HHS Public Access

Author manuscript

Int Rev Neurobiol. Author manuscript; available in PMC 2018 October 08.

Published in final edited form as:

Int Rev Neurobiol. 2018 ; 139: 255–296. doi:10.1016/bs.irn.2018.07.024.

Pain Modulation: From Conditioned Pain Modulation to Placebo and Nocebo Effects in Experimental and Clinical Pain

Janie Damien[*], **Luana Colloca**[†,‡], **Carmen-Édith Bellei-Rodriguez**[*], and **Serge Marchand**[*,§,1]

[*]Research Center of the Centre hospitalier universitaire de Sherbrooke (CHUS), Department of Surgery, Faculty of Medicine and Health Sciences, Université de Sherbrooke, Sherbrooke, QC, Canada

[†]Department of Pain Translational Symptom Science, School of Nursing, University of Maryland, Baltimore, MD, United States

[‡]Departments of Psychiatry and Anesthesiology, School of Medicine, University of Maryland, Baltimore, MD, United States

[§]Fonds de Recherche du Québec—Santé (FRQS), Montréal, QC, Canada

Abstract

Accumulating evidence reveal important applications of endogenous pain modulation assessment in healthy controls and in patients in clinical settings, as dysregulations in the balance of pain modulatory circuits may facilitate pain and promote chronification of pain. This article reviews data on pain modulation, focusing on the mechanisms and translational aspects of pain modulation from conditioned pain modulation (CPM) to placebo and nocebo effects in experimental and clinical pain. The specific roles of expectations, learning, neural and neurophysiological mechanisms of the central nervous system are briefly reviewed herein. The interaction between CPM and placebo systems in pain inhibitory pathways is highly relevant in the clinic and in randomized controlled trials yet remains to be clarified. Examples of clinical implications of CPM and its relationship to placebo and nocebo effects are provided. A greater understanding of the role of pain modulation in various pain states can help characterize the manifestation and development of chronic pain and assist in predicting the response to pain-relieving treatments. Placebo and nocebo effects, intrinsic to every treatment, can be used to develop personalized therapeutic approaches that improve clinical outcomes while limiting unwanted effects.

1. INTRODUCTION

Recently, there have been many new developments in our understanding of the area of the endogenous mechanisms of pain modulation. From nociceptive stimulation to perception, multiple endogenous pain systems modulate our experience of pain. The perception of pain is the result of several endogenous pain inhibitory and facilitatory mechanisms that trigger pain at all levels of the central nervous system. Conditioned pain modulation (CPM) is one unique form of endogenous descending inhibitory pathway (Bannister & Dickenson, 2017;

[1]Corresponding author: serge.marchand@usherbrooke.ca.

Willer, Le Bars, & De Broucker, 1990). The use of the CPM paradigm in scientific research for evaluating the inherent pain inhibition ability of individuals is highly relevant for understanding normal functioning and various disease states, including the development, persistency and treatment of chronic pain. The cognitive modulation of endogenous pain control mechanisms, illustrated by placebo analgesia, have greatly helped uncover its components and its neurophysiological mechanisms, which have generated enormous implications for personalizing pain management. Every treatment is inherently influenced by placebo and nocebo effects; the unpleasant component of pain as well as the expectation of pain or analgesia following an intervention contribute significantly to clinical outcomes. Aside from being relevant clinically, the study of CPM and placebo effects improved our understanding of the multiple factors and systems that interact and mediate the pain-modulatory effects of expectancies. While CPM and placebo effects are both influenced by expectations to a certain extent, evidence suggests they are not correlated (Skyt et al., 2018) and they implicate different mechanisms. This article aims to provide current and updated work on both mechanisms and translational aspects of endogenous mechanisms of pain modulation, from CPM to placebo and nocebo effects in experimental and clinical pain (also see Marchand, 2012).

2. THEORY OF PAIN MODULATION

Our current multidimensional and circular model of pain recognizes that information about pain, from sensory input to perception, does not travel in a linear way in the nervous system (Marchand, 2012). Nociceptive stimuli, first transformed into chemoelectric energy, travel as a nerve impulse along nerve fibers from the periphery to the spinal cord, from the spinal cord to the brainstem and the thalamus, and finally, from the thalamus to the cortex where the information is interpreted as pain. Along this path, the afferent noxious stimuli are modulated by neurons in the endogenous pain controls. Inhibitory cells, which modulate nociceptive inputs, are recruited by stimulation of non-nociceptive afferents (Aβ-fibers) and inhibited by stimulation of nociceptive afferents (Aδ- and C-fibers). The Gate Control Theory (Melzack & Wall, 1965) stipulates that a peripheral mechanism in the dorsal horns of the spinal cord as well as descending systems from the reticular formation modulate nociceptive information.

As described in Loeser's model, pain is the result of four components: nociception (nociceptive component), pain (sensory-discriminatory component), suffering (motivo-affective component) and pain behaviors (cognitive-behavioral component) (Loeser, 1980). Marchand (2012) highlighted how each component are best represented as a circular rather than linear model, existing independently, but also interacting with each other. Mere activation of nociceptive fibers does not necessarily cause pain. Inversely, phantom limb pain is an example of suffering that does not require nociceptive stimuli. The neuromatrix theory of pain is useful to outline the mechanisms of phantom or chronic pain (Melzack, 1990, 2001) that is produced, not solely by sensory input evoked by injury, inflammation, or pathology and the peripheral nervous system that surrounds it, but rather by the output of a neural network in the brain that is genetically determined and then modified by sensory experience, called the neuromatrix (Melzack, 2001). Placebo analgesia, for instance, could

be understood as resulting from a complex set of sociocultural beliefs, expectations and conditioning behaviors that influence the neuromatrix of the brain.

3. ENDOGENOUS MECHANISMS OF PAIN MODULATION

Modulation of nociceptive information in the central nervous system may be excitatory or inhibitory of the nociceptive signal before it reaches the higher centers of the brain, resulting in pain perceived as more or less intense. Inhibition of nociceptive afferents can be best understood under three types of endogenous mechanisms: (1) spinal mechanisms, (2) descending inhibitory controls, and (3) mechanisms of the higher centers (Marchand, 2012). These mechanisms of endogenous pain modulation controls have greatly improved our understanding of normal and dysregulated modulation of pain in healthy individuals and in patients with chronic pain conditions. The conditioned pain modulation and placebo effects, which are the focus of this chapter, result from the activity of descending pain control systems and pain modulatory mechanisms from the higher centers, respectively.

CPM, previously known as “diffuse noxious inhibitory control (DNIC)” or “DNIC-like” effects (Yarnitsky, 2010), was first studied in animals by Le Bars, Dickenson, & Besson (1979a, 1979b). In 2015, experts recommended the term CPM for human application of DNIC protocols (Yarnitsky et al., 2015). A noxious stimulus applied in one part of the body can inhibit pain in another part of the body, by activating the descending inhibitory system (DNIC or CPM). In this sense, CPM refers to any approach based on the application of a localized painful stimulation that produce a diffuse analgesic effect beyond the stimulation period and body location (muscles, joints and viscera) independently of the site of application (diffuse), i.e., “pain inhibits pain” phenomenon or “counter-irritation.”

This principle underlies numerous types of stimulation, ranging from acupuncture and deep massages to analgesic hyperstimulation and high intensity Transcutaneous Electrical Nerve Stimulators (TENS) or TENS-acupuncture. These approaches apply intense painful peripheral stimuli, which recruit nociceptive afferences (Aδ- and C-fibers) and produce diffuse analgesic effects (Marchand, 2012).

4. ASSESSMENT OF ENDOGENOUS CPM

Pain modulation, in particular the inhibitory modulatory mechanisms (generally termed endogenous analgesia), can be investigated in experimental settings using quantitative sensory tests (QSTs) based on the psychophysical paradigm of CPM. Using “pain inhibits pain” models, CPM is tested using a noxious conditioning stimulus (CS) to influence another painful test stimulus (TS), upon which the analgesic effect is tested (Nir & Yarnitsky, 2015; Yarnitsky, 2010). The TS is typically of short duration, milliseconds to seconds, during which the pain response is typically recorded by means of subjective pain ratings or nociceptive withdrawal reflexes (RIII reflex) elicited by painful stimuli to the sural nerve (Jurth, Rehberg, & von Dincklage, 2014) and more recently by changes of cortical evoked brain potentials (Höffken, Özgül, Enax-Krumova, Tegenthoff, & Maier, 2017). The CPM effect correspond to the CS-induced changes in these pain responses. It has been suggested that reflex responses reflect spinal nociception while subjective pain ratings

integrate more cognitive influences even though they are both reliable measures (Biurrun Manresa et al., 2014; Jurth et al., 2014).

In addition to being valuable for quantifying individuals' endogenous inhibition of pain, the evaluation of CPM effect in individuals has provided us important insight on the development of pain disorders and the response to analgesic treatment (Yarnitsky, 2015). Thus, CPM testing could help develop personalized pain management strategies based on individuals' endogenous analgesia capacity.

Although our knowledge on pain modulation has improved significantly over the years, the various CPM protocols employed and the lack of normative values limit the comparison of findings (Klyne, Schmid, Moseley, Sterling, & Hodges, 2015) and the utilization of CPM as a prognostic factor in experimental and clinical pain studies (Granovsky, Miller-Barmak, Goldstein, Sprecher, & Yarnitsky, 2016; Kennedy, Kemp, Ridout, Yarnitsky, & Rice, 2016). Further research on CPM methodology and its reliability is required to find a standard measurement of CPM and its main parameters such as the timing, modality, intensity, duration, and location of the stimuli.

5. TEST STIMULUS

The most studied test stimuli are pressure pain threshold and contact heat pain (Kennedy et al., 2016), but thermal, mechanical, electrical or chemical stimuli are also very common TS (Yarnitsky, 2015). The modality and intensity of test stimulus might influence CPM or DNIC reliability (Marcuzzi, Wrigley, Dean, Adams, & Hush, 2017) or magnitude (Okada, 2005), though it has been generally considered that CPM effect does not depend on characteristics of the TS as long as it is considered painful and not intolerable.

6. CONDITIONING STIMULUS

Researchers have also used various modalities as conditioning stimuli, such as cuff inflation, ischemia, capsaicin injection (Yarnitsky, 2015), with painful cold water immersion of a limb being one of the most potent (Nilsen, Olsen, Solem, & Matre, 2014) and reliable stimuli currently used (Kennedy et al., 2016; Lewis, Heales, Rice, Rome, & McNair, 2012). It has been found that the longer CS duration with the highest intensity (7/10 on a 0–10 pain rating scale) result in a more pronounced CPM in women only (Razavi, Hansson, Johansson, & Leffler, 2014), although these results need to be replicated. The intensity of the CS has been shown to be unrelated or positively correlated to the magnitude of CPM (Yarnitsky, 2015). It is believed that once CPM is induced by a minimal noxious load, even mild pain elicited by tonic heat pain with intensities around the pain threshold (Kunz et al., 2014), CPM might not be further activated by increased conditioning pain levels, hence CPM is considered a saturable phenomenon (Nir, Granovsky, Yarnitsky, Sprecher, & Granot, 2011).

7. CPM PROTOCOLS

CPM response is unrelated to individual sensitivity and adaptability to pain (Zheng, Wang, Yao, Xue, & Arendt-Nielsen, 2014). Nonetheless, modality-specific CPM responses are influenced by different psychological factors. Specifically, CPM responses evoked by

pressure, heat and electrical stimuli were associated with anxiety, depression and catastrophizing levels, respectively (Nahman-Averbuch, Nir, Sprecher, & Yarnitsky, 2016). Overall younger adult age, male gender, ovulatory phase of the menstrual cycle in women, positive expectations, attention to the CS, and carrier of the serotonin-transporter-linked polymorphic region (5-HTTLPR) long allele are other characteristics associated with larger CPM responses, according to a systematic review of 36 studies (Hermans et al., 2016). Data from a large population-based study of the Danish adult general population also found better CPM in males and in individuals with higher level of education and higher pain ratings on the visual analog scale (Skovbjerg et al., 2017). Therefore, it has been suggested that different underlying mechanisms might account for CPM responses (Nahman-Averbuch et al., 2016).

CPM is not influenced by stimuli location, except for ipsilateral homo-topic sites (Klyne et al., 2015). To reflect an ascending–descending long tract activity, CPM is preferably triggered by a heterotopic nociceptive conditioning stimulation (HNCS) in which the TS and CS are applied on two remote and separate anatomic regions of the body. However, some studies using spatial summation ipsilaterally also activate endogenous inhibitions (Marchand & Arsenault, 2002). CPM measurement is reliable, but varies depending on stimulation parameters and study methodology (Kennedy et al., 2016). The combination of heat pain test or handheld or cuff pressure pain and the cold pressor test (CPT) are reliable methods to induce CPM, whereas electrical and heat pain combined with cuff do not yield significant CPM effects (Gehling et al., 2016; Imai, Petersen, Mørch, & Arendt Nielsen, 2016; Petersen, Vaegter, & Arendt-Nielsen, 2017).

The different test protocols limit generalization of findings and thus a group of experts in the field presented recommendations regarding a standard measurement of CPM in healthy individuals and pain patients (Yarnitsky et al., 2010, 2015). Preferably, mechanical and heat TS should be delivered either at a fixed pain intensity of 40 on a 0–100 pain rating scale or at an ascending intensity and discontinued when pain intensity of 40/100 is reached. Subsequently, to induce a conditioning analgesic effect, the CS needs to be at least mildly to moderately painful (>20/100 pain score). The CS should be given as rapidly as possible after the second TS as the duration of CPM effects is short (Yarnitsky et al., 2015) and varies across testing protocols. For instance, 6–9min after the end of the conditioning period, the inhibition of the pain response (e.g., nociceptive reflex) recovered its baseline value (Willer et al., 1990). A sequential protocol in which the second TS is applied immediately at the end of the CS is preferred over a parallel method, wherein both stimuli are administered simultaneously. The latter method yields larger CPM effects, most likely from biases (distraction effects) (Yarnitsky, 2015).

8. HOW DOES IT WORK? THE ORIGINS

The information from nociceptive stimulation of a mechanical, chemical or thermal nature is sent from the periphery, through the primary neuron, and to the posterior horns of the spinal cord where there is a first synaptic contact with the secondary neuron. The second neuron will also establish synaptic contacts in different regions of the brainstem such as the periaqueductal gray (PAG) and the nucleus raphe magnus (NRM), a part of the rostral

ventromedial medulla (RVM). Then the information passes through the medulla/spinal cord to the thalamus, where it establishes synaptic contact with the tertiary neuron before being transported to the higher centers of the brain. At each synaptic contact, the information is integrated and undergoes inhibitory or excitatory influences (Marchand, 2012).

