Heliyon 10 (2024) e25156

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Body-site effect on CPM efficiency in healthy subjects: Central vs. peripheral stimulation

Y. Granovsky [a,b,*], E. Sprecher [b], N. Yarovinsky [b], M. Shor [b], S. Crystal [a]

[a] Laboratory of Clinical Neurophysiology, Bruce Rappaport Faculty of Medicine, Technion, Israel Institute of Technology, Haifa, Israel
[b] Department of Neurology, Rambam Health Care Campus, Haifa, Israel

A R T I C L E I N F O

Keywords:
CPM
Pain
Stimulation
Limb
Trunk
Tonic heat
Pressure pain threshold

A B S T R A C T

Background: Structural changes in the peripheral nerve system in neuropathic states alter sensory capacity of the affected area, thus biasing results of conditioned pain modulation (CPM) responses. The aim of this study was to evaluate CPM efficiency of central (i.e. trunk) vs. peripheral (i.e. limb) application of 'test' and 'conditioning' stimuli. **Methods:** Healthy volunteers (ages 18–73 yrs) underwent two CPM protocols: 'CPM Limb' and 'CPM Trunk'. Each included two types of test stimuli (Ts) (pressure pain threshold: PPT; and contact heat) conditioned either to hand immersion in cold noxious water (CPM limb), or to noxious contact heat applied on lower back (CPM trunk). **Results:** Both protocols generated efficient pain inhibition for each of the applied Ts; the PPT-based protocol induced more efficient CPM when the conditioned stimulus was applied on the trunk ($p = 0.016$). Moreover, the PPT-based CPM responses were significantly correlated ($\rho = 0.349$; $p = 0.007$). **Conclusions:** An efficient CPM induced by both central and peripheral stimulation, along with significant correlation between PPT-based responses, advances using the central 'CPM Trunk' protocol in patients with peripheral neuropathy.

1. INTRODUCTION

Individual capability for endogenous analgesia in humans can be assessed by testing conditioned pain modulation (CPM) [1,2] a human surrogate marker of the 'diffuse noxious inhibitory control' (DNIC) response [3]. One important factor that may affect CPM efficiency is application of the noxious stimuli in affected versus non-affected body sites in cases of peripheral neuropathies. This is because the "hardware" changes in the innervation and sensory loss alter the sensory function serving the affected area, lowering the sensory capacity of the affected area. Moreover, in cases of neuropathic pain, the affected area might also suffer "software" changes due to central neuronal sensitization, such that the stimulus perceived in the central system will be further changed vs. stimulus applied on the unaffected area. Thus, the interpretation of the CPM results, where either a test or a conditioning stimulus is applied on the affected body area, will be equivocal. A handful of reports indicated that the application of test or conditioning stimuli on allodynic or painful body areas in neuropathic pain patients may result in efficient CPM [4,5]. These reports are in line with our recently published findings on efficient CPM in a large group of patients with painful diabetic neuropathy [6]. This is in contrast to the common notion that patients with chronic non-neuropathic pain have less efficient CPM [7–9]. Thus, there is need to develop a CPM protocol which can be performed remote from sites of pathological sensory alterations, the most common of which is distal involvement due to

* Corresponding author. The Laboratory of Clinical Neurophysiology, Technion Faculty of Medicine, Department of Neurology, Rambam Health Care Campus, Haifa, Israel.

E-mail address: y_granovsky@rambam.health.gov.il (Y. Granovsky).

https://doi.org/10.1016/j.heliyon.2024.e25156
Received 15 August 2023; Received in revised form 4 January 2024; Accepted 22 January 2024
Available online 25 January 2024
2405-8440/

polyneuropathy.

Only a few studies previously addressed the effect of proximal (thigh) test stimulus application [10], or body core (lower back) vs. peripheral (forearm) application for test or conditioned stimuli [11] on CPM efficiency. These reports indicated that CPM was preserved among patients with trapezus myalgia [10], and that CPM efficiency was similar regardless of the body site application of test or conditioning stimuli [11]. These studies, however, concentrated on young participants [11] or very small patient cohorts [10]. Moreover, none of these studies tested relationships between the CPM efficiency from various protocols.

This study aimed to assess and compare the results of central (i.e. trunk-directed) vs. the 'routine' peripheral (i.e. limb-directed) CPM protocols, tested on a large (N = 58) and wide-range age cohort of healthy participants.

2. Methods

2.1. Participants

Sixty-one participant signed the consent form, and were defined as healthy according to the published criteria [12]. The final study sample included 58 participants, as detailed in the Results section.

Participants were recruited for study from the community through advertisement in the local press between September 2017 and June 2018, and received monetary compensation for their participation. Recruited were subjects of both sexes, age 18–80 years. Exclusion criteria were: (1) history of chronic pain, (2) pregnant or breastfeeding women, (3) having significant neurological or psychiatric disorders (psychosis, dementia or similar disorders), (4) use of analgesic or psychiatric medication on a regular basis, (5) communication or language difficulties that could affect performance on the various tests, and (6) prior participation in CPM-related studies. Participants were asked to avoid analgesic medication at least 24 h prior to the experiment. The study was approved by the Institutional Helsinki Committee at Rambam Health Care Campus, Haifa, Israel. All subjects signed an informed consent.

2.2. Study design

All participants underwent a single lab session. Demographic information (age, sex and years of education) was collected prior to psychophysical assessment. Tests instructions were standard and were read to subjects prior to the test to ensure consistency.

Each participant underwent two CPM protocols; first the routine peripheral 'CPM Limb' protocol (referring to the *stimuli applied on the upper limb*) and then, after a 30-min pause, a central *'CPM Trunk'* protocol (referring to the *stimuli applied on the para-median lower back*). During this time break, the subjects remained in the laboratory room without exposure to other subjects; no special instructions were provided.

