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## The neuroscience of placebo effects: connecting context, learning and health

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### Abstract

Placebo effects are beneficial effects that are attributable to the brain–mind responses to the context in which a treatment is delivered rather than to the specific actions of the drug. They are mediated by diverse processes — including learning, expectations and social cognition — and can influence various clinical and physiological outcomes related to health. Emerging neuroscience evidence implicates multiple brain systems and neurochemical mediators, including opioids and dopamine. We present an empirical review of the brain systems that are involved in placebo effects, focusing on placebo analgesia, and a conceptual framework linking these findings to the mind–brain processes that mediate them. This framework suggests that the neuropsychological processes that mediate placebo effects may be crucial for a wide array of therapeutic approaches, including many drugs.

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*I would rather know the person who has the disease than the disease the person has.*  
Hippocrates

Modern medicine has been very successful at treating many forms of disease, particularly those for which the physiological mechanisms can be identified and the pathology objectively assessed. However, it has proved difficult to treat the pain and psychological distress that are integral to many diseases<sup>1</sup> and to treat related disorders such as depression, chronic pain, anxiety and fatigue. Unlike diseases in which the pathology occurs primarily in peripheral organs, pain and distress are rooted in complex brain functions. They are influenced by brain pathology, internal thoughts and brain states, and conceptions of the social and environmental context. As a result, we lack objective physiological measures for disorders that are characterized by pain and distress, and a comprehensive understanding of the brain mechanisms underlying their generation and regulation.

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#### Competing interests statement

The authors declare no competing interests.

#### SUPPLEMENTARY INFORMATION

See online article: S1 (table) | S2 (box)

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New inroads are being made through the multidisciplinary study of placebo effects — that is, the effects of manipulating the informational context surrounding a medical treatment. Placebos are drugs, devices or other treatments that are physically and pharmacologically inert. Placebo interventions do not, by definition, have any direct therapeutic effects on the body. However, all treatments are delivered in a context that includes social and physical cues, verbal suggestions and treatment history (FIG. 1). This context is actively interpreted by the brain and can elicit expectations, memories and emotions, which in turn can influence health-related outcomes in the brain and body. Placebo effects are thus brain–body responses to context information that promote health and well-being. When brain responses to context information instead promote pain, distress and disease, they are termed *nocebo effects*.

Understanding placebo and *nocebo* effects is important for both clinicians and neuroscientists. Placebo responses are substantial across diverse clinical disorders<sup>2–4</sup> and, in some cases, are related to objective pathology<sup>5</sup> and survival<sup>6</sup>. A large part of the overall therapeutic response to drugs<sup>7–10</sup>, surgery<sup>11,12</sup>, psychotherapy<sup>13</sup> and other treatments may be due to the treatment context — and thus mechanisms shared with placebo effects — rather than the specific treatment itself. Even when attempting to understand the effects of drugs or other treatments is the primary goal, considering placebo effects is crucial, as drug effects occur alongside or even interact with internal psychological and brain processes<sup>7,14–18</sup>. In some cases, individuals who show the largest drug effects also show the largest placebo effects<sup>19</sup>, which is one indicator that some drugs and placebos may share mechanisms. If so, obtaining reliable drug effects may require establishing a suitable treatment context (for example, the right type of psychological or social support), and screening to remove placebo responders in clinical trials may eliminate those who most benefit from active drug treatment.

For neuroscientists, placebo studies provide a way to investigate how the brain systems that process contextual information influence physiology and clinically relevant outcomes. Humans are endowed with uniquely powerful systems for representing context<sup>20</sup>, which help to tailor our responses to the needs of a given situation<sup>21</sup>. Clinical contexts in particular integrate diverse psychological elements (FIG. 1), including learned associations between cues (for example, a doctor’s white coat) and past positive and negative experiences, conceptual knowledge based on verbal suggestions that induce expectations about treatment outcomes, and social interactions (for example, the patient–care provider relationship). Placebo effects on health-related outcomes such as pain and affective physiology, which we focus on in this Review, share many similarities with context effects on visual perception<sup>22–24</sup>, memory<sup>25</sup>, decision making<sup>26–28</sup>, athletic<sup>29</sup> and cognitive<sup>30</sup> performance, and other processes. Together, these studies provide a foundation for an integrated science of context processing, and studies of placebo may shed light on mechanisms of context effects that do not involve placebo manipulations<sup>20,31</sup>.

Here, we present a brain systems-oriented view of the mechanisms underlying placebo effects. The neuroscience of placebo effects is a new and rapidly evolving field that integrates diverse areas of human and animal neuroscience, and complements studies of placebo effects on peripheral physiology<sup>5</sup>, clinical pharmacology<sup>2</sup> and other outcomes<sup>20,31</sup>.

We first briefly discuss the behavioural, clinical and physiological outcomes that are affected by placebo treatments. Then, we review neuroimaging evidence relating to the systems-level neurobiology that underlies placebo effects; we focus primarily on pain, which has been most extensively studied. Next, we relate the resulting consensus view on the neural architecture of placebo effects in pain to brain placebo effects in depression, emotion and Parkinson disease (PD). Finally, we present a framework for mapping the psychological processes underlying placebo effects onto brain systems and highlight several areas for further research.

## Clinical and laboratory placebo effects

Placebos have been used throughout the history of medicine to soothe the emotions of troubled patients and are still used for this purpose today<sup>32</sup>. It is widely believed that placebos can make people ‘feel better’, but is that the extent of their clinical importance? What kinds of health-related outcomes can placebo treatments affect? For some, the presence of a placebo effect suggests that symptoms were not caused by ‘real’ or ‘organic’ disease. For example, patients who report pain relief after placebo treatment might be judged to be malingerers<sup>33</sup>. However, this inference is only valid if placebo treatments have no actual effects on pain pathophysiology or experience.

As we explain below, clinical studies have demonstrated meaningful placebo effects in multiple disorders, and laboratory studies have provided evidence for placebo effects on health-relevant behavioural, autonomic, endocrine and immune measures (Supplementary information S1 (table); see also REFS 5,34). These studies suggest that it is implausible — and perhaps unethical — to dismiss placebo responses as irrelevant to health and pathology.

### Placebo effects in clinical studies

Most clinical trials are not suitable for estimating placebo effects because they lack natural history controls. However, a small subset of clinical studies with appropriate controls (FIG. 2) have demonstrated causal effects of placebo treatment on measures that are typically used as primary disease end points<sup>35,36</sup> in multiple forms of chronic pain<sup>37–40</sup>, depression<sup>10,41–43</sup>, PD<sup>44,45,161</sup> and asthma<sup>5,46,47</sup> (but see REF. 48). Placebo effects can be as large as the effects of accepted drug treatments<sup>40,49</sup> or larger<sup>42,43</sup>, and can reduce disability and increase quality of life over a period of months or longer<sup>38,43</sup>. In some cases, particularly in cardiovascular disease<sup>6,50,51</sup>, adherence to placebo medication is associated with reduced mortality.

Placebo-related factors are also an important component of standard clinical treatments that are administered in hospitals and clinics, which are typically provided ‘open-label,’ with full information about drug delivery and its expected benefits. In many cases, hidden drug administration, which eliminates patients’ treatment expectations, markedly reduces the effects of drugs<sup>8,17,40,52,53</sup> and other treatments. These clinical results demonstrate the important functional improvements that are caused by the brain’s interpretation of the treatment context.

## Autonomic responses

The autonomic and neuroendocrine systems are governed by the brain, including ‘higher’ brain regions such as the prefrontal cortex (PFC)<sup>54,55</sup>, and can be influenced by threatening psychological contexts<sup>56</sup> and verbal instructions<sup>57,58</sup>. Several studies have found that placebo analgesia is associated with changes in autonomic activity<sup>59–61</sup>, and other studies have found evidence for diverse autonomic effects of placebo (see REFS 5,34 and Supplementary information S1 (table)). One such study assessed pain, autonomic responses and electroencephalography (EEG) across three levels of placebo ‘strength’ (REF. 60). Participants received three identical, inert (placebo) creams that they believed to vary in strength. A painful stimulus was then applied to the skin that was treated with the creams. During the training phase, the intensity of painful stimulation was reduced to differing degrees for the three placebo creams — not at all for the ‘control’ cream, slightly for the ‘weak placebo’ cream and markedly for the ‘strong placebo’ cream — creating differential expectations and associations of relief. In the subsequent test phase, stimulus intensity was identical across skin treated with each cream, but the authors observed a graded reduction in noxious stimulus-evoked skin conductance, pupil diameter and EEG N1–P2 amplitudes in proportion to the placebo ‘dose’. This paradigm, which we refer to as *response conditioning* (FIG. 2), experimentally manipulates associative learning and cognitive expectancy, and is the most popular experimental paradigm for studying placebo effects in the laboratory.

