



# Placebo (and nocebo) in <sup>acute</sup> pain



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# The King's touch







*METALLIC-TRACTORS.*

# Elisha Perkins

- Rare metal alloy
- “draw off the noxious electrical fluid that lay at the root of suffering”
- Wood as good
- ‘Power of the imagination’

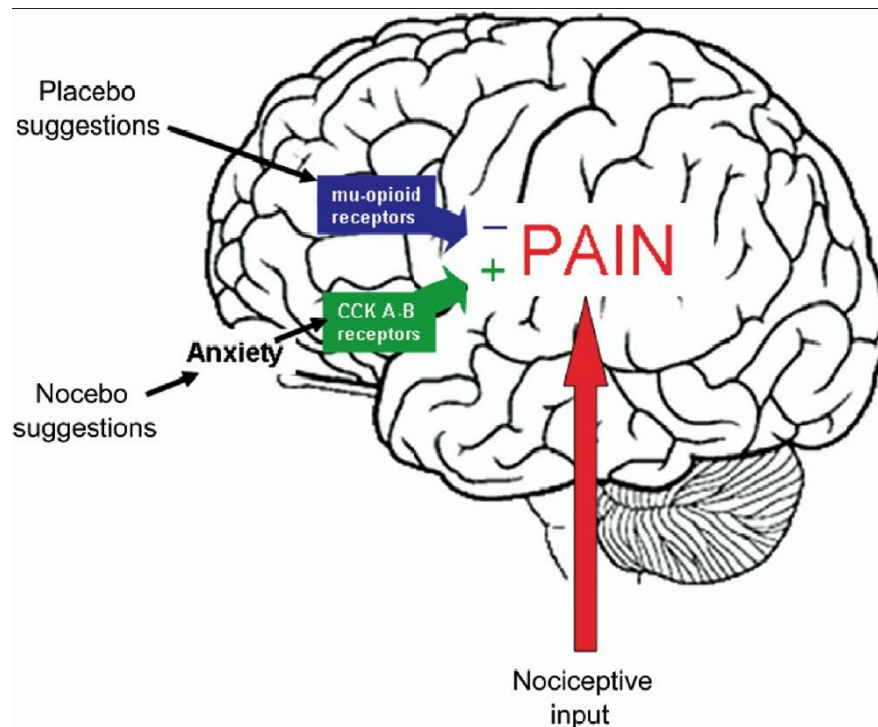


# Placebo in war

- Beecher noted the relative lack of soldiers asking for analgesia in WWII compared to civilians with similar injuries (25% vs 80%)
- Soldier
  - leaving war zone alive, repatriation
- Civilian
  - social and financial
- “The powerful placebo”



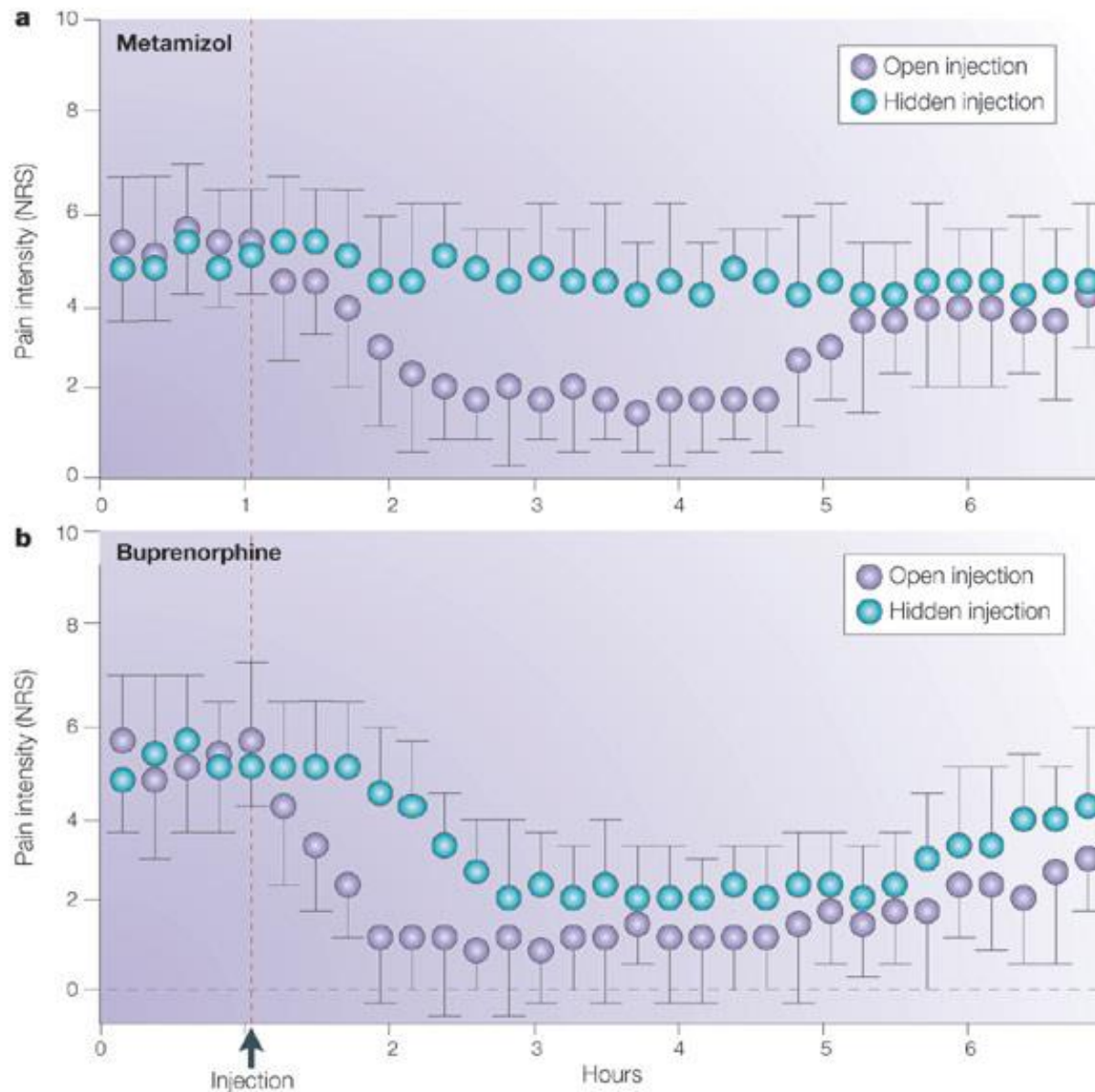
Beecher 1955,1956



Best evidence is for pain

Cochrane Database Syst Rev. 2010 Jan 20;(1):CD003974.  
Placebo interventions for all clinical conditions.  
Hrobjartsson and Getzache





# Placebo effect on OA

- Change in baseline in placebo group
- Change in baseline in no treatment group
- Placebo worked, effect size 0.5 (0.03 no Rx)
- Better in
  - Larger trials
  - Better active group
  - Needle/injection placebo

