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Abstract

Introduction: Offset analgesia (OA) and conditioned pain modulation (CPM) are frequently used paradigms to assess the descending pain modulation system. Recently, it was shown that both paradigms are reduced in chronic pain, but the influence of acute pain has not yet been adequately examined.

Objectives: The aim of this study is to investigate OA and CPM after exercise-induced pain to evaluate whether these tests can be influenced by delayed-onset muscle soreness (DOMS) at a local or remote body site.

Methods: Forty-two healthy adults were invited to 3 separate examination days: a baseline appointment, the consecutive day, and 7 days later. Participants were randomly divided into a rest (n = 21) and an exercise group (n = 21). The latter performed a single intensive exercise for the lower back. Before, immediately after, and on the following examination days, OA and CPM were measured at the forearm and the lower back by blinded assessor.

Results: The exercise provoked a moderate pain perception and a mild delayed-onset muscle soreness on the following day. Repeated-measurements analysis of variance showed no statistically significant main effect for either OA or CPM at the forearm or lower back ($P > 0.05$).

Conclusion: Delayed-onset muscle soreness was shown to have no effect on the inhibitory pain modulation system neither locally (at the painful body part), nor remotely. Thus, OA and CPM are robust test paradigms that probably require more intense, different, or prolonged pain to be modulated.

Keywords: Offset analgesia, Conditioned pain modulation, Exercise, Delayed-onset muscle soreness

1. Introduction

The descending pain modulating pathway is essential for the regulation of human pain perception.[54] A variety of paradigms has been developed to experimentally evaluate pain modulation, including conditioned pain modulation (CPM) and offset analgesia (OA). Conditioned pain modulation can be described as a systemic "pain inhibits pain" phenomenon, whereby a painful stimulus applied to a remote area of the body (conditioning stimulus) inhibits the pain response to another (testing)

stimulus.[50] By contrast, OA is characterized as a disproportional pain reduction after a small decrease of a noxious stimulus, measured locally.[22] Both paradigms are used to quantify descending pain inhibition; however, the way these paradigms process the afferent nociceptive information is different.[44]

For both, OA and CPM, it has repeatedly been shown that pain modulation is impaired in a range of chronic pain disorders.[32,43,52,61] Using CPM as a paradigm to assess pain modulation, previous research also included patients with chronic back pain,[4,35,56,63] although some contrary findings exist.[21,42] Whether this is exclusively limited to chronic pain conditions[29,34,40,42] and whether the localization of the test area plays a role[3,11,19] is a matter of ongoing debate.

Because of confounding factors in acute or chronic pain, such as psychological, cognitive, and social aspects, experimental pain models are advantageous when underlying mechanisms of pain are to be investigated.[55] Thus, experimentally induced pain models are often used to assess controlled psychophysical, behavioral, or neurophysiological responses.[6] In addition, experimental pain models might help us to understand the timeframe for pain inhibition impairment. So far, OA was not influenced by experimental pain models, such as tonic cold pain[51] or capsaicin application,[37] but the OA response seems to be dependent on the localization of tonic heat pain.[73] For CPM, painful electrical stimulation does not seem to have an influence,[53] but also, comparable with OA, this is traditionally assessed outside of the affected area, eg, low back patients are assessed at the forearm. In comparison with thermal, chemical, or

electric noxious stimulation stimuli, a more ecologically valid pain model to assess musculoskeletal pain is delayed-onset muscle soreness (DOMS),[12,14–16] which has been used reliably to induce acute, experimental low back pain following excessive physical effort.[1,26,65] This experimental model elicits a deep and movement-related pain with functional impairment that mimics mild nonspecific low back patient.[8,39] Although no studies on experimental, acute, or chronic back pain exist for OA, it was shown for CPM that acute exercised-induced back pain did not affect the systemic effect of CPM.[39] This, however, was only investigated when the test stimulus was applied to a body region other than the painful area.

Central sensitization has been linked to chronic pain,[5,49] and measuring pain inhibition can be used as a surrogate marker to identify altered pain modulation in chronic back pain.[13] Therefore, it seems crucial to investigate whether these processes are influenced by an acute pain model and whether there are regional differences. This study is aiming to investigate—in a randomized controlled and blinded manner—the influence of exercise-induced pain on locally as well as remotely applied OA and CPM paradigms. It was hypothesized a priori that experimental pain, at the painful site but not the nonpainful site, will decrease the magnitude of OA and CPM.

