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Conditioned pain modulation is more efficient in patients with painful diabetic polyneuropathy than those with nonpainful diabetic polyneuropathy

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Abstract

Endogenous pain modulation, as tested by the conditioned pain modulation (CPM) protocol, is typically less efficient in patients with chronic pain compared with healthy controls. We aimed to assess whether CPM is less efficient in patients with painful diabetic polyneuropathy (DPN) compared with those with nonpainful DPN. Characterization of the differences in central pain processing between these 2 groups might provide a central nervous system explanation to the presence or absence of pain in diabetic neuropathy in addition to the peripheral one. Two hundred seventy-one patients with DPN underwent CPM testing and clinical assessment, including quantitative sensory testing. Two modalities of the test stimuli (heat and pressure) conditioned to cold noxious water were assessed and compared between patients with painful and nonpainful DPN. No significant difference was found between the groups for pressure pain CPM; however, patients with painful DPN demonstrated unexpectedly more efficient CPM_{HEAT} (-7.4 ± 1.0 vs -2.3 ± 1.6; $P = 0.008$). Efficient CPM_{HEAT} was associated with higher clinical pain experienced in the 24 hours before testing ($r = -0.15$; $P = 0.029$) and greater loss of mechanical sensation ($r = -0.135$; $P = 0.042$). Moreover, patients who had mechanical hypoesthesia demonstrated more efficient CPM_{HEAT} ($P = 0.005$). More efficient CPM among patients with painful DPN might result from not only central changes in pain modulation but also from altered sensory messages coming from tested affected body sites. This calls for the use of intact sites for proper assessment of pain modulation in patients with neuropathy.

Keywords: Conditioned pain modulation, Neuropathic pain, Diabetic polyneuropathy, Sensory loss

1. Introduction

Diabetic polyneuropathy (DPN) is a common complication of diabetes mellitus, affecting up to 50% of patients.[8,34,35,40] Of these patients, up to half will experience neuropathic pain.[14,16,34,35,38,40] The exact pathophysiological mechanisms of neuropathic pain in diabetes mellitus remain unclear, and it is unclear why some patients suffer from chronic pain, whereas others are pain-free.[6] However, factors associated with pain in DPN include altered endogenous pain modulation and the severity of the peripheral sensory loss.[21,39]

Endogenous pain modulation refers to the ability of the central nervous system to reduce or augment pain.[1,17] Descending pain modulation can be assessed in humans through the conditioned pain modulation (CPM) paradigm,[30,46] a psychophysical equivalent of the assessment of diffuse noxious inhibitory control (DNIC) in animals. Conditioned pain modulation testing can assist in predicting pain acquisition, characterizing pain syndromes, and predicting response to pain treatment.[7,18,48,49,51] Several systematic reviews and meta-analyses concluded that CPM is less efficient in patients with various pain syndromes when compared with healthy controls.[24,44,50]

Less efficient CPM has been reported in patients with neuropathic pain of various etiologies, for example, chemotherapy-induced neuropathy,[25] neuropathic low back pain,[36] and spinal cord injury.[13] Little is known about CPM in patients with painful DPN; however, recent studies demonstrated that among these patients, less efficient CPM is associated with a shorter chronic pain duration,[11] they have reduced exercise-induced analgesia,[19] and deficient CPM can be restored with efficient pharmacological analgesia.[25,26,50]

To the best of our knowledge, there are no published studies comparing the CPM efficiency in patients with DPN with vs those

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without neuropathic pain. In this article, we aimed to characterize CPM efficiency in patients with painful and nonpainful DPN in a large cohort of patients from 2 centers. In line with other chronic pain syndromes, we hypothesized that patients with painful DPN will demonstrate less efficient CPM.

2. Methods

2.1. Study population

Patients with painful and nonpainful DPN were studied in 2 clinics, Rambam Medical Center, Technion, Haifa, Israel, and Imperial College Hospital, London, United Kingdom. Patients were recruited from local diabetes clinics and general practice surgeries through advertising in local newspapers (Israel) and specialist national diabetic publications (United Kingdom). Inclusion criteria were a diagnosis of diabetes mellitus (type I or II) with symptoms of peripheral polyneuropathy. Patients had to be aged at least 18 years (for more detailed recruitment information see published study protocol[29]). Patients were excluded if they had insufficient mental capacity or proficiency of either Hebrew or English language to obtain consent (in Israel and United Kingdom, respectively), significant neurological disorders other than DPN, psychiatric disorders, and moderate to severe pain from other causes that may confound assessment or pain reporting.

