PLACEBO EFFECTS & TRANSCRANIAL MAGNETIC STIMULATION

INTENSIVE COURSE IN TRANSCRANIAL MAGNETIC STIMULATION

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Please do not copy
Placebo Effects in Medicine
Ted J. Kaptchuk and Franklin G. Miller, Ph.D.

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.
1. Neurobiology of Placebo Effects
   - Definitions
   - Mechanisms of action
   - Evidence and theories
2. “Differential” Placebo Effects
   - Historical context
   - Meta-analytic approaches
   - Prospective approaches
3. TMS and Placebo Effects
   - Sham devices
   - Quantifying magnitude
   - Implications on clinical trial results
"Do you have that placebo I've heard so much about?"
PLACEBO EFFECTS

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

Tor D. Wager and Lauren Y. Atlas

External context

Verbal suggestions:
“This is going to make you feel better”

Place cues:
Doctor’s office

Social cues:
• Eye gaze
• Body language
• Voice cues
• White coat

Internal context

• Outcome expectancies:
  “My pain will go away”
• Emotions:
  “I am less anxious”
• Meaning schema:
  “I am being cared for”
• Explicit memories
• Pre-cognitive associations

Treatment cues:
• Syringe
• Needle puncture
Placebo Terminology

- Placebo “Response” vs. Placebo “Effects”

The latter requires a comparison to “no-treatment” controls to delineate placebo effects from other nonspecific changes:

- Regression to the mean
- Spontaneous changes
- Elevation bias (higher reported symptom severity at initial/baseline assessment than actually experienced)
- Hawthorne effects (changes in outcomes associated with the act of being studied/observed)
NEUROIMAGING STUDIES

Placebo and Opioid Analgesia
Predrag Petrovic, Eija Kalso, Kari Tolvanen, R. E. Courage, R. V. Hyvärinen, T. S. Hyvärinen, 
and P. M. Hammersley

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

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

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

Falk Eippert,†,‡ Ulrike Bingel,† Eszter D. Schoell,† Juliana Yacubian,‡ Regina Klinger,§ Jürgen Lorenz,¶ and Christian Büchel†

A

Day 1: Manipulation

- Placebo cream
- Control cream

Behavioral: 6 trials each

Unbearable pain

Day 2: Manipulation

- Placebo cream
- Control cream

fMRI „off“: 6 trials each

Day 2: Test

- Placebo cream
- Control cream

fMRI „on“: 15 trials each

Stimulus intensity: 80% 40%

Administration of naloxone / saline

No pain

60% 60%
BIOLOGICAL MECHANISMS

- Opioid, dopamine, cannabinoid, serotonergic, neuroendocrine, and neuro-immunological pathways (+ others) have all been implicated in placebo effects.

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

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

- Two major theories to explain placebo effects:
  - Expectation
  - Learning/Conditioning
“Placebo effects generally correspond to people’s knowledge or beliefs about the kind of drug they believe they are receiving, and for that reason, a causal relation between expectancy and placebo reaction has generally been assumed...”
**Open-Hidden Paradigms**

**Hidden Administration of Drugs**

F. Benedetti, E. Carlini, and A. Pollo

- **TOLD** → Saline → Ret
- **GET** → Remifentanil → Ret

No expectation

**Pain reduction**

0

**Hidden application**

Medication is administered by a machine (unbeknown to the patient)

**Open application**

Medication is administered by a physician

**Drug Labeling Changes in Migraine Attacks**

Enck et al. 2013

- pill
- Maxalt pill
Two major theories to explain placebo effects:

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

Julia Kirchhof\textsuperscript{a}, Liubov Petrakova\textsuperscript{a}, Alexandra Brinkhoff\textsuperscript{b}, Sven Benson\textsuperscript{a}, Justine Schmidt\textsuperscript{a}, Maike Unterberdörster\textsuperscript{c}, Benjamin Wilde\textsuperscript{b}, Ted J. Kaptchuk\textsuperscript{d}, Oliver Witzke\textsuperscript{e}, and Manfred Schedlowski\textsuperscript{a,f,1}

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

March 7, 2018
Two major theories to explain placebo effects:

- **EXPECTATION**
- **LEARNING/CONDITIONING**

“Rather than being viewed as an alternative to expectancy, classical conditioning can be understood as one method by which expectancies are formed”
Placebo Effect Grows in U.S., Thwarting Development of Painkillers

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

By Jo Marchant, Nature magazine on October 7, 2015
Placebo Effects: From the Neurobiological Paradigm to Translational Implications

Fabrizio Benedetti¹,²
¹Department of Neuroscience, University of Turin Medical School, Turin, Italy
²Correspondence: fabrizio.benedetti@unito.it
http://dx.doi.org/10.1016/j.neuron.2014.10.023

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

NATURE REVIEWS | DRUG DISCOVERY

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, Emiliano Santarnecchi, Ph.D.
CURE ALL?
Figure 1. Schema for Study Interventions.
The time between blocks varied, but was generally 3 to 7 days.
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.
PLACEBO EFFECTS?

