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The Cognitive Neuroscience of Placebo Effects: Concepts, Predictions, and Physiology

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Abstract

Placebos have been used ubiquitously throughout the history of medicine. Expectations and associative learning processes are important psychological determinants of placebo effects, but their underlying brain mechanisms are only beginning to be understood. We examine the brain systems underlying placebo effects on pain, autonomic, and immune responses. The ventromedial prefrontal cortex (vmPFC), insula, amygdala, hypothalamus, and periaqueductal gray emerge as central brain structures underlying placebo effects. We argue that the vmPFC is a core element of a network that represents structured relationships among concepts, providing a substrate for expectations and a conception of the situation—the self in context—that is crucial for placebo effects. Such situational representations enable multidimensional predictions, or priors, that are combined with incoming sensory information to construct percepts and shape motivated behavior. They influence experience and physiology via descending pathways to physiological effector systems, including the spinal cord and other peripheral organs.

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INTRODUCTION

Placebos—sham medical treatments—have been used throughout the history of medicine to “gratify” patients (Dorland 1951, p. 1164). Egyptian patients were treated with balms as various as lizard’s blood, crocodile dung, and the teeth of swine (Shapiro 1959). According to Shapiro, industrial-age Europeans administered equally colorful treatments, ranging from animal (earthworms, wood lice) to uniquely human (saliva of a fasting man, powdered mummy). Naturally, it is only with the hindsight of modern medicine that we recognize these treatments as shams; but we are not immune to using sham treatments even today. Notable sports stars regularly use so-called energy bracelets and necklaces to improve their performance. Widely used procedures like arthroscopic knee surgery and spinal steroid injections have been found to perform no better than placebo (Bicket et al. 2013, Moseley et al. 2002). And physicians still prescribe placebos regularly (Linde et al. 2014), presumably for the same reasons as they have throughout history: to provide care and convince the patient, and the world, that things will get better.

The use of sham treatments has done unquestionable harm. Yet, to the degree that a leavening of expectation and emotion can improve patients’ condition, they may also confer substantial benefits. This may partly explain the persistence of these treatments and popularity of those administering them. Because placebos by definition do not contain any active medication, their effects are based on processes that occur inside the patient’s brain—beliefs and expectations, perceptions of the social and physical environment, and generalization from past experiences (Colloca & Benedetti 2005, Enck et al. 2008, Wager & Atlas 2015). Placebo effects therefore constitute a fascinating puzzle for neuroscientists: How does the central nervous system (CNS) convert an inert sugar pill into physiological changes in the brain and body.

A placebo is a sham treatment without any active ingredients. This can be the classic sugar pill or even the implantation of a deep brain stimulator that is turned off. Although the placebo treatment itself is inactive, receiving a placebo treatment can nevertheless cause an effect. Hence, the mechanisms have to invoke the cognitive representation of that particular treatment, including its psychosocial context. Many clinical studies include patients treated with placebo, usually to control for nonspecific effects of active drugs, and patients on placebo often improve dramatically and for substantial periods of time (for reviews, see Enck et al. 2013, Finniss & Benedetti 2005, Vase et al. 2009). Such improvements do not constitute evidence that the placebo itself had any effect, however; for that, the placebo treatment must be compared with a natural history

Placebo: a sham medical or therapeutic treatment that appears similar to an actual treatment and evokes expectations of benefit

Expectation: a consciously accessible prediction, requiring mental representation of a future state or outcome

Placebo effect: the measurable improvement in symptoms that is due to the administration of the placebo, compared to a no-treatment control condition

condition to control for spontaneous recovery and various statistical artifacts. The difference in symptom improvement between the placebo and matched control groups (or conditions, in within-person designs) constitutes an estimate of the causal effect of the placebo (Colloca et al. 2007, Wager & Fields 2013). These effects likely originate in the brain's conception of the treatment context.

In clinical trials, placebo effects are sometimes as large as drug effects, although there is substantial variation among disorders and types of outcome measures (Meissner et al. 2007). Experimental studies designed to investigate placebo effects often reveal yet larger effects (Vase et al. 2009) across a wide variety of conditions, including pain (Amanzio & Benedetti 1999, Levine et al. 1978), Parkinson's disease (Benedetti et al. 2004, de la Fuente-Fernández et al. 2001, Lidstone et al. 2010), nausea (Quinn & Colagiuri 2016), major depression (Rutherford et al. 2016), autonomic activity (Geuter et al. 2013, Nakamura et al. 2012), immune responses (Albring et al. 2014, Goebel et al. 2002), and cognitive performance (Shiv et al. 2005, Stern et al. 2011). The ubiquity of placebo effects suggests that they are important and substantial and that they can indeed be harnessed in clinical practice for patients' benefit (Enck et al. 2013, Finniss et al. 2010).

This review first describes key psychological processes underlying placebo effects, including expectations, learning, and their interactions. We argue that predictions are central to all these processes and that many of these predictions are conceptual and multidimensional in nature. At least in some instances of placebo effects, these predictions are sent to lower levels of the CNS hierarchy and effector systems via descending pathways. We then outline the brain systems involved in placebo and endogenous control of physiological systems, with an emphasis on descending pathways linking prefrontal and limbic brain areas to nociceptive, autonomic, and immune regulatory systems in the brainstem. Finally, we build on information processing-centered views of placebo (Brown et al. 2008, Büchel et al. 2014, Koban et al. 2012, Petrovic et al. 2010) to develop the idea that conceptual representations form multidimensional priors related to the self-in-context—predictions about the meaning of stimuli for personal well-being. At a neural level, these priors are represented in the ventromedial prefrontal cortex (vmPFC) and associated networks and influence sensory and visceromotor pathways via their multiple descending projections to brainstem centers.

