



“Top down” or “bottom up”: Possible specific and unspecific mechanisms in acupuncture related pain control

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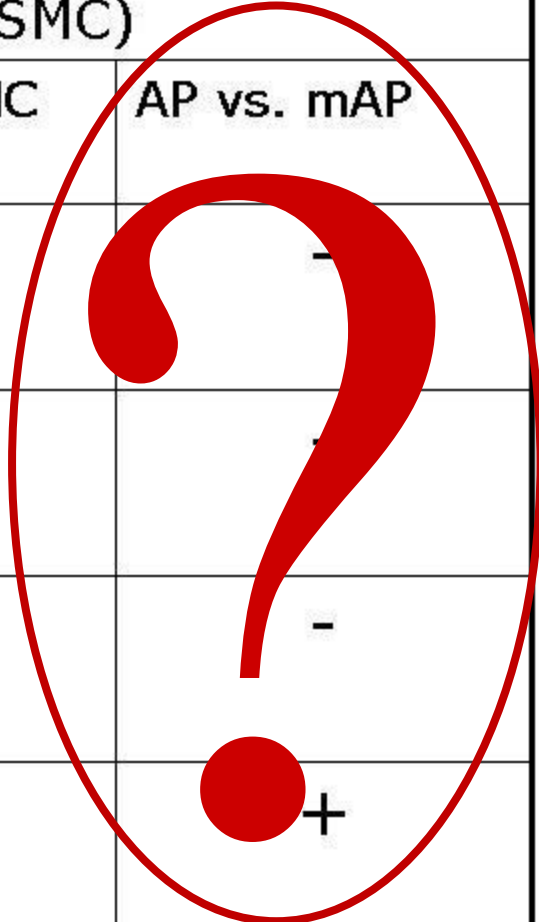
NOSF 8.-9. Januar 2015, Oslo



The problem....

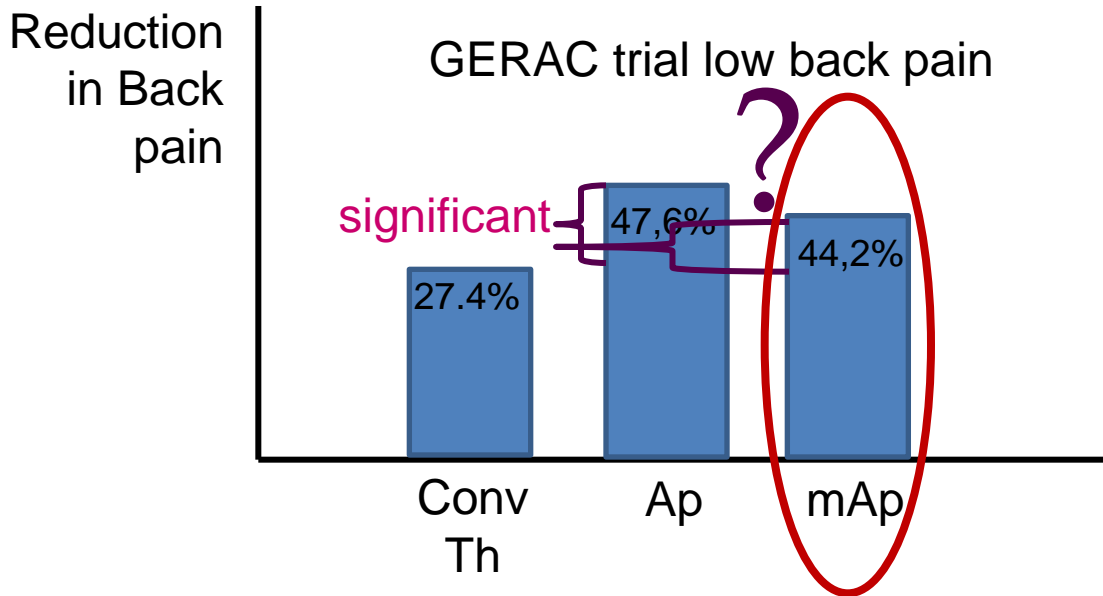
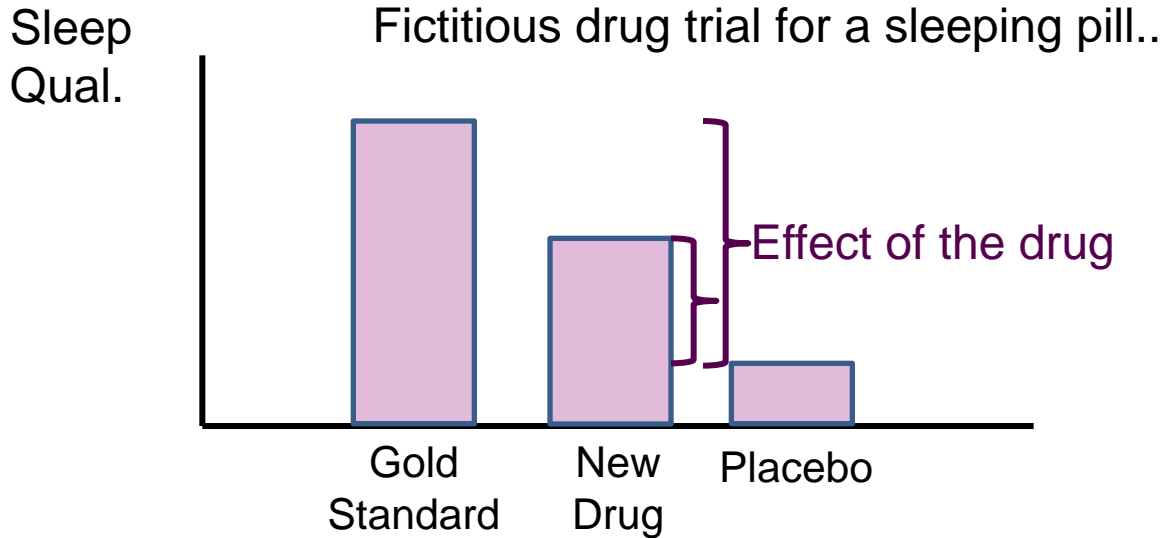
Results of the German acupuncture trials

acupuncture (AP) vs. minimal-acupuncture (mAP) vs. standard medical care (SMC)			
	AP vs. SMC	mAP vs. SMC	AP vs. mAP
Migraine	+	+	-
Tension headache	+	+	+
Back pain	+	+	-
Knee- arthritis	+	+	+



Some methodological considerations....

The problem with the control condition....

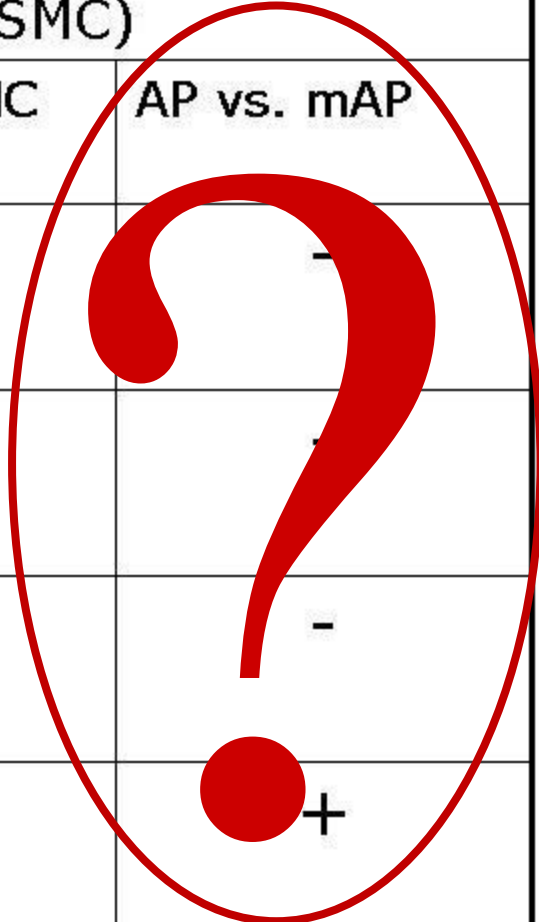


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Haake et al. German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. Arch Intern Med. 2007 Sep 24;167(17):1892-8. Erratum in: Arch Intern Med. 2007 Oct 22;167(19):2072.

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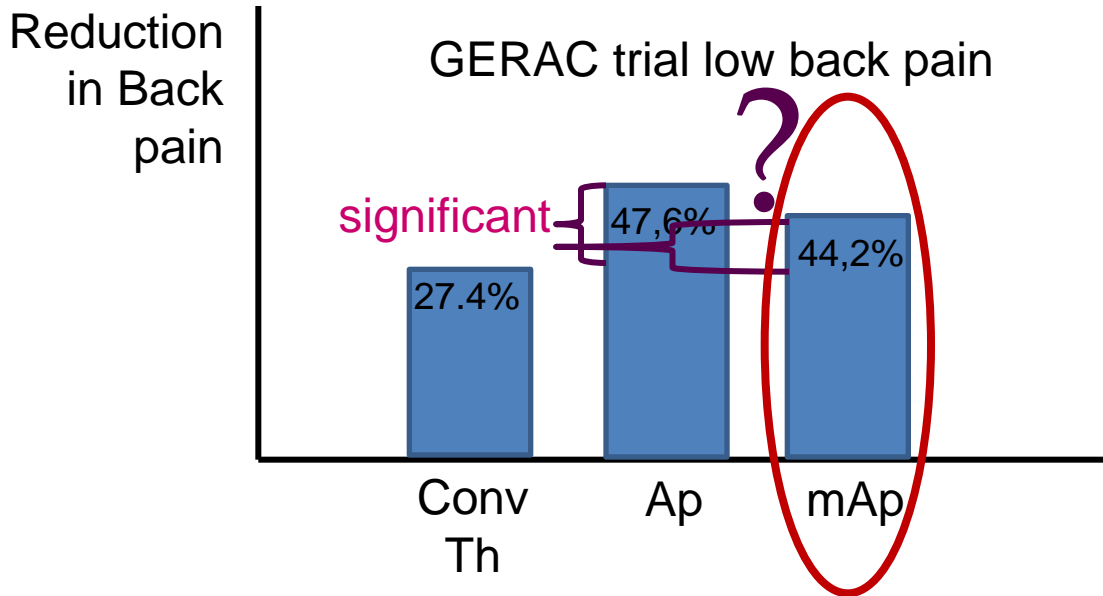
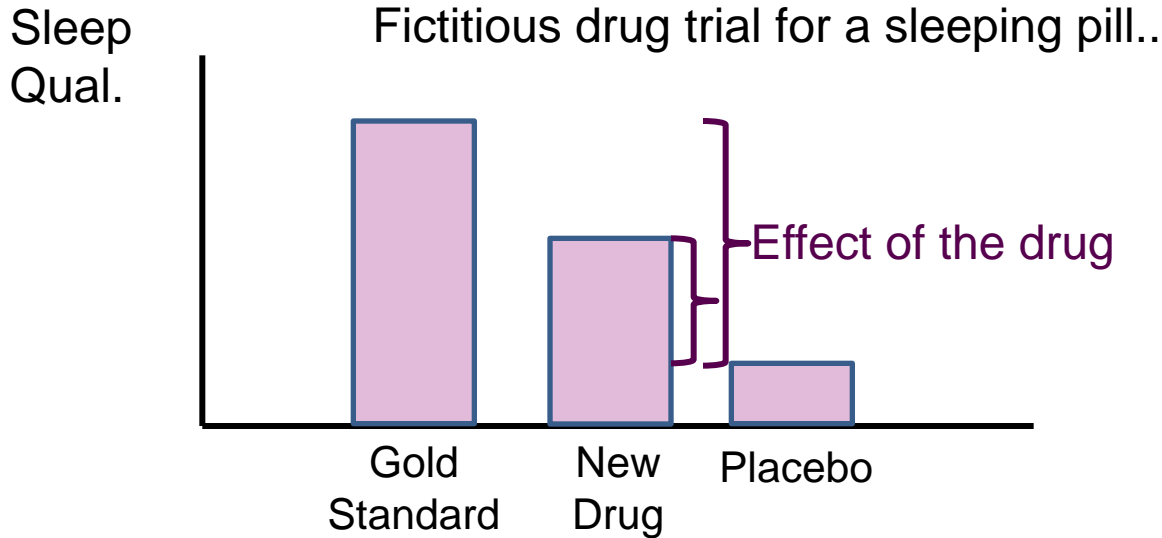
The problem:

Why is minimal/sham/etc.
acupuncture so effective in the
treatment of pain states?