## Neuroendocrine responses

Placebo treatments can also affect hormonal responses that are mediated via forebrain control of hypothalamus–pituitary–hormone systems (Supplementary information S1 (table)). Nocebo suggestions that a treatment will increase pain can increase peripheral cortisol levels in humans<sup>62,63</sup>, an effect that is blocked by the anxiolytic benzodiazepine diazepam<sup>62</sup>. Strikingly, this effect was induced with verbal instructions alone, without requiring conditioning, but in other cases associative learning might be crucial (Supplementary information S1 (table)). For example, the serotonin receptor agonist sumatriptan increases blood levels of cortisol and growth hormone. After repeated injections of sumatriptan, injections of saline alone can induce increases in the levels of both hormones, even when suggestions induce expectations for opposing responses<sup>65</sup>. These hormonal effects also have parallels in animal models, which use pharmacological conditioning to associate context cues with drug effects. In rats, after repeated injections of morphine, injections of saline alone reduce pain behaviours and the levels of adrenocorticotrophic hormone and corticosterone<sup>64</sup>.

Placebos might also affect other hormone systems, including those that regulate appetite. In one study, participants who drank a milkshake labelled as ‘indulgent’ showed reduced levels of the pro-hunger hormone ghrelin compared with those who drank an identical milkshake labelled as ‘sensible’ (REF. 66). These findings complement animal work on anticipatory brain regulation of appetitive hormones such as insulin, which is in many cases mediated by autonomic output to the periphery<sup>67</sup>.

## Immune responses

The autonomic and neuroendocrine systems interact with the immune system in multiple ways, providing a substrate for placebo effects on immune responses. The most compelling demonstrations of such interactions come from pharmacological conditioning studies (FIG. 2) in which taste cues, such as a uniquely flavoured drink, have been paired with immunosuppressive drugs (in particular, cyclosporin A). In both humans and rodents<sup>68–70</sup>, subsequent exposure to the taste cues alone suppresses peripheral immune responses, particularly T lymphocyte proliferation and the release of interleukin-2 and interferon- $\gamma$  from peripheral lymphocytes. Relatively little is known about the brain mechanisms underlying such effects, although recent work suggests that they are mediated by noradrenergic sympathetic efferents<sup>71</sup>, require the insula and hypothalamus for their expression<sup>72</sup> and may be correlated with anxiety<sup>73</sup>, implicating forebrain control of the response.

Other recent studies suggest that placebo manipulations may influence inflammatory responses, an aspect of immune function that is implicated in multiple aspects of health. In one study, exposure to pro-drug advertising materials coupled with administration of a placebo ‘antihistamine’ reduced the size of skin wheal responses to an allergen challenge<sup>74</sup>. In another study, verbal suggestions about altitude-induced headaches increased blood levels of prostaglandin, an important inflammatory mediator, which were reversed by administration of a placebo<sup>213</sup>. Notably, in this study, the suggestions were provided to one participant and were transmitted by social communication to others, demonstrating the power of social influences. Together, these studies suggest that psychological context may have more pervasive effects on physiology than is currently recognized.

## Placebo effects and decision making

Despite the physiological effects reviewed above, most demonstrations of placebo effects depend primarily on patient self-reports, mainly because self-reports are the accepted ‘gold standard’ for measuring pain and distress. One still-common view is that these placebo effects amount to various forms of ‘decision bias’ — effects on decision making — in the absence of meaningful changes in pathology or function. For example, if patients report less pain after a placebo treatment, it may be because they evaluate their experience relative to a different reference point<sup>75,76</sup>, combine information about experience and prior expectations into their reporting decisions (a Bayesian response bias)<sup>21</sup>, judge that it is more costly to over-report pain than under-report it (a reporting bias), or decide to simply report less pain to please the experimenter (a demand characteristic)<sup>214</sup>. Thus, part of the effects of placebos on symptom reporting and behaviour undoubtedly arise from effects on decision making or other central processes that are involved in the construction of subjective experiences<sup>77,78</sup>.

Even without immediately affecting pathology, placebo effects on decision making can have profound impacts on health. They can strongly influence choices about what to eat and drink<sup>26,28</sup>, how to exercise and socialize, which medications are preferable and will continue to be taken, and whether others in our environment are seen as enemies or friends<sup>79</sup>. Such effects on decision making can compound over time to influence health in important ways.

Nonetheless, the complexity of self-report provides a compelling rationale for studying placebo effects on objective measures that are more directly linked to specific aspects of pathology, perception and function. Direct measures of brain function, in particular, can provide both objective measures related to pain, suffering and brain disorders, and clues about the mechanisms by which suggestions and cues are translated into relief.

## Neuroimaging evidence

Modern neuroimaging techniques, including functional MRI (fMRI), molecular imaging of glucose, dopamine and opioid activity using positron emission tomography (PET), EEG and magnetoencephalography (MEG), offer new insights into the neural mechanisms of placebo effects. Over the past 12 years, nearly 40 PET and fMRI studies of placebo effects on pain have provided an emerging picture of the brain systems that are involved in placebo analgesia and hyperalgesia (FIG. 3; see Supplementary information S2 (box)). These are accompanied by a small but growing literature on the effects of placebo on emotion<sup>80–84</sup>, PD<sup>44,45,85</sup> and depression<sup>86,87</sup>, which provides converging evidence on the functions of the brain systems affected by placebo.

There are three major aims of these studies. One aim is to provide direct measures of the brain processes that give rise to pain and other clinical symptoms, providing objective targets for studies of placebo effects and other interventions. The second aim is to identify the functional systems that are engaged by placebo treatments and thus provide information on the mechanisms by which context can influence health and well-being. The third aim is to identify the factors that differentiate placebo responders from non-responders — or, equivalently, identify brain features that predict the magnitude of an individual's placebo response.

## Placebos reduce pain-related brain responses

Among the processes that show substantial placebo effects, pain is particularly amenable to study, because of its broad clinical relevance, experimental tractability and well-studied neural circuits and mechanisms. Established 'pain-processing' systems, which receive direct or indirect input from spinal nociceptive pathways (BOX 1) and encode the intensity of painful stimulation<sup>88</sup>, provide pain-related targets for tests of placebo interventions. These targets include the medial thalamus, the primary somatosensory cortex (S1) and the secondary somatosensory cortex (S2), as well as the dorsal posterior insula (dpINS), the mid- and anterior insula (aINS) and the dorsal anterior cingulate cortex (dACC) (FIG. 3).

Placebo treatments can reduce pain-related activity in all of these regions, with the most consistent effects occurring in the dACC<sup>53,61,89–95</sup>, the thalamus<sup>90,94,96</sup> and the aINS<sup>53,61,90,97,98</sup> (FIG. 3). In many of these studies, large placebo analgesic responses were correlated with large decreases in brain responses to noxious stimulation in specific regions (the dACC<sup>53,90,94</sup>, the thalamus<sup>53,61,99–101</sup> and the insula<sup>53,90,100,102</sup>). Several quantitative meta-analyses on a subset of the studies that are depicted in FIG. 3 indicate that these findings are reliable across paradigms and laboratories<sup>103–105</sup>. EEG and MEG studies have also shown that placebo treatments cause reductions in the amplitude of event-related

potentials in response to painful laser stimuli<sup>60,77,107–110</sup>, indicating that such treatments have an effect on rapid (~150–300 ms) sensory and cognitive responses to painful events.

These placebo effects on pain-related responses are promising. However, pain is a complex sensory experience that also involves affect and decision making, and it remains unclear which aspects of the pain construction and evaluation process are affected by which types of placebo treatments. Many of the regions that normally generate pain and show the strongest placebo effects are involved in a range of other cognitive and affective processes that are distinct from pain, including basic perceptual and decision-making tasks<sup>111–114</sup> and emotional responses that are independent of pain<sup>115</sup>. The regions most directly linked to nociceptive processing<sup>116</sup> and most specific to pain<sup>112</sup> are the dpINS and S2. Although placebo treatments have been shown to affect these regions<sup>61,101</sup>, such effects are not consistently identified in meta-analyses<sup>103</sup>, pointing to variability across studies and individuals. Some placebo paradigms — for example, those that involve extended conditioning or particularly powerful manipulations of belief — may have more profound effects on the sensory transmission of pain, whereas others may primarily affect emotion and decision making. Advances in neuroimaging methods, which are beginning to identify more precise signatures for pain and other affective processes (BOX 2), will permit stronger tests of which placebo paradigms influence pain-specific versus more general affective processes.

### Placebos engage endogenous pain modulation circuitry

A wealth of animal research has established numerous brain systems for the modulation of pain at multiple levels of the neuraxis, from the spinal cord up to the PFC<sup>117–120</sup> (BOX 1). One important set of systems are descending pain modulation systems, which comprise projections from the brainstem to the spinal cord that can facilitate or reduce spinal nociceptive responses (for example, see REF. 120). These systems involve multiple pathways and neurochemical systems, including opioids, serotonin, dopamine, noradrenaline, oxytocin, cholecystokinin and neurokinin 1 (for a review, see REF. 2). Particularly important among them is a central opioidergic pathway from the midbrain periaqueductal grey (PAG) through the rostroventral medulla (RVM) to the spinal cord. The PAG receives direct projections from the ventromedial PFC (vmPFC), ventrolateral PFC (vlPFC), amygdala, nucleus accumbens (NAc) and hypothalamus<sup>55,121,122</sup>, permitting prefrontal cortical and limbic control over both afferent input and central pain circuitry. Beyond pain, PAG circuitry is critical for several other motivated behaviours<sup>122,123</sup> and is activated during human emotional responses<sup>124–126</sup>.

