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Practitioner warmth and empathy attenuates the nocebo effect and enhances the placebo effect

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Abstract

Augmented patient–practitioner interactions that enhance therapeutic alliance can increase the placebo effect to sham treatment. Little is known, however, about the effect of these interactions on maladaptive health outcomes (i.e., the nocebo effect). Healthy participants ($N = 84$) were randomised to a 3-day course of Oxytocin nasal drops (actually, sham treatment) in conjunction with a high-warmth interaction (Oxy-HW: $N = 28$), a low-warmth interaction (Oxy-LW: $N = 28$) or to a no treatment control group (NT: $N = 28$). All participants were informed that the Oxytocin treatment could increase psychological well-being but was associated with several potential side effects. Treatment-related side effects, unwarned symptoms, and psychological well-being were measured at baseline and all post-treatment days. Side effect reporting was increased in the Oxy-LW condition compared to the other groups across all days. Conversely, increased psychological well-being was observed in the Oxy-HW condition, relative to the other conditions, but only on Day 1. Among those receiving treatment, positive and negative expectations, and treatment-related worry, did not vary by interaction-style, while psychological well-being and side effect reporting were inversely

associated at the level of the individual. Results have important implications for practice, suggesting poorer quality interactions may not only reduce beneficial health outcomes but also exacerbate those that are maladaptive.

KEYWORDS

empathy, expectations, nocebo effect, patient–practitioner interaction, placebo effect, therapeutic alliance

INTRODUCTION

Interpersonal communication between patients and medical professionals forms an integral part of most treatment settings. Therapeutic alliance, the quality of this interaction, is known to modulate health outcomes (Derksen et al., 2013; Di Blasi et al., 2001; Elliott et al., 2018; Kelley et al., 2014). Successful therapeutic alliance is thought to comprise both affective and cognitive components, with the former including practitioner warmth, empathy and compassion, and the latter professional competence (Di Blasi et al., 2001; Howe et al., 2019). However, these key dimensions are likely intercorrelated, with most research combining the two (Kelley et al., 2014).

Effective practitioner–patient communication has been found to be associated with improved adherence to treatment in meta-analysis (Zolnierek & Dimatteo, 2009), while correlational research has suggested that interactions actively including the patient are associated with improved health outcomes in conditions such as lupus (Ward et al., 2003) and breast cancer (Street & Voigt, 1997). Similarly, interactions that comprise greater practitioner warmth and empathy have been associated with improved outcomes in diabetes (Hojat et al., 2011), common cold (Rakel et al., 2011), and chronic low back pain (Ferreira et al., 2013). Finally, RCTs employing interventions to enhance practitioner communication skills have been found to improve outcomes associated with respiratory tract infection, asthma, somatic symptoms, osteoarthritis-related pain and depression among cancer patients (Aiarzaguena et al., 2007; Cals et al., 2009; Chassany et al., 2006; Cleland et al., 2007; Fujimori et al., 2014). As such, it appears that the interpersonal qualities expressed by the health practitioner during the patient–practitioner interaction can alter components of the treatment setting in a manner that enhances the effect of an active treatment or intervention.

Recent research has also demonstrated that the patient–practitioner interaction can augment the placebo effect elicited in response to inert treatment. The placebo effect refers to the phenomenon whereby health improvements are driven by features of the treatment context, independent of the active ingredients associated with a medication, treatment, or intervention (Price et al., 2008). With respect to patient–practitioner interaction, research regarding the placebo effect has systematically varied the content of verbal and non-verbal information expressed by the health professional, such that participants receive either an augmented interaction designed to increase therapeutic alliance, or a limited interaction more akin to standard care independent of these interpersonal qualities. Among clinical samples, patients with irritable bowel syndrome (IBS) reported increased quality of life, and decreased symptom severity, when placebo acupuncture in conjunction with an augmented interaction was compared to placebo

acupuncture alone (Kaptchuk et al., 2008). Consistent with these results, those with chronic low back pain benefitted more from sham interferential current therapy when combined with an augmented interaction than when administered independently (Fuentes et al., 2014). In both studies, however, time spent in the physical presence of the patient varied between conditions, with longer durations in the augmented interaction.

Research with healthy participants has shown similar benefits of augmented interactions while controlling for interaction time. Participants administered an inert cream described as an analgesic reported higher pain tolerance to a cold pressor task when the cream was applied with an augmented, relative to a limited, interaction style (Czerniak et al., 2016). Similarly, participants administered an inert cream described as reducing allergic reaction were found to have a smaller wheal size after a histamine skin prick test when the practitioner displayed high, relative to low, empathy and competence (Howe et al., 2017). Comparable effects have been observed for placebo interventions that are more abstract in nature. For instance, videos containing moving green shapes, provided with the rationale that their colour would activate emotional schemata, have been demonstrated to lead to improvement in mood, but only when delivered by an empathetic experimenter (Gaab et al., 2019). Furthermore, studies concerning interpersonal synchrony have provided tentative evidence that the strength of neural and physiological concurrence between the practitioner and patient is associated with enhanced placebo effects, implicating interpersonal connection at a level not accessible to self-report perceptions (Chen et al., 2019; Ellingsen et al., 2020, 2023).

In summary, the way in which a practitioner and patient interact can have a powerful effect on the patient's health, including via enhancement of the placebo effect. However, several gaps in the literature remain. First, while theoretical review has identified positive expectancies as a primary mechanism through which patient–practitioner interaction might increase the placebo effect (Howe et al., 2019; Wampold, 2021), direct exploration of mechanisms has received limited empirical attention. Instead, the modulation of expectancies have tended to be inferred as a result of the manipulation, rather than directly measured (e.g., Howe et al., 2017), which is common for the literature (Rooney et al., 2022). One study has combined practitioner warmth and empathy with positive treatment information leading to increased treatment expectations (Verheul et al., 2010). However, this study involved hypothetical scenarios and did not test for a placebo effect to treatment. Second, among studies that control for the length of the patient–practitioner interaction, primary outcomes have been measured at the end of a single laboratory-based session (e.g., Czerniak et al., 2016; Gaab et al., 2019; Howe et al., 2017). Medical consultations often involve an in-person appointment, where patients are prescribed a treatment to take home, but little is known about the longevity of the patient–practitioner interaction on the placebo effect expressed under these conditions. Third, it follows that if positive patient–practitioner interactions can enhance health outcomes through the placebo effect, then more negative interactions may lead to poorer health outcomes through the nocebo effect; a phenomenon whereby components of the treatment context trigger a worsening of health outcomes (Faasse, Helfer, et al., 2019). If patient–practitioner interactions of poorer quality are associated with a reduced placebo effect *and* have the capacity to increase maladaptive health outcomes, such as adverse events to treatment, then this would have significant implications for the way in which healthcare provision is deployed.

