Imperial College London

Somatosensory system: pathways, sensory loss and nociception

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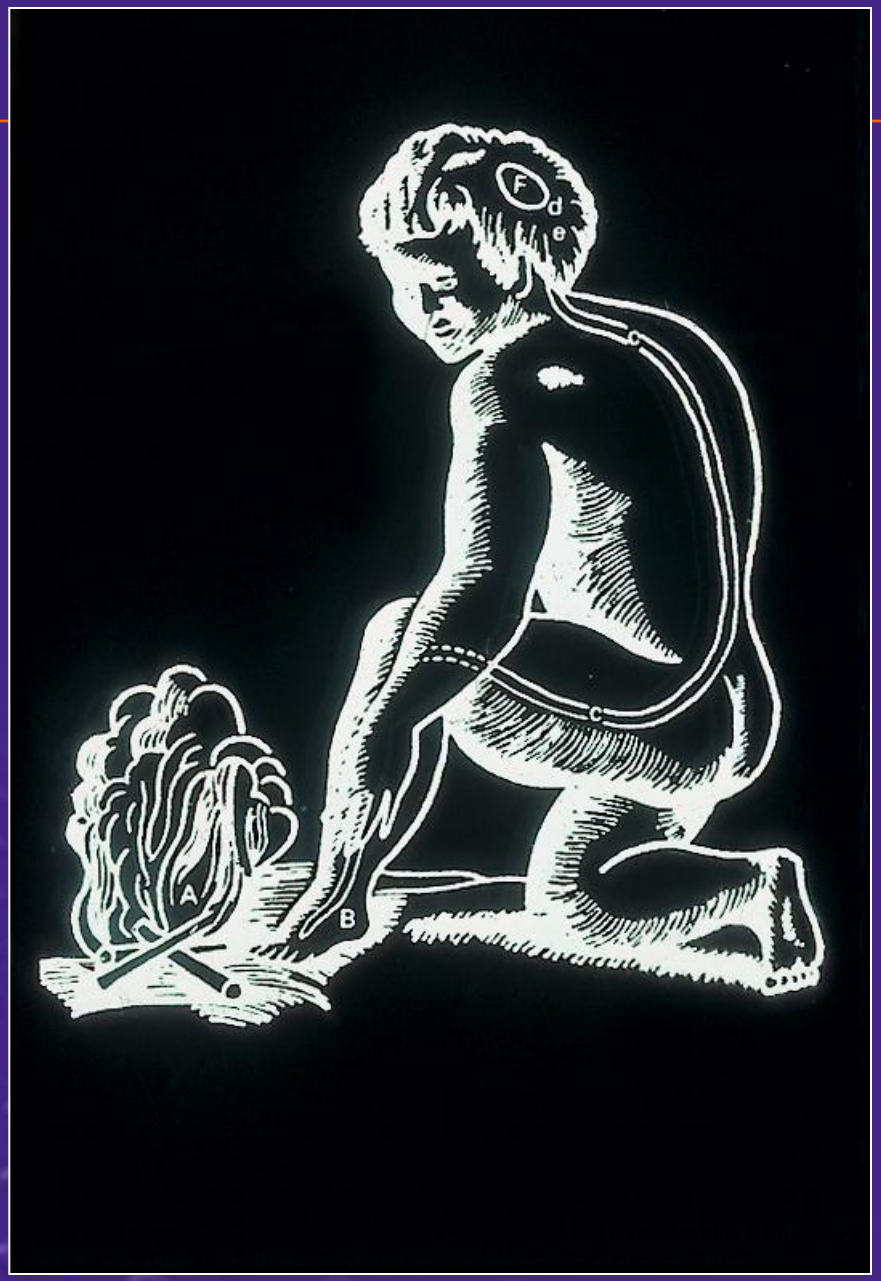
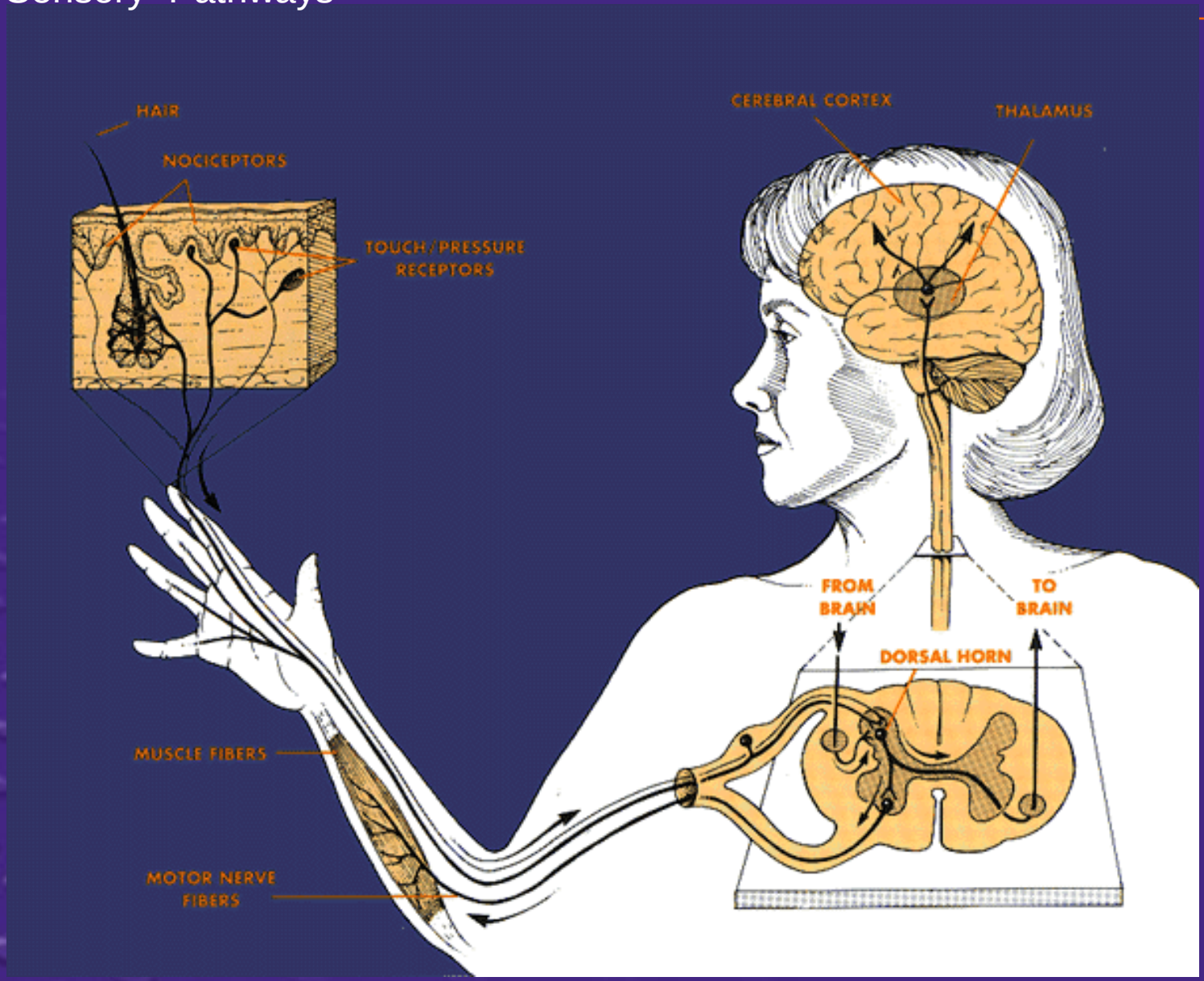
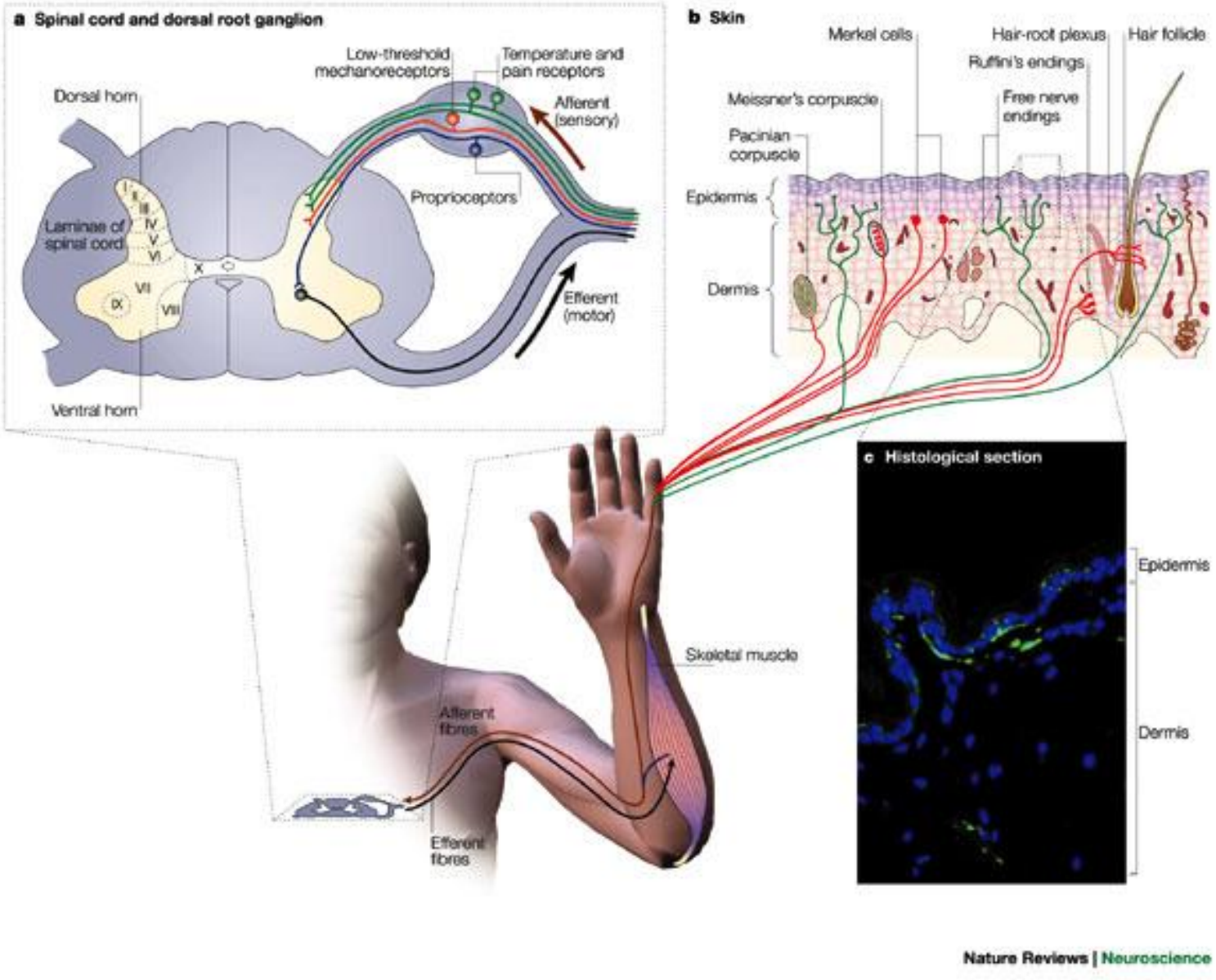
Descartes' model



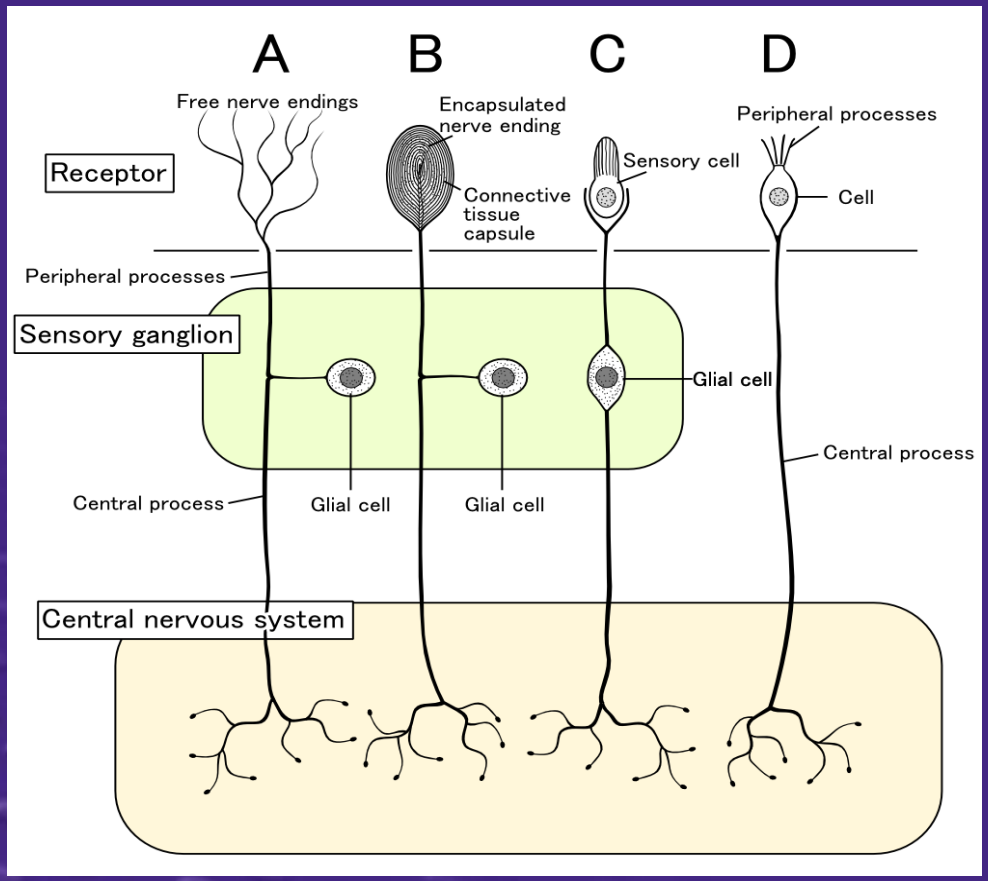
Sensory Pathways



Anatomic and Functional organisation of sensation



Sensory transmission



Sensory transmission - mechanoreceptors

By morphology

Ruffini's end organs detect tension deep in the skin.

Meissner's corpuscles detect changes in texture (vibrations around 50 Hz) and adapt rapidly.

Pacinian corpuscles detect rapid vibrations (about 200–300 Hz).

Merkel's discs detect sustained touch and pressure.

Mechanoreceiving free nerve endings detect touch, pressure and stretching

Hair follicle receptors are located in hair follicles and sense position changes of hairs.

