Genetic and environmental influences on the transition from acute to chronic pain

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Presentation outline

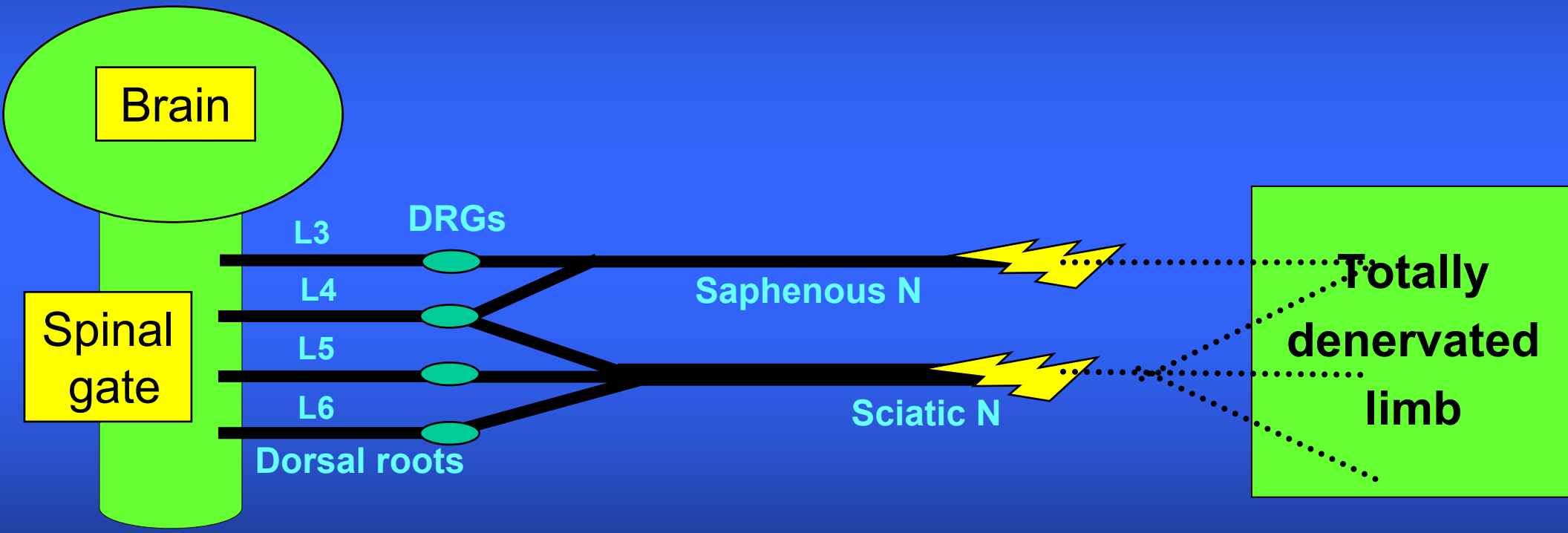
- Pathophysiology of the transition from acute to chronic pain
- Comparative pain genetics
  - Animal models
- Heritability and genetic assays
- Expected gains for pain medicine

Brief update

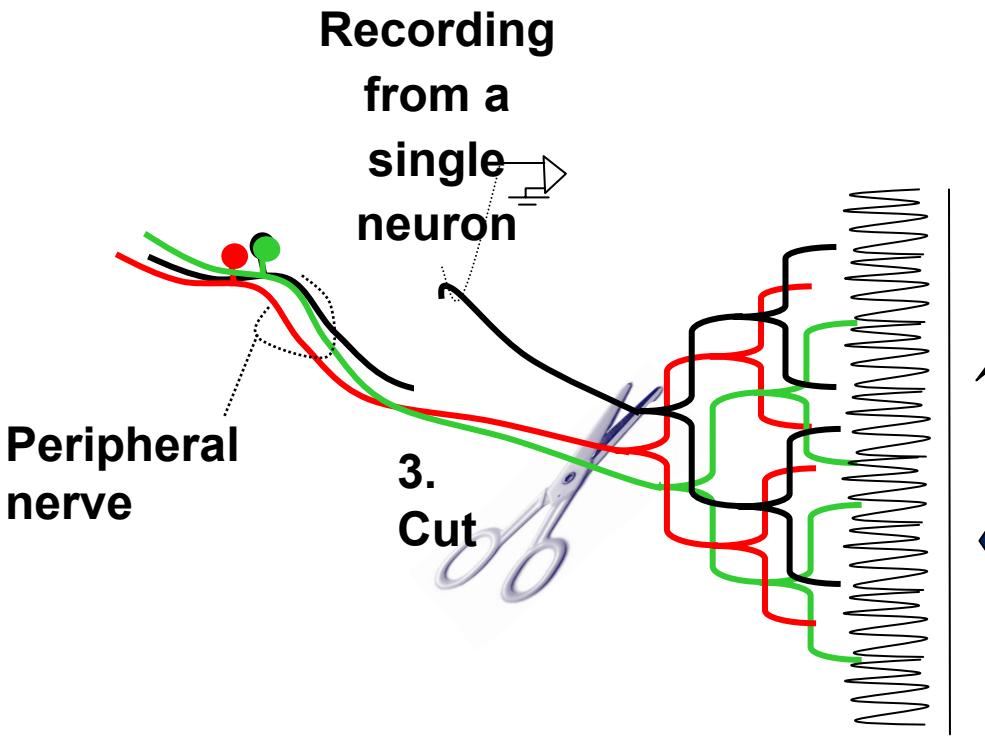
Pathophysiology of the transition from acute to chronic pain

What triggers the transition? - I

- Electrical signal (“Injury discharge”; online/msec)

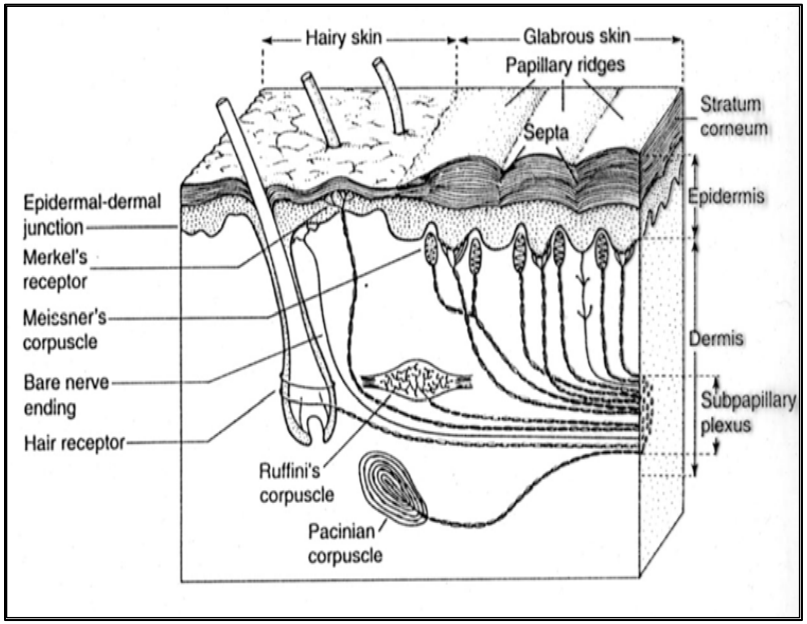


Injury discharge



2. Electrical shock to determine fiber class: Aβ-δ; C

1. Noxious & nonnoxious stimuli



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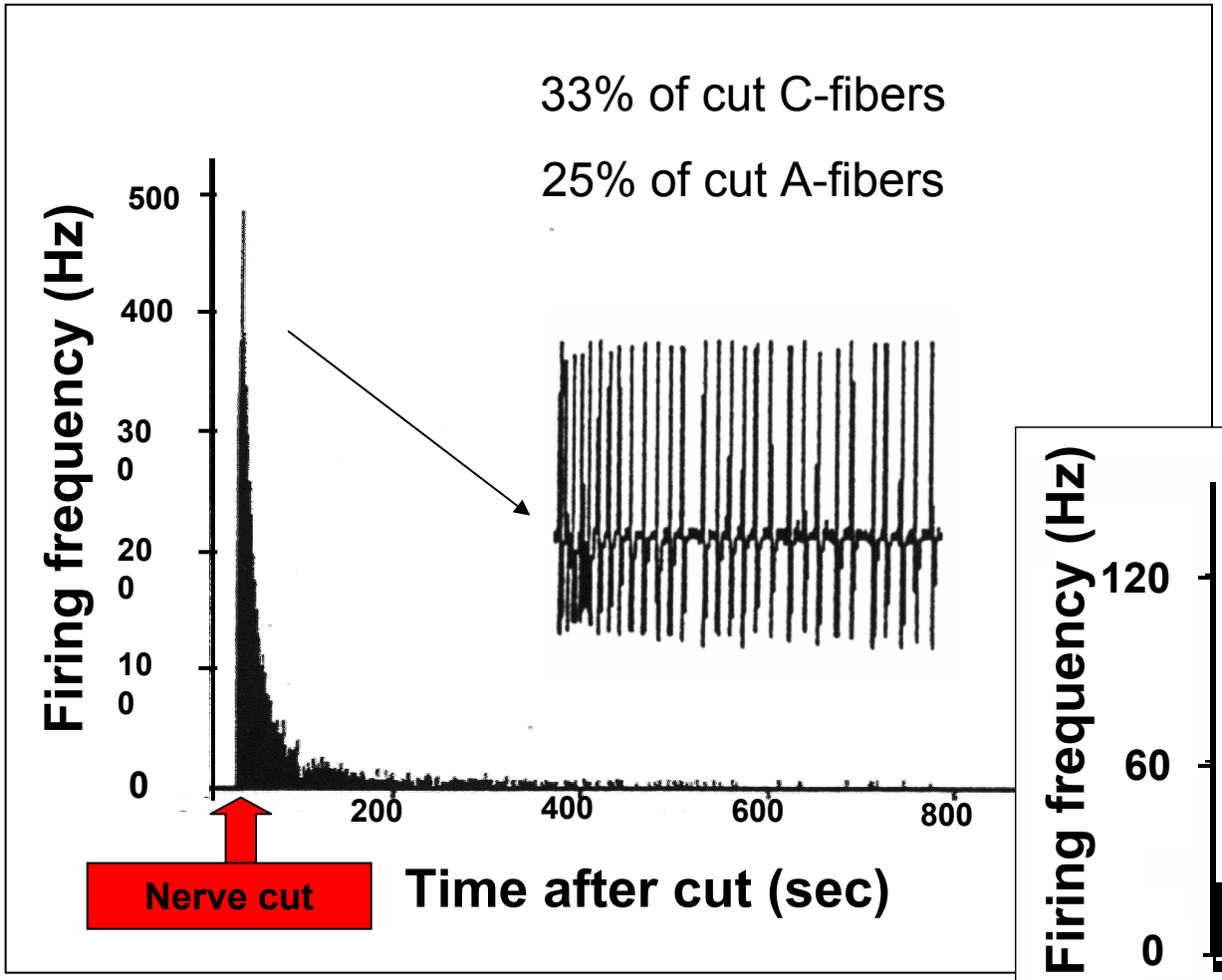
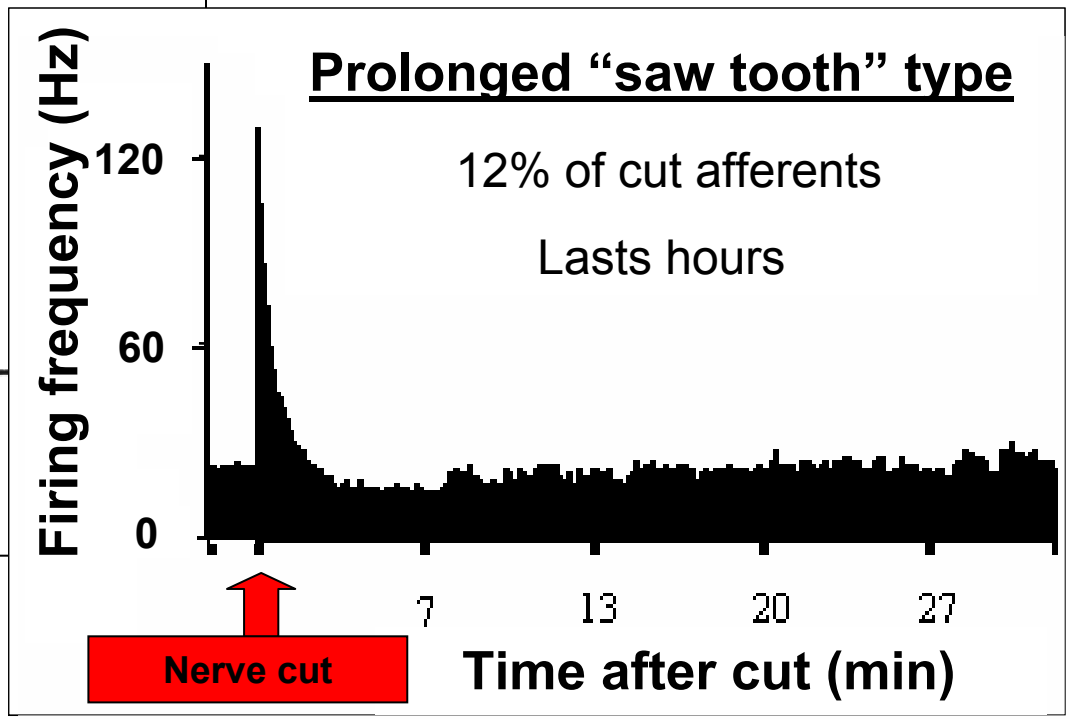
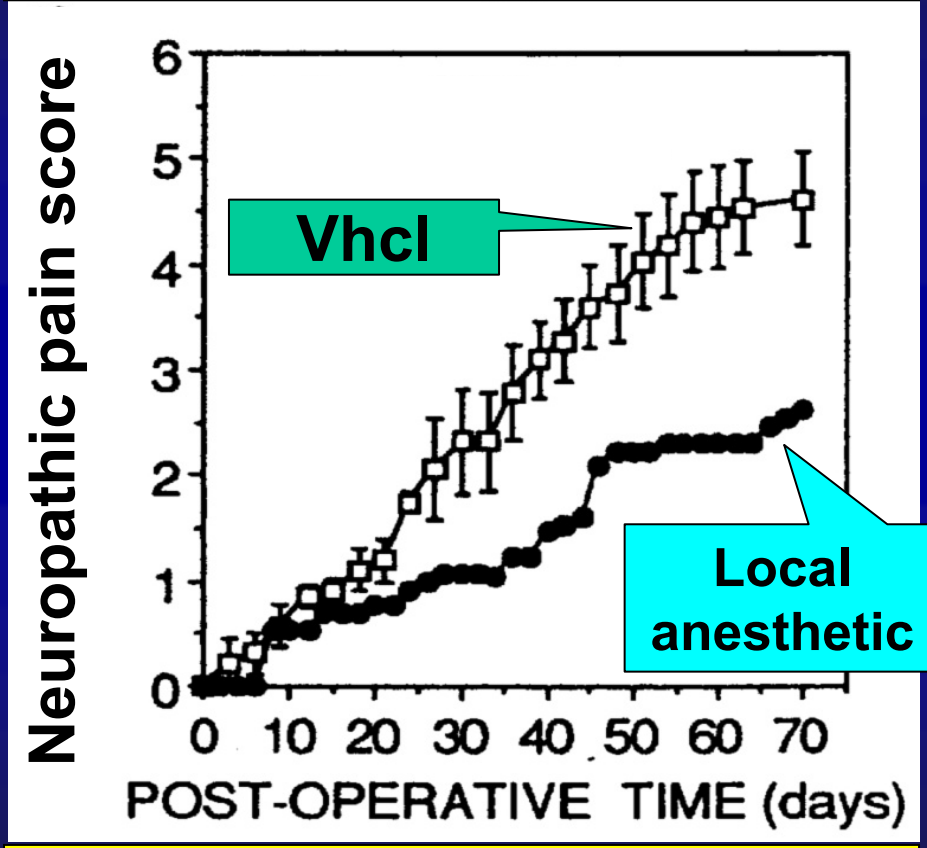




