Original Experimental

Anders Galaasen Bakken, Iben Axén, Andreas Eklund, Anna Warnqvist and Søren O'Neill*

Temporal stability and responsiveness of a conditioned pain modulation test

A secondary study of conservative treatment of neck pain patients

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Abstract

Objectives: Conditioned pain modulation is a commonly used quantitative sensory test, measuring endogenous pain control. The temporal stability of the test is questioned, and there is a lack of agreement on the effect of different pain conditions on the conditioned pain modulation response. Thus, an investigation of the temporal stability of a conditioned pain modulation test among patients suffering from persistent or recurrent neck pain is warranted. Further, an investigation into the difference between patients experiencing a clinically important improvement in pain and those not experiencing such an improvement will aid the understanding between changes in pain and the stability of the conditioned pain modulation test.
Methods: This study is based on a randomized controlled trial investigating the effect of home stretching exercises and spinal manipulative therapy vs. home stretching exercises alone. As no difference was found between the interventions, all participants were studied as a prospective cohort in this study, investigating the temporal stability of a conditioned pain modulation test. The cohort was also divided into responders with a minimally clinically important improvement in pain and those not experiencing such an improvement.
Results: Stable measurements of conditioned pain modulation were observed for all independent variables, with a mean change in individual CPM responses of 0.22 from baseline to one week with a standard deviation of 1.34, and −0.15 from the first to the second week with a standard deviation of 1.23. An Intraclass Correlation Coefficient (ICC3 – single, fixed rater) for CPM across the three time points yielded a coefficient of 0.54 ($p<0.001$).
Conclusions: Patients with persistent or recurrent neck pain had stable CPM responses over a 2 week course of treatment irrespective of clinical response.

Keywords: conditioned pain modulation; manual therapy; neck pain; quantitative sensory testing.

Introduction

In the context of pain research, *quantitative sensory testing* (QST) typically consists of a controlled painful stimulus (e.g. mechanical pressure) and a standardized measure of the pain experience (e.g. a numerical pain rating scale). Such QST procedures permit for a semi-objective psychophysical assessment of pain sensitivity and responsiveness. Of the different QST protocols in use, the *conditioned pain modulation* (CPM) paradigm is arguably of particular interest as it reflects short-term neuroplasticity of nociceptive modulation [1]. A robust CPM response suggests that a test-subject's pain sensitivity is malleable and affected by endogenous pain control, at least on a shorter time scale [1].

CPM is a test setup that quantifies the pain inhibits pain paradigm and is measured as a difference in pain elicited by a test stimulus before and after a conditioning stimulus. CPM can be used to assess pain inhibitory mechanisms, mediated by the lower brainstem and influenced by higher cortical structures [2–4], affecting incoming nociceptive signals from the entire body [5].

The literature on CPM responses between clinical groups is not in agreement: A recent systematic review on

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***Corresponding author: Søren O'Neill**, DC, M.Rehab, PhD, Spine Centre of Southern Denmark, University Hospital of Southern Denmark, Østre Hougvej 55, DK-5500 Middelfart, Denmark, E-mail: soren@oneill.dk. https://orcid.org/0000-0002-8064-7001
Anders Galaasen Bakken, Iben Axén and Andreas Eklund, Department of Environmental Medicine, Unit of Intervention and Implementation Research for Worker Health, Karolinska Institutet, Stockholm, Sweden, E-mail: Anders.Galaasen.Bakken@ki.se (A.G. Bakken)
Anna Warnqvist, Division of Biostatistics, Karolinska Institutet, Stockholm, Sweden

CPM responses in low back pain [6] concluded that three of seven studies reported decreased CPM responses, whereas four did not. Regarding neck pain, there is less available evidence, but the results are also discordant. For instance, Heredia-Rizo et al. [7] found decreased CPM responses in women with chronic neck/shoulder pain which was amenable to exercise therapy. Coppieters et al. [8] also found decreased CPM responses in patients with persistent or recurrent neck pain, but only when associated with whiplash trauma. By contrast, Shahidi et al. [9] found that low CPM responses were a pre-existing characteristic and predictor of future development of neck pain.

