

Placebo Analgesia: A Predictive Coding Perspective

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This Perspective reviews recent findings in placebo hypoalgesia and provides a conceptual account of how expectations and experience can lead to placebo hypoalgesia. In particular, we put forward the idea that the ascending and the descending pain system resembles a recurrent system that allows for the implementation of predictive coding—meaning that the brain is not passively waiting for nociceptive stimuli to impinge on it but is actively making inferences based on prior experience and expectations. The Bayesian formulation within the predictive coding framework can directly account for differences in the magnitude but also the precision of expectations that are known to influence the strength of placebo hypoalgesia. We discuss how modulatory neurotransmitters such as opioids might be related to the characterization of expectations with an emphasis on the precision of these expectations. Finally, we develop experimental strategies that are suited to test this framework at the behavioral and neuronal level.

Introduction

Placebo effects are a powerful illustration of the strong influence that expectations can have on treatment outcome and have therefore received enormous attention over the last decade, resulting in many comprehensive reviews on placebo effects in general (Benedetti, 2013; Colloca and Benedetti, 2005; Enck et al., 2013; Oken, 2008; Price et al., 2008), placebo hypoalgesia in particular (Carlino et al., 2011; Colloca and Benedetti, 2005; Kong et al., 2007), and the possible neurobiological mechanisms underlying placebo hypoalgesia (Tracey, 2010; Wager and Fields, 2013). Importantly, expectancy effects are not limited to inert (placebo) treatments but can significantly affect the behavioral and neural outcome of real treatments (Bingel et al., 2011; Schenk et al., 2014; but see Atlas et al., 2012). Although most authors speak of placebo analgesia, the term seems technically incorrect as most placebo effects in the domain of pain lead to a decreased pain sensation (i.e., hypoalgesia) and not to the absence of pain (i.e., analgesia). We will thus use the term placebo hypoalgesia throughout this article.

This Perspective reviews the neurobiology of placebo hypoalgesia, as this is the field of placebo mechanisms in which most neurobiological data is available. Placebo effects in the context of pain have been intensively studied using functional neuroimaging (for a recent meta-analysis, see Amanzio et al., 2013). fMRI studies in healthy volunteers have revealed contributions of spinal (Eippert et al., 2009a; Geuter and Büchel, 2013) and supraspinal (Bingel et al., 2006; Eippert et al., 2009b; Ellingsen et al., 2013; Kong et al., 2006; Lu et al., 2010; Lui et al., 2010; Petrovic et al., 2002; Wager et al., 2004; Watson et al., 2009) areas to placebo-induced pain modulation in healthy volunteers. Furthermore, combining these imaging approaches with pharmacological challenges (Eippert et al., 2009b), as well as using molecular imaging techniques based on positron emission tomography (PET) (Peciña et al., 2013; Scott et al., 2007, 2008; Wager et al., 2007; Zubieta et al., 2005), revealed information about the involvement of different neurotransmitter systems.

Information on the temporal aspects of these effects has been gained by studies using electroencephalogram (Colloca et al., 2008; Watson et al., 2007). Taken together, these studies have provided evidence for a very early hypothesis (Levine et al., 1978), namely that placebo hypoalgesia recruits an opioidergic system of descending pain control (Bee and Dickenson, 2009; Ren and Dubner, 2009), the activation of which leads to inhibition of nociceptive processing at the level of the spinal cord and thus reduces neural responses in pain-responsive brain regions as well as the experience of pain.

A Conceptual Framework for Placebo Hypoalgesia

In the following, we will take this idea further and propose that a hierarchical Bayesian framework of brain function based on the idea of predictive coding (Jehee and Ballard, 2009; Rao and Ballard, 1999; Srinivasan et al., 1982) can account for many facets of placebo hypoalgesia. In essence, we suggest that placebo hypoalgesia is the result of combining top-down prior expectations or predictions of pain (relief) with bottom-up sensory signals at multiple levels of the neural hierarchy.

An important aspect of this framework is that not only the mean of the predictions and sensory signals but also their precision (i.e., inverse variance) is important. We will show that recent findings in placebo hypoalgesia are in agreement with such a framework and furthermore suggest a possible neuronal implementation. Although the precise nature and implementation of the model in neurobiological terms must remain speculative at this time, the model as outlined below generates testable hypotheses for future studies on placebo hypoalgesia.

While the proposed framework will be applicable to placebo effects in other domains than pain, we focus on placebo hypoalgesia, because of the extensive literature on effect sizes (Vase et al., 2002, 2009) and neurobiological mechanisms (Colloca and Benedetti, 2005; Tracey, 2010; Wager and Fields, 2013). It is important to note at the outset that we are only considering acute pain in the healthy state and for now leave aside the implications of this framework for chronic pain states.

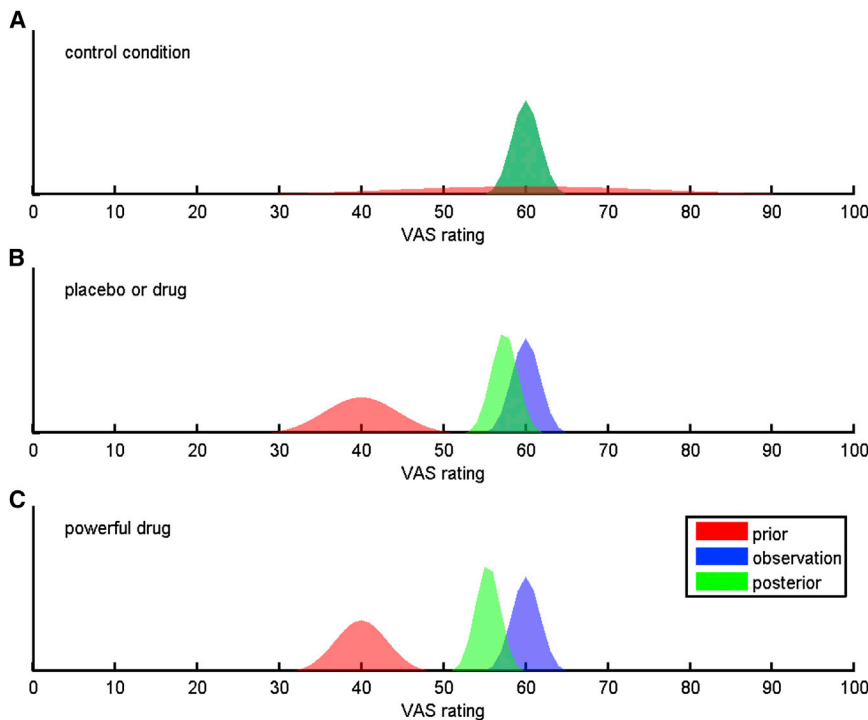


Figure 1. The Effect of Precision of Prior Expectations for Placebo Hypoalgesia

Based on Pollo et al. (2001). The blue distribution characterizes the incoming sensory data (observation/likelihood); the red distribution characterizes the expectation (prior). Integrating this information in a Bayesian fashion leads to the posterior distribution (green) that resembles the effect of the placebo manipulation (for simplicity, we plot estimated perceived pain intensity, whereas in the original study the placebo effect size was estimated by required medication). In the control condition (A), no expectation is generated, and a (flat) prior is centered on the mean of the stimulus. Consequently, the perceived pain (green) is identical to the stimulus (blue, hidden). Telling volunteers that they either perceive drug or placebo creates a more variable prediction (red distribution in B) as compared to an instruction in which volunteers are told that they will definitely get the drug (red distribution in C), which consequently leads to a stronger placebo effect (green distribution shifted further toward less painful VAS ratings). Note that in (B), a second prior (red) centered on VAS 60 could have been modeled to account for the fact that 50% of the patients received no treatment. Note that this figure is only an illustrative example and does not represent the actual placebo effect size from Pollo and colleagues (2001).

The Bayesian Framework

In information processing, it is useful to integrate new incoming information with already existing knowledge or expectations. For example, if a volunteer expects pain on a visual analog scale (VAS) around 40 (Figure 1), Bayes theorem can be used to estimate the level of perceived pain, taking prior knowledge into account (see O'Reilly et al., 2012 for an intuitive introduction). A Bayesian system estimates the posterior probability of the perceived pain, given an observation and a prior (expectation):

$$p(\text{pain}|\text{sensory input}) \propto p(\text{pain})p(\text{sensory input}|\text{pain}) \quad (\text{Equation 1})$$

In other words, the posterior probability $p(\text{pain}|\text{sensory input})$ is proportional to the product of the prior probability $p(\text{pain})$ and the likelihood of $p(\text{sensory input}|\text{pain})$.

