

# Does my mouse have a headache?

## Translational models of migraine

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NINDS Pain Consortium, May 31 2016



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SCHOOL OF MEDICINE

Headache & Neuro-Ophthalmology  
Department of Neurology

Translational Neuroscience  
Department of Neurology

# Outline

- Overview – what is migraine?
- Modeling migraine
  - The attack
  - The aura
- Future directions
  - Integrated models

# Features of migraine

## Premonitory

Euphoria/irritability  
Hunger/thirst  
Cognitive

## Aura

Visual  
Somatosensory  
Language  
Motor  
Vestibular/  
Cerebellar?  
Cognitive?  
Arousal?

## Attack

Pain  
Nausea/vomiting  
Conjunctival injection/  
tearing/rhinorrhea  
Flushing/sweating/pallor  
Photophobia  
Phonophobia  
Allodynia

## Postdrome (and Rebound)

Pain  
Photophobia  
Phonophobia  
Allodynia

## Interictal (Modulation Chronification Recovery)

Hormonal  
(Menstruation  
Pregnancy  
Menopause)  
Stress/Affective  
(Anxiety  
Depression)

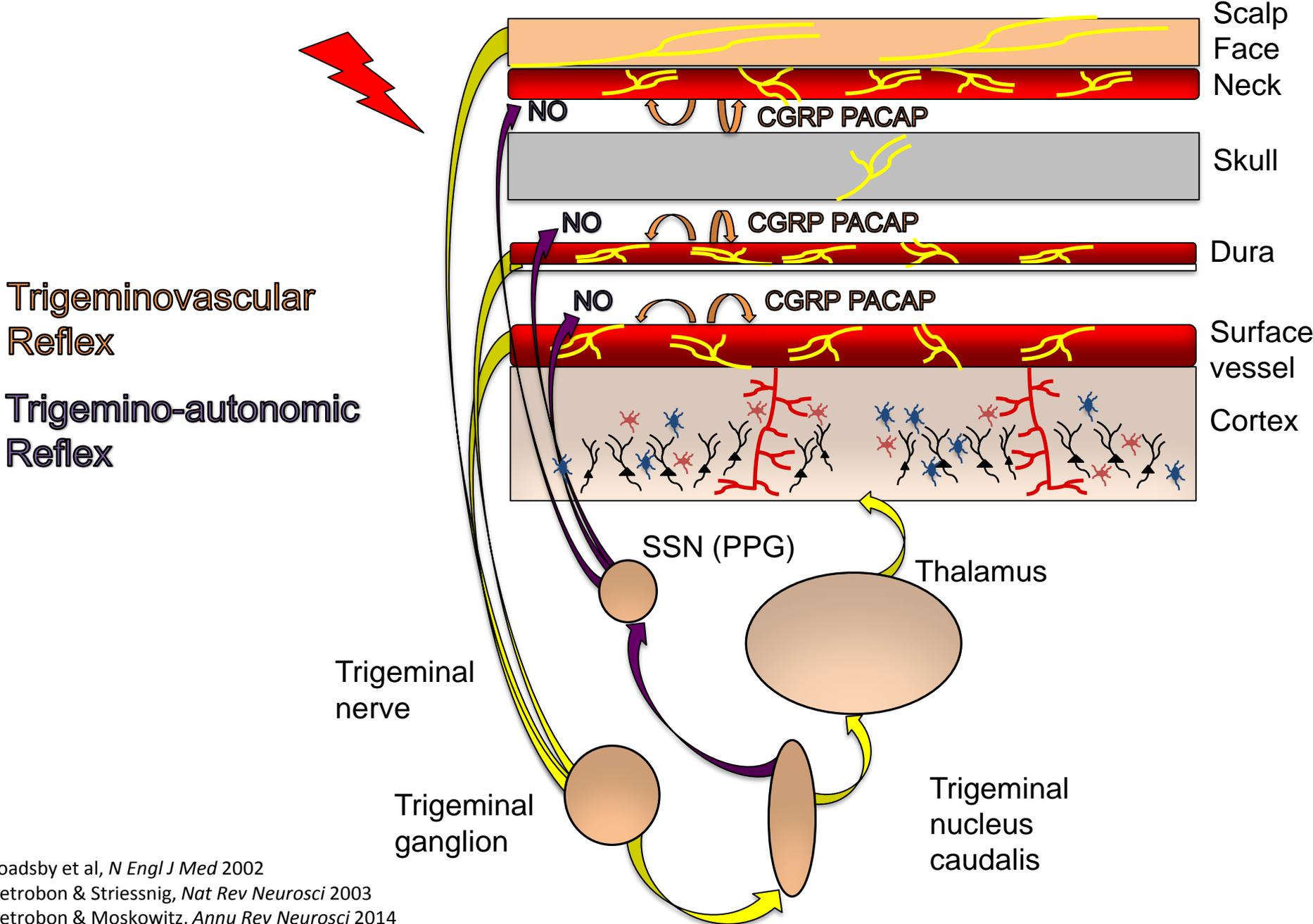
Comorbidities  
Medication  
overuse  
Trauma  
Infection