PSYCHOLOGICAL THEORIES OF PLACEBO EFFECTS

Placebo effects are shaped by many different sources. The most important processes include patients' expectations, learning history, instructions by caregivers, and social context (Benedetti 2014, Enck et al. 2013, Wager & Atlas 2015). Historically, placebo effects have sometimes been considered as a form of classical conditioning (Voudouris et al. 1990), which can influence pain, hormone release, and other behaviors in humans and animals (Benedetti et al. 2003, Herrnstein 1962). Indeed, a treatment's reinforcement history—particularly its association with increases or reductions in pain or active drug effects—is an important determinant of whether it will elicit a placebo effect. Pairing treatment cues (e.g., an intravenous injection) with a real drug induces associations between the cues and drug effects that can be elicited by the cues alone. This is the basis of many studies of conditioned placebo analgesia and other effects including conditioned motor function (Benedetti et al. 2016) and immunosuppression (Ader & Cohen 1975, Goebel et al. 2002). A variant of this paradigm does not use drugs during the conditioning phase but instead uses a placebo throughout and reduces the stimulus intensity during the conditioning phase (e.g., Price et al. 1999). In line with theories of associative learning, the number of associative pairings increases the magnitude of placebo effects (Colloca et al. 2010, Schafer et al. 2015). In some studies, even subliminally presented cues can elicit placebo effects (Jensen et al. 2012), or placebo

Prediction:

a representation of a likely future state of the organism and its environment

vmPFC:

ventromedial prefrontal cortex

Associative learning:

the detection of regularities in the environment in order to form and improve predictions



effects can be elicited even after participants cease to believe that the treatment is real (Schafer et al. 2015). Placebo effects in these studies and in rodents (Guo et al. 2010, 2011; I.-S. Lee et al. 2015) are likely to arise from precognitive associative processes.

Although classical conditioning is important, pairing cues and outcomes is often not sufficient to induce robust placebo effects, and appropriate instructions must also be present (Montgomery & Kirsch 1997). Several lines of evidence suggest that a conceptual model of the treatment and its consequent expectations are critical for many forms of placebo effects. The first line is based on the close relationship between explicit expectations about pain reductions and subsequent changes in pain perception (Amanzio & Benedetti 1999, Price et al. 1999), including findings that expectations are complete mediators of informational cues on pain perception (Jepma & Wager 2015, Koban & Wager 2016). The second line comes from studies that manipulate expectations using cues and verbal suggestions alone, without any explicit conditioning using drugs or primary reinforcers. In some cases, suggestions about the analgesic effects of placebos can have strong influences on pain, anxiety, and associated autonomic responses (Aslaksen et al. 2015, Jepma & Wager 2015, Schenk et al. 2014). A third line of evidence comes from studies that use suggestions to manipulate cognitive attribution. Participants in these studies experience a placebo treatment associated with low pain and a control treatment associated with high pain. Some groups are told that the experienced pain relief is caused by the placebo, and others are told that the pain relief is caused by the experimenters reducing the painful stimulus intensity. In a subsequent test of pain under placebo versus control treatment, the placebo only reduces pain when patients attribute the pain reductions they experienced during learning to the placebo (Montgomery & Kirsch 1997, Watson et al. 2009). Prior verbal information can also guide associative learning in placebo analgesia and placebo effects on motor performance (Benedetti et al. 2003). Furthermore, in probabilistic reward learning paradigms, incorrect information about the cue-reward contingencies can mislead the learning process so that participants learn the wrong associations (Doll et al. 2009, Staudinger & Büchel 2013). This suggests that the associative learning during conditioning is guided by causal attribution—an inherently cognitive, conceptual process.

All these examples converge on the notion that conceptual processes are important for placebo effects in most instances. As discussed above, the attribution of the symptom relief to the placebo and its plausibility are critical in eliciting placebo effects. Patients will integrate their prior knowledge (e.g., effects from creams are mainly local) with the information extracted from the situation (e.g., left hand is treated with cream) into a conceptual representation of the treatment (e.g., pain should be lower on the left compared to the right hand) (Montgomery & Kirsch 1996). This situational representation allows the formation of expectations, which are accessible as measurements of the underlying, latent representation.

Expectations about treatments are flexible because they are conceptual and model based. They can be induced via many routes, including verbal instructions, social observations, and contextual cues, and they can be updated rapidly when new information is presented. One of the predictions arising from this framework is that expectancy-based placebo effects are stable as long as the meaning and confidence remain stable. For example, when the same physician administers an analgesic via two different routes, placebo analgesia can be comparable in both cases (Kessner et al. 2013). However, the flexible nature of the cognitive processes involved in placebo also confers a vulnerability. The magnitude of a placebo effect for a given person can change dramatically when small changes in cues afford larger changes in their meaning [e.g., changing the brand name (Whalley et al. 2008) or the economic value (Geuter et al. 2013) of placebo creams can change the magnitude of placebo effects from one test to the next within the same participants]. Such concept-based placebo effects share features like flexible outcome predictions with so-called model-based learning in the reinforcement learning literature (Dayan & Berridge 2014).

Of course, not all types of placebo effects are purely conceptual. Some arise from learned precognitive associations in multiple brain systems. One study demonstrated pharmacological conditioning-based placebo effects on growth hormone release and plasma cortisol levels; verbally inducing expectations that countermanded the conditioning procedure had no effects (Benedetti et al. 2003). Similarly, suggestions alone are not sufficient to induce placebo immunosuppression (Albring et al. 2012), though pharmacological conditioning is effective and requires descending input from the brain (Pacheco-López et al. 2005). Learning through classical conditioning mostly depends on learned associations between particular sensory features and outcome valence and is often considered to be model-free in the reinforcement learning literature, in the sense that no explicit mental model of future state contingencies need be developed. Placebo effects based solely on associative learning are thus expected to generalize along a perceptual similarity gradient but are not expected to transfer based on conceptual similarity.

However, even with relatively simple forms of associative learning, what is learned may go beyond a basic encoding of action value. Results from revaluation studies suggest that learned associations in rodents can also retain information about the expected nature of outcomes, not just about whether they are to be approached or avoided. In a seminal study by Robinson & Berridge (2013), rats learned to associate the appearance of a nonfunctional metal lever with an intraorally delivered squirt of aversive salt water. After the injection of drugs that led to a sodium depletion state, the rats immediately approached the lever and started licking it (Robinson & Berridge 2013), suggesting an instantaneous switch in incentive salience that requires a model-based representation (Dayan & Berridge 2014). This suggests that placebo effects based on associative learning could also involve a model or conceptual representation of the treatment context. In this case, hallmarks of so-called model-based learning should be observable with placebo effects, including rapid, context-dependent reversal of responses. In contrast, if purely conditioned placebo effects solely rely on so-called model-free learning, they are expected to reverse slowly following repeated experiences (Dayan & Berridge 2014, Jensen et al. 2012). As we discuss above, both types of learning play important roles in placebo effects (Schafer et al. 2015), but conceptual processes are particularly important (Montgomery & Kirsch 1997, Whalley et al. 2008).