Beginning with the work of Levine, Gordon and Fields<sup>127</sup>, multiple studies have shown that placebo analgesia can be blocked by the opioid antagonist naloxone (for example, see REF. 128), implicating opioidergic pathways in placebo effects. Neuroimaging studies that examine fMRI and opioid activity in brain areas rich in opioids, particularly the PAG and RVM, have complemented and expanded on this work. PET studies have found placebo-induced increases in  $\mu$ -opioid activity (measured as decreases in binding of <sup>11</sup>C-carfentanil) in the PAG<sup>129–131</sup>. Consistent placebo-induced increases in blood oxygenation level-dependent (BOLD) activity in the PAG during both the anticipation<sup>90,94</sup> and experience<sup>61,103</sup> of pain have been observed in fMRI studies, and several studies have shown that placebo-

induced increases in PAG BOLD activity are correlated with the strength of analgesia<sup>61,90,132</sup> (although not always; see REF. 53). Placebos have also been found to increase activity in the vicinity of the RVM<sup>61</sup>. Importantly, the placebo effects on PAG and RVM activation, as well as on pain-related brain activity, can be reversed by naloxone<sup>61</sup>. These findings directly implicate endogenous opioid responses in the brainstem as a mechanism of placebo analgesia.

In rodents and primates, activation of the endogenous opioid system can in some cases reduce the transmission of nociceptive signals in the dorsal horn of the spinal cord, which prevents them from reaching the brain. A small set of recent studies suggest that placebos can also engage this type of descending modulatory control. Placebo treatments can reduce spinal responses to painful stimuli<sup>133</sup> and reduce secondary hyperalgesia around a site of painful stimulation<sup>134</sup>, which is thought to be spinally mediated in many cases. Conversely, nocebo suggestions of hyperalgesia can increase spinal fMRI responses to painful events<sup>59</sup> and reverse the effects of normally analgesic procedures on spinal nociceptive reflexes<sup>135</sup>. Although later-stage modulation of pain in the cerebrum is still likely to contribute to many types of placebo effects<sup>77,78</sup>, these findings strongly suggest that placebos can influence spinal nociception and modulate ascending pain-related signals.

In addition to the evidence on descending modulatory systems, there is now substantial evidence that placebo treatments engage multiple systems in the PFC, NAc and amygdala, and influence the functional connectivity between them. Such engagement may include both changes in ‘mindset’, perhaps reflected in changes in tonic metabolic activity (for example, see REF. 136), and alterations in responses to distinct events.

Thus far, it has not been possible to identify direct correlates of tonic states. Most studies have focused on how responses during the anticipation and experience of pain are altered by placebo treatment by comparing pain responses under placebo with pain responses during a control condition. The most consistent placebo-related increases in response during pain occur in cortical regions: the dorsolateral PFC (dlPFC) and ventrolateral PFC (vlPFC)<sup>61,94,96,99,136–138</sup>; the vmPFC, including the rostral and pregenual cingulate and medial orbitofrontal cortex (OFC)<sup>61,94,99,138,139</sup>; and the mid-lateral OFC (mlOFC)<sup>17,61,95,96,98,102,136</sup> (FIG. 3). In many cases, the increases in activity in these areas (lateral PFC<sup>17,53,94,99</sup>, vmPFC<sup>17,53,94,99</sup> and mlOFC<sup>99</sup>) are correlated with the magnitude of reported analgesia. Many of these regions show anticipatory increases in activity before pain, and responses in these regions can predict the magnitude of placebo analgesia across individuals<sup>100</sup>.

Both lateral and medial prefrontal regions may have important roles in placebo analgesia, particularly through their connections with the brainstem. High-frequency stimulation (10 Hz) of the dlPFC in humans using transcranial magnetic stimulation (TMS) can reduce pain<sup>140</sup>, and low-frequency stimulation (1 Hz; which may have inhibitory effects) of this area may reverse placebo-induced analgesia<sup>141</sup>. Placebo-induced dlPFC activity is associated with increased activity in the PAG<sup>90</sup>, and a recent study using diffusion tensor imaging found that strong placebo responses were associated with greater integrity in the white matter tracts that connect both the dlPFC and the vmPFC with the PAG<sup>142</sup>. Placebo



treatment also strengthens functional connectivity between the vmPFC and PAG, which can be measured in terms of correlations in fMRI time series<sup>61,139</sup>, and increases the correlation between the dACC and PAG<sup>129</sup> in levels of opioid binding, which is consistent with central opioid release. Placebo-induced vmPFC–PAG connectivity is also reversible by naloxone<sup>61</sup>, further implicating opioid mechanisms. All of these findings are consistent with placebo-induced central opioid release under the control of the PFC.

These findings have parallels in animal models that corroborate the importance of PFC–PAG connectivity in pain control. Stimulation of the lateral orbital PFC in rats can reduce nociceptive responses, and these effects require opioid release in the PAG<sup>143</sup>. Other work in rodents indicates that lateral PFC–brainstem projections may mediate some of the analgesic effects of thalamic stimulation<sup>144</sup>. These findings imply that projections from the PFC to the PAG might be important for many forms of pain control beyond placebo analgesia (BOX 1).

The amygdala, NAc and ventral striatum (VS) are also closely connected to the medial PFC (for example, see REF. 122). Across studies, placebo analgesic treatments reliably reduce activity in the amygdala and increase activity in the NAc–VS<sup>103</sup> (as these nearby regions are difficult to distinguish reliably with fMRI, we refer to them together), although they are discussed less frequently than the cortical regions discussed above.

In the amygdala, placebo treatments increase endogenous opioid responses (that is, they reduce opioid receptor binding), as observed by PET<sup>129</sup>, and reduce fMRI activity during pain<sup>16,17,61</sup>, an effect that can be blocked by naloxone<sup>61</sup>. Larger placebo-induced reductions in BOLD fMRI correlate with stronger placebo-induced analgesia<sup>53,100</sup>. The amygdala has a central role in encoding and maintaining sensory associations with potential threat (for example, see REF. 145), and placebo treatments may reduce the threat value and/or salience of pain cues. Opioid signalling in the amygdala, and projections to the PAG–RVM system, are also crucial for pain inhibition in animal models of threat-conditioned analgesia<sup>146</sup>. Together, these studies suggest that amygdala circuitry is important for both placebo and other analgesic effects that arise from competing motivational states. Further work is needed to determine whether placebo- and threat-related analgesia are mediated by opposing or similar influences on amygdala circuits.

A different pattern of placebo effects is found in the NAc–VS: placebo treatments cause increases in NAc–VS fMRI responses during pain<sup>53,96,103</sup> and in opioid<sup>129–131</sup> and dopamine<sup>130</sup> activity as measured by PET. Dopamine and fMRI activity increases in the NAc–VS have been strongly linked with appetitive learning<sup>147</sup>, desire<sup>148</sup>, social rewards<sup>149</sup> and motivational engagement<sup>150,151</sup>, as well as positive shifts in emotion<sup>152</sup> and pain reduction induced by self-regulation<sup>106</sup>. The NAc may also have a particularly important role in the motivational and behavioural aspects of pain<sup>119,153,154</sup>. For example, in animal models, chronic inflammation and nerve injury induce signs of depression and fatigue (for example, reduced reward seeking) that are accompanied by structural changes in the NAc<sup>154</sup> and vmPFC<sup>155</sup>. Strikingly, blocking the neuropeptide galanin in the NAc reversed both these structural and motivational effects<sup>154</sup>. In humans, fMRI-measured functional connectivity between the vmPFC and the NAc–VS predicts the development of chronic back pain 1 year later<sup>156</sup>, implicating this circuit in long-term pain-related behaviour. Thus, findings of

placebo effects in the NAc-VS may have important consequences on pain-related behaviour and other motivational processes.

The NAc-VS may also be important for predicting individual differences in the strength of placebo effects (that is, identifying placebo responders). Strong placebo analgesic responses are predicted by NAc-VS structure and function, including stronger placebo-related opioid<sup>129,131</sup> and fMRI activity<sup>17,53</sup> responses during pain, increased grey matter volume<sup>157</sup> and stronger fMRI responses in a reward-pursuit task unrelated to pain<sup>158</sup>. NAc-VS grey matter volume and placebo-induced opioid responses are also positively correlated with personality measures related to optimism, reward seeking and resilience<sup>132,157</sup>. These findings suggest that inter-individual differences in NAc-VS structure and function may provide clues as to why some individuals are placebo responders and others are not. In addition, activation of the NAc-VS during pain predicts the magnitude of opioid analgesia<sup>159</sup>, providing support for the notion that brain reward circuitry is implicated in both placebo effects and other forms of pain modulation.

### **Beyond pain: placebo effects on motivational systems**

Although placebo effects on brain function have been most extensively investigated in the context of pain, a select group of studies has begun to show that many of the systems discussed above are involved in placebo effects in other areas too, including emotion<sup>80,82–84,160</sup>, motor performance<sup>45,161</sup> and learning<sup>85</sup> in PD, and depression<sup>86,87</sup>.

