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Published in:
Pain

DOI (link to publication from Publisher):
10.1097/j.pain.0000000000001737

Publication date:
2020

Document Version
Accepted author manuscript, peer reviewed version

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000001737

Alterations in pro-nociceptive and anti-nociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis

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Disclosures: Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). Nocitech is partly owned by Aalborg University.

Systematic review paper for: PAIN

Manuscript Pages: 36 + tables (2), figures (3) and supplementary material (6)

Tables: 2 + 4 supplementary

Figures: 3 + 2 supplementary

Abstract

Altered pro-nociceptive and anti-nociceptive mechanisms are often implicated in painful conditions and have been increasingly studied over the past decade. For some painful conditions alterations are well-established, but in low back pain (LBP) populations there remains considerable debate whether these mechanisms are altered. The present systematic review aimed to address this issue by identifying studies assessing Conditioned Pain Modulation (CPM) and/or Temporal Summation of Pain (TSP) in LBP patients, comparing to either a healthy control group or using a method with reference data available. Qualitative synthesis and quantitative meta-analysis of group differences were performed. For CPM and TSP, 20 and 29 original articles were eligible, with data for meta-analysis obtainable from 18 (1500 patients, 505 controls) and 27 (1507 patients, 1127 controls) studies, respectively. Most studies were of poor-to-fair quality with significant heterogeneity in study size, population, assessment methodology and outcome. Nonetheless, CPM was impaired in LBP patients compared to controls (standardized mean difference = -0.44 [-0.64, -0.23], P<0.001), and the magnitude of this impairment was related to pain chronicity (acute/recurrent versus chronic, P=0.003), duration (R=-0.62, P=0.006) and severity (R=-0.54, P=0.02). TSP was facilitated in LBP patients compared to controls (standardized mean difference = 0.50 [0.29, 0.72], P<0.001), and the magnitude of this facilitation was weakly related to pain severity (R=0.41, P=0.04) and appeared to be influenced by test modality (P<0.001). Impaired CPM and facilitated TSP was present in LBP patients compared to controls, though the magnitude of differences was small which may direct future research on the clinical utility.

Keywords: Conditioned pain modulation; temporal summation of pain; low back pain; systematic review with meta-analysis; pain mechanisms

INTRODUCTION

In the past decade, research into pro-nociceptive and anti-nociceptive mechanisms among patients with pain has increased dramatically. These mechanisms have been identified and implicated, in particular, in nociplastic pain states where there is an absence of clear peripheral tissue injury but a severe clinical pain experience [37]. As a result, enhanced pro-nociceptive profiles are commonly purported to be a highly relevant factor contributing to both current experience and future development of disabling clinical pain states [4; 88]. In some specific painful conditions, such as fibromyalgia syndrome, findings of altered nociceptive processing have been near universal [56]. However, in other painful conditions, such as low back pain (LBP), findings are inconsistent, with debate around both the presence and significance of alterations in these mechanisms [64].

Several sensory testing parameters have been used to characterize the balance between pro-nociception and anti-nociception. For example, much research has focused on sensory detection and pain thresholds across a range of modalities, such as mechanical, thermal, electrical, some of which have been shown to be altered among LBP patients [32; 45; 54]. However, these thresholds only give a static indication of sensitivity, which may be influenced by a number of factors (e.g. time of day [5], subcutaneous fat [59; 72]) that are likely irrelevant to the condition at hand. Alternatively, assessments of dynamic pain sensitivity using the Conditioned Pain Modulation (CPM) and Temporal Summation of Pain (TSP) paradigms give insight into the relative responsiveness of the nervous system to painful stimuli, potentially better indicating hypersensitivity.

Prior systematic reviews investigating CPM and TSP have focused on chronic pain generally [42], other specific populations, such as irritable bowel syndrome [43] or fibromyalgia [56], or on pertinent testing considerations, such as methodological [34] or personal [29] influences. In LBP

populations specifically, existing reviews have looked primarily at the static forms of quantitative sensory testing [30; 44; 45], as at the time of publication of these reviews, very few articles investigating CPM or TSP were available. The focus of these reviews has also varied, with aims to investigate early somatosensory changes [45], prognostic value of sensory testing [44] or the relation of sensory testing to pain-related factors [30], though conclusions have been consistently inconclusive due to a paucity of evidence. As many studies are now available comparing these mechanisms between patients with LBP and pain-free controls, a systematic review and meta-analysis was warranted to clarify whether alterations are in fact present in these individuals and to what magnitude.

This review aimed to systematically identify, evaluate the quality of, and meta-analyze data from studies assessing CPM and TSP in LBP patients, which compared to pain-free controls or used standardized methodology with available reference data, to establish whether alterations were present in this patient group. Additional sub-analyses aimed to evaluate if differences in CPM and TSP between LBP patients and controls were related to pain chronicity, severity and test methodology.

METHODS

This systematic review and meta-analysis was pre-registered on PROSPERO (CRD42018118142) and reported after the PRISMA statement [50].

