How negative experiences influence the brain in pain: neuroimaging and biobehavioral insights

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Chapter 1.

General introduction

Learning decisively shapes the way individuals experience the world around them and how they respond to various external stimuli, including pain [1–3]. Increased pain sensitivity can result from negative experiences creating negative expectations about an environmental stimulus, such as a treatment, a phenomenon termed nocebo hyperalgesia [1–3]. Nocebo has been described as the negative counterpart to placebo. Nearly a century into the proliferation of placebo-controlled studies [4–6], research has shown that learned expectations regarding inert treatments may not only have positive placebo effects, but may also mimic negative treatment outcomes, such as medication side-effects [7–9]. Nocebo responses may thus produce deleterious effects on a variety of symptoms, as a result of learning mechanisms that are not yet fully understood. For example, it remains unclear how negative expectations on a cognitive level influence pain processing in the brain, or what the involvement of relevant emotions may be. Due to a known involvement of learning in the experience of pain [1,10–12], it is important to study and better understand the biobehavioral mechanisms that underly nocebo hyperalgesia.

In this general introduction, first, nocebo hyperalgesia will be framed as a multifaceted phenomenon that can be part of the intricate mechanisms of pain processing. Cognitive-emotional pain processing is described in the context of learned nocebo responses and as complimentary to sensory-discriminatory nociceptive processing. The state of the art in experimental nocebo research and the relevance of experimental learning mechanisms are then outlined. Experimental models that are typically implemented to investigate the cognitive and emotional aspects of nocebo hyperalgesia are described. Cognitive processes such as learning, as well as emotional processes such as fear, are then presented as major putative underlying factors in nocebo hyperalgesia, as indicated by experimental findings. Biobehavioral underpinnings of nocebo effects are then discussed in relation to current neurobiological literature; gaps in knowledge are highlighted. Finally, an outline of the current dissertation is presented.

Nocebo hyperalgesia and its involvement in pain

Nocebo hyperalgesia seems to be an intricate component of pain processing. Due to the multifaceted, subjective, and often unpredictable nature of pain, recovery from pain and chronic conditions are especially difficult to manage [13]. Pain has been described to arise in response to a nociceptive signal from the body, but this is not always a direct path. Rather, the experience of pain is heavily influenced by an array of processes within the nervous system [14]. These intricate processes do not merely rely on information regarding the nature of the nociceptive stimulus, but may include pain processing based on past experiences or cognitive-emotional factors such as fear [13]. We start by outlining the basic mechanisms of pain processing, in order to examine how these may be influenced by cognitive and emotional elements under nocebo hyperalgesic conditions.

Due to the multifactorial nature of pain, processing of nociceptive input involves a large, distributed neural network that is not yet fully understood [15]. Pain pathways have been extensively investigated via neuroimaging methods such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) and are thought to encompass numerous brain regions and processes. One neural system that has been implicated in pain processing relays sensory-discriminatory functions that are mainly involving nociceptive stimulus information. A second, more distributed system, is thought to be involved in cognitive-evaluative processes [16,17] and these could relate to learning and behavioral underlying factors. It should be noted that these networks and systems are not clearly defined, and that the literature contains inconsistencies regarding the exact brain areas that may be included in these systems [17]. Nevertheless, sensory-discriminatory processes and cognitive-evaluative processes have been extensively researched and are often found to play important roles in pain perception [16–18] and in nocebo hyperalgesia [19–21].

Further insights come from biobehavioral studies illustrating that the experience of pain arises from a combination of bottom-up processes (for example, the type and intensity of nociceptive stimulation) [22–27] and top-down processing (for example nocebo-related processes such as learning or emotional modulation of incoming pain signals) [23,26,28–31]. As one potential product of this interplay between sensory perception, cognition, and emotion, nocebo hyperalgesia is a complex phenomenon, and sophisticated experimental methods are required to understand its influence on pain.

Experimental learning mechanisms

Research typically induces nocebo effects by use of experimental learning models. Experimental models refer to simulations of conditions or responses to treatment that resemble clinical conditions and are induced in healthy individuals, artificially, in a laboratory. In nocebo research, learning manipulations consistently induce nocebo hyperalgesic responses. Typically, conditions in which a sham treatment is associated with pain aggravation are created by use of well-established learning techniques such as classical conditioning or providing negative verbal or written information. Experimentally induced nocebo hyperalgesia in healthy subjects enables researchers to examine these effects, in order to disentangle the mechanisms by which learning can affect pain sensitivity.

In the most robust experimental models of nocebo hyperalgesia, classical conditioning forms and reinforces pain expectations through associative learning [11,32–34]. In conditioning models of nocebo hyperalgesia, an association between a high-intensity pain stimulus (unconditioned stimulus, UCS) and a nocebo (inert treatment) conditioned stimulus (CS) is formed by repeatedly pairing the two stimuli. After repeated trials, an association between the nocebo

stimulus and the worsening of pain is formed and the nocebo stimulus can evoke changes in perceived pain (conditioned response, CR), similar to the previous pain stimulus (**Figure 1**) [35,36]. The powerful associative learning mechanisms employed by classical conditioning serve to recreate learned hyperalgesic responses to a specific stimulus. Classical conditioning thus attempts to recreate a putative clinical context in which not only physical injury but also memories of previous experiences and expectations about the future could have a strong impact on pain symptoms.

