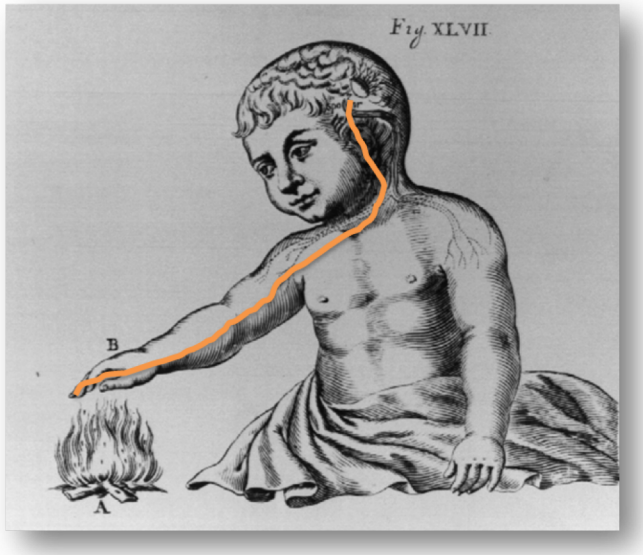
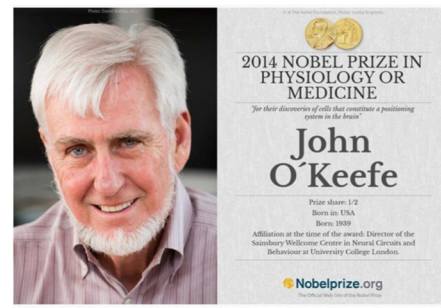
The discovery of *Central Sensitization* and its implications

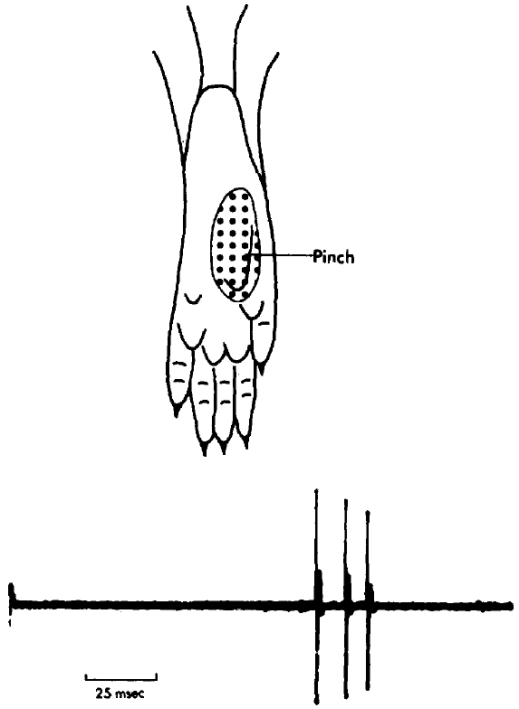


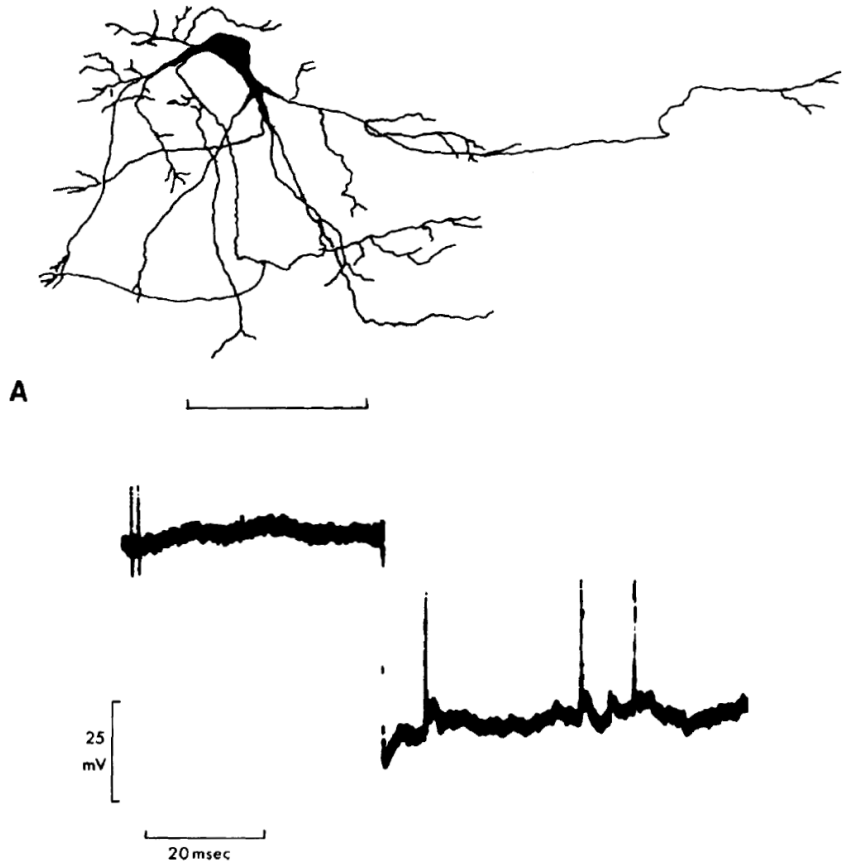
Clifford Woolf


2014 NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE
"for their discoveries of cells that constitute a positioning system in the brain"
John O´Keefe
Prize share: 1/2
Born in: USA
Born: 1939
Affiliation at the time of the award: Director of the Sainsbury Wellcome Centre in Neural Circuits and Behaviour at University College London.
Nobelprize.org

