PLACEBO EFFECTS AND NEUROMODULATION:

IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE

MATTHEW BURKE, MD FRCPC

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NEUROPSYCHIATRY LEAD, UNIVERSITY OF TORONTO NEUROLOGY
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SUNNYBROOK HEALTH SCIENCES CENTRE
ASSISTANT PROFESSOR, UNIVERSITY OF TORONTO

Sunnybrook HEALTH SCIENCES CENTRE

UNIVERSITY OF TORONTO Psychiatry

U of T NEUROLOGY

Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL

DISCLOSURES

- No relevant conflicts of interest
- Paid consulting relationships within past 5 years
  - Consultant Neurologist, NBA Toronto Raptors
  - Neuropsychiatry Medicolegal Expert
- Research Funding Sources:

Psychiatry UNIVERSITY OF TORONTO

SIDNEY R. BAER, JR. FOUNDATION

Sunnybrook FOUNDATION

Liu Fu Yu Charity Foundation
Louise and Peter Walters

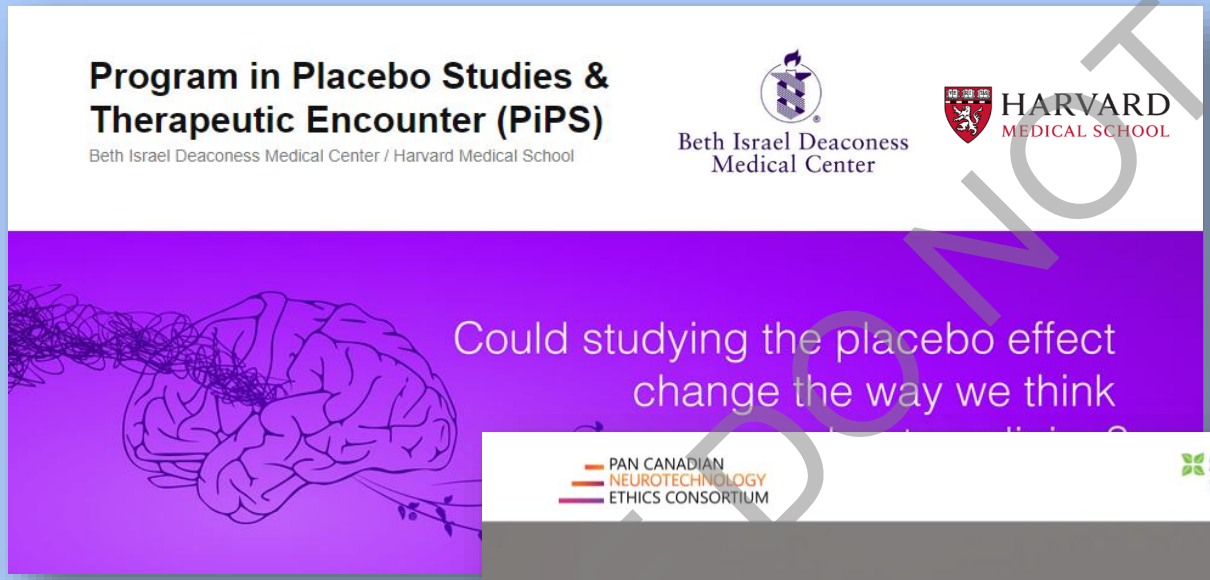
Kimel-Schatzky Family

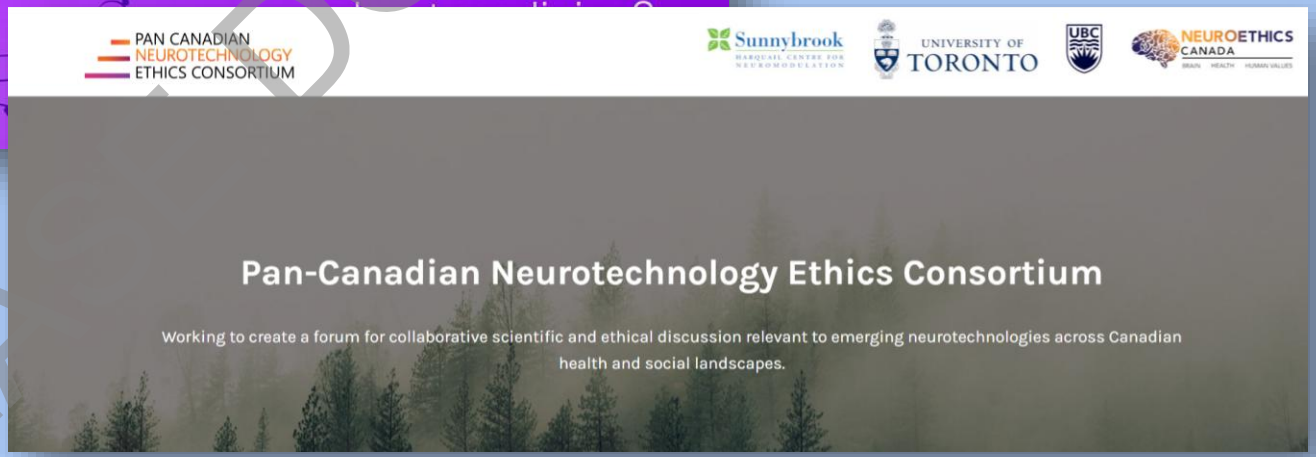
CIHR IRSC
Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

ONTARIO BRAIN INSTITUTE | INSTITUT ONTARIEN DU CERVEAU

NIH National Institute of Mental Health

RELEVANT AFFILIATIONS



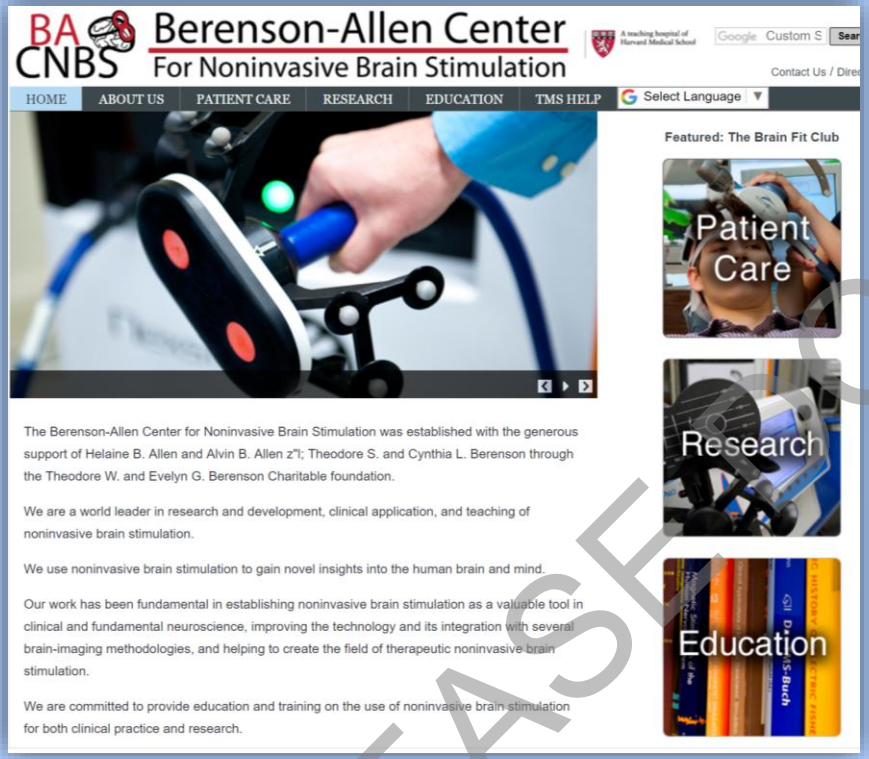


OBJECTIVES

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



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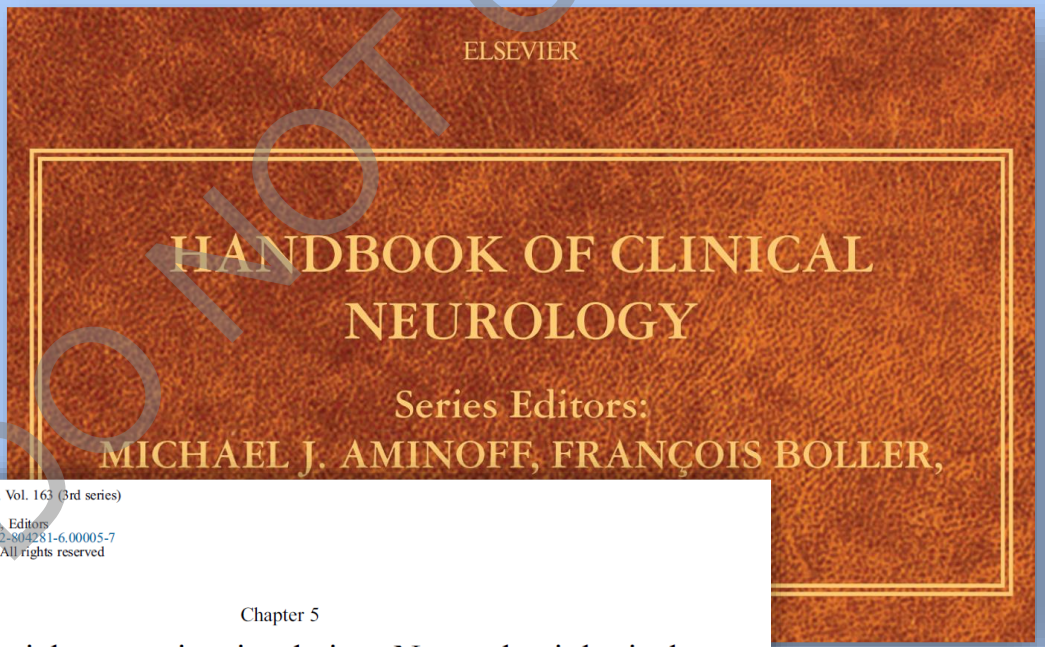
Dr. Alvaro Pascual-Leone

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

Chapter 5

Transcranial magnetic stimulation: Neurophysiological and clinical applications

MATTHEW J. BURKE[1], PETER J. FRIED[1], AND ALVARO PASCUAL-LEONE[1,2,3]*

[1]*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*

[2]*Guttmann Brain Health Institute, Institut Guttmann de Neurorehabilitacio, Universitat Autonoma de Barcelona, Barcelona, Spain*

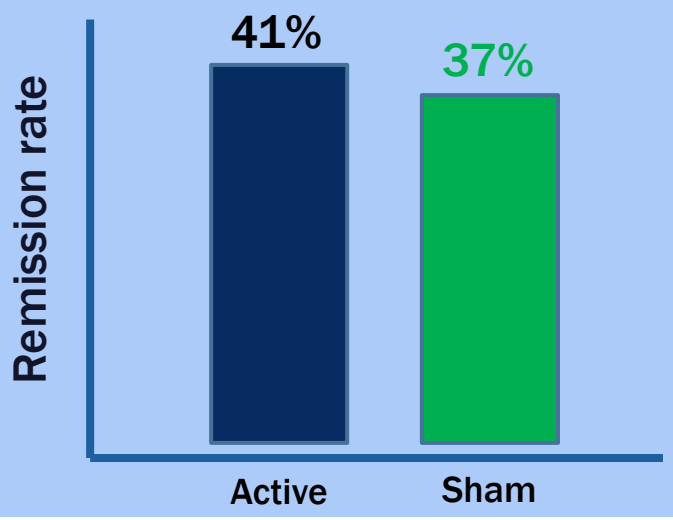
[3]*Marcus Institute for Aging Research, Hebrew Senior Life, Harvard Medical School, Boston, MA, United States*

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

Randomiz
Repetiti

Richard L. Harvey, MD;
Joel Stein,
Ana Durand-Sa
Gerard E. Fr

Nexstim

PATIENTS HEALTHCARE PROFESSIONALS RESEARCH NEWS

09/03/2018

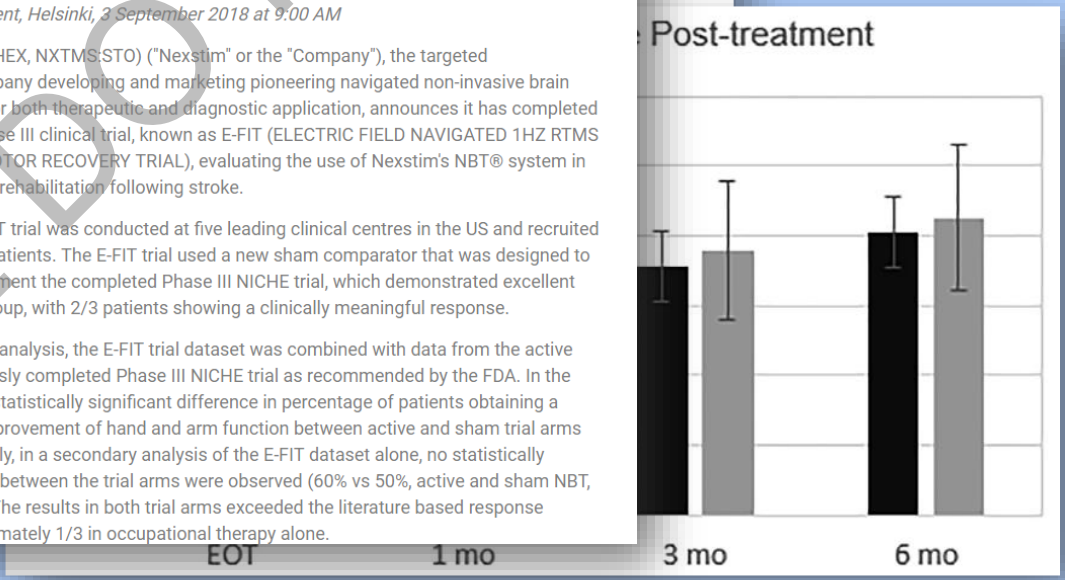
Nexstim Plc reports results of the supplementary Phase III E-FIT trial

Company announcement, Helsinki, 3 September 2018 at 9:00 AM

Nexstim Plc (NXTMH:HEX, NXTMS:STO) ("Nexstim" or the "Company"), the targeted neuromodulation company developing and marketing pioneering navigated non-invasive brain stimulation systems for both therapeutic and diagnostic application, announces it has completed its supplementary Phase III clinical trial, known as E-FIT (ELECTRIC FIELD NAVIGATED 1HZ RTMS FOR POST-STROKE MOTOR RECOVERY TRIAL), evaluating the use of Nexstim's NBT® system in upper extremity motor rehabilitation following stroke.

The supplemental E-FIT trial was conducted at five leading clinical centres in the US and recruited a planned total of 60 patients. The E-FIT trial used a new sham comparator that was designed to provide data to supplement the completed Phase III NICHE trial, which demonstrated excellent results in the active group, with 2/3 patients showing a clinically meaningful response.

In the primary efficacy analysis, the E-FIT trial dataset was combined with data from the active trial arm of the previously completed Phase III NICHE trial as recommended by the FDA. In the combined dataset no statistically significant difference in percentage of patients obtaining a clinically important improvement of hand and arm function between active and sham trial arms were observed. Similarly, in a secondary analysis of the E-FIT dataset alone, no statistically significant differences between the trial arms were observed (60% vs 50%, active and sham NBT, respectively, p=0.62). The results in both trial arms exceeded the literature based response expectation of approximately 1/3 in occupational therapy alone.



