Musculoskeletal
Research Paper

OPEN

PAIN REPORTS

Association between temporal summation and conditioned pain modulation in chronic low back pain: baseline results from 2 clinical trials

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Abstract

Introduction: Temporal summation (TS) and conditioned pain modulation (CPM) represent different aspects of central pain processing. Their relationship and differential performance within distinct body locations are not well understood.

Objectives: To examine the association between TS and CPM in chronic low back pain and the influence of testing location on this relationship.

Methods: We analyzed *baseline* data from 2 clinical trials on participants with chronic low back pain (n = 264; 47.3% female; mean age = 41 years, SD = 12; mean pain = 5.3/10, SD = 1.4). Measures used included questionnaires assessing pain and negative affect, phasic thermal TS at the hand (thenar) and the lower back (lumbar), followed by CPM that included a thermal testing stimulus (Heat-6, the temperature where pain rating is 6/10) and a cold-pressor conditioning stimulus. Nonparametric, proportional odds logistic regression was used to model thenar, and separately, lumbar TS, using CPM, Heat-6, negative affect, and demographics.

Results: Our models revealed a small association (βs = 0.17, $P = 0.01$) between reduced CPM and heightened TS at both testing sites, regardless of demographics or negative affect.

Conclusion: Results suggest a modest association between TS and CPM, irrespective of anatomical testing location, demographics, and negative affect. These findings will help improve the methodology and interpretation of TS and CPM measurement in clinical pain populations.

Keywords: Thermal temporal summation, Conditioned pain modulation, Individualized heat stimulus, Chronic low back pain, Testing location, Negative affect

1. Introduction

Temporal summation (TS) and conditioned pain modulation (CPM) are 2 dynamic quantitative sensory testing (QST)[2,3] measures that approximate key aspects in central pain processing.[29,33] Temporal summation refers to a behavioral test in which human participants experience increased pain to a rapid succession (frequency >0.3 Hz) of identical noxious stimuli.[55] Temporal summation is considered a behavioral correlate of wind-up, an ascending pain facilitatory process at the spinal dorsal horn identified in animal studies.[46] Conditioned pain modulation refers to the human behavioral phenomenon commonly known as "pain inhibits pain," wherein the pain evoked by a testing stimulus is reduced by the application of a second, conditioning noxious stimulus.[60] Conditioned pain modulation is a behavioral correlate of diffuse noxious inhibitory control, a descending pain inhibitory pathway involving the brain stem and the spinal dorsal horn originally identified in rodents.[31]

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.painrpts.com).

PR9 6 (2021) e975

http://dx.doi.org/10.1097/PR9.0000000000000975

Given these properties, TS and CPM are often characterized simultaneously in clinical populations as paired behavioral markers to profile complementary aspects of an individual's central pain regulatory state.[5,16,18,42,60–62] Increased TS and decreased CPM are often observed independently or together in chronic pain conditions and may indicate central pain dysregulation.[45]

Chronic low back pain (CLBP) is the most prevalent chronic pain condition, and it is the primary cause of disability worldwide.[38,52] Treatment for CLBP remains challenging, in part due to a discrepancy between findings of structural abnormality on spine imaging and the presence or severity of back pain.[7,9,58] Researchers have hypothesized that altered central pain processing may contribute to the development and maintenance of CLBP,[50] and such hypotheses have been supported by poor outcomes for several structurally based interventions (eg, disc replacement and spinal fusion),[6,9] alterations in brain systems involved with pain modulation,[24,57] and good efficacy for central-acting pain medications (eg, duloxetine).[53,54] Heightened TS and reduced CPM in CLBP compared with healthy controls[11,21,36] lends further support to a hypothesis of altered central pain processing, although the mechanisms are not well characterized. For instance, few studies have examined the relatedness between TS and CPM.[35,39]

Temporal summation and CPM both exert influences at the wide-dynamic range neurons at the spinal dorsal horn, with the former being facilitatory the latter inhibitory. The identical location of action and opposite effect on nociceptive transmission suggest that TS and CPM may be inversely related. However, only a handful of studies to date have addressed the relationship between TS and CPM and primarily focused on the impact of a noxious conditioning stimuli (CPM) on TS and not the direct relationship between TS and CPM.[20,40] Whether TS and CPM represent 2 sides of the same coin (intimately and oppositely related) or 2 orthogonal processes has not been extensively studied. The current study therefore aims to directly examine the relationship between TS and CPM and the impact of experimental and individual factors on this relationship. Specifically, the body location for evoked pain paradigms,[4,15] thermal sensitivity, demographics, and negative affect, including depression[17] and anxiety,[26] are known to influence QST broadly. However, their impact on the association between TS and CPM is less well characterized. We hypothesize that TS and CPM are inversed related, and this relationship is independent from the aforementioned factors. In a post hoc exploratory analysis, we also examined the bivariate relationship between these dynamic QST measures and pain outcomes, as well as between TS measured at 2 different body locations.