Contemporary theories of brain function employ this Bayesian idea and suggest that neuronal assemblies implement perception and learning by constantly matching incoming sensory data with the top-down predictions of an internal or generative model (Clark, 2013; Huang and Rao, 2011; Knill and Pouget, 2004). This is known as predictive coding and the model is called generative because top-down predictions are generated by a hierarchical model whose variables and parameters are optimized on different timescales. In other words, the brain has a model of the world that it continuously tries to optimize using sensory inputs (Friston, 2010). Initially, this model is defined by various genetic and epigenetic factors (Clark, 2013; Friston et al., 1994), which are then continuously refined over the lifespan through associative plasticity and neurodevelopmental learning. This enables more efficient pre-

diction as the brain learns the causal structure and regularities underlying sensations.

A key element of this framework is the mismatch between descending predictions and ascending sensory signals, which can be seen as a prediction error reporting the “surprising” (because it was not predicted) aspect of the sensory information. This part of the signal is forwarded to higher areas to adjust the predictions (for perceptual inference) and parameters (for perceptual learning), which in turn minimizes prediction errors.

Another important aspect of predictive coding is its Bayesian formulation that allows incoming data to be considered in the context of prior knowledge. These prior beliefs are entailed by the descending predictions. Importantly, both prior beliefs and sensory evidence are represented in terms of probability density functions. This is important because it means the brain has to encode the uncertainty about sensory signals (and prior predictions) in terms of their precision. Precision is the confidence or inverse variance of a probability distribution. The problem of how priors are specified de novo is circumvented by the hierarchical nature of the generative model, in which the posterior beliefs at any level of the hierarchy constitute (empirical) prior beliefs for the level below. This is formally identical to the empirical Bayes framework in statistics in which priors are estimated from the data (Efron, 2009). An important aspect of predictive coding—from the current perspective—is that both the content of sensory input and its context have to be predicted. This mandates descending predictions of both the incoming sensory signals and their precision. The balance of sensory evidence, against descending empirical prior beliefs, is controlled by the precision at the respective levels of the hierarchy. In biological implementations of predictive coding, precision is thought to

correspond to the neuromodulatory gain of populations encoding prediction errors.

Predictive coding can be considered as a consequence of the free-energy principle (Friston, 2010). The free-energy principle states that self-organizing systems that are in a homeostatic state must minimize their free energy (i.e., resist the natural tendency to increase their disorder or entropy). In this formulation, minimizing prediction errors lead to better models that allow the system to resist their tendency to disorder by being good predictors of the sensory environment. This theory goes beyond predictive coding, as it explicitly incorporates actions as a mean of minimizing prediction errors.

Although experimental data supporting such a framework have mostly been observed in the visual system (Egner et al., 2010; Hesselmann et al., 2010; Knill and Pouget, 2004; Rao and Ballard, 1999; Sterzer et al., 2008; Summerfield et al., 2006), there is growing support for the role of such a framework in explaining, for example, auditory (Moran et al., 2013; Todorovic et al., 2011) and interoceptive (Seth et al., 2011) responses. Furthermore, predictive coding and active inference has been employed to account for various neuropsychiatric disorders and symptoms such as functional motor and sensory symptoms (FMSSs) (Edwards et al., 2012), delusions (Schmack et al., 2013), hallucinations in psychosis (Adams et al., 2013; Corlett et al., 2009), and disorders of agency (Seth et al., 2011). With respect to FMSS, Edwards and colleagues (2012) suggested that abnormally “precise” expectations can be the basis of pain in these patients, in analogy to the notion that abnormal assignment of salience to nociceptive input (Borsook et al., 2013) might contribute to the formation of chronic pain. Crucially, all of these accounts focus on the optimization of the precision or confidence afforded to prediction errors at sensory and higher hierarchical levels. Last but not least, even processes in the social domain have been framed in terms of predictive coding (Brown and Brüne, 2012; Koster-Hale and Saxe, 2013; see also Krahé et al., 2013 for a perspective on the interplay of social factors and pain). As predictive coding accounts have been successful in explaining neuronal responses at retinal (Srinivasan et al., 1982), thalamic (Jehee and Ballard, 2009), and cortical levels (Rao and Ballard, 1999), one could expect that predictive coding is a general strategy employed by the CNS and thus applicable to pain as well (Seymour and Dolan, 2013).

The nociceptive system originates in the body periphery, from where primary afferent nociceptors transmit signals to the dorsal horn of the spinal cord, where they activate second-order neurons that project to supraspinal structures. These “bottom-up” pathways are numerous (with the spinothalamic tract being the most prominent one), and axons terminate, for example, in brainstem, midbrain, and diencephalic regions such as the rostral ventromedial medulla (RVM), the noradrenergic cell groups, the parabrachial area, the periaqueductal gray (PAG), the amygdala (AMY), the hypothalamus (HT), and the thalamus (THA) (Dostrovsky and Craig, 2013; Lima, 2009). From here, higher-order neurons project to various medial and lateral cortical regions that are thought to mediate different aspects of pain (Tracey and Mantyh, 2007).

This ascending (“bottom-up”) system is complemented by a descending (“top-down”) system that can exert both inhibitory

and facilitatory influences (Bee and Dickenson, 2009; Heinricher and Fields, 2013; Ren and Dubner, 2009; for the sake of brevity we are simplifying anatomical matters here, as there are other routes of descending control, for example, via noradrenergic cell groups). It originates in cortical areas, including the rostral anterior cingulate cortex (rACC) and anterior insula (AI), and projects—via subcortical regions such as the AMY and HT—to the PAG. The PAG in turn sends massive projections to the RVM (Basbaum and Fields, 1984), which modulates signal transmission at the dorsal horn of the spinal cord.

We propose that it is possible to reframe the dichotomy of ascending versus descending systems in terms of a recurrent system as it is required for a predictive coding framework (Friston, 2010; Mumford, 1992). First, in line with the principle of reciprocity of corticocortical connections (Felleman and Van Essen, 1991), the above-mentioned areas are not connected in a unidirectional fashion, as for example the term “descending system” suggests: for example, the rACC to PAG to RVM pathway also contains reciprocal connections (i.e., RVM to PAG to rACC; Beitz, 1982a; Herrero et al., 1991). Second, the involvement of the primary neuromodulators for pain—endogenous opioids—is not only evident in the classic PAG to RVM to spinal cord pathway but in nearly all regions of both the descending and ascending systems (with the notable exception of primary somatosensory cortex; Baumgärtner et al., 2006; Zubieta et al., 2001). Third, cortical regions such as the AI and dorsal ACC that often show placebo-induced decreases in response to pain (Amanzio et al., 2013; Wager and Fields, 2013) are also involved in modulatory functions (Eippert and Buchel, 2013). Finally, even the most central element of descending control—the PAG—is strongly responsive to nociceptive stimulation and involved in ascending relay of nociceptive information, as evidenced by both fMRI (Ritter et al., 2013) and electrophysiological data (Johansen et al., 2010). Taken together, this suggests that a classification of brain areas into “pain responsive” (as part of the ascending system) and “pain modulatory” (as part of the descending system) might be too simplistic and obscures the “reciprocal nature of many interconnecting pathways” (Millan, 2002).

Precision Matters

Many neuroimaging studies have modulated the magnitude of expected pain in nonplacebo contexts (Atlas et al., 2010; Keltner et al., 2006; Koyama et al., 2005; Lorenz et al., 2005; Yoshida et al., 2013) and can show that perceived pain intensity and concomitant neural responses are influenced by cue information. Lorenz and colleagues (2005) used two different pain intensities and cued them by different tones. They observed that the cue influenced pain perception such that high-intensity stimuli were perceived as less painful and low-intensity stimuli as more painful following invalid compared to valid cues. However, an expectation is not only characterized by its magnitude but also by its precision or certainty. This was studied by Brown and colleagues (2008), who employed different pain intensities with either certain or uncertain expectations. In agreement with Bayesian integration, they observed that high-intensity painful stimuli were perceived as more painful with a “certain” expectation, whereas low-intensity painful stimuli were perceived as less painful in the context of the “certain” expectation. A recent study

investigating the role of judgments from other volunteers on perceived pain intensities (Yoshida et al., 2013) also reported that a Bayesian model outperformed a mean model; however, in contrast to Brown and colleagues (2008), they observed that uncertainty increased perceived pain for the high-intensity pain stimulus, which might be related to the vicariously observed mean and uncertainty of the pain stimulus.