A diagnosis of DPN was confirmed according to the established minimal criteria of DPN: signs and symptoms of DPN and supportive clinical findings including either abnormal nerve conduction studies or abnormal findings on thermal quantitative sensory testing (QST).[37] To be classified as painful diabetic neuropathy, patients had to positively answer the question: "*Are you currently troubled by pain in your hands or feet either all the time or on and off?*"[29] meet the NeuPSIG criteria for probable or definite neuropathic pain,[9] and have no other cause for peripheral pain or neuropathy other than diabetes. To be classified as nonpainful diabetic neuropathy, patients had to be diagnosed as DPN as given above and have negatively answered the question regarding pain given above.

2.2. Study design

The protocol of this observational cross-sectional study was approved by the local ethics committees, in accordance with the Declaration of Helsinki: the Institutional Review Board of Rambam Health Care Campus (No. 0052-15) and London—Bromley Research Ethics Committee, NHS Health Research Authority, England (REC ref: 16/LO/1470). This article refers to the shared data collection in both centers and is part of the larger DOLORisk multicenter observational study that aimed to understand the risk factors and determinants of neuropathic pain. The full protocol of this study can be found elsewhere.[29] Participants were initially screened through a phone call. Written informed consent was obtained from each participant at the beginning of the study session before data collection or assessment. Study sessions took place at the Laboratotry of Clinical Neurophysiology, Rambam Health Care Campus and Technion Faculty of Medicine, Israel (the "Technion" site), and in the Department of Pain Medicine, Imperial College, Chelsea and Westminster Hospital Campus, London ("Imperial college" site). Study participants attended one study session that included the following:

1. A structured lower limb neurological examination and scoring using the Toronto Clinical Neuropathy Score (TCNS). The TCNS is a reliable and valid clinical tool to capture symptoms and signs of diabetic sensorimotor polyneuropathy.[3]
2. Quantitative sensory testing was conducted according to a previously published protocol of the German Research Network of Neuropathic Pain (DFNS) on the dorsal aspect of the foot identified by the participant as most affected by neuropathy. If the patient could not identify the most affected foot, the laterality of the DFNS assessment was chosen randomly. This battery of quantitative sensory tests consists of 13 parameters (including thermal and mechanical tests to determine detection thresholds for cold, warmth, touch, and vibration) and helps identify somatosensory phenotypes of patients with neuropathic pain.[32,43] In this article, we will report only the results of sensory threshold assessment. In brief, cold detection and warm detection thresholds (CDT and WDT, respectively) were assessed using devices that increased or decreased temperature by 1°C per second (TSA 2001-II; Medoc, Ramat Yishay, Israel; thermode contact area of 30 × 30 mm) used at Technion site and MSA (Somedic AB, Norra Mellby, Sweden; thermode contact area of 25 × 50 mm) used at Imperial site; both thermodes are based on the Peltier elements. Thermal thresholds were calculated as the step taken from the adaptation temperature of 32°C. Quantitative sensory testing data collected from the most affected foot were entered into the data analysis system Equista provided by the DFNS. Equista transforms the raw QST data into *z* scores normalized for age, sex, and body site.

