Temporal properties of painful contrast enhancement using repetitive stimulation

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Summary:

The temporal contrast enhancement of pain and electrodermal activity can be provoked by stimuli that are clearly separated in time.

Abstract

Offset analgesia is characterized by a disproportionately large reduction in pain following a small decrease in a heat stimulus and is based on the phenomenon of temporal pain contrast enhancement (TPCE). The aim of this study is to investigate whether this phenomenon can also be induced by repetitive stimulation, i.e., by stimuli that are clearly separated in time. With this aim, the repetitive TPCE paradigm was induced in healthy, pain-free subjects (n=33) at the volar non-dominant forearm using heat stimuli. This paradigm was performed applying three different interstimulus intervals (ISIs): 5, 15, and 25 seconds. All paradigms were contrasted with a control paradigm without temperature change. Participants continuously rated the perceived pain intensity. In addition, electrodermal activity was recorded as a surrogate measure of autonomic arousal. Temporal pain contrast enhancement was confirmed for both ISI 5 seconds ($p < 0.001$) and ISI 15 seconds ($p = 0.005$), but not for ISI 25 seconds ($p = 0.07$), however the magnitude of TPCE did not differ between ISIs ($p = 0.11$). Electrodermal activity was consistent previous pain ratings, but showing significantly higher autonomic activity being measured. Thus, the phenomenon of temporal contrast enhancement of pain can also be induced by repetitive stimulation. Both the involvement of the autonomic nervous system and the involvement of habituation processes are conceivable, which consequently points to both central and peripheral mechanisms of TPCE.

1. Introduction

Acute and chronic pain perception depend on an interaction between peripheral noxious afferents and the processing in the central nervous system [6]. Pain perception can be influenced by faciliatory (pro-nociceptive) and inhibitory (anti-nociceptive) aspects of endogenous descending pain modulation [60] and may therefore be a main contributing factor in the development and maintenance of persistent pain [2,36,59]. One frequently used paradigm reflecting those aspects of anti-nociceptive pain modulation is offset analgesia (OA). Offset analgesia is defined as a disproportionately large reduction in pain perception after a small decrease in the noxious stimulation [15]. It has been described to play a crucial role in the pathological processing of pain symptoms, as it has been shown to be reduced in various chronic pain conditions (see for review [52]). Offset analgesia is based on a robust inhibitory filtering mechanism of nociceptive information using temporal pain contrast enhancement (TPCE) [4,49,62]. However, the underlying mechanisms of OA - or the TPCE phenomenon on which it is based - are not fully understood, but some research is showing that OA seems to be dominated by a complex interplay of interdependent systems at different locations along the neuroaxis, including peripheral [3,29], spinal [49] and supra-spinal mechanisms [10,28,61].

Typically, OA is tested with a tonic heat stimulus traditionally lasting for 30 to 40 seconds. The pain response of OA is often contrasted with a constant heat trial without intensity modification to control for pain adaptation, i.e., a reduction in the pain response due to a relatively long-lasting stimulus [52]. In contrast to adaptation, habituation to pain describes a reduction in pain after repeated stimulations including an interstimulus interval (ISI) [9]. In OA, the temporal contrast enhancement phenomenon has been shown with repetitive electrical stimuli [37], however a frequency of 100Hz was used which is perceived as a tonic stimulation. It remains unclear whether a continuous tonic stimulus is necessary to achieve temporal contrast enhancement of pain or the effect can also be produced via a series of clearly separated stimuli as it has been shown in other sensory modalities, e.g. in taste [47], auditory [30] and visual systems [13].

The aim of this study was to investigate whether TPCE can be observed by repetitive stimulation. It is assumed that during a repetitive TPCE stimulation, a disproportionate reduction in pain and electrodermal activity (EDA) occurs after a small reduction in heat stimuli when stimuli are clearly separated over time. In this context, it is also assumed that a shorter time interval between stimuli will show a more pronounced TPCE effect, although this effect will also be observed with longer intervals.

2. Methods

Study design and procedure

This cohort study was conducted in a randomized within-subject repeated-measurement design. Following verification of eligibility criteria, oral and written information on study procedures, and informed consent, a sample of healthy pain-free participants were exposed to a heat-based repetitive TPCE paradigm using three different interstimulus intervals (ISI) in a randomized and counterbalanced sequence. Participants were seated on a chair at a table in front of a white wall during the entire procedure. All interventions and measurements were performed in an air-conditioned (temperature controlled) and quiet room. The principles of the Declaration of Helsinki were respected at all times of this study [58] and all participants could discontinue the study at any time without stating reasons. The methodology of this study was preregistered in the Open Science Framework Database (https://osf.io/4ghq3) and approved by the Ethics Committee of the University of Luebeck (21-177, 18th May, 2021).

