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The Use of Placebo effect in Chronic Pain: Theories and Strategies

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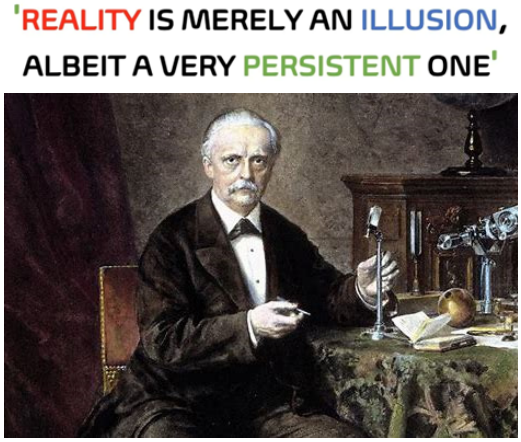
In my previous article "Effective *Listening affects patient outcomes*", I reported three case histories where the placebo effect was part and parcel of my therapeutic strategy. In this essay I wanted to revisit some of the recent theories regarding the neuroscience behind the placebo effect and possible theories as to its effectiveness [1]. Placebos have shown significant potential in managing chronic pain, offering a complex and intriguing avenue for treatment. I will review modern computational constructs of the mind body interaction in order to explain the effects of placebos. 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 competing theories.

I am not claiming that that empirical scientific evidence is somehow untrue, but rather that they are the product of our subjective interpretations of the probable causality for the observable phenomenon we are experiencing. In other words, what we infer the causality to be, is based on observed empirical evidence, are still biased by '*that which the Observer is able to perceive'*.

After reviewing the theories below we will return to the issue of the placebo effect and its specific application when dealing with chronic pain, itself a poorly understood pathological syndrome, from an empirical standpoint.

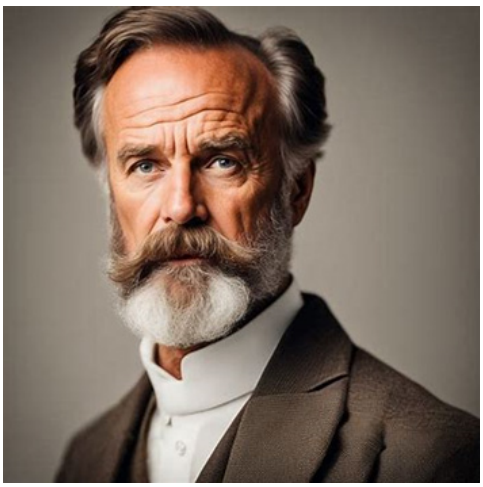


History

An approach to visual perception that bridges this apparent divide, proposed indeed more than a century ago by Helmholtz (1866/1962), puts an emphasis on the formation of a percept within a process of evaluation.

On Helmholtz's suggestion, the evaluation involves a test of a hypothesis about what is being seen based on "inductive inferences" gained from "sensations". By inductive inference Helmholtz meant *that perceptions are conclusions based not only on present sensations but also with reference to past sensations of the objects perceived*. Latent within this conceptualization is the idea that the perceived image is at least partly the outcome of stored information – a stored representation, that is a memory – of that object or of similar objects in similar contexts.

This was potentially the first proposal of a top-down influence in perception. It regards perception not primarily as a sensory phenomenon but as perceptual inference relying on internal models built through past experience. Helmholtz's idea of perceptual inference has been revived by computational models of perception relying on statistical inference [2].



A contemporary of, and indeed, student of Helmholtz, was William James, the American Physiologist turned Psychologist. During 1867–68 James went to Germany for courses with the physicist and physiologist Hermann von Helmholtz, who formulated the law of the conservation of energy. This trip sparked a flame in James, and he spent the next 25 years dedicated to decoding the human psyche. This resulted in the 2 volume, 1,200 page long 'The Principles of Psychology' which he published in 1890, after having toiled with its conception for 10 years, trying to get it finished. When the book was published in 1890, it became an instant success among the growing populous with interest in the new field of Psychology.

In 1890 William James wrote: "*Whilst part of what we perceive comes from the object before us, another part (and it may be the larger part) always comes out of our own head*", a statement sometimes referred to as William James' Law of Perception. The Principles, which was recognized at once as both definitive and innovating in its field, established the functional point of view in psychology. It assimilated mental science to the biological disciplines and treated thinking and knowledge as instruments in the struggle to live. At one and the same time it made the fullest use of principles of psychophysics (the study of the effect of physical processes upon the mental processes of an organism) and defended, without embracing, free will. [Encyclopedia Britannica].

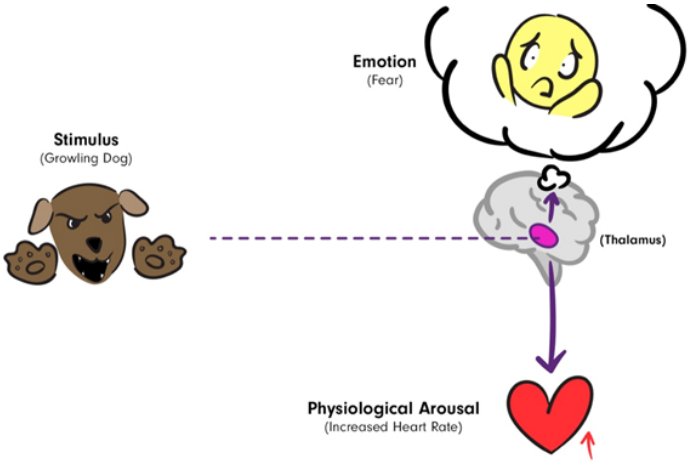
Cognitive neuroscientists now view the brain as a statistical organ that generates hypotheses or fantasies that are tested against sensory evidence. This perspective can be traced back to Helmholtz and the notion of unconscious inference (Helmholtz, 1866/1962). In the past decades this approach has been formalized to cover deep or hierarchical Bayesian inference about the causes of our sensations and how these inferences induce beliefs and behavior.

