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Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans

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The perception of pain is subject to powerful influences. Understanding how these are mediated at a neuroanatomical and neurobiological level provides us with valuable information that has a direct impact on our ability to harness positive and minimize negative effects therapeutically, as well as optimize clinical trial designs when developing new analgesics. This is particularly relevant for placebo and nocebo effects. New research findings have directly contributed to an increased understanding of how placebo and nocebo effects are produced and what biological and psychological factors influence variances in the magnitude of the effect. The findings have relevance for chronic pain states and other disorders, where abnormal functioning of crucial brain regions might affect analgesic outcome even in the normal therapeutic setting.

Pain does not exist 'out there' by itself but is generated within the brain, akin to pleasure, warmth and other experiences felt subsequent to environmental stimuli. The same goes for relief and analgesia. These subjective, private, multidimensional experiences are observed and measured by behavioral responses or by individual reporting. The complexity of the relationship between the nociceptive input, the resultant pain experience and the subsequent report of pain or pain relief is what leads to many of the problems in pain research and clinical management—concerns over 'report bias' can influence judgment. The problem is that although nociception is usually the cause of pain, it is neither necessary nor sufficient and is very often not linearly related to the resulting pain. This is because of the many factors that influence nociceptive processing along the pathway from the nociceptor to the spinal cord and brain, including peripheral and central sensitization, genetics, cognition and emotions[1] (**Fig. 1b**).

In pain relief, the same problem exists in that analgesia can also arise without any obvious 'cause', therefore calling into question the original pain report, the exemplar being placebo analgesia. Placebos have had a rocky historical path, having been equated to 'fake' in the thirteenth century, from where the term placebo originates[2], and having been first described within a medical context only in the eighteenth century, highlighting the potential of the mind to influence physiology[3]. The adoption of the randomized controlled trial after World War II brought the placebo effect into the mainstream[4], and subsequent work has shown that it is a genuine psychobiological event attributable to the overall therapeutic context in which a treatment is given, which itself comprises many factors such as patient-physician interaction and treatment environment[5,6]. What a placebo intervention does is to simulate these factors so that the influence they have on the brain and body is the same as that produced by an active treatment within the same therapeutic context. Many experimental placebo designs exist, but most clinical trials use the simple placebo-controlled format, in which it is imperative that placebo effects are not falsely attributed to other factors, such as natural course of disease, symptom fluctuation, regression to the mean, response bias or other concurrent treatments, which should all be controlled for as well[6,7].

It is noteworthy that most placebo and 'nocebo' (that is, negative outcome) manipulations have been examined within the field of pain, and our neurobiological understanding of the mechanisms underpinning placebo and nocebo effects has largely come from studies on placebo analgesia and nocebo hyperalgesia—data that have relevance for other clinical conditions subject to placebo and nocebo influences beyond those involving subjective responses, including Parkinson's disease, respiration and the cardiovascular system[2,8].

Over the past 15 years, studies exploring the neural basis for how humans experience pain and its relief via pharmacological and psychological means have contributed substantially to our neurobiological understanding of these experiences and provide a mechanistic framework for understanding placebo and nocebo effects in humans[1,9–12]. These studies are firmly placing the origin of pain as an emotional, cognitive and sensory experience back into the brain. Several brain areas show increased activity, often bilaterally, during pain in humans (**Fig. 1a**)[1,13]. Decreased activity in part of this network, commonly referred to as the 'pain matrix', is often observed

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during analgesia induced via pharmacological or psychological interventions, but, as described later in this Review, attenuation of activity within the 'pain matrix' is not necessary or conditional for changing the pain experience during reappraisal.

Pain modulatory mechanisms relevant to placebos and nocebos

Nociceptive inputs to the dorsal horn of the spinal cord are subject to powerful descending control from supraspinal regions. This descending control, unique to pain, and involving among other areas the rostral anterior cingulate cortex (rACC), hypothalamus, amygdala and periaqueductal gray (PAG), is combined in the brainstem rostral ventromedial medulla (RVM), where its output influences spinal nociceptive processing and consequently input to the brain according to the particular behavioral circumstance; importantly, it involves the endogenous opioid system[14,15]. Such antinociception is crucial during stress, fear, intense exercise or escape; however, the same network can facilitate nociception during inflammation and nerve injury[16,17]. Although such facilitation can be protective during recovery, promoting tissue healing, we are now aware that its failure to resolve may contribute to a chronic pain state[18–20].

