PLACEBO EFFECTS AND NEUROMODULATION: IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE

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NEUROPSYCHIATRY LEAD, UNIVERSITY OF TORONTO NEUROLOGY
ASSOCIATE SCIENTIST, HURVITZ BRAIN SCIENCES PROGRAM
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ASSISTANT PROFESSOR, UNIVERSITY OF TORONTO
DISCLOSURES

- No relevant conflicts of interest
- Paid consulting relationships within past 5 years
  - Consultant Neurologist, NBA Toronto Raptors
  - Neuropsychiatry Medicolegal Expert
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  - CIHR IRSC
  - Sunnybrook Foundation
  - University of Toronto Psychiatry
  - ONTARIO BRAIN INSTITUTE
  - INSTITUT ONTARIEN DU CERVEAU
  - SIDNEY R. BAER, JR. FOUNDATION

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RELEVANT AFFILIATIONS

Program in Placebo Studies & Therapeutic Encounter (PiPS)
Beth Israel Deaconess Medical Center / Harvard Medical School

Could studying the placebo effect change the way we think?

Pan-Canadian Neurotechnology Ethics Consortium
Working to create a forum for collaborative scientific and ethical discussion relevant to emerging neurotechnologies across Canadian health and social landscapes.
OBJECTIVES

1. Gain an understanding of placebo effects terminology, principles and neurobiology

2. Appreciate the factors that contribute to placebo effects in clinical settings

3. Develop a framework for how placebo effects impact clinical trials and measurements of efficacy in research

4. Appreciate specific placebo-related issues relevant to the field of non-invasive brain stimulation

5. Debate ethical considerations of placebo effects in medicine and society
SECRET OBJECTIVE
TRAINING IN NEUROMODULATION & BRAIN STIMULATION
Chapter 5

Transcranial magnetic stimulation: Neurophysiological and clinical applications

MATTHEW J. BURKE¹, PETER J. FRIED¹, AND ALVARO PASCUAL-LEONE¹,²,³a

¹Berenson-Allen Center for Noninvasive Brain Stimulation and Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States

²Günnthers Brain Health Institute, Institut Günnthers de Neurorehabilitació, Universitat Autonoma de Barcelona, Barcelona, Spain

³Marcus Institute for Aging Research, Hebrew Senior Life, Harvard Medical School, Boston, MA, United States
REVIEWING CLINICAL TRIALS

JAMA Psychiatry | Original Investigation

Effect of Repetitive Transcranial Magnetic Stimulation on Treatment-Resistant Major Depression in US Veterans: A Randomized Clinical Trial

Jerome A. Yesavage, MD; J. Kaci Fairchild, PhD; Zhibao Mi, PhD; Kousick Biswas, PhD; Anne Davis-Karim, PharmD; Ciaran S. Phibbs, PhD; Steven D. Forman, MD, PhD; Michael Thase, MD; Leanne M. Williams, PhD; Amit Etkin, MD, PhD; Ruth O’Hara, PhD; Gerald Georgette, RN; Tamara Beale, MA; Grant D. Huang, MPH, PhD; Art Noda, MS; Mark S. George, MD; for the VA Cooperative Studies Program Study Team

- **Active** Remission rate: 41%
- **Sham** Remission rate: 37%

PLEASE DO NOT COPY
Placebo Effect Grows in U.S., Thwarting Development of Painkillers

Analgesics struggle to get through clinical trials as the response to sham treatments has become stronger

By Jo Marchant, Nature magazine on October 7, 2015
Placebo Effects in Medicine
Ted J. Kaptchuk and Franklin G. Miller, Ph.D.

What if the Placebo Effect Isn’t a Trick?
New research is zeroing in on a biochemical basis for the placebo effect — possibly opening a Pandora’s box for Western medicine.
A fundamental change is needed for appraising placebo responses in psychiatry

Matthew J Burke

Published: May, 2023 • DOI: https://doi.org/10.1016/S2215-0366(23)00068-8
"Do you have that placebo I've heard so much about?"
The neuroscience of placebo effects: connecting context, learning and health

Tor D. Wager¹ and Lauren Y. Atlas²

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
NEUROIMAGING STUDIES

**Placebo and Opioid Analgesia**

*Science* 295 (5560), 1737-1740.
DOI: 10.1126/science.1067176

**Expectation and Dopamine Release: Mechanism of the Placebo Effect in Parkinson's Disease**
Raúl de la Fuente-Fernández, Thomas J. Ruth, Vesna Sossi, Michael Schulzer, Donald B. Caine and A. Jon Stoessl

*Science* 293 (5532), 1164-1166.
DOI: 10.1126/science.1060937

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**Table 1.** Striatal D2R binding potential (mean ± SD) of PD patients (group 1) scanned at open baseline and after receiving placebo (n = 6).

