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Placebo response

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Introduction

The placebo response can be described as a treatment effect caused not by the physical properties of treatment but by the meaning ascribed to it. This short review will focus on placebo analgesia in relation to its physiological validity, mechanisms and clinical relevance.

The use of placebos for pain therapy is probably as long-established as our civilisation. Some of the best known studies of placebo analgesia came from Beecher [1] during and after the Second World War when he was forced to use saline instead of morphine because he ran out of morphine. He found that placebo injections had remarkably sustained analgesic effects even in the context of severe trauma. Unfortunately his studies were uncontrolled and, therefore, difficult to interpret but they laid the foundation for recent interest in this important phenomenon. Since these remarkable studies, and until relatively recently, the placebo effect has been regarded more as a nuisance in the context of clinical trials than a subject worthy of study. The problems with placebo analgesia are often expressed in terms of its variability in magnitude and specificity (that is, some subjects will respond differently to differently coloured tablets) [2]. This has led some authors to question its biological significance and others to suggest that it is not a real physiological phenomenon but merely a product of regression to the mean or habituation [3]. Recent studies have established placebo as a potent physiological phenomenon [4]. The variability of placebo analgesia turns out to be its strength in that this provides us with a powerful means of using placebo analgesia as a manipulable physiological window into some of our brain-driven endogenous control mechanisms [5].

Pain perception

Pain perception is different to other types of sensory perception in that the sensation of pain is almost always associated with unpleasantness. However, in other respects it is quite similar in that the perceptual experience is an integration of actual sensory input with anticipated experience. Like other sensory experiences there is, therefore, a virtual reality component to the way in which pain is processed. Functional brain imaging has provided us with a detailed knowledge of the 'pain matrix' [6] in the brain that is responsible for pain perception. The 'pain matrix' is a dynamic parallel processing system that is as influenced by psychological cues (top-down) as it is by nociceptive information from the peripheral nervous system (bottom-up). This means that we need to take a 'whole-systems' approach to assessing pain, to understanding the mechanisms of pain and in treating it.

Placebo analgesia: physiological phenomenon or artefact?

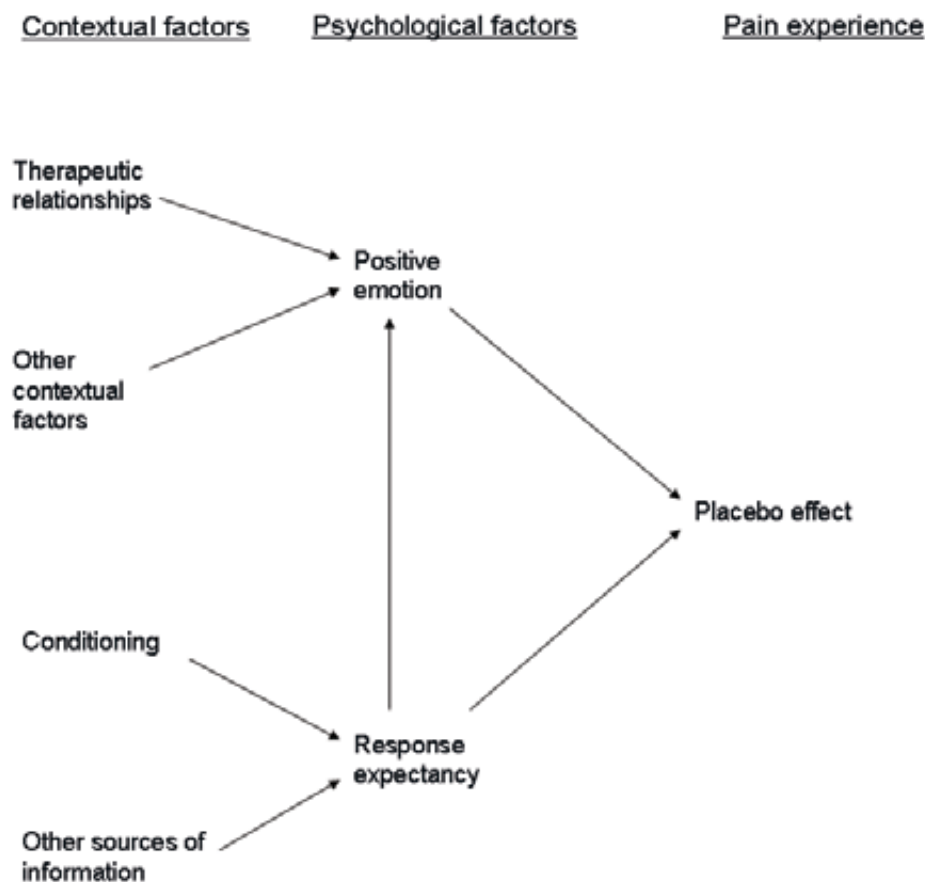
In this context it is, therefore, not surprising that the 'top-down' effects can have significant and lasting effects on the way we perceive pain. In subjects who are very suggestible, pain can be induced experimentally without any nociceptive input, activating the same areas of the pain matrix as are activated during noxious stimulation. In a similar way, pain can be reduced experimentally by placebo medications just by the suggestion that they may have an analgesic effect [7]. One potential explanation for these effects is that this is not a physiological response but is due to increased compliance. In other words, the subject or patient gives the response they think is required, without actually feeling it differently. An alternative explanation is that placebo analgesia is due to habituation or just regression to the mean. Recent combined behavioural, electrophysiological and functional imaging studies suggest that placebo analgesia is a robust physiological phenomenon due to very specific changes in cortical and sub-cortical activity [4, 8]. This provides us with the exciting prospect of understanding some powerful endogenous pain control mechanisms by studying placebo analgesia in greater detail.

