Placebo Analgesia

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Running Head: PLACEBO ANALGESIA

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SUMMARY

The expectation of pain relief can exert a powerful analgesic effect, even when pain is severe. Depending on the nature of experiences and instructions provided, a placebo analgesic effect can be elicited acutely in a very large percentage of individuals, in both experimental and clinical contexts. Placebo analgesia has been linked with activity in the prefrontal cortex, endogenous opioid release in both descending antinociceptive systems and forebrain structures, and reduced responses to noxious stimulation in regions of anterior cingulate and insular cortex, thalamus, spinal cord that correlate with the reported relief of pain. Thus, placebo responses can affect pain via both inhibition of ascending nociceptive pathways and modulation of forebrain and limbic pain-generation circuits. However, placebo responses are heterogeneous, and the degree to which each mechanism is involved likely depends in part on (a) the combination of conditioning and expectation elicited by the treatment context, and (b) inter-individual differences in optimism, receptivity to the placebo, and brain opioid and dopamine systems, as well as other factors. A more complete understanding of the placebo analgesic response could lead to new treatments that exploit psychological methods for activating pain-modulating circuitry and for ethically and optimally enhancing the placebo component of active treatments.

Introduction

For a patient experiencing pain, the perception that an effective treatment has been administered is often sufficient to produce significant analgesia. To the extent that the

analgesia is due to the psychobiological effects of the treatment process, as opposed to an active property of the treatment, the person can be said to have experienced a placebo analgesic response. The actual treatment manipulation can take a variety of forms: a dummy tablet, nasal spray, surgical procedure, magnetic treatment, or topical cream.

Whatever the form, the most critical determinants of the analgesic efficacy of a placebo are a) the presence of sensory cues that have been associated with effective treatment or pain relief in the past and b) the expectation of pain relief.

The concept of placebo implies that there is a mismatch between what the patient expects and the treatment's actual intrinsic efficacy. If the patient believes that the placebo treatment may be effective, positive expectations of analgesia are created, and these are linked to pain relief. This, in turn, implies that the patient is deceived. However, it is also possible to create placebo effects through conditioning, the process of learning that sensory cues associated with the treatment context are linked with pain relief. In such cases, placebo effects may be independent of the patients' conscious belief (Benedetti, et al., 2003), and it is thus possible in some cases to obtain placebo effects without explicit deception (Kaptchuk, et al., 2010).

It may also be possible to obtain expectancy (or treatment context-related benefits) in the context of active drug treatment, as is the case with patient-controlled analgesia (White, 1988) and as demonstrated by studies of overt vs. hidden drug treatment (Colloca, Lopiano, Lanotte, & Benedetti, 2004). In these cases, even though the active treatment cannot be called a placebo in the strict sense, the analgesic response it elicits in the patient may be said to have a placebo component. Finally, the effects of expectations might, in some cases, interact with the active pharmacological mechanisms of drug

treatments to produce synergistic effects (Kleijnen, de Craen, van Everdingen, & Krol, 1994). One striking example is a study of the drug proglumide, a CCK-antagonist shown to relieve pain better than placebo alone when given overtly, with full patient awareness, but performs more poorly than placebo when given without patients' awareness (Benedetti, Amanzio, & Maggi, 1995).

In our view, placebo effects can thus arise in several situations—concomitant with conscious expectations about treatment (Kirsch, 1985), following conditioning of pain relief with explicit sensory cues (with or without awareness of expectation; Benedetti, et al., 2003), and associated with the psychosocial context and ritual that surrounds treatment (Barrett, et al., 2006; Moerman & Jonas, 2002). It is true that according to this definition, the conceptual lines dividing placebo effects and effects of psychological therapies are blurred (Hrobjartsson, 2002), but this definition respects the common origin of these effects in the brain of the patient. The brain mechanisms of the various psychological influences on pain, and whether they arise from common or distinct sources, is an empirical matter.

Although sham treatments can produce a powerful analgesic effect, in a typical clinical situation it is usually not obvious whether the improvement observed in a patient is due to a placebo response. As we describe below, this is often true even when the patient is known to have received a placebo treatment. Failure to appreciate this point has created confusion about what effects placebos do and do not have. Because of this, the first part of this chapter will deal at length with definitions and with the phenomena that are most commonly confused with placebo analgesic responses. The second part of the chapter focuses on recent advances in understanding the neurobiology of the placebo

response.

Terminology

The term placebo is most likely derived from the Latin stem placebit ('it will please'). Since the beginning of medicine, health professionals have knowingly deceived patients by giving them sham treatments—sometimes with well-meaning intentions and other times for self-serving purposes. However, the longevity of many treatments with likely no active effects (Shapiro, 1959) and the success of the physicians that prescribed them suggests that patients must have attributed some benefit from these ministrations. And perhaps it is possible that psychobiological effects can confer concrete physiological health benefits, and even be an integral part of treatment. For example, Kong et al. (2009) ~~(Kong, et al., 2009)~~ cite the classic ancient Chinese text on acupuncture, the 1st-centure BCE Yellow Emperor's Inner Classic, as saying, 'if a patient does not consent to therapy [acupuncture] with positive engagement, the physician should not proceed as the therapy will not succeed.' The study of placebo treatments, which have been selected to have no direct therapeutic benefit, is the study of the psychobiological effects of the treatment itself.

In this chapter we differentiate between the placebo, the placebo effect, and the placebo response. The placebo itself is a dummy treatment such as a sham surgery or sugar pill. The placebo *effect* is an observable difference between groups attributable to the efficacy of the placebo—e.g., the difference in mean treatment effect between a group that has received a placebo treatment and one that received no treatment. The placebo analgesic *response* refers to the pain relief in an individual that results from the expectation of effectiveness of the therapeutic intervention.

The terminology surrounding placebo research can be confusing, as some authors use the term 'placebo response' to mean any type of improvement in a placebo group in a clinical trial, even if that improvement is related to statistical artifacts such as sampling bias and regression to the mean or to the natural history of a clinical condition. Here, we reserve the term 'response' for an active neurobiological process that occurs as a result of placebo treatment. Thus, from the standpoint of understanding mechanisms, it is the placebo response of the individual that is the most interesting and informative object of study.

Active placebo responses vs. statistical artifacts

The placebo response is widely misunderstood. This is due in part to modern clinical trials methodology and in part to a lack of understanding of the proximate mediating causes of clinical improvement. In clinical trials, the use of placebo treatment comparison groups is commonplace. The idea is to control for non-specific factors related to administration of the treatment and to the patient's perception of the treatment. Often, in clinical trials of pain and a variety of other disorders, patients in the placebo group improve (Fournier, et al., 2010; Hrobjartsson & Gotzsche, 2004; Hróbjartsson & Gøtzsche, 2001; Walsh, Seidman, Sysko, & Gould, 2002). The confusion begins with the assumption that the reason such patients improve is because they received a placebo. This assumption is often unwarranted.

There are several reasons that patients in the placebo group might improve. First, they might show improvement that would have happened with no treatment at all, due to the natural history of the disease. Second, patients tend to enroll in trials or treatment when pain is at its worst, resulting in apparent improvements with time due to regression

to the mean. Third, patients may benefit from the positive psychosocial context of being enrolled in a study, which usually means increased medical attention, care and assessment, and, increasingly, additional social support from other patients connected through Internet-based social media (the classic Hawthorne effect is a related phenomenon; Roethlisberger & Dickson, 1939).

To illustrate the problem, consider the common condition of idiopathic headache. In most people, the headaches they experience will arise and subside completely without treatment. Thus any treatment given at the peak of headache severity (or no treatment) will tend to be followed by improvement. This is true whether the treatment is a starch pill or an active analgesic. In order to assess whether the placebo treatment had any actual psychobiological effects, it is necessary to compare improvement in a placebo-treatment group with that in a no-treatment group (Fig.27.1). This comparison can estimate the magnitude of the placebo *effect*, i.e., the benefit due specifically to taking the placebo, whereas improvement in the placebo group reflects a composite of many factors.

