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# How Is Pain Influenced by Cognition? Neuroimaging Weighs In

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## Abstract

Neuroimaging can inform cognitive theories to the extent that particular patterns of brain activity are sensitively and specifically associated with particular types of cognitive processes. We illustrate the utility of neuroimaging data in one specific case: understanding cognitive influences on pain. We first argue that pain self-reports are often inadequate to fully characterize pain experience and the processes that underlie it. Then, we describe how neuroimaging measures have been used to corroborate the effects of psychological manipulations on pain by focusing on placebo treatments and demonstrating effects on the best available correlates of pain experience. In addition, using placebo analgesia as an example, we argue that brain evidence is useful for building psychological theories likely to yield valid and generalizable predictions, because biologically informed theories are grounded in the constraints inherent in the relevant physiological systems. Finally, we suggest that neuroimaging findings will become increasingly useful for constraining psychological inference as brain patterns diagnostic of particular types of mental events are identified and characterized. In our view, the relationships between biological findings and cognitive theory are empirically based and must develop through an iterative process of synthesis across studies, topics, and methods.

## Keywords

placebo, neuroimaging, pain, analgesia, fMRI

Imagine your grandmother is in the hospital being treated for injuries due to a fall. She's feeling quite shaken up, but when given a fentanyl drip she manages to say that it is helping to reduce the pain quite a bit. You would probably feel relieved—she's receiving medical care and the treatment is helping. But if her doctor told you that he has actually given her a placebo and it seems to be working, would you still feel confident that she is receiving adequate treatment?

If the answer to this question is “no,” you are caught in the paradox of pain. The paradox is this: Pain is a subjective experience, accessible only through patient report. Perhaps any intervention that reduces experienced pain should be considered a valid treatment. But pain reports have complex determinants. They are subject to biases related to (a) limited introspective access to the qualities of experience and their underlying causes (Ericsson & Simon, 1980), (b) cultural and interpersonal variations in attitudes about pain (Bates, Edwards, & Anderson, 1993; Tai-Seale, Bolin, Bao, & Street, 2011), (c) cognitive influences on judgment and decision-making processes (Tversky & Kahneman, 1981), and (d) social and economic influences on decision making (Allan & Siegel, 2002). Once one acknowledges that these factors may drive pain reports independent of the noxious event and cause

individuals to report more or less pain than they otherwise would, the use of pain report as the sole outcome measure seems insufficient. Compassionate care requires an attempt to differentiate effects on pain experience from effects on the social cognitive process of deciding what to report to a care provider.

## Neuroimaging Weighs In

To assess pain independent of self-report, one needs to be able to measure the hidden biological processes that cause and define pain. Although specialized sensory receptors register nociceptive input, the experience of pain is constructed in the brain. Thus, direct biological measures of brain function are likely to be particularly useful. Other autonomic and behavioral measures, including indices of autonomic responses (Donaldson et al., 2003), are useful in their own right, but in many cases they have an indirect relationship with pain

