

Power of Words: Influence of Preexercise Information on Hypoalgesia after Exercise—Randomized Controlled Trial

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ABSTRACT

VAEGTER, H. B., P. THINGGAARD, C. H. MADSEN, M. HASENBRING, and J. B. THORLUND. Power of Words: Influence of Preexercise Information on Hypoalgesia after Exercise—Randomized Controlled Trial. *Med. Sci. Sports Exerc.*, Vol. 52, No. 11, pp. 2373–2379, 2020. **Purpose:** Exercise increases pressure pain thresholds (PPT) in pain-free individuals, known as exercise-induced hypoalgesia (EIH). Positive preexercise information can elicit higher EIH responses, but the effect of positive versus negative preexercise information on EIH is unknown. The primary aim of this randomized controlled trial was to compare EIH at the exercising thigh muscle after an isometric squat exercise between individuals receiving positive versus negative preexercise information about the effect of exercise on pain. Secondary aims were to compare EIH at nonexercising muscles between groups, and to investigate the relationship between participants' expectations and EIH. **Methods:** Eighty-three participants were randomly assigned to brief positive ($n = 28$), neutral ($n = 28$) or negative ($n = 27$) verbal information. The neutral information group was included in the study as a reference group. Pressure pain thresholds at the thigh and trapezius muscles were assessed before and after the intervention (i.e., preexercise information+squat exercise). Expectations of pain relief were assessed using a numerical rating scale (−10 [most negative] to 10 [most positive]). **Results:** Change in quadriceps and trapezius PPT after the squat exercise showed a large difference between the positive and negative information groups (quadriceps, 102 kPa; 95% confidence interval, 55–150; effect size, 1.2; trapezius, 41 kPa; 95% confidence interval, 16–65; effect size, 0.9). The positive information group had a 22% increase in quadriceps PPT whereas the negative information group had a 4% decrease. A positive correlation was found between expectations and increase in PPT. **Conclusions:** Negative preexercise information caused hyperalgesia after the wall squat exercise, whereas positive or neutral preexercise information caused hypoalgesia. Positive preexercise information did not change the magnitude of EIH compared with neutral information. **Key Words:** EXERCISE-INDUCED HYPOALGESIA, EXPECTATIONS, PAIN THRESHOLD, PAIN TOLERANCE, PAIN SENSITIVITY

Exercise is a guideline-recommended treatment for a range of chronic pain conditions (1). Clinically important improvements in pain are typically observed after 8 to 12 sessions of exercise therapy (2), but as little as one

session of exercise can influence the pain sensitivity. In pain-free individuals, a single bout of aerobic or isometric exercise consistently results in higher pain thresholds and pain tolerance (3–8). This phenomenon is known as exercise-induced hypoalgesia (EIH) (9–12). Several mechanisms potentially responsible for hypoalgesia after exercise have been hypothesized and investigated in humans including the release of endogenous opioids (13–15), and the “pain inhibits pain” or conditioned pain modulation (16–18) phenomenon. In patients suffering from chronic pain conditions, the EIH response has been reported to be lower or that exercise even elicits a negative effect on pain thresholds or pain tolerance (i.e., hyperalgesia) (9,19,20).

It is well documented that specific pretreatment information can modulate the experience of pain (21–24) likely mediated by expectations of pain relief, and previous research has reported that positive information about the effect of an acute bout of exercise on the pain sensitivity elicits higher EIH

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responses (25). Currently, it is unknown how negative preexercise information influences the EIH response. The lower EIH response from exercise observed in patients with chronic pain (20) may be influenced by specific beliefs and negative expectations built on inappropriate narratives, previous experiences with ineffective treatments, and episodic hyperalgesia in response to exercise (26–28).

The primary aim of this randomized controlled trial was to investigate if individuals receiving positive preexercise information about the effect of an isometric squat exercise on pain would experience a larger EIH response compared with individuals receiving negative preexercise information. In addition, we aimed to investigate if the EIH response was confined to the exercising muscle, if a graded relationship between groups (EIH in positive information group > EIH in neutral information group > EIH in negative information group) existed, and if the EIH response was associated with expectations of pain relief from the squat exercise.

MATERIALS AND METHODS

The Consolidated Standards of Reporting Trials of Non-pharmacological Treatments (CONSORT NPT) were used as a guideline for reporting this trial (29). The trial was preregistered at ClinicalTrials.gov (ID: NCT03678662), approved by the Danish Data Protection Agency (18/49726) and the local ethics committee (S-20180019). All participants provided written informed consent.

Participants

Pain-free individuals were recruited for this trial through advertisements on social media, posters on billboards at the University of Southern Denmark and University College Lillebaelt, Odense, Denmark. Individuals were eligible for participation if they met the following inclusion criteria: between 18 and 50 yr of age and adept in Danish language both verbally and written. Individuals were excluded if any of the following criteria were present: pregnancy, former or present addictive behavior, suffering from neurological or cardiovascular diseases, currently suffering from acute or chronic pain, previous participation in pain and exercise studies. Eligible participants were presented with written information about the study and procedures, but the true aim of the study was not revealed to the participants.