This formulation of placebo effects has parallels to a recent account of reinforcement learning proposing that animals learn associations between cues and latent causes of the stimuli (Gershman et al. 2015). According to their account, a new latent cause is inferred if the posterior probability of a new latent cause is higher than that of the currently assumed cause. The association of outcomes (e.g., analgesia) to latent causes (e.g., presumed action of the alleged drug) resembles the activation of treatment concepts through contextual cues, which in turn generate outcome expectations and enable placebo effects.

Despite their different origins and functional characteristics, expectations and other, precognitive forms of associative learning share a fundamental functional property: They serve the formation of internal predictions (i.e., the brain's tendency to foresee future external and internal states), thereby reducing uncertainty about which actions are most adaptive (Friston 2010, Wolpert et al. 2011).

PLACEBO EFFECTS AND MULTIDIMENSIONAL PRIORS

A central question that must guide theories on placebo effects and their brain organization is the question of why they exist at all. One answer is that the nervous system, from the spinal cord and retina to the cortex, is adapted to make inferences about the behaviors that are optimal given the environment. Part of this adaptation is the use of context information and prior knowledge to constrain perception, which confers potential advantages in both speed and accuracy in noisy



sensory environments. This principle is even used by retinal ganglion cells that do not simply respond to stimulation but rather anticipate the position of a moving stimulus (Berry et al. 1999). Another answer is that modulation of sensory input aids the prioritization of competing goals and actions; it allows animals to focus on currently more important needs and behaviors (Crombez et al. 2012, Fields 2006). For example, it is helpful to suppress pain while running away from a bear.

Contextual knowledge shapes perception in many ways. Participants judge the length of distances as being greater when they are wearing a heavy backpack (Proffitt et al. 2003), a person's height to be greater if that person is male (Biernat et al. 1991), and the color of an object to be more yellow when it is shaped like a banana (Bruner et al. 1951). Motion perception is shaped by verbal suggestions about what participants should see (Schmack et al. 2013, Sterzer et al. 2008). In each case, these effects are apparent even though visual reference information that should have eliminated the bias was clearly visible. If the context information is reliable, such influences can improve perception and judgment, which are inherently noisy. However, a potential negative consequence of low-level modulation of sensory input is the emergence of hallucinations and delusions (Edwards et al. 2012, Schmack et al. 2013). It is therefore important to strike a balance between internal predictions and sensory evidence to ensure optimal functioning in changing environments.

Bayesian models of perceptual decision making provide one way to describe these effects using their computational advantages (**Figure 1b,c**) (Bastos et al. 2012, Friston 2005, Knill & Pouget 2004, Summerfield & de Lange 2014) and have been suggested as a framework for understanding placebo effects (Büchel et al. 2014). These hierarchical Bayesian models explain the types of biases discussed here as a helpful adaptation—in an underconstrained and noisy environment, it is helpful to bias perception toward expected values (priors) based on the precision of the expected value distribution. This will increase the fidelity of perceptual representations if the conceptual representation of the context is correct.

Expected pain, for example, constitutes a prior prediction that is combined with sensory evidence, producing a posterior perception of pain. Application of a credible placebo introduces a prior expectation of lower pain, which shifts uncertain sensory information towards the expected value. As long as the posterior estimate of the perception is compatible with the concept of an effective treatment, the current representation of the treatment remains unchanged. Predictions and placebo effects are thus expected to be stable under normal circumstances in many clinical and experimental settings (Büchel et al. 2014, Edwards et al. 2012). For example, Montgomery & Kirsch (1997) observed that placebo analgesia did not extinguish over the course of their experiment. Similarly, placebo analgesia resists extinction when induced via a partial reinforcement schedule (Au Yeung et al. 2014). One explanation for such findings is that partial reinforcement increases the estimated variance in the treatment efficacy, which makes it more plausible under a wider range of experienced outcomes. The placebo effect will thus extinguish more slowly. By contrast, the internal representation and expected treatment efficacy are expected to change drastically when the stimulation is too intense and the mismatch between prediction and sensory input causes rejection of the current model (Büchel et al. 2014). In practice, pain perception appears to be quite malleable, and there are few empirical demonstrations of this process.

The integrative nature of what it means to conceptualize a treatment context, and the variety of the input channels, suggest that it represents expectations and other appraisals in a multidimensional way—not only how bad an outcome is, but what outcome is expected, and what types of visceral and emotional responses are required (**Figure 1a,d**). These concepts are thus inherently multidimensional, in the sense that they integrate multiple sensory and internal events over time into a conceptual representation of the treatment situation (Hasson et al. 2015, Roy et al. 2012)