   In addition to the DFNS protocol, the Technion site assessed sensory detection thresholds (CDT, WDT, and mechanical detection threshold [MDT]) at the dominant forearm. CDT and WDT were measured 3 times each using TSA-II (Medoc) with a Peltier 30 × 30 mm contact thermode according to the method of limits.[47] The baseline temperature of 32°C decreased or increased at a rate of 1.0°C per second. Participants were instructed to press the response button when warm or cold sensation was perceived. Detection thresholds were calculated as the mean values of the 3 measurements. The MDTs were measured using von Frey filaments. Consecutive filaments were applied until the patient reported that sensation was perceived. Each filament was applied 3 times until the filament pressure was detected in at least 2 of the 3 trials. The first filament to be detected at ≥2 out of 3 times was determined as the MDT. The sensory detection thresholds from the forearm were analyzed as raw scores.
3. Conditioned pain modulation assessment: The test stimulus consisted of a combination of 3 measurements of pressure pain threshold (PPT $Ts_{stand\text{-}alone}$) delivered on the trapezius muscle with an interstimulus interval of 3 to 5 seconds followed by a 20-second tonic heat stimulus delivered to the dominant volar forearm (Heat $Ts_{stand\text{-}alone}$). The tonic heat stimulus was given at individually predetermined temperature that evoked the pain intensity of Pain50 on a 0 to 100 numerical pain scale. The pressure stimuli were delivered with a pressure algometer (Medoc and Wagner Instruments, Riverside, CT), gradually increasing the pressure by 0.5 kg per seconds until the patient reported pain. Heat stimuli were delivered with a 3 × 3 cm contact (TSA probe; Medoc and MSA probe; Somedic AB, Imperial), with a ramp up of 2°C per second and ramp down of 8°C per second. After a 5-minute break, the "conditioning stimulus" (Cs) was applied by immersion of the nondominant hand in a cold-water container (8–12°C; the water temperature was adjusted during initial familiarization to evoke pain perception in the range of 20–80 on the numerical pain scale). After 10 seconds, while the Cs was still applied, 3 PPT measurements were taken followed by the thermal test stimulus rating. Pain ratings of the heat stimulus were obtained at 2 seconds, 10 seconds, and 20 seconds

Table 1

Clinical characteristics of patients with painful and nonpainful diabetic polyneuropathy.

	Painful DPN	Nonpainful DPN	*P*
TCNS*	11.4 ± 4.3	9.3 ± 4.0	<0.001
CDT†	−1.9 (−2.1, −1.8)	−1.5 (−1.7, −1.2)	0.004
WDT†	−1.5 (−1.6, −1.4)	−1.3 (−1.4, −1.1)	0.012
MDT†	−1.7 (−2, −1.4)	−0.8 (−1.2, −0.5)	0.001
VDT†	−2.2 (−2.5, −1.8)	−1.8 (−2.4, −1.2)	0.293

* TCNS (mean ± SD).
† The QST results presented in *z* scores—mean (lower 95% CI, upper 95% CI).
CDT, cold detection threshold; CI, confidence interval; DPN, diabetic polyneuropathy; MDT, mechanical detection threshold, QST, quantitative sensory testing; TCNS, Toronto Clinical Neuropathy Score; VDT, vibration detection threshold; WDT, warm detection threshold.

postinitiation. Pain ratings of the Cs were obtained at 10 seconds after hand immersion (for the detailed CPM protocol please see https://www.youtube.com/watch?v=jL9GgdsyHtA). Two CPM scores were calculated as the difference between the 'test stimuli' (mean score of the last 2 heat pain ratings; CPM_{HEAT} and mean PPT value; CPM_{PPT}) obtained during the "Cs" vs the baseline stimulus. Positive CPM_{PPT} score and negative CPM_{HEAT} score indicated efficient CPM.

4. Assessment of physiological and psychological aspects of pain and pain perception using a battery of questionnaires.[29]

2.3. Statistical analysis

JMP (SAS Institute, Cary, NC) was used for statistical analyses. Demographic and clinical parameters were compared using the *t* test or through nonparametric comparisons, when applicable. Analysis of variance (ANOVA) models explored the influence of age, sex, status (painful or nonpainful DPN), and recruiting center (Technion and Imperial College) on CPM and CPM-related parameters (such as $Ts_{stand\text{-}alone}$, Ts given under Cs, and Cs). These models were performed after excluding the abnormal residuals based on the Cook D influence. In addition, CPM_{HEAT} calculation was performed only for patients whose mean pain score to the test stimulus was ≥20, as has previously been published,[12,15] because a low stand-alone test pain leads to a floor effect on the CPM.

The QST *z* scores were compared between 2 groups using independent group *t* tests. The QST *z* score data were expressed as mean ± 95% confidence interval.

