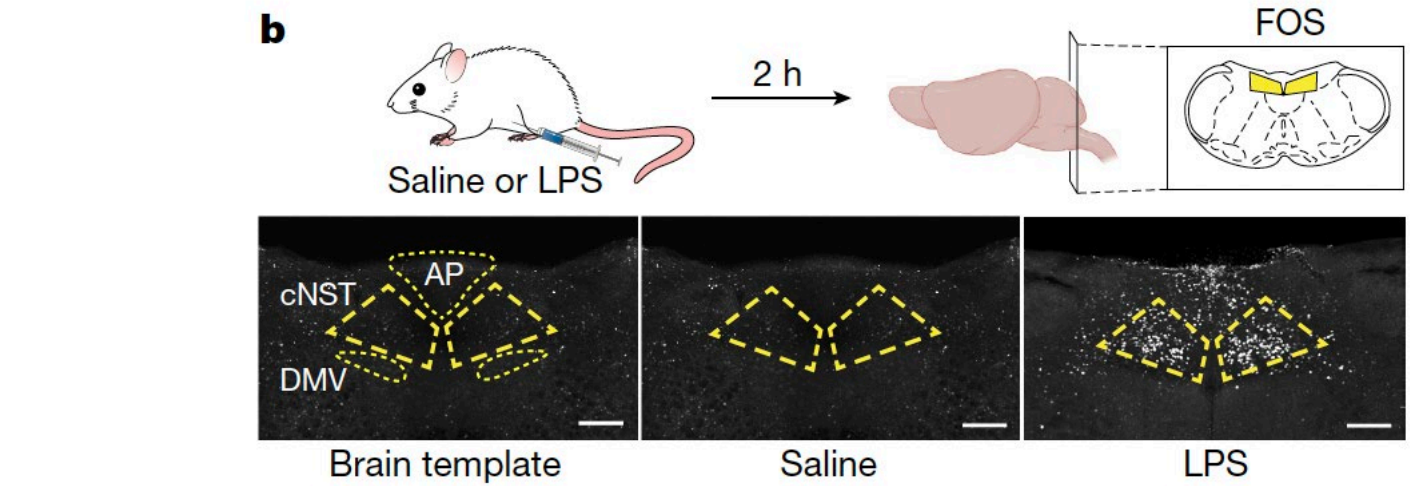
Hao Jin[1,2,3,5,6]✉, Mengtong Li[1,2,3,6], Eric Jeong[1,2,3], Felipe Castro-Martinez[4] & Charles S. Zuker[1,2,3]✉

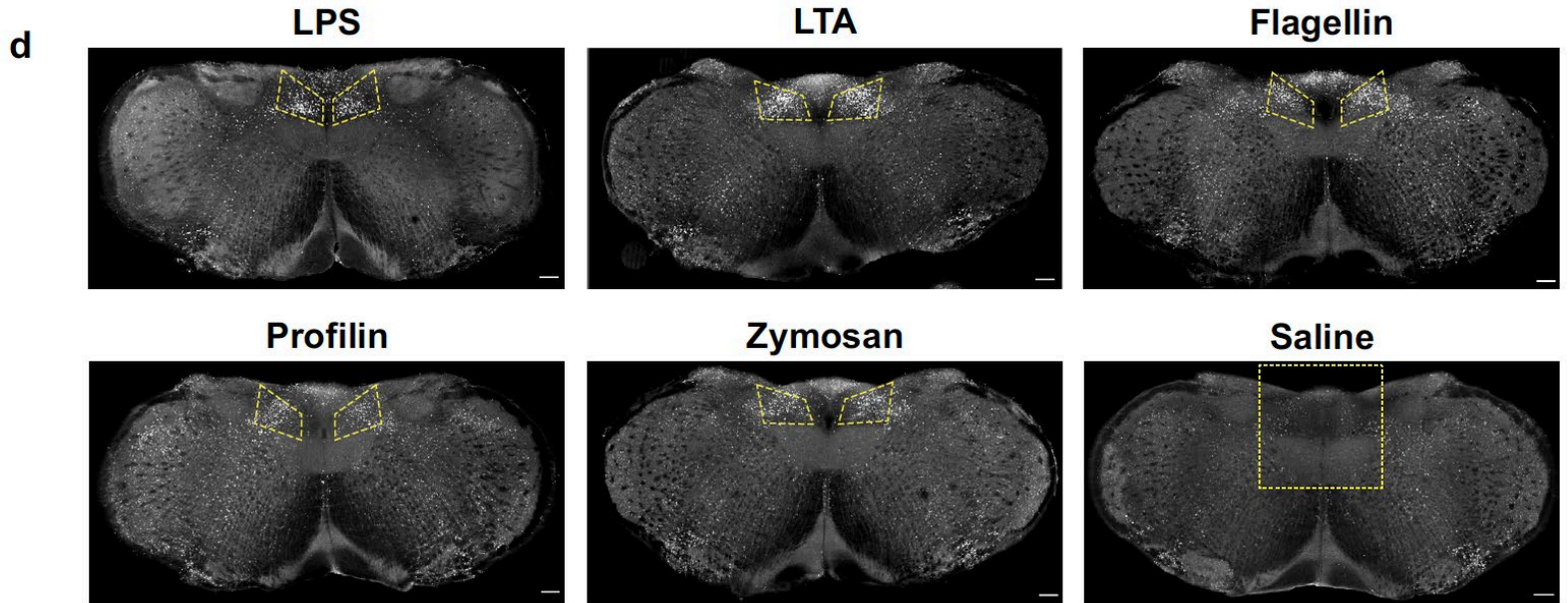
- Can a peripheral immune insult activates the body-brain axis to regulate immune responses?

