

A portrait of Ram Burstein, a middle-aged man with short, light-colored hair, smiling slightly. He is wearing a light-colored button-down shirt. The background is a solid blue color.

# The Neurobiology of Migraine – From Pathophysiology to Choice of Treatment

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Vice-Chairman – Neuroscience. Department of Anesthesia and Critical Care, Beth Israel Deaconess Medical Center

President-Elect, The International Headache Society

# Disclosures

① **Consultant / adviser**: Alder, Allergan, AbbVie, Allay, Amgen, Novartis, Avanir, Biohaven, Depomed, Dr. Reddy Laboratories, Electrocore, Eli Lilly, Ipsen, Johnson & Johnson, Neurolief,, Percept, Revance, Teva, Theranica, Trigemina

② **Stock holdings**: Allay, Percept,

③ **Patents / licenses**: US9061025, WO11732265.1, US10,766,952 B2, US10806890, US2021-0015908, WO21007165, US2021-0128724, WO21005497

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⑤ **Writing payment**: None

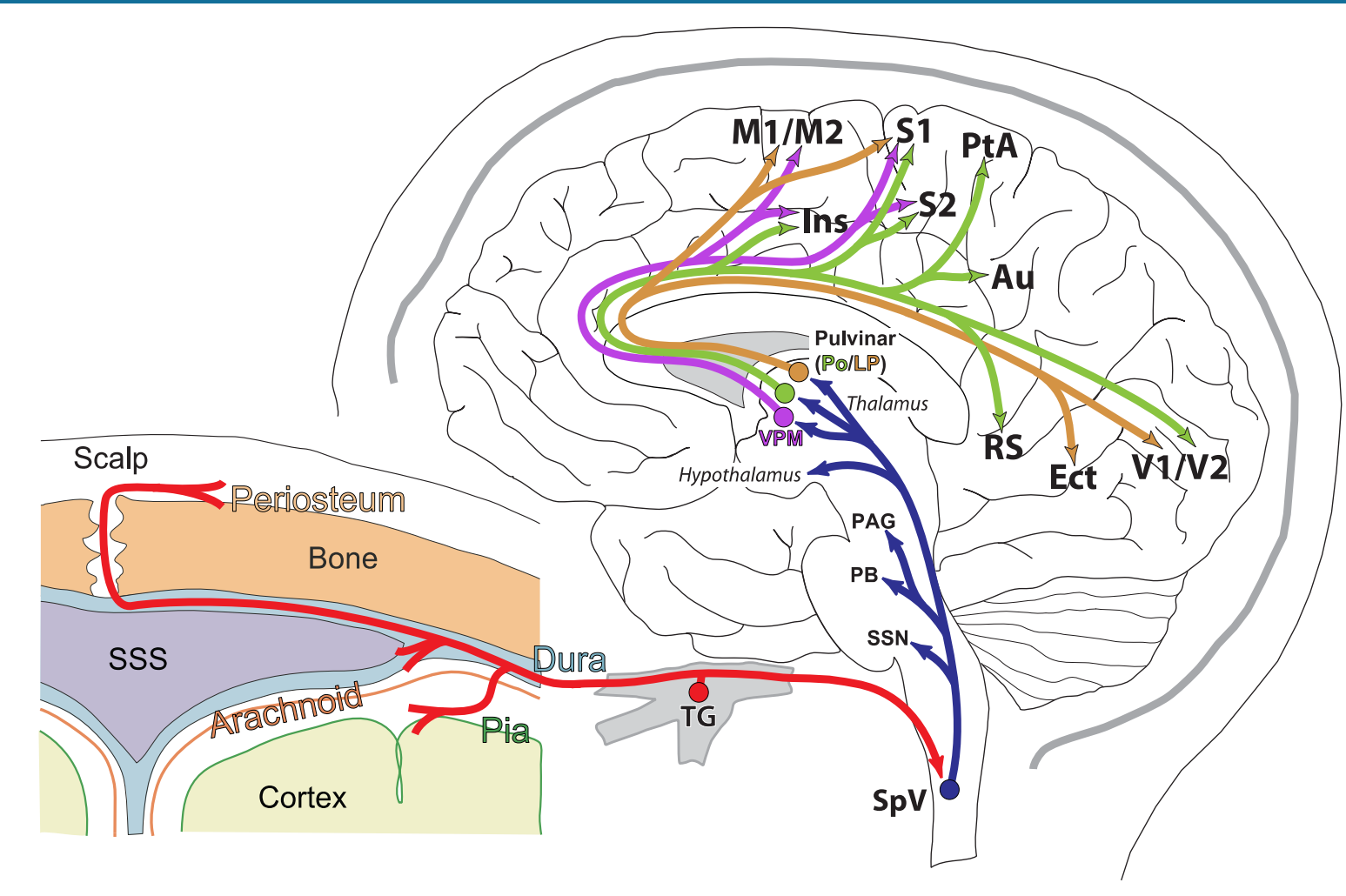
⑥ **Research grants**: NINDS, Allergan/AbbVie, Eli Lilly, Teva,

⑦ **Scholarship funds**: None

⑧ **Endowed chair**: Harvard Medical School

⑨ **Gifts**: Multiple grateful patients

# The trigeminovascular pathway explains the complexity of migraine

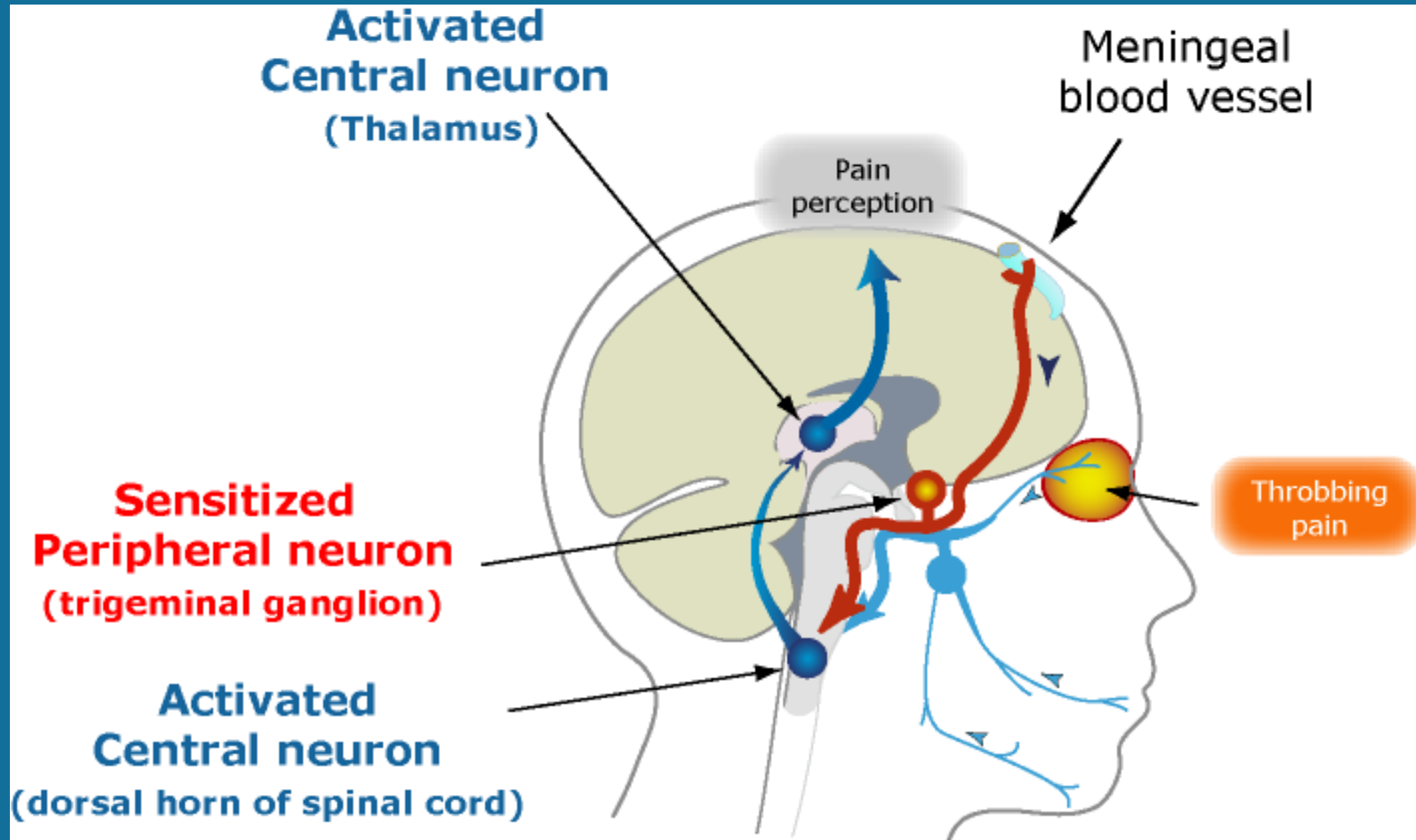


- Photophobia (V1/V2)
- Phonophobia (Au)
- Osmophobia/olfactory hallucination (Ect)
- Clumsiness/spatial orientation (PtA)
- "Brain fog", transient amnesia, difficulty with speech production and comprehension (RSA)
- Modulation of cortical processing of pain (Ins)

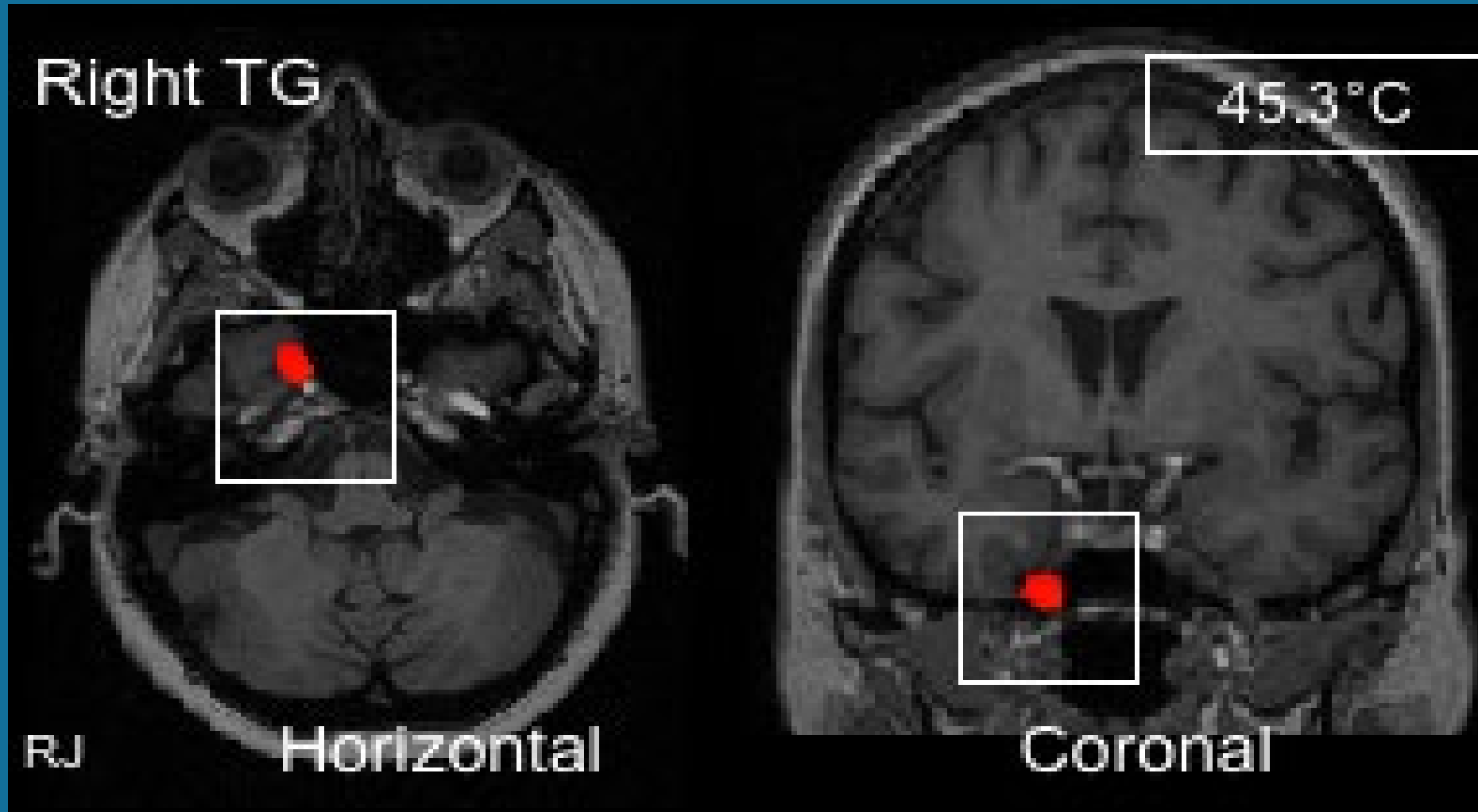
(1) Irritability, (2) Anger, (3) Anxiety, (4) Fear, (5) Low energy and tiredness, (6) Depression, (7) Yawning, (8) Frequent urination, (9) Teary eyes, (10) Loss of appetite, (11) Nausea, (12) Sleep disturbances

# **Peripheral and central sensitization role in migraine pathophysiology**

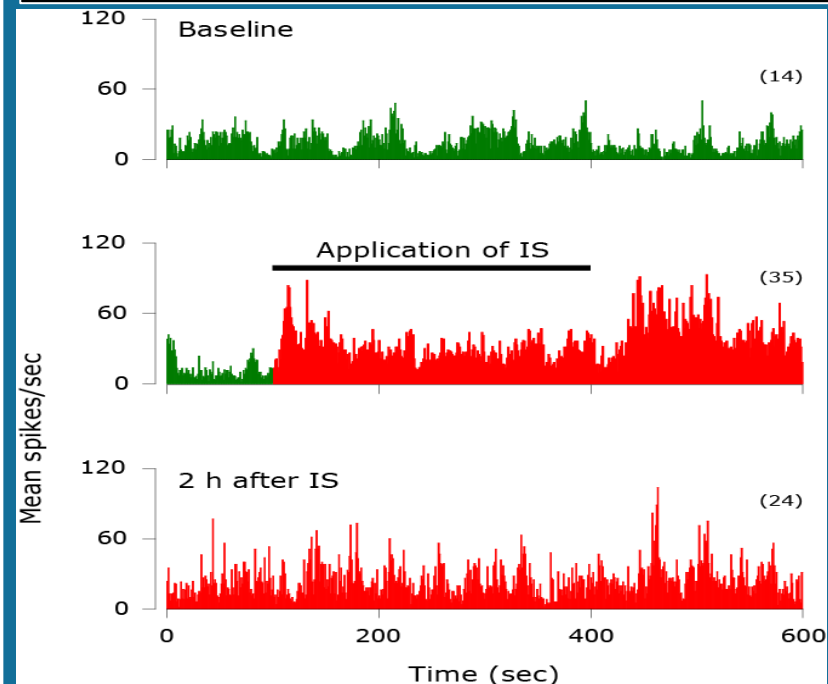
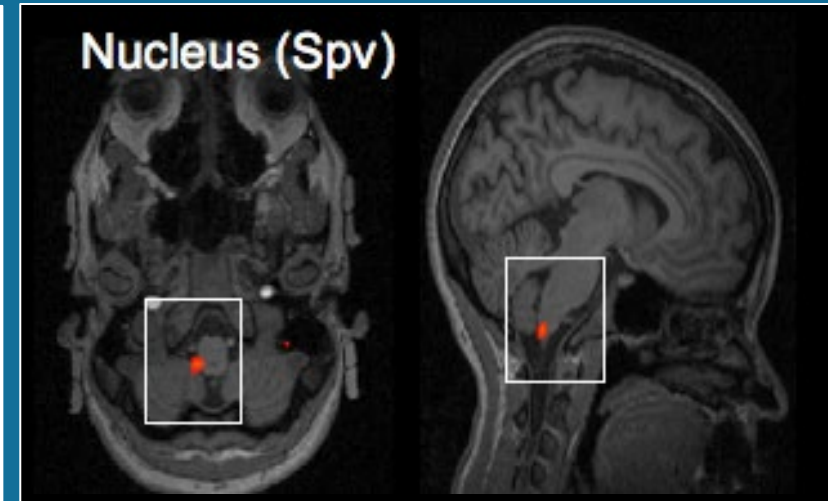
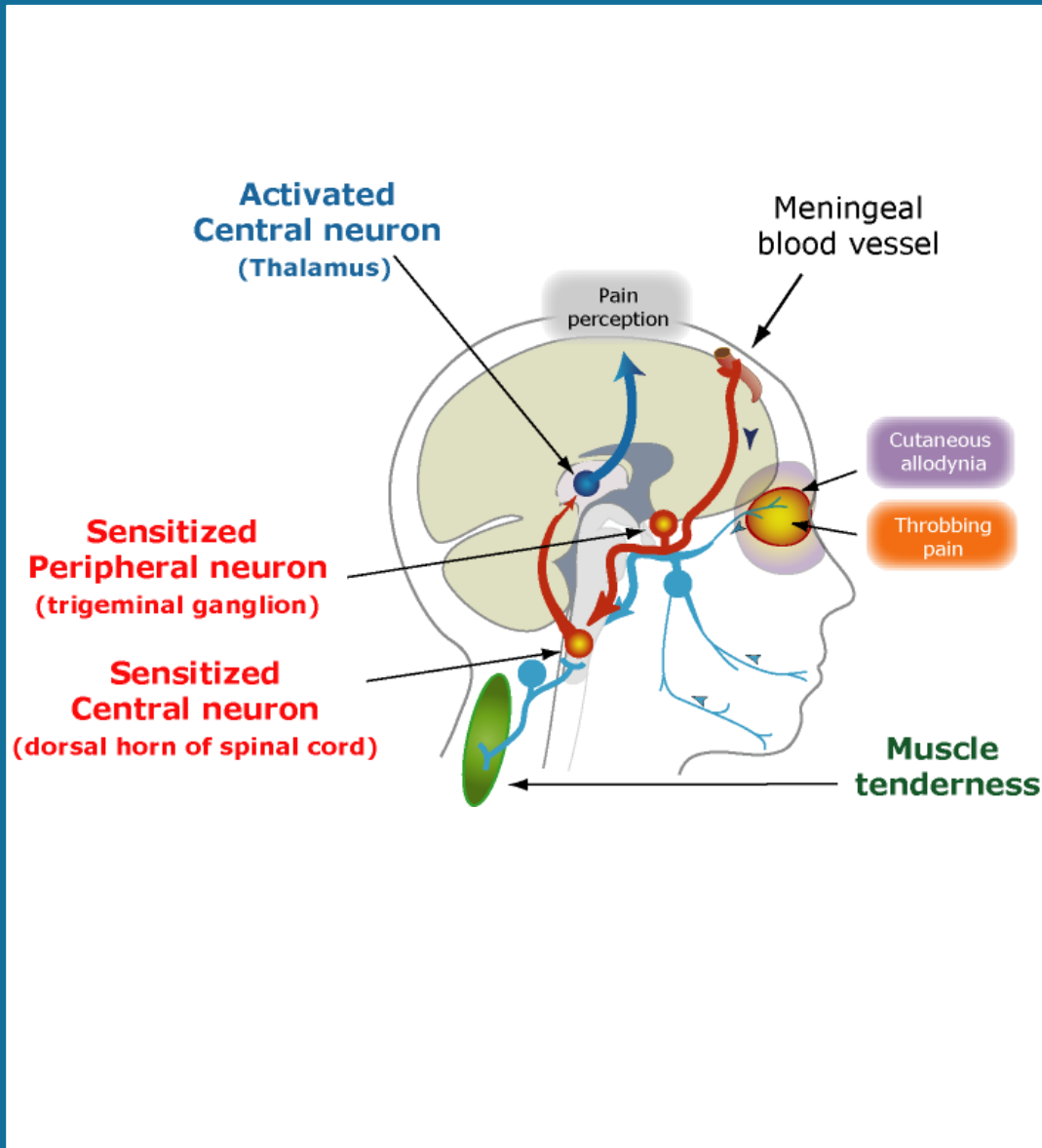
# Peripheral sensitization mediates the throbbing pain