<table>
<thead>
<tr>
<th>Site</th>
<th>Open baseline</th>
<th>Placebo</th>
<th>Mean percent change (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head of caudate</td>
<td>1.964 ± 0.221</td>
<td>1.638 ± 0.230</td>
<td>16.6 (8.4–25.1)</td>
</tr>
<tr>
<td>Putamen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rostral</td>
<td>2.398 ± 0.342</td>
<td>1.976 ± 0.321</td>
<td>17.6 (5.3–26.3)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.621 ± 0.438</td>
<td>2.142 ± 0.389</td>
<td>18.2 (7.4–27.0)</td>
</tr>
<tr>
<td>Caudal</td>
<td>2.095 ± 0.269</td>
<td>1.646 ± 0.261</td>
<td>21.2 (8.8–32.6)</td>
</tr>
</tbody>
</table>
CURRENT NEUROIMAGING

Wager and Atlas 2015, Ashar et al 2017

NATURE REVIEWS | NEUROSCIENCE

S2-dpINS: somatic pain intensity
mThal: pain and affect integration
dIPFC: goal context; expectancy
aINS: motivation; decision; affect
dACC: avoidance value
vmPFC: meaning ‘schema’

PAG: emotion; regulation of pain and autonomic
RVM: spinal control of pain and autonomic
IOFC

Wager and Atlas 2015, Ashar et al 2017
Biological, clinical, and ethical advances of placebo effects

Damien G Finniss, Ted J Kaptchuk, Franklin Miller, Fabrizio Benedetti

Lancet 2010; 375: 686-95

Figure 2: Receptor pathways activated by both psychosocial context and drugs

Social stimuli around the treatment might activate, through expectation or conditioning mechanisms, several receptor pathways in different diseases and therapeutic interventions (the involvement of serotonin [5-hydroxytryptamine; SHT] receptors in hormonal responses and depression is not definitive). These receptors are the same to which different drugs bind, suggesting that psychosocial factors are capable of modulating the action of drugs. This interference has implications for our understanding of drug action: when a drug is prescribed, the very act of giving it to a patient (i.e., the psychosocial context) might affect the system and change the response to the drug. Reproduced with permission from reference 39. IFNy=interferon γ, IL2=interleukin 2. CCK=cholecystokinin.
DOSE-RESPONSE RELATIONSHIP

Augmented = placebo + “patient-practitioner relationship augmented by warmth, attention, and confidence”
KNOCK-OUT MODELS

Hidden Administration of

TOLD → Saline
GET → Remifentanil

Hidden application

Open application

No expectation

Pain reduction

Expectancy-related (placebo) effect
Pharmacological effect

Medication is administered by a physician

Enck et al. 2013

Placebo pill
Maxalt pill

Enck et al. 2013
Placebo and Nocebo Effects
Luana Colloca, M.D., Ph.D., and Anhur J. Barsky, M.D.

Placebo and nocebo effects are the effects of patients' positive and negative expectations, respectively, concerning their state of health. These effects occur in many clinical contexts, including treatment with an active agent or a placebo in clinical practice or in a clinical trial, the informed-consent process, the provision of information about medical treatments, and public health campaigns. Placebo effects cause beneficial outcomes, and nocebo effects cause harmful and dangerous outcomes.

Variation in the ways that patients respond to treatments and experience symptoms is partly attributable to placebo and nocebo effects. The frequency and intensity of placebo effects in clinical practice are difficult to determine, and the range of effects in experimental settings is wide. In many double-blind clinical trials of treatments for pain or psychiatric disorders, for example, the responses to placebo are similar to the responses to active treatment, and up to 19% of adults and 26% of elderly persons taking placebos report side effects. Furthermore, as many as one quarter of patients receiving placebo in clinical trials discontinue it because of side effects, suggesting that a nocebo effect may contribute to discontinuation of or lack of adherence to active treatments.
Expectancies can be acquired in a number of ways:

1. **Prior experience of treatment effects** (e.g., analgesia after taking a medication)

