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Research paper

Generalization and enhancement of the effects of an active placebo nasal spray on sadness

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ABSTRACT

Introduction: The placebo effect, i.e., the psychobiological response arising from administering an inert treatment, influences various domains, such as pain perception and emotional regulation. Positive framing might enhance this effect. This study tested whether the effect of an active placebo (mimicking drug side effects to enhance treatment credibility) on is generalized between two different contexts of sadness induction and if positive framing of side effects enhances this effect.

Methods: Ninety-six healthy participants were randomly assigned to one of three groups: Placebo+positive framing (PPF), Placebo+standard information (PSI), or no treatment control (NTC). Participants underwent a sadness induction protocol during an in-person lab session and a 20-min online follow-up at home six hours later. Primary outcome was self-reported sadness, secondary outcome was self-reported side effects.

Results: Both the PPF and PSI groups showed a significant decrease in sadness compared to the NTC group after placebo administration during the lab session ($p < 0.001$) and at follow-up ($p < 0.05$). At follow-up, only the PPF group did not experience a significant increase in sadness. Positive framing did not improve side effect tolerability.

Limitations: Self-reported measures introduce subjective bias. The sample restriction to healthy volunteers limits generalizability. The six-hour period may not capture clinically relevant long-term effects.

Conclusions: The active placebo nasal spray effectively reduced sadness, with effects persisting for six hours and across different contexts. Positive framing did not enhance side effect tolerability but may have helped maintain effectiveness at follow-up. Further research is needed in clinical populations and to explore long-term effects.

1. Introduction

Antidepressant treatments have long been regarded as effective solutions for managing depression. However, growing evidence suggests that the perceived benefits of these medications may be substantially driven by the placebo effect (Kirsch, 2019; Matsingos et al., 2024; Rief et al., 2009b). In clinical trials evaluating antidepressant drugs, the distinction in improvement between the active drug and a placebo often lacks clinical significance (Kirsch, 2019). Antidepressants also have an unpleasant profile of side effects, which, to a substantial extent, can be attributed to the counterpart of the placebo effect, known as the nocebo effect (Rheker et al., 2017; Rief et al., 2009a). Indeed, evidence points to how simply informing patients about side effects can increase the likelihood of their occurrence through nocebo mechanisms (e.g., Petrie and Rief, 2019). On the other hand, positive treatment expectations, as the primary mechanism of the placebo effect (Bingel, 2020) present a promising approach for decreasing the likelihood of nocebo effects while enhancing the efficacy of antidepressant treatments. For example, a positive patient-clinician communication may serve as a tool to optimize treatment expectations by boosting both the efficacy and tolerability (e.g. reduction of unwanted side effects) of antidepressant medication (Manaï et al., 2019). However, it is ethically questionable not to inform patients about side effects in order to avoid nocebo effects (Leibowitz et al., 2021), Therefore, it is of relevance to examine how on the one hand patients can be given the necessary information concerning side effects while on the other hand reducing or even preventing the onset of nocebo effects.

A practical solution that has recently been proposed to solve this

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conundrum is positive framing. Side effect information can be positively framed, e.g., by informing patients that treatment side effects mark the beginning of the desired effect, and should be considered as 'onset sensations' (Wilhelm et al., 2018), namely, as a sign that the effects of a treatment are on course and are active in the body. Remarkably, this approach has been found to improve patients' side effect profile (Howe et al., 2019), and also boost the pain-relieving qualities of a medication (Fernandez et al., 2019).

When treating patients with depression, a positive framing of side effects might be a particularly helpful strategy to counteract the high risks and serious side effects of antidepressant medication (Andrews et al., 2012; Braun et al., 2016; Fava and Belaise, 2018; Maslej et al., 2017; Molero et al., 2015). In fact, these side effects may accompany the healing process for weeks, and even months (Leibowitz et al., 2021). Moreover, patients with depression are often overly focused on somatic sensations, show a tendency to somatization, and expect negative treatment outcomes, to the point of even thinking that they deserve such negative outcomes (Barsky et al., 2002; Löwe et al., 2008) Thus, the positive framing of side effects as onset sensations, may be a useful strategy for reducing nocebo effects in patients suffering from depression.