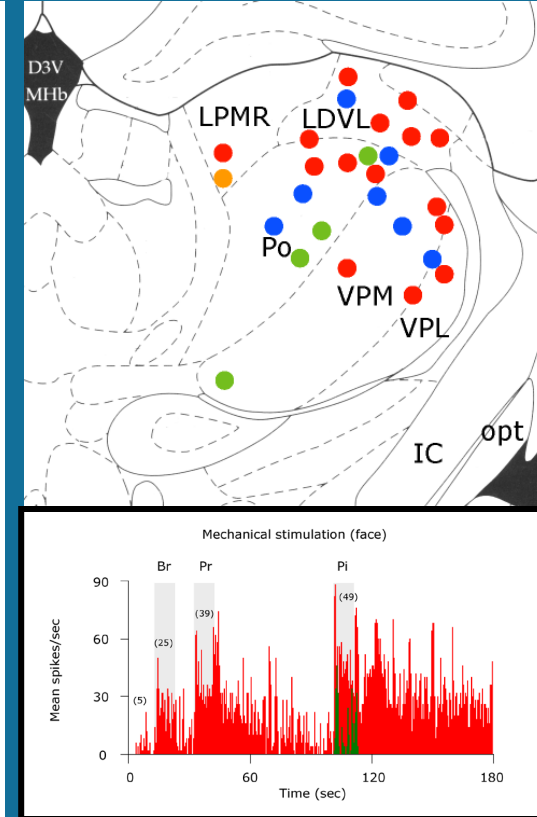
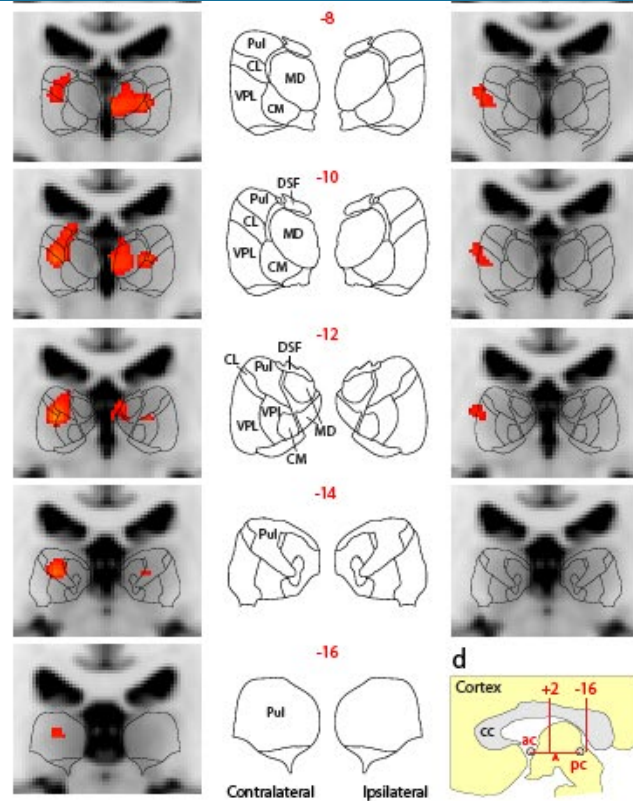
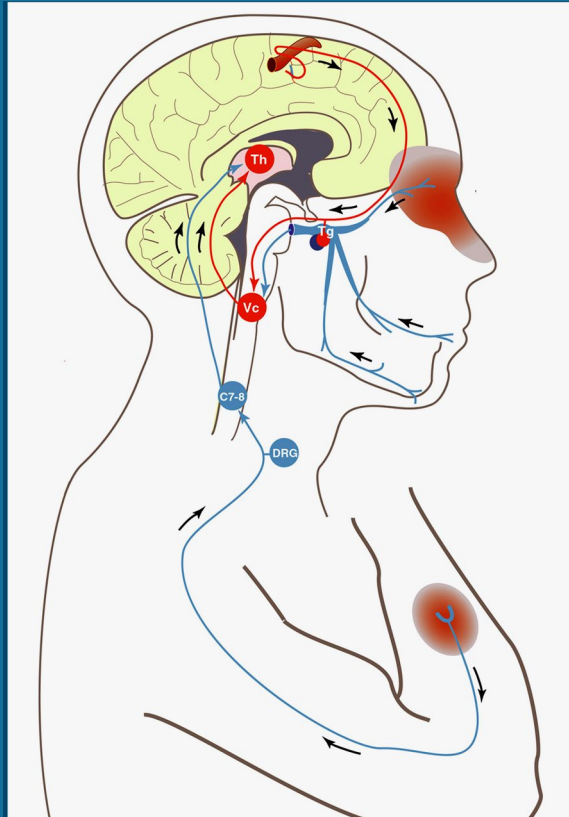
# Imaging peripheral sensitization in migraine



# Central sensitization in the spinal cord mediates skin hypersensitivity and muscle tenderness



# Sensitization of thalamic trigeminovascular neurons mediates whole-body allodynia

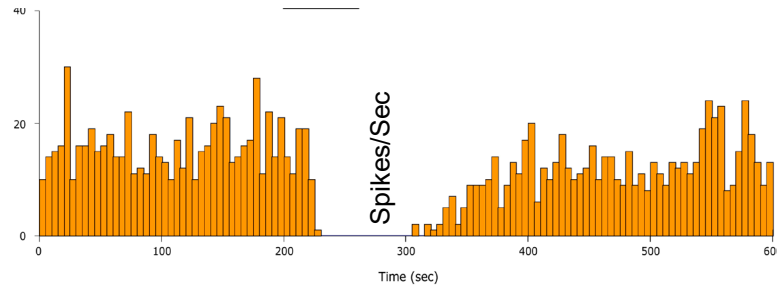


## Summary

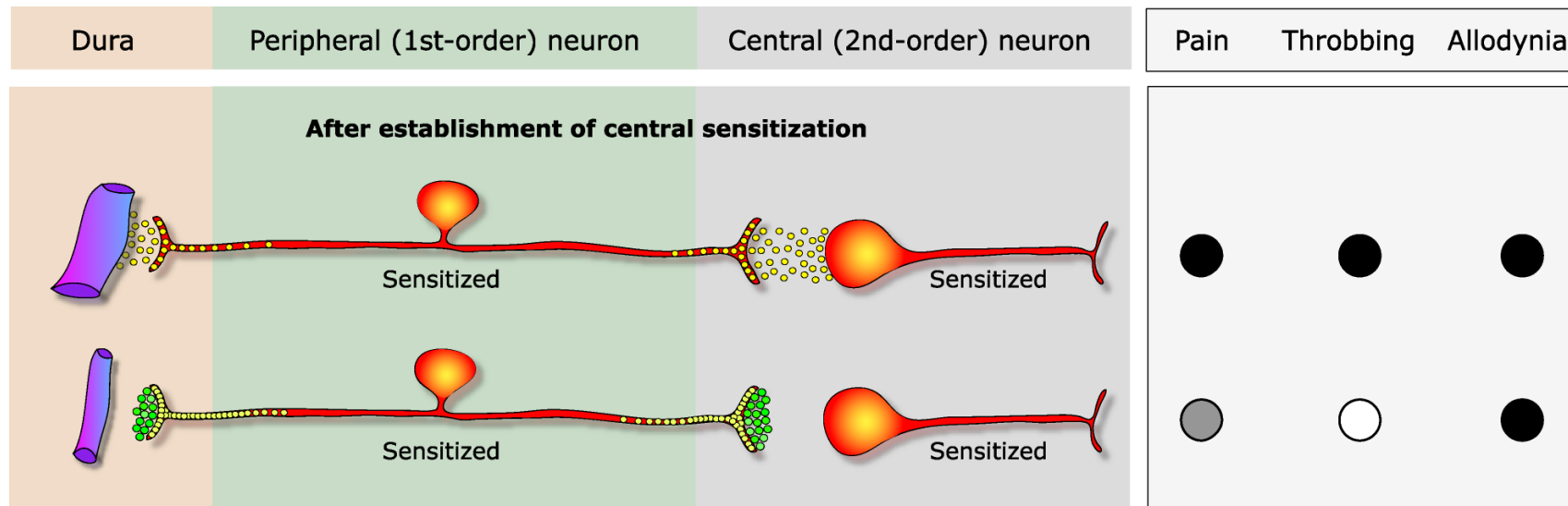
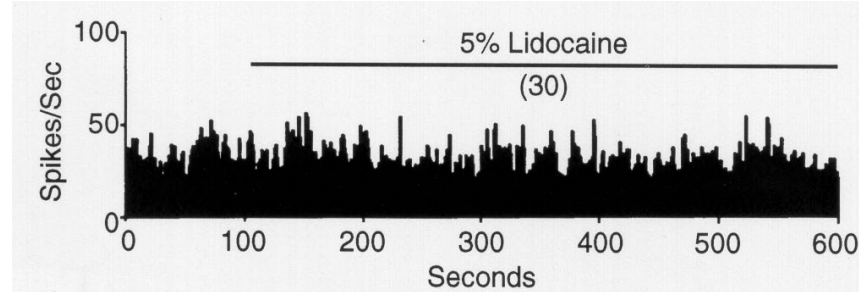
- **Peripheral sensitization mediates the throbbing pain of migraine**
- **Sensitization of central trigeminovascular neurons in the spinal cord mediates cephalic allodynia and muscle tenderness**
- **Sensitization of thalamic trigeminovascular neurons mediates whole-body allodynia.**

# Topical application of lidocaine onto the dura inhibits ongoing activity in sensitized peripheral but not central trigeminovascular neurons

Dura-sensitive Neuron in the Trigeminal ganglion



Dura-sensitive Neuron in the Spinal trigeminal nucleus

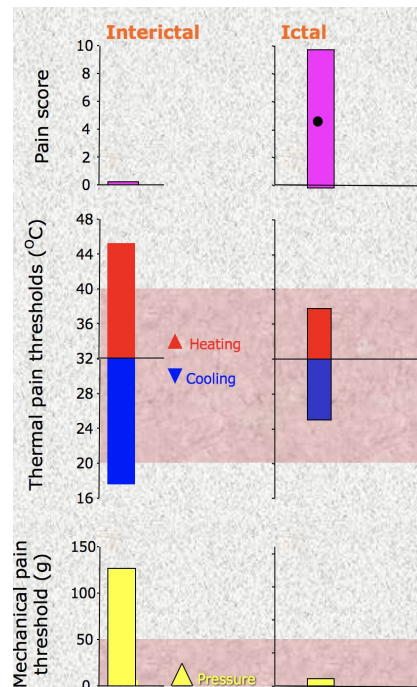


**We don't have an answer to central sensitization**

# Progression of disease: chronic state of central sensitization leads to interictal allodynia and background headache

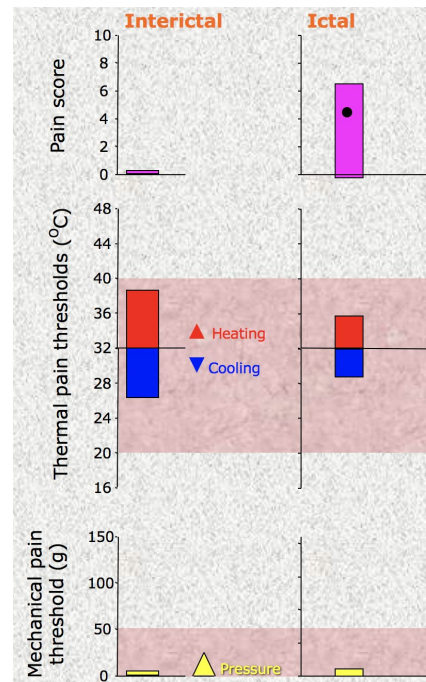
Episodic migraine

no  
allodynia    allodynia

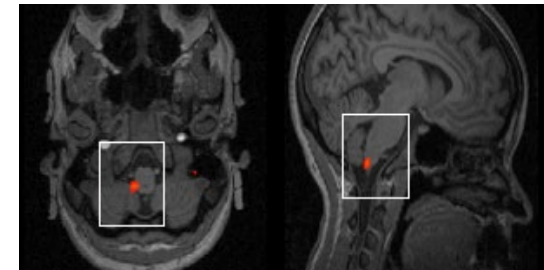


Chronic migraine

allodynia    allodynia



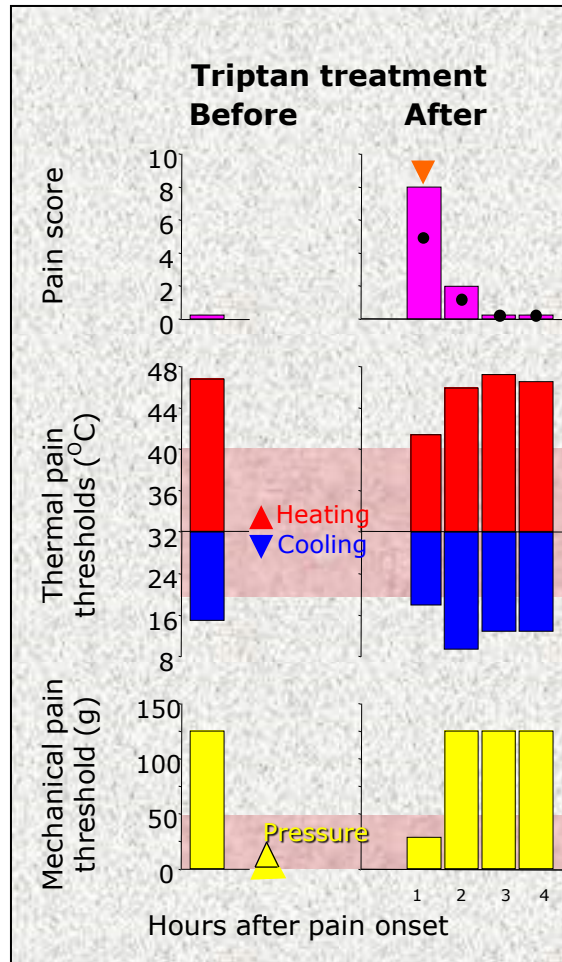
Chronically sensitized spinal trigeminal nucleus mediates the ongoing headache and the interictal cephalic allodynia



