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Temporal Aspects of Endogenous Pain Modulation During a Noxious Stimulus Prolonged for 1 Day

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Abstract

Background

This study investigated (a) if a prolonged noxious stimulus (24-hr topical capsaicin) in healthy adults would impair central pain inhibitory and facilitatory systems measured as a reduction in conditioned pain modulation (CPM) and enhancement of temporal summation of pain (TSP) and (b) if acute pain relief or exacerbation (cooling and heating the capsaicin patch) during the prolonged noxious stimulus would affect central pain modulation.

Methods

Twenty-eight participants (26.2 ± 1.0 years; 12 women) wore a transdermal 8% capsaicin patch on the forearm for 24 hr. Data were collected at baseline (Day 0), 1 hr, 3 hr, Day 1 (post-capsaicin application) and Day 3/4 (post-capsaicin removal) that included capsaicin-evoked pain intensity, heat pain thresholds (HPTs), TSP (10 painful cuff pressure stimuli on leg) and CPM (cuff pressure pain threshold on the leg prior vs. during painful cuff pressure conditioning on contralateral leg). After 3 hr, cold (12°C) and heat (42°C) stimuli were applied to the capsaicin patch to transiently increase and decrease pain intensity.

Results

Participants reported moderate pain scores at 1 hr (2.5 ± 2.0), 3 hr (3.7 ± 2.4), and Day 1 (2.4 ± 1.8). CPM decreased 3-hr post-capsaicin ($p = .001$) compared to Day 0 and remained diminished while the capsaicin pain score was reduced (0.4 ± 0.7 , $p < .001$) and increased (6.6 ± 2.2 , $p < .001$) by patch cooling and heating. No significant differences occurred for CPM during patch cooling or heating compared to initial 3HR; however, CPM during patch heating was reduced compared with patch cooling ($p = .01$). TSP and HPT did not change.

Conclusions

This prolonged experimental pain model is useful to provide insight into subacute pain conditions and may provide insight into the transition from acute to chronic pain.

Significance

During the early hours of a prolonged noxious stimulus in healthy adults, CPM efficacy was reduced and did not recover by temporarily removing the ongoing pain indicating a less dynamic neuroplastic process.

1 INTRODUCTION

Central pain modulation involves a balance of systems that inhibit and facilitate pain. In patient populations, the balance between antinociceptive and pronociceptive mechanisms is a dynamic process with a transition over time that often results in a net decrease in inhibition (Arendt-Nielsen et al., [2018](#)). While many people with chronic pain have impaired pain modulation (Arendt-Nielsen et al., [2018](#); Lewis, Rice, & McNair, [2012](#)), the temporal aspects of these deficiencies and transition are not clear.

The antinociceptive and pronociceptive aspects of endogenous pain modulation in humans may be studied via quantitative sensory testing that includes conditioned pain modulation (CPM) and temporal summation of pain (TSP), respectively (Bannister & Dickenson, [2017](#)). Studies on chronic pain patients have found that pain intensity and duration might drive CPM impairment (Albu, Gomez-Soriano, Avila-Martin, & Taylor, [2015](#); Arendt-Nielsen et al., [2015](#), [2010](#); Kosek & Ordeberg, [2000](#); Skou et al., [2013](#)). Young women with long-standing patellofemoral pain had similar TSP but impaired CPM compared with young pain-free women (Rathleff, Petersen, Arendt-Nielsen, Thorborg, & Graven-Nielsen, [2016](#)). Similarly, neuropathic pain patients who suffered more than a year had less efficient CPM, but similar TSP, compared with patients suffering less than 1 year (Mlekusch et al., [2016](#)). For chronic pain patients, TSP is often augmented such as in fibromyalgia (Staud, [2012](#)). Thus, the overall deficit in pain modulation with chronic pain may be characterized by enhanced TSP, impaired CPM or both.

