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Anatomy and disorders of the placebo system: How placebos influence mind, brain and behavior.

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Abstract

How can the sole administration of a sham treatment – a placebo, trigger psychological and physiological changes that mimic the action of active medication? Placebo effects are a well-known phenomenon from clinical research to everyday life. In this chapter we define the placebo effect as behavioral and physiological responses to a person's external (e.g., place, social cues, physical attributes of the treatment) and internal (e.g. thoughts, memories, emotions, expectancies) world during treatment. We describe where in the brain, and how a placebo gets translated into an effect from the pain domain to neurological disease such as Parkinson's disease to everyday life behavior – outside the medical domain. We discuss how psychological processes such as learning, prognostic expectancies and motivation together with their associated brain activation potentially mediate placebo effects. The overview of the growing literature on placebo effects and closely related phenomena reveals that placebo effects are an umbrella term for many different subprocesses, which may engage different and interacting brain systems. Identifying and probing the psychological and neurophysiological factors that determine placebo effects is an intriguing scientific puzzle that shed lights on mind-brain-body interactions, and how they shape human behavior.

Placebos—fake medical treatments—are well known from randomized clinical trials during which they are administered to control for non-specific effects of the active treatment, such as a new drug, a surgical intervention, or a specific psychotherapeutic treatment.

However, placebo effects are a double-edged sword. On the one side, they are a source of noise during clinical trials engendering both economic and medical costs. On the other side placebo effects are usually larger than improvements observed in waitlist control groups, indicating that they are not always driven by statistical artefacts such as regression to the mean or spontaneous remission and thus reveal a powerful endogenous effect that can potentially be harnessed for treatments. Clinical research has shown now and again how effective placebos are in comparison to non-treatment control arms for improving neurological and psychiatric disorders (Benedetti et al., 2004; 2016), autonomic nervous system function (Meissner, 2011), or even survival from heart failure (Pressman et al., 2012).

The fact that placebo effects are not only a nuisance presents an intriguing scientific puzzle: How come that an inactive treatment can be powerful enough to change experience and even physiology? While the idea to use placebos in clinical practice to sooth a patient's distress is controversial given that the patient-caregiver dyad is built on trust and non-deception, answering this question provides an opportunity to understand the effects of psychological factors of a treatment such as beliefs and expectancies more broadly. Shedding light on these psychological factors promises helpful for the development of medical strategies to improve the pharmacological effects of a treatment on health across many conditions, especially those where more conventional treatments have failed.

A growing body of literature from domains such as neurological disease, physiology, consumer, cognitive, social and affective neurosciences proposes that placebo effects are induced by multivariate factors. These multivariate factors are linked to the psychosocial cues of the specific treatment contexts (Benedetti, 2008; 2010; Enck et al., 2008) that are external to a person such as place (i.e. a doctor's office, hospital), type of treatment (i.e. surgery, drug, psychotherapy), social signals (i.e. eye gaze, medical caregiver empathy) or verbal suggestion (Wager and Atlas, 2015). The external cues have been shown to generate positive anticipations of a treatment outcome, also called "prognostic expectancies" (Kirsch, 1985), that are potentially learned from past experiences.

In this chapter we define the placebo effect as behavioral and physiological responses to a person's external (e.g., place, social cues, physical attributes of the treatment) and internal (e.g. thoughts, memories, emotions, expectancies) world during treatment. We outline what is known about the brain correlates of placebo effects from the pain domain, neurological disease such as Parkinson's disease and from everyday life behavior – outside the medical domain. We discuss the interactions between social and psychological processes, and how they mediate placebo effects. This overview of the growing literature on placebo effects and closely related phenomena reveals that placebo effects are an umbrella term for many different subprocesses, which may engage different and interacting brain systems.

The brain correlates of placebo effects

When facing a non-significant difference between the active treatment and the placebo arm of clinical trials, researchers typically conclude that the active treatment is inefficient. This is because the placebo arm is considered as an inactive control for nonspecific effects of treatment administration. Yet, paralleling the finding that placebos are more effective than waitlist control conditions, research on the neuroscience of placebo effects has provided evidence that a placebo effect is mediated by *active* processes in the brain.

