Pain and the Placebo

what we have learned

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ABSTRACT Despite the recent blossoming of rigorous research into placebo mechanisms and the long-standing use of placebos in clinical trials, there remains widespread and profound misunderstanding of the placebo response among both practicing physicians and clinical researchers. This review identifies and clarifies areas of current confusion about the placebo response (including whether it exists at all), describes its phenomenology, and outlines recent advances in our knowledge of its underlying psychological and neural mechanisms. The focus of the review is the placebo analgesic response rather than placebo responses in general, because much of the best established clinical and experimental work to date has been done on this type of placebo response. In addition, this subfield of placebo research offers a specific neural circuit hypothesis capable of being integrated with equally rigorous experimental work on the psychological (including social psychological) and clinical levels. In this sense, placebo analgesia research bears all the marks of a genuine multilevel interdisciplinary research paradigm in the making, one that could serve as a model for research into other kinds of placebo responses, as well as into other kinds of mind-body responses.

OVER THE PAST TWO DECADES, the placebo effect has been transformed from a nuisance factor in the setting of clinical research to a type of poster child for the emerging research field of mind-body medicine. As such, it has provided

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compelling evidence of the contributions made by psychological, neural, and social factors to health and healing. This appropriate elevation in status, however, has been accompanied by a certain amount of hyperbole and romanticizing—hyperbole that has in turn provoked renewed skepticism and censure, equally ill-founded.

Thus in 2000, the Sunday *New York Times Magazine* announced in a cover article that "the powerful placebo" had come of age, and suggested that medicine should make regular use of it (Talbot 2000). This piece prompted a spate of enthusiastic copycat articles on the same theme. A year later, however, the *New England Journal of Medicine* published an article that suggested that the placebo in fact might be "powerless" (Hrobjartsson and Gotzsche 2001). That article in turn prompted a wave of new editorializing in the media that now questioned the very existence of a placebo effect (Goodman 2001; Grossman 2001; Henderson 2001; *New York Times* 2001; *Statesman* 2001; Trafford 2001).

In light of such developments, one could be forgiven for supposing that very little must be known about the placebo effect: whether it is powerful or relatively powerless, how it works, when it works, and so on. That impression, however, would be mistaken. In fact, significant progress has already been made in laying down foundational knowledge about this important phenomenon. This progress is most evident in the area of pain research. There are at least three reasons for this: (1) clinically, placebo-induced pain reduction is probably the best verified instance of this general response; (2) methodologically, the most elegant experimental work on the placebo response has used pain reduction as its paradigm; and (3) conceptually, we have more insight into the brain mechanisms underlying placebo analgesia than we have for any other placebo response.[1]

Pain is not the only, or indeed necessarily the most interesting, arena in which to study placebo responses. However, if we want to take stock of what is currently reliably known about the placebo response, then we must begin with a review of the literature on placebo analgesia. By beginning here, moreover, we can clarify what may be required methodologically to study the placebo response well and how these same rigorous approaches can be applied more consistently beyond the area of pain research.

[1]An anonymous reviewer of an earlier draft of this paper noted that there is one methodological disadvantage to using pain as a model for studying the placebo effect, namely, that pain is typically evaluated subjectively and therefore might be perceived as a less exacting outcome measure than physiological measures that can be recorded objectively. That said, scales measuring changes in pain intensity have been shown to be highly reliable. There also exists at least one objective correlate of change in pain intensity—respiratory depression—that has been used to good experimental effect; it is discussed later in this paper.

The Placebo Effect versus the Placebo Response: A Plea for Clear Terminology

Much of the literature speaks indiscriminately about placebo effects and placebo responses as if they were the same thing. Building on previously published work by Levine and others, we aim to draw what we believe to be a useful distinction between the two terms (Fields and Levine 1981; Levine et al. 1978, 1979, 1981). The term "placebo effect" will be used to refer to any average improvement in the condition of a *group of subjects* that has received a placebo treatment. It is an inference based on the assumption that, had the placebo not been given, no such improvement would have been observed. In contrast, "placebo response" refers to the change *in an individual* caused by a placebo manipulation. Clearly, it is the placebo response—its psychology and neurobiology—that is most interesting to researchers today.

Things Mistaken for the Placebo Response

To learn more about the placebo response, many researchers have turned to the clinical trials literature. It is important to remember, however, that the focus of the clinical trial is not on placebos and how they work, but rather on how the active ingredient being tested contributes to the overall treatment outcome. Often, researchers find significant degrees of improvement in both placebo and "active" treatment groups. It is then said that there is a significant *placebo effect* for the intervention in question. However, findings like these actually tell us little or nothing definite about the magnitude of the *placebo response*. This is because clinical trials that simply compare treatment outcomes in a placebo group to those in an active treatment group are methodologically incapable of determining to what extent a given change is due to one of three well-established phenomena: true placebo responses, natural history, and the phenomenon of regression to the mean. Let us clarify what is meant by each of the other two effects—effects frequently mistaken for a true placebo response.

Natural History

If a person has a classic idiopathic headache, the pain typically peaks and then eventually subsides in the absence of any treatment manipulation. This "spontaneous" temporal course is known as the "natural history" of the headache. If a person with a headache of this sort were to take medication (including placebo medication) close to the time when his or her discomfort reaches its peak, he or she may well experience relief soon afterwards. But given what we know about the natural history of his or her headache, we might conclude that some or all of the decline in pain intensity was likely to have occurred in the absence of any manipulation and therefore cannot be reliably attributed to the placebo intervention (Figure 1, top curve).