It is unclear whether changes in CPM and/or TSP occur during a subacute or prolonged noxious stimulus. Existing experimental pain models can provoke intense pain for a short duration, which is seen in the hypertonic saline or acid pain models (Arendt-Nielsen, Sluka, & Nie, [2008](#); Asaki et al., [2018](#); Izumi, Petersen, Arendt-Nielsen, & Graven-Nielsen, [2014](#)). Whether a prolonged noxious stimulus over many hours produces changes in central pain modulation or could potentially act as a conditioning painful stimulus that produces CPM-like effects remains to be seen. For example, after 2 days with exercise-induced muscle soreness, participants reported mild pain without significant changes in CPM or TSP (McPhee & Graven-Nielsen, [2018](#)). No studies have focused on combining the study of pain modulation with a prolonged model of moderate spontaneous pain. Recent studies using topical capsaicin for 24 hr observed prolonged episodes of moderate pain and hyperalgesia (Andersen, Marker, Hoeck, Elberling, & Arendt-Nielsen, [2017](#); Henrich, Magerl, Klein, Geffrath, & Treede, [2015](#)) that can be further modulated by applying normally nonpainful heat or cold to the sensitized area (Dirks, Petersen, & Dahl, [2003](#); Petersen & Rowbotham, [1999](#)). Thus, topical capsaicin for 24–48 hr may be used as a novel human experimental pain model to induce prolonged ongoing pain and study CPM and TSP simultaneously.

The first aim of this study was to investigate if a prolonged noxious stimulus (24-hr topical capsaicin) in healthy adults would impair central pain inhibitory and facilitatory systems measured as a reduction in CPM and enhancement of TSP, respectively. The second aim was to identify if acute pain relief or exacerbation (cooling and heating capsaicin patch) during the prolonged noxious stimulus would affect central pain modulation.

2 METHODS

2.1 Participants

Power analysis (80% power and $p = .05$) was done prior to initiating participant recruitment to determine that 24 participants were needed to investigate the changes in pain modulation (e.g. CPM) during the prolonged noxious stimulus. Twenty-eight participants were included (26.2 ± 1.0 years; 12 women) and completed the protocol. All participants were healthy and free of any medical diagnoses. Exclusion criteria included acute or chronic pain, neurologic, musculoskeletal, or mental illnesses, skin diseases, current itch and pregnancy or lactation. All participants received written and oral information, and informed consent was obtained prior to starting the study. The protocol was conducted in accordance with the Declaration of the World Medical Association and approved by the institutional review boards at Marquette University and the North Denmark Region Committee on Health Research Ethics (N-20170020).

2.2 Experimental design

Participants wore a transdermal capsaicin patch for 24 hr on their forearm and participated in five experimental sessions. On Day 0, participants completed three sessions; the capsaicin patch was applied at the end of the first session and participants returned for two more sessions 1 hr (1HR), and 3 hr (3HR) post-capsaicin application. The data collection sequence in each session included: Capsaicin-evoked pain intensity, heat pain thresholds (HPTs) assessed contralateral to the capsaicin application, TSP on the dominant leg and CPM (unconditioned stimulus on nondominant leg and conditioning stimulus on dominant leg) (Figure [1](#)). During the 3HR session, cold and heat stimuli were applied onto the capsaicin patch to increase and decrease capsaicin-evoked pain intensity, respectively. After completing the day 1 session (Day 1), the capsaicin patch was removed. Recovery measurements were done after 3 or 4 days from Day 0 (Day 3/4).

Experimental Design

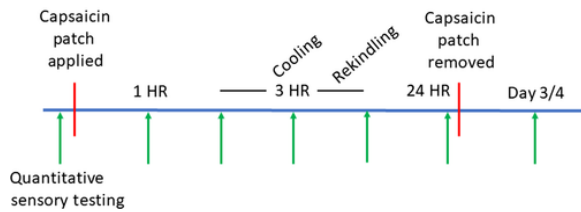


Figure 1. Experimental design. Participants wore a transdermal capsaicin patch on their right forearm and completed five experimental sessions; three sessions during Day 0 [capsaicin application, 1-hr (HR) and 3-hr post application], one session 24 hr after capsaicin application and one session post-capsaicin removal (Day 3/4). Quantitative sensory testing (green arrow) was done at each session that included heat pain threshold contralateral to the capsaicin patch, temporal summation of pain and conditioned pain modulation. During the 3HR session, cold and heat stimuli were applied onto the capsaicin patch to increase and decrease capsaicin-evoked pain intensity, respectively, during which CPM and TSP were re-assessed. CPM, conditioned pain modulation; TSP, temporal summation of pain