Of direct relevance to placebo and nocebo effects, this facilitatory (pronociceptive) and inhibitory (antinociceptive) descending modulatory system remains the major route by which cognitive and contextual influences change a pain experience, as shown by functional magnetic resonance imaging (fMRI) studies[10,21,22]. Additionally, frontal and limbic brain regions are involved during the cognitive control of pain,[10] and, as these regions are reciprocally connected to the brainstem, they too can exert a descending influence on spinal nociception. This supports a regulatory role of prefrontal-limbic regions in pain experiences[22–24].

Emotions can also change a pain experience. Emotion regulation involves the conscious or unconscious increase and decrease of emotions, and strategies for regulating emotions include either attentional control or cognitive change[25]. Attentional processes drive distraction from an unpleasant stimulus without the need for much cognitive change, but volitional re-interpretation of negative material relies on cognitive change; this involves cognitive reappraisal of the stimulus, such that reinterpretation of the importance or meaning of adverse and unpleasant events, such as painful experiences, occurs. Cognitive reappraisal seems to involve activation of right lateral prefrontal cortex (PFC)[26,27], which then either inhibits limbic activity (for example, amygdala) or generates alternative contents to replace emotions[25,27]. In support of this, the ventrolateral PFC (vlPFC) is activated during analgesia that arises from the belief that pain can be controlled or has had the 'suffering' element removed via emotional detachment[11,28]. Such successful regulation of emotional responses seems to be mediated by the vlPFC interacting with the nucleus accumbens and suppressing amygdala activation[29,30]. Limiting fear about pain involves the ventral-medial PFC (vmPFC)[31,32], but when this fails it leads to stimulus generalization and anxiety, which can exacerbate a pain experience via parahippocampal mechanisms[33]. In contrast, the orbitofrontal cortex (OFC) seems to be associated with evaluation and reward information, suggesting its role is more in affective or motivational responses to anticipation of pain and perhaps is relevant for how the factor of desire for relief is important in placebo analgesia[34]. Desire for relief is an interesting mechanism associated with placebo effects, as it is thought to both amplify expectations and strengthen placebo effects and also conflict with expectations during nocebo manipulations and reduce their effects[35].

In summary, cognitive and emotional mechanisms mediate their influence on pain experiences via prefrontal-limbic-brainstem interactions.

Expectation and its link to placebo and nocebo effects

Negative and positive expectations are powerful modulating factors that influence behavior, and many experiments have used simple verbal cues to manipulate expectations in both experimental and clinical pain studies not involving placebo or nocebo manipulations. For example, it has been shown that an expectation of decreased pain reduces both the subjective report as well as activation of sensory, insula and cingulate ('pain matrix') cortices[36]. Studies examining the neural basis by which negative expectations or increased anticipation and anxiety influence behavioral pain reports provide a possible neuroanatomical framework from which we can interpret nocebo interventions and effects[33,37,38]. One fMRI study[37] used two levels of noxious thermal stimulation (high and low) and two corresponding levels of expectancy (high and low); the results provided a clear demonstration of how beliefs (expectancy) influenced pain perception and report via altered activity within the brain's 'pain matrix' and frontal-limbic-brainstem network.

During expectation of high pain, subjects are likely to feel threatened and anxious; therefore, understanding how anxiety influences pain is crucial for understanding nocebo effects. Heightened anxiety and anticipation make the pain experience worse via increased activity within the parahippocampal, entorhinal and brainstem network[33,39]. Unfortunately, not as many nocebo experiments have been reported compared to placebo, but behavioral studies have highlighted a dominant role for cholecystokinin in nocebo hyperalgesia via anticipatory anxiety mechanisms[40,41]. A recent neuroimaging study has shown that nocebo effects are mediated by the hippocampus and regions involved with anticipatory anxiety and, as such, are distinct from placebo effects at a neural level[42]. How negative verbal cues or anxiety activates the cholecystokinin system to consolidate negative expectations is, as yet, not known and is a future area of investigation.