Questions:

- Is the acupuncture treatment of **chronic pain** (somatosensory system!) a „**placebo-intervention**“?

The problem with the control condition....



Vickers et al. for the Acupuncture Trialists' Collaboration. Acupuncture for Chronic Pain: Individual Patient Data Meta-analysis. Arch Intern Med. 2012 Sep 10;172(18):1333-41. doi:10.1001/archinternmed.2012.3654. PubMed PMID: 22965186.

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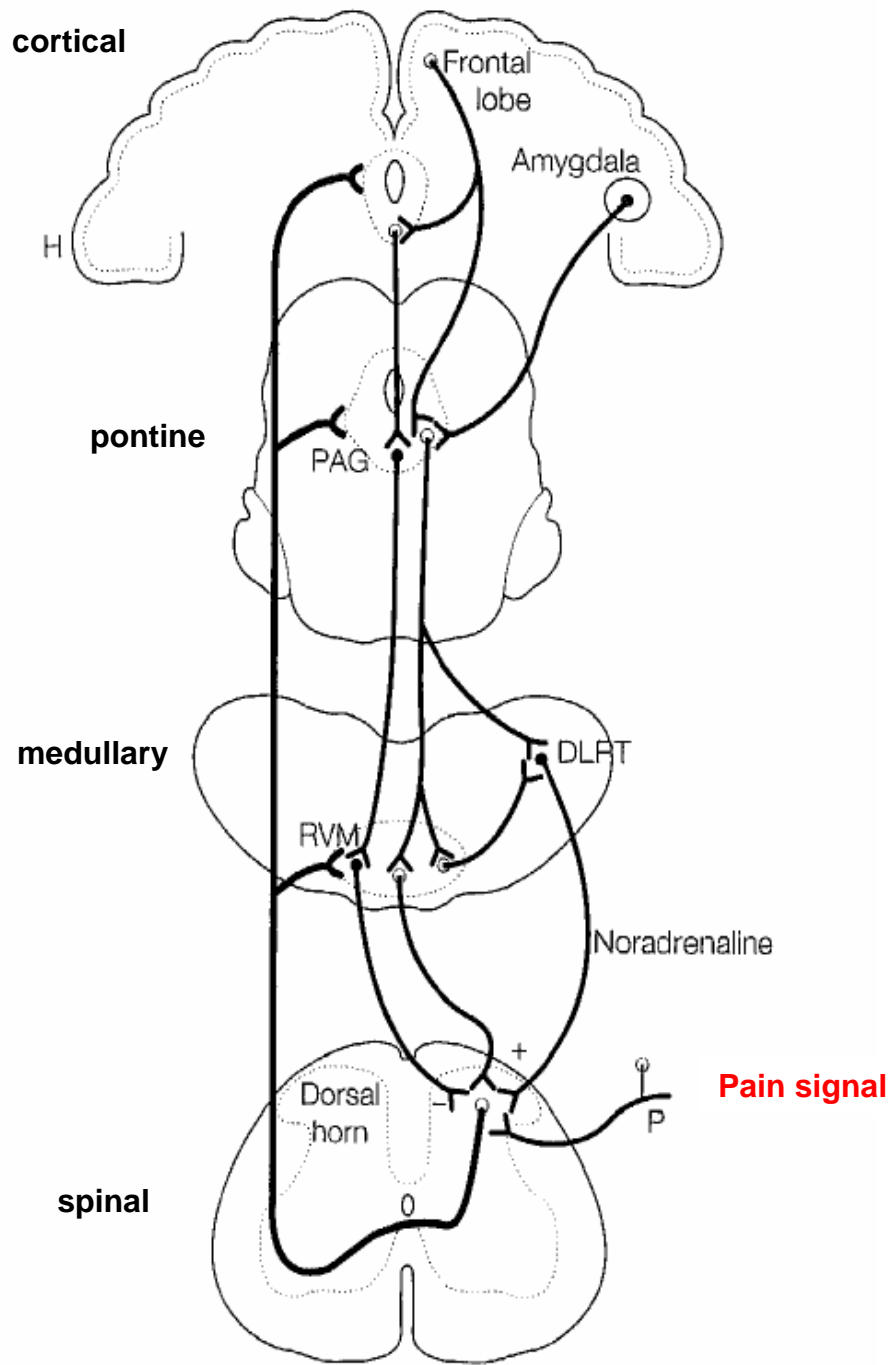
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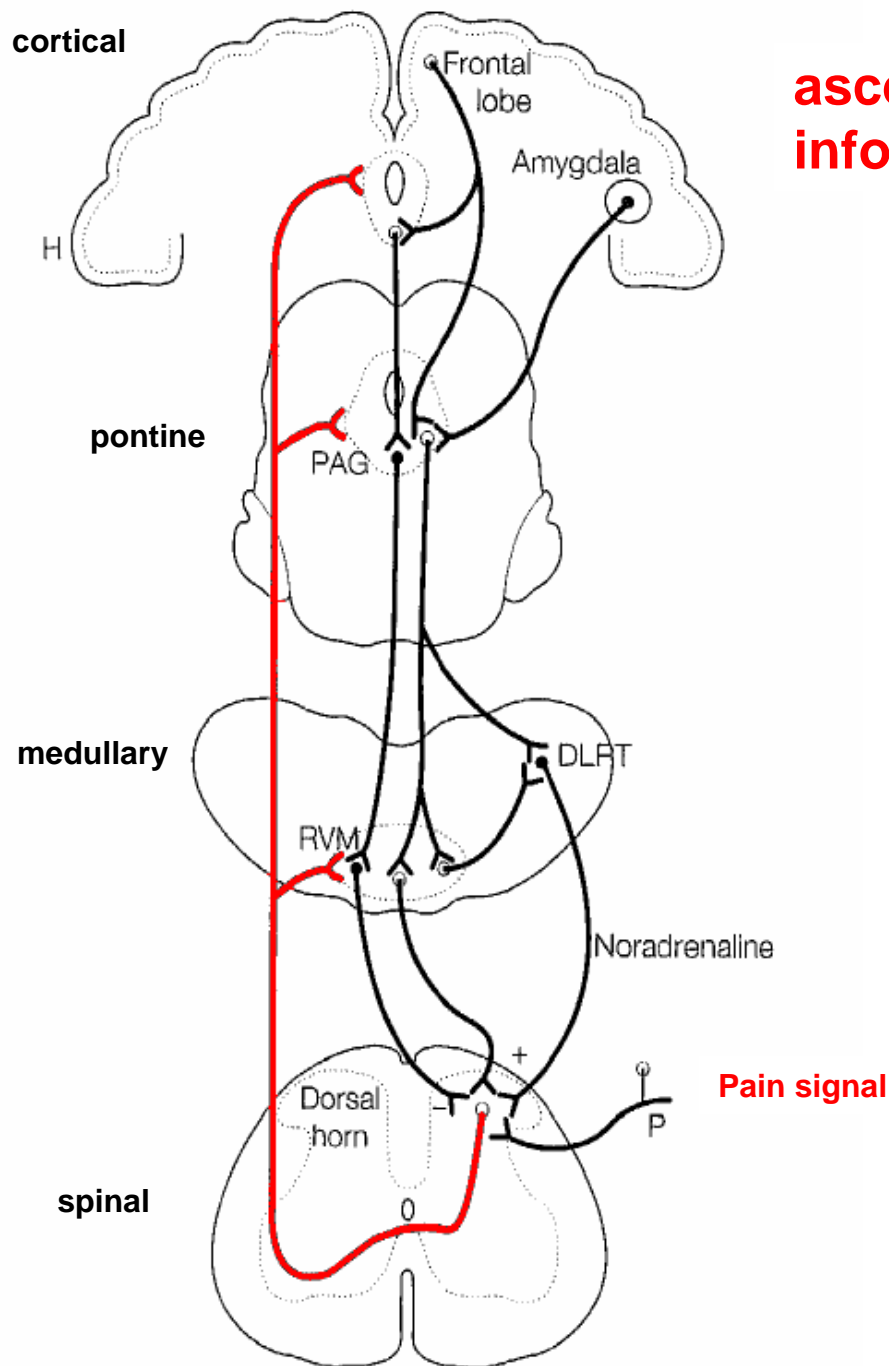
Questions:

- Is the acupuncture treatment of **chronic pain** (somatosensory system!) a „**placebo-intervention**“?
- Is there an **acupuncture specific** mechanism which can **explain the results** of the German acupuncture trials and which is well described in **classical physiology**?

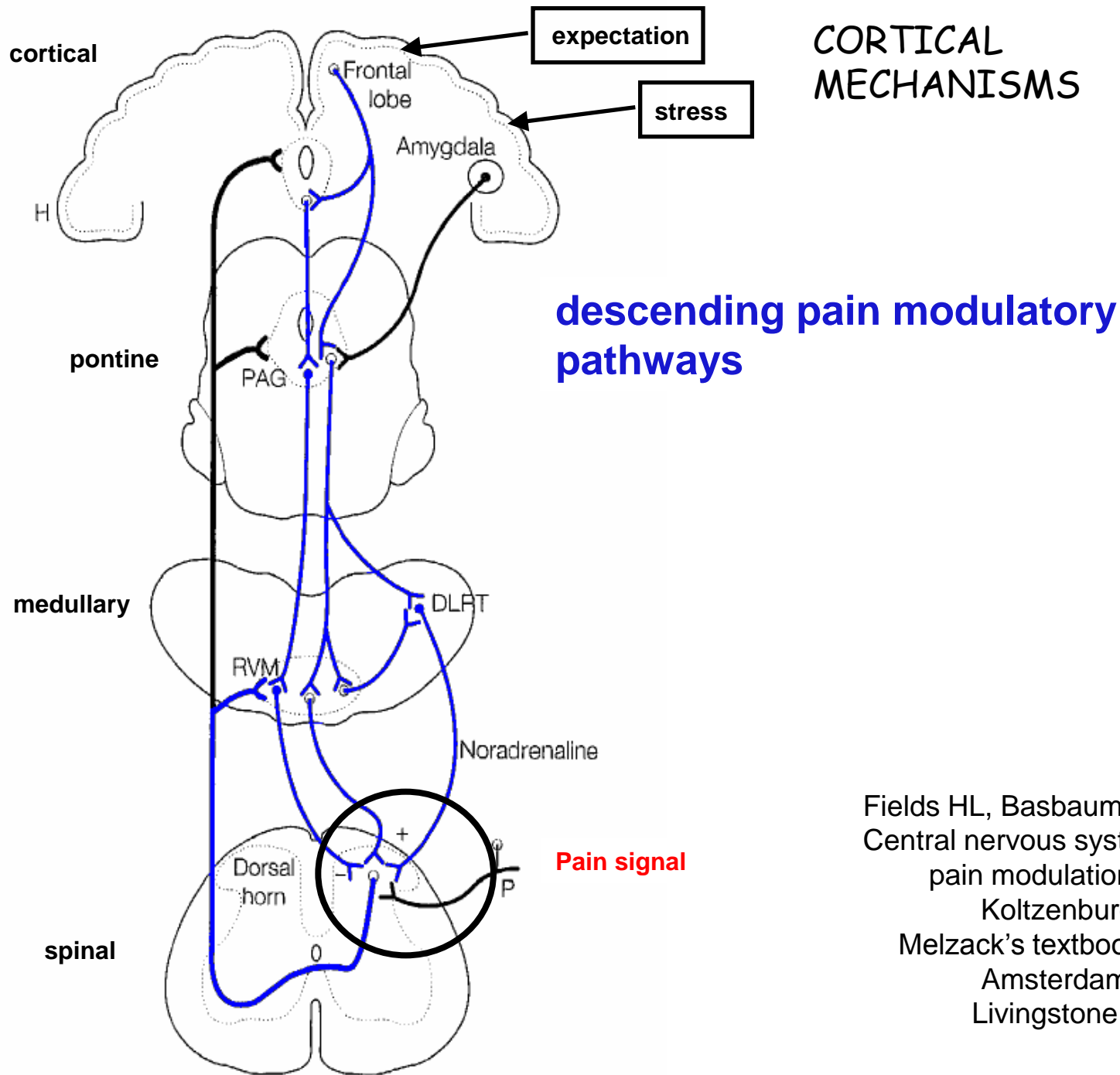
The somatosensory system and pain



Fields HL, Basbaum AI, Heinricher MM:
Central nervous system mechanisms of
pain modulation; in McMahon S B,
Koltzenburg M (eds): Wall and
Melzack's textbook of Pain. 5th edn.,
Amsterdam, Elsevier Churchill
Livingstone, 2005, pp 125-142.