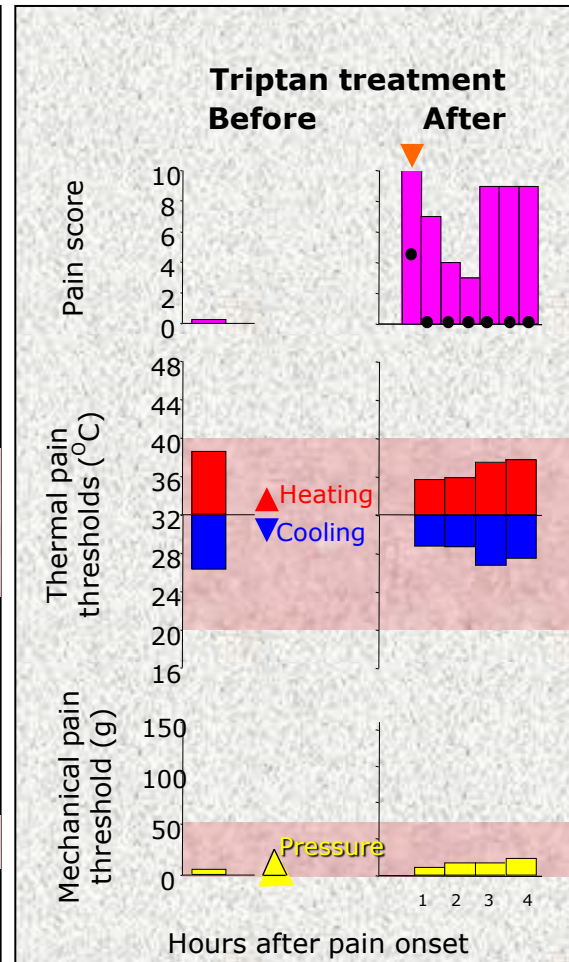
Spinal trigeminal nucleus

# Lessons learned from triptan therapy – Treat Early

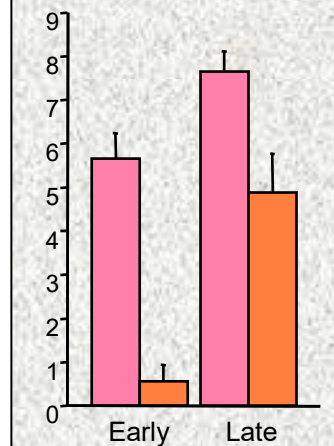
## Episodic migraine



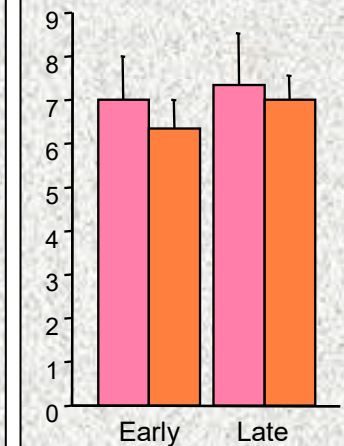
## Chronic migraine




Episodic migraine patients respond if treated early enough in the attack



Chronic migraine patients do not respond



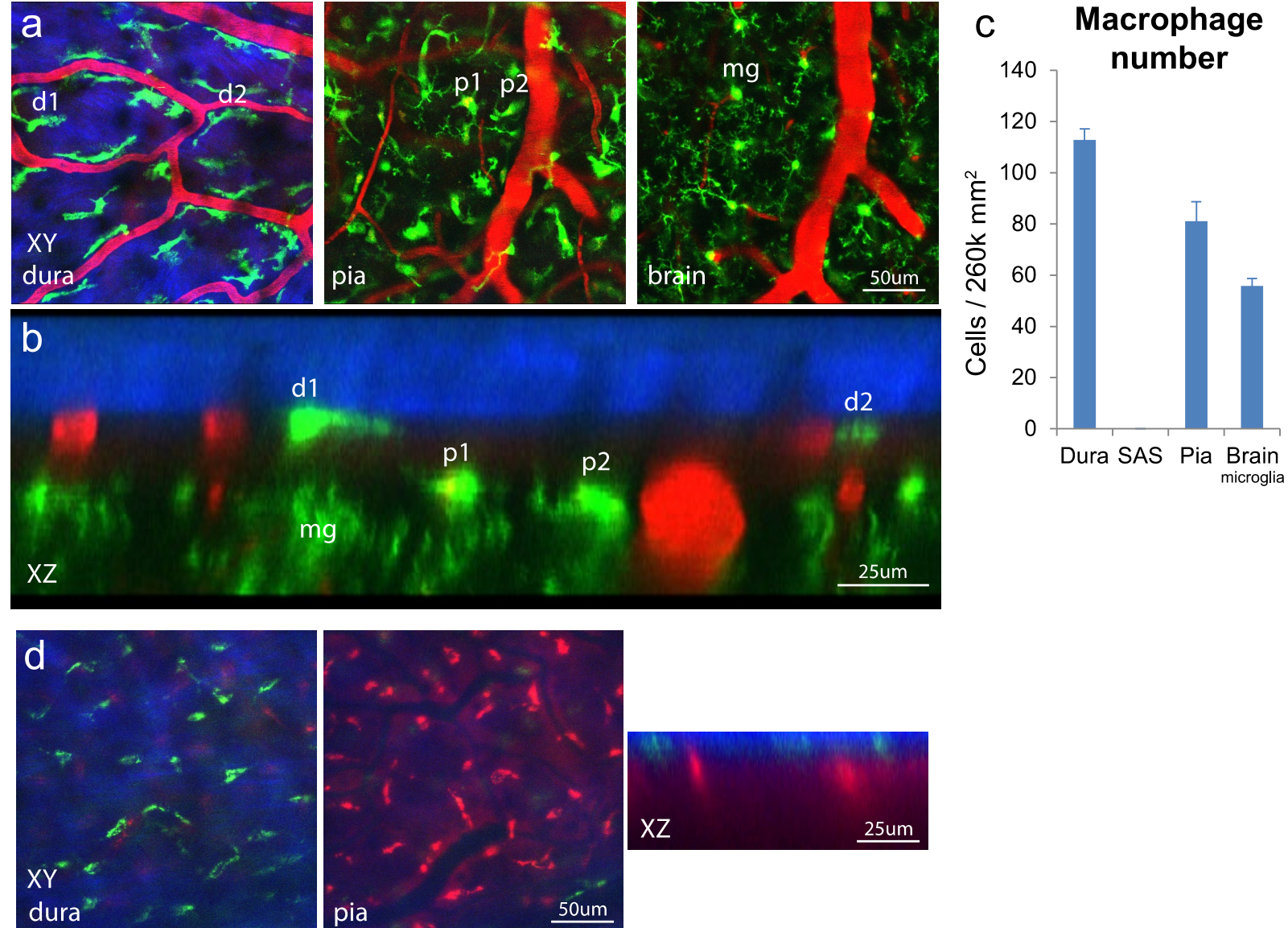
Before treatment      After treatment



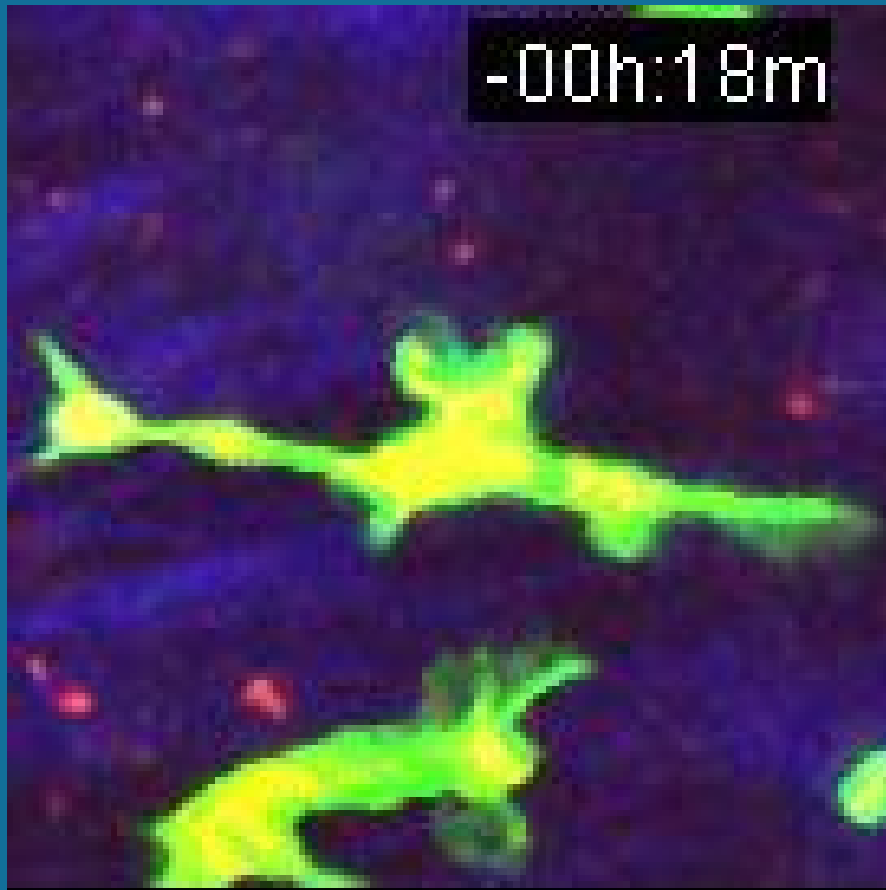
# **Bridging the gap between aura and headache or CSD and activation of meningeal nociceptors:**

*Activation of pial and dural macrophages and dendritic cells by CSD*

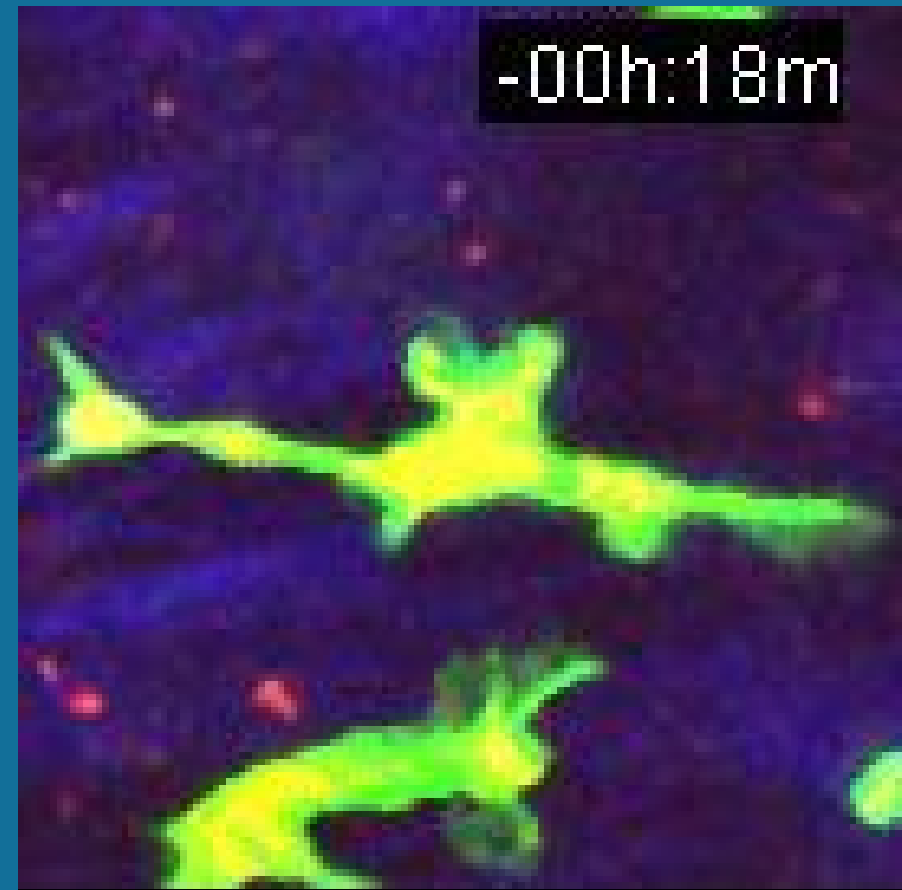
# Macrophages form monolayers in the dura and pia



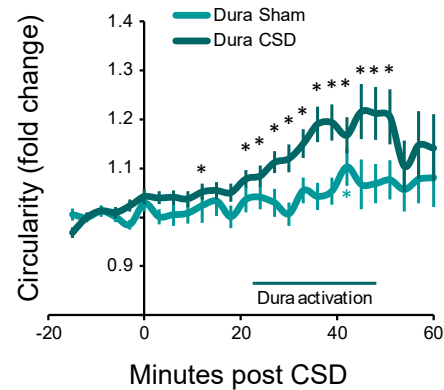
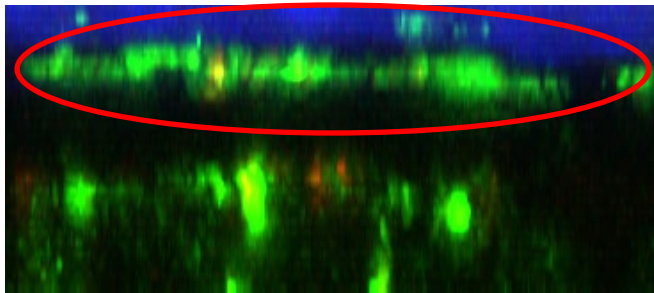
## Macrophage behavior before CSD



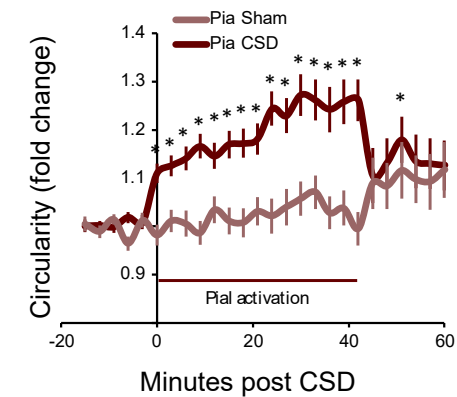
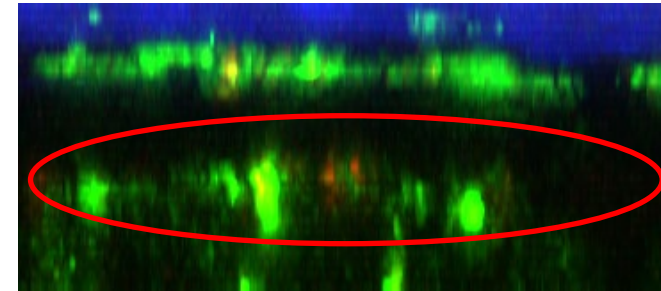
## Macrophage behavior after CSD



