Pain and executive function

No association between remote exercise-induced hypoalgesia and cognitive inhibition in pain-free participants
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Objectives: Cognitive inhibition, which denotes the ability to suppress predominant or automatic responses, has been associated with lower pain sensitivity and larger conditioned pain modulation in humans. Studies exploring the association between cognitive inhibition and other pain inhibitory phenomena, like exercise-induced hypoalgesia (EIH), are scarce. The primary aim was to explore the association between cognitive inhibition and EIH at exercising (local) and non-exercising (remote) muscles after isometric exercise. The secondary aim was to explore the association between cognitive inhibition and pressure pain sensitivity.

Methods: Sixty-six pain-free participants (28.3 ± 8.9 years old, 34 women) completed two cognitive inhibition tasks (stop-signal task and Stroop Colour-Word task), a 3-min isometric wall squat exercise, and a quiet rest control condition with pre- and post-assessments of manual pressure pain thresholds at a local (thigh) and a remote site (shoulder). In addition, cuff pressure pain thresholds, pain tolerance and temporal summation of pain were assessed at baseline.

Results: No association was found between remote EIH and cognitive inhibition (Stroop interference score: r=0.12, [-0.15; 0.37], p=0.405, BF01=6.70; stop-signal reaction time: r=−0.08, [-0.32; 0.17], p=0.524, BF01=8.32). Unexpectedly, individuals with worse performance on the Stroop task, as indicated by a higher Stroop interference score, showed higher local EIH (r=0.33; [0.10; 0.53], p=0.007, BF01=0.29). No associations were observed between pain sensitivity and any of the cognitive inhibition performance parameters.

Conclusions: The present findings do not support previous evidence on positive associations between exercise-induced hypoalgesia and cognitive inhibition, as well as baseline pain sensitivity and cognitive inhibition.

Keywords: endogenous pain modulation; executive function; exercise-induced hypoalgesia; pressure pain threshold; quantitative sensory testing; response inhibition; stimulus inhibition.

Introduction

Exercise-induced hypoalgesia (EIH) delineates a short-term decrease in pain sensitivity after a single bout of exercise [1]. Effect sizes of EIH are larger when assessed locally at the exercising muscles, i.e. local EIH, but smaller effects are also observed at assessment sites remote from the exercising muscle, i.e., remote EIH [2]. Centrally mediated descending pain inhibition has been suggested to mediate remote EIH, whereas a composition of central and peripheral pain inhibitory processes have been suggested to mediate local EIH [3]. Thus, EIH has been suggested to reflect endogenous pain inhibition [4].

Although EIH seems to vary considerably between pain-free individuals [2], diminished EIH is consistently reported in populations with chronic pain [2, 4].
Therefore, understanding individual modulators of EIH in pain-free individuals might provide more insight into the clinical problem of pain exacerbation after exercise. Diminished EIH in individuals with chronic pain might correspond to clinical reports of pain exacerbations after exercise in some individuals with chronic pain [5]. Concurrently, a large body of research suggests that individuals with chronic pain suffer from cognitive impairment, most pronounced in the domain of cognitive inhibition [6]. Cognitive inhibition delineates the ability to suppress dominant, automatic or pre-potent responses [7]. Regarding pain as an automatic, affective response, one might propose that cognitive inhibition might endorse pain inhibition [8]. Previous research has shown that pain-free individuals with stronger cognitive inhibition seem to show lower pain sensitivity as measured by threshold and tolerance [9–12], as well as larger conditioned pain modulation [13, 14].

Considering that cognitive functions emerge in the supraspinal CNS, cognitive inhibition might be an individual modulator of centrally mediated EIH. Therefore, the strongest association should be observed between remote EIH effects and cognitive inhibition. This hypothesis was recently supported by a smaller study from our laboratory, observing an association between better performance in a cognitive inhibition task and higher remote EIH after aerobic bicycling [15]. However, as this study was an exploratory study within a larger investigation, additional studies are warranted. In addition, the previous study (1) was not designed to differentiate between local and remote EIH, as no local assessment site was used, and (2) the exercise condition used to explore EIH after isometric exercise was not sufficient to produce an EIH response.

Therefore, the primary aim of this study was to explore the association between cognitive inhibition and EIH assessed at exercising muscles (local site) and EIH at non-exercising muscles (remote site) after an isometric exercise that has previously demonstrated more robust EIH. A secondary aim was to extend previous findings on associations between baseline pain sensitivity and cognitive inhibition by complementary assessments of pressure pain sensitivity, i.e., thresholds, tolerance and temporal summation of pain. We expected that better cognitive inhibition abilities would be associated with higher EIH, higher pain thresholds and tolerance, and with lower temporal summation of pain. Additionally, regarding EIH, it was hypothesized that the association between cognitive inhibition and EIH would be stronger at the remote than at the local assessment site.

Methods

Participants

An a-priori power analysis was conducted based on the primary aim of this study. To determine the sample size required for achieving a power of 0.9 with an effect size of r=0.35, we took the previous study from our lab [15] as the best available estimate for effect size. This resulted in a sample size of n=63.

The study was performed in the laboratory at the Pain Center at the University Hospital Odense in Denmark. Testing took place from February to March 2019. Sixty-eight participants were recruited via word of mouth and social media to allow for exclusion of participants with poor performance in cognitive tasks or due to other reasons. None of the included participants suffered from ongoing neurological or psychiatric disease, cardiovascular disease, infectious disease, metabolic diseases or thyroid malfunction, nor did participants have any pain or use pain medication prior to the week of testing. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee (S-20180171). Two participants had scheduling conflicts during the study period and did not participate. Therefore, 66 individuals participated in the study. All participants provided written informed consent and were asked to refrain from physical exercise, caffeine or alcohol on the day of the experiment.

