USASP
US ASSOCIATION FOR THE STUDY OF PAIN
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 24, No 6 (June), 2023: pp 1080–1093
Available online at www.jpain.org and www.sciencedirect.com

The Importance of the Treatment Rationale for Pain in Animal-Assisted Interventions: A Randomized Controlled Trial in Healthy Participants

Cora Wagner,* Jens Gaab,* and Karin Hediger[†,‡,§,¶]

[*]Division of Clinical Psychology and Psychotherapy, Faculty of Psychology, University of Basel, Basel, Switzerland, [†]Division of Clinical Psychology and Animal-Assisted Intervention, Faculty of Psychology, University of Basel, Basel, Switzerland, [‡]Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Allschwil, Switzerland, [§]Faculty of Psychology, Open University, Heerlen, Netherlands, [¶]Clinic for Neurorehabilitation and Paraplegiology, REHAB Basel, Basel, Switzerland

Abstract: **Animal-assisted interventions (AAIs) is a promising treatment approach for pain, but possible mechanisms still need to be elucidated. This study set out to investigate the analgesic effects of an animal provided with a treatment rationale in a randomized controlled trial employing a standardized experimental heat-pain paradigm. We randomly assigned 128 healthy participants to: dog treatment (DT), placebo treatment (PT), dog and placebo treatment (DPT), and no treatment (NT). Primary outcomes were heat-pain tolerance and the corresponding self-reported ratings of pain unpleasantness and intensity. Results revealed no differences in heat-pain tolerance between the conditions. However, participants in the DT condition experienced heat-pain as significantly less unpleasant at the limit of their tolerance compared to participants in the NT condition (estimate = -0.96, CI = -1.58 to 0.34, *P* = .010). Participants in the DT condition also showed lower ratings of pain intensity at the limit of their tolerance compared to participants in the NT condition (estimate = -0.44, CI = -0.89 to 0.02, *P* = .060). This study indicates that a dog has analgesic effects on pain perception when integrated into the treatment rationale. We assume that providing a treatment rationale regarding the animal is important in AAIs for pain.**

Perspective: ***This study shows that the presence of an animal is not sufficient for animal-assisted interventions (AAIs) to have an analgesic effect on pain unless they are provided with a treatment rationale. This could imply that not only the animal but also contextual factors are important in AAIs.***

Trial registration: ***Clinical Trials NCT04361968.***

Key words: *Meaning, expectation, mechanism, placebo, contextual factor.*

Animal-assisted interventions (AAIs) are "goal-oriented and structured interventions that intentionally incorporate animals in health, education, and human service for the purpose of therapeutic gains in humans."[26] AAIs are currently gaining increased attention and are increasingly being incorporated in various healthcare settings, such as hospitals,[32,58] psychotherapeutic settings,[54,64] rehabilitation clinics,[23,55] emergency departments,[28] and nursing homes.[1,36,51,67] While AAIs include all kinds of animals, dogs are most commonly involved.[3]

Several studies have examined the effects of AAIs with dogs in patients across all age groups.[6,7,20,37,48,53] While it is assumed that AAIs could be a promising treatment approach for pain management in different settings and populations,[65] the evidence base for the analgesic effects of AAIs is weak.

Received April 28, 2022; Revised December 12, 2022; Accepted January 4, 2023.
Conflict of interest statement: The authors declare no conflicts of interest.
Address reprint requests to Cora Wagner, PhD, Clinical Psychology and Psychotherapy, Faculty of Psychology, University of Basel, 4055 Basel, Switzerland. E-mail: cora.wagner@unibas.ch
1526-5900/$36.00

https://doi.org/10.1016/j.jpain.2023.01.004

First, the results on the effects of AAIs on pain are mixed: Some studies have shown promising effects of AAIs on pain such as in adult patients with fibromyalgia,[38] after total joint arthroplasty,[20] and with chronic joint paint,[48] and in children diagnosed with leukemia or solid tumors,[53] in an acute pediatric setting,[6] or after surgery.[7] Other studies, however, have not found any analgesic effects, such as in hospitalized children,[2] children undergoing dental[22] or blood-collection procedures,[59] or in healthy adults in an experimental setting.[63]

Second, it has been widely hypothesized that the animal is responsible for the reported analgesic effects, but the factors responsible for the potential analgesic effects of AAIs have not been investigated.[65]

In a previous randomized controlled trial, we investigated whether the analgesic effects of AAIs are based on the mere presence of a dog, ie, by providing social support to the participant or by strengthening the alliance between participant and study investigator (Wagner et al., 2021). The results showed that a dog alone is not sufficient to lead to pain reduction in healthy participants, neither in the context of pain assessment nor in placebo-induced placebo analgesia. Moreover, the presence of a dog also did not strengthen the alliance between participant and study investigator.

Findings from intervention research highlight the importance of a treatment rationale, ie, a verbal suggestion, to treatment responses.[8,18,25,27,33,56] With the treatment rationale, a meaning is attributed to the intervention at hand, which in turn affects the expectations and outcomes of the treatment.[40] Expectations are especially powerful with regard to pain, as they predict the outcomes of analgesic treatments[10,42,44] and have been identified as a core mechanism in placebo analgesia.[60,61]

To date, the role of the treatment rationale has not been investigated in AAIs. Since our previous study demonstrated that the mere presence of an animal, ie, without a treatment rationale, does not contribute to pain relief in a standardized experimental heat-pain placebo paradigm,[63] we hypothesize that it might not be the animal itself that contributes to pain relief but rather *how* the animal is embedded in the treatment rationale such that the animal has a meaning and patients have a treatment expectation about the animal.

The aim of the present study was to examine the effect of the treatment rationale on pain in an AAI. Using an experimentally induced heat-pain placebo paradigm, we compared participants in 4 conditions either receiving a dog treatment (DT), placebo treatment (PT), dog and placebo treatment (DPT), or no treatment (NT). The placebo treatment was an inert cream, but participants believed that the cream was analgesic. Except for the NT condition, all conditions received a treatment rationale. Primary outcomes were post-treatment heat-pain tolerance and the corresponding self-reported ratings of unpleasantness and intensity at the limit of heat-pain tolerance. We defined post-treatment heat-pain tolerance and the corresponding self-reported ratings of unpleasantness and intensity as primary outcomes since heat-pain tolerance has been related to affective and motivational aspects[21] and associated with pathological pain.[14] Secondary outcomes were post-treatment heat-pain threshold, expectations of pain unpleasantness, intensity at the limit of tolerance, and the trustworthiness of the investigator.

We assumed that if the treatment rationale is important in AAIs, the presence of a dog embedded in the treatment rationale should have a similar analgesic effect as a placebo. This led us to our hypotheses that we investigated: We hypothesized that DT and PT would lead to increased heat-pain tolerance and to decreased self-reported ratings of unpleasantness and the intensity at the limit of participants' heat-pain tolerance at post-treatment compared to no treatment (primary hypothesis). As secondary hypotheses we assumed the post-treatment heat-pain threshold, the intensity at the heat-pain threshold, the expectations of pain unpleasantness, and the intensity at the limit of tolerance after the treatment to be lower, and the trustworthiness of the investigator to be higher in the DT and PT groups compared to NT. Further, we used the condition where a dog treatment and a placebo treatment were administered together (DPT) to investigate whether the combination of 2 expectancy-induced treatments leads to a greater effect compared to only one expectancy-induced treatment.

Methods

Design

We conducted a randomized controlled trial on healthy participants, which were randomly assigned to one of 4 conditions (for details, see below). The study was conducted between June 2020 and November 2020. The study protocols and the informed consent of the study were approved by the Ethics Committee of Northwest and Central Switzerland (ID number: 2020-00642). Since the study was conducted during the Covid-19 pandemic, the study's protective protocol measures were approved by the Ethics Committee of the Faculty of Psychology at the University of Basel, Switzerland. The study protocol ensured the dog's welfare at all times. We conducted all sessions with a dog according to the guidelines of the International Association for Human −Animal Interaction Organizations.[26] The study was preregistered as a clinical trial on www.clinicaltrials.gov (Identifier: NCT04361968).

