PLACEBO EFFECTS
& TRANSCRANIAL MAGNETIC STIMULATION

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Intensive Course in Transcranial Magnetic Stimulation, 10/26/18
DISCLOSURES

None
CONTEXT

Dr. Alvaro Pascual-Leone
Director of the Berenson-Allen Center for Noninvasive Brain Stimulation

Dr. Ted Kaptchuk
Director of the Harvard University Program in Placebo Studies
THE TIME IS NOW...
OUTLINE

1. Neurobiology of Placebo Effects
   - Definitions
   - Mechanisms of action
   - Evidence and theories

2. “Differential” Placebo Effects
   - Historical context
   - Meta-analytic approaches
   - Prospective approaches

3. TMS and Placebo Effects
   - Sham devices
   - Quantifying magnitude
   - Implications on clinical trial results
"Do you have that placebo I've heard so much about?"
The neuroscience of placebo effects: connecting context, learning and health

Tor D. Wager\textsuperscript{1} and Lauren Y. Atlas\textsuperscript{2}

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
Placebo and Opioid Analgesia--Imaging a Shared Neuronal Network
Predrag Petrovic, Eija Kalso, Karl Magnus Petersson, and Martin Ingvar

*Science* 295 (5560), 1737-1740.
DOI: 10.1126/science.1067176 Originally published online February 7, 2002
BIOLOGICAL MECHANISMS

- Opioid, dopamine, cannabinoid, serotonergic, neuroendocrine, and neuro-immunological pathways (+ others) have all been implicated in placebo effects.
Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia

Falk Eippert, Ulrike Bingel, Eszter D. Schoell, Juliana Yacubian, Bernd Klinger, Jürgen Lorenz, and Christian Böchel
Two major theories to explain placebo effects:

- Expectation
- Learning/Conditioning
“Placebo effects generally correspond to people’s knowledge or beliefs about the kind of drug they believe they are receiving, and for that reason, a causal relation between expectancy and placebo reaction has generally been assumed...”
OPEN-HIDDEN PARADIGMS

Enck et al. 2013
Two major theories to explain placebo effects:

- **Expectation**
- **Learning/Conditioning**
Learned immunosuppressive placebo responses in renal transplant patients

Julia Kirchhof, Liubov Petrakova, Alexandra Brinkhoff, Sven Benson, Justine Schmidt, Maike Unteroberdörster, Benjamin Wilde, Ted J. Kaptchuk, Oliver Witzke, and Manfred Schedlowski

Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, 45122 Essen, Germany; Department of Nephrology, University Hospital Essen, University of Duisburg-Essen, 45122 Essen, Germany; Clinic of Neurosurgery, University Hospital Essen, University of Duisburg-Essen, 45122 Essen, Germany; Program in Placebo Studies, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA 02215; Department of Infectious Diseases, University Hospital Essen, University of Duisburg-Essen, 45122 Essen, Germany; and Department of Clinical Neuroscience, Karolinska Institutet, 171 77 Stockholm, Sweden

Baseline

Acquisition

Evocation

days 1

time am pm

2 am

pm

2 d

1 pm 5 pm

blood samples (11 am, 3 pm, 7 pm)

Baseline

Acquisition

Evocation

days 1

time am pm

2 am

pm

2 d

1 pm 5 pm

blood samples (11 am, 3 pm, 7 pm)

CsA/Tac, Placebo, CS
THEORIES OF PLACEBO EFFECTS

- Two major theories to explain placebo effects:
  - EXPECTATION
  - LEARNING/CONDITIONING

“Rather than being viewed as an alternative to expectancy, classical conditioning can be understood as one method by which expectancies are formed”
Placebo Effects: From the Neurobiological Paradigm to Translational Implications

Fabrizio Benedetti¹,
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*Correspondence: fabrizio.benedetti@unito.it
http://dx.doi.org/10.101

Placebo Effects in Medicine
Ted J. Kaptchuk and Franklin G. Miller, Ph.D.

