The Placebo Effect: A Psychosocial and Neurobiological Review Emphasizing Pain

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Abstract

The placebo effect is currently understood as a psychosocial and neurobiological interaction in which individuals' expectation of effective treatment initiates a biological response to facilitate symptomatic relief. In this review, the literature describing the placebo effect in experimental and clinical pain is synthesized. The various methods of inducing placebo, including verbal suggestion, social cues, expectancy manipulations, open/hidden administration, and classical conditioning are included. Both opioid and non-opioid placebo mechanisms are explored based on studies using naloxone and proglumide to investigate opioid presence. Finally, an overview of neuroimaging studies is presented in which positron emission tomography, event-related potential, and functional magnetic resonance imaging findings are discussed. Conclusions and implications of the studies reviewed are presented at the end.

Keywords: analgesia, expectation, naloxone, pain, classical conditioning, placebo, verbal suggestion

Historically, the placebo effect has been shown in negative light. Hooper's Medical Dictionary (1811) defines it as "an epithet given to any medicine adapted more to please than to benefit the patient" (Wolf, 1959). Currently, a theme in medicine has emerged that a doctor should keep a detached perspective when administering treatment, since clinical practice is overwhelmingly distressing with too much emotional involvement (Cheng, Lin, Liu, Hsu et al., 2007). The role of administering treatment, however, may be underplayed, in that the investigation of the placebo effect has shown growing implications for clinical practice. For instance, the magnitude of placebo response is a key factor in deciding the difference between a new treatment and revealing a sham drug (Kleijnen, de Craen, van Everdingen and Krol, 1994). Alternatively, the placebo effect can be a means of investigating the mechanisms essential in understanding effective treatments. As an example, changes in brain activity during placebo in patients with depression have been a recent focus of investigations looking for effective means of treatment (e.g., Andrews, 2001). In these two respects alone, the placebo effect is more than a quirk in human psychology; it represents the power of the mind-body interaction as well as a porthole into clinically relevant therapy.

Finding a working definition of the placebo effect has been an ongoing problem in the literature. Price, Finniss, and Benedetti (2008) define the placebo response as alleviation in symptoms or change in the condition of an individual caused by a simulation of treatment with no active ingredient. For research purposes, the placebo effect is defined as the difference between the natural history of an individual (i.e., untreated) and their condition after

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simulated treatment with an inert substance. These kinds of definitions, however, may not be comprehensive, demonstrating limitations by the complexity in the literature. For instance, covertly using an active therapy shows a weaker alleviation of symptoms than an open therapy, demonstrating a placebo type effect with active ingredients, and that placebo is not strictly involved with inert drugs (e.g., Bingel, Wanigasekera, Wiech, Mhuircheartaigh et al., 2011). In addition, different administrations of inert substances can yield different magnitudes of symptom alleviation. For example, it has been shown that placebo pills are less effective than placebo surgery (Kaptchuk, Goldman, Stone & Stason 2000).

Another challenge in describing the placebo response regards the number of different conditions in which placebo response can be tested. Clinically, the placebo effect has been demonstrated in a number of conditions, including clinical depression, Multiple Sclerosis, and Parkinson's Disease (Andrews, 2001; Noseworthy, Ebers, Vandervoort, Farquhar et al., 1994; Diamond, Markham & Treckiokas, 1985) while experimentally, placebo has been induced using heat pain, ischemic pain, and electric shock pain among others (Price, Milling, Kirsch, Duff et al., 1999; Benedetti, 1997; Zubieta, Bueller, Jackson, Scott et al., 2005). These conditions represent a significant number of permutations in which the placebo magnitude and neurological basis could exist. Ideally, an integration of data on placebo effects covering all domains would serve to further validate conclusions. However, considering all the double-blind clinical trials which may describe some placebo effects, much of the clinical research is beyond the scope of this review. Thus, the main focus of this review will be on pain and placebo analgesia, a key area in experimental research and a significant portion of clinical research. Finally, the reviewed studies were included based on sampling the major psychological and conditioning methods for inducing placebo, major subjective pain rating and objective methods of measuring placebo, as well as surveying previous reviews of placebo as a starting point (e.g. Benedetti, Mayberg, Wager, Stohler & Zubieta, 2005; Price at al., 2008). In addition to synthesizing both psychological and neurobiological mechanisms in placebo, the present review also describes evidence for alternative views such as report bias and its ethical implication for placebo study.