Dural macrophages are activated after a delay

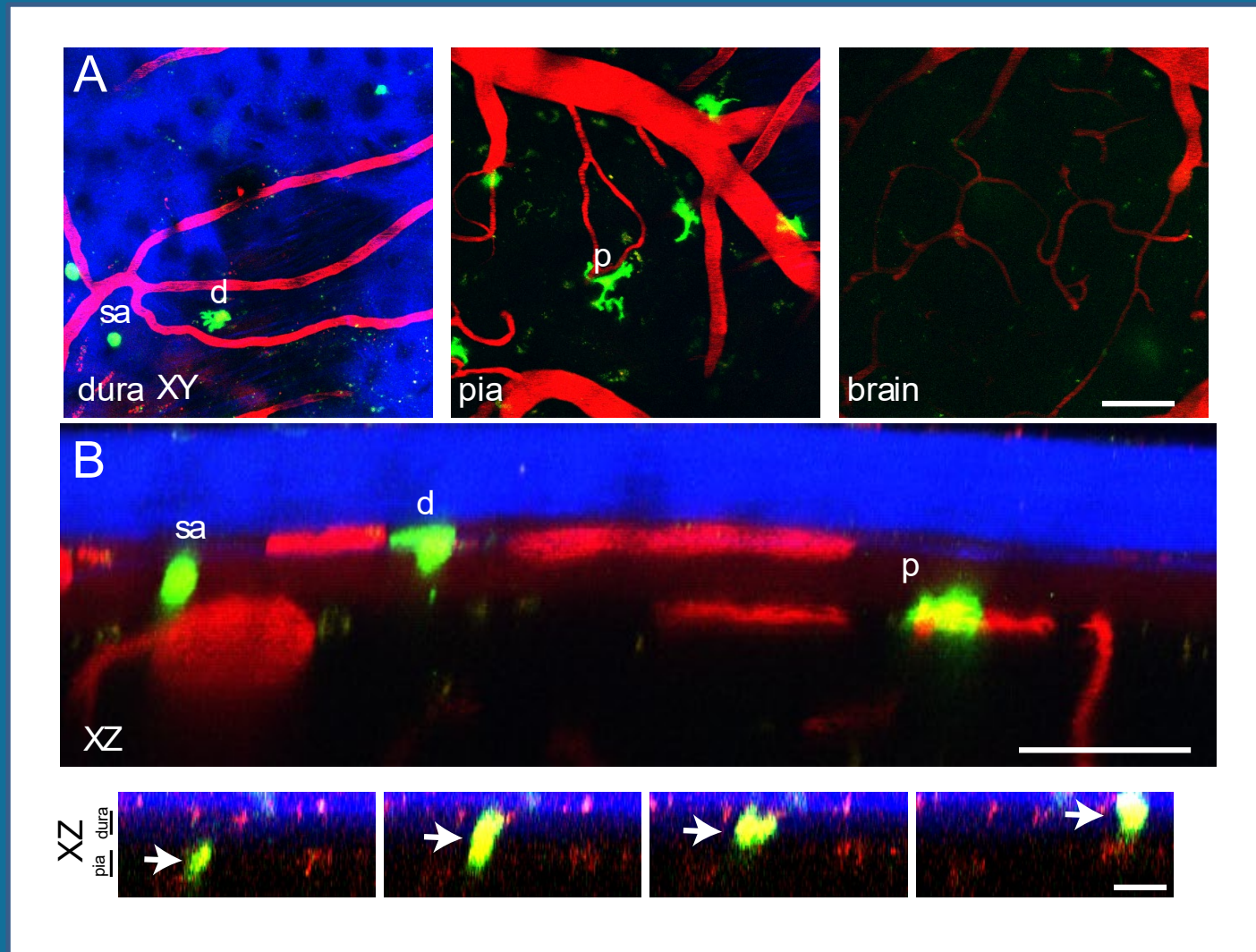


Pial macrophages are activated immediately

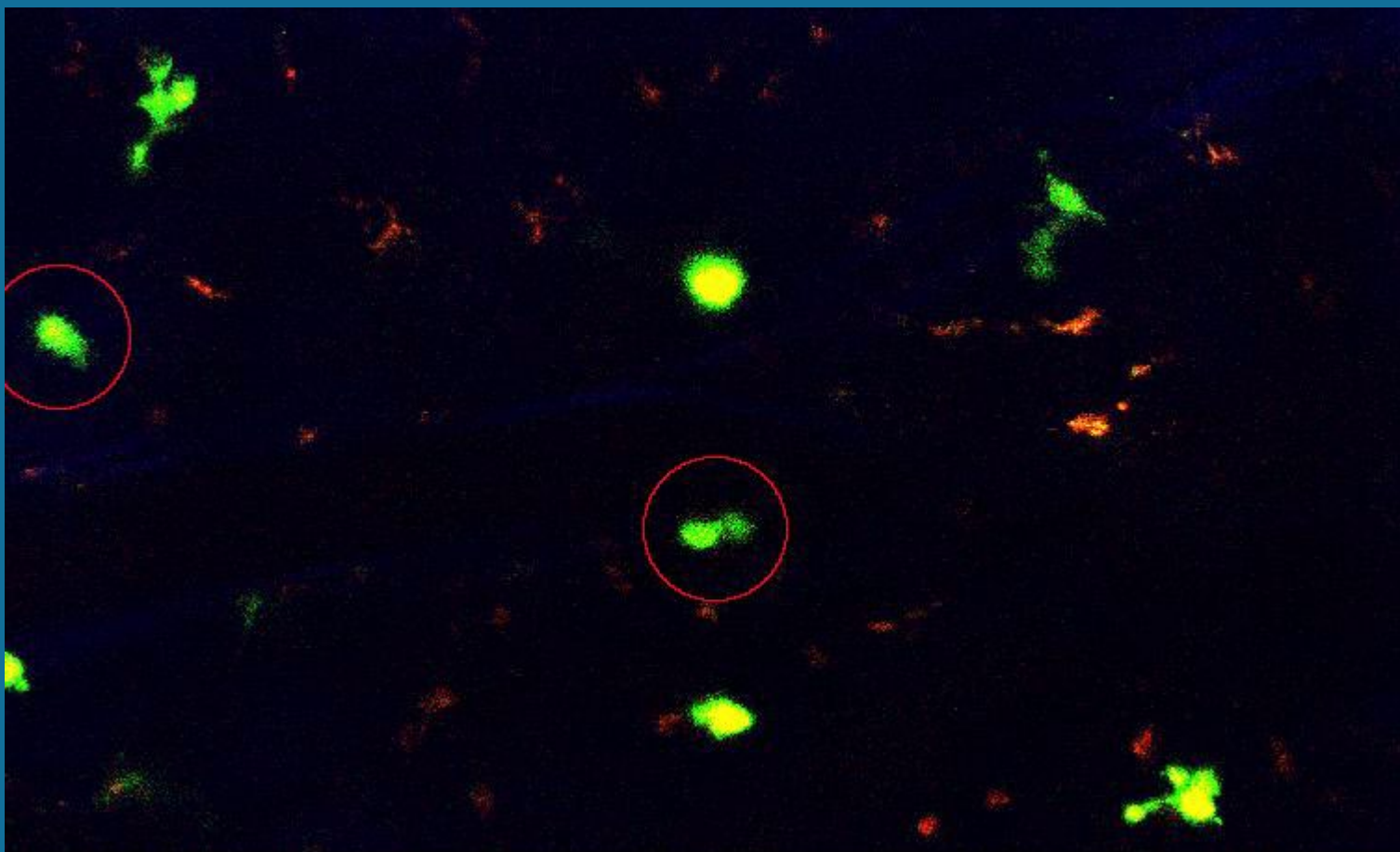


**We don't have drugs that block activation of meningeal macrophages**

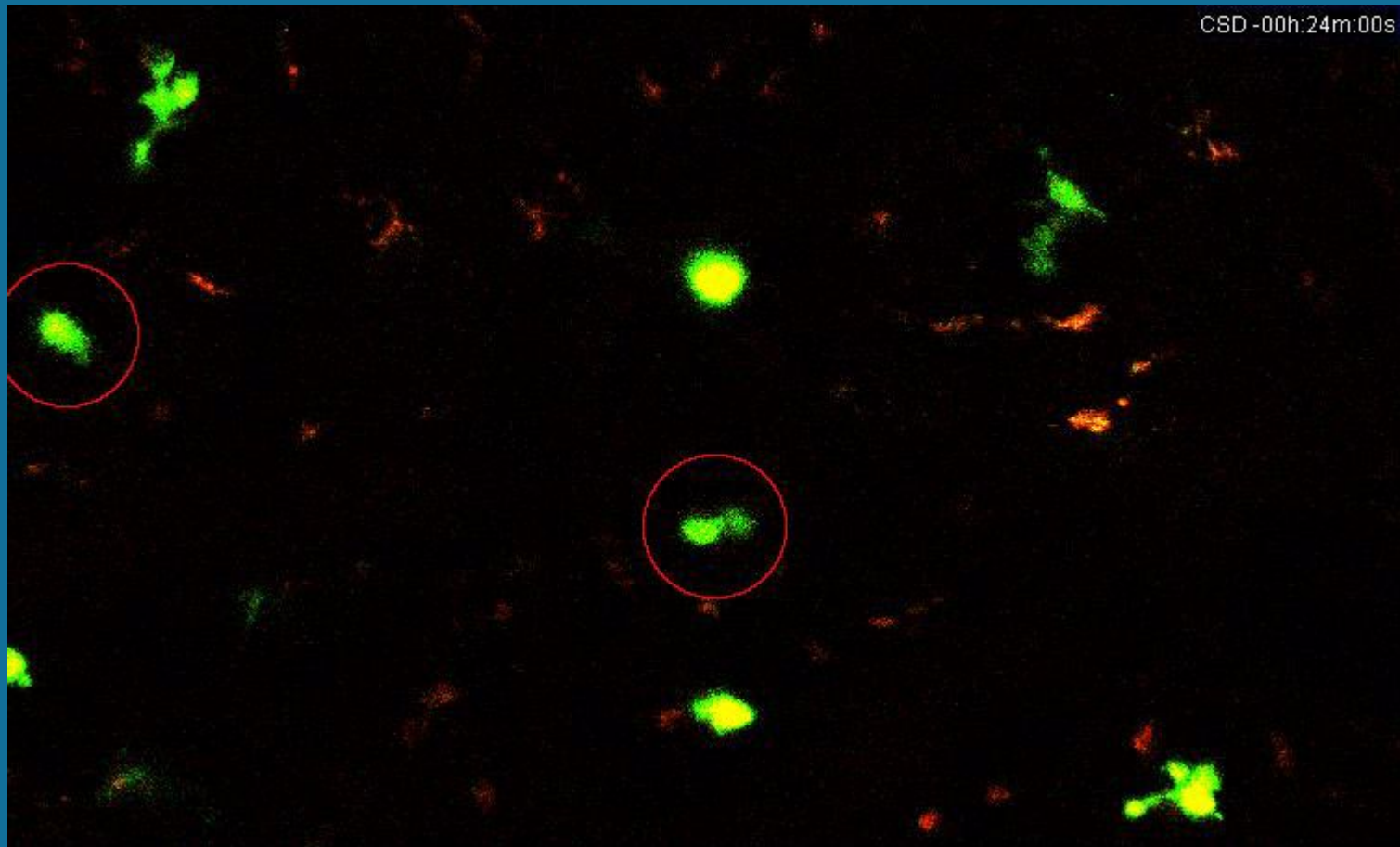
# Multiphoton *in vivo* imaging of dendritic cells in CSD



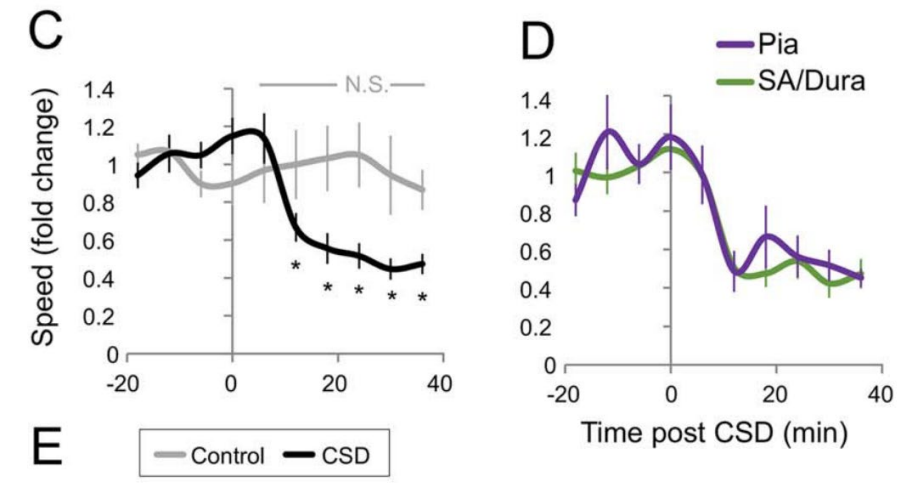
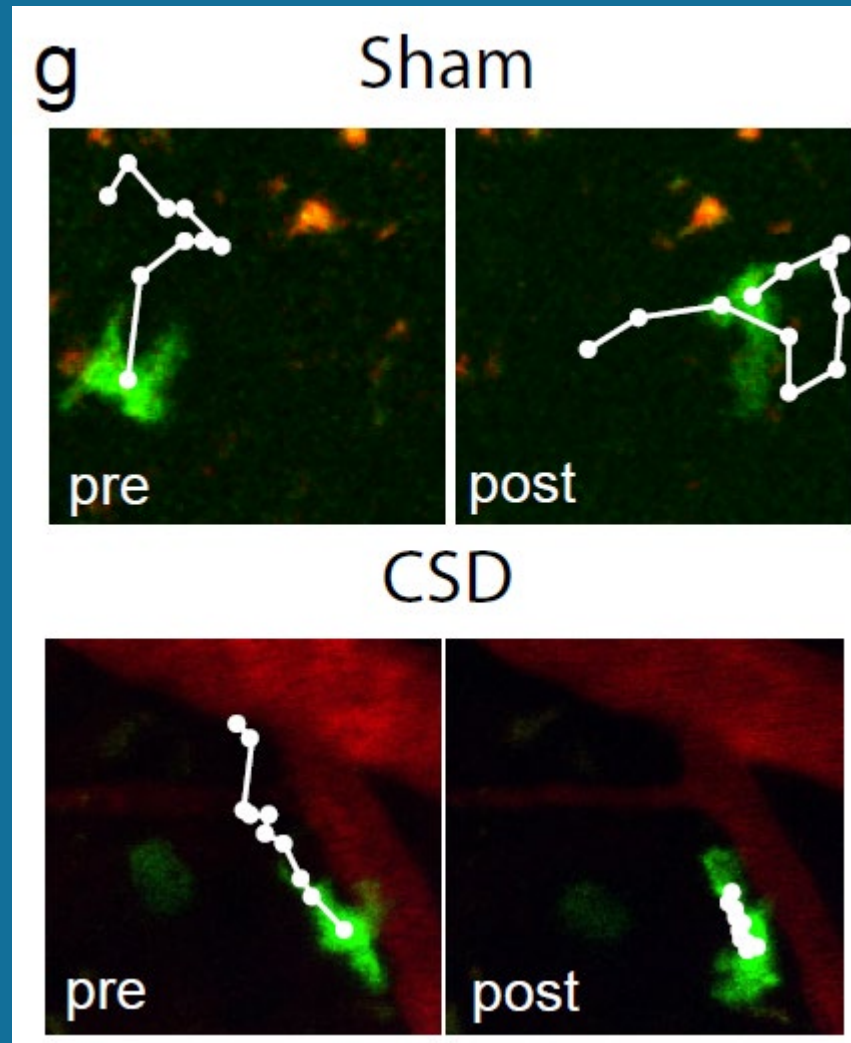
# A subset of dendritic cells are highly migratory



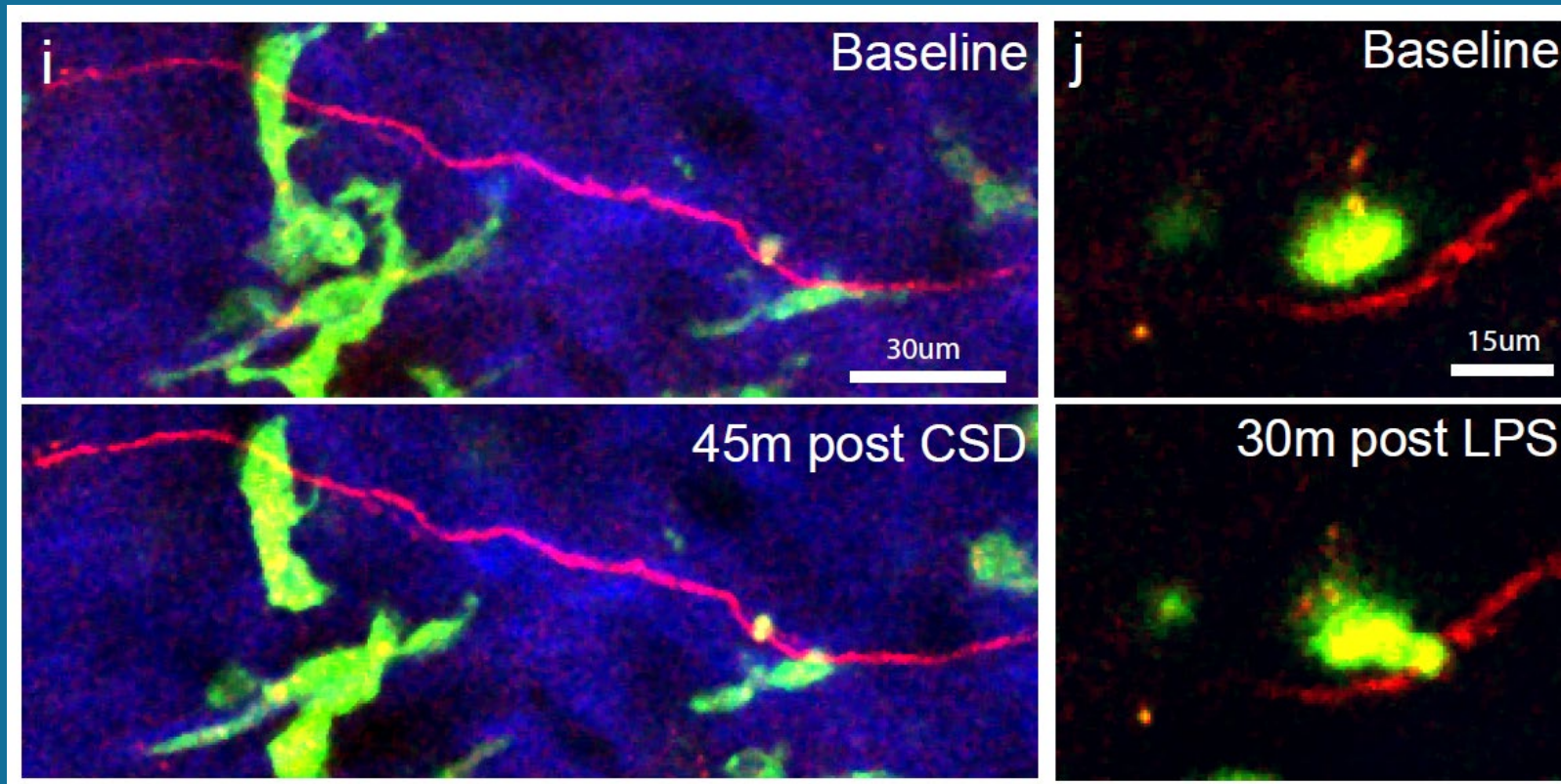
# Dendritic cells stop migrating after CSD



# Pial and dural DC are activated after a short delay



# Macrophages and DC are in close proximity to dural TRPV1-positive fibers



## SUMMARY

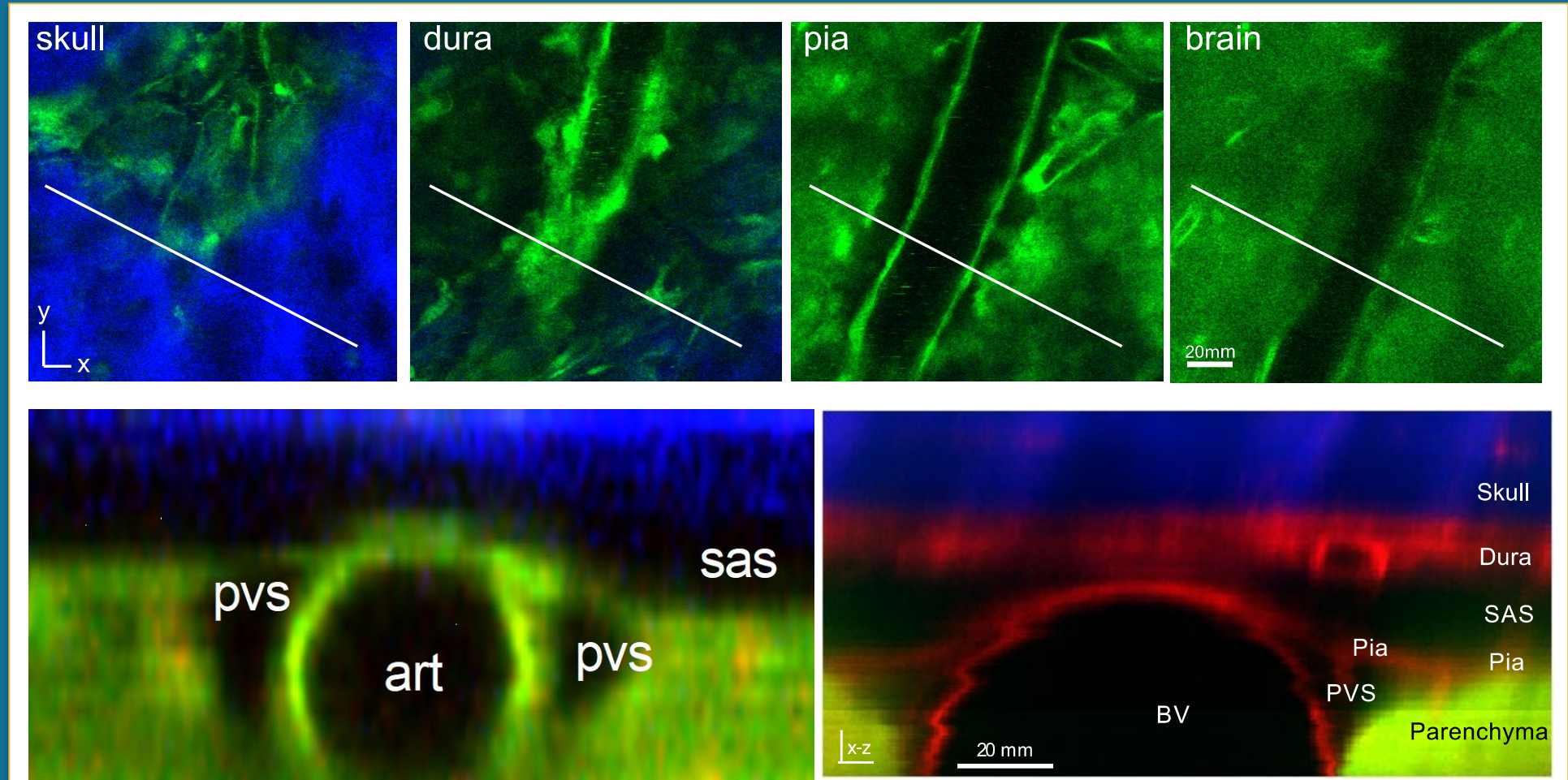
- Macrophages form monolayers in the dura and pia
- Activated meningeal macrophages retract their processes and become circular; activated meningeal Dendritic cells (DCs) stop migrating
- Dendritic cells are antigen-presenting cells capable of transferring inflammatory reactions from inside the BBB to the outside where they stimulate and attract T cells
- CSD activates pial macrophages instantaneously, pial, subarachnoid, and dural DCs 6-12 minutes later, and dural macrophages 20 minutes later.



