PLACEBO EFFECTS AND NEUROMODULATION: IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE

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DISCLOSURES

- No relevant conflicts of interest

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  - ONTARIO BRAIN INSTITUTE
  - INSTITUT ONTARIEN DU CERVEAU
  - NIH National Institute of Mental Health
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 about health and illness?

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
TRAINING IN NEUROMODULATION & BRAIN STIMULATION

Dr. Michael Fox
Dr. Alvaro Pascual-Leone
Dr. Emiliano Santarnecchi
Chapter 5

Transcranial magnetic stimulation: Neurophysiological and clinical applications

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

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
2Guttmann Brain Health Institute, Institut Guttmann de Neurorehabilitacio, Universitat Autonoma de Barcelona, Barcelona, Spain
3Marcus Institute for Aging Research, Hebrew Senior Life, Harvard Medical School, Boston, MA, United States
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. Philbs, PhD; Steven D. Forman, MD, PhD; Michael Thase, MD; Leanne M. Williams, PhD; Amit Etkin, MD, PhD; Ruth O’Hara, PhD; Gerald George, RN; Tamara Beale, MA; Grant D. Huang, MPH, PhD; Art Noda, MS; Mark S. George, MD; for the VA Cooperative Studies Program Study Team

Remission rate

- Active: 41%
- Sham: 37%
Randomized Sham-Controlled Trial of Navigated Repetitive Transcranial for Motor Recovery

The NICTHES Trial

Richard L. Harvey, MD; Dylan Edwards, PhD, PhD; Joel Stein, MD; Jarmo Laine, MD; Haimi Hietanen, MD; Ana Durand-Sanchez, MD; Marcia Bock, MD; Gerard E. Francisco, MD; Carolyn L. Smith, MD; on behalf of the NICTHES Investigators.

Change in Fugl-Meyer Score Post-treatment

- NBT
- SHAM

<table>
<thead>
<tr>
<th></th>
<th>EOT</th>
<th>1 mo</th>
<th>3 mo</th>
<th>6 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>NBT</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>SHAM</td>
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<td></td>
</tr>
</tbody>
</table>

Graph showing changes in Fugl-Meyer Score at EOT, 1 mo, 3 mo, and 6 mo for NBT and SHAM groups.
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
HARVARD PROGRAM IN PLACEBO STUDIES

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
INTRODUCTION TO PLACEBO EFFECTS

"DO YOU HAVE THAT PLACEBO I'VE HEARD SO MUCH ABOUT?"
The neuroscience of placebo effects: connecting context, learning and health

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

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

Treatment cues:
- Syringe
- Needle puncture
NEUROIMAGING STUDIES

**Placebo and Opioid Analgesia**
Predrag Petrovic, Eija Kalso, R. Mark Dingemanse, R. Mark Dingemanse

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

**Expectation and Dopamine Release: Mechanism of the Placebo Effect in Parkinson's Disease**
Ruáil 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

**Table 1.** Striatal RAC 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

NATURE REVIEWS | NEUROSCIENCE

- S2-dPLNS: somatic pain intensity
- mThal: pain and affect integration
- dIPFC: goal context; expectancy
- aINS: motivation; decision affect
- dACC: avoidance value
- vmPFC: meaning "schema"
- NAc-VS: motivational and hedonic value
- RVM: spinal control of pain and autonomic
- PAG: emotion; regulation of pain and autonomic
- IOFC

Wager and Atlas 2015, Ashar et al 2017
CURRENT NEUROIMAGING

Romanella et al. 2022

A
Connectivity of Activation Clusters in Placebo

B
Connectivity of Deactivation Clusters in Placebo

VS
VAN
SM
LIM
FPCN
DMN
DAN

% Overlap

0 10 20 30

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; 5HT] 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. IFNγ = interferon γ, IL2 = interleukin 2, CCK = cholecystokinin.
**DOSE-RESPONSE RELATIONSHIP**

