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Original Research

Conditioned Pain Modulation (CPM) Paradigms: Reliability and Relationship With Individual Characteristics

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ABSTRACT

Purpose: Conditioned Pain Modulation (CPM) is a useful tool for testing the functionality of endogenous pain modulation. However, inconsistent results have been obtained in clinical populations, possibly due to the wide variety of CPM protocols used and the influence of demographic and psychological characteristics of the individuals assessed.
Methods: We tested the sensitivity and reliability of four commonly used CPM paradigms in a sample of 58 healthy participants. We also checked how these measures were related to Temporal Summation of Second Pain (TSSP), sociodemographic (age and sex) and psychological variables (anxiety and stress).
Results: CPM results were influenced by the test stimulus used, with tests using pain pressure threshold (PPT) obtaining a greater number of responders (over 65%) and being the most sensitive (higher size effect: Cohen's d > 0.5). However, all measures showed excellent intrasession reliability, with strong agreement between the CPM magnitudes. CPM indices were not correlated with TSSP, age or sex, and the psychological scales did not differentiate CPM responders and non-responders.
Conclusions: Although the CPM indices showed good reliability, construction of a large database with standardized values for healthy individuals seems necessary for the use of CPM in clinical settings.

Pain has been defined as an unpleasant sensory and emotional experience associated with (or resembling that associated with) actual or potential tissue damage (International Association for the Study of Pain, 2020). Pain perception is the result of a series of nociceptive processes at peripheral, spinal and supraspinal levels (Romera et al., 2000; Apkarian et al., 2005; Kandel, 2013; Viera and Guirola, 2017), as well as of descending pain modulation mechanisms (Schweinhardt and Bushnell, 2010; Ossipov et al., 2010; Bushnell et al., 2013). These involve areas such as the hypothalamus, amygdala, locus coeruleus, rostral anterior cingulate cortex (rACC), periaqueductal grey region (PAG) and rostroventromedial medulla (RVM), which project to the spinal cord to alter the flow of nociceptive information and modify the painful experience (Heinricher et al., 2009; Ossipov et al., 2010; Ossipov et al., 2014). Some clinical pain manifestations may be explained by an imbalance between the inhibitory (antinociceptive) and facilitatory (pronociceptive) pathways controlled by those areas (Staud et al., 2008; Denk et al., 2014; Potvin & Marchand, 2016). In particular, the reciprocal PAG-RVM connections seem to explain endogenous descending pain modulation (Fields et al., 2005; Bodnar and Heinricher, 2022).

The efficacy of endogenous pain modulation can be measured by quantitative sensory testing (QST) involving dynamic paradigms such as conditioned pain modulation (CPM), a phenomenon that occurs when a second noxious stimulus (conditioning stimulus, CS) produces a decrease in the perceived pain evoked by a first stimulus (test stimulus, TS) applied to a heterotopic region (Staud et al., 2014). CPM has been examined as a way of differentiating between patients with chronic pain (CP) and healthy controls, and it has been proposed as a biomarker for pain pathologies and increased pain sensitivity (Lewis et al., 2012; Granovsky, 2013; Harper et al.,

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2018; Ramaswamy & Woodehouse, 2021). In addition, the temporal summation of second pain (TSSP) is a paradigm used to measure pain facilitation, known to represent a perceptive correlate of the wind-up process in the dorsal horn of the spinal cord (Price et al., 1994; Eckert et al., 2017). The TSSP is a progressive increase in perceived pain intensity after reiterative stimulation of peripheral C-fibers using repeated or continuous noxious stimuli (Price et al., 1977; Arendt-Nielsen et al., 1994; Nie et al., 2009). This paradigm provides some insight into the central sensitization processes (Coderre et al., 1993; Latremoliere and Woolf, 2009; Arendt-Nielsen, 2015) and the effect has been found to be greater in CP patients than in healthy controls (Staud et al., 2008; Potvin & Marchand, 2016; Fingleton et al., 2017; Staud et al., 2021).

However, the results obtained with CPM in the previous literature are clearly marked by methodological differences, due to the heterogeneity of the protocols used (Popescu et al., 2010; Nahman-Averbuch et al., 2013). The variety of types of CS (cold or hot water, tourniquets) and TS (pressure, heat, cold, mechanical, electrical) used and differences in the order of stimulus presentation (sequential, parallel) prevent robust conclusions being made about the clinical relevance of CPM (Fernandes et al., 2019). In a recent study, the superior sensitivity of the parallel paradigm (simultaneous presentation of CS and TS) as a biomarker of fibromyalgia was shown (Gil-Ugidos et al., 2024). Nevertheless, the optimal CS-TS combination remains to be identified and a standardized methodology must be developed to facilitate comparisons and make progress in the field.

In addition to methodological questions, demographic and psychological inter-individual differences can affect CPM, as evidenced in clinical and healthy populations. Regarding age, some studies indicated a greater efficiency of CPM at younger ages, with a progressive decline until reaching the lowest point at elderly ages (Riley III et al., 2010; Khan et al., 2018; Hackett et al., 2020), although this effect has not been consistent (Ibancos-Losada et al., 2020; Mertens et al., 2021). Some studies report that CPM may be more efficient (Hermans et al., 2016) and stable (Valencia et al., 2013) in men, but differences related to sex are also not consistent (Umeda & Okifuji, 2023; Uzawa et al., 2024). Although age and sex seem to influence CPM responses, the direction of this influence is not consistent in previous literature. Thus, it is important to explore whether the various CPM paradigms are differentially influenced by those variables. Finally, CPM may be influenced by the participant's mental state (Nahman-Averbuch et al., 2016): thus, CPM has been found to be negatively correlated with anxiety (Bogdanov et al., 2015) and decreases with increased acute stress (Mertens et al., 2020). Again, it would be interesting to explore whether different CPM paradigms are differentially related to those psychological variables.