A systematic review and meta-analyses from 2021 [10] reported impaired CPM responses with large effect sizes in patients with different chronic pain states. By contrast, another recent review on the correlation between CPM response and clinical pain parameters found no such correlation in 69% of analyses [11]. When a correlation was observed, reduced CPM responses were associated with worse clinical pain. Taken together, these findings could indicate that a CPM response is more of an all-or-nothing response elicited only with a sufficiently strong stimulus, as opposed to a graded response function of conditioning stimulus intensity. Such findings have previously been reported in an experimental study when investigating the role of the conditioning pain in the induction and magnitude of conditioned pain modulation [12]. CPM testing is also generally sensitive to differences in methodology which might go some way to explain conflicting findings [13, 14].

For CPM to be a meaningful clinical assessment tool, it should be sufficiently stable over time but also be sufficiently sensitive to change. In healthy individuals, Marcuzzi et al. [15] reported high temporal stability over a period of 4 months for *static* QST procedures like pressure, heat, and cold pain thresholds, but dynamic QST procedures like CPM were found to be less stable. Marcuzzi et al. [15] concluded specifically that “Assessment of CPM using pressure pain threshold (PPT) as the test stimulus did not show adequate reliability, suggesting that this test paradigm may be less useful for monitoring individuals over time”. It should be noted, however, that the conditioning stimulus used was a cold pressor test at 10.5 Celsius, which arguably is not cold enough to induce a robust CPM response. By contrast, Imai et al. [16] reported that from a number of different CPM protocols repeated at 45 min intervals, a setup with handheld pressure pain threshold as the test stimulus and cold pressor test as the conditioning stimulus was the most useful. Others have reported different temporal stability over weeks, which depended upon the sex and age of the test subjects [17–20]. Whilst age and sex does influence the CPM response, inter-individual variation (true score variance) is considerably greater [21].

The aim of this study was to examine the temporal stability of the CPM paradigm in a clinical cohort of neck pain patients over a 2 week course of treatment.

We hypothesized that patients that experienced a clinically important reduction in neck pain would exhibit increasing CPM responses compared to patients experiencing no such improvement in pain.

Methods and materials

This study is a secondary analysis of data from a randomized controlled clinical trial (RCT) [22] conducted at five multi-professional rehabilitation clinics, part of the Stockholm regional health service. Participants were randomized to receive either (a) spinal manipulation and home stretching exercises or (b) home stretching exercises only. The trial was registered at ClinicalTrials.gov with the registration number: NCT03576846 and data were collected between January 2019 and April 2020.

The RCT on which this study is based found no difference in changes in clinical pain between groups, and thus the total study population was investigated as a single cohort in this study [22].

Participants

Participants were primarily recruited through local newspapers or the clinics’ newsletters, distributed via email or Facebook. Some subjects were recruited through other therapists at the clinics or were invited to the study when seeking care. Collaborating General Practitioners’ clinics were also asked to recommend this study to their patients.

The study population consisted of subjects with persistent or recurrent neck pain for at least six months, undergoing treatment for their neck pain.

Inclusion criteria were:

(1) At least eighteen (18) years of age
(2) Able to read and understand Swedish
(3) No chiropractic treatment in the preceding three months
(4) Not diagnosed with cardiovascular disease, hypertension, or diabetes
(5) Not medicated with steroids, β-blockers, or antidepressants
(6) Self-reported BMI below 30
(7) Not pregnant
(8) Not suffering from any other serious competing diagnoses or recent development of headache, dizziness, drop-attacks, or acute cervical radiculopathy

Responder status

Participants were categorized as either *responders* or *non-responders* on the basis of changes in clinical neck pain intensity as reported using a numeric rating scale (NRS-11) at baseline and at two-week follow-up (end of the intervention period). The cut-point for responder status was set on the basis of a minimal clinically important difference (MCID) [23] defined as a reduction of two or more NRS points on a 0–10 scale, after four treatments over a two-week period. In other words, an

increase in pain or a reduction of less than two was considered a clinical *non-responder*.