2.3 Cuff pressure pain sensitivity

The pressure stimuli were applied using a computer-controlled cuff algometer (Nocitech, Aalborg University) including two 13-cm wide tourniquet cuffs (VBM). The skin is minimally provoked by stimulation of the cuff, and the stress and strain distributions are focused at deeper structures (i.e. muscles) rather than the skin (Manafi Khanian, Arendt-Nielsen, Kjaer Petersen, Samani, & Graven-Nielsen, [2016](#); Manafi-Khanian, Arendt-Nielsen, Frokjaer, & Graven-Nielsen, [2015](#); Manafi-Khanian, Arendt-Nielsen, & Graven-Nielsen, [2016](#)). In addition, this methodology has consistently demonstrated good-to-excellent reliability when assessed on the same day and in between days (Graven-Nielsen, Izumi, Petersen, & Arendt-Nielsen, [2017](#); Graven-Nielsen, Vaegter, Finocchietti, Handberg, & Arendt-Nielsen, [2015](#); Imai, Petersen, Morch, & Arendt, [2016](#)). An electronic visual analogue scale (VAS, Aalborg University) was used for recording of the pressure-induced pain intensity. The cuffs were placed at the level of the head of the gastrocnemius muscle. The VAS was 10 cm long and sampled at 10 Hz; 0 cm indicated 'no pain', and 10 cm indicated 'maximum pain'. The pressure was increased by 1 kPa/s and the participants were instructed to rate the pain intensity continuously on the electronic VAS until the tolerance level was reached. The participants were further instructed to press a stop button when reaching the tolerance intensity. The pressure pain detection threshold (PDT) was defined as the pressure at which the VAS score exceeded 1 cm (Graven-Nielsen et al., [2017](#)). The pain tolerance threshold (PTT) was defined when the participant pressed the stop button. PDT and PTT were assessed bilaterally.

2.4 Temporal summation of pain

Using a cuff algometer (Nocitech and Aalborg University), 10 short-lasting cuff pressure stimuli (1 s each) at the level of the PTT were given at the dominant leg with a 1 s break between stimuli. The PTT used was recorded immediately prior to each TSP using the same pressure increase (1 kPa/s) as described under cuff pressure pain sensitivity. The participants were instructed to continuously rate the pain intensity of the sequential stimuli using the electronic VAS and not to return to zero during the breaks. TSP was quantified by summing the VAS from the 10 stimuli after normalization to the VAS rating of the first stimulus. Specifically, normalization was done by subtracting VAS1 from all 10 stimuli and then summed.

2.5 Conditioned pain modulation

Conditioned pain modulation magnitude was assessed as the changes in PDT with and without a conditioning stimulus (cuff pressure stimulation). The PDT was assessed on the nondominant lower leg, and the conditioning stimulus was applied to the contralateral lower leg (Graven-Nielsen et al., [2017](#); Imai et al., [2016](#)). CPM was calculated as the difference in PDT with versus without the conditioning stimulus.

2.6 Heat pain sensitivity

A thermal stimulator (30x30 mm probe; PATHWAY Model ATS, Medoc Ltd, Israel) was used to assess HPT on the left volar forearm. The baseline temperature was 32°C and heat pain ramp stimuli were applied at an increase rate of 1°C/s. Participants were instructed that they would first feel a warm sensation and to press the stop button as soon as they perceived any pain. Once the HPT was reached, the temperature return rate was 3°C/s. A total of three trials were performed, and the average value was used for analysis.

2.7 Experimental pain model

A transdermal 8% capsaicin patch ('Qutenza', Grünenthal, 4 × 4 cm) was applied to the middle of the volar aspect of the right forearm (Andersen et al., [2017](#); Henrich et al., [2015](#)) and covered with two perpendicular strips of medical tape (Fixomull stretch, BSN). Participants were instructed that they might feel a prolonged burning sensation in the capsaicin patch area and to avoid getting the patch wet as well as heavy exercise. Participants were asked to rate their current, average and maximum capsaicin-evoked pain intensity at the start of the remaining four sessions using a 0–10 numerical rating scale (NRS) anchored with 0 as 'no pain' and 10 as 'worst imaginable pain'.

During the 3HR session, a thermal stimulator (30 × 30 mm probe; PATHWAY Model ATS, Medoc Ltd) was placed over the capsaicin patch to cool and then heat the area causing acute pain relief or exacerbation, respectively (Dirks et al., [2003](#)). For both protocols, the baseline temperature of the probe was 32°C and the temperature changed at a 3°C/s rate to 12°C (non-noxious) or 42°C. After 30 s of either cooling or heating, participants reported pain intensity in the capsaicin area. While the probe remained at the cooling or heating temperature, CPM and TSP were assessed. The return rate for both protocols was 5°C/s. The patch cooling and heating protocols were done consecutively without a break between the two protocols.

