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Effects of stimulation area and temperature rates on offset analgesia

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Abstract

Introduction: Offset analgesia describes the effect of a slightly reduced nociceptive stimulus, resulting in a disproportionate large reduction in the pain perception. This effect may be associated with descending pain inhibition, but parameters influencing this phenomenon are poorly understood.

Objectives: In this study, 2 separate experiments were conducted to investigate both, the spatial aspects of offset analgesia and the influence of different rates of temperature rise.

Methods: In both experiments, 29 healthy participants received individualized and heat-based offset analgesia paradigms applied to the forearm, with continuous assessment of pain intensity. In experiment 1, offset analgesia paradigms with 3 different rates of temperature rise were applied, whereas in experiment 2, offset analgesia paradigms with 2 different heat application areas were used.

Results: The results of experiment 1 showed that different temperature rates had no effect on the offset analgesia response ($P > 0.05$). Experiment 2, however, showed the influence of the size of a stimulated area on offset analgesia ($P = 0.009$), which can be explained mainly by the influence of spatial summation of pain and habituation processes.

Conclusions: The study showed a lack of influence of different temperature rates on offset analgesia; however, spatial aspects of offset analgesia could be identified. These are most likely based on spatial summation of pain and altered adaptation to pain.

Keywords: Offset analgesia, Pain modulation, Peripheral, Central, Temporal contrast enhancement

1. Introduction

Offset analgesia (OA) is understood as an antinociceptive aspect of endogenous pain modulation, involving the modulation of pain via temporal contrast enhancement.[37] Grill and Coghill described OA as a disproportionately large reduction in pain after a small offset of a noxious stimulus.[11]

Functional imaging studies showed spinal cord[26] and brain activations in several cortical and subcortical regions[8,21,36,41]—or its functional connectivity[17]—induced by OA. However, centrally acting pharmaceuticals showed no influence on the OA response.[16] A much more understudied component of OA may be attributed to peripheral influences because it was shown that the OA response at the palm (glabrous) was nonexistent in contrast to nonglabrous skin sites in young[2,23] and in older populations.[2,23] It is assumed that nonglabrous skin is rich in C and high as well as low threshold A-δ-mechano-heat nociceptors (AMH-I and AMH-II), whereas glabrous skin lacks AMH-II nociceptors.[3,25,30,31] The fact that OA seems to be suppressed if studied in glabrous skin indicates that peripheral components (AMH-II fibers) are crucial for shaping the magnitude of the OA effect. However, the exact physiological

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mechanisms of OA are not fully understood, even though publications on OA have increased enormously in the last decade.

Another aspect that contributes to this uncertainty of mechanisms might be the fact that various OA protocols have been used[28] and the parameters influencing the OA effect are still not adequately identified. It has been shown that parameters such as the length of the stimulation intervals[2,14] or the amount of the temperature increment[7] seem to have a direct influence. However, the influences of other parameters remain unknown, as seen, eg, regarding stimulation areas and temperature rates, which are often applied differently.[28] Thus, in 2 consecutive experiments, firstly, the influence of different temperature rates on OA were investigated and, secondly, it was tested whether the size of the stimulation area influenced the OA response. It was expected that (1) higher temperature rates and (2) a larger stimulation field would lead to an increased OA response.

2. Methods

2.1. Design, participants, and equipment

This study was performed using 2 distinct experiments. All participants underwent both experiments successively in a randomized order. Between each experiment, participants had a 15-minute break. An overview of both experiments can be found in **Figure 1**. Both experiments were preregistered and can be viewed on the Open Science Framework (OSF): https://osf.io/nmpqj and https://osf.io/38xyb. The protocol was approved by the Ethics Committee of the University of Lübeck (20-493). Twenty-nine healthy and pain-free adults participated in this study. Inclusion criteria were aged between 18 and 65 years. Participants were excluded if they had any acute or chronic pain or other neurological, cardiovascular, psychiatric, or systemic diseases.

All thermal stimuli in both experiments were delivered using a Pathway CHEPS (Medoc, Ramat Yishai, Israel). The CHEPS was attached to the nondominant forearm and shifted to a distinct skin area after each stimulation. During the heat stimuli, the participants were asked to continuously rate their pain via a computerized visual analogue scale (CoVAS; Medoc). All participants were instructed to observe and rate every small difference in pain intensity but were not aware of the study aim.

