Temporal aspects of endogenous pain modulation during a noxious stimulus prolonged for 1 day

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Background: This study investigated 1) if a prolonged noxious stimulus (24-hour 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 2) 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 hours. Data were collected at baseline (Day0), 1-hour, 3-hours, Day1 (post-capsaicin application), and Day3/4 (post-capsaicin removal) that included capsaicin-evoked pain intensity, heat pain thresholds (HPT), TSP (10 painful cuff-pressure stimuli on leg), and CPM (cuff-pressure pain threshold on the leg prior versus during painful cuff-pressure conditioning on contralateral leg). After 3-hours, 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-hour (2.5±2.0), 3-hours (3.7±2.4), and Day1 (2.4±1.8). CPM decreased 3-hours post-capsaicin ($p=0.001$) compared to Day0 and remained diminished while the capsaicin pain score was reduced (0.4±0.7, $p< 0.001$) and increased (6.6±2.2, $p<0.001$) 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 ($p=0.01$). 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.

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TEMPORAL ASPECTS OF ENDOGENOUS PAIN MODULATION DURING A NOXIOUS STIMULUS PROLONGED FOR ONE DAY

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Conflict of Interest: There is no conflict of interest to report.

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.

INTRODUCTION

Central pain modulation involves a balance of systems that inhibit and facilitate pain. In patient populations, the balance between anti-nociceptive and pro-nociceptive 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 et al., 2012), the temporal aspects of these deficiencies and transition are not clear.

The anti-nociceptive and pro-nociceptive 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 and Dickenson 2017). Studies on chronic pain patients have found that pain intensity and duration might drive CPM impairment (Albu et al., 2015; Arendt-Nielsen et al., 2015; Arendt-Nielsen et al., 2010; Kosek and Ordeberg 2000; Skou et al., 2013). Young women with long-standing patellofemoral pain (PFP) had similar TSP but impaired CPM compared with young pain-free women (Rathleff et al., 2016). Similarly, neuropathic pain patients that suffered more than a year had less efficient CPM, but similar TSP, compared with patients suffering less than one 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 for the hypertonic saline or acid pain models (Arendt-Nielsen et al., 2008; Asaki et al., 2018; Izumi et al., 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 two days with exercise-induced muscle soreness, participants reported mild

pain without significant changes in CPM or TSP (McPhee and 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 hours observed prolonged episodes of moderate pain and hyperalgesia (Andersen et al., 2017; Henrich et al., 2015) that can be further modulated by applying normally nonpainful heat or cold to the sensitized area (Dirks et al., 2003; Petersen and Rowbotham 1999). Thus, topical capsaicin for 24-48 hours 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-hour 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), 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.

METHODS

Participants

Power analysis (80% power and p= 0.05) was done prior to initiating participant recruitment to determine that twenty-four participants were needed to investigate the changes in pain modulation (e.g., conditioned pain modulation) 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 (Milwaukee, Wisconsin, USA) and the North Denmark Region Committee on Health Research Ethics (N-20170020).

Experimental Design

Participants wore a transdermal capsaicin patch for 24 hours 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- hour (1HR), and 3-hours (3HR) post-capsaicin application. The data collection sequence in each session included: Capsaicin-evoked pain intensity, heat pain thresholds (HPT) assessed contralateral to the capsaicin application, TSP on the dominant leg, and CPM (unconditioned stimulus on non-dominant 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, respectively. After completing the day 1 session (Day1), the capsaicin patch was removed. Recovery measurements were done after 3 or 4 days from Day0 (Day3/4).

Cuff Pressure Pain Sensitivity

The pressure stimuli were applied using a computer-controlled cuff algometer (Nocitech, Aalborg University, Denmark) including two 13-cm wide tourniquet cuff (VBM, Sulz, Germany). The skin is minimally provoked by stimulation of the cuff, and the stress and strain distribution are focused at deeper structures (i.e. muscles) rather than the skin (Manafi-Khanian et al., 2015; Manafi-Khanian et al., 2016; Manafi Khanian et al., 2016). In addition, this methodology has consistently demonstrated good-to-excellent reliability when assessed on the same day and in between days (Graven-Nielsen et al., 2017; Graven-Nielsen et al., 2015; Imai et al., 2016). An electronic visual analogue scale (VAS, Aalborg University, Denmark) 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 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.