Abandoning the ADC approach

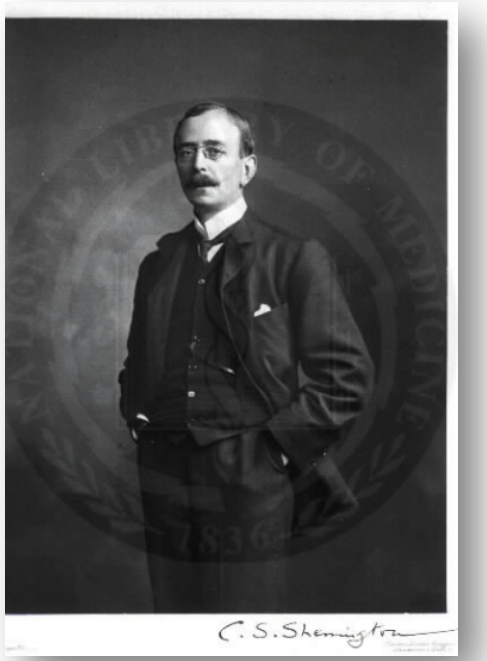
Maria Fitzgerald

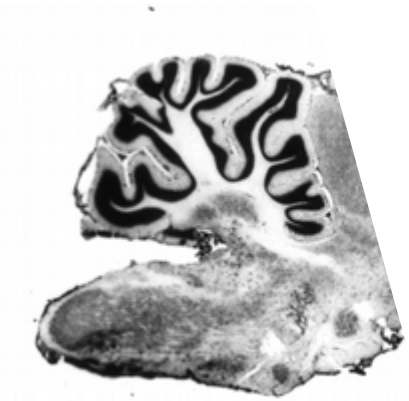


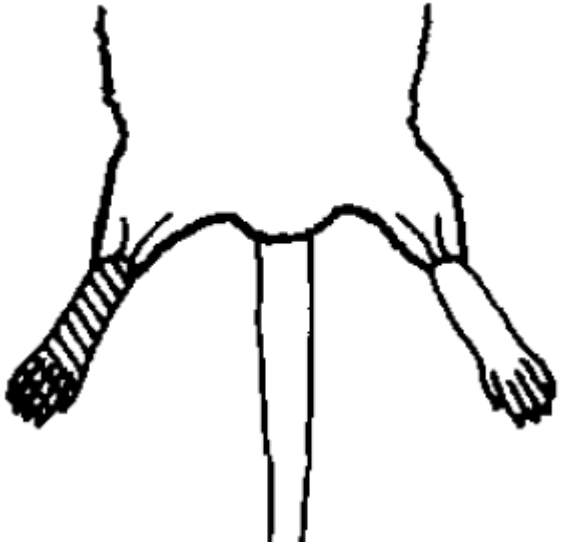


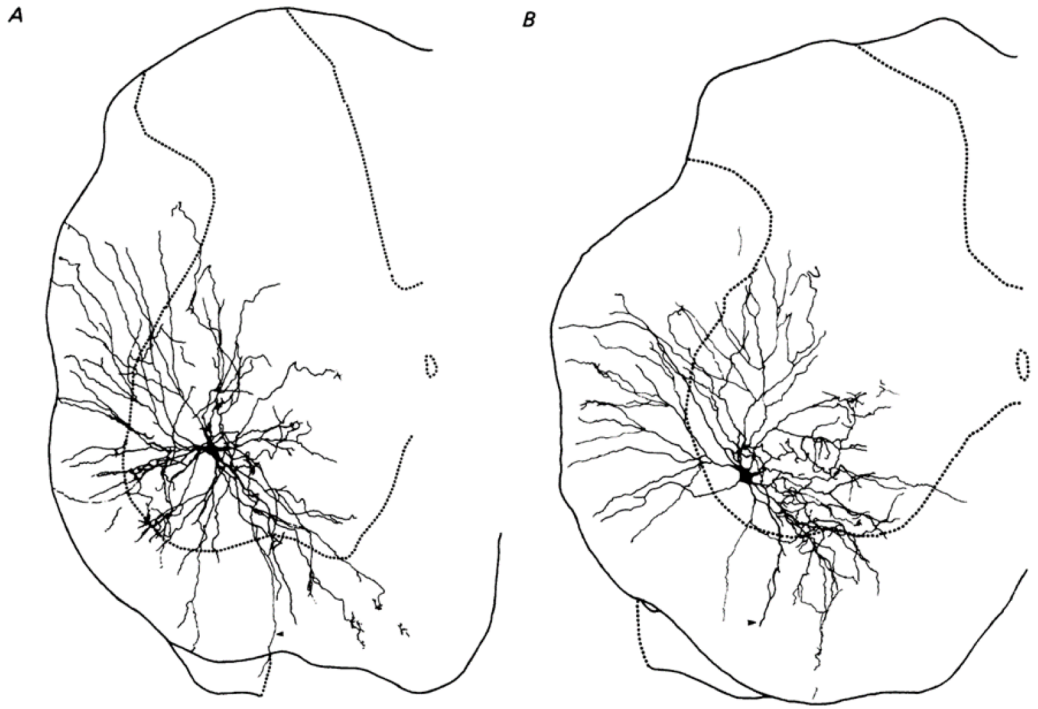
Woolf CJ, Fitzgerald M. **The properties of neurones recorded in the superficial dorsal horn of the rat spinal cord.** J Comp Neurol. 1983 Dec 10;221:313-28.