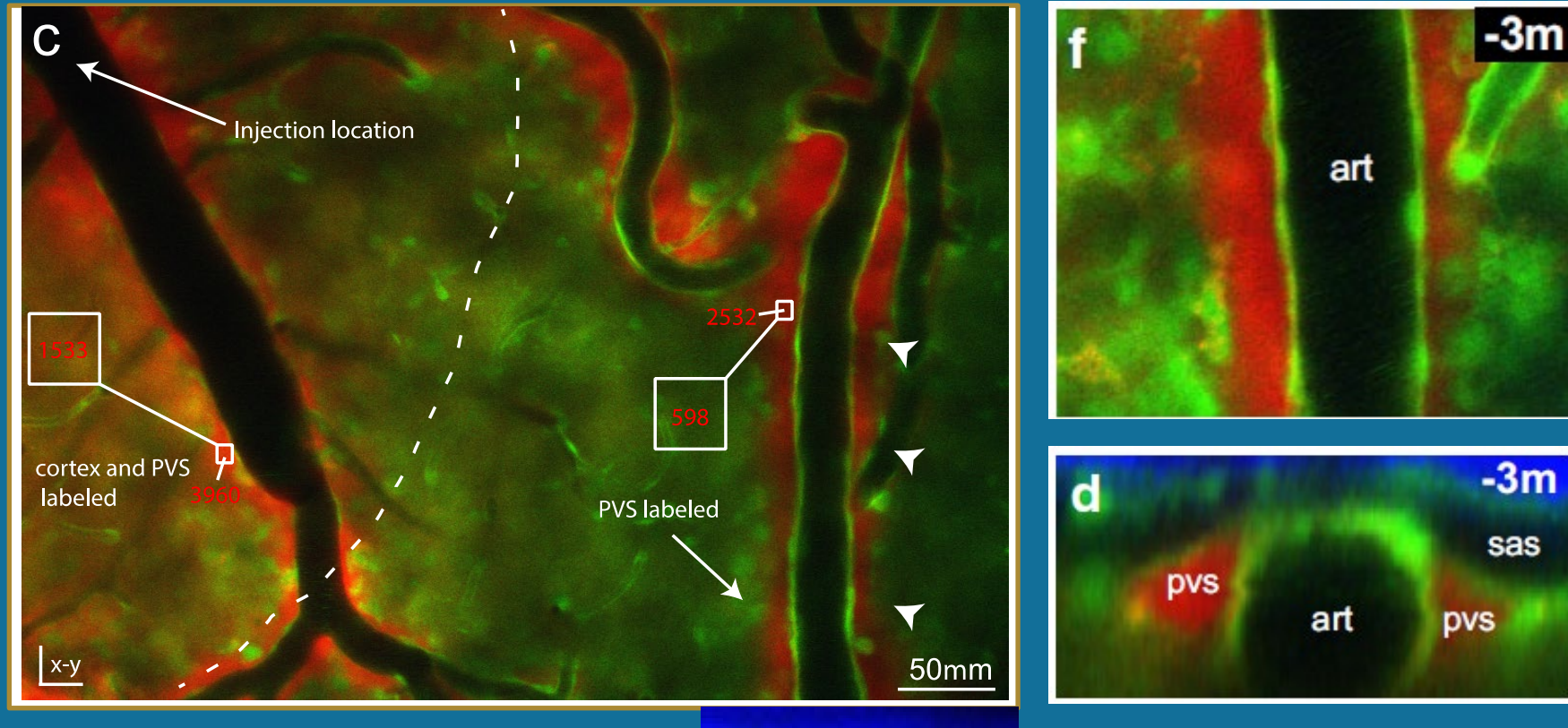
# Migraine and the Glymphatic System

*Cortical spreading depression closes the  
paravascular space and impairs  
glymphatic flow*

# The glymphatic system consists of tunnels that follow pial, dural and cortical blood vessels – called the paravascular space

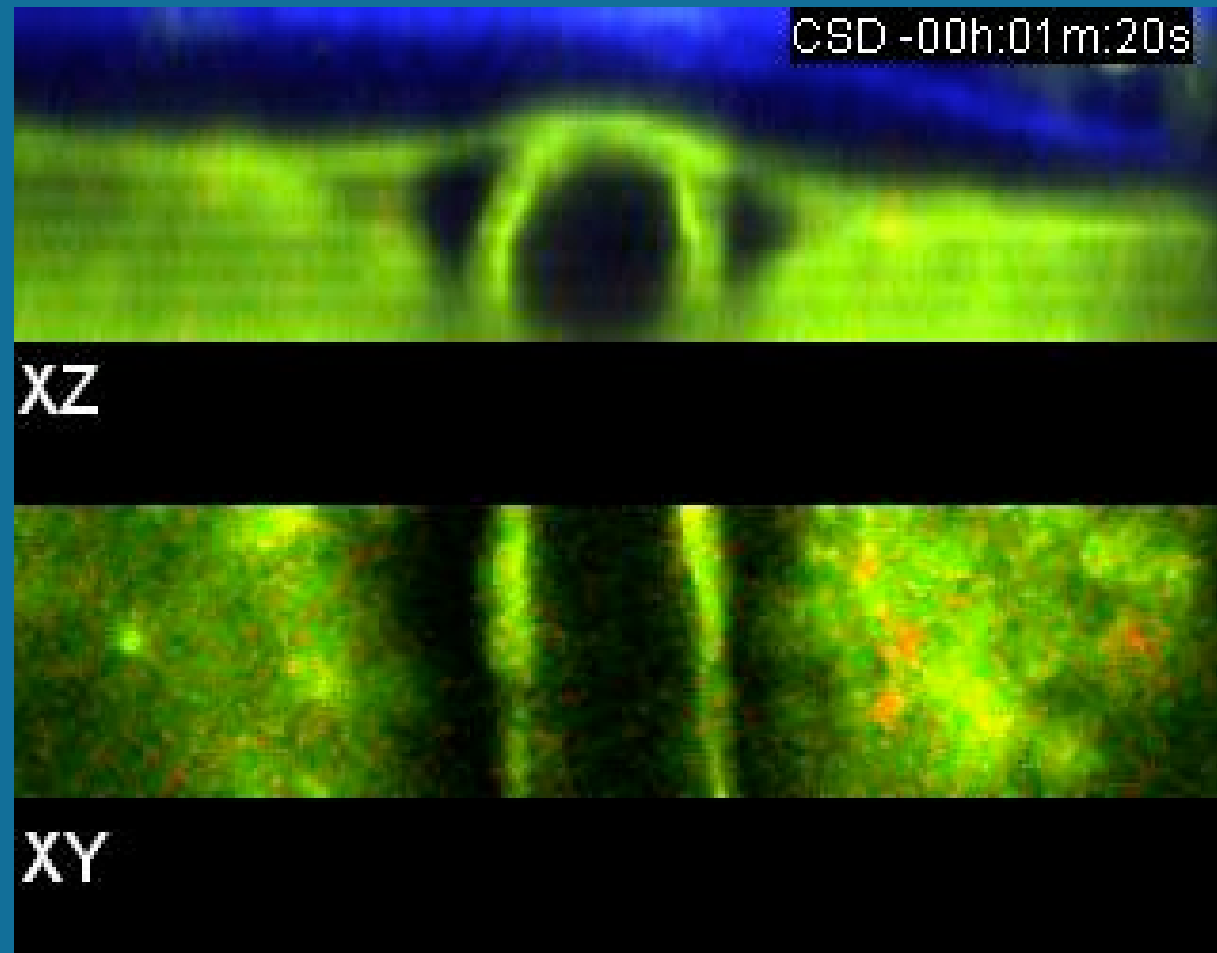


# Paravascular space labeled with dye following intracortical injection

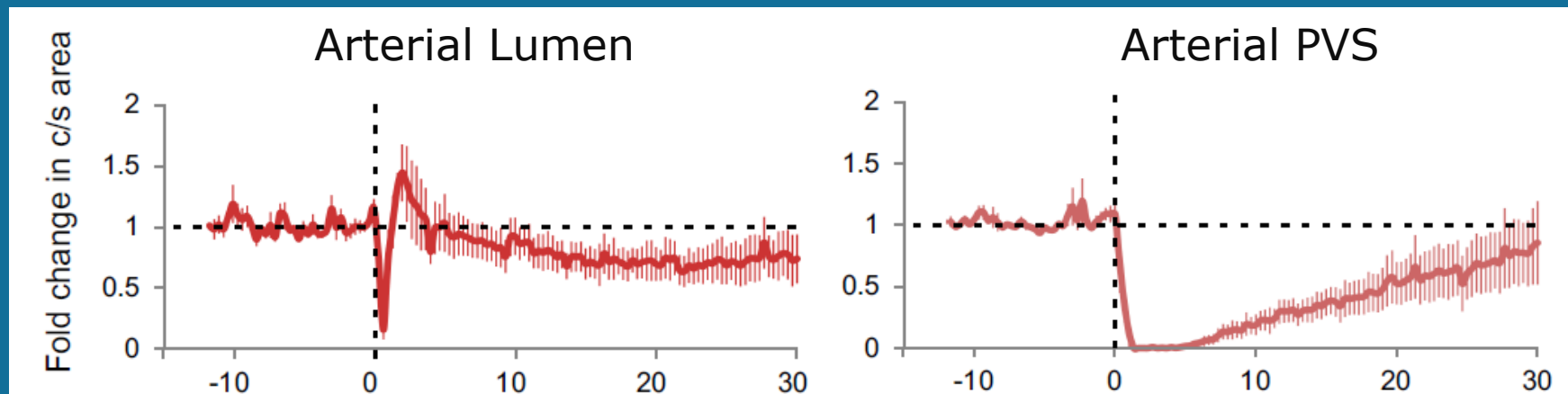
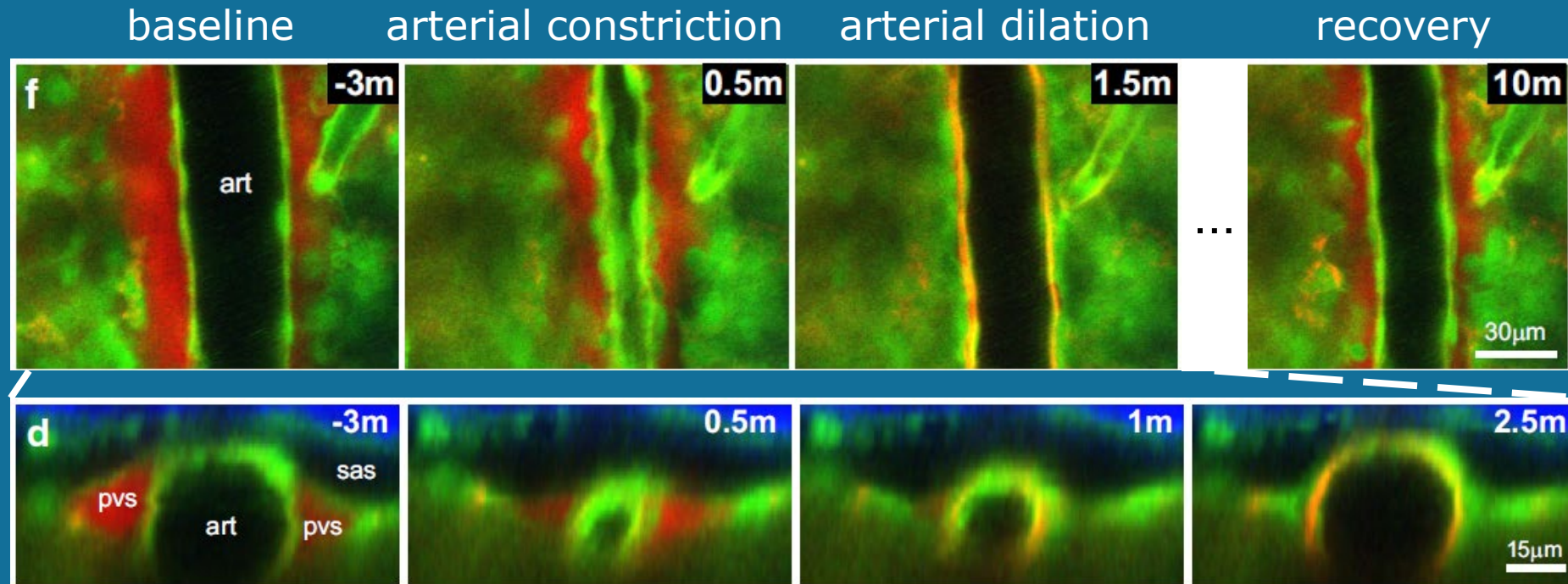


Note the anatomical separation between the paravascular space (red) and the arterial lumen (dark)

# Imaging cortical spreading depression

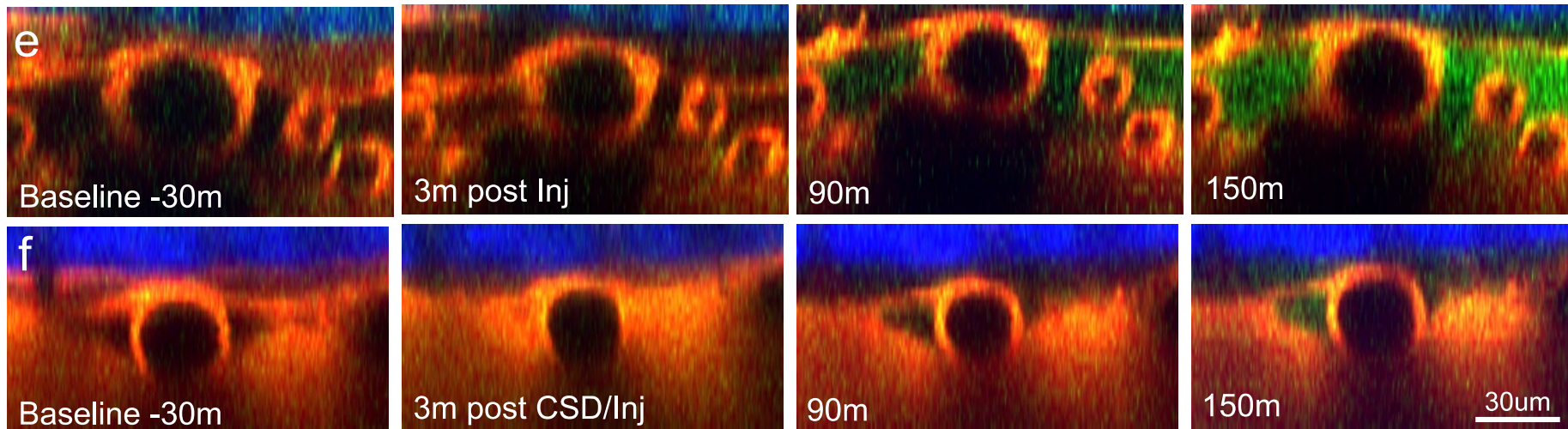
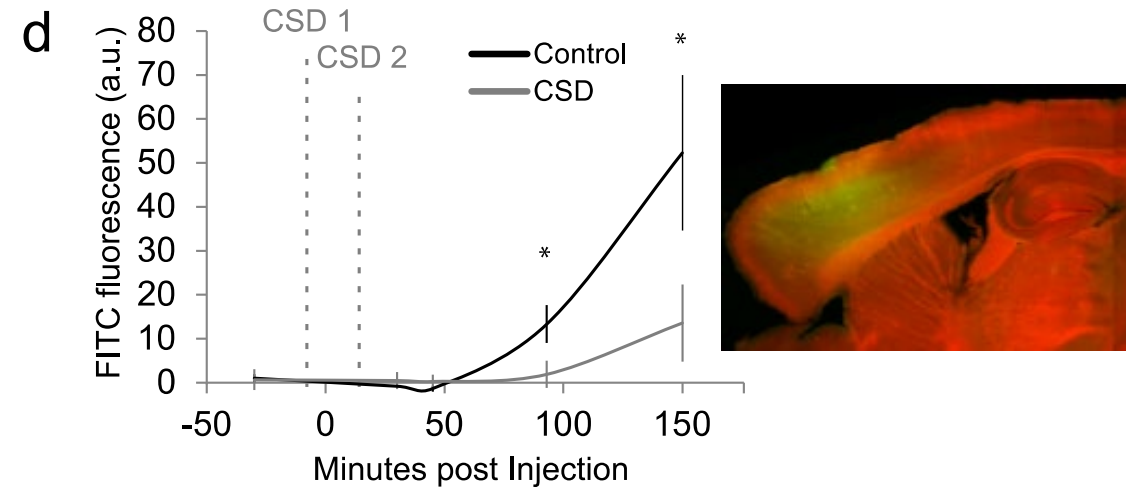
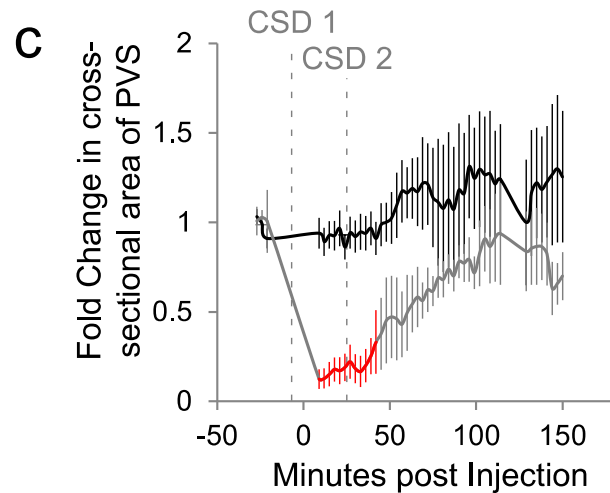