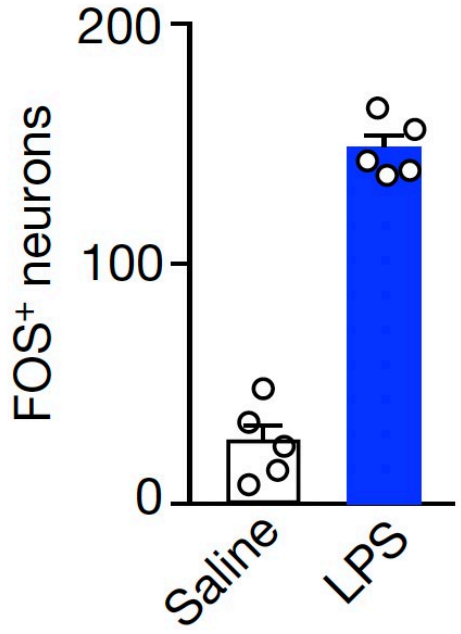
In vivo model to induce inflammation



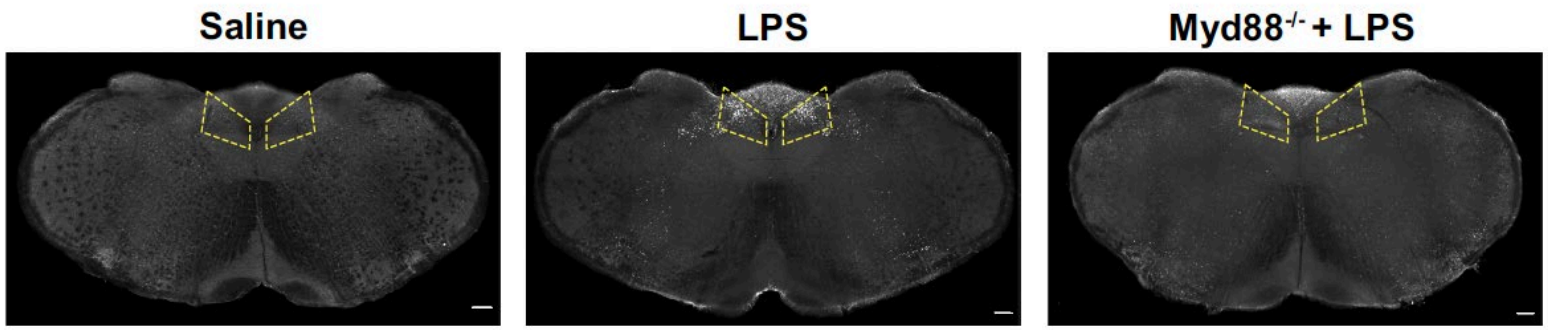
LPS activates neurons (cFos+) in the caudal nucleus of the solitary tract

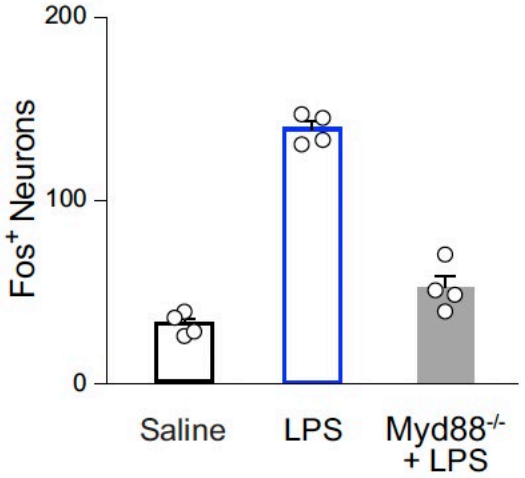






LPS **does not** activate neurons (cFos+) in the caudal nucleus of the solitary tract in Myd88$^{-/-}$ mice





