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Opposite effects of isometric exercise on pain sensitivity of healthy individuals: the role of pain modulation

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Abstract

Introduction: Exercise-induced hypoalgesia (EIHypo) among healthy individuals is well documented; however, the opposite effect of exercise, ie, exercise-induced hyperalgesia (EIHyper), has mainly been described in patients with chronic pain or after intense/painful exercise.

Objectives: We investigated the extent to which EIHypo and/or EIHyper occur among healthy participants and whether these responses are associated with individuals' pain modulation capacity.

Methods: Fifty-seven participants (mean age 29.20 ± 5.21 years) underwent testing of pressure pain threshold as an index of EIHypo/EIHyper: pain adaptation, offset analgesia (OA), and conditioned pain modulation as indices of pain modulation, prior to and immediately postsubmaximal isometric exercise (n = 40) or rest (n = 17, control group). Body awareness and exercise-evoked stress were also evaluated. Test–retest repeatability of the pain modulation indices was performed as well.

Results: Twenty-four participants (60%) exhibited EIHypo, whereas 16 (40%) exhibited EIHyper. Pressure pain threshold did not change in the control group. Baseline (preexercise) OA efficacy predicted EIHypo/EIHyper. Furthermore, OA significantly decreased postexercise in the EIHyper subgroup and slightly increased in the EIHypo subgroup. Exercise-induced hypoalgesia was associated with magnitude of daily exercise while EIHyper was associated with increased exercise-evoked stress and body awareness.

Conclusion: Submaximal isometric exercise can induce opposite effects on pain sensitivity among healthy participants—EIHypo or EIHyper. Descending pain inhibition pathways, and top-down influences over these pathways, seem to be involved in EIHypo/EIHyper effects. As such isometric exercise is often preferred in early stages of rehabilitation, preliminary screening individuals' vulnerability to this exercise is important; OA test may be used for this purpose.

Keywords: Exercise, Pain perception, Descending modulation, Stress, Interoceptive

1. Introduction

Physical exercise is an important component of health promotion and disease prevention programs[2,46] as well as pain management and rehabilitation,[36,47] and it is often the preferred intervention given pain medications' adverse effects. In addition to its functional benefits, studies have reported exercise-induced analgesia or exercise-induced hypoalgesia (EIHypo)—the elevation in pain threshold and/or pain tolerance after an acute bout of aerobic, isometric, or resistant exercise.[19,41,44,61] The opposite phenomenon, exercise-induced hyperalgesia (EIHyper), can also occur, however, more often among chronic pain patients[48,52] or healthy participants after maximal intensity/painful exercise.[25,33,34] Given that greatest EIHypo occurs with moderate/submaximal exercise,[44] which is the preferred exercise for athlete preparation and rehabilitation postorthopedic injuries,[38,48] it is important to understand whether such exercise can also lead to EIHyper among healthy individuals.

The mechanisms underlying EIHypo are also unclear. The role of descending pain modulation pathways has been suggested based on the elevation in serum endorphins and endocannabinoids

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postexercise in individuals[12,28] although naloxone did not necessarily block EIHypo.[12,30] Animal studies too have recorded the release of inhibitory neurotransmitters, as well as reduction in neuronal excitability after exercise, providing additional evidence for the involvement of the pain modulation pathways, although the contribution of stress response in these effects was difficult to control over.[36] Studies using experimental paradigms assessing pain modulation capacity, eg, conditioned pain modulation (CPM) and offset analgesia (OA), have yielded inconsistent results. Exercise-induced hypoalgesia either correlated with baseline pain modulation capacity[35,45,55] or did not[1,26,59] and exercise of various sorts either reduced this capacity[1,57] or did not.[26,39,56] Given these inconsistencies, the relations of exercise and the pain modulation pathways remain undetermined.

The aim was, therefore, to systematically study among healthy individuals, the interactions of exercise and pain modulation pathways using their known experimental indicators. Given that isometric exercise, in particular, is favorable in rehabilitation of various pain conditions, eg, fibromyalgia[50] and patellofemoral pain[58] as it allows a monitored strengthening without the need of joint motion,[38] we focused on this exercise type. Specifically, we investigated the extent to which EIHypo and/or EIHyper occur among healthy participants. We further investigated whether these responses are (1) predicted by baseline pain inhibition capacity, (2) affected by top-down influences of this capacity, and (3) influence pain modulation capacity. Given the study's longitudinal nature, test–retest reproducibility of the pain inhibition indices was also analyzed.

2. Methods

2.1. Participants

Fifty-seven healthy people participated. The participants were recruited by advertisements posted around the university campus, and initial screening for eligibility was done over the phone to prevent bias, and considering gender balance. Participants with acute or chronic pain, present or previous pathology in the hands (testing site), diseases causing potential neural damage (eg, diabetes), systemic and mental illnesses (eg, depression), and communication disabilities were excluded. The study was approved by the institutional review board of Tel Aviv University. Written informed consent was obtained from all participants after they received explanations of the study's protocol and goals.

2.2. Equipment

Sensory testing was conducted using (1) Peltier-based computerized thermal stimulator (Q-sense Medoc Ltd, Ramat-Ishay, Israel) with a 30 × 30-mm probe, (2) 10-L circulator water bath (Chillsafe; ScanVac, Ballerup, Denmark), and (3) handheld pressure algometer (Algometer type II; Somedic Sales AB, Sosdala, Sweden) with a 1 cm^2 probe.