Pearson correlation analyses examined the relationships between the clinical parameters and CPM efficiency. The level of significance was set at $P < 0.05$. The data for descriptive statistics or *t* test comparisons are presented as mean ± SD or, if nonnormally distributed, as median (min, max). The values from the ANOVA are presented as mean ± SE. ANOVA effect size is presented as eta-squared (η^2).

3. Results

3.1. Demographic characteristics

Two hundred seventy-one patients participated in this study: 198 patients from Technion and 73 from Imperial College. The distribution of patients with painful (N = 195) vs nonpainful (N = 76) DPN was similar across both centers: 143 (72%) and 55 (28%) at the Technion and 52 (71%) and 21 (29%) at Imperial College (χ^2 $P = 0.880$), respectively. In line, the ratio of males to females among patients with painful vs nonpainful DPN was not statistically different (136 males [70%] and 59 females [30%], painful DPN vs 61 males [80%] and 15 females [20%], nonpainful DPN; χ^2 $P = 0.095$). The patients with painful DPN were slightly but significantly younger (63.5 ± 10.6 vs 66.5 ± 9.5, $P = 0.033$). Among the whole study sample, 22 patients with DPN (8%) had type I diabetes.

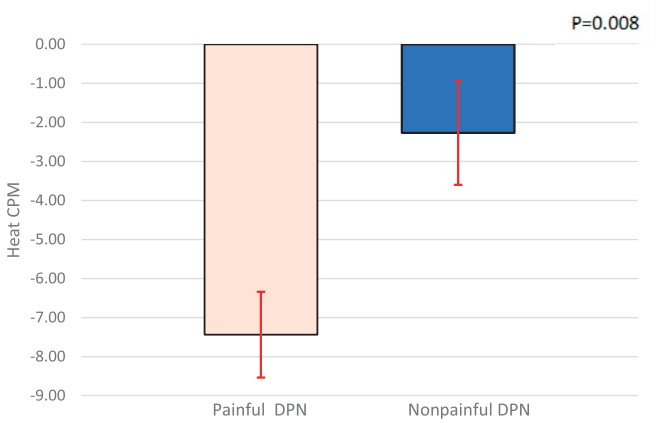

Figure 1. CPM_{HEAT} among patients with painful DPN and nonpainful DPN. Patients with painful DPN demonstrated more efficient CPM (mean, SD) than patients with nonpainful DPN. CPM, conditioned pain modulation; DPN, diabetic polyneuropathy.

3.2. Clinical characteristics of painful and nonpainful diabetic polyneuropathy

Patients with painful DPN had significantly higher TCNS scores and higher absolute CDT, WDT, and MDT compared with patients with nonpainful DPN. There were no statistically significant differences between patients with painful DPN and nonpainful DPN for VDT (**Table 1**).

3.3. Conditioned pain modulation in painful vs nonpainful diabetic polyneuropathy

No significant difference was found for the CPM_{PPT} (0.8 ± 0.1 vs 0.8 ± 0.1; ANOVA $P = 0.883$; $\eta^2 < 0.001$) between patients with painful and nonpainful DPN. CPM_{HEAT} responses were different between the 2 groups (ANOVA $P = 0.008$; $\eta^2 = 0.031$), with patients with painful DPN demonstrating a more efficient CPM than patients with nonpainful DPN (−7.4 ± 1.0 vs −2.3 ± 1.6; **Fig. 1**).

Table 2

Descriptive statistics of conditioned pain modulation-related parameters (mean and SD).

Parameter	Painful DPN	Nonpainful DPN
PPT $Ts_{stand\text{-}alone}$ (kg/cm^2)	4.6 ± 1.8	5.0 ± 1.8
PPT $Ts_{conditioned}$ (kg/cm^2)	5.3 ± 2.1	5.8 ± 2.2
Pain50 Ts temperature (°C)	45.8 ± 2.6	46.0 ± 2.8
Heat $Ts_{stand\text{-}alone}$ (NPS)	52.7 ± 15.4	54.2 ± 15.2
Heat $Ts_{conditioned}$ (NPS)	43.9 ± 19.6	49.1 ± 19.9
Cs (NPS)	47.7 ± 26.6	44.3 ± 25.3

CPM, conditioned pain modulation; Cs, conditioning stimulus; DPN, diabetic polyneuropathy; Heat Ts, tonic heat stimulus; NPS, numerical pain scale; Pain50 Ts, pain 50 tonic stimulus; PPT Ts, pressure pain threshold test stimulus.