The earliest studies of the brain mechanisms underlying placebo effects in domains other than pain examined placebo effects in PD and depression. One landmark PET study of dopamine activity<sup>45</sup> found that placebo administration increased striatal dopamine binding in patients with PD, particularly in those who perceived an improvement in clinical status with placebo treatment. Subsequent studies found that individuals with PD who showed placebo-induced improved motor performance also showed placebo-induced increases in subthalamic nucleus firing<sup>161</sup>, that PD patients' therapeutic expectations are correlated with placebo-induced striatal dopamine release<sup>44</sup> and that placebos mimic the effects of dopamine drugs on reward-learning signals in the striatum and vmPFC<sup>85</sup>. An adjacent region of the vmPFC, in the subgenual cingulate cortex, also showed placebo-related reductions in glucose metabolism in depression<sup>86</sup>. This region is thought to be a critical hub for depression<sup>162</sup>, and subgenual cingulate cortex stimulation has shown great promise as an intervention for treatment-resistant depression<sup>163</sup>. These studies provide promising links between the effects of placebo treatments on medial prefrontal–striatal circuitry and improvements in psychopathology.

Studies of placebo effects on emotion processing also dovetail with findings relating to placebo-mediated analgesia. In one study, a placebo 'anxiolytic' reduced both the unpleasantness of negative images and amygdalar and extrastriate cortical responses to the images<sup>80</sup>. These effects were also associated with increased activity in the lateral OFC and dACC, regions that are also implicated in placebo analgesia<sup>164</sup>. In another series of studies, treatment with a placebo 'anti-nausea' pill reduced ratings of disgust in response to negative images<sup>83,84</sup>. These effects were accompanied by reductions in insular and visual cortical activation and reduced functional connectivity between the insula and both the amygdala and

visual cortices. Finally, a placebo nasal spray, paired with suggestions of increased touch pleasantness and reduced pain, produced similar increases in vmPFC, NAc–VS, amygdala and PAG activity during both pleasant and painful touch<sup>165</sup>. However, somatosensory cortical activity increased during pleasant touch and decreased during pain. Thus, placebo effects on pleasant touch may engage similar forebrain motivational circuitry but have opposite effects on somatosensory processes.

Together, these studies elucidate the neural circuitry underlying placebo effects. Converging evidence indicates that placebo treatments engage prefrontal–subcortical systems that are involved in valuation, emotion and expectation. These systems can affect both sensory aspects of pain, via descending brainstem and spinal modulation, and functional and affective aspects of pain as well as other emotional and motivational processes, via interactions with the striatum and amygdala. Placebo effects in cortical–brainstem systems depend in part on opioid involvement: placebos can cause central opioid release in the cortex, NAc–VS and PAG<sup>129</sup>, and placebo effects on both pain-related increases and decreases in fMRI activity are blocked by naloxone<sup>61</sup>. However, a range of other neurochemicals, including dopamine, cholecystokinin and oxytocin, are also likely to be involved in the placebo response<sup>2</sup> (BOX 1); for example, one recent study found that intranasal oxytocin enhanced placebo analgesia<sup>166</sup>. Studies of placebo can also be viewed in conjunction with other forms of affective and perceptual regulation by context and expectancy, such as value-based modulation of hedonic responses<sup>28</sup> and cue-based modulation of visual and auditory perception<sup>23,24,167,168</sup>, although full consideration of all of these studies is beyond the scope of this Review.

## New frontiers in placebo research

The emerging neuroscience of placebo effects suggests a remarkable consistency in the brain systems engaged across studies and health-related domains, including pain, PD, depression and emotion. However, this apparent consistency belies a deep complexity, the untangling of which has barely begun. Placebo studies widely differ in both the outcomes that are assessed and the likely psychological processes involved. As Benedetti writes<sup>2</sup>: “There is not one placebo effect, but many.” To move forward, we must jointly consider the variety of psychological mechanisms that are involved in placebo effects and how they relate to brain systems.

In this section, we provide a framework that includes three types of psychological antecedents that give rise to placebo effects — *pre-cognitive associations*, *conceptual processes* (for example, expectancies) and *affective or motivational states* — with different brain substrates. These antecedents give rise to placebo effects on three kinds of outcomes: disease-related symptoms (for example, pain), physiological signs and other behaviours. Using this framework as a platform, we explore several frontiers and areas of new opportunity. The first frontier concerns differences across types of outcomes. We ask whether placebo effects on different outcomes really share common mechanisms, and what functional roles the regions consistently activated by placebos, such as the PFC, might have. The second frontier concerns the requisite antecedents for placebo effects. We explore the hypothesis that both conceptual and learning processes are required for many kinds of

placebo effects and discuss how these may relate to brain systems. Finally, although in many cases placebo effects require learning — driven by experienced benefit after receiving the placebo — in some cases placebo effects persist despite contrary experiences. We ask what the mechanisms underlying such ‘self-reinforcing’ placebo effects might be.

### Mapping psychological mechanisms onto brain systems

The principal building blocks of laboratory placebo paradigms include three elements: presentation of sensory cues associated with positive outcomes (for example, pain relief) or negative outcomes (for example, shock) through classical conditioning; verbal suggestions designed to induce expectations of therapeutic improvement or symptom exacerbation; and the delivery of placebo manipulations in a context that includes both rich associative cues (for example, a hospital setting) and information about the interpersonal relationship (for example, knowledge that treatment is provided by an expert caregiver). These ‘treatments’ can elicit a range of therapeutically relevant internal brain processes (FIG. 4a). One useful distinction is between processes that are pre-cognitive — that is, independent of what a person expects or believes — or conceptual — that is, dependent on thoughts, expectations and memories. Conditioned cues can elicit pre-cognitive associations, which are simple forms of memory that are supported by neuroplastic changes in specific circuits throughout the brain and the spinal cord. These associations can trigger multiple types of responses, depending on the nature of the circuit and its location in the brain, including autonomic and neuroendocrine responses, emotions and motivated behaviours. Verbal suggestions and background beliefs about the treatment context can engage multiple conceptual processes: expectations of specific outcomes, appraisals of the significance of both symptoms and treatment, and explicit memories of prior experiences. If they are sufficiently relevant for survival and well-being, both pre-cognitive associations and conceptual thought can induce emotional and motivational states, which may underlie some forms of placebo effects<sup>158,169</sup>. These mediating processes differentially influence different classes of observable outcomes, including reported experiences (for example, symptoms), behaviour and physiology.

Although placebo effects may engage similar classes of processes (for example, expectancies) across disorders and outcomes, resulting in substantial convergence in the neurobiological systems typically involved, no single process or system mediates all types of placebo effects. A challenge for the next generation of placebo studies will be to specify which psychological antecedents produce placebo effects on specific brain systems and outcomes.

### Different mechanisms for different outcomes?

Although placebo effects can encompass symptom reports, physiological signs and other behaviours, it is far from clear which brain pathways are essential for the effects on each type of outcome. Most placebo studies have examined symptoms such as pain as a behavioural end point, and brain correlates of the strength of placebo effects<sup>104</sup> are thus largely limited to the correlates of changes in symptoms. Direct comparisons of the brain mechanisms underlying placebo effects across outcomes (for example, pain, PD symptoms and emotion) and types of outcomes (for example, symptoms and physiology) have seldom been carried out.

It is thus still unclear whether brain regions such as the PFC and NAc, which seem to be consistently associated with placebo effects in pain, dopaminergic systems and beyond, are really engaged in the same way across disorders. The vmPFC and other prefrontal areas are critical hubs for conceptual meaning-making processes<sup>170</sup> (FIG. 4b), making them natural candidates for common antecedents of placebo effects across outcomes. However, very few studies make direct comparisons across outcomes. A pair of studies<sup>82,160</sup> have provided another kind of evidence on shared mechanisms: they examined whether placebo suggestions about one outcome (pain) influence another (emotion). A placebo ‘analgesic’ reduced the unpleasantness of negative images and the magnitude of the P2–N2 complex, an EEG marker of early visual processing<sup>82</sup>. Subsequent fMRI<sup>160</sup> scans revealed that placebo administration reduced amygdala and insula responses to unpleasant images and increased activation in the subgenual ACC, a part of the vmPFC zone. Thus, this provides some initial evidence that placebos engage brain mechanisms in a way that transfers across outcomes.

A related question is which aspects of placebo-induced changes in fronto–striatal–brainstem systems are related to effects on pathophysiology, internal states that drive behaviour in meaningful ways or decision bias — effects of conceptual processes on symptoms, without concomitant effects on behaviour and pathophysiology. For some researchers, vmPFC activation might be taken as an indicator of decision bias. Responses of the vmPFC during the viewing of desirable items predict how much a participant is willing to pay for the item<sup>171</sup> and are sensitive to beliefs about the object (for example, the price of a bottle of wine<sup>26</sup>) and one’s goals (for example, dieting goals when viewing food items<sup>172</sup>). However, vmPFC activation in placebo studies might also indicate effects of more enduring significance, in two ways. If conceptual processes affect health behaviours (for example, choices about food, exercise and social behaviour)<sup>150</sup>, they can have a lasting, long-term impact on disease. For example, smokers who showed larger vmPFC responses during viewing of anti-smoking advertisements were more likely to subsequently attempt to quit smoking, and vmPFC responses were more predictive than standard focus-group responses to the advertisements<sup>173</sup>. Despite their prominent role in decision making, vmPFC responses in placebo studies may also be related to influences on pathophysiology, including nociception and physiological responses (BOX 1). The vmPFC projects directly to the PAG, hypothalamus and other autonomic centres<sup>54</sup>, and its connections with the PAG mediate some kinds of conceptually driven autonomic responses, such as social evaluative threat<sup>56</sup>. Thus, one may ask, which potential outcomes is vmPFC (or lateral PFC, or NAc) activity related to in any given placebo study?