Despite recent positive findings, evidence is lacking on whether a positive framing of side effects can lead to effects that are sustainable over time. For example, (Faasse et al., 2019) showed that positive framing of side effects of placebo benzodiazepine reduces specific nocebo side effects in the short term during the experiment, but not in the 24 h follow-up. Moreover, additional symptoms that were not mentioned in the framing procedure occurred in the follow-up. Therefore, an investigation of the effects of positive framing, as well as of potential predictors for the duration of the framing effect should be considered a priority in the current research agenda.

A series of studies also explored placebo effects in the affective system and found that manipulating treatment expectations, combined with an active placebo nasal spray, can counteract feelings of sadness. Of note, an active placebo is an intervention whose pharmacological properties are not relevant to the purported condition, but which is administered to trigger physiological sensations that resemble those of the real medication, thus boosting patients' expectations. In one study (Glombiewski et al., 2019) participants were either given a deceptive placebo nasal spray or no placebo before sadness was induced through a film clip. The manipulation of treatment expectations had a protective influence on sadness in healthy participants, with those expecting an antidepressant effect from the nasal spray showing a lower increase in self-reported sadness (Glombiewski et al., 2019). In a follow-up study with patients diagnosed with major depression, inducing positive expectations had even stronger preventive effects against sadness, with a significant decrease in self-reported sadness compared to baseline (Haas et al., 2020). These results were confirmed when self-deprecating statements were used as a strategy to induce sadness, with effects on physiological parameters such as skin conductance (Göhler et al., 2021). More recently, the protective properties of an active placebo nasal spray against sadness were demonstrated in an open label placebo design (Hahn et al., 2022).

Despite the excellent groundwork done on the nasal spray-active placebo paradigm, it remains unclear whether the sadness protective effect of the active placebo can be generalized to different contexts, and whether positive framing can be leveraged as a strategy to augment the sadness protecting effect. The primary objective of the present study was, therefore, to investigate whether the sadness-protecting effects of an active placebo nasal spray could be generalized to different contexts using two sadness induction protocols that were delivered through different modalities and were spaced out by 6 h. Additionally, the study aims to explore whether the sadness protecting effects of the active placebo may be enhanced by framing common side effects as onset sensations, while also reducing the incidence of side effects.

2. Methods

2.1. Participants

Ninety-six healthy volunteers were recruited via flyers and e-mail advertisement addressed to students and university staff members based on the cover story that a low-dose antidepressant, known to protect from feelings like sadness and low mood, was to be tested.

Inclusion criteria were age between 18 and 65 years and fluency in German. Students of medicine, pharmacy, and psychology from the fifth semester onwards were excluded. Further exclusion criteria were food intolerances (to filter for allergies to capsaicin or sesame, i.e., the substances contained in the actual nasal spray), mental disorders (including any prior or current intake of antidepressants), symptoms of cold, or intake of psychotropic medication. To strengthen the credibility of the cover story (the administration of an "antidepressant" nasal spray), typical contraindications of antidepressants were also listed as exclusion criteria (i.e., use of MAO inhibitors, cardiovascular diseases such as congenital heart rhythm disorders or previously occurred episodes of heart rhythm disturbances; use of medications to treat heart rhythm disturbances or medications that can affect the heart rhythm; use of linezolid (an antibiotic) within the last 14 days; current pregnancy, suicidal thoughts, epilepsy, or severe lung or kidney disease).

All participants were informed about the study procedure, gave written informed consent, and were compensated with €30 or credit points. The experiment was conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013) and approved by the local ethics committee. The study was pre-registered in the German Register of Clinical Studies (Deutsches Register Klinischer Studien, ID: DRKS00028711). Participants were randomly assigned to three groups: the first group received the active placebo nasal spray, general information on side effects, and a positive framing of these side effects (placebo + positive framing group; PPF); the second group only received the nasal spray and general information on side effects, without positive framing (placebo + standard information group; PSI); the third group received no nasal spray and no information on side effects (no treatment control group; NTC).

2.2. Study procedure

At first, participants completed a 60-min laboratory experiment following a standardized procedure. Six hours after the laboratory session, participants underwent a 20-min online follow-up protocol. Primary (i.e., sadness) and/or secondary (i.e., side effects) outcomes were assessed at four different time points (see Fig. 1): T0 (baseline, prior to any manipulation); T1 (after the placebo nasal spray administration); T2 (after the first sadness induction); T3 (after 6 h, before the second sadness induction); T4 (after the second sadness induction). All questionnaires were made available to participants at www.soscisurvey.de (Leiner, 2022). During the in-person laboratory session, the experimenter wore a white lab coat, informed participants about the exclusion criteria of the study, and measured their blood pressure to enhance the credibility of the cover story. Subsequently, participants received verbal and written information on the study objective, and were told about the nasal spray and its sadness-protecting properties. After answering baseline questionnaires, participants received more detailed information on the nasal spray and on its supposed side effects. Afterwards, participants were informed that they had been randomized to either receive the antidepressant nasal spray, to receive a placebo nasal spray, or to a no treatment control group where no nasal spray would be administered. Participants in the nasal spray groups were then informed that the correct nasal spray is made available by a colleague and that the experimenter is blind to the group allocation.