Participants

Through online advertisements, 363 persons were recruited for "an efficacy study of a new innovative treatment method on individual pain perception of healthy participants" on the website of the University of Basel. The online advertisement did not contain any information about the possible presence of a dog to prevent attracting only participants with an affinity for dogs. The advertisement contained a link to a short

questionnaire. Persons interested in participating had to complete this questionnaire first to check for eligibility and inclusion and exclusion criteria. In order to participate in the study, participants had to be right-handed[43] and between 18 and 65 years old. Exclusion criteria were 1) any acute or chronic disease as well as skin pathologies, 2) current medications or current psychological or psychiatric treatment, 3) pregnancy, 4) nursing, 5) current or regular drug consumption, 6) insufficient German-language skills, 7) a fear of dogs, 8) dog-hair allergies, and 9) previous participation in studies using a heat-pain paradigm.

Of the total 363 screened persons, 206 met the inclusion criteria (see Fig 1). All eligible persons received the study information, which contained the whole study procedure, the mandatory Covid-19 safety measures, the aims, participants' rights, notification of the possible presence of a dog, and a selection of study appointments. Of the 206 persons, 63 declined to participate in the study after receiving the study information as they did not answer our e-mails. One hundred forty-three persons who were still willing to participate were asked to sign in for a study appointment. As soon as the predefined number of participants (N = 128) was included, the remaining persons were informed that there were no further appointments available. All participants attended one appointment with a duration of 70 minutes. The study compensation was CHF 50. Psychology students had the opportunity to obtain credit points for their bachelor's program.

Participants were blinded regarding the aims of our study and the placebo treatment. At the end of the study, all participants provided written delayed informed consent, in which they were debriefed about the aims of the study. Participants had the possibility to withdraw data from the study if they did not consent to participate after being debriefed.

Randomization

We used an adaptive randomization to apportion male participants over all 4 conditions because we expected more women than men to participate in the study. This approach automatically considered the previous gender allocation in the 4 conditions and influenced the probability of the next gender allocation to ensure equal representation in all 4 conditions (each n = 32). The randomization was conducted with Microsoft Excel for Mac, version 16.58. The first author entered each participant's code and gender into an Excel file that then automatically allocated participants to one of the 4 conditions. Participants did not know in which

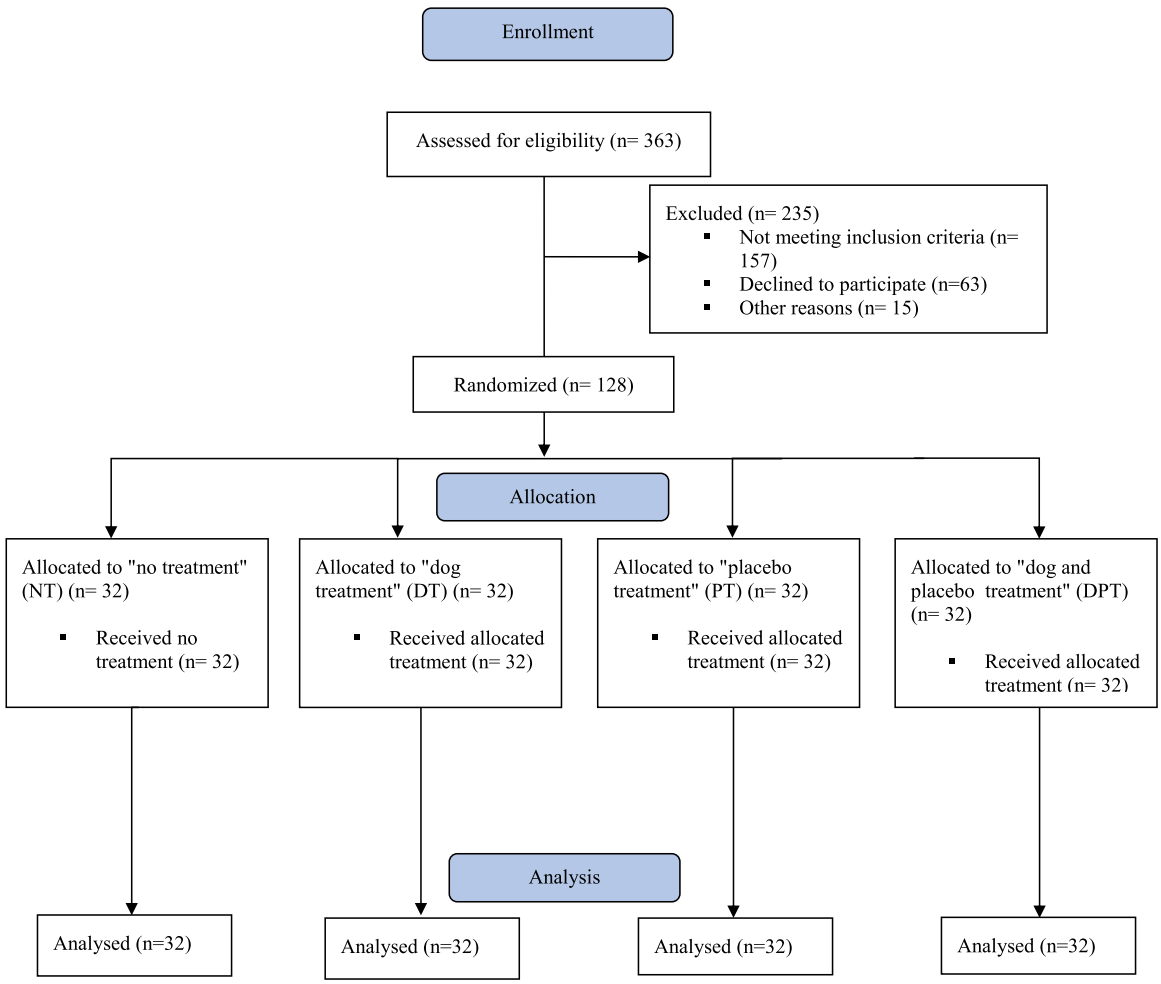

Figure 1. Flow chart.

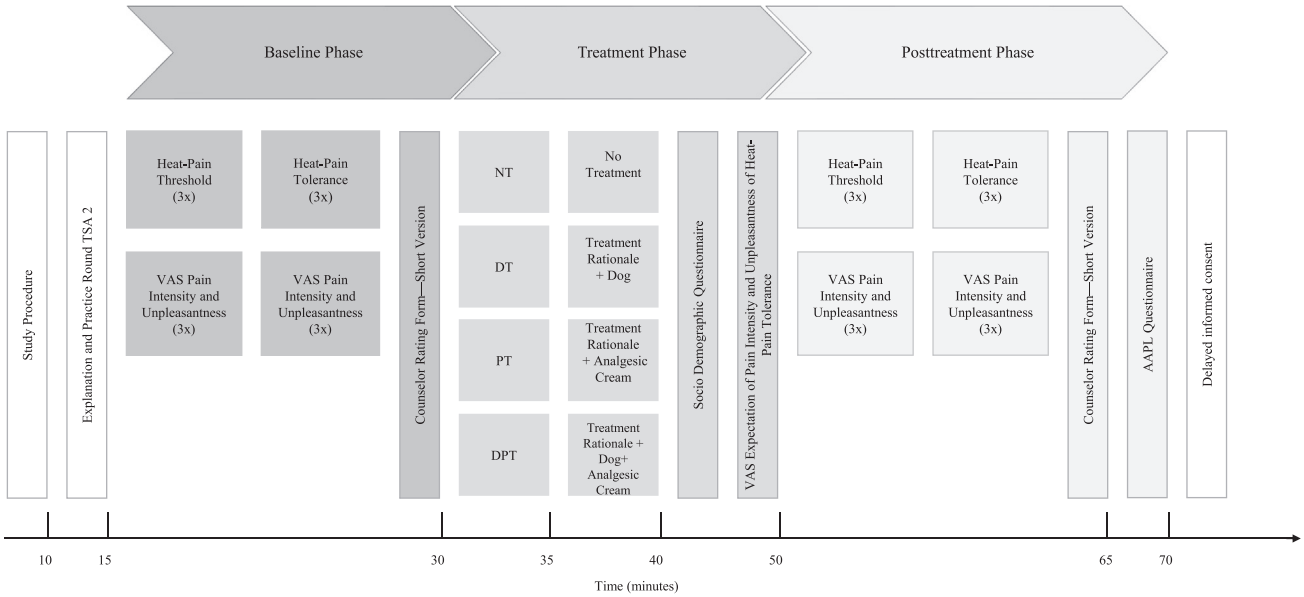

Figure 2. Timeline of the study procedure.

condition they were until the treatment phase. The study investigators, however, knew in which condition each participant was.