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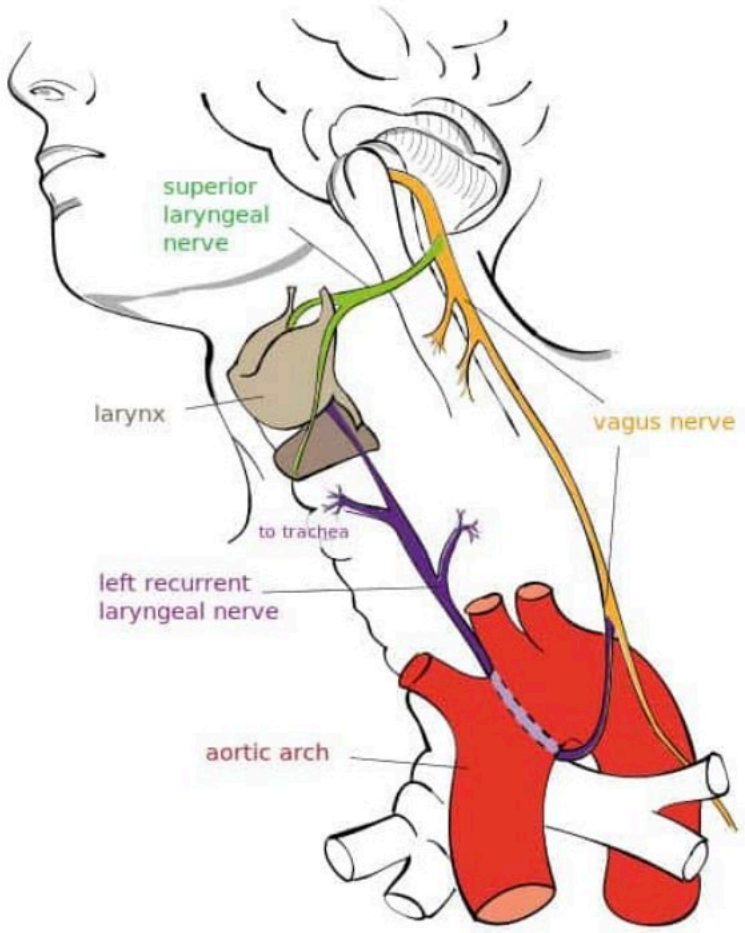
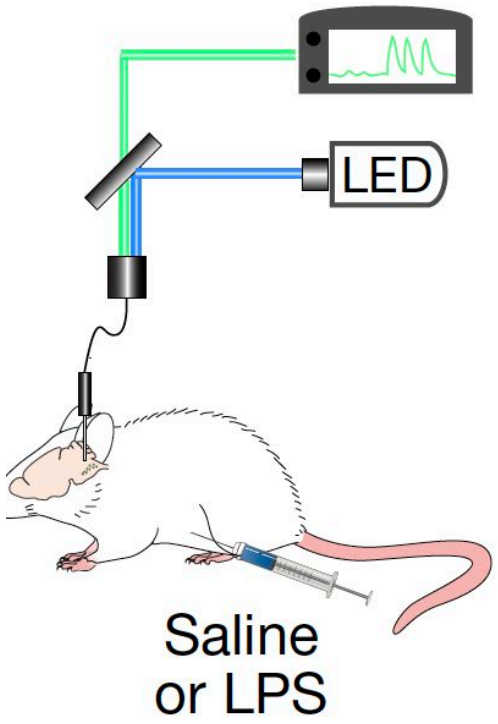
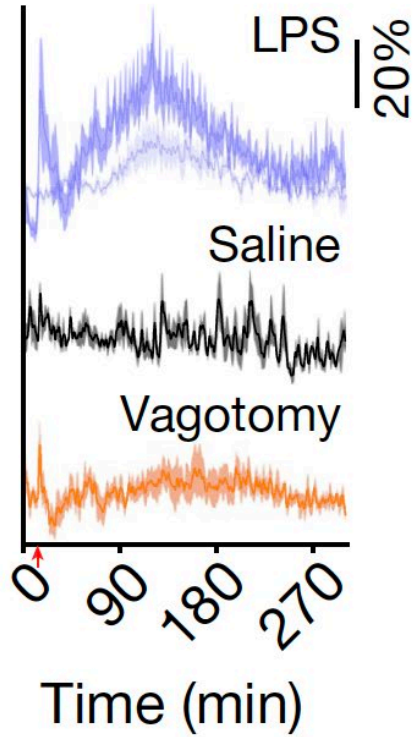
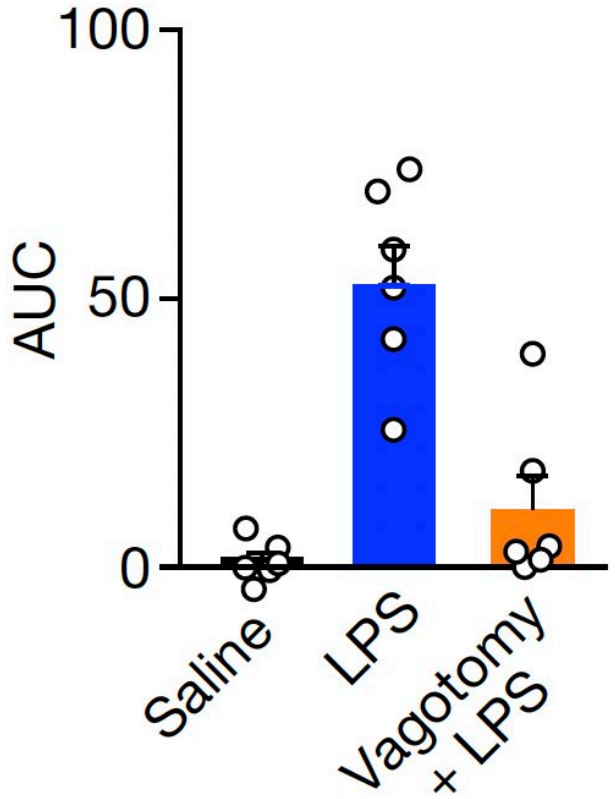
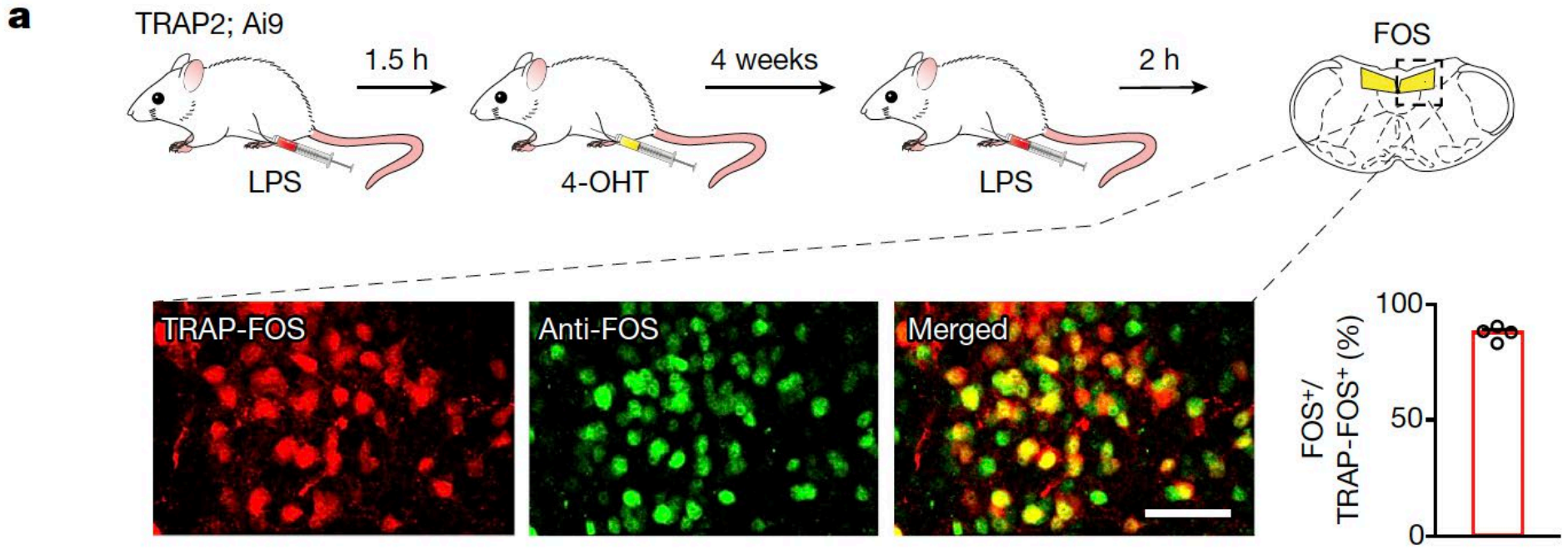




