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Understanding Placebo and Nocebo Responses for Pain Management

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Abstract

Placebo analgesia makes individuals experience relief of their pain simply by virtue of the anticipation of a benefit. A reduction of pain can occur also when placebos follow the administration of active and effective painkillers. In fact, studies indicate that placebos mimic the action of active treatments and promote the endogenous release of opioids in both humans and animals. Finally, social support and observational learning also lead to analgesic effects. Thus, different psychological factors and situations induce expectations of analgesia facilitating the activation of the top-down systems for pain control along with the release of endogenous mediators crucially involved in placebo-induced benefits. Recent scientific investigation in the field of brain imaging is opening new avenues to understanding the cognitive mechanisms and neurobiological substrates of expectation-induced pain modulation. Gaining deeper knowledge of top-down mechanisms of pain modulation has enormous implications for personalizing and optimizing pain management.

Keywords

Keywords Brain Imaging; Cannabinoids; Conditioning; Dopamine; Expectation; Genetics; Interpersonal interactions; Learning; Psychological traits; Opioids; Social observation; Oxytocin

Introduction

The terms placebo and nocebo effects refer respectively to the positive and negative cognitive modulation of behaviors and outcomes [1••]. Placebo and nocebo effects in the arena of pain are triggered by verbal instructions, conditioning, social observation, and interactions [1••, 2•]. Verbal instructions suggesting pain relief can induce placebo analgesia by recalling a prior experience of analgesia and increasing the desire to get better. Placebo analgesia (and likewise expectations of pain relief) [3] can be enhanced by conditioning, in

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which a simulation of benefit (e.g. an analgesic cream paired with a decrease of the intensity of painful stimuli) evokes analgesia when a control level of pain is delivered. Typically, conditioned placebo effects induce stronger and longer-lasting (up to 4–7 days) effects [4] compared with verbal suggestions alone in pain [5-9] and tactile perception [10, 11]. A recent study investigated the role of awareness in conditioned placebo analgesic effects and found that visual cues that are unconsciously perceived elicit analgesic responses, suggesting that learning mechanisms trigger these effects by partially operating outside of awareness [12]. When conditioning paradigms involve repetitive exposure to pharmacologic treatments, the result is a drug-like effect associated to the administration of a placebo that acts as a dose-extender of the effect of drug inherent to the treatment under investigation [5, 13]. For example, a placebo given after a repetitive administration of nonopioid drugs such as aspirin or ketorolac produces an aspirin- or ketorolac-like effect, respectively, while a placebo given after the opioid drug morphine produces morphine-like effects such as reduction of pain and morphine-induced adverse events [14, 15••, 16, 17]. The fact that placebos given after pharmacologic conditioning trigger drug-like physiological effects has tremendous value at a theoretical level as well as potential for the clinical practice.

Placebo effects also occur without direct first-hand experience via social observations, which may facilitate the process of building up expectations of analgesia. Colloca and Benedetti demonstrated that placebo analgesia is observable in healthy patients who have observed a benefit in another person [18]. When tested for pain, the observers showed placebo analgesia and the magnitude of observationally-induced analgesia was comparable with that induced by a conditioning procedure, in which patients directly experienced the benefic effect. Notably, placebo analgesic effects were correlated with empathy scores, suggesting that the ability to empathize another's feelings may facilitate these effects. However, the effect of empathy only seems to play a role when interpersonal interactions are involved [18, 19], since placebo effects following the observation of a video are not linked to the level of individual empathy [20]. Interestingly, behavioral nocebo effects are also modulated by observing another person in pain [21] suggesting that common brain mechanisms might account for these effects. Psychosocial cues and the entire set of interpersonal interactions contribute to induce expectations and potentially recall memories of analgesia. This phenomenon also occurs in clinical situations whereby interacting with the physician can trigger the mechanisms underlying placebo analgesia with relevant clinical effects [22-24]. Importantly, the results derived from research on placebo analgesia apply also to the nocebo counterpart, whereby negative expectations can elicit increase of pain experience [22, 24-26].

In this review, we present the most recent advances in placebo and nocebo that have been achieved toward neurobiological research. We focus primarily on the brain mechanisms of top-down regulation of sensory processing, the neurochemistry underlying these changes, and the psychological and genetic variables associated with proneness to respond to placebo and nocebo.