Broadly speaking, both human and non-human animals have been demonstrated to be extremely sensitive to social cues, which in turn have been shown to have a modulatory effect on physiological outcomes. For example, witnessing pain and fear in another is known to modulate both the pain and fear response of the observer (Keysers & Gazzola, 2023; Pärnamets

et al., 2020), including the nocebo effect (e.g., Vögtle et al., 2013). As such, this sensitivity towards negative social interactions may also exacerbate the nocebo effect in response to patient–practitioner interactions lacking warmth and empathy. Direct empirical evidence for this specific association, however, is currently lacking. Only one study has investigated the effect of practitioner warmth and competence in conjunction with negative treatment information (Howe et al., 2017, see above). A factorial design was employed that manipulated treatment information (a cream that increased vs. decreased allergy), practitioner competence (high vs. low) and practitioner warmth (high vs. low). When the treatment was described as *increasing* allergic reaction, wheal size did not appear to vary significantly across the factors of warmth or competence. Conversely, when the treatment was described as *reducing* allergic reaction, the high competence and warmth condition was associated with a greater reduction in wheal size than the low competence and warmth condition (high warmth/low competence, and vice versa, demonstrated intermediary effects). These results suggest that practitioner warmth and empathy may have limited effect on health outcomes when in conjunction with negative treatment information. The absence of a no treatment control condition systematically crossed with the factors of competence and empathy, however, complicates the assessment of placebo and nocebo effects per se. Furthermore, two separate treatments were tested, one increasing and one decreasing allergic reaction. The former is likely to be less familiar to participants as it is uncommon to apply a treatment that makes a condition worse, which may have led to between-group differences in the success of the manipulation. The point of note is that nocebo effects can occur in two different forms: primary and secondary (Faasse, Helfer, et al., 2019). Most studies, including that of Howe et al. (2017), focus on primary effects, where maladaptive health outcomes are the primary action of a given treatment. Experimental designs that elicit secondary nocebo effects (i.e., where negative outcomes, such as side effects, are a corollary to positive treatment outcomes) have the benefit of allowing for the modulatory effect of patient–practitioner interaction to be tested for a single treatment at the level of the individual participant, with the potential for placebo and nocebo effects to be simultaneously elicited.

To bridge the identified gaps in the literature, participants were recruited to a randomised-controlled study ostensibly investigating the role of Oxytocin nasal drops (actually, sham treatment) on psychological well-being (i.e., levels of stress and anxiety). All participants were informed that they would be randomised to a treatment or no treatment condition, and that the Oxytocin nasal drops, while decreasing stress and anxiety, were associated with several potential side effects. Practitioner warmth and empathy was the primary focus, with participants engaging in either an augmented (high warmth) or limited (low warmth) interaction, as in previous research (e.g., Howe et al., 2017; Verheul et al., 2010). Based on the results of Kaptchuk et al. (2008), who demonstrated an increase in global improvement among IBS patients receiving both a limited and augmented interaction, relative to waitlist control, an overall placebo and nocebo effect was anticipated in Oxytocin-treated participants, irrespective of interaction, when compared to the no treatment control. It was further hypothesised that the augmented interaction involving warmth and empathy, when compared to the limited interaction, would increase the placebo effect, measured as a decrease in stress and anxiety. Conversely, the limited, relative to augmented interaction, was expected to increase the nocebo effect, measured as an increase in reported side effects associated with the treatment. It was anticipated that the augmented interaction would increase positive expectancies, while the limited interaction would increase negative expectancies and treatment-related worry.

METHODS AND MATERIALS

Design

A mixed 3 × 3 design was employed with one between-subjects factor (Condition: No Treatment [NT], Oxytocin High Warmth [Oxy-HW]; Oxytocin Low Warmth [Oxy-LW]) and one within-subjects factor (Trial Day: 1–3). Participants were informed that they were taking part in a study investigating the effects of Oxytocin on stress and anxiety. In actuality, the Oxytocin nasal drops administered constituted a placebo consisting of inert saline. Block randomisation was employed (blocks of 12) to achieve roughly equal allocation of participants to experimental condition, with the random sequence generated by a researcher not otherwise involved in the study. Participants were first randomised to a High- vs. Low-Warmth Condition on a 1:1 ratio. Interaction-Style (i.e., High vs. Low Warmth) was anticipated to have limited effect on the health outcomes of those randomised to the NT group. Participants were subsequently randomised to Treatment or No Treatment on a 2:1 ratio, respectively. This meant half the NT group received the High Warmth and half the Low Warmth interaction.

As a primary aim of health interventions is to enhance health outcomes, all participants received verbal instruction that the nasal drops administered as part of the study contained '*Oxytocin, a hormone which helps to regulate stress responses and reduce anxiety by encouraging social engagement, increasing feelings of interpersonal trust, and improving sleep quality*', as in previous research (Darragh et al., 2016). Participants were also informed that the nasal drops could lead to potential side effects, including (1) headache; (2) nausea; (3) vomiting; (4) rapid heartbeat; (5) feeling faint or lightheaded; (6) skin itching or rash; (7) nasal irritation or discomfort. Participants randomised to the Treatment Conditions (Oxy-HW and Oxy-LW) were instructed to self-administer intra-nasal Oxytocin for three consecutive days. Primary outcomes regarding participant well-being were collected at baseline (in-person session) and remotely (via Qualtrics) each evening of the study. To reduce any confounding effects regarding individual differences in the expression of warmth and empathy between research personnel, a single experimenter delivered the study information. As such, they were not blind to Interaction-Style (High vs. Low Warmth). However, to minimise bias, care was taken to (1) collect all outcomes using online questionnaire software with the experimenter not present (including the in-person consultation); (2) follow standardised scripts when delivering information (see Supporting Information); (3) only unblind the experimenter to treatment allocation at the end of the in-person session, after both the baseline measures and the primary Interaction-Style manipulation were complete.

