PAIN® 154 (2013) 1022–1029

PAIN®

www.elsevier.com/locate/pain

Alterations in endogenous pain modulation in endurance athletes: An experimental study using quantitative sensory testing and the cold-pressor task

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 19 September 2012
Received in revised form 26 February 2013
Accepted 7 March 2013

Keywords:
Athletes
Pain perception
Quantitative sensory testing
QST
Cold-pressor task
Conditioned pain modulation

ABSTRACT

There is evidence for long-term alterations in pain tolerance among athletes compared with normally active controls. However, scientific data on pain thresholds in this population are inconsistent, and the underlying mechanisms for the differences remain unclear. Therefore, we assessed differences and similarities in pain perception and conditioned pain modulation (CPM) at rest in endurance athletes and normally active controls.

The standardised quantitative sensory testing protocol (QST) of the 'German-Research-Network-on-Neuropathic-Pain' was used to obtain comprehensive profiles on somatosensory functions. The protocol consisted of thermal and mechanical detection as well as pain thresholds, vibration thresholds, and pain sensitivity to sharp and blunt mechanical stimuli. CPM (the diffuse-noxious-inhibitory-control-like effect) was measured using 2 tonic heat pain test stimuli (at the temperature exceeding a subjective pain rating of 50/100) separated by a 2-min cold-pressor task (CPM-TASK; conditioning stimulus). Pain ratings were measured with a numerical rating scale. Endurance capacity was validated by assessment of maximum oxygen uptake (VO_2max). Participants included 25 pain-free male endurance athletes (VO_2max > 60 mL/min * kg) and 26 pain-free normally active controls (VO_2max < 45 mL/min * kg) matched based on age and body mass index.

Athletes were significantly less sensitive to mechanical pain but showed higher sensitivity to vibration ($P < 0.05$). In athletes, CPM was significantly less activated by the conditioning stimuli ($P < 0.05$) when compared with normally active controls.

Our data show that somatosensory processing in athletes differs in comparison with controls, and suggest that the endogenous pain inhibitory system may be less responsive. This finding may explain the paradoxical propensity of athletes to develop chronic widespread pain.

1. Introduction

Pain is a common phenomenon in athletes [3,22,26,51,60,67]. This is paradoxical, as physical activity is part of most multimodal pain treatment programmes. Thus, on the one hand, physical activity might be the origin of a variety of pain syndromes in athletes who engage in rigorous physical activity [3,22,26,51,60,67], whereas on the other hand, physical activity also represents an important therapeutic concept in pain syndromes [20,21,43,55]. Therefore, increased knowledge concerning the role of physical activity on pain perception and processing may impact the medical care of pain patients in general, and athletes in particular.

There has been consistent evidence that after an episode of intense exercise, pain perception is reduced for a limited period of time, i.e., 'acute exercise-induced analgesia' [29,31]. It has been theorised that physical activity activates some generalised endogenous pain-modulatory mechanisms, e.g., conditioned pain modulation (CPM; formerly termed 'diffuse noxious inhibitory control') [5,29], baroreflex-mediated analgesia [7,30], stress-induced hypoalgesia [29], or attentional factors [29,31]. Although different mechanisms have been proposed [29,30], CPM is of special interest, as alterations in this system have been reported for a variety of chronic pain conditions [19,27,28,36,40,41,44,63,71]. Moreover, a deficit in this system is associated with chronic widespread pain (CWP) [44], which is frequently reported in athletes (prevalence 31% [23]).

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0304-3959/$36.00
http://dx.doi.org/10.1016/j.pain.2013.03.014

To date, research has focused on pain perception during physical activity rather than the potential long-term consequences of regular exposure to physical activity on pain processing at rest. In particular, the endogenous pain inhibitory system is a little-researched issue in athletes and, to date, no data have been published about CPM.

Researchers have postulated that long lasting physical activity may alter pain perception at rest and have often concluded that athletes possess higher pain thresholds and a higher pain tolerance in general [50,53]. A recent meta-analysis confirmed significantly higher pain tolerance in athletes at rest and specific alterations in pain thresholds [57]. But, although some studies have reported elevated pain tolerance or pain thresholds [16,18,56], there are also data demonstrating normal [49] or even lower [45] pain thresholds in athletes. This ambiguity may be because different pain induction methods with non-standardised and non-validated testing paradigms have been used [10,11,16,18,45,49,50,66]. The situation is aggravated because the definition of an athlete in most pain studies has been characterised arbitrarily, and to date, there are almost no pain studies in which physical fitness has been assessed objectively [57].

