Introduction to Medical Psychology
Lecture 11: Placebo

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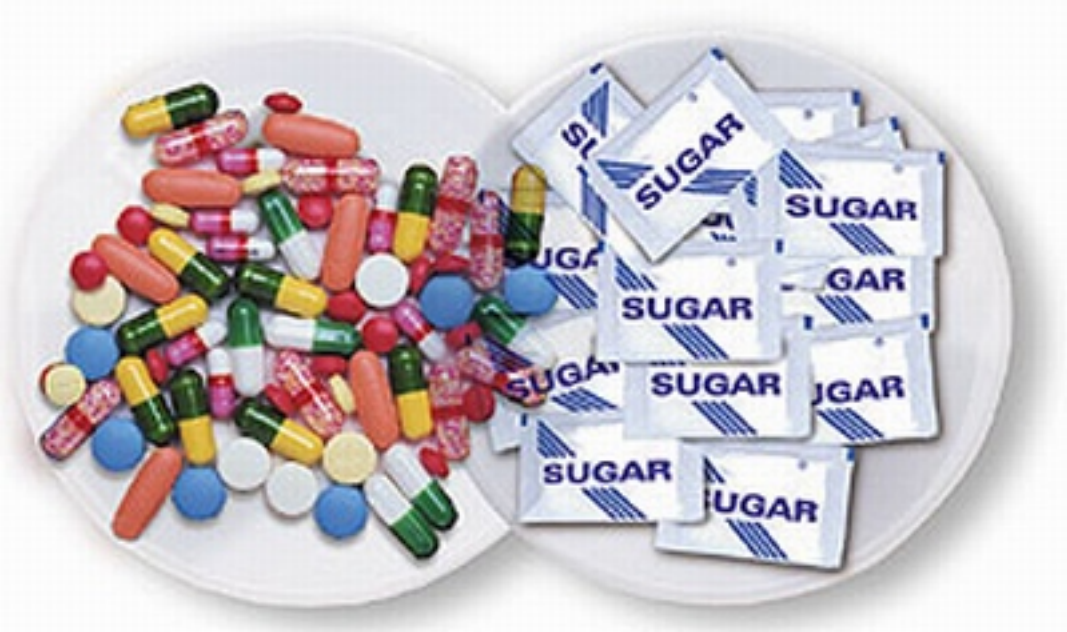
https://youtu.be/GXwYPd6cg9E

Lecture video at above link.

Today: Placebo! (and nocebo)

Placebo and Nocebo

- Definitions
- Examples
- Mechanisms



Before we start:
Do you know about placebo?

- What is the “placebo effect”?

- What is “nocebo”?

- Have you ever experienced a placebo effect or do you know examples?

Placebo / Nocebo

Placebo: “I shall please” (Latin), is a sham treatment or an inert substance (e.g., sugar pill or saline injection), that leads to a **placebo effect** → improvement of a symptom after placebo treatment.

Nocebo: “I shall harm” (Latin), is a sham treatment or an inert substance, that leads to a **noxious** effect. For example, adverse side effects after treatment with an inert substance.

Placebo Effect

Henry Beecher was a medic in World War II. When he ran out of morphine (pain killer), he injected saline solution instead but told the wounded soldiers that it was morphine.

To his surprise, 40% of the soldiers reported an improvement of their pain.

Importance for real drug/treatment trials: Why give drug if placebo works?

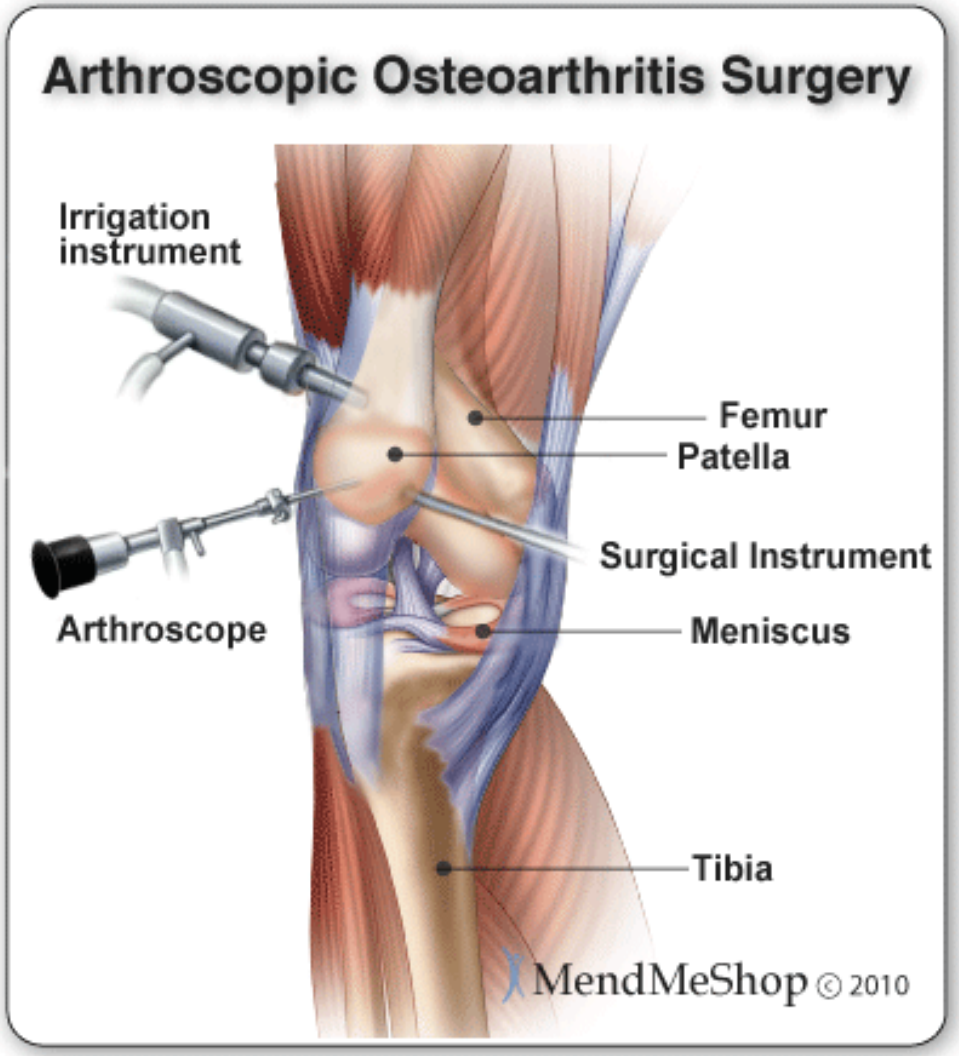
Osteoarthritis is a joint disorder with joint pain (e.g., knee pain) and stiffness.

Often, the reasons are not clear, MRI findings may sometimes be incidental.

In 1996, **arthroscopic surgery** was performed 650,000 times/year in the USA for the treatment of osteoarthritis.

Cost per operation: 5000$

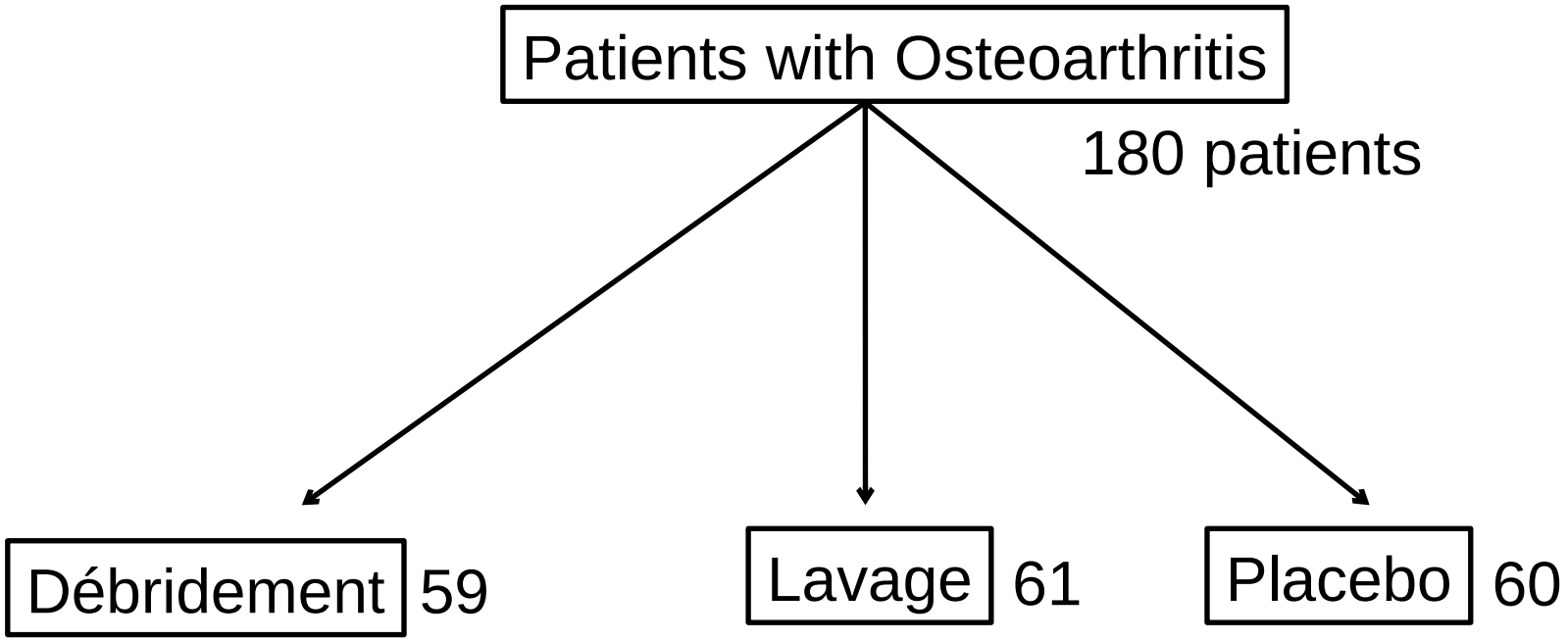
However, the benefits of this treatment were under debate.



