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Highlights

- Animal-assisted interventions are considered a promising approach for pain relief.
- Previous findings show that the mere presence of a dog had no analgesic effects.
- In this study, a dog had analgesic effects if included in the treatment rationale.
- It is not the animal but the meaning given to it that leads to analgesic effects

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

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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, $p = 0.010$). 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, $p = 0.060$).

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.

Trial registration: Clinical Trials NCT04361968.

Keywords: meaning₁, expectation₂, mechanism₃, placebo₄, contextual factor₅

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.

INTRODUCTION

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 departments²⁸, and nursing homes^{1, 36, 51, 67}. While AAIs include all kinds of animals, dogs are most commonly involved³.

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 populations⁶⁵, the evidence base for the analgesic effects of AAIs is weak.

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 fibromyalgia³⁸, after total joint arthroplasty²⁰, and with chronic joint pain⁴⁸, and in children diagnosed with leukemia or solid tumors⁵³, in an acute pediatric setting⁶, or after surgery⁷. Other studies, however, have not found any analgesic effects, such as in hospitalized children², children undergoing dental²² or blood-collection procedures⁵⁹, or in healthy adults in an experimental setting⁶³.

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 investigated⁶⁵.

In a previous randomized controlled trial, we investigated whether the analgesic effects of AAIs are based on the mere presence of a dog, i.e., 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, that is, 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 treatment⁴⁰. 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, i.e., without a treatment rationale, does not contribute to pain relief in a standardized experimental heat-pain placebo paradigm⁶³, 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 four 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 posttreatment heat-pain tolerance and the corresponding self-reported ratings of unpleasantness and intensity at the limit of heat-pain tolerance. We defined posttreatment 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 aspects²¹ and associated with pathological pain¹⁴. Secondary outcomes were posttreatment 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 posttreatment compared to no treatment (primary hypothesis). As secondary hypotheses we assumed the posttreatment 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 two 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 four 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 Organizations²⁶. 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-handed⁴³ and between 18 and 65 years old. Exclusion criteria were (a) any acute or chronic disease as well as skin pathologies, (b) current medications or current psychological or psychiatric treatment, (c) pregnancy, (d) nursing, (e) current or regular drug consumption, (f) insufficient German-language skills, (g) a fear of dogs, (h) dog-hair allergies, and (i) previous participation in studies using a heat-pain paradigm.

Of the total 363 screened persons, 206 met the inclusion criteria (see Figure 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 four conditions because we expected more women than men to participate in the study. This approach automatically considered the previous gender allocation in the four conditions and influenced the probability of the next gender allocation to ensure equal representation in all four 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 four conditions. Participants did not know in which 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 four 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 four conditions).

After the treatment phase, posttreatment 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 Figure 2 for the timeline).

Conditions

Participants were allocated to one of the following four 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, that is, 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 four investigators: study investigator CW conducted 44 appointments (11 per condition), and study investigators AH, MR, and MB each conducted 28 appointments (7 per condition). CW was the owner of the study dog and performed all dog appointments on her own (DT and DPT). The other three 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

Posttreatment 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 aspects²¹ and has been associated with pathological pain, as there is an inverse relationship between ischemic pain tolerance and the perceived severity of clinical pain¹⁴. We assessed heat-pain tolerance and heat-pain threshold following the design of a previous study⁶³. 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 two 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 posttreatment 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 posttreatment measurement. The reason for moving the thermode was to avoid effects of sensitization or habituation

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 three times in a row³³. 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 three times in a row. To avoid physical injury, the pain-tolerance measurement stopped at a temperature of 52 °C³⁰. Heat-pain tolerance was defined as the average of the three measurements²⁴.

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 studies⁴⁵. Unpleasantness refers to the affective dimension of pain, whereas intensity refers to cognitive dimensions of pain⁴⁷. 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 posttreatment 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 three 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 four 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 posttreatment heat-pain measurements, we assessed demographic variables (i.e., 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 tolerance⁶⁵ according to our primary hypothesis.

The primary outcomes (posttreatment 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 four 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 (i.e., “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 posttreatment 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 four 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 0.05. We decided a priori to treat results with a probability error equal to or lower than 10% ($p < 0.10$) 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 posttreatment 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 , $p = 0.634$) or from the mean in the PT condition (difference = -0.06, $CI = -0.56$ to 0.43 , $p = 0.800$). Further, there was no interaction effect of the dog and the placebo (difference = 0.09, $CI = -0.53$ to 0.71 , $p = 0.786$) on posttreatment heat-pain tolerance. Further, there was no significant difference in posttreatment 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 , $p = 0.077$).