To overcome some of these shortcomings, this study assessed for the first time pain perception and endogenous pain modulation in athletes using a comprehensive standardised quantitative sensory testing protocol (QST [47]) and an objective evaluation of 'physical fitness.' The aim of this study was (1) to examine whether there are differences in pain perception at rest between athletes and normally active controls, and if so, (2) to determine if endogenous pain-modulating mechanisms are involved. It was predicted that athletes are characterised by specific sensory profiles and that the endogenous pain modulation of athletes is significantly different compared with normally active controls.

2. Methods

2.1. Study population

In the present study, 25 endurance athletes and 26 normally active controls were included. Athletes were recruited from regional sport clubs. Healthy normally active controls were recruited via flyers posted in the local community. Inclusion criteria were as follows: male sex, age 18-35, and without pain. The study sample was restricted with respect to sex and age, as QST and CPM are sex- [9,46] and age-dependent [8,48]. Athletes trained for at least 3 h/wk for more than 3 years and were characterised by a maximal oxygen consumption (VO_2max) >60 mL/min $*$ kg. Controls were age- and BMI-matched, did not engage in regular physical activity, and had a VO_2max < 45 mL/min $*$ kg.

Study participants were screened using a questionnaire, physical examination, and electrocardiogram to rule out acute or chronic pain; in addition, data concerning regular medication use, diseases affecting sensory processing (e.g., diabetes, polyneuropathy) or contraindications to treadmill testing were used to screen patients. Subjects were excluded if they reported any history of injury of the hand dorsum or arm, as this was the area tested in our paradigm. Participants were advised not to take any medication 24 h prior to the investigation and to refrain from intensive or prolonged training on the day prior to each test.

2.2. Instruments

2.2.1. Assessment of athletic performance

Maximal oxygen consumption (VO_2max, mL/min $*$ kg) was measured in a ramp protocol on a motor-driven treadmill (Quasar med, H/P/Cosmos, Traunstein, Germany). After warming-up for 2 min at 4 km/h at an incline of 1.5%, the test began at a speed of 7.2 km/h, and the speed was increased by 0.6 km/h over 30 s until volitional exhaustion. Oxygen consumption was measured using a metabolic card (Ergostik, Geratherm Respiratory GmbH, Bad Kissingen, Germany). VO_2 max related to body weight was considered to be the highest VO_2 over a period of 30 s during the test. Prior to each test, both sensors were calibrated according to the manufacturer's instructions. During the treadmill test, a continuous 12-lead ECG was recorded.

Specifications of physical activity were also captured using a questionnaire that included a detailed self-report of the type, frequency, intensity, and duration of physical activities.

2.2.2. Assessment of pain perception

Somatosensory function was assessed using the comprehensive QST protocol, which was developed as part of the German Research Network on Neuropathic Pain (DFNS) [47]. It covers all relevant aspects of the somatosensory system, including large and small fibre functions, and signs of central sensitisation (dynamic tactile allodynia, punctate mechanical hyperalgesia, and paradoxical heat sensations). In this manner, detailed profiles of somatosensory function for the tested body areas were obtained. The dorsum of the dominant hand was tested.

To familiarise participants with the test procedure, all tests were first conducted over an area that was not tested later during the QST session.

The tests for thermal detection thresholds (warm detection threshold, WDT, and cold detection threshold, CDT), thermal pain thresholds (heat pain threshold, HPT, and cold pain threshold, CPT), and paradoxical heat sensations (PHS) were conducted using a TSA 2001-II (MEDOC, Israel) thermal sensory testing device [72]. All thresholds were obtained using ramped stimuli (1°C/s, 32°C baseline, 0°C and 50°C cut-offs, 8 cm^2 thermode), which were terminated when participants pressed a button. The mean of 3 consecutive measurements was calculated. Thermal sensory limen (TSL), a test with alternating warming and cooling ramps, was used as a provocative test to induce PHS.

The mechanical detection threshold (MDT) was measured with a standardised set of modified von Frey filaments (Optihair$_2$-Set, Marstock Nervetest, Germany), which exert forces between 0.25 and 256 mN [13]. The contact area was of uniform size and shape (round, 0.5 mm diameter). The threshold was the geometric mean of 5 series of ascending and descending stimulus intensities.

The mechanical pain threshold (MPT) was measured using a set of weighted pinprick stimulators with a flat contact area of 0.25 mm diameter, which exert forces between 8 and 512 mN [4]. Again, using the method of limits, the threshold was the geometric mean of 5 series of ascending and descending stimulus intensities.