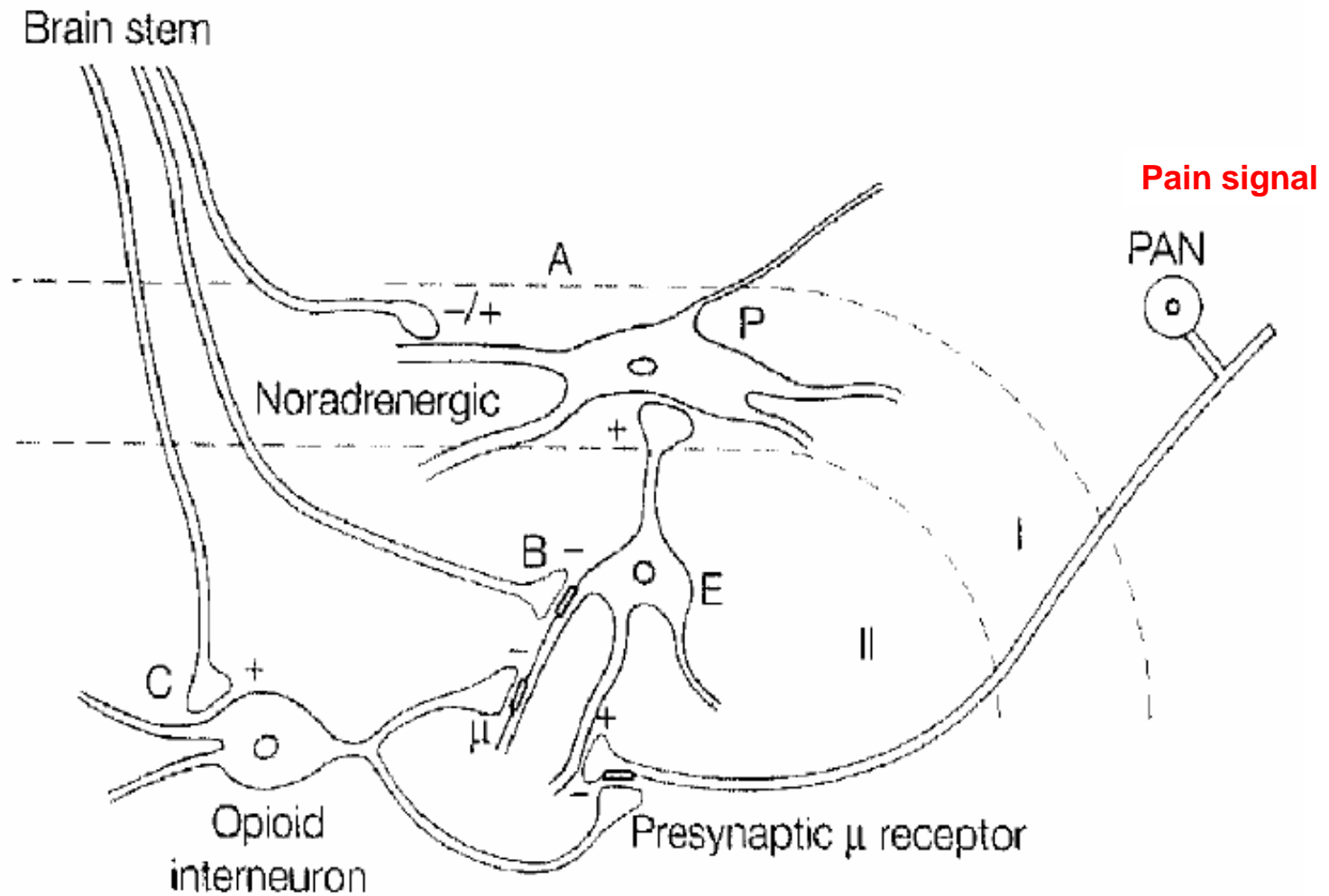


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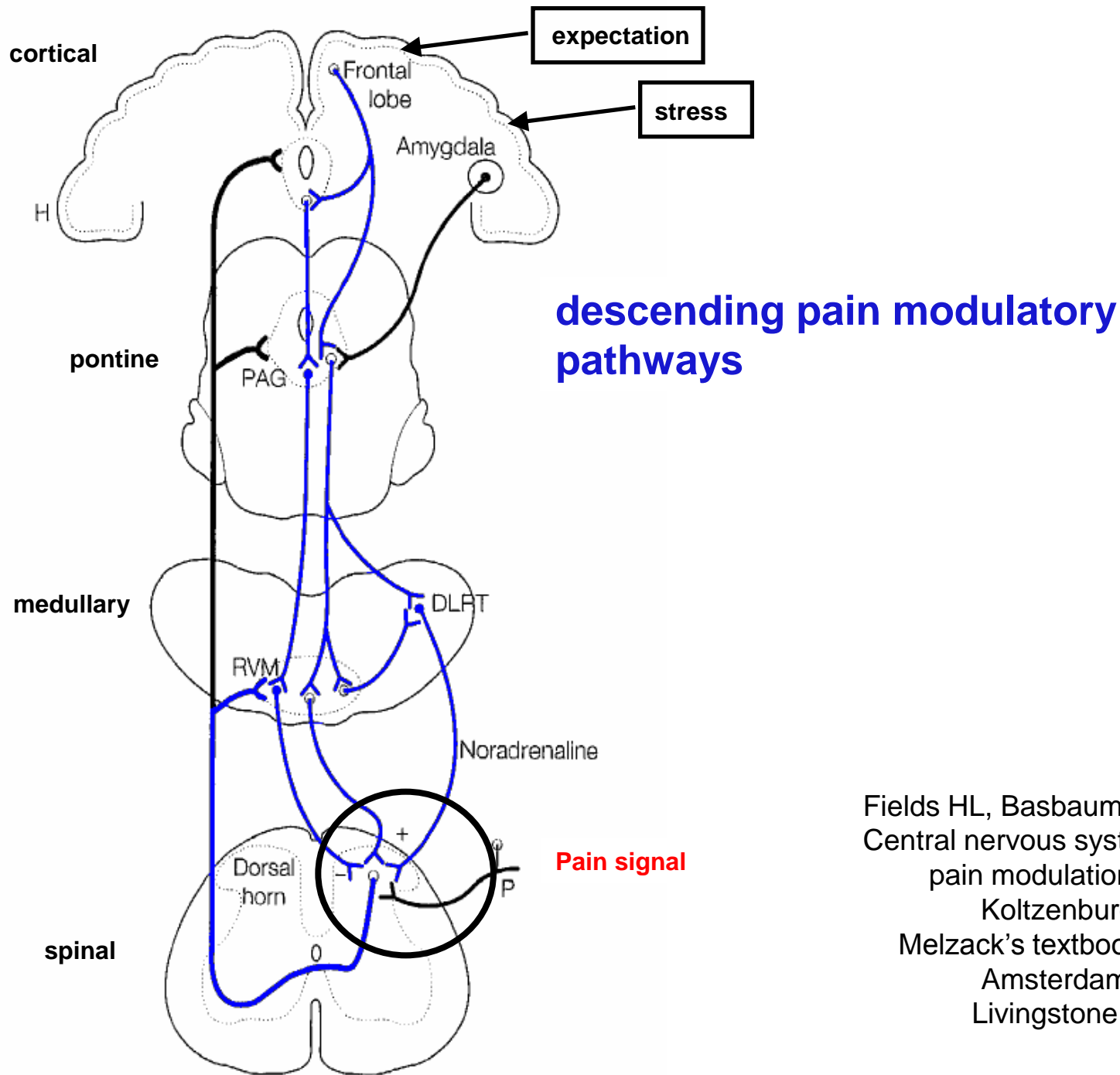
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dorsal horn

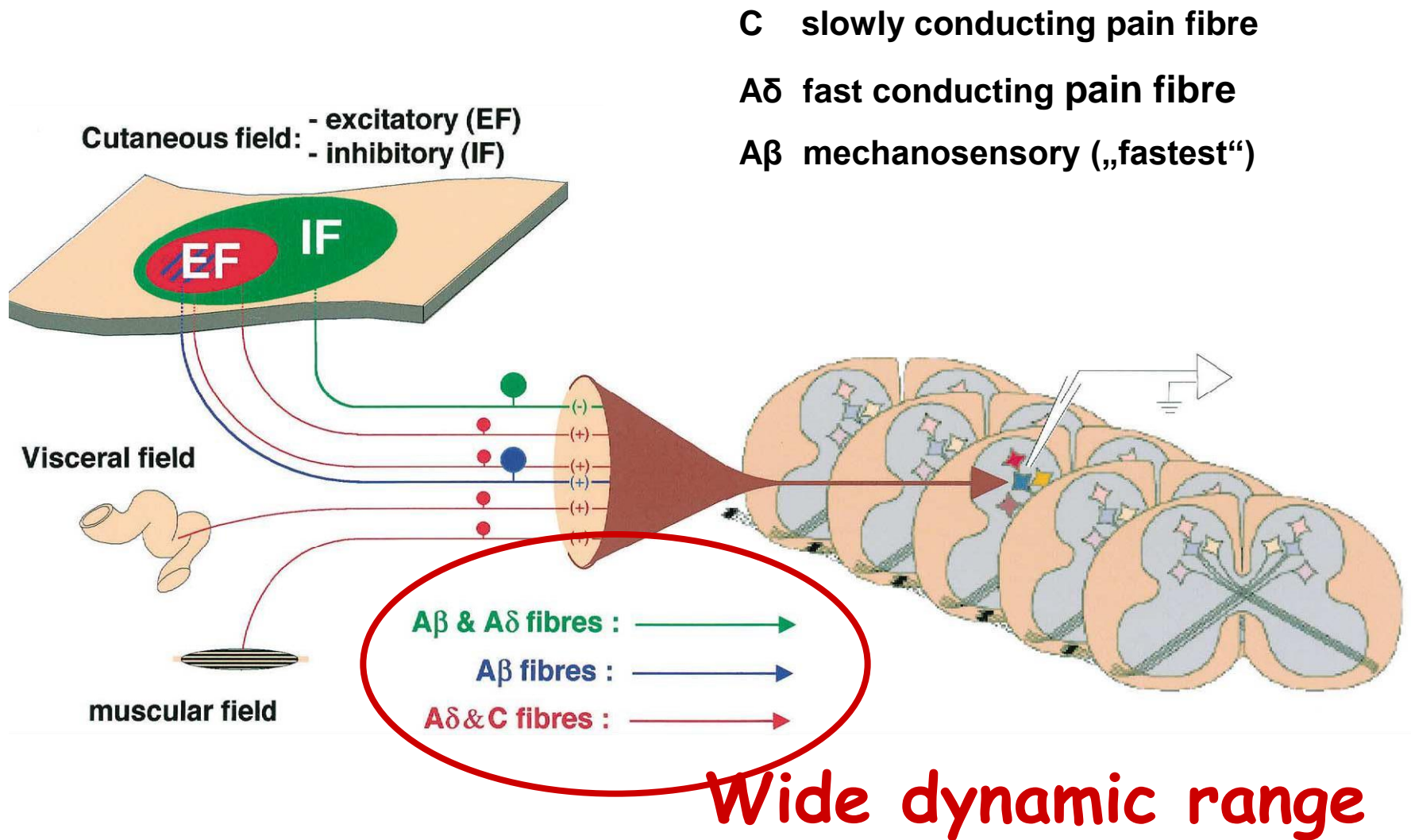


Subcortical mechanisms....