The various types of artifacts that can be mistaken for active placebo responses are described in more detail elsewhere (Atlas & Wager, 2009; Atlas, Wager, Dahl, & Smith, 2009), but it is worthwhile to elaborate briefly on regression to the mean, a pervasive problem illustrated in Fig.27.2. Imagine patients in a clinical trial for treatment of Irritable Bowel Syndrome (IBS), a condition in which symptoms fluctuate over time but may be stable over a period of years (Agreus, et al., 2001). In this thought experiment, imagine that there is *no* change in the average symptom severity over time, only fluctuation around a stable value. Patients tend to enroll when symptoms are relatively severe, as marked by the arrows in Fig 27.2A. Because the symptoms fluctuate around a

stable mean value, symptom severity on subsequent measurements will tend to be closer to the mean, and thus symptoms will appear to improve over time (Fig 27.2B). Thus, even if there is no true improvement in the population over time, the time of study enrollment is not randomly sampled with respect to symptoms, and there is apparent improvement (Fig 27.2C).

The clinical significance of regression to the mean in chronic pain is illustrated by the work of Whitney & Von Korff (1992). They conducted a population- and clinic-based study of people with temporo-mandibular disorders, comparing 147 patients who had been referred for treatment of 'facial ache or pain in the jaw muscles, the joint in front of the ear or inside the ear (excluding infection)' with 95 community cases identified in a random sample telephone survey of individuals who reported the same complaints but did not seek treatment. All subjects rated their pain severity at study entry and 1 year later. Pain severity at 1 year was much less than at entry for both treated and untreated groups. The greatest improvement occurred in those with the highest level of pain at study entry, and when the subjects were matched for initial pain severity, there was no difference in pain levels at 1-year follow-up between treated and untreated groups. However, at 4–6 weeks, many patients with temporomandibular disorders in the clinic group reported improvement and attributed their improvement to the treatment received.

Thus, improvement in placebo-treated groups in clinical trials is confounded with both natural healing processes and statistical artifacts such as regression to the mean. In a typical randomized placebo-controlled clinical trial of headache treatment, large numbers of patients in the placebo control group report improvement (e.g. de Craen, Tijssen, de Gans, & Kleijnen, 2000). Based on such improvement, it is frequently stated that a

certain percentage of subjects or patients in a treatment trial are placebo responders. In fact, Beecher's oft quoted survey of clinical analgesic trials, from which he concluded that an average of 30% of patients respond to placebo treatments (Beecher, 1955), is based on just such an estimate. In fact, assessing the benefits due to taking a placebo requires comparison with a no-placebo group, which controls for natural history, regression to the mean, and other effects of enrolling in the study, or manipulation of the the type of placebo intervention (e.g., de Craen, et al., 2000; Kaptchuk, et al., 2008).

Evidence for placebo analgesia

Placebo effects in experimental and clinical studies

Consistent placebo analgesic effects have been demonstrated for dental postoperative pain, post-thoracotomy pain, low-back pain, IBS pain, chronic neuropathic pain, and experimental somatic pain caused by noxious heat, laser, electric shock, intramuscular saline injections, rectal distention, esophageal stimulation, and exercise under ischaemic conditions. There are many well-controlled, experimental studies that demonstrate such effects (Atlas, et al., 2009; Benedetti, 2009; Enck, Benedetti, & Schedlowski, 2008; Finniss, Kaptchuk, Miller, & Benedetti, 2010; Price, Finniss, & Benedetti, 2008; Vase, Petersen, Riley, & Price, 2009; Zubieta & Stohler, 2009). Because placebo effects in experimental studies are quite well established, we devote space here to discussing the more contentious issue of whether placebo effects exist in clinical pain states.

Several meta-analyses have identified clinical trials with no-treatment control groups and have used these to estimate the magnitude of placebo analgesia (Hrobjartsson

& Gotzsche, 2004; Hróbjartsson & Gøtzsche, 2001; Vase, Riley, & Price, 2002). These show significant but modest placebo analgesia, with effect sizes estimated at $d = 0.25$ (Hrobjartsson & Gotzsche, 2004) and $d = 0.15$ (Vase, et al., 2002) (d is the mean effect divided by its standard deviation). The effect sizes also varied significantly across trials. By contrast, studies of clinical pain with placebo treatments designed to elicit placebo analgesia have reported larger effects (e.g., Gracely, Dubner, & McGrath, 1979; Kaptchuk, et al., 2008; Levine, Gordon, & Fields, 1978; Vase, Robinson, Verne, & Price, 2005). Experimental studies of placebo analgesia have reported even larger placebo effects ($d = 0.95$ and $d = 1.00$; Vase, et al., 2009; Vase, et al., 2002). The larger effects in placebo analgesia studies and the substantial heterogeneity in placebo effects across clinical trials is likely related to the instructions and context given to participants; those in placebo analgesia studies are typically told that the treatment will or may powerfully reduce pain, leading to stronger expectations of analgesia. In addition, a direct comparison between placebo effects in experimental and clinical low-back pain showed larger placebo effects for clinical pain (Charron, Rainville, & Marchand, 2006). This finding fits with meta-analysis results showing that placebo effects are larger with more sustained pain and in the presence of hyperalgesia (Vase, et al., 2009).

In sum, placebo treatments can have a positive impact on clinical pain, with the most evidence to date on chronic low back pain and IBS. The presence of hyperalgesia and the psychological context in which placebo treatments are given also appears to matter considerably. In the clinical situation, the enthusiasm and belief of the physician and what is verbally communicated to the patient are critical, as are conditioning effects due to prior exposure to an active (or inactive) analgesic drug. Other factors that probably

influence the placebo effect include the physical properties of the placebo and how it is administered (Kaptchuk, et al., 2006).

Cognitive bias as a source of placebo effects

One limitation of the studies discussed above, however, is that they all use patient-reported pain as an outcome. However, the judgment process that influences reports of pain and other phenomena can be biased in a number of ways. For example, judgments of simple facts such as "how far away is the moon?" are biased by suggested reference points (Tversky & Kahneman, 1981), and judgments of economic value and basic perceptual similarity are biased by a number of cognitive variables, including the order in which options are presented and the presentation of reference values that serve as anchors (Cheng, 1985; Tversky, 1977; Tversky & Kahneman, 1981). Thus, under placebo treatment, patients may a) establish a lower cognitive anchor point for pain and fail to sufficiently override their prior beliefs when making reporting decisions; b) over-weight moments with lower pain experience when judging overall pain due to increased cognitive availability of experiences that match expectations; c) desire to report what they believe the experimenter expects, in part because they believe this conforms to 'correct' or normative behavior; d) desire to be consistent with prior behavior, which could include decreased reports of pain during prior treatment; e) bias their reports towards what they would like to happen (Metcalfe, 1998). All of these could create a placebo effect on reported pain independent of internal nociceptive processing and pain experience.

Consistent with these ideas, several studies have used sensory decision theory (SDT) analyses to separate placebo effects on sensory discriminability—i.e., the ability to

accurately detect which of two stimuli is more intense—from effects on pain report. These studies found that although placebo treatment decreases reported pain, it does not affect sensory discriminability (Clark, 1969; Feather, Chapman, & Fisher, 1972). Though these studies provide some support for cognitive biases as a source of placebo effects (Allan & Siegel, 2002), one conceptual difficulty is that it is possible that sensory/discriminative processes remain intact but nociceptive processes are truly influenced by placebo (e.g., Gracely, 2005). Thus, in sum, it is possible that in at least some cases what is mainly influenced by placebo treatments are cognitive judgments of pain, rather than the brain processes that give rise to pain.

Placebo effects on brain correlates of pain

The use of physiological markers of pain has become increasingly important as a way to gain leverage on whether placebo treatments produce meaningful changes in how nociceptive input to the brain is processed. The question of whether placebo responses reflect altered transmission in pain pathways has been addressed using event-related potentials (ERPs), magnetoencephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). These studies show a) reductions in pain-related activity in most brain correlates of pain experience; b) activation with placebo treatment of areas important for modulation of pain-related regions and engagement of pain modulating circuits; and c) activation of endogenous opioid and dopamine systems with placebo treatment. We review point (a) in this section, and cover the others in the following section on mechanisms of placebo analgesia.

