Brain mechanisms and implications of the placebo effect

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S.D.G.

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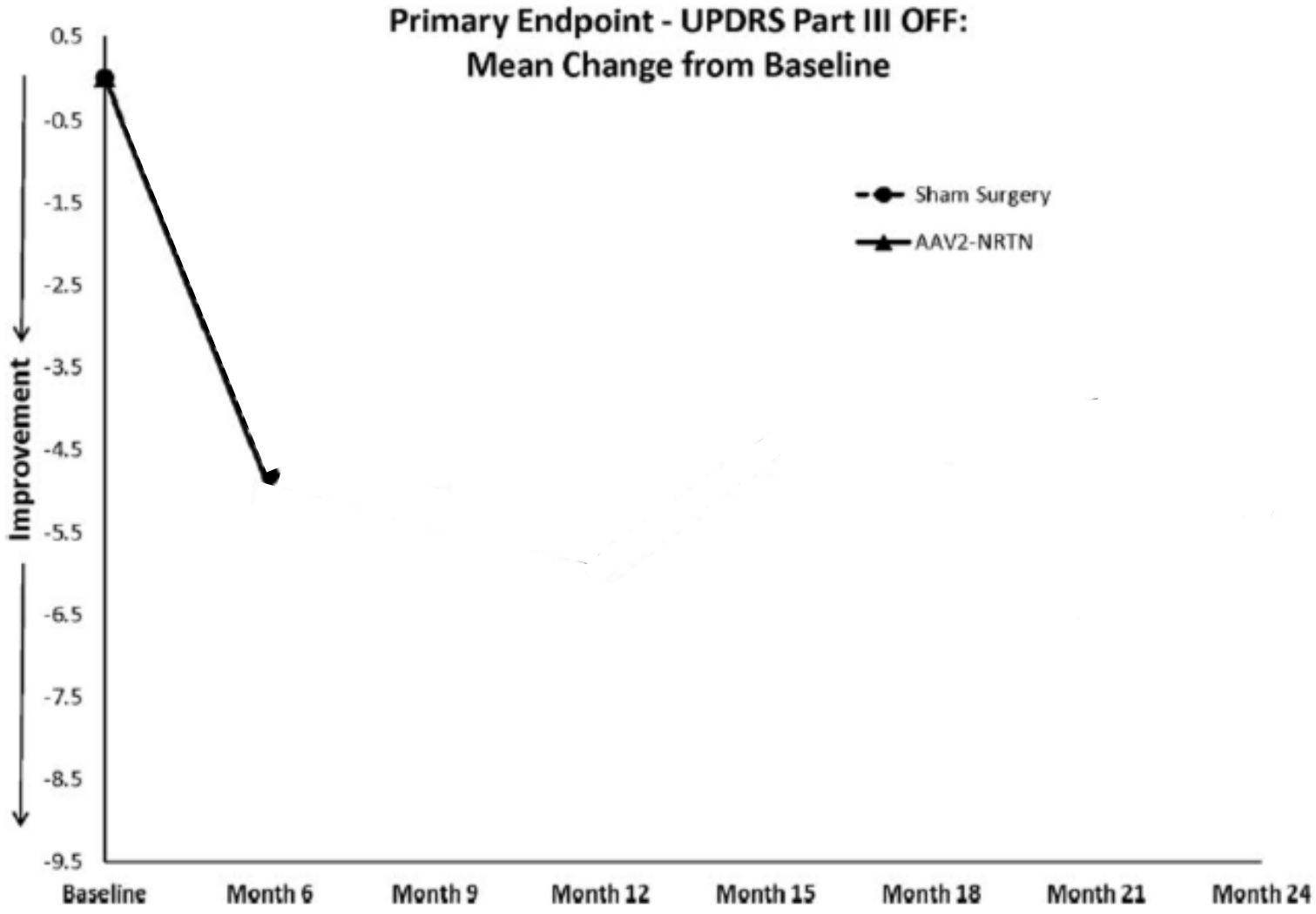
“…the patient, though conscious that his condition is perilous, may recover his health simply through his contentment with the goodness of the physician”

Hippocrates. Volume II: on decorum and the physician. London:William Heinemann, 1923.

• S.D.G.

Gene therapy for Parkinson's disease: A randomized, placebo-controlled trial



Olanow et al. 2015

45%

…of physicians reported using placebo treatments in clinical practice in 2007

Sherman & Hickner, 2007

45%

…of Americans use prayer
for health reasons

Barnes PM, Powell-Griner E, McFann K, Nahin RL. Complementary and alternative medicine use among adults: United States, 2002

Faith by the numbers

$235,400,000,000

U.S. pharmaceutical sales (2004)

$89,000,000,000

Pharma R&D budget (2004)

$4,746,000,000

NIH behavioral science spending, 2013 (est).

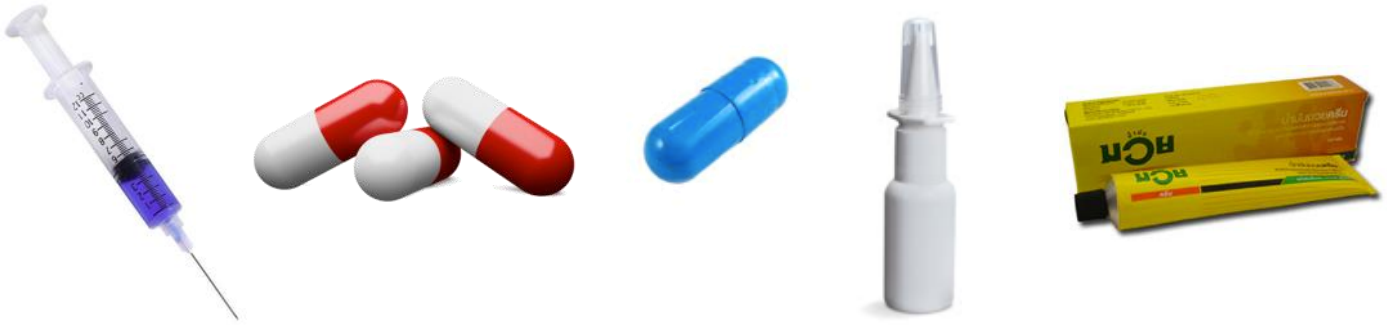
- Most research directed towards molecular/genetic causes and treatments, rather than psychology and behavior
- …even when we know behavior is very important (heart disease, lung cancer, pain, depression, anxiety)

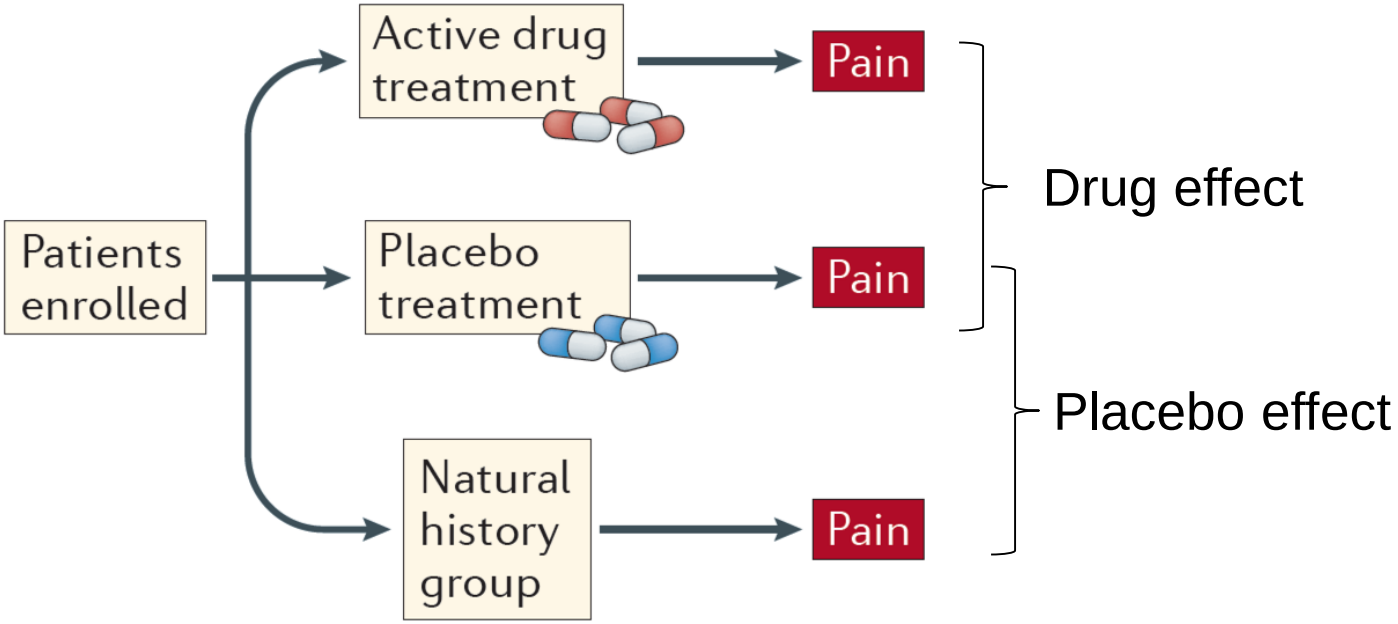
Crow, Nature, 2011

Gagnon, Lexchin et al. 2008 (2004 data)
InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems; CDC Advance Data Report #343. 2004; NIH

Placebo effects: A common thread

- Causal effect of a treatment context on outcomes

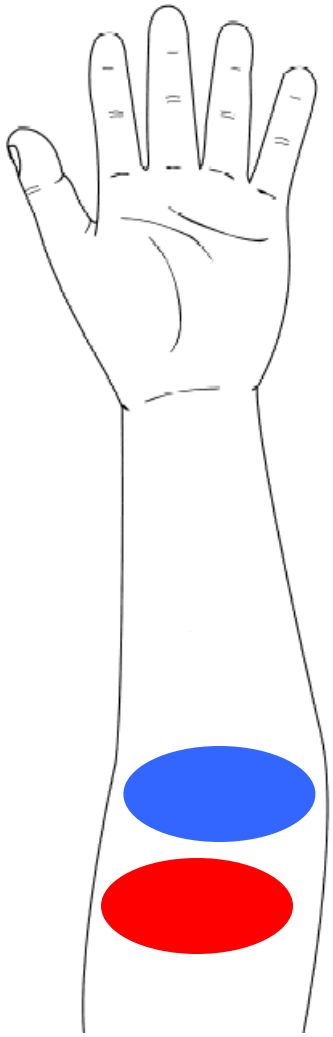




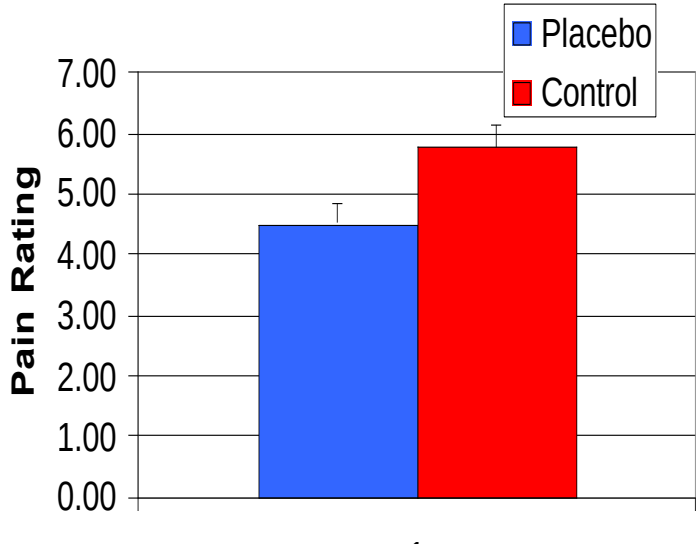
Experimental manipulation of expectation: Placebo analgesia

Placebo cream
"This is lidocaine"

Control cream
"Will have no effect"



Identical temperatures



Assimilation to expectations

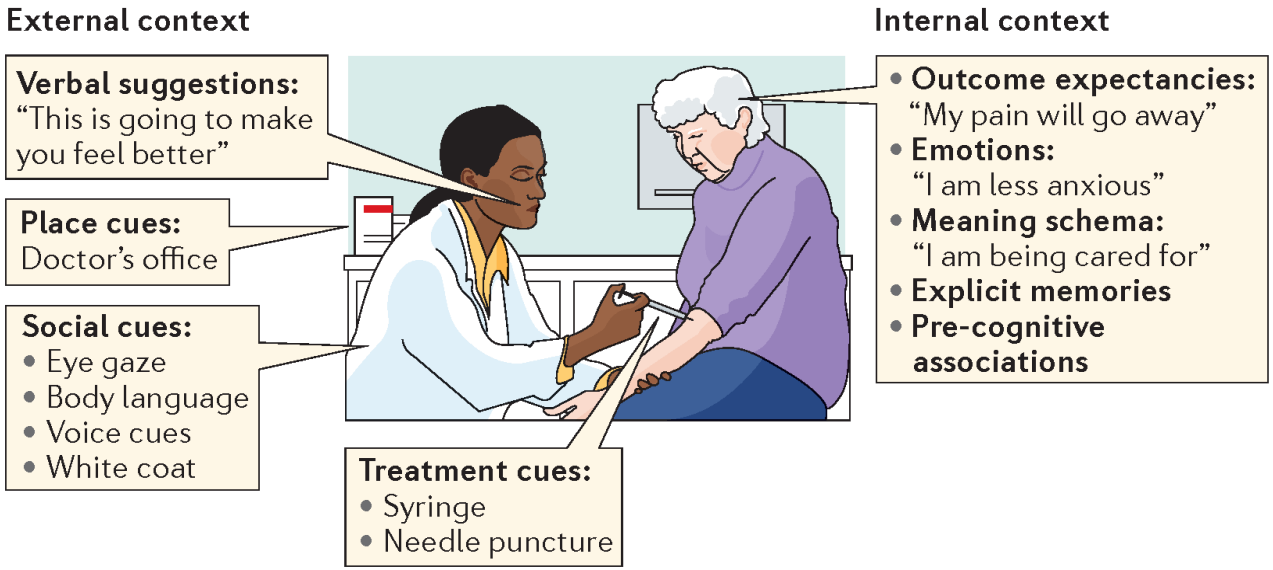
Benedetti et al., 1999; Bingel et al., 2006; Price et al. 1999, Montgomery and Kirsch, 1996; Vase et al., 2003; Voudouris et al., 1990; Wager et al., 2004, 07; many others

Placebo effects across domains

- Pain (Benedetti, 2007; Benedetti & Amanzio, 1997; De Pascalis, Chiaradia, & Carotenuto, 2002; Liberman, 1964; Montgomery & Kirsch, 1997; Price et al., 1999; Vase, Robinson, Verne, & Price, 2005; Voudouris, Peck, & Coleman, 1985; Wager, Matre, & Casey, 2006; Wager, Scott, & Zubieta, 2007, many more)
- Asthma (Kemeny et al., 2007; cf. Kaptchuk 2011 NEJM)
- Depression (Mayberg et al., 2002; Kirsch 2008; Rutherford and Roose 2008, 2010)
- Parkinson's Disease (Benedetti et al., 2004; Colloca, Lopiano, Lanotte, & Benedetti, 2004; de la Fuente-Fernandez et al., 2001; Pollo et al., 2002; Lidstone et al. 2010; Schmidt et al. 2014)
- Conditioned immunosuppression (Goebel et al., 2002, 2005; Exton et al. 2011)
- Insomnia (Storms & Nisbett, 1970)
- Autonomic responses (Benedetti et al., 1998; Benedetti, Amanzio, Baldi, Casadio, & Maggi, 1999; Lanotte et al., 2005; Pollo, Vighetti, Rainero, & Benedetti, 2003; Meissner et al. 2011; Nakamura et al., 2010)
- Cortisol release (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006; Benedetti et al., 2003; Johansen, Brox, & Flaten, 2003)
- Hormone modulation (Benedetti et al. 2003 [growth hormone]; Crum et al. 2013 [ghrelin])

