This work is a preprint that has not been peer-reviewed yet.

Placebo analgesia does not generalise from pain to interoceptive abilities

Helena Hartmann[1-3+*], Alessio Proposito[1,4+], Federica Riva[1], & Claus Lamm[1,5]

[1] *Social, Cognitive and Affective Neuroscience Unit, Department of Cognition, Emotion, and Methods in Psychology, Faculty of Psychology, University of Vienna, Vienna, Austria*

[2] *Clinical Neurosciences, Department for Neurology, University Hospital Essen, Germany*

[3] *Center for Translational and Neuro- and Behavioral Sciences (C-TNBS), University Hospital Essen, Germany*

[4] *Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, Netherlands*

[5] *Vienna Cognitive Science Hub, University of Vienna, Vienna, Austria*

[+] These authors contributed equally to this submission.

* Corresponding author: helena.hartmann@uk-essen.de, Clinical Neurosciences, Department for Neurology and Center for Translational and Behavioral Neuroscience, University Hospital Essen, Hufelandstraße 55, 45147 Essen, Germany

Abstract

Placebo pills reliably reduce pain. Pain perception is tied to increased arousal and heart rate, whose perception is closely related to interoceptive signals processing nociception and autonomic regulation. However, no studies so far have systematically examined the generalising vs specific effects of placebo analgesia in transferring from pain to the interoception of other bodily signals. In this preregistered study, we aim to investigate whether the placebo analgesia effect on pain may generalise to the perception of one's own heartbeat. We recruited 88 healthy participants (47 female, 41 male), of which half (23 female, 21 male) underwent a placebo analgesia induction. Using the Heartbeat Counting Task, we derived three interoceptive dimensions, interoceptive accuracy, sensibility and awareness. Despite a robust placebo analgesia effect, no difference between the placebo and the control group was found in any of the interoceptive dimensions. These findings were supported by post-hoc Bayesian analyses, which indicated moderate evidence for this absence of a group difference. Our findings thus do not indicate a generalisation of the placebo analgesia effect from pain to cardiac interoceptive awareness. Limitations and strengths of the work are discussed. Studies such as the present one are important to better understand the perception of different bodily systems and their connection in humans.

Keywords

heartbeat perception, heartbeat tracking, pain, placebo analgesia, interoception

1 Introduction

Placebo analgesia, first-hand pain reduction through nonpharmacological treatments, has been extensively documented (Colloca et al., 2013; Colloca & Benedetti, 2006). Pain sensations are directed to the central nervous system through the lamina I spinothalamocortical system. This circuit is also responsible for delivering other physiological sensations to the brain, such as temperature, itch, muscular and visceral sensations (Craig, 2002). This suggests that the lamina I spinothalamocortical system is the common peripheral pathway underlying interoceptive sensations (Li et al., 2017). Pain sensations, which entail bodily responses such as increased arousal and heart rate, could be considered part of interoception, the sensing of internal states of the body, and ranging from perceptible up to nociceptive signals. Interoception is distinguished from exteroception, which refers to the perception of the external environment, and proprioception, the sensing of the position of the body in space (Craig, 2007; Garfinkel et al., 2015). Interoception is a complex construct that can be operationalised using different dimensions. Regarding conscious interoception, Garfinkel and colleagues (Garfinkel et al., 2015) proposed a model entailing three different components: interoceptive accuracy, interoceptive sensibility and interoceptive awareness. The first one refers to the *objective* ability to correctly perceive our own bodily states, the second one indicates the *subjective* belief about our own interoceptive accuracy, while the third one represents a meta-cognitive measure of the correspondence between the first two measures.

The association between pain and interoception was investigated in few studies (Pollatos et al., 2012; Weiss et al., 2014) and is relevant in terms of the joint goal of maintaining homeostasis (Khalsa et al., 2018). Prior results suggest that enhanced sensitivity and decreased tolerance to pain in healthy subjects are associated with higher state interoceptive accuracy (Pollatos et al., 2012). Reduced interoceptive scores on a cardiac task were found in somatoform patients who showed stronger pain tolerance, compared to controls (Weiss et al., 2014). These findings point towards a connection between one's ability to perceive pain signals and one's interoception. However, previous studies merely provided correlative evidence and it is still unclear whether one's own pain perception causally influences one's general ability to perceive other bodily states that are not painful. In fact, studies such as (Werner et al., 2009) report pain and interoception to be at least partially independent. One study (Rütgen et al., 2021) provided causal evidence that placebo analgesia even generalises to reducing emotions associated with unpleasant touch. The authors also found that placebo analgesia reduced neural activity in the bilateral insular cortex. The insular cortex is, in turn, widely considered a crucial hub for the processing of interoceptive signals and their awareness (Caseras et al., 2013; Critchley et al., 2004; Ernst et al., 2013; Pollatos et al., 2007; Stern et al., 2017; Tan et

al., 2018; Wiebking et al., 2014, 2015; Zaki et al., 2012). These results call for a systematic investigation of the causal relationship between pain sensitivity and interoception.

In this preregistered study, we investigated whether placebo analgesia generalises to the perception of heartbeats, an interoceptive signal that could be considered neutral/unrelated to pain and affective states. Specifically, we formulated two competing hypotheses: 1) Participants under placebo analgesia might show reduced interoceptive abilities, due to a transfer of the blunting analgesic effect to a general reduction in the perception of bodily sensations. 2) The knowledge of having taken pain medication might increase participants' focus on their interoceptive signals (e.g. via side effect alertness (Webster et al., 2016)), resulting in enhanced interoceptive abilities.

2 Materials and Methods

2.1 Participants

This project was part of a bigger study conducted with multiple tasks, where the interoception task was performed last, which is why the procedures described in the following are equal to those in (Hartmann et al., 2022). Each participant was first screened for exclusion criteria using a thorough online questionnaire sent via email. Exclusion criteria were a past or present enrolment in academic studies including psychology, pharmaceutics or medicine (veterinary, dental, human, etc.) as well as other medical-related training (e.g. nurse), any neurological or psychiatric conditions, past or present substance abuse (alcohol more than daily use, drugs weekly or daily use), the intake of psychopharmacological medication (besides oral contraceptives) within the last three months, and past participation in at least one placebo study or a study involving similar deceptive elements. Furthermore, participants above the clinical cut-offs of the following questionnaires were excluded: Beck's Depression Inventory II (BDI-II; cut-off = 14 (Kühner et al., 2007)); Autism Quotient (AQ-k; cut-off = 17 (Freitag et al., 2015)); Toronto Alexithymia Scale (TAS-20; cut-off = 51 (Bach et al., 1996)).

Our preregistered target sample size was 90 participants (45 participants per group), excluding placebo analgesia non-responders and participants expressing doubts about the deceptive elements of the study. Precise a-priori power calculations were not possible due to the absence of previous studies investigating our research question and thus a lack of fitting effect size estimates. We therefore based our group sizes on previous studies using placebo analgesia in a between-subjects design to investigate transfer effects on empathy (Rütgen, Seidel, Riečanský, et al., 2015; Rütgen, Seidel, Silani, et al., 2015). Once deemed eligible, participants were pseudorandomly allocated to either the placebo or control group. A document with subject codes and group allocation was created beforehand, where placebo and control sessions were alternated (Subject_01 = control, Subject_02 = placebo, Subject_03 = control, etc.). Dropouts in each group were replaced and added at the end of this document until the final group sizes were reached. We recruited a total of 124 participants, 34 of whom were

excluded during data collection due to procedures described in (Hartmann et al., 2022) relating to another task (e.g. because of doubts about the cover story or given placebo). Two additional participants were not included in the analyses described here because of missing ECG data during the performance of the interoceptive task. The two groups were matched closely regarding age (mean age ± standard deviation = 23.54 ± 2.94 (placebo group) and 24.02 ± 4,37 (control group)) ($t(86)= -0.60$, $p = .549$), gender ($\chi^2(1) = 0.00$, $p = 1.000$), and trait interoceptive abilities (mean total score ± standard deviation = 4.07 ± 0.54 (placebo group) and 4.04 ± 0.58 (control group)) ($t(86)= 0.25$, $p = .799$), measured with the German version of the Multidimensional Assessment of Interoceptive Awareness (MAIA) (Mehling et al., 2012)). Participants were neurotypical, German-speaking, right-handed young adults with normal or corrected-to-normal vision who were currently enrolled in an Austrian university (Table 1). The final sample included $n = 88$ participants (placebo group: $n = 44$; control group: $n = 44$). The present study included no patient or public involvement.

Table 1. Overview of the sample and its characteristics.