Considering all of the above, the main objective of this study was to analyze the sensitivity and reliability of four CPM paradigms in a sample of healthy participants (to prevent the influence of possible dysfunctions in chronic pain patients). The second objective was to determine whether CPM and TSSP indices, related to antinociceptive and pronociceptive mechanisms respectively, are correlated. The third objective was to examine whether the age or sex of the participants is associated with the magnitude obtained in the different CPM paradigms and whether CPM responders and non-responders differed in measures of anxiety and stress.

Material and Methods

Participants

The sample comprised 58 healthy controls. Exclusion criteria were diagnosis of any chronic pain disorder, ongoing or planned pregnancy, history of drug abuse, unstable medical conditions (e.g. uncontrolled diabetes, uncompensated cardiac issues, heart failure or chronic obstructive pulmonary disease), implanted intracranial devices or stimulators, history of neurosurgery, brain injury with loss of consciousness or cortical lesions, family history of epilepsy or active epilepsy and presence of diagnosed psychiatric disorders. The present research represents a pilot study conducted prior to a clinical trial of transcranial electric stimulation in patients with chronic pain (registered at https://clinicaltrials.gov/; ID number: NCT05099406). The above exclusion criteria were established because the group considered in the present study acted as the control group in the trial. We used a sample of healthy participants because we did not want the sensitivity/reliability results to be affected by the alterations in pain modulation that typically occur in patients with chronic pain.

We publicized the study in social networks (X, Instagram, LinkedIn, WhatsApp), by placing advertising leaflets in sociocultural centers of the city of Santiago de Compostela (Spain), by disseminating information to participants of other ongoing studies and using a snowball procedure (research participants were asked to spread the study among their circle of contacts). We provided an incentive of 30 euros to those who met the criteria for participation and completed the assessments. All the included participants signed an informed consent form prior to the experiment, and their data were coded for pseudonymization. The assessments were carried out in the facilities of the Brain and Pain Lab of the Faculty of Psychology (University of Santiago de Compostela, Spain) in the period from December 2021 to July 2023, and the procedures were not harmful, since all the stimuli intensities were defined according to the individual participant's threshold. The study followed the Declaration of Helsinki and was approved by the Research Ethics Committee of Santiago-Lugo, with code 2021/021.

Instruments

CPM test stimulus (TS)

Two different pain threshold indices were used as the TS:

The Heat Pain Threshold (HPT) was reached using the Thermal Cutaneous Stimulator (TCS II.1.b, Probe T 08; https://www.qst-lab.eu/tcs-technical-description). A heat stimulus with increasing temperature (baseline 30°, with an increase of 1°C/s) was used. Participants were required to hold the stimulator, placed over the thenar eminence (base of the thumb) of their dominant hand (whether right or left-handed), and to press the response button with the other hand just when they began to feel pain. The procedure was applied three times, each separated by 20 seconds, and the mean HPT was calculated.

The Pressure Pain Threshold (PPT) was reached using a digital algometer (ALGOMED Computerized Pressure Pain Algometer, Medoc). The area of stimulation was a 1 cm^2 patch on the dominant forearm, over the belly of the extensor carpi radialis longus (near the elbow joint), and the pressure velocity (rate) was 35 kPa/s. Stimulation was delivered three times, each separated by 20 seconds, and the patients responded when they started to feel pain. The pressure value was registered digitally on the Medoc Main Station platform, and the PPT was calculated as the mean value of the 3 applications. The protocol was applied by a previously trained researcher.

CPM conditioning stimulus (CS)

Two different types of stimuli were used as CS. Both types were applied over the contralateral dermatome, which has been shown to provide the most reliable results (Nuwailati et al., 2020):

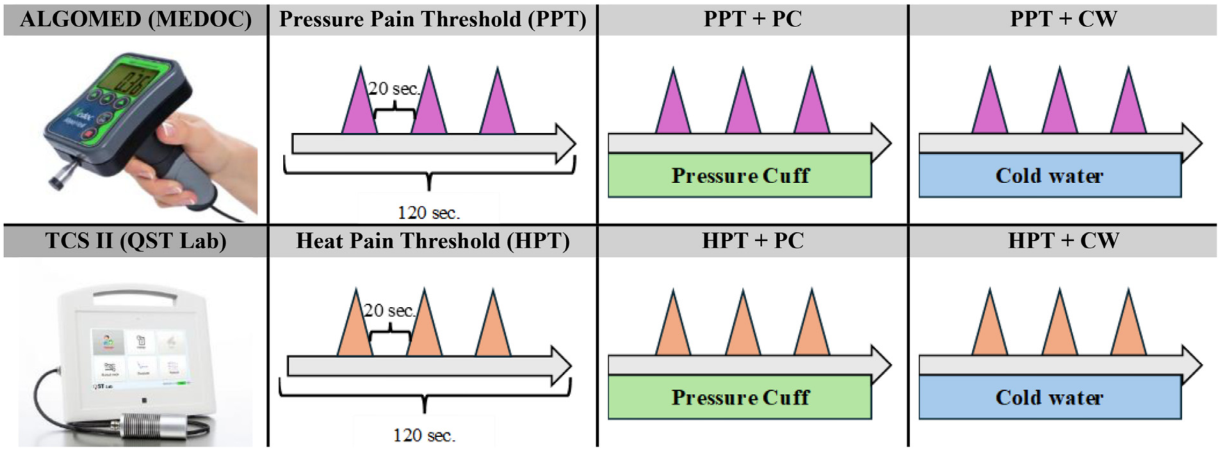

Figure 1. Conditioned Pain Modulation (CPM) procedures used.