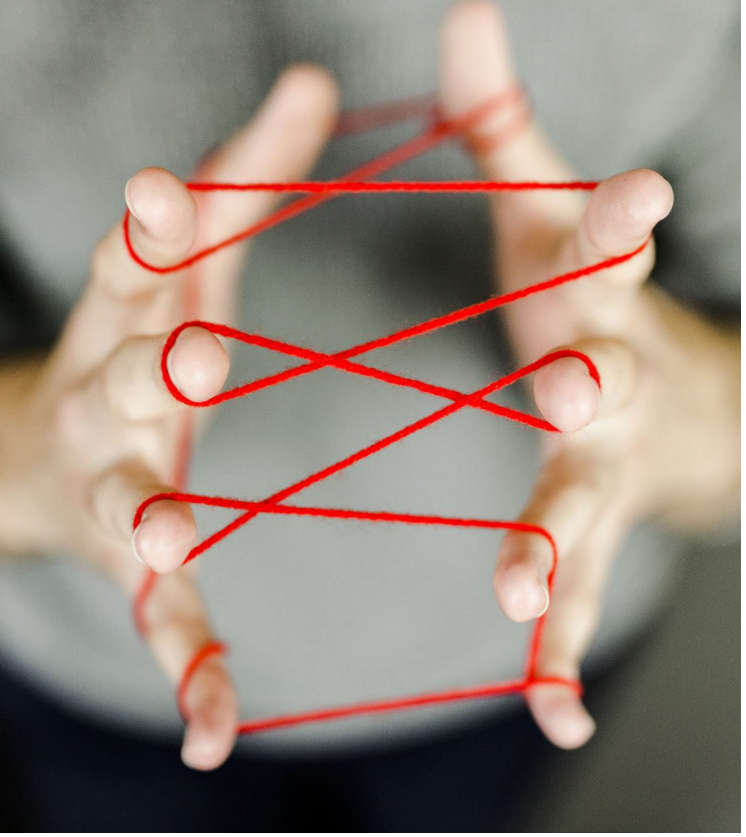




The recombination in active populations (TRAP) system



- Used for anatomical visualization of the neurons that got activated with the exogenus stimuli

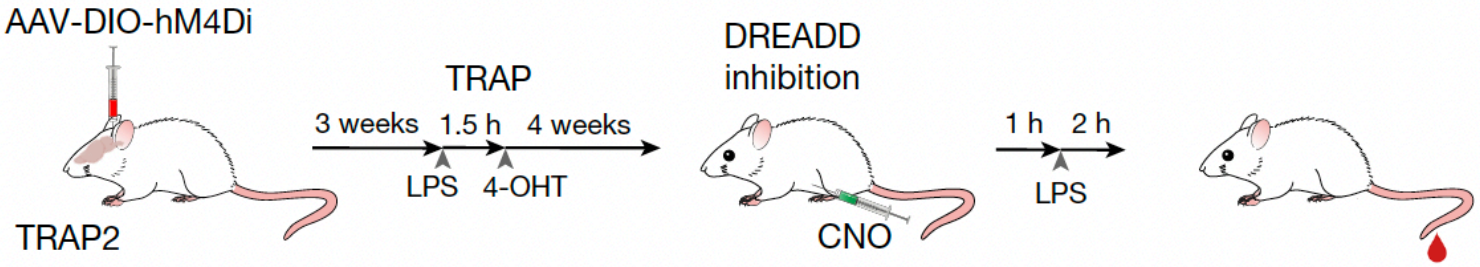


The combination of the (TRAP) system with DREADDs to explore the cNST function:

DREADDs (Designer Receptors Exclusively Activated by Designer Drugs) are **engineered so that the G-protein–coupled receptors (GPCRs)**:

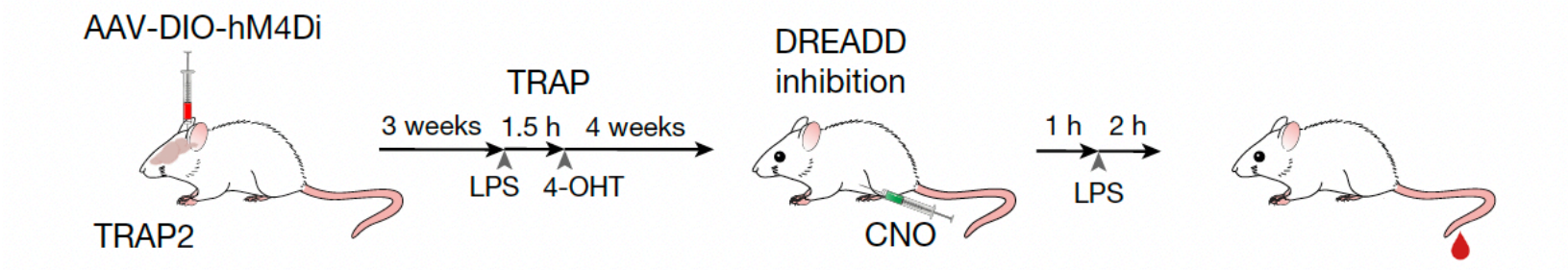
- **do not respond** to any endogenous neurotransmitter,
- **only respond** to a synthetic ligand (a “designer drug”).

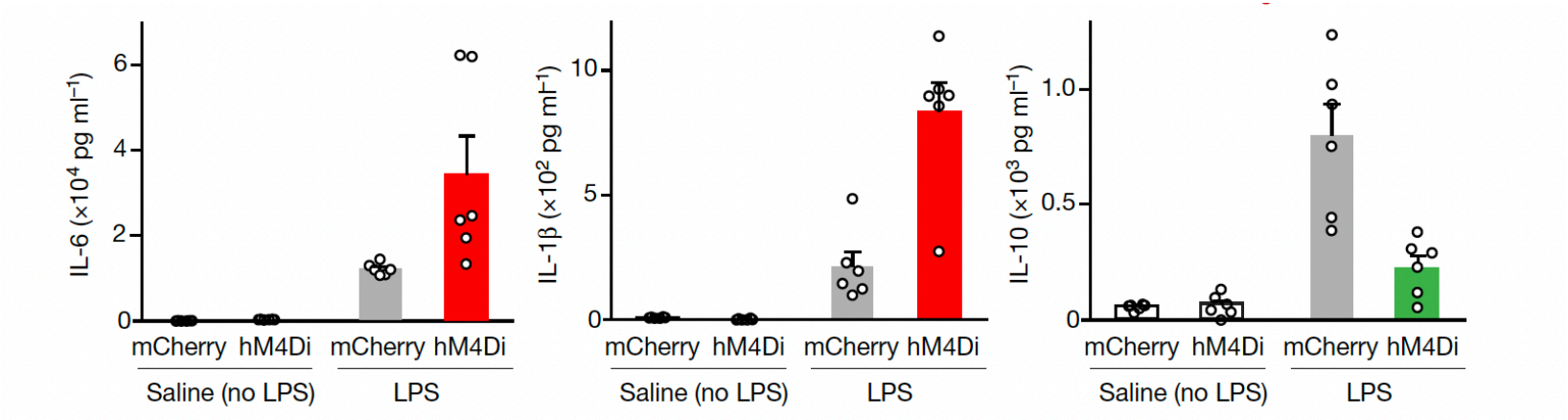
The authors used iDREADD system, a Cre-dependent inhibitory system