2. Methods

2.1. Subjects

This study was conducted at the University of Lübeck (Germany) and the Jerzy Kukuczka Academy of Physical Education in Katowice (Poland). Forty-two healthy and pain-free participants between 18 and 45 years were recruited through advertisement at the campus. Excluded were subjects with a history of pain (more than 6 months), any kind of acute pain within the last week including headache and toothache, acute or chronic disease including neurological and psychiatric disease, and any current medication (excluding contraceptives). Before the start of the study, the inclusion and exclusion criteria were evaluated by an investigator with a previously prepared checklist. All subjects were asked to refrain from additional exercise during the data collection period. The protocol for this study was prospectively registered at the German Clinical Trial Register (DRKS00014755) and was approved by the local research ethics authority. Written informed consent was obtained from all participants before taking part.

2.2. Procedure

Participants were invited to 3 separate sessions: a baseline appointment (day I), 24 to 48 hours later (day II), and 7 days later (day III). At day I, participants were introduced to the study procedures and divided in a randomized counterbalanced manner into 2 groups: an exercise group (n = 21) and a rest group (n = 21). In addition, questionnaires for demographic characteristics, physical activity (Tegner Activity Scale[9]), sleep behavior (Pittsburgh Sleep Quality Index[10]), and depression (Patient Health Questionnaire-9[33]) were provided. An assessor, blinded to the group allocation, evaluated OA and CPM at the nondominant volar forearm and the nondominant side of the lower back on day I before and after the intervention, as well as on the following examination days (day II and III). The order of tests and body regions (eg, OA forearm, OA back, CPM forearm, and CPM back) was also randomized and counterbalanced, but kept constant within each subsequent testing day. The sequence is shown in **Figure 1**.

2.3. Offset analgesia

The primary outcome defined in this study was a three-temperature OA paradigm. All thermal stimuli were delivered using a TSA-II (Medoc Inc., Ramat Yishai, Israel) using a 30″30-mm² peltier device. All participants were first familiarized with a series of thermal stimuli on the nondominant forearm (35°C, 43–48°C, each 5 seconds) to demonstrate the heat stimuli and to train the use of the computerized visual analogue scale.[36] To determine the individualized test temperature (Pain60), the temperature was increased slowly (0.5°C/second) from 32°C to the individual perceived pain intensity of 60/100 twice (with 20-second interstimulus interval) at the center of the nondominant forearm and at the nondominant back-extensor side (L3 level). If the temperature of Pain60 (average of 2 measurements) was higher than 48°C or lower than 43°C, these temperatures (48°C and 43°C, respectively) were used. Three sets of offset trials and 3 sets of constant trials (CT) were provided in a seated position in a pseudorandomized sequence. During this procedure, the thermode was attached to the forearm or lower back with a velcro strap and moved by approximately 1 cm after each trial to avoid local skin reactions. The offset trial (OT) consisted of 5 seconds at Pain60 (T1), 5 seconds at a temperature +1°C from T1 (T2), and 20 seconds again at the same temperature as T1 (T3). Constant trials consisted of a 30-second stimulus at Pain60 (T1). It has been shown that these are the most frequently used time-related parameters for the OA paradigm.[61] Rise and fall rates were 10°C/second. Participants were asked to simultaneously (real time) evaluate the perceived pain intensity using a computerized visual analog scale (VAS, 0–100, "no pain" to "most intense pain sensation imaginable"). Details on the offset paradigm were not explained to participants, instead participants were instructed to focus on the pain sensation and to rate its intensity continuously as precisely as possible.

2.4. Conditioned pain modulation

The CPM paradigm was designed following international recommendations[72]: In a counterbalanced manner, the second-ary outcome CPM was performed by an assessor blinded to the group allocation. Test stimuli were applied to the nondominant forearm in a supine position and at the nondominant side of the back in prone on a therapy plinth. The same test areas were used as for the OA paradigm. A handheld pressure algometer (Wagner Instruments, Greenwich, United Kingdom) with a stimulation area of 1 cm² was used as the test stimulus by increasing the pressure (250 g per second[62]) to a pain intensity of Pain40 (40 out of 100 on a VAS). Participants were informed to say "stop" as soon as they perceived a pain intensity of 40 out of 100 (Pain40). The test stimulus procedure was repeated twice on each side of the body before and immediately after the conditioning stimulus. For the conditioning stimulus, a 60-second cold-water immersion (approx. 8°C: exercise group 8.1°C [SD 0.08]; rest group: 8.0°C [SD 0.9]) of the dominant hand to wrist level was used as the conditioning stimulus. Immediately at the end of this cold pressor task, subjects reassessed the painfulness (VAS) induced by the conditioning stimulus.

