UNIVERSITÉ LAVAL

Institut universitaire en santé mentale de Québec

# Microglia gating pain… and beyond

Université Laval, Québec, Canada
Yves De Koninck

**Dominic Boudreau**
**Jeffrey Coull**
**Annie Castonguay**
**Nicolas Doyon**
**Francesco Ferrini**
**Florence Keller**
**Sophie Laffray**
**Louis-Etienne Lorenzo**

**Martin Beaulieu**
**Thomas Del'Guidice**
**Cathy Cahill**
**Anna Taylor**
**Alexandra Mattioli**
**Paul De Koninck**
**Jeffrey Mogil**
**Serge Rivest**
**Michael W. Salter**
**Simon Beggs**
**Tuan Trang**
**Ipek Yalcin**
**Ji Zhang**

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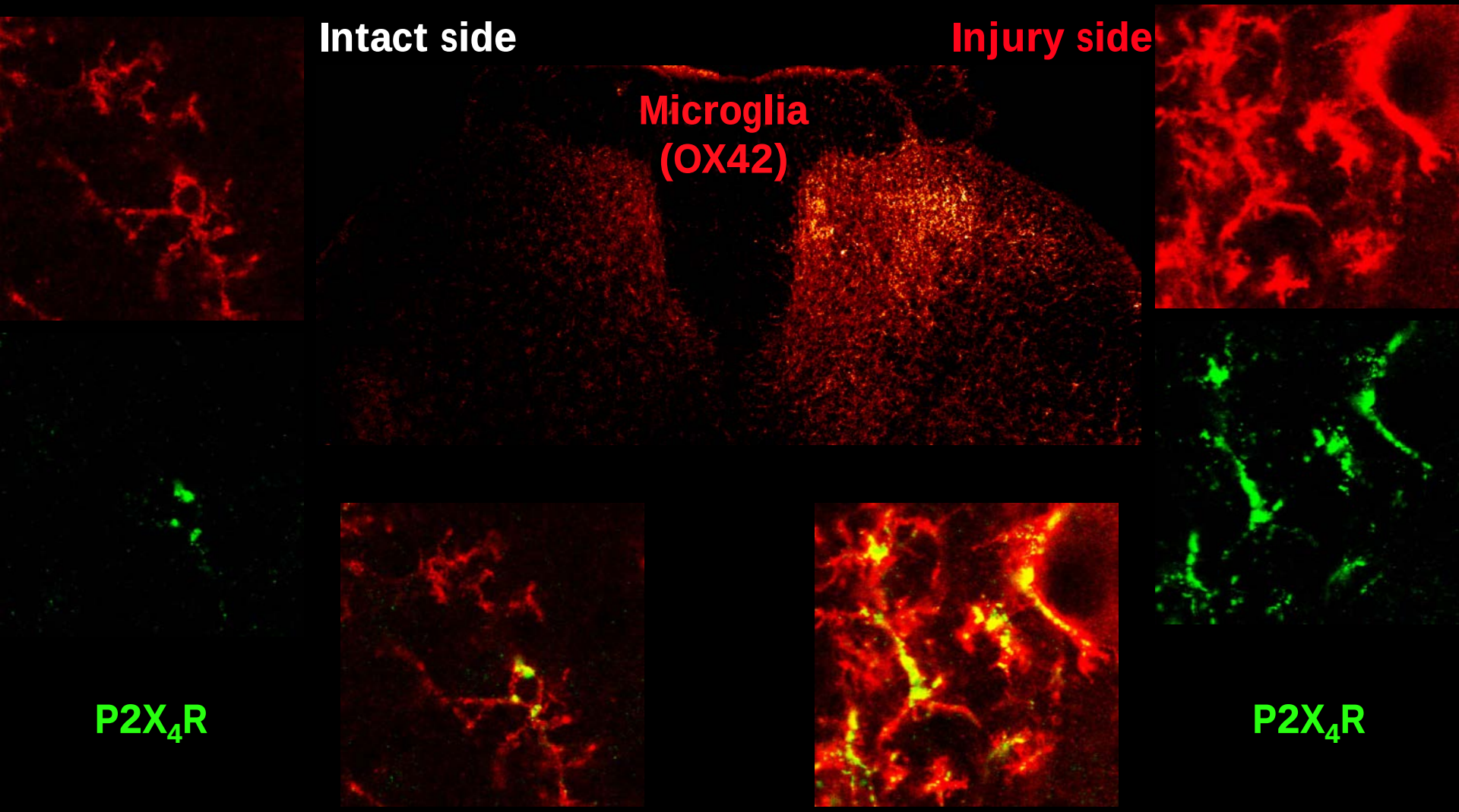
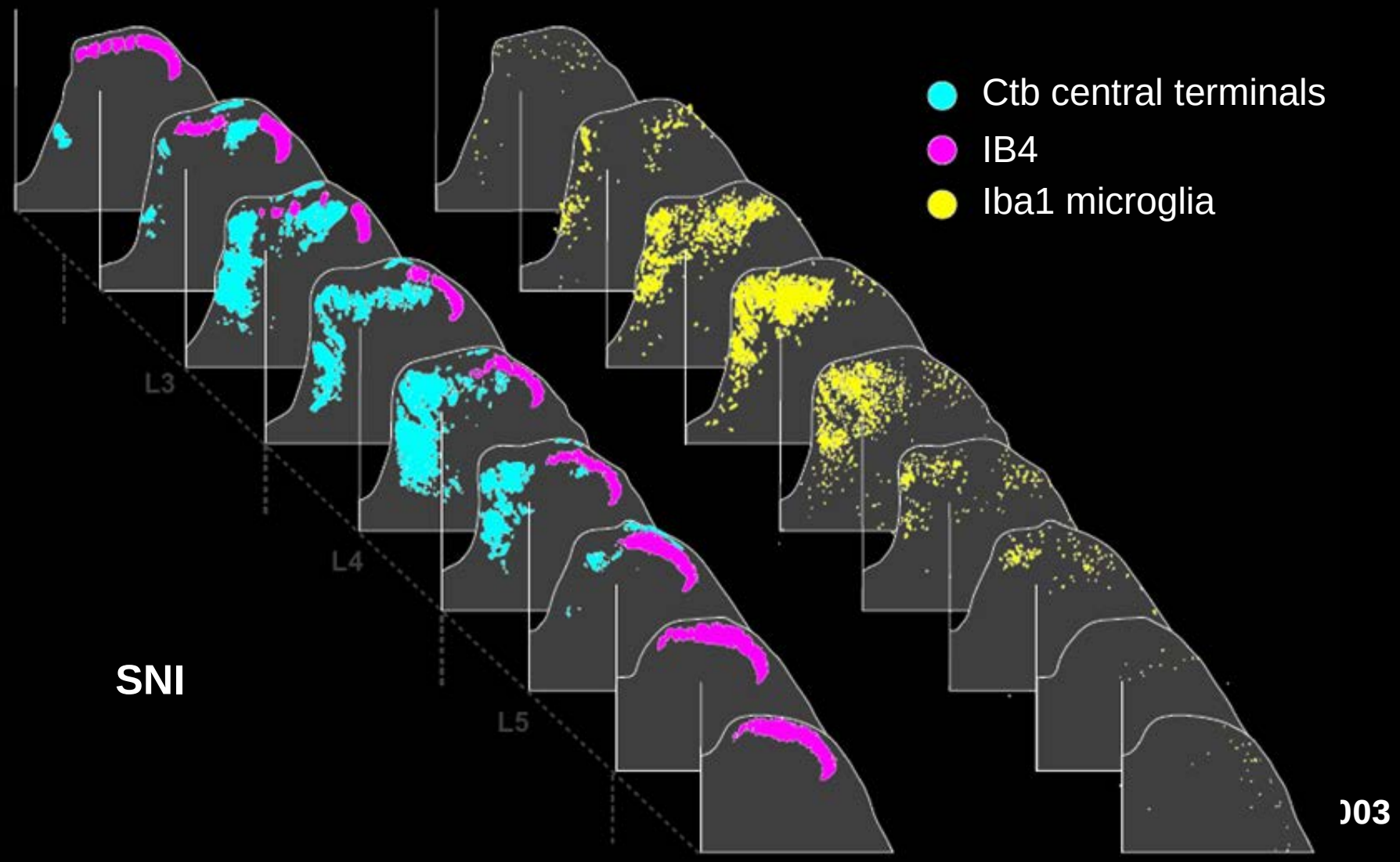
# Inflammation in the spinal cord after nerve lesion



