Does Conditioned Pain Modulation (CPM) correlate with clinical pain? A systematic review of the Literature

Carina Fernandes[1], Marina Pidal-Miranda[2], Noelia Samartin-Veiga[2], María Teresa Carrillo-de-la-Peña[2*]

[1]Laboratory of Neuropsychophysiology, Faculty of Psychology and Education Sciences, University of Porto; [2]Brain and Pain (BaP) Lab, Department of Clinical Psychology and Psychobiology, Universidad de Santiago de Compostela, Spain

*CORRESPONDING AUTHOR: mteresa.carrillo@usc.es

INTRODUCTION

Conditioned pain modulation (CPM) is a test used to assess the functionality of endogenous pain inhibition in the central nervous system.

During this paradigm, a **nociceptive (test) stimulus (TS)** is administered in the absence and after/during the application of a second **painful (conditioning) stimulus (CS)**, which is applied in a remote region of the body (Fig. 1).
In a healthy nociceptive system, the amount of pain experienced with the test stimulus will decrease during/after the application of the conditioning stimulus, reflecting the **efficacy of the endogenous pain inhibitory pathway**.

Although there is solid evidence **on deficits in pain modulation in several chronic pain diseases**, it is unclear whether the CPM can be considered a good predictor of pain manifestations, and thus a valid biomarker of clinical pain.
In this sense, we conducted a systematic review of studies that correlated CPM and clinical manifestations of pain (pain intensity, duration, disability due to pain, and number of painful areas).

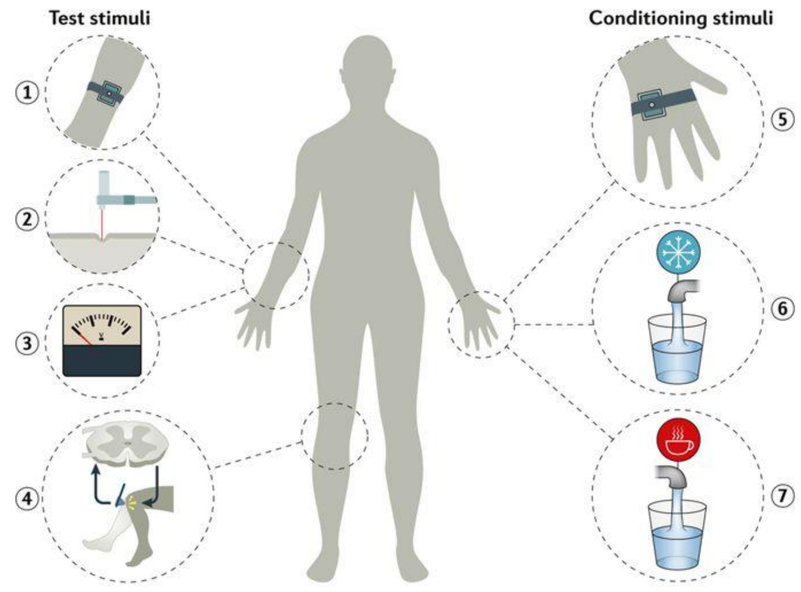


Fig. 1. Schematic representation of the CPM (Colloca et al., 2017)

METHODS

Literature Search, Inclusion and Exclusion Criteria

Systematic search on PubMed, Web of Knowledge and EBSCOhost in January 2019 (Fig. 2). The **search expression was** ("Conditioned pain modulation" or CPM or "endogenous pain modulation" or DNIC or "diffuse noxious inhibitory control" or "Quantitative Sensory Testing" or "temporal summation") AND (phenotyp* or subgroup* or "clinical pain" or "pain intensity" or "pain duration" or "chronic pain" or prediction or biomarker or "treatment response" or "treatment outcome").
We **included** observational case-control, cross-sectional and cohort studies, randomized and non-randomized controlled trials that have assessed CPM in patients with chronic pain, written in English, Portuguese or Spanish. We **excluded** studies without a group of adults with chronic pain, that did not assess CPM, without information about the correlation between CPM and clinical manifestations of pain, theoretical articles, and articles with duplicated data.