	Overall (N = 88)	**Placebo** (N = 44)	**Control** (N = 44)	**Group Comparison**
Gender (F = female, M = male)				
Frequency	F = 47, M = 41	F = 23, M = 21	F = 24, M = 20	$\chi^2(1) = 0.00$, $p = 1.000$
Age (years)				
Mean (SD)	23.78 (3.71)	23.54 (2.94)	24.02 (4.37)	$t(86) = -0.60$, $p = .549$
Body Mass Index				
Mean (SD)	22.8 (3.04)	22.62 (2.55)	22.97 (3.48)	$t(86) = -0.52$, $p = .603$
Education level				
Frequency	1 = 1 2 = 57 3 = 22 4 = 8	1 = 1 2 = 25 3 = 15 4 = 3	1 = 0 2 = 32 3 = 7 4 = 5	$\chi^2(3) = 5.27$, $p = .153$

Note. The placebo and the control groups included the same number of participants and showed no difference in age, gender, education, and BMI. Two-sample t-tests were used to test group differences in age and BMI, and a chi-squared test to test if the gender and education level distribution differed in the placebo and control group. The different levels of education were categorised in this way: 1 (vocational training), 2 (high school diploma), 3 (Bachelor's degree), and 4 (Master's degree).

2.2 Procedure

We conducted a cross-sectional, experimental study. Eligible participants answered questionnaires online prior to coming to the testing session in the lab. They were asked to refrain from alcohol, drugs and medication intake (except oral contraceptives) in the 24 hours leading up to the experiment and to refrain from smoking, food, caffeine, and any drinks other than water 1 hour before the experiment. The behavioural testing session started with general instructions and calibration of individual pain threshold (see below for thorough descriptions of each step). Depending on the group, this was either followed by the placebo induction (placebo group) or an equal waiting time (control group). Blinding of participants or experimenters regarding the placebo/control conditions was not possible, as both parties needed to know this information for targeted instructions and conditioning. After completing another task unrelated to this study, participants completed the heartbeat counting task on a computer alone in a quiet chamber. The session ended with follow-up questions and feedback from the participants. The whole experiment lasted around 3 hours and participants received 35€ for their participation. The local ethics committee of the University of Vienna approved all procedures beforehand (application number 00412). The present research was conducted in accordance with the Declaration of the World Medical Association and all participants gave written consent before participation.

2.2.1 Pain calibration

The pain calibration was identical to the one described in (Hartmann et al., 2022) where electrical stimulation was given to the dorsum of the non-dominant, left hand in multiple trials, moving up stepwise from a rating from 0 = 'not perceivable' until the stimulus is rated as 8 = 'extremely painful but bearable'. The experimenter started by delivering stimuli at a low intensity of 0.05 mA, with the step size individually chosen for each participant, so that each rating was experienced at least once. This was repeated a second time with a small break in between to avoid habituation/sensitization and followed by varying (seemingly “random”) stimulation in the before calibrated rating range from 1 to 8. This procedure allowed us to gain valid averages for values the participant rated as 1 = 'noticeable but not painful', 4 = 'medium painful' and 7 = 'very painful'. Average intensities rated as 1 and 4 were then used during the placebo conditioning procedure, and average intensities rated as 1 and 7 were used in the pain task for non-painful and painful stimulation, respectively.

2.2.2 Placebo analgesia induction

The placebo group underwent a placebo analgesia induction using a pill presented as an “effective and powerful painkiller”, combined with verbal suggestions by a medical student (presented as a doctor working at the Faculty of Psychology) and, after a waiting time of 10 minutes for the pill “to take effect”, a conditioning procedure in regard to the treatment. This

conditioning procedure involved the participants receiving electrical stimulation in the same location as during calibration. Participants were told they would receive high stimulation intensities, but in reality received stimulation of a medium intensity (rated as 4 before) and corresponding feedback (e.g. “This stimulus was rated as more painful/very painful before”) to suggest a pain reduction by means of the given treatment. These conditioning trials were repeated for a minimum of two and up to a maximum of four times until the subject did not respond with values higher than 5 to the conditioning stimulus, i.e. they experienced a pain reduction. In reality, the pill did not contain any active pharmacological components, but a natural sugar-alcohol (Mannitolum, 40G per pill). The control group did not receive a pill or any type of induction but had equal waiting times to keep the session length the same.

2.2.3 Pain task

The pain task was a shortened version of the one used in (Rütgen, Seidel, Silani, et al., 2015) with a total of 20 trials (5 per condition) and the trials where the participants received pain first-hand were used as a manipulation check to ensure that we had reduced pain in the placebo group through the treatment. The original task also contained an empathy condition that is reported in (Hartmann et al., 2022). This task was completed right before the Heartbeat Counting Task. Trials were shown in a pseudorandomized order (four sequences were created manually for each task and alternated over all participants in an a-priori defined order). We asked participants to evaluate: 'How painful was this stimulation for you?' on a 9-point rating scale from 0 = ‘not noticeable’ to 8 = ‘extremely painful/unpleasant’.

2.2.4 Heartbeat counting task

To measure interoceptive abilities, we used the classic Heartbeat Counting Task (HCT; (Schandry, 1981) but see (Ferentzi et al., 2022)) with an interoceptive condition (counting one’s own heartbeat) and an exteroceptive control condition (counting tones heard over headphones). Importantly, and in response to the criticism about the HCT, we used modified instructions that underlined to the participants that they should not use any help while counting their heartbeat (like feeling the pulse), and that they should only report the beats they really felt and under no circumstances guess or estimate (Corneille et al., 2020; Desmedt et al., 2018). This could mean reporting no beat at all, some beats or as many beats as were actually counted.

Participants completed a training, where they first underwent a 5-minute resting phase. During this phase, participants were asked to sit comfortably in their chair, close their eyes and concentrate on their heartbeat while relaxing. This was followed by a sound calibration to adjust the volume of the tones heard later in the task to make the exteroceptive and interoceptive conditions as equally difficult as possible. A set of tones of increasing or decreasing volume was played while participants wore headphones. Participants were asked to immediately press

a button when they (1) heard the tones for the first time (volume increase) or (2) did not hear the tones anymore (volume decrease) (order: decrease – increase – decrease – increase). An average volume was calculated from these four trials and after that, 10 single tones were played in this average volume, with the participant indicating for each of them whether they had heard a tone or not. The participant was told that sometimes a tone would be played and sometimes not. If the participant perceived 9 or 10 tones, the average volume was decreased by two steps (chosen volume step = 0.5 % of the maximum volume); if the participant perceived 7 or 8 tones, the average volume was decreased by one step; if the participant perceived 4, 5 or 6 tones (i.e., he/she perceived 40-60 % of all tones), the average volume was not changed; if the participant perceived 2 or 3 tones, the average volume was increased one step; and if the participant perceived 0 or 1 tone(s), the average volume was increased by two steps. Then again, five single tones were played in the same fashion in the adjusted volume and another correction was applied, depending on the number of total tones perceived: If the participant perceived 5 tones, the average volume was decreased by two steps; if the participant perceived 4 tones, the average volume was decreased one step; if the participant perceived 2 or 3 tones (= he/she perceived 40-60 % of all tones), the average volume was not changed; if the participant perceived 1 tone, the average volume was increased one step; and if the participant perceived 0 tones, the average volume was increased two steps. The resulting volume was used in the following training and task (see Figure 1).

Then, participants completed a short practice (4 trials, each condition twice) and then the main task with 12 trials, 6 for each condition (interoceptive, exteroceptive), using 3 different trial durations. The durations differed for the two conditions to avoid transfer/learning from one condition to the other (durations were 25/35/45s and 28/38/48, respectively, and were counterbalanced between subjects). After each trial, participants were asked to report the number of heartbeats or tones they counted, followed by a brief rest period of 20 seconds before the next trial. In every other trial, participants were also asked how confident they felt about their given answer (to measure interoceptive sensibility) on a continuous visual analogue scale (200 points) with the anchors “not confident” and “confident”. Our approach therefore assessed (1) performance in accuracy and (2) subjective beliefs about it (Murphy et al., 2019). Trials of the interoception task were shown in a pseudorandomized order (four sequences were created manually for each task and alternated over all participants in an a-priori defined order). We measured the actual heart rate to identify heartbeat peaks in each trial of the interoceptive condition using Mobi, a measurement system for electrophysiological signals (Twente Medical Systems International, Netherlands).

