Thoughts as things: Placebo effects and the brain systems that regulate pain and emotion

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If you are distressed by anything external, the pain is not due to the thing itself, but to your estimate of it; and this you have the power to revoke at any moment.

– Marcus Aurelius
“…if a patient does not consent to therapy with positive engagement, the physician should not proceed as the therapy will not succeed.”

Yellow Emperor’s Inner Classic (Kong et al., 2009)
“…the patient, though conscious that his condition is perilous, may recover his health simply through his contentment with the goodness of the physician”

“The physical affirmation of a disease should always be met with the mental negation. … Stand porter at the door of thought.”

- Mary Baker Eddy

Science and Health, p. 392
…of physicians reported using placebo treatments in clinical practice in 2007
The Dangerous Cure

- Over 4,000 ancient remedies
- Almost all effects now attributed to placebo
- Many deadly

*Arthur Shapiro; in Harrington, Anne (ed.), The placebo effect*
Can beliefs be helpful in relieving pain in a meaningful way?
Sham acupuncture

German Acupuncture Trials (GERAC) for Chronic Low Back Pain

Randomized, Multicenter, Blinded, Parallel-Group Trial With 3 Groups

Von Korff Chronic Pain Grade Scale at 6 months

Haake et al., 2008. N = 1162, 387 per group
Placebos Prove So Powerful Even Experts Are Surprised

New Studies Explore the Brain's Triumph Over Reality

Placebo Effect Is More Myth Than Science, Study Says

By GINA KOHL

In a new report that is being met with a mixture of astonishment and sometimes disbelief, two Danish researchers say the placebo effect is a myth.

The investigators analyzed 114 published studies involving about 7,500 patients with 10 different conditions. The report found no support for the common notion that, in general, about a third of patients improve on a placebo. "Maybe it is one of the urban legends of medicine," he said.

But others, like David Freedman, a statistician at the University of California, said he was not convinced. Professor Freedman said the statistical method the Danish researchers used, pooling data from many studies and using a statistical tool called metaanalysis to examine them, could give

A challenge to mind-body beliefs underlying some tenets on healing.
Contributions of Neuroscience

1) **Mechanism.** What systems are involved? Where and how should we intervene?

2) **Intermediate markers.** How early? Which brain processes?

Preliminary intermediate markers for pain processing

Wager lab, N=115, Thermal pain on left arm, p < .05 FWE corrected

e.g., Apkarian et al. 2005; Coghill et al. 1999, many others
Placebo fMRI Study Procedures

Study 1: Electric Shock, Right arm
N = 24 in fMRI

Study 2: Thermal Pain, Left arm
N = 22 in fMRI
fMRI trial design

Anticipatory activity

Cue

Ready!

1 s

Anticipation

1-16 s

\( \bar{x} = 9.77 \)
SD = 6.04

Heat

20 s

\( \bar{x} = 6.82 \)
SD = 4.18

Rest

1-12 s

Report-related activity

Rate pain

4 s

Rest

40 - 50 s

Time during Trials
Placebo analgesia: fMRI setup

- Calibration
  - Choose temperatures
  - Subjective Levels 2, 5, and 8 on 10-point scale

- Manipulation
  - Increase expectancy
  - Stim. At Level 8 on Control region
  - Reduce temperature to Level 2 on Placebo region

- Test
  - Stimulation at Level 5 on both Placebo and Control regions; order counterbalanced
Experimental manipulation of expectation: Placebo analgesia

Placebo cream
“This is lidocaine”

Control cream
“Will have no effect”

Identical temperatures

Assimilation to expectations

Benedetti et al., 1999; Bingel et al., 2006; Price et al. 1999, Montgomery and Kirsch, 1996; Vase et al., 2003; Voudouris et al., 1990; Wager et al., 2004, 07; many others
Placebo analgesia: Key results

Reduced response to painful stimulation

- Insula
- PHCP, Thalamus
- rACC

Increases during anticipation

- Opioids and PAG are major

Benedetti (1999); Fields & Levine (1981); Eippert et al., 2009; cf. Gracely et al. (1984)
Placebo analgesia: Key results

Reduced response to painful stimulation

- rACC
- Insula
- PHCP, Thalamus

Increases during anticipation

- Opioid release (PET)
- OFC
- PAG
- rACC

Wager, Scott, & Zubieta, 2007, PNAS; See also Scott et al., 2007, 2008

Regions of interest

- Green: Regions of interest
- Yellow: P < .05 corrected
- Orange: P < .005
- Red: P < .05
Evidence for spinal cord involvement in placebo analgesia

Eippert et al. Science 2009
Circuit dynamics of negative vs. positive expectation
Pain expectancy supported by conditioning

Expectancy effects on pain processing

Expectancy effects on pain processing

Cues
High – Low

Pain

Hypothal.