2.5. Exercise

The first task for participants in the exercise group was the supervised Biering-Sorensen test.[30] In short, the BST procedure requires an isometric contraction of the muscles of the lower back and the hip extensors. In a prone position with arms folded over the
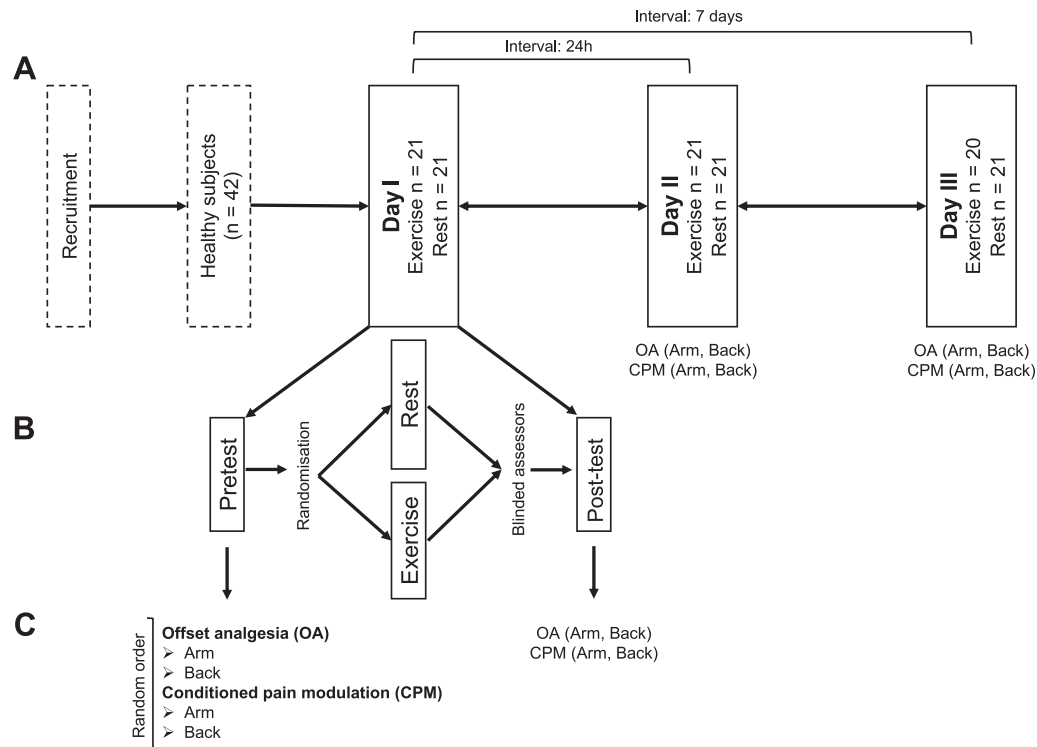
Figure 1. Flowchart of study sequence. Forty-two healthy volunteers were randomized in a counterbalanced manner into 2 groups. The exercise group (n = 21) performed an exercise protocol for the lower back while the other group (n = 21) rested. Offset analgesia (OA) and conditioned pain modulation (CPM) were evaluated before, immediately after, and on the following examination days at the nondominant forearm and the nondominant side of the lower back. (A) between day design, (B) randomization procedure at Day I, (C) pain modulation paradigms used.

chest, participants were instructed to hold the unsupported upper body (from the crista iliaca) in a horizontal position while the lower body is attached to a bench with 3 straps: below the crista iliaca, at the center of the hamstrings, and across the ankles. Subjects were encouraged to hold this position for at least 4 minutes (240 seconds). After a 30-second break, participants were asked to perform a set of the maximum number of repetitions (5 seconds per repetition) of dynamic (concentric/eccentric) back-extensor movements. As a final step and after another rest interval of 30 seconds, the maximum number of eccentric repetitions (concentric movement supported by supervisor) was performed. Immediately after performing the test, participants rated the intensity of muscle pain, global physical effort, and physical effort of the back-extensor muscles on a VAS. Participants in the rest group performed no task but instructed to rest for 10 minutes. At the beginning of day II and day III, all test persons were asked to rate the current perceived intensity of muscle pain related to muscle soreness and muscle fatigue in the lower back on a VAS. These data were collected by a person who was not otherwise involved in the data collection and who remained blinded.