Participants

Ninety-three University of New South Wales undergraduate psychology students gave consent to participate in the study for course credit, after having been screened for the following eligibility criteria: (1) 18 years of age or older; (2) fluent in English; (3) not pregnant or breastfeeding; (4) no known allergies to Oxytocin or saline; (5) no existing diagnosis of anxiety or depressive disorder; (6) not taking any prescribed medications; (7) willing to abstain from alcohol and other drugs for the duration of the study. A condition of ethical approval was that participants comprise a sub-clinical sample. As such, participants ($N = 9$) who scored in the severe or extremely severe range of the depression (≥11), anxiety (≥8) or stress (≥13) sub-scales of the

Depression Anxiety Stress Scale (DASS-21), measured directly after consent, were ineligible to participate and did not progress with the full-study. The mean age of those participants who completed the full study ($N = 84$) was 21 years ($SD = 5.5$; range = 18–52). Forty-five (54%) identified as female and 39 (46%) as male. No participants identified as another gender or declined to answer. Most identified as Asian (52%), Australian (29%), or European (12%) ethnicity. As all participants were students, SES and educational attainment were not measured. Ethical approval was obtained from the UNSW HREC (HC180036).

Materials and manipulations

Placebo nasal drops

The nasal drops, described as Oxytocin, contained isotonic saline solution, and were provided to participants in a 5 ml sealed transparent bottle. A medication label was designed to uphold the cover story. It detailed the primary ingredient (Oxytocin), a batch number, expiry date, and a generic warning *('For medical use only, keep out of the reach of children')*. Participants assigned to the Treatment condition received information to administer three drops of the Oxytocin fluid to each nostril by shaking the Oxytocin bottle, tilting their head back, holding their other nostril shut, and inhaling. Participants were instructed to administer the treatment each morning of the study, between 6 and 11 AM.

Interaction-style

Throughout the initial 30-min consultation, the interaction between the experimenter and participant was manipulated using verbal and non-verbal cues. Protocols for the delivery of this information were developed based on previous research (Howe et al., 2017; Verheul et al., 2010) and are detailed in Table 1, with standardised scripts freely available (see Supporting Information).

Interaction-style: Manipulation check

To assess the efficacy of the Interaction-Style manipulation, all participants were asked to complete a 'research feedback questionnaire' at the end of the in-person consultation regarding their experience during the study session. The survey comprised of a modified version of the Consultation and Relational Empathy (CARE) Measure relating to warmth and empathy (Mercer et al., 2004). It included six items assessing the experimenter's ability to make participants feel at ease, comfortable to disclose information, listened to, understood, cared for, and able to express their thoughts freely. Responses were collected on a 6-point scale ranging from 0 (*very poor*) to 5 (*excellent*), with an overall sum-score calculated. Two final single-item measures were included regarding the experimenter's warmth and empathy, rated on a 11-point scale ranging from 0 (*not at all*) to 10 (*very*). This type of feedback questionnaire is not dissimilar from teaching evaluation questionnaires regularly provided to students and therefore should not have appeared at odds with the context.

TABLE 1 Experimental manipulation of warmth and empathy.

	High warmth/empathy	Low warmth/empathy
Verbal cues	• Participant greeted by first-name • Experimenter introduces themselves by their first name • Experimenter uses a warm and friendly interaction style throughout • Experimenter responds empathically to anxiety/stress related questions, show understanding and validation • Experimenter employs an appropriate and variable intonation of voice throughout	• Participant not greeted by name • Experimenter does not introduce themselves • Experimenter uses an abrupt interaction style throughout • Experimenter responds with minimal empathy to stress and anxiety questions • Experimenter employs a monotonous, monotone voice throughout
Non-verbal cues	• Handshake upon arrival • Experimenter maintains appropriate eye contact throughout • Appropriate use of facial expressions to match the information being conveyed by the participant	• No handshake upon arrival • Minimal eye contact made with the participant experimenter frequently looks down or out of the window • Neutral facial expression used across all interactions with the participant

Primary and secondary outcomes

Primary nocebo outcome: Physical symptoms

A modified version of the Generic Assessment of Side Effects questionnaire (GASE; Rief et al., 2011) was employed as the primary outcome to measure the nocebo effect. At baseline, participants completed a 48-symptom measure on a scale from 0 (*not at all*) to 3 (*severe*). This comprised the original 38 item GASE and an additional 10 symptoms commonly reported (see: Petrie et al., 2014). At the three post-treatment time-points, a shorter 16-item measure was employed. From this, a 7-item metric, 'Listed Side-Effects', was calculated containing the GASE items that overlapped with the side effects participants were warned about: '*headache*', '*nausea*', '*vomiting*', '*palpitations/rapid heartrate*', '*feeling faint or lightheaded*', '*dizziness*', '*skin rash or itching*'. Nasal irritation or discomfort was not measured as this may have legitimately resulted from administration of the saline solution. The remaining 9-items were sum-scored as a metric of 'Unwarned Symptoms' (i.e., those symptoms not mentioned as Oxytocin side effects). These consisted of '*confusion*', '*difficulty breathing*', '*hives*', '*abdominal pain*', '*puffiness or swelling of the eyes, face, lips or tongue*', '*chest pain or discomfort*', '*coughing*', '*difficulty swallowing*', '*wheezing*'. In both cases, higher values indicated greater symptom experience.

Primary placebo outcome: Psychological well-being

The Depression Anxiety Stress Scale-21 (DASS-21) was used as the primary outcome to measure the placebo effect. The measure assesses negative mood states (Henry & Crawford, 2005;

Lovibond & Lovibond, 1995) and consists of 21 items (e.g., '*I found it hard to wind down*') measured on a four-point scale from 0 (*never*) to 3 (*almost always*). Lower scores indicate increased psychological well-being. Responses were sum-scored and then doubled to make them comparable to the full measure, the DASS-42 (as published elsewhere; Barnes, Babbage, et al., 2023). Baseline scores assessed psychological well-being over the past week. The three post-treatment surveys made assessments with respect to the current day of the study.