   ![Overlap with learning/conditioning](image)
CONDITIONING

Morphine  Morphine  Morphine  Saline

Pain
Expectancies be acquired in a number of ways:

1. **Prior experience of treatment effects** (e.g., analgesia after taking a medication)

2. **Verbal instructions or suggestion** (e.g., being told that a treatment will reduce pain)

3. **Social observation** (e.g., observing symptom relief in another person taking same medication)
PLACEBO EFFECTS IN MEDICINE
TWO MAIN CONSIDERATIONS

The Patient

The Treatment
A CURE ALL?
PATIENT POPULATIONS OF INTEREST

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

Chronic Pain
Anxiety Disorders
Irritable Bowel Syndrome
Depression
Parkinson’s Disease
Asthma
Fibromyalgia
Migraine
Functional Neurological Disorder
Concussion
Insomnia
Allergy syndromes
Chronic Fatigue
...
IN PSYCHIATRY...

JAMA Psychiatry | Original Investigation

Differential Outcome Across 9 Psychiatric Disorders: A Systematic Review

Tom Bschor, MD; Lea Nagel, MD; Joseph Lecrubier, MD

Figure 1. Random-Effects Meta-Analysis Estimates of Pooled Pre-Post Placebo Effect Sizes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Study participants, No.</th>
<th>Q</th>
<th>I², %</th>
<th>ES (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD</td>
<td>1598</td>
<td>47.9</td>
<td>81</td>
<td>1.40 (1.24-1.56)</td>
</tr>
<tr>
<td>GAD</td>
<td>1457</td>
<td>61.4</td>
<td>85</td>
<td>1.23 (1.06-1.41)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>1307</td>
<td>20.8</td>
<td>57</td>
<td>0.92 (0.81-1.02)</td>
</tr>
<tr>
<td>ADHD</td>
<td>1189</td>
<td>7.3</td>
<td>0</td>
<td>0.88 (0.81-0.95)</td>
</tr>
<tr>
<td>PTSD</td>
<td>655</td>
<td>99.8</td>
<td>91</td>
<td>0.84 (0.53-1.15)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>1180</td>
<td>34.7</td>
<td>74</td>
<td>0.72 (0.59-0.85)</td>
</tr>
<tr>
<td>Mania</td>
<td>967</td>
<td>53.1</td>
<td>83</td>
<td>0.68 (0.51-0.85)</td>
</tr>
<tr>
<td>OCD</td>
<td>819</td>
<td>29.6</td>
<td>70</td>
<td>0.65 (0.51-0.78)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>888</td>
<td>50.0</td>
<td>82</td>
<td>0.59 (0.41-0.76)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 88.50$ (P<.01)
CASE EXAMPLE 1

“FUNCTIONAL” BRAIN DISORDERS

Dr. Matthew Burke, a neurologist who teaches at the University of Toronto and has written about the dissolution of patient-physician trust, said flippant clips about healthcare, made and shared by healthcare professionals, are emblematic of a broader issue within medicine.

"This is just really symptomatic of this bigger problem: The fact that patients with complex, medically unexplained symptoms ... they're often dismissed, and a lot of mainstream physicians think that patients are faking it," he told CNN. "And that has gradually eroded some of the patient-physician relationships."
“Science’s first placebo-controlled blind study delivered two important revelations:
1. Animal magnetism does not seem to exist.
2. Individuals can in some mysterious way become healthier all on their own if they believe they are receiving effective treatment.”
CASE EXAMPLE 2
“STRUCTURAL” BRAIN DISORDER

Placebo responsiveness ≠ “fake” disorder
CASE EXAMPLE 3
GENERAL MEDICAL DISORDER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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
PLACEBO EFFECTS?

**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. Error bars indicate standard errors.
PATIENT LEVEL HETEROGENEITY

Genetics and the placebo effect: the placeboome
Kathryn T. Hall¹,², Joseph Loscalzo³, and Ted J. Kaptchuk¹,²

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

<table>
<thead>
<tr>
<th>Placebo pathway</th>
<th>Gene name</th>
<th>Gene symbol</th>
<th>Chromosomal</th>
<th>Placebo SNPs</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Catechol-O-methyltransferase</td>
<td></td>
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<tr>
<td></td>
<td>Monoamine oxidase</td>
<td></td>
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<tr>
<td></td>
<td>Dopamine B hydroxylase</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Dopamine receptor 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Brain-derived neurotrophic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>factor A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>Tryptophan hydroxylase</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>5-Hydroxytryptamine</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>5-Hydroxytryptamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serotonin transporter 50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>polymorphic region</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Opioid</td>
<td>Opioid receptor</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Endocannabinoid</td>
<td>Fatty acid amidine hydrolase</td>
<td></td>
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</tbody>
</table>

