Pain and the context

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Abstract | Pain is a sensory and emotional experience that is substantially modulated by psychological, social and contextual factors. Research now indicates that the influence of these factors is even more powerful than expected and involves the therapeutic response to analgesic drugs as well as the pain experience itself, which in some circumstances can even be a form of reward. Different experimental approaches and models, both in the laboratory and in the clinical setting, have been used to better characterize and understand the complex neurobiology of pain modulation. These approaches include placebo analgesia, nocebo hyperalgesia, hidden administration of analgesics, and the manipulation of the pain–reward relationship. Overall, these studies show that different neurochemical systems are activated in different positive and negative contexts. Moreover, pain can activate reward mechanisms when experienced within contexts that have special positive meaning. Because routine medical practice usually takes place in contexts that use different rituals, these neurobiological insights might have profound clinical implications.

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Introduction

A variety of cognitive and emotional factors, as well as a number of sensory inputs, modulate pain perception.[1,2] Mood and attention to pain might be important determinants of the experience of pain, and sensory stimuli such as pleasant and unpleasant odours might lead to different degrees of pain.[3,4] Negative emotions can cause or exacerbate pain, and lead to neural changes in different regions of the brain.[5] All cognitive, emotional and sensory processes that affect pain perception arise from the context surrounding the painful experience, such that different contextual factors might have an important role in the perception of pain. Not only does this hold true for pain perception itself, but also for the response to analgesic treatments. Balint *et al.*[6] referred to the context surrounding the patient and the therapy as "the whole atmosphere" around the treatment. This context includes the physical properties of the medication, such as colour, shape, taste and smell, the characteristics of the hospital room, the sight of health professionals and medical instruments and the interaction between patient and doctor.[7]

In the last two decades, the powerful influence of the context on the response to pharmacological, and other treatments, has been investigated by using the placebo effect as a model.[8] In this Review we focus our attention on experimental approaches and models that have helped understand how pain and analgesia are modulated by different contexts, with particular emphasis on the neurobiology. This is not a comprehensive Review, but a selection of exciting models and novel concepts that include placebo and nocebo effects, hidden administration of drugs, and the interaction between pain and reward. In fact, these experimental approaches are excellent models to investigate both context-induced modulation of pain and its possible clinical implications. These approaches help us to better understand the effect of positive contexts, negative contexts, contexts with special meanings, and the lack of a therapeutic context. Other comprehensive reviews on these topics are available.[9–17]

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Positive therapeutic context

The placebo response is an excellent model to study the effects of the context on therapeutic outcome. To study the placebo response is to study the psychosocial context of the patient and the therapy.[8,17,18] Several sensory and social stimuli, such as the doctor's words, including their meaning and tone, the hospital environment and the medical facilities 'tell' the patient that a treatment is being performed.

At least two important mechanisms create a positive context for the therapeutic outcome. The first is a conscious mechanism that involves positive expectations,[19] whereby positive contextual elements forecasting benefit may either reduce anxiety or activate reward mechanisms.[8,17] The second mechanism is unconscious and involves classical conditioning. A round, white pill containing acetylsalicylic acid, for example, leads to a conditioned placebo response, whereby any round and white pill will produce the same effect, even if there is no active ingredient.[8,17]

Both context-induced positive expectation and context-induced conditioning produce brain changes that are associated with the activation of at least two neurochemical systems, the endogenous opioid and endocannabinoid systems.[20] This differential activation takes place in different sub-contexts. If a placebo, for example, is administered after pharmacological pre-exposure to

Key points

- Pain is modulated by a variety of contextual factors
- Positive contexts, such as those related to placebo administration, have been found to activate a number of endogenous antinociceptive systems
- Negative contexts, such as those related to nocebo effects, activate endogenous systems that increase pain
- Contexts with positive meanings might even turn pain into a rewarding experience
- If therapy has no positive context, so that patients have no expectations of benefit, the effectiveness of treatment is reduced
- Consultations, diagnostic procedures and treatments are carried out within a context; this context might be a crucial determinant of symptom perception and therapeutic outcome