To test the efficacy of arthroscopic surgery, Moseley et al. conducted a randomized controlled trial:

Randomized: assignment of patients to treatment and placebo arms was random.

Controlled: there was a control group, placebo surgery.



Moseley et al., New England Journal of Medicine, 2002

Randomized Controlled Trial: Arthroscopic Surgery

Outcome measure: pain symptoms were tested with a knee-specific pain scale:

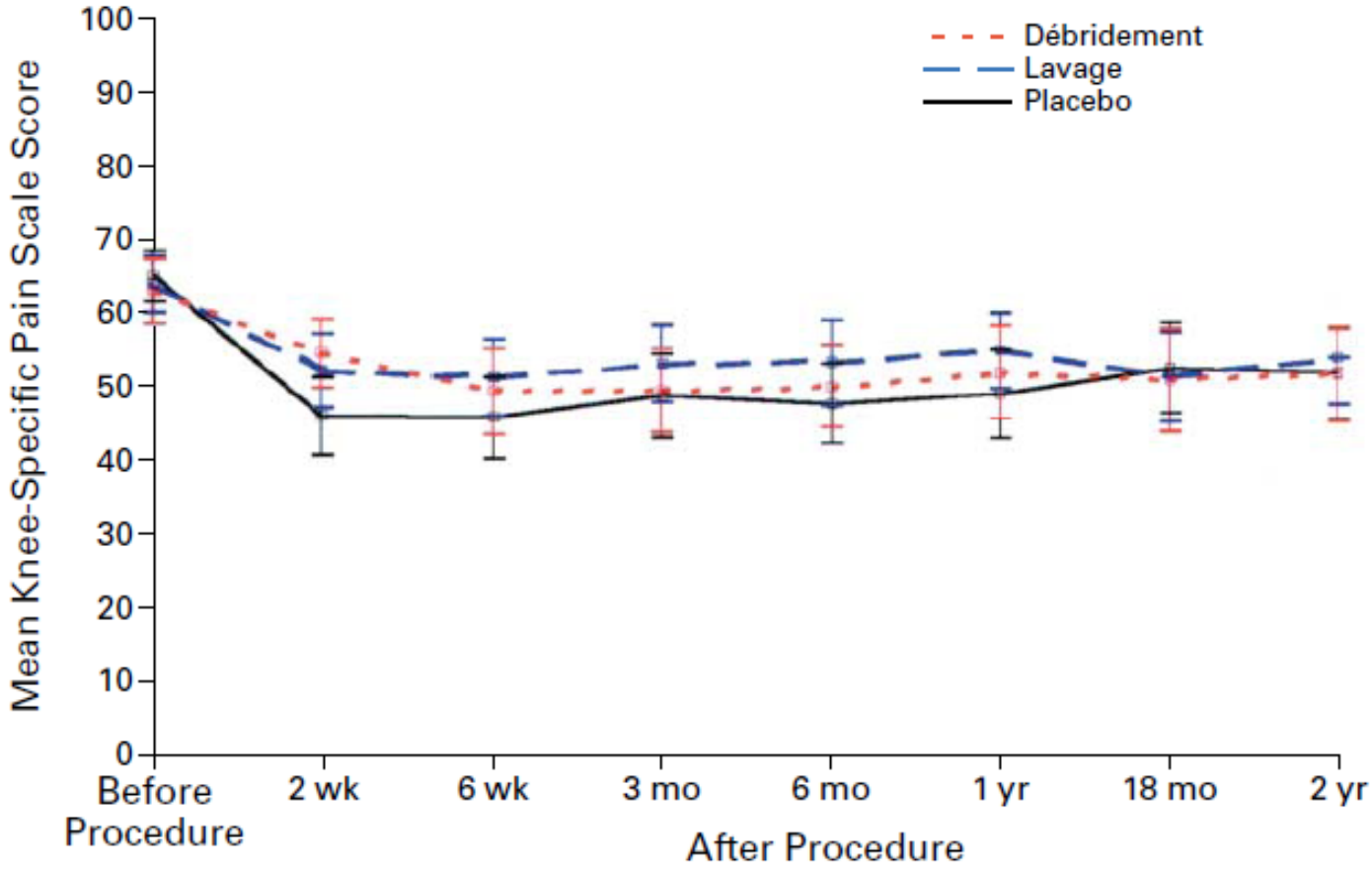
KNEE-SPECIFIC PAIN SCALE.*

ITEM	RANGE OF RESPONSES	MEANING OF RESPONSES
Pain magnitude		
Pain intensity		
1. How much pain are you currently having in your left/right knee?	1–7	Severe pain to no pain
2. At the present time (right now), how intense is your left/right knee pain?	0–10	No pain to bad as could be
3. In the past week, how intense was your worst left/right knee pain?	0–10	No pain to bad as could be
4. In the past week, on the average, how intense was your left/right knee pain?	0–10	No pain to bad as could be
Pain frequency		
5. On about how many days have you had knee pain in the past week in your left/right knee?	0–7	No days to all days
6. On days when you've had knee pain in the past week, how many hours were you usually in pain in your left/right knee?	0–24	No hours to all hours
7. On about how many days in the past week have you been kept from your usual activities (work, school, housework) because of the pain in your left/right knee?	0–7	No days to all days
Pain distastefulness		
8. Compared to other people your age, do you rate your situation regarding pain as . . .	1–5	Very poor to excellent
9. How satisfied are you with your current situation regarding pain?	1–5	Very satisfied to very dissatisfied
10. How pleased are you with your current situation regarding pain?	1–5	Very displeased to very pleased
11. How much of a problem do you have with pain because of your left/right knee?	1–6	None to very severe
12. In the past week, how unpleasant or distressing was your left/right knee pain?	1–10	No pain to bad as could be

*To calculate the total score, subtract the scores for items 1, 8, and 10 from the highest possible scores for those items +1 (to reverse the direction of scores, in keeping with the scores for the other items), rescale all items to a 0-to-10 scale, and add the scores for the items in each group (intensity, frequency, and distastefulness). Then average the scores for intensity and frequency to create the final pain-magnitude score, and average the sums of the pain-magnitude and pain-distastefulness scores to generate a total score. Each patient received a survey regarding his or her study knee; only the word "left" or "right" was included on each survey.

Moseley et al., New England Journal of Medicine, 2002

Randomized Controlled trial: Arthroscopic Surgery

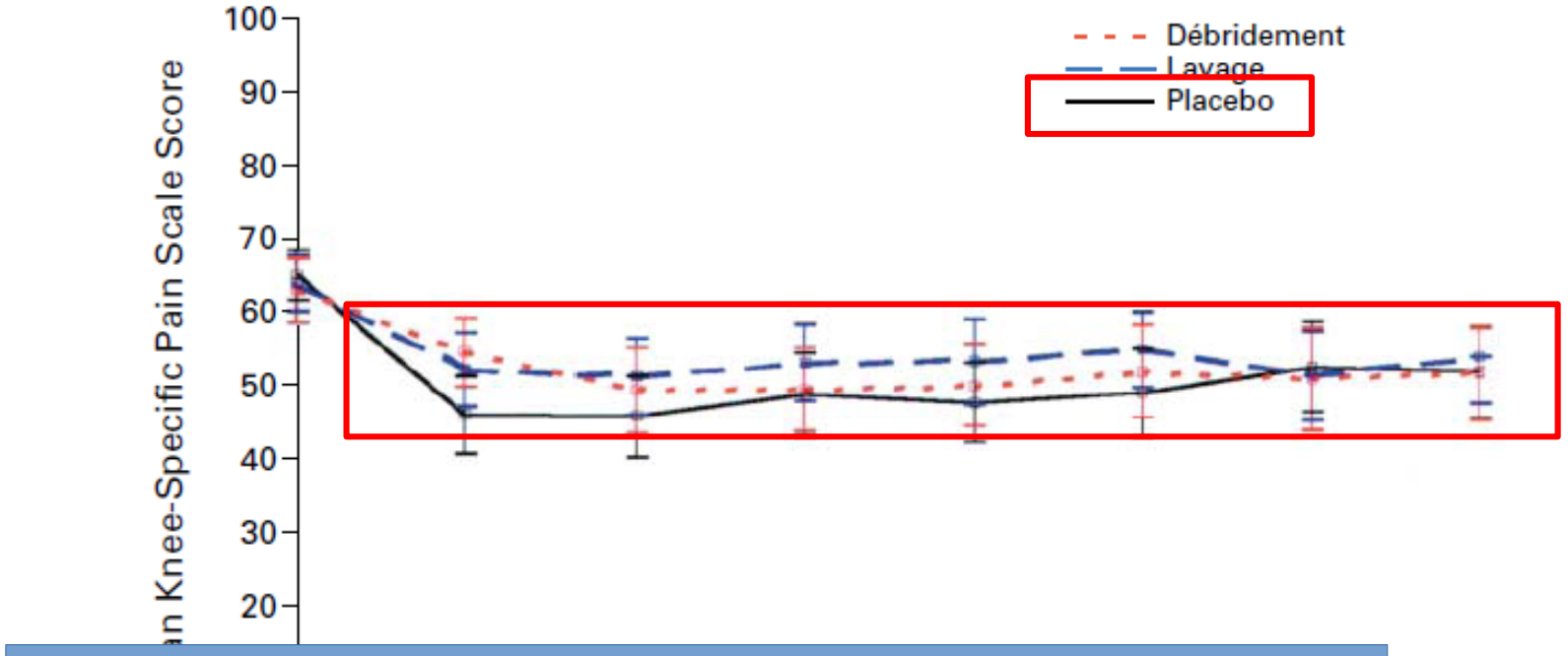


No. at Risk (number of patients)

Placebo	60	59	57	56	57	53	52	55
Lavage	61	59	57	59	59	57	56	55
Débridement	58	59	59	58	56	50	51	53

Figure 1. Mean Values (and 95 Percent Confidence Intervals) on the Knee-Specific Pain Scale. Assessments were made before the procedure and 2 weeks, 6 weeks, 3 months, 6 months, 12 months, 18 months, and 24 months after the procedure. Higher scores indicate more severe pain.