Many of these active brain processes basically mimic the specific effect of a pharmacologically active medication. One milestone finding about placebo effects on pain was that placebo hypoalgesia (i.e., the reduction of pain experiences due to a placebo pain medication) can be blocked by the opioid receptor antagonist naloxone indicating that opioid pathways in the brain are a key mechanism of placebo action on pain mimicking the effects of opioid pain medication (Levine et al., 1978). Another seminal brain imaging study has demonstrated overlapping brain effects of the opioid remifentanyl and placebo analgesia in orbitofrontal cortex and rostral anterior cingulate cortex (Petrovic et al., 2002). Placebo effects on neurological diseases such as Parkinson's disease, on the other hand, have been shown to be mediated by enhanced activity in dopaminergic pathways (de la Fuente-Fernandez et al., 2001; Lidstone et al., 2010), and decreased neuronal firing in the subthalamic nucleus (Benedetti et al., 2004; 2016).

A lot more about the brain correlates of placebo effects is known from studies that use nociceptive pain as a model. For several reasons. First, pain is one of the most important symptoms across many clinical conditions. Second, pain can be easily evoked experimentally with minimal invasiveness and without causing lasting discomfort. Third, the ascending nociceptive pathways and neurophysiological correlates of pain are well established and thus provide a compelling test to probe the brain mechanisms of placebo effects.

Placebo hypoalgesia is accompanied by reductions in several brain areas that are related to the affective component of pain such as insula and anterior cingulate cortex (Wager et al., 2004; Meissner 2011). In addition, placebo hypoalgesia also seems to affect non-nociceptive components of the brain responses to pain, as quantified by a multivariate brain signatures of both nociceptive and non-nociceptive (i.e., expectancies, perceived control over pain) aspects of pain (Zunhammer et al., 2018). Specifically, placebo hypoalgesia is mediated by an increase in the non-nociceptive brain regions such as the ventromedial and dorsolateral prefrontal cortex and the ventral striatum (Meissner, 2011; Wager and Atlas 2015; Benedetti et al. 2005). The activation of these prefrontal cortex areas under placebo hypoalgesia is thought to engage a descending pain regulatory system (Fields et al., 2006) by their interaction with brainstem areas such as the periaqueductal gray (Bingel, et al. 2006; Eippert et al., 2009). High resolution fMRI of the spinal cord showed that decreased pain self-reports under a placebo pain medication was associated with reduced nociceptive activation of the dorsal horn (Eippert et al., 2009). These results favor the hypothesis that neural pain processing at very early stages is shaped by a form of gate-control through which ascending, nociceptive information from the periphery is modulated by descending, cortical top-down pathways associated with psychological factors of pain perception.

Beyond pain, a small but growing body of research has provided evidence that the activation of the vmPFC, dlPFC and ventral striatum also mediates placebo effects on other domains of behavior and experiences such as decision-making, emotion, pleasantness experiences and reward learning (Schmidt et al., 2017, 2014; Shiv et al., 2005; Li et al. 2011; Petrovic et al., 2005; Meyer et al., 2015, Koban et al., 2017). These findings suggest that there may be some ground for brain mechanisms that mediate different types of placebo effects across domains.

In theory, the vmPFC is an important hub to integrate all incoming information into "a coherent schema that informs and is informed by responses at other processing levels" (Wager and Atlas, 2015). This notion is in line with the idea from decision neuroscience studies that the vmPFC integrates different information into a valuation signal that drives behavior such as choices (Rangel, 2013; Lebreton et al., 2015), learning (Schmidt et al., 2014) or effort allocation (Schmidt et al. 2012). Furthermore, the vSTR might be specifically linked to a valuation process underlying placebo effects. Known a common neural currency for motivation (Schmidt et al., 2012), the vSTR could encode a kind of "wanting" to believe that one has received a painkiller that then indeed translates into a less painful experience. This idea is in line with the linking of striatal activation to dopamine functioning, that has been shown to be important for both