Verbally delivered negative information can also alter pain expectations through instructional learning. Negative suggestions typically involve explaining the pain-enhancing effect of a (sham) treatment. Suggestions are used to induce nocebo hyperalgesia by themselves or to enhance the effectiveness of nocebo conditioning [9,37,38]. The combination of conditioning and verbal suggestions is found to create the strongest experimental model of nocebo hyperalgesia [7,39]. This points towards a complex interplay of diverse learning processes that may underlie nocebo effects.

Experimental models are thus suited for examining pain aggravation under nocebo hyperalgesic conditions, but they can also shed light on pain chronification due to nocebo. Experimental attenuation models of conditioned effects have shown that learning may be involved in the persistence of pain over time. Paradigms that employ extinction or counterconditioning methods may provide valuable insights into the factors that contribute to nocebo responses [40–43]. In a typical extinction paradigm, associations between the UCS and CS are discontinued, and learned effects would be expected to become extinct over multiple trials that are no longer negatively reinforced [7,39]. This type of behavioral paradigm represents that, even classical conditioning has been discontinued, increased pain sensitivity can persist in response to a learned nocebo stimulus, over a prolonged period of extinction [42,44]. The

clinical implications of negative pain effects that are resistant to extinction or other forms of nocebo attenuation remain unclear [1].

Cognitive-emotional factors

Experimental nocebo models that include conditioning and negative suggestions also enable the study of diverse cognitive and emotional factors that may be involved in nocebo hyperalgesia. Cognitive manipulations, such as varying the type of learning, can shed a light on the intricate processes that give rise to the experience of pain. Factors that contribute to the formation or the persistence of nocebo effects can be studied using manipulations within experimental models. For instance, studies have shown that consistent and repetitive learning methods, such as classical conditioning with continuous reinforcement of an association, induces the strongest nocebo responses [42]. However, interrupted or inconsistent learning is still able to induce nocebo hyperalgesia to some extent [42,45], which may be important from a clinical perspective, where pain and learning may be less consistent than in experimental settings. Partially reinforced learning has been shown to slow down the extinction or minimization of learned effects [45], including nocebo effects [46].

Learning as an underlying cognitive factor contributing to the formation of nocebo effects may also be investigated at a neurobiological level. Brain plasticity has long been shown to be non-unitary [47–50], with multiple mechanisms and processes being involved in different types of memorization, learning, as well as recall [48,51,52]. Given this multifaceted nature of learning, precise manipulations, targeting associative aspects of learning, hold the potential of enriching our understanding of hyperalgesic pain responses. For example, structures such as the N-Methyl-D-aspartate (NMDA) receptor and neurochemicals such as glutamate have been consistently implicated in a broad array of brain

plasticity processes, including learning by association [53–54]. Pharmacological manipulation of these receptors has been proven fruitful for enhancing learning during exposure therapy [53–55] and may also prove useful in the examination of the precise neurocognitive mechanisms, such as specific receptors and localized learning processes, that may facilitate nocebo hyperalgesia.

Emotional underlying factors, such as fear of pain symptoms, may additionally tie into the processing of pain based on prior experiences and expectations. Through the common theme of learning, nocebo hyperalgesia bares some similarities to the formation of phobias [56–58]. Nocebo and phobic responses may both be characterized by a key involvement of cognitive-affective components such as aversive learning and fear of a stimulus [12,53,59]. Indeed, neural correlates of nocebo hyperalgesia show some involvement of fear processing. This is especially evident by the consistent involvement of the amygdala in both nocebo responses [19,20,60] and fear responses [61–64]. Similarly to nocebo conditioning, pain-related fear can be acquired through associative learning [65–68]. Pain-related fear may thus be relevant to nocebo effects because it may arise in experimental models as a result of experienced pain or as a result of threatening information regarding upcoming pain. Fear experienced during nocebo conditioning may thus potentially augment the acquisition of negative expectations, but experimental studies on this are lacking so far. This makes fear an especially important factor to study in relation to nocebo hyperalgesia.