Search Strategy

PubMed, Scopus, EMBASE and the Cochrane Register of Clinical Trials were searched, for English-language articles from inception to present, using combinations of keywords pertaining to CPM, TSP and LBP (see Supplementary Table S1 for full list of search terms, available as supplemental digital content at http://links.lww.com/PAIN/A901) in December 2018. All identified citations were exported to a library, and duplicates were removed. Due to the high number of

potential inclusions, articles were initially screened on title to remove irrelevant and non-English language items, then on abstract to further remove items that clearly did not investigate LBP or sensory testing. Full-text articles were screened against selection criteria and were tentatively included if they examined TSP and/or CPM with any method in any form of clinical LBP. Both online citations and reference lists from these articles were hand-searched for additional missed articles.

Eligibility Criteria

Articles were required to have a full-text available in English, to use human subjects, and to test at least one of the paradigms of interest (CPM or TSP) in a clinical population of majority (>50%) LBP patients, not due to menstruation, malignancy, vertebral fractures or serious underlying pathology. Articles could include subgroups of patients with other pain conditions, provided LBP data could be extracted separately. For CPM paradigms, articles needed to broadly detail applying a painful experimental test stimulus prior to and during (parallel paradigm) or following (sequential paradigm) the application of a painful conditioning stimulus at another body site. For TSP paradigms, articles needed to detail measuring pain or reflex activity in response to repeated (frequency >0.33Hz) or sustained painful experimental stimuli (i.e. not endogenous provocations of pain summation such as repeated movement).

Only original research articles were included, though no restrictions were made in relation to article type or purpose. Data was assumed to be from independent samples and thus publications from the same research group were only excluded if explicitly stated as duplicate in text. Articles were separated into those with a pain-free comparator group (n = 20), and those without (n = 29). If a pain-free comparator group was included in the study, the article was automatically eligible for inclusion in the review and meta-analysis. To maximize available usable data, for articles without a comparator group, methodology and sample characteristics were assessed to identify those either: (a) using identical assessment methods, with a similar sample, performed by the same research

group as another included article with healthy comparators, or (b) using a standardized assessment method for which there is published reference data on pain-free individuals (sample size >100). These articles were also eligible for inclusion in the review and meta-analysis.

Data Extraction

Data extraction of administrative information, study and sample characteristics (including low back pain eligibility criteria, pain duration, severity and neuropathic pain features), methodology, results and conclusions, was performed by one reviewer (MEM) and checked by a second reviewer (HBV). When possible, group means and standard deviations for CPM and TSP effects (as delta or percentage change scores) at baseline (prior to any intervention or exposure) were extracted directly from the manuscript, or derived from available values (medians, IQR, 95% CI, etc.) using appropriate estimation formulas [83]. If articles reported data from more than one assessment site (e.g. back and hand) or over more than one repetition at baseline, then aggregate mean data was used for overall comparison. If articles assessed and reported both parallel and sequential CPM paradigms, then parallel values were used for meta-analysis. Similarly, if articles assessed sequential CPM and reported multiple assessments after the cessation of conditioning, then the first available post-measurement was used. For TSP, if both raw stimulus scores and change or ratio data was presented, then the change or ratio data was used. If not available in-text, change or ratio data was extracted from available graphs and figures using free online plot digitizing software (https://apps.automeris.io/wpd/). If still not obtainable, or if only raw stimulus data (not delta values) were presented, then group means and standard deviations were requested from corresponding authors. If no control group was included, but a suitable reference dataset was identified, then relevant reference data were extracted from manuscripts and entered to correspond with the matching papers. Data were first entered into excel, then into RevMan (Review Manager v5.3, The Nordic Cochrane Centre, Copenhagen, DK) for meta-analysis.

Quality Assessment

To assess the risk of bias and general quality of included studies, the Newcastle-Ottawa tool for case-control studies was used [84], modified in a similar manner to previous reviews on this topic [42; 56] (see supplementary Table S2 for full criteria, available as supplemental digital content at http://links.lww.com/PAIN/A901). Quality assessment was performed on all included articles by two independent reviewers (MEM and HBV), with consultation of a third reviewer (TGN) in the event that consensus could not be achieved through discussion. Articles received a total score out of 9, with articles not including control groups being allowed a maximum of 6. To be considered high quality with low risk of bias, articles had to have a score of minimum 6 and needed to fulfil at least three *Selection*, one *Comparability* and two *Exposure* criteria. Fair quality articles needed to have a score of minimum 4, fulfilling at least two *Selection*, one *Comparability* and one *Exposure* criteria. While articles obtaining scores of 3 or less, or failing to fulfil any criteria in a single subcategory obtained a poor quality rating indicating high risk of bias [80]. For articles including measures of both CPM and TSP, a score was given for each measure separately.