Conditioned pain modulation

The specifics of the CPM test utilized in this study are similar to those described by O'Neill and O'Neill in 2015 [24]:

Test stimulus: The pressure pain intensity (PPI) was measured using a spring-operated clamp (two 2.8 cm × 1.9 cm pads). The clamp used is commercially available, procured by Clas Ohlson (article number 40-7211) and exerts a force of 7.3 kg at a 2.6 cm opening. The clamp was placed on the subject's thumbnail for 10 s. Caution was taken to prevent the clamp from putting pressure on the eponychium but still placed as close to the eponychium as possible. The pain was rated on the NRS-11 from 0 (no pain) to 10 (worst imaginable pain) as an overall pain score of the PPI procedure. This was performed before (step 1) and immediately after (step 2) the cold pressor test.

Conditioning stimulus: The cold pressor test utilized a 40 L water container (Mobicool B4 230/12 V compressor) to keep the water at a stable temperature between 0 and 2 °C, monitored using a mercury thermometer. The container also contained a small submersible pump (Barwig Typ 03 0333, 720 L/h, 6 m), to keep the water circulating during tests. The subjects were asked to lower the opposite hand of the initial PPI test in the cold water and keep it there for at least 1 min or until the pain became unbearable. The pain intensity was recorded continuously as a VAS score (0 (no pain) to 100 (worst imaginable pain)) on a computer with a sampling rate of 1 Hz. Pain with the cold pressor test was summarized as the duration (tolerance) and summated pain scores over time, described as area under the curve.

The difference in NRS-11 between step 1 and step 2 of the test stimulus was calculated as the CPM response by subtracting step 1 from step 2.

All participants received the same instructions which followed a prepared manuscript. The measurement procedure and instructions were rehearsed by two researchers performing the measurements. The two testers also observed each other in a pilot study to ensure high and similar measurement quality.

Sample size calculation

The study sample size was determined a-priori as that of the RCT of which this study is a secondary analysis [25].

Statistical methods

Continuous variables were reported with means and standard deviations, and categorical variables were reported as counts and percentages.

The temporal stability of the first PPI, cold pressor test time, max cold pressor test pain, cold pressor test area under the curve, and CPM response, were presented as the mean and standard deviation for each repeat-test and combined.

The temporal stability of CPM for individuals and the study population is further illustrated using spaghetti plots (all participants) and box plots (population).

The individual CPM change between repeat-tests is tabulated is frequency tabulation.

Temporal stability was analyzed using ICC3 and CPM data were analyzed as a multivariate linear regression (repeated measures MANOVA type III), with five CPM variables (first PPI, cold pressor test time, max cold pressor test pain, cold pressor test area under the curve, and CPM response) as dependent variables and with clinical responder status, RCT group allocation, and test day as independent variables.

Ethics

This study was approved by The Regional Ethical Review Board (Stockholm) (2018/2137-31). A written informed consent form was signed by all subjects. The study was conducted in accordance with the Helsinki declaration [26].

Results

Participants

One hundred thirty-one subjects were recruited of which four subjects dropped out during the intervention period. A further two participants had incomplete data, leaving one-hundred-and-twenty-five (n=125) for analyses.

As evident from Table 1, 47 participants (38%) were categorized as clinical responders compared to 78 non-responders (62%). For a summary of descriptive variables sub-grouped by responder status, please see Table 1.

Quantitative sensory testing and temporal stability of CPM

Raw data for cold pressor test, mechanical pressure pain intensity and conditioned pain modulation are summarized in Table 2. Changes over time in the primary outcome for this study (conditioned pain modulation) are presented in Table 3. The raw CPM data and change over time are illustrated in Figure 1 as a spaghetti plot. CPM data population distribution is illustrated in Figure 2 as box plots.