Isometric exercise was performed with a calibrated, Jamar Hydraulic Hand Dynamometer (Jamar, Chicago, IL) (up to 200 lbs/90 kgs), which is considered the gold standard for testing isometric force as it has the highest retest reliability and precision.[37]

2.3. Experimental procedures

Previous studies demonstrated moderate to strong effect size for the effect of acute exercise on pain perceptions, ranging between 0.41 and 0.79, for both EIHypo and EIHyper.[33,41] The ample size calculation for conducting repeated measures analysis of variance with within & between interaction, considering α = 0.05, 80% power and moderate effect size, was 50 participants. The sample was increased to include 57 participants.

For each participant, data collection was done in a single testing day (**Fig. 1**). After a training session, all participants underwent 2 baseline quantitative sensory testing (QST) sessions (T1 and T2) with a 15- to 20-minute break between them for test–retest repeatability analysis. The exercise group underwent a third QST session (T3) immediately after the isometric exercise. For the exercise group, T2-QST session was considered "preexercise" evaluation and T3-QST was "postexercise" evaluation. The effect of exercise on pain modulation was controlled twice: by having the exercise group performing QST also after rest and by having control group performing QST after rest. The QST measures (pressure pain threshold [PPT], CPM, OA, and pain adaptation [PA]) were executed in random except for the stimulus-response function, which always preceded CPM/OA/adaptation because we needed to extract stimulation intensities from the functions in order to perform these tests. The testing sites (the 2 forearm) were also randomized. Nevertheless, the random order that was individually set for each participant in evaluation 1 was kept the same for evaluation 2 and 3.

Perceived effort and perceived stress were evaluated immediately postexercise (and prior to T3-QST) using a 0 to 10 numerical rating scale (NRS); its end points being 0 = not at all and 10 = maximal. In addition, the participants completed 2 questionnaires, which may affect performance during physical exercise. The short form of the international physical activity questionnaire (IPAQ) includes 4 generic questions in which participants are asked to report the number of times per week and the duration (minutes/hours) dedicated in the last 7 days to vigorous and moderate physical activity, walking, and sitting. The score can be divided into each category or can be summed up for all the categories (reported reliability 0.80).[11] The body awareness questionnaire includes 18 items (scored on a 1–7 scale), which evaluate attentiveness to body reactions, ability to detect small changes in normal functioning (eg, physical effort, temperature, and energy level), and ability to anticipate bodily reactions. The total scale score is calculated as a sum of the items; higher scores reflect higher interoceptive awareness (reported reliability 0.82).[51]

2.4. Exercise

Isometric exercise intensity was individually adjusted to 30% of maximal voluntary contraction (MVC) of the hand's flexor muscles, which has been reported to produce EIHypo.[57] Maximal voluntary contraction was defined as the highest trial in which the participants squeezed the handheld dynamometer as forcefully as possible for 5 seconds (3 repetitions, intertrial interval of 1–2 minutes). For the exercise task, the participants squeezed the dynamometer at 30% MVC, for 3 consecutive minutes while being able to adjust their effort as necessary to maintain the requested force.

2.5. Quantitative sensory testing

2.5.1. Pressure pain threshold

Pressure pain threshold was measured as an indicator for EIHypo/EIHyper.[1,5,43] Based on the modified method of limits, a gradual pressure was applied over the volar aspect of the nondominant forearm, using the pressure algometer (baseline