Secondary outcomes: Treatment expectations and worry

Treatment expectations and worry were measured among those randomised to receive Oxytocin. Expectations were measured regarding the placebo effect ('*How much do you think the Oxytocin nasal drops will reduce your stress and anxiety over the next three days?*') and the nocebo effect ('*How likely are you to experience side effects as a result of the Oxytocin?*'). Worry about taking the Oxytocin was also measured ('*How worried are you about taking the Oxytocin?*'). All three items were measured on a 5-point scale from 1 (*not at all/extremely unlikely*) to 5 (*a great deal/extremely likely*). These secondary measures were collected once at the end of the initial in-person consultation.

Filler questionnaires

Several measures were included to maintain the cover story that reductions in stress and anxiety associated with Oxytocin occur through '*encouraging social engagement, increasing feelings of interpersonal trust, and improving sleep quality*'. These served to detract from the items regarding expectations and experimenter warmth and empathy. As these were not the primary outcomes of Oxytocin stressed to participants throughout the study, they were not submitted to analysis. Filler measures were as follows: The Social Interaction Anxiety Scale (SIAS; Mattick & Clarke, 1998); The General Trust Scale (GTS; Yamagishi & Yamagishi, 1994); Insomnia Severity Index (ISI; Morin et al., 2011).

Procedure

Participants attended an ~30-min in-person consultation, held in a research room at the UNSW Psychology Clinic. The experimenter was dressed in accordance with the clinic dress code and therefore presented themselves in a professional manner comparable to all other clinicians in attendance. At the beginning of the consultation, the experimenter opened an opaque envelope to reveal the Interaction-Style for that session (i.e., whether the participant had been randomised to the High or Low Warmth condition). Please note, at this point the experimenter was unaware of whether the participant had been randomised to receive sham-treatment. In both instances, the participant was blind to condition. After providing written consent, all participants received standardised information regarding the nasal drops. This emphasised the positive effects of Oxytocin (reduced stress and anxiety) as well as the supposed common side effects. They subsequently completed the baseline measure of the DASS-21 which functioned as the primary outcome for the placebo effect and as a screener. In accordance with the conditions of the obtained ethical approval, those reporting scores within the '*severe*' or '*extremely severe*

range' ($N = 9$) were informed of their ineligibility to participate. They were credited for their time, but did not progress with the study. Participants subsequently provided demographic information and completed primary and secondary baseline measures.

A series of questions served as an opportunity for the experimenter to modulate their interaction with the participant in line with the Interaction-Style to which they had been assigned (High Warmth vs. Low Warmth; see Table 1). Participants were asked seven questions verbally regarding their stress and anxiety, including their worries, their difficulty controlling worry, avoidance of situations that increase worry, any physiological symptoms associated with thinking about worrying situations, and any coping strategies that they had for dealing with stress (see Supporting Information). The participant's answers were not recorded.

Finally, the researcher opened a sealed envelope containing information regarding whether the participant had been randomised to receive Oxytocin or No Treatment. Those randomised to Treatment were provided with additional instruction regarding the administration and return of the Oxytocin nasal drops. They were advised that they should administer the drops each morning, three drops per-nostril, for three consecutive days. They were also informed that they would receive text message reminders each morning as a prompt to take the medication and complete the follow-up questionnaire that would arrive via email each evening at 5 pm. A card with the principal investigator's contact details was provided, with participants told that, if they should seek medical attention for side effects, they should give the card to the medical practitioner. They were asked to return the Oxytocin bottle to a set location at the end of the study. Participants assigned to the NT group were told that they would not be taking the Oxytocin nasal drops but would be asked to complete the follow-up questionnaire each evening. To control for level of communication, participants in the NT group also received a text message reminder each morning to remind them of the follow-up survey. To conclude the in-person consultation, the treatment expectation measures were completed by those in the Treatment groups, and the '*research feedback questionnaire*' (Interaction-Style manipulation check) by all participants.

Follow-up questionnaires enquired about the participant's experience over the previous 24 h. These comprised the GASE (Listed Side Effects and Unwarned Symptoms), the DASS-21, and the secondary filler questionnaires regarding social anxiety, interpersonal trust, and sleep quality, to uphold the Oxytocin cover-story. Those assigned to Treatment were additionally asked about their adherence ('*Did you administer the Oxytocin nasal drops this morning*': '*Yes*'/'*No*'). Finally, all participants responded to a free-response question regarding the purpose of the study, with none identifying the true aims. All email and text message correspondence with participants followed a set template and was augmented to supplement the in-person interaction to emulate the effect that repeated interactions may have (e.g., genial greeting versus no greeting and friendly wording versus abrupt and succinct wording). All participants were debriefed after data collection. No participants elected to withdraw their data on finding out the true nature of the study.

Statistical analysis, missing data and sample size

Analysis of the nocebo and placebo effect took the form of Linear Mixed-Effects Models (LMEs), containing the Baseline measure (mean centered) of the primary outcomes as the

covariate, slopes for Trial Day (intercept at Day 1), and orthogonal contrasts for the effect of Condition: Contrast (1) overall nocebo/placebo comparison (NT vs. both Treatment groups); Contrast (2) augmented treatment effect (Oxy-HW vs. Oxy-LW). Participant-level random intercepts were included in the model. Main effects and contrasts were estimated first. A second model was subsequently run including the interaction between Trial Day and Condition (including the two orthogonal contrasts), with Trial Day and Condition in this model representing conditional effects. It was anticipated that the nocebo and placebo effect would be strongest at Day 1, directly following the manipulated interaction, and dissipate over time. As the main effects and contrasts associated with the LMEs are averaged over all Trial Days, a secondary simplified model, comprising a between-subjects ANCOVA, was completed using the Day 1 data to estimate the placebo and nocebo effect at its strongest, as performed elsewhere (e.g., Colagiuri et al., 2015; Faasse, Huynh, et al., 2019).