2. Method

2.1. Overview

The Stanford Center for Back Pain is an NIH-funded effort with the goal of characterizing the shared and distinct mechanisms of nonpharmacologic treatments for CLBP in 2 clinical trials using the same participant eligibility criteria (ClinicalTrials.gov registration number NCT02503475). The 2 clinical trials investigated 4 centrally acting, integrative medicine therapies for CLBP: mindfulness-based stress reduction vs cognitive behavioral therapy (Mackey et al., under review); and real vs sham electroacupuncture.[28] While the main, prespecified aim of the Stanford Center for Back Pain is to delineate the central mechanisms of these interventions via neuroimaging and behavioral testing (including TS and CPM), the current secondary analyses uses only baseline data. The Stanford University Institutional Review Board approved the protocol, and the study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained before enrolling each participant.

2.2. Participants

The main inclusion criteria were 21 to 65 years of age, English fluency, and chronic low back pain as the chief pain complaint, with pain duration $\geq$3 months and pain intensity $\geq$4 on a 0 to 10 numeric rating scale. The chronicity of the low back pain was defined by self-report, as a back pain problem that has persisted at least 3 months and has resulted in pain on at least half the days in the past 6 months.[18] The main exclusion criteria were receipt of acupuncture in the past 5 years, radicular symptoms, and ongoing legal or disability claims related to CLBP. Additional details on the inclusion or exclusion criteria, as well as the screening and consent processes are published elsewhere.[28]

2.3. Timeline of the experiment and choice of anatomical testing locations

After informed consent, participants completed questionnaires assessing back pain symptoms, demographics, and psychosocial functioning, followed by QST, which included TS and CPM (**Fig. 1**).

Importantly, we varied the TS location: proximal to the pain location in the lower back ("lumbar") and distal to the pain location on the thenar eminence of the hand ("thenar"). In contrast, for CPM, we selected the testing and condition locations to be both heterotopic and contralateral (nondominant hand and contralateral foot, respectively) to ensure reliable CPM[25] and did not vary these locations.

2.4. Data collection

2.4.1. Measures

The following questionnaires were administered within 1 to 2 days before or on the day of the psychophysical testing.

2.4.1.1. Back pain bothersomeness

Back pain bothersomeness was assessed on a 0 (not bothersome at all) to 100 (extremely bothersome) scale[12] over the preceding week. It was the prespecified, primary behavioral outcome of the mind–body intervention clinical trials.

2.4.1.2. The Roland Morris Disability Questionnaire

The Roland Morris Disability Questionnaire (RMDQ) was assessed on a 0 (no disability) to 24 (maximum disability) scale on the day of testing. It is a commonly used questionnaire to assess disability specific to CLBP[49] and was the prespecified primary functional outcome.

2.4.1.3. The NIH Patient-Reported Outcomes Measurement Information System

The NIH Patient-Reported Outcomes Measurement Information System (PROMIS) measures[8] were administered using computer-adaptive testing. We assessed the PROMIS depression and anxiety over the preceding 7 days as measures for

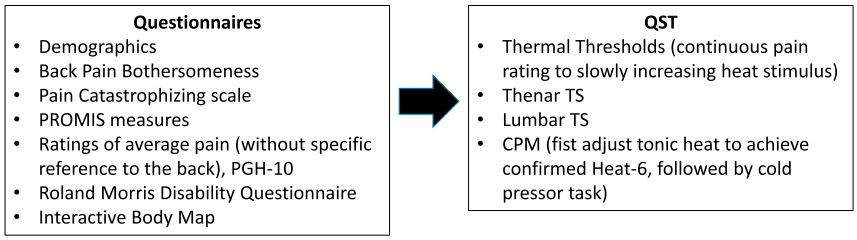

Figure 1. Experimental flow. CPM, conditioned pain modulation; Heat-6, the temperature at which a 30-second tonic stimulus resulted in pain ratings around 6 (between 5 and 7); PGH-10, the 10th item from PROMIS global health short form; PROMIS, Patient-Reported Outcomes Measurement Information System; TS, temporal summation.

negative affect.[14,59] Other PROMIS measures (pain interference, pain behavior, fatigue, and sleep-related impairment) were used to describe the study sample.