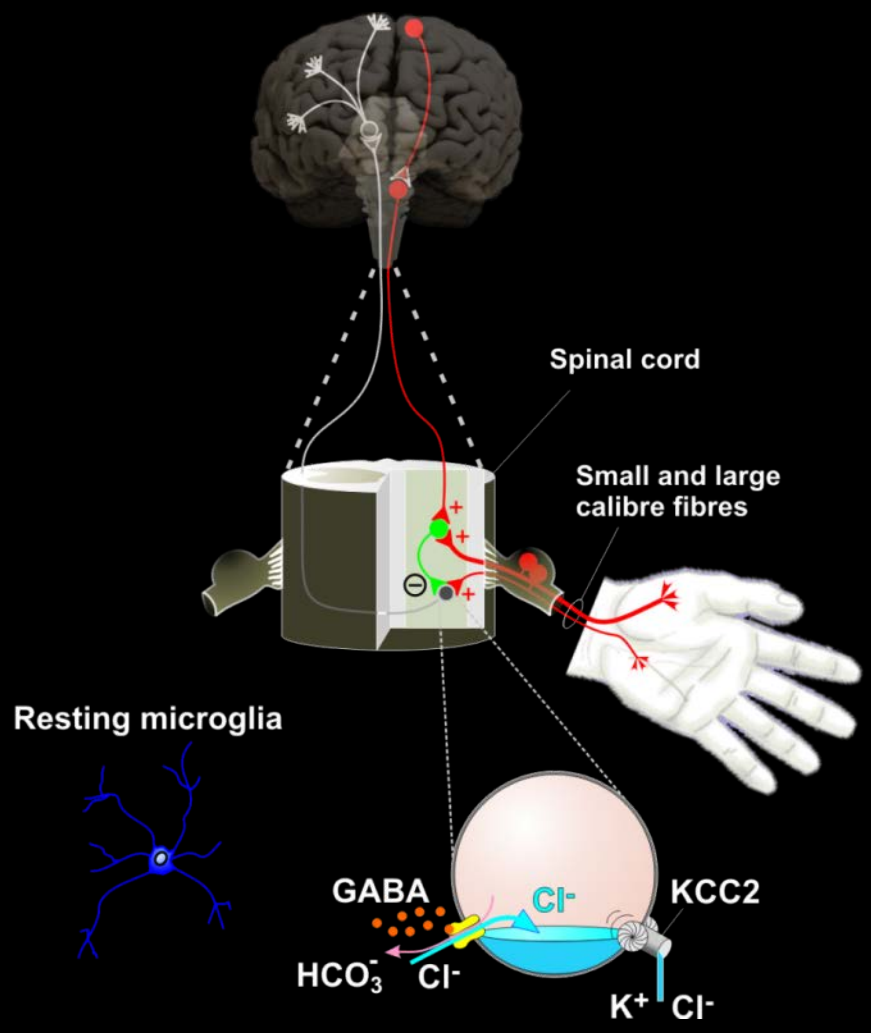

Tsuda, …, Salter & Inoue, *Nature* 2003

# Inflammation in the spinal cord after nerve lesion

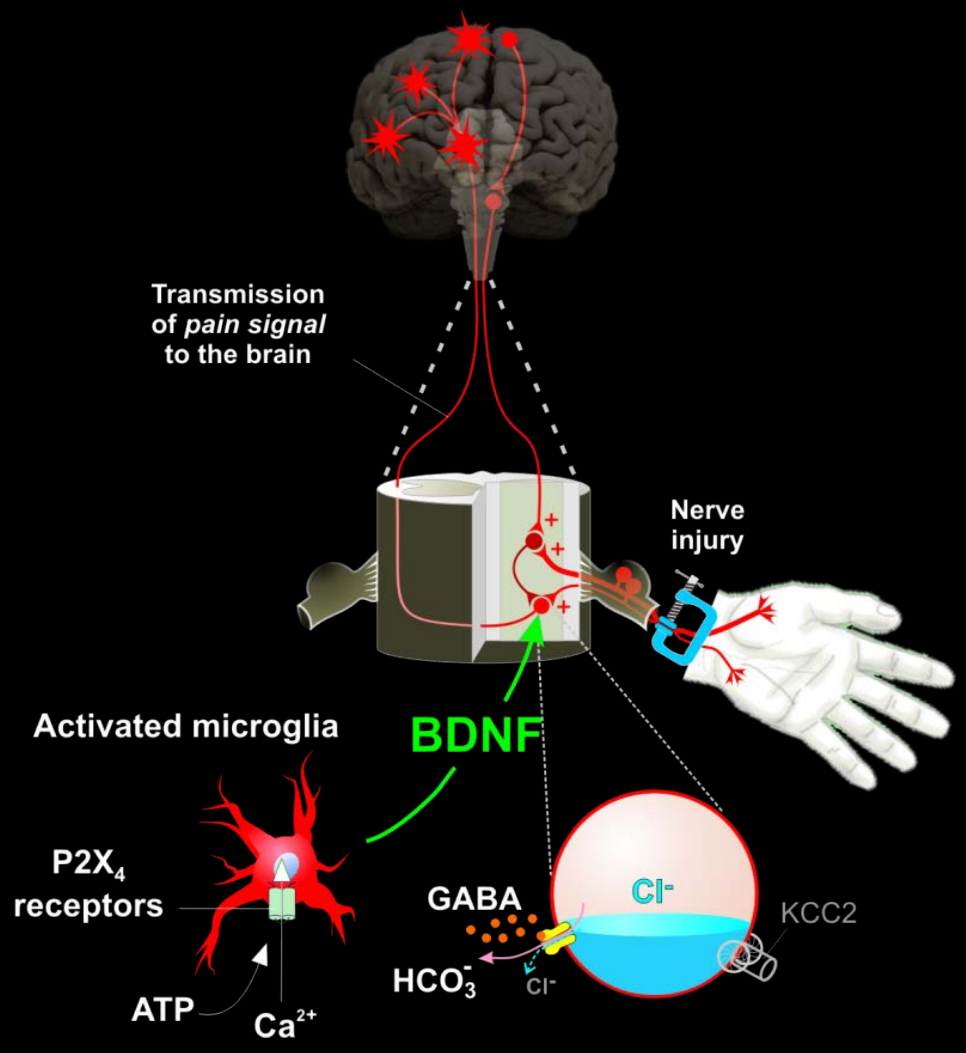



Beggs & Salter, *Brain Behav. Immun.* 2007

## Normal pain



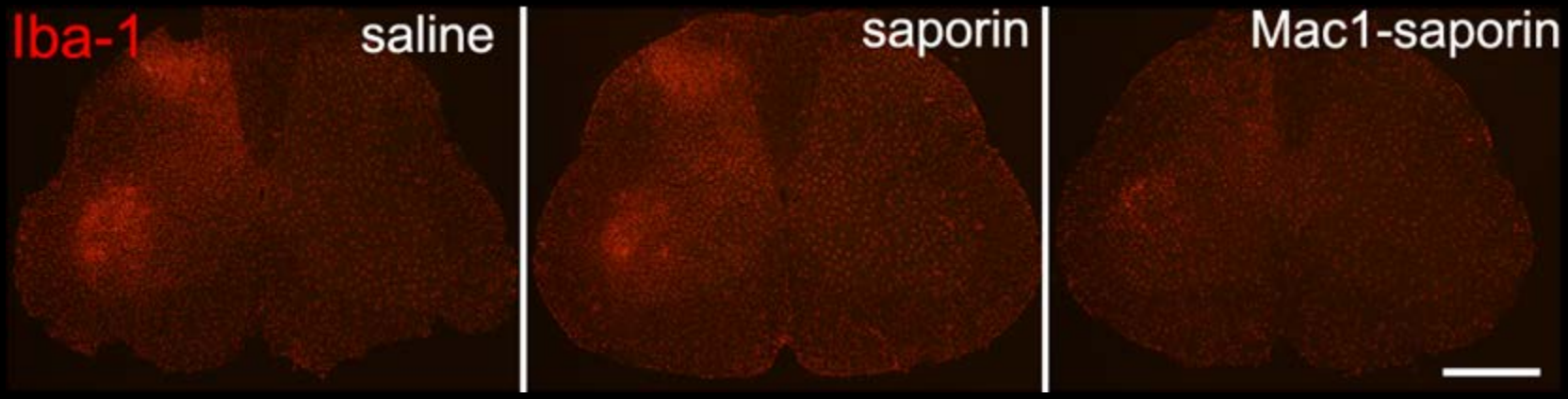

## Pathological pain

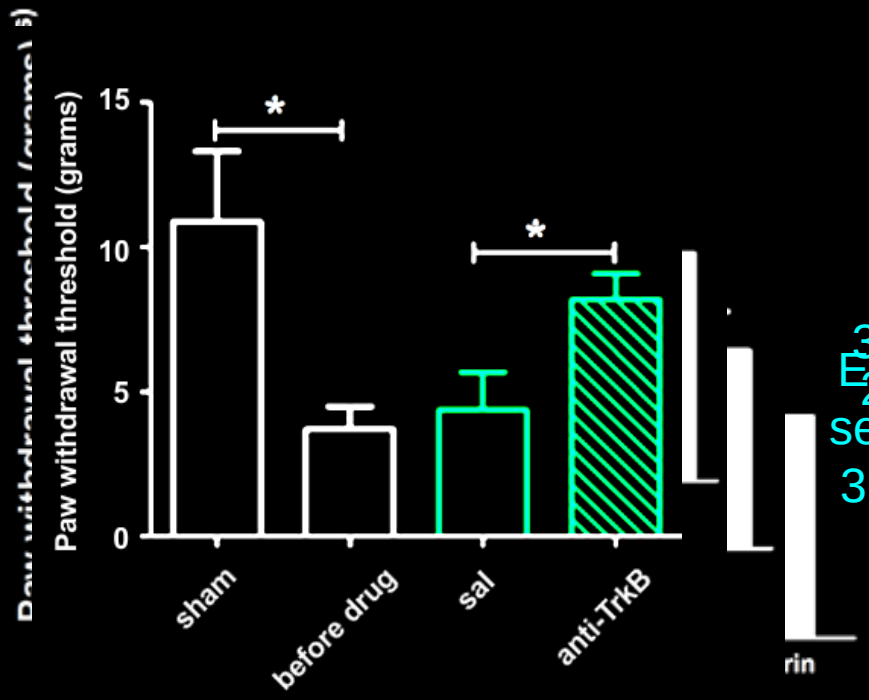



Coull, Beggs et al., *Nature* 2005

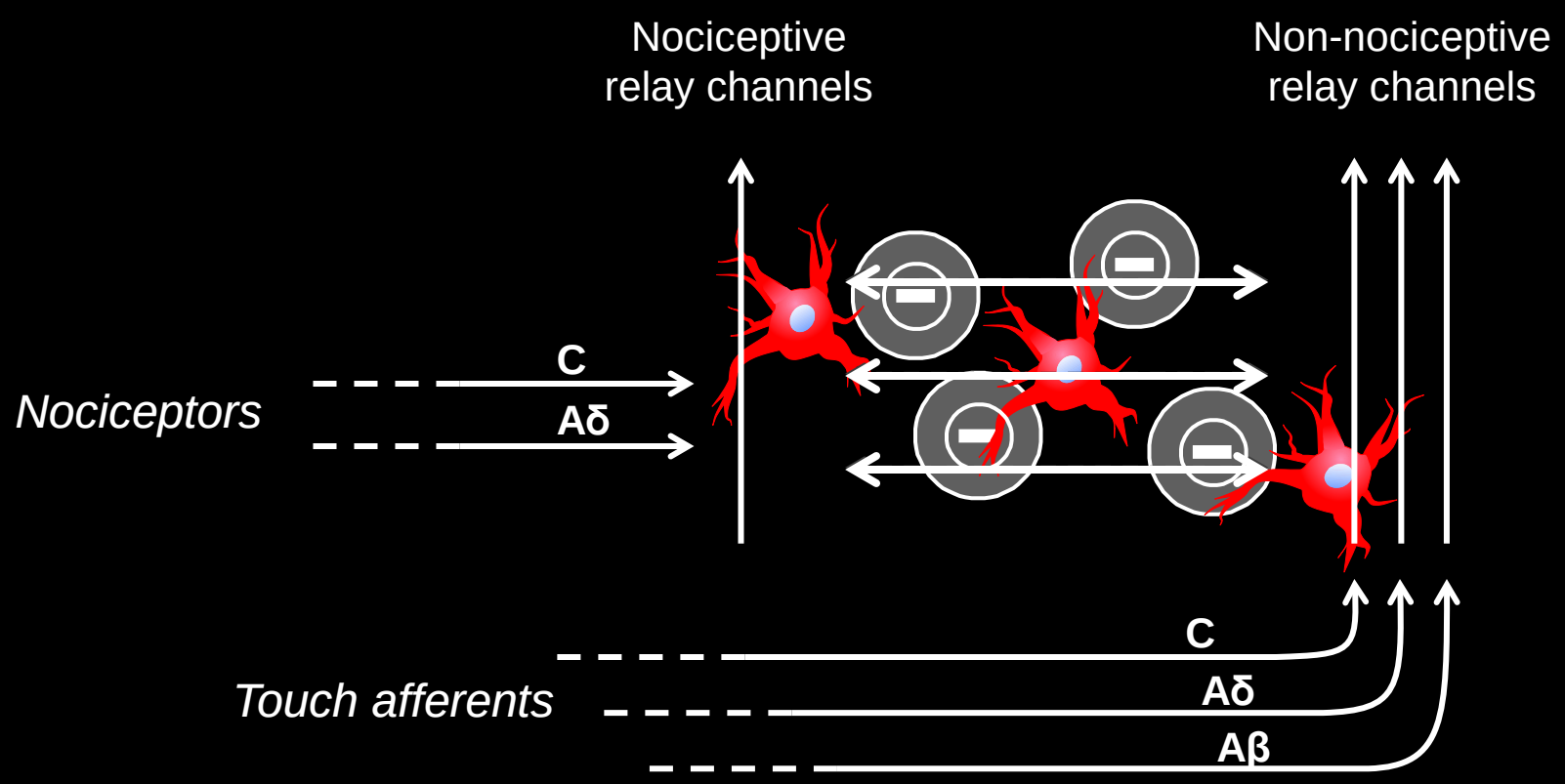
# Can microglia depletion reverse nerve injury-induced pain hypersensitivity?

Ji Zhang




Even
3 **months** after injury
Even ongoing BDNF
2 weeks after injury
secretion is involved
3 **months** after injury




**Labrakakis et al In *Inhibitory Synaptic Plasticity* 2011**

The Journal of Neuroscience, January 12, 2005 • 25(2):430 – 435

Brief Communication

# Morphine-Induced Chemotaxis and Brain-Derived Neurotrophic Factor Expression in Microglia

**Naoko Takayama and Hiroshi Ueda**

Division of Molecular Pharmacology and Neuroscience, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki 852-8521, Japan

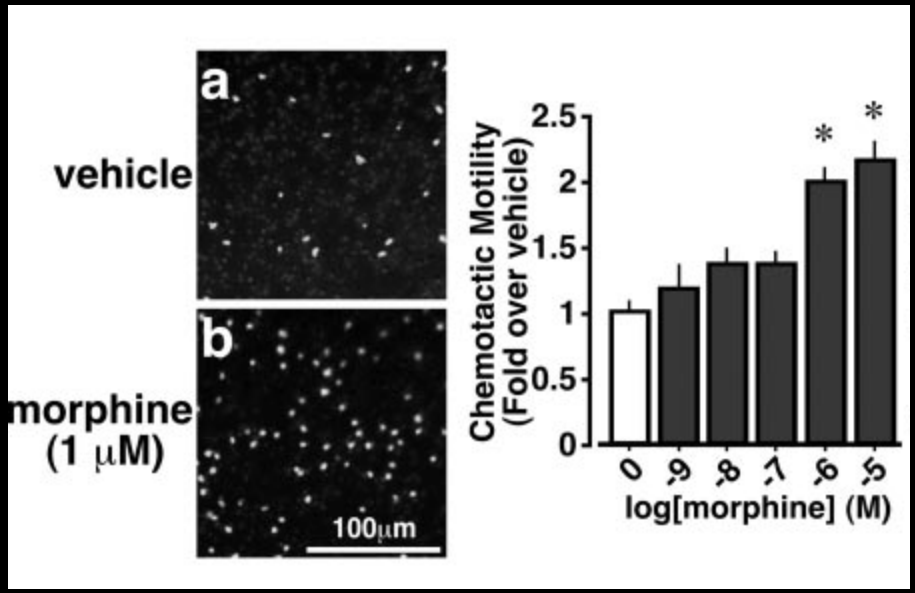



**Figure 2.** Morphine-induced chemotaxis of microglia in the Boyden Chamber. Microglia were stimulated with DMEM or 1μM morphine for 90 min…

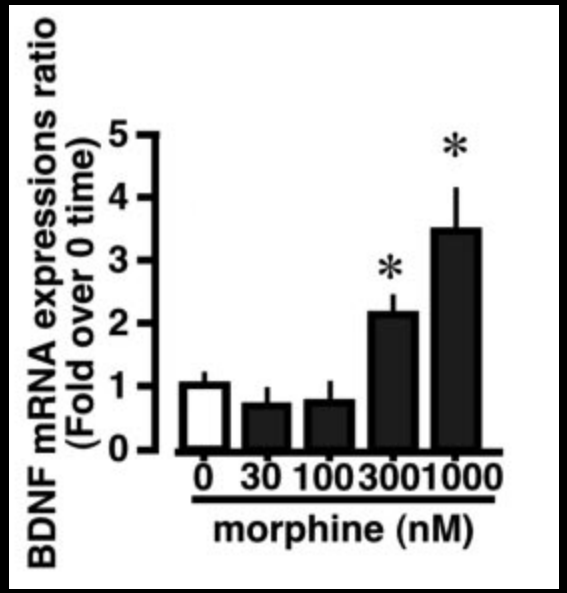
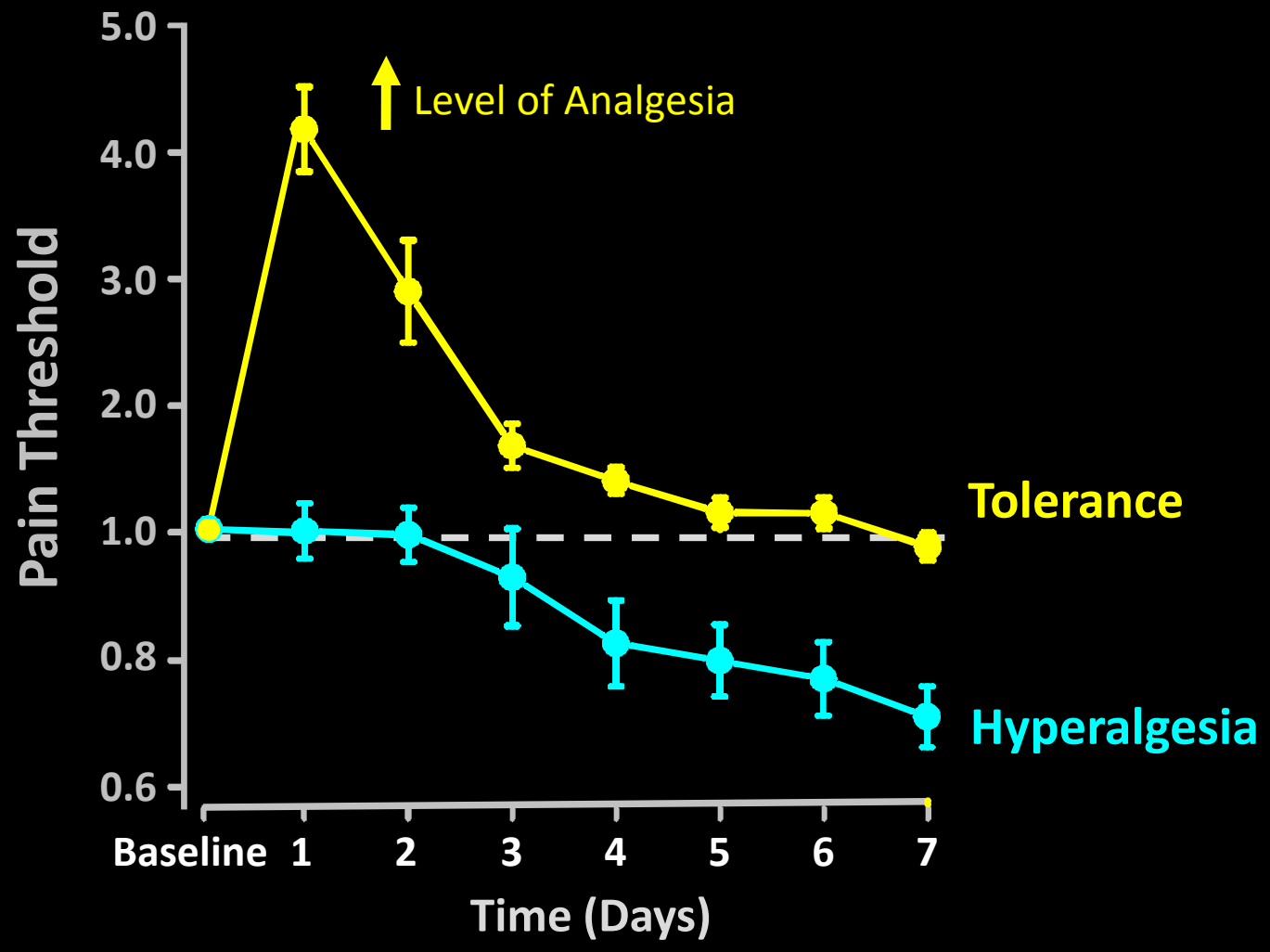