Placebo effects on fMRI responses to noxious stimuli. Several fMRI studies (summarized in Table 27.1 and Fig 27.3) have shown reduced processing of noxious somatic stimuli with placebo treatment as compared to a no-placebo control. These studies have typically tested the same individuals at two different times, once with placebo treatment and once with control, using intensity-matched stimuli. The placebo treatments used have included placebo cream, intravenous administration of saline, and sham acupuncture, and the control treatments have consisted of matched cream application/injection with different instructions (e.g., "This cream will have a powerful pain-reducing effect" in the placebo condition vs. "This cream will have no effect" in the control condition.) Though we include sham acupuncture effects, we note that sham acupuncture may act as a counter-irritant, complicating its interpretation as a pure placebo treatment.

Wager et. al. (2004) studied decreases in fMRI responses to noxious stimuli in two experiments. In Study 1, a sample of 24 community volunteers experienced noxious shock to the right arm under placebo and control conditions. Each participant served as their own control in a within-subjects design. In Study 2, to increase the magnitude of the placebo effect, a conditioning procedure (surreptitious lowering of stimulus intensity when inert cream was applied; Voudouris, Peck, & Coleman, 1985; Voudouris, Peck, & Coleman, 1989) was used to associate the application of a placebo cream with effective pain relief. In this case, noxious heat was delivered on the left arm. fMRI results were similar in studies 1 and 2. Placebo-induced reductions were found in the contralateral anterior insula, medial thalamus, and rostral dorsal cingulate (corresponding to Vogt's

anterior midcingulate region). As with all studies discussed here, the locations of placebo-relevant brain effects are plotted with numbers coding for each unique study contrast in Figure 27.3. The precise contrasts tested (i.e., the comparison of conditions that produced the statistical map of brain placebo effects) are listed by number in Table 27.1. This study, for example, corresponds to Contrasts 3-10 in Table 27.1 and Figure 27.3. In addition, importantly, this and all other studies showing decreases in pain-processing showed significant placebo analgesia effects on reported pain, replicating other, purely behavioral findings (e.g., Benedetti, 2008; Benedetti, et al., 1998; Benedetti, Arduino, & Amanzio, 1999; Benedetti, et al., 2005; Montgomery & Kirsch, 1997; Morton, 2010; Price, et al., 1999; Voudouris, et al., 1985; Voudouris, et al., 1989).

Since then, other studies have replicated these reductions. Price et al. (2007; Contrast 4 in Table 27.1/Figure 27.3) found decreases in the same regions (aINS, rdACC, and medial thalamus) accompanying large behavioral placebo effects in IBS patients. They reported decreases in SII and several other pain-responsive regions as well, though it was unclear if these changes were due to placebo or habituation over time. Lu et al. (2009; Contrast 26) found substantial placebo-induced reductions in these regions, as well as sensorimotor regions around S1/S2. Eippert et al. (2009b; Contrasts 16-19) replicated decreases in each region. Furthermore, decreases in each region (and in peri-S1/S2) were blocked by the opiate antagonist naloxone, implicating the opioid system. High verbally induced expectations were associated with reductions in some overlapping areas, including the rdACC, nearby dorsomedial prefrontal cortex, and other areas, including the amgydala and ventral striatum. Watson et al. (2009), Contrast 28) also reported placebo-induced reductions that correlated with the magnitude of placebo

analgesia in rdACC and peri-S1. In addition, in a re-analysis of the combined individual-differences data across both studies from Wager et al. (2004a), Wager et al. (2011) found correlations between placebo-induced reductions in signal magnitude in a number of pain-processing regions and reported placebo analgesia; these included the anterior cingulate and thalamus. Even larger correlations were found between reduced pain and reduced activity in the ventral striatum, potentially implicating valuation and learning systems distinct from those that typically encode the intensity of noxious stimulation.

Findings from all these studies are summarized in Figure 27.3A, with numbers corresponding to contrasts listed in Table 27.1 for each study. Figure 27.3B shows regions in which placebo-induced decreases were replicated in at least 3 separate study maps. A close-up view of individual study results in the key regions around the insula, cingulate, thalamus, and striatum is shown in Figure 27.3C. In summary, while results vary, there is clear consensus on decreased processing of noxious stimuli in typical "pain-processing regions" including rdACC, aINS, medial thalamus, and also reductions in pain-responsive regions of ventral striatum, amygdala, and sensorimotor cortex.

Placebo effects on ERP responses to noxious stimuli. In addition to their role in processing nociceptive input, both the rostral cingulate and insula are increasingly viewed as cortical 'hubs' that contribute to a variety of auxiliary processes, including perceiving others in pain, non-pain-related social or economic loss, conflict detection, and behavioral decision-making. Thus nociception related patterns of activity in these regions must be interpreted with caution and their role in placebo analgesia may not be straightforward. Second, the time resolution of fMRI is poor relative to that of the

underlying neural activity. For example, the imaging studies reviewed above did not have the ability to resolve events at a lower time resolution than several seconds, which leaves ample time for evaluative processes beyond nociception to influence the observed signals. In this respect, ERP studies provide an important complement to fMRI studies due to their excellent time resolution.

In fact, ERP studies have found encouragingly replicable results on early nociception-related components. Wager, Matre, & Casey (2006), using a brief conditioning manipulation, tested placebo effects on noxious laser-evoked potentials (LEPs), specifically the N2/P2 complex, a midline potential sensitive to noxious stimulus intensity that occurs at around 180 msec (N2) and 250-300 msec (P2) and whose likely neural generator is the anterior cingulate (Garcia-Larrea, Frot, & Valeriani, 2003). They found evidence for placebo-induced reduction of the P2 that decreased over time as the P2 habituated. Watson, El-Deredy, Vogt, & Jones (2007) replicated these findings in a Pre- vs. Post-placebo treatment design, finding reduced N2 and P2 potentials after placebo treatment, but not after an inactive control treatment. They found no evidence for habituation in the control group, arguing against a habituation-related explanation for placebo effects. Colloca et al. (2008b) also used a between-groups design to test for placebo-induced reduction of the N1 and N2/P2 complex with suggestion alone (Group 1) or conditioning to reduced stimulus intensity (Group 2), compared with a no-placebo control (Group 3). They found N2/P2 reductions that were particularly large in Group 2 and correlated with placebo analgesia ($r = 0.54$) in Group 1. Morton et al. (2010) tested placebo effects on laser-evoked potentials in two separate sessions at least two weeks apart. Reductions in LEP Pre- to Post-placebo treatment were correlated with placebo

analgesia (r = .040 and 0.41 in each session). Also of note was that both placebo analgesia and LEP reductions were reliable across the two sessions (r = 0.75 and r = 0.41, respectively). Finally, Aslaksen, Bystad, Vambheim, & Flaten (2011) also found reductions in N2/P2 potentials and accompanying reductions in self-reported stress, but only in males (experimenters were female.) These studies are complemented by other ERP studies of learned expectations not strictly classified as 'placebo' because the expectations are not about treatment. For example, Lorenz et al. (2005) found expectancy-based modulation of MEG activity around 165 ms post-noxious laser stimulation localized to SII. Overall, the evidence indicates that placebo treatments can modulate responses to early nociceptive processes.

Placebo effects on spinal nociceptive processes. The neurophysiological effects described above provide evidence that pain-related processing is reduced with placebo analgesia, and these reductions are correlated in some cases with reductions in pain experience. However, these studies do not address the question of whether and to what degree these brain changes reflect decreased aversion, reactivity, or attention to pain at the supra-spinal level, and to what degree they activate descending antinociceptive mechanisms that can reduce pain at the spinal level (Heinricher & Fields, Chapter 8 of this volume).