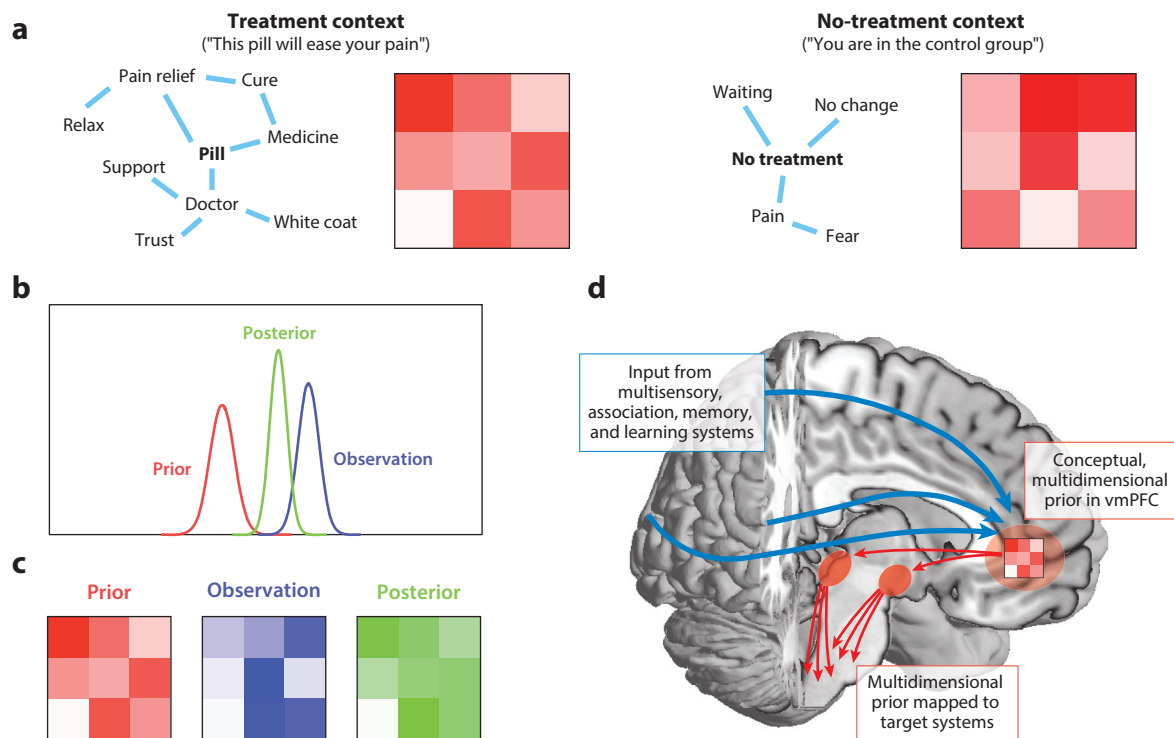


Figure 1

Multidimensional predictions as conceptual priors. (a) (Left) Placebo treatment, along with other medical and therapeutic procedures, activate a set of interconnected conceptual representations relevant for the situation. Example concepts include pain relief, medicine, doctor, and support. This relational map forms a representation of the self-in-context, providing a prior conception of the situation that guides action selection and physiological activity. Currently active representations may be decoded through analyses of spatial activity patterns. (Right) The no-treatment context activates a different set of interconnected representations and results in a different activation pattern. (b) Bayesian integration of predictions and sensory input. Priors (predictions, red) and sensory input (blue) are combined to estimate the posterior belief (percept or experience, green). Priors and observation are weighted by their precision (i.e., the inverse of their variance) during integration. (c) A multidimensional extension of the concept of conceptual priors. Multidimensional priors are rich representations that encode not only the quantitative intensity of expectation along one dimension but also the quality of the situation and potential behavioral and visceral actions, resulting in a high-dimensional conceptual space. Please note that colors in the square matrices indicate only the mean of a distribution and that the variance is not depicted here. (d) We propose that multidimensional priors (relational map of representations) are situated in the vmPFC and associated regions [although priors relevant for different outcome systems (e.g., spatial attention) may be encoded in different systems]. These representations generate predictions, which are projected to the hypothalamus, amygdala, nucleus accumbens, and PAG, influencing more specific representations of sensory experience and, in some cases, physiological effector systems in the lower brainstem and spinal cord. Abbreviations: PAG, periaqueductal gray; vmPFC, ventromedial prefrontal cortex.

and allow multidimensional predictions of bodily states. The placebo identity and related concepts are important for shaping autonomic, neuroendocrine, and affective responses in particular ways (Figure 1d). As we argue below, the vmPFC is particularly well suited to integrate diverse streams of information (Roy et al. 2012, Schoenbaum et al. 2009), form new concepts (Barron et al. 2013), and integrate conceptual knowledge with predictions arising from associative learning circuits (Atlas et al. 2016, Golkar et al. 2016, Milad & Quirk 2012).

dIPFC: dorsolateral prefrontal cortex

PAG: periaqueductal gray

BRAIN CIRCUITS FOR DESCENDING CONTROL

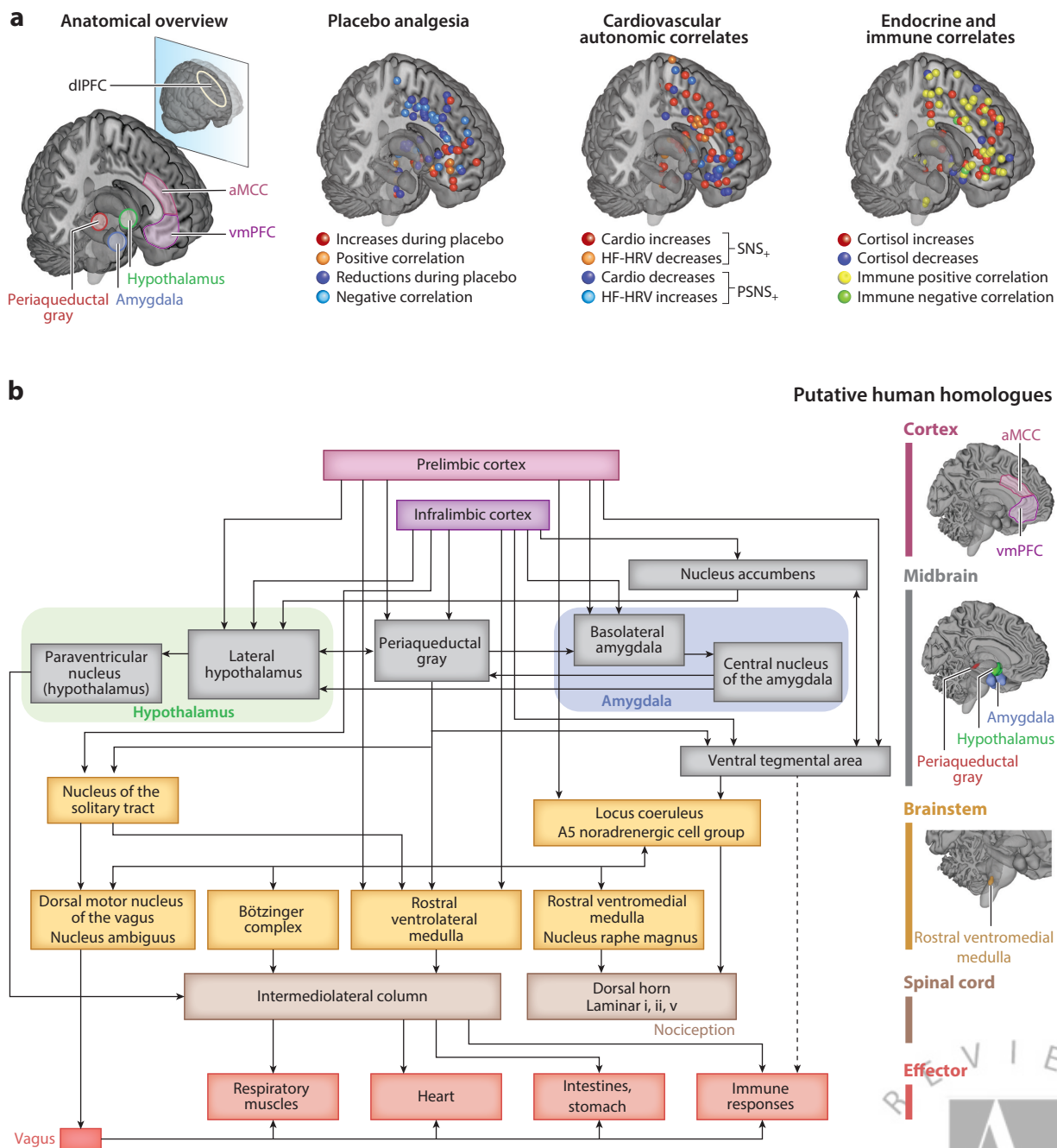
As the two major classes of mechanisms of placebo effects—flexible conceptual processes and pre-cognitive associative learning—have different functional characteristics, it is not surprising that the underlying neurotransmitter systems can be separated under certain circumstances. For example, some forms of placebo analgesia, particularly those supported by verbal suggestions, are blocked by opioid antagonists (Amanzio & Benedetti 1999, Eippert et al. 2009a, Levine et al. 1978). In other cases, particularly analgesia resulting from conditioning with nonopioid drugs, analgesia appears to be opioid independent (Amanzio & Benedetti 1999, Vase et al. 2005) but may be blocked by cannabinoid antagonists (Benedetti et al. 2011). These results suggest that multiple pathways can induce placebo analgesia, depending on the specific learning history and expectations. Researchers have made progress in identifying brain pathways that contribute to placebo analgesia—particularly a cortical-brainstem system involving the dorsolateral prefrontal cortex (dIPFC), vmPFC, lateral orbitofrontal cortex (IOFC), nucleus accumbens (NAC), periaqueductal gray (PAG), and rostral ventral medulla (RVM) (see Wager & Atlas 2015 for a recent review). However, it is not yet clear whether there is a single core system common to placebo effects across different domains.