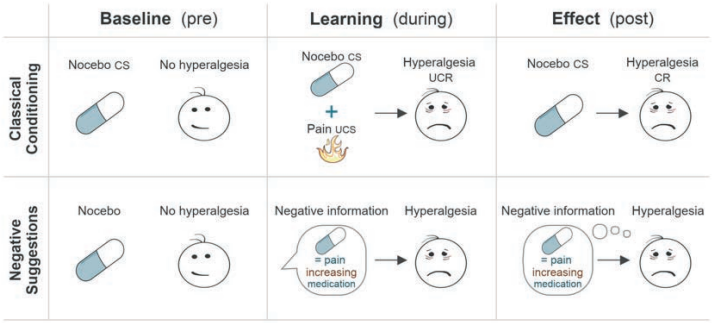

Figure 1. A representation of typical experimental procedures for delivering classical conditioning and negative suggestions. At baseline before any intervention, an inert treatment has no effect. In the case of a conditioning paradigm this becomes a conditioning stimulus, CS, but in verbal suggestion paradigms no conditioning takes place and suggestions can be delivered once, verbally or in writing. A nocebo treatment is here represented as an inert pill. During a learning paradigm, the negative association between the nocebo treatment and pain aggravation (unconditioned stimulus, UCS) is experienced by the subject (unconditioned response, UCR). If learning a negative association comes in form of a verbal suggestion, continuous learning is not required, and one suggestion can in principle suffice. Thereafter, a nocebo effect on pain (conditioned response, CR in the case of classical conditioning) is formed, as a result of learned negative expectations regarding the nocebo treatment.

Biobehavioral underpinnings

In recent years, fundamental research has focused on unravelling how nocebo responses are formed and how they may integrate in pain processing. In order to reach a better understanding of the neurocognitive components of nocebo effects, it is imperative to build on previous nocebo research, by utilizing consistent experimental models. In this way, results are comparable, and the reliability of findings can be tested over multiple studies. Theories and findings from the nocebo literature should also be connected to what is currently known about overlapping cognitive and emotional processes. Comprehensive reviews of the current state of research into the neural correlates of

nocebo hyperalgesia can thus be very valuable, next to neurobiological studies that build upon this accumulation of knowledge.

Research to date has highlighted some key areas that may be involved in nocebo hyperalgesia. Pain-specific processing has been implicated in the presentation of nocebo hyperalgesic responses. For instance, the dorsal horn of the spinal cord, the secondary somatosensory cortex, and the dorsolateral prefrontal cortex (dlPFC) all seem to be activated during nocebo responses [11,15]. This may indicate that pain reports under nocebo hyperalgesic conditions closely resemble typical pain processing. Concurrently, nocebo responses have also been shown to involve brain areas such as the anterior cingulate cortex (ACC), amygdala, and hippocampus [11,69], which supports an involvement of cognitive-emotional factors in nocebo effects, which are also involved in pain processing and integration. Nocebo hyperalgesia also seems to involve chemical systems, such as prostaglandins, cortisol, and dopamine [69,70], while electrophysiological correlates point towards an involvement of alpha and gamma brain rhythms [71–73]. It is thus evident, albeit not surprising, that nocebo hyperalgesia largely overlaps with pain processing. The involvement of a wide network of cognitive-emotional processing is also supported by neurophysiological findings. However, replicating findings from one nocebo study to the next seems challenging due to the implementation of diverse experimental models and distinct learning mechanisms between different studies. Employing diverse methods helps clarify specific aspects of nocebo hyperalgesia but also leads to inconsistencies and gaps in the literature, rendering nocebo hyperalgesia a phenomenon that is still poorly understood on a neurocognitive level.

With learning and the formation of expectations being at the heart of the most robust nocebo theories [1,11,72,74,75] it is important to observe and interpret similarities between these cognitive processes and nocebo effects. Limbic system structures, and especially the amygdala, are

known to play a crucial role in learning and memory formation [76–79]. More specifically, the amygdala and hippocampus, structures sometimes implicated in nocebo effects [20,21], play essential roles in the formation of new memories based on past experiences [80–82]. At the same time, the consistent involvement of the ACC in nocebo effects may be drawing together prior memories, expectations, and information processing. The ACC is an area that is largely interconnected to the limbic system and may play a key role in cognitive control and conflict monitoring [83,84]. These neuroscientific similarities may indicate that nocebo hyperalgesia involves a complex cognitive network that is responsible both for memory formation and for the recall and integration of learned expectations and incoming sensory information. Brain plasticity, learning, and cognitive-emotional factors, seem to form an interconnected, cortical-subcortical network that may be involved in nocebo hyperalgesia and in pain processing [21,60,62,85] (**Figure 2**).

Yet, inconsistencies and a lack of replicability between nocebo studies do not permit for firm conclusions to be drawn. Cognitive and emotional components, such as learning and fear, seem have a critical role in the formation of nocebo hyperalgesia. Nevertheless, there is uncertainty regarding the specific learning mechanisms that may be involved, how they affect brain plasticity, and how learning networks may integrate with pain processing. This is evident in the large disparity in neurophysiological findings of fMRI and EEG studies. Inconsistencies in the literature also lead to uncertainty regarding the impact of fear, as compared to related cognitive-emotional responses such as anxiety. It is important for systematic experimental research to actively manipulate states of brain plasticity, learning, memory, and other cognitive processes. While a comprehensive overview of the state-of-the-art in nocebo research is valuable, pharmacological manipulations and other methods that directly manipulate cognitive states may be central components in the strive to unravel the specific neurocognitive mechanisms of nocebo hyperalgesia.

