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Published in:
Scandinavian Journal of Pain

DOI (link to publication from Publisher):
10.1515/sjpain-2021-0025

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

Original Experimental

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https://doi.org/10.1515/sjpain-2021-0025
Received February 1, 2021; accepted April 22, 2021;
published online May 27, 2021

Abstract

Objectives: The literature on conditioned pain modulation (CPM) is inconclusive in relation to low-back pain and it is unclear how CPM affects temporal summation as a proxy of central pain integration. The aim of this study was to examine whether the CPM effect would be different on pain induced by temporal summation than single stimuli in a group of low back pain patients.

Methods: A total of 149 low-back pain patients were included. CPM was examined using single, repeated and temporal summation (repeated-single difference) of mechanical pressure pain as test stimuli at an individualized, fixed supra-pain-threshold force, before and after 2 min of cold pressor test (0–2 degrees Celsius). Participants were categorized as CPM responders or non-responders according to three different criteria: *simple* (any pain inhibition), *strict* (pain inhibition of more than 10VAS) and *reversed* (pain inhibition or facilitation of less than 10VAS). Clinical data on back pain was collected for correlation and descriptive purposes.

Results: Significant modulation was observed for all three test stimuli. Effects sizes were comparable in relative terms, but repeated pressure pain modulation was greater in absolute terms. No correlations to clinical data were observed, for any measure.

Conclusions: The current data suggests that repeated pressure pain may be better suited as the CPM test stimuli, than single pressure pain and temporal summation of pressure pain, as the CPM effect in absolute terms was greater. Employing temporal summation as the test stimulus in a CPM paradigm may be more sensitive than a single test stimulus.

Keywords: chronic pain; diffuse noxious inhibitory control; low back pain; pain measurement; pain threshold; postsynaptic potential summation.

Introduction

The *Conditioned Pain Modulation* (CPM) test paradigm quantifies the pain-inhibits-pain effect of an intense conditioning stimulus on a test stimulus. CPM is considered a reflection of brainstem mediated, diffuse descending inhibition of nociception [1] and as such may play a role in clinical pain conditions.

The literature on CPM in clinical cohorts seems more disparate than that of simpler *Quantitative Sensory Tests* (QST) and controversies exist in the field of low-back pain. A recent systematic review of QST in *Low Back Pain* (LBP) [2] found that *Pressure Pain Thresholds* (PPT) were almost uniformly lower compared to healthy controls. By contrast, group differences in CPM effects were found in two [3, 4] out of four studies. Differences in CPM effects have been reported within LBP populations and Gerhardt et al. [5] speculate that it "might be because many patients with [chronic low back pain] report pain in further areas of the body, and altered CPM might influence spatial extent of pain rather than chronic back pain per se."

The reliability of CPM tests has been reported as good or excellent but "is heavily dependent on stimulation parameters and study methodology" [6] and Martel et al. [7] reported important differences in the temporal stability of

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CPM responses between the sexes. Despite concerns about the robustness of CPM, it arguably could have important clinical relevance. Although LBP is a heterogeneous diagnostic group, widespread hyperalgesia and painful comorbidity are common findings [2, 8], which arguably could result from such attenuated CPM effects.

Most CPM procedures employ a simple test stimulus such as the detection threshold of pressure pain or heat pain. Perhaps more complex testing stimuli which rely on spinal integration of noxious stimuli could have different sensitive to CPM effects than simpler stimuli. Temporal summation is one such complex pain test, reflecting an additive or facilitatory effect of repeated stimuli on wide-dynamic range (WDR) neurons in the spinal dorsal horn [9]. The descending noxious inhibition which CPM test procedures are intended to induce are also believed to affect the WDR neurons, albeit in an inhibitory fashion [10]. Temporal summation and CPM thus likely exert opposing effects on the WDR neurons. As TS of pain is typically perceived as more painful than single stimuli, the CPM could arguably be more pronounced on TS, although this is uncertain.

Little has been published on the CPM effect on complex pain stimuli like TS in humans, and two smaller human volunteer studies reported conflicting findings. Holden et al. [11] found no CPM effect on TS, whereas Sirucek et al. [12] did. Attenuated descending pain inhibition could be an explanation for widespread increased pain sensitivity in chronic low back pain patients. To our knowledge no studies have been published on CPM effects on TS in a clinical population.

The present study investigated the CPM effect on three different test stimuli: Single- and repeated pressure pain intensity and temporal summation of pressure pain intensity.

The hypothesis was that the CPM effect would be different on pain induced by temporal summation compared to single stimuli. Secondarily, we examined whether being a CPM responder or non-responder was associated with clinical pain measures.

Methods

A cross-sectional, experimental study of a consecutive, convenience sample of low back pain patients. The study was approved by the Regional Committee on Health Research Ethics, Denmark (ref. number S-20180098).

Participants

All patients referred between February and October (2019) to the Spine Center of Southern Denmark, Lillebaelt Hospital with low back pain as the primary complaint were invited to participate in the study. The Spine Center of Southern Denmark is a large regional spine-care unit which attends to patients on referral from other hospital departments and general medical practitioners, chiropractors and medical consultants in private practice.