To date, there is limited direct evidence for spinal inhibition. In one study, Matre, Casey, & Knardahl (2005) assessed placebo effects on the area of secondary mechanical hyperalgesia created by sustained painful heat. The heat created a hypersensitive area on each participant's arm, and a subsequent test for pain induced by light touch was

performed without participants looking at the arm. Placebo treatment reduced the size of the hyperalgesic area, which the authors' argued implies reductions in central sensitization of pain at the spinal level. Goffaux and Marchand (2007) assessed the effects of instructions on Diffuse Noxious Inhibitory Control (DNIC, created here by a cold water bath) suppression of RIII reflex responses to sural nerve stimulation. They found signficant biasing of reflex amplitude by placebo treatment, but this was primarily driven by 'nocebo' conditions in which subjects were instructed that the cold-water bath would amplify their pain. Finally, Eippert, Finsterbusch, Bingel, & Buchel (2009c) used fMRI to directly image the cervical spinal cord during painful heat with and without placebo. They found that placebo treatment significantly reduced spinal fMRI activity in response to heat.

Though these are promising results, questions remain. If placebo treatment reduces nociception at the spinal level, one might expect it to reduce pain-related activity in all relevant areas of the cerebrum. However, studies have not yet unequivocally demonstrated reductions in pain-related processing in the sensory thalamus, SII, and dorsal posterior insula. Importantly, these are the areas activated most specifically by noxious somatic stimulation (e.g., Hua, et al., 2005; Kross, et al., 2011). It is possible that widespread effects of spinal inhibition are masked by placebo-related activity increases driven by cortical sources (some of which could reflect the metabolic demands of, e.g., activation of inhibitory interneurons) or paradoxically reduced thresholds in specific nociceptive pathways.

Ingredients of placebo analgesia: What makes a placebo responder?

A number of processes contribute to the creation of placebo analgesia at both the psychological and neural levels, and different factors may influence the magnitude of the placebo response in different situations. Relationships between placebo effects and personality measures have proven inconsistent (Liberman, 1964; Shapiro, Struening, & Shapiro, 1979), and placebo responses are not highly correlated across types of pain and variations in situational context. For example, Liberman (1964) assessed placebo response magnitude in the same group of women in three kinds of pain, and found that placebo responses were uncorrelated across the types of pain. More recently, Whalley, Hyland, & Kirsch (2008) tested for correlations in placebo responses in the same pain modality, but with different *brand names* for the placebo. Responses were uncorrelated.

However, another set of new studies suggest a number of promising psychological correlates of placebo response magnitude, including *suggestibility* (De Pascalis, Chiaradia, & Carotenuto, 2002; Morton, El-Deredy, Watson, & Jones, 2010), *optimism* (Morton, et al., 2009), *expectation* (Atlas, Bolger, Lindquist, & Wager, 2010; Morton, et al., 2010; Vase, Robinson, Verne, & Price, 2003; Zubieta, et al., 2005), *behavioral activation* (Schweinhardt, et al., 2009), *desire for relief* (Vase, et al., 2003), reductions with placebo treatment in anticipatory anxiety (Lyby, Aslaksen, & Flaten, 2010), and sensitivity to opiate drugs (Amanzio & Benedetti, 1999). These factors may underlie some of the brain correlates described elsewhere in this chapter—i.e., increased optimism and positive expectations may be linked to greater anticipatory fronto-striatal activity and reduced anticipatory anxiety, thereby potentiate the release of endogenous opioids through prefrontal-brainstem pathways, and reduce noxious stimulus-induced activity in pain-processing regions and learning and motivation-related ventral striatal circuits.

How can these apparently conflicting findings be reconciled? Placebo effects are influenced by both stable individual differences such as optimism and past experiences with pain, treatments, and treatment contexts and cues. These two kinds of predisposing factors contribute to psychological and brain processes that shape the emotional, sensory, and evaluative processing of pain. Thus, placebo responses are likely to be elicited in individuals who are receptive to the particular treatment context offered. For example, person A might be responsive to placebo injections in part because of positive past experiences with injected analgesics. Person B might be more responsive to a placebo cream. Person A might be quite optimistic and show strong placebo responses to laboratory pain, but have anxiety about the pain of childbirth that block placebo responses in that context, whereas Person B might have different predispositions toward childbirth that permit placebo responses to develop. This notion is consistent with a fundamental idea in psychology that personality traits alone are insufficient to describe how a person will respond, and person x situation interactions must be considered (Mischel, 2004). Thus, a number of predisposing factors might combine to elicit stronger or weaker expectations about pain in the moment, which may be proximal mediators of how strong the placebo effect will be for a given person in a given situation (e.g., Wager, et al., 2011). However, we might not expect a person to respond similarly to different situations and different types of pain (Liberman, 1964).

Much attention has been given to how prior experiences with drug and context cues influence placebo effects. The process of learning that drug cues signal pain relief and/or drug-induced changes in the brain's neurochemistry is known as conditioning. Conditioned cues can have strong influences on pain in basic and clinical contexts

(Amanzio & Benedetti, 1999; Atlas, et al., 2010; Voudouris, et al., 1985; Voudouris, Peck, & Coleman, 1990; Wickramasekera, 1980). The clearest evidence for conditioning effects in the clinical situation is derived from placebo-controlled crossover trials of analgesic medications. In a study of acute pain in hospitalized patients, Kantor and colleagues (1966) and Laska & Sunshine (1973) compared placebo and several different doses of an active analgesic. What they found was a clear conditioning effect. When placebo was given as a second treatment 24h after administration of an active analgesic, the magnitude of placebo analgesia was positively correlated with the dose of the previously administered active medication. These results indicate a conditioning effect of pairing the treatment context (the hospital, physician, nurse and capsule) with the analgesic effect of the drug through its direct action on the central nervous system. This is similar to classical conditioning of drug effects as described by Pavlov (Pavlov & Anrep, 1927). One could thus consider such a placebo manipulation to be a conditioned response. In this case, the contextual cues (white coat, pill or needle) are the conditional stimuli, the direct drug effect on the brain is the unconditioned stimulus, and the analgesic effect of the drug is the unconditional response.

Pharmacological conditioning is well documented in humans (Amanzio & Benedetti, 1999; Colloca & Benedetti, 2006) and animals (e.g., Guo, Wang, & Luo, 2010; Herrnstein, 1962). However, conditioning trials with analgesic drugs are not required to produce subsequent placebo analgesic responses. Voudouris and coworkers produced conditioned analgesia by simulating an analgesic effect (Voudouris, et al., 1990). They first applied a noxious stimulus to the skin to determine the subject's pain threshold. They then applied an inert cream to the skin and reapplied the stimulus, but

surreptitiously reduced its intensity to suggest to the subject that the cream had an analgesic effect. After this simulated analgesia, the placebo 'analgesic' cream was applied and the original noxious stimulus was delivered to the same area of skin. Compared with a group given the cream with no conditioning, the conditioned group showed significant pain reduction by the placebo cream. This same basic conditioning paradigm can influence both pain and pain-related physiology (Table 27.1, Figure 27.3). Furthermore, larger numbers of conditioning trials create larger placebo effects that are more resistant to extinction (Colloca, et al., 2010). Thus, cues associated with the experience of reduced pain per se can have a substantial analgesic effect when presented during later pain. However, critical, unanswered questions remain. Little is known about the precise mechanisms of pharmacological conditioning vs. conditioning to reduced pain (see Wager et al., 2007, supplement, for a discussion). In addition, it is unknown why cues that signal reduced pain elicit opioid-mediated analgesia, whereas in other studies, cues that signal *increased* pain produce opioid-mediated analgesia (Fanselow, 1986). Both are likely to be at least in part conditioned responses, but they have opposite effects on pain.

