Modulation of Pain Perception and Tolerance Following Treadmill Running with Different Intensities

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Abstract

Objective: This study investigated the acute and follow-up exercise induced hypoalgesia (EIH) effects of treadmill running with various intensities and durations in healthy individuals, and evaluated the relation between the endogenous pain modulation and the EIH effects.

Methods: A total of 66 healthy female individuals were enrolled in this study. Participants were randomly assigned into 3 intervention groups, and performed a running session at the intensity of 40% reserved heart rate (HRR), 55% HRR and 70% HRR for 35min. The EIH effects were evaluated by the changes of pressure pain thresholds (PPT) and pressure pain tolerance thresholds (PPTol) before running, every 5min during running and 5min, 10min, 24h follow-ups. And the conditioned pain modulation (CPM) was also measured to determine the changes of endogenous pain modulation functions.

Results: Compared with baseline, there was a significant increase of PPT and PPTol at arm and leg in all groups during running and 5-10min follow-ups. The PPT and PPTol changes of moderate and low intensity groups were significantly higher than the high intensity group during running and 24h after running. While the CPM responses of high intensity group were significantly reduced compared with other groups at 24h follow-up.

Conclusion: Moderate and low intensity running may trigger the endogenous descending inhibition and elicit EIH effects following running and persisting over 24h. While the high intensity running only induced limited EIH effects for the activation of both descending pain inhibition and facilitation, with reduced CPM at 24h follow-up. And the improvement of PPTol might also contributed by the reward circuit in the pain cognitive processing, and might be limited by the fatigue induced via high intensity running.

Key words: exercise induced hypoalgesia; endogenous pain modulation; treadmill running; pain thresholds; pain tolerance thresholds; analgesic effects

Introduction

Various exercises have been induced as essential parts of the chronic pain management. Through the exercise-induced hypoalgesia (EIH)[1], individuals who suffering from pain can attenuate their pain perception[2] and improve their emotional state after global aerobic exercises[3] or local resistance exercises[4]. Both the endogenous pain modulation[5] and the cortex cognitive modulation[6] participated in the EIH process, where exercise with different intensity and duration can trigger the endogenous descending inhibition to the nociceptive signals from the spinal cord dorsal horn[7], and activate the reward circuits[8] of the corticolimbic systems.

In asymptomatic individuals, the analgesic effect tends to be positively correlated with exercise intensity and duration within a range[9,10], while the emotional aspects of pain can be significantly improved during light physical activity[11]. However, the EIH in pain patients can be attenuated via the impaired endogenous pain modulation[12], or related psychological factors[13] including pain catastrophizing, fear, anxiety, and depression. Particularly, exercises with higher intensity often failed to increase the pain thresholds in chronic pain patients[14], while low-intensity activities can still improve the emotional aspect of pain[15], and increase the tolerance to the experimental pain stimulus.

Differences in EIH effects between various individuals and exercises might be contributed by the mechanisms of endogenous pain modulation, which have different activation thresholds towards perception stimulus[16]. The ventromedial nucleus (VM) of thalamus can be activated by inputs from both noxious and non-noxious C fibers and induce the descending pain inhibition, while the mediodorsal nucleus (MD) of thalamus can trigger descending pain facilitation with inputs from noxious C fibers. And the neurons in periaqueductal gray (PAG)[17] and rostral ventromedial medulla (RVM)[18] can modulate the nociception signals through the projection to the dorsal horn of spinal cord and change the pressure, heat, or cold pain threshold (PPT, HPT and CPT).

Considering the threshold of descending facilitation is relatively lower than the inhibition[19], the activation of pain inhibition usually requires high intensity painful stimulus (conditioned stimulus), which is called conditioned pain modulation (CPM). Thus, exercise with high intensity may activate the opioid[20] systems in the PAG and RVM[21], then induce the pain inhibition, but not in the pain patients with impaired CPM function[22]. And the high intensity exercise may also trigger the pain facilitation[23], which may decrease both EIH and CPM responses, lead to the mechanical allodynia[24] and even produce the delayed onset muscle soreness (DOMS)[25] in asymptomatic individuals[26].

However, the moderate or low intensity stimulus may still activate the cannabinoid[27] , and 5-HT[5] systems, and trigger the descending pain inhibition via the temporal summation[28] of non-noxious C fibers inputs, without triggering the nociceptors and descending facilitation. And the inhibition-only EIH effects following moderate or low intensity exercise might not induce the mechanical allodynia or DOMS, which have not been verified in human studies yet.

Apart from the activation of endogenous pain modulation, the exercise with moderate or voluntarily-controlled intensity[29] can also activate the reward circuits by enhancing the dopamine (DA) released from the ventral tegmental area (VTA) to the nucleus accumbens (NAc)[30], which can also increase the pressure, heat or cold pain tolerance (PPTol, HPTol or CPTol), and attenuate pain-related fear and avoid behavior.

Considering the potential modulation of EIH effect in exercises with different intensities, this study aimed to compare the changes of PPT and PPTol in asymptomatic individuals following running exercises with various intensities. And we were also investigated changes of the CPM responses before and 24h after the running sessions.

We hypothesized that: (1) Low-, moderate- and high-intensity running exercise might elicit EIH responses and increase the PPT and PPTol. (2) The analgesic effects of moderate or low intensity exercise might persist at 24h follow-up, while the high intensity exercise might decrease the pain threshold in the next day. (3) The CPM responses at 24h following high intensity running might attenuated compared with the low and moderate intensity running.

Methods

This study has been approved (2023023H) by Sports Science Experimental Ethics Committee of Beijing Sport University (supplemental file 1).

Study design

This study is designed as a randomized controlled trial. A total of 69 participants included in this study were invited to perform exercise interventions with different intensities and durations. Before the start, all participants would fill in a questionnaire including age, height, weight, and injury history, and finish the baseline measurement including resting-heart rate (HRrest), age-adjusted maximum-heart rate (HRmax), reserved heart rate (HRR) and CPM responses. The HRmax of all participants was estimated using the formula[31]: HRmax=202.5-0.53*age, and the HRR was calculated as HRR=HRmax-HRrest. To avoid potential long-lasting analgesic effects of the CPM test, all the exercise interventions will perform 1 week after the baseline measurements.

All individuals who conformed to this study were randomly assigned to 3 experimental groups (A, B, and C) with different exercise intensity in a 1:1:1 ratio by a computer. And the participants would execute the low-intensity treadmill running with 40% HRR in group A, moderate-intensity (55% HRR) in group B, or high-intensity (70% HRR) in group C, while the speed of the running would be determined in coherence with the target heart rate (THR) during the baseline measurements. All participants would perform a single exercise session with predetermined intensity for 30min.

The outcome measures including PPT and PPTol were assessed before, during, and after running session. And the CPM responses were tested via cold pressure methods in baseline sessions, and

24h after running session. The HR would also be recorded during the running session. (Figure 1)

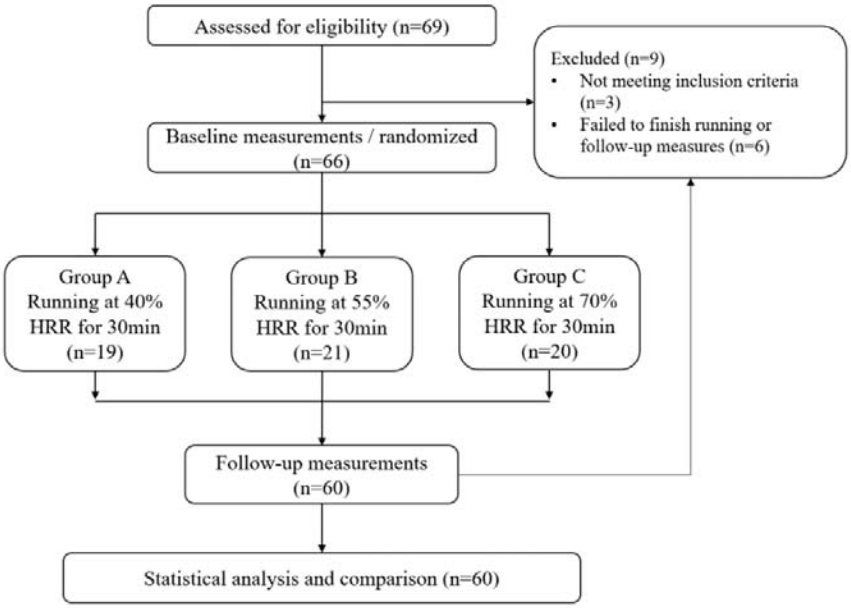

Figure 1. Flowchart of the experiment

Participants

According to the previous studies[32,33], the effect size of PPT changes by aerobic exercise is in the range of 0.20–0.38. PPTol size is in the range of 0.20. In this study, we used G-Power Software: F-test, ANOVA: two-way repeated measures (within factors) with the following parameters: effect size = 0.38; test level = 0.05; test efficacy = 0.95; group numbers = 3, number of measurements = 7. The total sample size of this study should be a minimum of 66 participants in the three groups, or 22 participants in each group.