motivation (Schultz et al., 2017) and placebo effects (Lidstone et al., 2010). In contrast, the activation of the anterior prefrontal cortex (antPFC) and dlPFC under placebo effects overlaps with findings from social and affective neuroscience that has shown that this set of frontal cortex regions underpins the cognitive regulation of affective states (Blair et al., 2007; Lévesque et al., 2003; Ochsner et al., 2009; Petrovic et al., 2005) and is associated with a variety of executive functions such as working memory (Wager and Smith, 2003; Gilbert and Burgess, 2008) and goal-directed action selection (Charron and Koechlin, 2010; Kouneiher et al., 2009). According to these findings, these frontal brain regions could form a “gateway” that integrates incoming information from the environment with individual information from long-term memory (Gilbert and Burgess, 2008). One possibility could be that a person recruits this brain region when reflecting on the external information provided by the treatment context and her subjective beliefs and memories about how efficient a drug or a good is to provide clinical or everyday life benefit, respectively.

Although, interpreting the brain activation observed under placebo effects across domains in terms of specific associated psychological processes such as valuation, motivation and cognitive self-regulation is compelling, more research is needed to establish them as causal neurocognitive mediators of placebo effects. To date, most research on placebo effects extensible debates the relative contribution and causality of other domain-general psychological processes to placebo effects (Montgomery and Kirsch 1997; Benedetti et al., 2010). Notably, learning and prognostic expectancies.

The placebo effect - a learning phenomenon.

Animal studies from the 1960s have set a foundation for the causal involvement of learning such as Pavlovian conditioning to placebo effects (Herrnstein, 1962). Pavlovian conditioning has since been used as a procedure to generate placebo effects in the laboratory. For example, the repeated pairing of a positive treatment outcome, say pain relief, with an initially pain-unrelated cue (the conditioned stimulus, CS: a symbol on a computer screen, a tone, the color, taste, sound or odor of a drug or shape of an acupuncture needle) generates (1) an association of that CS with low pain, and (2) a consciously, accessible expectancy of the outcome when the CS appears. The robust, and replicable placebo hypoalgesia resulting from this procedure has been extensively harnessed to investigate the underlying brain mechanisms. Moreover, the repeated pairing of the ingredient-unrelated attributes of a drug or intervention with positive treatment outcomes is thought to occur also outside the lab generating placebo effects during clinical practice and everyday life.

Recent work in cognitive and affective neuroscience has advanced our understanding of how other types of learning beyond Pavlovian conditioning contribute to placebo effects. For example, the observation of other people, and even pure instructions and suggestions—what other people tell us to do or suggest us to expect—can influence behavior and experience (Koban et al., 2017; Necka and Atlas, 2018; Schenk and Colloca, 2020).

Observational learning refers to instances in which we learn by observing other people's actions, behaviors, and outcomes (Bandura, 1977). Regarding its brain correlates, it has been suggested that learning by observation involves similar mechanisms than learning by one's own aversive experience (Olsson and Phelps, 2007; Haaker et al. 2017). In the domain of placebo effects, several studies have adapted the standard passive cue-conditioning paradigm, in which one cue is conditioned to predict high and another cue to predict low pain, to an observational learning paradigm (Schenk and Colloca, 2020). In these observationally learned placebo studies, participants—instead of experiencing different heat pain stimulations themselves—learn about the consequences of different predictive cues from observing another person. Their results show that observational learning is as effective as learning by one's own experience, and more effective to induce placebo effects than a simple instruction

(Colloca and Benedetti, 2009). For example, Schenk and Colloca (2020) investigated the brain systems underlying social learning of placebo effects and have shown that increased connectivity between TPJ and dlPFC underlies this effect.