Participants

Healthy, pain-free participants between the ages of 18 and 45 years were eligible to participate if they subjectively stated that they were healthy and pain-free on the day of examination. Participants were excluded if they had a history of chronic pain (>3 months) within the last two years, had experienced any kind of pain event (lasting longer than 30 min) within the last week and were diagnosed with neurological, cardiovascular, psychiatric or systemic diseases. Furthermore, participants were told to refrain from caffeine and cigarettes for 4 hours and from alcohol, exercise and painkillers for 24 hours before the assessment. All of them had no previous knowledge about the study aim.

Thermal stimulation

All thermal stimuli were delivered using a Pathway CHEPS (Contact Heat -Evoked Potential Stimulator) via a 27 mm diameter contact surface (Medoc, Ramat Yishai, Israel). The CHEPS was attached to the non-dominant volar forearm (5 cm distal to the elbow). A sphygmomanometer was applied and inflated to 25 mmHg in order to standardize the contact between the skin and the thermal probe without causing pain, paresthesia or any sensory disturbances [53]. The volunteers were asked to continuously rate their pain intensity during every heat stimulus with the dominant hand on a computerized visual analogue scale (CoVAS; Medoc, Ramat Yishai, Israel) anchoring at "no pain" (=0) and "worst pain imaginable" (=100).

Participants were previously familiarized with the use of the CoVAS. They were also instructed to rate pain consistently while receiving five training stimuli (familiarization: 45°C - 49°C, each 5 seconds).

For the repetitive TPCE, a protocol including two separate series of heat trials was applied: i. repetitive offset series (OS), and ii. repetitive constant series (CS). Repetitive OS included twelve consecutive heat trials, each lasting 5 seconds (s) with an ISI of 5s. The first three trials in that series were performed with an intensity of 47°C, followed by three trials with an intensity of 49°C and the final six trials with an intensity of 47°C. Repetitive CS included twelve identical heat stimuli of 47°C. The repetitive TPCE paradigm described above was administered with additional ISI of 15s and 25s. All heat stimuli were applied at identical temperature rates (rise: 70°C/s; fall: 40 °C/s). After each series, the thermal probe was moved to a new skin site to avoid interactions. A pause time of 2 minutes was applied between each series (OS, CS) and 10 minutes between each TPCE paradigm (ISI: 5s, 15s and 25s). The order of paradigms as well as the order of series within the paradigms was randomized and counterbalanced. An overview is provided in **Fig. 1**. All participants were instructed to detect small differences in pain and rate them on the CoVAS as accurately as possible.
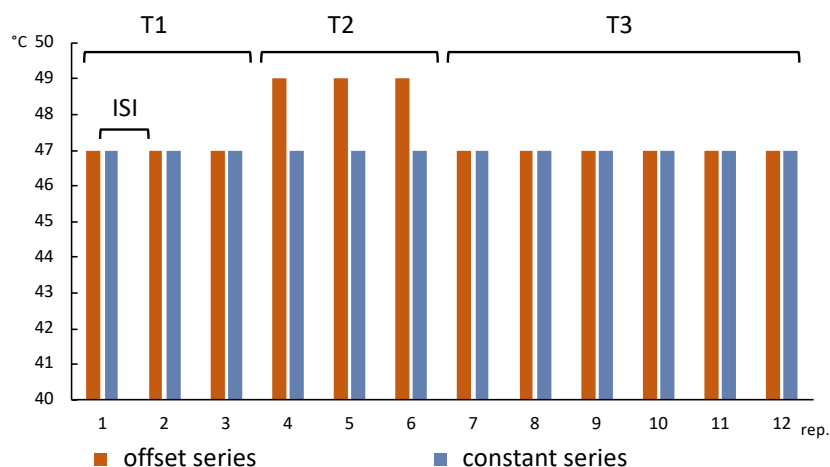

Fig. 1. ***A schematic overview of the repetitive temporal pain contrast enhancement (TPCE).*** *Two different heat stimulus series were applied: offset series (OS) and constant series (CS). Each of these series were applied with an interstimulus interval (ISI) of 5, 15 and 25 seconds in random order. The initial three heat stimuli repetitions (rep.) corresponded to the first interval (T1), the 4th to 6th heat stimuli formed the second interval (T2) and the remaining the third interval (T3). Each stimulus lasted 5 seconds. Temperatures of 47°C (T1 and T3 for OS and CS, as well as T2 for CS) and 49°C (T2 for OS) were contrasted.*

Electro dermal activity

During each repetitive paradigm, the respiBAN Professional (Plux, Lisbon, Portugal; a chest-worn device that registers various physiological modalities at a sampling rate of 1000 Hz) was used to collect physiological data. Electrodermal activity (EDA) signal was measured using two Ag/AgCl hydrogel electrodes (Covidien / Kendall, Dublin, Ireland) at the medial phalanx of index and middle finger of the non-dominant arm [14,40]. Electrodermal activity is dependent on sweat secretion, which is closely related to the activity in the autonomic nervous system [40]. Participants were asked to wash their hands with ordinary soap immediately before attaching the electrodes. During data collection, participants were asked not to speak and to breathe comfortably. EDA recordings was synchronized with thermal stimuli application using "opensignals" software (PLUX Wireless Biosignals, S.A., Portugal).

