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Nocebo and pain: an overview of the psychoneurobiological mechanisms

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Abstract

Introduction: Nocebo effects are defined as adverse events related to negative expectations and learning processes that are involved in the modulation of the descending pain pathways. Research over the last couple of decades has illustrated that behavioral, psychoneurobiological, and functional changes occur during nocebo-induced pain processing.

Objectives: We aimed to review published human and nonhuman research on algesia and hyperalgesia resulting from negative expectations and nocebo effects.

Methods: Herein, we searched and comprehensively reviewed scientific literature providing informative knowledge about the psychoneurobiological bases of the nocebo effect in the field of pain with an emphasis on how pain processes are shaped by both cognitive and noncognitive factors.

Results: Negative expectations are formed through verbal suggestions of heightened pain, prior nociceptive and painful experiences, and observation of pain in others. Susceptibility to the nocebo effect can be also influenced by genetic variants, conscious and nonconscious learning processes, personality traits, and psychological factors. Moreover, providers' behaviors, environmental cues and the appearance of medical devices can induce negative expectations that dramatically influence pain perception and processing in a variety of pain modalities and patient populations.

Conclusion: Importantly, we concluded that nocebo studies outline how individual expectations may lead to physiological changes underpinning the central integration and processing of magnified pain signaling. Further research is needed to develop strategies that can identify patients with nocebo-vulnerable pain to optimize the psychosocial and therapeutic context in which the clinical encounter occurs, with the ultimate purpose of improving clinical outcomes.

Keywords: Negative expectations, Hyperalgesia, Allodynia, Nocebo effects, Pain modulation

1. Introduction

Multiple psychosocial and environmental factors encompassed within a clinical encounter create a context through which patients develop negative or positive expectancies about treatments and clinical outcomes. Nocebo effects, which arise from negative expectancies elicited through verbal suggestion, conditioning and/or social observation,[25] have the potential to significantly influence pain pathways by triggering physiological changes that could consequently affect not only pain perception but also pharmacological efficacy and clinical outcomes in the context of pain management.[28] A better understanding of the nocebo mechanisms would relevantly inform clinical practice. Just as the multifaceted dimensions of the clinical encounter can have a powerful therapeutic placebo analgesic effect,[22,29] components of the clinical encounter can also produce algesic and hyperalgesic nocebo effects. Following an introduction of the nocebo effect and its methodology (eg, definition and identification criteria), this review focuses on describing the neurobiological changes driving this phenomenon, as well as the psychological and cognitive factors influencing negative expectancies. Altogether, these factors lead to alterations in descending pain pathways and individual pain experiences.

Merely disclosing the potential to experience higher pain can itself produce negative expectations and worsening of pain outcomes. Research on the mechanisms of the nocebo effect brings attention to multiple influencing factors within clinical settings that are relevant for any health care provider. By recognizing the impact of communication and interpersonal

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interactions in unsuccessful therapeutic outcomes, health care providers may develop important strategies to mitigate nocebo effects in the field of pain medicine. The purpose of this review is to report published human and nonhuman research describing neurobiological changes associated with algesia and hyperalgesia occurring as a consequence of negative expectations and nocebo effects.

We searched PubMed using nocebo, pain and negative expectancy as key words. The abstracts were therefore reviewed independently by 2 authors and the articles that were considered most relevant for understanding the psychoneurobiological mechanisms underpinning nocebo effects were described in detail in this narrative review.

By collating the factors and mechanisms that have been linked to nocebo effects, this review provides a concise contextual framework that can guide health care practitioners, physicians, and investigators in optimizing their interventional strategies. By paying careful attention to an individual's behavior and by being aware to the wide variety of factors and mechanisms that may influence responses to clinical interactions and treatments, practitioners, and researchers can tailor therapeutic strategies and deliver information with appropriateness to reduce the risk for negative outcomes or undesired effects.

2. Definitions and methodological considerations

The term nocebo effect was introduced in the literature to indicate the negative counterpart of the placebo effect and to contrast the adverse from the positive placebo effect.[53,54]

A "nocebo" refers to an inert substance, such as a sugar pill, as well as to an intervention or procedure intended to create negative expectations about health outcomes either intentionally (eg, disclosure of side effects) or unintentionally (eg, exposure to therapeutic encounters where a patient has experienced an adverse event). In laboratory settings, a nocebo can refer, for example, to the delivery of a conditioned stimulus in which a study participant experiences higher pain along with the delivery of an experimental noxious unconditioned stimulus. Nocebo effects also refer to negative effects of a drug that cannot be attributed to the pharmacokinetics of the drug (eg, reduction of expected efficacy; negative outcome expectancies; verbal and nonverbal negative cues in the clinical encounter). Furthermore, nocebo effects can be induced by social interactions and observational learning whereby study participants interact and/or observe another person experiencing a negative outcome (eg, increased pain) or receiving negative disclosures related to a treatment (eg, explanation of side effects of a painkiller).

Also, it is important to distinguish the nocebo effect from the nocebo response. As outlined by Colloca and Miller, the nocebo effect refers to the negative psychosocial context around the patient and the treatment as well as its neurobiological bases,[32] whereas the nocebo response refers to unspecific factors that can produce worsening of symptoms (eg, headache).

