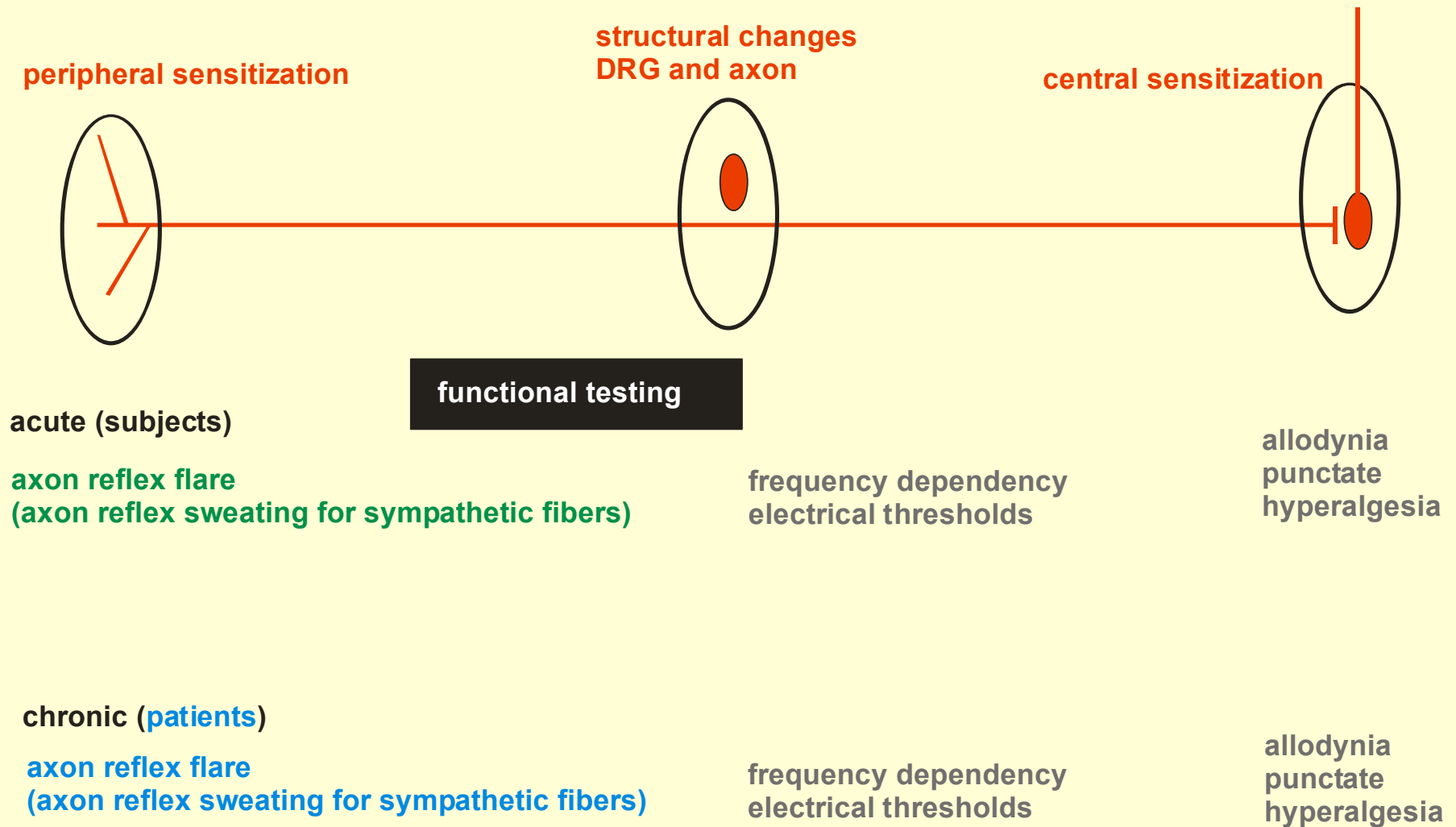




Translating Preclinical Targets to Human Experimental Models of Analgesic Efficacy in Healthy Volunteers

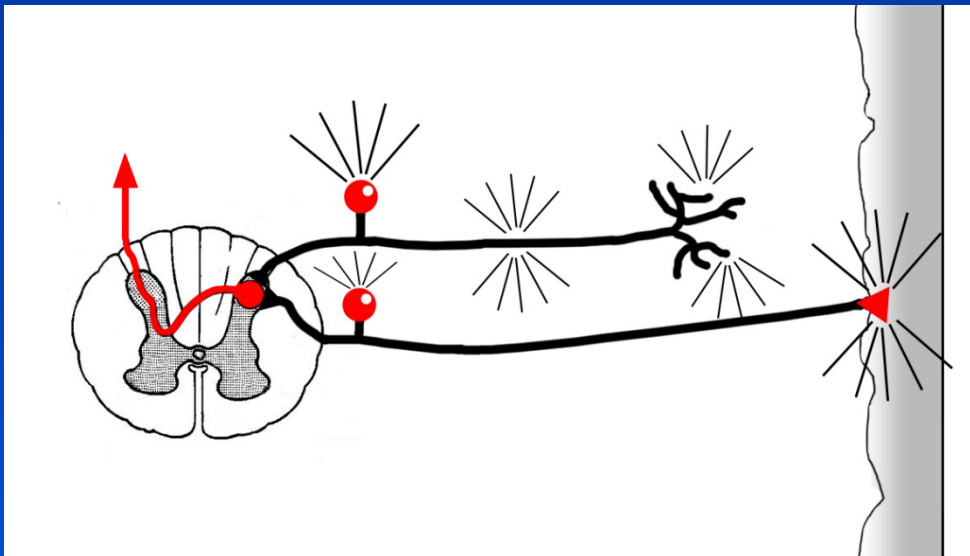
Martin Schmelz

Human pain models: what is the mechanism of pain to be modelled



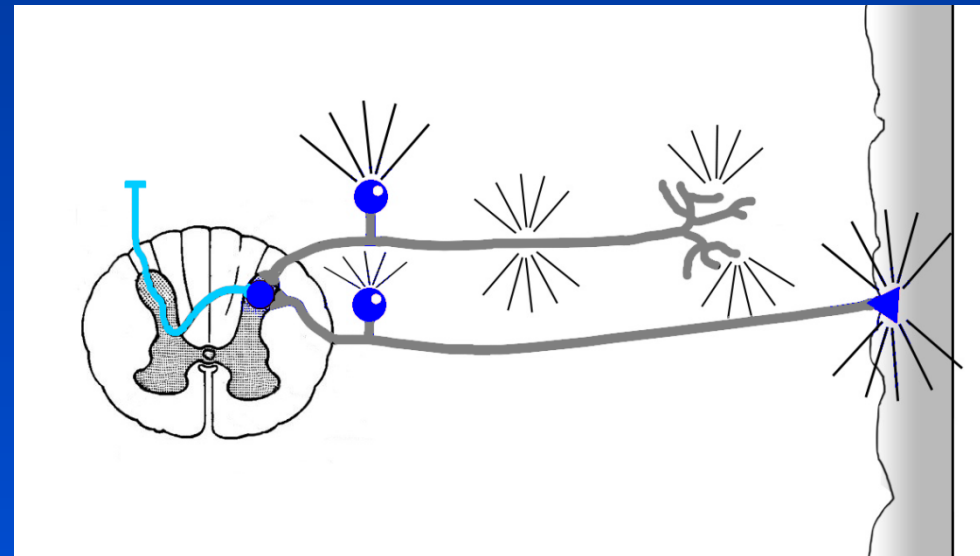
Painful neuropathy

Sites of sensitization/
spontaneous activity



- Spontaneous pain
- Peripheral sensitization
- Central sensitization

Sites of desensitization



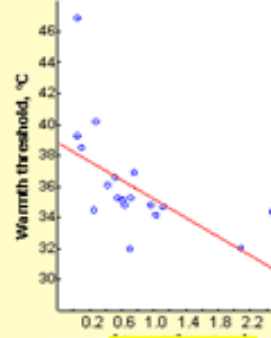
- Hyp- Anaesthesia
- Hyp- Analgesia
- numbness