**Figure 4.** Morphine-induced BDNF mRNA expression in microglia.

# Adaptation to chronic morphine

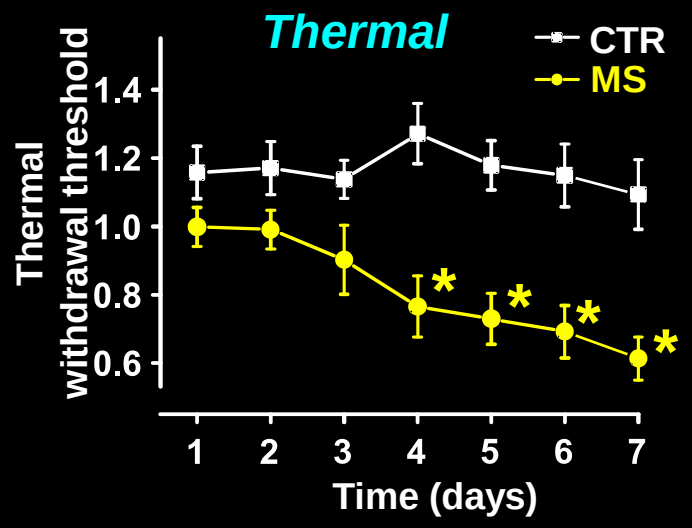
Francesco Ferrini

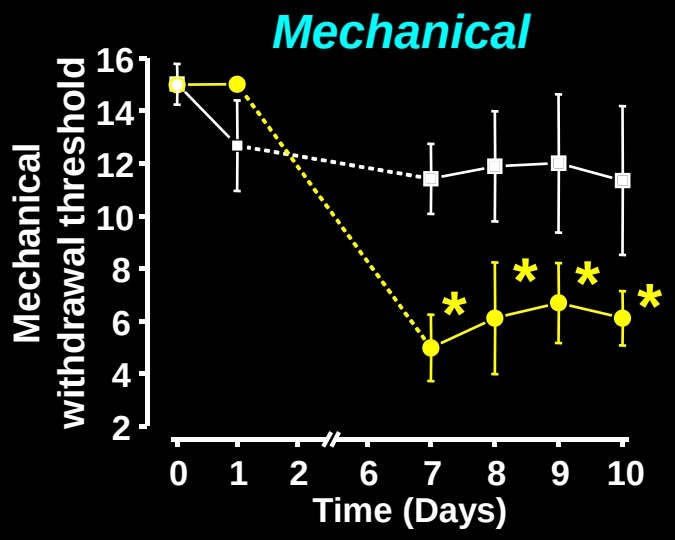


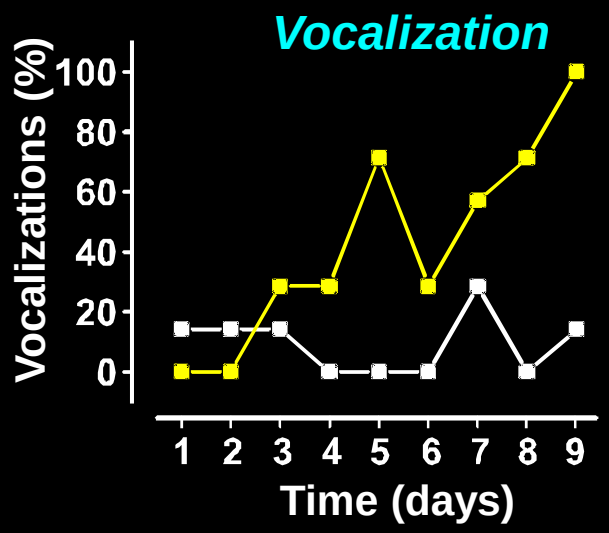
# Chronic morphine treatment : hyperalgesia

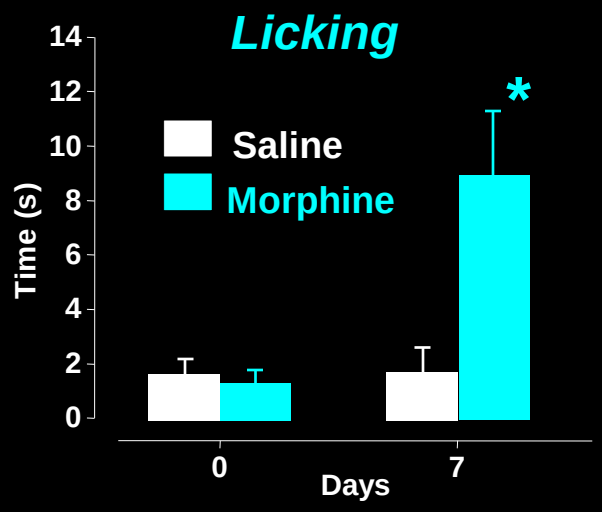
*Testing every morning, just before injections of morphine*

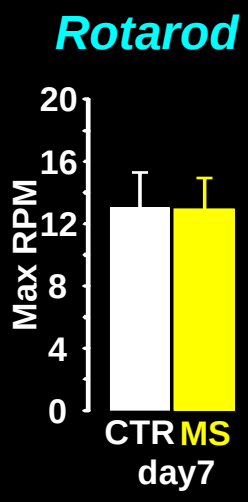
Francesco Ferrini



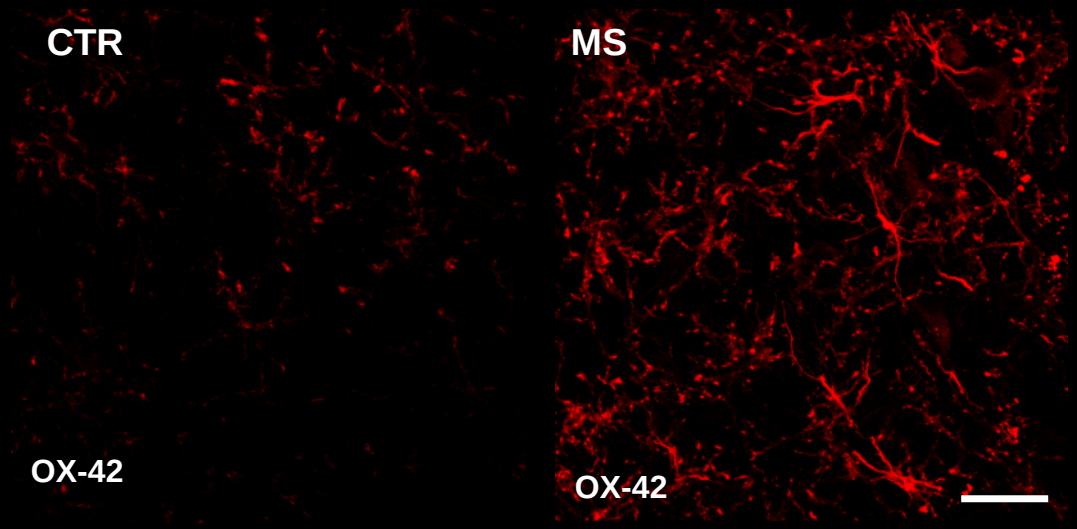



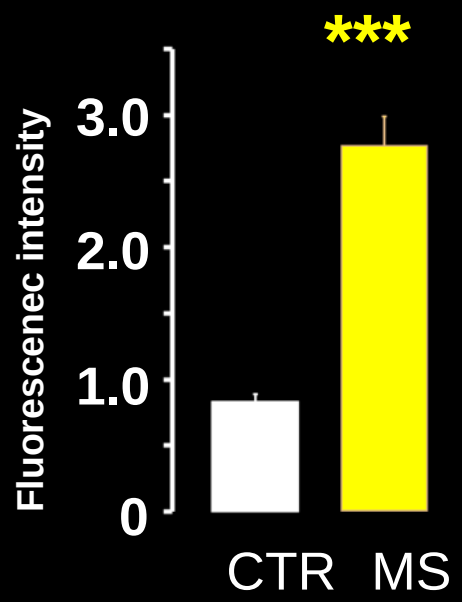



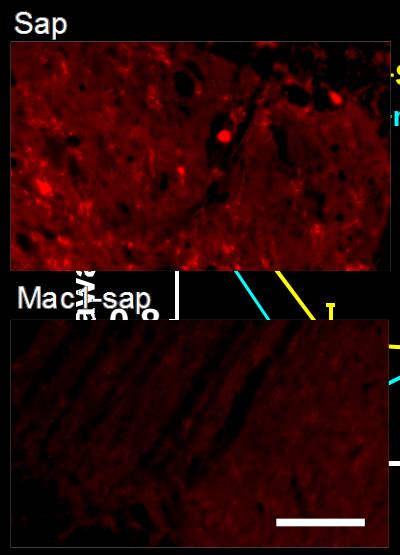



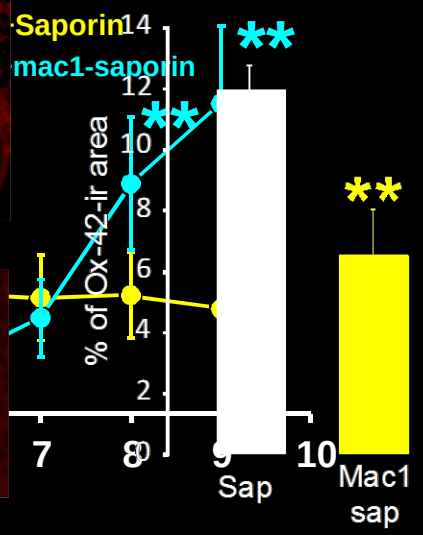
# Chronic morphine causes microglial activation

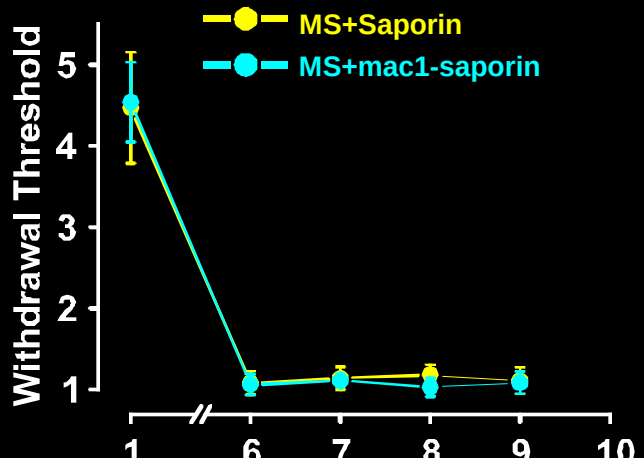
Francesco Ferrini, Alexandra Mattioli



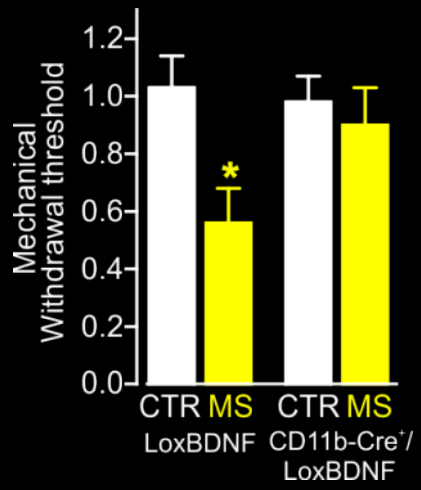



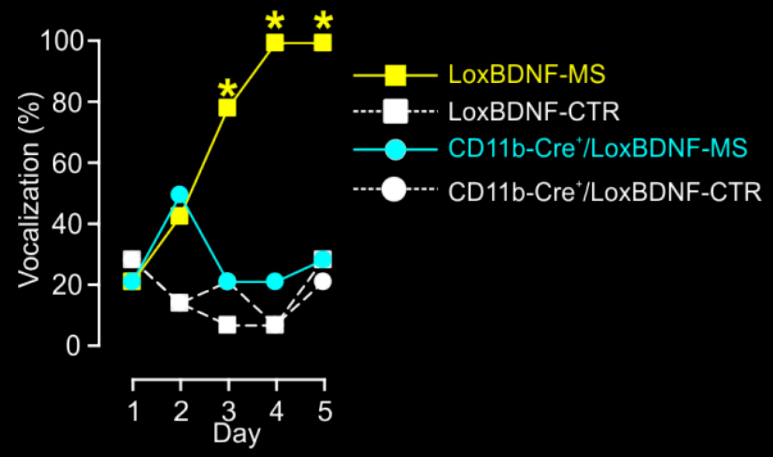



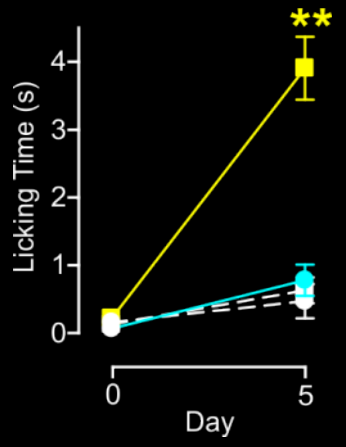
# BDNF from microglia; necessary for morphine hyperalgesia?

