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Placebo hypoalgesia: above and beyond expectancy and conditioning

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Abstract

Placebo hypoalgesia provides pain relief for individuals via the expectation of a beneficial or therapeutic outcome, while nocebo hyperalgesia results in increased pain in response to anxious anticipation of harmful outcomes. These forms of placebo pain modulation can be induced through repeated associations, verbal cues, and social interactions. Understanding these methods of pain modulation can provide greater insight into the psychosocial contexts of pain modulation, as well as develop novel approaches to pain management.

Keywords

Conditioning; Expectation; Learning; Pain; Placebo; Social observation; Interpersonal Interactions

Introduction

The terms placebo (Latin for *I shall please*) and nocebo (Latin for *I shall harm*) describe the positive and negative aspects of cognitive modulation of behaviors, responses, and outcomes [1]. Since the pioneering publication by physician Henry K. Beecher in 1955 highlighted the significant evidence suggesting the tangible benefits induced by placebos [2], placebo research has propelled experimental and clinical use to reduce symptoms in a variety of conditions including asthma[3], irritable bowel syndrome [4], anxiety [5], Parkinson's Disease [6], depression [7], and addiction [see Ref. 8].

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Conflicts of Interest
None.

The most studied and clinically applied placebo and nocebo knowledge is centered on pain [1,9–15]. Pain is an incredibly subjective experience, often being molded by a variety of components that creates a unique sensation for the individual (See Figure 1). Placebo-induced hypoalgesia and nocebo-induced hyperalgesia, refer to the reduction and heightening of pain experience due to cognitive modulations [1]. From a psychological standpoint, two broad mechanisms, namely expectancy and conditioning, have been reported as the primary mechanisms that elicit placebo and nocebo effects [4,11,16–18]. Only until recently the two broad mechanisms of expectancy and conditioning have not been simplistically reduced and viewed as alternative and conflicting forces, but rather complementary in their essential roles for forming placebo and nocebo effects [19]. More specifically, learning can be cognitively mediated and can elicit analgesia when relationships between events are acquired and verbal instructions can amplify the effect of automatic processes [20]. Here, we illustrate the psychosocial and behavioral mechanisms behind placebo-induced hypoalgesia and nocebo-induced hyperalgesia, as well as point to future areas of later research.

Conditioning

Ivan Pavlov's seminal experiment with dogs developed the classical conditioning paradigm that now forms the basis for a major mechanism facilitating placebo-induced hypoalgesia. In this classic experiment, Pavlov noticed that a dog begins to salivate (i.e. the unconditioned response - UR) when it saw and smelled of food (i.e. unconditioned stimulus - US). Pavlov began to pair the scent and sight of food with the sound of a bell (i.e. the neutral stimulus - NS). Eventually, Pavlov began to only ring the bell (i.e. conditioned stimulus - CS) and was able to elicit a salivary response from the dog [21].

A similar conditioning process has been performed to induce pain modulation in numerous human and nonhuman experiments, often using simple visual cues as the neutral stimulus. For example, an experimental painful stimulus, such as a shock [22,23], ischemic arm pain [16], thermal stimulation [15,24–26] may be paired with a certain color or text, while a non-painful stimulus, is associated with another. During the test phase, the same painful stimulus is applied surreptitiously, regardless of the change in visual stimuli and their associated meanings of pain. When this experimental paradigm is applied, subjects consistently reported lower levels of when the stimulus associated with low pain was made presented. In an earlier study, it was determined that certain visual cues paired with painful stimuli conditioning treatments may induce a robust placebo analgesia, strong enough to last for up to 4–7 days in length [9].

In placebo research, pharmacological conditioning has been used before the brain imaging advent. Pain medication or other pain treatments (US) cause pain reduction (UR). Pairing an inert substance (NS), taking the form of a pill, gel, cream, or other delivery device, with the active pain medication over a process of time, acts as the conditioning process. The unconditioned stimulus can be removed and the inert substance (CS) begins to exhibit similar drug-like physiological effects (CR). Working within the conditioning framework, further proof-of-concept studies refine understanding of this process.

