The impact of what we tell patients: Potentielle nocebo effekter i kommunikationen mellem klinikere og patienter med smerte

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Learning objectives

This lecture focuses on the psychoneurobiological mechanisms of nocebo effects.

Objectives:

1. Examine how nocebo effects are generated behaviorally and at the level of brain mechanisms

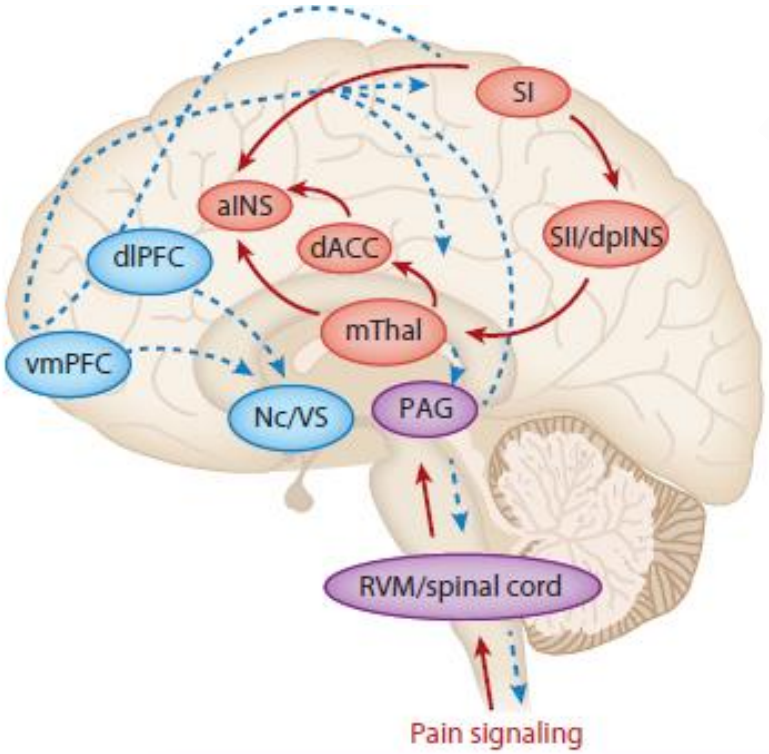
2. Comment on the implication of nocebo effects

Pain modulatory systems

- Verbal suggestions
- Therapeutic prior experiences
- Observation of benefits in others
- Contextual and treatment cues
- Interpersonal interactions

Expectancies

Demographics
Psychological traits



GENES

Descending pathways
Ascending pathways
Increased activation
Decreased activation
Increased/decreased activation

Pharmacological, integrative, psychological, and surgical interventions

Colloca, Annu. Rev. Pharmacol. Toxicol. 2019, 59:161-1621

NEUROSCIENCE

Nocebo effects can make you feel pain

Negative expectancies derived from features of commercial drugs elicit nocebo

By **Luana Colloca**

The mysterious phenomenon known as the nocebo effect describes negative expectancies. This is in contrast to positive expectancies that trigger placebo effects (*1*). In evolutionary terms, nocebo and placebo effects coexist to favor perceptual mechanisms that anticipate threat and dangerous events (nocebo effects) and promote appetitive and safety behaviors (placebo effects). In randomized placebo-controlled clinical trials, patients that receive placebos often report side effects (nocebos) that are similar to those experienced by patients that receive the investigational treatment (*2*). Information provided during the informed consent process and divulgence of adverse effects contribute to nocebo

ferential nocebo effects between the expensive and cheaper treatments. Expectancies of higher pain-related side effects associated with the expensive cream may have triggered a facilitation of nociception processes at early subcortical areas and the spinal cord [which are also involved in placebo-induced reduction of pain (*8*)]. The rACC showed a deactivation and favored a subsequent activation of the PAG and spinal cord, resulting in an increase of the nociceptive inputs. This suggests that the rACC–PAG–spinal cord axis may orchestrate the effects of pricing on nocebo hyperalgesia.

The anticipation of painful stimulation makes healthy study participants perceive nonpainful and low-painful stimulations as painful and high-painful, respectively (*9*). Verbally induced nocebo effects are as strong as those induced

administration was inter
findings provide evidenc
tion of treatment discont
least in part, lead to noce
gravation of symptoms.

In placebo-controlled
cebo effects can influenc
outcomes and treatment
shown in a clinical trial t
duced in the same indivic
of muscle-related adverse
blinded (i.e., patients kne
atorvastatin), nonrandom
up phase but not in the in
phase when patients an
unaware of the treatment
tatin or placebo) (*14*). Fur
ing information about sid
via public claims has led t
tinuation and an increase
heart attacks (*14*).

Given that nocebo eff
perceived side effects a

Colloca, Science, 6 OCTOBER 2017 • VOL 358 ISSUE 6359

Nocebo effects vs nocebo responses

- **Nocebo responses**: Changes in ***clinical trial*** outcomes that result from biases, regression to the mean, natural history, and co-interventions - **no inclusion of a no-treatment arm**

- **Nocebo effects**: Changes in neurobiological and clinical outcomes that result from patients' perception, **expectations**, **prior experience** and the therapeutic encounter - **inclusion of a no-treatment group**

Adverse Events (AEs) in antidepressant trials

Both active and placebo arms of TCA had higher rates of AEs than SSRI trials, suggesting a link between informed consent and AEs.

Dry mouth: 19.2% in placebo TCA vs 6.4% in placebo SSRI arm

Rief et al. Drug Saf. 2009;32:1041-1056

For a review see: Blasini et al. PAIN Reports 2017 Volume 2 - Issue 2 - p e585
http://journals.lww.com/painrpts/Fulltext/2017/03000/Nocebo_and_pain___an_overview_of_the.2.aspx

Nocebo responses in Randomized Clinical Trials

Disease	Treatment	Nocebo Responses	Drop-out	Ref.
Migraine	**symptomatic treatments** **preventive treatments**	**18.45%** **42.78%**	**0.33%** **4.75%**	**Mitsikostas DD et al. Cephalalgia. 2011**
Tension-type headache	preventive treatments	23.99%	5.44%	Mitsikostas DD et al. Cephalalgia. 2011
Fibromyalgia	Symptomatic treatments	67.2%	9.5%	Mitsikostas DD et al. Eur J Neurol. 2011

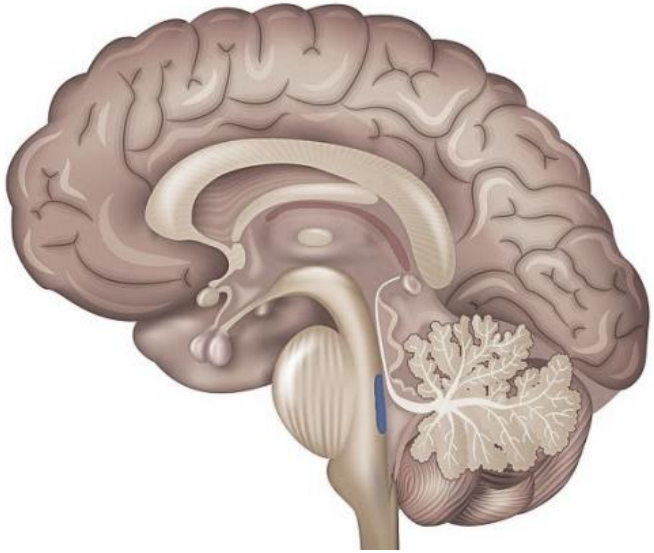
Colloca and Miller, Psychosom Med. 2011 :73(7):598-603