Peripheral nerve fibres - Motor

- **Motor**
- Lower motor neurons have two kind of fibres:
- Motor fibre types Type
- Erlanger-Gasser Classification Diameter Myelin Conduction velocity Associated
- Aα 13-20 µm 80–120 m/s Extrafusal muscle fibers
- Aγ 5-8 µm 4–24 m/s Intrafusal muscle fibers

Peripheral nerve fibres - sensory

- Different sensory receptors are innervated by different types of nerve fibres.
- Proprioceptors are innervated by type Ia, Ib and II sensory fibres,
- mechanoreceptors by type II and III sensory fibres and
- nociceptors and thermoreceptors by type III and IV sensory fibres.
- Sensory fiber types Type Erlanger-Gasser
  Classification Diameter Myelin Conduction velocity Associated sensory receptors
- Ia Aα 13-20 µm 80–120 m/s Primary receptors of muscle spindle
- Ib Aα 13-20 µm 80–120 m/s Golgi tendon organ II
- Aβ 6-12 µm 33–75 m/s Secondary receptors of muscle spindle
- A delta and C All cutaneous mechanoreceptors III Aδ 1-5 µm Thin 3–30 m/s
- Free nerve endings of touch and pressure Nociceptors Cold thermoreceptors IV C 0.2-1.5 µm No 0.5-2.0 m/s Warmth receptors

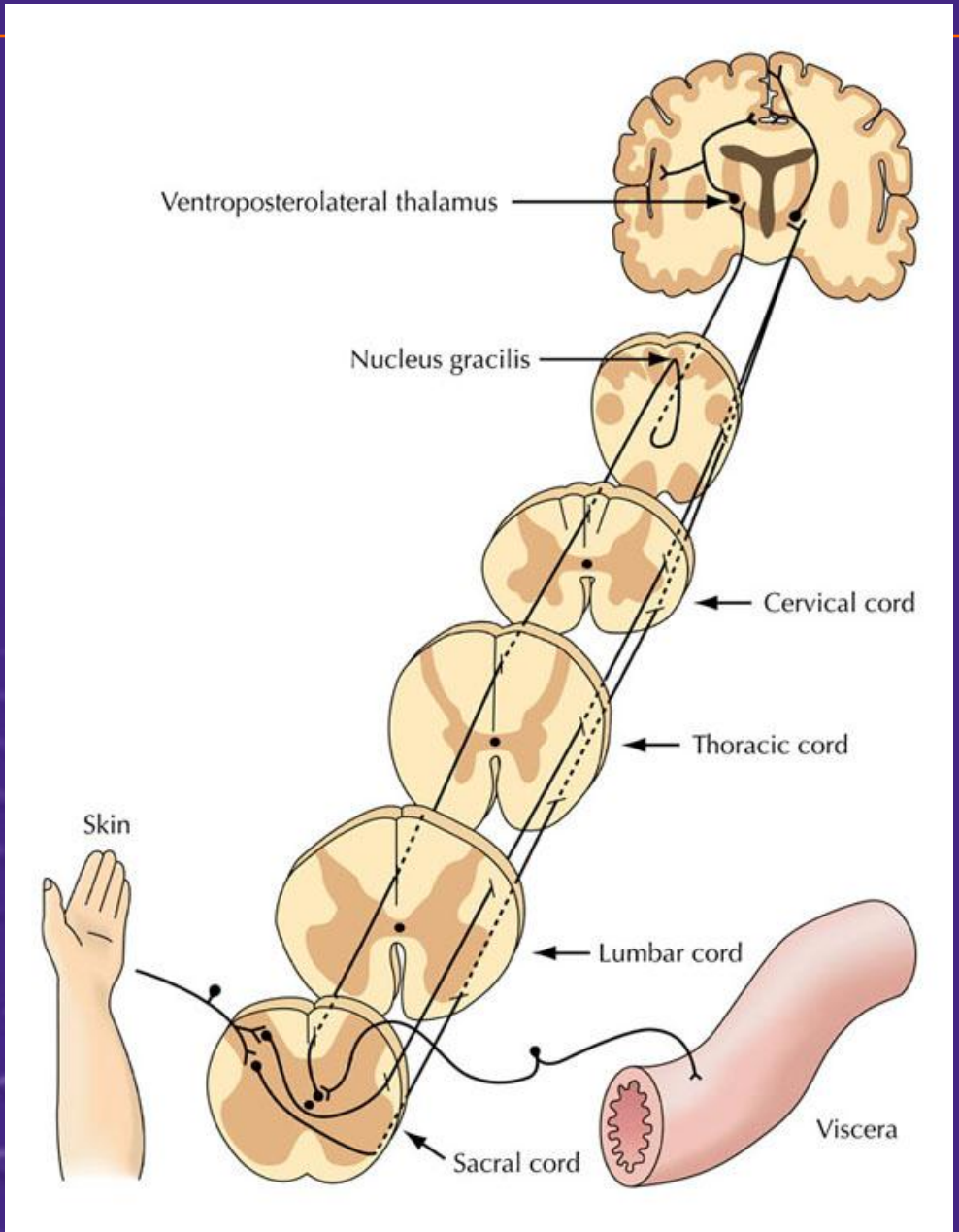
Peripheral nerve fibres - a**utonomic**

- **Autonomic**
- Autonomic nervous system has two kind of peripheral fibres:
- Type Erlanger-Gasser
  Classification Diameter Myelin Conduction velocity
- preganglionic fibers B 1-5 µm 3–15 m/s
- postganglionic fibers C 0.2-1.5 µm 0.5-2.0 m/s

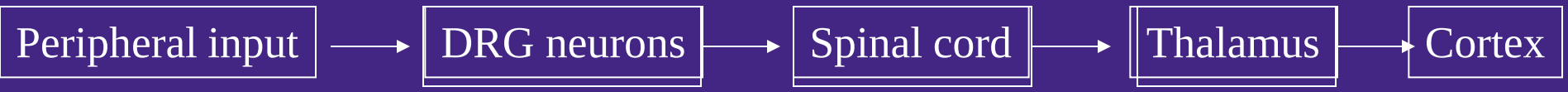
Two-point discrimination

- ability to discern that two nearby objects touching the skin are truly two distinct points, not one.
- It is often tested with two sharp points during a neurological examination
- and reflects how finely innervated an area of skin is
- The smallest and most dense sensory units are located in those areas that have the greatest somatosensory cortical representation
- Normally, a person should be able to recognize two points separated by as little as 2-4 mm on the lips and finger pads, 8-15 mm on the palms and 30-40 mm on the shins or back (assuming the points are at the same dermatome).
- Lesions of the sensory cortex will increase the distance.

Visceral Pain Pathways



Pain pathway

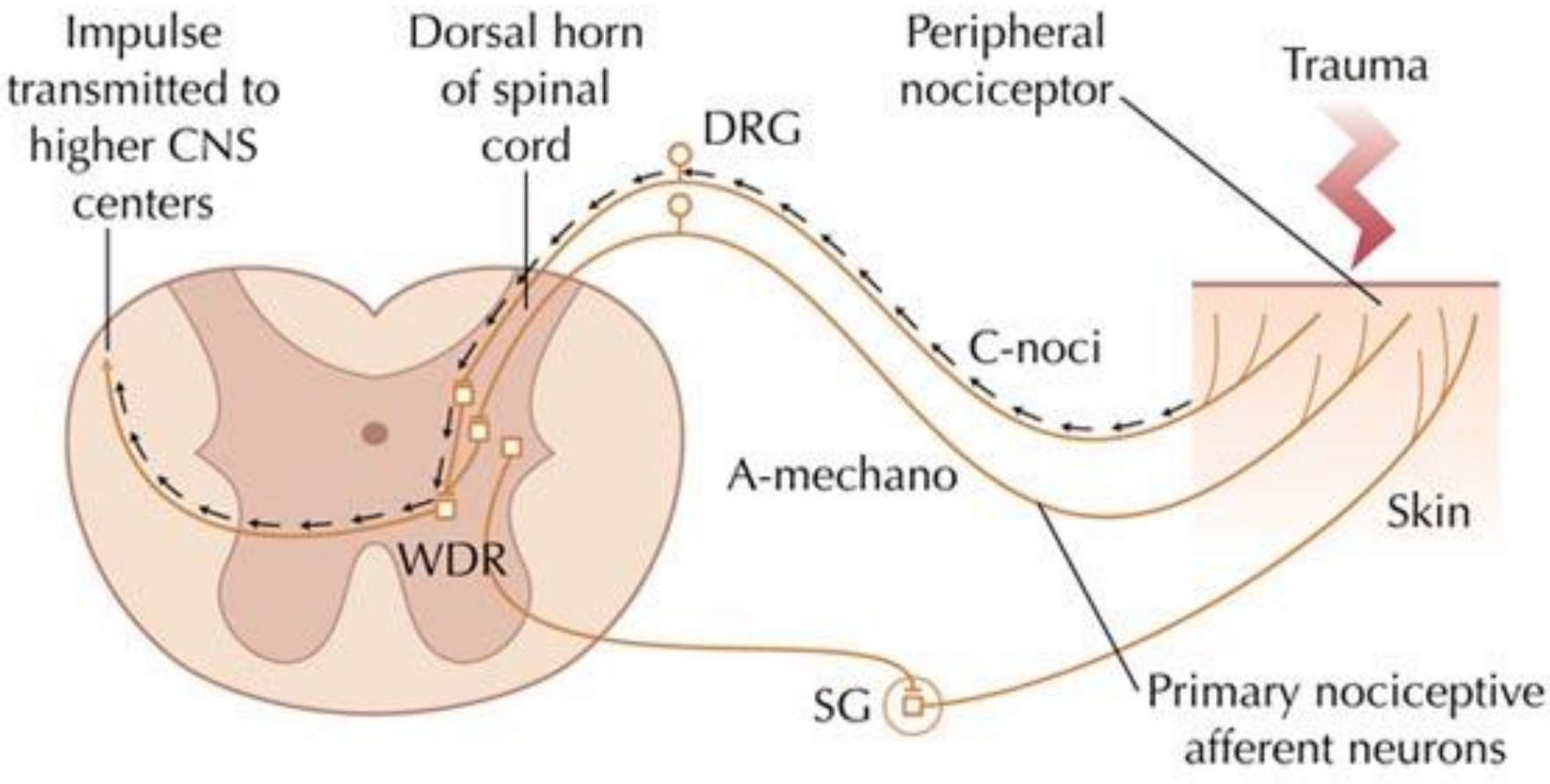


Normal pain sensation in the presence of painful stimuli (nociception)

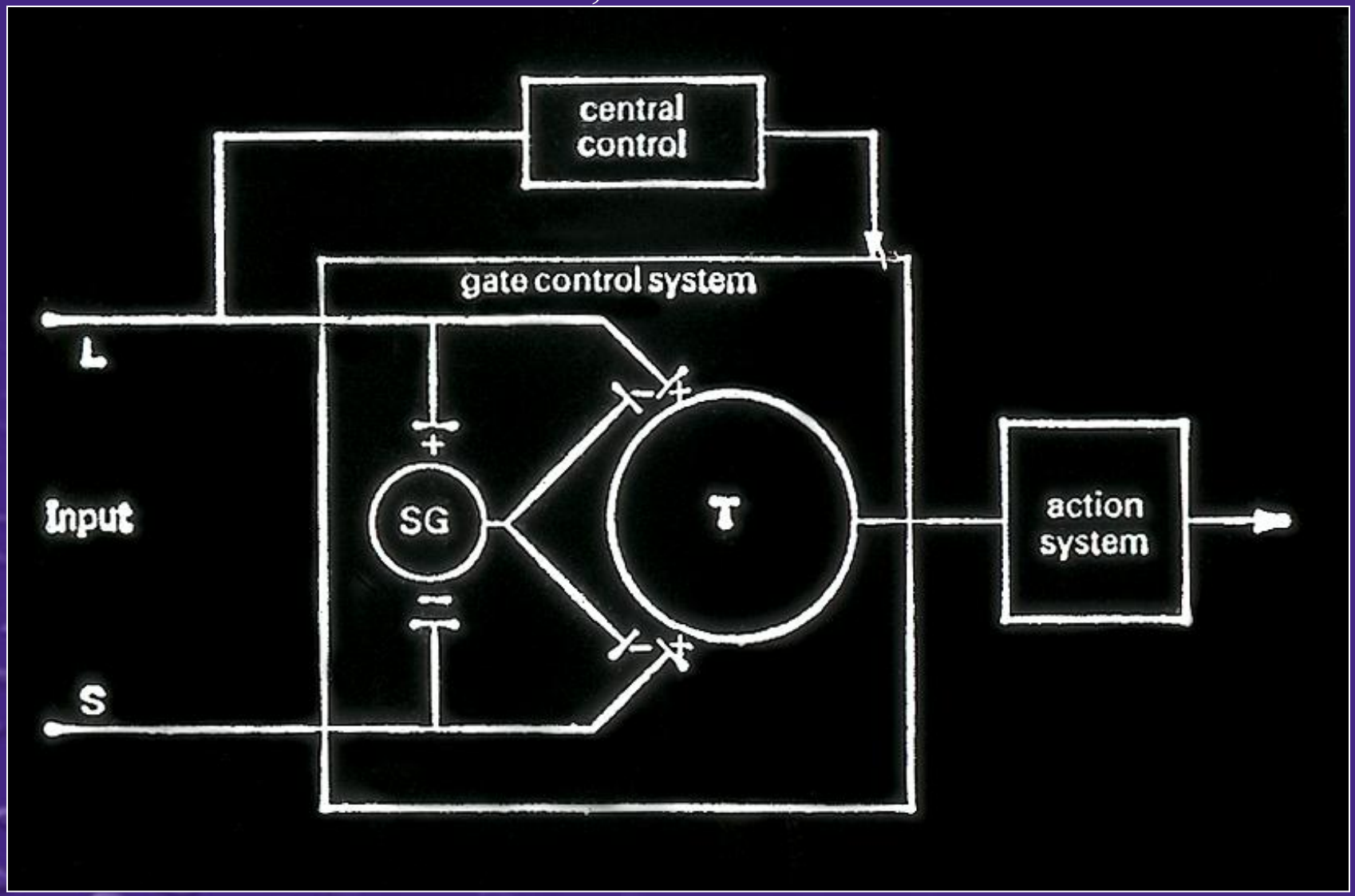
Inflammatory pain ⇒ sensitisation until healing of tissue