Our working model is that a system for conceptual appraisal is involved in representing the treatment context and generating predictions across many forms of expectancy-mediated placebo (Ashar et al. 2017). This system is centered on the vmPFC but includes the dIPFC, IOFC, precuneus, and temporoparietal junction, regions associated with cognitive appraisals that generate emotion. This system appears to influence associative learning structures and connects with effector systems that can exert multiple effects on perception, emotion, and physiological responses (**Figure 2a**). Which effector systems are engaged depends on the specific nature of the placebo manipulation, and which ones are relevant depends on the outcome being measured.

Figure 2

Human neuroimaging findings and pathways for placebo influences on physiology. (a) Overview of human brain systems in placebo effects, based on summary coordinates from published neuroimaging studies. (Left) An anatomical overview of important brain regions involved in placebo effects. (Center left) Coordinates from neuroimaging studies of placebo analgesia (adapted from Wager & Atlas 2015 by permission of Nature Publishing Group). Warm and cool colors represent placebo-related increases and decreases, respectively. vmPFC activity increases for placebo analgesia compared to control during the pain stimulation period. Pain processing areas in midcingulate cortex show less activity under placebo. (Center right) Coordinates from studies of brain-cardiovascular correlations (adapted from Gianaros & Wager 2015 by permission of SAGE Group). Warm colors reflect correlations with sympathetic activation, and cool colors reflect correlations with parasympathetic activation. (Right) Coordinates from studies of brain-endocrine (cortisol) and brain-immune correlations. Red and blue regions show positive and negative correlations with cortisol, respectively. Yellow and green markers show positive and negative correlations of peripheral immune measures (e.g., IL-6, IL-1), respectively. Coordinates from the same study within 12 mm were averaged to avoid redundancy. (b) Major descending projections from medial prefrontal cortex to effector systems potentially implementing descending control in placebo effects. Selected descending pathways are based on rodent neuroanatomical studies, as summarized in the BAMS Atlas (Bota et al. 2005) and original papers. The right column shows putative human homologues of key regions from the pathway diagram. Shown are projections originating from IL and PL zones of the medial prefrontal cortex. Putative human homologues of IL and PL are vmPFC and aMCC, respectively. Descending pathways also originate from forebrain structures, including the NAC and amygdala. Important elements of these descending pathways include the hypothalamus, PAG, and RVLm. The latter projects to preganglionic sympathetic neurons in the IML of the spinal cord, and from there to organs. The parasympathetic division innervates most visceral organs via the vagus nerve. The VTA regulates immune responses, probably via sympathetic innervation, but the exact pathway is unknown. Other pathways, including those through the RVM and LC, modulate spinal neurons important for nociception and immune surveillance. Abbreviations: aMCC, anterior midcingulate cortex; dIPFC, dorsolateral prefrontal cortex; HF-HRV, high-frequency heart-rate variability; IL, infralimbic; IML, intermediolateral column; LC, locus coeruleus; NAC, nucleus accumbens; PAG, periaqueductal gray; PL, prelimbic; PSNS, parasympathetic nervous system; RVLm, rostral ventrolateral medulla; RVM, rostral ventromedial medulla; SNS, sympathetic nervous system; vmPFC, ventromedial prefrontal cortex; VTA, ventral tegmental area.

There are two major types of effector systems: (a) direct neuronal control, for example, in placebo analgesia; and (b) indirect control via endocrine glands releasing hormones into the blood stream, for example, in conditioned immunosuppression. In both cases, placebo effects can involve descending modulatory pathways that shape incoming sensory input at lower levels (Eippert et al. 2009b, Geuter & Büchel 2013, Muckli et al. 2015, Schmack et al. 2013, Tracey et al. 2002). Such



descending pathways can extend to cortical regulation of hormone release and other transmitters into the blood. In one exemplary study, suggestions of hyperalgesia increased plasma cortisol and adrenocorticotrophic hormone levels (Benedetti et al. 2006a). In the following section, we outline descending pathways and their potential role in mediating placebo effects.