2.8 Statistical analysis

All statistical analyses were performed with IBM SPSS version 25. Normality was visually assessed with Q-Q plots. Repeated measure analysis of variance (RM-ANOVA) was done to assess capsaicin-evoked NRS pain scores over the repeated four sessions (session: 1HR, 3HR, Day 1, and Day 3/4) as well as HPT, PDT, PTT, CPM, and TSP measures over the five repeated sessions (session: Day 0, 1HR, 3HR, Day 1 and Day 3/4) and during the 3HR session (time: 3HR, 3HR-cool and 3HR-heat). If the sphericity assumption was violated, the Greenhouse-Geisser correction was used. When a significant effect was found, post-hoc analyses were done using paired sample *t* tests. For statistical significance, $p \leq .05$ was initially used (i.e. for RM-ANOVA); however, a more rigorous alpha level was selected ($p \leq .02$) to minimize type I and II errors with multiple group comparisons (i.e. post-hoc analyses) and multiple correlations (Alsouhibani, Vaegter, & Hoeger Bement, [2018](#); Avin & Law, [2011](#)). Intraclass correlations (ICC) two-way mixed model based on absolute agreement were done to evaluate reliability of parameters between Day 0 and Day 3/4. Data are reported as mean ± standard deviation within the text and mean ± standard error of the mean in Figures [2](#) and [3](#).

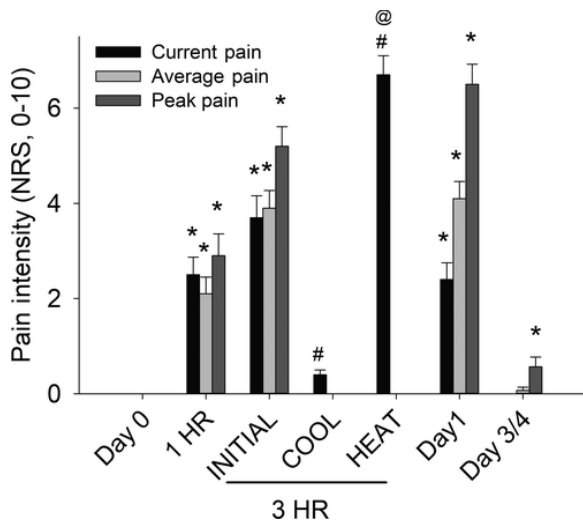


Figure 2. Capsaicin-evoked pain intensity. Mean (+SEM) numerical rating scale (NRS) scores of the current, average and peak capsaicin-evoked pain intensity. Subjects reported moderate pain intensity at 1 hr, 3 hr and Day 1. Patch cooling and patch heating decreased and increased pain intensity, respectively. Baseline (Day 0); 1 hr (1HR), 3 hr (3HR) and Day 1 (post-capsaicin application); Day 3/4 (post-capsaicin removal). During the 3HR session, the capsaicin patch was cooled (cool) and heated (heat). *, significantly different from Day 0 ($p < .001$); #, significantly different from 3HR initial ($p < .001$); @, significantly different between cooling and heating protocols ($p < .001$)

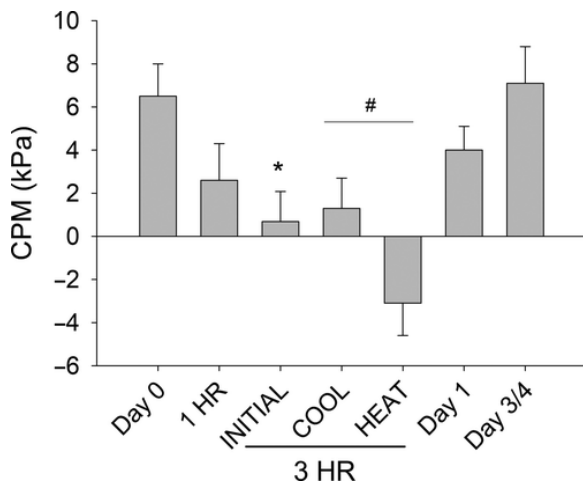


Figure 3. Conditioned pain modulation (CPM). Mean (\pm SEM) effect of CPM (conditioned pain detection threshold minus unconditioned pain detection threshold). CPM effect decreased 3-hr post-capsaicin compared to Day 0 (*, $p = .001$), and CPM during patch heating was reduced compared with patch cooling (#, $p = .012$). Baseline (Day 0); 1 hr (1HR), 3 hr (3HR) and Day 1 (post-capsaicin application); Day 3/4 (post-capsaicin removal). During the 3HR session, the capsaicin patch was cooled (cool) and heated (heat)