The PSI group received deceptive information on the sadness-protecting properties of the nasal spray along with a standard description of side effects (e.g., prickling and burning sensations in nose and

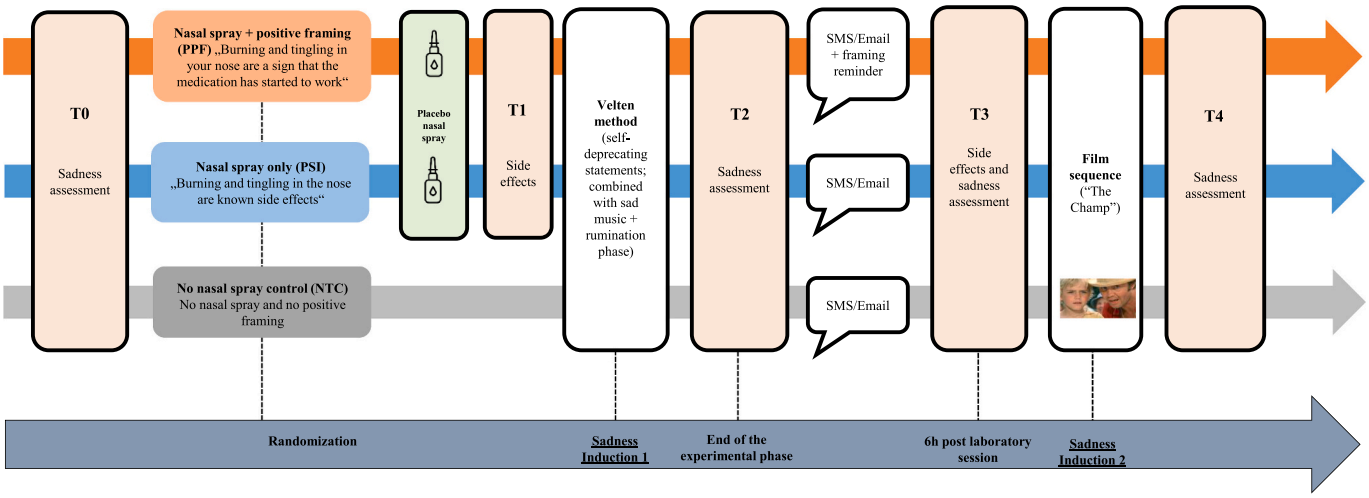

Fig. 1. Experimental design.

throat). Instead, the PPF group received the same information though with an additional positive framing of side effects (“the prickling and burning sensations in nose and throat are a sign that the medication has started to work”). Participants of the NTC group were told that they had been assigned to the control condition and that they would not receive the nasal spray, and thus not be protected against sadness and unpleasant feelings for the following 24 h. Prior to the first sadness induction protocol, all participants were asked to fill out a questionnaire assessing side effects, and to self-monitor their sensations for the following 15 min. Then, all groups were exposed to the modified Velten method (see details below) to induce sadness. Immediately afterwards, participants rated their current feelings of sadness and were reminded about the upcoming follow-up session six hours later.

During the follow-up session, participants were first asked to rate side effects and their current emotional state. Next, they were exposed to a video clip extrapolated from the movie “The Champ” (see details below), to induce feelings of sadness for a second time. The viewing of the movie was followed by an assessment of their current emotional state. Afterwards, participants were presented with a debriefing video that explained the cover story, the true study objectives, and their group assignment.