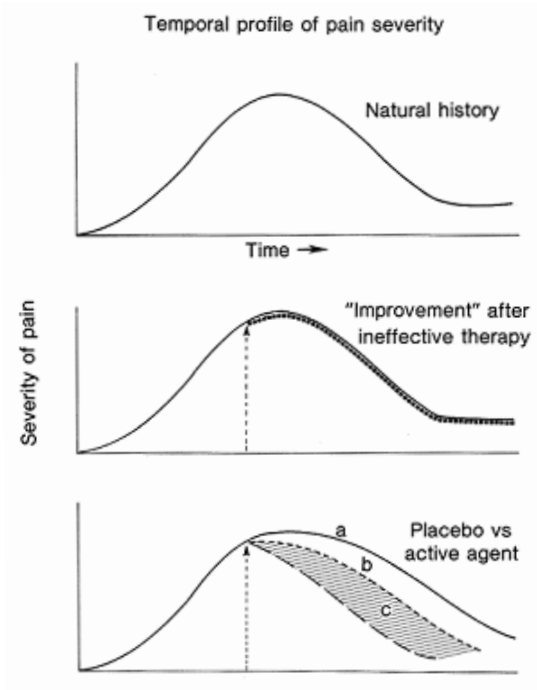

FIGURE 1

*Natural history and the placebo effect. Many painful conditions may be associated in spontaneous relapses and remissions in the absence of any treatment manipulation (top panel). In such cases, a wholly ineffective therapy will be followed by improvement (middle panel), and such improvement may mistakenly be attributed to the therapy. To demonstrate a placebo effect (lower panel) one must show a difference between the natural history (*a*) and the placebo (*b*). If there is a further improvement following a specific therapy, such as the administration of active medication (*c*), this can be attributed to a specific active component in the therapy.*

Regression to the Mean

In most clinical conditions and some experimental settings, individuals typically show "spontaneous" fluctuations in pain levels, and those levels tend on average toward a mean. Assuming that individuals tend to receive their initial clinical assessment (or enter treatment trials) when their pain is at or near its greatest intensity, then the statistical phenomenon of regression to the mean predicts that their pain level is likely to be lower when they return for a second pain assessment. Obviously, however, this improvement cannot reliably be attributed to any intervention they might have undergone (Whitney and Von Korff 1992). Thus, in clinical practice and in unblinded, uncontrolled trials, the so-called "success rate" reported may be due to one or more of the following: the specific efficacy of the treatment, the placebo manipulation, the natural history of the disorder in question, or regression to the mean (Figure 2).

The only reliable way within the framework of a clinical trial to see what proportion of an observed improvement might actually be attributable to the

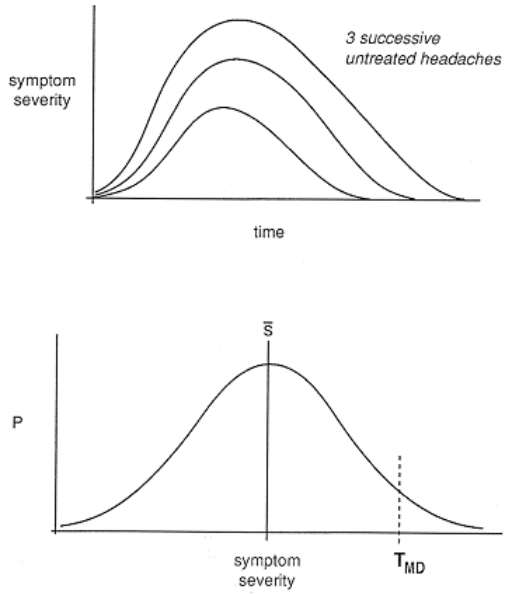

Figure 2

The concept of regression to the mean. This phenomenon also assumes a relapsing remitting course with wide variability in peak pain intensity, such as is observed with idiopathic headache (top). Peak severity (p, lower trace) varies around a mean (s̄). Only the most severe headaches (those with severity above T_{MD}) prompt medical attention. In this case, subsequent headaches will tend to have a lower severity.

placebo manipulation is to compare a group of patients receiving a placebo to a group that has received no treatment (vida infra). In fact, in their meta-analysis of clinical trials that had included so-called "no-treatment" groups, Hrobjartsson and Gotzsche (2001) concluded that there often was little difference between improvement levels in the placebo group and those in the no-treatment group. The one notable exception they made was for trials involving pain treatment. While this study has been criticized on methodological grounds (Kirsch 2002; *New England Journal of Medicine* 2001), the fact remains that as a matter of methodological principle, studies of the placebo effect (group effects) that lack a no-treatment control are as apt to mislead as to illuminate.

At the same time, introducing a no-treatment control condition into a clinical trial design is not without problems of its own. The major drawback is that it reintroduces the possibility of subject and observer reporting bias. The classical clinical trial (which rarely includes no-treatment controls) addresses the problem of observer and reporting bias and controls for it through the use of double-blind methods. Even though questions have been repeatedly raised about the actual ability of both patients and researchers to "guess" which group is which in a double-blind trial (Margraf et al. 1991; Ney, Collins, and Spensor 1986), there is patently no way for both patients and researchers to be ignorant

of which is the no-treatment group. In addition, a patient's perception of what it means to be in the "untreated" group may in turn bias how he or she reports changes in his or her condition.