Inclusion criteria were: 18+ years of age, ability to speak and understand Danish, referred with a primary complaint of low back pain (defined as dorsal pain, muscle tension, or stiffness localized below the lower costal margin and above the inferior gluteal folds, with or without sciatica), a completed SpineData questionnaire [13], written consent for the use of SpineData for research, and no severe psychiatric disorders.

Patients were excluded from the study if they later withdrew their consent for participation, if the experimental procedure was not tolerated, or in the event of unexpected technical difficulties.

Descriptive and clinical data

Descriptive and clinical data was collected using an electronic, online questionnaire (SpineData). Descriptive data included age, sex, height and weight. Clinical data included current LBP intensity, worst and average LBP intensity over the last 14 days (0–10 Visual analog scale), pain area (quantified from digital pain drawings as *convex hull polygons* [14]) and LBP duration [13].

QST protocol

Participants were assessed by a research assistant trained in performing a standardized QST test protocol. The current study represents a pre-planned limited analysis of data collected as part of a larger QST test battery. An overview of the complete QST test protocol will be published elsewhere.

For the current analyses, the following QST data were included (see Figure 1):

Pressure pain threshold: Participants were instructed to point out the most clinically painful area or the center of clinical pain in the lower back. Pressure was applied just lateral to the midline at that segment, on the most painful side. Patients unable to identify a most painful area, were tested at the L4 segment. If a patient could not identify a most painful side, pressure was applied on the dominant side.

A series of 10 custom built, spring-loaded pressure probes were used to apply pressure for assessment of pain threshold and intensity with single and repeated pressure. The probes were constructed in a manner to allow for precise calibration by increasing or decreasing the pre-tension of the steel spring. The 10 probes were calibrated using a digital weighing cell mounted in a test-bench, to apply pressure from 1 to 10 kg in steps of 1 kg. The probe contact surface was flat, circular with an area of 1 cm^2, had slightly rounded edges and were covered in 2 mm thick hard foam material. Pressure was increased smoothly over approximately ½ s, perpendicular to the skin, and maintained for approximately 1 s, before being discontinued.

Participants were instructed to indicate verbally whether an applied stimulus was perceived as painful or non-painful and the pressure pain threshold was determined using a 'split-middles' approach: Initially the 5 kg probe was applied. If the participant perceived this as being non-painful, the middle probe of the heavier probes (6–10 kg) was used (7.5 kg rounded up to the 8 kg probe). If the

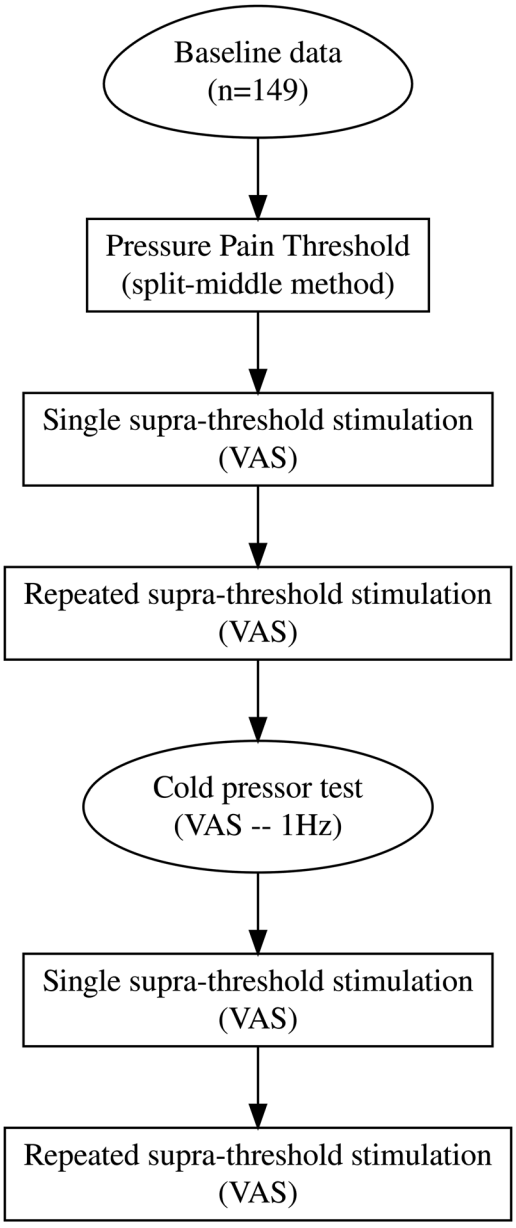

Figure 1: Study flow diagram.

8 kg probe was perceived as painful, the middle probe of the lighter probes (6–7 kg) was used (6.5 rounded up to the 7 kg probe). Conversely, if the participant perceived the initial 5 kg stimuli as painful, the middle lighter probe (1–4) was applied (2.5 kg rounded up to 3 kg). PPT was determined as the smallest pressure perceived as painful by the participant. Two trials were performed and the mean was calculated (mPPT).

