

# PLACEBO EFFECTS AND NEUROMODULATION: IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE



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SUNNYBROOK HEALTH SCIENCES CENTRE  
ASSISTANT PROFESSOR, UNIVERSITY OF TORONTO



# DISCLOSURES

- No relevant conflicts of interest
- Research Funding Sources:



Liu Fu Yu Charity Foundation  
Louise and Peter Walters



# RELEVANT AFFILIATIONS

## Program in Placebo Studies & Therapeutic Encounter (PiPS)

Beth Israel Deaconess Medical Center / Harvard Medical School



Beth Israel Deaconess  
Medical Center



HARVARD  
MEDICAL SCHOOL



Could studying the placebo effect  
change the way we think

PAN CANADIAN  
NEUROTECHNOLOGY  
ETHICS CONSORTIUM

Sunnybrook  
HOSPITAL CENTER FOR  
NEUROREHABILITATION

UNIVERSITY OF  
TORONTO



NEUROETHICS  
CANADA  
BRAIN HEALTH HUMAN VALUES

## Pan-Canadian Neurotechnology Ethics Consortium

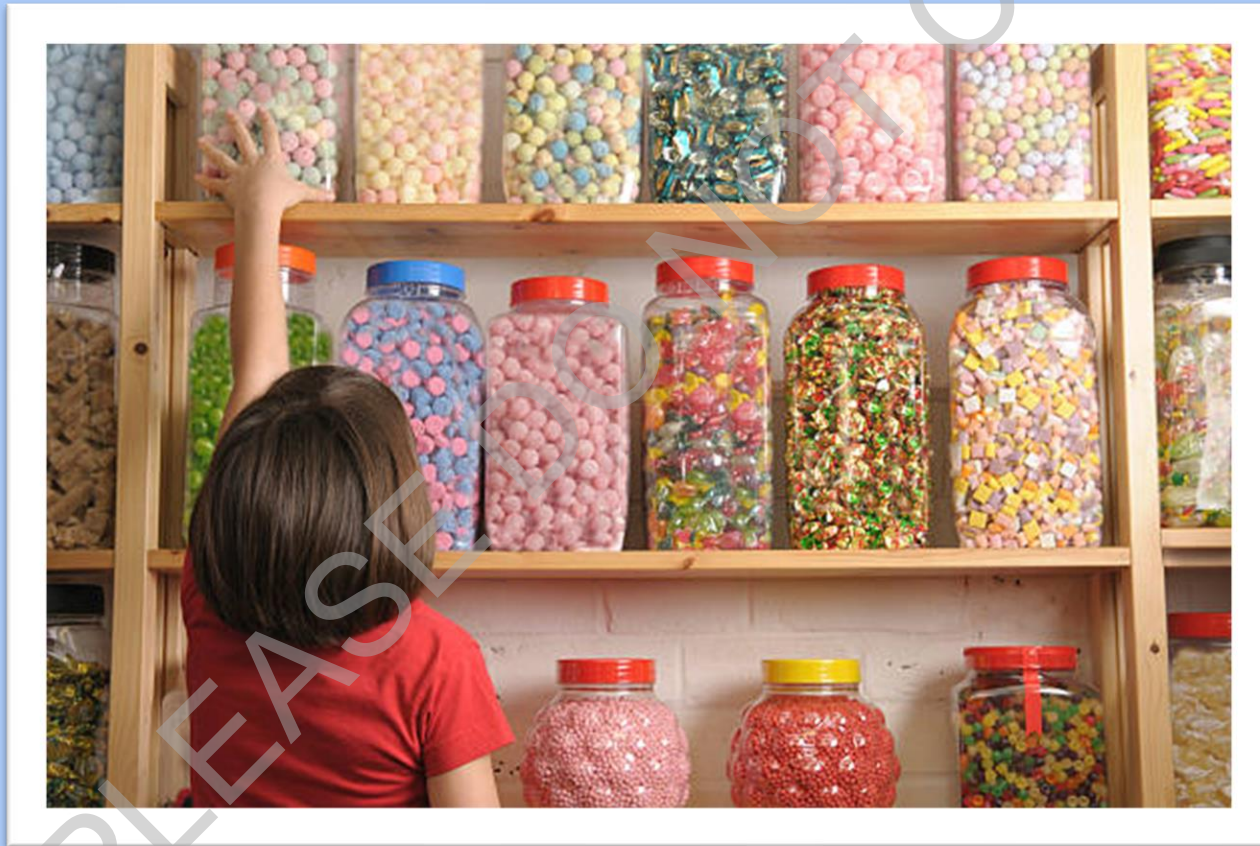
Working to create a forum for collaborative scientific and ethical discussion relevant to emerging neurotechnologies across Canadian health and social landscapes.

# OBJECTIVES

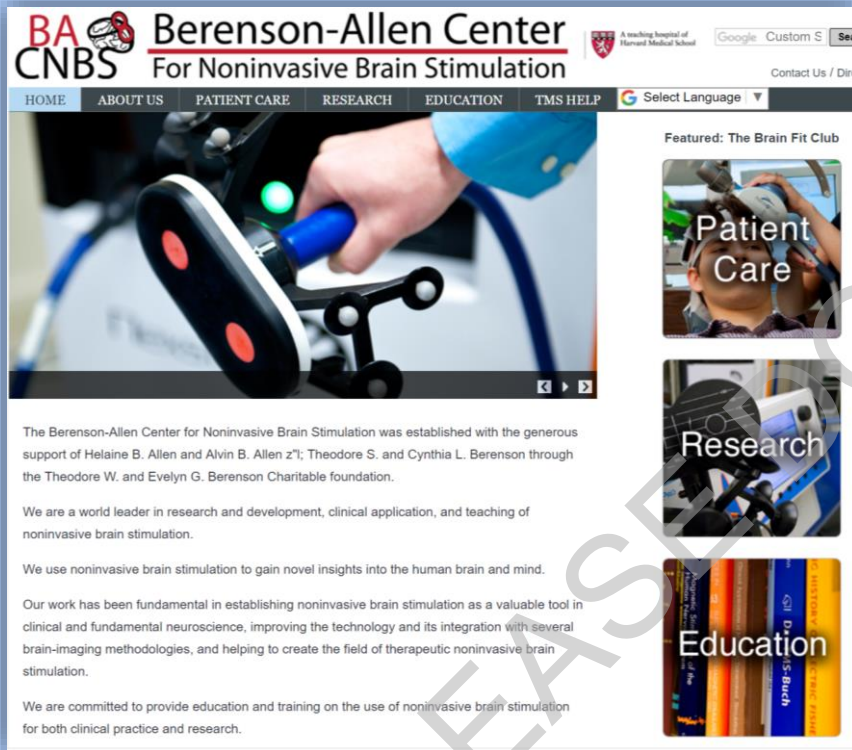
1. Gain an understanding of placebo effects terminology, principles and neurobiology
2. Appreciate the factors that contribute to placebo effects in clinical settings
3. Develop a framework for how placebo effects impact clinical trials and measurements of efficacy in research
4. Appreciate specific 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



**BA CNBS Berenson-Allen Center**  
For Noninvasive Brain Stimulation

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Featured: The Brain Fit Club

Patient Care

Research

Education

The Berenson-Allen Center for Noninvasive Brain Stimulation was established with the generous support of Helaine B. Allen and Alvin B. Allen z"l; Theodore S. and Cynthia L. Berenson through the Theodore W. and Evelyn G. Berenson Charitable foundation.

We are a world leader in research and development, clinical application, and teaching of noninvasive brain stimulation.

We use noninvasive brain stimulation to gain novel insights into the human brain and mind.

Our work has been fundamental in establishing noninvasive brain stimulation as a valuable tool in clinical and fundamental neuroscience, improving the technology and its integration with several brain-imaging methodologies, and helping to create the field of therapeutic noninvasive brain stimulation.

We are committed to provide education and training on the use of noninvasive brain stimulation for both clinical practice and research.



Dr. Alvaro  
Pascual-Leone



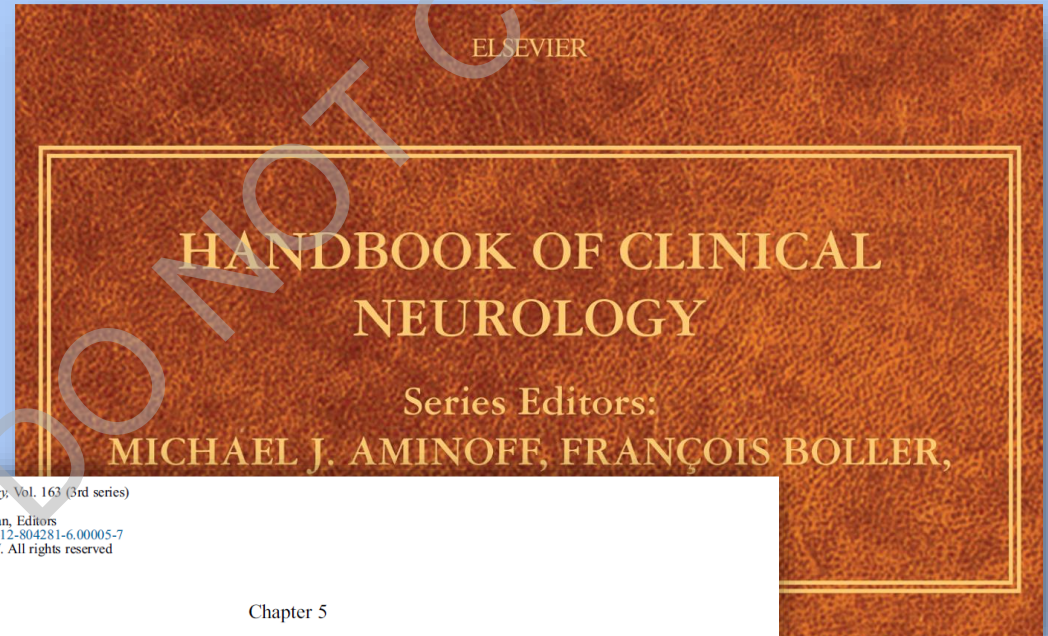
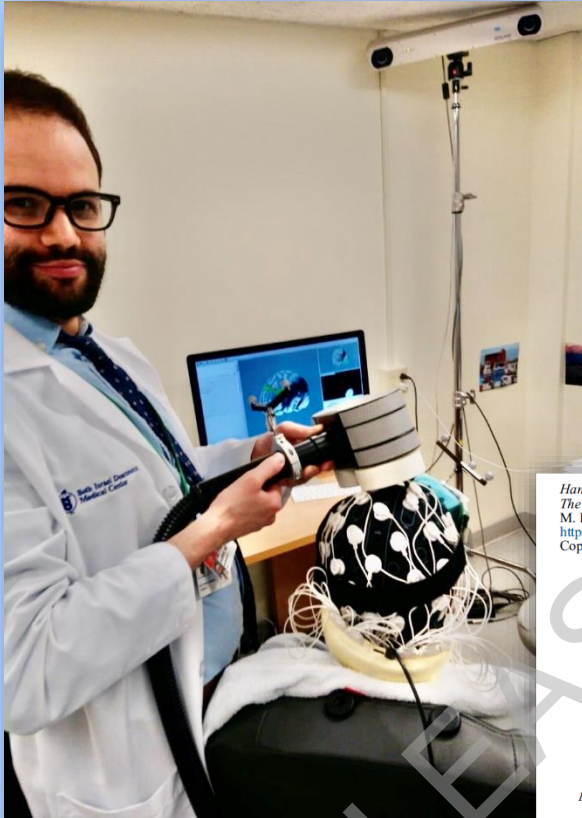
Dr. Michael Fox