3 RESULTS

3.1 Capsaicin-evoked pain intensity

All 28 participants completed the entire experiment without any adverse events or excessive discomfort. Capsaicin evoked significant current (session: $F(2.2, 59.6) = 47.2, p < .001$), average (session: $F(2.2, 58.7) = 73.2, p < .001$) and peak (session: $F(2.4, 65.7) = 103.3, p < .001$) NRS pain scores (Figure 2). Current and average pain were significantly different from baseline at 1HR, 3HR and Day 1 ($p < .01$). Peak pain NRS scores were significantly different from baseline at 1HR, 3HR, Day 1 and Day 3/4 ($p < .01$). While wearing the capsaicin

patch, participants reported mild-to-moderate average pain at 1HR (2.1 ± 1.8), 3HR (3.9 ± 2.0) and Day 1 (4.1 ± 1.9). During the recovery session (Day 3/4), pain ratings returned to baseline levels (i.e. no pain). Compared with the 3HR recordings, transient cooling reduced (0.4 ± 0.7 , $p < .001$) and transient heating increased (6.6 ± 2.2 , $p < .001$) the current NRS scores of the capsaicin-evoked pain intensity (time: $F(2, 54) = 124.4$, $p < .001$). During the 3HR session, pain intensity during cooling and heating was significantly different from 3HR (initial) and between the cool and heating protocols ($p < .01$).

3.2 Heat pain sensitivity

HPTs at baseline contralateral to the capsaicin administration area ($42.6 \pm 3.6^\circ\text{C}$), 1HR ($42.7 \pm 3.2^\circ\text{C}$), 3HR ($42.7 \pm 3.3^\circ\text{C}$), Day 1 ($42.8 \pm 3.7^\circ\text{C}$) and Day 3/4 ($42.9 \pm 3.8^\circ\text{C}$) did not change systematically (session: $F(2.3, 61.4) = 0.137$, $p = .90$).

3.3 Cuff pressure pain sensitivity

Despite a session effect for unconditioned PDT ($F(4, 108) = 2.6$, $p = .04$), post-hoc analysis showed there was no significance with baseline values ($p > .05$; Table 1). During the 3HR session, unconditioned PDT differed (time: $F(2, 54) = 13.6$, $p < .001$) and was higher during the patch heating than patch cooling ($p = .001$). For conditioned PDT (session: $F(2.6, 69.1) = 4.9$, $p = .001$), the 3HR session ($p = .007$) and Day 1 ($p = .02$) were lower compared to baseline. Conditioned PDT (time: $F(2, 54) = 7.5$, $p = .001$) was also higher during patch heating compared to the beginning of the 3HR session ($p = .001$).

Table 1. Mean (\pm SEM) for the pain detection threshold (PDT), pain tolerance threshold (PTT), conditioned PDT, conditioned pain modulation (CPM) and temporal summation of pain (TSP) assessed at baseline (Day 0), 1 hr (1HR), 3 hr (3HR), Day 1 (post-capsaicin application) and Day 3/4 (post-capsaicin removal)

	Unconditioned PDT (kPa)	PTT (kPa)	Conditioned PDT (kPa)	CPM (kPa)	TSP
Day 0	24.9 \pm 14.7	60.5 \pm 23.2	31.4 \pm 18.3	6.5 \pm 7.8	13.3 \pm 13.9
1HR	26.6 \pm 15.4	62.2 \pm 23.2	29.2 \pm 16.1	2.6 \pm 9.1	17.3 \pm 12.5
3HR	26.7 \pm 14.2	61.5 \pm 23.4	27.4 \pm 15.1 ^a	0.7 \pm 7.4 ^a	17.4 \pm 12.6
3HR-Cool	28.6 \pm 14.7	65.8 \pm 22.9 ^c	29.9 \pm 14.6	1.3 \pm 7.5	17.5 \pm 13.5
3HR-Heat	35.2 \pm 20.6 ^b	68.0 \pm 21.8 ^{b, c}	32.0 \pm 17.1 ^c	-3 \pm 8.1 ^b	17.7 \pm 14.6
Day 1	23.0 \pm 12.0	57.5 \pm 24.3	27.1 \pm 15.3 ^a	4.0 \pm 6.1	14.4 \pm 14.8
Day 3/4	25.7 \pm 13.7	56.3 \pm 23.8	32.8 \pm 21.1	7.1 \pm 9.2	10.6 \pm 12.1

Note. During the 3HR session, the capsaicin patch was cooled (3HR-Cool) and heated (3HR-Heat).