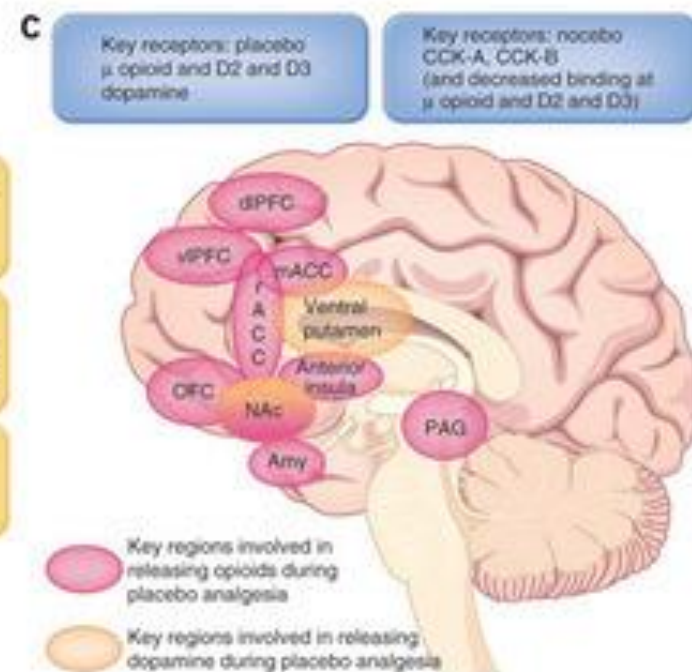
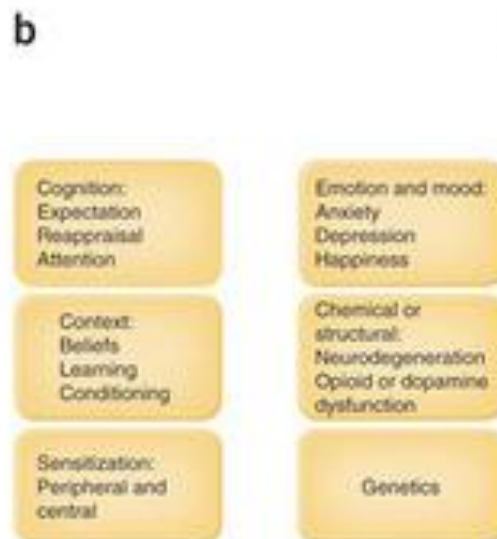
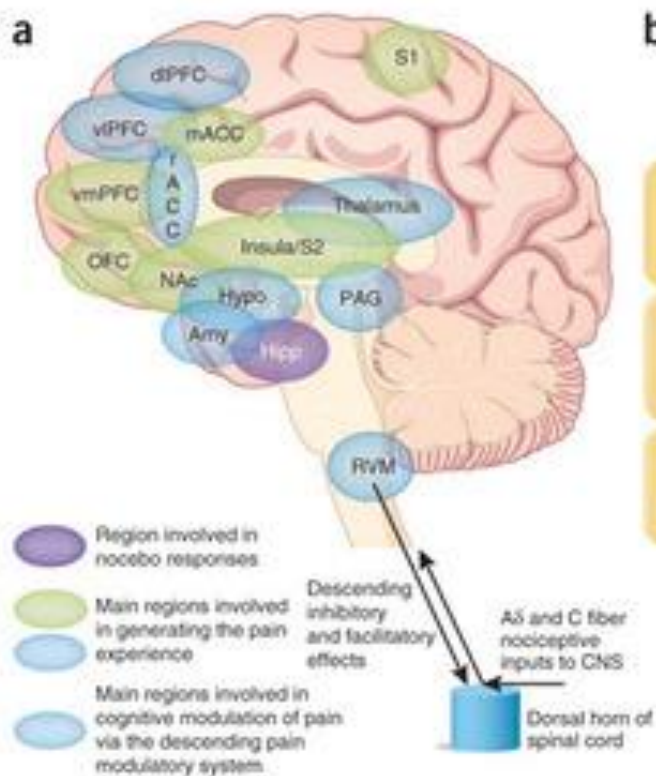
Zhang et al 2008