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nature

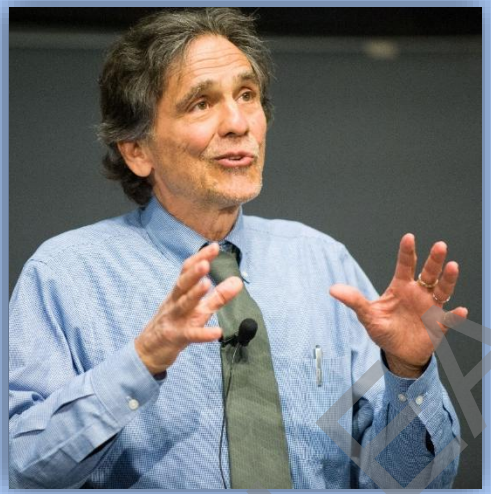
HEALTH

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

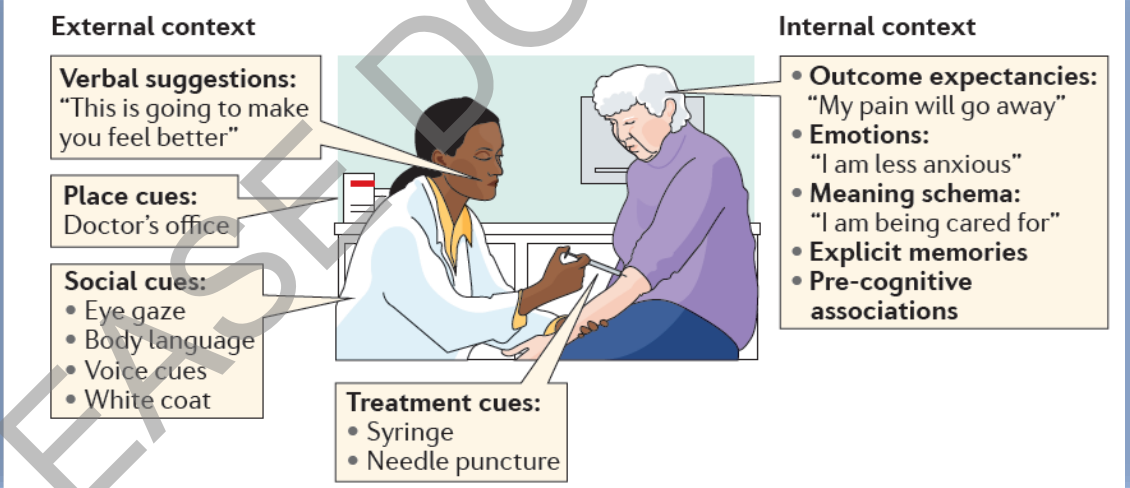
1 INTRODUCTION TO PLACEBO EFFECTS

PLACEBO EFFECTS

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

Tor D. Wager[1] and Lauren Y. Atlas[2]

NATURE REVIEWS | NEUROSCIENCE



NEUROIMAGING STUDIES

Science

Placebo and Opioid An

Predrag Petrovic, Eija Kalso, K

Science **295** (5560), 1737-174
DOI: 10.1126/science.106717

Science

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. Calne and A. Jon Stoessl

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

A Opioid ne

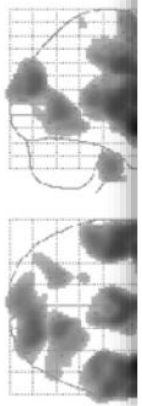
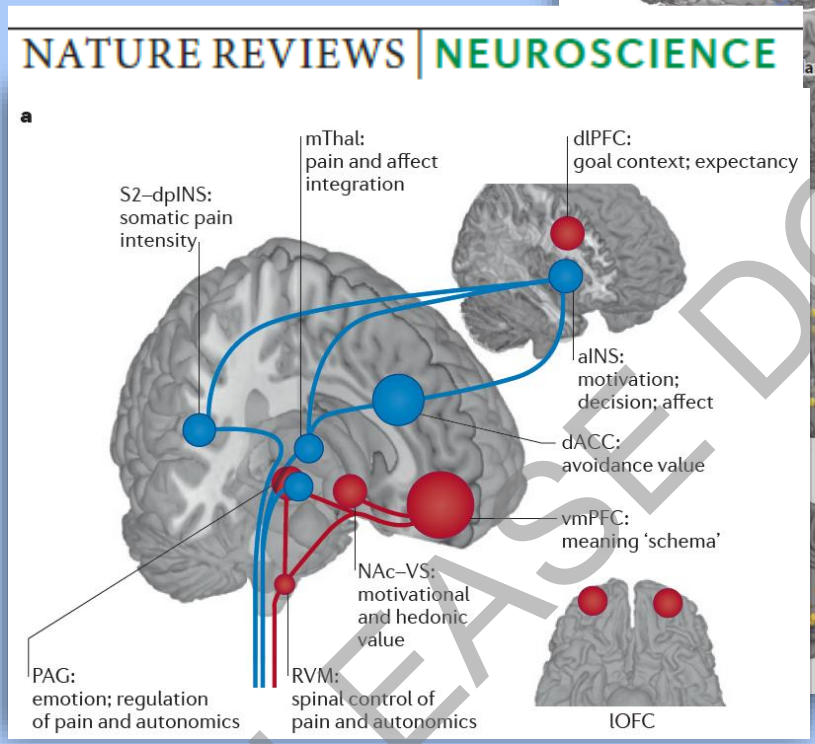
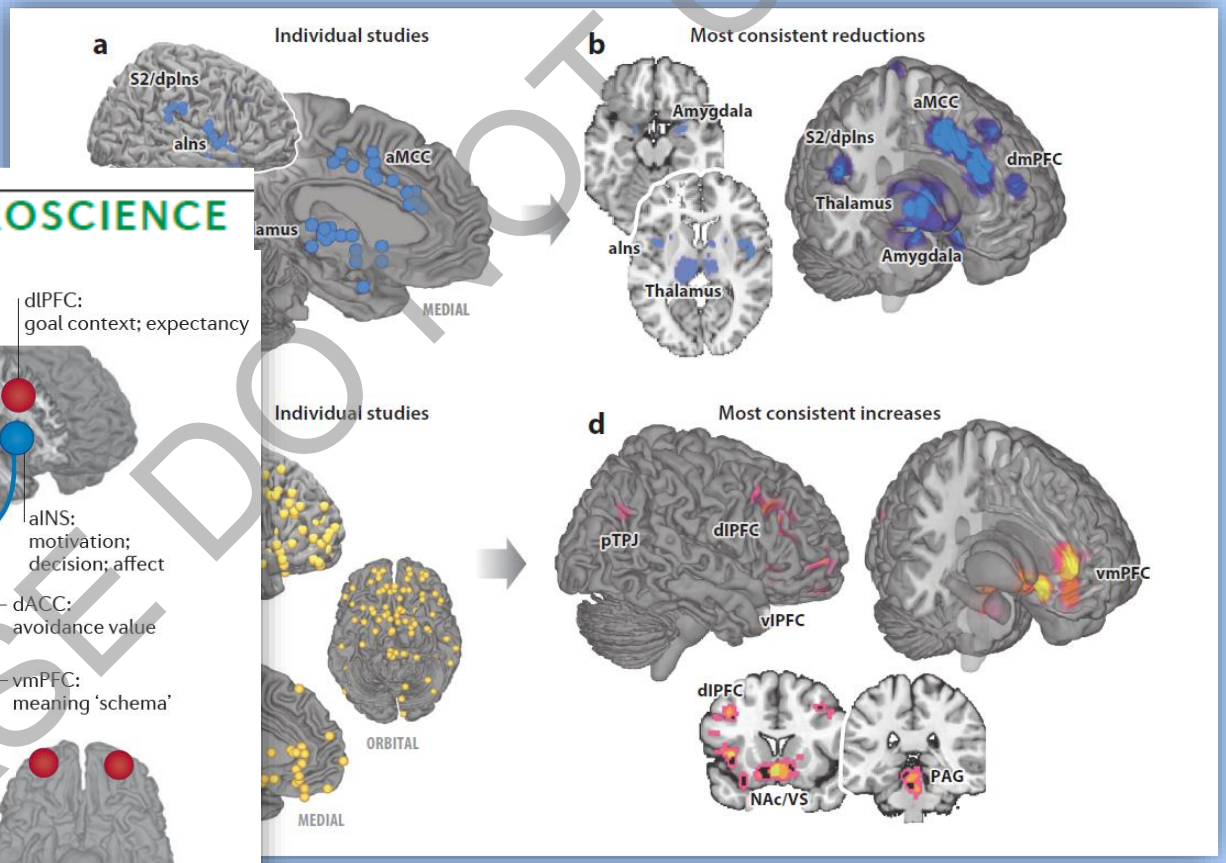


Table 1. Striatal RAC binding potential (mean ± SD) of PD patients (group 1) scanned at open baseline and after receiving placebo ($n = 6$).

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

CURRENT NEUROIMAGING





Wager and Atlas 2015, Ashar et al 2017

BLOCKING STUDIES

Biological, clinical, and ethical advances of placebo effects

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

Lancet 2010; 375: 686–95

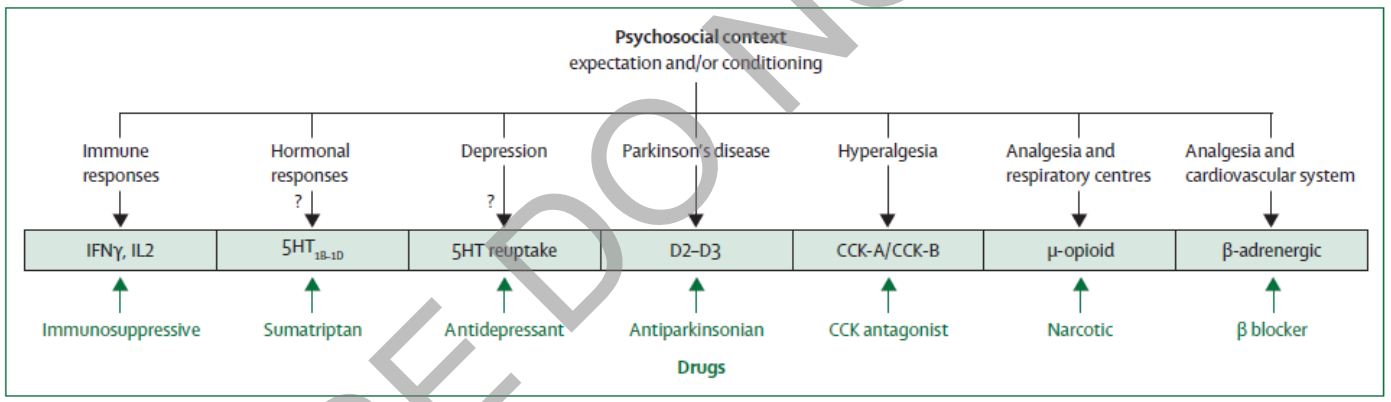


***Figure 2*: Receptor pathways activated by both psychosocial context and drugs**
Social stimuli around the treatment might activate, through expectation or conditioning mechanisms, several receptor pathways in different diseases and therapeutic interventions (the involvement of serotonin [5-hydroxytryptamine; 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. IFNγ=interferon γ. IL2=interleukin 2. CCK=cholecystokinin.

DOSE-RESPONSE RELATIONSHIP

BMJ

Components of placebo effect
in patients with irritable bowe

Ted J Kaptchuk, associate professor of medicine,[1] Joh
statistics,[2] Lisa A Conboy, instructor of medicine,[1] Ro
biostatistics,[3] Catherine E Kerr, instructor of medicine,
psychology,[5] Rosa N Schyner, research associate,[1] B
research fellow,[1] Min Park, research coordinator,[1] And
research coordinator,[1] Efi Kokkotou, assistant profes
medicine,[6] Peter Goldman, professor emeritus ,[7] Ant

Fig 2 | Outcomes at three week end point

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

KNOCK-OUT MODELS

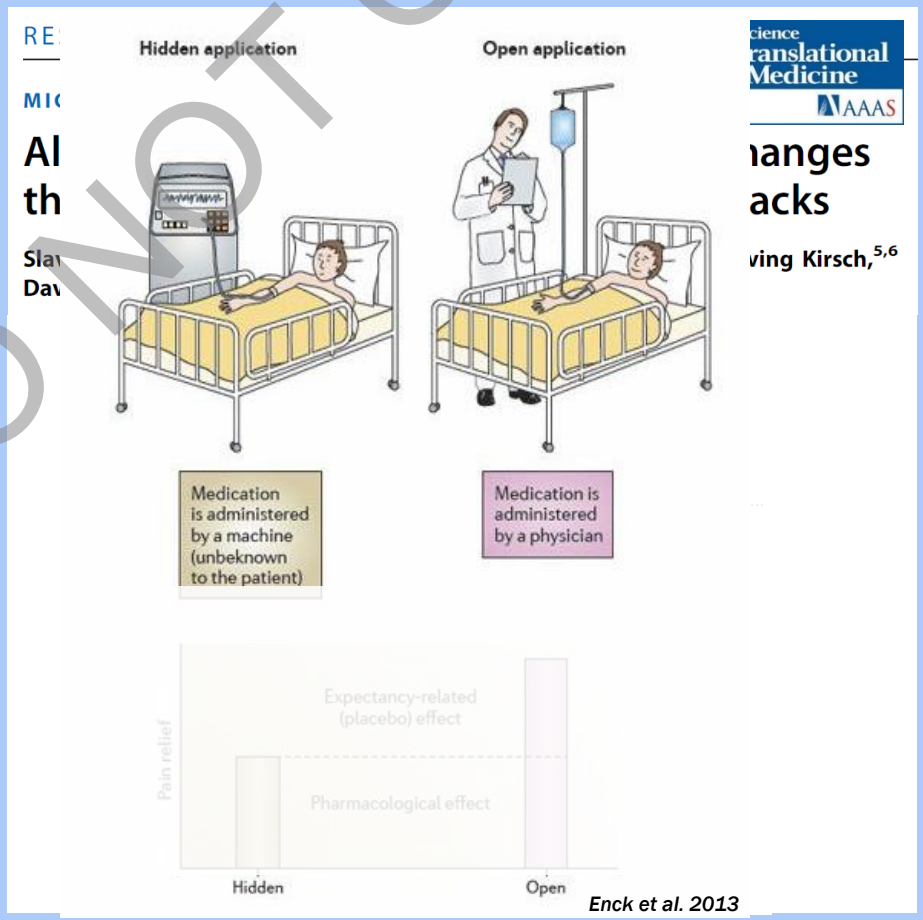
Hidden Administration of Drugs

F Benedetti[1,2], E Carlino[1,2] and A Pollo[1,2]

TOLD →	Saline	Remifentanil
GET →	Remifentanil	Remifentanil

No expectation

Positive expectation



Enck et al. 2013

HOT TOPIC!

Article

nature

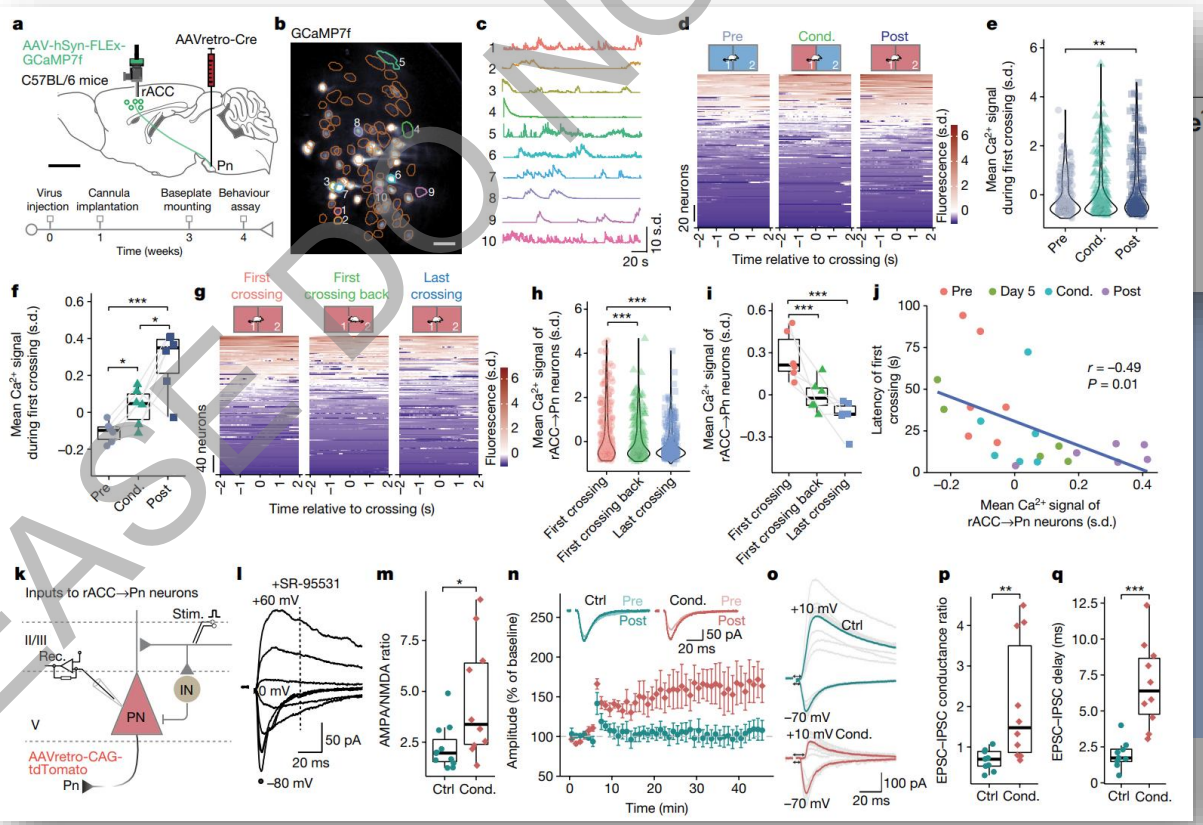
Neural circuit basis of placebo pain relief

https://doi.org/10.1038/s41586-0

Received: 7 December 2022

Accepted: 11 July 2024

Published online: 24 July 2024



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U of T NEUROLOGY

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

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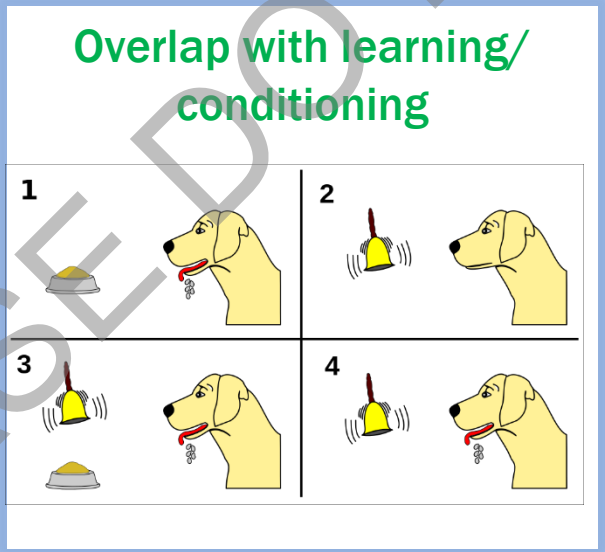
EXPECTANCIES

- Expectancies be acquired in a number of ways:

  1. **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 American M

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 adve... cific 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 placebos produce adverse side effects, offers some insight into non...

tions. These nonspecific side effects distress patients, add to the burden of their illness, and increase the costs of their care. They may lead to nonadherence, cause physicians to discontinue what is otherwise an appropriate therapy, or 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.