Dr. Emiliano Santarnecchi



# NON-INVASIVE BRAIN STIMULATION



*Handbook of Clinical Neurology*, Vol. 163 (3rd series)  
*The Frontal Lobes*  
M. D'Esposito and J.H. Grafman, Editors  
<https://doi.org/10.1016/B978-0-12-804281-6.00005-7>  
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Chapter 5

## Transcranial magnetic stimulation: Neurophysiological and clinical applications

MATTHEW J. BURKE<sup>1</sup>, PETER J. FRIED<sup>1</sup>, AND ALVARO PASCUAL-LEONE<sup>1,2,3\*</sup>

<sup>1</sup>*Berenson-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*

<sup>2</sup>*Guttmann Brain Health Institute, Institut Guttmann de Neurorehabilitacio, Universitat Autònoma de Barcelona, Barcelona, Spain*

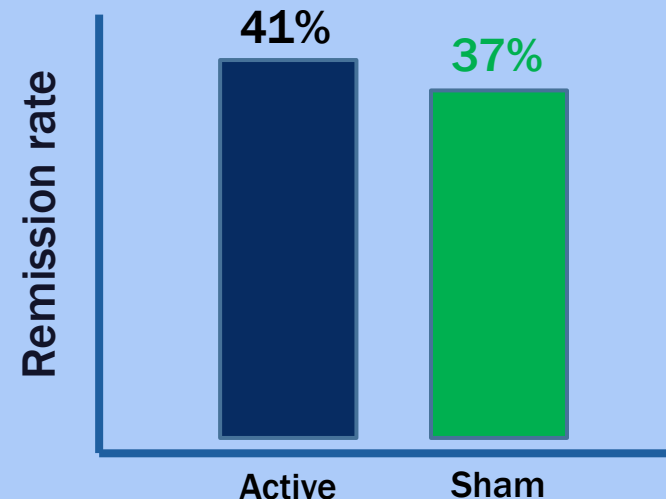
<sup>3</sup>*Marcus Institute for Aging Research, Hebrew Senior Life, Harvard Medical School, Boston, MA, United States*

# 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



# AND IN NEUROLOGY...



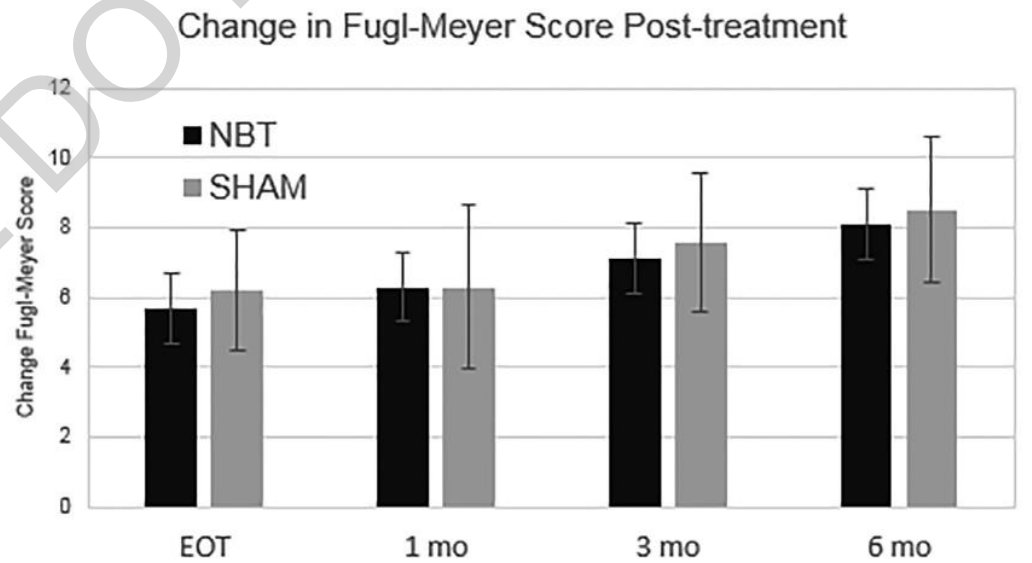
## Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



### Randomized Sham-Controlled Trial of Navigated Repetitive Transcranial Magnetic Stimulation for Motor Recovery in Stroke: The NIC Trial

Richard L. Harvey, MD; Dylan Edwards, PhD, PT; Joel Stein, MD; Jarmo Laine, MD; I. Ana Durand-Sanchez, MD; Marcia Bockholt, MD; Gerard E. Francisco, MD; Carolyn L. Semler, MD, on behalf of the NIC Trial Group



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nature  
HEALTH

## 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



The New York Times Magazine

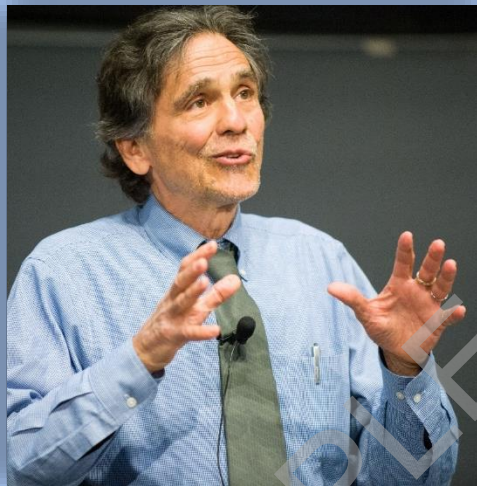


## Placebo Effects in Medicine



Ted J. Kaptchuk and Franklin G. Miller, Ph.D.

N ENGL J MED 373;1 NEJM.ORG JULY 2, 2015



FEATURE

## 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.





# RECENT BRIEF SYNOPSIS

THE LANCET  
Psychiatry

CORRESPONDENCE | VOLUME 10, ISSUE 5, P316-317, MAY 2023

## 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](https://doi.org/10.1016/S2215-0366(23)00068-8)



# 1 INTRODUCTION TO PLACEBO EFFECTS



# PLACEBO EFFECTS

## The neuroscience of placebo effects: connecting context, learning and health

Tor D. Wager<sup>1</sup> and Lauren Y. Atlas<sup>2</sup>

NATURE REVIEWS | NEUROSCIENCE

### 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

Science

Science

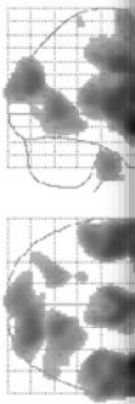
## Placebo and Opioid Antagonist Expectation and Dopamine Release: Mechanism of the Placebo Effect in Parkinson's Disease

Predrag Petrovic, Eija Kalso, K. Raúl de la Fuente-Fernández, Thomas J. Ruth, Vesna Sossi, Michael Schulzer, Donald B. Calne and A. Jon Stoessl

*Science* 295 (5560), 1737-1741  
DOI: 10.1126/science.1067176

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

A Opioid ne

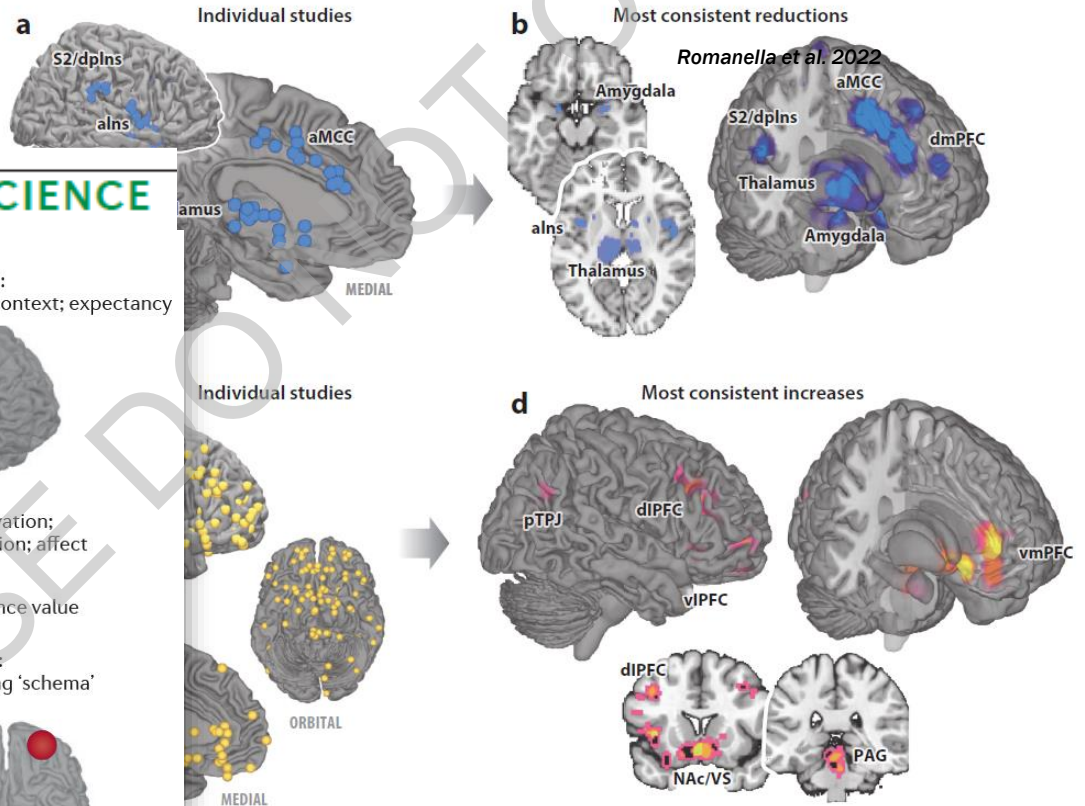
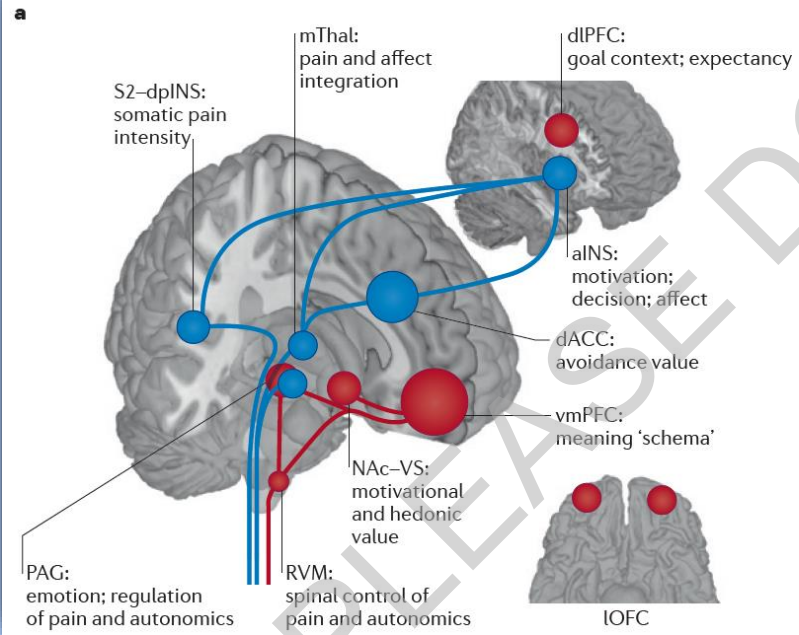


**Table 1.** Striatal RAC binding potential (mean  $\pm$  SD) of PD patients (group 1) scanned at open baseline and after receiving placebo ( $n = 6$ ).

