

Effects of fitness level and exercise intensity on pain and mood responses

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Abstract

Background: The phenomenon of exercise-induced hypoalgesia and concomitant mood changes is well-established. How exercise-induced hypoalgesia and affective responses are shaped by the intensity of an acute exercise bout and individual fitness levels is as yet not well-understood. This study investigates whether heat pain threshold (PTh), pain tolerance (PTol) and affective parameters are modulated by the intensity of an acute exercise bout and/or individuals' fitness level. Stronger analgesic responses are hypothesized after high-intensity exercise in physically fitter subjects, possibly in sync with concomitant mood changes.

Methods: Thirty-three healthy men were recruited (sedentary: $N = 17$ or recreational: $N = 14$; mean age: 25.3 ± 4.4 years). After a fitness assessment on a cycle ergometer, subjects underwent three experimental conditions on separate days: high (20 min exercise 20% above lactate threshold), low (20 min exercise 20% below lactate threshold) and control (seated rest). Before and after each intervention Positive and Negative Affect Schedule, PTh and PTol (cold water immersion test) were assessed.

Results: Results indicate an increase of the Positive Affect Scale (high: 26.7 ± 9.0 vs. 32.9 ± 7.1 , $p < .001$; low: 26.3 ± 7.2 vs. 32.0 ± 7.0 , $p < .001$) and PTh (high: $45.1 \pm 3.1^\circ\text{C}$ vs. $46.0 \pm 2.6^\circ\text{C}$, $p = .003$; low: $45.4 \pm 2.7^\circ\text{C}$ vs. $45.9 \pm 2.6^\circ\text{C}$, $p = .012$) after both exercise conditions. In an exploratory analysis, PTol significantly increased only after the high exercise condition (51.2 ± 33.7 s vs. 72.4 ± 64.0 s, $p = .045$). Fitness level was positively correlated with the increase in PTol from pre to post high-intensity exercise ($r = .59$, p (one-tailed) = .002).

Conclusion: Exercise-induced hypoalgesia depends on exercise intensity and appears to be influenced by individual fitness status, independent of mood responses.

Significance: Antinociceptive effects can be elicited by physical exercise and have been extensively investigated in the literature. However, the relation between exercise intensity, fitness status, and the degree of antinociception is not well-understood. This randomized intervention provides novel evidence that antinociceptive effects indeed depend on exercise intensity, but also on general fitness status. Data extend the existing literature by highlighting aspects of exercise

behaviour that promote antinociception. Effects do not simply mirror positive affective responses induced by exercise, hence, indicating partially distinct underlying mechanisms.

1 | INTRODUCTION

Acute exercise bouts lead to a temporary reduction in pain sensitivity, a phenomenon, referred to as exercise-induced hypoalgesia (EIH) (Koltyn, 2000; Koltyn, Brellenthin, Cook, Sehgal, & Hillard, 2014; Naugle, Fillingim, & Riley, 2012), that can be observed in different pain models, e.g. electrical, thermal, pressure and ischaemic pain (Wonders & Drury, 2011). EIH manifests as local and/or remote changes in heat or cold pain thresholds during and/or following acute exercise bouts (Droste, Greenlee, Schreck, & Roskamm, 1991; Pertovaara, Huopaniemi, Virtanen, & Johansson, 1984). A majority of studies investigating EIH applied (isometric) resistance exercise, but aerobic endurance exercise is suggested to be particularly effective (Koltyn, 2002) with a minimal duration of at least 10 min (Jeukendrup, Craig, & Hawley, 2000; Koltyn et al., 2014). Importantly, there are indications that EIH depends on exercise intensity, with a higher analgesic response for greater physical efforts (Kodesh & Weissman-Fogel, 2014; Koltyn, 2002; Koltyn, Garvin, Gardiner, & Nelson, 1996). Previous studies and reviews recommend exercise intensities of 50%–75% $\text{VO}_{2\text{peak}}$ or a workload of >220 W (Hoffman et al., 2004; Koltyn, 2002) to elicit EIH.

As yet, experimental evidence on the relation between the intensity of endurance exercise and the occurrence of EIH is still limited, in particular regarding randomized experimental protocols. One study tested aerobic exercise at two randomized submaximal intensities (i.e. $\pm 10\%$ of heart rate at lactate threshold): a significant increase of heat pain threshold (PTh) ratings was found in both conditions, independent of the submaximal exercise intensity (Wonders & Drury, 2011). Work by Hoffman et al. (2004) tested pain ratings on a visual analogue scale (VAS) at 10 s intervals during 2-min pressure pain exposure before and after a cycling intervention. There was only a significant pain reduction after 75% $\text{VO}_{2\text{max}}$ exercise of 30 min duration, when compared to shorter (10 min at 75% $\text{VO}_{2\text{max}}$) and less intense (30 min 50% $\text{VO}_{2\text{max}}$) exercise bouts (Hoffman et al., 2004). Dose response effects (comparisons between: [a] stationary cycling at 70% heart rate reserve (HRR), [b] stationary cycling at 50% HRR, or [c] quiet rest [control]) were also studied by Naugle, Naugle, Fillingim, Samuels, and Riley (2014), probing pressure pain thresholds, suprathreshold pressure pain, continuous heat pain and repetitive pulse heat pain in healthy young adults. Both exercise conditions, the vigorous (70% HRR) and the

moderate-intensity exercise (50% HRR) conditions reduced pain ratings associated with static continuous heat stimuli and repetitive heat pulse stimuli on a VAS scale. Importantly, the reported effects were larger in the vigorous (70% HRR) condition, which was shown to also increase pressure pain thresholds. None of the two exercise intensities, however, had an effect on the suprathreshold pressure pain ratings, suggesting differential effects of exercise for different pain systems. These results were supported by Vaegter, Handberg, and Graven-Nielsen (2014), who investigated the effects of cycling at low (50% $\text{VO}_{2\text{max}}$) and high intensity (75% $\text{VO}_{2\text{max}}$) on pressure pain thresholds. Both exercise intensities resulted in EIH, whereas the high-intensity exercise condition resulted in larger EIH effects than the low-intensity exercise condition.