„Wide Dynamic Range“ (WDR)
neurons in the spinal cord,
„Gate-Control“ und „Diffuse
Noxious Inhibitory Controls
(DNIC)“

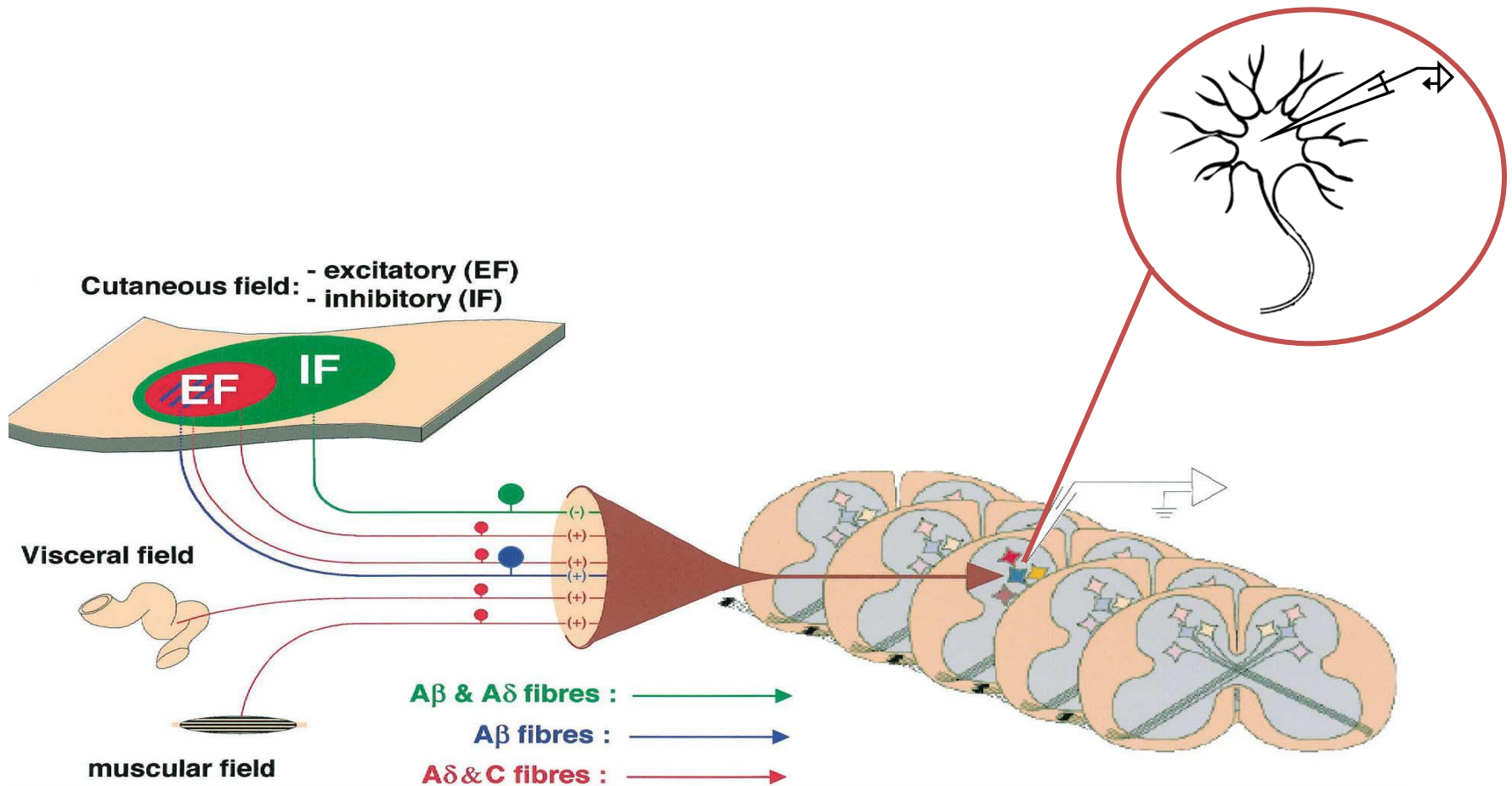


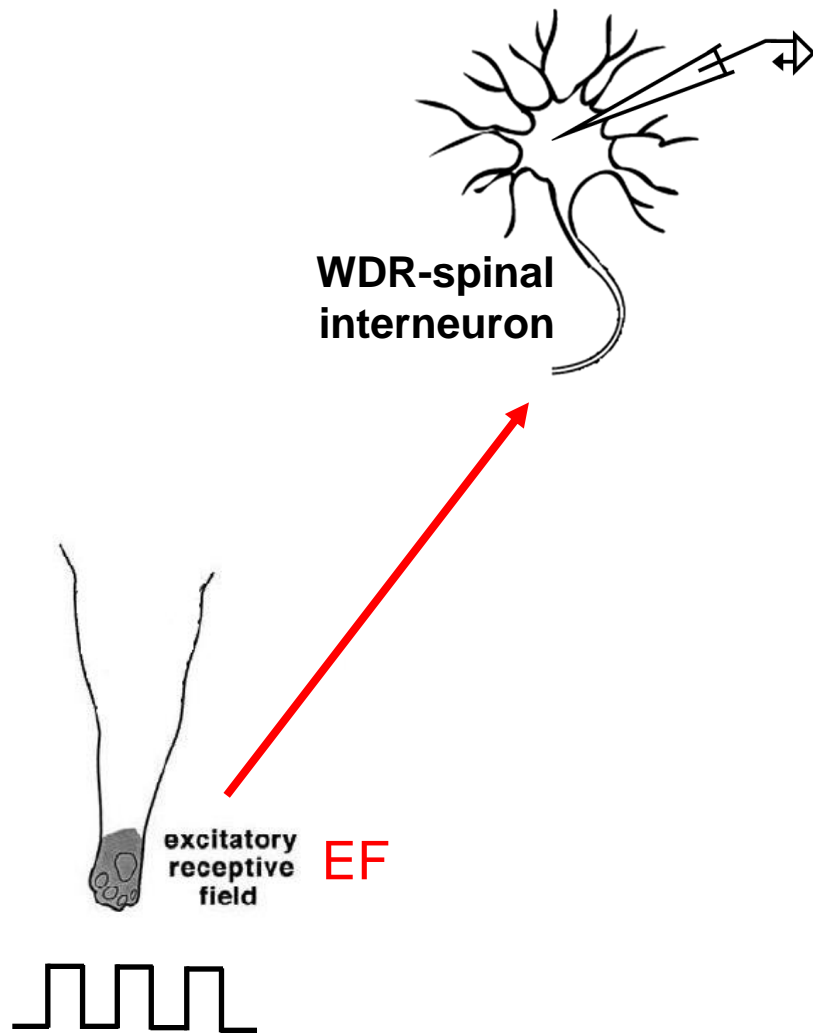
Fields HL, Basbaum AI, Heinricher MM: Central nervous system mechanisms of pain modulation; in McMahon S B, Koltzenburg M (eds): Wall and Melzack's textbook of Pain. 5th edn., Amsterdam, Elsevier Churchill Livingstone, 2005, pp 125-142.



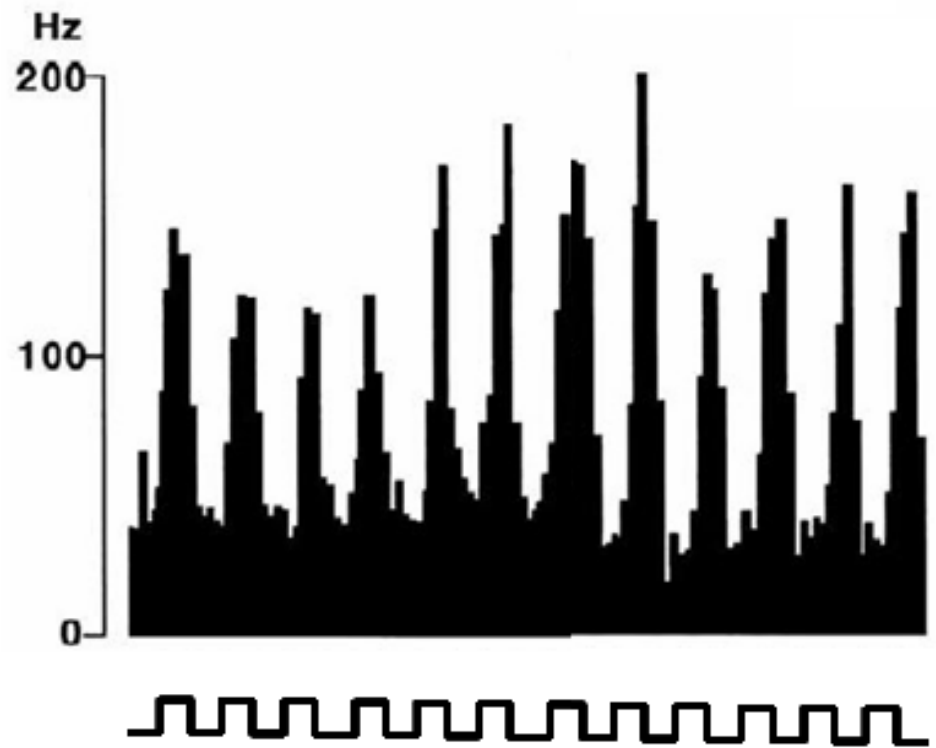
LeBars D: The whole body receptive field of dorsal horn multireceptive neurons. Review. Brain Research Reviews 2002;40:29-44.

Wide dynamic range Neuron





Aδ – Stimulation (fast conducting pain fibre)



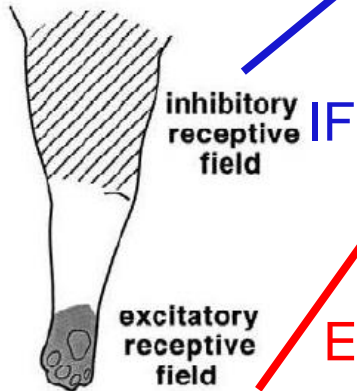
Firing rate of the WDR neuron

(Glutamate dependent / NMDA Receptor)

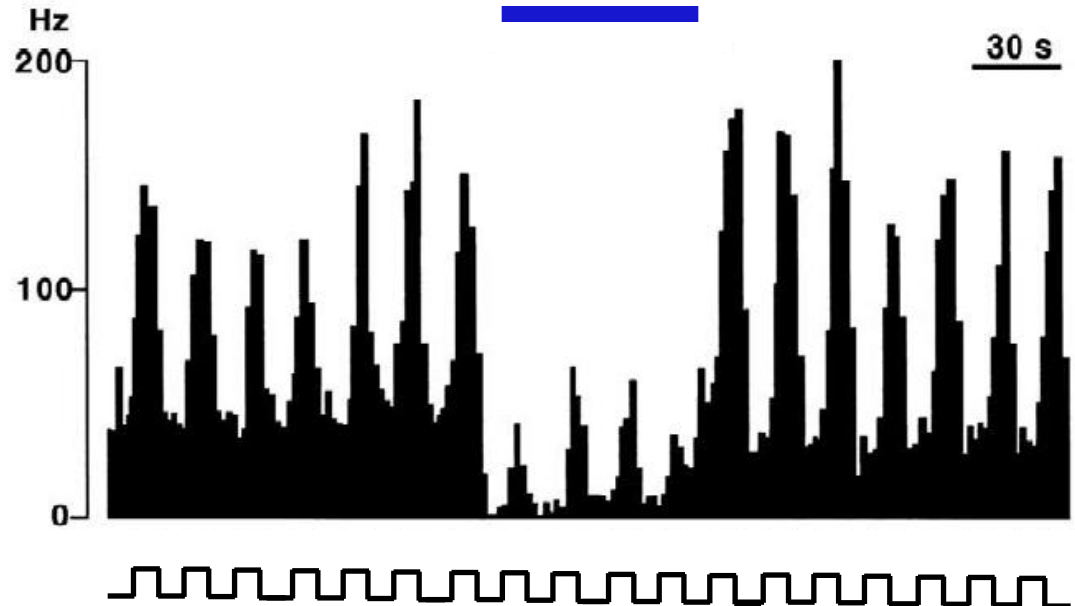
WDR-spinal
interneuron

„Gate-Control“
segmental, homotopic

mechanosensitive $A\beta$ –
stimulation (faster than
the pain fibre)



$A\delta$ – Stimulation (fast
conducting pain fibre)



Firing rate of the WDR neuron

also:
Neurons in the
caudal medulla

WDR-spinal
interneuron

additional **A δ & C** – Stimulation
heterotopic (from somewhere!)