Adapting the FMN approach









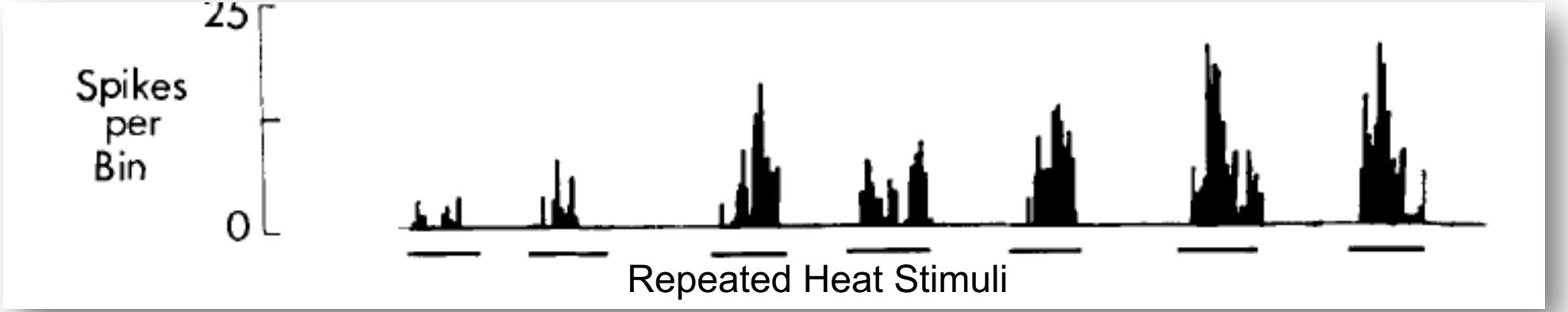
Woolf CJ, Swett JE. **The cutaneous contribution to the hamstring flexor reflex in the rat: an electrophysiological and anatomical study**. Brain Res. 1984 303:299-312.

Location and properties of the cutaneous receptive fields responsible for eliciting the flexor withdrawal reflex examined in unanaesthetized decerebrate rats, spinalized at T10-T11. Single alpha-motoneurone efferents recorded and responses to hindlimb skin stimulation investigated.

Efferents had low or absent background discharge and all had mechanoreceptive fields on **ipsilateral foot**. The mechanical threshold of these fields was **high with no response to light touch or brush.**

The flexor reflex in the spinal rat provides a useful model therefore, for studying how the input in nociceptive afferents is processed and transformed within the spinal cord to produce appropriate outputs.

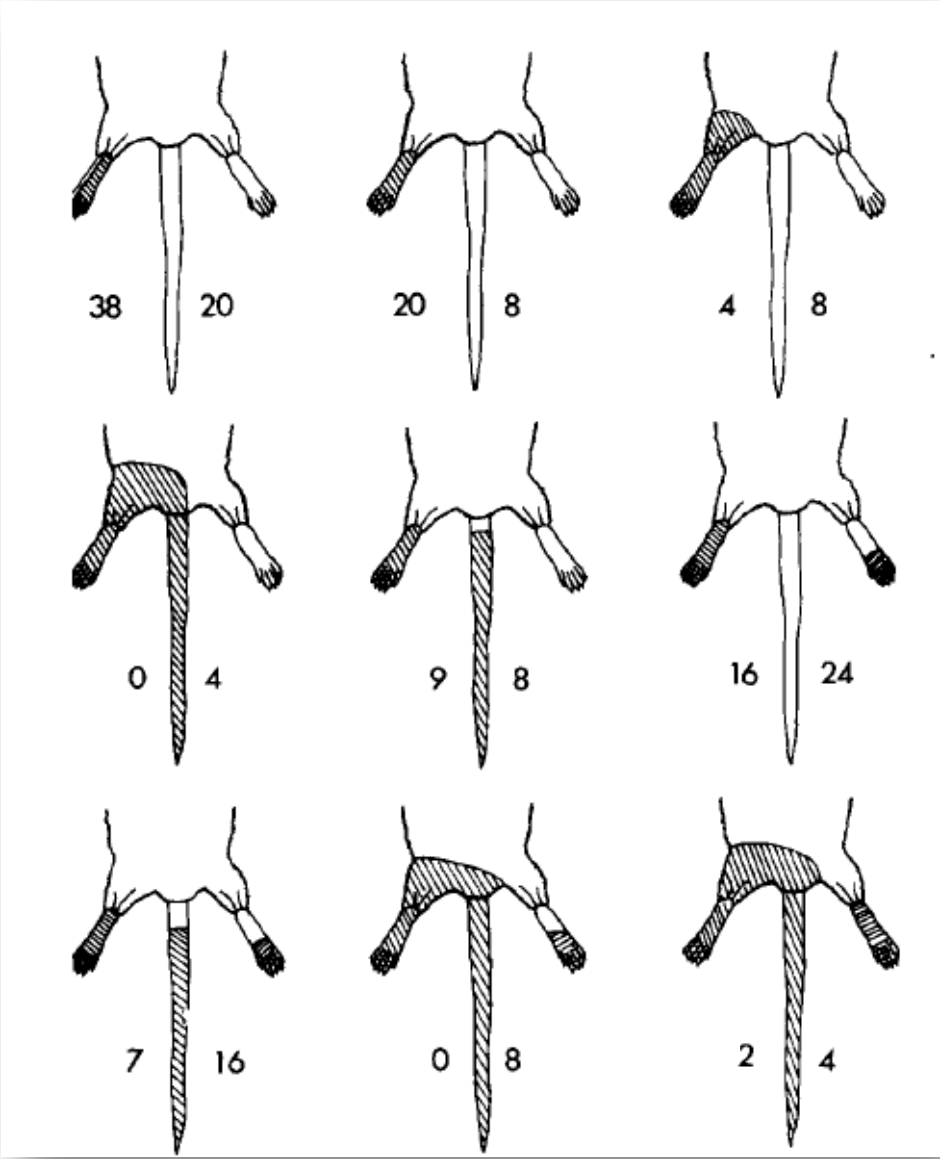
Peripheral sensitization?