An integrative model for nocebo effects

Experiential learning

Instructional learning

Vicarious learning



Decoding Information processes

NEGATIVE EXPECTATIONS

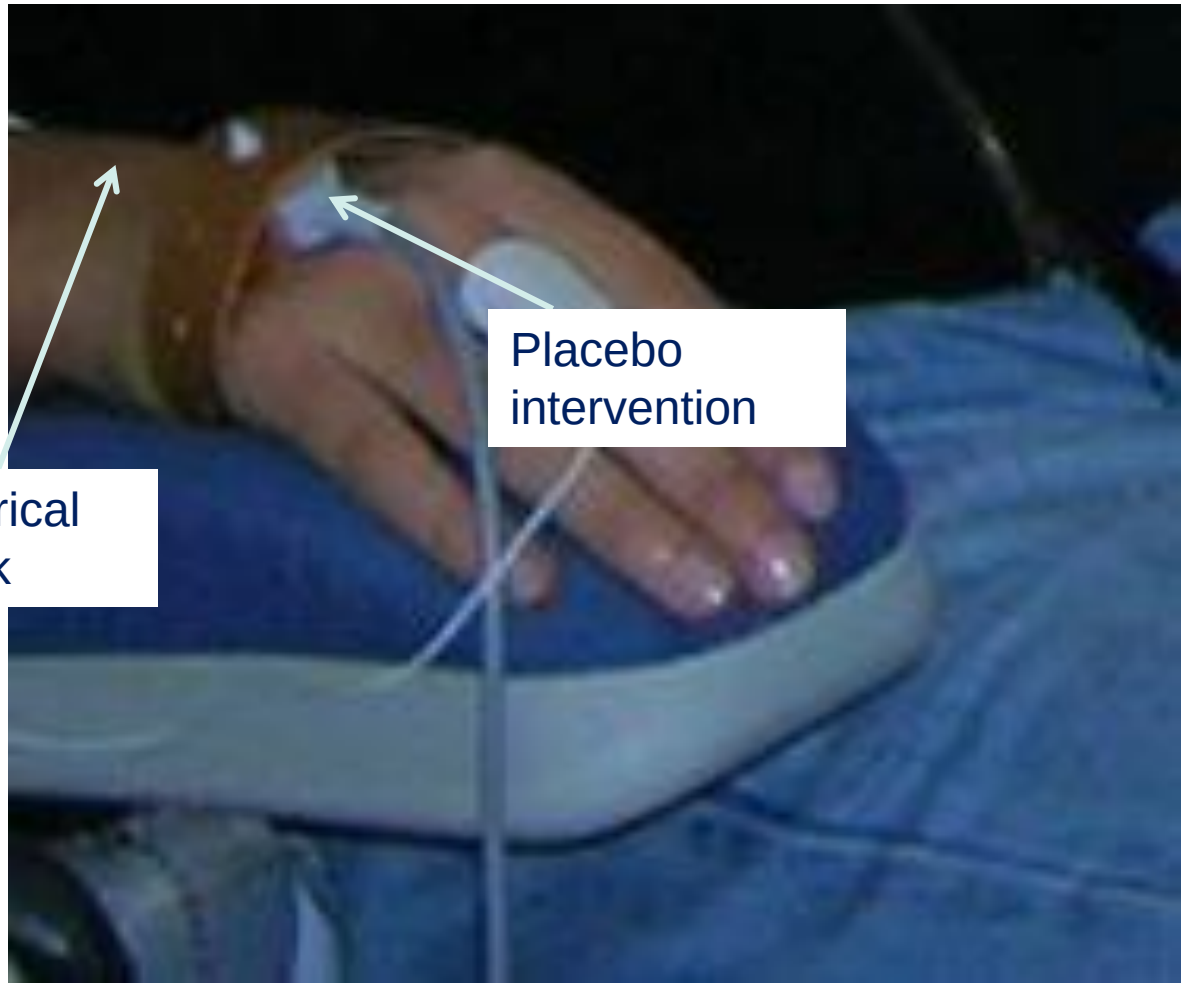
NOCEBO EFFECTS

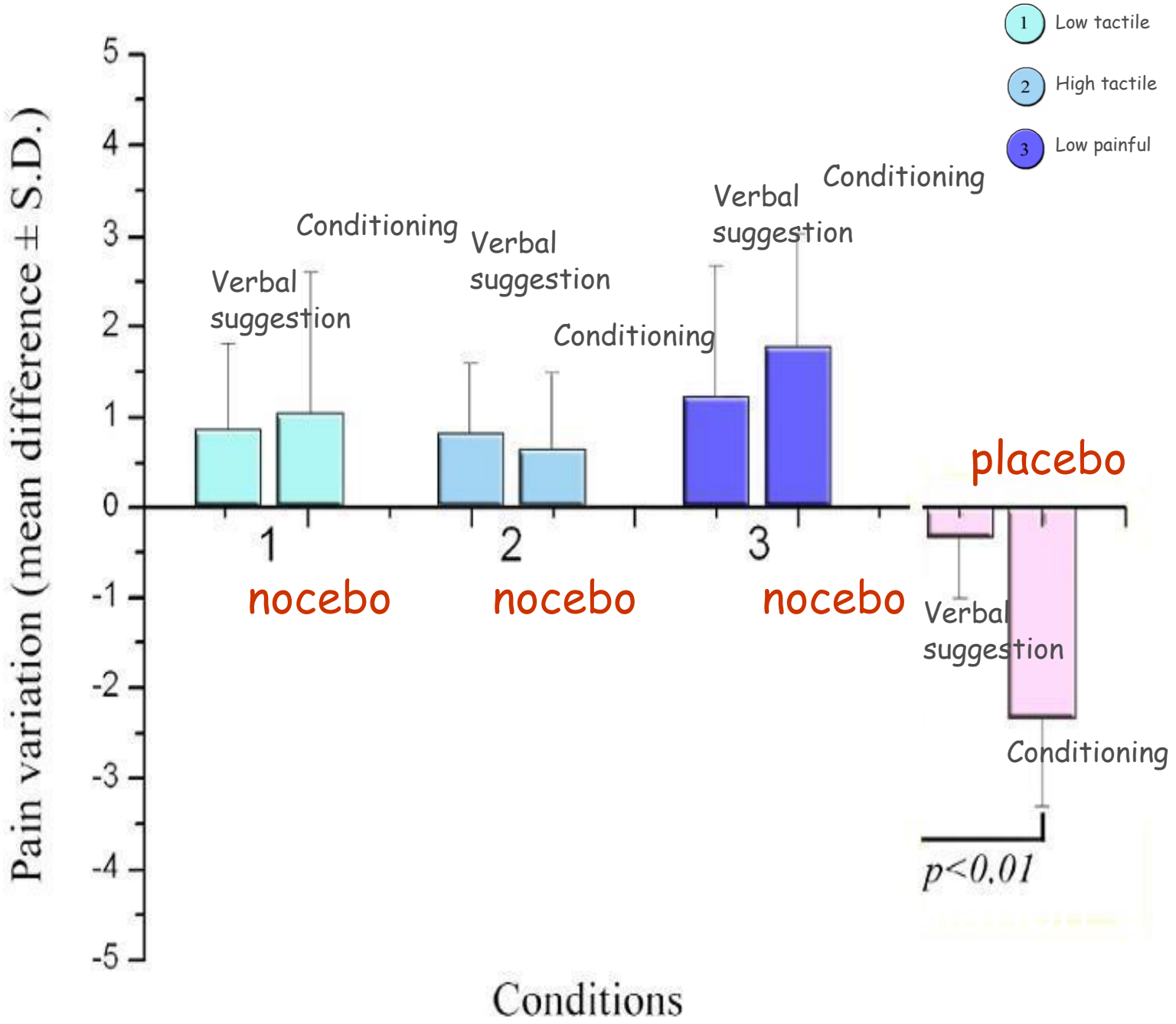
Negative Behavior and/or clinical outcome changes

Colloca and Miller, Phil Trans R. Soc. B 2011 ; 2011:366 1859-1869

Verbal suggestions and conditioning in nocebo effects

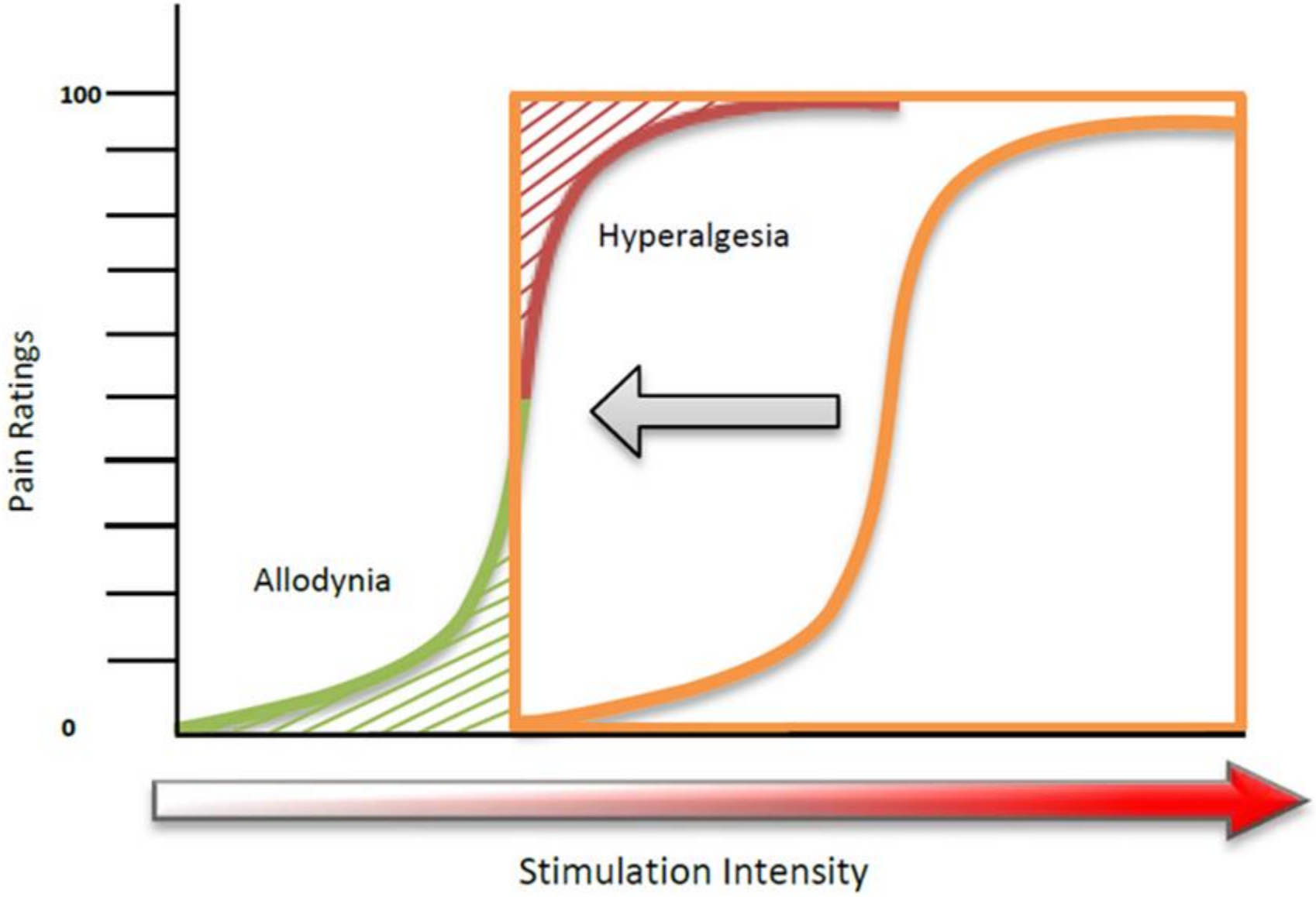
1. Low tactile
2. High tactile
3. Low painful