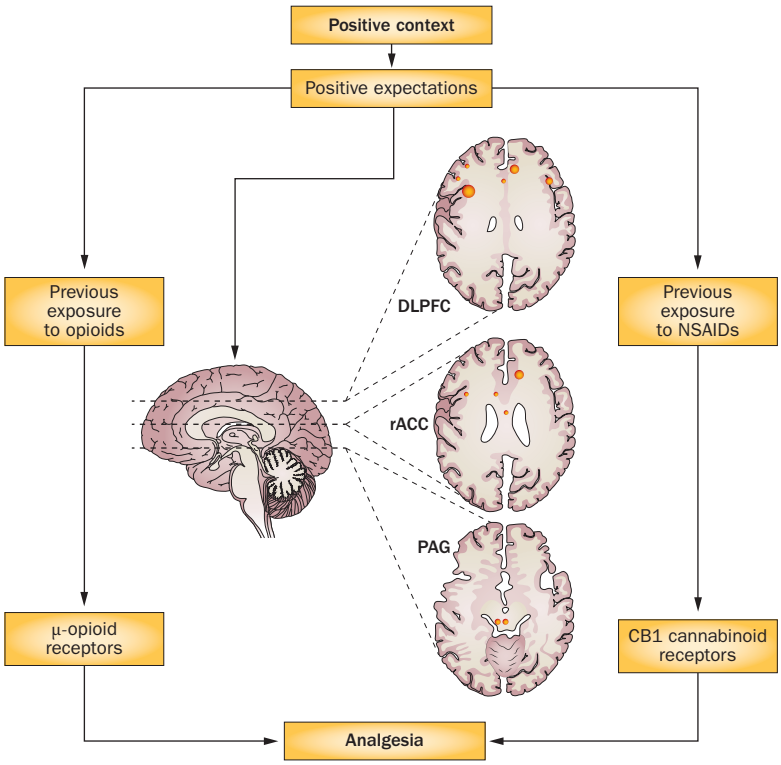

Figure 1 | The positive context. A positive therapeutic context induces positive expectations, which activate different brain regions, including the DLPFC, the rACC and the PAG. This is an inhibitory pain modulating network that can be mediated by two different neurochemical receptor systems, either the μ-opioid receptors or the cannabinoid receptor 1, depending on previous exposure to pharmacological agents. Abbreviations: DLPFC, dorsolateral prefrontal cortex; PAG, periaqueductal grey; rACC, rostral anterior cingulate cortex.

μ-opioid receptor agonists, the response is mediated by the μ-opioid receptor, whereas if the placebo is given after NSAIDs, it is mediated by the cannabinoid receptor 1,[21] which is activated by NSAIDs (Figure 1).

Little is known about the placebo-activated endocannabinoid system. One study investigated psychophysical, dopaminergic and opioid responses to pain and placebo-induced analgesia, and the influence of the common functional missense mutant Pro129Thr of *FAAH*, which encodes fatty acid amide hydrolase 1, the major endocannabinoid-degrading enzyme. *FAAH* Pro129/Pro129 homozygotes had higher analgesic responses to placebo and more positive emotions immediately and 24 h after administration. In regions of the brain known to be involved in the placebo response, Pro129/Pro129 homozygotes also had greater placebo-induced μ-opioid receptor activation, but not dopaminergic receptor activation.[22]

The placebo-activated opioid system has been investigated in more detail than the placebo-activated endocannabinoid system. Some analgesic responses to placebo, such as those following opioid pre-conditioning, are blocked by naloxone.[23] Cholecystokinin (CCK) has been found to reduce placebo analgesia with its anti-opioid action.[24,25] Complementary results have been obtained in animal models of placebo analgesia, in which the placebo response was blocked by naloxone administration.[26–28] From a neuroanatomical viewpoint, there is now agreement that administration of a placebo along with positive verbal suggestions activates a descending pain modulating network, which is known to have a crucial role in modulation of the ascending nociceptive inputs.[29–33] Three important regions of the brain are involved in this network, the dorsolateral prefrontal cortex, the rostral anterior cingulate cortex, and the periaqueductal grey (Figure 1), although many other areas of the brain are also activated or deactivated by the placebo response.[14,34–45]

Dopamine also has a role in placebo responsiveness. In particular, it depends, at least in part, on the function and efficiency of the reward system.[40] The dopaminergic system in the nucleus accumbens is activated during placebo analgesia.[41] Different neurotransmitters and neuromodulators, therefore, seem to be activated by placebos in different contexts. The challenge for placebo researchers is to identify which neurotransmitters are activated following the administration of a placebo, and when and how they are activated and released.