Association between personality traits and placebo effects: a preregistered systematic review and meta-analysis
Heemin Kang⁵,⁶, Miriam Sophie Miksch⁶, Dan-Mikael Ellingsen⁵,⁶,⁷,⁸
TWO MAIN CONSIDERATIONS

The Patient

The Treatment
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.
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'Brien, III, MD, Richmond, VA; Priscilla Ray, MD, Houston, TX; Sherie Smallay, 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 Mainzer, Council Staff Associate; Sam Saiden, Council Staff Associate.
Effect of Spinal Cord Burst Stimulation vs Placebo Stimulation on Disability in Patients With Chronic Radicular Pain After Lumbar Spine Surgery: A Randomized Clinical Trial

Sozaburo Hara, MD; Hege Andresen; RN, MSc; Ole Solheim, MD, PhD; Sven M. Carlsen, MD, PhD; Terje Sundstrøm, MD, PhD; Greger Lønne, MD, PhD; Vettle V. Lønne, MD; Kristin Taraldsen, PT, PhD; Erling A. Tronvik, MD, PhD; Lise R. Øie, MD, PhD; Agnete M. Gulati, MD, PhD; Lisa M. Sagberg, RN, PhD; Asgeir S. Jakola, MD, PhD; Tore K. Solberg, MD, PhD; Øystein P. Nygaard, MD, PhD; Øyvind O. Salvesen, MSc, PhD; Sasha Gulati, MD, PhD
“Meta-regression analyses showed that larger effects of placebo interventions were associated with physical placebo interventions” (e.g. sham devices)
Conclusion: 1) little/no mention of placebo effects AND/OR 2) there must be something “active” about our sham?

"When faced with two equally good hypotheses, always choose the simpler."
OTHER FACTORS

- Cost, perceived innovation, branding, pill shape/colour...

**Placebo effect of medication cost in Parkinson disease**

*A randomized double-blind study*

**ABSTRACT**

*Objective:* To examine the effect of cost, a traditionally “inactive” trait of intervention, on the response to therapeutic interventions.

*Methods:* We conducted a prospective double-blind study in 12 patients with moderate Parkinson disease and motor fluctuations (mean age 62.4 ± 7.9 years; mean duration of disease 11 ± 6 years) who were randomized to a “cheap” or “expensive” subcutaneous dopamine agonist placebo (normal saline). Patients were crossed over to the alternative supplement approximately 4 hours later. Blinded motor assessments in the “practically dead” state before and after each intervention, included the Unified Parkinson’s Disease Rating Scale subscale, the Purdue Pegboard Test, and a tapping task. Measurements of bradykinesia performed using a feedback-based visual-motor association learning functional effect was examined using stratified analysis.

*Results:* Although both placebo improved motor function, benefit was greater in the “expensive” placebo, with a magnitude halfway between levodopa and placebo. Brain activation was greater upon first-given cheap but not expensive placebo or levodopa. Regardless of order of administration, only cheap placebo increased activation in the left lateral sensorimotor cortex and other regions.

*Conclusion:* Expensive placebo significantly improved motor function and decreased brain activation in a direction and magnitude comparable to, albeit less than, levodopa. Perceptions of cost are capable of altering the placebo response in clinical studies.

*Classification of evidence:* This study provides Class III evidence that perception of cost is capable of influencing motor function and brain activation in Parkinson disease. *Neurology* 2015;84:794-802
Presenting a sham treatment as personalised increases the placebo effect in a randomised controlled trial

Dasha A Sandra¹*, Jay A Olson²†, Ellen J Langer², Mathieu Roy³

¹Integrated Program in Neuroscience, McGill University, Montreal, Canada;
²Department of Psychology, Harvard University, Cambridge, United States;
³Department of Psychology, McGill University, Montreal, Canada
Our trials show that the new drug performs no better than placebo. Maybe we should invest in placebos.
PLACEBO TERMINOLOGY FOR RCTS

Placebo “Response” vs. Placebo “Effects”