Conditioned pain modulation test stimuli: Test stimuli consisted of mechanical pressure pain intensity, quantified using an electronic visual analogue pain scale (0–100 VAS), anchored as 'No pain' and 'Worst pain imaginable' at either end, and quantified numerically as integers between 0 and 100.

For test stimuli, the individual mean pressure pain threshold (mPPT) rounded up to nearest probe plus 1 kg (max 10 kg) was used. Thus, pain intensities were tested using a supra-threshold stimulus.

Three different test stimuli were quantified: Pain intensity with a *single stimulation*, *repeated stimulation* and *temporal summation*.

Initially, a single stimulation of 1 s of mechanical pressure was applied and the participant indicated pain intensity on the electronic VAS – this was recorded as Single Stimulation pain intensity. After a short pause (10 s), 10 repeated stimulations of 1 s duration (with 1 s intervals) were applied and the participant indicated pain intensity on the VAS as it changed over time – the VAS recording at the final stimulation was recorded as Repeat Stimulation pain intensity. An illustrative video of the test procedure (with a different pressure probe and test site) is available at http://www.smerteforskning.dk/videolicens/TS.mp4.

Temporal summation (TS) was calculated as the difference between repeated and single stimuli: $TS = VAS_{stim10} - VAS_{stim1}$, i.e. positive numbers for an increase in pain intensity and vice versa.

Cold-pressor test: *Cold Pressor Test* (CPT) was used as the conditioning stimulus.

A 5 L water container was kept refrigerated at 0–2 °C (Mobicool C40; Dometic WAECO, Dubai, United Arab Emirates), with the temperature monitored using a thermometer. Water was kept circulating using a submersible pump (Barvig Tauchpumpe model 03, 12 V, 0.6 bar, 12 L/min). Participants were instructed to immerse their non-dominant, non-clenched hand to the wrist in the circulating water and to keep their hand immersed for 2 min, or until the pain became unbearable.

CPT pain was assessed continuously using an electronic (0–100) VAS with a frequency of 1 Hz. The CPT pain data was stored electronically and summarized as Cold Pain Detection Threshold (time from immersion to first VAS>0), Maximum Cold Pain Intensity (maximum VAS recorded), Time to Maximum Cold Pain Intensity (time from immersion to first maximum VAS recorded) and Area Under the Curve (Sum of VAS over immersion time).

Conditioned pain modulation: Pain responses to single and repeated stimuli were assessed at baseline and again immediately following completion of the CPT.

Conditioned pain modulation (CPM) was calculated as the difference between pressure pain intensity before and after the cold-pressor test, for both single and repeated stimuli and temporal summation. The CPM was calculated as $CPM = VAS_{after} - VAS_{before}$, i.e. positive numbers for an increase in pain intensity and vice versa.

The change in pain sensitivity (CPM response) is a continuous variable with no obvious or *natural* cut-off point for defining CPM responders and non-responders. Therefore, participants were categorized as CPM *non-responders* (and by inference as CPM *responders*) in relation to both *Single* and *Repeated stimuli* as well as *Temporal summation* by three different criteria: A *simple* criteria in which no change or any increase in test stimulus pain intensity ($CPM \geq 0$) was categorized as a CPM non-response. A *strict* definition in which only an increase of 10 VAS or more was categorized as a CPM non-response ($CPM \geq 0$). And a *reverse* definition in which any increase or even a small drop in VAS ($CPM \geq -0$) was categorized as a CPM non-response.

QST instructions

The participant information about the QST procedures followed a fixed, pre-authored manuscript, which is available (in Danish) on request.

Data management

Study data were collected and managed using REDCap electronic data capture tools hosted by 'Open,' a research support initiative in the Region of Southern Denmark. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [15, 16].

Statistical analyses

Comprehensive summary statistics of QST data and descriptive variables are presented as both parametric and non-parametric data. Distribution of QST data are presented as density plots.

The assumptions of homoscedasticity and normality of residuals for a two-way, repeated-measures ANOVA test were not fulfilled by the data. Most likely this is a result of the nature of the visual analogue pain scale, which is bounded at both ends, resulting in left-skewed data.

Instead data is presented visually and analyzed using non-parametric tests, which do not permit for analysis of variance or interactions and have less power.

Distributions are presented graphically as *density plots*. Density plots can be thought of as histograms which have been *smoothed out* and have the benefit of not being affected by the arbitrary number of bins used in histogram plotting. Also, density plots allow for simultaneous, comparative presentation of several distribution plots without obscuring overlaying plots.

CPM responder/non-responder group differences in clinical variables were analyzed non-parametrically (Wilcoxon test). Comprehensive summary statistics thereof are provided in appendix.

Results

Descriptive summary statistics

A total of 149 patients participated in the study (60 women, and 89 men).

Descriptive data is summarized in Table 1. A frequency table of clinical ICD10 diagnoses (primary and secondary) are presented in Appendix. The most common diagnoses were *Low back pain*, *Muscle strain*, *Lumbago with sciatica*, *Lumbar and other intervertebral disc disorders with radiculopathy*, *Other spondylosis*, *Spinal stenosis*, *Other spondylosis with radiculopathy* and *Other biomechanical lesions*.