Negative context

The nocebo response is a phenomenon that is opposite to the placebo response and is induced by negative expectations. If a placebo is given within a negative context, for example along with a negative verbal suggestion of pain, a nocebo response can occur. There are many examples of negative contexts that lead to negative expectations. For example, negative diagnoses and prognoses can lead to an amplification of pain intensity, and can have important effects on the emotional state of patients.[46,47] Nocebo and nocebo-related effects can also occur when patients distrust medical personnel or the prescribed therapy. The health reports commonly issued in Western societies can have nocebo effects; negative warnings sent out by the mass media may have an important impact on people's perceived symptoms. Headaches, for example, can be caused by believing that there are health risks associated with the use of mobile phones.[48] Similarly, some negative expectation-inducing procedures, such as voodoo magic aimed at producing illness, could exacerbate symptoms. In clinical trials of analgesic agents, there are frequent reports of adverse events from patients who receive placebo. One study of clinical trial data compared the rate of adverse events for three classes of antimigraine drugs

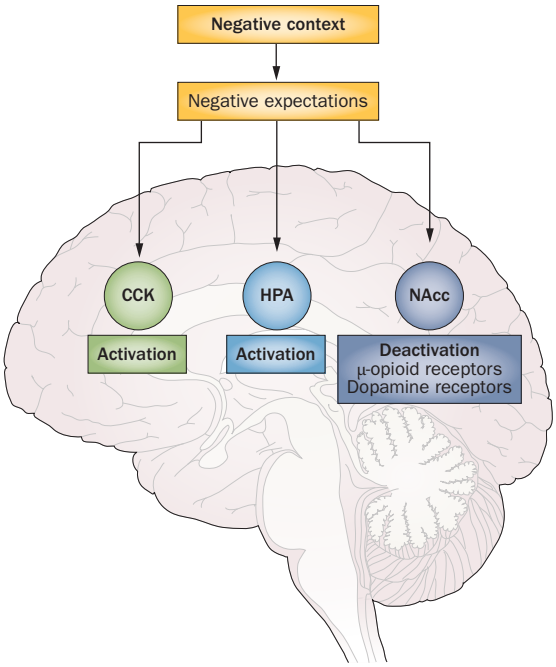

Figure 2 | The negative context. A negative context induces negative expectations and activates CCK, which has a facilitating effect on pain transmission, and the HPA, which is related to anticipatory anxiety. Negative expectations also reduce μ-opioid receptor and dopamine receptor signalling in the NAcc. Abbreviations: CCK, cholecystokinin; HPA, hypothalamic–pituitary–adrenal axis; NAcc, nucleus accumbens.

(NSAIDs, triptans and anticonvulsants) and found that the adverse events in the placebo-treated patients corresponded to those of the antimigraine medication against which the placebo was compared.[49] For example, anorexia and memory difficulties, which are typical adverse events following the use of anticonvulsants, only occurred in the placebo treated patients in these trials. This is in line with the expectation theory of the nocebo effect. In fact, in a clinical trial, both the patients who receive the true treatment and those who receive the placebo read an identical informed consent with a list of adverse events, which leads them to expect specific negative effects.