Randomization

This randomized controlled trial with a three-parallel group design and 1:1:1 group allocation was conducted in the laboratory at the Pain Center at Odense University Hospital, Denmark from September 2018 to November 2018.

The randomization sequence was computer generated in blocks of 6 and 9, prepared by an independent study secretary who had no other involvement in the trial. The randomization sequence was distributed and stored in sealed opaque envelopes handled only by experimenter 1 (C.H.M.) who after group allocation delivered the preexercise-specific group information. Experimenter 1 was not involved in the recruiting

or enrollment of the participants. All outcome measurements (pain sensitivity and expectation ratings) were done by experimenter 2 (P.T.) who was unaware of the participants' group allocation at all time. In addition, the researcher (J.B.T.) responsible for the statistical analyses was blinded to group allocations.

Interventions

All participants participated in one session lasting approximately 30 min (Fig. 1). At the beginning of the session, a thorough introduction to the procedures both verbally and via visual drawings and demonstrations was given, and all participants were familiarized with the definitions of pain threshold and pain tolerance. Moreover, one pressure pain threshold assessment at the nondominant thigh which was not used for further assessment was performed. Participants were also familiarized to the squat exercise through a picture, but did not perform the squat exercise during the familiarization procedure.

After the baseline pain sensitivity assessments, participants were randomized into one of three groups. The three groups received either (A) brief positive verbal suggestion on how previous studies have shown that exercise can reduce the experience of pain (i.e., hypoalgesic information), (B) neutral information elaborating on how to perform the exercise condition, or (C) brief negative verbal suggestion on how previous studies have shown that exercise can induce pain (i.e., hyperalgesic information) (see Table, Supplemental Digital Content 1, which describes the preexercise information given to the three groups, <http://links.lww.com/MSS/B994>). The neutral information group was included as a reference group which would help clarify whether a difference between the positive and negative information groups was due to an increase or decrease in EIH. The information lasted 2 to 3 min and was closely matched in duration for the positive, neutral and negative information groups.

Next, all participants performed a 3-min isometric wall squat exercise that has previously demonstrated robust EIH responses in pain-free individuals (8,30). Participants were instructed to stand upright with their back against the wall, heels 45 cm from the wall, feet parallel and shoulder-width apart, and hands by their sides. A goniometer was aligned with the lateral epicondyle of the right femur, and participants were instructed to lower their back down the wall until their hips were just above the knees, and a knee joint angle of 100° flexion was reached. All participants were asked to maintain this position for a maximum of 3 min or until fatigue. Just before beginning, the wall squat exercise participants were instructed to rate pain intensity in the legs on a 0 to 10 numerical rating scale (NRS), with 0 defined as “no pain” and 10 “as worst imaginable pain.” Pain intensity in the legs was assessed at 1, 2, and 3 min during the exercise.

Outcomes

The primary outcome in this trial was pressure pain threshold (PPT) at the dominant quadriceps muscle and secondary

