Neurophysiologie Clinique/Clinical Neurophysiology 51 (2021) 197—208

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COMPREHENSIVE REVIEW

Conditioned pain modulation—A comprehensive review

Shankar Ramaswamy*, **Theresa Wodehouse**

1St Bartholomew's Hospital, Bart's Health NHS Trust, London, EC1A 4AS, UK

Received 14 May 2020; accepted 28 November 2020
Available online 14 December 2020

KEYWORDS
Central sensitization;
Conditioned pain modulation;
Pain modulation profile;
Phenotypic profile;
Pronociceptive profile

Summary Conditioned pain modulation (CPM) is a centrally processed measure of the net effect of the descending pain pathway. This comprises both the facilitatory as well as the inhibitory effect. In the past, CPM or similar effects have been previously described using different terminologies such as diffuse noxious inhibitory control (DNIC), heterotopic noxious conditioning stimulation (HNCS) or endogenous analgesia (EA). A variety of patient-related factors such as age, gender, hormones, race, genetic and psychological factors have been thought to influence the CPM paradigms. CPM paradigms have also been associated with a wide range of methodological variables including the mode of application of the 'test' as well as the 'conditioning' stimuli. Despite all these variabilities, CPM seems to reliably lend itself to the pain modulation profile concept and could in future become one of the phenotypic biomarkers for pain and also a guide for mechanism-based treatment in chronic pain. Future research should focus on establishing consistent methodologies for measuring CPM and thereby enhancing the robustness of this emerging biomarker for pain.

Introduction

Conditioned pain modulation (CPM) is the modern terminology to describe the net effect of the endogenous pathways that enhance or diminish the effects of afferent noxious stimuli. The concept of CPM has evolved enormously in recent times and currently we are at a stage where there is a need to investigate this concept further, understanding both its scientific relevance as well as its pitfalls. There is a lack of standardization in the research on CPM, both in terms of the techniques used to measure CPM and the research methodologies applied, resulting in a heterogeneity that affects interpretation of the results and also our ability to confidently perform a pooled analysis. In addition, CPM is developing as an important biomarker for pain outcomes. Given the emerging importance of CPM, we feel there is a need to comprehensively address a broad range of topics relevant to CPM. We have chosen to write this review in a narrative style for that reason. The specific objectives

* Corresponding author.
E-mail address: Shankar.ramaswamy@nhs.net (S. Ramaswamy).

https://doi.org/10.1016/j.neucli.2020.11.002

of this review are to look at the evolution of the concept of endogenous pain modulation circuits, exploring the underlying neurophysiological mechanisms, variability and clinical usefulness of CPM paradigms and also the future needs and directions in the field of pain research, particularly with reference to phenotyping patients using CPM paradigms.

Evolution of the concept of endogenous pain modulation

In 1965 Melzack and Wall, in their landmark paper on the gate control theory, conceptualized the inhibitory role of non-nociceptive fibers over signals from pain fibers, which could thereby inhibit pain [64]. Subsequently, Wall in his re-examination and re-statement of the gate control theory, acknowledged the role of the descending control systems in modulating the excitability of the cells transmitting information about the injury [106]. Fields and colleagues extensively investigated endogenous analgesic pathways, which are organized in the midbrain, medulla and spinal cord. Electrical stimulation, opiates and psychological factors were thought to activate the periaqueductal grey matter (PAG) in the medulla, which in turn activates the rostral medulla, partly via the serotonergic pathways, which then inhibits the trigeminal and the spinal pain-transmission neurons. As part of the negative feedback loop, pain itself was thought to be involved in the pain-suppression system [7]. Le Bars and colleagues looked at neuronal activity at the lumbar convergent neurons-lamina V-wide dynamic range (WDR) in anaesthetized rats, using the counter-irritation mechanism, to demonstrate the concept of 'pain-inhibits-pain'. They showed that the neuronal activity at lamina V (WDR) can be completely blocked with a second noxious stimulus applied to a different part of the body. They coined the term diffuse noxious inhibitory control (DNIC) [53,54].

It is challenging to do similar recordings of dorsal horn neuron activity in humans as a measure of DNIC. However, it is also not clear if the measurement of such neuronal activity correlates with the manifestation of pain, both in the clinical and the experimental setting. So, there was a need to rely on surrogate markers to measure the DNIC response. This has resulted in the emergence of different methodologies to assess the endogenous pain pathway. Several terminologies have also been used in the past to describe these effects, such as DNIC, heterotopic noxious conditioning stimulation (HNCS), endogenous analgesia (EA) and DNIC-like effect [116]. In 2010, a panel of experts looked into the various terminologies used to describe psychophysical DNIC testing [116]. The term DNIC was originally coined to refer to the inhibitory effect mediated by the lower brainstem centers used in animal research. Subsequently, ''DNIC'' was extensively used in a variety of human psychophysical research settings where the exact mechanism was either unclear, or where this perhaps involved both complex facilitatory and inhibitory processes. ''HNCS'' has specific requirements referring only to the conditioning stimulation, in particular to the application of an extra-segmental conditioning stimulation at a remote location. Hence the panel of experts recommended the use of standard terminologies to describe 'test stimulus' (TS), 'conditioning stimulus' (CS) and the actual phenomenon as 'conditioned pain modulation (CPM)'. The current recommendation is to use the term DNIC only to describe the neurophysiological phenomenon and to evaluate objective outcome, and the term CPM to describe the psychophysical paradigm for evaluation of subjective outcomes. Based on these recommendations, CPM is the most modern and accepted terminology.