Compared with placebo analgesia, much less is known about nocebo hyperalgesia, mainly due to ethical limitations. The induction of placebo responses is often acceptable, whereas the induction of nocebo responses is an anxiogenic procedure. From a pharmacological viewpoint, the nocebo hyperalgesic effect can be mediated by CCK,[50,51] and can be blocked by the CCK antagonist, proglumide, and the antianxiety drug, diazepam, suggesting that anticipatory anxiety has an important role in nocebo hyperalgesia (Figure 2). Adrenocorticotropic hormone and cortisol plasma concentrations measured during nocebo responses indicate that hyperactivity of the hypothalamic–pituitary–adrenal axis is involved.[51] Similar findings were obtained in a social-defeat model of anxiety in rats, in which CI-988, a selective CCK type B receptor antagonist, prevented anxiety-induced hyperalgesia.[52] Nocebo effects are also associated with a decrease in dopamine and opioid activity in the nucleus accumbens (Figure 2), highlighting the role of the reward and motivational circuits in nocebo responses.[41]

Actual discrepancy between anxiety-induced hyperalgesia and stress-induced analgesia might not exist. Stress is known to induce analgesia and increase the pain threshold in a variety of situations, both in animal models and in humans. The nature of the stressor plays a central role. Whereas hyperalgesia might occur when anxiety is due to anticipation of pain,[51,53–55] analgesia might occur when anxiety is about a stressor that shifts attention away from the pain.[56–58] We should, therefore, use these definitions in two different ways, as has been recently emphasized.[59] In the case of anxiety-induced hyperalgesia, attention is focused on the impending pain, and the biochemical link between this anticipatory anxiety and the pain increase involves CCK. Conversely, stress-induced analgesia is a general state of arousal that stems from the focus of attention on an environmental stressor. Experimental evidence exists that this type of stress-induced analgesia results from activation of endogenous opioid systems.[56,57]

Neuroimaging studies have found that negative expectations increase the activity of brain regions involved in pain processing and emotional regulation, including the prefrontal cortex, anterior cingulate cortex and insula, along with the increase in pain perception.[53–55,60–69] Nocebos have also been found to affect the dorsal horn in the spinal cord, thus interacting at very early stages of nociception.[70]

Contexts with special meanings

Contextual factors can have special symbolic meanings that powerfully influence the pain experience. In a study of hand holding, in which married women were subjected to the threat of electric shock while holding either their husband's hand, the hand of an anonymous male experimenter, or no hand at all, the spouse's hand decreased the feeling of unpleasantness compared with no hand-holding, whereas holding the stranger's hand had no such benefit.[71] In addition, brain imaging found attenuation of activation in the neural systems that support emotional and behavioural threat responses when the women held their husband's hand. A more limited attenuation of activation occurred when they held the hand of a stranger. Interestingly, the effects of spousal hand-holding on these neural threat responses also varied as a function of marital quality. Higher marital quality was associated with less threat-related neural activation in the right anterior insula, superior frontal gyrus and hypothalamus during spousal hand-holding, but not with stranger hand-holding. It should be noted that hand-holding by a close relative or friend is not always necessary for these effects, the presence of a loved one is enough. In patients with fibromyalgia, pain sensitivity as well as subjective pain ratings are reduced in the presence of the patient's family and friends, compared with the rating of pain when the patient is alone.[72]

The meaning that a patient interprets from a symptom can be crucial. Cancer-related pain can be perceived as