A total of 69 female students (age 18-30 years) from Beijing Sport University were included in this study, and 66 of them were finally enrolled. The following eligibility criteria were used to include the participants: (1) had no pain or pain-related syndrome within 3 months; (2) had no injury history of lower extremities within 1 year; (3) had no neurological disability, including anxiety, depression or cognitive impairments; (4) had no potential or confirmed heart disease, or recovered from a heart disease less than 1 year.

The exclusion criteria were: (1) failed to maintain or tolerant the exercise intensity during the treadmill running; (2) showed serious exertion or fatigue in 24h after exercise sessions; (3) showed intolerable pain during the pain perception test or the CPM test.

Interventions

All participants would perform a single running session, while the participants in different groups

executed treadmill running with different intensities, which were set by individuals' THR. The THR was 40% HRR in group A, 55% HRR in group B, and 70% HRR in group C, which would be calculated and displayed on the screen for each participant during the baseline measurements in order to determine the running speed. Participants would wear an HR belt during the test and running session, which was linked to the computer and a screen to show and record the real-time HR. (Figure 2)

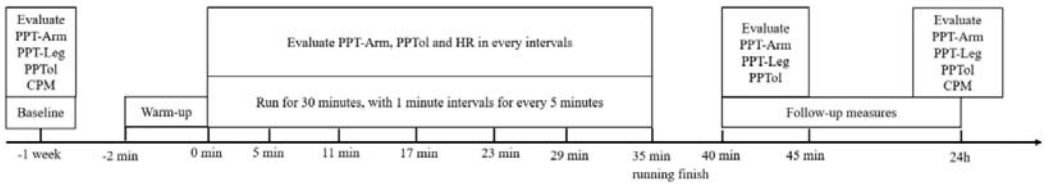

Figure 2. Flowchart of the intervention

Pre-exercise PPT and PPTol were measured 10 min before the exercise session, and the CPM responses were tested in baseline measurement to avoid potential long-lasting analgesic effects. The exercise session consisted of 30min running with 5 interval periods (at the speed of 4 km/h for 1 min) in every 5min (35min in total). And the HR, PPT, and PPTol during exercises were measured in each interval period.

After exercise session, participants were asked to sit down and rest, while the post-exercise PPT and PPTol were measured at 5min and 10min after the exercise. The HR would keep recorded at 5min intervals during the whole exercise session. And the PPT, PPTol and CPM would be also measured at 24h following the exercise session.

Outcome measures

PPT

PPT was measured by a quantitative sensory testing protocol[34] via handheld pressure algometer (Baseline Dolorimeter, Fabrication Enterprises, USA) with a 1 cm^2 metal probe and applied at a rate of 0.5kg/s. PPT was measured at the extensor carpus radialis (remote limb) and the peroneus longus (local limb) on the right side. Participants were instructed to report as soon as they perceived a pain intensity by visual analog score 30 out of 100 (Pain30) during pressure application, where the pressure thresholds would be recorded as PPT.

PPTol

PPTol was measured by a quantitative sensory testing protocol[35] via handheld pressure algometer (Baseline Dolorimeter, Fabrication Enterprises, USA) with a 1 cm^2 metal probe and applied at a rate of 0.5kg/s. PPTol was measured at the extensor carpus radialis on the left side. Participants were instructed to report as soon as they perceived a pain intensity by visual analog score 70 out of 100 (Pain70) during pressure application, where the pressure thresholds would be recorded as PPTol.

CPM

The CPM response was measured by quantitative sensory testing protocol, using the cold pressor procedure[36] (CPT), where the test stimulation was applied by mechanical pressure and conditioned stimulation was applied by cold water immersion. Participants first receive pressure stimulation at the ipsilateral extensor carpus radialis and report a PPT at Pain30 as a test stimulus. Then participants were instructed to immerse the contralateral hand into cold water at 8□ for 1 min, and report the PPT at Pain30 when the pressure was applied again at the threshold after 1 min of immersing. The difference between the two PPTs was recorded as the response of CPM.

Statistical analysis

Normality of all data was assessed by means of the 1-sample Kolmogorov-Smirnov test. The difference in baseline data (height, weight, HRrest, CPM, PPT and PPTol) between groups was verified by the one-way ANOVA test. The one-way repeated measured ANOVA was applied to examine whether there was a significant difference within the 3 groups considering the PPT and PPTol with the variables as running times and following-up times. The changes of CPM responses were tested by the one-way ANCOVA, while the baseline measurements were set as covariates. The Bonferroni method was applied in the post-hoc multiple comparison. All data were processed using SPSS Version 21.0, and the statistical significance was set at $p<0.05$ for all tests.

Results

Baseline and intervention characteristics

Of the 66 participants enrolled in this study, 19 of them in group A completed running for 30min with low intensity, 21 of them in group B completed running for 30min with moderate intensity, 20 of group C completed running for 30min with high intensity, and 6 participants did not complete running sessions or follow-up measurements and dropped out of this study. All of baseline characteristics, including age (p=0.097), height (p=0.797), weight (p=0.576), HRrest (p=0.814), PPT of arms (p=0.949), PPT of legs (p=0.799), PPTol (p=0.740) and CPM (p =0.998), did not present significant differences between the groups. During the running periods, the HR were recorded for every interval and differed between groups considering the intensities. (Table 1)

Table 1. Baseline and intervention measurement (M±SD) [1]

Measurements	A (n=19)	B(n=21)	C(n=20)	P
Age (y)	21.63±2.01	22.52±2.06	21.10±2.20	0.097
Height (cm)	166.95±7.31	166.48±7.27	165.55±4.93	0.797
Weight (kg)	59.05±9.67	56.05±9.23	57.55±8.02	0.576
PPT-Arm (kg/cm^2)	2.31±0.16	2.33±0.13	2.32±0.17	0.949
PPT-Leg (kg/cm^2)	4.40±0.53	4.51±0.48	4.46±0.48	0.799
PPTol (kg/cm2)	4.57±0.42	4.68±0.49	4.61±0.40	0.740
CPM (kg/cm^2)	0.70±0.15	0.70±0.16	0.71±0.17	0.998
HRrest (beats/min)	81.11±0.89	82.71±6.86	81.95±7.79	0.814

THR (beats/min)	125.26±5.32	142.03±3.07	158.51±2.40	<0.001
HR of 5min (beats/min)	125.85±5.75	143.95±5.96	161.00±4.67	<0.001
HR of 11min (beats/min)	126.36±6.01	143.38±6.67	163.35±3.92	<0.001
HR of 17min (beats/min)	126.00±6.45	142.62±5.69	164.00±4.34	<0.001
HR of 23min (beats/min)	125.32±6.80	143.95±5.98	165.01±4.52	<0.001
HR of 29min (beats/min)	126.11±6.43	143.71±4.66	165.95±3.79	<0.001
HR of 35min (beats/min)	126.47±5.86	144.14±5.34	166.15±4.15	<0.001

[1]: 1-way ANOVA, significant difference was set by $p \leq 0.05$.

Changes of PPT of arm following running

During the running periods, the one-way repeated-measures ANOVA revealed significant main effects ($F=264.74$, $p<0.001$) for the running time at PPT of arm, which indicated that the running for 30min increased global PPT significantly. And the interaction effect ($F=13.55$, $p<0.001$) of the running intensity and time at PPT of arms was also significant. Results of post-hoc comparisons showed that changes of PPT in moderate intensity group were significantly higher than low ($p=0.003$) and high ($p<0.001$) intensity groups, while the low intensity running also induced higher PPT ($p<0.001$) than the high intensity running.

During the acute follow-up periods, the one-way repeated-measures ANOVA revealed significant main effects ($F=385.83$, $p<0.001$) for the running time at PPT of arm, which indicated that the improvements of global PPT persisted for at least 10min. And the interaction effect ($F=25.35$, $p<0.001$) of the running intensity and time at PPT of arm was also significant. Results of post-hoc comparisons showed that changes of PPT in high intensity group were significantly lower ($p<0.001$) than other groups, but not differed between low and moderate groups ($p=0.09$).

