Brain mechanisms and implications of the placebo effect

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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”

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

Primary Endpoint - UPDRS Part III OFF: Mean Change from Baseline

- Sham Surgery
- AAV2-NRTN

Olanow et al. 2015
45% of physicians reported using placebo treatments in clinical practice in 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

$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)


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”

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


- **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. 2012 [ghrelin])

Placebo effects: Windows into treatment context

- 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

Plasticity: The automation of everything useful
- Sensations
- Action tendencies
- Autonomic responses
- Hormones

Appraisal: The meaning of things
- Emotion
- Motivation
- Affective state
- Expectations
- Appraisals
- Memories

Pathophysiology (signs) → Pre-cognitive association

Behaviour

Reported experience (symptoms)

'Vegetative stream'
Placebo, context and brain

Conceptual pattern generators: Situational schemas

Social context

DMPFC

Memory, place context

vmPFC

Affective pattern generators

Hipp

Expected future events

Interoceptive context

Insula

Plasticity:
Pathways that are used become stronger

Visceral pattern generators

Thermoregulation, emesis, nociception

PAG

Amy

NAC

Fight, escape, submit, pursue, recover, etc.

Appraisal:
Situational meaning
“Self in context”

Expression:
Emotion, autonomic and neuroendocrine responses, decisions
The dance of the placebos

**Plasticity:**
The automation of everything useful

**Appraisal:**
The meaning of things
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

- **dIPFC**: Goal context, expectancy
- **mThal**: Pain and affect integration
- **aINS**: Motivation, decision, affect
- **dACC**: Avoidance value
- **vmPFC**: Meaning ‘schema’
- **S2/dpINS**: Somatic representation
- **PAG**: Emotion, regulation of pain, autonomies
- **RVM**: Spinal control of pain, autonomies
- **NAC**: Motivational and hedonic value
- **Orbitofrontal**: Outcome expectancy
- **mlOFC**: Outcome expectancy
- **mThal**: Pain and affect integration
- **vmPFC**: Meaning ‘schema’
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Placebo analgesia: Key results

Reduced response to painful stimulation

- rACC
- Insula
- PHCP, Thalamus

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

rACC

Insula

PHCP, Thalamus

Increases during anticipation

Opioid release (PET)

PAG

OFC

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

Wagerlab.colorado.edu
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
Descending pathways from ventromedial prefrontal cortex: Pain regulation

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

Modulation: Descending control

Optogenetic activation of vmPFC (prelimbic)-accumbens pathway reduces allodynia and depression-like behavior after spared nerve injury.
Ventromedial prefrontal cortex:
Appraisal, emotion, and decision-making

Modulatory connections

**aMCC:** Action policy

**vmPFC:** Avoidance value (expectation)

**PAG:** Aversive prediction errors

- dmPFC
- vmPFC
- OFC
- putamen

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

Noxious input
Expected probability of avoidance

Modulatory connections

aMCC: Action policy

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

Stressor

Working memory engagement

Performance

Weaker with stress
Engaged with stress

Heart Rate

PAG

vmPFC

aMC

IPS

dlPFC

vmPFC

Stress

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

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

Schmidt et al. 2014, Nat Neuro
Operant learning task

**Fixation**

3000 to 6000

**Response**

Reaction time (RT)

**Choice**

3000-RT

**Outcome**

+10 $

*Reward learning:* Which symbols are associated with reward?
Results: Learning performance

<table>
<thead>
<tr>
<th>BIN1</th>
<th>BIN2</th>
<th>BIN3</th>
<th>BIN4</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFF drug</td>
<td>ON Placebo</td>
<td>ON Drug</td>
<td></td>
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Learning from reward

Learning from punishment

Optimal Choice (%)

Time (bins of 8 trials)
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

Innervation of Organs:
- Cholinergic system (Ach), Vagus
- Adrenergic system (NE), sympathetic

Direct:
- Visceromotor and neuroendocrine

Indirect:
- Motivation, decision-making, health behaviors

Blood, saliva
- Biochemical: cortisol

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?

Expectancy reversal
“The Reveal”

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

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

Symbolic conditioning:
Conditioning to a cognitive representation of pain

‘Symbolic conditioning’ phase:

CS\textsubscript{low} trials:

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{shape_low.png}
\caption{Shape-heat associations are learned, but with no primary reinforcement.}
\end{figure}

CS\textsubscript{high} trials:

\begin{figure}[h]
\centering
\includegraphics[width=0.2\textwidth]{shape_high.png}
\caption{Heat intensity matched across cues
Test causal effects of cue value on pain}
\end{figure}

Test phase: Noxious heat

CS\textsubscript{low} trials:

\begin{itemize}
\item 50% 47°C
\item 50% 48°C
\end{itemize}

Jepma & Wager, 2015, Psych Sci
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?

Response → Right appraisal → Learning → Reduced symptoms → Response

- Immediate
  - Acute responses
- Long-term
  - Stable, learned responses
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Placebo analgesia: fMRI setup

**Apply creams**

**fMRI Scanning**

- **Placebo**
  - Control
- **Control**
  - Placebo

**Calibration**

**Manipulation**

- **Stim. At Level 8** on Control region; Reduce temperature to Level 2 on Placebo region

**Test**

**Choose temperatures**

Subjective Levels 2, 5, and 8 on 10-point scale

**Increase expectancy**

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*