S2

Ventral striatum

Amygdala

Pons, Rostral ventral medulla

Lateral PFC

Insula

Cerebellum

Atlas et al., J Neurosci 2010

HM-LM: t(17) = 8.59, p < .0001
Mediators of expectancy effects on pain
Multi-level mediation

Noxious heat (Medium) → PREDICTIVE CUE High – Low → Reported pain

Mediation: 3 significant effects:
• $a$: Effect of cue on brain
• $b$: Brain predicts behavior
• $a*b$: Mediation effect

Atlas et al., J Neurosci 2010

Lauren Atlas
Consistent placebo effects across laboratories: Decreases in ‘pain matrix’, increases in regulatory systems

- Reduced pain-related activity
- Cingulate, thalamus, insula
- Somatosensory regions?

- Valuation and context
- Orbitofrontal and cingulate
- Brainstem (PAG)
- Lateral prefrontal cortex

Wager & Fields, in press, Textbook of Pain; Meissner et al., 2011, J Neuro
connections
Beyond pain: Ventromedial prefrontal cortex and affective meaning

**Autonomic/endocrine**
- Sympathetic
- Parasympathetic
- Endocrine

**Valuation**
- Now > Later
- Money, trinkets, snacks
- Expected value/conceptual knowledge

**Threat/threat regulation**
- Conditioned SCRs
- Instructed fear
- Fear extinction

**Memory/Self-projections**
- Theory of mind, default mode, autobiographical memory
- Imagining future remembering past
- Self-reflection

**Mediators of reappraisal success**
- Opioids/Placebo

**Mediators of HR increases during social-evaluative threat**
- Speech preparation (SET)
- Heart Rate

**Mood and anxiety disorders**
- Fear extinction recall PTSD < controls
- Hypo- and hyper-activations in PTSD
- Decreases/increases in CBF during depression

Roy, Shohamy, & Wager 2012
"Systems for survival"
Placebos engage a general system for affective appraisal

Innervation of Organs:
- Cholinergic system (Ach), Vagus
- Adrenergic system (NE), sympathetic

Blood, saliva

Endocrine system

Medial/Orcbital Prefrontal Network:
Context-based evaluation of survival-relevance
Context learning

Hypothalamus

Periaqueductal gray (PAG)

Brainstem nuclei

Affective appraisal circuits:
- Threat/reward representation, basic motivation, learning
- Extended amygdala, insula, nucleus accumbens, ventral striatum/pallidum, medial thalamus

Homeostatic regulation:
Coordinate brain and peripheral response via autonomic and endocrine systems

e.g., J. Price, 1999

http://psych.colorado.edu/~tor
wagerlab.colorado.edu
Beyond pain: Clues from examining brain function across psychological states

neurosynth.org

Yarkoni et al., Nature Methods 2011
Ventromedial prefrontal cortex: Translating concepts into affective meaning

N=1152 studies

Roy, Shohamy, & Wager, TICS 2012
Placebo connections

• Example of conceptually generated modulation of affective responses

• Cortical-subcortical interactions affecting pain processing (and possibly other conditions) in profound ways

• Establishes connections between cognitive processes (valuation, memory, learning, decision-processes, ‘meaning’) and health-related outcomes.
towards better approaches:
fMRI-based Biomarkers
Towards better approaches: fMRI-based Biomarkers

fMRI activity can help determine whether placebo treatments affect pain...

...to the degree that brain patterns are biomarkers for pain

...also true for reward, emotion, perception, etc.

Biomarker: physiological process that is objectively measured as an indicator of normal or pathological responses.
The problem with current approaches

- These brain results are not biomarkers

- **Definition**: We do not agree on precisely what these patterns are (which voxels?)