Models

There are many computational perspectives that could be called upon to characterize psychopathology. These range from neural network and dynamical systems theory to reinforcement learning and game theory. A recent paradigm shift in cognitive neuroscience provides a sort of theory that allows one to talk about false beliefs and understand how these arise from synaptic pathophysiology.

Büchel, Geuter, Sprenger and Eippert have proposed that a hierarchical Bayesian framework of brain function based on the idea of predictive coding can account for many facets of placebo hypoalgesia [3].

They 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.



Theory: The Bayesian Brain Hypothesis

The Bayesian Brain Hypothesis considers the brain as a statistical organ of hierarchical inference that predicts current and future events on the basis of past experience.

Perceptual Inference

Perceptual inference refers to the ability to infer sensory stimuli from predictions that result from internal neural representations built through prior experience [2].

Perceptual Inference was a term first used by, marking a re-emergence of the Helmholtzian view of perception as inductive inference, a notion re-articulated by as the "Helmholtz Machine". These models described perception as hypothesis testing using the Bayes rule, the latter incorporating ideas on hierarchical coding from neuroscience. Expectation was introduced by and predictive coding by. A subsequent theoretical framework of "active inference" was developed by [4] from the ideas of statistical decision theory and predictive coding in a series of recent publications. 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 [5,6]. 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 [4]. Initially, this model is defined by various genetic and epigenetic factors [5,7], which are then continuously refined over the lifespan through associative plasticity and neurodevelopmental learning. This enables more efficient prediction 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.

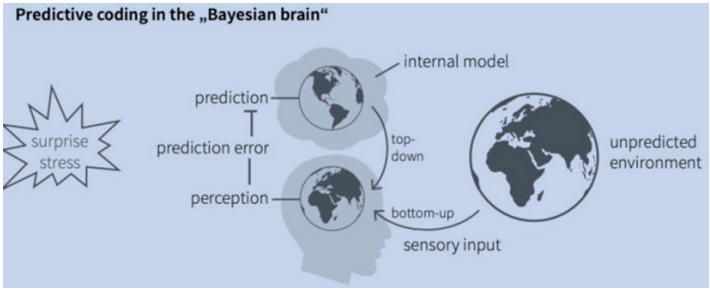
Predictive coding can be considered as a consequence of the free-energy principle [4]. The free-energy principle states that self-organizing systems that are in a homeostatic state must minimize their free energy (i.e., resist the natural tendency to increase their disorder or entropy). In this formulation, 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.

Perceptual Inference in the Sensorimotor System

The Bayesian statistical models were developed partially in physics, artificial vision, and artificial intelligence and partially in relation to experimental psychophysics, where the model observer has to passively predict an input and the world acts as an instructor. Information flows unidirectionally from the world to the brain. In these simplified situations, the visual stimulus was until recently regarded as a feedforward input. The classical view in experimental studies of the sensorimotor system has been quite the reverse. The sensory input has been traditionally regarded as feedback while the top-down motor commands have been regarded as the feedforward action that causes an interaction with the world. The result of that interaction between the motor command and the sensory feedback is the minimisation of corrections (essentially the same as the minimisation of error or optimisation of precision) [2].

The Bayesian Brain Hypothesis Overview

According to this theory, the mind makes sense of the world by assigning probabilities to hypotheses that best explain (usually sparse and ambiguous) sensory data and continually updating these hypotheses according to standard probabilistic rules of inference. This fine-tuning (optimization) of perception and action operates under the single imperative of minimizing surprise (free energy) and uncertainty; thereby maximizing statistical and thermodynamic efficiency. Learning in the Bayesian brain differs from reinforcement (and machine) learning because it occurs with understanding. Mental models of past experience use these experiences to anticipate new experiences, as opposed to being shaped by them. Continual optimisation of the models also enables efficient exchange with the environment in a self-organised, self-evidencing and unsupervised fashion.



Predictive Coding and the Bayesian brain

Modern formulations of Helmholtz's ideas usually appeal to theories such as predictive coding. Predictive coding describes how the brain processes sensory information by optimizing explanations for its sensations. In predictive coding, neuronal representations in higher levels of cortical hierarchies generate predictions of representations in lower levels. These top-down predictions are compared with representations at the lower level to form a prediction error (associated with the activity of superficial pyramidal cells).

The ensuing mismatch signal is passed back up the hierarchy, to update higher representations (associated with the activity of deep pyramidal cells). This recursive exchange of signals suppresses prediction error at each and every level to provide a hierarchical explanation for sensory inputs. In computational terms, neuronal activity is thought to encode beliefs about states of the world that cause sensations. The simplest encoding corresponds to the expected value or *expectation* of a (hidden) cause. These causes are referred to as *hidden* because they have to be inferred from their sensory consequences.