Throbbing  
unilateral  
pain  
Perspiration  
Flushing  
Tearing



Phonophobia  
Photophobia  
Speaks in low voice  
to avoid aggravating  
pain

# What makes a migraine attack?



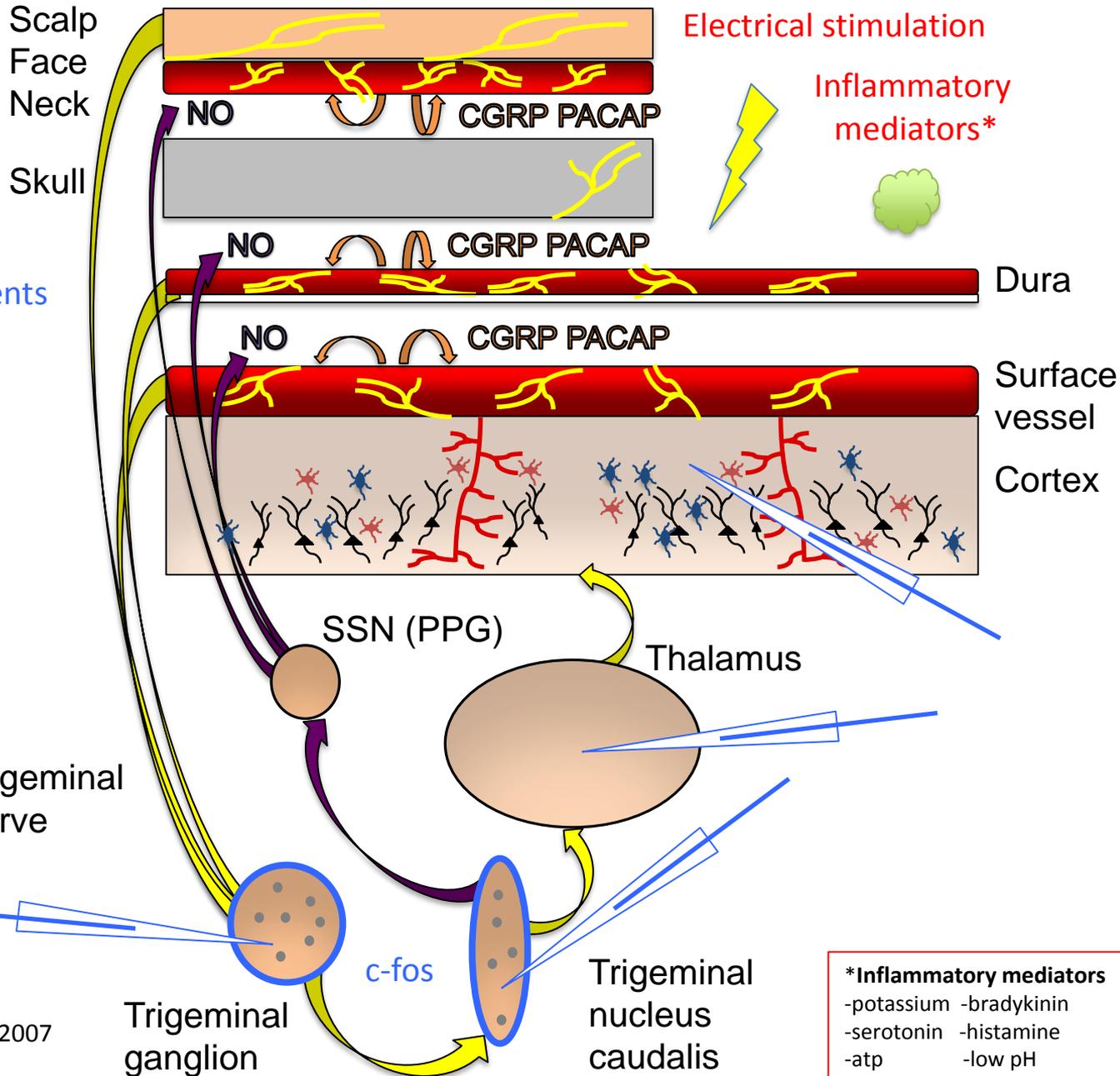
Goadsby et al, *N Engl J Med* 2002  
 Pietrobon & Striessnig, *Nat Rev Neurosci* 2003  
 Pietrobon & Moskowitz, *Annu Rev Neurosci* 2014

# Trigeminovascular Physiology, Pharmacology

**Sensory stimulation**  
 -mechanical  
 -thermal  
 -electrical

**Imaging, perfusion measurements**  
 -laser doppler flowmetry  
 -intravital microscopy  
 -two photon microscopy

**Electrophysiology**  
 -extracellular recordings  
 -whole cell recordings



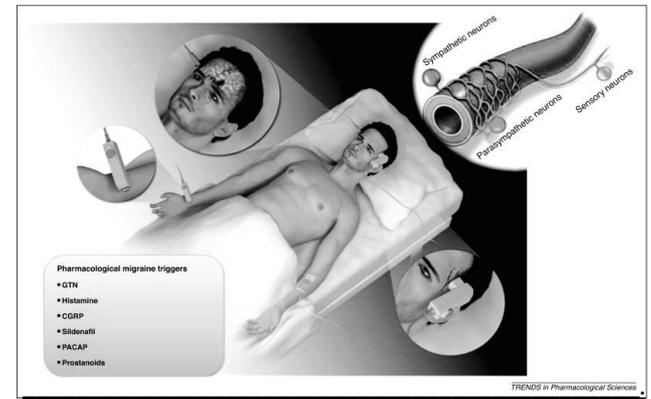
**\*Inflammatory mediators**  
 -potassium -bradykinin  
 -serotonin -histamine  
 -atp -low pH

Goadsby & Edvinsson *Ann Neurol* 1993  
 Strassman et al *Nature* 1996  
 Cumberbatch MJ *Br J Pharmacol* 1999  
 Oshinsky & Gomonchareonsiri *Headache* 2007  
 Nosedá Burstein *Nat Neurosci* 2010

# Modeling migraine behavior

## Migraine-inducing substances in humans

- nitroglycerin (NTG; NO donor)
- CGRP
- PACAP
- migraine in migraineurs; not in controls
- triptan sensitive

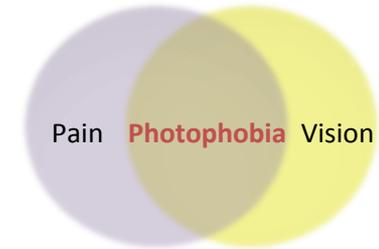
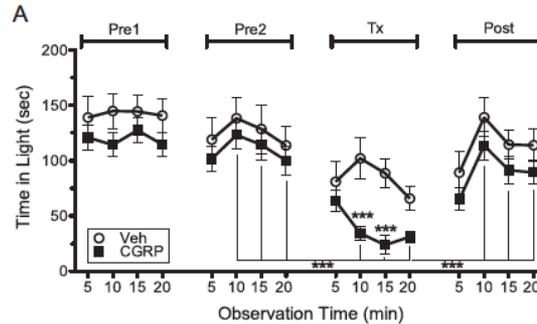
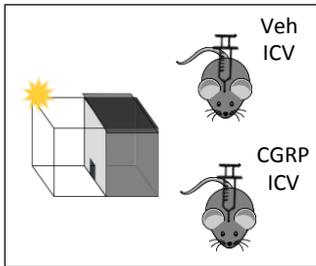


Iversen and Olesen *Cephalalgia* 1996

Olesen and Ashina *Trends Pharmacol Sci* 2011

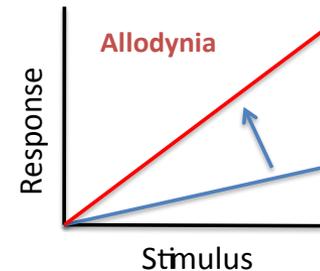
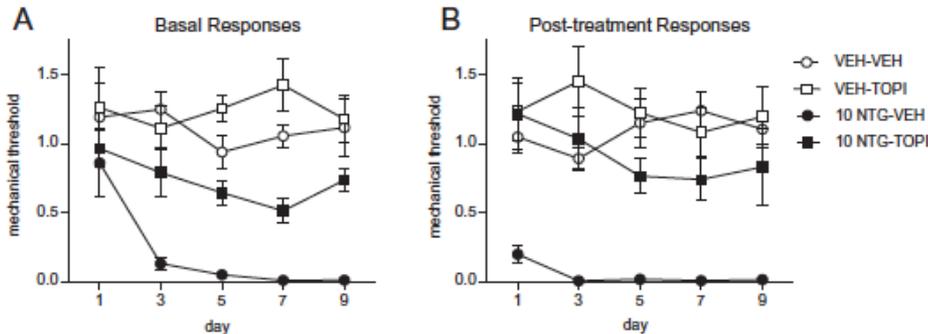
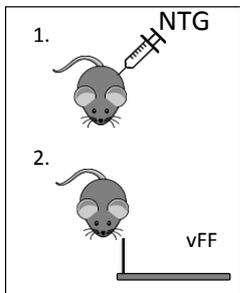
## Migraine analog behavior

