Original experimental

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Exercise does not produce hypoalgesia when performed immediately after a painful stimulus

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Abstract

Background and aims: Exercise-induced hypoalgesia (EIH) and conditioned pain modulation (CPM) are assumed to reflect descending pain inhibition. Potential interactions between EIH and CPM may be important in the therapy of chronic pain, as reduced CPM and increased pain after exercise are frequently observed. This study compared the EIH response after CPM was activated using a cold pressor task with the EIH response after a control condition.
Methods: Thirty-one participants (age: 27.7 ± 9.8; 15 female) completed two sessions: a cold pressor task (CPT) session, i.e. testing EIH with preceding CPM activation induced using a 2 min CPT at approximately 2 °C, and a control session, i.e. testing EIH after a control condition (2 min of quiet rest). EIH was induced using a 15 min bicycling exercise at a target heart rate corresponding to 75% VO2 max. Repeated measures ANOVAs on pressure pain thresholds (PPTs) at the hand, back and leg were used to determine the effects of exercise after the cold pressor test and control condition. Furthermore, correlations between CPM and EIH, in the CPT session as well as control session, were calculated at each assessment site.
Results: A significant time x condition interaction ($F(1, 30) = 43.61$, $p < 0.001$, partial $\eta^2 = 0.59$), with Bonferroni-corrected *post-hoc t*-tests showed that PPTs increased after exercise in the control session ($p < 0.001$), but not in the CPT session ($p = 0.125$). Furthermore, there was a small positive correlation of EIH in the control session and CPM at the hand ($r = 0.37$, $p = 0.043$). There was a moderate negative correlation of EIH in the CPT session and CPM at the hand ($r = -0.50$, $p = 0.004$), and smaller negative correlations at the back ($r = -0.37$, $p = 0.036$) and at the leg ($r = -0.35$, $p = 0.054$).
Conclusions: Attenuated EIH after the CPM activation in comparison to a control condition suggests that EIH and CPM may share underlying pain inhibitory mechanisms on a systemic level. This assumption is further supported by the finding of small to moderate significant correlations between EIH and CPM at the hand. The attenuated EIH response furthermore suggests that these mechanisms are exhaustible, i.e. that its effects decline after a certain amount of inhibition.
Implications: In patients with chronic pain, assessing the current capacity of the descending pain inhibitory system – as indicated by the CPM response – may aid to make better predictions about how patients will respond to exercise with respect to acute pain reduction.

Keywords: exercise-induced hypoalgesia; conditioned pain modulation; cold pressor task; endogenous pain inhibition; pressure pain sensitivity; pressure pain threshold.

1 Introduction

Physical exercise is an important component in treatment and rehabilitation of patients with chronic pain [1]. In pain-free individuals, acute exercise can transiently reduce pain sensitivity, known as exercise-induced hypoalgesia (EIH) [2]. EIH is often reported when assessed at non-exercising muscles, but greater increases in pressure pain thresholds (PPTs) are seen at the exercising muscles [3–7]. This suggests that EIH involves – in addition to peripheral or segmental pain modulatory processes – a systemic component of central descending inhibition, which is reflected in EIH effects at non-exercising muscles.

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The existence of EIH in subjects with chronic pain is still controversial [1]. Clinically, it is well known that some patients report increasing pain after exercise. This is in agreement with studies observing that a subset of patients with chronic pain demonstrates impaired EIH responses [2, 8–10], or even hyperalgesia after exercise [11] compared with pain-free controls.

A reason for EIH being reduced when pain is present could be related to aberrant conditioned pain modulation (CPM). CPM delineates a decrease in pain sensitivity after a painful stimulus. As CPM is observable at stimulated and non-stimulated body parts, it has been suggested that it mainly operates on a systemic level and reflects descending pain inhibition [12]. More consistently than attenuated EIH, reduced CPM responses characterize patients with chronic pain [13, 14]. Taken together, these observations have led to the question whether EIH and CPM share underlying mechanisms. Accordingly, small positive correlations were reported between EIH and CPM in pain-free subjects [15–17] and subjects with musculoskeletal pain [18]. These findings imply that EIH and CPM may be related to each other on a systemic level [19].

