Predictive validity of Conditioned Pain Modulation (CPM) as a biomarker of chronic pain: A systematic qualitative review

María Teresa Carrillo-de-la-Peña[1*], Noelia Samartin-Veiga[1], Marina Pidal-Miranda[1], Carina Fernandes[2]
[1]Brain and Pain (BaP) Lab, Department of Clinical Psychology and Psychobiology, Universidade de Santiago de Compostela, Spain; [2]Laboratory of Neuropsychophysiology, Faculty of Psychology and Education Sciences, University of Porto, Portugal
*CORRESPONDING AUTHOR: mteresa.carrillo@usc.es

INTRODUCTION

Given the modest efficacy of the available treatments for chronic pain, the pinpointing of **predictors of treatment response** and the implementation of individualized treatments based on the patients' characteristics are crucial to improve pain therapy. **Conditioned pain modulation (CPM)** has attracted increasing interest as a biomarker of central pain inhibitory mechanisms: it is simple to obtain and consistently discriminates chronic pain patients from healthy controls. Nevertheless, there is not enough information concerning **its predictive validity**. Therefore, the objective of the present systematic qualitative review was to analyze the evidence on the power of pre-intervention CPM to predict treatment outcomes.

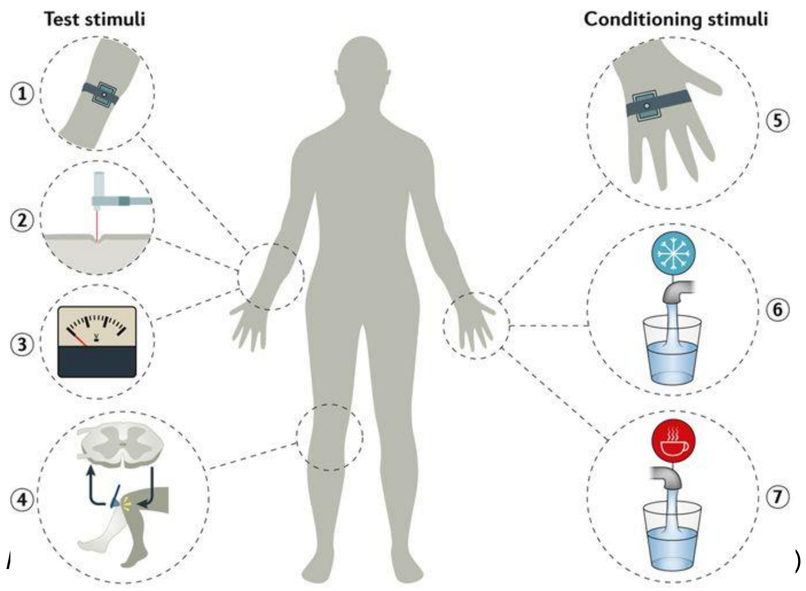

Fig. 1. Schematic representation of the CPM (Colloca et al., 2017)

METHODS

Literature Search, Inclusion and Exclusion Criteria

Systematic search on PubMed, Web of Knowledge and EBSCOhost in February 2018. 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").

Inclusion criteria: type of study (longitudinal prospective cohort studies, cross-over case-control studies, as well as randomized (RCT) and non-randomized controlled trials (CCT), **measures** (CPM assessed pre-intervention as predictor of clinical pain assessed post-intervention, **population** (adult patients with pain), **language** (English, Portuguese or Spanish).

Exclusion criteria: **wrong population** (studies considering other pain manifestations different from stable chronic pain, such as acute, experimental or provoked pain on healthy subjects), **wrong measure** (studies that did not assess pain modulation using heterotopic noxious stimulation such as distraction analgesia); **lack of data** (studies that did not provide data on the relationship of pre-intervention CPM with treatment outcomes; **wrong publication type** (as reviews, letters, commentaries, abstracts, case reports, case series, methods, or corrigendum).

Procedure

Screening and selection of records performed blindly by two researchers using Rayyan QCRI (Cohen's kappa = .65)

Data extraction: General characteristics of the studies (such as country and lab, study design, type of intervention), sample characteristics (sex, age, chronic pain condition, disease duration, medication), CPM measurements (test and conditioned stimuli, place and duration of stimulation), outcome assessment (type of outcomes, measures used, time of post-treatment measure), and main results.

Risk of bias assessment following the guidelines for assessing the quality of prognostic studies proposed by Hayden et al., (2006).