Neurogenic pain ⇒ maladaptive plasticity, damage or dysfunction of the pathway

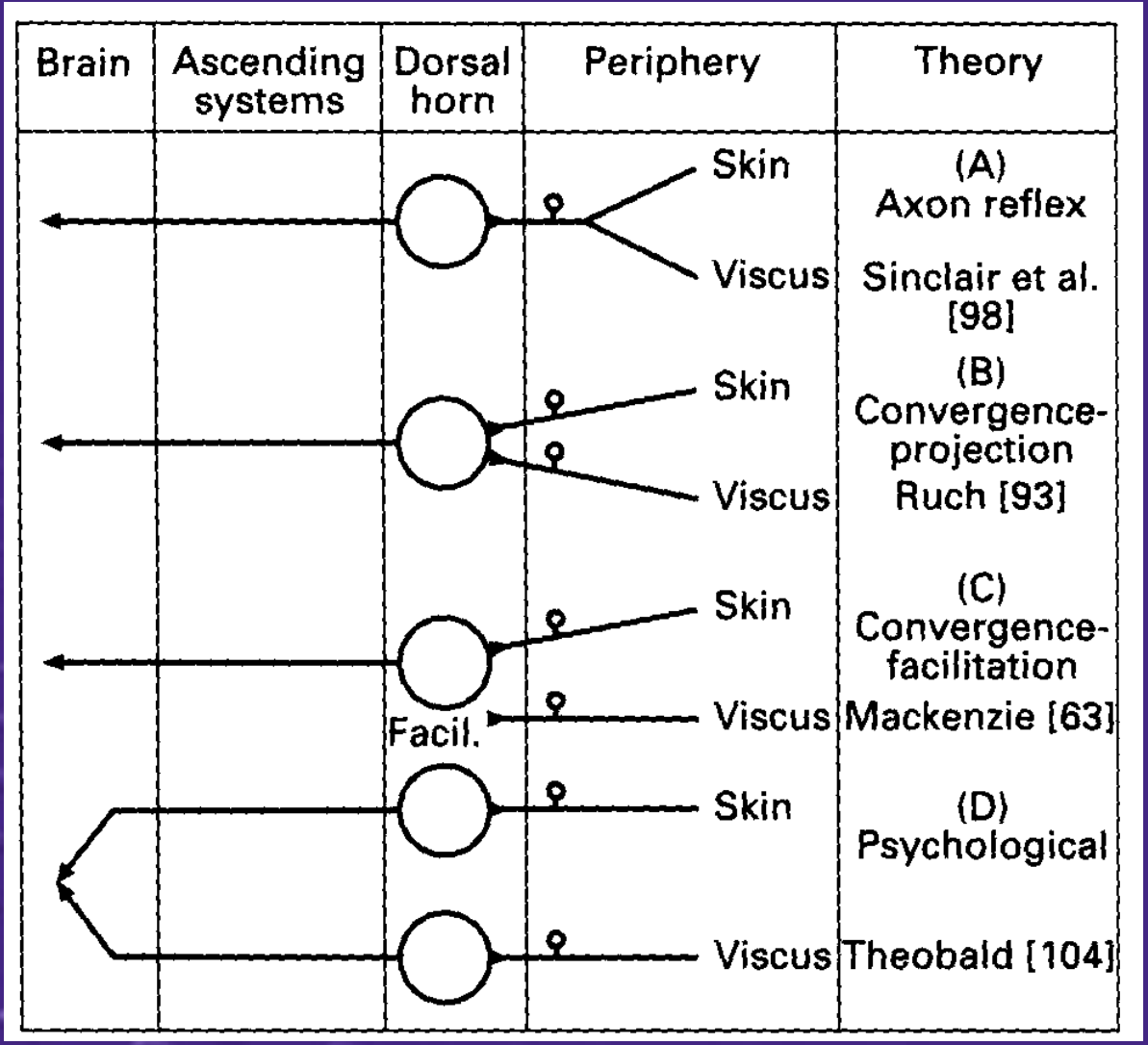
Nociceptive transmission



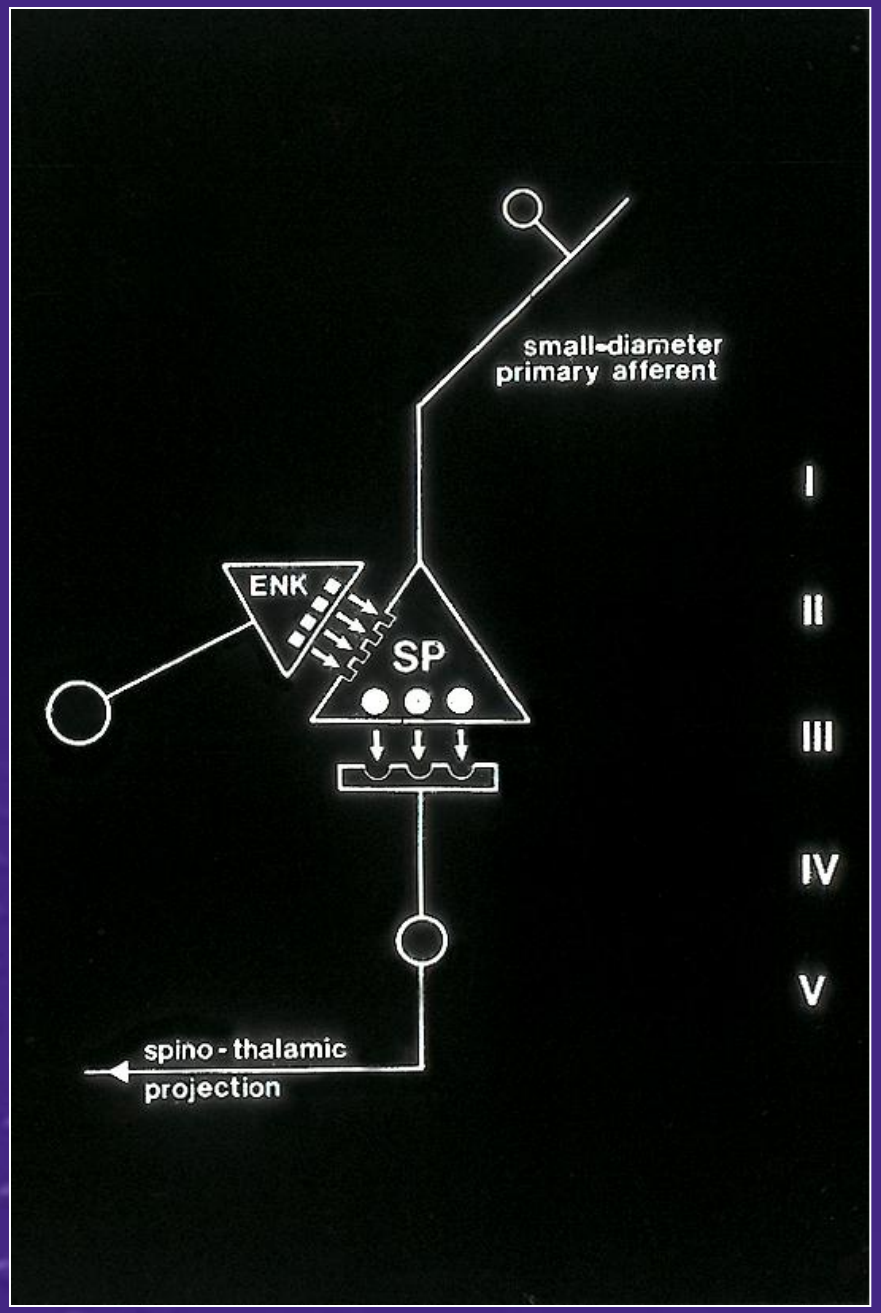
Gate control theory of pain
Wall and Melzack, 1965



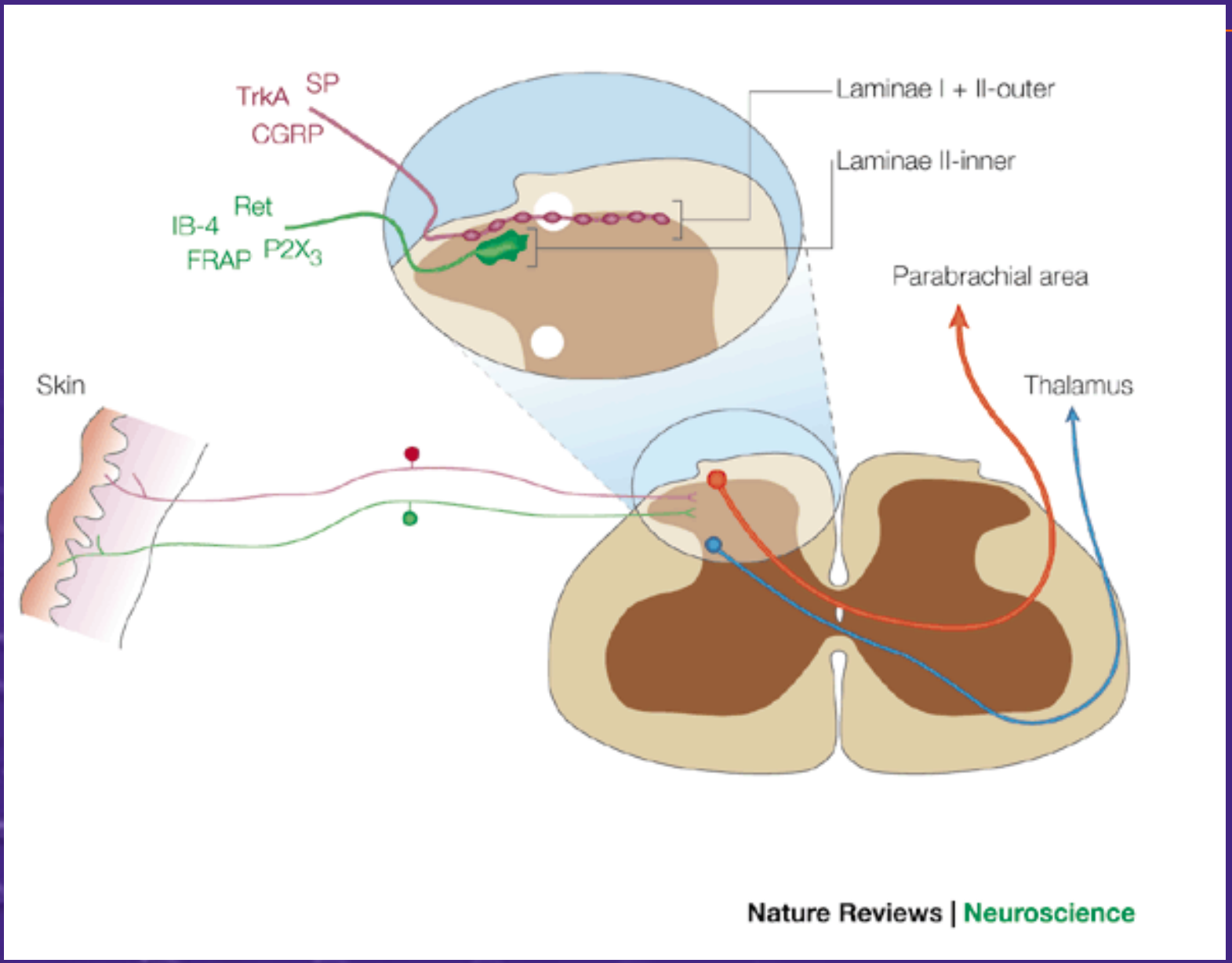
Referred Pain

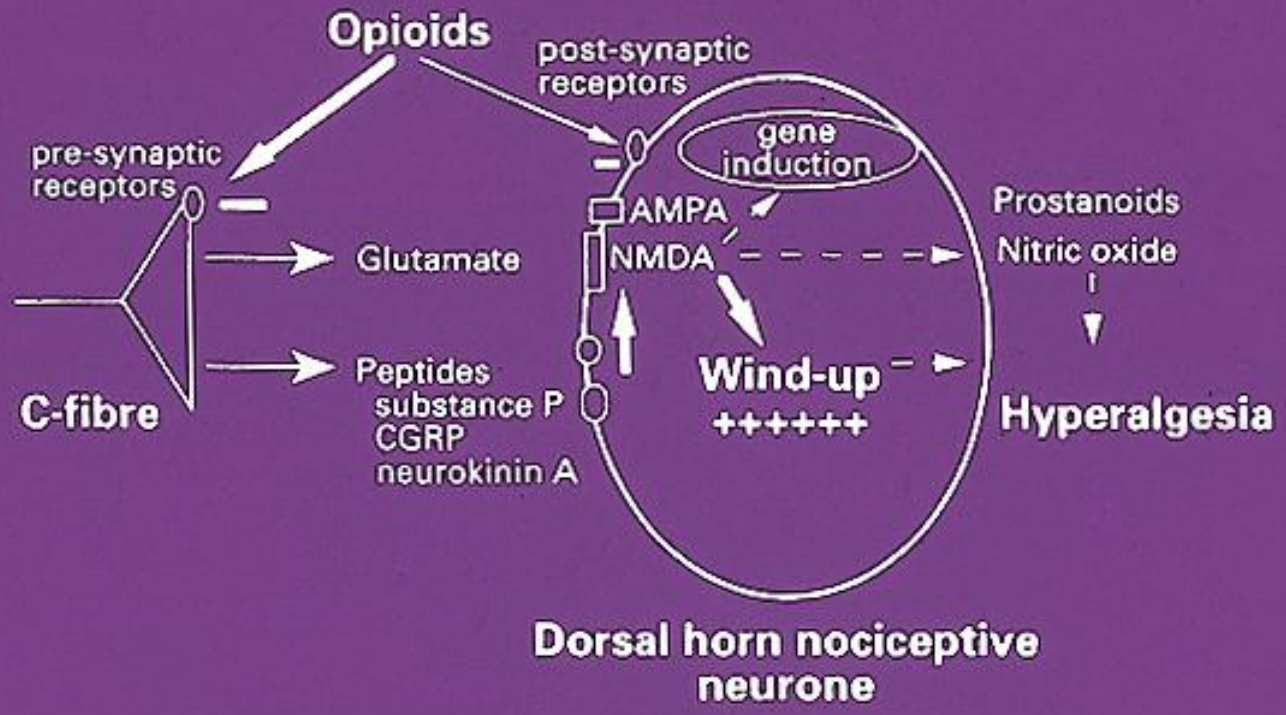


"Chemical labelling" of the Gate-control Theory of Pain



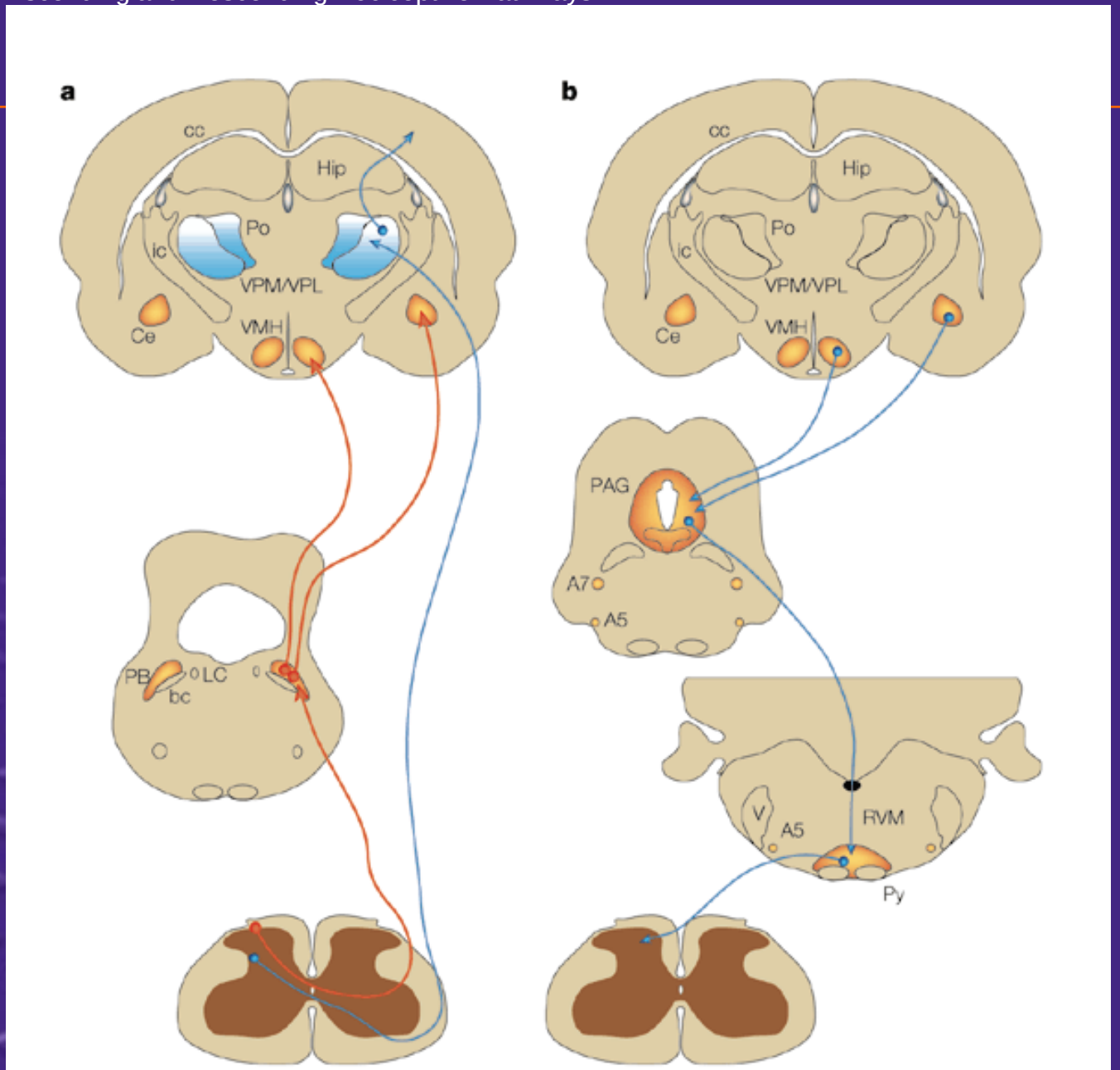
C Fibres and Dorsal Horn of Spinal Cord



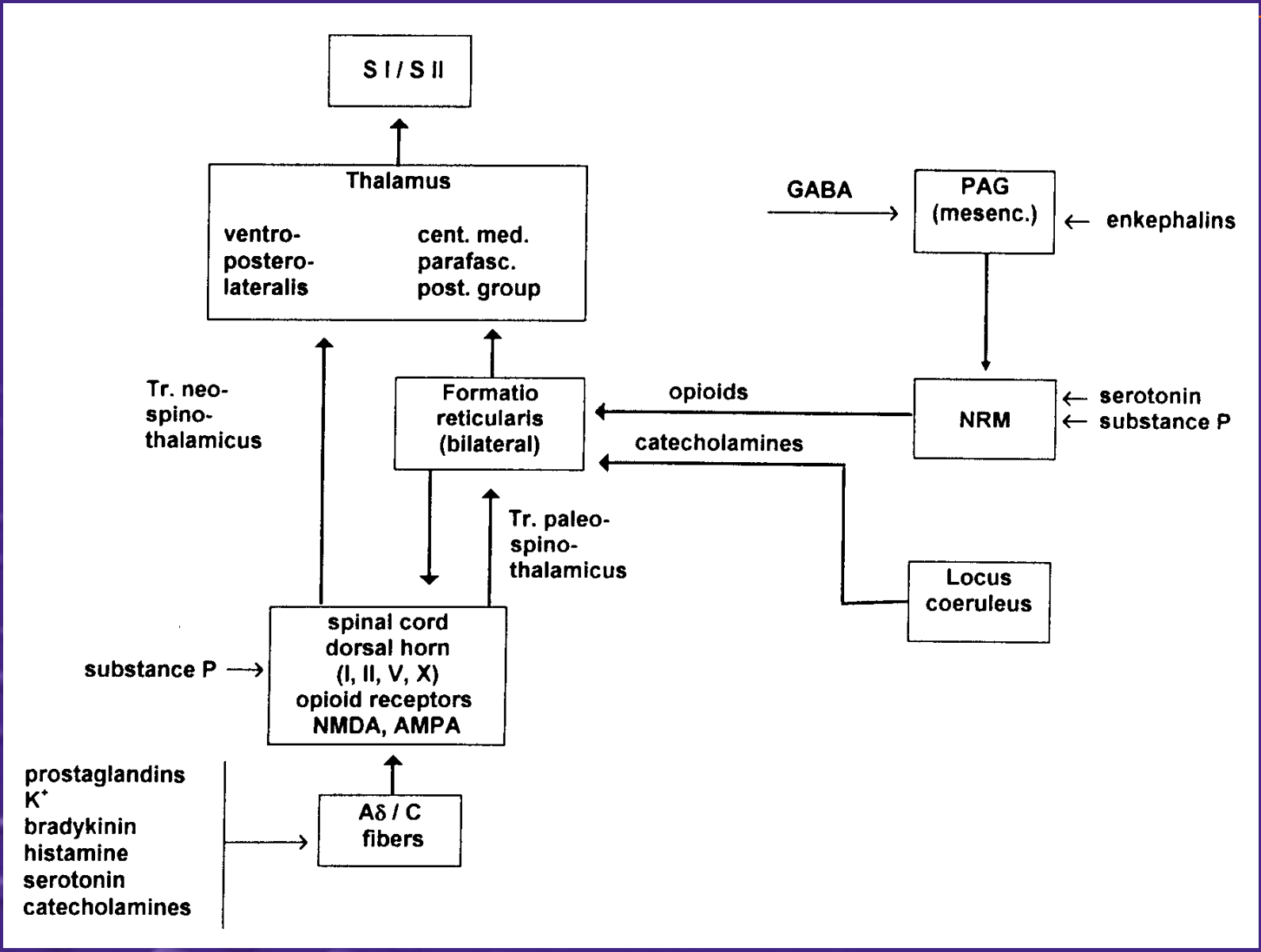


A schematic diagram illustrating the release of the excitatory transmitters from C-fibres and the subsequent effects on a dorsal horn nociceptive neurone. The predominant pre-synaptic action of opioids (reducing the release of these transmitters) and the post-synaptic action (reducing neuronal activity) are shown.