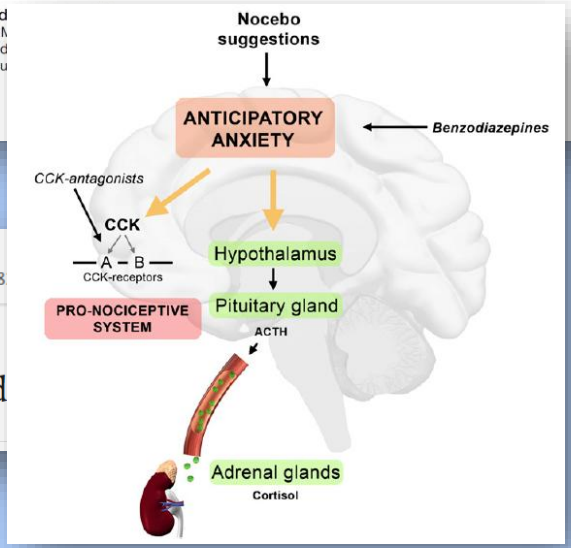
JAMA. 2002;287:622-627 www.jama.com

Neuron
Review

Cell PRESS

New Insights into the Placebo and Nocebo Responses

Paul Enck,[1,*] Fabrizio Benedetti,[2] and Manfred
[1]Department of Internal Medicine VI: Psychosomatic M
[2]Department of Neuroscience, University of Turin Med
[3]Institute of Medical Psychology and Behavioral Immu
47048 Duisburg-Essen, Germany
*Correspondence: paul.enck@uni-tuebingen.de
DOI 10.1016/j.neuron.2008.06.030



The NEW ENGLAND JOURNAL of MEDICINE

November 26, 2020
N Engl J Med 2020; 38

CORRESPONDENCE

N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Sid

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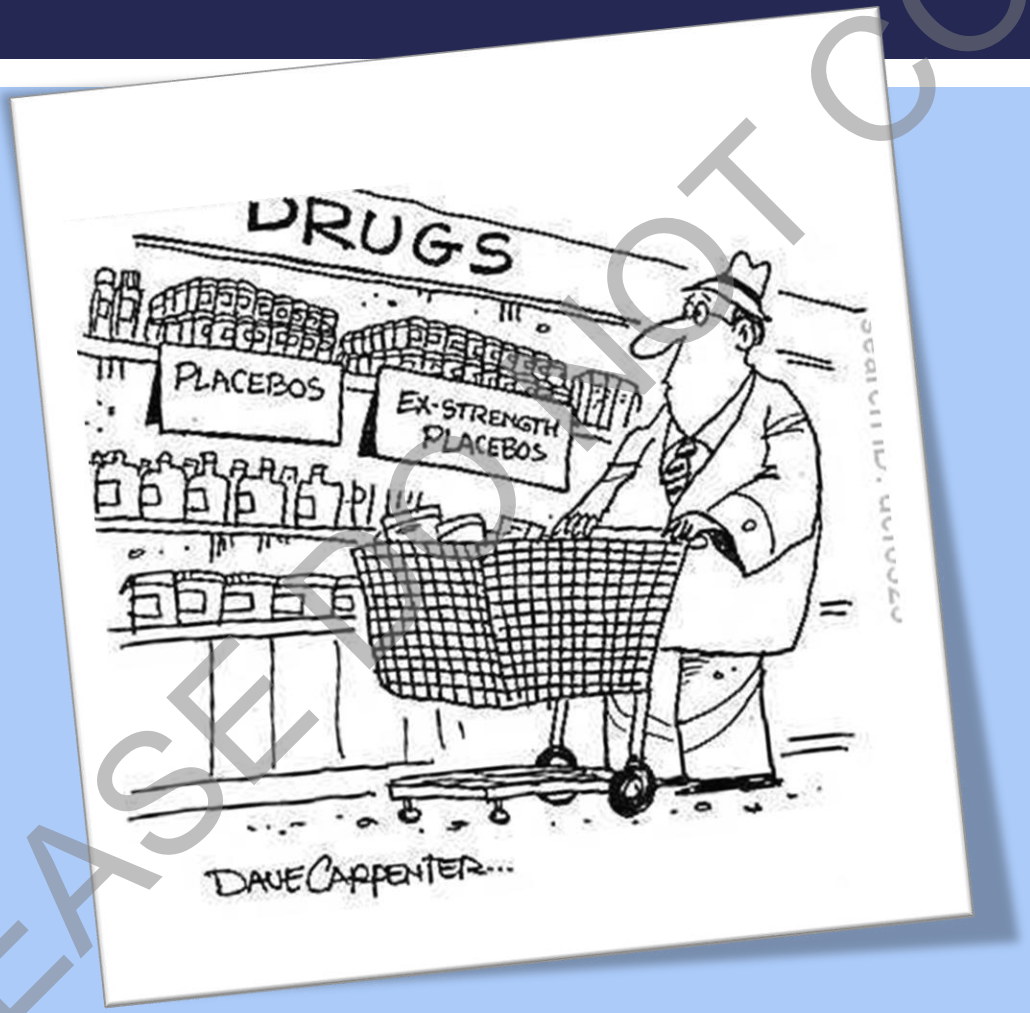
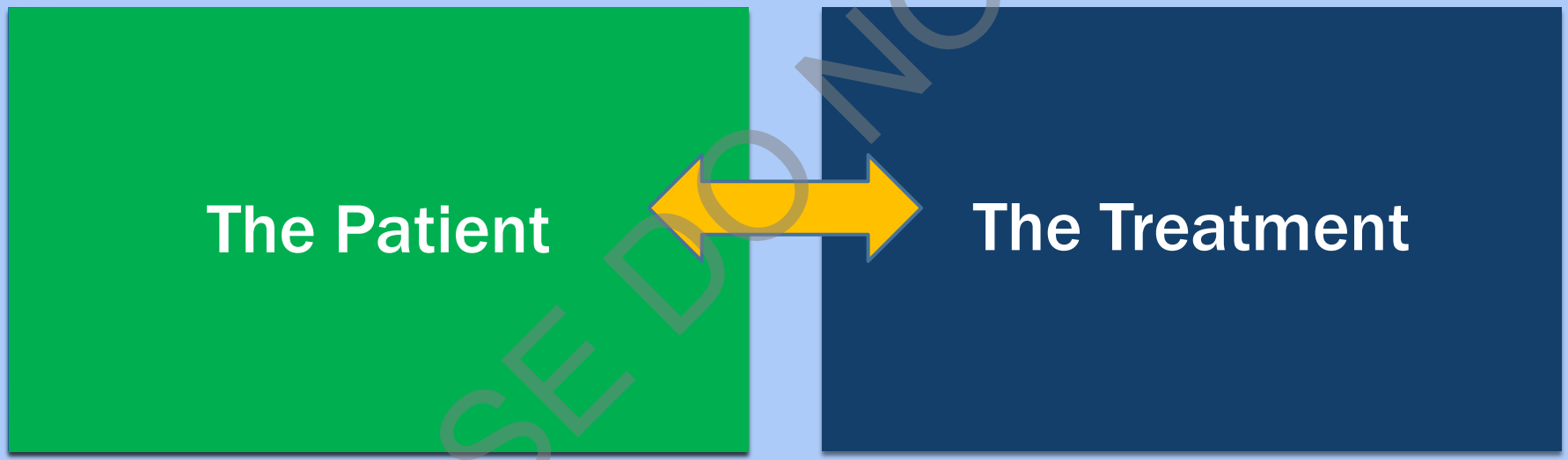
UNIVERSITY OF TORONTO

UofT NEUROLOGY

2 PLACEBO EFFECTS IN MEDICINE



TWO MAIN CONSIDERATIONS



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…

Research

JAMA Psychiatry | Original Investigation

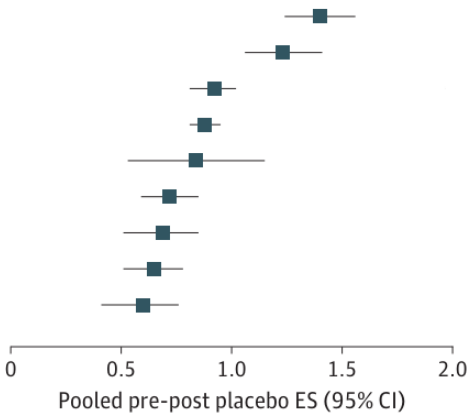
Differential Outcon
Across 9 Psychiatri
A Systematic Reviev

Tom Bschor, MD; Lea Nagel, MD; Josep

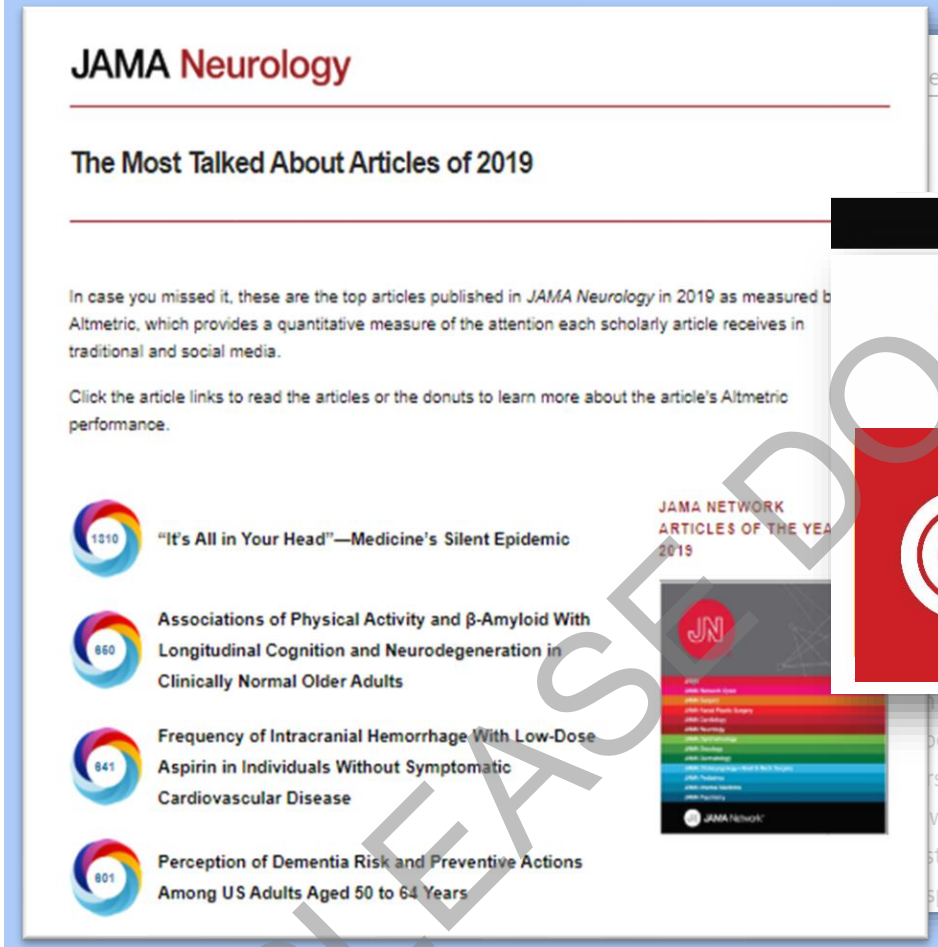
Figure 1. Random-Effects Meta-Analysis Estimates of Pooled Pre-Post Placebo Effect Sizes

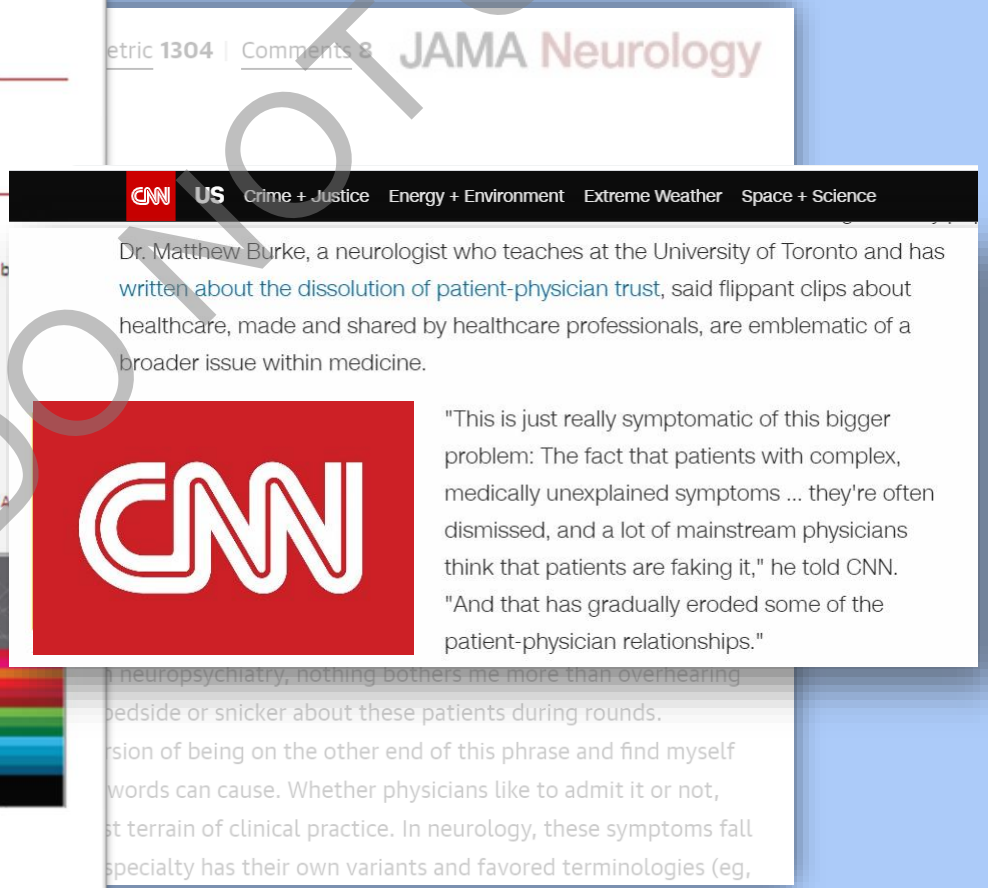
Diagnosis	Study participants, No.	Q	I^2, %	ES (95% CI)
MDD	1598	47.9	81	1.40 (1.24-1.56)
GAD	1457	61.4	85	1.23 (1.06-1.41)
Panic disorder	1307	20.8	57	0.92 (0.81-1.02)
ADHD	1189	7.3	0	0.88 (0.81-0.95)
PTSD	655	99.8	91	0.84 (0.53-1.15)
Social phobia	1180	34.7	74	0.72 (0.59-0.85)
Mania	967	53.1	83	0.68 (0.51-0.85)
OCD	819	29.6	70	0.65 (0.51-0.78)
Schizophrenia	888	50.0	82	0.59 (0.41-0.76)