In the thalamus, the nuclei of the ventro-basal complex receive their afferences from the spinothalamic pathway and project toward the primary and secondary somatosensory cortices (SI and SII), with precise receptor fields. The SI and SII regions are mainly responsible for the localization and the perception of the sensory-discriminative aspect of pain, a stable component related to the evaluation of the intensity of pain as well as to the spatial and temporal characteristics of pain. The other important group of nuclei in the thalamus, those of the centromedian or intralaminar complex of the somatosensory thalamus, receive their afferences from the spino-reticular pathway and project, with large receptor fields, to structures of the brainstem and the limbic system, including the thalamus, frontal cortex, anterior cingulate cortex (ACC) and insular cortex (IC). The latter connects with the SI, SII, cingulate cortex and limbic structures like the amygdala and the perirhinal complex. The spinoreticular pathway is mainly involved in the motivo-affective component of pain modulation that is related to the evaluation of the unpleasantness of pain. The PAG is partly responsible for the unpleasantness of pain; its stimulation causes strong uncomfortable feelings of distress to be perceived as pain (Marchand, 2012).

CPM is based on the DNIC spinobulbospinal mechanisms originally investigated in rats by Le Bars and colleagues (Le Bars et al., 1979a, 1979b; Villanueva & Le Bars, 1986) who argued that a painful stimulation conducts the nociceptive information to the higher centers of the brain via the spinothalamic pathway and the transmission of afferences to brainstem structures including the PAG and NRM, which send inhibitory efferences to spinal segments and finally produces diffuse inhibition (with the help of inhibitory interneurons). CPM triggered by HNCS affect all convergent neurons recorded in the dorsal horn of the spinal cord or the nucleus caudalis of the trigeminal system (Villanueva & Le Bars, 1986). Reynolds (1969) helped unravel the neurophysiological mechanisms of CPM when he realized CNS stimulation of the midbrain central gray (PAG) produced sufficient analgesia to perform abdominal surgery in the rat without any other form of anesthesia.

Numerous studies have completed this model. PAG and NRM have been targeted for serotonergic and noradrenergic descending pathways, respectively. These pathways recruit enkephalinergic interneurons in the spinal cord and produce an analgesic response by reducing the activity of nociceptive afferents. However, studies of lesions performed at different levels of the brainstem in rodents suggest that CIDN use caudal spinal bulb structures, and therefore would not require midbrain PAG input. A recent study using functional magnetic resonance imaging (fMRI) to determine the precise brainstem sites responsible for CPM in healthy individuals observed an association between expression of analgesia and reduction of signal in brainstem regions following counter-irritation: the caudalis subdivision of the spinal trigeminal nucleus, i.e., the primary synapse, the region of the subnucleus reticularis dorsalis (SRD) and the dorsolateral pons in the region of the parabrachial nucleus (Youssef, Macefield, & Henderson, 2016a). In comparison to subjects exhibiting CPM analgesia, those with impaired CPM showed greater signal intensity

increases in the mid-cingulate and dorsolateral prefrontal cortices and increased functional connectivity with the SRD following counter-irritation (Youssef, Macefield, & Henderson, 2016b). The SRD conveys widespread descending inhibition to spinal secondary neurons via the dorsolateral funiculi (Nir & Yarnitsky, 2015). Descending pain modulation induces analgesia by activation of opioid receptors in the medullary reticularis nucleus dorsalis (MRD) (Villanueva, Bouhassira, & Le Bars, 1996). In animal studies, the opioid receptor antagonist naloxone injected into the MRD prevented DNIC, while naloxone injection into the RVM did not affect DNIC analgesia (de Resende, Silva, Sato, Arendt-Nielsen, & Sluka, 2011). Using a spatial summation paradigm, systemic naloxone blocked endogenous inhibitions (Julien & Marchand, 2006). Administration of lidocaine, a local analgesic, within the RVM, reversed allodynia induced by spinal nerve litigation in rats, suggesting that activation of descending inhibition from the RVM protects against chronic neuropathic pain in animals (De Felice et al., 2011). In patients with neuropathic pain and dynamic mechano-allodynia, the clinical CS (brushing or pressure within the allodynic area) reduced the pain sensation but did not inhibit the electrophysiological responses, while the experimental CS (cold pressor or tourniquet tests) inhibited both painful sensations and the RIII reflex, suggesting supraspinal mechanisms involved in the CPM effect of this pain condition (Bouhassira, Danziger, Attal, Guirimand, & Atta, 2003).

Pain inhibition by CPM rely partly on the orbitofrontal cortex (OFC) and the amygdala (Moont, Crispel, Lev, Pud, & Yarnitsky, 2011). Pich e, Arsenault, and Rainville (2009) argue for at least two neural mechanisms underlying the effects of CPM on pain and spinal nociception in humans. Conditioning stimulus inhibits shock pain perception and RIII reflex amplitude (spinal nociception) only in a subset of individuals. Moreover, sustained activation of the OFC induced by the CS was predictive of pain decrease while sustained activity in SI and the PAG predicted nociceptive reflex modulation (Piché et al., 2009).

In another study, the conditioning stimulus induced reductions of blood oxygen level dependent (BOLD) responses in classical pain-responsive regions but increases in BOLD responses in sub-regions of the ACC. During the CS, decreased pain was positively correlated with the increase in strength of functional coupling between the subgenual ACC and structures of the descending pain control system. These results demonstrate the contribution of higher-order brain regions (supraspinal mechanisms) in the activation of CPM (Sprenger, Bingel, & Büchel, 2011). The strength of the PAG resting functional connectivity can explain some of the normal variability in CPM; higher resting connectivity between the PAG and cortical pain processing regions correlates with greater CPM efficacy (Harper et al., 2018). CPM scores are also correlated with the modulation of the laser-induced BOLD response in left posterior insula/SII (Bogdanov et al., 2015).

During CPM, the nociceptive stimulation activates the nociceptive neurons corresponding to the spinal segment they innervate but also other nociceptive neurons in the spinal cord serving the rest of the body. Descending modulatory effects act on wide dynamic range neurons in the spinal dorsal horn where nociceptive C-, Aδ- and Aβ-fibers converge. It has been demonstrated that during HNCS, the perceived intensity of nociceptive Aδ- and C-fiber nociceptive inputs, but also Aβ-non-nociceptive fiber inputs is reduced, as paralleled by inhibited pain perception and event-related potentials (ERPs) (Rustamov, Tessier,

Provencher, Lehmann, & Piché, 2016). Since Aβ-fibers are related to primary afferents that send the noxious information upward directly through the dorsal columns to reach second-order neurons in the dorsal column nuclei without being relayed at spinal level. The pain modulatory responses may not be attributed only to descending spinal mechanisms (Torta, Churyukanov, Plaghki, & Mouraux, 2015).

CPM inhibits pain through cerebral/supraspinal and cerebrospinal mechanisms, reflecting activation of the endogenous analgesia system, where ascending pain-induced activity evokes descending pathways, which subsequently elicit inhibitory effects on spinal nociceptive inputs. However, the underlying mechanisms of CPM in human and DNIC in animals are still incompletely understood.

9. CLINICAL RELEVANCE OF PAIN MODULATION

9.1 Post-surgical Acute and Chronic Pain

An individual's endogenous pain inhibitory capacity can be reliably assessed by CPM protocols. However, the stability of CPM might be greater for women than for men (Martel, Wasan, & Edwards, 2013), requiring further investigation. Although DNIC seem to be more effective in animals after tissue injury, CPM is often impaired in humans with chronic pain (de Resende et al., 2011; Staud, 2012). Nevertheless, it is important to note that the criteria characterizing normal and deficient CPM using QST vary largely among the different studies (Gierthmühlen et al., 2015).

Chronic pain may develop following surgical and medical procedures, particularly those involving nerve injuries. The incidence and intensity of chronic neuropathic pain developed after a surgery may be predicted by pre-operative CPM efficacy (Granovsky, 2013). CPM efficacy may predict lower risk of developing chronic pain after thoracotomy (Yarnitsky et al., 2008), while less efficient CPM is sometimes associated with acute or chronic postoperative pain (Yarnitsky, 2010), emphasizing the clinical relevance of using CPM to help identify individuals at risk of developing chronic post-surgical pain. In contrast, others have found no consistent associations between most CPM parameters and prediction of pain after injuries (e.g., stroke) or surgeries (e.g., funnel chest repair) (Grosen, Vase, Pilegaard, Pfeiffer-Jensen, & Drewes, 2014; Roosink et al., 2011; Sangesland, Støren, & Vaegter, 2017).

9.2 Chronic Pain

Even though assessing endogenous analgesia in chronic pain conditions is complicated by the presence of spontaneous ongoing pain, Edwards, Ness, Weigent, and Fillingim (2003) have found CPM to be the only consistent predictor of health-related quality of life among several laboratory pain variables. Greater CPM responses were related to less clinical pain, better physical functioning, and better self-rated health (Edwards et al., 2003).

A growing body of knowledge has revealed consistent low pain inhibitory capacity underlying various chronic pain states such as fibromyalgia, irritable bowel syndrome, migraine, tension-type headache, temporomandibular joint disorders, osteoarthritis and muscle pain, whiplash-associated disorders, interstitial cystitis, cancer pain (Nir & Yarnitsky,

2015; Yarnitsky, 2010). However, the altered function of endogenous pain modulation mechanisms might depend on the pathophysiological mechanisms of clinical pain (Bouhassira et al., 2003).

9.3 Idiopathic Pain Syndromes

Substantial evidence supports a decreased CPM efficacy in idiopathic pain syndromes. In a recent meta-analysis and numerous studies, a significant alteration of pain modulation mechanisms (CPM or temporal summation) is present in patients with fibromyalgia (FM) or chronic widespread pain (O'Brien, Deitos, Triñanes Pego, Fregni, & Carrillo-de-la-Peña, 2018). While major depressive disorder is not associated with CPM deficits (Normand et al., 2011), patients with FM and comorbid depression have more pronounced deficits in pain inhibition (de Souza, Potvin, Goffaux, Charest, & Marchand, 2009). Moreover, pain facilitation during CPM procedure is reported by twice as many FM patients than healthy subjects (42% versus 21%) (Potvin & Marchand, 2016). Less gray matter volume in a cluster encompassing the PAG as well as greater PAG resting functional connectivity to the caudal pons/rostral medulla could explain the pain-facilitative CPM in FM (Harper et al., 2018). Endogenous pain inhibition mechanisms are significantly impaired in fibromyalgia patients, but only in a subgroup of them (Potvin & Marchand, 2016). In fact, the study showed that a group of patients with FM (e.g., 41.7%) experience pain facilitation during the CPM procedure that induces pain inhibition mechanisms in physiological conditions. Those patients experiencing pain facilitation during the CPM did not differ from FM patients who experienced pain inhibition. The two subgroups were comparable with respect to sociodemographic characteristics, pain intensity, depression, and psychophysical measures (except the CPM-induced change in pain perception).

In keeping with this line of findings, irritable bowel syndrome (IBS) and provoked vestibulodynia are other chronic pain conditions with a woman predominance in which facilitatory CPM are reported in only a subgroup of patients (Gougeon, Gaumond, Goffaux, Potvin, & Marchand, 2016). More women than men suffer from chronic pain conditions and experience less endogenous analgesia (Skovbjerg et al., 2017). In patients suffering from IBS, CPM is linked to the clinical severity of symptoms (Bouhassira et al., 2013). In addition, compared to healthy subjects, IBS patients have an increased risk of suffering from temporomandibular disorder (TMD), another chronic pain syndrome unknown origin (Gallotta et al., 2017). The function of CPM mechanisms is sometimes preserved in rheumatoid arthritis (up to 5 years after diagnosis) (Leffler, Kosek, Lerndal, Nordmark, & Hansson, 2002) and in osteoarthritis (OA), but impaired in temporomandibular joint (TMJ) arthralgia patients (Kothari et al., 2016) at sites with chronic pain but not at pain-free sites (Oono et al., 2014). Knee OA has sometimes been associated with reduced CPM and enhanced temporal summation of pain (Edwards et al., 2016), which predicts less pain relief after total knee replacement (Petersen, Graven-Nielsen, Simonsen, Laursen, & Arendt-Nielsen, 2016). Even though OA patients might not report a pain reduction following painful CS (provoked OA pain), magneto-encephalography and electroencephalography techniques indicate a decreased activation of the cingulate gyrus (Quante, Hille, Schofer, Lorenz, & Hauck, 2008).

9.4 Nociceptive

A pro-nociceptive pattern of amplified pain facilitation (central sensitization) and reduced endogenous pain inhibition is also common in carpal tunnel syndrome, chronic pancreatitis (Soon, Vicenzino, Schmid, & Coppieters, 2017), whiplash-associated disorders (Daenen et al., 2013; Ng, Pedler, Vicenzino, & Sterling, 2014; Yarnitsky, 2015) and in primary headaches such as migraine, chronic tension-type headache and chronic post-traumatic headache following mild traumatic brain injury (Sandrini et al., 2006). In patients with acute and chronic low back pain, CPM effect is triggered following counter-irritation, but its duration is significantly reduced compared to healthy individuals (Mlekusch et al., 2016). Moreover, CPM efficacy may predict the analgesic effect of pregabalin treatment for painful chronic pancreatitis (Olesen et al., 2013).

9.5 Neuropathic Pain

Evaluation of pain modulation capabilities by CPM protocols is particularly relevant in cases of chronic neuropathic pain (Granovsky, 2013) caused by a nerve lesion or disease of the somatosensory system, including peripheral fibers (Aβ-, Aδ- and C-fibers) and central neurons. In addition to being increasingly prevalent (currently affecting 7–10% of the general population), neuropathic pain is caused by a multitude of factors, including alterations in the modulation of pain by the CNS and in the excitatory and inhibitory somatosensory signaling, complexifying the treatment of its symptoms (Colloca et al., 2017). Dysregulated spinal endogenous inhibitory systems and ongoing primary afferent activity are related to the intensity and duration of central sensitization (dorsal horn neuron hypersensitivity) present in neuropathic pain (Taylor, 2009). Psychophysical and electrophysiological approaches reveal impaired potency and duration of CPM in patients with postherpetic neuralgia (Pickering, Pereira, Dufour, Soule, & Dubray, 2014), in individuals with acquired neuropathic pain following spinal cord injury (Albu, Gómez-Soriano, Avila-Martin, & Taylor, 2015), in patients with painful diabetic polyneuropathy (DPN) of short duration (less than 2 years) (Granovsky, Nahman-Averbuch, Khamaisi, & Granot, 2017) and in cancer survivors with painful neuropathy acquired after chemotherapy (Nahman-Averbuch et al., 2011). The duration of DPN pain correlated positively with CPM efficacy, suggesting improvement of endogenous analgesia with chronicity of the pain syndrome (Granovsky et al., 2017). Moreover, in patients with DPN, deficient descending pain inhibition measured by CPM responses improved following four weeks of daily treatment with tapentadol sustained-release (Niesters et al., 2014).