# CSD produces a rapid closure of the PVS around pial arteries and veins.



# Clearance of interstitial fluid (molecular waste) from the brain parenchyma, through the PVS to cervical lymph nodes

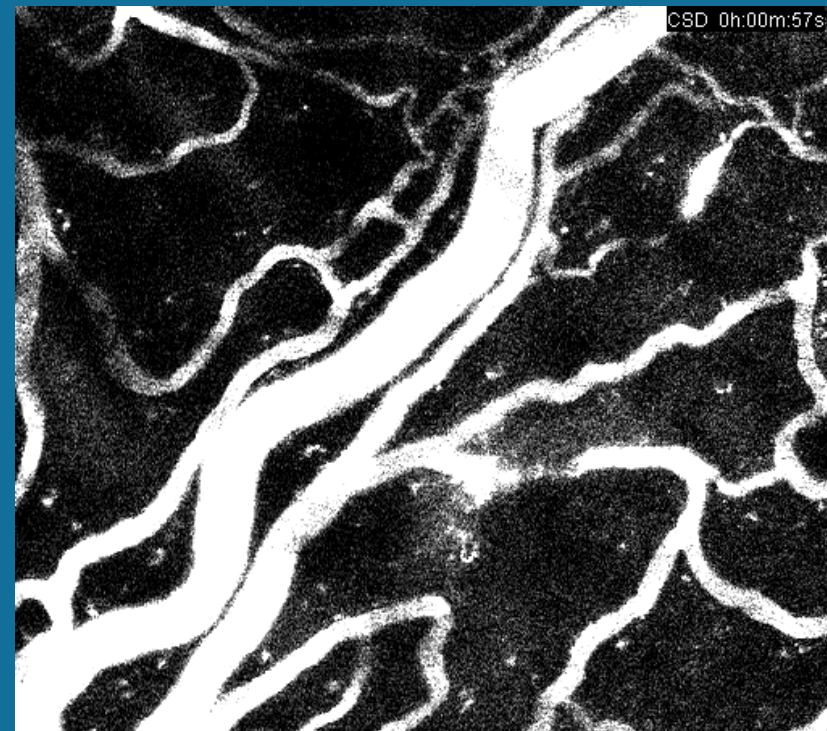
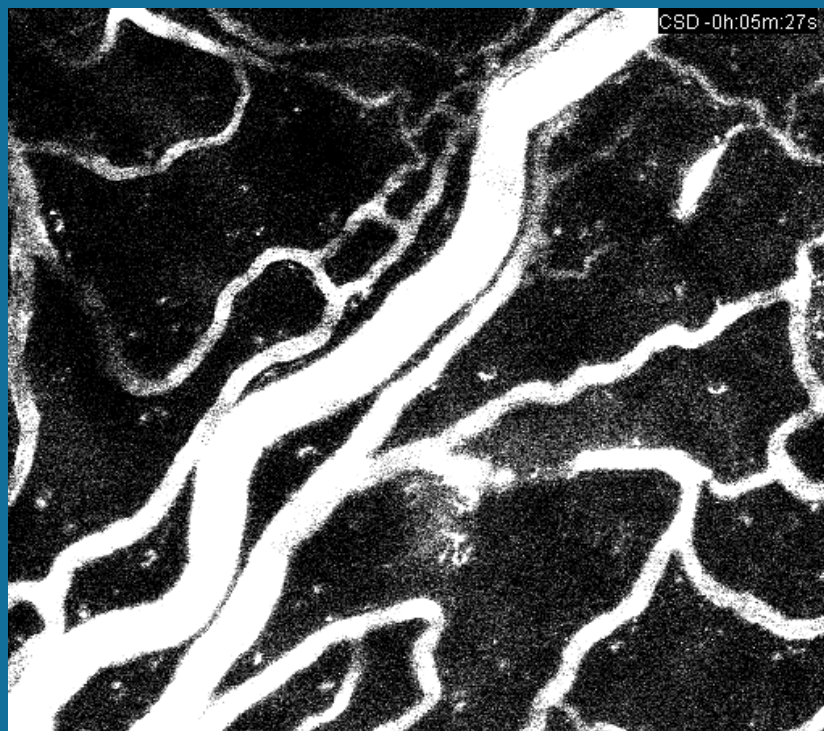
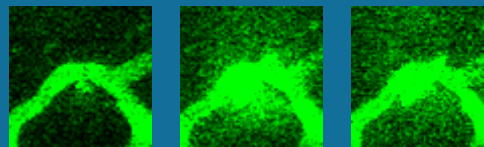
(CSD causes reduction in flow of interstitial fluid within the PVS)



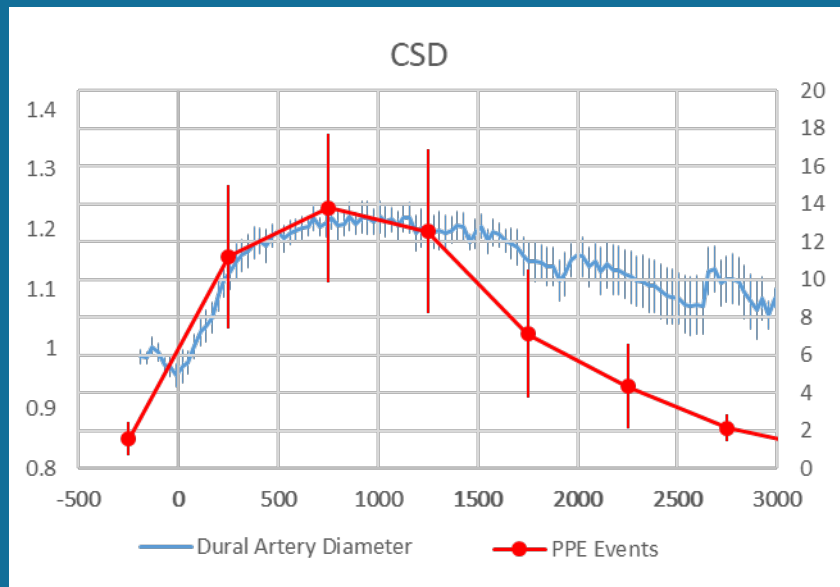


# Plasma protein extravasation

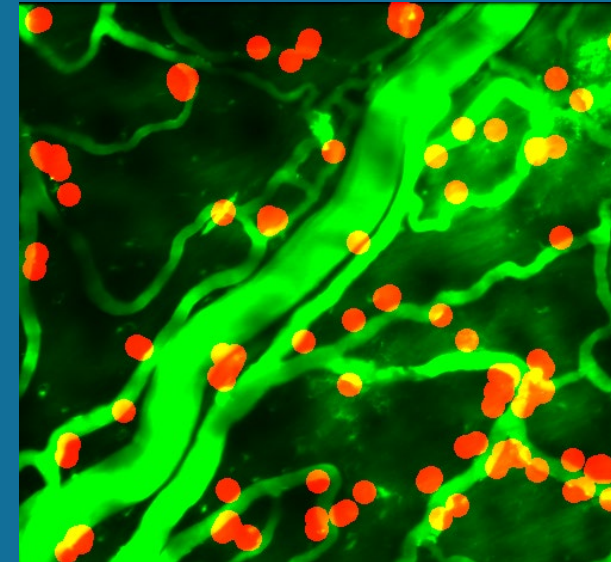
# Plasma protein extravasation during CSD in the rat



# Plasma protein extravasation and dilatation of dural arteries



● PPE Event

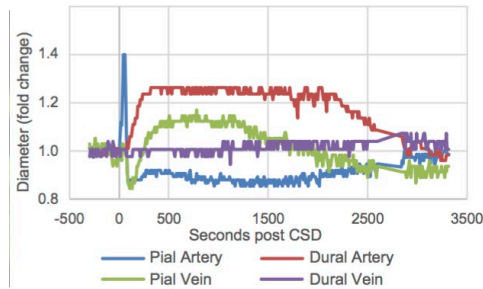




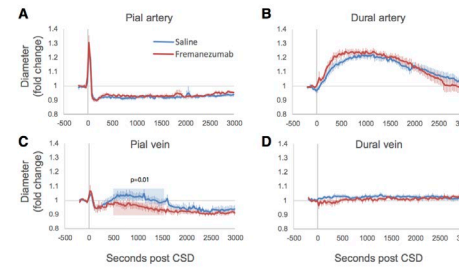
# Vascular responses

# CGRP-mAbs effects on meningeal blood vessels and plasma protein extravasation

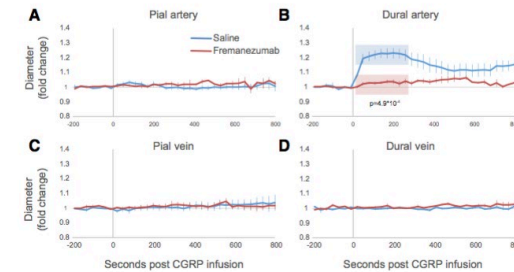
## 1. CSD-induced vascular dilatation



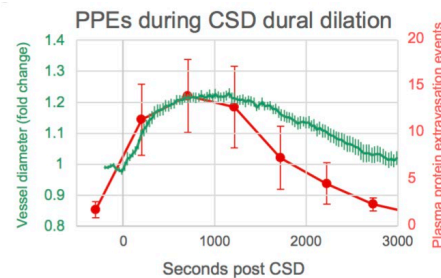
## 2. CSD-induced vascular dilatation is not affected by CGRP-mAb



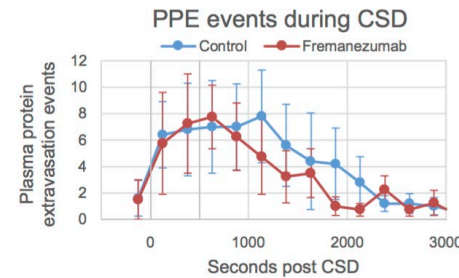
## 3. CGRP-induced vascular dilatation is limited to dural arteries (outside the bbb)



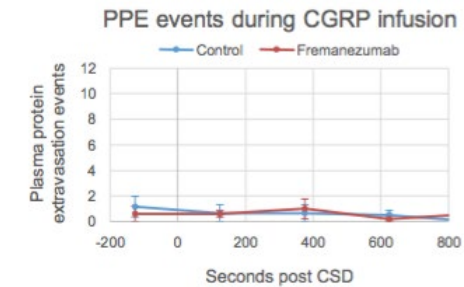
## 4. CSD-induced plasma protein extravasation



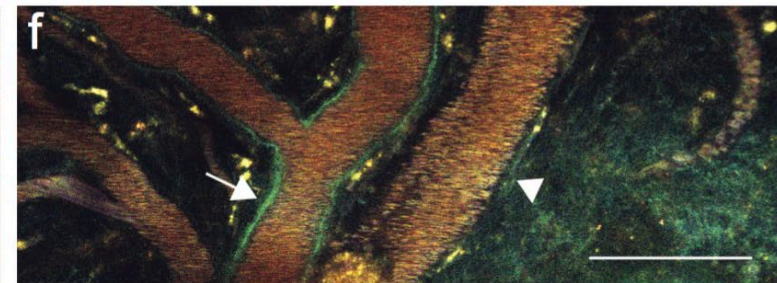
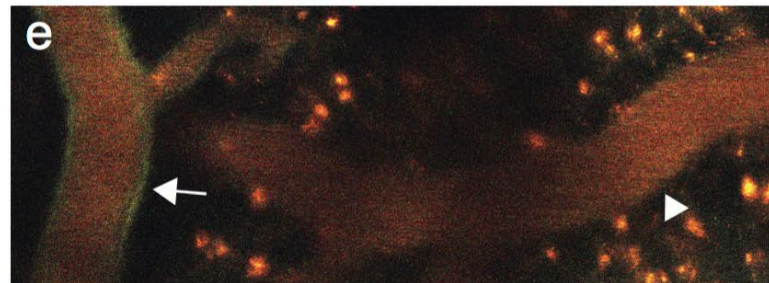
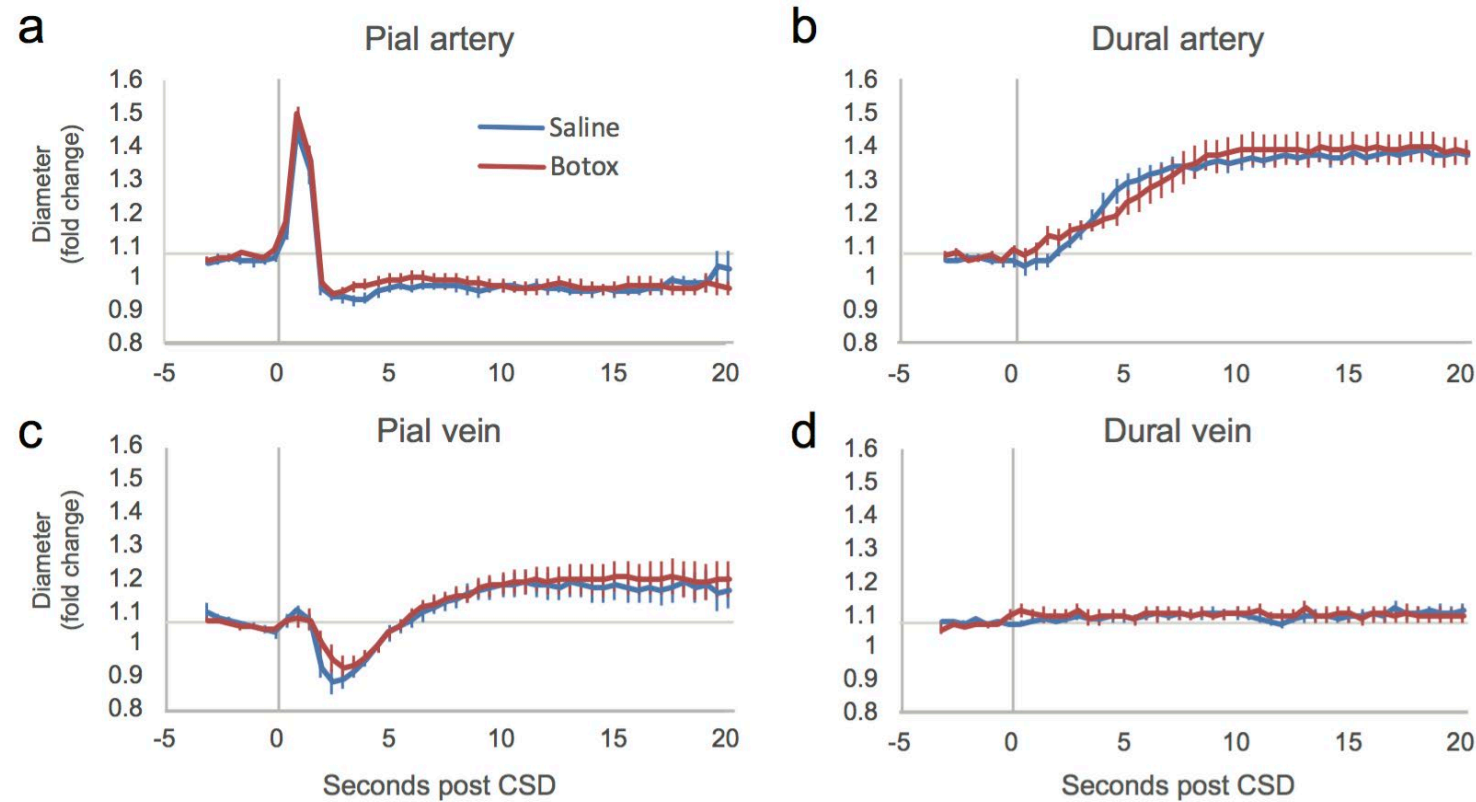
## 5. CSD-induced plasma protein extravasation is not affected by CGRP-mAb