As described by Colloca and Miller,[32] nocebo effects can be either apparent or true, and accurate detection of the true placebo effect, from a methodological perspective, requires comparison with a no-treatment control group. For example, when a patient reports headache as a side effect when beginning a new medication, this headache may be in fact the result of quality-of-life–related factors, personal distress, normal physiological processes, or of the natural history of a condition, and might have already been present prior to, or occurred regardless of, the initiation of the new medication regimen.[7,64] Thus, these reported side effects can either be biased by misattribution, or they could represent a true response to the nocebo effect.[43] Adverse effects may be more difficult to be evaluated compared to target outcomes because of biases related to memory effects on retrospective symptom reporting.[75,79] Moreover, the researcher responsible for evaluating and reporting these side effects and symptoms may add another level of bias by having to subjectively attribute relevance to such reports in terms of symptom intensity and possibility of it being drug-related.[64] Altogether, these factors may cloud true nocebo effects and also potentially affect data quality. Also, it has been described that the methods or tools employed for measuring side effects can also have an impact on patient nocebo effects (eg, increased pain reports).[64] These circumstances then suggest the need for standardized assessments that would allow for between-trial comparison of adverse effects as well as potential nocebo effects and responses.[32] As explained above, true nocebo effects can be identified in studies which include either a no-treatment group or a group that is not disclosed about the side effects related to a certain treatment. Nonetheless, nondisclosed groups should still be told about the intentional concealment of information to prevent any potential violation of patients' rights.[32]

3. Theoretical bases to understand the nocebo phenomenon

The basic psychological mechanisms underlying the formation of negative expectations and thus, nocebo effects, are anticipation of and information about negative outcomes,[34,76] prior lack of therapeutic effectiveness,[33,34] and observation of other patients' pain worsening.[42,60,74,77,78] A recent systematic review of 89 studies on nocebo effects found that besides from higher negative expectancies, clear suggestions of possible symptoms and observing others develop symptoms, higher perceived dose of exposure is also a strong predictor of nocebo effects.[80]

In the following section, we describe the psychological and psychobiological underpinnings of nocebo effects. Although promoting placebo responses may be an intentional and desirable aspect of clinical practice, health care providers should avoid producing undesirable nocebo effects. An understanding of the psychobiological mechanisms of nocebo algesia and hyperalgesia is of critical importance when evaluating aspects of clinical care that could be impacting patients' satisfaction with care and overall well being.

4. Negative expectancies shaped via verbal suggestions

Nocebo effects can result from verbal instructions or suggestions that promote the formation of negative expectancies or the absence of positive expectancies.

One of the earliest studies on nocebo comes from Schweiger and Parducci, who reported a localized pain in healthy study participants informed that an electrical current passing through their heads could cause headache as a possible side effect.[69] These findings have been recently reproduced. In a study, participants experienced headache when going through sham exposure to radiofrequency when in fact the radiofrequency from the amplifier was absorbed by a load, thus suggesting that expectations created discomfort and head pain.[73]

Namely, verbal instructions can also paradoxically modify the action of drugs. Study participants who believed that they were given a stimulant perceived an increase of their tension, despite having taken a muscle relaxant.[44] This paradoxical effect has

also been observed with other types of medication. For example, the typical action of 33% nitrous oxide (N_2O) was reversed from analgesia to hyperalgesia—low level of pain perceived as higher—when healthy study participants received misleading information about the possibility of experiencing an increase of pain.[39]

Verbal suggestions are strong enough to reverse conditioned placebo analgesia after 2 days of exposure to nonopioid analgesic ketorolac.[16] Benedetti et al showed that pain experience is highly manipulable via instructions. The authors investigated pain tolerance against ischemic arm pain after an acquisition phase involving a verum pain-reducing medication given along with either positive or negative verbal suggestions ("you will receive a medication which will increase your pain" vs "you will receive a medication which will decrease your pain"). While the placebo procedure led to nearly the same pain reduction as the pain medication, the nocebo information ruled out this positive effect.[16]

Other studies have also revealed strong nocebo effects induced by verbal suggestions.[8,76] In the study by van Laarhoven et al, negative verbal suggestions were designed to induce higher expectations for itch or pain, and it was revealed that higher itch and pain expectancies led to higher reports of both events. Evaluation of both nocebo effects revealed stronger effects for itch when compared to pain.[8,76] Negative verbal information can convert typically painless stimulations into painful ones and induce nocebo responses as strong as those induced by direct experience of negative outcomes.[34,65]

5. Negative expectancies shaped via conditioning

Research has shown that similarly to placebo analgesia, both verbal suggestion and learning-conditioning paradigms can produce nocebo hyperalgesia and allodynia, although verbal suggestions seem to play a bigger role in the development nocebo hyperalgesia when compared to placebo analgesia (**Figs. 1A and B**).[34]

Although it has been documented that conditioning processes may lead to noncognitive learning that produces placebo responses without influencing conscious expectancies, interesting differences between the placebo and nocebo phenomena have been observed. For example, learning appears to influence both the occurrence of nocebo and placebo effects; however, the repetition of associations is less important in promoting nocebo hyperalgesia than in consolidating placebo analgesia.[24] Experimental evidence suggests that negative expectations elicited by verbal suggestions are generally powerful enough to produce nocebo effects of higher effect size when compared to the placebo effect, for which it is critical to have a first-hand experience where a positive outcome is learned and consolidated.[34,51] Nocebo responses can also derive from prior unsuccessful experiences associated with certain medications and interventions. Learned negative associations can condition a patient to subsequently experience algesic nocebo effects and therefore reduce the expected positive outcome of a pain treatment. The duration of prior events marked with exposure to pain is also relevant for the development and perpetuation of nocebo-induced algesia.[24,26,33–35] Furthermore, conditioning mechanisms appear to create more nocebo effects in women, whereas these effects may be driven more by expectations in men.[56]