Sackstein et al (1999)

Injury discharge triggers neuropathic pain - I

Preemptive analgesia

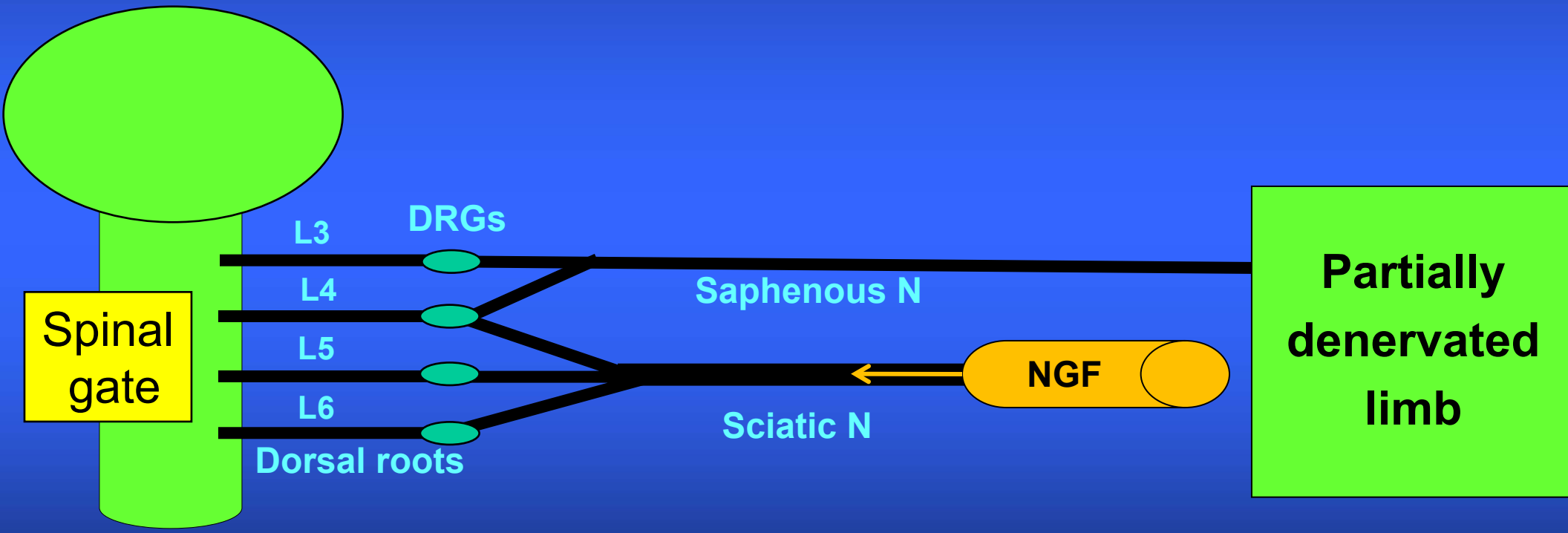


Efficacy of preemptive analgesia in humans is debated in the literature

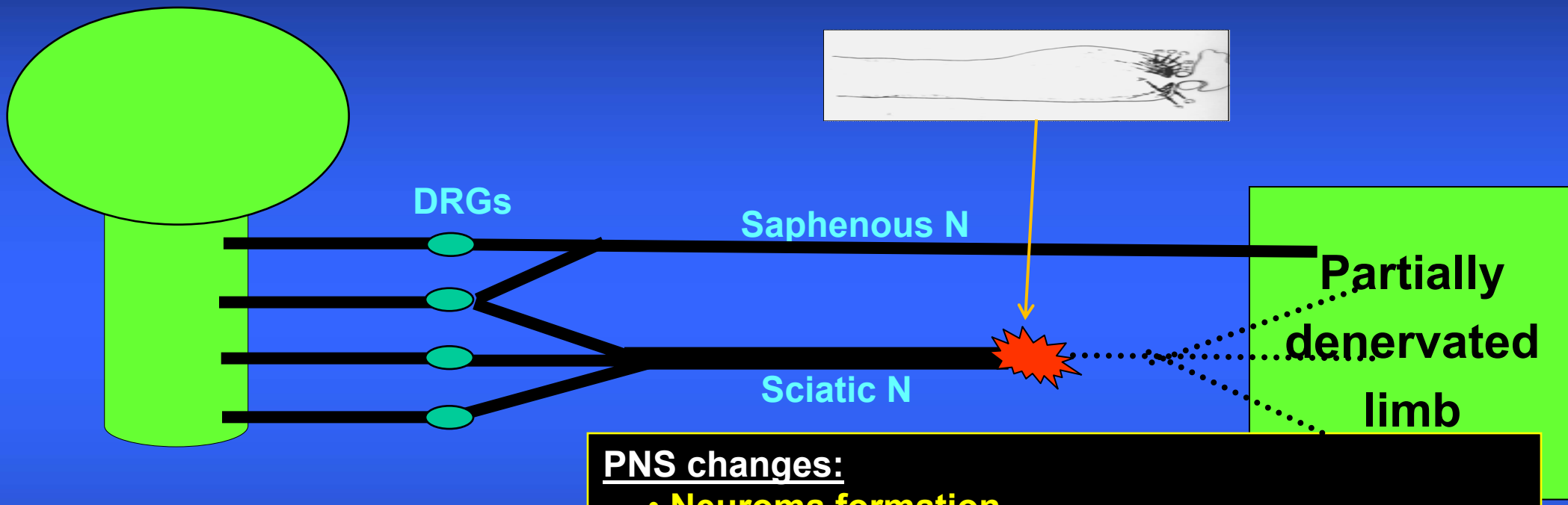
Seltzer et al (1990a)

What triggers the transition? - II

- Chemical signal(s) (Neurotrophic factors: e.g., NGF; hrs/days)



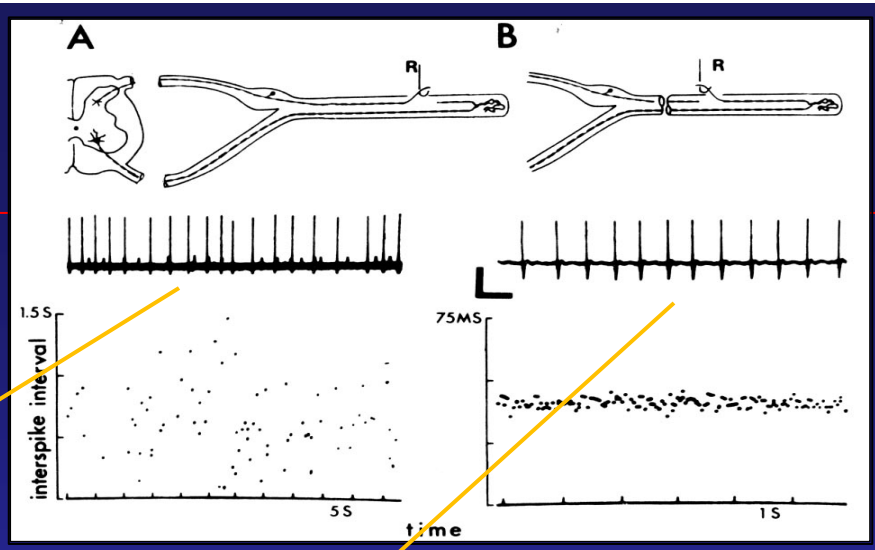
Neuroplastic changes following nerve injury



PNS changes:

- **Neuroma formation**

Neuroplastic changes following nerve injury



DRGs

Sciatic N

Partially denervated limb

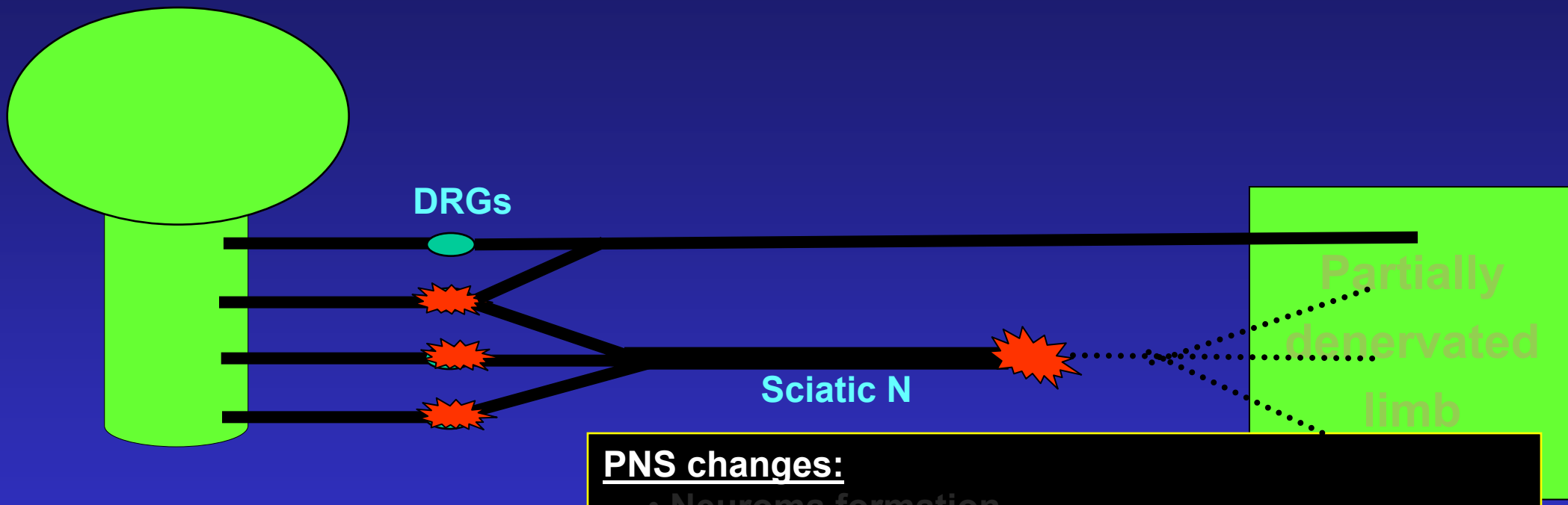
PNS changes:

- Neuroma formation
- Spontaneous firing

Production of novel Na^+ channels

Assembly in neuroma and DRG

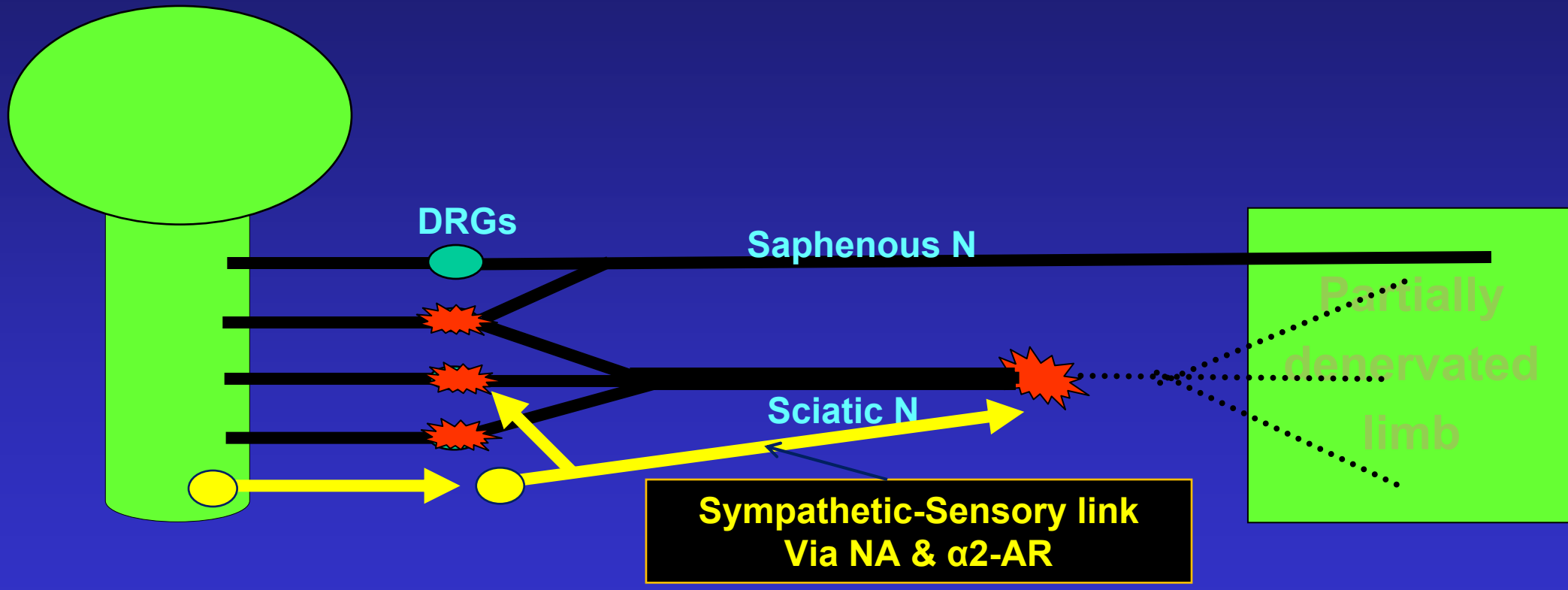
Neuroplastic changes following nerve injury



PNS changes:

- Neuroma formation
- Spontaneous firing
- **Firing induced by**
  - **chemical mediators (histamine, bradykinin…)**
  - **Mechanical stimuli (e.g., malfitting prosthesis)**
  - **electrical stimuli (cross-talk, ephapses)**

Neuroplastic changes following nerve injury (cont.)



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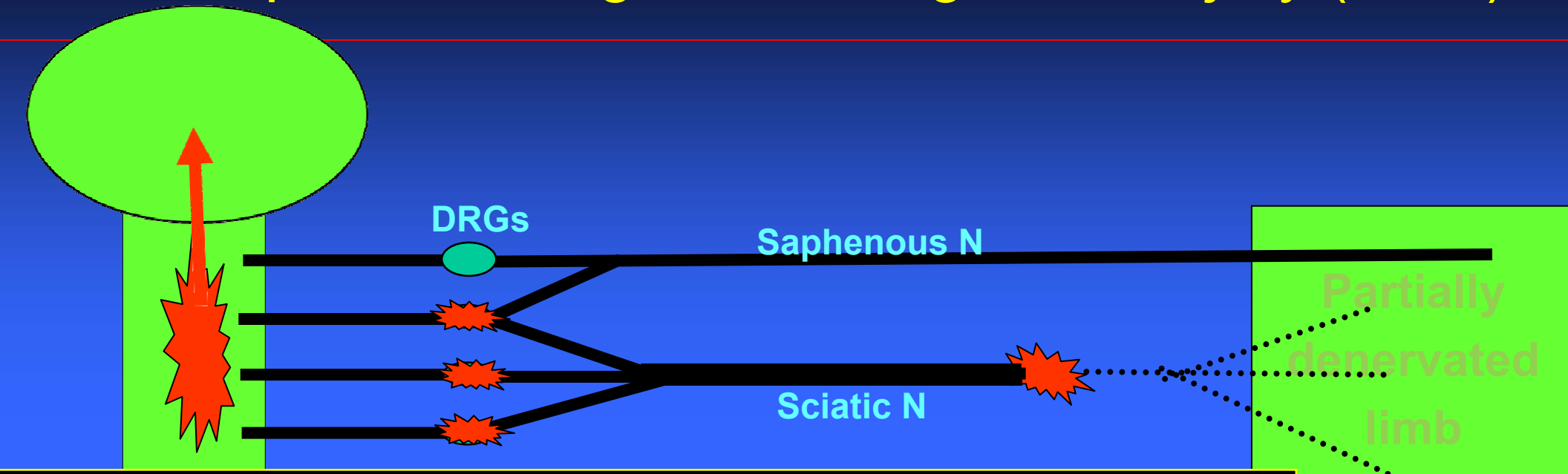
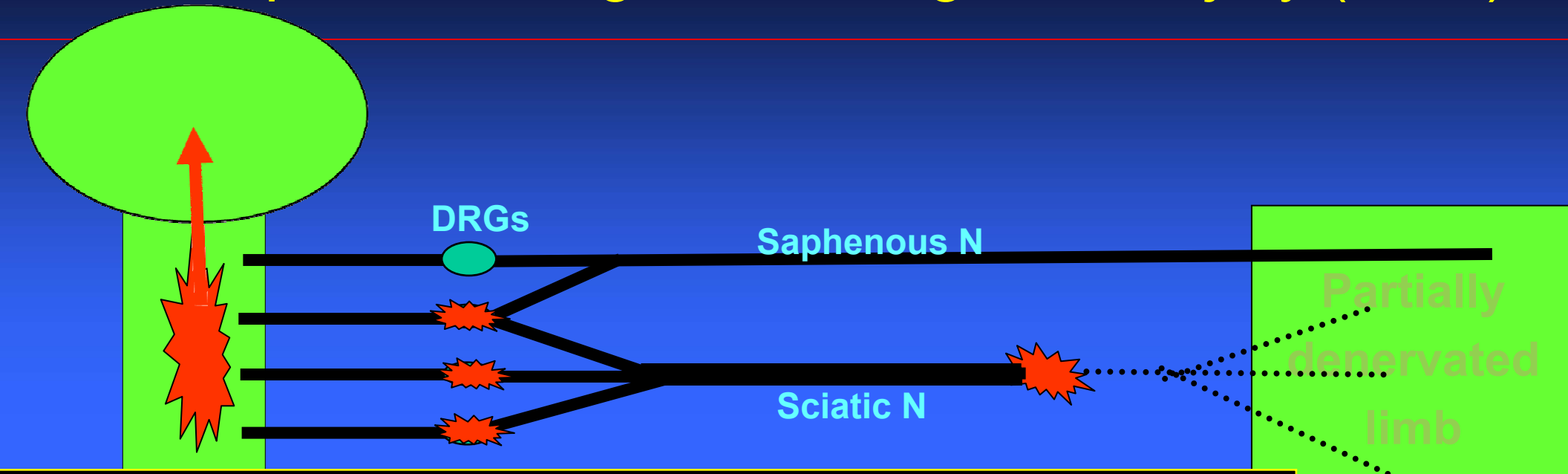


CNS changes:

- **Loss of I^o & II^o / microglia reaction / astroglia**
- **Loss of receptors (e.g., opioid rec.)**
- **↓↑ mediators + phenotypic switch (e.g., GABA depolarizes)**

Neuroplastic changes following nerve injury (cont.)



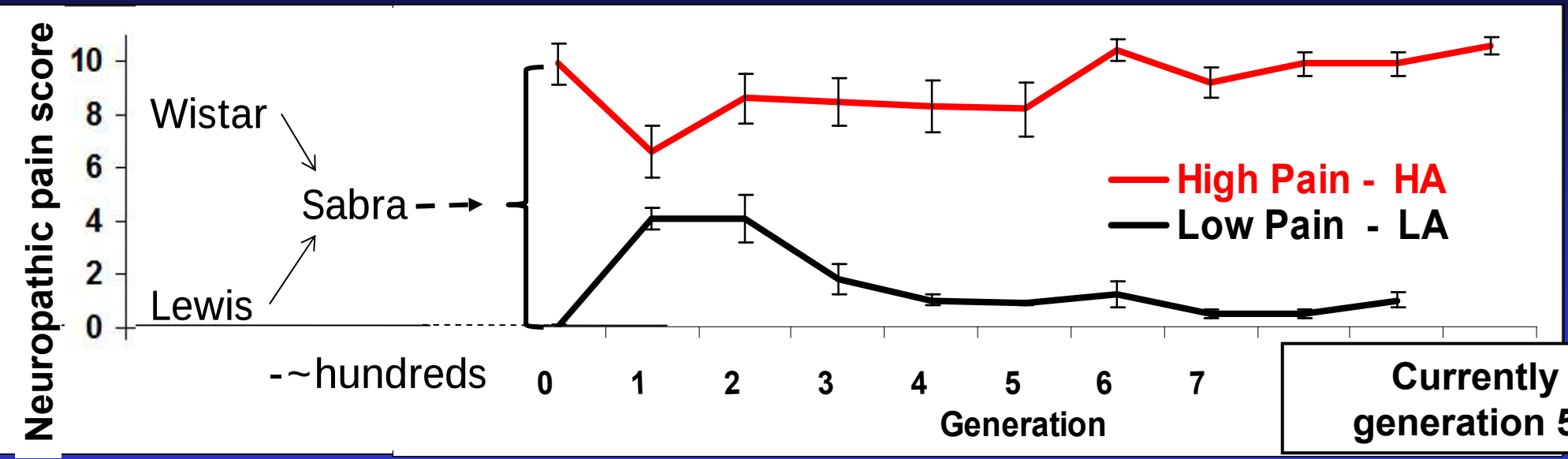
CNS changes:

- Loss of I^o & their terminals / microglia reaction / astroglia
- Loss of receptors (e.g., opioid rec.)
- ↓↑ mediators + phenotypic switch (e.g., GABA depolarizes)
- **Rewiring of the pain network:**
  - ⇔ tuning curves; novel modalities
  - ⇔ RFs
  - segmental disinhibition
  - central sensitization
  - reduced efficacy of descending inhibition

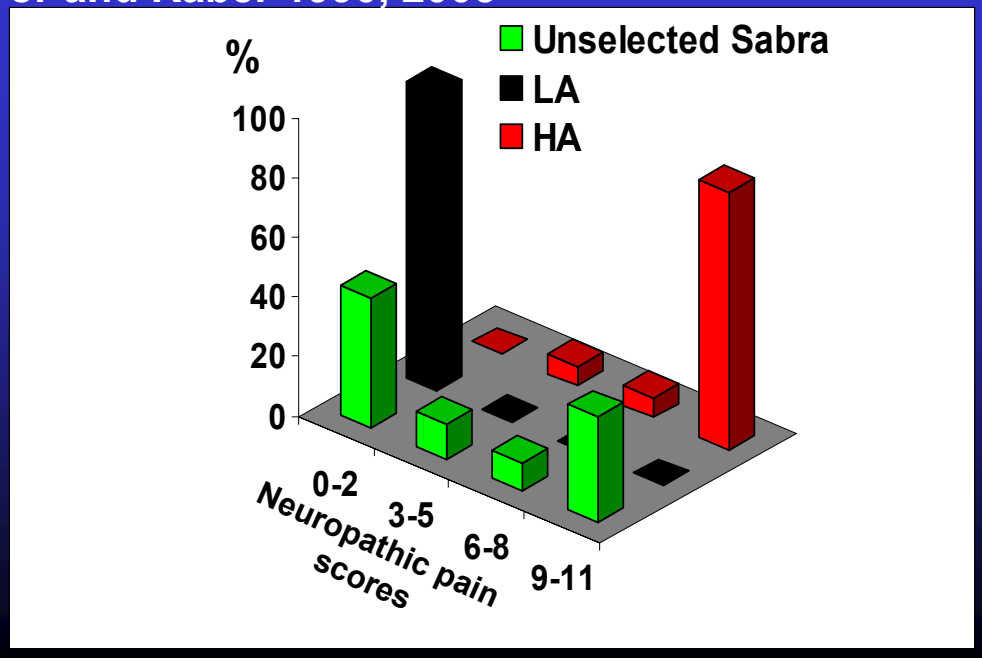
Comparative approach:

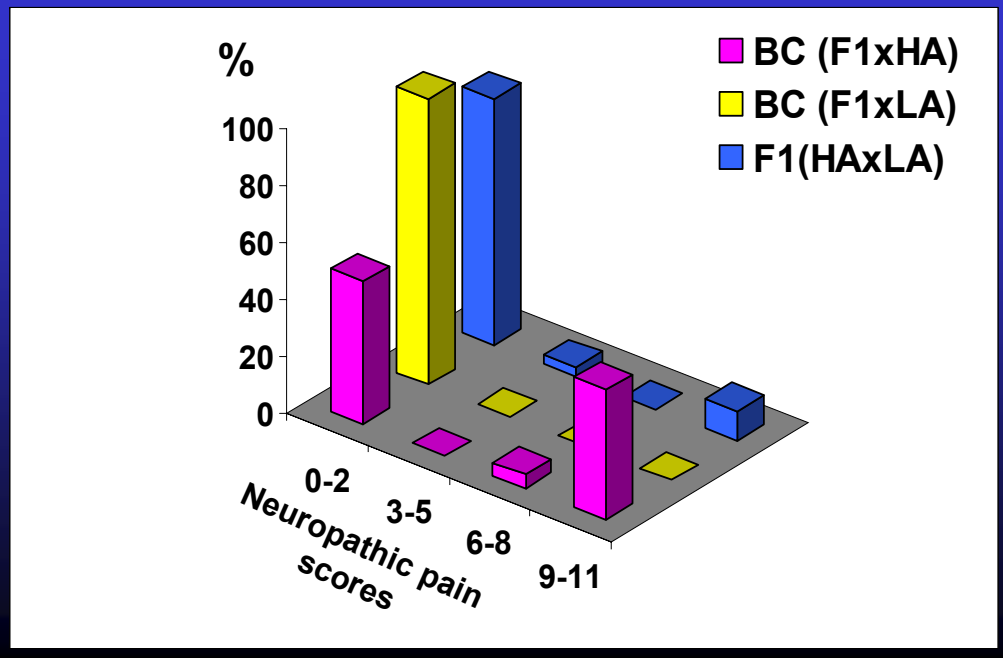
Animal models used in pain genetics

Genetic selection based on **spontaneous** neuropathic pain

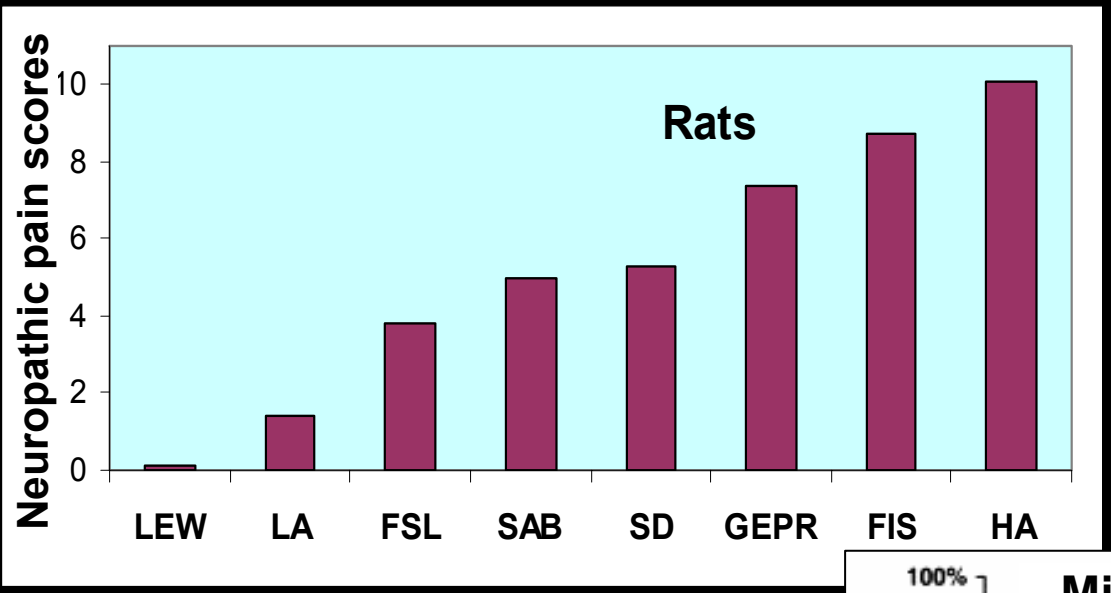


Devor and Raber 1990, 2005



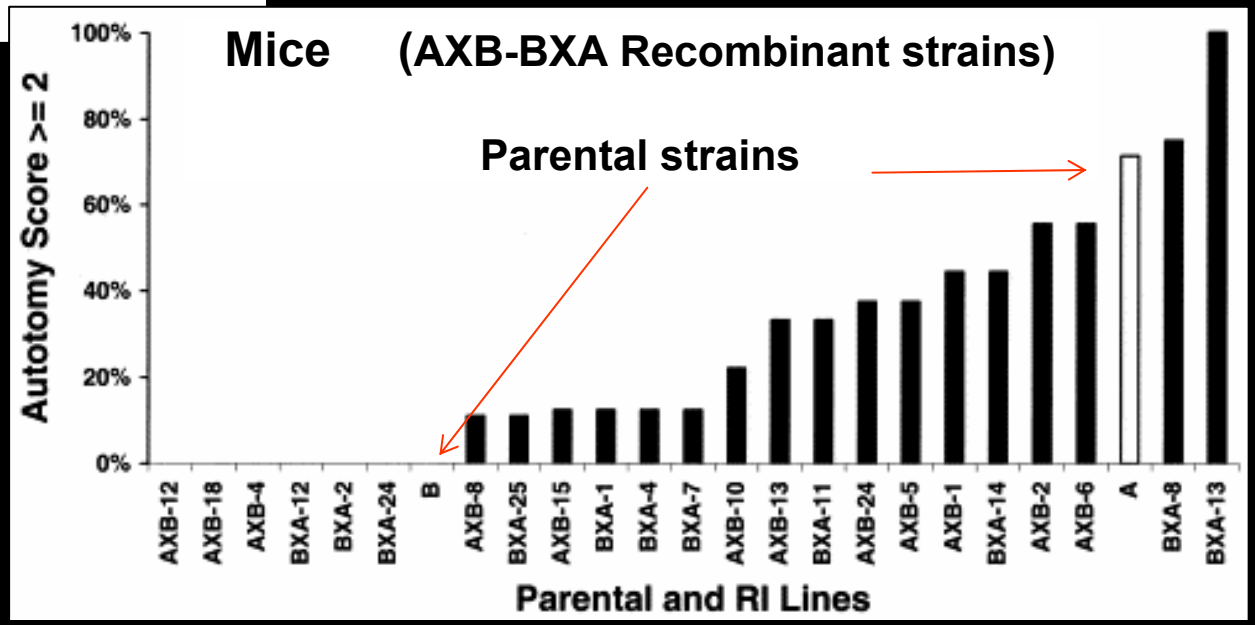


Neuropathic pain levels are strain specific / 2 species



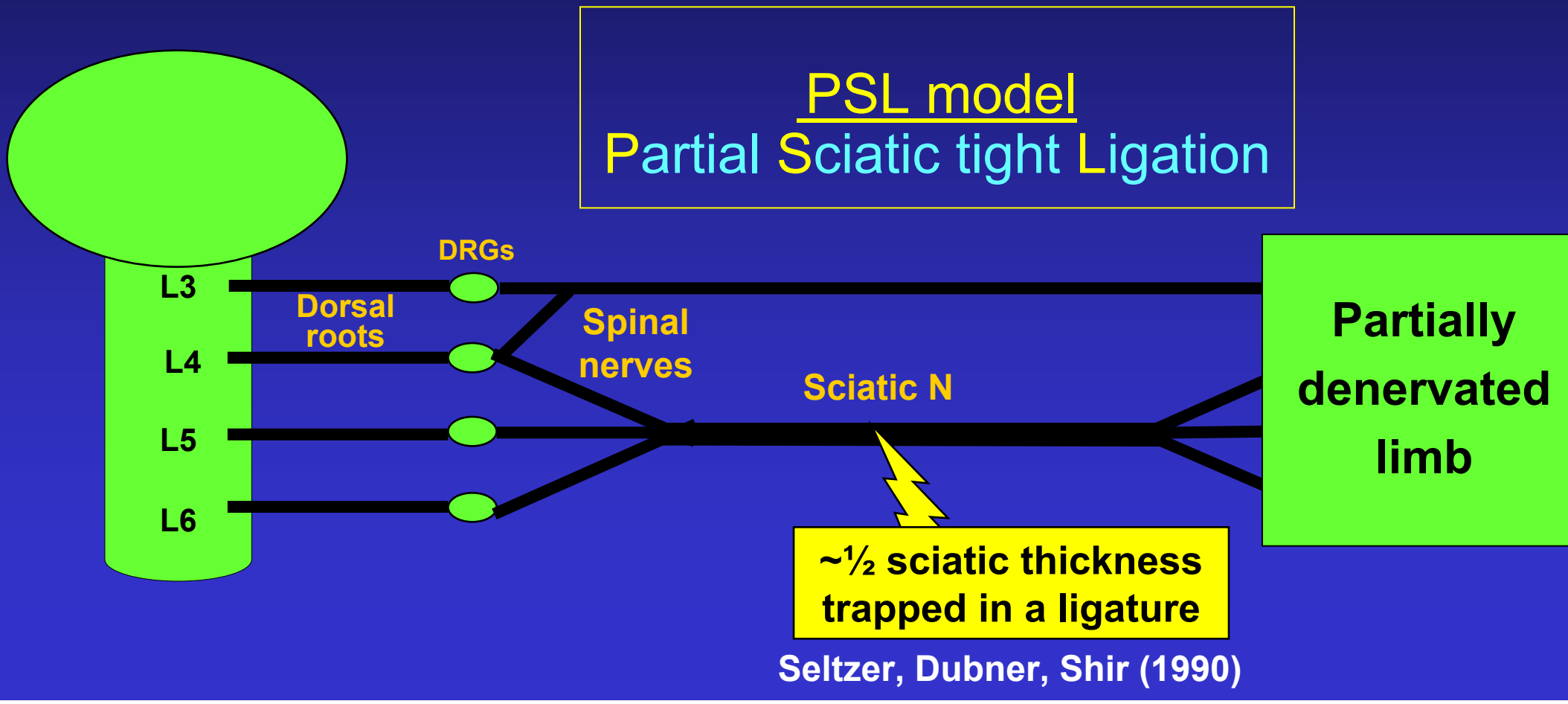
Seltzer & Shir (1998)

$$Var_{Pain} = Var_{Gen} + \cancel{Var_{Env}}$$



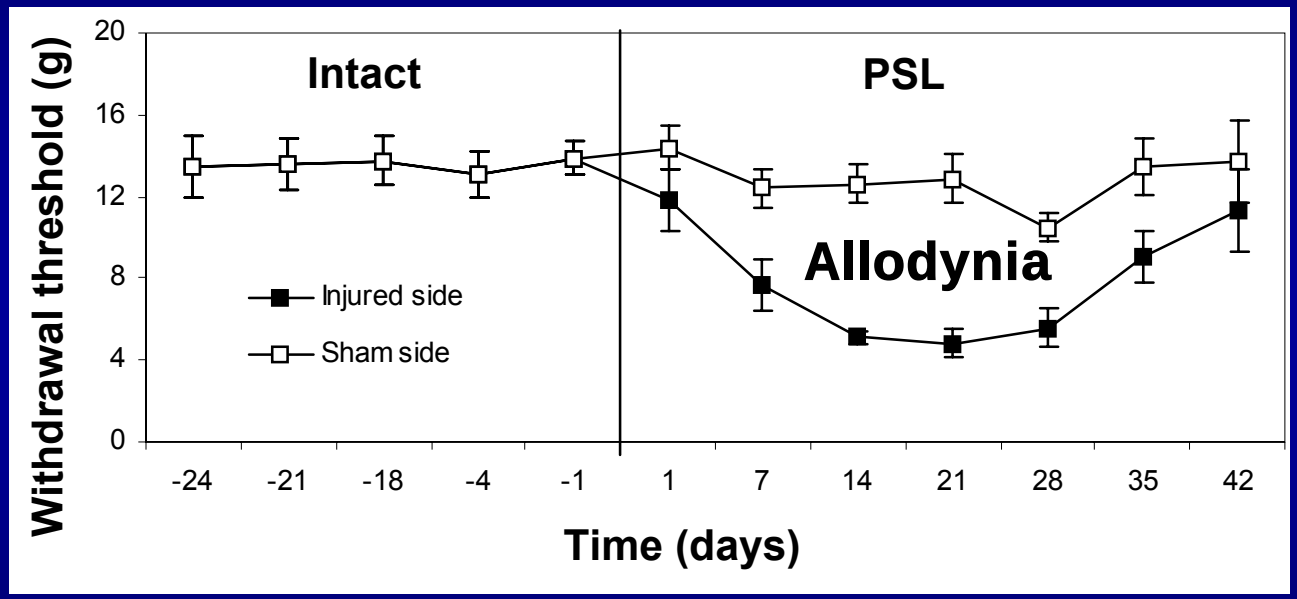
Seltzer et al (2001)

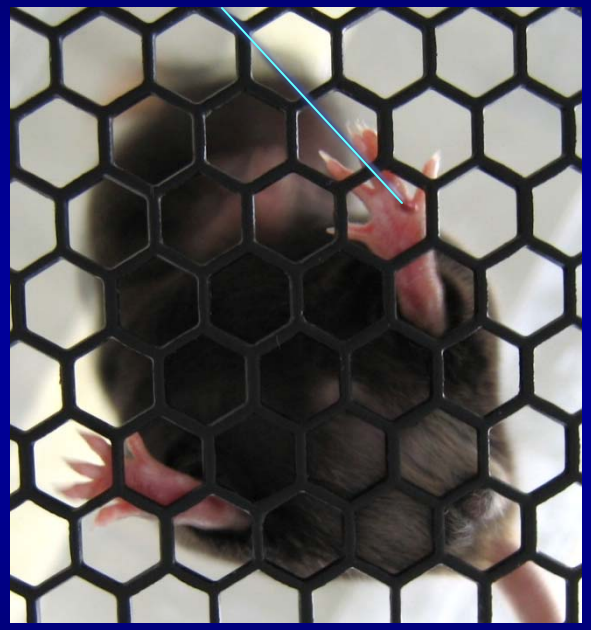
Stimulus-evoked chronic pain is also determined genetically



Pain abnormalities in the PSL model - I

Tactile allodynia:

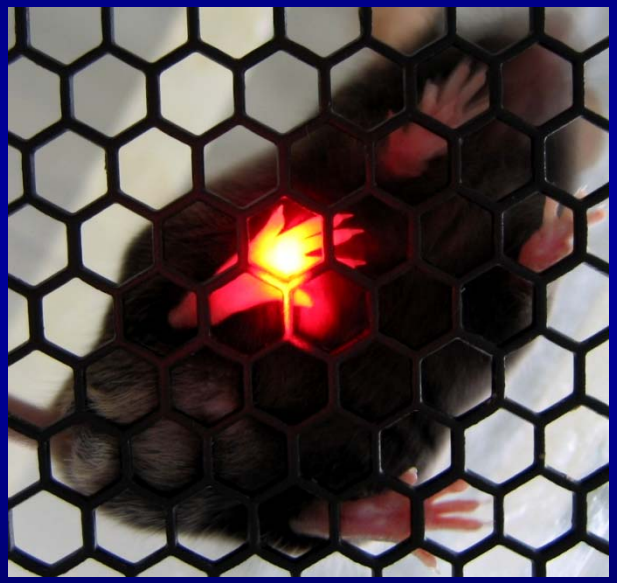


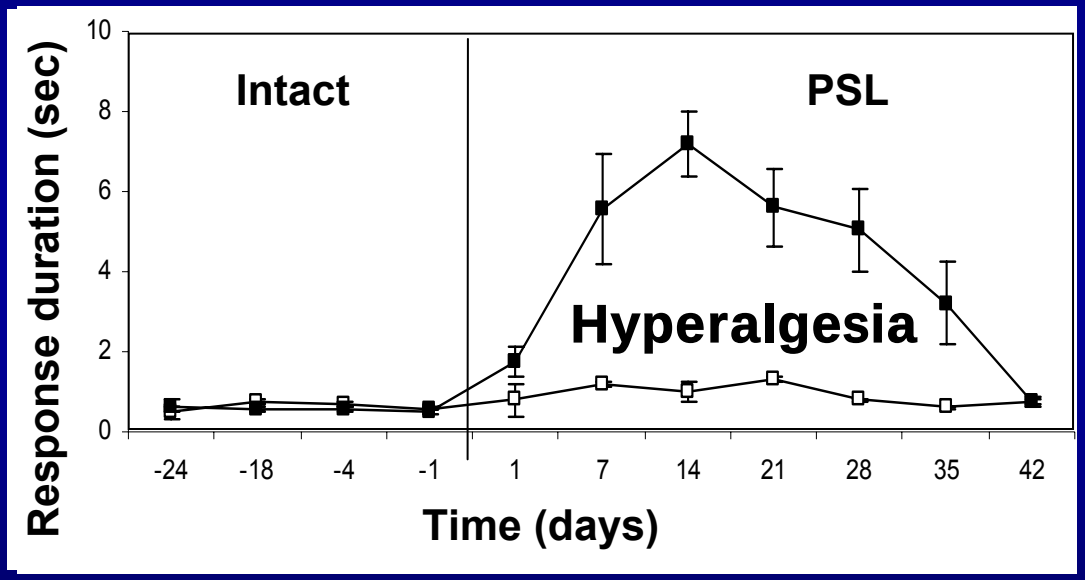


Shir & Seltzer (1998

Pain abnormalities in the PSL model - II

Heat hyperalgesia:

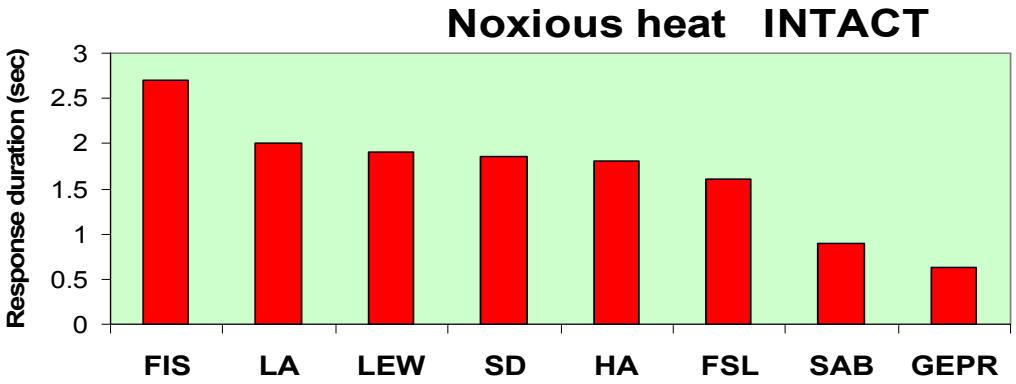


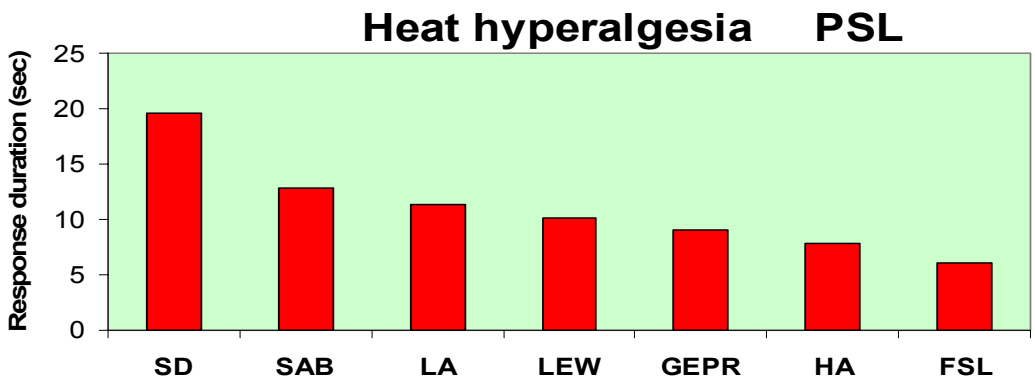


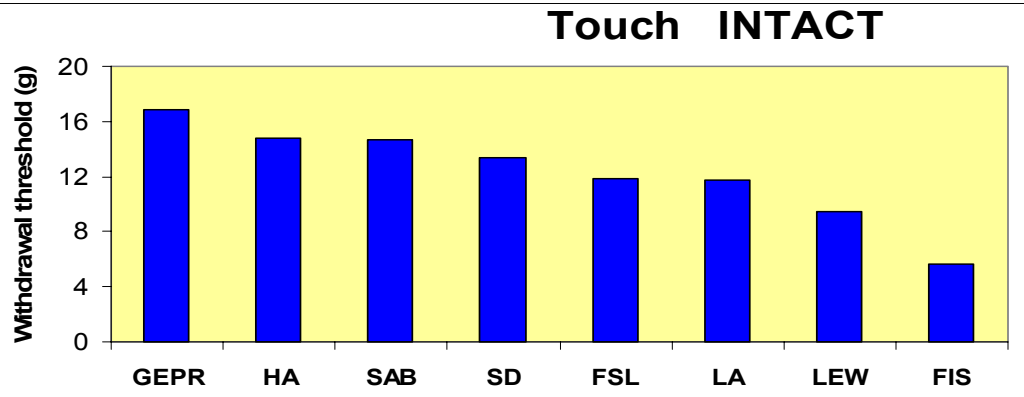
Shir & Seltzer (1998)

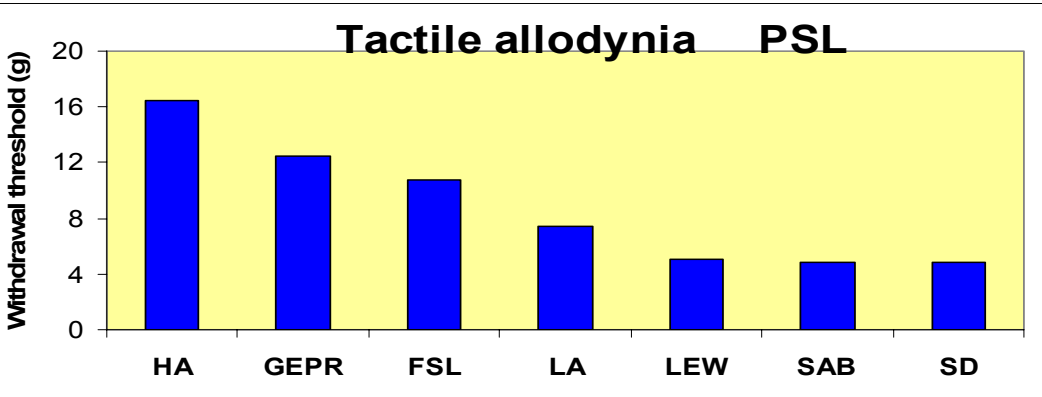
Acute pain - Tactile allodynia - Heat hyperalgesia - Spontaneous pain

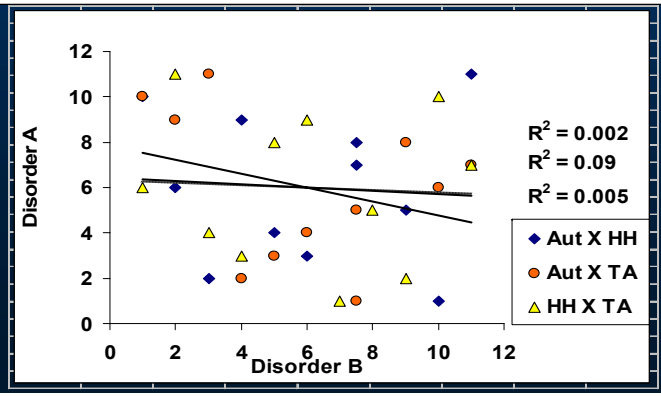
RATS (Mogil et al. in mice)

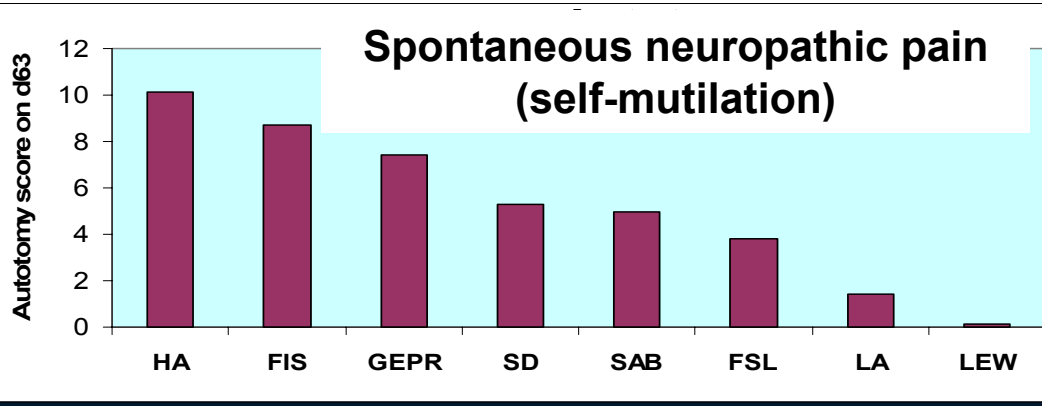












hir et al (2001)

Conclusions

1. **Acute** pain sensitivity does not predict levels of **chronic** pain (3 different chronic pain models, 2 stimulus modalities, 2 species, 2 research groups).

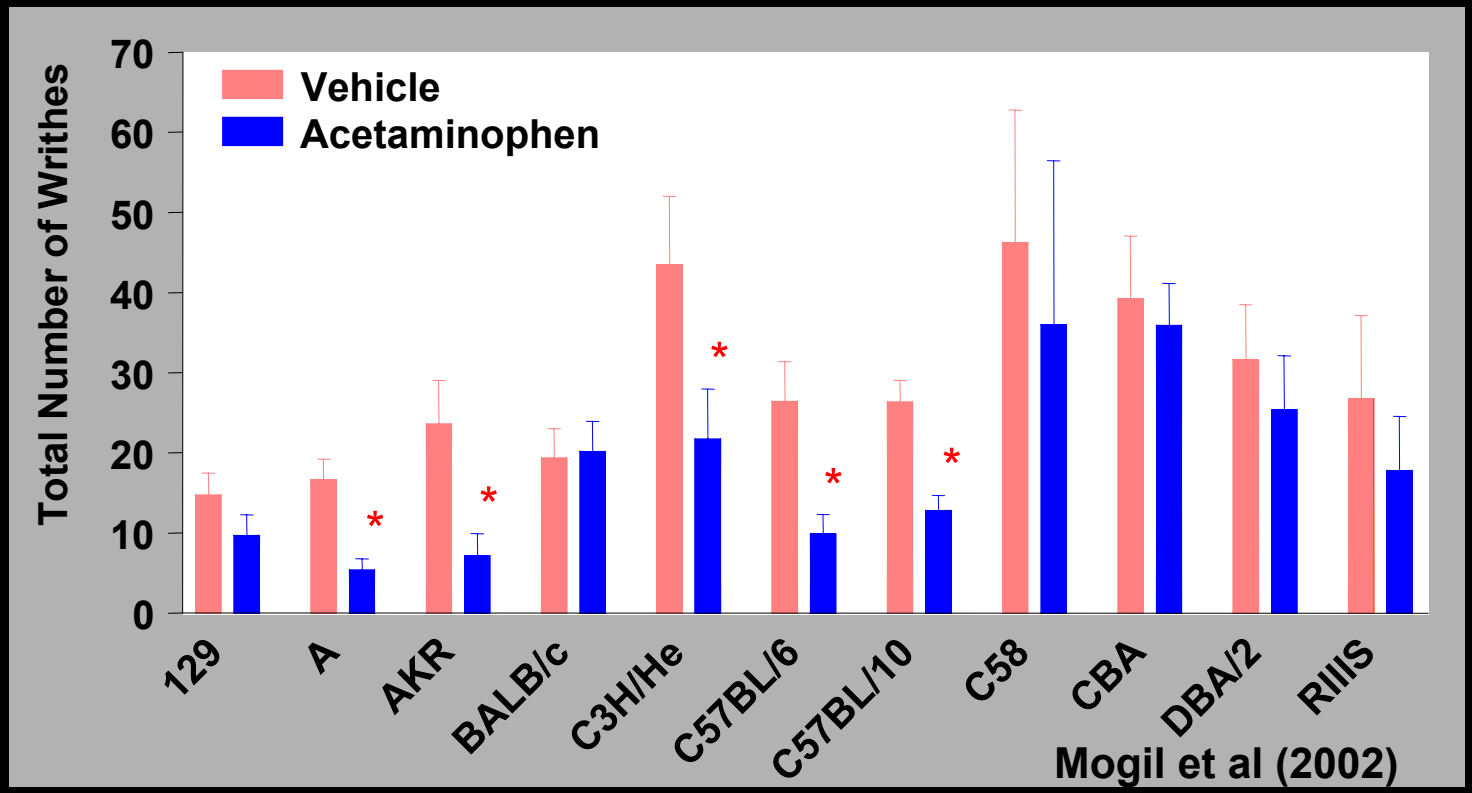
2. Levels of **spontaneous** chronic pain are not correlated with levels of **stimulus-evoked** chronic pain.