Repeated Heat Stimuli

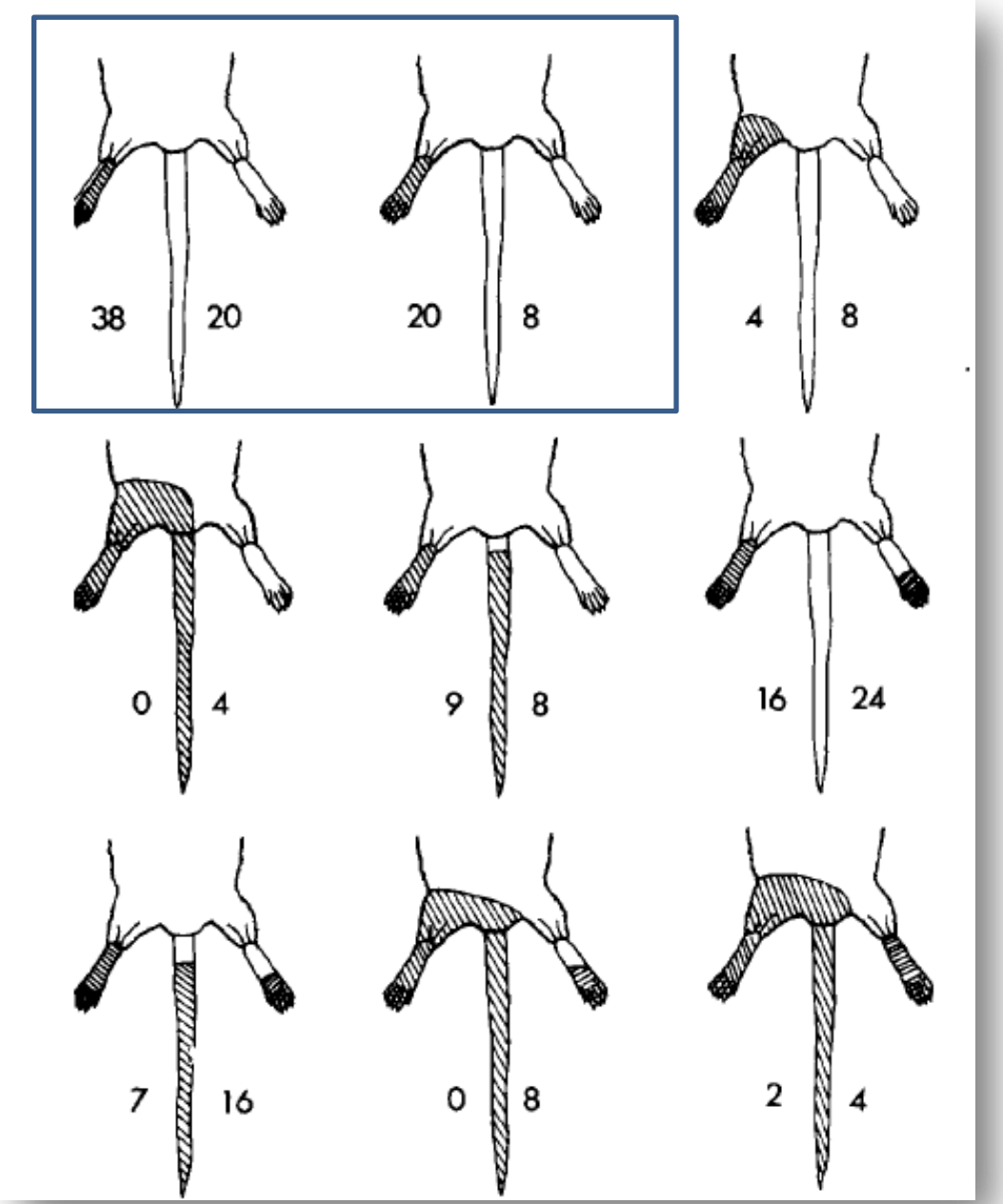
Ed Perl

Confusion!



Resolution!

72% early
28% late



28% early
72% late

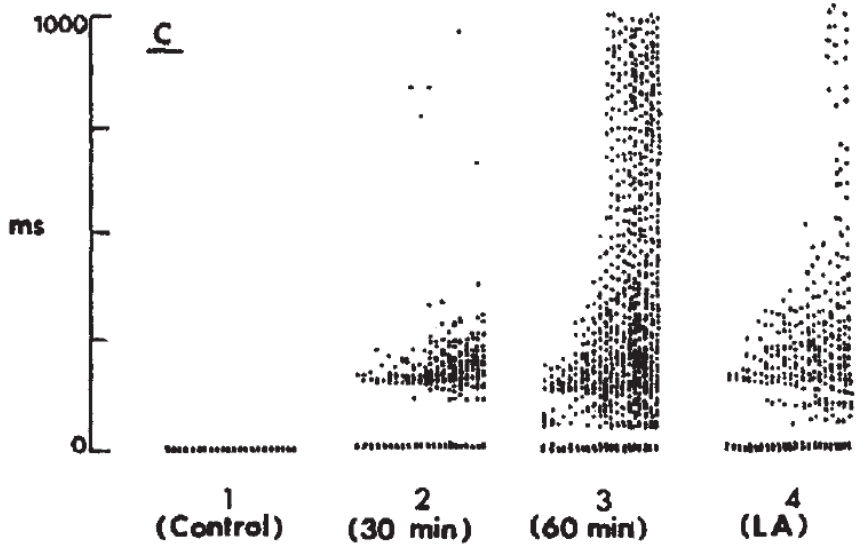
NATURE VOL. 306 15 DECEMBER 1983

Evidence for a central component of post-injury pain hypersensitivity

Clifford J. Woolf

Department of Anatomy, University College London, London WC1E 6BT, UK

Proof of CNS hyperexcitability



Woolf CJ **Evidence for a central component of post-injury pain hypersensitivity**. Nature 1983 Dec 15-21;306:686-8.