One possibility is that conditioned analgesia is mediated by changes in brain connectivity in nociceptive or affective circuits that reduce pain in a relatively unconscious, automatic way. Conditioned placebo effects that are insensitive to verbal instructions revealing that the treatment is a sham have been demonstrated in other domains (Benedetti, et al., 2003), and recently, Kaptchuk et al. (2010) found substantial placebo effects in IBS pain even when patients were told they were being given placebo. On the other hand, other studies have demonstrated that suggestion alone is enough to

produce some degree of analgesia (Amanzio & Benedetti, 1999; Wager, et al., 2004b) and possibly opioid release (Zubieta, et al., 2005). Conscious expectations of relief are correlated with reduced anticipatory responses in brain regions linked with anticipatory anxiety and reduced placebo analgesia (Wager, et al., 2011), with prefrontal activity that mediates cue-evoked changes in pain (Atlas et al., 2010), and with placebo-induced opioid release in limbic and paralimbic regions (Zubieta, Yau, Scott, & Stohler, 2006). These studies suggest that conditioning can work in at least two different ways—by eliciting conscious expectations of drug relief, and by brain mechanisms independent of conscious expectations (Stewart-Williams & Podd, 2004).

Just as conditioning can produce positive expectations and brain changes that reduce pain, it can also produce negative expectations and brain changes that increase pain. Such phenomena have often been referred to as 'nocebo' effects, and reduction of anxiety-related hyperalgesia is one potential mechanism of action for placebo treatments (Aslaksen & Flaten, 2008; Vase, et al., 2005), though more complex relationships between placebo analgesia and anxiety are also possible (Benedetti & Amanzio, 1997; Staats, Staats, & Hekmat, 2001).

One clear example of nocebo expectations is the study of Dworkin and colleagues on the effect of nitrous oxide on pain elicited by tooth pulp stimulation (Dworkin, Chen, LeResche, & Clark, 1983). Using verbal instruction, these investigators were able to turn the effect of nitrous oxide from analgesia to hyperalgesia. Several recent experimental studies have yielded similar results. Goffaux et al. (2007) found that the largest effects of instructions on spinal reflexes were nocebo effects: Instructions that a normally analgesic counterstimulation treatment would create hyperalgesia offset or reversed the effects of

the treatment. Bingel et al. (2011) found that nocebo instructions offset or reversed the normally analgesic effects of remifentanil on pain reports and fMRI responses associated with pain. Finally, nocebo instructions appear to have larger and longer-lasting effects than placebo instructions (Colloca, et al., 2010; Colloca, Sigaudo, & Benedetti, 2008a) and produce stronger physiological responses, e.g., on cortisol (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006; Johansen, 2003).

Mechanisms of placebo analgesia

Engagement of evaluative and visceromotor brain systems

Thus far, we have reviewed evidence on whether placebos can produce reductions in biological markers of nociceptive processes and some of the likely ingredients of placebo analgesia. Brain-based studies of placebo can also elucidate the proximal mechanisms by which placebo treatments work, including changes in brain activity, brain connectivity, and neurochemistry. Understanding these mechanisms is likely to be essential for understanding what brain-body processes placebos can affect, how placebo responses can be triggered in patient care, and how placebo-related interventions can be combined with standard medical treatments. Important insights into the mechanisms of placebo analgesia have come from studies that use PET and fMRI to measure brain activity and neurochemistry, pharmacological manipulations to manipulate neurochemistry, and transcranial magnetic stimulation (TMS) to manipulate brain electrical activity.

The brain circuits important for creating and maintaining expectations, re-evaluating the significance of noxious stimuli, and activating endogenous antinociceptive

systems are likely to show increased metabolic activity when anticipating and experiencing pain under placebo conditions, as increased activity is usually tightly correlated with increased processing load in the brain. Figure 27.4A summarizes consistent findings on increases in fMRI and PET in placebo vs. control conditions. Consistent increases in placebo conditions are found in the bilateral posterior dorsolateral prefrontal cortex (DLPFC), anterior prefrontal cortex, and orbitofrontal cortex (OFC), the pre-genual anterior cingulate cortex (pgACC), and the midbrain periaqueductal gray (PAG; red in Figure 27.4; see Table 27.1 for details of numbered effects on the figure). In each of these regions, activity increases in at least one study—and typically more—were correlated with the magnitude of placebo analgesia in reported pain (yellow in Fig. 27.4). These regions constitute a likely control circuit that generates expectations of pain relief and altered appraisals of imminent and ongoing pain in the placebo context. The involvement of the PAG points to possible activation of descending control systems and altered affective-motivational states.

Further evidence on the functional significance of activity for analgesia comes from correlations between individual differences in the magnitude of brain increases and placebo analgesia. The most extensive treatment of predictors of individual differences in placebo analgesia to date was done by Wager et al. (2011; #34 in Fig. 27.4A), who used multivariate patterns of activation to predict, and quantify the ability to predict placebo analgesia. The strongest links were between placebo analgesia and placebo-related activity increases during anticipation of pain in anterior PFC and superior parietal cortex, confirming the importance of anticipatory evaluative processes. Both placebo analgesia and pre-scan expectations of analgesia were also associated with reduced

anticipatory activity in pregenual anterior cingulate (pgACC), a region linked with anticipatory value, anxiety, and cardiovascular responses in other studies. These patterns explained up to 44% of the variance in individual placebo analgesia, suggesting that these brain changes might be reliable enough to be clinically useful.

This pattern of placebo-related influences is consonant with current models of affect regulation in other domains. DLPFC, operating in conjunction with the parietal cortex, has been linked to the maintenance of context information in short-term memory in numerous other studies, and may play a large role in establishing the cognitive set that generates placebo analgesia. Recently, Krummenacher et al. (2009) reported that transcranial magnetic stimulation to left DLPFC, which is thought to disrupt or inhibit ongoing processing in the stimulated region, blocked placebo analgesia without affecting baseline pain, corroborating the fMRI findings. Stimulation of the lateral prefrontal cortex in the rat also produces analgesia blocked by naloxone infusion in the PAG (Zhang, Tang, Yuan, & Jia, 1997a, 1998; Zhang, Tang, Yuan, & Jia, 1997b). The mid-lateral OFC has also been implicated in the generation and updating of reward value and hedonic processes, with neurons that encode both appetitive and aversive qualities of reinforcers. Recently, Petrovic et al. (2010) noted that this area was more reliably activated by placebo than verum opiate treatment, raising the possibility that placebos can engage evaluative mechanisms that could complement active treatment.

The heaviest anatomical connections with PAG and other parts of the descending nociception-control systems, however, are in the pgACC and other areas within the ventromedial prefrontal cortex (VMPFC), which has been termed ‘visceromotor’ cortex by virtue of its influences on brainstem neuroendocrine and autonomic systems (Price,

2005). This area is heavily connected with lateral OFC, and also with the amgydala, nucleus accumbens, ventral pallidum and striatum, PAG, hypothalamus, and other brainstem nuclei involved in pain regulation such as the parabrachial complex and rostral ventral medulla. Reliable metabolic increases here were first noted by Petrovic, Kalso, Petersson, & Ingvar (2002) in the first neuroimaging study of placebo analgesia and were co-localized with areas showing opiate-induced increases. Activity in the more ventral parts of this region reliably track anticipated hedonic value and the desirability of economic outcomes, whereas activity more dorsal in the anterior cingulate responds to a variety of manipulations that increase anticipatory anxiety and stressor-evoked physiological changes (see Wager, et al., 2009) . Several neuroimaging studies have found evidence for increased functional coupling beween the VMPFC or nearby dorsal cingulate cortex and PAG or pontine areas under placebo conditions (Bingel, et al., 2006; Petrovic, et al., 2002; Wager, Scott, & Zubieta, 2007), providing additional support for placebo engagement of cortical-brainstem pain-regulatory circuits.