There was no missing data from the primary outcomes at Baseline. Missing data was present for the GASE at Day 1 ($N = 3$: NT = 1| Oxy-LW = 2) and Day 3 ($N = 2$: both Oxy-HW). Missing data was present from the DASS-21 at Day 1 ($N = 3$: NT = 1|Oxy-LW = 2) and Day 3 ($N = 2$: both Oxy-HW). Consequently, data from a minority of participants are missing from the models. A small number of participants failed to rate their adherence on Day 1 ($N = 2$: both Oxy-LW), Day 2 ($N = 2$: Oxy-HW = 1|Oxy-LW = 1) and Day 3 ($N = 2$: both Oxy-HW). Due to technical error, the first five participants enrolled in the study did not receive the single-item measures regarding experimenter warmth and empathy (NT = 2|Oxy-LW = 1|Oxy-HW = 1) but did receive the CARE measure.

To check that the Interaction-Style manipulation had no effect on the primary outcomes of those assigned to NT, LMEs were run to compare the data of those not assigned to Treatment who received a High vs. Low Warmth interaction. To determine whether participants perceived the Low Warmth interaction to be less warm, *t*-tests with one between-subjects factor (High Warmth vs. Low Warmth; collapsing across Treatment/No Treatment) were run on the manipulation check items (CARE and single-item warmth and empathy measures). Differences between treatment groups (Oxy-HW and Oxy-LW) with respect to treatment worry as well as positive and negative expectancy, were analysed via *t*-tests.

Based on the results of our primary analyses, exploratory contrasts were run to test for a placebo effect in the Oxy-HW group, and a nocebo effect in the Oxy-LW group, both relative to NT, at Day 1. After confirming the presence of these two effects, a final exploratory analysis was run assessing the interrelationship between positive and negative health outcomes at the level of the Oxytocin-treated individuals. Further detail regarding these analyses is presented in the results section.

Sample size (estimated $N = 75$; 25 per group) was calculated via a priori power analysis (80% power, alpha = 0.05, effect size $\eta^2 = 0.25$) based on results from Darragh et al. (2016) concerning the effect of a take-home '*Oxytocin*' placebo-treatment on stress and anxiety. An additional nine participants (three per-condition) were recruited to account for potential non-adherence and missing data.

All analyses reported were performed using R (version 4.3.1; R Core Team, 2023). The lme4 package (Bates et al., 2015) was used to estimate the LMEs. ANCOVAs were run with the afex package (Singmann et al., 2023) in conjunction with the emmeans package (Lenth, 2023) to test the specified contrasts. An alpha level of .05 was used for all tests. Data is publicly available and can be accessed at https://osf.io/ud4af/?view_only=da8d398905244f849a49b07feb60bc99.

RESULTS

Demographics and baseline scores

Participants randomised to the Oxy-HW, Oxy-LW, and NT conditions did not differ by age or gender ($ps > .55$), nor did they differ in their baseline scores on the GASE or DASS-21 ($ps > .82$). Full statistical information, including descriptive statistics for all primary and secondary outcomes can be found in Supporting Information.

Treatment adherence

All but one participant (Oxy-HW; Day 3 only) randomised to receive the sham Oxytocin reported being adherent across all follow-up days of the study (98.8% adherence). However, it is noted that uncertainty exists regarding adherence in the minority of participants included in the primary analyses who did not provide responses to this question (sample proportion = 3.6%).

Manipulation check: Perceived warmth and empathy

Compared to those who received the High Warmth Interaction-Style, those who received the Low Warmth Interaction rated the experimenter significantly lower on the CARE measure ($t[82] = 11.27$, $p < .001$, Cohen's $d = 2.46$), as well as the single-item measures regarding perceived empathy ($t[77] = 11.74$, $p < .001$, Cohen's $d = 2.03$) and warmth ($t[77] = 13.68$, $p < .001$, Cohen's $d = 2.42$). In line with expectations, therefore, the Interaction-Style manipulation appeared successful at modulating the participant's perceptions. See Figure S1.

Manipulation check: Effect of interaction-style on no treatment outcomes

The effect of Interaction-Style was not expected to significantly impact the primary outcomes of those randomised to the NT condition. There was no main effect of Condition on the GASE (Listed Side Effects: $B = .33$, $t(25.2) = 0.78$, $p = .441$, 95% CI [−1.14, 0.48]| Unwarned Symptoms: $B = .30$, $t(25.2) = 0.50$, $p = .625$, 95% CI [−1.44, 0.85]) nor was there a Condition x Day interaction (Listed Side Effects: $B < .01$, $t(53.8) < 0.01$, $p = .998$, 95% CI [−0.71, 0.71]|Unwarned Symptoms: $B = .14$, $t(53.8) = 0.25$, $p = .800$, 95% CI [−0.91, 1.19]). Similar applied to the DASS-21, with no main effect of Condition ($B = 3.50$, $t(25.0) = 0.88$, $p = .389$, 95% CI [−11.17, 4.16]) and no Condition x Day Interaction ($B = .99$, $t(53.1) = 0.67$, $p = .506$, 95% CI [−3.88, 1.89]).

Primary analysis, the nocebo effect: GASE listed side effects

There was a main effect of Condition on Listed Side Effects ($F[2, 80.4] = 3.62$, $p = .031$, $\eta_p^2 = .04$). As presented in Figure 1, this was represented in Contrast 2 (Oxy-HW vs. Oxy-LW: $B = -0.39$, $t[80.6] = -2.61$, $p = .011$, 95% CI [−0.25, −0.10]) with greater side effect reported in the Oxy-LW group. Contrary to our hypothesis, Contrast 1 was not significant (Overall