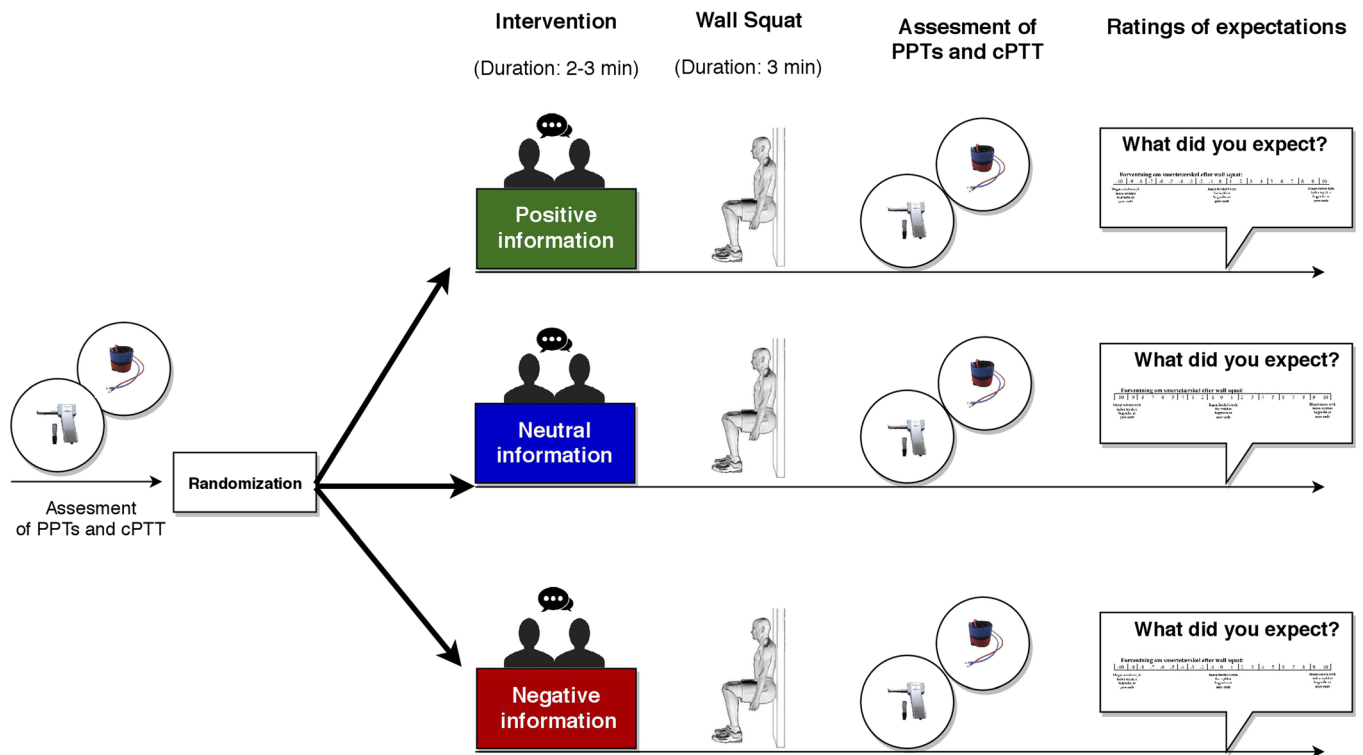


FIGURE 1—Illustration of the experimental procedure. PPT were assessed at the thigh and shoulder with handheld algometry, and cPTT were assessed at the lower leg with computer-controlled cuff algometry. PPT and cPTT were assessed before randomization and after the information interventions.

outcomes were PPT at the nondominant trapezius muscle, cuff pressure pain tolerance (cPTT) at the right lower leg, and ratings of expectations about EIH. Order of the assessments was as presented above. Leg dominance was assessed by asking the participant what leg they would use to kick a ball.

Seated with arms resting in the lap and without footrest, PPT were assessed with handheld pressure algometer (Somedic Sales AB, Sweden). Two assessment sites were located and marked. Site 1 was located in the middle of the dominant quadriceps muscle, 15 cm proximal to the base of patella. Site two was located in the nondominant upper trapezius muscle, 10 cm from the acromion in direct line with the 7th cervical vertebra. The stimulation area was 1 cm², and the rate of pressure increase was 30 kPa·s⁻¹. The first time the pressure was perceived as minimal pain, the participant pressed a button and the pressure intensity defined the PPT. Two PPT assessments were completed for each site, and the average was used for statistical analysis.

Computer-controlled cuff algometry (CPAR, Nocitech, Denmark) was used to assess cPTT. Due to positioning of the plinth and the cuff algometer cPTT was always performed on the right leg. A 10-cm blood pressure cuff (VBM, Sulz, Germany) connected to an air tank was placed 8 cm distally from the base of the patella around the right calf muscle. The pressure increased with a rate of 1 kPa·s⁻¹, and the maximal limit of pressure was 100 kPa; participants were unaware of this limit. Participants quantified the pain intensity induced by the pressure using an electronic 0- to 10-cm visual analog scale with 0 indicating “no pain” and 10 “maximal pain.”

When the pain intensity reached the extreme of 10 cm on the visual analog scale, the pressure was terminated, and the pressure value was defined as the cPTT.

To assess the effect of the intervention on expectations of EIH, a manipulation check was performed immediately after the postintervention pain assessment. Participants were asked to retrospectively rate how they had expected the wall-squat exercise to affect PPT at the quadriceps and trapezius muscles and cPTT at the lower leg. The questions for pain threshold and pain tolerance were asked as “If you think back to the time just before you did the squat exercise. What impact did you expect that the squat exercise would have on how much pressure would be needed before you experienced the first sensation of pain?” and “If you think back to the time just before you did the squat exercise. What impact did you expect that the squat exercise would have on how much pressure would be needed before you could not tolerate more pressure?” Each question was scored from -10 to +10, where -10 indicated the expectation of a lot less pressure needed to reach PPT or cPTT (hyperalgesia), and +10 indicated the expectation of a lot more pressure needed to reach PPT or cPTT (hypoalgesia). Zero indicated no change in pressure needed to reach PPT or cPTT.

Statistical Analysis

The study was powered to detect a large difference in EIH response (i.e., effect size of 0.80) between the group exposed to positive verbal information and the group exposed to negative verbal information. Using G*power (version 3.1.9.2.,

TABLE 1. Baseline characteristics and pain intensity during wall squat for the three groups.