DESCENDING MODULATION OF PAIN

The afferent nociceptive pathways originating from nociceptive neurons in the dorsal horn of the spinal cord are complemented by a descending modulatory system that can both reduce and enhance nociceptive signaling. Key elements of this descending system originate in the cingulate cortex and vmPFC projecting directly and indirectly to the PAG (**Figure 2b**). The PAG receives further input from subcortical regions including the amygdala, NAC, and hypothalamus—all of which have extensive bidirectional connections with the vmPFC (Büchel et al. 2014, Ossipov et al. 2010, Tracey 2010). The PAG in turn sends projections to the RVM and the locus coeruleus (LC), which synapse onto neurons located in the spinal cord dorsal horn. Two distinct cell populations in the RVM, so-called ON- and OFF-cells, give rise to opposite effects on nociceptive signaling. ON-cell activity facilitates pain behavior in rats, whereas OFF-cell activity inhibits pain behavior (Heinricher et al. 2009). For an in-depth treatment of this system, we refer the reader to several excellent reviews (e.g., Heinricher & Fields 2013, Millan 2002, Ossipov et al. 2010, Willis & Westlund 1997).

Evidence for the involvement of this descending pain modulatory system in placebo analgesia comes from neuroimaging studies that observed increased activity in key regions of the descending modulatory network under placebo compared to control (**Figure 2a**). Brain regions showing placebo-related increases in activation include the cingulate cortex, vmPFC, dlPFC, anterior insula, PAG, RVM, and NAC (Amanzio et al. 2013, Atlas & Wager 2014, Bingel & Tracey 2008, Bingel et al. 2006, Büchel et al. 2014, Eippert et al. 2009a, Geuter et al. 2013, Kong et al. 2006, Wager & Atlas 2015), with the vmPFC and cingulate cortex being the most consistently placebo-related areas (Atlas & Wager 2014). Positron emission tomography studies using a tracer binding specifically to μ -opioid receptors extended these findings by demonstrating that opioidergic neurotransmission in the vmPFC, IOFC, amygdala, NAC, and PAG is increased under placebo (Scott et al. 2008, Wager et al. 2007, Zubieta et al. 2005). Furthermore, several studies showed increased functional coupling between the vmPFC and PAG under placebo (Bingel et al. 2006, Petrovic et al. 2002, Wager et al. 2007), and this functional coupling is sensitive to opioid receptor antagonists and correlates with placebo analgesia (Eippert et al. 2009a). Increased functional coupling of the vmPFC and PAG was also observed for placebo hyperhedonia, an increased pleasantness of touch induced by suggestions of pleasure (Ellingsen et al. 2013). These findings suggest overlap in the neural regulation of pain and pleasure. Furthermore, vmPFC activity is important for placebo effects on anxiety (Petrovic et al. 2005) and reward learning in Parkinson's disease (Schmidt et al. 2014). In addition to its consistent involvement in placebo analgesia and other placebo effects, optogenetic vmPFC activation reduces pain in rats (M. Lee et al. 2015). The vmPFC is also a key region for many conceptual processes, integrating inputs from multiple other high-level regions (Roy et al. 2012) suggesting that the vmPFC is part of a more general system for conceptual regulation (see the sidebar titled New Evidence for vmPFC's Role in Conceptual Processing).

DESCENDING MODULATION OF AUTONOMIC AND CARDIOVASCULAR FUNCTION

The autonomic nervous system (ANS) innervates and regulates activity in peripheral organs, including the skin, heart, lymphatic tissue, and others (Sternberg 2006). The sympathetic and

NEW EVIDENCE FOR VMPFC'S ROLE IN CONCEPTUAL PROCESSING

The vmPFC plays a central role in emotional and nonemotional processes that, together, suggest that this region represents structured relationships between concepts in a dimensional space.

The vmPFC is not only involved in semantic memory retrieval (Binder et al. 2009), which is well described by a network of relations among concepts. The vmPFC also tracks the trajectory of current relevant states (Schuck et al. 2016). It may also play a role in spatial navigation, which requires a representation of dimensional space. Doeller et al. (2010) found fMRI evidence for grid cell–like activity during spatial navigation in the vmPFC. This is significant because grid cells have receptive fields aligned along a hexagonal grid (Hafting et al. 2005), which provides an efficient way to encode distances in space. In another study (Constantinescu et al. 2016), participants learned structured relationships among items embedded in a conceptual space of abstract associations. vmPFC activity tracked movement through this conceptual space as predicted for a grid cell–like dimensional representation.

The vmPFC is also activated consistently during self-referential cognition (Denny et al. 2012), in proportion to the closeness of a word or person to oneself. It is thus uniquely positioned to represent the self in relation to events in the environment.

parasympathetic nervous system (SNS and PSNS) divisions have mainly opposing effects on each organ, with SNS activity alerting the body. For example, SNS inputs to the adrenal medulla cause it to release epinephrine and norepinephrine into the bloodstream, which not only increase heart rate and blood pressure but also influence immune system activity (see below). Although placebo effects on ANS activity have been demonstrated (Meissner 2009, 2011), the exact neural pathways are still unknown. We outline known descending pathways regulating ANS activity and discuss links to brain regions involved in placebo effects.

Sympathetic efferents originate in the intermediolateral column (IML) of the spinal cord, whereas parasympathetic efferents leave the CNS via cranial nerves. The vagus nerve is the most important nerve of the parasympathetic division, carrying both afferent and efferent projections. Interestingly, both divisions of the ANS receive input from the same set of brainstem nuclei, including the rostral ventrolateral medulla (RVLM), A5 region (including the LC), and medullary raphe nuclei (**Figure 2b**) (Saper 2002). These centers mediate the influences of the PAG, amygdala, and paraventricular and lateral hypothalamus on autonomic responses (Critchley & Harrison 2013, Saper 2002). The PAG is particularly important here because it has been consistently linked to placebo effects in neuroimaging studies (Wager & Atlas 2015). Stimulation of the ventrolateral PAG in rats induces a reduction of blood pressure, heart rate, and skeletal muscle tone, whereas stimulation of the lateral portion leads to increased blood pressure (Saper 2002). Electrical stimulation of the ventrolateral PAG in humans also reduces blood pressure and increases heart rate variability (Patel et al. 2011, Pereira et al. 2010).

Cortical regions involved in ANS control include the vmPFC, cingulate gyrus, OFC, and anterior insula (Barrett & Simmons 2015, Critchley 2009, Saper 2002, Seth et al. 2011). A recent study identified a multisynaptic pathway connecting the vmPFC, and several motor and premotor areas, to the adrenal medulla (Dum et al. 2016). The authors were able to identify projections from cortical layer V connecting to the adrenal medulla, via relays most likely located in the hypothalamus, RVLM, and PAG. This study thus provides evidence for a direct link between cortical areas critical for conceptual and emotional processing and a major endocrine gland.