EXPERIMENTAL STUDIES OF PLACEBO ANALGESIA: A SIGNIFICANT EFFECT

Fortunately, clinical trials are not the only methodology available to this field. In recent decades, laboratory studies have been able to circumvent many of the stumbling blocks one encounters in the clinical trial format and have provided important and reliable data about placebo responses (Amanzio and Benedetti 1999; Amanzio et al. 2001; Benedetti 1996; Benedetti, Arduino, and Amanzio 1999; Petrovic et al. 2002). Experimental studies typically use either a standard surgical procedure (often dental) or experimenter-induced pain (e.g., the cutaneous injection of capsaicin or restriction of blood flow in one arm while the subject repeatedly contracts his forearm muscles). The advantage of investigator-induced pain is that it can be experimentally controlled by the investigator and has a highly reproducible time course.

The placebo manipulation is typically initiated by telling the subject that he will receive a "powerful painkiller" through (for example) a solution administered via a previously placed intravenous line or through application of a topical cream rubbed onto the skin at the source of the pain. In both scenarios, however, neither the intravenous solution nor the cream contains any active analgesic ingredients. In some (arguably better designed) experiments, a separate randomly assigned group of subjects does receive an active analgesic drug (e.g., morphine). The inclusion of such an active treatment group allows the investigator to state in the consent form that one of the treatments the subject will receive may be a powerful painkiller. It also ensures that both the experimenter and the subject are blind as to the actual nature of the infusion.

The best designed placebo studies make use of an experimental no-treatment group. The no-treatment group undergoes the pain challenge while receiving no treatment manipulation and no suggestion that a treatment for pain has been surreptitiously administered. It is assumed that this no-treatment group will reveal the probable time course of pain in the absence of a placebo manipulation. The difference between this and the time course of pain in the placebo group is the placebo analgesic effect.

Using standard psychophysical pain rating scales (such as the visual analog scale or the numerical rating scale), or a behavioral measure (e.g., pain tolerance time or the amount of analgesic medication requested), individuals receiving a placebo treatment typically experience a significantly greater reduction in pain than those in a no-treatment group (Amanzio and Benedetti 1999; Benedetti 1996; Benedetti, Amanzio, and Maggi 1995; Benedetti, Arduino, and Amanzio 1999; Benedetti et al. 1998, 1999; Gracely et al. 1983; Levine and Gordon 1984;

Levine et al. 1979; Pollo et al. 2001). The results are similar across studies looking at moderate to severe pain, in dental postoperative pain and post-thoracotomy pain, and in experimental capsaicin-induced and ischemic arm pain.

Still, subjective and behavioral rating scales are what they are; they do not wholly eliminate concerns about reporting biases. Two studies have recently pushed the methodological boundaries of placebo research further by using changes in respiratory rate as an indirect objective measure of placebo-induced analgesia. Mild respiratory depression is a typical physiological concomitant of an opioid-mediated analgesic response, but at a level that is generally not discernible to subjects. Nevertheless, when subjects in two studies were given an open administration of saline along with the "information" that it was an analgesic drug with which they had experience, they exhibited respiratory depression relative to a no-treatment group (Benedetti et al. 1998, 1999). Although subjects were aware that their respiration was being monitored, they presumably did not know that the investigators were interested in their respiratory rate rather than their pain levels, and they almost certainly did not know what was "supposed" to happen to their respiration.

A further innovation that addresses the issue of subject reporting bias is the surreptitious use of drugs that either enhance or block placebo-induced analgesia. The elegant experimental work that has made use of these methods will be described later.

Looking at Individuals: Responders and Non-Responders

Since the earliest clinical observations, it has always been assumed that there are placebo responders and non-responders, and that responders represent a minority of all individuals. In many clinical studies, however, the assumption has been based on a comparison of group averages. This point is important because identical differences between groups might be seen if either (1) all individuals in the placebo group exhibit a moderate response, or (2) a relatively small subset of individuals in that group exhibit a large magnitude response. In the second scenario, it is plausible to think that some individuals in the placebo group might have experienced no response at all (Benedetti 1996; Levine et al. 1979).

At the moment, the second scenario seems to be the correct one. In laboratory studies where it has been possible to determine the distribution of individual responses, mean placebo effects tend to be a product *not* of modest responses in all the individuals in the group, but of relatively large responses within a *subset* of individuals in that group. In every placebo group, there tends also to be a subset of individuals who show no evident response to the placebo manipulation—in other words, they fare no better on average than individuals in the no-treatment group (Benedetti 1996; Levine et al. 1979). From a research standpoint, it is critical for investigators to be able to identify those individuals who

are actually responding to a placebo manipulation. This is because it is at the individual response level that we are most able to gain insights into the possible psychological and neural mechanisms of placebo-induced analgesia.