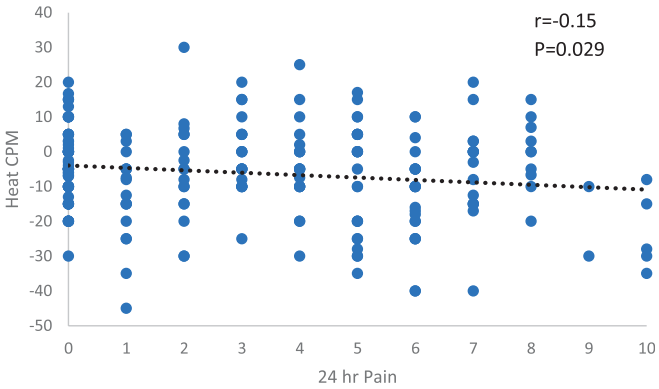

Figure 2. Scatter plot of clinical pain and CPM_{HEAT}. Higher self-reported foot pain in 24 hours before CPM testing was correlated with more efficient CPM_{HEAT}. CPM, conditioned pain modulation.

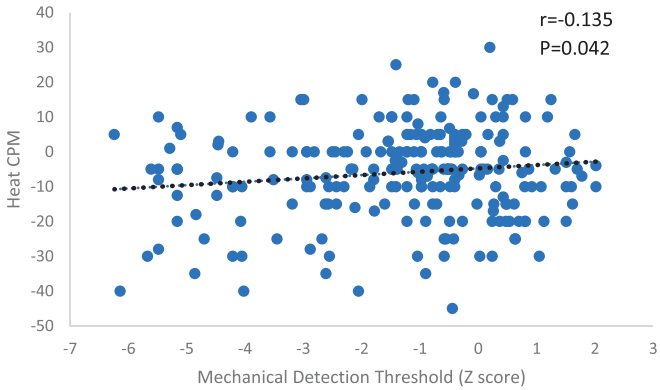

Figure 3. Scatter plot of mechanical detection threshold and CPM_{HEAT}. Impaired mechanical detection threshold was correlated with more efficient CPM_{HEAT}. CPM, conditioned pain modulation.

Differences between patients with painful and nonpainful DPN for CPM_{HEAT} were confirmed by an ANOVA model that included age, sex, the testing center (Technion or Imperial College), and CPM (model $P = 0.002$; CPM_{HEAT} differences $P = 0.036$; $\eta^2 = 0.019$). This also demonstrated a less efficient CPM_{HEAT} in older patients ($P = 0.005$; $\eta^2 = 0.033$) irrespective of whether they had painful or nonpainful DPN. No effect of the testing center on CPM_{HEAT} efficiency was observed.

Additional ANOVA models were tested to examine whether the observed CPM_{HEAT} differences were related to parameters that comprise the CPM response, such as Pain50 temperature and the pain scores to Cs. No significant group differences were detected for any of these parameters. The descriptive statistics of CPM-related parameters are presented in **Table 2**.

3.4. Associations between the CPM_{HEAT} efficiency and clinical parameters

In line with the described group differences for CPM_{HEAT}, efficient CPM_{HEAT} was associated with higher clinical pain experienced in past 24 hours ($r = -0.15$; $P = 0.029$, **Fig. 2**) and greater loss of mechanical sensation ($r = -0.135$; $P = 0.042$, **Fig. 3**).

Furthermore, for each QST parameter, patients were classified as either normal or hypoesthetic, based on their z scores.[31] Patients who had mechanical hypoesthesia demonstrated more efficient CPM_{HEAT} ($P = 0.005$), **Figure 4**. No such differences were observed between normal and hypoesthetic patients for thermal or vibratory parameters.