Separating pain intensity and degree of neuropathy

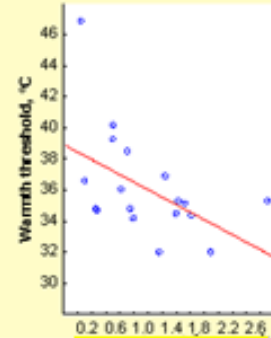
Pain intensity

„excitability“ tests

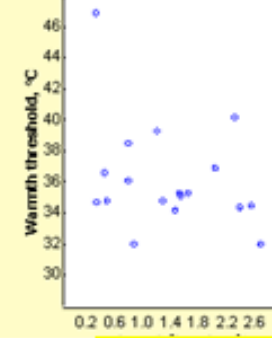
Warm threshold, °C



epidermal



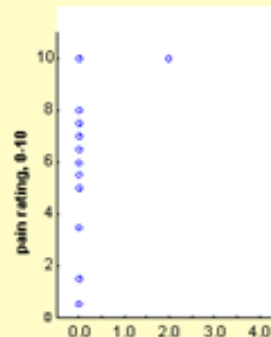
upper dermal



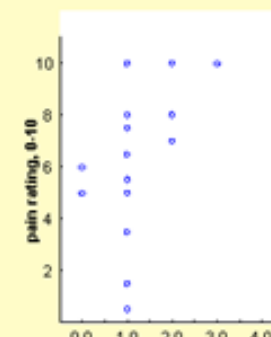
deep dermal

Nerve fiber density

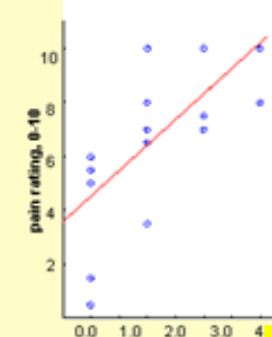
Intensity of electrically induced pain



epidermal



upper dermal



deep dermal

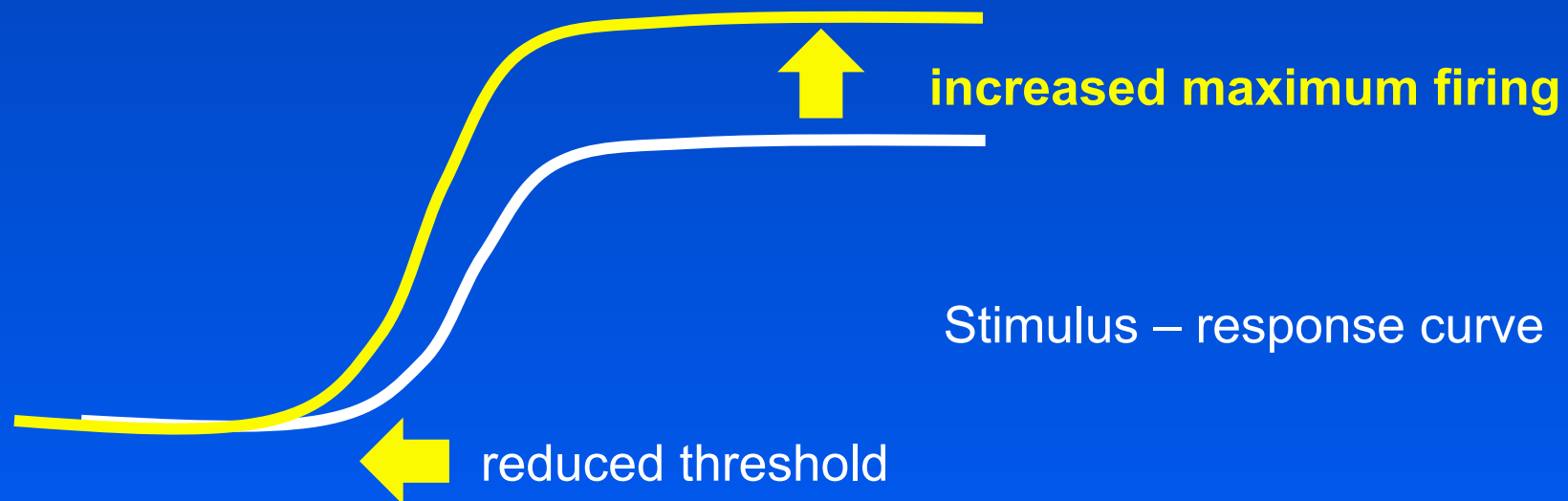
CGRP staining intensity

QST, Skin biopsy (IENF)

Neuropathy

Clinically relevant read outs for the models

- ~~Excitation thresholds~~
- Supra-threshold encoding - “evoked pain”
- Spontaneous activity - “spontaneous pain”



Microneurography technique

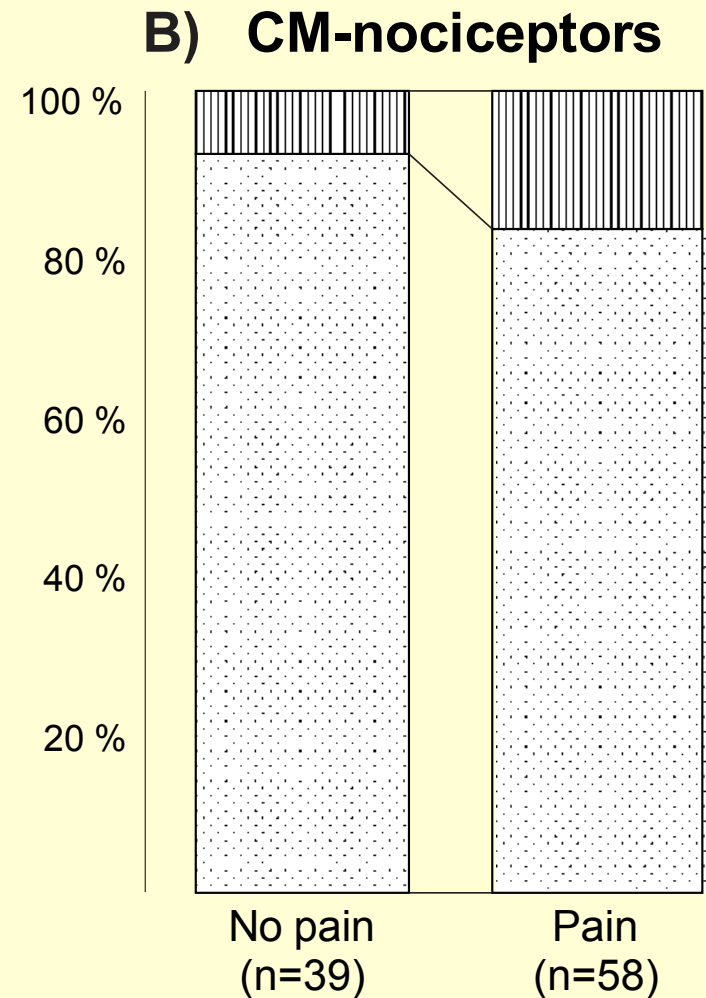
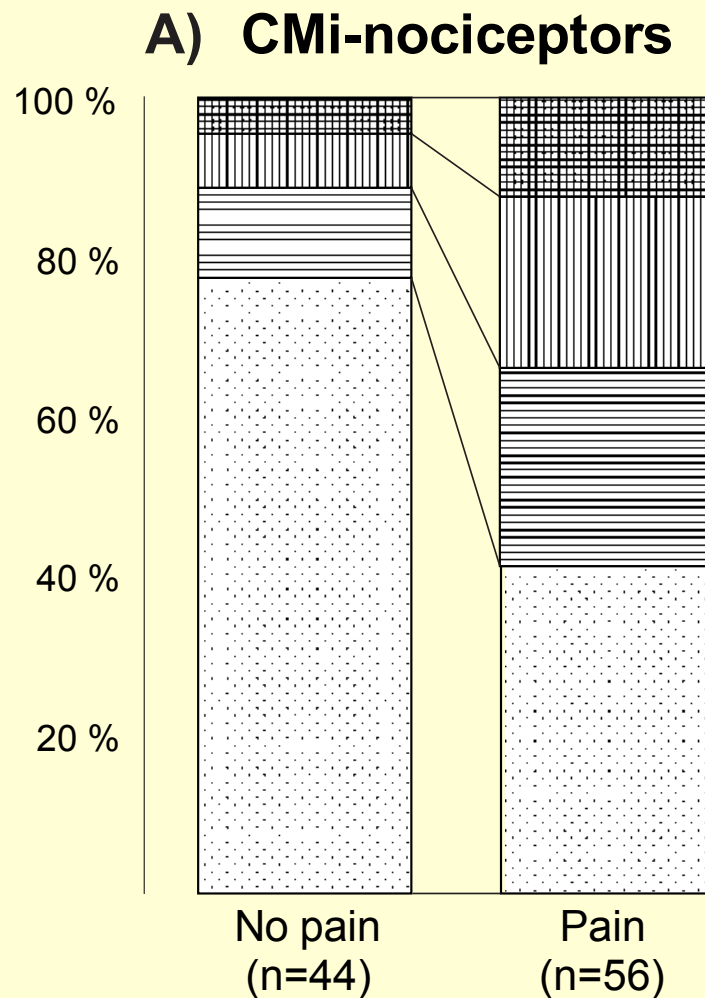