Apart from cue-based pain studies, Bayesian integration can also be observed in placebo hypoalgesia. Pollo and colleagues (2001) demonstrated that different levels of precision of verbal instructions about the analgesic effect of a treatment can produce different placebo effect sizes (Figure 1). The more precise instruction telling patients that the infusion contains a potent painkiller led to a more pronounced placebo effect as the less precise instruction in which volunteers were told that the infusion was either a powerful painkiller or a placebo.

A similar effect of variability of the instructions was observed in irritable bowel syndrome (IBS) patients who were exposed to clinically relevant abdominal pain by means of rectal balloon distension under different expectation conditions. In one study, patients were told, “this *may be* an active agent or an inactive placebo agent” (Verne et al., 2003). In another one they were told that “the agent you have just received *is known to* significantly reduce pain in some patients” (Vase et al., 2003). As the second suggestion created a more precise expectation, the observed placebo analgesic effect was larger in this study. These examples illustrate that the effect size of placebo responses can be maximized by the magnitude and the precision of the prior expectation.

The Site of Modulation

Pain is a psychologically constructed experience that includes extensive processing at the cortical level (Apkarian et al., 2005; Tracey and Mantyh, 2007). A mechanism subserving placebo hypoalgesia could therefore theoretically be implemented at the cortical or subcortical level. In agreement with this idea, initial studies on placebo hypoalgesia firmly established the involvement of the rACC and prefrontal cortex (PFC) with projections to the PAG in placebo hypoalgesia (Bingel et al., 2006; Petrovic et al., 2002; Wager et al., 2004). These early studies supported the view that “a major portion of the placebo effect may be mediated centrally by changes in specific pain regions” (Wager et al., 2004). However, several years later, a series of placebo hypoalgesia experiments demonstrated effects in relation to placebo hypoalgesia in the medulla (Eippert et al., 2009b; note that Petrovic and colleagues, 2002 already observed placebo-related signal changes in an area close to the RVM) and even at the spinal cord level (Eippert et al., 2009a; Matre et al., 2006). These observations speak against a model in which placebo hypoalgesia is an exclusively supraspinal phenomenon, but rather suggest that placebo hypoalgesia is implemented through a hierarchical recurrent system including cortical (rACC and AI), subcortical (AMY, HT, and THA), midbrain (PAG), medulla (RVM), and spinal sites. This is reminiscent of the visual system, in which a recurrent hierarchical system including the retina, the lateral geniculate nucleus, primary visual cortex, and higher-order visual areas are likely to implement a predictive coding framework for visual perception (Jehee and Ballard, 2009; Rao and Ballard, 1999; Srinivasan et al., 1982).

The Generation of Expectations: Learning and Experience

The placebo effect is based on expectation and experience, where the latter is a form of learning and often implemented by conditioning in experimental placebo studies. After a debate about the importance of each factor (Stewart-Williams and Podd, 2004), there seems to be agreement that both can be important contributors to the placebo effect.

The proposed framework suggests that expectations (i.e., predictions) are the consequence of experience (i.e., parameters of the internal model). This is best exemplified in the context of conditioning in placebo hypoalgesia (Colloca and Benedetti, 2006; Stewart-Williams and Podd, 2004). Through the pairing of an analgesic treatment (e.g., analgesic drug or simply reduction of the afferent painful stimulus) with a sensory cue (e.g., the visual and tactile information that a “treated” skin patch is stimulated), an expectation of hypoalgesia is formed (Meissner et al., 2011) and consequently the parameters of the internal model are updated to account for this effect.

In a series of studies, the role of conditioning (Colloca and Benedetti, 2006; Colloca et al., 2010) has been investigated. During the conditioning phase of the first study, Colloca and Benedetti (2006) observed pain ratings for the cued treatment at a level of about 1 (due to a reduction of stimulus intensity), whereas the cued pain trials scored 6 on their scale (i.e., a “treatment”-related difference of 5 between both cues). In the following test block with equal stimulus intensities, they observed a significant placebo hypoalgesic effect indicated by a difference between both cues of 3.5. In the presented framework, the perceived level of pain during the test phase (around 3.5) represents the combination of prior expectation (about 1) and the incoming sensory information (around 6). What is observed is the posterior, i.e., the statistically optimal combination of the prior information and the incoming sensory data. Although the authors observed no within block extinction, after 4–7 days the placebo hypoalgesic effect was reduced (i.e., a difference of 2 between both cues), which according to our model resembles either the loss of precision or a decrease in magnitude of the prior information, both of which result in a percept that is closer to the incoming data. This might be related to the observation of Harrison and colleagues (2006) showing uncertainty encoding in the hippocampus, a memory-related structure involved in placebo hypoalgesia (Peciña et al., 2013).

In a later study, Colloca and colleagues (2010) were able to show that four conditioning trials lead to stronger placebo effect as compared to a single conditioning trial. In addition, volunteers who received a single conditioning trial showed more rapid extinction compared to the group receiving four conditioning trials. Importantly, the reduction of stimulus intensity during the conditioning phase was identical in both groups. Therefore, the only difference between groups was the amount of precision that volunteers assign to the conditioning phase. Thus, in agreement with our model, the group receiving four conditioning trials forms a more precise prior expectation and thus shows the stronger placebo hypoalgesic effect.

Finally, the role of experience for placebo effects has also been established in a more clinically oriented context (Kessner et al., 2013a). In this study, the effect of previous treatment

success or failure on current treatment was investigated. In agreement with the view that positive experience with previous treatment generates predictions on treatment success in the current setting, the authors observed a strong positive effect of prior experience, i.e., previous successful treatment predicted current treatment success. This observation illustrates that the important concept of a hierarchical model in which data are used to generate priors is also present in the time domain, or in simpler words, a past posterior can be used as a current prior.

The Limits of Placebo Hypoalgesia and Individual Differences

In agreement with the predictive coding framework [Crombez and Wiech \(2011\)](#) argued that expectations can bias perception but sensory evidence can also update expectations. According to our model, the placebo hypoalgesic effect is caused by matching a predictive model with incoming data by explaining away the discrepancy (i.e., prediction error). It is now interesting to speculate what would happen if the incoming sensory data is “too far away” from the current model. This would be the case when during conditioning an expectation of placebo hypoalgesia was generated with a very low-intensity stimulus and subsequently during the test phase a very high-intensity stimulus was used. In these cases, volunteers might question the efficacy of the treatment and as a consequence generate a disbelief in the placebo treatment. In our suggested model, this phenomenon resembles a dramatic revisiting of the model to explain the incoming data, i.e., the initial model of “a real treatment reducing pain” might be replaced by a model that entails a deception and that no treatment has been applied. This model would thus dramatically reduce the prediction error. This can be seen in analogy to shifts in explanatory models that are thought to underlie the perceptual dynamics in binocular rivalry ([Clark, 2013; Hohwy et al., 2008](#)) or viewing of ambiguous figures such as the face-vase illusion ([Kleinschmidt et al., 1998](#)), in which competing percepts can partially satisfy two different models (one for each stimulus). However, as the system has not been exposed to this rather artificial situation, each model leaves a considerable prediction error, resulting in switches between percepts.

A breakdown of placebo hypoalgesia can also be anticipated from a different perspective in the predictive coding scheme: simulations in the visual system have shown that elimination of prediction signals from higher areas leads to a breakdown of the “explaining-away” component of prediction errors in lower areas ([Rao and Ballard, 1999](#)). It is thus tempting to explain recent finding in placebo hypoalgesia in this light: a diminished function of the PFC (as found under repetitive transcranial magnetic stimulation ([Krummenacher et al., 2010](#)) or in Alzheimer’s disease ([Benedetti et al., 2006a](#)) has been shown to lead to a loss of placebo hypoalgesic effects. Along these lines, the structural integrity of white matter pathways from PFC to lower areas has been shown to be related to placebo hypoalgesia ([Stein et al., 2012](#)). Together, these data suggest that a failure of downward message passing of predictions from a higher area will lead to exacerbated prediction errors and thus a higher influence of sensory signals, i.e., a higher level of pain.