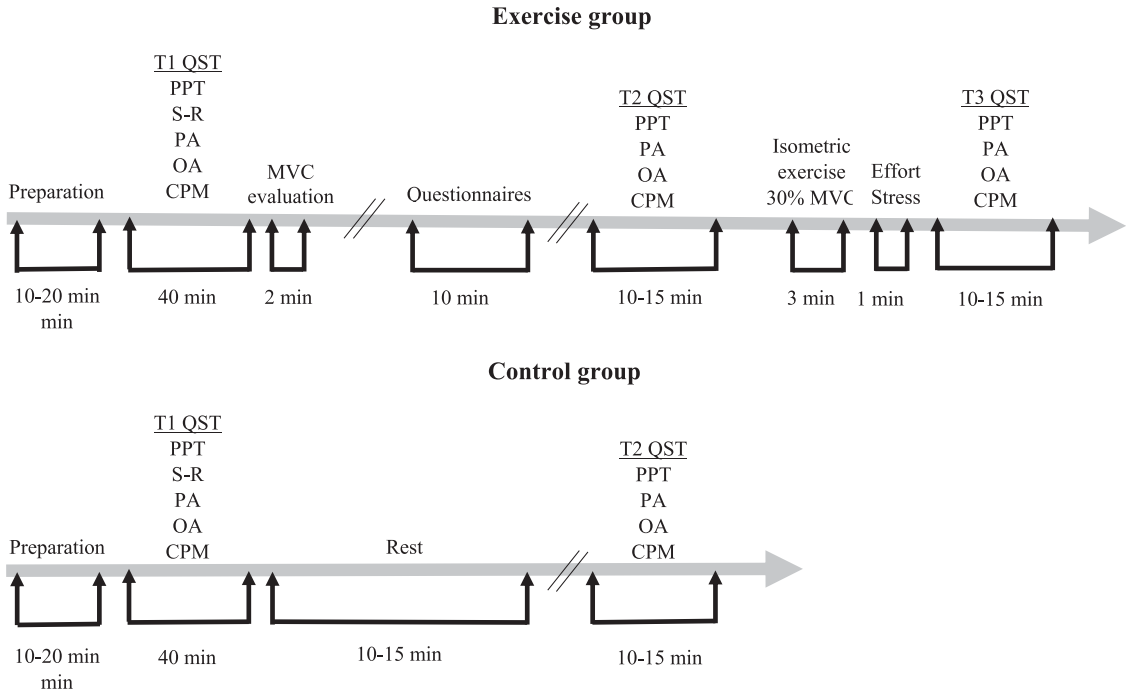

Figure 1. Experimental protocol. Preparations included explanations on the study and equipment, an interview regarding demographics and general health status, and a training session in quantitative sensory testing (QST). The exercise group performed T1, T2, and T3 QST evaluations, and the control group performed T1 and T2 QST evaluations. Each QST evaluation included the measurement of CPM, conditioned pain modulation; MVC, maximal voluntary contraction; OA, offset analgesia; PA, pain adaptation; PPT, pressure pain threshold; S-R, stimulus response function for heat pain; effort/stress, self-report scales (0–10). The break between the different phases lasted 2 to 5 minutes.

intensity—0 kPa, rate—30 kPa/s, 3 repetitions, interstimulus interval—45 seconds). Participants pressed a switch when the first pain sensation was perceived. Pressure pain threshold was the average reading of 3 consecutive measurements. The tip of the algometer was moved by 0.5 cm each repetition to prevent changes in skin sensitivity due to recurrent pressure.[14] The effect of exercise on PPT was indicated by the difference in PPT (kPa) between T2 and T3 measurements.

2.5.2. Stimulus-response functions

Participants received a series of thermal stimuli using the thermal stimulator and rated their perceived pain after each stimulus with NRS (0 = no pain sensation, 10 = the most intense pain imaginable). The stimuli rose from 35°C to a destination temperature ranging between 40°C (lowest destination temperature) to the intensity eliciting 7 to 8 on the NRS (highest destination temperature) at a rate of 2°C/sec (5 seconds in destination, interstimulus interval—30 seconds). The temperatures eliciting pain of 3 to 4 and 5 to 6 in the NRS were extracted for subsequent testing.[21]

2.5.3. Conditioned pain modulation

Conditioned pain modulation reflects the pain modulation pathway involving the subnucleus reticularis dorsalis and parabrachial nucleus.[63,64] Conditioned pain modulation was induced by applying a noxious test stimulus (TS) to one forearm using the thermal stimulator (an individually adjusted heat equivalent to 5–6/10 NRS for 5 seconds) and evaluating its perceived intensity twice: alone, and during immersion of the contralateral hand in hot water bath (conditioning stimulus), which is expected to inhibit the TS. The bath was set to 46°C, and immersion duration was 30 seconds (pain ratings at the moment of hand immersion was 6.18 ± 2.05 on the NRS). The second application of the TS occurred 25 seconds after hand immersion. The magnitude of CPM was calculated by subtracting the NRS rating of the TS in the presence of the conditioning stimulus from the NRS rating of the TS alone.[24] The effect of exercise on CPM was indicated by the difference in NRS between T2 and T3 measurements.

2.5.4. Offset analgesia

Offset analgesia reflects the pain modulation pathway involving the periaqueductal grey (PAG)/rostroventral medulla (RVM).[15,23] Offset analgesia was induced by applying a noxious heat stimulus equivalent to 6/10 NRS using the thermal stimulator (individually adjusted, for 5 seconds = T1), which then increased by 1°C (5 seconds = T2), and afterwards decreased by 1°C to the initial intensity (additional 20 seconds = T3). The participants rated the amount of perceived pain (on NRS) at T1, T2, and during T3. Offset analgesia magnitude was the difference in NRS between T1 and T3 NRS ratings.[15,49] Note, that the complete OA protocol, which includes 2 control conditions, was confirmed in a preliminary study.[49] The effect of exercise on OA was indicated by the difference in NRS between T2 and T3 measurements.

2.5.5. Pain adaptation

Pain adaptation reflects the pain modulation pathway involving the PAG-raphe nucleus and/or PAG-RVM network.[4,9] Pain adaptation was induced by applying a noxious heat stimulus of a fixed intensity using the thermal stimulator (an individually adjusted heat equivalent to 3–4/10 NRS for 60 seconds) and

evaluating the amount of perceived pain (NRS) every 10 seconds, which is expected to gradually diminish. The participants were not informed of the time elapsed from the beginning of stimulation. Pain adaptation magnitude was the difference in NRS between the first and last rating.[24] The effect of exercise on PA was indicated by the difference in NRS between T2 and T3 measurements.

3. Statistical analysis

Sample size was calculated using G*Power version 3.1. Data were processed with IBM SPSS statistics software version 27 (IBM, New York, NY). Normal distribution was evaluated with the Kolmogorov–Smirnov test. Reproducibility of the pain outcomes (PPT, CPM, OA, PA) was evaluated by calculating standard error of measurement (SEM) for T1-T2 evaluations. Standard error of measurement, which is the aggregate of factors (environmental, examiner, and examinee related) that collectively blurs the true value of the measurement, and which takes into account the dispersion around the mean and the degree of correlation between the 2 measurements serves as an indicator for true, clinically significant change.[17] The SEM thus supplies context when interpreting data from longitudinal measurements by indicating how much the score needs to change before one can be reasonably certain that a true change has occurred. Standard error of measurement was calculated as follows: $SEM = SD\sqrt{(1 - ICC)}$, wherein SD is the standard deviation of the combined T1-T2 measurements, and ICC is the intraclass correlation coefficients (2 way mixed model) of T1-T2.