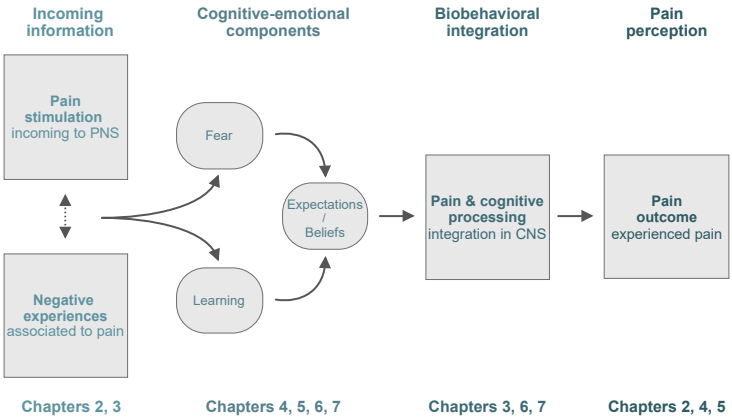

Figure 2. The working theoretical model of this dissertation. In the process of pain perception, incoming information to the Peripheral Nervous System (PNS) regarding a pain stimulus (bottom-up information), in combination with negative experiences, are influenced by nocebo-related cognitive-emotional factors (top-down information). Based on these factors of interest, integrative processing of pain takes place in the Central Nervous System (CNS), with the potential of giving rise to negative pain outcomes related to learned nocebo responses.

The current dissertation

In this dissertation, we address biobehavioral aspects of nocebo hyperalgesia, using neuroimaging as well as behavioral science methods. First, a systematic review and meta-analysis provides a novel examination of nocebo effect sizes and relevant factors in experimental studies. Thereafter, a literature review aims to comprehensively summarize what is currently known about the neurobiological correlates of nocebo hyperalgesia. Subsequently, a series of experimental studies attempt to directly manipulate and study cognitive and emotional factors involved in nocebo, by use of innovative methods. Fear and pharmacological manipulations of specific learning mechanisms are utilized for the first time in these studies, while original

electrophysiological methods reveal biomarkers of nocebo effects. The aim of this dissertation was to further the knowledge on the neurochemical, electrophysiological, and cognitive-emotional processes that underlie nocebo hyperalgesia, with a specific focus on cognition, emotion, and brain plasticity.

In **Chapter 2** we explore the state of the art in behavioral nocebo research with a systematic review and meta-analysis of nocebo literature on somatosensory sensations, including pain. We aim to address the efficacy of different experimental learning methods for the induction of nocebo effects. We systematically summarize results from dozens of studies that investigated these effects, and we discuss the implications of their findings. This meta-analysis showed that across sensations, the magnitude of nocebo responses is affected by the type of learning, with classical conditioning being more potent than verbal suggestions alone. We discuss the lack of explanatory or moderation factors found in the literature. Our analysis served to illuminate the extent to which learning processes induce nocebo effects on different sensations and what the practical and theoretical implications of a lack of moderating factors identified may be for research and clinical practice.

In **Chapter 3**, we review the neurobiological literature on nocebo hyperalgesia. This comprehensive review article summarizes neurobiological findings from studies that utilized (f)MRI, EEG, magnetoencephalography (MEG), as well as pharmacological and biochemical measures. The review provides a comprehensive overview and serves to highlight consistent neural correlates of nocebo hyperalgesia across a variety of different experimental nocebo models. In this way, this overview aims to provide an up-to-date picture of the biobehavioral correlates of nocebo effects. We outline the evidence from this field and give an overview of similarities and differences between nocebo research and learning/memory research.

Building on previous nocebo studies as described in the first chapters of this dissertation, **Chapter 4** presents a randomized controlled trial investigating distinct learning schedules. This experiment aimed to examine the role of continuous versus partial learning and the consequences of such learning schedules for the persistence of nocebo hyperalgesia. For this purpose, both the induction and the attenuation of nocebo hyperalgesia are experimentally manipulated via distinct learning methods. Healthy participants were randomized to receive conditioning on nocebo effects with continuous reinforcement, partial reinforcement, or sham conditioning. In attenuation, counterconditioning (i.e., positive conditioning of the nocebo conditioned stimulus) was compared to extinction for the attenuation of nocebo hyperalgesia. This study provided important insights into the effect that different learning schedules may have on the acquisition and attenuation of nocebo responses.

In **Chapter 5** an experimental study of cognitive-emotional processes is presented. Here, we aimed to investigate how fear can augment nocebo responses and how this may affect the persistence of these responses over time. We experimentally manipulated fear of pain during the induction of nocebo responses. We used two distinct fear inductions. One fear induction method was to manipulate pain levels with the aim of inducing fear of the high pain stimulations. The other fear induction included a threat manipulation that convinced participants that their skin is critically sensitive to pain. This study provided insights into the role of specific types of fear in the acquisition and extinction of nocebo hyperalgesia, which may be of important relevance given the relationship between fear and pain in clinical practice.