Summary statistics of QST

The median pressure probe employed for CPM test stimuli was the 8 kg probe (individual pressure pain threshold + 1 kg) (n=149, median=8, q1=6, q3=10, min=3, max=10).

Distributions of pain intensity (VAS) with single and repeated pressure stimulation before and after CPM are illustrated in Figure 2 as density plots.

Summary statistics of quantitative sensory testing is presented in Tables 2 and 3.

CPM and TS effects

Two-way repeated measures ANOVA (Pillai statistic) indicated statistically highly significant effects of both TS, CPM and their interaction. However, as described in the Method section, the underlying assumptions of ANOVA were not fulfilled.

Table 1: Clinical data.

Variable	n	Min	Max	Median	q1	q3	IQR	Mad	Mean	SD	SE	CI
Age, years	149	21	81	58.0	45.00	69.0	24.00	17.79	55.99	15.13	1.24	2.45
Current LBP, VAS	145	0	10	5.0	4.00	7.0	3.00	2.96	5.23	2.53	0.21	0.42
Typical LBP, VAS	142	0	10	7.0	5.00	8.0	3.00	1.48	5.95	2.44	0.20	0.41
Worst LBP, VAS	145	0	10	8.0	6.00	9.0	3.00	1.48	7.11	2.69	0.22	0.44
Pain area (pixels)	149	0	25,212	1,433.0	522.00	3,428.0	2,906.00	1,690.16	3,123.64	4,437.25	363.51	718.35
Duration, days	144	0	11,355	365.0	120.75	1834.5	1713.75	449.23	1,410.35	2,261.85	188.49	372.58
Height, cm	146	155	200	175.0	169.00	182.0	13.00	10.38	175.53	9.26	0.77	1.51
Weight, kg	146	44	143	83.5	74.00	96.0	22.00	17.05	85.01	17.35	1.44	2.84

Summary of descriptive and clinical data. q1=first (25%) quartile, q3=third (75%) quartile, IQR, inter-quartile range; MAD, median absolute deviation.

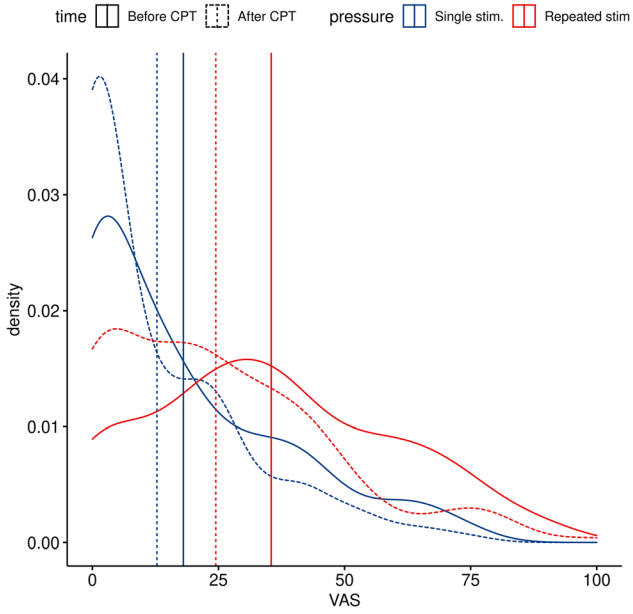

Figure 2: Density plot (smoothed histogram) of pain scores (VAS) for mechanical pressure pain, before/after cold pressor test and with single/repeat stimulation. Vertical lines represent mean values.

Unpaired, single-sample Wilcoxon rank-sum test (mu=0) support significant effects of both Temporal Summation and Conditioned Pain Modulation. See Table 4.

Unpaired, single-sample Wilcoxon rank-sum test (mu=0) support significant effects of both Temporal Summation and Conditioned Pain Modulation. See Table 4. Significant differences in the CPM effect was observed when comparing single and repeated stimuli (Paired Wilcoxon test, p<0.0001) and when comparing repeated stimuli to temporal summation (Paired Wilcoxon test, p<0.0001), but not when comparing single stimulus to temporal summation (Paired Wilcoxon test, p≥0.05). Similarly, a significant difference in the effect of temporal summation was observed before/after CPM (Paired Wilcoxon test, p<0.0001).

Figure 3 illustrates the distribution of the CPM effect for both single and repeated (TS) stimulation. As evident from Table 4, a significant CPM effect was observed for both test stimuli.

Similarly, Figure 4 illustrates the distribution for the TS effect on pressure pain before and after CPM. As evident from Table 4, a significant TS effect was observed at both points in time.

The effect of Temporal Summation was found to be significantly attenuated after CPT (paired Wilcoxon test, p<0.0001), with the mean TS effect dropping from 17.42 δVAS to 11.67 δVAS.