Because sensitization of peripheral receptors occurs following injury, a peripheral mechanism is widely held to be responsible for post-injury hypersensitivity.

Developed an animal model where changes occur in the threshold and responsiveness of the flexor reflex following peripheral injury that are analogous to the sensory changes found in man.

Electrophysiological analysis of injury-induced increases in excitability of the flexion reflex shows that it arises from changes in the activity of the spinal cord.

Long-term consequences of noxious stimuli result, therefore, from central as well as from peripheral changes.

Woolf CJ, McMahon SB. **Injury-induced plasticity of the flexor reflex in chronic decerebrate rats**. Neuroscience. 1985 16:395-404.

Hindlimb-flexor-withdrawal reflex elicited by stimulation of skin of hindpaw examined in chronic decerebrate rats. Once threshold of skin exceeded, a brief burst of activity with short afterdischarge occurs in flexor motoneurones and the threshold, duration and responsiveness of the reflex remains stable when tested repeatedly.

Tissue injury/local inflammation result in marked and long-lasting (several weeks) alterations in the ipsilateral withdrawal reflex. **The mechanical threshold necessary to elicit the falls so that light touch or brush can now elicit a response instead of the firm pressure or pinch required pre-injury**. **Suprathreshold stimuli to the inflamed skin now generate a sustained oscillating pattern of flexion in contrast to the brief flick found in control animals.**

Populations of single cutaneous mechanoreceptive C-primary afferents recorded both from untreated decerebrate rats and from rats with an inflamed hindpaw **are indistinguishable in terms of their response properties**.

Wall PD, Woolf CJ. **Muscle but not cutaneous C-afferent input produces prolonged increases in the excitability of the flexion reflex in the rat.** J Physiol. 1984 Nov;356:443-58.

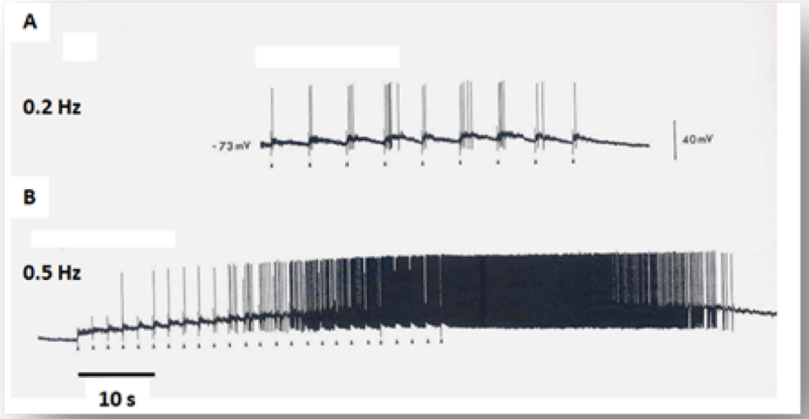
Cook AJ, Woolf CJ, Wall PD. **Prolonged C-fibre mediated facilitation of the flexion reflex in the rat is not due to changes in afferent terminal or motoneurone excitability** Neurosci Lett. 1986 Sep 25;70(1):91-6.

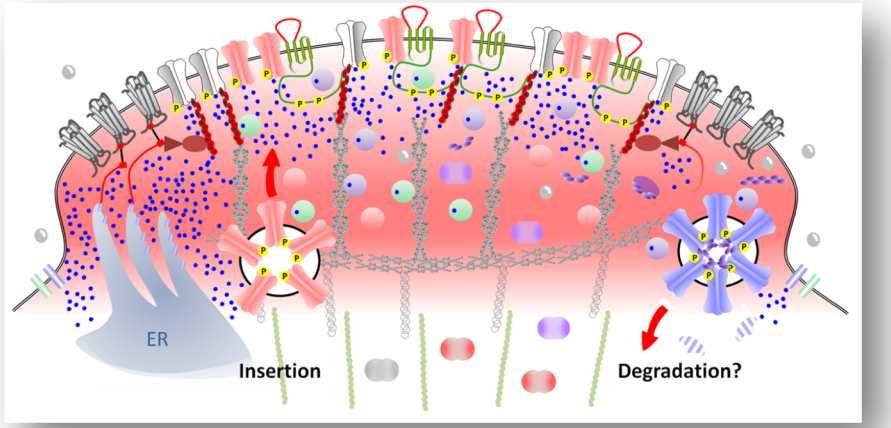
Cook AJ, Woolf CJ, Wall PD, McMahon SB. **Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input**. Nature. 1987 Jan 8-14;325(7000):151-3.

Woolf CJ, Thompson SW, King AE. **Prolonged primary afferent induced alterations in dorsal horn neurones, an intracellular analysis in vivo and in vitro**. J Physiol (Paris). 1988/9; 83(3):255-66