Furthermore, it has been proposed before that CPM might be exhaustible, meaning that once a certain amount of descending inhibition is reached, no further inhibition is possible [20–23]. In chronic pain, the CPM system might be constantly active due to clinical pain, which is reflected in reduced CPM responses. Likewise, EIH responses might be reduced in chronic pain because they vary depending on pre-existing activation of the CPM system. A recent study supports this hypothesis by demonstrating that patients with knee osteoarthritis, who showed no CPM response, also showed hyperalgesia after exercise at remote assessment sites [24].

By contrast, however, there are also studies suggesting that EIH and CPM affect pain sensitivity independently [25], showing no correlations between EIH and CPM responses [3, 20, 26]. Still, studies testing direct interactions between EIH and CPM in pain-free participants are rare. However, such studies might contribute to better understand EIH in chronic pain, as it is possibly related to aberrant CPM. Thus, the aim of this study was to investigate EIH responses at exercising and non-exercising body parts after CPM was activated in pain-free subjects. We hypothesized that EIH would be reduced when exercise was performed immediately after activation of CPM compared to EIH after a control condition. Furthermore, we expected that CPM activation would affect the subsequent EIH response at non-exercising muscles to a greater extent than at the exercising muscles.

2 Materials and methods

2.1 Subjects

Thirty-one healthy subjects (age: 27.7 ± 9.8 years; 15 women) participated in this study. Subjects were recruited via personal contacts of KN as a part of her medical dissertation. All subjects were naive to experimental pain testing. None of the included subjects suffered from neurological, psychological or cardiovascular diseases or had experienced pain during the weeks prior to participation. Before the experiment, participants were asked to refrain from any pain medication and vigorous exercise for 24 h, and caffeine for 4 h. The study was conducted in accordance with the Declaration of Helsinki and approved by ethical review board of the psychological faculty at the Ruhr-University of Bochum (application #242). All subjects gave written informed consent before participating in the study.

2.2 Protocol

In this repeated-measures within-subject study design, all participants completed two experimental sessions separated by 1–2 weeks. However, due to scheduling conflicts, in one subject the sessions were separated by 6 weeks. In each of the two sessions, subjects performed an aerobic bicycling exercise with a duration of 15 min, preceded by either a cold pressor task (CPT) or a duration-matched control condition (Fig. 1). The order of the sessions was randomized and counterbalanced. Pressure pain thresholds (PPTs) were used to assess pain sensitivity before and after the control condition, the cold pressor task and the bicycling exercise.

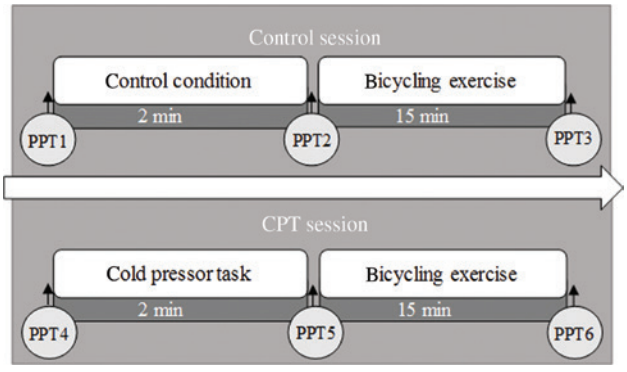

Fig. 1: Schematic illustration of the experimental protocol performed during the two experimental sessions. Pressure pain thresholds (PPTs) were assessed on three assessment sites (hand, back and leg) before and immediately after cold pressor task, a control condition, and exercise.

First, all subjects were introduced to the protocol for assessment of PPTs, where they were told that the experimenter would slowly increase the pressure on the respective muscles. Subjects were instructed to say "stop" as soon as the perception of pressure changed into the first perception of pain. The experimenter emphasized that the PPT was not a measure of how much pain they could tolerate. After the instruction subjects completed a practice trial at the middle of the thenar eminence of the right hand to ensure that they understood the procedure. In each session, subjects were familiarized with the PPT procedure 5 min before the first assessment.