Randomized Controlled trial: Arthroscopic Surgery



Why do dangerous surgery if placebo works the same?

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Randomized Controlled trial: Arthroscopic surgery

At no point did either arthroscopic-intervention group have greater pain relief than the placebo group (Fig. 1, Table 2, and Supplementary Appendix 2). For example, there was no difference in knee pain between the placebo group and either the lavage group or the débridement group at one year (mean [±SD] KSPS scores, 48.9±21.9, 54.8±19.8, and 51.7±22.4, respectively; P=0.14 for the comparison with the lavage group, and P=0.51 for the comparison with the débridement group) or at two years (mean KSPS scores, 51.6±23.7, 53.7±23.7, and 51.4±23.2, respectively; P=0.64 and P=0.96, respectively). Similarly, there was no significant difference in arthritis pain between the placebo group and the lavage group or the débridement group at one or two years (Table 2).

Placebo Issues: Ethical Considerations

Placebo Procedure

To preserve blinding in the event that patients in the placebo group did not have total amnesia, a standard arthroscopic débridement procedure was simulated. After the knee was prepped and draped, three 1-cm incisions were made in the skin. The surgeon asked for all instruments and manipulated the knee as if arthroscopy were being performed. Saline was splashed to simulate the sounds of lavage. No instrument entered the portals for arthroscopy. The patient was kept in the operating room for the amount of time required for a débridement. Patients spent the night after the procedure in the hospital and were cared for by nurses who were unaware of the treatment-group assignment.

Postoperatively, there were two minor complications and no deaths. Incisional erythema developed in one patient, who was given antibiotics. In a second patient, calf swelling developed in the leg that had undergone surgery; venography was negative for thrombosis. In no case did a complication necessitate the breaking of the randomization code.

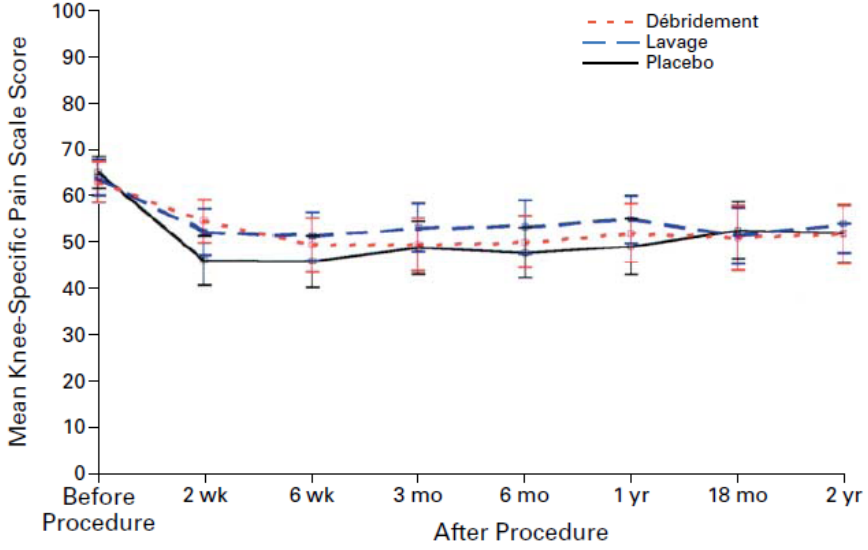
Postoperative care was delivered according to a protocol specifying that all patients should receive the same walking aids, graduated exercise program, and analgesics. The use of analgesics after surgery was monitored; during the two-year follow-up period, the amount used was similar in the three groups.

Moseley et al., New England Journal of Medicine, 2002

Randomized Control Trial: Arthroscopic Surgery

The study by Moseley et al.(2002) is an example of a placebo-controlled trial of a surgery technique:

- in this case there was no significant difference between surgeries and placebo.
- ethics committees will allow sham surgery (high risk of side effects/infections) only when there is considerable doubt in a method



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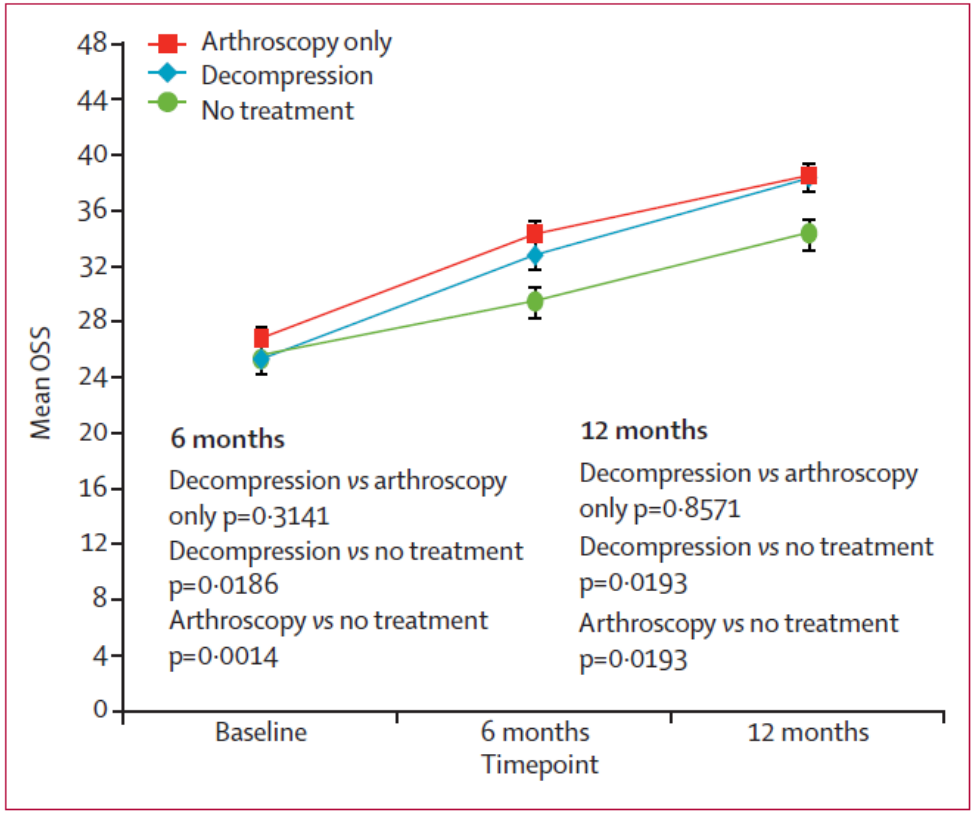
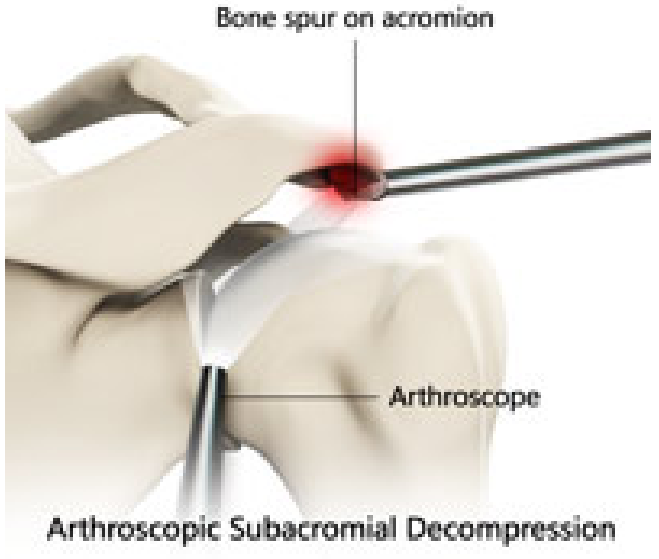
Another Example: Arthroscopic Surgery for shoulder pain

A recent study investigated subacromial (below an extension of the shoulder blade) decompression as a surgery to relieve subacromial shoulder pain.

Their results indicate that under the investigated conditions, the procedure had no benefit in comparison to arthroscopy only (placebo).