Two new research directions may provide important clues. The first is examination of PFC–brainstem connectivity. Enhanced vmPFC–PAG connectivity in placebo studies suggests descending regulation of pain physiology or autonomic or neuroendocrine responses. In future studies, it may be possible to separate patterns of prefrontal activity that differentially relate to brainstem or spinal cord responses and measures of pathophysiology, symptom reports independent of pathophysiology and long-term placebo-induced changes in behaviour.

The second direction is the development of brain measures that provide new markers of neuropathophysiology for mental health and neurological disorders (BOX 2). In pain, these

include brain indices of early nociception<sup>59,133</sup> and central pain-construction processes<sup>174</sup>. In PD, they include measures of dopamine activity<sup>45</sup> and dopamine-linked brain processes<sup>85</sup>. The brain correlates of placebo effects on these new measures may be similar to or different from those related to self-reported outcomes. For example, in one recent study of placebo analgesia, the brain patterns predictive of the magnitude of placebo effects on pain reports versus pain-related brain responses were distinct, although frontal cortical systems were involved in both<sup>100</sup>.

### Understanding the role of conceptual processes

Another frontier is understanding which types of placebo mechanisms — including pre-cognitive associations, conceptual thought and emotional states — are required to elicit changes in brain processes that are relevant to health and disease. Nearly all of the studies that produced convincing placebo-induced decreases in pain-related brain responses and increases in activity in pain- and emotion-modulatory circuitry (FIG. 3) utilized the response conditioning procedure, which involves both creating expectations via verbal suggestions and reinforcing those expectations through classical conditioning. Although conditioning is frequently thought of as creating ‘hard-wired’ associations in neural circuits, decades of empirical work suggests that in many cases conditioned responses in humans and rodents alike depend on the information value of the cue — that is, the expected outcome — rather than obligatory, pre-cognitive associations<sup>175–178</sup>. Thus, it is still unknown whether placebo-induced neuromodulation is created by the belief in the placebo, expectations of positive outcomes or specific associations learned through reinforcement.

Conditioning and expectancy have traditionally been offered as competing alternatives for placebo effects<sup>179–182</sup>. However, there is growing evidence that a combination of pre-cognitive associations and conceptual processes may be required. Placebo effects elicited by verbal suggestions alone have been reported, including some effects on physiology (Supplementary information S1 (table)), but on the whole these effects are weak and inconsistent across studies. The most compelling example — that is, the induction of cortisol release by suggestions of strong upcoming pain — may have worked by eliciting strong emotional responses. Perhaps surprisingly, reinforcement alone without verbal instructions does not often yield robust placebo effects either; adding verbal instructions to reinforcement alone typically produces much stronger effects<sup>109,183,184</sup>.

In addition, conditioned placebo effects can often be reversed by verbal suggestions. For example, autonomic responses can be conditioned in humans and animals by pairing previously neutral sensory cues (for example, lights) with shocks. Such responses can be reversed in a single trial by instructing participants that the light– shock contingency is no longer in effect<sup>58</sup> (for a review of related paradigms, see REF. 178). In a minority of cases, placebo effects may be insensitive to beliefs: for example, in conditioned immunosuppression<sup>185</sup> and some forms of pharmacological conditioning<sup>65,186</sup>. However, even in these cases, verbal suggestions may support conditioning during learning; thus, having the right belief may still support the formation of placebo effects in these systems.

One way in which conceptual processes may interact with experiences (that is, reinforcement) is by guiding attributions — beliefs about the nature of the events that

caused pain relief or other therapeutic outcomes. For example, imagine that you take a pill to relieve a headache and an hour later the headache disappears. You must decide whether to attribute the relief you feel to the pill or the natural course of events. Attributions such as this probably guide what we learn from experiencing outcomes with multiple potential causes in many situations. Several placebo studies<sup>184,187,188</sup> have found that response conditioning — pairing a cream with reductions in the intensity of painful stimuli — resulted in placebo analgesia (and reduced EEG potentials<sup>188</sup>) during a later test, but only as long as participants were not aware of the reduction and believed that the stimuli were just as intense on the placebo-treated site. When participants were informed that the stimulus intensity would be reduced, no placebo analgesia occurred, although the conditioning procedure was otherwise identical. Conditioned analgesia required both the experience of reduced symptoms and the attribution of efficacy to the cream. Thus, another potential function of prefrontal cortical activation after placebo treatment is to guide attributions of efficacy; if they favour the treatment, learned placebo may be strengthened in other systems, including the amygdala, the NAc–VS and the brainstem.

Attribution may be important in appetitive learning as well as in pain: a positive outcome following what one believes is a good choice reinforces the choice, but a positive outcome following a bad choice may be attributed to luck. Several recent studies suggest that this type of attribution shapes appetitive learning: participants learn the reward values of cues faster when reward feedback is compatible with prior beliefs induced by verbal suggestion<sup>189–191</sup>. These studies imply that dopaminergic reward learning is enhanced by prior beliefs in the reward value of the cues. All of these effects are consistent with the idea that suggestions influence the credit-assignment process during learning and suggest that conditioned placebo responses in the NAc–VS, and possibly other regions, may depend on attribution of benefit to the placebo.

### **Self-reinforcing placebo effects?**

One of the mysteries surrounding placebo effects is that they can sometimes be stable or even increase in magnitude over time<sup>184,192,193</sup>. But if placebo effects are a conditioning phenomenon that is learned during a training phase, then they should extinguish during subsequent testing, when symptoms (such as experienced pain) are higher than expected in placebo conditions. Although it remains largely unexplored at the brain level, two of the mechanisms discussed here might be particularly important for creating self-reinforcing placebo effects that last through time. First, if experienced benefits are attributed to a treatment when they match prior beliefs (for example, when pain experience is low) but not otherwise (for example, when pain is high), then disconfirmatory experiences will be discarded and belief in the placebo will persist. Second, if placebo treatments have deep effects on the sensory processes that give rise to symptoms (for example, spinal responses to painful events), belief in the placebo will not be disconfirmed because the ascending noxious input will be dampened. These conditions allow placebo effects to become self-fulfilling prophecies. Much work remains to test these mechanisms and the brain processes that support them, but doing so could help us to understand and ultimately harness the power of belief for creating positive, long-term change.

## Conclusions

A substantial part of the therapeutic benefit patients experience when undergoing medical treatment is caused by their brain's response to the treatment context. Laboratory investigations of placebo effects provide a way of examining the brain mechanisms underlying these effects. Consistent findings across studies include reduced activity in brain areas associated with pain and negative emotion, and increased activity in fronto-striatal-brainstem circuits. In most cases, the creation of robust placebo effects across disorders and outcomes seems to require appropriate conceptual beliefs — maintained in prefrontal cortical networks — that are supported by experience-dependent learning in striatal and brainstem circuits. However, the critical ingredients for eliciting placebo effects, at both the psychological and brain level, are just beginning to be understood. These ingredients may differ substantially depending on whether the outcomes are symptoms, behaviours or changes in physiology. A better understanding of the neuroscience of placebo could yield rich benefits for both neuroscience and human health.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Glossary

### Context

The combination of all of the elements surrounding a given event that can be psychologically meaningful, including interpersonal dynamics, situational features owing to a place or location, memories, goals for the future and internal body or brain states.

### Cues

Stimuli that signify the occurrence, or evoke a representation, of another stimulus or internal experience.

### Emotions

Coordinated responses to biologically relevant events (such as threats and opportunities) that involve changes in multiple systems, including peripheral physiology.

### Nocebo effects

Deleterious outcomes (for example, an increase in pain or an increase in negative side effects) owing to beliefs about the treatment context.

### Placebo responders



Individuals who show an improvement in symptoms after receiving inert treatments (that is, placebos).

**Placebo analgesia**

A reduction in pain that can be attributed to the treatment context.

**Response conditioning**

The process of associating neutral stimuli with biologically meaningful outcomes, through which neutral stimuli may begin to induce anticipatory responses that are associated with the outcomes themselves.

**Expectancy**

A conscious, conceptual belief about the future occurrence of an event. It is a subclass of predictive processes, which may be conscious or unconscious.

**Analgesia**

Pain relief, which can be caused by many factors, including medical treatments (for example, opioid analgesia), features of the treatment context (placebo analgesia) and affective states (for example, stress-induced analgesia).

**Nociceptive**

Receiving input from stimuli that can cause damage to tissues.

**Descending pain modulation systems**

Endogenous, biological mechanisms for suppressing ascending nociceptive information at the level of the spinal cord.

**Pre-cognitive associations**

Links between events and/or objects that exist outside conscious awareness. These links are generally created through conditioning procedures or innate (evolutionarily afforded) associations.

**Conceptual processes**

Processes that depend on an interpretation of the situational context and its relationship to prior information (for example, memories and rules), including interoceptive cues from the body, and which can be updated in response to verbally presented or symbolic information.