Figure 3. Percent Change in Maximum Forced Expiratory Volume in 1 Second (FEV₁) with Each of the Four Interventions.

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

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

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

<table>
<thead>
<tr>
<th>Placebo pathway</th>
<th>Gene name</th>
<th>Gene symbol</th>
<th>Chromosomal location</th>
<th>Placebo SNPs</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Catechol-O-methyltransferase</td>
<td>COMT</td>
<td>22q11.2</td>
<td>rs4680</td>
<td>[38]</td>
</tr>
<tr>
<td></td>
<td>Monoamine oxidase</td>
<td>MAO-A</td>
<td>Xp11.3</td>
<td>rs6323, rs6609257</td>
<td>[43,55]</td>
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<tr>
<td></td>
<td>Dopamine B hydroxylase</td>
<td>DBH</td>
<td>9q34</td>
<td>rs2873804</td>
<td>[43]</td>
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<tr>
<td></td>
<td>Dopamine receptor 3</td>
<td>DRD3</td>
<td>3q13.31</td>
<td>rs6280</td>
<td>[69]</td>
</tr>
<tr>
<td></td>
<td>Brain-derived neurotropic factor</td>
<td>BDNF</td>
<td>11p14.1</td>
<td>rs6285</td>
<td>[66]</td>
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<tr>
<td>Serotonin</td>
<td>Tryptophan hydroxylase-2</td>
<td>TPH2</td>
<td>12q21.1</td>
<td>rs4570625</td>
<td>[75]</td>
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<td></td>
<td>5-Hydroxytryptamine transporter</td>
<td>SLC6A4</td>
<td>17q11.2</td>
<td>rs4251417</td>
<td>[43]</td>
</tr>
<tr>
<td></td>
<td>5-Hydroxytryptamine receptor 2A</td>
<td>HTR2A</td>
<td>13q14.2</td>
<td>rs2296972, rs622337</td>
<td>[43]</td>
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<td>Serotonin transporter gene-linked</td>
<td>5-HTTLPR</td>
<td>17q11.2</td>
<td>Variable tandem</td>
<td>[75]</td>
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<tr>
<td></td>
<td>polymorphic region</td>
<td></td>
<td></td>
<td>nucleotide repeat</td>
<td></td>
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<tr>
<td>Opioid</td>
<td>Opioid receptor</td>
<td>OPRM1</td>
<td>6q25.2</td>
<td>rs510769</td>
<td>[69]</td>
</tr>
<tr>
<td>Endocannabinoid</td>
<td>Fatty acid amide hydrolase</td>
<td>FAAH</td>
<td>1p33</td>
<td>rs324420</td>
<td>[73]</td>
</tr>
</tbody>
</table>
APPROACHES

1) “Deceptive” Placebo

2) “Open-label” Placebo

3) Extracting Placebo
Placebos could save lives and health care dollars: so why can’t mainstream medicine put them to better use?

ERIN ANDERSSON
PUBLISHED OCTOBER 28, 2019

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
5. OPINION: Why I think Canada will avoid a recession next year and the loonie
The concept that different types of placebos may yield different magnitudes of placebo effects.
Challenges of Differential Placebo Effects in Contemporary Medicine: The Example of Brain Stimulation

Matthew J. Burke, MD,¹ Ted J. Kaptchuk,² and Alvaro Pascual-Leone, MD, PhD¹
A Double-Blind Study of the Treatment of Hypertension

Raymond F. Grenfell, M.D., Arthur H. Briggs, M.D., and William C. Holland, M.D., Jackson, Miss.
Surgical “Placebo” Controls

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

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

Rasha Al-Lamee, David Thompson, Hakim-Moulay Debbi, Sayan Sen, Kere Tang, John Davies, Thomas Keeble, Michael Mielewczik, Raffi Kaprielian, Iqbal S Malik, Sukhjinder S Nijjer, Ricardo Petrosco, Christopher Cook, Yousef Ahmad, James Howard, Christopher Baker, Andrew Sharp, Robert Gerber, Sumeil Talwar, Ravi Assomull, Jarnil Moyet, Roland Wensel, David Collier, Matthew Chun-Shin, Simon A Thom, Justin E Davies, David P Francis, on behalf of the ORBITA investigators