Participants initially underwent a short familiarization with the experimental stimuli which included: (a) exposure to three short contact-heat stimuli at 43 °C, 45 °C, and 47 °C, each lasting 7 s, given on the non-dominant forearm (b); exposure to one pressure

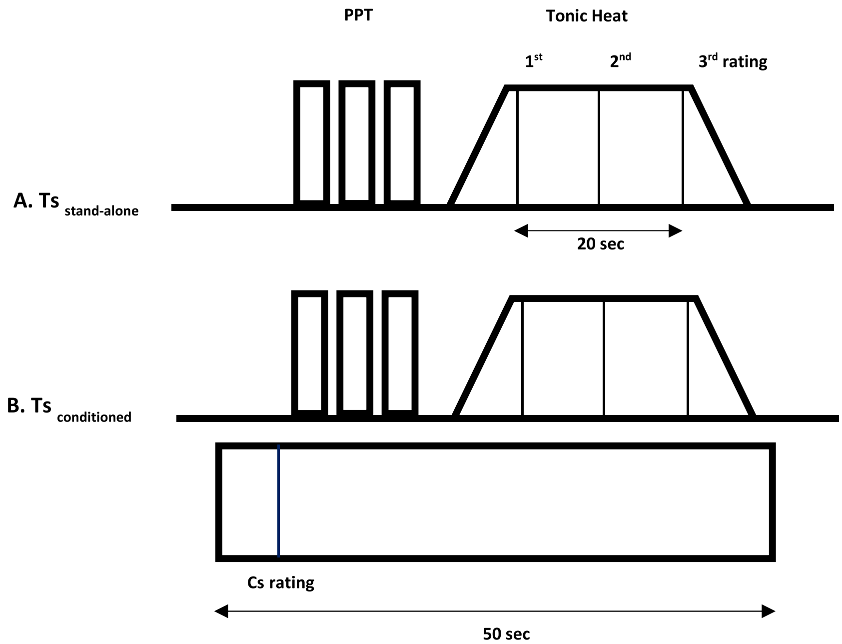


Fig. 1. Schematic representation of the stimulation details
(A) Ts $_{\text{stand-alone}}$ and (B) Ts $_{\text{conditioned}}$ components of the CPM assessment.

stimulus at non-dominant trapezius muscle with a gradual increaseof pressure by 0.5 kg/s until the patient reported pain (pressure pain threshold, PPT) and (c) 10-s exposure to cold water (8–12 °C) by non-dominant hand immersion up to the wrist into a plastic water bath, after which they were asked to rate pain intensity (0–100 verbal numerical pain scale, NPS). After the familiarization, additional set of contact-heat stimuli were given at the dominant forearm in order to determine the intensity of the test stimulus, that evokes a pain intensity of 60 on a 0–100 NPS (pain-60). Initial triplet of stimuli consisted of 46 °C, 45 °C, and 47 °C. Participants were asked to report their pain level to each stimulus. If none evoked a pain-60 response, additional triplet of stimuli was applied, at higher or lower temperatures, accordingly. The temperature found to evoke pain-60 response served as the intensity of the test-stimulus (Ts) in the 'CPM Limb' protocol.

'CPM Limb' protocol; was based on two types of Ts delivered at the fixed order: (i) mechanical stimuli, consisting of three PPT measurements on the dominant trapezius muscle, followed by (ii) 20-sec contact heat stimulus delivered to the ventral surface of the dominant forearm at the individually-predetermined pain-60 temperature. During the contact heat stimulation, participants reported verbally their pain at 2, 11, and 18 s. A mean value of three PPT measurements composed the PPT Ts; the mean value of two last score for the heat stimulation composed the Heat Ts. Conditioning stimulus (Cs) was cold water immersion of the non-dominant hand, up to the wrist, in a water container for a period of 50 s (8–10 °C; if during familiarization phase this temperature failed to evoke a pain level of more than 20/100, water temperature was lowered to 4–6 °C). At the beginning of Cs, the subjects were asked to rate the water pain intensity. For the CPM measurement, the test-stimuli were administered twice; first stand-alone ($Ts_{\text{stand-alone}}$), then repeated after 10 min break, in parallel to contralateral hand immersion in cold noxious water ($Ts_{\text{conditioned}}$).

'CPM Trunk' protocol: the procedure was similar to the CPM Limb protocol in terms of the Ts methodology but differ in the sites of the stimuli application; both PPT- and Heat-Ts were delivered on the dominant trapezius, conditioned to the contact heat applied on lower back. The determination of the stimulation temperature for the Heat Cs based on the pain-60 determination on the lower back.

For all the protocols, the CPM was calculated as a subtraction of the Ts values $_{\text{stand-alone}}$ from the Ts given under Cs; a positive value for the CPM_{PPT} and negative value for the CPM_{Heat} indicated efficient CPM.

All the tests were performed by Sh.C, a PhD student.

The scheme of the CPM assessment paradigm (regardless of the applied protocol) is presented in Fig. 1 (A, B).

2.3. Instruments

The following instruments were used.

1 **Pressure Algometer** (Wagner Instruments, FDX, Greenwich, CT) was used for PPT assessment. The device with round rubber disc, contact area 1 cm^2, was pressed upon the skin at the base of neck, on the upper trapezius muscle. The PPT calculation was based on the averaged responses of three repetitions delivered at inter-stimulus intervals of 5 s.
2 **Thermal sensory analyzer** (TSA, Medoc, Ramat Yishai, Israel) was used to deliver thermal painful stimuli through a square, 30 × 30 mm, Peltier surface probe. The probe was attached with a Velcro strap to the ventral surface of the mid dominant forearm, or the dominant trapezius muscle or non-dominant lower back 5 cm lateral to the spinal processes (see explained locations below). Baseline temperature was set to 32.0 °C, and maximal temperature to 48.0 °C. Temperature increase rate was 2.0 °C/s, and decrease rate was 8.0 °C/s.