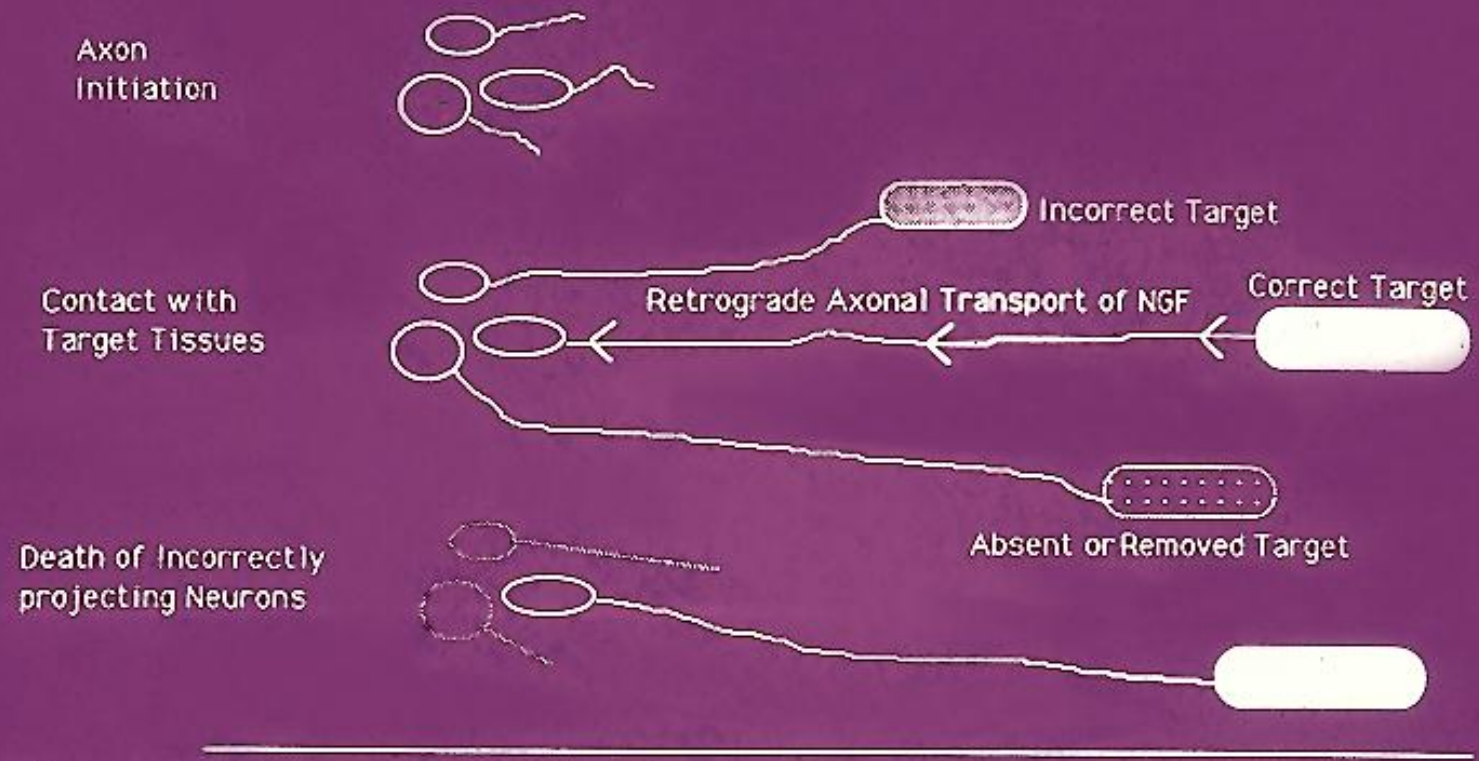
Main Ascending and Descending Nociceptive Pathways



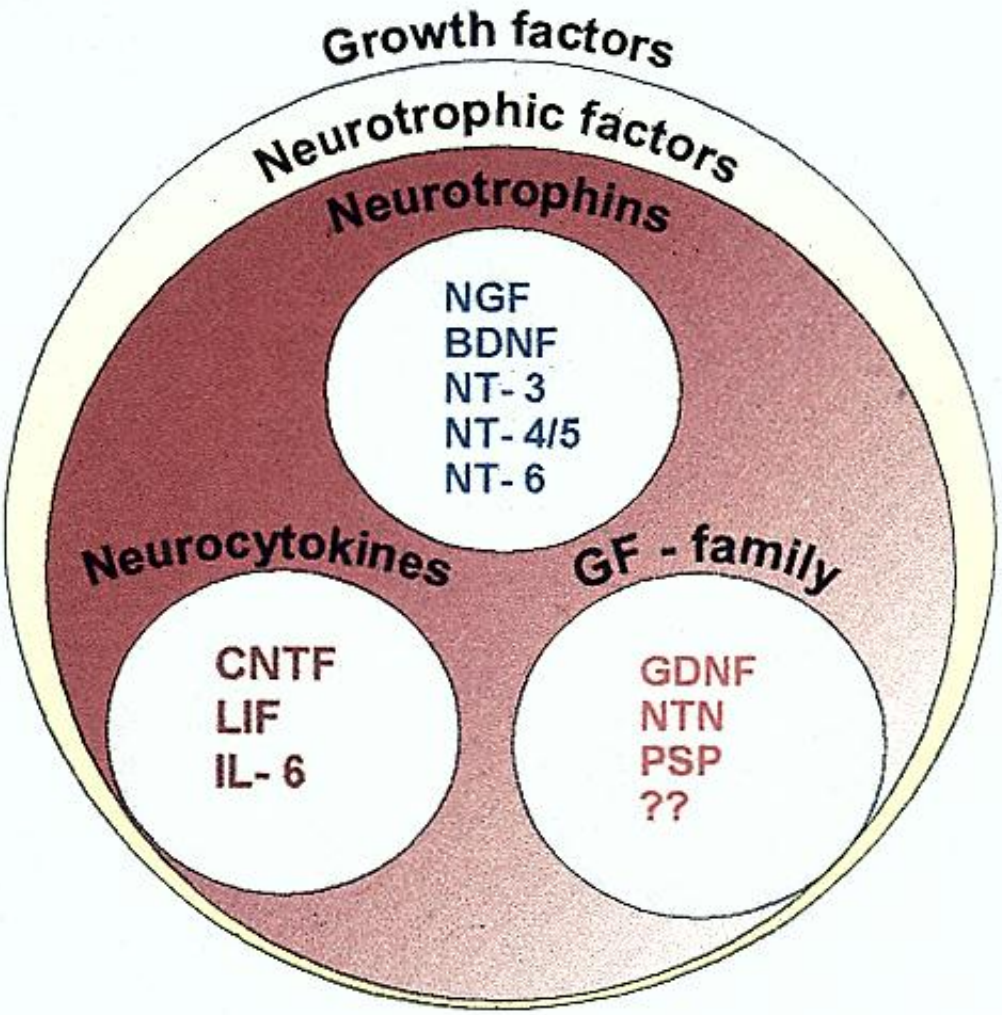
Pain Pathways



Neurotrophic Theory



The neurotrophic theory of cell death based on the actions of NGF suggests that target tissues release the neurotrophic factor, which is taken up by receptor-mediated endocytosis and transported back to the cell body, where it has its effect on the nucleus to cause survival.


Growth factors
Neurotrophic factors
Neurotrophins
NGF
BDNF
NT- 3
NT- 4/5
NT- 6
Neurocytokines
CNTF
LIF
IL- 6
GF - family
GDNF
NTN
PSP
??

Three-year old boy

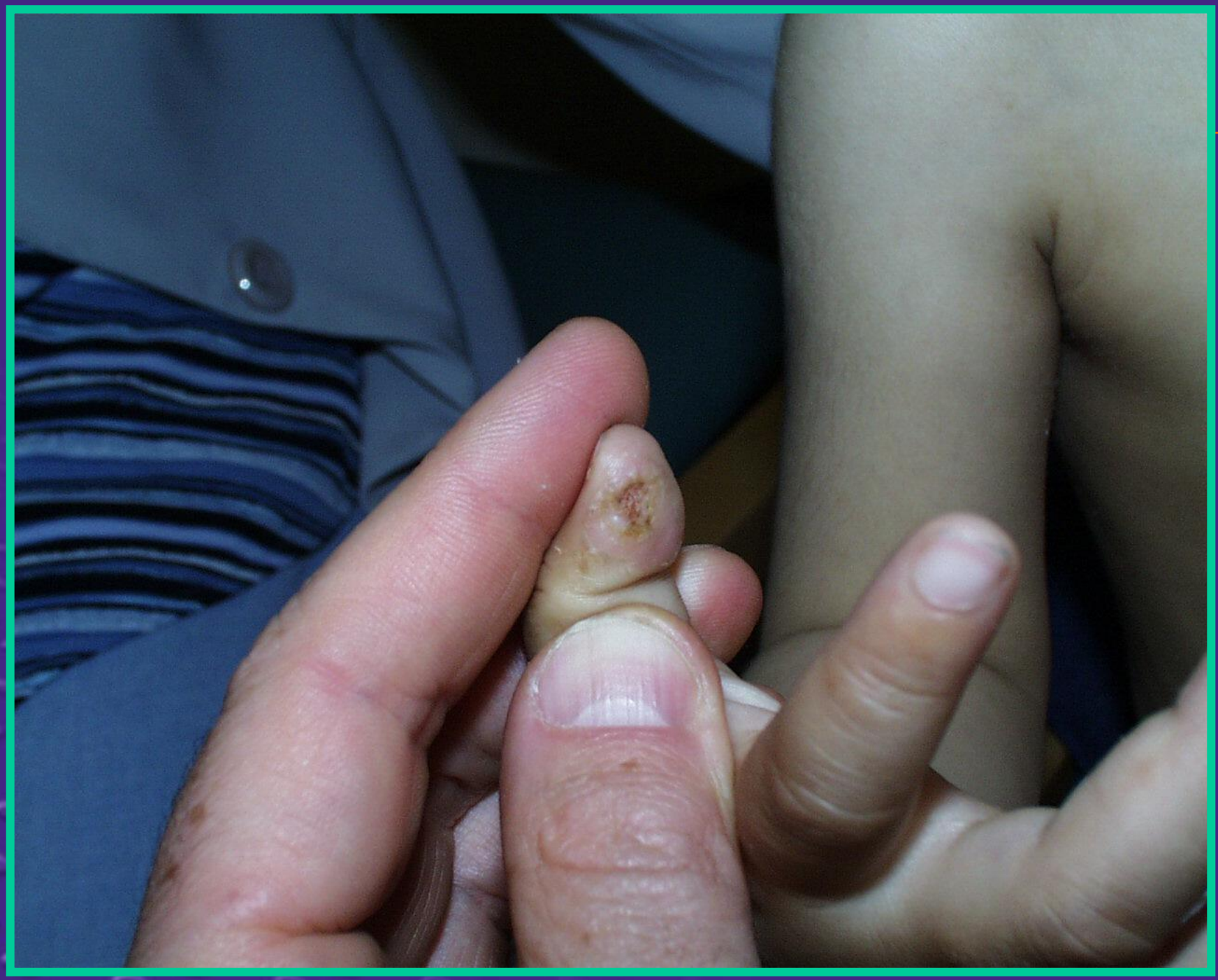
Lack of appropriate behavioural response

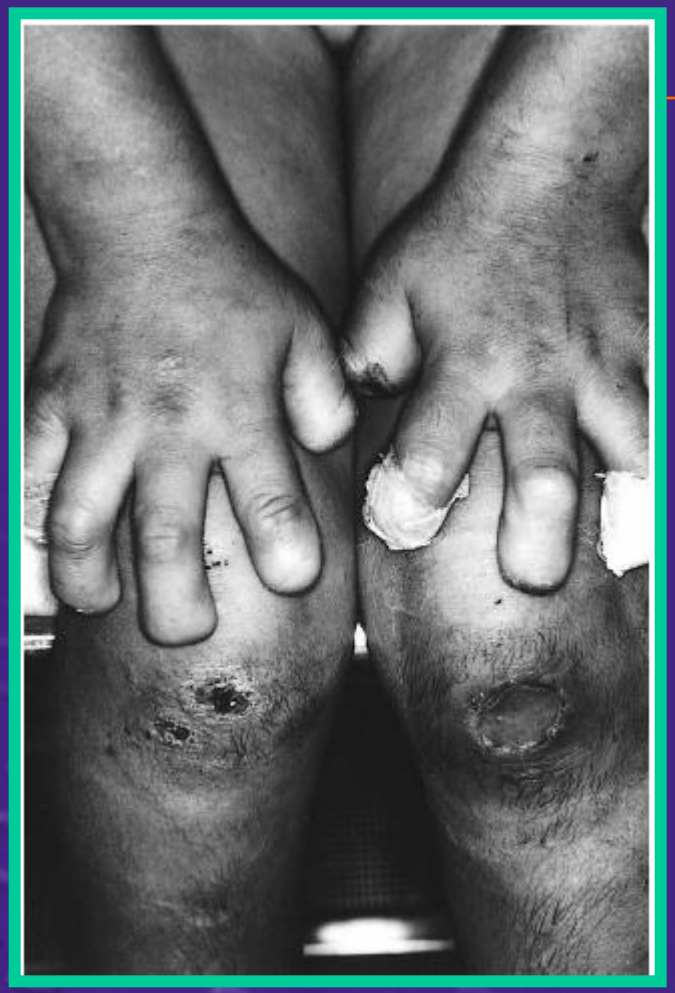
to mechanical and thermal injuries

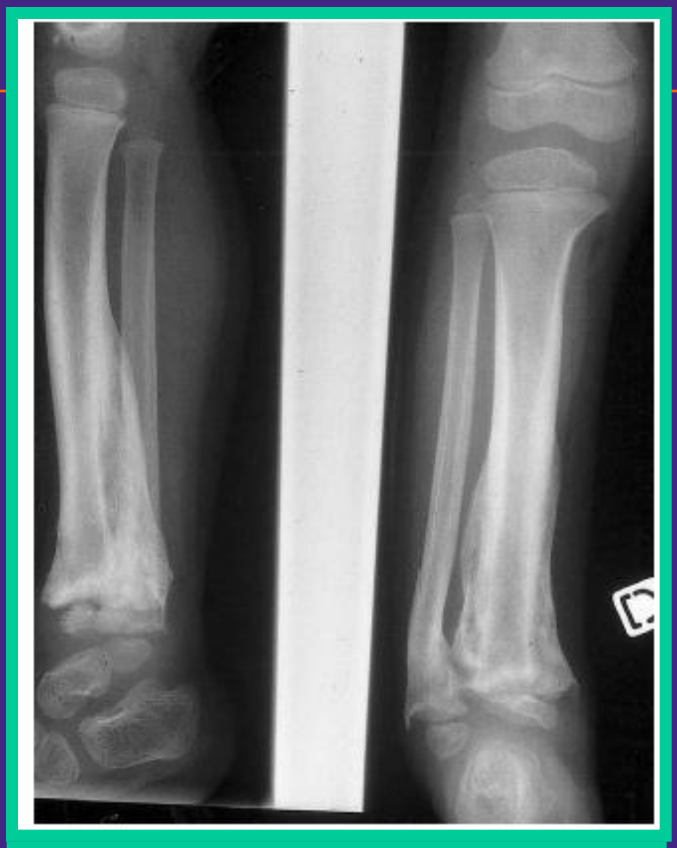
and noxious stimuli

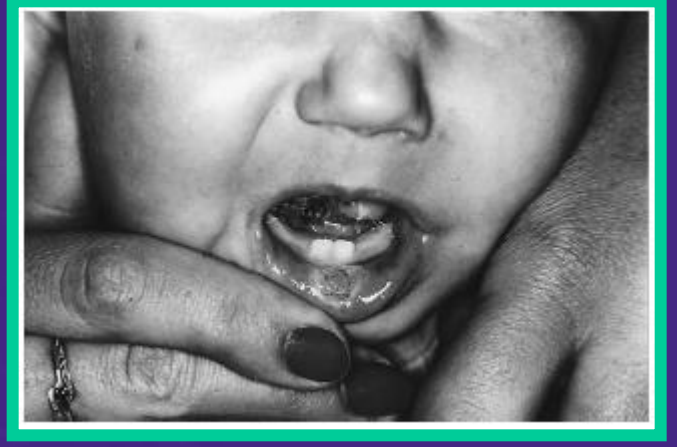
Main clinical features when referred to Hammersmith:

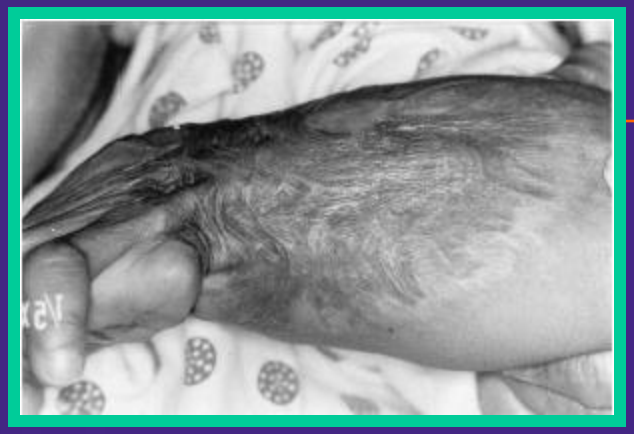
- Impaired sense of pain: frequent bruises and injuries from falls
  - Fracture of his L arm went unnoticed for almost 1 week
  - Placed hand in hot oven and “did not mind”
- Mild/moderate global developmental delay
  - ? Gait unsteadiness
  - Slow to develop speech
- Recurrent lower respiratory tract infections
- Silent aspiration with fluids

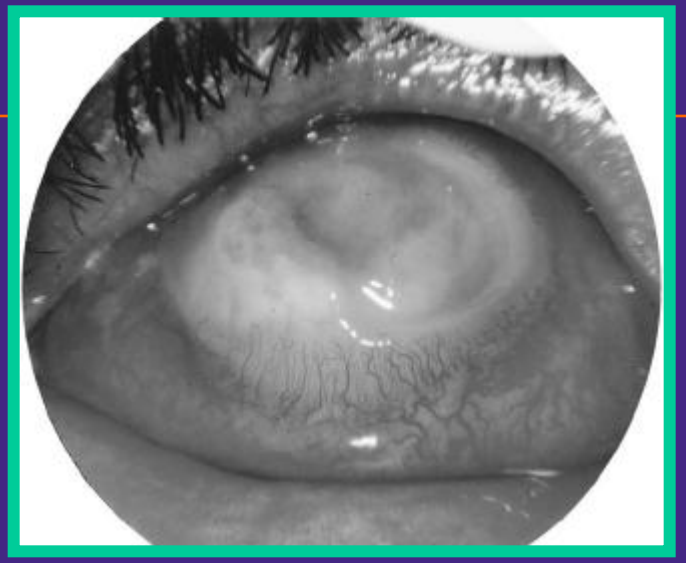












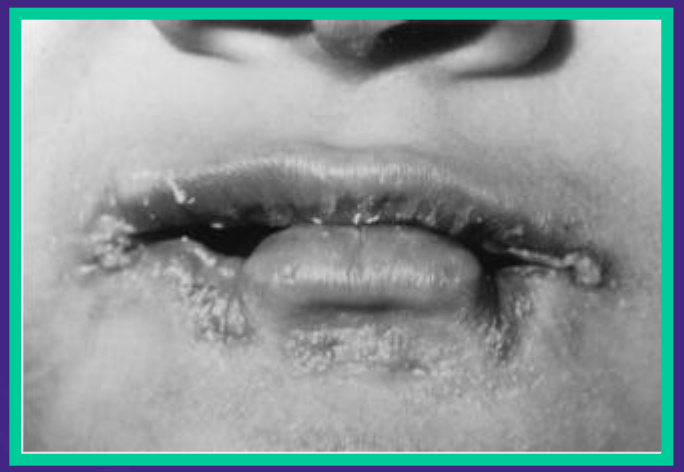


Table 1
Types of HSAN

	Inheritance	Sensory deficits	Autonomic deficits	Reflexes	Tissue damage	Nerve fibers affected
HSAN I *Hereditary sensory radicular neuropathy*	Autosomal dominant	Distal loss of pain sensitivity Distal loss of thermal sensitivity Distal proprioceptive deficits Distal light touch deficits	None known	Absent/weak	Severe ulceration of extremities Painless injuries	All (smaller diameters affected more)
HSAN II	Autosomal recessive	Distal loss of pain sensitivity Distal loss of thermal sensitivity Distal proprioceptive deficits Diffuse light touch deficits	None known	Absent/weak	Severe ulceration of extremities Painless injuries	Myelinated fibers
HSAN III *Riley-Day syndrome* *Familial dysautonomia*	Autosomal recessive	Diffuse pain insensitivity Diffuse thermal insensitivity	Excessive sweating Defective lacrimation Postural hypotension Recurrent fevers Feeding problems	Absent/weak	Corneal ulceration Painless injuries	Unmyelinated fibers Large myelinated fibers
HSAN IV *Congenital pain insensitivity w/ anhidrosis*	Autosomal recessive	Diffuse pain insensitivity Diffuse thermal insensitivity	Anhidrosis Recurrent fevers	Weak/normal	Ulceration of extremities Painless injuries Self-mutilation	Unmyelinated fibers Small myelinated fibers
HSAN V	Autosomal recessive	Distal pain insensitivity Distal thermal insensitivity	None known	Normal	Ulceration of extremities Painless injuries	Small myelinated fibers

Conclusion

- ***The ability to perceive pain has great survival value***
- HSAN IV and V are rare Autosomal Recessive disorders
- No cure for the condition ? NGF
- Prevention of trauma, meticulous foot care and proper skin care

Diseases of peripheral nerves leading to sensory loss

- Injury and entrapment
- Diabetes / Metabolic
- Inflammatory
- Demyelinating
- Inherited
- Toxic
- Neoplastic / Paraneoplastic

Diabetic neuropathy

- "Established" neuropathy
- Focal and multifocal neuropathies
- - cranial mononeuropathies
- - thoracoabdominal neuropathies
- - focal limb neuropathies
- - assymetric proximal lower limb (amyotrophy)
-
- Symmetric neuropathies
- - sensory/autonomic polyneuropathy
- - proximal lower limb motor neuropathy

Diabetic sensory neuropathy

- Chronic insidious sensory neuropathy with progressive development of unpleasant sensations, often with pain, in the legs and feet

- 2 groups:
- 1 paraesthesiae and discomfort
- 2 pain

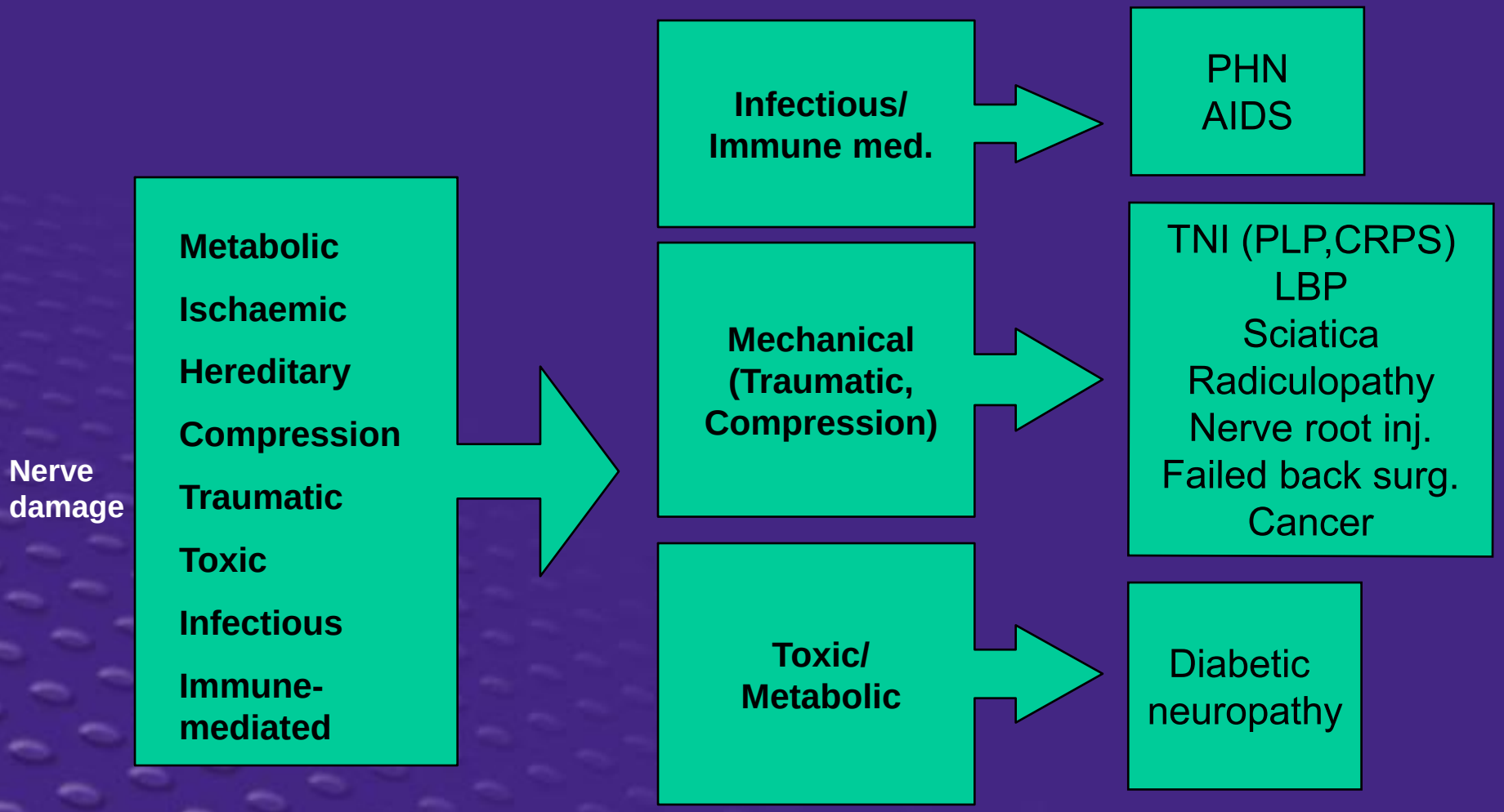
- SYMPTOMS

- "tingling, burning, cramps, shooting, tearing, bone-deep"
- touch painful (e.g. bed-clothes)
- mainly in legs, feet
- worse at night, prevent sleep
- depression

Diabetic neuropathy - assessment

a	history, clinical examination, diary, VAS, McGill
b	nerve conduction studies (peroneal,tibial,ulnar summated CMAP)
c	vibration thresholds (feet, hands)
d	touch thresholds (von Frey), record allodynia
e	thermal thresholds to warm/cold: pain thresholds
f	intradermal capsaicin- and histamine-evoked axon reflex vasodilatation (? < 50% decrease initially)
g	autonomic function tests: sweating, cardiovascular (including cardiac beat to deep breathing)
h	diabetic status, including glucose and HbA_1

Neuropathies and Pain



Epidemiology of neuropathic pain

- Estimated prevalence 2–4% of the population[1]
- Represents at least 25% of patients attending pain clinics[2]
- Incidence increases with age[3]

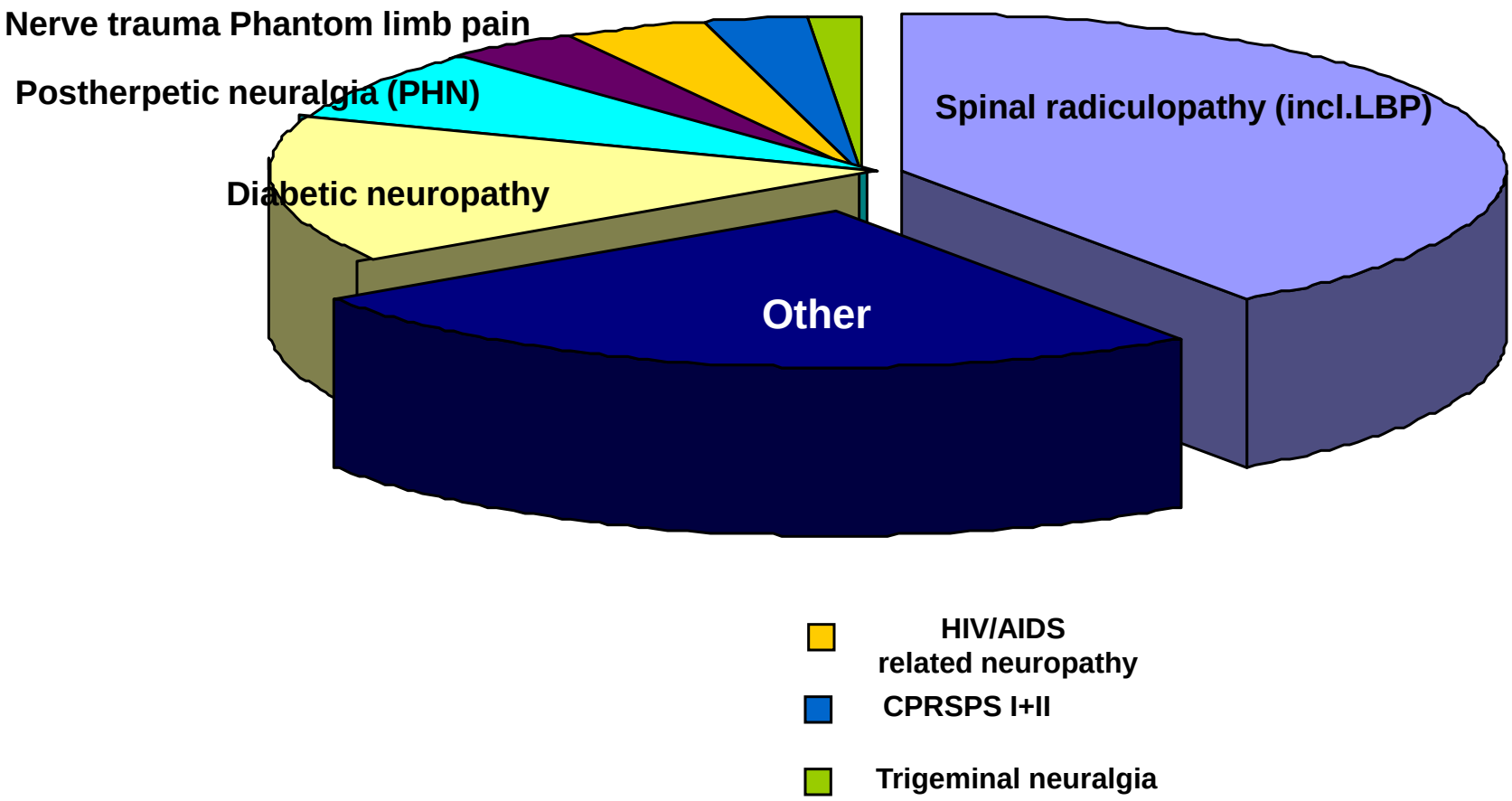
1. Serpell M. Peripheral neuropathy: neuropathic pain. Neuropathy Trust. 2. Bowsher D. Brit Med Bull 1991; 47(3): 644–666. 3. Booker CK and Keen A. Pain Society, 2004.

