Imaging Biomarkers for Assessment of the Placebo Response

Ariana E. Anderson, Ph.D.
Assistant Professor
University of California, Los Angeles
Disclosures

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Overview

- Placebo response/effect:
  - Definitions
  - Differentiation

- Placebo response observed in:
  - Pain
  - Depression
  - Parkinson’s Disease

- New work: Measuring placebo response using fMRI

- Conclusions

-Now that's what I mean... You live for two weeks with a placebo version of me - and you don't even notice!
Placebo Controlled Trials
Placebo Response

“An improvement in symptoms caused *in part* by a set of mind-brain processes.”

![Graph showing treatment response over time with lines for placebo response, temporal-statistical effects, placebo effect, and drug effect.](image)
Temporal/Statistical Effects:

- spontaneous, endogenous improvement
- sampling bias, regression to the mean
- natural symptom fluctuation (e.g., patients may enroll in trials when symptoms are at their worst and subsequently improve)
Placebo Effect

- “The placebo effect is a psychobiological phenomenon that can be attributable to different mechanisms, including expectation of clinical improvement and Pavlovian conditioning.” Benedetti et al., 2005
Placebo Mechanisms
Placebo Expectations

fMRI Predicting Analgesia Placebo Responders

fMRI Depression: Duloxetine

- Default Mode Network
- Task Positive Network

Parkinsons’ Mechanisms

Endogenous Dopamine in PD PET Imaging

Measuring the Placebo using fMRI

- Smoking cessation study: bupropion, placebo, CBT
- Use fMRI to measure treatment effects:
  - Generalized Placebo Response: temporal/statistical effects
  - Pill Placebo Effect: Effects from receiving a blinded pill
  - CBT Effect
  - Drug Effect
- Can fMRI measure placebo within drug and CBT group?
Experimental Design

INDEPENDENT COMPONENTS ANALYSIS (ICA)

data are decomposed into a set of 
spatially-independent maps and a set of 
time courses.

IC Spatial Maps
Independent Component Analysis (ICA)

- ICA: $Y = DX$, $D =$ time series weights
- Estimation in fMRI usually by maximizing negentropy (FAST-ICA) or minimizing mutual information (INFOMAX)
- Independence is assumed on the voxel level - $p(x_1, x_2, \ldots x_k) = p(x_1)p(x_2)\ldots p(x_k)$
- This necessarily assumes that the ability of a voxel to contribute to any network is not affected by its contribution to any other networks.
The functional architecture of the human brain: Correspondence between resting FMRI and task-activation studies

Stephen M. Smith¹  Peter T. Fox²
Karla L. Miller¹  David C. Glahn³,²  P. Mickle Fox²  Clare E. Mackay¹
Nicola Filippini¹  Kate E. Watkins¹  Roberto Toro⁴
Angela R. Laird²  Christian F. Beckmann⁵,¹
Placebo Brain Changes

Is CBT a Placebo?

Network Changes with CBT

fMRI-measured Treatment Effects

fMRI measured changes significantly increased ability to predict treatment response.

Conclusions:

- Brain imaging can
  - Predict placebo responders
  - Identify placebo group response patterns
  - Measure placebo response within subjects receiving medications
- Phase 1 (n of 1 studies, rare diseases): brain imaging can separate drug effects from placebo responses.
- Placebo response may mimic effective treatments.
- Brain imaging can localize, predict, and measure placebo response.
- fMRI placebo changes are sensitive to conditioning, disorder, and stimulus.
- Most studies using fMRI may not translate well clinically.
- EEG would be ideal for such biophysical measurements given its cost and availability.
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