- ^a Significantly different compared with Day 0.
- ^b Significantly different between patch cooling and heating.
- ^c Significantly different from initial 3HR.

For PTT, there was a significant session effect (session: $F(2.6, 71.3) = 5.9$, $p = .002$); however, there was no significance from baseline with post-hoc analysis (Table 1). PTT differed during patch cooling and patch heating (time: $F(1.6, 44.3) = 28.0$, $p < .001$) with higher PTT during patch cooling and heating compared to the beginning of the 3HR session ($p < .001$) and higher PTT during heating than cooling ($p = .002$).

3.4 Temporal summation of pain

There was a session effect for TSP (session: $F(2.8, 75.0) = 3.4$, $p = .03$); however, there was no significance from Day 0 with post-hoc analysis (Table 1). TSP was similar during patch cooling and patch heating (time: $F(2, 54) = 0.02$, $p = .98$).

3.5 Conditioned pain modulation

Conditioned pain modulation magnitude differed across sessions (session: $F(2.4, 66.7) = 5.3, p = .004$; Figure 3); CPM was lower during the 3HR session than baseline (Day 0; $p = .001$) indicating that descending inhibitory function was compromised. During the 3HR session, CPM also differed (time: $F(2, 54) = 3.8, p = .03$) between the patch cooling and patch heating protocols ($p = .012$) but not with CPM at the start of the 3HR session.

3.6 Repeatability across days

PTT, unconditioned PDT and conditioned PDT had strong reliability between Day 0 and Day 3/4 (ICC = 0.91, 0.84 and 0.91, respectively). CPM and HPT had moderate reliability (ICC = 0.67 and 0.71, respectively), and TSP had poor reliability (ICC = 0.35).

4 DISCUSSION

This is the first study to demonstrate impaired CPM after 3 hr of prolonged episodes of experimental pain. Interestingly, after 1 day with experimental pain, the CPM adapted towards baseline measures and recovered fully a few days after the experimental pain vanished. The impaired CPM after 3 hr was not reversed by temporarily reducing the intensity of experimental pain, as demonstrated by similar CPM at the beginning of the three 3HR session and during patch cooling. Increasing the experimental pain transiently via patch heating impaired the CPM further.

4.1 Pain sensitivity

In accordance with recent studies, high-concentration 8% topical capsaicin was well-suited as a safe model providing subacute mild-to-moderate pain (Lo Vecchio, Andersen, & Arendt-Nielsen, **2018**). Previous research has shown that transient application of capsaicin may act either as a conditioning or test noxious stimulus producing CPM effects (Baad-Hansen, Poulsen, Jensen, & Svensson, **2005**; Kempainen, Waltimo, Waltimo, Kononen, & Pertovaara, **1997**). For instance, ice water immersion decreased pain intensity associated with 5% capsaicin applied to the gingiva for 9 minutes (Baad-Hansen et al., **2005**). Similarly, an approximate 25 minutes application of 1% capsaicin decreased the tooth-pulp-evoked pain sensations (Kempainen et al., **1997**). In the current study, prolonged application of high-concentration capsaicin did not act as a conditioning stimulus and produced CPM-like effects when paired with another noxious stimulus (i.e. HPT). However, CPM-like effects occurred when the capsaicin-induced pain intensity (conditioning stimulus) was transiently exacerbated during patch heating as demonstrated by an increase in unconditioned PDT (test stimulus) during the patch heating compared with patch cooling (i.e. the additional capsaicin pain may have caused additional conditioning). One caveat is that the capsaicin pain intensity without the heating procedure may not have been high enough to induce a robust CPM response; Granot and colleagues have shown that mild pain levels do not induce CPM (Nir, Granovsky, Yarnitsky, Sprecher, & Granot, **2011**).