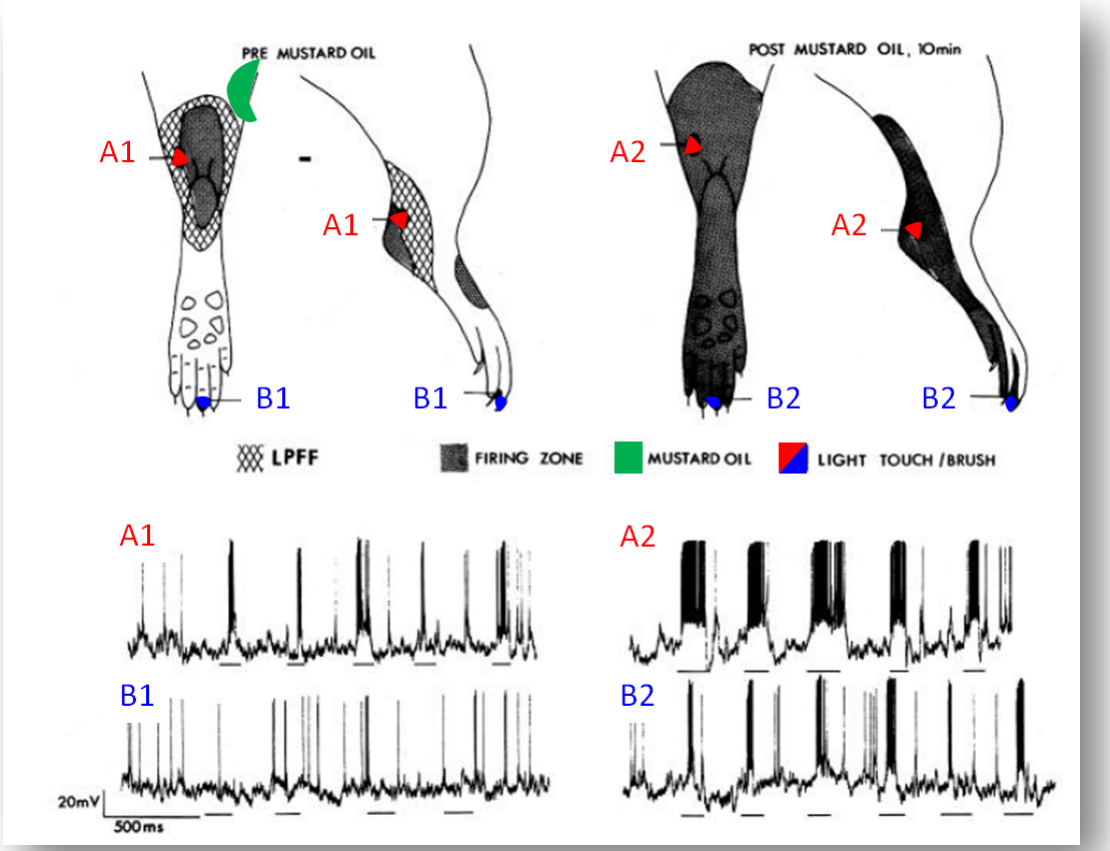
Two mechanisms contribute to post-injury hypersensitivity syndrome; sensitization of the peripheral terminals of high threshold primary afferents and an increase in the excitability of the spinal cord; **central sensitization**.

In dorsal horn neurones recorded intracellularly in an isolated hemisected spinal cord, stimulation of a dorsal root produces in some neurones a **prolonged facilitation** with both an augmentation of the response to the conditioning root (**homosynaptic potentiation**) and to adjacent test roots (**heterosynaptic potentiation**)





Woolf CJ, King AE **Dynamic alterations in the cutaneous mechanoreceptive fields of dorsal horn neurons in the rat spinal cord**. J Neurosci. 1990 Aug;10(8):2717-26.



Subliminal input – functional reservoir

LaMotte RH, Lundberg LE, Torebjörk HE. Pain, hyperalgesia and activity in nociceptive C units in humans after intradermal injection of capsaicin. J Physiol. 1992 448:749-64.

Woolf CJ, Thompson SW. **The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation; implications for the treatment of post-injury pain hypersensitivity states**. Pain. 1991 Mar;44(3):293-9.

Park KM, Max MB, Robinovitz E, Gracely RH, Bennett GJ. Effects of intravenous ketamine, alfentanil, or placebo on pain, pinprick hyperalgesia, and allodynia produced by intradermal capsaicin in human subjects. Pain. 1995 Nov;63(2):163-72.

Willert RP, Woolf CJ, Hobson AR, Delaney C, Thompson DG, Aziz Q. The development and maintenance of human visceral pain hypersensitivity is dependent on the N-methyl-D-aspartate receptor. Gastroenterology. 2004 Mar;126(3):683-92.

García-Henares et al Effects of Ketamine on Postoperative Pain After Remifentanil-Based Anesthesia for Major and Minor Surgery in Adults: A Systematic Review and Meta-Analysis. Front Pharmacol. 2018 Aug 17;9:921

Pendi et al Perioperative Ketamine for Analgesia in Spine Surgery: A Meta-analysis of Randomized Controlled Trials. Spine 2018 Mar 1;43(5):E299-E307

Brunelli M, Castellucci V, Kandel ER
Synaptic facilitation and behavioral sensitization in Aplysia: possible role of serotonin and cyclic AMP.
Science. 1976 194:1178-81.

Woolf CJ, Walters ET. **Common patterns of plasticity contributing to nociceptive sensitization in mammals and Aplysia**. Trends Neurosci. 1991 Feb;14(2):74-8

In contrast to innocuous stimuli, which only have transient effects when applied to the body surface, noxious stimuli generate persistent changes in the nervous system. This **nociceptive memory** manifests itself most prominently as a **post-injury sensitization** where, after tissue damage, the avoidance reaction and pain that result from subsequent stimuli are exaggerated and prolonged and can be initiated by low intensity stimuli. **Similarities between nociceptive sensitization in mammals (including humans) and the mollusc Aplysia californica suggest that fundamental mechanisms contributing to injury-induced behavioral modifications might be widespread in the animal kingdom.**

THE NOBEL ASSEMBLY AT THE KAROLINSKA INSTITUTE
9 October 2000

The Nobel Assembly at Karolinska Institutet has today decided to award **The Nobel Prize in Physiology or Medicine for 2000**

Arvid Carlsson, Paul Greengard and **Eric Kandel** for their discoveries concerning “signal transduction in the nervous system”

Eric Kandel is rewarded for his discoveries of how the efficiency of synapses can be modified, and which molecular mechanisms that take part. With the nervous system of a sea slug as experimental model he has demonstrated how **changes of synaptic function are central for learning and memory.** Protein phosphorylation in synapses plays an important role for the generation of a form of short term memory. For the development of a long term memory a change in protein synthesis is also required, which can lead to alterations in shape and function of the synapse.