See Wager & Atlas (2015) Nature Reviews Neuroscience

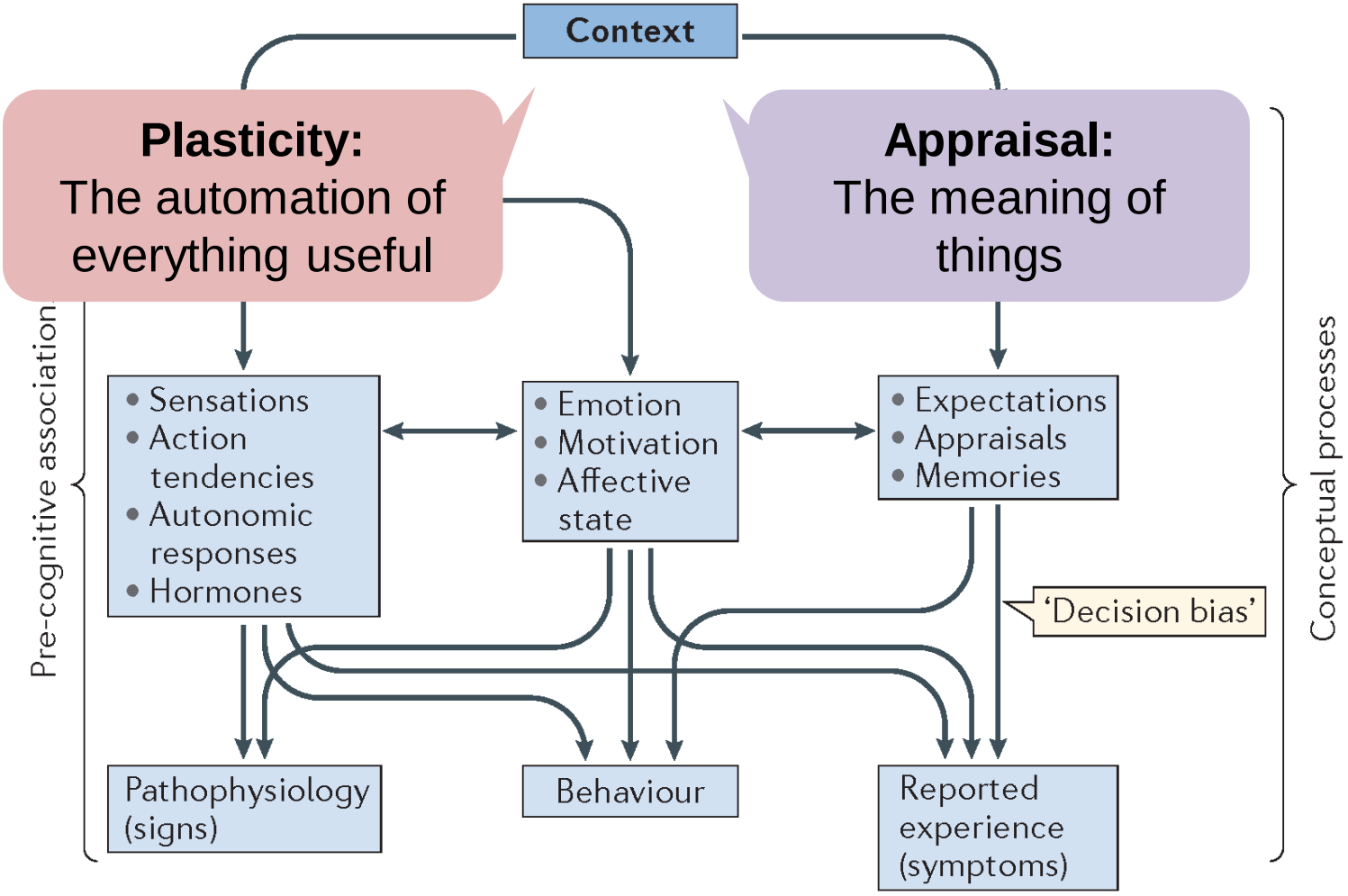
Placebo effects: Windows into treatment context



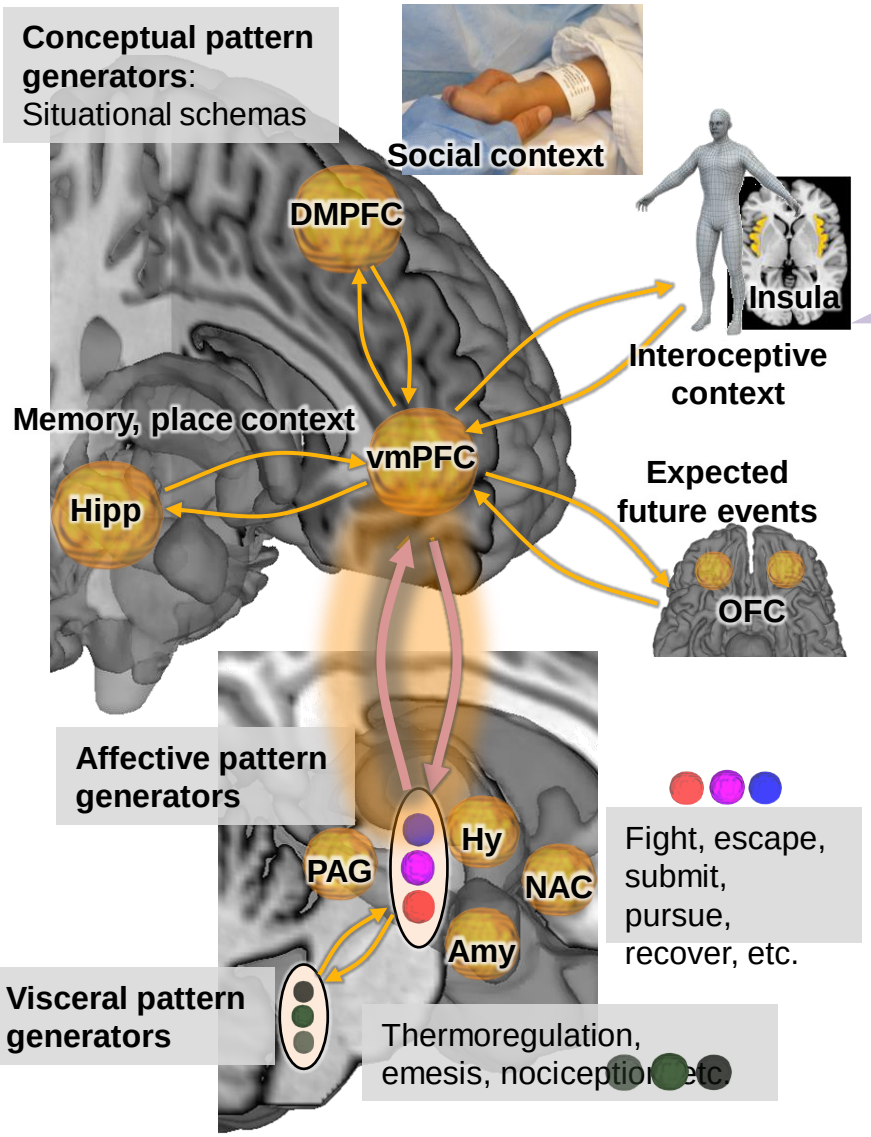
Nature Reviews | Neuroscience

- Giving fake drugs (patient deception) is not a viable strategy
- But there are many aspects of treat context that should be used!

Many effects, many mechanisms



Placebo, context and brain



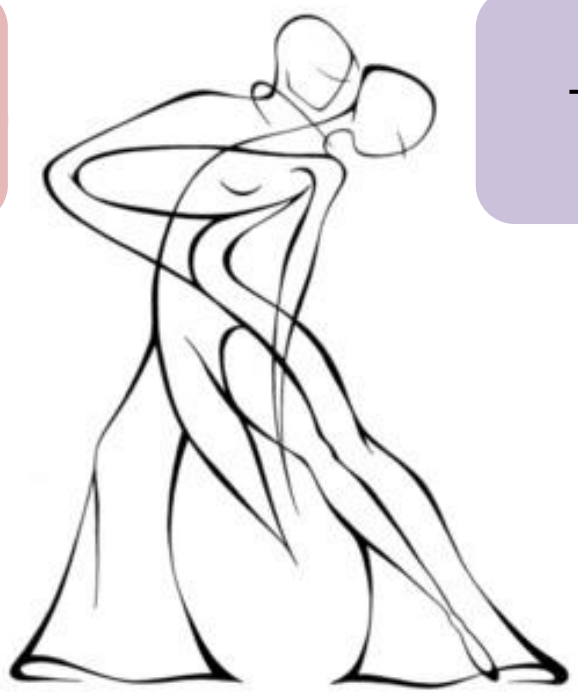
Appraisal:
Situational *meaning*
"Self in context"

Expression:
Emotion, autonomic and neuroendocrine responses, decisions

Plasticity:
Pathways that are used become stronger

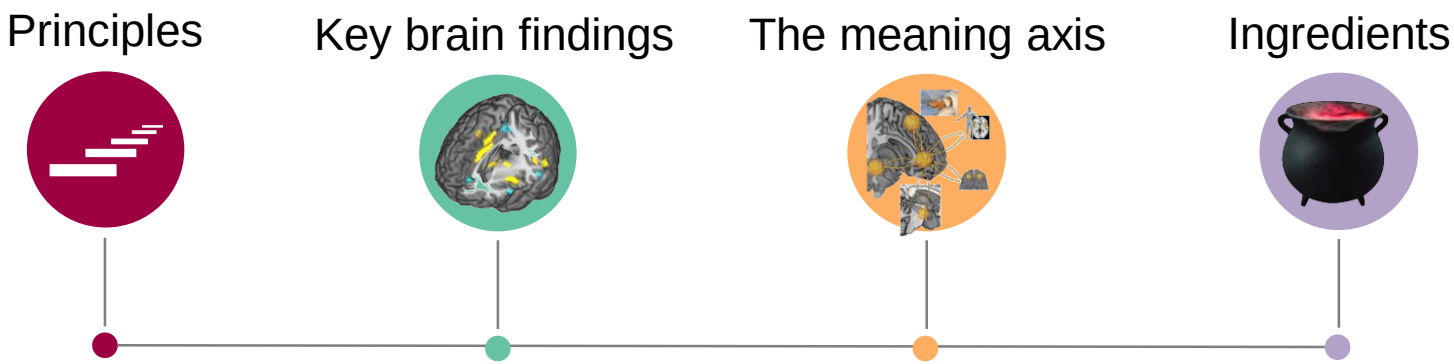
The dance of the placebos

Plasticity:
The automation of everything useful



Appraisal:
The meaning of things

Outline



1. Two principles: Appraisal and plasticity
2. Key brain findings
3. The meaning axis
4. Two ingredients

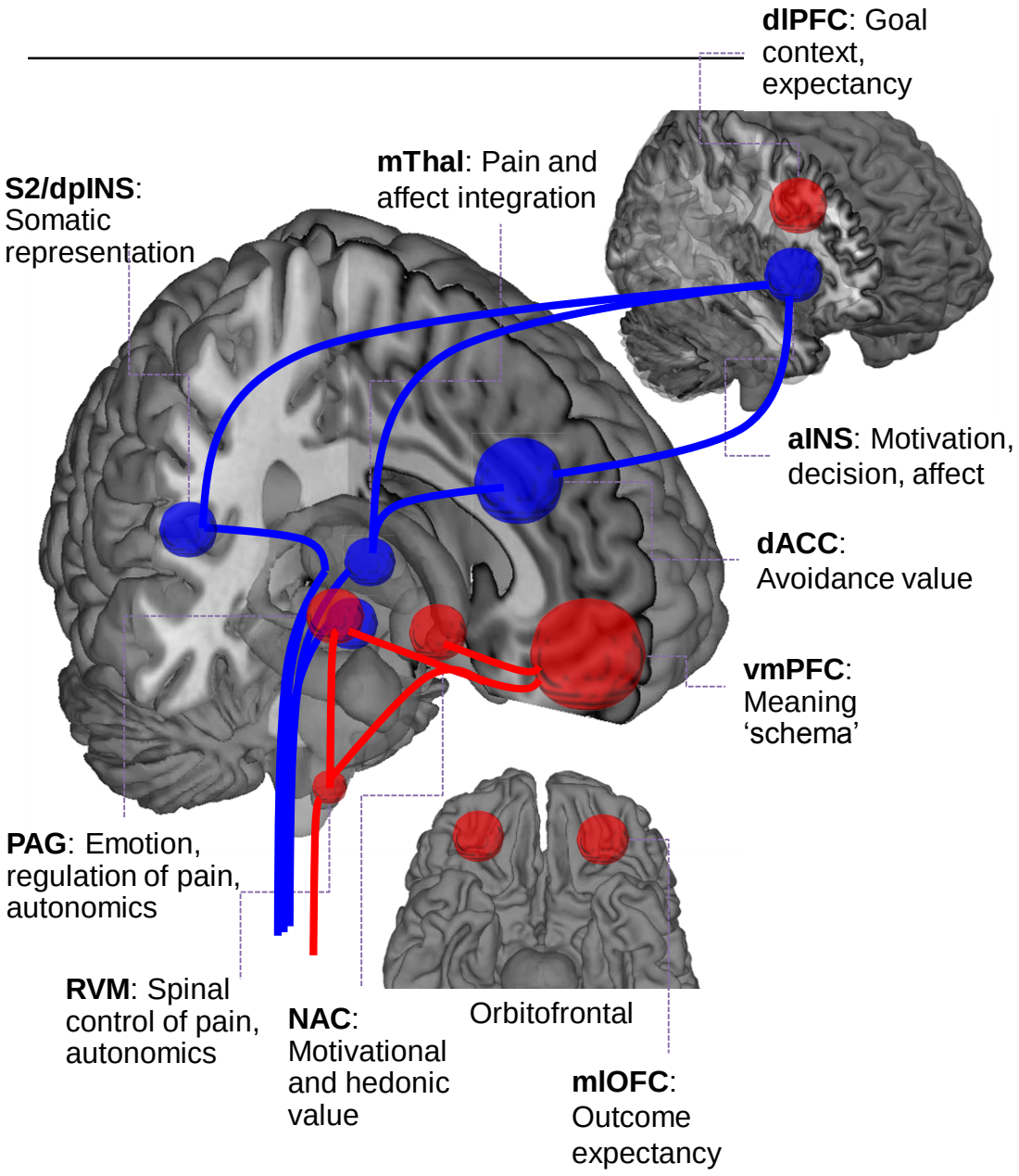
Outline

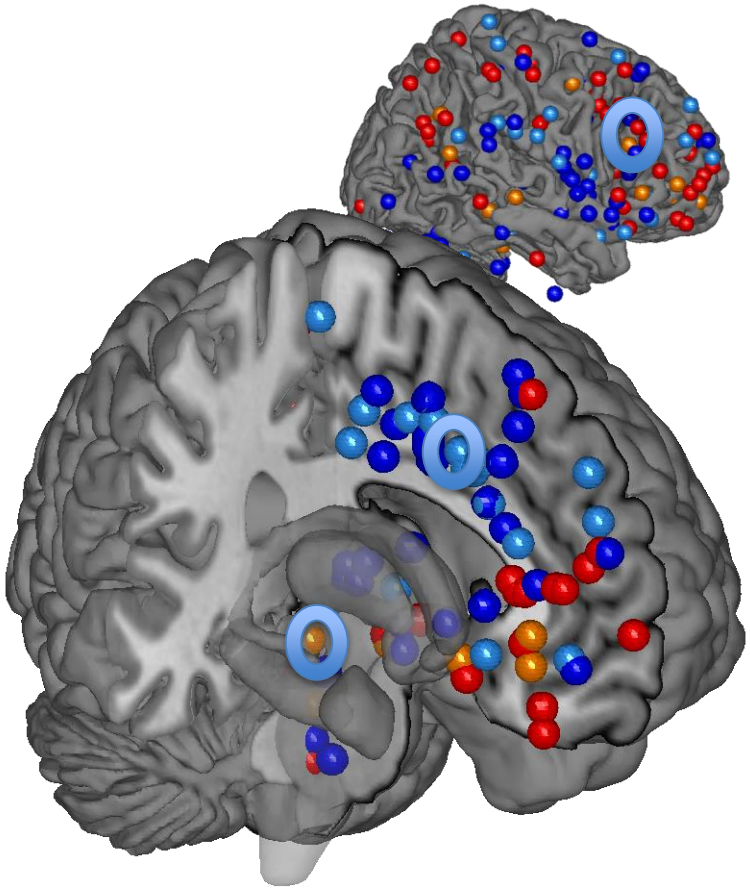
Principles

Key brain findings

Placebo fMRI Study Procedures

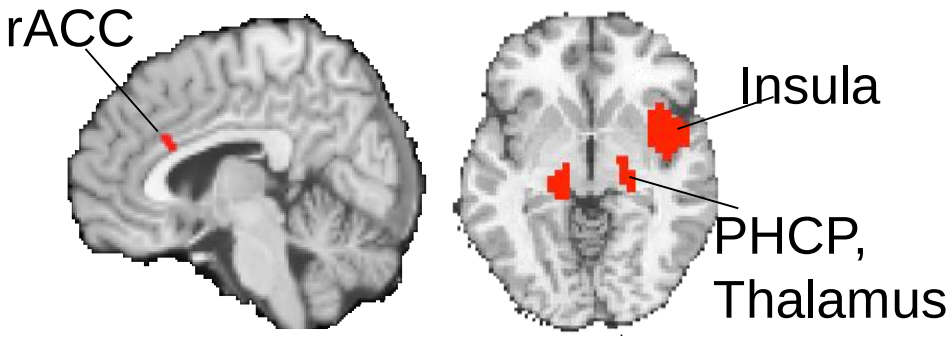
The neurophysiology of placebo analgesia