Colloca L, et al. Pain 2008; 136:211-8

Nocebo suggestions create allodynia and hyperalgesia



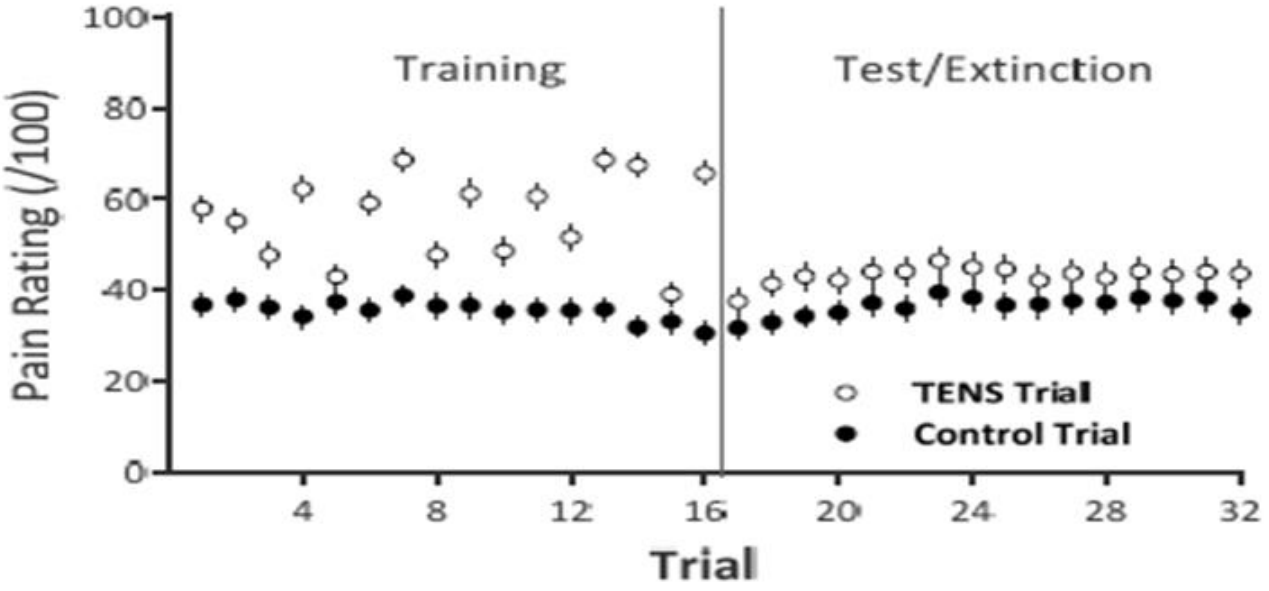
Colloca L, et al. Pain 2008; 136:211-8

Nocebo effects and partial reinforcement

Group	Verbal suggestion	Conditioning	Extinction
CRF	✓	16 TENS → 60% 16 No TENS → 100%	16 TENS → 100% 16 No TENS → 100%
PRF (62.5%)	✓	10 TENS → 60% 6 TENS → 100% 16 No TENS → 100%	16 TENS → 100% 16 No TENS → 100%
Control	×	16 TENS + 16 No TENS → 100% 16 TENS + 16 No TENS → 60%	

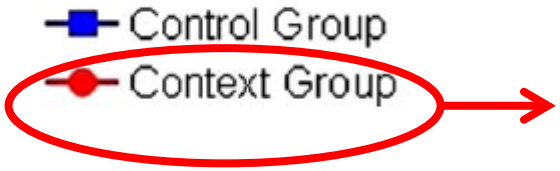
Au Yeung et al. Pain. 2014;155(6):1110-7

Negative partial reinforcement

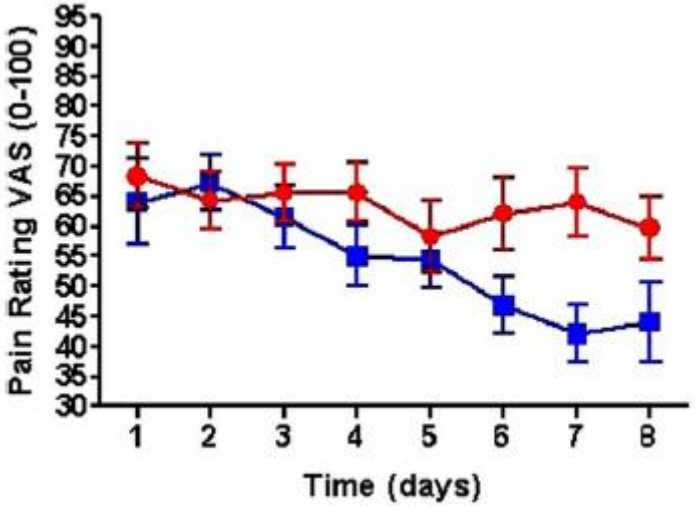


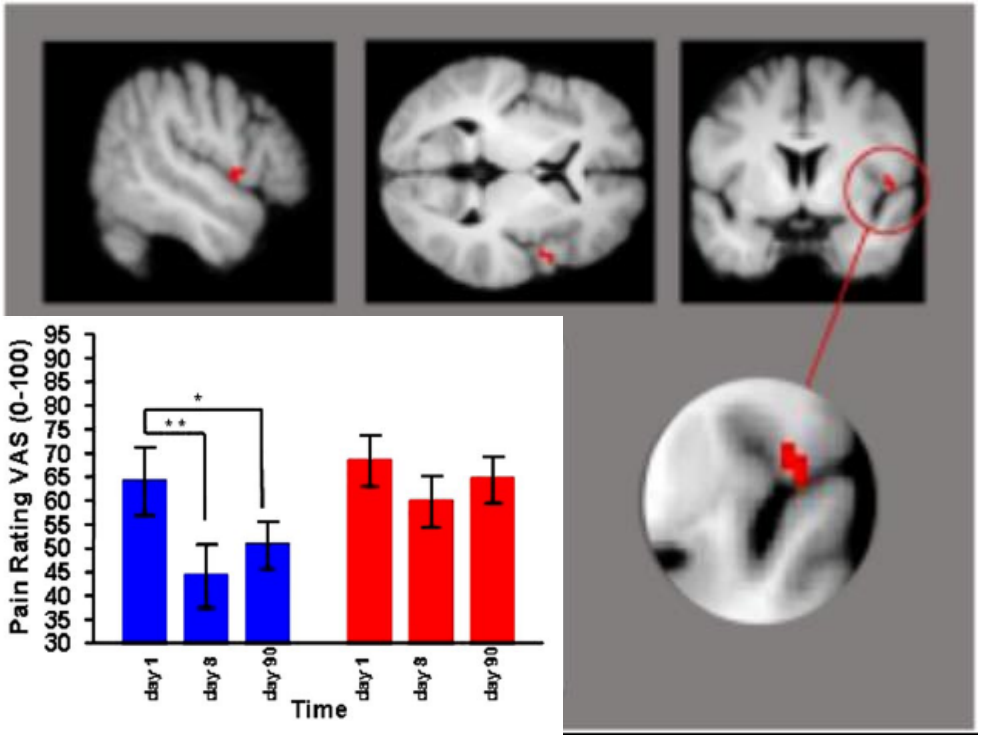
Colagiuri et al. J Pain 2015; 16*:* 995-1004