The large majority (81%) were observed to change by no more than a single NRS point, i.e. ±1 NRS in CPM response over time, and less than 6% changed by 3 NRS points or more.

The mean change in individual CPM responses was 0.22 from baseline to Week 1 (SD=1.35), and −0.15 from Week 1 to Week 2 (SD=1.24). An Intra-class Correlation Coefficient (ICC3 – single, fixed rater) for CPM across the three time points yielded a *moderate* or *fair* reliability coefficient of 0.54 ($p<0.001$) – see Table 4.

Table 1: Summary of descriptive variables.

	MCID improved (n: 47)	Not MCID improved (n: 78)
Age: mean, SD	59 (16)	59 (13)
Female: n (%)	25 (53)	44 (56)
Received SMT and stretching exercises: n (%)	24 (51)	41 (53)
Baseline NRS-11: mean, SD	5.5 (1.6)	3.7 (2.0)
NRS-11 change score: mean, SD	−3.3 (0.2)	0.2 (0.2)
Neck disability change score: mean, SD	−4.2 (0.75)	1.6 (0.53)
Mcgill change score: mean, SD	−4.5 (1)	0.7 (1)
EQ-5D change score: mean, %	−0.004 (0.006)	0.001 (0.009)
Also reporting arm pain: n (%)	29 (62)	46 (59)
Also reporting pain in the mid back: n (%)	21 (48)	50 (67)
Also reporting pain in the low back: n (%)	23 (52)	46 (61)
Pain duration		
Reporting with less than 6 months: n (%)	0 (0)	1 (1)
Reporting with more than 6 months: n (%)	6 (13)	12 (15)
Reporting several years: n (%)	40 (87)	65 (83)
Years with neck pain: mean, SD	12 (12)	12 (9)
STarT back categories		
Categorized as low risk: n (%)	34 (77)	54 (72)
Categorized as medium risk: n (%)	5 (11)	12 (16)
Categorized as high risk: n (%)	2 (5)	5 (7)
Type of occupation		
Reporting no job: n (%)	15 (32)	24 (31)
Reporting mostly hard labour: n (%)	1 (2)	2 (3)
Reporting mostly a variation between hard and easy labour: n (%)	4 (9)	5 (6)
Reporting mostly standing and walking: n (%)	9 (19)	11 (14)
Reporting mostly sitting: n (%)	18 (38)	36 (46)
Sick leave the previous year		
Reporting do not work: n (%)	13 (28)	18 (23)
Reporting no sick leave: n (%)	32 (68)	51 (65)
Reporting yes, between 1 and 7 days: n (%)	2 (4)	3 (4)
Reporting yes, between 8 and 14 days: n (%)	0 (0)	3 (4)
Reporting yes, more than 15 days: n (%)	0 (0)	3 (4)

Summary of descriptive variables of 125 patients with neck pain, sub-grouped into clinical responders (improved at the level of a Minimal Clinically Important Difference – MCID) and non-responders (not improved at MCID level). Data were collected at baseline, except for change scores for NRS-11, NDI, McGill and EQ-5D which represent changes over the course of treatment.

Table 2: Quantitative sensory testing.