Temporal Summation of Pain

Using a cuff algometer (Nocitech and Aalborg University, Denmark), ten 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 subtraction VAS1 from all 10 stimuli and then summed.

Conditioned Pain Modulation

CPM magnitude was assessed as the changes in PDT with and without a conditioning stimulus (cuff pressure stimulation). The PDT was assessed on the non-dominant 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.

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 warmth 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 used for analysis.

Experimental Pain Model

A transdermal 8% capsaicin patch ('Qutenza', Grünenthal, 4x4 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, Hamburg, Germany). 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 (30x30 mm probe; PATHWAY Model ATS, Medoc Ltd, Israel) 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.

Statistical Analysis

All statistical analyses were performed with IBM SPSS version 25 (Armonk, NY, USA). 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, Day1, and Day3/4) as well as HPT, PDT, PTT, CPM, and TSP measures over the repeated five sessions (session: Day0, 1HR, 3HR, Day1, and Day3/4) and during the 3HR session (time: 3HR, 3HR-cool, and 3HR-heat). If the sphericity assumption was violated, the Greenhouse-Geiser correction was used. When a significant effect was found, post-hoc analyses were done using paired sample t-tests. For statistical significance, $p \leq 0.05$ was used initially (i.e., for RM-ANOVA); however, a more rigorous alpha level was selected ($p \leq 0.02$) to minimize type I and II errors with multiple group comparisons (i.e., post hoc analyses) and multiple correlations (Alsouhibani et al., 2018; Avin and Law 2011). Intraclass correlations (ICC) two-way mixed model based on absolute agreement were done to evaluate reliability of parameters between Day0 and Day3/4. Data are reported as mean ± standard deviation (SD) within the text and mean ± standard error of the mean (SEM) in figures 2 and 3.

RESULTS

Capsaicin-Evoked Pain Intensity

All twenty-eight participants completed the entire experiment without any adverse events or excessive discomfort. Capsaicin evoked significant current (session: $F(2.2, 59.6)= 47.2$, $p< 0.001$), average (session: $F(2.2, 58.7)= 73.2$, $p< 0.001$), and peak (session: $F(2.4, 65.7)= 103.3$, $p< 0.001$) NRS pain scores (Figure 2). Current and average pain were significantly different from baseline at 1HR, 3HR, and Day1 ($p<0.01$). Peak pain NRS scores were significantly different from baseline at 1HR, 3HR, Day1, and Day3/4 ($p<0.01$). While wearing the capsaicin patch, participants reported mild-to-moderate average pain at 1HR (2.1 ± 1.8), 3HR (3.9 ± 2.0), and Day1 (4.1 ± 1.9). During the recovery session (Day3/4), pain ratings returned to baseline levels (i.e. no pain). Compared with the 3HR recordings, transient cooling reduced (0.4±0.7, $p< 0.001$) and transient heating increased (6.6±2.2, $p< 0.001$) current NRS scores of the capsaicin evoked pain intensity (time: $F(2,54)= 124.4$, $p< 0.001$). During the 3HR session, pain intensity during cooling and heating was significantly different from 3HR (initial) and between the cool and heating protocols ($p<0.01$).

Heat Pain Sensitivity

HPTs at baseline contralaterally to the capsaicin administration area (42.6 ± 3.6 °C), 1HR (42.7 ± 3.2 °C), 3HR (42.7 ± 3.3 °C), Day1 (42.8 ± 3.7 °C) and Day3/4 (42.9 ± 3.8 °C) did not change systematically (session: $F(2.3, 61.4)= 0.137$, $p= 0.90$).

Cuff Pressure Pain Sensitivity

Despite a session effect for unconditioned PDT ($F(4, 108)= 2.6$, $p=0.04$), post-hoc analysis showed there was no significance with baseline values ($p> 0.05$; Table 1). During the 3HR session, unconditioned PDT differed (time: $F(2,54)= 13.6$, $p< 0.001$) and was higher during the patch heating than patch cooling ($p=0.001$). For conditioned PDT (session: $F(2.6, 69.1)= 4.9$, $p= 0.001$), the 3HR session ($p= 0.007$) and Day 1 ($p= 0.02$) were lower compared to baseline. Conditioned PDT (time: $F(2,54)= 7.5$, $p= 0.001$) was also higher during patch heating compared to the beginning of the 3HR session ($p= 0.001$).