Chapter 6 presents an electrophysiological investigation into nocebo hyperalgesia. We aimed to explore alterations in EEG biomarkers during the anticipation, acquisition, and evocation of nocebo hyperalgesia. This thorough investigation served to unravel multiple electrophysiological

aspects of nocebo effects, thereby shedding light on novel aspects of brain processing under nocebo hyperalgesic conditions. We induced nocebo hyperalgesia by use of conditioning and negative suggestions and recorded EEGs before, during, and after nocebo acquisition and evocation. This EEG study enriched our understanding of the role that learning and nociceptive processing play in nocebo hyperalgesia.

In **Chapter 7** we present a pharmacological fMRI study that investigated neurochemical correlates of learning in nocebo hyperalgesia. In this randomized clinical trial, we aimed to pharmacologically manipulate NMDA receptors, known for mediating certain types of learning, such as associative learning involved in classical conditioning. fMRI methods allowed for the exploration of brain activations during nocebo acquisition and extinction. We used classical conditioning and negative suggestions to induce nocebo hyperalgesia in a group receiving a low dose of D-cycloserine (a known partial NMDA receptor agonist) and in a group receiving placebo. These manipulations and imaging methods served to explore how NMDA-dependent learning influences the formation of nocebo effects and several potentially relevant brain processes were identified.

Chapter 8 is a general discussion relating to this dissertation. In this chapter the results of the conducted studies are summarized and connected to the aims of this PhD project. We then further discuss these aims in light of theoretical and practical implications.

References

1. Colloca L, Sigaudo M, Benedetti F. The role of learning in nocebo and placebo effects. Pain. 2008;136(1):211-218. doi:10.1016/j.pain.2008.02.006
2. Hadamitzky M, Lückemann L, Schedlowski M, Engler H. How learning shapes immunity. Neuroforum. 2020;0(0). doi:10.1515/nf-2020-0017
3. LaFreniere LS, Newman MG. Probabilistic Learning by Positive and Negative Reinforcement in Generalized Anxiety Disorder. Clinical Psychological Science. 2019;7(3):502-515. doi:10.1177/2167702618809366
4. Blease C. Consensus in Placebo Studies: Lessons from The Philosophy of Science. Perspectives in Biology and Medicine. 2018;61(3):412-429. doi:10.1353/pbm.2018.0053
5. Gaab J, Locher C, Blease C. Placebo and Psychotherapy: Differences, Similarities, and Implications. In: International Review of Neurobiology. Vol 138. Academic Press Inc.; 2018:241-255. doi:10.1016/bs.irn.2018.01.013
6. Cousins S, Blencowe NS, Tsang C, et al. Reporting of key methodological issues in placebo-controlled trials of surgery needs improvement: a systematic review. Journal of Clinical Epidemiology. 2020;119:109-116. doi:10.1016/j.jclinepi.2019.11.016
7. Blythe JS, Peerdeman KJ, Veldhuijzen DS, van Laarhoven AIM, Evers AWM. Placebo and nocebo effects on itch. Itch. 2019;4(3):e27. doi:10.1097/itx.0000000000000027
8. Atlas LY, Wager TD. How expectations shape pain. Neuroscience Letters. 2012;520(2):140-148. doi:10.1016/J.NEULET.2012.03.039
9. Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: Unraveling the mechanisms of the nocebo effect. Neuroscience. 2007;147(2):260-271. doi:10.1016/j.neuroscience.2007.02.020
10. Koban L, Kusko D, Wager TD. Generalization of learned pain modulation depends on explicit learning. Acta Psychologica. Published online October 10, 2018. doi:10.1016/j.actpsy.2017.09.009
11. Icenhour A, Labrenz F, Ritter C, et al. Learning by experience? Visceral pain-related neural and behavioral responses in a classical conditioning paradigm. Neurogastroenterology and Motility. 2017;29:e13026. doi:10.1111/nmo.13026
12. Aslaksen PM, Lyby PS. Fear of pain potentiates nocebo hyperalgesia. Journal of pain research. 2015;8:703-710. doi:10.2147/JPR.S91923
13. Price TJ, Inyang KE. Commonalities between pain and memory mechanisms and their meaning for understanding chronic pain. In: Progress in Molecular Biology and Translational Science. Vol 131. Elsevier B.V.; 2015:409-434. doi:10.1016/bs.pmbts.2014.11.010
14. Malfliet A, Coppieters I, Van Wilgen P, et al. Brain changes associated with cognitive and emotional factors in chronic pain: A systematic review. European Journal of Pain (United Kingdom). 2017;21(5):769-786. doi:10.1002/ejp.1003
15. Geuter S, Buchel C. Facilitation of Pain in the Human Spinal Cord by Nocebo Treatment. Journal of Neuroscience. 2013;33(34):13784-13790. doi:10.1523/JNEUROSCI.2191-13.2013
16. Jones AKP, Kulkarni B, Derbyshire SWG. Pain mechanisms and their disorders. British Medical Bulletin. 2003;65(1):83-93. doi:10.1093/bmb/65.1.83