What does CPM actually measure?

CPM is a measure of the efficacy of descending pain pathways, which have both facilitatory as well as inhibitory effects. What we measure as CPM is perhaps the net effect of the descending pathway. The clinical value of CPM is in being a surrogate measure of the brain's capacity for activating endogenous analgesia, possibly via the descending tracts, which is important for the chronification of pain [66]. Impaired descending pain modulatory pathways is thought to contribute to the development and maintenance of central sensitization and therefore also important for the development of clinical pain conditions [107,80,6,3].

CPM can be calculated using a dynamic quantitative sensory testing (QST) technique that involves agitation of the pain-perceiving system and also by using few other non-QST based objective techniques as detailed later in this review [116,19,33,73]. Dynamic QST includes tests of central integration such as temporal and spatial summation and a test of descending control or CPM. CPM refers to the observation that the net effect of the descending pain pathway can be strongly modulated by an intensive pain stimulus outside the subject's peripheral receptive field. This is the basis for the 'pain-inhibits-pain' mechanism [53,54].

A typical CPM measurement requires a test stimulus (TS) and a conditioning stimulus (CS) applied using a consistent protocol. An ischemic arm technique is an example of a method used to measure CPM, using the pressure pain threshold (PPT) as TS and a tourniquet pressure as the conditioning stimulus applied to the upper arm [90]. To evoke the CS, the blood pressure cuff is inflated over the upper arm above systolic pressure (200 mmHg) for up to 10 min, or until a Numerical Rating Scale (NRS) of 6/10 is achieved. A consistent site is then chosen to apply the TS, such as a PPT using an algometer until the patient feels a certain level of pain such as P40 (pain level of 40/100). The conditioned TS is either applied immediately after the CS (which is the preferred and 'cleaner' technique, free of distraction effects) or in parallel to the CS [117]. The cuff is deflated to terminate the CS. The difference between the PPT measurements (pre-cuff inflation minus post-cuff inflation PPT) is taken as the absolute value of CPM response. A negative value suggests that CPM is efficient, and the patient is likely to have an anti-nociceptive profile. On the contrary, a positive value suggests that CPM is inefficient, and the patient is likely to have a pro-nociceptive profile.

Central processing and mechanisms of CPM and DNIC

Central nervous system pathway of CPM

CPM is a central phenomenon, as it can only be demonstrated in animals with intact brain and not in spinal animals [52]. The main centers in the central nervous system (CNS)

involved in the descending inhibitory pathway include PAG, rostral ventromedial medulla (RVM), locus coeruleus (LC) and subnucleus reticularis dorsalis (SRD) [99,79,25,105]. In patients with tetraplegia, heterotopic nociceptive stimulation was not associated with depression of the RIII reflex (a nociceptive receptor reflex which measures the spinal withdrawal reflex by stimulating the A-delta fibers, as measured by electromyography) [105]. Also, in patients with lesions in the brainstem or thalamus with unilateral analgesia, nociceptive CS applied to the affected side did not produce a CPM effect but when applied to the unaffected side elicited a normal CPM response [105].

Stimulation of the PAG in rats was shown to produce an analgesic effect [79]. The PAG sends inputs to the RVM and LC. RVM sends the serotonergic mediated descending inhibitory signals to the spinal cord and LC sends the noradrenaline mediated inhibitory signals to the spinal cord. SRD also forms an important link in descending inhibition. It is situated in the caudal medulla and is part of the spinobulbar-spinal loop, which is activated via neurons with a 'whole-body receptive field'. The descending neuronal pathway from the SRD terminates at all levels in the dorsal horn of the spinal cord. This makes CPM a 'bottom-up' activation process for the pain modulatory system as part of the descending endogenous analgesia system [99].

Role of opioidergic pathway in CPM

Numerous studies have explored the influence of the opioidergic pathway on CPM in healthy volunteers as well as in patients with chronic pain, although the relationship has not been consistent or straightforward [60,46,8,39]. Both PAG and the RVM have opioidergic receptors and hence we would expect opioids to have an influence on pain modulation.