In sum, CPM deficits could reflect a predisposing factor primary to acquisition of chronic pain (Pickering et al., 2014) and help identify patients at risk for developing chronic pain (van Wijk & Veldhuijzen, 2010), but mechanisms and neurochemical correlates of this deficit are still only partially understood (Yarnitsky, 2010). It may also help optimize pain management, as chronic pain patients may benefit more from pharmacological agents that target and enhance the specific dysfunctional pain modulation mechanism. The descending pain inhibitory system is impaired in chronic pain and it is important to know how analgesics interact with this system (Nir & Yarnitsky, 2015). A systematic literature study including 12 articles of good to moderate quality provide limited evidence suggesting that decreased CPM efficacy is improved after chronic pain (and not acute pain) is surgically

removed (Goubert et al., 2015). An improvement in clinical pain levels by analgesic treatments is accompanied by an improvement in CPM specific to the treated mechanism and not to a more generalized response to pain relief (Nir & Yarnitsky, 2015).

10. A FEW OTHER PHARMACOLOGICAL AND THERAPEUTIC APPLICATIONS

According to a recent systematic literature review, some pain inhibitory medication (e.g., ketamine) and oral contraceptives inhibit the CPM mechanism (Goubert et al., 2015) and facilitate pain responses (Niesters et al., 2011). In a sample of chronic neuropathic pain patients with inefficient CPM, treatment with ketamine, morphine, and placebo were effective in improving significantly CPM responses (Niesters, Aarts, Sarton, & Dahan, 2013). The opioid treatments buprenorphine and fentanyl also potentiate CPM in healthy male volunteers (Arendt-Nielsen et al., 2012). Pregabalin, a GABAergic medication used to treat neuropathic pain and fibromyalgia among other conditions, may also produce its analgesic effect by enhancing CPM. Importantly, pregabalin efficacy is influenced by initial CPM efficacy, such that individuals with less efficient CPM benefit more from the drug (Sugimine, Saito, Araki, Yamamoto, & Obata, 2017).

In summary, dysfunctions in pain modulation systems exist in individuals with and without chronic pain, and importantly, these deficits may be improved with drugs modulating the dysfunctional pain modulatory system, especially in individuals with less efficient CPM initially, highlighting the implication of CPM enhancement in pain management.

10.1 Neurotransmitters of Pain Modulation

Multiple neurotransmitters, including monoamines and opioids, are involved in the modulation of pain by endogenous descending inhibitory pathway.

10.1.1 Monoamines: Serotonin, Noradrenaline and Dopamine—Endogenous descending pain inhibitory systems originating in midbrain and brainstem regions (e.g., PAG and NRM) rich in amino biogenic transmitters, including serotonin and norepinephrine, are activated by bulbospinal monoaminergic pathways that project onto the spinal cord. In rats, DNIC is affected by clinical doses of adrenergic agonists (e.g., dexmedetomidine and phenylephrine), suggesting an involvement of adrenergic neurons in DNIC (Sanada, Kohase, Makino, & Umino, 2009). Catecholamines like norepinephrine and epinephrine signal through the α2-adrenergic receptors (Vo & Drummond, 2016) concentrated in the spinal cord to produce an inhibitory effect. Neurons of the dorsal horn in the spinal cord are directly inhibited by serotonin (from serotoninergic neurons) which, through its action on facilitatory spinal 5-HT3 receptors, influences the expression of CPM (Bannister & Dickenson, 2017). Measures of monoamines in men before a prostate surgery, the levels of monoamines, particularly adrenergics, was correlated to the efficacy of CPM (Parent et al., 2015).

10.1.2 Dopamine—A growing body of literature support the role of dopaminergic neurotrans-mission in the modulation of pain, however, the underlying mechanisms need

further investigation. In healthy subjects, CPM effect was significantly more important following apomorphine, a non-specific dopamine agonist, than placebo administration (27% versus 4%, respectively) (Treister, Pud, & Eisenberg, 2013). Inversely, the inhibition of dopaminergic neurotransmission in healthy human subjects using acute phenylalanine and tyrosine depletion (APTD) induced decreases of cerebral dopaminergic activity accompanied by increases of pain unpleasantness but not pain intensity (Tiemann, Heitmann, Schulz, Baumkötter, & Ploner, 2014). Even though parts of the descending pain inhibitory system involve dopaminergic pathways, no dysregulations in CPM contribute to altered pain processing in Parkinson's disease (PD), a pathology mainly characterized by lower secretion of dopamine. However, the akinetic-rigid subtype of PD is associated, at a trend level, to impairment of pain inhibition (Grashorn et al., 2015).

10.1.3 Catecholamines—Some patients with chronic pain conditions such as fibromyalgia display reduced CPM efficacy as well as lower concentration of serotonin and noradrenaline in the cerebrospinal fluid (Marchand, 2012). A recent study found a relationship between CPM efficacy and basal monoamine levels in blood, specifically blood-bound norepinephrine and metanephrine concentrations. Patients with chronic pain and deficits in CPM presented lower peripherally (plasma) acting norepinephrine and metanephrine concentrations (Parent et al., 2015). Lower CPM-mediated pain inhibition has also been linked to expression of a polymorphism in the serotonin transporter (5-HTT) gene (SLC6A4) (Lindstedt et al., 2011), but this association is not observed in all samples (Locke et al., 2014).

Pharmacological treatments engaging descending noradrenergic and serotonergic control pathways have shown some efficacy in the treatment of pain, demonstrating the importance of serotonin and norepinephrine in pain modulation (Bannister & Dickenson, 2017; Kirkpatrick et al., 2015). Antidepressants such as tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors are used for pain management in chronic pain conditions such as neuropathic pain, migraines, and fibromyalgia (Dharmshaktu, Tayal, & Kalra, 2012). Duloxetine,a serotonin–norepinephrine reuptake inhibitor (SNRI),benefited more patients with painful diabetic polyneuropathy and deficient CPM than subjects with efficient CPM. Furthermore, drug efficacy correlated with improvement in CPM efficacy (Yarnitsky, Granot, Nahman-Averbuch, Khamaisi, & Granovsky, 2012).

10.1.4 Opioids—The functioning of descending controls induced by counter-irritation include the analgesic action of endogenous opioid release, including enkephalins, B-endorphin, and dynorphins. Opioid receptors are contained on several primary afferents in the dorsal horn of the spinal cord, in particular the PAG and probably also the rostro-ventral gray matter of the bulb. Dorsal horn neurons mediated by serotonergic neurons act on interneurons that contain enkephalins which limit the discharge transmitted from the primary afferents to the cells of the dorsal horn (Marchand, 2012). In rats, plasticity of spinal serotonergic neurotransmission can modulate spinal mu-opioid receptors mechanisms (Aira et al., 2012).

In humans, pain inhibition and decrease in the nociceptive reflex induced by CPM can be completely blocked by naloxone hydrochloride, a non-selective and competitive opioid receptor antagonist after 5min from the administration. These findings led Willer et al. (1990) to believe that the supraspinal CPM phenomenon involves an opioidergic system. Similarly, the endogenous pain inhibitory systems activated by spatial summation is mediated by an opioid pathway (Julien & Marchand, 2006). Basal mu-opioid receptor availability in the amygdala predicts pain-related brain activity (on the P260 component of somatosensory evoked potentials reflecting activity in the ACC) during CPM but does not affect the nociceptive reflex. The authors argue that the inhibition of pain-related brain activity induced by activation of mu-opioid receptors in the amygdala may depend on a cerebral mechanism different from descending modulation (Piché et al., 2014). King et al. (2013) further reported only a partial blockage of the CPM effect by naltrexone, a long-term opioid antagonist, highlighting the importance of endogenous opioid release in the expression of CPM with the effects of naltrexone being moderated by levels of pain catastrophizing.

In healthy individuals, the mu-opioid receptor *agonist* morphine impairs CPM expression, while tapentadol, a combined mu-opioid receptor agonist and noradrenaline reuptake inhibitor, does not affect CPM (Martini et al., 2015). Conversely, tapentadol enhances pain inhibition in chronic pain patients with diabetic polyneuropathy (Niesters et al., 2014). In patients with chronic fatigue syndrome/fibromyalgia and rheumatoid arthritis, morphine produced anti-hyperalgesia effects (comparable to placebo), but neither morphine nor naloxone affected CPM. Findings suggest that the opioid system might not be responsible for impaired CPM in these patients (Hermans et al., 2018). Repeated use of opioids in the course of chronic pain treatment may lead to decreased capacity for endogenous analgesia. Patients with chronic pain using oral opioids express smaller CPM responses than patients with chronic pain using other analgesics (Ram, Eisenberg, Haddad, & Pud, 2008). Moreover, the dosage and duration of opioid treatment correlate negatively with CPM efficacy in men. The finding that CPM is affected by opioid use might hint at mechanisms of pain modulation and opioid-induced hyperalgesia phenomenon (Ram et al., 2008).

10.1.5 Cannabinoids—In producing antinociception, the neural circuitry activated by endogenous opioids and cannabinoids overlap (Ibrahim et al., 2005; Manning, Martin, & Meng, 2003; Sáez-Cassanelli, Fontanella, Delgado-García, & Carrión, 2007). Evidence of an implication of endogenous cannabinoids (endocannabinoids) in inhibitory pain modulation (Grotenhermen, 2004) arises primarily from animal studies. In the rat, the endogenous descending pain-modulatory pathways that includes PAG, its projection to downstream RVM neurons, and their inhibitory projections to the dorsal horn of the spinal cord (Palazzo, Luongo, Novellis, De Rossi, & Maione, 2010), play an important role in antinociception modulated by endocannabinoids (Calejesan, Kim, & Zhuo, 2000; Escobar et al., 2012; Hohmann, Tsou, & Walker, 1999; Manning et al., 2003) by actions primarily at the cannabinoid receptors type 1 (CB1) (Hohmann et al., 1999; Palazzo et al., 2010).

Cannabinoid receptor activation by endocannabinoids regulate the mode and the probability of g-aminobutyric acid (GABA) release within the midbrain PAG (Aubrey, Drew, Jeong, Lau, & Vaughan, 2017) and modulate GABA release in the RVM neurons (Li, Suchland, &

Ingram, 2017). Cannabinoids produce antinociception in the superficial dorsal horn also by modulation of the descending noradrenergic pathways (Gutierrez et al., 2003). CB1 receptors on GABAergic neurons play a role in the electroacupuncture effect of pain alleviation and improvement of DNIC function in a mouse model of knee osteoarthritis (Yuan et al., 2018). Neuropathic pain in rats may be reduced by action of the spinal endocannabinoid anandamide (AEA) on CB1 or transient receptor potential vanilloid 1 (TRPV1) receptors, depending on its local concentration (Maione et al., 2006; Starowicz et al., 2012). Several ventrolateral PAG neurons co-express TRPV1 and CB1 receptors (Maione et al., 2006; Palazzo, Rossi, & Maione, 2008) to produce spinal antinociception (Horvath, Kekesi, Nagy, & Benedek, 2008). Some of the therapeutic action of the pain treatment metamizole (Escobar et al., 2012) or the triptans for migraines may act via endocannabinoid containingneurons and CB1 receptors in the lateral–ventrolateral PAG (Akerman, Holland, Lasalandra, & Goadsby, 2013).

11. ROLE AND MANIPULATION OF EXPECTANCIES

Physiological pathways interact with psychological-cognitive ones to produce subjective pain experience. Neuroimaging studies support the modulation of CPM by certain regions of the limbic system (e.g., anterior cingulate cortex (ACC)) and the insula involved in the motivational-affective component of pain (Moont, Pud, Sprecher, Sharvit, & Yarnitsky, 2010). Reports link pain modulation with cognitive factors, including expectation, distraction, and attention, even though CPM effects are not due to attentional or distraction processes (Lautenbacher, Prager, & Rollman, 2007; Moont et al., 2010). Several studies have shown that conditioned modulation of pain is mediated by changes in expectancies (Jepma & Wager, 2015; Koban & Wager, 2016).

Expectancy refers to beliefs that something is going to happen or is likely to happen. Expectancies can be implicit or explicit. Implicit expectancies refer to beliefs based on what usually occurs in the individual’s environment (Schwarz, Pfister, & Büchel, 2016). These beliefs can also be built by social observation (Colloca & Benedetti, 2009; Schwarz et al., 2016) where people adapt their behavior partially based on these sort of statistical probabilities. Explicit expectancies refer to personal beliefs about oneself, the others and the environment. There are two categories of explicit expectancies: the first one refers to the beliefs consciously used to make decisions and the second one refers to the beliefs that will “incidentally” influence the decision making (Schwarz et al., 2016). Oneself expectancies can also be influenced by someone else’s expectancies (Pygmalion effect), like a therapist’s expectation concerning a patient or a teacher’s expectation concerning a student (Schwarz et al., 2016).

Expectancies can modulate conditioned pain modulation. When individuals with and without chronic back pain are asked, prior to testing if they expect ischemic pain (CS) would increase, decrease or not change their heat pain (TS), those who anticipate lower pain during ischemia report significantly more pain inhibition in heat pain than those with no expectancies or with pain augmentation expectancies. Administration of placebo, naloxone, or morphine did not affect these results. These findings reveal an important contribution of expectancy in CPM that is not mediated by opioid mechanisms (France et al., 2016),

supporting evidence from previous studies. Expectancies of pain augmentation can counteract an analgesic treatment (Cormier, Piché, & Rainville, 2013; Goffaux, Redmond, Rainville, & Marchand, 2007). *A priori* expectancies strongly correlate with CPM-induced analgesia, such that expectancies of hyperalgesia verbally induced through suggestions can enhance the nociceptive reflex amplitude and shock pain (thus blocking the analgesia normally activated by CPM), while suggestions of analgesia enhance the decrease in nociceptive reflex amplitude (Cormier et al., 2013). Changes in expected pain predict changes in pain outcomes mediated by descending pain modulation affecting spinal processes (Taylor, Chang, Rainville, & Roy, 2017). Findings suggest that while positive expectancies (analgesia) and lower stress are related to a greater pain reduction induced by CPM, negative expectancies (e.g., expectation of enhanced pain, hyperalgesia) enhance pain intensity. Interestingly, expectation of decreased or enhanced pain following a conditioning stimulation might produce the corresponding effect only in women (Bjørkedal & Flaten, 2012). However, further studies are needed to confirm a potential dysmorphic effect. The influence of expectancies on CPM seems to decrease in elderly individuals, while the deterioration of descending pain inhibitory mechanisms occurs (Grashorn, Sprenger, Forkmann, Wrobel, & Bingel, 2013).