RESULTS

Study Selection

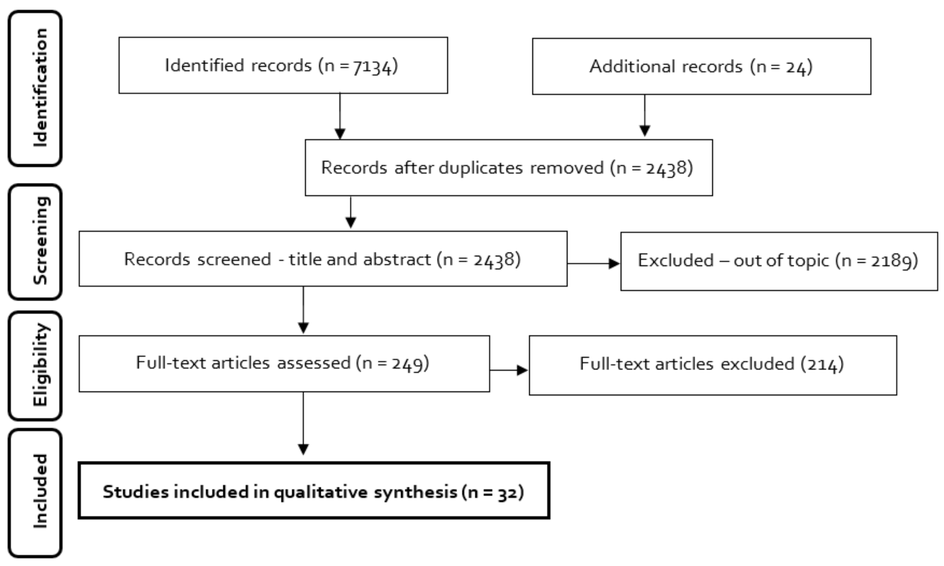
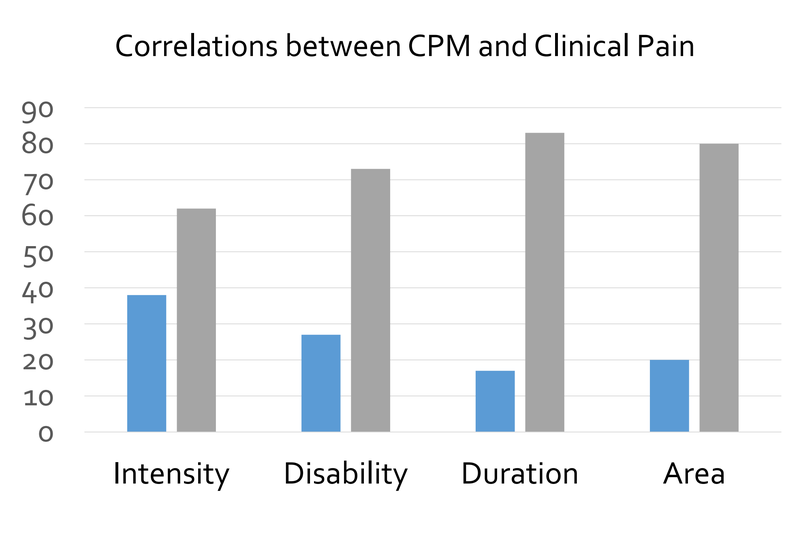
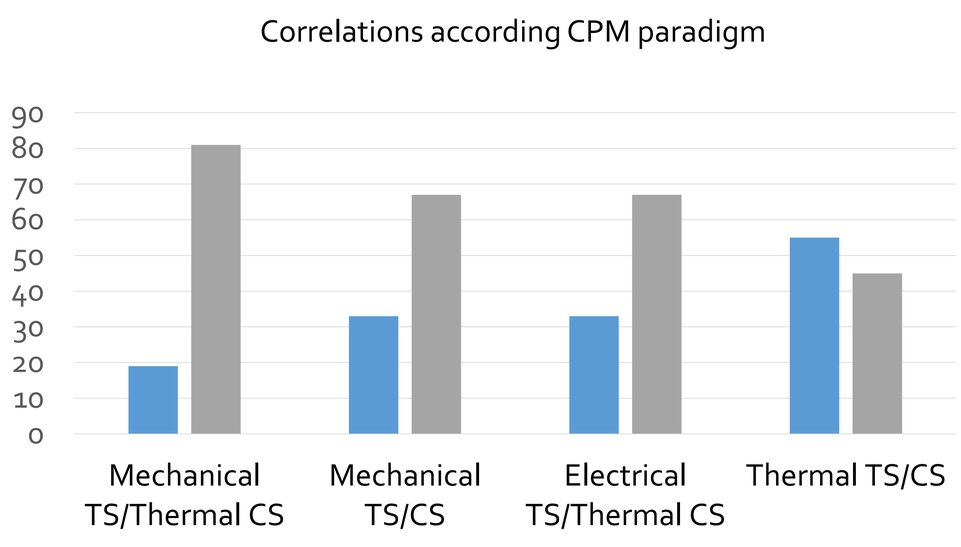