Communication of pain induces long-lasting hyperalgesia



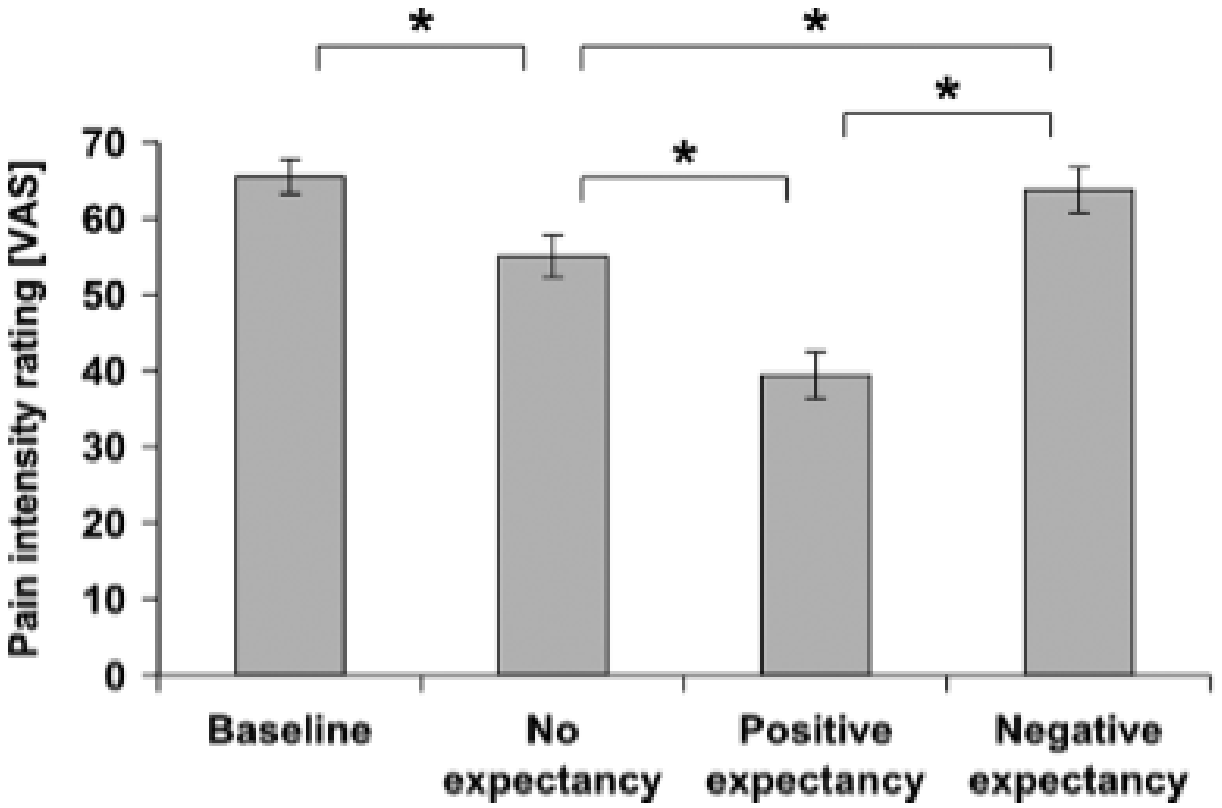
'Repeated pain over several days will increase your pain sensation over time e.g., from day to day'





Rodriguez-Raecke et al., J Neurosci. 2010; 30:11363-11368

Effect of negative treatment expectations on drug efficacy



Effect of remifentanil alone

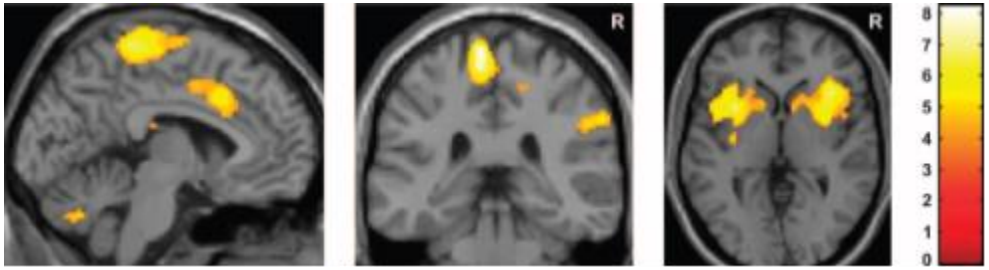
Positive expectations + remifentanil

Negative expectations + remifentanil

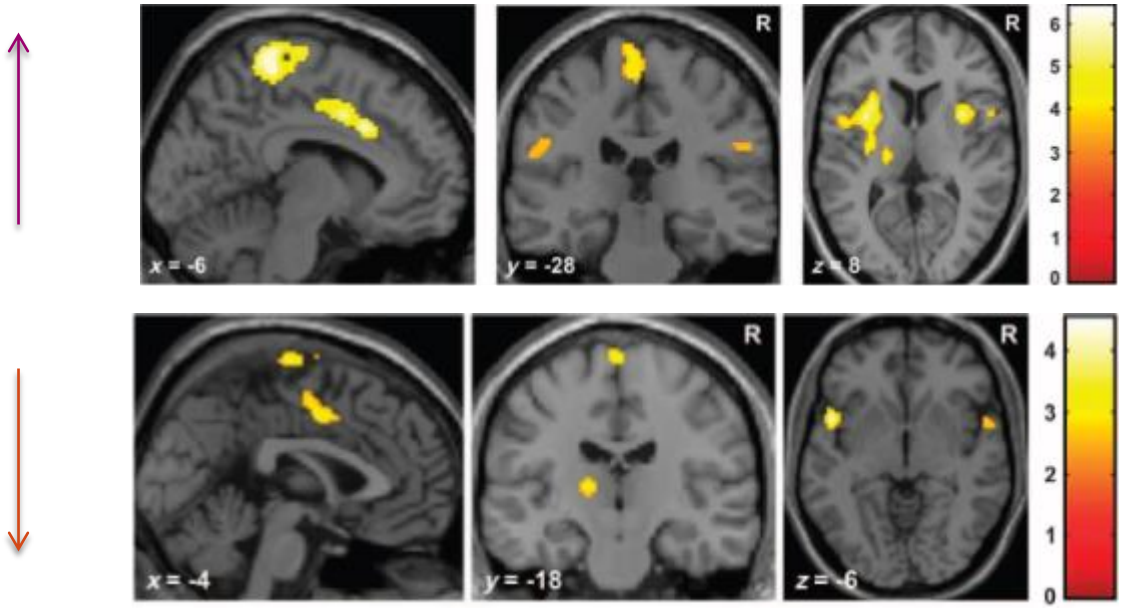
Bingel et al. Sci Transl Med (2011) 3, 70ra14