Other areas are likely to be involved in this circuit as well—such as the ventral striatum/nucleus accumbens, parahippocampal cortex, and brainstem areas including the rostral ventral medulla. Placebo-related activity increases in each of these areas has been reported (Figure 24.4A). Though not yet replicated multiple times, these areas are heavily interconnected with the ventromedial prefrontal cortex (and pgACC) and insula, and neuropharmacological results described below suggest their importance in placebo analgesia. In addition, other studies reinforce the importance of ventral striatum/accumbens, which are heavily implicated in approach and avoidance motivation and value-driven learning, in placebo analgesia. The ventral striatum/accumbens is

robustly activated by cues that predict monetary gain (Knutson, Adams, Fong, & Hommer, 2001) and loss (Jensen, et al., 2007), perhaps in different local regions (Seymour, et al., 2007; cf. Yacubian, et al., 2006), shock (whether or not it can be avoided; Jensen, et al., 2003), and pain relief (Baliki, Geha, Fields, & Apkarian, 2010). In addition, it is specifically activated in response to better-than-expected outcomes (Hare, et al., 2008; Rutledge, Dean, Caplin, & Glimcher, 2010) and loss-avoidance (Pessiglione, et al., 2006), but also during pain itself (Becerra, et al., 2001). Together, these findings suggest a central role for this structure in regulating responding to sensory stimuli with intrinsic motivational salience. Since relief of pain is negatively reinforcing, the expectation of pain relief might be viewed as reward predictive, and placebo treatment would be expected to activate the ventral striatum. Additionally, if the ventral striatum is critical for learning the motivational value of pain relief-related cues, it might play an important role in the development of placebo effects.

Schweinhardt et al. (2009) found that gray-matter density in human ventral striatum/accumbens was positively correlated with both placebo analgesia and a composite personality measure essentially reflecting approach motivation and risk-seeking. Paralleling these findings, Wager et al. (2011) reported that reduced ventral striatal responses during pain were among the strongest correlations between activity during pain and placebo analgesia (perhaps indicating reduced aversive processing or reduced demand for pain-avoidance learning in ventral striatum). In another study, Atlas et al. (2010) manipulated expectations about pain intensity with predictive cues. They found robust effects of high-pain cues on pain and responses in classic 'pain-processing' circuits, including rdACC, medial thalamus, anterior insula, and SII. These effects were

mediated by anticipatory increases in the ventromedial prefrontal cortex (near pgACC) and ventral striatum (near the accumbens), tracing a pathway from anticipatory processes in these 'value-related' regions and responses in the established pain circuitry. This study and other similar ones (e.g., Keltner, et al., 2006; Koyama, McHaffie, Laurienti, & Coghill, 2005) were not included in Fig. 27.3 because they do not manipulate expectations about a treatment *per se*, as in the classic placebo paradigm, but the pain expectancy-manipulation paradigm is nearly indistinguishable from other recent studies that used conditioning to similar cues to elicit placebo effects (e.g., Lui, et al., 2010).

Neurochemical mechanisms of placebo analgesia

One of the first discoveries that implied a role for placebos in shaping nociceptive processing was the finding of Levine, Gordon and Fields (Levine, et al., 1978) that placebo effects could be reversed by the opiate antagonist naloxone, implicating the endogenous opioid system. Other studies have since replicated and extended this finding in humans and animals (Amanzio & Benedetti, 1999; Benedetti & Amanzio, 1997; Guo, et al., 2010), though placebo effects are not always sensitive to naxolone (Vase, et al., 2005), particularly when they are created via pharmacological conditioning with a non-opiate drug (Amanzio & Benedetti, 1999).

More recently, neuroimaging studies have directly assessed activity at mu-opioid and dopamine D2 receptors using PET imaging with radioactively labeled compounds that bind to these receptors. Results from these studies are shown in Fig.27.4B, and they implicate many of the same brain structures as the fMRI studies. Zubieta et al. (2005; Contrast 36 in Fig27.4B) compared binding of the mu-opioid receptor specific agonist

carfentanil during intramuscular pain induced by injecting saline into the masseter muscle in the jaw. Subjective pain levels were matched using an adaptive procedure, and the higher saline infusion rate required to maintain pain provided evidence for a placebo effect on pain. The higher rate of infusion was accompanied by decreases in binding (evidence for increased opioid-system activation) in pgACC, nucleus accumbens, DLPFC, and other areas, many of which were found to be correlated with subjective pain (Zubieta, et al., 2006). Wager et al. (2007; Contrast 37) imaged mu-opioid binding with carfentanil during matched levels of noxious thermal heat with and without placebo (the typical design used in the fMRI studies described above), and found opioid-system increases in these areas, and in bilateral OFC, medial thalamus, and PAG. This latter finding was particularly important as PAG is a major source of opioids in the brain. They also found evidence for increased correlation in carfentanil binding between the rostral anterior cingulate and PAG (as in Bingel, et al., 2006 and Kong, et al., 2008) and between a number of other placebo-responsive regions, consistent with the idea that placebo treatment causes central opioid release.

More recently, Scott et al. (2007, 2008; Contrasts 38-39) provided additional evidence implicating both endogenous opioid and dopamine systems in placebo analgesia. In the first paper, they used raclopride PET to image dopamine binding, and scanned the same subjects with fMRI in a monetary incentive delay task to assess nucleus accumbens responses to impending reward. They found correlations between dopamine activity and fMRI responses in the accumbens, which were also correlated with the magnitude of placebo analgesia in a separate test. Subsequently, they imaged subjects in a placebo paradigm with both carfentanil and raclopride PET, in separate sessions. They

replicated the finding of placebo-induced increases in PAG, and reported correlated responses in the nucleus accumbens of both dopamine and opioid systems. In general, these results fit with other fMRI studies showing correlations between pain-related decreases in ventral striatum/pallidum and placebo analgesia (Wager, et al., 2011), correlations with ventral striatal gray-matter density measures and placebo analgesia (Schweinhardt, et al., 2009), and ventral striatal mediation of the effects of pain-predictive cues (which elicit expectations of higher vs. lower pain) on pain-processing and pain report (Atlas, et al., 2010). As opioids typically exert a local inhibitory effect on neural transmission, increased opioid responses might be expected to be associated with reduced fMRI activity during pain; however, the relationships between tonic and phasic dopamine, opioid, and fMRI responses are likely to be complex and remain to be fully elucidated.

Finally, Eippert et al. (Eippert, et al., 2009a) compared fMRI responses to noxious heat under placebo and control (inert instruction) conditions, as in previous studies, but this time with two groups: One group was treated with naloxone before testing, and the other was treated with saline. In addition to reversing pain-related decreases in established pain-processing regions, as discussed above, naloxone reversed placebo-related increases in pgACC, DLPFC, and several brainstem regions including the PAG, pons, and rostral ventral medulla. These latter findings are important because they establish links with descending anti-nociceptive systems (Fields, 2004), and they were detected in a unique, brainstem-specific analysis, which is a promising approach for future studies.

The placebo response in clinical practice

There is very little published information on the extent to which placebo effects contribute to outcome in clinical practice, but studies of clinical treatments suggest that their effects might be quite large (Haake, et al., 2007; Kaptchuk, et al., 2008). The deliberate enhancement of the placebo component of an active clinical treatment is usually accomplished when the healthcare professional makes positive suggestions about the treatment's efficacy, leading to an increase in the patient's expectation of pain relief, or when attention is paid to the context cues and route of administration associated with treatment, including the place, time, and look and feel of the treatment. The extent to which health professionals actually make positive statements (or for that matter, negative statements) likely varies considerably, and both positivity and attention to the treatment context play a much larger role in alternative than standard allopathic medicine, perhaps explaining the popularity of complementary and alternative practices for pain management. Thus, in contrast to the overall view and conclusions of Hrobjartsson & Gotzsche (2001), it is likely that at least some physicians, psychologists, physical therapists and nurses elicit strong placebo effects, and that improved pain management at least in the short term could occur by teaching such professionals about the relevant factors.

Several obvious factors related to the doctor-patient relationship and patients' expectations may have an important impact on treatment outcome. First, the more ineffective treatments a patient receives, the more likely it is that future treatments will fail. This means that it is important to find the optimal therapy early in the course of treatment, and it is important that patients believe that they can improve. This can be a

major challenge for patients whose pain has persisted through many different therapies. Second, it is important for the person who is providing the treatment to communicate to the patient why a particular therapeutic approach is being used. If the practitioner doubts the efficacy of the treatment, and this doubt is communicated to the patient, it may negatively impact treatment. Third, explaining the effect of expectancy to patients may be helpful, particularly if there is reason to believe that expectancy may be contributing to the resistance of the patient to treatment. Fourth, the use of prognostic drug infusions may be helpful in demonstrating to the patient that relief is possible. It is also possible that a conditioning effect of such infusions could add to the efficacy of the same class of drug when given orally. Of course, if the infusions don't work, the conditioning will work in the wrong direction.

