

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

Tor D. Wager Department of Psychology and Neuroscience The University of Colorado, Boulder

http://psych.colorado.edu/~tor

• S.D.G.

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"

Hippocrates. Volume II: on decorum and the physician. London:William Heinemann, 1923.



"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



45%

...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?

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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



Science Times

The New Hork Eimes



Expanded

Placebos Prove So Powerful Even Experts Are Surprised

The Body Heals Itself Now studies show the placebo afficit at work from head to too in officerent collumes around the work

New Studies Explore the Brain's Triumph Over Reality

Placebo Effect Is More Myth Than Science, Study Says

By GINA KOLATA

In a new report that is being metwith a mixture of astonishment and sometimes disbelief, two Danish researchers say the placeboeffect is a myth.

The investigators analyzed 114 published studies involving about 7,500 patients with 40 different conditions. The report found no support for the continon notion that, in general about a third of natients true to num. "Maybe it is one of the urban legends of medicine." he sold

But others, like David Freedman, a statistician at the University of California, said he was not convinced. Professor Freedman said the <u>statistical</u> method the Danish researchers used, pooling data from many studies and using a statistical tool called metanniysis to examine them, could give books asserted that placebo effects were so powerful that, on average, 35 percent of patients would improve simply if they were told that a dummy treatment was real. The investigators began asking where this assessment came from. Every paper. Dr. Hrobjartsson said, seemed to refer to other papers. And those papers referred bim to other papers. He began peeling back the onion, finally...

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

Contributions of Neuroscience



- 1) <u>Mechanism</u>. What systems are involved? Where and how should we intervene?
- 2) <u>Intermediate markers</u>. How early? Which brain processes?

Preliminary intermediate markers for pain processing



e.g., Apkarian et al. 2005; Coghill et al. 1999, many others http://pwagerlab.colorado.edu

Placebo fMRI Study Procedures <u>Study 1</u>: Electric Shock, Right arm N = 24 in fMRI

<u>Study 2</u>: Thermal Pain, Left arm N = 22 in fMRI

fMRI trial design



Time during Trials

Placebo analgesia: fMRI setup



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

Reduced response to painful stimulation



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



Effects on potential descending modulatory systems





C6 ipsilat to stimulation

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





HM-LM: t(17) = 8.59, p<.0001

Atlas et al., J Neurosci 2010

Mediators of expectancy effects on pain Multi-level mediation

Lauren Atlas



Mediation: 3 signifiant effects:

- a: Effect of cue on brain
- b: Brain predicts behavior
- a*b: Mediation effect

Atlas et al., J Neurosci 2010



dACC Insula mThal

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

- Activity decreases
 Activity increases
- Consistent findings: At least three studies within 10 mm

Wager & Fields, in press, Textbook of Pain; Meissner et al., 2011,, J Neuro



connections

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Beyond pain: Ventromedial prefrontal cortex and affective meaning





Roy, Shohamy, & Wager 2012

"Systems for survival" Placebos engage a general system for affective appraisal





e.g., J. Price, 1999

Beyond pain: Clues from examining brain function across psychological states



In

neurosynth.org

Yarkoni et al., Nature Methods 2011

~ J

Ventromedial prefrontal cortex: Translating concepts into affective meaning



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 healthrelated outcomes.



towards better approaches: fMRI-based Biomarkers

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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.

Biomarker definitions working group, 2011

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(brain | psychological event)?
- Specificity: We do not know if observed patterns are specific enough to be useful as biomarkers. P(brain | absence of psych)?
- Thus, we do not know their diagnostic value.
 - P(psych | brain)?

A new approach



Machine learning: Key to specificity



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

Predicting the orientation of perceived lines



Figure 5 Orientation preference map on flattened cortical surface. The color maps depict the orientation preference of individual voxels on the flattened surface of left ventral V1 and V2 for subjects S2 and S3 (scale bar, 1 cm).

Kamitani & Tong, 2005

Predicting the semantic category of words, pictures

Predicting Human Brain Activity Associated with the Meanings of Nouns

Tom M. Mitchell,¹* Svetlana V. Shinkareva,² Andrew Carlson,¹ Kai-Min Chang,^{3,4} Vicente L. Malave,⁵ Robert A. Mason,³ Marcel Adam Just³

Mitchell et. al, 2008 3 wagerlab.colorado.edu³

Analysis framework



Multivariate approach: Multiple brain regions predict pain





• Standard diagnostic testing framework:

• Sensitivity pain; more activ



- Specificity: Low probability of activation in the absence of pain; selective activation
- Use available data within and across studies

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

Study 1, Biomarker results predicting new individuals



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



Results: Generalization to Study 2 Exact replication: No free parameters

- Pain vs. warm: 93% sensitivity/specificity
- 90+% sensitivity/specificity for 1 degree increments

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• Tracks pain more closely than temperature

- Standard diagnostic testing framework:
- Sensitivity: High probability of activation during pain; more activity with greater pain report
- Specificity absence of pair
 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

Ethan Kross

Kross et al., 2011, PNAS

Α

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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

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 wagenab.colorado.edu

Application to Study 3

Does the biomarker trained on Study 1 discriminate high vs. low pain the Kross et al. experiment? Is it specific to physical pain?

Common regions, different patterns

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

Atlas et al., 2012, J Neuro. Unpublished: collaboration with Jin Fan, Marina Lopez-Sola, Jesus Pujol, Etienne Vachon-Presseau, Pierre Rainville

- 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

Cognitive reappraisal of pain

Results: Does reappraisal influence PPBN?No.

* Reappraisal does have other effects; ask for detailstp://pwagerlab.colorado.edu

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
- Does pain biomarker response mediate effects of cues on pain report? Multilevel mediation on single-trial responses.

Does biomarker response mediate the effects of cues on pain report?

integration

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The 'placebo brain:' Vertical integration

e.g., Fields, 2004, NRN

Fronto-parietal systems

Ventromedial prefrontal cortex (VMPFC)

Nucleus accumbens/ventral striatum (NAC)

Periaqueductal gray (PAG)

Multiple kinds of self-regulation: Different effects at different levels

e.g., Fields, 2004, NRN

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/decisionmaking 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

The same sign to the same sign

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Apkarian, 2011

Analysis framework

Analysis framework

Typical brain mapping approach: Not really what we want...