2.4. Statistical analysis

Statistical analyses were performed using JMP version 15.1.0 (SAS Institute, Cary, NC). Diagnostics for all tests were examined to ensure appropriateness of parametric techniques. The CPM_{Heat} calculation was performed only for patients whose pain score to the Heat $Ts_{\text{stand-alone}}$ was ≥20, as has previously been published [13], since a low pain level of the $Ts_{\text{stand-alone}}$ may have a floor effect on the CPM efficiency [14].

In order to evaluate differences between CPM paradigms and its components, we used the Wilcoxon Signed Rank test, due to the non-normal distribution of the variables. The presented P values are uncorrected for multiple comparisons. We applied Spearman correlation to test for associations between two protocols CPM (Limb vs Trunk stimulation), for each Ts modality. ANOVA model was applied to test the effect of age, sex, and the interaction between them, on the CPM efficiency, separately for each CPM paradigm. Spearman correlation tested the association between the CPM efficiency and education level reflected by the number of education years.

The sample size estimates for this study were based on our experience with pain modulation-focused studies suggesting that at least 27–33 healthy subjects would be enough to detect systematic differences between various methods for CPM assessment [15–19], which could be also applied to the effect of body sites. We over-enrolled recruitment to protect against data loss.

3. Results

3.1. Subjects

Out of a total of 61 patients who signed consent, three were excluded due to low pain responsiveness and inability to determine pain-60 temperature. Thus, 58 healthy subjects were included in the study (30 females, age range 18–73 years, mean age 47.3 ± 15.2 years).

3.2. Psychophysical results

Comparing the pain scores between Ts $_{stand-alone}$ and Ts $_{conditioned}$ we determined that both CPM protocols (CPM Limb or CPM Trunk) of CPM $_{PPT}$ and CPM $_{Heat}$ generated efficient pain inhibition (Table 1). There were no statistical differences between the CPM efficiency tested with the Limb vs. Trunk protocols for CPM $_{Heat}$. As for the CPM $_{PPT}$, it was more efficient for the CPM Trunk protocol ($p = 0.016$) (Table 2). Significant correlation was observed between the Limb and Trunk protocols for the CPM $_{PPT}$ ($\rho = 0.349$; $p = 0.007$), but not for the CPM $_{Heat}$ responses ($\rho = 0.012$; $p = 0.933$), see Fig. 2 (A, B).

There was a significant difference in the Cs pain levels between two CPM protocols; the contact heat stimulation on the lower back (Trunk Cs) was significantly more painful than the cold water hand immersion (Limb Cs) ($p < 0.001$), Table 2.

3.3. The effect of demographic parameters on the CPM responses

Neither sex nor participant's age influenced the efficiency of any of four tested CPM paradigms; the significance levels of each of the ANOVA models were >0.05. Among all paradigms, only the CPM $_{PPT}$ of the Limb protocol correlated significantly with education – more efficient CPM was associated with more years of education ($\rho = 0.384$; $p = 0.005$).

4. Discussion

This study shows that both CPM protocols (the peripheral, upper limb-directed and the central, body trunk-directed) induced inhibitory pain modulation in a wide-age range of a healthy population. For the CPM $_{Heat}$ paradigms, both protocols were of similar efficiency, though uncorrelated. In contrast, for the CPM $_{PPT}$ paradigms, the central protocol (the conditioning stimulus was applied on the trunk) evoked more efficient CPM than the peripheral protocol (the conditioning stimulus was applied on the limb); both CPM $_{PPT}$ responses were inter-correlated. None of the CPM responses were related to sex or age but the value of CPM $_{PPT}$ tested peripherally, correlated with the years of education. The results of our study suggest that both protocols might be efficiently used in healthy subjects, suggesting a certain advantage for the PPT-based central CPM paradigm for testing patients with peripheral neuropathies.

Application of the noxious stimuli centrally for inducing efficient CPM is not novel. For example, applying mechanical (PPT) or thermal (heat pain threshold and suprathreshold heat) on the thigh in a small group of patients with trapezus myalgia, Leffler et al. (2002) reported efficient CPM to both types of the test stimuli conditioned to the ischemic pain at forearm, in patients and controls alike [10]. Later, for a group of healthy young subjects, Klyne et al. (2015) reported efficient CPM responses using several stimulation protocols in which both test (PPT or suprathreshold contact heat) and conditioning stimuli (contact heat) were applied either at lower back or peripherally (at forearm), regardless of stimulated body site. An additional conclusion of this study wasthat the PPT-based CPM was more valid than the contact heat-based CPM responses, as its efficiency was associated with the Cs intensity (noxious but not neutral stimulation temperature) [11]. Taking these results further, bearing in mind that the CPM repeatability is better for the Ts is of shorter duration [19], a significant correlation between the efficiency of central and peripheral CPM $_{PPT}$ paradigms support the advantage of using PPT as a test-stimulus for CPM assessment.