Recently, it has been also demonstrated that nocebo effects persist over time independently of the experimental reinforcement procedure. In fact, both partial and continuous classical conditioning paradigms produced nocebo effects that did not extinguish over the entire experimental sessions.[21] A different trend has been observed for positive partial reinforcement in which placebo effects persisted over time when established throughout partial reinforcement, but not after continuous reinforcement.[5]

Importantly, nocebo effects induced via conditioning can occur without the conscious formation of negative expectancies. Recent research has shown that unconscious processes modulate placebo and nocebo effects differently.[40,45,50] Evolutionarily, nocebo responses and placebo responses may represent 2 opposite pathways that coexist in the organism. The placebo phenomenon may promote appetitive and safety behaviors, while nocebo effects may favor perceptual mechanisms that are initiated to prevent dangerous events and negative outcomes.[23]

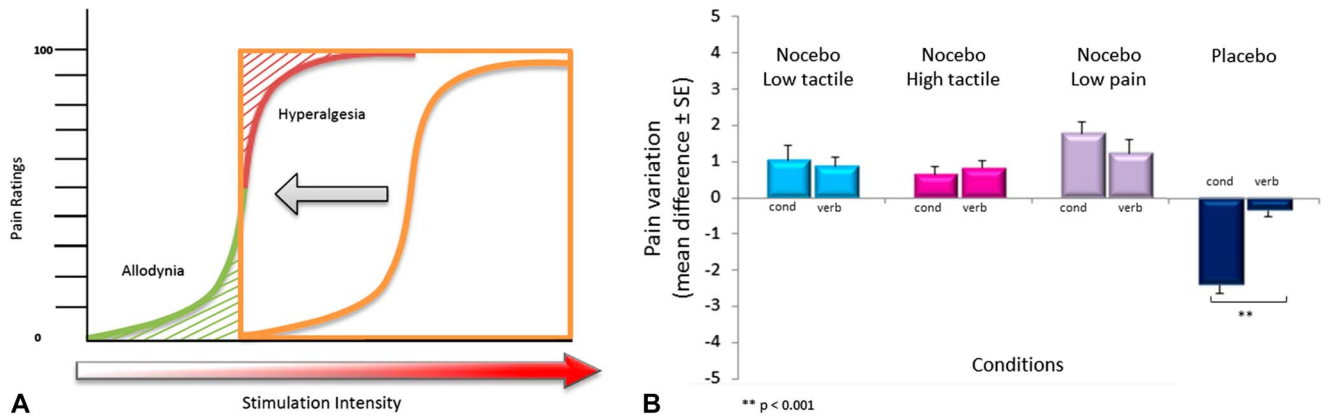

Figure 1. Verbal suggestions and conditioning elicit the same magnitude of nocebo effects. (A) Allodynic and hyperalgesic pain profiles. Allodynia refers to pain in response to a stimulus that does not normally elicit any pain and hyperalgesia refers to increased pain from a stimulation that normally induces low pain. Adapted from Ref. 66 (Republished with permission of The American Physiological Society, from Sandkuhler J. Models and mechanisms of hyperalgesia and allodynia. Physiol Rev 2009;89:707–58. Permission conveyed through Copyright Clearance Center, Inc. (B) Contribution of verbal suggestions and classical conditioning to nocebo responses. Low and high nonpainful tactile stimuli were turned into painful experiences after study participants were told about the possibility to experience high pain. Similarly, low pain was perceived as painful ones, with or without being exposed to high pain via the classical conditioning. Thus, allodynic and hyperalgesic effects may be triggered by suggestions alone. A different trend was observed in the placebo analgesia condition in which experience matters more than being informed about pain relief. Data from Ref. 34. The red arrow indicates the stimulation intensity. The gray arrow indicates the switch between allodynia and hyperalgesia.

6. Negative expectancies and social learning

Nocebo effects can be the result of negative expectancies or the failure of developing positive expectancies, and can be shaped by social observation and vicarious learning. Pain is influenced by social interactions and can be modulated through the observation of others.[37] Observational learning is defined as changes in behavioral patterns that are a consequence of observing the behavior of others. Through an observation of a particular situation, an individual acquires information about that circumstance and about the consequences of specific actions.[6] There are some indications about how pain-related beliefs and attitudes are affected by the observation of others in pain.[48] More specifically, the observation of a painful experience in another person, whether through a live or video demonstrator or a confederate, can cause a more painful sensation in the observer when he or she experiences the same situation.