Procedure

Participants completed one testing session, which began with familiarization to the assessment of manual pressure pain thresholds (PPT). Five minutes after familiarization, baseline pain sensitivity measures were obtained using cuff algometry, as well as manual PPTs. Following a 5 min break, the main three experimental parts were administered, that is, (1) an exercise condition with a 3-min isometric wall squat exercise, (2) a duration-matched control condition of seated rest, and (3) the cognitive inhibition tasks. In order to evenly allocate potential risks of carry-over effects between the three experimental parts, they were administered in counterbalanced and randomized order.

Local and remote PPTs using manual algometry were assessed immediately before and immediately after the isometric wall squat and quiet rest, respectively. Manual algometry was chosen as a dependent measurement in the EIH paradigm in order to maintain comparability to a previous study with this exercise [16]. Cognitive inhibition was assessed with a stop-signal task and a Stroop Colour-Word task. The two cognitive tasks were always performed in one block, but their order was randomized (see Figure 1). All R/Matlab scripts are available in an open research repository: https://osf.io/eqwjr/?view_only=79f8e16866cd675aaab064f3b39710049.
Familiarization PPT

Baseline pain assessment
(approx. 10 minutes)
cPPT, cPTT, cPTL, cTSP
PPT

Exercise (approx. 7 minutes)
PPT Wall squat (3 minutes) PPT

Control (approx. 7 minutes)
PPT Quiet rest (3 minutes) PPT

Cognitive tasks (approx. 1 hour)
Stop-signal task # Stroop task

Figure 1: Flow chart of experimental parts in the present study. PPT, manual pressure pain threshold; cPPT, cuff pressure pain threshold; cPTT, cuff pressure pain tolerance; cPTL, cuff pressure pain tolerance limit; cTSP, temporal summation of cuff pressure pain. # Indicates that the order between the respective experimental parts was randomized (for a detailed description, see Section Procedure).

Cognitive inhibition tasks

It has been recommended to use several tasks measuring the construct of cognitive inhibition, as cognitive tasks are not process-pure, each measuring slightly different sub-facets of cognitive inhibition along with other, unrelated processes [17]. Therefore, two different tasks were used in this study to measure cognitive inhibition: the stop-signal task [18] and the Stroop Colour-Word task [19]. In the stop-signal task, participants typically build up the pre-potent response of a button press during the experiment, which must be inhibited in the presence of the stop-signal [18]. Therefore, performance in the stop-signal task is also referred to as response inhibition [20]. In contrast, in the Stroop Colour-Word task, participants are required to inhibit the reading of words, which is a behavioural tendency that has presumably long built up throughout participants’ learning history. The reading process is automatically triggered by presenting a familiar word, which is why Stroop Colour-Word task performance is also referred to as stimulus inhibition [20].

Both cognitive tasks were administered in Octave [21] using the Psychophysics Toolbox extensions [22] (Kleiner, Brainard, Pelli, Ingling, & Murray, R., Broussard, C., 2007). The tasks were run in Ubuntu Linux (version 18.04) on an Acer® TravelMate Laptop (5740 series; Acer Inc., Xizhi, New Taipei, Taiwan) with an Intel® Core™ i5 CPU M 520 processor @ 2.60 GHz. An approximate viewing distance to the screen of 65 cm was maintained for all participants. All stimuli were displayed on a gray background in the screen center. Text stimuli were presented in Arial (font size 25).

Stop-signal task (SST): The stop-signal task administered here has been described in detail elsewhere [15]. Essentially, on each trial a black square or circle was presented along with a black square-shaped frame around the shape cues. On 75% of all trials (go trials) participants had to indicate the shape displayed. On the remaining 25% (stop trials) the square-shaped frame changed to blue, denoting the stop signal, at a variable interval from stimulus onset (stop signal delay). On stop trials participants were asked to refrain from responding. In contrast to Gajsar et al. (2020), this time participants performed 12 experimental blocks of 64 trials (768 trials in total). Each block consisted of 8 stop trials and 24 go trials per shape (circle vs square) and every two blocks participants were given a break of 30 s. Before the experimental task participants underwent one block of practice. The practice phase was identical to the experimental phase, except that feedback was provided after each trial. Specifically, ‘incorrect’ was displayed following erroneous responses on go trials, whereas ‘correct’ was displayed following accurate responses on go and successful stop trials. Response omissions on go trials and responses on stop trials prompted ‘respond’ and ‘stop’ messages, respectively. Feedback was displayed in white lower-case font for 250 ms.