At 24h after running, the one-way ANCOVA revealed significant between-groups differences ($F=16.52$, $p<0.001$) considering the running intensities. And the results of post-hoc comparisons showed that changes of PPT in high intensity group were significantly lower ($p<0.001$) than other groups, but not differed between low and moderate groups ($p=0.80$). (Table 2, Table 3 and Figure 3)

Table 2. Changes of PPT-Arm following running exercise (M±SD)

Measurements	A (n=19)	B(n=21)	C(n=20)	P
Baseline	2.31±0.16	2.33±0.13	2.32±0.17	
5min in running[1]	2.81±0.21	3.09±0.27	2.72±0.30	
11min in running[1]	3.10±0.33	3.45±0.30	2.87±0.32	
17min in running[1]	3.32±0.35	3.68±0.31	2.98±0.32	<0.001[1]
23min in running[1]	3.46±0.42	3.78±0.32	3.05±0.32	
29min in running[1]	3.60±0.34	3.80±0.32	3.00±0.31	
35min in running[1]	3.51±0.23	3.79±0.29	2.95±0.29	
5min in follow-up[2]	3.38±0.35	3.61±0.35	2.80±0.28	<0.001[2]
10min in follow-up[2]	3.27±0.34	3.52±0.36	2.79±0.31	

24h in follow-up[3]	2.73±0.23	2.83±0.33	2.26±0.31	<0.001[3]

[1]: 1-way Repeated measures ANOVA, significant difference was set by p≤0.05.

[2]: 1-way Repeated measures ANOVA, significant difference was set by p≤0.05.

[3]: 1-way ANCOVA, significant difference was set by p≤0.05.

Table 3. Between-group comparison results of PPT-Arm following running exercise

Measurements	Groups		Mean Difference	Std. Error	Sig.	95% CI	
						Lower Bound	Upper Bound
0-35min in running[1]	A	B	-0.254	0.073	0.003	-0.435	-0.073
		C	0.317	0.074	<0.001	0.134	0.500
	B	C	0.571	0.072	<0.001	0.393	0.750
5-10min in follow-up[2]	A	B	-0.162	0.073	0.091	-0.342	0.018
		C	0.351	0.074	<0.001	0.169	0.533
	B	C	0.513	0.072	<0.001	0.336	0.691
24h follow-up[3]	A	B	-0.103	0.092	0.800	-0.329	0.123
		C	0.478	0.093	<0.001	0.249	0.707
	B	C	0.581	0.090	<0.001	0.358	0.804

[1]: 1-way Repeated measures ANOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.

[2]: 1-way Repeated measures ANOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.

[3]: 1-way ANCOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.

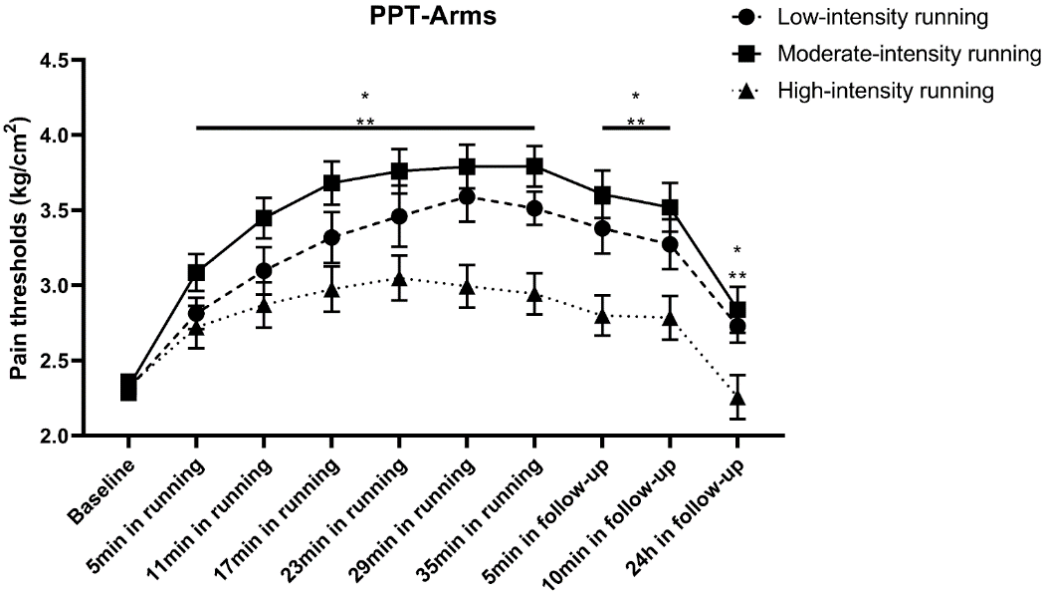

Figure 3. Changes of PPT of arms following running

*: PPT in low intensity group significantly higher than high intensity group

**: PPT in moderate intensity group significantly higher than high intensity group

Changes of PPT of leg following running

At the end of running, the one-way ANCOVA revealed significant between-groups differences ($F=19.25$, $p<0.001$) considering the running intensities. And the results of post-hoc comparisons showed that changes of PPT in high intensity group were significantly lower than low ($p=0.002$) and moderate ($p<0.001$) intensity groups.

During the acute follow-up periods, the one-way repeated-measures ANOVA revealed significant main effects ($F=181.03$, $p<0.001$) for the running time at PPT of leg, which indicated that the improvements of local PPT persisted for at least 10min. And the interaction effect ($F=18.65$, $p<0.001$) of the running intensity and time at PPT of leg was also significant. Results of post-hoc comparisons showed that changes of PPT in high intensity group were significantly lower than low ($p=0.007$) and moderate ($p<0.001$) intensity groups.

At 24h after running, the one-way ANCOVA revealed significant between-groups differences ($F=38.11$, $p<0.001$) considering the running intensities. And the results of post-hoc comparisons showed that changes of PPT in high intensity group were significantly lower ($p<0.001$) than other groups. (Table 4, Table 5 and Figure 4)

Table 4. Changes of PPT-Leg following running exercise (M±SD)

Measurements	A (n=19)	B(n=21)	C(n=20)	P
Baseline	4.40±0.53	4.51±0.48	4.46±0.48	
35min in running[1]	5.87±0.74	6.21±0.66	5.29±0.48	<0.001[1]
5min in follow-up[2]	5.71±0.71	5.95±0.73	4.85±0.43	<0.001[2]
10min in follow-up[2]	5.56±0.67	5.88±0.53	4.81±0.45	
24h in follow-up[3]	5.19±0.56	5.37±0.50	4.21±0.49	<0.001[3]

[1]: 1-way ANCOVA, significant difference was set by $p\leq0.05$.

[2]: 1-way Repeated measures ANOVA, significant difference was set by $p\leq0.05$.

[3]: 1-way ANCOVA, significant difference was set by $p\leq0.05$.

Table 5. Between-group comparison results of PPT-Leg following running exercise

Measurements	Groups		Mean Difference	Std. Error	Sig.	95% CI	
						Lower Bound	Upper Bound
0-35min in running[1]	A	B	-0.272	0.169	0.336	-0.688	0.144
		C	0.614	0.170	0.002	0.195	1.034
	B	C	0.886	0.166	<0.001	0.477	1.296
5-10min in follow-up[2]	A	B	-0.226	0.162	0.507	-0.626	0.174
		C	0.519	0.164	0.007	0.115	0.924
	B	C	0.745	0.160	<0.001	0.351	1.140
24h follow-up[3]	A	B	-0.119	0.135	>0.999	-0.453	0.214
		C	1.009	0.136	<0.001	0.672	1.345
	B	C	1.128	0.133	<0.001	0.800	1.456

[1]: 1-way ANCOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.
[2]: 1-way Repeated measures ANOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.
[3]: 1-way ANCOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.