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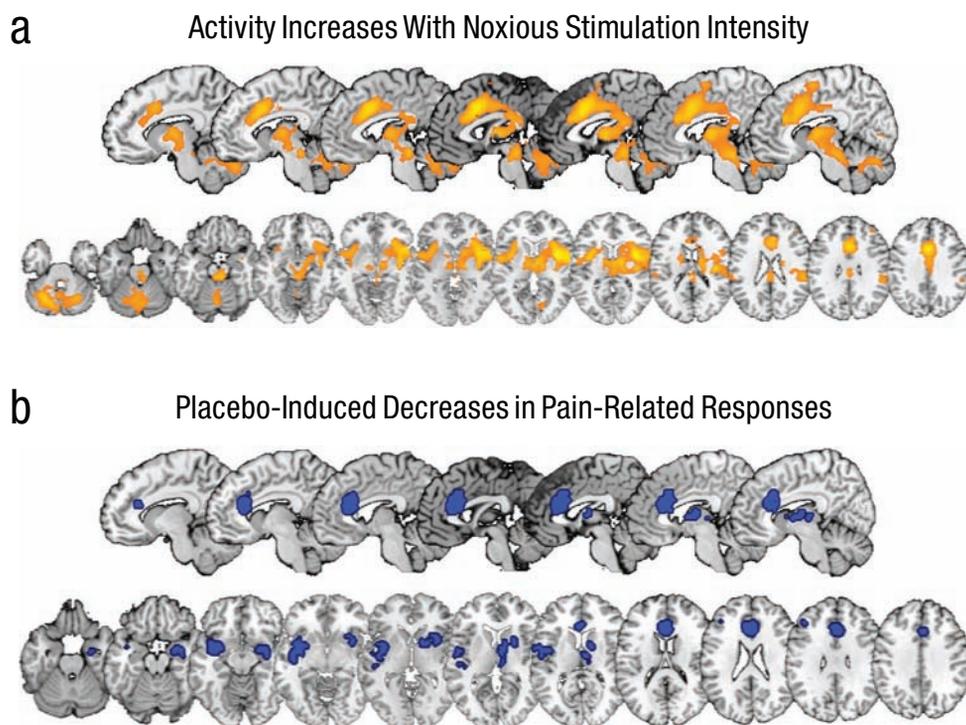
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experience (Brown, Chatterjee, Younger, & Mackey, 2011). In addition, direct measures of brain activity may predict future outcomes—such as aberrant plasticity that leads to sensitization and chronic pain—in a way that pain behaviors and other less direct measures do not.

One goal of neuroimaging research is to provide a biological marker of pain experience under normative conditions. Such markers are being actively developed and involve a distributed pattern of activity in specific parts of the insula, anterior cingulate, thalamus, and somatosensory cortices (Brown et al., 2011; Marquand et al., 2010; see Fig. 1A). Once such a marker is available, one can use it for *theory testing*—that is, one can ask whether the brain correlates of pain are influenced by placebo treatments and other types of cognitive manipulations that influence the context surrounding pain. As an example, the work we describe below provides tests of whether placebo treatments—which involve a mix of cognitive expectations, affective appraisals, and learning processes—can influence the best currently available biomarkers of pain experience in several neuroimaging modalities: functional magnetic

resonance imaging (fMRI), event-related potentials (ERPs), magnetoencephalography (MEG), and positron emission tomography (PET). Though our example centers on placebo effects, we use the more general term *cognition* in the title of this article because the concept of using neuroimaging for theory testing could equally apply to understanding any kind of psychological treatment that has traditionally not been considered on par with drug treatments for pain, such as distraction, acceptance, cognitive-behavioral therapy, and others.

In addition, neuroimaging can inform theories about pain and pain modulation in ways that go beyond using brain activity to corroborate pain experience. It can be used for theory building to constrain the space of possible theories about how placebos work at the psychological level and suggest new avenues for behavioral and psychological testing. For example, do placebo effects involve endogenous opioid release? Do they engage “descending control” systems involved in the inhibition of nociception at the spinal level? The answer to these biological questions have important implications for understanding what placebo effects are psychologically, their



**Fig. 1.** Placebo-induced reductions in target regions for pain processing in the brain. A: Regions activated by high-intensity or low-intensity painful heat across five samples in the Wager laboratory (combined  $N = 115$ ; adapted from Atlas, Bolger, Lindquist, & Wager, 2010). Activity evoked by painful events in these regions constitutes a preliminary biomarker for pain-related processing. Though different regions likely play different functional roles, activity in this network is generally highly intercorrelated during pain experience across diverse types of pain. Though activation in many of these gross anatomical regions is not specific to pain, the pattern of activity across regions is likely to be specific to somatic pain-related processes (e.g., Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011), and work is underway to identify patterns that are increasingly diagnostic of pain. B: Consensus regions in which placebo-induced reductions in pain-related activity has been found in at least three separate contrasts (most frequently from three separate studies, all reporting peak effects within 10 mm of one another; adapted from Meissner et al., 2011). In each panel, the top row shows sagittal slices from left ( $x = -9$ ) to right ( $x = 9$ ) in 3-mm increments. The bottom row shows axial slices from bottom ( $z = -30$ ) to top ( $z = 36$ ) in 6-mm increments.