We found a statistically relevant difference in the self-reported ratings of pain unpleasantness at the limit of heat-pain tolerance at posttreatment 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 , $p = 0.003$). There was no significant difference between the conditions PT and NT (difference = -0.40, $CI = -0.97$ to 0.17 , $p = 0.168$). 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, $CI = 0.33$ to 2.05 , $p = 0.007$) (see Table 2 and Figure 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 , $p = 0.340$).

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 posttreatment. 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, $p = 0.060$). 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, $p = 0.153$). 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, $p = 0.077$) (see Table 2 and Figure 4). There was no significant difference in the self-reported ratings of pain intensity when including the different investigator conditions (“dog owner only” vs. “study investigator + dog owner”) (difference = -0.13, CI = -0.53 to 0.27, $p = 0.534$).

Secondary outcomes

As illustrated in Table 3, we found no significant differences in the posttreatment 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, $p = 0.688$) or the mean in the PT condition (difference = -0.22, CI = -1.53 to 1.09, $p = 0.739$). Further, there was no interaction effect of the dog and the placebo on the posttreatment heat-pain threshold (difference = 0.90, CI = -0.97 to 2.76, $p = 0.342$).

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, $p = 0.088$): 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, $p = 0.128$). 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 to 0.187, $p = 0.027$) (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, $p = 0.939$) or from the mean in the PT condition (difference = -0.24, CI = -0.81 to 0.32, $p = 0.391$). There was also no interaction effect of the dog and the placebo (difference = 0.39, CI = -0.59 to 1.37, $p = 0.430$) (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 posttreatment compared to participants in the NT condition (DT vs. NT: difference = -1.44, CI = -2.30 to -0.59, $p < 0.001$; PT vs. NT: difference = -2.18, CI = -2.96 to -1.40, $p < 0.001$).

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 to 3.28, $p < 0.001$) (see Table 4 and Figure 5).

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 posttreatment compared to participants in the NT condition represented by a statistical trend (difference = -0.86, CI = -1.73 to 0.01, $p = 0.051$). 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, $p < 0.001$). 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 to 2.80, $p = 0.003$) (see Table 4 and Figure 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, $p = 0.096$). 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 to 1.14, $p = 0.008$). 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, $p = 0.327$) (see Table 5).

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, $p = 0.586$). 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, $p = 0.507$) (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 posttreatment 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' posttreatment 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 present⁶³. 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 effectivity⁶². The treatment rationale is considered to be an important factor in providing therapeutic meaning and in shaping the overall treatment context⁴¹. The impact of the treatment rationale on treatment response has been demonstrated in diverse interventions, for example, in psychotherapy⁵⁶, placebo treatments¹⁸, and open-

label placebo treatments^{8, 25, 27, 33}. Interestingly, the effect of the treatment rationale can go in either direction: it can elicit a positive treatment response or a negative one⁴⁹. 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 pain⁴. “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 support⁶⁸ as explanatory mechanisms for AAIs. However, based on our findings and evidence stressing the importance of the treatment context⁶², 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 suggests that animals positively influence how we perceive others, but it contradicts the results from two studies with a real dog where no such effect was found^{19, 63}. However, in those two 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 posttreatment at the limit of participants' heat-pain tolerance and at their heat-pain threshold as well as in the expected unpleasantness posttreatment 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 AAIs³⁵, and there is a recognized lack of high-quality studies on the effects of AAIs on pain and the relevant mechanisms⁶⁵. 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 pain⁴⁴, 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 owner performed dog appointments on her own while the other three study investigators only performed dog appointments in the presence of the dog owner. It is possible that the dog 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 perception⁹. Moreover, only one 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 AAI, and further research is required to better understand the impact of contextual factors in AAI and to make these potential benefits available in the clinical application of AAI. Since AAI 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 AAI 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

J. G., C. W., and K. H. conceived the study. C. W., K. H., and J. G. designed it. C. W. acquired the data, carried out the analyses, and drafted the manuscript. K. H. and J. G. 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.