### Acute CGRP ICV reduces time spent in light



Kaiser et al *J Neurosci* 2012

### Chronic NTG IP reduces mechanical thresholds, topiramate sensitive



Pradhan et al *Pain* 2014

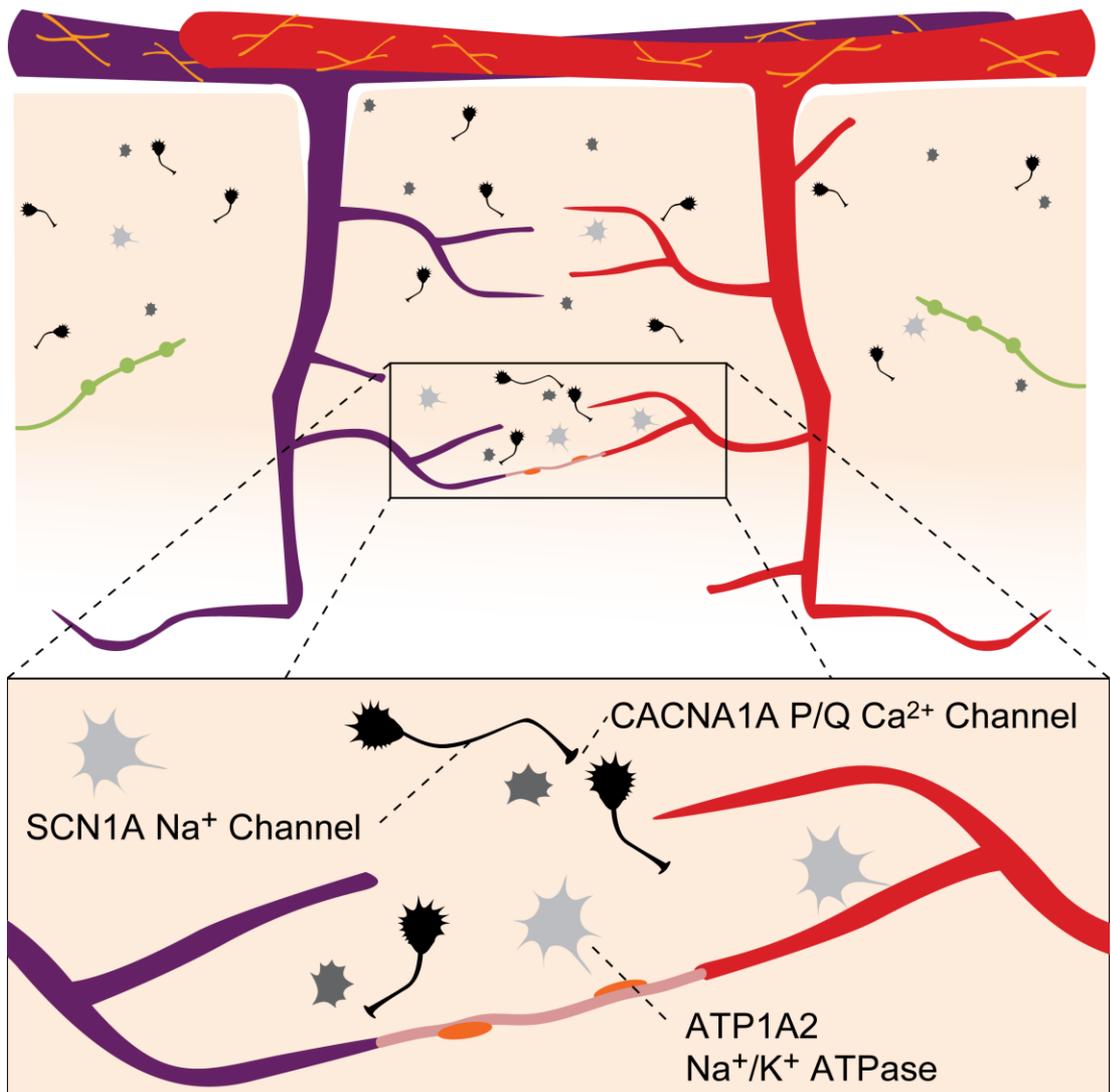
# Migraine genetics

## Familial migraine

TRESK  
 Lafraniere et al Nat Med 2010  
 Casein kinase 1 delta  
 Brennan et al Sci Transl Med 2013

## Susceptibility loci (GWAS)

PRDM16  
 TRPM8  
 LRP1  
 ZNF555  
 GRM7  
 MEF2D  
 ADARB2  
 ASTN2  
 TGFBR2  
 PHACTR1  
 HTR7  
 Review:  
 Schurks J Headache Pain 2012