2.2.1. Sadness induction

Two different techniques were used to induce sadness and unpleasant feelings during the laboratory session and the online follow-up. For the former, a modified and reduced version of the Velten method combined with sad music was employed (Velten Jr, 1968; Seibert and Ellis, 1991; Göhler et al., 2021; Westermann et al., 1996). The Velten method is a self-referential statement technique that instructs participants to empathize with the feelings evoked by sentences with a negative connotation (e.g., “everything I do goes wrong” or “I feel worthless”). The reduced form of the Velten method consists of 25 self-deprecating statements presented in a 20-s interval. Previous studies have shown that the Velten Method, combined with congruent sad music, is effective in inducing sadness (Göhler et al., 2021; Westermann et al., 1996). In this study, the presentation of the statements was accompanied by two pieces of music: *Piano Sonata No. 14* (“Moonlight Sonata”) by Ludwig van Beethoven at the beginning and *Adagio For Strings* by Samuel Barber at half speed at the end. These two musical compositions have proved effective in inducing sadness in past studies (Göhler et al., 2021; Västfjäll, 2001). The present study closely followed the validated form of the Velten Method of Seibert and Ellis (1991). Following the induction of sadness, participants were asked to think about the experience and reflect on the feelings evoked by the self-deprecating statements during a two-minute ruminative phase, adapted from the work of (Göhler et al., 2021).

The second technique to induce sadness at the follow-up session differed from the first, so as to avoid a decrease in the effect due to a repetition of the procedure. As such, a 2.51-min film sequence from “The Champ”(Zefirelli, 1979) was employed. This film sequence has been widely recognized as an effective paradigm for inducing sadness in previous studies (Flohr et al., 2017; Gross and Levenson, 1995; Hewig et al., 2005; Koushiou et al., 2019) and has already been used in several similar experimental studies to induce sadness (Glombiewski et al., 2019; Haas et al., 2020).

2.2.2. Placebo administration

An active placebo, reported to provide a new application form of “citalopram”, but containing sesame oil and a low dose of capsaicin (0.0007 %) was used to induce mild side effects (prickling and burning sensations in nose and throat). This type of active placebo has proved effective in several studies (Glombiewski et al., 2019; Göhler et al., 2021; Haas et al., 2020; Hahn et al., 2022; Rief and Glombiewski, 2012). Participants receiving the placebo nasal spray were informed that it had antidepressant properties and would protect against unpleasant feelings, such as sadness. Moreover, they were asked to self-administer the nasal spray under supervision, and to monitor their sensations for 15 min – described as the time needed for experiencing the effects of the treatment.

2.2.3. Positive framing

All participants in the three groups received written information about the side effects of citalopram, as stated in the package leaflet of citalopram. To enhance the credibility of the cover story, the original side-effect information of citalopram was supplemented with a description of noticeable side effects related to the active placebo, such as nasal tingling, burning in the nose, and a scratchy throat. In the PPF group, after participants were made aware of the general side effects of citalopram, they received verbal and graphically-supported explanations with regards to two specific side effects, which were the ones to be positively framed: nose tingling and burning. Importantly, these two side effects were described as being the most common, and were depicted as a sign that the treatment had started to be effective and was ‘doing its job’ (“Tingling and/or burning in the nose are the most commonly reported side-effects of the citalopram nasal spray. If you experience nose tingling and/or nose burning, consider it a sign that the active component of citalopram is being metabolized by your body and that the treatment has started to work”).

2.3. Measures

2.3.1. Sadness

Sadness was measured subjectively using the sadness subscale of the German version of the valid and reliable Positive and Negative Affect Schedule (PANAS-X; (Röcke and Grühn, 2003; Watson and Clark, 1994) expanded with three distractor items, successfully applied in other studies on the matter (Glombiewski et al., 2019; Haas et al., 2020) to make it less obvious that the study revolves around sadness and hence reduce response bias.

The sadness subscale consists of five items ("To what extent do you feel: sad, downhearted, lonely, alone, or blue"). Responses are recorded using a visual analog scale ranging from not at all (1) to very much (101). Participants select a position on the scale using a slider. The total score of the scale, obtained by summing the responses, ranges from 5 to 505, with higher scores indicating greater sadness. The original scale (five-point) was adapted to increase the sensitivity and variance of the measurement instrument, as successfully implemented in studies by Glombiewski et al. (2019) and Haas et al. (2020). This modified version demonstrated good reliability in the study by Glombiewski et al. (2019) with $\alpha = 0.87$.

2.3.2. Side effects

Side effects were assessed using an extended version of the Generic Assessment of Side Effects Scale (GASE; Rief et al., 2011; Wilhelm et al., 2018).