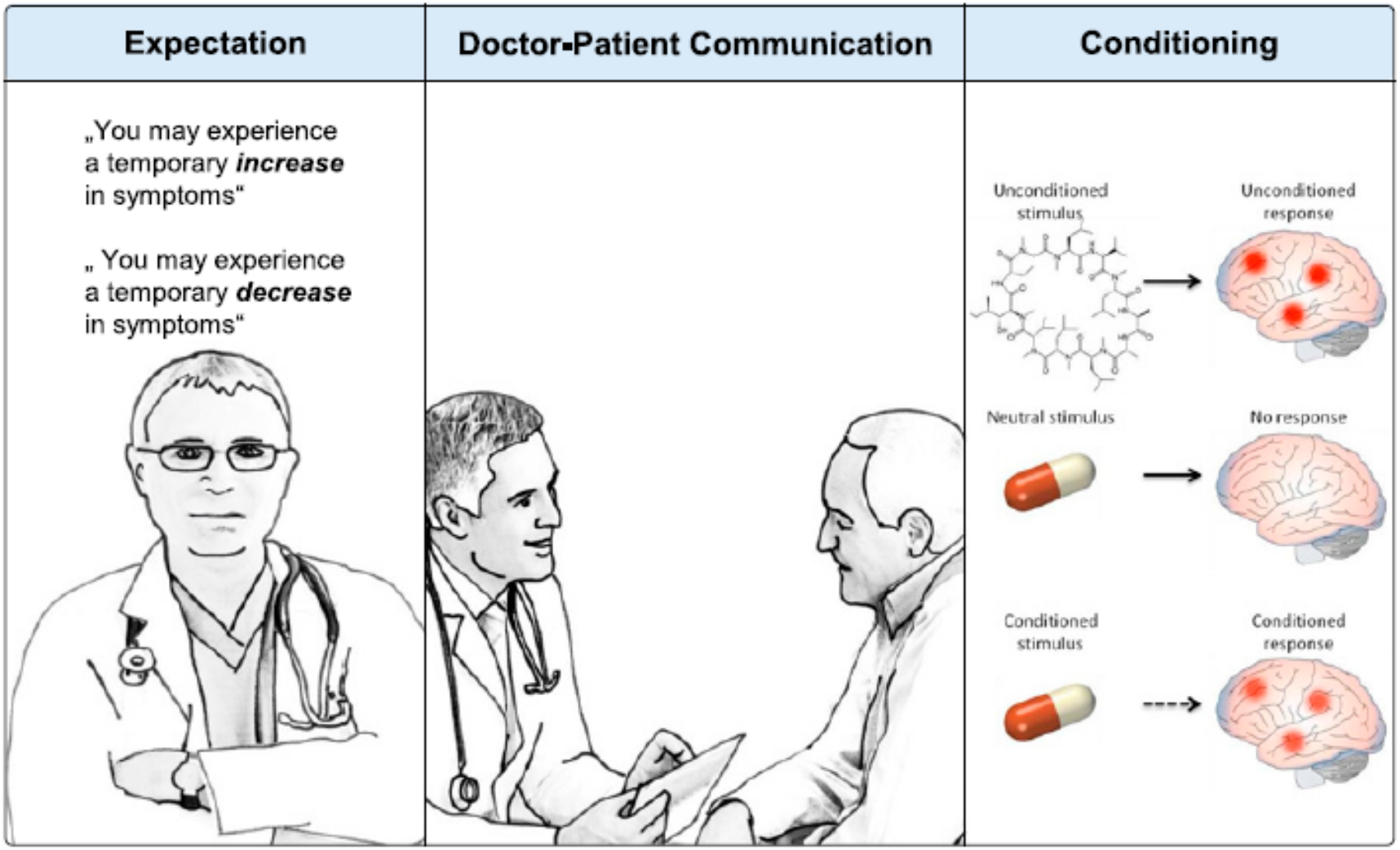
www.arthrohealth.com.au

N = 313 patients

OSS: Oxford shoulder score (higher scores indicate less pain and more functionality)

Beard et al., Lancet, 2017

Mechanism(s) of Placebo Effect



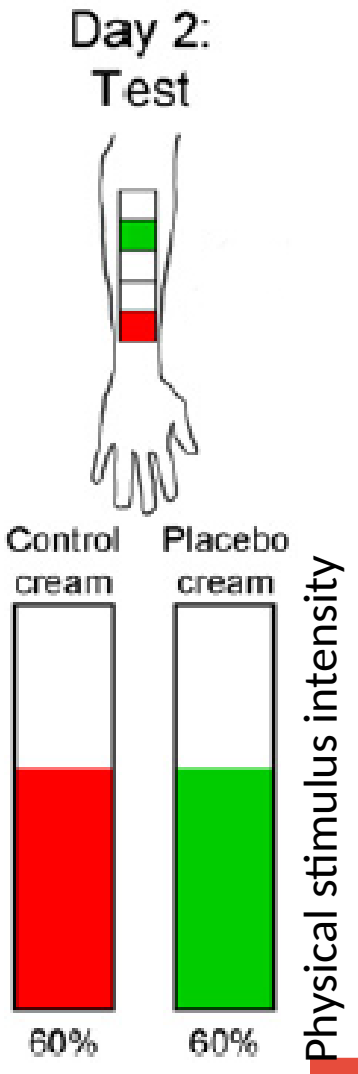
Schedlowski et al., Pharmacological Reviews, 2015

Placebo Example: Pain Suppression (Analgesia)

A placebo cream can decrease pain perception, for example in response to thermal stimulation -> placebo analgesia.

In the study by Eippert et al. (2009), participants were told that one patch of skin would receive a “highly effective pain killer” (placebo cream) and a control cream without effect. Indeed, both creams were the same.

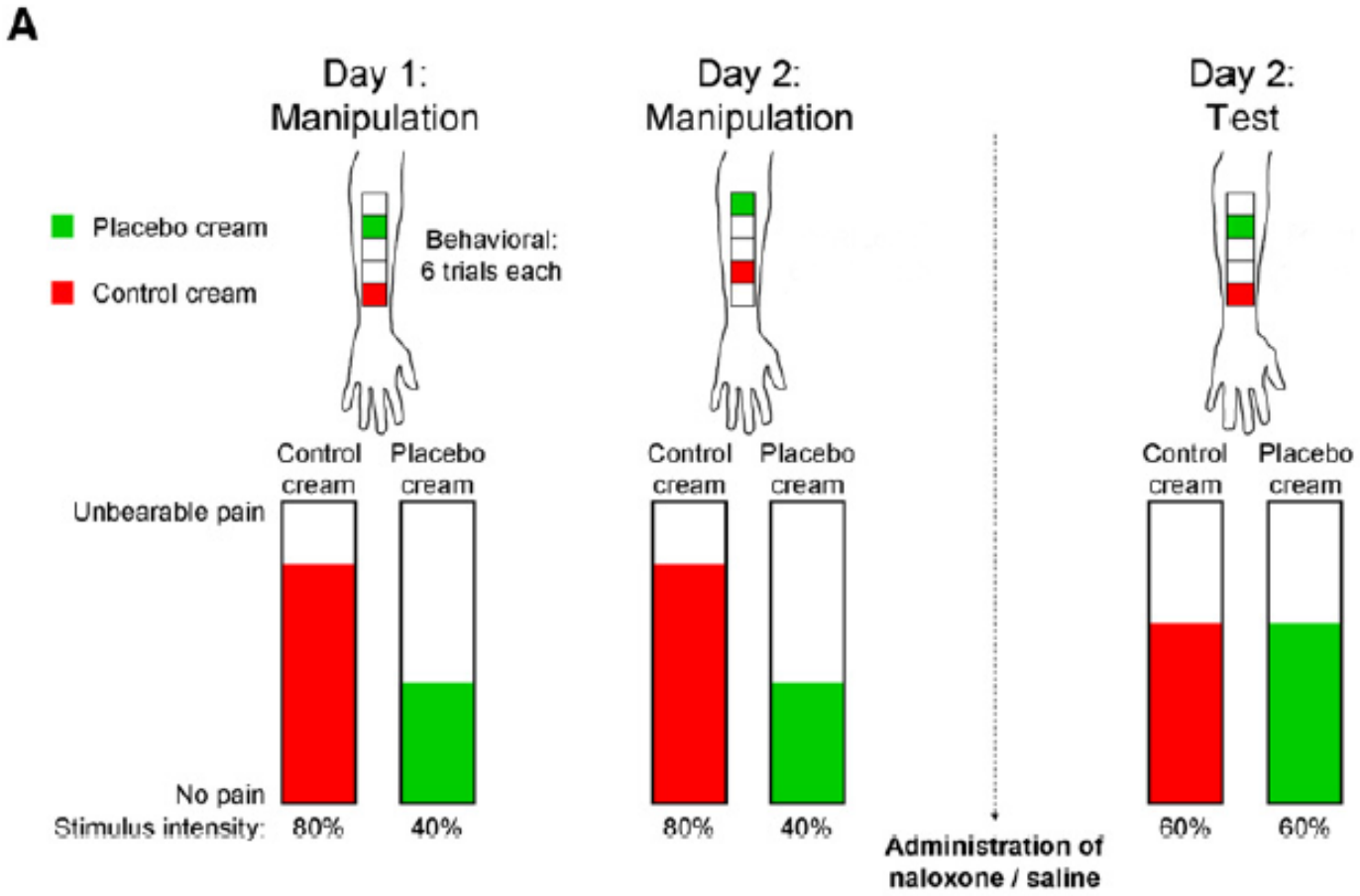
They then had to judge the pain on a visual analog scale (0%: nothing, 100%: unbearable pain).