## Familial hemiplegic migraine

DeFusco et al. *Nat Genet* 2003

Van den Maagdenberg et al. *Neuron* 2004

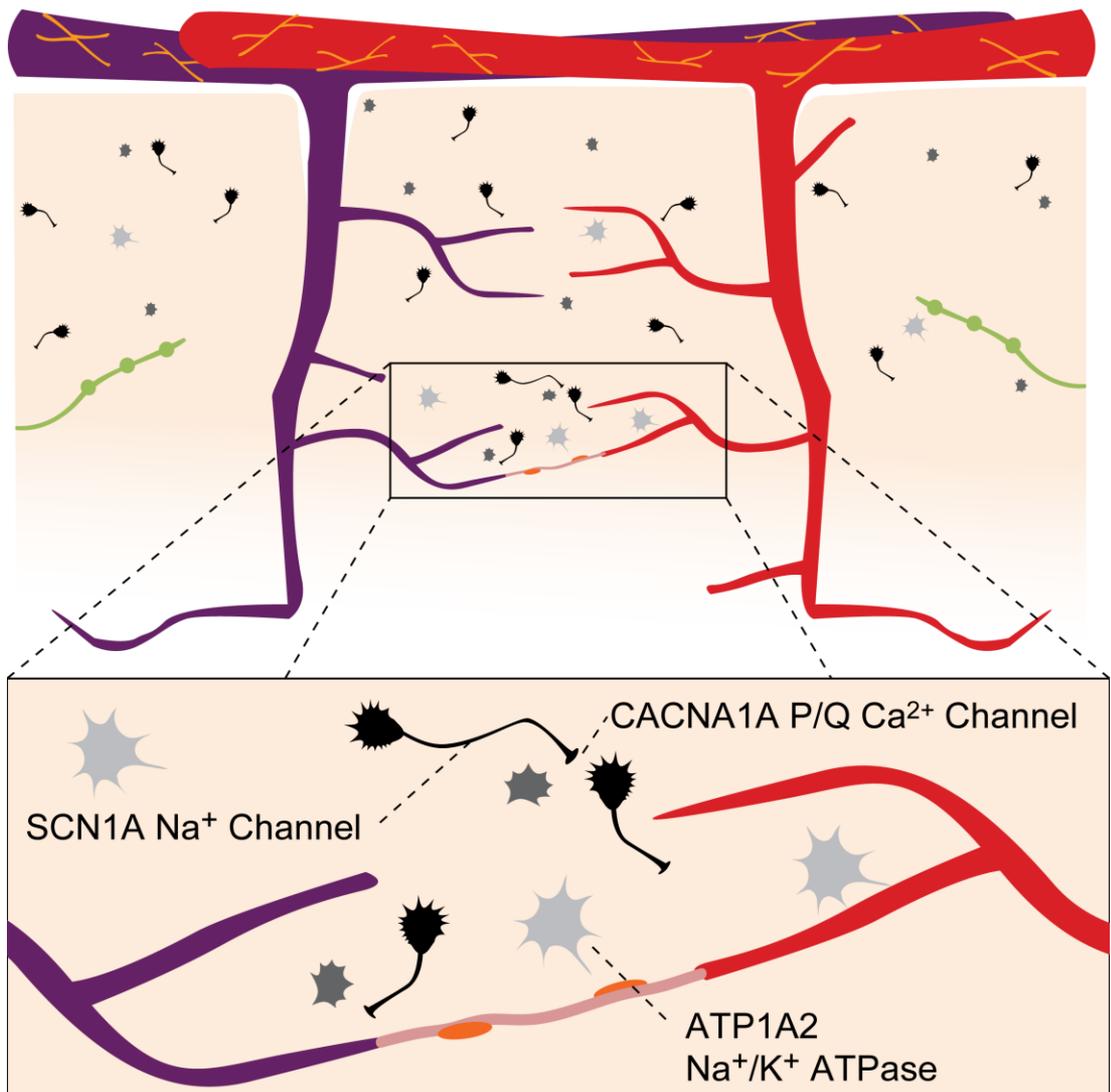
Dichgans et al. *Lancet* 2005

# Migraine genetics

## Migraine mouse models

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 Lafraniere et al Nat Med 2010  
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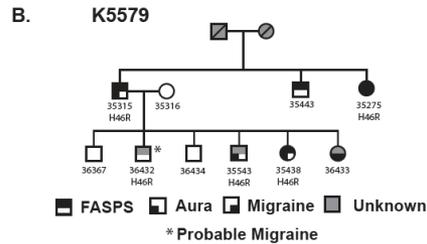
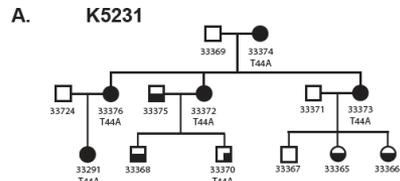
Van den Maagdenberg et al. *Neuron* 2004

Dichgans et al. *Lancet* 2005

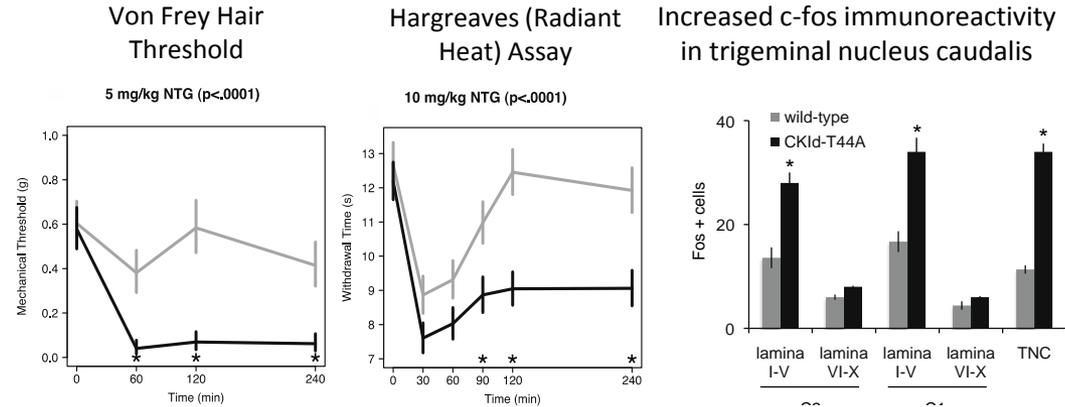
# Casein kinase 1 delta (CK1δ) mouse

## Migraine relevant nociception in CK1δ mice

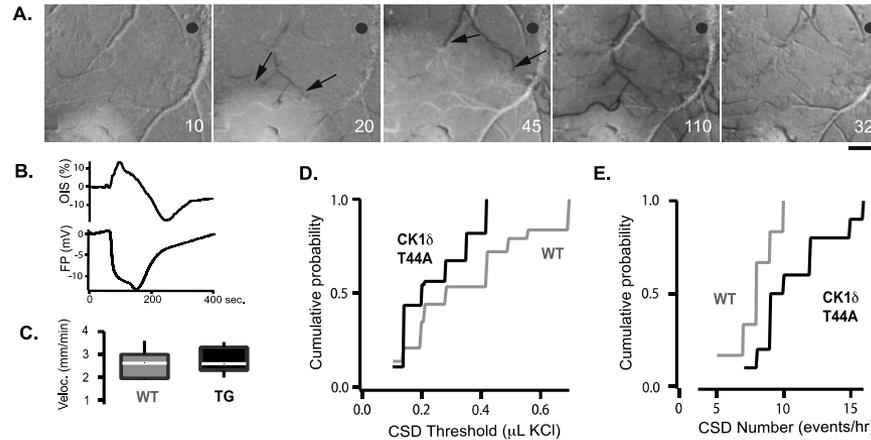
Casein kinase 1 delta (CK1δ) mutations in two families with familial migraine and advanced sleep phase



Alleles not present in >2600 control chromosomes  
 -thousand genomes database  
 -CGI 60 whole genomes  
 -250 additional controls



## Increased CSD susceptibility and arterial dilation in T44A CK1δ transgenics



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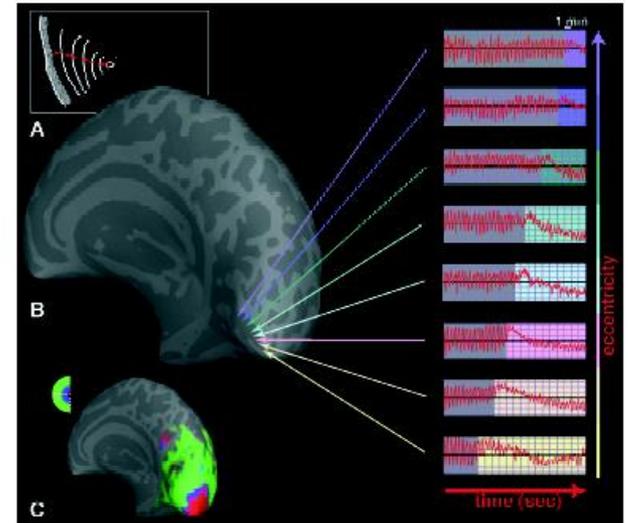
Phonophobia  
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pain

# Cortical spreading depression and migraine aura

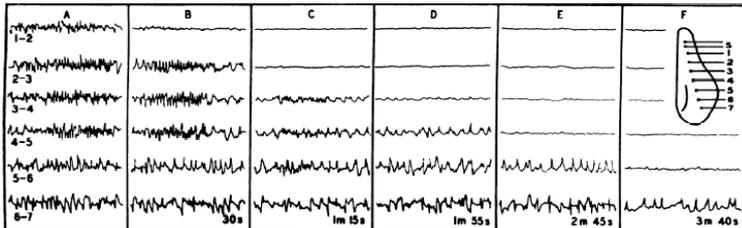


"[scotomata] sketched at brief intervals during an attack suggest that a wave of intense excitation is propagated at a rate of about 3 mm per minute across the visual cortex. This wave is followed by complete inhibition of activity..."