2.4.1.4. Overall pain intensity

Average pain intensity "in general" was assessed on a 0 (no pain) to 10 (worst pain imaginable) numeric rating scale. Note this item is the 10th item from the PROMIS global health short form ("How would you rate your pain on average")[19] and did NOT restrict the areas of pain rating to the low back.

2.4.1.5. Pain Catastrophizing Scale

The Pain Catastrophizing Scale[56] includes 13 items, with each item rated on a 0 (not at all) to 4 (all the time) scale. The total Pain Catastrophizing Scale score ranges from 0 to 52, with higher scores indicating greater pain catastrophizing.

2.4.1.6. Body map

A standardized, interactive visual body map assessed the number of currently painful body locations (on the day of survey),[51] with a minimum of zero and maximum of 74.

2.5. Quantitative sensory testing

The current study analyzes the TS and CPM data and related thermal measures from the full QST protocol that included other measures.[37] The detailed TS and CPM protocols are published elsewhere[33] and briefly described below.

2.5.1. Temporal summation

Temporal summation of heat pain was assessed using a Medoc Pathway Analyzer (Medoc, Ltd, Ramat Yishai) with a 2.9 cm-diameter circular thermode using individualized heat pulses via constant contact. First, to minimize floor and ceiling effect, the baseline and peak temperature of the heat pulse for each participant were adjusted to achieve TS between 30 and 70 out of 100. Next, TS was assessed on the thenar eminence by repeating the individualized heat pulses 10 times, with pulse duration of 0.5 seconds and peak-to-peak interstimulus interval of 2 seconds. Thenar TS was assessed twice, first on the nondominant hand, followed by the dominant hand 5 minutes later. During each trial, participants were asked to rate the heat pain continuously using a 0 to 100 visual analog scale on a horizontal lever device provided by Medoc (COVAS). The magnitude of TS from each trial was computed by subtracting pain of the first heat pulse from peak pain of the 10-pulse train. The TS from each trial was then averaged to obtain the final thenar TS magnitude.

The same procedure was then repeated on the low back (lumbar), approximately 2 to 3 inches lateral to the L4-5 interspace. The heat pulse temperatures for the lumbar TS was also individually adjusted as with the thenar TS.

2.5.2. Conditioned pain modulation

Conditioned pain modulation was assessed on the nondominant thenar eminence using a 30-second calibrated Heat-6 stimulus (test stimulus, via the same Medoc device as above) and on the contralateral foot using a cold-pressor task (submersion in a cold water bath) at 10°C for 2 minutes (conditioning stimulus). Before the CPM and TS tasks, Heat-6 was determined for each participant where the heat pain from the thermode applied to the hand for 30 seconds was rated at 6 ± 1 out of a 0 to 10 scale. The Heat-6 stimulus was applied twice, before and during the last 30 seconds of the 2-minute conditioning stimulus. The participant was asked to rate the heat stimulus on a scale from 0 to 10 verbally, immediately after each application. Conditioned pain modulation was calculated as the change in the pain rating of the Heat-6 as a result of the conditioning stimulus, ie, (pain during) − (pain before).

2.6. Statistical analysis

2.6.1. Missing data

We analyzed data from all participants who completed CPM testing. Little's Missing Completely At Random[32] test was conducted with all other continuous variables listed under Measures and QST sections above, $\chi^2 = 104.01$, $P = 0.903$, suggesting missing values were considered missing at random. Overall, the missing rates were minimal: 2.3% for thenar TS and lumbar TS and ≤4.5% for survey data. We therefore imputed the missing values using the mean values of the sample. We used imputed data only for the proportional odds regression analysis. We used raw data (unimputed) for the descriptive statistics.