Effect size for opioids in non cancer chronic pain  
 $\leq 0.5$



# Placebo involves Giving





**Placebo**  
μ opioid receptor  
D2/D3 receptors

Tr

**Nocebo**  
CCK-A/CCK-B



# Maximise placebo effect?

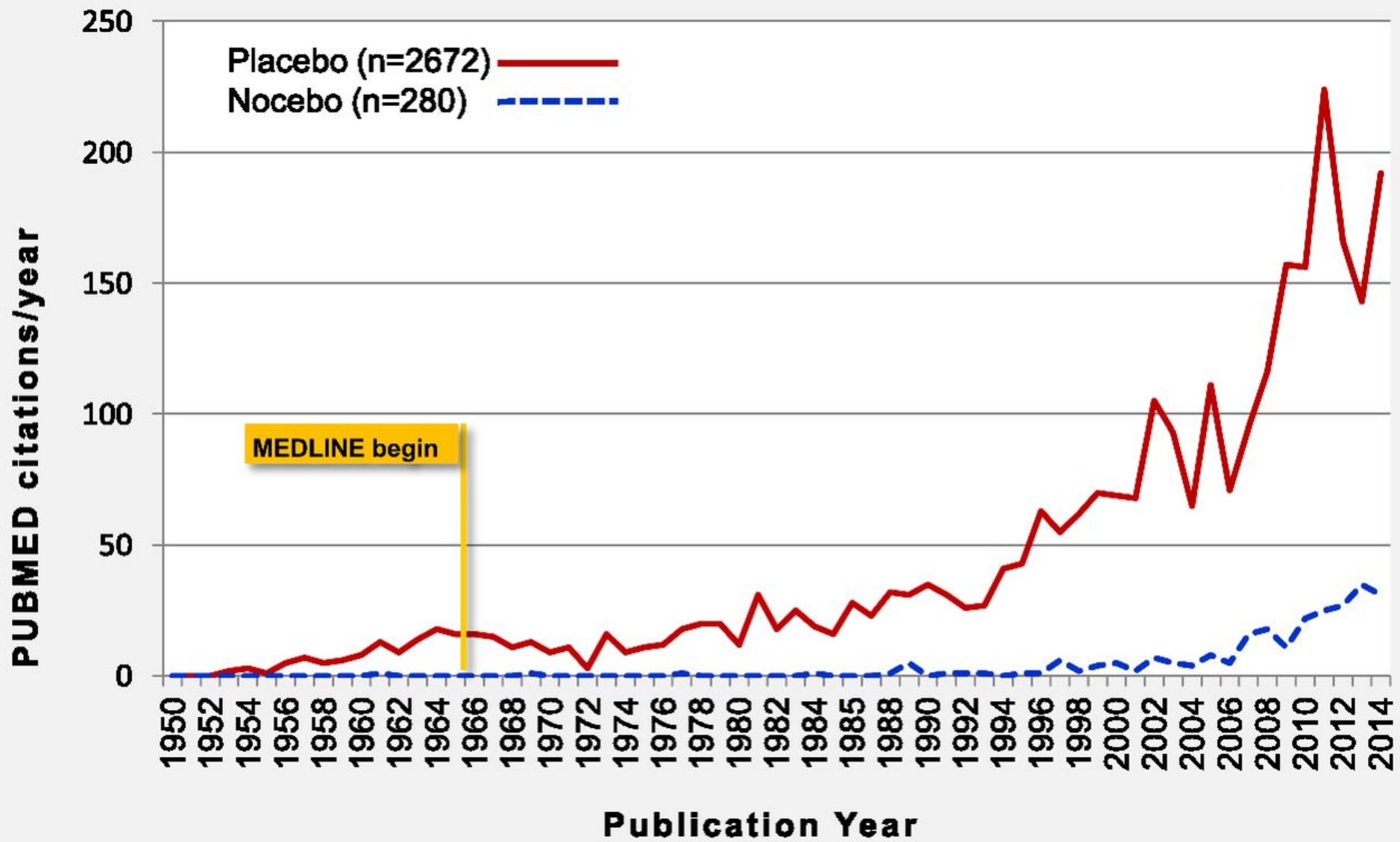


# **Nocebo :**

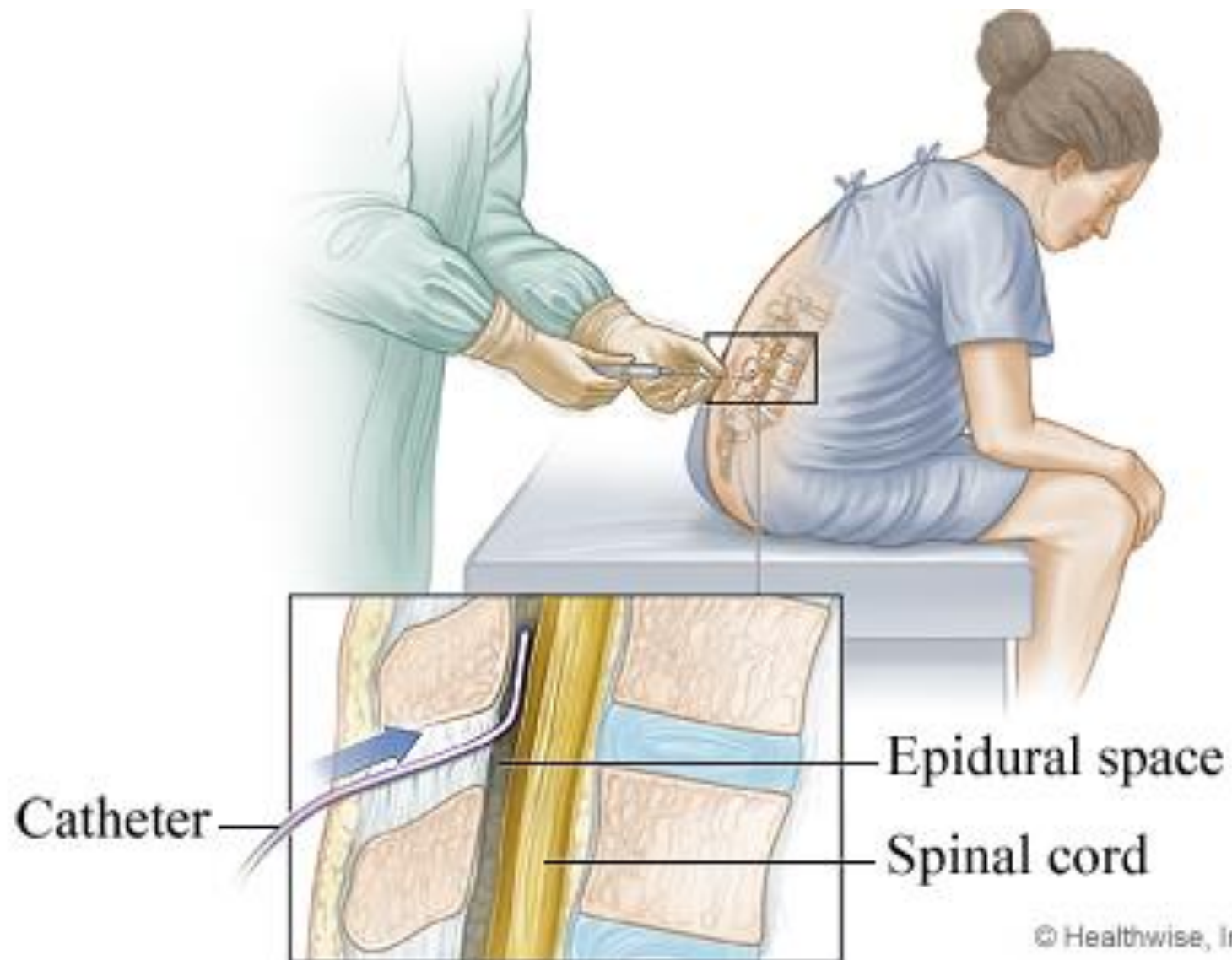
**A harmless thing  
that causes harm**

**because you believe it's harmful.**





Schedlowski et al 2015

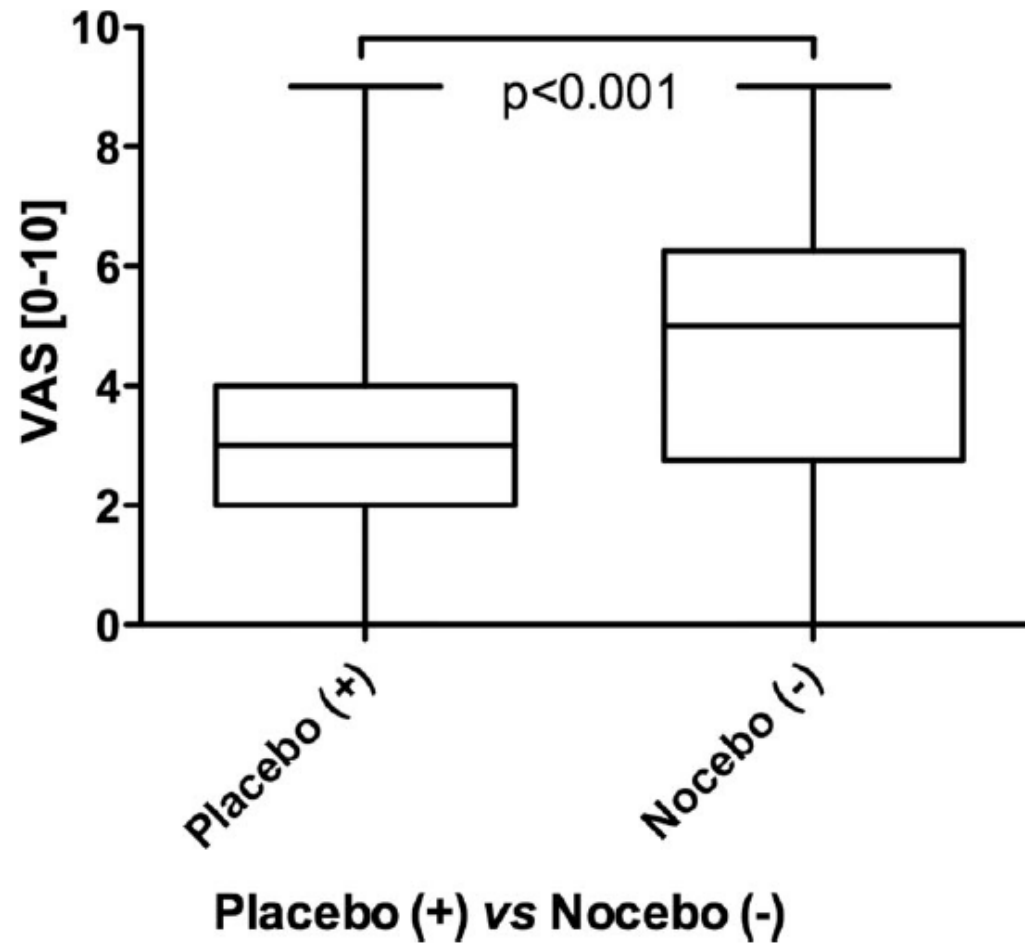


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HUMAN HEALTH

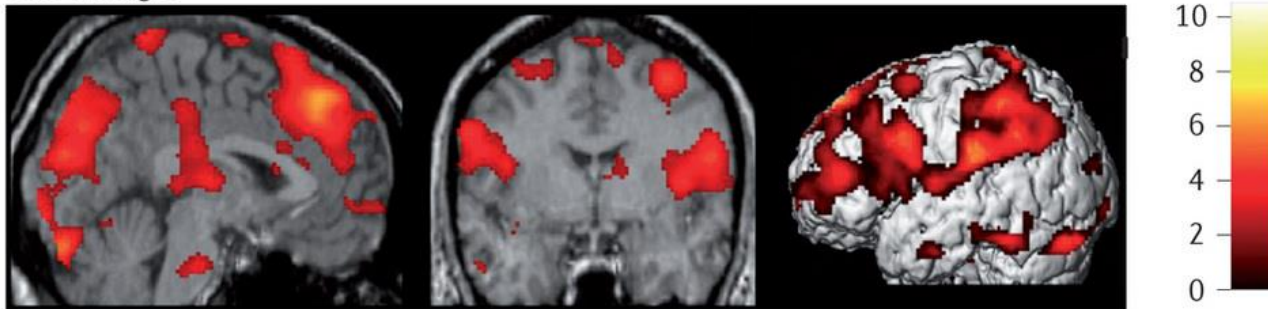


# Nocebo



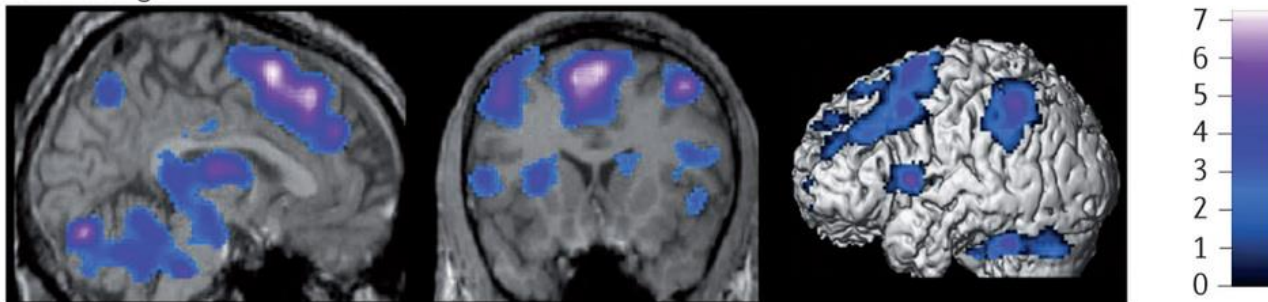
### Physically induced pain

Pain rating 5

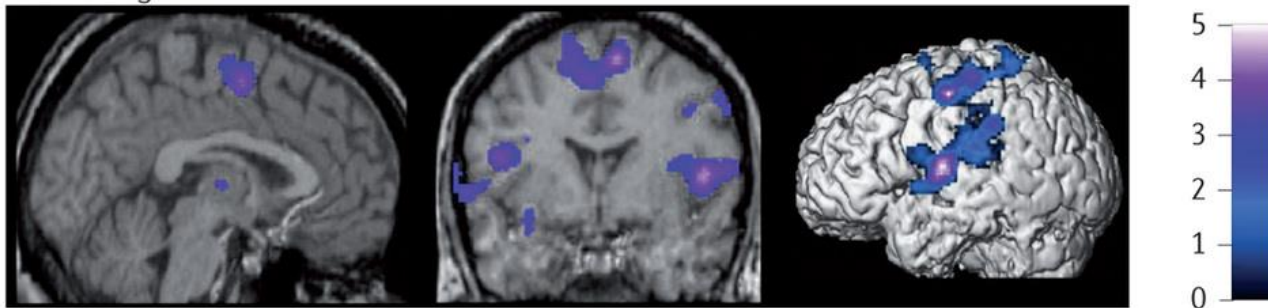


### Hypnotically induced pain

Pain rating 5




Pain rating 1









If you believe it will affect you  
**it will**

If you don't  
**it won't**



## Novel tasting green 'slop'



Albring et al PLOS 2012

# Benedetti

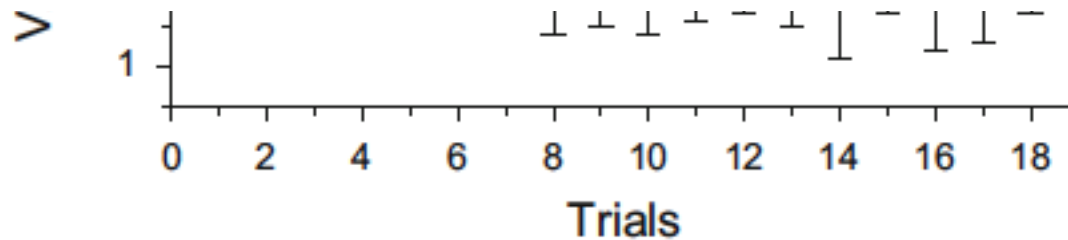
- Hypoxia
- Symptoms and PGE2 increases
- 'Fake' oxygen
- Symptoms improved
- PGE2 decreases