For PTT, there was a significant session effect (session: $F(2.6, 71.3)= 5.9$, $p= 0.002$); however there was no significance from baseline with post-hoc analysis (Table 1). PTT differed during patch-cooling and patch-heating (time: $F(1.6, 44.3)= 28.0$, $p< 0.001$) with higher PTT during patch cooling and heating compared to the beginning of the 3HR session ($p< 0.001$) and higher PTT during heating than cooling ($p= 0.002$).

Temporal Summation of Pain

There was a session effect for TSP (session: $F(2.8, 75.0)= 3.4$, $p= 0.03$); however there was no significance from Day 0 with post-hoc analysis (Table 1). TSP was similar during patch-cooling and patch-heating (time: $F(2, 54)= 0.02$, $p= 0.98$).

Conditioned Pain Modulation

CPM magnitude differed across sessions (session: $F(2.4, 66.7)= 5.3$, $p= 0.004$; Figure 3); CPM was lower during the 3HR session than baseline (Day0; $p= 0.001$) indicating that descending inhibitory function was compromised. During the 3HR session, CPM also differed (time: $F(2,54)= 3.8$, $p= 0.03$) between the patch-cooling and patch-heating protocols ($p= 0.012$) but not with CPM at the start of the 3HR session.

Repeatability Across Days

PTT, unconditioned PDT, and conditioned PDT had strong reliability between Day0 and Day3/4 (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).

DISCUSSION

This is the first study to demonstrate impaired CPM after 3 hours of prolonged episodes of experimental pain. Interestingly, after one 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 hours 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.

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 et al., 2018).

Previous research has shown that transient application of capsaicin may act as either as a conditioning or test noxious stimulus producing CPM effects (Baad-Hansen et al., 2005; Kemppainen et al., 1997). For instance, ice water immersion decreased pain intensity associated with 5% capsaicin applied to the gingiva for nine minutes (Baad-Hansen et al., 2005). Similarly, an approximate twenty-five-minute application of 1% capsaicin decreased tooth-pulp-evoked pain sensations (Kemppainen et al., 1997). In the current study, prolonged application of high-concentration capsaicin did not act as a conditioning stimulus and produce 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 et al., 2011).

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 hours after fatiguing exercise) compared with the baseline session (Alappattu et al., 2011; McPhee and 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 non-painful areas (Bisset et al., 2018; Raphael et al., 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 and 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).

Conditioned Pain Modulation

CPM decreased 3 hours 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 hour 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 that 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 four months, CPM declined in a linear fashion in healthy adults (Marcuzzi et al., 2017). In contrast, in patients with painful posttraumatic trigeminal neuropathy, CPM was less in patients that suffered for a longer duration (i.e., greater than one 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 Day1. 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.

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 and Arendt-Nielsen 2010). In addition, Arendt-Nielsen et al. 2015, assessed patients with non, mild, moderate and severe osteoarthritic pain and found more pronounced CPM impairment in the severe pain patients (Arendt-Nielsen et al., 2015). Finally, Kosek et al. 2000 and Graven-Nielsen et al., 2012 found that CPM was normalized following pain recovery after total joint replacements (Graven-Nielsen et al., 2012; Kosek and 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 et al., 2015; Petersen et al., 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 et al., 2018; Meints et al., 2019), which complicates 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 causes 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.

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 Day3/4 (ICC= 0.35) may have been due to pain felt after removal of the capsaicin patch. Interestingly, acceptable intraclass correlation coefficients (baseline versus Day3/4) 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.

Conclusion

Topical capsaicin applied over a 24-hour period produced prolonged mild-to-moderate pain. There was a decline in CPM after 3 hours that returned to baseline levels when the pain vanished, whereas temporal summation of pain 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 influences 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.

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).