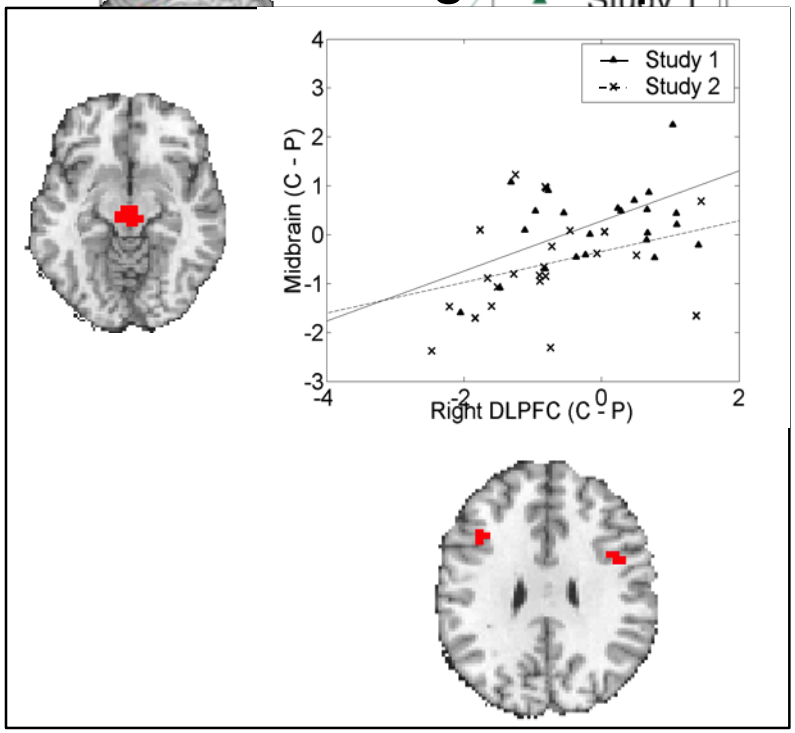


Placebo analgesia: Key results

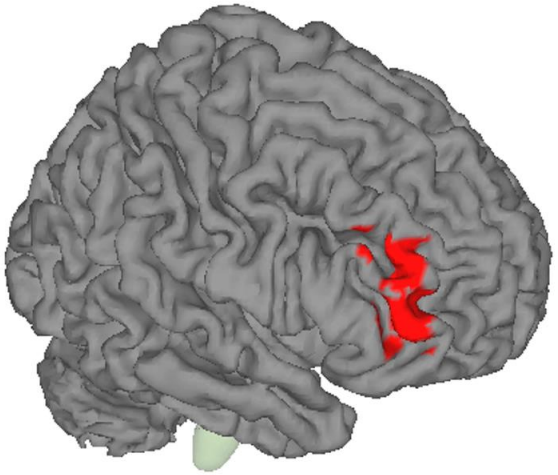
Reduced response to painful stimulation



Increases during anticipation



- Opioids and PAG are major

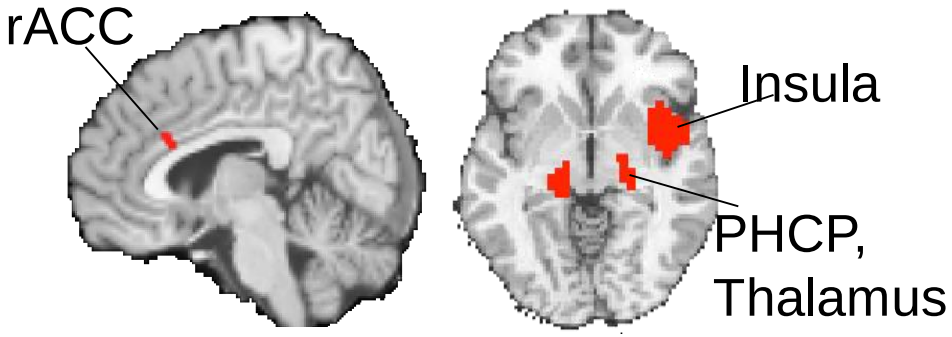


Benedetti (1999); Fields & Levine (1981); Eippert et al., 2009; cf. Gracely et al. (1984)

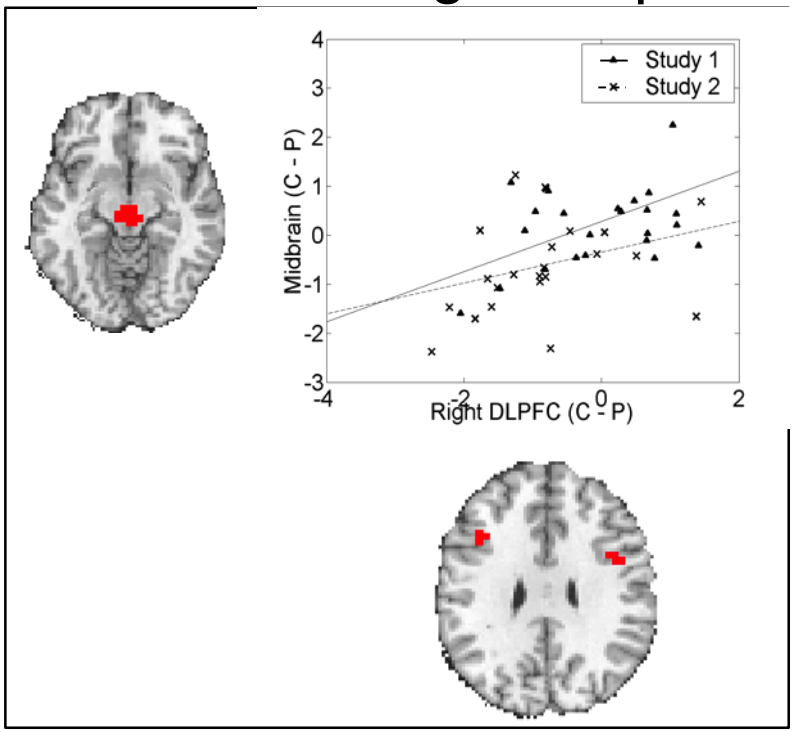
Wager et al. 2004, Science

Placebo analgesia: Key results

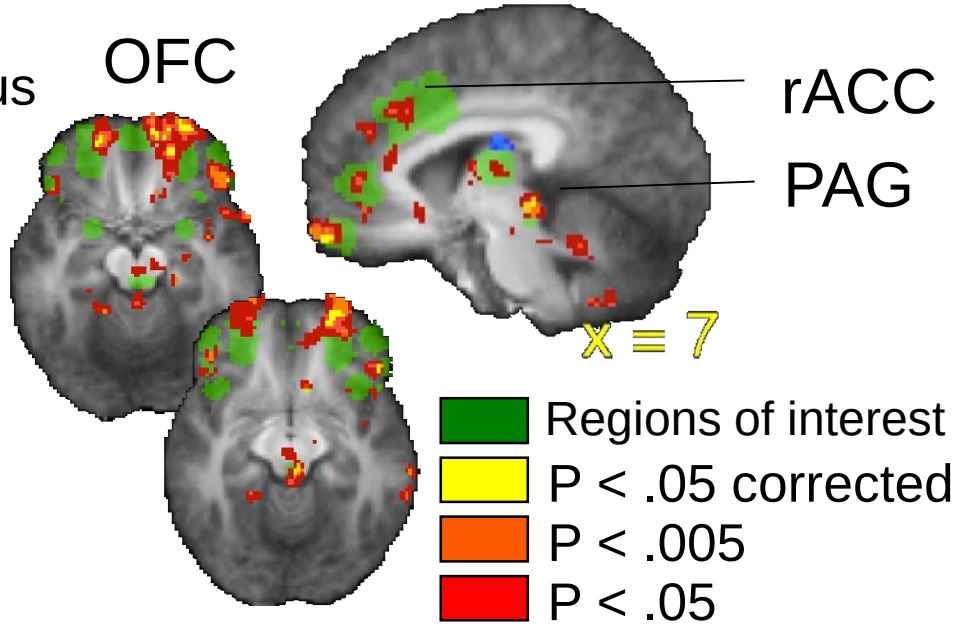
Reduced response to painful stimulation



Increases during anticipation



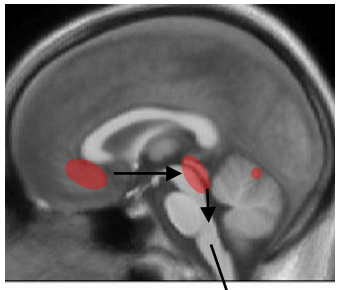
Opioid release (PET)

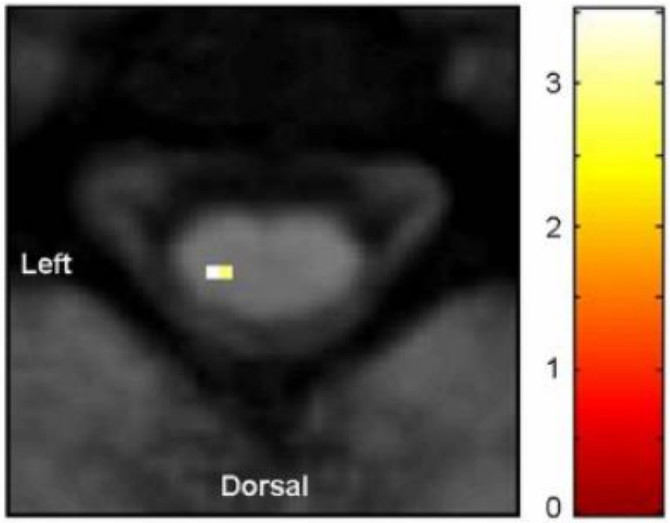


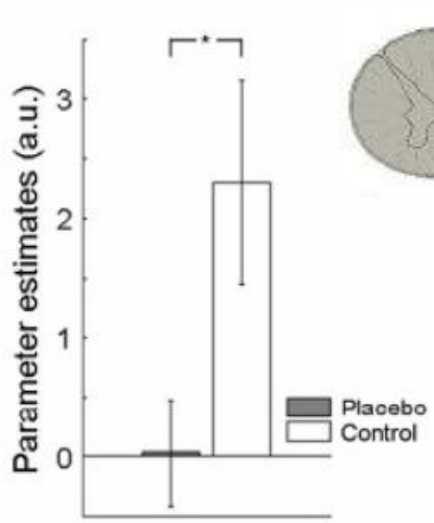
Wager, Scott, & Zubieta, *2007, PNAS;*
See also Scott et al., 2007, 2008