# Observing enhances placebo/nocebo

10 - Live observation -



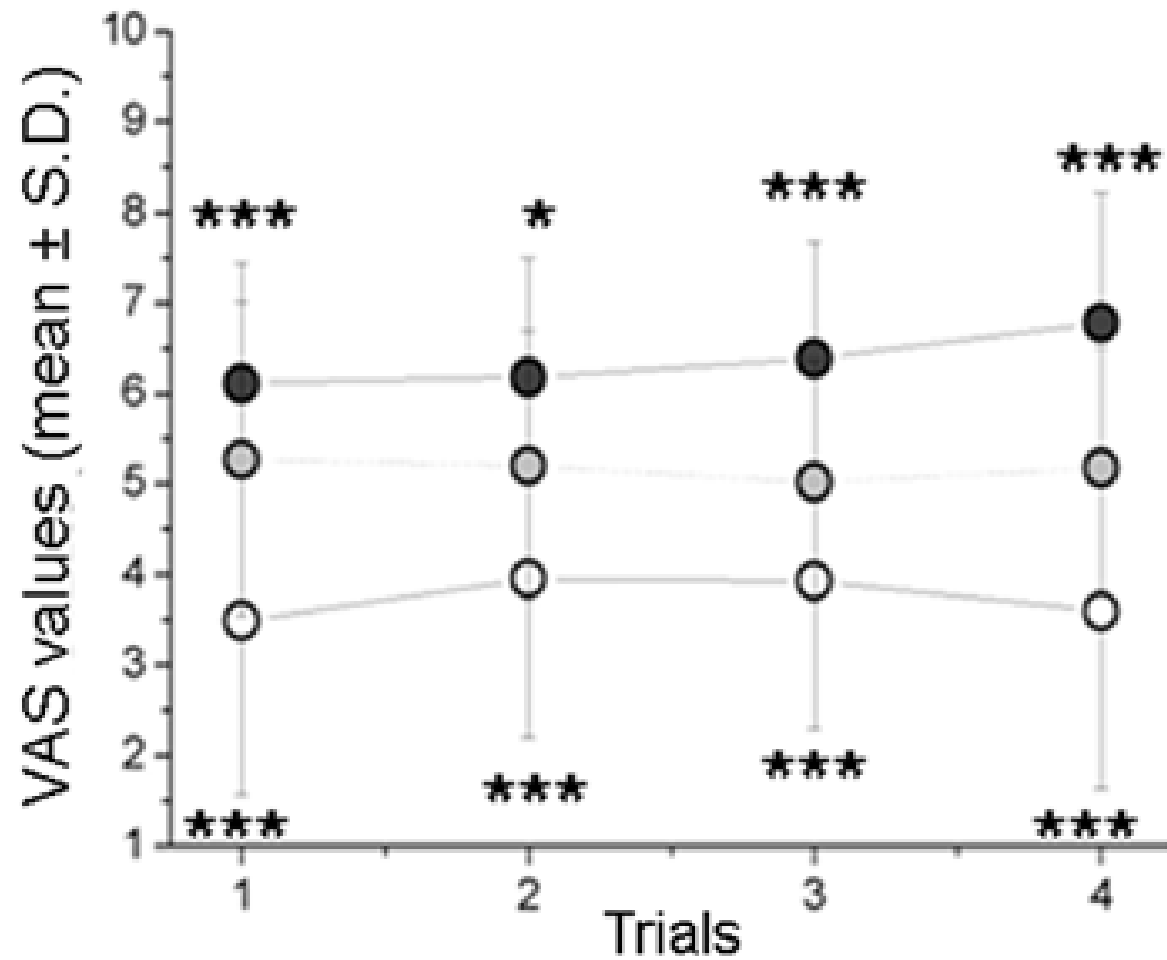
# Conditioning effects

- Painful stimulus (and non painful) on foot with dummy electrodes on ankle that would 'modulate' the pain
- Red light indicated increasing perception of stimulus
- Green light reducing perception of stimulus
- Yellow light 'inactivated' ankle electrode
- Group 1 single conditioning
- Group 2 multiple conditioning

Colloca et al 2010

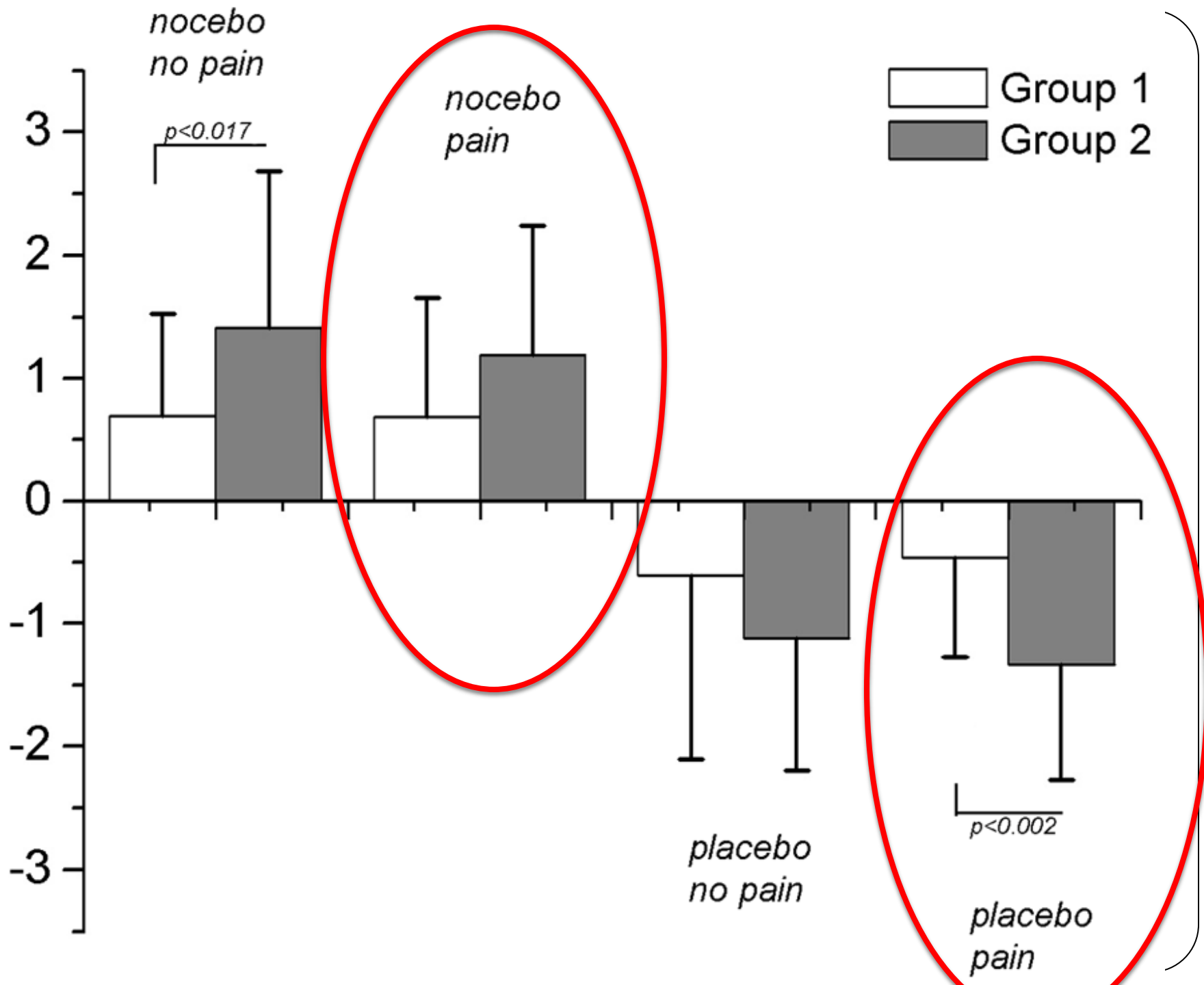
D

- Yellow stimuli
- Red stimuli
- Green stimuli





VAS variations (mean difference  $\pm$  S.D.)