For the stop signal task, outliers were removed, in a first step, at the individual subject level. In this step extreme “raw” go RT and signal-respond RT scores were deleted for a given participant. Extreme scores were detected based on the threshold advocated by Leys et al. (2013; median ± 2.5 × median absolute deviation). This resulted in, on average, 5% of go RTs (± 9%) and 8% of signal-respond RTs (± 13%) being removed. Mean go RTs were then computed for correct go trials and mean signal-respond RTs for incorrect stop trials. Next, we checked for any participants violating the independence assumption of the horse race model following the guidelines by 18 [18]. For this, in line with the guidelines, any participants exhibiting larger mean RTs on incorrect stop trials than on go trials were removed. Mean RTs used for this comparison comprised all trials with a key press (i.e., also choice errors and premature responses), as advocated by the authors. Two participants were removed from any subsequent analyses as a result of the assumption check. In a second step of our outlier procedure participants were excluded at the group level to increase the reliability of SSRT estimates [23]. Here, participants showing sub-optimal performance levels, as defined by the lenient criteria from 23 [23], were excluded. This resulted in the removal of 8 participants due to sub-optimal task performance. One further participant was excluded due to technical issues. Overall, we excluded a total of 11 participants in the SST (2 for violations of the assumptions of the horse-race model, 8 for exhibiting sub-optimal performance and 1 for technical issues). There was no significant difference in any of the study variables after exclusion of these 11 participants (all ps > 0.200).
Stroop colour-word task: In the Stroop Colour-Word Task [19, 24], each trial began with a white fixation cross displayed for 500 ms. Next, colour words (red, green, blue, yellow) were shown until response in lower case letters (maximum duration: 7,000 ms). All colour words were printed in a uniform font colour: either red (RGB: 200, 0, 0), green (RGB: 0, 200, 0), blue (RGB: 0, 0, 240) or yellow (RGB: 240, 240, 0). This yielded trials with a match between colour word and font colour (congruent, e.g., the word blue printed in blue font) and trials with a mismatch between colour word and font colour (incongruent, e.g., the word blue printed in red font). Overall, there were 20 experimental blocks with 26 trials each (i.e., 480 trials in total). For every block a given colour word was presented six times, three times in the congruent colour and once in each of the three incongruent colours. Congruent and incongruent trials were thus presented with equal frequency. For every five experimental blocks participants could take a break. For participants 1 to 6, these breaks were self-paced. Due to timing issues (i.e., prolonged duration of the experiment), these breaks were restricted to 30 s for the remaining participants. Participants were instructed to determine the font colour of each stimulus whilst ignoring the written word. They were asked to respond as fast and accurately as possible. Participants pressed the response keys ‘Q’ and ‘E’ with their left index and middle fingers for blue and red font colours, respectively. For green and yellow responses, they respectively pressed the keys ‘I’ and ‘P’, using the corresponding fingers on the right hand. To facilitate stimulus–response mapping, the response keys were labelled with the relevant colours. Prior to the experimental participants completed a practice phase of two blocks (48 trials). Practice trials were identical to experimental trials with one exception: during the practice phase response feedback, the words ‘correct’ or ‘incorrect’ displayed in white font, was provided at the end of each trial for 250 ms.

For the Stroop Colour-Word Task, reaction time (RT) outliers along with the corresponding accuracy scores were removed at the individual subject level, as described for the stop signal task. This led to the removal of 6% (± 3%) of “raw” RT (accuracy) scores. Mean RTs for correct trials and mean accuracy were then computed. On the group level, participants with extreme mean RT (accuracy) scores in at least one condition were excluded (i.e., median ± 2.5 × median absolute deviation; [25]). This led to the exclusion of 2 participants due to extreme RT or accuracy scores.

Exercise-induced hypoalgesia

Isometric wall squat exercise: Three minutes of isometric wall squat exercises were performed by all participants. This task has previously demonstrated robust local and remote EIH [16]. Participants were instructed to stand upright with their back against the wall, heels approximately 45 cm from the wall, feet parallel and shoulder-width apart, and hands by their sides. Participants were instructed to lower their back down the wall until a knee joint angle of approximately 100° flexion was reached. All participants were asked to maintain this position for a maximum of 3 min or until fatigue. Just before the exercise condition, the participant was instructed to rate pain intensity in the legs on a 0–10 numerical rating scale (NRS), with 0 defined as “no pain” and 10 “as worst imaginable pain”. Pain intensity in the legs was also assessed after one, two, and 3 min. Pain intensity in the thigh due to the isometric wall squat was obtained as the ratio from the first NRS pain rating after minute one to the NRS pain rating after minute three (NRS ratio wall squat, 16). Immediately before and after 3 min of wall squat, PPT assessments at the thigh and shoulder muscles were performed as described below (see Manual pressure algometry).

Quiet rest: Participants were instructed to relax in a seated position in a comfortable armchair for 3 min in a temperate and undisturbed room. PPT assessments were performed as described, before and immediately after the quiet rest condition.

Pain assessment at baseline

Cuff pressure algometry: A computer-controlled cuff pressure algometer (CPAR, NociTech, Denmark,) was used to apply deep tissue pressure pain and assess baseline experimental pain sensitivity. These were cuff pressure pain thresholds (cPPT), cuff pressure pain tolerance (cPTT), cuff pressure pain tolerance limit (cPTL), and temporal summation of cuff pressure pain (cTSP). The experimenter (HG) wrapped a 13-cm wide silicone tourniquet cuff (VB M, Sulz, Germany) with an equal-sized proximal and distal chamber around the right lower leg with an 8-cm distance to the tibial tuberosity.