Procedure

To comply with mandatory Covid-19 safety measures, participants had to wash their hands and put on a mask before entering the lab room. Upon arrival, study investigators explained the study procedure and participants were told that the study's aim was to investigate if the presence of a dog has a similar effect on pain perception and experience as an established analgesic cream. Then baseline measurements of participants' heat-pain tolerance and threshold as well as their corresponding self-reported ratings of pain unpleasantness and intensity were collected. After these baseline measurements, we conducted the treatment phase. Participants were allocated to one of the following 4 conditions: no treatment (NT), dog treatment (DT), placebo treatment (PT), or dog and placebo treatment (DPT). Except for participants in the NT condition, all participants received a positive treatment rationale for pain relief (see chapter 2.5 for a detailed description of the 4 conditions).

After the treatment phase, post-treatment heat-pain measurements and the corresponding self-reported ratings of pain unpleasantness and intensity were performed in an identical manner to the baseline assessments (see Fig 2 for the timeline).

Conditions

Participants were allocated to one of the following 4 conditions:

- No treatment (NT): In the NT condition, participants were told that they were in the no-treatment group and that they would not receive any treatment.
- Dog treatment (DT): In the DT condition, participants were informed that they were in the dog treatment. After this information, the study investigators shortly left the room to retrieve the dog. The dog was a 2-year-old female Golden Retriever that was experienced in interacting with strangers. To standardize the interaction between the participants and the dog, all participants were asked to greet and pet the dog as soon as the dog entered the room. We explained that it would be easier for the dog to relax on a blanket when allowed to greet the new person in the room. The duration of the interaction between the participant and the dog was kept to a minimum, ie, under 3 minutes. During the greeting phase, study investigators also interacted with the dog if the dog approached the investigator. While participants interacted with the dog, the study investigators gave participants the treatment rationale for the dog's presence. They explained that previous studies had shown that the presence of a dog could lead to pain reduction in patients and that this could be because of the contact with a dog or because just seeing an animal can increase our oxytocin level, which is a hormone that can also have an anti-inflammatory effect. For that reason, we wanted to examine if the presence of a dog could also lead to pain reduction in this study. After giving the treatment rationale for the dog's presence, the dog was asked to lie on her blanket, which was always in the participants' field of vision. The participants did not touch the dog during the further procedure. The study investigators also did not interact with the dog during the further procedure.
- Placebo treatment (PT): In the PT condition, participants were told that they were in the analgesic-cream-treatment condition, which was in fact a placebo provided with a treatment rationale. The study investigators explained that the cream contains the active ingredient lidocaine and that the efficacy of

lidocaine has been proved in several high-quality studies. Then the study investigators applied the placebo cream on participants' left volar forearms.

- Dog and placebo treatment (DPT): In the DPT, participants received the placebo provided with a treatment rationale while in the presence of the dog with a treatment rationale for the dog's presence. Participants were introduced to the dog and received the treatment rationale for the dog, then the treatment rationale for the placebo cream, and the cream application.

Study Investigators

Four study investigators carried out the 128 study appointments. Appointments were randomly distributed across all 4 investigators: study investigator CW conducted 44 appointments (11 per condition), and study investigators A.H., M.R., and M.B. each conducted 28 appointments (7 per condition). C.W. was the owner of the study dog and performed all dog appointments on her own (DT and DPT). The other 3 study investigators each performed the dog appointments (DT and DPT) in the presence of the dog owner to ensure that the dog was not stressed. Leaving the dog in a setting with unfamiliar individuals without the dog's owner would have been inappropriate from an ethical standpoint. In these cases, the dog owner sat quietly in a chair, did not interact with participants (except for greetings and goodbyes), and avoided being in the participants' field of vision.

Heat-Pain Tolerance and Threshold and the Corresponding Self-reported Ratings of Unpleasantness and Intensity

Post-treatment heat-pain tolerance and the corresponding self-reported ratings of unpleasantness and intensity at the limit of heat-pain tolerance (see below for more information) were defined as primary outcomes. Heat-pain tolerance is related to affective and motivational aspects[21] and has been associated with pathological pain, as there is an inverse relationship between ischemic pain tolerance and the perceived severity of clinical pain.[14]

We assessed heat-pain tolerance and heat-pain threshold following the design of a previous study.[63] Both heat-pain tolerance and threshold were determined using a Thermal Sensory Analyser (TSA 2, Medoc, Ramatishai, Israel). Heat-pain threshold was measured prior to heat-pain tolerance in order to minimize interference between the two outcomes.[31,33] The TSA 2 is a pain management system for the qualitative assessment of pain and measures sensory threshold such as heat-induced pain. The employed heat stimuli did not entail any significant danger and have already been used in previous studies in our lab.[17,18,31,33,34] Participants were able to stop the stimuli at any time during each experimental run.

The study investigator administered the heat stimuli to the left volar forearm of the participant using a 30 × 30 mm Peltier device. The thermode of the TSA 2 was fixed at 2 different locations (locations Y and X, determined using a positioning device). Location Y was placed one-third of the way down the forearm from the elbow, while location X was placed two-thirds of the way down the forearm from the elbow. Half of the participants were randomly assigned to start with location Y for the baseline heat-pain measurement and to switch then to location X for the post-treatment heat-pain measurement. The other half of the participants started with the opposite location, location X, for the baseline heat-pain measurement and then switched to location Y for the post-treatment measurement. The reason for moving the thermode was to avoid effects of sensitization or habituation.[15]

Before starting with the actual heat-pain measurement, participants performed a practice round to experience how the heat stimuli work and how to handle the device including how to stop the heat stimuli. After this practice round, we started with the baseline measurements. We first assessed participants' heat-pain threshold by determining limits. Participants were instructed to press the button to determine the turning point from perceiving warmth to perceiving pain. The temperature was increased from the baseline (32°C) at a rate of 0.5°C/s. When participants indicated that the pain threshold had been reached, the device returned to its baseline (32°C) and began to rise again at a rate of 0.5°C/s. This procedure was repeated 3 times in a row.[33] The heat-pain threshold was defined as the average of the three measurements.

Afterward, heat-pain tolerance was determined using limits. Participants were asked to stop the increasing heat stimulus at the moment they could not stand the heat any longer. The temperature increased from the baseline (32°C) at a rate of 0.5°C/s. As soon as participants indicated that their pain tolerance had been reached, the device returned its baseline (32°C) and began to rise again at a rate of 0.5°C/s. This procedure was again repeated 3 times in a row. To avoid physical injury, the pain-tolerance measurement stopped at a temperature of 52°C.[30] Heat-pain tolerance was defined as the average of the 3 measurements.[24]

Further, we assessed self-reported ratings of unpleasantness and intensity at the heat-pain threshold and the limit of heat-pain tolerance, which represent common pain parameters in heat-pain-paradigm studies.[45] Unpleasantness refers to the affective dimension of pain, whereas intensity refers to cognitive dimensions of pain.[47] After each heat-pain tolerance and threshold measurement, participants had to rate pain unpleasantness and intensity on a visual analogue scale (VAS). The VAS ranged from 1 to 10 (1 = "not unpleasant at all" or "not intense at all"; 10 = "the most unpleasant pain I have ever experienced" or "the most intense pain I have ever experienced").

Measures and Questionnaires

After the baseline measurements and again after the post-treatment measurements, we assessed participants'

perception of the study investigator with the Counselor Rating Form—Short Version (CRF-S).[11] The CRF-S is a 12-item questionnaire for measuring an individual's perception of the therapist on the following 3 subscales: *trustworthiness, expertness*, and *attractiveness*. The questionnaire contains items on a 7-point Likert scale, ranging from 1 (not very) to 7 (very). For this study, only the subscale *trustworthiness* was analyzed, because it seems most central to the therapeutic alliance. For example, studies have indicated that patient trust in the physician is of particular importance in clinical practice.[5,12,39] The subscale *trustworthiness* included the following 4 items: *honest, reliable, sincere*, and *trustworthy.*

Previous studies have shown that the presence of an animal positively influences how we perceive others and have suggested that this could strengthen the therapeutic alliance between the patient and the treatment provider.[13,19,29] Since the therapeutic alliance is important for the treatment outcome, we used the CRF-S to control for whether a possible change in the perception of the study investigator could also explain the analgesic effects.