A-fiber response



C-fiber response

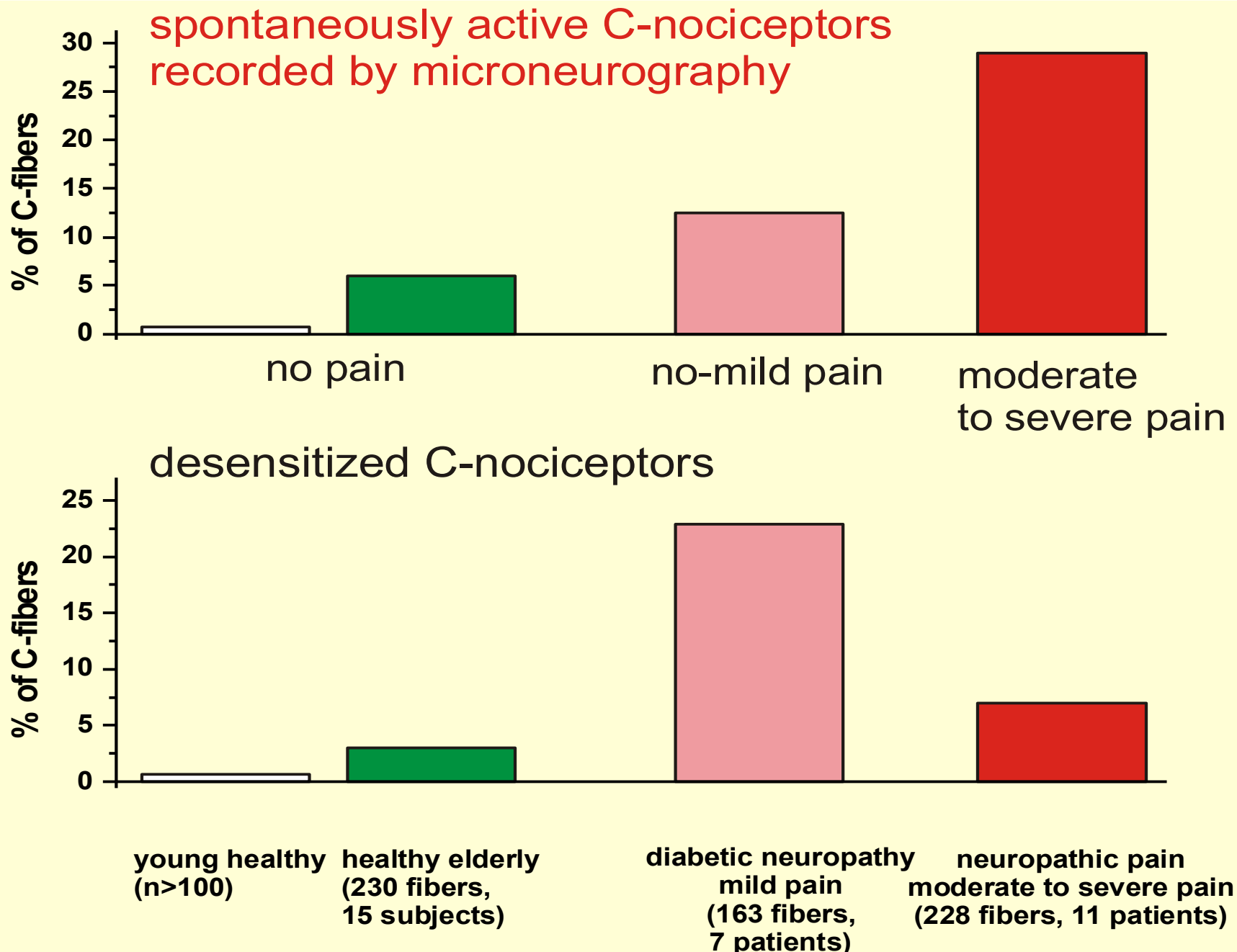
More spontaneous activity in nociceptors in painful vs. Non-painful neuropathy