- **Sensitivity**: We do not know how big the effects of our manipulations are. $P(\text{brain} \mid \text{psychological event})$?

- **Specificity**: We do not know if observed patterns are specific enough to be useful as biomarkers. $P(\text{brain} \mid \text{absence of psych})$?

- Thus, we do not know their diagnostic value.
  - $P(\text{psych} \mid \text{brain})$?
A new approach

- Identify precise patterns for testing in new datasets
- Characterize sensitivity and specificity
- Maximize sensitivity, specificity, interpretability, robustness
- Use biomarkers to understand mental phenomena
Machine learning: Key to specificity

- Machine learning oriented towards
  a) Optimizing prediction, b) assessing specificity across defined alternatives

Predicting the orientation of perceived lines

Kamitani & Tong, 2005

Predicting the semantic category of words, pictures

Mitchell et. al, 2008
Analysis framework

Multivariate approach: Multiple brain regions predict pain

Manipulation

Noxious input

Brain

Anterior cingulate

Thalamus

Anterior insula

Posterior insula/SII

Behavior

Pain reports

...etc.

- Many predictors (200,000!!)
- Use machine learning to stabilize maps
- Test generalization: Train on some subjects, test on others
A plan for developing fMRI-based biomarkers

- Standard diagnostic testing framework:
  - **Sensitivity**: High probability of activation during pain; more activity with greater pain report
  - **Specificity**: Low probability of activation in the absence of pain; *selective* activation

- Use available data within and across studies

---

Can fMRI reliably track subjective pain experience when cognitive biases are minimized?
Study 1: Predicting pain

- N = 20 healthy individuals
- Thermal pain on left arm
- 12 trials at each of 4 temperatures
- Warm, Low, Medium, High pain
- Standard GLM -> resp. to heat

Time during Trials

Anticipatory activity

Pain-related activity

Report-related activity
Study 1, Biomarker results predicting new individuals

Predicting pain: new individuals

Tests applied to new individuals:
- Forced-choice: Which is more painful?
- Hyperalgesia, allodynia

Threshold for display: $q < .05$ FDR (bootstrap)

Predicting pain: Single trials

Pain report

Predicted pain

$r = 0.74$
Study 2: Generalization

- N = 33 healthy individuals
- Thermal pain on left arm
- 72 trials across 6 temperatures
- Different scanner (3T Phillips)
- Standard GLM -> resp. to heat

Pain-related activity

<table>
<thead>
<tr>
<th></th>
<th>Heat</th>
<th>Rest</th>
<th>Pain yes/no, intensity</th>
<th>Rest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time during</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trials</td>
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<td></td>
<td>+</td>
<td>+</td>
<td>6 s</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>10 s</td>
<td>12-18 s</td>
<td>8-12 s</td>
<td></td>
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</tbody>
</table>
Results: Generalization to Study 2
Exact replication: No free parameters

Biomarker response by condition

- Pain vs. warm: 93% sensitivity/specificity
- 90+% sensitivity/specificity for 1 degree increments
- Tracks pain more closely than temperature
A plan for developing fMRI-based biomarkers

- Standard diagnostic testing framework:

- **Sensitivity**: High probability of activation during pain; more activity with greater pain report

- **Specificity**: Low probability of activation in the absence of pain; selective activation

Can fMRI patterns be specific for physical pain?

- Use available data within and across studies
Study 3: Social pain

N = 40 participants
All romantically rejected

Viewed pictures of ex-partners and friends
Painful and non-painful heat

<table>
<thead>
<tr>
<th>Fixation Cross</th>
<th>Ex-Partner (vs. Friend)</th>
<th>Rating</th>
<th>Visuospatial Control Task</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>15</td>
<td>5</td>
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Kross et al., 2011, PNAS
Rejection is very similar to physical pain

Regions activated in both [Hot vs. Warm] and [Reject – Friend] contrasts

Kross et al., 2011, PNAS
Pain-specific S2/dpINS activated by rejection

Red: Physical pain and emotional pain overlap
Blue: OP1 anatomical ROI (reported to be specific for pain vs. touch; Eickhoff, 2009)

\[ t(39) = .72, \ p = .48 \]

Kross et al., 2011, PNAS
S2 and dorsal posterior insula: Specific to pain

Mazzola et al., 2011. 4160 stimulations in 162 patients over 12 years.
Does the biomarker trained on Study 1 discriminate high vs. low pain in the Kross et al. experiment? Is it specific to physical pain?