- Nocebo the same with single conditioning stimulus
- Placebo more effective with 4 conditioning stimuli
- Nocebo more easily set up
- Nocebo effect correlated with state-trait anxiety
- Placebo with empathy

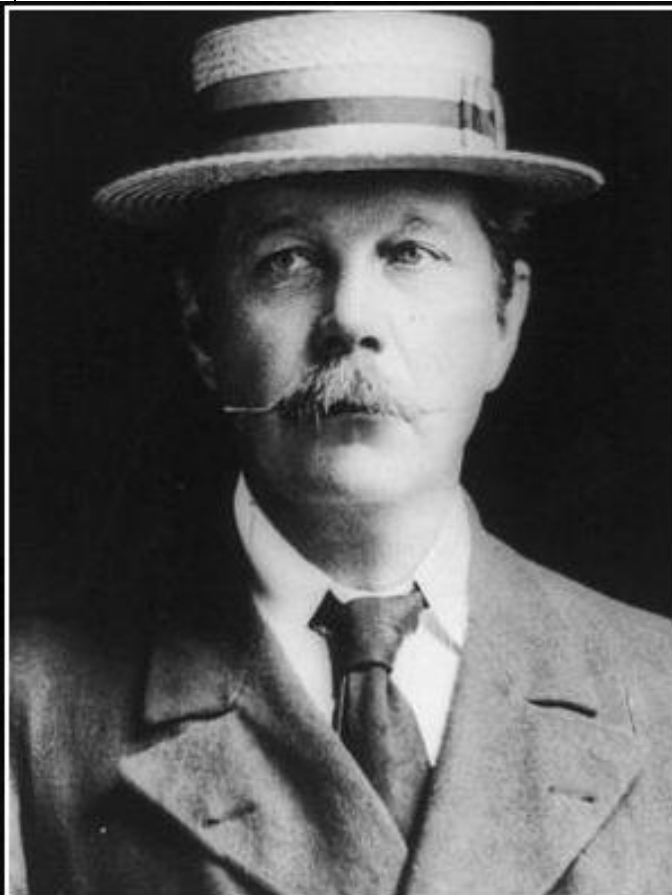
# Nocebo related to anxiety





# Empathy

- Group 1 observation green light reducing others pain and then they had green light with pain
- Group 2 conditioning green light associated with lesser stimulus to make them believe it worked
- Group 3 verbal only to expect benefit from green light
- Placebo effect for group 1 the same as group 2 with strong correlation with empathy



I'm not a psychopath, I'm a fully



# Validation and Invalidation

- Stressful maths, physiology and mood
- Is it safe?
- Feedback
  - Validating
  - Invalidating
  - None

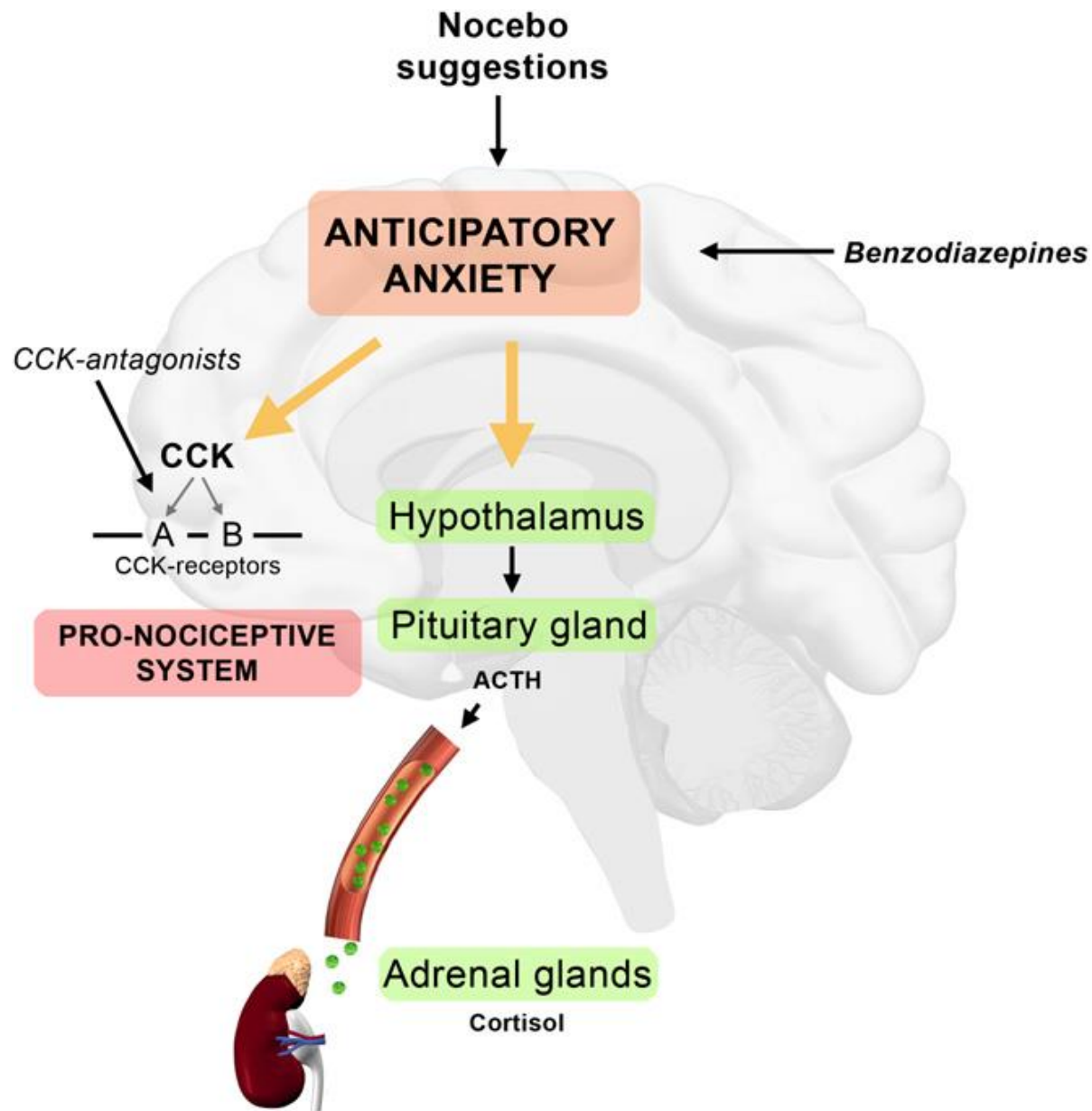
Little effect of validation but invalidation significant effects - low mood, low safety, not do again



# Importance of invalidation

- Doctor-patient interactions that are invalidating (i.e. that do not successfully communicate acceptance and understanding to the patient) facilitate the nocebo.
- The power of negative communication is stronger than positive communication.
- It is important to focus on *not* invalidating patients (rather than simply focusing on compassion, empathy and validation).