3. If these results are translatable to humans, **genes are 'syndrome-specific'**. Pharmaco-genetic solutions will have to be tailored per syndrome.

Heritability of chronic pain

How much of the variance is accountable by genetics?

Heritability in rodents



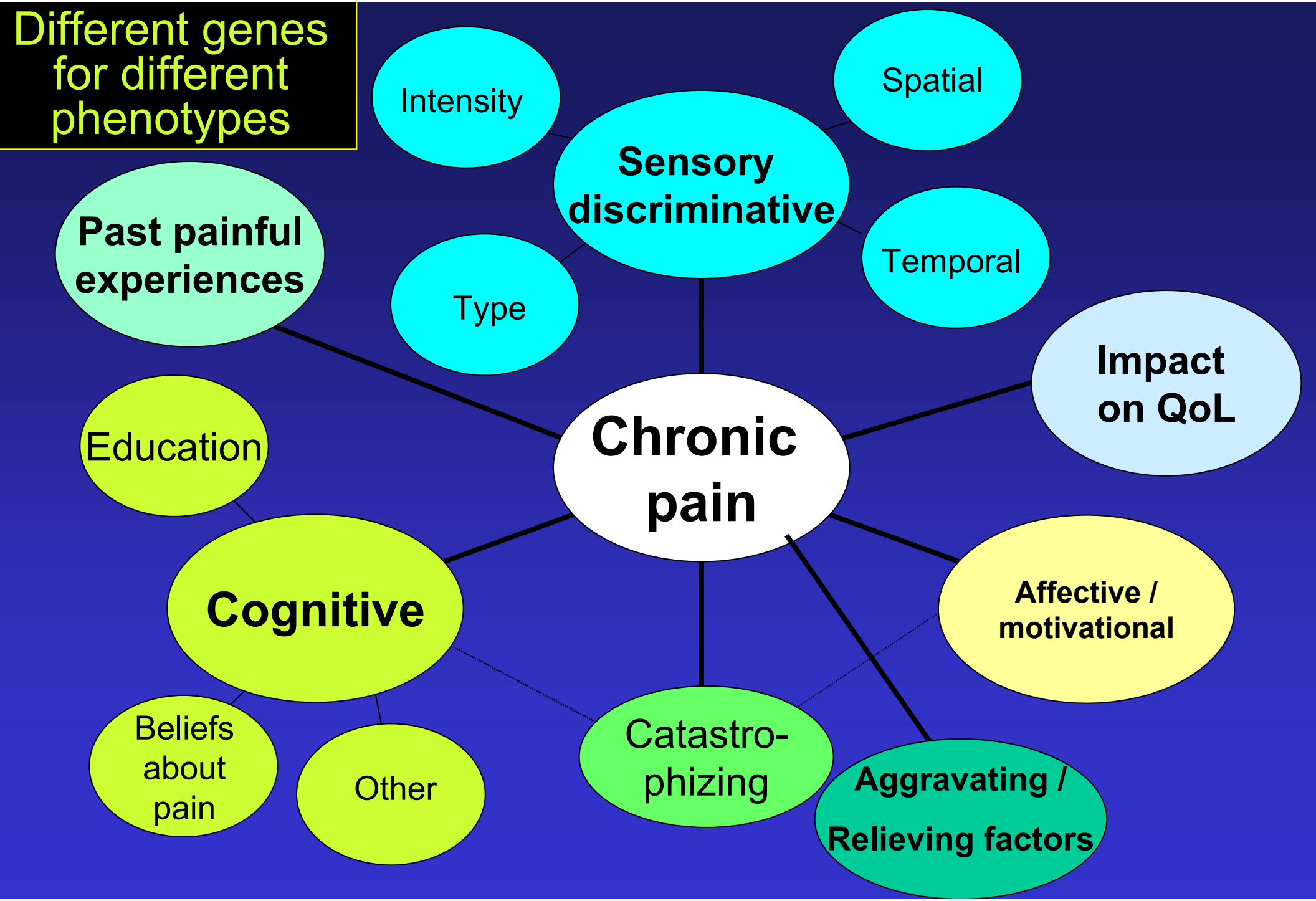
– Nociception: 30-76% mean ~ 53%
– Anti-nociception / analgesia: 23-68% mean ~ 45%
– Neuropathic pain (SNL, Autotomy, PSL): ~ 30-70% mean ~50%

Heritability of pain in humans

Pedigree analyses / twins studies: h^2 ~ 0.2-0.7 (mean ~50%)

- Sciatica
- Diabetic neuropathy
- Carpal tunnel syndrome
- "Burning feet" syndrome
- Post-herpetic neuralgia (HLA)
- CRPS (HLA)
- Fibromyalgia (HLA; *5HTTP1*)
- Low back pain / Sciatica (*GCH1; BDNF*)
- Migraine *(Cacna1a, ATP1A2, …)*
- TMD - Temporo-Mandibular Pain Disorder *(COMT)*
- Phantom limb pain / stump pain (HLA, *GCH1, GDNF*)
- Post-Mastectomy Pain Syndrome *(COMT, GCH1)*

Phenomics of chronic pain as a complex trait


Different genes for different phenotypes
Intensity
Spatial
Sensory discriminative
Temporal
Type
Past painful experiences
Impact on QoL
Education
Chronic pain
Cognitive
Affective / motivational
Beliefs about pain
Other
Catastro-phizing
Aggravating / Relieving factors

Chronic pain phenomics

Choosing the right phenotypes for genetics:

- **Clinical relevance**
- **Mechanism-based**
- **N traits *vs.* multiple comparisons ("Bonferroni correction")**
- **Pooling / Indexing / Loosing resolution**
- **Endophenotypes**

The Human Pain Phenome Project

- Detailed registry of previous chronic pain episodes
- Aetiology and medical history
- Detailed phenotypes
- Tests (QST, electrodiagnosis, imaging, biochemistry)
- Treatment effects
- Additional traits: life style, personality / character
- Bioinformatics / data mining

Expected gains in pain genetics

- Diagnostic kits
- Prognostic kits
- Preventive pain medicine
- Novel painkillers
- New mechanisms
- Gene therapy
- Better animal models
- Faster / cheaper clinical trials

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United States Congress declared:
2001-2010: The Decade of Pain Control and Research

The Human Genome Project has developed methodological templates that can be transposed immediately to pain genetics.

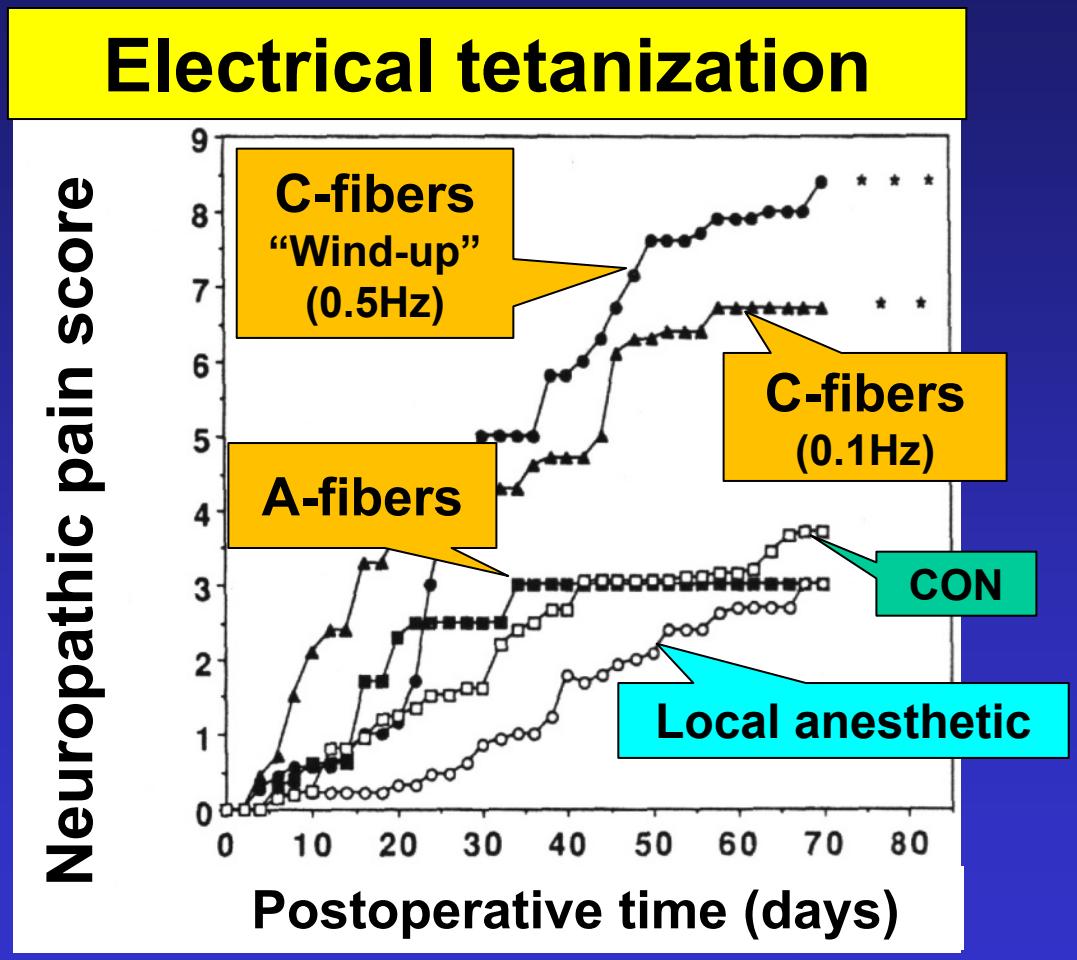
This is the time to:

- Establish new research teams
- Support the collections of DNA samples / multicenter approach
- Finance genome-wide screens using microarray chips
  (1,000 samples X $ 500/ sample = $ 0.5 million / syndrome)

Proposed goal for 2010: First draft listing all major chronic pain genes in humans and mice.
Given the right support – this is achievable !