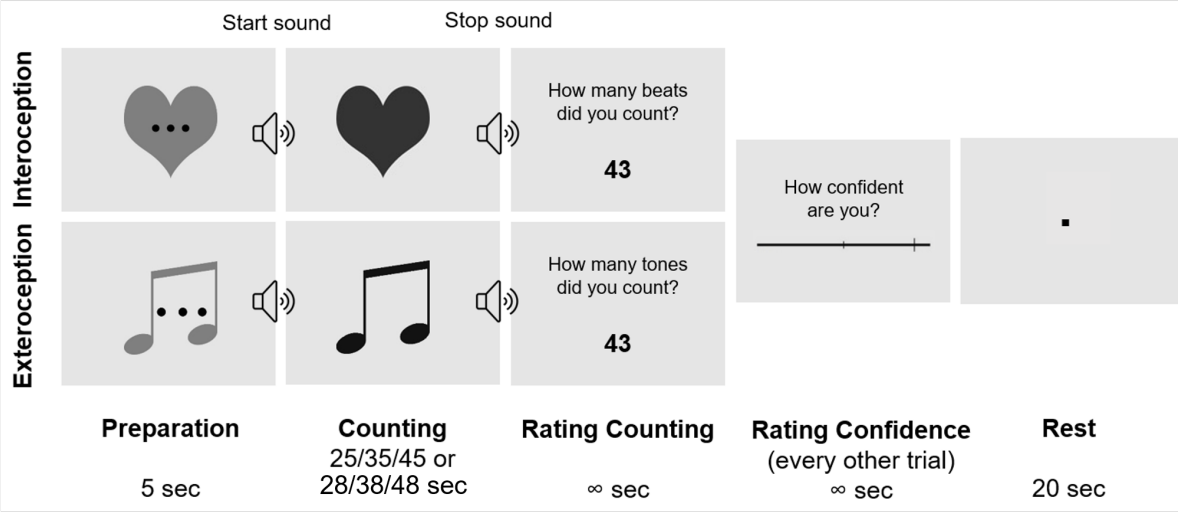

Figure 1. Overview of the Heartbeat Counting Task. Participants either counted their own heartbeats or tones audible over headphones and then reported the number of beats/tones that they counted, and, every other trial, also their confidence in their reported number.

We then calculated interoceptive accuracy scores for each subject according to the standard formula: 1/total number of time intervals Σ (1–(|actual heartbeats – reported heartbeats|)/actual heartbeats). The score ranges between 0 and 1, with higher numbers representing higher accuracy. The same formula was used for the exteroceptive condition. Interoceptive sensibility scores were calculated as a mean of all confidence ratings of one condition.

2.3 Data acquisition and analysis

Data were processed and analysed using RStudio (Version 1.4.17 (R Core Team, 2020)). All *p*-values were interpreted as two-sided, as we had two competing hypotheses.

2.3.1 Nonresponder identification

Non-responders were determined by procedures equal to the ones used in (Hartmann et al., 2022). In brief, a combination of three measures was employed: First, we recorded any verbally expressed doubts about the treatment or study setup (e.g. confederate or other deceptive parts) by means of feedback questions at the end of the study. If a participant expressed doubts in any of these domains, we asked them to elaborate these further and participants with strong doubts were excluded. Second, differences in the belief scores about the effectiveness of the placebo before and after the induction procedure as well as at the end of the session were analysed. Here, total belief scores (sum of pre- and post-conditioning scores) lower than 66.6 (values can range from 0 to 200) and strong decreases between the first and second measure (pre- score minus post-conditioning score bigger than 33.3) served as a measure for lack of responding. Third, we took the number of placebo conditioning trials into account. If participants responded with a value greater than 5 on a 9-point rating scale from 0 = ‘not noticeable’ to 8 = ‘extremely painful, but bearable’ to the conditioning stimulus

(delivered at a medium intensity of 4), we deemed the conditioning trial as non-successful, waited another few minutes for the “medication to take effect”, and then repeated the trial. This was repeated a maximum of four times or until participants responded with values below 6 to the conditioning stimulus in the current trial. If more than three of these trials were necessary, this was taken as an indication of non-responding.

2.3.2 Manipulation check

Placebo analgesia effect. We operationalized the placebo effect by subtracting the first-hand pain rating from the value 7 (i.e., the rating corresponding to the pain intensity delivered, as determined during prior individual pain calibration, see also the mediation analysis in (Hartmann et al., 2022)), leading to a placebo analgesia score where higher values mean higher analgesia. The validity of the placebo analgesia induction on the subjective pain score was assessed with a two-sample *t*-test comparing the analgesia scores of the placebo and control group. Exclusively for the placebo group, we asked the participants about their beliefs in the effectiveness of the placebo pill at three different time points of the experiment: after the administration of the pill (pre-conditioning), after the conditioning procedure and at the end of the session. This was done as a manipulation check on the strength of the first-hand placebo effect (not preregistered).

2.3.3 Control variables

We investigated the comparability of our two groups and included several control measures. These analyses were not preregistered.

BMI. Previous studies found a significant effect of the Body-Mass-Index on interoceptive abilities, with higher BMI being associated with lower cardiac awareness (Kleckner et al., 2015; Rouse et al., 1988). For this reason, we measured the BMI of participants (using self-report of weight and height) and included it as a covariate in the mixed analysis of variance described in the next section.

Clinical questionnaires. To assess that the placebo and control groups do not differ in any of the clinical questionnaires administered (see Table 2 for the complete list), we performed two-sample *t*-tests separately per each of the 11 questionnaires. In addition, any possible relationship between the clinical questionnaires and the main interoceptive dimensions was investigated with Pearson’s correlations, both within the total sample and separately for the placebo and control groups. To control for the potential effects of clinical symptoms on HCT performance, the main questionnaire scores of the BDI, STAI-T and TAS were included separately as covariate in the main analyses described in the next section. These analyses were not preregistered, but we considered them necessary to control for baseline group differences and to assess possible confounding relationships.

Post-session questionnaires. During the debriefing at the end of the session, we asked participants how hard vs. easy they perceived the interoceptive and exteroceptive condition, respectively, whether they felt the heartbeats in a specific location and/or generally in the body, and to what extent they estimated or guessed when they didn't feel their heartbeat (Desmedt et al., 2018). For each question, participants indicated their answer on a rating scale going from 1 (hard) to 5 (easy) for the first question, and 1 (never) to 9 (always) for the second and third questions. To assess that the two groups did not differ in the evaluation of the difficulty of the two conditions of the HCT, as well as in their strategy to count heartbeats, two-sample *t*-tests were used to compare the groups' score for each of the follow-up questions.

2.3.4 Preregistered analyses

State Interoceptive accuracy. The (interoceptive and exteroceptive) accuracy (IAcc) scores were analysed with a parametric mixed-model analysis of variance (ANOVA). As independent variables we included *treatment* (placebo, control) as a between-subjects factor and *condition* (interoceptive, exteroceptive) as a within-subject factor. We controlled for BMI by including it as a covariate. To check for the presence of ceiling effect (i.e., people having 100% accuracy scores), we adopted a threshold for a minimum of 15% of participants having the highest accuracy value (i.e., 100% or 1) (Lim et al., 2015).

State interoceptive sensibility. The second ANOVA analysed the confidence ratings collected during the HCT. These scores define a state measure of interoceptive sensibility (IS-s) construct because they are related to the current performance of the HCT. As independent variables, we again included treatment and condition as in the above ANOVA.

2.3.5 Exploratory analyses

Trait interoceptive sensibility. Interoceptive sensibility as the general belief in one's own interoceptive ability (IS-t) was operationalized by means of the MAIA questionnaire (Mehling et al., 2012). This measure is unrelated to the performance of a specific interoceptive task and can thus be defined as a trait. We specifically focused on three subscales investigating interoceptive aspects that relate to our study and tasks: Noticing (awareness of uncomfortable, comfortable, and neutral body sensations), Attention Regulation (ability to sustain and control attention to body sensations) and Body Listening (active listening to the body for insight). Group differences were calculated with two-sample *t*-tests.

Interoceptive awareness. To investigate the metacognitive awareness of interoceptive abilities, we derived two measures. The first measure returns an individual index of interoceptive awareness (IAwa), calculated with a within-participant Pearson correlation between the IAcc and IS-s scores, as introduced by (Garfinkel et al., 2015). Since we acquired confidence ratings only every other trial (6 out of 12 total trials), we failed to balance this

measurement between the interoceptive and exteroceptive conditions. Therefore, analytic constraints permitted only participants with at least three confidence ratings for the interoceptive condition to be included in the analysis. This led to a reduced sample of 56 participants (placebo group: n = 26; control group: n = 30) for this measure. Individual correlation coefficients were averaged to define group specific interoceptive awareness. Then, to determine if interoceptive awareness is present or absent (following the procedure of (Garfinkel et al., 2015)), a one-sample *t*-test was used to establish if the correlations between confidence and accuracy were significantly different from zero. This was performed on both the entire sample and on the two groups separately (resulting in a total of three one-sample *t*-tests). Finally, to assess if the placebo and control group differ in IAwa, we used a two-sample *t*-test.

Since this first measure of interoceptive awareness did not include all participants, we calculated a second measure which reflects the index of correspondence between subjective and objective accuracy at the group level, and was calculated with a Pearson correlation between the individual mean of interoceptive accuracy scores and confidence ratings, separately for the placebo and control group. This method allowed us to include ratings from all participants, as well as the ones with fewer than three confidence ratings per condition. We then tested if the relationship between these dimensions differed in the groups by means of the test statistic *z*, comparing the two correlation coefficients with each other (see Figure 4).