CMI_norm
 CMI_sens
 CMI_spont
 CMI_spontsens

CM_norm
 CM_spont

Spontaneous activity of nociceptors correlates to pain level in patients



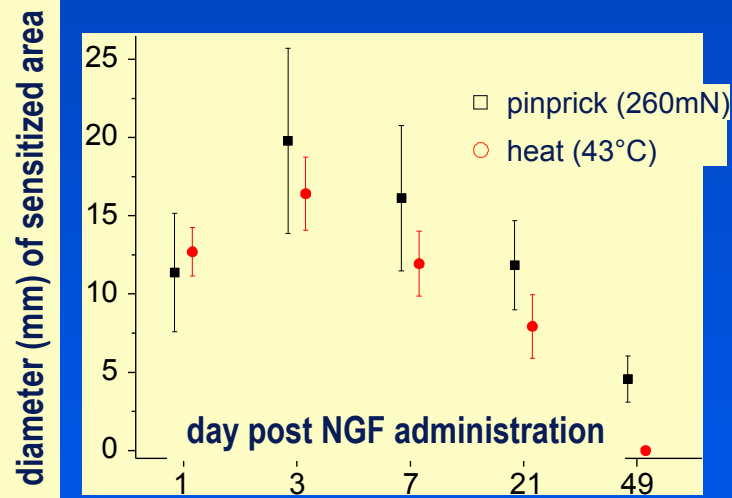
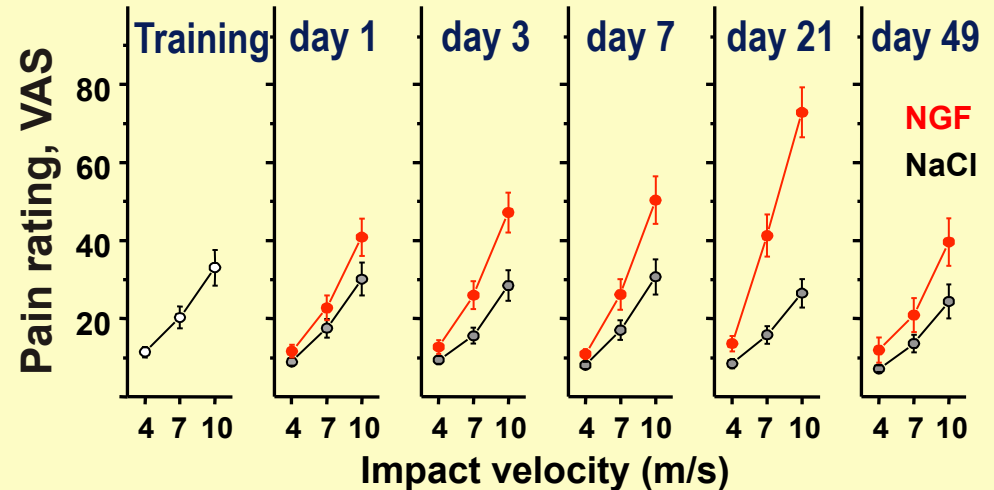
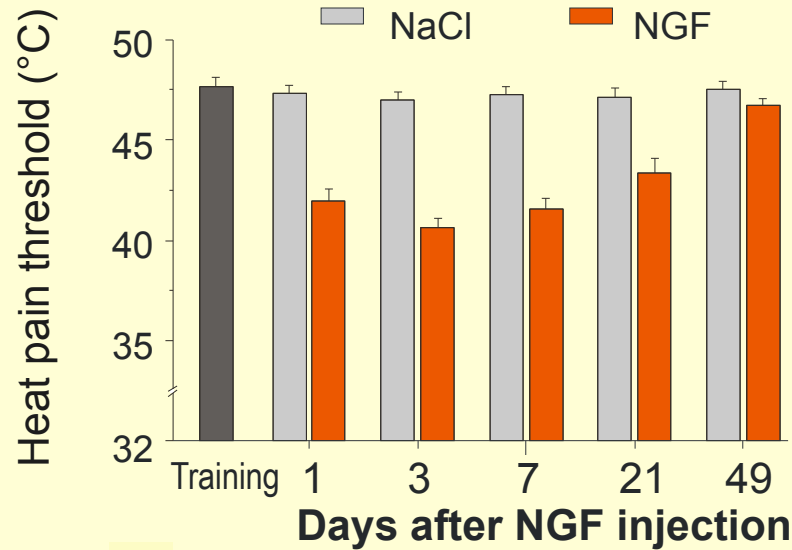
Dissecting neuropathy and pain

Neuropathic pain patients in microneurography:

- Correlation of pain intensity and spontaneous activity
- Sensitization of mechano-insensitive nociceptors

Effects of Nerve Growth factor in human skin

(1 μ g/50 μ l, n=16)



Acute effects:

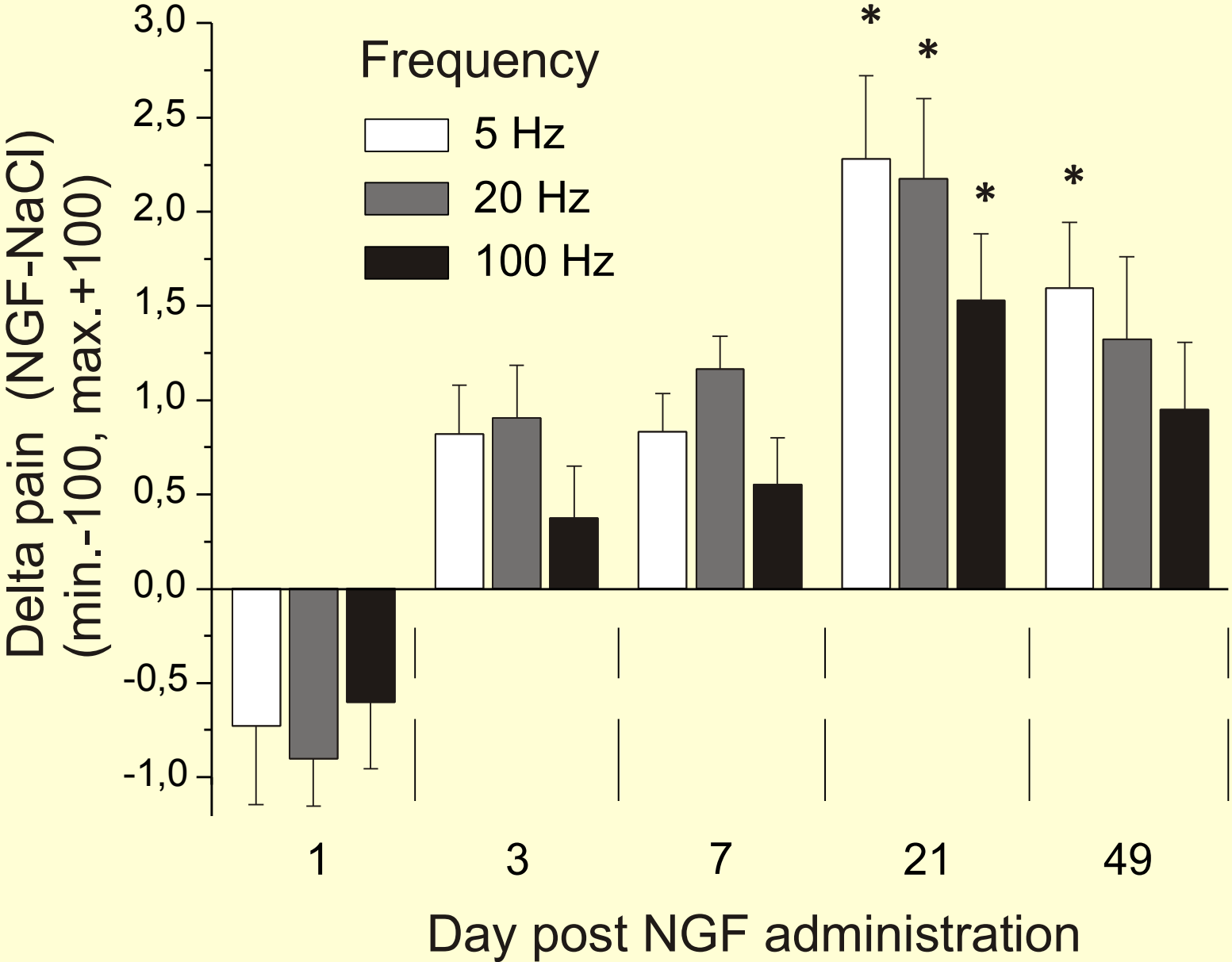
no spontaneous pain, no axon reflex flare, no inflammation

Long term sensitization

- rapid heat hyperalgesia (peak at day 3)
- mechanical hyperalgesia to impact (**peak day 21**)
- **static allodynia**, but no brush evoked allodynia
- no secondary hyperalgesia
- no sensitized axon reflex