On the one hand, a *pressure cuff*, with a constant pressure of 240 mm hg (30 kPa), was applied on the opposite arm for 120 seconds.

On the other hand, we used as CS the immersion of the non-dominant hand in a tank of *cold water* (8°C) for 120 seconds. The water temperature was controlled with a portable electric cooler and the desired temperature was confirmed to have been reached with a digital thermometer.

Questionnaires and NRS measurement

The participants completed several online self-reported questionnaires, all of which were administered in the corresponding Spanish-validated versions:

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983; Sánchez-López et al., 2015) was used to assess the presence of anxiety. The HADS is a 14-item Likert type scale (response range, 0-3), enabling patients to describe the feelings they had experienced during the previous week. The total score ranges from 0-42, and higher scores are associated with greater severity of symptomatology. The scale is divided into two 7-item subscales (score range 0–21 for each), one for anxiety (HADS-A) and other for depression (HADS-D). In this study, we considered only HADS-A. This subscale has an adequate reliability/ internal validity ($\alpha = 0.84$).

The Perceived Stress Scale (PSS-14; Cohen et al., 1983; Remor, 2006) is a self-report instrument that assesses the level of stress perceived during the past month. It consists in a 14-item Likert type scale (response range between 0-4) that refers to feelings and thoughts related to stress over the past month. Higher scores correspond to higher perceived stress levels in the range 0 to 56. This questionnaire has an adequate reliability (internal consistency, $\alpha = 0.81$, and test-retest, $r = 0.73$), validity (concurrent), and sensitivity.

In addition, the participants completed *ad hoc NRS (0-10)* related to their *anticipatory anxiety* before the session.

Procedure

CPM

The TS was assessed before and during the application of the CS, as a previous study has shown that the parallel application of TS and CS is more likely than sequential application to produce CPM responses (Gil-Ugidos et al., 2024). In the present study, we tested 4 CPM combinations: PPT + pressure cuff (PPT+PC), PPT + cold water (PPT+CW), HPT + pressure cuff (HPT+PC) and HPT + cold water (HPT+CW) (see Fig. 1). All 4 paradigms were delivered to all participants, in a counterbalanced order and with an inter-protocol interval of 10 min. The second application of the TS did not begin until the participant indicated that the CS caused intense pain (of a minimum of 7 on a numerical scale of 0-10) or had been applied for 20 s.

We extracted the CPM magnitude for each experimental paradigm by calculating the mean for the TS during the presentation of the CS minus the mean for the TS before the CS. Positive values ($CPM > 0$) indicated elevation of the threshold, i.e. an inhibitory response due to the application of the CS.

Pain5 estimation for TSSP

We conducted a brief test session to select the temperature to be used for each person. Participants were asked to verbally rate (using a Numerical Rating Scale- NRS) thermal stimuli applied to their dominant hand, from 0 to 10 (with 0 indicating not painful at all and 10 unbearable pain). Participants were instructed to pay attention to the “second pain” that appeared just after the initial peak of pain provoked by the stimuli. Starting at the HPT temperature, the participants were assessed with different stimuli at variable temperatures, with a duration of 1 second for each exposure, and following an adapting staircase approach focused on finding an approximate temperature that they would stably score as 5 out of 10 (Pain 5).

TSSP

Test runs of 12 heat stimuli (each of 1 sec. duration) were presented to the participants. The temperature was adjusted for each participant individually, using the temperature established as Pain 5. Participants rated the pain caused by the first stimulus (S01) and the last stimulus (S12) of each series on a computerized NRS ranging from 0 to 10 (see Fig. 2), clicking on a computer mouse to indicate the score. The interval between nociceptive stimuli was randomized, ranging from 1.5 to 2.3 seconds (except the interval after the first stimulus, in which the participant had to rate the perceived pain). The magnitude of TSSP was calculated as the difference between NRS-S12 and NRS-S01.

Data Analysis

Means and standard deviations were used to describe the quantitative variables, while absolute frequencies and percentages were used for the qualitative measures. The normality and distribution of the data were also checked, and the two subjects who were extreme outliers for any of the variables analyzed were excluded.

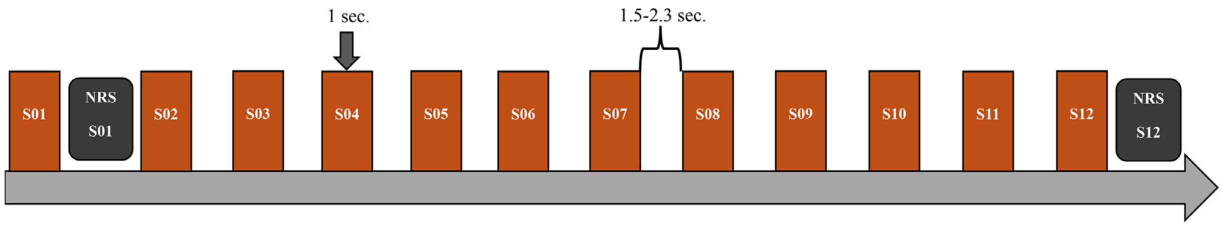

Figure 2. Temporal Summation of Second Pain (TSSP) procedure used.