The effect of treatment expectations on drug efficacy

Intrinsic effect of remifentanil

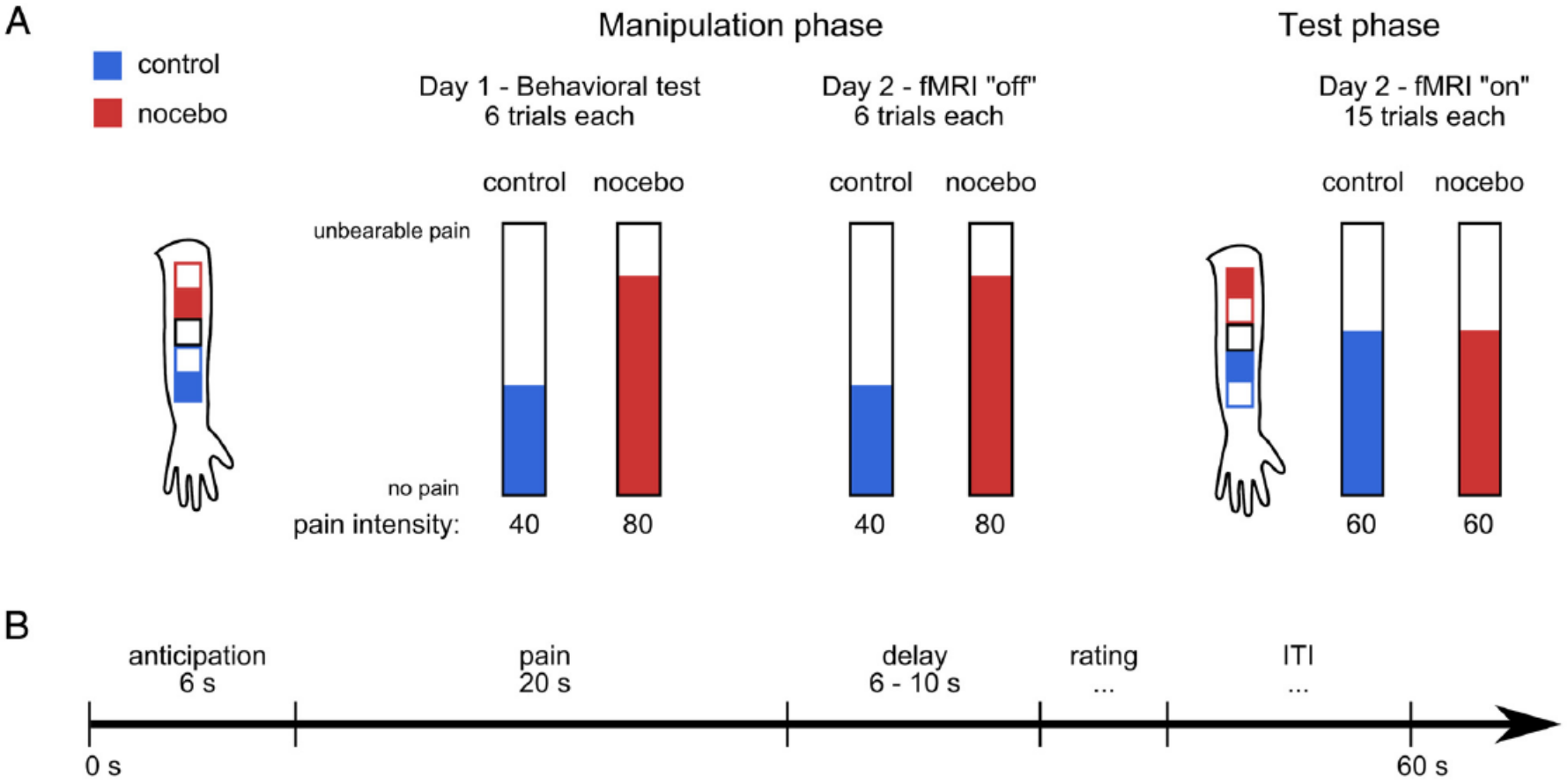


Expectancy modulation of remifentanil



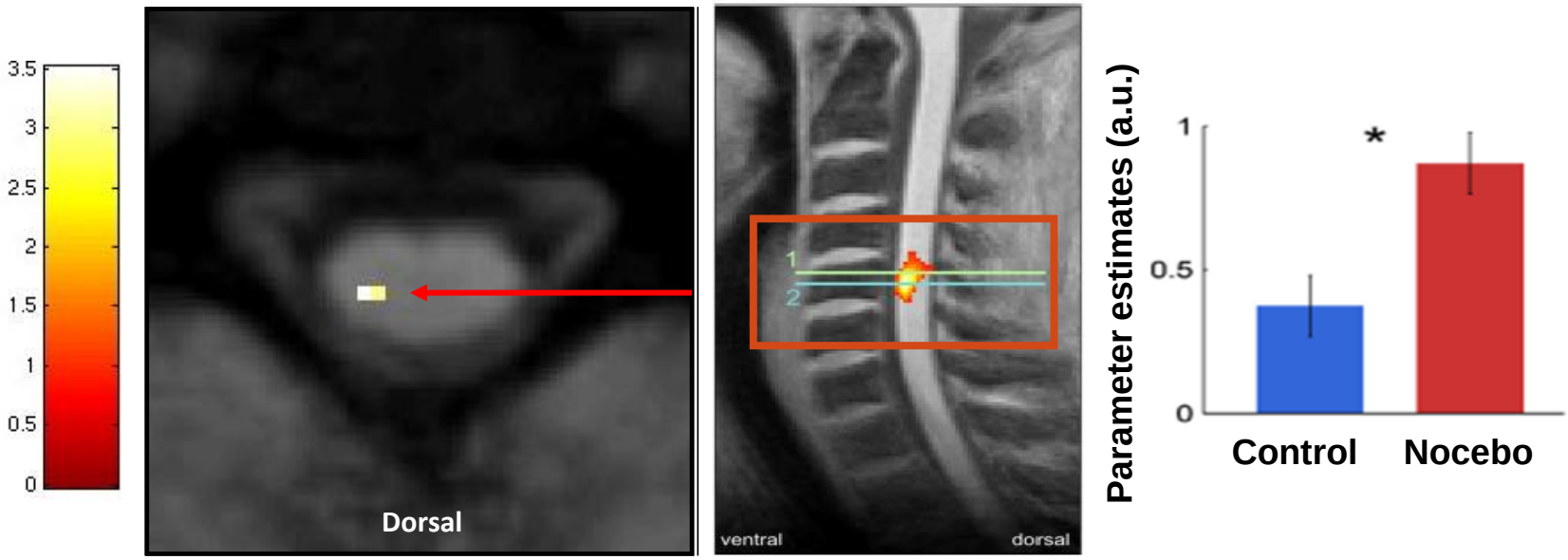
Bingel et al. Sci Transl Med (2011) 3, 70ra14

Nocebo hyperalgesia – a spinal cord study



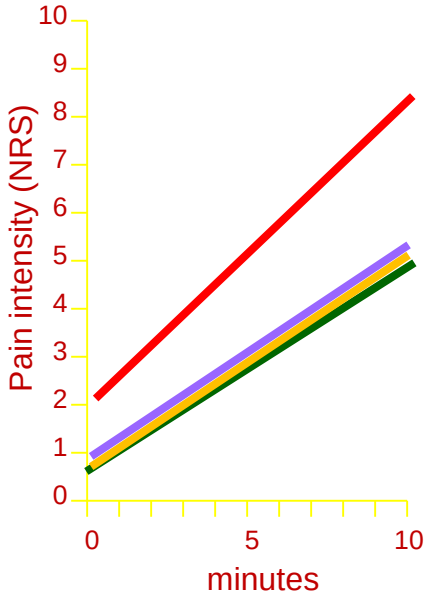
Geuter and Buchel. J. Neurosci. 2013;33(34):13784-90

Facilitation of pain in human spinal cord

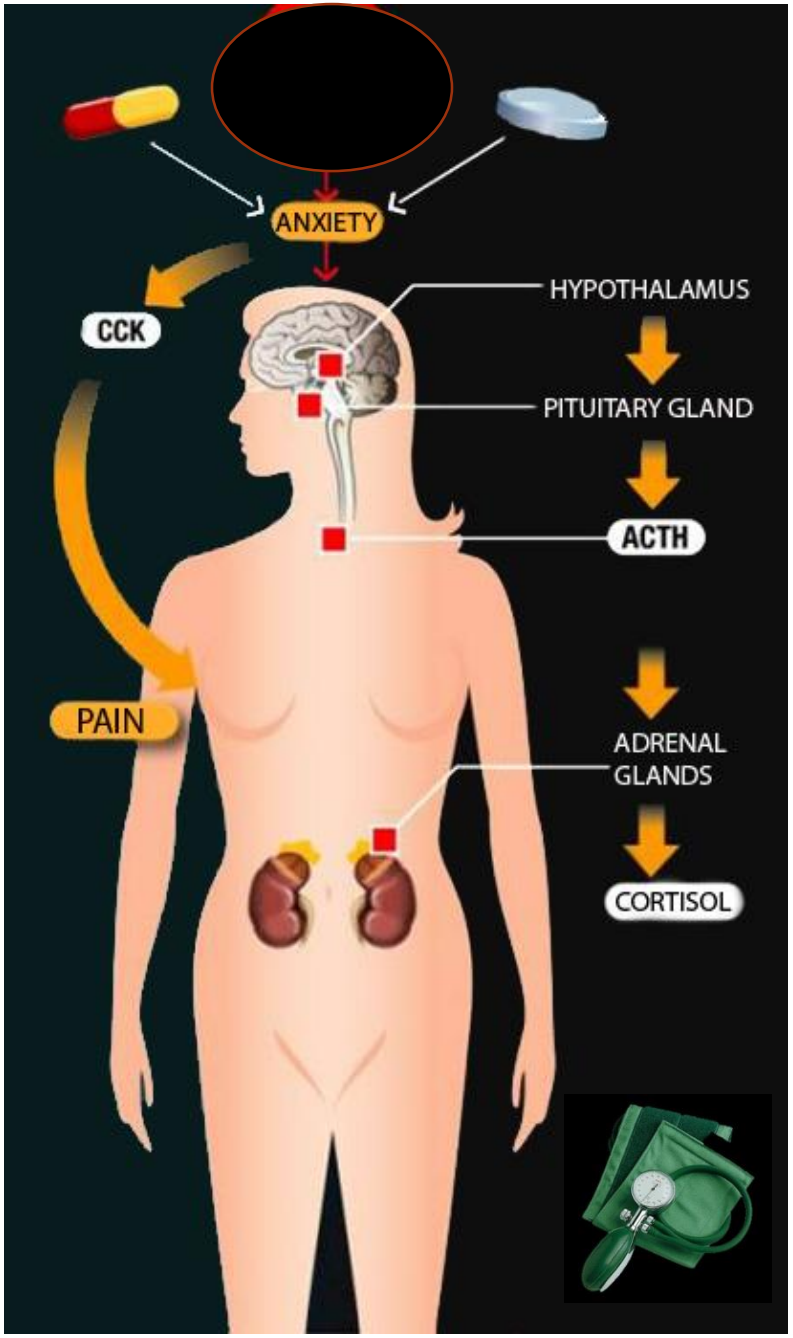


Geuter and Buchel. J. Neurosci. 2013;33(34):13784-90

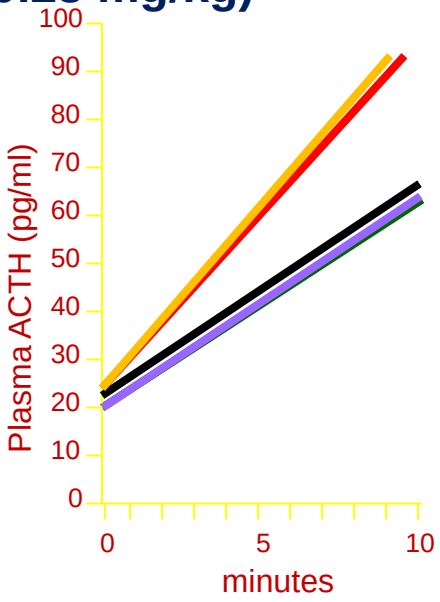
PROGLUMIDE (1.5 mg/kg)