2.6.2. Analytical approach

R version 3.6.1 was used for all analyses. First, Shapiro–Wilk tests were conducted to examine normality of CPM, thenar TS and lumbar TS data, which significantly violated normality assumption ($P < 0.001$), and was not fixable by transformation. Therefore, Mann–Whitney *U* tests and Wilcoxon signed rank tests were used to compare variables in the descriptive statistics.

We examined the relationship between TS and CPM by performing 2 proportional odds logistic regression (POLR) analyses with TS at the thenar, then the lumbar site as the

dependent variable, and negative affect and CPM as the independent predictors, while adjusting for baseline demographics. Note that the POLR is a class of generalized modeling without distribution assumptions on either the dependent or the independent variables. Because of the nonnormal distribution of TS, we were unable to use linear regression and instead performed ordinal regression (POLR) where the raw TS magnitudes were converted into quartiles. The differences in the corresponding coefficients between the 2 models (eg, β for Heat-6 in the thenar vs lumbar TS model) were computed according to the study by Paternosterand Clogg.[10,41] In all cases, 2-tailed *P* values of ≤0.05 were considered statistically significant.

Finally, in an exploratory post hoc analysis, we examined the association between TS at the lumbar and at thenar location, and between TS and CPM and the primary clinical outcomes including back pain bothersomeness and RMDQ via nonparametric Spearman correlations. The effect of multiple comparisons was accounted for by the Holm–Bonferroni method.

3. Results

3.1. Participant characteristics

3.1.1. Demographics

For the purpose of this study, we included only the participants who completed the CPM task (n = 264) from a total sample of 326 participants (**Table 1**). Of the 264 participants, about half were male (53.0%), half were White or Caucasian (51.5%), and half were married (55.3%). The mean age was 40.7 years (SD = 12.4). Only 11 participants reported taking prescription opioids (4.2%). Comorbid pain conditions, including neck pain, joint pain, or other pain, were reported in 23.1% of the participants.

3.1.2. Behavior outcomes

Our participants demonstrated moderate level of pain and disability with mean of back pain bothersomeness 59.8 (SD = 16.8) and mean RMDQ 5.3 (SD = 1.4) (**Table 2**). They endorsed having on average 7.5 pain sites (SD = 4.7), and 99.2% endorsed having more than one pain area. Our interactive body map included 6 regions designated for the low back. Because 133 of the 264 participants reported pain in ≥7 body areas, it is inferred that >50% of the participants experienced pain beyond the low back.

3.1.3. Quantitative sensory testing outcomes

Large variability was seen in the response to the TS and CPM tasks (**Fig. 2**). Sixty-two participants were excluded because they could not tolerate the 2-minute cold conditioning at 10°C. For those who completed the CPM task, efficient CPM, defined as reduction of pain ratings due to the conditioning stimulus (ie, negative CPM values), was observed in 208 participants (78.8%), and 27 (10.2%) and 29 (11.0%) reported no change or increased pain during CPM testing. Furthermore, the median value of CPM in our study was −1.8 (IQR: −3.0 to −1.0) on a 0 to 10 numerical rating scale.

During TS testing, 6 of the 264 participants (2.3%) could not tolerate the heat pulses in the thenar paradigm and another 6 could not tolerate heat pulses in the lumbar paradigm. Only 1 individual failed to tolerate both thenar and lumbar TS. Of those who completed TS testing, 15 participants (5.8%) did not demonstrate summation (ie, TS = 0) at the thenar location, and 18 participants (7.0%) did not summate at the lumbar location. TS values were significantly higher at the thenar location (median = 32.9, IQR: 18.9–48.1) than at the lumbar location (median = 22.6, IQR: 9.3–37.1), with $P < 0.0001$, 95% confidence interval (CI, 5.3–10.7).

3.1.4. Regressions to estimate thenar and lumbar temporal summation by conditioned pain modulation

Final regression models for thenar and, separately, lumbar TS using CPM and additional measures are shown in **Table 3**. Both models were superior to their respective null models, as indicated by a smaller Akaike information criterion (AIC). The *P*-values for the log likelihood tests were <0.05.