„DNIC“

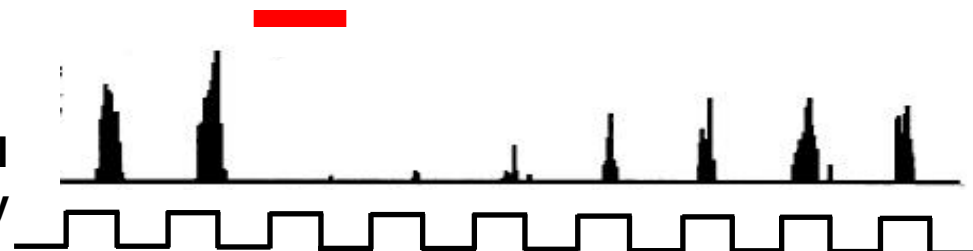
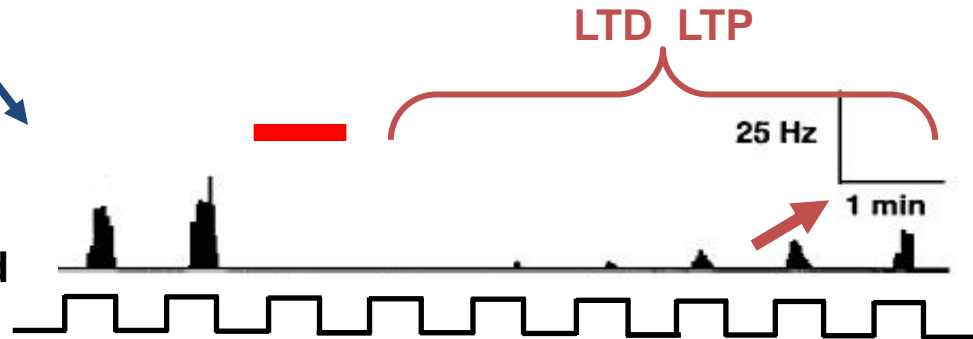
excitatory
receptive
field **EF**

Contralateral
extremity



A δ – Stimulation (fast
conducting pain fibre)

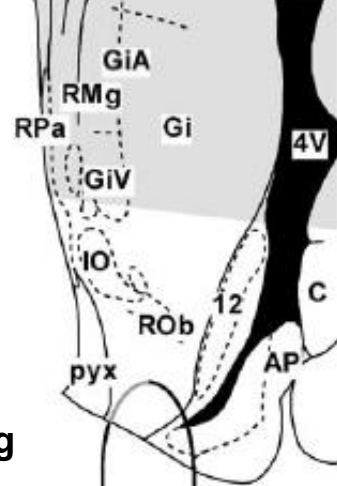
Head



Firing rate of the WDR neuron

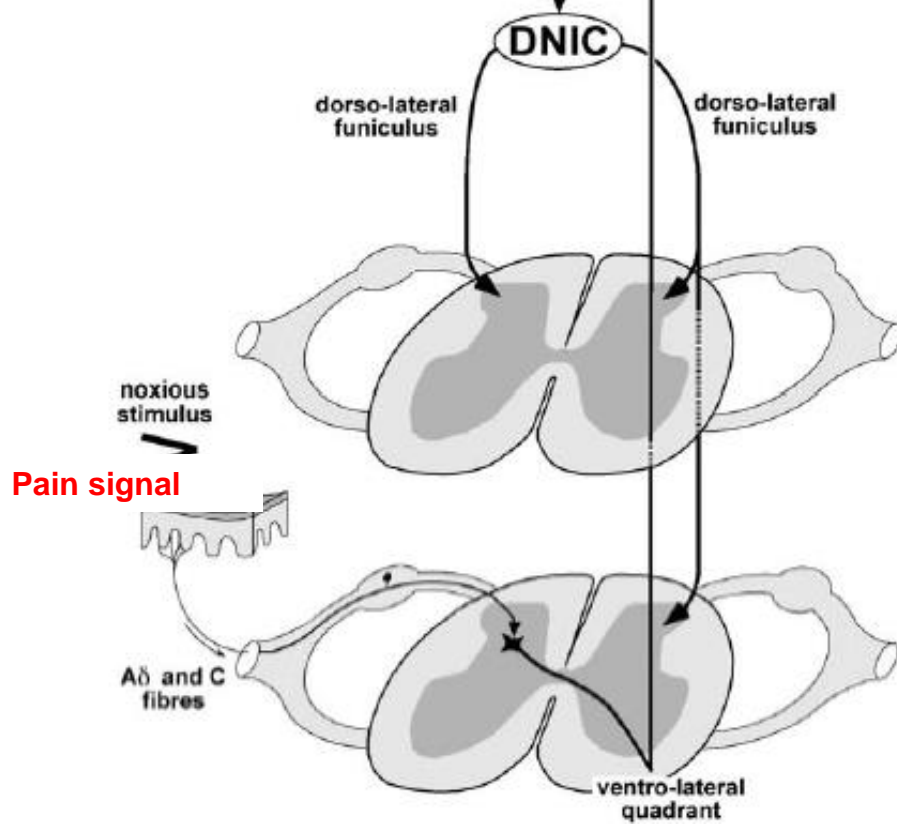
Diffuse Noxious Inhibitory Controls

- The **nociceptive (A δ & C stimulation)** dependent activity of the spinal WDR neurons can be **suppressed** by an **additional, short lasting noxious stimulation** outside its receptive field.
- **This inhibition lasts much longer than the additional stimulation.** Synaptic changes such as LTP, LTD are very likely, especially since glutamate and the **NMDA receptor** are involved. The mechanisms are **similar to the ones hypothesized for allodynia and hyperalgesia**. The character of the noxious stimulation is irrelevant (electrical, thermal, mechanical, chemical).
- In contrast to mechanosensory A β – stimulation and gate control is **DNIC** mediated through **supraspinal mechanisms** (caudal Medulla, Ncl. Reticularis dorsalis). It is hypothesized that these medullary cells have a **„whole body“ receptive field**.

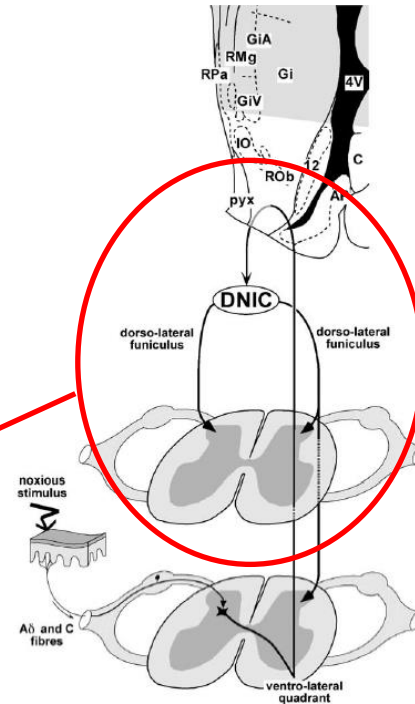
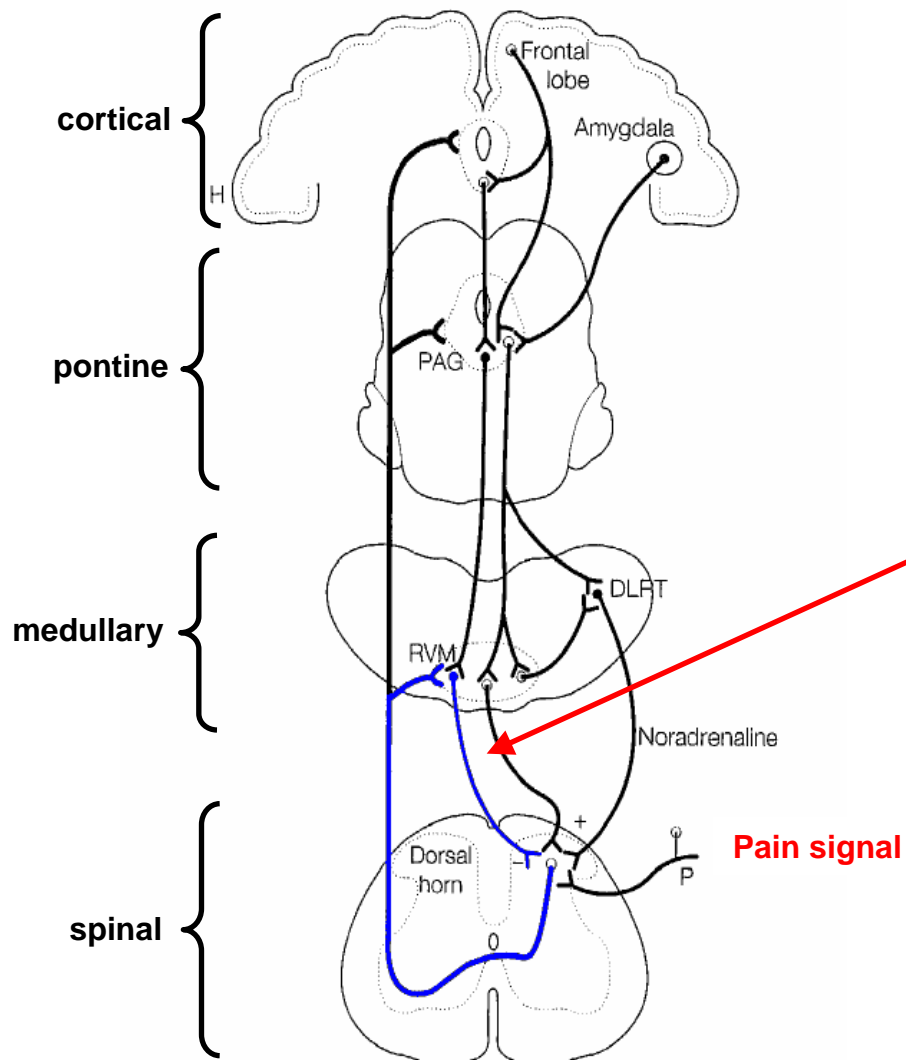