2.2. Experiment 1

A calibration procedure was performed to individualize the heat stimuli for each participant at the nondominant ventral side of the forearm at a level of 50 of 100 ($pain_{50}$).[27] Individualization of the temperature was chosen to match the intensity of pain both within and between experiments. The following 2 trials were applied 3 times to the nondominant forearm—constant trials (CTs): 30 seconds with an individual temperature eliciting pain of $pain_{50}$ and offset trials (OTs): 10 seconds $pain_{50}$ (T1) followed by 5 seconds $pain_{50}$ +1°C (T2) and again 15 seconds $pain_{50}$ (T3). Offset trials were performed 3 times each with 3 different temperature rates during the T2 interval. Temperatures were increased and decreased by 1°C within T2 by 0.9°C/s (slow), 6.5°C/s (moderate), or 40°C/s (fast). Once the respective target temperature was reached, the T2 time interval started, resulting in a total stimulation time of T2, which was identical for all OTs. These temperature rates were chosen because it was shown in animal models that stimuli with a temperature rise rate of 6.5°C/s activated Aδ fibres, while C fibres were associated with slower rise rates (0.9°C/s).[20,38–40] To create a contrast between these 2 rates, a much faster rate (40°C/s) was also used in the OA paradigm in this study. The remaining temperature rates (ie, in T1 and T3) were performed at 6.5°C/s. Between each trial (OT and CT) was a pause interval of approx. 2 minutes. Participants provided continuous ratings of pain intensity with the CoVAS during every stimulus (CT and OT). The order between stimuli was randomized.

2.3. Experiment 2

In experiment 2, thermode covers were used to provide 2 different stimulation areas[24]: full stimulation area (full = 6.6 cm^2) and semicircular stimulation area (half = 3.3 cm^2)[29] (for more information see supplementary material S1, available at http://links.lww.com/PR9/A176). Here, the calibration process was repeated twice, once for half and once for the full stimulation area (random order). Within experiment 2, 3 OTs and 3 CTs were applied to the full (6.6 cm^2) and again to the half stimulation area (3.3 cm^2) in a random order. All individualized stimuli were applied to the nondominant forearm with the identical temperature rates (6.5°C/sec).

2.4. Statistical analysis

Analyses were performed with the IBM Statistical Package for Social Science (SPSS Version 26, Armonk, NY). The following average pain values of the different time intervals were extracted: 5 to 9 seconds (T1), 10 to 14 seconds (T2), and 21 to 30 seconds (T3). These intervals were chosen to obtain the most accurate pain ratings possible and to account for time delays in heat pain ratings. The first 5 seconds of T1 and T3 were not considered because of still increasing (T1) or still decreasing (T3) pain

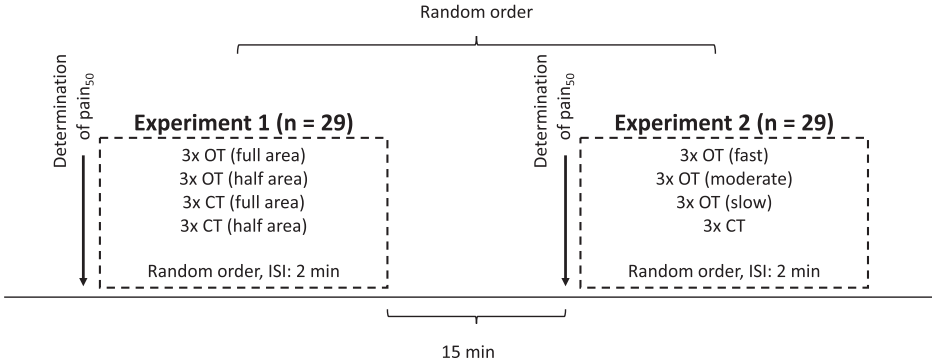

Figure 1. Overview of experiments 1 and 2. Constant trials (CTs), offset trials (OTs), full (6.6 cm^2) and half stimulation area (3.3 cm^2); temperature rates: 40°C/s (fast), 6.5°C/s (moderate), and 0.9°C/s (slow); ISI, interstimulus interval.

responses. A 10-second time window was chosen to determine a relative stable OA effect. The OA effect was defined as the difference between OT and CT in T3 and was analyzed using dependent *t* tests in both experiments. In experiment 1, the within-factor "temperature rates" (fast, moderate, or slow) was analyzed for the OA effect using a repeated-measures analysis of variance. If statistically significant differences were detected, Bonferroni corrected post hoc *t* tests were calculated. In experiment 2, paired samples *t* tests was used to test significant differences between the OA effect of the half and full stimulation area. The significance level was set at 0.05 for all comparisons.

3. Results

Twenty-nine participants (mean age 26.7 [SD 9.3] years, 69.0% female) were assessed in both experiments. In experiment 2, the pain response of one subject had to be excluded from the analysis because of a software error during data collection. Sensitization and habituation for the pain response could not be shown within and between the experiments (supplementary materials S2, available at http://links.lww.com/PR9/A176). Each pain response of T1, T2, and T3 of both experiments are located in the supplementary materials S3 (available at http://links.lww.com/PR9/A176).