It is apparent from what has been discussed so far that cognitive and emotional circuits are involved in generating and modulating the pain experience, and specific mechanisms involved, such as expectation and reappraisal, are likely to be integral to generating placebo and nocebo effects (**Fig. 1a**,**b**). Such knowledge provides a solid neuroanatomical framework for interpreting the data generated by placebo and nocebo interventions. But, given that many placebo effects exist[43], other mechanisms must be present, such as conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction, beliefs and meaning[6,8,44–47]. In addition, we are beginning to appreciate how personality and psychological traits, such as dispositional optimism, interact with these mechanisms to provide a further means by which these effects are amplified, reduced, habituated or sustained over time[48]. To date, however, the principal mechanisms for generating placebo and nocebo effects that have been extensively studied and are well supported by behavioral data are expectancy and classical conditioning. As discussed above, manipulation of expectations has been powerfully applied within the placebo and nocebo fields[35,46,49,50], but by including a classical Pavlovian conditioning design to increase the expectation of relief or pain, researchers can observe larger placebo or nocebo effects[50]. Classical conditioning, whether in animals[51] or humans[44,52,53], results in learned associations between a neutral stimulus and an active drug such that the neutral stimulus alone can elicit a response characteristic of the drug, even in unconscious processes.

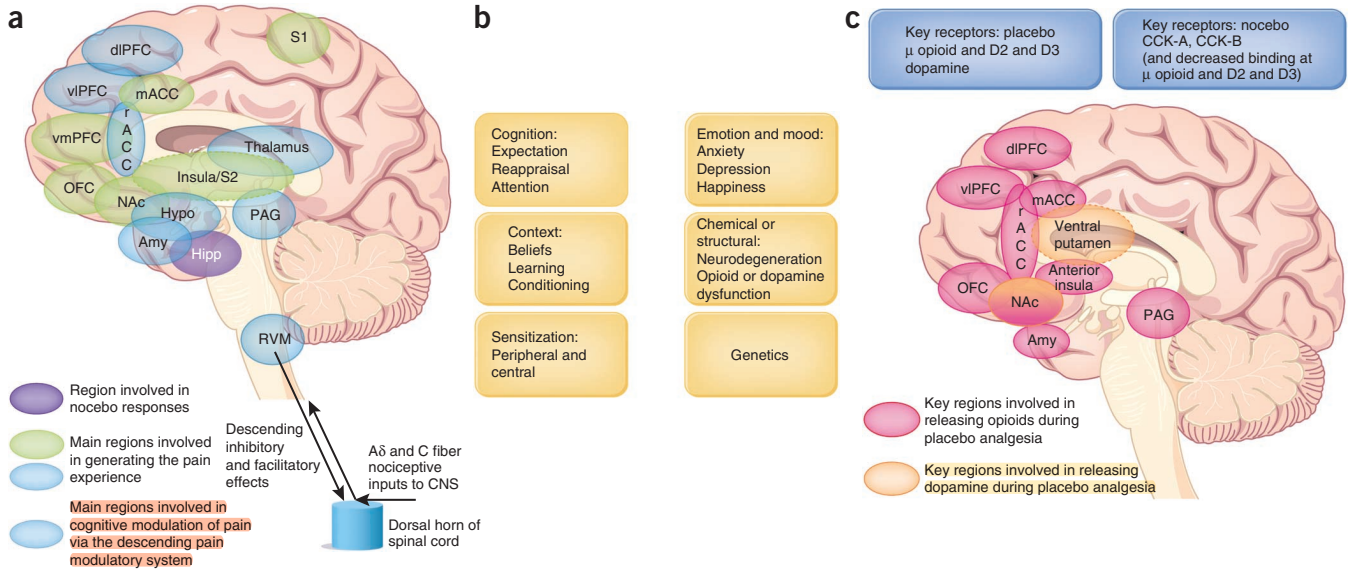

Figure 1 Factors influencing pain perception and the neural basis for endogenous pain modulation, placebo and nocebo effects. (**a**,**b**) Schematic illustration of key brain regions involved in generating a pain experience (green, blue and purple) with core brain regions that comprise the cognitive and descending pain modulatory networks (blue) (**a**) and a description of the various factors that influence the pain experience listed in the text boxes (**b**). (**a**) The regions highlighted in blue indicate the core descending endogenous pain and cognitive modulatory networks that many of these factors, including placebo and nocebo effects, use to elicit their influence on nociceptive processing and resultant pain perception. The hippocampal region (purple) is important for amplifying pain experiences during nocebo or increased anxiety. (**c**) Schematic illustration indicating where endogenous opioid and dopamine neurotransmission occurs in the human brain during placebo analgesia. Note the overlap with many of the brain regions involved in cognitive modulation of pain, and for some brain regions (NAc) there is a bidirectional response of both opioid and dopamine release that produces either placebo (increased release) or nocebo (decreased release) effects. vmPFC, ventromedial prefrontal cortex; Amy, amygdala; Hypo, hypothalamus; Hipp, hippocampus; S2, secondary somatosensory cortex; S1, primary somatosensory cortex; dlPFC, dorsolateral prefrontal cortex; rACC, rostral anterior cingulate cortex; mACC, midanterior cingulate cortex; CCK, cholecystokinin.