Eippert et al., Neuron, 2009

Pain: Placebo analgesia

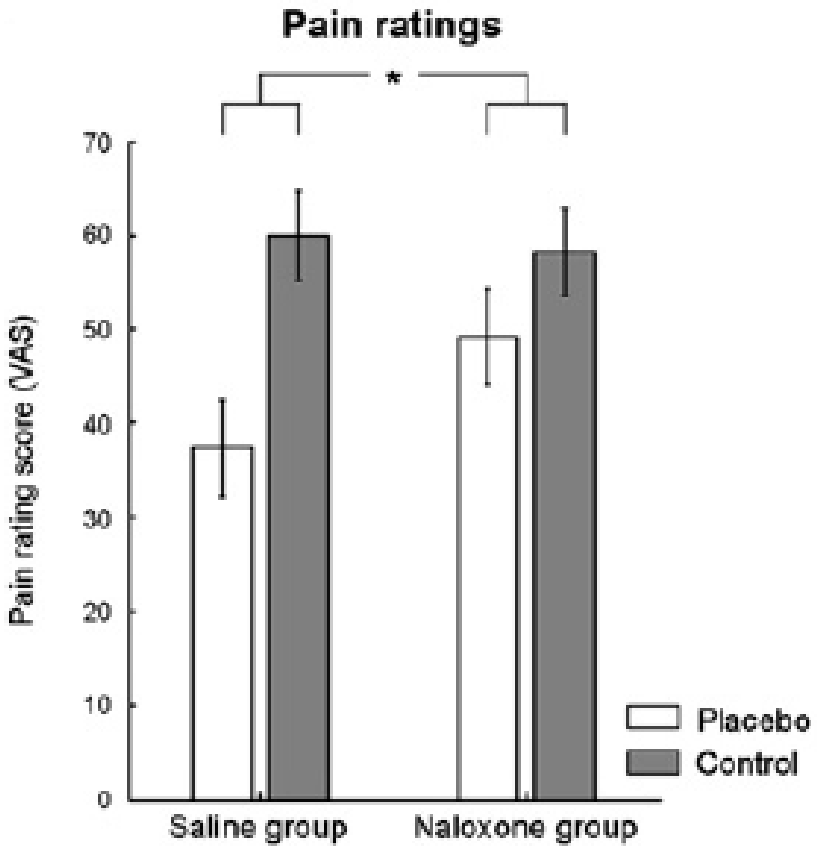
To strengthen the analgesic expectation for the placebo cream, the authors played a “trick” on the participants: on the days before, the same experiment was done, but the placebo cream was always paired with a less painful stimulus.

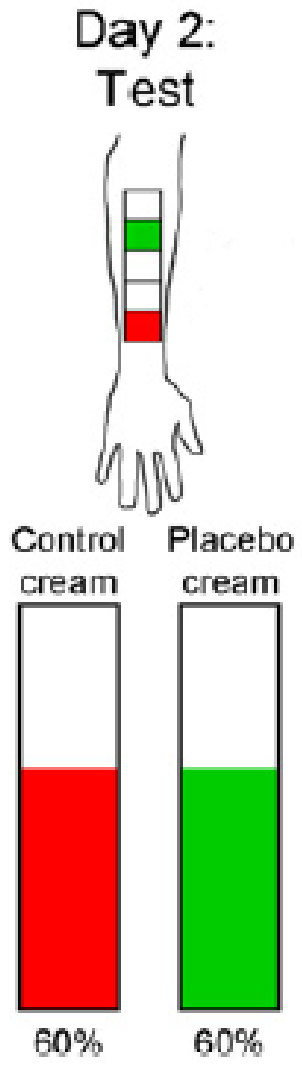


Eippert et al., Neuron, 2009

Pain: placebo analgesia

Pain ratings of thermal stimulation were much lower for the placebo (~37) compared to the control cream (~60), even though they were the same and during this test thermal stimulation intensities were the same.



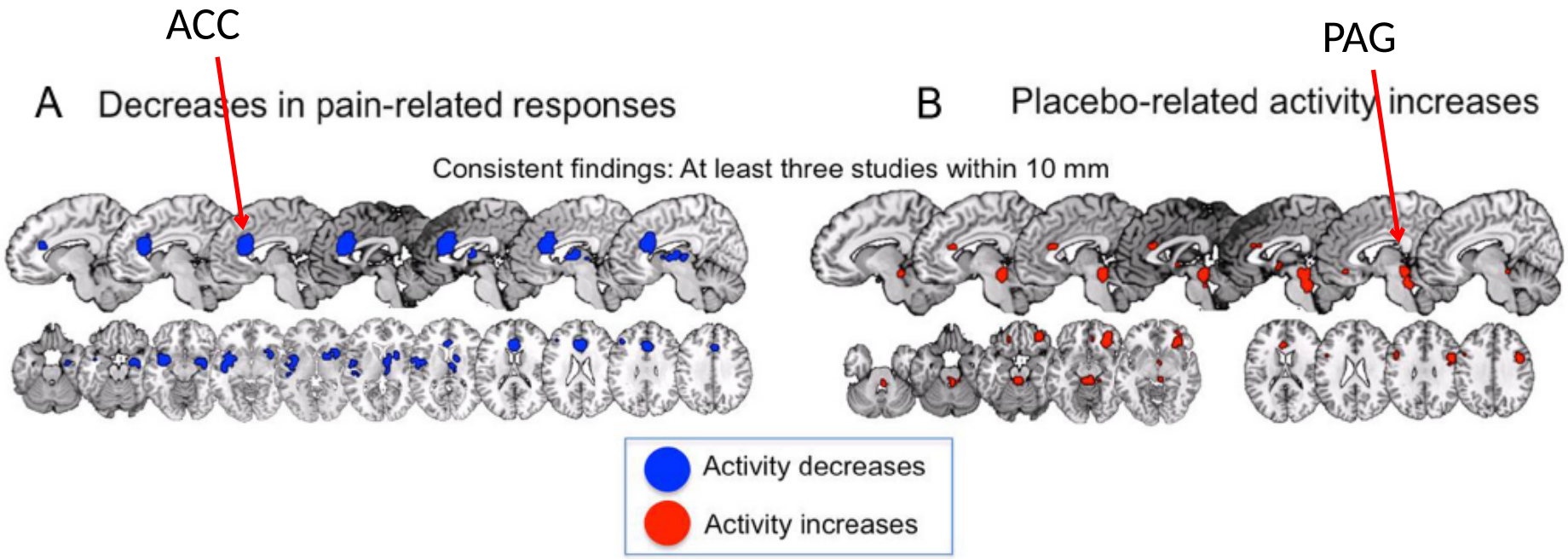


Eippert et al., Neuron, 2009

Pain: placebo analgesia

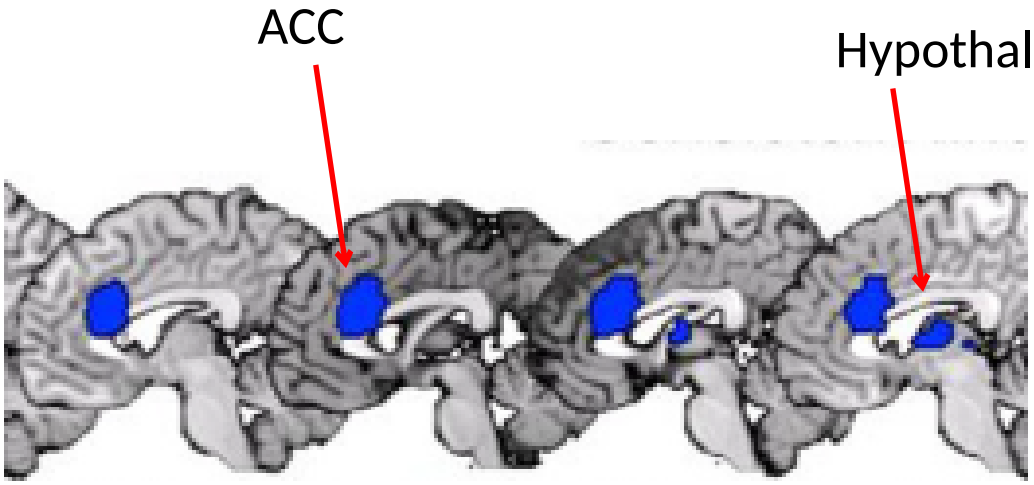
Neuroimaging studies on placebo analgesia show modulation of brain responses in particular in the anterior cingulate cortex (ACC) and the periaquaeductal gray (PAG).

Further areas involved include frontal regions, insula, hypothalamus and hippocampus. These neuroimaging studies induced placebo analgesia by placebo analgesic creams, sham acupuncture, etc.



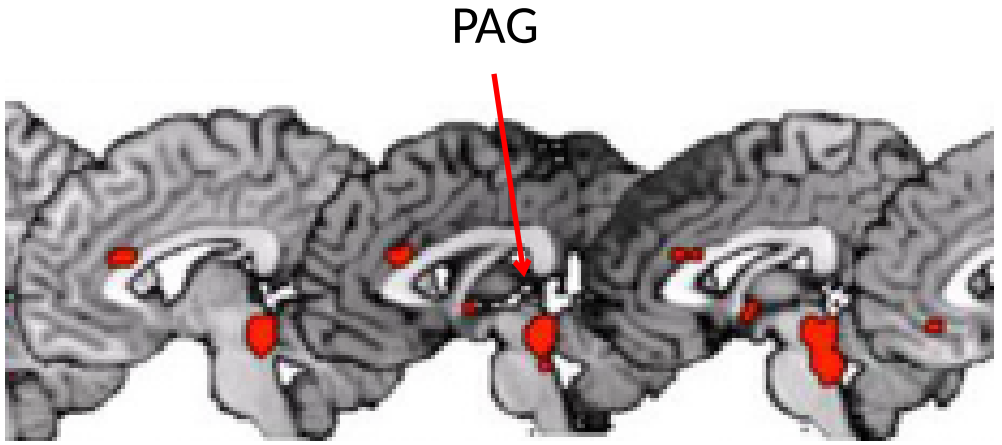
after Wager and Fields, 2011

Pain: placebo analgesia



Blue areas show decreased responses during pain stimulation when a placebo is given.

Red areas show increases related to placebo during anticipation or pain.