The patients were classified as responders or non-responders for each of the paradigms. For a participant to be considered a CPM responder, the difference between the TS before and during the CS had to be greater than the standard deviation for the mean of the threshold to the isolated TS for the individual (CPM Magnitude > SD of the isolated TS measurements), as done by Gil-Ugidos et al (2024). This was conceived considering the intrinsic standard error of any psychophysical measurement, aimed to ensure that any differences in pain thresholds were due to the application of the CS. The percentage of change was also calculated for each participant, with the formula {([CPM TS - TS] / TS) * 100}, and the standardized size effects (Cohen's d) for the different CPM magnitudes were determined.

To assess the reliability of the protocols used to obtain CPM, we calculated the intraclass correlation coefficient (ICC). The ICC provides information about the strength of a correlation, considering the magnitudes of each variable. We considered that ICC < 0.5 represents poor reliability, a value between 0.51 and 0.75 represents moderate reliability, a value between 0.76 and 0.90 good reliability, and an ICC > 0.90 excellent reliability (Koo and Li, 2016). Thus, following a 2-way mixed effects model (absolute agreement; 95% CI), this statistic allowed us to check the reliability of the 3 measurements of TS and CS in each CPM paradigm and of the different CPM indices.

We therefore constructed Bland-Altman plots (Bland & Altman, 1986; Ludbrook, 2002) and used simple linear regression to check for homoscedasticity (absence of correlation between the size of error and the magnitude of the scores; Weir, 2005). This allowed us to check the degree of agreement between measures that share TS, both graphically (by plotting the limits of agreement or LOA) and statistically (β, r, p-value). For this test, non-significant values indicate an absence of discrepancy between scores, in other words, agreement between scores.

After that, we calculated the correlation between the magnitudes of CPM and TSSP, and between the CPM magnitudes and the age of the participants using Spearman's correlation coefficient (as the data were not normally distributed). Also, we determined the correlations between sex and the CPM magnitude obtained from each protocol using point-biserial correlations, due to the dichotomic condition of the sex variable.

Finally, we compared the profiles of CPM responders and non-responders in the different NRS and questionnaires using classical and Bayesian one-way ANOVAs, applying the Bonferroni-Holm correction to the values obtained.

Data were analyzed using the SPSS statistical package (v.29.0; IBM Corporation, Armonk, NY, United States) and JASP (v.0.18; The JASP Team).

Results

Sample Characteristics

The descriptive statistics for the participants' data regarding the demographic, QST and self-reported measures are summarized below (see Table 1; n varied due to missing data). The sample was composed of 37 females and 21 males, aged between 25 and 65 years (mean age 39.11 years).

Sensitivity and Reliability of the CPM Paradigms

Distribution of responders, percentage of change and size effect for each CPM paradigm

Table 1
Descriptive Statistics for Sociodemographic, QST and Self-Reported Characteristics of Healthy Participants (n = 58).

Quantitative Variables						Qualitative Variables				
Variable	N	Minimum	Maximum	Mean	Std. Deviation	Variable	N	Category	n	%
Age (years)	58	25	65	39.11	12.50	Sex	58	Female	37	63.8
Weight (kg)	56	44	107	69.91	14.97			Male	21	36.2
Height (cm)	56	148	186	165.95	8.97	Dominant hand	58	Right	56	96.6
PPT (kgf/cm²)	58	0.81	5.54	2.78	1.07			Left	2	3.4
PPT+PC: magnitude (kgf/cm²)	58	−0.87	2.40	0.58	0.69	Civil status	56	Single	32	57.1
PPT+PC: pressure cuff pain (NRS 0-10)	58	1	9.67	6.17	2.39			Married	18	32.1
PPT+CW: magnitude (kgf/cm²)	58	−1.19	2.73	0.59	0.70			Divorced	3	5.4
PPT+CW: cold water pain (NRS 0-10)	58	1	10	6.93	2.04			Common-law partner	3	5.4
HPT (°C)	58	37.73	52.03	45.66	3.05	Educational level	56	High school	4	7.1
HPT+PC: magnitude (°C)	58	−9.27	6.00	.64	2.99			Bachelor's degree	4	7.1
HPT+PC: pressure cuff pain (NRS 0-10)	58	1	10	6.30	2.41			College degree	21	37.5
HPT+CW: magnitude (°C)	58	−10.24	5.91	0.27	3.00			Master's degree	27	48.2
HPT+CW: cold water pain (NRS 0-10)	58	1	10	6.72	1.93	Occupation	56	Full-time job	30	53.6
TSSP magnitude (NRS 0-10)	58	−0.33	6.41	2.47	1.77			Part-time job	8	14.3
PSS	37	13	39	24.78	5.67			Student	12	21.4
HADS-Anxiety	54	1	17	7.13	3.74			Unemployed	5	8.9
Anticipatory anxiety (NRS 0-10)	56	0	8	1.82	2.43			Retired	1	1.8

PPT: Pain Pressure Threshold; PC: Pressure Cuff; CW: Cold Water; NRS: Numerical Rating Scale; HPT: Heat Pain Threshold; TSSP: Temporal Summation of Second Pain; PSS: Perceives Stress Scale; HADS: Hospital Anxiety and Depression Scale

Table 2
Distribution of Responders and Nonresponders for Each CPM Paradigm, Percentage of Change and Results of Cohen's d Test for Effect Size for Each of the CPM Paradigms (N = 58).