In some studies, the authors have demonstrated placebo effects when telling participants explicitly that they will receive

a placebo ([Kaptchuk et al., 2010](#)). The authors told volunteers explicitly about the effectiveness of placebo and thus created a treatment expectation. However, as this study took place in a clinical environment, it is highly likely that volunteers also created an expectation based on experience with this environment, which would interact with the placebo treatment. Most people associate hospitals with effective medical treatment and symptom reduction and thus a covert expectation of pain relief might have been generated. In agreement with the suggestion that unconscious expectations can drive placebo hypoalgesia, a recent study from this group showed that nonconscious cues are indeed sufficient to trigger pain modulation ([Jensen et al., 2012](#)). A similar, implicit expectation is seen in studies investigating classical conditioning in which volunteers generate predictions and prediction errors but are not aware of the expectation (i.e., pairing of sensory stimulus with shock) ([Morris et al., 2001](#)).

Placebo effects in general vary across and within individuals ([Atlas and Wager, 2012](#)). Early studies ([Levine et al., 1978](#)) report that around one-third of all volunteers showed a placebo hypoalgesia effect. This rate is similar in recent studies ([Benedetti, 1996; Bingel et al., 2006; Price et al., 2008](#)). Interestingly, it has been observed that although volunteers differ in their individual placebo effects for different contexts ([Liberman, 1964](#)), they show stable responses when repeatedly tested in these contexts ([Atlas and Wager, 2012; Whalley et al., 2008](#)). This is easily integrated in the predictive coding model: volunteers will have formed a specific model for different contexts. If repeated treatments provided by Doctor X were beneficial, the generated model will predict a successful treatment by Doctor X in the future. However, this does not necessarily involve the same model in other patients in which the experience with Doctor X was either less positive or variable ([Kessner et al., 2013a](#)). However, it is important to note that the model is not necessarily stable, as over time the organism will receive additional information either directly linked to this context (e.g., newspaper report that Doctor X is involved in a malpractice suit) or indirectly (e.g., newspaper reports on bad performance by doctors in general). It is therefore not surprising that the test-retest correlation for placebo is not higher than $R^2 = 0.55$ ([Morton et al., 2009](#)).

The Role of the PAG-RVM-Spinal Pathway and Opioids

The common assumption about the role of opioids is that placebo hypoalgesia is paralleled by a release of endogenous opioids and that these are responsible for the perceived pain reduction by acting as endogenous analgesics. This hypothesis is supported by data showing that opioid antagonists can at least partially block placebo hypoalgesia ([Benedetti et al., 1999; Eippert et al., 2009b](#)).

However, another mechanism is suggested by studies investigating conditioned analgesia ([Bolles and Fanselow, 1982; Fanselow, 1986](#)). In classical conditioning, the conditioned stimulus (CS, usually a neutral sensory cue) that is repeatedly paired with an unconditioned stimulus (US, usually a painful shock) comes to predict the shock and also elicits the release of endogenous opioids. Initially, it was thought that the release of endogenous opioids decreases the discrepancy (i.e., prediction error) between the expectation generated by the CS and the painful US by reducing the impact of the pain of the US through

analgesia (Fanselow, 1986). Consistent with the notion that prediction errors drive learning in a delta rule learning model (Rescorla and Wagner, 1972), the application of the opiate antagonist naloxone can block this effect and facilitate learning (Eippert et al., 2008; McNally et al., 2004a, 2011). However, for this mechanism to be universally correct, naloxone should have no effect on procedures in which there is no US present and thus its impact cannot be modulated (neither by endogenous opioids nor by naloxone). Yet this is not the case, as experimental data clearly show that endogenous opioids interfere with second-order fear conditioning (Cicala et al., 1990) and that naloxone reduces extinction (McNally et al., 2004b), i.e., showing exactly the opposite effect as in conditioning. To reconcile these data with a delta rule learning model (Rescorla and Wagner, 1972), a viable alternative explanation is that opioidergic neurotransmission is involved in modulating the prediction (i.e., the CS) rather than affecting the outcome alone (i.e., the US) (McNally et al., 2004b).

In agreement with these observations from classical conditioning, we propose that in addition to a direct analgesic effect (as for example exerted on synaptic terminals of nociceptive afferents in the dorsal horn), opioids play an additional role in signaling top-down predictions in a generative model, namely representing the precision of the top-down prediction (or the precision-weighted prediction errors) in the PAG-RVM-spinal cord system. This is also in agreement with an earlier notion that the role of opioids is to “gate” sensory information (Bolles and Fanselow, 1982; Lewis et al., 1981).

The final segments of the descending pain modulatory system comprise the PAG, RVM, and the spinal cord dorsal horn. The RVM (as well as the PAG) is characterized by distinctive cells (Fields et al., 1983; Heinricher et al., 1987) that show a pause of firing (Off cells) or a burst of firing (On cells) just before a nociceptive withdrawal reflex occurs in the anesthetized animal (Fields, 2004; but see Mason, 2012). Other cells show a neutral behavior, but it has been shown that this allocation is dynamic as neutral cells can become On cells in certain circumstances (Bee and Dickenson, 2009). Both On and Off cells can be modulated by opioids, but it is the activation of Off cells that is critical for opioid-mediated analgesia (Heinricher et al., 1994). In case of Off cells, a presynaptic opioidergic inhibition of GABAergic projections explains the activation of Off cells by opioids. In contrast, On cells are directly inhibited by morphine through a postsynaptic opioidergic effect. Consequently, opioid agonists activate Off cells (and silence On cells) and this effect leads to analgesia as indicated by reduced withdrawal responses. Importantly, the effect of morphine on Off cells can be blocked by an NMDA antagonist (Heinricher et al., 2001). The projections from the RVM to the dorsal horn are mainly GABAergic, glycinergic, and serotonergic (Aicher et al., 2012; Kato et al., 2006; Ossipov et al., 2010), but a clear assignment of these neurotransmitters to the On or Off system is lacking and possibly nonexistent (Gao and Mason, 2000; Morgan et al., 2008; Pedersen et al., 2011). Similarly, the effects on spinal processing do not follow an all-or-none regime but are very specific in terms of inhibition of noxious versus innocuous responses, deep versus superficial laminae, and type of afferent fiber (for review, see Heinricher et al., 2009). It is also interesting to note that cholecystokinin

(CCK), which is often portrayed as an antioioid and whose actions underlie nocebo hyperalgesia (Benedetti et al., 2006b), acts in this RVM-spinal circuit, also in combination with serotonin (Dogrul et al., 2009; Marshall et al., 2012). Most placebo hypoalgesia studies have investigated brain activity changes with respect to pain modulation shortly before (i.e., anticipation) or during the application of the painful stimuli. This seems to be at odds with the initial observations of tonic activations of the On-Off cell system. However, recent studies in awake animals (Mason, 2012) have revised this picture and indicate a more phasic response profile of this system, which might explain why fMRI studies investigating evoked responses are able to observe activations related to pain modulation.

Bayesian models including predictive coding and the free-energy principle not only rely on a representation of the magnitude of the prediction but also on its precision or variance. It has been suggested that feedback signaling in the hierarchy through NMDA is responsible for the specification of the priors (or predictions) (Corlett et al., 2009; Friston, 2010) and that the precision of these predictions is implemented through modulatory neurotransmitters (Corlett et al., 2009; Edwards et al., 2012; Friston, 2010). Extending these ideas to placebo hypoalgesia, we suggest that the NMDA part of the Off cell system could represent the prior or prediction signal and that the opioidergic component of this system represents the precision of this prediction. Currently, this notion is obviously speculative, but future studies investigating opioidergic effects (either using PET or pharmacological challenges) in combination with an independent manipulation of the magnitude and the precision of the top-down prediction (i.e., experimental manipulation of placebo hypoalgesia) could test this hypothesis.