**Test accuracy using biomarker from Study 1**

- Test Hot vs. Warm
- Test Reject vs. Friend

**Pain biomarker expression**

- High Pain
- Low Pain

**Biomarker response**

- Rejector
- Friend

http://psych.colorado.edu/~tor
Common regions, different patterns

Discrimination accuracy

Correlations in predictive patterns

Physical pain  Social pain

Test Hot vs. Warm
Test Reject vs. Friend
Additional biomarker validation

- **Treatment effects**
  - Responds to opiate drug

- **Transfer** across modalities
  - Shock
  - Mechanical pain

- **Specificity** – no response to:
  - Observed pain/“pain empathy”
  - Emotional images

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Full circle: Psychological modulation

Do psychological processes modulate pain at a neurobiologically “deep” level?
Study 2: Effects of reappraisal

- Also manipulated pain appraisal

- “Appraise-up:” imagine your skin is burning, sizzling, melting

- “Appraise-down:” imagine spreading warmth, like your skin is under a warm blanket on a cold day

![Graph showing pain rating against temperature](image)

![Bar chart showing relative effect sizes](image)
Cognitive reappraisal of pain

If yes: Appraisal may work at a “deep” level

If no: Appraisal mainly influences post-nociception judgment
Results: Does **reappraisal** influence PPBN? **No.**

* Reappraisal *does* have other effects; ask for details.
Example 2: Modulation by expectancy?

- Apply pain biomarker to expectancy dataset (Atlas et al., 2010)
- Robust effects of conditioned high- vs. low-pain cues on pain perception

\[
\text{Mediation: } p < .01 \text{ (bootstrap test, 10,000 samples)}
\]
Does biomarker response mediate the effects of cues on pain report?

Medium-temperature trials only

Biomarker Response

Low cue  High cue

< median pain  > median pain

Low cue  High cue
The ‘placebo brain:’ Vertical integration

- Nucleus accumbens/ventral striatum (NAC)
- Ventromedial prefrontal cortex (VMPFC)
- Periaqueductal gray (PAG)

e.g., Fields, 2004, NRN

http://wagerlab.colorado.edu
Multiple kinds of self-regulation: Different effects at different levels

e.g., Fields, 2004, NRN

Cognitive therapy
Cognitive reappraisal
Acceptance therapy
Music
Mindfulness
SSRIs
Catastrophizing
Anxiety
Conditioning
Meditation
Opiate drug treatment
Virtual reality
Anti-inflammatory treatments
Anxiolytics

PAG, PBN, NTS, Amy, VMPFC

http://wagerlab.colorado.edu
Implications

- Biomarker is sensitive and specific to physical pain across a range of tests and studies

- Biomarker response is influenced by some psychological manipulations (conditioned placebo), but not others (cognitive reappraisal)

  - *Manipulations have differential effects on “deep” modulation of affective systems vs. judgment/decision-making systems*

  - *Hope for disentangling nociceptive (affective) from evaluative systems*
Implications (2)

- Can compare drugs and psychological manipulations on the same (brain) outcomes

- Which psychological manipulations have “deep” effects?
  - Combined belief + experience works…cognitive goal does not.
  - Placebo as a learning process: Hope for understanding interactions between expectancies and learning
"I would rather know the person who has the disease than know the disease the person has."

– Hippocrates
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Analysis framework

Manipulation

Noxious input

Brain

Anterior cingulate

Thalamus

Anterior insula

Posterior insula/SII

...etc.

Behavior

Pain reports
Analysis framework

Typical brain mapping approach: Not really what we want…

Manipulation

- Noxious input
- Noxious input
- Noxious input
- Noxious input

Brain

- Anterior cingulate
- Thalamus
- Anterior insula
- Posterior insula/SII

Behavior

- Pain reports
- Pain reports
- Pain reports
- Pain reports

Temperature effects

Correlations with report

...etc.