Paradigm	Responders		Non-Responders		Change % (SD)	Cohen's d
	N	%	N	%		
PPT+PC	38	65.5	20	34.5	27.65 (34.45)	0.535
PPT+CW	38	65.5	20	34.5	27.26 (31.33)	0.541
HPT+PC	28	48.3	30	51.7	5.85 (21.80)	0.194
HPT+CW	23	39.7	35	60.3	4.16 (22.39)	0.087

PPT: Pain Pressure Threshold; PC: Pressure Cuff; CW: Cold Water; HPT: Heat Pain Threshold.

Table 3
ICC Tests Between the 3 Intra-session Measurements of Each Stimulus (Thresholds to the Test Stimulus - PPT or HPT - or to TS during CS - PC or CW -), and NRS for CS in each Combination of Stimuli.

	1st measurement mean (SD)	2nd measurement mean (SD)	3rd measurement mean (SD)	ICC (95% CI)	*p*
Isolated PPT (kgf/cm²)	2.877 (1.109)	2.772 (1.247)	2.715 (1.065)	0.935	<.001
PPT+PC (kgf/cm²)	3.318 (1.049)	3.326 (1.222)	3.265 (1.137)	0.912	<.001
PPT+CW (kgf/cm²)	3.362 (1.241)	3.476 (1.262)	3.299 (1.193)	0.908	<.001
Isolated HPT (C°)	45.253 (3.190)	45.871 (3.043)	46.122 (3.164)	0.943	<.001
HPT+PC (°C)	45.393 (3.732)	46.393 (3.782)	47.172 (3.447)	0.922	<.001
HPT+CW (°C)	45.446 (2.763)	46.039 (3.147)	46.241 (3.231)	0.920	<.001
PPT+PC: Pressure Cuff pain (NRS 0-10)	6.086 (2.406)	6.189 (2.471)	6.233 (2.416)	0.985	<.001
PPT+CW: Cold water pain (NRS 0-10)	6.293 (1.991)	7.052 (2.154)	7.457 (2.179)	0.937	<.001
HPT+PC: Pressure Cuff pain (NRS 0-10)	6.155 (2.469)	6.319 (2.516)	6.439 (2.444)	0.971	<.001
HPT+CW: Cold water pain (NRS 0-10)	6.155 (1.945)	6.776 (2.050)	7.241 (2.109)	0.920	<.001

PPT: Pain Pressure Threshold; PC: Pressure Cuff; CW: Cold Water; HPT: Heat Pain Threshold; NRS: Numerical Rating Scale.

To enable comparison of the effects obtained by each of the CPM paradigms used at the participant level, we classified the participants into responders and non-responders. After that, we calculated the percentage of change (increase in threshold values after the CS), and standardized effect sizes for the different CPMs using Cohen's d (see Table 2).

The results showed that the two CPM paradigms using the PPT as the TS (PPT+PC and PPT+CW) yielded a higher proportion of responders (more than 65%). For the paradigms with HPT as TS (HPT+PC and HPT+CW), the proportion was less than 50%. On the other hand, we found a medium effect size for PPT+PC (.535) and PPT+CW (.541) and a very small effect size for HPT+PC (.194) and HPT+CW (.087).

Intrasession reliability for TS and CS measurements

We checked the intrasession reliability by calculating the ICC for the 3 presentations of the different isolated TS (PPT and HPT), for each of the CPM indices (thresholds) and NRS to the CS (see Table 3). The ICC values (greater than 0.9 and with $p < .001$ in all presentations for both TS) corroborated the excellent reliability of the 3 threshold measures obtained for each TS and for all of the CPM indices.

Reliability and agreement between the different CPM paradigms

We subsequently checked whether the results obtained by the participants in the different CPM paradigms were concordant, performing ICC tests (see Table 4). To enable comparison between the different CPM, we converted the magnitude results to Z-scores. The ICC values showed that all the CPM paradigms, even those using different test stimuli, were significantly associated and that the reliability was at least moderate. The ICC values also showed a high degree of reliability both between CPM indices obtained using PPT as the TS (ICC = 0.911, excellent reliability; $p \leq .001$) and between CPM indices using the HPT (ICC = 0.900, excellent reliability; $p < .001$). Regarding ICC values for CS (NRS 0-10 for pressure cuff or cold water), all comparisons showed good reliability (ICC > 0.75), and the correlation between PPT+PC and HPT+PC (the paradigms using pressure cuff as CS) indicated excellent reliability (ICC = 0.968; $p < .001$).

Finally, we constructed Bland-Altman plots (see Fig. 3) for visual comparison of the agreement between protocols using the same TS but different CS. The related statistics are shown in Table 4. The results indicated agreement between the magnitude of the CPM responses obtained in PPT+PC vs. PPT+CW ($\beta = -0.018$; $p = .895$) and also between those obtained in HPT+PC vs. HPT+CW ($\beta = 0.005$; $p = .969$).

Relationship Between CPM Magnitudes and Participants' Characteristics

Correlation between CPM magnitude and TSSP magnitude, age and sex

We subsequently carried out a series of Spearman's correlation analysis between the CPM magnitudes obtained and the TSSP magnitudes and age of participants. In addition, we carried out a Point-Biserial correlation test between the CPM magnitudes and the sex of the participants. Results of the correlation analysis are presented in Table 5. There were no significant relationships between TSSP, age or sex and any of the CPM paradigms used.