A possible mechanism by which placebo hypoalgesia could be implemented was already introduced 50 years ago in Melzack and Wall's gate control theory (1965). As this mechanism posited a crucial modulatory stage at the spinal cord, its involvement in placebo hypoalgesia was questioned for a long time, as no spinal involvement in placebo hypoalgesia had been observed until a few years ago (Eippert et al., 2009a; Matre et al., 2006). While it is important to note that originally this model was intended to explain local control through large- and small-diameter fibers at the spinal cord (Melzack and Wall, 1965), the authors also postulated a “central control trigger” i.e., a fast afferent system, which would precede the ordinary signal processing route and could thus “set the receptivity of cortical neurons for subsequent afferent volleys” and “by way of central-control efferent fibers, also act on the gate control system” (Melzack and Wall, 1965). Through this putative mechanism “it is possible for central nervous system activities subserving attention, emotion, and memories of *prior experience* to exert control over the sensory input.” Although this model has shown great explanatory power, it seems important to add a few details that make this theory compatible with a full hierarchical predictive coding model. The main point of a predictive coding model is the hierarchical organization in which prior information can be estimated from the data at each level. Taking the original authors' suggestion that interactions take place at many levels (Melzack and Wall, 1965), we propose that instead of a single modulatory effect at the spinal cord, the intimate connections of the top-down and

bottom-up pain system form a hierarchical recurrent model in which the modulation related to placebo hypoalgesia is implemented not at a single stage but throughout the system. Consequently, our framework suggests a single system rather than separate top-down and bottom-up systems. This is in agreement with functional neuroimaging studies that have observed pain modulatory signal changes at all levels of this system (Amanzio et al., 2013; Wager et al., 2013), such as the spinal cord (Eippert et al., 2009a), the PAG-RVM system (Bingel et al., 2006; Eippert et al., 2009b; Petrovic et al., 2002; Tracey et al., 2002; Wager et al., 2004; Yelle et al., 2009), the nucleus cuneiformis (Keltner et al., 2006), the AMY (Bingel et al., 2006), the rACC (Bantick et al., 2002; Bingel et al., 2006; Eippert et al., 2009b; Geuter et al., 2013), THA (Lorenz et al., 2003; Valet et al., 2004), and the PFC (Eippert et al., 2009b; Wager et al., 2004).

The Mesolimbic System: Linking Value to Placebo Hypoalgesia

Apart from the opioidergic system, several studies have linked the dopaminergic (DA) system to placebo hypoalgesia using MRI (Schweinhardt et al., 2009) or PET (Scott et al., 2007, 2008). DA is the main modulatory neurotransmitter in the mesolimbic system including the substantia nigra, the ventral tegmental area (VTA), the ventral striatum (VS), and frontal areas such as the ventromedial prefrontal cortex (vmPFC). In the context of a predictive coding framework, it has been proposed that DA can signal the precision of predictions (Adams et al., 2013; Edwards et al., 2012; Friston, 2010) in a similar manner as we suggested for opioids in the PAG-RVM-spinal cord system. Such a role of DA could also be involved in placebo hypoalgesia, as a study showed that individual expectations of analgesia prior to placebo administration were correlated with placebo-related DA activation in the VS (Scott et al., 2007). It is conceivable that these expectation ratings also indicated the volunteers' confidence in the treatment, which can be seen in analogy to the precision of the prediction (Brown et al., 2008).

In a study investigating opioidergic and dopaminergic effects of placebo hypoalgesia (Scott et al., 2008), opioidergic and dopaminergic effects were demonstrated in many subcortical and cortical areas. In particular, in the VS both DA and opioidergic effects were observed. Based on this observation, the authors suggest that VS dopaminergic responses represent a "trigger" that can then entail downstream adaptive responses. These responses are most likely opioidergic, but dopaminergic modulation of the dorsal horn has also been observed (Tamae et al., 2005). Our model would offer a similar, yet simpler, explanation: both opioids and DA as modulatory neurotransmitters are ideally suited to signal the precision of predictions (Corlett et al., 2009; Edwards et al., 2012; Friston, 2010). It is thus likely that in some areas (e.g., the VS) they both signal the precision of predictions, whereas in other areas (RVM-PAG system) opioids more exclusively take this role, possibly together with other neurotransmitters such as cannabinoids (Benedetti et al., 2011). This is also in accord with recent experimental data that suggest that at different levels of the hierarchy separate neuromodulatory systems are related to precision-weighted prediction errors (Iglesias et al., 2013). Importantly, PET studies (Scott et al., 2008; Wager et al., 2007; Zubieta

et al., 2005) suggest that opioids not only play a role in signaling the precision of predictions in areas lower in the hierarchy as compared to the VS but also in areas higher in the hierarchy such as the rACC and the AI.

In the context of dopaminergic effects on placebo hypoalgesia, it has been discussed that projections between the vmPFC and the VS play an important role in updating the effectiveness of the treatment over time (Wager and Fields, 2013), which the authors relate to subjective value of the treatment. Value in general can be seen as an attribute for states and maximizing value (or being in a valuable state) is the goal of the optimization scheme underlying the free-energy principle (Friston, 2010), an extension of the predictive coding framework. Minimizing free energy in this framework is to ensure that organisms spend most of their time in valuable states such as being satiated and pain-free to maintain their homeostasis. This is conceptually linked to reinforcement learning (Friston, 2010) and temporal difference models and DA signaling (Schultz et al., 1997). In essence, the idea is that neuronal value systems enable the brain to label a sensory state as valuable, if it leads to another valuable state. This ensures that agents move through a succession of states (e.g., specific path in a maze) that have acquired value to access states with an innate value (e.g., food). This notion can be related to the desire-belief model of placebo hypoalgesia, where it is argued that the overall desire of volunteers is to avoid painful experience as much as possible (Price et al., 2008). It should be noted that avoiding a painful experience "as much as possible" is a relative rather than absolute concept of value, as for example illustrated in a recent study showing that if a painful stimulus is less painful than the maximally possible painful stimulus, it can even be perceived as pleasant (Leknes et al., 2013).

Furthermore, value can be an attribute of the treatment in placebo hypoalgesia (Wager and Fields, 2013), rendering the placebo effect more or less effective. This is best illustrated through a behavioral study in which two different inert treatments were tested (Waber et al., 2008). One treatment was described as having a high monetary value (i.e., "regular price"); the other one was described as "low price." This study convincingly showed that the magnitude of placebo hypoalgesia was increased for the "regular price" treatment. This behavioral finding was followed up in an fMRI study (Geuter et al., 2013). Here again one treatment was declared as low in value and another one was described as high in value. Similar to a previous study (Price et al., 1999), a congruent experience to these verbal instructions was introduced in a conditioning phase, allowing volunteers to experience the superior effect of the high-value treatment. To directly assess the perceived individual value of both treatments, volunteers participated in a typical auction setup as used in behavioral economics to identify their willingness-to-pay (WTP). Both experimental treatment creams (i.e., placebos) were presented alongside other useful medical products such as Band-Aids, sunscreen, or insect repellent. Importantly, it was observed that the estimated WTP predicted the perceived pain reduction on an individual level. In addition, a choice task analogous to the one used by Chib and colleagues (2009) was performed to obtain a neuronal value signal (Figure 2A). On a neuronal level, the rACC, during the placebo

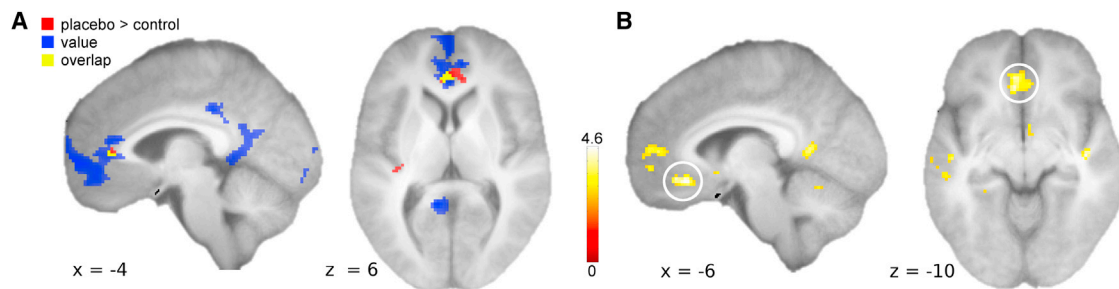


Figure 2. Placebo-Induced BOLD Responses and Value Signal

Based on data reported in Geuter and colleagues (2013).