17. Tracey I, Mantyh PW. The Cerebral Signature for Pain Perception and Its Modulation. Neuron. 2007;55(3):377-391. doi:10.1016/J.NEURON.2007.07.012
18. Apkarian AV, Bushnell MC, Treede R-D, Zubieta J-K. Human brain mechanisms of pain perception and regulation in health and disease. European Journal of Pain. 2005;9(4):463-463. doi:10.1016/j.ejpain.2004.11.001
19. Tinnermann A, Geuter S, Sprenger C, Finsterbusch J, Büchel C. Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. Science. 2017;358:105-108.
20. Jensen KB, Kaptchuk TJ, Chen X, et al. A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. Cerebral Cortex. 2015;25(10):3903-3910. doi:10.1093/cercor/bhu275
21. Kong J, Gollub RL, Polich G, et al. A Functional Magnetic Resonance Imaging Study on the Neural Mechanisms of Hyperalgesic Nocebo Effect. Journal of Neuroscience. 2008;28(49):13354-13362. doi:10.1523/JNEUROSCI.2944-08.2008
22. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: A bilateral, distributed mechanism. Journal of Neurophysiology. 1999;82(4):1934-1943. doi:10.1152/jn.1999.82.4.1934
23. Mouraux A, Diukova A, Lee MC, Wise RG, Iannetti GD. A multisensory investigation of the functional significance of the "pain matrix." NeuroImage. 2011;54(3):2237-2249. doi:10.1016/j.neuroimage.2010.09.084
24. Brooks J, Tracey I. REVIEW: From nociception to pain perception: imaging the spinal and supraspinal pathways. Journal of Anatomy. 2005;207(1):19-33. doi:10.1111/j.1469-7580.2005.00428.x
25. Iannetti GD, Zambreanu L, Wise RG, et al. From The Cover: Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. Proceedings of the National Academy of Sciences. Published online 2005. doi:10.1073/pnas.0506624102
26. Longo MR, Iannetti GD, Mancini F, Driver J, Haggard P. Linking pain and the body: Neural correlates of visually induced analgesia. Journal of Neuroscience. 2012;32(8):2601-2607. doi:10.1523/JNEUROSCI.4031-11.2012
27. Iannetti GD, Mouraux A. From the neuromatrix to the pain matrix (and back). Experimental Brain Research. 2010;205(1):1-12. doi:10.1007/s00221-010-2340-1
28. Bäckryd E, Ghafouri B, Larsson B, Gerdle B. Do low levels of beta-endorphin in the cerebrospinal fluid indicate defective top-down inhibition in patients with chronic neuropathic pain? A cross-sectional, comparative study. Pain Medicine (United States). 2014;15(1):111-119. doi:10.1111/pme.12248
29. Ossipov MH. The Perception and Endogenous Modulation of Pain. Hindawi Publishing Corporation. 2012;12:1-25. doi:10.6064/2012/561761
30. Walter C, Oertel BG, Felden L, et al. Brain mapping-based model of Δ 9-tetrahydrocannabinol effects on connectivity in the pain matrix. Neuropsychopharmacology. 2016;41(6):1659-1669. doi:10.1038/npp.2015.336
31. Peng W, Babiloni C, Mao Y, Hu Y. Subjective pain perception mediated by alpha rhythms. Biological Psychology. 2015;109:141-150. doi:10.1016/j.biopsycho.2015.05.004
32. Stockhorst U. Classical conditioning of endocrine effects : Current Opinion in Psychiatry. Current Opinion in Psychiatry. 2005;18(2).
33. Stockhorst U, Steingrueber H-J, Enck P, Klosterhalfen S. Pavlovian conditioning of nausea and vomiting. Autonomic Neuroscience. 2006;129(1-2):50-57. doi:10.1016/j.autneu.2006.07.012