4V – 4. ventricel

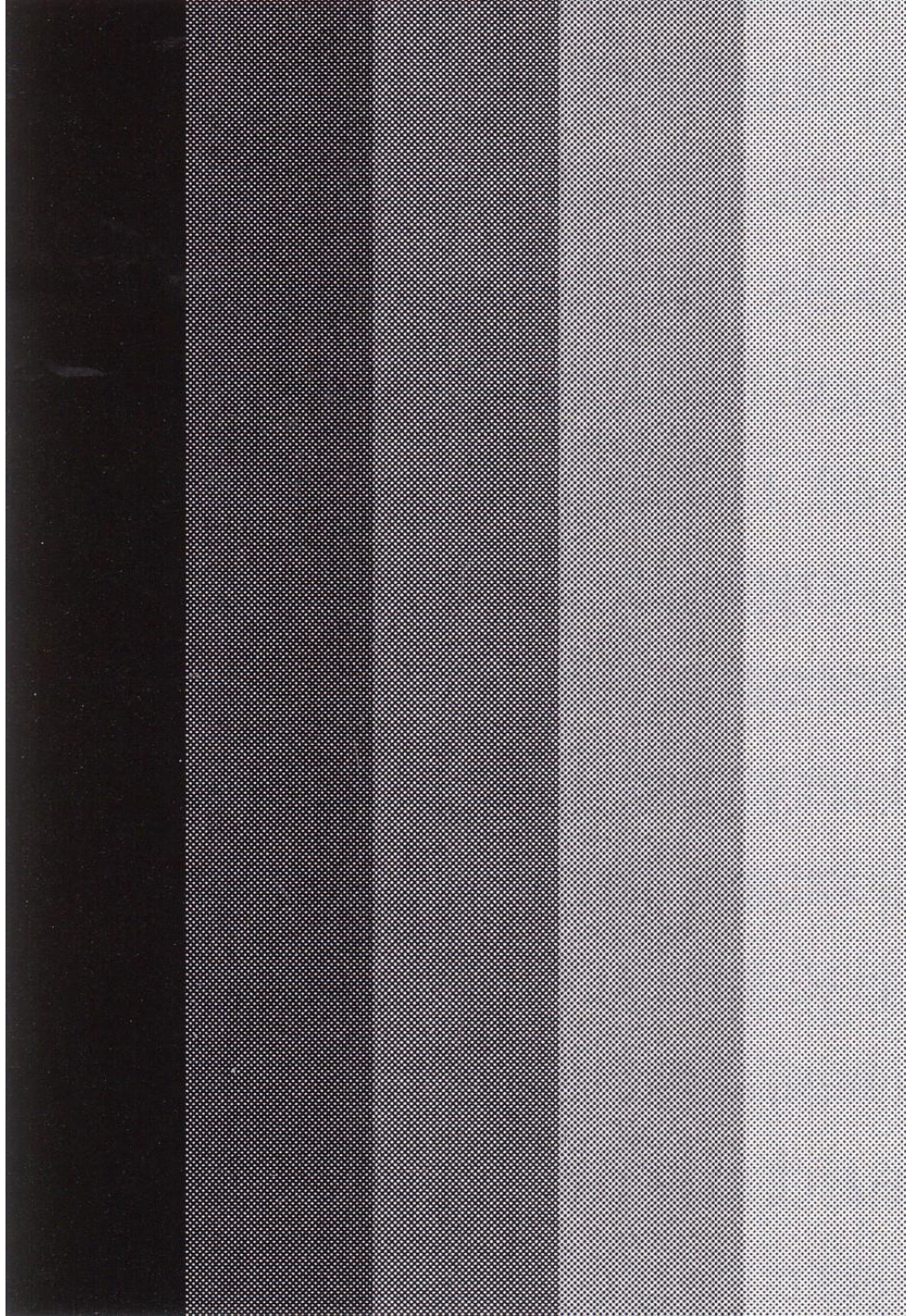
pyx – Pyramidal crossing



DNIC is a spino-medullary subcortical loop

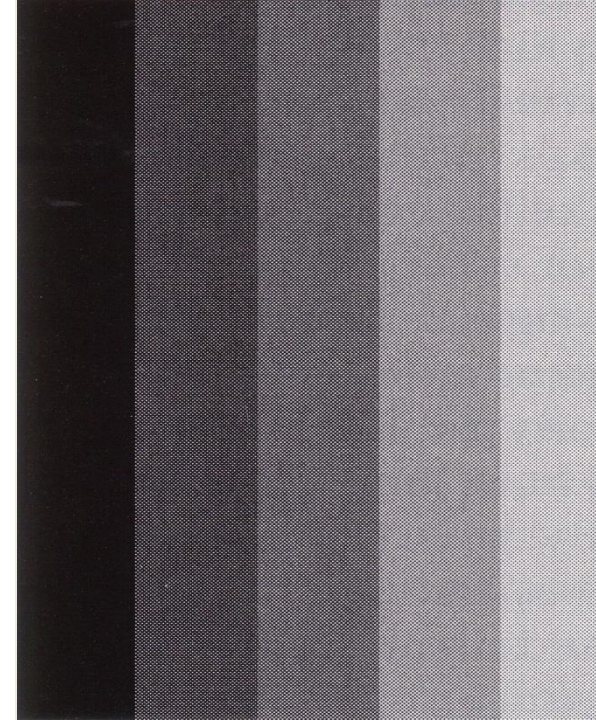






The **Context** determines, how
bright a surface appears

Brightness is an active
perceptual effort of the visual
system!



Mach-bands-illusion

➡ **Simultaneous contrast!**

Diffuse Noxious Inhibitory Controls: biological significance

- It is of **vital importance** to **detect** an **additional pain stimulus** on the **background of an ongoing pain process**
- The **attention** needs to be **shifted** towards the **newly occurring pain signal**, in order to prevent further damage to the body's integrity
- **If there would a summation of the signal, no new injury could be detected!**
- **DNIC** is very likely a **simultaneous perceptual contrast in the somatosensory system**, in order to **protect** the body from further **tissue damage!**
- That means, that it can probably even be **provoked by very light noxious stimuli** (Le Bars & Cadden, 2007)

DNIC in humans....

Diffuse Noxious Inhibitory Controls in humans (examples)

- A **DNIC like effect** has been shown for humans (on RIII-Reflex)

LeBars D, Willer J-C (2002) Pain modulation triggered by high-intensity stimulation: implication for acupuncture analgesia? International Congress Series 2002;1238:11-29.

- In patients with **spinal cord injuries** the effects can be **predicted depending on the localisation** of the lesion

Le Bars D and Willer JC. Diffuse Noxious Inhibitory Controls (DNIC). In: Basbaum A et al. editors. The senses: a comprehensive reference, vol 5: Pain. Amsterdam: Elsevier Churchill Livingstone; 2007. p. 762-773.

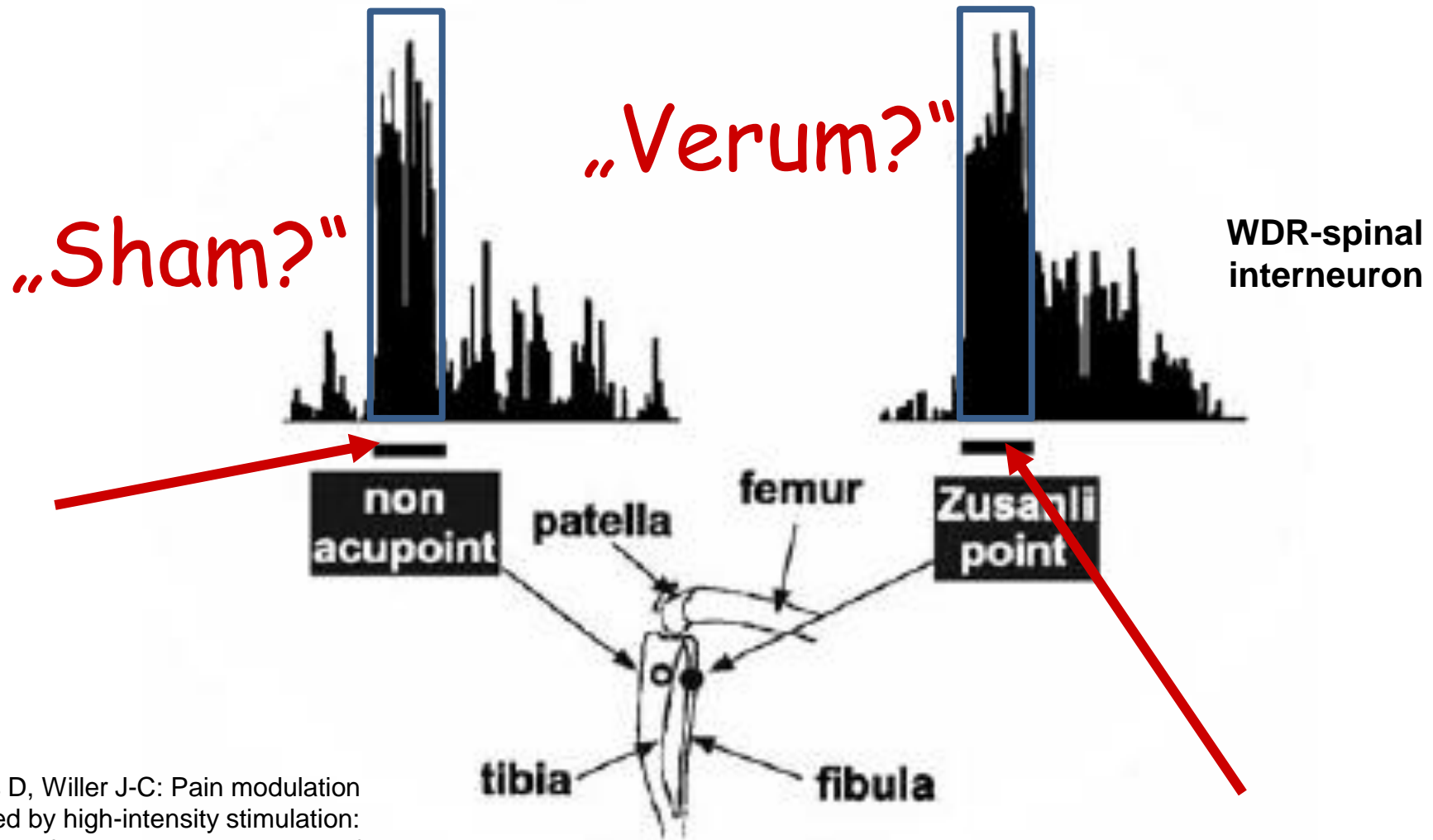
DNIC / „Counter Irritation“

- Le Bars D, Willer JC, De Broucker T, Villanueva L. Neurophysiological mechanisms involved in the pain relieving effects of counterirritation and related techniques including acupuncture. In: Stux G, Pomeranz B, eds. Scientific bases of acupuncture. Heidelberg, Berlin: Springer; 1989. p. 79-112.
- Le Bars D. The whole body receptive field of dorsal horn multireceptive neurons. Brain Res Brain Res Rev 2002;40:29-44.
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- Le Bars D and Cadden SW (2007) What is a wide-dynamic-range cell? In: Basbaum A et al. editors. The senses: a comprehensive reference, vol 5: Pain. Amsterdam: Elsevier Churchill Livingstone; 2007. p. 331-338.
- Mann F. Reinventing acupuncture. Oxford: Butterworth Heineman; 1993
- Etc.

DNIC and the GERAC trials



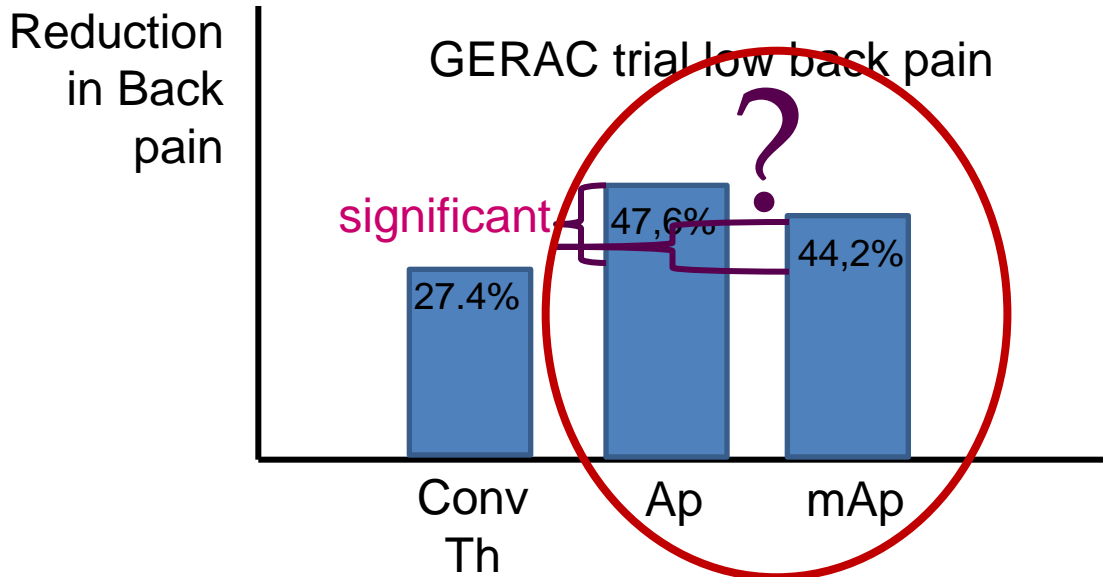
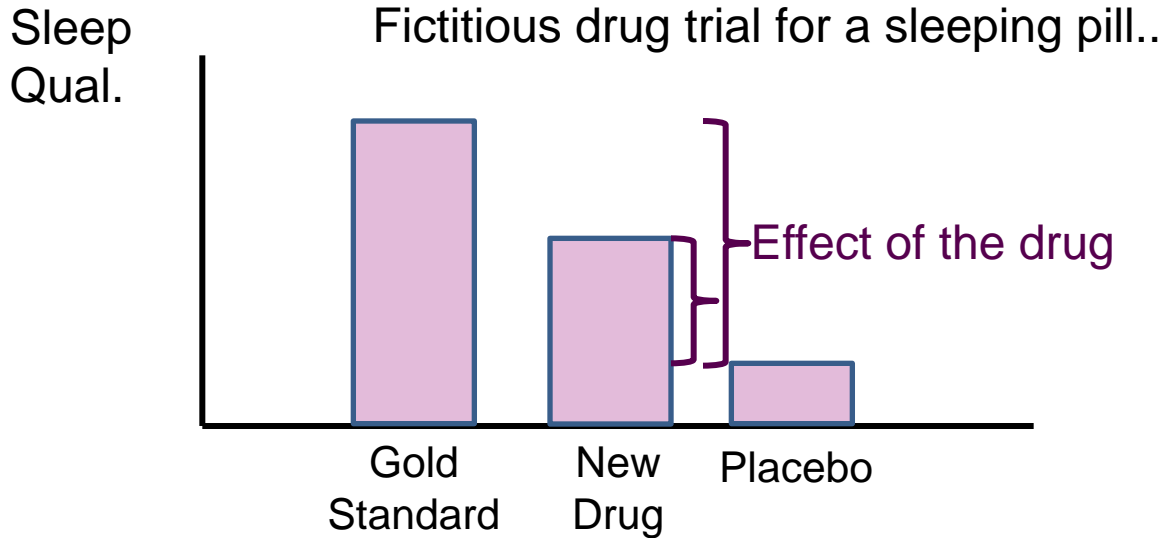
Particularly **effective** and long lasting **reactions of the WDR-neurons** from the „acupuncture point“!