For cPPT, cPTT and cPTL, cuff pressure was increased by the device at a rate of 1 kPa/s; the maximal pressure limit was 96.5 kPa. The participants were instructed to use an electronic visual analog scale (VAS) to rate their pressure-induced pain intensity in a continuous fashion. The electronic VAS was sampled at 10 Hz. Zero- and 10-cm extremes on the VAS were defined as “no pain” and as “maximal, intolerable pain,” respectively. Participants were also instructed that when they reached the cPTL of VAS=10, i.e. the pain was intolerable, the pressure would be released from the cuff. The pressure value when the participant rated the sensation of pain as 1 cm on the VAS was defined as the cPPT, when the cPTL=VAS 10 the pressure inflation was defined as the cPTT. The pain intensity at the time of termination was defined as the cPTL. Participants (n=5) with cPTL>10 were excluded from analysis of pain tolerance, as they did not reach the pain threshold within the pressure capacity of the cuff system.

cTSP was assessed immediately after the assessment of cPPT and cPTT. Ten repeated cuff pressure stimulations (2 s duration and 1 s interval between stimuli) were delivered to the leg by the computer-controlled cuff pressure algometer with an intensity equivalent to the cPPT recorded during the previous assessment. Participants rated their pressure pain intensity continuously during the sequential stimulation on the electronic VAS. Participants were also instructed to not return the VAS to zero in-between the stimulations. In the period between stimuli, a constant non-painful pressure of 5 kPa was kept to ensure that the cuff did not move. The VAS score immediately after each stimulus was extracted. cTSP scores were calculated for the main statistical analysis as the ratio between the pain intensity rating of the 10th and the 1st repetition of pressure. Positive cTSP scores thus reflect a higher summation of pain ratings and negative scores a decrease in pain ratings. Due to technical issues, cTSP was not completed in one participant.

Manual pressure algometry: Manual pressure pain thresholds (PPTs) were assessed with a handheld pressure algometer (Somedic Sales AB,
Hörby, Sweden) on a stimulation area of 1 cm². The increment rate of pressure was kept at approximately 30 kPa/s. The first time the pressure was perceived as pain, the participant pressed a button; the actual pressure intensity defined the PPT. Two PPT assessments were completed for each assessment site, and their average was used for statistical analysis. Twenty second intervals were maintained between the assessments. 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 the patella. Site 2 was located in the middle of the dominant upper trapezius muscle, 10 cm from the acromion in direct line with the seventh cervical vertebra.

Statistical analysis

Data preparation: All data analyses were conducted using SPSS Statistics Version 25 (IBM, Armonk, NY) and R (R Core Team, 2019). Descriptive statistics are reported as means ± standard deviations. The pain sensitivity data (cPPT, cPTT, cPTL, cTSP and PPTs) were checked for plausibility. Furthermore, potential effects of the experimental administration order (see Procedure) were scrutinized by comparing cognitive task parameters divided by administration order using one-way ANOVAs.

In order to validate the EIH protocol used in this study, the effect of exercise on PPTs compared with the control condition was assessed using a 2 × 2 factorial repeated measures analysis of variance (rmANOVA) with time (pre vs post) and condition (wall squat exercise vs quiet rest) as within-subject factors for each assessment site. Here, a time × condition interaction was deemed to indicate EIH, with a larger increase in PPTs after the wall squat exercise condition compared with quiet rest condition. Bonferroni-corrected post-hoc t-tests were used for probing a significant interaction.

To obtain single values of EIH for further analyses, absolute and relative EIH change scores (ΔPPTabs and ΔPPTrel, respectively) were calculated for each assessment site, as

\[ \Delta \text{PPT}_{\text{abs}} = \text{PPT}_{\text{postexercise}} - \text{PPT}_{\text{preexercise}} \]

and

\[ \Delta \text{PPT}_{\text{rel}} = \frac{\Delta \text{abs}}{\text{PPT}_{\text{preexercise}}} \times 100. \]

Thus, positive values of ΔPPT represent an increase in pain threshold after exercise, i.e., higher EIH. Both ΔPPTabs and ΔPPTrel were calculated and are presented. As the absolute change provides a more puristic indicator of pain inhibition, only ΔPPTabs was used in further statistical analysis.

Stop-signal reaction times (SSRTs) were used as an index of cognitive inhibition in all analyses reported here. We used the block-based integration method to estimate SSRTs [26]. This procedure has been described in detail elsewhere [15]. In a minor deviation to 15 [15], throughout the manuscript we used ‘real’ mean SSDs (also for estimating SSRTs) to reflect the genuine screen presentation times (see [18]). For ease of use we will refer to ‘real’ mean SSDs simply as mean SSDs in the remainder of this manuscript.

To validate the interference effect in the Stroop Colour-Word task, a dependent samples t-test was performed on RTs (accuracy) between the congruent and incongruent conditions. To obtain a single measure of cognitive inhibition, Stroop interference scores were then calculated by subtracting RTs (accuracy) in the congruent condition from mean RTs (accuracy) in the incongruent condition.

Main analysis: The association between EIH/pain sensitivity and cognitive inhibition was tested using bivariate correlation coefficients with one-tailed confidence intervals and significance testing. Spearman’s rho correlation coefficients were used in case of non-normal distribution of variables. Bonferroni corrections were used to adjust for multiple testing. Furthermore, we performed complementary Bayesian analyses, using a β prior of 1 for correlations [27]. The Bayes factor (BF) indicates the relative strength of evidence for 2 alternative theories. A Bayes factor score of n, comparing the null to the alternative hypothesis (BF01) means that the data are n times more likely under the null hypothesis than the alternative hypothesis. BF01 values much <1 allow us to conclude that there is strong evidence for the alternative over the null. Conversely, BF 01 values substantially >1 provide strong evidence in favour of the null over the alternative. For example, a BF 01 of 0.2 shows that the data are 5 times more likely under the alternative hypothesis than under the null hypothesis.