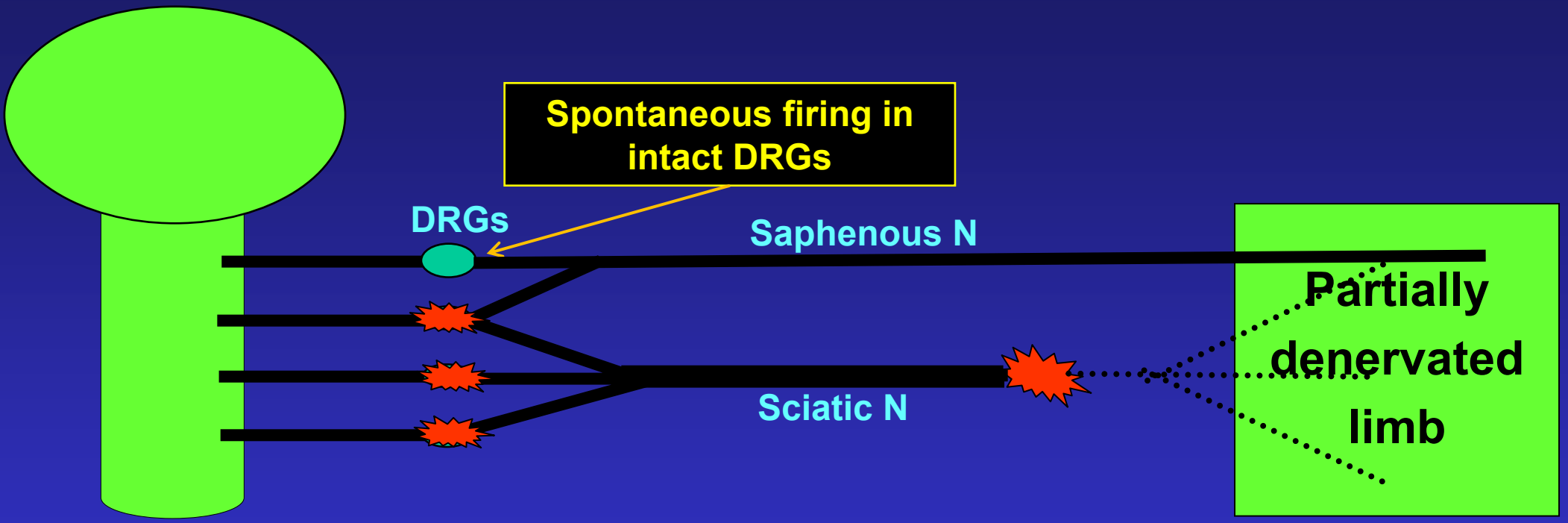

Thank
Thank
You!
THANK YOU

Injury discharge triggers neuropathic pain - II

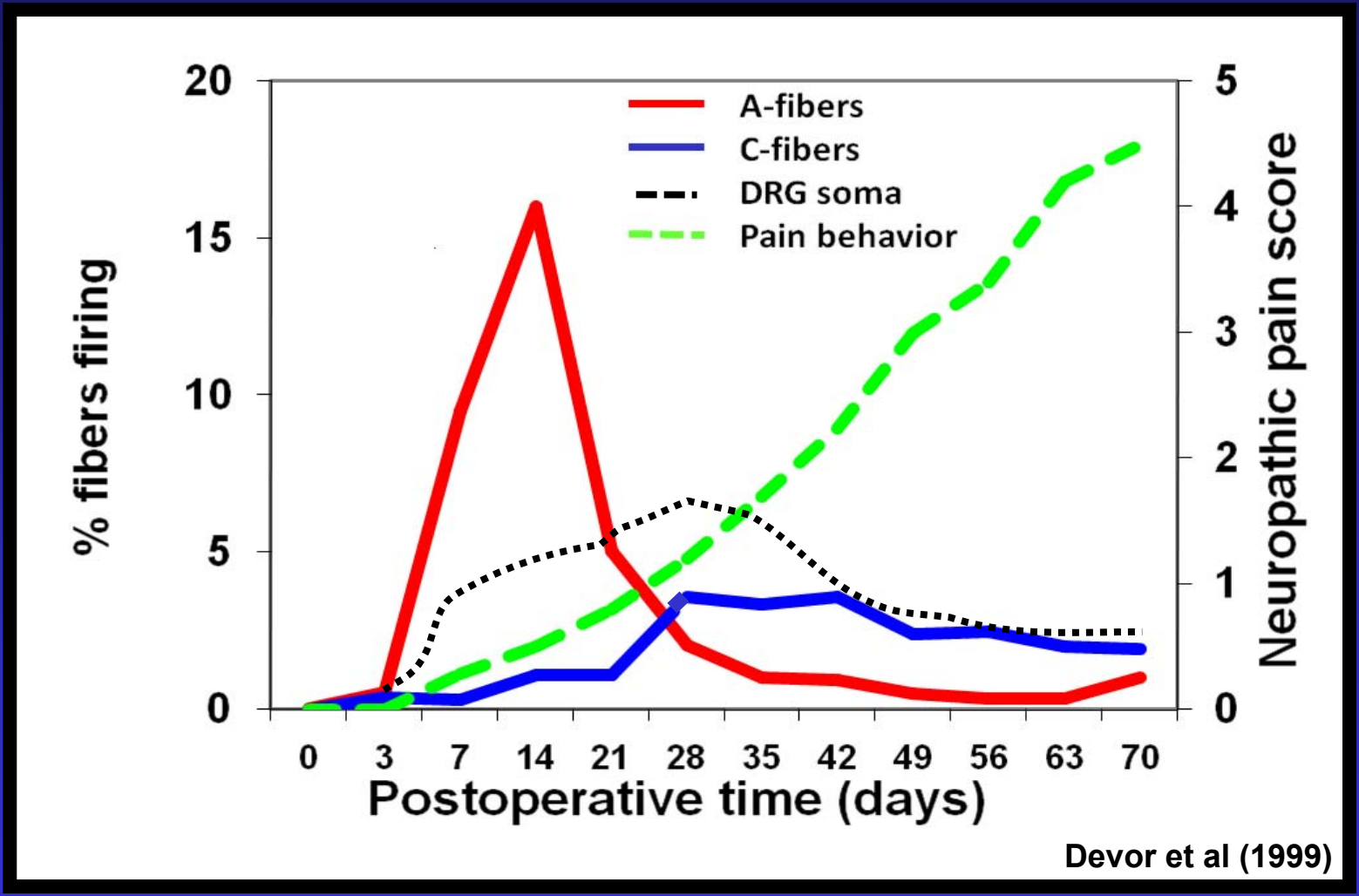


Seltzer et al (1990b)

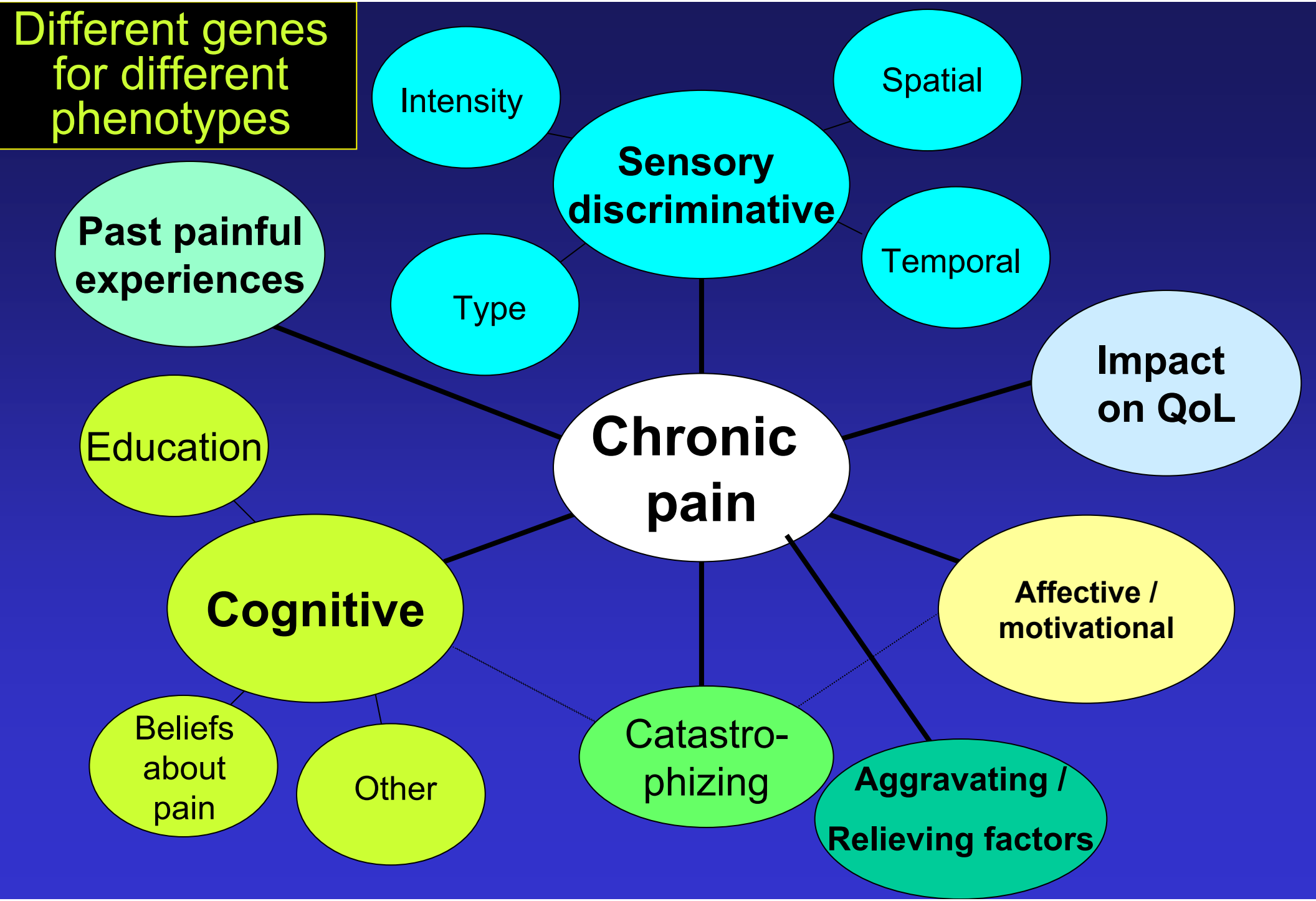
Neuroplastic changes following nerve injury (cont.)



Activity in neuroma and DRG causes pain



Resection / RF / neurolysis of painful neuroma & GG - sometime successful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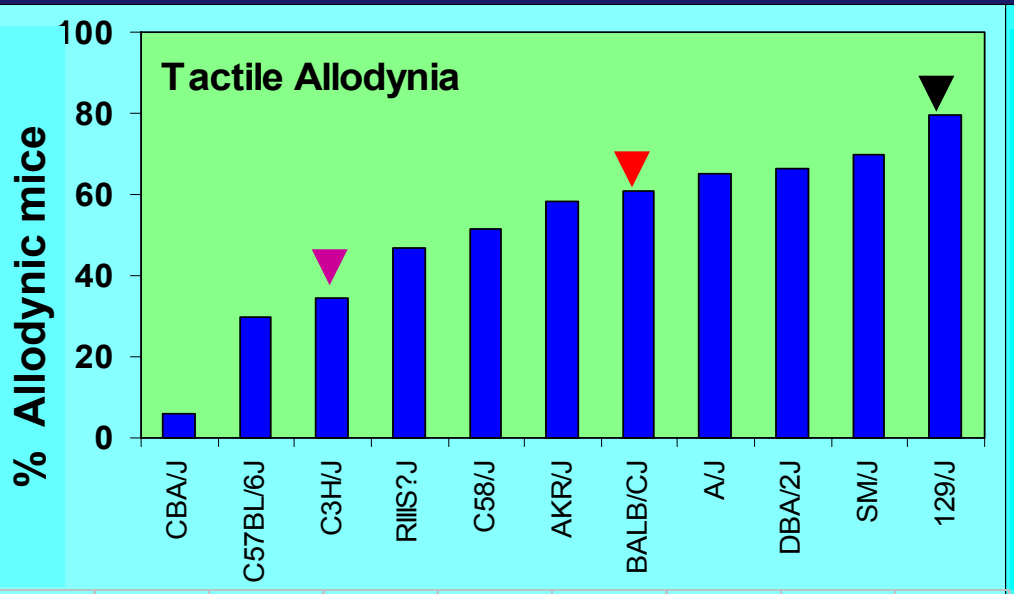
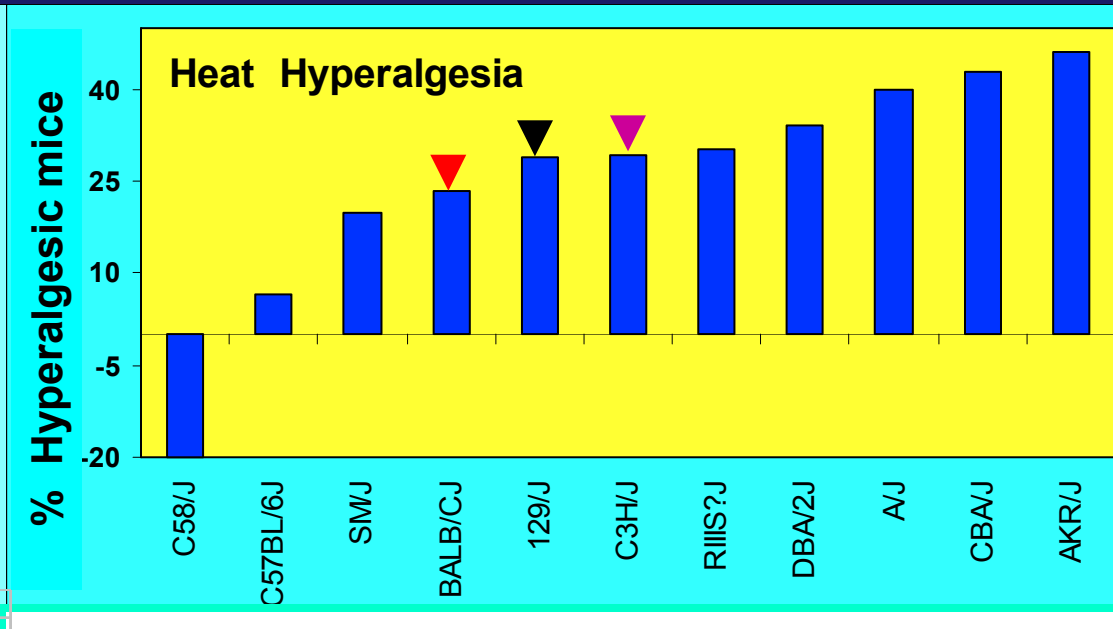
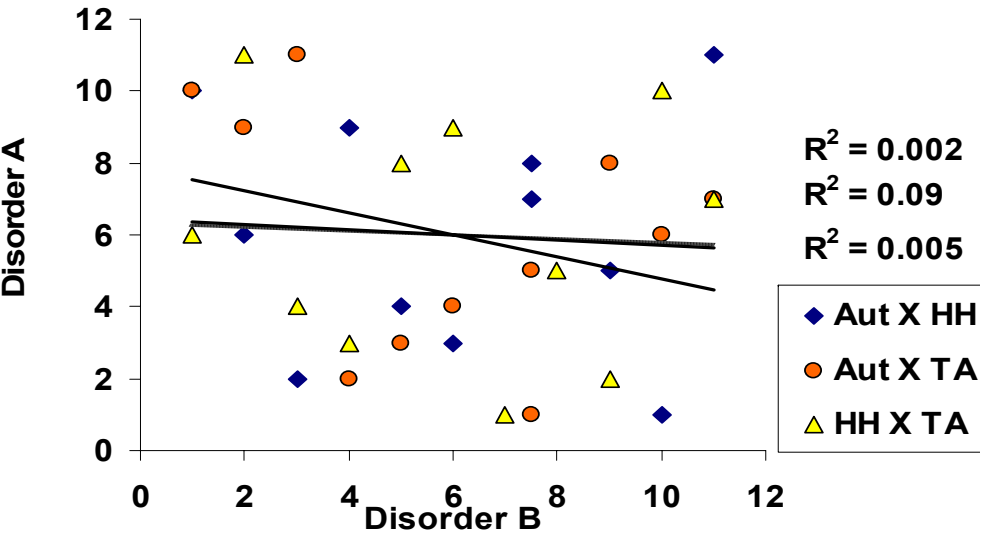
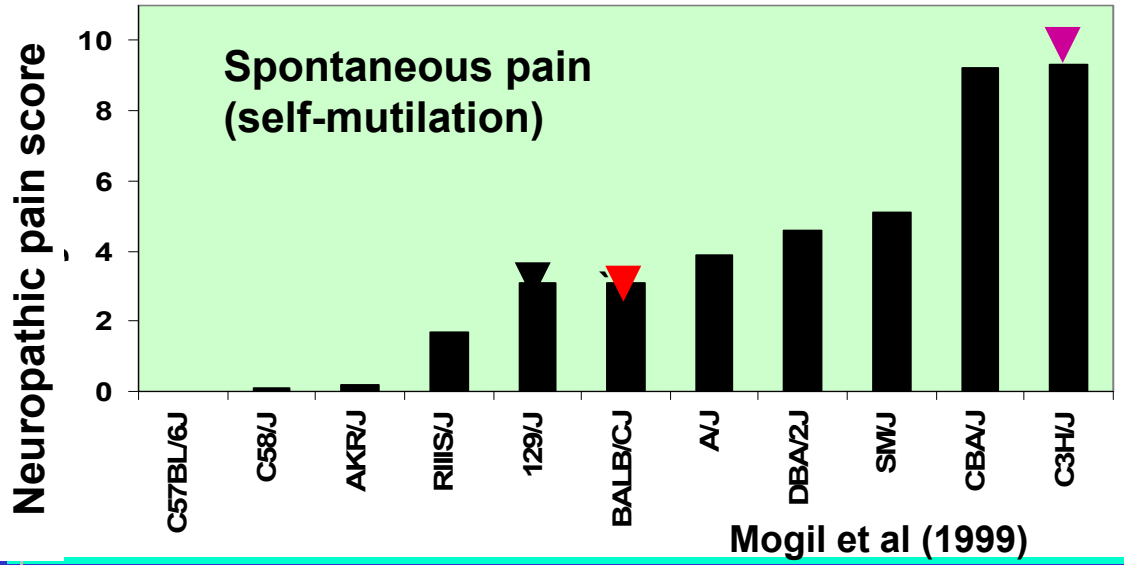
Acute pain - Tactile allodynia - Heat hyperalgesia - Spontaneous pain