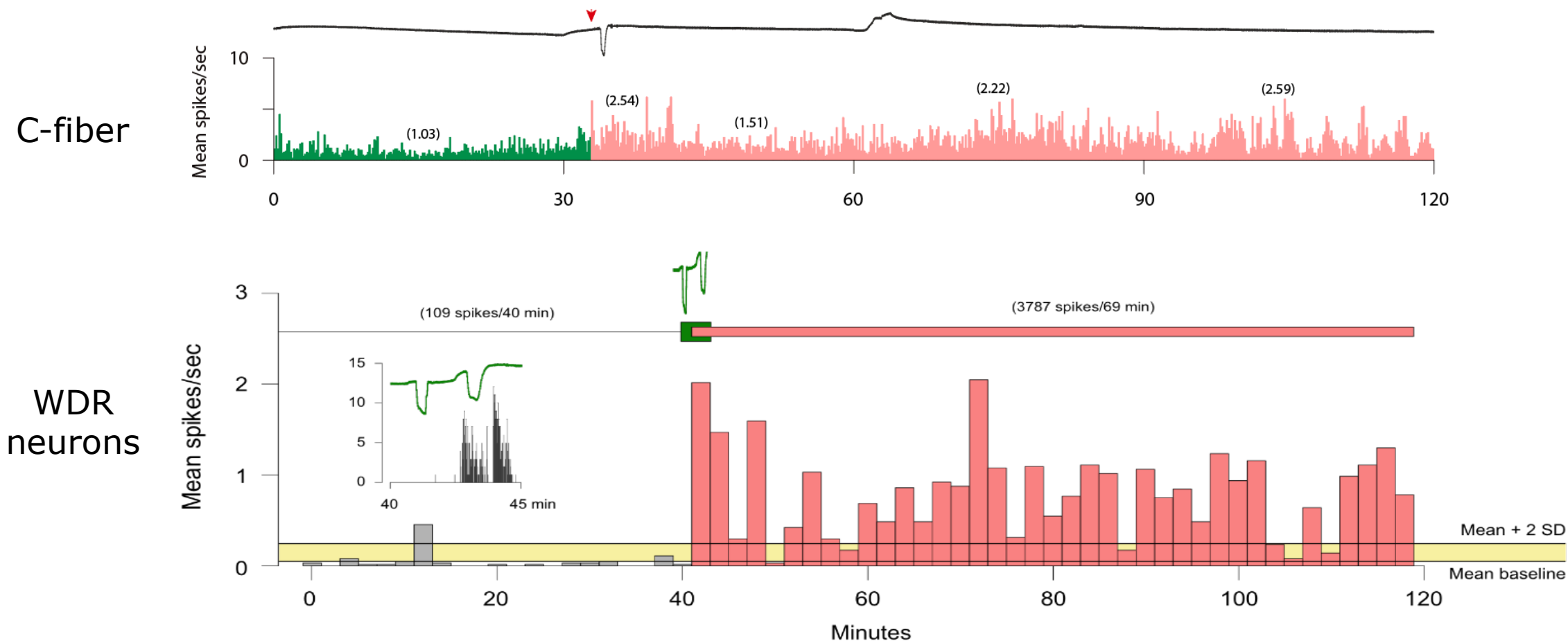
## 6. CGRP does not induce plasma protein extravasation



## OnabotulinumtoxinA does not affect vascular responses to CSD

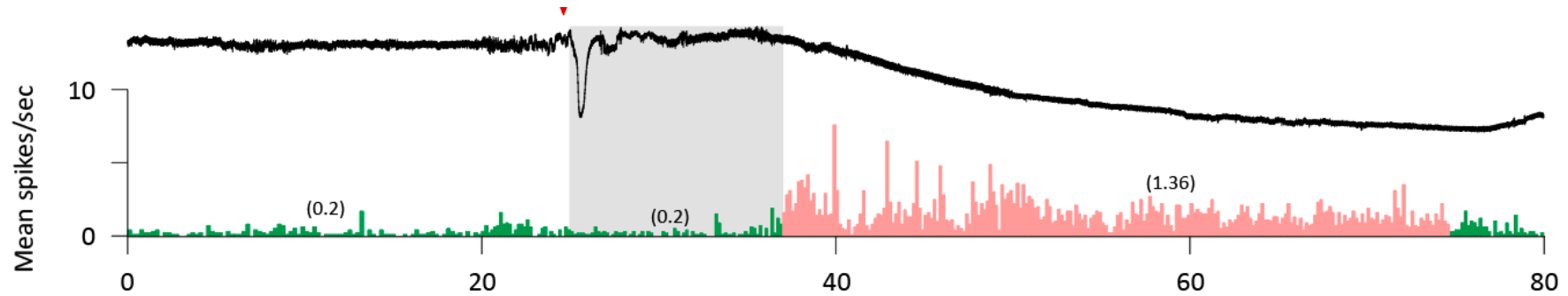


## CSD-induced immediate activation of C-class meningeal nociceptor and WDR trigeminovascular neuron

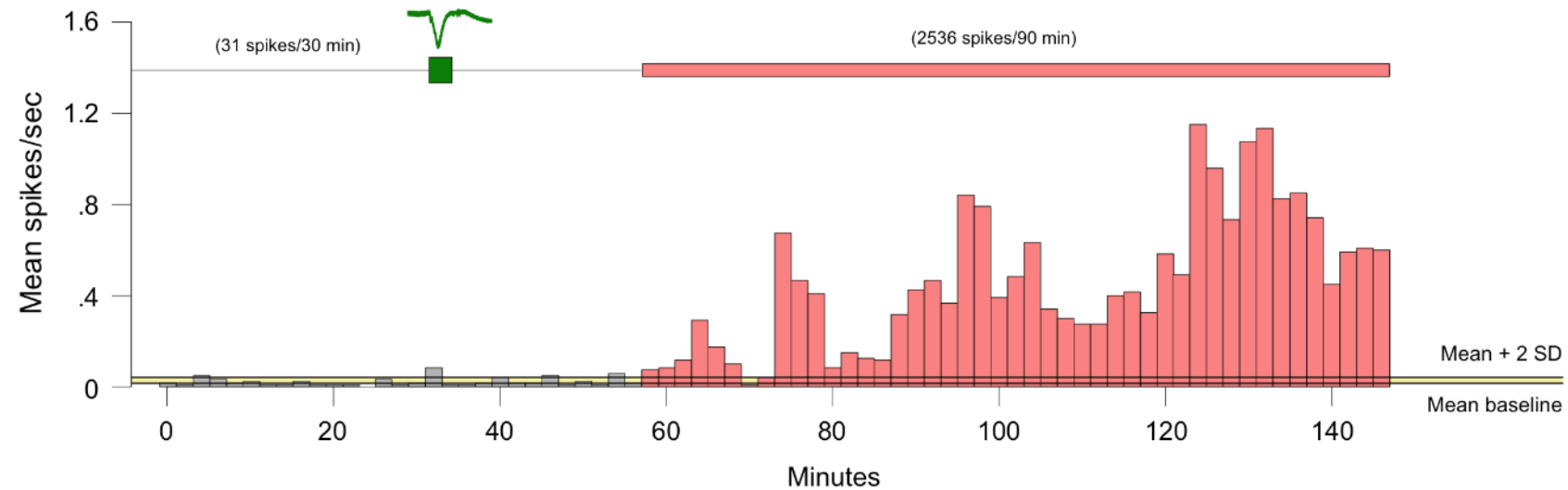


# CSD-induced delayed activation of A $\delta$ -meningeal nociceptor and high-threshold trigeminovascular neuron

A $\delta$ -fiber

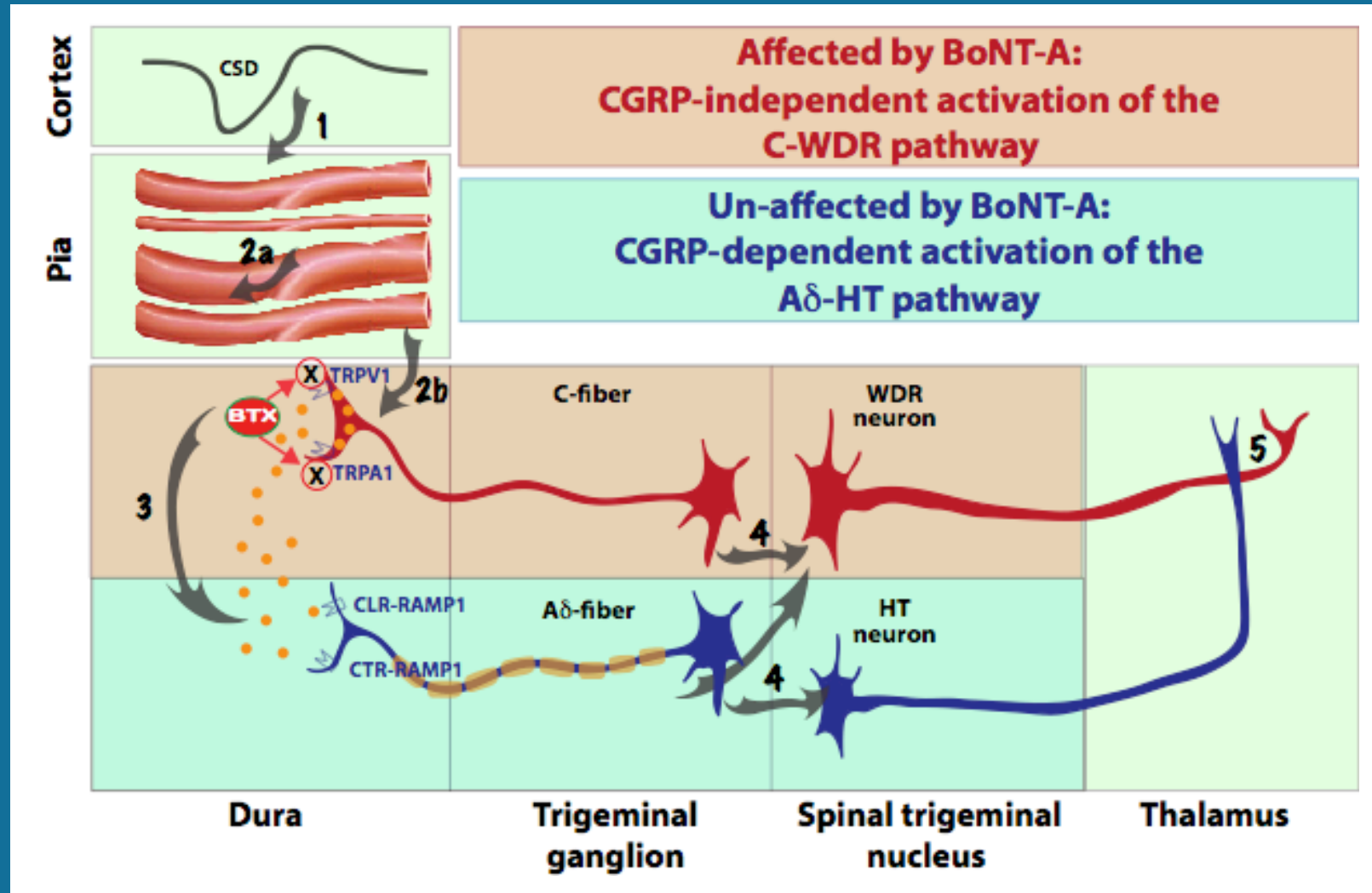


HT  
neurons



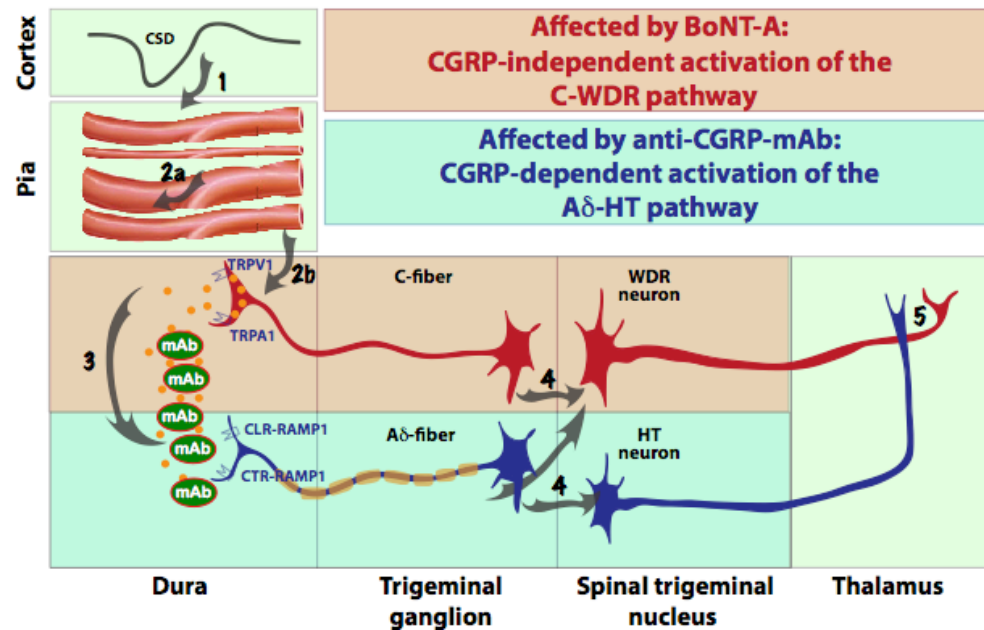
Zhang et al., J. Neuroscience 2010; Zhang et al., Ann. Neurol. 2011

# OnabotulinumtoxinA prevents activation and sensitization of C- but not A $\delta$ -fibers

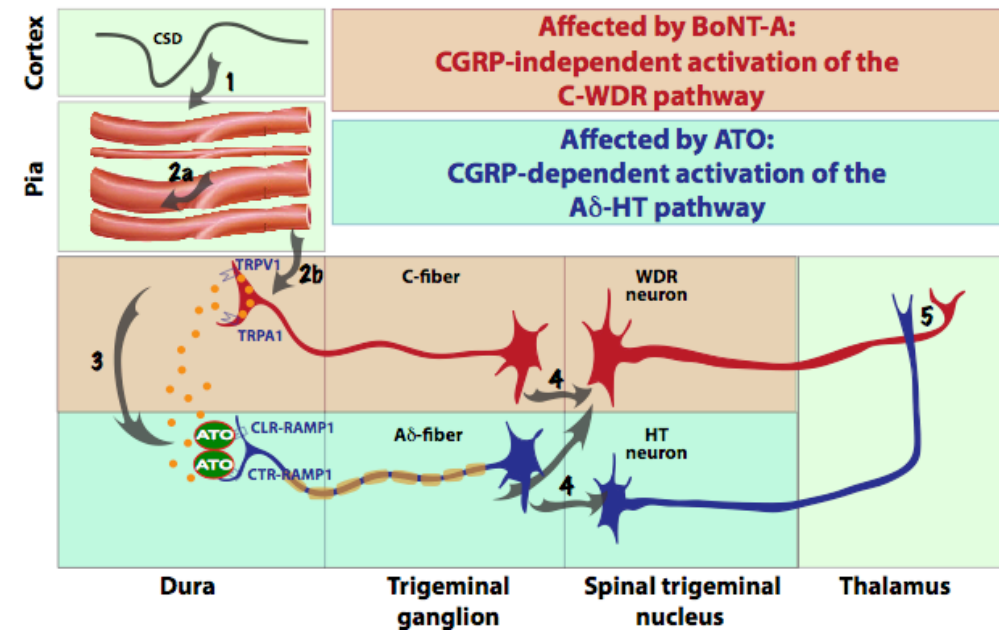


# CGRP monoclonal antibodies and small molecule CGRP receptor antagonists prevent activation of A $\delta$ - but not C-fibers

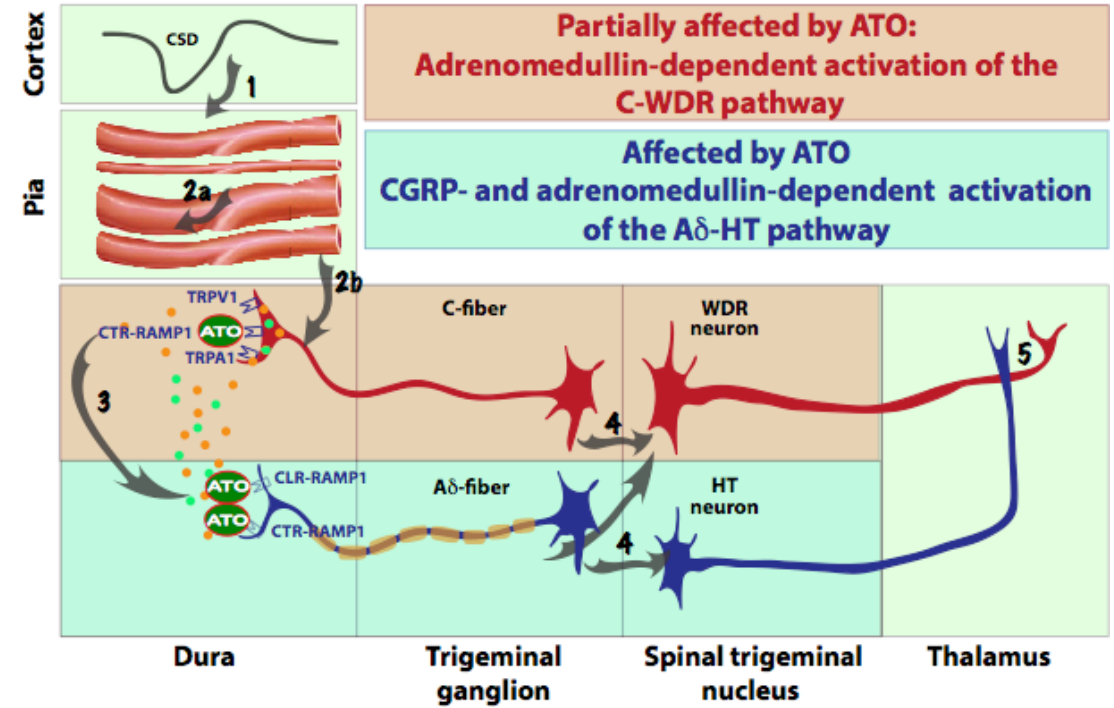
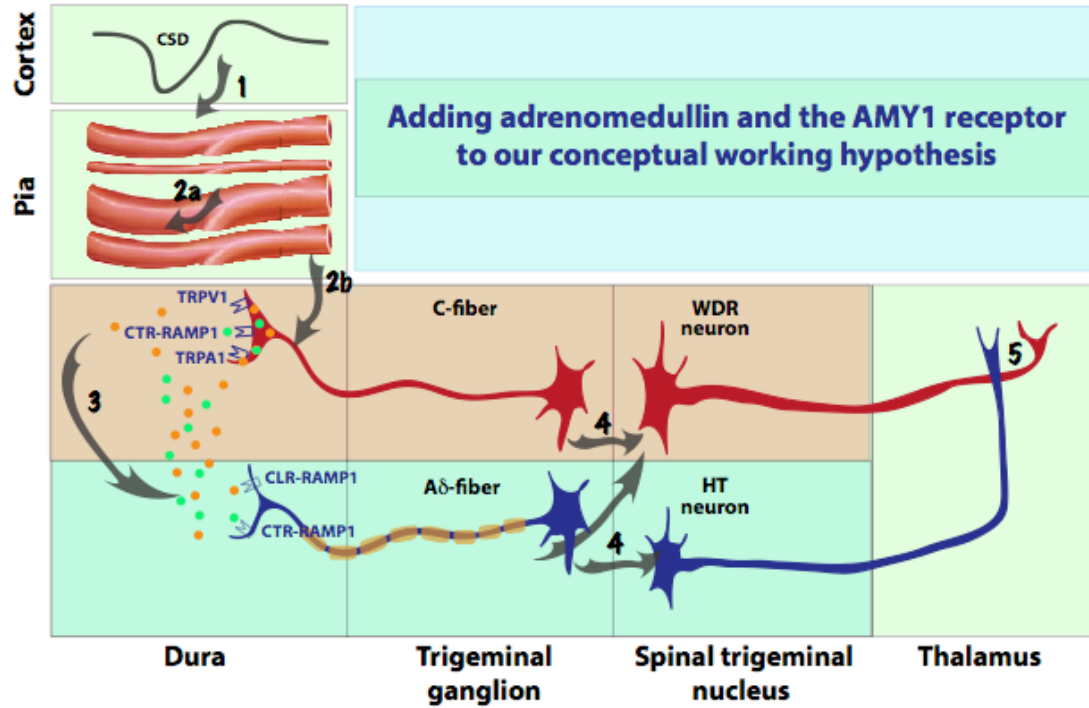
## Option 1. Drugs that neutralize the peptide



