Is conditioned pain modulation (CPM) a useful paradigm in women? A TRiPP study exploring CPM in pain-free women and those living with chronic pelvic pain

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Introduction

Conditioned pain modulation (CPM) is a frequently used paradigm which assesses the function of descending inhibitory pain pathways. We performed CPM in a cohort of women as part of the Translational Research in Pelvic Pain (TRiPP) project and hypothesised that we would see effective CPM in all healthy control participants, but only in a subset of those with chronic pelvic pain (CPP).

However, there are many variables which may influence the CPM response and contribute to variation between studies[1]. Recent work investigating the reliability of the CPM paradigm in healthy participants demonstrated poor intra- and intersession reliability of within-subject CPM[2]. Additionally, to account for measurement error within the paradigm, a threshold of 2 x standard error of measurement (SEM) was proposed to determine a 'true' CPM effect.

In addition, we investigated serotonin abundance with respect to the CPM response. Serotonin abundance has previously been associated with CPM inhibition in participants with chronic low back pain, and may in part facilitate our understanding of the mechanisms underlying CPM.

This study aims to:

1. Calculate the SEM of the CPM response, to determine how many participants (n,%) had a true CPM effect
2. Assess the intrasession reliability of the CPM effect
3. Further investigate known factors which may contribute to the CPM effect in healthy controls

Methods

Participants: Women between ages 18-50 years old, from one of three TRiPP study sites (Oxford, UK; Porto, Portugal; Boston, USA, REC Reference: 19/TH/0030)

Questionnaires: Participants completed a brief questionnaire which included questions about pain, mood, current medications used and comorbidities. Questionnaires were completed at a dedicated study visit just prior to the conditioned pain modulation paradigm

Conditioned pain modulation paradigm: A pressure algometer test stimulus (TS) was applied to the dorsal foot three times and a mean was calculated. An ischemic pressure cuff conditioning stimulus (CS) was applied to the left arm until painful, and maintained for 60 seconds prior to deflating the cuff and repeating the TS. Stimuli were applied sequentially.

Serotonin abundance and rs255531: Serotonin relative abundance was quantified using Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy by Metabolon Inc[3] in two batches with pooled plasma matrix used as a control. Log[2] transformed abundance was used in analysis. To determine rs25531 expression, Plasma serum samples were genotyped using Illumina Global Screening Array (38 samples) and earlier genotyping experiments (Affymetrix Axiom - 2 samples, Affymetrix Precision - 3 samples) of biobanked samples.

Statistical analyses: CPM effect was calculated as the percentage change, and absolute difference in pressure pain threshold (PPT). A +/-2SEM threshold was calculated for controls. Individual CPM effect for pain and control participants was compared against this threshold and categorised as non-responders, inhibitory (+2SEM) or facilitatory (-2SEM) responders accordingly. Intra-session reliability of the CPM effect was determined using the kappa statistic. Continuous variables were assessed for normality using the Shapiro-Wilks test. Differences between pain and control groups were analysed using an unpaired t-test. Differences in demographic and pain data were compared between responder groups using the Kruskal-Wallis test. Data from all women with CPP were amalgamated into a single group as we had no prior evidence to suggest differences in CPM between the CPP subgroups. Data were analysed using PRISM 9.

Results

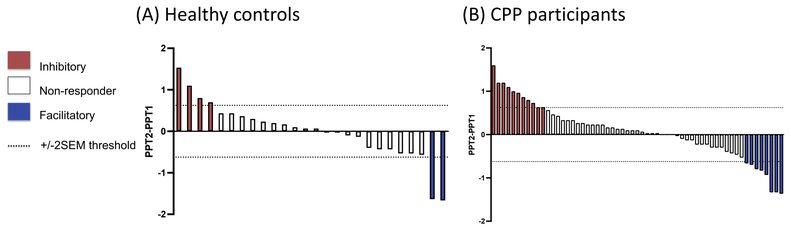
- CPM was performed on 85 women; n=59 with CPP and n=26 healthy controls
- No significant difference in median age between groups (p=0.124)

Participant characteristics and CPM parameters

Table 1. (A) Participant characteristics CPP; chronic pelvic pain participants. IQR; interquartile range. CPM; conditioned pain modulation. (B) CPM parameters by pain group. kPA;kilopascals, IQR;interquartile range