In short, predictive coding represents a biologically plausible scheme for updating beliefs about the world using sensory samples. The figure here, tries to convey the basic idea behind predictive coding in terms of minimizing prediction errors.

Computational Models

Since 2010, the research in Neuroscience into the depth of how the human brain computes the information it receives, have made extraordinary landfall, especially in the area of Perception and Action.

Peter Vang outlines the key principles of Bayesian theory [8]. Perceptual inference refers to the ability to infer sensory stimuli from predictions that result from internal neural representations built through prior experience [2].

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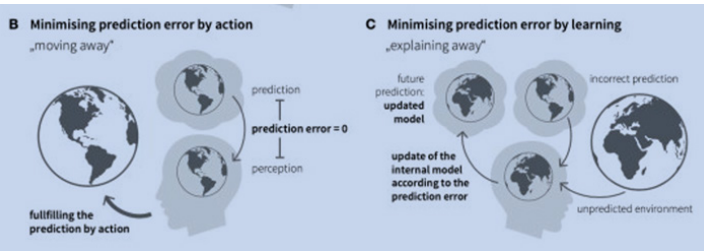
Active Inference

Active inference seeks to explain brain function in terms of predictive coding, the brain always seeking to minimise prediction error or "free energy" through the optimisation of precision (prediction accuracy) in attention and in motor commands.

Predictive Coding

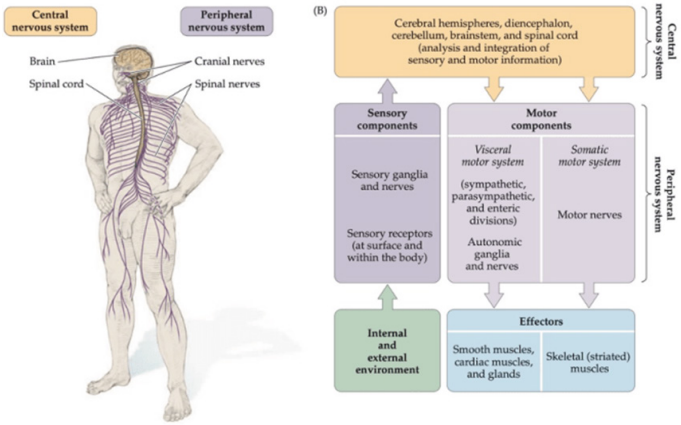
Perception arises in prediction error minimization where the brain's hypotheses about the world are stepwise brought closer to the flow of sensory input caused by things in the world. This is an elegant idea because it gives the brain all the tools it needs to extract the causal regularities in the world and use them to predict what comes next in a way that is sensitive to what is currently delivered to the senses. This idea can be explicated in more complex terms of minimizing surprisal to ensure agents sample sensory inputs that are characteristic of their phenotype. This can be cast in terms of minimizing the divergence between hypotheses or probabilistic representations of the world and the true posterior probability, given sensory evidence a minimization that necessarily invokes a Bayesian brain perspective on perception and places the role of probabilistic representations centre stage. This perspective provides an account in terms of the overall way prediction error bounds the creature's surprisal. This idea of a bound-on surprise is something we will return to a number of times.



The Constructed Mind

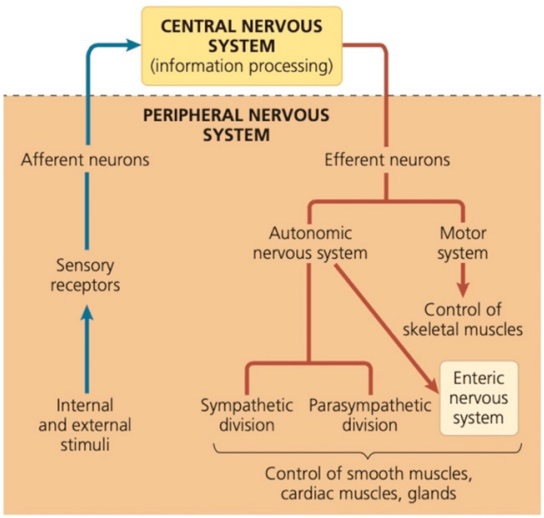
The Constructed Mind approach is an extension of the Theory of Constructed Emotion, which itself began as a more modest theoretical proposal, called the Conceptual Act Theory. Built from psychological and social construction approaches, the conceptual act theory proposed that the human mind transforms feelings of affect into instances of emotion by categorizing them with situation-specific, embodied emotion concepts. Following publication of the initial papers outlining the conceptual act theory, however, a deeper understanding of nervous system structure and function suggested that instances of emotions do not arise from categorizing affect. Instead, they emerge in a brain as it continually makes meaning of sense data from its body and the world by categorizing those data with situation-specific concepts, thereby constructing experience and guiding action.