Meta-analysis

Data was extracted from included articles and reference papers as detailed above and entered for overall meta-analysis of each aggregate measure (CPM and TSP). In addition, data was separated into groups for comparison, based on: Pain chronicity (as defined within articles as acute or recurrent versus chronic >3 months), pain severity (mean current or average LBP rating equivalent to numerical rating scale of ≤5/10 or >5/10), test and conditioning stimulus modalities (cold, heat, pressure, or electrical), test site (painful segment or extra-segmental for TSP) and assessment procedure (parallel or sequential for CPM). If studies included multiple subsets within these factors (e.g. both acute and chronic patients), they were separated for subgroup analysis. Variables were entered as positive or negative dependent on the direction of favorable outcome such that higher numbers entailed greater inhibition (CPM) and facilitation (TSP).

Using RevMan5.0, an overall effect size estimate (Z statistic) using an inverse variance random-effects model (due to known between-study heterogeneity) and significance level of differences between patients and controls was calculated from standardized mean differences, based on entered group mean and standard deviation data and sample sizes, both with and without studies requiring reference data for comparison. Degree of between-study variance (Tau^2) and degree of between-study inconsistency (I^2) were used as assessments of study heterogeneity. Effects of other factors (chronicity, severity, modality, test site, and assessment procedure) were analyzed by determining effect size estimates for comparisons between-groups within a factor. Effect size estimates were then compared between sub-groups via chi-square tests.

For chronicity and pain severity, a further correlational analysis was undertaken, whereby mean pain severity (normalized to a 0-10 scale from the presented visual analogue or numeric rating scale data for current or average pain intensity) and mean pain duration (normalized to a number of years from presented duration) were extracted from each article (where available) and correlated to between-group standardized mean difference (SMD) in CPM and/or TSP. Further, correlations between alterations in CPM and TSP were performed for studies assessing both variables. Spearman's correlation coefficients were used due to non-normality of pain duration data on Shapiro-Wilks testing. Significance was accepted at $P<0.05$, data is reported as SMD and 95% confidence intervals (SMD [95%CI]).

RESULTS

Included Study Characteristics

This review initially identified 4905 articles, screened 3690 articles on title through to full-text and included 20 eligible articles for CPM [13; 14; 17; 20; 27; 36; 38; 39; 46; 48; 49; 51; 55; 57; 58; 61; 62; 65; 81; 82] and 29 eligible articles for TSP [6; 8; 9; 11; 12; 16; 21; 24; 27; 31; 33; 35; 46; 51; 54; 55; 58; 60; 65; 70; 71; 73-76; 78; 79; 81; 82] (see Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram in Figure 1). Studies varied considerably in terms

of purpose and design, with by far the most being observational cross-sectional comparative studies (CPM: n = 9, TSP: n = 17), but also including interventional trials (CPM: n = 3, TSP: n = 6), test-retest reliability studies (CPM: n = 1, TSP: n = 2), longitudinal cohort studies (CPM: n = 4, TSP: n = 3), and some experimental trials (CPM: n = 3, TSP: n = 1). A summary of additional study characteristics is provided in Supplementary Table S3-S4 (available as supplemental digital content at http://links.lww.com/PAIN/A901).

---------- *Insert Figure 1 approximately here* ----------

Quality of Included Studies Assessing CPM

Most studies were of poor (n = 15) to fair (n = 4) quality, with only one high quality study (n = 1, Table 1). All studies (n = 20) provided adequate descriptions of the CPM protocol and did not appear to have unexplained drop-outs. The vast majority of studies (n = 18) also provided appropriate descriptions of inclusion requirements for LBP patients. However, only near half of the included studies recruited patients in a randomized or consecutive manner (n = 9), and many studies failed to fulfill criteria for appropriate control participant selection, with especially few studies (n = 2) reporting the use of prior LBP as an exclusion criteria. Notably, none of the included studies appropriately adjusted analyses for known influential factors, and only near half of those with an internal control group (n = 6) controlled for between-group age and gender. Studies were rarely blinded (n = 2), but in some cases (n = 4) used automated measurement systems limiting assessor-related bias.

---------- *Insert Table 1 approximately here* ----------

Quality of Included Studies Assessing TSP

Similar to CPM studies, most studies assessing TSP were of poor (n = 20) to fair (n = 7) quality, with few high quality studies (n = 2, Table 2). The majority of studies (n = 25) adequately defined inclusion criteria for LBP patients and either appropriately detailed or did not have dropouts, though

under half of studies (n = 12) reported appropriate random or consecutive patient selection procedures. Approximately two thirds of studies (n = 19) either used blinded assessors or more commonly used automated stimuli, and similarly two thirds (n = 19) provided a clear description of TSP methodology. Some studies (n = 9) controlled for participant age and gender, while only few (n = 2) adjusted for confounding factors. Many problems were noted with control participant selection, with relatively few studies (n = 4) selecting controls from similar populations to patients and no studies using LBP history as an excluding feature.