2.3 Assessment of pressure pain thresholds

PPTs were assessed at 1) the thenar eminence of the non-dominant hand, 2) the lower back at the non-dominant side approximately 2 cm adjacent to the spine at the level of the 3rd lumbar vertebra, and 3) the middle of the non-dominant biceps femoris muscle. PPTs were assessed with a handheld algometer (Somedic Sales AB, Horby, Sweden). The stimulation area was 1 cm^2 and the rate of pressure increase was kept to approximately 50 kPa/s. PPTs were assessed with the subject lying in prone position on the examination table and the order of assessment was counterbalanced and randomized. Two PPT assessments were completed for each assessment site and the mean of these was used for analysis [27]. Twenty-second intervals between assessments were maintained. All assessments were performed by female assessors (KN and HG).

2.4 Bicycling exercise

The bicycling exercise lasted for 15 min. Prior to the exercise, the age-related target heart rate was determined for each subject. Based on a previously used aerobic exercise protocol demonstrating robust EIH [16], a target heart rate of approximately 86% of the maximal age-related heart rate was chosen. This target heart rate corresponds to 75% VO_{2max} [28]. Subjects performed the exercise on a stationary ergometer with a build in heart rate monitor using a heart rate belt that was strapped around the chest (Corival cpet, Lode, Groningen, the Netherlands). The subjects were asked to maintain a pedal rate of 70 rounds per minute throughout the 15 min.

The first 2 min of the exercise were used as a warm-up. After the 2 min, resistance was increased over the next 3 min until the target heart rate was reached. The heart rate was monitored continuously and resistance was altered in order to maintain the target heart rate if needed. Thirty seconds before completion of the exercise, subjects were asked to rate their level of perceived exertion due to the exercise (Borg 6–20 RPE scale [29]).

2.5 Cold pressor task and the control condition

Subjects performed the 2 min cold pressor task (CPT) in a sitting position. Subjects were asked to immerse their dominant hand to 2 cm above the wrist into an in-house custom made water bath with circulating ice water. The temperature was kept constant at approximately 2 °C. The instruction was to not move the hand or the joints of the fingers while performing the cold pressor task. Just before removing the hand, subjects were asked to rate the pain intensity caused by the ice water bath on a numerical rating scale ranging from 0 to 10, with 0 indicating no pain and 10 indicating the worst pain imaginable.

For the control condition, subjects were instructed to relax comfortably in sitting position for 2 min in an undisturbed room, which was the same in which the CPT was performed.

2.6 Statistical analysis

All statistical analyses were performed using SPSS (Version 25, IBM, Armonk, NY, USA). Results are presented as means and standard deviations, unless otherwise specified. To assess potential differences in PPT values at baseline (PPT1 vs. PPT4, see Fig. 1), a two-way repeated measures analysis of variance (rm-ANOVA) was conducted with the *assessment site* (hand, back and leg) and *session* (control session, CPT session) as within-subject factors.

In order to validate the CPM protocol in a first step, a three-way rm-ANOVA with the within-subject factors *time* (pre, post), *session* (CPT session, control session) and *assessment site* (hand, back, leg) was performed. This analysis was used to determine whether the activation of CPM was successful, i.e. whether the cold pressor task induced a significant increase in PPTs compared to the control condition at each assessment site.

In the main analysis, the effect of a preceding CPT vs. control condition on the subsequent EIH response was analyzed using a three-way rm-ANOVA with the within-subject factors *time* (pre, post exercise), *session* (CPT session, control session) and *assessment site* (hand, back, leg).

Greenhouse-Geisser corrections were used in case of sphericity violations and p-values less than 0.05 were

considered significant. Partial η^2 (η_p^2) was used to estimate the effect size of main effects or interactions in the rm-ANOVAs. In case of significant factors or interactions in the rm-ANOVAs, *post-hoc* comparisons incorporating Bonferroni-corrections for the multiple comparisons were performed with paired *t*-tests. Cohen's d was calculated in order to estimate the effect sizes of pairwise comparisons.