How exercise-induced decreases in pain thresholds and/or subjective pain assessed by VAS ratings (see previous paragraph) translate into improved pain tolerance (PTol), which is defined as the ability to sustain noxious input as long as possible, awaits to be explored in similarly designed experimental procedures. The cold pressor task is an established experimental procedure for quantifying PTol via the measurement of the time in seconds, a subject can sustain cold pain after immersion of the hand in ice-cold water. The resulting measure of cold pressor is pain sustainability time, rather than a subjective rating of pain intensity, i.e. the ability to cope with pain as long as possible in a physiologically meaningful situation. Increase in PTol times in the cold pressor task were described after 6 min of acute sub-maximal exercise (Pokhrel et al., 2013). Although, no change in PTol time was observed in habitual runners as compared to normally active controls (Janal, Glusman, Kuhl, & Clark, 1994), an interesting study by Geva and Defrin was able to describe longer pain sustainability in middle-aged endurance athletes compared to sedentary control subjects (Geva & Defrin, 2013), suggesting an influence of fitness on PTol. The only study comparing the effects of aerobic exercise at different intensities (low and high) on pain tolerance reported increased pressure pain tolerance after both exercise conditions, without a significant difference between low and high intensity (Vaegter, Handberg, & Graven-Nielsen, 2015).

To draw on and extend this previous research, our experimental study had a specific focus on PTol as a behaviourally relevant parameter of pain (together with PTh and affective parameters), and to examine the effects of two different

exercise intensities thereupon. Moreover, we wanted to assess how the EIH response is affected by the individuals' fitness level. We hypothesized the strongest analgesic response to occur in more trained subjects during high-intensity exercise and concomitant affective responses to be correlated with the antinociceptive effects.

2 | METHODS

2.1 | Participants

A total of 33 healthy sedentary and recreationally active men were recruited for the study. Two subjects needed to be excluded due to a lack of German language skills, resulting in a final sample size of $N = 31$ ($N = 17$ sedentary and $N = 14$ recreational). Inclusion criteria were an age between 18 and 40 years and either a sedentary (no exercise at all or no exercise on a regular basis) or recreational leisure behaviour, while latter had to have cycling experiences of at least two years (training of at least 3 days/week for approx. 60 min). Group affiliation was based on a self-rating activity questionnaire and objective classification of peak power output (PPO) in an exercise test (Jeukendrup et al., 2000). According to the Edinburgh Handedness Inventory (Oldfield, 1971), $N = 30$ subjects were right handed/right dominant (mean laterality quotient 76.41 ± 16.33). For one subject, accidentally, no Edinburgh Handedness Inventory value was performed. The participants were fully informed

TABLE 1 Participants' characteristics

	Recreational ($N = 14$)	Sedentary ($N = 17$)
	$M \pm SD$	$M \pm SD$
Age (years)	26.1 ± 4.3	24.7 ± 4.4
Height (cm)	182.0 ± 6.6	182.2 ± 6.7
Body mass (kg)	78.5 ± 9.7	81.6 ± 17.5
BMI	23.7 ± 2.4	24.6 ± 4.8
Exercise/week (hours)*	4.6 ± 1.6^a	0.1 ± 0.3
PPO (W)*	268 ± 32	225 ± 62
PO at LT (W)*	156 ± 26	89 ± 29
BDI	1.8 ± 2.5	2.4 ± 2.9
STAI trait	29.9 ± 5.4	33.3 ± 6.2^b
EHI	79.1 ± 16.6	74.0 ± 16.2^c
GVT	109.4 ± 8.1	106.1 ± 11.4

Abbreviations: BMI, body mass index; BDI, Becks Depression Inventory; EHI, Edinburgh Handedness Inventory; GVT, German vocabulary test; PPO, peak power output; PO at LT, power output at lactate threshold; STAI, state trait anxiety inventory.

*Significant group difference $p \leq .001$; a: $N = 12$ due to missing values, b: $N = 15$ due to missing values, c: $N = 16$ due to missing values.

of the purposes and risks associated with the study design before providing written, informed consent. Participants' characteristics are summarized in Table 1. The study conformed to current local guidelines and the Declaration of Helsinki and was approved by the Clinical University Bonn Ethics Advisory Committee (Lfd. 377/16).

2.2 | General procedures

The study consisted of five testing days that were accomplished within a minimum of two weeks and a maximum of four weeks. On the first day participants were asked to complete a set of psychiatric questionnaires to ensure participants mental health: Mini International Neuropsychiatric Interview, German Version 5.0.0 (MINI) (Sheehan et al., 1998), State and Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) and Becks Depression Inventory (BDI) (Hautzinger, Bailer, Worall, & Keller, 1994). Participants also underwent a medical healthcare check involving a short anamnestic questionnaire, an auscultation of the lung and heart, and a resting electro cardiogram to exclude major physical health risks for subsequent exercise tests and interventions.