Probability of Response

Given that not all individuals respond to a placebo, do we have any sense of the typical proportion of those who do? Unfortunately, Beecher's (1955) widely cited survey of clinical analgesic trials, from which he concluded that an average of 30% of patients respond to placebo treatments for pain, is impossible to interpret because none of the studies he referenced were controlled by a no-treatment group. Fortunately, since Beecher, others have returned to the question with the following results: Levine et al. (1979), using a no-treatment control in a dental postoperative pain model, found that 39% of patients had an analgesic response to placebo treatment (their pain either decreased or increased by less than 0.2 cm on a 10 cm visual analog scale, as measured against the controls who experienced steadily increasing pain). In a study of normal volunteers using ischemic arm pain, Benedetti (1996) found that 27% of the subjects responded to a placebo analgesic, as compared to a large no-treatment control group in which there were no responders at all (a "responder" was here defined as a subject with a pain rating lower than 7 on a scale of 0 to 10).

Another study involving cutaneous heating of the left hand found that 56% of subjects responded to the placebo treatment, as compared to the no-treatment controls, who experienced a 10% or less decrease in pain (Petrovic et al. 2002). It is important to realize that these data do not allow us to conclude that responsivity to a placebo intervention is a fixed personality trait. On the contrary, subjects who reliably respond to a placebo intervention in one kind of trial or setting might fail to respond in another. The fact that we see such variation in the percentages of responders across different studies further underscores the need for more research designed to tease out the contextual and other factors that affect the likelihood of a response.

Magnitude of Response

Historically, questions about the magnitude of response to placebos have been addressed using group comparisons. Using this approach, several studies have found that the mean magnitude of the placebo analgesic effect across all individuals is 2 out of 10 units on a visual analog scale or numerical rating scale (Benedetti, Amanzio, and Maggi 1995; Benedetti et al. 1998; Gracely et al. 1983; Levine and Gordon 1984). Using subcutaneous injection of capsaicin to induce pain, Benedetti, Arduino, and Amanzio (1999) found that application of a placebo cream caused a mean reduction of ~46% to ~57% in pain, compared to no treatment. In another study using ischemic arm pain, intravenous saline infusion caused an average increase of 3.5 minutes in the duration of pain tolerated compared to a no-treatment group (Amanzio and Benedetti 1999).

If not everyone responds to a placebo manipulation, what is the magnitude of pain relief that placebo analgesic manipulations can produce in that subset of individuals who *do* respond? Benedetti (1996) addressed this issue by looking only at responders, and found an average placebo effect magnitude of 5 units on the 10 unit numerical rating scale. This is similar to the data reported by Levine et al. (1981), using a dental post-operative pain model. Here an approximately 3.3 cm (out of 10) lower mean post-treatment visual analog scale score for placebo responders was found compared to non-responders. This study did not have a no-treatment comparison group, but subsequent work using the same pain model indicated that the placebo non-responder group had pain levels identical to a no-treatment group (Levine et al. 1979).

When a group of subjects given morphine is compared to one given placebo, morphine is superior to placebo (Amanzio and Benedetti 1999). Nevertheless, the interpretation of this finding (not itself surprising) remains unclear. The average response to morphine might be greater than that to placebo in trials because more people in a group on average have a response to morphine than they do to placebo; it might be greater because morphine produces a greater analgesic response in some individuals; or it might be both. This question has not been systematically addressed; however, one study found that the magnitude of individual analgesic responses to a placebo manipulation actually were remarkably similar to those seen in response to morphine (Levine et al. 1981).

Type and Severity of Pain

It is commonly assumed that placebo analgesics will be more apt to work on mild pain than severe pain. The experimental evidence, however, suggests just the opposite. Levine et al. (1979) found a highly significant positive correlation between severity of pre-treatment levels of post-operative pain and the likelihood of a placebo response for post-operative pain. Numerous other studies have shown that placebo manipulations have a significant effect on severe clinical pain, including dental postoperative and thoracotomy pain (Benedetti, Amanzio, and Maggi 1995; Benedetti et al. 1998; Gracely et al. 1983). These pains are likely more severe and threatening than those experienced by subjects in the more controlled setting of the laboratory. The full significance of these findings remains unclear. It could be that placebos simply work more effectively on severe than on mild pain. Alternatively, it is possible that the stress of severe pain is an independent factor enhancing placebo analgesic responses.

Psychological Mechanisms Involved in Placebo-Induced Analgesia

Given that the placebo analgesic response is robust, what has been learned about the underlying psychological processes? Early work focused on the possibility that there are stable personality traits—suggestibility, acquiescence, anxiety, hypnotiz-

ability—that distinguished a placebo responder from a non-responder. The results were rarely consistent from study to study, and, in any event, most did not include a natural history control group, and so could not reliably identify individual responders (Harrington 1997). One recent study that did use such a control group found a positive correlation between "suggestibility" and the magnitude of placebo analgesia (De Pascalis, Chiaradia, and Carotenuto 2002). However, more nuanced work is needed to determine whether "personality" is a variable worth resurrecting in this area.

The primary focus of work on the psychology of placebo analgesia has been framed within a larger debate on the relative roles played by prior classical conditioning versus conscious expectancy in the moment. Advocates of the classical conditioning model claim that placebo responses arise after an individual is repeatedly exposed to pairings of neutral sensory cues (the shape of a pill, the environment of a doctor's office) with effective treatment manipulations (such as morphine). This model asks no questions about the subject's awareness and, indeed, was first developed in animal work carried out within a strictly behaviorist paradigm (Herrnstein 1962). Instead, it is supposed that, after a sufficient number of such pairings, the sensory cues alone (now the "placebo" manipulation) automatically elicit an analgesic response (Ader 1997). In contrast, those who emphasize the importance of expectancy hold that conscious expectation of improvement—reportable "anticipations of automatic reactions to particular situational cues" (Kirsch 1999)—is required for placebo responses to occur (Kirsch 1997).