Evidence of the effect of expectancies on pain modulation was elegantly provided by Goffaux et al. (2007). Expectancies of hyperalgesia completely blocked the typical CPM response on subjective pain ratings as well as spinal nociceptive reflexes and somatosensory evoked brain potentials; whereas expectancies of analgesia did not affect spinal nociception. The blockade of the analgesic effect by expectancies both at the spinal level (nociceptive reflex) and at the cortical level (somatosensory evoked potentials) suggests a physiological effect of expectancies related to spinal nociceptive signal processing rather than to the reinterpretation of nociceptive messages by the cortex (Goffaux et al., 2007).

Analgesia induced by CPM activation might depend mainly on the subjective perception of the painfulness of the CS rather than its physical intensity. Participants randomized to one of four cognitive interventions aimed at manipulating only the perception of pain intensity of the CPM conditioning component (and not its physical component); placebo (CS less painful after application of a local anesthetic cream); nocebo (CS more painful); and the informed control groups. Placebo and nocebo interventions respectively decreased and increased the perceived CS painfulness, however, only the placebo suggestions were paralleled by changes in CPM magnitude (Nir, Yarnitsky, Honigman, & Granot, 2012). These opposite effects of placebo analgesia and nocebo hyperalgesia are supported by brain mapping studies which generate a divergent pattern of cerebral activation after the administration of placebo and nocebo (Nir et al., 2012).

Expanding on these findings, Rattanavong (2013) manipulated the motivational-affective component of pain, while rendering untouched the intensity of pain, the sensory-discriminative component of pain. Suggestions of increase, decrease or no change in CS unpleasantness following inactive cream application were made. Consequently, a decrease in perceived unpleasantness significantly reduces the effectiveness of CPM mechanisms. The manipulation of the affective component of pain, through specific suggestions, modulates the analgesic efficacy of CPM, however, an initially effective analgesic response is not

enhanced by increased unpleasantness of the stimulus, indicating a ceiling effect (Rattanavong, 2013).

It is hypothesized that a change in pain intensity affects pain unpleasantness. The sensory and affective components of pain can be dissociated by hypnotic suggestions. When it is suggested, via hypnosis, that pain induced by a CS will be as intense as the previous one, but not unpleasant, the corresponding changes are observed in pain ratings and brain activity. The reduction of pain unpleasantness is associated with reduced activity in the cortical regions involved in the emotional component of pain (e.g., ACC), while the unaltered sensory component of pain is consistent with the absence of change in the activity of the SI. In contrast, hypnotic suggestions used to modulate the sensory component of pain reduce perception and brain activity associated with both the sensory and affective components of pain (Rainville, Carrier, Hofbauer, Bushnell, & Duncan, 1999). The analgesic effect of hypnosis is thought to activate descending inhibitory mechanisms, among other mechanisms (Kiernan, Dane, Phillips, & Price, 1995). Moreover, CPM-induced analgesia is more pronounced in subjects highly susceptible to hypnosis (Fidanza, Varanini, Ciaramella, Carli, & Santarcangelo, 2017).

According to the literature, expectancies and CPM effects are generally correlated (Bjørkedal & Flaten, 2012; Hermans et al., 2016). It has been suggested that “reduced inhibitory CPM can be due to contextually induced cognitive and emotional factors and not necessarily to a dysfunction of descending inhibitory pathways” (Bjørkedal & Flaten, 2012).

A recent study has examined the relationship between CPM responses and the magnitude of placebo effects induced by open and hidden applications of lidocaine and a control analgesic in individuals with neuropathic pain. Even though patients expressed efficient CPM and placebo effects, the CPM response did *not* predict the occurrence and magnitude of individual placebo effects, suggesting similar behavioral effects but most likely different mechanisms underlying CPM and placebo effects (Skyt et al., 2018). A very recent study in our laboratory also suggest that placebo-induced analgesia does not vary as a function of CPM in healthy adults, suggesting different pain inhibitory mechanisms (Damien, Léonard, Chalaye, Colloca, & Marchand, 2018). Evidence on the capacity of placebo and nocebo effects to act on descending pain modulation mechanisms is important for the prevention and treatment of pain considering that the capacity to trigger endogenous pain modulation mechanisms may help predict chronic pain. The extensive research on the placebo effect has contributed to the recognition of its strength and its ability to produce significant therapeutic benefits in managing experimental and clinical pain. In fact, as there are different CPM, there exists many placebo effects, with different mechanisms (Benedetti, Carlino, & Pollo, 2011). Recent experimental and clinical studies begin to unravel the psychoneurobiological mechanisms underlying placebo analgesic effects (Elsenbruch & Labrenz, 2018; Medoff & Colloca, 2015).

While placebo effect varies between people with different characteristics (Corsi & Colloca, 2017; Geers, Kosbab, Helfer, Weiland, & Wellman, 2007) and within the same person when receiving more than one treatment (Whalley, Hyland, & Kirsch, 2008), the evaluation of the effect of expectancies is a challenge in research (Schwarz et al., 2016). Nevertheless, as

mentioned elsewhere, numerous studies reveal that expectancies also modulate placebo and nocebo effects (Bartels et al., 2014; Bartels, van Laarhoven, Heijmans, et al., 2017; Bartels, van Laarhoven, Stroo, et al., 2017; Bingel et al., 2011; Bräscher, Witthöft, & Becker, 2018; Fiorio et al., 2012). Expectancies are induced by verbal instructions, social observation (for reviews see, Colloca & Grillon, 2014; Medoff & Colloca, 2015) and distinct forms of learning (for example, Benedetti et al., 2003; Egorova et al., 2015; Morton, El-Deredy, & Jones, 2014; Reicherts, Gerdes, Pauli, & Wieser, 2016). Expectancies and placebo-related mechanisms and specific effects of therapies or drugs may partially overlap to affect therapeutic outcome (Benedetti et al., 2011). Drug actions and placebo effects may interact additively or synergistically in some conditions, such that a treatment is less effective if the placebo component is absent. Therefore, patients' beliefs and expectancies should be exploited to optimize treatment outcomes (Bingel et al., 2011) in adult as well as pediatric populations (Simmons et al., 2014).

The extensive research on the placebo effect has contributed to the recognition of its strength and its ability to produce significant therapeutic benefits in managing experimental and clinical pain. There exists different CPM and placebo effects (Benedetti et al., 2011). Not only is placebo research helpful for personalizing and optimizing pain management, it also contributes to the understanding of the endogenous mechanisms of analgesia involved in normal functioning and pain states (Benedetti, 2007; Colloca & Grillon, 2014) and in the context of clinical trials (Gourion & Mouchabac, 2016).

12. EXPERIMENTAL AND CLINICAL PLACEBO STUDIES

Placebo effects have been described both in different experimental settings and multiple clinical conditions (Murray & Stoessl, 2013). A positive placebo effect is observed in almost half of patients with Parkinson's disease (PD), pain syndromes, and depression, particularly in states of advanced disease or during invasive procedures (Diederich & Goetz, 2008). The placebo and nocebo effects in clinical trials for migraines are also substantial (Antonaci, Chimento, Diener, Sances, & Bono, 2007). Placebo analgesic effects are usually greater in studies investigating placebo analgesic mechanisms compared with clinical trials in which placebos served as a control (Vase, Riley, & Price, 2002).

Placebo effects have been suggested to affect more strongly postoperative or clinical pain than experimental pain. Several studies demonstrate higher and more enduring placebo effects in patients as compared to healthy participants (Sauro & Greenberg, 2005). Expectancy-induced placebo effects elicited a large placebo analgesic effect to both acute experimental and chronic pain, however, the placebo effects were unrelated to each other (Müller et al., 2016). Charron, Rainville, and Marchand (2006) examined changes in the intensity and unpleasantness of pain in patients with low back pain undergoing a placebo treatment consisting of a saline injection presented as a potent painkiller in one session or as an inactive substance in the control session. Following the injection, comparable pain relief was expected for clinical and experimental pain. Nonetheless, reported ratings of pain intensity, pain unpleasantness, and perceived relief demonstrated a more potent placebo effect in clinical pain versus experimental pain (Charron et al., 2006).

12.1 Clinical Pain

Longer exposure to fibromyalgia pain is associated with lower placebo-induced analgesia in addition to low pain inhibitory capacity, which is depicted by less efficient CPM (Kosek et al., 2017; Yarnitsky, 2010), highlighting the need for early interventions (Kosek et al., 2017). Similarly, patients with Alzheimer's disease or dementia with impaired prefrontal lobe functions show reduced expectancy-induced placebo responses, underlying the need to compensate for the loss of the endogenous placebo-related mechanisms in this condition in order to optimize therapeutic benefits (Benedetti et al., 2006, 2011). Placebo effects obtained after a conditioning procedure on pain tolerance can be transferred to other modalities such as motor endurance, emphasizing the potential implications of placebo analgesic procedures in pathological conditions such as chronic fatigue or Parkinson's disease (Carlino, Guerra, & Piedimonte, 2016).

In contrast, major depressive disorder is a condition that is highly responsive to placebos in clinical trials; placebo response rates can attain up to 30–40% (Gourion & Mouchabac, 2016). In this condition, placebo effects can partially mimic selective serotonin reuptake inhibitor-mediated brain activation (Diederich & Goetz, 2008). Depressive symptoms as well as trait anxiety, pain catastrophizing, and pain disability appear to be associated to deficits in endogenous opioid function, which may be improved by opioid analgesic treatment (e.g., morphine) (Burns et al., 2017). Placebo effects and particularly nocebo effects are important in clinical trials for sexual dysfunctions and migraine or acute headache treatments (Colloca & Miller, 2011; Diener, Schorn, Bingel, & Dodick, 2008; Mitsikostas, 2012).

12.1.1 Open-Label Placebos Clinical Trials—According to a recent systematic reviews and meta-analysis, open-label placebos (without deception) positively influence clinical effects (e.g., mean global improvement scores, severity of symptoms and pain relief) in comparison to the absence of treatment across many clinical conditions: irritable bowel syndrome, depression, allergic rhinitis, back pain, and attention deficit hyperactivity disorder (Charlesworth et al., 2017; Colloca & Howick, 2018; Kaptchuk et al., 2010). Open-label and dose-extending placebos do not raise the typical ethical dilemmas usually associated with deceptive placebos because patients are explicitly informed of the nature the placebo treatment and the rationale of receiving the placebo (Carvalho et al., 2016; Colloca & Howick, 2018). Thus, the use of clinically meaningful placebo effects with potential benefits and limited adverse events (Colloca & Miller, 2011) may be a helpful strategy for pain management (Carvalho et al., 2016). Laboratory and clinical studies on placebo analgesia might benefit from using open-label and dose-extending placebos to potentiate the placebo effect in therapeutic regimes (Colloca & Howick, 2018).

In clinical practice, patients always expect to receive an active drug, whereas they are informed about the possibility of receiving an active drug or a placebo in clinical trials, resulting in reduced treatment efficacy. Nonetheless, active placebos inducing minor sensations versus inert/passive placebo substances can make participants believe they received an active drug and enhance pain relief induced by placebo effects (Rief & Glombiewski, 2012).

In clinical trials, placebo responses have increased thereby making it difficult to attain superior analgesic effects with new drugs (Tuttle et al., 2015; Vase et al., 2015). Various individual factors influence the placebo response in clinical trials, such as patients' expectation, baseline pain intensity, age, gender, geographical distribution. General characteristics and methodology of randomized controlled trials (RCTs) impact the placebo response, including design (studies with a parallel design yield higher placebo response than cross-over studies), blinding, randomization ratio, treatment allocation, route of application of drugs (Diener et al., 2008; Vase et al., 2015), adverse effects and discontinuation, washout length and number of planned face-to-face visits (Vase et al., 2015) and countries where the trials are ran (Tuttle et al., 2015).

A pioneering Cochrane review including randomized placebo trials on 60 clinical conditions (including pain, nausea, phobia, asthma, depression, smoking, dementia, obesity, hypertension, insomnia and anxiety) found a very variable effect of placebo interventions on pain, from negligible to clinically important. Larger effects of placebo interventions were found in studies with physical placebo interventions (e.g., sham acupuncture), outcomes reported by patients rather than by observers, small trials, and trials that did not inform patients about the possibility of placebo treatment (Hróbjartsson & Gøtzsche, 2010).

In contrast, a meta-analysis of RCTs in the treatment of depression with selective serotonin reuptake inhibitors (SSRIs) found no significant difference in effect size between clinical trials that excluded placebo responders after the placebo run-in phase and those trials that did not (Lee, Walker, Jakul, & Sexton, 2004). A recent study has shown that it is possible to estimate patients' expectancies toward treatment efficacy and hence predict the magnitude of the placebo response in RCTs (Vase et al., 2015).

Weimer, Colloca, and Enck (2015) evaluated 75 systematic reviews and meta-analyses on the predictors of the placebo response in major medical areas (neurology, psychiatry, internal medicine) known for high placebo response rates and concluded that a younger age may contribute to placebo response rate in some conditions (psychiatric conditions but not in depression, and internal medicine but not in gastroenterology), but found no supporting evidence of an effect of sex or older age in placebo response. Importantly, lower symptom severity at baseline, a randomization ratio that selected more patients to drugs than to placebo, and more frequent study visits were common predictors of placebo response (Weimer et al., 2015).

12.1.2 Psychological Variables—The large variability in placebo effects and responses is partially mediated by individual variables, although the factors identified are unlikely to be exhaustive. For instance, aspects of pain catastrophizing including feelings of helplessness and magnification of pain are associated with the efficacy of pharmaceutical and natural placebos in reducing pain intensity (Watkinson, Chapman, & Horne, 2017). Higher anxiety also contributes to greater placebo and nocebo effects, in part, via activation of the CCK pathway (Colloca & Miller, 2011). Heightened anxiety and autonomic arousal are involved in the persistence of nocebo hyperalgesia (Colagiuri & Quinn, 2017). Personality traits such as resiliency, altruism, straightforwardness, and hostility explain some variance in placebo analgesic responses that is related to activations in endogenous opioid

systems (Peciña et al., 2013). Biological markers contributing to interindividual variations in placebo-induced pain modulation and the pain-related neurotransmission of endogenous opioid and dopamine have been identified. For instance, the A118G mu-opioid receptor gene (*OPRM1*) polymorphism has been linked to psychological factors associated with placebo analgesia and brain activity changes (Peciña, Love, Stohler, Goldman, & Zubieta, 2015). Similar endogenous MOR mechanisms are activated by the analgesic effects of placebo and real transcranial direct current stimulation (tDCS) of the primary motor cortex M1 (DosSantos et al., 2014).