The effect of exercise (exercise group) or rest (control group) on PPT, CPM, OA, and PA was calculated with repeated measure analyses of variance and corrected *t* tests. Delta T2-T3 values of PPT, CPM, OA, and PA were compared to their calculated SEM; delta values greater than SEM were considered as true changes postexercise/rest. A linear regression analysis was used to assess the ability of baseline variables (preexercise CPM, OA, and PA as well as perceived effort, perceived stress, IPAQ, body awareness) to predict the delta PPT pre- and postexercise. All the independent variables were entered in one step. Parametric and nonparametric models were used to compare the background variables (age, gender, marital status, education, and employment), exercise-related variables (perceived effort, perceived stress, MVC, IPAQ), and pain modulation indices (CPM, OA, PA) between the ElHypo and ElHyper subgroups. Corrected post hoc tests were conducted using 2-tailed *t* tests for the continuous variables, and Mann–Whitney or χ^2 tests for ordinal or dichotomous variables, respectively. Effect size was evaluated with Cohen d. Correlation coefficients between pairs of variables were calculated using two-tailed Pearson correlations.
P-values <0.05 were considered statistically significant.

4. Results

4.1. Sample characteristics and test–retest reproducibility

The exercise and control group did not differ in any of the background variables (**Table 1**). Agreement level for test–retest was good for PPT, PA, and OA and moderate for CPM. The SEM of these indices (**Table 1**) was used to evaluate whether the change in these indices pre- and postexercise signified a real difference.

4.2. The effect of exercise on pressure pain threshold

On a group level (n = 40), PPT significantly increased after exercise ($t = -1.96$, $P < 0.05$, Cohen $d = -0.31$), indicating ElHypo, whereas PPT of the control group did not change after rest (**Fig. 2A**). Nevertheless, the increase in PPT among the exercise group (delta of 14.25 kPa) was smaller than the SEM of PPT (26.50 and 25.90 kPa, respectively, for the exercise and the control groups) and, therefore, may not signify a true change.

Individual PPT pre- and postexercise values revealed a high within-group variability (**Fig. 2B**). Consequently, 2 subgroups emerged out of the exercise group, with opposite effects: subgroup ElHypo (n = 24) whose PPT significantly increased postexercise by 41.6 kPa ($t = -6.22$, $P < 0.001$, $d = -1.26$) and subgroup ElHyper (n = 16) whose PPT significantly decreased postexercise by 27.9 kPa ($t = 6.02$, $P < 0.001$, $d = 1.52$) (**Fig. 2C**, data on **Table 2**), both changes above the SEM calculated for the

Table 1

Background variables and repeatability analysis of the outcome measures among the exercise and control groups.

Background variables	Exercise group		Control group	
Number	40		17	
Gender (female, %)	19, 47.5%		10, 58.8%	
Age years (mean ± SD)	29.60 ± 6.91		28.8 ± 9.39	
Education years (mean ± SD)	15.93 ± 3.25		16.34 ± 4.1	
Family status (single, %)	26, 65.0%		7, 41.2%	
Employment (yes, %)	35, 87.5%		13, 76.5%	
BAQ (mean ± SD)	71.59 ± 19.1		75.09 ± 22.3	
IPAQ min/wk (mean ± SD)	245 ± 250		219 ± 226	
Perceived effort (mean ± SD)	6.72 ± 1.9		—	
Perceived stress (mean ± SD)	2.72 ± 2.7		—	
Repeatability analysis	**ICC**	**SEM**	**ICC**	**SEM**
Pressure pain threshold (kPa)	0.85	26.50	0.88	25.91
Pain adaptation (NRS)	0.83	0.61	0.79	0.87
Offset analgesia (NRS)	0.83	0.86	0.90	0.71
Conditioned pain modulation (NRS)	0.51	1.10	0.53	1.05

BAQ, body awareness questionnaire; ICC, intraclass correlation coefficients; IPAQ, international physical activity questionnaire; NRS, numerical rating scale; SEM, standard error of measurement.