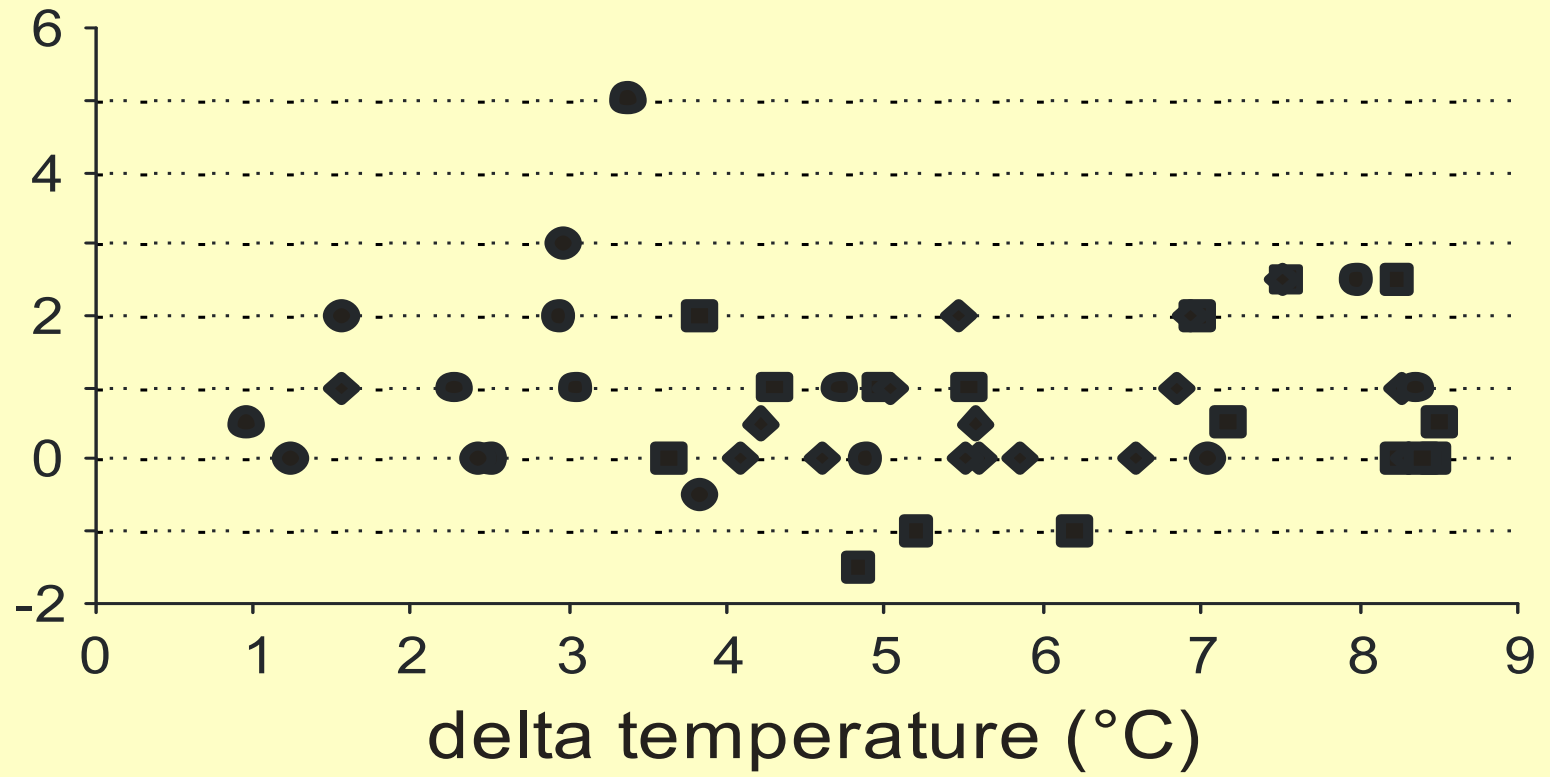
Rukwied et al. Pain, 2010

Electrical hyperalgesia at NGF injection site

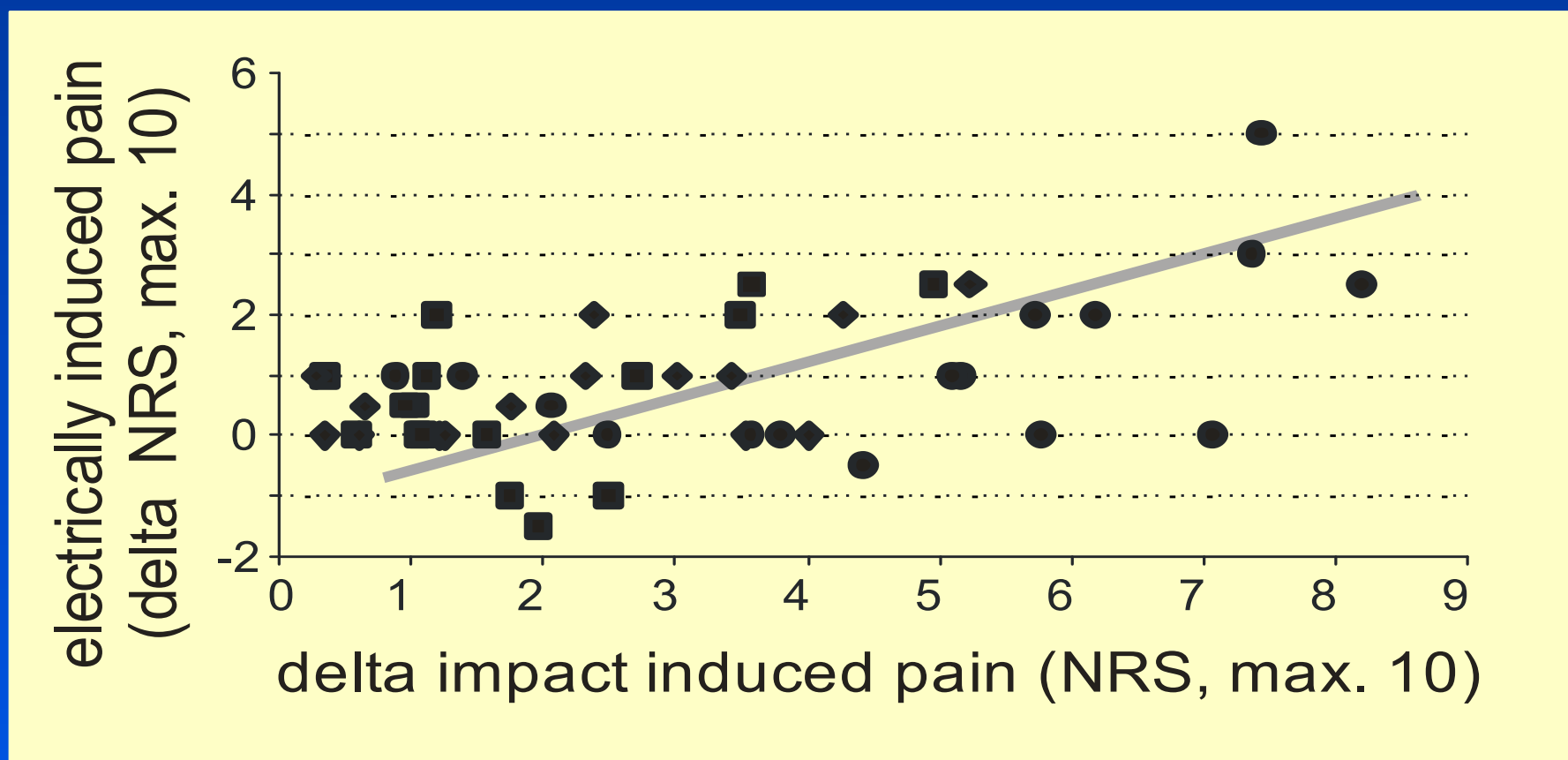


No correlation between axonal hyperexcitability and heat pain threshold

electrically induced pain
(delta NRS, max. 10)