time course and spatio-temporal specificity, how deeply they influence pain and its diverse effects on the brain and body, and the potential for mitigating the long-term sequelae of pain. Another type of theory building involves comparing treatments at the brain level that are difficult to directly compare in other ways. Are placebo effects identical to the effects of opiate drugs? Are they similar to other cognitive interventions that affect pain, such as distraction, perceived control, acceptance, or hypnosis? Understanding the biological similarities between treatments can provide clues about their psychological similarity at a deep level, whether they appear to be psychologically similar at first glance or not.

### Theory testing

Several authors have argued that placebo effects on pain reflect report biases and shifts in decision making (Feather, Chapman, & Fisher, 1972; Hrobjartsson & Gotzsche, 2004). Your ailing grandmother might report less pain on an intravenous placebo drip simply because she is now receiving medical attention or because she doesn't want to worry her family or seem ungrateful. If placebo treatments and related manipulations of expectations influence the best available biological correlates of pain experience, it is likely that they influence the sensory and affective aspects of pain rather than simply affecting decisions about pain experience.

We tested this hypothesis in two fMRI experiments (Wager et al., 2004) by first identifying a set of brain regions that responded to high or low-intensity noxious stimulation and then testing these areas for reductions in stimulus-evoked responses under placebo treatment—a skin cream coupled with instructions that the cream was a potent analgesic—as compared with a matched control that was physically identical but without the same instructions about efficacy. Placebo-induced reductions in brain activity were found in several pain-related regions, including the contralateral anterior insula, medial thalamus, and rostral dorsal cingulate. Since then, other fMRI studies have replicated these reductions in clinical samples (Price, Craggs, Verne, Perlstein, & Robinson, 2007) and healthy controls (Eippert, Bingel, et al., 2009; Lu et al., 2009), and some researchers have reported that these reductions are correlated with the magnitude of placebo analgesia (i.e., reductions in reported pain; Watson et al., 2009) and blocked by the opiate antagonist naloxone (Eippert, Bingel, et al., 2009). Finally, one recent study reported placebo-induced reduction of pain-related activity in the spinal cord (Eippert, Finsterbusch, Bingel, & Buchel, 2009), which would be difficult to explain other than by engagement of descending pain-modulation systems. Several meta-analyses have demonstrated convergence in the affected areas across studies (Amanzio, Benedetti, Porro, Palermo, & Cauda, 2011; Wager & Fields, in press; Fig. 1B).

ERP and MEG studies provide converging evidence that placebo treatments can influence nociception. Wager,

Matre, and Casey (2006) tested placebo effects on noxious laser-evoked potentials (LEPs) by focusing specifically on the N2/P2 complex, a midline potential sensitive to noxious stimulus intensity that occurs between 150 and 300 ms poststimulus. Placebo treatment reduced the P2 amplitude. Subsequent studies have replicated these effects (Aslaksen, Bystad, Vambheim, & Flaten, 2011; Colloca et al., 2008; Watson, El-Deredy, Vogt, & Jones, 2007) and found correlations between brain reductions and placebo analgesia (Colloca et al., 2008). At least one other study (Lorenz et al., 2005) has examined even earlier potentials thought to be localized to the second somatosensory area and/or the dorsal posterior insula, cortical regions with a relatively high degree of specificity to pain and touch (Kross, Berman, Mischel, Smith, & Wager, 2011). Lorenz et al. found expectancy-based modulation of MEG activity around 165 ms postnoxious laser stimulation, and dipole modeling localized the source of this activity to the second somatosensory area.

Collectively, these studies move beyond simple reliance on reported pain as the sole indicator of nociceptive processing and experience and demonstrate effects on relevant brain responses. Furthermore, they provide a foundation for more elaborated views of pain encoded in multiple brain regions and systems and potential modulatory mechanisms whereby placebo treatments can have their effects.