---------- *Insert Table 2 approximately here* ----------

Methodological Aspects of Included Studies

Studies used a variety of different outcomes, modalities, sites and paradigms to assess CPM and TSP. For CPM (see Supplementary Figure S1 for illustration, available as supplemental digital content at http://links.lww.com/PAIN/A901) the most common conditioning stimulus was the Cold Pressor Task (immersion of an extremity in cold water, n = 14), though the temperature, location and duration of application varying. In the majority, temperatures used were at or below 2°C, though one study used 7°C, while others adjusted temperatures on an individual basis to achieve a desired pain intensity. Similarly, the majority of studies encouraged participants to withstand this stimulus for 2 minutes, while others used shorter, longer, repeated or individually tailored timeframes. In terms of test stimuli, the majority of studies used pressure-based measures (n = 14), while the remainder used either heat (n = 4) or electrical stimuli (n = 2). Precise outcomes were inconsistent though, with some studies using detection thresholds, others tolerance thresholds, and some pain ratings of supra-threshold stimuli.

For TSP (see Supplementary Figure S2 for illustration, available as supplemental digital content at http://links.lww.com/PAIN/A901) the most common stimulus modality was mechanical (n = 16), though this varied between monofilaments, pin-prick stimulation, and handheld or cuff pressure algometry. Heat (n = 5) and electrical stimuli (n = 9) were also used less frequently.

Stimulus duration and frequency varied in relation to modality, with all repetitive stimuli being applied at frequencies between 0.33 Hz and 2.4 Hz, and one study using a constant stimulus. Outcome and site of application similarly varied with modality, but in most cases (n = 21) the outcome was a pain rating relative to a single stimulus.

Study Conclusions on Alterations in CPM and TSP

Many studies were not interested in group comparisons for CPM and TSP and thus did not conclude on alterations in these measures. Of those that did comment on differences in CPM between LBP patients and controls, three suggested CPM was impaired [13; 38; 61], three more suggested a degree of impairment either in subgroups of patients or only in specific time-related or methodological approaches [36; 48; 58], while others suggested no CPM impairment was observed [17; 27; 39; 46; 57; 81].

For TSP, eight articles indicated LBP patients had facilitated TSP [9; 11; 16; 54; 58; 71; 73; 81], two more indicated facilitation in specific LBP subgroups with widespread pain or trauma exposure [24; 74], and three suggested no difference from controls [27; 31; 46].

Meta-analysis of CPM in Patients with Low Back Pain compared to Controls

A total of 1500 patients with LBP and 505 control participants were included in the 18 studies assessing CPM with data available for meta-analysis. In aggregate analysis of all data, CPM was impaired in patients with LBP compared to controls ($Z=3.97$, $P<0.001$), however the difference in CPM magnitude between patients and controls was small (SMD=-0.44 [-0.64, -0.23], Figure 2). When only including studies with a within-study control group (n = 13), the effect size was reduced, though still showed CPM impairment in patients with LBP compared to controls (SMD=-0.34 [-0.59, -0.10], $Z=2.75$, $P<0.01$).

---------- *Insert Figure 2 approximately here* ----------

Meta-analysis of TSP in Patients with Low Back Pain compared to Controls

A total of 1507 patients with LBP and 1127 control participants were included in the 27 studies assessing TSP available for meta-analysis, and reference data was obtained from 4 additional studies [3; 28; 53; 63]. In aggregate analysis, TSP was facilitated in patients with LBP compared to controls ($Z=4.56$, $P<0.001$), however, the difference in TSP between patients and controls was small (SMD=0.50 [0.29, 0.72], Figure 3). Similar to CPM, when only including studies containing within-study control groups (n = 16), the effect size was reduced, but still showed significant facilitation of TSP in LBP patients compared to controls (SMD=0.40 [0.17, 0.63], $Z=3.38$, $P<0.001$).

---------- *Insert Figure 3 approximately here* ----------

Effects of Pain Chronicity on alterations in CPM and TSP in the Meta-analysis

For CPM there were 6 studies reporting data from acute or recurrent LBP patients, and 14 studies reporting data from chronic patients. For the acute or recurrent LBP subgroup (n = 287) there was no difference in CPM from controls (SMD=-0.11 [-0.30, 0.08], $Z=1.17$, $P=0.24$), though CPM was impaired in the chronic LBP subgroup (n = 1113) compared to controls (SMD=-0.57 [-0.82, -0.33], $Z=4.66$, $P<0.001$). Effects of acute or recurrent LBP on CPM were thus different from chronic LBP ($X^2_1=8.74$, $P=0.003$, Figure 2), with greater impairment observed for chronic patients. Further, extracted mean pain durations were moderately correlated with between-group SMD in CPM ($R_S=-0.621$, $P=0.006$).

For TSP there were 8 studies reporting data from acute or recurrent LBP patients, and 18 studies reporting data from chronic LBP patients. Both the acute or recurrent LBP subgroup (n = 315, SMD=0.51 [0.16, 0.85], $Z=2.87$, $P<0.01$) and the chronic LBP subgroup (n = 933, SMD=0.55 [0.30, 0.81], $Z=4.20$, $P<0.001$) showed facilitation of TSP compared to controls. Effects of chronicity on TSP were thus not significant, with no difference observed between subgroups

(X^2_1=0.04, P=0.84, Figure 3). Similarly, extracted mean pain durations showed no clear association with between-group SMD in TSP (R_S=-0.034, P>0.86).