An exciting research avenue is represented by pharmacological conditioning and dose-extending placebos. It is important to note that the concept of dose-extending placebos was posited by Robert Ader. Indeed, Ader and Cohen observed that merely giving a placebo such as a sweet-tasting saccharine solution following the administration of cyclophosphamide, an immunosuppressant and chemotherapy agent, induced a measurable immunosuppression response in rats [27]. Interestingly, there was a dose-response effect: rats that received two doses of cyclophosphamide during the conditioning phase had greater conditioned immunosuppression responses than those that received one dose of cyclophosphamide, suggesting that the stronger the US, the more robust the CR [27]. More recently, Ader et al. completed a recent clinical trial that demonstrated the effectiveness of conditioning with corticosteroids in patients with psoriasis [28]. Patients were treated under experimental arms that varied in dosing and drug administration schedules. A group of patients were treated under a partial reinforcement schedule, in which a full dose of corticosteroid was given 25%–50% of the time and placebo medication other times; dose control group received 25–50% of the initial dose but no placebos; and a continuous reinforcement group (active drug every time) receiving 100% of the initial dose. The partial schedule of pharmacotherapeutic reinforcement with corticosteroid administration and placebos given only one quarter or half as frequently as currently prescribed was sufficient to treat psoriasis. Indeed, the results were clinically comparable to the reduction in symptoms induced by a full-dose of corticosteroids. Pharmacological conditioning creates a *memory* of the learned response that can be re-evoked over time.

Guo et al. investigated the differences in effect caused by prior pharmacological conditioning by administering an opioid or non-opioid drug to mice [29]. Mice were subjected to a form of the widely-used hot plate testing scheme, measuring the time it takes for the mice to react to the noxious heat stimulus as the response latency. Conditioned cues were paired with either morphine hydrochloride, the opioid agonist, or aspirin, the non-opioid nonsteroidal anti-inflammatory drug (NSAID). Naloxone, an opioid antagonist, was administered to the mice in both experimental conditions. The results demonstrated that the mice that underwent pharmacological conditioning via morphine administration not only experienced placebo analgesic responses, but these responses were antagonized by naloxone. These findings suggest that the endogenous opioid system mediates this effect. By contrast, after conditioning with the NSAID aspirin, the conditioned placebo effects were not blocked by naloxone, indicating that the substance used during the conditioning phase triggers the appropriate underlying systems leading to a specific effect.

Amanzio and Benedetti showed that the administration of morphine for two consecutive *days* produced substantial placebo responses when the placebo is given on the third day [16]. Future research demonstrated prolonged conditioning schedules consequently led to longer lasting placebo effects. In 2007, Benedetti et al. [30] applied the principles of pharmacological conditioning from a clinical setting to the simulation of a sports competition, where the subjects, or *test athletes* underwent different training regimens, with or without the administration of morphine, and then competed in a mock competition where their performance (i.e. pain tolerance to ischemic arm pain) was assessed. The experimental group receiving intramuscular morphine twice over two weeks during the pre-competition conditioning, and finally a placebo during the competition itself, performed the best with

greatest pain tolerance out of all four of the experimental groups. Another result from this study was gleaned from the crucial distinction that one experimental group partook in a pre-competition conditioning scheme with the morphine; however, on the day of the competition, the placebo and naloxone were administered. This experimental group performed similarly to the experimental groups that did not receive the pre-competition conditioning at all; this result suggests that the placebo-induced analgesia from pharmacological conditioning results in the release of endogenous opioids within the body itself. This echoes the aforementioned literature on pharmacological conditioning. The effect of pharmacological conditioning managed to significantly influence the subjects' pain endurance several days after the last active analgesic dose.

Colloca et al. demonstrated that similar effects can be elicited with a nonpharmacological-based conditioning paradigm, whereby the experience of analgesia is induced by electrical stimulation and coupled with a surreptitious reduction of pain to create the conditioned response [19]. Thus it has been determined that the number of conditioning trials is positively correlated with the strength and the length of the placebo and nocebo effects experienced by the subjects [32]. The longer and more pronounced effects the conditioning trials elicited, the more powerful the placebo effect for the individual. The clinical applications of these findings may allow for higher quality, both in terms of duration and efficacy, placebo-induced analgesia. In the case of pharmacological conditioning, it is important to note that the drug-induced pain relief rather than the drug per se drives placebo effects. It has been demonstrated that individuals have to perceive an effective drug response in order to observe a pharmacological conditioned response [1]. In terms of non-pharmacological conditioning, naloxone antagonizes conditioned placebo effects that are elicited by prior exposure to hypoalgesic stimulations providing further evidence that endogenous opioids are also released during non-pharmacological conditioning in pain and placebo settings [32]

Expectancy

Kirsch originally posited an earlier alternative perspective to the conditioning framework based on an expectancy model: a placebo or nocebo produces an effect because the individual expects it to do so [18]. The individual in question must synthesize information from the external environment, as well as internal beliefs and prior experiences, to form a response expectancy [18]. The expectancy model involves mechanisms that facilitate potential placebo and nocebo effects. Complex psychosocial interaction lies in the center of the expectancy model. Verbal cues and suggestions have successfully produced placebo-induced analgesia, causing individuals to form expectations of pain relief by recalling prior experiences or treatments.