- Placebo Effects
- Other Effects
  1. Regression to the mean
  2. Spontaneous changes
  3. Hawthorne effects
  4. Elevation bias
  5. Unknown
CHALLENGES TO CONVENTIONAL FRAMEWORK
1) BLINDING INTEGRITY

THE LANCET

CONSORT 2010 changes and testing blindness in RCTs

Kenneth F Schulz, Douglas G Altman, David Moher, Dean Fergusson

Published: March 24, 2010  DOI: https://doi.org/10.1016/S0140-6736(10)60413-8

EJN EUROPEAN JOURNAL OF NEUROSCIENCE

TECHNICAL SPOTLIGHT

Challenges of proper placebo control for non-invasive brain stimulation in clinical and experimental applications

Nick J. Davis, Edward Gold, Alvaro Pascual-Leone and R. Martyn Bracewell
### SHAM TMS GROUPS, FROM 0 TO 50% IMPROVEMENT??

<table>
<thead>
<tr>
<th>Source</th>
<th>Baseline No.</th>
<th>Baseline Mean (SD)</th>
<th>Baseline SD</th>
<th>End point No.</th>
<th>End point Mean (SD)</th>
<th>End point SD</th>
<th>Hedges g (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baeken et al.⁸⁰ 2013</td>
<td>11</td>
<td>26.45 (8.71)</td>
<td></td>
<td>11</td>
<td>22.36 (10.01)</td>
<td></td>
<td>0.42 (-0.39 to 1.23)</td>
<td>1.46</td>
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<tr>
<td>Bakim et al.³¹ 2012</td>
<td>12</td>
<td>25.58 (3.82)</td>
<td></td>
<td>12</td>
<td>19.5 (7.83)</td>
<td></td>
<td>0.95 (0.13 to 1.77)</td>
<td>1.45</td>
</tr>
<tr>
<td>Blumberger et al.²⁵ 2012</td>
<td>22</td>
<td>25.2 (2.8)</td>
<td></td>
<td>15</td>
<td>18.9 (6.4)</td>
<td></td>
<td>1.34 (0.63 to 2.05)</td>
<td>1.68</td>
</tr>
<tr>
<td>Blumberger et al.²⁶ 2016</td>
<td>41</td>
<td>25.5 (3.6)</td>
<td></td>
<td>35</td>
<td>20.5 (3.64)</td>
<td></td>
<td>1.37 (0.87 to 1.86)</td>
<td>2.25</td>
</tr>
<tr>
<td>Boutros et al.³⁷ 2002</td>
<td>9</td>
<td>31.7 (4.9)</td>
<td></td>
<td>7</td>
<td>26.4 (12.4)</td>
<td></td>
<td>0.56 (-0.39 to 1.52)</td>
<td>1.20</td>
</tr>
<tr>
<td>Chen et al.³⁸ 2013</td>
<td>10</td>
<td>24.9 (6.3)</td>
<td></td>
<td>10</td>
<td>12.3 (4.7)</td>
<td></td>
<td>2.17 (1.10 to 3.25)</td>
<td>1.03</td>
</tr>
<tr>
<td>Concerto et al.³⁹ 2015</td>
<td>15</td>
<td>21 (5)</td>
<td></td>
<td>15</td>
<td>20 (7)</td>
<td></td>
<td>0.16 (-0.54 to 0.86)</td>
<td>1.71</td>
</tr>
<tr>
<td>Fitzgerald et al.⁴² 2012</td>
<td>20</td>
<td>22.9 (2.1)</td>
<td></td>
<td>17</td>
<td>22.6 (5)</td>
<td></td>
<td>0.08 (-0.55 to 0.71)</td>
<td>1.87</td>
</tr>
<tr>
<td>Garcia-Toro et al.⁴³ 2001</td>
<td>18</td>
<td>25.6 (4.92)</td>
<td></td>
<td>16</td>
<td>23.83 (3.78)</td>
<td></td>
<td>0.39 (-0.27 to 1.05)</td>
<td>1.79</td>
</tr>
<tr>
<td>Garcia-Toro et al.²⁶ 2006</td>
<td>10</td>
<td>25.1 (7.28)</td>
<td></td>
<td>10</td>
<td>23.6 (7.79)</td>
<td></td>