Colloca and Benedetti[26] showed that the participants who were observing an analgesic effect in another person when a light flashed, displayed analgesia when they were exposed to the same light paired with high level of pain. The social observation (vicarious learning) played an important role in the development of placebo effects. In particular, the placebo analgesia generated in the observer positively correlated with the grade of empathy of the observer. Social learning produced placebo effects of the same magnitude as classical conditioning.[26]

Similarly, vicarious learning can favor an increase of pain experience. Yoshida et al found strong hyperalgesic effects that were correlated with observed uncertainty following an indirect social-observation paradigm in which participants saw a group of 8 people rate their pain levels to painful stimuli that they will later receive on themselves. Brain imaging findings revealed that these effects were positively correlated with periaqueductal gray activity.[82]

Recently, another study sought to evaluate socially induced nocebo hyperalgesia through a similar social-observation paradigm.[78] Ninety-seven women were exposed to either a nocebo condition or control condition, through which participants observed a video portraying a female model experiencing more pain after application of an ointment in the fingers of the right or left hand, and less pain when no ointment was applied. Women in the nocebo condition saw the female model express high pain when the ointment was applied, whereas those in the control condition observed the female model report low pain throughout the procedure. Investigators also measured multiple personality traits and cognitive styles to evaluate the potential relationship between these and elicitation of nocebo effects and included pain catastrophizing, hypochondriacal concerns, and empathy, as well as depression and anxiety as control measures. Unspecific somatic complaints were also assessed. Results demonstrated a significant difference in the pain ratings as an effect of group condition, and also as an effect of ointment applications within each condition. Women within both the nocebo and control conditions reported more pain with application of the ointment. Furthermore, ratings of pain were higher in the nocebo condition than that in the control condition, which suggests a potentiated perception of pain related to the social observation.

In this study, nocebo responses were correlated with hypochondriacal trepidations as well as somatic complaints in the control condition group but not in the nocebo group.[78] Nonetheless, contradictory results have been observed in regard to the psychological factors correlated with nocebo effects. In a different study, the same research group found that the nocebo response was positively associated with pain catastrophizing.[77] The role of personality factors in the nocebo effect is further discussed in the next section.

Another study documented that nocebo hyperalgesia was found in a group who observed a male or female model receive less painful stimulations with the appearance of a green-light, and higher pain intensities with appearance of a red-light, for a period of about 5 minutes prior to receiving the stimuli themselves. Results showed that participants who observed the model rated the red-stimuli as more painful when compared to the control groups who did not engage in the social observation period. A sex effect was also apparent, as the hyperalgesic effects were more potent after observing the male model receiving the painful stimulations, regardless of the sex of the participants. Moreover, psychological assessments revealed that empathetic traits were a predictor of the level of nocebo hyperalgesia.[74]

Recently, an investigation conducted by Faasse et al showed that social modeling influences both placebo and nocebo effects, from a physiological and behavioral standpoint. In the study, 82 participants were administered a placebo tablet described as a fast-acting beta-blocker which was presented as either a branded or a generic counterpart and were told that the purpose of the study was to evaluate the effects of the medication on pre-examination anxiety. Following the ingestion of placebo, groups were randomized to either see a female participant—who was in reality a confederate—describe adverse effects related to the ingestion of the same medication, or not. Participants were informed that the medication would lower both their blood pressure and heart rate, leading to greater feelings of relaxation, and that they could experience multiple mild side effects such as headache, tiredness, drowsiness, nausea, stomach pain, among others. Investigators measured blood pressure, heart rate, anxiety, and physical symptoms and found that participants in the group exposed to the female confederate reported both more total symptoms and more symptoms attributed to medication side effects than those who were not exposed to such event. Moreover, a significant association between sex and reported symptoms was observed, with female participants who were exposed to the female confederate reporting about twice as much total number of symptoms and medication-attributed side effects than the other groups.

Interestingly, sex-specific nocebo effects have been observed in other social modeling and observation paradigms. Lorber et al showed an increase in both specific and nonspecific symptoms in participants who were randomly assigned to inhale an inert placebo that was described as an alleged environmental toxin. Half of the participants also observed a female confederate inhale the supposed toxin and express specific symptoms. It was found that following the observation of the female confederate, women but not men reported a significant increase in specific symptoms. In this particular study, authors were evaluating, in a laboratory setting, the effects of expectancy and modeling in mass psychogenic illness, which has been previously observed to affect women more than men.[59]

In all the above described instances, social observational learning stimulated both specific and nonspecific nocebo effects and responses. This “social contagion of negative emotions” could have strong implications in the management of individual clinical outcomes, particularly for pain management, when considering the interplay between the social environment as well as the interpersonal interactions of patients.[10]

Social modeling through multiple media outlets, such as medical information retrieved from the internet and shared among social media, as well as pharmacological advertisements and descriptions of health-related environmental factors and

warnings through television channels are strongly involved in socially induced nocebo effects.[42] For example, Fassee et al described the "thyroxine health scare" that affected New Zealand following manufacturing-related modifications of Eltroxin, the medication used in the country for thyroid replacement therapy in patients with hypothyroidism. The drug's size, shape, taste, and color were different, although bioequivalence was ascertained. In 18 months, there had been a 2000-fold increase in adverse events attributed to the medication. The reported effects, which subsided almost completely in a year and a half, were the result of a complex interplay of circumstances that shaped patients' expectations and beliefs about the medication and the company involved in its manufacture, all of which were influenced by the following: (1) misinformation regarding the actions to be taken by the national agency controlling medication implementation; (2) patient's prior negative suspicions surrounding one of the involved companies' financial motives and actions; (3) constant and increased media attention and propagation of detailed information about reported side effects across the country through TV and radio, including false rumors alleging that the drug's manufacturing was taking place in India, and that genetically modified ingredients as well as monosodium glutamate were being added to the medication; (4) a health care professional figure actively attributing side effects to the newly implemented medication in the media; (5) changes in drug appearance; (6) and from inaccessibility to different pharmacological agents for the same condition.[41]