Once these and other factors that contribute to placebo analgesia have been identified and studied in the clinical setting, they could be optimized in clinical practice. While optimizing clinician-patient interactions is likely to be complex and involve an understanding of the various reactions patients may have to the same information, we are optimistic that placebo-related psychological principles could be systematically employed to patients' benefit. In addition, these priciples may be employed without deception, by using conditioning procedures (Amanzio & Benedetti, 1999; Benedetti, et al., 1998) and by providing positive, supporting information (Kaptchuk, et al., 2010; Vase, et al., 2003). The potential utilization of these techniques in clinical practice is an area ripe for future investigation.

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Table 27.1: Neuroimaging studies of placebo analgesia

Study	Contrast number on figure 27.3 & 27.4	Contrast description
Petrovic et al., 2002	1	(Pain + Placebo) - (Pain alone)
	2	[(Pain + Placebo) - (Pain alone)] - [(Warm + Placebo) - (Warm alone])
Wager et al., 2004, Study 1	3	(Control - Placebo) - (Intense - Mild Shock)
	4	(Control - Placebo) during pain correlated with Placebo Analgesia
	5	(Placebo - Control) during anticipation correlated with Placebo Analgesia
Wager et al., 2004, Study 2	6	(Placebo - Control) during anticipation
	7	(Control - Placebo) during early pain
	8	(Control - Placebo) during late pain
	9	(Control - Placebo) during early pain correlated with Placebo Analgesia
	10	(Control - Placebo) during late pain correlated with Placebo Analgesia
Lieberman et al., 2004	11	(Before - After) placebo treatment correlated with symptom improvement
Bingel et al., 2006	12	(Placebo - Control) during laser stimulation
Kong et al., 2006	13	(After - Before placebo treatment) - (Placebo - Control site)
	14	(After - Before) placebo - (Placebo - Control site) correlated with Placebo Analgesia
Price et al., 2007	15	Pre-placebo (B1) - Placebo during pain AND Post-placebo (B2) - Placebo; ROIs
Eippert et al., 2009a	16	(Control - Placebo) during early pain
	17	(Control - Placebo) during late pain
	18	(Control - Placebo) - (Saline - Naloxone group) during early pain
	19	(Control - Placebo) - (Saline - Naloxone group) during late pain
	20	(Placebo - Control) early pain
	21	(Placebo - Control) - (Saline - Naloxone) early pain
	22	(Placebo - Control) during pain, brainstem-specific
	23	(Placebo - Control) - (Saline - Naloxone) during pain, brainstem-specific
	24	(Placebo - Control) during pain, brainstem, correlated with Placebo Analgesia
	25	(Placebo - Control) correlation with Placebo Analgesia, Saline > Naloxone
Lu et al., 2009	26	(Control - Placebo) during pain
Watson et al., 2009	27	(Placebo - Control) during anticipation
	28	(Control - Placebo) correlated with Placebo Analgesia
Kong et al., 2009a	29	Placebo acupuncture group (N=12), (Pre - Post-placebo) x (Placebo - Control) site
Craggs et al., 2008	30	Placebo - Baseline during pain
Kong et al., 2009b	31	Verum acupuncture (High-Low expectancy) groups, (Pre - Post-treatment)
	32	Verum acup high-expectancy group, (Pre - Post-treatment) - (Expected - Control site)
	33	ME of expectancy on high-expectancy site, (pre - post treatment)

Wager et al., 2011	34	(Placebo - Control) during anticipation correlated with Placebo Analgesia
	35	(Control - Placebo) during pain correlated with Placebo Analgesia
Zubieta et al., 2005	36	(Placebo - Control) opioid increase; carfentanil binding decrease
Waget et al., 2007	37	(Placebo - Control) opioid increase, (Painful - Nonpainful Heat)
Scott et al., 2008	38	(Placebo - Control) opioid increase; carfentanil binding decrease
	39	(Placebo - Control) dopamine increase (raclopride binding decrease)
Harris et al., 2009	40	Opioid increase (binding decrease) After - Before sham acupuncture
Eippert et al., 2009a	41	(Placebo - Control) - (Saline - Naloxone Group), brainstem-specific analysis
	42	(Placebo - Control) - (Saline - Naloxone) correlated with Placebo Analgesia; brainstem
	43	(Placebo - Control) - (Saline - Naloxone) in early pain

Note: Results from each of these studies are coded by the specific comparisons between conditions used (contrasts) and plotted in Figures 27.3 and 27.4.

Figure Captions

Figure 27.1 Estimating the placebo effect. The graph shows the time course of pain severity after enrollment in a clinical trial in three hypothetical groups. The No-treatment group, shown in orange, may improve spontaneously due to a combination of the natural time-course of the condition and regression to the mean. The vast majority of clinical trials do not contain such a group, but in those that do, the *natural history effect* is estimated as the change in pain severity relative to pain levels on enrollment. The Placebo group, shown in blue, may show greater pain relief than the No-treatment group due to active psychological/brain processes. The difference between the Placebo group and the No-treatment group thus defines the *placebo effect.* By contrast, the *placebo response* is the total change from enrollment levels in the Placebo group, i.e., the placebo effect plus the natural history effect, and does not necessarily reflect any active psychological/brain changes induced by the placebo. The Drug group, shown in green, shows more rapid and complete pain reduction in trials of effective medications. The difference in pain severity between the Drug and Placebo groups after treatment defines the *drug effect.* The drug effect is the outcome of primary interest in nearly all clinical trials, and thus most clinical trials only compare the Drug and Placebo groups. Without a No-treatment group, however, it is impossible to isolate the active psychobiological effects of the placebo.

Figure 27.2. Natural history and regression to the mean. A) The time course of pain severity in four hypothetical patients (P1 – P4) who experience fluctuating levels of pain over time, but no change in their long-term average pain. The dashed arrow marks a likely point of enrollment in treatment for each person, which often occurs when pain is higher than average. In this hypothetical example, we assume a normal distribution of pain values that fluctuates slowly around a constant average for each patient. B) The time course of pain following enrollment for each person (black lines) and the group average (orange line). In this case the trial would show a substantial natural history effect. If the individuals shown had received a placebo treatment, the trial would appear to show a substantial placebo response. As there is no true, long-term improvement in any patient, this effect is due to regression to the mean. C) The true population average across time (dashed orange line), vs. the apparent natural history effect. The dashed orange line is flat because there is no true average change across time in this hypothetical

example, only symptom fluctuation. The solid orange line shows pain reduction over time because of regression to the mean, i.e., patients tend to enroll when their pain is extreme, and thus tends to be less extreme on repeated measurements.

Figure 27.3. Modulation of pain processing-related brain activity by placebo treatments. A) Reported stereotactic coordinates reflecting placebo-induced decreases in fMRI activity during painful stimulation. Coordinates from statistical contrasts showing reduced activity with placebo (e.g., [Placebo < Control]) in group analyses are shown in blue, and coordinates showing correlations between reduced brain activity and placebo analgesia in subjective reports are shown in green. Contrasts are numbered according to the specific comparisons listed in Table 27.1. In this and all Figures, coordinates from the same contrast within 12 mm were averaged together before plotting. B) Consensus regions showing effects within 10 mm in at least three separate contrast maps. The map shows decreased activity during pain in (from bottom to top in the brain) the amygdala and basal forebrain, anterior insula and operculum, medial thalamus, striatum, anterior cingulate, and parts of the prefrontal cortex. C) Detail showing individual study findings (numbered as in Table 1) around the insula, thalamus, and striatum.