Furthermore, absolute change scores were calculated in order to quantify the EIH responses following the control and the CPT condition, as well as to quantify the CPT alone. The EIH response after the control condition was calculated as PPT3 minus PPT2; the EIH response after the CPT condition was calculated as PPT6 minus PPT5. The CPM response was calculated as PPT5 minus PPT4 (see Fig. 1).

Finally, bivariate correlation coefficients were used to determine the relationship between the EIH response in both conditions and the CPM response, for each assessment site. In case of normally distributed change scores, Pearson's r was computed, and in case of non-normally distributed change scores, Spearman's rho was computed.

3 Results

3.1 Baseline characteristics

All subjects completed both sessions. At baseline, a significant main effect of *assessment site* was found ($F(2, 58) = 24.91$, $p < 0.001$, $\eta_p^2 = 0.46$), with lower PPTs at the hand (302 ± 103 kPa) than at the back (391 ± 178 kPa, $p < 0.001$), and at the leg (414 ± 177 kPa, $p < 0.001$). There further was a trend towards a significant difference in baseline PPTs between *sessions* ($F(1, 30) = 3.31$, $p = 0.086$, $\eta_p^2 = 0.10$) with higher PPTs in the CPT session. Table 1 shows the raw mean PPTs and SD across time, conditions and assessment sites.

3.2 Conditioned pain modulation

The mean pain intensity reported during cold pressor task was 7.5 ± 1.7. Table 1 shows the raw mean PPTs and SD across time, conditions and assessment sites. Results of the three-way rm-ANOVA on PPTs with the within-subject factors *time* (pre, post), *session* (CPT session, control session) and *assessment site* (hand, back, leg) showed a significant *time* × *session* × *assessment site* interaction (Fig. 2; $F(2, 60) = 6.78$, $p = 0.002$, $\eta_p^2 = 0.18$).

Post-hoc tests with a Bonferroni-adjusted α level of $\alpha = 0.008$ for six comparisons showed no significant change in PPTs at the hand ($p = 0.022$, Cohen's d = 0.15), the back ($p = 0.700$, Cohen's d = 0.02), nor at the leg ($p = 0.892$, Cohen's d = 0.01) after the control condition compared with before the control condition. After the CPT, there was a significant increase compared to before the CPT in PPTs at the hand ($p < 0.001$, Cohen's d = 0.28), and at the back ($p < 0.001$, Cohen's d = 0.31). However, there was no significant increase in PPTs at the leg ($p = 0.344$, Cohen's d = 0.07).

3.3 Exercise-induced hypoalgesia in control session and cold pressor task session

Subjects reported a mean perceived exertion after the bicycling exercise in both conditions of 15.87 ± 1.23 on the Borg 6-20 RPE scale. The perceived exertion due to exercise in

Table 1: Means (M) and standard deviations (SD) of pressure pain thresholds (PPTS), at baseline, after CPT or control condition and after exercise across conditions and assessment sites.

Session	Assessment site	Baseline	After control condition or CPT	After exercise
				M (SD)
		PPT1	PPT2	PPT3
Control	Hand	287.68 (107.47)	272.13 (101.71)	312.31 (99.76)
	Back	377.95 (179.11)	380.73 (184.12)	444.50 (210.59)
	Leg	388.63 (169.67)	387.18 (175.86)	440.77 (187.50)
		PPT4	PPT5	PPT6
CPT	Hand	315.77 (109.63)	373.66 (116.48)	332.73 (103.20)
	Back	404.87 (201.57)	465.31 (184.44)	457.56 (197.71)
	Leg	439.37 (197.45)	452.50 (171.25)	465.44 (216.95)

The numerations (PPT1-PP6) correspond to the schematic experimental protocol in Fig. 1.