Heterogeneity: $\chi^8_2 = 88.50$ ($P < .01$)

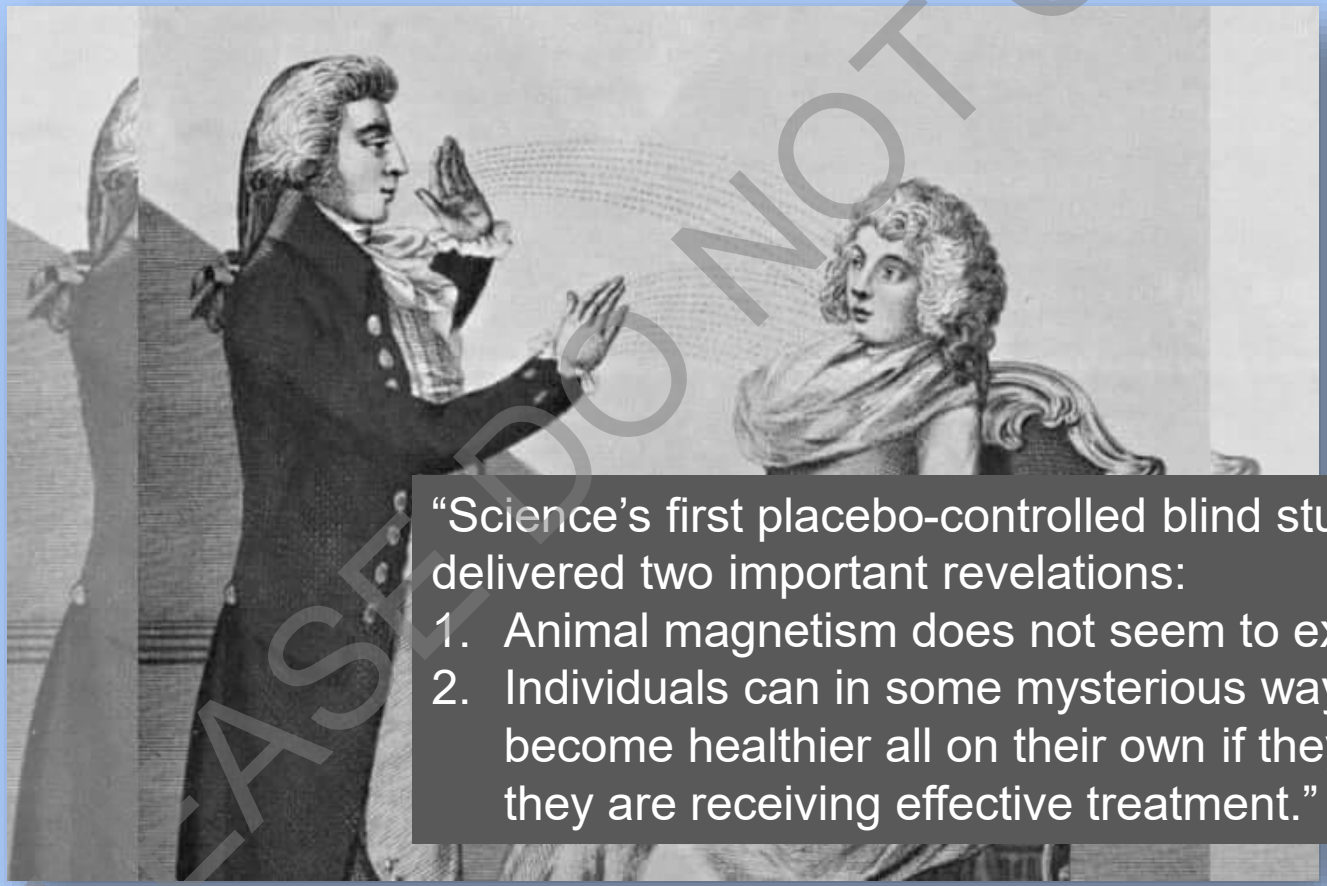


CASE EXAMPLE 1
"FUNCTIONAL" BRAIN DISORDERS





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 Neurobiolo
Functional Neurological Disorder: A

Matthew J. Burke, M.D., Vanda Faria, Ph.D., Davide Cappo
Ted J. Kaptchuk, and Emiliano Santarnecchi, Ph.D.

CLINICAL AND RESEARCH REPORT

Harnessing Placebo Effects for the Treatment of Functional Cognitive Disorder: A Feasibility Pilot Study

Matthew J. Burke, M.D., Davide Cappon, Ph.D., David L. Perez, M.D., M.M.Sc., Alvaro Pascual-Leone, M.D., Ph.D., Emiliano Santarnecchi, Ph.D.

NATURE REVIEWS | NEUROLOGY VOLUME 18 | OCTOBER 2022

Functional neurological disorder and placebo and nocebo effects: shared mechanisms

Mirta Fiorio, Miriam Braga, Angela Marotta, Bernardo Villa-Sánchez, Mark J. Edwards, Michele Tinazzi and Diletta Barbiani

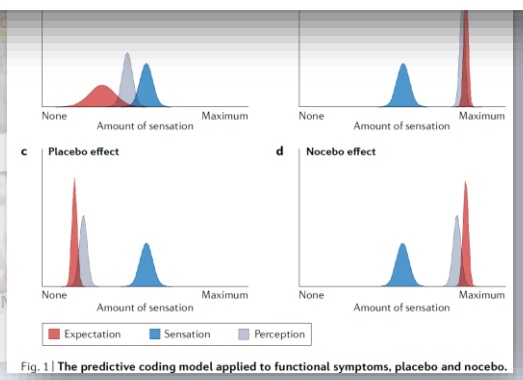
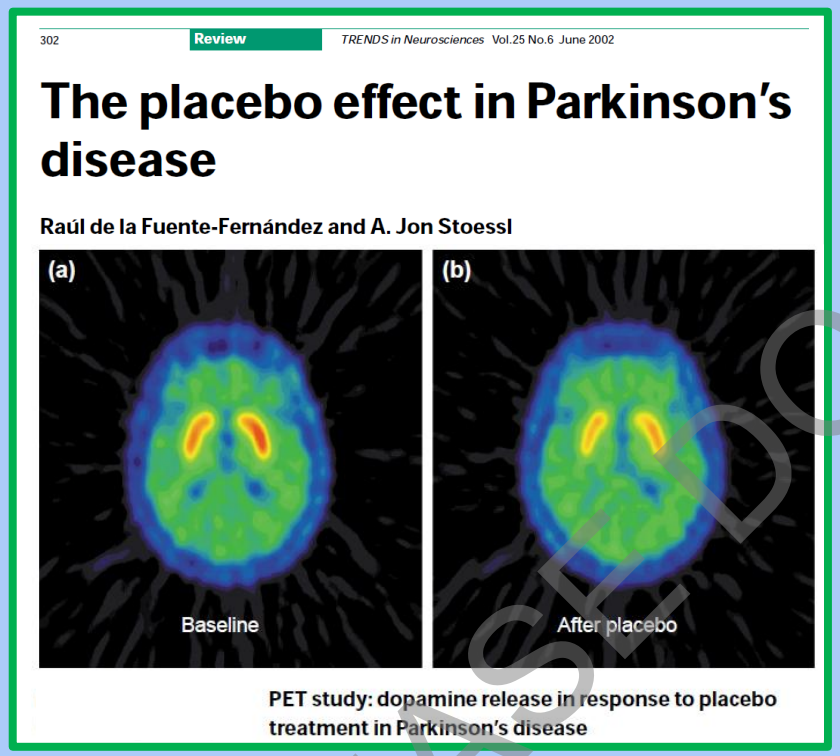


Fig. 1 | **The predictive coding model applied to functional symptoms, placebo and nocebo.**

CASE EXAMPLE 2
"STRUCTURAL" BRAIN DISORDER

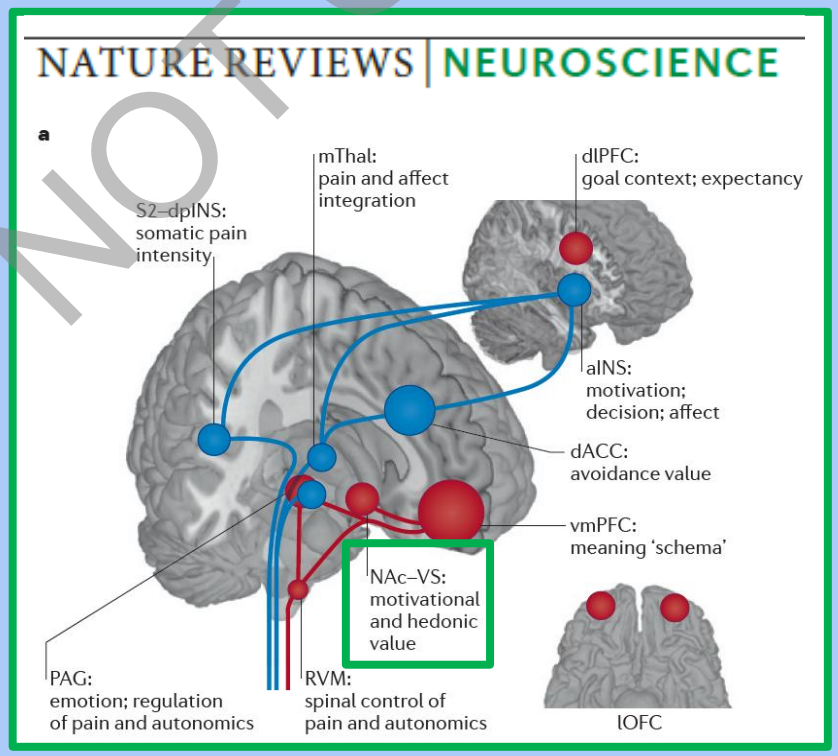


302 Review *TRENDS in Neurosciences* Vol.25 No.6 June 2002

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

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?

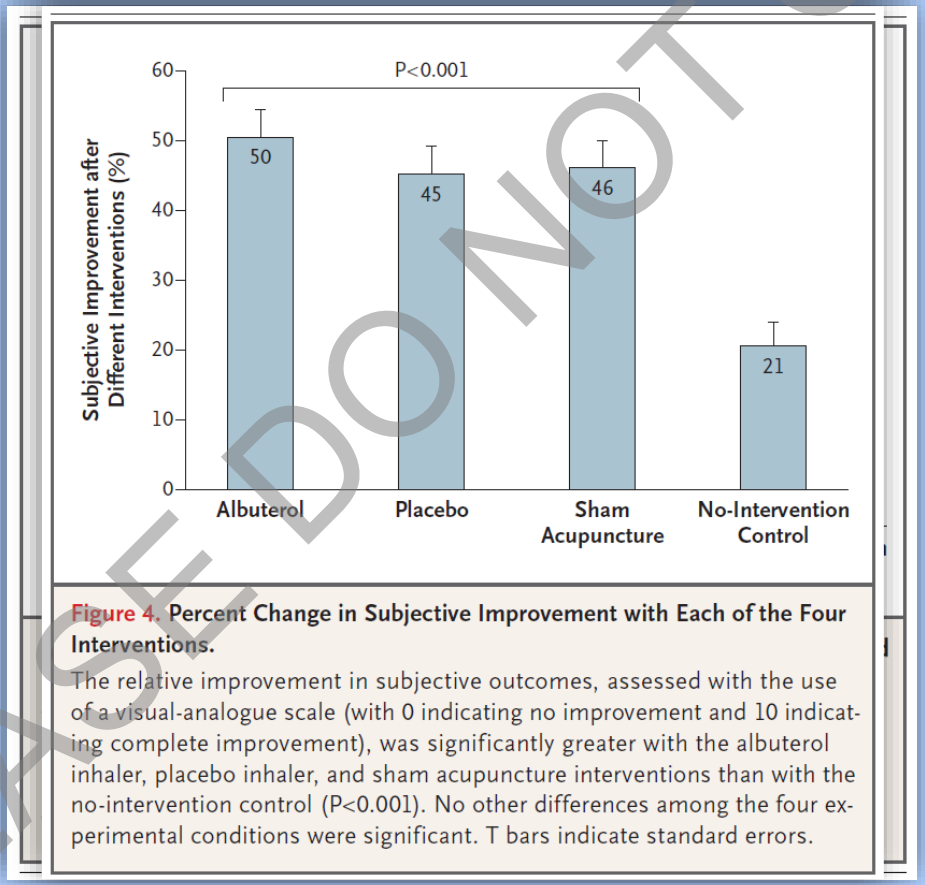


Figure 4. Percent Change in Subjective Improvement with Each of the Four Interventions.

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. T bars indicate standard errors.

PATIENT LEVEL HETEROGENEITY

Review

CellPress

Genetics and the placebo effect: the placebome

Kathryn T. Hall[1,2], Joseph Loscalzo[3], and Ted J. Kaptchuk[1,2]

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

Placebo pathway	Gene name	Gene symbol	Chromosomal location	Placebo SNPs	Refs
Dopamine	Catechol-O-methyltra				
	Monoamine oxidase				
	Dopamine B hydroxyl				
	Dopamine receptor 3				
	Brain-derived neurotr				
Serotonin	Tryptophan hydroxyla				
	5-Hydroxytryptamine				
	5-Hydroxytryptamine				
	Serotonin transporter polymorphic region				
Opioid	Opioid receptor				
Endocannabinoid	Fatty acid amide hydr				

Systematic Review and Meta-Analysis

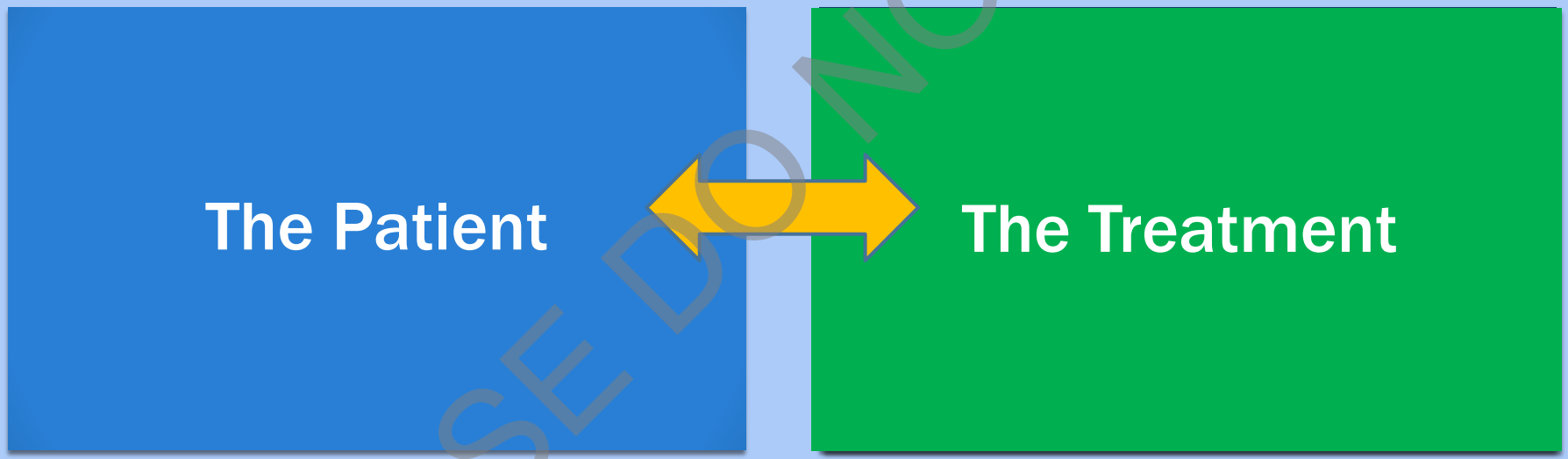
March 2023 • Volume 164 • Number 3

PAIN®

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

Heemin Kang[a,b], Miriam Sophie Miksche[a], Dan-Mikael Ellingsen[a,c,d,*]