Bayesian analyses. The surprising absence of any difference in the interoceptive dimensions between the two groups, going against our preregistered hypotheses, was followed up using a complementary Bayesian approach (e.g. (Wagenmakers et al., 2018)) that explored the relative evidence for either the null or the alternative hypothesis of no group difference. Four Bayesian two-sample *t*-tests were used to compare IAcc, IS-s, IS-t and IAwa between the two groups. A standard Cauchy (0,1) prior to 1 was used as the effect size. This refers to a 50% chance of observing an effect size that falls between −1 and 1 (e.g., (Rouder et al., 2009)). Bayesian *t*-tests generate a Bayes Factor comparing the relative evidence between the alternative and null hypothesis (BF_{10}, H1 vs. H0; (Mac Giolla & Ly, 2019)). To interpret these values, it was proposed that a $BF_{10} < 3$ indicates weak evidence, a $BF_{10} > 3$ positive evidence, and a $BF_{10} > 150$ shows strong evidence for the alternative hypothesis (Jarosz & Wiley, 2014). To investigate the evidence for the null compared to the alternative hypothesis (BF_{01}, H0 vs. H1) the Bayes factor was calculated as $BF_{01} = 1/BF_{10}$.

Association between pain and interoception. We tested the relationship between the analgesia score and the four interoceptive dimensions within both the total sample and the placebo and control group separately by means of Pearson correlations.

3 Results

3.1 Manipulation check

Placebo analgesia effect. First, we aimed to make sure that our placebo manipulation reliably reduced pain in the placebo group, compared to the control group. This check was not included in the preregistration, but we routinely employed it in previous studies (Hartmann et al., 2021, 2022). The placebo group reported a mean placebo analgesia score of 1.7 (*SD* = 1.64, max = 5.8, min = -0.4) while the control group had a mean of 0.7 (*SD* = 1.13, max = 3.6, min = -1), resulting in a strong group difference (t(86)= 3.33, *p* = .001), which confirmed the validity of the placebo analgesia induction on the subjective pain scores (see panel A in Figure 2). When looking at the duration of the placebo effect, participants in the placebo group reported stronger beliefs of the effectiveness of the placebo pill in the post-conditioning time point compared to the pre-conditioning (t(86)= 3.43, *p* < .001). At the end of the session (post-session time point) the beliefs of the medication effectiveness were significantly reduced compared to the post-conditioning phase ((86)= 2.70, *p* = .008), but not lower than the initial pre-conditioning belief (t(86)= 0.37, *p* = .715) (see panel B in Figure 2).

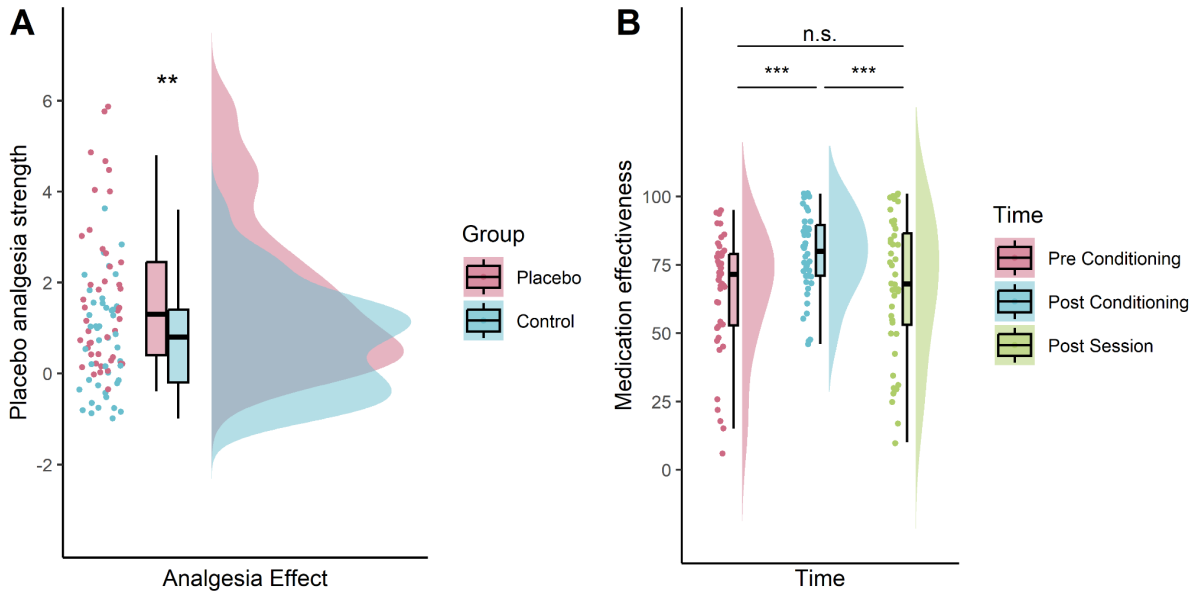

*Figure 2. Manipulation checks of the placebo analgesia effect. A) The placebo group showed a higher analgesia effect compared to a control group without such an induction. Participants who received placebo medication rated painful electrical stimuli as significantly less painful compared to participants who did not receive the medication. B) Beliefs in the effectiveness of the administered alleged painkiller were rated by the placebo group at three time points during the experiment: after oral ingestion and verbal suggestions by the medical cover (pre-conditioning), after the conditioning procedure (post-conditioning) and during the debriefing at the end of the session (post-session). This revealed a significant increase in beliefs after the conditioning. Although the beliefs significantly decreased until the end of the session, they did not drop significantly lower than initial belief levels. ** (p ≤ .01), *** (p ≤ .001), n.s. (not significant, p > .05). The boxes in the plots showed the interquartile range (IQR) of the data, where the upper and lower edges correspond to the first and third quartiles respectively. The*

horizontal line inside the boxes represents the median, while the whiskers outside the boxes indicate the range of non-outliers data points (i.e. data not exceeding 1.5 times the IQR range).

3.2 Control variables

BMI. The total sample reported a BMI average of 22.8, falling into the range of what is considered healthy body weight (Peterson et al., 2016)(see Table 1). No significant difference was found between the placebo and control group ($t(86) = -0.52$, $p = .603$; placebo: $M = 22.62$, $SD = 2.55$; control: $M = 22.96$, SD = 3.48). The results of the ANOVAs, described in the *Preregistered analyses* section, did not change when including BMI as covariate.

Clinical questionnaires. Between the placebo and control group, no significant difference was found in the score of all questionnaires administered (see Table 2 for the complete list) (all *p's* > .126). In the total sample and in the placebo group, there was no significant relationship between the interoceptive dimensions and a measure of depression (BDI), alexithymia (TAS) and anxiety (STAI-T) (total sample: $r < \pm .17$, all *p's* > .104, placebo group: $r < \pm .27$, all *p's* > .073). In the control group, a negative trend was evident between alexithymia and interoceptive sensibility (i.e., confidence ratings) ($r = -.29$, $p = .054$). When adding separately the main questionnaire scores (BDI, STAI-T and TAS) as covariate in the ANOVA used to analyse the HCT performance, results did not differ from those described in the next section.

Post-session questionnaires. No group difference was found in the evaluation of the difficulty of the interoceptive and exteroceptive conditions of the HCT ((86) < 0.96, *p's* > .337). However, all participants rated the interoceptive condition significantly more difficult than the exteroceptive one ((174)= -29.78, $p < .001$), which indicates that the difficulty level between the two conditions was not correctly balanced. No group differences were found when asking if the counted heartbeats were felt in a specific location or generally in the body ((86) < 1.34, *p's* > .184). Regarding the strategies used to count heartbeats, both groups reported a similar level of guessing and estimation strategies whenever they didn't feel any heartbeat ((86) < 1.45, *p's* > .151) (guessing strategies: placebo: $M = 1.23$, $SD = 0.47$; control: $M = 1.45$, SD = 0.93; estimation strategies: placebo: $M = 1.57$, $SD = 0.95$; control: $M = 1.64$, SD = 1.01). The little use of these strategies implies good compliance with the task instructions.

Table 2. Overview of the administered behavioural and clinical questionnaires .

Questionnaire	Placebo Mean (SD)	Control Mean (SD)	Group comparison
IRI- EC	18.36 (4.81)	18.32 (4.79)	$t(86) = 0.04$, $p = .96$
IRI-PT	18.61 (4.71)	18.27 (3.99)	$t(86) = 0.36$, $p = .71$

HAS	78.64 (8.78)	78.61 (9.61)	t(86) = 0.01, p = .99
AMI-BA	2.59 (0.6)	2.51 (0.68)	t(86) = 0.61, p = .54
AMI-SM	2.87(0.62)	2.65 (0.71)	t(86) = 1.54, p = .12
AMI-ES	6.73 (3.72)	6.70 (2.94)	t(86) = -0.47, p = .64
SD3 - P	18.34 (3.67)	19.57 (5.39)	t(86) = -1.25, p = .21
MAIA	4.07 (0.54)	4.04 (0.58)	t(86) = 0.25, p = .79
TAS	38.39 (6.54)	40.11 (6.84)	t(86) = -1.20, p = .23
AQ	6.73 (3.72)	6.70 (2.94)	t(86) = 0.03, p = .97
BDI	4.32 (3.7)	4.61 (4.1)	t(86) = -0.36, p = .72
STAI-T	36.82 (8.75)	39.48 (7.91)	t(86) = -1.49., p = .14

Note. Placebo and control group did not differ in any of these self-report measures (all p's > .126). Questionnaire abbreviations: IRI-EC = Interpersonal Reactivity Index - Empathic concern, IRI-PT = Perspective taking, HAS = Prosocial behaviour, AMI-BA = Apathy Motivation Index - Behavioural Activation, AMI-SM = Social Motivation, AMI-ES = Emotional Sensitivity, SD3 = Short Dark Triad - Psychopathy, MAIA = Multidimensional Assessment of Interoceptive Awareness - Trait Sensibility, TAS = Toronto Alexithymia Scale, AQ = Autism Quotient, BDI = Beck's Depression Inventory, STAI-T = Trait Anxiety Inventory.