Correlation of axonal hyperexcitability and mechanically induced pain



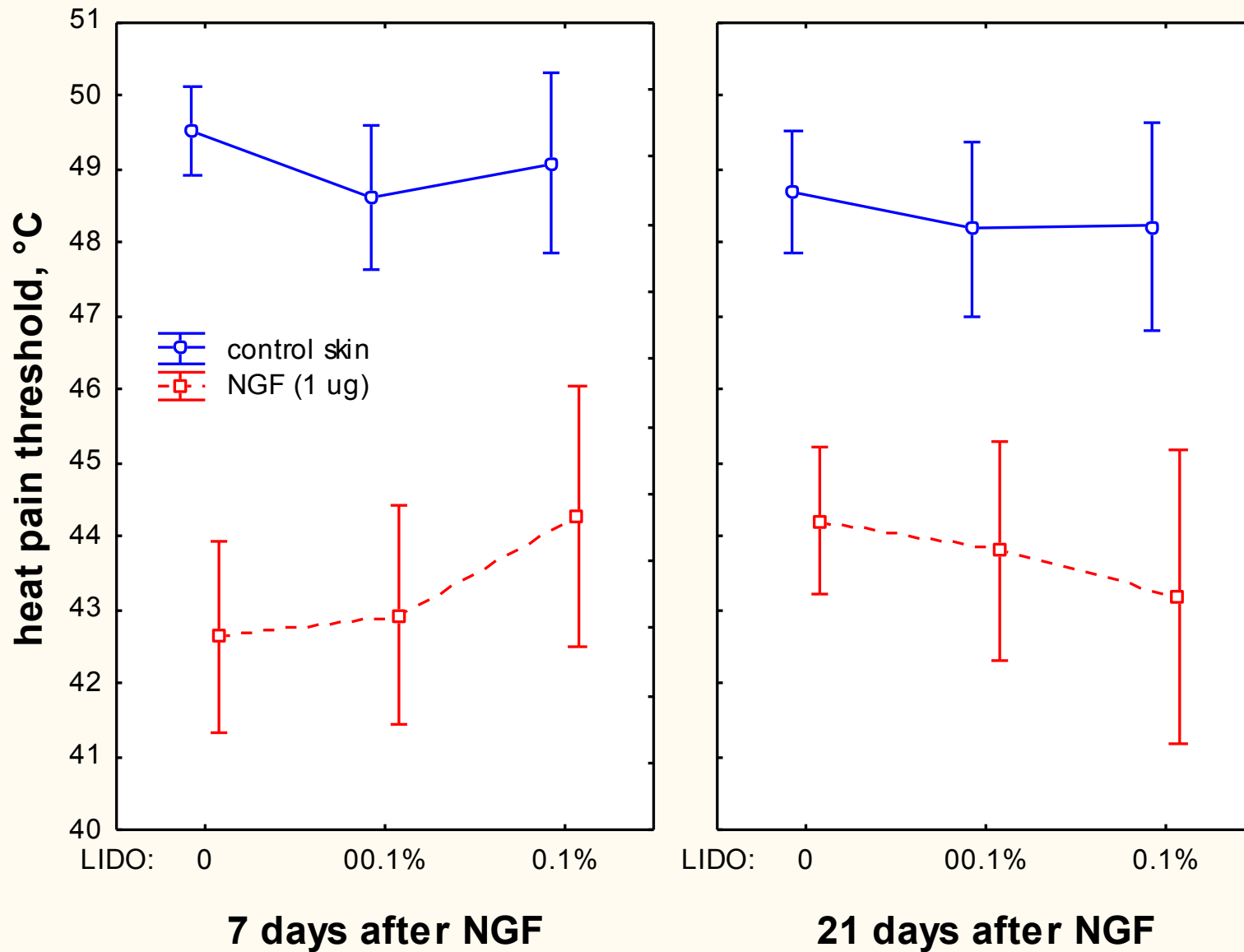
NGF sensitization model in humans

- Localized sensitization – no secondary hyperalgesia to brush or pin-prick
- No enhanced axon reflex flare at the NGF-injection site
- Augmented pain upon electrical stimulation at day 21 - axonal sensitization

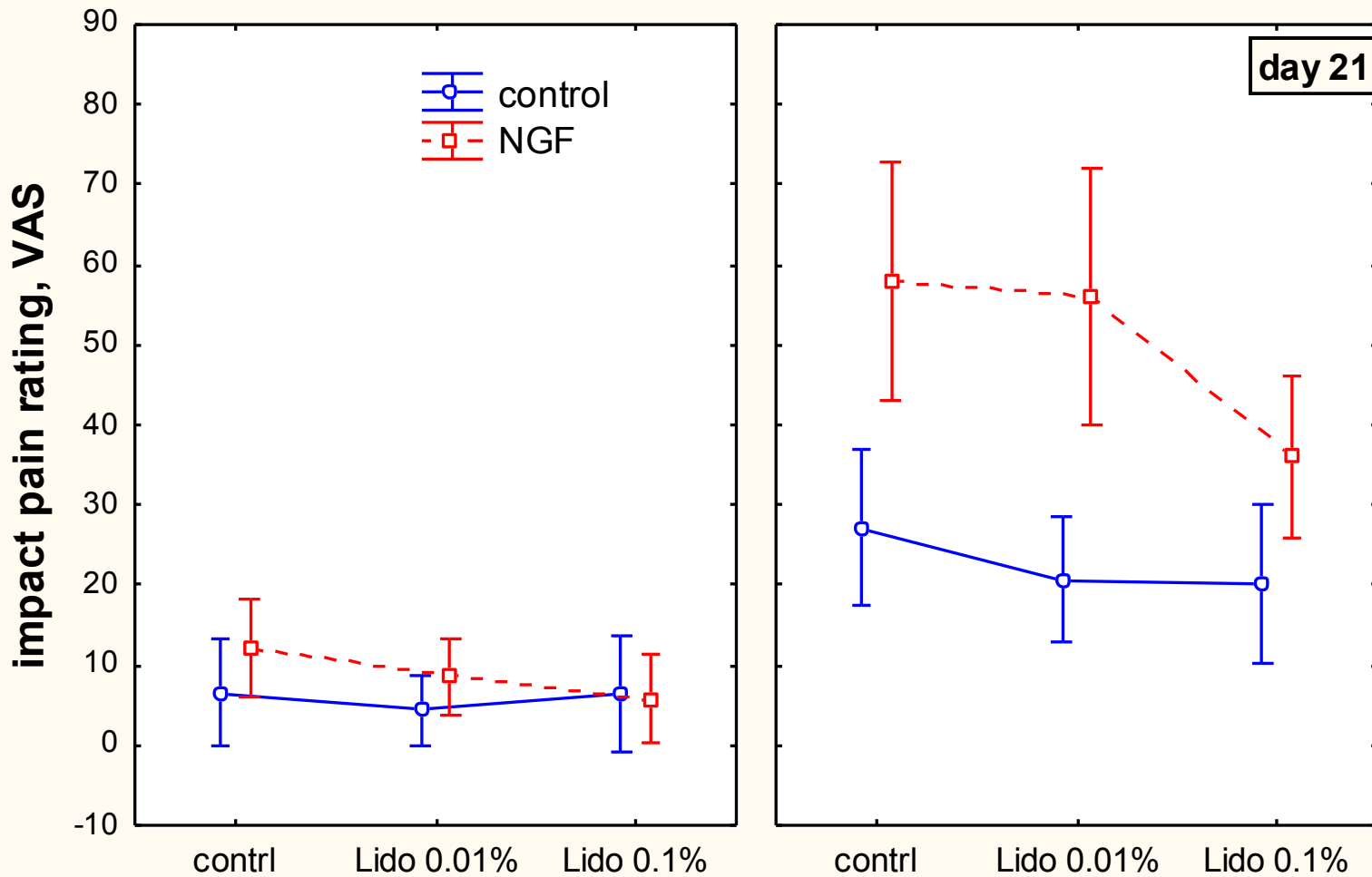
NGF induced sensitization in human pharmacological intervention