Endurance performance and lactate threshold (LT) were determined on the second day within a graded exercise test (GXT) until volitional exhaustion on a cycle ergometer. The third, fourth and fifth day followed a similar structure (Figure 1) but the order of intervention (high, low, control) was counterbalanced and randomly assigned. First, PTh and PTol (cold pressor task and visual analogue scale, VAS) were determined. To minimize any influences of the pain measurements on the acquisition of the mood questionnaire, subjects had a 60 min resting period between the pain measurement and the acquisition of the Positive and Negative Affect Schedule (PANAS) (Tausch, Krohne, Egloff, & Kohlmann, 1996). The PANAS is a self-report questionnaire that consists of a positive and a negative scale. Each scale includes 10-items for affect and each item is rated on a 5-point scale of 1 (not at all) to 5 (very much). Afterwards, participants completed one of the three interventions, followed again by ratings of mood, measurements of PTh and PTol in the same order as pre-intervention.

2.3 | Heat pain threshold determination

Measurements of PTh before and after the interventions were performed using a MEDOC-TSA II thermal pain stimulation device (Medoc, Ramat-Yishai, Israel). The "ascending methods of limits" option with a temperature increase of 0.5°C per second was used, starting at a temperature of 32°C . To this end, a 9 cm^2 contact thermode was placed at the non-dominant left volar forearm 2 cm below

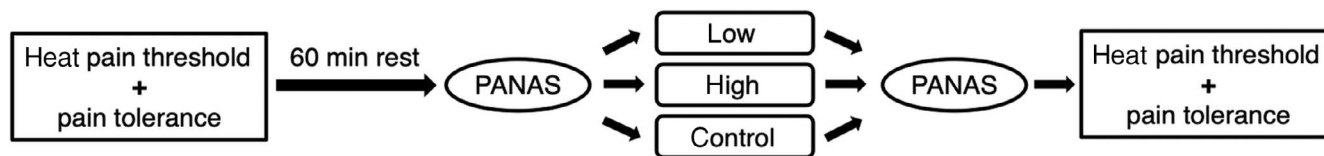


FIGURE 1 Illustration of the experimental procedure performed on three testing days

the arm bend. Subjects were instructed to press a button with their right hand as soon as the thermal heat perception was accompanied for the first time by a painful sensation. Three test trials were followed by five main trials for the PTh assessments. The test trials allowed the participants to familiarize with the protocol and were not included in the data analysis. The five main trials were averaged to determine the respective PTh.

2.4 | Pain tolerance determination

For the assessment of PTol, subjects were asked to place their left hand in 2°C cold water using a commercially available refrigerated circulating bath (temperature stability $\pm 0.01^\circ\text{C}$; AD15R-30-V12V, VWR International, Pennsylvania, USA). Subjects were instructed to retrieve their hand from the water as soon as the perceived pain was no longer tolerable. The elapsed time was measured. During the test, subjects were requested to indicate the perceived pain on VAS (pain intensity) with their right hand every 20 s to validate the PTol measurements. For safety reasons the maximal time of testing was set at 4 min.

2.5 | Exercise testing

Prior to the exercise tests, body height and body mass were measured and recorded. A GXT was completed on an electronically braked cycle ergometer (Electronic premium 8i, Daum Electronic GmbH®, Fuerth, Germany). Subsequent to a low-intensity warm-up phase (5 min) at 30 W for sedentary participants and at 50 W for recreationally active participants, the GXT started with an initial workload of 30 W for untrained and 60 W for recreationally active participants and was increased every 5 min in 30 W increments until volitional exhaustion. These different starting workloads were used to account for the different level of fitness of the two participant groups.

Heart rate (HR) was continuously measured by a HR monitor (RS200sd; POLAR, Büttelborn, Germany). To determine blood lactate concentration (BLa), capillary blood samples (20 μl) were extracted from the hyperemic fingertip at the end of each 5 min stage and analyzed (BIOSSEN C-line; EKF, London, UK). Rating of perceived exertion (RPE) was evaluated using the Borg-scale 6–20 (Borg, Hassmen, & Lagerstrom, 1987). HR, BLa and RPE were recorded within the last 30 s of each stage. Volitional exhaustion was considered with the

attainment of at least two of the following criteria: high levels of BLa (8–10 mmol/L); a perceived rate of exertion of ≥ 18 and/or a HR of ± 10 bpm of age-predicted maximum ($220 - \text{age}$) (Hollmann, Knigge, Knicker, & Strüder, 2012) and a drop in cadence of 10% under 90 rpm (Neptune & Hull, 1999). Test results were used to determine participants' endurance performance and to identify individual LT. The LT was determined as a clear threshold increase in blood lactate from plots of blood lactate against cycle work load via visual inspection (Jones & Doust, 1998).

2.6 | Exercise intervention

The exercise intervention started with a low-intensity warm-up of 5 min similar to the exercise testing. This was followed by a constant load exercise of 20 min and again a low-intensity cool-down of 5 min. The workload during the constant load exercise corresponded to either 20% under LT or 20% above LT or a control condition without any exercise and was completed on the third, fourth and fifth day in counterbalanced and randomized order. HR, BLa and RPE were measured and recorded every five minutes. The exercise intensity and duration were chosen based on previous studies in healthy subjects that have mostly shown EIH at these exercise protocols (Hoffman et al., 2004; Koltyn et al., 1996). Notably, we chose an exercise intensity of 20% above LT, since a previous randomized study found no intensity-dependent effects on EIH for constant-load trials at 10% above or below lactate threshold (Wonders & Drury, 2011).