3.3 Preregistered analyses

State interoceptive accuracy. The total sample reported for the interoceptive condition and the exteroceptive condition a mean accuracy score of 0.52 (*SD* = .32, max = .98, min = 0) and 0.97 (*SD* = .06, max = 1, min = .7) respectively. No group difference in the HCT performance was found in the main effect of group (F(1,86) = 0.10, p = .754, $\hat{\eta}^2_G$ < .001) (see panel A in Figure 3), neither in the group x condition interaction (F(1,86) = 0.18, p = .677, $\hat{\eta}^2_G$ < .001). Instead, a strong difference between conditions was found (main effect of condition: F(1,86) = 175.35, p < .001, $\hat{\eta}^2_G$ = .498), with an overall better performance for the exteroceptive condition compared to the interoceptive condition. We observed a ceiling effect (36.36% of participants had a perfect score, i.e., an accuracy of 100%) for the exteroceptive condition which indicates a disproportion in the difficulty level between the two conditions (similar as in other studies, e.g. (Sojka et al., 2024)).

State interoceptive sensibility. There was no group difference in the confidence ratings (F(1,86) = 0.25, p = .617, $\hat{\eta}^2_G$ = .002) (see panel B in Figure 3) and the group x condition interaction was found not significant (F(1,86) = 0.53, p = .468, $\hat{\eta}^2_G$ = .003). Like above, only

the difference between conditions was significant ($F(1,86) = 154.21$, $p < .001$, $\hat{\eta}^2_G = .465$), meaning that participants were more confident about their exteroceptive performance compared to the interoceptive performance in the HCT.

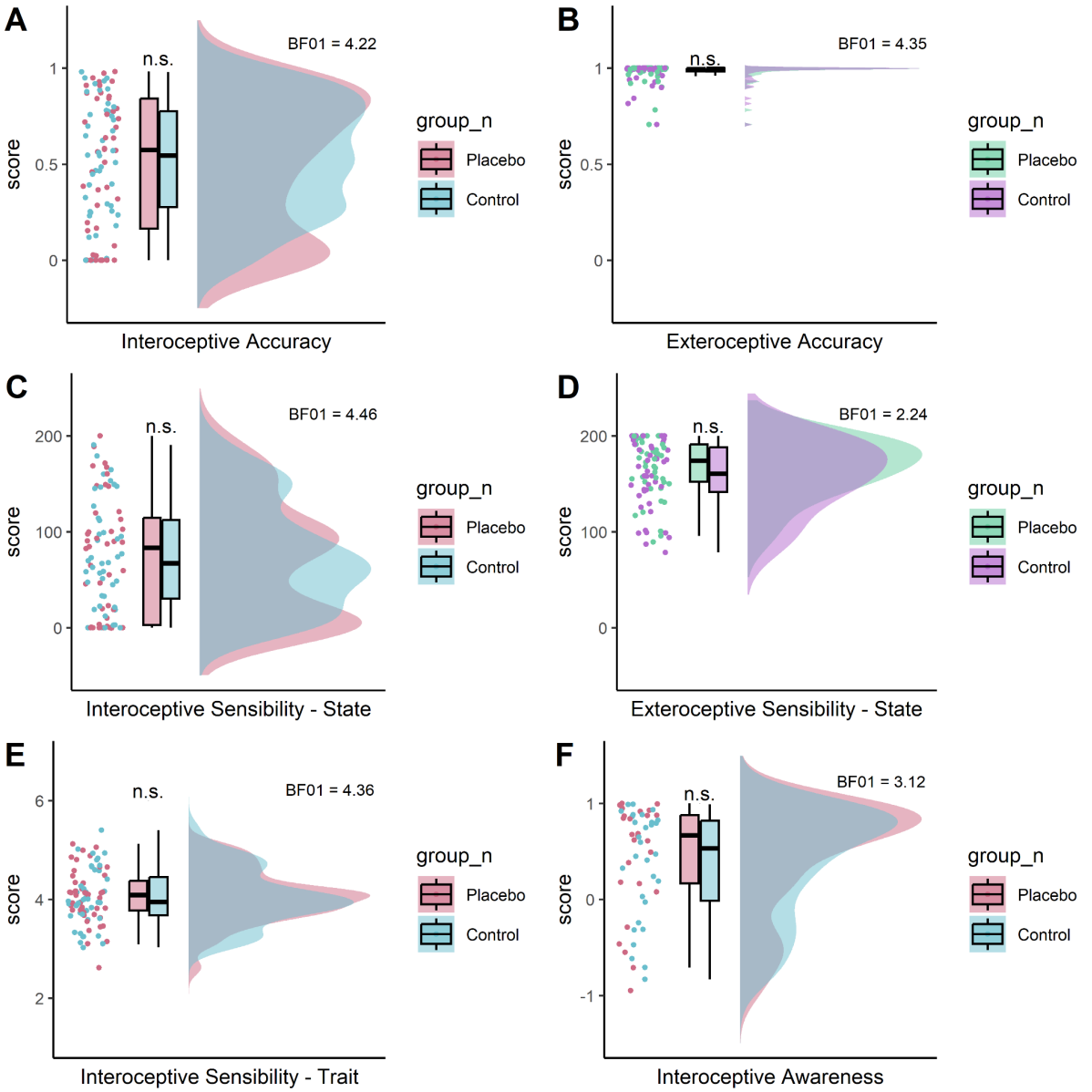

Figure 3. No effects of placebo analgesia on the four dimensions of interoception. A) State interoceptive accuracy (objective performance in the heartbeat counting task). B) State exteroceptive accuracy. C) State interoceptive sensibility (the subjective perception of one's performance in the heartbeat counting task). D) State exteroceptive sensibility. E) Trait interoceptive sensibility (general subjective perception of one's interoceptive abilities in a questionnaire). F) Interoceptive awareness (the correlation between objective performance and its subjective perception). Correspondent bayer factors are indicated in the top right corner of each plot. All values were higher than 3 in the interoceptive dimensions indicating positive evidence for the null hypothesis (i.e. no group difference in the interoceptive dimensions). For the exteroceptive dimensions, the exteroceptive accuracy also showed a Bayes factor higher than 3, while for the state exteroceptive sensibility, the value is 2.24 indicating anecdotal evidence for the null hypothesis. Note. The boxes in the plots showed the interquartile range (IQR) of the data, where the upper and lower edges correspond to the first and third quartiles respectively. The horizontal line inside the boxes represents the median, while the whiskers outside the boxes indicate the range of non-outliers

data points (i.e. data not exceeding 1.5 times the IQR range). n.s. = not significant (p > .05), BF01 = evidence for the null relative to the alternative hypothesis.

3.4 Exploratory analyses

Interoceptive sensibility - trait. Interoceptive sensibility as a trait was operationalized by means of the MAIA questionnaire. Placebo and control groups did not differ in the total score ((86) = -0.25, p = .79) (see panel C in Figure 3) as well as in the subscales of interest (Noticing, Attention Regulation and Body Listening) (t(86) < ± 1.39, *p's* > .17).

Interoceptive awareness. We found a significant positive correlation between confidence ratings and interoceptive accuracy in both the total sample (r = .38, p < .001) and in the placebo (r = .35, p = .019) and control group (r = .42, p = .004).