- Microdosing
- Local injection of 150 μ l of Lidocaine
0.1 or 0.01%

NGF - heat hyperalgesia: sensitization by lidocaine



NGF- mechanical hyperalgesia: more sensitive to lidocaine



impact stimulation:
4m/s NGF, 8m/s control

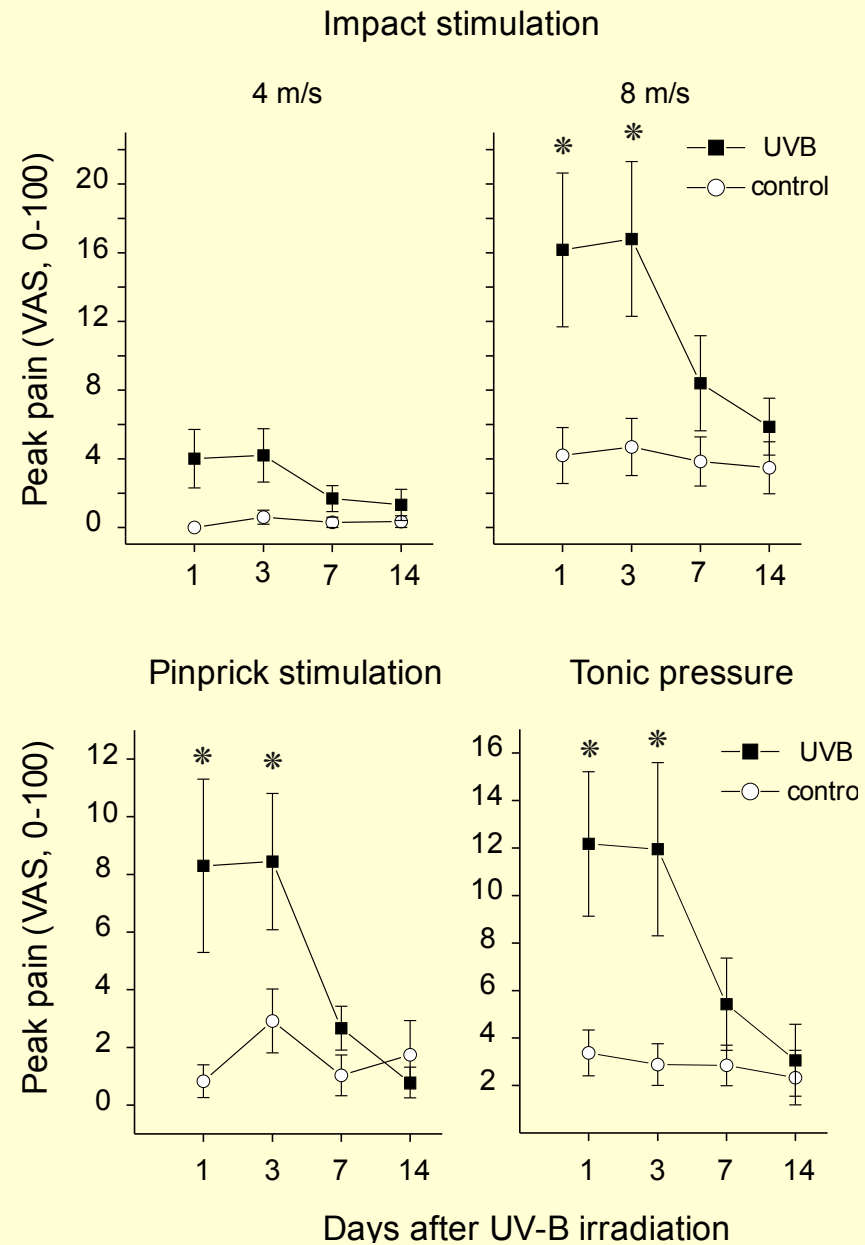
impact stimulation:
8m/s NGF, 12m/s control

conclusions

- Long lasting local sensitization
- Non-inflammatory
- Long lasting hyperalgesia suitable for microdosing approach
- Increased responsiveness to chemical stimulation (low pH and cowhage)