**Schema**

A conceptual, 'situational' pattern — inferred from a combination of sensory cues, internal motivation, interoceptive information and thoughts — that can activate scripts that guide behaviour based on the nature of the situation rather than any single cue.

**Attributions**

Inferred causality; the process of assigning an observed effect (for example, a symptom) to an underlying cause or mechanism.

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## Biographies

Tor D. Wager is a professor of psychology and neuroscience, and a faculty member in the Institute for Cognitive Science at the University of Colorado, Boulder, USA. He received his Ph.D. from the University of Michigan, Ann Arbor, USA, in cognitive psychology in 2003, and served as an assistant and associate professor at Columbia University, New York, USA, from 2004 to 2009. Since 2010, he has directed Boulder’s Cognitive and Affective Neuroscience Laboratory. He has a deep interest in how thinking influences affective experiences, affective learning and brain–body communication. His laboratory also focuses on the development and deployment of analytical methods, and has developed several

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### Box 1 | Converging circuitry and common mechanisms for analgesia and affective states

Interactions among the prefrontal cortex (PFC), the forebrain and the periaqueductal grey (PAG)–rostromedial medulla (RVM)–spinal cord axis underlie multiple forms of analgesia, including placebo effects. These circuits are also integral to generating affective and motivational states. Likewise, the neurochemical systems implicated in placebo analgesia<sup>2</sup> — including opioid (OP), dopamine (DA), serotonin, cholecystikinin (CCK) and oxytocin systems — have diverse roles in motivated behaviour beyond pain. Seen in this light, placebo-based modulation of pain is one example of a broader pattern of regulation of affect, perception and behaviour by cognitive and motivational context.

The context-based modulation of pain and motivation is supported by convergence between ‘bottom-up’ sensory processes and ‘top-down’ context at multiple levels of the neuraxis. Nociceptive afferents from the spinal cord project to brainstem regions (including the PAG and RVM), thalamic nuclei and forebrain regions (including the hypothalamus (HYP), amygdala (AMY) and ventromedial PFC (vmPFC))<sup>194,195</sup> (see the figure, part **a**). These regions also receive monosynaptic inputs from the vmPFC<sup>55,196</sup>. Thus, brainstem and forebrain centres integrate input from the ‘lowest’ and ‘highest’ levels of the neuraxis, providing multiple convergence zones for sensory input and contextual information.

The PAG–RVM–spinal cord axis is important for many forms of pro- and anti-nociception in non-human animals, paralleling involvement in human placebo and nocebo effects, including forms of ‘stress’ analgesia present even in decerebrate animals<sup>197</sup>. This axis is, in turn, governed by evolutionarily newer forebrain neural and neurochemical systems, which interact with the PAG–RVM pathway to mediate diverse types of pain-modulatory effects (see the figure, part **b**). For example, in intact animals, both footshock-induced analgesia and morphine analgesia require OP–DA interactions in the ventral tegmental area (VTA) and nucleus accumbens (NAc)<sup>198,199</sup>, which influence ‘pain off’ spinal projection neurons in the RVM. Threat- or fear-conditioned analgesia relies on the release of OPs<sup>146,200</sup> and cannabinoids (CBs)<sup>201</sup> in the AMY and PAG, respectively, which also activates RVM ‘pain off’ neurons. Analgesia related to noxious stimulation<sup>202</sup> and massage-like touch<sup>203</sup> depends on oxytocin (labelled ‘Oxy’) release from hypothalamic projections to the PAG and subsequent OP release<sup>204</sup>. The PAG–RVM circuit also mediates some kinds of pro-nociceptive actions. CCK antagonizes OPs in this system<sup>205</sup> and may underlie nocebo hyperalgesia<sup>62</sup>, OP hyperalgesia<sup>215</sup> and safety signal-mediated hyperalgesia<sup>206</sup>. Other motivational states related to hypothalamic and forebrain circuits — including food pursuit<sup>207</sup>, micturition, and social conflict and defeat<sup>208,209</sup> — can also influence nociception, providing additional clues that pain control circuits evolved as part of an integrated system governing adaptive behaviour. IOFC, lateral orbitofrontal cortex; PBN, parabrachial nucleus.

## Box 2 | Brain-based biomarkers for pain and affect

To study pain, depression and other conditions that affect the brain, we must first identify biomarkers — observable physiological measures — for the processes that give rise to them<sup>174</sup>. For example, functional MRI (fMRI) responses during pain in the dorsal anterior cingulate cortex (dACC) and anterior insula (aINS) are commonly used as markers for pain. When activity in these regions is affected by placebo, or other treatments, it is assumed that the treatment affects pain-related neural activity in these areas, and thus it is inferred that the placebo affects ‘pain processing’.

At first, this seems reasonable, as the dACC and aINS contain neurons that encode nociceptive information<sup>210</sup>. However, there are two central problems with this inference. First, each ‘voxel’ in a typical neuroimaging study contains approximately 5.5 million neurons<sup>211</sup>. Neurons in the dACC and other ‘pain-processing’ regions encode diverse forms of information, some unrelated to pain. The examination of fMRI activity across thousands of studies has revealed that the dACC and aINS are among the most frequently activated areas in the brain, regardless of the psychological task<sup>111–114</sup>. Second, pain is likely to be encoded in a distributed circuit, and it is unclear whether measures in individual brain regions — whether fMRI or cellular — are sufficient to capture the mechanisms underlying pain experience.

For a pattern of brain activity to be useful as a biomarker for pain, the pattern must be sensitive and specific to pain. These criteria, and other related metrics that can be derived from them (‘precision’ and ‘recall’, and positive and negative predictive value), are the bedrock of any diagnostic test. Sensitive measures of pain respond reliably, with large effect sizes that track the intensity of pain, and thus show a high probability of being present when pain is experienced. Specific measures respond only to pain and have a low probability of being present when pain is not present.

Recently, it has been demonstrated that distributed patterns of fMRI activity can be identified that are both sensitive and specific to pain. One pattern, termed the ‘neurologic pain signature’ (NPS)<sup>174</sup>, can be applied to individual participants to make accurate predictions about pain intensity and has been validated across several studies. Although it is activated by painful events and reduced by opioid treatment, it does not respond to other emotionally salient events<sup>115,174</sup>, demonstrating specificity to pain.

Markers such as the NPS provide more precise targets for a new generation of placebo studies. Thus far, there are few tests of placebo effects on such markers; but, in one study, a placebo manipulation that affected reported pain had no effect on responses in the NPS<sup>174</sup>. In another, cognitively ‘rethinking’ pain, a psychological intervention related to placebo, strongly affected pain reports but also had no effect on the NPS<sup>106</sup>. Rather, the effects of cognitive regulation were mediated by brain signals in an independent pathway connecting the ventromedial prefrontal cortex and nucleus accumbens. These findings suggest that the NPS was only influenced in a subset of studies in which pain reports were affected. Whereas placebos may affect nociception in fundamental ways in some

cases, they may independently affect the evaluation and functional consequences of pain in others; such effects may be mediated by separate brain pathways.