Characteristic	CPP (n=59)	Controls (n=26)	p-value
Age (median, IQR)	34 (13)	29.5 (12.5)	0.124
Pain rating before CPM paradigm	2 (4)	0 (1.5)	0.0336
Change in PPT (after CS (u, SD)			
Absolute (kPA)	0.47 (0.413)	0.5 (0.483)	
% Change (%)	12.74 (15.08)	11.88 (11.12)	0.795
Ischaemic pain rating (Median, IQR)	5 (5)	3 (3)	0.0070
Pressure (mmHg) of CS (u, SD)	202.5 (63.49)	161.9 (40.10)	0.0036

Conditioned pain modulation effect using +/-2SEM threshold



Relationship between CPM response and mood in healthy controls

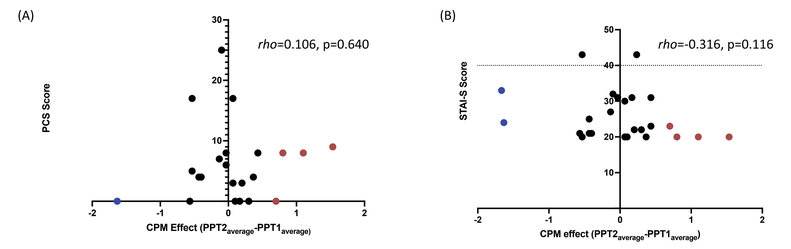


Figure 3. (A) Pain catastrophizing scale score by CPM effect in healthy controls, and (B) STAI-State scores by CPM effect in healthy controls

Comorbidities and Medications by CPM response in healthy controls

Comorbidities	Inhibitory (n=4)	No-response (n=20)	Facilitatory response (n=2)
Anxiety requiring medication or therapy	3 (75)	5 (25)	1 (50)
Depression requiring medication or therapy	1 (25)	4 (20)	0
Number (%) with at least one diagnosis	4 (100)	11 (55)	2 (100)
Common medications			
Anti-depressants/mood stabilisers	2 (50)	6 (30)	0
Anti-histamine	0	5 (25)	0
Number (%) using hormonal contraception	3 (75)	8 (40)	1 (50)
Number (%) taking at least one medication	1 (25)	5 (25)	0

Serotonin abundance by CPM response

- Median (IQR) time between sample collection and CPM paradigm was 4.34 (1.9 years)
- Only a weak negative correlation was found between plasma serotonin and CPM inhibition in the entire cohort
- No significant difference in rs25531 single nucleotide polymorphism between CPM response groups

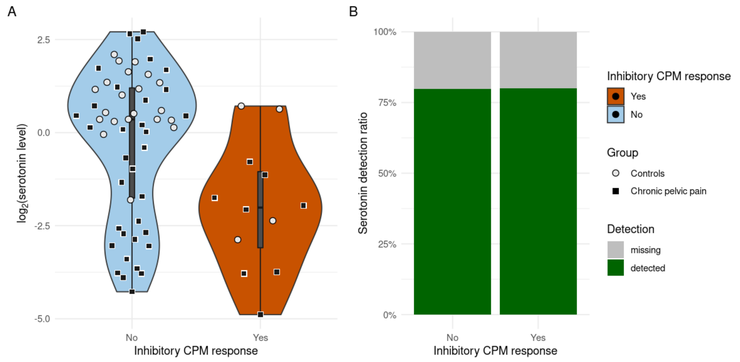


Figure 4. (A) Serotonin abundance and (B) detection ratio (%) by CPM response status

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Conclusions

- There was no significant difference in the CPM response (PPT2-PPT1) between CPP and control participants
- Using a robust statistical approach, only 23.1% of healthy control participants had a 'true' CPM effect
- Upon investigation, no single covariate could explain why so few healthy control participants exhibited in tact CPM
- Although not formally assessed, many participants found the CPM paradigm unpleasant, particularly amongst a battery of other psychophysical pain testing (i.e. QST, ANS)
- A more detailed understanding of the value of CPM in women is needed to justify its continued use in clinical studies

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