The neurobiology of placebo and nocebo effects

Our understanding of the underlying mechanisms and neurobiology involved in generating placebo and nocebo effects is evolving quickly. A seminal study showed that placebo analgesia was blocked by the opioid receptor antagonist naloxone and provided the first evidence that the endogenous opioid system was involved in the production of placebo-induced analgesia[54]. Furthermore, these naloxone-reversible placebo effects were not generalized but rather body-region specific[49,55], suggesting a targeted endogenous opioid release within the spinal cord. However, a nonopioid-based mechanism seems to have a role in some circumstances[54,56–58]. For example, expectation cues after morphine administration produce analgesic responses that are naloxone reversible, but if the subjects are conditioned with the nonsteroidal anti-inflammatory drug ketorolac, only partial blockage of the placebo effect by naloxone is achievable—and ketorolac conditioning alone (without additional expectation cues) produces naloxone-insensitive analgesia[50]. Furthermore, subjects treated with cholecystokinin antagonists show a potentiated placebo effect[59,60]. Such studies show that conditioning recruits additional mechanisms to expectation-driven activation of endogenous opioid systems.

Imaging placebo and nocebo effects

Over the past decade there has been an explosion of studies using positron emission tomography (PET), fMRI, magnetoelectroencephalography and electroencephalography in humans to understand the neural basis for placebo and nocebo effects. These studies support the involvement of a frontal-limbic-brainstem network capable of driving endogenous opioid and dopamine release.

Frontal-limbic-brainstem networks in placebo analgesia. Activity within the rACC is common to both opioid administration and placebo analgesia, suggesting a link to common opioid-based pathways within the brain. There is covariation in activity between the rACC and the brainstem in the placebo but not pain-only condition, supporting a descending rACC-PAG-pons-medulla pain-modulating circuit as being involved in placebo analgesia[61]. In this same study, subjects who show high placebo analgesic responses also show greater responses to the opioid drug, suggesting a possible genetic basis for individual differences in the concentration or function of μ-opioid receptors. Additionally, studies examining the neural mechanisms underlying the effect of expectations of placebo analgesia showed that during the anticipation phase of the placebo analgesic response there is activation in a 'cognitive-evaluative' network, which includes the prefrontal-brainstem regions identified as relevant for modulating pain (**Fig. 1a**); such activity probably accounts for the decreased activity in core pain processing regions in response to noxious stimulation during placebo analgesia[62]. These studies illustrate the difficulty in unraveling which brain regions are the source or target of placebo effects, as overlapping structures can be active during expectation of placebo analgesia, as well as during placebo analgesia itself.

Nevertheless, these early observations and others[63,64] provided the first indirect evidence for the recruitment of the endogenous pain modulatory opioid network during placebo analgesia.

Endogenous opioids and placebo effects. To study the molecular mechanisms underpinning a regionally specific placebo effect and the basis for individual variations in placebo responses, researchers used PET imaging to determine the regional activation of endogenous opioid neurotransmission[65]. They showed that expectation-induced placebo

analgesia was associated with marked activation of μ-opioid receptor mediated neurotransmission in an extensive set of brain regions[65] (**Fig. 1c**). Notably, they found that opioid-related activities in several brain regions within this network correlated with changes in specific behavioral measures of placebo analgesia, such as pain intensity and unpleasantness, as well as measures of subjects' emotional states[65]. Importantly, the nucleus accumbens was identified as a key structure mediating these effects.

Therefore, placebo treatment affects endogenous opioid activity in many brain regions, including the prefrontal cortex, PAG and amygdala[66]. As noxious stimulation produces endogenous opioid release, it is important to know whether placebo analgesia is mediated via potentiation of this normal release. One study has provided evidence this is the case and further highlighted that placebo analgesia increases the functional connectivity between the PAG and the rACC and between limbic regions, as well as between some limbic and prefrontal regions during placebo analgesia[66].