Three main results from **Table 3** are highlighted. First and foremost, both the thenar and the lumbar TS models contained CPM as a significant predictor with similar βs (0.17) and *P*-values (0.01), representing a negative relationship between TS and CPM, ie, less efficient (ie, greater positive value of) CPM was associated with greater TS. Second, unlike the lumbar TS model that only contained CPM as a significant predictors, the thenar TS model also included Heat-6 and the stimulating temperatures of the heat pulses as significant predictors. Third, when comparing the coefficient for Heat-6 between the thenar and lumbar TS models, the results in **Table 4** showed a significant difference ($P = 0.007$, 95% CI = [0.30–0.33]), with greater β for Heat-6 in the thenar model. In contrast, CPM influences TS to a similar degree (βs = 0.17, *P*s = 0.01) between the lumbar and the thenar models. The coefficients for CPM magnitude in predicting thenar and lumbar TS were not statistically different ($P = 0.98$, 95% CI = [−0.062 to 0.075]).

We also evaluated the effects of sequentially removing negative affect variables (depression and anxiety), demographics, and Heat-6 from the original model on the model performance, as well as on the coefficient and *P*-value for CPM in the prediction models (Supplemental Materials, available at http://links.lww.com/PR9/A139). We found that the removal of negative affect or demographics did not change the performance of the models (AIC ~ 716–718) or the significance level for the CPM predictor, around 0.01 (Suppl Mat'l 3a, 3b, available at http://links.lww.com/PR9/A139). However, removal of a single predictor variable,

Table 1

Baseline demographics.

	n (%)	Responders (n)
Sex Male/female	139 (52.7%)/125 (47.3%)	264
Race or ethnicity White or Caucasian	136 (51.5%)	257
Marital status Married	146 (55.3%)	262
Employment Currently employed	215 (82.1%)	262
Education College or higher	191 (73.5%)	260
Comorbid pain* Any	61 (23.1%)	261
	M (SD)	
Age (y)	40.7 (12.4)	257
BMI (kg/m^2)	25.0 (4.3)	262

* Comorbid pain conditions include neck pain (5.7%), upper back pain (4.6%), shoulder pain (3.4%), knee pain (3.4%), and the others (<2%).
BMI, body mass index.

Table 2

Summary statistics on participants' characteristics including quantitative sensory testing.

	M	SD	Min	Max
Back pain bothersomeness (0–100)	59.8	16.8	10.0	100.0
Average pain intensity (PGH-10, 0–10)	5.3	1.4	2.0	9.0
RMDQ (0–24)	7.8	4.5	0.0	24.0
PCS total scores (0–52)	14.7	9.3	0.0	48.0
Number of pain areas (0–74)	7.5	4.7	0.0	34.0
PROMIS (T-scores)				
Depression	51.5	7.7	34.2	69.5
Anxiety	54.0	7.6	32.9	73.4
Pain interference	59.2	5.1	47.0	74.1
Fatigue	56.1	7.9	24.3	79.0
Sleep impairment	55.8	8.0	26.2	76.4
CPM				
Confirmed Heat-6 (°C)	44.2	1.7	36.5	48.5
CPM (−10.0 to 10.0 NRS)	−1.8	1.9	3.0	−7.0
TS thenar				
Base temperature (°C)	40.2	2.5	33.0	44.8
Δ temperature (°C)	9.7	1.7	5.6	13.0
TS (0–100 VAS)	33.3	21.8	0.0	99.9
TS lumbar				
Base temperature (°C)	38.3	2.6	30.0	44.0
Δ temperature (°C)	9.9	1.4	0.5	13.0
TS (0–100 VAS)	25.2	19.1	−8.7	87.5

CPM, conditioned pain modulation; Heat-6, the temperature at which a 30-second tonic stimulus resulted in pain ratings around 6 (between 5 and 7); PCS, Pain Catastrophizing Scale; NRS, numerical rating scale; PGH-10, the 10th item from PROMIS global health short form, assessing average intensity of pain (not specified to the back); PROMIS, Patient-Reported Outcomes Measurement Information System; RMDQ, Roland Morris Disability Questionnaire; TS, temporal summation, Δ temperature, the difference between the individualized base and peak temperature in the heat pulse to general thermal TS.

Heat-6, led to a loss of performance for the thenar TS model (AIC increased from 708 to 723–726) while not appreciably changing the lumbar TS model performance, with AIC decreasing from 718 to 717 (Suppl mat's 2, 3c, available at http://links.lww.com/PR9/A139). Therefore, Heat-6 is a significantly explanatory variable for the thenar TS model but not the lumbar TS model.