Clamp pressure pain intensity (NRS-11)	Baseline (n=125)	Follow-up 1 (n=125)	Follow-up 2 (n=125)	Combined (n=375)
Mean, SD	4.64 (2.08)	4.28 (2.17)	4.31 (2.30)	4.41 (2.18)
Median [range]	4.00 [1.00, 10.0]	4.00 [1.00, 10.0]	4.00 [0, 10.0]	4.00 [0, 10.0]
Missing values: n (%)	2 (1.6%)	4 (3.2%)	7 (5.6%)	13 (3.5%)
Cold-pressor test duration, s	**(n=125)**	**(n=125)**	**(n=125)**	**(n=375)**
Mean, SD	80.7 (36.7)	86.7 (36.4)	88.6 (35.9)	85.2 (36.4)
Median [range]	70.0 [10.0, 120]	100 [10.0, 120]	120 [1.00, 120]	90.0 [1.00, 120]
Missing values: n (%)	2 (1.6%)	4 (3.2%)	7 (5.6%)	13 (3.5%)
Cold-pressor test max pain, VAS	**(n=125)**	**(n=125)**	**(n=125)**	**(n=375)**
Mean, SD	85.7 (11.5)	84.2 (11.2)	82.5 (13.2)	84.1 (12.0)
Median [range]	88.0 [13.0, 100]	88.0 [51.0, 100]	87.0 [19.0, 100]	87.0 [13.0, 100]
Missing values: n (%)	3 (2.4%)	5 (4.0%)	10 (8.0%)	18 (4.8%)
Cold-pressor test area under the curve	**(n=125)**	**(n=125)**	**(n=125)**	**(n=375)**
Mean, SD	5670 (2720)	5670 (2720)	−5600 (2800)	5500 (2810)
Median [range]	5010 [26.0, 11400]	5590 [186, 11200]	5660 [28.0, 10800]	5420 [26.0, 11400]
Missing values: n (%)	4 (3.2%)	5 (4.0%)	10 (8.0%)	19 (5.1%)
Conditioned pain modulation (NRS-11)	**(n=125)**	**(n=125)**	**(n=125)**	**(n=375)**
Mean, SD	−1.39 (1.42)	−1.18 (1.28)	−1.36 (1.44)	−1.31 (1.38)
Median [range]	−1.00 [−8.00, 2.00]	−1.00 [−6.00, 1.00]	−1.00 [−7.00, 1.00]	−1.00 [−8.00, 2.00]
Missing values: n (%)	3 (2.4%)	6 (4.8%)	7 (5.6%)	16 (4.3%)

Suwmmary statistics of QST procedures presented for each of three test days and combined. Time-series data (1 Hz) for cold-pressor test are summarized as duration (tolerance), max pain score during test and cumulated pain score during test (area-under-curve). Conditioned pain modulation is difference in pain intensity with mechanical pressure of the thumb nail before and after cold-pressor test (negative values indicate a drop in pain intensity).

Table 3: Quantitative sensory testing.

	−5	−4	−3	−2	−1	0	1	2	3	4	5
BL-W1	1	0	3	3	23	41	31	12	3	0	1
W1-W2	0	3	1	8	27	44	24	7	1	0	0

Tabulated frequencies of change in CPM over time. Rows represent change in CPM from baseline to week 1 (BL-W1) and from week 1 to week 2 (W1-W2). Columns represent the observed change in CPM response (from −5 to +5 on an 11 point NRS scale) and cells list the statistical frequency (n) of observations.

Factors affecting CPM response

Statistical modeling

The multivariate linear regression model included five dependent QST variables: (clamp pressure pain intensity, cold pressor test duration, -max pain, -area under the curve and conditioned pain modulation). The effects of three independent predictor variables were included: clinical responder status in relation to the MCID (reduction of 2+ points in NRS in clinical pain), group allocation in the randomized trial (stretching exercises alone or in combination with manual therapy), and time (test day as baseline, follow-up day 1 or 2). As evident from Table 5, no significant effects were found.

A uni-variate linear regression model using only the CPM response as a dependent variable yielded similar results (not presented).

Adverse events

One subject fainted during the cold pressor test. This was later diagnosed as a stress-induced event following an unrelated medical examination. The subject was excluded from further CPM testing due to this. No lasting ill effects were reported.