The possible role of the Ts modality on the interaction between peripheral and central CPM protocols is intriguing. We believe that several factors may affect the CPM reliability across both protocols and explain the lack of correlation between the CPM $_{HEAT}$ of both protocols. These factors include the relatively long (20 s) duration of the Ts, the different locations of the Ts (arm vs. upper back), and the different location (hand vs. trunk) and modality (cold water vs. noxious heat) of the Cs. In contrast, methodological differences between central and peripheral protocols for the CPM $_{PPT}$ can be mainly attributed to the characteristics of the conditioning rather than test stimuli. Both Trunk- and Limb-CPM $_{PPT}$ paradigms used the same Ts methodology (PPT) and were applied on the same bodysite (trapezius muscle). This, along with the reports that the Ts of short duration (phasic stimuli or pain detection threshold) elicit more reliable CPM responses [20–22], including the use in PPT as a test stimulus [22,23], explains why the central and peripheral CPM PPT responses in our study were correlated. In addition, higher efficiency of the CPM $_{PPT}$ tested with the central protocol can be attributed to higher Cs pain level evoked by trunk (noxious contact heat) vs. limb stimulation. Indeed, despite certain disagreements [24,25], the results of animal and human studies point to a positive association between the actual or perceived conditioning pain level and CPM/DNIC efficiency [26–29]. This relationship suggests that highly noxious stimuli evoke more intense activation of the spino-bulbo-spinal pathway, thus resulting in more efficient descending control of pain. It is worth noting that the effect of perceived Cs intensity on CPM efficiency may be modulated, or mimicked, by the Ts stimulation characteristics. This may explain why the

Table 1
CPM responses obtained in the Limb and Trunk CPM protocols.

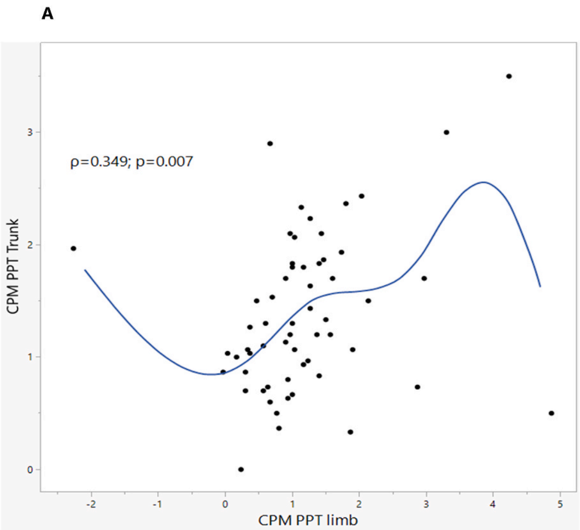
Body site	PPT (kg/cm^2)			Heat (NPS)		
	Ts $_{stand-alone}$	Ts $_{conditioned}$	P	Ts $_{stand-alone}$	Ts $_{conditioned}$	P
Limb median (range)	3.7 (1.7–7)	5.0 (1.8–10)	**<0.001**	49.9 (20–75)	40.0 (0–85)	**<0.001**
Trunk median (range)	3.6 (1.5–7.6)	5.0 (2.3–10)	**<0.001**	45 (20–71.5)	36.3 (0–70)	**0.012**

*P value of Wilcoxon Signed Rank test between Ts $_{stand-alone}$ and Ts $_{conditioned}$.
Ts - test stimulus; PPT - pressure pain threshold; NPS - Numerical Pain Scale.
N = 58 for PPT and Heat Limb Ts $_{stand-alone}$ and Ts $_{conditioned}$.
N = 54 for Heat Trunk Ts $_{stand-alone}$ and Ts $_{conditioned}$.

Table 2
Comparison between CPM efficiency tested at Limb vs. Trunk.

Parameter	Limb median (range)	Trunk median (range)	P
CPM $_{PPT}$ (kg/cm^2)	1.0 (−2.3–4.9)	1.2 (0–3.5)	**0.016**
CPM $_{Heat}$ (NPS)	−7.5 (-65–30)	−5 (−71.5–25)	0.311
Pain-60 T Temp (°C)	47 (43–49)	47.5 (43–49)	0.229
Cs (NPS)	40 (10–90)	57.5 (20–90)	**<0.001**

*P value of Wilcoxon Signed Rank test between CPM Limb and CPM Trunk.
CPM - Conditioned pain modulation; Ts - test stimulus; Cs - Conditioning stimulus.
PPT - pressure pain threshold; NPS - numerical pain scale.
N = 58 for CPM $_{PPT}$ in the Limb and Trunk and CPM $_{Heat}$ in the Limb.
N = 54 for CPM $_{Heat}$ in the Trunk.



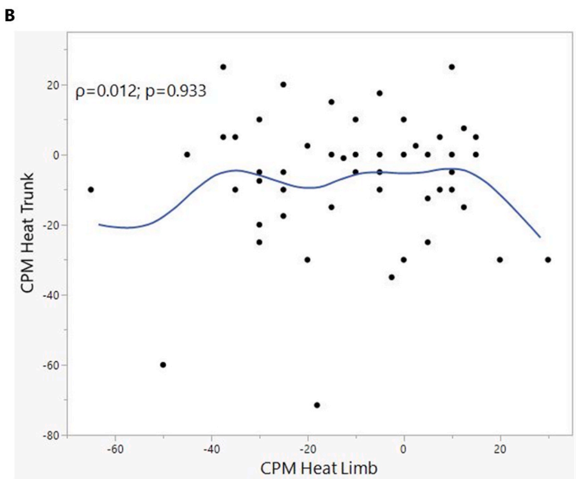


Fig. 2. Correlation between the central (Trunk stimulation) vs. peripheral (Limb stimulation) protocols
(A) CPM $_{PPT}$ paradigms; (B) CPM $_{Heat}$ paradigms
The solid line represents a spline fit relating both protocols.

efficiency of central vs. peripheral CPM $_{Heat}$ paradigms was similar, despite the higher painfulness of the Cs of the CPM Trunk protocol. The Cs modality may also influence the CPM efficiency, regardless of perceived intensity. However, the findings in this regard are inconclusive. For example, using the same Ts, some studies reported more efficient CPM evoked by noxious cold water Cs vs. mechanical, ischemic [30,31], or experimental muscle pain modalities [32]. Others, however, found no difference in CPM responses to cold water vs. hot water or ischemic Cs modalities [33], vs. contact heat Cs [34], or found it less efficient [35]. Therefore, the question of how the Ts or Cs stimuli metrics affect CPM efficiency remains to be explored.