Mechanical pain sensitivity (MPS) was tested using the same weighted pinprick stimuli as that for MPT. To obtain stimulus response function, these 7 pinpricks were applied in balanced order 5 times each. The participant was asked to rate each stimulus for pain on a 0 to 100 numerical rating scale (0 indicating 'no pain,' and 100 indicating 'most intense pain imaginable'). The geometric mean of the 35 pain ratings was the final value for MPS. Stimulus response functions for dynamic mechanical allodynia (DMA) were determined using a set of 3 light tactile stimulators [4,34]. They were intermingled with the pinprick stimuli in a balanced order, and participants were asked to give a rating on the same numeric rating scale.

The vibration detection threshold (VDT) was determined with a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale), which was placed over the bony prominence of the processus styloideus radii of the dominant hand 3 times. Subjects indicated the time at which they no longer experienced vibratory sensations.

2.2.3. Assessment of conditioned pain modulation

To test CPM (the term CPM rather than diffuse noxious inhibitory control/DNIC is chosen based on the recent recommendations of Yarnitsky et al. [70]), we used the protocol of Tousignant-Laflamme et al. [59] and consulted the guidelines for the cold-pressor task (CPM-TASK) as an experimental pain stimulus [65]. The CPM-TASK activates the diffuse noxious inhibitory control-like effect (CPM), as it is a strong nociceptive stimuli that takes place over a lengthy span of time [69] and is applied over a large body surface area [39]. Thus, the CPM-TASK allows us to modify the endogenous pain-modulating system. To quantify CPM, we evaluated the pain intensity of two tonic heat pain (THP) test stimuli separated by a CPM-TASK. Even if the THP may lead to both habituation and sensitisation according to the dual process theory, the THP is a reliable stimulus to induce CPM [59].

CPM-TASK: The cold-pressor task was used as a conditioning stimulus to elicit a strong and prolonged pain sensation to trigger CPM. The CPM-TASK consisted of immersing the non-dominant hand and wrist and approximately 5 cm of the forearm in circulating cold water (22 L + circulating with 15 L/min) for 2 min (informed ceiling task). To maintain the water temperature at 12 ± 0.2°C, we used an immersion cooler and a thermostat to control for temperature variations in both directions (Immersion cooler FT 200 and clip thermostat model ED, Julabo, Seelbach, Germany). The temperature of the water was set at 12°C to ensure that the CPM-TASK was sufficiently painful to elicit CPM while tolerable enough to be endured for 2 min. To control depth of immersion, the hand was placed on a grid (rubber isolated metal grid) that permitted the circulation of water on all sides of the immersed hand. Participants were instructed to lay their hand loosely on the grid and were asked to not move the hand or explore their grid. An armrest of silicone made testing more comfortable and prevented participants from changing the depth of immersion. During the test, subjects verbally rated their pain intensity every 5 s using the numerical rating scale ($NRS_{0/100}$). The rating scale ranged from 0, i.e., 'no pain,' to 100, i.e., 'most intense pain imaginable.' The experimental setup was approved by our local medical engineering department.

THP: To determine the temperature for the 2-min THP, an initial pre-test was completed. To familiarise participants with the testing procedure, participants were asked to continuously rate their pain intensity using the $NRS_{0/100}$, while the temperature of the thermode was gradually increased from 32°C to 50°C (0.3°C/s). The procedure was conducted twice. After participants were acclimated to the procedure and after a short break, we determined the temperature at which participants rated the THP with a score of 50/100 (0 'no pain' to 100 'most intense pain imaginable'). This procedure was performed until the temperature in 2 consecutive runs did not differ by more than ±1°C. The mean temperature eliciting pain ratings of 50/100 on the $NRS_{0/100}$ ($Temp_{50}$) was used for the THP. After a short break, the first THP (Pain baseline, THP_0) was applied to the palm of the dominant forearm (Peltier Thermode, TSA II, Medoc, Advanced medical systems, Israel). Participants were instructed that the temperature could increase, decrease, or remain constant. Then, the temperature of the thermode was increased from 32°C at a rate of 0.3°C/s to the individually determined temperature. Thereafter, the pain stimulus remained constant for 2 min. Pain intensity was measured every 5 s using the $NRS_{0/100}$. Following the first THP (THP_0), the CPM-TASK was used to trigger CPM. One minute after the CPM-TASK, we applied the second THP (THP_1). We quantified the amount of CPM by subtracting the mean pain rating of the first THP before the CPM-TASK (THP_0) from the second THP after the CPM-TASK (THP_1).