The history of treatment is another important factor to consider in experimental and clinical modulation of placebo and nocebo effects. In healthy individuals, prior positive experiences with effective treatment enhance the placebo effect. In patients with chronic pain, a more negative pain-related treatment history was associated with larger placebo effects for the relief of clinical pain (Müller et al., 2016). Clinically, the efficacy of sham rTMS for neuropathic pain relief could be improved by being administered following a successful active rTMS (André-Obadia, Magnin, & Garcia-Larrea, 2011). Furthermore, the persistence of placebo and nocebo effects is associated to the length of conditioning (i.e., number of exposures) to prior effective (and ineffective) interventions (Colloca, Petrovic, Wager, Ingvar, & Benedetti, 2010). In any treatment, learned placebo responses following exposure to an active therapy or drug should be maximized by using a conditioned strategy of therapeutic effects, so that placebos can acquire properties of active treatments (like in dose-extending placebos) and extend their clinical benefits, especially in conditions of chronic diseases (Colloca, Enck, & DeGrazia, 2016).

Translational placebo research should also consider the common nocebo effects that can arise from information about side effects. Nocebo effects can negatively influence clinical outcomes, by attenuating the perceived pain relief, consequently causing a decreased effectiveness of pain-management interventions and increase nonadherence or discontinuation of trials (Colloca & Miller, 2011). To improve patient care, Klinger, Blasini, Schmitz, and Colloca (2017) suggest multiple strategies to minimize nocebo effects in the treatment of patients with chronic pain, focusing on communication and interactions between patients and clinicians during treatment and minimizing negative information, cues, context and lack of positive information.

13. CONCLUSION

In recent years, there have been many new exciting discoveries to advance our understanding of the area of the endogenous mechanisms of pain modulation. Cumulative evidence in research on pain modulation substantiate similar and divergent mechanisms in the various conditioned pain modulation and placebo effects. CPM and placebo effects are both influenced by expectancies of analgesia built up through verbal suggestions, past personal experience, contextual cues, socio-affective and learning processes (e.g., conditioning and social observation). Expectancies of pain relief in CPM and placebo effects activate subcortical nuclei in the descending pain inhibitory system, including brainstem regions such as the RVM and PAG, which send inhibitory projections to the spine and produce diffuse analgesic responses important for endogenous pain modulation (Fazeli & Büchel,

2018). Multiple neurotransmitters, including endogenous monoamines, opioids and cannabinoids, are involved in the modulation of pain by endogenous inhibitory pathway in animals and humans. In contrast, nocebo hyperalgesic effects activate release of the cholecystokinin system (CCK), among other neurotransmitters. Although CPM and placebo or nocebo effects induce similar behavioral pain reduction or enhancements, the related analgesic effects are not correlated and they activate distinct endogenous pain inhibitory systems (e.g., activation of descending pain control systems from spinobulbospinal and higher centers, respectively).

Placebo effects inherently contribute to every treatment and clinical outcomes. Pre-treatment assessment of CPM efficacy and the functioning of descending pain inhibitory pathways may provide the ability to predict the development of clinical pain in patients and the magnitude of analgesic effects in response to treatments. Therefore, the knowledge of the interaction between placebo and CPM systems in the descending pain inhibitory pathways is of high clinical relevance yet remains to be fully elucidated. Exploring the action of placebo and nocebo effects along with CPM on different parts of descending pain inhibition systems can reveal whether the engagement of potential common pathways limits the overall analgesic effect (e.g., a ceiling effect), or alternatively, results in a potentiation of the inhibitory response (e.g., additive effects). The ultimate goal of this research is to minimize the experience of pain in patients and help optimize pain management strategies based on inhibitory pain modulation mechanisms.

REFERENCES

Aira Z, Buesa I, García del Caño G, Salgueiro M, Mendiable N, Mingo J, et al. (2012). Selective impairment of spinal mu-opioid receptor mechanism by plasticity of serotonergic facilitation mediated by 5-HT2A and 5-HT2B receptors. Pain, 153(7), 1418–1425. 10.1016/j.pain.2012.03.017. [PubMed: 22520172]

Akerman S, Holland PR, Lasalandra MP, & Goadsby PJ (2013). Endocannabinoids in the brainstem modulate dural trigeminovascular nociceptive traffic via CB1 and “triptan” receptors: Implications in migraine. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 33(37), 14869–14877. 10.1523/JNEUROSCI.0943-13.2013. [PubMed: 24027286]

Albu S, Gómez-Soriano J, Avila-Martin G, & Taylor J (2015). Deficient conditioned pain modulation after spinal cord injury correlates with clinical spontaneous pain measures. Pain, 156(2), 260–272. 10.1097/01.j.pain.0000460306.48701.f9. [PubMed: 25599447]

André-Obadia N, Magnin M, & Garcia-Larrea L (2011). On the importance of placebo timing in rTMS studies for pain relief. Pain, 152(6), 1233–1237. 10.1016/j.pain.2010.12.027. [PubMed: 21342747]

Antonaci F, Chimento P, Diener H-C, Sances G, & Bono G (2007). Lessons from placebo effects in migraine treatment. The Journal of Headache and Pain, 8(1), 63–66. 10.1007/s10194-007-0360-4. [PubMed: 17361384]

Arendt-Nielsen L, Andresen T, Malver LP, Oksche A, Mansikka H, & Drewes AM (2012). A double-blind, placebo-controlled study on the effect of buprenorphine and fentanyl on descending pain modulation: A human experimental study. The Clinical Journal of Pain, 28(7), 623–627. 10.1097/AJP.0b013e31823e15cb. [PubMed: 22156892]

Aubrey KR, Drew GM, Jeong H-J, Lau BK, & Vaughan CW (2017). Endocannabinoids control vesicle release mode at midbrain periaqueductal grey inhibitory synapses. The Journal of Physiology, 595(1), 165–178. 10.1113/JP272292. [PubMed: 27461371]

Bannister K, & Dickenson AH (2017). The plasticity of descending controls in pain: Translational probing. The Journal of Physiology, 595(13), 4159–4166. 10.1113/JP274165. [PubMed: 28387936]

Bartels DJP, van Laarhoven AIM, Haverkamp EA, Wilder-Smith OH, Donders ART, van Middendorp H, et al. (2014). Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. PLoS One, 9(3), e91727 10.1371/journal.pone.0091727. [PubMed: 24646924]

Bartels DJP, van Laarhoven AIM, Heijmans N, Hermans D, Debeer E, van de Kerkhof PCM, et al. (2017). Cognitive schemas in placebo and nocebo responding: Role of autobiographical memories and expectations. Clinical Therapeutics, 39(3) 502–512.e1 10.1016/j.clinthera.2017.02.004. [PubMed: 28341522]

Bartels DJP, van Laarhoven AIM, Stroo M, Hijne K, Peerdeman KJ, Donders ART, et al. (2017). Minimizing nocebo effects by conditioning with verbal suggestion: A randomized clinical trial in healthy humans. PLoS One, 12(9), e0182959 10.1371/journal.pone.0182959. [PubMed: 28910291]

Benedetti F (2007). Placebo and endogenous mechanisms of analgesia. Handbook of Experimental Pharmacology, 177, 393–413. 10.1007/978-3-540-33823-9_14.

Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, Rainero I, et al. (2006). Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. Pain, 121(1–2), 133–144. 10.1016/j.pain.2005.12.016. [PubMed: 16473462]

Benedetti F, Carlino E, & Pollo A (2011). How placebos change the patient's brain.Neuropsychopharmacology, 36(1), 339–354. 10.1038/npp.2010.81. [PubMed: 20592717]

Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, & Rainero I (2003).Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 23(10), 4315–4323. 10.1523/JNEUROSCI.23-10-04315.2003. [PubMed: 12764120]

Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. (2011). The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. Science Translational Medicine, 3(70), 70ra14 10.1126/scitranslmed.3001244.

Biurrun Manresa JA, Fritsche R, Vuilleumier PH, Oehler C, Mørch CD, Arendt-Nielsen L, et al. (2014). Is the conditioned pain modulation paradigm reliable? A test-retest assessment using the nociceptive withdrawal reflex. PLoS One, 9(6), e100241 10.1371/journal.pone.0100241. [PubMed: 24950186]

Bjørkedal E, & Flaten MA (2012). Expectations of increased and decreased pain explain the effect of conditioned pain modulation in females. Journal of Pain Research, 5, 289–300. 10.2147/JPR.S33559. [PubMed: 23049277]

Bogdanov VB, Viganò A, Noirhomme Q, Bogdanova OV, Guy N, Laureys S, et al. (2015). Cerebral responses and role of the prefrontal cortex in conditioned pain modulation: An fMRI study in healthy subjects. Behavioural Brain Research, 281, 187–198. 10.1016/j.bbr.2014.11.028. [PubMed: 25461267]

Bouhassira D, Danziger N, Attal N, Guirimand F, & Atta N (2003). Comparison of the pain suppressive effects of clinical and experimental painful conditioning stimuli. Brain: A Journal of Neurology, 126(Pt. 5), 1068–1078. [PubMed: 12690047]

Bouhassira D, Moisset X, Jouet P, Duboc H, Coffin B, & Sabate J-M (2013). Changes in the modulation of spinal pain processing are related to severity in irritable bowel syndrome. Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society, 25(7), 623 10.1111/nmo.12123. [PubMed: 23551988]

Bräscher A-K, Witthöft M, & Becker S (2018). The underestimated significance of conditioning in placebo hypoalgesia and nocebo hyperalgesia. Pain Research & Management, 2018, 6841985 10.1155/2018/6841985. [PubMed: 29670678]

Burns JW, Bruehl S, France CR, Schuster E, Orlowska D, Buvanendran A, et al. (2017). Psychosocial factors predict opioid analgesia through endogenous opioid function. Pain, 158(3), 391–399. 10.1097/j.pain.0000000000000768. [PubMed: 27898491]

Calejesan AA, Kim SJ, & Zhuo M (2000). Descending facilitatory modulation of a behavioral nociceptive response by stimulation in the adult rat anterior cingulate cortex. European Journal of Pain (London, England), 4(1), 83–96. 10.1053/eujp.1999.0158.

Carlino E, Guerra G, & Piedimonte A (2016). Placebo effects: From pain to motor performance. Neuroscience Letters, 632, 224–230. 10.1016/j.neulet.2016.08.046. [PubMed: 27574730]

Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, & Kirsch I (2016). Open-label placebo treatment in chronic low back pain: A randomized controlled trial. Pain, 157(12), 2766–2772. 10.1097/j.pain.0000000000000700. [PubMed: 27755279]

Charlesworth JEG, Petkovic G, Kelley JM, Hunter M, Onakpoya I, Roberts N, et al. (2017). Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. Journal of Evidence-Based Medicine, 10(2), 97–107. 10.1111/jebm.12251. [PubMed: 28452193]

Charron J, Rainville P, & Marchand S (2006). Direct comparison of placebo effects on clinical and experimental pain. The Clinical Journal of Pain, 22(2), 204–211. [PubMed: 16428957]

Colagiuri B, & Quinn V (2017). Autonomic arousal as a mechanism of the persistence of nocebo hyperalgesia. The Journal of Pain: Official Journal of the American Pain Society, 19(5), 476–486. 10.1016/jjpain.2017.12.006. [PubMed: 29269281]

Colloca L, & Benedetti F (2009). Placebo analgesia induced by social observational learning. Pain, 144(1–2), 28–34. 10.1016/j.pain.2009.01.033. [PubMed: 19278785]

Colloca L, Enck P, & DeGrazia D (2016). Relieving pain using dose-extending placebos: A scoping review. Pain, 157(8), 1590–1598. 10.1097/j.pain.0000000000000566. [PubMed: 27023425]

Colloca L, & Grillon C (2014). Understanding placebo and nocebo responses for pain management. Current Pain and Headache Reports, 18(6), 419 10.1007/s11916-014-0419-2. [PubMed: 24771206]

Colloca L, & Howick J (2018). Placebos without deception: Outcomes, mechanisms, and ethics. InternationalReviewofNeurobiology, 138, 219–240. 10.1016/bs.irn.2018.01.005.

Colloca L, Ludman T, Bouhassira D, Baron R, Dickenson AH, Yarnitsky D, et al.(2017) Neuropathic pain. Nature Reviews Disease Primers, 3, 17002 10.1038/nrdp.2017.2.

Colloca L, & Miller FG (2011). Harnessing the placebo effect: The need for translational research. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 366(1572), 1922–1930. 10.1098/rstb.2010.0399. [PubMed: 21576150]

Colloca L, Petrovic P, Wager TD, Ingvar M, &Benedetti F (2010). How the number of learning trials affects placebo and nocebo responses. Pain, 151(2), 430–439. 10.1016/j.pain.2010.08.007. [PubMed: 20817355]

Cormier S, Piché M, & Rainville P (2013). Expectations modulate heterotopic noxious counter-stimulation analgesia. The Journal of Pain: Official Journal of the American Pain Society, 14(2), 114–125. 10.1016/jjpain.2012.10.006. [PubMed: 23260452]

Corsi N, & Colloca L (2017). Placebo and nocebo effects: The advantage of measuring expectations and psychological factors. Frontiers in Psychology, 8, 308 10.3389/fpsyg.2017.00308. [PubMed: 28321201]

Daenen L, Nijs J, Roussel N, Wouters K, Van Loo M, & Cras P (2013). Dysfunctional pain inhibition in patients with chronic whiplash-associated disorders: An experimental study. Clinical Rheumatology, 32(1), 23–31. 10.1007/s10067-012-2085-2. [PubMed: 22983264]

Damien J, Leonard G, Chalaye P, Colloca L, &Marchand S (2018). In Sex differences in analgesia induced by conditioned pain modulation, hypnosis and placebo treatments. Presented at the Canadian Pain Society's (CPS) 39th Annual Scientific Meeting, Montreal: Canadian Journal of Pain 10.1080/24740527.2018.1476313.