Prevalence of neuropathic pain in different conditions

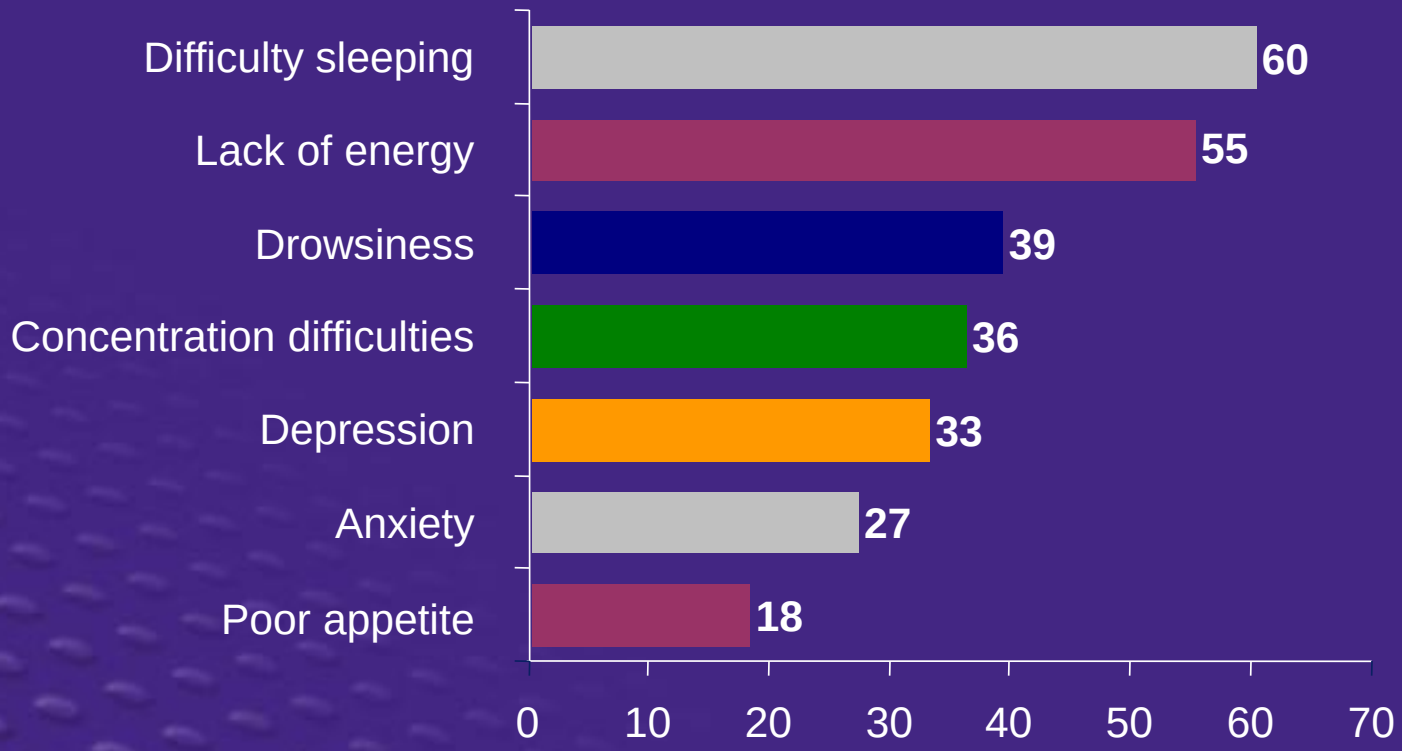
- 20–24% of diabetics experience PDN[1]
- 25–50% of patients >50 years with herpes zoster develop PHN (3 months after healing of rash)[1]
- 20% of women develop post-mastectomy pain[2]
- One-third of cancer patients have neuropathic pain (alone or with nociceptive pain)[3]

1. Schmader KE. Clin J Pain 2002; 18: 350–354. 2. Stevens PE *et al*. Pain 1995; 61: 61–68. 3. Davis MP and Walsh D. Am J Hosp Palliat Med 2004; 21(2): 137–142.

Neuropathic Pain



Co-morbidity associated with peripheral neuropathic pain



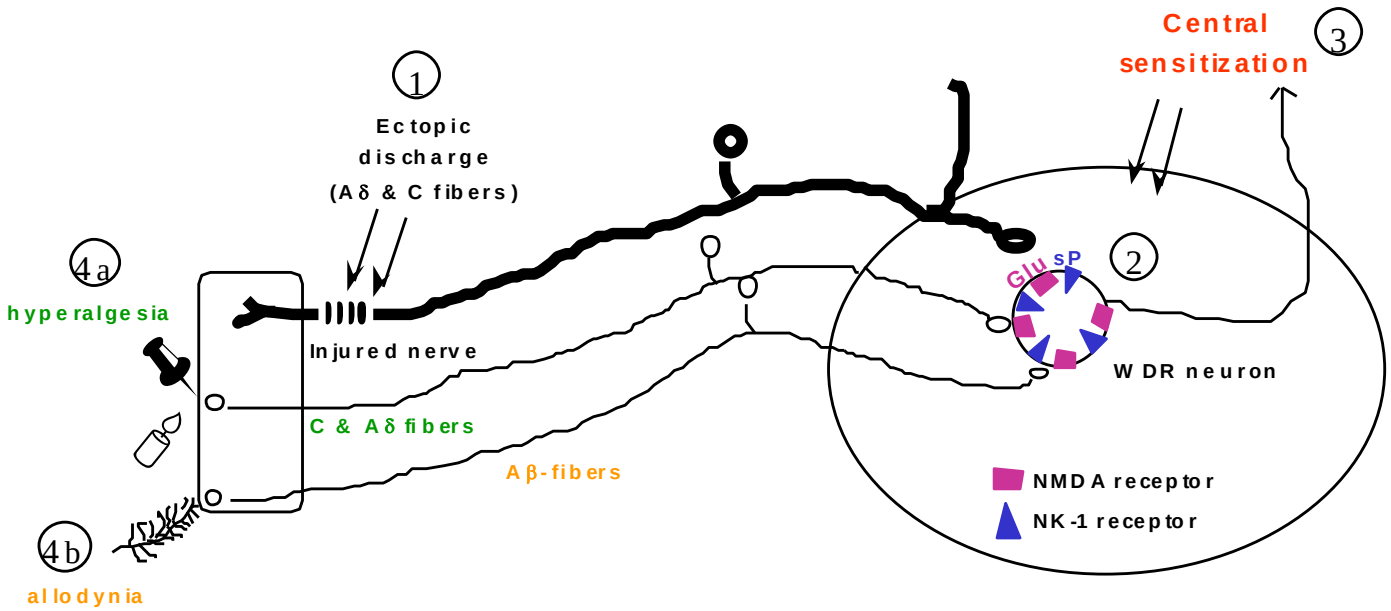
% patients with moderate to very severe discomfort due to symptoms (n=126)

Meyer-Rosberg K *et al*. Eur J Pain 2001; 5: 379–389.

Features of Neuropathic Pain

- Nerve Injury/Disease – *pain is a symptom*
- Spontaneous pain / no spontaneous pain
- With or without:
  - Allodynia
    - **Mechanical Static vs. Dynamic**
    - **Thermal – cool > warm**
  - Hyperpathia
  - “wind-up” – clinical vs. neurophysiological

Neuropathic Pain



1. Nerve injury-evoked C fiber ectopic discharge to dosal horn spinal cord
2. Neurotransmitters release [Glutamate (Glu) & substance P (sP)]
3. Central sensitization
   - 4a. C & Aδ stimulus → hyperalgesia
   - 4b. Aβ stimulus → allodynia

Neurogenic Pain Mechanisms

- Peripheral and central sensitisation

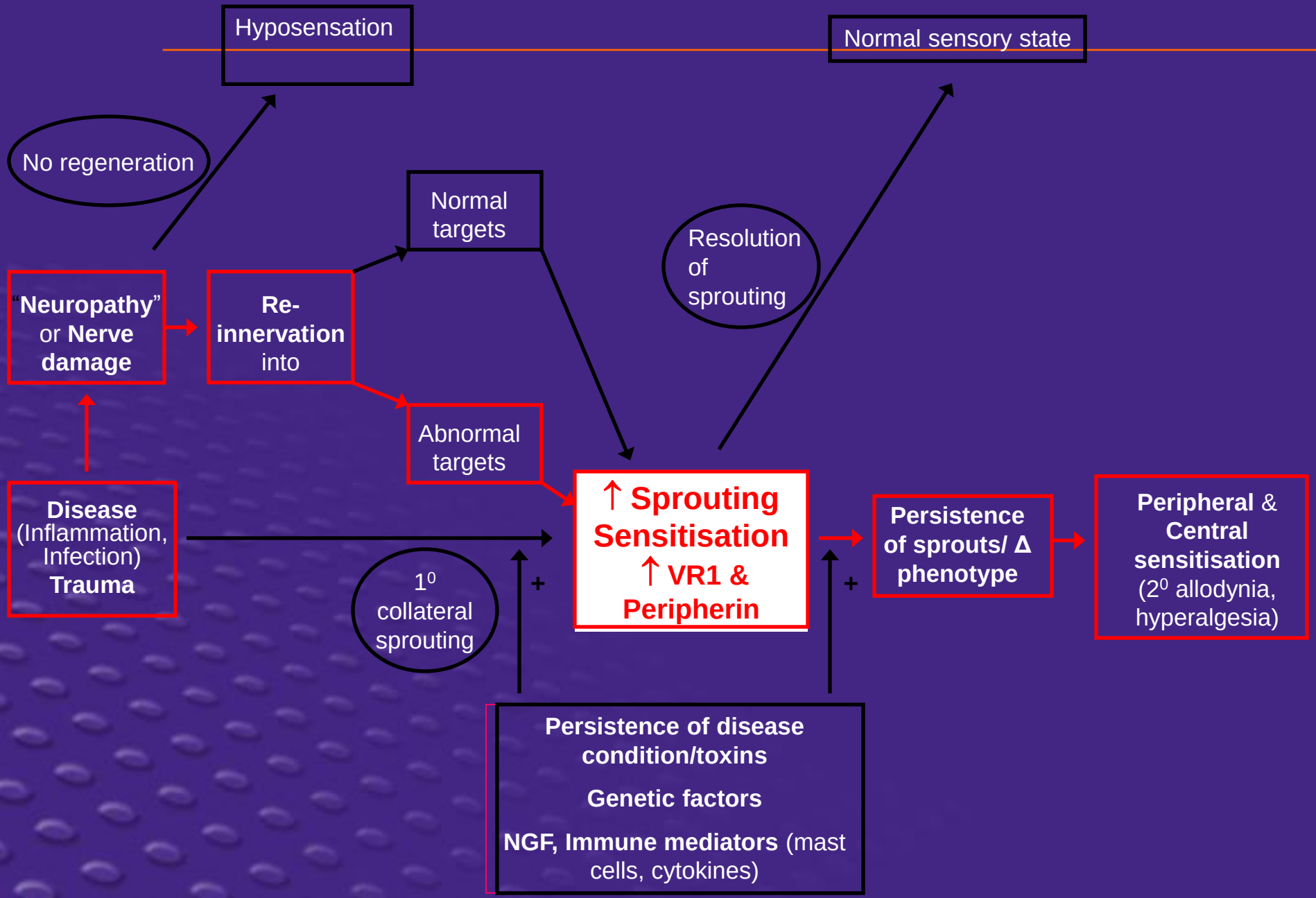
  neuronal spontaneous activity or hyper-excitability related to change in receptor phenotype
- Nerve Sprouting

  Aβ-fibres in dorsal horn after axotomy

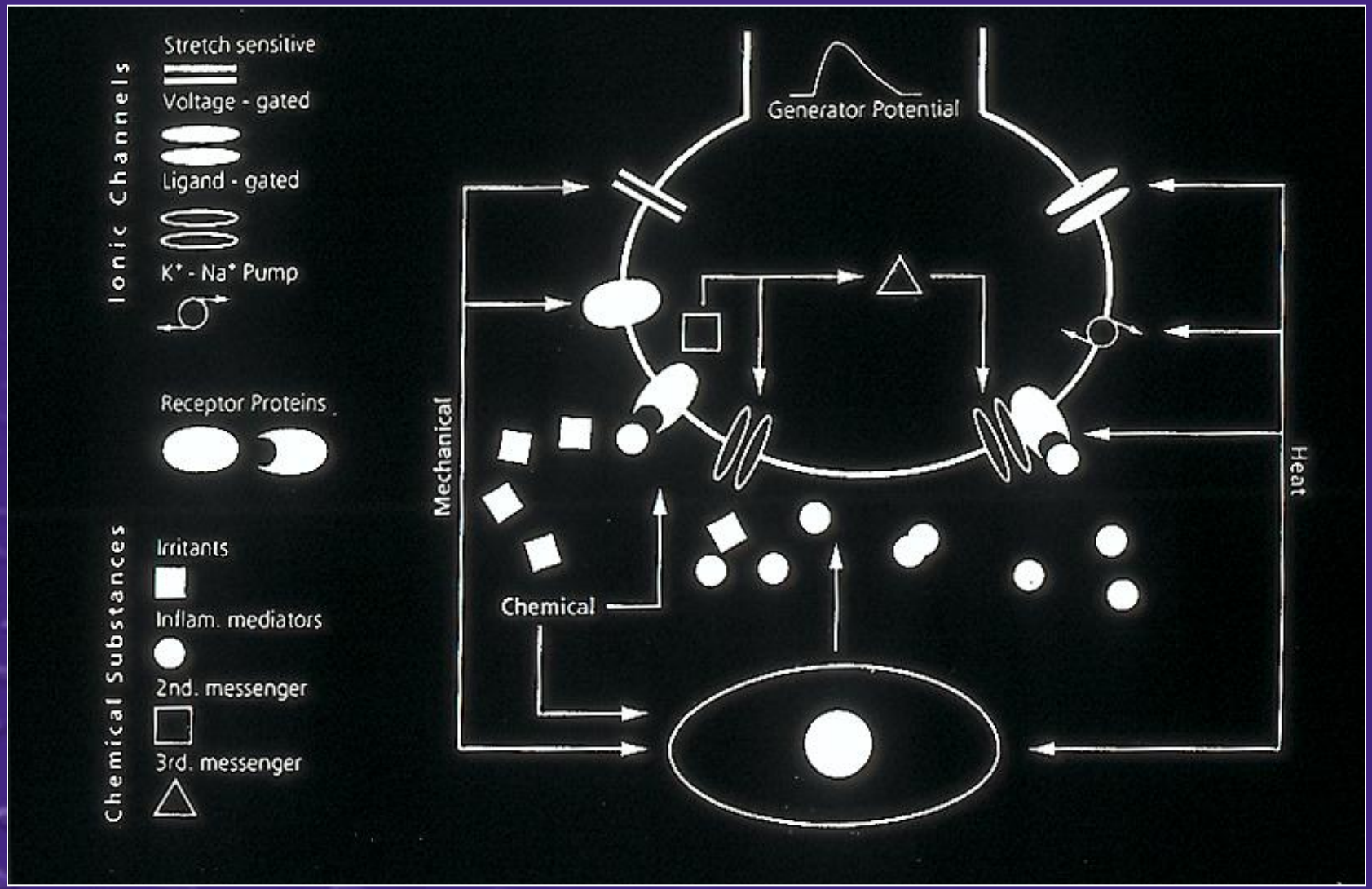
  peripheral sprouting
- Loss of inhibition

Targeting of the specific underlying causes of pain rather than just the symptoms for a better management of painful syndromes.