2.6. Statistical analysis

Because of the lack of reference data for the primary outcome OA in acute muscle pain, the sample size calculation was based on a recent meta-analysis comparing OA in healthy subjects and those with chronic pain.[61] With an expected effect size of 0.9 (80% power; alpha 0.05), a total of 42 (21 per group) participants was estimated to detect the interaction.

Offset analgesia data were preprocessed using MATLAB R2017b (MathWorks, Inc, Natick, Massachusetts) and analyzed by the IBM Statistical Package for Social Science (SPSS Version 24, Armonk, NY). Unless otherwise stated, mean and SD were

reported in the text and tables. For parametric, normally distributed data, an independent t test was performed to verify baseline group differences, whereas for nonparametric data, the Mann–Whitney U test was used. Nominal data were analyzed with the χ^2 test. Regarding the OA paradigm, for OT and CT, maximum pain ratings for T2 ($T2_{max}$), minimum pain ratings for T3 ($T3_{min}$), as well as for the $T2_{max}$-corrected percentage difference between $T2_{max}$ and $T3_{min}$ [OT% and CT%: ($T2_{max} - T3_{min}$)/$T2_{max}$ $\times$ 100) were obtained. The magnitude of the OA response was reported as the difference between OT and CT to control for heat pain adaptation during the OT trial. Regarding the CPM effect, the mean of the 2 pressure measurements of the first test stimuli (before the conditioning stimulus) were subtracted from the mean of the second test stimulus and divided by the mean of the first test stimulus (CPM%: [($TS_{post} - TS_{pre}$)/TS_{pre}] $\times$ 100%). The magnitude of the CPM response was defined as the difference between the test stimuli before and after the conditioned stimulus. Positive percentages for OA and CPM response indicate an existing effect related to endogenous pain modulation. Normal distribution was tested with the Kolmogorov–Smirnov test. If data were not normally distributed, it was transformed using log transformation. The effect of CPM and OA was analyzed with a two-way dependent t test. A repeated-measurement analysis of variance with "group" (exercise; rest) and "time" (day I pre, day I post, day II, and day III) and the interaction between "group" and "time" were performed to investigate the main effect of OA and CPM separately for the arm and the lower back. Using an identical analysis approach, a subgroup analysis was performed to determine whether the test sequence of OA and CPM (OA first or CPM first) confirmed the findings ("group" $\times$ "time"). An additional explorative analysis was also performed for DOMS responders (participants who subjectively indicated to have DOMS-like

symptoms in the back), only. Bonferroni-corrected post hoc tests were performed, as required. Correlation analysis between DOMS, OA, and CPM were performed with the Pearson correlation (2-sided). For all the above analyses, *P*-values less than 0.05 were considered significant.

3. Results

3.1. Participant characteristics

From the original 21 participants of the exercise group, 20 completed the study. One subject was unable to participate on day III due to scheduling limitations. All subjects from the rest group were evaluated at all time points. Several baseline comparisons showed no significant differences between the groups (**Table 1**).

3.2. Exercise and delayed-onset muscle soreness

After the first examination, but before the exercise, it was reconfirmed that both groups were entirely pain-free. Participants in the exercise group performed the Biering-Sorensen test for an average of 198.8 seconds (SD 53.9) and subsequently performed 26.0 (SD 16.0) dynamic and 12.8 (SD 5.6) eccentric repetitions. The average pain intensity during the exercise was 50.9 (SD 23.6, VAS), the general muscle fatigue 55.0 (SD 22.0, VAS), and the lower back fatigue 63.4 (SD 23.4, VAS), immediately after exercise. On the

Table 1

Baseline characteristics.