Effects on potential descending modulatory systems

Spinal cord fMRI





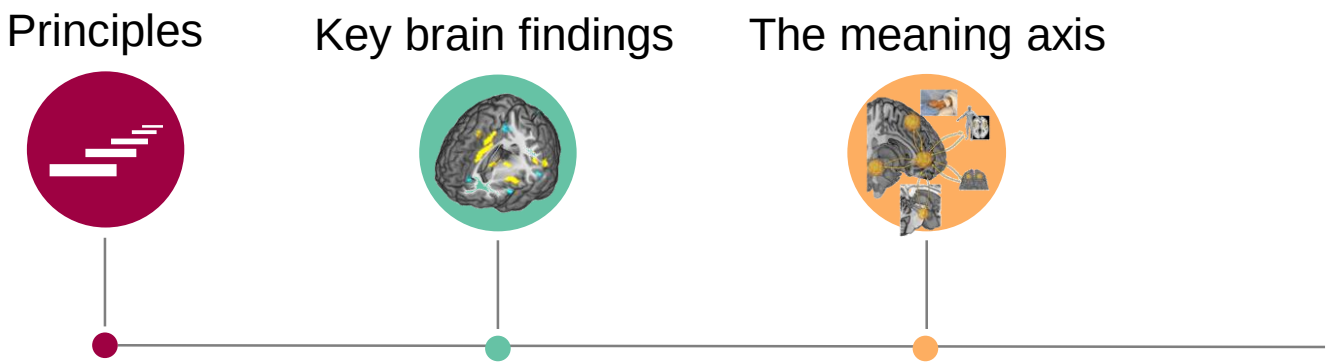


C6 ipsilat to stimulation

Evidence for spinal cord involvement in placebo analgesia

Eippert et al. Science 2009

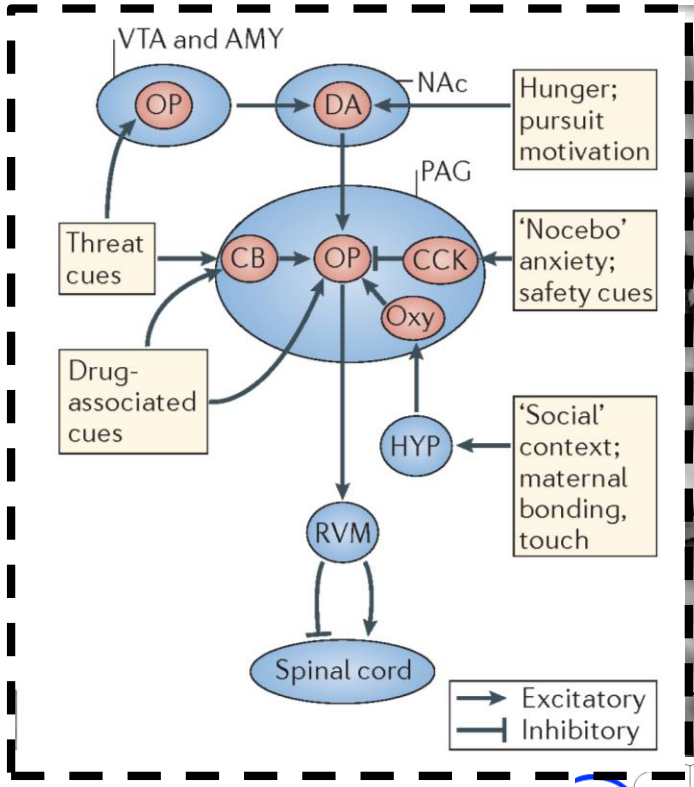
Outline

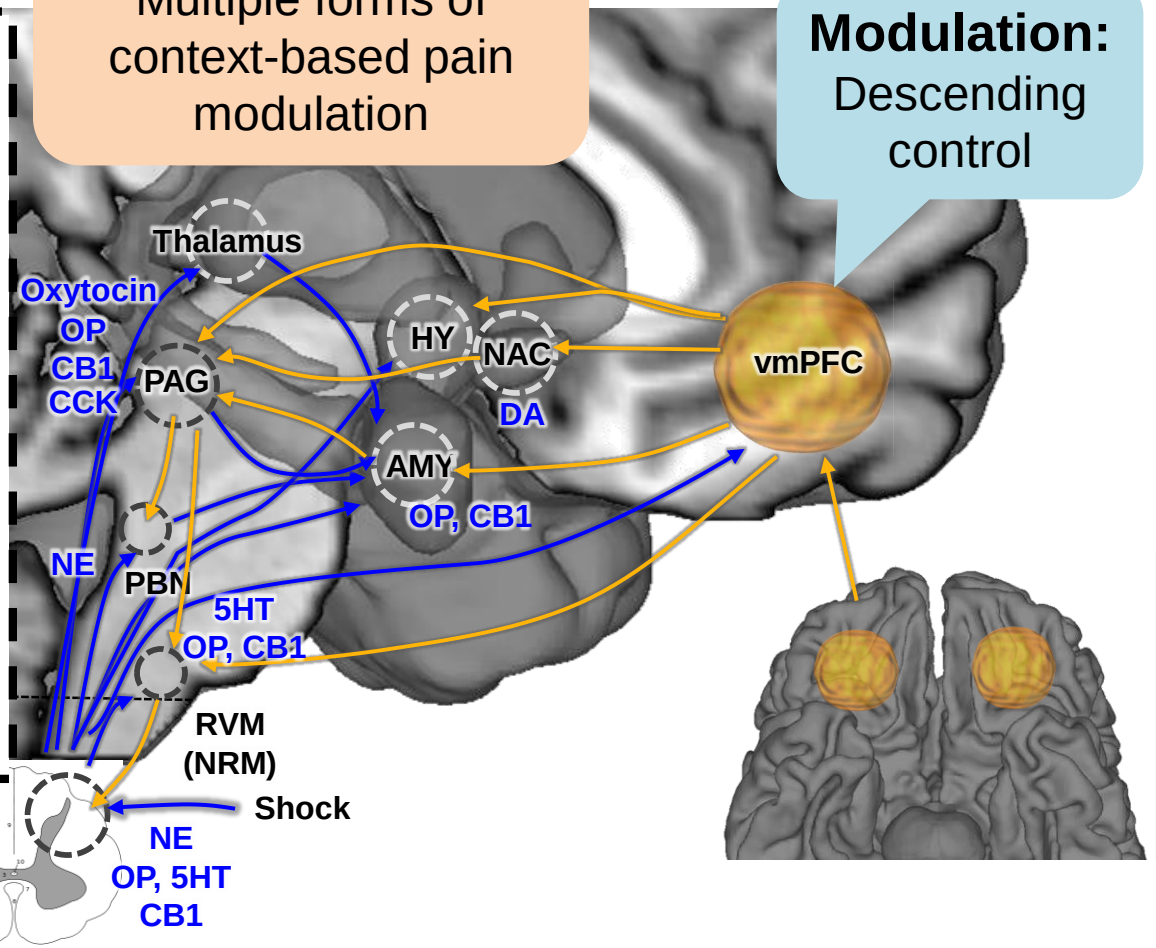


Descending pathways from ventromedial prefrontal cortex:
Pain regulation

PAG-RVM axis:
Multiple forms of context-based pain modulation

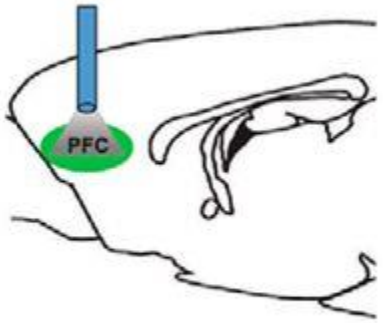
Modulation:
Descending control



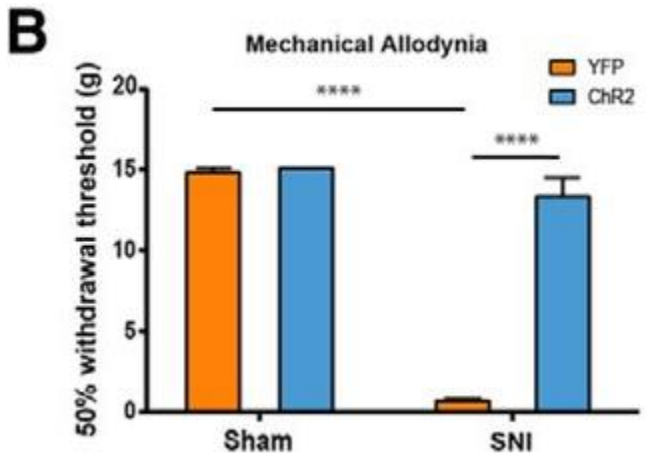


Wager & Atlas 2015, NRN; Fields 2004; Heinricher & Fields 2013; Bushnell 2013 NRN; Altier & Stewart 1999; Willis & Westlund 1997

Brain stimulation:
Optogenetic stimulation of vmPFC-NAC pathway and pain relief



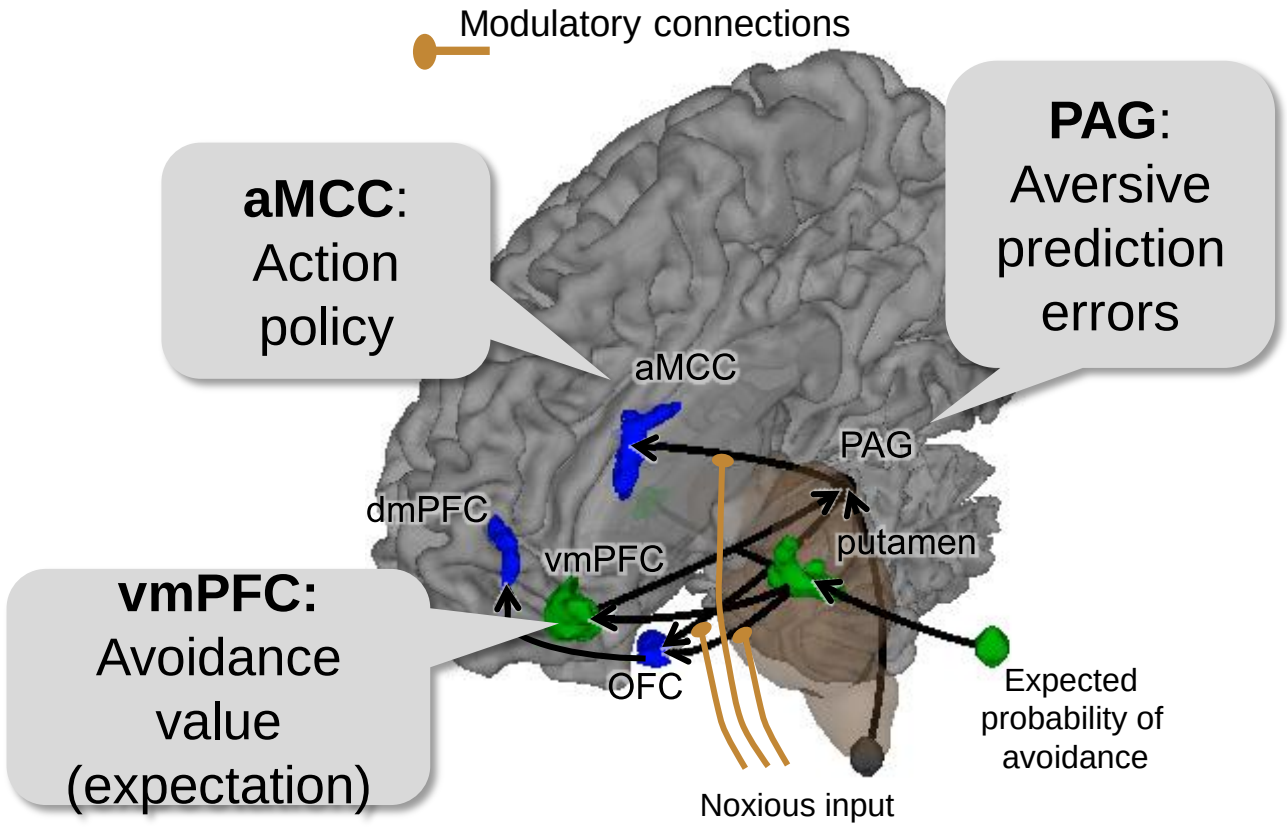
Lee et al. 2015, J Neuro



Optogenetic activation of vmPFC (prelimbic)-accumbens pathway reduces allodynia and depression-like behavior after spared nerve injury

See also Schwartz et al. 2014 *Science*; Wei 2008 *J Neuro*; Goffer 2013 *J Neuro*; Chang et al. 2014 *Pain*

Ventromedial prefrontal cortex:
Appraisal, emotion, and decision-making

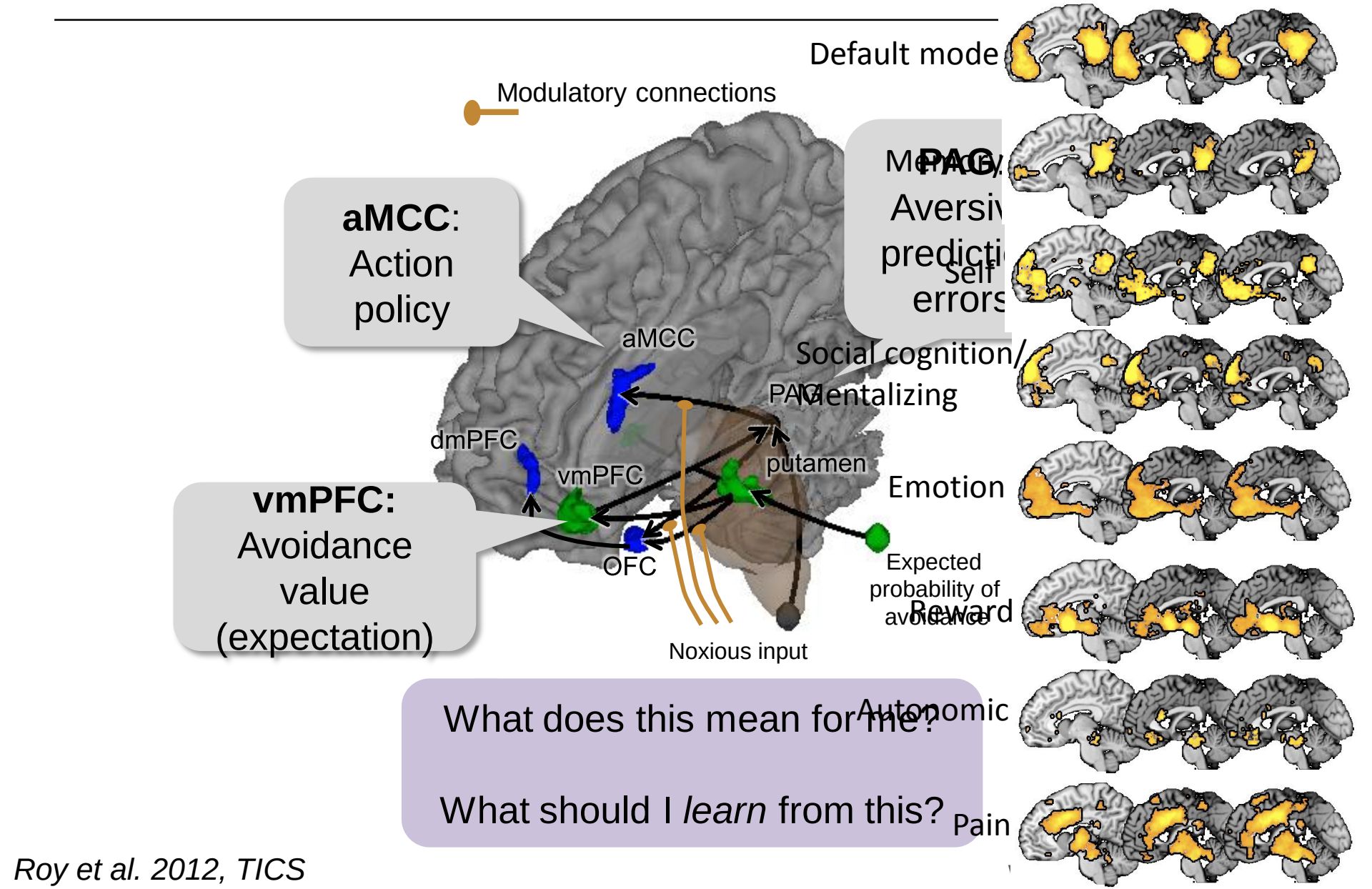


What does this mean for me?

What should I *learn* from this?

Roy et al. 2014, Nat

Ventromedial prefrontal cortex:
Appraisal, emotion, and decision-making



aMCC: Action policy

PAG: Aversiv predicti errors

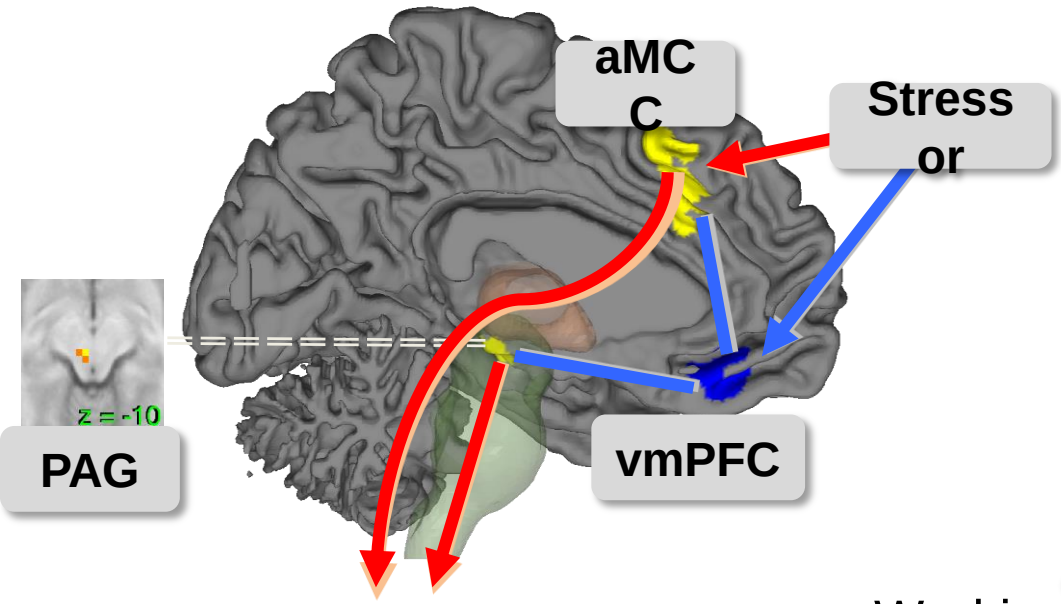
vmPFC: Avoidance value (expectation)

What does this mean for me?

What should I *learn* from this?