The role of expecting the positive benefits from therapy is evident in the overt versus covert administration of active medication [6]. Colloca et al. discussed the differences between open and hidden injections of four painkillers: buprenorphine, tramadol, ketorolac, and metamizol. When the drug was openly administered, the doctor stated that the drug was a powerful analgesic. When the drug was hiddenly administered, the drug was pumped through an automatic infusion machine without any clinician in the room to signal the

presence of the drug's use. The authors found that a 50% higher dose was needed for the hidden injection to induce similar analgesic effects as the open injection [for a review, see 6].

Conversely, prior negative treatment experiences may jade future attempts, reducing the therapeutic benefits and potentially increasing likelihood the harmful effects. Bingel et al. investigated the mechanisms regarding differing patient's beliefs and expectations may alter their likelihood of experiencing beneficial or harmful effects of a drug [24]. Bingel et al. administered the analgesic opioid remifentanyl to healthy volunteers in three experimental conditions: first, no expectation of pain relief, second, positive expectations of pain relief, and third, negative expectations of pain relief. The opioid remifentanyl and its potential therapeutic benefits, or lack thereof, were pitted against a constant source of painful thermal stimulation. Using fMRI, Bingel et al. mapped the brain activity of the patients and found that positive expectancy of the treatment doubled the effects of the drug, while negative expectations severely reduced the efficacy of the drug. These results suggest that a patient's beliefs and expectations can greatly influence the therapeutic potential of the treatment [24].

Treatment history often shapes an individual's expectations, as previous positive experiences may further enhance or ensure future positive experiences. André-Obadia et al. highlighted the importance of timing when administering a placebo by comparing the analgesic effect of using repetitive transcranial magnetic stimulation (rTMS), to treat chronic neuropathic pain either before or after a sham rTMS [10]. The research group found that pain relief was significant only if the sham rTMS followed a successful active rTMS treatment, while pain increased when the sham rTMS was administered after an unsuccessful rTMS treatment. In fact, patients with more positive experiences with the rTMS treatment reported 11% pain reduction, while patients with negative or unsuccessful rTMS treatment sessions reported a 6% increase in pain. This result not only indicates the existence of placebo analgesia, but also nocebo hyperalgesia [10]. However, there is no systematic evaluation of the impact of explicit contingency on the conditioning for placebo effects. Nevertheless, we do know that when expectation is successfully boosted by conditioning, there is a positive relationship between expectations and placebo effects.

Social learning

Social observational learning involves gaining, processing, and synthesizing information from others as an observer without experiencing the event first hand [see Ref. 33]. Colloca and Benedetti performed the first experiment to determine the role of observational social learning in placebo-induced analgesia [34]. The subjects were divided into three experimental groups, each assigned an unique means of inducing placebo analgesia: first, observing a demonstrator showing an analgesic effect when painful stimuli were paired with a green light, second, conditioning via visual stimuli, or third, expectancy via verbal suggestion. The results demonstrated that the participants assigned to the observational social learning paradigm produced similar placebo effects to those assigned to the conditioning treatment indicating that placebo effects can be finely shaped by mechanisms that go beyond first-hand experiences.

Hunter et al. performed the first study to compare the use of pre-recorded observation versus in-person observation in the role of placebo-induced analgesia [35]. The research group assigned 60 healthy women to four experimental arms: first, social observation via video, second, social observation via person, third, verbal suggestions, and fourth, a control/natural history group. A unique low pain stimulus was associated with a green visual cue and a unique high pain stimulus was associated with a red visual cue. However, during the actual test, the same painful shock was delivered to induce a pain response in the participants in each other the experimental arms, regardless of the type of visual cue. The magnitude of pain reduction was greatest for the subjects that experienced social observational learning by witnessing the in-person demonstrator, confirming early results. However, social observational learning via pre-recorded videos also induced similar levels of pain relief; the magnitude of pain relief was much greater than the pain relief experienced from verbal suggestions alone. This was the first study to demonstrate that pre-recorded videos could have a significant placebo-induced analgesia effect [35].