The goal of The Constructed Mind Theory is ***not*** *to reduce every mental phenomenon to energy regulation* but rather to *highlight energy regulation as a key element in the* ***state space*** *of a brain*:



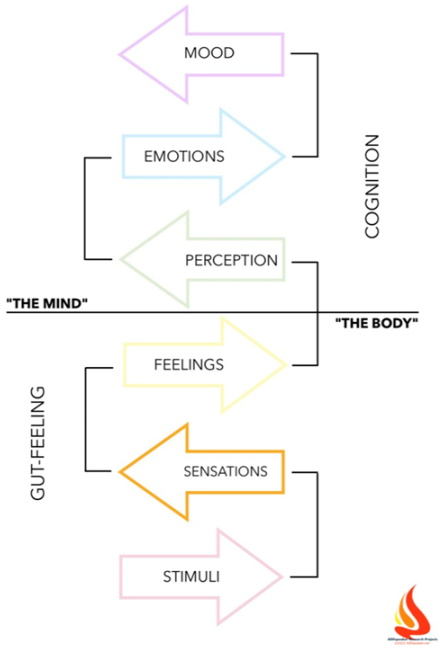
Optimization

The Nervous System must generate a response that effectively addresses the stimulus, only if necessary, as quickly and accurately as possible, and with the least consumption of resources. To improve performance, the Nervous System has developed multiple biological mechanisms in architecture and dynamics (**memory**, **pattern recognition**, **predictive systems**, **feedback**, **feedforward**, **mirror system**, **automaticity**). The three levels of response (**automatic**, **mentalized**, and **automated**) allows the Nervous System to optimize the three critical variables **(activation threshold**, **reaction time** and **accuracy**) and their **interdependence**.



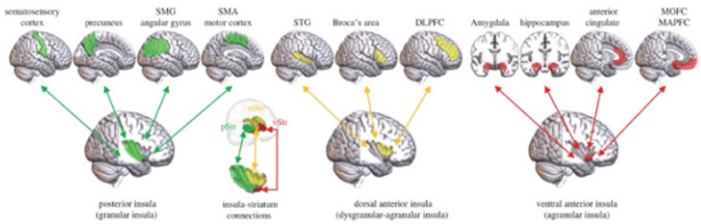
The Structural and Functional Schematics of the Bayesian Brain Hypothesis

The model can be used to see the process from Stimuli to Mood (Sense-of-Self), and the clever feature is, that you can input both Sensory Signals [taste, smell, sound, sight, touch, and vestibular] as well as Neuronal Signals [thoughts or emotions] into the STIMULI box at the bottom of the model, and then just follow the steps in the process up the chain. This is possible due to the fact, that the MIND does not distinguish between what is 'real' and what is 'imagined' when evaluating the impact of the Object on the State-of-Affairs in Core Affect, it just handles its business regardless.



The BRAIN is a physical organ which resides inside the Skull, isolated from the physical External World

The **CNS** is connected to the Peripheral Nervous System (**PNS**) through which it interacts with both the internal world [called **Interoception**] and the external world [called **Exteroception**] through the Somatic Nervous System (**SNS**), as well as receiving information of the current **State-of-Affairs** of the **BODY** through the Autonomic Nervous System (**ANS**).



The MIND is a non-physical entity, which is conceptualized as consisting of various neural networks within the BRAIN, which in unison gives rise to consciousness, or the SELF.

The SELF is a non-physical, mentalization of the BODY in the world, as defined by the MIND

Cognition, as it is used here, broadly encompasses every mechanism of mind including (but not limited to) perception, attention, motivation, planning, deliberation, metacognition, action selection, and motor control, as well as the embodiment of all of these activities. "Cognition" then is meant to cover the entirety of the agent's mental life including its embodiment and embodied actions.

Consciousness is the result of the Executive Functions of COGNITION, used by the MIND to construct our Subjective, Experienced, Embodied Sense-of-Self

Summary

Recent research has proposed "predictive coding" and "Bayesian brain" models as unified frameworks to explain placebo effects, particularly in chronic pain. Here are the key points about these models:

Predictive Coding Model

- This model suggests that the brain actively makes inferences based on prior experience and expectations, rather than passively waiting for sensory input.
- It inverts the traditional view of the brain as a stimulus-driven organ, proposing instead that perception relies heavily on learned, top-down cortical predictions.
- In this framework, both chronic pain and its alleviation through placebo are explained as centrally encoded, mostly non-conscious Bayesian biases.

Bayesian Brain Perspective

- The Bayesian aspect of predictive coding can account for differences in both the magnitude and precision of expectations, which are known to influence placebo effects.
- This model predicts that the extent to which perception is biased toward prior expectations depends on the expectation's precision: more certain expectations have a stronger influence on perception.

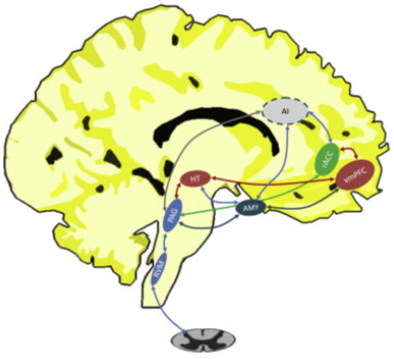
Application to Placebo Analgesia

- Studies have shown that placebo effects are larger when expectations are more precise (less variable).
- The periaqueductal gray (PAG), an opioid-rich brain region, has been found to correlate with the "attraction weight" - a quantity sensitive to the precision of both prior expectations and incoming sensory data.
- This framework can explain why conditioning and verbal suggestions different impacts on placebo outcomes may have, as they shape expectations differently.