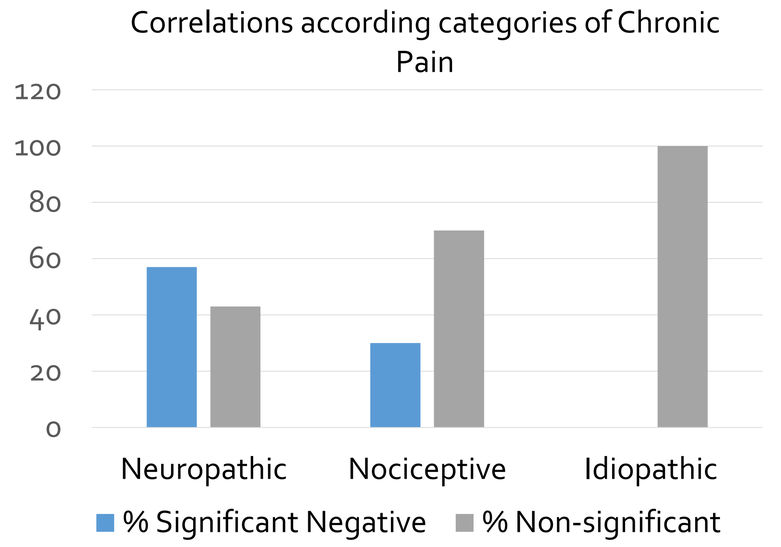
Fig. 2. Flowchart of the systematic search, results and the selection of the studies

Synthesis of CPM Results

- **1958 chronic pain patients** (1161 females), with a **mean age of 50.1 years**; 88% of the studies included males and females. Most common chronic pain conditions: Knee Osteoarthritis (25%) and Chronic Back Pain (low or widespread; 22%). 38% did not include a control group. From the remaining studies, **70% found significant differences in CPM efficacy between chronic pain patients and healthy controls**, 10% found a significant reduction in CPM for one experimental group, and 20% of the studies did not find significant differences between patients and controls.
- We extracted **62 correlations between CPM and clinical manifestations of pain**: pain intensity (and severity), disability (and interference) due to pain, duration and number of areas with pain. **The majority of these correlations were non-significant (69%)**, suggesting that CPM efficiency and clinical manifestations of pain may be relatively independent. **The remaining correlations were significant and negative**, showing that less efficient pain inhibition was associated with worse symptoms of clinical pain.







DISCUSSION

The majority of the studies found significant differences in CPM efficacy between patients and controls, and 31% of the correlations were significant and negative, showing less efficient pain inhibition associated with worse symptoms of pain. This percentage increased for neuropathic pain, when we analyzed the results based on the type of pain. However, in general, the majority of the correlations were non-significant throwing doubts on the validity of CPM as a biomarker of clinical pain.
Considering the high heterogeneity among the included studies and their unclear risks of bias, future studies need to be conducted with the specific goal of testing the correlation between CPM responses and clinical manifestations of pain, including standardized measures of clinical pain and CPM, and controlling for confounding factors such as medication intake, sex or type of chronic pain disease. We recommend the use of thermal CPM protocols, stimulation of non-painful areas, and stable measures of clinical pain (comprising at least the last month), taking attention to the characteristic of pain (localized vs. generalized) and gender.

FUNDING: This work was supported by a Grant from the IACOBUS, Ministerio de Economía y Competitividad (PSI2016-75313-R) and Galician Government (GRC (GI-1807-USC); REF: ED431-2017/27).

REFERENCES: Colloca et al., Nat Ver Dis Primers 2017;3:1-19. doi:10.1038/nrdp.2017.2; **Fernandes et al., 2019. doi: 10.1097/j.pain.0000000000001664**