Functional imaging studies correlating measures of autonomic activity—principally heart rate, heart rate variability, and skin conductance—have identified several associated brain regions (**Figure 2a**), including the amygdala, anterior insula, and vmPFC (Beissner et al. 2013, Critchley

& Harrison 2013, Gianaros & Sheu 2009, Thayer et al. 2012). Sympathetic activity seems to be driven most strongly by an axis from the anterior midcingulate cortex to the PAG to lower brainstem centers, whereas parasympathetic activity is associated most strongly with activity in the vmPFC (Gianaros & Wager 2015, Thayer et al. 2012), although all these regions likely play more complex roles in both sympathetic and parasympathetic activity (Beissner et al. 2013, Napadow et al. 2013, Wager et al. 2009).

The importance of expectations for autonomic responses is evident from numerous experimental paradigms in which the mere expectation of an aversive event induces profound changes in autonomic activity. For example, the expectation of having to give a public speech induces a marked increase in sympathetic activity, similar to a nocebo effect (Wager et al. 2009). Furthermore, placebo effects have been reported on a variety of outcomes governed by autonomic activity, including blood pressure, gastric motility, and nausea (Meissner 2011). For example, in a group of patients with stable hypertension, injections of saline lead to a long-lasting reduction in blood pressure (Grenfell et al. 1961). Manipulating expectations about blood pressure has also been shown to affect systolic blood pressure (Amigo et al. 1993). Furthermore, successful induction of placebo analgesia leads to reductions in skin conductance and pupillary responses to painful stimuli (Nakamura et al. 2012).

DESCENDING MODULATION OF IMMUNE RESPONSES

Researchers have discovered close interactions between the CNS and the immune system only during the past few decades. There is still a considerable degree of uncertainty regarding the pathways underlying conditioned placebo effects on immune responses, and multiple, different pathways may be involved (Schedlowski & Pacheco-López 2010, Vits et al. 2011). However, three principal routes of efferent immune control are likely candidates mediating placebo immune responses: neuroendocrine control [e.g., the hypothalamic-pituitary-adrenal (HPA) axis], the sympathetic-medullary-adrenal (SMA) axis, and direct autonomic-to-immune communication. HPA-axis activation results in cortisol release from the adrenal gland, which inhibits proinflammatory cytokines (Sternberg 2006). Corticosteroids can have diverse effects on immune function, with phasic increases in corticosteroids increasing some immune functions and tonic adrenal hyperactivity resulting in reduced immune functioning (Marques-Deak et al. 2005). SMA-axis activation, recently found to originate in both the vmPFC and motor cortices (Dum et al. 2016), can also result in the release of cortisol, epinephrine, and norepinephrine into the bloodstream, as well as cytokines (Sternberg 2006).

The ANS exerts direct influences via the vagus nerve and sympathetic innervation of lymphoid organs (e.g., bone marrow, thymus, and spleen) (Elenkov et al. 2000, Sternberg 2006). Immune cells express several receptors that are sensitive to neurotransmitters, including catecholamines and acetylcholine (Sternberg 2006, Tracey 2009), enabling regulation by the ANS. Norepinephrine released by sympathetic postganglionic terminals binds to β -adrenergic receptors expressed on lymphoid cells, which leads to a suppression of proinflammatory cytokine release (Sternberg 2006). In line with the common opposition of the SNS and PSNS, parasympathetic activation of the vagus nerve induces the release of acetylcholine that inhibits the production of proinflammatory cytokines via nicotinic receptors (Tracey 2009).

Brainstem centers that project onto preganglionic sympathetic neurons located in the IML of the spinal cord include the RVLM and the noradrenergic A5 region (**Figure 2b**). Retrograde tract tracing studies confirmed that the spleen receives indirect input from the RVLM, A5 region, and paraventricular nucleus of the hypothalamus (Cano et al. 2001). Besides the pathway from the vmPFC to the adrenal medulla (Dum et al. 2016), another recent study implicated ventral

tegmental area (VTA) activation in immune responses (Ben-Shaanan et al. 2016). In this study, VTA activation by designer receptors exclusively activated by designer drugs (DREADDs) led to an increase in Type 1 (antipathogen) immune activity, including increased interferon- γ levels and reduced bacterial load in vivo after an *Escherichia coli* challenge. VTA modulation of immune responses in this study was mediated at least partially by sympathetic norepinephrine signaling (Ben-Shaanan et al. 2016). Furthermore, the NAC, which has reciprocal connections with the VTA, has been shown to mediate opiate-related immune reactions (Saurer et al. 2008, 2009). These regions, which have been associated consistently with reward and motivation in the cognitive neuroscience literature, thus also appear to contribute directly to immunomodulation (**Figure 2a**). These pathways provide a potential functional neuroanatomical foundation for placebo effects on immune function.

Several studies have demonstrated placebo effects on the immune system in humans, including in immunosuppression (Albring et al. 2014, Goebel et al. 2002), psoriasis (Ader et al. 2010), asthma (Kemeny et al. 2007, cf. Wechsler et al. 2011), and the modulation of inflammatory cytokine release by emotion induction (Mittwoch-Jaffe et al. 1995). Conditioned immunosuppression using cyclosporine A (CsA) is the best studied model in humans and rats. In this model, the immunosuppressant CsA is paired with a distinctively flavored drink serving as a conditioned stimulus. Reexposure to the conditioned stimulus then leads to reduced IL-2 production in stimulated blood samples, mimicking the effects of CsA (Goebel et al. 2002). This conditioned response extinguishes over time, but the speed of extinction can be slowed substantially by administering subtherapeutic CsA doses during the evocation (Albring et al. 2014).

In line with the idea that sympathetic innervation of the spleen is a critical pathway for conditioned immunosuppression, complete splenic denervation blocked conditioned immunosuppression in rats, as did the blockade of β -adrenergic signaling (Exton et al. 2002). With regard to brain regions involved, the critical role of the amygdala in other forms of associative learning (Bechara et al. 1995) suggests that it may mediate acquisition of conditioned immunosuppression as well. Indeed, amygdala lesions prior to, but not after, conditioning prevented conditioned immunosuppression (Pacheco-López et al. 2005). By contrast, the hypothalamus is critical for the expression of conditioned immunosuppression, whereas the insula is important both for acquisition and expression (Pacheco-López et al. 2005). This key role for the insula in conditioned immunosuppression fits well its other functions, namely storing associative taste memories (Shema et al. 2007) and processing interoceptive information (Critchley & Harrison 2013). In sum, the neuroscience of immunomodulation is an exciting field, and much remains unknown—including whether the regions involved depend on the type of cues (e.g., taste), type of output (e.g., IL-2), or other factors.