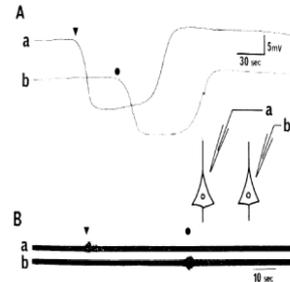
Lashley KS. *Arch Neurol Psychiatry* 1941



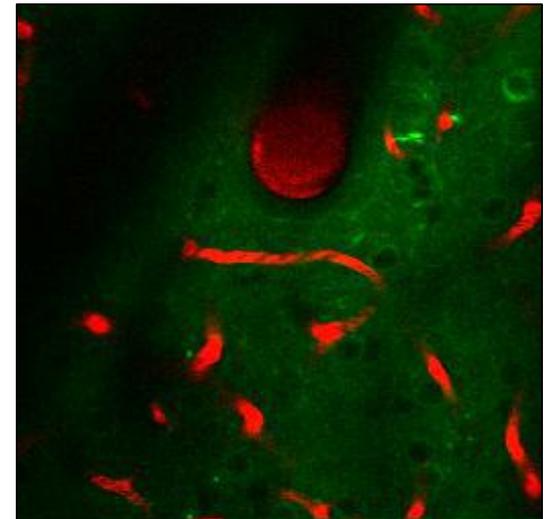
Hadjikhani N, *Proc Nat Acad Sci* 2001



Leao A.A.P., *J Neurophysiol* 1944

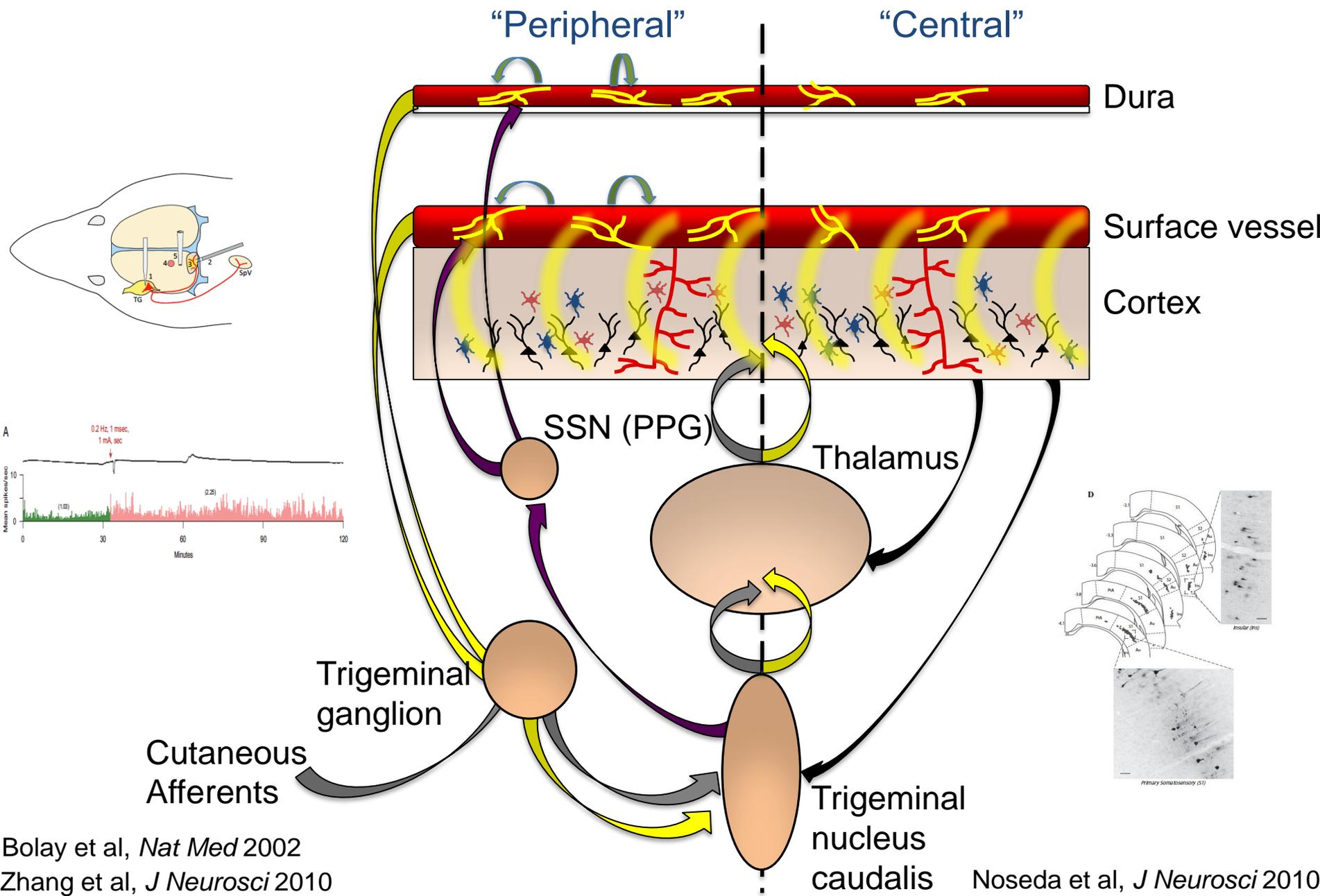


Sugaya E  
*J Neurophysiol* 1975



GCaMP6F, Tx Red Dextran  
210x210um, 2.96Hz

# How does CSD cause pain?



Bolay et al, *Nat Med* 2002  
 Zhang et al, *J Neurosci* 2010

Nosedá et al, *J Neurosci* 2010

# CSD and sensory plasticity

*A network disrupted by spreading depression*



Jeremy Theriot

Possible consequences  
for migraine

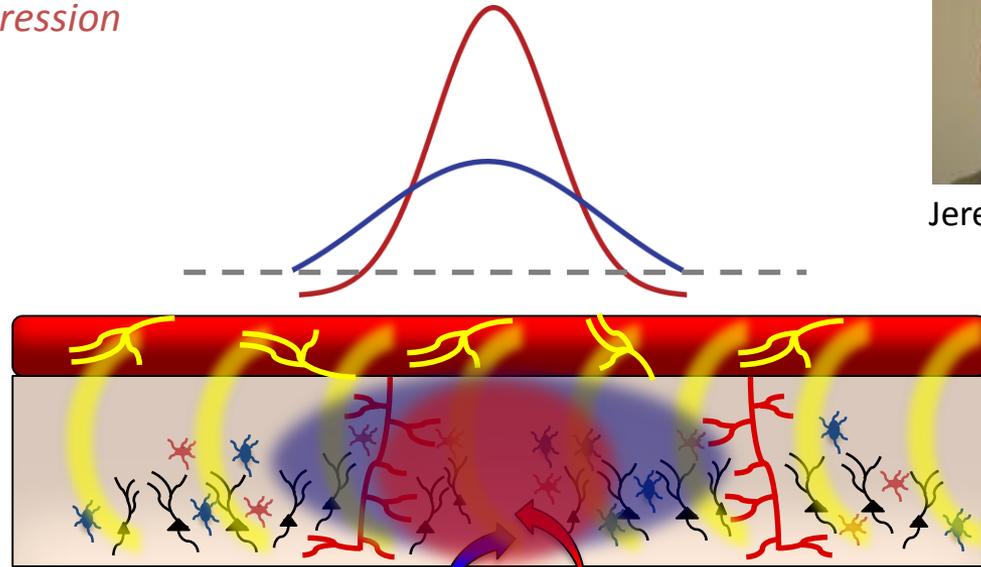
*Direct cortical effects*



Phonophobia

Photophobia