A recent high-resolution fMRI study has shown activity within all key regions of the descending pain modulatory system (rACC, hypothalamus, PAG and RVM) during placebo analgesia, with this activity being significantly decreased when naloxone was present during the placebo intervention[67]. rACC-PAG coupling was significantly increased during placebo analgesia but was not different versus control in the presence of naloxone during the placebo intervention[67].

These studies provide evidence that placebo analgesia is associated with activation of the endogenous opioid system and with μ-opioid receptors, within a number of brain regions, including prefrontal-limbic-brainstem regions. Furthermore, the activity changes in these brain regions are correlated to reductions in the physical and emotional aspects of a pain experience, indicating that variation in endogenous opioid transmission relates to variances in placebo effects across individuals.

Linking variances in placebo effects to neurobiology. Multiple factors contribute to the generation of the placebo effect in a given individual. One study showed that the largest proportion of the variance in regional endogenous opioid activity was explained by the degree of affective quality of the pain report and pain sensitivity[68]. Therefore, the individual's pain sensitivity and affective experience during pain are key predictors of the magnitude of their subsequent placebo analgesia.

In an examination of how the expected analgesia related to the experienced analgesia, a possible key role for the nucleus accumbens (NAc) has been identified: the magnitude of opioid activity within the NAc and PAG correlated with the subjects' expected analgesia, whereas activity within the rACC, NAc and OFC correlated with placebo-induced changes in pain intensity[69]. If one classifies subjects according to the magnitude of their placebo analgesia as 'high' or 'low' responders (high meaning greatest placebo analgesia), then opioid activity in the NAc best distinguishes the two groups. The NAc also showed opposite responses between placebo (activation) and nocebo (deactivation) responders. These studies, although in their infancy, highlight the powerful roles endogenous opioid activation have in terms of producing expectations of analgesia, changing those expectations over time and driving placebo-induced analgesia.

Spinal fMRI: specific target for placebo analgesia. During placebo analgesia, pain-related activity in the human spinal cord is markedly reduced. This suggests that cognitive factors mediate their effects early in the nociceptive pathway and that spinal inhibition may be one possible mechanism of placebo analgesia[70].

Linked to these findings are results using higher temporal resolution techniques, such as electroencephalography and magneto-electroencephalography, that show placebo-induced modulation of nociceptive processing before or at the very earliest stages of awareness and perception of pain within the brain[71,72].

Dopaminergic mechanisms related to placebo and nocebo effects

The PET opioid studies described above indicate that the NAc is a prominent player in eliciting placebo analgesia and has a role in explaining individual variances. As the NAc is involved in response to rewards, salient stimuli and updates in reward expectations[73] and has high levels of dopamine innervation from the ventral tegmental area, it is probably involved with encoding the saliency or reward aspects of any placebo intervention. In fact, if one considers the anatomical position of the NAc, it is ideally placed to galvanize placebo analgesic effects via its connections to the OFC, ventral pallidum and the amygdala and its ability to interface with sensorimotor and limbic circuits, which are themselves connected to core pain processing regions[74].

But is there a role for NAc dopamine in placebo effects? Basal ganglia dopamine release has been reported in the placebo arm of a clinical trial in people with Parkinson's disease[75], and subsequent PET and fMRI work in a range of disorders confirmed that the NAc is involved in placebo effects[76,77] and expectations of anxiety relief in subjects preconditioned with an anxiolytic drug[78]. Given these data, a PET study aimed to specifically explore dopamine's role during placebo analgesia showed activation of dopamine neurotransmission in ventral caudate, ventral putamen and NAc.[69] The extent of NAc dopamine activation correlated positively with both individual expectations of analgesia and their updates, as well as with the magnitude of analgesia and the increase in positive effect ratings during placebo (**Fig. 1c**), mirroring results from the opioid system. Examining both regional opioid and dopamine responses for their contribution to placebo analgesia, it emerged that dopamine release in the NAc is the most predictive region and neurotransmitter.[69] Perhaps NAc dopamine responses to placebo interventions constitute a 'trigger' for downstream opioid responses? Further work is needed to clarify the interactions and integration of these two major neurotransmitter systems during placebo analgesia.