### Theory building

Tests of opioid system involvement in placebo analgesia can constrain theories about what outcomes placebos influence and how they work in a particularly powerful way. The opioid system is the best-known antipain system in the brain, and drugs that activate opioid receptors are the oldest and best-known analgesics in the modern pharmacopea. The opioid-rich periaqueductal gray (PAG) in the midbrain is a major driver of both opioid and nonopioid brainstem systems that can reduce or enhance pain based on central nervous system activity and, by extension, psychological context. Several pharmacological studies have suggested that placebo effects can be blocked by opioid receptor antagonists (Benedetti, Arduino, & Amanzio, 1999; Levine, Gordon, & Fields, 1978), but opioids may have pervasive effects on arousal and decision making, and it is unclear whether placebos engage opioid antipain systems specifically.

PET studies using the mu-opioid selective agonist carfentanil have shown that placebo treatment causes endogenous opioid activation in the PAG and other forebrain areas (Scott et al., 2008; Wager, Scott, & Zubieta, 2007). Paralleling these findings, placebo treatments increase fMRI activity in the PAG and other brainstem areas consistent with engagement of descending control systems (Bingel, Lorenz, Schoell, Weiller, & Buchel, 2006; Eippert, Bingel, et al., 2009; Wager et al., 2004). In addition, the opioid antagonist naloxone blocks other placebo-induced decreases in pain processing in the brain (Eippert, Bingel, et al., 2009). Together, these studies provide

new evidence that placebos engage opioid antipain systems and thus have meaningful effects on pain.

In addition to providing evidence on the clinical importance of placebo analgesia, these neuroimaging studies provide a plausible mechanism. Evidence on the biological mechanisms, in turn, places additional constraints on psychological theories and raises new questions. For example, anticipatory activity in prefrontal brain systems most closely associated with emotional appraisal in a meta-analysis of neuroimaging studies predicts placebo analgesia (Wager, Atlas, Leotti, & Rilling, 2011). However, the prefrontal cortex is heterogeneous; the prefrontal regions associated with cognitive control in the meta-analysis appear to be distinct (see Fig. 2) and do not predict placebo analgesia in this study. This suggests that placebo effects may be distinct from cognitive manipulations such as distraction.

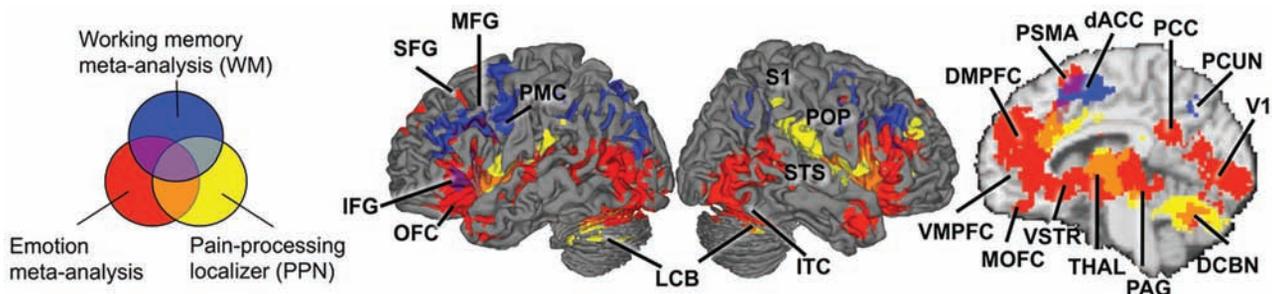
Behavioral studies can directly test these “brain-derived” ideas. One study (Buhle et al., 2012) compared distraction and placebo treatments by crossing a placebo treatment with a demanding secondary task (the N-back). Both relieved pain, but they had additive effects: Placebo effects were just as large when executive attention was consumed by task performance. These findings converge with other brain findings suggesting that they may depend on separate mechanisms. The additive behavioral results alone do not provide compelling evidence for separate mechanisms, but together the behavioral and brain results make a stronger case than either alone.