Brain, Nociception and Pain Experience

Placebo analgesia produces activity changes and enhanced functional coupling in areas of the brain such as the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex (ACC) and subcortical regions including the hypothalamus, amygdala and the periaqueductal grey (PAG) [27-30]. The DLPFC initiates the placebo analgesic response as demonstrated by different groups and approaches [31, 32]. The rACC is connected with the PAG and correlates with the modulation of placebo analgesia [27, 29]. Moreover, placebo analgesia decreases pain-enhanced activity in areas such as the thalamus (Th), insula (INS) and the somatosensory cortex [27, 29, 30, 32], showing a neural correlation with the subjective reduced perception. Recent studies show that the activity at the level of the spinal cord is modulated by placebo analgesia with changes in the ipsilateral dorsal horn, corresponding to the area of stimulation [33]. Using functional magnetic resonance imaging of the human spinal cord, Eippert et al. showed that placebo analgesia results in a reduction of nociceptive processing in the spinal cord suggesting that top-down mechanisms suppress pain processing in the central nervous system at the earliest stages [33].

Notably, the local application of an inert cream on the forearm along with negative suggestions and manipulation of pain intensity increased pain ratings compared with a control cream inducing a nocebo hyperalgesic effect. This nocebo modulation induced a strong activation in the spinal cord at the level of the stimulated dermatomes C5/C6 [34••]. Pain and nocebo effects spatially overlapped and the comparison between pain stimulation under nocebo and control condition showed an enhanced pain-related activity in the ipsilateral dorsal horn of the spinal cord [34••]. These findings emphasize the negative and positive modulatory effects of expectations from frontal areas to the spinal cord extending and corroborating earlier pioneering suggestions and evidence [35-38].

Interestingly, several studies have recently correlated placebo analgesia with brain structure (e.g. grey matter density) and used *functional* connectivity as a predictor of individual placebo analgesia. Using voxel-based morphometry, Schweinhardt and colleagues found that grey matter density in brain areas such as the DLPFC, INS, and Nucleus Accumbens (NAc) correlated with greater placebo analgesic effects [39]. Structural differences in NAc and DLPFC were in turn correlated with dopamine related traits, including novelty seeking and behavioral activation [39]. It would be interesting to investigate in future studies whether dopamine agonists and antagonists modulate placebo analgesia. More recently, Kong and colleagues investigated how pretest resting-state functional connectivity was linked to expectations and cue-mediated placebo analgesia [40]. An increased baseline resting-state *functional* connectivity of the right fronto-parietal network with the rostral ACC correlated positively with the magnitude of expectation of analgesia, whilst connectivity between the somatosensory areas and the cerebellum correlated with pain reduction induced by the cues of analgesia [40]. *Functional* connectivity is also relevant in predicting placebo analgesic responses in patient population. Patients with chronic back pain were studied during a 2-week placebo treatment [41]. The *functional* connectivity between the dorsomedial PFC and bilateral INSs cortices predicted the magnitude of placebo analgesia and the probability to recover from low back pain. In fact, the patients who responded to the 2-week placebo treatment, showed a lower connectivity between

dorsomedial PFC and INSs compared with those who did not respond to placebo and did not recover [41]. Furthermore, patients who recovered from the episode of low back pain under placebo treatment showed a high-frequency activity in the left DLPFC and the midcingulate cortex. The connections between dorsomedial PFC-INS and DLPFC-midcingulate cortex seem to predict the resolution of low back pain with high accuracy (about 90%) [41].

Recently, Stein et al using a tract-finding algorithm that measured local white matter anisotropy and *structural* connectivity between a priori cortical and subcortical regions of interest, showed that placebo analgesia correlated with higher fractional anisotropy in the rostral ACC and in left DLPFC, and with stronger fiber connections of these 2 regions with the periaqueductal grey (PAG) [42•].