The neurophysiological basis of the CPM phenomenon is not unequivocal, but depends on the nature of the nociceptive mechanisms brought into play. According to the results from animal studies, DNIC is primarily triggered by peripheral C and A-delta fibers initiating medullar descending pathways [29,36,37]. Therefore, in our case, superior efficiency of the CPM $_{PPT}$ conditioned to the noxious contact heat over noxious cold water can be also partially related to physiological properties of peripheral transmission of the noxious heat, which is mediated by both types of nociceptors suggesting, therefore, more significant sensory barrage to the pain modulating brain structures. This opposes to the initiation of CPM via the Cs of cold water hand immersion as the noxious cold mainly activates A-delta nociceptors [38]. It worth noting that the results of in vitro studies point on the activation of the transient receptor potentials channels of polymodal C mechano-heat-cold nociceptors in response to cold stimuli [39] as well. However, the physiological role of C fiber activation to cold is under debate [40].

Another interesting finding of this study is the relationship between more efficient CPM and the level of education. It has been established that higher education level (which is intuitively associated with more years of education) contributes to advanced executive functioning and cognitive reserve, and is associated with higher grey matter volume and stronger functional connectivity [41–43]. In turn, the results of functional imaging studies show overlap between brain regions involved in cognition and top-down pain regulation [44–46]. These findings are supported by reports on the association between executive cognitive functioning and CPM efficiency [47–49]. Note that, the positive association between CPM and education level in our study was only significant for CPM $_{PPT}$ delivered with Limb protocol. Bearing in mind that the Limb protocol was always tested first, and the PPT Ts always preceded the contact heat Ts we may hypothesize that the relationship between the CPM and the level of education is best established for "naïve" rather than repetitive CPM assessment.

It is worth noting that none of the CPM paradigms tested in our study related to subjects' age, nor were they sex-dependent, thus, contributing to the potential universal and direct applicability of these paradigms. Knowledge of age and sex effects on CPM efficiency is ambiguous at best. The general assumption is that CPM efficiency declines at older age [50–52] possibly due to enhanced central sensitization among older cohorts [53]. Others, however, indicated no such relationship [54,55], or very limited and inconclusive effects [56]. A large body of evidence suggests sex differences in pain processing exist at the molecular, cellular, and hormonal levels [57]. These differences are observed in clinical and experimental settings, having an impact on general pain sensitivity and efficiency of inhibitory pain modulation, mainly associated with greater sensitivity and deficient pain inhibition in females [58,59], though the magnitude of these differences varies across studies [60]. Importantly, the reported sex differences in CPM efficiency could be in opposite directions, even within the same study, depending on stimulation parameters [54,55].

Our study has several limitations. First, the sample size is relatively small and can potentially affect generalizability of the results. Further research with larger and more diverse participant groups would enhance the validity of the findings. Second, without full control conditions (i.e. sham conditioning stimulation or control session), the influence of measurement error on repeated test stimulus application cannot be dismissed [61–63].

To conclude, we aimed to introduce a protocol for testing CPM in polyneuropathy patients using central (trunk) stimulation for both test and conditioning stimuli. We assumed these sites are less affected in the distally dominated polyneuropathy. We found that the central stimulation protocol induced more efficient CPM when using PPT as a test stimulus. There was a significant correlation between CPM $_{PPT}$ efficiency across central and peripheral protocols. Also, the peripheral CPM $_{PPT}$ efficiency correlated with education level, but none of the CPM paradigms were related to age or sex. This suggests their potential applicability in the general population. However, the clinical relevance of testing CPM centrally can only be confirmed in patients with peripheral polyneuropathies.

Ethical approval

The study was approved by the Institutional Helsinki Committee at Rambam Health Care Campus, Haifa, Israel (ethics approval reference number 0381-16-RMB).

Data availability

The data are available upon request (please contact the corresponding author).

Funding

This research was supported by the Israel Science Foundation (grant No.1415/15).

CRediT authorship contribution statement

Y. Granovsky: Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization. **E. Sprecher:** Writing – review & editing, Formal analysis, Data curation. **N. Yarovinsky:** Validation, Methodology. **M. Shor:** Project administration, Investigation. **S. Crystal:** Writing – original draft, Project administration, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The authors thank Professor David Yarnitsky, MD for help with the study logistics and the manuscript preparation.