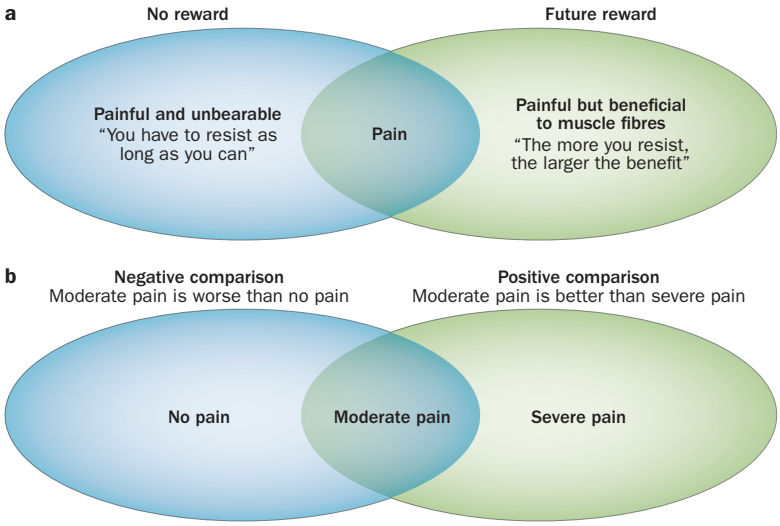

Figure 3 | Pain is perceived in different contexts according to special meanings. **a** | If pain is associated with a future reward, tolerance is increased through the activation of the endogenous opioid and cannabinoid systems.[79] **b** | When moderate pain is compared with the absence of pain, it is the worst possible outcome. When moderate pain is compared to severe pain, it is the best possible outcome; accordingly, it activates reward mechanisms and can be experienced as pleasant.[80]

more unpleasant than postoperative pain,[73–75] because of the association with the prognosis, illness or death on one hand and healing on the other, respectively. An individual's interpretation of the meaning of pain is not always associated with prognosis. Different religions and cultures attribute different meanings to pain and suffering, and this can lead to different experiences of pain.[76–78] For example, certain religions inspire self-flagellation, which can have a positive meaning of redemption and salvation.

In order to investigate the neurobiological effects produced by different meaningful contexts, one study manipulated patient interpretations of the meaning of pain.[79] The subjects had to tolerate ischaemic arm pain for as long as they could bear. One group of patients was pre-informed of the pain of ischaemia, as is ordinarily required in such studies, whereas the other group was told that ischaemia would be beneficial to the muscles, thus that there was a future reward in the pain endurance task (Figure 3a). Pain tolerance was significantly higher in this group compared with the first group, an effect that was partially blocked by the opioid antagonist, naltrexone, or by the cannabinoid antagonist, rimonabant, and completely blocked by a combination of the two drugs. These data suggest that the expectation of a future reward reduces the pain experience through the co-activation of the opioid and cannabinoid systems. Interestingly, there was a negative correlation between the effects of the opioid antagonist and those of the cannabinoid antagonist, according to the rule 'the larger the effect of the opioid antagonist, the smaller the effect of the cannabinoid antagonist', which suggests that individuals preferentially use either opioid or cannabinoid systems.

In a study of pain perception, skin conductance and brain activation patterns in response to moderate pain, two different contexts were used for analysis.[80] 'Control context' participants had a 50% chance of receiving a moderate painful stimulation or a nonpainful warm stimulation, whereas 'relative relief context' participants had a 50% chance of receiving a moderate or highly painful stimulation (Figure 3b). Moderate pain was perceived as painful and elicited negative feelings in the control context (perceived as the worst outcome) but it was perceived as surprisingly pleasant in the pain relief context (perceived as the best outcome) and similar in magnitude to the nonpainful warm stimulation in the control context. The measured change in skin conductance during moderate noxious stimulation was considerably lower in the relative relief context compared to the control context. Moreover, when moderate pain was perceived as pleasant, activity in the insula and dorsal anterior cingulate cortex was attenuated, whereas the activity in the reward circuitry, including the medial orbitofrontal and ventromedial prefrontal cortices, was substantially increased.

These studies show that even pain can be perceived as a rewarding experience if it is presented within a context in which there is special positive meaning.[79,80] The relationship between pain and reward is well documented,[13,81–83] and relief from pain can be a form of reward.[84] Analgesia can activate the same mesolimbic reward network as stimuli including food, money and drugs of abuse. In addition, endogenous opioids and cannabinoids are both located in regions of the brain that are involved with pain and reward, and they overlap in the neural processing of antinociception and reward behaviour.[85–89] The fact that pain can have a positive meaning in the appropriate context suggests that the context can be manipulated to therapeutically benefit the patient.

Lack of a meaningful context

The crucial role of expectation in the outcome of analgesic treatment is highlighted by the decreased effectiveness of treatment when a meaningful context is eliminated. This involves giving an analgesic covertly, so that the patient is unaware a drug is being injected. The outcome is then compared, either with other patients or with the same patient at a different time, with the outcome following an expected administration of the drug. In this sense a meaningful context is related to all available information, including sensory and social stimuli, a context that tells the patient that therapy is in progress. If therapy is administered without the patient's awareness, the context loses its positive meaning, such as can occur in patients with dementia.