The magnitude of the placebo effect is highly variable and dependent on the psychological context of the study design. High levels of verbal reinforcement or suggestion will have a positive effect on the magnitude of placebo analgesia [9]. In general placebo analgesic responses are reported as providing a mean reduction in pain of between 20-30 %, depending on the levels of reinforcement. Because of the variability in the placebo response it has been assumed that it is not reproducible within individuals and is not related to personality traits [10]. Recent studies suggest that when experimental conditions including suggestion are carefully controlled, the placebo analgesia is highly reproducible in individuals and positively related to optimism [11].

Mechanisms

The primary mechanisms for the placebo response have to be brain derived, although there is evidence for secondary mechanisms involving modulation of descending inhibitory control [12]. The brain mechanisms appear to be related to a number of interacting processes related to altered expectation, mood, desire for pain relief, somatic focus and conditioning. It is likely that there is a hierarchy of related mechanisms that help to mediate placebo analgesia. The role of reduced expectation of pain in placebo analgesia has been demonstrated by a number of experiments where the subjects' expectation of pain relief were highly correlated with actual relief [13]. However, alterations of mood, particularly in relation to reduced anxiety, have been implicated by a number of studies. Although altered expectation would appear to be more important than classical conditioning in placebo analgesia, there is evidence for classical conditioning playing a more important part in other aspects of the placebo response, for instance in relation to a neuro-immune response that can be demonstrated in human and animals [14]. It is, therefore, possible to construct simple and more complex models of placebo response (Figure 1).

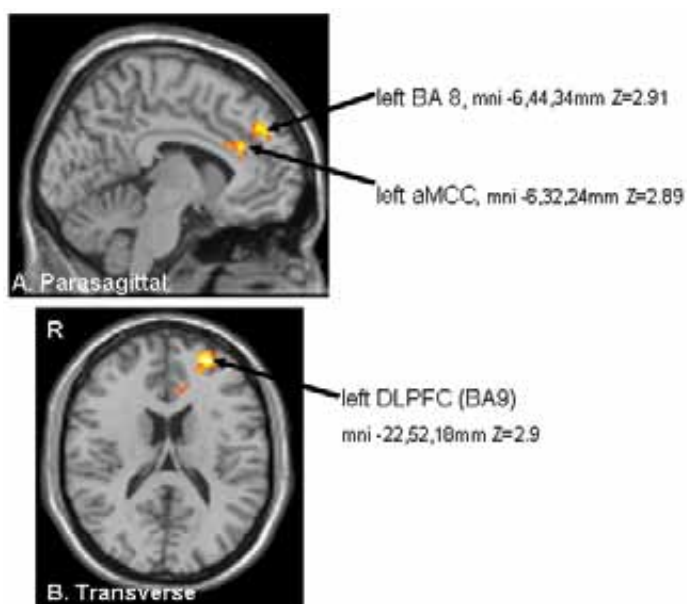
Figure 1



A simple construct of a possible model of the placebo response.
Kirsch I. *The emperor's new drugs: exploding the antidepressant myth*. London: Random House, (in press).