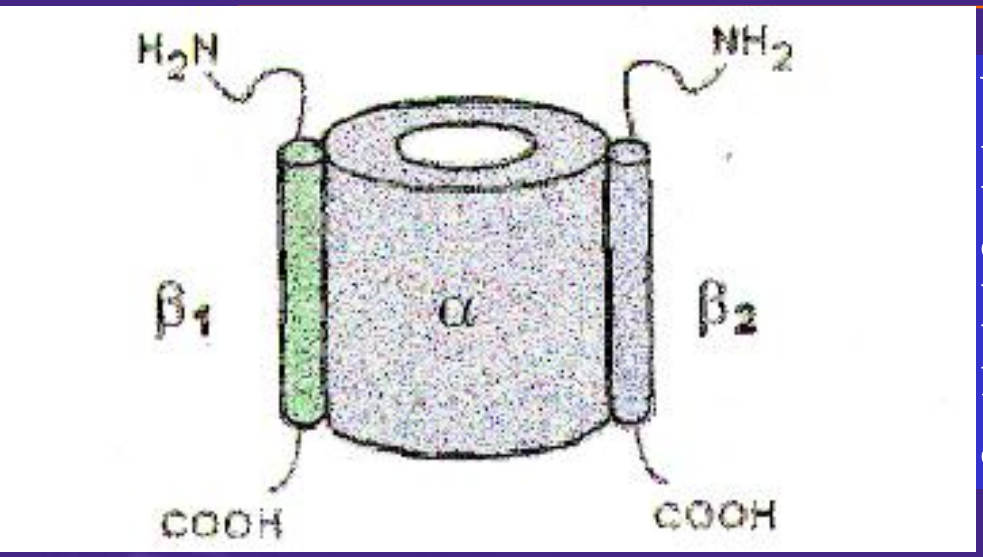
Proposed mechanisms of chronic hypersensitivity



Signal transduction at nerve terminals

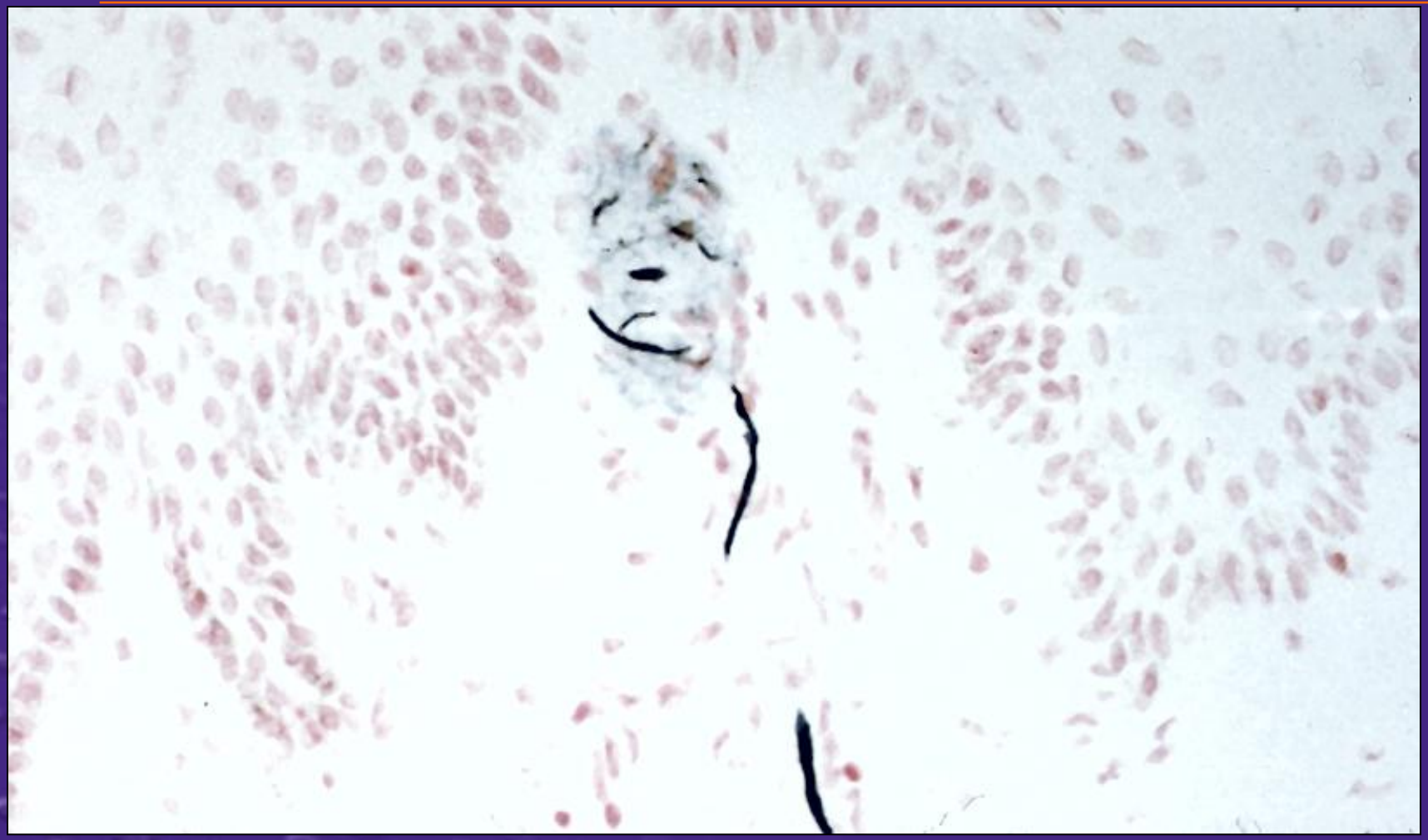


Na^+ channels



Voltage-gated sodium channel. Heteromeric receptors which activation leads to an increase in Na^+ permeability therefore facilitating the transmission of action potentials.

In human nerve injury SNS1, NaN TTX-r subunits accumulate at the nerve endings



Temperature Ranges and Temperature Sensors

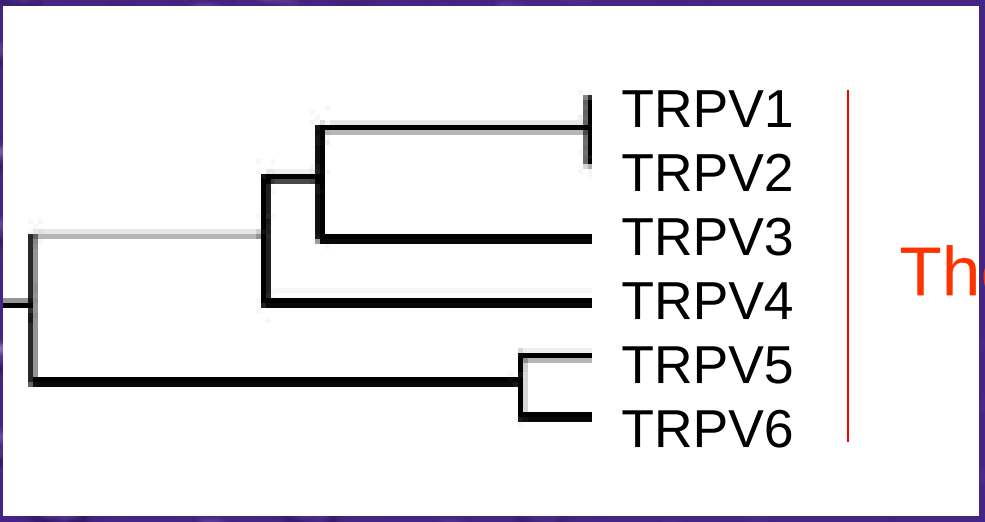
VR1 threshold for activation

Cold

Hot

ANKTM1	CMR1 TRPM8	TRPV3, TRPV4	TRPV1 VR1	TRPV2 VRL1
~ 10 °C	~ 25 °C	30 -> 40 °C	~ 43 °C	~ 53 °C
noxious cold	cold	warm	noxious heat	

modulators



The Vanilloid Receptor family

Vanilloid receptors

- Temperature sensitive, cation channels.
- VR1 (TRPV1), the capsaicin receptor, responds to high temperature (>42), H^+ and anandamide as endogenous agonist.
- VR6 respond to moderate heat.
- Thought to form heteromers (variability at single channel level, differences neurons vs. transfected cells).
- Distributed mainly in small and medium neurons and fibres but recently characterised also in skin epidermal cells and other non neuronal cell types.

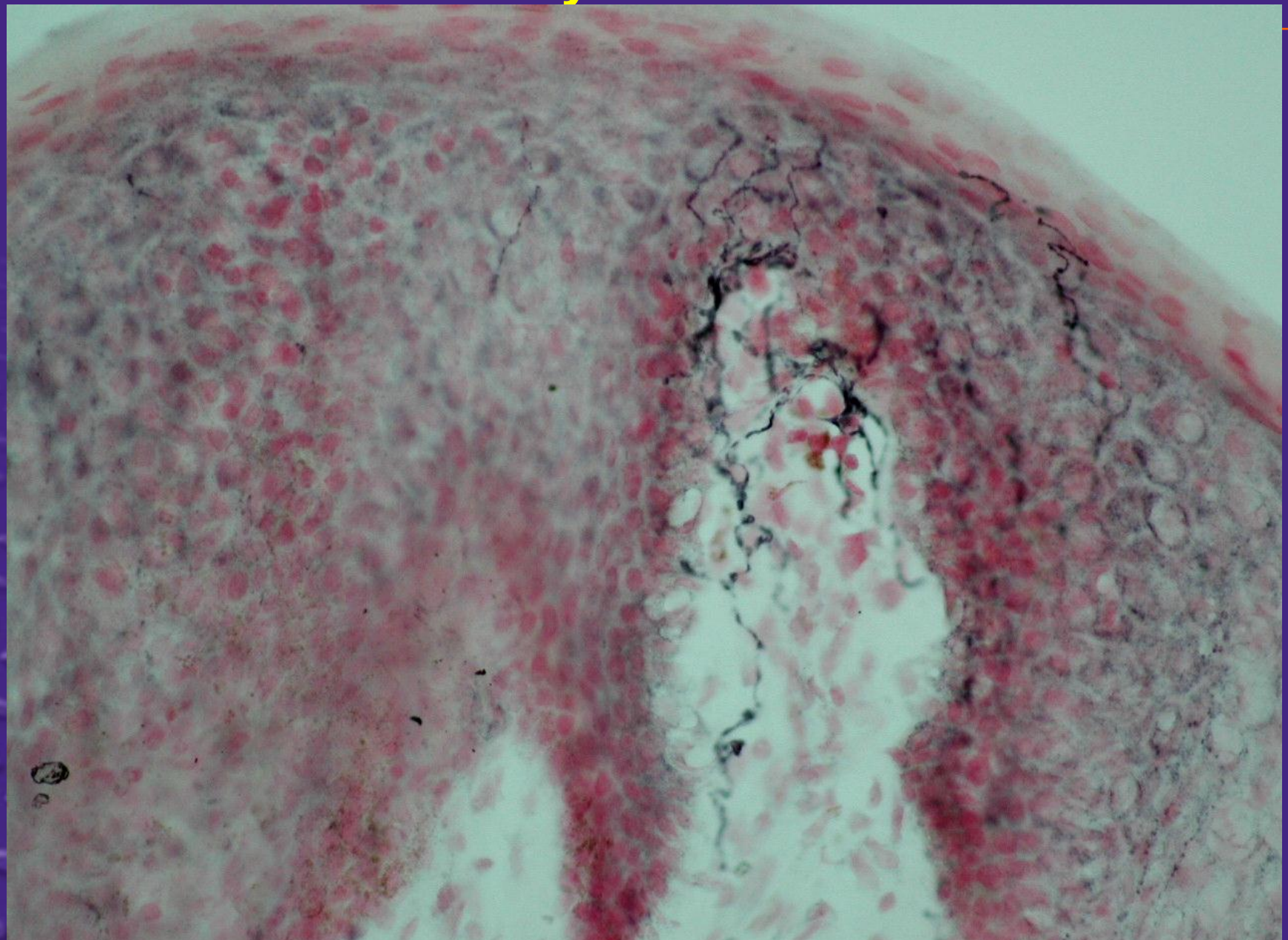
VR1 (TRPV1) receptor

Results from animal models

- after axotomy is down-regulated in damaged neurons but over-expressed in undamaged neurons
- Expression is NGF-dependant (also GDNF)
- involved in thermal hyperalgesia (knock-out) check.

Validation in humans

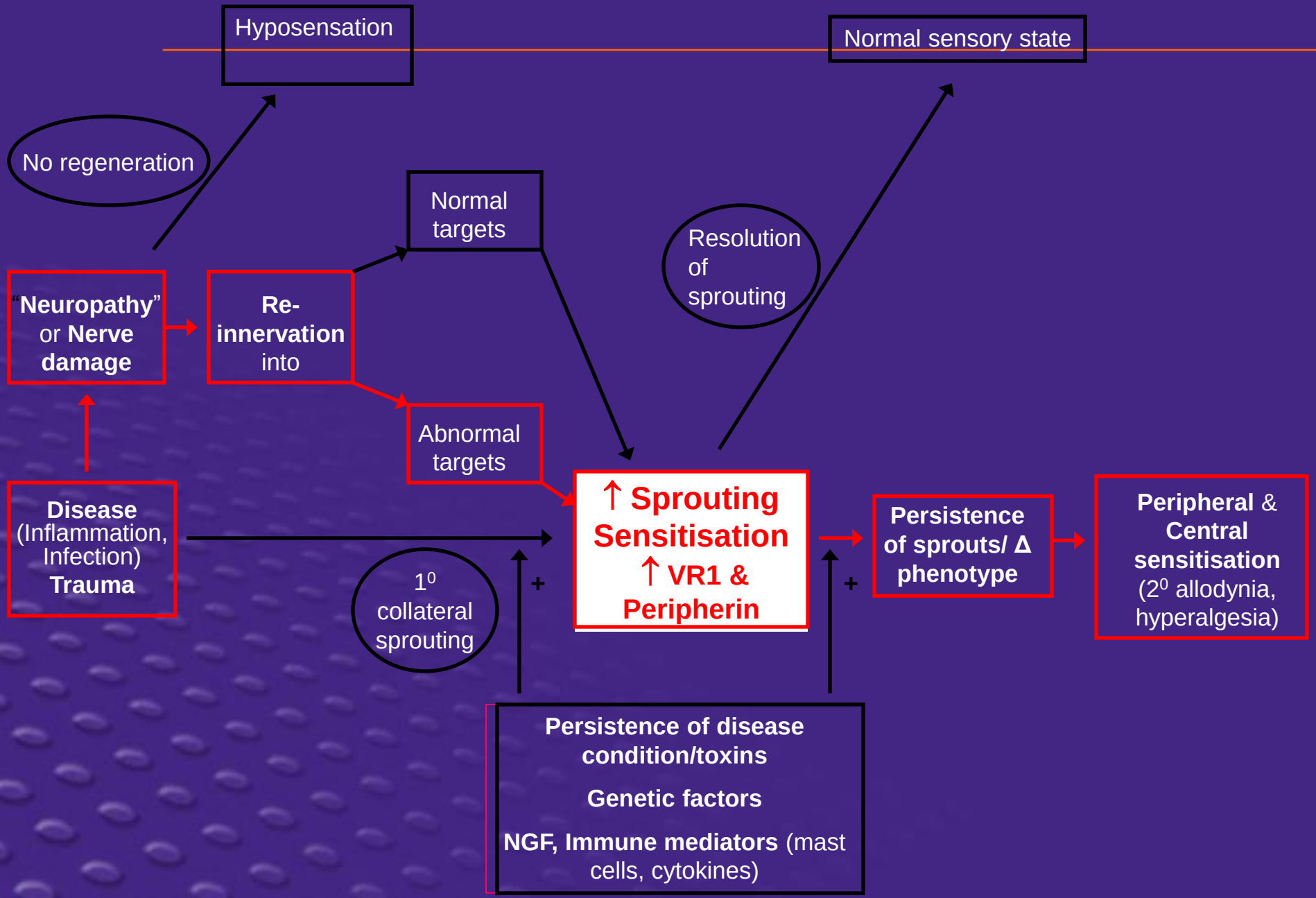
TRPV1 fibres in vulvodynia



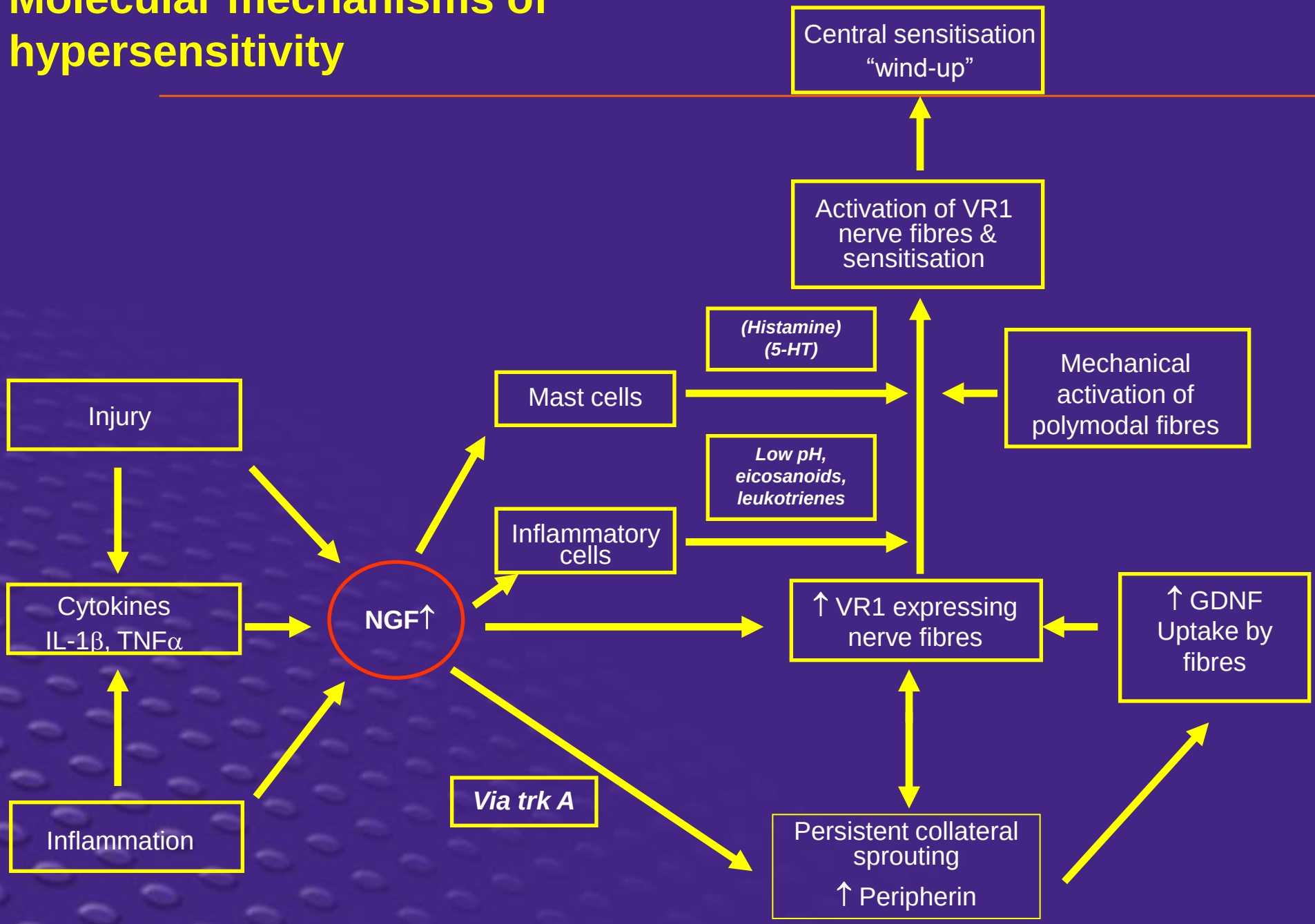
- Overall up-regulation in nerve after injury by accumulation and/or over-expression in undamaged and regenerating fibres.