FIGURE LEGENDS

Figure 1. Experimental Design. Participants wore a transdermal capsaicin-patch on their right forearm and completed five experimental session; three sessions during Day 0 [capsaicin application, 1-hour (HR) and 3-hour post application], one session 24 hours 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.

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-hour, 3-hours, and Day 1. Patch cooling and patch-heating decreased and increased pain intensity, respectively. Baseline (Day0); 1-hour (1HR), 3-hours (3HR), and Day 1 (post-capsaicin application); Day 3/4 (post-capsaicin removal). During the 3 HR session, the capsaicin patch was cooled (cool) and heated (heat). *, significantly different from Day 0 ($p< 0.001$); #, significantly different from 3 HR initial ($p< 0.001$); @, significantly different between cooling and heat protocol ($p< 0.001$).

Figure 3. Conditioned Pain Modulation (CPM). Mean (+/- SEM) effect of CPM (conditioned pain detection threshold minus unconditioned pain detection threshold). CPM-effect decreased 3-hours post-capsaicin compared to Day0 (*, $p= 0.001$), and CPM during patch-heating was reduced compared with patch-cooling (#, $p= 0.012$). Baseline (Day 0); 1-hour

(1HR), 3-hours (3HR), and Day 1 (post-capsaicin application); Day 3/4 (post-capsaicin removal). During the 3 HR session, the capsaicin patch was cooled (cool) and heated (heat).

REFERENCES

Alappattu MJ, Bishop MD, Bialosky JE, George SZ, Robinson ME. Stability of behavioral estimates of activity-dependent modulation of pain. J Pain Res 2011;4: 151-157.

Albu S, Gomez-Soriano J, Avila-Martin G, Taylor J. Deficient conditioned pain modulation after spinal cord injury correlates with clinical spontaneous pain measures. Pain 2015;156: 260-272.

Alsouhibani A, Vaegter HB, Hoeger Bement M. Systemic Exercise-Induced Hypoalgesia Following Isometric Exercise Reduces Conditioned Pain Modulation. Pain Med 2018.

Andersen HH, Marker JB, Hoeck EA, Elberling J, Arendt-Nielsen L. Antipruritic effect of pretreatment with topical capsaicin 8% on histamine- and cowhage-evoked itch in healthy volunteers: a randomized, vehicle-controlled, proof-of-concept trial. Br J Dermatol 2017;177: 107-116.

Arendt-Nielsen L, Egsgaard LL, Petersen KK, Eskehave TN, Graven-Nielsen T, Hoeck HC, Simonsen O. A mechanism-based pain sensitivity index to characterize knee osteoarthritis patients with different disease stages and pain levels. Eur J Pain 2015;19: 1406-1417.

Arendt-Nielsen L and Graven-Nielsen T. Translational musculoskeletal pain research. Best Pract Res Clin Rheumatol 2011;25: 209-226.

Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, Wells C, Bouhassira D, Mohr Drewes A. Assessment and manifestation of central sensitisation across different chronic pain conditions. Eur J Pain 2018;22: 216-241.

Arendt-Nielsen L, Nie H, Laursen MB, Laursen BS, Madeleine P, Simonsen OH, Graven-Nielsen T. Sensitization in patients with painful knee osteoarthritis. Pain 2010;149: 573-581.

Arendt-Nielsen L, Sluka KA, Nie HL. Experimental muscle pain impairs descending inhibition. Pain 2008;140: 465-471.

Asaki T, Wang K, Luo Y, Arendt-Nielsen T, Graven-Nielsen T, Arendt-Nielsen L. Acid-induced experimental knee pain and hyperalgesia in healthy humans. Exp Brain Res 2018;236: 587-598.

Avin KG and Law LA. Age-related differences in muscle fatigue vary by contraction type: a meta-analysis. Phys Ther 2011;91: 1153-1165.

Baad-Hansen L, Poulsen HF, Jensen HM, Svensson P. Lack of sex differences in modulation of experimental intraoral pain by diffuse noxious inhibitory controls (DNIC). Pain 2005;116: 359-365.

Bannister K and Dickenson AH. The plasticity of descending controls in pain: translational probing. J Physiol 2017;595: 4159-4166.

Bisset L, Carty M, Smith A. Unilateral Lateral Epicondylalgia Shows a Pro-nociceptive Pain Profile: A Case-control Observational Study. Clin J Pain 2018;34: 954-959.