Note that in the cognitive tasks, SSRTs/Stroop interference scores were analyzed as reaction time (RT) based parameters, where lower RTs generally indicate better performance in cognitive inhibition. As higher EIH and lower baseline pain sensitivity were hypothesized to be associated with better cognitive inhibition, we expected a negative correlation between EIH/cPPT/PPT/cPTT/PTL and SSRT/Stroop interference score. As higher cTSP scores indicate higher pain sensitivity, a positive relationship was expected between cTSP and SSRT/Stroop interference score. Significant correlations were then further probed using stepwise hierarchical multiple linear regression. As both EIH and cognitive inhibition have been suggested to decline with increasing age [2, 28], participant’s age was controlled in regression analysis of EIH and SSRT/Stroop interference score. Homoscedasticity was inspected visually using scatterplots of standardized predicted values against standardized residuals, respectively. Variance inflation factors were checked regarding multicollinearity.

Effect sizes were calculated as Cohen’s d and r/rho. For Cohen’s d [29], d<0.20 were considered no effect, d=0.20–0.50 a small effect, d=0.50–0.80 a moderate effect, and d>0.80 a large effect. For r/rho, r/rho<0.09 were considered no effect, r/rho=0.10–0.30 a small effect, r/rho>0.30–0.50 a moderate effect, and r/rho>0.50 a large effect (Cohen, 1988). The level of significance was set to p=0.05.

Results

Descriptive statistics and preliminary analyses

The overall study sample consisted of 66 participants [28.3 ± 8.9 years old (range 18–57 years); average body mass index (BMI) 23.2 ± 2.7 kg/m² (range 17.3–30.1); 34 women].

Cognitive inhibition tasks

In the stop-signal task, the percent of omissions (1 ± 2 %) and choice errors (2 ± 2 %) on go trials was very low for included participants, indicating that the participants performed well on go trials and built up a prepotent go
response. On stop trials, participants successfully withheld their responses on 48 ± 3% of the trials, indicating that the tracking procedure was successful. Stop-signal reaction times (SSRTs) were normally distributed and had a mean of 242.46 ± 30.02 ms (range: 186.20–317.35 ms). Detailed task parameters are displayed in the supporting material (Supporting Material A, Table S1).

Regarding the Stroop Colour-Word Task, reaction times (RTs) where significantly longer in the incongruent condition (600 ± 89 ms) than in the congruent condition (660 ± 105 ms, p<0.001). This validates the interference effect of the incongruent condition on response latency, with a mean Stroop interference score of 60 ± 39 ms (range: 7±172 ms). In contrast, there was no interference effect on performance accuracy, as indicated by comparable accuracy between the congruent (96 ± 3%) and incongruent conditions (96 ± 3%, p=0.116). Therefore, only the Stroop interference score on RTs was analyzed in the following.

Table 1: Means and standard deviations (M ± SD), 95% confidence intervals (95% CI) of pain measures at baseline as well as pressure pain thresholds (PPTs) throughout the exercise-induced hypoalgesia protocol, i.e. before and after isometric wall squat at the thigh (local assessment site) and the shoulder (remote assessment site). The last column shows rmANOVA statistics for testing the EIH effect, consisting in an increase in PPTs from the pre wall squat to the post wall squat, but not from the pre quiet rest to the post quiet rest.

<table>
<thead>
<tr>
<th>Pain measures</th>
<th>M ± SD</th>
<th>95% CI</th>
<th>ANOVA time × condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIH thigh (local assessment site)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPT pre wall squat</td>
<td>451±192</td>
<td>402 to 501</td>
<td>Pre vs. post: d=0.37, p&lt;0.001</td>
</tr>
<tr>
<td>PPT post wall squat</td>
<td>535±237</td>
<td>474 to 597</td>
<td>Pre vs. post: d=0.02, p=0.707</td>
</tr>
<tr>
<td>PPT pre quiet rest</td>
<td>472±206</td>
<td>419 to 252</td>
<td></td>
</tr>
<tr>
<td>PPT post quiet rest</td>
<td>472±181</td>
<td>426 to 519</td>
<td></td>
</tr>
<tr>
<td>ΔPPTabsEIH</td>
<td>84±106</td>
<td>57 to 111</td>
<td></td>
</tr>
<tr>
<td>ΔPPTrefEIH</td>
<td>20.3±22.4%</td>
<td>14.5 to 26.1%</td>
<td></td>
</tr>
<tr>
<td>ΔPPTabsControl</td>
<td>0±74</td>
<td>–18 to 19</td>
<td></td>
</tr>
<tr>
<td>ΔPPTrefControl</td>
<td>2.3±14.2%</td>
<td>–1.4 to 6.0%</td>
<td></td>
</tr>
<tr>
<td>EIH shoulder (remote assessment site)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPT pre wall squat</td>
<td>355±149</td>
<td>317 to 394</td>
<td>Pre vs. post: d=0.17, p&lt;0.001</td>
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<tr>
<td>PPT post wall squat</td>
<td>391±162</td>
<td>348 to 432</td>
<td>Pre vs. post: d=0.00, p=0.979</td>
</tr>
<tr>
<td>PPT pre quiet rest</td>
<td>370±166</td>
<td>372 to 410</td>
<td></td>
</tr>
<tr>
<td>PPT post quiet rest</td>
<td>372±151</td>
<td>332 to 411</td>
<td></td>
</tr>
<tr>
<td>ΔPPTabsEIH</td>
<td>35±65</td>
<td>18 to 52</td>
<td></td>
</tr>
<tr>
<td>ΔPPTrefEIH</td>
<td>12.1±22.6%</td>
<td>6.3 to 18.0%</td>
<td></td>
</tr>
<tr>
<td>ΔPPTabsControl</td>
<td>1±51</td>
<td>–11 to 15</td>
<td></td>
</tr>
<tr>
<td>ΔPPTrefControl</td>
<td>1.9±13.9%</td>
<td>–1.7 to 5.5%</td>
<td></td>
</tr>
<tr>
<td>NRS ratio exercise</td>
<td>2.9±1.5 (NRS)</td>
<td>2.5 to 3.3 (NRS)</td>
<td></td>
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<tr>
<td>Baseline pain sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cuff pressure pain threshold (cPPT)</td>
<td>20.7±8.4</td>
<td>18.6 to 22.9</td>
<td></td>
</tr>
<tr>
<td>Cuff pressure pain tolerance (cPPT)</td>
<td>60.6±18.6</td>
<td>55.8 to 65.4</td>
<td></td>
</tr>
<tr>
<td>Temporal summation of cuff pressure pain (cTSP)</td>
<td>1.9±2.0</td>
<td>1.4 to 2.4</td>
<td></td>
</tr>
<tr>
<td>Manual pressure pain threshold (PPT)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigh</td>
<td>490±198</td>
<td>439 to 541</td>
<td></td>
</tr>
<tr>
<td>Shoulder</td>
<td>381±141</td>
<td>345 to 418</td>
<td></td>
</tr>
</tbody>
</table>