In this study, two side effects of the active placebo nasal spray (nasal tingling and nose burning) were included as items in the questionnaire. The modified GASE were assessed at two time points (Fig. 1): T1: post-nasal spray application ("symptoms in the last 15 minutes"); T3: at the beginning of follow-up ("symptoms in the last hours").

2.4. Statistical analysis

The data was analysed using IBM SPSS Statistics (Version 20). To test for group differences in self-reported sadness at different time points repeated measures analyses of variance (ANOVA) were carried out with Group (PSI, PPF and NTC) as a between-subject factor and Time (T0, T2, T3, T4) as a within-subject factor. In all analyses, because hypotheses exist as to which groups differ with respect to sadness experience at specific measurement time points, to explore significant effects and interactions, post hoc tests were calculated if ANOVA was statistically significant using paired sample *t*-tests. In particular, to determine whether sadness scores within a group differ between measurement time points, sadness scores at T0, T2, T3, and T4 were compared within each group. Six paired t-tests were calculated for each group. This analysis is exploratory, as no hypotheses are available. Since all measurement time points are to be compared and thus six pairwise comparisons are made per group, correction is made for multiple testing. For this purpose, the *p*-values are adjusted with the Bonferroni correction.

With regards to side effects, three sum scores were calculated from the GASE data, namely number, intensity, and perceived threat of medication-attributed symptoms. The number of drug-attributed symptoms is calculated by summing up all symptoms assessed with an intensity >0 and attributed to the nasal spray. The sum score ranges from 0 to 38. The intensity and perceived threat sum scores were calculated by summing the ratings (0–3) of each drug-attributed symptom. Both sum scores range from 0 to 114.

3. Results

Ninety-six participants were recruited. Table 1 shows demographic variables and sadness values at baseline. Age ranged from 19 to 58 years. Sadness scores at baseline ranged from 6.00 to 338.00. A one-way ANOVA confirmed that there were no significant differences in sadness scores at baseline ($p > 0.05$).

Table 1
Descriptive sample characteristics.

	PPF ($N = 30$)	PSI ($N = 32$)	NTC ($N = 34$)
Age in years, M (SD)	26.20 (8.12)	22.44 (2.58)	23.41 (3.77)
Number of Females, N (%)	12 (40 %)	19 (59.4 %)	21 (61.8 %)
Baseline sadness, M (SD)	129.33 (84.52)	96.81 (71.87)	124.09 (98.37)

Note: M = mean; SD = standard deviation, N = sample size; PPF = placebo + positive framing group; PSI = placebo + standard information group; NTC = no treatment control group.

3.1. Sadness

Sadness scores were significantly different across sessions (effect of Session: $F(3) = 28.83$, $p < 0.001$, $\eta p2 = 0.24$). There was a significant Group × Time interaction ($F(6, 279) = 4.45$, $p = 0.001$, $\eta p2 = 0.09$). Post hoc tests revealed that sadness levels were significantly higher in the NTC group than in the PPF group (T2: $p = 0.015$, $d = -0.67$; T4: $p = 0.026$, $d = -0.61$) and the PSI group (T2: $p < 0.001$, $d = -0.96$; T4: $p = 0.009$, $d = -0.73$) during the laboratory session and at follow-up (Figs. 2A and 2B). See Table 2 for an overview of sadness scores across groups at the different time points. T0 and T3 represent the time points before the sadness induction, while T1 and T4 show measurements after the respective sadness induction.

A within-group analysis revealed significant temporal changes in sadness. For the NTC group, there was a significant increase in sadness from T0 to T2 ($p < 0.001$, $d = -0.83$). However, for both the PPF and the PSI group, this increase was not significant ($p > 0.05$) (Fig. 2A). Overall, these results provide evidence in favor of a short-term protective effect of the active placebo nasal spray against sadness.

Sadness ratings did not differ between the groups at T3 (for all comparisons, $p > 0.05$). At follow-up, sadness significantly increased in both the PSI group ($p < 0.001$, $d = -0.73$) and the NTC group ($p < 0.001$, $d = -0.92$) after the second sadness induction (from T3 to T4). Conversely, the PPF group did not display a significant increase in sadness ($p > 0.05$) (Fig. 2B), suggesting that the sadness-protective effects of positive framing went beyond those of expectations alone, making participants of the PPF group less susceptible to re-experience sadness after 6 h.