Another line of research on distraction provides an example of both theory testing and theory building. Sprenger et al. (2012) used fMRI to image the spinal cord during pain and found that, as with placebo, a distracting N-back task reduced spinal responses to painful events. This led them to ask

whether the opioid system was involved, and a second behavioral study demonstrated that naloxone selectively blocked distraction-induced reductions in reported pain.

A third example demonstrates that although placebo and opiate drugs interact with the endogenous opioid system, they do not work in exactly the same way. In a recent study (Atlas et al., 2012), we combined a placebo manipulation with administration of a potent opiate, remifentanyl, in an open-hidden design. Remifentanyl produced strong decreases in most pain-processing regions, with the strongest effects in the anterior cingulate (strongly associated with pain affect) and the weakest effects on somatosensory regions (S2/dorsal posterior insula). Expectancies, revealed by comparing open and hidden administration, instead activated lateral and ventromedial prefrontal cortices and reduced responses in amygdala and pain-processing thalamic and somatosensory regions. Overall, expectancies and opiates seemed to be clearly dissociable at the neurophysiological level. A second behavioral study demonstrated significant, additive effects of expectancies and opiates on pain, supporting the idea that they involve separable effects.

In these cases, information about the brain mechanisms informs models of what processes are involved and how they are interrelated and inspires further behavioral research. Together, these data provide the basis for an emerging model, in which (a) both placebo and distraction can produce deep effects on pain; (b) opioids are at least partially required for both placebo and distraction effects, and they reduce pain in a behavioral state-dependent manner rather than simply blocking sensation; and (c) opioid drug effects, distraction, and placebo involve dissociable cortical and subcortical generators, even if they have some common effects on pain, and can thus



**Fig. 2.** Meta- and mega-analytic maps of working memory, emotion, and physical pain, and their overlap (adapted from Wager, Atlas, Leotti, & Rilling, 2011). These are based on Wager and Smith’s (2003) meta-analysis on working memory and Wager et al.’s (2008) meta-analysis of emotion (2008), as well as a mega-analysis of thermal pain (Atlas, Bolger, Lindquist, & Wager, 2010). The analyses show nonoverlapping regions of the prefrontal cortex and posterior areas, demonstrating potentially reliable neuroanatomical differences across these types of processes. A very similar set of maps was used in Yarkoni, Poldrack, Nichols, Van Essen, and Wager (2011) to predict which of the three types of tasks individual participants performed (with ~80% classification accuracy overall). Only activity in regions within the emotion map predicted placebo analgesia. DCBN = deep cerebellar nuclei; DMPFC = dorsomedial prefrontal cortex, dACC = dorsal anterior cingulate cortex, IFG = inferior frontal gyrus, MFG = middle frontal gyrus, SFG = superior frontal gyrus, ITC = inferior temporal cortex, LCB = lateral cerebellum, MOFC = medial orbitofrontal cortex, OFC = orbitofrontal cortex, PAG = periaqueductal gray, PCC = posterior cingulate, PCUN = precuneus, PMC = premotor cortex, POP = parietal operculum (covering S2 and dorsal posterior insula), PSMA = presupplementary motor cortex, STS = superior temporal sulcus, S1 = primary somatosensory area, THAL = thalamus, V1 = primary visual cortex, VMPFC = ventromedial prefrontal cortex, VSTR = ventral striatum.

be used side-by-side to regulate pain. It is difficult to imagine how such a rich model could be developed based on behavior alone.

More broadly, the brain evidence provides a grounding in physiology that complements and constrains psychological theory. And psychological theory, so constrained, has increased potential for valid predictions about untested cases and generalization to new contexts.