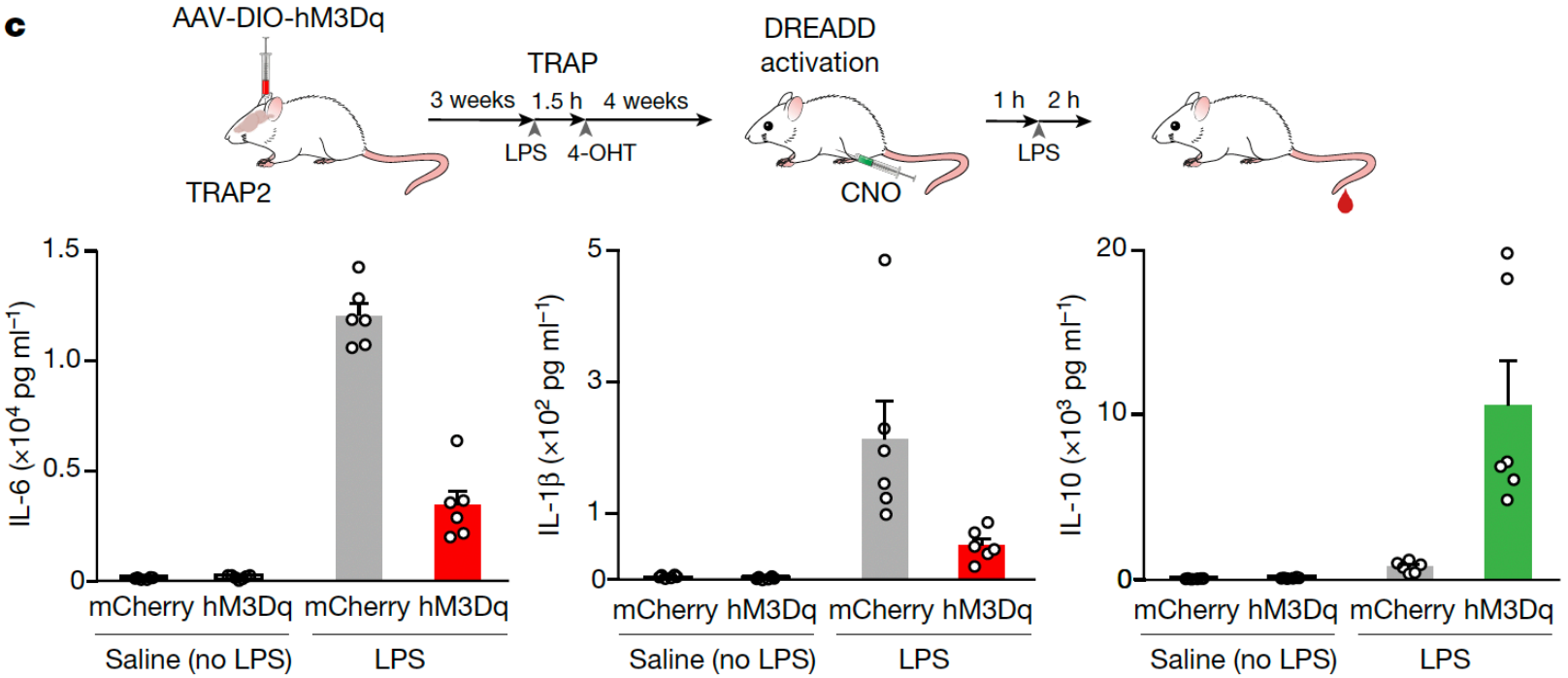
Cytokine levels detection

TRAP + iDREADD



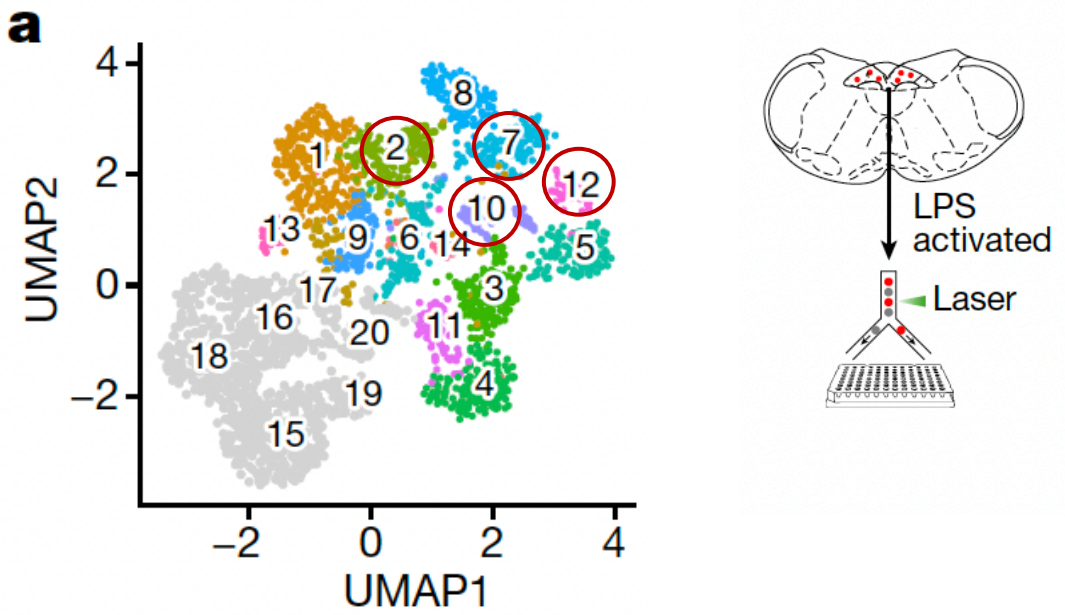


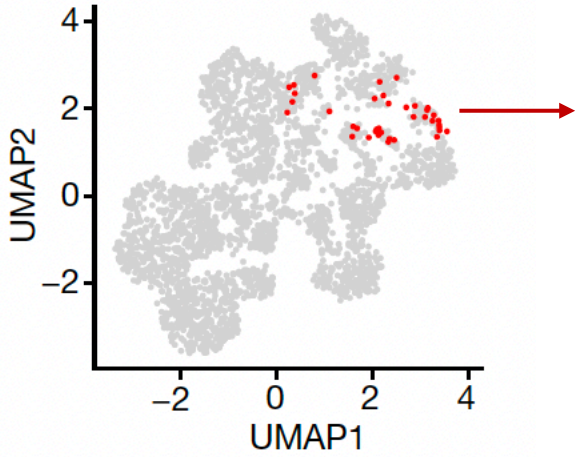
TRAP + DREADD activation



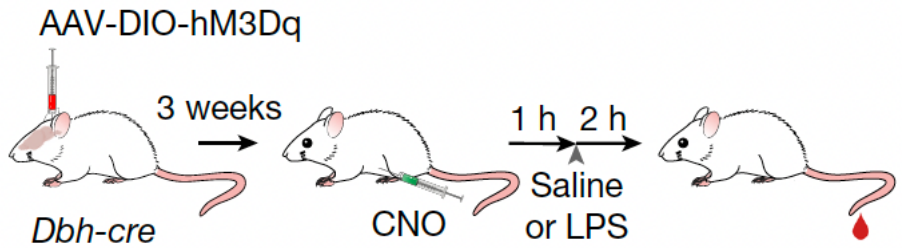
- These results suggest that the cNST function as a homeostatic neural control of the peripheral immune response