- Interesting to analyse VR1 expression in peripheral fibres, close to the source of NTFs

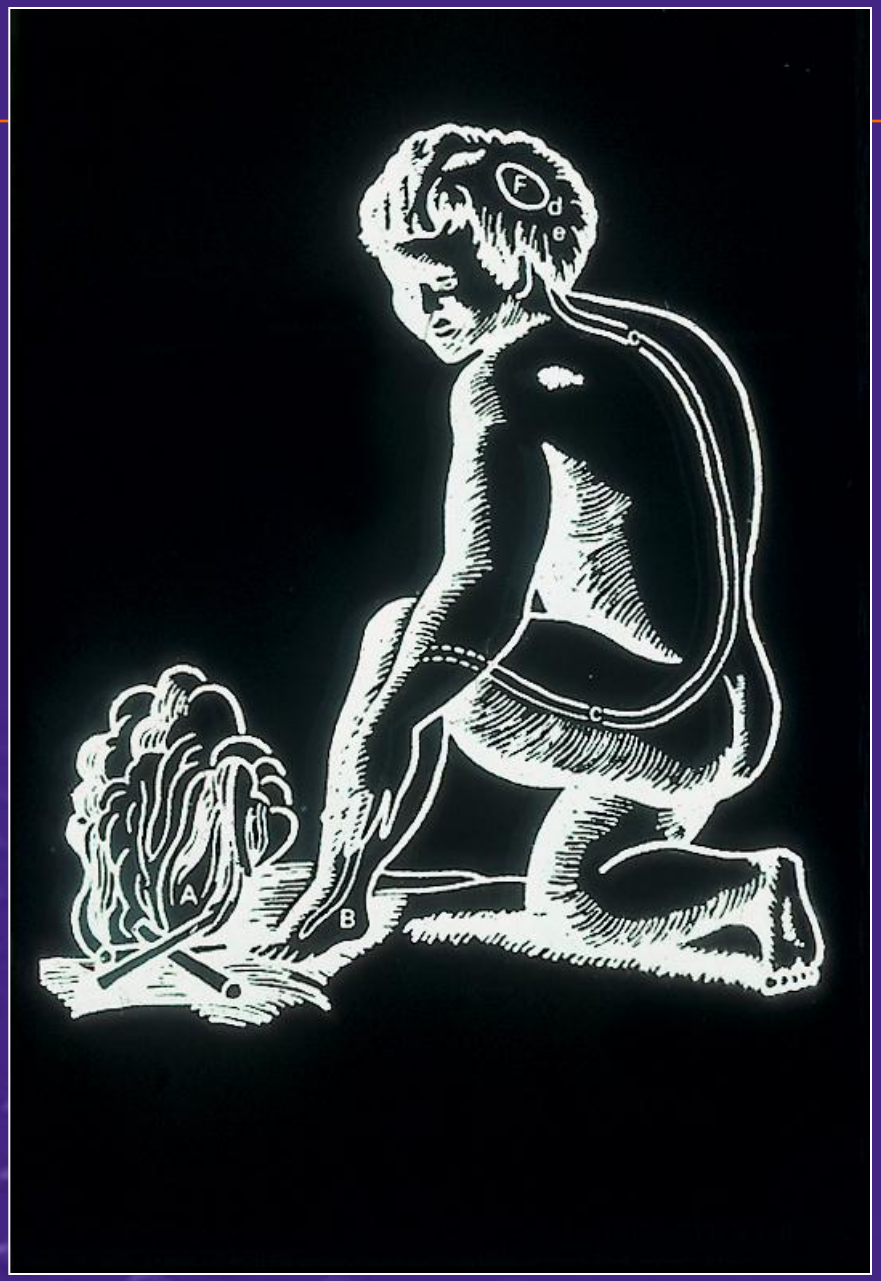
Proposed mechanisms of chronic hypersensitivity



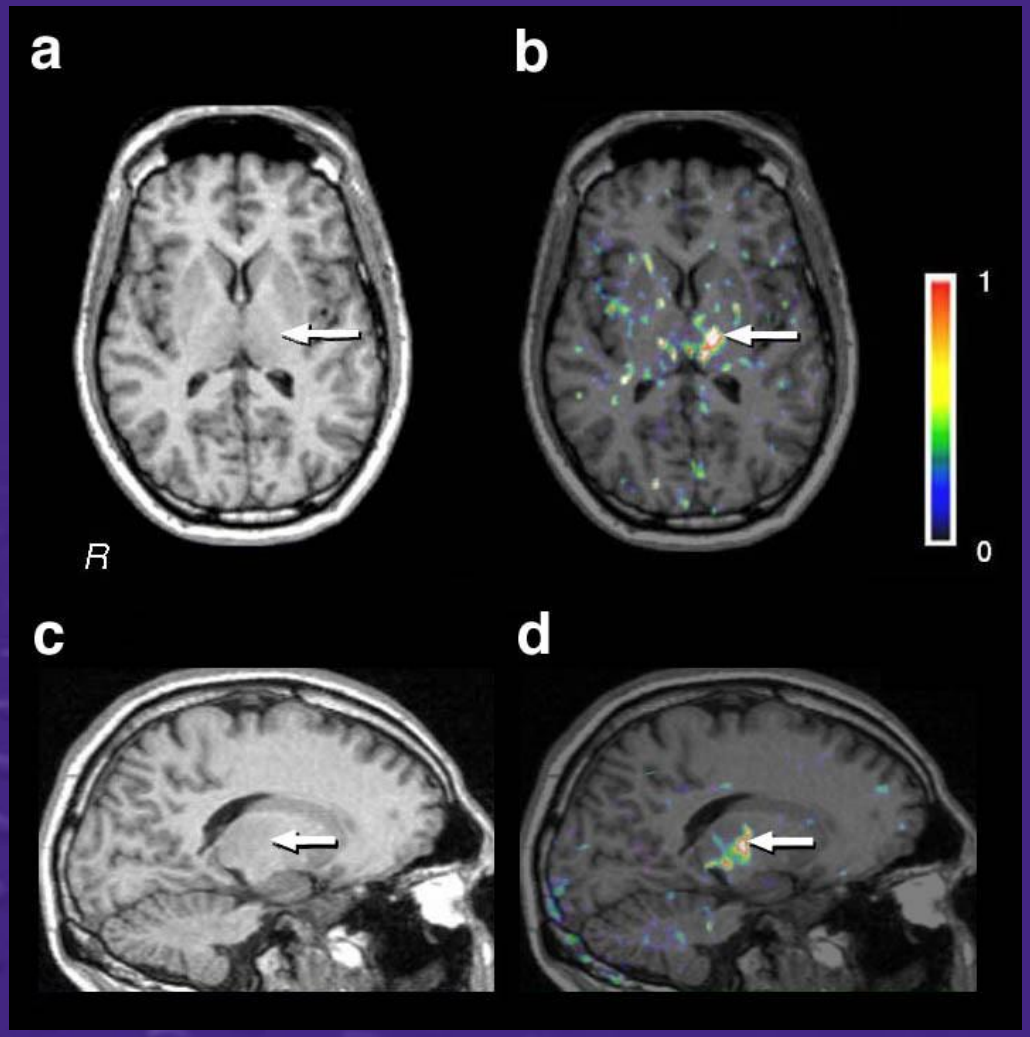
Molecular mechanisms of hypersensitivity



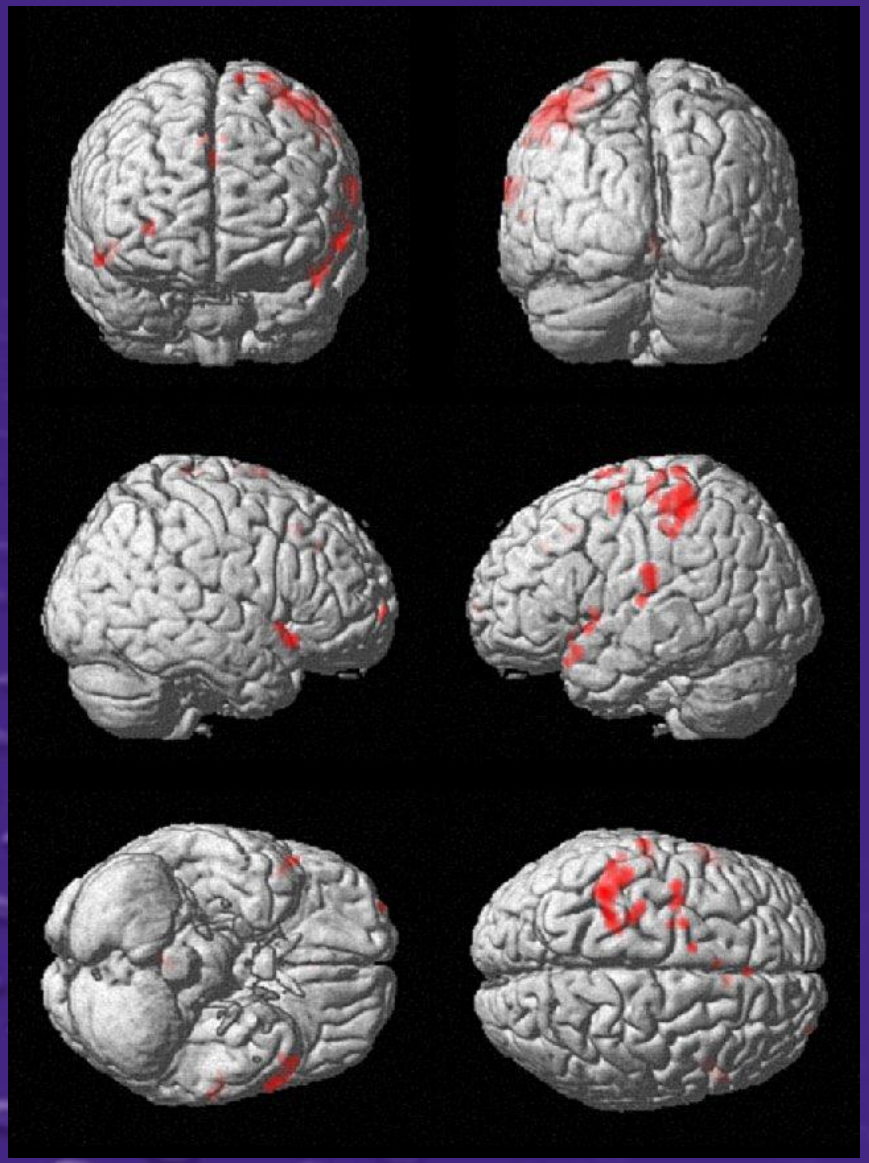
Descartes' model



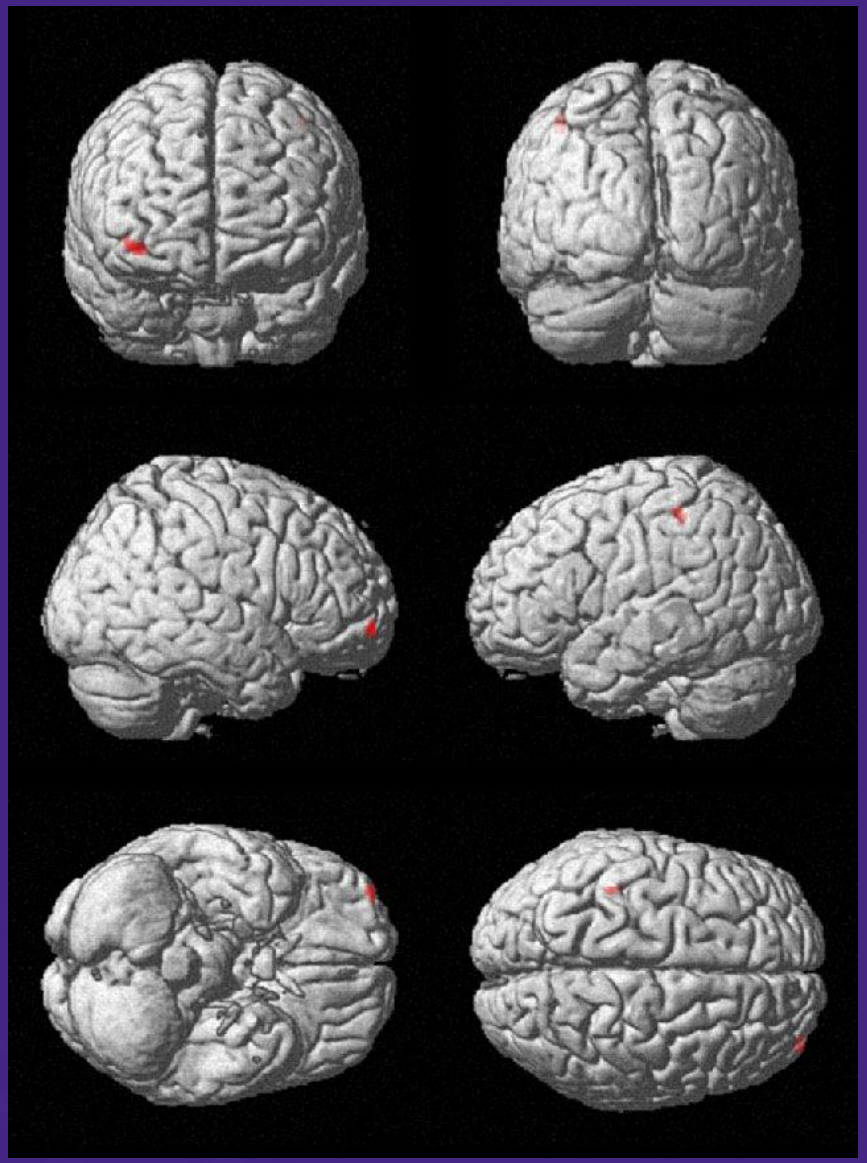
PK11195 PET in Nerve Injury



Allodynic stimulation - i.v.saline



Allodynic stimulation - i.v. lidocaine



Medicinal strategies for neuropathic pain relief

- 1 **Empirical**

  e.g. gabapentin in diabetic neuropathy, other anticonvulsants, anti-depressants, opioids

- **2 Mechanistic**

  e.g. sodium channel blockade in allodynia; sympathetic blockade for causalgia; pregabalin after gabapentin

- **3 Homeostatic / restorative**

  e.g. NGF in HIV neuropathy

Stimulation and Surgical Procedures

- **Stimulation**

  TENS

  Spinal cord / CNS

- **Surgical e.g. DREZ, infusion pumps**

Numbers Needed to Treat (NNT) &
Numbers Needed to Harm (NNH)

$$\frac{1}{\text{Response (Active RX) - Response (Control)}}$$

Example: 50 % of patients in active treatment group & 25 % in the placebo group are relieved with treatment. i.e. NNT= 4

$$\frac{1}{0.5 - 0.25}$$

NNT/ NNH Analysis
Diabetic Neuropathic Pain

Therapy	50% **[NNT]**	PGIC **[NNT]**	%Drops /AE's **[NNH]**
Gabapentin	48% **[3.6]**	47% **[4.5]**	8.3 **[45]**
Placebo	20%	25%	6.1

Meta-Analysis (McQuay et. al.)

Tricyclic Antidepressants

8 Studies (N=143) NNT Range: **[1.7 to 6.0]** NNH Range**[4 to Infinity]**

Anticonvulsants

3 Studies (N=82) NNT Range: **[2.1 to 3.3]** NNH Range: **[6 to 15]**

Novel Pain Targets: the near future

- **Sodium channels, calcium channels, TRP receptors, purinergic receptors, glutamate receptor subtypes, monoamine systems, anti-NGF, etc. etc….**

- **Multiple mechanisms - rational basis for polypharmacy**

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Thank you