Characteristics and Questionnaires

The height, weight, limb dominance and the general fear of pain measured on a 0 (=none at all) to 100 (=highest possible fear) Numerical Rating Scale (NRS) were collected before starting the heat assessment. Furthermore, the following questionnaires were administered: the Pain catastrophizing scale (PCS) includes questions about catastrophizing and ruminations to pain [22], the Patient Health Questionnaire (PHQ-9) contains questions on depression [44], the Pain and Vigilance Awareness Questionnaire (PVAQ) addresses awareness, consciousness, vigilance and pain monitoring [19], the Pain Sensitivity Questionnaire (PSQ) contains self-reported pain sensitivity based on imagined painful daily life situations [46], the Working Memory Questionnaire (WMQ) addresses three dimensions of working memory: short-term storage, attention and executive control [56].

Data extraction and analysis

Based on the effect size for the OA response of $d = 0.76$ [15], an estimated group size of n=25 participants was required for this study (α=5%, β=95%). This was increased to n=33, in order to avoid a loss of statistical power if the previously determined effect was underestimated [1], especially given the fact that repetitive OA paradigm was not assessed previously.

Pre-processing of the CoVAS and EDA data was performed using Python Libraries. Pain rating for each millisecond was averaged to obtain one pain rating per second. All other statistical analyses were performed with the IBM Statistical Package for Social Science (SPSS

Version 25, Armonk, NY). Pain ratings (CoVAS, 0-100) as well as EDA values (microsiemens, µS) were expressed as the Area Under the Curve (AUC). The time interval was chosen from the start of the corresponding heat stimulus (temperature increment from the baseline temperature) to the start of the next heat stimulus (twelve AUC values in total). This allows for a comparability between pain and EDA data, as especially the latter show a response latency. Present repetitive temporal pain contrast enhancement (ΔrTPCE) was defined as the difference between CS and OS of AUC (pain and EDA) at the 7th heat stimulus (after stimulus reduction). According to the pre-registered analysis plan, this difference was analyzed using dependent two-tailed student's t-tests (including Cohen's d effect sizes) separately for the three different ISIs (pain: CS vs. OS, EDA: OS vs. CS). The mean AUC from the 8th to the 12th stimulus was also analyzed. Also, an existing habituation effect in pain, both within the T1 interval (1st vs. 3rd heat stimulus), and the T2 interval (4th vs. 6th) was examined by comparing corresponding mean values using two-tailed student's t-tests. A repeated measure analysis of variance (rANOVA) of the ΔrTPCE response was performed including all three ISIs (5s, 15s and 25s) as within-subject factor "ISI". Effect sizes were expressed as partial η^2_p. If statistically significant differences were detected, Bonferroni corrected post-hoc t-tests were performed. Pearson's correlation (r_p) analysis was used to evaluate the possible correlations among parametric data, whereas Spearman's correlation analysis (r_s) was used for not normally distributed data. Data were presented as mean and standard deviation (SD) in text and tables and as mean and standard error of the mean (SEM) in figures. The level of significance was set at p = 0.05.

3. Results

3.1. Characteristics of participants

33 healthy pain-free participants (n = 28, 85% women, n = 31, 94% right-handed) were investigated. The mean age of the subjects was 25.2 (SD 4.0) years. Further characteristics are shown in **Table 1**. No data were missing. No subject terminated the study before completion. No side effects of noxious stimulations were observed.

Table 1. **Descriptive statistics.**

Variable	Mean (SD)
Height (cm)	168.1 (28.2)
Weight (kg)	68.3 (12.7)
Fear of pain (VAS)	34.1 (17.3.)

Variable		Median (IQR)
PVAQ		32.0 (28.5 - 38.0)
PHQ-9		4.0 (3.0 - 6.5)
PCS		10.0 (7.5 - 13.0)
PSQ		51.0 (36.0 - 65.5)
WMQ	total	22.0 (14.5 - 28.0)
	storage domain	7.0 (4.0 - 10.0)

IQR - interquartile range, PCS - Pain Catastrophizing Scale, PSQ - Pain Sensitivity Questionnaire, PVAQ - Pain Vigilance and Awareness Questionnaire, SD - standard deviation, VAS - Visual Analogue Scale, WMQ - Working Memory Questionnaire.