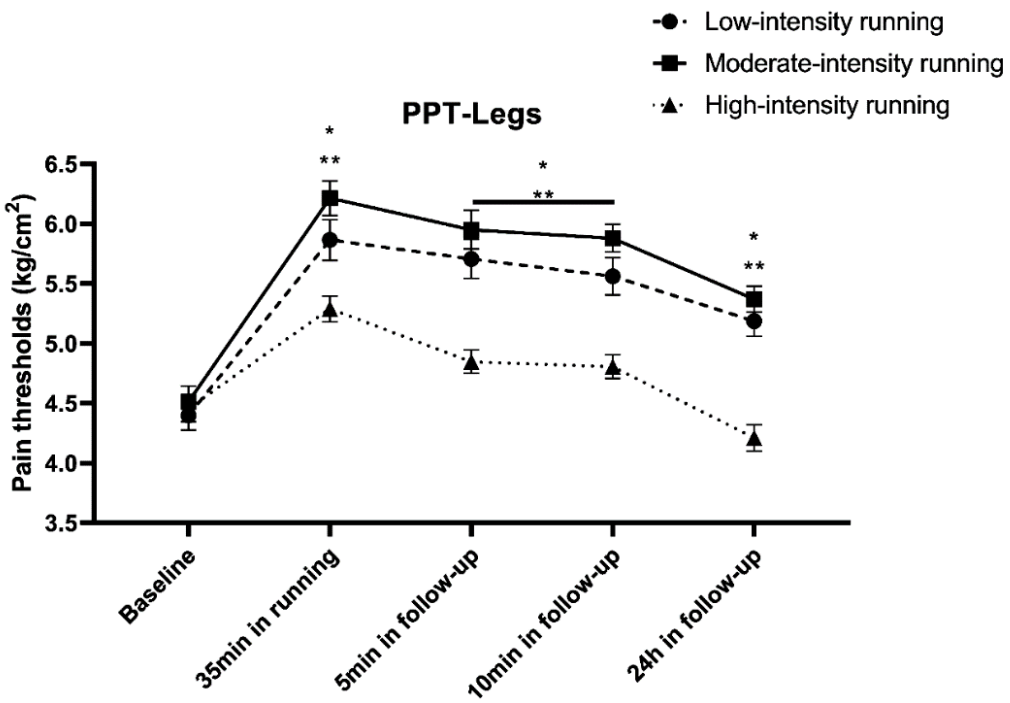

Figure 4. Changes of PPT of legs following running
*: PPT in low intensity group significantly higher than high intensity group
**: PPT in moderate intensity group significantly higher than high intensity group

Changes of PPTol following running

During the running periods, the one-way repeated-measures ANOVA revealed significant main effects (F=122.93, p<0.001) for the running time at PPTol, which indicated that the running for 30min increased PPTol significantly. And the interaction effect (F=3.90, p<0.001) of the running intensity and time at PPTol was also significant. Results of post-hoc comparisons showed that changes of PPTol in moderate intensity group were significantly higher (p=0.008) than high intensity groups, but there were no significant differences between low and high intensity groups (p=0.129), or low and moderate intensity groups (p=0.256)

During the acute follow-up periods, the one-way repeated-measures ANOVA revealed significant main effects (F=150.96, p<0.001) for the running time at PPTol, which indicated that the improvements of PPTol persisted for at least 10min. And the interaction effect (F=4.18, p=0.02) of the running intensity and time at PPTol was also significant. Results of post-hoc comparisons showed that changes of PPTol in moderate intensity group were significantly higher (p=0.006) than high intensity groups, but there were no significant differences between low and high intensity groups (p=0.140), or low and moderate intensity groups (p=0.199)

At 24h after running, the one-way ANCOVA revealed significant between-groups differences (F=13.58, p<0.001) considering the running intensities. And the results of post-hoc comparisons showed that changes of PPTol in high intensity group were significantly lower than moderate (p<0.001) and low (p<0.001) intensity groups, and were not differed between low and moderate intensity groups (p=1.000). (Table 6, Table 7 and Figure 5)

Table 6. Changes of PPTol following running exercise (M±SD)

Measurements	A (n=19)	B(n=21)	C(n=20)	P
Baseline	4.57±0.42	4.68±0.49	4.61±0.40	
5min in running[1]	5.23±0.52	5.45±0.61	5.21±0.57	
11min in running[1]	5.57±0.62	5.73±0.69	5.38±0.74	
17min in running[1]	5.76±0.64	5.96±0.63	5.36±0.67	<0.001[1]
23min in running[1]	5.88±0.63	6.09±0.69	5.50±0.78	
29min in running[1]	5.97±0.72	6.18±0.69	5.44±0.66	
35min in running[1]	5.94±0.69	6.23±0.50	5.51±0.62	
5min in follow-up[2]	5.74±0.59	6.04±0.51	5.40±0.55	<0.001[2]
10min in follow-up[2]	5.63±0.60	5.86±0.56	5.22±1.00	
24h in follow-up[3]	5.27±0.47	5.33±0.54	4.58±0.57	<0.001[3]

[1]: 1-way Repeated measures ANOVA, significant difference was set by p≤0.05.

[2]: 1-way Repeated measures ANOVA, significant difference was set by p≤0.05.

[3]: 1-way ANCOVA, significant difference was set by p≤0.05.

Table 7. Between-group comparison results of PPTol following running exercise

Measurements	Groups		Mean Difference	Std. Error	Sig.	95% CI	
						Lower Bound	Upper Bound
0-35min in running[1]	A	B	-0.201	0.175	0.256	-0.552	0.150
		C	0.273	0.177	0.129	-0.082	0.628
	B	C	0.474	0.173	0.008	0.128	0.821
5-10min in follow-up[2]	A	B	-0.208	0.160	0.199	-0.529	0.113
		C	0.243	0.162	0.140	-0.082	0.567
	B	C	0.451	0.158	0.006	0.134	0.767
24h follow-up[3]	A	B	-0.002	0.156	>0.999	-0.387	0.382
		C	0.711	0.157	<0.001	0.323	1.098
	B	C	0.713	0.153	<0.001	0.335	1.091

[1]: 1-way Repeated measures ANOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.

[2]: 1-way Repeated measures ANOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.

[3]: 1-way ANCOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.

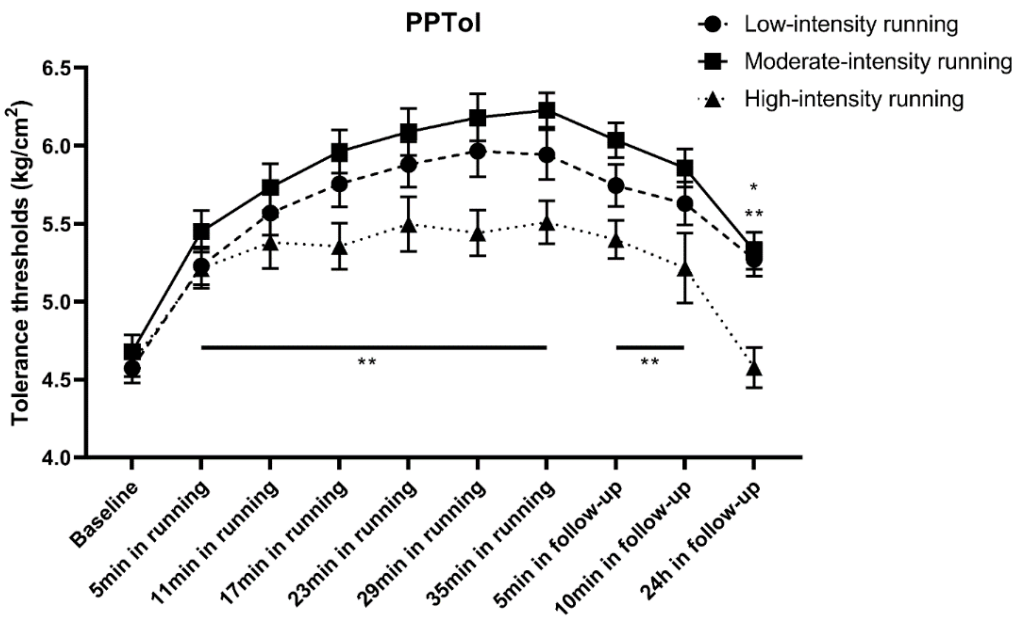

Figure 5. Changes of PPTol following running

*: PPTol in low intensity group significantly higher than high intensity group

**: PPTol in moderate intensity group significantly higher than high intensity group

Change of CPM following running

At 24h after running, the one-way ANCOVA revealed significant between-groups differences (F=27.17, p<0.001) considering the running intensities. And the results of post-hoc comparisons showed that changes of CPM in high intensity group were significantly lower (p<0.001) than other groups. (Table 8, Table 9 and Figure 6)

Table 8. Changes of CPM following running exercise (M±SD)

Measurements	A (n=19)	B(n=21)	C(n=20)	P
Baseline	0.70±0.15	0.70±0.16	0.71±0.17	
24h in follow-up[1]	0.91±0.25	0.90±0.22	0.41±0.14	<0.001[1]

[1]: 1-way ANCOVA, significant difference was set by p≤0.05.

Table 9. Between-group comparison results of CPM following running exercise[1]

Groups		Mean Difference	Std. Error	Sig.	95% CI	
					Lower Bound	Upper Bound
A	B	0.011	0.065	1.000	-0.150	0.171
	C	0.506	0.066	<0.001	0.344	0.668
B	C	0.496	0.064	<0.001	0.337	0.654

[1]: 1-way ANCOVA, adjusted by Bonferroni. significant difference was set by p≤0.05.