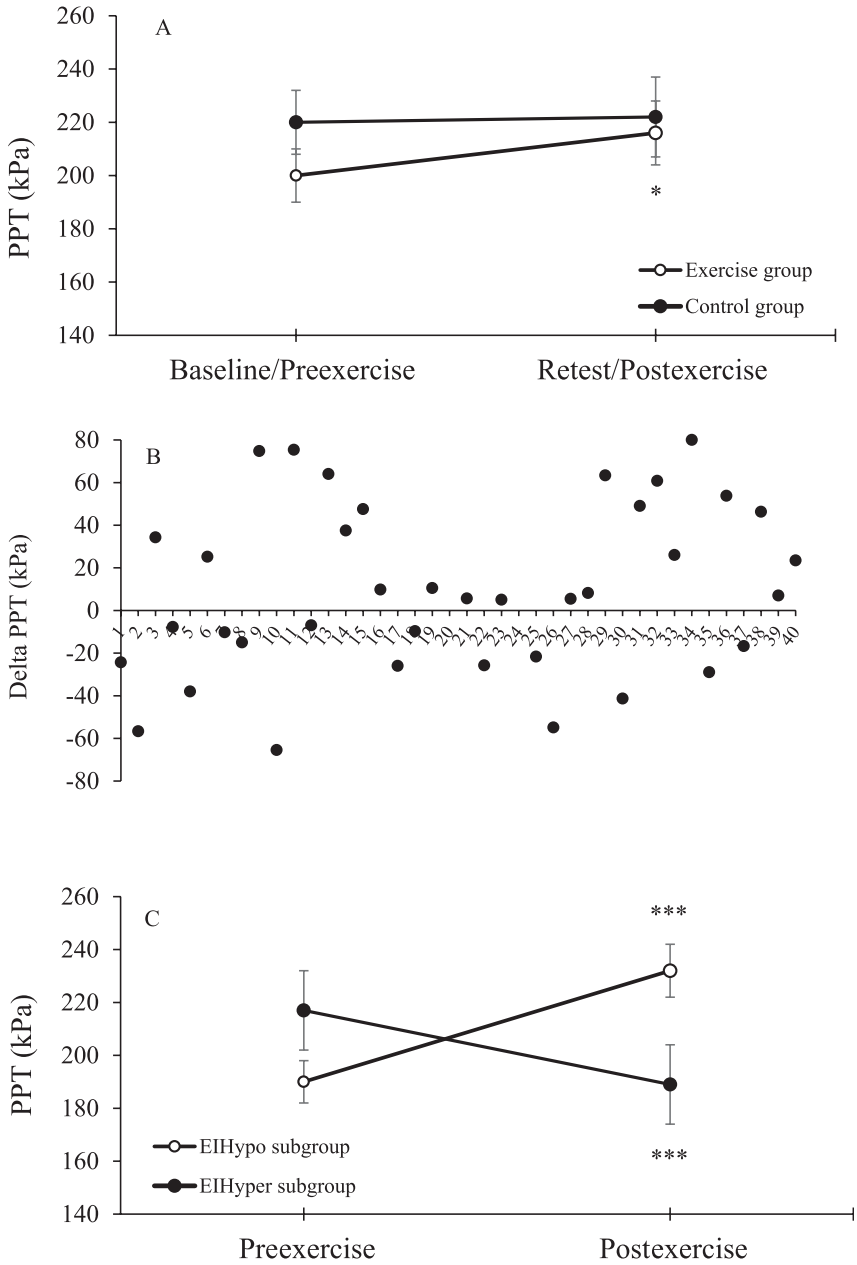

Figure 2. Change in pressure pain threshold (PPT) pre- and postisometric exercise or rest (control group) (A). Delta PPT pre- and postexercise of individual participants (B). The significant changes in PPT pre- and postexercise among the exercise-induced hypoalgesia (EIHypo) and exercise-induced hyperalgesia (EIHyper) subgroups (C). Values for (A and C) are group average ± SE. *$P < 0.05$, ***$P < 0.001$.

exercise and the control groups. The smallest increase or decrease in PPT postexercise in each subgroup was ~5 kPa.

The EIHypo/EIHyper subgroups did not differ in demographic characteristics: age (30.6 ± 8.66 and 28.1 ± 2.55 years, respectively, $P = 0.26$), education (16.00 ± 3.61 and 15.81 ± 2.530 years, $P = 0.86$), gender distribution (13/24 and 7/16 men, $P = 0.67$), marital status (13/24 and 13/16 unmarried, $P = 0.07$), or employment status (21/24 and 14/16 employed, $P = 1.00$). The EIHypo/EIHyper subgroups also did not differ in level of perceived effort (6.51 vs 7.03, respectively, $t = -0.81$, $P = 0.42$), perceived stress (2.62 vs 2.87, $t = -0.28$, $P = 0.78$), body awareness (70.9 ± 18.4 and 72.9 ± 19.9, $P = 0.74$), or in exercise habits: weekly duration of vigorous (201.7 ± 270.3 and 101.3 ± 108.9 minutes, respectively, $P = 0.17$), moderate (77.1 ± 97.7 and 41.4 ± 89.1, $P = 0.29$), or light physical activity (530.4 ± 551.6 and 362.5 ± 492.8, $P = 0.33$).

4.3. Prediction of pressure pain threshold change pre- and postexercise

Table 3 presents the results of the linear regression predicting the continuous variable delta pre- and postexercise PPT (n = 40) using baseline pain modulation indices and exercise-related variables. As can be seen, OA was the only predictor. According to the unstandardized β, for every 1 visual analogue scale unit increase in OA value (less efficient OA), PPT increased by 11.34 kPa. In other words, the probability of responding with EIHypo was best predicted with a less efficient OA.

Table 2

Group mean values of pre- and postexercise quantitative sensory testing for the exercise-induced hyperalgesia and exercise-induced hypoalgesia subgroups.