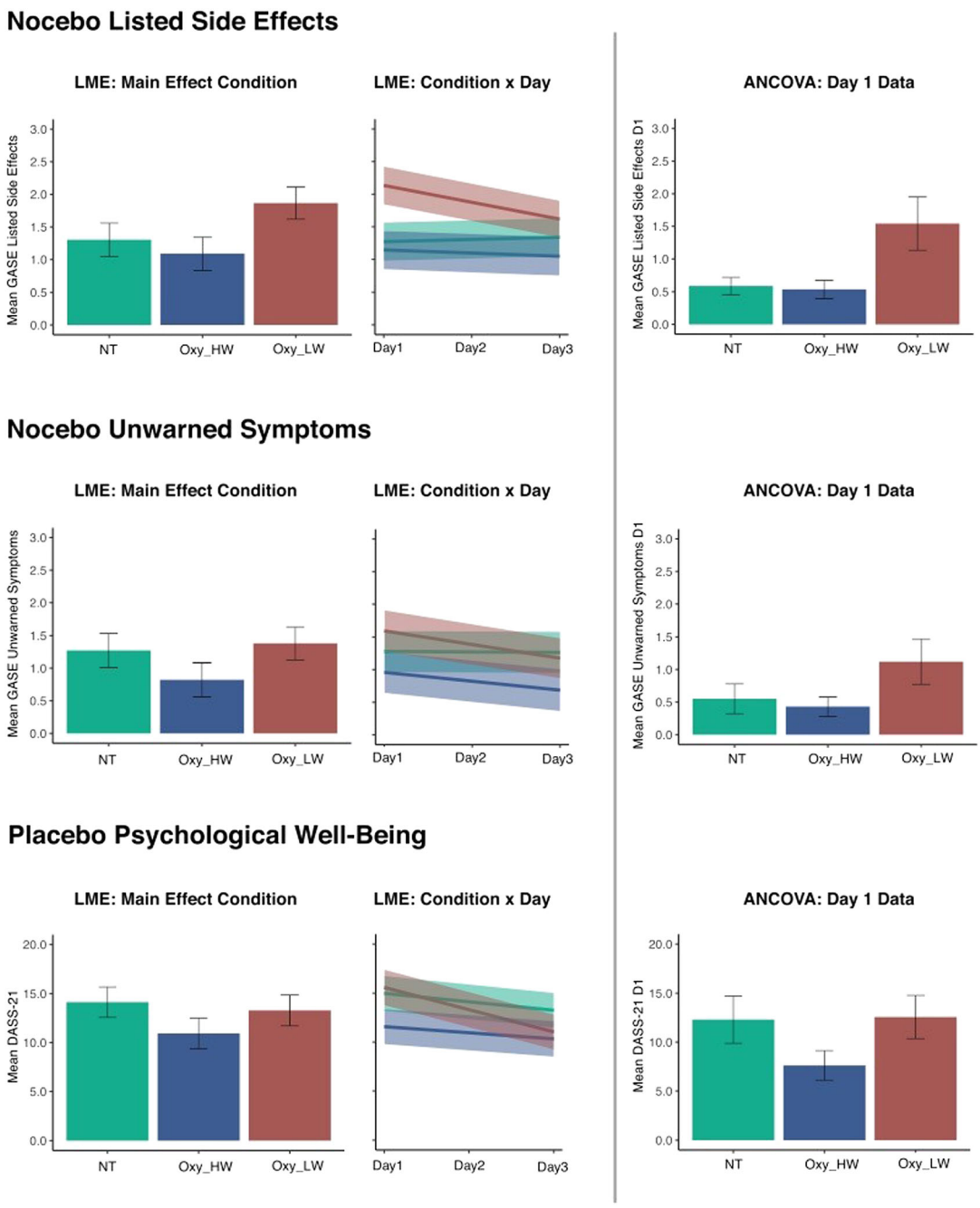

FIGURE 1 Depicts the model predicted values from the LMEs concerning the main effects of condition and day (bar graph, collapsed across all trial days) and the condition × day interaction (line graph) on the left, and the model predicted means from the Day 1 ANCOVAs on the right. Error bars represent ±1 SEM. [Color figure can be viewed at wileyonlinelibrary.com]

Nocebo Effect: $B = -0.12$, $t[80.2] = -0.68$, $p = .497$, 95% CI [−0.49, 0.21]). There was no main effect of Day ($B = -0.10$, $t[164.1] = -1.12$, $p = .265$, 95% CI [−0.25, 0.07]), nor was there an interaction between Day and Condition, nor Day and the two contrasts (all $ps > .25$). When

Day 1 was considered in isolation, there was a main effect of Condition ($F[2, 77] = 5.70$, $p = .005$, $\eta_p^2 = .13$). Contrast 1 did not reach statistical significance (Overall Nocebo: $t[77] = 1.57$, $p = .121$, Cohen's $d = 0.36$), while Contrast 2 did (Oxy-HW vs. Oxy-LW: $t[77] = 3.02$, $p = .003$, Cohen's $d = 0.69$). The Oxy-LW group reported higher average side effects ($M = 1.54$; $SE = 0.24$) than the Oxy-HW group ($M = 0.54$; $SE = 0.23$).

Primary analysis, the nocebo effect: GASE unwarned symptoms

There was no main effect of Condition on Unwarned Symptoms ($F[2, 80.6] = 1.91$, $p = .155$, $\eta_p^2 = .02$). Neither Contrast 1 (Nocebo Effect: $B = 0.11$, $t[80.3] = 0.65$, $p = .517$, 95% CI [−0.22, 0.45]) or Contrast 2 (Oxy-HW vs. Oxy-LW: $B = -0.28$, $t[80.9] = -1.84$, $p = .069$, 95% CI [−0.57, 0.01]) reached statistical significance. There was no main effect of Day, and no interaction between Day and the main effect or Condition or the contrasts (all $ps > .23$). When Day 1 was considered alone, there was no statistically significant main effect of Condition ($F[2, 77] = 2.90$, $p = .061$, $\eta_p^2 = .07$) on Unwarned Symptoms. However, Contrast 2 (Oxy-HW vs. Oxy-LW: $t[77] = 2.27$, $p = .026$, Cohen's $d = 0.52$), but not Contrast 1 (Overall Nocebo: $t[77] = 0.85$, $p = .396$, Cohen's $d = 0.19$), reached statistical significance. The Oxy-LW group reported higher average symptoms not listed with Oxytocin administration ($M = 1.12$; $SE = 0.22$) compared to the Oxy-HW group ($M = 0.43$; $SE = 0.21$).