COMPARISON OF DESCENDING MODULATORY PATHWAYS

As outlined above, placebos can affect various organs and systems via descending control, in particular through the ANS. Brain regions that are jointly involved in placebo effects on pain, the immune system, and autonomic processes include the PAG, amygdala, hypothalamus, and insula (see **Figure 2b**). The amygdala is a key region supporting associative learning (Büchel et al. 1998, Milad & Quirk 2012). Because most experimental placebo studies so far have used elements of associative learning, the prominence of the amygdala is not surprising. Furthermore, downstream projections from the amygdala to the hypothalamus and PAG provide important connections with the endocrine, autonomic, and nociceptive systems (Milad & Quirk 2012). In fear conditioning studies, the hypothalamus mediates the conditioned arterial pressure response, whereas the PAG is necessary for behavioral freezing responses (LeDoux et al. 1988). These subcortical regions



could thus constitute a core network for placebo effects that is involved in associative learning processes relevant for placebo effects.

Whereas the above brain regions seem to be involved across multiple placebo domains, differentiations are likely to arise in terms of the specific effectors engaged. For example, different columns of the PAG evoke very different responses (e.g., as discussed above on blood pressure). Furthermore, autonomic efferent projections are separable by target organs within multiple brainstem nuclei (Saper 2002).

Despite the different effector system, the processes that initiate placebo effects are probably more general—the generation of internal predictions based on associative learning and conceptual representations of the treatment context. Connections from higher brain regions, including the vmPFC, to these parallel descending systems allow the orchestration of multifaceted responses using neuronal pattern generators (Saper 2002).

Interestingly, all the regions above receive direct input from the vmPFC, which is a consistently activated area in the neuroimaging literature on placebo (Amanzio et al. 2013, Wager & Atlas 2015). Although we have outlined pathways connecting the vmPFC with the immune system, this pathway has not yet been tested in the context of placebo effects. However, several examples suggest that conceptual representations and the vmPFC could play a role in immunological and endocrine placebo effects as well. First, vmPFC activity is affected by immune challenges and correlates with immune measures in humans (Eisenberger & Cole 2012, Gianaros & Wager 2015). Second, cognitive manipulations similar to placebo treatments, can affect immunological and hormonal responses. For example, exposure to commercials for an anti-histaminic drug without any conditioning increased the subsequent efficacy of this drug as measured by skin reactivity to a histamine challenge (Kamenica et al. 2013). Similarly, a cognitive intervention that reduced stress through affirmation of values and beliefs led to a reduction in markers of endothelial cell damage (Spicer et al. 2016). In summary, we have outlined several potential pathways from the vmPFC to sympathetic control of immune function, involving projections from the vmPFC to the NAC, VTA, and hypothalamus, and thence to lower brainstem autonomic centers including the RVLM and IML sympathetic chain in the spinal cord. All these projections are evident in rodent neuroanatomical studies (**Figure 2b**). If the vmPFC is involved in immune regulation, it would provide a brain substrate for the regulation of immune function by conceptual thought.

CONCEPTUAL REPRESENTATIONS IN PREFRONTAL CORTEX

Reduced placebo effects following disruption of prefrontal function by either Alzheimer's disease (Benedetti et al. 2006b) or transcranial magnetic stimulation (Krummenacher et al. 2010) show the dependence of placebo effects on these regions. Functional imaging studies consistently show increases in prefrontal areas following placebo treatment, especially in the dlPFC and vmPFC (Büchel et al. 2014, Tracey 2010, Wager & Atlas 2015). Whereas the dlPFC is important for control and monitoring of skeletomotor action and spatial attention, the vmPFC is particularly important for visceromotor action, homeostatic processes, emotional evaluation, and decision making (Price & Drevets 2010, Roy et al. 2012). Because of its unique ability to integrate conceptual information (Abitbol et al. 2015, Barron et al. 2013, Schuck et al. 2016) and its connection to multiple descending modulatory systems, we argue that the vmPFC is critical for expectation-dependent placebo analgesia (**Figure 1a**).

The vmPFC's diverse connections from the OFC and limbic areas allow the integration of somatic and mnemonic information. For example, emotional meaning (Roy et al. 2012), outcome expectations (Schoenbaum et al. 2009), emotion regulation (Etkin et al. 2011, 2015), value representation (Gläscher et al. 2009, Kable & Glimcher 2007), the formation of new concepts (Barron

et al. 2013), the representation of current states (Schuck et al. 2016), and conceptualizing future states of the self (Andrews-Hanna et al. 2010, Schacter et al. 2007) are all related to vmPFC activity. Furthermore, the vmPFC represents and regulates autonomic and interoceptive states in coordination with the insula (Barrett & Simmons 2015, Critchley & Harrison 2013) and is connected to associative learning systems, including the amygdala and NAC (Price & Drevets 2010).

Thus, several lines of evidence converge on the idea that the vmPFC encodes structured relationships among concepts in a dimensional space (see the sidebar titled New Evidence for vmPFC's Role in Conceptual Processing). The vmPFC is hence well positioned to represent the self in relation to events in the environment, consciously or unconsciously. The closer a stimulus or event is to one's self-concept, the more it matters—and the stronger the vmPFC activity (Krienen et al. 2010, Tamir & Mitchell 2010). This provides a substrate for the vmPFC to help appraise the self-relevance of pain and medical treatment and provide nuanced control over the NAC, PAG, and other subcortical regions. In a musical analogy, the latter have been likened to the keys of an affective keyboard (Berridge & Kringelbach 2015); if so, the vmPFC and its associated network are the pianists, and brainstem nuclei are the piano wires.

CONCLUSIONS

We have outlined several descending pathways involved in placebo analgesia and their convergence on a set of conceptual and associative brain regions, particularly a network centered on the vmPFC that is involved in appraising the significance of symptoms, treatment, and context for the self. Multidimensional predictions generated in this network and in associative learning structures serve as priors that shape incoming sensory information and action tendencies and may be critical for determining which specific physiological and behavioral processes a placebo treatment affects.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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