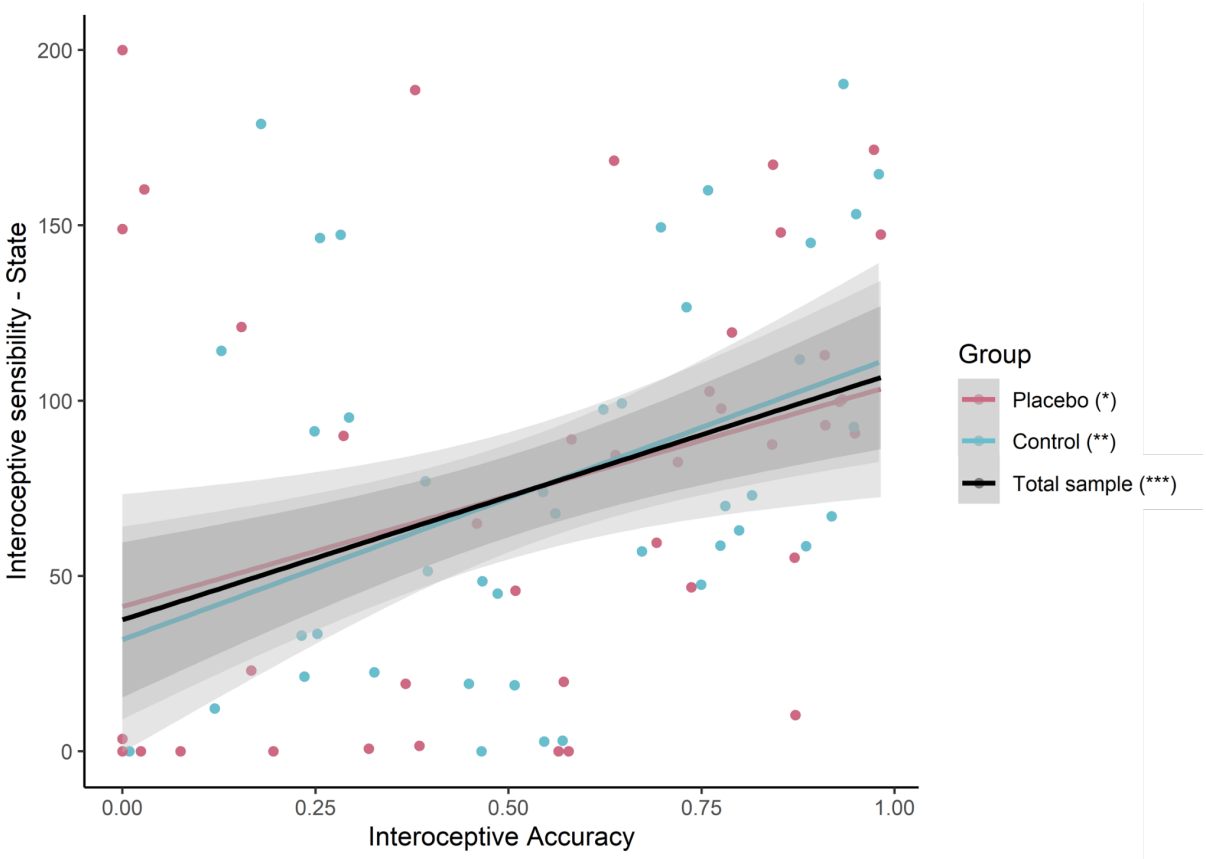

*Figure 4. C*orrespondence between subjective and objective interoceptive abilities at the group level in the placebo and control group as well as for the whole sample. The total sample showed a significant relationship between state interoceptive accuracy and state interoceptive sensibility (r = .38, p < .001) as well as the placebo group (r = .35, p = .019) and the control group (r = .42, p = .004). However, no group difference was found when directly comparing the two correlation coefficients (Fisher's z = -0.40, p = .689). The black line represents the average line between the two groups. ** (p ≤ .05), ** (p ≤ .01), *** (p ≤ .001).*

However, the correlation coefficients did not differ between the two groups (Fisher's z = -0.40, p = .689), indicating that the correspondence between subjective and objective interoceptive abilities in the placebo and control group is not statistically different (Figure 4).

Individual interoceptive awareness determined from confidence-accuracy correlation (Pearson's *r*) significantly differed from zero at the total sample level (56 participants, (55) = 5.30, $p < .001$) and in the placebo (26 participants, $t(25) = 3.90$, $p < .001$) and control group (30 participants, $t(29) = 3.56$, $p = .001$). When comparing interoceptive awareness between the two groups, no significant difference was found ((54)= 0.52, $p = .603$) (see panel D in Figure 3).

Bayesian follow-up analyses. The absence of group difference in all interoceptive dimensions (i.e., state interoceptive accuracy, state interoceptive sensibility, and interoceptive awareness) was further explored with Bayesian two-sample *t*-tests for each dimension separately. All results showed moderate evidence against the alternative hypothesis, with the null hypothesis being more than three times more likely than the alternative hypothesis in our sample (IAcc: $BF_{01} = 4.22$; IS-s: $BF_{01} = 4.46$; IS-t: $BF_{01} = 4.36$; Iawa: $BF_{01} = 3.12$). Furthermore, moderate evidence against the alternative hypothesis was found also for the exteroceptive condition in the HCT ($BF_{01} = 4.35$), while the related confidence ratings showed anecdotal evidence ($BF_{01} = 2.24$).

Association between pain and interoception. No significant correlations were found between the placebo analgesia effect and the interoceptive dimensions in both the total sample and in the placebo and control group separately ($r < \pm .17$, all $p's > .265$).

4 Discussion

We investigated whether placebo analgesia, the reduction of first-hand pain by means of a placebo pill presented as a "strong painkiller" and a related conditioning procedure, would generalise to neutral bodily states unrelated to pain or affective states, such as heartbeat perception. Using a combination of frequentist and Bayesian statistical approaches, we observed consistent moderate evidence of absence for such a transfer in all three interoceptive dimensions.

The placebo and control group did not differ in their interoceptive accuracy, i.e., their objective performance of counting their heartbeats. Matching the above finding, the groups did not differ regarding state or trait interoceptive sensibility, i.e., how confident they felt in correctly counting their heartbeats during a cardiac interoceptive task and how they rated their general interoceptive ability in a self-report trait questionnaire, respectively. Similarly, the two groups did not show differences regarding their interoceptive awareness, i.e., how well people's subjective perception and objective performance match in the counting task. At the group level, we did find that both the placebo and control group showed a significant positive correlation between confidence reports and task performance. This correlation indicated that people who were more accurate in counting their heartbeats were also more confident in their performance, or vice versa. However, the correlation coefficients of the two groups were not different when

statistically compared. These null findings in the three interoceptive dimensions were corroborated by moderate Bayesian evidence for the null hypothesis (which was 3-4x more likely than the alternative hypothesis), and further evidenced by the absence of a significant correlation between the placebo analgesia effect score and the measure of any interoceptive dimension.

Our findings are in line with the study (Werner et al., 2009) who reported no difference between participants with high and low interoceptive sensitivity regarding pain sensitivity, pain tolerance, and subjective pain experience of tonic heat stimuli. Also they found no significant correlation between pain sensitivity and cardiac interoceptive sensitivity. According to some accounts, pain applied on the skin might primarily be considered an exteroceptive sensation (Ceunen et al., 2016). These findings possibly highlight the limits and extent that our own pain processing affects heartbeat perception, proposing that distinct mechanisms are at play. Perceiving one's heartbeat might thus rely, in presumably large parts, on different mechanisms than pain perception, even though some neural processing might rely on similar brain regions (Legrain et al., 2011). Here, we tested the causal influence of reduced pain perception via a placebo on interoceptive abilities in a conscious heartbeat tracking task. Perceiving one's heartbeats is only one facet of interoception, and we cannot generalise our findings to other, more internal or unconscious forms of interoception (e.g., visceral or gut interoception, (Smith et al., 2021); or unconscious interoception (Azevedo et al., 2017)). Moreover, it could also be that people with better interoceptive abilities feel pain more intensely and are thus more sensitive or accurate when perceiving pain. This notion, however, will have to be tested in future work, for example, by strategically collecting and comparing data from individuals "better" or "worse" at interception.

In connection with this, research has shown that placebo analgesia also reduces the first-hand experience of unpleasant, but not pleasant, touch (Rütgen et al., 2021). This suggests a valence-specific categorization and modulation of incoming sensations into positive and negative. Our results extend this knowledge to the neutral domain of heartbeat perception, but do not exclude the possibility that placebo analgesia may generalise to states of higher arousal, such as the perception of negative affect.

These findings seem intuitive from an evolutionary standpoint: while some generalisations of bodily perception may be helpful, they may be overly cautious in other cases: distinguishing heartbeat perception from the perception of pain is useful, as only the latter serves as a warning and warrants concrete action. Moreover, while heartbeats are a signal that is automatically regulated by the body, acute pain often demands conscious attention, at least in otherwise healthy individuals. The picture might look different in chronic pain patients, where pain has lost its warning function and has been shown to be related to interoceptive conditions and sensations ((Di Lernia et al., 2016) for a review; (Borg et al., 2018) for fibromyalgia; (Grabli

et al., 2021) for back pain; (Weiss et al., 2014) for somatoform disorder). Future work should also focus on further teasing apart the connection between increased vs. decreased pain and interoception in health vs. disease.