Further, a growing number of studies have tested how learning interacts with effects of social influence on behavior, valuation, and emotional states underlining placebo effects in a broader sense. A long tradition in social psychology has demonstrated the powerful effects of social norms on behavior and self-reported preferences (Cialdini and Kallgren, 1994). Recent brain imaging studies have shown that social influence such as disagreeing with peers increases activity in the anterior cingulate cortex and anterior insula, which are brain areas associated with the signaling of negative prediction errors or the need for adjustments (Klucharev et al., 2009; Campbell-Meiklejohn et al., 2010). On the contrary, agreeing with peers increases activation of brain areas associated with positive prediction errors such as the ventral striatum (Nook and Zaki 2015; Klucharev et al. 2009; Falk et al., 2010). These results indicate that this kind of social influence acts on brain systems that are also involved in direct learning, and potentially play a role for placebo effects.

Moreover, several studies have shown that social influence effects go beyond changes in overt behavior or self-reported preferences but also affect physiological and neurophysiological signals that indicate changes on 'deeper' levels. For example, Zaki et al. (2010) showed that social influence effects on self-reported liking are paralleled by changes in the brain's valuation systems, notably in the ventral striatum (Zaki et al., 2010). Moreover, the brain networks underlying social information and learning effects on pain can be partially separable (Koban et al., 2019). Whereas on a behavioral level, both social information and learning generate self-reported changes in prognostic expectancies about the efficiency of a pain medication, on the neurophysiological level different networks mediated social and learning effects. Specifically, learned expectations influenced pain via areas related to associative learning areas such as the hippocampus, whereas frontoparietal areas played a central role in mediating social influence effects on pain (Koban et al., 2019). This suggests that social influence effects may bypass learning mechanisms and directly engage frontal association areas to represent expectations and influence experience and behavior.

Instructions and learning may also interact in multiple ways in a kind of model-based, conceptual learning of pain modulation. In a study by Jepma et al. participants learnt to associate an abstract cue with a symbolic (or conceptual) representation of heat (a drawing of a thermometer indicating different heat levels). Importantly, during a test phase the abstract cues were followed by different levels of heat confirming and disconfirming the learnt expected pain, respectively (Jepma et al., 2015). The results showed that the same heat was perceived as more painful when preceded by the congruent cue that was associated with the symbolic representation of high heat, compared to the incongruent cue that was associated with the symbolic representation of low heat. Thus, conceptual learning might be as powerful as conditioning to shape expectations and modulate pain under treatment and placebo.

The placebo effects - an expectancy phenomenon

Both learning and instructions jointly and separately can lead to the formation of declarative memories, beliefs and anticipations of positive treatment outcomes that are termed prognostic expectancies. For instance, telling participants that a treatment was actually an inert cream strongly reduces the effects of conditioned placebo analgesia (Schafer et al., 2015), in line with evidence showing conditioning effects on pain are often mediated by consciously accessible expectations about pain (Kirsch 1985; Montgomery and Kirsch, 1997; Koban and Wager, 2016).

Whereas, the role of a person's prognostic expectancies about treatment efficiency, is an undeniable healing factor and a well-documented psychological mechanism of placebo effects, it is unclear whether the link between a person's placebo responses and his/her prognostic expectancy about a treatment outcome is linear. For example, not a lot is known about whether sweet spots of optimal expectancies exist that determine when a person is going to respond to a placebo, while below this sweet spot a person remains unresponsive to treatment. This is also important because holding too strong expectancies about a treatment outcome can lead to delusions and nocebo responses — defined as negative effects of a fake treatment based on the negative expectation of side effects (Hird et al., 2019). Furthermore, expecting analgesia from a pain medication comes with a varying degree of certainty, that is also shaped by the likelihood and amount of incoming sensory evidence (Yoshida et al., 2013).