3.1. Experiment 1

The mean calibrated temperature for $pain_{50}$ in experiment 1 was calculated as 45.9°C (SD 1.0). For fast ($t_{28} = 4.19$, $P < 0.001$, d = 0.78), moderate ($t_{28} = 3.71$, $P = 0.001$, d = 0.69), and slow temperature rates ($t_{28} = 2.86$, $P = 0.008$, d = 0.53), a significant difference between the T3 intervals in CTs and the corresponding OTs was shown, indicating an OA effect at each temperature rise rate. A significant difference regarding the OA effect (difference of CT and OT in T3) was not found between the temperature rates ($F_{[2,56]} = 1.24$, $P = 0.298$, $\eta_p^2 = 0.042$). The pain responses from experiment 1 are visualised in **Figure 2**.

3.2. Experiment 2

In experiment 2, the mean calibrated temperature ($pain_{50}$) was 45.5°C (SD 0.6) for the full stimulation area and 46.9°C (SD 0.9) for the half stimulation area. A significant difference ($P < 0.001$) indicated a spatial summation of pain effect (SSP).[24] For half ($t_{27} = 6.63$, $P < 0.001$, d = 1.25) and full stimulation areas ($t_{27} = 3.36$, $P = 0.002$, d = 0.64), a significant difference between the T3 intervals in CT and the corresponding OTs was shown (**Fig. 3**). An additional paired-samples *t* test showed a significant difference between the OA effect obtained from the half compared with the full stimulation area ($t_{27} = 2.79$, $P = 0.009$, d = 0.53).

4. Discussion

The aim of these 2 experiments was to investigate whether different parameters can determine the OA response. The results of experiment 1 showed that including different temperature rates had no effect on the OA response. All temperature rates elicited a significant and comparable OA response. Experiment 2, showed a spatial influence on OA. Interestingly, a larger stimulus area, did show a smaller OA response. In addition to new insights for future designing OA paradigms, both results can be explained by the assumption of central and peripheral mechanisms.

Based on previous animal models, it has been shown that specific nociceptive nerve fibers are activated by specified rates of temperature increase. At temperature rise rates of 0.9°C/s, mainly C fibers and above rise rates of 6.5°C/s, mainly A fibers are recruited.[38,38,40] As a contrast to these 2 rates, a considerably faster rate was added in this current experiment, as applied in previous studies to achieve a fiber-specific stimulus.[5,9,24] Furthermore, Yarnitsky et al.[34,35] provided translational evidence for fiber-specific activation in humans as a consequence of temperature rates. However, it also has been debated whether this experimental manipulation of the 2-fiber systems can be selectively activated because because these assumptions are mainly based on animal in vitro studies (1).[38,39] Furthermore, it was not supported by fiber-specific pain qualities (2)[5] and rapidly increasing laser stimulation does not exclusively activate A fibers (3).[22] With different rates of heat stimulation, it was shown that the periaqueductal grey (PAG) shows marked differences in the descending control of spinal nociception mediated by C and Aδ fibers[19,32] with the activation of functionally distinct neuron populations (4).[13] The latter, in particular, seems interesting because it has also been shown that OA underlies an endogenous inhibitory mechanism originating in the PAG,[8,36] a key structure for descending pain inhibition.[18]

It is conceivable that a smaller stimulation field leads to an increased OA response because of the higher stimulation temperature via the less efficient SSP effects[1] and varied pain adaptation processes.[33] Spatial summation of pain refers to the ability of the nervous system to integrate nociceptive information from large areas or distinct areas of the body.[24] Consequently, the smaller area had to be stimulated with a significantly higher temperature to achieve a comparable perceived pain intensity. The neural mechanism of SSP is not yet thoroughly understood. Recent research suggests a dominant mechanism specific to peripheral nerve fibers being mediated by the cingulate cortex, as seen in electroencephalography responses.[9] Interestingly, for

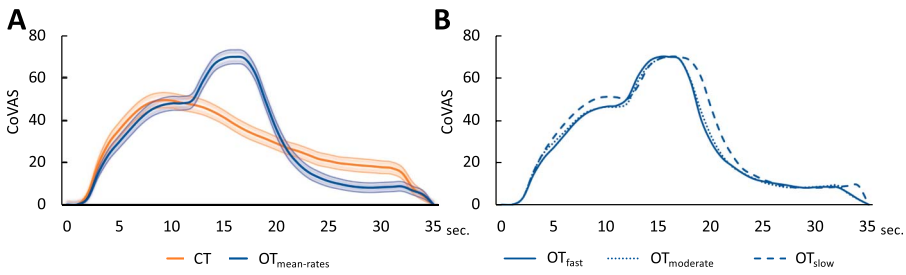

Figure 2. Pain ratings of the different temperature rise rates (experiment 1, n = 29). On the left (A), pain responses (mean, SEM) using the computerized visual analog scale (CoVAS) for the mean of the constant trials (CTs) and for the mean value of the offset trials of all temperature rates ($OT_{mean\text{-}rates}$) are presented. On the right (B), pain responses (means) are shown separately for the offset trials with the temperature rates 40°C/s (OT_{fast}), 6.5°C/s ($OT_{moderate}$), and 0.9°C/s (OT_{slow}).