Psychological differences between responders and non-responders to CPM paradigms

The classical and Bayesian one-way ANOVAs carried out to compare responders and non-responders in the questionnaires and anticipatory anxiety NRS found no significant differences (see Table 6).

Discussion

Research in the field of pain management has highlighted CPM as a tool for assessing the functionality of endogenous pain modulation pathways (Granovsky, 2013; Lewis et al., 2012). However,

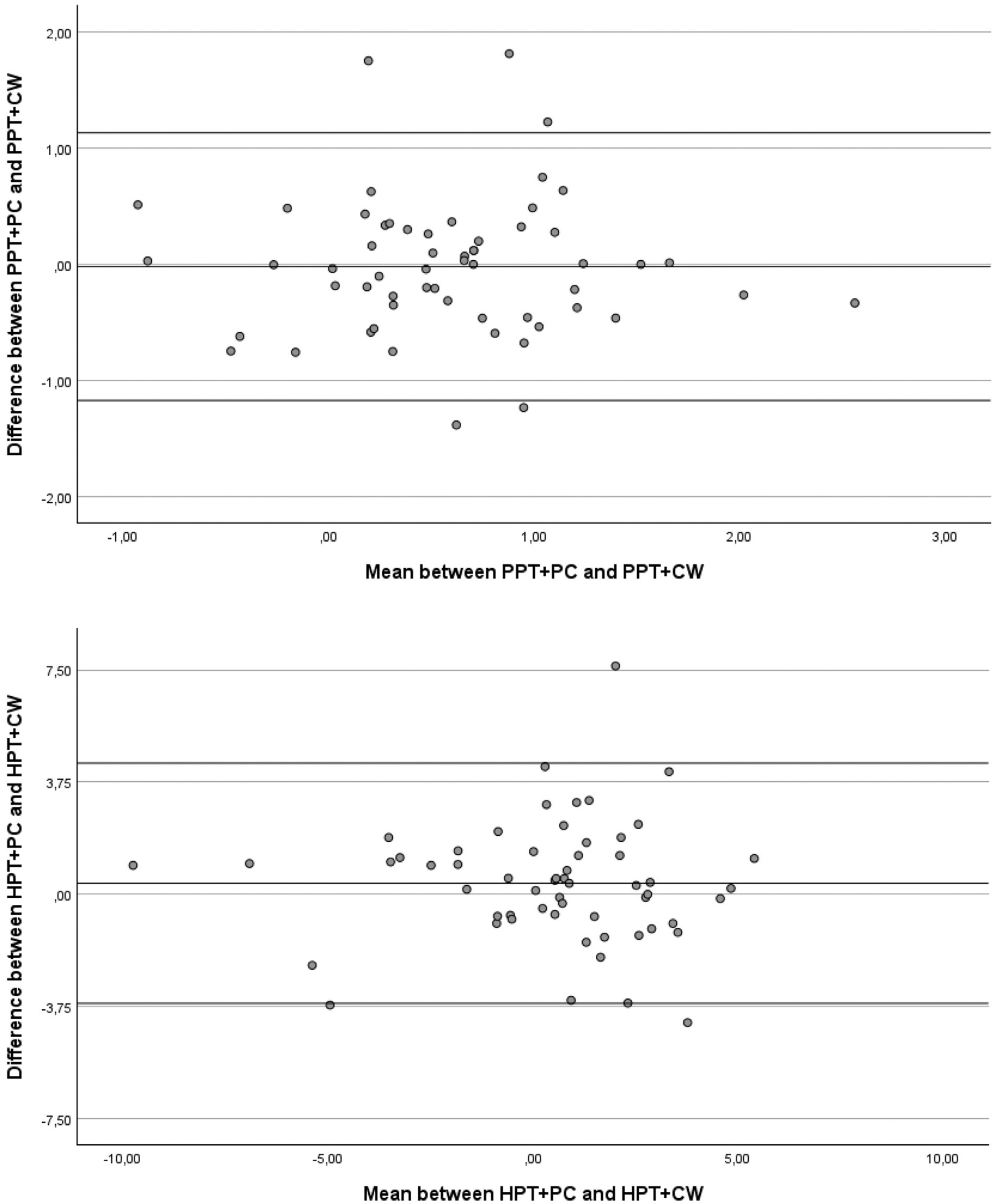

Figure 3. Bland-Altman plots for PPT+PC and PPT+CW (upper, in Kg/cm2) and HPT+PC and HPT+CW (bottom, in C°).
PPT: Pain Pressure Threshold; PC: Pressure Cuff; CW: Cold Water; HPT: Heat Pain Threshold.

Table 4
ICC Results for the Pairwise Comparison Between Scores Obtained in the Different CPM Paradigms, Limits of Agreement (LOA), Simple Linear Regression and Beta Scores for CPM Paradigms Paired by TS.