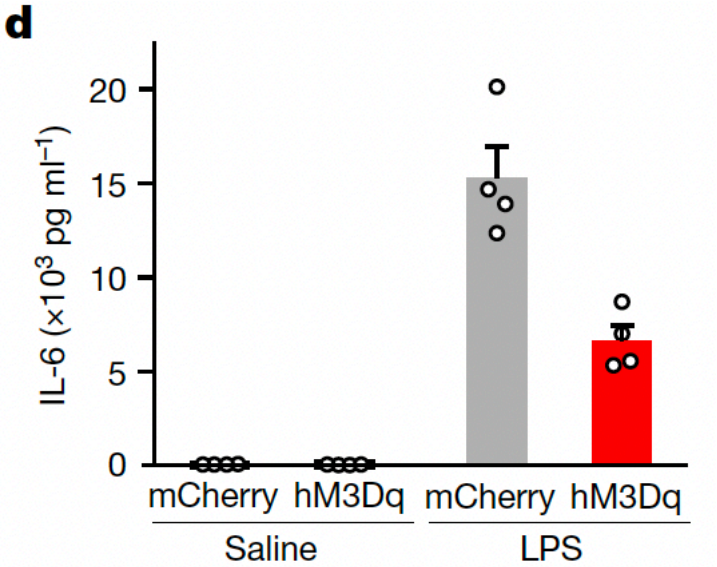
scRNA-sequencing reveals that glutamatergic neurons Dbh+ responds to LPS