	Positive Information Group (n = 28)	Neutral Information Group (n = 28)	Negative Information Group (n = 27)
Female, n (%)	17 (60.7)	13 (46.4)	15 (55.6)
Age (yr)	27.9 ± 5.0	28.0 ± 6.0	26.0 ± 4.7
BMI (kg·m ⁻²)	25.2 ± 3.5	24.4 ± 3.1	24.5 ± 2.9
Pain intensity during wall squat exercise			
1 min (NRS, 0–10)	3.3 ± 1.4	2.9 ± 1.1	3.2 ± 1.4
2 min (NRS, 0–10)	6.1 ± 1.8	5.6 ± 1.6	6.0 ± 1.8
3 min (NRS, 0–10)	7.9 ± 1.7	7.3 ± 1.7	7.7 ± 1.5

BMI, body mass index; NRS, Numeric Rating Scale.

Dusseldorf, Germany), we estimated that 26 participants were required in each group to be able to detect such a difference with a power of 80% and a two-sided significance level of 0.05. In addition, a similar number of individuals were recruited for a reference group receiving neutral information. To account for a ceiling effect in the assessment of pain tolerance in approximately 8% of the participants (6), we planned to include a total of 84 participants (i.e., 28 participants per group).

Main analysis on the primary outcome. To investigate the effect of the intervention on the primary outcome, the absolute change (before vs after the squat exercise) in PPT at the quadriceps muscle was compared between the two positive and negative information groups using Student’s unpaired *t* test as change score in quadriceps PPT was normally distributed (Shapiro–Wilk test, *P* > 0.05).

Exploratory analyses on the primary outcome. To explore the hypothesis of a graded quadriceps EIH response between all three groups (EIH in positive information group > EIH in neutral information group > EIH in negative information group), a linear test for trend (linear regression) was performed. In addition, to explore whether a difference in the primary outcome was due to an increase or decrease in EIH after positive or negative information, the absolute change in PPT was also compared between the neutral information group and the positive information group, and between the neutral information group and the negative information group, respectively using Student’s unpaired *t* test.

Exploratory analyses on secondary outcomes. For exploration of secondary outcomes, the absolute change (before vs after the squat exercise) in PPT at the trapezius muscle and cPTT at the lower leg were compared between the two positive and negative information groups using Student’s unpaired *t* tests as change scores in trapezius PPT and cPTT were normally distributed (Shapiro–Wilk test, *P* > 0.05). As for the primary outcome, the absolute changes in trapezius PPT and cPTT were also explored between the neutral information group and the positive information group, and between the neutral information group and the negative information group, respectively, using Student’s unpaired *t* test. As we did not hypothesize a graded EIH response on the secondary outcomes, tests for trend were not performed.

For primary and secondary outcomes, Cohen’s *d* effect sizes (ES) were calculated and categorized as large (ES ≥ 0.80), moderate (ES = 0.5), and small (ES = 0.2) using Cohen’s criteria (31). To explore differences between all three groups

in ratings of expectations and pain intensity experienced during the wall squat exercise separate one-way ANOVA were used. In case of significant ANOVA, Bonferroni-corrected *t*-tests were used for between-group comparisons. Pearson’s correlation coefficients were used to investigate correlations between the expectation ratings and the EIH responses after the wall squat exercise. Effect sizes for Pearson product–moment correlations coefficients were categorized as large (ES ≥ 0.50), moderate (ES = 0.3), and small (ES = 0.1) using Cohen’s criteria (31). All statistical analyses were performed using Stata 15.1 (StataCorp, College Station, TX), and *P* values of 0.05 or less were considered significant unless otherwise specified.

RESULTS

Eighty-four individuals were assessed for eligibility, but one was excluded due to pregnancy. A total of 83 participants underwent randomization into one of the three information groups (Table 1). All participants completed the pain sensitivity assessments and the full 3-min wall-squat exercise, and no adverse events were reported. The 3-min wall squat exercise was rated as moderately painful (Table 1) with no significant differences between groups at any time during the squat exercise (one-way ANOVA: *F*(2,82) < 1.11; *P* > 0.33).

Primary outcome. A large difference in change in PPT (ES, 1.2) at the quadriceps muscle was observed between the positive and negative information groups (102 kPa; 95% confidence interval [CI], 55–150, *P* < 0.001). The positive information group experienced a 22% increase in thigh PPT (85 kPa; 95% CI, 46–125), whereas the negative information group experienced a 4% decrease in thigh PPT (–16 kPa; 95% CI, –43 to 11). A graded response between groups were observed in thigh PPT (positive information > neutral information > negative information) (test for trend, *P* < 0.001) (Fig. 2 and Table 2). Compared with the neutral information group, the negative information group had a significantly smaller EIH response at the exercising quadriceps muscle

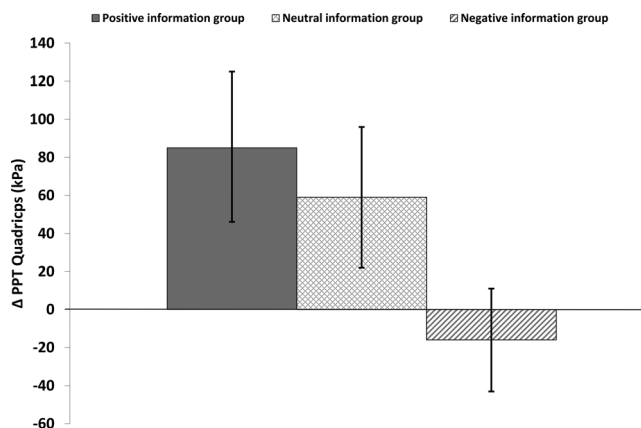


FIGURE 2—Absolute mean change (95% CI) in PPT at the exercising quadriceps muscle for the positive information group (n = 28), the neutral information group (n = 28), and the negative information group (n = 27) assessed with handheld algometry after a 3-min isometric wall squat exercise. *Significantly different compared with other groups.