King et al., in their placebo-controlled study including 33 healthy volunteers, demonstrated that the efficiency of CPM (measured by rating heat pain as TS and cold water immersion as CS) was reduced by opioid antagonists such as naltrexone [46]. However, interestingly, the endogenous opioidergic system influenced the CPM only in low catastrophizing subjects, suggesting a differential influence. This perhaps supports the important role played by the endogenous opioids on pain modulation in healthy individuals but also highlights that the degree of influence is multifactorial, depending on other complex circumstances.

Based on a cross-sectional study involving 190 patients with chronic back or neck pain, opioid use was associated with less efficient CPM, suggesting a dampening effect on the endogenous pain modulatory system [60]. This is not surprising, as the utility of opioids as an analgesic in chronic pain conditions is being currently questioned by the various guidelines. Opioids are also thought to compromise functioning as well as the inter-relationships of the endogenous pain modulation systems [60]. Hermans et al. conducted a double-blind, randomized, placebo-controlled, cross-over study in patients with fibromyalgia, chronic fatigue syndrome and rheumatoid arthritis which showed little impact of morphine and naloxone on CPM, suggesting minimal influence of the opioidergic system in modulation in patients with these chronic pain conditions [39].

Berna et al., in a double-blind, placebo-controlled, crossover study including twenty healthy volunteers given intravenous naloxone versus saline, identified opioid-independent and opioid-mediated mechanisms for pain modulation based on the differential effect of naloxone on different pain modulation tasks [8]. For instance, mental imagery influenced the CPM independent of the opioidergic pathway while the expectation-related analgesia relied on the opioidergic pathway. This perhaps highlights that different therapeutic options may use different mechanisms (opioidergic or non-opioidergic) to influence CPM.

Clinically, different opioids are known to have different effects on CPM. Tapentadol is a novel opioid, which also has a noradrenaline re-uptake inhibitory action and thereby could potentially have a greater effect on the descending inhibitory pathway. In a randomized controlled trial including 24 patients with painful diabetic neuropathy, CPM was found to be inefficient at baseline. After 4 weeks of treatment with tapentadol, there was a significant activation of the CPM, which coincided with significant improvements in pain levels [72]. In studies involving human volunteers, tapentadol administration was associated with an efficient CPM, which was comparable to placebo (20—30% reduction in pain ratings following application of the CS). In contrast, morphine administration was associated with a less efficient CPM effect, whereas naloxone normalized the CPM and in fact increased the pain inhibition following an administration of morphine [62,32]. This confirms the differential mechanism of tapentadol compared to morphine, supporting its effect on the descending noradrenaline inhibitory pathway.

The effect of endogenous opioids on CPM has also been shown to depend on the method used to measure CPM, as discussed later in the review.

Role of the autonomic nervous system in CPM

Studies have shown that reduced blood pressure response to conditioning stimulus is associated with less efficient CPM, suggesting a correlation between cardiovascular reactivity to pain and efficiency of CPM [22,21]. This could be partially related to the effect of the sinoaortic baroreceptor reflex on the descending pain inhibitory pathway. Brain imaging studies have also shown that the increased activities seen in the centers implicated in the control of autonomic cardiovascular regulation in the brain such as the anterior cingulate cortex, orbitofrontal cortex and the amygdala are also associated with the magnitude of CPM. This perhaps suggests a role for the sympathetic system in mediating the CPM response but needs further evaluation [21].

Factors influencing the CPM paradigm

A number of inconsistencies have been noted in aspects of CPM paradigm measurements. To begin with, different terminologies have been confusingly used to explain similar phenomena as described above. The CPM paradigms are known to be influenced by a number of different factors including unmodifiable patient related factors such as age, gender, hormones, race and genetic makeup; psychological factors including anxiety, depression and catastrophizing;

methodological and procedural factors such as testing site, surface area/ duration; nature of CS and TS; concurrent medications and underlying medical problems including pre-existing chronic pain condition. These can be broadly divided into 'subjected-related' factors or 'method-related' factors.

Subject-related factors influencing CPM paradigms

A recent systematic review (including 36 studies with a methodological quality score of 72.5%) looking into the different personal traits affecting CPM showed that the factors associated with more efficient CPM include younger adult age, male gender, ovulatory phase, positive expectations, attention to the CS, and carrier of the 5-HTTLPR long allele [40]. Various subject-related factors are known to influence CPM as detailed below.

Age

CPM effect seems to be consistently more efficient in the younger age group, with a progressive decline with age, resulting in an inefficient or absent CPM in the elderly [96]. It is postulated that the balance between the facilitatory and the inhibitory effect could vary with age and increased facilitatory effect, due to multiple noxious stimuli and a diminished inhibitory effect contributing to the higher levels of pain perception in the elderly.

Gender

The effect of gender on CPM paradigm has yielded inconsistent results, with some studies demonstrating no influence and some suggesting that men have a more efficient CPM effect than women [40]. Menstrual cycle also seems to have an inconsistent effect on CPM [93,112]. CPM paradigm has been found to be more stable in females with clinical pain and in healthy males [104]. There are also a number of reported gender differences in chronic pain and hence the gender differences in the CPM paradigm itself are not surprising [29]. This needs further clarification in future studies.