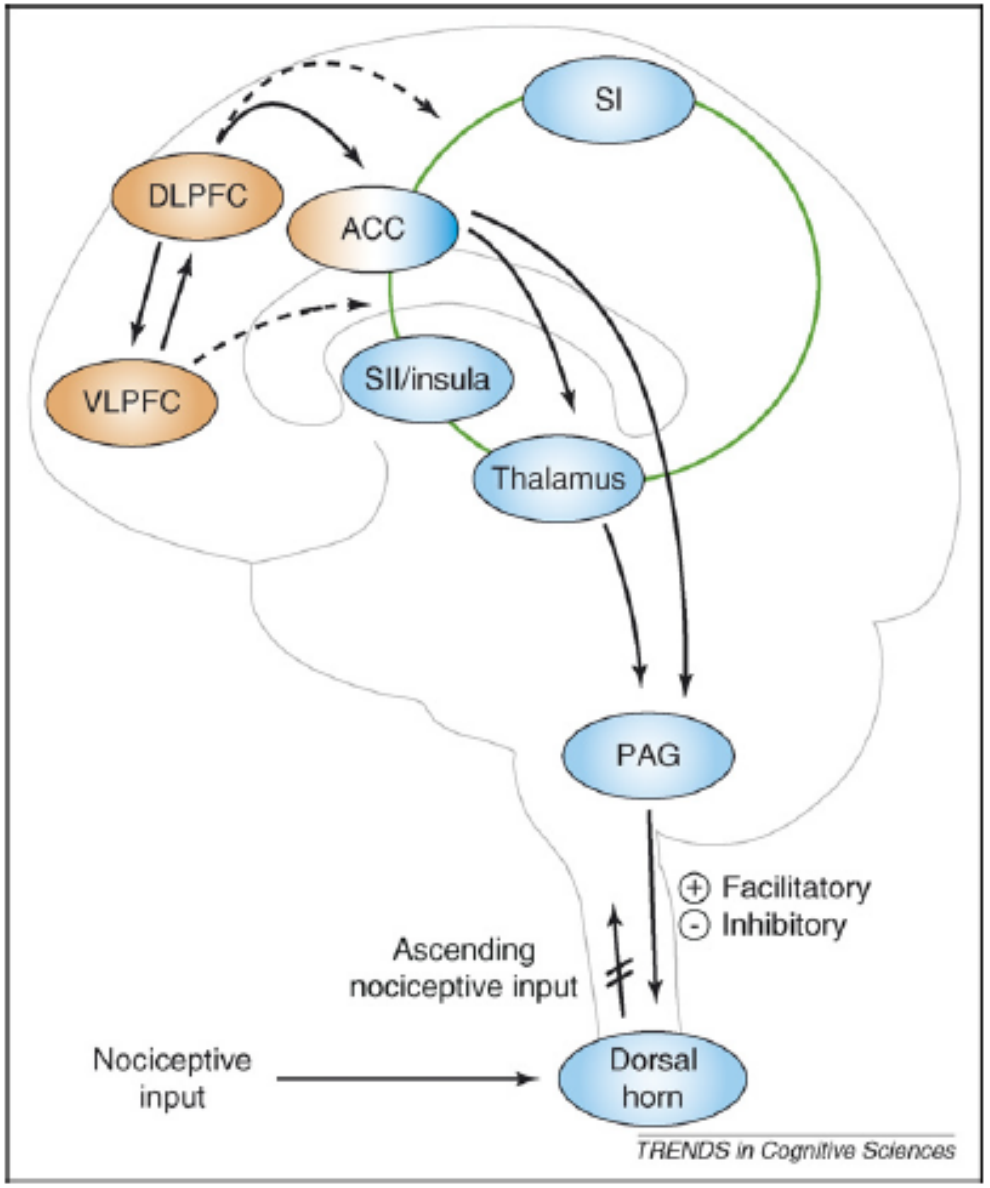
after Wager and Fields, 2011

Cortical control of pain perception

Remember what we learned in class 9 (chronic pain):

Somatosensory cortex (SI, SII), anterior cingulate cortex (ACC), and insula are modulated by prefrontal areas, and in turn modulate ascending pain perception via the PAG (periaquaeductal gray).

The PAG contains opioid receptors and modulates ascending pain input.



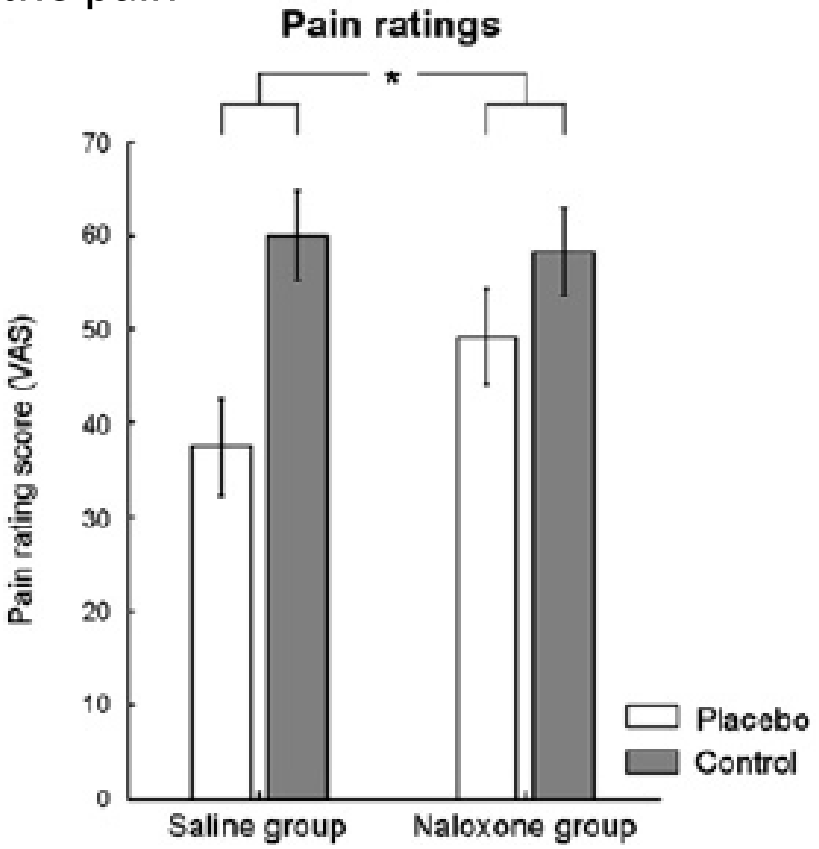
Wiech et al., TICS, 2008

Placebo analgesia and opiod neurotransmitter system

Eippert et al. (2009) had two experimental groups: in the saline group participants were injected with saline, in the naloxone group participants were injected with naloxone before the pain stimulation.

Naloxone inhibits the effect of opioids. The placebo effect (difference between placebo and control) was much smaller in the naloxone group.

This suggests that placebo analgesia is mediated at least in part by the opioidergic descending control system (the system that controls pain perception using opioids as transmitters).

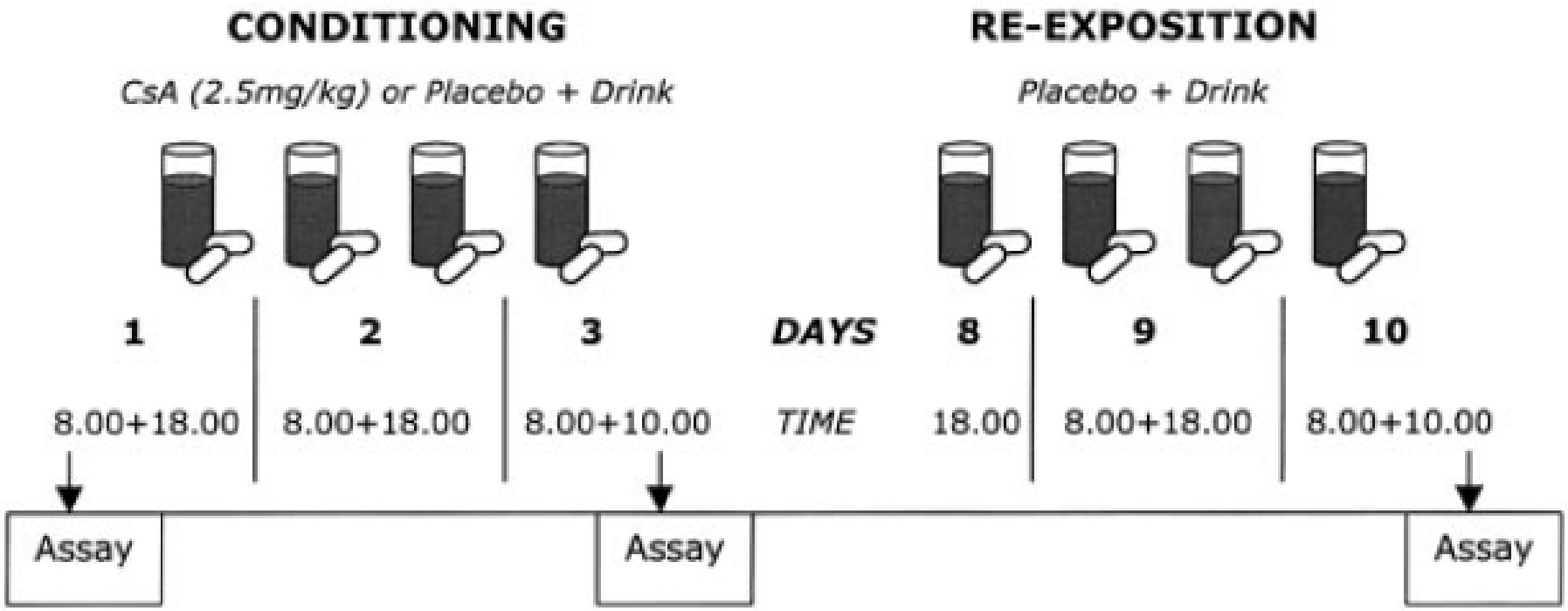


Eippert et al., Neuron, 2009

Placebo effects on immune system

Goebel et al. (2002) were able to condition immune responses in humans:
During conditioning they paired the immunosuppressive drug cyclosporine A (CsA) as unconditioned stimulus (US) with a distinctively flavored drink as conditioned stimulus (CS).