2.2.4. Assessment of pain experience

To evaluate different aspects of the pain experience, the Pain Experience Scale ('Schmerzempfindungsskala,' SES), a well-validated instrument used in pain research, was administered. The SES consists of 24 items and distinguishes between the affective and sensory dimensions of pain [14]. The response format was 4-staged, from 1 'not applicable,' to 4 'absolutely applicable.' To calculate values for the affective (items 1–14, e.g., ''exhausting,'' 'cruel') and sensory (items 15–24, e.g., 'hot,' 'stabbing') subscales, items for each subscale were summed. We asked participants to rate the SES after assessment of CPM. Participants were instructed to rate 'pain sensations during testing.' The SES is sensitive to change and has proven validity and reliability for the affective and sensory subscales ($\alpha = 0.81$ and 0.92 respectively) [14].

2.3. Study design

All tests were performed at the same time in the afternoon. Before starting the tests, the subjects rested for half an hour in their respective environments. The test procedure began with the QST protocol and was followed by an assessment of conditioned pain modulation. Directly after the assessment of CPM, pain experience was evaluated with the SES. Maximal oxygen consumption was determined 30 min after the pain assessment procedure. The present study was approved by the Ethics Research Committee of the Faculty of Medicine, University of Heidelberg and was carried out in accordance with the Declaration of Helsinki. All participants gave written informed consent and received an allowance of 30 Euros (approximately 40 dollars) for their participation.

2.4. Statistical analysis

All analyses were conducted using SPSS for Windows (Version 19.0). Descriptive statistics are presented as the means and standard deviations for continuous variables, and absolute numbers and percentages for categorical variables. All analyses were explorative and not of confirmatory nature.

CPM was determined by subtracting the mean pain intensity of the THP prior to the CPM-TASK from the mean pain intensity of the THP after the CPM-TASK. Therefore, negative values indicate inhibitory conditioned pain modulation. Between group differences with respect to the CPM were tested using *t* tests, and paired *t* tests were used to determine within group differences. Variables that exhibited a non-normal distribution were analysed using non-parametric Mann–Whitney *U* tests. Most QST parameters (CDT, WDT, TSL, MPT, MPS, DMA, WUR, PPT, and MDT) are log-normally distributed and were therefore log-transformed [47]. Group differences between athletes and normally active controls were tested using *t* tests. We also standardised all QST measures of athletes using a *z*-transformation referring to the mean and standard deviation of the control group. This procedure allowed for direct comparison between sensory tests that are measured in different units (e.g., °C and mN) as well as judgement of a gain or loss of function in profiles between athletes and normally active controls. Hyperfunction is indicated by *z*-values above '0,' i.e., patients are more sensitive to the tested parameter compared with controls (lower thresholds, gain of function), whereas *z*-scores below '0' indicate hypofunction and therefore a loss of or lower sensitivity of the patient compared with controls (higher thresholds). Whenever log-transformed scores were calculated, the log-scores were used for *z*-standardisation and *t* tests.

Because of the explorative nature of the study, we abstained from adjustment for multiple testing and interpreted *P*-values cautiously as descriptive measures of effect. Statistical significance was accepted if $P < 0.05$.

3. Results

3.1. Subjects

A total of 25 male endurance athletes (14 triathletes, 10 runners, and 1 cyclist) and 26 age- and BMI-matched normally active subjects were included in the analysis. Descriptive statistics for demographic and clinical variables are summarised in Table 1. Athletes were characterised by a mean training time of 9.6 ± 3.5 h/wk and a mean frequency of 5.4 ± 1.6 training d/wk. All athletes had participated regularly in competitions during the previous 3 years. Maximal oxygen uptake (VO_2max) was significantly higher (62%) in athletes compared with normally active controls (65.9 ± 4.6 mL/min ∗ kg and 40.6 ± 6.2 mL/min ∗ kg, respectively, $P < 0.001$). Values indicate a highly trained population of athletes, whereas normally active controls were characterised by an appropriate level of inactivity. There were no significant differences in age, BMI, or skin temperature between athletes and normally active controls. In control subjects, 21 of the 286 QST parameters were outside the published reference range for age- and gender-matched subjects [37], which is close to the expected value of 5%. That about 5% are outside the published reference data range indicates that our controls are representative for the published reference data of healthy controls, and thus underpins the representativeness and quality of our data [37].

3.2. Comparison of QST values

As shown in Table 2 and Fig. 1, *t* tests revealed significant group differences for the mechanical pain threshold (MPT) and for the vibration detection threshold (VDT). Compared with normally active controls, athletes showed an elevated pain threshold with respect to pinprick stimulation (MPT: $P < 0.05$), but increased sensitivity to vibration stimuli (VDT: $P < 0.05$). Athletes did not differ significantly from controls for cold and heat stimuli (CDT, WDT, CPT, HPT, and TSL), non-painful mechanical stimuli (MDT), mechanical pain sensitivity (MPS), and mechanical pain induced by blunt pressure (PPT).