Biochemical Aspects of Placebo Analgesia

The above described findings corroborate the notion that cortical brain regions and their connections to the descending pain inhibitory system including the brainstem are extremely important for endogenous pain modulation. Indeed, expectations induce brain changes by triggering and regulating the interplay of endogenous brain neuropeptides underlying placebo analgesia. It has been extensively demonstrated that placebo analgesia is due to the endogenous release of neuropeptides such as opioids [29], cholecystokinins [43], oxytocin [44], and cannabinoids [15••]. Indirect pharmacologic approaches have provided evidence that placebo analgesia can be antagonized by naloxone thus, indicating that opioids are crucially involved in these kinds of expectancy-driven placebo analgesic effects. The role of the opioidergic system has been confirmed by pharmacologic fMRI and PET studies using an in vivo receptor binding with opioidergic ligands [29, 45, 46]. The placebo analgesia has been also associated with the release of cannabinoids [15••]. In the circumstance in which placebo analgesia is elicited by a non-opioid pharmacologic conditioning with the nonsteroidal anti-inflammatory drug (NSAID) ketorolac, the cannabinoid receptor 1 (CB1) antagonist SR 141716A (rimonabant) blocks placebo analgesia, thus, indicating that the effects elicited by placebo given after NSAID ketorolac are due to the release of endogenous cannabinoids [15••]. Recently, it has been shown that oxytocin agonists given intranasally enhance behavioral placebo analgesia in men [44], suggesting that the oxytocinergic system, which is involved in the modulation of social behaviors [47, 48] might play a role in placebo. Further research is needed to determine whether oxytocin produces similar effects in women, how a dose of oxytocin influences outcomes and what the physiological and brain mechanisms responsible for these effects are.

The nocebo phenomenon is influenced by the cholecystokinin (CCK) system, a system involved in the modulation of anxiety and hyperalgesia. In fact, the block of the CCK A and B receptors with the type A/B receptor antagonist proglumide blocks nocebo hyperalgesia [43].

Genetic Factors

Variation in genetic polymorphisms can to some extent determine the probability of forming a placebo analgesic response and triggering the cascade of events related to placebo-induced reduction of pain [49]. Patients with irritable bowel syndrome (IBS) randomized to no-

treatment ('waitlist'), placebo treatment with a business-like doctor-patient relationship and placebo treatment with an enhanced and supportive doctor-patient relationship were studied. Pain was measured as indicated by the changes from baseline in IBS-Symptom Severity Scale following 3 weeks of treatment, and the number of methionine alleles in the COMT Val158Met polymorphism (rs4633) was considered. Patients with Met/Met alleles had robust placebo analgesic effects and benefited from the enhanced and supportive doctor-patient relationship. Patients with Val/Val alleles minimally benefited from placebo responses and doctor-patient relationship, potentially opening the way to personalized therapeutic approaches [50].

Recently, it has been suggested that a single-nucleotide polymorphism in the fatty acid amide hydrolase (*FAAH*) gene, *C385A* (rs324420), that regulates the release of endogenous cannabinoids can be a good predictor of opioid-mediated placebo analgesia [51]. Endogenous cannabinoids and opioids are thought to regulate antinociception synergistically. Zubieta et al examined the link between cannabinoid polymorphisms and μ-opioid mediated placebo analgesia in a positron emission tomography (PET) study using selective radiotracers labeling MOR and $D_{2/3}$ receptors. The authors found that a μ-opioid-mediated placebo analgesia in regions such as preFC, rostral, dorsal, and subgenual ACC, INS, thalamus, and NAc. Activation of the μ-opioid neurotransmission was also observed in areas associated with reward-motivated learning and memory processing such as the mammillary region, the anterior thalamic nuclei, CC, and hippocampal and parahippocampal gyrus. The endogenous opioid release in these brain areas was significantly correlated with placebo analgesia and *FAAH* Pro129/Pro129 homozygosity. Interestingly, Pro129/Pro129 homozygotes with lower cannabinoid levels [52], showed higher psychophysical placebo analgesia and regional μ-opioid activation during placebo administration, compared with Pro129/Pro129 heterozygotes [51].

Beyond pain, serotonin-related gene polymorphisms have been found to influence the placebo response in social anxiety, at both the behavioral and neural level [53, 54]. Polymorphisms modulating monoaminergic tone have been linked to the degree of placebo responsiveness in patients with major depressive disorder [55]. It remains a critical need to achieve a deeper understanding of the role of genetic influences in predicting placebo responses in the field of pain and associated disorders (eg, anxiety and depression) at multiple levels including psychometric phenotypes and brain responses. Clarifying the reliability and reproducibility of the genetic predictors represents an important goal both in neuroscience research and for randomized clinical trials.