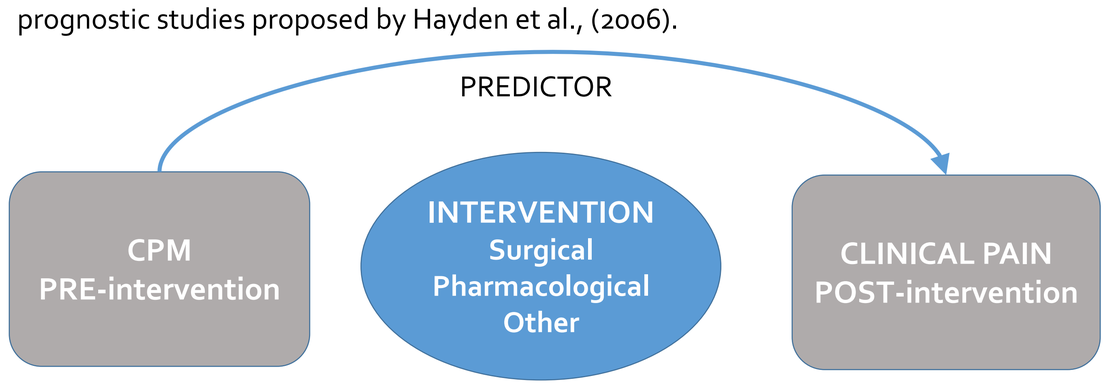

Figure 2. Design of the included studies

RESULTS

Selected Studies

- 14 studies published between 2008 and 2017 (71% in the last 5 years).
- 667 patients involved (mostly in their 50's-60's; 52.9% of females).
- Knee osteoarthritis was the chronic pain condition most studied (50% of the publications).
- Mostly performed in two labs (Aalborg University, DK participated in 57.1 % of the studies, and Technion Institute, IL participated in 14.3%)
- Two types of studies: CPM used to predict clinical future pain in surgical patients or CPM used to predict responsiveness (pain relief) to a given treatment.
- 6 studies used surgical interventions, 6 pharmacological treatments, and 2 other interventions (exercise, spinal cord stimulation).

Synthesis of Results

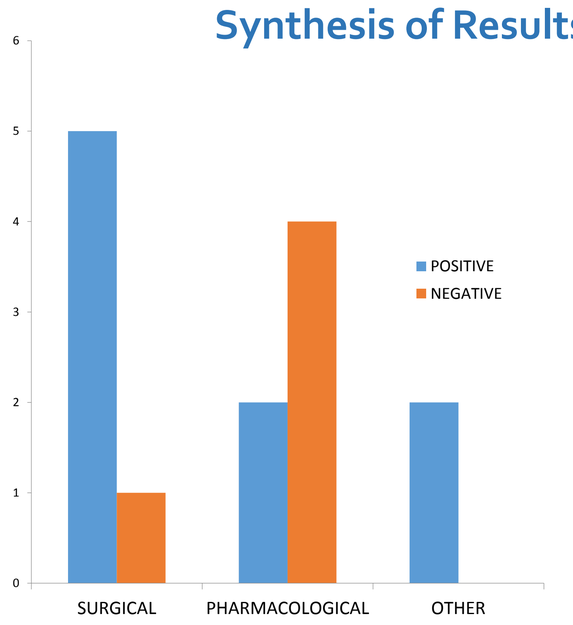

Figure 3. Number of studies with results supporting (positive) or not (negative) the predictive power of pre-intervention CPM

- For surgical interventions, CPM, alone or in combination with temporal summation assessment, is a good predictor of future clinical pain, even in pain-free subjects before surgery.
- Using pharmacological interventions, the contradictory results do not support the predictive power of CPM.
- With other non-pharmacological interventions, we found that lower CPM was associated with reduced pain ratings 3 months after spinal cord stimulation while baseline CPM predicted exercise-induced hypoalgesia within the same session.

Risk of Bias and Limitations of the Studies

- The majority of the studies made an adequate control of the potential sources of bias, being the appropriate identification and control of confounders the most critical issue.
- There is large methodological heterogeneity among the studies in CPM measurement (which may influence the results).
- There is not a homogenous pattern concerning management of the patient's current medication.

DISCUSSION AND CONCLUSIONS

- ❑ **The predictive validity of CPM strongly depends on the type of intervention, with more positive results for surgical and non-pharmacological interventions. As also concluded in a previous review using non-dynamic quantitative sensory testing (QST) measures (Grosen et al., 2013), the evidence so far is not strong enough to recommend the use of CPM as a predictor of future clinical pain.**
- ❑ **Although promising, the results need to be replicated in independent research groups, who should adequately address the possible contaminating effect of previous or concomitant pain medication, using longitudinal, prospective designs and following standardized and common procedures for CPM measurement.**
- ❑ **The predictive validity of CPM as a biomarker of central pain inhibitory mechanisms should be also tested using treatments that target central sensitization specifically.**

REFERENCES: Colloca et al., 2017. Nat Ver Dis Primers 3:1-19. Grosen et al., 2013. Eur J Pain,17:1267-1280. Hayden et al., 2006. Ann Intern Med 144:427-437.

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).