These effects may be of special relevance in inpatient clinical settings where patients observe other patients interacting with the health care personnel, as well as their responses to pain and pain treatments. Indeed, negative expectations that are induced by the medical staff also lead to the formation of nocebo effects.[15,31] In clinical settings, expecting side effects from medical treatments is consistently associated with higher reports of nocebo effects. Expectations about side effects, that produce nocebo effects, can be induced through verbal suggestion[15] or written information,[20] the latter including information provided during the informed consent process about potential adverse events.[7] The expectations of the patients receiving a treatment are of particular importance, but the health care provider's belief about negative outcomes can also produce nocebo effects. Therefore, the relationship between patient and medical staff has the power to influence the patient's experience of treatment side effects.[17] Additionally, failure to give positive instructions associated with painkillers can be of utmost importance in reducing positive expectations. In contexts where computerized pumps, which contain pain medication and are connected directly to a patient's intravenous line, the patient–clinician interaction and communication is limited. In such cases, the pump is set to deliver painkillers on demand jeopardizing the positive psychosocial context associated with treatments. The open-hidden paradigm serves as an empirical model for exploring the role of the psychosocial context. Seeing, feeling, smelling, or tasting a medication tends to create higher placebo effects. Information helps patients to direct their attention to these features, in turn forming expectations of effectiveness that would minimize nocebo effects.[11,12,30]

7. Personality factors

Factors such as choice of a medication[9] and higher perceived dose of exposure, explicit suggestions that the exposure triggers arousal or symptoms, observing people experiencing symptoms from the exposure, and higher expectations of symptoms have been listed as critical variables for inducing nocebo effects associated with medication or other interventions according to a recent systematic review.[80] In laboratory settings, recent studies have begun to provide evidence that personality and psychological factors are critically associated with aversive responses to pain and proneness to nocebo effects.[26] Suggestibility, a trait-like characteristic facilitating body sensations (eg, physical suggestibility), has been linked to nocebo effects.[36] Catastrophizing, an important psychological factor for pain management therapies, was also found to be relevant for nocebo effects.[77] Corsi and Colloca (under review) have recently

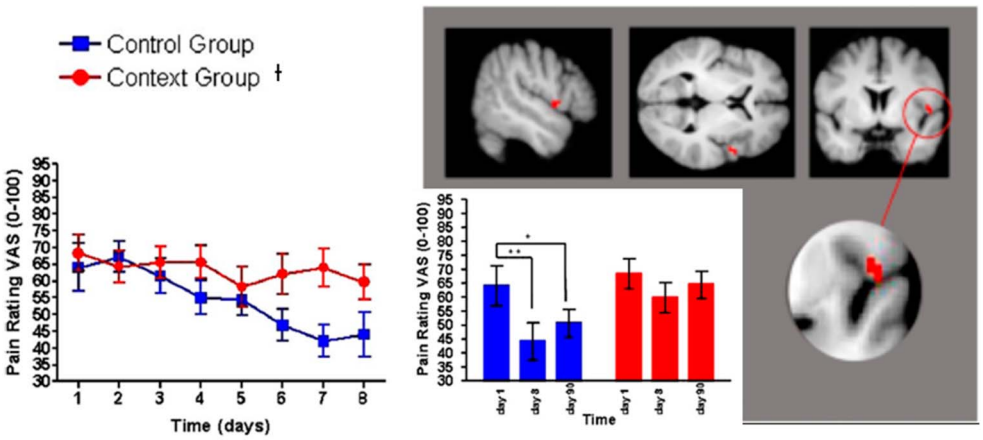

Figure 2. Nocebo effects persist over time. Pain reports for the context group (red) and the control group (blue). The left part shows the pain reports on a visual analog scale from 0 (no pain) to 100 (worst pain imaginable) during 8 consecutive days of experimental testing. The same participants were tested for pain sensitivity after 90 days and the control group showing habituation to pain but not the context group. Importantly, the fMRI data indicated a higher activation of the right parietal operculum compared to the control group. Adapted from Ref. 65. Republished with permission of The Society for Neuroscience, from Rodriguez-Raecke R, Doganci B, Breimhorst M, Stankewitz A, Buchel C, Birklein F, May A. Insular cortex activity is associated with effects of negative expectation on nociceptive long-term habituation. J Neurosci 2010;30:11363–8. Permission conveyed through Copyright Clearance Center, Inc. The red marks indicate the activation in the right pariental operculum and the red circle shows a zoomed activation area.

demonstrated that anxiety sensitivity, physiological suggestibility, and catastrophizing (eg, rumination, helplessness, and total catastrophizing) are associated with nocebo hyperalgesic effects contributing to report medium pain as an experience of harmful intense pain. Further research is needed to explore the role of anxiety, suggestibility, and catastrophizing on the formation of nocebo effects. Importantly, higher expectations—belief that something will happen or is likely to happen[68]—of pain were associated with larger nocebo effects, and these effects were independent of prior exposure to pain increases occurring as part of the acquisition phase of a conditioning paradigm.