Tuan Trang

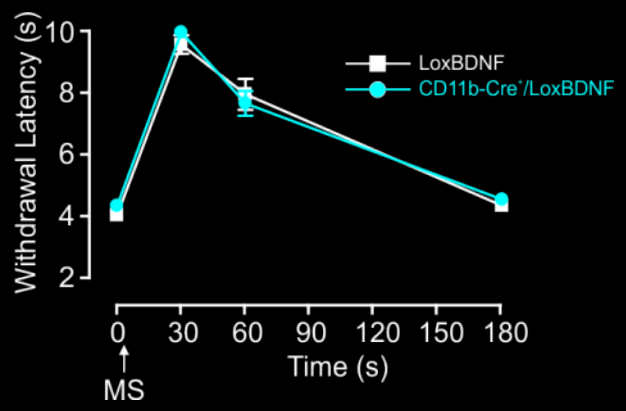
## CD11b-Cre+/LoxBDNF mice do not develop morphine –induced hyperalgesia

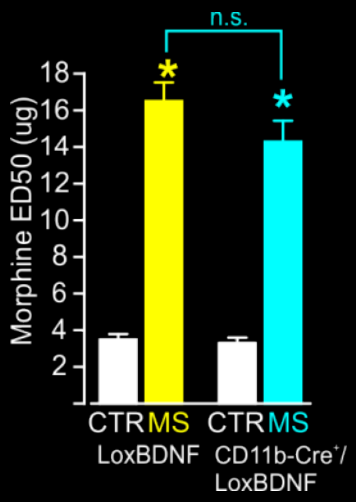



## *Yet, morphine analgesia is intact*

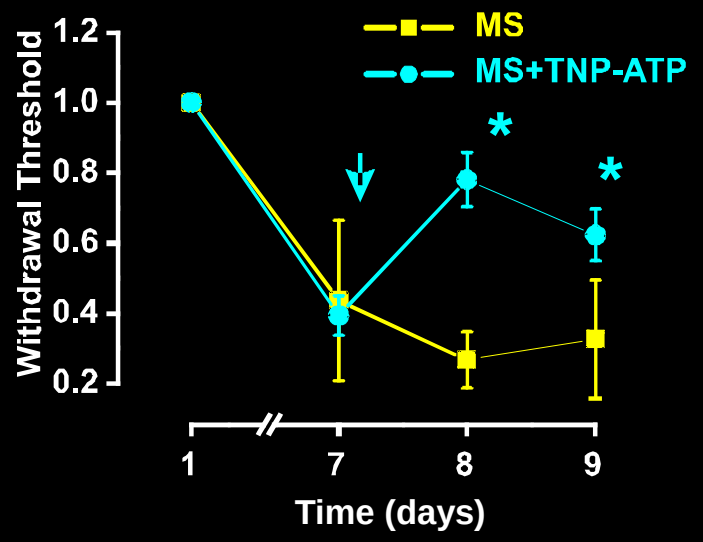


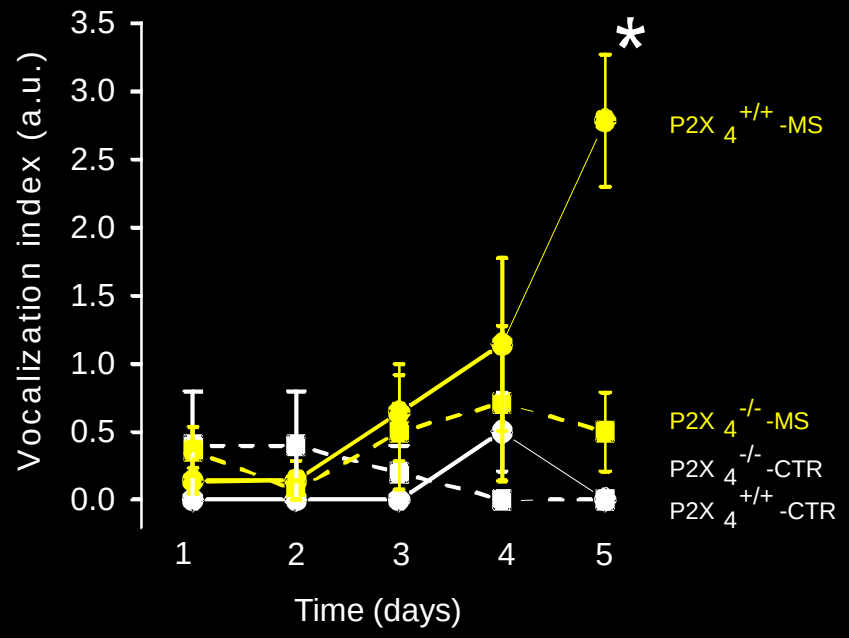
# $P2X_4$ receptors; necessary for morphine hyperalgesia

Sophie Laffray

## Reversing established hyperalgesia *in vivo*

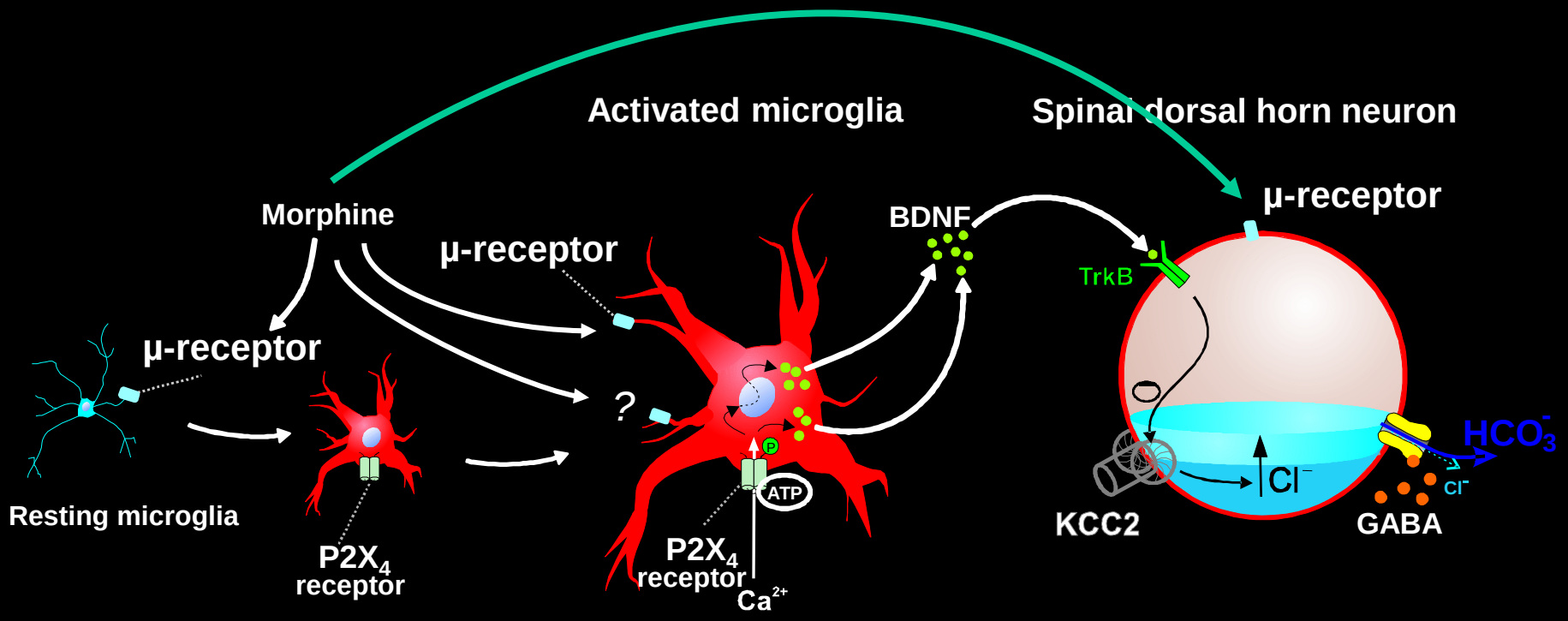



## P2X4 -/- mice do not develop hyperalgesia



# Morphine causes paradoxical hyperalgesia… by triggering a central inflammatory response… that leads to impaired $Cl^-$ homeostasis…

Francesco Ferrini
Tuan Trang




Ferrini et al, *Nature Neuroscience* 2013

# What about the brain ?

# Disrupted $Cl^-$ homeostasis in opiate-dependence

© 2004 Nature Publishing Group

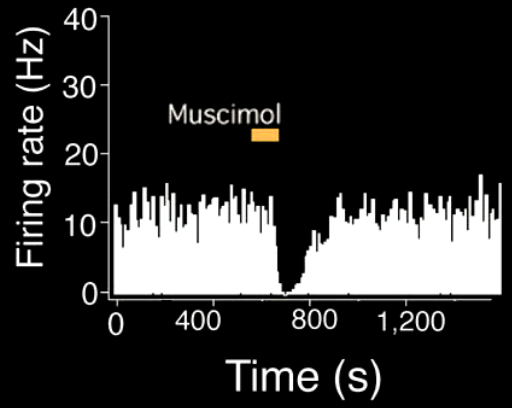
## Opiate state controls bi-directional reward signaling via $GABA_A$ receptors in the ventral tegmental area

Steven R Laviolette[1], Roger A Gallegos[2], Steven J Henriksen[2] & Derek van der Kooy[1,3]

The neural mechanisms that mediate the transition from a drug-naive state to a state of drug dependence and addiction are not yet known. Here we show that a discrete population of $GABA_A$ receptors in the mammalian ventral tegmental area (VTA) serves as a potential addiction switching mechanism by gating reward transmission through one of two neural motivational systems: either a dopamine-independent (opiate-naive) or a dopaminergic (opiate-dependent or opiate-withdrawn) system. Bi-directional transmission of reward signals through this $GABA_A$ receptor substrate is dynamically controlled by the opiate state of the organism and involves a molecular alteration of the $GABA_A$ receptor. After opiate exposure and subsequent withdrawal, the functional conductance properties of the rat VTA $GABA_A$ receptor switch from an inhibitory to an excitatory signaling mode.

160 VOLUME 7 | NUMBER 2 | FEBRUARY 2004 NATURE NEUROSCIENCE

**Opiate naive**




**Opiate dependent / withdrawn**

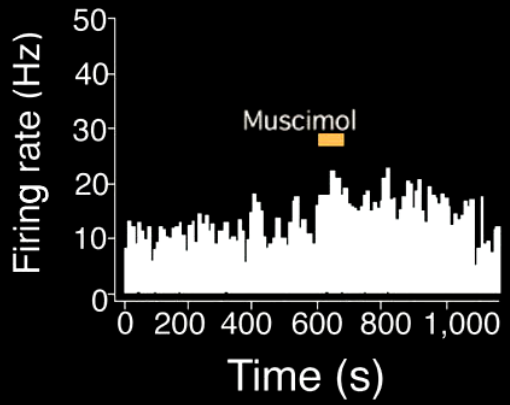
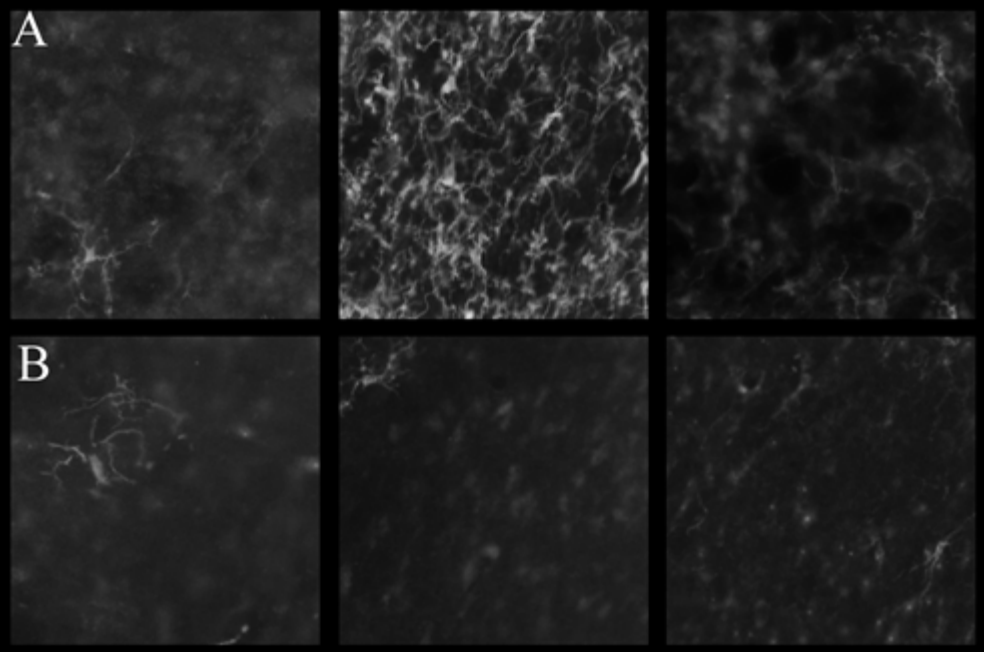



**Figure 6** Single-unit extracellular recordings of VTA GABAergic neurons shows that a subpopulation of these neurons respond with excitatory depolarization to receptor activation in the opiate-dependent/withdrawn state.