2.7 | Data analysis

All statistical analyses were performed using SPSS 25 (SPSS Inc., Chicago, Illinois). Criteria for parametric tests were verified by Shapiro-Wilk test (normal distribution), Mauchley test (sphericity) and Levene test (homogeneity of variance). Since simulation studies have shown that ANOVA with repeated measure is relatively robust to normal distribution assumption violations (Vasey & Thayer, 1987), data were processed using parametric tests. Effect sizes were calculated by Pearson's correlation coefficient r for the t tests and partial eta square for the ANOVAs. Differences were considered significant at $p \leq .05$.

2.8 | Exercise intervention

Changes in HR, RPE and BLA during exercise were analyzed using the Friedman test (warm-up, 5, 10, 15, and 20 min intervention). In case of significance, Wilcoxon signed rank test was used to test the single time points against each other and to compare the interventions with each other.

2.9 | PANAS

Data of the positive scale were analyzed using a 2 (time) $\times$ 3 (condition) repeated measures ANOVA. Additionally, post-hoc one-tailed paired *t*-tests with Bonferroni correction were performed. To test for group differences delta of "post-pre"

were entered in an independent one-tailed *t* test for each condition. The data of the negative affect scale were not normally distributed and the assumptions of homogeneity and sphericity were violated. These violations result from a "floor effect" in the data (Figure 2b). Mean changes from pre to post intervention are less than one point on the negative scale (Figure 2c). For the above stated formal reasons, no statistical analysis for the negative scale of the PANAS was performed.

2.10 | Heat pain threshold and pain tolerance

A two-way (condition $\times$ time) ANOVA with repeated measures was carried out. Pairwise comparisons were used