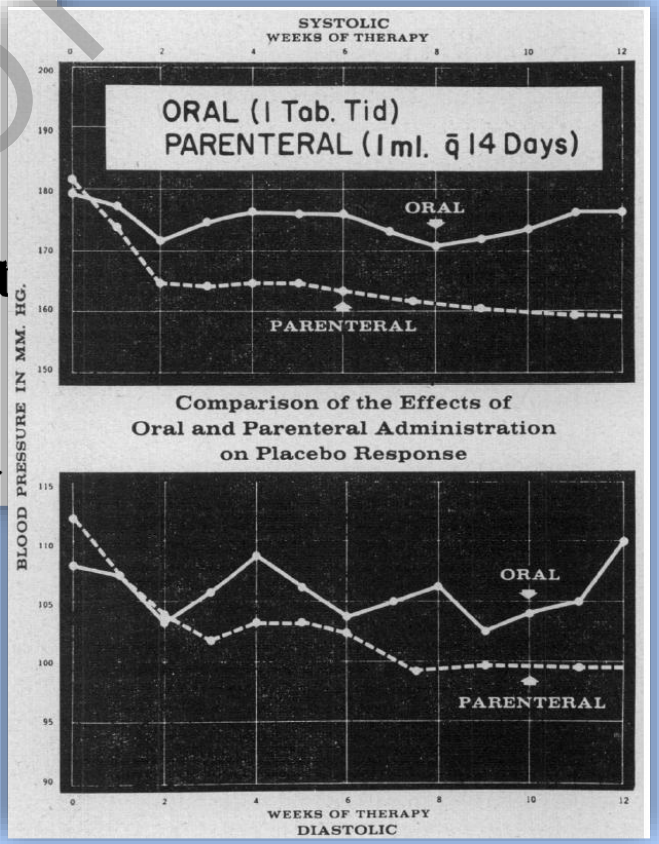
TWO MAIN CONSIDERATIONS



FACTORS IMPACTING PLACEBO EFFECTS

A Double-Blind Study of the Treatment of Hypertension

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

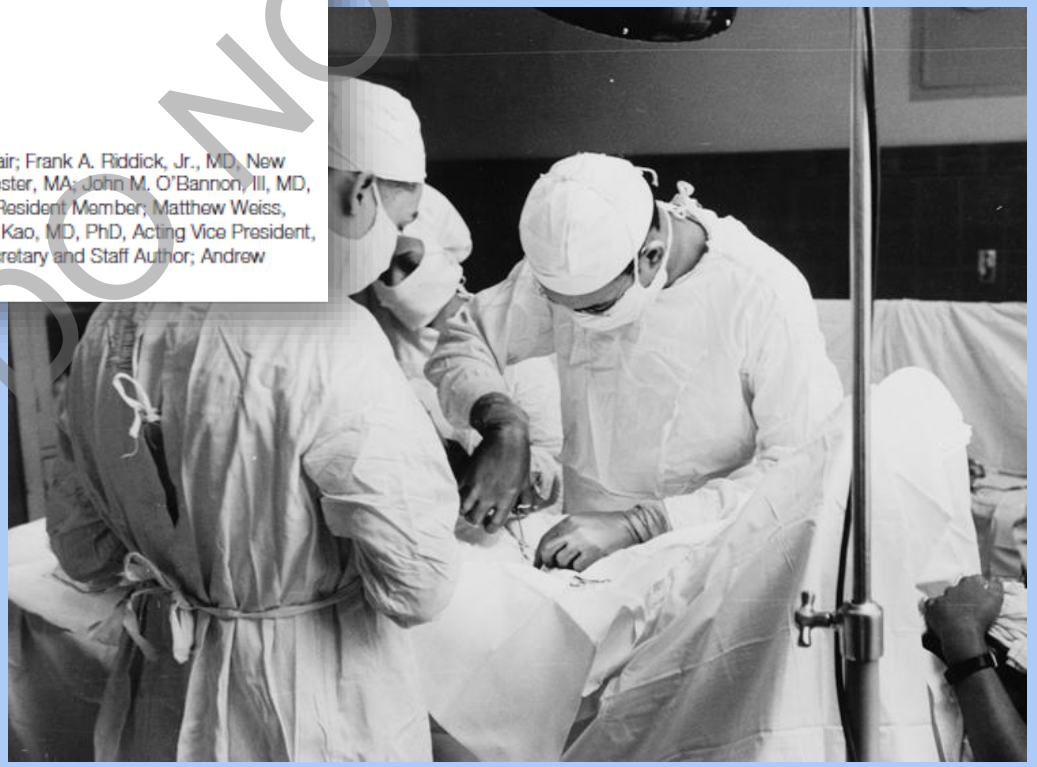


SHAM-CONTROLLED SURGICAL TRIALS

ANNALS OF SURGERY
Vol. 235, No. 2, 303–307

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, LLM, Council Secretary and Staff Author; Andrew Maixner, Council Staff Associate; Sam Seiden, Council Staff Associate.

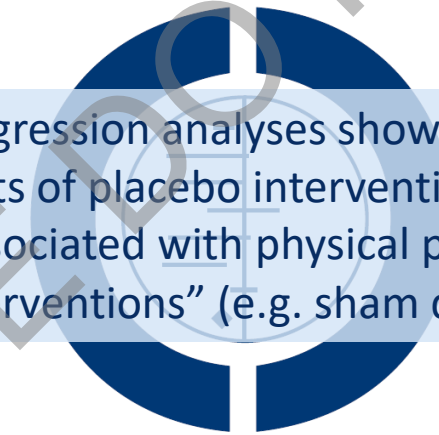


SHAM-CONTROLLED SURGICAL/PROCEDURAL TRIALS

TREATMENT INTENSIVENESS

Placebo interventions for all clinical conditions (Review)

Hróbjartsson A, Gøtzsche PC

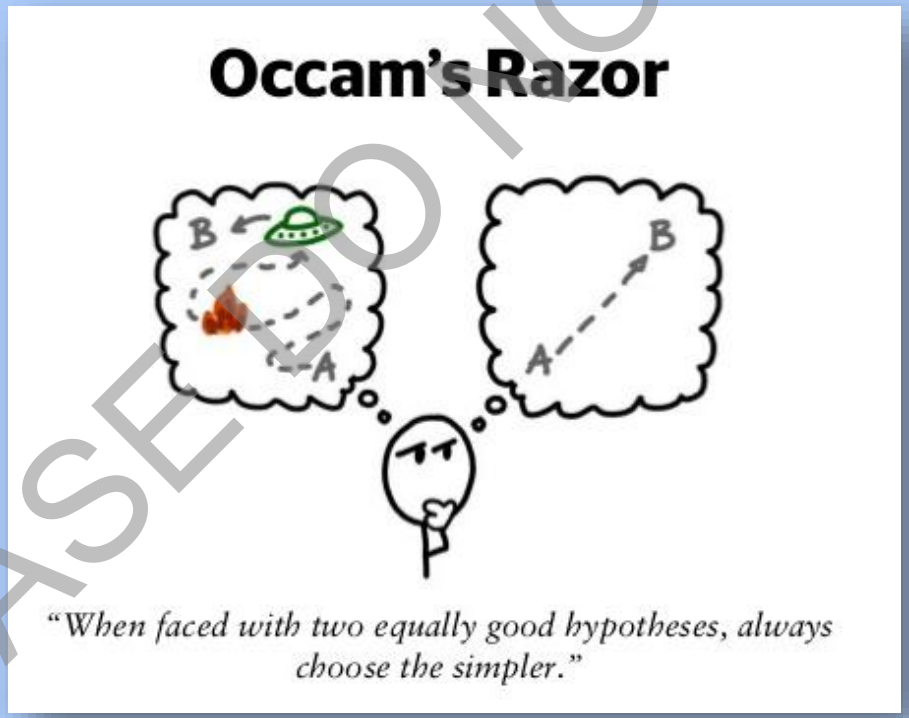


THE COCHRANE COLLABORATION®

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

COMMON DENOMINATOR

- Conclusion: 1) little/no mention of placebo effects AND/OR 2) there must be something "active" about our sham?



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

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

ABSTRACT

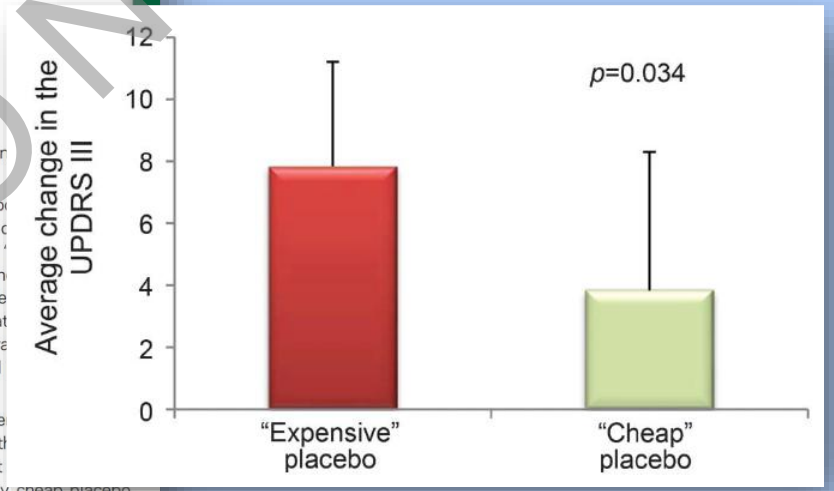
Objective: To examine the effect of cost, a traditionally "inactive" trait of interver utor to the response to therapeutic interventions.

Methods: We conducted a prospective double-blind study in 12 patients with mo Parkinson disease and motor fluctuations (mean age 62.4 ± 7.9 years; mean d 11 ± 6 years) who were randomized to a "cheap" or "expensive" subcutaneous dopamine agonist" placebo (normal saline). Patients were crossed over to th approximately 4 hours later. Blinded motor assessments in the practically de before and after each intervention, included the Unified Parkinson's Disease Rat subscale, the Purdue Pegboard Test, and a tapping task. Measurements of bra performed using a feedback-based visual-motor associative learning functional effect was examined using stratified analysis.

Results: Although both placebos improved motor function, benefit was greate were randomized first to expensive placebo, with a magnitude halfway between t cebo 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



PERSONALIZED, TAILORED MEDICINE

eLife

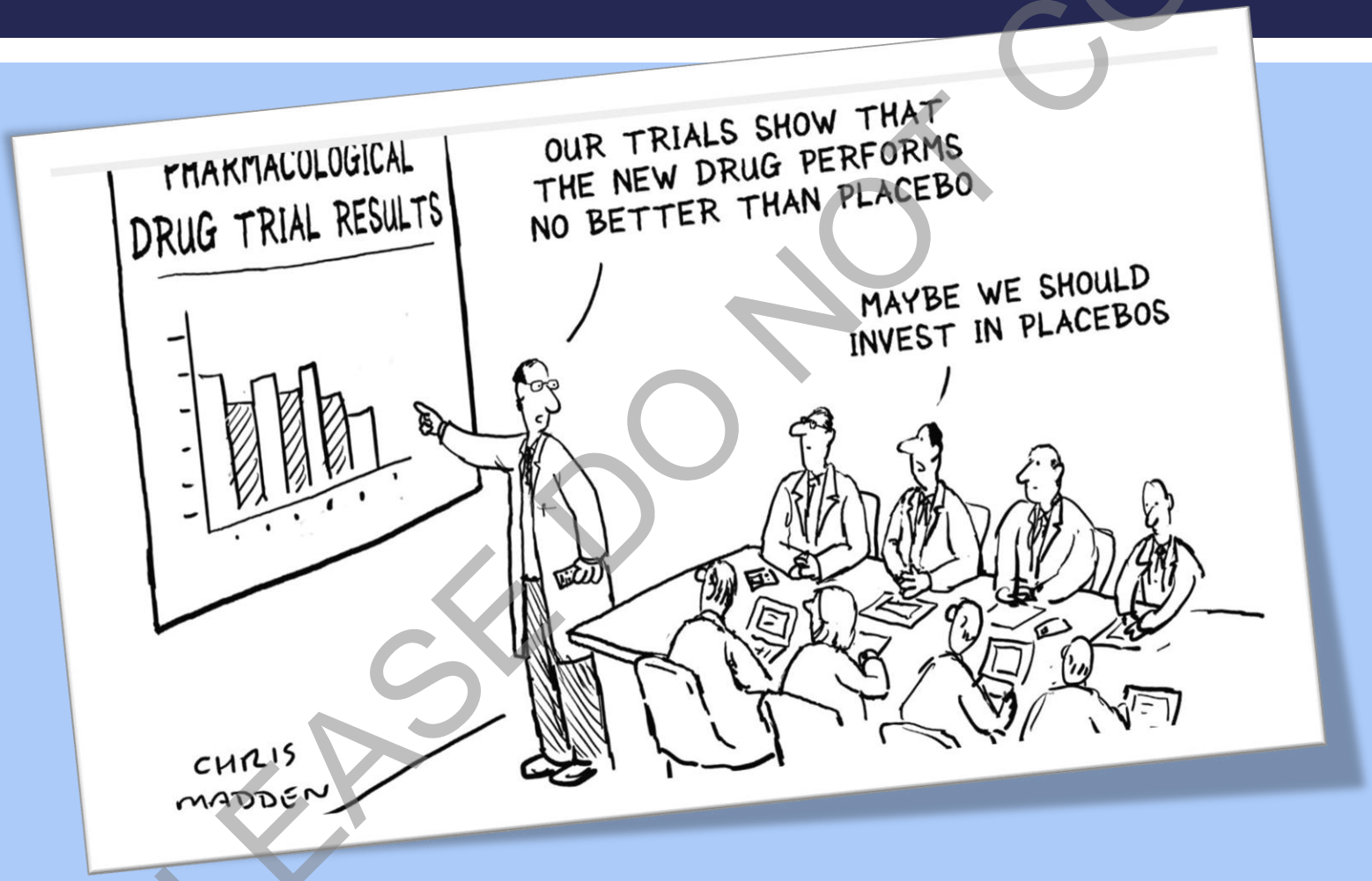
RESEARCH ARTICLE

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

Dasha A Sandra[1]*, Jay A Olson[2†], Ellen J Langer[2], Mathieu Roy[3]

[1]Integrated Program in Neuroscience, McGill University, Montreal, Canada;
[2]Department of Psychology, Harvard University, Cambridge, United States;
[3]Department of Psychology, McGill University, Montreal, Canada

3 PLACEBO EFFECTS IN RESEARCH

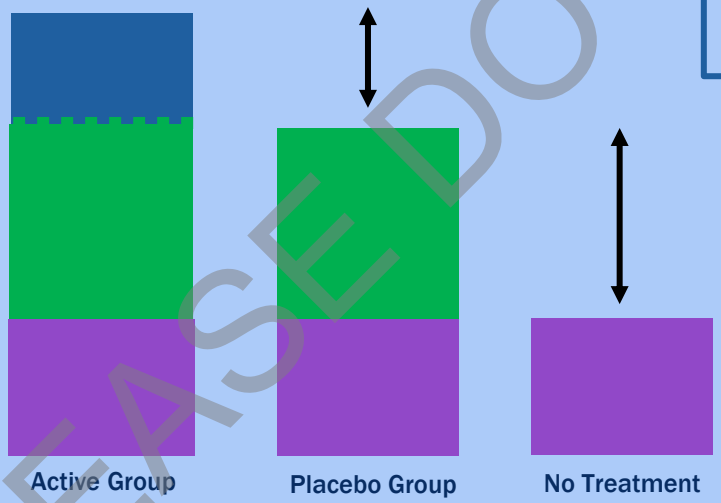


Edsurge

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

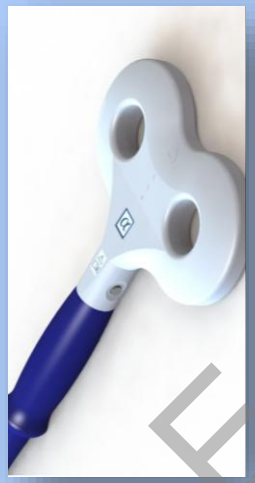
THE LANCET

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



EJN fens EUROPEAN JOURNAL OF NEUROSCIENCE

European Journal of Neuroscience, Vol. 38, pp. 2973–2977, 2013 doi:10.1111/ejn.12307

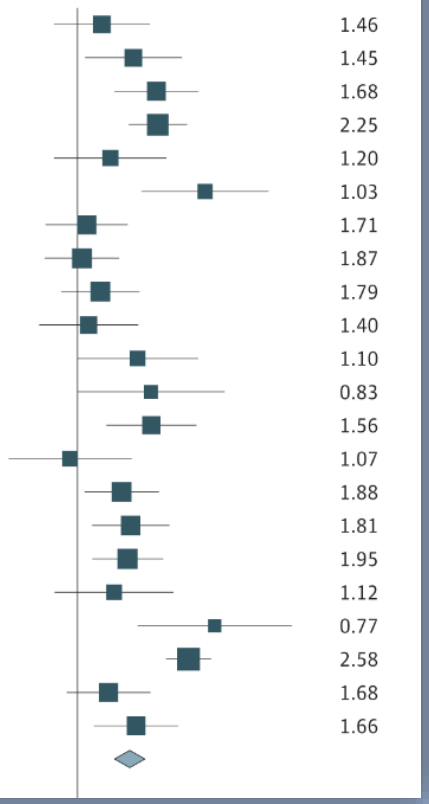
TECHNICAL SPOTLIGHT

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

Nick J. Davis,[1] Edward Gold,[2] Alvaro Pascual-Leone[2] and R. Martyn Bracewell[1,3,4]

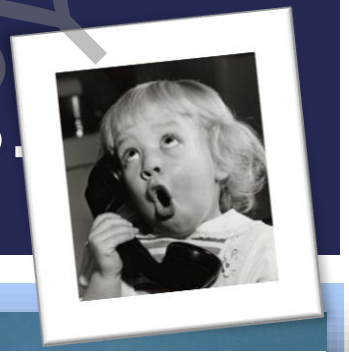
SHAM TMS GROUPS, FROM 0 TO 50% IMPROVEMENT??