Allodynia

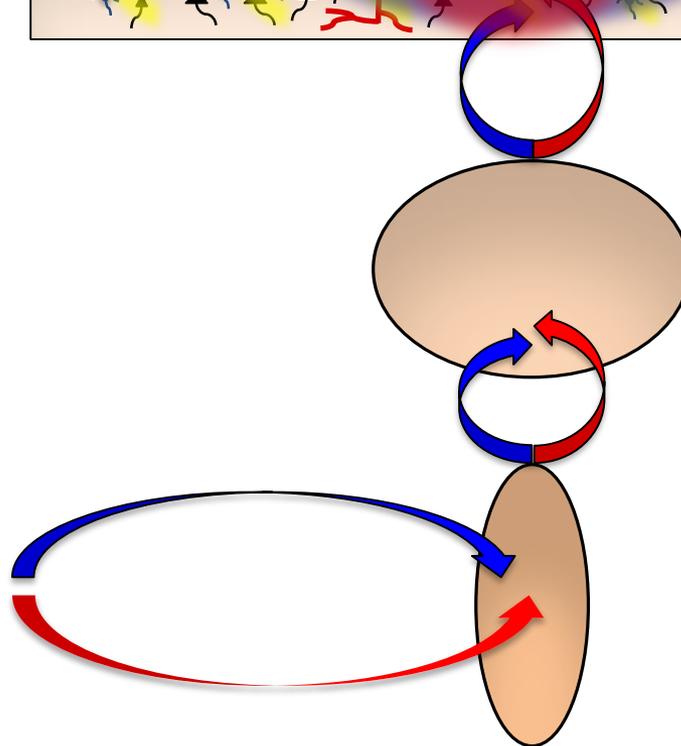


*Cortical modulation of  
lower structures*

- Pain
- Photophobia
- Phonophobia
- Allodynia

*A mechanism  
for migraine  
chronification?*

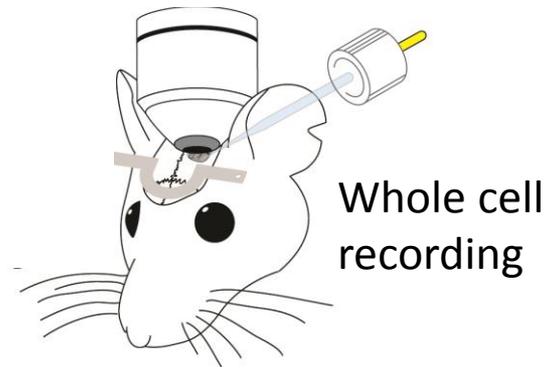
Sensory  
Afferents



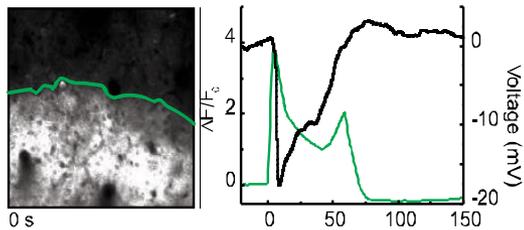
Pre-SD  
Post-SD

# Effects of CSD at cellular resolution *in vivo*

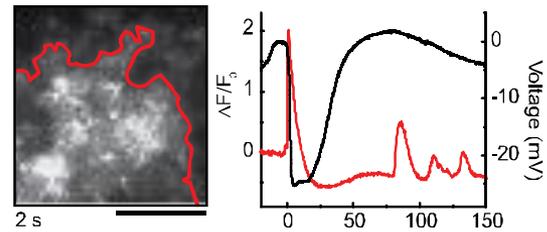
## Two photon microscopy



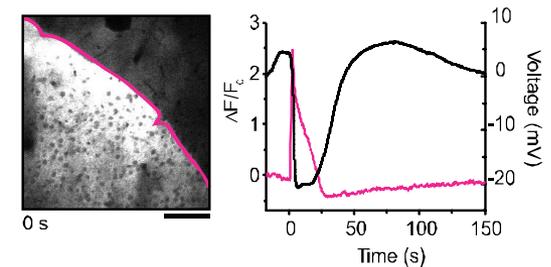
### Neuronal calcium and field potential



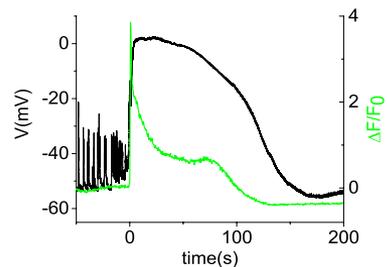
### Astrocyte calcium and field potential



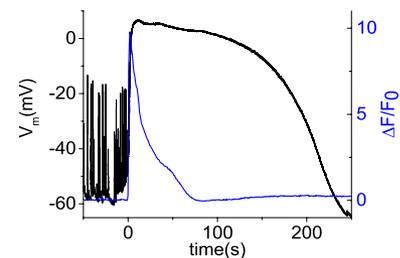
### Extracellular glutamate and f.p.