3.2. Side effects

Side effects were measured at T1 after application of the nasal spray. Contrary to our hypotheses, *t*-tests for independent groups between the nasal spray groups (PPF and PSI) did not reveal significant differences (number and intensity: $p > 0.05$). Interestingly, however, a significant difference in the occurrence, number, and intensity of side effects was observed at T3. In particular, the PPF reported more numerous and frequent side effects ($p = 0.024$, $d = 0.62$), as well as more intense side effects ($p = 0.018$, $d = 0.65$), than the PSI group at T3.

4. Discussion

Our findings revealed a notable impact of an active placebo nasal spray, whose sadness protecting effects persisted up to six hours post-administration and in a different context. In comparing the nasal spray (PSI and PPF) groups with the no treatment control (NTC) group, it is obvious that the active placebo nasal spray induced a protective effect against sadness after both sadness induction protocols. In particular, during the in-person laboratory session, the NTC group exhibited higher levels of sadness as compared to the PSI and PPF, a difference that was preserved over time in the online follow-up session. Notably, in this latter scenario, only the PPF group appeared to be less susceptible to experiencing sadness after the viewing of the video clip, possibly suggesting that positive framing further enhanced the sadness protecting effect of the active placebo nasal spray.

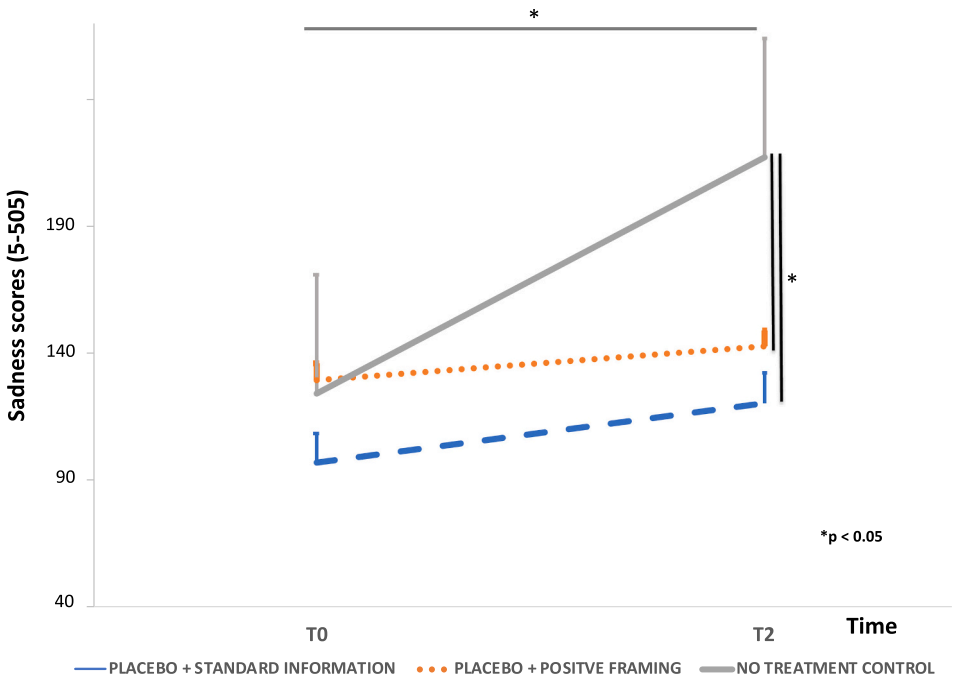

Fig. 2A. Sadness scores across groups from T0 (baseline) to T2 (after the first sadness induction). Both the PSI and PPF groups showed a non-significant increase in sadness scores from T0 to T2 ($p > 0.5$). Instead, sadness scores in the NTC group increased significantly following exposure to the first sadness induction protocol (Velten Method). Moreover, sadness scores at T2 were significantly higher in the NTC group than in the PSI and PPF groups ($p < 0.001$), suggesting that the active placebo procedure – both in itself and in combination with positive framing – was effective in protecting participants against feelings of sadness.

Table 2
Sadness scores by group and time point.

	T0 (before sadness induction 1)	T2 (after sadness induction 1)	T3 (before sadness induction 2)	T4 (after sadness induction 2)
PPF, *M* (*SD*)	129.33 (84.52)	142.53 (111.41)	88.07 (78.69)	111.17 (79.11)
PSI, *M* (*SD*)	96.81 (71.87)	120.28 (89.17)	62.26 (48.61)	103.35 (69.16)
NTC, *M* (*SD*)	124.09 (98.37)	217.15 (111.24)	98.88 (84.38)	168.41 (104.96)

Note: M = Mean; SD = Standard deviation; PPF = placebo + positive framing group; PSI = placebo + standard information group; NTC = no treatment control group.