Later, during re-exposition they tested immune function after taking a placebo pill + drink.



Goebel et al., FASEB J, 2002

Placebo effects on immune system

As immune markers they looked at production of the cytokines

interleukin-2 (IL-2) and

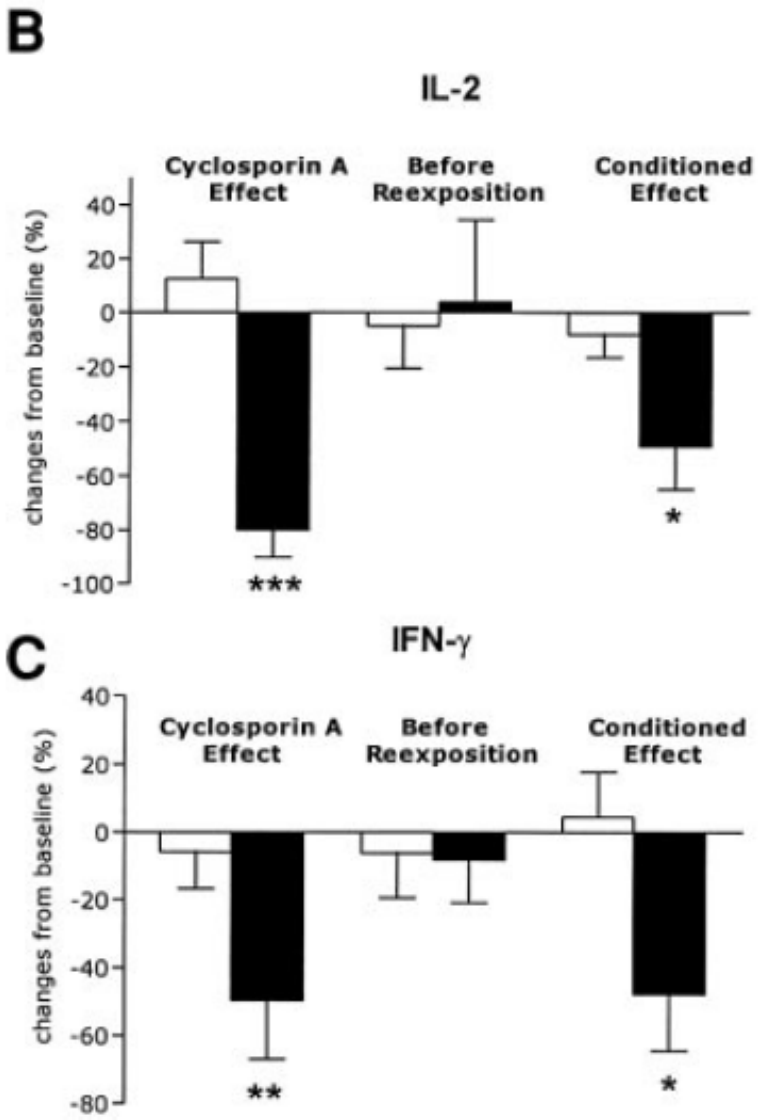
interferon-gamma (IFN-γ),

important for signaling in the immune system.

The placebo group (white bars) showed no reduction of immune markers at any time (they always got the placebo).

The conditioned group (black bars) showed a reduction of immune markers when they got the immunosuppressive drug, but also exhibited a conditioned effect when taking placebo+drink.

Figure: Cyclosporin A Effect = day 3,
Before reexposition = day 8,
Conditioned effect = day 10



Goebel et al., FASEB J, 2002

Mechanisms of placebo effect

1) **Expectations**
   Expectations can be shaped by doctors, our experience, the media, and people and the context around us. It is not necessary to have experienced the drug effect.

2) **Doctor-patient communication**
   Good doctor-patient communication improves therapeutic efficacy, possibly due to reduced fear, positive emotions, feeling of being socially supported, and the feeling of being in control (being able to make important health decisions).
   However, our health system is not well equipped for good communication: 50% of patients say they haven't fully understood the doctor's explanation, an interruption occurs on average after around 23 sec (USA; Bodenheimer, 2008).

3) **Conditioning**
   For conditioning to occur, we have to experience the initial drug effect. Extinction (loss of conditioned response) occurs after repeated exposure to inert substance. Conditioning can override our beliefs: even if we know we take a placebo pill it can have an effect.

Nocebo

In 2007, clinical researchers reported the case of Derek Adams (26) who participated in a clinical trial for antidepressants.

After his girlfriend split up with him, he swallowed 29 pills of the “antidepressant” and was taken to hospital because of poisoning symptoms and a sudden fall in blood pressure.

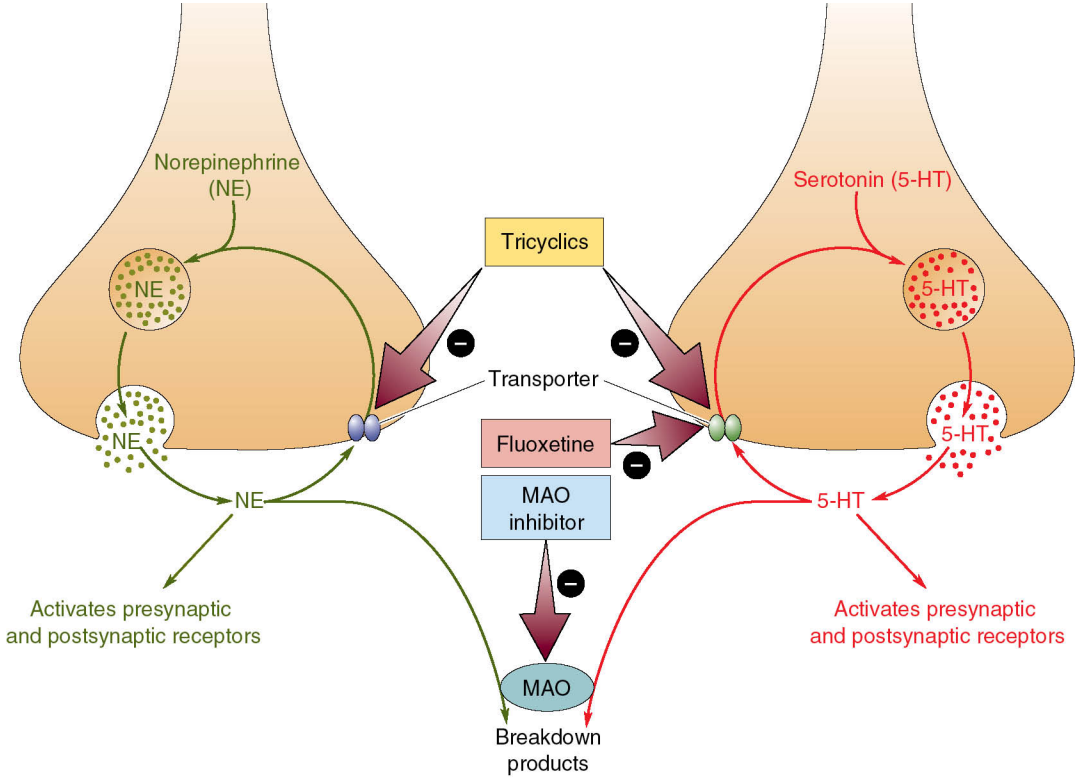
It turned out that he was in the “placebo arm”: he did not receive the antidepressant, but rather a placebo.

After this became clear to him, he recovered within minutes.

Nocebo

Rief et al. (Drug Safety, 2009) analyzed the placebo arms of several randomized clinical trials in terms of side effects to tricyclic and SSRI (e.g., Fluoxetine) antidepressants.

Synaptic mechanism of antidepressants

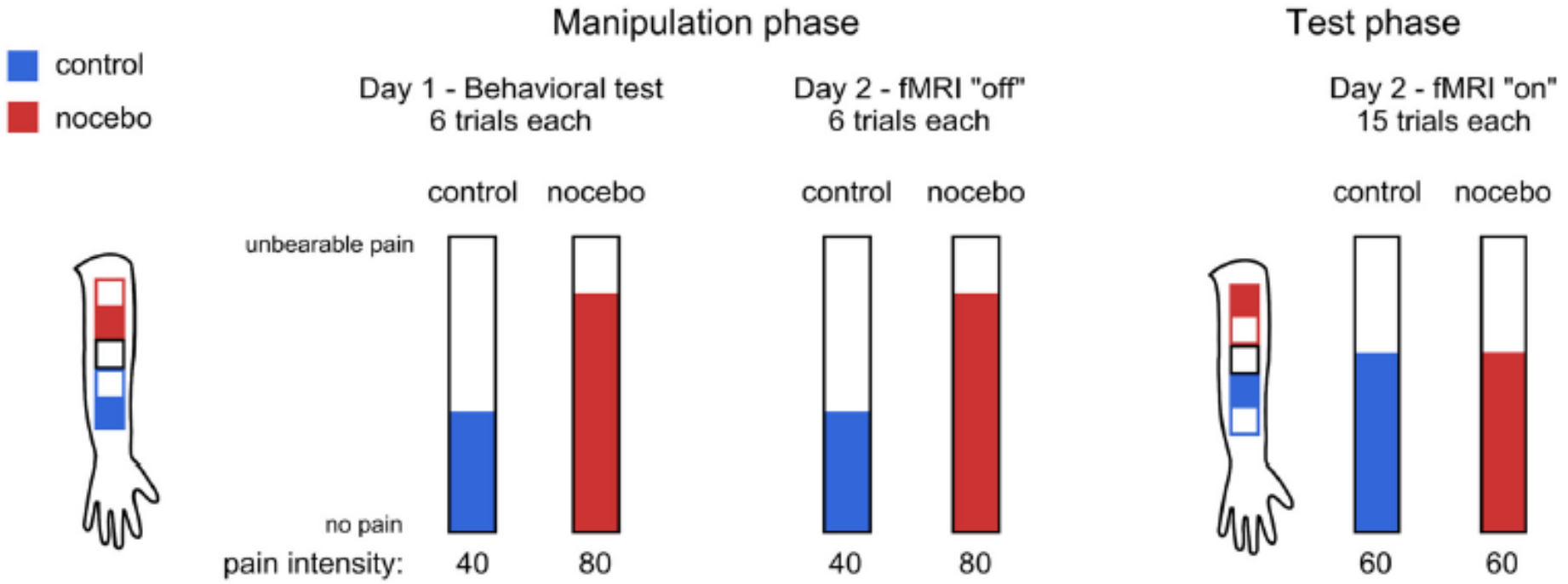


Expected side effects are much more severe for tricyclics (dry mouth, constipation, drowsiness, sexual problems) than for SSRI antidepressants.