34. Bräscher A-K, Witthöft M, Becker S. The Underestimated Significance of Conditioning in Placebo Hypoalgesia and Nocebo Hyperalgesia. Pain Research and Management. 2018;2018:1-8. doi:10.1155/2018/6841985
35. Rief W, Hofmann SG, Nestoriuc Y. The Power of Expectation – Understanding the Placebo and Nocebo Phenomenon. Social and Personality Psychology Compass. 2008;24(10):1624-1637. doi:10.1111/j.1751-9004.2008.00121.x
36. Rescorla RA. Pavlovian conditioning: It's not what you think it is. American Psychologist. 1988;43(3):151-160. doi:10.1037/0003-066X.43.3.151
37. Bräscher A-K, Becker S, Desch S, Kleinböhl D, Hölzl R. Classically conditioned hyperalgesia-learning a nocebo response without verbal suggestion. European Journal of Pain Supplements. 2011;5(1):281.
38. Van Laarhoven AIMM, Vogelaar ML, Wilder-Smith OH, et al. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain. 2011;152(7):1486-1494. doi:10.1016/j.pain.2011.01.043
39. Bartels DJP, van Laarhoven AIM, Haverkamp EA, et al. Role of Conditioning and Verbal Suggestion in Placebo and Nocebo Effects on Itch. Sakakibara M, ed. PLoS ONE. 2014;9(3):e91727. doi:10.1371/journal.pone.0091727
40. Kerkhof I, Vansteenwegen D, Baeyens F, Hermans D. Counterconditioning: An effective technique for changing conditioned preferences. Experimental Psychology. 2011;58(1):31-38. doi:10.1027/1618-3169/a000063
41. Bartels DJP, van Laarhoven AIM, Stroo M, et al. Minimizing nocebo effects by conditioning with verbal suggestion: A randomized clinical trial in healthy humans. Darragh M, ed. PLOS ONE. 2017;12(9):e0182959. doi:10.1371/journal.pone.0182959
42. Colagiuri B, Quinn VF, Colloca L. Nocebo Hyperalgesia, Partial Reinforcement, and Extinction. The Journal of Pain. 2015;16(10):995-1004. doi:10.1016/J.JPAIN.2015.06.012
43. Thomaidou MA, Veldhuijzen DS, Peerdeman KJ, Sifra Wiebing NZ, Blythe JS, Evers AWM. Learning mechanisms in nocebo hyperalgesia: The role of conditioning and extinction processes. PAIN. Published online March 5, 2020:1. doi:10.1097/j.pain.0000000000001861
44. Au Yeung ST, Colagiuri B, Lovibond PF, Colloca L. Partial reinforcement, extinction, and placebo analgesia. Pain. 2014;155(6):1110-1117. doi:10.1016/j.pain.2014.02.022
45. Robbins D. Partial Reinforcement: A Selective Review of the Alleyway Literature since 1960. Vol 76. American Psychological Association; 1971.
46. Colagiuri B, Quinn VF, Colloca L. Nocebo Hyperalgesia, Partial Reinforcement, and Extinction. The Journal of Pain. 2015;16(10):995-1004. doi:10.1016/J.JPAIN.2015.06.012
47. Paulsen O, Sejnowski TJ. Natural patterns of activity and long-term synaptic plasticity. Current Opinion in Neurobiology. 2000;10(2):172-180. doi:10.1016/S0959-4388(00)00076-3
48. McClelland JL, McNaughton BL, O'Reilly RC. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychological Review. 1995;102(3):419-457. doi:10.1037/0033-295X.102.3.419
49. Conway MA, Loveday C. Remembering, imagining, false memories & personal meanings. Consciousness and Cognition. 2015;33:574-581. doi:10.1016/j.concog.2014.12.002
50. Groome D, Eysenck M. An Introduction to Applied Cognitive Psychology. Psychology Press; 2016.

53. Nave AM, Tolin DF, Stevens MC. Exposure therapy, D-cycloserine, and functional magnetic resonance imaging in patients with snake phobia: a randomized pilot study. The Journal of clinical psychiatry. 2012;73(9):1179-1186. doi:10.4088/JCP.11m07564
54. Ebrahimi C, Koch SP, Friedel E, et al. Combining D-cycloserine with appetitive extinction learning modulates amygdala activity during recall. Neurobiology of Learning and Memory. 2017;142(pt.B):209-217. doi:10.1016/j.nlm.2017.05.008
55. Guastella AJ, Dadds MR, Lovibond PF, Mitchell P, Richardson R. A randomized controlled trial of the effect of d-cycloserine on exposure therapy for spider fear. Journal of Psychiatric Research. 2007;41(6):466-471. doi:10.1016/J.JPSYCHIRES.2006.05.006
56. Schienle A, Höfler C, Übel S, Wabnegger A. Emotion-specific nocebo effects: an fMRI study. Brain Imaging and Behavior. 2018;12(1):180-187. doi:10.1007/s11682-017-9675-1
57. Field AP. Is conditioning a useful framework for understanding the development and treatment of phobias? Clinical Psychology Review. 2006;26(7):857-875. doi:10.1016/j.cpr.2005.05.010
58. LoLordo VM, Droungas A. Selective associations: Taste aversions and phobias . In: Klein SB, Mowrer RR, eds. Contemporary Learning Theories: Instrumental Conditioning Theory. Vol 2. Routledge; 1989.
59. Craske MG, Treanor M, Conway CC, Zbozinek T, Vervliet B. Maximizing exposure therapy: an inhibitory learning approach. Behaviour research and therapy. 2014;58:10-23. doi:10.1016/j.brat.2014.04.006
60. Schmid J, Bingel U, Ritter C, et al. Neural underpinnings of nocebo hyperalgesia in visceral pain: A fMRI study in healthy volunteers. NeuroImage. 2015;120:114-122. doi:10.1016/j.neuroimage.2015.06.060
61. Barad M, Gean PW, Lutz B. The Role of the Amygdala in the Extinction of Conditioned Fear. Biological Psychiatry. 2006;60(4):322-328. doi:10.1016/j.biopsych.2006.05.029
62. Sigurdsson T, Doyère V, Cain CK, LeDoux JE. Long-term potentiation in the amygdala: A cellular mechanism of fear learning and memory. Neuropharmacology. 2007;52(1):215-227. doi:10.1016/j.neuropharm.2006.06.022
63. Davis M. The role of the amygdala in fear-potentiated startle: implications for animal models of anxiety. Trends in Pharmacological Sciences. 1992;13(C):35-41. doi:10.1016/0165-6147(92)90014-W
64. Davis M. The role of the amygdala in fear and anxiety. Annual Review of Neuroscience. 1992;15(1):353-375. doi:10.1146/annurev-neuro-080317-062245
65. Linnman C, Rougemont-Bücking A, Beucke JC, Zeffiro TA, Milad MR. Unconditioned responses and functional fear networks in human classical conditioning. Behavioural Brain Research. 2011;221(1):237-245. doi:10.1016/J.BBR.2011.02.045
66. Karos K, Meulders A, Vlaeyen JWS. Threatening social context facilitates pain-related fear learning. Journal of Pain. 2015;16(3):214-225. doi:10.1016/j.jpain.2014.11.014
67. Meulders A, Vlaeyen JWS. The acquisition and generalization of cued and contextual pain-related fear: An experimental study using a voluntary movement paradigm. Pain. 2013;154(2):272-282. doi:10.1016/j.pain.2012.10.025
68. Ohman A, Mineka S. Fears, phobias, and preparedness: toward an evolved module of fear and fear learning. Psychological review. 2001;108(3):483-522.
69. Scott DJ, Stohler CS, Egnatuk CM, Wang H, Koeppe RA, Zubieta J-KK. Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses.