4.2 Temporal summation of pain

During the prolonged noxious stimulus, TSP was not significantly different across all sessions as well as during the heating and cooling protocols when measured at a distal site. Conversely, whether TSP would have changed if measured at the capsaicin area is not known. Others have shown that TSP appears to be a more stable phenomenon especially when compared with CPM for musculoskeletal and neuropathic clinical pain (Nasri-Heir et al., **2015**; Rathleff et al., **2016**). Similar findings were reported with an exercise-induced pain model in healthy participants; no differences in TSP occurred following exercise-induced muscle pain (48 hr after fatiguing exercise) compared with the baseline session (Alappattu, Bishop, Bialosky, George, & Robinson, **2011**; McPhee & Graven-Nielsen, **2018**). Therefore, the stability of TSP in this prolonged experimental pain model is comparable with other subacute experimental models and certain chronic pain conditions.

Enhanced TSP may occur more frequently in chronic pain conditions that have a more defined area of pain, and TSP may be more sensitive in the pain region compared with nonpainful areas (Bisset, Carty, & Smith, [2018](#); Raphael, Janal, Anathan, Cook, & Staud, [2009](#)). Furthermore, facilitated TSP is well-documented in multiple chronic pain conditions and it has been suggested that a prolonged (years) peripheral input is needed to initiate a spreading of the sensitization of central mechanisms including facilitated TSP (Arendt-Nielsen & Graven-Nielsen, [2011](#); Arendt-Nielsen et al., [2018](#)). In the current study, TSP was unaffected when measured at a site distant from the capsaicin patch; however, TSP may have been enhanced if measured at the site of the prolonged noxious stimulus (i.e. capsaicin).

4.3 Conditioned pain modulation

Conditioned pain modulation decreased 3 hr after the application of the capsaicin patch. Arendt-Nielsen and colleagues have shown less effective CPM during two concurrent conditioning stimuli (Arendt-Nielsen et al., [2008](#)). Therefore, in the current study, CPM may have been reduced due to the simultaneous noxious stimulation produced by the capsaicin. This is, however, not likely since the CPM impairment was not found after 1 hr with capsaicin pain and reducing the pain intensity briefly at 3HR did not recover the CPM. The reduced CPM efficiency was different from baseline only during the 3HR session when the capsaicin-evoked pain intensity was at the moderate level. This result suggests CPM to be more of a state-dependent phenomenon than previously assumed.

While the prolonged noxious stimulus produced by capsaicin resulted in less efficient CPM in young healthy adults, the temporal effects of CPM in patient populations are less clear. Patients with acute or chronic low back pain have similar CPM as healthy adults immediately after a conditioning stimulus, although the magnitude of CPM declined more rapidly in the patient groups than the controls (Mlekusch et al., [2016](#)). Additionally, over a span of 4 months, CPM declined in a linear fashion in healthy adults (Marcuzzi, Wrigley, Dean, Adams, & Hush, [2017](#)). In contrast, in patients with painful post-traumatic trigeminal neuropathy, CPM was less in patients who suffered for a longer duration (i.e. greater than 1 year) compared with those for a shorter duration (Nasri-Heir et al., [2015](#)). In the same study, TSP did not differ between the two groups. Thus, CPM appears to be a more dynamic process compared with TSP during prolonged noxious stimulation as well as in certain patient populations.

Despite the prolonged noxious stimulus of the capsaicin patch, CPM was not significantly different from 1HR recordings and increased towards baseline levels at Day 1. Others have shown that the CPM magnitude is correlated with the conditioning stimulus intensity rather than the pain reported with the conditioning stimulus (Nir et al., [2011](#)). Importantly, the cuff pressure pain tolerance was not significantly different across days meaning that the conditioning intensity was not significantly adjusted as a potential factor explaining the difference in CPM.

4.4 Dynamic characteristics of impaired conditioning pain modulation

At the start of the 3HR session, participants reported moderate pain intensity and impaired CPM compared to the baseline assessment. While cooling the area, participants reported minimal/no pain but there was no effect on the CPM response. Previous research shows that CPM improves following an acute pain intervention, if CPM is deficient (Goubert et al., [2015](#)). Consequently, the lack of CPM effect after alleviating pain in this subacute pain model does not align with previous findings in clinical pain patients due to several differences between the models. One important difference is the temporal aspects of the pain relief were immediate and transient in the current study and more prolonged following surgical interventions. Therefore, brief exposure to an analgesic intervention does not appear to alter central pain modulation unlike more long-lasting interventions, although it is important to note that cooling the area is unlikely to reverse the agonizing effects of capsaicin on the TRPV1 receptors. This suggests that the CPM impairment after a while is less dependent on the peripheral drive, and