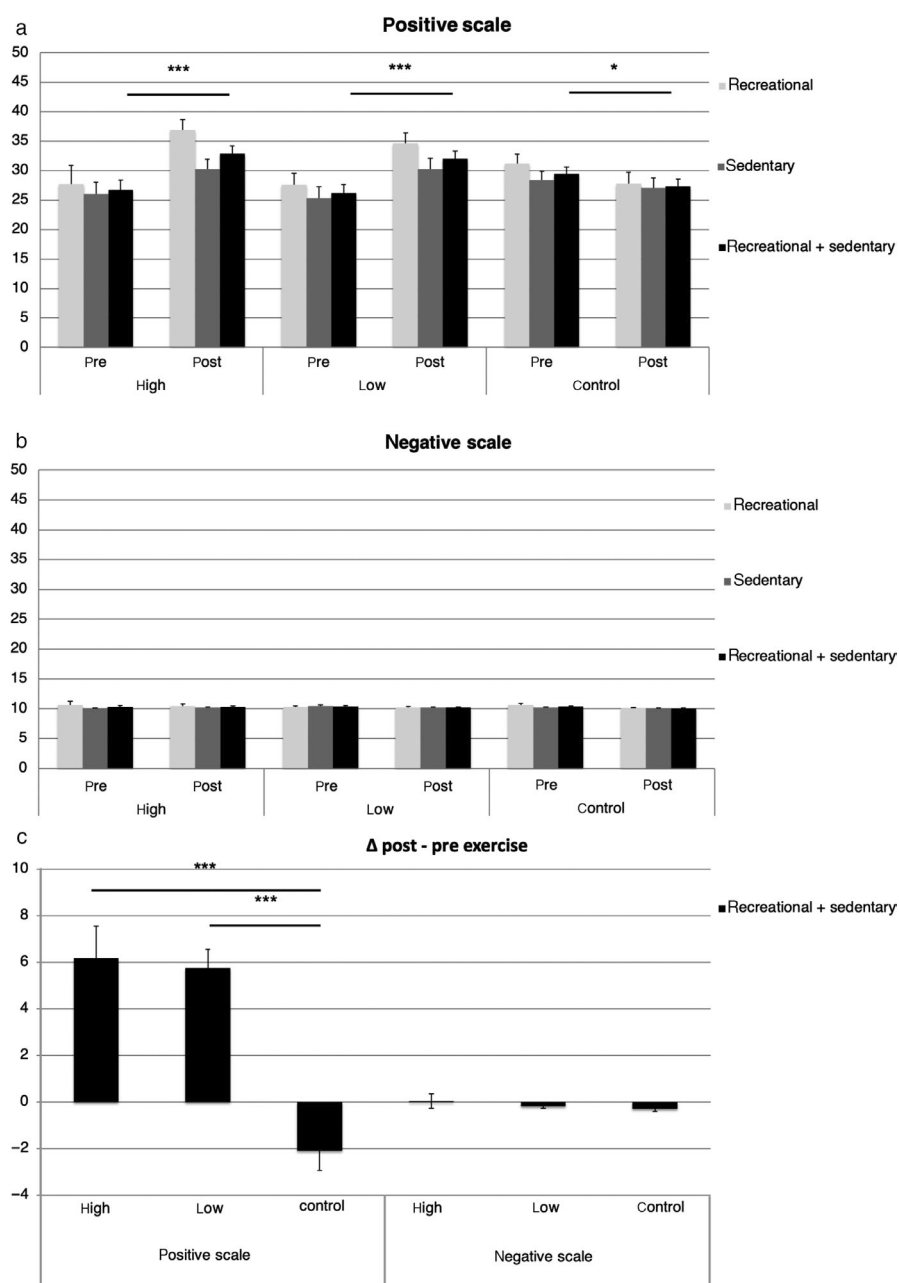


FIGURE 2 Scores of the PANAS questionnaire pre and post each intervention (high, low, control). (a) positive affect scale: pre and post values for each group separately (sedentary/recreational) and all subjects together (recreational + sedentary), (b) negative affect scale: pre and post values for each group separately (sedentary; $N = 17$ /recreational: $N = 11$) and all subjects together (recreational + sedentary; $N = 28$), (c) delta post-pre exercise for all subjects together (recreational + sedentary; $N = 28$) in positive and negative scale; error bars indicate standard error of the mean; *** $p < .001$; * $p < .05$

to assess differences pre to post intervention and between conditions using a one-tailed paired t tests with Bonferroni correction. To test for group differences delta of “post-pre” were entered in an independent one-tailed t test for each condition.

2.10.1 | Correlations with fitness level

To investigate whether the individual fitness level, indexed as the power output at lactate threshold (PO at LT/kg) in GXT, is associated with the amount of change in PTh, PTol, and PANAS (positive scale) during the three conditions (high, low, control), additional non-parametric one-tailed correlation analyses were performed. The power output at lactate threshold was chosen, as it represents both the reference point for the applied exercise intensity and individuals' fitness in the aerobic exercise range.

2.10.2 | Correlations with affect scores

To investigate whether affect is associated with the amount of change in PTh and PTol during the three conditions (high, low, control) we performed non-parametric one-tailed correlation analyses using the delta from pre to post of positive affect scale.

3 | RESULTS

None of the 31 participants showed results indicating psychiatric diseases (MINI). At study entrance, the volunteers' mean score for BDI was 2.13 ± 2.69 ($M \pm SD$), indicating that all participants scored below the threshold value for clinical relevant depression (score ≤ 9 : no depression). STAI trait scores were on average 31.7 ± 6.0 (range: 20 = not being afraid to 80 = maximum intensity of anxiety). Mean verbal intelligence quotient estimated by a German vocabulary test was 107.6 ± 1.8 (Schmidt & Metzler, 1992), showing normal verbal intelligence.

3.1 | Exercise Intervention

The HR during exercise increased significantly over time during the low-intensity condition ($\chi^2(4) = 78.44$; $p < .001$) and during the high-intensity condition ($\chi^2(4) = 111.29$; $p < .001$). Post hoc testing showed a significantly higher HR at each time point compared with the previous time point ($p < .05$) in both conditions (low and high). The interventions (low and high) differed at each time point significantly from each other ($p < .01$).

Ratings of perceived exertion increased over time during the low-intensity condition ($\chi^2(4) = 107.90$; $p < .001$) and during the high-intensity condition ($\chi^2(4) = 114.64$; $p < .001$). Post hoc testing showed a significantly higher RPE values at each time point compared with the previous time point ($p < .01$) in both conditions (low and high). The interventions (low and high) differed at each time point significantly from each other ($p < .001$), except after the warm-up.

Values of BLA increased over time during the high-intensity condition ($\chi^2(4) = 46.92$; $p < .001$), but not during the low-intensity condition ($\chi^2(4) = 7.72$; $p = .102$). Post hoc testing showed only a significantly higher BLA between warm-up and 5 min of intervention in the high condition ($p < .01$). The interventions (low and high) differed at each time point significantly from each other ($p < .001$), except after the warm-up. Data are summarized in Table 2.

3.2 | PANAS

Due to missing values we had to exclude three subjects resulting in a final sample size of $N = 28$ ($N = 11$ sedentary; $N = 17$ recreational) subjects. The ANOVA for the PANAS positive scale revealed a main effect of time ($F_{1,27} = 39.33$; $p < .001$, $\eta_p^2 = 0.593$) and a significant time $\times$ condition interaction. Mauchly's test indicated that the assumption of sphericity had been violated for the interaction time $\times$ condition ($\chi^2(2) = 8.39$, $p < .05$). Therefore, degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = 0.78$, $F_{1.65,42.32} = 17.87$, $p < .001$, $\eta_p^2 = 0.398$). Post-hoc t -tests revealed a significant increase in positive mood after low ($t_{27} = -7.18$, p (one-tailed) $< .001$, $r = .81$) and high ($t_{27} = -4.48$, p (one-tailed) $< .001$, $r = .65$) exercise intensity intervention and a significant decrease after seated rest ($t_{27} = 2.66$, p (one-tailed) $= .020$, $r = .46$) (Figure 2a). Additionally, both exercise interventions resulted in a significant change in positive mood compared to seated rest (low versus control: $t_{27} = 6.19$, p (one-tailed) $< .001$, $r = .77$; high versus control: $t_{27} = 4.31$, p (one-tailed) < 0.001 , $r = .64$) (Figure 2c). Between group comparisons did not reveal any significances for any of the conditions.