Evidence for Psychosocial Factors Mediating Subjective Pain

Far less attention in the placebo literature has focused on non-opioid mechanisms. The studies that characterize this response mainly implicate classical conditioning as a key element in their potentiation. In placebo analgesia by classical conditioning, the active analgesic first provided is the unconditioned stimulus (US), and its accompanied analgesic effect the unconditioned response (UR). When the similar looking placebo replaces the analgesic, it becomes the conditioned stimulus (CS), which produces the conditioned analgesic response (CR). Illustrating this, Amanzio and Benedetti (1999) conducted an experiment using the paradigm of ischemic arm pain in healthy participants, while manipulating the use of expectancy cues, opiate conditioning, and non-opiate conditioning. That is, some participants received only expectation cues and no conditioning, some participants received drug conditioning, either opiate (morphine) or non-opiate (ketorolac), without expectancy cues, and some participants received both expectancy cues and drug conditioning (either opiate or non-opiate). Placebo was found with expectancy cues alone, which itself was naloxone (opiate antagonist) reversible. Expectancy and morphine conditioning combined placebo responses were also naloxone reversible. However, expectancy and ketorolac combined placebo response was only partially reversible, while ketorolac drug conditioned placebo response alone was naloxone insensitive. Thus, when ketorolac (US; a non-opioid analgesic) was used to inhibit pain (UR) and subsequently replaced with placebo (CS), the analgesic effect that resulted could not be reversed by naloxone. This seems to indicate expectations induced by psychosocial cues rely exclusively on endogenous-opioid systems, while conditioning can initiate either opioid or non-opioid mediated placebo response sub-systems.

In another study comparing and contrasting classical conditioning and verbal suggestion, Benedetti et al. (2003) have shown that verbal suggestion can antagonize conditioning procedures. Conditioning of analgesia in healthy volunteers experiencing experimental ischemia as well as conditioning of increased motor performance in Parkinson's patients was disrupted when verbal suggestion revealed the conditioning procedure used a sham drug. However, when conditioning the hormonal drug secretion of serotonin agonist sumatriptan (acting on the $5\text{-}HT_{1B/1D}$ receptor that produces increased growth hormone and decreases cortisol secretion), subsequent antagonistic verbal suggestions of opposite hormonal changes were found to have no antagonizing effects during a subsequent placebo trial. While the findings suggest that conscious processes like subjective pain and motor performance may be in the purview of expectancy manipulation, unconscious processes like hormone secretion and non-opioid analgesia may be beyond the scope of expectancy effects, but rather in the scope of conditioning effects. Furthermore, it indicates separate systems of conscious and unconscious learning in the placebo response.

Classical conditioning in placebo has also been shown to have a host of autonomic effects, including changes in blood flow, blood pressure, heart rate, respiration, skin conductance, immunological function, and gastric activity (Ronel, Mehilli, Ladwig et al., 2011; Meissner & Ziep, 2011; Kemeny, Rosenwasser, Panerrieri, Rose et al., 2007; Mikalsen, Bertelsen, & Flaten, 2001; Vits, Cesko, Enck, Hillen et al., 2011; and Meissner, 2009). However, the distinction between placebo effect and classical conditioning requires elucidation, especially considering Montgomery and Kirsch's (1997) argument that placebo is exclusively mediated by expectation. Placebo effect, by definition (Price et al., 2008), seems to require a level of cognitive expectancy and conscious awareness of active treatment administration. Alternatively, classical conditioning readily occurs in animals that do not seem to grasp the concepts of an inert drug or active ingredient and the idea of revealing the inert nature of a drug (Bitterman, 1964; Pavlov, 1927). Conditioning may induce expectation, but expectation need not be induced by conditioning. For this reason, it should be questioned if classical conditioning without expectation should be considered as a true placebo effect.

At first glance, one complication in dismissing conditioning without expectancy has been suggested in that the doctor-patient relationship is built by conditioning, with or without awareness. From the youngest ages, the efficacy of drugs and the word of doctors coincide to create the overall association that a visit to the doctor will make us well. It should be noted, however, that even in the presence of a physician, hidden administration of non-analgesics like proglumide routinely fail to yield an endogenous-opioid response (e.g., Benedetti et al., 1995), and thus serve as a reminder that it is the procedure (e.g., sham pill, sham injection, sham surgery) that induces expectancy. Conditioning is a large part of placebo response in medicine, but the simple correlation does not establish firm causation. Overall, there are a number of subtleties involved in treatment, many of which lie in the definitions applied to terms like awareness, expectancy, and conditioning. Still, the elucidation of underlying mechanisms in the placebo response would benefit from a clearer framework of these concepts.