Roy et al. 2012, TICS

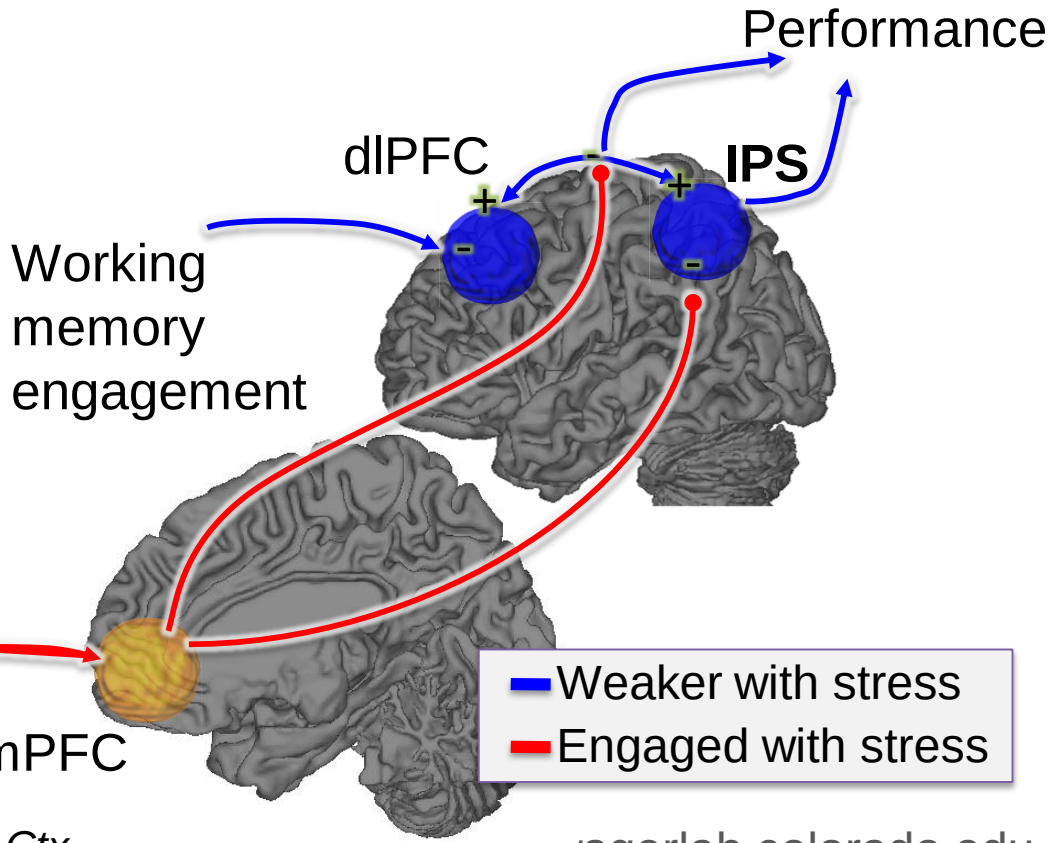
Key regions and pathways



Stress-related regulation of the heart

Positive relationship

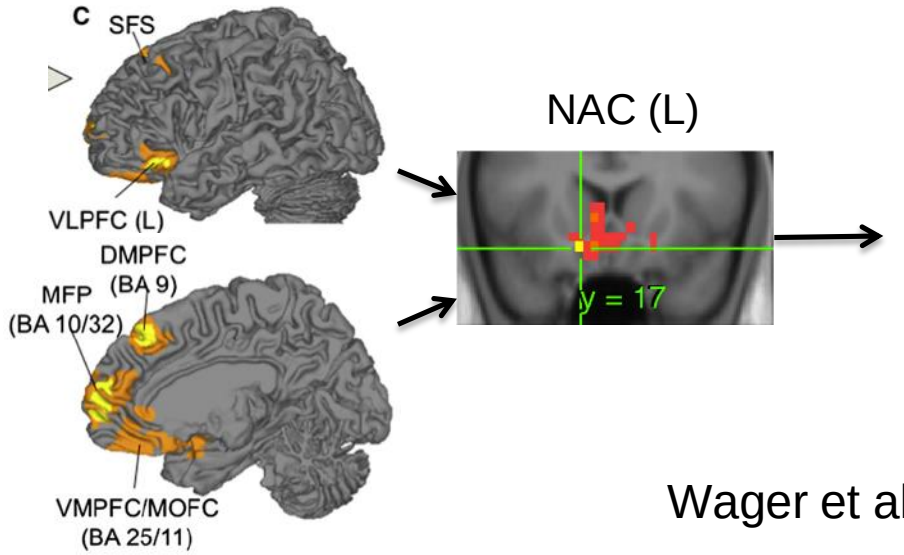
Negative relationship



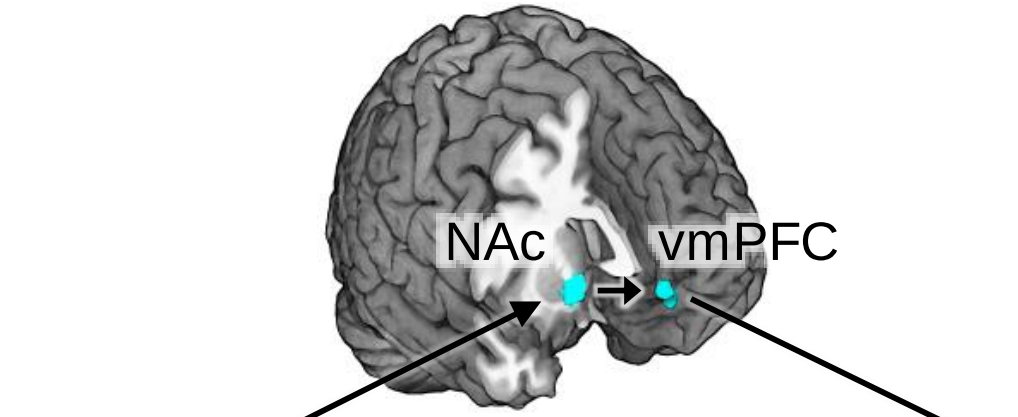
Stress-related memory impairment

Wager et al. 2009; van Ast et al. 2014, Cer Ctx

Links with cognitive self-regulation



Wager et al. 2008 Neuron

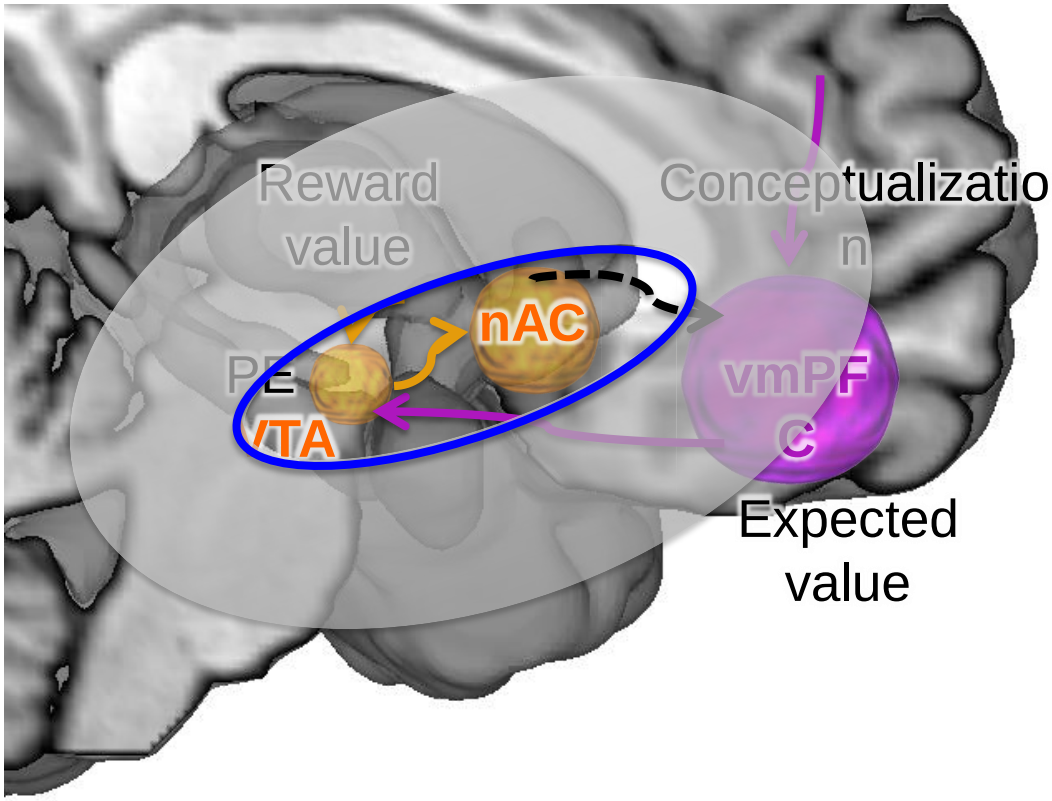


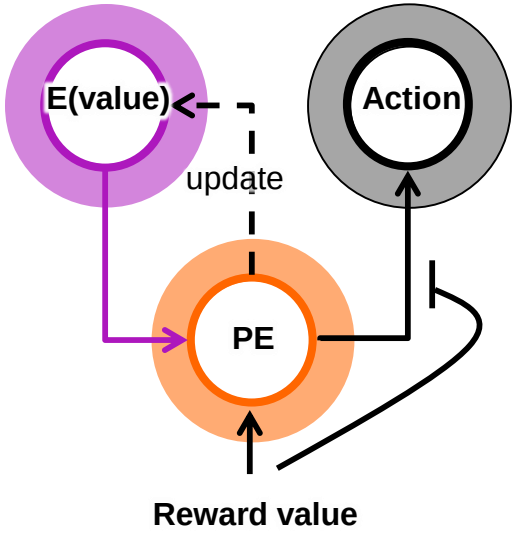
Woo et al. 2015 PLoS Biol

Parkinson's Disease and reward learning

Different disorder, similar circuit?

Mesolimbic prediction error (PE) closely associated with dopamine

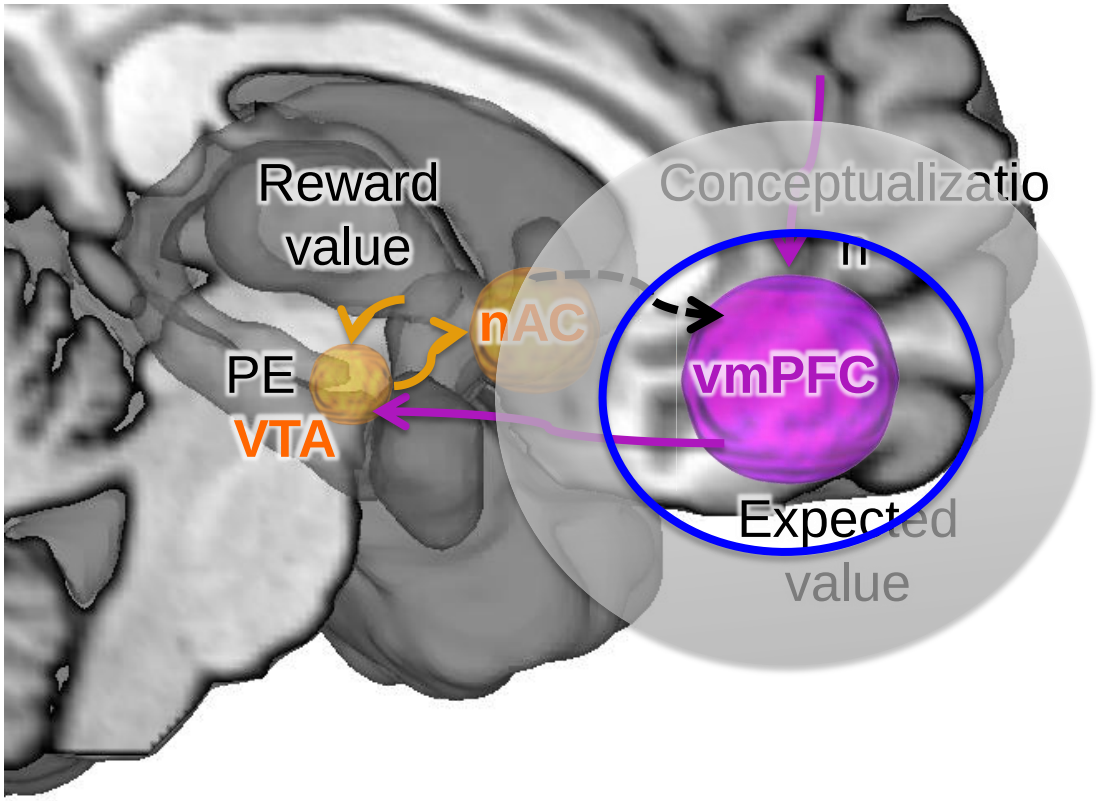


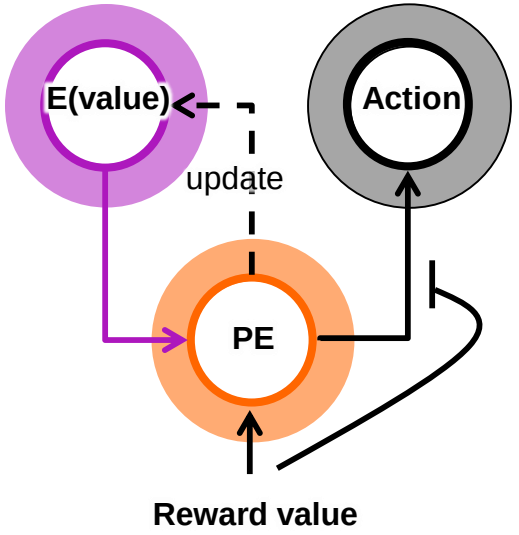


Parkinson's Disease and reward learning

Different disorder, similar circuit?

vmPFC 'value' related circuit: expected value of potential gain, reliable placebo effects in pain studies