Nocebo effects can also be that participants that engaged in the social observational learning paradigm experienced greater pain intensities than those that were given only verbal. Vögtle et al. examined the potential nocebo effects garnered from social observational learning [36]. An inert ointment was placed on the arms of subjects and accompanied by one of three conditions: first, no comment on the ointment's characteristics, second, verbal instruction that the ointment will heighten pain sensitivity to pressure pain, and third, social observational learning via a video with a demonstrator undergoing the same procedures as the subject. Subjects that underwent the social observation learning experienced greater pain intensities than those in the other experimental arms.

Colloca's first study on social learning [34] and the following line of research derived from this study, challenged the dualism between expectancy and conditioning introducing the concept of rethinking of placebo and nocebo effects in an integrative way [1,37].

Beyond expectancy versus conditioning

While expectancy and conditioning models are often pitted against one another as opposing theories, more research has begun to detail the interactions between the models [1,37]. Conditioning paradigms contribute to expectancy held since learning through prior experience can influence internal beliefs regarding treatments, clinicians, and other environmental factors. Klinger et al. demonstrated this with a study involving subjects with or without atopic dermatitis, as the subjects were assigned to different experimental groups, with all groups being given an inert ointment to treat the pain, yet were told different briefings, ("Ointment is neutral" vs "Ointment reduces pain") [38]. It was found that only briefing the subjects was not enough to cause pain relief, as only the experimental group that also received some form of conditioning experienced pain relief [38].

Kirsch et al. attempted a new experiment in order to clarify the purposes and roles of expectancy and conditioning in placebo-induced analgesia with experimental pain relief through verum (i.e. true) acupuncture or sham acupuncture, were able to conclude that conditioning altered the effect of expectancy substantially [19].

These and other studies support the concept that the role of conditioning in relation to expectations is that conditioning can be viewed as the *process of generating* expectancies [11].

Do we people respond differently to placebos?

Personality traits have only recently been linked to the occurrence of placebo responsiveness in individuals. Links between hypnotic suggestibility, dispositional optimism, and empathy have all been correlated (yet no causal effects) to placebo hypoalgesia. Dispositional optimism refers to an individual's ability to have confidence about the positive or successful outcome of the future. Past literature have shown a correlation between an individual's degree of dispositional optimism and the magnitude of the placebo effects they experience as a result of treatment [39–41]. Geers et al. further explored this development by randomly assigning optimists and pessimists to a placebo expectation condition or a no expectation condition before a completing a cold pressor task. The results of the study suggested that optimism was not only associated with the higher likelihood of evocation of placebo effects, but also a lower pain magnitude when compared to pessimists [40]. Later research conducted by Hanssen tested the ability to induce optimism in subjects through writing about and visualizing a future best self before subjecting them to the similar pain cold pressor task paradigm. The results of the experiment suggested that not only was a statistically significant difference between optimism scores pre- and post- manipulation, but those that did achieve this temporary state of optimism reported less pain intensity when completing the cold pressor task [42].

Hypnotic suggestibility may have a role in modulation expectations as well, increasing the likelihood of experiencing placebo effects. In a study experimenting with the role of suggestibility and its role in placebo analgesia [43], placebo analgesia was produced via a conditioning procedure with electrical shocks. Pairing electrical shocks with placebos did successfully induce placebo analgesia; however, differences in pain intensity reports when compared between the subject were found in subjects with high suggestibility [43]. Interestingly, highly suggestible subjects tended remember the initial pain intensity to be much higher than they originally were. Another important distinction is that children tend to be more suggestible than adults; a heat pain paradigm revealed the resulting magnitude of the placebo effects (e.g. heat pain tolerance and heat pain threshold) being several times greater than that of adults [44].

The empathy trait allows individuals to understand and grasp how another being is feeling. In an aforementioned study [34], the authors found that the beneficial effects of in-person social observational learning were positively correlated with empathy scores the individual produced from the questionnaires. Although in-person social observation leaning also seems to be positively correlated with empathy and greater magnitudes of analgesic effects, social observational learning via pre-recorded video does not seems to correlate the variables of empathy scores and analgesic effects [35]. In an aforementioned article illuminating the interaction between social observation and placebos [35], the authors found no significant correlation between empathy scores and nocebo responses. The authors found no significant correlation between empathy scores and nocebo responses [36]. This may suggest that while

empathy is an important factor for grasping how another being is feeling, placebo effect and nocebo effects may not be influenced by a person's ability to empathize.