One interesting exception to the largely opioid-mediated placebo response has been described by Vase, Robinson, Verne, and Price (2005). Patients with unusually large placebo effects in an irritable bowel syndrome (IBS) procedure were found to be naloxone resistant. That is, some, but not all, of the placebo response was eliminated following naloxone administration. However, little is offered in terms of explanation for these effects. It may be that alternative, non-opioid, analgesic endogenous neuropeptides are involved (e.g. a variant of ketorolac). On the other hand, it may be a case of report bias, as in an exceptionally large number of false positives compared to correct rejections. Clark (1969) investigated the hypothesis that the placebo effect results from an abundance of false positives using signal detection theory (SDT), which are often found in the medical field reported both by physicians and patients (for a review of signal detection theory with placebo response, see Allan and Siegel, 2002). In the case of placebo, a false positive is indicated with reported treatment effect where no active ingredient is present. Using SDT, Clark replicated the traditional placebo response, finding that participants report less pain in a placebo condition relative to natural history. However, the conclusion that pain sensitivity was reduced was not called for. Rather, sensitivity to pain remained the same between natural history and placebo conditions while the response criterion, or report bias, was significantly shifted, a finding that was independently replicated (Feather, Chapman, & Fisher, 1972). Similarly misleading is the common occurrence of a substantial portion of non-responders in the placebo condition. Non-responder rates have been described at 39% (Levine et al., 1979), 26.9% (Benedetti, 1996), 30% (Beecher et al., 1955), and 50% (Petrovic et al., 2002). While non-responder rates vary between verbal suggestion, conditioned, social observation, and other placebo-induced mediums, they serve as a reminder that means alone may fail to tell the whole truth. Thus, the incorporation of SDT and non-response rates in placebo studies should be prioritized.

Functional Neuroanatomy and Neuroimaging Studies

Some of the first investigations of the neurobiology in placebo involved direct measurement of endogenous opioids, as well as Positron Emission Tomography (PET). In the measurement of opioids present in a placebo response, Lipman et al. (1990) found greater amounts of endogenous opioids in the cerebrospinal fluid of individuals who had responses to placebo treatment than those who did not show analgesic responses. Investigating brain activation in drug and placebo expectancy, Volkow et al. (2003) tested cocaine abusers (with conditioned expectancies following cocaine administration) who were told they were receiving either placebo or stimulant drug methylphenidate, and actually received either placebo or drug. Monitoring areas of brain metabolism via PET, expectation of the drug and receiving the drug produced ~50% larger brain activations in the cerebellum and thalamus compared to placebo administration. When expecting placebo and receiving the drug, increased activation was found in the left lateral orbitofrontal cortex compared to expecting and receiving the drug. Overall, increased brain metabolism when drug administration is expected and received than when drug

administration is hidden represents the mechanisms of expectancy facilitating placebo response. These results would indicate that expectations have a neurobiological base that enables a stronger physiological response compared to drug administration kept out of awareness, which is consistent with open/hidden placebo paradigms.

In a PET study more specific to endogenous opioid release, Petrovic, Kalso, Petersson, and Ingvar (2002) demonstrated an increase of regional cerebral blood flow of the rostral anterior cingulate cortex (rACC) by both systematic administration of the opiate analgesic remifentanil, as well as with placebo trials following remifentanil administration. Covariation between the brainstem and the rACC was found in remifentanil and placebo administration, but not during a pain-only condition. In fact, those who showed a greater response to placebo also showed greater reactivity in the rACC to remifentanil administration. Together, these results implicate responses of the μ-opioid receptor system, localized to the rACC and extending pathway to the brainstem as a cognitively top-down mediator of the placebo effect.

In another PET study conducted by Zubieta et al. (2005), a μ-opioid receptor selective radiotracer was employed to evidence opiate-specific neurotransmitter activation. This was shown by reduced availability of *in vivo* synaptic μ-opioid receptors to bind with the radiotracer (Bencherif et al., 2002). Opioid activation was compared between sustained pain and sustained pain with placebo in healthy males. It was found that significantly greater activation with placebo occurred in the ipsilateral dorsolateral prefrontal cortex (DLPFC), contralateral rACC, contralateral anterior insular cortex (AIC), and the ipsilateral nucleus accumbens. Importantly, these regions have been shown to house populations of μ-opioid receptors and facilitate endogenous opioid neurotransmission (Gross-Isseroff et al., 1990; Gabilondo et al., 1995). In addition, the anterior cingulate gyrus and AIC have also been implicated in the subjective perception and affective components of pain regulation (Decety, 2011). These converging results suggest that endogenous opioids activated by placebo administration may mediate subjective pain by modulating pain systems involved in the interpretation and control of pain perception.