3.2. Pain ratings

An illustration of the mean pain ratings per trial is shown in **Figure 2**. For all ISIs, no significant difference was found between OS and CS at the 1st heat stimulus ($p > 0.05$) indicating that the baseline sensitivity was comparable between different series. In contrast to ISI of 25s ($t_{(32)} = -1.852$, $p = 0.073$, $d = 0.32$), a significant difference between OS and CS at the 7th heat stimulus was found in the ISI of 5s ($t_{(32)} = -5.11$, **$p < 0.001$**, $d = 0.89$) and 15s ($t_{(32)} = -3.01$, **$p = 0.005$**, $d = 0.52$). These results indicate that ΔrTPCE at ISI of 25s is abolished, however application of the shorter ISI preserves the ΔrTPCE effect. **Figure 3** provides an overview of the pain ratings for the OS and CS of the 7th heat trial, as well as the corresponding values for the AUC for ΔrTPCE.
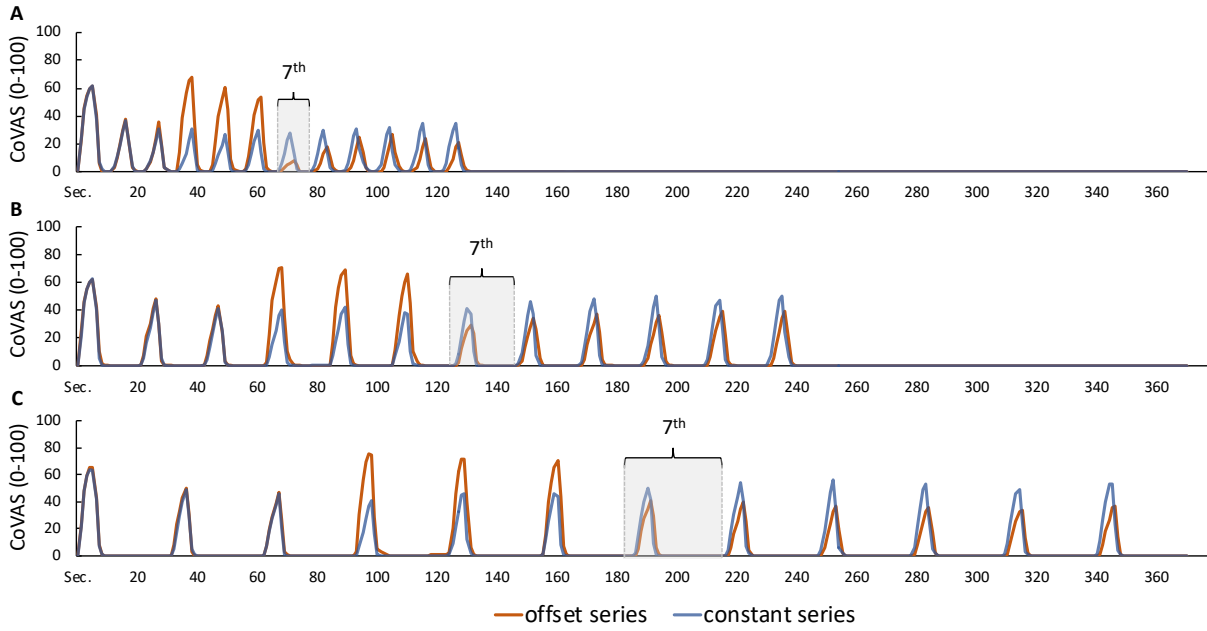
Figure 2. Pain ratings for all heat trials. *Both the constant series (12 identical heat stimuli at a temperature of 47°C, 5 seconds each) and the offset series (3 heat stimuli at a temperature of 47°C, followed by 3 heat stimuli at 49°C and again 6 stimuli at 47°C) are presented using ratings recorded by the computerized Visual Analog Scale (CoVAS). Interstimulus intervals (ISI) of 5 (A), 15 (B) and 25 seconds (C) are compared. The pain response to the 7th heat trial is indicated.*