All values are provided in kilo Pascal (kPa), except noted otherwise.
assessment site with respective rmANOVAs to test for EIH effects.

In the analysis of EIH effects, there were significant time × condition interactions at each assessment site (thigh (local): $F(65, 1)=24.71$, $\eta^2_p=0.28$, $p<0.001$; shoulder (remote): $F(1, 65)=10.41$, $\eta^2_p=0.14$, $p<0.05$). These consisted in a significant increase in PPTs after isometric wall squat (thigh (local): pre vs. post: $p<0.001$; shoulder (remote): pre vs. post: $p<0.001$), but no change in the quiet rest condition (thigh (local): pre vs. post: $p=0.707$; shoulder (remote): pre vs. post: $p=0.979$). The effect size at the local assessment site was larger ($d=0.37$) than at the remote assessment site ($d=0.17$).

**Pain sensitivity measures at baseline**

Descriptive statistics of pain sensitivity at baseline are shown in Table 1. Regarding cTSP, a rmANOVA with the factor time (first vs second vs third average) showed a significant main effect, $F(1.74, 11.34)=35.25$, $p<0.001$, $\eta^2_p=0.36$. This effect consisted in a significant increase in pain ratings on a 0–10 NRS from the first (4.00 ± 2.13) to the second average of pain ratings (5.03 ± 2.17, $p<0.001$), as well as from the second to the third average (5.42 ± 2.10, $p=0.007$), thus validating the cTSP protocol.

**Main analyses: associations between exercise-induced hypoalgesia, baseline pain sensitivity and cognitive inhibition**

Correlation coefficients with confidence intervals and p-values, quantifying the association between EIH scores at the local and remote assessment sites and cognitive inhibition are displayed in Table 2. Regarding EIH, there was a significant correlation with a small effect size between EIH at the thigh and the Stroop interference score ($r=0.33$, 95% CI 0.09 to 0.53, $p=0.007$, BF=0.29), supporting the alternative hypothesis. This indicates that participants with worse performance in the cognitive inhibition task showed a higher EIH effect at the local assessment site. Figure 2 displays scatterplots on the correlations between EIH and cognitive inhibition.

As shown in Table 2 and Figure 3, none of the other correlations between EIH and cognitive inhibition reached significance. Scrutiny of Bayes factors suggested moderate evidence for the null hypothesis in all other correlations. Scatterplots corresponding to each correlation between baseline pain sensitivity, respectively, and cognitive inhibition are displayed in Figure 3.

Hierarchical multiple linear regression on EIH at the thigh resulted in a final model, $R^2=0.18$, adjusted $R^2=0.15$, with baseline PPT at the thigh, $\beta=0.31$, 95% CI 0.04; 0.27, $p=0.011$; and Stroop interference scores as significant predictors, $\beta=0.25$; 95% CI 0.01; 1.21, $p=0.045$ and with a
significant change in $F$ from mean, $p=0.003$, when controlling for age. Inspecting Cook’s distances, no influential cases were identified. Residuals were independent (Durbin Watson=1.65) and normally distributed, as indicated by Kolmogorov–Smirnov tests of standardized residuals ($p>0.200$) in this model. Homoscedasticity was given, as inspected by scatterplots of standardized predicted values against standardized residuals. Variance inflation factors indicated that multicollinearity was not an issue ($VIF=1.00–1.02$).

No significant correlations between baseline pain sensitivity as measured by cPTT, cTSP, cPPT and PPT and SST or Stroop interference score were found (see Table 2). All data are available in an open research repository: https://osf.io/eqwjr/?view_only=79f8e16866cd475aab064f3b39710049.

### Table 2: Pearson’s $r$ correlation coefficients ($r$), with 95% confidence intervals (95% CI), significance test (p), Bayes factor scores (BF), as well as the number of included participants ($n$), testing the association between cognitive inhibition and pain measures at baseline and exercise-induced hypoalgesia, respectively.