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Figure legends

Journal Pre-proof

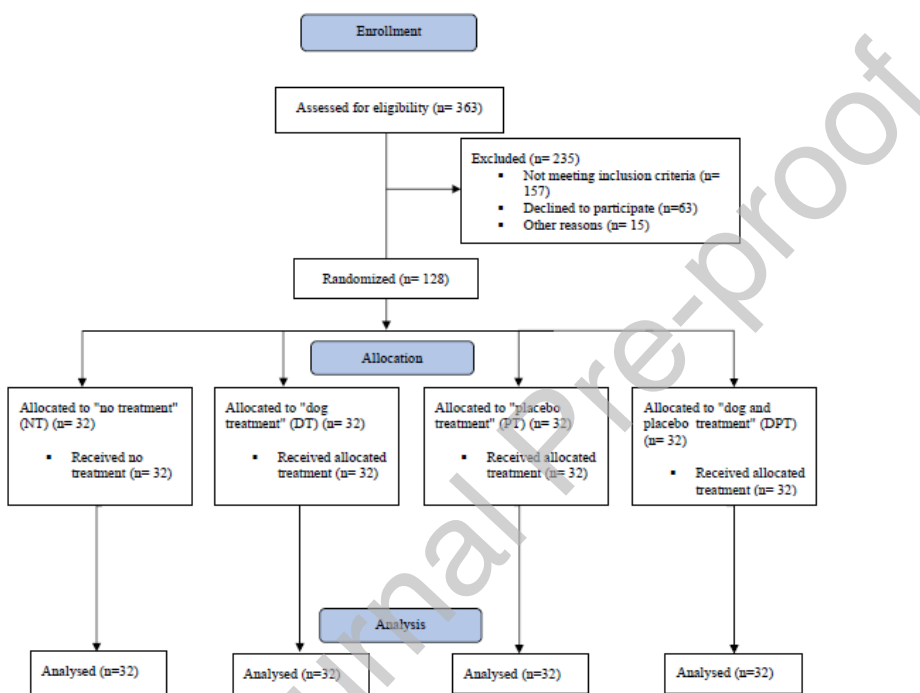


Figure 1. Flow chart

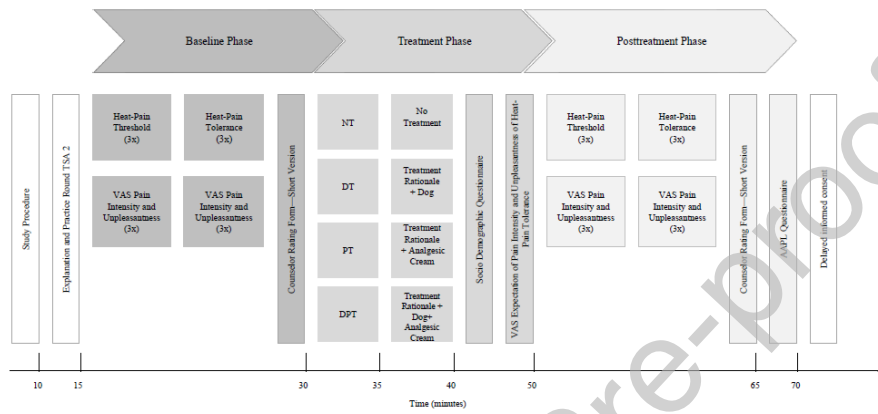


Figure 2. Timeline of the study procedure

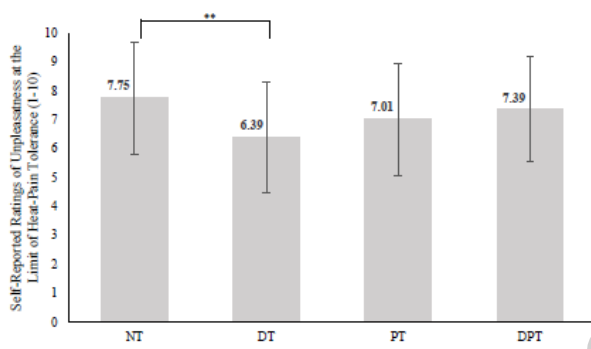


Figure 3. Self-reported ratings of pain unpleasantness at the limit of heat-pain tolerance. For each condition (NT = no treatment, DT = dog treatment, PT = placebo treatment, DPT = dog and placebo treatment), the respective mean and standard deviation are displayed. ** = p value < 0.01

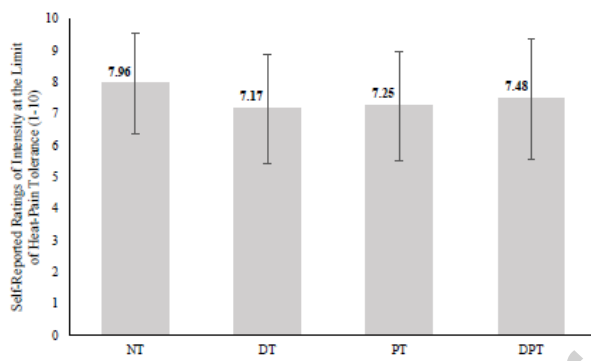


Figure 4. Self-reported ratings of pain intensity at the limit of heat-pain tolerance. For each condition (NT = no treatment, DT = dog treatment, PT = placebo treatment, DPT = dog and placebo treatment), the respective mean and standard deviation are displayed.