8. Biochemical and neurophysiological mechanisms

The behavioral studies described in the previous sections are supported by psychopharmacological[14,15] and neuroimaging research.[38,65]

Neuropharmacological studies of the nocebo have detailed some of the mechanisms underlying hyperalgesia.[13,14] The oral administration of an inert talc pill given along with verbal suggestions of hyperalgesia induced an increase of cortisol plasma concentrations and hyperactivity of adrenocorticotropic hormone release. Both nocebo hyperalgesia and hypothalamic–pituitary–adrenal axis (HPA) hyperactivity were blocked by the benzodiazepine diazepam, indicating that anxiety plays a role in these effects. The mixed cholecystokinin (CCK) type-A/B receptor antagonist, proglumide blocked nocebo hyperalgesia with no effect on cortisol and adrenocorticotropic hormone supporting the direct role of CCK in the hyperalgesic nocebo effect.[14] Animal studies have also showed that the CCK antagonist CI-988 prevents anxiety-induced hyperalgesia with an effect that was similar to that produced by the established anxiolytic chlordiazepoxide.[2]

Brain imaging studies have shed light on the neuroanatomical areas that are involved in the modulation of innocuous stimulations,[67] as well as the exacerbation of pain when study participants expect a high-intensity noxious stimulus. Increased anxiety and alertness lead to changes in perceptual processing, creating an augmentation of pain experience and processing.[52,58,63] For example, the mere expectation to feel more pain after the administration of an inert medication affects a laser-induced pain experience and related laser-evoked potential amplitude in the treated hand.[62] The magnitude of nocebo effects were not potentiated by conditioning as occurs for the positive placebo effects.[34] Changes in EEG activity, namely, an enhancement of low alpha (8–10 Hz) activity have been linked to nocebo manipulations that increase intensity and unpleasantness of heat-induced pain.[1]

Informing study participants about the occurrence of heightened pain, even if given only once, interferes with the natural habituation that can be experienced when painful stimulations are repetitively delivered, and produces hyperactivity of the insular cortex over time periods as long as 8 and even 90 days (**Fig. 2**).[65] Expectancies also impact the interruptive function of pain that negatively affect cognitive task performance. Positive expectation abolished the detrimental effects of pain on cognition by changes in functional connectivity between rostral anterior cingulate cortex (ACC), posterior fusiform cortex and the hippocampus. Connectivity between ACC and fusiform gyrus during painful stimulation decreased in the negative expectancy group, indicating that verbal instructions related to pain deserve further investigation.[71] Startle reflex[3] and electroencephalogram[1] are modulated by negative expectancies and have been associated with nocebo hyperlagesia.

Moreover, Bingel and colleagues studied the effect of expectancies (expectancy of a positive analgesic effect and expectation of hyperalgesia or exacerbation of pain) on a fixed concentration of the μ-opioid agonist remifentanil on constant heat pain. Positive expectancy doubled the analgesic response to remifentanil, while expectancy of pain exacerbation blocked the remifentanil analgesic action. The fact that brain analgesic effects induced by μ-opioid agonist remifentanil were completely over-ridden when study participants were told that the drug infusion was stopped (when it had not) indicated that negative expectations can robustly interfere with the pharmacodynamic profile of painkillers.[19] The negative effect was mirrored by an activation of the hippocampus, an area previously linked to the nocebo effect.[57]

It has been postulated that changes in cortical pain responses may be secondary to earlier amplification of incoming pain signals within the spinal cord. A recent study combined a conditioning paradigm using painful contact hear stimulations with spinal

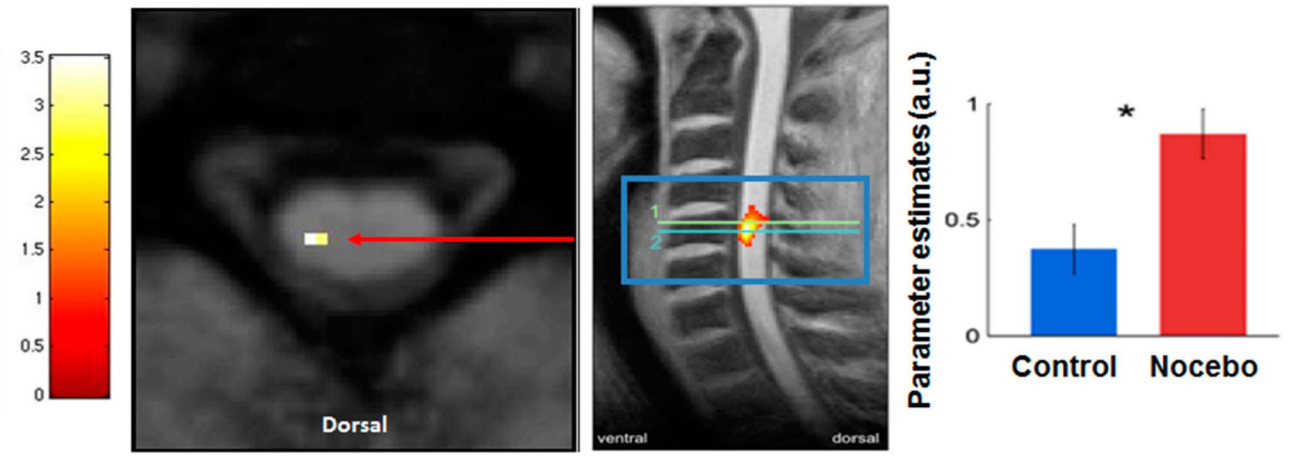

Figure 3. Nocebo effects at the level of spinal cord. Study participants were informed that a cream would increase pain experience. During the acquisition phase, the level of pain was surreptitiously enhanced to simulate increased pain because of the cream. During the testing phase in the fMRI, the pain intensities were identical. Participants reported higher pain to the heat stimuli delivered to a lower intensity level. The fMRI results indicated an increase of activity in the left ipsilateral dorsal horn, suggestive of nocebo-induced hyperactivity. Adapted from Ref. 47. Republished with permission of The Society for Neuroscience, from Geuter S, Buchel C. Facilitation of pain in the human spinal cord by nocebo treatment. J Neurosci 2013;33:13784–90. Permission conveyed through Copyright Clearance Center, Inc. The red arrow indicates activity in the ipsilateral dorsal horn and the blue box indicates the spinal sagittal section. *$p < 0.050$.