Enck et al 2008





# Placebo

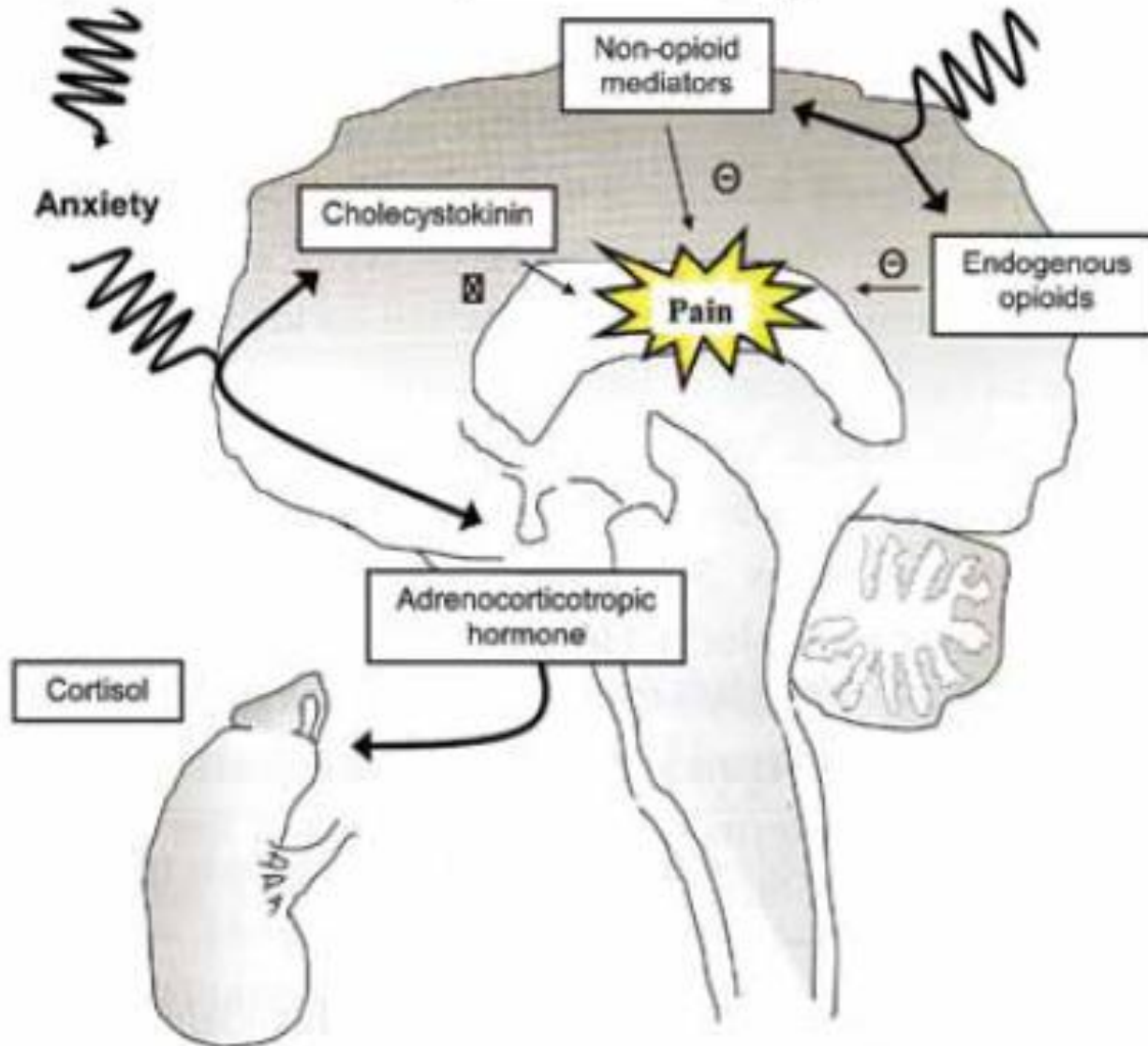
- Brain reward circuitry
- Anticipation of pain areas in ACC
- Endogenous activation of opioids for placebo
- CCK antagonists increase placebo
- Endogenous activation of CCK for nocebo
- Anxiolysis reduces nocebo
- Decrease dopamine in nucleus accumbens nocebo

## NOCEBO

Suggestion of hyperalgesia

## PLACEBO

Expected or conditioned analgesia



- **Placebo**
- Empathy
- Conditioning

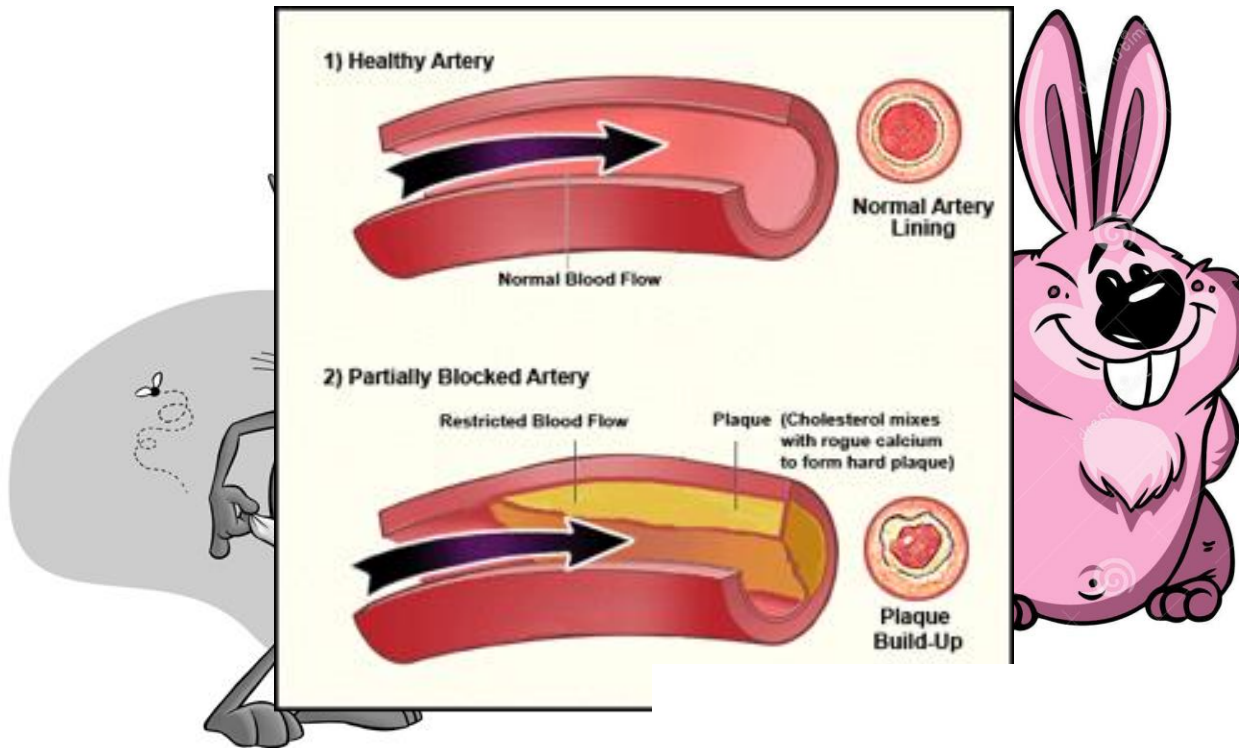


- **Nocebo**
- Invalidation ————— Validation
- Anxiety —————> Reduce anxiety

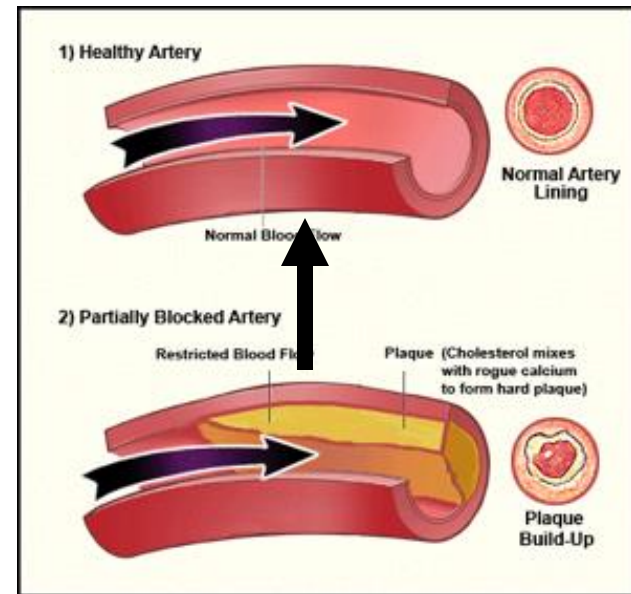


# Even in animals?

- Atheroma



# ‘Just giving’





HAPPINESS IS A THUMB AND A BLANKET.