# Microglial activation in the ventral tegmental area (VTA) of acute and chronic drug exposure

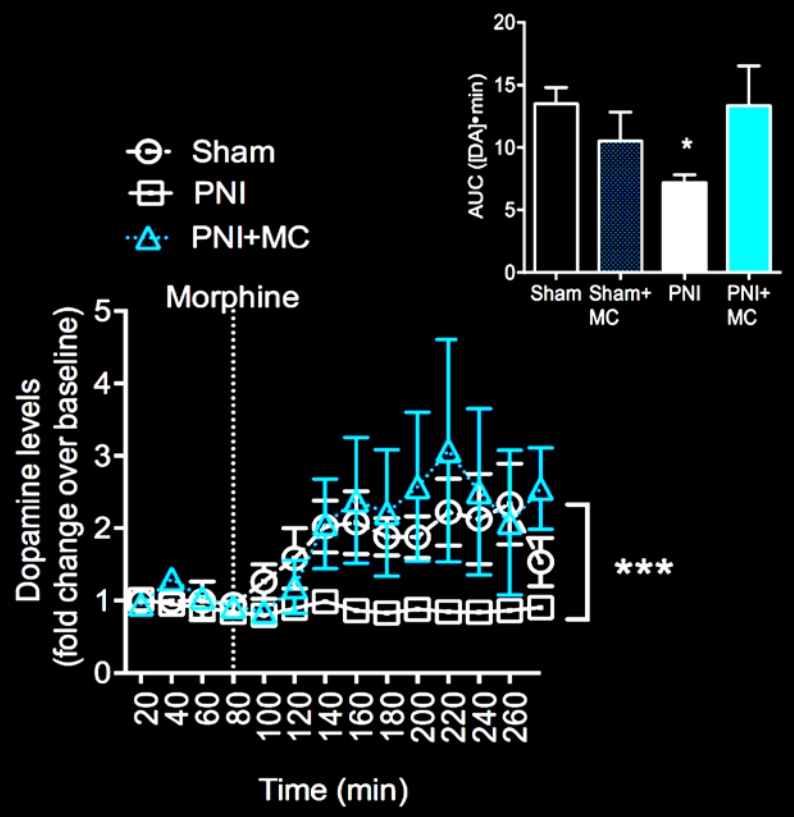
Anna Taylor
(Cathy Cahill)



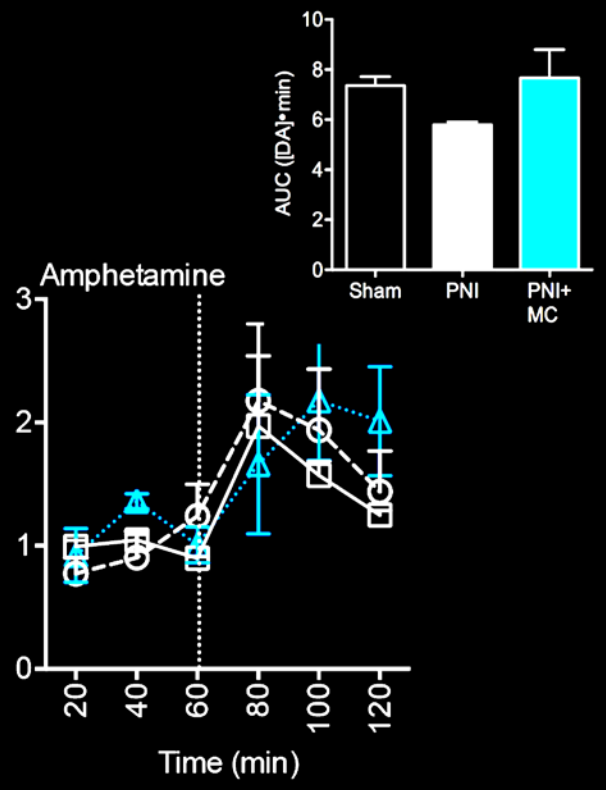
# Impaired morphine-evoked dopamine release in animals with peripheral nerve injury

Anna Taylor
(Cathy Cahill)

## Morphine

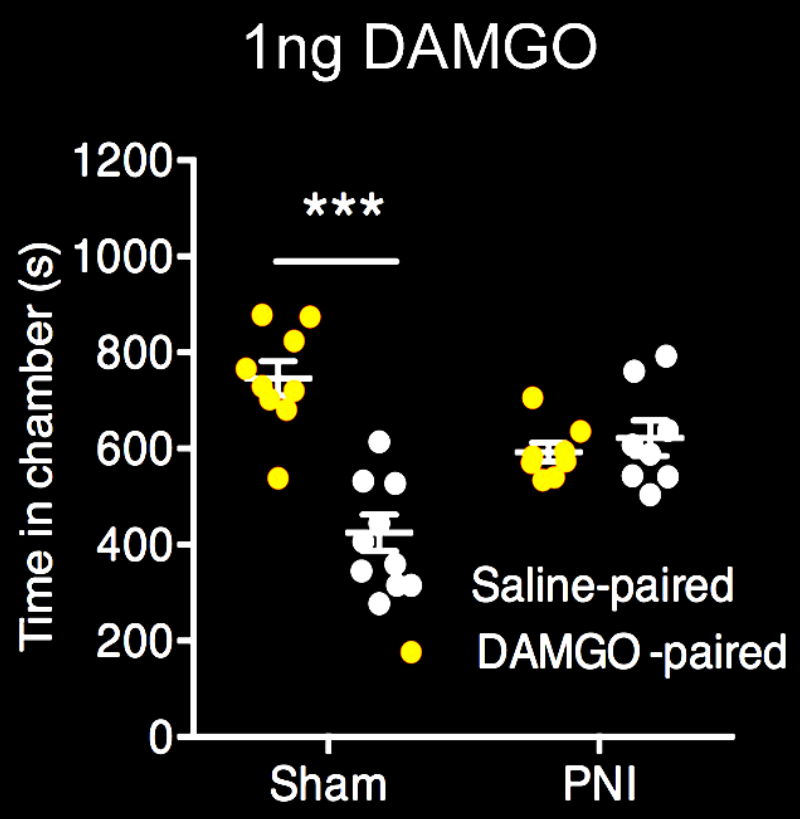


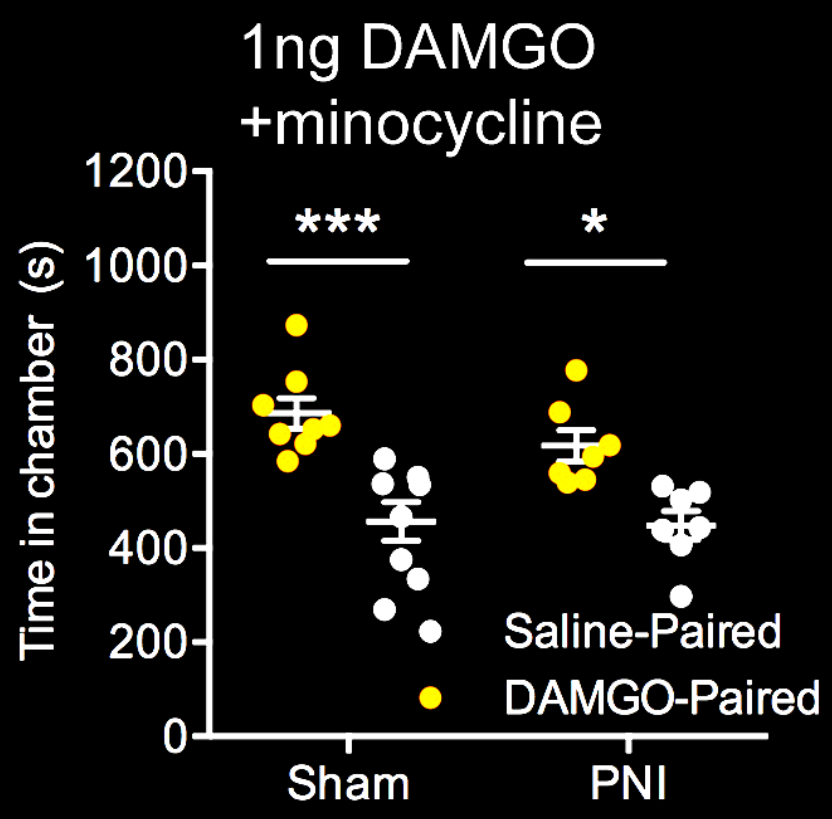

## Amphetamine



# Intra-VTA opiate injection fails to produce place preference in animals with peripheral nerve in jury

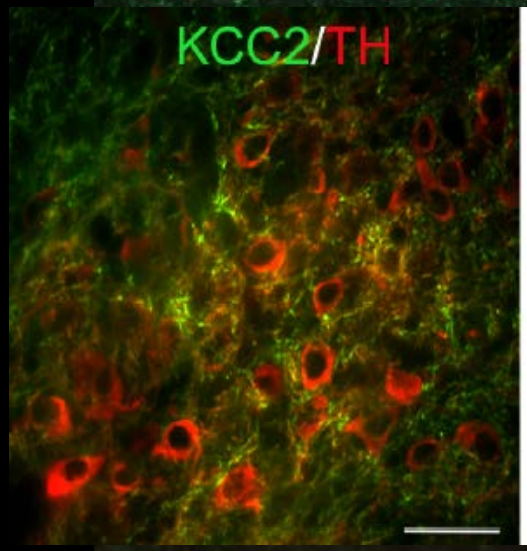
Anna Taylor
(Cathy Cahill)

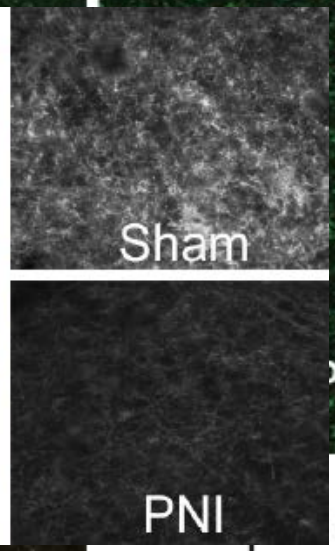


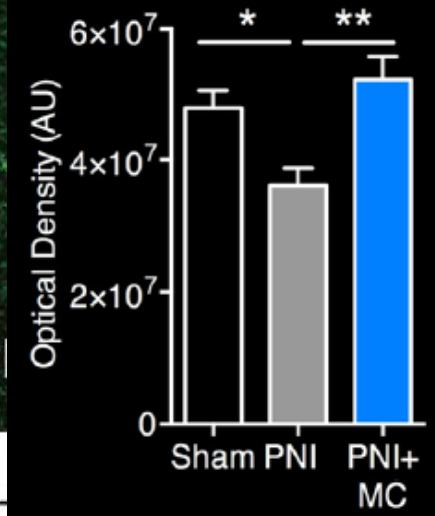



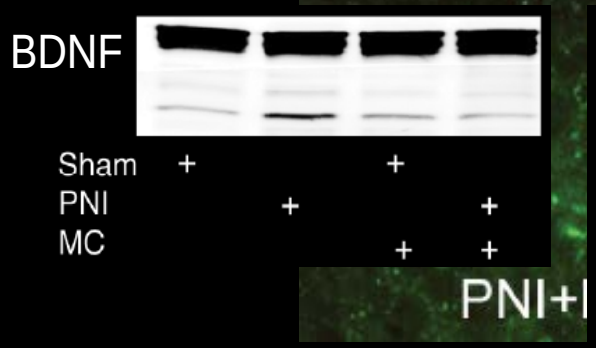
# Microglia-BDNF-KCC2 cascade in the ventral tegmental area (VTA) in animals with peripheral nerve injury

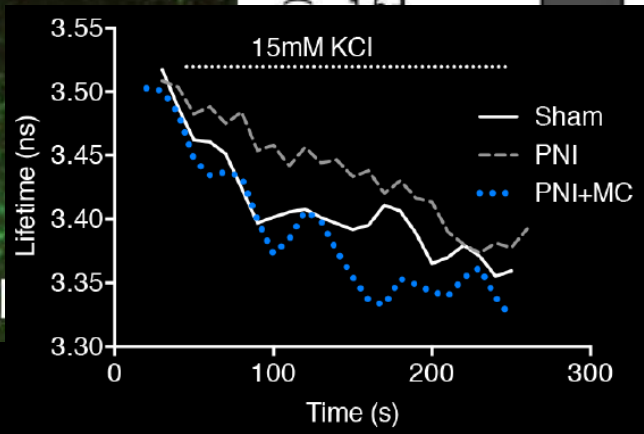
Anna Taylor
(Cathy Cahill)

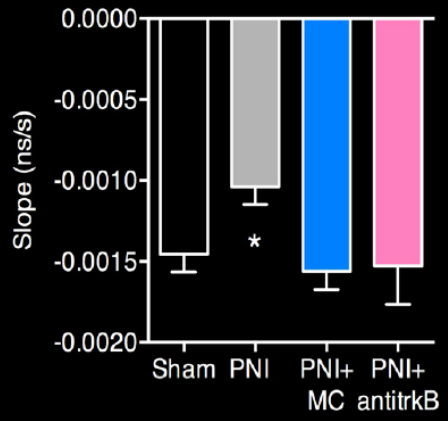


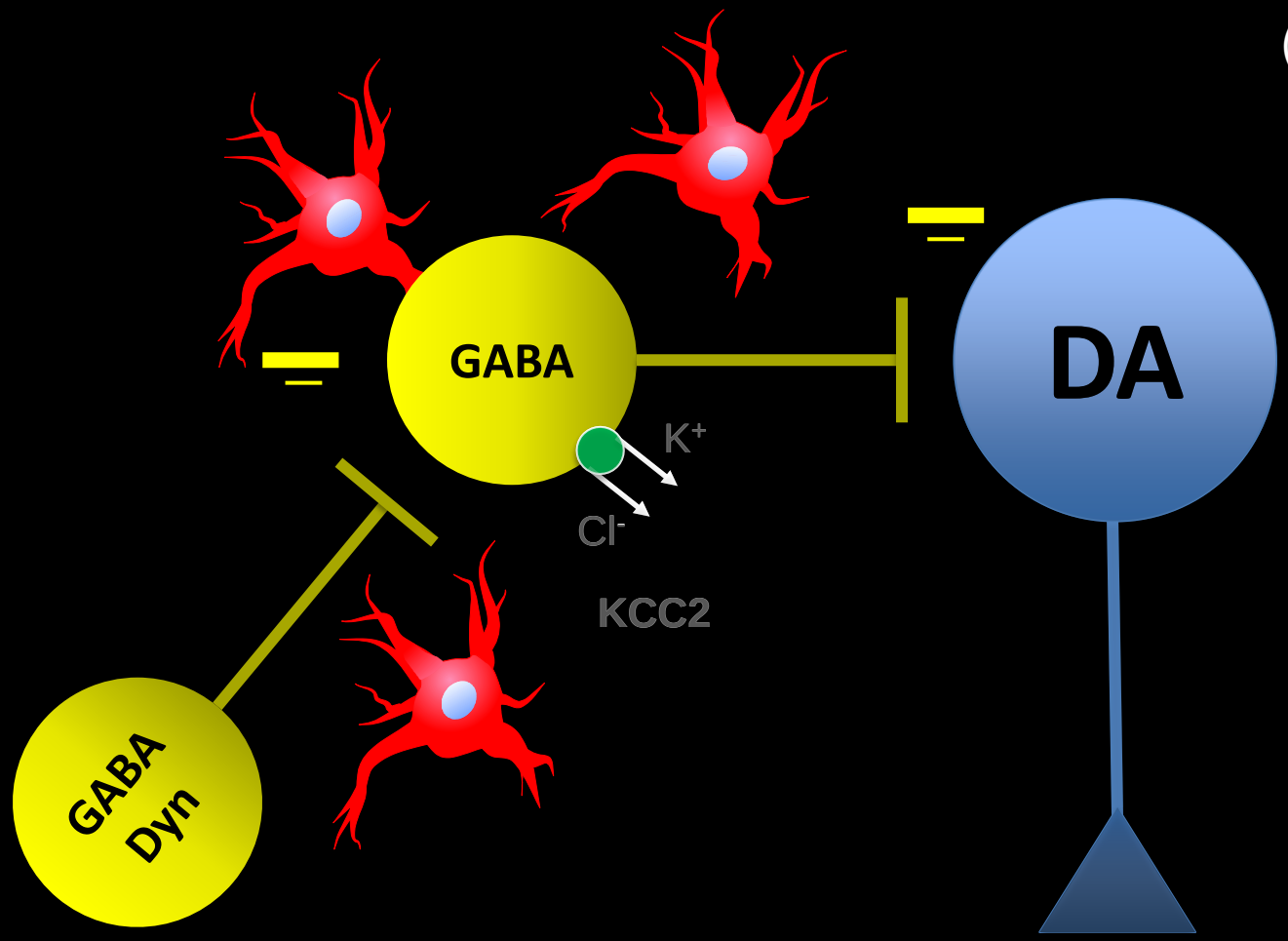



# Neuropathic pain-induced $Cl^-$ dysregulation in VTA GABAergic neurons blunts the reward response

Anna Taylor
(Cathy Cahill)