We are just beginning to understand the brain substrates of placebo analgesia. A number of functional brain imaging studies have shown reductions in activity within the pain matrix during placebo response. A more interesting question is what circuitry initiates and maintains these responses. There is now evidence for a number of brain regions that appear to be responsible for at least a part of the neuromodulation during placebo response which include the dorsolateral prefrontal cortex (DLPF), medial prefrontal cortex, orbito-frontal cortex (OFC) and cingulate cortex (CC). These areas are involved in memory, executive control, self-appraisal, attention and reward, as well as nociceptive processing (DLPF, CC) [15]. Work from our group [15] has looked at the whole sequence of experimental placebo from pre-conditioning (noxious stimulation), conditioning (administration of inactive cream with instruction that it may contain anaesthetic after which the pain stimulation energy is turned down) and post-conditioning (return to previous level of noxious stimulation). There would appear to be a common circuitry involving the DLPF, OFC, anterior mid cingulate (aMCC) that is responsible for the modulation of expectation during conditioning and the post-conditioning (Figure 2) (OFC being activated during anticipation only during post-conditioning). Only aMCC is modulated during expectation (during conditioning and post-conditioning) and placebo analgesia and represents the interaction between these two processes. It is possible that the aMCC mediates the interactions between higher cognitive control mechanisms and placebo analgesia and self-appraisal. This would fit well with its functions in emotional control and the high concentrations of opioid receptors in this area of the cingulate cortex [16]. Structures necessary for the placebo response are activated in terms of memory comparison with previous experience and locations (post-cingulate, DLPF), stimulus appraisal and error monitoring (aMCC), and control of attention (aMCC, DLPF) and affect (aMCC, MFC) and maintenance of belief (DLPF) and reward (OFC). If the reward is the reduction in pain which elevates mood, then this may be what drives the higher control centres to reduce attention to the mismatch between expected stimulus intensity and actual stimulus intensity with consequent modulation of nociceptive processing within the pain matrix.

Figure 2



Common brain areas activated during pain anticipation in both the placebo conditioning and post-conditioning stages compared to the pre-treatment stage. DLPFC (left dorsolateral prefrontal cortex) (mni -22, 52, 18, BA 9), left BA 8, mni -6,44,34) and left aMCC (mni -6,32,24)). The images are shown in axial and sagittal orientation and radiological convention (right side of the brain on the left side of the picture). This image has been accepted for publication in an Elsevier journal.

The neurochemical mediators of placebo response

The first evidence that the placebo effect may be mediated by endogenous opioids was provided by Levine and colleagues [17] using naloxone to block the placebo analgesic effects of infusions of saline. These have been variably reproduced by subsequent pharmacological studies since, but naloxone has been found not to completely block placebo analgesic effects [18]. This may be because of incomplete blockade of mu and other receptor subtypes or because there are other neurochemical mediators. Recent PET studies [19] have provided more direct evidence of placebo analgesia being associated with changes in endogenous opioid activity, particularly within structures associated with reward, motivational processing and control of executive function such as the aMCC, ACC (pre-genual cingulate) and orbito-frontal cortices. Interestingly it would appear that negative suggestion effects (nocebo) have different modulators and are blocked by cholecystokinin antagonists which have no effect on placebo analgesia.

Clinical relevance

The clinical relevance of this is that suggestion and empathy have key effects on the efficacy and even the valence of therapeutic interventions. This means that the way in which a therapeutic intervention is introduced will often have a significant effect on the positive and negative effects on the patient. The skill of the physician is, therefore, to balance the information given about therapy with sufficient positive reassurance to maximise the clinical benefit [20]. The development of new pharmaceutical agents, that inhibit the breakdown of endogenous opioids in the brain, provides the possibility of enhancing the brain's own endogenous control mechanisms, including placebo effects. This will provide an interesting challenge to clinical trial design. Placebo analgesia provides a difficulty to clinical trials. There is a suggestion that a significant proportion of the most recent 18 trials of new analgesics failed because of a high placebo response in the control arm. The assumption of any controlled trial is that there will be an equal proportion of placebo responders in each group. The larger the trial, the greater is the likelihood that this is going to be true. However, because of the variability of placebo effects it is not possible at the moment to estimate the point for any therapeutic intervention where this becomes adequate to test the null hypothesis. However, with further studies of placebo analgesia in different clinical and non-clinical populations it should be possible to substantially reduce the uncertainty of clinical trials of pain therapies.