While a sense of rivalry prevails in the literature between these two perspectives on the psychology of placebo responses, it is important to realize that they actually are not mutually exclusive. Some researchers (e.g., Rescorla 1988) have even theorized that classical conditioning may function *via* the mediating mechanism of expectancy—by altering expectancies of the individual. While that perspective remains controversial, most who have studied the matter agree that both conditioning and expectancy can contribute to the eliciting of an analgesic response, and, when used in concert, that the two processes amplify each other (Amanzio and Benedetti 1999; Benedetti et al. 2003; De Pascalis, Chiaradia, and Carotenuto 2002; Montgomery and Kirsch 1997; Price et al. 1999; Voudouris, Peck, and Coleman 1990).

A study by Amanzio and Benedetti (1999) illustrated this interaction. In this study, one group received "expectation alone" (a saline infusion with the verbal communication that it was a powerful painkiller); a second received "conditioning alone" (two days of conditioning trials in which morphine was paired with a saline infusion that the subjects believed was an antibiotic designed to "clean their blood"); a third group received "conditioning plus expectation." As compared to a fourth, no-treatment group, the "expectation alone" and the "conditioning alone" group each had small but significant increases in pain tolerance. However, the group that received both conditioning and expectation had an increase in pain tolerance double that of the other two groups.

That said, when expectation and conditioning pull in opposite directions, available evidence suggests that expectancy is the more powerful factor. In an elegant study, Montgomery and Kirsch (1997) surreptitiously lowered the intensity of an initially painful electrical cutaneous stimulus in a group of normal volunteers after administering an inert placebo cream (which the subjects were told was an analgesic) to the area of stimulation. After a few of these pairings, the placebo cream elicited an analgesic response when the electrical stimulation was applied at its original intensity. The subjects were then divided into two subgroups. One of these was informed of the subterfuge and the other was not. In the next trial, the individuals who had been debriefed had lost their analgesic response to the placebo cream. The others did not. The conditioning model of placebo analgesia predicts that changes in conscious expectation should have little effect on conditional responses—and yet, evidently they do.

While the current controversies over the relative roles of expectancy versus conditioning have been useful, they have also had a narrowing effect on thinking and work in this area. There is much that we still do not know and should be investigating. For example, we know little about the extent to which the conscious expectancies created by verbal suggestion may interact with expectancies generated from other kinds of environmental cues. Questions about the possibility of unconscious expectancy remain unresolved, as do questions about the role played by different levels of motivation in generating placebo responses. The effort to conceptualize the phenomenology of the placebo effect within the context of thinking about its possible biological (evolutionary) function is also in the very early stages (Humphrey 2002). Finally, promising work remains to be done on the more implicit expectancies generated through social modeling and long-term socialization into the belief systems of one's culture, especially those concerned with understandings of efficacy and power in healing (Moerman 2002).

Neural Mechanisms Underlying Placebo-Induced Analgesia

In 1975, Hughes et al.(1975) discovered that the brain synthesizes endogenous opioid peptides that act at the same receptor site as powerful exogenous opioid analgesics like morphine. These opioid peptides and the receptor that mediates their action are distributed at discrete sites in the brain that are known to underlie the analgesic action of morphine (Fields and Basbaum 1999). These sites are thus part of a pain-modulating network that depends upon release of endogenous opioids for its normal function (Figure 3). This knowledge has been exploited to address the neural circuitry that mediates the placebo analgesic response.

Strategy 1: Naloxone

The first approach takes its starting point from the hypothesis that the placebo response depends upon the activation of the above-described opioid-mediated

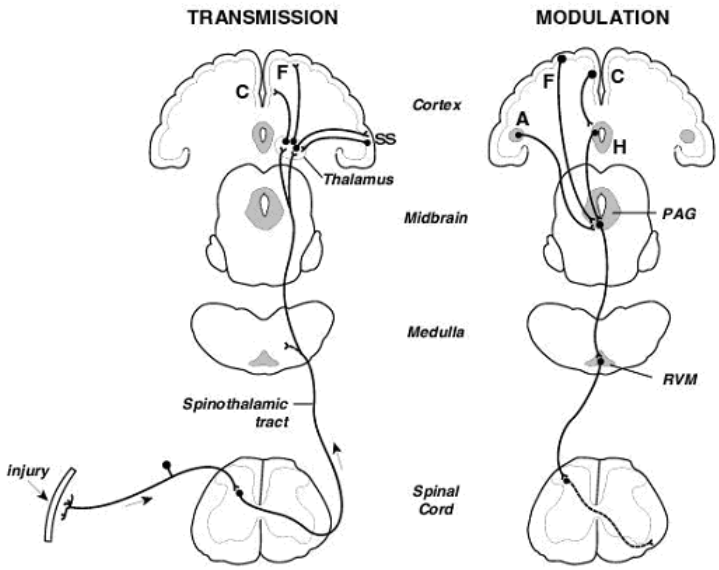

FIGURE 3

*Pain transmission and modulatory pathways. Tissue injury initiates activity in pain receptors that is transmitted to the central nervous system and via the spinothalamic pathway to thalamus and cortical targets (*C, *anterior cingulated;* F, *frontal insular; and* SS, *somatosensory). A distinct top-down pain modulatory system arises in frontal and anterior cingulate cortex and limbic structures such as the amygdala and hypothalamus. It connects via brainstem structures—midbrain periaqueductal gray (*PAG*) and rostral ventromedial medulla (*RVM*)—to directly control the pain transmission system. The modulatory system has high concentrations of endogenous opioid peptides and opioid receptors.*