These results are consistent with previous research demonstrating the effects of placebo treatments in managing negative affect (Colloca and Miller, 2011; Glombiewski et al., 2019; Göhler et al., 2021; Haas et al., 2020). Importantly, our study provides further evidence that the placebo effect persists and can be retrieved in a different context (online and outside the lab). The results also suggest that positive framing may have contributed to the preservation of the placebo effect, which can first of all be enhanced by positive treatment expectations (Bingel, 2020; Leibowitz et al., 2021; Petrie and Rief, 2019).

Contrary to the initial expectations, positive framing did not reduce side effect ratings, to the point that the PPF group reported a higher number, occurrence, and intensity of side effects with respect to the PSI and the NTC groups. One possible explanation could be that the active placebo nasal spray did not induce substantial side effects, leading to a potential floor effect. At the same time, the emphasis on describing side effects as onset sensations in the PPF group might have led to more side effects being noticed due to a higher attention to bodily sensations (Doering et al., 2015).

This is in accordance with evidence that attention that is directed towards the body may increase the probability for expected sensations to be detected (Geers et al., 2011), and also further amplify them (Edwards et al., 2013; Fiorio et al., 2022). This observation raises legitimate questions regarding the interaction between the physical and cognitive aspects of side effect perception, opening up an intriguing pathway for future studies in the context of patient-clinician-communication.

4.1. Limitations

The use of self-reported measures, although common in studies of this nature, could be prone to subjective bias. Future studies should be aimed at exploring whether the effects of positive framing could also extend to objective physiological outcomes such as heart rate variability and skin conductance (Göhler et al., 2021). Furthermore, the sample was restricted to healthy volunteers (primarily students and university staff), limiting the generalizability of the findings. Most importantly, the applicability of our findings should be tested in clinical populations in which sadness and depression represent core symptoms, e.g., not only in patients with clinical depression (Haas et al., 2020) but also in patients with other maladies who are more than often susceptible to experiencing depressive symptoms. It would also be valuable for future research to explore these effects in a more diverse sample that allows to account for factors such as educational level and cultural background. Another limitation could be that a time frame of 6 h is not wide enough to mark clinically relevant effects of active placebo or positive framing, thus the inclusion of longer time windows (e.g., 24 h) could represent a sounder methodological approach for testing long-term effects of such paradigms. Another limitation could have been the experimenter bias, e.g., introduced through subtle variations in instructions during the nasal spray administration, which could have influenced participants' responses. However, the impact of such bias was minimized by employing a standardized study protocol for the entire interaction between the experimenter and participants and the online follow-up assessment, conducted in a different context without a face-to-face contact with the experimenter's, in which the effects observed were comparable to those