In addition, sensory detection thresholds for warm and mechanical stimulation on the forearm (tested for Technion patients only) correlated with the CPM_{HEAT} efficiency; higher WDT (**Fig. 5**) and MDT (**Fig. 6**) values were associated with more efficient CPM ($r = -0.20$; $P = 0.009$ and $r = -0.201$; $P = 0.009$). The latter should be considered with some caution because a robust regression analysis suggested substantial influence of potentially outlying results ($P = 0.0669$).

4. Discussion

This is the first study, to the best of our knowledge, to characterize CPM efficiency in patients with painful vs nonpainful DPN. We expected to find less efficient CPM among patients with painful DPN; however, conversely, we found more efficient CPM_{HEAT} in this group and no difference between groups for pressure CPM. The positive correlation found between the more efficient CPM_{HEAT} and neuropathy severity identified by the increased average pain scores over the past 24 hours and greater loss of mechanical sensation corroborates with these findings, alongside increased CPM_{HEAT} efficiency in patients with mechanical hypoesthesia. In line with previously reported findings,[39] patients with painful DPN had higher neuropathy severity as measured by the sensory loss, higher CDT, WDT, and MDT when compared with patients with nonpainful PDN (**Table 1**).

The traditional view is that less efficient CPM occurs in patients with chronic pain when compared with healthy controls. The reason for this is believed to be either that an underlying, inherent less efficient CPM makes these individuals more susceptible to developing chronic pain or that the presence of chronic pain has "exhausted" the pain inhibition resources to the point of demonstrating a less efficient to nonefficient test result.[48] A combination of both factors is also possible. It has to be noted that the studies showing less efficient CPM for patients with chronic pain, including patients with painful DPN (data in preparation), compared patients to healthy controls. Interestingly, in this study, healthy controls are not used; rather, the comparison is between 2 groups of patients with DPN, those with and those without pain. Unexpectedly, we have demonstrated that patients with painful DPN have more efficient CPM when compared with patients with nonpainful DPN. The likely explanation to our findings relates to the fact that stimuli are given to

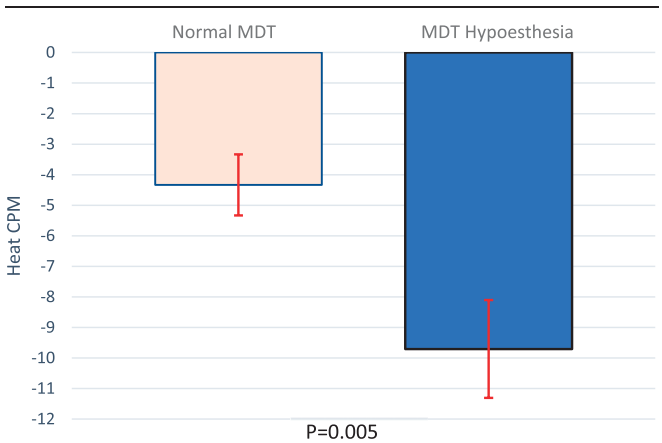

Figure 4. CPM_{HEAT} in patients with normal and hypoesthetic mechanical detection thresholds. Patients with mechanical hypoesthesia demonstrated more efficient CPM (mean, SD). CPM, conditioned pain modulation; MDT, mechanical detection threshold.

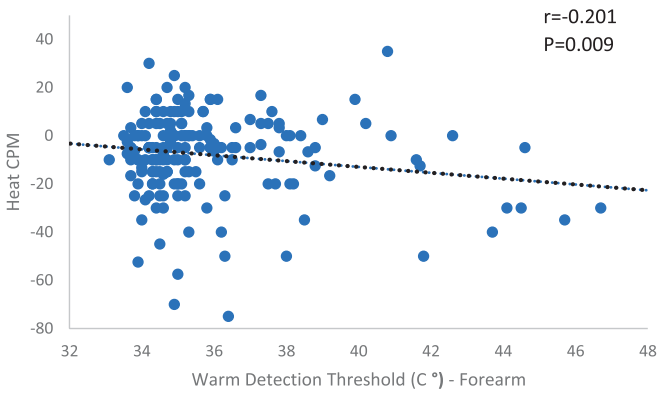

Figure 5. Scatter plot of warm detection thresholds in the forearm and CPM_{HEAT}. Higher warm detection threshold at the site of CPM testing was correlated with more efficient CPM_{HEAT}. CPM, conditioned pain modulation.