Another area of study is how dopamine and its link to reward are related to individual variations in reward expectation and placebo response outcomes: in short, if one is reward biased, does he or she get a larger placebo response? An elegant study showed that individuals whose NAc was activated to a greater extent during monetary reward anticipation in one imaging experiment also had the greatest placebo responses, as measured by behavior, in a different imaging experiment. What was particularly striking was the finding that the NAc activity during anticipation of monetary reward in the fMRI study correlated with placebo-induced dopamine activity in the other experiment for the same group of individuals. Moreover, the difference between anticipated and perceived placebo analgesia correlated with the NAc activation during reward expectation. Combined, these results support a strong relationship between the NAc, reward expectation and placebo analgesic outcome that is robust across time for an individual. This has relevance for subject or patient selection in clinical trials, where placebo effects might need to be minimized[79].

Consistent with this theme, some fascinating recent work examined the relationships between brain gray matter volume, placebo

analgesic response and personality traits associated with dopamine neurotransmission. It was shown that dopamine-related traits predict a substantial portion of placebo analgesia, the magnitude of which was related to gray matter density in several brain regions, including the ventral striatum and prefrontal cortex. Again, these findings offer ways of identifying subjects who are likely to show large placebo analgesic responses in clinical trials[80].

These results further define the neurobiological basis for individual variations in placebo responses and indicate a key role for the NAc, a region highlighted recently as important for judging the value of pain and analgesia due to its altered behavior to noxious stimulation in the presence of chronic pain[81].

Factors contributing to variances in placebo and nocebo effects

Excluding the above, it has not been easy to identify specific personality and trait factors that are relevant for influencing both the placebo response and its reproducibility over time. Factors that play a part may include psychopathology, dispositional optimism and social desirability[82–84]. A recent study has shown that dispositional optimism and state anxiety are significant predictors of placebo analgesia and contribute to the reproducibility of the effect[48]. It is possible to hypothesize that increased positive expectations will lead to lower anticipated anxiety, and, combined, these provide resilience and perhaps increased placebo and decreased nocebo responses.

Chronic pain patients and disease changes that affect placebo effects

It is clear from the discussion so far that placebo analgesia is a true antinociceptive effect and does not reflect mere report bias. Although neuroimaging data is limited in patient placebo studies, a report showing a positive correlation between blood flow increases in the right vlPFC after placebo treatment and symptom improvement in people with irritable bowel syndrome has been shown[85]. Further, reductions in brain activation within pain-related regions induced by rectal distension during placebo analgesia[86] support findings from studies conducted in healthy subjects.

Data from human neuroimaging studies in individuals with chronic pain have highlighted the consequences of living with this condition in terms of maladaptive plasticity, neurotoxicity and neurodegeneration[87]. Intriguingly, the PFC is a major site of potential neurodegeneration in people with chronic pain[88,89], but understanding cause and effect is difficult, and relevant factors can only be dissected in carefully controlled, longitudinal studies in preclinical pain models, which so far confirm the human volumetric changes[90,91]. There is considerable evidence for altered functional activation of the PFC in humans with chronic pain (reports of hypoactivity[92] and hyperactivity[93]), which is perhaps not surprising considering its key role in pain modulation. For someone with chronic pain, being able to regulate cognition and emotions during episodes of pain is crucial if he or she is to adapt well to the condition, yet we know there is abnormal brain neurochemistry in the opioidergic and dopaminergic systems in a range of chronic pain states and this probably affects the individual's ability for adaptive regulation[94–98].

The relationship between these alterations in structure, function and neurochemistry within brain regions identified as necessary for eliciting placebo analgesia begs the question of whether this affects their capacity to generate a placebo response. Supporting this notion, a study showed that a reduced score of frontal cortex cognitive function was related to reduced placebo analgesia in people with Alzheimer's disease receiving a local anesthetic (overtly or covertly) after venipuncture. When reduced connectivity was found specifically for prefrontal regions, this related to no placebo analgesia, highlighting that a functional prefrontal cortex is crucial for a contextually driven placebo effect. Importantly, these results alert us to the fact that we might not be adequately treating such patients, as they are not benefiting from the additional context-driven analgesia produced in a normal medical therapeutic setting and require more analgesics as a consequence[99].