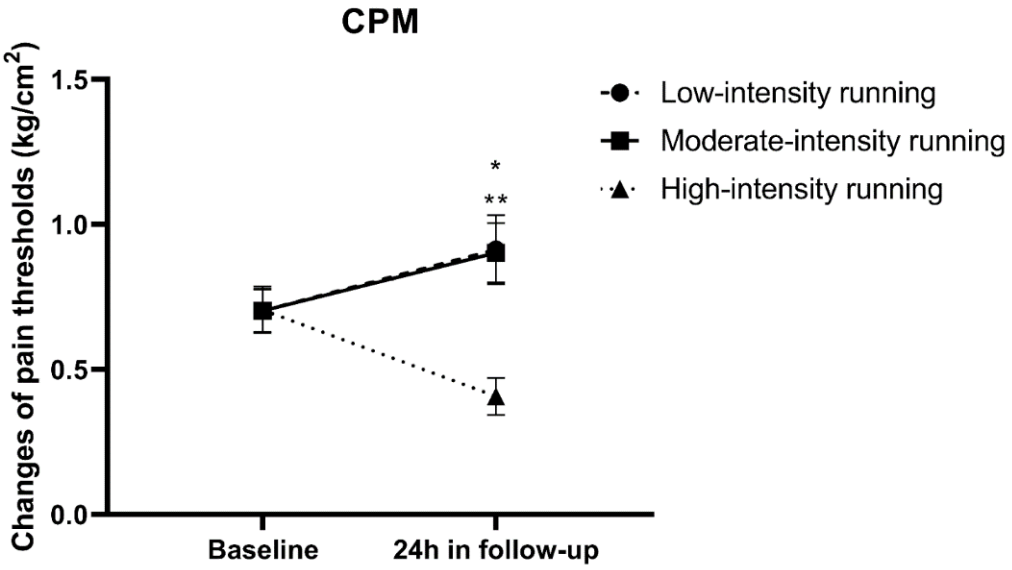

Figure 6. Changes of CPM following running

*: CPM in low intensity group significantly higher than high intensity group

**: CPM in moderate intensity group significantly higher than high intensity group

Discussion

This study investigated the modulation of EIH effects following running exercises with different intensities in healthy individuals. Interestingly, the results showed that the changes of PPT and PPTol had the temporal summation effects, which both increased along with the running time. The PPT and CPM responses of the moderate and low intensity running were significantly higher than the exercise with high intensity during running session and follow-ups. And the improvements of PPTol following moderate intensity running were also significantly greater than high intensity running. These results suggested the EIH effects might be modulated by different central mechanisms considering the context of exercises.

The PPT changes in healthy individuals following aerobic exercise with different intensities have been discussed in previous studies. In a certain range, the EIH may be positively correlated with the exercise intensity. Hoffman et al[37] compared the PPT changes during the running, and found that running with 75% VO_2max elicited greater EIH effects than the running of 50% VO_2max. However, Kruger et al[26] found that the maximal endurance cycling induced mechanical allodynia, and a cross-over study by Hviid et al[33] showed that fast walking over 60 mins can increase the PPT significantly. It has also been reported that exercise with moderate to low intensity seems to induce the EIH more effectively in patients with pain conditions[12,15].

As the muscle contraction during the exercise can activate the C fibers[38], the exercise with high intensity may upregulate the opioids[39,40] in PAG and induce the descending inhibition, but it may also induce the descending facilitation for the activation of noxious C fibers, which may decrease the EIH and CPM responses eventually. While the moderate and low intensity exercises with enough time may still summate the stimulus of non-noxious C fibers, activate the descending

inhibition with the triggering of cannabinoid[41] and 5-HT[5,42] receptors in the PAG and RVM, which would enhance the CPM responses and analgesic effects. (Figure 7)

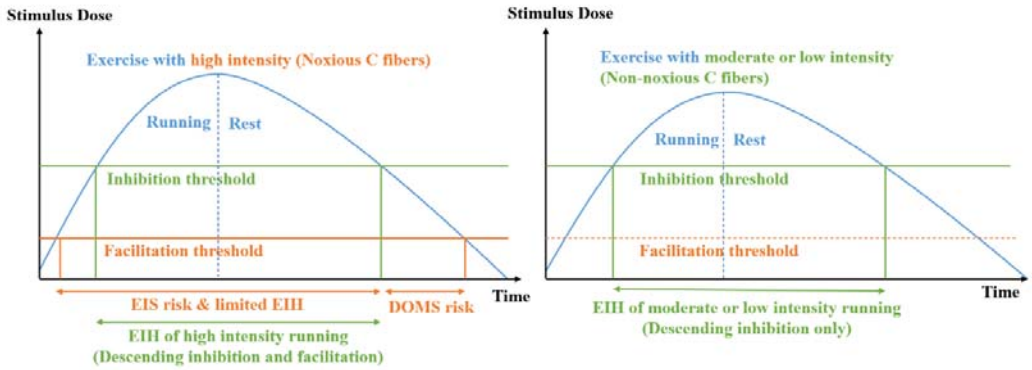

Figure 7. Mechanisms of EIH induced via running with different intensities

Considering the role of CPM responses in the EIH effects, Lemley et al[43] compared the EIH responses in healthy individuals referring to the CPM levels, and found that adults with greater CPM were more likely to report greater EIH, which were also consistent with the findings in our study. Thus, the descending inhibition might contribute to the PPT and PPTol changes during the aerobic exercises in our study, which might be modulated by the intensity and duration of exercises in healthy individuals.

Besides, the low or moderate intensity exercises can also improve the pain tolerance in patients with pain conditions, Vaegter et al[44] tested the PPT and PPTol changes during exercises in patients with high- and low- pain intensity, and the PPTol increased in all patients after both aerobic and resistance exercises despite the attenuation of the PPT levels. Similar to the pain patients, the PPTol can also increase following various exercises in healthy individuals. Vaegter et al[45] investigated the EIH responses in the submaximal isometric exercises, and the results showed that the increase in pain tolerance was the major contributor to the EIH of low-intensity exercises, and Hviid et al[33] also found that the changes in PPTol can be elicited by walking exercise in relatively low intensity, but not the PPT.

The changes of pain tolerance might be contributed by the improvement of cognitive process[6] related to pain perception in brain areas of "Pain Matrix"[46] including the modulation of the prefrontal cortex (PFC)[47], ventral tegmental area (VTA)[48], amygdala (Amgy)[8], nucleus accumbens (NAc), hippocampus (HIP) and insular[49]. A rodent study by Kami et al[50] reported that the voluntary exercise of neuropathic pain mice activated the DA neurons in VTA and the GABA neurons in the NAc shell, which is related to the pain tolerance and emotional aspects including anxiety, depression and fear related to pain perception[51]. Besides, Baiamonte et al[9] also found that the changes of PPTol during the resistance exercises were negatively related to the HR and rating of perceived exertion (RPE) levels, indicated that the fatigue of exercises might attenuate the EIH effects and reduce the tolerance to pain perceptions.

There were several limits in this study. First, due to limited funds and equipment, the indicators of

the pain tests were cut down, for instance, adding the heat pain detection and tolerance thresholds might give a more complete description of the changes in pain perception. Second, the results of individuals' pain tolerance thresholds might be diversified by the former pain experiences and subjective emotional perceptions. Lastly, all of the participants were female, and the gender difference of EIH and CPM responses following running exercise should be considered in future studies.

Conclusion

The finding of our study suggested that the changes of PPT and PPTol in healthy individuals differed from running exercises with various intensities and durations, which might be modulated by both descending pain inhibition and cognitive process considering the context of exercises. The changes of PPT, PPTol and CPM indicated that the high intensity running may activate the descending facilitation and the inhibition effects, limit the EIH effects and attenuate CPM responses. While the moderate and low intensity exercise with sufficient time can also induce the endogenous descending inhibition and reduce the pain perceptions. The improvement of PPTol might also contributed by the reward circuit in the pain cognitive processing, and might be limited by the fatigue induced via high intensity running.