De Felice M, Sanoja R, Wang R, Vera-Portocarrero L, Oyarzo J, King T, et al. (2011). Engagement of descending inhibition from the rostral ventromedial medulla protects against chronic neuropathic pain. Pain, 152(12), 2701–2709. 10.1016/j.pain.2011.06.008. [PubMed: 21745713]

de Resende MA, Silva LFS, Sato K, Arendt-Nielsen L, & Sluka KA (2011). Blockade of opioid receptors in the medullary reticularis nucleus dorsalis, but not the rostral ventromedial medulla, prevents analgesia produced by diffuse noxious inhibitory control in rats with muscle inflammation. The Journal of Pain: Official Journal of the American Pain Society, 12(6), 687–697. 10.1016/jjpain.2010.12.009. [PubMed: 21330219]

de Souza JB, Potvin S, Goffaux P, Charest J, &Marchand S (2009). The deficit ofpain inhibition in fibromyalgia is more pronounced in patients with comorbid depressive symptoms. The Clinical Journal ofPain, 25(2), 123–127. 10.1097/AJP.0b013e318183cfa4.

Dharmshaktu P, Tayal V, & Kalra BS (2012). Efficacy of antidepressants as analgesics: A review. Journal of Clinical Pharmacology, 52(1), 6–17. 10.1177/0091270010394852. [PubMed: 21415285]

Diederich NJ, & Goetz CG (2008). The placebo treatments in neurosciences: New insights from clinical and neuroimaging studies. Neurology, 71(9), 677–684. 10.1212/01.wnl.0000324635.49971.3d. [PubMed: 18725593]

Diener H-C, Schorn CF, Bingel U, & Dodick DW (2008). The importance of placebo in headache research. Cephalalgia: An International Journal of Headache, 28(10), 1003–1011. 10.1111/j.1468-2982.2008.01660.x. [PubMed: 18727647]

DosSantos MF, Martikainen IK, Nascimento TD, Love TM, DeBoer MD, Schambra HM, et al. (2014). Building up analgesia in humans via the endogenous μ-opioid system by combining placebo and active tDCS: A preliminary report. PLoS One, 9(7), e102350 10.1371/journal.pone.0102350. [PubMed: 25029273]

Edwards RR, Dolman AJ, Martel MO, Finan PH, Lazaridou A, Cornelius M, et al. (2016). Variability in conditioned pain modulation predicts response to NSAID treatment in patients with knee osteoarthritis. BMC Musculoskeletal Disorders, 17, 284 10.1186/s12891-016-1124-6. [PubMed: 27412526]

Edwards RR, Ness TJ, Weigent DA, & Fillingim RB (2003). Individual differences in diffuse noxious inhibitory controls (DNIC): Association with clinical variables. Pain, 106(3), 427–437. 10.1016/j.pain.2003.09.005. [PubMed: 14659526]

Egorova N, Park J, Orr SP, Kirsch I, Gollub RL, & Kong J (2015). Not seeing or feeling is still believing: Conscious and non-conscious pain modulation after direct and observational learning. Scientific Reports, 5, 16809 10.1038/srep16809. [PubMed: 26578164]

Elsenbruch S, & Labrenz F (2018). Nocebo effects and experimental models in visceral pain. International Review of Neurobiology, 138, 285–306. 10.1016/bs.irn.2018.01.010. [PubMed: 29681331]

Escobar W, Ramirez K, Avila C, Limongi R, Vanegas H, & Vazquez E (2012). Metamizol, a non-opioid analgesic, acts via endocannabinoids in the PAG-RVM axis during inflammation in rats. European Journal of Pain (London, England), 16(5), 676–689. 10.1002/j.1532-2149.2011.00057.x.

Fazeli S, & Büchel C (2018). Pain related expectation and prediction error signals in the anterior insula are not related to aversiveness. The Journal ofNeuroscience: The Official Journal of the Society for Neuroscience, 38(29), 6461–6474. 10.1523/JNEUROSCI.0671-18.2018.

Fidanza F, Varanini M, Ciaramella A, Carli G, & Santarcangelo (2017). Pain modulation as a function of hypnotizability: Diffuse noxious inhibitory control induced by cold pressor test vs explicit suggestions of analgesia. Physiology & Behavior, 171, 135–141. 10.1016/j.physbeh.2017.01.013. [PubMed: 28082248]

Fiorio M, Recchia S, Corra F, Simonetto S, Garcia-Larrea L, & Tinazzi M (2012). Enhancing non-noxious perception: Behavioural and neurophysiological correlates of a placebo-like manipulation. Neuroscience, 217, 96–104. 10.1016/j.neuroscience.2012.04.066. [PubMed: 22569155]

France CR, Burns JW, Gupta RK, Buvanendran A, Chont M, Schuster E, et al. (2016). Expectancy effects on conditioned pain modulation are not influenced by naloxone or morphine. Annals of Behavioral Medicine: A Publication of the Society of Behavioral Medicine, 50(4), 497–505. 10.1007/s12160-016-9775-y. [PubMed: 26809850]

Gallotta S, Bruno V, Catapano S, Mobilio N, Ciacci C,& Iovino P (2017). High risk of temporomandibular disorder in irritable bowel syndrome: Is there a correlation with greater illness severity? World Journal of Gastroenterology, 23(1), 103–109. 10.3748/wjg.v23.i1.103. [PubMed: 28104985]

Geers AL, Kosbab K, Helfer SG, Weiland PE, & Wellman JA (2007). Further evidence for individual differences in placebo responding: An interactionist perspective. Journal of Psychosomatic Research, 62(5), 563–570. 10.1016/jjpsychores.2006.12.005. [PubMed: 17467411]

Gehling J, Mainka T, Vollert J, Pogatzki-Zahn EM, Maier C, & Enax-Krumova EK (2016). Short-term test-retest-reliability of conditioned pain modulation using the cold-heat-pain method in healthy subjects and its correlation to parameters of standardized quantitative sensory testing. BMC Neurology, 16, 125 10.1186/s12883-016-0650-z. [PubMed: 27495743]

Gierthmühlen J, et al. (2015). Who is healthy? Aspects to consider when including healthy volunteers in QST-based studies—A consensus statement by the EUROPAIN and NEUROPAIN consortia. Pain, 156(11), 203–2211. 10.1097/j.pain.0000000000000227. [PubMed: 25599440]

Goffaux P, Redmond WJ, Rainville P, & Marchand S (2007). Descending analgesia—When the spine echoes what the brain expects. Pain, 130(1), 137–143. 10.1016/j.pain.2006.11.011. [PubMed: 17215080]

Goubert D, Danneels L, Cagnie B, Van Oosterwijck J, Kolba K, Noyez H, et al. (2015). Effect of pain induction or pain reduction on conditioned pain modulation in adults: A systematic review. Pain Practice: The Official Journal of World Institute of Pain, 15(8), 765–777. 10.1111/papr.12241. [PubMed: 25387406]

Gougeon V, Gaumond I, Goffaux P, Potvin S, & Marchand S (2016). Triggering descending pain inhibition by observing ourselves or a loved-one in pain. The Clinical Journal ofPain, 32(3), 238–245. 10.1097/AJP.0000000000000244.

Gourion D, & Mouchabac S (2016). Placebo effect: Clinical, biological and therapeutical involvements in depression. L'Encephale, 42(1 Suppl. 1), 1S24–30. 10.1016/S0013-7006(16)30016-1.S24-1S30.

Granovsky Y (2013). Conditionedpain modulation: A predictor for development and treat-ment of neuropathic pain. Current Pain and Headache Reports, 17(9), 361 10.1007/s11916-013-0361-8. [PubMed: 23943407]

Granovsky Y, Miller-Barmak A, Goldstein O, Sprecher E, & Yarnitsky D (2016). CPM test-retest reliability: "Standard" vs "single test-stimulus" protocols. Pain Medicine, 17(3), 521–529. 10.1111/pme.12868. [PubMed: 26272736]

Granovsky Y, Nahman-Averbuch H, Khamaisi M, & Granot M (2017). Efficient conditioned pain modulation despite pain persistence in painful diabetic neuropathy. Pain Reports, 2(3), e592 10.1097/PR9.0000000000000592. [PubMed: 29392208]

Grashorn W, Schunke O, Buhmann C, Forkmann K, Diedrich S, Wesemann K, et al. (2015). Influence of dopaminergic medication on conditioned pain modulation in Parkinson's disease patients. PLoS One, 10(8), e0135287 10.1371/journal.pone.0135287. [PubMed: 26270817]

Grashorn W, Sprenger C, Forkmann K, Wrobel N, & Bingel U (2013). Age-dependent decline of endogenous pain control: Exploring the effect of expectation and depression. PLoS One, 8(9), e75629 10.1371/journal.pone.0075629. [PubMed: 24086595]

Grosen K, Vase L, Pilegaard HK, Pfeiffer-Jensen M, & Drewes AM (2014). Conditioned pain modulation and situational pain catastrophizing as preoperative predictors of pain following chest wall surgery: A prospective observational cohort study. PLoS One, 9(2), e90185 10.1371/journal.pone.0090185. [PubMed: 24587268]

Grotenhermen F (2004). Pharmacology of cannabinoids. Neuro Endocrinology Letters, 25(1–2), 14–23. [PubMed: 15159677]

Gutierrez T, Nackley AG, Neely MH, Freeman KG, Edwards GL, & Hohmann AG (2003). Effects of neurotoxic destruction of descending noradrenergic pathways on cannabinoid antinociception in models of acute and tonic nociception. Brain Research, 987(2), 176–185. 10.1016/S0006-8993(03)03324-9. [PubMed: 14499961]

Harper DE, Ichesco E, Schrepf A, Hampson JP, Clauw DJ, Schmidt-Wilcke T, et al. (2018). Resting functional connectivity ofthe periaqueductal gray is associated with normal inhibition and pathological facilitation in conditioned pain modulation. The Journal of Pain: Official Journal of the American Pain Society, 19(6), 635e1–635.e15 10.1016/j.jpain.2018.01.001. [PubMed: 29360608]

Hermans L, Nijs J, Calders P, De Clerck L, Moorkens G, Hans G, et al. (2018). Influence of morphine and naloxone on pain modulation in rheumatoid arthritis, chronic fatigue syndrome/fibromyalgia, and controls: A double-blind, randomized, placebocontrolled, cross-over study. Pain Practice: The Official Journal of World Institute of Pain, 18(4), 418–430. 10.1111/papr.12613. [PubMed: 28722815]

Hermans L, Oosterwijck JV, Goubert D, Goudman L, Crombez G, Calders P, et al. (2016). Inventory ofpersonal factors influencing conditionedpain modulation in healthy people: A systematic literature review. Pain Practice: The OfficialJournal of World Institute of Pain, 16(6), 758–769. 10.1111/papr.12305. [PubMed: 26011523]

Höffken O, Özgul ÖS, Enax-Krumova EK, Tegenthoff M, & Maier C (2017). Evoked potentials after painful cutaneous electrical stimulation depict pain relief during a conditioned pain modulation. BMC Neurology, 17(1), 167 10.1186/s12883-017-0946-7. [PubMed: 28851323]

Hohmann AG, Tsou K, & Walker JM (1999). Cannabinoid suppression of noxious heat-evoked activity in wide dynamic range neurons in the lumbar dorsal horn of the rat. Journal of Neurophysiology, 81(2), 575–583. 10.1152/jn.1999.81.2.575. [PubMed: 10036261]

Horvath G, Kekesi G, Nagy E, & Benedek G (2008). The role of TRPV1 receptors in the antinociceptive effect of anandamide at spinal level. Pain, 134(3), 277–284. 10.1016/j.pain.2007.04.032. [PubMed: 17533116]

Hróbjartsson A, & Gøtzsche PC (2010). Placebo interventions for all clinical conditions. The Cochrane Database of Systematic Reviews, 3, CD003974 10.1002/14651858.CD003974.pub3.

Ibrahim MM, Porreca F, Lai J, Albrecht PJ, Rice FL, Khodorova A, et al. (2005). CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. Proceedings of the National Academy of Sciences of the United States of America, 102(8), 3093–3098. 10.1073/pnas.0409888102. [PubMed: 15705714]

Imai Y, Petersen KK, Mørch CD, & Arendt Nielsen L (2016). Comparing test-retest reliability and magnitude of conditioned pain modulation using different combinations of test and conditioning stimuli. Somatosensory & Motor Research, 33(3–4), 169–177. 10.1080/08990220.2016.1229178. [PubMed: 27650216]

Jepma M, & Wager TD (2015). Conceptual conditioning: Mechanisms mediating conditioning effects on pain. Psychological Science, 26(11), 1728–1739. 10.1177/0956797615597658. [PubMed: 26381506]

Julien N, & Marchand S (2006). Endogenous pain inhibitory systems activated by spatial summation are opioid-mediated. Neuroscience Letters, 401(3), 256–260. 10.1016/j.neulet.2006.03.032. [PubMed: 16600506]

Jurth C, Rehberg B, & von Dincklage F (2014). Reliability of subjective pain ratings and nociceptive flexion reflex responses as measures of conditioned pain modulation. Pain Research & Management, 19(2), 93–96. [PubMed: 24555177]

Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, et al. (2010). Placebos without deception: A randomized controlled trial in irritable bowel syndrome. PLOS ONE, 5(12), e15591 10.1371/journal.pone.0015591. [PubMed: 21203519]

Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, &Rice ASC (2016). Reliability ofconditionedpain modulation: A systematic review. Pain, 157(11), 2410–2419. 10.1097/j.pain.0000000000000689. [PubMed: 27559835]

Kiernan BD, Dane JR, Phillips LH, & Price DD (1995). Hypnotic analgesia reduces R-III nociceptive reflex: Further evidence concerning the multifactorial nature of hypnotic analgesia. Pain, 60(1), 39–47. [PubMed: 7715940]

King CD, Goodin B, Kindler LL, Caudle RM, Edwards RR, Gravenstein N, et al. (2013). Reduction of conditioned pain modulation in humans by naltrexone: An exploratory study of the effects of pain catastrophizing. Journal of Behavioral Medicine, 36(3), 315–327. 10.1007/s10865-012-9424-2. [PubMed: 22534819]

Kirkpatrick DR, McEntire DM, Hambsch ZJ, Kerfeld MJ, Smith TA, Reisbig MD, et al. (2015). Therapeutic basis of clinical pain modulation. Clinical and Translational Science, 8(6), 848–856. 10.1111/cts.12282. [PubMed: 25962969]

Klinger R, Blasini M, Schmitz J, & Colloca L (2017). Nocebo effects in clinical studies: Hints for pain therapy. Pain Reports, 2(2), e586 10.1097/PR9.0000000000000586. [PubMed: 29034363]

Klyne DM, Schmid AB, Moseley GL, Sterling M, &Hodges PW (2015).Effect of types and anatomic arrangement of painful stimuli on conditioned pain modulation. The Journal of Pain: Official Journal of the American Pain Society, 16(2), 176–185. 10.1016/j.jpain.2014.11.005. [PubMed: 25464158]

Koban L, & Wager TD (2016). Beyond conformity: Social influences on pain reports and physiology. Emotion (Washington, DC), 16(1), 24–32. 10.1037/emo0000087.