Race

A number of studies have looked into the impact of race on CPM, which have so far yielded conflicting results [18,68]. African—Americans seem to have less efficient CPM than non-Hispanic whites, although this has not been consistent across all studies [18]. This again needs further investigation in the future especially in the light that certain races have been shown to have lower pain sensitivity.

Genetic

There is also some reported genetic influence on CPM paradigms. CPM was associated with certain common polymorphisms in serotonin (5-HTT) transporter gene (*SLC6A4*) or 5HTTLPR and opioid receptor genes (OPRM1 rs589046T allele) [59,40,75]. Healthy subjects with low levels of 5-HTT-expression exhibited significantly less efficient CPM-mediated pain inhibition for pressure pain threshold (PPT) and heat-pain. Hermans and colleagues identified carriers of the 5HTTLPR long allele as one of the personal factors influencing CPM in healthy people [40]. Genetic polymorphisms could be one of the reasons contributing to the large inter-individual variability in the CPM, pain perception sensitivity and regulation.

Psychological factors

Patients with elevated catastrophizing scores have higher pain intensities with less efficient CPM, which may contribute to higher pain levels as well as poor outcomes, following chronic pain interventions [31,108]. A meta-analysis of the psychological factors and CPM in patients with and without pain revealed that there was no correlation between CPM and the various psychological factors. However, the subgroup analysis of healthy individuals showed that different modalities of CPM measurements were influenced by different psychological factors such as anxiety, depression and catastrophizing levels [69].

Exercise

Similar to CPM, exercise is also associated with modulation of the descending pain pathways [94]. A number of spatial and temporal differences have been identified in the way that exercise and CPM influence the descending pathway, which suggests either a distinct or only a partially overlapping neurophysiological mechanism between exercise and CPM. The impact of exercise in producing hypoalgesia (exercise induced hypoalgesia, EIH) seems more consistent in pain-free patients than in patients with chronic pain. Also, patients with efficient CPM seems to have greater EIH [56].

Polypharmacy

Most patients with chronic pain take a variety of different medications that could have an effect on the CPM. A systematic review by Goubert et al., 2015, reported that dexmedetomidine, lignocaine, bupivacaine, morphine, ketamine, opioids, and oral contraceptives might reduce the efficiency of CPM and thereby reduce the effect of pain inhibition; pregabalin and tropisetron had no effect on the CPM [32].

Method-related factors influencing CPM paradigms

There has relatively little consistency in the methods used for the measurement of CPM [116,85,45], as detailed below.

Differences with the use of CS

Various differences have been noted in the literature with regard to the type, design and parameters used for CS.

Nature or type of CS

Different CS techniques have been used, such as the cold pressor pain (CPP) (immersion of the upper limb into cold water, which is the commonest mode used), noxious heat stimulation (using a contact thermode or a water bath), the ischemic arm technique (using mechanical stimulation or PPT), or the use of control condition.

Intensity of CS
Although the CS must be noxious, the intensity of the CS has been shown to have mixed effects on the degree of CPM response [77,91,30,86,5,34]. It is not clear if the intensity of the CS is associated with the magnitude of CPM effect, with some studies showing a positive correlation and some studies showing no correlation. Even mild or non-painful CS has been shown to produce some degree of CPM effect [12,50,51]. There also seems to be a ceiling effect, with the degree of CPM response varying with increasing intensity of the CS. Giving two different CS simultaneously has in fact produced a facilitatory effect [4]. A relationship between the intensity of the CS and the degree of DNIC response has been shown in animal studies [55]. In healthy volunteers, there was a significant linear relationship between the intensity of the nociceptive CS and the intensity of the CPM effect as elicited by spinal nociceptive reflex (RIII reflex); non-nociceptive CS did not elicit any CPM effect [111].

Impact of CS as 'pain inhibits pain' vs distraction
Application of a second stimulus as a CS can potentially act as a mere distraction rather than having a physiological influence on descending modulation. The CPM effect with and without distraction has been studied in human volunteers in a four-arm study comprising of test pain alone, with CS alone, with distraction alone, and with both CS and distraction [67]. This showed an additive effect of CPM and distraction but the CPM effect itself was found to be independent of distraction. Thus, although distraction can to an extent decrease pain perception, it alone cannot explain the entire CPM effect and there is an element of the additional role of 'pain-inhibits-pain'.