### Neuronal membrane potential and Neuronal calcium

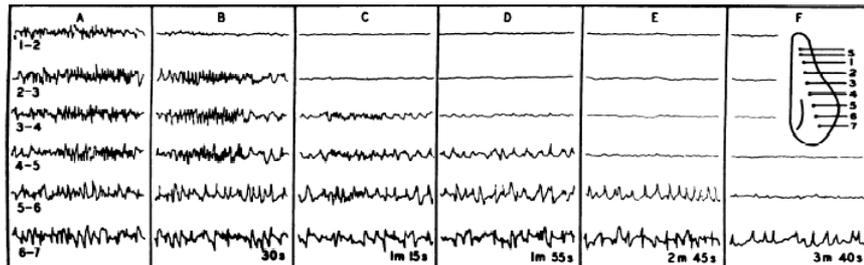


### Neuronal membrane potential and glutamate



# Why is it called cortical spreading *depression*?

*What causes the cortical silencing after SD*

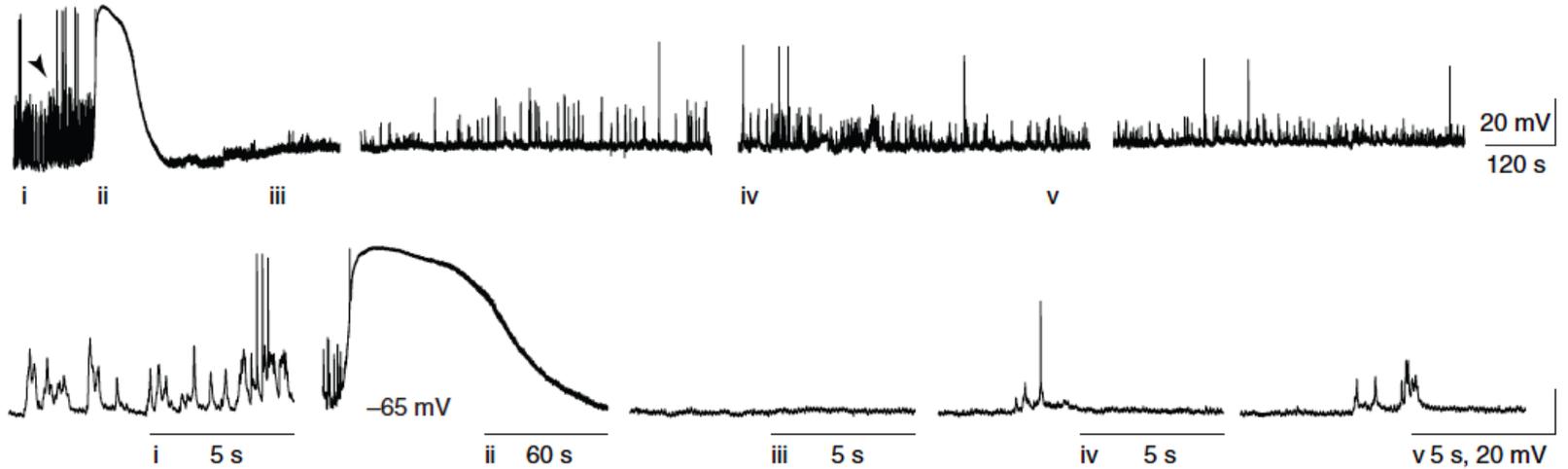
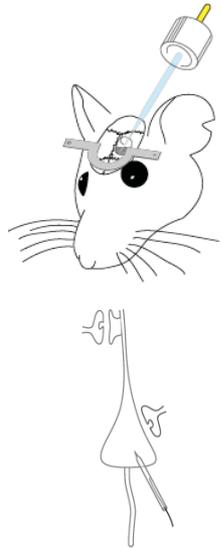


Leao A.A.P., *J Neurophysiol* 1944

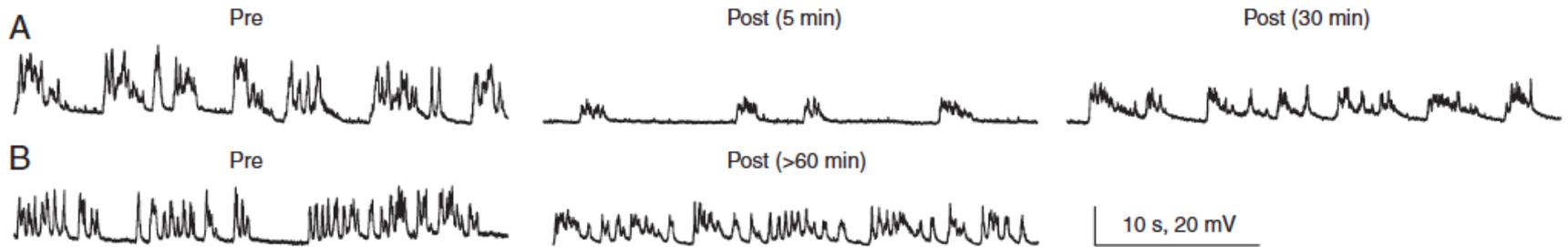


Punam Sawant

*In vivo* whole-cell recordings (current clamp)  
layer 2/3 pyramidal neurons of somatosensory cortex



Suppression of spontaneous synaptic activity after SD  
Changes last over an hour