To validate the results for MPT, post hoc analysis for mechanical pain sensitivity stratified for stimulus-force revealed that athletes were less sensitive to low stimulus intensities but did not differ for higher stimulus intensities. Therefore, as differences were restricted only to the lower forces and not to higher stimulus intensities, group differences in MPS did not reach the level of significance. Analysis for outliers showed that 1 subject in the control group had an MPT outside the 95% confidence interval (CI). This highlights the validity of a loss of function among the athlete group, indicating that the results were not based on pathological outliers. With respect to VDT, 1 control subject and 1 athlete reported a loss of function that was outside the 95% CI. This also highlights the validity of the gain of function in athletes, as it is not explainable by outliers within the respective groups. Correlation analyses of VO_2max with sensory parameters revealed a significant correlation only for VDT ($r = 0.419$, $P = 0.008$).

No signs of central sensitisation (dynamic tactile allodynia, punctate mechanical hyperalgesia or paradoxical heat sensations) were found for athletes or the control group. In addition, there was no difference in the temporal summation of pain (WUR) between the 2 groups.

Table 2
Somatosensory profiles obtained by quantitative sensory testing of athletes and normally active healthy controls.

		Athletes		Controls		ES	*P*-value
		Mean	SD	Mean	SD		
CDT	Δ°	−0.03	0.26	−0.02	0.17	−0.05	0.931
WDT	Δ°	0.19	0.25	0.17	0.22	−0.09	0.771
TSL	°C	0.35	0.23	0.32	0.24	−0.13	0.725
CPT	°C	11.35	10.66	15.79	10.43	−0.42	0.148
HPT	°C	44.06	3.87	43.44	4.08	−0.16	0.581
PPT	kPa	2.58	0.14	2.55	0.12	−0.23	0.332
MPT	mN	1.92	0.53	1.58	0.49	−0.67	0.027
MPS	$NRS_{0/100}$	−0.18	0.38	-0.02	0.44	−0.4	0.187
WUR		0.34	0.23	0.41	0.3	−0.26	0.356
MDT	mN	0.15	0.5	0.11	0.38	−0.09	0.72
VDT	/8	7.81	0.29	7.58	0.46	0.61	0.047

CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold; $NRS_{0/100}$, numeric rating scale; mN, millinewton; kPa, kilopascal.
Data are given as log-transformed values (mean ± SD) except PHS, HPT, CPT, and VDT, which are listed as absolute values according to [43].
Two-tailed Student *t* test was used to determine level of significance.
Effect sizes (ES) were calculated as Hedge's *g*.

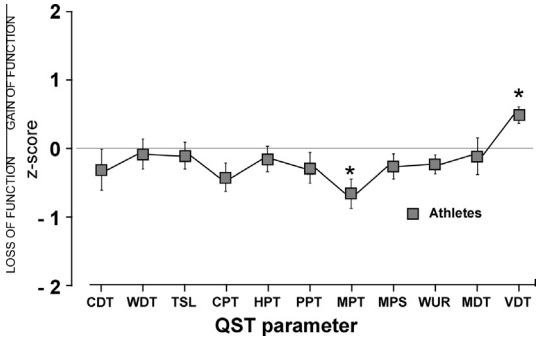

Fig. 1. Quantitative sensory testing (QST) profiles in athletes. Somatosensory profiles at hand dorsum in athletes. Values are mean ± SEM. To obtain *z*-values, athletes' values were standardised according to mean and standard deviation of normally active controls. $^*P < 0.05$, *t* test vs normally active controls. CDT, cold detection threshold; WDT, warm detection threshold; TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; MDT, mechanical detection threshold; VDT, vibration detection threshold.

Table 1
Demographic and clinical variables of athletes and controls.

		Athletes (n = 25)	Controls (n = 26)	*P*-value
Age	(years)	27.8 ± 4.1	28.0 ± 4.5	0.920
BMI	(kg/m^2)	22.1 ± 1.5	22.7 ± 2.2	0.229
VO_2max	(mL/min ∗ kg)	65.9 ± 4.6	40.6 ± 6.2	<0.001
VCO_2max	(mL/min ∗ kg)	5.4 ± 0.5	3.8 ± 0.6	<0.001
VE	(L/min)	158 ± 17	115 ± 24	<0.001
Training hours	(h/wk)	9.6 ± 3.5	<0.5	<0.001
Number of training	(d/wk)	5.4 ± 1.6	–	–
Training since when	(mo)	119.6 ± 82.9	–	–

BMI, body mass index; VO_2max, maximal oxygen uptake; VCO_2 max, maximal carbon dioxide production; VE, maximal air ventilation.
Data are indicated as the mean ± standard deviation.
A two-tailed Student *t* test was used to determine level of significance.