TABLE 2. Handheld PPT at the exercising quadriceps muscle and the nonexercising trapezius muscle as well as change in computer-controlled cPTT at the right lower leg after 3 min of isometric wall squat exercise in participants receiving different preexercise information.

	Positive Information Group (n = 28)			Neutral Information Group (n = 28)			Negative Information Group (n = 27)		
	Baseline, Mean ± SD	After Wall Squat, Mean ± SD	Absolute Change from Baseline, Mean (95% CI)	Baseline, Mean ± SD	After Wall Squat, Mean ± SD	Absolute Change from Baseline, Mean (95% CI)	Baseline, Mean ± SD	After Wall Squat, Mean ± SD	Absolute Change from Baseline, Mean (95% CI)
Quadriceps PPT (kPa)	394 ± 154	479 ± 195	85 (46 to 125)	426 ± 201	484 ± 212	59 (22 to 65)	419 ± 229	403 ± 246	-16 (-43 to 11)*
Trapezius PPT (kPa)	252 ± 95	277 ± 121	25 (6 to 44)	257 ± 83	283 ± 97	25 (5 to 46)	245 ± 101	229 ± 113	-16 (-32 to 1)*
Lower leg cPTT (kPa) (n = 66)	59.0 ± 20.4	66.5 ± 19.7	7.5 (4.5 to 10.4)	66.2 ± 15.2	74.3 ± 19.4	8.2 (3.9 to 12.4)	61.3 ± 14.1	62.6 ± 18.6	1.2 (-4.6 to 7.1)*

Data are reported as raw values at baseline (i.e., before randomization, information and exercise), after exercise and absolute change scores from baseline.

*Significantly different compared with other groups.

(-75 kPa; 95% CI, -122 to -28; $P = 0.002$), whereas there was no significant difference between the positive information group and the neutral information group (26 kPa; 95% CI, -28 to 81; $P = 0.33$).

Secondary outcomes. Change in the nonexercising trapezius PPT showed a large difference (ES, 0.9) between the positive and negative information groups (41 kPa; 95% CI, 16-65; $P = 0.002$). The positive information group had a 10% increase in trapezius PPT, whereas the negative information group had a 7% decrease in PPT (Fig. 3 and Table 2). Compared with the neutral information group, the negative information group had a significantly smaller EIH response at the nonexercising trapezius muscle (-41 kPa; 95% CI, -67 to -158; $P = 0.002$), whereas there was no significant difference between the positive information group and the neutral information group (0 kPa; 95% CI, -27 to 27; $P = 0.98$).

Seventeen (21%) participants, six in the positive information group, six in the neutral information group and 5 in the negative information group reached the maximum capacity of the computer-controlled cuff algometry (100 kPa) at baseline and were therefore not included in the pain tolerance analysis. Change in cPTT at the lower leg showed a moderate difference (ES, 0.6) between positive and negative information groups (6.3 kPa; 95% CI, -0.1 to 12.6; $P = 0.054$). The positive information group had a 13% increase in lower-leg cPTT, whereas the negative information group had a 2% increase in cPTT (Table 2). Compared with the neutral information group, the negative information group had a smaller change in pain tolerance after exercise (-7.0 kPa; 95% CI, -13.9 to -0.01; $P = 0.050$), whereas there was no significant difference between the positive information group and the neutral information group (-0.7 kPa; 95% CI, -5.7 to 4.37; $P = 0.78$).

Participants receiving positive information or neutral information had higher expectations to the effect of the squat exercise on pain sensitivity compared with the negative information group. The difference in expectations between participants receiving positive information or neutral information was not significant (Table 3; one-way ANOVA: $F(2,82) > 7.80$, $P \leq 0.001$).

A positive correlation of moderate size was observed between expectation ratings and change in quadriceps PPT ($r = 0.35$, $P = 0.002$) and a positive correlation of small-moderate size was observed between expectation ratings and change in cPTT ($r = 0.26$, $P = 0.03$) after the wall squat exercise. No correlation between ratings of expectations and change in trapezius PPT ($r = -0.02$, $P = 0.84$) was observed.