Effects of Pain Severity on Alterations in CPM and TSP in the Meta-analysis

For CPM there were 10 studies with LBP patients reporting a high mean pain intensity (>5/10), and 6 studies with LBP patients reporting a low mean pain intensity. CPM was impaired compared to controls in those studies with high patient-reported pain intensities (SMD=-0.63 [-0.96, -0.31], Z=3.78, P<0.001), but not in those with low pain intensities (SMD=-0.10 [-0.30, 0.10], Z=0.95, P=0.34). Pain severity thus impacted the magnitude of impairment in CPM (X^2_1=7.40, P<0.01). Consistent with this, a moderate association was observed between mean pain severity and between-group SMD in CPM (R_s=-0.538, P=0.021), suggesting higher pain severity was associated with greater impairment in CPM compared to controls.

For TSP there were 10 studies with LBP patients reporting a high mean pain intensity (>5/10), and 13 studies with LBP patients reporting a low mean pain intensity. TSP was facilitated compared to controls in both studies with high patient-reported pain intensities (SMD=0.54 [0.12, 0.95], Z=2.54, P=0.01) and low patient-reported pain intensities (SMD=0.48 [0.21, 0.75], Z=3.52, P<0.001), with no difference observed due to severity (X^2_1=0.04, P=0.84). However, a weak correlation was also observed between pain severity and between-group SMD in TSP (R_S=0.411, P=0.041), whereby higher pain severities were associated with more facilitation compared to controls.

It should be noted that pain severity was not correlated with pain duration (R_S=0.087, P>0.61), so these results should not be interpreted as reflective of the same relationship. Further, among studies with available data for both CPM and TSP (n = 6), these variables were not correlated (R_S = 0.143, P>0.75).

Effect of Stimulus Modality on Alterations in CPM and TSP in the Meta-analysis

Adequate data was available to compare studies assessing CPM using cold (n = 13) versus hot (n = 4) conditioning stimuli, though this factor did not significantly alter magnitude of CPM impairment (X^2_1=1.64, P=0.20). Similarly, sufficient data was available to compare studies assessing CPM using pressure detection thresholds (n = 4), pressure tolerance thresholds (n = 5), other pressure-based assessment methods (n = 4), and heat pain ratings (n = 4). No significant subgroup differences were noted between these different test modalities (X^2_3=4.51, P=0.21).

Sufficient data was available to compare studies assessing TSP using heat (n = 4), mechanical (n = 13), pressure-based (n = 3) and electrical (n = 8) test stimuli. Test modality had a significant effect on the magnitude of facilitation of TSP compared to controls (X^2_3=36.95, P<0.001), with much stronger facilitation among LBP patients observed in articles using electrical stimuli especially those with reflex threshold (mA) as the outcome (SMD=1.07 [0.94, 1.20], Z=16.45, P<0.001), rather than pressure or mechanical stimuli. Though this may be explained by the lack of relativity in this modality (i.e. not compared to the first evoked response).

Effect of Other Methodological Variations on Alterations in CPM and TSP in the Meta-analysis

No subgroup differences in effect size were observed based on whether articles used a parallel (n = 13) or sequential (n = 5) assessment of CPM (X^2_3=0.19, P=0.67). Articles assessing TSP over the lower back (n = 10), upper limb (n = 13) or lower limb (n = 14) were compared, but no differences in effect size were observed on the basis of test site (X^2_2=2.29, P=0.32).

Heterogeneity in the Meta-analysis

High levels of heterogeneity and inconsistency were noted for both outcome measures (CPM: Tau^2=0.18, X^2_{16}=78.65, P<0.001, I^2=80%; TSP: Tau^2=0.28, X^2_{16}=225.77, P<0.001, I^2=88%), though the majority of this heterogeneity can be attributed to true variance between study results,

rather than within-study error. This was expected, given the known heterogeneity in sampling, study sizes, modalities and protocols.

DISCUSSION

This paper presents the most extensive systematic review and meta-analysis of CPM and TSP data in LBP patients compared to controls to date. Studies were considerably heterogeneous in design, purpose, assessment methodology, LBP population included and findings, and the vast majority were considered to have moderate to high risk of bias for the outcomes investigated. On qualitative synthesis, conclusions on CPM and TSP comparisons were inconsistent with studies reporting alterations at the group level, only under specific conditions, or not at all. Nevertheless, in the meta-analysis comparing with healthy controls or reference data, patients with LBP showed significantly impaired CPM and significantly facilitated TSP, though the magnitudes of these differences were small. Chronicity and pain severity seemed to impact the magnitude of difference between LBP patients and controls most for CPM, whereas test modality impacted observed differences for TSP.

Quality Improvement

Overall, study quality was poor with only very few studies demonstrating low risk of bias. The primary reason for increased risk of bias across studies was a failure to appropriately select control participants, with very few articles explicitly requiring an absence of LBP history in the control group and few selecting controls from similar populations to the LBP patients. Although this consideration may seem trivial, the question of whether alterations in CPM and TSP precede and contribute to, or are consequential to, LBP development remains to be answered, and thus it is not clear how individuals with a history of LBP should be expected to behave relative to normal. Further, despite known influences of various demographic, personal and lifestyle factors, such as age, gender, physical activity, psychological distress and sleep quality on CPM and TSP [22; 29;

36; 52; 68; 77], and the fact these characteristics may be altered in different population groups and by painful conditions, these were rarely properly considered or controlled for in analyses.