3.3 | Heat pain threshold

The 2 (time) $\times$ 3 (condition) ANOVA for PTh revealed a significant main effect of time ($F_{1,30} = 17.13$, $p < .001$, $\eta_p^2 = 0.364$) and a significant time $\times$ condition interaction ($F_{2,29} = 3.75$, $p = .036$, $\eta_p^2 = 0.206$). There was no main effect of condition. Post-hoc comparisons showed a significant increase in PTh from the pre ($45.4 \pm 2.7^\circ\text{C}$) to post ($45.9 \pm 2.6^\circ\text{C}$) low ($t_{30} = -2.89$, p (one-tailed) $= .012$, $r = .47$) and the pre

TABLE 2 Physiological parameters during the exercise interventions (low and high) for recreational ($N = 14$) and sedentary subjects ($N = 17$)

	Low						High					
	After warm-up	After 5 min of intervention	After 10 min of intervention	After 15 min of intervention	After 20 min of intervention	After 5 min of intervention	After 10 min of intervention	After 15 min of intervention	After 20 min of intervention	After 5 min of intervention	After 10 min of intervention	After 15 min of intervention
Heart rate (bpm)												
Sedentary	110 ± 15	118 ± 15	122 ± 17	124 ± 17	127 ± 17	114 ± 15	136 ± 17	142 ± 18	145 ± 19	149 ± 20		
Recreational	94 ± 10	115 ± 9	118 ± 11	120 ± 12	122 ± 13	98 ± 11	140 ± 11	147 ± 14	151 ± 14	154 ± 14		
Blood lactate (mmol/L)												
Sedentary	1.94 ± 0.74	2.18 ± 0.89	2.18 ± 1.14	2.10 ± 1.07	2.13 ± 0.98	1.99 ± 0.74	3.51 ± 1.53	3.75 ± 1.98	3.98 ± 2.21	3.77 ± 2.26		
Recreational	1.34 ± 0.63	1.88 ± 0.68	1.83 ± 0.79	1.75 ± 0.82	1.88 ± 1.02	1.43 ± 0.60	3.98 ± 1.38	4.98 ± 2.99	4.68 ± 2.32	4.70 ± 2.46		
Rating of perceived exertion												
Sedentary	9 ± 2	11 ± 2	12 ± 2	13 ± 3	13 ± 3	9 ± 2	12 ± 2	14 ± 1	15 ± 2	16 ± 2		
Recreational	7 ± 1	10 ± 2	12 ± 3	12 ± 2	13 ± 2	7 ± 1	12 ± 2	15 ± 1	16 ± 2	16 ± 2		

($45.2 \pm 3.1^{\circ}\text{C}$) to post ($46.0 \pm 2.6^{\circ}\text{C}$) high ($t_{30} = -3.38$, p (one-tailed) = .003, $r = .53$) exercise intervention (Figure 3a). There was no significant difference from pre to post seated rest. Only exercising at a high intensity ($0.8 \pm 1.3^{\circ}\text{C}$), but not at low intensity, was associated with significantly stronger increases in PTh compared to the seated rest ($0.1 \pm 0.7^{\circ}\text{C}$) condition ($t_{30} = 2.57$, p (one-tailed) = .023, $r = .42$) (Figure 3b). Between group comparisons did not reveal any significances for any of the conditions.

3.4 | Pain tolerance

Subjects who were able to hold their hands in the cold water for 4 min already at the beginning of the study (pre-exercise) were excluded from statistical analyses (ceiling effect). The final group size included $N = 23$ subjects ($N = 13$ sedentary; $N = 10$ recreational). The 2 (time) $\times$ 3 (condition) ANOVA for PTol revealed a significant main effect of time ($F_{1,22} = 4.80$, $p = .039$, $\eta_p^2 = 0.179$). There was no main effect of condition and no interaction. However, due to the similar patterns in the deltas of “post-pre” exercise in PTh and PTol, we exploratively performed post-hoc tests comparing pre versus post in each condition. Analyses revealed that subjects could sustain pain significantly longer only after high exercise (pre: 51.2 ± 33.7 s; post: 72.4 ± 64.0 s) intervention ($t_{22} = -2.28$, p (one-tailed) = 0.045, $r = .44$). Pre versus post low exercise or pre versus post seated rest did not reveal a significant change (Figure 4a). All participants reached a maximum value of 10 on the VAS in both pre and post measurements. Between group comparisons did not reveal any significances for any of the conditions.

3.5 | Correlation analysis with fitness level

Performing an outlier analysis over all subjects revealed that two subjects needed to be removed for the correlation analysis of the PTol, resulting in a sample size of $N = 21$ subjects. Non-parametric correlation analyses of individual fitness levels identified a significant positive correlation with the increase in PTol from pre to post during the high-intensity exercise intervention ($r = .59$, p (one-tailed) = .002) (Figure 5). No significant correlation was evident for the low exercise intensity intervention ($r = .14$, p (one-tailed) = .26) or control condition ($r = -.05$, p (one-tailed) = .42). Moreover, no significant correlations were found for PTh (high: $r = -.10$, p (one-tailed) = .30; low: $r = -.13$, p (one-tailed) = .24; control: $r = -.09$, p (one-tailed) = .31) or PANAS positive scale (high: $r = .27$, p (one-tailed) = .08; low: $r = .16$, p (one-tailed) = .22; control: $r = -.06$, p (one-tailed) = .37).