DISCUSSION

The main finding of the present study was that participants receiving negative preexercise information experienced hyperalgesia (i.e., a decrease in PPT) after the wall squat exercise compared with individuals receiving positive or neutral preexercise information. Importantly, positive information did not change the magnitude of EIH compared with neutral information. Exercise expectations matched the EIH response on a group level supporting that expectations are likely a large contributor to the observed EIH response. The absence of EIH after negative information was observed in the exercising body part as well as in a remote nonexercising body part indicating that negative expectations influence pain-inhibitory mechanisms on a more systemic level. This is the first study investigating the effect of negative preexercise information on the pain response of exercise and the complete blockage of EIH after negative information is similar to what has been demonstrated for conditioned pain modulation (32).

The observed changes in the neutral information group in PPT and pain tolerance at the exercising and nonexercising muscles after the 3-min wall squat exercise are in line with the magnitude of hypoalgesia previously observed after isometric exercises (4,8,16,33). Previous research exploring the effect of verbal suggestions and manipulation of expectations has reported that verbal suggestion can induce positive expectations of hypoalgesia with small to large treatment effects (34). Our

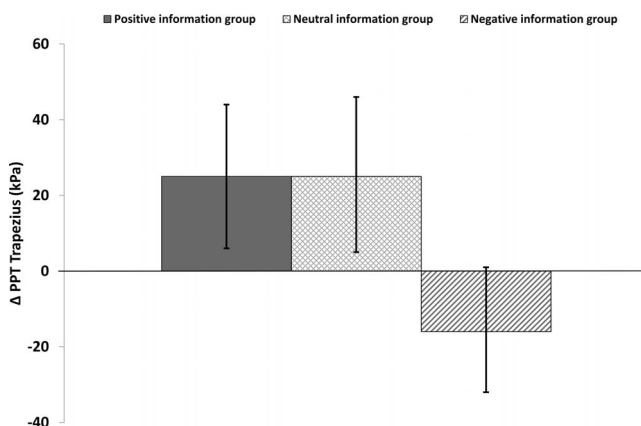


FIGURE 3—Absolute mean change (95% CI) in PPT at the nonexercising trapezius muscle for the positive information group (n = 28), the neutral information group (n = 28), and the negative information group (n = 27) assessed with handheld algometry after a 3-min isometric wall squat exercise. *Significantly different compared with other groups.

TABLE 3. Participant-rated expectations about change in PPT at the exercising quadriceps muscle and the nonexercising trapezius muscle as well as in cPTT at the right lower leg after 3 min of isometric wall squat exercise.

	Positive Information Group (<i>n</i> = 28), Mean ± SD (95% CI)	Neutral Information Group (<i>n</i> = 28), Mean ± SD (95% CI)	Negative Information Group (<i>n</i> = 27), Mean ± SD (95% CI)
Exp Δ Quadriceps PPT (NRS, -10 to 10)	4.6 ± 4.1 (3.0 to 6.2)	3.1 ± 4.4 (1.4 to 4.9)	-0.6 ± 4.4 (-2.3 to 1.2)*
Exp Δ Trapezius PPT (NRS, -10 to 10)	2.4 ± 3.7 (0.9 to 3.8)	2.0 ± 2.9 (0.8 to 3.1)	-0.7 ± 2.7 (-1.8 to 0.34)*
Exp Δ Lower leg cPTT (NRS, -10 to 10)	4.8 ± 4.2 (3.1 to 6.4)	3.0 ± 4.2 (1.3 to 4.6)	-0.4 ± 4.6 (-2.2 to 1.4)*

The questions for pain threshold and pain tolerance were asked as “If you think back to the time just before you did the squat exercise. What impact did you expect that the squat exercise would have on how much pressure would be needed before you experienced the first sensation of pain?” and “If you think back to the time just before you did the squat exercise. What impact did you expect that the squat exercise would have on how much pressure would be needed before you could not tolerate more pressure?” Each question was scored from -10 to +10 where -10 indicated the expectation of a lot less pressure needed to reach PPT or cPTT (hyperalgesia) and +10 indicated the expectation of a lot more pressure needed to reach PPT or cPTT (hypoalgesia). Zero indicated no change in pressure needed to reach PPT or cPTT.

Exp, expectations; NRS, Numeric Rating Scale.

*Significantly different compared with other groups.

results are comparable to a previous study observing enhanced hypoalgesia after positive preexercise EIH education (25); however, although we observed a graded response in EIH at the quadriceps the between group difference (i.e., positive vs negative information) was primarily caused by the hyperalgesic response after negative information rather than an increase in EIH after positive information. The modest effect of the positive information in this study could be due to the relative short information intervention (i.e., 2–3 min) compared to previous studies using a positive EIH education lasting for 15 min (25), suggesting a larger effect after an intervention with longer duration, however the influence of duration is currently unknown. However, the expectation ratings corresponded well to the group allocation with a clear polarization between the positive and negative information groups validating the brief verbal information intervention used in our study. Of note, although clear group differences in EIH were observed the correlations between expectations and EIH were less clear with a moderate correlation between expectation ratings and change in quadriceps PPT and no correlation between expectation ratings and trapezius PPT. This may be explained by the fact the exercise intervention was focused on the quadriceps muscle and that participants for that reason had less clear expectations about the effect on the nonexercising trapezius muscle.