(A) Overlay of the placebo > control contrast (red; rACC $p < 0.005$; all p values small-volume corrected as reported in Geuter and colleagues (2013) and the WTP correlate (blue; vmPFC $p < 0.011$; rACC $p < 0.003$; VS $p < 0.003$). WTP and placebo activation overlapped in the rACC (yellow; rACC $p < 0.046$).

(B) Correlation of placebo-induced activation (placebo > control) with the individual neural value estimates from vmPFC. Here, activity in the rACC correlated with the value signal ($p < 0.01$). Statistical t -maps are overlaid on an average structural image at $p < 0.005$ (uncorrected).

manipulation, showed a graded response, which was larger for the expensive placebo treatment. In addition, the value-related activation level of the vmPFC (ROI based on Chib et al., 2009) during the valuation task was extracted. It was then tested whether this neuronal value signal (from the valuation scan) predicted the placebo-related signals in the frontal cortex during the placebo scan. Importantly, the placebo and the valuation scans were performed in separate sessions. The data show that indeed a neuronal value signal in the vmPFC was predictive of the placebo-related activation in the rACC (Figure 2B) or, in other words, a neural signature of value-predicted activation related to placebo hypoalgesia.

In some studies, naloxone had no effect on placebo hypoalgesia (Benedetti et al., 2011; Vase et al., 2005), suggesting that other neurotransmitter systems also play a role. Even in studies that report effects of high doses of naloxone, the opioid antagonist was only able to attenuate placebo hypoalgesia (Eippert et al., 2009b), but not to completely block it. These observations can be accounted for by our model. Given the hypothesis that modulatory neurotransmitters signal the precision of the top-down predictions in the proposed Bayesian framework, blocking those neurotransmitters would not erase the prediction but would attenuate its precision and thus lead to a decrease in placebo hypoalgesia. However, as described above for the VS in which both opioids and DA might play a role in signaling the precision of a prediction, the precision signals in other areas might be mediated by other modulatory neurotransmitters such as oxytocin (Kessner et al., 2013b), cannabinoids (Benedetti et al., 2011), etc. This implementation would equip the system with additional flexibility and redundancy and could also account for the observed interindividual differences in placebo responses and blocking them with various drugs. A study employing the monetary incentive delay task (Knutson et al., 2000) showed that individual responsiveness in the dopaminergic system during this task was predictive of the placebo hypoalgesic effect (Scott et al., 2007). It is tempting to speculate that volunteers showing a large contribution of dopaminergic effects to placebo hypoalgesia would demonstrate a high vulnerability to a DA antagonist (e.g., haloperidol), whereas others could be more naloxone sensitive. Further studies are required to test the hypothesis that different individuals employ different

modulatory neurotransmitter systems in placebo hypoalgesia. Such a finding could potentially explain the large interindividual differences that have been observed in this domain (Enck et al., 2013).

Reporting Bias

Placebo effects (Hróbjartsson and Gøtzsche, 2004) and placebo hypoalgesia in particular (Clark, 1969) have been criticized to simply reflect a reporting bias. Based on a study in which the effects of placebo hypoalgesia were estimated using signal detection theory, the authors argued that this analysis indicated that the reduced number of pain responses in the placebo condition reflected an increase in the amount of noxious stimulation volunteers were willing to endure before calling it pain, rather than a decrease in their thermal sensitivities (Clark, 1969). Many years later it has been argued that providing direct central nervous (Benedetti, 2013; Eippert et al., 2009b; Wager et al., 2004) or autonomic (Eippert et al., 2009b; Nakamura et al., 2012) measures in placebo studies can favor a sensory discrimination effect and make an exclusive reporting bias unlikely. The proposed hierarchical predictive coding framework takes a more neutral position and would argue that the decision and the sensory discrimination component are not separable in a meaningful sense, or in other words, there is no clear point in a hierarchical system where sensory processing ends and the decision process begins; both the sensory perception and the decision component are implemented throughout the hierarchy. In other words, signal changes in both the spinal cord and the rACC are probably responsible for what Clark (1969) describes as "... an increase in the amount of noxious stimulation S_s [subjects] were willing to endure before calling it pain."

A Putative System

Converging anatomical data from rats, cats, and monkeys suggests a strong degree of reciprocity in the connective architecture of the "descending system," as evidenced between spinal cord and RVM (Basbaum and Fields, 1979; Basbaum et al., 1978; Carlton et al., 1985; Craig, 1995; Sugiyama et al., 2005), RVM and PAG (Abols and Basbaum, 1981; Basbaum et al., 1976; Beitz, 1982a, 1982b; Mantyh, 1982, 1983a), PAG and AMY (Aggleton et al., 1980; Beitz, 1982b; Hopkins and Holstege, 1978; Mantyh, 1983b; Rizvi et al., 1991; Volz et al., 1990), PAG and HT (Aimone et al., 1988; Cameron et al., 1995; Mantyh,

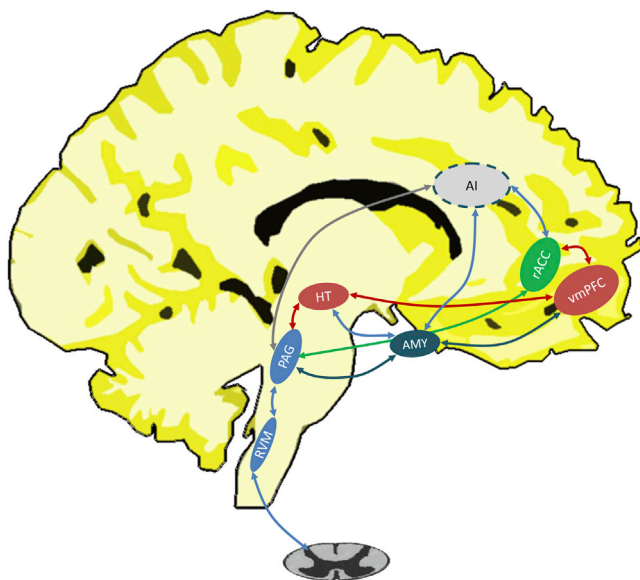


Figure 3. A Putative System Mediating Placebo Hypoalgesia

Note the recurrent nature of all connections in the hypothetical system (simplified by omitting several connections and areas). Whereas the cortical and subcortical projections all converge onto the PAG-RVM-spinal cord system, there are many cortical systems potentially mediating different aspects of placebo hypoalgesia. For instance, the projections from the rACC to the PAG (green) might resemble expectation effects in a more general fashion, whereas the projections from the vmPFC and the HT (red) might mediate the value aspect of placebo hypoalgesia.

1982, 1983b; Sakai et al., 1990), AMY and AI and rACC/vmPFC (Aggleton et al., 1980; Carmichael and Price, 1995; Krettek and Price, 1977; McDonald et al., 1996; Mufson et al., 1981; Russchen, 1982), as well as HT and AI and rACC/vmPFC (Floyd et al., 2001; Jasmin et al., 2004; Kita and Oomura, 1981; Mesulam et al., 1983; Musil and Olson, 1988; Ongür et al., 1998; Room et al., 1985); note that due to brevity, we are not discussing all projections (such as direct ones between rACC/vmPFC and PAG) here. There are only very few exceptions to this reciprocity, such as rather light connections from the dorsal horn of the spinal cord to the RVM (Lima, 2009; but these could for example be compensated by spinal input to PAG and HT: Dostrovsky and Craig, 2013; Lima, 2009) or inconclusive evidence for reciprocal connections between HT and AI in the cat.

The notion of a recurrent hierarchical model also shifts the focus from the analysis of regional activity toward the analysis of interregional effects. In agreement with this notion, many studies have consistently observed placebo hypoalgesia-related changes of functional coupling in human functional neuroimaging studies (Bingel et al., 2006; Craggs et al., 2007; Petrovic et al., 2002; Wager et al., 2007). The interregional coupling between the rACC and the PAG was found to be increased during placebo hypoalgesia (Bingel et al., 2006; Petrovic et al., 2002; Wager et al., 2007). Furthermore, this increased coupling was attenuated by naloxone and furthermore correlated to behavioral reports of hypoalgesia and activation changes in sensory-related pain-processing areas (SII) (Eippert et al., 2009b).