3.2. Exploratory analyses

The Spearman correlations and the corresponding *P*-values (with and without adjustment for multiple comparisons) between thenar and lumbar TS, between CPM and clinical outcomes, and between TS (both thenar and lumbar) and clinical outcomes are shown in **Table 4**. As expected, thenar and lumbar TS are highly correlated ($r = 0.422$, adjusted $P < 0.001$). Conditioned pain modulation correlated modestly with back pain bothersomeness ($r = 0.14$, adjusted $P = 0.048$). No significant correlations were found between the clinical outcomes and TS at either thenar or lumbar site.

4. Discussion

We identified a modest association between efficient CPM and reduced TS via nonparametric regression modeling, irrespective of testing location, demographics, or negative affect in 264 individuals with moderate CLBP. Importantly, with individualized pulsatile thermal TS and a common CPM paradigm involving individualized heat and CPT, we observed variability in response to these dynamic QST paradigms that might reveal individual differences in central pain processing.

4.1. Relationship between temporal summation and conditioned pain modulation

Our primary analyses (POLR) demonstrated that augmented TS was associated with less efficient CPM, independent of testing location on the body, demographics, or negative affect. Our results echoed those by Naugle[39] (51 healthy adults) and Martel[35] (190 adults with any back or neck pain) and extended their findings by using a conservative, nonparametric regression technique, which also allowed us to assess the influence from other factors, including testing location, peripheral heat sensitivity, demographics, and affect. For example, Martel assumed normality and used linear regression and Pearson correlation in evaluating the relationship between TS and CPM, whereas Naugle only evaluated the relationship between TS and CPM using Spearman correlation. Therefore, our study, via nonparametric logistic regression, confirmed an, intrinsic, modest association between heightened TS and inefficient CPM suggested by earlier studies with less stringent analytical techniques.

Although both TS and CPM are often used to describe an individual's central pain regulatory state, it is not clear whether TS and CPM are 2 sides of the same coin (ie, intimately related) or

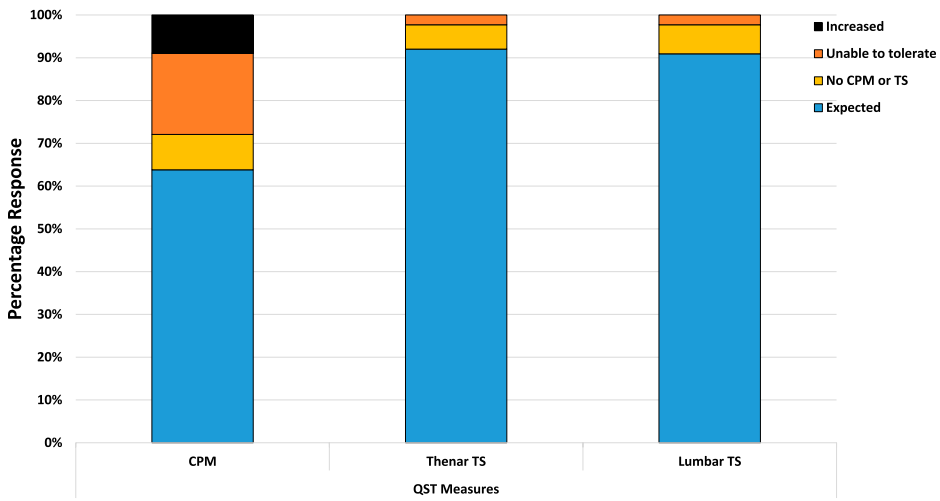

Figure 2. Variability in participants' response to TS and CPM tasks. CPM, conditioned pain modulation; QST, quantitative sensory testing; TS, temporal summation.

Table 3

Proportional Odds Linear Regression models to estimate lumbar temporal summation and thenar temporal summation.