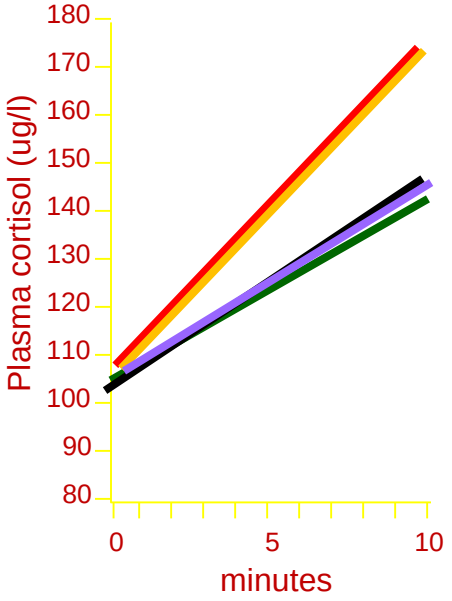


Control (NH)
Verbal suggestion
PROGLUMIDE
DIAZEPAM



DIAZEPAM (0.28 mg/kg)

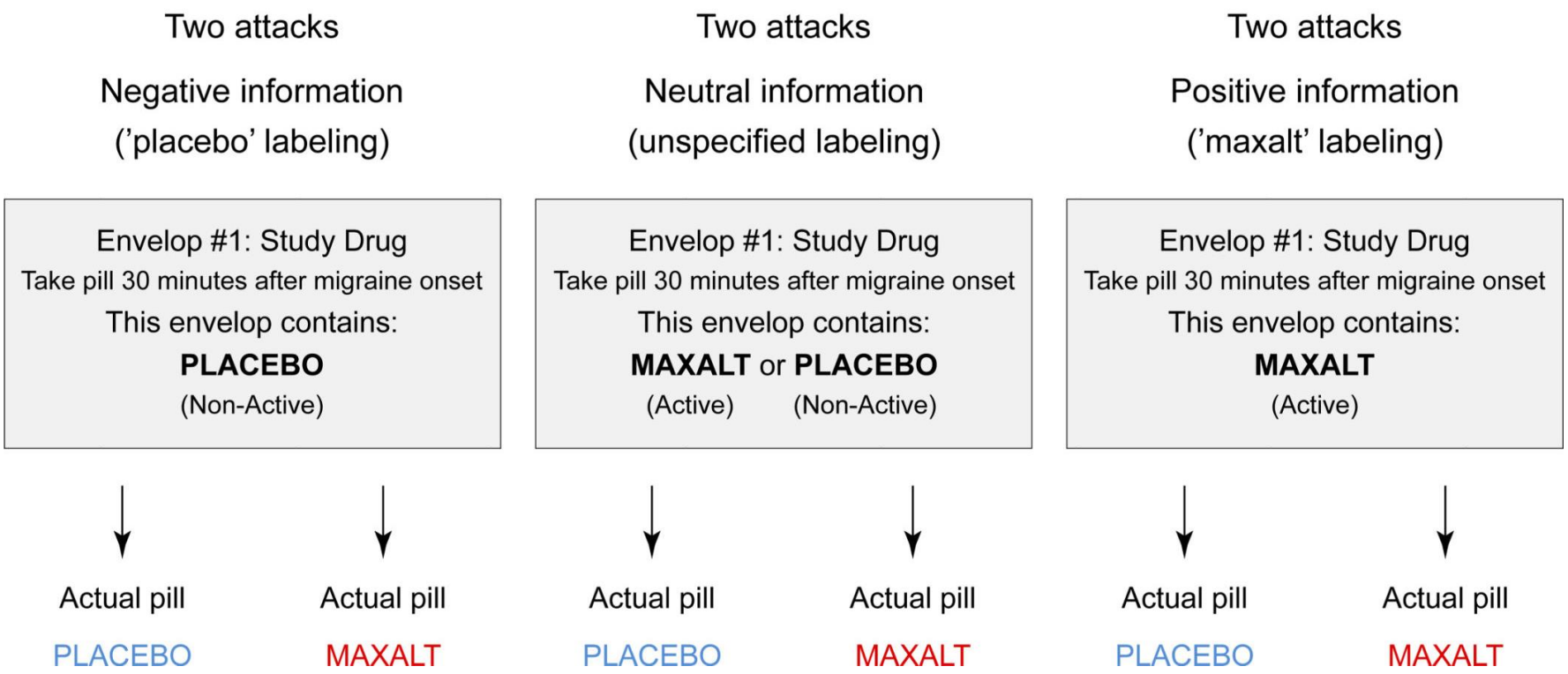




Benedetti et al (2006) J Neurosci 26: 12014-12022

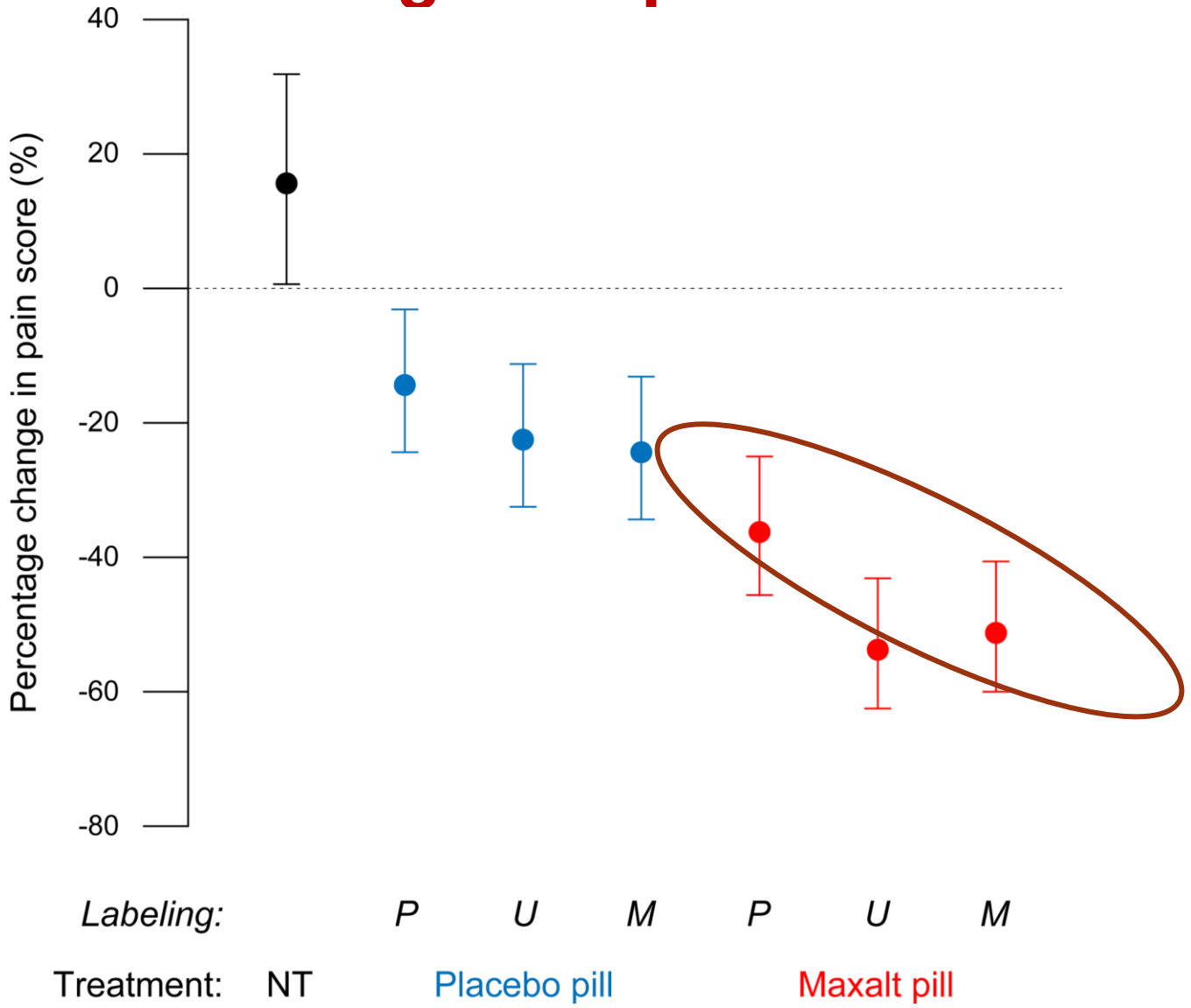
Medication labeling affects drug effects in migraine

Prospective, within-subjects, repeated-measures study of 66 subjects with episodic migraine and 459 documented attacks