<table>
<thead>
<tr>
<th>Pain measures</th>
<th>SSRT</th>
<th>Stroop interference score (RT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$r$ 95% CI p-Value BF01 n</td>
<td>$r$ 95% CI p-Value BF01 n</td>
</tr>
<tr>
<td>EIH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta$PPT$_{abs}$ thigh (local)</td>
<td>$-0.13$ –0.38 to 0.14 0.355 6.18 55</td>
<td>$0.33$ 0.09 to 0.53 0.007 0.29 64</td>
</tr>
<tr>
<td>$\Delta$PPT$_{abs}$ shoulder (remote)</td>
<td>$0.12$ –0.15 to 0.37 0.405 6.70 55</td>
<td>$-0.08$ –0.32 to 0.17 0.524 8.32 64</td>
</tr>
<tr>
<td>Pain sensitivity at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cPPT</td>
<td>$0.01$ –0.26 to 0.26 0.947 9.44 55</td>
<td>$-0.13$ –0.36 to 0.12 0.321 6.24 64</td>
</tr>
<tr>
<td>cPTT</td>
<td>$-0.02$ –0.26 to 0.29 0.899 9.05 51</td>
<td>$-0.10$ –0.36 to 0.16 0.467 7.58 60</td>
</tr>
<tr>
<td>cTSP</td>
<td>$0.02$ –0.25 to 0.29 0.908 9.31 54</td>
<td>$0.07$ –0.18 to 0.31 0.580 8.67 63</td>
</tr>
<tr>
<td>PPT thigh</td>
<td>$0.02$ –0.25 to 0.29 0.903 9.22 53</td>
<td>$0.14$ –0.11 to 0.38 0.264 5.39 62</td>
</tr>
<tr>
<td>PPT shoulder</td>
<td>$0.20$ –0.07 to 0.44 0.151 9.37 54</td>
<td>$0.10$ –0.15 to 0.34 0.415 7.26 63</td>
</tr>
</tbody>
</table>

### Exercise-induced hypoalgesia and cognitive inhibition

We expected that individuals with better cognitive inhibition abilities would show a greater EIH response, and that this association would be more pronounced when EIH was assessed systemically, i.e., at the remote assessment site. This hypothesis was not confirmed. This is the first study investigating this association when EIH after isometric exercise is successfully induced. The result is in contrast with a previous finding reported by our group [15], where better performance in the stop-signal task (SST), was found to be associated with remote EIH after aerobic bicycling. These disparate results might be explained by a difference between the studies in exercise modality. It has previously been suggested that different mechanisms drive isometric vs. aerobic EIH [30]. Therefore, it might be that cognitive inhibition is associated with mechanisms of aerobic EIH, but not isometric EIH. However, the power in the present study was higher than in the previous study, which speaks in favour of the null hypothesis. This is in line with a recent study by Pinto et al., demonstrating that performance in SST and Stroop colour-word task were not associated with pain attenuation during motor execution [31]. Instead, it might be worthwhile to consider working memory capacity as an individual predictor of systemic EIH, as a number of previous studies have demonstrated that successfully engaging working memory in cognitively demanding tasks induces pain inhibition, which is a psychological and scientific way to describe distraction [32–35]. This corresponds with a proposed account of EIH as a form of “embodied distraction”, where attention is directed away from painful stimuli towards other bodily sensations such

### Discussion

The present study explored the association between exercise-induced hypoalgesia and cognitive inhibition, as well as baseline pressure pain sensitivity and cognitive inhibition. In general, no associations between cognitive inhibition and EIH were observed. However, unexpectedly, we found a small but significant correlation between worse Stroop task performance and higher EIH at the thigh. Cognitive inhibition was also not associated with baseline pressure pain sensitivity.
Figure 3: Scatterplots displaying the association between pain sensitivity measures at baseline (cuff pressure pain threshold, cuff pressure pain tolerance, temporal summation of cuff pressure pain, manual pressure pain threshold at thigh and shoulder) and cognitive inhibition measures (stop-signal reaction time and stroop interference score).
as heart pounding and sweating, resulting in reduced pain sensitivity [36]. If distraction is a cognitive mechanism in EIH, working memory capacity could be a factor in the individual EIH response.

Regarding local EIH, there was an unexpected negative association between performance in the Stroop task and EIH. This means that individuals with worse performance in the Stroop Colour-Word task, had higher EIH scores at the thigh. This association is in the opposite direction to our hypothesis and warrants explanation. It is conceivable that exhaustive effects between cognitive inhibition task performance and EIH might have played a role as the assessment of cognitive inhibition and EIH were performed in a single session. That is, high performance in the cognitive inhibition tasks might have caused reduced EIH effects afterwards and, vice versa, a high EIH response might have caused poor performance in the cognitive inhibition tasks afterwards. The assumption of shared and limited inhibitory resources mediating EIH and cognitive inhibition underly both scenarios, and stems from former observations of exhaustive EIH [37, 38] and exhaustive cognitive inhibition performance [39]. However, as the current study was not designed to test exhaustive effects, this account remains speculative. Overall, the results of this study do not support the hypothesis that individuals with better cognitive inhibition show a higher EIH response.

**Cognitive inhibition and experimental pain sensitivity at baseline**

No correlations were observed between pressure pain sensitivity and cognitive inhibition, as assessed as pain threshold, pain tolerance and temporal summation of pain. Therefore, the findings contrast with earlier work, which showed that individuals with stronger cognitive inhibition had higher pain tolerance [9, 11–13] as well as a higher pain threshold [9, 10]. This was therefore an unexpected finding that warrants explanation.