Subgroup	EIHyper		EIHypo	
Condition	Preexercise	Postexercise	Preexercise	Postexercise
Pressure pain threshold (kPa)	217.41 (71.53)	189.43 (74.01)***	190.05 (62.19)	231.61 (80.77)***
Condition pain modulation (NRS)	−2.53 (1.51)	−2.31 (1.20)	−2.81 (1.88)	−2.75 (1.55)
Offset analgesia (NRS)	−5.05 (1.54)	−4.01 (2.09)**	−3.81 (2.11)	−4.26 (2.18)*
Pain adaptation (NRS)	−3.65 (1.55)	−3.75 (1.78)	−3.81 (1.33)	−3.46 (1.66)

Values are mean and SDs.

Asterisks are paired *t* tests within groups *$P = 0.15$, **$P < 0.05$, ***$P < 0.0001$.

EIHypo, exercise-induced hypoalgesia; EIHyper, exercise-induced hyperalgesia; NRS, numerical rating scale (0–10).

4.4. The effect of exercise on pain inhibition indices

Repeated measure analyses of variance revealed no significant effects of exercise on the pain inhibition indices (CPM: $F(1,38) = 0.28$, $P = 0.59$; OA: $F(1,38) = 1.04$, $P = 0.31$; PA: $F(1,38) = 0.34$, $P = 0.56$) nor did subgroup type affected these indices (CPM: $F(1,38) = 0.67$, $P = 0.42$; OA: $F(1,38) = 1.15$, $P = 0.20$; PA: $F(1,38) = 1.01$, $P = 0.32$) (raw data on **Table 2**). However, there was a significant exercise × subgroup interaction for OA: $F(1,38) = 4.33$, $P < 0.05$ (**Fig. 3A**). Offset analgesia efficacy significantly decreased postexercise in EIHyper subgroup ($t = -1.67$, $P < 0.05$, $d = 0.51$, above SEM) and did not significantly change, albeit showed a trend towards increase in the FIHypo subgroup ($t = 1.03$, $P = 0.15$, $d = -0.26$). Furthermore, preexercise OA was significantly more efficient in the EIHyper subgroup than in the EIHypo subgroup (-5.05 ± 1.5 vs -3.8 ± 2.1, $P < 0.05$). **Figure 3B** presents the magnitude of change in OA within each subgroup; delta OA differed between the subgroups ($t = 2.11$, $P < 0.05$, $d = 0.68$).

4.5. Correlations between exercise-related variables and pain-related variables

On a group level, the change in PPT pre- and postexercise did not correlate with any of the exercise-related variables (perceived effort, perceived stress, IPAQ, body awareness). However, the change in OA pre-and postexercise correlated with IPAQ score ($r = 0.33$, $P < 0.05$) and with body awareness level ($r = -0.40$, $P < 0.05$), and the change in CPM pre- and postexercise correlated with perceived stress ($r = -0.36$, $P < 0.05$).

Given that PPT and OA exhibited opposite trends in the EIHypo/EIHyper subgroups, we examined correlations between changes in QST pre- and postexercise and exercise-related variables within these subgroups (**Table 4**). In the EIHyper subgroup, the greater the perceived stress, the greater the decrease in PPT (hyperalgesia). Furthermore, the greater the body awareness, the greater the decrease in OA efficacy postexercise. In addition, the greater the perceived effort, the greater the decrease in PA efficacy. Thus, in the EIHyper subgroup, performance was associated with enhanced distress and body awareness. In the EIHypo subgroup, the greater the daily activity, the smaller the increase in PPT (hypoalgesia) and the greater the improvement in OA efficacy. Thus, in the EIHyper subgroup, performance was associated with daily activity habits.

5. Discussion

The results reveal that (1) submaximal isometric exercise can induce both EIHypo and EIHyper among healthy participants and (2) isometric exercise's responses interact with pain inhibition capacity.

5.1. Effects of isometric exercise on pain sensitivity

For the entire exercise group, isometric exercise induced a significant increase in PPT (EIHypo) albeit at a magnitude smaller than the SEM of PPT, calculated for both the exercise and the control group. Given that the SEM value indicates by how much the score needs to change before one can be reasonably certain that a true change has occurred,[17] the observed EIHypo on a group level may not represent a true change. Close inspection of individual data revealed that group level analysis may be misrepresentative as 2 opposite effects of exercise on PPT have emerged: 60% of the participants experienced a significant increase in PPT, namely EIHypo, and 40% experienced a significant decrease in PPT, namely EIHyper; changes that were above the SEM of PPT, deeming them real changes above and beyond error/variance of the measure.

It is widely agreed upon that isometric exercise[1,6,19,26,54,59,62] as well as aerobic exercise[20,29,42,59] induce EIHypo among healthy participants. However, the opposite effect of exercise, EIHyper, was reported mainly among chronic pain patients, particularly, when exercise involved the painful body regions.[44,52,54] EIHyper among healthy participants is seldom reported; the few relevant studies reveal that EIHyper occurred under particular conditions. For example, pain threshold decreased after maximal endurance exercise done to exhaustion,[33] maximal speed exercise against resistance that was meant to cause negative emotions,[3] or after dozens of maximal isokinetic eccentric contractions that were meant to cause muscle pain.[34] Furthermore, after painful wall squat, although the group overall exhibited EIHypo, 26% responded with EIHyper.[25] Pain threshold also decreased among elite athletes after repeated sprints of the highest possible power, which were immediately followed by

Table 3

Logistic regression for the prediction of exercise-induced hypoalgesia/exercise-induced hyperalgesia using baseline pain modulation variables and exercise-related variables.