The results of Zubieta et al. (2005) are generally confirmed by an fMRI study conducted by Wager, Rilling, Smith, and Sokolik et al. (2004). Combining data from two experiments, experiment one using a conditioning manipulation in combination with electric shock pain, and experiment two using a heat pain and conditioning manipulation, more than 70% of participants elicited the placebo response with decreased pain by 22% on average. Particular brain regions shown to significantly differ from the no treatment group included the contralateral AIC, contralateral thalamus, and the anterior cingulate cortex (ACC). Especially in the second experiment, where administered heat pain occurred over a longer course of time, increased activity was found in the DLPFC, orbitofrontal cortex, and rostral dorsal ACC, and lateral and medial prefrontal changes were shown to persist through pain. These areas have been shown to be involved with cognitive expectancy, attentional control, and perceptual processing (Posner et al., 1980; Allport et al., 1989; Handy et al., 2001; Desimone & Duncan, 1995), which support both endogenous opioid mechanisms as well as cognitive reappraisal of affective pain interpretation in placebo response. Interestingly, activity in the secondary somatosensory cortex was found to increase compared to the no treatment condition, suggesting that bottom-up processes in pain may be less involved in placebo response than top-down processing, although both play an interactive role.

Criticism of the Wager et al. (2004) study has been made because the results of brain changes overlapped with given pain ratings, perhaps indicating that differences found were due to report bias instead of placebo (Price et al., 2007). To investigate this criticism, Price et al. (2007) conducted their own fMRI study with IBS patients. In the placebo condition, subjects demonstrated decreased activity in the thalamus, AIC, ACC, and somatosensory cortices during pain stimulation. These results support Wager et al. (2004) in concluding that the brain changes found in placebo are not due to report bias, which furthermore directly contrasts with the SDT results demonstrated by Clark (1969). These conflicting findings would benefit from an fMRI study which includes SDT and an explanation for this discrepancy.

In further investigation of neural mechanisms in placebo response, including direct nociceptive pain inhibition, cognitive appraisal of pain, or report biases, Wager, Matre, Kenneth, and Casey (2006) employed a laser-evoked pain stimulus and recorded event-related potentials (ERPs) at the mid-scalp line, comparing the P2 and N2 peaks between a no treatment and a placebo group. They hypothesized that if placebo is due to early attenuation of nociceptive pain, then pain-evoked (P2) ERPs (~200 to 300ms) should be reduced in the placebo condition, whereas late processing of cognitive appraisal or cognitive judgments in pain intensity would be demonstrated by changes in N2 ERPs (~400 to 600ms). In fact, it was the case that P2 ERPs were significantly reduced in the placebo condition, suggesting that early nociceptive pain processing was attenuated by the ACC, replicating results obtained by Wager et al. (2004). While no differences in N2 ERP peaks were detected, it is unclear whether this reflects a lack of cognitive evaluation due to the selective location of scalp recording. Still, P2 findings would suggest early modulation of nociception, likely via

the ACC and insula. Because the cingulate and insular regions have been implicated in emotion and pain processing (Wager et al., 2004; Decety, 2011), these results generally align with other descriptions of the neural correlates involving the placebo effect mediated by subjective pain interpretation.

Using both experimental and clinical approaches in placebo, the relevance of the frontal anatomy also has a significant role in mediating placebo response. For instance, employing repeated administrations of disruptive transcranial magnetic stimulation to the prefrontal cortex during heat-generated pain has been shown to block placebo response induced by verbal suggestion (Krummenacher, Candia, Folkers et al., 2010). Similarly, Benedetti, Arduino, Costa, Vighetti et al. (2006) demonstrated similar findings in an Alzheimer's disease population with reduced frontal volume. By employing both correlational and experimental methodology, the importance of frontal lobe, especially in maintaining expectancy and cognitive appraisal functioning, seems to be critical to generating the placebo effect.

Very recent technological advances involving fMRI of the spinal cord have also been used to investigate placebo mechanisms. Eippert et al. (2009) reported that significantly reduced activity in the ipsilateral dorsal horn under placebo compared to a no treatment group when pain is induced. The direct down regulation of spinal activity suggests that placebo may act at the earliest stages of central nervous system processing, in line with the findings of Wager et al. (2006). In addition, significant coupling of the rACC with the periaqueductal grey (PAG) has also been identified (Amanzio & Benedetti, 1999; Wager et al., 2004; Eippert et al., 2009), perhaps mediating subjective pain interpretation. These findings further support the hypothesis for expected pain reduction mediating top-down regulation via descending pathways.