Table 3
Conditioned pain modulation in athletes and normally active controls.

		Athletes (n = 25)	Controls (n = 26)	*P*-value
Pain baseline T_0 (THP_0)	($NRS_{0/100}$)	34.2 ± 21.9	38.8 ± 15.7	0.411
Conditioned pain modulation (CPM)	(T_1-T_0)	−3.1 ± 8.7	−9.6 ± 12.2	0.020[a]
Pain CPM-TASK	($NRS_{0/100}$)	58.6 ± 24.0	68.9 ± 15.6	0.088

Data are indicated as the mean ± standard deviation.
THP: the tonic heat pain stimulus was applied as test stimulus at individual determined temperature (temperature at which participants rated the THP with 50 of 100 on the $NRS_{0/100}$) for 2 min by a thermode on the palm of the dominant forearm.
Conditioned pain modulation (CPM): CPM was quantified by subtracting the mean pain rating of the first THP (THP_0) before the CPM-TASK from the second THP (THP_1) after the CPM-TASK. Therefore, negative values indicate inhibitory CPM.
CPM-TASK: pain ratings during the cold-pressor task; the CPM-TASK as conditioning stimulus consisted in the immersion of the non-dominant hand for 2 min in circulating 12°C cold water.
Variables that were normally distributed were analysed using independent samples *t* test, whereas variables that exhibited non-normal distribution were analysed using non-parametric Mann–Whitney *U* tests ([a]). Difference in CPM remained significant ($P < 0.05$) even after controlling for cold-pressor test pain intensity.

However, although the majority of differences did not reach the conventional level of significance, there were trends for significance for all of these variables towards a loss of function (hypoesthesia, hypoalgesia) in athletes.

3.3. Comparison of conditioned pain modulation (CPM)

Table 3 shows that there was a significant difference in CPM between athletes and normally active controls ($P < 0.05$). There was a strong activation of CPM by the CPM-TASK in controls ($P < 0.001$), whereas CPM was only slightly induced by CPM-TASK in athletes ($P = 0.091$, Fig. 2). The effect size of the CPM on the differences in mean THP ratings before and after the CPM-TASK was small in athletes (Cohen's d = 0.14), whereas the inhibitory effects of this paradigm in controls were characterised by a moderate effect size (Cohen's d = 0.55).

There were no significant differences in the temperature of the $Temp_{50}$ stimulus ($P = 0.212$), the mean THP pain ratings prior to the CPM-TASK ($P = 0.411$) or in the mean pain rating for the CPM-TASK (conditioning stimulus, $P = 0.088$). However, because of the marginal difference in CPM-TASK ratings between athletes and normally active controls, we repeated the analysis for CPM and entered the CPM-TASK pain intensity as a covariate in the analysis of covariance. Differences in CPM, with less activity activated in athletes, remained significant ($P < 0.05$) even after controlling for CPM-TASK pain intensity. The intensity of the CPM-TASK was not significantly associated with CPM. Correlation analysis of CPM with CPM-TASK pain intensity ($r = 0.032$, $P = 0.833$) or with VO_2max ($r = 0.161$, $P = 0.348$) showed no association. Athletes and controls did not differ in THP_0. None of the participants attained complete pain relief after conditioning stimulus. Exploratory analysis showed that in the control group there was a gain in 3 subjects and a loss in 20 subjects, whereas in athletes there was a gain in 7 subjects and a loss in 16 subjects. Outlier analysis revealed that in each group, 1 subject experienced a gain and 1 loss of function outside the 95% CI. This confirms the validity of the results.

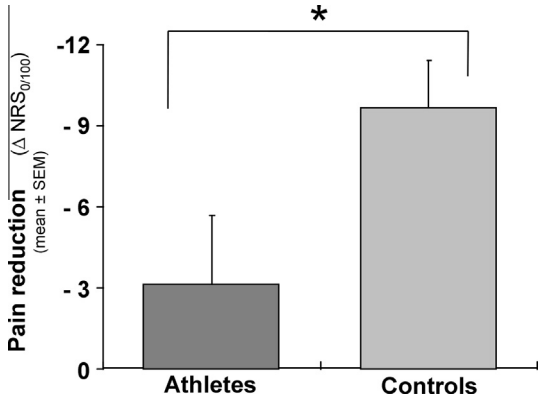

Fig. 2. Conditioned pain modulation (CPM). Reduction in pain intensity (conditioned pain modulation) between thermal pain measures (test stimulus) obtained before and after the cold-pressor task (CPM-TASK, conditioning stimulus). Controls (n = 26) had a 25% reduction (Cohen's d = 0.55) in thermal pain following the CPM-TASK, whereas there was only a small change (9%, Cohen's d = 0.14) for athletes (n = 25). *$P < 0.05$.