Pretreatment information is a well-recognized factor known to modulate treatment outcome (22,35–37), which the results of the present study support. Former experiences and treatment history may shape individual expectations and these seem to persist over time and transfer to other therapeutic approaches (38). Some individuals with chronic pain may have expectations shaped by previous unhelpful information or narratives from healthcare professionals, non-evidence-based web sources or negative treatment experiences which may explain why the EIH response is less consistent in individuals with chronic pain (9,26).

Clinical implications. The findings of this study have important clinical implications. The participants in the neutral information group reported positive expectations of the effect of exercise suggesting that the general impression is that exercise is beneficial for pain. However, this impression or expectation may easily be changed. The participants receiving negative information had no expectations of a hypoalgesic response to exercise, consistent with the observed hyperalgesic response. The results suggest that expectations were greatly affected

by the information given to the participants and play an important role in the pain response to an acute exercise bout.

To our knowledge, this is the first study investigating the effect of negative preexercise information on the pain response of exercise and reporting a complete absence of EIH after negative information. This could be related to the psychological phenomenon of “bad is stronger than good” previously proposed by Baumeister and co-workers (39). Clinicians should therefore be careful how they frame information about exercise and pain to avoid negative narratives, but also be aware that positive information did not change the magnitude of EIH compared with neutral information. Likely this also applies to information in relation to delivery of other types of treatment interventions. The results highlight that clinicians should thoroughly and systematically assess expectations, knowledge, previous experiences, and exercise preferences before any exercise prescription in order to optimize the outcome.

Limitations. This study has limitations. First, the ratings of EIH expectations were completed at the end of the experimental session as a manipulation check, and it may, therefore, not reflect the true preexercise expectations, potentially enhancing the relationship between expectations and EIH. However, had expectations been assessed before the exercise, it could have revealed the hypothesis of the trial to the participants. Second, an unexpected high number of participants reached the cuff-algometry’s maximum capacity at baseline resulting in a smaller sample for the analysis of pain tolerance. Third, participants were pain-free young adults; therefore, results cannot be directly transferred to a clinical population.

CONCLUSIONS

Participants receiving negative preexercise information experienced hyperalgesia after the wall squat exercise compared with individuals receiving positive or neutral preexercise information. The difference between groups in exercise response was primarily driven by the absence of an EIH response in those receiving negative information as positive information did not change the magnitude of EIH compared with neutral information. The findings have clinical implications as clinicians should consider how they frame information about exercise and pain to avoid negative outcomes. Future studies should investigate interactions between information, expectations, and EIH in individuals with chronic pain.

The authors declare that the results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by ACSM.

The authors declare no conflicts of interest. No funding to report for this study.

Trial registration number: NCT03678662.