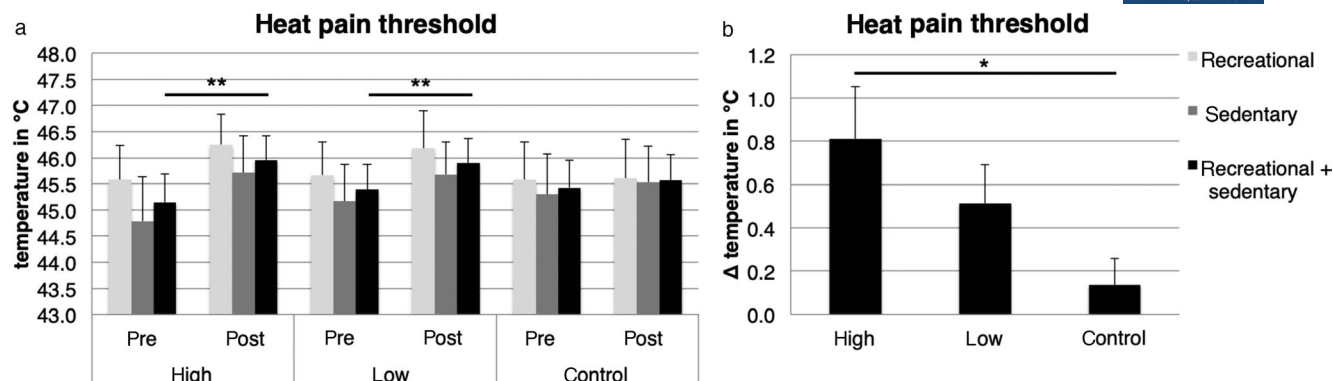


FIGURE 3 Heat pain thresholds for each test condition (high, low, control). (a) pre and post values for each group separately (sedentary: $N = 17$ /recreational: $N = 14$) and all subjects together (recreational + sedentary), (b) delta post-pre exercise of the heat pain threshold for all subjects together (recreational + sedentary; $N = 31$); error bars indicate standard error of the mean; ** $p < .01$; * $p < .05$

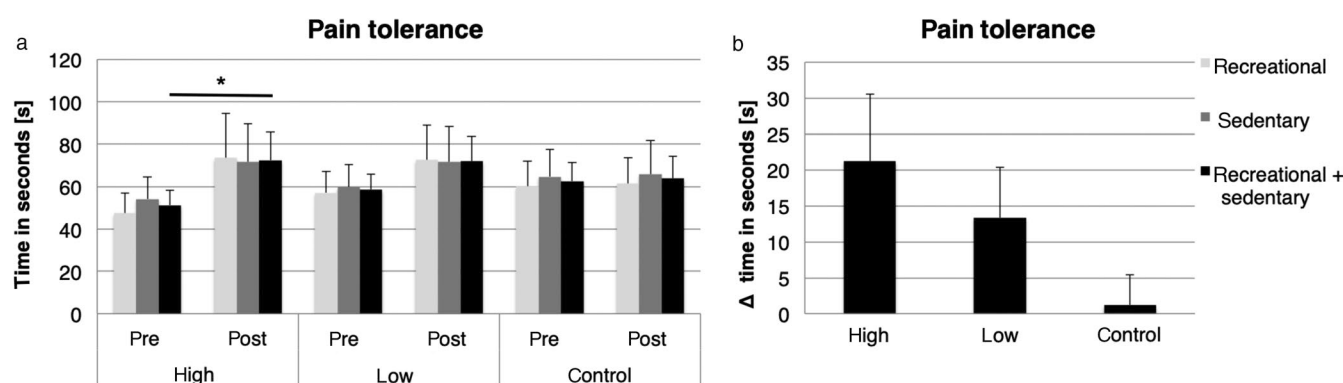


FIGURE 4 Pain tolerance for each test condition (high, low, control). (a) pre and post values for each group separately (sedentary: $N = 13$ /recreational: $N = 10$) and all subjects together (recreational + sedentary), (b) delta post-pre exercise of the heat pain threshold for all subjects together (recreational + sedentary); error bars indicate standard error of the mean; $N = 23$; * $p < .05$

3.6 | Correlation analysis with affect score

PANAS positive affect scale scores did not correlate significantly with PTol (high: $r = .04$, p (one-tailed) = .43; low: $r = .04$, p (one-tailed) = 0.43; control: $r = -.33$, p (one-tailed) = .08) or PTh (high: $r = .23$, p (one-tailed) = .12; low: $r = .15$, p (one-tailed) = .22; control: $r = .12$, p (one-tailed) = 0.27) for either of the exercise interventions or the seated control condition.

4 | DISCUSSION

Despite a large body of literature in the field of EIH, so far only few studies meet the methodological criteria that are required for inclusion in high quality meta-analyses, i.e. randomized experimental setups, individually prescribed exercise and control conditions, etc. This randomized controlled psychophysical study fills some open gaps in the literature, in particular by focusing on PTol as a behaviourally relevant aspect of central pain modulation. In this study we

investigated the effects of two different, individually titrated exercise intensities and the influence of physical fitness status on EIH: PTh increases occurred in both, sedentary and recreationally active young men after 20 min of cycling above and below LT (as compared to a non-exercising control condition), confirming previous findings (Hoffman et al., 2004; Koltyn et al., 1996). The intensity of the acute exercise bout determined the magnitude of the PTh, i.e. larger effects were encountered in the high-intensity condition, supporting the notion that exercise intensity is an influential factor determining the magnitude of the PTh response as an important component of EIH. In an exploratory analysis, PTol time prolongations were also found to depend on exercise intensity, as PTol time significantly increased only in the high-intensity exercise condition. Thus, our findings translate into behaviourally relevant outputs, such that a high-intensity bout produces a higher level of centrally mediated antinociception allowing the individual to sustain pain to a larger degree. This is further supported by the interesting observation that individual fitness levels correlated with the degree of PTol in the high-intensity exercise condition, suggesting that the fitness level in recreationally active

endurance athletes compared to sedentary control subjects (Geva & Defrin, 2013), again not comparing different exercise intensities. Findings from this randomized intervention study provides initial evidence that the ability to sustain nociceptive input after exercise might depend on the intensity of the exercise bout, bringing these experimental findings to a broader, i.e. behaviourally relevant, level. The only study comparing the effects of aerobic exercise at low and high intensities on pressure pain tolerance reported increased pressure pain tolerance after both exercise conditions, without a significant difference between low and high intensity (Vaegter et al., 2015).