References

[1] D. Yarnitsky, et al., Recommendations on terminology and practice of psychophysical DNIC testing, Eur. J. Pain 14 (4) (Apr. 2010) 339, https://doi.org/10.1016/j.ejpain.2010.02.004.
[2] D. Yarnitsky, M. Granot, Y. Granovsky, Pain modulation profile and pain therapy: between pro- and antinociception, Pain 155 (no. 4) (2014) 663–665, https://doi.org/10.1016/j.pain.2013.11.005. Elsevier B.V.
[3] S. Ramaswamy, T. Wodehouse, Conditioned pain modulation—a comprehensive review, Neurophysiol. Clin. 51 (no. 3) (Jun. 01, 2021) 197–208, https://doi.org/10.1016/j.neucli.2020.11.002. Elsevier Masson s.r.l.
[4] B. Tuveson, A.S. Leffler, P. Hansson, Heterotopic noxious conditioning stimulation (HNCS) reduced the intensity of spontaneous pain, but not of allodynia in painful peripheral neuropathy, Eur. J. Pain 11 (4) (May 2007) 452–462, https://doi.org/10.1016/j.ejpain.2006.06.007.
[5] N. Witting, P. Svensson, T.S. Jensen, "Differential recruitment of endogenous pain inhibitory systems in neuropathic pain patients,", Pain 103 (no. 1–2) (2003) 75–81, https://doi.org/10.1016/S0304-3959(02)00421-9.
[6] Y. Granovsky, et al., "Conditioned pain modulation is more efficient in patients with painful diabetic polyneuropathy than those with nonpainful diabetic polyneuropathy,", Pain 163 (5) (May 2022) 827–833, https://doi.org/10.1097/j.pain.0000000000002434.
[7] G.N. Lewis, D.A. Rice, P.J. McNair, "Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis,", J. Pain 13 (10) (Oct. 2012) 936–944, https://doi.org/10.1016/j.jpain.2012.07.005.
[8] ME McPhee, HB Vaegter, T Graven-Nielsen, Alterations in pronociceptive and antinociceptive mechanisms in patients with low back pain: a systematic review with meta-analysis, Pain 161 (3) (2020 Mar) 464–475.
[9] A. Marcuzzi, et al., "Conditioned pain modulation (CPM) is reduced in Irritable Bowel syndrome: a systematic review and meta-analysis of CPM and the role of psychological factors.,", J. Clin. Gastroenterol. 53 (6) (Jul. 2019) 399–408, https://doi.org/10.1097/MCG.0000000000001181.
[10] A.S. Leffler, P. Hansson, E. Kosek, "Somatosensory perception in a remote pain-free area and function of diffuse noxious inhibitory controls (DNIC) in patients suffering from long-term trapezius myalgia,", Eur. J. Pain 6 (2) (2002) 149–159, https://doi.org/10.1053/eujp.2001.0312.
[11] D.M. Klyne, A.B. Schmid, G.L. Moseley, M. Sterling, P.W. Hodges, "Effect of types and anatomic arrangement of painful stimuli on conditioned pain modulation,", J. Pain 16 (2) (2015) 176–185, https://doi.org/10.1016/j.jpain.2014.11.005.
[12] J. Gierthmühlen, et al., "Who is healthy? Aspects to consider when including healthy volunteers in QST-based studies - a consensus statement by the EUROPAIN and NEUROPAIN consortia,", Pain 156 (11) (2015) 2203–2211, https://doi.org/10.1097/j.pain.0000000000000227.
[13] Y. Granovsky, E. Sprecher, A. Sinai, "Motor corticospinal excitability: a novel facet of pain modulation?,", Pain Rep 4 (no. 2) (Mar. 2019) https://doi.org/10.1097/PR9.0000000000000725.
[14] L. Honigman, O. Bar-Bachar, D. Yarnitsky, E. Sprecher, Y. Granovsky, "Nonpainful wide-area compression inhibits experimental pain,", Pain 157 (9) (Sep. 2016) 2000–2011, https://doi.org/10.1097/j.pain.0000000000000604.
[15] M. Granot, Y. Granovsky, E. Sprecher, R.R. Nir, D. Yarnitsky, "Contact heat-evoked temporal summation: tonic versus repetitive-phasic stimulation,", Pain 122 (3) (2006) 295–305, https://doi.org/10.1016/j.pain.2006.02.003.
[16] M. Granot, et al., "Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter?,", Pain 136 (no. 1–2) (May 2008) 142–149, https://doi.org/10.1016/j.pain.2007.06.029.
[17] R.R. Nir, Y. Granovsky, D. Yarnitsky, E. Sprecher, M. Granot, "A psychophysical study of endogenous analgesia: the role of the conditioning pain in the induction and magnitude of conditioned pain modulation,", Eur. J. Pain 15 (5) (2011) 491–497, https://doi.org/10.1016/j.ejpain.2010.10.001.
[18] H. Nahman-Averbuch, D. Yarnitsky, Y. Granovsky, E. Gerber, P. Dagul, M. Granot, "The role of stimulation parameters on the conditioned pain modulation response,", Scand J Pain 4 (1) (2013) 10–14, https://doi.org/10.1016/j.sjpain.2012.08.001.
[19] Y. Granovsky, A. Miller-Barmak, O. Goldstein, E. Sprecher, D. Yarnitsky, "CPM test-retest reliability: 'standard' vs 'single test-stimulus' protocols,", Pain Med. 17 (3) (2016) 521–529, https://doi.org/10.1111/pme.12868.
[20] S. Cathcart, A.H. Winefield, P. Rolan, K. Lushington, "Reliability of temporal summation and diffuse noxious inhibitory control,", Pain Res. Manag. 14 (6) (2009) 433–438, https://doi.org/10.1155/2009/523098.
[21] J.A. Biurrun Manresa, et al., "Is the conditioned pain modulation paradigm reliable? A test-retest assessment using the nociceptive withdrawal reflex,", PLoS One 9 (6) (2014) 1–9, https://doi.org/10.1371/journal.pone.0100241.
[22] G.N. Lewis, L. Heales, D.A. Rice, K. Rome, P.J. McNair, "Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways,", Pain Res. Manag. 17 (2) (2012) 98–102, https://doi.org/10.1155/2012/610561.
[23] M. Kovacevic, L. Klicov, D. Vuklis, R. Neblett, A. Knezevic, "Test-retest reliability of pressure pain threshold and heat pain threshold as test stimuli for evaluation of conditioned pain modulation,", Neurophysiol. Clin. 51 (5) (Oct. 2021) 433–442, https://doi.org/10.1016/j.neucli.2021.06.005.
[24] M. Umeda, A. Okifuji, "Exploring the sex differences in conditioned pain modulation and its biobehavioral determinants in healthy adults,", Musculoskelet Sci Pract 63 (July 2022) (Feb. 2023) 102710, https://doi.org/10.1016/j.msksp.2022.102710.
[25] J. Vollert, et al., Conditioned pain modulation and offset analgesia: influence of sex, sex hormone levels and menstrual cycle on the magnitude and retest reliability in healthy participants, Eur. J. Pain 26 (9) (Oct. 2022) 1938–1949, https://doi.org/10.1002/ejp.2014.
[26] D. Le Bars, "The whole body receptive field of dorsal horn multireceptive neurones,", Brain Res. Rev. 40 (1–3) (Oct. 2002) 29–44, https://doi.org/10.1016/S0165-0173(02)00186-8.
[27] M. Granot, et al., "Determinants of endogenous analgesia magnitude in a diffuse noxious inhibitory control (DNIC) paradigm: do conditioning stimulus painfulness, gender and personality variables matter?,", Pain 136 (1–2) (May 2008) 142–149, https://doi.org/10.1016/j.pain.2007.06.029.
[28] R.-R.R. Nir, D. Yarnitsky, L. Honigman, M. Granot, "Cognitive manipulation targeted at decreasing the conditioning pain perception reduces the efficacy of conditioned pain modulation,", Pain 153 (1) (Jan. 2012) 170–176, https://doi.org/10.1016/j.pain.2011.10.010.
[29] L. Villanueva, D. Le Bars, "The activation of bulbo-spinal controls by peripheral nociceptive inputs: diffuse noxious inhibitory controls.,", Biol. Res. 28 (1) (1995) 113–125.
[30] Y. Oono, H. Nie, R.L. Matos, K. Wang, L. Arendt-Nielsen, "The inter- and intra-individual variance in descending pain modulation evoked by different conditioning stimuli in healthy men,", Scand J Pain 2 (4) (2011) 162–169, https://doi.org/10.1016/j.sjpain.2011.05.006.
[31] M.D.R. Ibancos-Losada, M.C. Osuna-Pérez, M.Y. Castellote-Caballero, Á. Díaz-Fernández, "Conditioned pain modulation effectiveness: an experimental study comparing test paradigms and analyzing potential predictors in a healthy population,", Brain Sci. 10 (9) (Sep. 2020) 1–18, https://doi.org/10.3390/brainsci10090599.
[32] L. Arendt-Nielsen, K.A. Sluka, H.L. Nie, "Experimental muscle pain impairs descending inhibition,", Pain 140 (3) (Dec. 2008) 465–471, https://doi.org/10.1016/j.pain.2008.09.027.