REFERENCES

1. Geneen LJ, Moore RA, Clarke C, Martin D, Colvin LA, Smith BH. Physical activity and exercise for chronic pain in adults: an overview of Cochrane reviews. *Cochrane Database Syst Rev*. 2017;4:Cd011279.
2. Sandal LF, Roos EM, Bøgesvand SJ, Thorlund JB. Pain trajectory and exercise-induced pain flares during 8 weeks of neuromuscular exercise in individuals with knee and hip pain. *Osteoarthr Cartil*. 2016;24(4):589–92.
3. Vaegter HB, Handberg G, Jorgensen MN, Kinly A, Graven-Nielsen T. Aerobic exercise and cold pressor test induce hypoalgesia in active and inactive men and women. *Pain Med*. 2015;16(5):923–33.
4. Vaegter HB, Hoeger Bement M, Madsen AB, Fridriksson J, Dasa M, Graven-Nielsen T. Exercise increases pressure pain tolerance but not pressure and heat pain thresholds in healthy young men. *Eur J Pain*. 2017;21(1):73–81.
5. Vaegter HB, Dorge DB, Schmidt KS, Jensen AH, Graven-Nielsen T. Test–retest reliability of exercise-induced hypoalgesia after aerobic exercise. *Pain Med*. 2018;19(11):2212–22.
6. Hviid JT, Thorlund JB, Vaegter HB. Walking increases pain tolerance in humans an experimental cross-over study. *Scand J Pain*. 2019. In press (Epub 2019/07/01).
7. Vaegter HB, Bjerregaard LK, Redin MM, Rasmussen SH, Graven-Nielsen T. Hypoalgesia after bicycling at lactate threshold is reliable between sessions. *Eur J Appl Physiol*. 2019;119(1):91–102.
8. Vaegter HB, Lyng KD, Yttereng FW, Christensen MH, Sorensen MB, Graven-Nielsen T. Exercise-induced hypoalgesia after isometric wall squat exercise: a test–retest reliability study. *Pain Med*. 2019; 20(1):129–37.
9. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. *Pain*. 2010;151(1):77–86.
10. Koltyn KF, Garvin AW, Gardiner RL, Nelson TF. Perception of pain following aerobic exercise. *Med Sci Sports Exerc*. 1996;28(11): 1418–21.
11. Koltyn KF, Arbogast RW. Perception of pain after resistance exercise. *Br J Sports Med*. 1998;32(1):20–4.
12. Koltyn KF. Analgesia following exercise: a review. *Sports Med*. 2000;29(2):85–98.
13. Black J, Cheshier GB, Starmer GA, Egger G. The painlessness of the long distance runner. *Med J Aust*. 1979;1(11):522–3.
14. Janal MN, Colt EW, Clark WC, Glusman M. Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. *Pain*. 1984;19(1):13–25.
15. Droste C, Greenlee MW, Schreck M, Roskamm H. Experimental pain thresholds and plasma beta-endorphin levels during exercise. *Med Sci Sports Exerc*. 1991;23(3):334–42.
16. Vaegter HB, Handberg G, Graven-Nielsen T. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. *Pain*. 2014;155(1):158–67.
17. Lemley KJ, Hunter SK, Hoeger Bement MK. Conditioned pain modulation predicts exercise-induced hypoalgesia in healthy adults. *Med Sci Sports Exerc*. 2015;47(1):176–84.
18. Ellingson LD, Koltyn KF, Kim JS, Cook DB. Does exercise induce hypoalgesia through conditioned pain modulation? *Psychophysiol*. 2014;51(3):267–76.
19. Kosek E, Ekholm J, Hansson P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. *Pain*. 1996;64(3):415–23.
20. Rice D, Nijs J, Kosek E, et al. Exercise-induced hypoalgesia in pain-free and chronic pain populations: state of the art and future directions. *J Pain*. 2019;20(11):1249–66.
21. Mondloch MV, Cole DC, Frank JW. Does how you do depend on how you think you'll do? A systematic review of the evidence for a relation between patients' recovery expectations and health outcomes. *CMAJ*. 2001;165(2):174–9.
22. Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanyl. *Sci Transl Med*. 2011;3(70):70ra14.
23. Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. *Pain*. 2001;93(1):77–84.
24. Amanzio M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J Neurosci*. 1999;19(1): 484–94.
25. Jones MD, Valenzuela T, Booth J, Taylor JL, Barry BK. Explicit education about exercise-induced Hypoalgesia influences pain responses to acute exercise in healthy adults: a randomized controlled trial. *J Pain*. 2017;18(11):1409–16.
26. Staud R, Robinson ME, Price DD. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. *Pain*. 2005;118(1–2):176–84.
27. Meeus M, Roussel NA, Truijzen S, Nijs J. Reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain: an experimental study. *J Rehabil Med*. 2010;42(9):884–90.
28. da Cunha Ribeiro RP, Franco TC, Pinto AJ, et al. Prescribed versus preferred intensity resistance exercise in fibromyalgia pain. *Front Physiol*. 2018;9:1097.
29. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial abstracts. *Ann Intern Med*. 2017;167(1):40–7.
30. Smith A, Ritchie C, Pedler A, McCamley K, Roberts K, Sterling M. Exercise induced hypoalgesia is elicited by isometric, but not aerobic exercise in individuals with chronic whiplash associated disorders. *Scand J Pain*. 2017;15:14–21.
31. Cohen J. *Statistical Power Analysis for the Behavioural Sciences. Chapter 2:24–27*. Hillsdale, NJ: Erlbaum; 1988.
32. Goffaux P, Redmond WJ, Rainville P, Marchand S. Descending analgesia—when the spine echoes what the brain expects. *Pain*. 2007;130(1–2):137–43.
33. Vaegter HB, Handberg G, Graven-Nielsen T. Isometric exercises reduce temporal summation of pressure pain in humans. *Eur J Pain*. 2015;19(7):973–83.
34. Peerdeman KJ, van Laarhoven AI, Keij SM, et al. Relieving patients' pain with expectation interventions: a meta-analysis. *Pain*. 2016; 157(6):1179–91.
35. Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. *Curr Opin Anaesthesiol*. 2007;20(5):435–9.
36. Eklund A, De Carvalho D, Page I, et al. Expectations influence treatment outcomes in patients with low back pain. A secondary analysis of data from a randomized clinical trial. *Eur J Pain*. 2019;23(7):1378–89.
37. Holm LW, Carroll LJ, Cassidy JD, Skillgate E, Ahlbom A. Expectations for recovery important in the prognosis of whiplash injuries. *PLoS Med*. 2008;5(5):e105.
38. Kessner S, Wiech K, Forkmann K, Ploner M, Bingel U. The effect of treatment history on therapeutic outcome: an experimental approach. *JAMA Intern Med*. 2013;173(15):1468–9.
39. Baumeister RF, Bratslavsky E, Finkenauer C, Vohs KD. Bad is stronger than good. *Rev Gen Psychol*. 2001;5(4):323–70.