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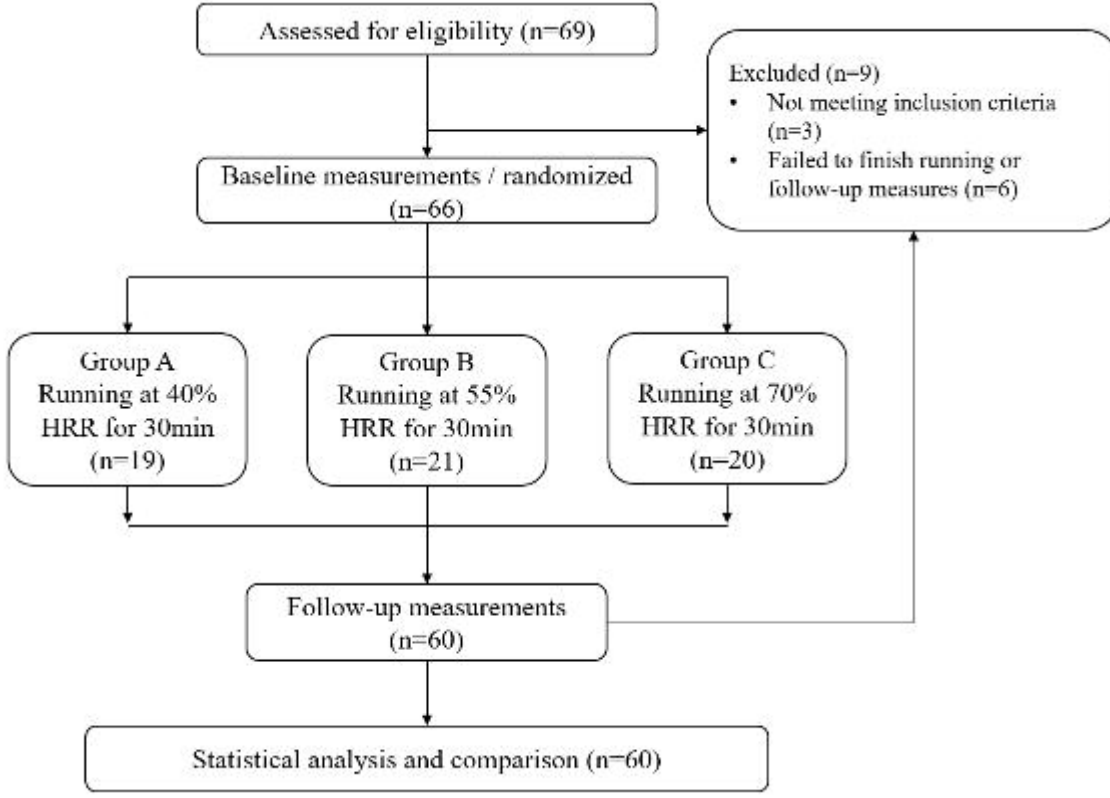
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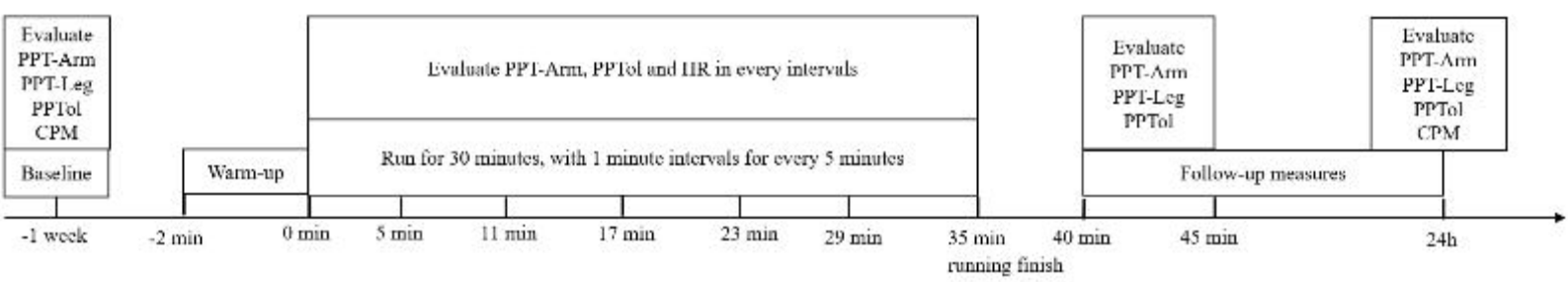
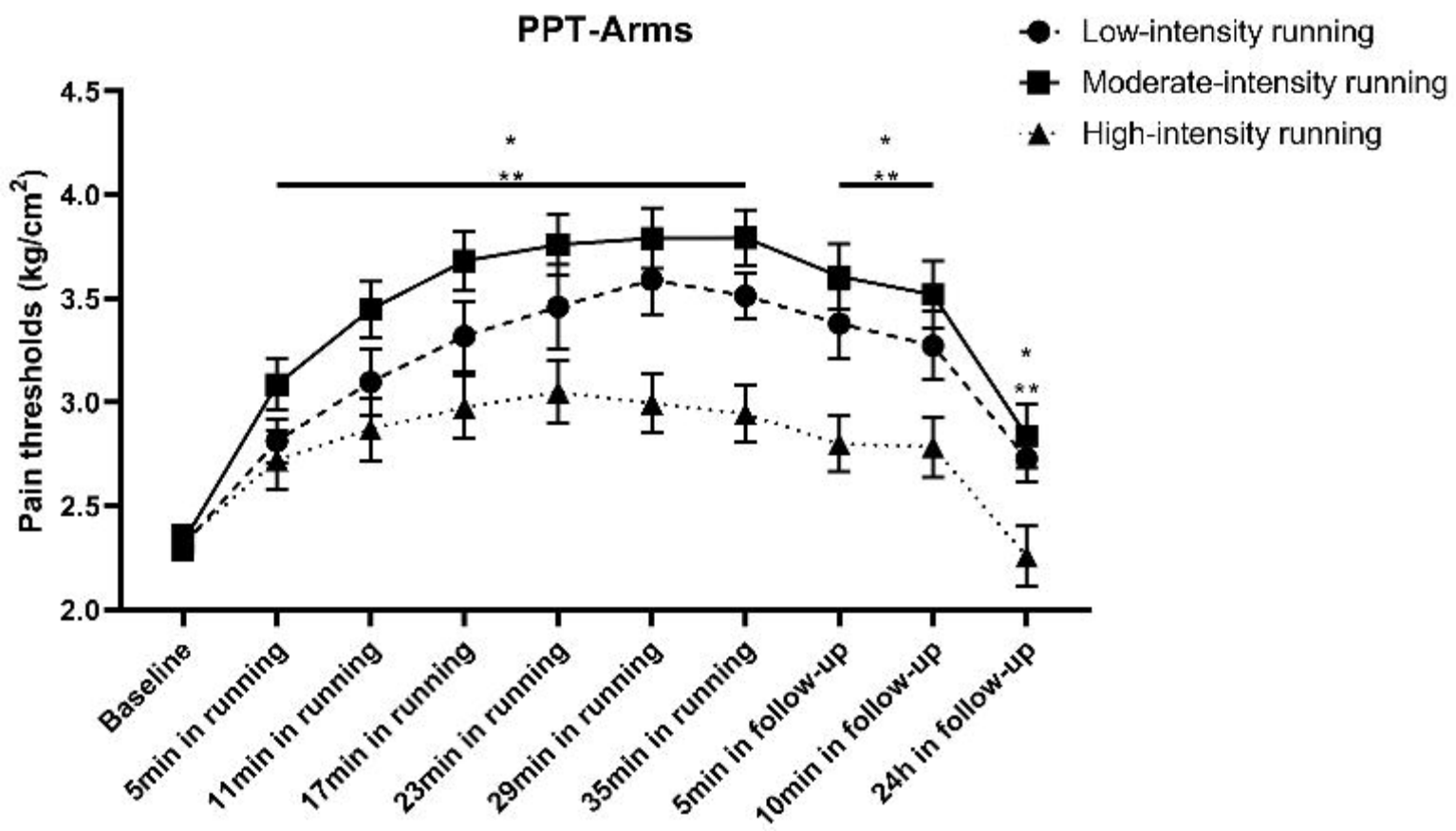
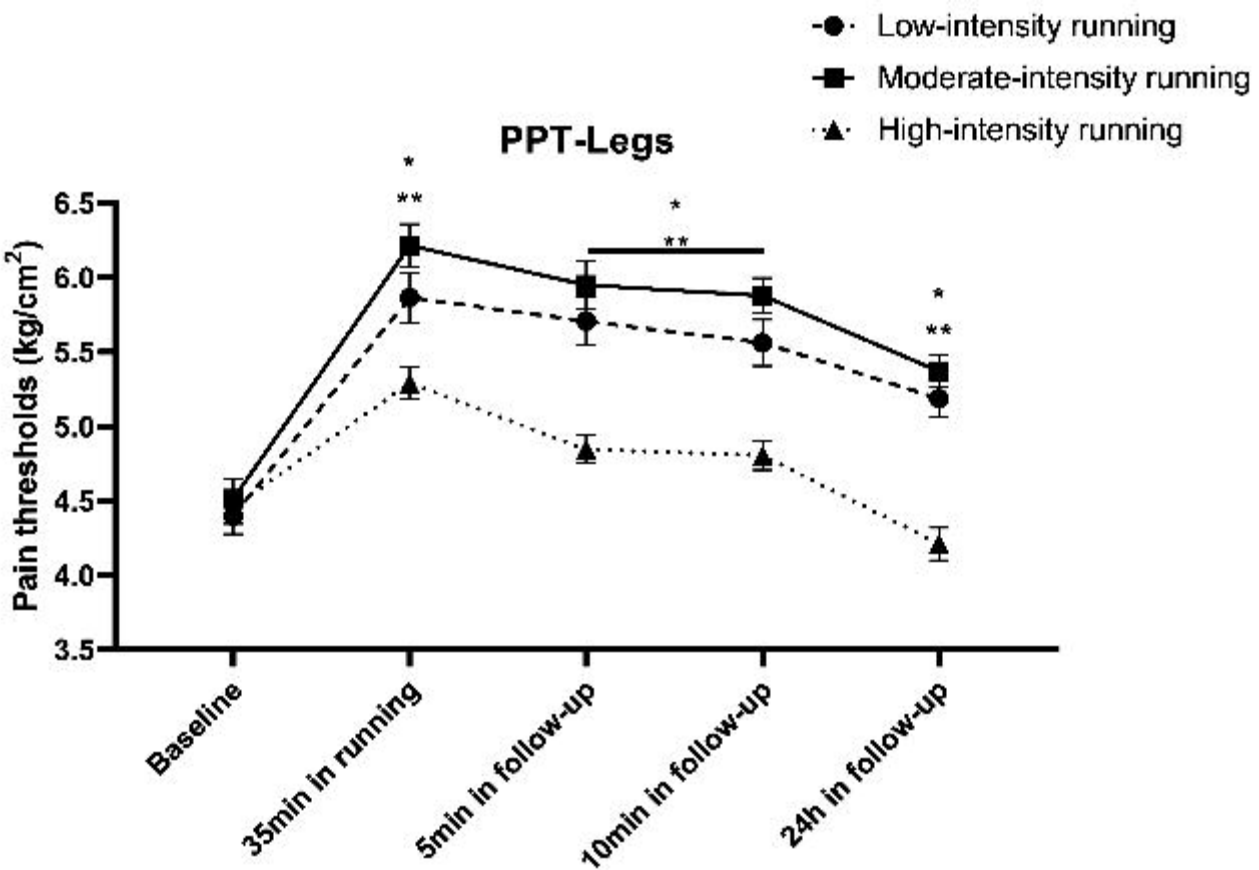
Excluded (n=9)
• Not meeting inclusion criteria (n=3)
• Failed to finish running or follow-up measures (n=6)
Baseline measurements / randomized (n=66)
Group A Running at 40% HRR for 30min (n=19)
Group B Running at 55% HRR for 30min (n=21)
Group C Running at 70% HRR for 30min (n=20)
Follow-up measurements (n=60)
Statistical analysis and comparison (n=60)