MICE



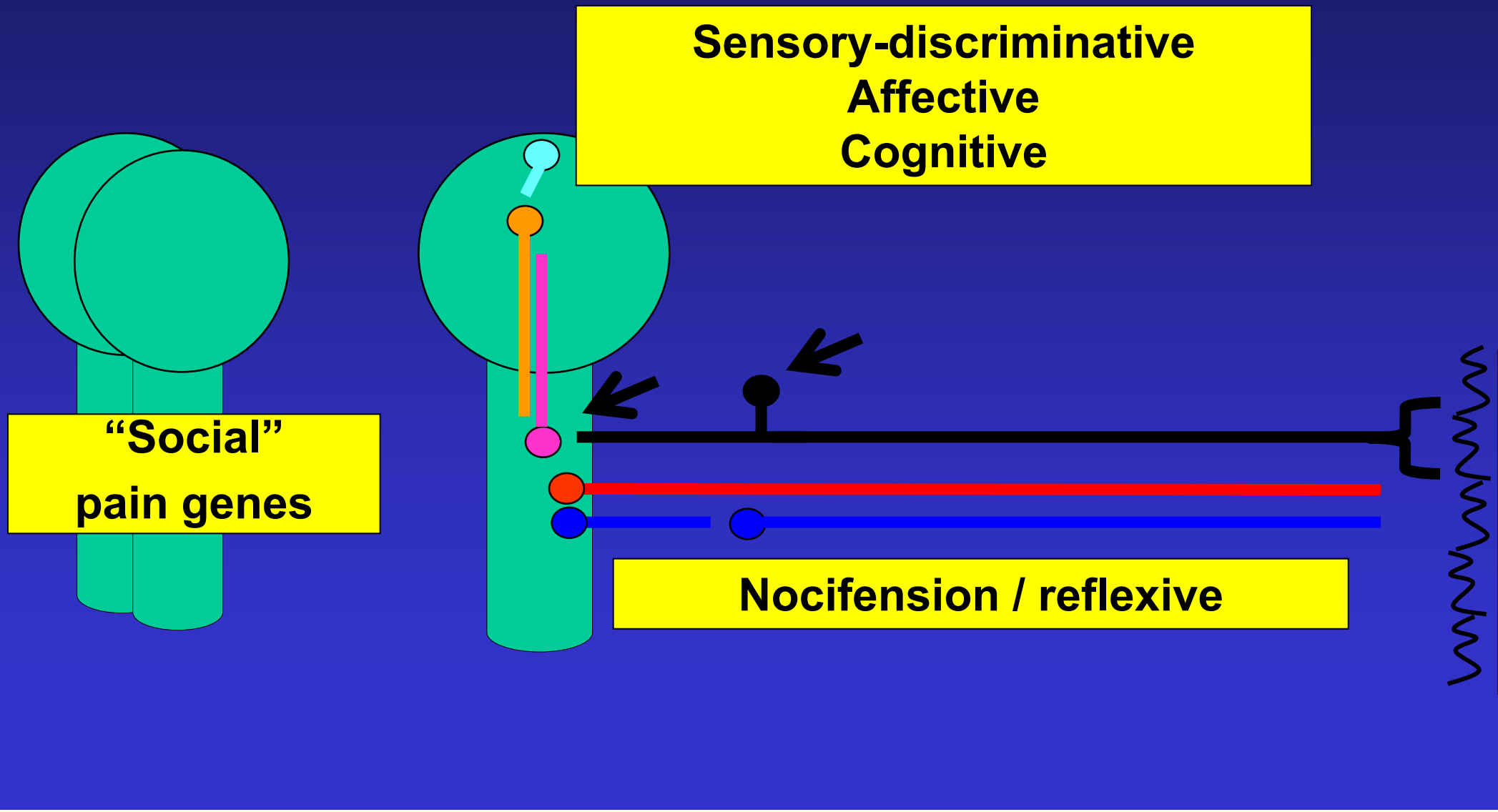






Mogil et al (1999)

Thousands/~25K genes in the human genome encode the chronic pain network



Shall we need to control thousands to treat pain ?

No

- **Most genes have been fixed throughout evolution**

  (e.g., *"Painless"* for noxious heat in the fly larva)

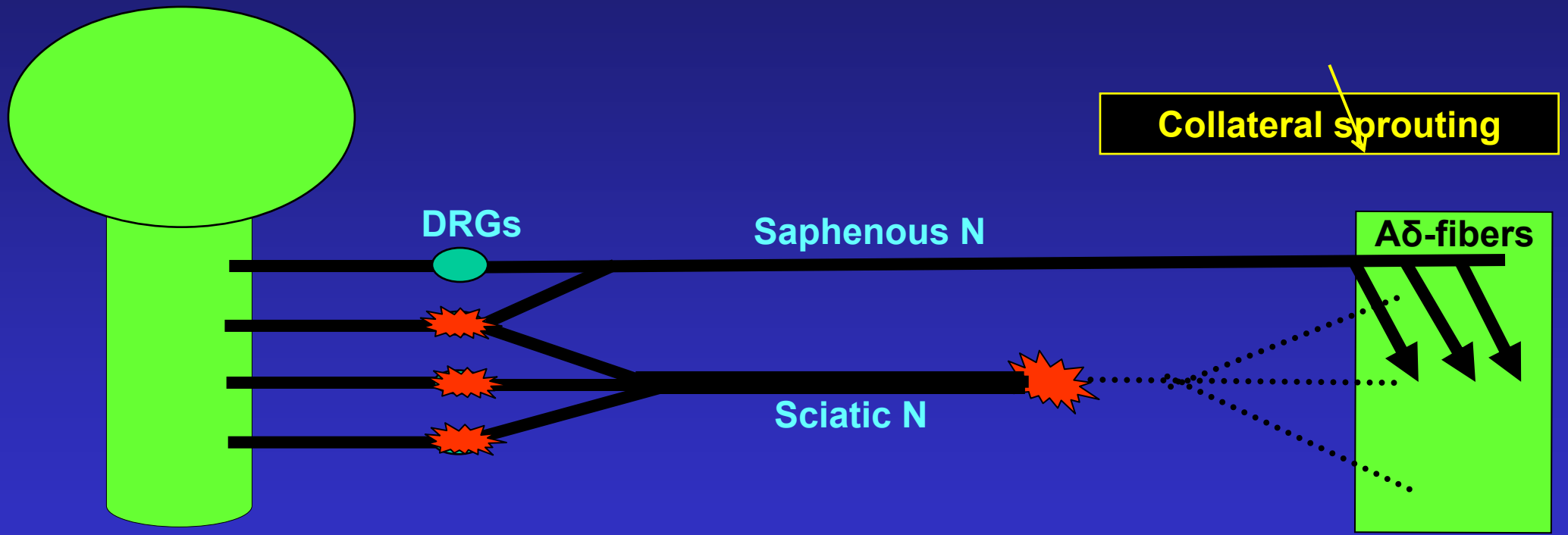
- **While many have Single Nucleotide Polymorphisms (SNPs)**
- **Only a small fraction are functional, even fewer clinically relevant**
- **So how many will have to treated to treat a given pain syndrome?**

Not known as of yet

Guess: ~5 'major' and up to ~15 'modifiers' per syndrome

How many genes would have to be pharmaco-genetically controlled to provide solutions for a pain syndrome?

Neuroplastic changes following nerve injury (cont.)



Genetic and environmental influences on the transition from acute to chronic pain

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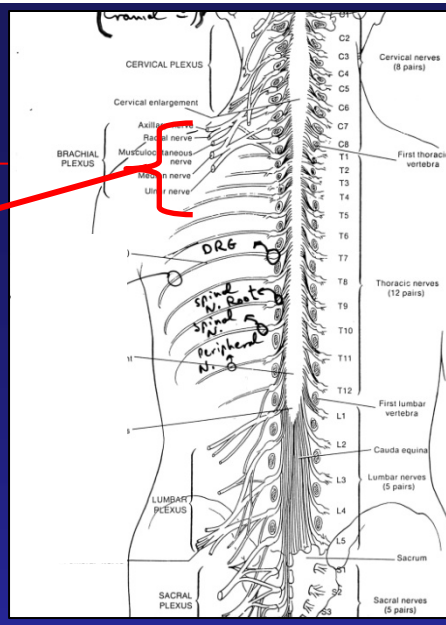
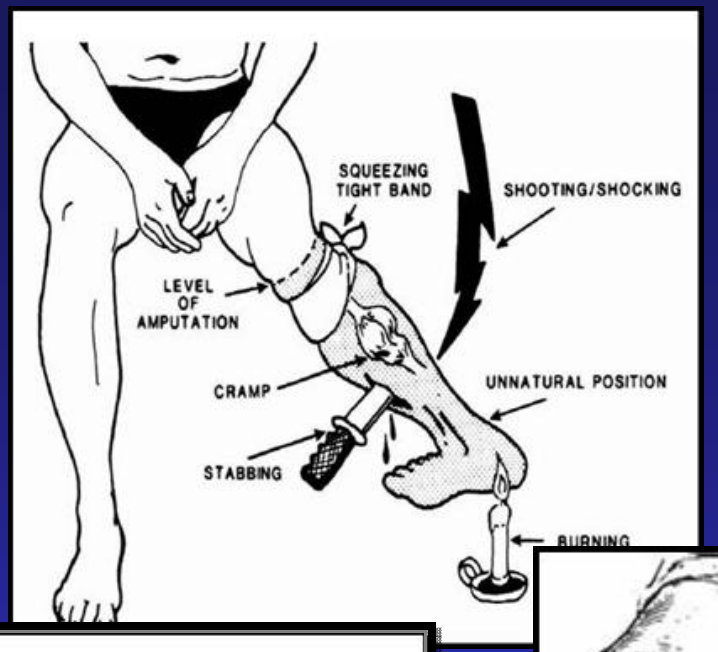
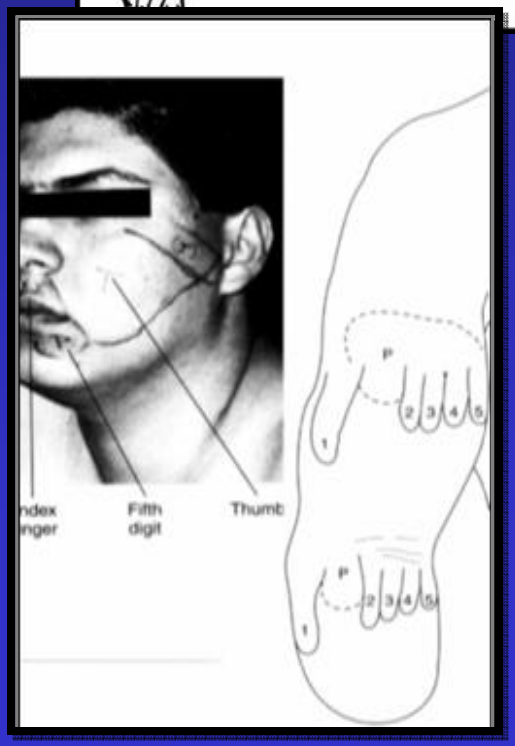
The case of Roni A. (male , age 44, contractor)

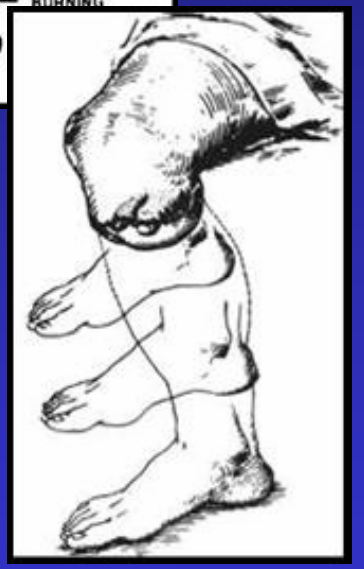
- 1995 - suffered an accident at work
  - L. brachial plexus avulsion
  - L. hand numb and painful
  - L. hand paralysed at an awkward position



- 1997 – surgical relocation of the arm
- 2002 – amputation of the hand
  - Telescoping
  - Triggering the phantom from the face/arm
  - Exacerbation of pain
    - When symp system aroused
    - Changing weather
    - When attempting to move phantom







No therapy has helped Roni get rid of the pain