The present study had some limitations and strengths worth mentioning. Regarding limitations, the interoceptive and exteroceptive conditions were unbalanced in terms of subjectively perceived difficulty. Even though we tried to match the two conditions as best as possible using an elaborate sound calibration procedure, ~36% of participants had the highest possible accuracy in the exteroceptive condition. We also observed higher confidence when counting tones vs. heartbeats over all participants, which matches the accuracy results. Another task-related limitation regards the different proportion of confidence rating measures across the participants. Since they were assessed in every other trial no matter the condition, we failed to balance this measurement between the interoceptive and exteroceptive conditions, resulting in the exclusion of some subjects from the analyses on interoceptive awareness. Moreover, placebo analgesia has been suggested to act mainly via higher-level regulatory mechanisms, as opposed to nociception (Zunhammer et al., 2021), which could be one of the reasons why we did not observe any causal effects in this study.

Finally, the Bayesian analyses showed Bayes Factors above three, which indicates moderate evidence for the null hypothesis. However, as these and other analyses in the study were done exploratory, replication in independent studies is warranted.

Regarding strengths, we successfully induced a placebo analgesia effect in the experimental group, as they rated electrical pain received on their hand as less painful compared to the control group, who did not receive any treatment. The placebo group also had a high belief in the “medication”, which significantly increased through the conditioning procedure and remained present until the end of the session. This validates our causal manipulation and strengthens the evidence of absence of a transfer of placebo analgesia to heartbeat perception. We further observed that participants complied with task instructions and completed the task as intended. Counting strategies such as guessing or estimating were similar in both groups. The groups were comparable regarding their BMI and personality traits such as depression, alexithymia and anxiety, and the inclusion of these variables as covariates did not change the overall findings. This homogeneity of the two groups regarding sociodemographics and trait measures allows for increased confidence in the observed state-related results.

In conclusion, we show causal moderate and consistent evidence of absence of a transfer of placebo analgesia to the perception of an inner bodily state such as the heartbeat. Studies such as the present one are important to better understand the perception of different bodily systems and their connection in humans.

5 Acknowledgements

We thank the two master students Magdalena Banwinkler and Elisabeth Löffler as well as numerous interns for helping with the data collection.

The present study was financially supported by the uni:docs scholarship (awarded to HH) of the University of Vienna, the Austrian Science Fund (FWF W1262-B29), and the Vienna Science and Technology Fund (WWTF VRG13-007). HH was additionally supported by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation - Project-ID 422744262 - TRR 289). None of the funders had any role in study design, data collection and analysis, interpretation, writing or decision to publish. The authors declare that they have no financial interests or potential conflicts of interest.

The data and code needed to run all analyses and reproduce the figures can be found on our Open Science Framework (OSF) project ((Hartmann et al., 2019); https://osf.io/fz73k/). We report how we determined our sample size, all data exclusions, all manipulations, and all measures in the study. This study was preregistered on the OSF prior to any creation of data and included an analysis plan (https://doi.org/10.17605/OSF.IO/GH4SF). In the methods and results, we clearly separate preregistered procedures and analyses from those added post hoc. A pilot study with nine subjects was conducted before the start of data collection and the upload of the preregistration to test the study procedure, especially for the placebo group. However, this data was not used in the final analysis.

6 References

Azevedo, R. T., Garfinkel, S. N., Critchley, H. D., & Tsakiris, M. (2017). Cardiac afferent activity modulates the expression of racial stereotypes. *Nature Communications*, *8*. https://doi.org/10.1038/ncomms13854

Bach, M., Bach, D., de Zwaan, M., & Serim, M. (1996). Validierung der deutschen Version der 20-Item Toronto-Alexithymie-Skala bei Normalpersonen und psychiatrischen Patienten. *PPmP: Psychotherapie*, 208–214.

Borg, C., Chouchou, F., Dayot-Gorlero, J., Zimmerman, P., Maudoux, D., Laurent, B., & Michael, G. A. (2018). Pain and emotion as predictive factors of interoception in fibromyalgia. *Journal of Pain Research*, *11*, 823–835. https://doi.org/10.2147/JPR.S152012

Caseras, X., Murphy, K., Mataix-Cols, D., López-Solà, M., Soriano-Mas, C., Ortriz, H., Pujol, J., & Torrubia, R. (2013). Anatomical and functional overlap within the insula and anterior cingulate cortex during interoception and phobic symptom provocation. *Human Brain Mapping*, *34*(5), 1220–1229. https://doi.org/10.1002/hbm.21503

Ceunen, E., Vlaeyen, J. W. S., & Van Diest, I. (2016). On the origin of interoception. *Frontiers in Psychology*, *7*(MAY), 1–17. https://doi.org/10.3389/fpsyg.2016.00743

Colloca, L., & Benedetti, F. (2006). How prior experience shapes placebo analgesia. *Pain*, *124*(1–2), 126–133. https://doi.org/10.1016/j.pain.2006.04.005

Colloca, L., Klinger, R., Flor, H., & Bingel, U. (2013). Placebo analgesia: Psychological and

neurobiological mechanisms. *Pain*, *154*(4), 511–514. https://doi.org/10.1038/jid.2014.371

Corneille, O., Desmedt, O., Zamariola, G., Luminet, O., & Maurage, P. (2020). A heartfelt response to Zimprich et al. (2020), and Ainley et al. (2020)'s commentaries: Acknowledging issues with the HCT would benefit interoception research. *Biological Psychology*, *152*(February), 107869. https://doi.org/10.1016/j.biopsycho.2020.107869

Craig, A. D. (2002). How do you feel? Interoception: the sense of the physiological condition of the body. *Nature Reviews Neuroscience*, *3*, 655–666. https://doi.org/https://doi.org/10.1038/nrn894

Craig, A. D. (2007). Interoception and Emotion: a Neuroanatomical Perspective. In *Handbook of Emotion*.

Critchley, H. D., Wiens, S., Rotshtein, P., Öhman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience*, *7*(2), 189–195. https://doi.org/10.1038/nn1176

Desmedt, O., Luminet, O., & Corneille, O. (2018). The heartbeat counting task largely involves non-interoceptive processes : Evidence from both the original and an adapted counting task. *Biological Psychology*, *138*, 185–188. https://doi.org/10.1016/j.biopsycho.2018.09.004

Di Lernia, D., Serino, S., & Riva, G. (2016). Pain in the body. Altered interoception in chronic pain conditions: A systematic review. *Neuroscience and Biobehavioral Reviews*, *71*, 328–341. https://doi.org/10.1016/j.neubiorev.2016.09.015

Ernst, J., Northoff, G., Böker, H., Seifritz, E., & Grimm, S. (2013). Interoceptive awareness enhances neural activity during empathy. *Human Brain Mapping*, *34*(7), 1615–1624. https://doi.org/10.1002/hbm.22014

Ferentzi, E., Wilhelm, O., & Köteles, F. (2022). What counts when heartbeats are counted. *Trends in Cognitive Sciences*, *26*(10), 832–835. https://doi.org/https://doi.org/10.1016/j.tics.2022.07.009

Freitag, C. M., Retz-Junginger, P., Retz, W., Seitz, C., Palmason, H., Meyer, J., Rösler, M., & von Gontard, A. (2015). Evaluation der deutschen Version des Autismus-Spektrum-Quotienten (AQ) - die Kurzversion AQ-K. *Zeitschrift Für Klinische Psychologie Und Psychotherapie*, *36*, 280–289. https://doi.org/10.1026/1616-3443.36.4.280

Garfinkel, S. N., Seth, A. K., Barrett, A. B., Suzuki, K., & Critchley, H. D. (2015). Knowing your own heart: Distinguishing interoceptive accuracy from interoceptive awareness. *Biological Psychology*, *104*, 65–74. https://doi.org/10.1016/j.biopsycho.2014.11.004

Grabli, F. E., Quesque, F., Borg, C., Witthöft, M., Michael, G. A., Lucas, C., Pasquier, F., Lebouvier, T., & Bertoux, M. (2021). Interoception and social cognition in chronic low back pain: a common inference disturbance? An exploratory study. *Pain Management*, *12*(4), 471–485. https://doi.org/https://doi.org/10.2217/pmt-2021-0090

Hartmann, H., Forbes, P., Rütgen, M., & Lamm, C. (2022). Placebo analgesia reduces costly prosocial helping to lower another's pain. *Psychological Science*. https://doi.org/https://doi.org/10.1177/09567976221119727

Hartmann, H., Proposito, A., Riva, F., & Lamm, C. (2019). *The Effects of Placebo Analgesia on Interoceptive Abilities.* Open Science Framework. osf.io/fz73k

Hartmann, H., Rütgen, M., Riva, F., & Lamm, C. (2021). Another's pain in my brain: No evidence that placebo analgesia affects the sensory-discriminative component in empathy for pain. *NeuroImage*, *224*, 1–44. https://doi.org/10.1016/j.neuroimage.2020.117397

Jarosz, A. F., & Wiley, J. (2014). What are the odds? A practical guide to computing and reporting Bayes factors. *Journal of Problem Solving*, *7*(1), 2–9. https://doi.org/10.1109/ICASSP.2005.1415890

Khalsa, S. S., Adolphs, R., Cameron, O. G., Critchley, H. D., Davenport, P. W., Feinstein, J. S., Feusner, J. D., Garfinkel, S. N., Lane, R. D., Mehling, W. E., Meuret, A. E., Nemeroff, C. B., Oppenheimer, S., Petzschner, F. H., Pollatos, O., Rhudy, J. L., Schramm, L. P., Kyle Simmons, W., Stein, M. B., … Participants, I. S. 2016. (2018). Interoception and mental health: A roadmap. *Biological Psychiatry: Cognitive Neuscience & Neuroimaging*, *3*(6), 501–513. https://doi.org/10.1016/j.bpsc.2017.12.004

Kleckner, I. R., Wormwood, J. B., Simmons, W. K., Feldman Barrett, L., & Quigley, K. S. (2015). Methodological recommendations for a heartbeat detection-based measure of interoceptive sensitivity. *Psychophysiology*, *52*(11), 1432–1440. https://doi.org/10.1111/psyp.12503

Kühner, P. D. C., Bürger, C., Keller, F., & Hautzinger, M. (2007). Reliabilität und Validität des revidierten Beck-Depressionsinventars (BDI-II). *Der Nervenarzt*, *78*(6), 651–656.