Key Learning Points

- Placebo analgesia is a powerful physiological phenomenon and is not due to habituation effects or increased subject compliance.
- The magnitude of placebo analgesia is highly dependent on the psychological context of the administration of the placebo.
- Early evidence suggests that reproducibility of placebo effects may be correlated with psychological traits such as optimism.
- The mechanisms of placebo analgesia are just beginning to be understood and appear to be related to adaptive changes within orbito-frontal structures in the brain concerned with reward, memory, attention and mood.
- The neurochemical basis of placebo analgesia is less well understood but there is some evidence that the release of endogenous opioids, which normally modulate nociceptive activity, may be enhanced during placebo analgesia.

References

1. Beecher HK. The powerful placebo. *J Am Med Assoc* 1955; 159: 1602-1606.
2. de Craen AJM, Roos PJ, de Vries AL, Kleijnen J. Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness. *BMJ* 1996; 313: 1624-6.
3. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001; 344: 1594-602.
4. Watson A, El-Derey W, Vogt BA, Jones AK. Placebo analgesia is not due to compliance or habituation: EEG and behavioural evidence. *Neuroreport* 2007; 18: 771-5.
5. Zubieta JK, Bueller JA, Jackson LR, et al. Placebo effects mediated by endogenous opioid activity on (micro)-opioid receptors. *Journal of Neuroscience* 2005; 25: 7754-62.
6. Kulkarni B, Bentley DE, Elliott R, et al. Attention to pain localization and unpleasantness discriminates the functions of the medial and lateral pain systems. *Eur J Neurosci* 2005; 21: 3133-42.
7. Watson A, El-Derey W, Bentley DE, Vogt BA, Jones AKP. Categories of placebo response in the absence of site-specific expectation of analgesia. *Pain* 2006; 126: 115-22.

8. Wager TD, Rilling JK, Smith EE, et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 2004; 303: 1162-7.
9. Price DD, Milling LS, Kirsch I, et al. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 1999; 83: 147-56.
10. Whalley B, Hyland ME, Kirsch I. Consistency of the placebo effect. *J Psychosom Res* 2008; 64: 537-41.
11. Morton DL, Watson A, El-Deredy W, Jones AK. Reproducibility of placebo analgesia: Effect of dispositional optimism. *Pain* 2008 (in press).
12. Goffaux P, Redmond WJ, Rainville P, Marchand S. Descending analgesia--when the spine echoes what the brain expects. *Pain* 2007; 130: 137-43.
13. Vase L, Robinson ME, Verne GN, Price DD. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients: An empirical investigation. *Pain* 2003; 105: 17-25.
14. Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta JK. Neurobiological mechanisms of the placebo effect. *Journal of Neuroscience* 2005; 25: 10390-402.
15. Watson A, El-Deredy W, Iannetti G, et al. Placebo conditioning and placebo analgesia modulate a common brain network during pain anticipation and perception. *Pain* 2008 (in press).
16. Casey KL, Svensson P, Morrow TJ, et al. Selective opiate modulation of nociceptive processing in the human brain. *J Neurophysiol* 2000; 84: 525-33.
17. Levine JD, Gordon NC, Fields HL. The mechanism of placebo analgesia. *Lancet* 1978; 2: 654-7.
18. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *Journal of Neuroscience* 1999; 19: 484-94.
19. Zubieta JK, Yau WY, Scott DJ, Stohler CS. Belief or need? Accounting for individual variations in the neurochemistry of the placebo effect. *Brain Behav Immun* 2006; 20: 15-26.
20. Benedetti F. How the doctor's words affect the patient's brain. *Evaluation & the Health Professions* 2002; 25: 369-86.