Site	Open baseline	Placebo	Mean percent change (range)
Head of caudate	1.964 $\pm$ 0.221	1.638 $\pm$ 0.230	16.6 (8.4–25.1)
Putamen			
Rostral	2.398 $\pm$ 0.342	1.976 $\pm$ 0.321	17.6 (5.3–26.3)
Intermediate	2.621 $\pm$ 0.438	2.142 $\pm$ 0.389	18.2 (7.4–27.0)
Caudal	2.095 $\pm$ 0.269	1.646 $\pm$ 0.261	21.2 (8.8–32.6)

# CURRENT NEUROIMAGING

NATURE REVIEWS | NEUROSCIENCE

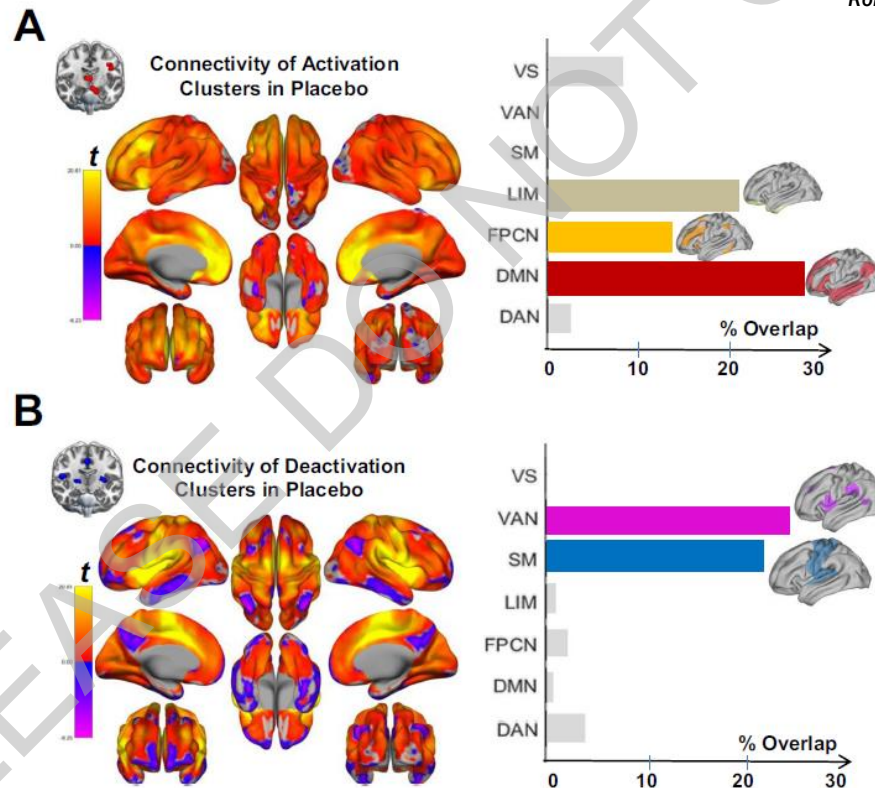


Wager and Atlas 2015, Ashar et al 2017

# CURRENT NEUROIMAGING

Cognitive, Affective, & Behavioral Neuroscience

Romanella et al. 2022

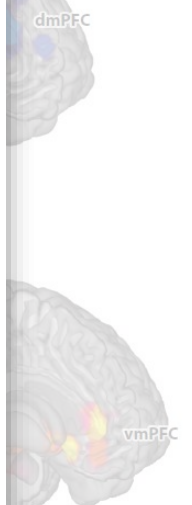


NATURE REVIEW

a

S2-dpINS:  
somatic pain  
intensity

PAG:  
emotion; regulation  
of pain and autonomies



wager and Atlas 2015, Ashar et al 2017

# BLOCKING STUDIES

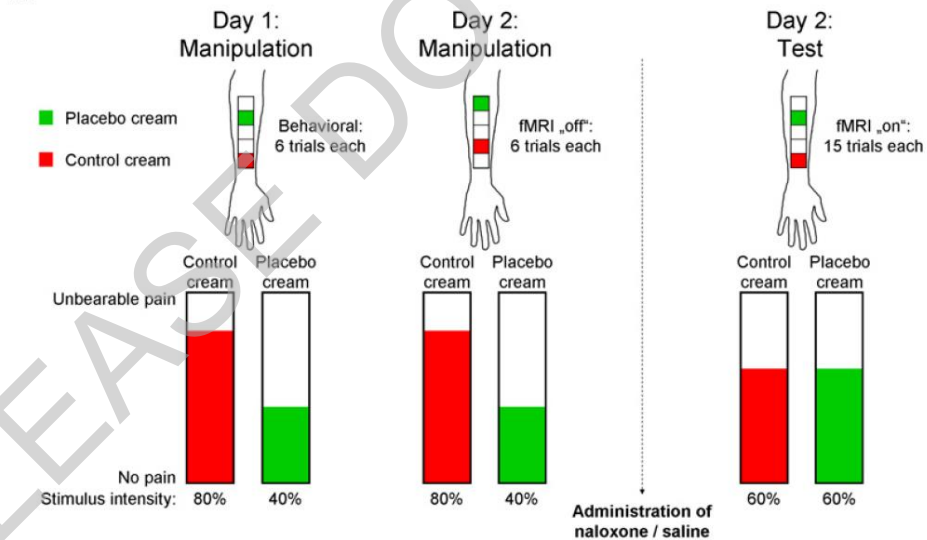
Neuron  
Article

Cell  
PRESS

## Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia

Falk Eippert,<sup>1,\*</sup> Ulrike Bingel,<sup>2</sup> Eszter D. Schoell,<sup>1</sup> Juliana Yacubian,<sup>1</sup> Regine Klinger,<sup>3</sup> Jürgen Lorenz,<sup>4</sup> and Christian Büchel<sup>1</sup>

A





# BLOCKING STUDIES

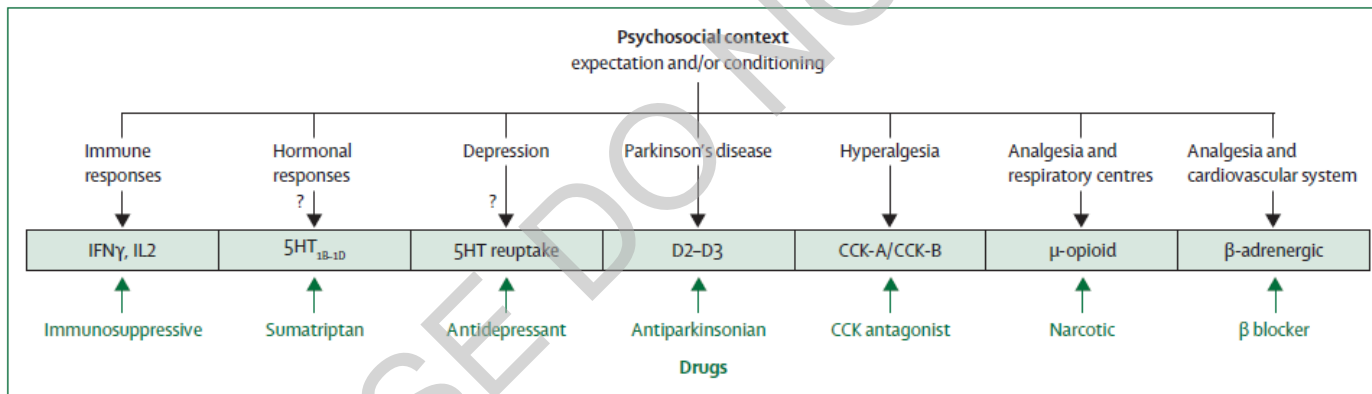
Neuron  
Article

Cell  
PRESS

## Biological, clinical, and ethical advances of placebo effects

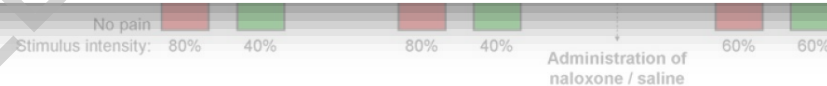
Damien G Finniss, Ted J Kaptchuk, Franklin Miller, Fabrizio Benedetti

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 (ie, the psychosocial context) might affect the system and change the response to the drug. Reproduced with permission from reference 39. IFN $\gamma$ =interferon  $\gamma$ . 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,<sup>1</sup> Jobst,<sup>2</sup> Lisa A Conboy, instructor of medicine,<sup>1</sup> Robert M. Hyman, professor of biostatistics,<sup>3</sup> Catherine E Kerr, instructor of medicine, psychology,<sup>5</sup> Rosa N Schyner, research associate,<sup>1</sup> Brian J. Goldstein, research fellow,<sup>1</sup> Min Park, research coordinator,<sup>1</sup> Andriana M. N. M. research coordinator,<sup>1</sup> Efi Kokkotou, assistant professor of medicine,<sup>6</sup> Peter Goldman, professor emeritus,<sup>7</sup> Ant

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

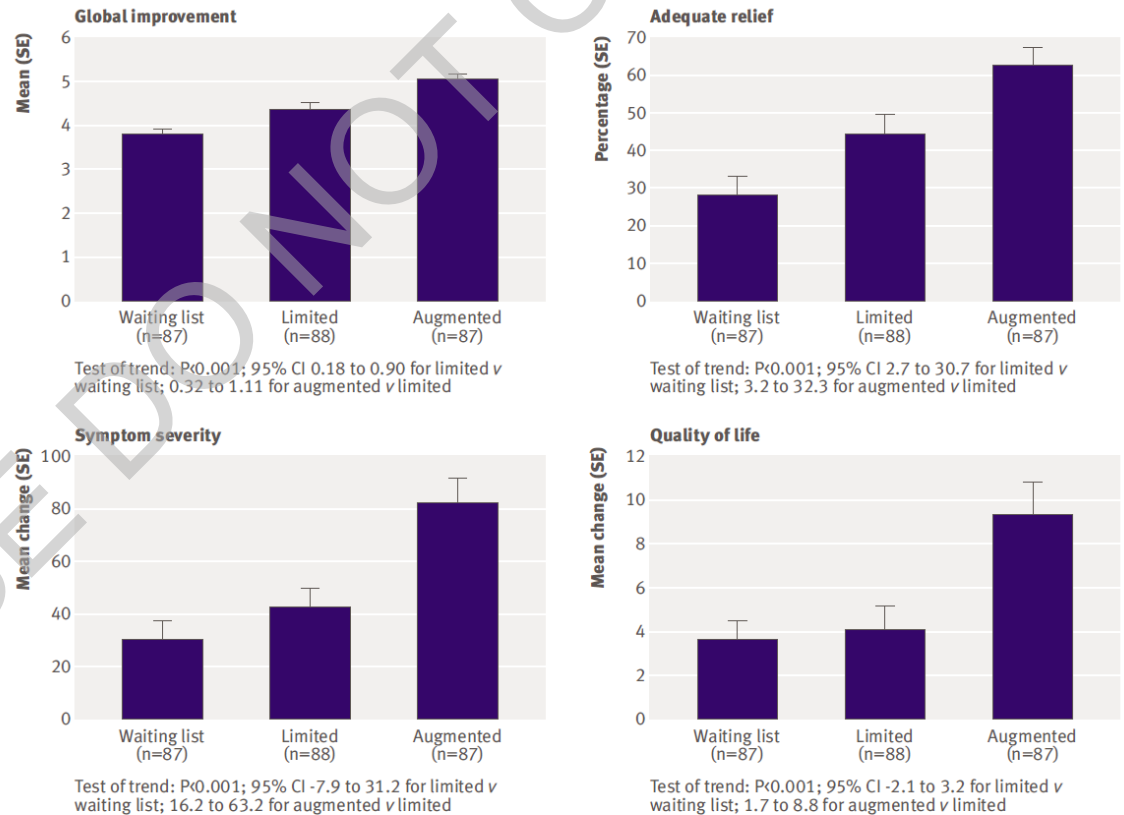


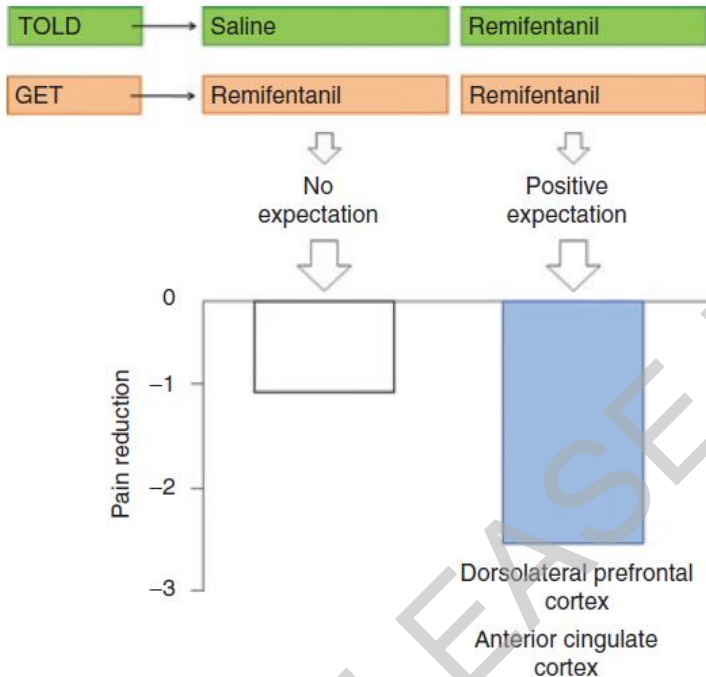
Fig 2 | Outcomes at three week end point