Temporal and residual effect of CS
TS and CS can be applied at the same time (parallel stimulation) or TS can be applied after the CS (sequential stimulation). CPM effect diminishes with time following the CS and hence parallel stimulation with CS and TS seems to produce a greater CPM effect as opposed to using a sequential paradigm [117]. However, the duration of the residual CPM effect has been found to be inconsistent [30,36,110,101]. Some studies have in fact shown that a CPM effect occurs only during the application of the CS with no residual effect [44,100]. Lewis and colleagues looked at the time course of the conditioned pain inhibition following stimulus removal. They demonstrated that the inhibition of PPT remained significant at 10 min post CS, returning to baseline at 15 min; this correlation was particularly good for CPP as opposed to ischemic arm technique [57]. With parallel stimulation we cannot separate the effects of distraction, however insignificant, from the direct 'pain-inhibits-pain effect' of CPM. The washout time for the CS is also not known and hence its impact on the intra-session reliability is unclear [20,57,102]. The current recommendation is to use a sequential protocol as opposed to a parallel protocol, with the TS applied immediately after the CS, which is thought to be a cleaner method with minimal bias due to distraction [117].

Differences with the use of TS

A number of differences have been noted in the literature with regard to the type, design and parameters used for TS.

Nature or type of TS
Thermal (heat or cold), mechanical (pressure), electrical, chemical or laser stimuli have been applied using a phasic, tonic or summation techniques. Different objective methods using laser or neurophysiological techniques such as electrical evoked potentials or the RIII reflex (a nociceptive receptor reflex which measures the spinal withdrawal reflex by stimulating the A-delta fibers as measured by electromyography) have been used as TS as detailed below.

End points used for TS
Different endpoints have been used for TS such as: (i) pain threshold or tolerance- a 'psychophysically anchored' variable stimuli applied to measure fixed threshold (e.g., pain-60, giving a pain score of 60/100) or tolerance (pain tolerance threshold or PPTol) for pain using a subjective pain rating scale (e.g., visual analogue scale- VAS or numerical rating scale- NRS). (ii) Fixed supra-threshold stimulus with same pain intensity. (iii) Spatial summation: hand immersed in cold water in an ascending fashion (from the fingertips to the shoulder) and then in a descending fashion (from the shoulder to the fingertips) which will act as both CS and TS [42]. (iv) Apart from using different types of test and conditioning stimuli, the same type of stimulus has been used with different end points and at different body parts. For example, temperature settings were used in different studies for both the TS and CS [45,85].

Tissue types and body parts used for TS
Both heterotopic (remote location) and homotopic (painful location) body part distribution as well as different tissue types including superficial/ skin or deep/ muscular or visceral structures have been used for applying TS.

Effect of different CS and TS on the magnitude of CPM effect

Different CS and TS have been reported to produce varying degrees of CPM effect. Aparecida da Silva and colleagues explored the differential effects of CPM using three different CS (with similar evoked-pain intensity): cuff-pressure pain stimulation (CuPS), cold pressor test (CoPT), and thermode-based cold painful stimulation (TCPS) using the same TS (supra-threshold heat pain stimulation with a contact-heat thermode) in thirty healthy volunteers. Significant differences in the intensity of CPM were noted for the three different CS, with CoPT inducing the most robust CPM effect [2]. Oono et al. looked at the inter- and intra-individual variance in descending pain modulation that was evoked by different CS such as CPP, tourniquet pain and mechanical pressure pain over the craniofacial region using a headband [76]. Of the numerous CS used, cold pressor pain (CPP) elicited the strongest CPM effect followed by ischemic arm using tourniquet and headband respectively. With regard to different TS, PPT elicited the strongest CPM effect followed by reduction in pain intensity (VAS) and PPTol. A CPM

effect was elicited using the TS at numerous sites, which also has been reported to have an impact in the magnitude of the CPM effect, with the highest effect seen at the tibialis anterior (TA). In summary, a combination of CPP as CS and PPT measured at TA as TS perhaps elicits the highest CPM effect [76]. One of the major limitations of this study was that it included only 12 healthy men aged 19—38 years and hence is difficult to extrapolate the results to wider groups of patients with chronic pain conditions.

Reliability of different CS and TS

Kennedy et al., in their systematic review looked at the inter-session reliability of different CS and TS [45]. The review included 10 heterogenous studies, which could not be pooled to obtain a meta-analysis. For CS, the reliability of pain ratings was reported as fair to excellent for immersion in a hot water bath, good to excellent for immersion in cold water, excellent for ischemic pain and poor for contact heat. Regarding TS, PPT threshold as a static endpoint had excellent intra-session reliability and good to excellent inter-session reliability, whereas the retest reliability for PPTol was poor to fair. Reliability of contact heat as TS depended on the type of application, with threshold technique having a fair to excellent reliability, but the subjective pain rating technique having a poor to fair reliability. Pain elicited reflex had good to excellent reliability.