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

David J Beard, Jonathan L Rees, Jonathan A Cook, Ines Rombach, Cushla Cooper, Naomi Merritt, Beverly A Shirley, Jenny L Donovan, Stephen Gwilym, Julian Savulescu, Jane Moser, Alastair Gray, Marcus Jepson, Irene Tracey, Andrew Judge, Karolina Wartolowska, Andrew J Carr, on behalf of the CSAW Study Group*
META-ANALYTIC APPROACHES

Drug vs. Inert Pill

Device/Procedure vs. Sham

VS.
META-ANALYTIC APPROACHES

Placebo Response in Parkinson’s Disease: Comparisons Among 11 Trials Covering Medical and Surgical Interventions

Differential Effectiveness of Placebo Treatments: A Systematic Review of Migraine Prophylaxis

Effectiveness and Implications of Alternative Placebo Treatments: A Systematic Review and Network Meta-analysis of Osteoarthritis Trials
“Meta-regression analyses showed that larger effects of placebo interventions were associated with physical placebo interventions” (e.g. sham devices)
Do medical devices have enhanced placebo effects?
Ted J. Kaptchuk\textsuperscript{a,},* Peter Goldman\textsuperscript{b}, David A. Stone\textsuperscript{a,b}, William B. Stason\textsuperscript{b}
\textsuperscript{a}Center for Alternative Medicine Research, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Avenue, Boston, MA 02215, USA
\textsuperscript{b}Harvard School of Public Health, Boston, MA, USA
Received 10 November 1999; received in revised form 5 January 2000, accepted 21 January 2000

Sham device \textit{v} inert pill: randomised controlled trial of two placebo treatments
Ted J Kaptchuk, William B Stason, Roger B Davis, Anna T R Legedza, Rosa N Schnyer, Catherine E Kerr, David A Stone, Bong Hyun Nam, Irving Kirsch, Rose H Goldman
OTHER FACTORS...

- Treatment cost, perceived innovation, branding, pill shape/colour...

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

A randomized double-blind study

**ABSTRACT**

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

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

**Results:** Although both placebos improved motor function, benefit was greatest in the "cheap" placebo, with a magnitude halfway between that of cheap placebo and levodopa. Brain activation was greater upon first-held cheap but not upon first-held 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
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.
TMS AND PLACEBO EFFECTS
Sham tDCS: A hidden source of variability? Reflections for further blinded, controlled trials

Clara Fonteneau, a, b, c, Marine Mondino, a, b, c, Martijn Arns, d, e, Chris Baeken, f, g, h, Marom Bikson, i, Andre R. Brunoni, j, k, Matthew J. Burke, l, Tuomas Neuvonen, m, Frank Padberg, l, Alvaro Pascual-Leone, l, Emmanuel Poulet, a, b, c, Giulio Ruffini, n, Emiliano Santarnecchi, l, Anne Sauvaget, o, p, Klaus Schellhorn, d, Marie-Françoise Suau-D-Chagny, a, b, c, Ulrich Palm, l, Jérôme Brunelin, a, b, c, *
EXEMPLIFICATION OF AN ELABORATE THERAPEUTIC TECHNOLOGY
Achieve blinding but avoid meaningful stimulation to the brain

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

Many different sham device techniques

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

Laís B. Razza\textsuperscript{a}, Adriano H. Moffa\textsuperscript{a}, Marina L. Moreno\textsuperscript{a}, Andre F. Carvalho\textsuperscript{b}, Frank Padberg\textsuperscript{c}, Felipe Fregni\textsuperscript{d}, André R. Brunoni\textsuperscript{a,c,s} (2018) 105–113

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

*No difference from sham group (37%)
PLACEBO MODULATION OF AMYGDALA

A follow-up fMRI study on the anxiolytic effect

Amygda Subregions Tied to SSRI and Placebo Response in Patients with Social Anxiety Disorder

Vanda Faria, Lieve Appel, Fredrik Åhs, Clas Linnman, Anna Pissota, Örjan Frans, Massimo Bani, Paolo Bettica, Emilio M Pich, Eva Jacobsson, Kurt Wahlstedt, Mats Fredriksson, and Tomas Furmark

Amygda subregions in anxiolysis

V Faria et al

<table>
<thead>
<tr>
<th>Change in amygdala blood flow, % (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left amygdala</td>
</tr>
<tr>
<td>Right amygdala</td>
</tr>
</tbody>
</table>

- Placebo nonresponders, n=26
- Placebo responders, n=11
- SSRI nonresponders, n=15
- SSRI responders, n=20
“Contrary to our primary hypothesis, the number of headache days decreased significantly more in the sham group than in the group treated with active rTMS-DLPFC at eight weeks. Average decrease in headache days was >50% in the sham group, indicating a powerful placebo response.”
EVIDENCE FOR “DIFFERENTIAL EFFECT”?