## Option 2. Drugs that block the receptor



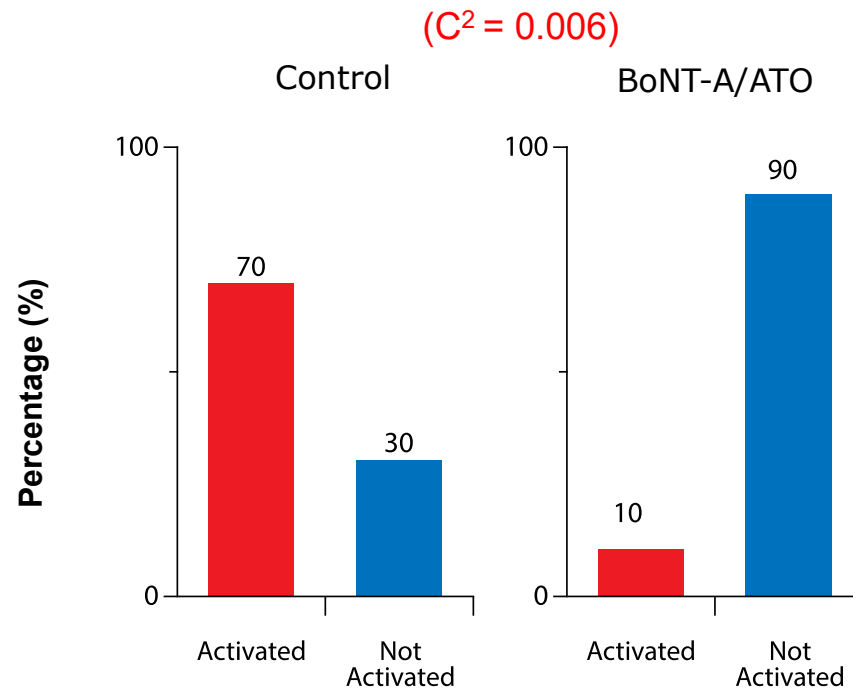
# Proposed mechanism for prevention of migraine by Atogepant



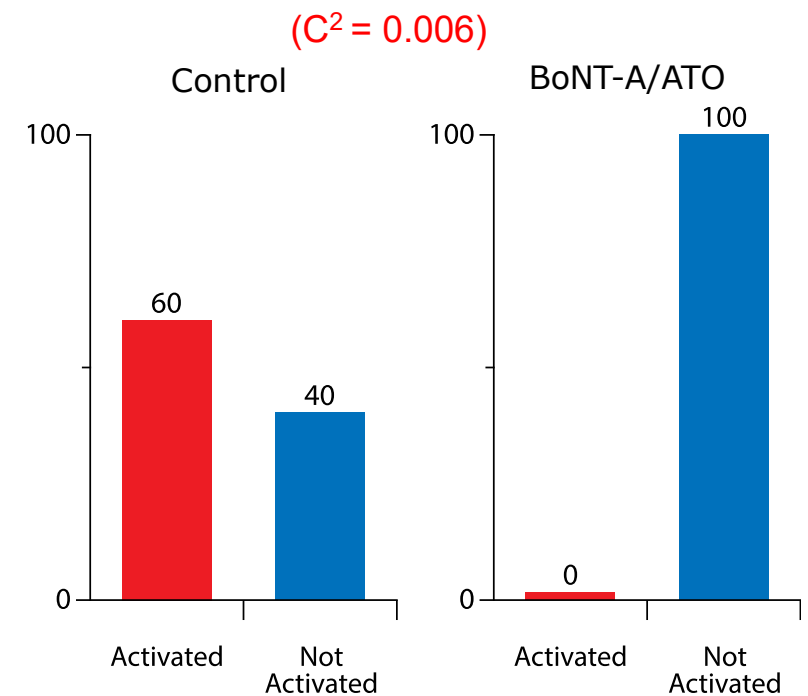
# Blocking A $\delta$ -fibers with onabotulinumtoxinA and C-fibers with atogepant attenuate activation and sensitization of HT and WDR neurons

## Incidence of activation by CSD

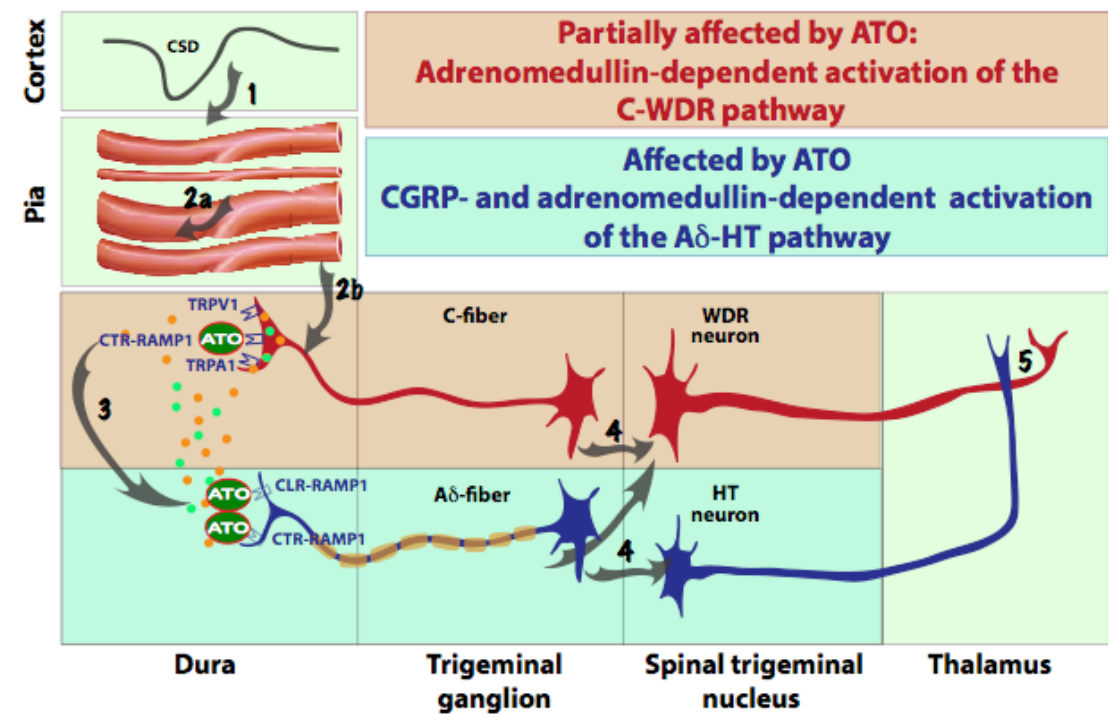
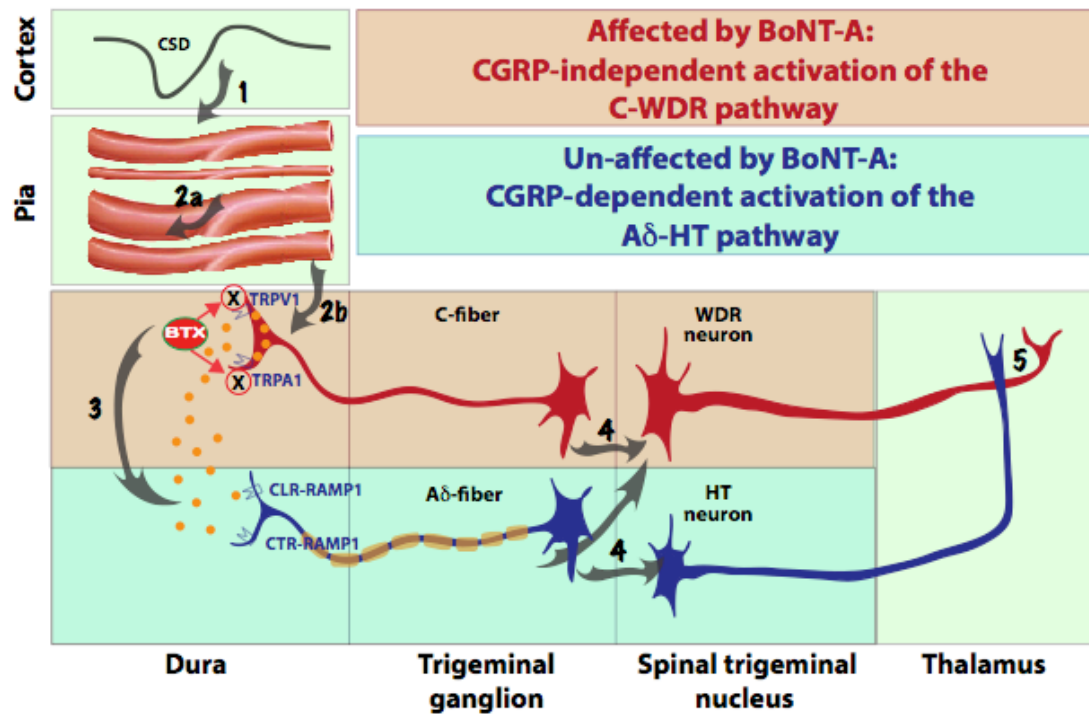
### HT Neurons



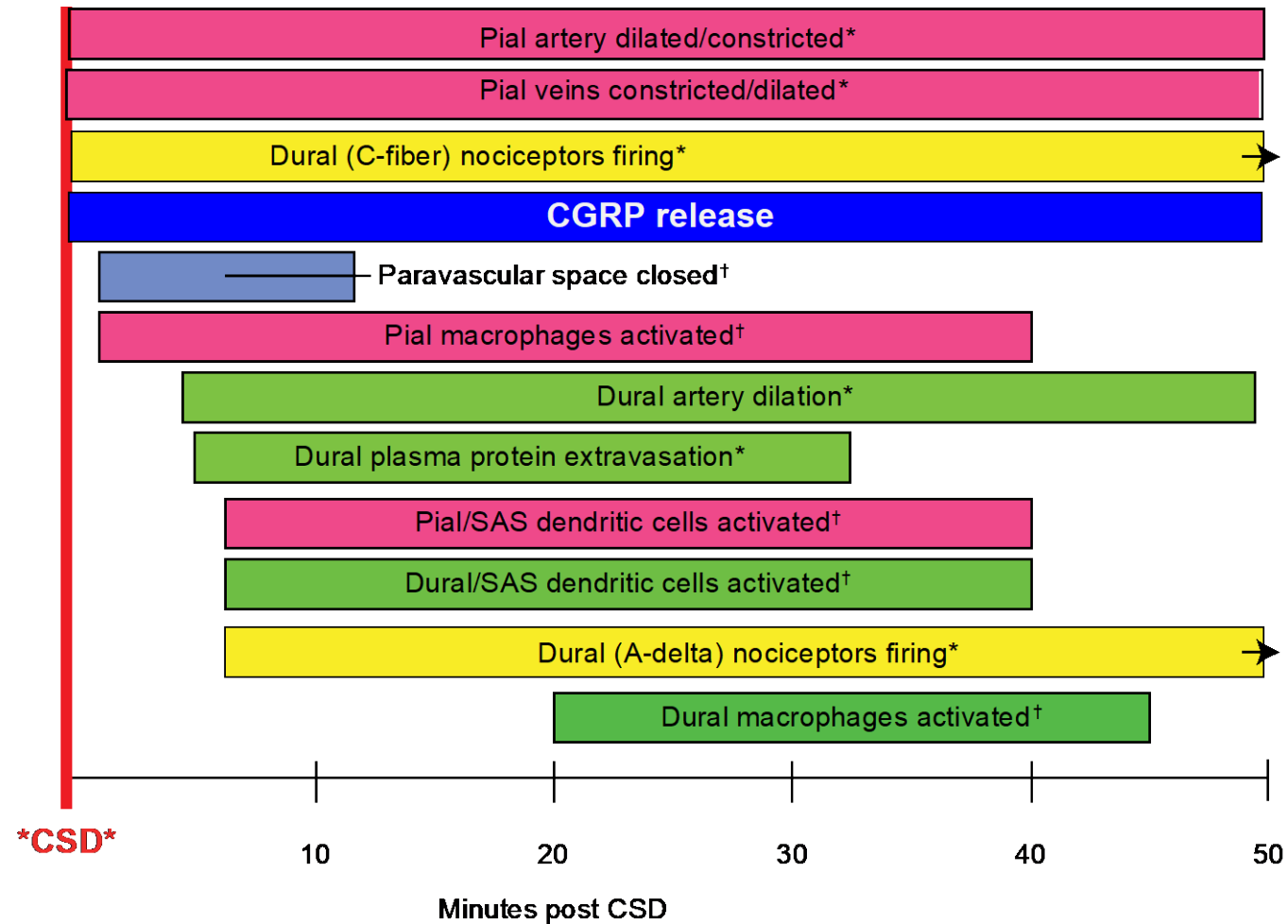
### WDR Neurons



# Scientific Rationale for combination therapy in migraine prevention



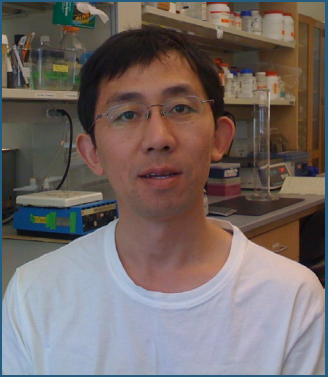
# Proposed sequence of events



## Opportunities:

- Centrally-acting drugs that reverse central sensitization
- Peripherally-acting drugs that attenuate activation of meningeal macrophages
- Peripherally-acting drugs that attenuate activation of meningeal dendritic cells
- Central, peripheral, or vascular acting drugs that prevent closure of the glymphatic system
- Drugs that prevent CSD (reduced impact on the nociceptors)
- Drugs that block activation of all nociceptors by all scenarios

# Acknowledgements



**XiChun Zhang**  
Neuroscience



**Andrew Strassman**  
Neuroscience



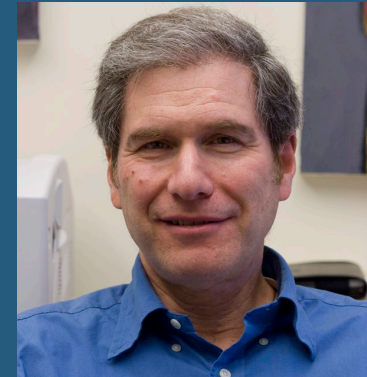
**Agustin Melo-Carrillo**  
Neuroscience



**Rodrigo Nosedá**  
Neurosciene



**Aaron Schain**  
Neuroscience



**Moshe Jakubowski**  
Neuroscience



**Vanesa Kainz**  
Neuroscience



**Jay Austen**  
Plastic surgery



**Lisa Gfrerer**  
Plastic surgery



**Carlton Perry**  
Plastic surgery



**Pamela Blake**  
Neurology



**Sait Ashina**  
Neurology



**Steve Papavassiliou**  
Neurosurgery



**Manoj Kumar**  
Bioinformatics

# Fundings

## **National Institutes of Neurological Disorders and Stroke:**

- |                   |             |       |
|-------------------|-------------|-------|
| 1. RO1- NS 010101 | (2023-2028) | PI    |
| 2. RO1-NS094198   | (2016-2022) | PI    |
| 3. R37-NS0796781  | (2012-2019) | PI    |
| 4. RO1-NS073977   | (2012-2018) | Co-PI |
| 5. RO1-NS095655   | (2015-2020) | Co-PI |
| 6. R21-NS091627   | (2017-2019) | Co-PI |

## **Industry Grants**

- |                             |             |    |
|-----------------------------|-------------|----|
| 1. Allergan/ AbbVie         | (2005-2025) | PI |
| 2. Teva Pharmaceutical      | (2016-2025) | PI |
| 3. Eli Lilly                | (2020-2025) |    |
| 4. Trigemina, LLC.          | (2016-2018) | PI |
| 5. Dr. Reddy's Laboratories | (2017-2020) | PI |