functional magnetic resonance imaging in healthy participants. The authors detected a strong activation in the spinal cord at the level of the stimulated dermatomes C5/C6 when a local topic inert nocebo cream was applied along with verbal suggestion of pain increases, and with exposure to high painful stimulations during the acquisition phase of the conditioning paradigm (**Fig. 3**). There was overlapping activation in the ipsilateral dorsal horn of the spinal cord during painful stimulations, supporting a potential direct evidence for a pain-facilitating mechanism in the human spinal cord in relation to nocebo effects.[47]

Nocebo responders showed a decrease of both mesolimbic dopaminergic and opioid system activations. The dopaminergic system showed reduced activity in areas of the brain such as the ventral basal ganglia, while the endogenous opioid system showed a reduction of activity in the rostral and subgenual ACC, orbitofrontal cortex, anterior and posterior insulae, medial thalamus, nucleus accumbens, amygdala, and periacqueductal area, as evidenced in a PET study.[70] Although data on the genetics involved in the nocebo effect are limited, a recent study by Wednt et al[81] suggested a role of the Catechol-O-Methyltransferase Val158Met Polymorphism in nocebo effects. In this study, 62 healthy Anglo-American men were given the immunosuppressant calcineurin inhibitor CsA during the acquisition phase of a pharmacological conditioning paradigm, followed by the placebo treatment. Results showed that those with the Val158/Val158 genetic variant reported more general and specific psychological and medical complaints at baseline as well as after medication intake, respectively. Moreover, Val158 homozygotes significantly reported more specific side effects following placebo intake when compared to the Met158/Met158 and Val158/Met158 groups. Importantly, these results were unrelated to treatment-related changes in psychological or biological parameters evaluated during the experimental session through anxiety and cardiovascular measurements. When compared to other genotypes, Val158 homozygotes appear to more strongly recognize naturally occurring somatovisceral sensations and to classify them as unpleasant or noxious.[81] Interestingly, Zubieta and colleagues previously observed that Met homozygotes presented with lower pain tolerance but higher μ-opioid receptor density when compared to Val homozygotes and heterozygotes.[83] The effects of the Val158/Val158 genetic variant of the catechol-O-methyltransferase gene on placebo effects appear to be different than nocebo effects. A recent study in individuals with irritable bowel syndrome showed that the largest placebo effect occurred in met/met homozygotes.[49] Although more studies with larger and more diverse samples need to be conducted, these finding adds to the literature describing important differences between the mechanisms of the nocebo and placebo phenomena, and highlights catechol-O-methyltransferase genetic variability as a mediator of both nocebo and placebo effects in an opposite fashion.

A thorough understanding of the mechanisms underlying nocebo effects can help characterize factors driving the interindividual variability that is distinctive of nocebo responses, with the scope of developing personalized interventions that are shaped based on patients' psychophysiological characteristics.