Psychological Traits

The attempt to find a psychological marker of placebo responsiveness has intrigued researchers for many years, although the results have been quite discouraging. Only recently, psychological traits such as dispositional optimism, hypnotic suggestibility, somatic focus, empathy, neuroticism, altruisms, and the locus of ego-reliance have been linked to placebo analgesia.

Optimism is associated with active behavioral and mental coping when individuals face adversity. Geers and colleagues examined healthy college student participants and their optimistic levels by hypothesizing that optimism is a moderator of placebo responsiveness, thus, a factor that influences the strength and/or direction of the relation between a predictor and placebo analgesia. The authors found that dispositional optimism was correlated with the magnitude of placebo analgesia [56, 57]. These results have been confirmed by the same and other authors [57, 58]. Hypnotic susceptibility, a psychological trait referring to the responsiveness to suggestions influences placebo analgesia [59] and can partially explain inter-individual differences in the neural conditioned placebo analgesic responses in healthy volunteers [60•]. Subjects with high hypnotic susceptibility, showed increased anticipatory activity in a right DLPFC focus, and the ability to reduce functional connectivity of that focus with brain regions related to emotional and evaluative pain processing such as the anterior mid-cingulate cortex and medial PFC. A reverse pattern of fMRI changes and functional connectivity was found in patients with low hypnotic susceptibility [60•].

Somatic focus that refers to the attention toward the body, correlated with larger placebo analgesic effects when pain expectancy was high [61]. Conversely, distraction reduced pain, but did not influence placebo analgesia, thus, suggesting that placebo analgesia and distraction work through distinct mechanisms [61].

Empathy, a vicarious emotion referring to feeling the same emotion as, or congruent with, the emotion of the other person, has also been investigated in the context of placebo research. Specifically, empathy concern of the recipient is a factor that modulates observational placebo analgesia. Interestingly, Colloca et al showed a strong positive correlation between analgesic responses and empathic concern for the live social observation conditions [18]. Most notably, a recent study demonstrated that watching a video modulates placebo analgesia but these video-induced effects were not correlated with dispositional empathy, indicating that empathy is a moderator of observationally-induced placebo analgesia in live interactions only [20].

Personality traits related to dopaminergic function such as novelty seeking, harm avoidance, behavioral drive, fun seeking, and reward responsiveness have been linked with both placebo analgesic effects and gray matter density in the basal ganglia and PFC [39]. More recently, Pecina and colleagues reported that 4 stable personality traits including high Ego-Resiliency, NEO Altruism, NEO Straightforwardness, and low NEO Angry Hostility predicted 25% of placebo responsiveness to pain and 27% of the NAc μ-opioid system activation during placebo administration thus, suggesting a link between behaviors and release of endogenous opioids [62•]. Further research is needed to understand the psychological predictors of nocebo effects, potentially allowing the prediction of unspecific adverse effects in clinical trials and practices [63, 64].

Clinical Pain and Placebo Analgesia

Every treatment is significantly modulated by placebo effects and drug actions and placebo effects interact additively or synergistically depending on the condition. In general, placebo effects seem to act as *reinforcers* of clinical outcomes. This point is clearly proven by open/

hidden models whereby identical concentrations of painkillers are given either covertly or overtly [23]. The former represents the situation in which the treatment is administered by a *computer-programmed pump of infusion*. The latter is the condition in which the patient is aware of receiving the medication that is administrated by a supportive health practitioner. The clinical response to covert and overt administrations of painkillers is different in terms of time-course reduction of pain. Patients in postoperative acute pain respond much better when their treatments are given by a physician (50% reduction in drug intake) compared with those treated in a socially-deprived context (eg, pump of infusion) [23]. These observations have been extended and corroborated by brain imaging studies showing that the mere awareness of receiving a treatment potentiates the pharmacologic analgesic effect in both healthy patients and patients in postoperative acute pain [65].

Amanzio et al (2001) analyzed the effects of covert and over administration in 4 painkillers that are widely used in clinics and that have distinct mechanisms of action (buprenorphine, tramadol, ketorolac, metamizol) in patients. The analgesic dose needed to reduce the clinical pain by 50% (AD_{50}) was higher with covert than overt infusions for all the classes of painkillers, indicating that the reinforcing effect of expectation is a widespread phenomenon. Amanzio et al (2001) tested the difference between open and hidden injections also in the laboratory setting by using the experimental model of ischemic arm pain in healthy volunteers [66]. Most importantly, the administration of 10 mg of the opiate antagonist, naloxone, reversed the effect of overt administration of ketorolac suggesting that the potentiation is likewise due to the release of endogenous opioids [66].