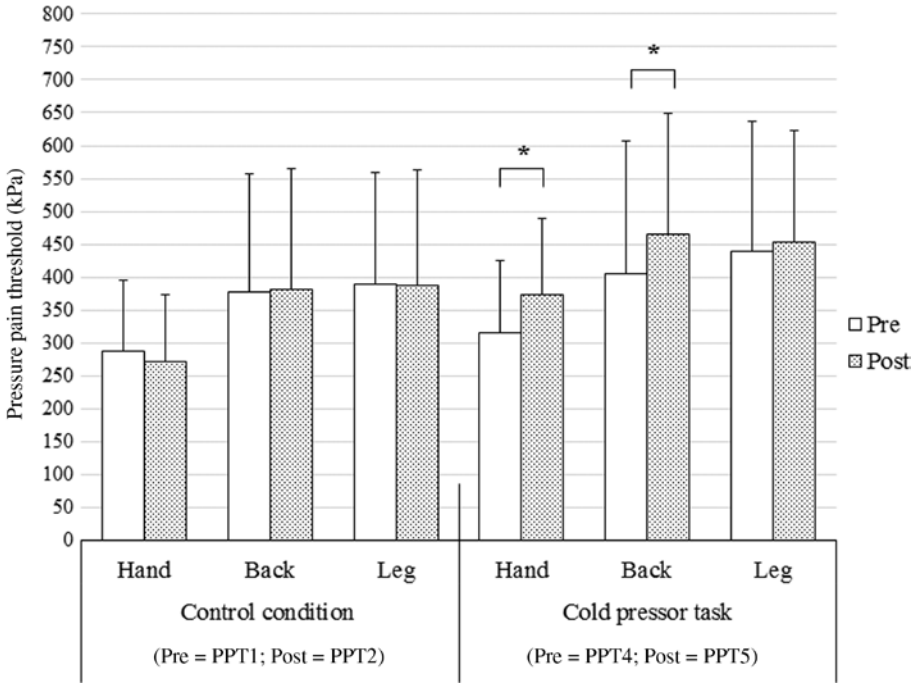

Fig. 2: Mean (±SD) pressure pain threshold (PPT) recorded at three assessment sites (hand, back and leg) before and immediately after a 2 min control condition and a 2 min cold pressor task. Significantly different between pre and post (*$p < 0.001$).

the CPT condition (15.81 ± 1.42) was comparable to the perceived exertion during exercise in the control condition (15.94 ± 1.36; $p = 0.587$, Cohen's d = 0.09).

Table 1 shows the raw mean PPTs and standard deviations (SDs) across time, session and assessment site. The three-way rm-ANOVA showed an interaction between

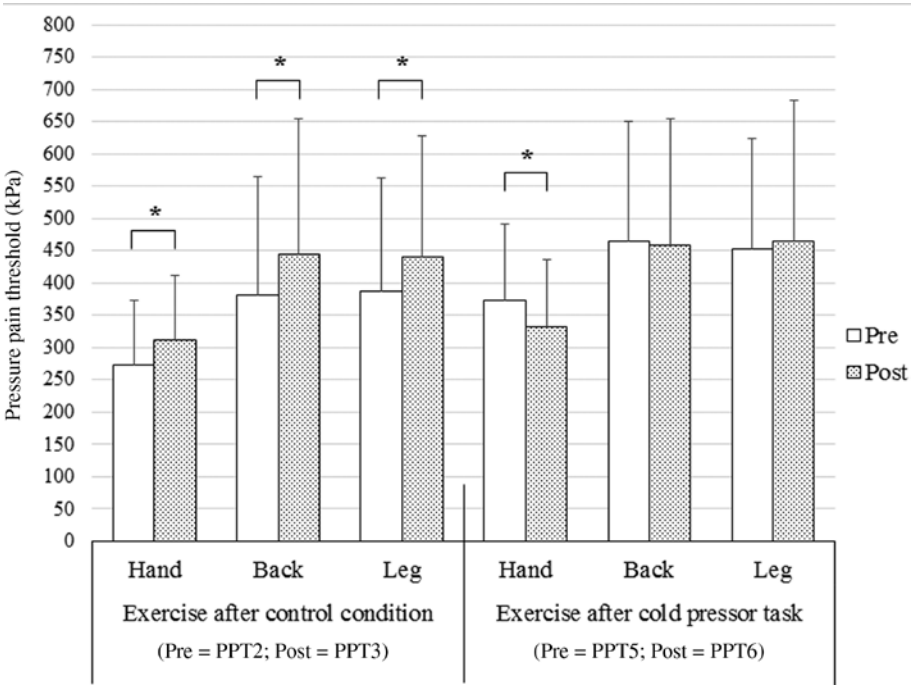

Fig. 3: Mean (±SD) pressure pain threshold (PPT) recorded at three assessment sites (hand, back and leg) after bicycling in the CPT session and the control session. Significantly different between pre and post (*$p < 0.001$).