Effect size

The mean CPM effect of cold-pressor pain on single pressure pain was −5.24 (VAS) (Table 4), corresponding to −29% of mean single pressure pain intensity before CPT (Table 2).

Similarly, the mean CPM effect of cold-pressor pain on repeated pressure pain was −10.99 (VAS) (Table 4), corresponding to −31% of mean repeated pressure pain intensity before CPT (Table 2).

Lastly, the mean CPM effect of cold-pressor pain on TS was −5.75 (VAS) (Table 4), corresponding to −33% of mean TS effect before CPT (Table 4).

Table 2: QST data.

Stimulus	Setting	n	Min	Max	Median	q1	q3	IQR	MAD	Mean	SD	SE	CI
Single stim.	Before CPT	149	0	74	12	1	31	30	17.79	18.04	19.71	1.61	3.19
	After CPT	149	0	74	4	0	22	22	5.93	12.80	16.60	1.36	2.69
Repeated stim.	Before CPT	149	0	93	33	19	53	34	28.17	35.46	24.01	1.97	3.89
	After CPT	149	0	100	22	5	37	32	25.20	24.47	21.80	1.79	3.53

Summary statistics of raw data: Experimental pressure pain intensity (VAS) grouped by test stimulus and setting. q1=first (25%) quartile, q3=third (75%) quartile, IQR, inter-quartile range; MAD, median absolute deviation; CPM, conditioned pain modulation; CPT, cold-pressor test; TS, temporal summation.

Table 3: Cold-pressor test.

CPT measure	n	Min	Max	Median	q1	q3	IQR	MAD	Mean	SD	SE	CI
AUC (VAS × sec)	149	0	10,162	3,728	1,532	6,305	4,773	3,426.29	4,011.28	2,789.00	228.48	451.51
Max VAS, VAS	149	0	100	87	70	100	30	19.27	79.62	23.22	1.90	3.76
Time, sec	149	10	120	119	36	120	84	1.48	81.90	43.19	3.54	6.99
Time to max VAS, sec	149	0	120	53	28	88	60	42.99	57.11	35.15	2.88	5.69

Summary statistics of raw data: Cold-pressor test pain intensity over time. q1=first (25%) quartile, q3=third (75%) quartile, IQR, inter-quartile range; MAD, median absolute deviation; CPT, cold-pressor test; AUC, area under the curve.

Table 4: Effects of CPM and TS.

Effect	…on	n	min	Max	Median	q1	q3	iqr	MAD	Mean	SD	SE	CI	p-Value
CPM effect	Single stim.	149	−74	29	−1	−11	0	11	7.41	−5.24	13.75	1.13	2.23	p<0.0001
	Repeated stim.	149	−50	21	−9	−20	0	20	13.34	−10.99	14.64	1.20	2.37	p<0.0001
	TS effect	149	−51	62	−4	−16	3	19	14.83	−5.75	16.73	1.37	2.71	p<0.0001
TS effect	After CPT	149	−28	78	9	0	19	19	13.34	11.67	15.38	1.26	2.49	p<0.0001
	Before CPT	149	−43	77	15	5	28	23	16.31	17.42	17.71	1.45	2.87	p<0.0001

Summary statistics of the effects of conditioned pain modulation (CPM) and temporal summation (TS) on experimental pressure pain intensity (VAS). q1=first (25%) quartile, q3=third (75%) quartile, IQR, inter-quartile range; MAD, median absolute deviation; CPT, cold-pressor test. p-Value from one-sample Wilcoxon test (μ=0).

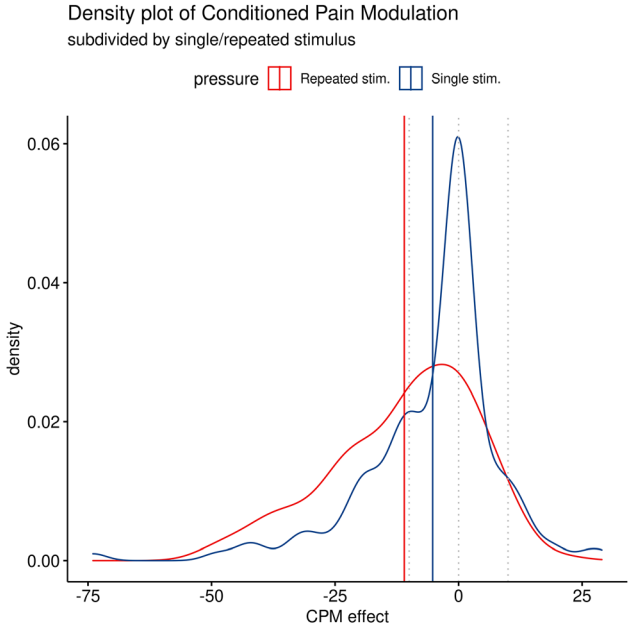

Figure 3: Distribution density plot (smoothed histogram) of the Conditioned Pain Modulation effect on single/repeat mechanical pressure stimulation, i.e. the individual change in pain before/after CPM. Vertical lines represent mean values.

