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# The role of stimulation parameters on the conditioned pain modulation response

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ABSTRACT

**Background and purpose:** Conditioned pain modulation (CPM) is a testing paradigm representing features of diffuse noxious inhibitory control. There is large diversity in the paradigms applied to induce CPM, and the consistency in CPM responses assessed by different paradigms is largely unknown. We aimed to characterize and explore the associations between the CPM responses assessed by different paradigms in the same cohort.
**Methods:** Thirty-three healthy middle-aged subjects underwent six CPM paradigms. The 'test-stimuli', consisted of thermal and mechanical modalities, using pain thresholds, suprathreshold pain and temporal summation types of measurements. The 'conditioning-stimulus' consisted of a contact heat stimulus applied to the thener of the left hand for 60 s at an intensity of 46.5 °C.
**Results:** Large variability was observed among the responses to the different CPM paradigms. Surprisingly, no correlations were found between the various CPM responses.
**Conclusions:** The variability in the CPM responses may suggest that the capacity of pain modulation is a multifaceted trait, whose expression varies with the application of different CPM paradigms.
**Implications:** Considering that CPM responses may represent different processes when assessed by different paradigms, we encourage the use of more than one CPM paradigm.


## 1. Introduction

Pain modulation processes have been recognized as a key factor in depicting the characteristics of the individual pain profile. One of the most explored mechanisms underlying the pain modulation system is the 'diffuse noxious inhibitory control' (DNIC), which is mediated by activation of the spino-bulbo-spinal loop [1]. The DNIC phenomenon is manifested as a decrease in pain sensation evoked by a 'test-stimulus' during or following the application of another noxious stimulus, termed the 'conditioning-stimulus'. This 'pain inhibits pain' phenomenon can be measured psychophysically in humans by the conditioned pain modulation (CPM) paradigm [2]. Less efficient DNIC was reported in various populations of idiopathic pain disorders, such as tempomandibular disorder [3–6]; irritable bowel syndrome [3,7,8]; fibromyalgia [9–13]; and tension-type headache [14]. Furthermore, less efficient DNIC was found to be associated with a higher self-report of pain history among healthy subjects [15]. Less efficient CPM was also found to predict the development of chronic post-surgical pain [16,17] and high response to some analgesics [18]. These findings further support the role of prospective assessment of CPM as a valuable laboratory test supporting assessment.

Along with the growing interest in the potential clinical relevance of CPM, a large variability in the techniques applied to induce the CPM response can be found (see a review by Pud et al. [19]); numerous types of 'test' and 'conditioning' stimuli are used to evoke CPM, with different psychophysical measures (pain threshold, pain scores of supra-threshold stimulus, pain tolerance, or temporal summation), various stimulation modalities (thermal, mechanical, electrical, or ischemic), and different body sites. Moreover, a large variability is found in the CPM extents [19], probably due to the use of different paradigms in the different laboratories. This study was conducted to address the question of consistency of individuals' expression of their pain modulation when induced by a variety of test protocols. We, therefore, aimed to characterize the results of CPM responses evoked by different paradigms in one cohort.

## 2. Methods

### 2.1. Subjects

Participants were 33 healthy subjects (18 women and 15 men), mean age 52.4 ± 7.5. They were recruited by advertisement and met

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**Table 1**
Characteristics of the various CPM protocols.

| CPM protocol | 'Test-stimulus' | 'Conditioning-stimulus' |
|---|---|---|
| HPT | Heat pain threshold | Contact heat |
| PPT | Pressure pain threshold | Contact heat |
| HP | Heat pain | Contact heat |
| PP | Pressure pain | Contact heat |
| tTS | Thermal temporal summation | Contact heat |
| mTS | Mechanical temporal summation | Contact heat |

the following inclusion criteria: (1) absence of chronic pain history; (2) no use of analgesic or psychiatric medication on a regular basis; (3) ability to communicate and understand the instructions of the study; and (4) age above 40. Subjects were asked to refrain from pain relief medications in the 24 h prior to the experimental trial.

### 2.2. Study design

The study was approved by the local Ethics Committee, and informed consent was obtained from all of subjects prior to the first experiment. The present study was part of a bigger research project involving ten CPM paradigms conducted in four sessions, each lasted approximately 1 h. The sessions were separated by at least three days. Here we present the analyses obtained from six different 'test-stimuli' used in parallel to a single 'conditioning-stimulus', The CPM paradigms were performed in random order by three examiners (H.N.-A., E.G., and P.D.), who were blind to the CPM results measured by the other examiners, Subjects completed the personality questionnaires in the first session.