# KNOCK-OUT MODELS

## Hidden Administration of Drugs

F Benedetti<sup>1,2</sup>, E Carlino<sup>1,2</sup> and A Pollo<sup>1,2</sup>



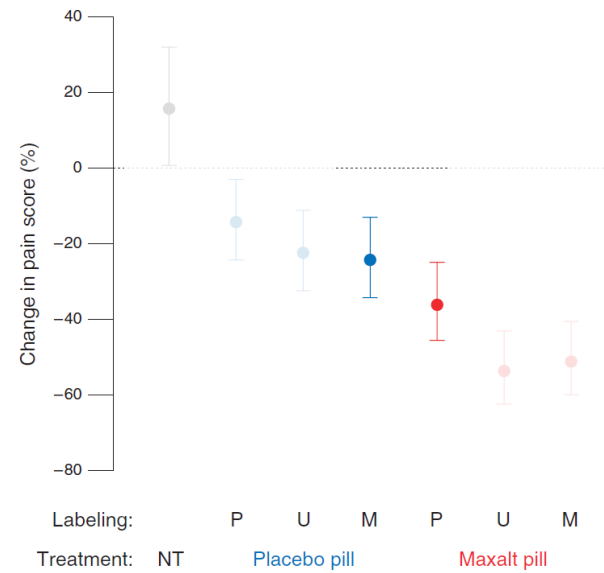
## RESEARCH ARTICLE



### MIGRAINE

## Altered Placebo and Drug Labeling Changes the Outcome of Episodic Migraine Attacks

Slavenka Kam-Hansen,<sup>1</sup> Moshe Jakubowski,<sup>2</sup> John M. Kelley,<sup>3,4,5</sup> Irving Kirsch,<sup>5,6</sup> David C. Hoaglin,<sup>7</sup> Ted J. Kaptchuk,<sup>5\*</sup> Rami Burstein<sup>2\*†</sup>



# UNDERLYING PRINCIPLES & MODELS

The NEW ENGLAND JOURNAL of MEDICINE

## REVIEW ARTICLE

Allan H. Ropper, M.D., *Editor*

### 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.<sup>1,2</sup> 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.<sup>3-6</sup> The frequency and intensity of placebo effects in clinical practice are difficult to determine, and the range of effects in experimental settings is wide.<sup>7</sup> In many double-blind clinical trials of treatments for pain<sup>8</sup> or psychiatric disorders,<sup>9</sup> 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.<sup>10</sup> Furthermore, as many as one quarter of patients receiving placebo in clinical trials discontinue it because of side effects,<sup>11,12</sup> suggesting that a nocebo effect may contribute to discontinuation of or lack of adherence to active treatments.

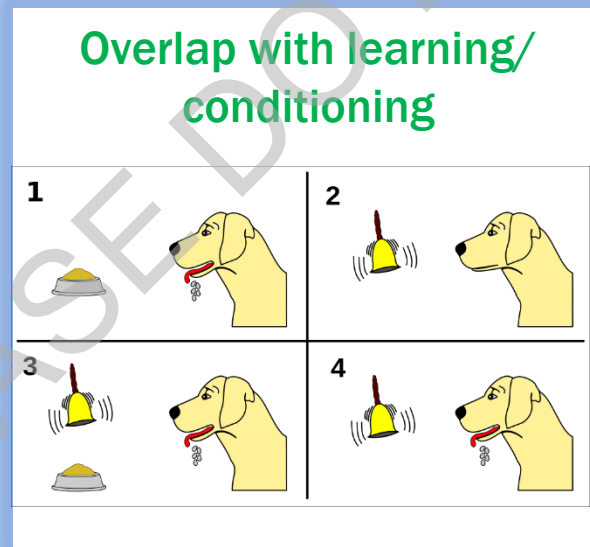
N ENGL J MED 382:6 NEJM.ORG FEBRUARY 6, 2020



# EXPECTANCIES

- Expectancies be acquired in a number of ways:

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



# CONDITIONING

Morphine



Morphine



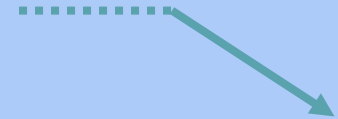
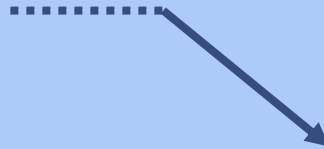
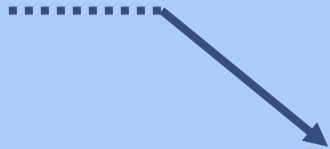
Morphine



Saline



Pain



# EXPECTANCIES

- 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

**Nocebo effects** = new or worsening symptoms in response to negative health-related information, beliefs, and/or experiences

**SPECIAL COMMUNICATION**

**JAMA** The Journal of the American Medical Association

## Nonspecific Medication Side Effects and the Nocebo Phenomenon

Arthur J. Barsky, MD  
Ralph Saintfort, MD  
Malcolm P. Rogers, MD  
Jonathan F. Borus, MD

Patients taking active medications frequently experience adverse nonspecific side effects that are not a direct result of the specific pharmacological action of the drug. Although this phenomenon is common, distressing, and costly, it is rarely studied and poorly understood. The nocebo phenomenon, in which placebo produces adverse side effects, offers some insight into...

November 26, 2020  
N Engl J Med 2020; 383:622-627

**CORRESPONDENCE**

### N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects

side effects to active medications by identifying in advance those patients most at risk for developing them and by using a collaborative relationship with the patient to explain and help the patient to understand and tolerate these bothersome but nonharmful symptoms.

JAMA. 2002;287:622-627

www.jama.com

**Neuron Review**

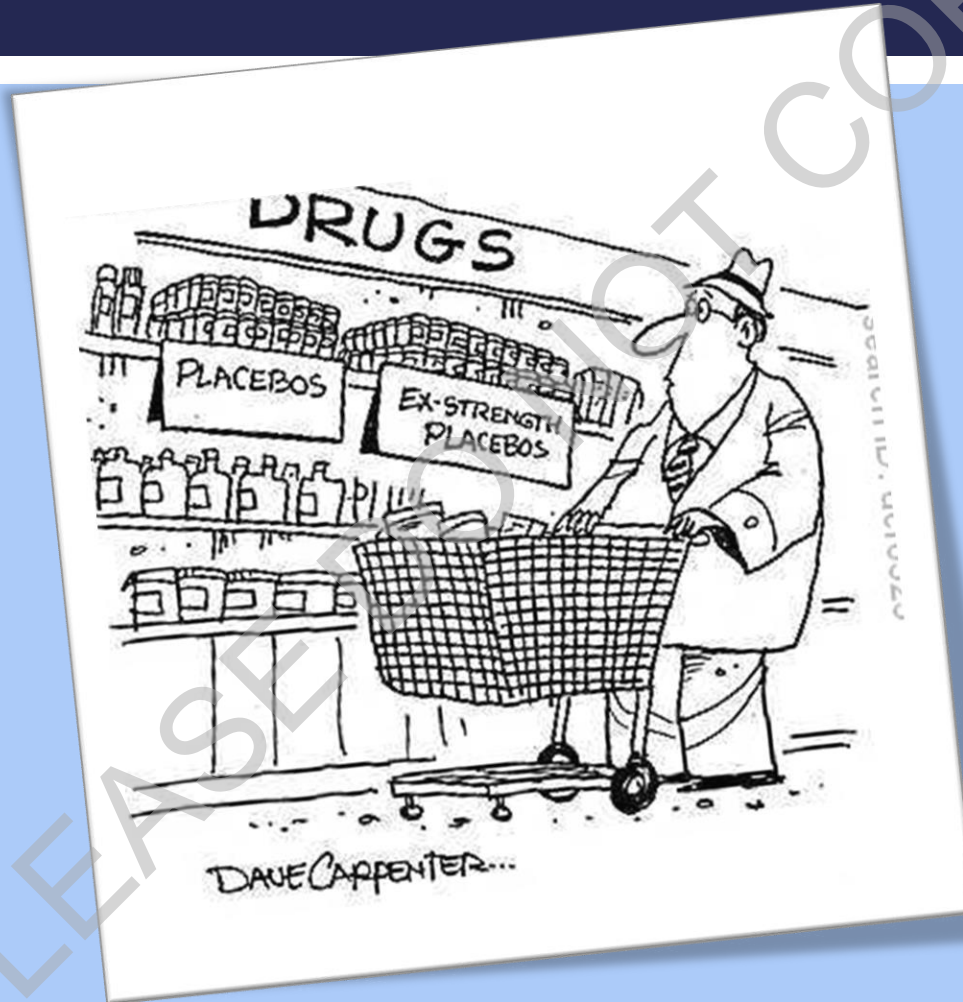
**Cell PRESS**

## New Insights into the Placebo and Nocebo Responses

Paul Enck,<sup>1\*</sup> Fabrizio Benedetti,<sup>2</sup> and Manfred Schedlowski,<sup>3</sup> Department of Internal Medicine VI: Psychosomatic Medicine, Department of Neuroscience, University of Turin Medical School, 10126 Turin, Italy; <sup>2</sup>Institute of Medical Psychology and Behavioral Immunology, 47048 Duisburg-Essen, Germany  
\*Correspondence: paul.enck@uni-tuebingen.de  
DOI: 10.1016/j.neuron.2008.06.030

The diagram illustrates the physiological pathway of a nocebo response. It begins with 'Nocebo suggestions' which lead to 'ANTICIPATORY ANXIETY' in the brain. 'Benzodiazepines' are shown to have an inhibitory effect on this anxiety. The anxiety then triggers the 'Hypothalamus', which sends signals to the 'Pituitary gland' to release 'ACTH'. ACTH then stimulates the 'Adrenal glands' to release 'Cortisol'. A 'PRO-NOCEPITIVE SYSTEM' is also shown to be involved in this pathway. 'CCK-antagonists' are shown to block 'CCK' from acting on 'CCK-receptors' in the hypothalamus, thereby modulating the response.