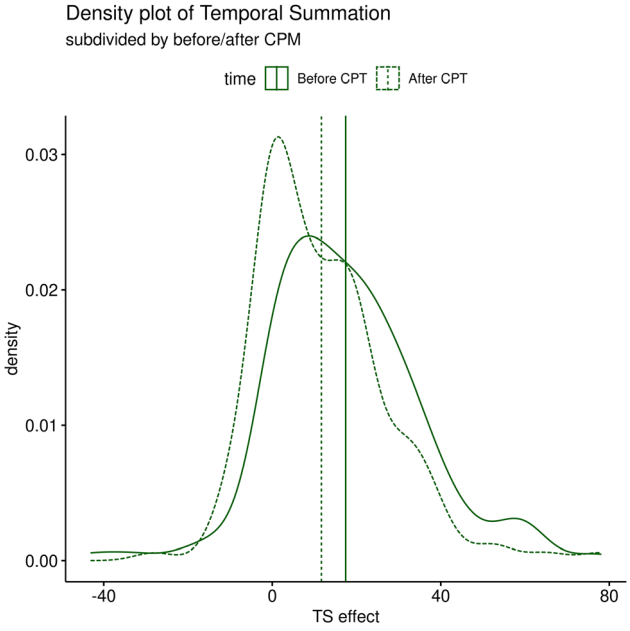

Figure 4: Distribution density plot (smoothed histogram) of the Temporal Summation effect before/after cold-pressor test, i.e. the individual difference in pain with single versus repeated pressure. Vertical lines represent mean values.

CPM responders/non-responders

Using the *simple CPM responder criteria*, the frequency (number) of CPM responders/non-responders was observed to be 75/74 for Single stimuli, 103/46 for Repeat stimuli, and 84/65 for Temporal summation respectively. For the *strict CPM responder criteria* the frequencies were 137/12, 142/7, and 124/25 respectively, and for the *reverse CPM responder criteria* 40/109, 64/85, and 55/94.

Group (CPM responder vs. non-responder) differences in clinical pain are presented in Table 5, subdivided into each of the three non-responder criteria (simple, strict, reversed) and each test stimulus (single, repeated and temporal summation). Significant differences were observed in only six of the 45 tests.

Discussion

In this large group of low-back pain patients, we found highly significant inhibitory effects of CPM on single- and repeated pressure stimuli, and on the temporal summation of pressure stimuli.

We hypothesized that the sensitivity of TS to the inhibitory effect of CPM would be different from that of a simple phasic test stimuli, but the relative effect size of CPM was comparable between all three test stimuli (single pressure pain, repeated pressure pain and temporal summation of pressure pain).

By contrast, in *absolute values* a more pronounced CPM effect was seen with repeated pressure pain as compared to both a single test stimulus and TS of pressure

Table 5: CPM responder status and clinical data.

Clinical pain	Test stim.	Responder criteria	CPM non-responder	n	Median	p-Value
Current pain, VAS	Single stim.	Simple	TRUE	72	5.0	0.40
			FALSE	73	6.0	
		Strict	TRUE	12	5.0	0.91
			FALSE	133	5.0	
		Reversed	TRUE	106	5.0	0.22
			FALSE	39	6.0	
	Repeated stim.	Simple	TRUE	44	4.5	0.03*
			FALSE	101	6.0	
		Strict	TRUE	7	4.0	0.54
			FALSE	138	5.0	
		Reversed	TRUE	82	5.0	0.05*
			FALSE	63	6.0	
	TS effect	Simple	TRUE	62	5.0	0.58
			FALSE	83	6.0	
		Strict	TRUE	24	5.0	0.69
			FALSE	121	6.0	
		Reversed	TRUE	91	5.0	0.54
			FALSE	54	5.0	
Typical pain, VAS	Single stim.	Simple	TRUE	70	7.0	1.00
			FALSE	72	6.5	
		Strict	TRUE	12	7.0	0.85
			FALSE	130	6.5	
		Reversed	TRUE	103	6.0	0.40
			FALSE	39	7.0	
	Repeated stim.	Simple	TRUE	44	6.0	0.03*
			FALSE	98	7.0	
		Strict	TRUE	7	6.0	0.78
			FALSE	135	7.0	
		Reversed	TRUE	80	6.0	0.03*
			FALSE	62	7.0	
	TS effect	Simple	TRUE	62	7.0	0.40
			FALSE	80	6.5	
		Strict	TRUE	24	6.5	0.67
			FALSE	118	7.0	
		Reversed	TRUE	89	6.0	0.51
			FALSE	53	7.0	
Worst pain, VAS	Single stim.	Simple	TRUE	72	8.0	0.86
			FALSE	73	8.0	
		Strict	TRUE	12	8.0	0.68
			FALSE	133	8.0	
		Reversed	TRUE	106	8.0	0.59
			FALSE	39	8.0	
	Repeated stim.	Simple	TRUE	44	7.5	0.01**
			FALSE	101	8.0	
		Strict	TRUE	7	8.0	0.37
			FALSE	138	8.0	
		Reversed	TRUE	82	8.0	0.01**
			FALSE	63	8.0	
	TS effect	Simple	TRUE	62	8.0	0.08
			FALSE	83	8.0	
		Strict	TRUE	24	8.0	0.31
			FALSE	121	8.0	
		Reversed	TRUE	91	8.0	0.33
			FALSE	54	8.0	
Pain duration, days	Single stim.	Simple	TRUE	72	365.0	0.82
			FALSE	72	336.0	