Objective measurement methods

The objective nociceptive response, such as evoked potentials or nocifensor reflex, has been explored to measure the CPM or the DNIC-like effect [92,43,41,27]. For instance, a CPM paradigm using painful cutaneous electrical stimulation as TS, looking at corresponding changes in the cortical evoked potentials (PCES-EP), has been found to be consistent with reduction in subjective pain ratings. Hoffken and colleagues looked at the CPM effect in 17 healthy subjects. They used immersion of the non-dominant hand in cold water at 10 °C or 24 °C as CS and electrical stimulation to dominant hand, inducing a pain score of 40—60 in NRS 0—100 as TS, along with the measurement of PCES-EP. In the 10 °C condition, there was a significant reduction in the pain level as well as the amplitude of PCES-EP ($P < 0.001$); in addition, there was a strong correlation between the subjective pain ratings and amplitude of PCES-EP ($r = 0.5$), and also with the intensity of CS ($r = 0.5$) [41,27]. Jurth and colleagues demonstrated good test-retest reliability with nociceptive flexion reflex (NFR) using painful electrical stimuli to sural nerve as TS, which was comparable to subjective pain ratings [43]. While NFR will purely focus on spinal nociception, subjective pain rating will also include the cognitive influence of CPM and hence the two techniques may look at different components of CPM. Dhondt and colleagues performed a systematic review looking at the effect of CPM on NFR in healthy subjects. The type of stimuli influenced impact of CPM on NFR with some evidence suggesting that the thermal and mechanical stimuli inhibit the NFR, with inconclusive evidence for the electrical stimuli [24]. Currently there are no accepted standards or methodology for the performance of CPM.

Is CPM a reliable measure despite variabilities, and do different methodologies measure the same thing?

In order for CPM paradigm to be used as a reliable phenotypic marker it should be reproducible and reliable with stable measurements. Differences in CPM values are well known in the normal population and it is not clear what we take as a normal value in the healthy population, especially in the light of several patient-related variables as mentioned above.

CPM paradigms have been found to have good test-retest reliability in young healthy adults [10]. In patients with chronic pain, a strong correlation between baseline and follow up CPM values has been demonstrated in women but not in men [61]. In clinical and experimental shoulder pain models, CPM was found to be a stable physiological parameter in females in the clinical cohort and in males in the experimental cohort, despite some fluctuations in reported pain intensities. [104]. A systematic review looking into the reliability of CPM paradigm found that CPM was a reliable parameter but that the degree of reliability was dependent on the stimulation parameters and study methodology; it was considered that there was a need to improve on the reporting of CPM reliability studies [45]. Lewis and colleagues reported a systematic review and meta-analysis including 30 studies (778 patients and 664 control participants), looking into the CPM paradigm in chronic pain population [58]. They reported a consistent reduction in CPM paradigms across all studies and the effect size was significantly influenced by age and gender but not the methodological variables such as the nature of TS and CS, degree of pain with the CS and type of outcome measure.

Previous fMRI studies have explored variability of CPM in the normal population as well as in patients with chronic pain [11,121,38]. Differential activation of the prefrontal cortex due to a variety of reasons such as trait anxiety and variations in the strength of the PAG resting functional connectivity could contribute to individual differences in CPM. The altered responsiveness of the prefrontal and the cingulate cortex, with an overall attenuation of pain inhibitory and amplification of pain facilitative processes could be responsible for less efficient or a pain-facilitative CPM effect observed in chronic pain patients [38].

It is not clear if the different methodologies measure the same CPM paradigm exploring the same underlying mechanism [113,114,82]. For instance, Pertovaara used the ischemic conditioning stimulus using an arm tourniquet and measured the response to three different test stimuli: electrical stimulation to the tooth; heat stimulation to the lip and mechanical stimulation to the contralateral arm. There was an increase in the threshold following both electrical and heat stimulation but only the response to heat stimulation was reversed with naloxone, suggesting that only the response to the heat stimulation was mediated by the endogenous opioidergic system [82].

Interestingly, no major differences were noted with the degree of pain reduction when measured subjectively using different techniques (psychophysical studies measuring CPM or DNIC-like response) or objectively (measuring a true DNIC effect using neurophysiological studies) [85]. The CPM effect

measured using supra-threshold test-pain reduction was 29% (10—55%), increase in pain threshold was 25% (3—100%) and the DNIC effect measured using neurophysiological techniques was 28.5% (10—60%). Overall, a higher degree of variation has been reported when using the threshold technique. CPM paradigm has been found to be abnormal in a number of chronic pain conditions including fibromyalgia, osteoarthritis and muscle pain, whiplash-associated disorders, irritable bowel syndrome, migraine, tension-type headache, temporomandibular joint (TMJ) disorders, chronic pain of specific etiology such as chronic pancreatitis, interstitial cystitis, patients with opioid induced hyperalgesia and HIV [58,13,14,70,88,118,1,74,81]. Patient at risk of developing chronic post surgical pain were also found to have an abnormal CPM [118].