As placebo hypoalgesia is subject to numerous influences such as expectations, motivations, and emotions (Price et al.,

2008), such a system might implement these modulatory effects in a parsimonious fashion, by drawing upon different cortical ensembles for different modulatory effects, but at the same time utilize a final common pathway such as the PAG-RVM-spinal cord system (Figure 3). This notion is supported by a comprehensive network analysis study (Wager et al., 2007). In this data set, an increase of opioid release in rACC, PAG, VTA, VS, and AMY was seen for heat stimuli only, whereas the lateral PFC, AI, and the AMY showed decreases to warm stimuli. The authors concluded that the mechanism for areas that only respond to heat stimuli is the potentiation of opioid release, whereas decreases that are related to warm stimuli could be related to the reduction of anticipatory threat. Our framework would offer a slightly different interpretation: the increase in opioid release would be related to signaling predictions along the rACC-PAG system, whereas the decreases of opioidergic release in AMY and AI would be related to signaling predictions of decreased threat (Lundh, 1987; Price et al., 2008).

Placebo effects have also been explained by referring to a desire expectation model of emotions (Price and Barrell, 1984; Price et al., 2008). In addition to simpler models relying mainly on expectations, this model adds a desire component implying that in analgesia studies, volunteers have the desire to terminate pain. Previous studies have shown that the interaction of “desire for pain relief” and “expected pain relief” contributes significantly to placebo hypoalgesia. The model further predicts a parallel decrease of negative emotions, which has been observed behaviorally (Vase et al., 2003; Verne et al., 2003) and has been suggested by fMRI studies showing signal changes in areas implicated in anxiety and emotion regulation in placebo hypoalgesia studies (Bingel et al., 2006; Price et al., 2008; Wager et al., 2011).

The role of negative emotions in mechanisms of the placebo effect is also part of a cognitive-emotion model (Flaten et al., 2011; Lundh, 1987). Here, it is argued that illness often involves negative psychological aspects such as anxiety, sadness, or depression and an important part of the placebo effect is the development of “healing” beliefs. These beliefs are thought to counteract negative psychological aspects and thus have a positive influence on physical health (i.e., pain in placebo hypoalgesia). Conceptually, these cognitive-emotion models are in agreement with a hierarchical Bayesian model of placebo hypoalgesia. Although we initially explained the idea of such models in a single chain of recurrent brain areas (i.e., rACC-PAG-RVM-spinal cord), this system is more complex, as many regions are not only connected to areas up or down in the hierarchy, but rather to other areas (Figure 3). This suggests that top-down predictions in this framework do not only originate from a single area higher up in the hierarchy but from many regions (e.g., AI, rACC, and AMY) converging on lower tier structures (and vice versa) (Adams et al., 2013). Many cortical and subcortical regions such as the AI, the rACC, the AMY, and the HT have recurrent connections with the PAG. It is thus possible that the manifold of contextual effects that are part of most psychological theories of placebo hypoalgesia (Flaten et al., 2011; Lundh, 1987; Price et al., 2008) such as anxiety reduction, emotions, beliefs, and desire are mediated by overlapping projections in this system. For instance, AMY and AI might be involved in signaling

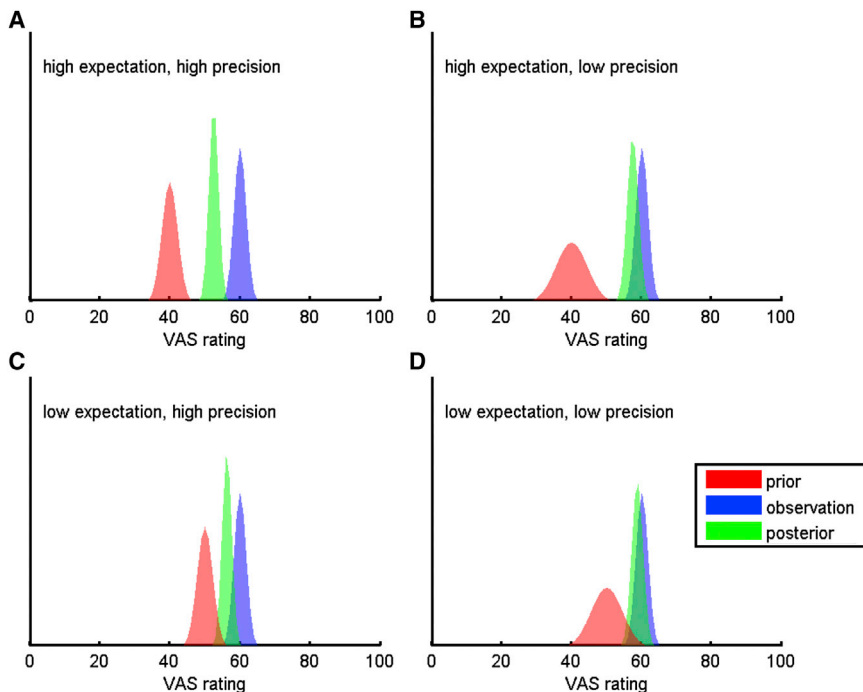


Figure 4. Predictions from the Bayesian Framework for Different Magnitudes and Precisions of the Prior Expectation in Placebo Hypoalgesia Experiments

The red Gaussian distribution characterizes the prediction (e.g., expectation; prior). Both different magnitudes (A and B versus C and D) and precisions (A and C versus B and D) are implemented. The blue Gaussian distribution characterizes the incoming sensory data (constant across conditions; likelihood). Based on the Gaussian model this leads to the posterior distribution (green) that resembles the placebo effect.

fear-related predictions (Figure 3, gray), whereas the vmPFC and HT might mediate predictions with respect to value or desire (Figure 3, red).

Predictions

The proposed Bayesian framework makes certain behavioral predictions that can be tested experimentally. Importantly, all these approaches have in common that the precision and the magnitude of either the prediction or the incoming sensory signals is varied independently. Only this allows testing crucial predictions from the model such as (1) how the precision of the prediction and the data affect placebo hypoalgesia, even when the magnitude is kept constant, and (2) how the precision of the prediction is mediated by modulatory neurotransmitter systems such as dopamine and opioids. Figure 4 summarizes these hypotheses in an experiment in which the precision of the placebo manipulation (e.g., previous experience or expectation) is varied. As there might be interactions between differences in magnitude and variability of the prediction, a full factorial 2×2 design is depicted.

Intuitively, all distributions can be interpreted as “approximated histograms,” e.g., in conditions A and B the average expectation is about 40 on a VAS, whereas it is 50 in conditions C and D. The width of the distribution indicates the variability (low precision in B and D as compared to A and C. The distribution of the painful stimulation with a mean of VAS 60 is identical for all conditions. According to our framework, high expectation with high precision should lead to the strongest placebo response (green posterior distribution in A), whereas a low expectation with low precision should lead to the weakest placebo response (green posterior distribution in D). As outlined above, this manipulation will have a limit, namely when the expectation (prior) is “too far away” from the incoming data (like-

likelihood). This would lead to a dramatic revisiting of the model to explain the incoming data, i.e., the initial model of a treatment reducing pain would be replaced by a model that entails a deception (i.e., no treatment).

Conversely, one could manipulate the magnitude and the precision of the incoming sensory data. This is relevant, as in clinical conditions such as IBS or fibromyalgia the precision of the sensory signal (i.e., ongoing pain) might be more variable as compared to well-defined

experimental pain stimuli. In this 2×2 design (Figure 5), the expectation (red) is kept constant across conditions. However, now the incoming sensory stimulus (blue) is varied in magnitude (i.e., intensity: A and B versus C and D or precision: A and C versus B and D. According to the presented model, the strongest placebo hypoalgesic effect should be obtained with a highly variable painful stimulus (low precision; green posterior in B and D).

On a related account, a meta-analysis has shown that a longer stimulus duration can result in a larger magnitude of placebo hypoalgesia (Vase et al., 2009). This could be due to a higher variability (i.e., lower precision) of average perception of longer stimuli, as volunteers have to integrate pain sensations over a longer time period. In future studies, it would be useful to obtain continuous ratings of perceived pain in paradigms with longer painful stimulation in order to assess the variability and to allow further model-based analyses (Cecchi et al., 2012).

Predictions for Population-Based Neuronal Data

Many studies have revealed behavioral evidence for predictive coding schemes (Clark, 2013; Knill and Pouget, 2004). Consequently, it would be interesting to reveal a possible neuronal implementation of this framework (O'Reilly et al., 2012). Using fMRI or other population-based techniques for this endeavor is not trivial, because both the top-down prediction and the bottom-up prediction error will contribute to the observed signal changes in such an area. The matter is further complicated by the fact that one cannot assume a simple 1:1 contribution of both processes (Egner et al., 2010).