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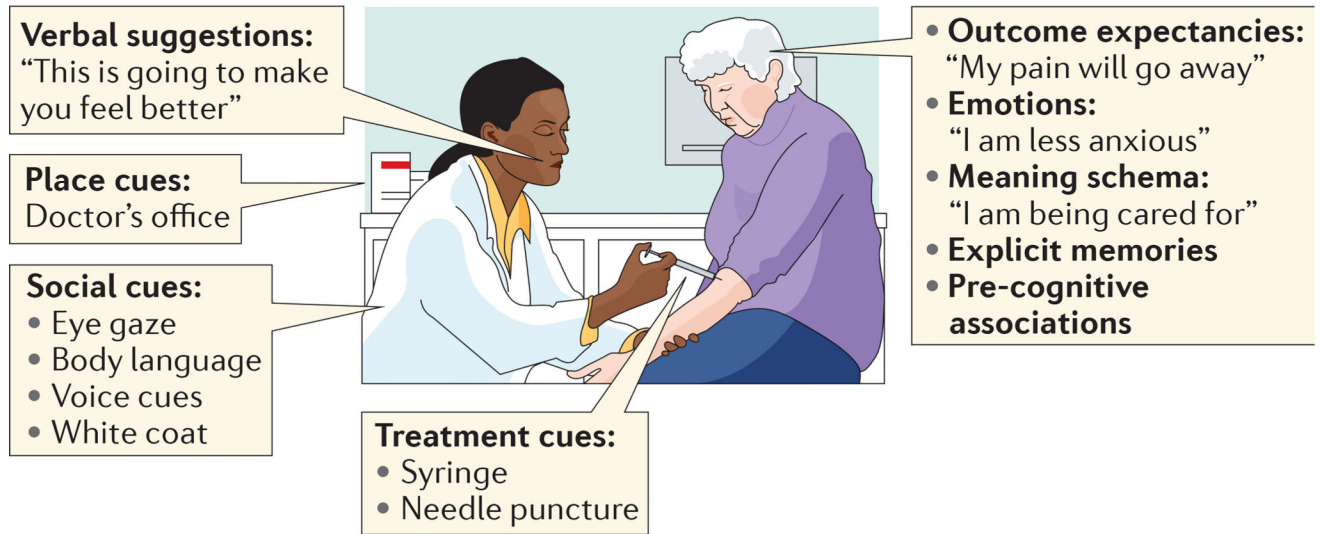
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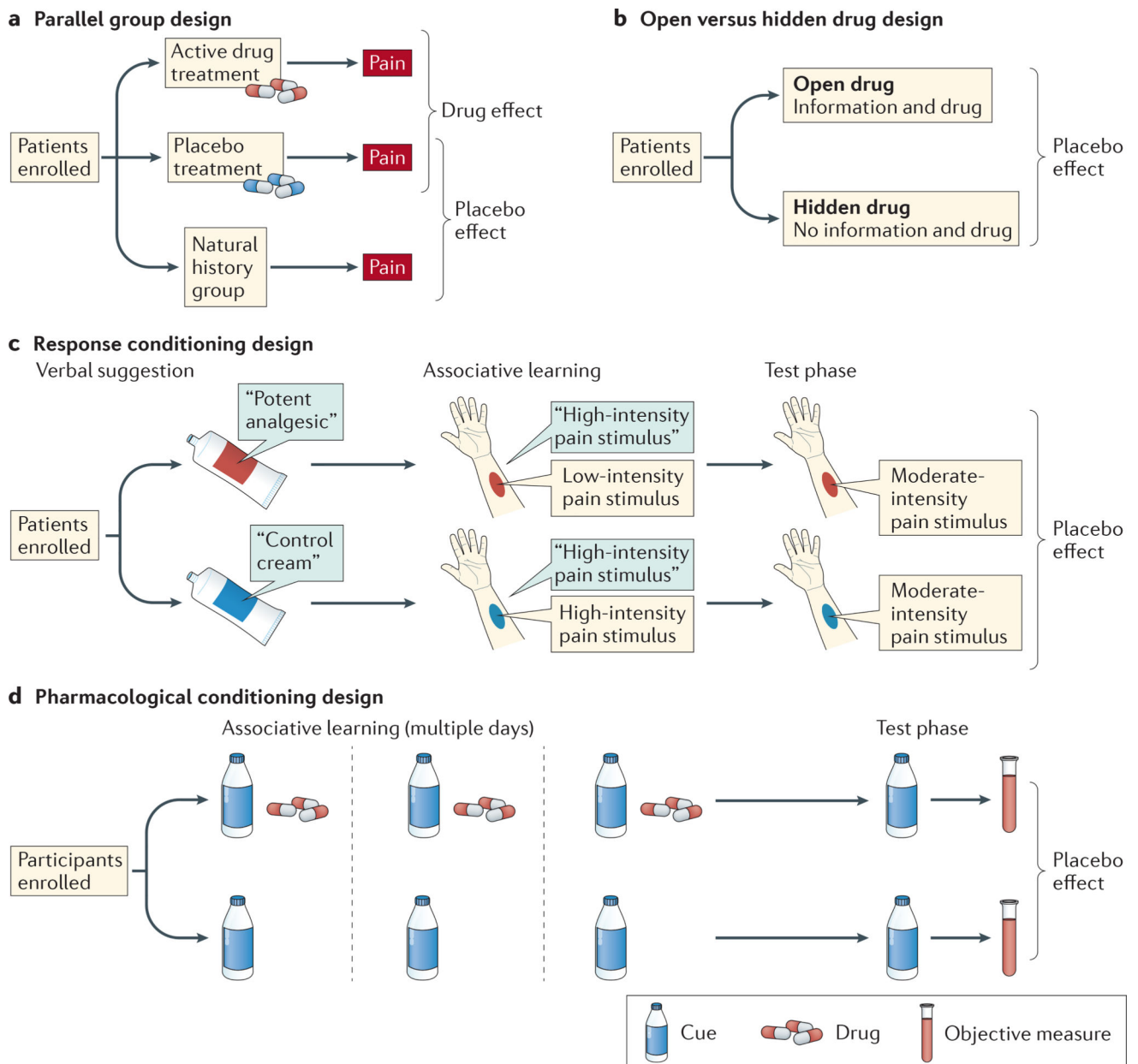
### Key points

- Placebo effects are effects of the context surrounding medical treatment. They can have meaningfully large impacts on clinical, physiological and brain outcomes.
- Effects of placebo treatments are consistent across studies from different laboratories. These effects include reduced activity in brain areas associated with pain and negative emotion, and increased activity in the lateral and medial prefrontal cortex, ventral striatum and brainstem.
- Placebo effects in pain, Parkinson disease, depression and emotion are enabled by engagement of common prefrontal–subcortical motivational systems, but the similarity across domains in the way these systems are engaged has not been directly tested.
- Meaningfully large placebo effects are likely to require a mixture of both conceptual belief in the placebo and prior experiences of treatment benefit, which engage brain learning processes.
- In some cases, placebo effects are self-reinforcing, suggesting that they change symptoms in a way that precludes extinction. The mechanisms that drive these effects remain to be uncovered, but doing so could have profound translational implications.



**External context****Figure 1. Elements of treatment context**

Whether treatment consists of an active drug or a placebo, the clinical setting that surrounds treatment includes multiple types of context information that are perceived and interpreted by the patient’s brain. The external context includes treatment, place and social cues, along with verbal suggestions. The internal context consists of memories, emotions, expectancies and appraisals of the meaning of the context for future survival and well-being. These features combine to make up the treatment context and are the ‘active ingredients’ of placebo effects.



**Figure 2. Paradigms for assessing placebo effects**

Most paradigms used to assess placebo treatments fall into one of four categories. **a** | In a parallel group design, placebo effects are measured by comparing outcomes in a placebo group with those in a no-treatment control group. This is the most common paradigm in clinical trials. **b** | In an open versus hidden design, drugs are delivered either with (open) or without (hidden) the knowledge of the patient. This design permits assessment of the effects of treatment context in clinical settings without withholding treatment. Extended designs such as the balanced placebo design<sup>9</sup> cross open versus hidden administration with verum versus sham drugs, enabling researchers to assess placebo–drug interactions. **c** | Response conditioning designs use instructions combined with reinforcement to maximize the effectiveness of placebo treatments. In a common variant, initial verbal instructions are

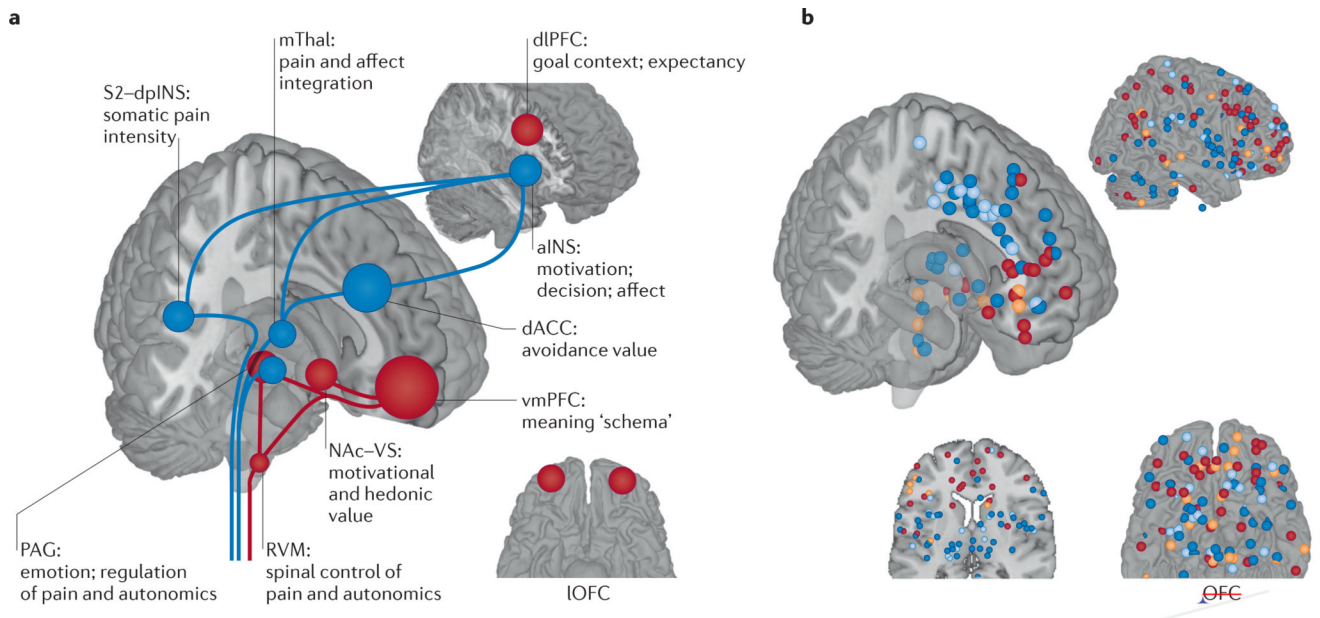
provided that one cream (the placebo) is an effective analgesic and another (the control) is not. Then, painful stimulation is given on both placebo-treated and control-treated skin sites. Participants are told that the stimulus intensity will be the same on both sites, but in fact it is surreptitiously reduced for the placebo-treated site, reinforcing belief in the placebo and associations with relief. During a final test phase, equivalent levels of painful stimulation are applied to both sites, and the effects of the placebo conditioning procedure are assessed. This is the most common paradigm used in neuroimaging studies; placebo and control treatments are often compared in a within-person crossover design. **d** | Pharmacological conditioning designs combine instructions and cues paired with active drugs during a conditioning phase, which often occurs over multiple days. Placebo effects are determined by presenting cues alone and comparing outcomes in drug-paired versus non-drug-paired groups. Response conditioning and pharmacological conditioning designs have been used in both humans and non-human animals.