Implications for Understanding Placebo Mechanisms

- These models suggest that modulatory neurotransmitters like opioids might be related to characterizing expectations, particularly their precision.
- They provide a unified explanation for various observations in placebo research, including the role of learning, expectation, and the patient-physician relationship.
- The predictive coding/Bayesian brain approach offers a more comprehensive explanation than simpler reinforcement learning models for placebo effects.

These emerging models from computational neurobiology offer a promising framework for understanding the complex and heterogeneous evidence on placebo effects, particularly in chronic pain management. They suggest that placebo responses are not merely psychological traits but reflect fundamental processes of how the brain processes information and generates perceptions.



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.

Chronic Pain Application

Predictive coding offers several key differences from traditional models in explaining placebo effects, particularly for chronic pain:

1. Active inference vs. passive processing:

Predictive coding views the brain as actively making inferences based on prior experience and expectations, rather than passively waiting for sensory input. This inverts the traditional view of the brain as primarily stimulus-driven.

2. Top-down vs. bottom-up:

In predictive coding, perception relies heavily on learned, top-down cortical predictions to infer the source of incoming sensory data. This contrasts with models that emphasize bottom-up processing of sensory information.

3. Precision of expectations:

The Bayesian aspect of predictive coding accounts for both the magnitude and precision of expectations. More certain expectations have a stronger influence on perception, which can explain variations in placebo response strength.

4. Integration of prediction errors:

Predictive coding models suggest that pain perception results from integrating both bottom-up sensory signals and top-down expectations. The mismatch between these (prediction error) is used to refine future expectations.

5. Unified framework:

Predictive coding offers a more comprehensive explanation for various observations in placebo research, including the roles of learning, expectation, and the patient-physician relationship. It provides a unified framework that can account for heterogeneous evidence on placebos.

6. Neurobiological basis:

The model suggests that modulatory neurotransmitters like opioids might be related to characterizing expectations, particularly their precision. This provides a potential neurobiological mechanism for placebo effects.

7. Non-conscious processing:

Predictive coding/Bayesian brain models explain both chronic pain and its alleviation through placebo as centrally encoded, mostly non-conscious Bayesian biases. This differs from models that emphasize conscious expectations.

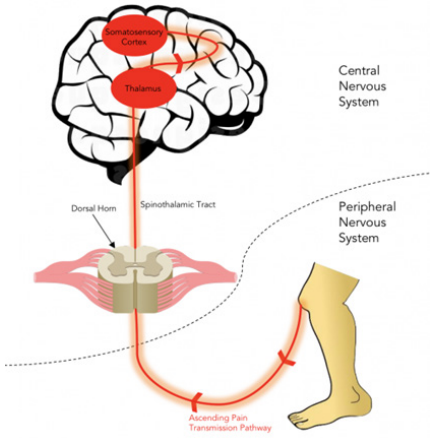
8. Explains persistent effects:

Unlike simple reinforcement learning models, predictive coding can account for self-reinforcing expectancies and persistent placebo effects even when not consistently reinforced.

By offering these unique perspectives, predictive coding provides a more nuanced and comprehensive framework for understanding placebo effects compared to traditional expectancy-based or conditioning models. Predictive coding offers a more comprehensive and flexible framework for modeling placebo effects, particularly in accounting for the role of expectation precision and persistent effects. However, both models continue to be useful in placebo research, with reinforcement learning providing valuable insights into learning processes involved in placebo responses.

Many health professionals consider a positive response to placebo a psychological trait related to neurosis and imagination. However, a decade of data suggests the placebo effect to be a powerful demonstration of how mental activity that is shaped by expectation, context and experience can measurably influence physiological functions. The current strategy, in particular in the design of clinical trials, is to minimize potential placebo effects and thus ignoring the positive effects of the placebo response.

Here a Bayesian perspective on placebo hypoalgesia is used and aims to explain fundamental findings in terms of a hierarchical neurobiological model based on the framework of predictive coding. This framework applies 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 [9] or psychological processes in chronic pain patients [10].

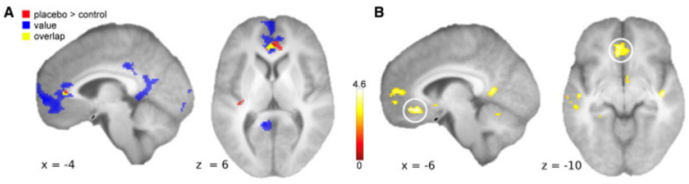


The Role of the PAG-RVM-Spinal Pathway and Opioids

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 [11,12].

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 [13,14].

A possible mechanism by which placebo hypoalgesia could be implemented was already introduced 50 years ago in Melzack and Wall's gate control theory. 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 [12]. 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, 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". 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."



Placebo-Induced BOLD Responses and Value Signal
Based on data reported in Geuter and colleagues (2013)

Current Understanding of Placebos in Clinical Management

Definition

A placebo is an inert treatment that is not designed to have any therapeutic value, such as inert tablets or injections, sham surgery, and other procedures with no therapeutic value. placebo is a substance, pill, or other treatment that appears to be a medical intervention but isn't one. Because a placebo isn't an active treatment, it shouldn't have a significant effect on the condition. Researchers can compare the results from the placebo to those from the actual drug. This helps them to determine if the new drug is effective.