On the Ethical Nature of Placebo Studies

As mentioned above, there is a minimal reporting of non-response rates as well as a poor acknowledgment of signal detection analysis studies amongst placebo literature, which may be of concern to the ethics behind placebo research. Pollo (2001) argues, among other reasons, his investigation was ethically sound because all patients reported equal analgesic effects. Considering that pain sensitivity may not diminish with placebo (Clark, 1969), and instead that the willingness to report less pain may be increased, directly opposes this justification. Similarly, Vase et al. (2003) argues there is ethical justification for their placebo research because their verbal suggestion that 'the agent you have been just given is known to significantly reduce pain in some patients' is not a lie, because the placebo truly does reduce pain compared to natural history. This is also in contention, considering the signal detection analysis results which are now over four decades old in publication.

In contrast, there is significant reason to believe that report bias is not the only mechanism of the placebo response. For instance, the presence of endogenous opiate release in placebo-responding patients (e.g., Lipman et al., 1990; Zubieta et al., 2005) as well as inhibition of nociceptive perceptual processing (e.g., Petrovic et al., 2002; Wager et al., 2004) lends some credence to Pollo and Vase et al. However, this is not the whole truth, either. Indeed, the potential for benefit in placebo research is overwhelmingly greater than its potential harm, granted the approval of a research ethics agency. First, placebo research allows for clinical trials to test drug efficacy. In addition, placebo studies aim to reveal biological and psychological mechanisms in pain and in other disorders such as IBS, clinical depression, and Parkinson's Disease, to name a few. In the end, open discussion of non-response in placebo and equal pain sensitivity between conditions demonstrated by SDT will further the benefits of this research far more than ignoring these results will minimize the perceived harm.

Future Directions

With the numerous advancements made in understanding placebo, there are still more questions raised. For instance, individual factors such as gender differences and the contrast between hyperalgesia in some clinical populations compared to nociceptive pain felt by healthy participants are not well represented in the neurobiological literature. In addition, the contrast between conditioned, social observation, and verbally suggested placebo lacks strong empirical investigation with fMRI or PET approaches, as well as combining SDT or non-responder differences in these methodologies. While the link between conditioning and non-opioid placebo response is developed, it remains a mystery what neural correlate is responsible for this placebo effect. It may be the case, however, that the non-opioid mediated placebo effects, as found in Vase et al. (2005), are a spurious result of report bias, and replication studies should be performed to establish the stability of this phenomenon.

In addition, the question has been raised as to what verbal suggestions are most appropriate for inducing a placebo response (Verne et al., 2003; Vase et al., 2003), or if other designs would be more efficacious. This question has implications for clinical trials, in which it is essential to demonstrate that an active treatment is more effective than placebo. If the placebo magnitude is in question, then

the efficacy of some active therapies may also be in question, which is of serious ethical import as well.

Conclusions

The conceptualization of the placebo effect has made great advances in the past few decades. The focus has shifted from administering an inert substance to the simulation of an active treatment (Price et al., 2008). Further, multiple types of placebo responses have been characterized including verbal suggestion, social cues, expectancy manipulation, classical conditioning, and open/hidden administration paradigms. In the focus of pain literature, it is incontrovertible that endogenous opioids play a major role in unconditioned responses. Alternatively, conditioning procedures have demonstrated that non-opioid mechanisms can play a distinct role, although the overlap between classical conditioning and expectancy in the placebo effect is a grey area.

In terms of neural mechanisms underlying the placebo response in placebo analgesia, it seems evident that areas of frontal activation are involved, perhaps supporting cognitive control, expectancy, evaluation, and attentional processes. In addition, limbic and paralimbic structures including the ACC and AIC are implicated, possibly supporting the representation of affective pain and pain regulation. Furthermore, the PAG and brainstem have also shown alteration in placebo response. Their function includes modulating the receptivity to pain stimulation in the earliest responses to pain stimulation. However, the top-down regulation of the PAG on the spinal cord has been challenged, since the PAG can exert bottom-up effects onto the telencephalon (Zubieta et al., 2005). In this way, there is evidence for both top-down regulation and bottom-up effects in the placebo response, where their interaction is likely.

Overall, the mechanisms of placebo are no longer entirely mysterious. The evidence presented supports the idea that psychosocial context can exert neurobiological effects in a sort of feedback loop. These neurobiological effects have been demonstrated beyond subjective pain report, for instance, with the release of endogenous opioids and corollary autonomic effects of the respiratory and cardiovascular systems. These effects have been shown to be naloxone reversible and enhanced by proglumide, even under hidden administration, but perhaps less understood are the factors responsible for individual variation. Additionally, some studies have shown non-opioid placebo effects without classical conditioning, which also requires attention. In conclusion, the placebo effect represents a stable phenomenon in human psychology and biology which bespeaks both psychosocial and neurobiological factors.

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