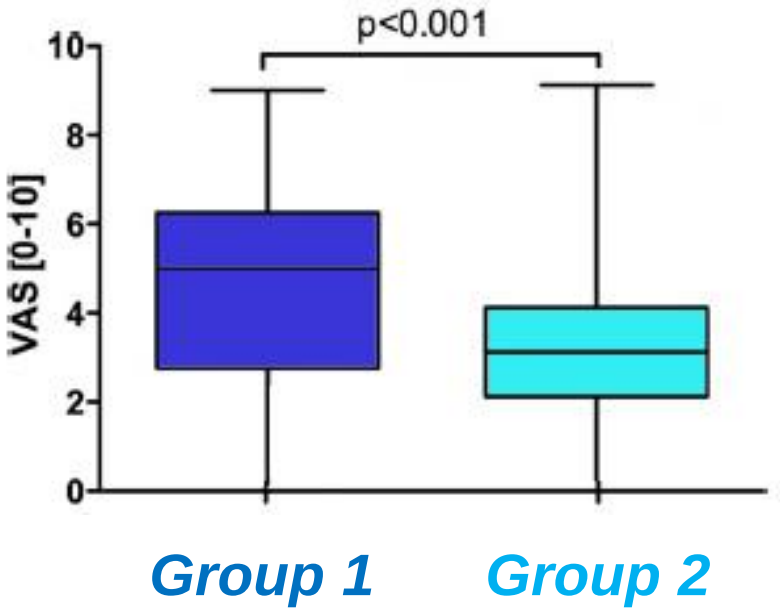
Kam-Hansen et al. Science Translational Medicine 2014: 6:128

Medication labeling modifies nocebo and drug effects in migraine patients



Kam-Hansen et al. Science Translational Medicine 2014: 6:128

Framing information and nocebo effects

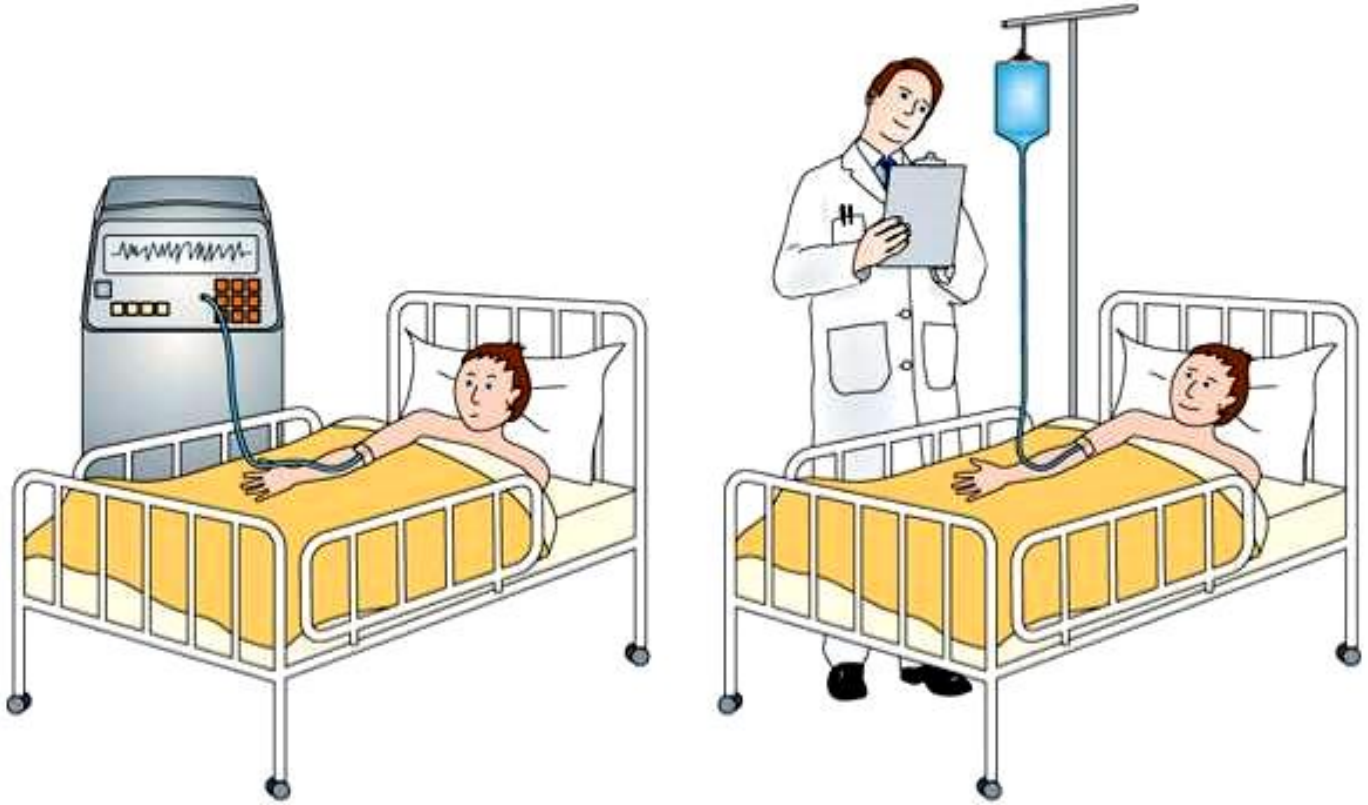


***Group 1**: "You are going to feel a big bee sting; this is the worst part of the procedure"*

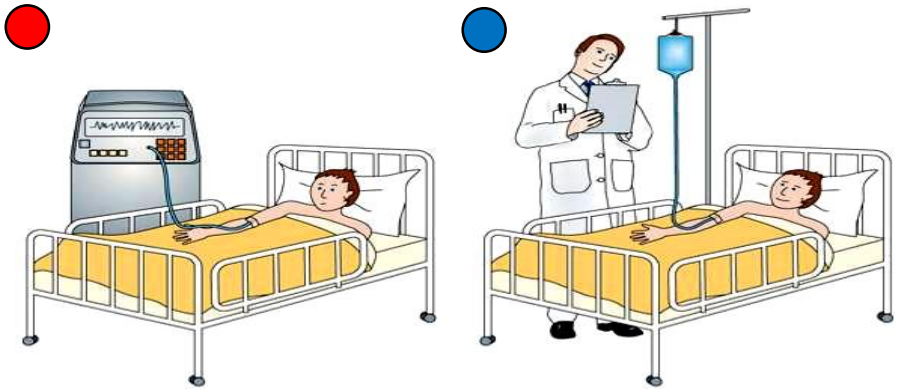
***Group 2**: "We are going to give you a local anesthetic that will numb the area and you will be comfortable during the procedure"*

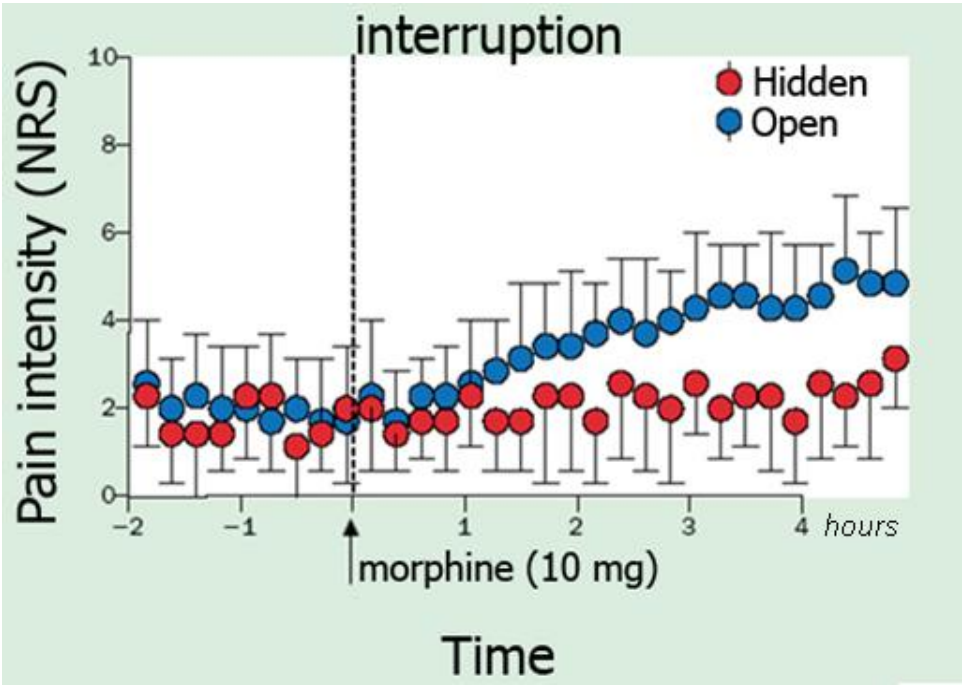
Varelmann et al., Anesth Analg 2010;110:868 –70

Hidden versus open interruption of medication
Contextual effects



Covert vs overt morphine *interruption*





Colloca L, et al. Lancet Neurol. 2004;679-84

Informing patients and clinicians about side effects

- ✓ In RCTs, treatment labels and advertisements can induce nocebo effects that influence patients clinical outcomes and treatment adherence

- ✓ A recently published large Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial showed that 10 mg open label *atorvastatin* and *placebo* induced an excess rate of muscle-related adverse events in the non-blinded non-randomized three year follow-up phase.