pain modulatory system (Levine, Gordon, and Fields 1978), and involves administering naloxone, an opioid receptor antagonist. The question is whether it also blocks placebo-triggered analgesia. Methodologically, it is critical to the interpretation of this type of experiment that subjects are unaware that they are receiving naloxone. Thus, in these experiments, subjects are given the drug covertly through an intravenous line already in place.

When this has been done, the placebo analgesic response is, in fact, blocked by naloxone. Levine and colleagues (1978) first demonstrated this using the dental postoperative pain model and a visual analog scale for pain magnitude, and naloxone reduction of placebo analgesia has since been confirmed using other pain models and methods of assessment (Amanzio and Benedetti 1999; Amanzio et al. 2001; Benedetti 1996; Benedetti, Arduino, and Amanzio 1999). Later studies confirmed the specificity and selectivity for placebo analgesia of the naloxone blocking effect by showing that, even as naloxone blocks or reverses placebo-induced analgesia, there is no enhancement of pain when naloxone is administered to a no-treatment group. Supporting the naloxone reversal studies is the evidence that placebo analgesic responsiveness correlates with an increase in the spinal fluid concentration of an endogenous opioid peptide (Lipman et al. 1990).

Such studies implicating endogenous opioid release have been of immense importance in changing how people think about and study the placebo effect. First, the fact that naloxone can be given in a double-blind manner has helped the field address the difficult issue of subject bias in a powerful way. Second, because this work has framed questions about the placebo effect in terms of a specific mechanistic hypothesis, it has helped locate placebo research more generally—and for the first time—within the field of neuroscience and biomedicine. For those who might previously have insisted that this phenomenon could never be more than a nuisance factor in modern medical research, the counterproposal is now firmly on the table that it is in fact fair game for modern biomedical research in its own right.

Strategy 2: Proglumide

An independent approach that supports the line of reasoning initiated by the naloxone studies has come from studies of the endogenous peptide cholecystokinin (CCK). Proglumide is a nonselective antagonist of CCK receptors. CCK itself is a peptide neurotransmitter within the CNS that tends to be released concomitantly with endogenous opioids and opposes their analgesic effect. Thus, proglumide functionally enhances opioid action.

This fact in turn suggests that if naloxone, an opioid antagonist, blocks placebo analgesia, then proglumide might enhance it. Two separate studies indicate that this is indeed the case. The first of these studied 93 post-thoracotomy patients and found that, 60 minutes after injection, proglumide approximately doubled the analgesia produced by a placebo alone (Benedetti, Amanzio, and Maggi 1995). Hidden proglumide alone had no effect on patients in the no-treatment group. These results were confirmed using an experimental pain paradigm, in which pain was induced via the tourniquet technique. While proglumide significantly potentiated the placebo effect, it had no effect in the no-treatment group (Benedetti 1996).

Brain Activity Correlated with Placebo Analgesia

The pharmacological evidence outlined above is compelling, but it does not directly address the question of the specific circuitry mediating placebo analgesic responses. Petrovic et al. (2002) investigated this matter directly using positron emission tomography (PET). In nine normal volunteers, they compared the brain areas activated by opioids with those activated when a placebo analgesic response was observed. Each subject underwent six conditions: (1) a painful heat stimulus on the hand; (2) a non-painful warm stimulus; (3) the painful stimulus plus an opioid drug (remifentanil); (4) the non-painful stimulus plus the same opioid; (5) the painful stimulus plus a placebo; and (6) the non-painful stimulus plus a placebo. Remarkably, largely overlapping brain areas were activated specif-

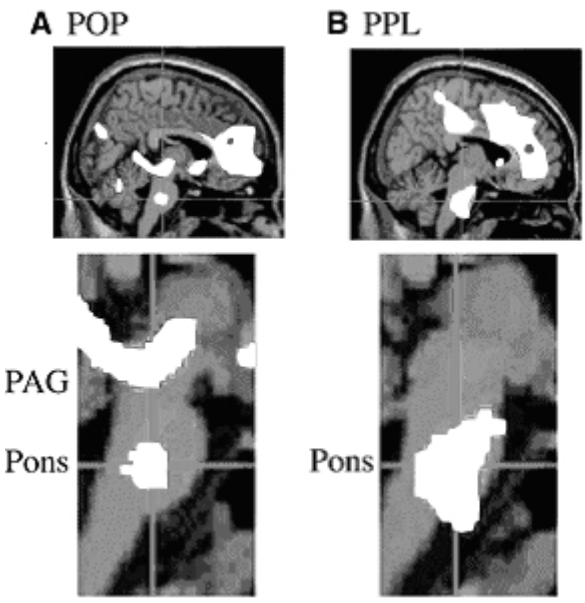

FIGURE 4

*Activation of pain modulatory structures by both opioid analgesics and a placebo analgesic manipulation. PET showing significant overlap of brain areas in the same subjects activated by the opioid analgesic remifentanyl (*POP*) and an infusion that they were told was a powerful analgesic (*PPL*) (Petrovic et al. 2002).*

ically during the opioid and placebo analgesia conditions. Both conditions were associated with increased activity in the rostral anterior cingulate cortex and the orbitofrontal cortex (Figure 4). In the pain plus placebo group, increased activity in the anterior cingulate occurred only in those subjects who had been independently categorized as placebo responders.