However, a finessed experimental design might allow some inferences about the interplay between prediction and prediction errors, which would suggest a predictive coding framework in the context of pain. In analogy with Egner and colleagues (2010), one could employ a painful and a nonpainful hot stimulus

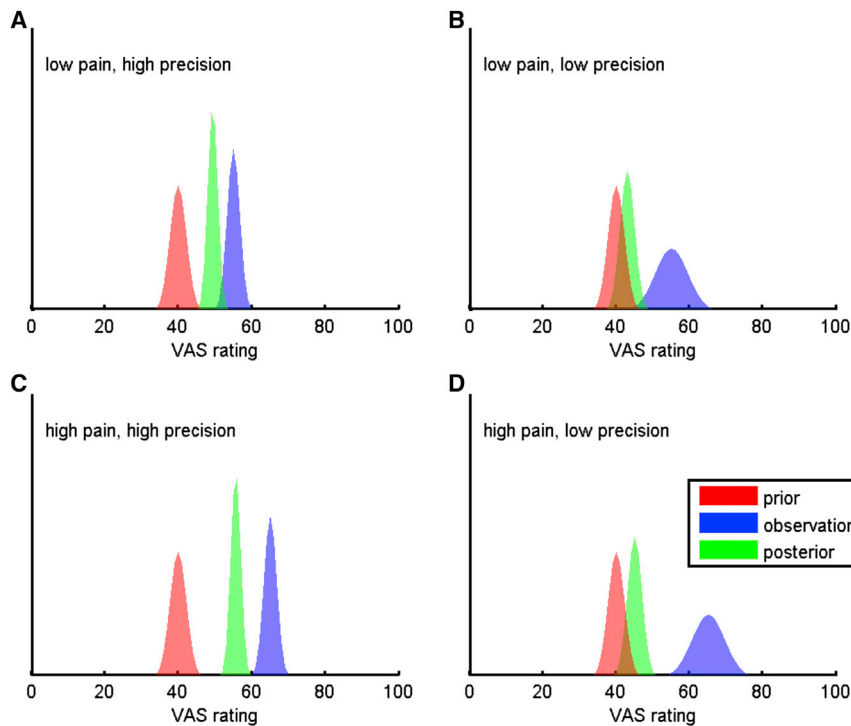


Figure 5. Predictions from the Bayesian Framework for Different Magnitudes and Precisions of the Incoming Sensory Information in Placebo Hypoalgesia Experiments

The blue Gaussian distribution characterizes the incoming sensory data (likelihood). Both different magnitudes (A and B versus C and D) and precisions (A and C versus B and D) are implemented. The red Gaussian distribution characterizes the prediction (e.g., expectation), which is kept constant across conditions. Based on the Bayesian model, this leads to the posterior distribution (green) that resembles the effect of the placebo manipulation.

in the context of different levels of pain expectation (Figure 6). A cortical region that shows nociceptive-specific responses, such as the posterior insula (Garcia-Larrea, 2012; Mazzola et al., 2012), should show a constant response to all painful stimuli irre-

spective of the expectation of pain. On the contrary, for hot stimuli the activity in this area should be dependent on the level of pain expectation. This distinction comes about because the response to the painful stimulus is a combination of prediction error or surprise (higher activation with low expectation; Figure 6A; see also Ploghaus et al., 2000 for an early study on prediction errors in the context of pain) and prediction (higher with high expectation; Figure 6B), leading to a constant response across expectation levels (Figure 6C). In contrast, nonpainful hot stimuli should lead to an increase in activation with increasing pain expectation. Importantly, if the assumption of pain specificity is violated (i.e., the region in question also

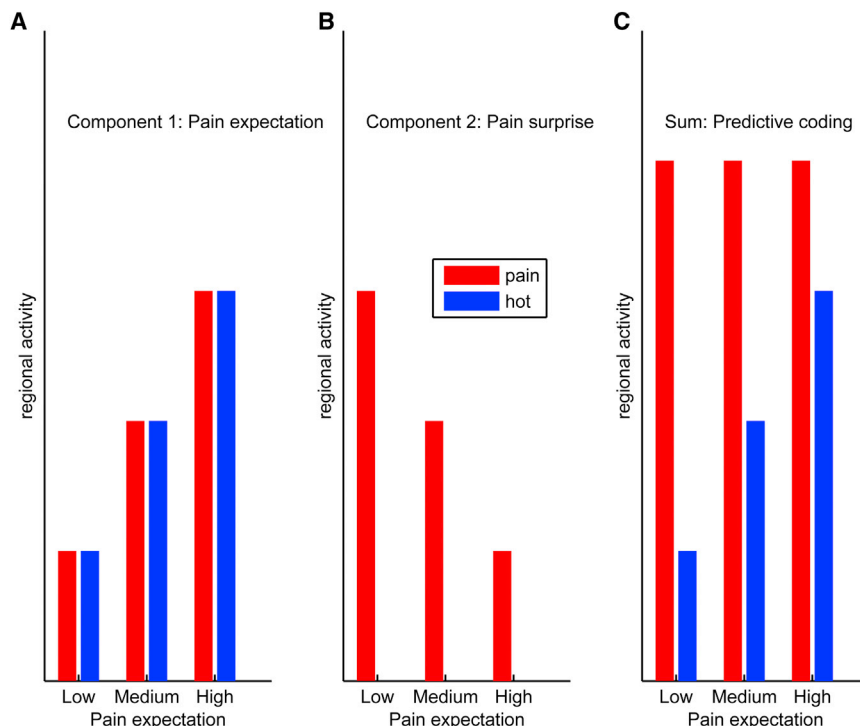


Figure 6. Predictions for Regional Activity Changes in a Predictive Coding Framework
Based on Egner et al. (2010).

(A) For a painful stimulus and a nonpainful stimulus, the signal component due to prediction increases with the expectation of pain. (B) In contrast, the signal component due to surprise decreases with increasing prediction but only for the painful stimulus. (C) Based on the sum of (A) and (B), an area involved in a predictive coding scheme should show a relatively constant activation for a painful stimulus and at the same time an increase for a nonpainful hot stimulus with increasing pain expectation. Note that in case of an area that responds equally well to pain and nonpainful hot stimuli, the response pattern for both should be identical.

responds to nonpainful hot stimuli), the ensuing activation pattern would not wrongly suggest a predictive coding framework but simply show identical activation levels for pain and non-painful hot stimuli (i.e., equal activation levels in Figure 6C). In addition, this experimental design could be adapted to a pharmacological fMRI study that would allow investigating the role of the dopaminergic and opioidergic system in the hypothesized effects.

Ongoing Activity

In a perceptual decision making study Hesselmann and colleagues (2010) observed that fluctuations in ongoing neural activity, as indexed by fMRI, biased perceptual decisions toward correct inference but not toward a specific percept: hits (detection of near-threshold stimuli) were preceded by significantly higher activity than both misses and false alarms. Based on this observation, they concluded that the observed activity probably corresponds to the precision of later-occurring prediction errors (see also Coste et al., 2011).

Translated into the context of our predictive coding framework for placebo hypoalgesia, we would predict that prestimulus activity fluctuations, e.g., in the PAG, are related to the placebo hypoalgesic effect. This seems plausible, as a previous study has already demonstrated the negative predictive value of prestimulus PAG activity for pain perception (Ploner et al., 2010; see also Brodersen et al., 2012). Furthermore, if the hypothesis that precision is mediated by opioidergic signaling in this system is correct, we would expect that the predictive value of prestimulus activity is not related to placebo hypoalgesia if volunteers were treated with an opioid antagonist.

Conclusion

Here we have taken a Bayesian perspective on placebo hypoalgesia and have aimed to explain fundamental findings in terms of a hierarchical neurobiological model based on the framework of predictive coding. We have applied this framework only to placebo hypoalgesia and in some cases to expectation-induced modulation of acute pain in healthy volunteers, leaving aside important topics such as central sensitization and pathophysiological (Woolf, 2011) or psychological processes in chronic pain patients (Morley, 2008). It will be an exciting endeavor to see how the ideas developed here and extensions thereof can be applied to clinical populations (Edwards et al., 2012).

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