	Exercise (n = 21)	Rest (n = 21)	P
Age, Years; x̄ (SD)	23.1 (3.8)	23.9 (3.5)	0.45
Weight, kg; x̄ (SD)	68.1 (9.3)	71.7 (14.2)	0.34
Height, cm; x̄ (SD)	175.0 (8.3)	174.5 (10.4)	0.88
Female, n (%)	13 (61.9)	10 (47.6)	0.35
PHQ-9, M (IQR)	4.0 (1.5–6.5)	5.0 (2.0–6.5)	0.87
PSQI, M (IQR)	4.0 (3.0–5.5)	4.0 (3.0–6.0)	0.69
TAS, M (IQR)	5.0 (4.0–5.5)	5.0 (4.0–6.5)	0.89
Pressure Pain40, kg/cm²; x̄ (SD)			
Forearm	4.3 (1.9)	4.7 (2.0)	0.44
Lower back	6.5 (2.4)	6.6 (2.4)	0.92
Heat Pain60, ℃; x̄ (SD)			
Forearm	46.5 (1.6)	46.6 (1.7)	0.93
Lower back	46.5 (1.8)	46.0 (1.9)	0.41
Cold-water immersion, VAS; x̄ (SD)			
Hand	55.7 (20.7)	56.6 (24.1)	0.90
CPM, %; x̄ (SD)			
Forearm	14.2 (24.5)	17.3 (20.5)	0.66
Lower back	11.2 (18.9)	12.1 (19.5)	0.89
OT%, %; x̄ (SD)			
Forearm	67.2 (30.5)	67.4 (28.5)	0.98
Lower back	64.6 (30.2)	70.6 (33.1)	0.55
CT%, %; x̄ (SD)			
Forearm	49.2 (30.5)	55.2 (35.1)	0.56
Lower back	44.8 (32.5)	58.7 (32.4)	0.19
OA response, %; x̄ (SD)			
Forearm	18.05 (24.3)	12.2 (23.5)	0.69
Lower back	19.8 (19.0)	11.9 (19.04)	0.20

x̄, mean; ℃, Celsius; CPM, conditioned pain modulation; CT%, consent trial; IQR, interquartile range; M, median; OA, offset analgesia; OA, response CT%-OT%; OT%, offset trial; PHQ-9, Patient Health Questionnaire-9; PSQI, Pittsburgh Sleep Quality Index; Pain40, pressure according to pain intensity 40/100; Pain60, temperature according to pain intensity 60/100; TAS, Tegner Activity Scale; VAS, visual analog scale (0–100).

following day (day II), participants reported an average back pain intensity of 17.3 (SD 16.3) and lower back fatigue of 14.3 (SD 19.9), which was decreased at the last assessment day to an average pain intensity of 4.9 (SD 7.6, VAS) and general fatigue of 4.7 (7.0, VAS). The pain intensity in the rest group (VAS 1.0 (SD 1.8)) was significantly different from the training group on day II ($P < 0.001$), but not on day III (VAS 2.9 (SD 5.2), $P = 0.33$). An additional explorative subgroup analysis of 17 DOMS responders (81.0%) showed an average low back pain intensity of 21.6 (SD 15.4, VAS) and back fatigue of 16.6 (SD 21.5, VAS) on Day II, which was decreased on the last assessment day to a pain intensity of 4.0 (SD 4.8, VAS) and fatigue of 4.4 (6.4, VAS). However, DOMs responders did not differ in pain intensity or muscle fatigue to the overall exercise group on day II or day III ($P > 0.05$).

3.3. Offset analgesia

At baseline, both the rest group and the exercise group showed significant differences between the OTs and the CTs, at the forearm, as well as at the back ($P < 0.05$). Thus, an OA response at both body parts was observed in all participants before the experimental manipulation. For the OA response, no significant main effects was found for "time" (forearm: F = 2.409; $P = 0.070$: $\eta_p^2 = 0.057$; lower back: F = 1.504; $P = 0.218$; $\eta_p^2 = 0.039$), "group" (forearm: F = 0.120; $P = 0.731$; $\eta_p^2 = 0.003$; lower back: F = 0.698; $P = 0.409$; $\eta_p^2 = 0.019$), or "time" × "group" (forearm: F = 0.455; $P = 0.707$; $\eta_p^2 = 0.011$; lower back: F = 0.310; $P = 0.800$; $\eta_p^2 = 0.009$). No significant correlations were shown between DOMS and CPM measured on day II (forearm: $r = -0.36$, $P = 0.880$; lower back: $r = 0.112$; $P = 0.608$). Details of each session can be found in **Table 2** and **Figures 2A and B**.

Subgroup analysis of participants who performed CPM before OA (exercise group n = 10; rest group n = 10) did not show statistically significant effects ("time" × "group") for the difference between OT and CT (forearm: F = 0.039; $P = 0.990$: $\eta_p^2 = 0.002$; lower back: F = 1.133; $P = 0.344$; $\eta_p^2 = 0.59$). The subgroup of DOMS responders (n = 17) showed no significant interaction effect for the OA response (difference between OT and CT) (forearm: F = 0.619; $P = 0.604$; $\eta_p^2 = 0.017$; lower back F = 0.349; $P = 0.790$; $\eta_p^2 = 0.01$).