**BMJ**

Components of placebo effect in patients with irritable bowel syndrome

Ted J Kaptchuk, associate professor of medicine,1 John F. Kane, PhD,2 Robert G. Greenwald, PhD,3 Lisa A Conboy, instructor of medicine,1 Roland M. Lorig, PhD,4 Catherine E. Kerr, instructor of medicine,5 Rosa N Schyler, research associate,6 Brianna Slavik, research fellow,7 Min Park, research coordinator,1 Andrew F. Lussier, MD,7 research coordinator,1 Efi Kokkotou, assistant professor of medicine,8 Peter Goldman, professor emeritus. 1Antoni Institute for Health Research, San Diego, California, USA; 2Harvard School of Public Health, Boston, Massachusetts, USA; 3University of Arizona, Tucson, Arizona, USA; 4University of California, Los Angeles, California, USA; 5University of Rochester, Rochester, New York, USA; 6University of California, San Francisco, California, USA; 7San Diego State University, San Diego, California, USA; 8University of Wisconsin, Madison, Wisconsin, USA.

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

![Graph showing outcomes at three week end point](image_url)

- **Global improvement**
  - Waiting list (n=87)
  - Limited (n=88)
  - Augmented (n=87)

- **Adequate relief**
  - Waiting list (n=87)
  - Limited (n=88)
  - Augmented (n=87)

- **Symptom severity**
  - Waiting list (n=87)
  - Limited (n=88)
  - Augmented (n=87)

- **Quality of life**
  - Waiting list (n=87)
  - Limited (n=88)
  - Augmented (n=87)
KNOCK-OUT MODELS

Hidden Administration of Drugs
F Benedetti\textsuperscript{1,2}, E Carlino\textsuperscript{1,2} and A Pollo\textsuperscript{1,2}

\begin{itemize}
  \item TOLD \rightarrow \text{Saline} \quad \text{Remifentanil}
  \item GET \quad \text{Remifentanil} \quad \text{Remifentanil}
\end{itemize}

\begin{itemize}
  \item No expectation
  \item Positive expectation
\end{itemize}

Dorsolateral prefrontal cortex
Anterior cingulate cortex

RESEARCH ARTICLE

MIGRAINE

Altered Placebo and Drug Labeling Changes the Outcome of Episodic Migraine Attacks
Slavenka Kam Hansen\textsuperscript{1}, Moshe Jakubowski\textsuperscript{2}, John M. Kelley\textsuperscript{3,4,5}, Irving Kirsch\textsuperscript{5,6}, David C. Hoaglin\textsuperscript{7}, Ted J. Kaptchuk\textsuperscript{5,*}, Rami Burstein\textsuperscript{2,*}

\begin{itemize}
  \item Change in pain score (%)
  \item Labeling: \text{NT Placebo pill Maxalt pill}
  \item Treatment: \text{NT Placebo pill Maxalt pill}
\end{itemize}
Placebo and Nocebo Effects

Luana Colloca, M.D., Ph.D., and Arthur 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 be acquired in a number of ways:

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

![Overlap with learning/conditioning]

- 1
- 2
- 3
- 4
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)
Nocebo effects = new or worsening symptoms in response to negative health-related information, beliefs, and/or experiences
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
Parkinson’s Disease
Asthma
Fibromyalgia
Depression
Migraine
Functional Neurological Disorder
Concussion
Insomnia
Allergy syndromes
Chronic Fatigue
...
CASE EXAMPLE 1

“FUNCTIONAL” BRAIN DISORDERS

Viewpoint

September 16, 2019

“It’s All in Your Head”—Medicine’s Silent Epidemic

Matthew J. Burke, MD, FRCPc1,2

Author Affiliations

1Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts
2Department of Psychiatry, Hurvitz Brain Sciences Program, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada


“It’s all in your head” is a phrase sometimes said by physicians to patients presenting with symptoms unexplained by medical disease. As a neurologist specializing in neuropsychiatry, nothing bothers me more than overhearing medical colleagues proclaim this one-liner at the bedside or snicker about these patients during rounds. Unbeknownst to them, I also hear my patients’ version of being on the other end of this phrase and find myself constantly trying to repair the damage that these words can cause. Whether physicians like to admit it or not, medically unexplained symptoms encompass a vast terrain of clinical practice. In neurology, these symptoms fall under functional neurological disorder, but every specialty has their own variants and favored terminologies (eg,
"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.”
OVERLAP IN IMPLICATED BRAIN REGIONS

Leveraging the Shared Neurobiology of Placebo Effects and Functional Neurological Disorder: A Call for Research

Matthew J. Burke, M.D., Vanda Faria, Ph.D., Davide Cappon, Ph.D., Alvaro Pascual-Leone, M.D., Ph.D., Ted J. Kaptchuk, and Emiliano Santarnecchi, Ph.D.

Functional neurological disorder and placebo and nocebo effects: shared mechanisms

Mirta Florio, Miriam Braga, Angela Marotta, Bernardo Villa-Sánchez, Mark J. Edwards, Michele Tinazzi and Diletta Barbiani
CASE EXAMPLE 2
“STRUCTURAL” BRAIN DISORDER

The placebo effect in Parkinson’s disease
Raúl de la Fuente-Fernández and A. Jon Stoessl

PET study: dopamine release in response to placebo treatment in Parkinson’s disease

Placebo responsiveness ≠ “fake” disorder
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. T bars indicate standard errors.
PATIENT LEVEL HETEROGENEITY

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

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

<table>
<thead>
<tr>
<th>Placebo pathway</th>
<th>Gene name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Catechol-O-Methyl Transfer</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Tryptophan</td>
</tr>
<tr>
<td>Opioid</td>
<td>Opioid receptor</td>
</tr>
<tr>
<td>Endocannabinoid</td>
<td>Fatty acid</td>
</tr>
</tbody>
</table>

Systematic Review and Meta-Analysis

Association between personality traits and placebo effects: a preregistered systematic review and meta-analysis
Heemin Kangᵃ,ᵇ, Miriam Sophie Mikscheᵃ, Dan-Mikael Ellingsenᵃ,c,d,*
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’Bannon, III, MD, Richmond, VA; Priscilla Ray, MD, Houston, TX; Sherie Smalley, 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; Karin Morin, LLM, Council Secretary and Staff Author; Andrew Maixner, Council Staff Associate; Sam Seiden, Council Staff Associate.
Percutaneous coronary intervention (PCI)

Clinical effectiveness of active Alpha-Stim AID versus sham Alpha-Stim AID in major depression in primary care in England (Alpha-Stim-D): a multicentre, parallel group, double-blind, randomised controlled trial

Richard Morris, Shilpa Patel, Clement Boutry, Priya Patel, Boliang Guo, Paul M Birkley, Deborah Butler, Michael Croven, Ashley Duncan, Christopher Griffiths, Fred Highton, Rebecca McNaughton, Neil Nixon, Vibhore Prasad, Kapil Soday, David Smart, Azhar Zafar, Joe Kie
“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?

“Occam’s Razor”

“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 11 ± 6 years) who were randomized to a "cheap" or "expensive" subcutaneous dopamine agonist placebo (normal saline). Patients were crossed over to the other approximately 4 hours later. Blinded motor assessments in the 'practically done' before and after each intervention, including 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 associative learning functional magnetic resonance imaging effect was examined using stratified analysis.

**Results:** Although both placebos improved motor function, benefit was greater with the placebo, with a magnitude halfway between the 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 3 evidence that perceptions of cost is capable of influencing motor function and brain activation in Parkinson disease. *Neurology* 2016;84:794-802
PLACEBO EFFECTS IN RESEARCH

Pharmacological Drug Trial Results

Our trials show that the new drug performs no better than placebo.

Maybe we should invest in placebos.