Archives of General Psychiatry. 2008;65(2):220-231. doi:10.1001/archgenpsychiatry.2007.34
70. Benedetti F, Durando J, Vighetti S. Nocebo and placebo modulation of hypobaric hypoxia headache involves the cyclooxygenase-prostaglandins pathway. Pain. 2014;155(5):921-928. doi:10.1016/j.pain.2014.01.016
71. Albu S, Meagher MW. Expectation of nocebo hyperalgesia affects EEG alpha-activity. International Journal of Psychophysiology. 2016;109:147-152. doi:10.1016/j.ijpsycho.2016.08.009
72. Pazzaglia C, Testani E, Giordano R, Padua L, Valeriani M. Expectation to feel more pain disrupts the habituation of laser-pain rating and laser-evoked potential amplitudes. Neuroscience. 2016;333:244-251. doi:10.1016/j.neuroscience.2016.07.027
73. Tu Y, Park J, Ahlfors SP, et al. A neural mechanism of direct and observational conditioning for placebo and nocebo responses. NeuroImage. Published online 2019. doi:10.1016/j.neuroimage.2018.10.020
74. Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. Pain. 2010;151(2):430-439. doi:10.1016/j.pain.2010.08.007
75. Amanzio M. Expert Review of Clinical Pharmacology Nocebo effects and psychotropic drug action Nocebo effects and psychotropic drug action. Expert Rev Clin Pharmacol. 2015;8(2):159-161. doi:10.1586/17512433.2015.992877doi.org/10.1586/17512433.2015.992877
76. Izquierdo I, Medina JH, Bianchin M, et al. Memory processing by the limbic system: Role of specific neurotransmitter systems. Behavioural Brain Research. 1993;58(1-2):91-98. doi:10.1016/0166-4328(93)90093-6
77. Kornhuber HH. Neural Control of Input into Long Term Memory: Limbic System and Amnestic Syndrome in Man. In: Zippel HP, ed. Memory and Transfer of Information. Springer US; 1973:1-22. doi:10.1007/978-1-4684-2052-4_1
78. Berger TW, Thompson RF. Neuronal plasticity in the limbic system during classical conditioning of the rabbit nictitating membrane response. I. The hippocampus. Brain Research. 1978;145(2):323-346. doi:10.1016/0006-8993(78)90866-1
79. Vinogradova OS. Functional Organization of the Limbic System in the Process of Registration of Information: Facts and Hypotheses. In: Isaacson RL, Pribram KH, eds. The Hippocampus. Springer US; 1975:3-69. doi:10.1007/978-1-4684-2979-4_1
80. Sutherland RJ, Rudy JW. Configural association theory: The role of the hippocampal formation in learning, memory, and amnesia. Psychobiology. 1989;17(2):129-144. doi:10.3758/BF03337828
81. Whitlock JR, Heynen AJ, Shuler MG, Bear MF. Learning induces long-term potentiation in the hippocampus. Science. 2006;313(5790):1093-1097. doi:10.1126/science.1128134
82. McClelland JL, McNaughton BL, O'Reilly RC. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychological Review. 1995;102(3):419-457. doi:10.1037/0033-295X.102.3.419
83. Devinsky O, Morrell MJ, Vogt BA. Contributions of anterior cingulate cortex to behaviour. Brain. 1995;118(1):279-306.
84. Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: An update. Trends in Cognitive Sciences. 2004;8(12):539-546. doi:10.1016/j.tics.2004.10.003
85. Sapolsky RM. Stress and Plasticity in the Limbic System. *Neuroch. Research.*