The predictive coding model of placebo effects potentially accounts for such non-linear links between an expectancy, incoming sensory information and pain experience under placebo conditions. Inspired by models for information processing in the visual cortex (Rao and Ballard, 1999), predictive coding proposes that the brain makes predictions about treatment outcomes (lesser pain) and the likelihood of incoming sensory information (damage to the skin) via top down cognitive and bottom up sensory projections (Büchel et al., 2014). A Bayesian inference drawn from the product of the likelihood of neural activity encoding the prognostic expectancy of clinical benefit and the likelihood of incoming sensory information is then thought to generate placebo effects. To put it differently, if the prior, how much and how certain one expects low pain, is stronger than the incoming sensory evidence, the posterior probability of the neural response encoding pain, and reflecting the neural placebo response, will be more similar to the prior, expected pain than to the sensory evidence. Such a predictive coding framework can explain if and how strong a person will respond to a placebo, and has been shown as a plausible mechanism for placebo effects in the pain (Anchisi and Zanon, 2015; Geuter et al., 2017; Eippert et al., 2009) and anxiety domains (Meyer et al., 2015). While predictive coding is an elegant model for how the brain makes sense out of external and internal information, its predictions remain to be tested in other less aversive domains of placebo effects beyond pain and anxiety.

Psychological processes contributing to placebo effects beyond learning and prognostic expectancies

A core statement of the classical placebo motivation model is that “patients who are motivated to get better are also more likely to get better” (Hyland 2011). This idea has been investigated by many studies in psychology to tackle the motives (goals) that potentially bias a patient's responses to treatment (see Hyland 2011 for review). It is unclear though what a patient's motivation to get better actually means in the face of chronic disease. One aspect of chronic, neuropathic pain for example is that a patient's motivation to avoid pain is delusional given the unavoidable neural damage that causes the pain. One may argue that chronic, neuropathic pain patients are then less sensitive to placebo effects. Though, a few, but well-controlled studies suggest that placebo effects in chronic pain can be quite substantial (see Vase et al., 2016 for review). An alternative hypothesis suggests that a doctor's suggestion of clinical benefit or learning may generate a motivational process that helps coping with the pain on an everyday life basis.

An important determinant of motivational processes is reward sensitivity. Reward sensitivity is defined by how much a person or the brain's hedonic valuation system, formed by brain areas such as the vmPFC and ventral striatum (Lebreton et al., 2015; Bartra and Kable, 2013), responds to the magnitude of expected or received reward. It can be measured with probabilistic monetary reward behavioral paradigms such as the motivational incentive task (MIT) task during which participants have to choose between three different cues. Each choice can lead to a reward with a likelihood of 30%. Thus, reward occurrence is always unexpected,

an incident that reliably activates the brain's hedonic valuation system (Knutson et al., 2001; Bartra et al., 2013). Importantly, the ventral striatum activation following unexpected, monetary reward scales with the strength of placebo effects across domains. For example, participants who show stronger ventral striatum activation in response to unexpected, monetary reward also self-report lesser pain under placebo pain medication (Scott et al., 2007, 2008). In line with these findings, studies from consumer neuroscience showed that the marketing placebo effect of a wine's price label on taste pleasantness is determined by inter-individual differences in the brain's hedonic valuation system's sensitivity to monetary reward (Plassmann et al., 2010; Schmidt et al., 2017).

Reward sensitivity is further determined by the neurotransmitter dopamine, which also plays a crucial role for placebo effects. For example, tonic dopamine levels in the ventral striatum are correlated to self-reported placebo hypoalgesia. Moreover, positron emission tomography (PET) using dopamine D1/D2 receptor markers such ^{11}C Raclopride have provided insights into the link between placebo effects and central dopamine levels in Parkinson's disease. ^{11}C Raclopride competes with dopamine on the binding to D1/D2 receptors in the basal ganglia. PD patients, who expected clinical benefit from a placebo, that was deceptively labelled as a dopaminergic drug, displayed a decreased binding potential of ^{11}C Raclopride in the basal ganglia (Fuente Fernandez et al., 2001; Lidstone et al. 2010). This finding indicated that the placebo triggered dopamine release potentially via the activation of midbrain dopamine neurons. One can draw two alternative conclusions from this finding. The dopamine release under placebo can be a domain-specific response that reflects the neural placebo response typical for PD patients, and mimics the effects of dopamine medication. Alternatively, midbrain dopamine neurons play a reward signaling role. Specifically, electrophysiological studies in monkeys have shown that midbrain dopamine neurons activate and release dopamine into the ventral striatum when the monkey receives an unexpected reward or sees a conditioned stimulus (CS) that is associated with reward (Schutz et al., 2017). In the context of placebo effects that are potentially generated by learning from prior positive treatment outcome experiences, a CS (e.g., the color, taste or odor of a drug, the white lab coat of the physician) associated with clinical benefit should thus trigger enhanced dopamine release into the brain via the activation of midbrain neurons. Yet, more research is needed to test such a causal role of midbrain dopamine learning signals for placebo effects.