Impacts on clinical trial design and ethics

It is clear that these placebo and nocebo effects are real and powerful. Therefore, at one ethical level we should not be shying away from harnessing or reducing (nocebo) them if they bring further relief to patients[6,100]. Indeed, most treatment scenarios include many factors involved in generating a placebo response component, which, if removed, will influence the efficacy of a drug's intrinsic pharmacodynamics (**Fig. 2a–c**). In a recent neuroimaging experiment using a μ-opioid agonist (remifentanil), we have confirmed that during a 'hidden-open' placebo nocebo intervention (a design that represents the best way to isolate the placebo effect as a context effect because the active agent is always present in both open and hidden conditions), the subjects' reported pain relief to an experimental pain stimulus increased significantly when they were told the drug infusion had started (when it already had), and, importantly, this benefit (that is, the drug- and context-induced benefit) was completely over-ridden

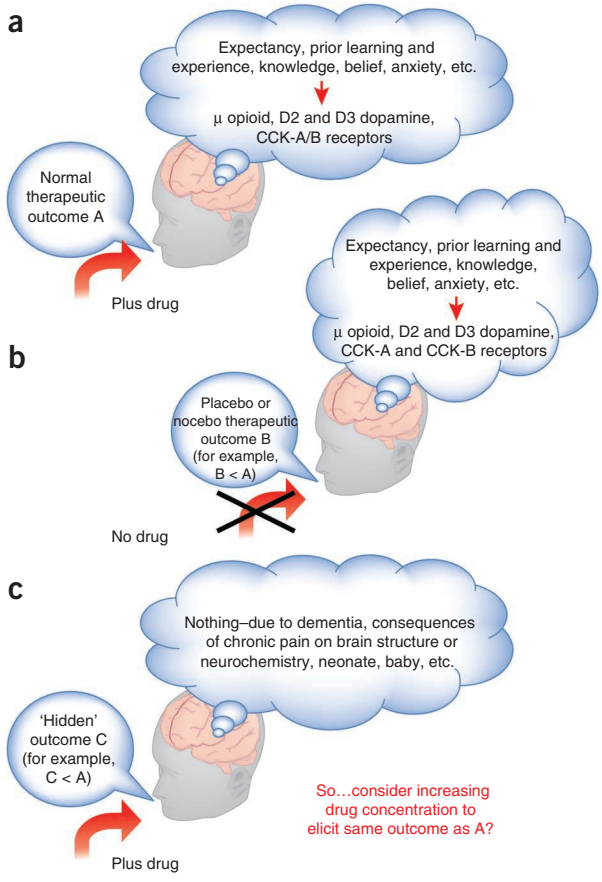

Figure 2 The patient environment. (**a**–**c**) Schematic of a treatment environment where both drug and therapeutic context interact to produce resultant pain report (**a**), where without drug only the therapeutic context influences pain report (**b**) and where, due to conditions that affect the key brain regions listed in **Figure 1**, there is only the drug and its pharmacodynamics able to influence the pain report (**c**).

when the subjects were told that the drug infusion had stopped (when it had not), with the neuroimaging results supporting the behavior. These data may have relevance for people with chronic pain, where success of the first encounter, observation of other patients' outcomes and repeated negative or positive therapeutic outcomes will create a store of negative or positive expectations that probably dictate a particular response to a new drug, irrespective of its mechanism or pharmacodynamic profile (U. Bingel, V. Wanigasekera, K. Wiech, R. Mhurcheartaigh, M.C. Lee, M. Ploner *et al.*, unpublished data).

Reappraising placebos—it's all about the meaning

Red placebo pills are more likely to act as stimulants compared with blue placebo pills, because red is interpreted as 'hot' and 'danger'. More expensive placebo treatments produce significantly more placebo analgesia than less expensive ones[101]. Therefore, placebo interventions induce particular expectations beyond those linked to their efficacy as 'drug', and these expectations depend, for example, upon the placebo's appearance and value, which are both influenced by prior learning and experiences. Interpreting these additional factors and conferring 'meaning' to them involves cognitive reappraisal, which involves activation of the vlPFC, which then either inhibits limbic activity or generates alternative contents. The fact that most studies imaging the placebo effect show activity within the vlPFC both in anticipation of and during placebo analgesia supports there being involvement of reappraisal in most placebo effects. Can we harness the powers of reappraisal outside traditional placebo interventions to gain pain relief?

Making pain pleasant

If cognitive reappraisal involves re-interpreting the importance or meaning of adverse events, such as painful experiences, then is it possible to not only reduce pain but perhaps also reverse completely the meaning of pain and make it pleasant? Such hedonic 'flipping' provides an alternative route by which re-interpreting the meaning of pain might produce startling changes in pain report[102]. Such studies coupled to further explorations of placebo and nocebo effects will provide new brain targets for possible pharmacological, surgical and brain interference tools in the years to come.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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