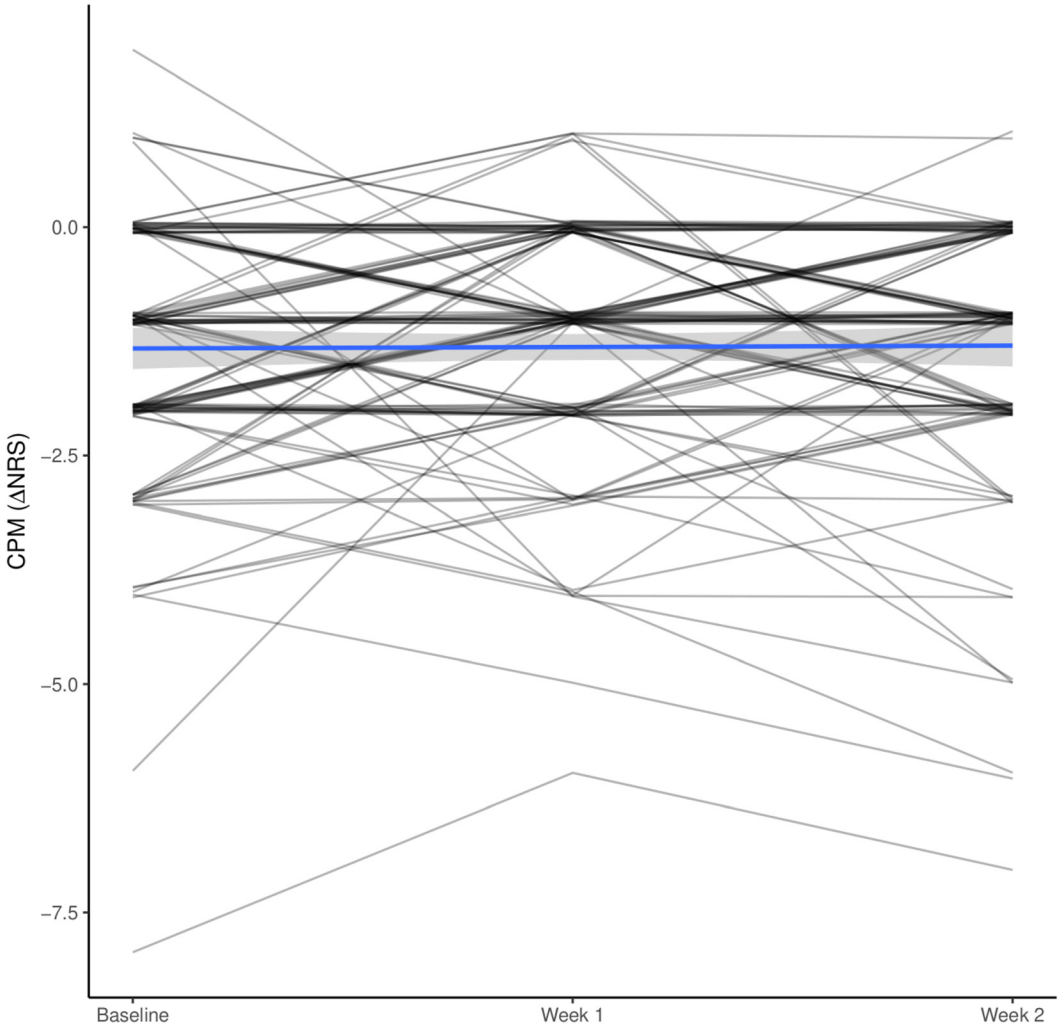

Figure 1: Conditioned pain modulation over time. Spaghetti plot of conditioned pain modulation for each individual participant over time. Lines are slightly jittered and semi-transparent to allow for illustration of multiple superimposed lines as darker lines. The y-axis CPM represents the difference in pressure pain intensity (ΔNRS) before/after cold pressor test. Linear regression is illustrated as a blue line with grey confidence interval.