3.4. Conditioned pain modulation

At baseline, significant differences between the test stimuli before and after the conditioned stimulus were shown for both test stimuli (forearm and lower back) within both groups ($P < 0.05$). In other words, a CPM response was observed in both parts of the body in all participants before experimental manipulation.

Repeated-measurement analysis of variance revealed no statistically significant main effects for "time" (F = 0.825; $P = 0.483$; $\eta_p^2 = 0.02$), "group" (F = 0.901; $P = 0.348$; $\eta_p^2 = 0.022$), or for the "time" × "group" interaction, neither at the forearm (F = 0.178; $P = 0.911$; $\eta_p^2 = 0.004$) nor at the lower back ("time": F = 1.335; $P = 0.266$; $\eta_p^2 = 0.032$; "group" (F = 0.754; $P = 0.391$; $\eta_p^2 = 0.018$) "time" × "group": F = 0.988; $P = 0.401$; $\eta_p^2 = 0.024$). No significant correlations were shown between DOMS and OA measured on day II (forearm: $r = 0.055$, $P = 0.823$; lower back: $r = -0.166$, $P = 0.498$). Results are detailed in **Table 2** and **Figures 2C and D**. Similarly, results for subgroup analysis of participants who performed the CPM before OA protocol (exercise group n = 11; rest group n = 11) did not show statistically significant effects at the forearm ("time" × "group": F = 0.474; $P = 0.702$; $\eta_p^2 = 0.022$) or at the lower back ("time" × "group": F = 0.346; $P = 0.792$; $\eta_p^2 = 0.016$). The subgroup

Table 2

Mean values and SDs of conditioned pain modulation and offset analgesia at all measurement time points.

	Exercise				Rest			
	Day I pre	Day I post	Day II	Day III	Day I pre	Day I post	Day II	Day III
Total participants								
n	21	21	21	20	21	21	21	21
CPM response								
Forearm	14.1 (24.5)	7.8 (14.9)	10.5 (17.6)	12.9 (18.7)	17.3 (20.5)	13.4 (23.4)	14.0 (20.7)	15.5 (12.5)
Lower back	11.2 (18.9)	1.7 (12.5)	13.8 (17.6)	7.6 (12.6)	12.1 (19.5)	8.1 (16.0)	8.0 (14.4)	11.1 (13.5)
Offset trial (OT%)								
Forearm	67.2 (30.5)	64.0 (30.6)	65.5 (32.7)	60.0 (36.3)	67.4 (28.5)	68.5 (33.6)	81.1 (26.6)	72.3 (33.8)
Lower back	64.6 (30.2)	76.9 (22.4)	70.4 (31.0)	57.4 (39.1)	70.6 (33.1)	80.6 (29.2)	85.2 (22.9)	71.8 (31.2)
Constant trial (CT%)								
Forearm	49.2 (30.5)	59.0 (28.8)	56.2 (40.3)	47.7 (36.5)	55.2 (35.1)	63.0 (38.6)	64.1 (32.3)	57.2 (34.4)
Lower back	44.8 (32.5)	62.9 (31.6)	57.5 (37.9)	48.4 (36.5)	58.7 (32.2)	68.9 (34.3)	70.5 (33.6)	67.1 (33.9)
OA response								
Forearm	18.0 (24.3)	5.0 (22.6)	9.3 (23.5)	12.3 (23.1)	12.2 (23.4)	5.2 (18.5)	16.1 (21.3)	14.4 (16.2)
Lower back	19.8 (19.0)	14.1 (20.8)	12.9 (21.2)	9.0 (28.5)	11.9 (19.0)	11.1 (21.0)	14.0 (21.9)	5.0 (20.4)

OA response expressed as the difference between offset trial (OT%) and constant trial (CT%) (for OT% and CT%: difference of the maximum pain ratings for T2 ($T2_{max}$) and minimum pain ratings for T3 ($T3_{min}$) corrected by $T2_{max}$ ($[(T2_{max} - T3_{min})/T2_{max}] \times 100\%$)). CPM response expressed as the difference of the first test stimuli (before the conditioning stimulus) and second test stimulus and divided by first test stimulus ($[(TS_{post} - TS_{pre})/TS_{pre}] \times 100\%$). Data are presented as mean values and SDs.
CPM, conditioned pain modulation; OA, offset analgesia.

of DOMS responders (n = 17) showed no significant interaction effect for CPM (forearm: F = 0.490; $P = 0.685$; $\eta_p^2 = 0.013$; lower back F = 1.151; $P = 0.332$; $\eta_p^2 = 0.031$).