Source	Baseline No.	Baseline Mean (SD)	End point No.	End point Mean (SD)	Hedges *g* (95% CI)	Weight, %
rTMS						
Baeken et al,[80] 2013	11	26.45 (8.71)	11	22.36 (10.01)	0.42 (-0.39 to 1.23)	1.46
Bakim et al,[31] 2012	12	25.58 (3.82)	12	19.5 (7.83)	0.95 (0.13 to 1.77)	1.45
Blumberger et al,[35] 2012	22	25.2 (2.8)	15	18.9 (6.4)	1.34 (0.63 to 2.05)	1.68
Blumberger et al,[36] 2016	41	25.5 (3.6)	35	20.5 (3.64)	1.37 (0.87 to 1.86)	2.25
Boutros et al,[37] 2002	9	31.7 (4.9)	7	26.4 (12.4)	0.56 (-0.39 to 1.52)	1.20
Chen et al,[38] 2013	10	24.9 (6.3)	10	12.3 (4.7)	2.17 (1.10 to 3.25)	1.03
Concerto et al,[39] 2015	15	21 (5)	15	20 (7)	0.16 (-0.54 to 0.86)	1.71
Fitzgerald et al,[42] 2012	20	22.9 (2.1)	17	22.6 (5)	0.08 (-0.55 to 0.71)	1.87
Garcia-Toro et al,[43] 2001	18	25.6 (4.92)	16	23.83 (3.78)	0.39 (-0.27 to 1.05)	1.79
Garcia-Toro et al,[76] 2006	10	25.1 (7.28)	10	23.6 (7.79)	0.19 (-0.65 to 1.03)	1.40
Holtzheimer et al,[46] 2004	8	20.8 (6.3)	7	15.3 (3)	1.02 (0.00 to 2.05)	1.10
Kauffmann et al,[47] 2004	5	18.2 (4.9)	5	11.8 (4.3)	1.25 (0.01 to 2.50)	0.83
Li et al,[48] 2014	15	23.8 (3.2)	15	19.66 (3.2)	1.26 (0.49 to 2.02)	1.56
Padberg et al,[78] 1999	6	22.2 (8.8)	6	23.5 (10.4)	-0.12 (-1.17 to 0.92)	1.07
Pallanti et al,[51] 2010	20	29.05 (3.54)	20	26.38 (3.4)	0.75 (0.12 to 1.38)	1.88
Theleritis et al,[56] 2017	20	29.4 (3.2)	18	25.4 (5.3)	0.91 (0.25 to 1.56)	1.81
Theleritis et al,[56] 2017	24	30.3 (3.6)	21	27 (4)	0.86 (0.25 to 1.46)	1.95
Triggs et al,[57] 2010 (left sham)	7	27.7 (3.5)	7	22 (11.6)	0.62 (-0.38 to 1.63)	1.12
Triggs et al,[57] 2010 (right sham)	7	27.3 (2.7)	7	13.4 (7.4)	2.34 (1.03 to 3.64)	0.77
Yesavage et al,[61] 2018	83	27.5 (5.1)	68	14.4 (8.6)	1.89 (1.51 to 2.27)	2.58
Zheng et al,[60] 2010	15	24.6 (2.8)	15	22.9 (3.4)	0.53 (-0.18 to 1.24)	1.68
van Eijndhoven et al,[58] 2020	16	22.7 (3.8)	16	18.6 (4.2)	1.00 (0.28 to 1.72)	1.66
Heterogeneity: $\tau^2 = 0.22$; $I^2 = 62.14\%$; $H^2 = 2.64$ Test of $\theta_i = \theta_j$: $Q_{21} = 63.57$; $P = .001$					0.89 (0.63 to 1.15)	



Jones et al 2021

NOT A UNIQUE ISSUE FOR TMS.



The NEW E

Trial of Psilo

Robin Carhart-Harris, Ph.D
Michelle Baker-Jo
Roberta Murphy, M.D
David Erri

nature medicine

OPEN

MDMA-assisted therapy
randomized, double-blin
phase 3 study

Jennifer M. Mitchell[1,2], Michael Bogenschutz
Sarah Kleiman[6], Kelly Parker-Guilbert[7], Marcela
Ingmar Gorman[11], Christopher Nicholas[12], Mich
Bruce Poulter[8,9], Ann Mithoefer[9], Sylvestre Que
Bessel van der Kolk[16], Keren Tzarfaty[9], Revital An
Joshua D. Woolley[2], Cole Marta[20], Yevgeniy Gelfa
Randall Brown[11], Scott Hamilton[25], Julie B. Wang
Alberdina de Boer[5], Berra Yazar-Klosinski[4], Amy

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 mental health

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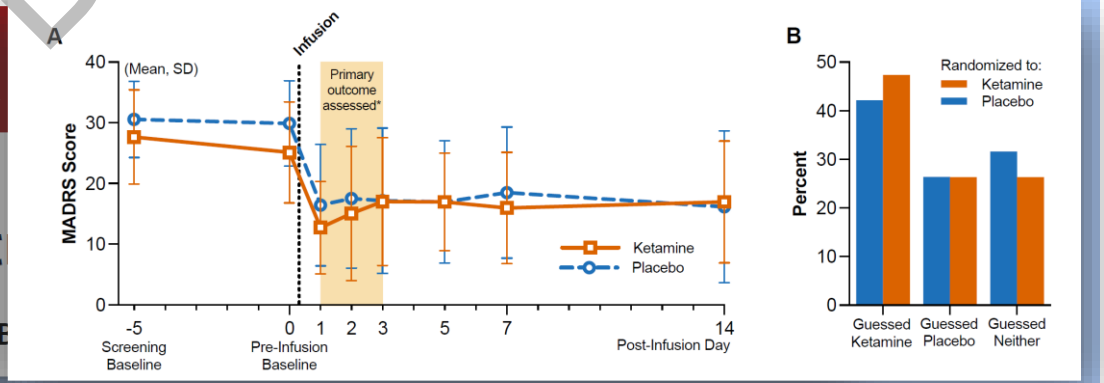
nature > nature mental health > articles > article

Article | Published: 19 October 2023

Randomized trial of ketamine masked by surgical anesthesia in patients with depression

Theresa R. Lii, Ashleigh E. Smith, Josephine R. Flohr, Robin L. Okada, Cynthia A. Nyongesa, Lisa J. Cianfichi, Laura M. Hack, Alan F. Schatzberg & Boris D. Heifets

Nature Mental Health 1, 876–886 (2023) | Cite this article



2) THE IMPACT OF DIFFERENTIAL PLACEBO EFFECTS

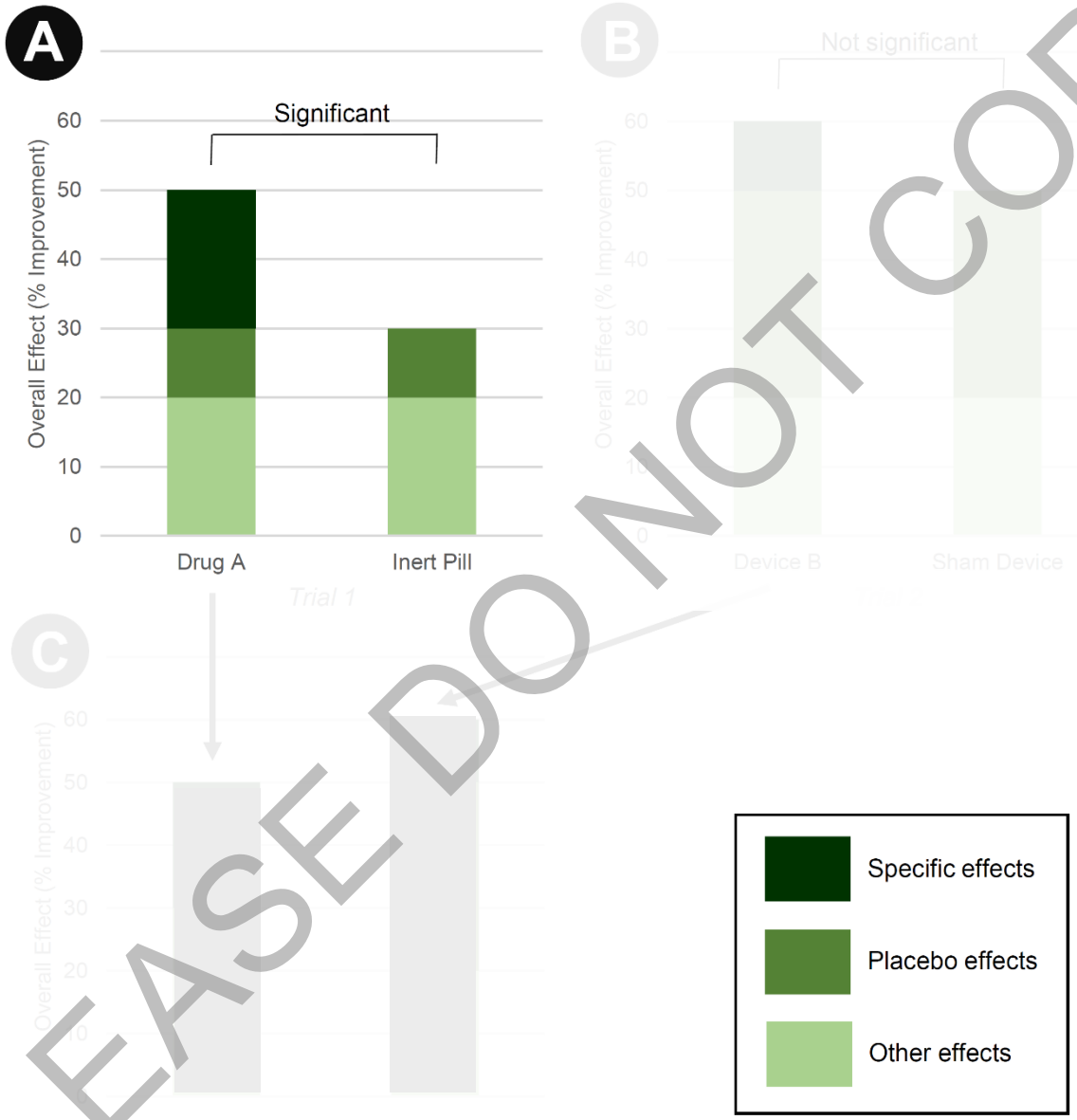
ANNALS *of Neurology* January 2019

NEUROLOGY GRAND ROUNDS

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

Matthew J. Burke, MD,[1] Ted J. Kaptchuk,[2] and Alvaro Pascual-Leone, MD, PhD[1]

BRAIN STIMULATION TECHNOLOGIES



Burke et al. 2019

3) IMPACT OF SHARED MECHANISMS BETWEEN PLACEBO EFFECTS & TREATMENT

Molecular Psychiatry

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[1,2,3,12]✉, Sara M. Romanella[3,4,12], Lucia Mencarelli[3,4], Rachel Greben[2], Michael D. Fox[3,5,6], Ted J. Kaptchuk[7], Alvaro Pascual-Leone[8,9,10] and Emiliano Santarnecchi[3,11]✉

BA CNBS Berenson-Allen Center For Noninvasive Brain Stimulation

Beth Israel Deaconess Medical Center

BWH

Harvard Medical School

Università di Siena 1240

University of Toronto

Sunnybrook Health Sciences Centre

Psychiatry University of Toronto

UofT Neurology

PLACEBO NEUROIMAGING META-ANALYSIS

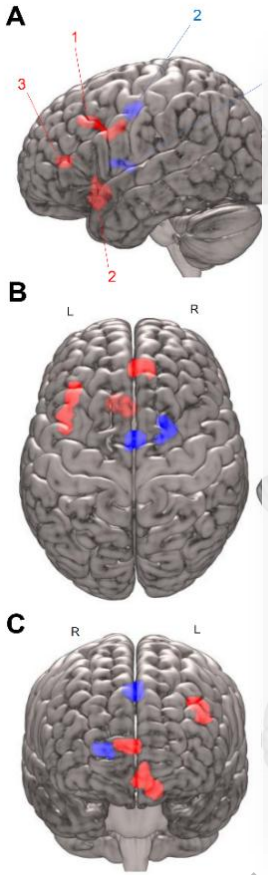
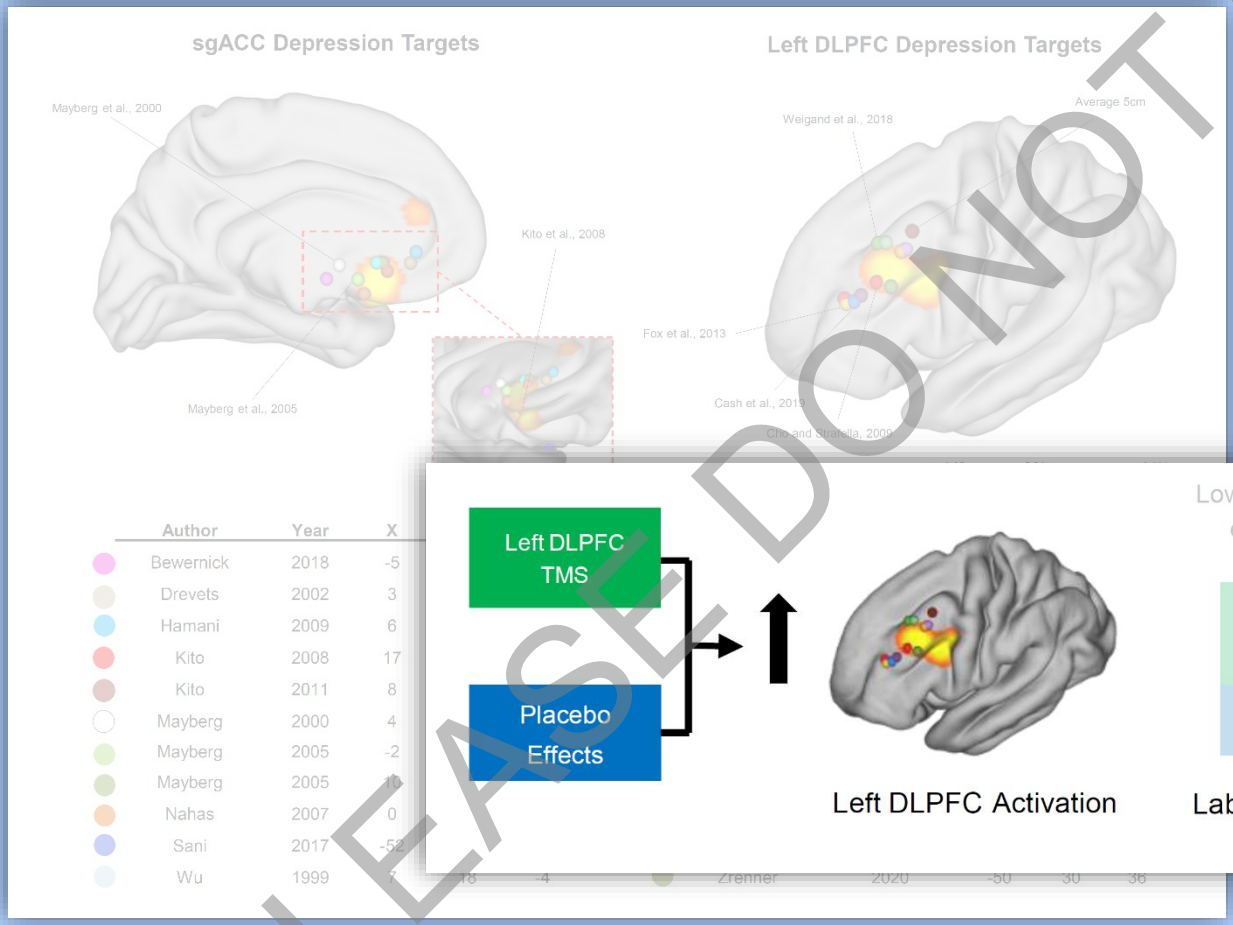