Evaluate
PPT-Arm
PPT-Leg
PPTol
CPM
Baseline
Warm-up
Evaluate PPT-Arm, PPTol and HR in every intervals
Run for 30 minutes, with 1 minute intervals for every 5 minutes
Evaluate
PPT-Arm
PPT-Leg
PPTol
Evaluate
PPT-Arm
PPT-Leg
PPTol
CPM
Follow-up measures
-1 week
-2 min
0 min
5 min
11 min
17 min
23 min
29 min
35 min
running finish
40 min
45 min
24h


PPT-Arms
Low-intensity running
Moderate-intensity running
High-intensity running
Pain thresholds (kg/cm²)
4.5
4.0
3.5
3.0
2.5
2.0
*
**
*
**
*
**
Baseline
5min in running
11min in running
17min in running
23min in running
29min in running
35min in running
5min in follow-up
10min in follow-up
24h in follow-up


Low-intensity running
Moderate-intensity running
High-intensity running
PPT-Legs
Pain thresholds (kg/cm2)
6.5
6.0
5.5
5.0
4.5
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3.5
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*
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Baseline
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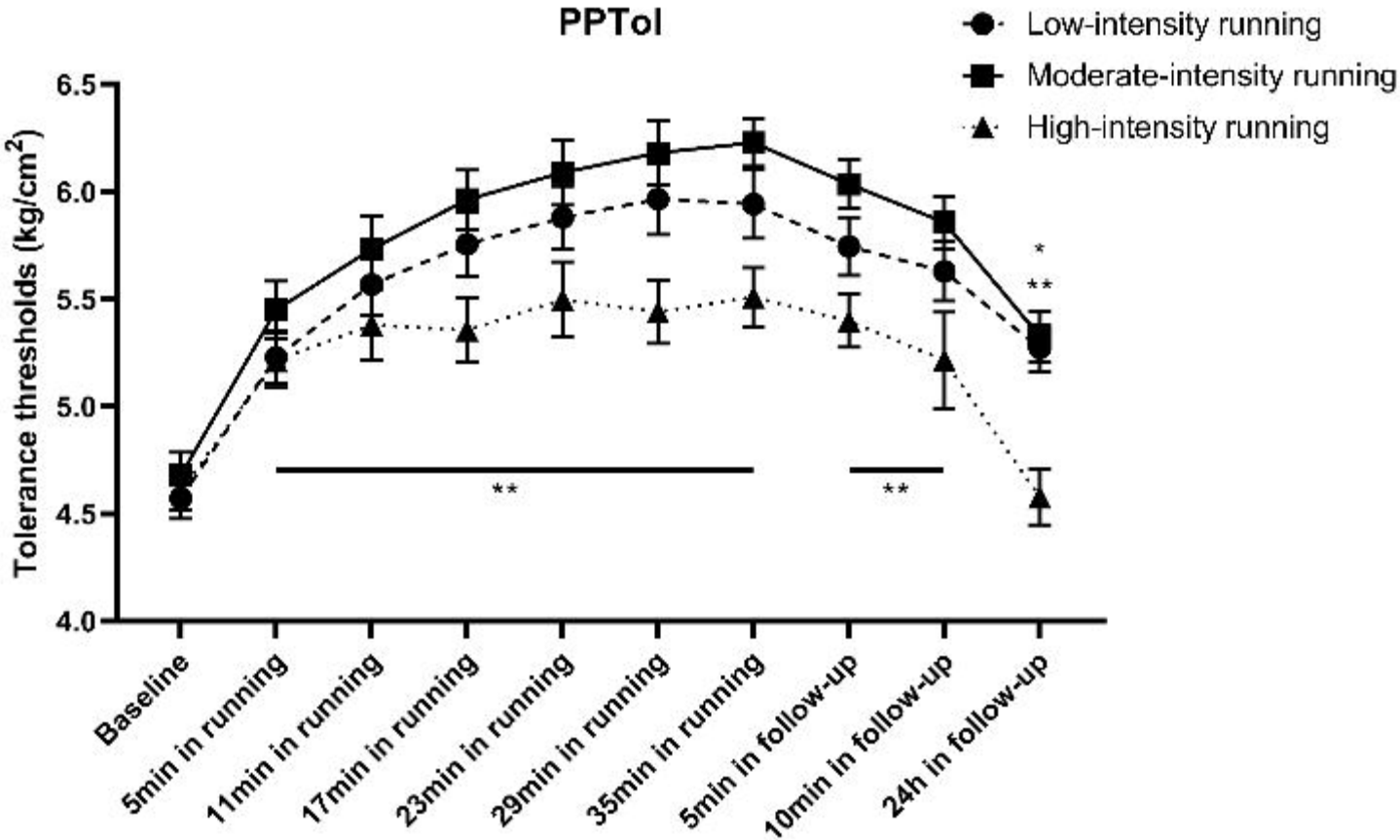
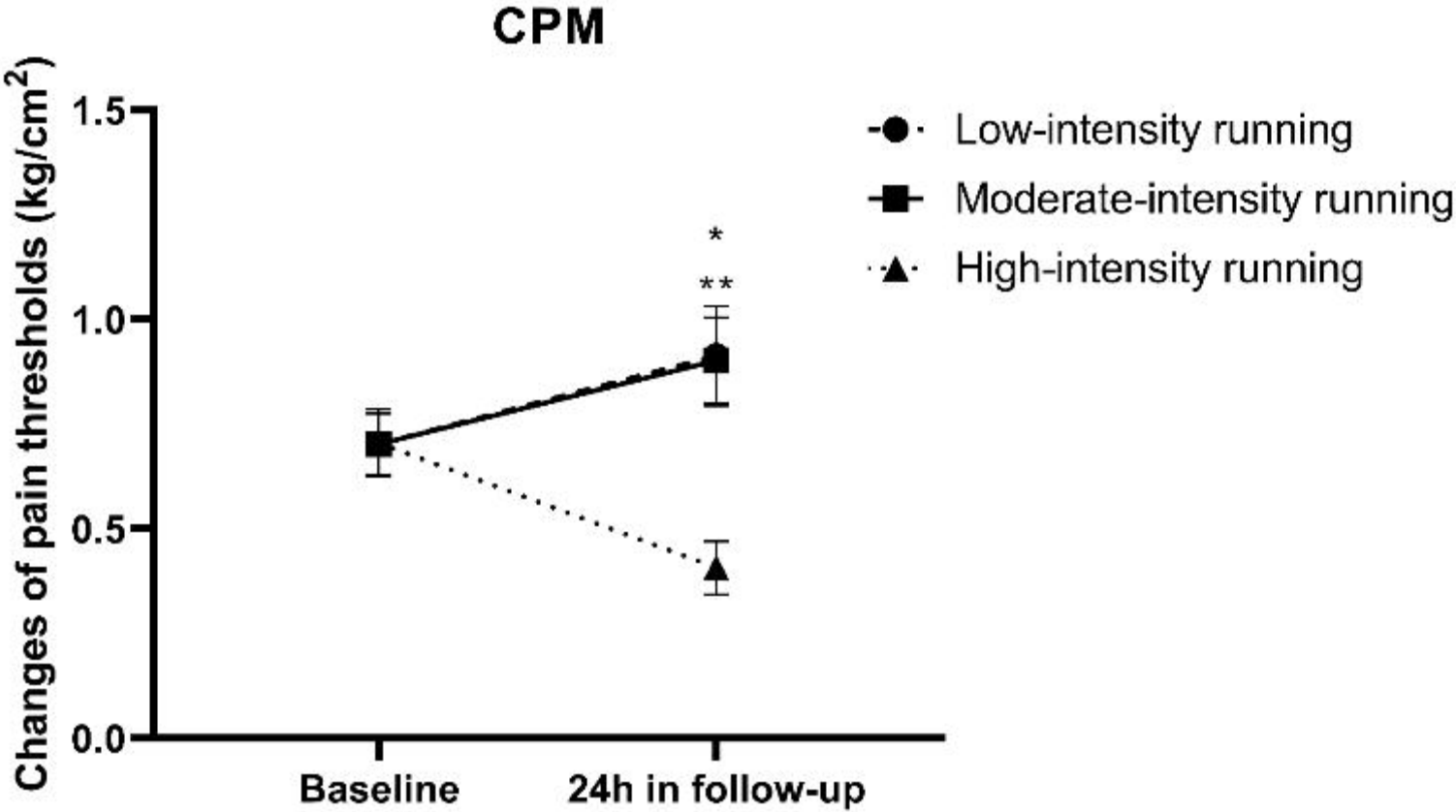
5min in follow-up
10min in follow-up
24h in follow-up