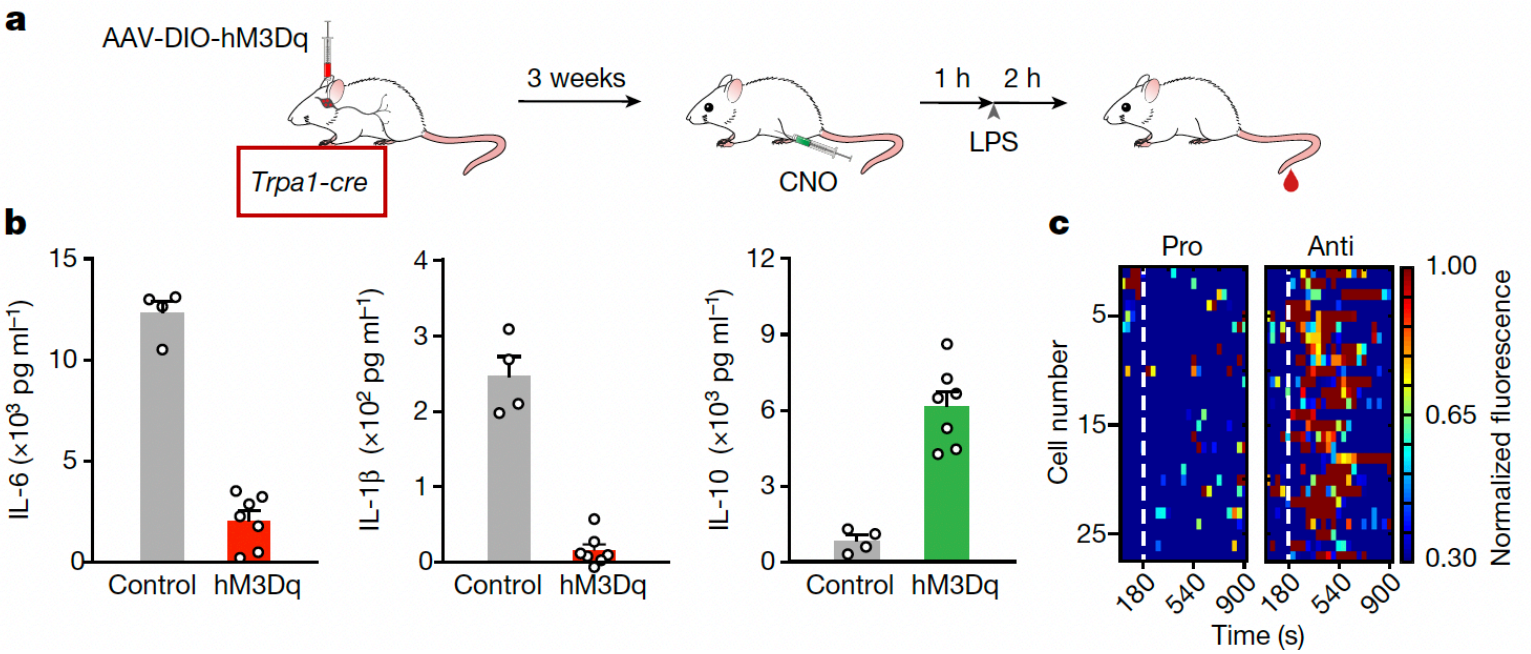


Glutamatergic neurons express dopamine β hydroxylase

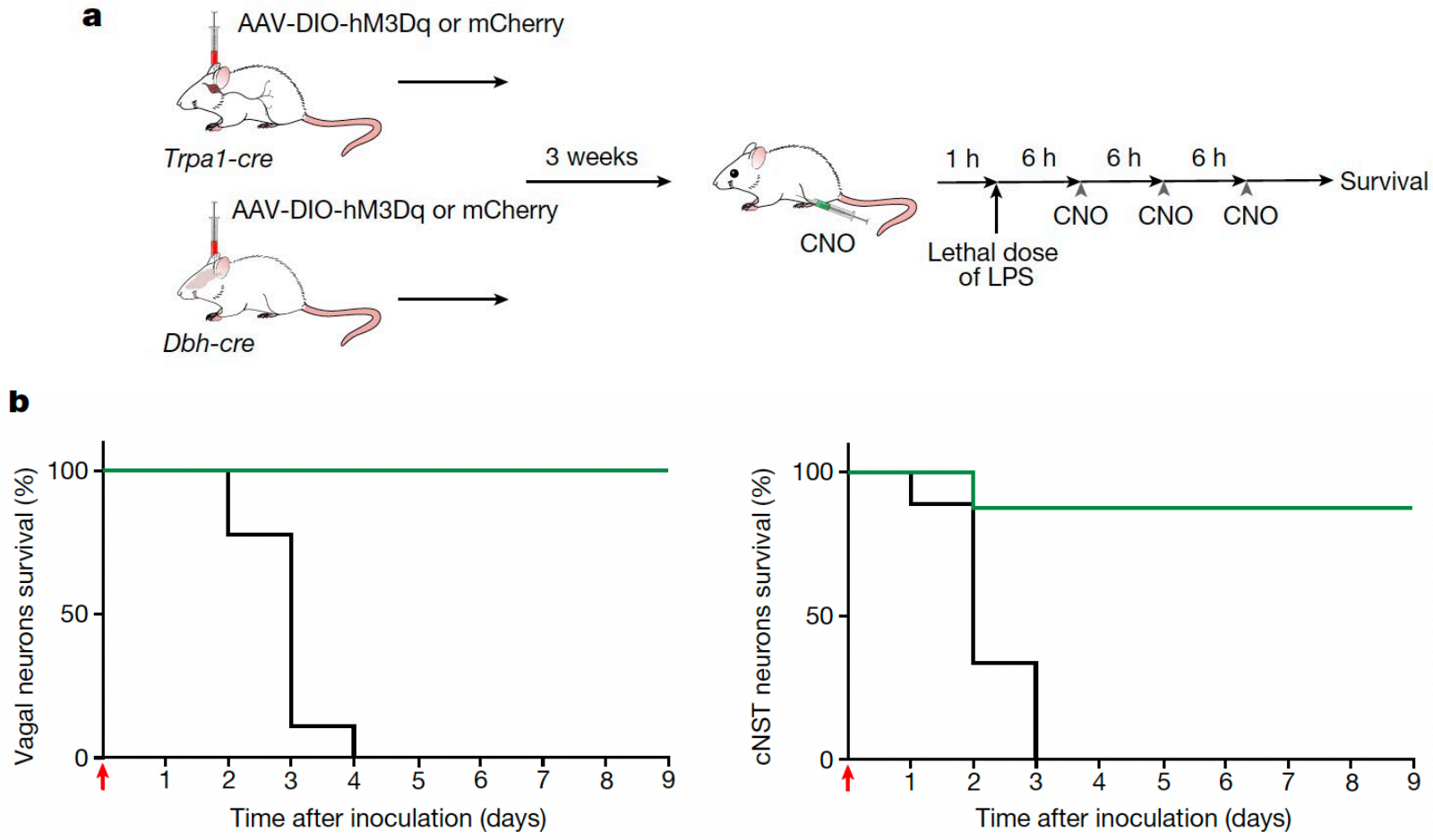




Vagal responses to immune cytokines



Restoring the immune balance through Trpa1 and Dbh protects mice from LPS-derived cytokine storm



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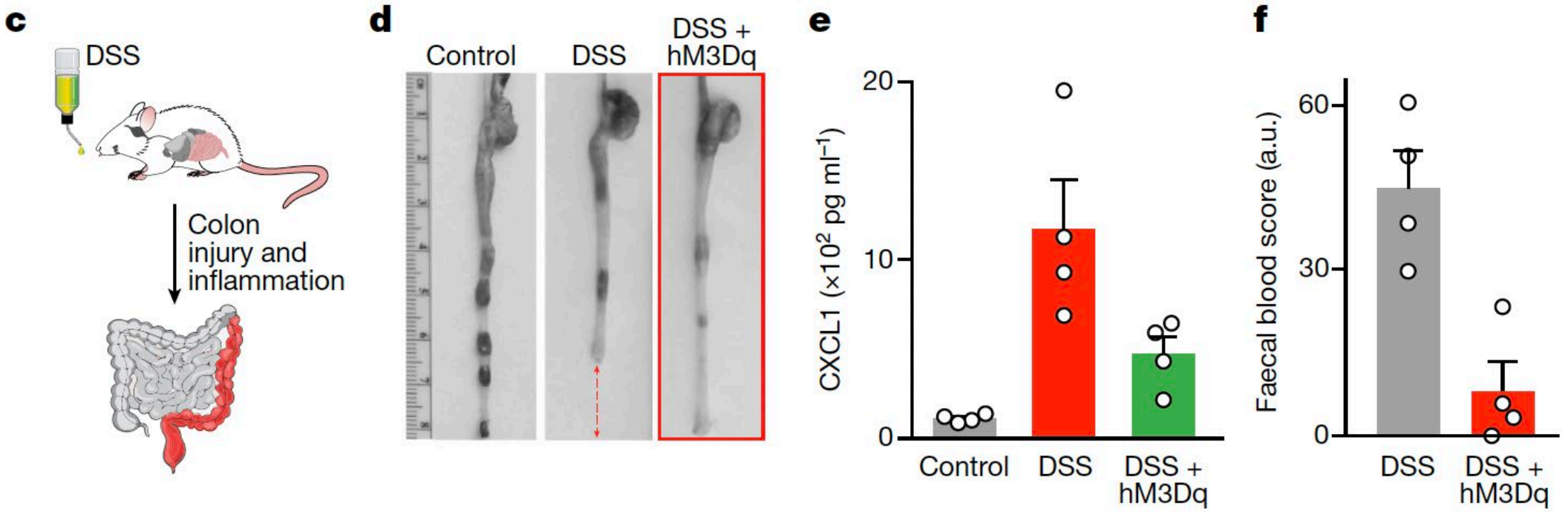

Summary

- Cytokines mediate the activation of the vagal–brain axis
- This body-brain circuit modulate the pro- and anti-inflammatory response
- This body–brain circuit monitors the development of an inflammatory response and ensures the homeostatic balance between the pro-inflammatory and anti-inflammatory states
- Removing this body–brain circuit during an innate immune challenge abolishes essential immune regulation

Thank you!