Kosek E, Rosen A, Carville S, Choy E, Gracely RH,Marcus H, et al. (2017). Lower placebo responses after long-term exposure to fibromyalgia pain. TheJournal ofPain: Official Journal of the American Pain Society, 18(7), 835–843. 10.1016/j.jpain.2017.02.434.

Kothari SF, Baad-Hansen L, Hansen LB, Bang N, Sørensen LH, Eskildsen HW, et al. (2016). Pain profiling of patients with temporomandibular joint arthralgia and osteoarthritis diagnosed with different imaging techniques. The Journal ofHeadache and Pain, 17(1), 61 10.1186/s10194-016-0653-6.

Kunz M, Mohammadian P, Renner B, Roscher S, Kobal G, & Lautenbacher S (2014). Chemo-somatosensory evoked potentials: A sensitive tool to assess conditioned pain modulation? Somatosensory & Motor Research, 31(2), 100–110. 10.3109/08990220.2014.887562. [PubMed: 24568199]

Lautenbacher S, Prager M, & Rollman GB (2007). Pain additivity, diffuse noxious inhibitory controls, and attention: A functional measurement analysis. Somatosensory & Motor Research, 24(4), 189–201. 10.1080/08990220701637638. [PubMed: 18097992]

Le Bars D, Dickenson AH, & Besson JM (1979a). Diffuse noxious inhibitory controls (DNIC). I. Effects on dorsal horn convergent neurones in the rat. Pain, 6(3), 283–304. [PubMed: 460935]

Le Bars D, Dickenson AH, & Besson JM (1979b). Diffuse noxious inhibitory controls (DNIC). II. Lack of effect on non-convergent neurones, supraspinal involvement and theoretical implications. Pain, 6(3), 305–327. [PubMed: 460936]

Lee S, Walker JR,Jakul L,& Sexton K (2004). Does elimination ofplacebo responders in a placebo run-in increase the treatment effect in randomized clinical trials? A meta-analytic evaluation. Depression and Anxiety, 19(1), 10–19. 10.1002/da.10134. [PubMed: 14978780]

Leffler A-S, Kosek E, Lerndal T, Nordmark B, & Hansson P (2002). Somatosensory perception and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from rheumatoid arthritis. European Journal of Pain (London, England), 6(2), 161–176. 10.1053/eujp.2001.0313.

Lewis GN, Heales L, Rice DA, Rome K, & McNair PJ (2012). Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. Pain Research & Management, 17(2), 98–102. 10.1155/2012/610561. [PubMed: 22518372]

Li M-H, Suchland KL, & Ingram SL (2017). Compensatory activation of cannabinoid CB2 receptor inhibition of GABA release in the rostral ventromedial medulla in inflammatory pain. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 37(3), 626–636. 10.1523/JNEUROSCI.1310-16.2016.. [PubMed: 28100744]

Lindstedt F, Berrebi J, Greayer E, Lonsdorf TB, Schalling M, Ingvar M, et al. (2011). Conditioned pain modulation Is associated with common polymorphisms in the serotonin transporter gene. PLoS One, 6(3), e18252 10.1371/journal.pone.0018252. [PubMed: 21464942]

Locke D, Gibson W, Moss P, Munyard K, Mamotte C, &Wright A (2014). Analysis of meaningful conditioned pain modulation effect in a pain-free adult population. The Journal of Pain: Official Journal of the American Pain Society, 15(11), 1190–1198. 10.1016/j.jpain.2014.09.001. [PubMed: 25241218]

Loeser JD (1980). Perspectives on pain In Turner P, Padgham C, & Hedges A (Eds.), Clinical pharmacology & therapeutics (pp. 313–316). London: Palgrave Macmillan.

Maione S, Bisogno T, de Novellis V, Palazzo E, Cristino L, Valenti M, et al. (2006). Elevation of endocannabinoid levels in the ventrolateral periaqueductal grey through inhibition of fatty acid amide hydrolase affects descending nociceptive pathways via both cannabinoid receptor type 1 and transient receptor potential vanilloid type-1 receptors. The Journal of Pharmacology and Experimental Therapeutics, 316(3), 969–982. 10.1124/jpet.105.093286. [PubMed: 16284279]

Manning BH, Martin WJ, & Meng ID (2003). The rodent amygdala contributes to the production of cannabinoid-induced antinociception. Neuroscience, 120(4), 1157–1170. 10.1016/S0306-4522(03)00356-7. [PubMed: 12927220]

Marchand S (2012). The phenomenon of pain. IASP Press.

Marchand S, & Arsenault P (2002). Spatial summation for pain perception: Interaction of inhibitory and excitatory mechanisms. Pain, 95(3), 201–206. [PubMed: 11839419]

Marcuzzi A, Wrigley PJ, Dean CM, Adams R, &Hush JM (2017). The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals. Pain, 158(7), 1217–1223. 10.1097/j.pain.0000000000000901. [PubMed: 28328574]

Martel M, Wasan A, & Edwards R (2013). Sex differences in the stability of conditioned pain modulation (CPM) among patients with chronic pain. Pain Medicine (Malden, Mass.), 14(11), 1757–1768. 10.1111/pme.12220.

Martini C, van Velzen M, Drewes A, Aarts L, Dahan A, & Niesters M (2015). A randomized controlled trial on the effect oftapentadol and morphine on conditioned pain modulation in healthy volunteers. PLoS One, 10(6), e0128997 10.1371/journal.pone.0128997. [PubMed: 26076171]

Medoff ZM, & Colloca L (2015). Placebo analgesia: Understanding the mechanisms. Pain Management, 5(2), 89–96. 10.2217/pmt.15.3. [PubMed: 25806903]

Melzack R (1990). Phantomlimbs and the concept ofaneuromatrix. Trends in Neurosciences, 13(3), 88–92. [PubMed: 1691874]

Melzack R (2001). Pain and the neuromatrix in the brain. Journal of Dental Education, 65(12), 1378–1382. [PubMed: 11780656]

Melzack R, &Wall PD. (1965). Painmechanisms: Anewtheory. Science (New York, N.Y.), 150(3699), 971–979.

Mitsikostas DD (2012). Nocebo in headaches: Implications for clinical practice and trial design. Current Neurology and Neuroscience Reports, 12(2), 132–137. 10.1007/s11910-011-0245-4. [PubMed: 22193945]

Mlekusch S, Neziri AY, Limacher A, Juni P, Arendt-Nielsen L, & Curatolo M (2016). Conditioned pain modulation in patients with acute and chronic low back pain. The Clinical Journal of Pain, 32(2), 116–121. 10.1097/AJP.0000000000000238. [PubMed: 26741741]

Moont R, Crispel Y, Lev R, Pud D, & Yarnitsky D (2011). Temporal changes in cortical activation during conditioned pain modulation (CPM), a LORETA study. Pain, 152(7), 1469–1477. 10.1016/j.pain.2011.01.036. [PubMed: 21339052]

Moont R, Pud D, Sprecher E, Sharvit G, & Yarnitsky D (2010). “Pain inhibits pain” mechanisms: Is pain modulation simply due to distraction? Pain, 150(1), 113–120. 10.1016/j.pain.2010.04.009. [PubMed: 20493631]

Morton DL, El-Deredy W, & Jones AKP (2014). Placebo analgesia: Cognition or perception. Handbook of Experimental Pharmacology, 225, 71–80. 10.1007/978-3-662-44519-8_4. [PubMed: 25304526]

Müller M, Kamping S, Benrath J, Skowronek H, Schmitz J, Klinger R, et al. (2016). Treatment history and placebo responses to experimental and clinical pain in chronic pain patients. European Journal of Pain (London, England), 20(9), 1530–1541. 10.1002/ejp.877.

Murray D, & Stoessl AJ (2013). Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. Pharmacology & Therapeutics, 140(3), 306–318. 10.1016/j.pharmthera.2013.07.009. [PubMed: 23880289]

Nahman-Averbuch H, Nir R-R, Sprecher E, & Yarnitsky D (2016). Psychological factors and conditioned pain modulation: A meta-analysis. The Clinical Journal of Pain, 32(6), 541–554. 10.1097/AJP.0000000000000296. [PubMed: 26340657]

Nahman-Averbuch H, Yarnitsky D, Granovsky Y, Sprecher E, Steiner M, Tzuk-Shina T, et al. (2011). Pronociceptive pain modulation in patients with painful chemotherapy-induced polyneuropathy. Journal of Pain and Symptom Management, 42(2), 229–238. 10.1016/j.jpainsymman.2010.10.268. [PubMed: 21458224]

Ng TS, Pedler A, Vicenzino B, & Sterling M (2014). Less efficacious conditioned pain modulation and sensory hypersensitivity in chronic whiplash-associated disorders in Singapore. The Clinical Journal of Pain, 30(5), 436–442. 10.1097/AJP.0b013e3182a03940. [PubMed: 23887342]

Niesters M, Aarts L, Sarton E, & Dahan A (2013). Influence of ketamine and morphine on descending pain modulation in chronic pain patients: A randomized placebo-controlled cross-over proof-of-concept study. British Journal of Anaesthesia, 110(6), 1010–1016. 10.1093/bja/aes578. [PubMed: 23384733]

Niesters M, Dahan A, Swartjes M, Noppers I, Fillingim RB, Aarts L, et al. (2011). Effect of ketamine on endogenous pain modulation in healthy volunteers. Pain, 152(3), 656–663. 10.1016/j.pain.2010.12.015. [PubMed: 21237568]

Niesters M, Proto PL, Aarts L, Sarton EY, Drewes AM, & Dahan A (2014). Tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. BritishJournal ofAnaesthesia, 113(1), 148–156. 10.1093/bja/aeu056.

Nilsen KB, Olsen IC, Solem AN, &Matre D (2014). Alarge conditionedpain modulation response is not related to a large blood pressure response: A study in healthy men. European Journal of Pain (London, England), 18(9), 1271–1279. 10.1002/j.1532-2149.2014.486.x.

Nir R-R, Granovsky Y, Yarnitsky D, Sprecher E, & Granot M (2011). A psychophysical study of endogenous analgesia: the role of the conditioning pain in the induction and magnitude of conditioned pain modulation. European Journal of Pain (London, England), 15(5), 491–497. 10.1016/j.ejpain.2010.10.001.

Nir R-R, & Yarnitsky D (2015). Conditioned pain modulation. Current Opinion in Supportive and Palliative Care, 9(2), 131–137. 10.1097/SPC.0000000000000126. [PubMed: 25699686]

Nir R-R, Yarnitsky D, Honigman L, & Granot M (2012). Cognitive manipulation targeted at decreasing the conditioning pain perception reduces the efficacy of conditioned pain modulation. Pain, 153(1), 170–176. 10.1016/j.pain.2011.10.010. [PubMed: 22119318]

Normand E, Potvin S, Gaumond I, Cloutier G, Corbin J-F, & Marchand S (2011). Pain inhibition is deficient in chronic widespread pain but normal in major depressive disorder. The Journal of Clinical Psychiatry, 72(2), 219–224. 10.4088/JCP.08m04969blu. [PubMed: 20816025]

O'Brien AT, Deitos A, Trinanes Pego Y, Fregni F, & Carrillo-de-la-Peria MT (2018). Defective endogenous pain modulation in fibromyalgia: A meta-analysis of temporal summation and conditioned pain modulation paradigms. The Journal of Pain: Official Journal of the American Pain Society, 19(8), 819–836. 10.1016/j.jpain.2018.01.010. [PubMed: 29454976]

Okada C (2005). The relationship between diffuse noxious inhibitory control effects and the magnitude of noxious stimuli. Kokubyo Gakkai Zasshi. The Journal of the Stomatological Society, Japan, 72(1), 49–55.

Olesen SS, Graversen C, Bouwense SAW, van Goor H, Wilder-Smith OHG, & Drewes AM (2013). Quantitative sensory testing predicts pregabalin efficacy in painful chronic pancreatitis. PLoS One, 8(3), e57963 10.1371/journal.pone.0057963. [PubMed: 23469256]

Oono Y, Wang K, Baad-Hansen L, Futarmal S, Kohase H, Svensson P, et al. (2014). Conditioned pain modulation in temporomandibular disorders (TMD) pain patients.Experimental Brain Research, 232(10), 3111–3119. 10.1007/s00221-014-3997-7. [PubMed: 24897946]

Palazzo E, Luongo L, Novellis V, De Rossi F, & Maione S (2010). The role of cannabinoid receptors in the descending modulation of pain. Pharmaceuticals (Basel, Switzerland), 3(8), 2661–2673. 10.3390/ph3082661.

Palazzo E, Rossi F, & Maione S (2008). Role of TRPV1 receptors in descending modulation of pain. Molecular and Cellular Endocrinology, 286(1–2 Suppl. 1), S79–S83. 10.1016/j.mce.2008.01.013. [PubMed: 18325659]

Parent AJ, Beaudet N, Daigle K, Sabbagh R, Sansoucy Y, Marchand, et al. (2015). Relationship between blood- and cerebrospinal fluid-bound neurotransmitter concentrations and conditioned pain modulation in pain-free and chronic pain subjects. The Journal of Pain: Official Journal of the American Pain Society, 16(5), 436–444. 10.1016/j.jpain.2015.01.007. [PubMed: 25659204]

Pecina M, Azhar H, Love TM, Lu T, Fredrickson BL, Stohler CS, et al. (2013). Personality trait predictors of placebo analgesia and neurobiological correlates. Neuropsychopharmacology, 38(4), 639–646. 10.1038/npp.2012.227. [PubMed: 23187726]

Pecina M, Love T, Stohler CS, Goldman D, & Zubieta J-K (2015). Effects of the mu opioid receptor polymorphism (OPRM1 A118G) on pain regulation, placebo effects and associated personality trait measures. Neuropsychopharmacology, 40(4), 957–965. 10.1038/npp.2014.272. [PubMed: 25308352]

Petersen KK, Graven-Nielsen T, Simonsen O, Laursen MB, & Arendt-Nielsen L (2016). Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief

after total knee replacement. Pain, 157(7), 1400–1406. 10.1097/j.pain.0000000000000531. [PubMed: 27331347]

Petersen KK, Vaegter HB, & Arendt-Nielsen L (2017). An updated view on the reliability of different protocols for the assessment of conditioned pain modulation. Pain, 158(5), 988 10.1097/j.pain.0000000000000833.