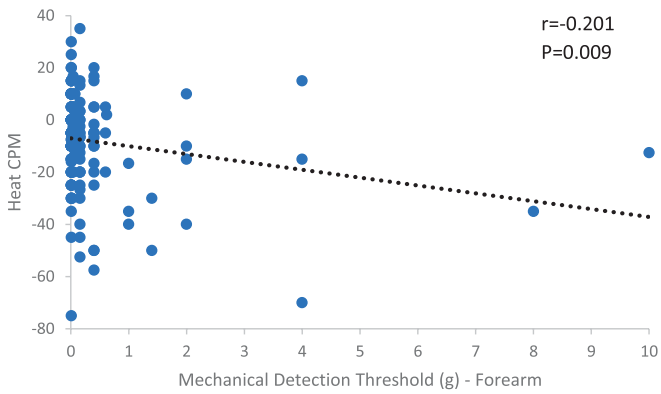

Figure 6. Scatter plot of mechanical detection thresholds in the forearm and CPM_{HEAT}. Decreased mechanical detection threshold at the site of CPM testing was correlated to more efficient CPM. CPM, conditioned pain modulation.

body areas affected by neuropathy, with alterations in sensory function, either gain or loss. If, on one hand, gain of function makes the perception of the conditioning water immersion more painful than normal, one should expect a more efficient CPM due to the peripheral neuropathic sensory changes. On the other hand, if loss of function dominates, then the conditioning will be perceived as less painful and the CPM effect will be lower. It is noted that the rating given by our patients with painful and nonpainful DPN for the Cs painfulness was similar, so it either nullifies the above explanation or we might be looking at different impacts of external stimuli on the cortex, ie, pain perception, and the brainstem, ie, activation of pain inhibition. Several studies have shown that thresholds for pain perception and for activation of pain inhibition differ, with the latter being lower than the former.[23,28] Thus, in healthy subjects, stimuli could be intense enough to activate the brainstem modulatory centers, but not intense enough to evoke a pain sensation. This gap could be larger or smaller in neuropathy with alterations in nociceptor function, generating a situation where different effects on the brainstem modulatory centers are not paralleled by different perceived pain. Similar line of considerations can be portrayed for the test stimuli, although we individually adjust the level of stimulus, providing a partial mitigation of the sensory alteration and making this factor less central than the Cs.

An additional explanation to the unexpected CPM efficiency in painful vs nonpainful DPNs might relate to the alteration in large fiber function due to the neuropathy. Studies in heathy subjects have shown that ongoing large fiber sensory input, mostly subconscious, happening as part of the normal proprioceptive function, is exerting pain inhibition. Applying lumbar spinal anesthesia led to higher pain perception in the intact body areas.[27] In line, mild pressure cuff blocks applied to lower limbs blocking large fiber sensory inflow inhibit experimental pain.[15] Thus, one would expect that in all patients with neuropathy, the loss of large fibers will lead to less efficient CPM. However, in those with pain, there is a combination of this factor with the gain of function that could lead to more efficient CPM.

In line with this rationale are animal models of inflammatory or neuropathic pain where mechanical or thermal conditioning stimulation of the affected hind paw induced an enhanced DNIC response on the activity of trigeminal convergent neurons.[5] Importantly, the DNIC potentiation was observed in parallel with behavioral signs of nerve injury–related central sensitization.[4] Similarly, brushing or pressure stimulation of allodynic area inhibits RIII nociceptive flexion reflex and concomitant painful sensation in patients with traumatic peripheral nerve injury.[2] The extent of this inhibition was comparable with the CPM efficiency when experimental pain conditioning stimuli were applied to the normal limb.[2]

Efficient pain inhibition in chronic neuropathic pain was also reported when conditioning stimuli were applied on pain-free body site and the test stimuli were applied on the neuropathic body area. For example, efficient CPM was reported in patients with chronic poststroke shoulder pain when the pain threshold assessment on the affected parts served as test stimuli.[33] An interesting finding comes also from the reports of modulation of evoked clinical pain; reduced intensity or area of brush-evoked allodynia was demonstrated for patients with painful peripheral neuropathy[41,45] and central poststroke pain.[42] Similar inhibitory effect was observed on the ongoing pain.[41]