After the treatment phase and before conducting post-treatment heat-pain measurements, we assessed demographic variables (ie, age, sex, nationality, family status, education level, employment situation, and income) with a sociodemographic questionnaire. At this point, we also asked participants to rate using a VAS how unpleasant and intense they expected heat-pain to be at the limit of their tolerance after the treatment. These self-reported ratings of their expectations of pain unpleasantness and intensity were made with a similar VAS (ranging from 1 to 10) as those for pain unpleasantness and intensity.[33,46] The self-reported ratings of expected heat pain at the limit of their tolerance were assessed to control for whether the expectation induction was successful.

The study investigator quantified the intensity of the contact between participant and dog during the greeting phase on a 5-stage Likert scale ranging from 1 = "no contact at all" to 5 = "very high intensity of contact." We also assessed participants' affinity for dogs at the end of the study with a short self-developed questionnaire. For that, we used a 5-stage Likert scale, with 1 indicating that participants liked dogs "not at all" and 5 indicating "very much." Both outcomes were used to investigate if participants in the DT and DPT conditions differed regarding the intensity of the contact with the dog during the greeting and regarding their general affinity for dogs.

Statistical Analyses

We estimated that a sample size of N = 128 with a power of 0.8, an alpha error of 5%, and a beta error of 20% would be necessary to detect a medium size effect of $f = 0.25$ between the conditions DT and PT compared to NT for heat-pain tolerance[65] according to our primary hypothesis.

The primary outcomes (post-treatment heat-pain tolerance and the corresponding self-reported ratings of pain unpleasantness and intensity at the limit of their heat-pain tolerance) were analyzed using linear models (analysis of covariance, ANCOVA) with the corresponding baseline outcomes as a covariate. For each outcome, we calculated prespecified separate models to analyze the dog effect, the placebo effect, and the interaction effect of the dog and the placebo. We quantified the dog effect by comparing the DT with the NT. The placebo effect was quantified by comparing the PT with the NT. The interaction effect of the dog and the placebo was estimated in a model that included all 4 conditions and in which the placebo and the dog served as between-subject factors. Further, for each primary outcome, we also analyzed post hoc whether the different study investigators influenced the outcomes (ie "dog owner only" vs "study investigator + dog owner") in order to assess the potential role of this confound by including the dog owner as a factor in the ANCOVA (not prespecified).

For the secondary outcomes (the post-treatment heat-pain threshold and the corresponding self-reported ratings of unpleasantness and intensity at the heat-pain threshold, expectations of pain unpleasantness and intensity at the limit of tolerance after the treatment, and the subscale from the CRF-S for trustworthiness), we also conducted linear models (ANCOVAs) to assess the dog, the placebo, and the interaction effects. In each model, the respective baseline outcome was used as a covariate.

The requirements for the analyses were tested using Levene's test to determine the variance homogeneity of the 4 conditions and the homogeneity of the regression slopes. The normal distribution of the variables and residuals was tested using Shapiro-Wilk's test and a quantile−quantile plot (Q−Q plot). All variables and residuals were normally distributed, and all prerequisites were met. We report our outcomes according to the Consolidated Standards of Reporting Trials (CONSORT). The mean difference (estimate) was used as the effect size, the confidence interval was defined at 95%, and the significance level was set at .05. We decided a priori to treat results with a probability error equal to or lower than 10% ($P < .10$) as indicating a trend. All statistical analyses were carried out using R for Mac, version 1.4.1103.

Results

Sample Characteristics

All 128 participants were included in the analysis. Participants had a mean age of 28.82 years (SD = 10.78). Eighty-four participants were female, and 44 were male (see Table 1).

Primary Outcome

As presented in Table 2, our analysis found no differences in the means of post-treatment heat-pain tolerance between the conditions. The mean in the NT condition did not statistically differ from the mean in the DT condition (difference = 0.09, CI = - 0.27 to 0.44,

Table 1. Sociodemographic Characteristics of Participants

Condition	N	Age mean (SD)	N (%) female	Family status N	Highest educational level N (%)	Employment level N (%)
NT	32	29.22 (12.51)	20 (62.5%)	Single: 27 Married: 5 Divorced: 0 Other: 0	Secondary: 19 (59.38%) Tertiary: 13 (40.62%)	Full-time: 10 (31.25%) Part-time: 16 (50%) None or student: 6 (18.75%)
DT	32	31.03 (12.55)	21 (65.63%)	Single: 29 Married: 2 Divorced:1 Other: 0	Secondary: 15 (46.88%) Tertiary: 17 (53.12%)	Full-time: 6 (18.75%) Part-time: 11 (34.38%) None or student: 15 (46.88%)
PT	32	29.06 (10.19)	21 (65.3%)	Single: 28 Married: 4 Divorced:0 Other: 0	Secondary: 18 (56.25%) Tertiary: 14 (43.75%)	Full-time: 3 (9.38%) Part-time: 11 (34.38%) None or student: 18 (56.25%)
DPT	32	25.97 (6.66)	22 (68.75%)	Single: 29 Married: 2 Divorced: 0 Other: 1	Secondary: 15 (46.88%) Tertiary: 17 (53.12%)	Full-time: 4 (12.5%) Part-time: 7 (21.88%) None or student: 21 (65.63%)

SD, standard deviation; N, number of participants; NT, no treatment; DT, dog treatment; PT, placebo treatment; DPT, dog and placebo treatment.

P = .634) or from the mean in the PT condition (difference = -0.06, CI = - 0.56 to 0.43, P = .800). Further, there was no interaction effect of the dog and the placebo (difference = 0.09, CI = -0.53 to 0.71, P = .786) on post-treatment heat-pain tolerance. Further, there was no significant difference in post-treatment heat-pain tolerance when controlling for the different investigators ("dog owner only" vs "study investigator + dog owner") (difference = -0.29, CI = -0.61 to 0.31, P = .077).

We found a statistically relevant difference in the self-reported ratings of pain unpleasantness at the limit of heat-pain tolerance at post-treatment between the conditions DT and NT, indicating that participants in the DT condition experienced heat-pain tolerance to be less unpleasant compared to participants in the NT condition (difference = -0.96, CI = -1.58 to -0.34, P = .003). There was no significant difference between the conditions PT and NT (difference = -0.40, CI = -0.97 to 0.17, P = .168). Further, we found a significant interaction of the dog and the placebo in the unpleasantness ratings, which were higher in the combined DPT than in the separate DT and PT (difference = 1.19, CI = 0.33−2.05, P = .007) (see Table 2 and Fig 3). There was no significant difference in the self-reported ratings of pain unpleasantness when including the different investigator conditions ("dog owner only" vs "study investigator + dog owner") (difference = -0.23, CI = -0.69 to 0.24, P = .340).

Finally, we found a trend but no statistically significant effect in the self-reported ratings of pain intensity at the limit of heat-pain tolerance at post-treatment. Participants in the DT condition rated pain intensity to be less intense compared to participants in the NT condition (difference = -0.44, CI = -0.89 to 0.02, P = .060). Again, no differences were found in the self-reported ratings of pain intensity between participants in the PT group and participants in the NT condition (difference = -0.33, CI = -0.79 to 0.13, P = .153). There was a trend but no statistically significant interaction of the dog and the placebo in the intensity ratings, which were higher in the combined DPT than in the separate DT and PT (difference = 0.71, CI = -0.05 to 1.47, P = .077) (see Table 2 and Fig 4). There was no significant difference in the self-reported ratings of pain intensity when including the different investigator conditions ("dog owner only"

Table 2. Primary Outcomes: Limit of Heat-Pain Tolerance and Corresponding Self-Reported Ratings of Pain Intensity and Unpleasantness. Values for Heat-Pain Tolerance are Presented in °C

		Condition			
		NT (N = 32)	DT (N = 32)	PT (N = 32)	DPT (N = 32)
Baseline	**Heat-pain tolerance** (mean, SD)	48.42 (1.56)	48.58 (1.05)	48.11 (1.55)	48.14 (1.51)
	Self-reported pain intensity at the limit of tolerance (mean, SD)	7.90 (1.61)	7.5 (1.52)	7.48 (1.64)	7.44 (1.54)
	Self-reported pain unpleasantness at the limit of tolerance (mean, SD)	7.62 (1.95)	7.1 (1.83)	7.22 (1.83)	7.38 (1.55)
Posttreatment	**Heat-pain tolerance** (mean, SD)	48.32 (1.36)	48.52 (1.10)	47.99 (1.88)	48.18 (1.48)
	Self-reported pain intensity at the limit of tolerance (mean, SD)	7.96 (1.60)	7.17 (1.72)	7.25 (1.72)	7.48 (1.90)
	Self-reported pain unpleasantness at the limit of tolerance (mean, SD)	7.75 (1.93)	6.39 (1.91)	6.39 (1.96)	7.39 (1.82)

SD, standard deviation; N, number of participants; NT, no treatment; DT, dog treatment; PT, placebo treatment; DPT, dog and placebo treatment.