<td>0.19 (-0.65 to 1.03)</td>
<td>1.40</td>
</tr>
<tr>
<td>Holtzheimer et al.⁴⁶ 2004</td>
<td>8</td>
<td>20.8 (6.3)</td>
<td></td>
<td>7</td>
<td>15.3 (3)</td>
<td></td>
<td>1.02 (0.00 to 2.05)</td>
<td>1.10</td>
</tr>
<tr>
<td>Kauffmann et al.⁴⁷ 2004</td>
<td>5</td>
<td>18.2 (4.9)</td>
<td></td>
<td>5</td>
<td>11.8 (4.3)</td>
<td></td>
<td>1.25 (0.01 to 2.50)</td>
<td>0.83</td>
</tr>
<tr>
<td>Li et al.⁴⁸ 2014</td>
<td>15</td>
<td>23.8 (3.2)</td>
<td></td>
<td>15</td>
<td>19.66 (3.2)</td>
<td></td>
<td>1.26 (0.49 to 2.02)</td>
<td>1.56</td>
</tr>
<tr>
<td>Padberg et al.²⁸ 1999</td>
<td>6</td>
<td>22.2 (8.8)</td>
<td></td>
<td>6</td>
<td>23.5 (10.4)</td>
<td></td>
<td>-0.12 (-1.17 to 0.92)</td>
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<tr>
<td>Pallanti et al.⁵¹ 2010</td>
<td>20</td>
<td>29.05 (3.54)</td>
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<td>20</td>
<td>26.38 (3.4)</td>
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<td>0.75 (0.12 to 1.38)</td>
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<tr>
<td>Thelertis et al.²⁶ 2017</td>
<td>20</td>
<td>29.4 (3.2)</td>
<td></td>
<td>18</td>
<td>25.4 (5.3)</td>
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<td>0.91 (0.25 to 1.56)</td>
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<tr>
<td>Thelertis et al.²⁶ 2017</td>
<td>24</td>
<td>30.3 (3.6)</td>
<td></td>
<td>21</td>
<td>27 (4)</td>
<td></td>
<td>0.86 (0.25 to 1.46)</td>
<td>1.95</td>
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<tr>
<td>Triggs et al.⁵⁷ 2010 (left sham)</td>
<td>7</td>
<td>27.7 (3.5)</td>
<td></td>
<td>7</td>
<td>22 (11.6)</td>
<td></td>
<td>0.62 (-0.38 to 1.63)</td>
<td>1.12</td>
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<tr>
<td>Triggs et al.⁵⁷ 2010 (right sham)</td>
<td>7</td>
<td>27.3 (2.7)</td>
<td></td>
<td>7</td>
<td>13.4 (7.4)</td>
<td></td>
<td>2.34 (1.03 to 3.64)</td>
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<tr>
<td>Yesavage et al.⁶¹ 2018</td>
<td>83</td>
<td>27.5 (5.11)</td>
<td></td>
<td>68</td>
<td>14.4 (8.6)</td>
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<td>1.89 (1.51 to 2.27)</td>
<td>2.58</td>
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<tr>
<td>Zheng et al.⁶⁰ 2010</td>
<td>15</td>
<td>24.6 (2.8)</td>
<td></td>
<td>15</td>
<td>22.9 (3.4)</td>
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<td>0.53 (-0.18 to 1.24)</td>
<td>1.68</td>
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<tr>
<td>van Eijndhoven et al.⁶⁸ 2020</td>
<td>16</td>
<td>22.7 (3.8)</td>
<td></td>
<td>16</td>
<td>18.6 (4.2)</td>
<td></td>
<td>1.00 (0.28 to 1.72)</td>
<td>1.66</td>
</tr>
</tbody>
</table>