Figure 27.4. Mechanisms of placebo analgesia revealed through neuroimaging. A) Coordinates from individual studies, numbered according to Table 1, associated with placebo-induced increases in activity. Overall activity increases in group analyses (e.g., [Placebo > Control] during anticipation or experience of pain) are shown in red, whereas activity increases correlated with the magnitude of placebo analgesia are shown in yellow. Subcortical structures are colored for visibility, and include the caudate (blue), thalamus (brown), brainstem (green), nucleus accumbens (darker green), hypothalamus (yellow), and amygdala (purple). Conistent changes in at least three separate contrasts were found in the dorsal pons, periaqueductal gray, bilateral mid-lateral orbitofrontal cortex, anterior insula, and bilateral poseterior lateral prefrontal cortex. B) Coordinates associated with placebo-induced increases in endogenous neurotransmitter/neuropeptide activity, including opioid increases (light blue) and dopamine increases (green). Also shown are coordinates associated with placebo-induced increases in activity that were blocked by naloxone (purple). Consistent changes in at least three separate contrasts were found in the dorsal pons, sugenual anterior cingulate, nucleus accumbens,

hypothalamus, and periaqueductal gray.

Figure Captions

Figure 27.1 Estimating the placebo effect. The graph shows the time course of pain severity after enrollment in a clinical trial in three hypothetical groups. The No-treatment group, shown in orange, may improve spontaneously due to a combination of the natural time-course of the condition and regression to the mean. The vast majority of clinical trials do not contain such a group, but in those that do, the *natural history effect* is estimated as the change in pain severity relative to pain levels on enrollment. The Placebo group, shown in blue, may show greater pain relief than the No-treatment group due to active psychological/brain processes. The difference between the Placebo group and the No-treatment group thus defines the *placebo effect.* By contrast, the *placebo response* is the total change from enrollment levels in the Placebo group, i.e., the placebo effect plus the natural history effect, and does not necessarily reflect any active psychological/brain changes induced by the placebo. The Drug group, shown in green, shows more rapid and complete pain reduction in trials of effective medications. The difference in pain severity between the Drug and Placebo groups after treatment defines the *drug effect.* The drug effect is the outcome of primary interest in nearly all clinical trials, and thus most clinical trials only compare the Drug and Placebo groups. Without a No-treatment group, however, it is impossible to isolate the active psychobiological effects of the placebo.

Figure 27.2. Natural history and regression to the mean. A) The time course of pain severity in four hypothetical patients (P1 – P4) who experience fluctuating levels of pain over time, but no change in their long-term average pain. The dashed arrow marks a likely point of enrollment in treatment for each person, which often occurs when pain is higher than average. In this hypothetical example, we assume a normal distribution of pain values that fluctuates slowly around a constant average for each patient. B) The time course of pain following enrollment for each person (black lines) and the group average (orange line). In this case the trial would show a substantial natural history effect. If the individuals shown had received a placebo treatment, the trial would appear to show a substantial placebo response. As there is no true, long-term improvement in any patient, this effect is due to regression to the mean. C) The true population average across time (dashed orange line), vs. the apparent natural history effect. The dashed orange line is flat because there is no true average change across time in this hypothetical

example, only symptom fluctuation. The solid orange line shows pain reduction over time because of regression to the mean, i.e., patients tend to enroll when their pain is extreme, and thus tends to be less extreme on repeated measurements.

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hypothalamus, and periaqueductal gray.

Figure 1.

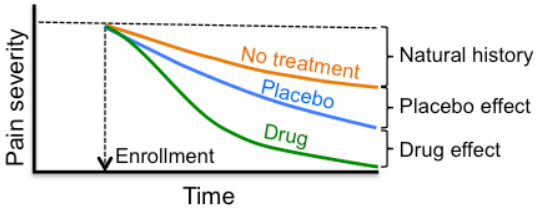
Pain severity
No treatment
Placebo
Drug
Enrollment
Time
Natural history
Placebo effect
Drug effect

Figure 2. Natural history and regression to the mean.

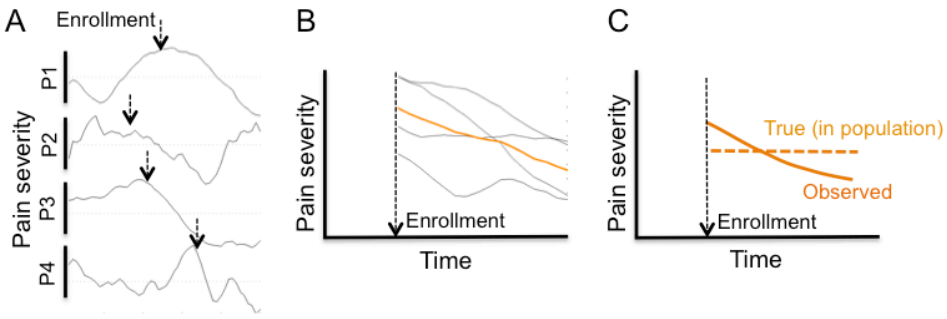

Figure 3. Placebo-induced decreases in brain activity during pain

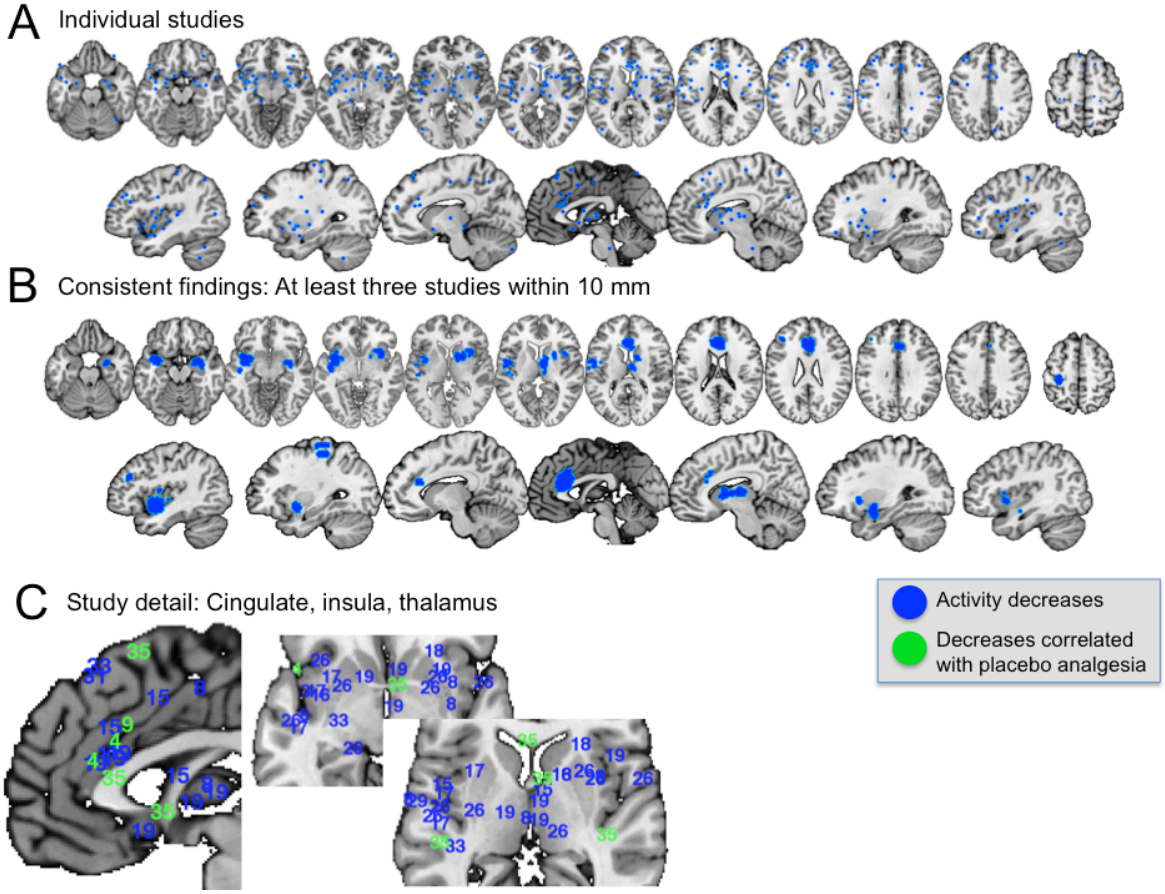

Figure 4. Placebo-induced increases in brain activity during anticipation and pain