Richmond CE, Bromley LM, Woolf CJ. **Preoperative morphine pre-empts postoperative pain.** Lancet. 1993 Jul 10;342(8863):73-5.

Pre-emptive analgesia

Moore KA, Kohno T, Karchewski LA, Scholz J, Baba H, Woolf CJ.
Partial peripheral nerve injury promotes a selective loss of GABAergic inhibition in the superficial dorsal horn of the spinal cord.J Neurosci. 2002 Aug 1;22(15):6724-31

Baba H, Ji RR, Kohno T, Moore KA, Ataka T, Wakai A, Okamoto M, Woolf CJ.**Removal of GABAergic inhibition facilitates polysynaptic A fiber-mediated excitatory transmission to the superficial spinal dorsal horn** Mol Cell Neurosci. 2003 Nov;24(3):818-30.

Disinhibiiton

Clinical manifestations

Dahl JB, et al **Pain sensation and nociceptive reflex excitability in surgical patients and human volunteers**. Br J Anaesth. 1992 Aug;69(2):117-21

Choe et al **Epidural morphine plus ketamine for upper abdominal surgery: improved analgesia from preincisional versus postincisional administration**. Anesth Analg. 1997 Mar;84(3):560-3.

Katz et al **Postoperative morphine use and hyperalgesia are reduced by preoperative but not intraoperative epidural analgesia: implications for preemptive analgesia and the prevention of central sensitization.** Anesthesiology. 2003 Jun;98(6):1449-60

Baykan et al **Characterization of Migraineurs Having Allodynia: Results of a Large Population-based Study**. Clin J Pain. 2016 Jul;32(7):631-5.

Gervais-Hupé et al **Validity of the central sensitization inventory with measures of sensitization in people with knee osteoarthritis.** Clin Rheumatol. 2018 Nov;37(11):3125-3132

Koltzenburg et al **Nociceptor modulated central sensitization causes mechanical hyperalgesia in acute chemogenic and chronic neuropathic pain**. Brain. 1994 Jun;117 (Pt 3):579-9

Woolf CJ. **What to call the amplification of nociceptive signals in the central nervous system that contribute to widespread pain?** Pain. 2014 Oct;155(10):1911-2.

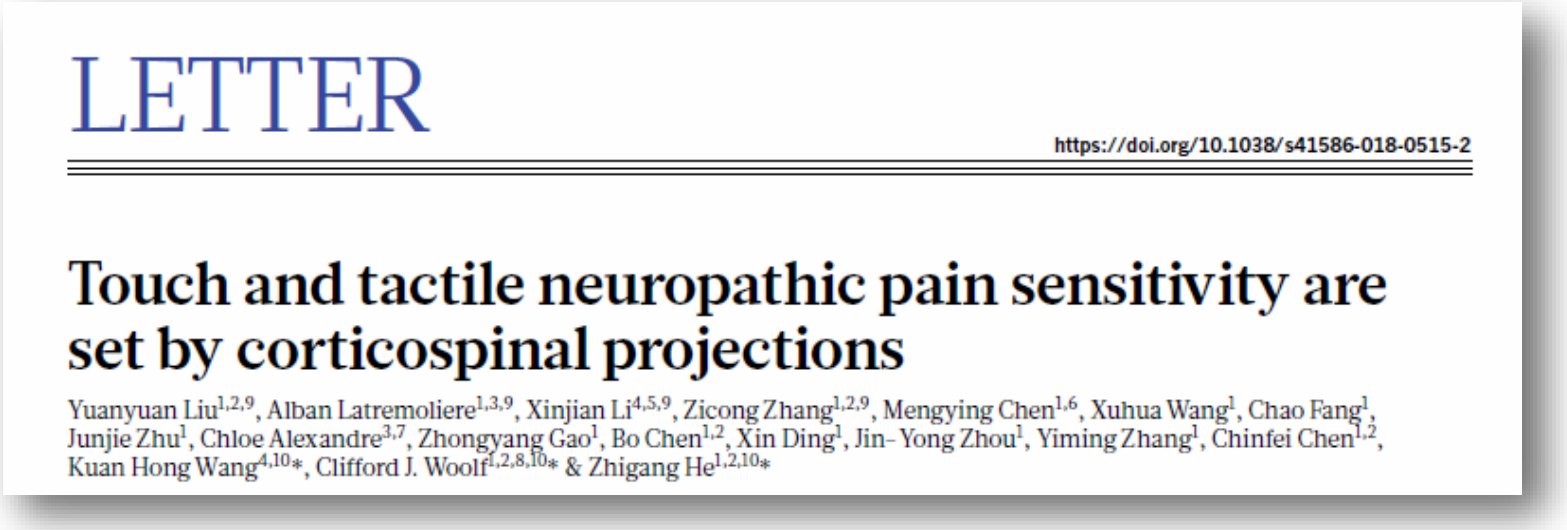
“What’s in a name? That which we call a rose by any other name would smell as sweet”

What is CS?