Contrasting the average of the remaining heat trials in the T3 interval ($\bar{X}$ 8th to 12th) between CS and OS revealed significant differences for all ISIs (ISI of 5s: $t_{(32)}$ = -4.13, **p < 0.001**, d = 0.72; ISI of 15s: $t_{(32)}$ = - 3.59, **p = 0.001**, d = 0.63; ISI 25s: $t_{(32)}$ = - 5.30, **p < 0.001**, d = 0.92). Interestingly, when the magnitude of the ΔrTPCE was compared regarding the different ISIs, no significant differences were observed. Namely, neither ΔrTPCE at the 7th trial ($F_{(2,64)}$ = 2.31, p = 0.11, 2p = 0.07) nor based on the average of the remaining trials of T3 (Δ $\bar{X}$ 8th to 12th) was found to be significantly different across ISIs ($F_{(2,64)}$ = 2.40, p = 0.10, η_p^2 = 0.07). Additionally, 36.4% (n = 12) of participants reported having full analgesia (no pain at all) at the 7th heat trial in the ISI of 5s sequence, only 3% (n = 1) at ISI 15s and none at ISI 25s. Pain was reported during all other 7th heat trials in all ISI sequences. The values for the AUC of the 7th trial as well as the average 8th to 12th trial can be found in Table 2.
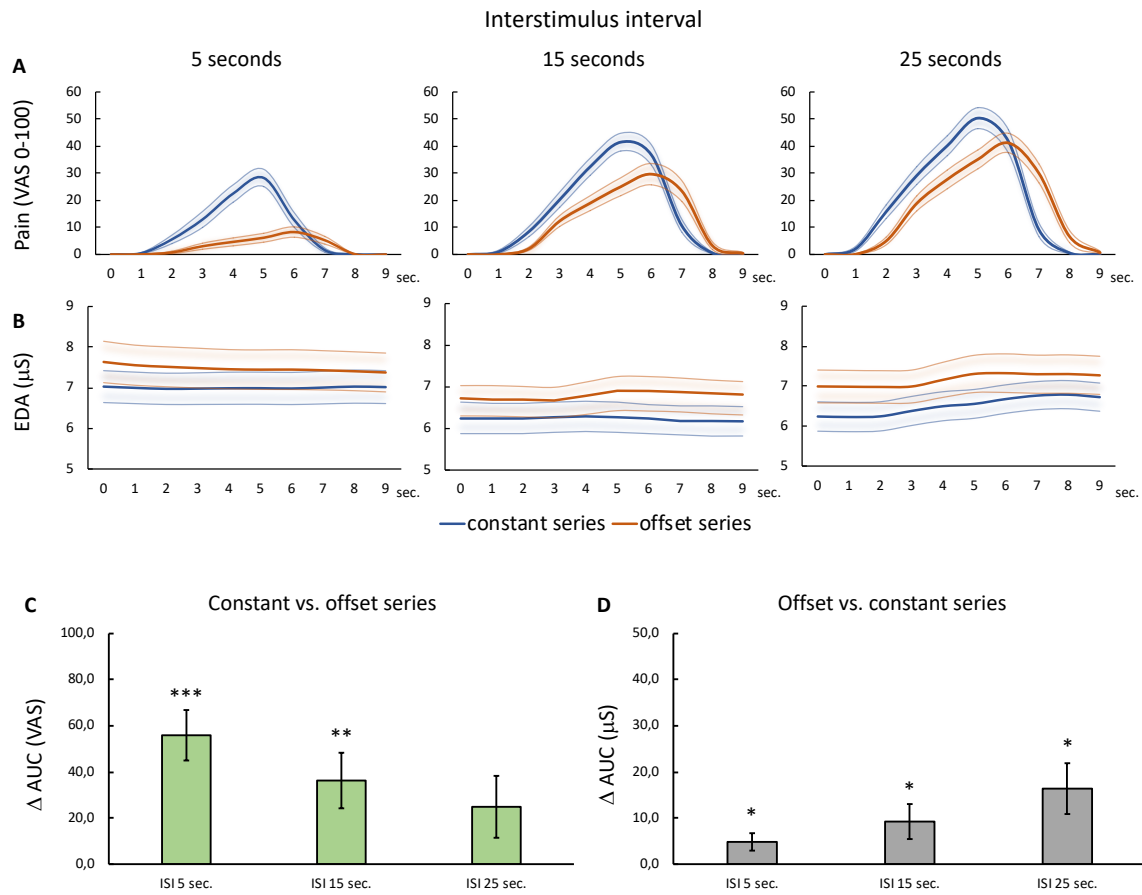
Figure 3. Pain ratings and electrodermal activity during the 7th heat trial. *In the upper and middle graphs, both the offset and constant series are shown using Computerized Visual Analog Scale (CoVAS) (A) and electrodermal activity (EDA) expressed in microsiemens (μS) (B) per interstimulus interval (ISI) 5, 15, and 25 seconds. At the bottom, the differences between the offset and the constant series for the area under the curve (AUC) for CoVAS (C) and μS (D) for each ISI are shown. All data are presented in mean values ($\overline{X}$) and standard error of the mean (SEM). Significant difference between OS and CS within each ISI: * p < 0.05, ** p < 0.01, *** p < 0.001. No differences were found between the ISIs.*

Table 2. Pain ratings and electrodermal activity presented as the Area Under the Curve (mean, SD)

			Interstimulus interval		
	Trial	**Repetition**	**5s**	**15s**	**25s**
AUC Pain (VAS)	OS	7th	28.3 (39.6)	115.2 (87.6)	165.2 (93.6)
	CS	7th	84.2 (64.7)	151.4 (73.4)	190.1 (92.5)
	ΔrTPCE [1]	Δ 7th	56.0 (62.9)	36.3 (69.2)	24.9 (77.1)
AUC EDA (μS)	OS	7th	81.6 (30.4)	132.1 (50.4)	203.7 (91.2)
	CS	7th	76.8 (24.9)	122.8 (46.1)	187.3 (78.9)
	ΔrTPCE [2]	Δ 7th	4.8 (10.9)	9.2 (21.8)	16.4 (31.7)
AUC Pain (VAS)	OS	$\bar{X}$ 8th to 12th	67.5 (53.1)	139.8 (93.3)	140.7 (87.2)
	CS	$\bar{X}$ 8th to 12th	102.9 (65.7)	173.0 (77.4)	201.4 (92.7)
	ΔrTPCE [1]	Δ $\bar{X}$ 8th to 12th	35.4 (49.2)	33.2 (53.1)	60.7 (66.1)
AUC EDA (μS)	OS	$\bar{X}$ 8th to 12th	74.3 (24.9)	123.6 (49.7)	182.0 (82.3)
	CS	Δ $\bar{X}$ 8th to 12th	69.8 (23.4)	117.9 (50.3)	175.9 (77.9)
	ΔrTPCE [2]	$\bar{X}$ 8th to 12th	-4.5 (12.2)	-5.7 (20.6)	-6.2 (29.7)