Previous studies have implicated both the rostral anterior cingulate and orbitofrontal cortex in the modulation of pain by suggestion and by opioid administration (by hypnosis and morphine, respectively; Adler et al. 1997; Casey et al. 2000; Faymonville et al. 2000; Peyron, Laurent, and Garcia-Larrea 2000; Rainville et al. 1999). In rodents, these cortical areas project directly or indirectly to the brainstem circuitry that produces analgesia through opioid-mediated processes. While the resolution of the PET technique is crude, Petrovic et al. (2002) also found that the increase in anterior cingulate activity during both placebo and opioid analgesia was correlated with increases in activity in areas of the midbrain and pons that overlap significantly with the location of pain-modulating circuits (Figure 4). Furthermore, a more recent study using the higher resolution technique of functional magnetic resonance imaging confirmed that the rostral anterior cingulate and the midbrain periaqueductal gray region are activated in subjects that experience a placebo-induced analgesic response (Wager et al. 2004). These imaging studies provide direct support for the hypoth-

esis that placebo-induced analgesia is mediated by the same modulating circuitry that controls pain transmission through endogenous opioid peptides. The human brain possesses, Petrovic et al. (2002) conclude, "a network that uses cognitive cues to activate the endogenous opioid system."

Conclusion

The extent to which administration of placebo treatments can result in real and clinically significant changes has been subject to both hype and controversy, but more has been learned about this phenomenon than is widely realized. Particularly in the area of pain and analgesia, impressive strides have been made in describing the magnitude, probability of occurrence, and potency of responses to placebos. Even more impressive are recent advances in understanding the underlying psychological and especially neural mechanisms that mediate placebo analgesic responses. Clinically, we know that the analgesic changes recorded in response to placebo treatments are not all simply a manifestation of the natural history of a condition. Nor can they all be dismissed as artifacts of patient or observer reporting bias. Psychologically, we know that classical conditioning and expectancy have both independent and interacting effects in mediating responses to placebos. We also have very strong direct evidence that effective placebo manipulations trigger the release of endogenous opioid peptides that act on the same receptors as synthetic opioid drugs such as morphine. Finally, there is evidence that both placebo analgesic responses and analgesic responses caused by morphine or another exogenous opioid are mediated by largely overlapping pain-modulating circuits in the brain.

Taken together, the literature on placebo-induced analgesia shows that the placebo effect can be studied, and that it can be studied rigorously. The value of this subfield of placebo research lies in the fact that it offers up a specific neural circuit hypothesis capable of being integrated with equally rigorous experimental work on the psychological, social, and clinical levels. In this sense, it bears all the marks of a genuine multilevel interdisciplinary research paradigm in the making, one that could serve as a model for research on non-analgesic placebo responses. It also may suggest ways of more rigorously researching other kinds of mind-body effects more generally. Serious discussion of the larger clinical implications of this work for treating pain and other disorders has hardly begun. Some sound foundations have already been laid down; the challenge now is for others to build on them.

References

Ader, R. 1997. The role of conditioning in pharmacotherapy. In *The placebo effect: An interdisciplinary exploration*, ed. A. Harrington, 138–65. Cambridge: Harvard Univ. Press.

Adler, L. J., et al. 1997. Regional brain activity changes associated with fentanyl analgesia elucidated by positron emission tomography. *Anesth Analg* 84(1):120–26.

Amanzio, M., and F. Benedetti. 1999. Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci* 19(1):484–94.

Amanzio, M., et al. 2001. Response variability to analgesics: A role for non-specific activation of endogenous opioids. *Pain* 90(3):205–15.

Beecher, H. K. 1955. The powerful placebo. *JAMA* 159:1602–6.

Benedetti, F. 1996. The opposite effects of the opiate antagonist naloxone and the cholecystokinin antagonist proglumide on placebo analgesia. *Pain* 64(3):535–43.

Benedetti, F., M. Amanzio, and G. Maggi. 1995. Potentiation of placebo analgesia by proglumide. *Lancet* 346(8984):1231.

Benedetti, F., C. Arduino, and M. Amanzio. 1999. Somatotopic activation of opioid systems by target-directed expectations of analgesia. *J Neurosci* 19(9):3639–48.

Benedetti, F., et al. 1998. The specific effects of prior opioid exposure on placebo analgesia and placebo respiratory depression. *Pain* 75(2–3):313–19.

Benedetti, F., et al. 1999. Inducing placebo respiratory depressant responses in humans via opioid receptors. *Eur J Neurosci* 11(2):625–31.

Benedetti, F., et al. 2003. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J Neurosci* 23(10):4315–23.

Casey, K. L., et al. 2000. Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol* 84(1):525–33.

De Pascalis, V., C. Chiaradia, and E. Carotenuto. 2002. The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. *Pain* 96(3):393–402.