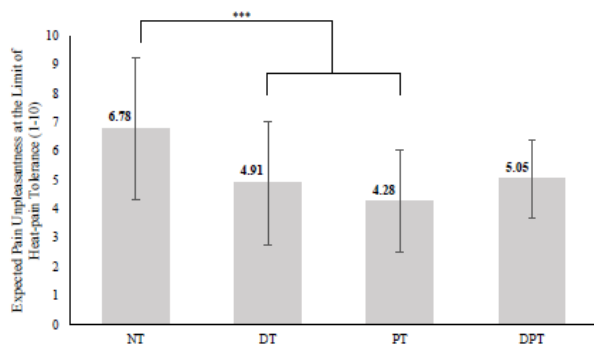


Figure 5. Self-reported ratings of expected pain unpleasantness at the limit of heat-pain tolerance. For each condition (NT = no treatment, DT = dog treatment, PT = placebo treatment, DPT = dog and placebo treatment), the respective mean and standard deviation are displayed. *** = p value < 0.001

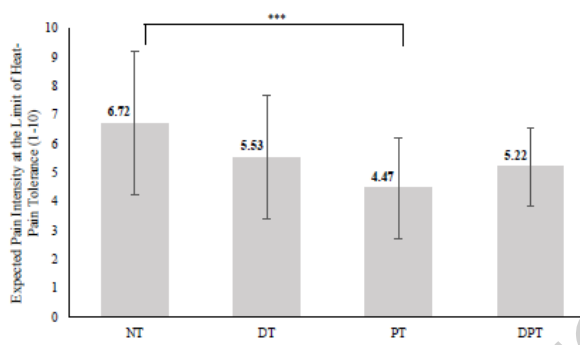


Figure 6. Self-reported ratings of expected pain intensity at the limit of heat-pain tolerance. For each condition (NT = no treatment, DT = dog treatment, PT = placebo treatment, DPT = dog and placebo treatment), the respective mean and standard deviation are displayed. *** = p value < 0.001

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Table 1. Sociodemographic characteristics of participants

Condition	<i>N</i>	Age mean (<i>SD</i>)	<i>N</i> (%) female	Family status <i>N</i>	Highest educational level <i>N</i> (%)	Employment level <i>N</i> (%)
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

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 (<i>N</i> = 32)	DT (<i>N</i> = 32)	PT (<i>N</i> = 32)	DPT (<i>N</i> = 32)
Baseline	Heat-pain tolerance (mean, <i>SD</i>)	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, <i>SD</i>)	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, <i>SD</i>)	7.62 (1.95)	7.1 (1.83)	7.22 (1.83)	7.38 (1.55)
Posttreatment	Heat-pain tolerance (mean, <i>SD</i>)	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, <i>SD</i>)	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, <i>SD</i>)	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

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, <i>SD</i>)	44.43 (2.24)	44.17 (2.31)	43.37 (2.88)	43.40 (2.92)
	Self-reported pain intensity at threshold (mean, <i>SD</i>)	4.98 (2.11)	4.19 (1.88)	4.06 (1.80)	4.38 (2.03)
	Self-reported pain unpleasantness at threshold (mean, <i>SD</i>)	4.88 (2.11)	4.01 (1.96)	3.67 (1.67)	4.20 (2.07)
Posttreatment	Heat-pain threshold (mean, <i>SD</i>)	43.47 (2.78)	43.02 (3.33)	42.53 (3.37)	43.18 (3.18)
	Self-reported pain intensity at threshold (mean, <i>SD</i>)	4.16 (2.26)	3.48 (1.98)	3.16 (1.59)	3.71 (2.22)
	Self-reported pain unpleasantness at threshold (mean, <i>SD</i>)	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 (<i>N</i> = 32)	DT (<i>N</i> = 32)	PT (<i>N</i> = 32)	DPT (<i>N</i> = 32)
Expected intensity at limit of heat-pain tolerance (mean, <i>SD</i>)	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, <i>SD</i>)	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

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

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