Covariates	Lumbar TS model		Thenar TS model	
	β (95% CI)	*P*	β (95% CI)	*P*
Baseline stimulating temperature (for TS)	0.005 (−0.11 to 0.12)	0.935	0.314 (0.12 to 0.51)	0.001
Δ T (pulse temperature for TS)	0.150 (−0.03 to 0.34)	0.122	0.280 (0.01 to 0.55)	0.039
Confirmed Heat-6	−0.070 (−0.22 to 0.08)	0.358	−0.381 (−0.56 to −0.21)	<0.001
CPM magnitude	**0.165 (0.04 to 0.29)**	**0.011**	**0.172 (0.05 to 0.30)**	**0.008**
Female sex	−0.418 (−0.87 to 0.03)	0.069	−0.073 (−0.53 to 0.39)	0.755
Age	−0.015 (−0.03 to 0.004)	0.125	−0.019 (−0.04 to −0.0001)	0.049
White race	0.254 (−0.23 to 0.74)	0.301	0.005 (−0.48 to 0.49)	0.985
PROMIS-anxiety	0.031 (−0.009 to 0.07)	0.126	−0.006 (−0.05 to 0.03)	0.761
PROMIS-depression	−0.014 (−0.05 to 0.03)	0.484	0.023 (−0.02 to 0.06)	0.271
Log likelihood test of models above compared with null	**Lumbar TS model**		**Thenar TS model**	
AIC of model above	718		708	
AIC of respective null model	721		721	
Degree of freedom	9		9	
χ^2	21.4		31.0	
P	0.011		<0.001	

Bold numbers highlight the statistically significant association between CPM and TS in each model. AIC, Akaike information criterion; CI, confidence interval; CPM, conditioned pain modulation; PROMIS, Patient-Reported Outcomes Measurement Information System; TS, temporal summation.

represent independent aspects of pain regulation. The elucidation of the precise relationship between TS and CPM therefore is critical for the interpretation of these dynamic QST data in the context of chronic pain pathophysiology. Our results, along with those by Martel and Nagle, are building a body of knowledge supporting the modest concordance between heightened TS and inefficient CPM across several pain conditions. This relationship is "heuristic" as suggested by Martel because either increased ascending pain facilitation (reflected by TS) or reduced descending pain inhibition (reflected by CPM) may be associated with a pro-nociceptive state.[62] However, the concordance between TS and CPM is limited ($\beta < 0.2$), suggesting that they measure mostly distinct pain regulatory pathways. Therefore, both TS and CPM should be measured when dynamic QST is considered, as either or both measures may be altered in an individual with chronic pain.

4.2. The influence of anatomical location on thermal temporal summation

Our study showed that, compared with the lumbar location, the thenar TS was more strongly influenced by peripheral heat sensitivity.

Phasic thermal TS (ie, heat pulses at frequency ≥0.33 Hz) paradigms are widely used in clinical research because of its ease to deliver and standardize. However, there were concerns regarding the difficulty by some subjects in distinguishing A-delta fiber–mediated sensations from that of C-fiber-mediated true TS.[1,26] For example, Robinson et al.[48] found strong correlation between TS (also measured at hand) and supra-threshold heat response, a purported measure of peripheral heat sensitivity, raising the possibility that phasic thermal TS may not be a purely central measure. Our results, especially from the regression model for thenar TS, support this possibility.

However, habituation to noxious heat may also explain our observation. Repetitive noxious heat administration may activate complex patterns of sensitization and habituation.[23,26,46] Our finding of higher TS at the thenar (nonpainful site) compared with the lumbar (painful site) is inconsistent with previous findings of greater TS at painful sites in patients with chronic pain.[47,48] Because thenar TS was measured before lumbar TS, habituation to heat pain may explain our results. Further thermal TS testing with randomized anatomical location is needed to confirm our findings.

Relevance of TS and CPM in clinical research and methodological considerations.

Table 4

Exploratory analysis: Spearman correlations among key quantitative sensory testing variables and clinical pain.

Key association examined	Variable 1	Variable 2	*r*	*P*	Adjusted *P**	Significance
TS of different locations	Thenar TS	Lumbar TS	0.422	2.40E-12	2.40E-12	***
CPM vs clinical outcome	CPM	Back pain bothersomeness	0.142	0.024	0.048	*
	CPM	RMDQ	0.068	0.271	0.542	
TS vs clinical outcome	Thenar TS	Back pain bothersomeness	0.102	0.112	0.448	
	Thenar TS	RMDQ	0.015	0.811	1	
	Lumbar TS	Back pain bothersomeness	0.029	0.645	1	
	Lumbar TS	RMDQ	−0.002	0.979	1	

* Holm–Bonferroni correction was used to account for multiple comparisons. Specifically, 2 comparisons were used to identify relationship between CPM and behavioral outcomes, and 4 comparisons were used to identify relationship between TS and behavioral outcomes. Because only 1 comparison was used to compute the association between thenar and lumbar TS, the adjusted *P* remained the same as the unadjusted.
CPM, conditioned pain modulation; RMDQ, Roland Morris Disability Questionnaire; TS, temporal summation.* p<0.05 but >0.01; ** p<0.01 but >0.001;*** p<0.001.