The placebo response in medicine: minimize, maximize or personalize?
Paul Enck, Ulrike Bingel, Manfred Schedlowski and Winfried Rief
HETEROGENEITY IN RESPONSES?
Genetics and the placebo effect: the placebome

Kathryn T. Hall\textsuperscript{1,2}, Joseph Loscalzo\textsuperscript{3}, and Ted J. Kaptchuk\textsuperscript{1,2}

Table 1. Polymorphisms in candidate genes that may be part of the placebo effect

<table>
<thead>
<tr>
<th>Placebo pathway</th>
<th>Gene name</th>
<th>Gene symbol</th>
<th>Chromosomal location</th>
<th>Placebo SNPs</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Catechol-O-methyltransferase</td>
<td>COMT</td>
<td>22q11.2</td>
<td>rs4680</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>Monoamine oxidase</td>
<td>MAO-A</td>
<td>Xp11.3</td>
<td>rs6323, rs6609257</td>
<td>[43,55]</td>
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<td></td>
<td>Dopamine B hydroxylase</td>
<td>DBH</td>
<td>9q34</td>
<td>rs2873804</td>
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<tr>
<td></td>
<td>Dopamine receptor 3</td>
<td>DRD3</td>
<td>3q13.31</td>
<td>rs6280</td>
<td>[69]</td>
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<tr>
<td></td>
<td>Brain-derived neurotrophic factor</td>
<td>BDNF</td>
<td>11p14.1</td>
<td>rs6285</td>
<td>[66]</td>
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<tr>
<td>Serotonin</td>
<td>Tryptophan hydroxylase-2</td>
<td>TPH2</td>
<td>12q21.1</td>
<td>rs4570625</td>
<td>[75]</td>
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<td></td>
<td>5-Hydroxytryptamine transporter</td>
<td>SLC6A4</td>
<td>17q11.2</td>
<td>rs4251417</td>
<td>[43]</td>
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<td>5-Hydroxytryptamine receptor 2A</td>
<td>HTR2A</td>
<td>13q14.2</td>
<td>rs2296972, rs622337</td>
<td>[43]</td>
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<td>Serotonin transporter gene-linked</td>
<td>5-HTTLP2</td>
<td>17q11.2</td>
<td>Variable tandem</td>
<td>[75]</td>
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<tr>
<td></td>
<td>polymorphic region</td>
<td></td>
<td></td>
<td>nucleotide repeat</td>
<td></td>
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<tr>
<td>Opioid</td>
<td>Opioid receptor</td>
<td>OPRM1</td>
<td>6q25.2</td>
<td>rs510769</td>
<td>[69]</td>
</tr>
<tr>
<td>Endocannabinoid</td>
<td>Fatty acid amide hydrolase</td>
<td>FAAH</td>
<td>1p33</td>
<td>rs324420</td>
<td>[73]</td>
</tr>
</tbody>
</table>
Active Albuterol or Placebo, Sham Acupuncture, or No Intervention in Asthma

Michael E. Wechsler, M.D., John M. Kelley, Ph.D., Ingrid O.E. Boyd, M.P.H., Stefanie Dutile, B.S., Gautham Marigowda, M.B., Irving Kirsch, Ph.D., Elliot Israel, M.D., and Ted J. Kaptchuk
Figure 3. Percent Change in Maximum Forced Expiratory Volume in 1 Second (FEV₁) with Each of the Four Interventions.

The relative improvement in FEV₁, achieved with albuterol was significantly greater than that achieved with each of the other three interventions (P<0.001). No other differences among the four experimental conditions were significant. T bars indicate standard errors.

Figure 4. Percent Change in Subjective Improvement with Each of the Four Interventions.

The relative improvement in subjective outcomes, assessed with the use of a visual-analogue scale (with 0 indicating no improvement and 10 indicating complete improvement), was significantly greater with the albuterol inhaler, placebo inhaler, and sham acupuncture interventions than with the no-intervention control (P<0.001). No other differences among the four experimental conditions were significant. T bars indicate standard errors.
The concept that different types of placebos may yield different magnitudes of placebo effects
A Double-Blind Study of the Treatment of Hypertension

Raymond F. Grenfell, M.D., Arthur H. Briggs, M.D., and William C. Holland, M.D., Jackson, Miss.