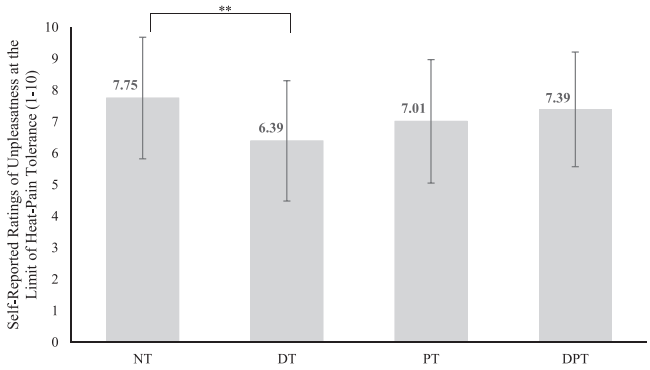

Figure 3. Self-reported ratings of pain unpleasantness at the limit of heat-pain tolerance. For each condition (NT, no treatment; DT, dog treatment; PT, placebo treatment; DPT, dog and placebo treatment), the respective mean and standard deviation are displayed. ** = *P* value <.01.

vs "study investigator + dog owner") (difference =-0.13, CI = -0.53 to 0.27, *P* = .534).

Secondary Outcomes

As illustrated in Table 3, we found no significant differences in the post-treatment heat-pain threshold between the conditions. The mean in the NT condition did not statistically differ from the mean in the DT condition (difference = -0.27, CI = -1.62 to 1.08, *P* = .688) or the mean in the PT condition (difference = -0.22, CI = -1.53 to 1.09, *P* = .739). Further, there was no interaction effect of the dog and the placebo on the post-treatment heat-pain threshold (difference = 0.90, CI = -0.97 to 2.76, *P* = .342).

With regard to the self-reported ratings of pain unpleasantness at the heat-pain threshold, we found a trend but no statistically significant effect between the DT and NT conditions (difference = -0.54, CI = -1.16 to 0.08, *P* = .088): participants in the DT condition reported a tendentially lower rating of pain unpleasantness compared to participants in the NT. However, we found no significant differences between the ratings of participants in the PT condition and the ratings of participants in the NT condition (difference = -0.41, CI = -0.93 to 0.12, *P* = .128). There was a significant interaction of the dog and the placebo in the unpleasantness ratings at the heat-pain threshold, which were higher in the combined DPT than in the separate DT and PT (difference = 0.99, CI = 0.12−0.187, *P* = .027) (see Table 3).

The analyses of the self-reported ratings of pain intensity at the heat-pain threshold revealed no statistically relevant findings. The mean in the NT condition did not differ statistically from the mean in the DT condition (difference = -0.03, CI = -0.72 to 0.66, *P* = .939) or from the mean in the PT condition (difference = -0.24, CI = -0.81 to 0.32, *P* = .391). There was also no interaction effect of the dog and the placebo (difference = 0.39, CI = -0.59 to 1.37, *P* = .430) (see Table 3).

With regard to expected pain unpleasantness, the findings show that participants in the DT and PT conditions expected heat-pain to be less unpleasant at the limit of their tolerance at post-treatment compared to participants in the NT condition (DT vs NT: difference = -1.44, CI = -2.30 to -0.59, *P* < .001; PT vs NT: difference = -2.18, CI = -2.96 to -1.40, *P* < .001).

Additionally, we found a significant interaction effect of the dog and the placebo regarding expected pain unpleasantness, which was lower in the combined treatment than in the separate DT and PT (difference = 2.19, CI = 1.09−3.28, *P* < .001) (see Table 4 and Fig 5).

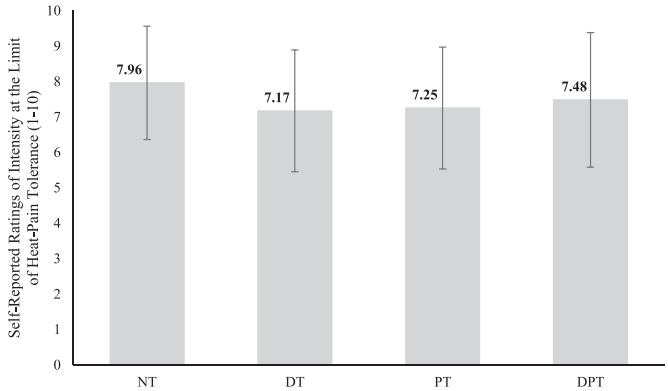

Figure 4. Self-reported ratings of pain intensity at the limit of heat-pain tolerance. For each condition (NT, no treatment; DT, dog treatment; PT, placebo treatment; DPT, dog and placebo treatment), the respective mean and standard deviation are displayed.

Table 3. Heat-Pain Threshold and Corresponding Self-Reported Ratings of Pain Intensity and Unpleasantness. Values for Heat-Pain Threshold are presented in °C.

		Condition			
		NT (N = 32)	*DT (N = 32)*	*PT (N = 32)*	*DPT (N = 32)*
Baseline	**Heat-pain threshold** (mean, SD)	44.43 (2.24)	44.17 (2.31)	43.37 (2.88)	43.40 (2.92)
	Self-reported pain intensity at threshold (mean, SD)	4.98 (2.11)	4.19 (1.88)	4.06 (1.80)	4.38 (2.03)
	Self-reported pain unpleasantness at threshold (mean, SD)	4.88 (2.11)	4.01 (1.96)	3.67 (1.67)	4.20 (2.07)
Posttreatment	**Heat-pain threshold (**mean, SD)	43.47 (2.78)	43.02 (3.33)	42.53 (3.37)	43.18 (3.18)
	Self-reported pain intensity at threshold (mean, SD)	4.16 (2.26)	3.48 (1.98)	3.16 (1.59)	3.71 (2.22)
	Self-reported pain unpleasantness at threshold (mean, SD)	3.97 (2.38)	2.74 (1.59)	2.54 (1.22)	3.34 (2.21)

SD, standard deviation; N, number of participants; NT, no treatment; DT, dog treatment; PT, placebo treatment; DPT, dog and placebo treatment.

Table 4. Self-Reported Ratings of Expected Unpleasantness and Intensity at the Limit of Heat-Pain Tolerance

	Condition			
	NT (N = 32)	*DT (N = 32)*	*PT (N = 32)*	*DPT (N = 32)*
Expected intensity at limit of heat-pain tolerance (mean, SD)	6.72 (2.25)	5.53 (2.02)	4.47 (1.8)	5.22 (1.26)
Expected unpleasantness at limit of heat-pain tolerance (mean, SD)	6.78 (2.46)	4.91 (2.13)	4.28 (1.76)	5.05 (1.35)

SD, standard deviation; N, number of participants; NT, no treatment; DT, dog treatment; PT, placebo treatment; DPT, dog and placebo treatment.

Similar results were found for expected pain intensity. Participants in the DT condition expected heat-pain to be less intense at the limit of their tolerance at post-treatment compared to participants in the NT condition represented by a statistical trend (difference = -0.86, CI = -1.73 to 0.01, $P = .051$). Further, we found that participants in the PT condition expected heat-pain to be significantly less intense at the limit of their tolerance than participants in the NT condition (difference = -1.90, CI = -2.68 to -1.13, $P < .001$). Moreover, we also found a significant interaction effect of the dog and the placebo for expected pain intensity, which was lower in the combined treatment compared to the PT (difference = -1.71, CI = 0.61 −2.80, $P = .003$) (see Table 4 and Fig 6).