- ✓ During the initial five year blinded randomized phase with patients and physicians unaware of the adverse events via public claims did not have the large proportion of muscle-related adverse events that the effects are related to nocebo rather than the atorvastatin.

Gupta *et al.*, Lancet 389, 2473-2481 (2017).

JAMA The Journal of the American Medical Association

Nocebo Effects, Patient-Clinician Communication, and Therapeutic Outcomes

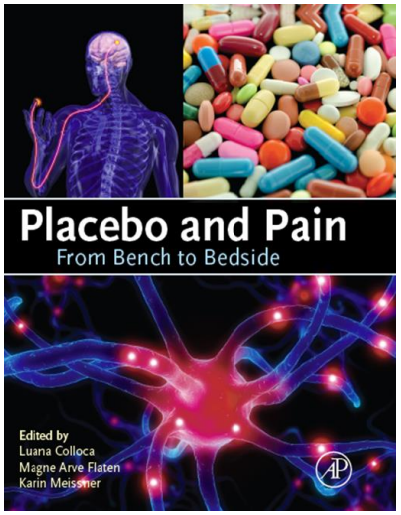
- ✓ Frame disclosures and informed consents to carefully to balance truthful information and expectancy empowerment
- ✓ Tailor the information delivery process to the needs of the patient and learn about her expectancies
- ✓ Educate health providers and patients about the potential role of endogenous systems in clinical encounters

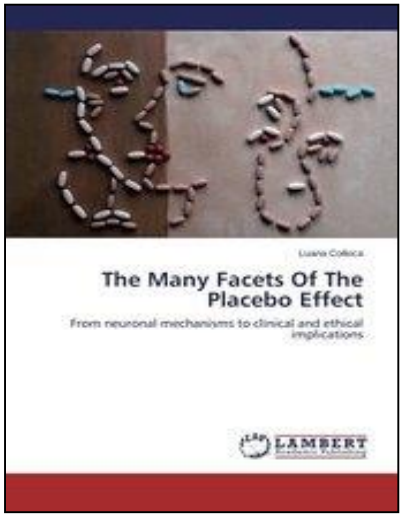
Colloca and Finniss, JAMA 2012:307(6):567-8

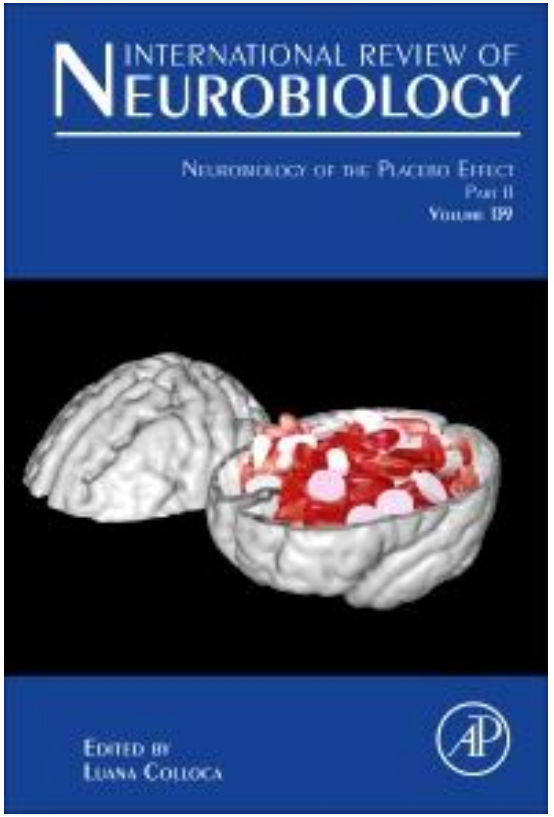
What we have learned…

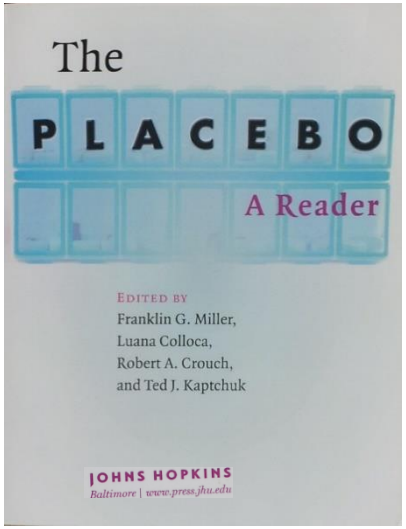
- ✓ Distinct learning mechanisms shape the formation of negative expectancies and nocebo effects
- ✓ Expectancies are dynamically updated contributing to the determination and magnitude of nocebo effects
- ✓ Nocebo research raises the attention to consider how to use doctor-patient communication to better handle unwanted side effects and negative prognoses in daily clinical practice and physiotherapy.

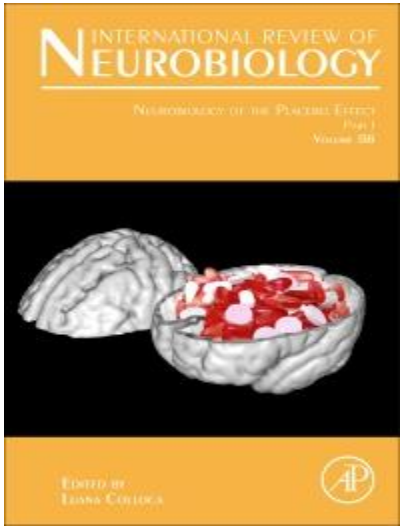
Educational tools











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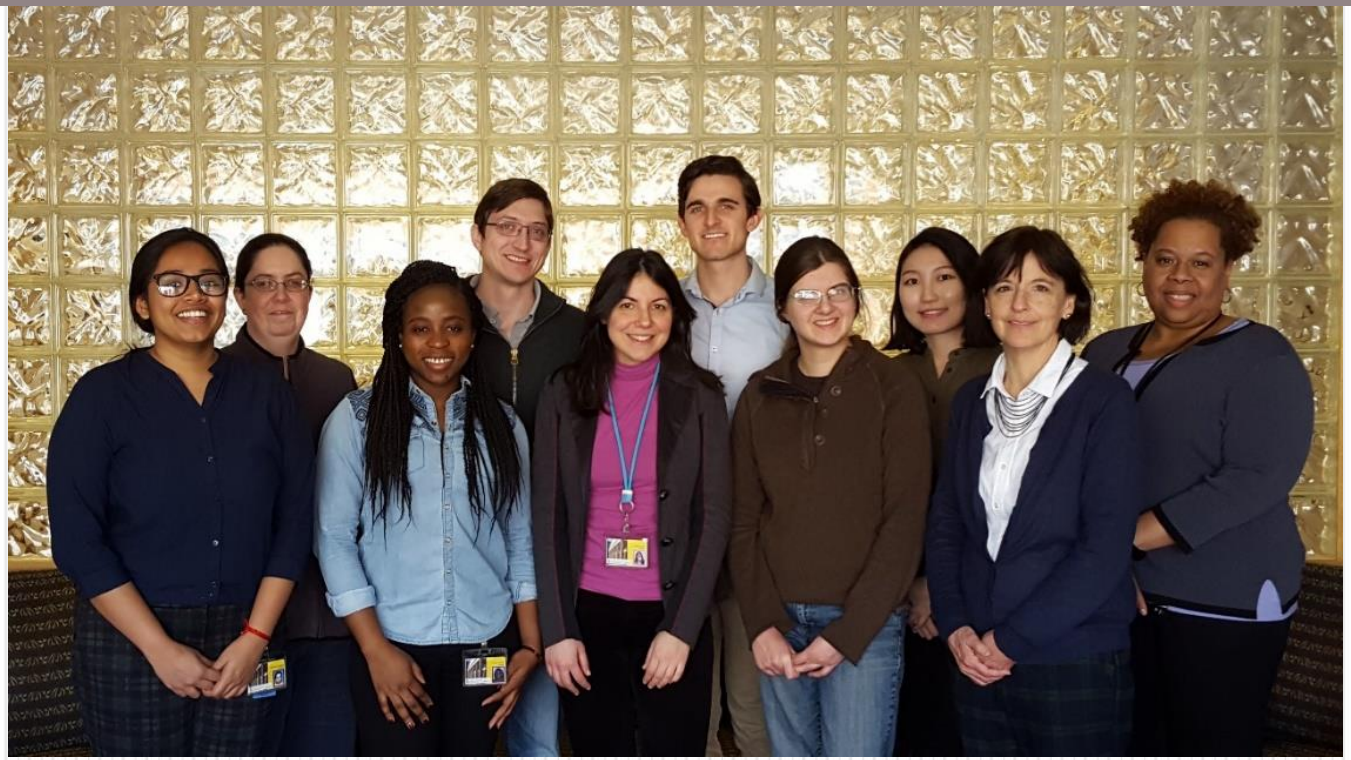

http://colloca.wixsite.com/colloca-lab/staff

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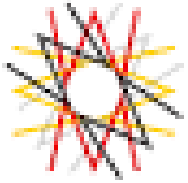

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