Taylor et al. *J.Neurosci.* (in press)

# What about the ACC?

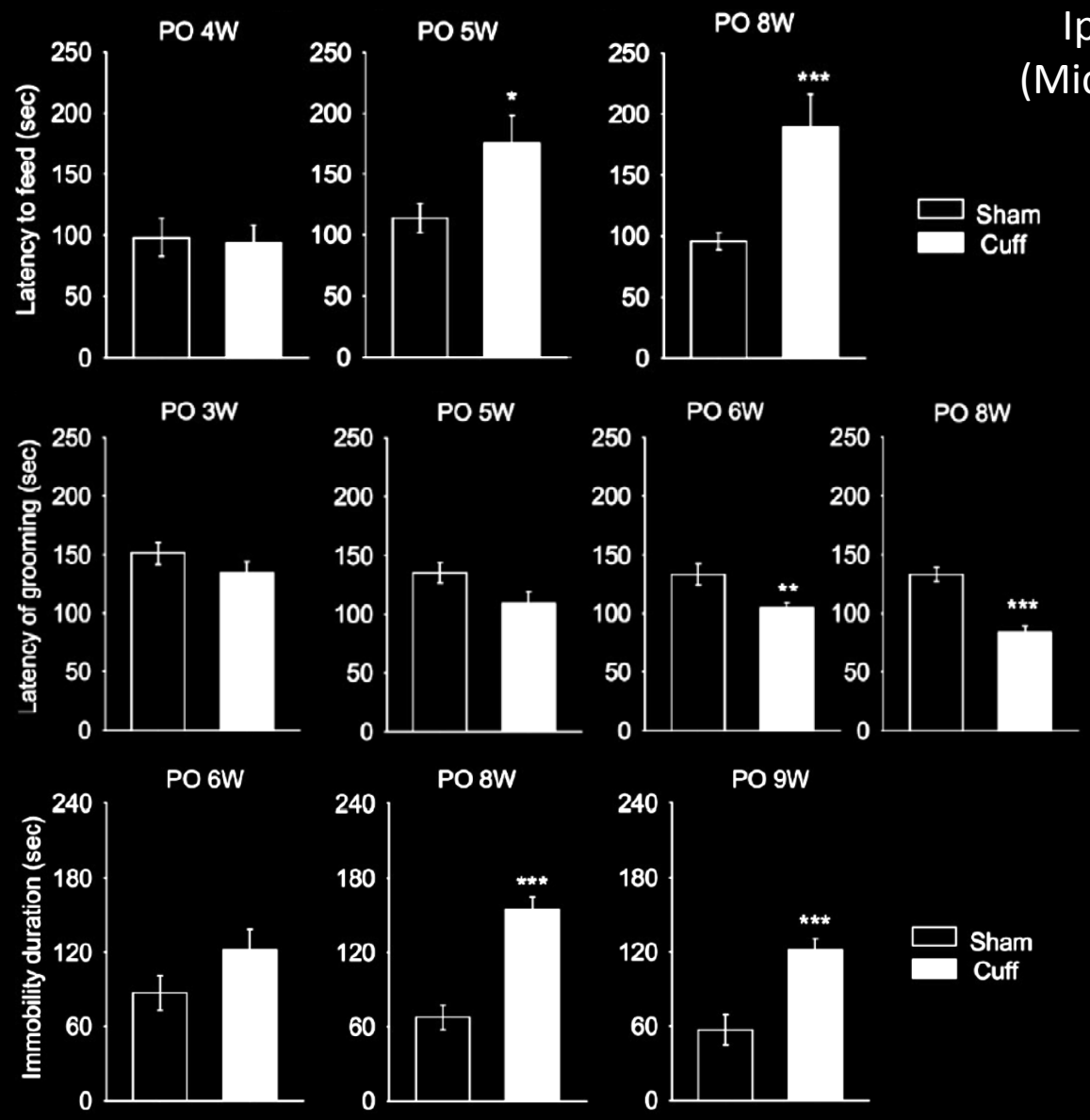
# Time-dependent development of anxio-depressive-like phenotypes

Ipek Yalcin
(Michel Barrot)

Novelty supressed feeding

Splash

Forced Swimming Test




Yalcin et al *Biol.Psych.* 2011

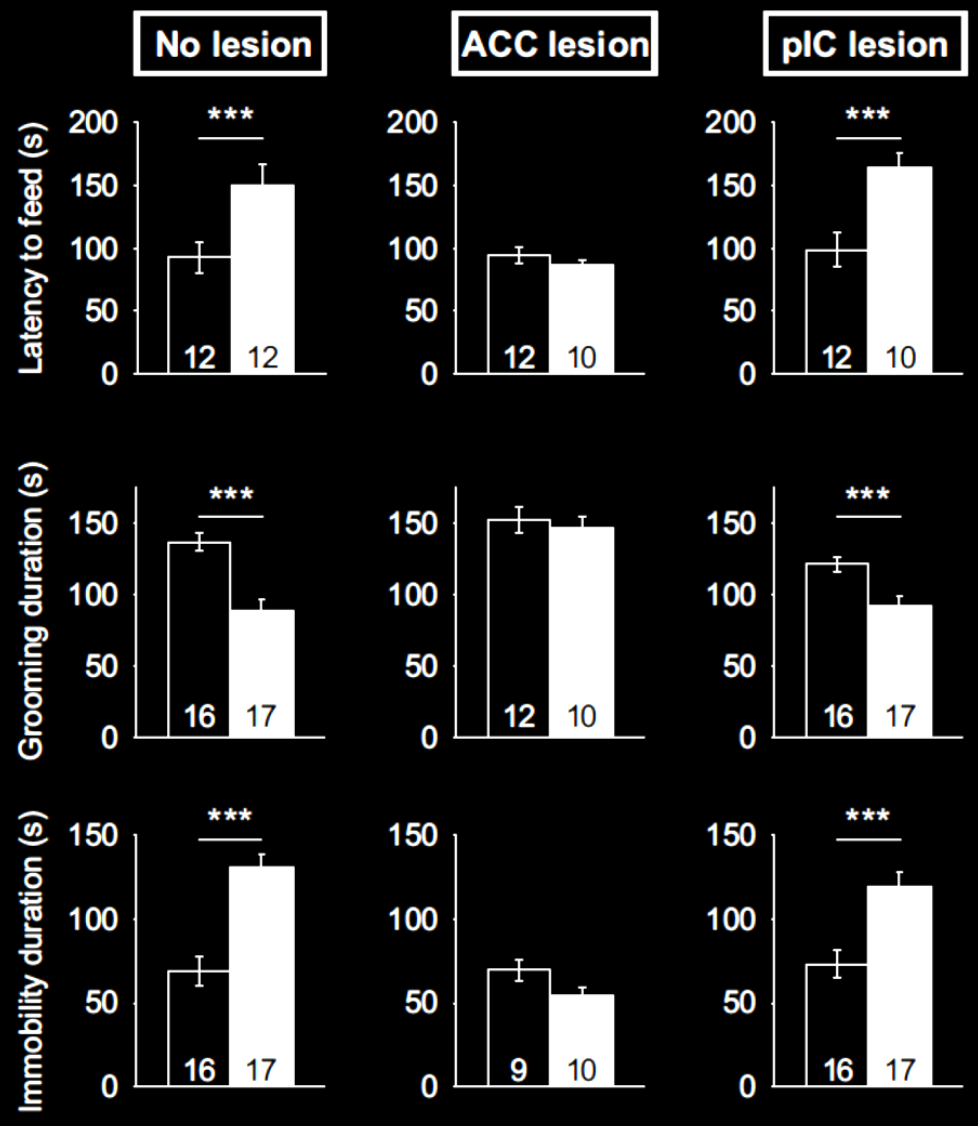
# Ablation of the ACC, but not the pIC blocks the anxio-depressive-like phenotype following nerve lesion