Perception of the Study Investigator

Analyses of the CRF-S showed differences among the conditions regarding perceptions of the study investigator. Participants in the DT condition tended to rate the study investigator to be more trustworthy compared to participants in the NT condition, but this effect is only a statistical trend (difference = 0.45, CI = -0.08 to 0.99, $P = .096$). Further, we also found that participants in the PT condition rated the study investigator to be significantly more trustworthy than participants did in the NT condition (difference = 0.66, CI = 0.18−1.14, $P = .008$). Analysis showed no interaction effect of the dog and the placebo on the trustworthiness of the study investigator (difference = -0.41, CI = -1.19 to 0.40, $P = .327$) (see Table 5).

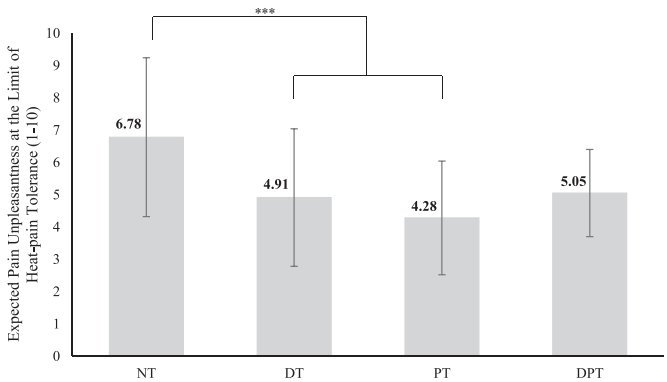

Figure 5. Self-reported ratings of expected pain unpleasantness at the limit of heat-pain tolerance. For each condition (NT, no treatment; DT, dog treatment; PT, placebo treatment; DPT, dog and placebo treatment), the respective mean and standard deviation are displayed. *** = *P value* <.001.

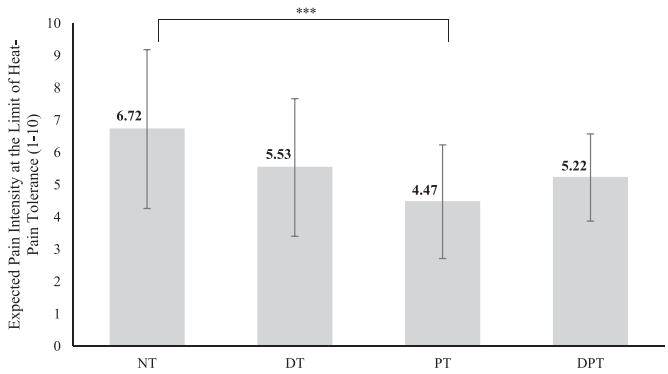

Figure 6. Self-reported ratings of expected pain intensity at the limit of heat-pain tolerance. For each condition (NT, no treatment, DT, dog treatment, PT, placebo treatment, DPT, dog and placebo treatment), the respective mean and standard deviation are displayed. *** = *P* value <.001.

Interaction with the Dog and Dog Affinity

We found no difference in the intensity of interaction with the dog between participants in the DT and the DPT conditions (difference = -0.12, CI = -0.58 to 0.33, *P* = .586). Further, there was no difference regarding the participants' dog affinity between the DT and the DPT conditions (difference = -0.12, CI = -0.50 to 0.25, *P* = .507) (see Table 6).

Discussion

The aim of this study was to examine the effect of the treatment rationale in AAIs on experimentally induced pain in healthy participants.

While no differences in post-treatment heat-pain tolerance were found, participants rated the heat-pain experienced at the limit of their tolerance to be significantly less unpleasant when the employed AAI was provided with a treatment rationale compared to participants in the no-treatment condition. Further, participants in the AAI conditions rated heat-pain tolerance to be less intense and differed by almost 5% from participants in the control condition. Further, participants in the AAI condition expected heat pain at the limit of their tolerance to be significantly less unpleasant compared to participants that received no treatment. They also expected heat pain at the limit of their tolerance to be less intense and differed in their ratings by almost 10% compared to participants in the control condition. With regard to participants' post-treatment heat-pain threshold, the same pattern was observed: participants did not differ in their heat-pain threshold, but participants in the dog treatment experienced the pain at their heat-pain threshold as less unpleasant and differed by 5% compared to participants in the no-treatment group. No differences were found in the ratings of pain intensity at participants' heat-pain threshold.

In a previous study, we conducted on an AAI with a dog in which the dog was not included in the treatment rationale, the presence of the dog had no positive analgesic effects on healthy participants. Instead, participants experienced heat pain to be more intense at the limit of their tolerance in the presence of the dog compared to when no dog was present.[63] Taken together with the findings of the present study, this leads us to hypothesize that AAIs need to provide a treatment rationale to have analgesic effects.

This hypothesis is in line with previous research stressing the importance of treatment contexts to effectivity.[62] The treatment rationale is considered to be an important factor in providing therapeutic meaning and in shaping the overall treatment context.[41] The impact of the treatment rationale on treatment response has been demonstrated in diverse interventions, for example, in psychotherapy,[56] placebo treatments,[18] and open-label placebo treatments.[8,25,27,33] Interestingly, the effect of

Table 6. Interaction With the Dog and Dog Affinity

	Condition	
	***DT** (N = 32)*	***DPT** (N = 32)*
Dog affinity (mean, SD)	4.56 (0.88)	4.69 (0.59)
Dog interaction (mean, SD)	2.91 (1.00)	3.03 (0.82)

SD, standard deviation; N, number of participants; DT, dog treatment; DPT, dog and placebo treatment.

Table 5. Counselor Rating Form—Short Version (CRF-S): Subscale trustworthiness

		Condition			
		***NT** (N = 32)*	***DT** (N = 32)*	***PT** (N = 32)*	***DPT** (N = 32)*
Trustworthiness	**Baseline** (mean, SD)	26.19 (2.61)	26.34 (1.70)	26.44 (1.88)	26.06 (2.56)
	Posttreatment (mean, SD)	25.94 (2.51)	26.53 (1.95)	26.81 (1.75)	26.59 (2.03)

SD, standard deviation; N, number of participants; NT, no treatment; DT, dog treatment; PT, placebo treatment; DPT, dog and placebo treatment.

the treatment rationale can go in either direction: it can elicit a positive treatment response or a negative one.[49] For example, the administration of a pain intervention with a positive meaning can induce positive expectations and lead to a positive analgesic response, whereas the administration of a pain intervention with no meaning or a negative meaning can induce no expectations or negative expectations that lead to an exacerbation or perpetuation of pain.[4] "Meaning making is central to every treatment,"[57] and our results suggest that this is also the case in AAIs for pain.

This understanding expands the common belief that animals are solely responsible for the analgesic effects in AAIs. Previous studies have proposed direct neuroendocrine responses,[6,7,20,53,68] cognitive distraction,[48,53,68] or social support[68] as explanatory mechanisms for AAIs. However, based on our findings and evidence stressing the importance of the treatment context,[62] it seems important to reevaluate the idea that animals are the panacea in AAIs. Instead, it should be acknowledged that the effects in AAIs are also influenced by contextual factors, such as the provision of a treatment rationale.

We found that participants tendentially rated the study investigator as more trustworthy in the presence of a dog compared to when no dog was present. As this is only a statistical trend, it must be interpreted with caution. However, it is in line with previous in vitro studies,[13,50] which suggest that animals positively influence how we perceive others, but it contradicts the results from 2 studies with a real dog where no such effect was found.[19,63] However, in those 2 studies, the presence of the dog was not part of the rationale. It is thus possible that including the animal in the treatment rationale is again important, in this case for positively impacting our perception of other people. Based on the mixed evidence, further research is needed to better understand if and how animals influence our perception.

Interestingly, we found no placebo effect in this study on pain. While this result was unexpected considering the fact that we employed a well-established and standardized paradigm, which has elicited placebo effects in previous studies in our lab,[17,18,31,33,34] it is possible that the strict Covid-19 measures impacted the interaction between the study personnel and the participants but not between the dog and the participants. This might not only have reduced possible placebo effects but also have led to the observed negative interaction effects in self-reported unpleasantness post-treatment at the limit of participants' heat-pain tolerance and at their heat-pain threshold as well as in the expected unpleasantness post-treatment at the limit of their heat-pain tolerance when both the dog and the placebo were administered.