Placebo Analgesia and Treatment History

Another important aspect to take into account is the link between placebo (and nocebo) effects and the history of treatment in both experimental and clinical settings. Prior positive experiences increase analgesic responses of a subsequent placebo, but negative previous experiences decrease the magnitude of placebo effects. Colloca and Benedetti designed a study in which one group received a simulation of effective treatment (in actuality, the intensity of painful stimulations was surreptitiously decreased) and a second group received a placebo intervention after a treatment perceived as ineffective (verbal suggestions with no manipulation of the intensity of painful stimulation was performed), producing 49.3% vs 9.7% pain reduction, respectively [4]. After a time lag of 4– 7 days, both groups were retested for placebo analgesia. After 4–7 days, the placebo responses following the effective procedure were significantly higher than those observed after the ineffective treatment (29% vs 18% pain reduction). These results indicate that placebo analgesic effects are finely shaped by prior experience (either positive or negative), and that the effect of initial treatment influences the magnitude of subsequent placebo responses even after several days [4].

Similarly, after randomization of healthy patients to two groups, either a positive or negative treatment experience with an inert patch treatment, Kessner et al introduced a new analgesic to test for the effect of treatment history in an fMRI study [67••]. The therapeutic effect of the tested treatment was lower in the negative compared with the positive treatment history group. The adverse effect of the negative treatment history was sustained in the brain by a

higher activation of the bilateral posterior INSs, regions related to afferent nociceptive processing, and a lower activation of the right DLPFC that is also involved in nociceptive inhibition processes and placebo analgesia [67••].

The causal relation between amount of previous successful pain relief experiences and placebo analgesia was further demonstrated in another study using a learning model with either 10 or 40 associations between a specific visual cue and analgesic experience [68]. The persistence of placebo and nocebo responses was firmly connected to the length of exposures to prior effective (and ineffective) interventions, thus, demonstrating that the size and the resistance to extinction of the ensuing placebo and nocebo responses is intrinsically connected with the number of conditioning trials [68].

It is interesting to consider how these concepts may apply to clinical contexts. For example, André-Obadia et al showed that the magnitude of placebo analgesia in patients with chronic neuropathic pain depended on prior exposure to either successful or unsuccessful treatment [69]. The placebo analgesia of repetitive transcranial magnetic stimulation (rTMS) was evaluated in a cross-over study design in which neuropathic pain patients resistant to pharmacologic treatment were assigned to one of two arms—sham rTMS delivered either before or after the conventional stimulation of the motor cortex. Carry-over effects of a single session of rTMS did not exceed a week. Those patients who received the sham rTMS after a session of real rTMS perceived an analgesic effect (11% pain reduction). By contrast, patients who received the sham session after the ineffective rTMS intervention experienced higher levels of pain (6% pain increase), indicating that the exposure to effective treatments induces the formation of analgesic placebo responses that are stronger compared with responses following placebos given first [69]. These findings are in line with the pioneering results by Laska et al suggesting the existence of a dose-response relationship between the delivery of the first medication and the response to a subsequent placebo.

Overall these studies seem to support the fact that positive and negative previous therapeutic experiences may confound the results of cross-over designs. Clinically speaking, it is worth appreciating that learned placebo analgesic effects can be elicited in patients suffering from neuropathic pain despite the fact that the pain was refractory to conventional pharmacologic interventions. These findings deserve further investigation for the potential to improve the design of clinical trials and likewise, optimize therapeutic strategies.

Conclusions

Current knowledge of placebo and nocebo effects provides direct evidence for a pain-inhibiting or facilitating mechanism in the human brain and spinal cord, which can be activated by cognitive manipulations of expectations through verbal suggestions, pharmacologic, and nonpharmacologic conditioning, and social learning. Brain changes are strategically linked to the release of endogenous opioids, cannabinoids, and CCKs. Psychological and genetic traits are likely to contribute to the occurrence of these inner processes potentially helping predict individuals who may activate these inner processes. More research is needed to expand this evidence to different kinds of pain and conditions

associated with clinical pain. Fruitful research in this field is likely to improve personalized therapeutic approaches to pain management.

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