4. Discussion

This study evaluated the effect of exercise-induced pain on the magnitude of OA and CPM, measured both locally and remotely. Before the intervention, intact endogenous pain modulation was shown for both paradigms at the forearm as well as at the lower back. Experimentally induced DOMS did not affect OA or CPM significantly, when compared with a control condition. In contrast to our previous hypothesis, endogenous pain modulation paradigms remained unaffected at the exercised, painful local area (lower back), and at the distant measurement site (forearm).

As described earlier, it is not yet sufficiently established whether endogenous pain modulation measured through CPM is impaired in chronic back pain.[13] This can be explained by different patient populations,[4] but also by different test procedures, such as test and conditioning stimuli, examination areas (eg, affected and nonaffected areas), and sequential or parallel testing of the CPM paradigm.[11,42] Studies examining (sub-) acute back pain in a clinical population showed a more distinct picture, which is in line with findings from this current study in experimental pain. Although methodological heterogeneity among studies was similar to chronic pain, CPM was shown
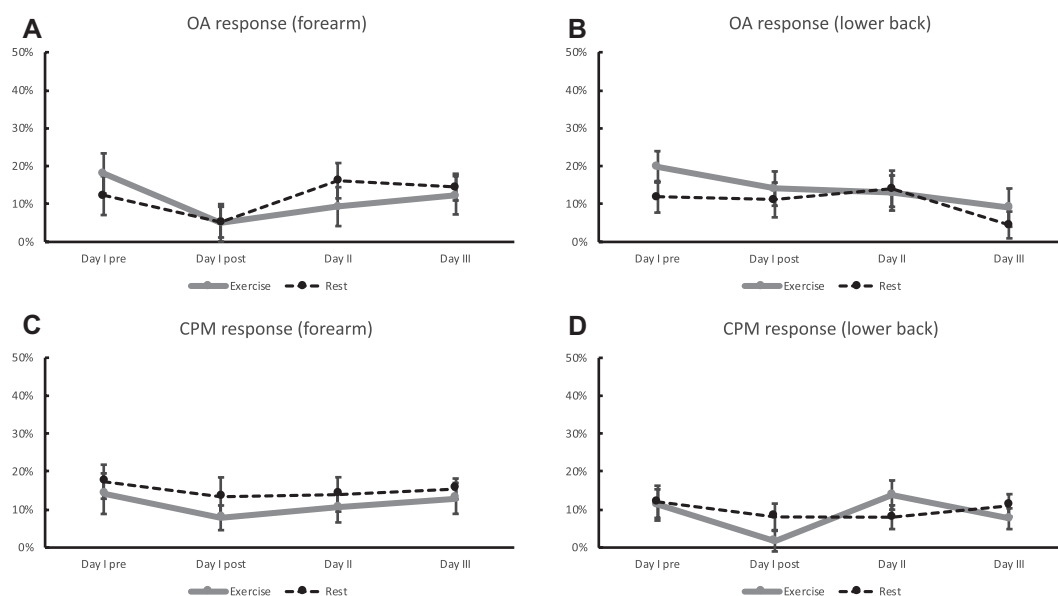

Figure 2. Conditioned pain modulation (CPM) and offset analgesia (OA) at all measurement time points. Offset analgesia response expressed as the difference between offset trial (OT%) and constant trial (CT%) (for OT% and CT%: difference of the maximum pain ratings for T2 ($T2_{max}$) and minimum pain ratings for T3 ($T3_{min}$) corrected by $T2_{max}$ ($[(T2_{max} - T3_{min})/T2_{max}] \times 100\%$). CPM response expressed as the difference of the first test stimuli (before the conditioning stimulus) and second test stimulus and divided by first test stimulus ($[(TS_{post} - TS_{pre})/TS_{pre}] \times 100\%$). OA response at the forearm (A) and the lower back (B), CPM response at the forearm (C) and the lower back (D). Data are presented as mean values and SEs (SEM).

not to be impaired in patients with acute pain compared with healthy controls[29,34,42,70] indicating that for the pain modulation impairment, the duration of clinical pain plays a crucial role.