Table 2: Means (M) and standard deviations (SD) of absolute change scores, before and after CPT (CPM response) as well as before and after exercise in the control condition (EIH response in the control condition) and the CPT condition (EIH response in the CPT condition) at each assessment site.

	CPM response	EIH response in control condition			EIH response in CPT condition		
		Hand	Back	Leg	Hand	Back	Leg
	M (SD)	40.18 (42.49)	63.77 (70.15)	53.60 (67.98)	−40.94 (45.77)	−7.74 (56.02)	12.94 (84.56)
Hand	57.89 (54.81)	r = 0.37[b]	–	–	r = −0.50[a]	–	–
Back	60.44 (73.47)	–	rho = −0.09	–	–	rho = −0.37[b]	–
Leg	13.13 (76.03)	–	–	rho = 0.25	–	–	rho = −0.35[c]

Significant correlation coefficients ([a]$p < 0.001$; [b]$p < 0.05$; [c]$p < 0.100$). The correlation coefficients between the CPM responses and the EIH responses in the control condition or CPT condition, respectively, are displayed for each assessment site (hand, back, leg).

the factors *time* × *condition* ($F(1, 30) = 43.61$, $p < 0.001$, $\eta_p^2 = 0.59$). Bonferroni-corrected *post-hoc* tests with an adjusted α level of $\alpha = 0.025$ for two comparisons indicated that in the control condition, there was a significant increase in PPTs after exercise ($p < 0.001$, Cohen's $d = 0.34$), while there was no significant change in PPTs after exercise in the CPT condition ($p = 0.125$, Cohen's $d = 0.07$).

Furthermore, there was a trend towards a significant *time* × *condition* × *assessment site* interaction ($F(1.54, 46.06) = 2.72$, $p = 0.089$, $\eta_p^2 = 0.083$). Subsequent analyses, with a Bonferroni-corrected α level of $\alpha = 0.008$ for six comparisons, indicated that in the control condition, an increase in PPTs after exercise occurred at each assessment site (hand: $p < 0.001$, Cohen's $d = 0.40$; back: $p < 0.001$, Cohen's $d = 0.29$; leg: $p < 0.001$, Cohen's $d = 0.29$; Fig. 3). By contrast, in the CPT condition, there was a significant decline in PPTs after exercise at the hand ($p < 0.001$, Cohen's $d = 0.36$), while there was no significant change in PPTs at the back ($p = 0.448$, Cohen's $d = 0.04$), nor at the leg ($p = 0.401$, Cohen's $d = 0.06$, Fig. 3).

3.4 EIH change scores and correlations between the CPM and EIH responses

Table 2 shows the EIH absolute change scores across conditions and assessment sites, as well as CPM absolute change scores at each site. Furthermore, the correlation coefficients between EIH responses in both conditions and the CPM responses at each assessment site are displayed.

Regarding the correlation between the EIH response in the control condition and the CPM response, there was a small positive correlation at the hand ($r = 0.37$, $p = 0.043$), but no significant correlations were seen at the back ($rho = -0.09$, $p = 0.641$), nor at the leg ($rho = 0.25$, $p = 0.179$).

In contrast, there was a moderate negative correlation between the CPM change score and the EIH change score following the CPT condition at the hand ($r = -0.50$, $p = 0.004$). At the back, there was a small negative but significant correlation ($r = -0.37$, $p = 0.036$). At the leg, there was a borderline significant negative correlation ($r = -0.35$, $p = 0.054$).