Fifteen minutes after the initial administration of the 'test-stimulus', the 'conditioning-stimulus' was delivered by contact heat, which was applied to the non-dominant thenar eminence for 60 s at an intensity of 46.5 °C. Subjects were asked to verbally rate their pain intensity, using a 0–100 Numerical Pain Scale (NPS), three times during the first 30 s of the stimulus (at 10, 20, and 30 s). The final pain score was calculated by averaging these three pain ratings. In parallel to the last 30 s of the 'conditioning-stimulus', the 'test-stimulus' was repeated. The CPM response was calculated as the difference between the pain scores of the two 'test-stimuli' (during the 'conditioning-stimulus' minus before it). A negative value for CPM response represents pain reduction with a more efficient CPM response. Each paradigm was termed according to the chosen 'test-stimulus'. The six CPM paradigms are presented in Table 1.

### 2.3. Characteristics of the various 'test-stimuli'

#### 2.3.1. Heat pain threshold (HPT)

Two contact heat stimuli were delivered to the dominant volar forearm, using the Thermal Sensory Analyzer (TSA) 2001 system (Medoc, Ramat Yishay, Israel), with a 30 × 30 mm Peltier surface stimulator. The rate of temperature increase was 1.5 °C/s, and the rate of its return to baseline (32 °C) was 10.0 °C/s. Subjects were instructed to identify the point when the stimulus was first perceived as painful by pressing the 'stop' button on the response unit. Heat pain threshold (HPT) was calculated by averaging the threshold temperatures (°C) of two successive trials.

#### 2.3.2. Pressure pain threshold (PPT)

Mechanical pressure stimulus of increasing intensity was applied to the forearm using a pressure algometer (Somedic, Sweden) with a probe diameter of 1 cm. The subjects were instructed to press the 'stop' button at the point when the stimulus was first perceived as painful. The pressure pain threshold (PPT) was calculated by averaging the threshold pressure (kPa) of four successive trials.

#### 2.3.3. Heat pain (HP)

Tonic heat pain (HP) stimulation was applied to the dominant volar forearm, using TSA with a 30 × 30 mm Peltier surface stimulator. The stimuli were administered at the intensity of *pain60*, which is the temperature that induces pain scoring at a magnitude of 60 on a 0–100 NPS. The *pain60* temperature was determined individually in the dominant volar forearm before application of the HP stimulation (for more details, see Granot et al. [20]). The 'test-stimulus' was delivered 10 min after determining the *pain60* temperature. The rate of increasing and decreasing the temperature from the baseline was 2 °C/s. The stimulation was applied for 30 s, during which subjects were asked to verbally rate their pain intensity on an NPS at 10, 20, and 30 s. The final 'test-stimulus' pain score was determined by averaging these three pain ratings.

#### 2.3.4. Pressure pain (PP)

Pressure pain (PP) stimulation was applied to the volar forearm, using a pressure algometer (Somedic, Sweden). Stimuli were administered at the *pain60* intensity, which is the kPa value that induces pain scoring at a magnitude of 60 on a 0–100 NPS in the dominant volar forearm. The 'test-stimulus' was delivered 10 min after individually determining the *pain60* intensity. Subjects were asked to verbally rate their pain intensity on an NPS at the peak of this phasic stimulus. The final pain scores were determined by averaging the results of two trials.

#### 2.3.5. Mechanical temporal summation (mTS)

In order to evoke mechanical temporal summation (mTS), a train of 10 identical pinprick stimuli was delivered to the dominant volar forearm, using Von Frey monofilaments (Stoelting, Wood Dale, IL) of 6.45 Nm (225.1 g). The stimuli were administered at an inter-stimulus interval (ISI) of 2 Hz within an area of 1 $cm^2$. The subjects were asked to verbally rate their pain intensity on an NPS for the first pinprick stimulus and then for the last stimulus in the series of ten. The mTS value was calculated as the difference between the pain scorings obtained for the last and the first pinprick stimuli (last minus first).

#### 2.3.6. Thermal temporal summation (tTS)

In order to induce thermal temporal summation (tTS), a series of 10 brief repetitive supra-threshold thermal stimuli was applied to the thenar eminence of the dominant hand, using the Pathway (Pain & Sensory Evaluation System, Medoc, Israel), with a 27 mm diameter round probe. Stimuli were administered at the *pain60* intensity, with an inter stimulus interval (onset-to-onset) of 2.5 s and a plateau duration of 0.7 s. The adaptation temperature was 39 °C, the increase rate was 20 °C/s, and the decrease rate was 40 °C/s. Last minus first rating was calculated as tTS.

### 2.4. Statistical analysis

Statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA, version 15). The CPM response was calculated as the difference between the pain scores of the two 'test-stimuli'. A negative value for CPM response represents pain reduction with a more efficient CPM response. Paired *t*-test was used in order to compare the difference between the 'test-stimulus' before and during the 'conditioning-stimulus'. Since the various CPM paradigms applied in the current study represent diverse physical units (i.e., °C, NPS, kPa), we standardized the response in each of the CPM paradigms into *z*-scores using the formula: $z = (x - \mu)/<\text{sigma}>$, where $x$ was the raw CPM response, $\mu$ was the mean of the population and <sigma> was the standard deviation of the population. This procedure allows us to more easily graphically compare differences in individual responses across paradigms. Furthermore, we examined the correlations between the CPM responses obtained