other central neuroplastic manifestations may explain the maintained CPM impairment. Studies have demonstrated that prolonged (years) pain leads to impaired CPM (Graven-Nielsen & Arendt-Nielsen, **2010**). In addition, Arendt-Nielsen et al., **2015** assessed patients with no, mild, moderate and severe osteoarthritic pain and found more pronounced CPM impairment in the severe pain patients (Arendt-Nielsen et al., **2015**). Finally, Graven-Nielsen, Wodehouse, Langford, Arendt-Nielsen, and Kidd (**2012**) and Kosek and Ordeberg (**2000**) found that CPM was normalized following pain recovery after total joint replacements (Graven-Nielsen et al., **2012**; Kosek & Ordeberg, **2000**). Conclusively, these studies suggest that CPM impairment is maintained by a peripheral driver. Contrary to this, studies have found that CPM is not normalized when clinical pain is reduced (Petersen, Arendt-Nielsen, Simonsen, Wilder-Smith, & Laursen, **2015**; Petersen, Simonsen, Olesen, Morch, & Arendt-Nielsen, **2019**), indicating that other factors might interfere with the impairment of CPM. For example, studies have suggested that pain catastrophizing or sleep impairment can impair CPM and many of these factors are rarely assessed in mechanistic pain studies (Eichhorn, Treede, & Schuh-Hofer, **2018**; Meints et al., **2019**), which complicate the interpretation of these findings.

In contrast to the cooling protocol, the heating protocol modified the CPM response. Specifically, while heating the area, participants reported moderate-to-severe pain intensity and less efficient CPM compared with the already reduced CPM. The heat protocol that significantly increased pain at the capsaicin patch may have acted as a conditioning like noxious stimulus that resulted in an increase in the unconditioned PDT. Others have shown that two conditioning stimuli cause less efficient CPM (Arendt-Nielsen et al., **2008**), which could explain the attenuated CPM during the heating protocol. Interestingly, the conditioning intensity was adjusted to current PTT, which was significantly higher during patch heating. Despite the increase in conditioning intensity, which could potentially cause an increase in the CPM effect, CPM was attenuated.

5 LIMITATIONS

The fact that no time series of assessments were done in a control group without application of topical capsaicin is a limitation to the current design. Previous studies, however, have demonstrated reliable repeated assessment of pressure pain sensitivity (Graven-Nielsen et al., **2015**), CPM assessment [18] and TSP (Graven-Nielsen et al., **2015**); although in the current study, TSP was not measured at the site of the capsaicin patch and the repeatability of TSP at Day 3/4 (ICC = 0.35) may have been due to pain felt after removal of the capsaicin patch. Interestingly, acceptable intraclass correlation coefficients (baseline vs. Day 3/4) were found for the parameters also modulated by capsaicin-induced pain, suggesting that at least for CPM and pressure pain sensitivity a control group would not have added to the current findings. Additionally, the capsaicin-induced pain intensity without the patch heating may not have been high enough to induce a robust CPM response. Finally, the explorative nature of the current findings also calls for a larger study including a better representative sample across different ages.

6 CONCLUSION

Topical capsaicin applied over a 24-hr period produced prolonged mild-to-moderate pain. There was a decline in CPM after 3 hr that returned to baseline levels when the pain vanished, whereas TSP and pain sensitivity at distant sites did not change significantly during the ongoing pain. CPM impairment was maintained even if capsaicin pain was temporally reduced. With patch heating, CPM was further attenuated compared with patch cooling demonstrating that brief intense changes in pain intensity influence CPM efficiency. Thus, CPM appears to be a more dynamic phenomenon compared to the more stable metrics of TSP in healthy participants. This prolonged experimental pain model is a useful tool in providing insight into subacute pain conditions and may provide insight into the transition from acute to chronic pain.

CONFLICT OF INTEREST

There is no conflict of interest to report.

AUTHOR CONTRIBUTIONS

All authors provided significant contributions to this manuscript; Marie Hoeger Bement (design of protocol, data collection, data analysis, preparation of manuscript), Kristian K. Petersen (Design of protocol, data analysis, preparation of manuscript), Line Bay Sørensen (data collection), Hjalte H. Andersen (design of protocol, data analysis) and Thomas Graven-Nielsen (design of protocol, data analysis, preparation of manuscript).

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