Blinding was also a major issue. Although a number of studies used automated stimuli, which can mitigate exposure bias to some extent, blinding of assessors to patient status would offer superior control; especially given expectations are known to alter outcomes [10; 41]. Generally, it appeared that studies with appropriate blinding or automation were less likely to show a significant within-study group difference, at least for CPM, but it was not possible to formally analyze this factor due to inherent modality differences and the small number of blinded studies. Lack of blinding has also been highlighted in previous reviews of quantitative sensory testing studies [56] and is a problem that needs to be addressed in future research to improve the strength of conclusions.

Population Considerations

As mentioned, other chronic pain populations (e.g. fibromyalgia syndrome, irritable bowel syndrome, knee osteoarthritis, etc. [4; 42; 43; 56]) show clearer relation to alterations in CPM and TSP than observed here. However, LBP might be considered a much more heterogeneous condition. As such, the included studies presented data from a range of LBP populations, with approximately two thirds focusing on chronic patients and the remainder looking at acute, recurrent, present and radicular LBP. Within each sub-population, inclusion criteria varied in terms of minimum/maximum pain duration, lower limits for pain intensity and disability, extent of pain radiation, presence of neuropathic features and comorbid complaints allowed. One could argue that this strengthens the generalizability of findings from this review to the broader LBP population, though this also questions the consistency of LBP definitions. In fact, many of the studies investigating ‘acute’ LBP patients used criteria in accordance with the proposed recurrent LBP definition [69], which brings into question whether alterations observed in this group really are reflective of immediate changes due to acute pain, or to progression of a recurring painful

condition. Furthermore, many studies chose to exclude patients with overt radiating pain or neuropathy, but few studies attempted to quantify neuropathic-like pain features. As has been stated previously [2; 69], better standardization in LBP definitions and inclusion/exclusion criteria, as well as consideration of more mechanism-based classification of pain features, would aid the comparison of outcomes across studies and allow for firmer conclusions to be made in relation to specific types of LBP with and without comorbid conditions.

Pain Chronicity and Severity

Pain chronicity and severity both seemed to affect the magnitude of alterations in CPM, while there was only weak indication of a relationship between pain severity and TSP. To some extent this opposes the work of Hubscher et al. [30], and prior experimental LBP studies [7; 47], where associations have been demonstrated between pain intensity and TSP, but not CPM. These studies were notably limited in sample size/available number of studies, but also performed more nuanced analyses than the crude subgroup comparisons and group mean correlations in the present review.

Relationships between pain duration and CPM impairment have previously been demonstrated in other painful conditions, such as knee osteoarthritis [19]. In the present work, this relationship is unclear, as there is evidence that CPM can become more impaired over time as pain persists and becomes chronic [67], but there is also evidence from musculoskeletal pain patients [23; 66] and surgical populations [87], that individuals with greater impairment in CPM prior to or soon after pain onset may be at increased risk for future chronic pain development. It could be the case that acute LBP patients represent a highly heterogeneous group with regard to CPM, such that those with appropriately functioning inhibitory systems recover while only those with impairments progress to develop recurring or ongoing pain. Alternatively, it may be such that there is a time-dependent impairment of CPM in these patients consequential to the transition to chronicity, though this is merely speculation. Interestingly, the lack of this relationship between pain duration and TSP, i.e. with clear facilitation of TSP present in both acute and chronic patients, would suggest that

facilitated TSP and pain presence are to some extent connected. The directional nature of this connection could be debated, however it seems plausible that ongoing nociception in either an acute or chronic state would give rise to facilitated TSP (consistent with original theories of wind-up[85]) and thus enhanced pain perception.

In terms of pain severity, higher pain levels may lead to greater disability levels and greater concurrent impairments in other factors [26; 40], such as mood, stress, sleep and physical activity that also influence CPM and TSP. Alternatively, impaired CPM and/or facilitated TSP may drive experiences of ongoing spontaneous pain [1] or the development of greater pain intensity and distribution [25]. It is, however, far beyond the scope of this review to tease out the contribution and directional relationship of each of these factors to the difference in sensory testing between acute/chronic or high/low severity LBP patients, but their consideration in future work is encouraged.

Methodological Considerations

A commonly cited methodological consideration among reviews on sensory testing is the heterogeneity in TSP and CPM assessment methods [18]. This review is no different with significant variation noted in modalities used, stimulus timing, number of trials or repetitions performed, and body site assessed. Many articles have called for standardization in assessment methods and as such standard quantitative sensory testing protocols [63] and guidelines for test methodology have been developed [86]. Despite this, there remain substantial gaps in knowledge, particularly regarding the relevance of different stimulus parameters to effect sizes in different pain conditions, and there is still ongoing debate around which methods are most reliable and valid. A recent review included only pressure-based assessment methods in low back pain patients, as these are often assumed to be most relevant to musculoskeletal conditions, though still results for TSP and CPM were mixed [15].