We may interpret the relevance of TS and CPM in clinical research by examining: (1) the proportion of individuals in whom these measures can be obtained; (2) the association between TS and CPM and clinical pain outcomes from our exploratory analysis.

Our individualized TS protocol resulted in a much larger proportion (>93%) of participants who provided TS data than published fixed protocols, which can miss up to 50% of participants.[1,26,27] However, TS from our sample did not correlate with any pain outcomes. This lack of correlation might result from the fact that we individualized thermal stimulating temperatures to achieve a standardized, moderate level of TS, thereby minimizing its between-individual variability.

Our CPM protocol with a cold conditioning stimulus missed 62 of 326 participants (19%) who could not tolerate the cold-pressor task. Of the remaining 264 participants included in our study, the proportion that displayed efficient CPM (79%) is at the higher end of the reported range of 24% to 89% for CLBP[34,35,44] and may reflect the moderate level of pain experienced by our participants. Regardless, we observed a small, negative correlation between efficient CPM and back pain bothersomeness. Although our correlation analyses were post hoc and should be considered exploratory, they are consistent with findings from a recent meta-analysis on TS and CPM in CLBP.[36]

Overall, our individualized TS method demonstrated an excellent success rate but no association between the resultant TS and clinical pain. In contrast, our CPM method using a fixed temperature conditioning stimulus missed about 20% of the participants but demonstrated a small association with clinical pain. Regardless, the magnitudes of the associations are so small that neither CPM nor the individualized TS temperature appears to be a suitable surrogate marker of clinical pain intensity.[36]

Importantly, our participants demonstrated varied profiles in the outcomes to TS and CPM paradigms. Previous studies showed that derangement in either TS[42,43] or CPM[30,63] may predict outcome to specific treatments whose mechanisms of action overlap with the pain processing pathway each of these QST measures represent. As such, TS and CPM might be better suited as predictive and prognostic markers of pain[22,29,35,44] and will be explored in subsequent articles from our research program.

4.3. Limitations

Our study has several limitations. First, most of our participants were employed (82%), had at least a college degree (74%), had moderate disability (mean RMDQ = 7.8), and did not take any opioid medications (95.8%). Therefore, our results may not be generalizable to patients with more disadvantage/disability or those taking opioids. Concurrent opioid consumption was associated with reduced CPM.[13] Second, we used phasic thermal TS and a CPM paradigm that also involved noxious heat as the test stimulus. The overlapping stimulus modality between our TS and CPM paradigms may have undue influence on their relationship identified in our primary analysis. Third, the greater influence of peripheral heat sensitivity on thenar compared with lumbar TS might be due to a fixed experiment order where the thenar TS was assessed before the lumbar TS. Finally, we excluded 19% of the original sample (62 of 326), who did not tolerate the cold-pressor task from CPM. Therefore, our results cannot apply to participants unable to tolerate the cold-conditioning stimulus. Importantly, not tolerating the conditioning stimulus is not equivalent to absent CPM.

5. Conclusion

Our study advances the current understanding of central sensitization in the context of chronic low back pain by demonstrating: (1) a modest association between efficient CPM and reduced TS, thus supporting the measurement of both in characterizing central pain processing; (2) large variability in the profile of response to a thermal TS paradigm and a conventional thermal or cold-conditioning CPM paradigm that may serve as individual signatures in characterizing central pain regulation; (3) possibly stronger influence of peripheral heat sensitivity in the measurement thermal TS at the thenar but not the lumbar site, although this will require subsequent confirmatory studies. Our findings will help improve the methodology and interpretation of TS and CPM in characterizing central pain processing in chronic pain.

Disclosures

The authors have no conflict of interest to declare. Of note, Dr. Darnall is Chief Science Advisor at AppliedVR and her consulting role with this company is unrelated to the current research.

NIH P01AT006651, K23AT008477, K23DA048972, K24DA029262, Redlich Pain Endowment.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A139.

Article history:
Received 31 May 2021
Received in revised form 21 September 2021
Accepted 10 October 2021

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