Another interesting finding in this context is the impact of the fitness status on the magnitude of PTol: the higher the individual fitness level the larger the PTol, i.e. indexed as prolonged immersion time after the high-intensity exercise condition. These significant findings thus support long-term training effects on the acute PTol, during which repeated opioidergic release is triggered, as discussed above. This may suggest a fitness-associated central opioidergic mechanism to be closely related to pain tolerance as a centrally mediated effect as compared to other peripheral measures of pain perception, as e.g. PTh. One may argue that regular physical trainings challenge the different antinociceptive mechanisms (as discussed above) in a repeated manner, thereby increasing the efficacy of the PTol. Such improved capacity of the PTol is particularly meaningful for strenuous exercise conditions that are prone to induce pain perceptions and, indeed, there are indications from previous work that tolerance for exercise intensity is positively correlated with (post exercise) pain tolerance (Baiaumont et al., 2017). In conclusion, acute EIH responses, evidenced as prolonged PTol, are associated with individual fitness levels, a finding that may be discussed in terms of biological adaptations and functional plasticity of underlying neuronal and neurohumoral systems in the human brain.

Whereas mutual connections between affect and pain processing are well-established in the literature (Wiech & Tracey, 2009), current results found no indications for exercise-intensity related affective responses: The PANAS positive scale was elevated directly post exercise, independent of the tested intensities (i.e. without significant differences between high and low), generally corroborating previous findings reporting similar mood scores after exercise regardless of intensity (Bixby, Spalding, & Hatfield, 2001), although not unambiguously (Saaniijoki et al., 2018). While high-intensity exercise bouts can be aversive, recent meta-analyses have generally reported that also vigorous training intensities go along with positive affective responses (Oliveira, Santos, Kilpatrick, Pires, & Deslandes, 2018). It is important to consider that mood was tested after the termination of the exercise bout and cool-down when potential aversive

effects during highly strenuous exercise intensities may have already leveled off. Steptoe and Bolton (1988) reported that tension/ anxiety ratings were increased immediately after high-intensity exercise, but then decreased subsequently during the recovery phase (Steptoe & Bolton, 1988). In a more recent study, affective valence during both high-intensity interval and high-intensity continuous exercise was less positive than during moderate-intensity continuous exercise. However, this effect tended to rebound rapidly and was no longer identifiable at 5 min post-exercise (Niven, Thow, Holroyd, Turner, & Phillips, 2018). Hence, our data may be affected by the time point of mood assessments, precluding any inferences regarding dynamic affective changes over time. No evidence was found for a correlation between PANAS positive scale, PTh or PTol, although significant increases were observed for all three measures after both exercise interventions. This negative finding may also indicate that mood effects, at least in the tested exercise ranges, are mediated also by other mechanisms than EIH, e.g. for instance serotonin signalling.

Methodologically, there are some limitations to be considered in the current study. First of all, the study population consisted only of males to exclude potential hormone cycle-linked humoral factors in this randomized intervention with three different experimental conditions. To be able to further generalize findings, future studies will thus need to investigate EIH in relation to exercise intensity in larger gender-balanced populations. Moreover, the investigated study population is rather small (sedentary: $N = 17$ /recreational: $N = 14$), thus, a statistical power issue cannot be excluded with certainty. This especially applies to the statistical analysis of PTol data, in which sample size was even smaller because subjects with a ceiling effect had to be excluded. Therefore, results of PTol analyses are to be regarded as preliminary and will need to be further substantiated in additional samples. In future, studies in larger and balanced cohorts should thus be envisaged, according to sample size estimations using appropriate a priori power calculations. Another methodological shortcoming is that the applied exercise conditions represent only two exercise intensities. Thus, future work may consider extending these findings to other (higher and lower) exercise intensities. Also, other stimuli to measure the EIH response should be considered, together with the extension to other age ranges.

In conclusion, the current results provide evidence that antinociceptive effects depend on the intensity of the exercise bout. Moreover, the magnitude of PTol appears to be associated with the individual fitness status. This is thought to represent a biological adaptation process induced by repeated exercise bouts, eventually fostering highly efficient antinociceptive effects that differentiate trained from untrained individuals.

CONFLICT OF INTEREST

All authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

A.S. contributed substantially to the design, analysis and interpretation of the data, wrote parts of the main manuscript text and prepared the figures. D.W. contributed substantially to the acquisition of the data. C.S. made substantial contributions to the data analysis and wrote parts of the main manuscript text. J.A.M. defined lactate threshold of each individual. U.S.-I. contributed to the data acquisition. H.B. contributed substantially to the design, interpretation of the data and wrote parts of the main manuscript text. All authors revised the text critically and gave final approval of the version to be published.

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