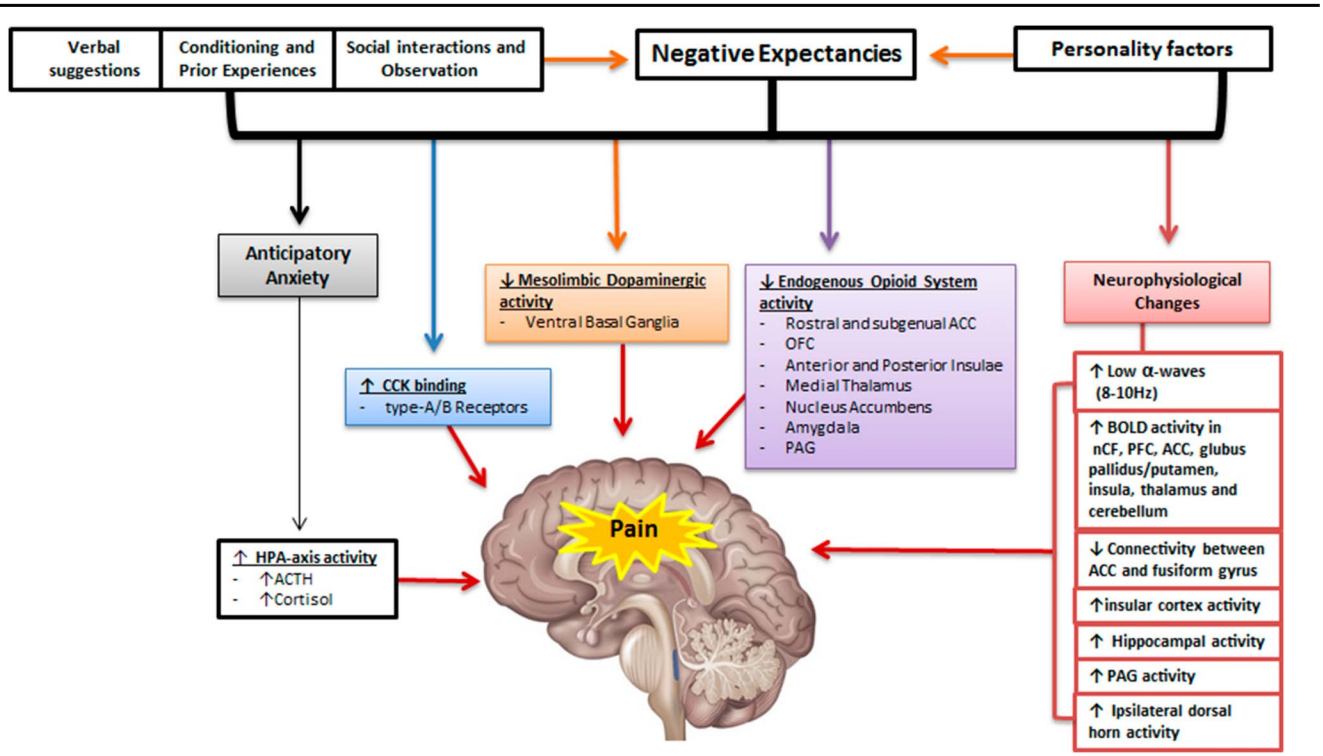

Figure 4. Nocebo algesia and hyperalgesia are triggered by an individual's negative expectancies around a treatment or intervention, its efficacy, and its potential outcomes. These expectations can be shaped by verbal suggestions or instructions, the individual's prior experience and conditioning with the same or related treatments, as well as by the observation of others in pain (social observation/vicarious learning) and individual psychological characteristics such as personality factors. This complex interplay of cognitive-affective factors leads to physiological changes that can initiate as well as promote algesic and hyperalgesic states including anxiety changes along with an activation of the hypothalamic–pituitary–adrenal (HPA) axis and the cholecystokinin (CCK) system. Hypoactivity of the mesolimbic dopaminergic and of the endogenous opioid systems have been observed following exposure to a nocebo procedure. Neurophysiological changes in the brain include increased activity of the nCF region, the insular cortex, the hippocampus, the periaqueductal gray area (PGA), the hippocampus and the ipsilateral dorsal horn, as well as decreased connectivity between the anterior cingulate cortex (ACC) and the fusiform gyrus. Finally, EEG recordings have also shown increased levels of low-frequency α-waves associated with nocebo-induced pain.

Further investigation on the genetic determinants of the nocebo effect holds promise for developing strategies to help identify individuals with specific genotypes and phenotypes that could negatively influence intervention outcomes. By doing so, clinicians could take actions that appropriately tailor the clinical environment for the benefit of the patient. The neurochemicals identified as influential factors in nocebo effects, such as dopamine and CCK, partake in a variety of complex pathways and systems associated with pain disorders and its related comorbidities. Thus, knowledge on the complexity of the endogenous pain modulation systems as they relate to cognitive-affective factors could serve as the foundation for understanding potential etiologies or disease-promoting elements, as well as for developing new intervention approaches and strategies. This way, there is more potential for controlling interventions in both specific and nonspecific ways to increase treatment effectiveness and positive outcomes.

9. Conclusions

The paucity of studies linking the psychological and neurobiological changes limits the transfer of knowledge from bench to beside. It is critical to define commonalities and differences across distinct ways to elicit nocebo effects. Exploring, for example, how verbally induced nocebo effects differ from those related to direct and vicarious learning can advance the overall knowledge of this phenomenon.

Expectations deriving from the clinical encounter can produce negative effects and outcomes. Verbal suggestions, the provider's behaviors, environmental conditioning cues, the appearance of medical devices, prior experiences of failed interventions, and social learning induce negative expectancies that are linked to the neurobiological modulation of pain pathways and circuitries (**Fig. 4**).

Additionally, affective and cognitive traits could be important as well. Some personality traits and psychological factors, such as anxiety,[61,72] harm avoidance and persistence,[36] pessimism,[36,46] and fear of pain,[4] may influence the responsiveness to nocebo.

Research described in this review focuses on mechanistic findings with the scope to raise awareness about the interplay between the changes occurring in the descending pain modulatory systems and the individual subjective pain experience. Specifically, research on the nocebo effect indicates that algesic and hyperalgesic effects can result from information as well as patient–clinician communication and clinical encounters surrounding the patient. Questions such as: How health care providers should frame verbal and nonverbal communication with their patients in light of the findings deriving from nocebo research and how we can accurately convey information about side effects while minimizing nocebo effects have been discussed somewhere else[18,27] and in detail in a related review specifically designed to cover the clinical implications of nocebo research.[55] These findings have the potential to help patients with chronic pain and other comorbidities where cognitive and affective processes act as major factors affecting pain clinical outcomes. Nocebo research would benefit from further mechanistic studies exploring the neural processes underlying negative changes in somatosensory perception, nociception, and pain signaling. Moreover, there is a critical need to explore how human behaviors can be "deconditioned" by using psychological interventions to reverse nocebo effects. Finally, further research on the neurobiology of fear-, stress-, and anxiety-related nocebo effects can help discover therapeutic targets to tailor the development of pharmacological treatments.

Disclosures

The authors have no conflicts of interest to declare.

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