## 2 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

**This Issue** Views **25,950** | Citations **0** | Altmetric **1304** | Comments **8**

**JAMA Neurology**

### Viewpoint

September 16, 2019

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

Matthew J. Burke, MD, FRCPC<sup>1,2</sup>

#### Author Affiliations

<sup>1</sup>Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

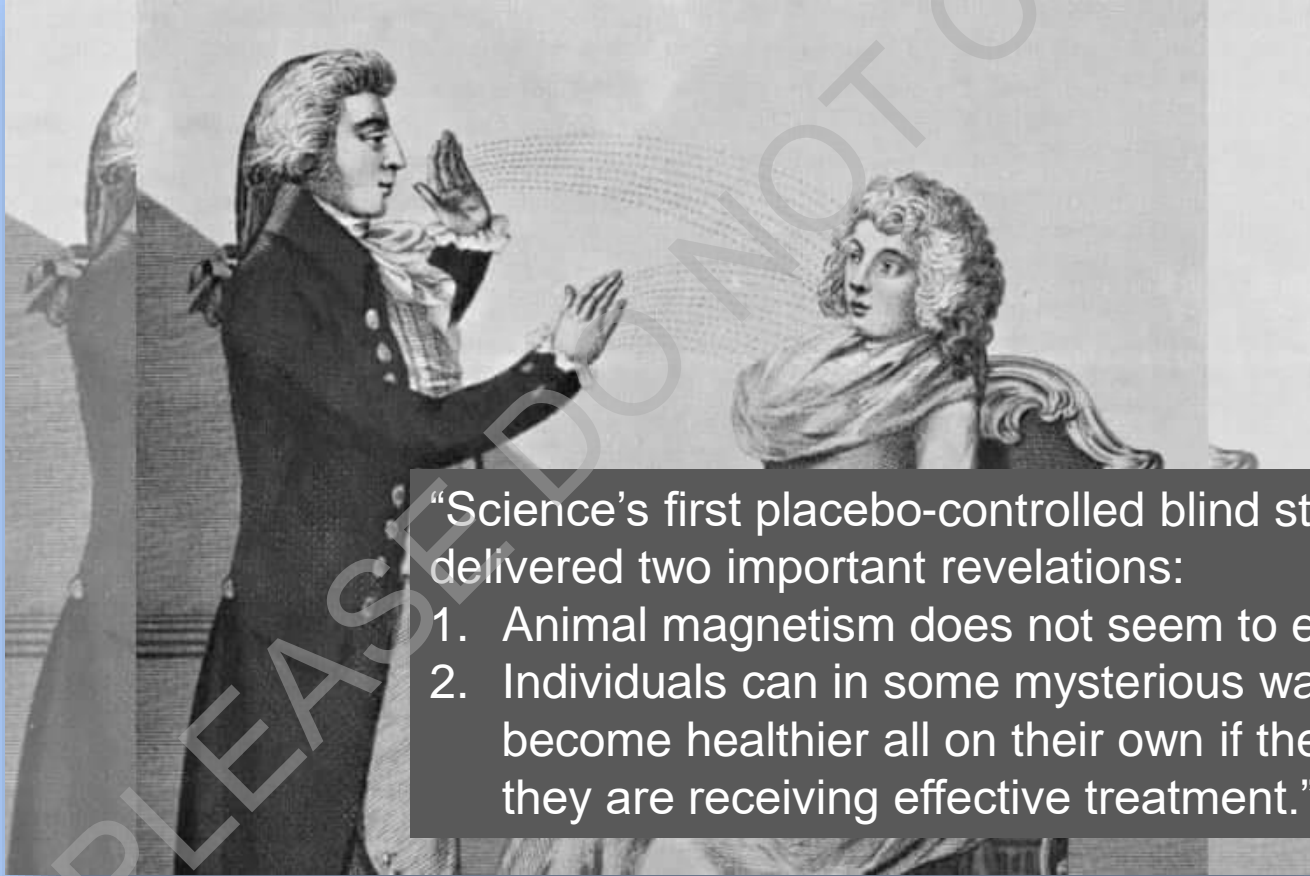
<sup>2</sup>Department of Psychiatry, Hurvitz Brain Sciences Program, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

*JAMA Neurol.* 2019;76(12):1417-1418. doi:10.1001/jamaneurol.2019.3043



“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,

# LONG AND DARK HISTORY RELATED TO PLACEBO EFFECTS



“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.”

Genetic Literacy Project

# OVERLAP IN IMPLICATED BRAIN REGIONS

The Journal of  
**Neuropsychiatry**  
and Clinical Neurosciences

OPINION





## 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.



NATURE REVIEWS | NEUROLOGY | VOLUME 18 | OCTOBER 2022

## 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

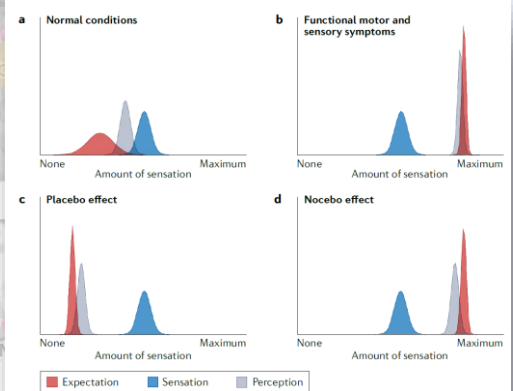
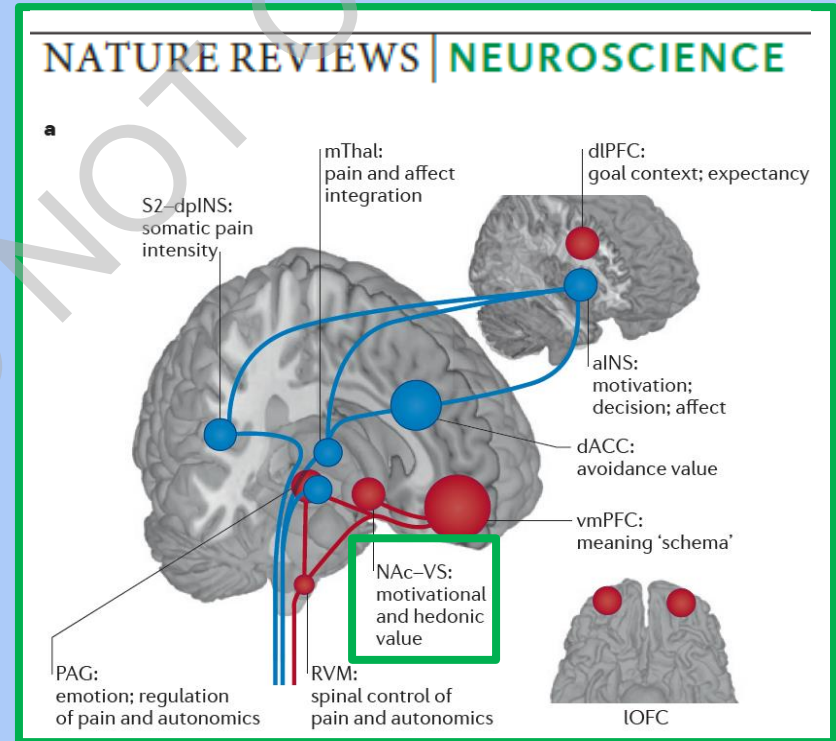
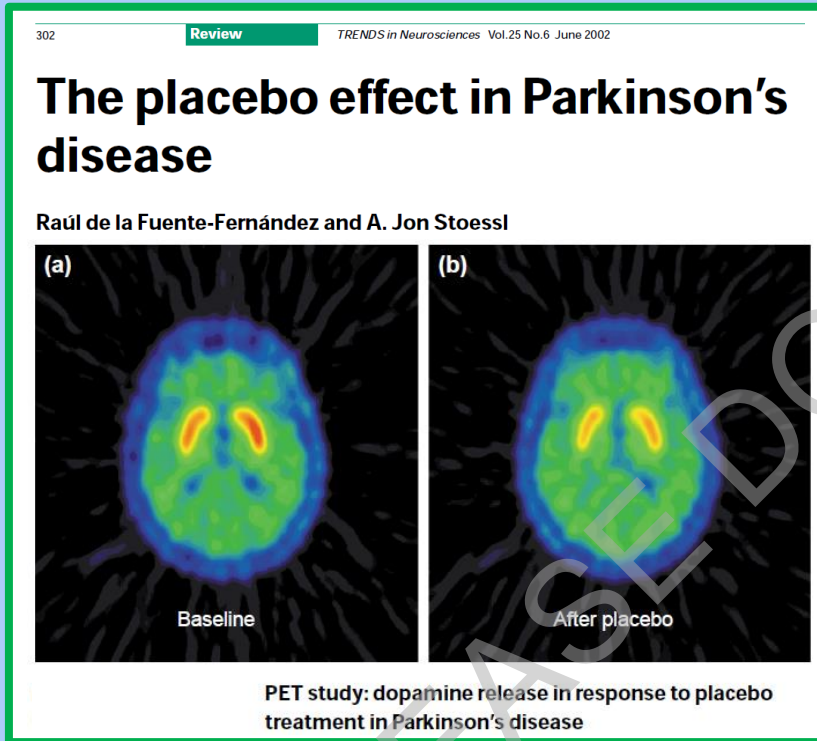


Fig. 1 | The predictive coding model applied to functional symptoms, placebo and nocebo.



# CASE EXAMPLE 2

## “STRUCTURAL” BRAIN DISORDER



Placebo responsiveness ≠ “fake” disorder

# CASE EXAMPLE 3

## GENERAL MEDICAL DISORDER

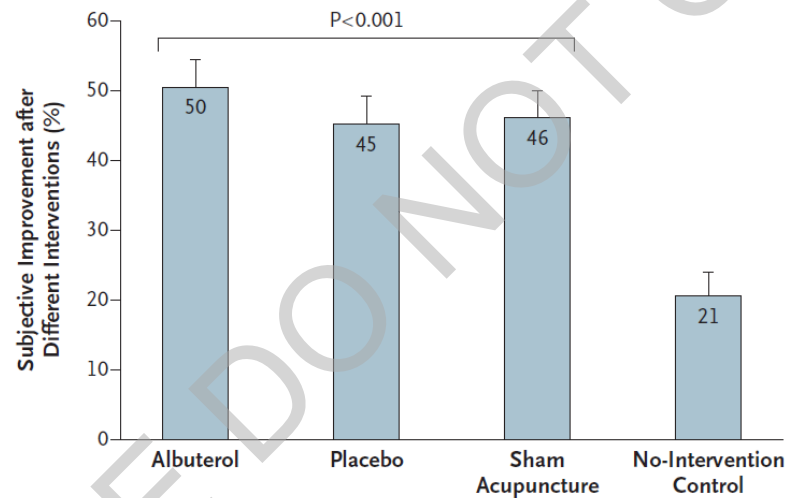
*The* NEW ENGLAND JOURNAL *of* MEDICINE

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 Dutilleul, 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

Review

CellPress

## Genetics and the placebo effect: the placebome

Kathryn T. Hall<sup>1,2</sup>, Joseph Loscalzo<sup>3</sup>, and Ted J. Kaptchuk<sup>1,2</sup>

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

Placebo pathway	Gene name
Dopamine	Catechol-O-
	Monoamine
	Dopamine E
	Dopamine r
Serotonin	Brain-derive
	Tryptophan
	5-Hydroxytr
	5-Hydroxytr
Opioid	Serotonin tr
	polymorphi
Endocannabinoid	Opioid rece
	Fatty acid a

Systematic Review and Meta-Analysis

March 2023 • Volume 164 • Number 3

**PAIN**<sup>®</sup>



## Association between personality traits and placebo effects: a preregistered systematic review and meta-analysis

Heemin Kang<sup>a,b</sup>, Miriam Sophie Miksche<sup>a</sup>, Dan-Mikael Ellingsen<sup>a,c,d,\*</sup>

# TWO MAIN CONSIDERATIONS

The Patient



The Treatment

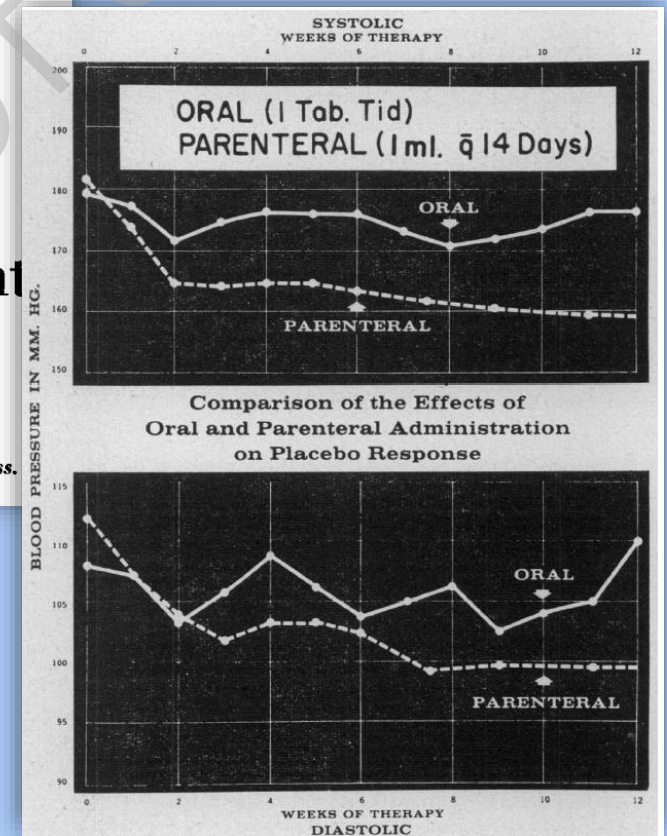
# FACTORS IMPACTING PLACEBO EFFECTS

124

J.A.M.A., April 15, 1961

## 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.



# SHAM-CONTROLLED SURGICAL TRIALS

ANNALS OF SURGERY  
Vol. 235, No. 2, 303-307  
© 2002 Lippincott Williams & Wilkins, Inc.