Comparison of the Effects of Oral and Parenteral Administration on Placebo Response
Surgical “Placebo” Controls

Robert Tenery, MD, Dallas, TX-Chair; Herbert Rakatansky, MD, Providence, RI-Vice-Chair; Frank A. Riddick, Jr., MD, New Orleans, LA; Michael S. Goldrich, MD, Highland Park, NJ; Leonard J. Morse, MD, Worcester, MA; John M. O’Bannon, III, MD, Richmond, VA; Priscilla Ray, MD, Houston, TX; Sherie Smalliey, MD, Salt Lake City, UT–Resident Member Matthew Weiss, Chicago, IL–Student Member. Staff to the Council on Ethical and Judicial Affairs: Audley Kao, MD, PhD, Acting Vice President, Ethics Standards Group, American Medical Association; Karine Morin, LLM, Council Secretary and Staff Author; Andrew Maixner, Council Staff Associate; Sam Seiden, Council Staff Associate.
RECENT ATTENTION...

**Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial**


**Arthroscopic subacromial decompression for subacromial shoulder pain (CSAW): a multicentre, pragmatic, parallel group, placebo-controlled, three-group, randomised surgical trial**

“Meta-regression analyses showed that larger effects of placebo interventions were associated with physical placebo interventions” (e.g. sham devices)
Do medical devices have enhanced placebo effects?

Ted J. Kaptchuk, Peter Goldman, David A. Stone, William B. Stason

Received 10 November 1999, revised 5 January 2000, accepted 21 January 2000

Sham device v inert pill: randomised controlled trial of two placebo treatments

Ted J Kaptchuk, William B Stason, Roger B Davis, Anna T R Legedza, Rosa N Schnyer, Catherine E Kerr, David A Stone, Bong Hyun Nam, Irving Kirsch, Rose H Goldman
TMS AND PLACEBO EFFECTS
EXEMPLIFICATION OF AN ELABORATE THERAPEUTIC TECHNOLOGY

Brainsight TMS
Achieve blinding but avoid meaningful stimulation to the brain

Goal: Mimic TMS’s visual and auditory (+/- tactile) experience but shield the brain from the magnetic fields

Many different sham device techniques

*Include a measure assessing success of blinding!
A systematic review and meta-analysis on placebo response to repetitive transcranial magnetic stimulation for depression trials

Laís B. Razza, Adriano H. Moffa, Marina L. Moreno, Andre F. Carvalho, Frank Padberg, Felipe Fregni, André R. Brunoni

(2018) 105–113

- 61 studies, large effect size of 0.8 (Hedge’s g)
- Meta-regression
  - Placebo response magnitude was positively associated with the year of publication (increasing sham TMS responses over time).
  - Studies that included patients with treatment-resistant depression had lower placebo responses
“41.0% of the veterans in the active treatment group achieved remission of depressive symptoms”*

*No difference from sham group (37%)
A follow-up fMRI study of placebo modulation of amygdala anxiolytic effect
“Contrary to our primary hypothesis, the number of headache days decreased significantly more in the sham group than in the group treated with active rTMS-DLPFC at eight weeks. Average decrease in headache days was >50% in the sham group, indicating a powerful placebo response.”
Compared inert pill group from escitalopram medication trials to the sham TMS group of TMS trials

Reported no significant difference...BUT

Methodological limitations

- Heterogenous patient populations – “refractory”
- Blinding – double vs single
- Dated (only included trials 2002-2008)
FURTHER RESEARCH?

- No studies comparing sham TMS to “no treatment” control
  - Needed to delineate placebo effects from “other” effects (including activation of coming to hospital for treatment)
Unfavorable impact on statistical power for sham controlled treatment trials

- RCT investigating a treatment with a large embedded placebo effect will generally need more subjects to prove efficacy than a treatment with a smaller placebo effect (Kaptchuk et al. 2000)
ONGOING ISSUES...

News and Events
Press Releases

Final Results from NICHE Phase III trial presented at the International Stroke Conference
23 February 2017
ISSUES REQUIRING CRITICAL REFLECTION...

How should we measure efficacy? New approaches?

How do we leverage enhanced placebo effects?