Together these findings allow us to suggest that the presently reported efficient CPM in patients with painful DPN may result from the mere location of stimuli in the CPM protocol, from central changes in pain inhibitory function, or both. It raises a question of fitting the CPM-assessing methodology to the clinical pain characteristics. The potential clinical value of the CPM assessment today is limited in part due to various combinations of the used modalities, body placement, and duration of test and conditioning stimuli. The results of our findings may point to a methodological bias of using the CPM protocols that involve peripheral pain stimulation emphasizing the need to apply the test and conditioning stimuli at nonaffected or minimally affected body sites. We propose therefore that further studies should try and test CPM in sensory nonaffected body areas that will allow more decisive interpretation of the results.

Because the CPM differences in this project were attributed to thermal but not pressure pain modality, we suggest that the CPM assessment methodology and modality must be considered when assessing disease symptomatology. This assertion is confirmed by some observation that when several CPM protocols are tested, the thermal CPM is more relevant for classification of neuropathic pain[41] and CPM protocols that involve deep tissue stimulation such as PPT testing are more relevant for musculoskeletal pain.[20,22] Although interesting, owing to different scoring systems and lack of standard reference values, the question whether the 2 CPM protocols significantly differed in producing differences between the patients with painful vs nonpainful DPN cannot be currently assessed; we consider this a study limitation and leave it open for future research.

Our study has several additional limitations. First, the negative findings on VDT for detecting the group differences might be related to the methodology used rather than the lack of actual

group differences. This is because the tuning fork method is likely not sensitive enough to study vibration perception as compared with the method of limits approach at the target frequency. Furthermore, a direct comparison between the VDT assessed by the 2 methods indicated an advantage of the method of limits vs tuning fork in diagnostic accuracy for detecting impaired proprioception in patients with central nerve system lesions.[10] Second, although statistically significant and being in line with other findings, the correlations between CPM and clinical pain or mechanical sensitivity are weak and might be explained by large intersubject variability in the responses.

In conclusion, we suggest that in cases of neuropathy, CPM testing is probably sensitive to the sensory function of body sites tested, either neuropathy-affected or intact. This makes the interpretation of the test more complex in the former and calls for the use of unaffected body parts as much as possible in future CPM assessments of neuropathic patients.

Conflict of interest statement

L. Shafran Topaz, Y. Granovsky, R. Zubiedat, S. Crystal, C. Buxbaum, N. Bosak, R. Hadad, and E. Domany have nothing to disclose. H. Laycock is an editor for Anesthesia, she was part funded by the Horizon 2020 European grant. M. Khamaisi and E. Sprecher have nothing to disclose. D.L. Bennett has acted as a consultant in the past 2 years for Amgen, Bristows, CODA therapeutics, LatigoBio, Lilly, Mundipharma, OliPass, Orion, Regeneron, and Theranexus on behalf of Oxford University Innovation. Additionally, D.L. Bennett has an Industrial Partnership grant with Astra Zeneca funded by the BBSRC. D. Yarnitsky holds shares in BrainsGate and Theranica. A. Rice's conflicts of interest occurring in the past 2 years include consultancy and advisory board work for Imperial College Consultants and remunerated work for Abide, Confo, Vertex, Pharmanovo, Lateral, Novartis, Mundipharma, Orion, Asahi Kasei, Toray, and Theranexis. In addition, A. Rice was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued on the acquisition of Spinifex by Novartis in July 2015. The final payment was made in 2019. He is also named as an inventor on patents: (1) Rice A.S.C., Vandevoorde S., and Lambert D.M Methods using N-(2-propenyl) hexadecanamide and related amides to relieve pain. WO 2005/079771 and (2) Okuse K. et al. Methods of treating pain by inhibition of vgf activity EP13702262.0/WO2013 110945.

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Appendix A Supplemental video content

Video content associated with this article can be found online at http://links.lww.com/PAIN/B457.

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