Dirks J, Petersen KL, Dahl JB. The heat/capsaicin sensitization model: a methodologic study. J Pain 2003;4: 122-128.

Eichhorn N, Treede RD, Schuh-Hofer S. The Role of Sex in Sleep Deprivation Related Changes of Nociception and Conditioned Pain Modulation. Neuroscience 2018;387: 191-200.

Goubert D, Danneels L, Cagnie B, Van Oosterwijck J, Kolba K, Noyez H, Meeus M. Effect of Pain Induction or Pain Reduction on Conditioned Pain Modulation in Adults: A Systematic Review. Pain Pract 2015;15: 765-777.

Graven-Nielsen T and Arendt-Nielsen L. Assessment of mechanisms in localized and widespread musculoskeletal pain. Nat Rev Rheumatol 2010;6: 599-606.

Graven-Nielsen T, Izumi M, Petersen KK, Arendt-Nielsen L. User-independent assessment of conditioning pain modulation by cuff pressure algometry. Eur J Pain 2017;21: 552-561.

Graven-Nielsen T, Vaegter HB, Finocchietti S, Handberg G, Arendt-Nielsen L. Assessment of musculoskeletal pain sensitivity and temporal summation by cuff pressure algometry: a reliability study. Pain 2015;156: 2193-2202.

Graven-Nielsen T, Wodehouse T, Langford RM, Arendt-Nielsen L, Kidd BL. Normalization of widespread hyperesthesia and facilitated spatial summation of deep-tissue pain in knee osteoarthritis patients after knee replacement. Arthritis Rheum 2012;64: 2907-2916.

Henrich F, Magerl W, Klein T, Greffrath W, Treede RD. Capsaicin-sensitive C- and A-fibre nociceptors control long-term potentiation-like pain amplification in humans. Brain 2015;138: 2505-2520.

Imai Y, Petersen KK, Morch CD, Arendt Nielsen L. Comparing test-retest reliability and magnitude of conditioned pain modulation using different combinations of test and conditioning stimuli. Somatosens Mot Res 2016;33: 169-177.

Izumi M, Petersen KK, Arendt-Nielsen L, Graven-Nielsen T. Pain referral and regional deep tissue hyperalgesia in experimental human hip pain models. Pain 2014;155: 792-800.

Kemppainen P, Waltimo A, Waltimo T, Kononen M, Pertovaara A. Differential effects of noxious conditioning stimulation of the cheek by capsaicin on human sensory and inhibitory masseter reflex responses evoked by tooth pulp stimulation. J Dent Res 1997;76: 1561-1568.

Kosek E and Ordeberg G. Lack of pressure pain modulation by heterotopic noxious conditioning stimulation in patients with painful osteoarthritis before, but not following, surgical pain relief. Pain 2000;88: 69-78.

Lewis GN, Rice DA, McNair PJ. Conditioned pain modulation in populations with chronic pain: a systematic review and meta-analysis. J Pain 2012;13: 936-944.

Lo Vecchio S, Andersen HH, Arendt-Nielsen L. The time course of brief and prolonged topical 8% capsaicin-induced desensitization in healthy volunteers evaluated by quantitative sensory testing and vasomotor imaging. Exp Brain Res 2018;236: 2231-2244.

Manafi-Khanian B, Arendt-Nielsen L, Frokjaer JB, Graven-Nielsen T. Deformation and pressure propagation in deep somatic tissue during painful cuff algometry. Eur J Pain 2015;19: 1456-1466.

Manafi-Khanian B, Arendt-Nielsen L, Graven-Nielsen T. An MRI-based leg model used to simulate biomechanical phenomena during cuff algometry: a finite element study. Med Biol Eng Comput 2016;54: 315-324.

Manafi Khanian B, Arendt-Nielsen L, Kjaer Petersen K, Samani A, Graven-Nielsen T. Interface Pressure Behavior During Painful Cuff Algometry. Pain Med 2016;17: 915-923.

Marcuzzi A, Wrigley PJ, Dean CM, Adams R, Hush JM. The long-term reliability of static and dynamic quantitative sensory testing in healthy individuals. Pain 2017;158: 1217-1223.