UVB-induced sensitization in human

UVB induced sensory sensitization

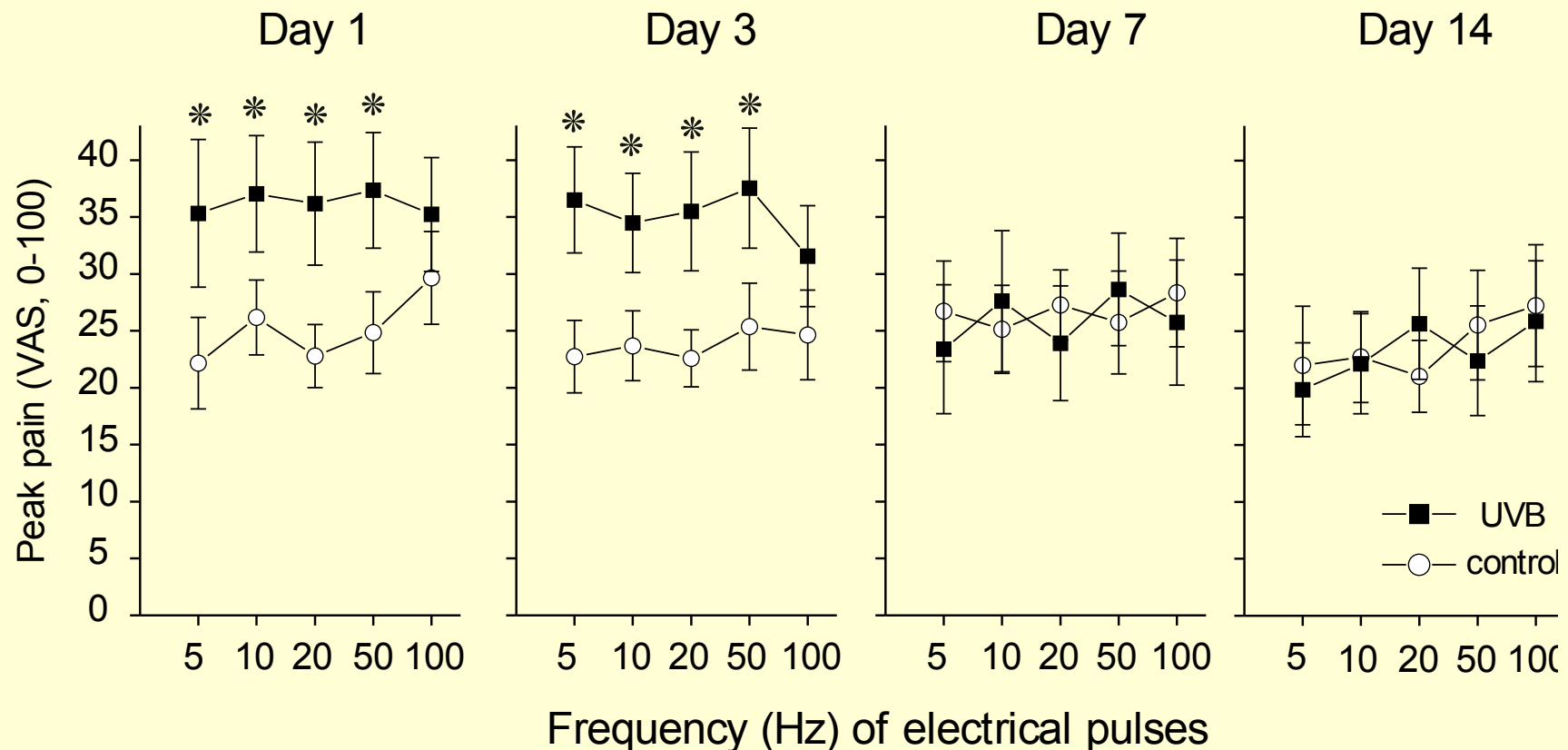


Weinkauf,
Rukwied,
submitted

UVB induced axonal sensitization

B

Pain upon electrical stimuli

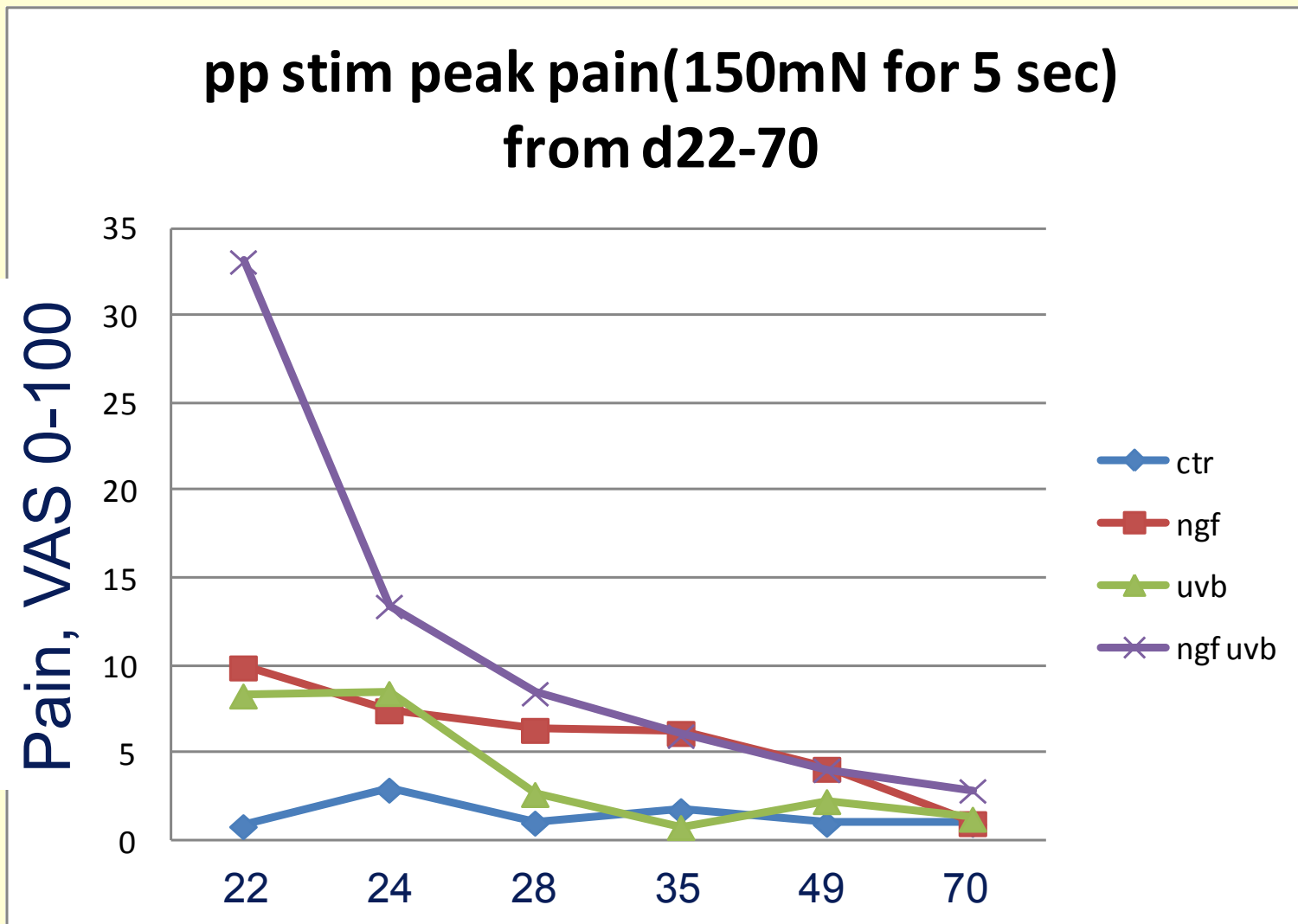


UVB-induced sensitization in human

- Primary hyperalgesia to mechanical and heat stimuli
- Axonal sensitization

- Combination of NGF and UVB

UVB in NGF pre-sensitized skin



UVB at day 21, 3 MED

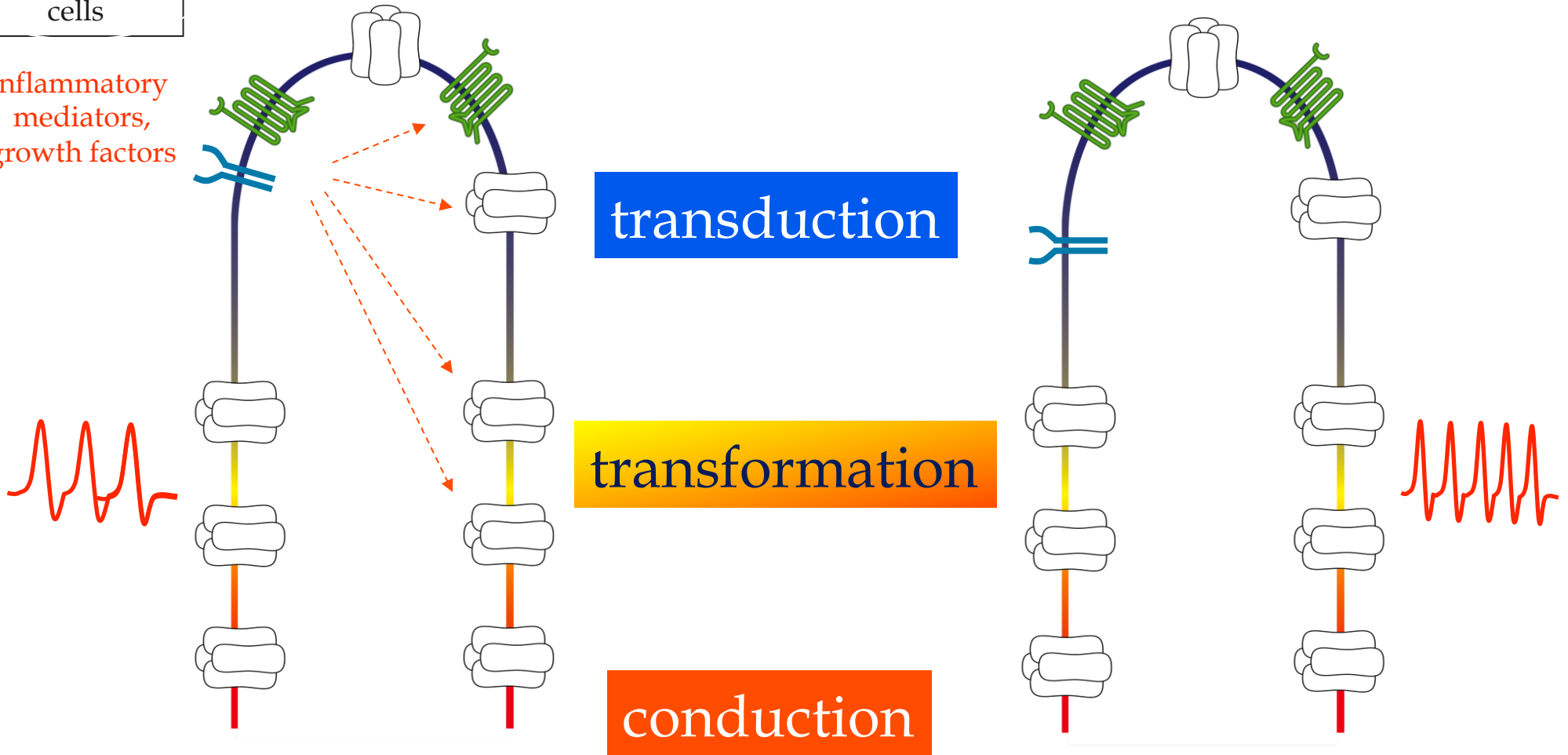
Days after NGF

Weinkauf,
Rukwied,
submitted

Sensory and axonal sensitization

Non-neuronal cells

Inflammatory mediators, growth factors



conclusion

- Key read outs:
spontaneous pain
suprathresholds encoding
- UVB and NGF models provide patterns of sensitization that reflects some aspects of pain patients
- Mechanisms in patients still unknown

anesthesiology

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E. Forsch

Single fiber ephys,
primate

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Baltimore

basic idea of experimental models