Ipek Yalcin

Novelty supressed feeding

Splash

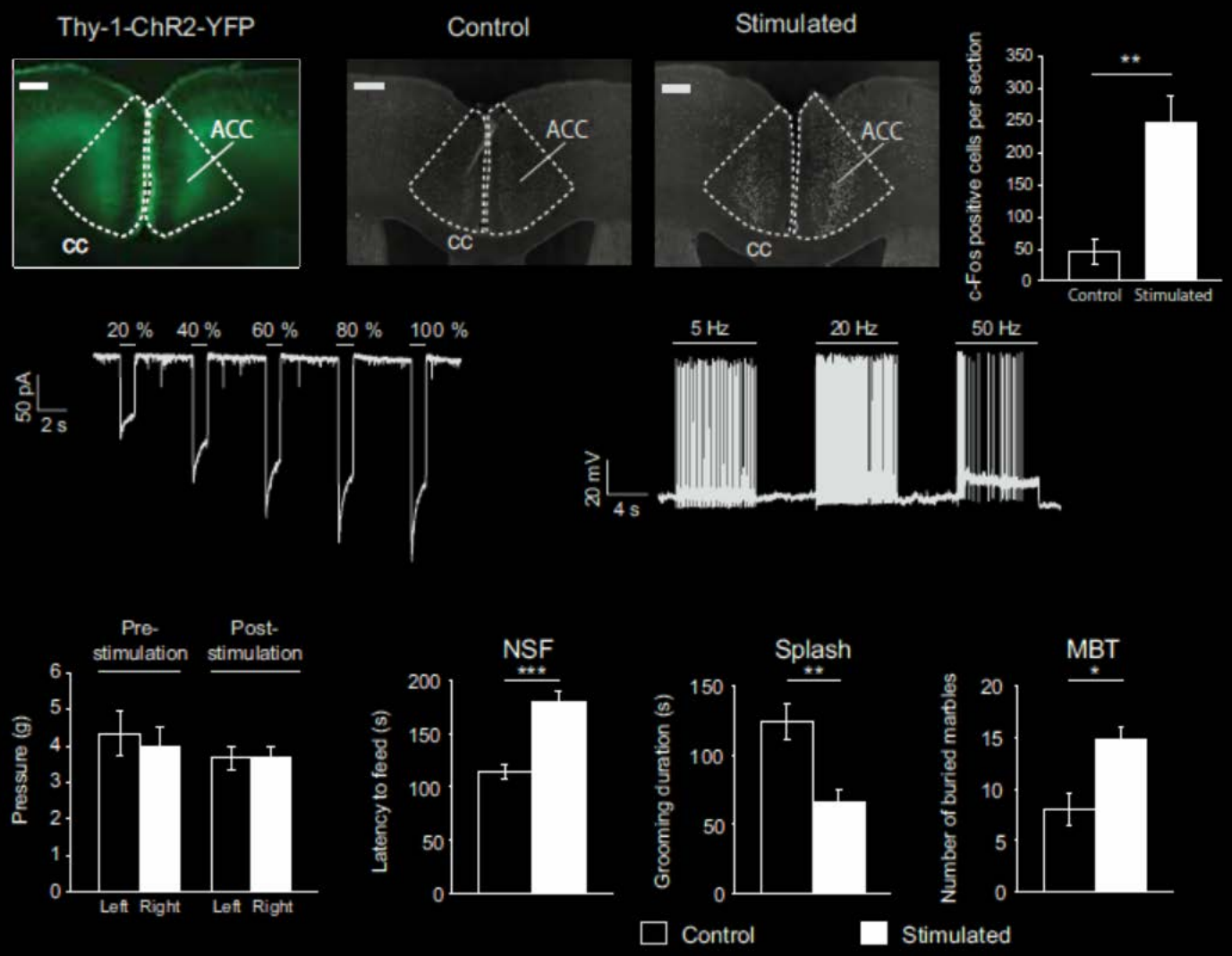
Forced Swimming Test




Barthas et al *Biol.Psych.* 2015

# Optogenetic stimulation of the ACC triggers anxio-depressive-like behaviours

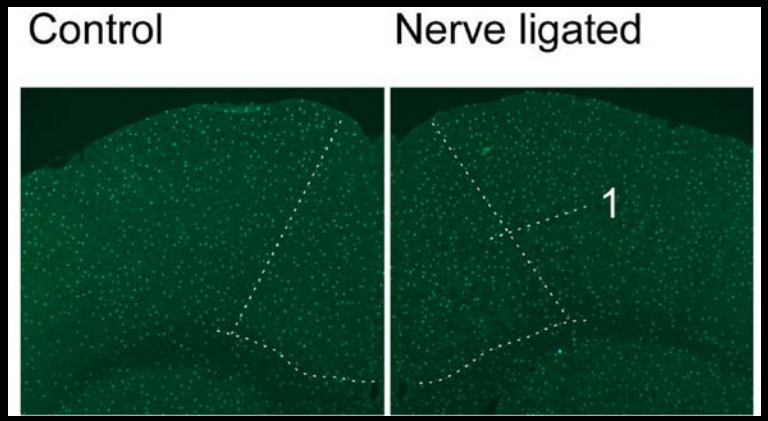
Ipek Yalcin

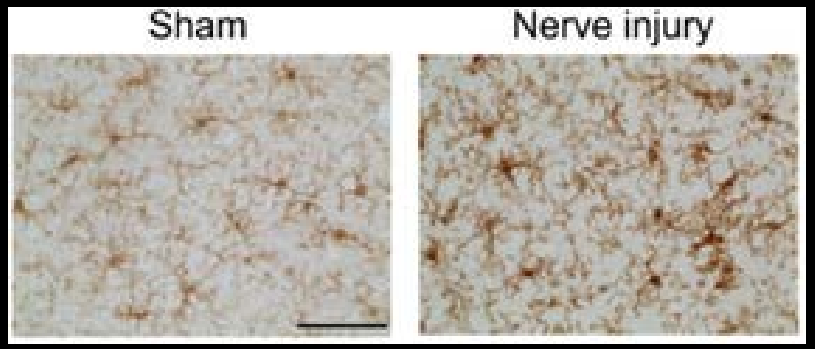



Barthas et al *Biol.Psych.* 2015

# Microglial activation in the ACC...

## ...Only several weeks after nerve injury




7 days

8 weeks

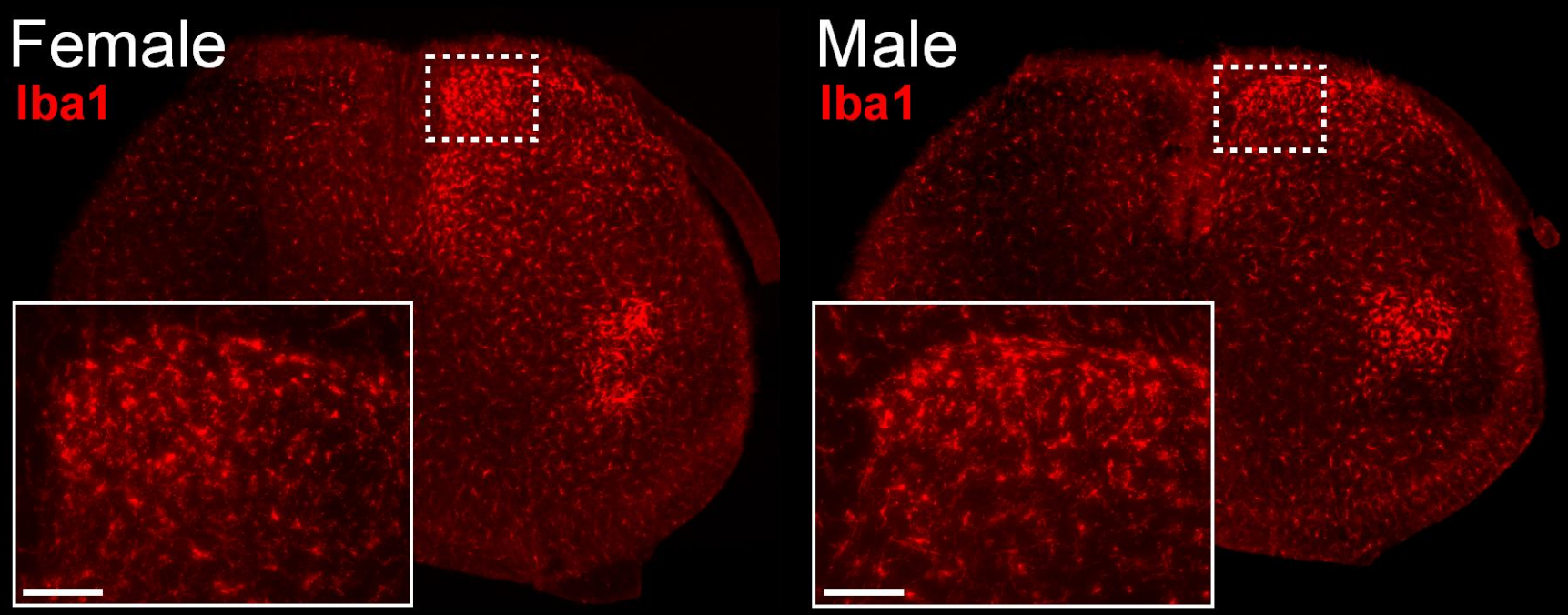
Zhang et al. *Mol. Pain* 2008

Ipek Yalcin

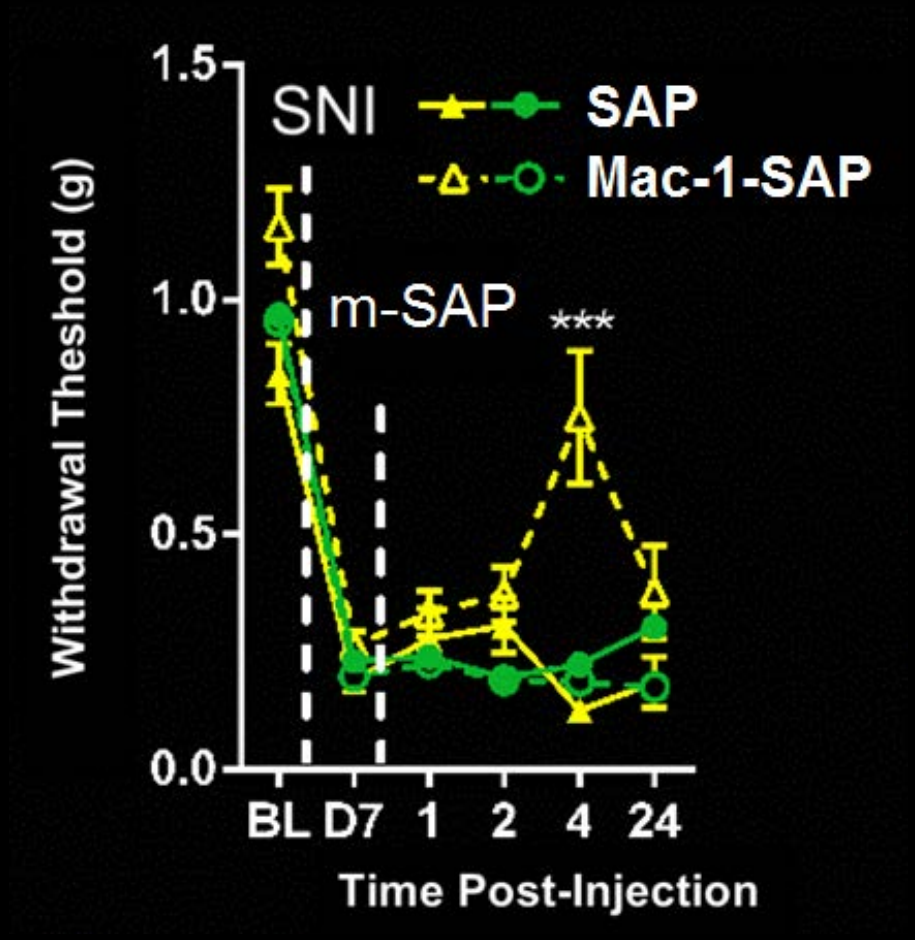
# What about sex?

# Microglia respond to peripheral nerve injury in females as well as in males

Robert Sorge
Josiane Mapplebeck
Simon Beggs
(Jeff Mogil)
(Michael Salter)

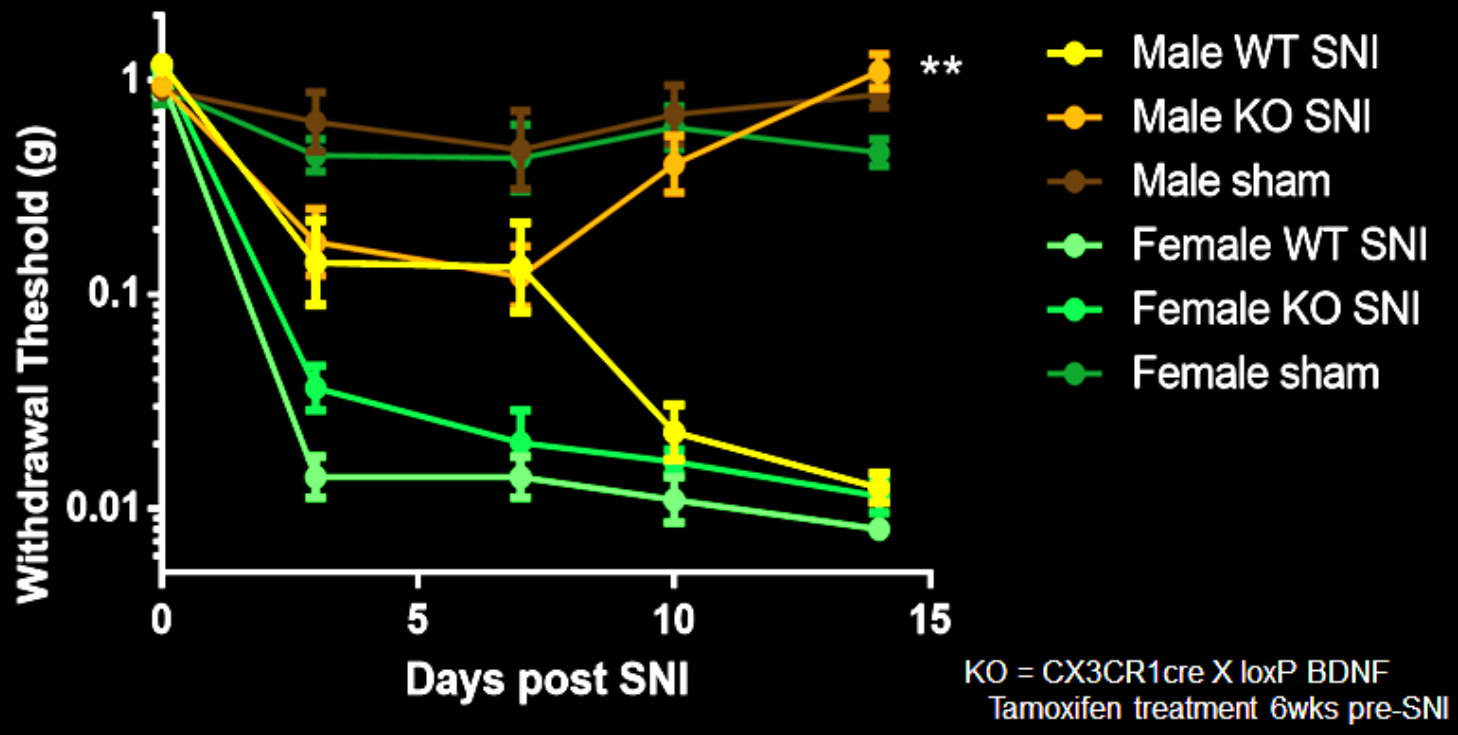


# Microglia depletion reverses pain hypersensitivity … but only in males…



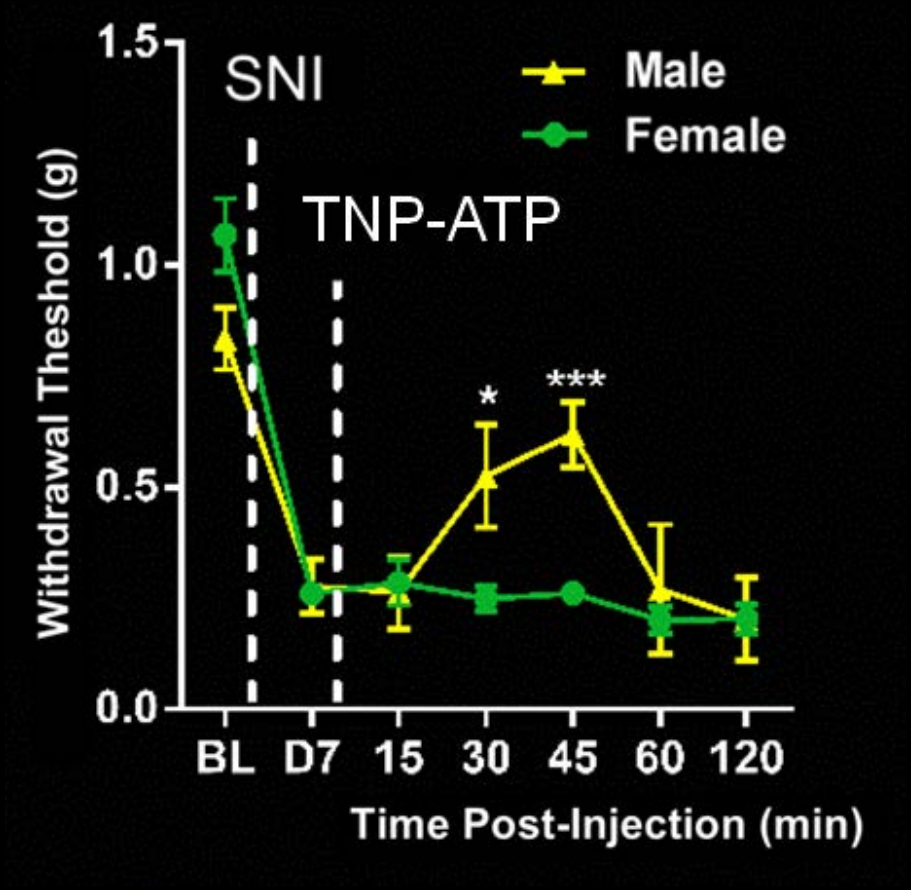

Sorge et al. unpublished

# Pain hypersensitivity prevented by microglia BDNF depletion in males only




Sorge et al. unpublished

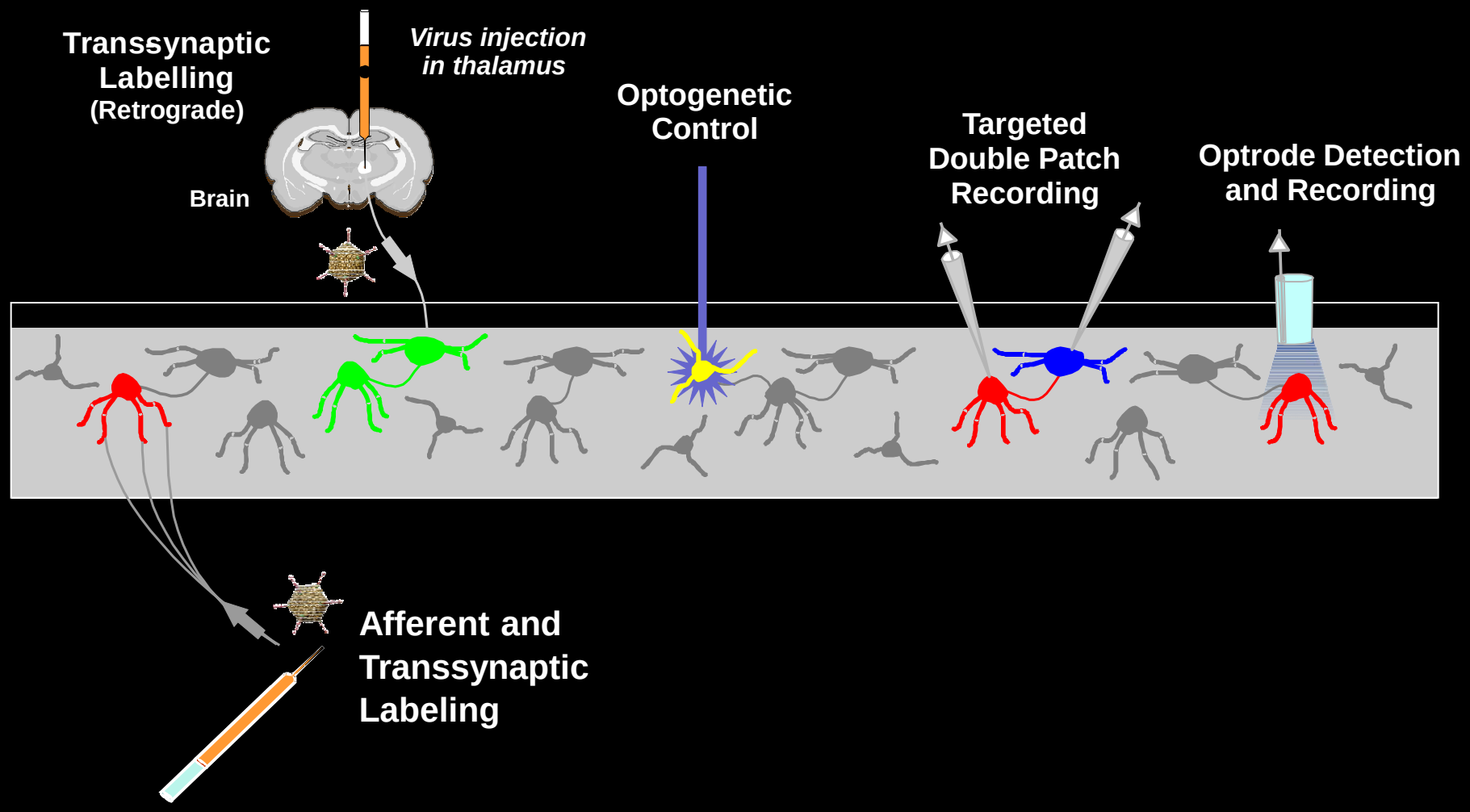
# Pain hypersensitivity reserved by P2X4 receptor blocker but only in males