It is important to understand that these studies only show an association between inefficient CPM and chronic pain, rather than showing a causative relationship. It could either be that a pre-existing increased facilitation causes a pronociceptive state resulting in the development of a chronic pain syndrome; or that the development of a chronic pain syndrome consumes all the antinociceptive activity, leading to a pronociceptive state. Yarnitsky and colleagues looked at 62 patients undergoing thoracotomy. Patients with no pre-operative pain but with efficient baseline CPM prior to having a thoracotomy had half the chance of developing chronic pain post-thoracotomy with an odds ratio of 0.52 [118]. Similarly, inefficient CPM was associated with increased incidence of postoperative pain and hyperalgesia following abdominal surgery and caesarean section [109,49]. Peters and colleagues looked into a CPM or DNIC-like effect in rat models with partial spinal nerve ligation [83]. The CPM effect was influenced by blocking/ablating the nor-adrenergic pathways in the spinal cord using idazoxan/antidopamine β-hydroxylase conjugated saporin (DβH-saporin). The study showed that descending endogenous noradrenergic signaling was deemed crucial for the recovery from the post-surgery hypersensitivity. These studies very much support that 'pronociceptive state' with inefficient CPM is responsible for the development of chronic pain. However, other studies have failed to demonstrate a correlation between pre-operative CPM and postoperative pain [95,84]. Overall, we need to bear in mind that the CPM is a net effect of the sum of inhibitory and facilitatory descending modulation, with an effective CPM being due to a combination of high inhibition and low facilitation and an ineffective CPM being due to a combination of low inhibition and high facilitation.

Yarnitsky et al. proposed the concept of 'pain modulation profile' based on the balance between pronociceptive and antinociceptive effect [119]. They recommended that the combination of inefficient CPM referring to decreased pain inhibition and enhanced temporal summation referring to increased pain facilitation will form a pronociceptive profile. These subjects will have a higher pain phenotype with increased risk of pain acquisition and developing chronic pain syndromes. Similarly, patients with efficient CPM and unenhanced temporal summation will fall into the antinociceptive category and hence into the category of a lower clinical pain profile. Despite large variability in the CPM in groups of patients, those with chronic low back pain were found to have a higher proportion of patients with pronociceptive profile compared to healthy controls as measured using the CPM paradigm and temporal summation [87].

CPM as a biomarker and its therapeutic modulation

The 'Biomarkers Development Working Group' defined biomarkers as characteristics which are ''objectively measured and evaluated as an indicator of normal biological process, pathogenic processes, or pharmacologic responses to a therapeutic intervention'' [9].

Valencia et al. and Oono et al. looked into the CPM paradigms in (sub) acute pain conditions [103,78]. In contrast to chronic pain conditions, removal of experimental or clinical acute pain does not seem to alter the CPM paradigm. This perhaps alludes to a time dependent effect on CPM, for it to first reduce after a prolonged period of pain, before being normalized by intervention [32].

Fernandes et al. performed a systematic review looking at the role of CPM as a biomarker for chronic pain [28]. The review looked at 32 studies including 1958 patients in total (2 randomized-controlled trials, 18 case-controlled studies and 12 cross-sectional studies). The review identified 62 correlations between CPM and different clinical manifestations of pain including pain intensity, duration, disability due to pain and number of areas with pain. The majority of the correlations were non-significant (69%) with the remaining showing a significant negative correlation between CPM and clinical pain manifestations. The review highlighted a large heterogeneity in the study methods similar to previous publications and recommended a concerted effort towards standardized methodologies as a prerequisite for considering CPM as a valid biomarker of pain. Given the complexity of chronic pain conditions, the biomarkers for pain are likely to be multifactorial and it is perhaps less likely that a single parameter such as CPM would be able to consistently predict or correlate with pain manifestations. The authors quite correctly reached a cautious conclusion in not rejecting the null hypothesis that CPM is not a reliable or a valid biomarker of chronic pain, citing the multitude of limitations in research. While this review has looked at the correlation between CPM and clinical pain symptoms, the remit of biomarkers itself is much broader. The Food and Drug Administration USA looks at biomarkers as having a diagnostic, prognostic, predictive and pharmacodynamics measures which requires much larger fulfillment requirements and clearly there is a long way to go before CPM can get close to fulfilling these requirements [98].

Few studies have shown that CPM has a predictive value or an association with a certain therapeutic response following an intervention, supporting its role as a biomarker. For instance, in patients with painful diabetic neuropathy, inefficient baseline CPM was predictive of favorable response to duloxetine [120]. There was a correlation between the baseline CPM and the efficacy of duloxetine ($r = 0.628$, $P < .001$, efficient CPM is marked negative), in a way that less efficient CPM predicted favourable response to duloxetine. There was also a correlation between the efficacy of duloxetine and improvement in CPM but only the patients with less efficient CPM demonstrated this improvement [120]. In another study, Campbell and colleagues showed that patients with

pronociceptive pain modulation profile with enhanced TS and reduced baseline CPM were associated with lower pain scores three months following spinal cord stimulation (SCS) [17]. We have also recently demonstrated that all patients with inefficient baseline CPM had a successful SCS implant whereas only 50% of patients with efficient CPM had a similar response [89]. Contrary to the above mentioned centrally acting therapies, pre-treatment CPM had an opposite effect to more peripherally active treatments. A recent open-label study looking at the effect of topical diclofenac for knee osteoarthritis showed that a more efficient pre-treatment CPM was predictive of a better analgesic response to the topically applied NSAID [26].