[33] M. G C A M Mertens, et al., "Comparison of five conditioned pain modulation paradigms and influencing personal factors in healthy adults,", Eur. J. Pain 25 (1) (Jan. 2021) 243–256, https://doi.org/10.1002/ejp.1665.

[34] J.L. Riley, Y. Cruz-Almeida, R. Staud, R.B. Fillingim, "Age does not affect sex effect of conditioned pain modulation of pressure and thermal pain across 2 conditioning stimuli,", Pain Rep 5 (no. 1) (2020) E796, https://doi.org/10.1097/PR9.0000000000000796.

[35] V. Aparecida da Silva, R. Galhardoni, M.J. Teixeira, D. Ciampi de Andrade, "Not just a matter of pain intensity: effects of three different conditioning stimuli on conditioned pain modulation effects,", Neurophysiol. Clin. 48 (5) (2018) 287–293, https://doi.org/10.1016/j.neucli.2018.06.078.

[36] D. Le Bars, L. Villanueva, D. Bouhassira, J.C. Willer, "Diffuse noxious inhibitory controls (DNIC) in animals and in man.,", Patol. Fiziol. Eksp. Ter. (4) (1992) 55–65, https://doi.org/10.1136/aim.9.2.47.

[37] D. Bouhassira, D. Le Bars, L. Villanueva, "Heterotopic activation of A delta and C fibres triggers inhibition of trigeminal and spinal convergent neurones in the rat.,", J Physiol 389 (1) (Aug. 1987) 301–317, https://doi.org/10.1113/jphysiol.1987.sp016658.

[38] L.U. Sneddon, "Comparative physiology of nociception and pain,", Physiology 33 (1) (Jan. 2018) 63–73, https://doi.org/10.1152/physiol.00022.2017.

[39] M. Campero, J. Serra, J.L. Ochoa, "C-polymodal nociceptors activated by noxious low temperature in human skin,", J. Physiol. 497 (2) (1996) 565–572, https://doi.org/10.1113/jphysiol.1996.sp021789.

[40] R. Xiao, X.Z.S. Xu, "Temperature sensation: from molecular thermosensors to neural circuits and coding principles.,", Annu. Rev. Physiol. 83 (Feb. 2021) 205–230, https://doi.org/10.1146/annurev-physiol-031220-095215.

[41] E. Gómez-Pérez, F. Ostrosky-Solís, "Attention and memory evaluation across the life span: heterogeneous effects of age and education,", J. Clin. Exp. Neuropsychol. 28 (4) (May 2006) 477–494, https://doi.org/10.1080/13803390590949296.

[42] E.M. Arenaza-Urquijo, et al., "Relationships between years of education and gray matter volume, metabolism and functional connectivity in healthy elders,", Neuroimage 83 (December) (Dec. 2013) 450–457, https://doi.org/10.1016/j.neuroimage.2013.06.053.

[43] L.B. Zahodne, Y. Stern, J.J. Manly, "Differing effects of education on cognitive decline in diverse elders with low versus high educational attainment.,", Neuropsychology 29 (4) (Jul. 2015) 649–657, https://doi.org/10.1037/neu0000141.

[44] A.V. Apkarian, M.N. Baliki, P.Y. Geha, "Towards a theory of chronic pain,", Progress in Neurobiology 87 (2) (Feb. 2009) 81–97, https://doi.org/10.1016/j.pneurobio.2008.09.018.