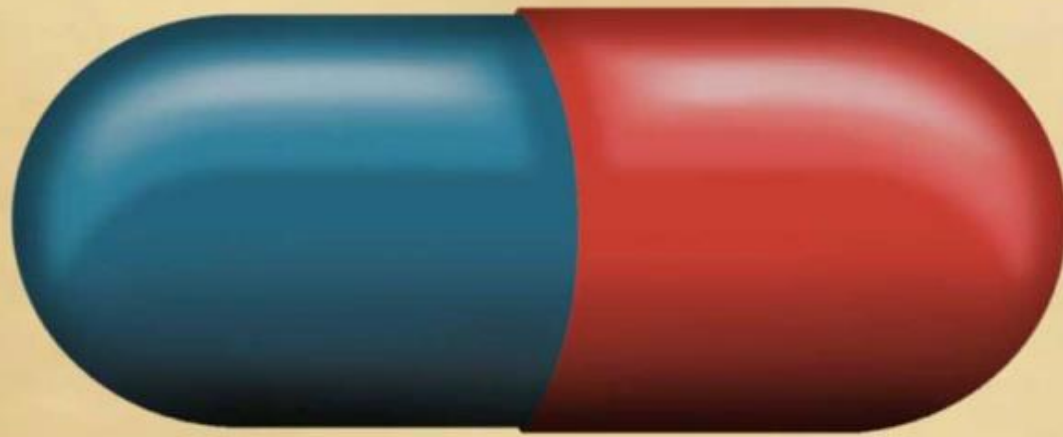








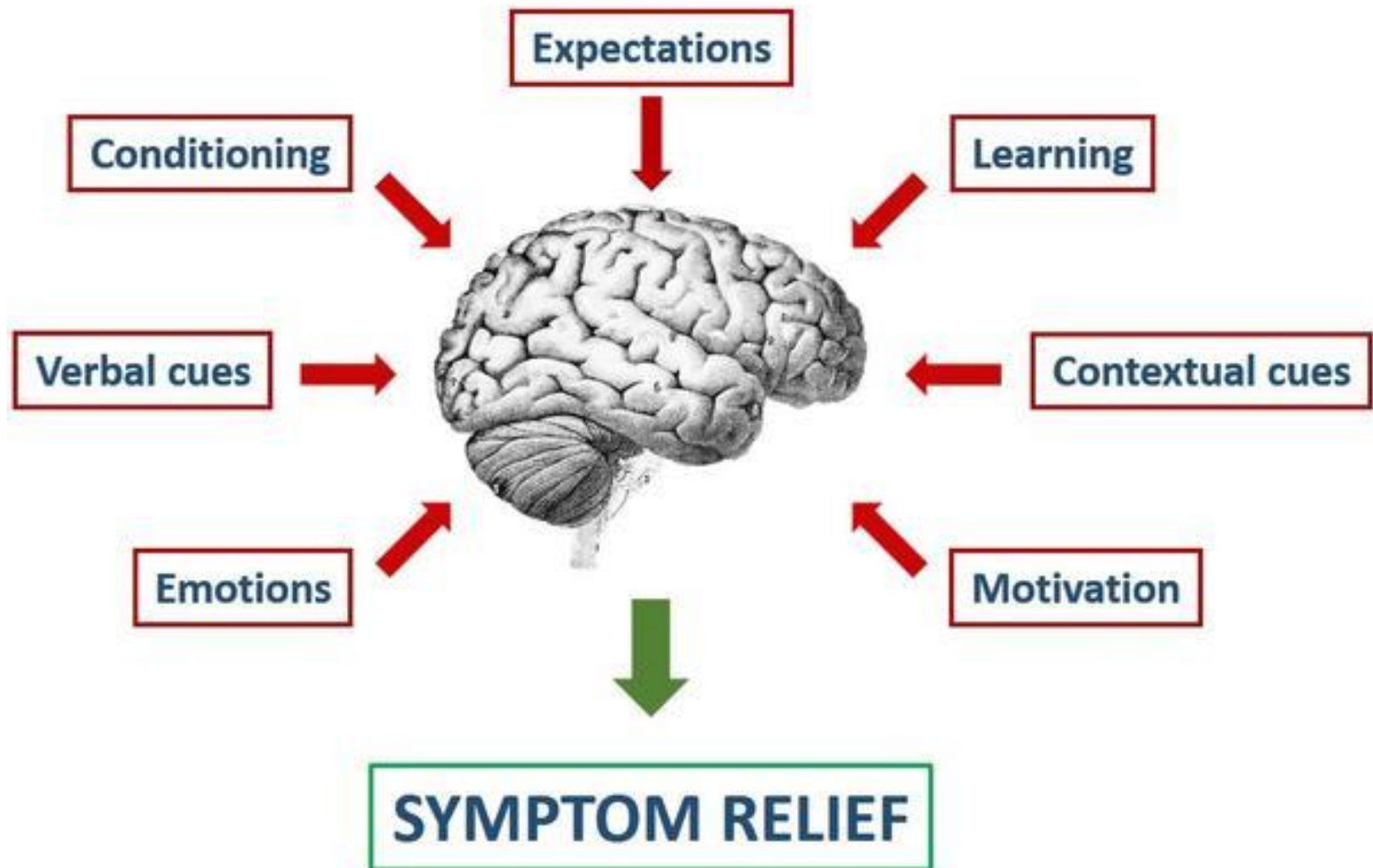
# Implications for Treatment?



*Ceci n'est pas une pilule.*

(This is not a pill.)

# PLACEBO EFFECT



## External context

**Verbal suggestions:**  
"This is going to make you feel better"

**Place cues:**  
Doctor's office

**Social cues:**

- Eye gaze
- Body language
- Voice cues
- White coat



**Treatment cues:**

- Syringe
- Needle puncture

## Internal context

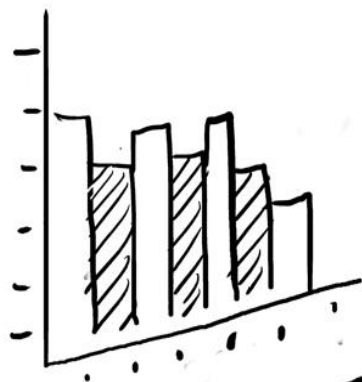
- **Outcome expectancies:**  
"My pain will go away"
- **Emotions:**  
"I am less anxious"
- **Meaning schema:**  
"I am being cared for"
- **Explicit memories**
- **Pre-cognitive associations**

Nature Reviews | Neuroscience

- Maximising
  - Expectation
  - Context
  - Verbal cues
- Minimising
  - Anxiety
  - No Validation



# PHARMACOLOGICAL DRUG TRIAL RESULTS



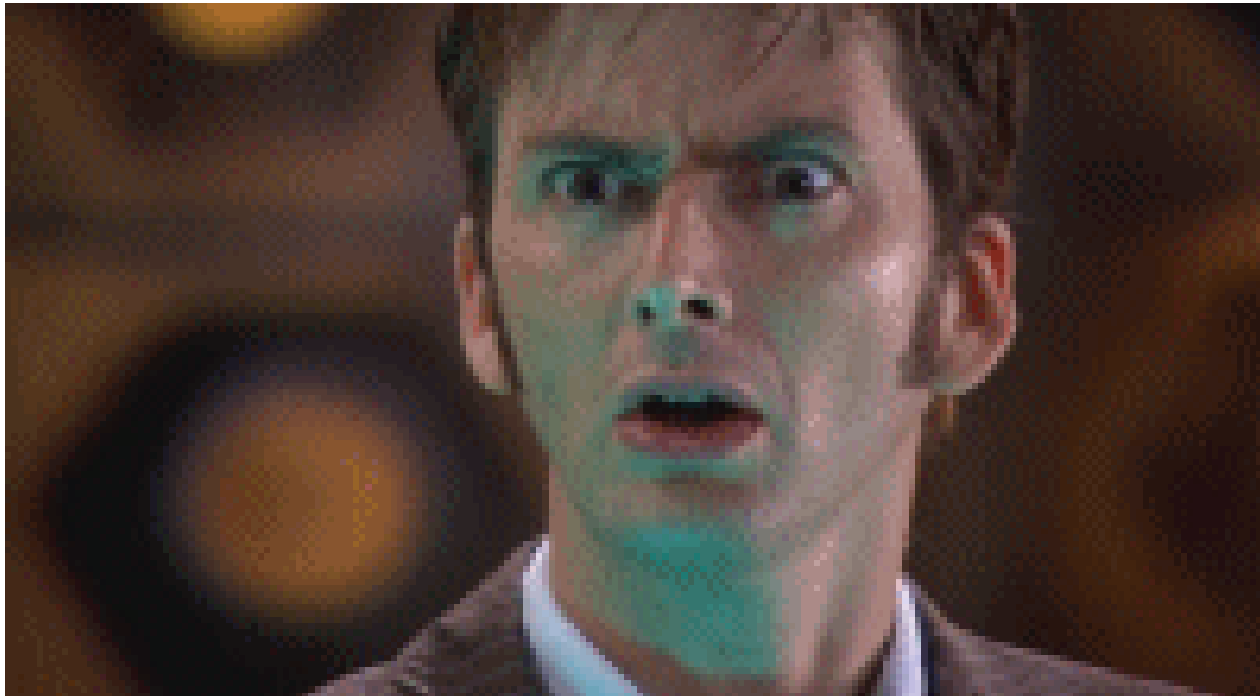
OUR TRIALS SHOW THAT  
THE NEW DRUG PERFORMS  
NO BETTER THAN PLACEBO

MAYBE WE SHOULD  
INVEST IN PLACEBOS

CHRIS  
MADDEN



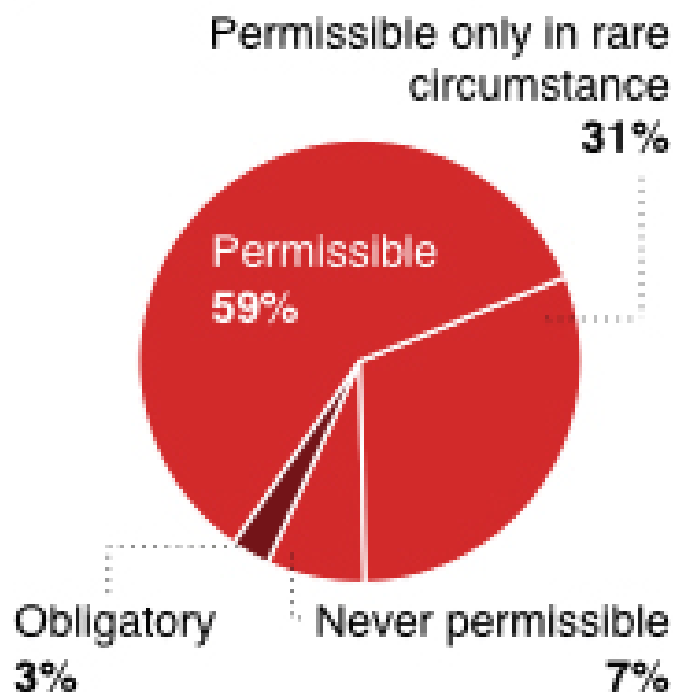
# Using placebos in clinical practice (? !)