McPhee M and Graven-Nielsen T. Alterations in Temporal Summation of Pain and Conditioned Pain Modulation Across an Episode of Experimental Exercise-Induced Low Back Pain. J Pain 2018.

Meints SM, Mawla I, Napadow V, Kong J, Gerber J, Chan ST, Wasan AD, Kaptchuk TJ, McDonnell C, Carriere J, Rosen B, Gollub RL, Edwards RR. The relationship between catastrophizing and altered pain sensitivity in patients with chronic low-back pain. Pain 2019;160: 833-843.

Mlekusch S, Neziri AY, Limacher A, Juni P, Arendt-Nielsen L, Curatolo M. Conditioned Pain Modulation in Patients With Acute and Chronic Low Back Pain. Clin J Pain 2016;32: 116-121.

Nasri-Heir C, Khan J, Benoliel R, Feng C, Yarnitsky D, Kuo F, Hirschberg C, Hartwell G, Huang CY, Heir G, Korczeniewska O, Diehl SR, Eliav E. Altered pain modulation in patients with persistent postendodontic pain. Pain 2015;156: 2032-2041.

Nir RR, Granovsky Y, Yarnitsky D, Sprecher E, Granot M. A psychophysical study of endogenous analgesia: the role of the conditioning pain in the induction and magnitude of conditioned pain modulation. Eur J Pain 2011;15: 491-497.

Petersen KK, Arendt-Nielsen L, Simonsen O, Wilder-Smith O, Laursen MB. Presurgical assessment of temporal summation of pain predicts the development of chronic postoperative pain 12 months after total knee replacement. Pain 2015;156: 55-61.

Petersen KK, Simonsen O, Olesen AE, Morch CD, Arendt-Nielsen L. Pain inhibitory mechanisms and response to weak analgesics in patients with knee osteoarthritis. Eur J Pain 2019.

Petersen KL and Rowbotham MC. A new human experimental pain model: the heat/capsaicin sensitization model. Neuroreport 1999;10: 1511-1516.

Raphael KG, Janal MN, Anathan S, Cook DB, Staud R. Temporal summation of heat pain in temporomandibular disorder patients. J Orofac Pain 2009;23: 54-64.

Rathleff MS, Petersen KK, Arendt-Nielsen L, Thorborg K, Graven-Nielsen T. Impaired Conditioned Pain Modulation in Young Female Adults with Long-Standing Patellofemoral Pain: A Single Blinded Cross-Sectional Study. Pain Med 2016;17: 980-988.

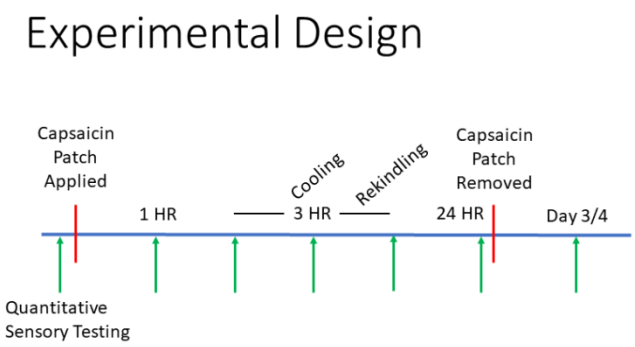
Skou ST, Graven-Nielsen T, Rasmussen S, Simonsen OH, Laursen MB, Arendt-Nielsen L. Widespread sensitization in patients with chronic pain after revision total knee arthroplasty. Pain 2013;154: 1588-1594.

Staud R. Abnormal endogenous pain modulation is a shared characteristic of many chronic pain conditions. Expert Rev Neurother 2012;12: 577-585.