PPTol
Low-intensity running
Moderate-intensity running
High-intensity running
Tolerance thresholds (kg/cm²)
6.5
6.0
5.5
5.0
4.5
4.0
*
**
**
**
Baseline
5min in running
11min in running
17min in running
23min in running
29min in running
35min in running
5min in follow-up
10min in follow-up
24h in follow-up


CPM
Changes of pain thresholds (kg/cm2)
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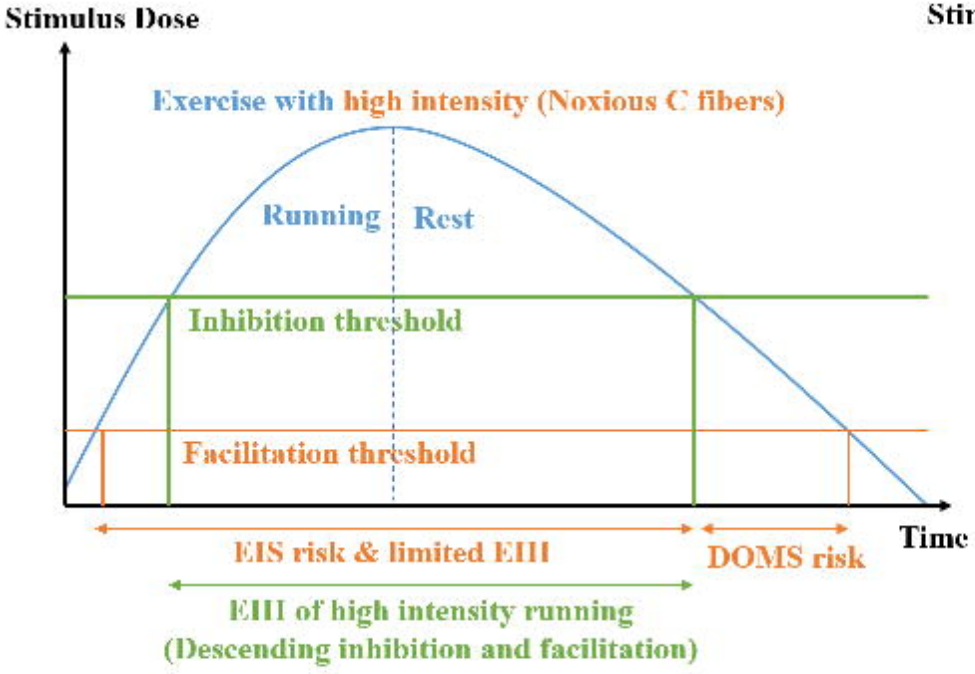
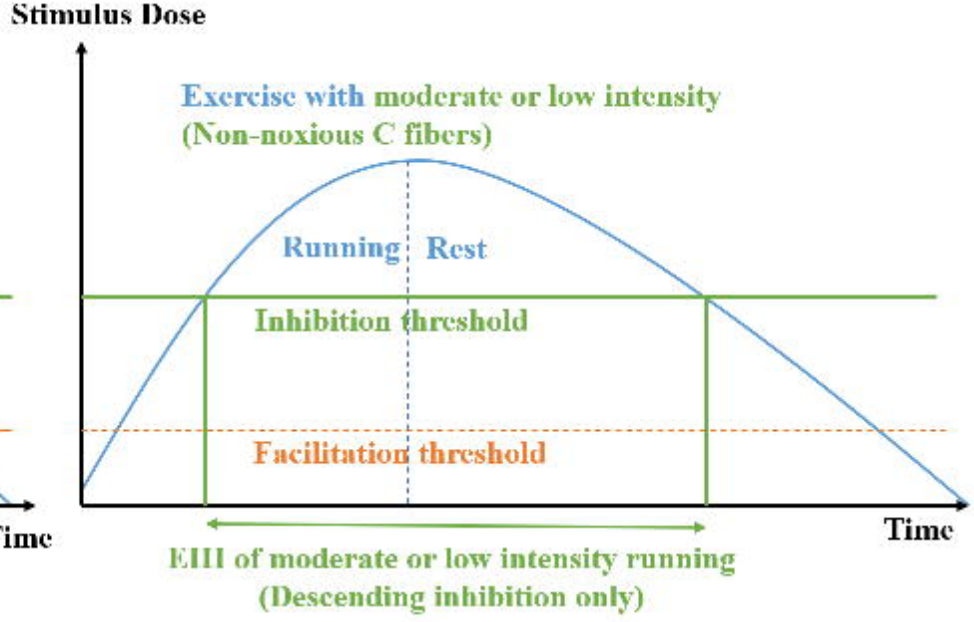
1.0
0.5
0.0
*
**
Baseline
24h in follow-up
Low-intensity running
Moderate-intensity running
High-intensity running


Stimulus Dose
Exercise with high intensity (Noxious C fibers)
Running
Rest
Inhibition threshold
Facilitation threshold
Time
EIS risk & limited EIH
DOMS risk
EIH of high intensity running
(Descending inhibition and facilitation)


Stimulus Dose
Exercise with moderate or low intensity
(Non-noxious C fibers)
Running
Rest
Inhibition threshold
Facilitation threshold
Time
EIH of moderate or low intensity running
(Descending inhibition only)