## 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: Audiey Kao, MD, PhD, Acting Vice President, Ethics Standards Group, American Medical Association; Karine Morin, LL.M., Council Secretary and Staff Author; Andrew Maixner, Council Staff Associate; Sam Seiden, Council Staff Associate.



# SHAM-CONTROLLED SURGICAL/PROCEDURAL TRIALS

THE NEW ENGLAND JOURNAL OF MEDICINE  
Vol. 260 No. 22 INTERNAL-MAMMARY-ARTERY LIGATION — COBB ET AL. 1115

Articles **IN BY A**

Percutaneous coronary intervention

(OR **Articles**

Rasha A  
Raffi Ka  
Andrew  
Justin E



**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, Shireen Patel, Clement Boutry, Priya Patel, Boliang Guo, Paul M Briley, Deborah Butler, Michael Craven, Ashley Duncan, Christopher Griffiths, Fred Highton, Rebecca McNaughton, Neil Nixon, Vibhore Prasad, Kapil Sayal, David Smart, Azhar Zafar, Joe Kai

Articles **Articles**

acromial  
parallel  
sed



L Donovan,  
Polowska, Andrew J Carr,



ri, M.D., William W. O'Neill, M.D.,  
, M.P.H., Barry T. Katzen, M.D.,  
auri, M.D., Manuela Negoita, M.D.,  
M.D., Krishna Rocha-Singh, M.D.,  
George L. Bakris, M.D.,  
Investigators\*

# TREATMENT INTENSIVENESS

## Placebo interventions for all clinical conditions (Review)

Hróbjartsson A, Gøtzsche PC

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

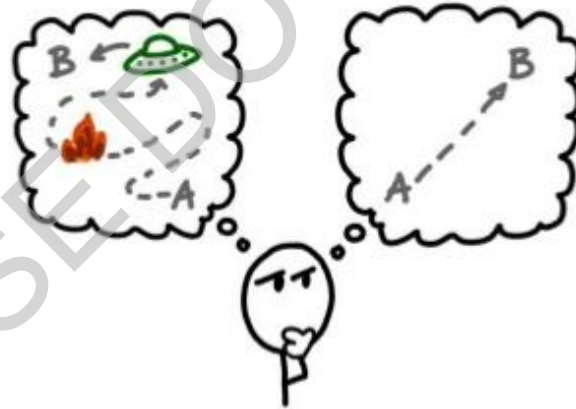
**THE COCHRANE  
COLLABORATION®**



# COMMON DENOMINATOR

- 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.”*

vectorstock

# OTHER FACTORS

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

## Placebo effect of medication cost in Parkinson disease

A randomized double-blind study



Alberto J. Espay, MD, MSc  
Matthew M. Norris, MEng  
James C. Eliassen, PhD  
Alok Dwivedi, PhD  
Matthew S. Smith, BS  
Christi Banks, CCRC  
Jane B. Allendorfer, PhD  
Anthony E. Lang, MD, FRCPC  
David E. Fleck, PhD  
Michael J. Linke, PhD  
Jerzy P. Szaflarski, MD, PhD

### ABSTRACT

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

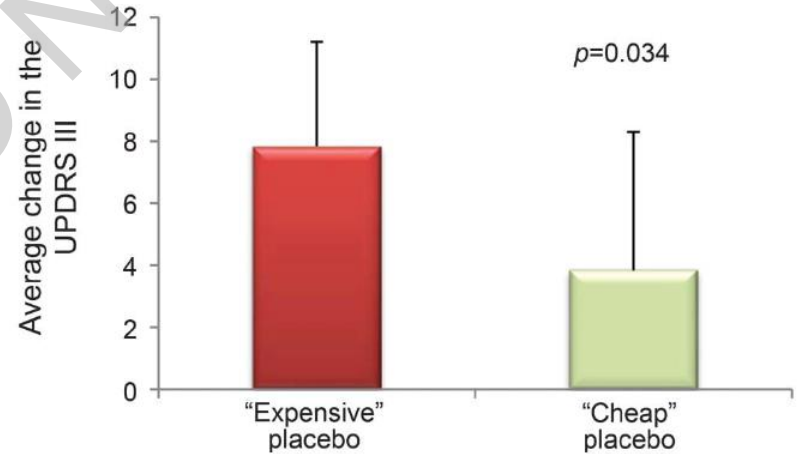
**Methods:** We conducted a prospective double-blind study in 12 patients with motor Parkinson disease and motor fluctuations (mean age  $62.4 \pm 7.9$  years; mean  $11 \pm 6$  years) who were randomized to a “cheap” or “expensive” subcutaneous dopamine agonist placebo (normal saline). Patients were crossed over to the approximately 4 hours later. Blinded motor assessments in the “practically de before and after each intervention, included the Unified Parkinson’s Disease Rating subscale, the Purdue Pegboard Test, and a tapping task. Measurements of brain effect was examined using stratified analysis.

**Results:** Although both placebos improved motor function, benefit was greater were randomized first to expensive placebo, with a magnitude halfway between placebo and levodopa. Brain activation was greater upon first-given cheap but not expensive placebo or by 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

Correspondence to  
Dr. Espay:  
alberto.espay@uc.edu



# 3

# PLACEBO EFFECTS IN RESEARCH

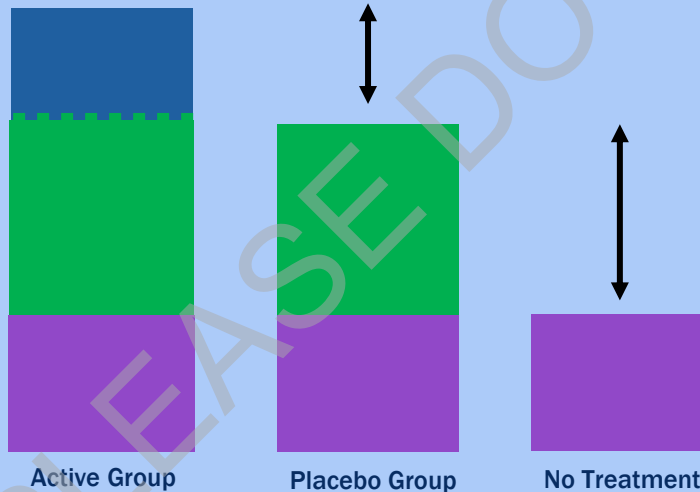
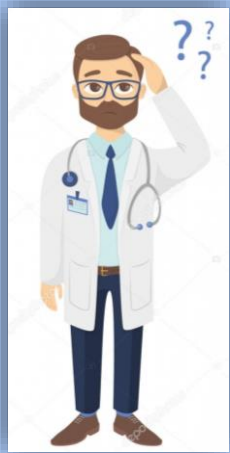


Edsurge

# 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

# CHALLENGES TO CONVENTIONAL FRAMEWORK



# 1) BLINDING INTEGRITY

## THE LANCET

COMMENT | VOLUME 375, ISSUE 9721, P1144-1146, 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](https://doi.org/10.1016/S0140-6736(10)60413-8)



EJN  EUROPEAN JOURNAL OF NEUROSCIENCE

*European Journal of Neuroscience*, Vol. 38, pp. 2973–2977, 2013

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,<sup>1</sup> Edward Gold,<sup>2</sup> Alvaro Pascual-Leone<sup>2</sup> and R. Martyn Bracewell<sup>1,3,4</sup>



# NOT A UNIQUE ISSUE FOR TMS.



The NEW ENGLAND JOURNAL OF MEDICINE

**nature medicine**

**OPEN**

## Trial of Psilocybin-assisted therapy in a randomized, double-blind phase 3 study

Jennifer M. Mitchell<sup>1,2,3,4</sup>, Michael Bogenschutz<sup>5</sup>, Sarah Kleiman<sup>6</sup>, Kelly Parker-Guilbert<sup>7</sup>, Marcela C. Ingmar Gorman<sup>8</sup>, Christopher Nicholas<sup>9</sup>, Michael Bruce Poulter<sup>10</sup>, Ann Mithoefer<sup>9</sup>, Sylvestre Quessada Bessel van der Kolk<sup>16</sup>, Keren Tzarfaty<sup>9</sup>, Revital Anand<sup>11</sup>, Joshua D. Woolley<sup>2</sup>, Cole Marta<sup>20</sup>, Yevgeniy Gelfand<sup>12</sup>, Randall Brown<sup>13</sup>, Scott Hamilton<sup>25</sup>, Julie B. Wang<sup>14</sup>, Alberdina de Boer<sup>5</sup>, Berra Yazar-Klosinski<sup>4</sup>, Amy

Robin Carhart-Harris, Ph.D.  
Michelle Baker-Jones  
Roberta Murphy, M.D.  
David Erritzano

The New York Times

## A Psychedelic Drug Passes a Big Test for PTSD Treatment

A new study shows that MDMA, known as Ecstasy or Molly, can bring relief when paired with talk therapy to those with severe post-traumatic stress disorder.

“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.”