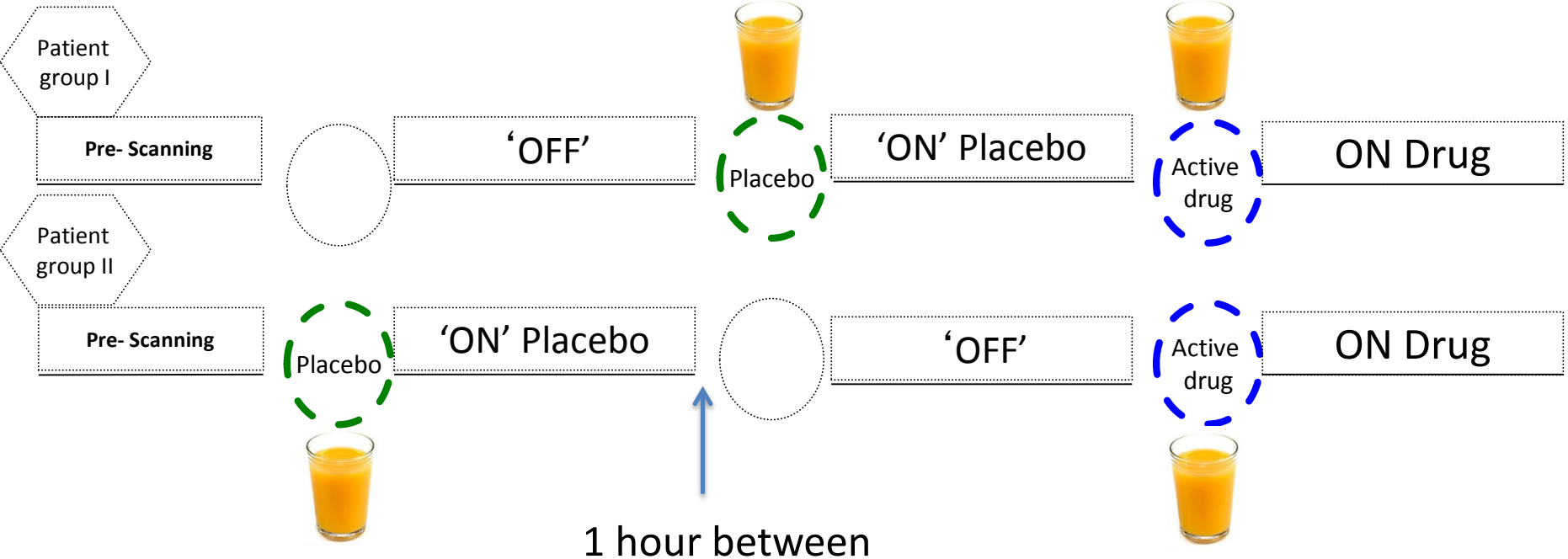


Parkinson's disease study: Experimental design

Liane Schmidt

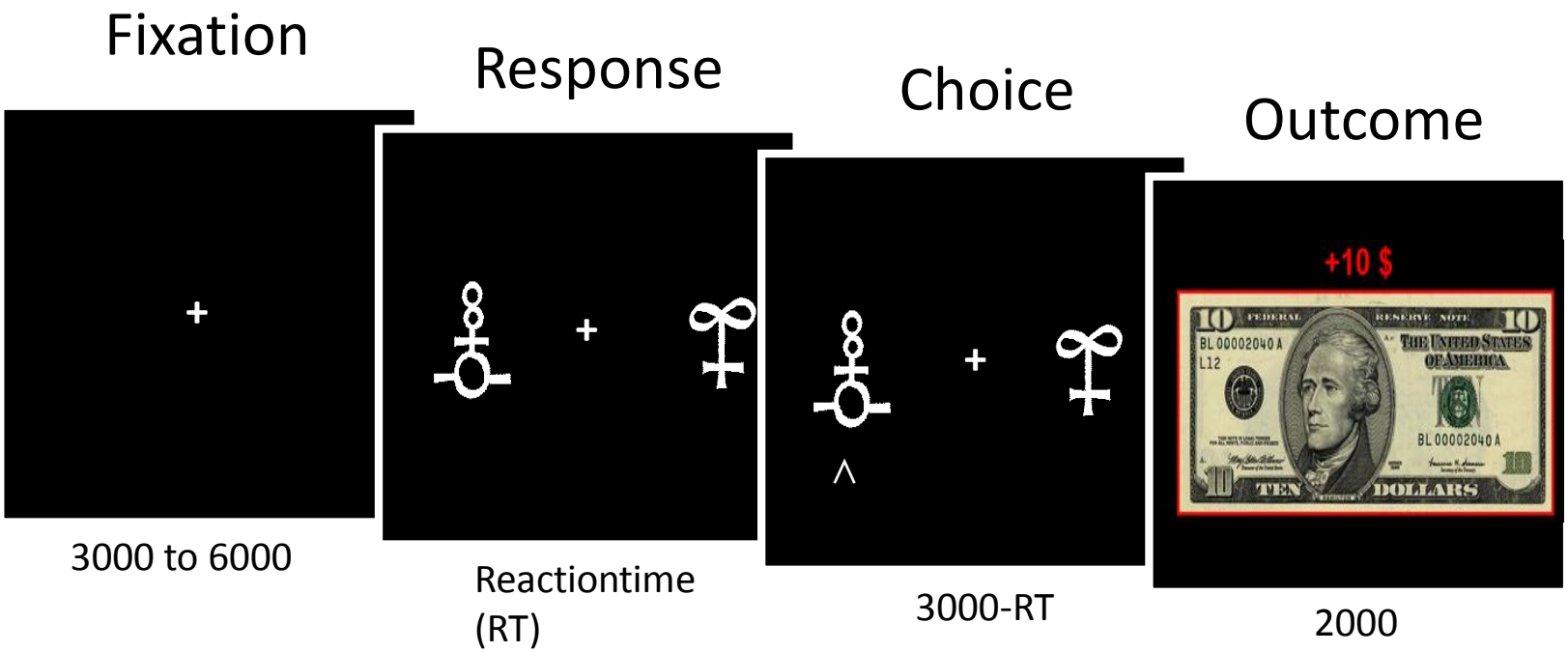
Daphna Shohamy

- Daily medication dissolved in orange juice
- Within-subject crossover design (placebo vs. control)



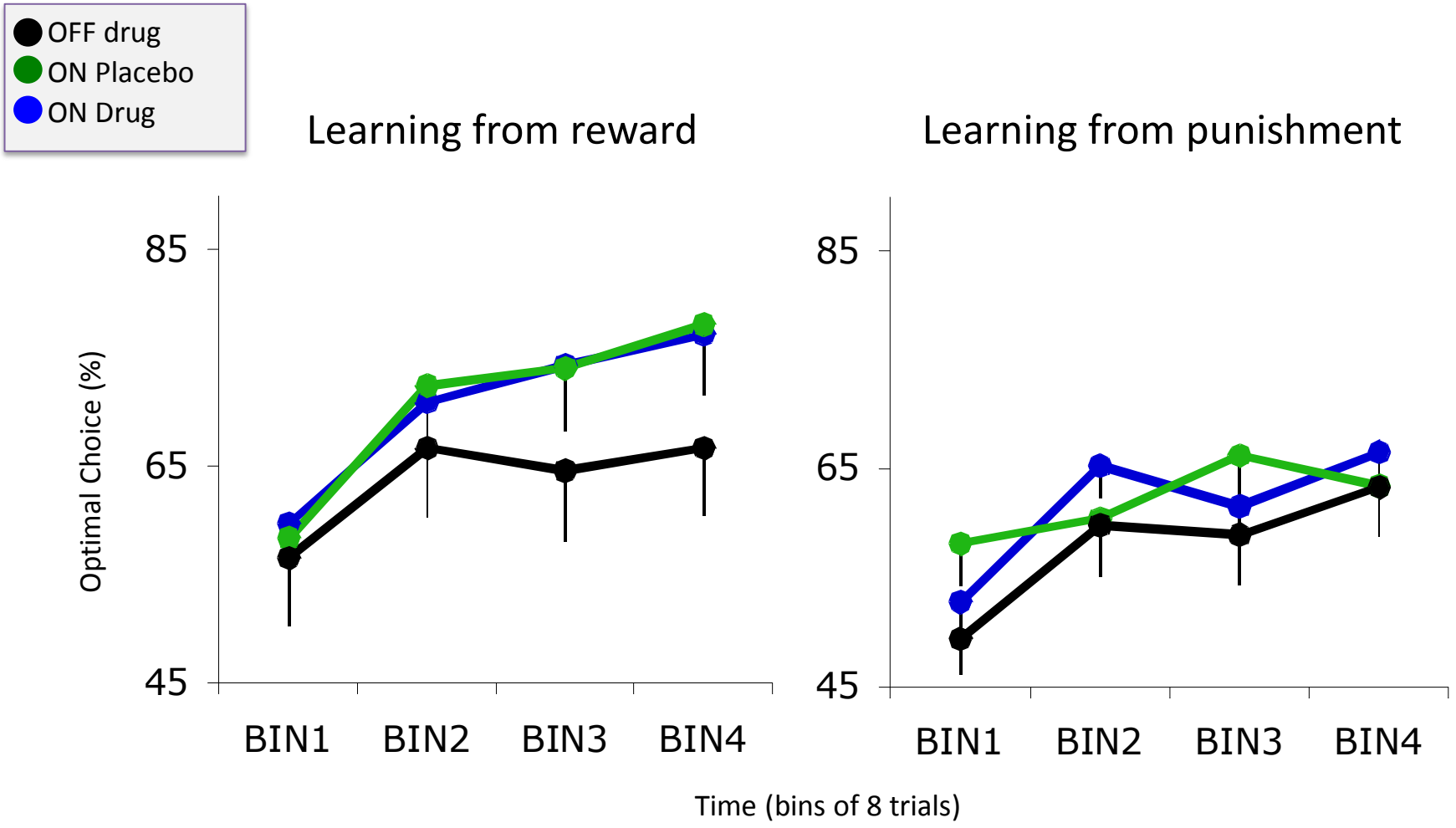
Schmidt et al. 2014, Nat Neuro

Operant learning task

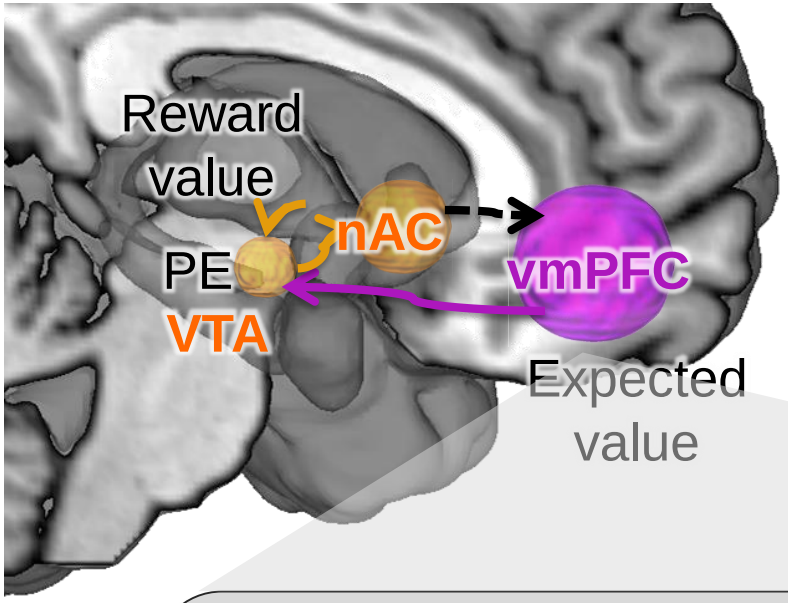


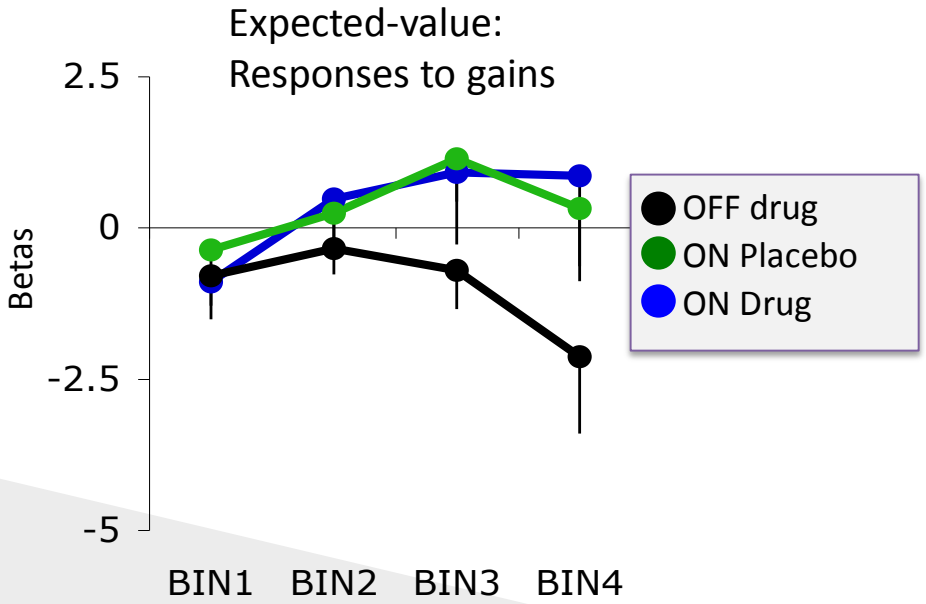
Reward learning: Which symbols are associated with reward?

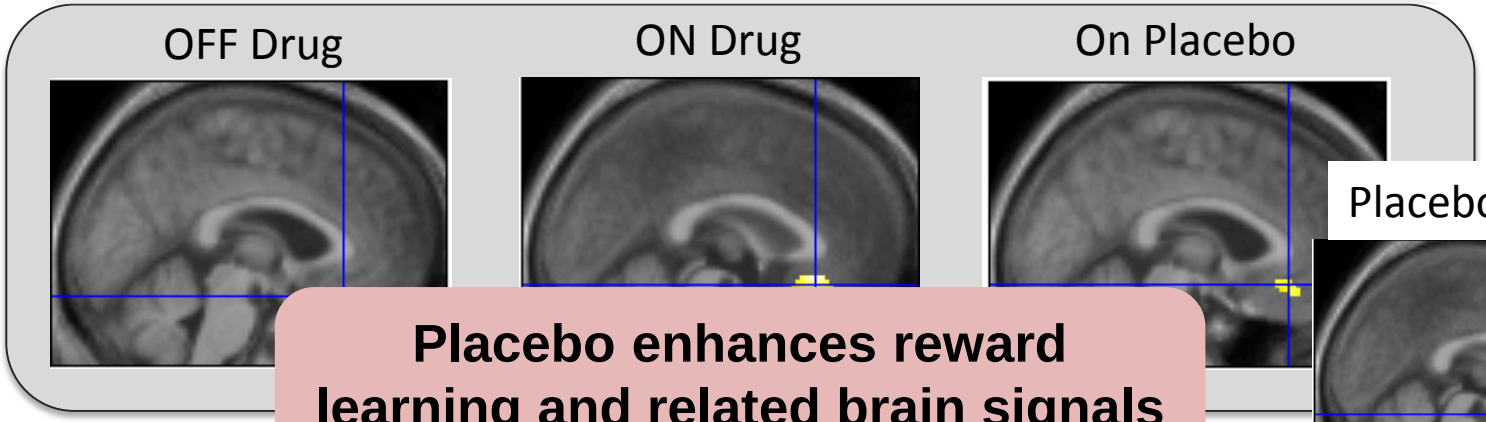
Results: Learning performance

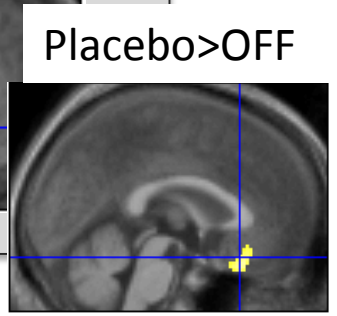


Placebo effects in Parkinson's Disease







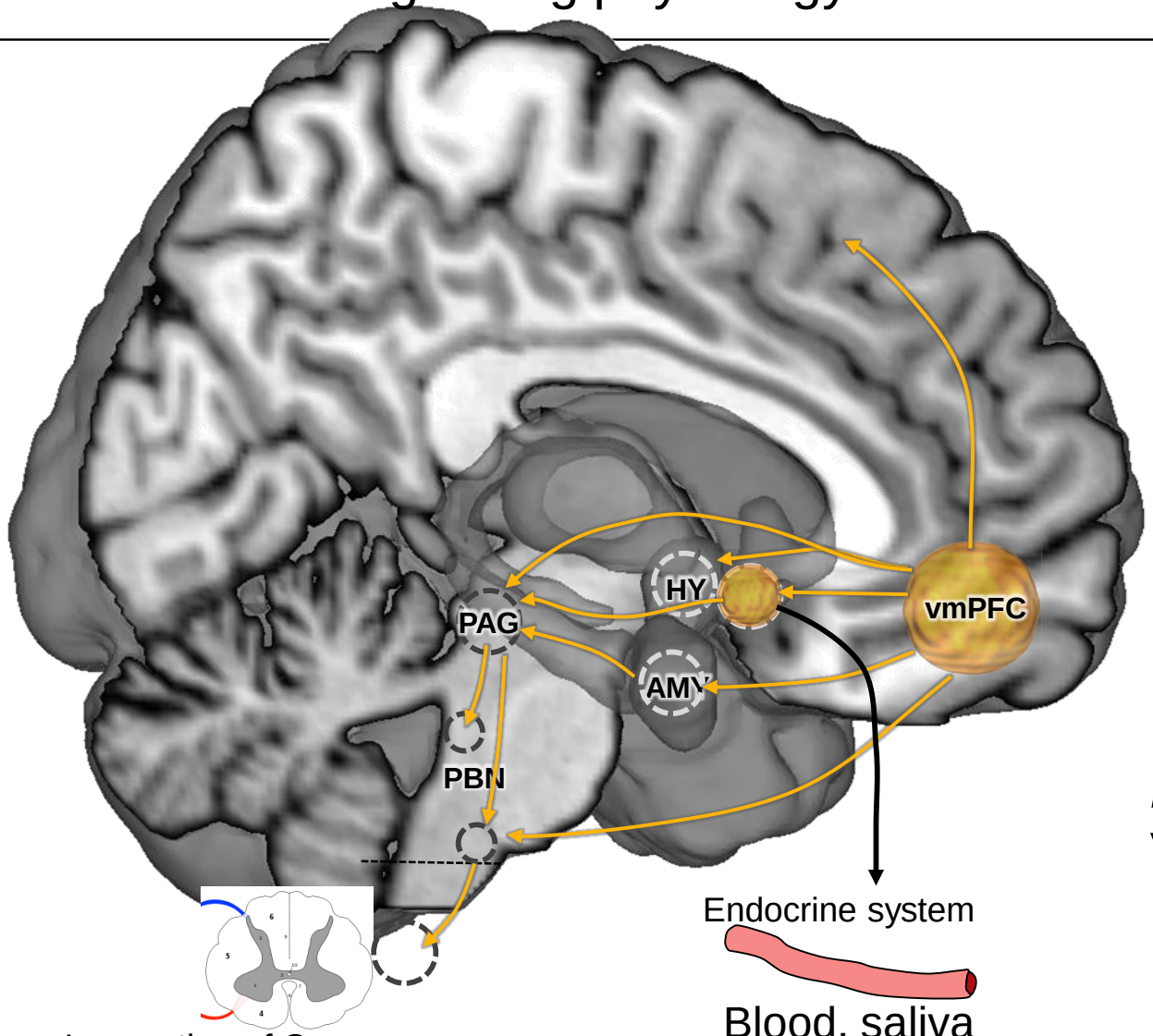


Placebo enhances reward learning and related brain signals in valuation/decision circuits