Amplification within the CNS of those circuits connecting sensory input from the periphery to those cortical areas where pain is perceived such that the degree of pain evoked by noxious stimuli is exaggerated (hyperalgesia), innocuous stimuli begin to elicit pain (allodynia), pain duration is extended and summates, and pain sensitivity spreads to undamaged/non inflamed tissue (secondary hyperalgesia)

Mechanistic underpinnings

Use-dependent synaptic facilitation driven by primary afferent input
Local disinhibition – reduced/altered gene expression, cell death
Distributed facilitation or reduced inhibition – change in circuit activity



LETTER

https://doi.org/10.1038/s41586-018-0515-2

Touch and tactile neuropathic pain sensitivity are set by corticospinal projections

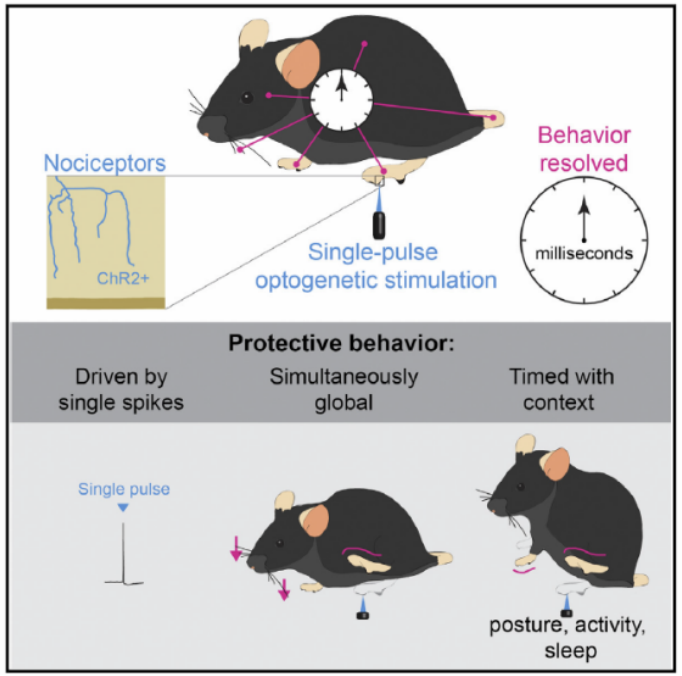
Yuanyuan Liu[1,2,9], Alban Latremoliere[1,3,9], Xinjian Li[4,5,9], Zicong Zhang[1,2,9], Mengying Chen[1,6], Xuhua Wang[1], Chao Fang[1], Junjie Zhu[1], Chloe Alexandre[3,7], Zhongyang Gao[1], Bo Chen[1,2], Xin Ding[1], Jin-Yong Zhou[1], Yiming Zhang[1], Chinfei Chen[1,2], Kuan Hong Wang[4,10]*, Clifford J. Woolf[1,2,8,10]* & Zhigang He[1,2,10]*

Article

Cell Reports

Time-Resolved Fast Mammalian Behavior Reveals the Complexity of Protective Pain Responses

Graphical Abstract



Authors

Liam E. Browne, Alban Latremoliere, Brendan P. Lehnert, ..., David P. Roberson, David D. Ginty, Clifford J. Woolf

Correspondence

liam.browne@ucl.ac.uk (L.E.B.), clifford.woolf@childrens.harvard.edu (C.J.W.)

In Brief

Browne et al. find that the responses evoked by noxious stimuli, when examined at a millisecond resolution, are not fixed, localized, or limited to reflex withdrawal but are instead coordinated globally across the body in a sub-second time frame to alert the animal and limit potential harm.

Diagnostic features

Disproportionate pain
Dynamic tactile allodynia/reduced pressure pain threshold/temporal summation/ secondary hyperalgesia
fMRI

Central Sensitization Inventory

Soni et al. Central Sensitization in Knee Osteoarthritis: Relating Presurgical Brainstem Neuroimaging and PainDETECT-Based Patient Stratification to Arthroplasty Outcome. Arthritis Rheumatol. 2019;71:550-560.

Nijs et al. Applying modern pain neuroscience in clinical practice: criteria for the classification of central sensitization pain. Pain Physician. 2014 17:447-457

Treatment options

Don’t treat site where pain is experienced but the locus and nature of the central amplification
NMDA receptor antagonists/Gabapentin/dual amine uptake inhibitors/Opioids
Disease modification – prevent establishment of persistent changes in CNS by early interventions

Drugs that act on Central Sensitization

Ketamine

Stubhaug et al. **Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery**. Acta Anaesthesiol Scand. 1997 41:1124-32

Morphine

Mercieri et al. **Low-dose buprenorphine infusion to prevent postoperative hyperalgesia in patients undergoing major lung surgery and remifentanil infusion: a double-blind, randomized, active-controlled trial**. Br J Anaesth. 2017 ;119:792-802

Gabapentin/Pregabalin

Gottrup et al **Chronic oral gabapentin reduces elements of central sensitization in human experimental hyperalgesia**. Anesthesiology. 2004 Dec;101(6):1400-8

Bouwense et al **Effects of pregabalin on central sensitization in patients with chronic pancreatitis in a randomized, controlled trial**. PLoS One. 2012;7(8):e42096.

Duloxetine

Koh et al **Duloxetine Reduces Pain and Improves Quality of Recovery Following Total Knee Arthroplasty in Centrally Sensitized Patients: A Prospective, Randomized Controlled Study**. J Bone Joint Surg Am. 2019 Jan 2;101(1):64-73

Anti-NGF

Anti-CGRP

Risk of developing chronic pain?

Clark J et al. **What Are the Predictors of Altered Central Pain Modulation in Chronic Musculoskeletal Pain Populations? A Systematic Review.** Pain Physician. (2017)

Manfuku et al. **Comparison of central sensitization-related symptoms and health-related quality of life between breast cancer survivors with and without chronic pain and healthy controls.** Breast Cancer. 2019 May 24.

Kramer et al. **Somatosensory profiles in acute herpes zoster and predictors of postherpetic neuralgia.** Pain. 2019 Apr;160(4):882-894

What's next?

Population network activity in freely behaving animals

Optogenetic control of circuits

AI/Neural network analysis of preclinical model phenotypes

Human stem cell based neuronal network models