3.4. Pain experience

Concerning differences in pain experience, assessed by the SES, there were no differences in affective (athletes: 20.1 ± 5.8, controls: 20.7 ± 6.3, $P = 0.762$, possible range 10–40) or sensory (athletes: 18.2 ± 4.3, controls: 18.5 ± 4.9, $P = 0.792$, possible range 14–56) pain experience for modified pain at T1 (THP_1) between athletes and normally active controls after the induction of CPM.

4. Discussion

This study has shown decreased sensitivity for MPT, increased sensitivity to vibration and a reduction in CPM in endurance athletes with validated athletic status.

No significant differences were found for heat, cold or pressure pain thresholds, or for temperature and mechanical detection thresholds. These findings are consistent with previous work, which also found no differences for heat [52,54] or pressure pain thresholds between athletes and normally active controls [38,49].

4.1. Sensory profiles in endurance athletes

The isolated loss of function for pinprick stimuli described in this study is an interesting finding, as MPT by pinprick has not been tested in athletes to date. An increase in MPT can result from both dysfunctions of the peripheral nociceptors and inhibition within the central nervous system [62,73]. The peripheral sensors for pinprick stimuli are a highly specific class of high threshold Aδ-mechanoreceptors with high relevance for protective guarding and withdrawal behaviour [61,73]. Alterations in peripheral nociceptors seem to be consistent with previous research, which has found abnormal nerve-conduction-tests in runners, suggesting asymptomatic neuropathy similar to that noted in subclinical entrapment neuropathy [6]. However, these data were restricted to the lower extremities of runners, whereas our data focused on the upper extremity. Moreover, researchers have not studied the peripheral nervous system in athletes systematically, and future studies on peripheral nociceptor function in athletes are recommended.

It is notable that most QST parameters showed a general trend towards a reduced sensitivity, indicating a 'loss of function', although the level of statistical significance was reached only for MPT.

It has been suggested that perception aberrations in athletes may be based on their lack of motivation ('stoicism') to report pain [24,25]. In this regard, 'stoic athletes' should feel as much pain as others but express their experience less. Therefore, if athletes offer fewer reports of pain, they would also experience a (pseudo-)reduction in their sensory response to noxious stimuli. In our study, pain reports relied on subjective pain ratings and may therefore have given the appearance of increased pain thresholds. Although there was a trend towards a 'loss of function,' the QST profiles observed in our study did not generally support the idea of stoicism to pain in athletes for several reasons. First, detection thresholds were shifted toward a loss of function in our study; however, detection thresholds do not exceed pain and therefore should not be affected by stoicism [24,25]. In addition, there was no difference in the affective dimension of pain experience between athletes and normally active controls as one might expect in the case of stoicism. Moreover, there was a significant decrease in VDT, suggesting that athletes were more sensitive to the detection of vibration than normally active controls.

The increased sensitivity to vibration is an interesting finding, as the vibration detection threshold was the only measure that was altered toward a gain of function (more sensitive perception). Vibration results in a small variation in muscle length, thereby activating low-threshold muscle spindle proprioceptors [12,64]. Decreased vibration-detection thresholds indicate an increased excitability of those non-pain-encoding proprioceptors or of the respective central projection pathways. There is evidence that vibration perception is associated with postural control [32,33]. Postural control is an important feature of the athlete's competence, and therefore specifically trained in athletes. In this regard, enhanced vibration sensitivity may be the result of a well-trained locomotive system. As a defective locomotive system is a key factor in the pathophysiology of restless leg syndrome, it is interesting to note that an increased sensitivity to vibration has also been demonstrated for patients suffering from restless leg syndrome [2]. However, this assertion is speculative, and further research is needed to better understand the underlying mechanisms.

4.2. Reduced CPM in athletes

Athletes were characterised by a significantly lower activation of the CPM induced by the CPM-TASK than normally active controls. Although, there is consistent evidence that intense physical activity results in the direct activation of endogenous pain inhibition for a limited period of time [29–31], the long-term consequences of the chronic activation of this system by regular high performance exercise have not been investigated thus far.