Table 5: (continued)

Clinical pain	Test stim.	Responder criteria	CPM non-responder	n	Median	p-Value
		Strict	TRUE	12	265.0	0.81
			FALSE	132	365.0	
		Reversed	TRUE	106	380.0	0.30
			FALSE	38	259.0	
	Repeated stim.	Simple	TRUE	44	396.5	0.93
			FALSE	100	349.5	
		Strict	TRUE	7	153.0	0.38
			FALSE	137	365.0	
		Reversed	TRUE	82	321.0	0.58
			FALSE	62	380.0	
	TS effect	Simple	TRUE	62	259.5	0.29
			FALSE	82	380.0	
		Strict	TRUE	24	198.0	0.15
			FALSE	120	380.0	
		Reversed	TRUE	91	335.0	0.24
			FALSE	53	394.0	
Pain drawing, pixels	Single stim.	Simple	TRUE	74	1,654.0	0.23
			FALSE	75	1,399.0	
		Strict	TRUE	12	2038.5	0.15
			FALSE	137	1,430.0	
		Reversed	TRUE	109	1,430.0	0.80
			FALSE	40	1,462.0	
	Repeated stim.	Simple	TRUE	46	1754.0	0.76
			FALSE	103	1,430.0	
		Strict	TRUE	7	2,533.0	0.10
			FALSE	142	1,393.5	
		Reversed	TRUE	85	1,491.0	0.80
			FALSE	64	1,393.5	
	TS effect	Simple	TRUE	65	1,433.0	0.76
			FALSE	84	1,456.5	
		Strict	TRUE	25	1,433.0	0.58
			FALSE	124	1,456.5	
		Reversed	TRUE	94	1,487.0	0.97
			FALSE	55	1,328.0	

pain. This adds to the controversies about how CPM should be assessed and presented.

Conditioned pain modulation of temporal summation of pain

Two previous publications about the CPM effect on TS [11, 12] were not in agreement. Holden et al. [11] reported no significant differences in TS, whereas Sirucek et al. [12] found a significant CPM induced inhibition of TS. The current data align with the findings of Sirucek et al.

Both Holden et al. and Sirucek et al. applied the conditioning and testing stimuli at the same segmental levels of spinal innervation, albeit on contra-lateral sides. By contrast, the current study applied the test and conditioning stimuli at different segments of spinal innervation. Applying the test and conditioning stimuli at the same segmental level could obfuscate any diffuse descending inhibitory effect of the conditioning stimulus: There is evidence that nociceptive input can lead to contralateral sensitization on the same segment [17] and it is thus conceivable that the intense pain of the conditioning stimulus could interfere with the integration of nociceptive input from the test stimulus and the descending diffuse noxious inhibitory control from higher centers.

The two previous and the current study are different in other ways, including the QST methods employed. As Kennedy et al. [6] observed CPM is sensitive to differences in test method and this could also account for the differences observed between the three studies.

Earlier publications have examined the effects of CPM on *second pain* elicited by electrical or heat stimulation on

healthy individuals [18] and fibromyalgia patients [19]. These authors reported greater inhibitory CPM effect on second pain than first pain, dependent on clinical status and sex. There may be an element of slow onset secondary pain to temporal pain summation and vice versa, but the test methods are not directly comparable and the findings should be compared with care.

All-in-all, there is some evidence to suggest that perturbations in CPM is a feature of chronic low-back, but CPM methodology is important and the literature is not in agreement [2].

Clinical considerations

Several other publications have used TS and CPM as indicators of perturbed central pain modulation in chronic clinical pain states – see e.g. O'Brien et al. [20] and den Bandt et al. [2] for reviews on fibromyalgia and low-back pain patients respectively. To our knowledge the effect of CPM on TS of pressure pain in a clinical population has not been reported before.

The current data is based exclusively on low-back pain patients seen in a specialized hospital spine center. It is therefore not possible to say whether the effects of CPM and TS differ from healthy individuals or other clinical populations.

In any clinical context however, the relevance of a CPM effect is likely to be in the distinction between individuals as *CPM responders* or *CPM non-responders* [21]. A CPM *non*-response could reflect an attenuated diffuse, descending noxious inhibitory control. This in turn is probably important for development of widespread hyperalgesia and chronification of pain [22].

On the face of it, the results presented in Table 5 suggested that significant differences in clinical presentation were observed between CPM responders and non-responders. However, on closer examination this must be questioned: The table included forty-five p-values, which suggests that it would be appropriate to correct for multiple statistical comparisons. Such correction methods (e.g. Bonferroni correction) generally rely on stricter significance criteria, and as the six significant p-values in Table 5 ranged from 0.01 to 0.05, they would likely be concluded insignificant using *any* correction method. Also, the three clinical measures in question were *current pain*, *typical pain* and *worst pain* which are not independent, but correlated (post-hoc Pearson correlation coefficient=[0.75; 0.9]).