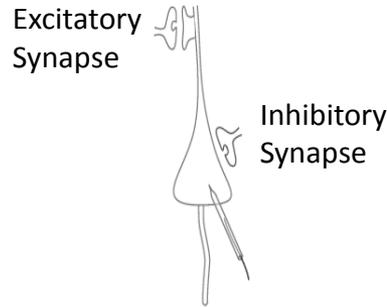


# Suppression of synaptic activity after SD

## Ratio of excitation/inhibition shifted toward inhibition

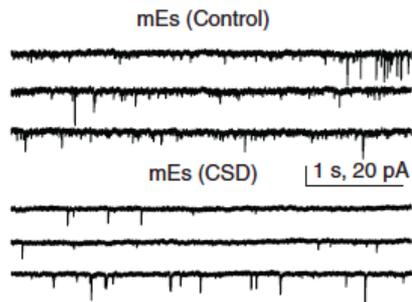


Pratyush  
Suryavanshi



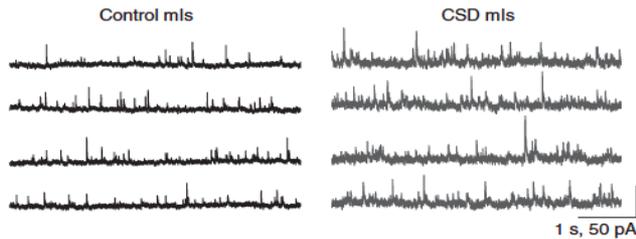
### Excitatory postsynaptic currents

*Miniature (AP independent)*



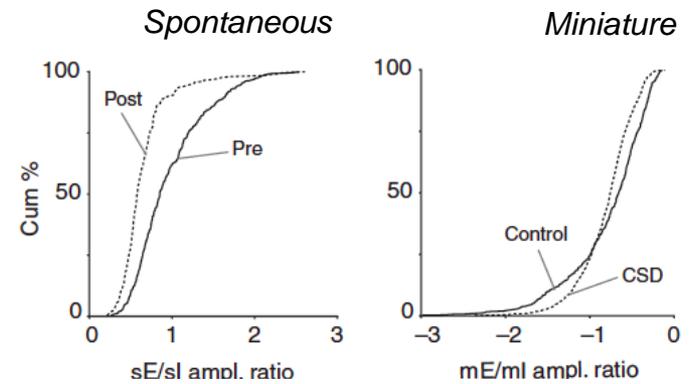
### Inhibitory postsynaptic currents

*Miniature (AP independent)*

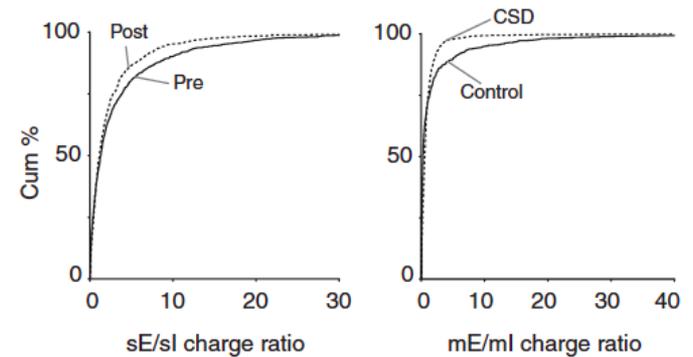


< frequency, > amplitude

### Amplitude ratio

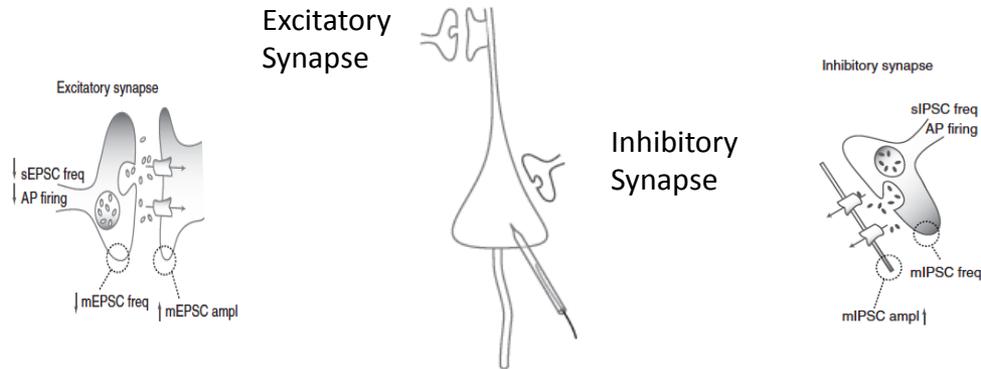


### Charge ratio

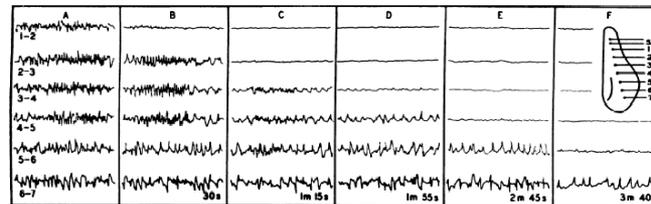


# Summary

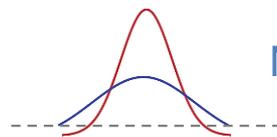
## Shift in synaptic balance toward inhibition after SD



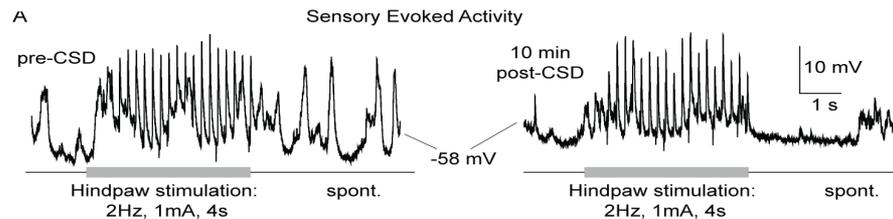
## An explanation for the depression in spontaneous cortical activity



Leao A.A.P., *J Neurophysiol* 1944

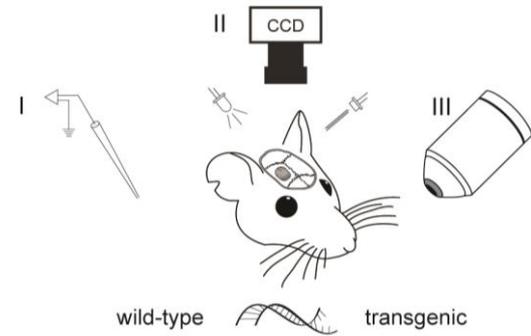


## Next: sensory evoked responses

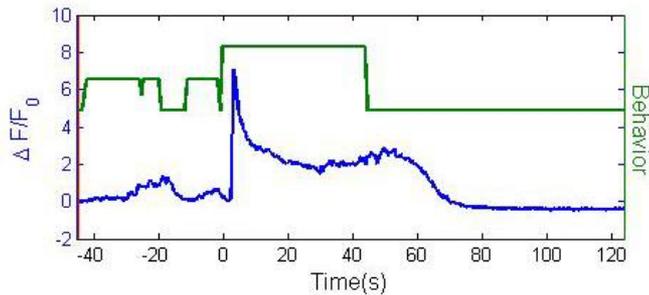


# Toward integrated, cellular resolution models

## Genetics, physiology, behavior

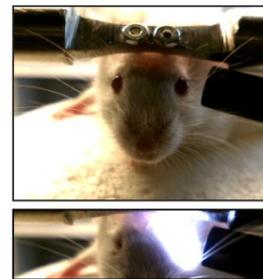


### Awake CSD under two photon

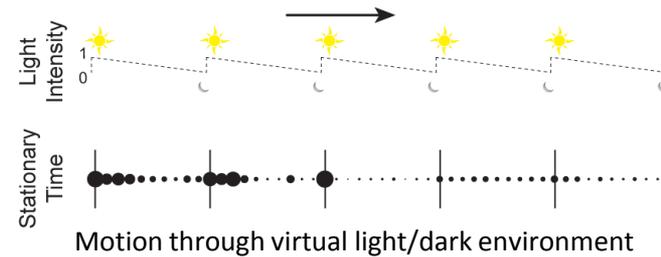
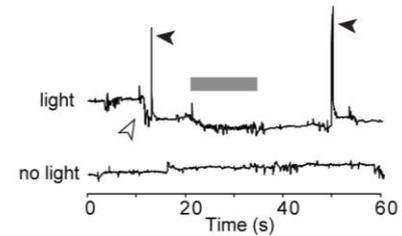


**Behavior:** down=quiet, middle=running, grooming, up=motor disruptions  
**Calcium:** GCaMP5G-synapsin

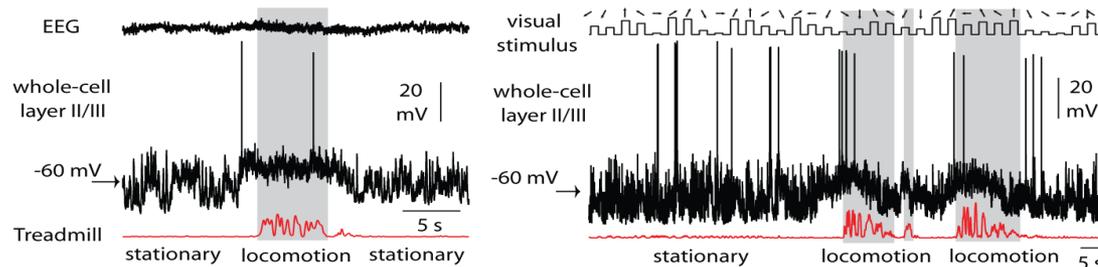
### Dynamic head fixed photophobia model



#### Automated blink detection



### Awake *in vivo* whole cell, visual stimulation



# Conclusions

Does my mouse have a headache?

Trigeminovascular physiology, pharmacology

Migraine relevant stimuli, behavior

Genetic models

Cortical spreading depression

Non-pain measure

Drives pain and other circuit alterations

Toward integrated models

Physiology, behavior, genetics

Cellular resolution

# Acknowledgements!

## Lab:

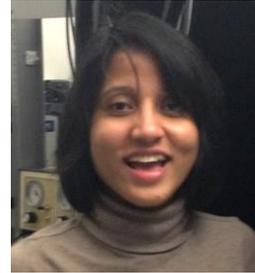
Jeremy Theriot  
Punam Sawant  
Dan Kaufmann  
Kyoungsook Park  
Pratyush Suryavanshi  
Patrick Parker  
Natalie Rea  
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Jed Hartings  
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Huaxiong Huang



Jeremy Theriot



Punam Sawant



Pratyush  
Suryavanshi

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