Placebos are widely used in clinical research to provide control arms when evaluating the effects of drugs and other interventions. In a clinical context, knowingly administering an inert treatment without the patient's explicit consent would be unethical, although the practice was widespread in the history of medicine until the first half of the 20th century as an accepted therapeutic strategy. Factors relevant to placebo mechanisms can also result in therapeutic advantage when active treatments are delivered non-

deceptively. The focus of this article is the usefulness of such responses in practice, which has been most widely researched in clinical and experimental pain settings.

Effectiveness of Placebos

- Placebos can be surprisingly effective in treating chronic pain:
- Some patients experience up to 30% pain relief from placebos, which is considered clinically significant and comparable to many active pain medications.
- In some studies, up to 32% of patients receiving saline injections (as a placebo) reported greater than 50% pain relief.

Mechanisms of Action

The placebo effect in chronic pain is thought to work through several mechanisms:

- **Expectation and Conditioning:** A person's beliefs and past experiences with treatments can influence their response to placebos.
- **Neurobiological Changes:** Placebos can trigger real physiological responses in the brain, including the release of pain-relieving neurotransmitters.

Predictive Factors

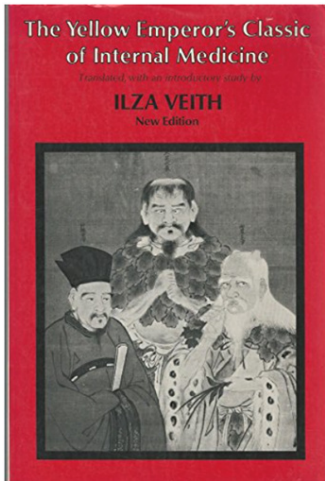
Recent research has identified factors that may predict a strong placebo response:

- **Brain Anatomy**: Certain brain structures, such as asymmetry in the subcortical limbic system, are associated with stronger placebo responses.
- **Personality Traits**: Individuals who are more emotionally self-aware, mindful of their environment, and sensitive to painful situations tend to respond better to placebos.

Clinical Applications

The use of placebos in clinical practice is evolving:

- **Open**-Label Placebos: Some studies suggest that placebos can be effective even when patients know they are receiving an inert treatment.
- **Enhancing Active Treatments**: Understanding placebo mechanisms can help optimize the overall therapeutic context of active treatments.



A very early allusion to contextual (not explicitly therapeutic) factors important to treatment success was from ancient Chinese medicine. The Yellow Emperor's Inner Classic (*Huang Di Nei Jing*) from the first century BCE: ***'If a patient does not consent to therapy [acupuncture] with positive engagement, the physician should not proceed as the therapy will not succeed'*** **[15]**.

This statement suggests an appreciation that contextual factors are relevant to treatment success, which increased in Western literature through the 19th and 20th centuries. In Henry Beecher's milestone 1955 paper, 'The powerful placebo', the placebo groups of 15 placebo-controlled trials were examined, and it was concluded that this effect averaging approximately 35% of patients was attributable to placebo. Although methodology and conclusion have since been questioned, the ubiquity and significance of placebo effects in trials, and clinical practice, are now established [16].

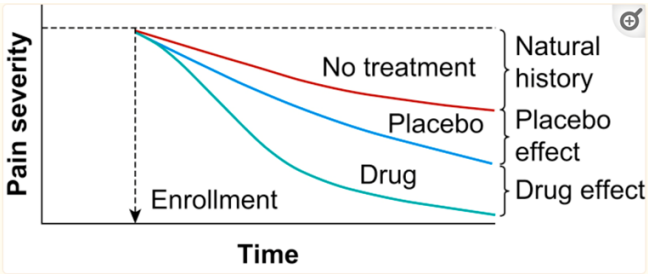
Placebo response is the response observed in the placebo arm of a research trial. In a clinical setting, it is a positive response noted in or described by a patient, which is not attributable to the active treatment itself. In contrast, placebo effect is the difference in the presence or severity of symptoms between the placebo group and an untreated control arm, and therefore controls for other factors, such as natural history of the condition [17].

The nocebo effect has also been described and is the negative counterpart of the placebo effect. Examples include adverse effects or worsening of symptoms not directly caused by a treatment, when compared with an untreated control arm. It has been studied to a lesser extent than the placebo effect, largely because of ethical considerations.

Natural History

J.S. Perfitt, N. Plunkett, and S. Jones write [18]:

The natural history of some symptoms is such that they are likely to resolve over time. If the natural history of the symptoms matches that of the study period, then it may appear that the symptoms of patients in the placebo group have improved as a result of placebo or treatment.



At the time of enrolment (the clinical corollary of which is the new patient assessment), pain severity is at its highest. Over time, even with no treatment, pain levels may reduce (natural history and perhaps regression to the mean). With treatment (drug or any treatment), the pain reduces to a greater degree, in part because of the 'intrinsic' treatment effect, and partly from the placebo effect [19].

Psychological Mechanisms

There have been two main schools of thought in relation to the psychological mechanisms of the placebo effect. These are conditioning and expectancy.