One possible explanation may be that tonically increased activation levels of the endogenous pain inhibitory system in athletes result in a ceiling effect: because of the continuous and heightened activation level of endogenous pain inhibition, additional activation as induced by the CPM-TASK may be truncated, and athletes failed to respond adequately when directly challenged using the CPM-paradigm. The 'elevated activation level hypothesis' of inhibitory pain control in athletes is consistent with our observation that all QST parameters, with the exception of VDT, showed a general trend towards reduced sensitivity. The constant activation of the descending pain inhibitory system in athletes might be the compensatory response to repeated noxious input induced by regular exhaustive training in these subjects. Without such continuous counter-regulatory pain inhibitory activity, athletes might not be able to endure daily physical activity.

Alternatively, there may be a shift in the activation threshold of the endogenous pain inhibitory system in athletes. The 'threshold hypothesis' postulates that the pain inhibitory system in athletes require higher stimuli to get activated or, using fixed stimulus intensity, the same stimulus will result in a lower activation of the pain inhibitory system in these subjects.

One may argue that it is easy to test this hypothesis directly by using more painful stimuli as conditioning stimuli. However, increased noxiousness of the conditioning stimuli results in an increased drop-out rate of subjects who are sensitive to pain, thus leading to a strong selection bias for the overall results. Nevertheless, the hypothesis is supported indirectly by the finding that the correlation between cold-pressor associated pain intensity and induced CPM was higher in the athlete group than for the entire sample ($r = 0.222$ vs $r = 0.032$). Accordingly, this might indicate that in some athletes the threshold to activate the CPM was not reached.

As chronic widespread pain, which is not rare in athletes [23], is often explained by exhaustion of CPM [44], the hypothesis of an elevated activation level may contain an interesting approach for future research on pain in athletes.

Notably, at present there are no accepted standards for the performance of CPM. There are different studies using either tonic [17,28,44,58,68] or phasic stimuli [1,15,35]. As the paradigm used in this study was based on a tonic heat stimulus as test stimulus, our findings cannot be extrapolated offhandedly to other kinds of stimuli. Further research is needed using other paradigms (e.g., phasic test stimuli) to induce such modulation, which might show different aspects of these systems, and, possibly, different clinical correlates.

4.3. Limitations

Limitations include lack of statistical power as a result of small sample sizes as well as risk of false positive results. Based on our explorative-descriptive approach, *P*-values should be interpreted more as a descriptive measure of effect than as a confirmatory judgement.

In addition, with the use of sensory measures at or near threshold to characterise pain sensitivity, the findings might not be transferable to pain tolerance. Moreover, the generalisability of our results to athletes in general is limited, as our study was restricted to male endurance athletes, accordingly, our results may not be representative for female athletes nor for other kind of sports (e.g., game or strength sports). Furthermore, although our athletes were characterised by both outstanding physical fitness and regular participation in official competitions, it should also be borne in mind, that 'athleticism' was not assessed explicitly in our study.

At last, determining the direction of causality of our findings is not possible given our study design. Whether athletes acquire altered pain perception because they engage in physical activity or whether they are able to engage in physical activity as a result of altered pain perception requires further longitudinal research.

4.4. Conclusions

The proposed alterations in endogenous pain modulation noted in our study may have consequences for future research. For example, various pain alleviating medications reduce pain through activation of pain-inhibitory circuits [42] and may therefore act differentially in athletes. Moreover, a chronic overstressing of the endogenous pain inhibitory pathways by heightened activation levels may eventually result in exhaustion over time. Such exhaustion may result in disinhibition of pain processing and in transition from acute to chronic pain conditions as well as spatial pain spreading, which are both common problems in athletes [33,22,26,51,60,67]. In contrast, a shift in the activation threshold

may protect the endogenous pain inhibitory pathways from chronic overstressing over the course of time and may thus contribute to an increase in the efficiency of pain inhibition on a continuing basis.

Together, the results of this research support the idea that athletes generally differ from non-athletes with respect to pain perception as well as pain processing and suggest a compensatory response of the endogenous antinociceptive system to the repeated noxious input induced by the regular exhaustive training in endurance athletes.

Conflict of interest statement

There are no conflicts of interest. No benefits in any form have been or will be received from a commercial party directly or indirectly related to the subject of this manuscript.

Acknowledgements

The authors wish to thank M. Ebert-Haselmayr, B. Schneiders and J. Vogt for excellent technical assistance. Involved coworkers were supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung; LOGIN consortium, FKZ: 01EC1010A). The submitted manuscript does not contain information about medical device(s)/drug(s).

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