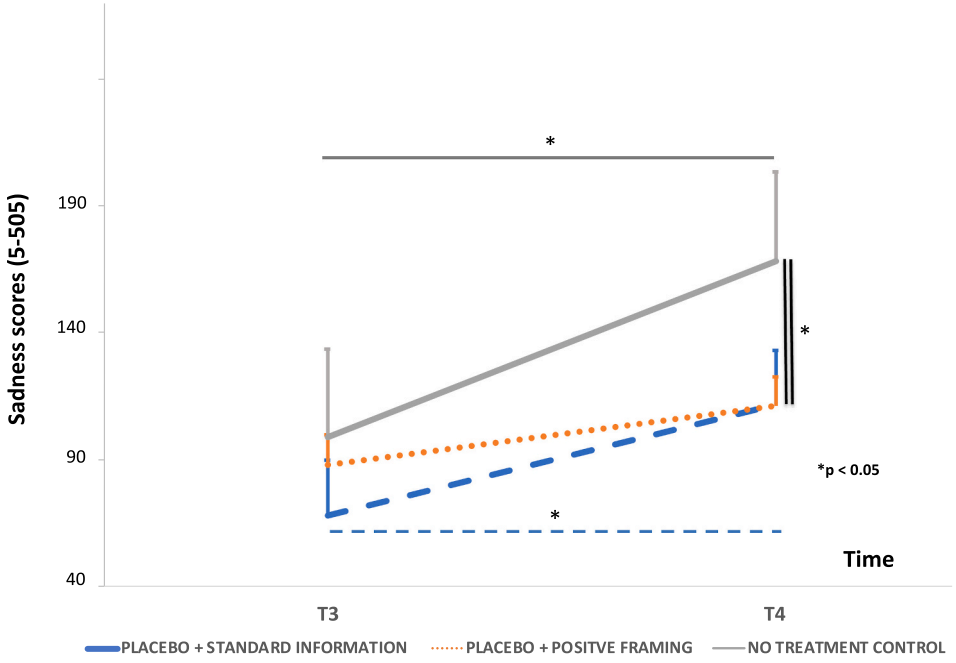

Fig. 2B. Sadness scores across groups at follow-up (from T3 to T4). After the second sadness induction (i.e., video clip), sadness scores significantly increased in both the PSI and NTC groups ($p < 0.001$). Conversely, no significant increase in sadness was observed in the PPF group ($p > 0.5$), possibly suggesting that the sadness protecting effect of the active placebo nasal spray was further enhanced by positive framing, which may have supported the transfer of the effect to a different context. When comparing the different groups at T4, both the PSI and PPF groups reported lower sadness scores than the NTC group, hinting, on the one hand, to the effects of the active placebo nasal spray, though, on the other, to the fact that positive framing was not effective enough to detect a difference in the susceptibility to sadness in the groups receiving the active placebo.

obtained in the lab.

Some strengths are also worth mentioning, for example, the use of rigorous sadness induction methods. The application of two different validated techniques for inducing sadness, i.e., the Velten method and the film sequence from The Champ, may have increased the reliability and validity of the sadness responses. Indeed, both methods have been used in similar studies but have never been successfully combined for a repeated measure of sadness, which could have helped to provide a more nuanced view of the temporal dynamics of this experience. Additionally, the follow-up was conducted in a different setting and after a significant time period, which adds to the robustness of the findings. Finally, the inclusion of a control group without nasal spray further validates the employed paradigm.

The findings of this study have interesting implications for future research and clinical practice. The results suggest that placebo mechanisms, could potentially be used as a strategy to manage negative emotions. While the implementation of deceptive placebos in clinical practice is ethically problematic, framing salient side effects as 'onset sensations' could be a strategy to increase the effect of real antidepressant medication, while overcoming the ethical barriers posed by the use of deception. For example, emphasizing the salience of side effects, such as dry mouth in the case of amitriptyline (Rheker et al., 2017), as a sign that the treatment is working, may play a crucial role in boosting the therapeutic efficacy of the drug. However, this study also underscores the need for caution, as an undue emphasis on the description of side-effect related bodily sensations may lead to a higher somatic focus, which could inadvertently make space for nocebo effects to take root. Indeed, this is different from directing attention to positive bodily signs (e.g., the ones associated to the positive effects of a treatment), which instead could lead to an enhancement of treatment effectiveness (Barbiani et al., 2024). Overall, if positive framing strategies will be translated in clinical practice it will be of utmost importance to select which symptoms/side effects are most suitable to be positively framed in terms of both minimizing a worrisome focus on bodily sensations and not overshadowing the positive expectations associated to receiving a specific treatment. On a more general note, it could be interesting for future research to explore the trade-offs between positively framed side effects described with a different degree of severity and/or likelihood of occurrence and the therapeutic effects of treatments. To explore this path, more experimental studies are needed, especially in clinical populations and with pharmacokinetic active substances. However, it should also be further investigated if the persistence of the active placebo nasal spray could last even beyond six hours. The possibility of a once-daily administration would strengthen the idea of exploiting this effect in clinical practice, especially in light of recent open label placebo findings (Hahn et al., 2022).

In conclusion, our study revealed that the use of an active placebo resulted in a protective effect against sadness compared to a no treatment control group, even six hours after placebo administration. Importantly, positive framing might have contributed to an enhancement of this effect. This finding underlines the potential value of placebo interventions in managing negative affective states, especially when coupled with positive framing, which may act as a crucial component in augmenting the impact of the clinician-patient-communication. Future research is required to explore these effects further, particularly in clinical populations and real-world contexts.

CRediT authorship contribution statement

Marcel Wilhelm: Writing – original draft, Visualization, Methodology, Conceptualization. **Sarah Mae Fischer:** Formal analysis, Conceptualization. **Winfried Rief:** Writing – review & editing, Supervision. **Mirta Fiorio:** Writing – review & editing, Supervision. **Diletta Barbiani:** Writing – review & editing, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

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