4 Discussion

4.1 Attenuated EIH response after cold pressor task (CPT)

This study sought to compare exercise-induced hypoalgesia (EIH) with and without preceding activation of conditioned pain modulation (CPM). Our data suggest that the EIH and CPM protocols in the present study, for the most part, induced the expected hypoalgesic responses when performed independently. In line with our first hypothesis, an attenuated EIH response occurred after activation of CPM compared to the EIH response without preceding activation of CPM. Previous research reported small positive correlations between independently assessed EIH and CPM responses [15, 16, 19], suggesting shared mechanisms. A similar correlation also emerged in the present study. Moreover, the activation of the CPM system affected the subsequent EIH response, implying that the EIH and CPM protocols have shared mechanisms.

Furthermore, the finding that EIH was attenuated after activation of the CPM system could suggest that the pain inhibitory systems was exhausted. Previous research has given some evidence for this notion. For instance, Valencia and colleagues reported that when a CPM protocol was performed twice within one experimental session, the second CPM response was reduced [30]. Furthermore, Arendt-Nielsen and colleagues observed a reduced CPM response when two concomitant conditioning stimuli

were applied compared to one conditioning stimulus alone [21]. Moreover, studies reported a reduction in the CPM response after exercise [20, 31], while in one study, this was only the case in individuals who showed systemic EIH [31]. In sum, these findings suggest that EIH and CPM protocols may target similar descending pain inhibitory mechanisms in an exhaustive manner.

Several observations regarding the mechanisms of EIH and CPM support this assumption. Both have been related to activation changes in similar cerebral structures associated with pain inhibition [32–34]; this coincides with the observation that both EIH and CPM show systemic effects [3, 5, 12]. The periaqueductal gray (PAG) is an opioid-sensitive midbrain structure which plays a pivotal role in descending pain inhibition [35, 36]. Cutaneous cold pain, as induced by CPT, activates thermal ascending pathways projecting to the PAG [21, 37], and CPM has been related to activity alterations in the PAG [34, 38, 39]. Similarly, nociceptive muscle afferents project to the PAG via the dorsal horn [37], and activity changes in the PAG have been related to EIH [32]. Therefore, opiodergic processes triggered in the PAG may be a candidate for descending pain inhibition that is common to both EIH and CPM.

Furthermore, the present study suggests that EIH and CPM may be exhaustible. Another study provides a further hint to opioidergic involvement in exhausted pain inhibition. Ram and colleagues [40] reported that a continuous intake of opioids resulted in reduced CPM responses in patients with chronic pain, proposing a mechanism for opioid-induced hyperalgesia. Taken together with this finding, the notion of exhaustibility emerging in the present study could aid to explain deficient descending pain inhibition in chronic pain. It has been proposed that a reduced capacity for pain inhibition is a precursor, not a result of chronic pain [13, 41]. However, a study by Kosek and Ordeberg [42] reported that patients with osteoarthritis showed reduced CPM in a painful state, but that CPM responses recovered in patients who experienced pain relief after surgery. Hence, in some individuals with chronic pain, descending pain inhibition may be in an exhausted state, possibly due to constant stimulation by nociceptive afferents that trigger the CPM system. A recent study by Fingleton and colleagues [24] reported that patients with knee ostheoarthritis, who had an impaired CPM response, showed a systemic hyperalgesic response after an isometric exercise. They concluded that in some patients with chronic pain, there might be a reduced capacity for descending pain inhibition, leading to both reduced CPM and EIH responses.

4.2 Site-specific attenuation of EIH after CPM

Unlike at the non-exercising body parts, PPTs did not decrease at the exercising body parts after exercise in the CPT condition, but remained stable. As the CPM response is rather short-living, not lasting longer than a few minutes after termination of the conditioning stimulus [3, 12], it seems like the exercise may have stabilized the CPM response which would otherwise have declined. Possibly, additional peripheral or segmental sources of pain inhibition, triggered by exercise, may have caused this effect. This is in accordance with previous research indicating that the EIH response is greater at exercising body parts, compared to non-exercising body parts [3]. This assumption is supported by another result of the Fingleton study [24]. They reported that CPM non-responders showed decreases in PPTs after exercise at non-exercising body parts, while there was no change in PPTs after exercise at exercising body parts. This result is somewhat comparable to the current findings, assuming that patients who are CPM non-responders have an exhausted capacity for systemic, descending pain inhibition.