Primary analysis, the placebo effect: Psychological well-being

There was no effect of Condition on DASS-21 scores ($F[2, 79.8] = 1.21$, $p = .304$, $\eta_p^2 = .01$). There was a main effect of Day ($B = -1.25$, $t(163.1) = -2.55$, $p = .012$, 95% CI [−2.22, −0.29]), with decreasing values across Conditions representing an increase in well-being over time, independent of the placebo effect (i.e., lower DASS-21 scores are indicative of increased well-being). When Day 1 scores were considered in isolation, there was a main effect of Condition ($F[2, 77] = 3.13$, $p = .049$, $\eta_p^2 = .06$), reflected in Contrast 2 (Oxy-HW vs. Oxy-LW: $t[77] = 2.20$, $p = .031$, Cohen's $d = 0.50$), but not Contrast 1 (Overall Placebo: $t[77] = 1.14$, $p = .259$, Cohen's $d = 0.26$). Those in the Oxy-HW group reported lower DASS-21 scores ($M = 7.61$; $SE = 1.56$), and therefore greater psychological well-being, than those in the Oxy-LW group ($M = 12.56$; $SE = 1.62$).

Secondary analysis: Treatment expectations and worry

The Oxy-HW and Oxy-LW groups did not differ significantly in their expectations for positive effects from treatment ($t[54] = 0.47$, $p = .642$, Cohen's $d = 0.12$), their expectations for side effects ($t[54] = 0.59$, $p = .555$, Cohen's $d = 0.16$) or their treatment-related worry ($t[54] = 0.24$, $p = .812$, Cohen's $d = 0.06$).

Placebo and nocebo effects in conjunction

Contrary to expectation, an overall placebo and nocebo effect in the sham-treated participants, relative to NT, was not apparent. Inspection of the error bars in Figure 1, however, suggests

that, relative to NT, there was a nocebo effect among the Oxy-LW group, and a placebo effect among the Oxy-HW group, at Day1. However, orthogonal contrasts did not directly test these comparisons. Supplementary comparisons demonstrated a significant placebo effect in the Oxy-HW group ($t[77] = 2.11$, $p = .038$, Cohen's $d = 0.48$), and a nocebo effect in the Oxy-LW group ($t[77] = 2.84$, $p = .006$, Cohen's $d = 0.65$), relative to NT. While these results suggest that increased practitioner warmth enhances the placebo effect, and lower warmth exacerbates the nocebo effect, they do not speak to the interrelationship between positive and negative health outcomes at the level of Oxytocin-treated individuals. An exploratory analysis was run correlating the raw DASS-21 and GASE scores at Day 1. This analysis collapsed across Oxy-HW and Oxy-LW to explore whether positive health outcomes after treatment decrease as negative health outcomes increase. The mean of the NT group was subtracted from each predictor so that scores less than zero represent higher well-being on the DASS-21, and lower symptoms on the GASE, than was observed on average after no treatment. DASS-21 scores were found to be positively associated with GASE scores (i.e., greater health benefits, lower symptoms: $r[52] = .36$, $p = .007$, 95% CI [0.11, 0.58]). For a scatter plot see Figure S2.

DISCUSSION

The present study tested the effect of practitioner warmth and empathy on positive and negative health outcomes occurring in response to sham Oxytocin treatment. Three notable results emerged: (1) side effect reporting was increased in the group receiving the low warmth interaction, relative to the groups receiving the high warmth interaction and no treatment; (2) psychological well-being was increased among those receiving the high warmth interaction, relative to the groups receiving the low warmth interaction and no treatment; (3) positive and negative expectancies did not vary between the sham-treated conditions, suggesting alternative mechanisms may be responsible for the observed differences in health outcomes. Results have ramifications for clinical practice, where patient–practitioner interactions lacking warmth and empathy have the capacity to attenuate health benefits, and exacerbate maladaptive health outcomes, leading to poorer prognosis.

The present study corroborates previous research demonstrating that augmented interactions designed to facilitate therapeutic alliance can enhance positive health outcomes, including the placebo effect to sham-treatment (e.g., Czerniak et al., 2016; Fuentes et al., 2014; Gaab et al., 2019; Howe et al., 2017; Kaptchuk et al., 2008). Contrary to the results of Kaptchuk et al. (2008), a placebo effect was not apparent in both sham-treated groups relative to NT, but was instead limited to those in the Oxy-HW condition. The former study comprised a clinical sample, with differences in the desire or need for treatment potentially explaining the discrepancy in results. Among healthy participants, placebo effects have been observed to be limited to high-warmth interactions (Gaab et al., 2019), suggesting the effect of augmented interactions may vary dependent on the sample selected.

The current results extend the literature by demonstrating that the nocebo effect can also be modulated via the quality of the patient–practitioner interaction, even when all other aspects of the treatment context are held constant. Of concern, the low-warmth interaction appeared to exacerbate the nocebo effect and block the placebo effect. This has practical implications for healthcare, particularly given the increasing move towards automated and eHealth solutions (e.g., Shalaby et al., 2022). As these solutions tend to lack the subtle non-verbal interpersonal cues that signify warmth and empathy, it will be important for future research to determine the

boundaries under which interpersonal connection facilitates positive, and circumvents negative, health outcomes to optimise patient outcomes.

The nocebo effect expressed by those in the Oxy-LW condition appeared most apparent in the side effects that participants were explicitly warned about. However, there was some evidence for the generalisation of the nocebo effect to a broader range of symptoms at Day 1, where the Oxy-LW group reported more unwarned symptoms than those assigned to the Oxy-HW group. This transient spreading of the nocebo effect has previously been observed in similar experimental paradigms (e.g., Faasse et al., 2018; Faasse, Huynh, et al., 2019). The increased negative health outcomes expressed by those in the Oxy-LW condition differs from previous research (Howe et al., 2017). In this study, an augmented interaction had limited effect on wheal size after the administration of a cream that supposedly increased allergic reaction. A primary difference concerns the method through which negative health outcomes were induced. Howe et al. (2017) compared two different treatments between-subjects, and not systematically to a no treatment control. The negative outcome selected (i.e., increased allergy) is likely to have differed in perceived familiarity, as well as prior experience, when compared to the common side effects selected here. Both familiarity and experience are factors known to modulate the placebo and nocebo effect (e.g., Reicherts et al., 2016; Stewart-Williams & Podd, 2004). Further, it is possible that objective physiological outcomes, such as wheal size, may be less amenable to nocebo suggestion than the self-report outcomes employed in the present study. Self-report and physiological measures have been found to covary in response to nocebo instruction across numerous studies (e.g., Barnes et al., 2021; Reicherts et al., 2016; Russell et al., 2022; Turnwald et al., 2019), including with respect to secondary nocebo effects (e.g., Faasse et al., 2015). However, results have varied with respect to the physiological measure selected (e.g., Bartley et al., 2016), and have not always been consistent (e.g., Mao et al., 2021; Russell et al., 2022). Further research is therefore required that systematically varies the type of nocebo induction (primary vs. secondary) while collecting both self-report and objective outcomes to determine the conditions under which low-warmth interactions are detrimental to different types of health outcome.