Experimental pain models have the potential to provide additional knowledge about acute pain by enabling the evaluation of a standardized condition of pain. This study shows for the first time that OA remains unaffected by experimental pain induced by DOMS, as already shown for CPM.[39,67,68] In addition, current results confirm that pain modulation paradigms remain intact not only at the typically investigated remote site (usually the forearm), but also in the area that has been (1) exercised and (2) affected by acute pain (in this case the lower back). Intact OA and CPM during experimentally induced muscle pain, indicates that altered pain inhibitory mechanisms in chronic pain are a phenomenon, which is "time dependent" rather than "pain dependent." Previous meta-analyses have confirmed impaired pain inhibition in chronic pain patients,[32,61] while previous clinical and experimental studies failed to show an influence of acute pain. Taken together these observations and findings of altered brain structure[71] and function[18,27] in long-lasting low back pain patients, one might conclude that only prolonged exposure to nociception and pain might change pain inhibition mechanisms.

Delayed-onset muscle soreness is a valid musculoskeletal pain model, although the intensity of the perceived pain is rather mild.[15,16] Typically, the DOMS-associated pain reaches its peak after 24 to 48 hours after the exercise stimulus and is no longer present after 1 week.[8] DOMS does not cause pain at rest. This is comparable with diseases of the musculoskeletal system, such as acute mild to moderate back pain, which also shows pain during movement or muscle contraction. In addition, it has been shown that self-reported pain and disability are comparable among clinical pain conditions and DOMS.[8] Further studies showed that neuroplastic changes in cortical sensory excitability[12] and functional changes among brain regions, which are also involved in pain modulation, are associated with DOMS-induced pain.[38,58,74] Although DOMS is comparable with clinical symptoms, the intensity of the pain experience is mild and could explain why pain modulation is not affected as it is in chronic clinical pain.

The study design allows to investigate not only the effect of experimental pain but also the influence of an exercise stimulus. The results of the current study are consistent with some of the earlier reports: both OA[23] and CPM[28,41,69] remained stable after exercise. As well as the influence of acute and chronic pain on CPM, the influence of training on CPM is discussed controversially.[2,3,28,41,57,69] Again, different methodological approaches were applied, and different populations were investigated. Furthermore, a clear relationship has been established between CPM and physical activity[2,7,17,20,46,59,64] as well as between CPM and exercise-induced hypoalgesia—known as the "exercise inhibits pain" phenomenon.[31,60,66]

Numerous influencing factors were investigated for both CPM and OA. Although influencing factors such as age, sex, sleep quality, hormone cycle, psychological factors, and physical activity have been described for CPM,[24,48] this is largely unclear for OA. Age seems to have an influence on OA,[45,48] but sex remains controversial.[25,45,47,48] Baseline comparisons, including sex and age, showed in our study that the exercise group and the control (rest) group did not differ significantly. These factors may, however, influence the baseline OA or CPM or may influence the effects of exercise or DOMS on OA or CPM. Further studies should be conducted to evaluate this potential.

5. Limitations

Although this study reveals numerous methodological strengths, such as an adequate randomization, the inclusion of a control group, and the blinding of assessors, it also has some limitations. First, although this is not in line with the study aim, the small sample size does not allow for an analysis of sex differences. Second, for methodological strength, the order of the paradigms was randomized and counterbalanced. Using an exploratory subgroup analysis, however, it was shown that the order is not relevant, even if the size of the subgroups is underpowered. Third, a limitation of our study could be the dosage and responsiveness to the muscle soreness task. Although all the subjects performed the task reaching their individual limits, some of the participants (19%) did not develop a pain response and the overall pain intensity was mild, which was, however, comparable with previously studies.[2,8,39,67,68] But again, the subgroup analysis showed no trend, although this subgroup was underpowered. In future studies, subjects with a limited number of sportive activities should be included, promising a greater pain stimulus. Because DOMS-related pain at rest is often minimal, future studies may benefit from provoking the muscles involved to generate a more intense experimental pain model.

6. Conclusions

An intensive exercise protocol for the muscles of the lower back with a subsequent mild experimental acute pain model showed to have no influence on the inhibitory pain modulation system. A difference between local and remote effects for both OA and CPM was not identified. Thus, it has been shown that both paradigms are robust that probably require more intense, different, or prolonged pain to be modulated.

Disclosures

Acknowledgments

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