Predictor	B	SE	β	t	*P*	95% CI	
						Lower	Upper
Offset analgesia	11.34	4.57	0.54	2.48	**0.01**	1.98	20.69
Pain adaptation	−1.75	6.7	−0.05	−0.26	0.79	−15.50	11.98
CPM	−6.75	4.79	−0.25	−1.40	0.16	−16.55	3.04
Perceived effort	−1.12	4.63	−0.04	−0.24	0.80	−10.61	8.35
Perceived stress	−2.67	3.28	−0.16	−0.81	0.42	−9.39	4.05
IPAQ average	0.00	0.03	0.03	0.18	0.85	−0.06	0.07
Body awareness	0.79	0.47	0.34	1.66	0.10	−0.18	1.77

Bold indicates statistical significance.

β, standardized beta; B, unstandardized beta coefficient; CI, confidence interval; CPM, conditioned pain modulation; EIHypo, exercise-induced hypoalgesia; EIHyper, exercise-induced hyperalgesia; IPAQ, international physical activity questionnaire (average score); p, p-value; SE, standard error; t, *t*test statistics.

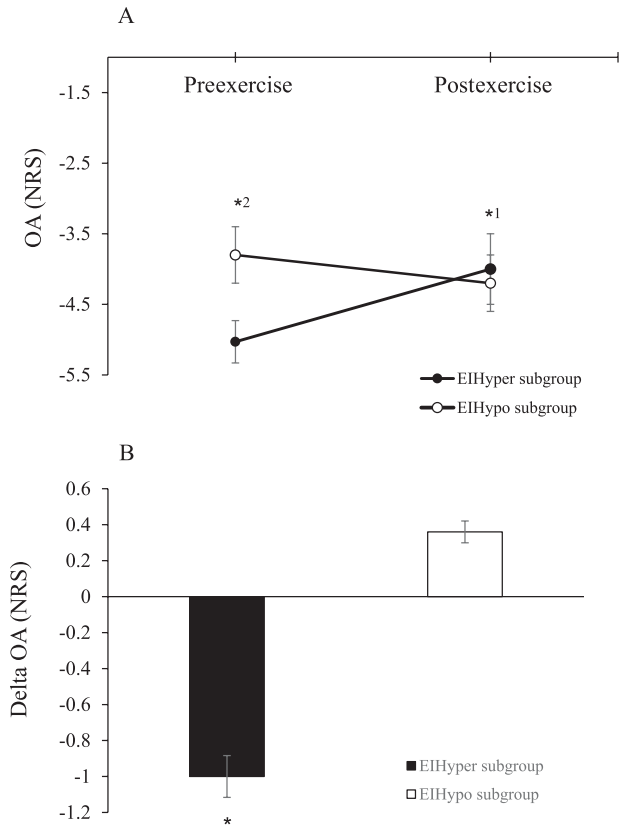

Figure 3. The change in offset analgesia (OA) pre- and postisometric exercise; the exercise-induced hypoalgesia (EIHypo) subgroup exhibited a slight increase in OA efficacy (greater inhibition), whereas the exercise-induced hyperalgesia (EIHyper) subgroup exhibited a significant decrease in OA efficacy (less inhibition) (*1). Furthermore, OA efficacy at baseline was significantly greater in the EIHyper subgroup (*2) (A). The difference between the subgroups in the magnitude of OA change was significant (B). Values are group average ± SE. *$P < 0.05$.

emersion in ice cold water.[31] In another study, aerobic exercise induced either EIHypo or EIHyper among the same 10 participants, depending on exercise strength.[40] It thus appears that EIHyper among healthy participants occurs after intense, strenuous/painful exercise. We found only one study in which EIHyper was reported after submaximal, isometric exercise, the type performed in the present study; however, the study population included older adults (ages 60–77 years) taking various medications.[43] The present study examined exercise effects at an individual level and is the first to report that submaximal isometric exercise can induce either EIHypo or EIHyper among healthy, pain-free participants, a finding that has clinical implications.

5.2. Possible underlying mechanism of exercise-induced hypoalgesia/exercise-induced hyperalgesia

Studies using similar exercise type,[5,6,32,54] intensity or duration[1,6] and similar PPT evaluation protocols[5,19,54,59] as herein, have reported EIHypo only. One explanation for this discrepancy might be that previous studies have looked at group level analysis, as did we initially. Alternatively, individual EIHyper responses may have been regarded as outliers. Nevertheless, considering the results of the control group and the SEM values, both EIHypo and EIHyper seem valid responses among healthy participants.

The EIHypo and EIHyper subgroups did not differ in background or exercise-related variables; therefore, these variables cannot explain the opposite responses. Yet EIHypo/EIHyper responses interacted with pain modulation indices in a different manner. The relationship of EIHypo/EIHyper with these indices was investigated by testing: (1) the ability of baseline pain inhibition indices to predict exercise effects, (2) the effects of exercise on pain inhibition indices, and (3) the correlation of these indices with exercise-related factors. First, the magnitude of baseline (preexercise) OA was the sole predictor of PPT change pre- and postexercise; less efficient OA predicted a larger increase in PPT postexercise and vice versa. This finding suggests that individuals with lesser OA may be more sensitive to the analgesic effects of exercise, or have a greater potential to exploit the analgesic effect of exercise than those with a more efficient OA, who could not improve further postexercise perhaps due to a ceiling effect. Second, OA exhibited an interaction effect; its efficacy significantly decreased in the EIHyper subgroup and slightly increased in the EIHypo subgroup. Szikszay et al. have also reported decreased OA efficacy postexercise, despite EIHypo. Harris et al., however, found no association between EIHypo and OA, perhaps because OA was not evaluated in the activated muscle as herein. As OA is said to be mediated by the PAG-RVM pathway,[15,23] perhaps different recruitment manners of this pathway underlie the opposite effects of isometric exercise.