AUC - area under the curve, EDA - electrodermal activity, CS - constant series, OS - offset series, s - seconds, VAS - visual analogue scale (0-100), μS - microsiemens, 7th - seventh trial within the OS, CS or their difference (Δ), 8th to 12th presents eighth to 12th trial within the OS, CS or (Δ), ΔrTPCE - repetitive temporal pain contrast enhancement expressed as [1] the difference between CS and OS or as [2] the difference between OS and CS. All data are presented in mean values ($\bar{X}$) and standard deviation (SD).

Secondary exploratory analyses showed that within T1, a significant habituation occurred in all series and ISIs (T1: 1st vs. 3rd, **$p < 0.001$**) and within T2 for all of the ISIs considering OS (T2: 4th vs. 6th, **$p < 0.002$**), as shown by the lower pain ratings in the third stimulus compared to the first stimulus in the T1 and T2 intervals, respectively. Significant correlations between OS and CS were shown for all ISIs regarding the pain response (ISI 5s: **$p = 0.035$**, $r_p = 0.368$; ISI 15s: **$p < 0.001$**, $r_p = 0.602$; ISI 25s: **$p < 0.001$**, $r_p = 0.650$). Furthermore, a significant correlation was shown between the rTPCE (25s) and the PVAQ ($r_s = -0.38$, **$p = 0.029$**). Interestingly, the ΔrTPCE did not correlate with the total WMQ ($r_s < 0.3$, $p < 0.05$), but when exclusively the domain "storage" was considered, significant correlations were shown for ΔrTPCE of 25s ($r_s = 0.42$, **$p = 0.016$**), but not the remaining ISI ($r_s < 0.3$, $p < 0.05$). No

correlation was found between ΔrTPCE and other included questionnaires or characteristics ($r_{p,s} < 0.3$, $p > 0.05$).

3.2. Electrodermal activity

Similarly, the 1st heat stimuli between OS and CS at all ISIs did not differ significantly for the EDA signal ($p > 0.05$). At the 7th heat stimulus significant differences between CS and OS could be shown for all ISIs (5s: $t_{(32)} = 2.55$, **p =0.016**, d = 0.44; 15s: $t_{(32)} = 2.43$, **p = 0.021**, d = 0.42, 25s: $t_{(32)} = 2.97$, **p = 0.006**, d = 0.52). This indicates an existence of rTPCE effect at all ISIs regarding EDA (**Table 2, Figure 3**). If the average of the remaining heat trials within T3 is also compared between CS and OS ($\Delta \bar{X}$ 8th to 12th), significant differences were shown exclusively for 5 seconds ($t_{(32)} = 2.12$, **p = 0.042**, d = 0.72), but not for the remaining ISIs ($p < 0.05$). As for the pain ratings, no significant differences between the three ISIs regarding the ΔrTPCE could be shown for the EDA ($F_{(2,64)} = 2.19$, p = 0.12, 2p = 0.06). Both the pain ratings and the corresponding EDA can be found for each heat trial (each series and ISIs) in **Figure 4.**
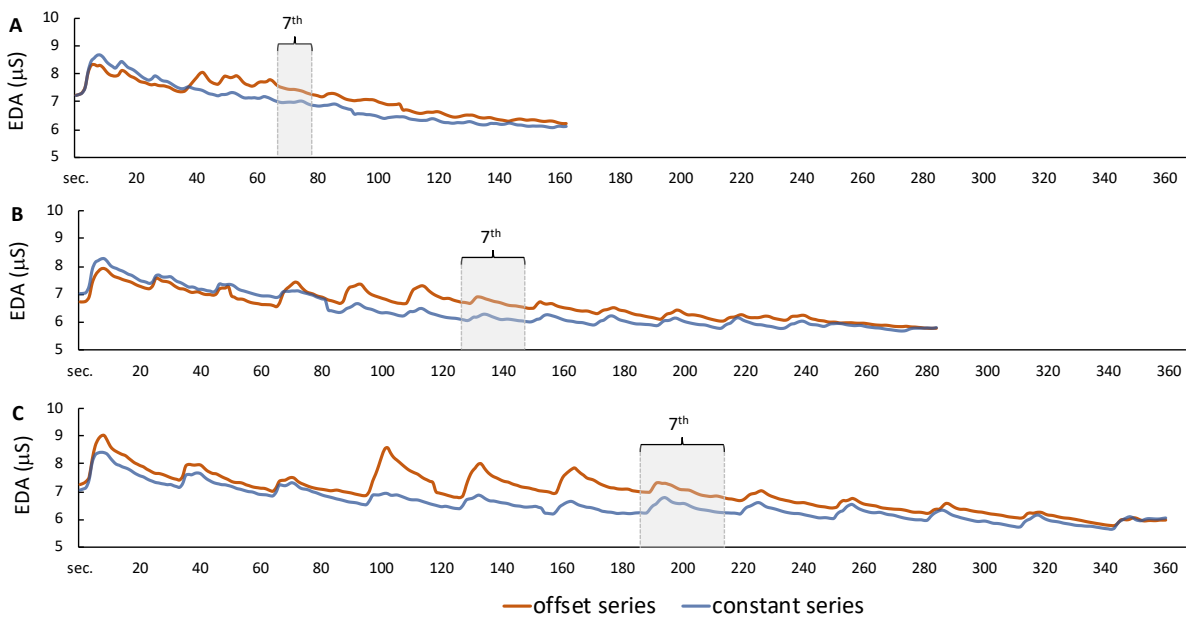