Regarding the best way to dichotomize CPM responses into *responders* and *non-responders*, the three criteria resulted in very different frequencies. With the *strict* criteria, very few patients (n=7–25 – see Results subsection CPM responders/non-responders) were categorized as non-responders. Conversely, with the reverse criteria more than half (n=85–109) were categorized as non-responders. As the current study did not include a healthy control group, we can not determine the CPM non-responder criteria with the best discriminatory ability. However, a previous study of healthy controls can be cautiously contrasted with the present study. Locke et al. [23] also used CPT to induce inhibitory CPM responses, but used pressure pain *thresholds* as the test stimuli (+5% *higher* thresholds corresponding to an inhibitory CPM effect) and was focused on identifying CPM responders. In other words, Locke et al. considered CPM non-responders to be those participants with either a small or no inhibitory CPM response, which would correspond to our *reverse* criteria. In contrast to our LBP population, Locke et al. found that only 7% of healthy controls were CPM non-responders by such *reverse* criteria. Even with the laxer *simple* criteria a considerably higher proportion of LBP patients (n=46–74) were categorized as CPM non-responders in our population.

No differences in reported LBP *duration* were found between CPM responders and non-responders, irrespective of the criteria. Additionally, Gerhardt et al. [5] suggested that altered CPM might drive pain extent (area), but we found no difference in pain extent between CPM responders and non-responders in the current data. At first look, this challenges the impact of pain duration on development of perturbed central pain modulation, but it should be recalled that the current study population consisted exclusively of chronic low-back pain patients in whom such perturbed modulation may be common.

Thus, no difference in clinical pain intensity, duration or extent between CPM responders and non-responders should be inferred from these data. We reiterate however, that the present data are from a select subgroup of chronic LBP patients. We can not rule out, that a comparison with healthy controls or acute LBP patients would demonstrate significant differences.

Restrictions imposed by a VAS

The CPM effect was most pronounced in relation to the pain induced by repeated pressure stimuli. This could possibly reflect an undesired characteristic of the Visual Analogue Scale or methodological caveat: As the VAS is fixed at both ends, there is a risk of flooring and ceiling effects which may limit the usefulness of standardized QST tests [24]. If the test stimulus pain intensity prior to CPM is low, there is little remaining *room* on the VAS to indicate even lower

scores following CPM. As the pain induced by repeated pressure was about double that of a single stimulus, there was more room available for a drop in pain scores following CPM. The similarity in *relative* effect size of CPM on single and repeated pressure stimuli could be interpreted as reflecting such a flooring effect. Thus, in CPM testing care should be taken to ensure that the intensity of the test stimuli is sufficiently high to avoid a flooring effect and ensuing type B error.

Strengths and weaknesses

Clinical pain status was recorded at a single point in time prior to QST testing and we can say nothing about the temporal development of clinical pain in relation to CPM responder/non-responder status.

As discussed above, only chronic LBP patients were included and whilst significant differences in CPM effect have been reported across different chronic pain diagnoses [25], important differences within pain patient groups have also been reported [5, 26, 27]. The current results should not be uncritically extrapolated to other populations and we can not draw conclusions regarding any potential differences between our study population and healthy individuals.

It is known that attention and expectations [28, 29] may influence the CPM response. No attempt was made to control or measure attention in the current study, but conversely a strict and uniform testing protocol was followed throughout.

Conclusions

A significant CPM effect of cold-pressor test was observed on single pressure pain, repeated pressure pain and temporal summation of pressure pain alike and no apparent difference in relative effect sizes were observed.

A more pronounced CPM effect in absolute terms was observed with repeated mechanical pressure as the test stimulus, possibly as a result of less flooring effect compared to single stimuli and temporal summation.

Categorization of participants as CPM responders or non-responders was not associated with significant group differences in clinical pain measures.

Research funding: Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). Liam Holm was funded by a research grant from the Danish Foundation for the Advancement of Chiropractic Research and Post-Graduate Education.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: We, the authors state no conflicts of interest in the preparation of this manuscript.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The study was approved by the Regional Committee on Health Research Ethics, Denmark (ref. number S-20180098).

Appendix A

Diagnoses

Frequency table of clinical diagnoses and sub-diagnoses.

ICD10	n
M54.5	46
M62.6	46
M54.4	27
M51.1	22
M47.8	21
M48.0	18
M47.2	14
M99.8	10
M43.1	9
M79.6	8
M99.6	8
M99.9	6
M16.9	5
M54.9	5
M99.7	4
M54.1	3
M47.	2
M51.2	2
M51.3	2
M53.1	2
M53.9	2
M54.2	2
M54.6	2
M54.8	2
M70.6	2
M99.4	2
M23.9	1
M40.0	1
M46.9	1
M47.9	1
M48.1	1
M53.3	1
M99.0	1

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