Comparison	CPM Magnitudes (Z Scores)		CS Ratings (NRS 0-10)				
	ICC (95% CI)	*p*	ICC (95% CI)	*p*			
PPT+PC vs. PPT+CW	0.911	<.001	0.806	<.001			
PPT+PC vs. HPT+PC	0.576	<.001	0.968	<.001			
PPT+PC vs. HPT+CW	0.579	<.001	0.788	<.001			
PPT+CW vs. HPT+PC	0.544	.002	0.796	<.001			
PPT+CW vs. HPT+CW	0.583	<.001	0.861	<.001			
HPT+PC vs. HPT+CW	0.900	<.001	0.809	<.001			
	Mean of difference (SD)	LOA	R	R square	F	Sig	Standardized β
PPT+PC−PPT+CW	−0.019 (.587)	1.151	0.018	.000	0.017	0.895	−0.018
HPT+PC−HPT+CW	0.374 (2.047)	4.012	0.005	.000	0.002	0.969	−0.005

PPT: Pain Pressure Threshold; PC: Pressure Cuff; CW: Cold Water; HPT: Heat Pain Threshold.

Table 5
Correlation of the Different CPM Paradigms With TSSP Magnitude, Age and Sex.

	Spearman's				Point-Biserial	
	With TSSP		With Age		With Sex	
	r	*p*	r	*p*	r	*p*
PPT+PC	−0.193	.147	0.037	.785	−0.051	.704
PPT+CW	0.075	.578	−0.038	.781	−0.220	.097
HPT+PC	−0.017	.901	−0.039	.776	0.190	.153
HPT+CW	−0.130	.331	0.005	.970	0.055	.683

PPT: Pain Pressure Threshold; PC: Pressure Cuff; CW: Cold Water; HPT: Heat Pain Threshold; TSSP: Temporal Summation of Second Pain.

Table 6
Classical and Bayesian One-Way ANOVA Results for the Questionnaires After Established Groups Based on Being a Responder or Nonresponder to the Different CPM Protocols

	Responder Vs Non-Responder											
	PPT+PC			PPT+CW			HPT+PC			HPT+CW		
	F	*p*	BF_{10}	F	*p*	BF_{10}	F	*p*	BF_{10}	F	*p*	BF_{10}
PSS	0.505	.482	0.396	0.109	.743	0.349	0.814	.373	0.440	2.298	.138	0.778
HADS-A	2.504	.120	0.785	0.035	.853	0.288	1.166	.285	0.444	0.873	.354	0.403
Anticipatory anxiety	2.078	.155	0.653	2.078	.155	0.653	0.040	.843	0.275	0.103	.749	0.286

PPT: Pain Pressure Threshold; PC: Pressure Cuff; CW: Cold Water; HPT: Heat Pain Threshold; PSS: Perceives Stress Scale; HADS: Hospital Anxiety and Depression Scale.

a wide variety of CPM protocols are used, and the discrepancies in the results observed in clinical populations may be attributed to methodological differences (Popescu et al., 2010; Nahman-Averbuch et al., 2016; Fernandes et al., 2019). Personal characteristics, both demographic and psychological, have also been observed to influence the results of quantitative sensory testing (Riley III et al., 2010; Valencia et al., 2013; Hermans et al., 2016; Nahman-Averbuch et al., 2016; Khan et al., 2018; Hackett et al., 2020). We therefore aimed to study the sensitivity and reliability of four commonly used CPM paradigms, and its relation to TSSP testing and to sociodemographic (age and sex) and psychological variables (anxiety and stress). The study was conducted with a sample of 58 healthy individuals aged between 25 and 65 years.

Our first objective was to test which CPM paradigm produced the largest increase in pain threshold after the CS and the greatest number of CPM responders (i.e. people with efficient pain modulation). To this end, we selected the test stimulus (TS) and conditioning stimulus (CS) most widely used in previous studies, and we established 4 TS+CS combinations: PPT + PC, PPT + CW, HPT + PC and HPT + CW. The study participants performed all tests and were subsequently classified as responders if the magnitude of their CPM response was above the threshold SD range for the TS. We found that the protocols that used pressure pain as TS produced the highest number of responders and larger effect sizes, and CPM paradigms using heat as the TS both produced smaller percentage of responders and effect sizes. This result suggests that CPM paradigms using pressure pain as TS may be more sensitive for assessing descending pain inhibition; indeed, pressure is the most widely used TS (Nuwailati et al., 2022). Regarding the CS, the paradigms using pressure cuff produced a slightly higher percentages of responders than those using cold water, but the difference was not significant. These results contradict those of many previous studies indicating the superiority of cold water in inducing the CPM effect (Ramaswamy & Woodehouse, 2021). The inconsistent results across studies may be due to the wide range of temperatures used for cold water as a CS in the studies in this field (Nuwailati et al., 2022) or even to inter-individual anatomical, perceptual or psychological differences.

We then tested the agreement between the 3 different TS measures recorded within sessions and between NRS ratings of the CS, by calculating intra-class correlations (ICC). All TS measurements, both those presented without and with CS, showed high within-session reliability as previously observed (Wylde et al., 2011; Imai et al., 2016; Nuwailati et al., 2022). Notably, the ICCs for all of the HPT related measures were slightly higher. This could be explained by the fact that execution of the PPT test relies on a trained researcher, who must keep the upward pressure within a certain range for the test to be considered correctly conducted.

This adds extra, inevitable variability that does not exist in the HPT test, which is performed automatically by a thermal stimulator. Likewise, for the NRS ratings related to the CS exposure, we also found excellent reliability in line with previous studies (Lewis et al., 2012; Kennedy et al., 2020). We also checked the reliability comparing the agreement between each pair of CPM protocols using ICC. The protocols using the same type of TS yielded stronger significant correlations, showing excellent reliability. A high level of agreement between the magnitudes was also observed, as can be seen in the Bland-Altman plots elaborated.