Even in the placebo arms of these studies, reported side effects were more severe for the tricyclics and according to the expected side effects.

Nocebo: mechanism

Using a similar paradigm as Eippert et al. (2009), Geuter and Büchel (2013) could induce a nocebo effect by telling participants that a nocebo cream would increase their pain.

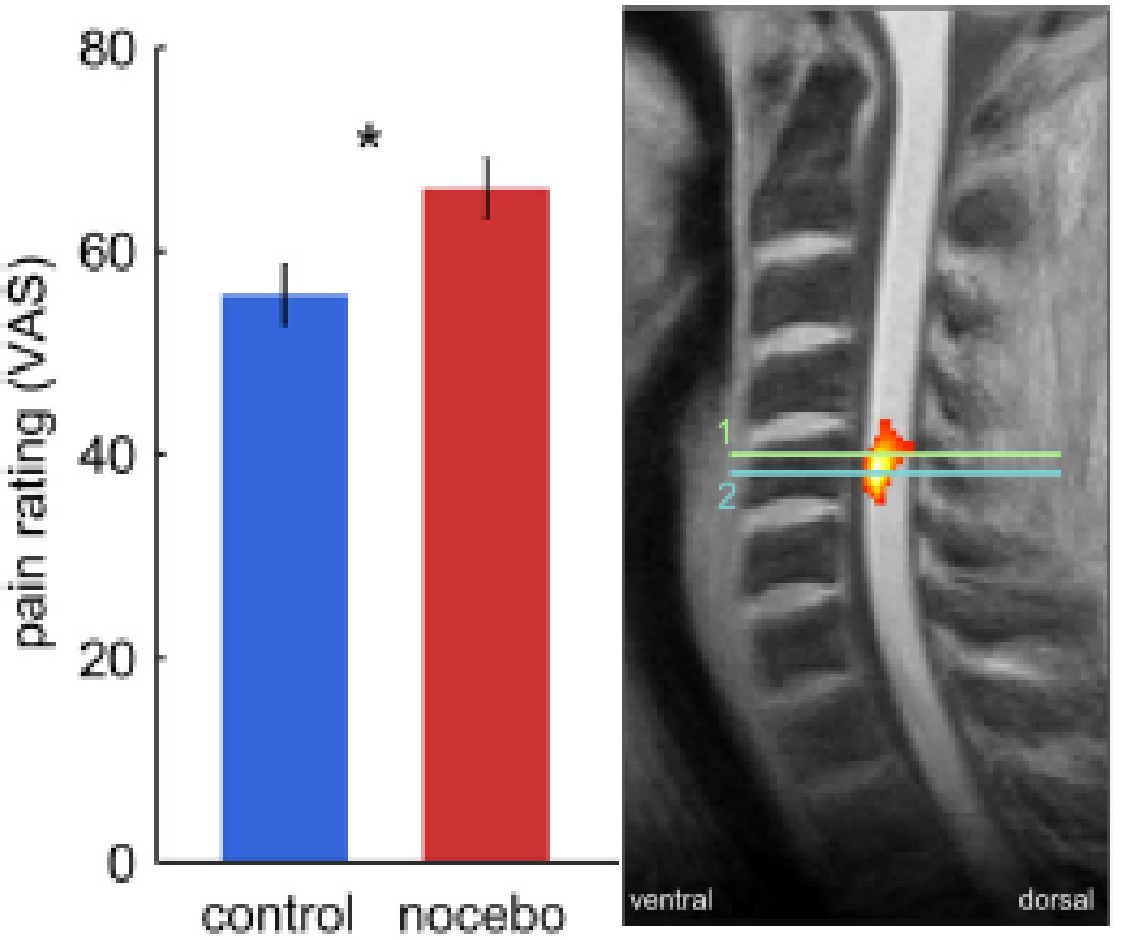


Geuter and Büchel, J Neuroscience, 2013

Nocebo: mechanism

In addition to increased pain ratings for thermal stimulation, enhanced neural activity for nocebo compared to control was observed at the level of the spinal cord, at the segments that innervate the arm.

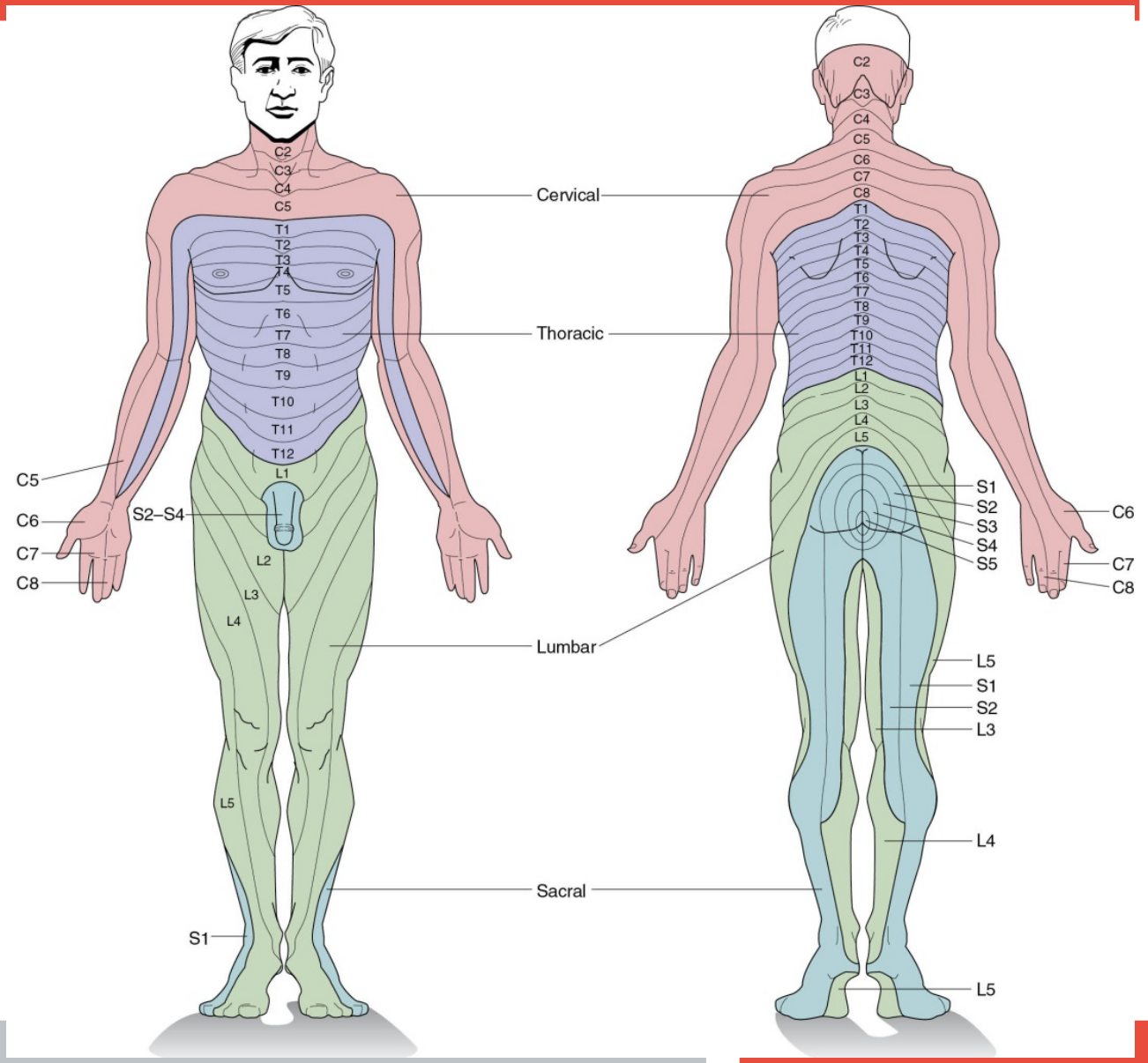
This suggests modulation of pain transmission by negative expectation at a very early stage, namely the spinal cord.



Geuter and Büchel, J Neuroscience, 2013

Nocebo: mechanism

The observed enhanced neural activity for nocebo was observed at segments C5/C6 (see figure).



Bear, Neuroscience

Summary: Placebo / Nocebo

Placebo and Nocebo

Definitions: placebo is a sham treatment or inert substance that can lead to symptom improvements; nocebo is a sham treatment or inert substance that can lead to harmful effects.

Examples: the placebo effect has been observed for example in the case of pain reduction and the immune response (others examples are: Parkinson's disease, anxiolytic and antidepressant effects).

Mechanisms: the placebo effect is mediated via expectations, quality of doctor-patient communication, and conditioning.