Given there is little consensus on how methodology impacts CPM and TSP, and that all methods claim to measure the same mechanisms; a meta-analysis was performed despite these differences. From this meta-analysis, it would appear that stimulus modality and timing did not have a clear impact on CPM findings. However, for TSP, studies assessing the nociceptive withdrawal reflex could show greater discrimination from controls than other mechanical or thermal modalities. This modality is argued to be more objective, as it relies on the magnitude of electromyographic responses rather than perceptual ratings, so may provide a cleaner measure of spinal hyper-excitability. One major factor that needs to be considered here, however, is that reflex thresholds are generally not relative. In TSP paradigms with subjective ratings it is normal practice to provide either a ratio or change score from a single stimulus to the repeated series. In these reflex studies, however, the outcome was given for the repeated series alone, not taking into account that electrical pain thresholds to single stimuli were also commonly altered in LBP patients [9; 54].

It is further worth noting that this meta-analysis combined continuous data representing group differences. Hence, while it was clear that CPM was lower and TSP was higher in LBP patients compared to controls, this does not indicate whether significant inhibition or facilitation was present within paradigms. In addition, some included studies were unable to demonstrate 'normal' responses to the paradigms in the control groups, so further consideration of best methodology and the development of larger normative datasets is warranted. Finally, few studies assessed both CPM and TSP, though among these the measures appeared independent and thus should both be investigated in future populations to elucidate the distinct value of each.

The value of CPM and TSP in LBP Populations

The overall magnitude of differences in CPM and TSP between LBP patients and controls were small, and there was considerable variation in whether individual studies were able to identify such a difference. Author conclusions in individual studies of facilitated TSP were more common than those of impaired CPM, but neither were consistently demonstrated across samples. As a result, the

value and utility of these measures in LBP remains to be clarified. If clear group differences exist only when data from hundreds of patients is synthesized, it may be that these measures are not individually discriminative of LBP diagnosis, but may offer utility in characterizing LBP phenotypes that respond differentially to treatments, which is yet to be fully explored. Further, there is room for methodological exploration to improve how influential factors are accounted for and determine the best assessment approach. It may also be that combinations of CPM and TSP with other outcomes provide greater utility in determining the extent of neuroplasticity in central pain mechanisms. As well, the present review cannot conclude on predictive or prognostic value of these measures which may be a more promising avenue [17; 46; 51; 70] and again remains to be fully elucidated. Finally, relationships between CPM, TSP, and pain chronicity or severity are intriguing, and deserve further exploration. Such associations may hint at a possibility to intervene with these mechanisms to prevent pain progression or reduce pain severity, but the question of cause versus consequence versus coincidence in these relationships remains to be answered.

Limitations

An extensive systematic search was undertaken and further hand-searching for relevant articles was conducted to retrieve as many eligible articles as possible, however, it is still possible that pertinent research was either missed or excluded. Some data was converted from different measures (median, IQR, SEM) to mean and standard deviation based on appropriate formulas. However, these formulas make assumptions about normality of the data and thus provide only an estimate of centrality which should be considered when interpreting the data. Quality assessment may also be skewed toward more negative results, given articles without control groups were also included and could only achieve a high quality rating by fulfilling all possible criteria. For this reason, care has also been taken to highlight these studies and consider their effect on conclusions in the meta-analysis. In some cases, studies conducted by the same research group were included from which some patient data may be replicated as this information was not specifically requested from authors.

Sub-group comparisons should further be interpreted with caution, as these reduce available sample sizes and hence increase the impact of methodological heterogeneity between-studies. Similarly, with regard to the correlations, these are based on available mean data which may not accurately reflect the same construct in all cases. For example, pain duration in acute patients was usually reported as the length of the current episode despite prior histories of LBP in many cases, where in recurrent or chronic patients it was often the full duration since initial episode or diagnosis despite possible periods without pain. Likewise, current or average pain severity were used when available, but these scores may vary dependent on question phrasing (e.g. with respect to timeframe), so these results should be considered only as indications of relationships that require further study.

Conclusion

CPM was impaired and TSP was facilitated in LBP patients compared to controls, though the magnitude of differences was small. There remains room for improvement in terms of LBP definition consistency, participant selection, assessment standardization and consideration of confounding influences among studies. Future research should focus on improving these aspects and investigating the relation of these measures to clinical pain parameters, along with further investigating the utility of these measures in treatment response and prognosis prediction.

ACKNOWLEDGEMENTS

Center for Neuroplasticity and Pain (CNAP) is supported by the Danish National Research Foundation (DNRF121). Nocitech is partly owned by Aalborg University.

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Figure Legends:

Figure 1: PRISMA Flow Diagram of study identification, screening, eligibility assessment and inclusion. As searches were conducted separately for conditioned pain modulation (CPM) and temporal summation of pain (TSP) keywords, duplicate articles between these factors may exist.