**nature medicine**

**MATTERS ARISING**

<https://doi.org/10.1038/s41591-021-01524-1>

Check for updates

## Caution at psychiatry’s psychedelic frontier

Matthew J. Burke<sup>1,2,3,4</sup> and Daniel M. Blumberger<sup>1,5</sup>

NATURE MEDICINE | [www.nature.com/naturemedicine](http://www.nature.com/naturemedicine)

## 2) THE IMPACT OF DIFFERENTIAL PLACEBO EFFECTS

*ANNALS of Neurology*

January 2019

NEUROLOGY GRAND ROUNDS

# Challenges of Differential Placebo Effects in Contemporary Medicine: The Example of Brain Stimulation

Matthew J. Burke, MD,<sup>1</sup> Ted J. Kaptchuk,<sup>2</sup> and Alvaro Pascual-Leone, MD, PhD<sup>1</sup>

# BRAIN STIMULATION TECHNOLOGIES



# HOW THE TREATMENT IS FRAMED



RESEARCH ARTICLE



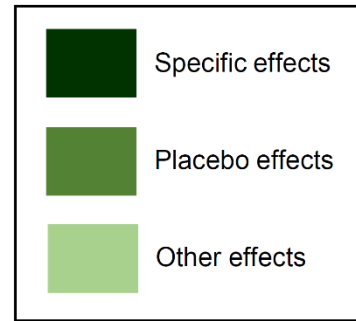
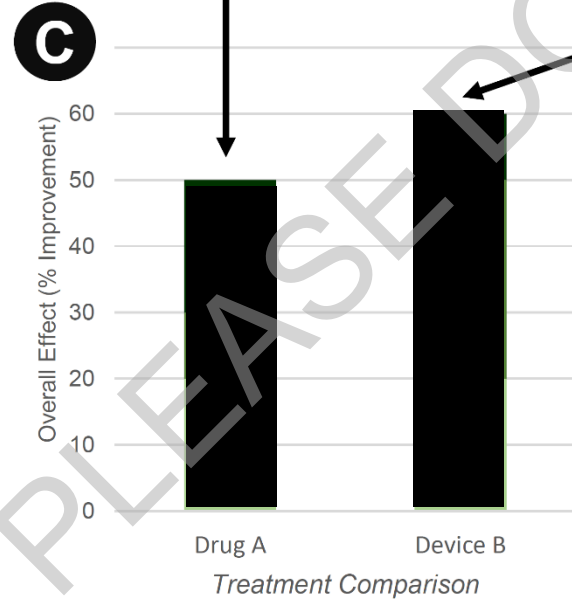
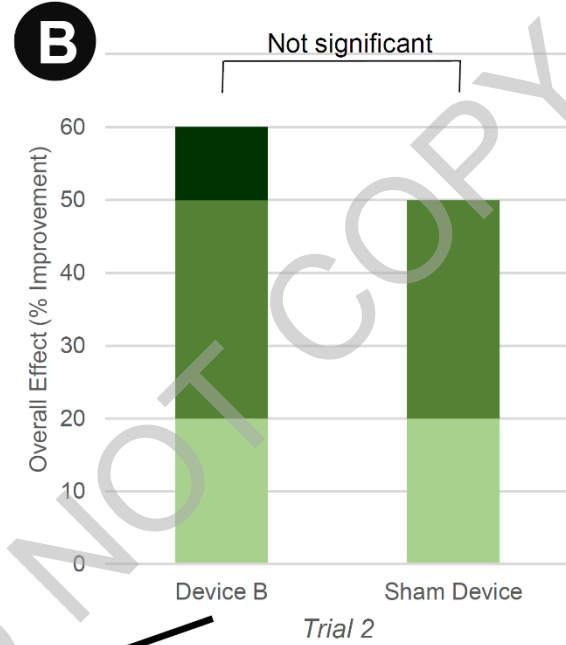
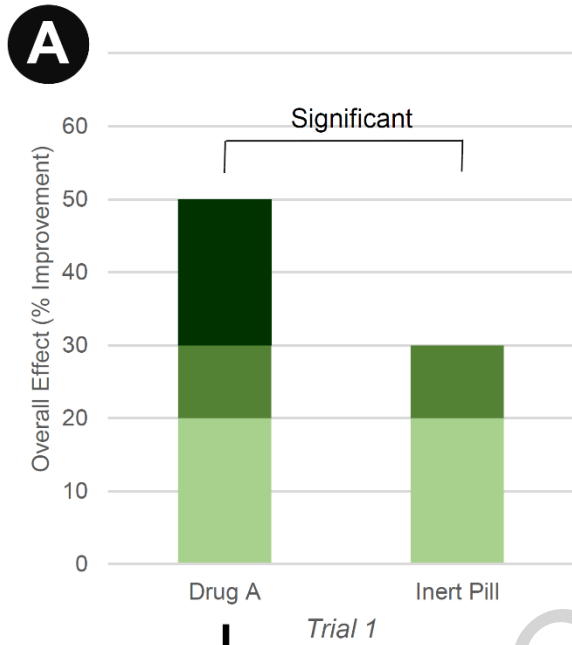
## Presenting a sham treatment as personalised increases the placebo effect in a randomised controlled trial

Dasha A Sandra<sup>1\*</sup>, Jay A Olson<sup>2†</sup>, Ellen J Langer<sup>2</sup>, Mathieu Roy<sup>3</sup>

<sup>1</sup>Integrated Program in Neuroscience, McGill University, Montreal, Canada;

<sup>2</sup>Department of Psychology, Harvard University, Cambridge, United States;

<sup>3</sup>Department of Psychology, McGill University, Montreal, Canada



# 3) IMPACT OF SHARED MECHANISMS BETWEEN PLACEBO EFFECTS & TREATMENT






Molecular Psychiatry

[www.nature.com/mp](http://www.nature.com/mp)  
nature portfolio

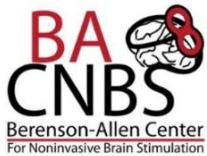
## ARTICLE

 Check for updates

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

Matthew J. Burke <sup>1,2,3,12</sup> , Sara M. Romanella<sup>3,4,12</sup>, Lucia Mencarelli<sup>3,4</sup>, Rachel Greben<sup>2</sup>, Michael D. Fox<sup>3,5,6</sup>, Ted J. Kaptchuk <sup>7</sup>, Alvaro Pascual-Leone<sup>8,9,10</sup> and Emiliano Santarnecchi <sup>3,11</sup> 

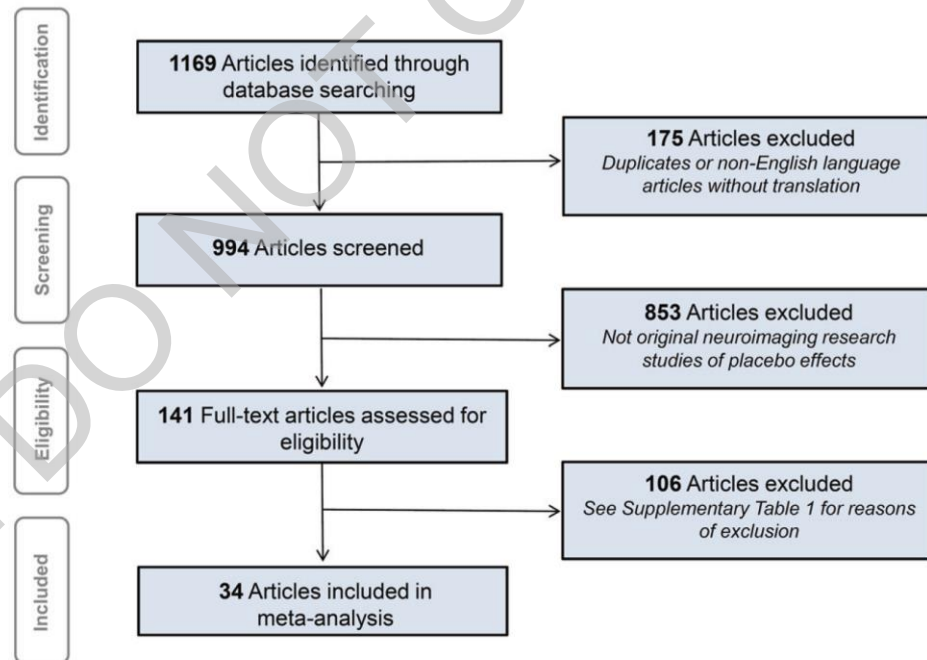
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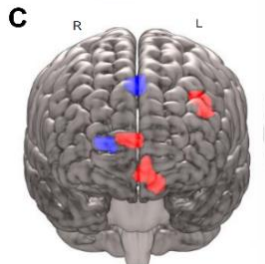
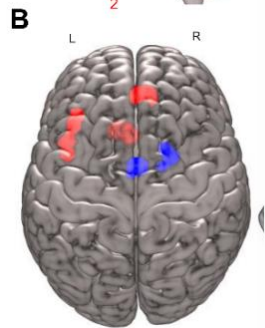
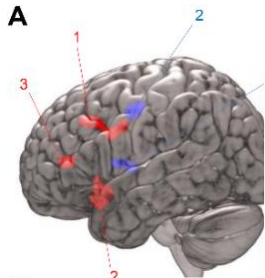
# PLACEBO NEUROIMAGING META-ANALYSIS

**Main search terms:** “placebo”, “expectation” combined with “functional magnetic resonance imaging”, “positron 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

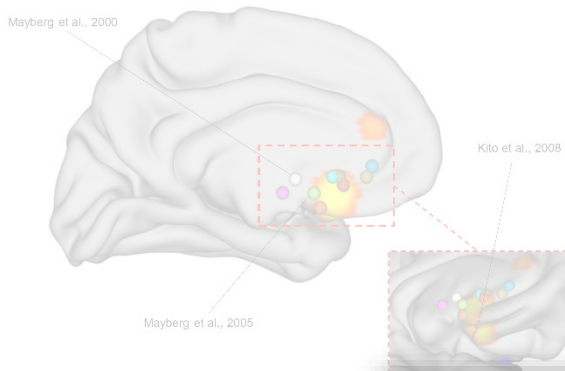


**Table 1.** Brain regions demonstrating activation or deactivation associated with placebo effects.

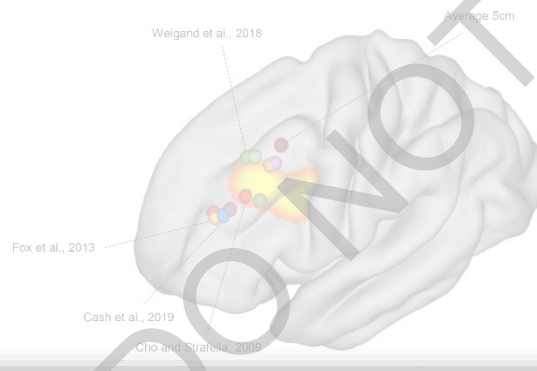
Cluster	Volume (mm <sup>3</sup> )	Center			Extrema Value	Extrema value coordinates			BA	Hemisphere	Neuroanatomic Label
		x	y	z		x	y	z			
<i>Activation Clusters</i>											
1	1888	-40.8	16.1	33.7							
					0.023	-42	4	34	6	L	→ DLPFC
					0.023	-38	22	36	9	L	
					0.021	-36	30	38	8	L	
					0.02	-44	12	28	9	L	
2	1768	-7.9	18	-14.7							→ Subgenual ACC/ventral striatum
					0.032	-12	18	-20	25	L	
					0.027	-4	16	-12	25	L	
3	808	4	42.2	9.5							Rostral ACC
					0.024	2	42	10	32	R	
<i>Deactivation Clusters</i>											
1	888	19.9	2.4	7							Basal Ganglia
					0.02	18	8	8		R	
					0.017	24	2	8		R	
					0.016	16	-4	4		R	
2	792	0.6	-4.6	45							Dorsal ACC
					0.02	2	-4	44	24	R	

# COMPARATIVE ANALYSES WITH NEUROMODULATION TARGETS

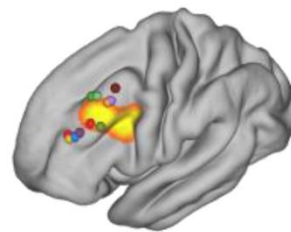
sgACC Depression Targets



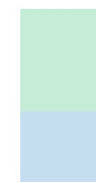
Left DLPFC Depression Targets



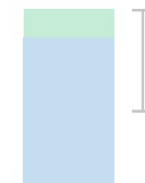
Author	Year	X
Bewernick	2018	-5
Drevets	2002	3
Hamani	2009	6
Kito	2008	17
Kito	2011	8
Mayberg	2000	4
Mayberg	2005	-2
Mayberg	2005	10
Nahas	2007	0
Sani	2017	-62
Wu	1999	7