The differential correlations of OA within the EIHypo/EIHyper subgroups may provide additional evidence for this pathway's

Table 4

Correlation matrix between delta pre- and postquantitative sensory testing values and exercise-related variables, within exercise-induced hyperalgesia (n = 16) and exercise-induced hypoalgesia (n = 24) subgroups.

	Stress	IPAQ	Awareness	PA change	OA change	CPM change	PPT change
Effort							
EIHyper	0.18	−0.50*	−0.16	−0.57*	0.05	−0.04	0.03
EIHypo	0.51†	−0.27	−0.05	−0.05	0.32	−0.36	0.09
Stress							
EIHyper		−0.31	0.03	0.05	−0.28	−0.19	−0.61†
EIHypo		−0.33	−0.18	−0.08	0.24	−0.39	0.24
IPAQ							
EIHyper			0.26	−0.40	0.03	−0.02	0.19
EIHypo			0.03	−0.20	0.50†	0.33	−0.45*
Awareness							
EIHyper				0.05	−0.52*	0.36	0.15
EIHypo				0.15	−0.29	−0.10	0.07

* Values are correlation coefficient and superscripts signify the 2-tailed significance level $P < 0.05$.
† Values are correlation coefficient and superscripts signify the 2-tailed significance level $P < 0.01$.
CPM, conditioned pain modulation; EIHypo, exercise-induced hypoalgesia; EIHyper, exercise-induced hyperalgesia; IPAQ, international physical activity questionnaire; OA, offset analgesia; PA, pain adaptation; PPT, pressure pain threshold.

involvement in the opposite exercise effects. In the ElHypo subgroup, OA improvement postexercise was associated with greater magnitude of daily activity. This finding corresponds with the greater inhibition observed in physically active vs sedentary animals, which correlated with mu-opioid expressing neurons in RVM.[53] In contrast, in the ElHyper subgroup, OA worsening postexercise was associated with greater body awareness. Relatedly, ElHypo magnitude (PPT increase) correlated with daily activity, whereas ElHyper magnitude (PPT reduction) correlated with perceived stress; the greater the stress, the stronger the ElHyper. Thus, opposite changes in pain inhibition postexercise herein are associated with different traits: those related to exercise habits or those related to attentiveness to bodily signals and stress, respectively. The latter result corresponds with the report that negative mood correlate with smaller ElHypo outcomes[6] and that positive reinforcement can induce hypoalgesia whereas negative reinforcement induces hyperalgesia.[60] Perhaps ElHyper occurs among participants who tend to be apprehensive and/or vigilant.

It is well known that descending inhibitory pathways are under top-down control by structures involved in psycho-cognitive processing.[8,10,64] The PAG-RVM can exert both inhibition or facilitation of nociceptive spinal neurons, via the ON-cells and OFF-cells, which are differentially recruited based on to-down control.[27] Perhaps this bidirectional top-down control was manifested in the present study in the ElHypo/ElHyper subgroups. The results combined thus suggest that the interaction of exercise with the descending pain inhibition pathways involves not only the physical components of exercise and its local events but also the psychological components related to individuals' appraisal.

Several lines of evidence from animal studies support the involvement of PAG-RVM in ElHypo.[27,36] ElHyper was associated with endogenous opioids and serotonin release in cerebrospinal fluid and in PAG and RVM.[7] Inhibition of ElHhypo occurred by blocking endocannabinoid receptors in the PAG.[16,18] Exercise has also been reported to reverse increased spinal excitability in neuropathic pain models.[22] In contrast, ElHyper in animal models was found to occur after fatiguing exercise or injury, which lead to local changes in the activated muscles,[13] an unlikely explanation for the ElHyper found herein. Taken together, exercise effects on the pain system seems to depend on individual variations in baseline capacity of the descending pain inhibition pathways and their top-down control.

5.3. Limitations, summary, and clinical implications

Several limitations exist. First, testing was performed in the active region, precluding systemic effects evaluation. Second, the results apply to isometric exercise only and to young adults. Third, there was ~5-minute difference in T2-T3 gap between exercise and control group. Yet, the study provides novel information: (1) submaximal isometric exercise produces either ElHypo or ElHyper among healthy participants, effects that are predicted by OA efficacy. (2) ElHyper response is related to individuals' interoceptive awareness and perceived stress. Isometric exercise is often preferred in pain management and rehabilitation, athlete preparations, and after orthopedic injuries, especially in early stages when joint movement is painful or restricted.[38] Thus, testing individuals' vulnerability to isometric exercise is important in order to prevent adverse effects such as hyperalgesia. The OA test and the body awareness questionnaire may be used to screen individuals' vulnerability. Testing the applicability of these findings among chronic pain patients is desirable in future studies.

Disclosures

The authors have no conflicts of interest to declare.

Data available within the article. Supporting data available on request from the authors.

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