Faymonville, M. E., et al. 2000. Neural mechanisms of antinociceptive effects of hypnosis. *Anesthesiology* 92(5):1257–67.

Fields, H. L., and A. I. Basbaum. 1999. Central nervous system mechanisms of pain modulation. In *Textbook of pain*, ed. P. Wall and R. Melzack, 243–57. Edinburgh: Churchill-Livingston

Fields, H. L., and J. D. Levine. 1981. The biology of placebo analgesia. *Am J Med* 70(4): 745–46.

Goodman, E. 2001. As medicine evolves, the "placebo effect" comes undone. *Boston Globe*, May 31.

Gracely, R. H., et al. 1983. Placebo and naloxone can alter post-surgical pain by separate mechanisms. *Nature* 306(5940):264–65.

Grossman, K. N. 2001. Placebos don't do much good after all. *Chicago Sun-Times*, May 24.

Harrington, A. 1997. Introduction. In *The placebo effect: An interdisciplinary exploration*, ed. A. Harrington, 1–11. Cambridge: Harvard Univ. Press.

Henderson, M. 2001. Dummy drug effect "a myth." *Times* (London), May 25.

Herrnstein, R. J. 1962. Placebo effect in the rat. *Science* 138:677–78.

Hrobjartsson, A., and P. C. Gotzsche. 2001. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 344(21):1594–1602.

Hughes, J., et al. 1975. Identification of two related pentapeptides from the brain with potent opiate agonist activity. *Nature* 258(5536):577–80.

Humphrey, N. 2002. Great expectations: The evolutionary psychology of faith healing and the placebo effect. In *The mind made flesh: Essays from the frontiers of psychology and evolution*, 255–88. Oxford: Oxford Univ. Press.

Kirsch, I. 1997. Specifying nonspecifics: Psychological mechanisms of placebo effects. In *The placebo effect: An interdisciplinary exploration*, ed. A. Harrington, 166–86. Cambridge: Harvard Univ. Press.

Kirsch, I. 1999. Response expectancy: An introduction. In *How expectancies shape experience*, ed. I. Kirsch, 3–13. Washington, DC: American Psychological Association.

Kirsch, I. 2002. Yes, there is a placebo effect, but is there a powerful antidepressant drug effect? *Prev Treatment* 5 (art. 22).

Levine, J. D., and N. C. Gordon. 1984. Influence of the method of drug administration on analgesic response. *Nature* 312(5996):755–56.

Levine, J. D., N. C. Gordon, and H. L. Fields. 1978. The mechanism of placebo analgesia. *Lancet* 2(8091):654–57.

Levine, J. D., et al. 1979. Role of pain in placebo analgesia. *Proc Natl Acad Sci USA* 76(7): 3528–31.

Levine, J. D., et al. 1981. Analgesic responses to morphine and placebo in individuals with postoperative pain. *Pain* 10(3):379–89.

Lipman, J. J., et al. 1990. Peak B endorphin concentration in cerebrospinal fluid: Reduced in chronic pain patients and increased during the placebo response. *Psychopharmacology (Berl)* 102(1):112–16.

Margraf, J., et al. 1991. How "blind" are double-blind studies? *J Consult Clin Psychol* 59(1):184–87.

Moerman, D. E. 2002. *Medicine, meaning and the "placebo effect."* Cambridge: Cambridge Univ. Press.

Montgomery, G. H., and I. Kirsch. 1997. Classical conditioning and the placebo effect. *Pain* 72(1–2):107–13.

New England Journal of Medicine. 2001. Letters to the editor. 345(17):1276–79.

New York Times. 2001. Study casts doubt on the placebo effect. May 24.

Ney, P. G., C. Collins, and C. Spensor. 1986. Double blind: Double talk or are there ways to do better research? *Med Hypotheses* 21(2):119–26.

Petrovic, P., et al. 2002. Placebo and opioid analgesia: Imaging a shared neuronal network. *Science* 295(5560):1737–40.

Peyron, R., B. Laurent, and L. Garcia-Larrea. 2000. Functional imaging of brain responses to pain: A review and meta-analysis. *Neurophysiol Clin* 30(5):263–88.

Pollo, A., et al. 2001. Response expectancies in placebo analgesia and their clinical relevance. *Pain* 93(1):77–84.

Price, D. D., et al. 1999. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 83(2):147–56.

Rainville, P., et al. 1999. Cerebral mechanisms of hypnotic induction and suggestion. *J Cogn Neurosci* 11(1):110–25.

Rescorla, R. A., 1988. Pavlovian conditioning: It's not what you think it is. *Am Psychol* 43(3):151–60.

Statesman (India). 2001. Fake pills no longer work: People given no treatment are just as likely to improve as those who receive placebos. May 29.

Talbot, M. 2000. The placebo prescription. *NY Times Mag*, Jan. 9.

Trafford, A. 2001. Reassessing our investment in the placebo effect. *Washington Post*, June 12.

Voudouris, N. J., C. L. Peck, and G. Coleman. 1990. The role of conditioning and verbal expectancy in the placebo response. *Pain* 43(1):121–28.

Wager, T. D., et al. 2004. Placebo-induced changes in FMRI in the anticipation and experience of pain. *Science* 303(5661):1162–67.
Whitney, C., and M. Von Korff. 1992. Regression to the mean in treated versus untreated chronic pain. *Pain* 50(3):281–85.