By using this approach in postoperative pain management, following the extraction of the third molar, intravenous injection of a 6–8 mg of morphine without patient awareness was found to have a similar effect to intravenous injection of saline solution (placebo) in full view of the patient.[90,91] In other words, telling the patient that a painkiller is being injected (with what is actually a saline solution) is as potent as a hidden injection of 6–8 mg of morphine that lacks a placebo benefit. Postoperative differences between open (expected) and

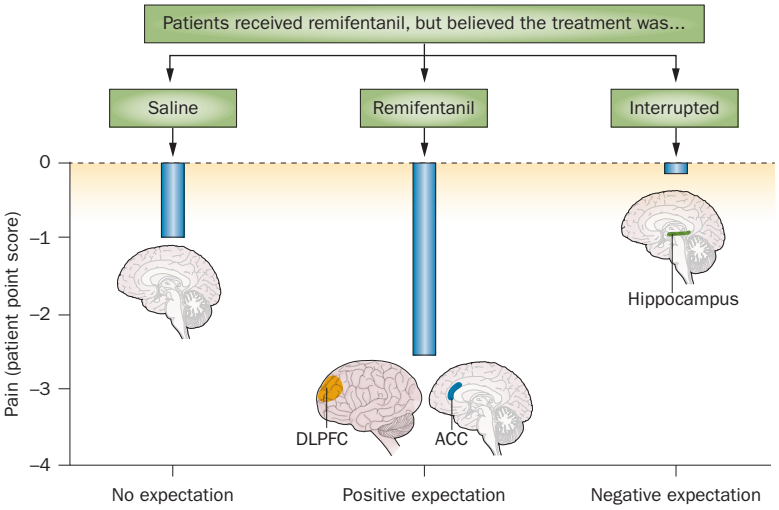

Figure 4 | Placebo response during pain reduction with remifentanil. Remifentanil was infused continuously, but when individuals were told the truth pain reduction was more pronounced than when they were told it was only saline solution. This is related to the activation of the DLPFC and the ACC, which are typically involved in the placebo response. When individuals are told that remifentanil has been interrupted, the analgesic effect disappears completely, and this is associated with activation of the hippocampus.[96] Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex.

hidden (unexpected) injections of five widely-used painkillers (morphine, buprenorphine, tramadol, ketorolac, metamizol) have been analysed.[92–95] Patients receiving expected injections were told that they were being injected with a powerful analgesic and that the pain would subside in a few minutes. In contrast, unaware patients were given hidden injections of the same analgesic at the same dose by an automatic infusion machine that started the painkilling infusion without any doctor or nurse in the room. The analgesic dose needed to reduce pain by 50% was found to be much higher with hidden infusions than with open infusions for all five painkillers tested, indicating that hidden administration is less effective than expected administration. The time-course of post-surgical pain was also found to be significantly different; during the first hour after administration the perception of pain was much higher with a hidden injection than with an open one.

Open and hidden administration of painkillers have also been studied in combination with neuroimaging.[96] Patients who were told that they were receiving remifentanil, and who did receive remifentanil, experienced less pain than patients who had no expectation because they were told they were receiving saline, but actually were given remifentanil. In addition, in patients who were told that their treatment was being interrupted, but in fact were continued on remifentanil, the analgesic effect of remifentanil was abolished. Neuroimaging of brain responses in these patients showed that enhancement of analgesia by positive expectation is associated with activity in the dorsolateral prefrontal cortex and pregenual anterior cingulate cortex, whereas negative expectation of interruption is associated with activity in the hippocampus (Figure 4).

The fact that hidden administration of a pharmacological agent is less effective than an open one suggests that there is a different action of the drug in the absence of expectations. The overall effect of a drug derives from its specific pharmacodynamic action plus the psychological (placebo) effect of its administration (meaningful context). One study suggests that these two components operate independently from each other.[97] In this study, the opioid agonist remifentanil was administered during experimental thermal pain, and participant knowledge of drug delivery was manipulated. Both remifentanil and expectation of remifentanil reduced pain, but the imaging showed that regions of the brain associated with pain processing were unchanged in response to drug effects as a function of expectation. Instead, expectations modulated activity in the frontal cortex, with a separable time course from drug effects. Therefore, both drugs and expectations influence clinical outcomes. Although drugs and expectations use the same type of receptors, such as μ-opioid receptors, these biochemical pathways are likely to be independent from each other and located in different areas of the brain.