Chris Madden

Edsurge
PLACEBO TERMINOLOGY FOR RCTS

Placebo “Response” vs. Placebo “Effects”

Placebo-controlled Trial

- Placebo Effects
- Other Effects
  1. Regression to the mean
  2. Spontaneous changes
  3. Hawthorne effects
  4. Elevation bias
  5. Unknown

Active Group
Placebo Group
No Treatment
CHALLENGES TO CONVENTIONAL FRAMEWORK
1) BLINDING INTEGRITY

THE LANCET

COMMENT | VOLUME 375, ISSUE 9723, P1144-1148, APRIL 03, 2010

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

doi:10.1111/ejn.12307

TECHNICAL SPOTLIGHT

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†,‡,§,†
“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, Ted J. Kaptchuk, and Alvaro Pascual-Leone, MD, PhD
BRAIN STIMULATION TECHNOLOGIES
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
THE EFFICACY PARADOX

A

\[
\begin{align*}
\text{Drug A} & : \text{Significant} \\
\text{Inert Pill} & : \text{Not significant}
\end{align*}
\]

B

\[
\begin{align*}
\text{Device B} & : \text{Not significant} \\
\text{Sham Device} & : \text{Not significant}
\end{align*}
\]

C

\[
\begin{align*}
\text{Drug A} & : \text{Not significant} \\
\text{Device B} & : \text{Significant}
\end{align*}
\]

Legend:
- **Specific effects**
- **Placebo effects**
- **Other effects**
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 Santarnecchi

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PLACEBO NEUROIMAGING META-ANALYSIS

Main search terms: “placebo”, “expectation” combined with “functional magnetic resonance imaging”, “position emission tomography”, their acronyms, and “functional neuroimaging”

Fig. 1 Flowchart outlining selection of placebo effects neuroimaging studies. After exclusions during screening and review, 34 articles were included for meta-analysis.
## PLACEBO NEUROIMAGING META-ANALYSIS

### Table 1. Brain regions demonstrating activation or deactivation associated with placebo effects.

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Volume (mm$^3$)</th>
<th>Center x</th>
<th>Center y</th>
<th>Center z</th>
<th>Extrema Value x</th>
<th>Extrema Value y</th>
<th>Extrema Value z</th>
<th>BA</th>
<th>Hemisphere</th>
<th>Neuroanatomic Label</th>
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<tr>
<td><strong>Activation Clusters</strong></td>
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<tr>
<td>1</td>
<td>1888</td>
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<td>42</td>
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<td>32</td>
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<tr>
<td><strong>Deactivation Clusters</strong></td>
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COMPARATIVE ANALYSES WITH NEUROMODULATION TARGETS

sgACC Depression Targets

Left DLPFC Depression Targets

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Left DLPFC TMS

Placebo Effects

Low placebo effects

High placebo effects

Potential capacity for TMS to modulate DLPFC

Left DLPFC Activation

Label Attributed to Activation
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 ON RESEARCH AND PRACTICE

SYNERGY

1 + 1 > 2
THE ART OF DELIVERING PLACEBO EFFECTS WITHOUT THE “PLACEBO”?

Placebo Effects in Psychotherapy: A Framework
Paul Enck* and Stephan Zipfel
Psychosomatic Medicine and Psychotherapy, Department of Internal Medicine VI, University of Heidelberg, Heidelberg, Germany

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

Viewpoint
May 23/30, 2017

FROM NUISANCE TO TREATMENT?

Perspective

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 MEANME TIME... 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 notice 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
Placebos could save lives and health care dollars: so why can’t mainstream medicine put them to better use?
THANKS!

Research Collaborators

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- Dr. Dan Blumberger

**UBC**
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**Harvard Medical School**
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- Dr. Michael Fox
- Dr. Emiliano Santarnecchi
- Dr. David Perez
- Dr. Davide Cappon
- Dr. Stefania Papatheodorou
- Dr. Fred Schaper
- Dr. Shan Siddiqi
- Sara Romanella
QUESTIONS

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