- Compared inert pill group from escitalopram medication trials to the sham TMS group of TMS trials
- Reported no significant difference...BUT
- Methodological limitations
  - Heterogenous patient populations – “refractory”
  - Blinding – double vs single
  - Dated (only included trials 2002-2008)
FURTHER RESEARCH?

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

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

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)

Jean-Pascal Lefaucheur a,b,*, Nathalie André-Obadia c,d, Andrea Antal e, Samar S. Ayache a,b, Chris Baeken f,g, David H. Benninger h, Roberto M. Cantello i, Massimo Cincotta j, Mamede de Carvalho k, Dirk De Ridder l,m, Hervé Devanne n,o, Vincenzo Di Lazzaro p, Saša R. Filipović q, Friedhelm C. Hummel r, Satu K. Jääskeläinen s, Vasilios K. Kimiskidis t, Giacomo Koch u, Berthold Langguth v, Thomas Nyffeler w, Antonio Oliviero x, Frank Padberg y, Emmanuel Poulet z,a, Simone Rossi a,b, Paolo Maria Rossini a,c,ad, John C. Rothwell ae, Carlos Schönfeldt-Lecuona af, Hartwig R. Siebner ag,ah, Christina W. Slotema al, Charlotte J. Stagg aj, Josep Valls-Sole ak, Ulf Ziemann al, Walter Paulus e,1, Luis Garcia-Larrea d,am,1
ILLUSTRATIVE EXAMPLE - PAIN

**Neuron Article**

Activation of the Opioidergic Descending Pain Control System Underlies Placebo Analgesia

Falk Eippert, Ulrike Bingel, Eszter D. Schoell, Juliana Yacubian, Regine Klinger, Jürgen Lorenz, and Christian Büchel

**Rapid Review**

Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques

Felipe Fregni, Steven Freedman, Alvaro Pascual-Leone
ISSUES REQUIRING CRITICAL REFLECTION...

What is the best way to measure efficacy in this context?

How can we leverage enhanced placebo effects?
Every field jumps to assuming that there must be something “active” about their placebo group...

Occam’s Razor: When presented with competing hypotheses, simpler solutions are more likely to be correct than complex ones
A FINAL COMPLICATING ISSUE...

- S2-dpINS: somatic pain intensity
- mThal: pain integration
- dIPFC: goal context; expectancy
- aIns: motivation; decision; affect
- dACC: avoidance value
- vmPFC: meaning ‘schema’
- NAc-VS: motivational and hedonic value
- PAG: emotion; regulation of pain and autonemics
- RVM: spinal control of pain and autonemics
- IOFC
MECHANISMS?

The Functional Neuroimaging of Depression

Helen S. Mayberg, M.D., F.R.C.P.C.
J. Arturo Silva, M.D.
Steven K. Brannan, M.D.
Janet L. Tekell, M.D.
Roderick K. Mahurin, Ph.D.
Scott McGinnis, B.S.
Paul A. Jerabek, Ph.D.

Objective: Cognitive malfunction in depression can result in impairments of executive, verbal, and motor functions that are not distinguishable from those of normal aging. The biological substrates of these impairments have not been fully defined.

Method: We examined functional brain activity, using positron-emission tomography (PET) of cerebral glucose metabolism in depressed women with melancholic features who were randomly assigned to be administered fluoxetine or placebo. Two-dimensional PET images of brain activity were obtained at three time points: baseline (day 1), and after 2 and 6 weeks of treatment. The study was divided into two parts: a double-blind placebo-controlled phase and an open-label phase.

Results: The analyses revealed a significant correlation between the changes in regional glucose metabolism and improvements in cognitive, motor, and affective symptoms. The changes were most pronounced in the frontal and anterior cingulate regions, which are known to be involved in the regulation of emotional and cognitive processes. In the placebo group, no significant changes in glucose metabolism were observed.

Fluoxetine Responders

Sagittal View Axial View Coronal View

Placebo Responders

Subgenual cingulate

Prefrontal

Subgenual cingulate

Subgenual cingulate

Subgenual cingulate

Subgenual cingulate

Y = +18

X = +2

Z = -14

Left

Figure 1. Changes in Regional Glucose Metabolism in Eight Depressed Patients Who Responded to Fluoxetine or Placebo Over 6 Weeks

a Slice location is in millimeters relative to the anterior commissure line. Increases in metabolism are in red; decreases are in yellow. Cortical increases and limbic-paralimbic decreases were seen under both conditions. Fluoxetine response was additionally associated with brainstem increases and hippocampal and striatal decreases.
QUESTIONS

Could studying the placebo effect change the way we think about medicine?

- The New Yorker on PiPS Research

mburke11@bidmc.harvard.edu  matthew.burke@sunnybrook.ca