Taken together, these finding suggest that in the exercising body parts, additional peripheral processes may undermine an otherwise stronger relationship between EIH and CPM. The finding that there were higher correlations between EIH and CPM at the remote assessment site than at the assessment sites at the exercising body parts, further corroborates this assumption. Stolzman and colleagues [19] have reported similar site-specific correlations of EIH and CPM, while another study did not observe site-specific differences in the correlations [16]. Therefore, future studies should investigate the relationship between EIH and CPM in a site-specific manner.

4.3 Conditioned pain modulation

After the CPT, there was an increase in PPTs at the hand and at the back, indicating that CPM was successfully activated. The amount of this increase was comparable at the hand and at the back, which is in accordance to the existing literature suggesting a systemic CPM effect [12]. However, no change in PPTs was measurable at the leg. This is an unexpected finding and could be related to the sequential methodology of the CPM protocol: unlike in many CPM protocols [43], the test stimulus, i.e. the PPT procedure, was applied immediately after, and not during the conditioning stimulus, i.e. the CPT. However,

guidelines for the practice of CPM assessment suggest to measure the CPM response after termination of the conditioning stimulus [12, 44]. Furthermore, there was an observable effect of the CPT on EIH at the leg compared to the control condition, which suggests that activation of CPM may have been successful nonetheless.

4.4 Limitations

Some methodological limitations should be considered when interpreting the results. First, a quiet rest condition after termination of the CPT without further stimulation by exercise, would allow more definite interpretations about the effect of CPM on the subsequent EIH response. Without a quiet rest control condition before exercise, our interpretations, especially regarding site-specific effects of CPM on EIH, remain somewhat speculative.

Furthermore, ceiling effects in the PPTs may account for the observation of no change or a decrease in pain sensitivity after exercise in the CPT condition; the PPTs before exercise in the CPT condition were elevated as a result of the immediately preceding CPT compared to the control condition. This account implies that PPTs cannot further increase after reaching a certain maximum, which may explain the present findings without an involvement of shared, exhaustible mechanisms [31]. A ceiling may result from hand algometry methodology: as PPTs increase, they progressively depend on the experimenter's manual strength to exert pressure on the respective muscles. However, this explanation seems improbable, as throughout the experiment, PPTs at the hand were significantly lower than at the back and at the leg. In contrast, a decrease in PPTs after exercise in the CPT condition only occurred at the hand, while at the back and at the leg, PPTs remained stable. Ceiling effects in PPTs due to limits in the experimenter's strength to exert pressure would imply the opposite, namely that the most pronounced ceiling effects would occur at those sites where the highest PPTs are assessed.

A third point of concern is that there was a trend towards higher baseline PPTs in the CPT session than in the control session. A systematic influence of habituation to the PPT procedure seems improbable, as the order of the sessions was randomized. However, there may have been effects of expectations, as the CPT was already visible at the time of assessment of baseline PPTs. To adjust these differences in future studies, a sham CPT should be incorporated as a control condition for the CPT in favor of quiet rest.

4.5 Conclusions and clinical implications

The current study is the first to study the direct effect of a painful stimulus on the subsequent EIH response in pain-free individuals. The results implicate that the systemic hypoalgesic effect of exercise is attenuated if CPM is activated before. If CPM responses in patients with chronic pain are reduced because the processes underlying the CPM response are continuously active in chronic pain, this may imply that these patients may not benefit from exercise with regard to acute pain reduction. This further supports the recent claim that the capacity for descending pain, as indicated by the CPM response, should be assessed in patients with chronic pain [13, 45, 46]. Specifically, the individual magnitude of the CPM response may aid clinicians to make individual treatment decisions as to whether exercise, or which kind of exercise will help to acutely reduce pain sensitivity and if counter-effects are to be expected.

Authors' statements
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Informed consent: All subjects gave written informed consent before participating in the study.
Ethical approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the ethical review board of the psychological faculty at the Ruhr-University of Bochum (application #242).

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