Figure 4. Electrodermal activity for all heat trials. *Both the constant series (12 identical heat stimuli at a temperature of 47°C, 5 seconds each) and the offset series (3 heat stimuli at 47°C, followed by 3 heat stimuli at 49°C and again 6 stimuli at 47°C) are shown in electrodermal activity (EDA) expressed in microsiemens (μS). Interstimulus intervals of 5 (A), 15 (B), and 25 seconds (C) are specified. The EDA to the 7th heat trial is indicated.*

4. Discussion

Temporal contrast enhancement of pain can be induced by stimuli that are clearly separated in time with up to 25s separation. Larger periods trend to reduce TPCE, whereas - contrary to our hypothesis - no statistically significant difference between intervals were observed. Interestingly, EDA data indicate that this effect can be replicated physiologically, showing an increased EDA response - as a marker of activity in the autonomic nervous system - during temporal contrast analgesia. The EDA marker of the behavioral effect followed a reversed direction: The longer the ISI the more pronounced the difference between constant and offset series.

Continuous temporal pain contrast enhancement

For OA, with its continuous temporal contrast enhancement of pain, again, both central and peripheral underlying mechanisms are discussed. Functional imaging studies including functional magnetic resonance imaging (fMRI) indicated the involvement of supra-spinal and spinal areas during OA [10,28,49,61,63]. Among other findings, a greater BOLD signal in the brainstem pain modulation circuit, including the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM), was observed [10,61]. It is therefore particularly interesting and somewhat surprising that centrally acting drugs did not affect the OA response [21,33,34]. On the other hand, there is some evidence that specific nerve fibers are involved in the traditional continuous OA response, in which glabrous and non-glabrous skin sites were contrasted [3,29]. Likewise, an existing TPCE effect, even with repeated stimulation, may indicate central as well as peripheral mediating mechanisms.

Pain habituation and repetitive temporal pain contrast enhancement

In general, repetitive application of noxious stimuli with an identical intensity can modulate the perceived pain intensity, which can lead to an increase (sensitization, summation) or a decrease (habituation) in reported pain [18]. There are multiple central and peripheral processes involved. One of them is temporal summation of second pain (summation via a delayed sensation of pain [41]), which involves repetitive stimulation of peripheral unmyelinated C-fibers [42]. During noxious heat, this pain summation is produced with ISIs of up to 3 seconds [32,45]. However, longer ISIs (as shown here), may lead to a reversed pain response: habituation to pain [7]. Proposed mechanisms of habituation are mainly based on central nervous system explanatory models (see [9] for a review), such as cognitive models and

non-associative learning [39], and also on descending pain inhibitory activity [24]. Interestingly, habituation of pain also occurs in the long term, i.e., as a contrast of pain from day to day [5], and habituation is not limited to the context of pain but can also be observed as a behavioral response across species, stimuli and responses [43].