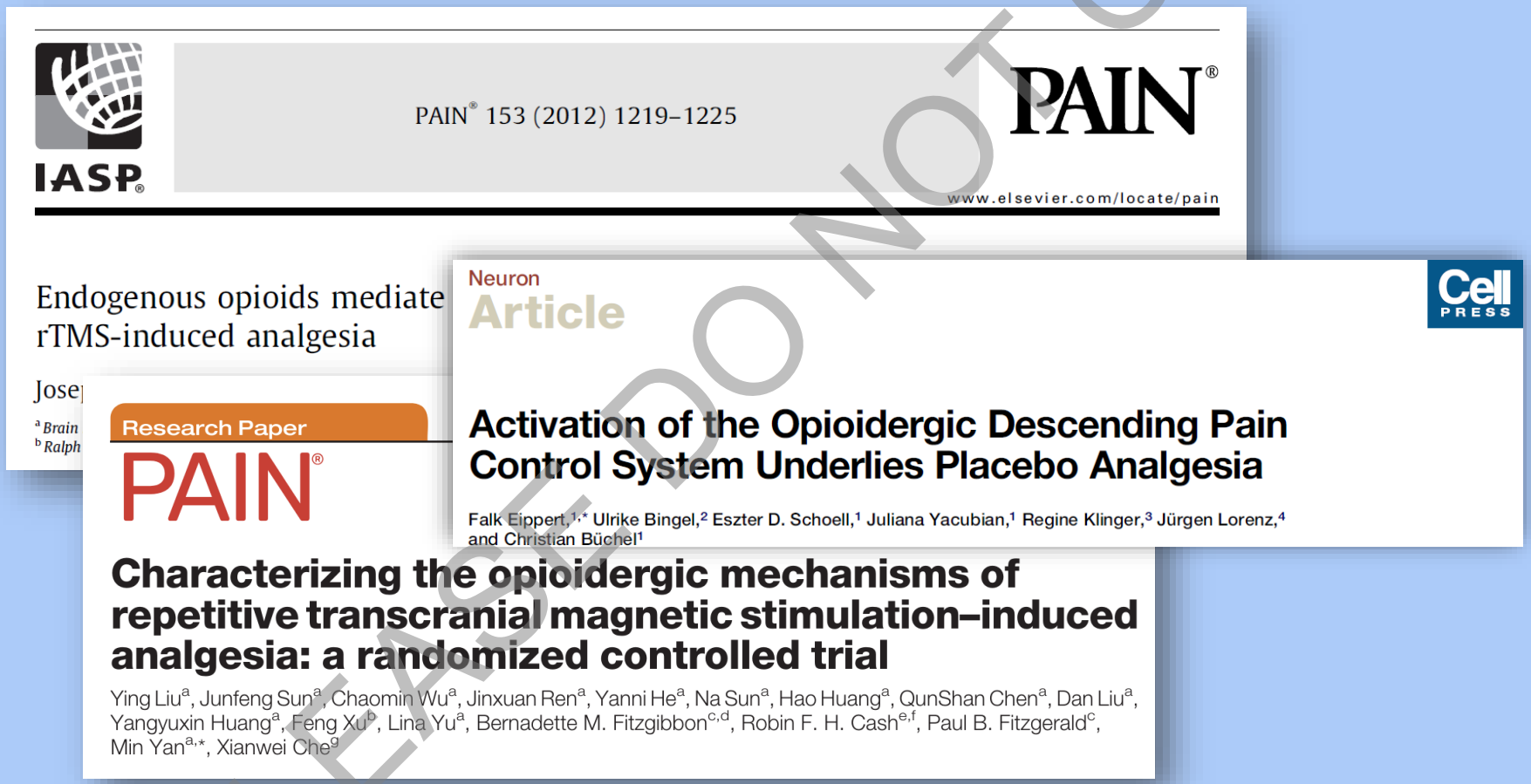
Table 1. Brain regions demonstrating activation or deactivation associated with placebo effects.

		Center				Extrema value coordinates					
Cluster	**Volume (mm^3)**	**x**	**y**	**z**	**Extrema Value**	**x**	**y**	**z**	**BA**	**Hemisphere**	**Neuroanatomic Label**
Activation Clusters											
1	1888	−40.8	16.1	33.7							DLPFC
					0.023	−42	4	34	6	L	
					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	
Deactivation Clusters											
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



POTENTIAL SHARED NEUROTRANSMITTER SYSTEMS



IASP

PAIN® 153 (2012) 1219–1225

PAIN®

www.elsevier.com/locate/pain

Endogenous opioids mediate
rTMS-induced analgesia

Jose

[a] Brain
[b] Ralph

Neuron

Article

Cell PRESS

Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia

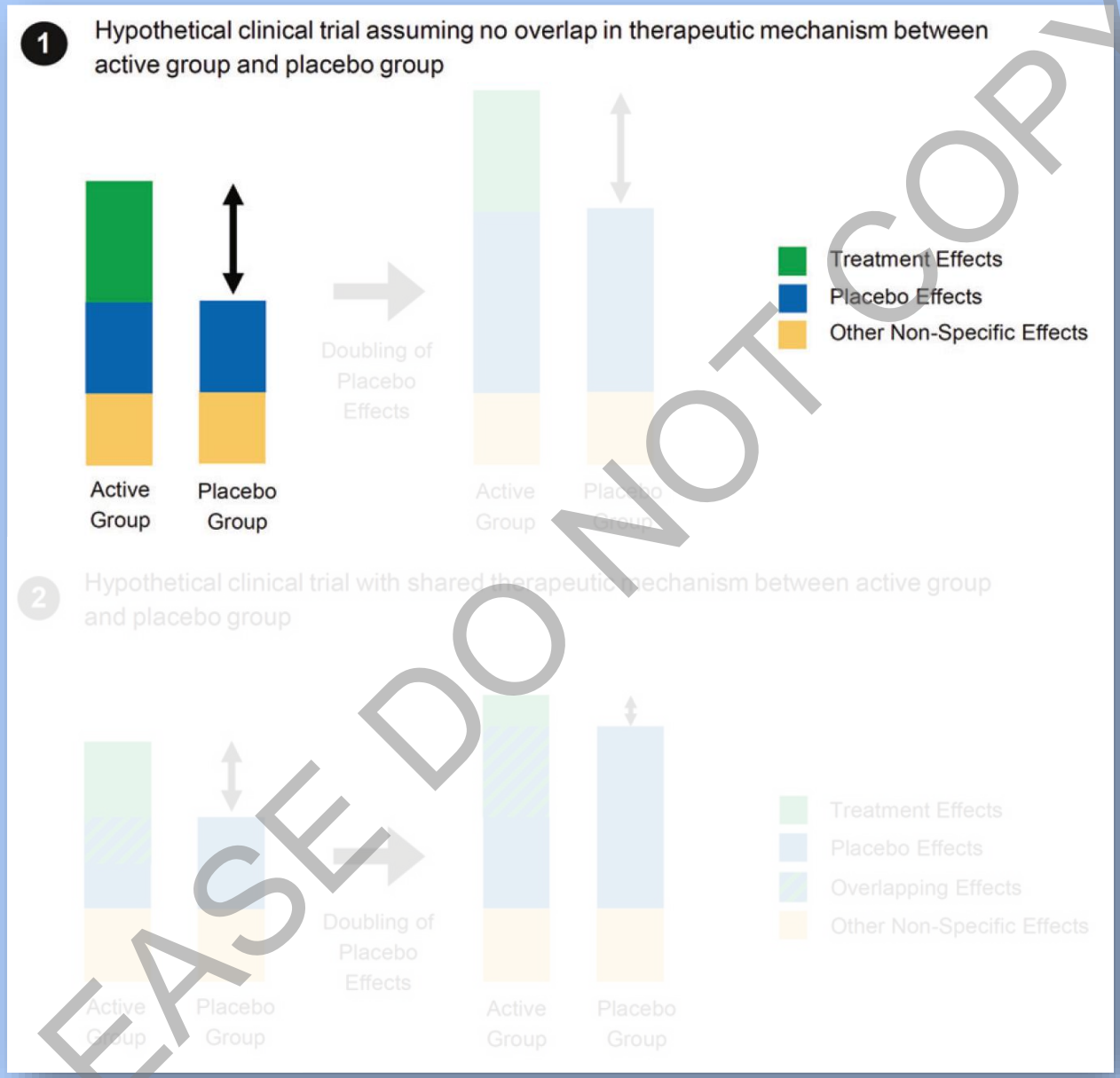
Falk Eippert,[1,*] Ulrike Bingel,[2] Eszter D. Schoell,[1] Juliana Yacubian,[1] Regine Klinger,[3] Jürgen Lorenz,[4] and Christian Büchel[1]

Research Paper

PAIN®

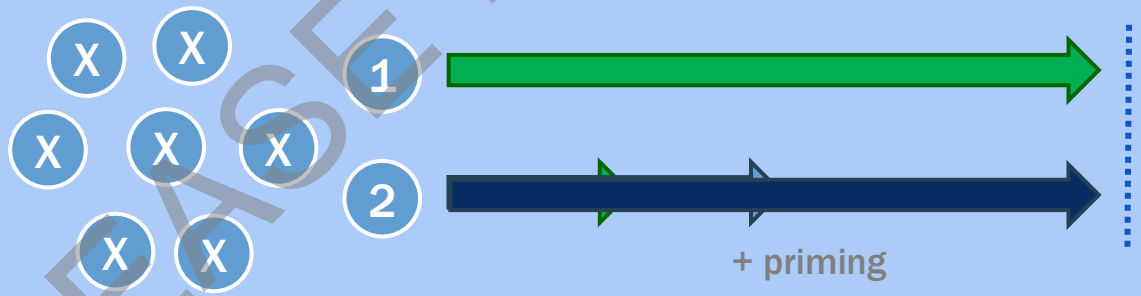
Characterizing the opioidergic mechanisms of repetitive transcranial magnetic stimulation–induced analgesia: a randomized controlled trial

Ying Liu[a], Junfeng Sun[a], Chaomin Wu[a], Jinxuan Ren[a], Yanni He[a], Na Sun[a], Hao Huang[a], QunShan Chen[a], Dan Liu[a], Yangyuxin Huang[a], Feng Xu[b], Lina Yu[a], Bernadette M. Fitzgibbon[c,d], Robin F. H. Cash[e,f], Paul B. Fitzgerald[c], Min Yan[a,*], Xianwei Che[g]



IMPLICATIONS OF OVERLAPPING MECHANISMS

OR



PRIMING THE NETWORK?

nature reviews neuroscience

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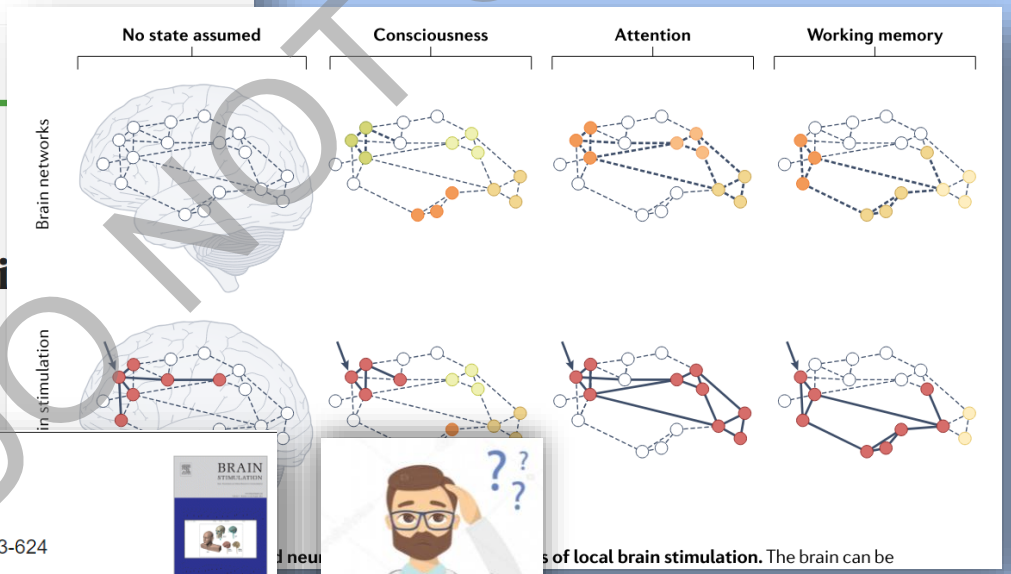
Review Article | Published: 16 May 2022

State-dependent effects of neural stimulati… function and cognition

Claire Bradley, Abbey S. Nydam, Paul E. Dux & Jason B. Mattingley



…of local brain stimulation. The brain can be

ELSEVIER

Brain Stimulation

Volume 7, Issue 4, July–August 2014, Pages 623-624

Letter to the Editor

It's All in Your Head: Reinforcing the Placebo Response With tDCS

H.M. Schambra, M. Bikson, T.D. Wager, M.F. DosSantos, A.F. DaSilva

1) *Measure*
2) *Leverage*

RECENT PUBLICATION

BRAIN STIMULATION

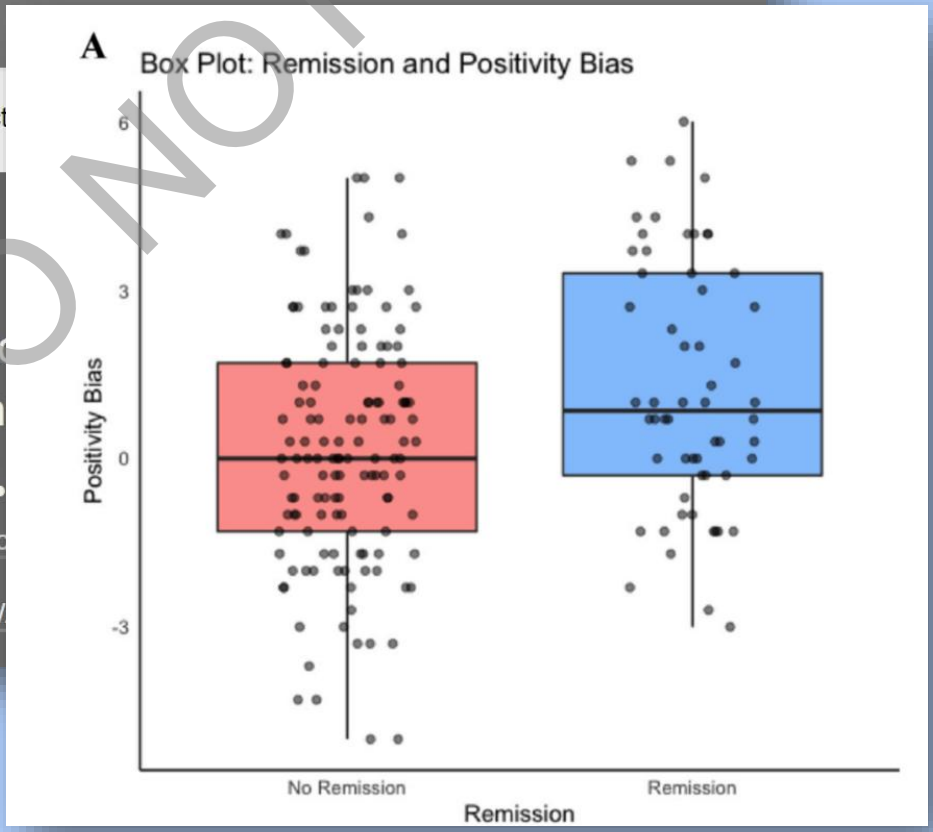
Articles Publish Multimedia About Contact

RESEARCH ARTICLE | ARTICLES IN PRESS

Treatment expectations and clini
transcranial magnetic stimulation

Adriano Mollica # • Enoch Ng # • Matthew J. Burke •
Peter Giacobbe • Show all authors • Show foc

Open Access • Published: June 18, 2024 • DOI: https:/



Psychiatry
UNIVERSITY OF TORONTO

UofT NEUROLOGY

THE ART OF DELIVERING PLACEBO EFFECTS WITHOUT THE "PLACEBO"?