CPM also has shown some interesting response to treatments in different clinical conditions. A number of studies have demonstrated that specific chronic pain intervention results in an improvement in CPM paradigm and the pronociceptive profile, in parallel with the alleviation of pain. Total hip and knee replacement were associated with an improvement in the CPM paradigm in parallel with the improvement in clinical pain levels [48,47,37]. In a small study involving 10 patients with peripheral neuropathic pain, CPM was found to be inefficient at baseline. Treatment with morphine, ketamine and placebo all produced improved CPM responses, which correlated with the magnitude and duration of pain relief [71]. We have previously demonstrated that SCS can convert inefficient CPM suggestive of a pronociceptive profile to efficient CPM suggestive of a antinociceptive profile [89]. Dorsal root ganglion intervention was also associated with improved CPM in patients with unilateral lumbosacral radicular pain [63]. We have also demonstrated that pregabalin can result in a significant improvement in CPM in patients with fibromyalgia [115]. Bouwense et al. showed that in patients with chronic pancreatitis, treatment with pregabalin did not produce a mean improvement in CPM compared to placebo [15]. The same group subsequently demonstrated a selective treatment-related improvement of CPM for pregabalin responders. That is, patients who responded to treatment with pregabalin, with significant improvement in pain levels also had a significant improvement in CPM [15,16]. In patients with fibromyalgia, active TENS was associated with a more efficient CPM, lower pain levels and fatigue at the time of the application [23].

The CPM also seems to have a real time impact with an ongoing therapy for pain management. For instance, switching 'on' of a spinal cord stimulator (active treatment state) has been associated with an improved CPM compared to 'switching off' position of the stimulator (inactive treatment state) [65,97].

Given the current literature on the role of CPM as a phenotypic biomarker, it is still quite early to consider its role in personalized medicine or mechanisms-based treatment in chronic pain. For instance, in the future there may be scope for targeting a dysfunctional pain modulation profile with specific therapy. Patients with decreased pain inhibition as suggested by an inefficient CPM could be targeted with selective noradrenaline reuptake inhibitors (SNRI) such as duloxetine and patients with increased pain facilitation as suggested by enhanced temporal summation could be targeted with drugs suppressing pain sensitization such as gabapentinoids and ketamine [73,119,120,35].

Limitations of CPM

There are a number of questions still to be answered with regard to CPM. When we phenotype patients based on CPM what are we actually measuring? Are we looking into any specific abnormality in the descending somatosensory system in terms of either the pathway or the neurotransmitter release? Also, is it a combined output of all descending control mechanisms (both facilitatory and inhibitory); does it have an implication on the placebo response, or can it be used as a marker for central sensitization? If this is the case, could it be used as a tool to screen patients in clinical trials?

There is also a 'chicken and egg situation' — did inefficient CPM result in chronic pain or the CPM became inefficient due to chronic pain? The fact that a successful intervention in a patient with chronic pain results in the restoration of efficient CPM perhaps suggests that chronic pain predates and possibly results in an inefficient CPM [45].

While there are a number of studies looking into the usefulness of CPM, currently there is no standardization of the technique for testing CPM, nor in the mode of presentation of the results. Hence there is a need to describe the test in detail at the time of writing the research methodology. It is also recommended to present the results as both absolute change as well as percentage change in the values following the application of the CS, along with a representation of the variability, stating whether the CS resulted in the facilitation or inhibition of pain processing [116]. It is now widely recognized that variability in research protocols is a barrier in pooled analysis and hence it is recommended to have a standardized protocol with regard to the nature of the TS (if possible, using mechanical and thermal stimulus), CS, use of sequential protocol and presentation of data [117]. This we hope will help with standardization of the CPM paradigms used in future research, enabling researchers to produce reliable and comparable results, which could be meaningfully pooled in systematic reviews.

Conclusions

CPM is indeed a useful bedside test as part of dynamic QST testing, as it can be effectively performed using portable equipment. Inefficient CPM is part of a pronociceptive pain modulation profile which could make the subject 'at risk' for developing chronic pain. CPM also has an emerging role as a phenotypic biomarker to predict response to chronic pain intervention, which in the future could point towards personalized medicine. The pitfalls in measuring CPM are well recognized and there have been excellent recommendations from experts in the field to standardize future research on CPM. This we hope will help facilitate pooled analysis of multiple studies with more homogenous methodologies.

Conflicts of interest

None.

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