Peripheral mechanisms in the processing of pain habituation are also reasonable, although rather secondary. It was shown, that both A and C fiber nociceptors show fatigue responses - increased with higher stimulation - when ISIs are below 30s [48]. Thus, this afferent fatigue response may contribute to the habituation effect and one can speculate that higher stimulation (here 49°C) even potentiates this fatigue response in the 7th trial (after the temperature reduction to 47°C). Furthermore, a correlation was found in the pain responses to the 7th heat trial between offset and constant series. A re-analysis of our previous OA studies [50,51,53] confirms this effect also for continuous TPCE: there is a strong correlation between the pain reduction in the offset trial and the adaptation to pain in the constant heat trial, without temperature change. Although the underlying mechanisms of adaptation to a sustained pain stimulus are not yet fully understood, again predominantly peripheral processes are hypothesized [16,57] as shown, for example, in certain A-delta nociceptors by electrophysiological studies [20,23,54,55]. However, both habituation and adaptation are strongly dependent on individual differences in pain perception with a strong tendency to inhibition. An association of habituation and the repetitive TPCE or adaptation and the continuous TPCE effect (OA) can nevertheless be hypothesized, at least in part, points to a common underlying mechanism. It should be clarified whether i) habituation and adaptation of pain are associated (our previous data suggest this), whether ii) OA and repetitive TPCE are associated, and whether iii) repetitive TPCE and OA show the same properties, such as impairment in chronic pain and unaffected by centrally acting drugs, like in OA [17].

Interesting observations made in the field of habituation point to the fact that this phenomenon can be easily disrupted. Indeed, successful habituation is impaired when repeated exposure to the same stimulus occurs through the introduction of a different or higher stimulus. This characteristic is also known as dishabituation [43]. Thus, with not just one but several higher stimuli within a habituation series (in our protocol three stimuli), the magnitude of the dishabituation produced can be expected to decrease and even become potentiated, in contrast to the original habituation. Additional associated features could be "habituation of dishabituation" and "potentiation" [9,43]. As with the mechanisms of habituation, repetitive TCPE was expected to decrease pain/irritation with more frequent stimulation over a longer

period of time (or stimulation with shorter ISI). This can be explained by a temporal contrast in which the current stimulus (consciously or unconsciously) is compared and evaluated with the previous stimulus. It is supported by the present association with short-term storage in working memory, which corresponds to the ability to retain information in short-term memory, and with the association of attention, vigilance and observation of pain (PAVQ), here at least for longer ISIs. For this, a trend but no significant difference between the presented ISIs could be shown. Reasons for this could be a high variance of the inter-individual pain responses [11]. Intentionally, no individualization was chosen in this experiment to allow a better relation between pain and the autonomic nervous system as this was shown to be more associated with stimulus intensity than with pain [31]. Further studies with an individualized stimulus are required to confirm this.

Autonomic function and repetitive temporal pain contrast enhancement

A behavioral effect described by TPCE was successfully shown by the physiological effect measured via EDA. A significantly higher autonomic arousal was observed after higher stimulus intensity (here 49 °C) compared to the condition wherein each stimulus had the same intensity of 47 degrees. This observation may indicate that TPCE has a central component driven by top-down processes likely originated in the PAG. Again, this brain region has been shown to be involved in conventional continuous TPCE (OA) [10,61] and seems to have a central role in both pain inhibition and (at least in part) in autonomic response [26,27]. Our data, however, indicate that the relationship between the contrast effect and autonomic arousal is inverse. Paradoxically, less pain 'means' more arousal. It is not surprising that a greater effect size (d= 0.52) was observed for longer stimuli delay. EDA reflects local changes in skin conduction that depend on sweat gland secretion. Typically, the half-recovery period is between 2 to 10s explaining why longer ISIs led to greater physiological contrast [8].

One can speculate that enhanced EDA responses in post-stimulus offset can serve as inhibitory markers. It can be assumed that the higher temperature (49°C) in trials four to six could serve as the conditioning stimulus that inhibits subsequent pain originated from trials seventh to twelve. This might be the local inhibition resembling pain-inhibiting-pain effect [35], in which remote stimulus of a higher intensity can trigger descending pain control lasting for as long as 5 minutes [12,25]. Whether indeed TPCE resembles the pain-inhibiting-pain effect must be determined in future experiments with longer ISIs.

Clinical implication

The investigation of repetitive TPCE may contribute to a better understanding of the descending pain modulation systems. Thus, it can be hypothesized that the underlying mechanisms of repetitive noxious stimulation leading to habituation to pain partially overlaps with the pain response of repetitive TPCE. This assumption is based on the repetitive nature, contrast to habituation, and anti-nociceptive properties of these two paradigms. However, a direct comparison between continuous and repetitive paradigms was not the subject of this work.

A large number of studies have described a possible relationship between preoperative quantitative sensory testing procedures and chronic postoperative pain (see for review [38]). In particular, it has been shown that descending pain modulation quantification procedures, such as temporal pain summation and pain inhibiting pain effect, have the most consistent predictive values for chronic postoperative pain and analgesic effect. Accordingly, in case of (dys)functionality, different and more effective therapeutic pathways should be offered in each individual clinical setting. Other testing procedures such as OA have not been studied in this regard, although different test paradigms seem to reflect different sub-aspects of pain modulation [53] and this might allow better phenotyping [59,60]. One reason for this could be that procedures such as OA are laborious procedures that require expensive equipment. This project, on the other hand, helps to provide the basis for easier and less expensive variants that could be applied within in a bedside manner using, for example, pressure algometry.

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