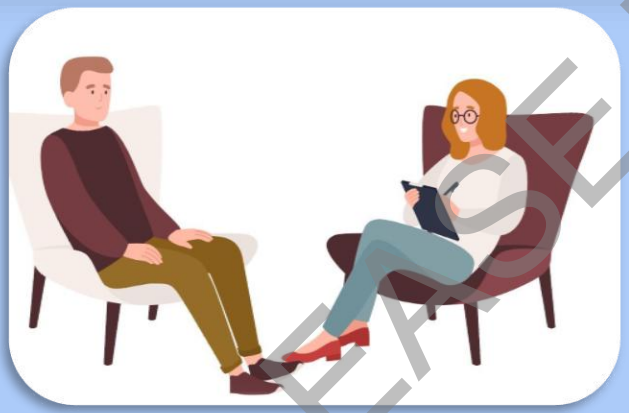
frontiers in Psychiatry

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

Placebo Effects in Psychotherapy: A Framework

Paul Enck and Stephan Zipfel*

Psychosomatic Medicine and Psychotherapy, Department of Internal Medicine VI, Unive



JAMA The Journal of the American Medical Association

This Issue | Views 16,578 | Citations 38 | Altmetric 162

Viewpoint

May 23/30, 2017

Changing Mindsets to Enhance Treatment Effectiveness

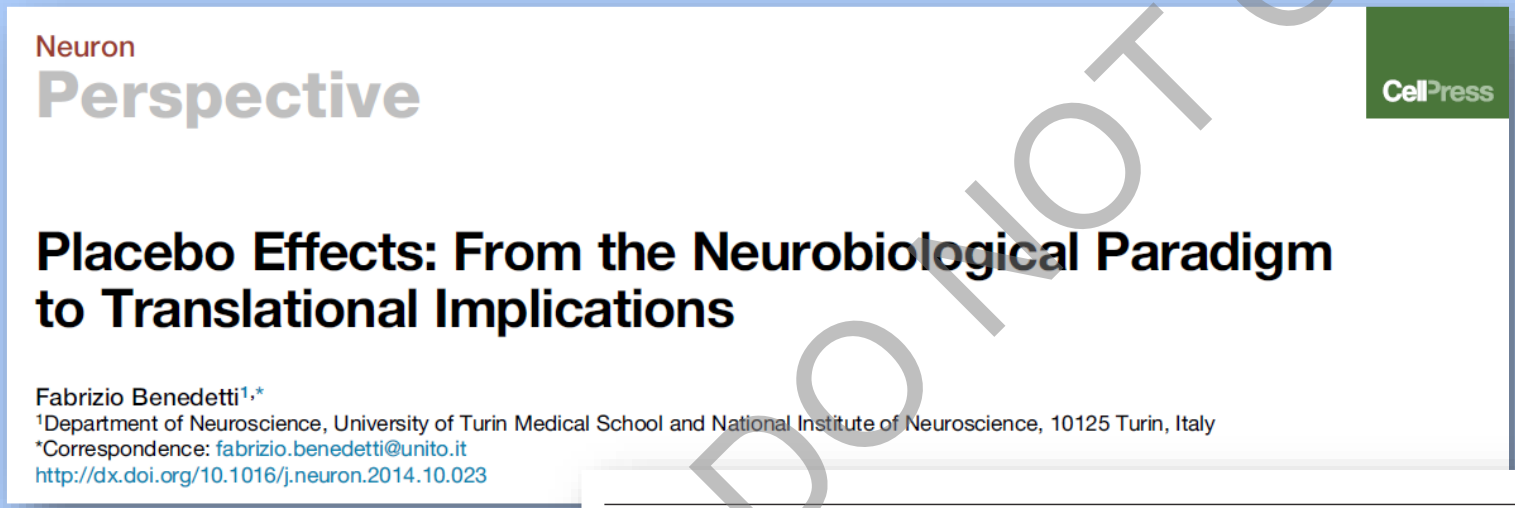
Alia Crum, PhD[1]; Barry Zuckerman, MD[2,3]

» 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[1,*]
[1]Department 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

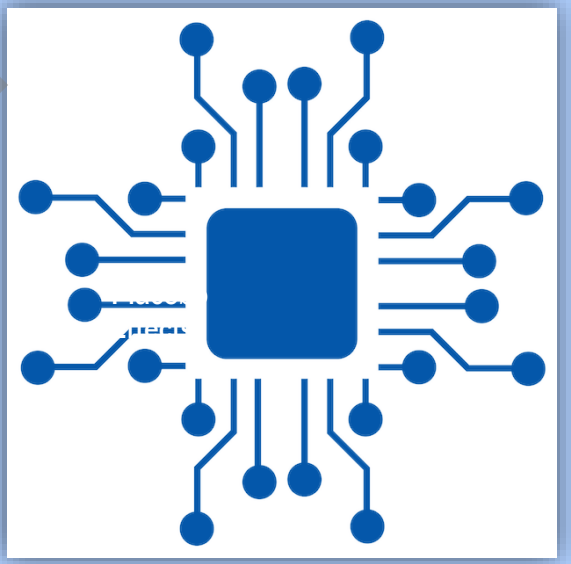
OPINION

NATURE REVIEWS | DRUG DISCOVERY

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

Paul Enck, Ulrike Bingel, Manfred Schedlowski and Winfried Rief

APPROACHES FOR HARNESSING PLACEBO EFFECTS



Ethics

ARE WE ALREADY DECEIVING?

BMJ

RESEARCH

Prescribing "placebo treatments": results of national survey of US internists and rheumatologists

Jon C Tilburt, staff scientist,[1] Ezekiel J Emanuel, director,[1] Ted J Kaptchuk, associate director,[2] Farr A Curlin, assistant professor of medicine,[3] Franklin G Miller, director, research ethics programme[1]

Is it appropriate to recommend treatment primarily to promote patients' expectations?:	
Obligatory	19/642 (3)
Permissible	380/642 (59)
Permissible only in rare circumstance	197/642 (31)
Never permissible	46/642 (7)

IN THE MEANTIME… REAL-WORLD DATA

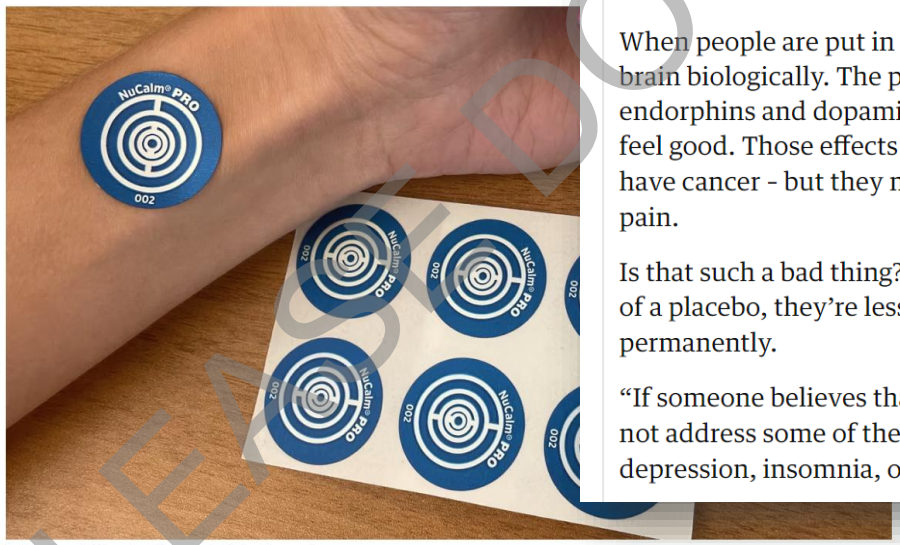
RECENT HEADLINES

Psychology

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

Alaina Demopoulos

Thu 7 Sep 2023 11.00 BST



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.

MINIMIZING NOCEBO EFFECTS

Annual Review of Psychology

Psychobiological Mechanisms of Placebo and Nocebo Effects: Pathways to Improve Treatments and Reduce Side Effects

Keith J. Petrie[1] and Winfried Rief[2]

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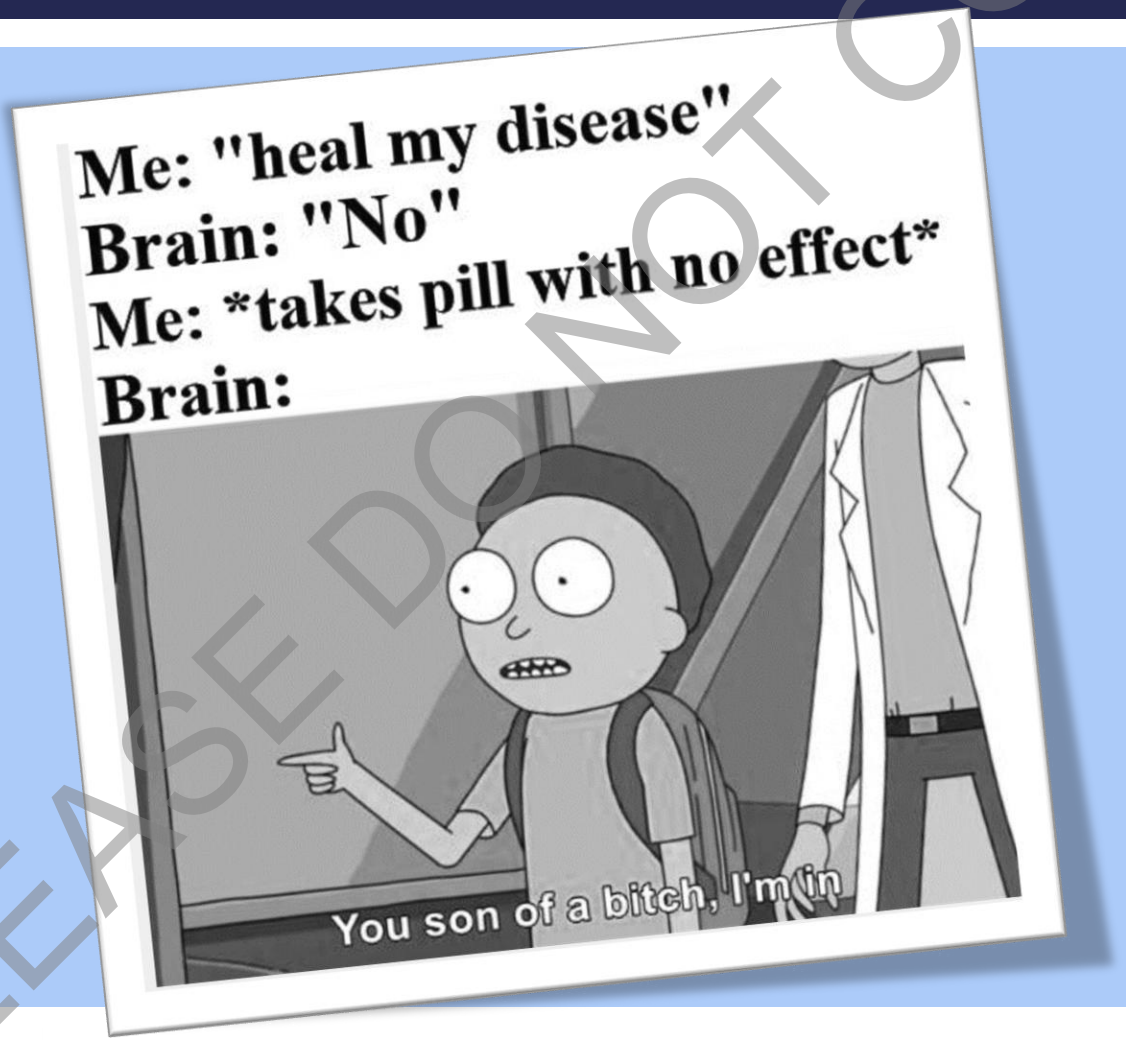
SO HOW DO WE MOVE FORWARD?



MOVING FORWARD IN NEUROMODULATION RESEARCH

- New trial design considerations
  - Priming, synergy and concurrent interventions
- Collect data on expectancy and potentially modulate it
- Change semantics –endogenous healing network, anti-depressant 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 Mollica[1,2], Rachel Greben[2,3], Marieve Cyr[4], Jay A. Olson[5] and Matthew J. Burke[1,2,6,7]

[1]Neuropsychiatry Program, Department of Psychiatry, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada, [2]Harquail Centre for Neuromodulation and Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Toronto, ON, Canada, [3]Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [4]Faculty of Medicine, McGill University, Montreal, QC, Canada, [5]Department of Psychology, McGill University, Montreal, QC, Canada, [6]Division of Neurology, Department of Medicine, University of Toronto, Toronto, ON, Canada and [7]Berenson-Allen Center for Noninvasive Brain Stimulation, Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

Table 2: Strengths and limitations of study designs for neuromodulation trials with a focus on placebo effects

Study design	Strengths	Limitations
Randomized sham-controlled trial		
Active treatment versus sham control group	Considered gold standard in evaluating effectiveness of active treatment	Requires careful design of sham technology to replicate the experience of active stimulation protocols, as well as assessment of blinding integrity
Placebo run-in trial		
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[63] Recently found to be no more effective in finding differences between drug and placebo groups than trials without placebo run-in periods for antidepressants[65]
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[66] 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.

SHIFTING THE SPIN

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could this change the way we think about modern medicine?

28 minutes

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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,

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
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Feedback

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

University Health Network
- Dr. Anthony Lang
- Dr. Robert Chen
- Dr. Sarah Lidstone

St. Michael's Hospital
- Dr. Saadia Sediqzadah

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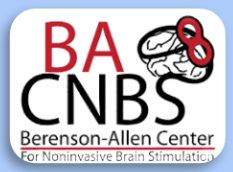
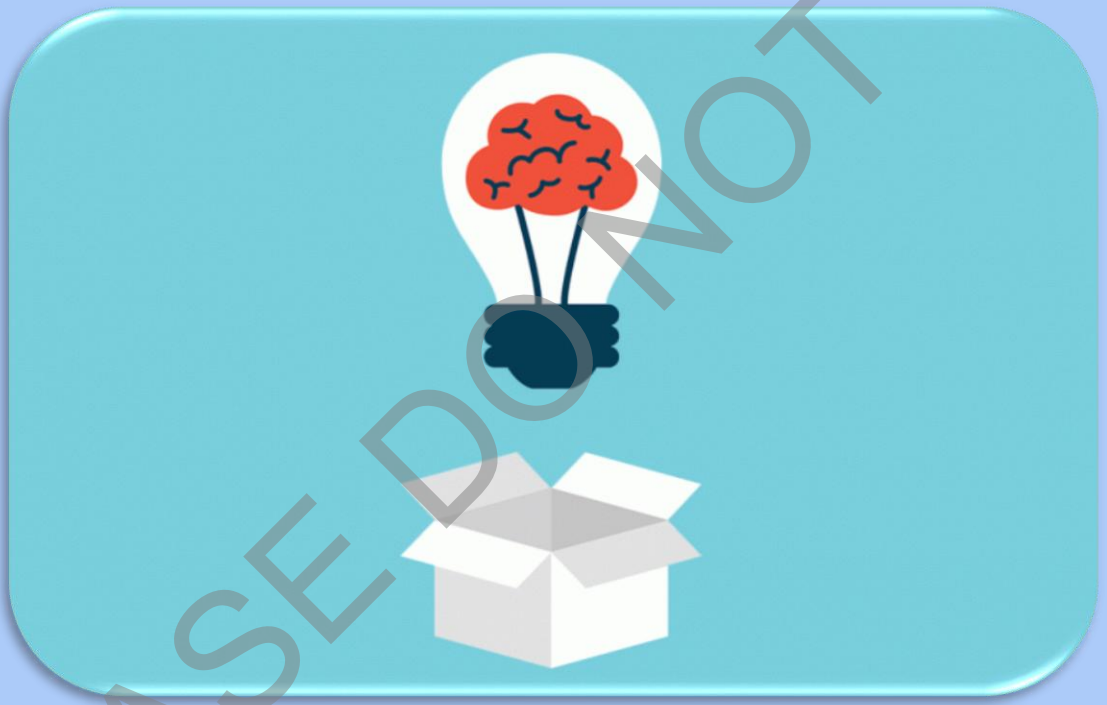


QUESTIONS



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