Firstly, previous studies reporting an association between pain sensitivity and cognitive inhibition have typically employed the cold pressor test to induce pain. This contrasts with the Bjekić et al. study [13] and the present study, which used cuff pressure pain. It is therefore possible that the association between lower pain tolerance and higher cognitive inhibition is specific to pain modality. Furthermore, cognitive inhibition has been proposed to be associated with pain inhibition by cognitive means, i.e. distraction, only if the painful stimulation is perceived as threatening [40]. In other words, it might be specific to threatening painful stimulation to trigger cognitive pain inhibitory mechanisms and therefore show an association with cognitive function. Therefore, one might speculate that stimulus modalities that are more psychologically aversive, i.e., perceived as more threatening and more unpleasant, such as the cold pressor test, have a stronger relationship with cognitive inhibition.

In that respect, Price et al. [41] postulated that the unpleasantness of nociceptive stimulations is influenced by the amount of autonomic activation they induce. As the cold pressor test is well known to induce cardiovascular activation [42], cold pressor pain might induce a more pronounced unpleasantness than other pain modalities. Taken together, this could provide an explanation for the differences in the relationships between cognitive inhibition and cold pressor pain and cuff pressure pain, respectively. In an earlier study, Rainville et al. [43] directly compared emotional responses to four different stimulus modalities. They reported that cold pressor pain was perceived as most unpleasant, but the perceived unpleasantness of cold pressure pain was not significantly different from the unpleasantness of cuff-induced ischemic pain. However, it seems reasonable that the ischemic pain protocol in the study by Rainville et al. [43] was probably more unpleasant than the cuff-pressure pain in the present study as it included additional muscle contractions during cuff occlusion, making this comparison somewhat invalid. Furthermore, recent evidence suggests that subjective threat value of pain stimulation is unrelated to the amount of pain inhibition [31].

Secondly, good reliability of the Stroop Colour-Word task [44] and excellent reliabilities of cold pressor pain threshold and tolerance have been reported [45], suggesting that measurement error is unlikely to have been a problem in the present study studies. However, it has been suggested that robust cognitive tasks are ill-suited to correlational designs, as they do not entail sufficient individual variation in performance, a prerequisite for individual differences research [44]. Therefore, future studies might explore the link between pain sensitivity and cognitive inhibition using performance measures with sufficient individual variation.

Thirdly, as proposed in Exercise-induced hypoalgesia and cognitive inhibition, it might be that cognitive inhibition is only weakly related or unrelated to pain sensitivity and pain inhibition, and other cognitive functions, such as working memory capacity, are of greater relevance to the pain experience [33].
Cognitive inhibition tasks

In this study, cognitive inhibition was measured as performance in two different tasks that require cognitive inhibition abilities. Based on this consideration and that the response to pain is highly automated, Bjekić et al. [9] proposed that stimulus inhibition in the Stroop Colour-Word task is more similar to pain inhibition than response inhibition in the stop-signal task, as reading and pain processing are automatic processes compared to the indexing task in the stop-signal task [20]. The present results partly confirm this proposal, as an association with EIH was only seen with the Stroop interference score – albeit in the opposite direction to our hypotheses. However, in contrast to Bjekić [9], Stroop interference was not associated with pain sensitivity. Although, as outlined above, pain modality might account for this discrepancy, it is difficult to interpret the present findings on the background of the Bjekić et al. (2018) study.

Furthermore, there was a significant interference effect in the Stroop Colour-Word task, meaning that reaction times (RT) were longer in the incongruent condition than in the congruent condition [24]. However, an interference effect was not observed on task accuracy. For this reason, only RT costs were analyzed in the correlational analyses of the present study. The dissociation between error costs and RT costs is in line with recent investigations pertaining to the Stroop Colour-Word task [46]. In that respect, our results further corroborate the suggestion that RT costs and error costs should be treated as independent constructs [46].

Limitations

There are several limitations that should be addressed in the present study. Firstly, in the stop-signal task (SST), outlier analysis produced a large dropout of eleven individuals, which could not be compensated, as the running time of the study was limited. Consequently, the analysis of the association between SSRTs and EIH after isometric exercise was underpowered, as was the previous study by our group on SSRTs and EIH after aerobic bicycling [15].

Secondly, baseline pain sensitivity measures, cognitive inhibition tasks as well as the EIH protocol were performed within a single session. Although the order of cognitive inhibition tasks, and the EIH protocol were randomized and counterbalanced, carryover effects from exhaustion cannot be ruled out in the present study. At least, order effects in cognitive tasks performance could not be observed (see Supporting Material A).

Conclusion

The present study investigated the association between exercise-induced hypoalgesia and cognitive inhibition as well as baseline pressure pain sensitivity and cognitive inhibition. Overall, no associations between cognitive inhibition and pain modulation induced by exercise or pain sensitivity were observed. These findings call previous findings of a positive association between cognitive inhibition and pain inhibition into question.

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Author Contributions: Hannah Gajsar mainly designed the research paradigm, conducted data acquisition, data analysis and interpretation, and drafted and revised the article, figures and tables from first to final versions. Marcel Meyer designed and programmed the cognitive tasks, ran preliminary analyses of the cognitive tasks including computation of task parameters, drafted the sections pertaining to the cognitive tasks (Stroop task and the SST) gave critical advice in the design of the research paradigm, data analysis and interpretation and reviewed the article from the first draft to the final version. Monika I. Hasenbring gave critical advice in the design of the research paradigm, data analysis and interpretation and reviewed the article from the first draft to the final version. Henrik B. Vaegter supervised the design of the research paradigm, provided resources for conduction of the studies and methods for the EIH paradigm, managed participant acquisition, gave critical advice in data analysis and interpretation and reviewed the article from the first draft to the final version.

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Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: Research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has
been approved by the local research ethical committee (S-20180171).

References


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