### **The Japanese sword**

What we have described so far is a sort of “Cognitive Neuroscience 1.0” use of neuroimaging data to test and build theories about pain. Critically, our ability to use brain activity patterns to test psychological theories depends on the specificity and sensitivity of brain responses to particular categories of psychological events. Such patterns could be considered biomarkers—physiological processes that are objectively measured as indicators of normal or pathological responses (Atkinson et al., 2001). The arguments for placebo influences on pain experience rely on identifying brain regions thought to reflect nociception or, more generally, pain processing. The use of brain activity to corroborate pain is similar to the use of activity in early visual cortex as a biomarker for the presence or modulation of visual perception (Kastner, De Weerd, Desimone, & Ungerleider, 1998; Kosslyn et al., 1993).

Often, such reverse inferences about psychological processes from brain activity are unwarranted (Poldrack, 2006; Sarter, Berntson, & Cacioppo, 1996). However, new techniques can increase precision in our understanding of the relationship between brain and behavior and can facilitate the development of brain biomarkers for psychological processes. A major new direction in the field is the use of quantitative procedures to assess the sensitivity and specificity of particular brain patterns for diagnosing particular classes of psychological processes and identify precise patterns of brain activity and connectivity designed to maximize sensitivity and specificity (e.g., Poldrack, Halchenko, & Hanson, 2009). The development of increasingly well-validated biomarkers for pain and other types of processes will provide increasingly precise and meaningful tests of psychological theories.

Establishing specificity is critical for psychologically useful biomarkers, and one way of establishing it is by using meta-analysis to aggregate findings across hundreds or thousands of studies (Yarkoni, Poldrack, Van Essen, & Wager, 2010). For example, we recently trained a classification algorithm to discriminate studies of pain, emotion, and working memory in a meta-analytic database. The algorithm identified maps very similar to those in Figure 2. Comparing new individual participants’ activity maps to the meta-analysis derived ones allowed us to predict which of the three task types was being performed or experienced with ~76% sensitivity and 88% specificity overall (Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). Once validated in this way, those patterns can be tested for effects in other tasks, and the more

sensitive and specific the pattern to one type of task, the more informative the test.

Other new techniques can also provide increasingly specific links between brain and behavior. One promising approach is mediation analysis, which can establish empirical relationships between experimental manipulations, brain activity, and behavior and thus can identify brain circuits likely to be involved in specific psychological processes. For example, a recent experiment (Atlas, Bolger, Lindquist, & Wager, 2010) used auditory cues to signal high or low levels of upcoming pain and found that the cues strongly colored pain perception toward the expected intensity. Pain-responsive portions of the anterior cingulate, insula, and thalamus increased during pain in response to high-pain cues. In addition, they mediated the relationship between cues and pain report, implying that they explained part of the effect of expectations on pain. These results showed close convergence with the placebo studies, but they go beyond them by linking cue effects and predictions of behavior in the same brain regions.

We envision the forging of validated links between neuroimaging activity, psychological processes, and behavior as an iterative process, with biomarkers designed to discriminate among specific types of processes (e.g., pain vs. negative emotion vs. touch) being developed and improved as more data becomes available and theories are refined. Just as the construction of the samurai swords of feudal Japan involved folding and reforging the molten metal hundreds of times, the construction of psychologically useful brain biomarkers will involve a cycle of refining the target brain patterns of interest and subsequently using them to probe the effects of placebo treatment and other psychological manipulations.

### **Conclusions**

In our view, behavioral research alone has not produced an adequate theory of what pain is, what its components are, how those components interact, and how various cognitive and affective processes influence those components. Likewise, there is no adequate psychological theory about how the various treatments that can modulate pain (expectancy, attention, hypnosis, acceptance, etc.) are related to one another and whether they influence the ingredients of pain in similar ways. Neuroimaging has been used to validate the notion that placebos and other cognitive interventions can produce real changes in pain processing and that holistic treatments that focus on patient expectations and well-being may be truly beneficial. In addition, neuroimaging has provided direct evidence for the involvement of endogenous antinociceptive systems (particularly the opioid system), which constrains psychological thinking about what placebo effects are, what processes they should affect, and when they should affect them. Finally, however, the use of brain activity to constrain psychological theory is seldom achieved in a single study—instead, there must be an iterative process of accumulating evidence across many studies and multiple methods.

## Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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