Negative health outcomes appeared most readily elicited in the present study. Side effect reporting among the Oxy-LW group was elevated relative to the Oxy-HW group across all days. Furthermore, this effect temporarily spread to symptoms that were not listed as being associated with treatment. This was not the case for health benefits, where two Oxytocin-treated groups only differed significantly on Day 1. Furthermore, relative to NT, the nocebo effect in the Oxy-LW group on Day 1 was associated with a numerically larger effect size (Cohen's $d = 0.65$) than the placebo effect in the Oxy-HW group (Cohen's $d = 0.48$). This is consistent with previous research concerning secondary nocebo effects (Faasse et al., 2018; Faasse, Huynh, et al., 2019) as well as other paradigms (Colagiuri & Quinn, 2018; Colloca et al., 2010). Results from these studies demonstrate that the nocebo effect is both stronger than the placebo effect, and more persistent over time. However, given the reliance on designs that elicit primary nocebo effects (Faasse, Helfer, et al., 2019), the association between the expression of placebo and nocebo effects at the level of the individual is currently unknown.

In the present study, exploratory analysis suggested that positive and negative health outcomes were inversely associated among those receiving sham-treatment. We note that this result is tentative and in need of replication. Specifically, studies that employ factorial designs to systematically cross information about health benefits and side effects are required to determine the direct association between co-occurring placebo and nocebo effects. Previous research, however, has shown that real-world reporting of side effects is associated with perceptions of

reduced treatment efficacy (e.g., Faasse et al., 2009; MacKrill et al., 2019) while experimentally, nocebo effects tend to emerge in studies where there is limited evidence of a placebo effect (e.g., Faasse et al., 2013, 2015, 2016). If such an inverse association exists, then interventions that aim to increase the placebo effect, such as those that tailor positive treatment information, harness learning mechanisms, or present personal recounts from other patients (e.g., Darnall & Colloca, 2018; Enck et al., 2013; Faasse et al., 2017; Kube et al., 2018), and interventions that aim to reduce the nocebo effect, such as those that employ attribute framing, increase choice over treatment, or deploy nocebo education (e.g., Barnes et al., 2019; Barnes, Faasse, & Colagiuri, 2023; Pan et al., 2019; Tang et al., 2022), may be able to counteract the effect of low-warmth interactions.

Expectancies have been implicated as a mechanism underlying the effect of practitioner warmth on the placebo effect in theoretical review (Howe et al., 2019; Wampold, 2021). No evidence for such a claim was found in the current study, with limited difference in positive or negative expectancies in the sham-treated groups. Given that the objective information regarding treatment-related outcomes was identical across the two conditions, this lack of expectancy modulation is perhaps unsurprising. As such, modulation of expectancies might not be necessary to induce a nocebo effect, with other mediatory variables responsible. One such candidate, previously linked to patient–practitioner interaction (Wampold, 2021), concerns affect (Geers et al., 2021). However, if affect is an underlying mechanism, it is likely to be a general one, as we found no difference in treatment-specific worry. Null results may alternatively be explained by the brief single-item measure employed. This methodological choice was intentional to avoid participants guessing the true nature of the study. While similar single-item expectancy measures have been associated with placebo and nocebo effects in similar paradigms (e.g., Barnes, Babbage, et al., 2023; El Brihi et al., 2019; Quinn et al., 2023), a more comprehensive measure, such as the Treatment Expectation Questionnaire may provide greater specificity (Jannis et al., 2020).

Other limitations of the study should be noted. The sample was limited to university students. Further, due to the conditions of the ethical approval granted, those with high levels of psychological distress could not be tested. As such, it is currently unclear how far the observed results generalise. Additional limitations include the use of a high vs. low warmth manipulation and a 30-min consultation time. While the manipulation was consistent with previous research (Gaab et al., 2019; Howe et al., 2017; Verheul et al., 2010), ratings regarding the experimenter's warmth and empathy were above average in the Oxy-HW, and below average in the Oxy-LW, conditions. Comparison to an entirely neutral interaction would be of benefit to future research, especially as this may be the more common form of medical interaction. Similar applies to study timeframe, where shorter durations of 10 min or less may be closer matched to medical consultation times. Further research is therefore required to understand the interaction between consultation time and the effect of warmth and empathy on the placebo and nocebo effect.

In summary, the present study demonstrates that the quality of the patient–practitioner interaction is likely to have a modulatory effect on both positive *and* negative health outcomes. Issues regarding communication are one of the most common types of complaint in the healthcare system, with one comprehensive review finding that shortcomings regarding the patient–practitioner relationship accounted for ~29% of reported grievances (Reader et al., 2014). As such, there appears to be plenty of opportunity for components of the treatment interaction to give rise to suboptimal health outcomes. Given the potential ramifications for

clinical care, future research should strive to understand the mechanisms underlying this effect to most appropriately optimise patient outcomes.

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CONFLICT OF INTEREST STATEMENT

All authors confirm that there are no actual or potential conflicts of interest associated with the publication of the present manuscript.

DATA AVAILABILITY STATEMENT

Data are openly available through OSF https://osf.io/ud4af/?view_only=da8d398905244f849a49b07feb60bc99.

ETHICS STATEMENT

Approval granted by the UNSW Human Research Ethics Committee (HC180036).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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