**Heterogeneity:** $I^2 = 0.22, \ P = 62.14\%; \ H^2 = 2.64$

**Test of $\theta = 0$: $Q_{21} = 63.57; \ P = .001$**

---

**Jones et al 2021**
NOT A UNIQUE ISSUE FOR TMS...

While most participants correctly guessed whether they received a placebo or MDMA, this did not undermine the study’s results or its methodology, which was agreed to in advance by the F.D.A.
Challenges of Differential Placebo Effects in Contemporary Medicine: The Example of Brain Stimulation

Matthew J. Burke, MD,¹ Ted J. Kaptchuk,² and Alvaro Pascual-Leone, MD, PhD¹
BRAIN STIMULATION TECHNOLOGIES
THE EFFICACY PARADOX

Burke et al. 2019
Molecular Psychiatry

ARTICLE
Placebo effects and neuromodulation for depression: a meta-analysis and evaluation of shared mechanisms

Matthew J. Burke, Sara M. Romanella, Lucia Mencarelli, Rachel Greben, Michael D. Fox, Ted J. Kaptchuk, Alvaro Pascual-Leone, and Emiliano Santar necchi

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PLACEBO NEUROIMAGING
META-ANALYSIS

<table>
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<tr>
<th>Cluster</th>
<th>Volume (mm$^3$)</th>
<th>Extrema Value</th>
<th>BA</th>
<th>Hemisphere</th>
<th>Neuroanatomic Label</th>
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<td></td>
<td></td>
<td>x</td>
<td>y</td>
<td>z</td>
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<tr>
<td><strong>Activation Clusters</strong></td>
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<td>-38</td>
<td>22</td>
<td>36</td>
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<td>0.027</td>
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<td><strong>Deactivation Clusters</strong></td>
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<tr>
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<td>0.02</td>
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<td></td>
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<td>0.017</td>
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<td>2</td>
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<td>0.016</td>
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<td>792</td>
<td>0.6</td>
<td>-4.6</td>
<td>45</td>
<td>0.02</td>
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</tbody>
</table>
COMPARATIVE ANALYSES WITH NEUROMODULATION TARGETS
Endogenous opioids mediate rTMS-induced analgesia

Characterizing the opioidergic mechanisms of repetitive transcranial magnetic stimulation–induced analgesia: a randomized controlled trial

Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia
Hypothetical clinical trial assuming no overlap in therapeutic mechanism between active group and placebo group

Hypothetical clinical trial with shared therapeutic mechanism between active group and placebo group
IMPLICATIONS OF OVERLAPPING MECHANISMS

OR

SYNERGY

1 + 1 > 2

+ priming
PRIMING THE NETWORK?

1) Measure
2) Leverage
RECENT PUBLICATION

Treatment expectations and clinical improvement following transcranial magnetic stimulation

Adriano Molica # • Enoch Ng # • Matthew J. Burke •
Peter Giacobbe • Show all authors • Show funding

Open Access • Published: June 18, 2024 • DOI: https://doi.org/
THE ART OF DELIVERING PLACEBO EFFECTS WITHOUT THE “PLACEBO”?

Placebo Effects in Psychotherapy: A Framework
Paul Enck* and Stephan Zipfel

Placebo Effects in Psychotherapy: A Framework
Paul Enck* and Stephan Zipfel

Psychosomatic Medicine and Psychotherapy, Department of Internal Medicine VI, University of Tübingen, Tübingen, Germany

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Viewpoint
May 23/30, 2017

Changing Mindsets to Enhance Treatment Effectiveness
Alia Crum, PhD1; Barry Zuckerman, MD2,3

Author Affiliations
FROM NUISANCE TO TREATMENT?

Placebo Effects: From the Neurobiological Paradigm to Translational Implications

Fabrizio Benedetti¹,*
¹Department of Neuroscience, University of Turin Medical School and National Institute of Neuroscience, 10125 Turin, Italy
*Correspondence: fabrizio.benedetti@unito.it
http://dx.doi.org/10.1016/j.neuron.2014.10.023

The placebo response in medicine: minimize, maximize or personalize?

Paul Enck, Ulrike Bingel, Manfred Schedlowski and Winfried Rief
IN THE MEANIME... REAL-WORLD DATA

Burke emphasizes that the changes from placebos are real and not imagined or mystical. "It's becoming clear that placebo effects in themselves are extremely meaningful. If you were to take a placebo during an fMRI scan, we would see specific areas of the brain light up," he said.

Having someone endorse the effectiveness of a product, fancy packaging and an expensive price tag can all increase the effectiveness of a placebo. In certain clinical settings, these effects have been shown to persist even when people know that they are getting a placebo.

Because of this, Burke thinks the summit could make a positive difference in people's health. "Absolutely, the summit could legitimately cause biological changes to the brain through the placebo effect." However, he warns, "this alone should not replace addressing other factors that may be contributing to an individual's symptoms or given health state."

Goop has no issue with this possibility. "If it's the placebo effect, that's great too," Chief Content Officer Elise Loehnen wrote in an email.
Burke, the neuroscientist, believes that a wellness sticker could potentially help someone chill out - though not for the reason advertised.

“If these products work, it’s almost certainly because of the placebo effect,” he said. “The likely explanation is that these stickers help people through the psychological intervention of making them feel like they are being treated.”