Schmidt et al. 2014, Nat Neuro

“Systems for survival”

Dual functions in regulating physiology and motivated behavior



Indirect:
Motivation, decision-making, health behaviors

Direct:
Visceromotor and neuroendocrine

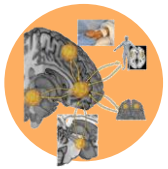
e.g., J. Price, 1999; Roy et al. 2012 TICS

Outline

Principles

Key brain findings

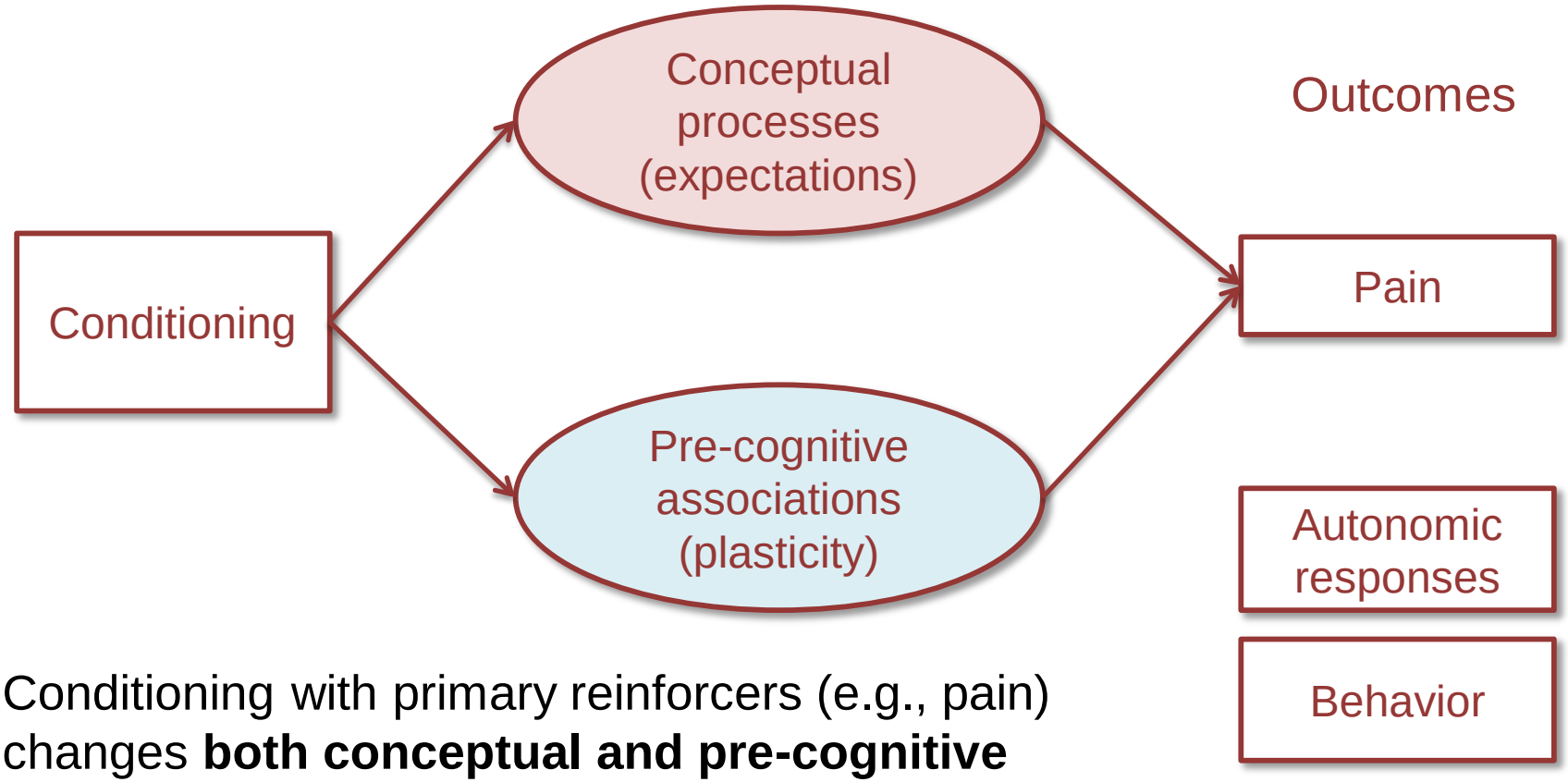
The meaning axis



Ingredients

Two key ingredients: Reinforcement and *Belief*

Modulation of pain and physiology without reinforcement?

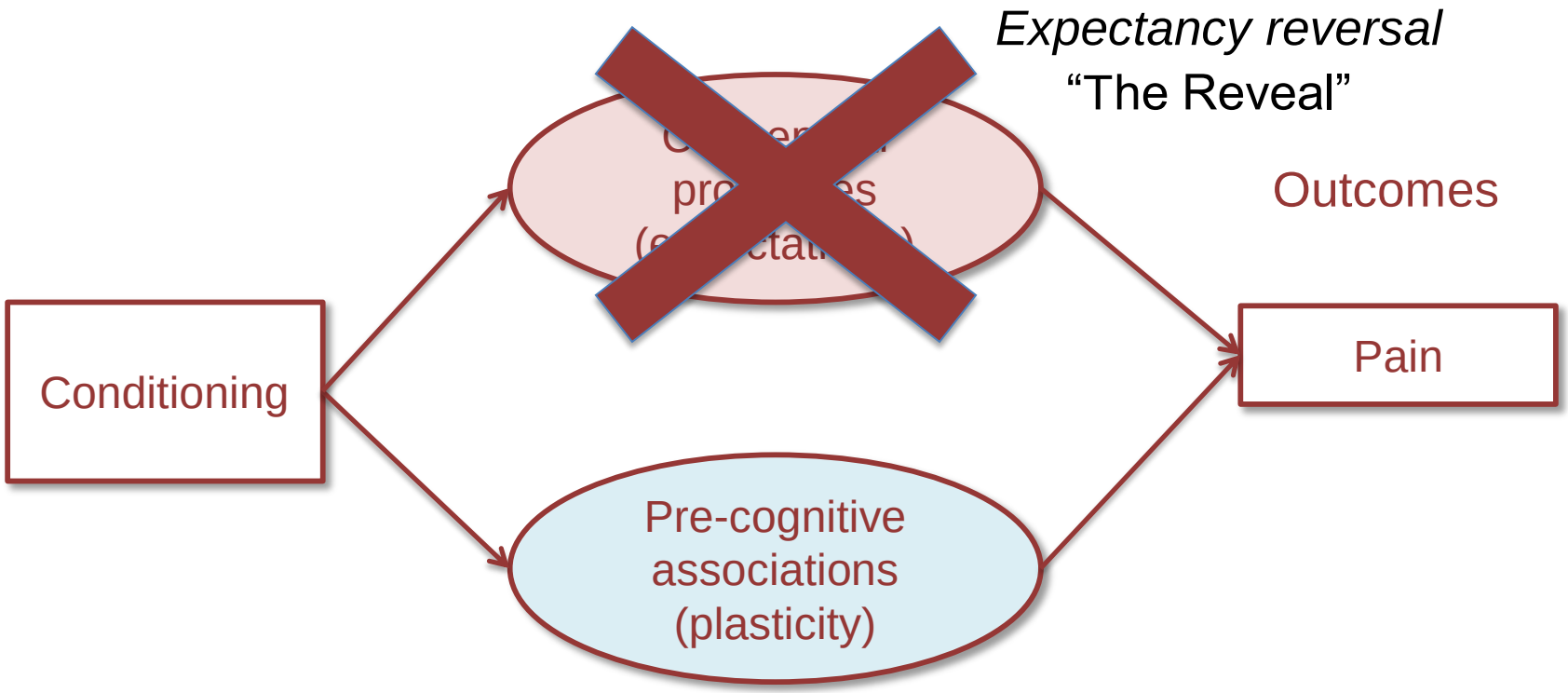


Conditioning with primary reinforcers (e.g., pain) changes **both conceptual and pre-cognitive processes**

e.g., Kirsch et al. 2004; Montgomery & Kirsch 1997

Ingredient 1: Reinforcement

Placebo without expectations?



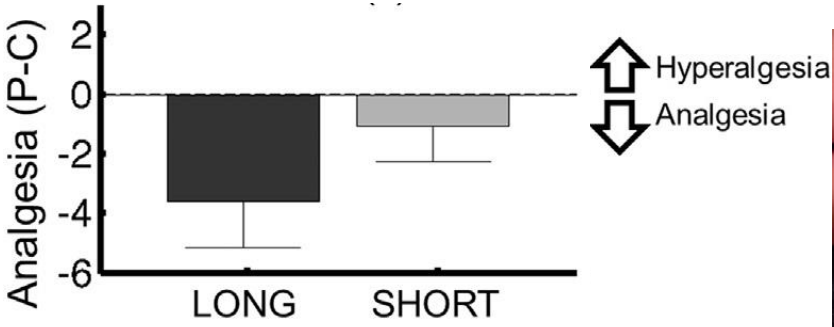
Schafer et al. 2015, J of Pain

Ingredient 1: Reinforcement

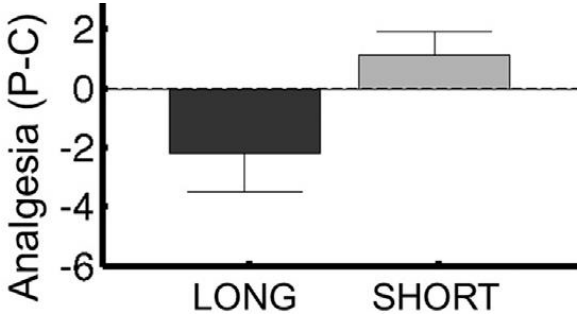
Placebo effects without expectations?

SHORT: Conditioning x 1 day → Placebo vs. control test

LONG: Conditioning x 4 days → Placebo vs. control test



"The Reveal"

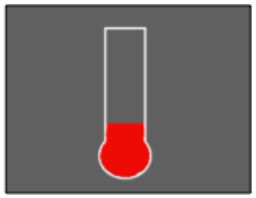


Yes: After 4 days of conditioning, placebo effects persist without expectations.

Schafer et al. 2015; See also: Colloca et al. 2008, 2010; Benedetti et al. 2003; Exton et al. 2011

Ingredient 2: Belief

Strengthening beliefs without conditioning



‘Symbolic Conditioning’

Conceptual processes (expectations)

Outcomes

Pain

Autonomic responses

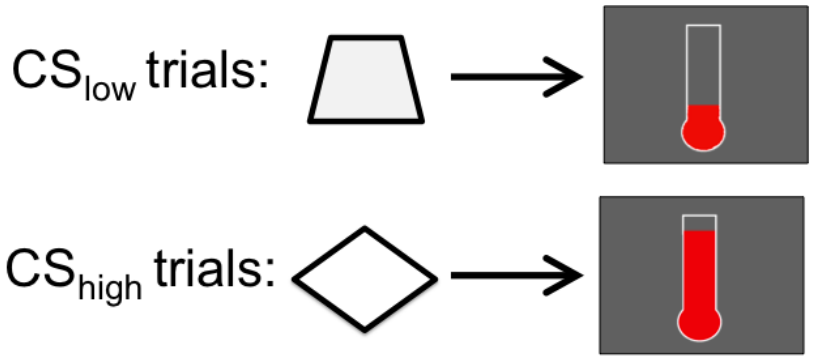
Reinforcement with conceptual cues (no affective value or associations with pain)

Symbolic conditioning:
Conditioning to a cognitive representation of pain

‘Symbolic conditioning’ phase:

CS_{low} trials:

CS_{high} trials:



Shape-heat associations are learned, but with *no primary reinforcement*.

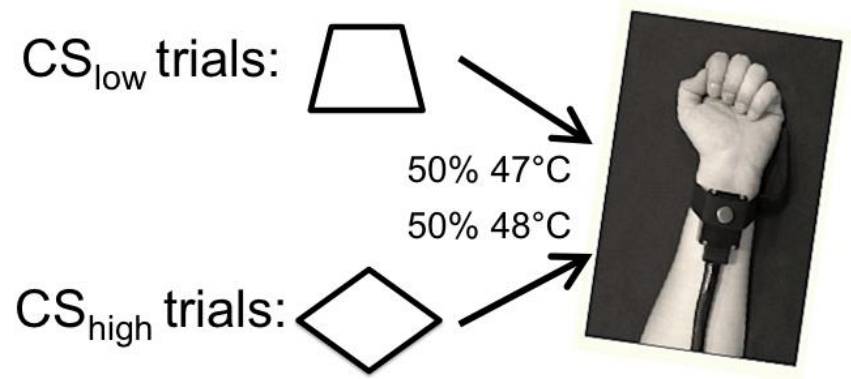
Test phase: Noxious heat

CS_{low} trials:

50% 47°C

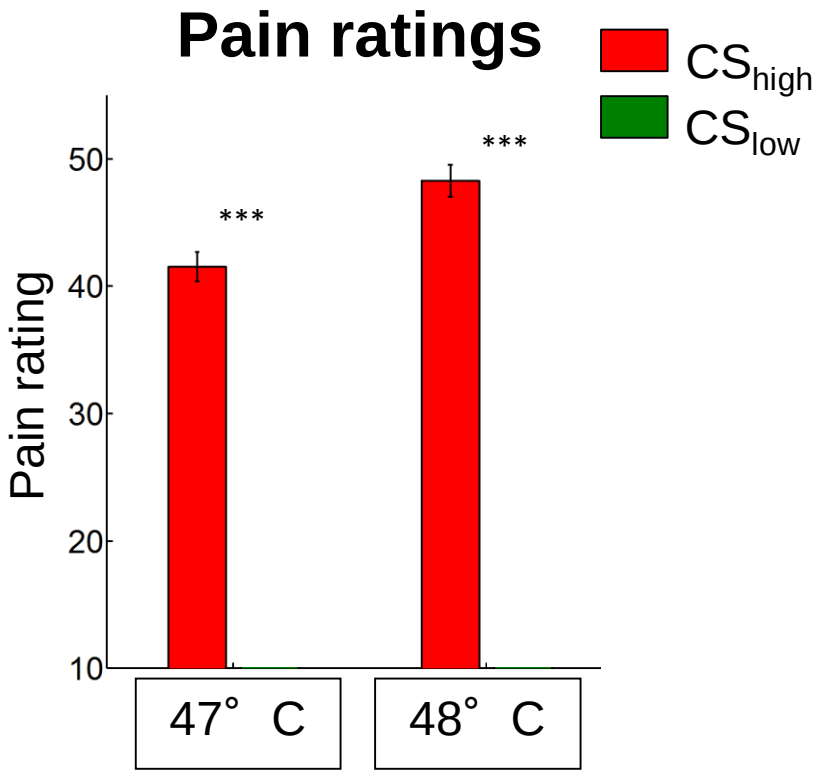
50% 48°C

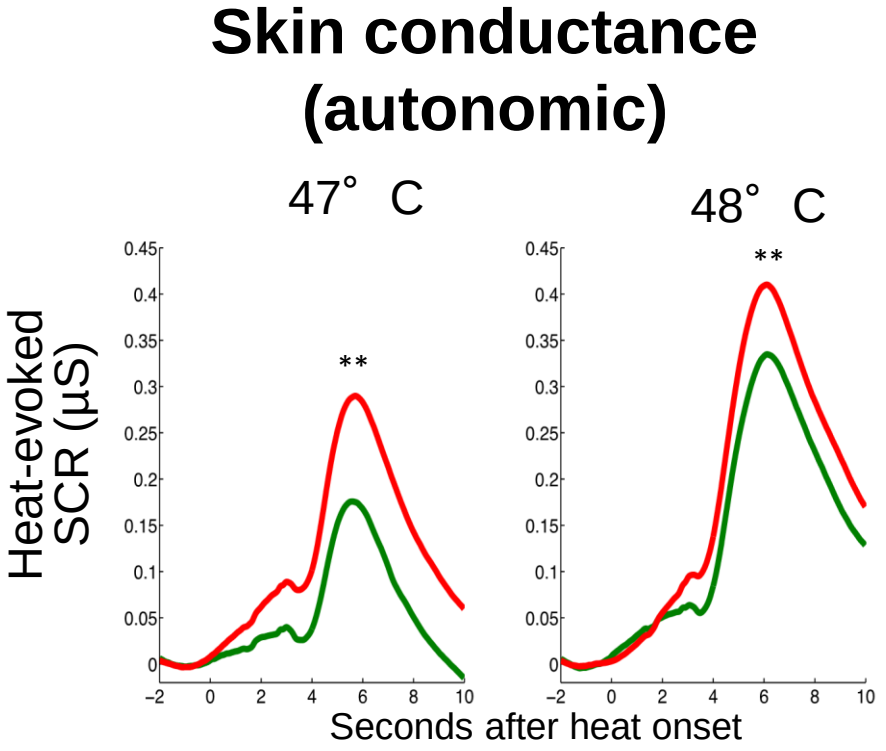
CS_{high} trials:



Heat intensity matched across cues
Test causal effects of cue value on pain

Symbolic conditioning:
Cue effects on pain and physiology in the test phase



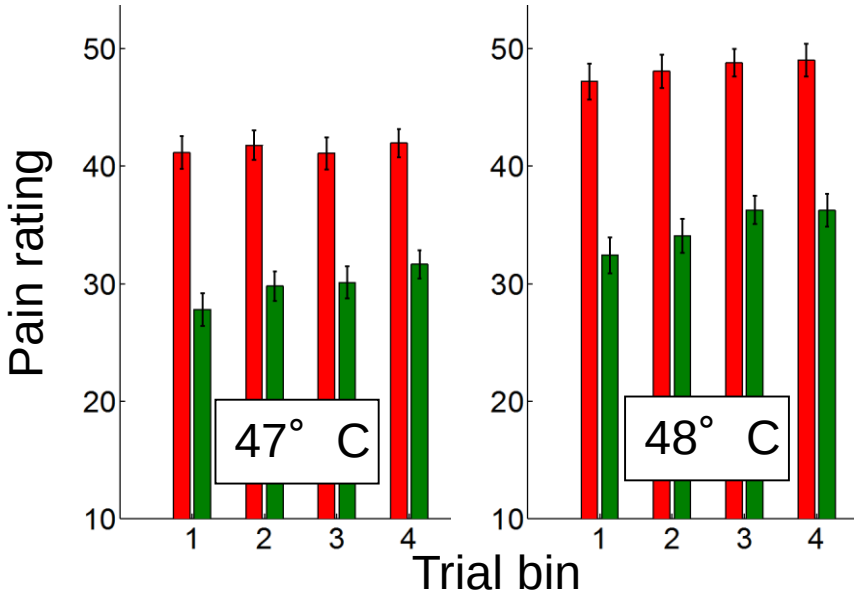


Both pain and skin conductance are:

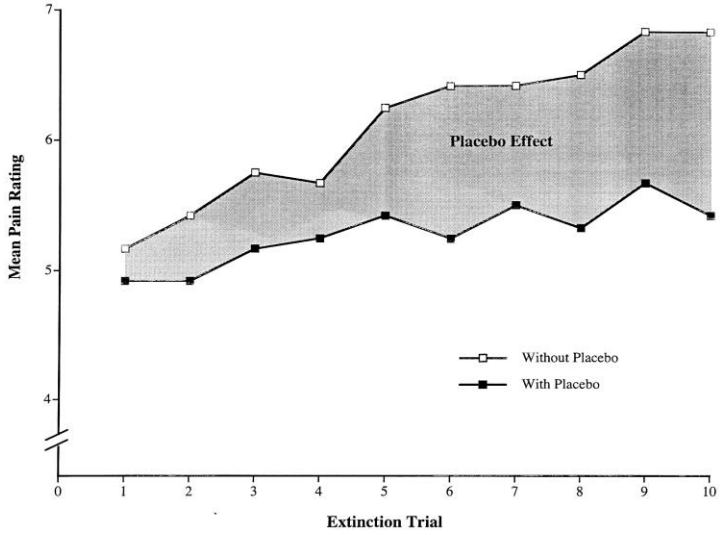
Primary reinforcers (e.g., shock/pain) are not required for conditioned pain modulation: Conceptual associations can have powerful effects

Stability across time: Self-reinforcing placebo effects?

Effects remain stable without reinforcement



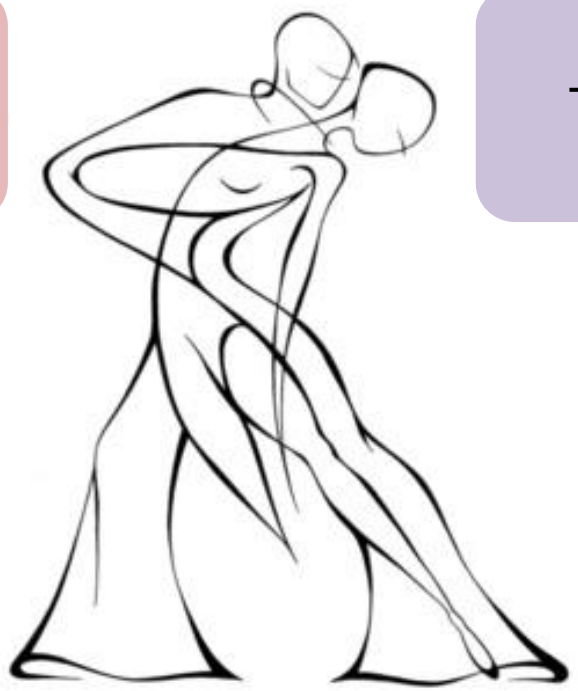
Placebo responses can be ‘self-reinforcing’



Montgomery & Kirsch, 1997

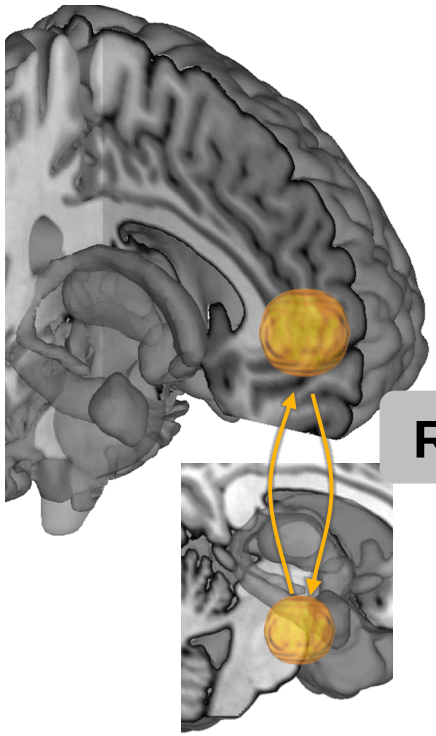
The dance of the placebos

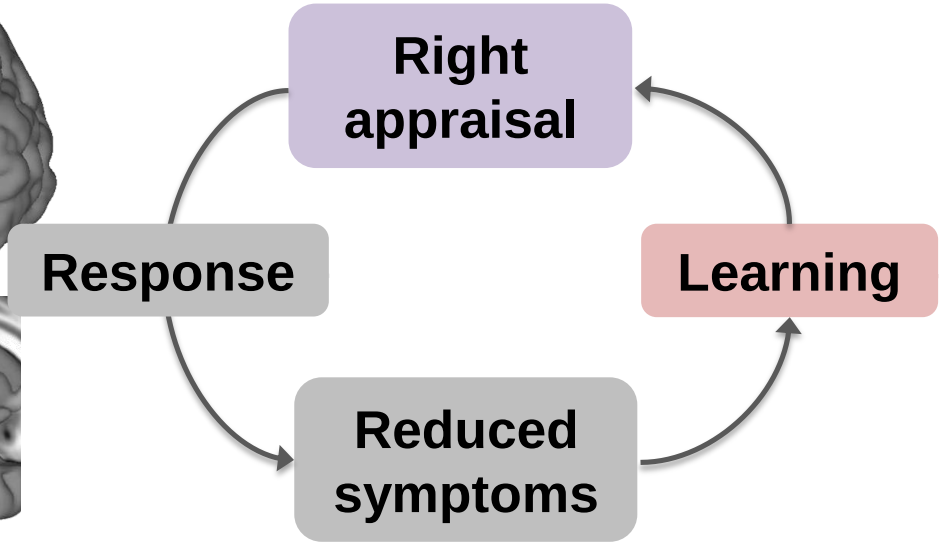
Plasticity:
The automation of everything useful



Appraisal:
The meaning of things

Stability across time: Self-reinforcing placebo effects?





Long-term
Stable, learned responses

Immediate
Acute responses

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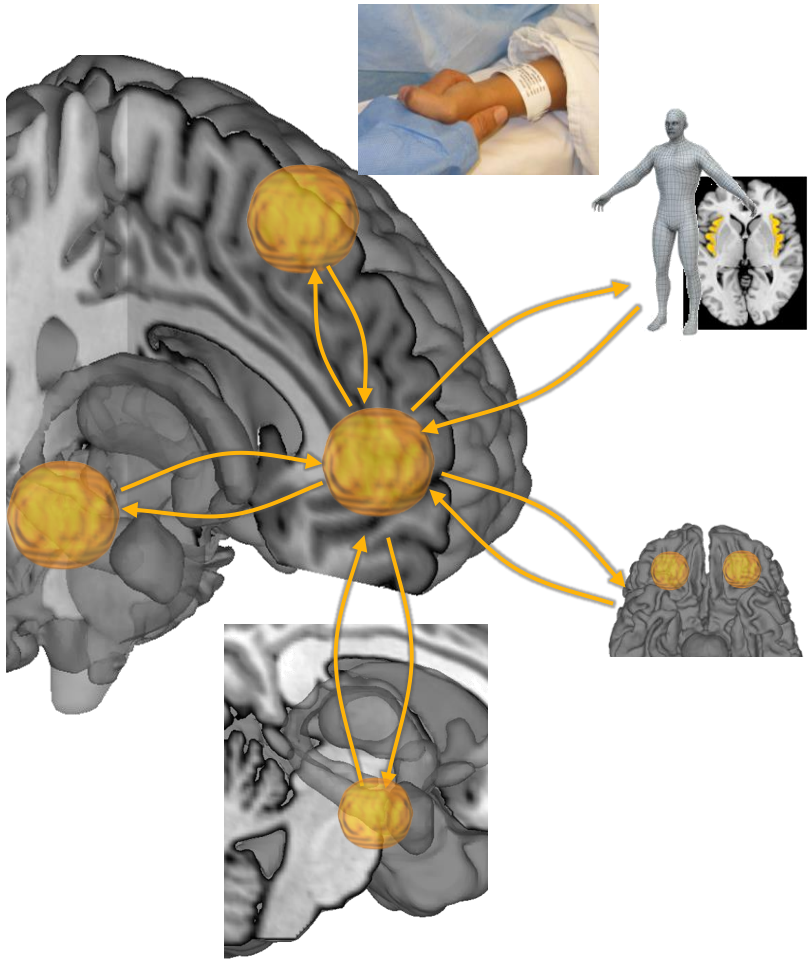
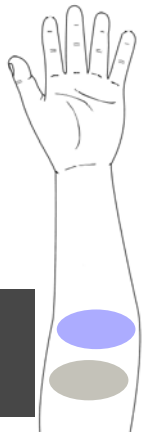


• S.D.G.

Placebo analgesia: fMRI setup

Apply creams

fMRI Scanning



Calibration → Manipulation → Test

Choose temperatures

Subjective Levels

2, 5, and 8 on 10-point scale

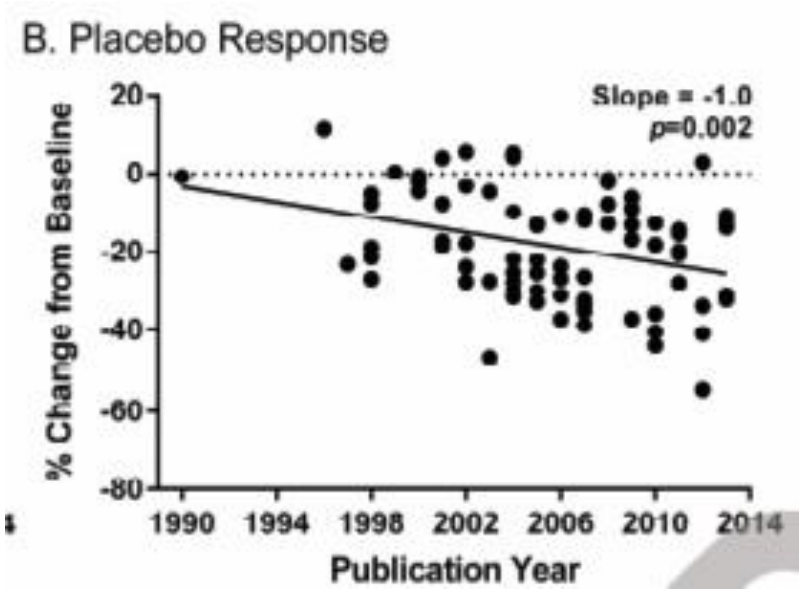
Increase expectancy

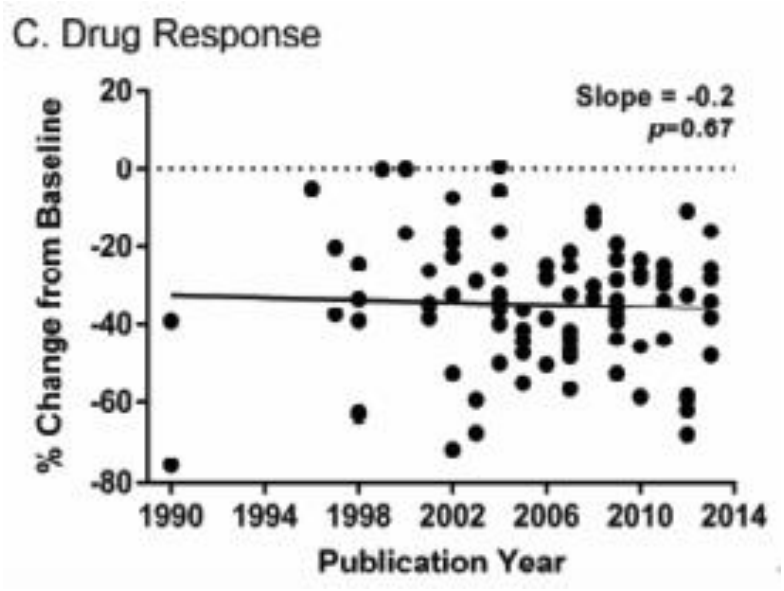
Stim. At Level 8 on Control region;

Reduce temperature to Level 2 on Placebo region

Stimulation at Level 5 on both Placebo and Control regions; order counterbalanced

Problems for clinical trials





Placebo responses in pain trials are growing across years

- Specifically in the U.S. (not Europe)
- Drug responses are not growing, causing more trials to fail
- One likely cause is direct-to-consumer marketing coupled with subjective pain measures

Tuttle et al. 2015, Pain