LeBars D, Willer J-C: Pain modulation triggered by high-intensity stimulation: implication for acupuncture analgesia? International Congress Series 2002;1238:11-29.

Rat-model

The problem with the control condition....



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DNIC:

A candidate for
a specific
acupuncture
effect



Diffuse Noxious Inhibitory Controls

- Even though DNIC can be induced from every localisation, acupuncture points are likely to be **more effective** in inducing **A δ – stimulation** (fast conducting pain fibre).
- **Possibly:** Many non-acupuncture points are as efficient as a few acupuncture points
- Points **distant to the pain** are likely to play an important role (**heterotopic** stimulation) in the acupuncture treatment of pain.

(a little) Discussion on point specificity

- DNIC is **not** entirely independent from point specificity. **Acupuncture points** induce a **stronger** and **longer** neuronal reaction!
- There is good evidence for point specificity in the **autonomic nervous system** (e.g. cardiovascular system: heart rate: Li et al., 2004, Li et al., 2006; blood flow: Agarwal-Kozlowski, Lange & Beck, 2009; nausea: e.g. Beissner et al, 2012; functional dyspepsia: Ma et al. 2012)
- The exclusiveness of point specificity may be **dependent** on the **physiological system** (e.g. somatosensory vs. autonomic nervous system)

Is acupuncture /
needling a
nociceptive/pain
signal



Is acupuncture / needling a nociceptive /pain signal?

- Acupuncture (e.g. ST 36) activates **pain related brain structures** (e.g. Biella et al., 2001, Pariente et al., 2005, Beissner et al., 2012; for overview and discussion see Wang, Kain & White, 2008; Theyson et al., 2014).
- The activation is depending on **needling sensation** (Beissner et al., 2012)
- A recent meta analysis across 28 fMRI studies of **acupuncture needling** showed an **activation of the pain matrix** (sensorimotor cortical network, including the insula, thalamus, anterior cingulate cortex, and primary and secondary somatosensory cortices). (Chae et al, 2013)

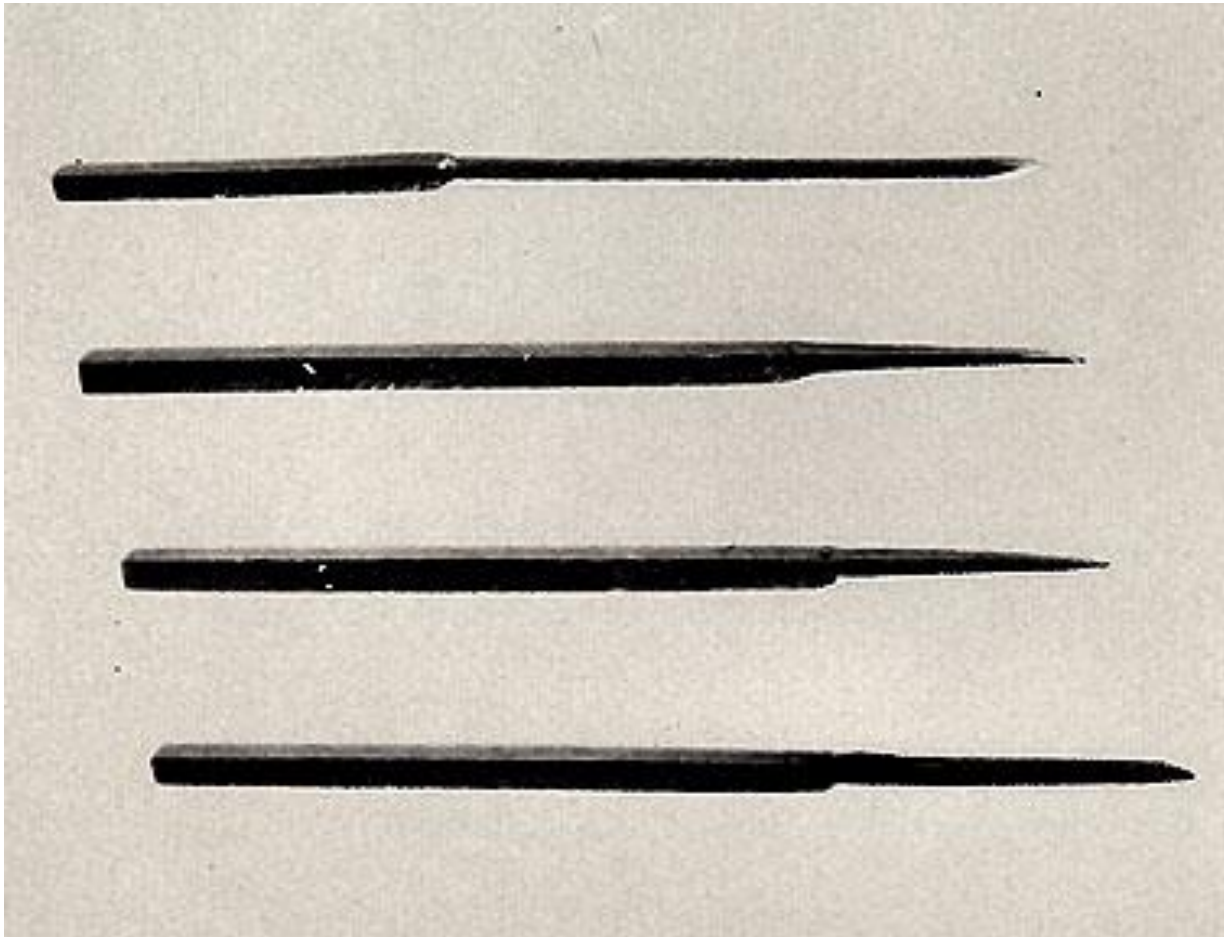
Chae Y, Chang DS, Lee SH, Jung WM, Lee IS, Jackson S, Kong J, Lee H, Park HJ, Lee H, Wallraven C. Inserting needles into the body: a meta-analysis of brain activity associated with acupuncture needle stimulation. J Pain. 2013 Mar;14(3):215-22.

Is acupuncture / needling a nociceptive /pain signal?

yes!

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Acupuncture needles 2nd century B.C.



Is a potential
needling induced
DNIC effect
clinically relevant in
chronic pain states



Conditioned Pain Modulation (the diffuse noxious inhibitory control-like effect): its relevance for **acute and chronic pain states** (review)

David Yarnitsky, Current Opinion in Anaesthesiology 2010, 23:611–615

- **reduced CPM efficiency** in idiopathic pain syndromes, such as irritable bowel syndrome, temporomandibular disorders, fibromyalgia, and tension type
- **Low CPM efficiency**, reflecting **low pain inhibitory capacity**, may be a common **pathogenetic factor**
- **Low CPM efficiency** was shown to be **predictive of acute and chronic postoperative pain**
- **Low CPM efficiency is associated with higher pain morbidity** and vice versa.
- The role of **CPM plasticity** and its relevance to selection and efficacy of pain therapy is to date unclear.

Does
Acupuncture
induce DNIC



- o DNIC is very likely to **add** to the **overall effect** of **acupuncture related pain control!**
- o It is probably **stronger in acute clinical pain** and in experimental laboratory pain **as compared to chronic pain.**
- o It **cannot be the only mechanism**, since e.g. chronic pain patients show a **reduced DNIC response** (e.g. Yarnitsky, 2010).
- o However, acupuncture may provide „**retraining**“ of DNIC in chronic pain.

More methodological considerations....

Implications for
experimental setups (mostly
performed in healthy controls)...

Always test acupuncture
on an **experimental pain
stimulus!**

„Treating pain with pain“ or „heterotopic conditioning stimulations“ (HCNS = the human experimental equivalent to DNIC)

- Acupuncture decreases somatosensory evoked potential amplitude to noxious stimuli in anesthetized volunteers (Meissner et al., Anesth Analg 2003). **Clear acupuncture effects in unconscious humans.**
- Modulation of cold pain (Zhang et al., Neuroreport 2003) and electrical pain (Theyson et al. 2014) in the human brain by electric acupoint stimulation: evidence from fMRI. **Less brain activity in somatosensory areas in response to acupuncture.**
- Etc.

Treating pain with pain: Supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimulations (Sprenger, Bingel & Büchel, PAIN, 2011)

- Tonic cold pressor task and phasic additional pain stimulation in an fMRI paradigm.
- Clear **HNCS effect** / marked endogenous analgesia
- Reduced activity in classical pain related brain structures
- In addition, recruitment of an **opiate dependent, descending pain control system** (naloxone blockade)

Some general implications: Take good care of your **control condition** (in experimental AND clinical trials)!!!

- Use a well established control, where the mechanism is known, such as e.g. a pharmacological gold standard (e.g. Musial et al., 2012, Electroacupuncture vs. Tramadol)
- If you go for non-pharmacological interventions, use one where the biomechanism is understood (e.g. Meditation; Choi et al, 2011)
- In experimental trials, always include a non-treatment control group, in clinical trials, minimally have a standard medical care group.

Is there a role
for placebo in
acupuncture
analgesia



Placebo effects: group of subjects

- regression to the mean
- natural history
- true **placebo response**

The effect is small to non-existent! (Hrobjartsson A, Gotzsche PC. Placebo interventions for all clinical conditions. Cochrane Database of Systematic Reviews. [ARTN CD003974;DOI.1002/14651858. CD003974.pub3]. 2010;1.



Placebo response: individual reaction

**variability / signal
to noise relation**

expectation
conditioning
suggestion
beliefs
etc.

⇒ **neurobiological basis**

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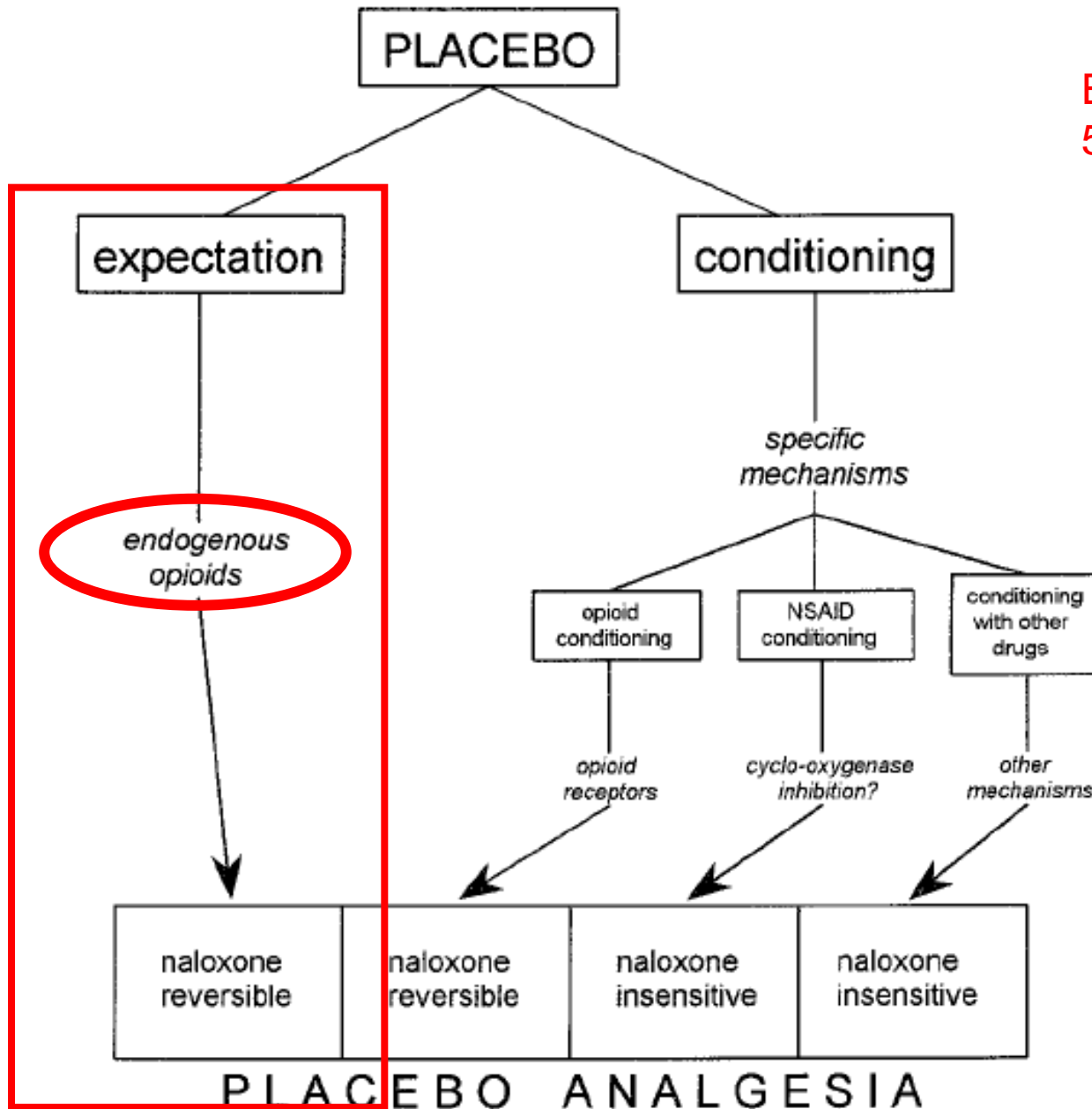
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variability / signal
to noise relation

expectation
conditioning
suggestion
beliefs
etc.