Strengths and Limitations

Other researchers have stated that there is a need to increase the internal validity of AAIs,[35] and there is a recognized lack of high-quality studies on the effects of AAIs on pain and the relevant mechanisms.[65] We therefore conducted a randomized controlled trial with a highly standardized study procedure to systematically control for confounding variables and to increase the internal validity. Further, this is the first study that investigated the impact of a treatment rationale for pain in an AAI. Hence, our findings bring new and important insights for future research on the mechanisms regarding pain in AAIs.

However, our study has several limitations. Our sample consisted of healthy participants that were not suffering from acute or chronic pain. While experimentally induced pain in healthy participants is regarded as a good model for clinical pain,[44] the results may not be generalizable to a clinical population. Further, the effects were only present in the self-reported pain ratings and not in heat-pain tolerance or threshold. This is in line, however, with previous placebo studies.[16,33,52,66] We found several statistical tendencies that must be interpreted with caution. Further, we expected a medium effect size between DT or PT and NT and powered the study for these models. For a comparison between DT and PT or to investigate the interaction, the study was underpowered and results thus must be seen as exploratory. The effect sizes are, however, often clinically meaningful and might have reached statistical significance with a larger sample size. We therefore suggest a replication of this study in the future. Further, the dog's owner performed dog appointments on her own while the other 3 study investigators only performed dog appointments in the presence of the dog owner. It is possible that the dog's owner also had an impact on the results, but we assume that the impact was very small since we did not find effects in our analyses. Moreover, findings from a meta-analysis of the analgesic effects of human social support suggest that the mere presence of a person is not sufficient to affect pain perception.[9] Moreover, only 1 dog participated in the study. This makes the dog treatment in this study highly comparable, but the results cannot be generalized to other dogs or other animal species.

Implications for Future Research

Our findings show that contextual factors matter in AAIs, and further research is required to better understand the impact of contextual factors in AAIs and to make these potential benefits available in the clinical application of AAIs. Since AAIs are increasingly accepted and used in clinical practice, we also see both the need and the potential to examine the impact of the treatment rationale and other contextual factors on the effects of AAIs in clinical conditions.

Conclusion

The results of our study show that the treatment rationale can significantly impact the analgesic effects of AAIs. When provided with a treatment rationale, the AAI resulted in less unpleasant and tendentially less intense pain at the limit of heat-pain tolerance, both in participants' experience and in their expectations.

This corresponds with the findings of a previous study, where the presence of a dog had no positive analgesic effects when it was not part of the treatment rationale. We thus conclude that the presence

of an animal is not sufficient for AAIs to have an analgesic effect on pain unless they are provided with a treatment rationale.

Author contributions

JG, CW, and **KH** conceived the study. **CW, KH**, and **JG** designed it. **CW** acquired the data, carried out the analyses, and drafted the manuscript. **KH** and **JG** provided critical advice and revised the manuscript. All authors read and approved the final manuscript.

Data statement

We would like to state that the data will be available online on Harvard Dataverse soon as the publication is accepted.

References

1. Banks MR, Banks WA: The effects of animal-assisted therapy on loneliness in an elderly population in long-term care facilities. J Gerontol Series A 57:M428-M432, 2002

2. Barker SB, Knisely JS, Schubert CM, Green JD, Ameringer S: The effect of an animal-assisted intervention on anxiety and pain in hospitalized children. Anthrozoös 28:101-112, 2015

3. Bert F, Gualano MR, Camussi E, Pieve G, Voglino G, Siliquini R: Animal assisted intervention: A systematic review of benefits and risks. Eur J Integrat Med 8:695-706, 2016

4. Bingel U, Wanigasekera V, Wiech K, Mhuircheartaigh RN, Lee MC, Ploner M, Tracey I: The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med 3:70ra14, 2011

5. Birkhäuer J, Gaab J, Kossowsky J, Hasler S, Krummenacher P, Werner C, Gerger H: Trust in the health care professional and health outcome: A meta-analysis. PLoS One 12:e0170988, 2017

6. Braun C, Stangler T, Narveson J, Pettingell S: Animal-assisted therapy as a pain relief intervention for children. Complement Therap Clini Pract 15:105-109, 2009

7. Calcaterra V, Veggiotti P, Palestrini C, De Giorgis V, Raschetti R, Tumminelli M, Mencherini S, Papotti F, Klersy C, Albertini R: Post-operative benefits of animal-assisted therapy in pediatric surgery: A randomised study. PLoS One 10, 2015

8. Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I: Open-label placebo treatment in chronic low back pain: A randomized controlled trial. Pain 157:2766-2772, 2016

9. Che X, Cash R, Chung S, Fitzgerald PB, Fitzgibbon BM: Investigating the influence of social support on experimental pain and related physiological arousal: A systematic review and meta-analysis. Neurosci Biobehav Rev 92:437-452, 2018

10. Cormier S, Lavigne GL, Choinière M, Rainville P: Expectations predict chronic pain treatment outcomes. Pain 157:329-338, 2016

11. Corrigan JD, Schmidt LD: Development and validation of revisions in the Counselor Rating Form. J Counsel Psychol 30:64-75, 1983

Disclosures

Karin Hediger received support from an Ambizione grant from the Swiss National Science Foundation (grant PZ00P1_174082).

Acknowledgments

The authors would like to thank Michelle Berns for her help with study preparation and recruitment, and Michelle Berns, Carmina Grob, and Mareike Rytz for conducting the experiments. The authors also thank the participants and the study dog, Romy, for her patience and for greeting every participant with her very friendly nature. We would also like to thank the reviewers for their valuable suggestions and input.

12. Coulter A: Patients' views of the good doctor: Doctors have to earn patients' trust. Br Med J Pub Group 325:668-669, 2002

13. Creary P: Thesis, 2017, University of Toronto*The influence of the presence of a dog or cat on perceptions of a psychotherapist* (Order No. 10255070). Available from ProQuest Dissertations & Theses A&I. (1931361291). Ann Arbor. Available at: https://www.proquest.com/dissertations-theses/influence-presence-dog-cat-on-perceptions/docview/1931361291/se-2. Accessed January 31, 2023.

14. Edwards RR, Doleys DM, Fillingim RB, Lowery D: Ethnic differences in pain tolerance: Clinical implications in a chronic pain population. Psychosom Med 63:316-323, 2001

15. Emerson NM, Zeidan F, Lobanov OV, Hadsel MS, Martucci KT, Quevedo AS, Starr CJ, Nahman-Averbuch H, Weissman-Fogel I, Granovsky Y: Pain sensitivity is inversely related to regional grey matter density in the brain. PAIN® 155:566-573, 2014

16. Foddy B: A duty to deceive: Placebos in clinical practice. Am J Bioeth 9:4-12, 2009

17. Gaab J, Blease C, Locher C, Gerger H: Go open: A plea for transparency in psychotherapy. Psychol Consciousness 3:175-198, 2016

18. Gaab J, Kossowsky J, Ehlert U, Locher C: Effects and components of placebos with a psychological treatment rationale—three randomized-controlled studies. Sci Rep 9:1421, 2019

19. Goldmann KM, Hatfield DR, Terepka A: The potential influence of a companion-animal's presence on aspects of the therapeutic alliance. Anthrozoös 28:661-672, 2015

20. Harper CM, Dong Y, Thornhill TS, Wright J, Ready J, Brick GW, Dyer G: Can therapy dogs improve pain and satisfaction after total joint arthroplasty? A randomized controlled trial. Clini Orthopaed Related Res® 473:372-379, 2015

21. Harris G, Rollman GB: The validity of experimental pain measures. Pain 17:369-376, 1983

22. Havener L, Gentes L, Thaler B, Megel M, Baun M, Driscoll F, Beiraghi S, Agrawal N: The effects of a companion animal on distress in children undergoing dental procedures. Issues Compr Pediatr Nurs 24:137-152, 2001

23. Hediger K, Wagner J, Künzi P, Haefeli A, Theis F, Grob C, Pauli E, Gerger H: Effectiveness of animal-assisted interventions for children and adults with post-traumatic stress disorder symptoms: a systematic review and meta-analysis. Eur J Psychotraumatol 12:1879713, 2021

24. Hermann C, Hohmeister J, Demirakça S, Zohsel K, Flor H: Long-term alteration of pain sensitivity in school-aged children with early pain experiences. Pain 125:278-285, 2006

25. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, Fontaine KR: Open-label placebo treatment for cancer-related fatigue: A randomized-controlled clinical trial. Sci Rep 8:2784, 2018

26. IAHAIO: The IAHAIO definitions for animal assisted intervention and guidelines for wellness of animals involved in AAI. IAHAIO White Paper. 2018. Available at: https://iahaio.org/wp/wp-content/uploads/2018/04/iahaio_wp_updated-2018-final.pdf. Accessed January 31, 2023.

27. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, Kowalczykowski M, Miller FG, Kirsch I, Lembo AJ: Placebos without deception: A randomized controlled trial in irritable bowel syndrome. PLoS One 5: e15591, 2010

28. Kline JA, Fisher MA, Pettit KL, Linville CT, Beck AM: Controlled clinical trial of canine therapy versus usual care to reduce patient anxiety in the emergency department. PLoS One 14:e0209232, 2019

29. Kruger KA, Serpell JA: Animal-assisted interventions in mental health: Definitions and theoretical foundations. Handbook on animal-assisted therapy. London, United Kingdom, Elsevier, 2010, pp 33-48

30. Krummenacher P, Candia V, Folkers G, Schedlowski M, Schönbächler G: Prefrontal cortex modulates placebo analgesia. Pain 148:368-374, 2010

31. Krummenacher P, Kossowsky J, Schwarz C, Brugger P, Kelley JM, Meyer A, Gaab J: Expectancy-induced placebo analgesia in children and the role of magical thinking. J Pain 15:1282-1293, 2014

32. Linder DE, Siebens HC, Mueller MK, Gibbs DM, Freeman LM: Animal-assisted interventions: A national survey of health and safety policies in hospitals, eldercare facilities, and therapy animal organizations. Am J Infect Control 45:883-887, 2017

33. Locher C, Nascimento AF, Kirsch I, Kossowsky J, Meyer A, Gaab J: Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. Pain 158:2320-2328, 2017

34. Locher C, Nascimento AF, Kossowsky J, Meyer A, Gaab J: Open-label placebo response—Does optimism matter? A secondary-analysis of a randomized controlled trial. J Psychosom Res 116:25-30, 2019

35. López-Cepero J: Current status of animal-assisted interventions in scientific literature: a critical comment on their internal validity. Animals 10:985, 2020

36. Majic T, Gutzmann H, Heinz A, Lang UE, Rapp MA: Animal-assisted therapy and agitation and depression in nursing home residents with dementia: a matched case-control trial. Am J Geriatr Psychiatry 21:1052-1059, 2013

37. Marcus DA: The role of volunteer services at cancer centers. Curr Pain Headache Rep 17:376, 2013

38. Marcus DA, Bernstein CD, Constantin JM, Kunkel FA, Breuer P, Hanlon RB: Impact of animal-assisted therapy for outpatients with fibromyalgia. Pain Med 14:43-51, 2013

39. Mechanic D, Schlesinger M: The impact of managed care on patients' trust in medical care and their physicians. JAMA 275:1693-1697, 1996

40. Moerman DE: The Meaning Response: Thinking About Placebos. Pain Practice. Wiley Online Library, 2006, pp 233-236

41. Moerman DE, Jonas WB: Deconstructing the placebo effect and finding the meaning response. Ann Intern Med 136:471-476, 2002

42. Mondloch MV, Cole DC, Frank JW: Does how you do depend on how you think you'll do? A systematic review of the evidence for a relation between patients' recovery expectations and health outcomes. CMAJ 165:174-179, 2001

43. Oldfield RC: The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 9:97-113, 1971

44. Peerdeman KJ, van Laarhoven AI, Keij SM, Vase L, Rovers MM, Peters ML, Evers AW: Relieving patients' pain with expectation interventions: A meta-analysis. Pain 157:1179-1191, 2016

45. Petersen GL, Finnerup NB, Nørskov KN, Grosen K, Pilegaard HK, Benedetti F, Price DD, Jensen TS, Vase L: Placebo manipulations reduce hyperalgesia in neuropathic pain. Pain 153:1292-1300, 2012

46. Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F: Response expectancies in placebo analgesia and their clinical relevance. Pain 93:77-84, 2001

47. Price DD: Psychological and neural mechanisms of the affective dimension of pain. Science 288:1769-1772, 2000

48. Rodrigo-Claverol M, Casanova-Gonzalvo C, Malla-Clua B, Rodrigo-Claverol E, Jové-Naval J, Ortega-Bravo M: Animal-assisted intervention improves pain perception in polymedicated geriatric patients with chronic joint pain: A clinical trial. Int J Environ Res Public Health 16:2843, 2019

49. Rossettini G, Carlino E, Testa M: Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. BMC Musculoskelet Disord 19:27, 2018

50. Schneider MS, Harley LP: How dogs influence the evaluation of psychotherapists. Anthrozoös 19:128-142, 2006

51. Schuurmans L, Enders-Slegers M-J, Verheggen T, Schols J: Animal-assisted interventions in Dutch nursing homes: A survey. J Am Med Dir Assoc 17:647-653, 2016

52. Schwarz KA, Büchel C: Cognition and the placebo effect—dissociating subjective perception and actual performance. PLoS One 10:e0130492, 2015

53. Silva NB, Osório FL: Impact of an animal-assisted therapy programme on physiological and psychosocial variables of paediatric oncology patients. PLoS One 13:e0194731, 2018

54. Templin JC, Hediger K, Wagner C, Lang UE: Relationship between patient satisfaction and the presence of cats in psychiatric wards. J Altern Complement Med 24:1219-1220, 2018

55. Theis F, Luck F, Hund-Georgiadis M, Hediger K: Influences of animal-assisted therapy on episodic memory in

patients with acquired brain injuries. Int J Environ Res Public Health 17:8466, 2020

56. Tondorf T, Kaufmann L-K, Degel A, Locher C, Birkhäuer J, Gerger H, Ehlert U, Gaab J: Employing open/hidden administration in psychotherapy research: A randomized-controlled trial of expressive writing. PLoS One 12:e0187400, 2017

57. Trachsel M, Holtforth MG: How to strengthen patients' meaning response by an ethical informed consent in psychotherapy. Front Psychol 10:1747, 2019

58. Uglow LS: The benefits of an animal-assisted intervention service to patients and staff at a children's hospital. Br J Nurs 28:509-515, 2019

59. Vagnoli L, Caprilli S, Vernucci C, Zagni S, Mugnai F, Messeri A: Can presence of a dog reduce pain and distress in children during venipuncture? Pain Manag Nurs 16:89-95, 2015

60. Vase L, Robinson ME, Verne GN, Price DD: The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients: An empirical investigation. Pain 105:17-25, 2003

61. Vase L, Vollert J, Finnerup NB, Miao X, Atkinson G, Marshall S, Nemeth R, Lange B, Liss C, Price DD, Maier C, Jensen TS, Segerdahl M: Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: A meta-analysis of the individual data from nine industrially sponsored trials. Pain 156:1795-1802, 2015

62. Wager TD, Atlas LY: The neuroscience of placebo effects: connecting context, learning and health. Nat Rev Neurosci 16:403-418, 2015

63. Wagner C, Gaab J, Locher C, Hediger K: Lack of effects of the presence of a dog on pain perception in healthy participants - a randomized controlled trial. Front Pain Res 2:714469, 2021

64. Wagner C, Lang UE, Hediger K: There Is a Cat on Our Ward": Inpatient and staff member attitudes toward and experiences with cats in a psychiatric ward. Int J Environ Res Public Health 16:3108, 2019

65. Waite TC, Hamilton L, O'Brien W: A meta-analysis of animal assisted interventions targeting pain, anxiety and distress in medical settings. Complement Therap Clini Pract 33:49-55, 2018

66. Wechsler ME, Kelley JM, Boyd IOE, Dutile S, Marigowda G, Kirsch I, Israel E, Kaptchuk TJ: Active albuterol or placebo, sham acupuncture, or no intervention in asthma. N Engl J Med 365:119-126, 2011

67. Wu AS, Niedra R, Pendergast L, McCrindle BW: Acceptability and impact of pet visitation on a pediatric cardiology inpatient unit. J Pediatr Nurs 17:354-362, 2002

68. Zhang Y, Yan F, Li S, Wang Y, Ma Y: Effectiveness of animal-assisted therapy on pain in children: a systematic review and meta-analysis. Int J Nurs Sci 8:30-37, 2020