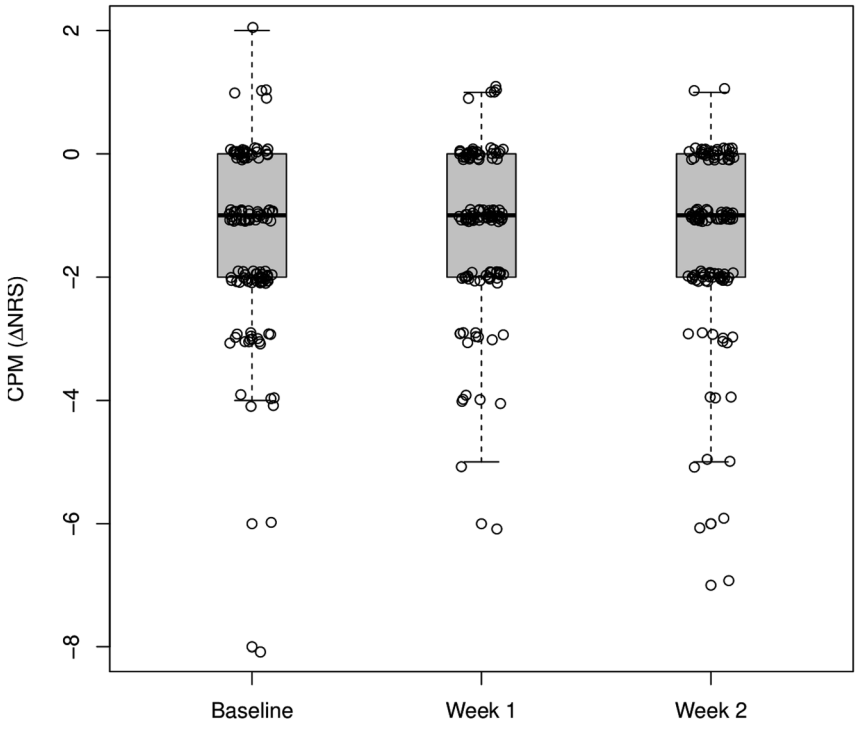

Figure 2: Distribution of conditioned pain modulation at baseline at follow-ups. Boxplot (median, inter-quartile range and 1.5xIQR) illustration of the distributions of conditioned pain modulation, i.e. the difference in pressure pain intensity (ΔNRS) before/after cold pressor test. . Raw data are superimposed and presented as slightly jittered circles to allow for visualization of overlying observations.

Table 4: Intraclass correlation coefficients.

	Type	ICC	F	df1	df2	p	Lower bound	Upper bound
Single_fixed_raters	ICC3	0.54	4.5	124	248	4.3e-24	0.44	0.63

Changes in conditioned pain modulation over time (baseline, follow-up at week 1 and 2) yielded a coefficient of 0.54, i.e. moderate reliability.

Table 5: Multivariate analyses of variance (n:125).

Type of III MANOVA tests: Pillai test statistics						
	Df	Test stat approx	F	Num Df	den Df	Pr(>F)
(Intercept)	1	0.43900	52.430	5	335	<2e-16
Time	1	0.01092	0.739	5	335	0.5943
Improved	1	0.00586	0.395	5	335	0.8522
Group	1	0.01591	1.083	5	335	0.3693
Time: improved	1	0.00487	0.328	5	335	0.8960
Time: group	1	0.00961	0.650	5	335	0.6618
Improved: group	1	0.00652	0.440	5	335	0.8207
Time: improved: group	1	0.00386	0.260	5	335	0.9346

Results of a multivariate linear regression model with five dependent QST variables: clamp pressure pain intensity, cold-pressor test duration, -max pain, -area under the curve and conditioned pain modulation. None of the predictors ("Time": baseline, follow-up day 1, follow-up day 2, "Improved": minimal clinically important difference for improved reached or not, "Group": allocated to stretching exercises with/without manual therapy) were significant.

Discussion

The current study quantified conditioned pain modulation at three points in time over a course of treatment for persistent or recurrent neck pain. We found that CPM effects were generally inhibitory but of small magnitude (mostly between 0 and −2 NRS) and remained moderately stable over time. Four out of five participants changed only a single CPM point on an 11-point numerical pain rating scale from one time point to the next, or not at all. This was not significantly related to occasion, treatment allocation or clinical response to treatment. Only a few participants showed more variation in CPM, but this was the exception.