Sorge et al. unpublished

# What microglia ?

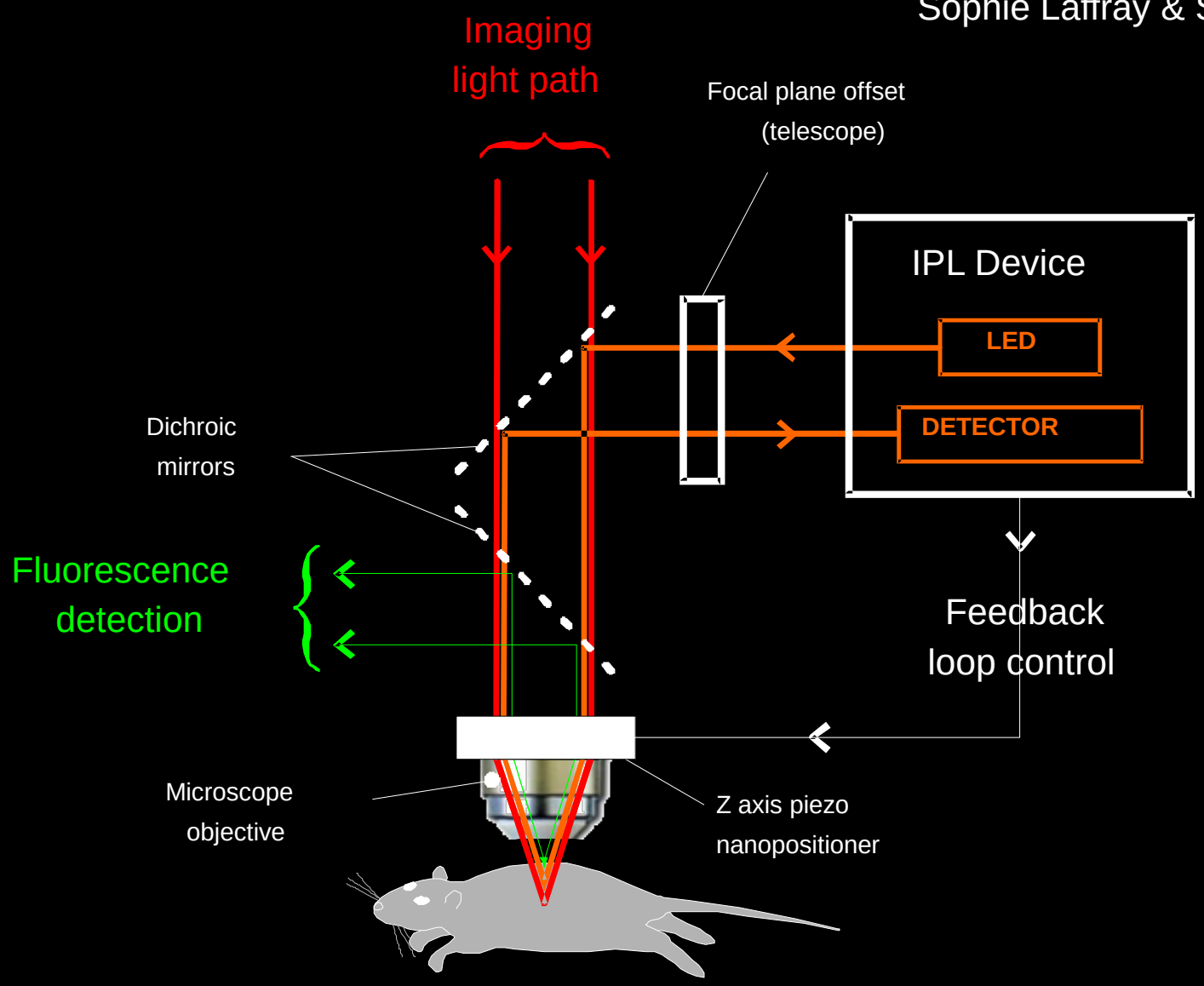
# The expanding optogenetic toolbox…




Prescott et al *Nat.Neurosci.* 2014

# Challenge: Functional imaging of cellular dynamics *in situ*

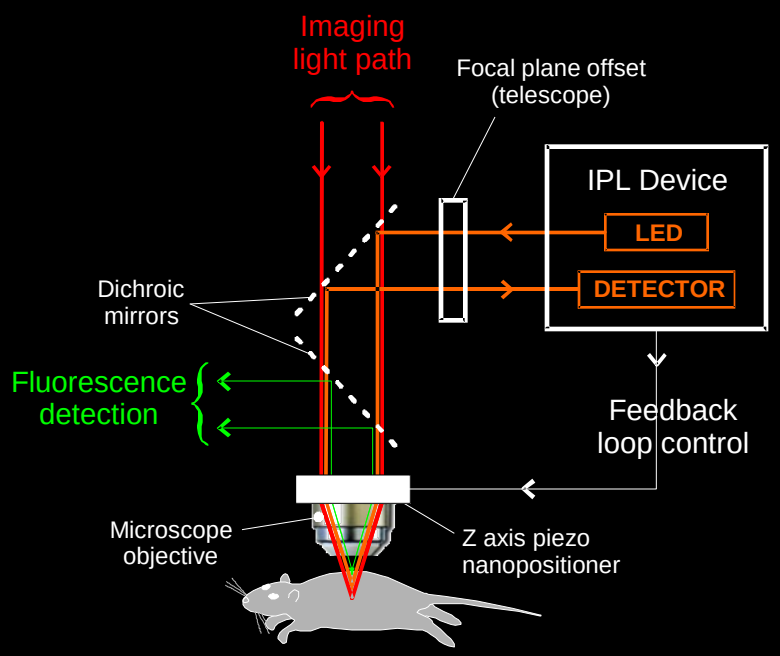
Sophie Laffray & Stéphane Pagès



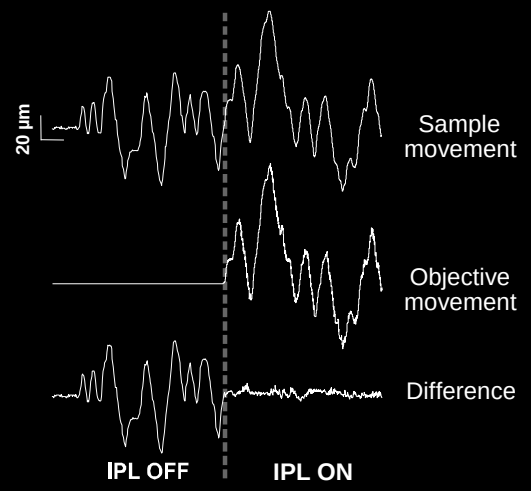

*Laffray, Pages et al. PLoS One* 2011

# In vivo functional imaging: dealing with movement…

Sophie Laffray & Stéphane Pagès




*Adaptive, real-time movement compensation*

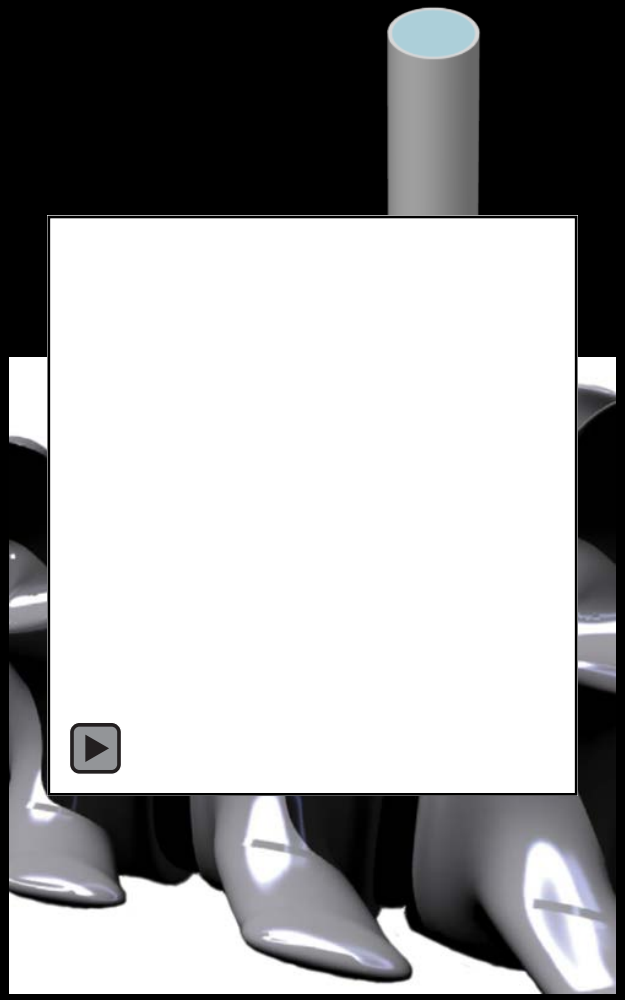


**Mov. compensation OFF**

*Laffray, Pages et al. PLoS One* 2011

# Challenge: Functional imaging of cellular dynamics in behaving animals

Erik Bélanger
Sophie Laffray



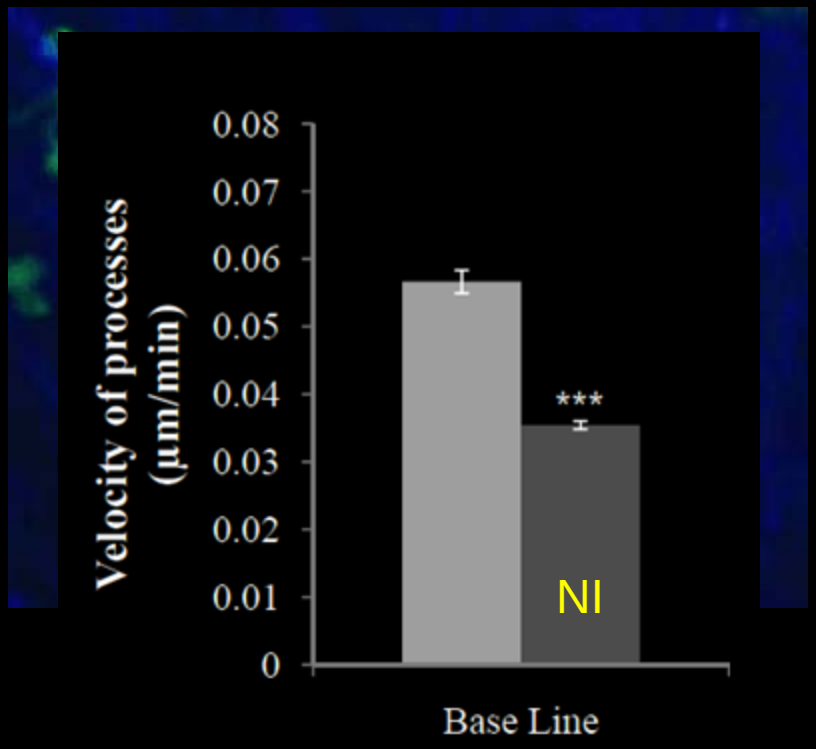
Bélanger et al, *J. Biomed. Opt.* 2012

# A characterization of microglia based on their dynamic behaviour

Sophie Laffray

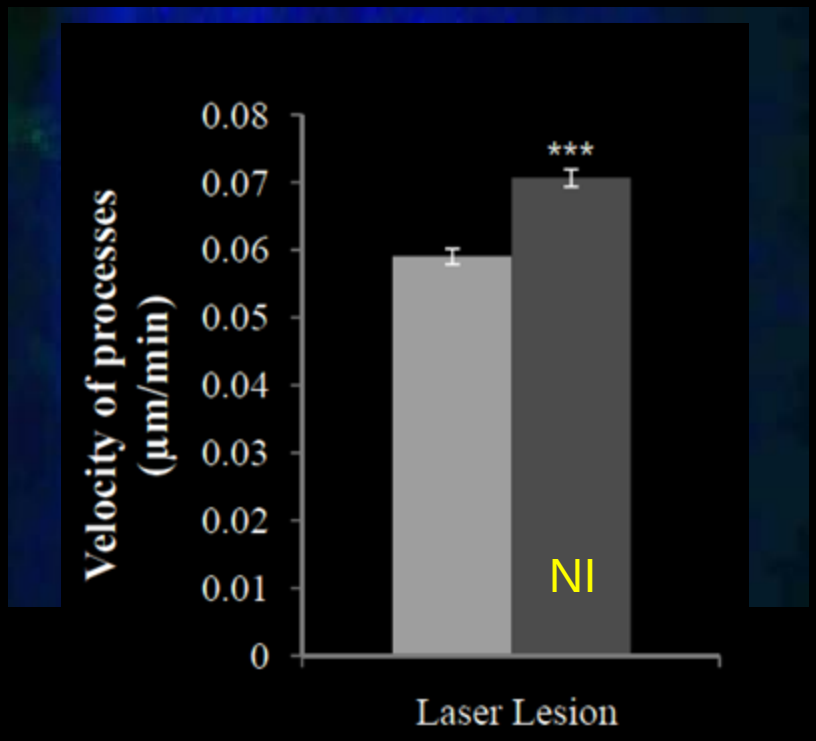
*In vivo* two photon imaging across the dura matter

**Normal surveillance mode**




After peripheral nerve injury (NI)

**Response to a focal laser lesion**




After peripheral nerve injury (NI)

Merci!