# Placebo treatment considered an option

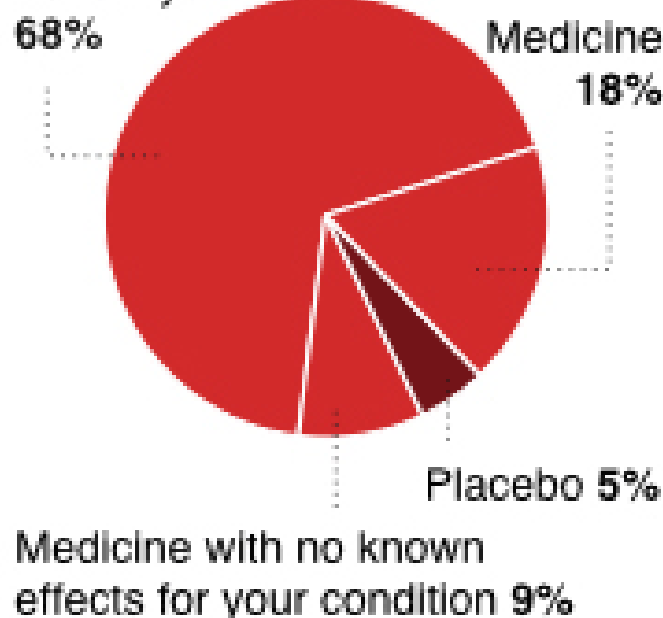
Nearly 60 percent of American doctors think prescribing placebo pills to patients to promote their expectations is ethically permissible.

## Appropriateness of recommending treatment primarily to promote patients' expectations



## How placebos are typically described to patients

Medicine not typically used for your condition but might benefit you 68%





NEW REPORT CLAIMS 50% OF DOCTORS HAVE PRESCRIBED PLACEBOS



The New England  
Journal of Medicine

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VOLUME 347

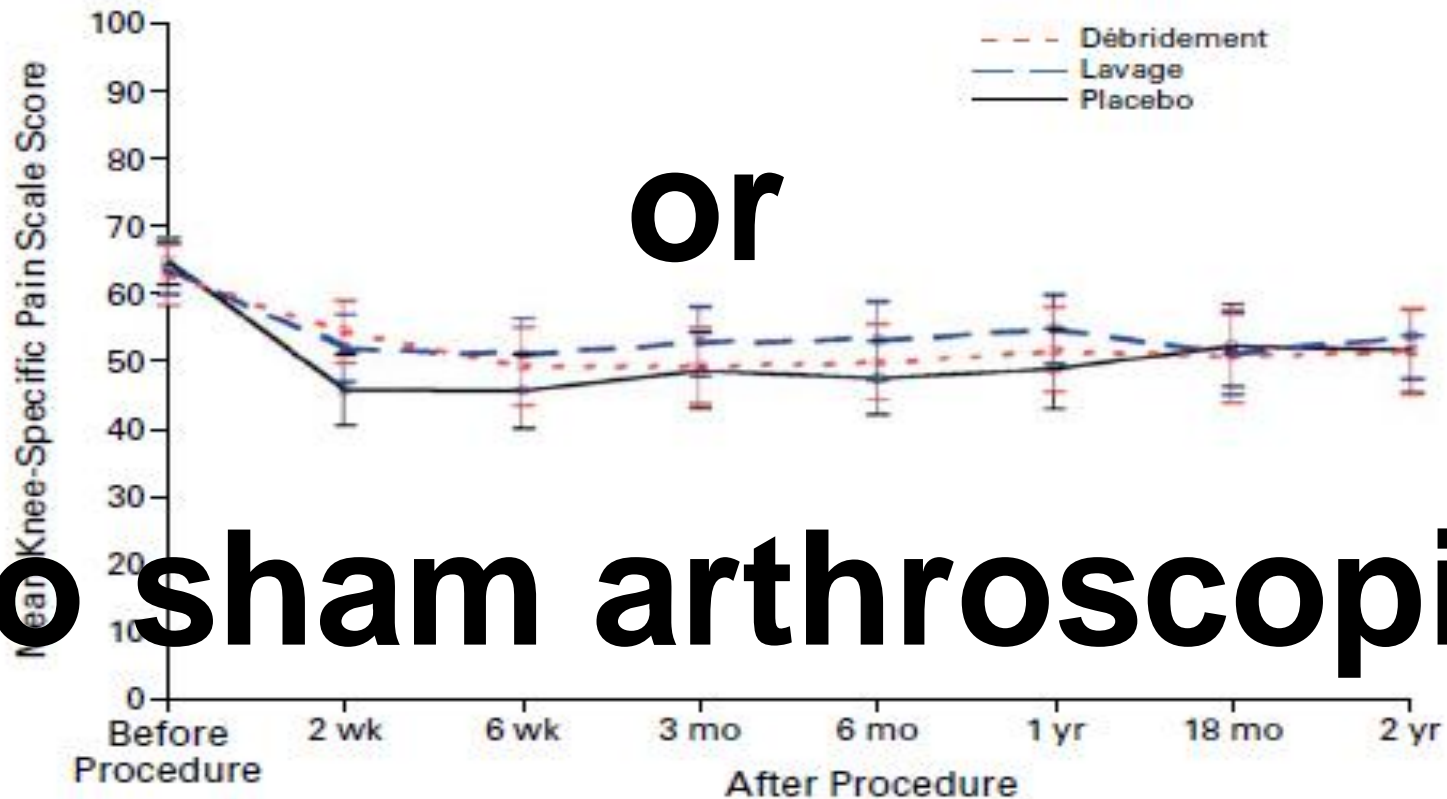
JULY 11, 2002

NUMBER 2

**Don't do arthroscopies**

**or**

**Do sham arthroscopies**



**ARE YOU THE  
PLACEBO?**



**AREN'T YOU?**





# NIH Public Access

## Author Manuscript

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Published in final edited form as:

*N Engl J Med.* 2009 August 6; 361(6): 569–579. doi:10.1056/NEJMoa0900563.

## **A Randomized Controlled Trial of Vertebroplasty for Osteoporotic Spine Fractures**

D.F. Kallmes<sup>1</sup>, B.A. Comstock<sup>2</sup>, P.J. Heagerty<sup>2</sup>, J.A. Turner, Ph.D.<sup>2</sup>, D.J. Wilson<sup>4</sup>, T.H. Diamond<sup>5</sup>, R. Edwards<sup>6</sup>, L.A. Gray<sup>1</sup>, L. Stout<sup>2</sup>, S. Owen<sup>4</sup>, W. Hollingworth<sup>3</sup>, B. Ghdoke<sup>2</sup>, D.J. Annesley-Williams<sup>7</sup>, S.H. Ralston<sup>8</sup>, and J.G. Jarvik<sup>2</sup>

- N=131, 68 vertebroplasty, 63 sham vertebroplasty
- Disability and pain no difference between groups
- More crossover from sham to ‘real’
- No difference in those who correctly guessed intervention

## RESEARCH ARTICLE

# Brain Connectivity Predicts Placebo Response across Chronic Pain Clinical Trials

Pascal Tétreault<sup>1</sup>, Ali Mansour<sup>1</sup>, Etienne Vachon-Pressseau<sup>1</sup>, Thomas J. Schnitzer<sup>2,3</sup>, A. Vania Apkarian<sup>1,2,4 \*</sup>, Marwan N. Baliki<sup>2,5 \*</sup>

1 Department of Physiology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois, United States of America, 2 Department of Physical Medicine and Rehabilitation, Northwestern University, Feinberg School of Medicine, Chicago, Illinois, United States of America, 3 Department of Internal Medicine, Northwestern University, Feinberg School of Medicine, Chicago, Illinois, United States of America, 4 Department of Anesthesia, Northwestern University, Feinberg School of Medicine, Chicago, Illinois, United States of America, 5 Rehabilitation Institution of Chicago, Chicago, Illinois, United States of America

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- OA knee pain
- Placebo effect from single blind placebo (50%)
- Placebo effect compared to duloxetine
- Duloxetine increased placebo in 50%
- Duloxetine reduced placebo response in 50%