⇒ **neurobiological basis**

Benedetti, Pain, 64 (1996)
535-543.



Opiate sensitivity, acupuncture and expectation induced placebo analgesia

- **Acupuncture analgesia** is **similar** to the **expectation-dependent placebo analgesia** in that it can be blocked by naloxone. Thus it is also **opiate dependent**.

For an overview see:

- Mayer D. Biological mechanisms of acupuncture. In: Mayer EA, Saper CB, editors. Progress in Brain Research. Amsterdam: Elsevier Churchill Livingstone; 2000. p. 122-32.
 - Stux G, Berman B, Pomeranz B. Basics of acupuncture. Berlin: Springer; 2003
 - Han Neurosci lett 2004; 361(1-3): 258-261.
- **Expectation-dependent placebo analgesia** exhibits some similarities to **acupuncture analgesia** and may utilize the **same mechanisms**.

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- **Tonic cold pressor** task and **phasic additional** pain stimulation in an fMRI paradigm.
- Clear **HNCS effect** / marked endogenous analgesia
- **Reduced activity** in classical pain related brain structures
- In addition, recruitment of an **opiate dependent, descending pain control system** (naloxone blockade)

Cortical substrates of acupuncture and expectation induced placebo analgesia

- Neuroimaging data in man indicate that **acupuncture analgesia** is mediated via the **same cortical areas** that process the **emotional-affective aspect of pain** (prefrontal cortex, anterior cingulate, insula) (e.g. Biella et al., 2001, Pariente et al., 2005, Beissner et al., 2012; Theyson et al., 2014; for overview and discussion see Wang, Kain & White, 2008; Chai et al, 2013)
- The activation is depending on **needling sensation** (Beissner et al., 2012)
- These areas are also **central to the mediation of expectation induced placebo analgesia** (e.g. Petrovic et al. 2002; Zubieta et al. 2005)

Acupuncture analgesia and placebo

- Are there **parallels** between **acupuncture analgesia** and **expectation induced placebo analgesia**?

Yes

- What does that **mean** for the interpretation of the **neurobiological mechanisms of acupuncture analgesia**?

?

When expectation becomes reality

(Koyama et al. 2005)....

Sensory **experiences** are to the same extent determined by

➤ **Sensory input**

as well as

➤ **Expectations**

Paradigm (Koyama et al. 2005)

- In a training session, heat stimuli (46, 48, 50 °C) were paired with time intervals of increasing length (7.5, 15, 30 sec.)

➤ Conditioning

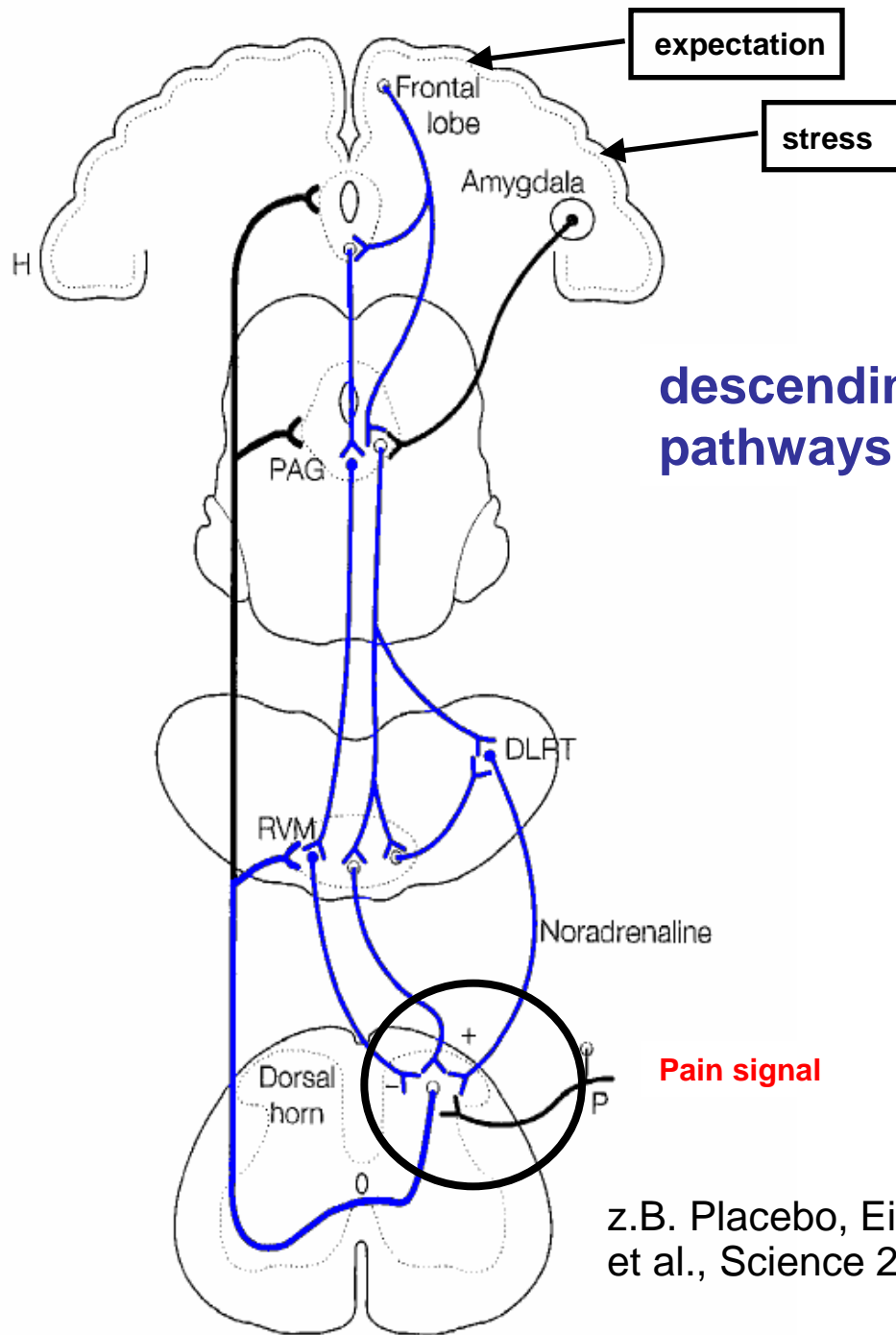
- 33 % of the trials with 48 °C and 50 °C were „announced“ wrongly (the intervals were exchanged)

➤ Expectation

Koyama et al. (2005) The subjective experience of pain: where expectations become reality. PNAS, 102 (36), 12950-12955.

Role of expectation in acupuncture....

- A successful acupuncture treatment in the past
- A good patient-practitioner relationship
- Social setting (...it helped me, why don't you try?)
- And so on...

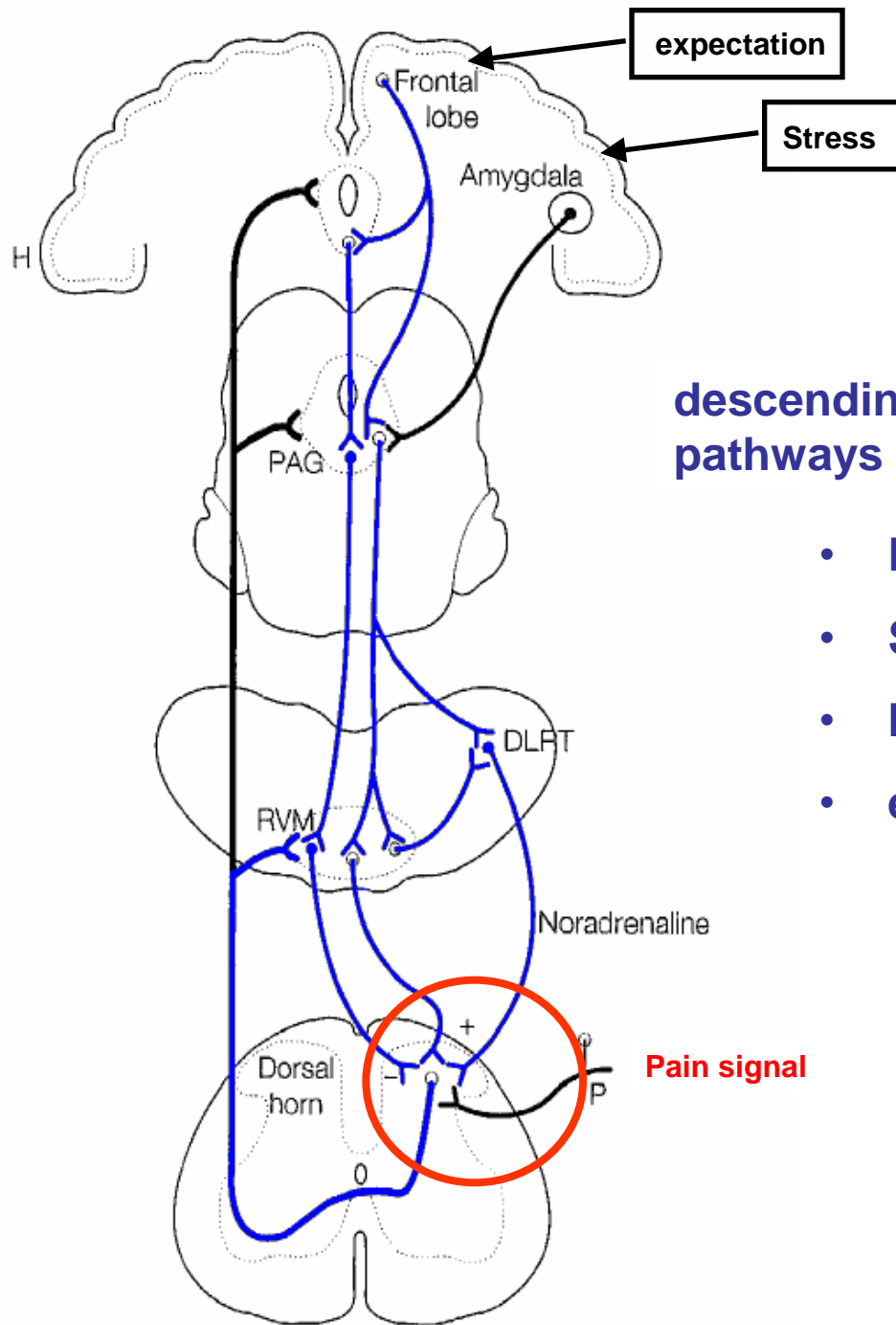


descending pain modulatory pathways

Pain signal

z.B. Placebo, Eippert et al., Science 2009

Fields HL, Basbaum AI, Heinricher MM: Central nervous system mechanisms of pain modulation; in McMahon S B, Koltzenburg M (eds): Wall and Melzack's textbook of Pain. 5th edn., Amsterdam, Elsevier Churchill Livingstone, 2005, pp 125-142.



descending pain modulatory pathways

- Expectation
- Stress
- Meditation
- etc.

Fields HL, Basbaum AI, Heinricher MM: Central nervous system mechanisms of pain modulation; in McMahon S B, Koltzenburg M (eds): Wall and Melzack's textbook of Pain. 5th edn., Amsterdam, Elsevier Churchill Livingstone, 2006, pp 125-142.



The acupuncture
setting

„Perfect“ Acupuncture-setting:

Top down

Expectation

descending pain
modulatory pathways

Bottom up

DNIC

Pain