Conditioning

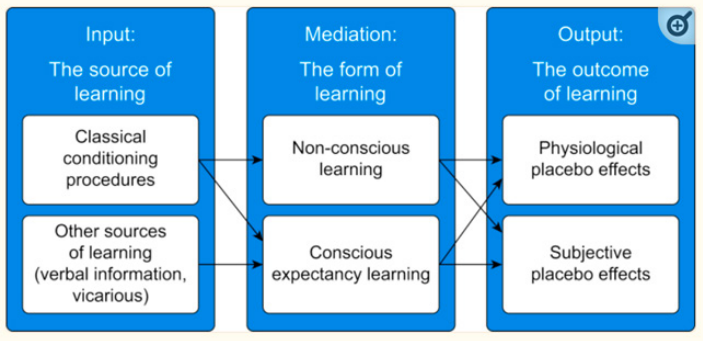
The conditioning hypothesis suggests that placebo responses result from automatic, unconscious pairing of stimuli via Pavlovian conditioning. An individual may experience a reduction in pain (unconditioned response) after an analgesic intervention, such as an injection (neutral stimulus) containing an analgesic agent (unconditioned stimulus). The pairing of the injection and a reduction in pain may lead the injection (conditioned stimulus) to result into a reduction in pain (conditioned response) without the presence of the original analgesic agent.

Expectancy

Expectancy theories of placebo consider the conscious expectation of a situation to impact the individual's responses within that context. Expectations are formed from prior experience; for example, previous positive experiences of visiting a doctor could lead to an expectation of further positive experiences. Social learning, such as responses to authority, others' experiences of healthcare, or how likely we are to experience positive outcomes, could all influence placebo responses according to expectancy theory.

Synthesis

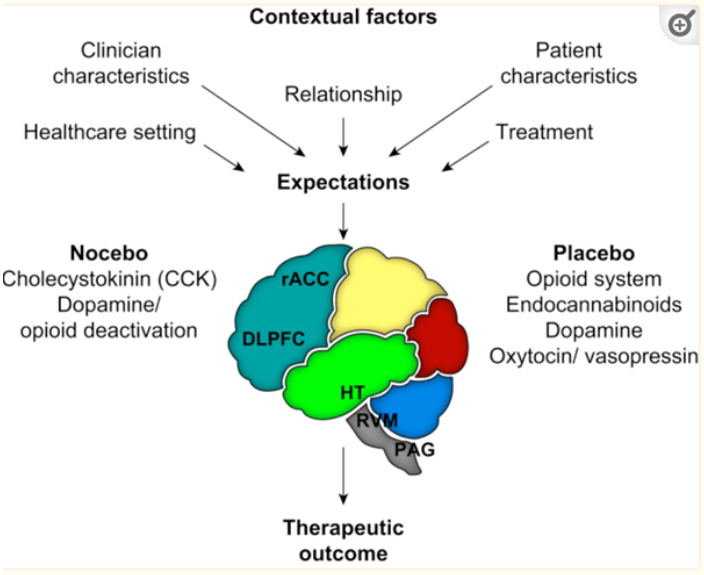
Previous research has suggested two distinct schools of thought regarding psychological mechanisms underpinning placebo effects. More recent debate has questioned whether they are mutually distinct mechanisms. Stewart-Williams and Podd proposed a model in which conditioning and expectancy theories complement and interact to produce an effect [20].



Stewart-Williams and Podd's (2004) combined model of placebo response

Within this combined model, individual differences can influence a general process upon which the response is underpinned (i.e. how our conscious experience can influence our unconscious physiological responses). Viewing the placebo response as a product of prior learning, expectation, and unconscious physiological conditioning helps clinicians and researchers to consider the placebo effect more in line with the prevailing models of chronic pain, which have grown from Engel's 1977 biopsychosocial model.

A synthesis of conditioning and expectation theories also complements work conducted on pain matrix conceptualisations of pain perception by Tiemann and colleagues, which have been shown to rely on top-down and bottom-up processing to modulate pain perception, and Miller and Kaptchuk's model of contextual healing [20]. In consideration of various factors that influence the placebo response, the evidence suggests that the context and environment interact with the individual's physiology, as depicted below [21].



Neuro-chemical mechanisms of placebo and nocebo

The neurobiology of the placebo effect was first demonstrated in 1978 when it was shown that giving the opioid antagonist naloxone could block the placebo response, indicating the involvement of endogenous opioids.[12] Subsequently, their role was shown to differ depending on the context, in which the placebo response was induced. In an experimental model of pain, naloxone blocked the placebo response related to expectation and conditioning with opioids. When the placebo response was induced with non-opioid conditioning using an NSAID, this response was naloxone insensitive [23].

Cholecystokinin (CCK) has known anti-endogenous opioid actions. Administration of the CCK antagonist proglumide was found to enhance placebo analgesia. Opioid-induced placebo analgesic response appears to be mediated by a balance between endogenous opioids and CCK [24]. Other neurotransmitters that have been found to be involved in the placebo effect include dopamine, oxytocin, and vasopressin. In patients with Parkinson's disease, increases in endogenous dopamine release in response to placebo administration were observed, comparable with those of therapeutic doses of levodopa or apomorphine [25].

Placebo Effects in Pain Management

Individual factors

Not all individuals display response to placebo. This can in part be explained by individual physiological differences, but also to psychological factors, as discussed earlier. Several studies have looked to identify particular psychological characteristics, which give insight into how an individual would respond to placebo. Corsi and Colloca found that placebo responses were negatively correlated with anxiety severity and pain [25].