Figure 2: Forest plot showing standardized mean differences (SMDs) and confidence intervals (CI) for low back pain (LBP) patients compared to controls, sub-grouped by study-defined chronicity, from articles assessing CPM. Greyed studies are those without an internal control group where reference data, as cited in Supplementary Table S3 (available as supplemental digital content at http://links.lww.com/PAIN/A901), has been used for comparison, with control participant numbers

from these studies denoted using R. Note: *Shows weighting in overall analysis as not included in a subgroup analysis.

Figure 3: Forest plot showing standardized mean differences (SMDs) and confidence intervals (CI) for LBP patients compared to controls from articles assessing TSP. Greyed studies are those without an internal control group where reference data, as cited in Supplementary Table S4 (available as supplemental digital content at http://links.lww.com/PAIN/A901), has been used for comparison, with control participant numbers from these studies denoted using R. *Shows weighting in overall analysis as not included in a subgroup analysis.

Table 1: Newcastle-Ottawa Quality Assessment of Included Studies assessing Conditioned Pain Modulation

	Selection Bias				*Comparability*		*Exposure*			
Author (Year)	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*Score*
Correa (2015)	+	-	-	-	-	+	-	+	+	4
Correa (2016)	+	+			-		-	+	+	4
Dubois (2016)	-	-	+	+	-	-	+	+	+	5
France (2016)	+	-	-	-	-	-	+	+	+	4
Goubert (2017)	+	-	-	-	-	-	+	+	+	4
Klyne (2018)	+	-	+	-	-	-	-	+	+	4
Krafft (2017	+	-	-	-	-	-	+	+	+	4
Ladouceur (2018)	+	-	-	+	-	+	+	+	+	5
Marcuzzi (2018)	+	+	+	-	-	+	+	+	+	7
Mlekusch (2013)	-	+			-		-	+	+	3
Mlekusch (2016)	+	+	-	-	-	-	-	+	+	4
Muller (2018)	+	+			-		-	+	+	4
Neziri (2012)	+	+			-		-	+	+	4
O'Neill (2013)	+	+	-	-	-	+	-	+	+	5
Owens (2016)	+	-	+	-	-	+	-	+	+	5
Rabey (2015, MT)	+	-	-	-	-	+	-	+	+	4
Rabey (2015, P)	+	-			-		-	+	+	3
Schliessbach (2018)	+	+			-		-	+	+	4
Vuilleumier (2015)	+	+			-		-	+	+	4
Vuilleumier (2017)	+	-	-	-	-	-	-	+	+	3

Note: See Supplementary Table S2 for full criteria, + = fulfilled, - = not fulfilled, = unable to assess (no within-study control group)

Table 2: Newcastle-Ottawa Quality Assessment of Included Studies assessing Temporal Summation of Pain

	Selection Bias				*Comparability*		*Exposure*			
Author (Year)	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	
Bialosky (2009)	+	-			-		+	+	+	4
Biurrun Manresa (2011)	+	-			-		+	+	+	4
Biurrun Manresa (2013)	+	+	-	-	+	-	+	-	+	5
Blumenstiel (2011)	+	+	+	-	-	-	-	+	+	5
Coronado (2014)	+	+			-		+	+	+	5
Diers (2007)	+	-	-	-	-	-	+	+	+	4
Freynhagen (2008)	-	-	-	-	-	+	-	-	+	2
Gerhardt (2016)	+	+	-	-	-	-	+	+	+	5
Goubert (2017)	+	-	-	-	-	-	-	+	+	3
Hubscher (2014)	+	-	-	-	-	+	+	+	-	4
Kapitza (2010)	+	-			-		-	+	+	3
Kleinbohl (2006)	-	-	-	-	-	+	+	-	-	2
Marcuzzi (2018)	+	+	+	-	-	+	+	+	+	7
Muller (2018)	+	+			-		+	-	+	4
Neziri (2012, RA)	+	+	+	-	+	+	+	-	+	7
Neziri (2012, IV)	+	+			-		+	-	+	4
Owens (2016)	+	-	+	-	-	+	-	+	+	5
Puta (2013)	+	-	-	-	-	+	-	+	+	4
Schliessbach (2018)	+	+			-		+	-	+	4
Starkweather (2016, CJP)	+	-	-	-	-	-	-	+	-	2
Starkweather (2016, BR)	+	-	-	-	-	-	-	-	-	1
Tesarz (2015)	+	-	-	-	-	+	+	+	+	5
Tesarz (2016)	+	-	-	-	-	+	+	+	+	5
Tschugg (2015)	+	+			-		-	+	+	4
Tschugg (2018)	-	+			-		-	+	+	3
Vaegter (2016)	-	-			-		+	+	+	3
Vaegter (2017)	+	-			-		+	+	+	4
Vuilleumier (2015)	+	+			-		+	-	+	4
Vuilleumier (2017)	+	-	-	-	-	-	+	-	+	3

Note: See Supplementary Table S2 for full criteria, + = fulfilled, - = not fulfilled, = unable to assess (no within-study control group)