Piché M, Arsenault M, & Rainville P (2009). Cerebral and cerebrospinal processes underlying counterirritation analgesia. The Journal of Neuroscience: The Official Journal of the Society for Neuroscience, 29(45), 14236–14246. 10.1523/JNEUROSCI.2341-09.2009. [PubMed: 19906971]

Piché M, Watanabe N, Sakata M, Oda K, Toyohara J, Ishii K, et al. (2014). Basal μ-opioid receptor availability in the amygdala predicts the inhibition of pain-related brain activity during heterotopic noxious counter-stimulation. Neuroscience Research, 81—82, 78–84. 10.1016/j.neures.2014.02.006.

Pickering G, Pereira B, Dufour E, Soule S, & Dubray C (2014). Impaired modulation of pain in patients with postherpetic neuralgia. Pain Research & Management, 19(1), e19–e23. [PubMed: 24427769]

Potvin S, & Marchand S (2016). Pain facilitation and pain inhibition during conditioned pain modulation in fibromyalgia and in healthy controls. Pain, 157(8), 1704–1710. 10.1097/j.pain.0000000000000573. [PubMed: 27045524]

Quante M, Hille S, Schofer MD, Lorenz J, & Hauck M (2008). Noxious counterirritation in patients with advanced osteoarthritis of the knee reduces MCC but not SII pain generators: A combined use of MEG and EEG. Journal of Pain Research, 1, 1–8. [PubMed: 21197282]

Rainville P, Carrier B, Hofbauer RK, Bushnell MC, & Duncan GH (1999). Dissociation of sensory and affective dimensions of pain using hypnotic modulation. Pain, 82(2), 159–171. 10.1016/S0304-3959(99)00048-2. [PubMed: 10467921]

Ram KC, Eisenberg E, Haddad M, & Pud D (2008). Oral opioid use alters DNIC but not cold pain perception in patients with chronic pain—New perspective of opioid-induced hyperalgesia. Pain, 139(2), 431–438. 10.1016/j.pain.2008.05.015. [PubMed: 18583047]

Rattanavong V (2013). Manipulation de la perception de la composante affective de la douleur (Master's thesis). Quebec, Canada: Universite de Sherbrooke, Sherbrooke.

Razavi M, Hansson PT, Johansson B,& Leffler A-S (2014). The influence ofintensity and duration of a painful conditioning stimulation on conditioned pain modulation in volunteers. European Journal of Pain (London, England), 18(6), 853–861. 10.1002/j.1532-2149.2013.00435.x.

Reicherts P, Gerdes ABM, Pauli P, &Wieser MJ (2016). Psychologicalplacebo and nocebo effects on pain rely on expectation and previous experience. The Journal of Pain: Official Journal of the American Pain Society, 17(2), 203–214. 10.1016/j.jpain.2015.10.010. [PubMed: 26523863]

Reynolds DV (1969). Surgery in the rat during electrical analgesia induced by focal brain stimulation. Science (New York, NY), 164(3878), 444–445.

Rief W, & Glombiewski JA (2012). The hidden effects of blinded, placebo-controlled randomized trials: An experimentalinvestigation. Pain, 153(12), 2473–2477. 10.1016/j.pain.2012.09.007. [PubMed: 23084328]

Roosink M, Renzenbrink GJ, Buitenweg JR, van Dongen RTM, Geurts ACH, & Ijzerman MJ (2011). Somatosensory symptoms and signs and conditioned pain modulation in chronic post-stroke shoulder pain. The Journal ofPain: Official Journal of the American Pain Society, 12(4), 476–485. 10.1016/j.jpain.2010.10.009.

Rustamov N, Tessier J, Provencher B, Lehmann A, & Piche M (2016). Inhibitory effects of heterotopic noxious counter-stimulation on perception and brain activity related to Aß-fibre activation. The European Journal of Neuroscience, 44(1), 1771–1778. 10.1111/ejn.13258. [PubMed: 27086672]

Sáez-Cassanelli JL, Fontanella GH, Delgado-García JM, & Carrion AM (2007). Functional blockage of the cannabinoid receptor type 1 evokes a kappa-opiate-dependent analgesia. Journal of Neurochemistry, 103(6), 2629–2639. 10.1111/j.1471-4159.2007.05000.x. [PubMed: 17953671]

Sanada T, Kohase H, Makino K, & Umino M (2009). Effects of alpha-adrenergic agonists on pain modulation in diffuse noxious inhibitory control. Journal of Medical and Dental Sciences, 56(1), 17–24. [PubMed: 19697515]

Sandrini G, Rossi P, Milanov I, Serrao M, Cecchini AP, & Nappi G (2006). Abnormal modulatory influence of diffuse noxious inhibitory controls in migraine and chronic tension-type headache patients. Cephalalgia: An International Journal of Headache, 26(7), 782–789. 10.1111/j.1468-2982.2006.01130.x. [PubMed: 16776692]

Sangesland A, Støren C, & Vaegter HB (2017). Are preoperative experimental pain assessments correlated with clinical pain outcomes after surgery? A systematic review. Scandinavian Journal ofPain, 15, 44–52. 10.1016/j.sjpain.2016.12.002.

Sauro MD, & Greenberg RP (2005). Endogenous opiates and the placebo effect: A meta-analytic review. Journal of Psychosomatic Research, 58(2), 115–120. 10.1016/j.jpsychores.2004.07.001. [PubMed: 15820838]

Schwarz KA, Pfister R, & Büchel C (2016). Rethinking explicit expectations: Connecting placebos, social cognition, and contextual perception. Trends in Cognitive Sciences, 20(6), 469–480. 10.1016/j.tics.2016.04.001. [PubMed: 27108268]

Simmons K, Ortiz R, Kossowsky J, Krummenacher P, Grillon C, Pine D, et al. (2014). Pain andplacebo in pediatrics: A comprehensive review oflaboratory and clinical findings. Pain, 155(11), 2229–2235. 10.1016/j.pain.2014.08.036. [PubMed: 25180010]

Skovbjerg S, Jørgensen T, Arendt-Nielsen L, Ebstrup JF, Carstensen T, & Graven-Nielsen T (2017). Conditioned pain modulation and pressure pain sensitivity in the adult Danish general population: The DanFund study. The Journal of Pain: Official Journal of the American Pain Society, 18(3), 274–284. 10.1016/j.jpain.2016.10.022. [PubMed: 27884690]

Skyt I, Moslemi K, Baastrup C, Grosen K, Svensson P, Jensen TS, et al. (2018). Does conditioned pain modulation predict the magnitude ofplacebo effects in patients with neuropathic pain? European Journal of Pain (London, England), 22(4), 784–792. 10.1002/ejp.1164.

Soon B, Vicenzino B, Schmid AB, & Coppieters MW (2017). Facilitatory andinhib-itory pain mechanisms are altered in patients with carpal tunnel syndrome. PLoS One, 12(8), e0183252 10.1371/journal.pone.0183252. [PubMed: 28854251]

Sprenger C, Bingel U, & Büchel C (2011). Treating pain with pain: Supraspinal mechanisms of endogenous analgesia elicited by heterotopic noxious conditioning stimulation. Pain, 152(2), 428–439. 10.1016/j.pain.2010.11.018. [PubMed: 21196078]

Starowicz K, Makuch W, Osikowicz M, Piscitelli F, Petrosino S, DiMarzo V, et al. (2012). Spinal anandamide produces analgesia in neuropathic rats: Possible CB(1)- and TRPV1-mediated mechanisms. Neuropharmacology, 62(4), 1746–1755. 10.1016/j.neuropharm.2011.11.021. [PubMed: 22178705]

Staud R (2012). Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. Expert Review ofNeurotherapeutics, 12(5), 577–585. 10.1586/ern.12.41.

Sugimine S, Saito S, Araki T, Yamamoto K, & Obata H (2017). Endogenous analgesic effect of pregabalin: A double-blind and randomized controlled trial. European Journal of Pain (London, England), 21(6), 997–1006. 10.1002/ejp.1007.

Taylor BK (2009). Spinal inhibitory neurotransmission in neuropathic pain. Current Pain and Headache Reports, 13(3), 208–214. [PubMed: 19457281]

Taylor VA, Chang L, Rainville P, & Roy M (2017). Learned expectations and uncertainty facilitate pain during classical conditioning. Pain, 158(8), 1528–1537. 10.1097/j.pain.0000000000000948. [PubMed: 28715353]

Tiemann L, Heitmann H, Schulz E, Baumkötter J, & Ploner M (2014). Dopamine precursor depletion influences pain affect rather than pain sensation. PLoS One, 9(4), e96167 10.1371/journal.pone.0096167. [PubMed: 24760082]

Torta DM, Churyukanov MV, Plaghki L, & Mouraux A (2015). The effect of heterotopic noxious conditioning stimulation on Aδ-, C- and Aß-fibre brain responses in humans. The European Journal of Neuroscience, 42(9), 2707–2715. 10.1111/ejn.13071. [PubMed: 26369522]

Treister R, Pud D, & Eisenberg E (2013). The dopamine agonist apomorphine enhances conditioned pain modulation in healthy humans. Neuroscience Letters, 548, 115–119. 10.1016/j.neulet.2013.05.041. [PubMed: 23727387]

Tuttle AH, Tohyama S, Ramsay T, Kimmelman J, Schweinhardt P, Bennett GJ, et al. (2015). Increasing placebo responses over time in U.S. clinical trials of neuropathic pain. Pain, 156(12), 2616–2626. 10.1097/j.pain.0000000000000333. [PubMed: 26307858]

van Wijk G,& Veldhuijzen DS (2010). Perspective on diffuse noxious inhibitory controls as a model ofendogenous pain modulation in clinical pain syndromes. The Journal ofPain: Official Journal of the American Pain Society, 11(5), 408–419. 10.1016/j.jpain.2009.10.009.

Vase L, Riley JL, & Price DD (2002). A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. Pain, 99(3), 443–452. 10.1016/S0304-3959(02)00205-1. [PubMed: 12406519]

Vase L, Vollert J, Finnerup NB, Miao X, Atkinson G, Marshall S, et al. (2015). Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: A meta-analysis of the individual data from nine industrially sponsored trials. Pain, 156(9), 1795 10.1097/j.pain.0000000000000217. [PubMed: 25955965]

Villanueva L, Bouhassira D, & Le Bars D (1996). The medullary subnucleus reticularis dorsalis (SRD) as a key link in both the transmission and modulation of pain signals. Pain, 67(2–3), 231–240. [PubMed: 8951916]

Villanueva L, & Le Bars D (1986). Indirect effects of intrathecal morphine upon diffuse noxious inhibitory controls (DNICs) in the rat. Pain, 26(2), 233–243. [PubMed: 3763236]

Vo L, & Drummond PD (2016). Involvement of a2-adrenoceptors in inhibitory and facilitatory pain modulation processes. European Journal of Pain (London, England), 20(3), 386–398. 10.1002/ejp.736.

Watkinson A, Chapman SCE, & Horne R (2017). Beliefs about pharmaceutical medicines and natural remedies explain individual variation in placebo analgesia. The Journal of Pain: Official Journal of the American Pain Society, 18(8), 908–922. 10.1016/j.jpain.2017.02.435. [PubMed: 28279704]

Weimer K, Colloca L, & Enck P (2015). Age and sex as moderators of the placebo response—An evaluation of systematic reviews and meta-analyses across medicine. Gerontology, 61(2), 97–108. 10.1159/000365248. [PubMed: 25427869]

Whalley B, Hyland ME, & Kirsch I (2008). Consistency of the placebo effect. Journal of Psychosomatic Research, 64(5), 537–541. 10.1016/jjpsychores.2007.11.007. [PubMed: 18440407]

Willer JC, Le Bars D, & De Broucker T (1990). Diffuse noxious inhibitory controls in man: Involvement of an opioidergic link. European Journal of Pharmacology, 182(2), 347–355. [PubMed: 2168836]

Yarnitsky D (2010). Conditioned pain modulation (the diffuse noxious inhibitory control-like effect): Its relevance for acute and chronic pain states. Current Opinion in Anesthesiology, 23(5), 611 10.1097/AC0.0b013e32833c348b. [PubMed: 20543676]

Yarnitsky D (2015). Role of endogenous pain modulation in chronic pain mechanisms and treatment. Pain, 156(Suppl. 1), S24–S31. 10.1097/01-j.pain.0000460343.46847.58. [PubMed: 25789433]

Yarnitsky D, Arendt-Nielsen L, Bouhassira D, Edwards RR, Fillingim RB, Granot M, et al. (2010). Recommendations on terminology and practice of psychophysical DNIC testing. European Journal of Pain (London, England), 14(4), 339 10.1016/j.ejpain.2010.02.004.

Yarnitsky D, Bouhassira D, Drewes A. m., Fillingim RB, Granot M, Hansson P, et al. (2015). Recommendations on practice of conditioned pain modulation (CPM) testing. European Journal of Pain, 19(6), 805–806. 10.1002/ejp.605. [PubMed: 25330039]

Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, et al. (2008). Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. Pain, 138(1), 22–28. 10.1016/j.pain.2007.10.033. [PubMed: 18079062]

Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, & Granovsky Y (2012). Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain, 153(6), 1193–1198. 10.1016/j.pain.2012.02.021. [PubMed: 22480803]

Youssef AM, Macefield VG, & Henderson LA (2016a). Pain inhibits pain; human brainstem mechanisms. NeuroImage, 124(Pt. A), 54–62. 10.1016/j.neuroimage.2015.08.060. [PubMed: 26343321]

Youssef AM, Macefield VG, & Henderson LA (2016b). Cortical influences on brainstem circuitry responsible for conditioned pain modulation in humans. Human Brain Mapping, 37(7), 2630–2644. 10.1002/hbm.23199. [PubMed: 27104478]

Yuan X-C, Zhu B, Jing X-H, Xiong L-Z, Wu C-H, Gao F, et al. (2018). Electroacupuncture potentiates cannabinoid receptor-mediated descending inhibitory control in a mouse model of knee osteoarthritis. Frontiers in Molecular Neuroscience, 11, 112 10.3389/fnmol.2018.00112. [PubMed: 29681797]

Zheng Z, Wang K, Yao D, Xue CCL, & Arendt-Nielsen L (2014). Adaptability to pain is associated with potency of local pain inhibition, but not conditioned pain modulation: A healthy human study. Pain, 155(5), 968–976. 10.1016/j.pain.2014.01.024. [PubMed: 24502842]

FURTHER READING

Amanzio M,& Benedetti F (1999). Neuropharmacological dissection of placebo analgesia: Expectation-activated opioid systems versus conditioning-activated specific subsystems. The Journal of Neuroscience: The Official Journal ofthe Society for Neuroscience, 19(1), 484–494.

Benedetti F, Amanzio M, Baldi S, Casadio C, & Maggi G (1999). Inducing placebo respiratory depressant responses in humans via opioid receptors. The European Journal of Neuroscience, 11(2), 625–631. [PubMed: 10051763]