They also reviewed other research that suggested that placebo was associated with optimism, suggestibility, empathy, openness to experience, and somatic focus, whilst nocebo was associated with pessimism, anxiety, and catastrophising. Whilst in a clinical setting it would be impractical to administer a battery of psychometric tests to each individual, it is important to consider how psychological factors can influence the response to treatment and how these factors could be incorporated into 'treatment as usual' within a clinical setting.

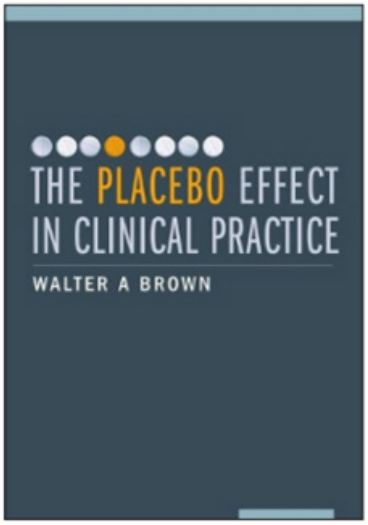
Using Placebo as an Additive Effect in Clinical Practice

- Describe basic mechanisms behind the treatment
- Give information stating that the particular treatment is effective, provided that this information is realistic
- Aim for an emotionally warm/empathetic style
- Try to reduce the amount of stress for the patient

Barrett et al [26]. suggest a list of eight specific and practical principles that doctors can use to elicit placebo effects. These include speaking positively about treatments, providing encouragement, developing trust, providing reassurance, supporting relationships, respecting uniqueness, exploring values, and "creating ceremony". The aim of using these principles is to create positive expectations, reduce anxiety/stress, and enhance the feeling of being cared for. These principles are fundamental and can be related to a biopsychosocial and patient-centered perspective.

It is important to communicate positive expectations regarding the outcome of the treatment and the patient's ability to cope with the disease and its treatment [27,28]. The doctor can do this, for instance, by providing information stating that a particular treatment is effective. As an example, Benedetti and Amanzio [29] recommend that negative suggestions should be substituted with positive hints. For instance "here is your pain medicine" can be changed to "Here's some medicine to help you get better". Patients should have a clear understanding of the treatment and the desired outcome [30]. A central principle is thus to communicate realistic optimism and hope. Positive patient experiences with treatment may also lead to more long-lasting placebo effects due to a psychological conditioning effect [31].

A trusting relationship between the doctor and the patient is central. Building confidence between patients and doctors is an important way of inducing placebo effects [32]. Kaptchuk et al. demonstrated this when they administered placebo without deception in patients with irritable bowel syndrome [33]. They obtained placebo effects based on the relationship between patients and health workers. Further, they found that switching from a technical style to a more emotionally warm/empathetic style increased the placebo effects from 42% to 82%. Employing a patient-centered approach involving a cooperative and empathetic interactional style may help reduce patients' anxiety and stress and thereby elicit additional positive placebo responses [34].



The placebo effect is the bane of clinical trial design because it causes many drug trials to fail. Nevertheless, researchers, clinicians and ethicists are increasingly interested in the use of placebos in clinical practice.

Brown challenges our attitudes about the placebo effect. He argues for the skilled use of placebos in clinical practice and suggests how to benefit from their scientifically proven effects [35]. Brown starts with a short history of placebos, reminding us that early medical practice was a catalog of placebo potions that worked because both physician and patient believed in their effectiveness. Early medical practice also established the link between patient and physician in the ritual of effective healing. Indeed, up until the mid-1950s, physicians published articles discussing how a placebo effect could be maximized in clinical practice they understood that 'deception for good' was necessary to elicit patient improvement. Brown argues, provocatively, that a large number of current therapies, such as psychotherapies and surgical interventions,

might essentially be placebos. Evidence of effectiveness over and above a placebo is unproven in many therapies owing to either ethical or practical difficulties. Arguably, placebos have become the bad boys of modern medicine after publication of Henry Beecher's seminal paper in JAMA in 1955, which assessed the results of 15 studies with over a thousand patients who had been treated with placebos. Beecher concluded that because the placebo effect is so powerful, a drug must beat the placebo effect if it is to be approved: thus, the placebo-controlled trial was born. Brown correctly points out the irony that just when the effectiveness of placebo treatments was quantitatively proven, forcing this new design into clinical research, they stopped being used clinically as therapeutic agents.

Brown discusses the importance of the treatment environment for eliciting the placebo response well, and he makes a plea to rebrand the placebo effect as a "response to treatment situation." The idea that this situation promotes possible activation of brain circuits involved in driving well-being and perhaps a return to homeostasis harks back to ancient understandings of the importance of the patient-physician interaction. The author cleverly indicates how this interaction is degraded in our current climate, where appointment time windows are cut too short for meaningful interactions to occur.

In my practice the ethical use of the placebo effect is part of the interventional strategy as much as injections infusions and medications.

The success of the treatment lies in the marriage of direct standard medical intervention and the judicious use of the placebo effect [36]. I leverage the placebo effect for therapeutic purposes. Ethically I justify this by demonstrating the reduced dependance upon opiates or multiple surgical interventions can only be good for the patient. In being fully transparent the patient enters the space of healing voluntarily knowing full well the implications of the use of the placebo because of the trust factor.

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