The finding that a placebo enhances dopamine levels in the basal ganglia points toward another interesting possibility. Dopamine is a necessary neurotransmitter for motivational processes that translate an expected reward into a behavioral activation (e.g. effort, choices, learning) (Haber et al., 2011; Schultz et al. 2017). For example, untreated PD patients display a deficit in motivation that is characterized by increased apathy on the clinical level, decreased learning from reward and attenuated effort allocation according to the magnitude of expected reward (Frank et al., 1999; LeBouc et al., 2016; Palminteri et al., 2009; Schmidt et al. 2008). The motivational deficit is reduced after treatment with levodopa (Frank et al., 1999; Palminteri et al., 2009), which is metabolized by the brain into dopamine. One hypothesis therefore is that a placebo, potentially via the activation of dopaminergic pathways enhances behavioral components of motivation such as reward learning (Schmidt et al. 2014; Turi et al. 2017). Schmidt et al., 2014 have tested this hypothesis by combining placebo and pharmacological manipulations with a well-characterized instrumental learning paradigm (Schmidt et al., 2014). The results indicated that a placebo in form of a sham dopaminergic drug administered together with verbal suggestions about its efficiency enhanced reward learning behavior and the activation of the reward value-encoding vmPFC. This result indicates that the mere expectation of clinical benefit can enhance a patient's incentive motivation for other types of expected reward such as money.

The finding that expectancies of clinical benefit enhance learning and learning-related signals in the brain further raises the potential of feedback cycles in which prognostic expectancies of positive treatment outcomes and experienced reward are mutually reinforcing. Such a

feedback cycle underpins the very human tendency to search for confirmation of beliefs also known as a self-fulfilling prophecy. Prior beliefs that bias or hinder learning based on novel sensory experiences have recently been studied in the domain of pain (Jepma et al., 2018). A study by Jepma et al., 2018 demonstrated that participants updated their expectations during learning more based on information that confirmed their prior beliefs than based on information that was not in line with those prior beliefs. Learning biased towards confirming rather than disconfirming prior beliefs can explain why expectation effects such as those seen in placebo effects do not extinguish over time and can then lead to persisting fake beliefs over time even in the presence of contradicting evidence.

Conclusion

Research on the cognitive and affective neuroscience of placebo effects has much advanced the understanding of the neurocognitive mechanisms that mediate placebo effects on behavior, experiences and physiology. While placebo effects are a well-recognized phenomenon, whether these underlying neurocognitive mechanisms are domain-specific or domain-general is an ongoing debate. The similarity of brain activation across different experimental contexts and types of placebo effects is compelling, but it does not allow generalization or inferences about the underlying causal mental states (Poldrack & Yarkoni, 2016). This is important, because such inverse inferences can seriously mislead the scientific understanding of placebo effects. A lot of work has been done for understanding placebo effects on pain, revealing that there is likely not a single underlying mechanism, but many different subprocesses that contribute to placebo effects. Investigating whether pain-unrelated neurocognitive processes also mediate placebo effects in other less aversive behavioral domains is important and should be addressed by more future research studies. In summary, identifying what and how mental and neurophysiological processes translate a placebo into a placebo response is useful for refining diagnosis and for developing treatment strategies that combine psychological and pharmacological factors. Such an approach also favors the development and recognition of more holistic treatment strategies that consider the person as a whole, and not only specific symptoms in order to promote health and well-being.

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