TABLE 1

	Unconditioned PDT (kPa)	**PTT (kPa)**	**Conditioned PDT (kPa)**	**CPM (kPA)**	**TSP**
Day0	24.9 ± 14.7	60.5 ± 23.2	31.4 ± 18.3	6.5 ± 7.8	13.3 ± 13.9
1HR	26.6 ± 15.4	62.2 ± 23.2	29.2 ± 16.1	2.6 ± 9.1	17.3 ± 12.5
3HR	26.7 ± 14.2	61.5 ± 23.4	27.4 ± 15.1*	0.7 ± 7.4*	17.4 ± 12.6
3HR-Cool	28.6 ± 14.7	65.8 ± 22.9@	29.9 ± 14.6	1.3 ± 7.5	17.5 ± 13.5
3HR-Heat	35.2 ± 20.6#	68.0 ± 21.8#@	32.0 ± 17.1@	-3 ± 8.1#	17.7 ± 14.6
Day1	23.0 ± 12.0	57.5 ± 24.3	27.1 ± 15.3*	4.0 ± 6.1	14.4 ± 14.8
Day3/4	25.7 ± 13.7	56.3 ± 23.8	32.8 ± 21.1	7.1 ± 9.2	10.6 ± 12.1

Table 1. Mean (± 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 (Day0), 1-hour (1HR), 3-hours (3HR), Day1 (post-capsaicin application), and Day 3/4 (post-capsaicin removal). During the 3HR session, the capsaicin patch was cooled (3HR-Cool) and heated (3HR-Heat). *, significantly different compared with Day0; #, significantly different between patch cooling and heating; @, significantly different from initial 3HR



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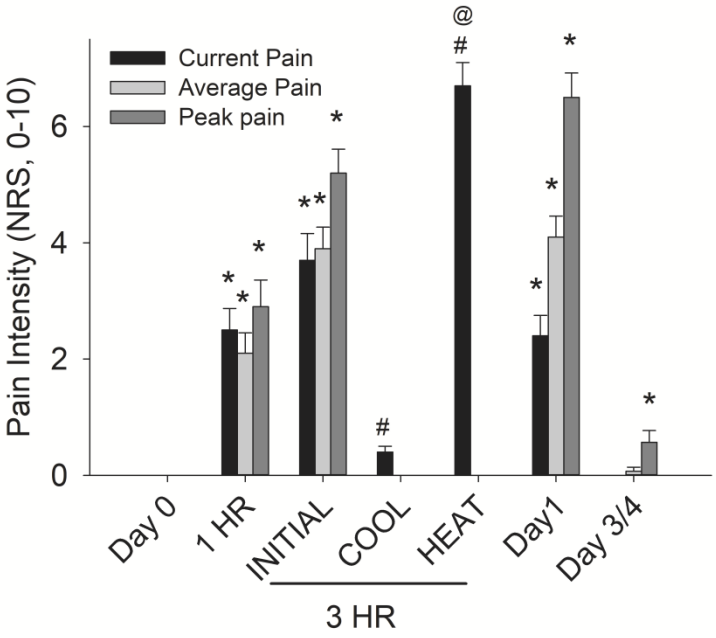

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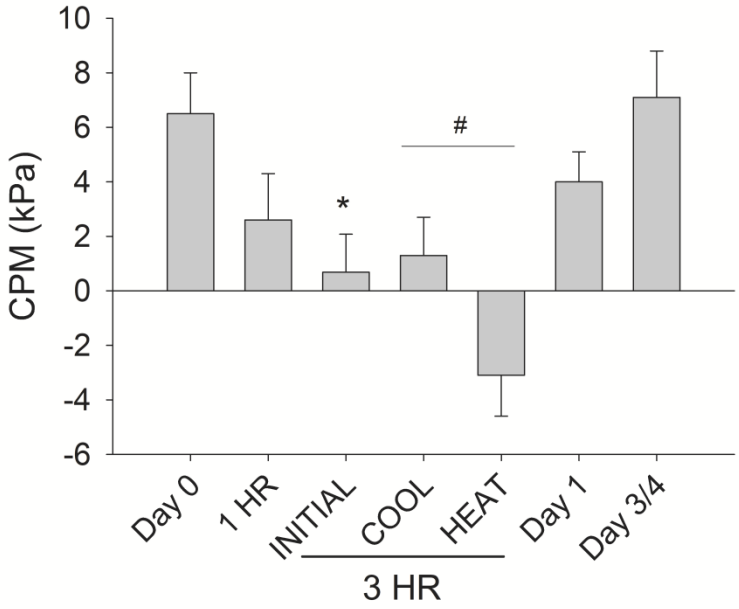

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