In the same way that patients are unaware of receiving a hidden injection, patients with cognitive impairment relating to dementia are often unaware of treatment. For these patients there is no meaningful context. Placebo analgesia is reduced, or even completely inhibited, in patients with Alzheimer disease and this correlates with cognitive status and functional connectivity of different brain regions, according to the rule 'the more impaired the prefrontal connectivity, the smaller the placebo response'.[98] The overall effect of analgesic treatment, therefore, is reduced owing to the loss of the placebo effect. In fact, the individual placebo analgesic effect was found, in one study, to correlate with white matter integrity, particularly in the right dorsolateral prefrontal cortex, left rostral anterior cingulate cortex, and the periaqueductal grey.[99] These studies demonstrate that disruption of prefrontal functioning can affect therapeutic outcome.

Implications for clinical rheumatology

Experimental models such as the placebo and nocebo phenomena and the pain–reward relationship have shed new light on the modulation of pain by different types of positive and negative contexts. Overall, the context surrounding the patient and the treatment is crucial in producing the experience of pain, and we are now beginning to understand the associated neurobiology. On the one hand different contexts can alternatively activate neurochemical systems, and on the other hand the context itself is amenable to manipulation. In fact, any consultation, diagnostic procedure or treatment is carried out within a context, a context which itself may be a crucial determinant of symptom perception and therapeutic outcome.

A major problem for rheumatologists is the management of pain in patients with fibromyalgia. These patients have high sensitivity to placebo and nocebo effects.[100–102] An analysis of 18 trials with 3,546 patients treated with placebo for fibromyalgia estimated that

18.6% of patients had a 50% reduction in pain, whereas 10.9% of these patients dropped-out of the study because of adverse events.[102] This might suggest that psychological factors substantially influence the therapeutic outcome of patients with fibromyalgia. Psychological factors include emphasizing the importance of empathetic relationships with patients, positive reinforcement during procedures, and the avoidance of communicating the potential adverse effects of prescribed medications to patients.

Most rheumatic pathology involves pain or discomfort associated with a variety of impaired functions, including limitation of motion of affected areas, stiffness of affected muscles and joints, symptomatic worsening in response to climatic factors and soreness to the touch of affected regions. The clinical significance of rheumatic pain traverses a spectrum from mild to serious discomfort and from acute to chronic conditions. Therefore, in routine medical practice, special attention should be paid to those psychological factors that either improve or worsen the symptomatology of pain.

Conclusions

A better understanding of the neurobiology of the endogenous antinociceptive and pronociceptive systems is a challenge for future pain research. In particular, we need to understand which psychological factors are capable of modulating the perception of pain and which neurochemical pathways are involved in this modulation. The fact that positive and negative contexts activate different endogenous systems, as assessed in the laboratory, should be a starting point for clinical research aimed at manipulating the context around the patient in order to improve the doctor-patient relationship and the therapeutic outcome. In other words, the knowledge gained in the laboratory must be applied in clinical practice, where the character of the clinician is centre stage, confirming, after more than half a century that "the physician is a vastly more important institution than the drug store".[103]

Review criteria

We searched PubMed for the following keywords: "placebo effect", "placebo response", "placebo analgesia", "nocebo effect", "nocebo response", "nocebo hyperalgesia", "pain reward" and "pain modulation". Then we selected those studies aimed at investigating the mechanisms by means of a neuroscientific approach, such as pharmacology, brain imaging and behavioural analysis. Because this Review is aimed at discussing the role of the context in pain perception by using placebos, nocebos and rewards as experimental models, we discarded all clinical trial studies in which the main objective was to compare the placebo response with the real treatment response.

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E.C. and E.F. planned, discussed and wrote the review. F.B. planned, discussed and wrote the review, and supervised the work.