Legrain, V., Iannetti, G. D., Plaghki, L., & Mouraux, A. (2011). The pain matrix reloaded: A salience detection system for the body. *Progress in Neurobiology*, *93*, 111–124. https://doi.org/10.1016/j.pneurobio.2010.10.005

Li, D., Zucker, N. L., Kragel, P. A., Covington, V. E., & LaBar, K. S. (2017). Adolescent development of insula-dependent interoceptive regulation. *Developmental Science*, *20*(5), 1–16. https://doi.org/10.1111/desc.12438

Lim, C. R., Harris, K., Dawson, J., Beard, D. J., Fitzpatrick, R., & Price, A. J. (2015). Floor and ceiling effects in the OHS: An analysis of the NHS PROMs data set. *BMJ Open*, *5*(7). https://doi.org/10.1136/bmjopen-2015-007765

Mac Giolla, E., & Ly, A. (2019). What to do with all these Bayes factors: How to make Bayesian reports in deception research more informative. *Legal and Criminological Psychology*, *3*, 1–7. https://doi.org/10.1111/lcrp.12162

Mehling, W. E., Price, C., Daubenmier, J. J., Acree, M., Bartmess, E., & Stewart, A. (2012). The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLoS ONE*, *7*(11), e48230. https://doi.org/10.1371/journal.pone.0048230

Murphy, J., Catmur, C., & Bird, G. (2019). Classifying individual differences in interoception: implications for the measurement of interoceptive awareness. *Psychonomic Bulletin & Review*.

Peterson, C. M., Thomas, D. M., Blackburn, G. L., & Heymsfield, S. B. (2016). Universal equation for estimating ideal body weight and body weight at any BMI. *American Journal of Clinical Nutrition*, *103*(5), 1197–1203. https://doi.org/10.3945/ajcn.115.121178

Pollatos, O., Füstös, J., & Critchley, H. D. (2012). On the generalised embodiment of pain: How interoceptive sensitivity modulates cutaneous pain perception. *Pain*, *153*(8), 1680–1686. https://doi.org/10.1016/j.pain.2012.04.030

Pollatos, O., Schandry, R., Auer, D. P., & Kaufmann, C. (2007). Brain structures mediating cardiovascular arousal and interoceptive awareness. *Brain Research*, *1141*(1), 178–187. https://doi.org/10.1016/j.brainres.2007.01.026

R Core Team. (2020). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing. https://www.r-project.org/

Rouder, J. N., Speckman, P. L., Sun, D., Morey, R. D., & Iverson, G. (2009). Bayesian t tests for accepting and rejecting the null hypothesis. *Psychonomic Bulletin and Review*, *16*(2),

225–237. https://doi.org/10.3758/PBR.16.2.225

Rouse, C. H., Jones, G. E., & Jones, K. R. (1988). The Effect of Body Composition and Gender on Cardiac Awareness. *Psychophysiology*, *25*(4), 400–407.

Rütgen, M., Seidel, E.-M., Riečanský, I., & Lamm, C. (2015). Reduction of empathy for pain by placebo analgesia suggests functional equivalence of empathy and first-hand emotion experience. *Journal of Neuroscience*, *35*(23), 8938–8947. https://doi.org/10.1523/JNEUROSCI.3936-14.2015

Rütgen, M., Seidel, E.-M., Silani, G., Riečanský, I., Hummer, A., Windischberger, C., Petrovic, P., & Lamm, C. (2015). Placebo analgesia and its opioidergic regulation suggest that empathy for pain is grounded in self pain. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(41), E5638–E5646. https://doi.org/10.1073/pnas.1511269112

Rütgen, M., Wirth, E.-M., Riečanský, I., Hummer, A., Windischberger, C., Petrovic, P., Silani, G., & Lamm, C. (2021). Beyond sharing unpleasant affect – evidence for pain-specific opioidergic modulation of empathy for pain. *Cerebral Cortex*, *31*(6), bhaa385. https://doi.org/10.1093/cercor/bhaa385

Schandry, R. (1981). Heart beat perception and emotional experience. *Psychophysiology*, *18*(4), 483–488.

Smith, R., Mayeli, A., Taylor, S., Al Zoubi, O., Naegele, J., & Khalsa, S. S. (2021). Gut inference: A computational modelling approach. *Biological Psychology*, *164*, 108152. https://doi.org/10.1016/j.biopsycho.2021.108152

Sojka, P., Serranová, T., Khalsa, S. S., Perez, D. L., & Diez, I. (2024). Interoceptive disruption in functional neurological disorder: a multimodal brain imaging study. *MedRxiv*, 2024.03.13.24303546. https://doi.org/10.1101/2024.03.13.24303546

Stern, E. R., Grimaldi, S. J., Muratore, A., Murrough, J., Leibu, E., Fleysher, L., Goodman, W. K., & Burdick, K. E. (2017). Neural correlates of interoception: Effects of interoceptive focus and relationship to dimensional measures of body awareness. *Human Brain Mapping*, *38*(12), 6068–6082. https://doi.org/10.1002/hbm.23811

Tan, Y., Wei, D., Zhang, M., Yang, J., Jelinčić, V., & Qiu, J. (2018). The role of mid-insula in the relationship between cardiac interoceptive attention and anxiety: evidence from an fMRI study. *Scientific Reports*, *8*(1), 1–12. https://doi.org/10.1038/s41598-018-35635-6

Wagenmakers, E.-J., Marsman, M., Jamil, T., Ly, A., Verhagen, J., Love, J., Selker, R., Gronau, Q. F., Smíra, M., Epskamp, S., Matzke, D., Rouder, J. N., & Morey, R. D. (2018). Bayesian inference for psychology. Part I: Theoretical advantages and practical ramifications. *Psychonomic Bulletin & Review Review*, *25*, 35–57. https://doi.org/10.3758/s13423-017-1343-3

Webster, R. K., Weinman, J., & James Rubin, G. (2016). A systematic review of factors that contribute to nocebo effects. *Health Psychology*, *35*(12), 1334–1355. https://doi.org/10.1037/hea0000416

Weiss, S., Sack, M., Henningsen, P., & Pollatos, O. (2014). On the interaction of self-regulation, interoception and pain perception. *Psychopathology*, *47*(6), 377–382. https://doi.org/10.1159/000365107

Werner, N. S., Duschek, S., Mattern, M., & Schandry, R. (2009). The relationship between pain perception and interoception. *Journal of Psychophysiology*, *23*(1), 35–42. https://doi.org/10.1027/0269-8803.23.1.35

Wiebking, C., de Greck, M., Duncan, N. W., Tempelmann, C., Bajbouj, M., & Northoff, G. (2015). Interoception in insula subregions as a possible state marker for depression—an

exploratory fMRI study investigating healthy, depressed and remitted participants. *Frontiers in Behavioral Neuroscience*, *9*(APR). https://doi.org/10.3389/fnbeh.2015.00082

Wiebking, C., Duncan, N. W., Tiret, B., Hayes, D. J., Marjańska, M., Doyon, J., Bajbouj, M., & Northoff, G. (2014). GABA in the insula - a predictor of the neural response to interoceptive awareness. *NeuroImage*, *86*, 10–18. https://doi.org/10.1016/j.neuroimage.2013.04.042

Zaki, J., Davis, J. I., & Ochsner, K. N. (2012). Overlapping activity in anterior insula during interoception and emotional experience. *NeuroImage*, *62*(1), 493–499. https://doi.org/10.1016/j.neuroimage.2012.05.012

Zunhammer, M., Spisak, T., Wager, T. D., Bingel, U., & The Placebo Imaging Consortium. (2021). Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. *Nature Communications*, *12*(1391), 1391. https://doi.org/10.1038/s41467-021-21179-3