Study population

Arguably, the study population was internally heterogeneous in so far as participants had received one of two

different treatments, but we suggest this was justified as there is no reason to expect that the treatments would have any *direct inherent* effects on the CPM responses. Rather, any effect of the treatments on CPM response would likely be the result of changes in clinical pain, but no significant difference in change in clinical pain was observed between treatment groups [27]. As reported above, the results of a linear regression model confirmed that treatment group allocation did not influence CPM responses.

It should be noted, that as no pain-free control group was included in the current study we can make no inferences about the magnitude of the observed CPM responses in our population, only that the CPM responses were not related to clinical response to treatment.

Temporal stability of CPM

The linear regression modeling indicated that the occasion (test days 1-to-3) was also not a significant effect/predictor for CPM response. In other words, the distribution of CPM responses on a population level remained stable over the study period.

Arguable this does not preclude greater changes over time within individuals if those changes are roughly equal in either direction. The analysis of variance, however, demonstrated that this was not the case, and the mean change in CPM response for individuals between tests was found to be relatively small.

A systematic literature review from 2016 [13] reported reliability between test sessions as ranging from fair to excellent in six different studies, but also noted that these employed different CPM test paradigms. Conversely, a systematic review and meta-analysis from 2022 [28] reported that whilst intra-session reliability was good-to-excellent with a mechanical pressure and cold-pressor test paradigm, the inter-session reliability was fair or less for all modalities and for both healthy participants and pain patients. There is also evidence, that the CPM effect is more pronounced or robust when employing cold-pressor test as the conditioning stimulus, as the case was in this study, compared to other methods [29]. The current data are thus in line with these previous findings and demonstrate a fair degree of stability over time, despite participants being engaged in a treatment program.

Responsiveness of CPM to changes in clinical pain

We hypothesized that patients who experienced a clinically important improvement in neck pain would also exhibit increases in CMP responses compared to those without clinical improvement. This hypothesis is not supported by our findings.

At face value, this suggests that CPM response is in fact not affected by clinical improvement in patients with persistent or recurrent neck pain.

However, there are a few caveats that should temper our interpretation: We defined a minimum clinically important change as a reduction in NRS of at least two on the 11-NRS scale and this was observed in 38% of participants with a mean change of −3.3 (0.2). It is possible that clinical pain intensity and/or duration in this cohort of neck pain patients was insufficient to lead to reduced CPM responses in the first place. However, with a mean baseline clinical pain intensity of 5.5 (1.6) and a neck pain duration of longer than six months, this is less likely. We can only speculate, but as generalized hyperalgesia seems common in patients with persistent pain, we would expect a degree of CPM attenuation in this population as well.

It is also possible that the changes in clinical pain following treatment were insufficient to effect changes in CPM responses robust enough to be statistically detectable.

QST technical considerations

As described in the Introduction, CPM testing is more complicated than simpler QST test paradigms and is sensitive to differences in methodology. This might go some way to explain conflicting findings in CPM research [13, 14]. Whilst CPT is commonly used as the conditioning stimulus in CPM paradigms, the use of a mechanical clamp as a test stimulus is not. Whilst CPM responses have previously been demonstrated using such a setup [24, 30], it is possible that the test stimulus was insufficiently intense to make a CPM response detectable (i.e. a flooring effect). However, with a clamp force of 7+ kg at 2.4 cm opening and overall mean pain of 4.41 at the first measurement, this seems unlikely.

Conclusions

In this cohort of patients with persistent or recurrent neck pain, we found that CPM responses were surprisingly stable over a 2 week course of treatment for the majority of patients.

Our hypothesis, that patients who experienced a clinically important reduction in neck pain would exhibit increasing CMP responses compared to patients experiencing no such improvement in pain, was not supported.

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Competing interests: Authors state no conflict of interest.

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

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the Regional Ethical Review Board (Stockholm) (reference approval no. 2018/2137-31).

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