Low placebo effects



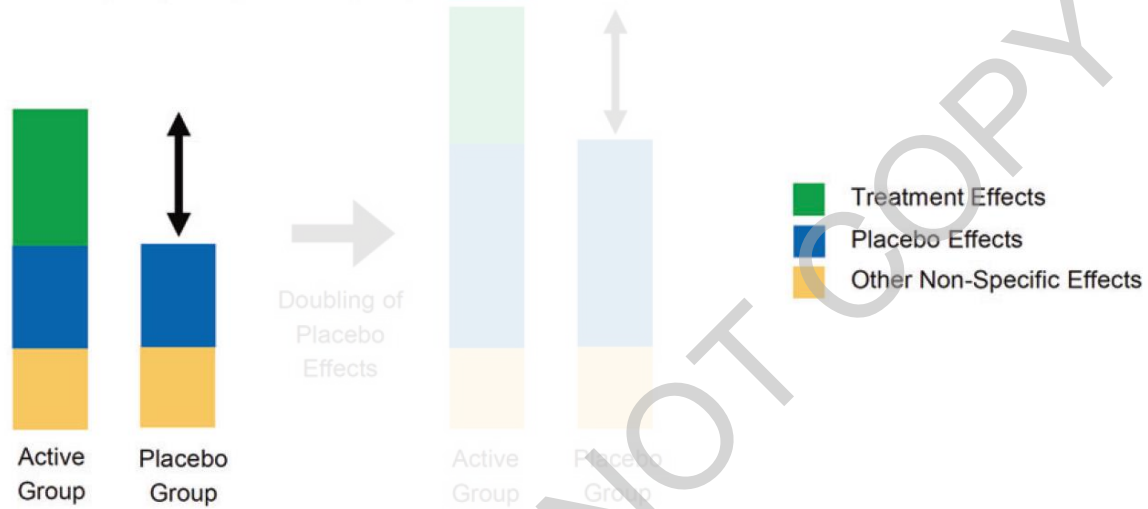
High placebo effects



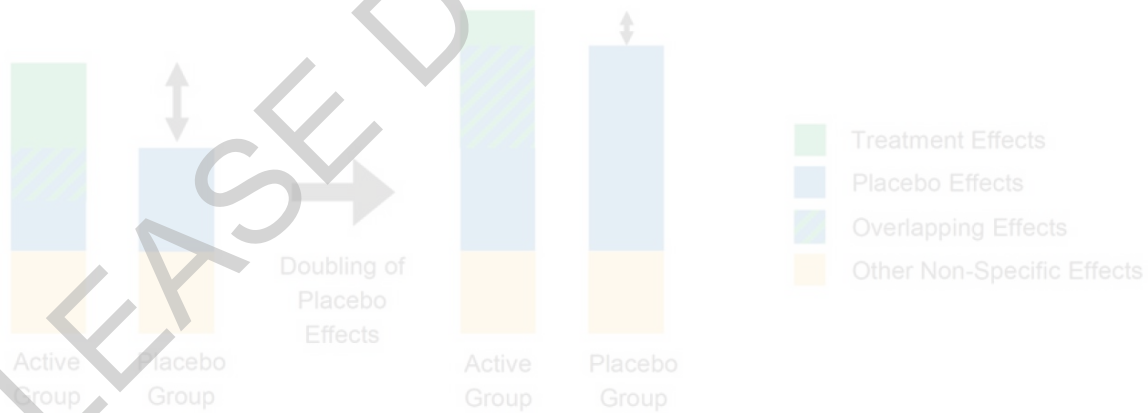
Potential capacity for TMS to modulate DLPFC

Label Attributed to Activation

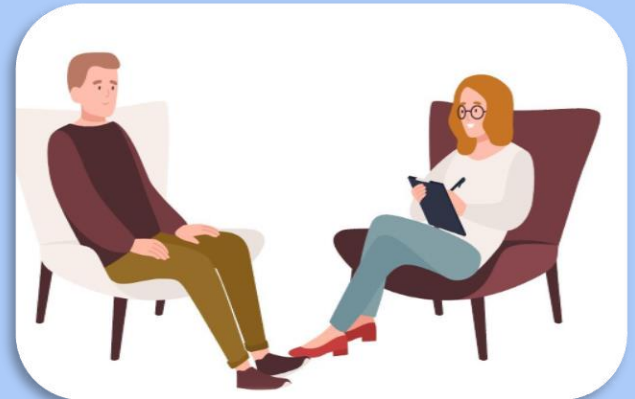
1 Hypothetical clinical trial assuming no overlap in therapeutic mechanism between active group and placebo group



2 Hypothetical clinical trial with shared therapeutic mechanism between active group and placebo group



# IMPLICATIONS ON RESEARCH AND PRACTICE



# THE ART OF DELIVERING PLACEBO EFFECTS WITHOUT THE “PLACEBO”?

 **frontiers**  
in Psychiatry

REVIEW  
published: 26 June 2019  
doi: 10.3389/fpsy.2019.00456



## Placebo Effects in Psychotherapy: A Framework

Paul Enck\* and Stephan Zipfel

*Psychosomatic Medicine and Psychotherapy, Department of Internal Medicine VI, University of Bonn*

**This Issue**

Views **16,578**

Citations **38**

Altmetric **162**

**JAMA** The Journal of the  
American Medical Association

### Viewpoint

May 23/30, 2017

## Changing Mindsets to Enhance Treatment Effectiveness

Alia Crum, PhD<sup>1</sup>; Barry Zuckerman, MD<sup>2,3</sup>

» [Author Affiliations](#)

JAMA. 2017;317(20):2063-2064. doi:10.1001/jama.2017.4545

Psychiatric Times



# FROM NUISANCE TO TREATMENT?

Neuron  
**Perspective**

CellPress

## Placebo Effects: From the Neurobiological Paradigm to Translational Implications

Fabrizio Benedetti<sup>1,\*</sup>

<sup>1</sup>Department of Neuroscience, University of Turin Medical School and National Institute of Neuroscience, 10125 Turin, Italy

\*Correspondence: [fabrizio.benedetti@unito.it](mailto:fabrizio.benedetti@unito.it)  
<http://dx.doi.org/10.1016/j.neuron.2014.10.023>

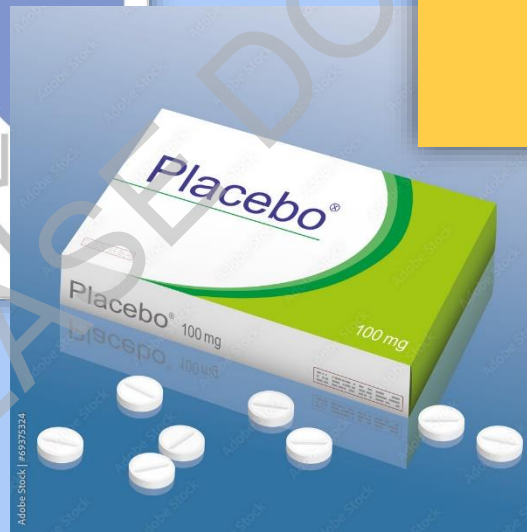
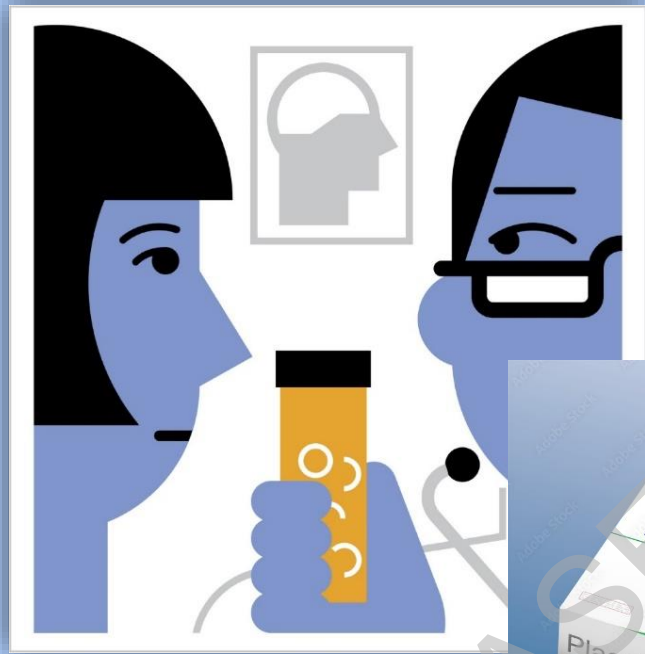
OPINION

NATURE REVIEWS | DRUG DISCOVERY

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

*Paul Enck, Ulrike Bingel, Manfred Schedlowski and Winfried Rief*

# APPROACHES



# IN THE MEANTIME... REAL-WORLD DATA

The image shows a screenshot of a Goop website article. The main article is titled "Does Goop Gwyneth Paltrow Feel Like This?" by Maggie Veatch and Roni S. It features a photo of Gwyneth Paltrow and a product image. A blue arrow points from the product image to a "Better Deal" section. A green arrow points from the bottom of the page to a "RETURN POLICY" link. A related article snippet is visible, discussing placebo effects and mentioning a summit.

**Does Goop Gwyneth Paltrow Feel Like This?**  
By Maggie Veatch and Roni S.  
Updated 5:51 AM ET, Sat Apr

Shop / Wellness / Vitamin

goop Wellness

**WHY AM I TIRED?**  
US \$90.00 / US \$75.00

Formulated with a variety of high dose of the B's), and herbs—including some Ayurveda—this is designed to balance in an overtaxed system. The nutrients your diet may lack can support energy levels. These can provide support d

• 1-month supply = 30  
• Note: Works for all

**Better Deal:** Sign up for

[RETURN POLICY](#)

[f](#) [p](#) [t](#) [e](#)

**Related Article:** Gwyneth Paltrow's Goop brand hit with penalties for 'unsubstantiated claims'

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.

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### Psychology

## 'Hardcore science' or 'just a sticker' - do anti-anxiety patches actually work?

Alaina Demopoulos

Thu 7 Sep 2023 11.00 BST



The image shows a person's forearm with a blue circular patch applied. The patch has a target-like design with the text 'NuCalm PRD' and '002'. Below the arm is a sheet of several more identical patches.

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**



# SHIFTING THE SPIN

The screenshot shows a BBC News article titled "Placebos could save lives and health care dollars: so why can't mainstream medicine put them to better use?". The article is by Erin Anderssen and was published on October 28, 2019. It has 19 comments and a share button. Below the article title is a video player featuring Dr. Matthew Burke, a man with a beard and glasses, sitting on a bed in his office. The video is 28 minutes long. To the right of the article is a "TRENDING" section with five items, including news about Jason Kenney's energy policies, Encana's headquarters move, and the impeachment of Donald Trump. The BBC logo and "HEALTH & FITNESS" category are visible at the top left of the article page.

**THE GLOBE AND MAIL** HEALTH & FITNESS

## Placebos could save lives and health care dollars: so why can't mainstream medicine put them to better use?

ERIN ANDERSSEN  
PUBLISHED OCTOBER 28, 2019

19 COMMENTS SHARE

Dr. Matthew Burke, seen here in his office at Sunnybrook Health Sciences Centre in Toronto on Friday, could this change the way we think about modern medicine? 28 minutes

**TRENDING**

- 1 Jason Kenney says Liberal energy policies to blame for Encana's move to U.S.
- 2 Encana to shift headquarters to U.S., change name as industry veterans lament 'heart-wrenching' decision
- 3 U.S. House approves impeachment inquiry against President Donald Trump
- 4 **OPINION**  
Taking a vacation? Think twice about relying on your credit card's travel medical insurance  
ROB CARRICK
- 5 **OPINION**  
Why I think Canada will avoid a recession next year and the loonie



# THANKS!

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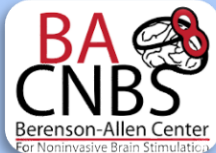
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# QUESTIONS



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