We also attempted to examine the relationship between the CPM indices and the TSSP effect. The Spearman's correlations were not significant in any case, suggesting the relative independence of pronociceptive and antinociceptive mechanisms, even though they share neural regions as the PAG or RVM (Fields, 2005; Staud et al., 2008, Denk et al., 2014, Potvin & Marchand, 2016) and both have been found to be altered in different chronic pain conditions (Potvin & Marchand, 2016; Fingleton et al., 2017; McPhee et al., 2020; Staud et al., 2021; Ramaswamy & Wodehouse, 2021; Zabala-Mata et al., 2021).

We also investigated whether the age and sex of the participants were associated with the CPM protocol. We found no significant correlation between the age of participants and the CPM effect, in line with some previous studies (Ibancos-Losada et al., 2020; Mertens et al., 2021) but contradicting others that reported a decline in the efficiency of pain modulation mechanisms over time (Riley III et al., 2010; Khan et al., 2018; Hackett et al., 2020). Similarly, there was no significant correlation between sex and the results obtained for any of the CPM protocols. This appears to contrast with previous evidence indicating higher CPM magnitudes in men (Hermans et al., 2016; Riley III et al., 2020) and a less efficient and stable CPM in women (Valencia et al., 2013; Hermans et al., 2016), although it has recently been argued that these differences do not appear consistently (Umeda & Okifiji, 2023; Uzawa et al., 2024).

On the other hand, we did not find significant differences between CPM responders and non-responders for anxiety/stress indices. However, previous studies with healthy participants found evidence of a relationship between higher scores of anxiety and greater heat pain (administered with a laser) during a CPM with heterotopic cold stimulation (Bogdanov et al., 2015). Additionally, a meta-analysis by Nahman-Averbuch et al. (2016) found that using pressure-based CPM (algometer + cold water) was associated with higher levels of anxiety and a more efficient CPM response. Regarding stress, a recent study by Mertens et al. (2020) reported a significant effect on pain sensitivity, with an increase in PPT and a decrease in pressure-based CPM efficacy (with pressure cuff as CS). These discrepancies may suggest the existence of specific connections between some of the psychological factors assessed and the effects caused by the stimulation sets used in the CPM paradigms, as the different characteristics could lead to variations in the inhibitory mechanisms triggered (Nahman-Averbuch et al., 2016).

The above results must be interpreted in regard to the limitations of the study. First, we used a sample that is unbalanced by sex, with only 36.2% of the sample being male. Although this imbalance may affect the results obtained, this variable was not significantly correlated with CPM. It would be interesting in future studies to check whether some CPM paradigms are more suitable depending on the sex of the participants, to optimize the protocols. On the other hand, despite the excellent reliability of the 3 manually controlled PPT measurements both before and during CS, as well as the strong agreement in the CPM index using these measures, we believe this method relies too heavily on the skill of trained researchers. Therefore, future studies should investigate the consistency of results obtained by different researchers, or even consider the inclusion of measures such as computer-controlled cuff-algometry (cPPT), which could maintain the reliability of the results while precluding any possible human-dependent variability in application. We also used pain threshold measurements as test stimuli, but it would be interesting to explore CPM using pain tolerance indices or fixed supra-threshold values and to stimulate other body areas (Ramaswamy & Wodehouse, 2021). Also, we used an individually adjusted temperature of 5 out of 10 for the TSSP stimulus. Given the difficulty in rating painful stimuli, more thorough training should perhaps be done to adapt the temperatures used more accurately to individuals and to explore the possible relationship between antinociceptive and pronociceptive mechanisms. Lastly, we used a sample of healthy participants, as our main objective was to test the sensitivity and reliability of the CPM paradigms. This decision avoided possible alterations in the results caused by altered pain modulation in chronic pain patients but limits the extrapolation of the results to this population. Future studies should test QST assays in clinical samples.

Clinical Implications

Since CPM has been proposed as a diagnostic and prognostic biomarker for chronic pain, it is important to have QST assessment procedures with good reliability. All the CPM indices obtained from the 4 different paradigms used in the present study with healthy individuals showed good reliability. It is necessary to advance in the construction of a large database with standardized values to enable the clinical use of CPM for diagnosis and prognosis purposes.

Conclusion

In summary, the study findings showed that the different effects of CPM could mainly depend on the type of test stimulus used. Thus, paradigms using PPT as the TS produced more responders (more than 65%) and a greater size effect, while those using HPT produced less than 50% of responders. The paradigms using pressure cuff as the CS produced more responders than the ones using cold water, although the difference was was not significant. The intra-session reliability between the 3 measurements of each TS was excellent, as was the reliability between the 4 CPM paradigms used. There seems to be relatively good agreement between the magnitudes obtained with CPMs using PPT as TS (PPT+PC and PPT+CW) and between those obtained with HPT as TS (HPT+PC and HPT+CW).

In addition, we found that the antinociceptive mechanisms reflected by the CPM might not correlate with the results obtained for the pronociceptive TSSP, which could indicate a certain degree of independence in these mechanisms, even though they share neural regions. Neither age nor sex were related to the magnitude of any of the CPM paradigms used. There was also no clear psychological responder profile for any of the paradigms, as there were no significant differences between responders and non-responders for any of the questionnaires and scales used for assessing anxiety and stress.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Antonio Gil-Ugidos: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Lara Rubal-Otero:** Writing – review & editing, Investigation, Data curation. **Alberto González-Villar:** Writing – review & editing, Methodology. **María Teresa Carrillo-De-la-Peña:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Conceptualization.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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