Applications of placebo effects

A crucial element to the formation of placebo-induced analgesia is the communication between the intended subject and the clinician or researcher involved. Often, a unique psychosocial interaction between patients and clinicians may elicit certain expectations of benefit and healing. Benedetti [45] explored the intricacies between placebos and the relationship between doctors and their patients, emphasizing the internal beliefs and memories held by the patient that meld with the sensory and social input, such as the sight of medical professionals, interaction with other patients, and other contextual factors that surround the therapy itself [45]. A four step process underlies the doctor-patient relationship: feeling seek, seeking relief, meeting the therapist, and finally receiving therapy [45]. Special emphasis is placed on the third and fourth steps since the factors that can elicit the placebo effect is most readily observable there. When a patient meets the therapist, a set of values and emotional responses are exhibited by both parties. The patient, feeling physically, emotionally, and/or mentally sick and uncomfortable, comes with trust and hope of potential relief; the doctor must hold compassion and empathy to understand how one may feel when witness such pain.

Enck et al. suggested enhancing the doctor-patient interaction by promoting respectful, meaningful, and collaborative discussion between the two parties involved is of the upmost importance when maximizing placebo effects, while minimizing nocebo effects [46]. Anticipation of negative or nonexistent treatment effects is sufficient to induce nocebo effects, such as listing symptoms of a condition or side effects of a medication [11]. Concerns arise when balancing the need to provide effective therapeutic care and the right of the patient to be aware as to what procedures or treatment plans they will potentially undergo. Wildly presenting a treatment in an optimistic manner by minimizing explanation of the potential negatives infringes on the patient's ability to make an adequately informed decision regarding treatments.

Because of the sensitivity of doctor-patient interactions, the risk for nocebo effects to cause undue harm is a serious ethical concern. Friesen and Blease [47] argued that health disparities due to the implicit biases held physicians and health care clinicians may place racial and ethnic minorities at a greater risk of being affected by nocebo effects than their white counterparts. Doctor-patient interactions were more likely to be of lower quality, typically lacking in warmth, empathy, support and patient interaction with individuals from racial and ethnic minorities, further increasing the likelihood of harm being experienced [47]. Although no direct cause or link has been determined, indirect inferences can be made based on the principles of the placebo and nocebo effects explored so far by research.

Gaps in placebo and nocebo research

There is lack of literature revealing interactions between psychiatric disorders and pain relief via placebo-induced hypoalgesia. Considering that in 2011, it was estimated that a little less

than 1 in 5 U.S. adults suffered from a mental illness in the previous year [8], a growing subset of the population will have psychiatric conditions that may or may not interfere with the potential therapeutic benefits gained from placebos indicating a need for a new avenue for future research. Also, nocebo effects are not studied nearly as frequently as placebo effects due to the potential ethical concerns. However, the experiment proving the potential to induce nocebo effects through media [see Ref. 35] opens new doors into further research on the depiction of pain and suffering and potential nocebo effects inflicted upon individuals and society at large.

Conclusions

With problematic and debilitating pain plaguing millions of individuals across the globe, the growing number of funding going towards researching novel methods of pain reduction validate the need to continue to push the boundaries of effective treatments. Once written off as a nuisance variable to control for or as a sham treatment meant to maliciously deceive, placebo effects have been validated to show remarkable effects on pain modulation. While various perspectives have revealed much needed details regarding the placebo effect, it is wise to believe that multiple components make up the overall placebo effect, rather than compete against one another.

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Highlights

- Placebo analgesia is changed through biological, cognitive, and social factors
- Pharmacological conditioning can produce placebo effects over time
- The quality of doctor-patient interactions can improve or impede treatment outcomes
- Placebos raise concerns in areas of clinical practice, disparities, and doping

Figure 1. Placebo hypoalgesia.

Pain is a subjective sensation unique to the person currently experiencing it. Three broad categories of factors can influence the placebo hypoalgesia: psychobiological (e.g. endogenous opioids, genetic polymorphisms of mu-opioid receptors, etc.), cognitive (e.g. attention to painful stimulus, emotional response to pain, etc.), and sociocultural (e.g. the context in which pain is applied, disparities in pain management, interpersonal interactions etc.) factors. These factors interact with one another as well, potentially amplifying, minimizing, or changing the painful experience.