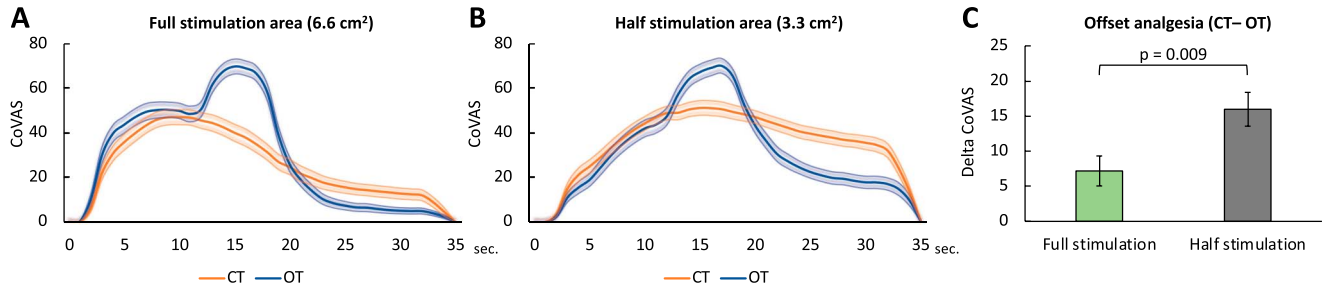

Figure 3. Pain ratings for the different stimulation areas (experiment 2, n = 28). On the left side (A), the pain responses using the computerized visual analog scale (CoVAS) for constant trials (CTs) and offset trials (OTs) of the full stimulation area (6.6 cm^2) and in the centre (B) for the half stimulation area (3.3 cm^2) were shown. On the right (C), offset analgesia was defined as the difference in average pain scores (Delta CoVAS) within a 10-second time interval after the stimulus offset (third time interval, T3) between CT and OT. A significant difference between full and half stimulation could be found ($P = 0.009$). Data were presented as mean and SEM.

both SSP and OA, a significant influence of specific peripheral fibers was described because of comparisons of glabrous and nonglabrous skin sites.[2,6,9,23,24] Thus, if peripheral mechanisms are involved in both OA and SSP, additive processes of these 2 paradigms, as in this study, might also be considered. Paradoxically, however, the increase in stimulation temperature in the small area compared with the larger area may result in increased activation in the neuron population.[4] It is conceivable that adjacent receptive fields are activated as a result of the higher intensity, which may even exceed the number of receptive fields activated in the larger stimulation area.

Constant noxious stimuli of fixed intensity may reduce the sensation of pain over time. This phenomenon is described as adaptation.[10,12] Within the 30-second heat stimulation of the constant trials, the participants adapted considerably more with the full stimulation area compared with the half stimulation area. Although the exact contributions of the peripheral and central components to pain adaptation are still unclear, it has been shown on the basis of electrophysiological studies that pain adaptation is primarily modulated peripherally.[15,31] An influencing factor on OA seems to be the pain adaptation behavior within the constant trials, as again, the OA effect was determined from the difference between offset and constant trial. Although numerous analytical approaches have been described to determine the magnitude of OA, subtracting CT from OT is, however, a well-established method to avoid overestimation of the OA effect.[28] In this manner, adaptation/sensitization could be subtracted from offset effects. However, the size of the stimulation area, the resulting higher stimulation temperature, and the associated adaptation seems to be an influencing parameter for the OA and should be considered in the design of future studies.

A limiting parameter that should be addressed is the overshoot that often occurs in the Medoc's Pathways system when fast rates are applied. This overshoot at a rate of 40°C/s is on average about ~0.3°C. However, it lasts for less than ~0.1 second in average.

5. Conclusion

It can be concluded that temperature rates are not mediating OA effect, but area of stimulations does. Both peripheral and central mechanisms may be involved in this. The spatial aspects of OA may be attributed to SSP and an altered adaptation of pain and should be considered when planning future OA studies.

Disclosures

The authors have no conflicts of interest to declare.

Appendix A. Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PR9/A176.

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