When people are put in a state where they expect to get better, it changes the brain biologically. The placebo effect kicks off a reaction that releases endorphins and dopamine, two neurotransmitters known for making people feel good. Those effects won’t cure anyone - a patient with cancer will still have cancer - but they might feel a little less depressed, more hopeful, in less pain.

Is that such a bad thing? Burke warned that when people feel good because of a placebo, they’re less likely to seek out treatment that might work more permanently.

“If someone believes that their bio-frequencies are out of whack, they might not address some of the actual underlying factors that might be driving their depression, insomnia, or pain,” Burke said.
SO HOW DO WE MOVE FORWARD?

Me: "heal my disease"
Brain: "No"
Me: *takes pill with no effect*
Brain:

You son of a bitch, I'm in
New trial design considerations

- Priming, synergy and concurrent interventions
- Collect data on expectancy and potentially modulate it
- Change semantics – endogenous healing network, antidepressant network etc.
- Adjust lens of critical appraisal...interrogate date in placebo arms, blinding integrity

Review Article

Placebo Effects and Neuromodulation: Ethical Considerations and Recommendations

Adriano Mollica1,2,*, Rachel Greben2,3, Marieve Cyr4, Jay A. Olsen5 and Matthew J. Burke1,2,6,7

1Neuropsychiatry Program, Department of Psychiatry, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada, 2Harquail Centre for Neuromodulation and Human Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada, 3Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada, 4Faculty of Medicine, McGill University, Montreal, QC, Canada, 5Department of Psychology, McGill University, Montreal, QC, Canada, 6Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada and 7Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA
<table>
<thead>
<tr>
<th>Study design</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized sham-controlled trial</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active treatment versus sham control group</td>
<td>Considered gold standard in evaluating effectiveness of active treatment</td>
<td>Requires careful design of sham technology to replicate the experience of active stimulation protocols, as well as assessment of blinding integrity</td>
</tr>
<tr>
<td><strong>Placebo run-in trial</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| All participants receive placebo prior to trial initiation | Potential to exclude patients with high placebo responsiveness in an attempt to increase the ability to find significant differences between active and placebo groups | Greater risks of unblinding and decreased external validity  
Recently found to be no more effective in finding differences between drug and placebo groups than trials without placebo run-in periods for antidepressants |
| **Three-arm trial with no-treatment control** |                                                                                                                                            |                                                                                                                                               |
| Active treatment versus sham control versus no treatment | Would help delineate the magnitude of placebo effects from the magnitude of other nonspecific effects in placebo trial arms (e.g., spontaneous changes, regression to the mean, elevation bias, Hawthorne effects) | More cumbersome trial design that may impact statistical power  
Ethical concerns regarding beneficence given those assigned to no-treatment control would potentially be exposed to relatively more harms than active treatment or placebo control |
| **Non-inferiority trial**            |                                                                                                                                            |                                                                                                                                               |
| A new intervention is compared with an established treatment as opposed to placebo control | Allows more ethical evaluation of treatment effectiveness for patients with more severe illness (e.g., acute suicidality) as participants would not be randomized to a placebo group.  
Bypasses need to develop sham stimulation that would replicate complex protocols (e.g., MST, FUS) | In order to achieve sufficient power, the sample size may need to be larger, and this would influence the costs associated with a trial.  
Provides no data on placebo response magnitude (placebo effects could drive improvement in both groups) |
| **Open-label placebo**               |                                                                                                                                            |                                                                                                                                               |
| Participants are truthfully told they will be receiving placebo, typically in comparison to a no-treatment control | Used for studying the efficacy of placebo effects, while avoiding the need for deception | Has not been used for evaluating the efficacy of neuromodulation interventions  
Requires careful controlling to ensure the effect measured is attributable to taking a placebo, rather than elements of the study design  
Non-standardized script with potential to alter expectations of a positive response  
Cannot blind investigator delivering the script  
OLP research remains in its early stages |

FUS = focused ultrasound; MST = magnetic seizure therapy; OLP = open-label placebo.
Placebos could save lives and health care dollars: so why can’t mainstream medicine put them to better use?

ERIN ANDERSEN
PUBLISHED OCTOBER 28, 2019

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- Dr. Anthony Feinstein
- Dr. Bojana Stefanovic
- Dr. Ben Davidson
- Dr. Adriano Mollica
- Dr. Maged Goubran
- Elke McClellan

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- Dr. Shan Siddiqi
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- Sara Romanella
QUESTIONS

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