[45] I. Coppieters, et al., "Differences in white matter structure and cortical thickness between patients with traumatic and idiopathic chronic neck pain: associations with cognition and pain modulation?,", Hum. Brain Mapp. 39 (4) (Apr. 2018) 1721–1742, https://doi.org/10.1002/hbm.23947.

[46] D.A. Seminowicz, K.D. Davis, "Pain enhances functional connectivity of a brain network evoked by performance of a cognitive task,", J. Neurophysiol. 97 (5) (May 2007) 3651–3659, https://doi.org/10.1152/jn.01210.2006.

[47] S. Lithfous, O. Després, T. Pebayle, A. Dufour, "Modification of descending analgesia in aging critical role of the prefrontal cortex,", Clin. J. Pain (2019).

[48] K. Ickmans, M. Meeus, M. De Kooning, L. Lambrecht, N. Pattyn, J. Nijs, "Associations between cognitive performance and pain in chronic fatigue syndrome: comorbidity with fibromyalgia does matter,", Pain Physician 18 (no. 5) (Sep. 2015) E841–E852, https://doi.org/10.36076/ppj.2015/18/e841.

[49] I. Coppieters, et al., "Cognitive performance is related to central sensitization and health-related quality of life in patients with chronic whiplash-associated disorders and fibromyalgia,", Pain Physician 18 (no. 3) (2015) E389–E402, https://doi.org/10.36076/ppj.2015/18/e389.

[50] J. Khan, O. Korczeniewska, R. Benoliel, M. Kalladka, E. Eliav, C. Nasri-Heir, "Age and gender differences in mechanically induced intraoral temporal summation and conditioned pain modulation in healthy subjects,", Oral Surg Oral Med Oral Pathol Oral Radiol 126 (2) (Aug. 2018) 134–141, https://doi.org/10.1016/j.oooo.2018.03.021.

[51] K.M. Naugle, T. Ohlman, B. Wind, L. Miller L, "Test-Retest instability of temporal summation and conditioned pain modulation measures in older adults,", 1, Pain Med. 21 (11) (2020) 2863–2876, https://doi.org/10.1093/pm/pnaa288. PMID: 33083842.

[52] J. Hackett, K.E. Naugle, K.M. Naugle, "The decline of endogenous pain modulation with aging: a meta-analysis of temporal summation and conditioned pain modulation,", J. Pain 21 (5–6) (2020) 514–528, https://doi.org/10.1016/j.jpain.2019.09.005.

[53] J.L. Riley, C.D. King, F. Wong, R.B. Fillingim, A.P. Mauderli, "Lack of endogenous modulation and reduced decay of prolonged heat pain in older adults,", Pain 150 (1) (Jul. 2010) 153–160, https://doi.org/10.1016/j.pain.2010.04.020.

[54] M. Kovacevic, L. Klicov, D. Vuklis, R. Neblett, A. Knezevic, "Test-retest reliability of pressure pain threshold and heat pain threshold as test stimuli for evaluation of conditioned pain modulation,", Neurophysiol. Clin. 51 (5) (Oct. 2021) 433–442, https://doi.org/10.1016/j.neucli.2021.06.005.

[55] M.D.R. Ibancos-Losada, M.C. Osuna-Pérez, M.Y. Castellote-Caballero, Á. Díaz-Fernández, "Conditioned pain modulation effectiveness: an experimental study comparing test paradigms and analyzing potential predictors in a healthy population,", Brain Sci. 10 (9) (Sep. 2020) 1–18, https://doi.org/10.3390/brainsci10090599.

[56] M. G C A M Mertens, et al., "Comparison of five conditioned pain modulation paradigms and influencing personal factors in healthy adults,", Eur. J. Pain 25 (1) (Jan. 2021) 243–256, https://doi.org/10.1002/ejp.1665.

[57] J.S. Mogil, "Sex differences in pain and pain inhibition: multiple explanations of a controversial phenomenon,", Nat. Rev. Neurosci. 13 (12) (2012) 859–866, https://doi.org/10.1038/nrn3360.

[58] E.J. Bartley, R.B. Fillingim, "Sex differences in pain: a brief review of clinical and experimental findings,", Br. J. Anaesth. 111 (1) (2013) 52–58, https://doi.org/10.1093/bja/aet127.

[59] R.B. Fillingim, C.D. King, M.C. Ribeiro-Dasilva, B. Rahim-Williams, J.L. Riley, "Sex, gender, and pain: a review of recent clinical and experimental findings,", J. Pain 10 (5) (2009) 447–485, https://doi.org/10.1016/j.jpain.2008.12.001.

[60] M. Racine, Y. Tousignant-Laflamme, L.A. Kloda, D. Dion, G. Dupuis, M. Choinire, "A systematic literature review of 10 years of research on sex/gender and experimental pain perception - Part 1: are there really differences between women and men?,", Pain 153 (3) (2012) 602–618, https://doi.org/10.1016/j.pain.2011.11.025.

[61] A. Marcuzzi, P.J. Wrigley, C.M. Dean, R. Adams, J.M. Hush, "The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals,", Pain 158 (7) (Jul. 2017) 1217–1223, https://doi.org/10.1097/j.pain.0000000000000901.

[62] D.L. Kennedy, H.I. Kemp, C. Wu, D.A. Ridout, A.S.C. Rice, "Determining real change in conditioned pain modulation: a repeated measures study in healthy volunteers,", J. Pain 21 (no. 5–6) (May 2020) 708–721, https://doi.org/10.1016/j.jpain.2019.09.010.

[63] T.M. Cummins, S.B. McMahon, K. Bannister, "The impact of paradigm and stringent analysis parameters on measuring a net conditioned pain modulation effect: a test, retest, control study,", Eur. J. Pain 25 (2) (Feb. 2021) 415–429, https://doi.org/10.1002/ejp.1681.