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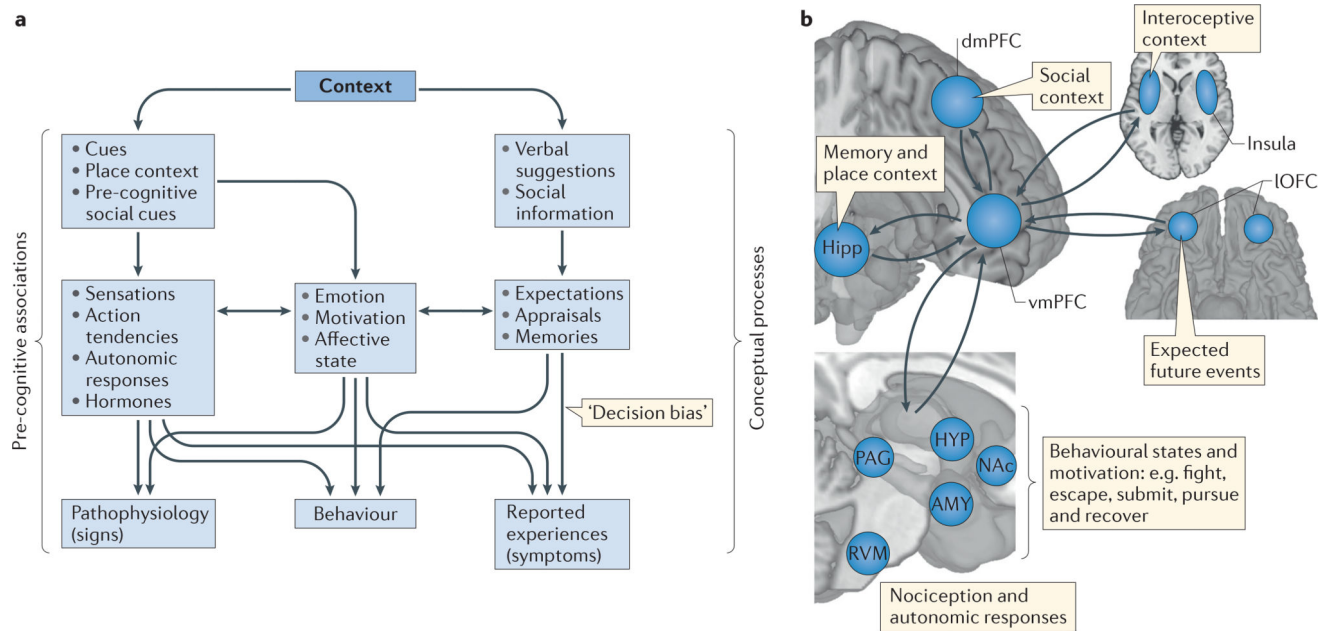
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### Figure 3. The neurophysiology of placebo analgesia

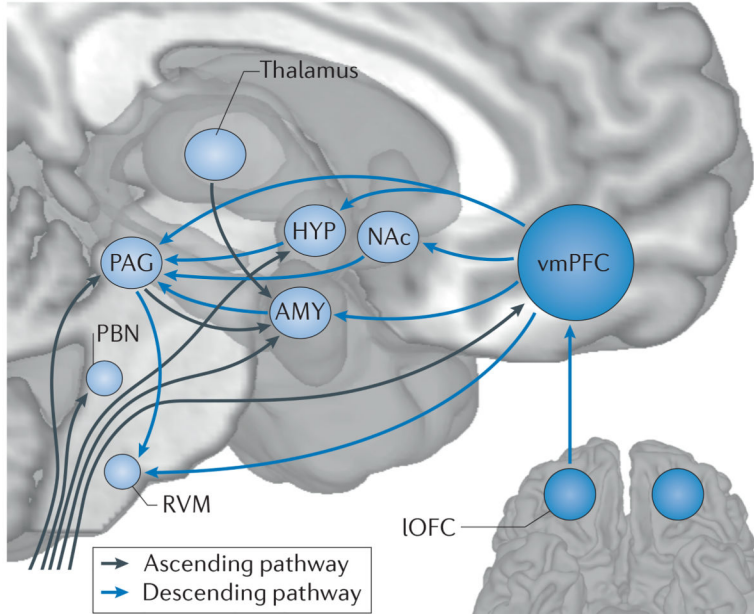
**a** | An overview of the brain regions involved in the placebo effects on pain and their potential functions in this context. The areas shown in blue respond to painful stimuli and, on that basis, are expected to show reduced responses to pain after placebo treatment. These areas include the medial thalamus (mThal), anterior insula (aINS), dorsal anterior cingulate cortex (dACC), periaqueductal grey (PAG) and secondary somatosensory cortex–dorsal posterior insula (S2–dpINS). Areas shown in red are associated with increases in response to placebo treatment (either before or during painful stimulation), and activity in these regions is thought to be involved with the maintenance of context information and the generation of placebo-related expectations and appraisals. They include the ventromedial prefrontal cortex (vmPFC), dorsolateral PFC (dIPFC), lateral orbitofrontal cortex (IOFC), nucleus accumbens–ventral striatum (NAc–VS), PAG and rostroventral medulla (RVM). Some regions, including the PAG and dACC, show different effects depending on the study and timing relative to painful stimulation. **b** | Results from neuroimaging studies of placebo-induced analgesia. Each point represents a finding from an individual study, reported in standard Montreal Neurological Institute space (all studies are listed in Supplementary information S2 (box)). Red points show increases in activity under placebo versus control treatment (that is, the same cream without the belief that it is a painkiller), and blue points identify decreases in activity under placebo. These comparisons involved randomized assignment to placebo or control conditions, and so they can test the causal effects of placebo treatment on brain activity. Some studies also examined correlations between the magnitude of placebo analgesia and the magnitude of placebo-induced changes in brain responses. Orange points identify positive correlations between the magnitude of an individual's activity increases under placebo versus control treatment and the magnitude of placebo analgesia. Light blue points identify negative correlations. These correlations do not necessarily reflect causal effects of placebo on brain activity but can provide important information on the nature of the individual differences that predispose a person towards showing a larger versus a smaller placebo response.



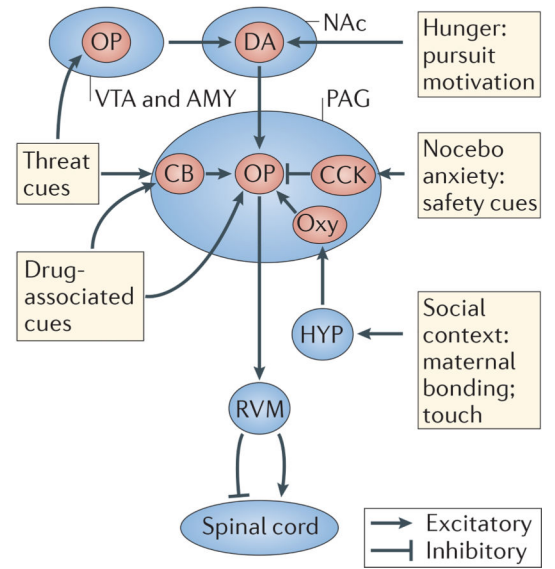
**Figure 4. Concepts, associations and the representation of context**

**a** | Patient outcomes, and hence placebo effects, are measured as a function of pathophysiology (signs), reported experiences (symptoms) and behaviour. These outcomes are influenced in various ways by the two primary components of the treatment context: conceptual processes and pre-cognitive associations. Conceptual processes can influence expectations, appraisals and memories, which can directly influence emotional states, reported decisions and behaviour. Pre-cognitive associations influence physiological processes outside conscious control, which can in turn influence emotion, motivation and affective states as well as outcome measures. Thus, some types of placebo effects may be mediated by affective and motivational states, whereas others may be independent of such states, depending on the nature of the context and the outcome. **b** | Conceptual processes have been difficult to define and measure precisely in the brain, because they depend on the integration of information associated with multiple systems into an overall schema, or conceptualization of the situation and its implications for well-being, which guides the meaning or significance of events. The ingredients of such ‘meaning responses’, which are thought to be critical for placebo effects<sup>212</sup>, include inferences about social information (dorsomedial prefrontal cortex (dmPFC)), interoceptive assessments of one’s body state (insula), expectancies (lateral orbitofrontal cortex (IOFC)) and autobiographical memories and place context information (hippocampus (Hipp)). The ventromedial PFC (vmPFC) is positioned to integrate these elements into a coherent schema that informs and is informed by responses at other processing levels<sup>170</sup>, including brainstem and subcortical centres that regulate sensory, autonomic and neuroendocrine responses. AMY, amygdala; HYP, hypothalamus; NAc, nucleus accumbens; PAG, periaqueductal grey; RVM, rostroventral medulla.

**a** Converging ascending and descending pathways



**b** Forebrain control of the PAG-RVM-spinal cord axis



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