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The nocebo effect and its consequences for clinical trials and clinical practice

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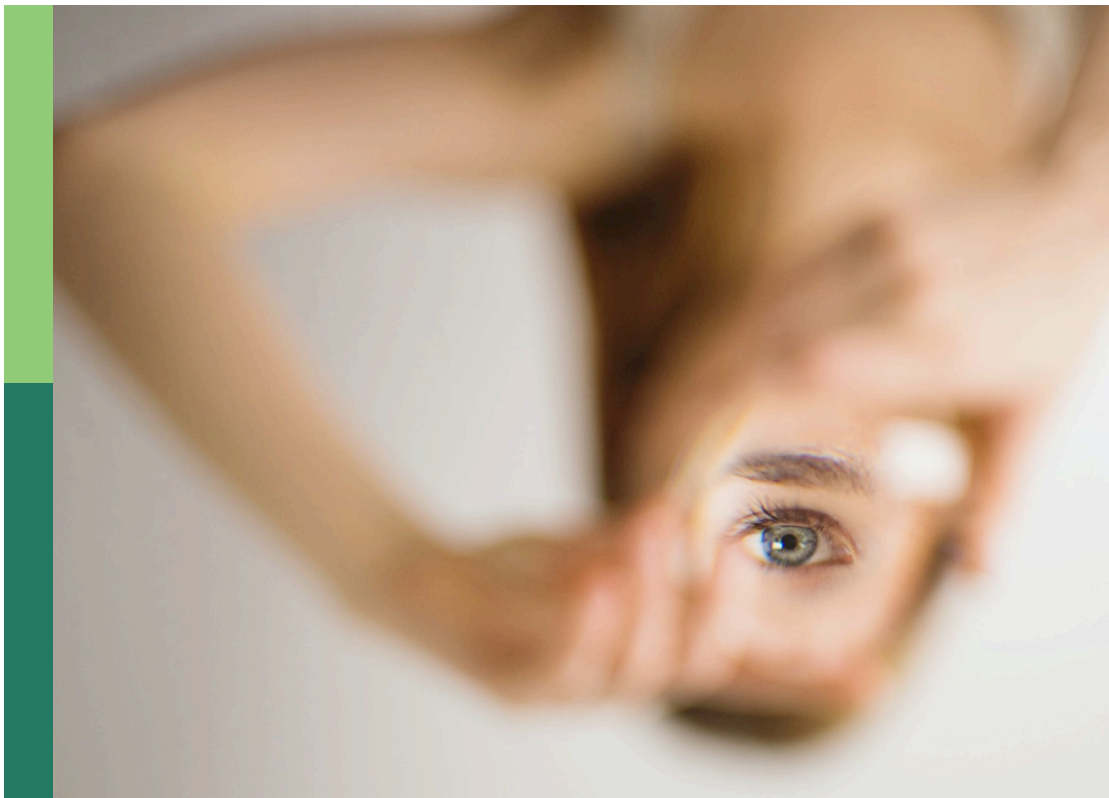

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The nocebo effect and its consequences for clinical trials and clinical practice

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Editorial: The nocebo effect and its consequences for clinical trials and clinical practice

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Editorial on the Research Topic
The nocebo effect and its consequences for clinical trials and clinical practice

Recently, there has been an increase in interest in the nocebo effect, with a subsequent rise in the number of publications on the subject (Sweeney et al., 2022). Our recent Research Topic focuses on the nocebo effect in clinical trials and practice.

The concept of a nocebo effect is not new. It was first used in Kennedy (1961), who wrote "(…) it is somewhat surprising that little attention has been drawn to the existence of the contrary effect [to the placebo]—which I may call the nocebo reaction." Kennedy recognized that the nocebo effect frequently contributes to the observed adverse effects but emphasized that these effects are inherent to the patient rather than the properties of the treatment and should not be confused with true pharmacological effects as this may lead to discarding useful drugs.

The nocebo effect is often called a negative placebo effect, but it is much more than just the flip side of the placebo effect. The nocebo effect causes negative or unfavorable reactions. These effects are not caused by the pharmacological or physical properties of a treatment, but they may resemble the effects of a treatment (Amanzio et al., 2009). Therefore, they are referred to as "non-specific side effects," "adverse reactions of non-specific characters," or "adverse non-drug reactions." The nocebo effect sometimes leads to reduced treatment efficacy. Moreover, the nocebo effect is underpinned by different psycho-biological mechanisms than the placebo effect, further indicating that it is a separate phenomenon (Colloca and Barsky, 2020).

This Research Topic focuses on the nocebo effects in clinical trials and practice.

In a perspective review, Amanzio et al. described psychological distress from negative contextual factors during the pandemic COVID-19 as predisposing factors for the occurrence of the nocebo phenomenon. The media provided dramatic and negative descriptions that increased discomfort and anxiety and decreased response to treatment.

Subsequently, data from randomized controlled trials of SARS-CoV-2 vaccines and from surveys of healthy individuals, health care workers, and patients with chronic pain disorders had confirmed this hypothesis (Amanzio et al., 2022).

A survey of university students and staff showed that a stronger belief of being infected with COVID-19, and potentially over-reporting of symptoms was linked to conscientiousness and health anxiety (Daniali and Flaten).

In their perspective article, Yetman et al. suggested that the nocebo effects evoked by information given by a healthcare professional may be affected by the perceived similarity or dissimilarity between the patient and the treatment provider, for example, different ethnicity. They called for more education of healthcare providers on the subject of nocebo, its links with clinical information about treatment and the potential strategies for management/mitigation.

The need for more extensive education on the subject of nocebo and its management was also emphasized in a survey of physiotherapists (Rossettini, Geri, et al.). The responders were aware of the existence of the nocebo effect, and only 18.6% said that it was "rarely," and 1.4% that it was "never" present in their practice. They recognized the importance of the treatment provider and reported that they actively try to minimize the nocebo effect by managing patients' negative expectations.

A series of experiments by Zech, Scharl, et al., Zech, Schrödinger, Hansen, and Zech, Schrödinger, Seemann, et al. demonstrated that negative information increase anxiety but also have a detrimental effect on functional measures such as muscle strength. People with higher health anxiety, tend to report more negative symptoms and this effect persists even after controlling for generalized anxiety and depression and independently of the potential for a financial reward through litigation (Lecci et al.). Anxiety and fear learning after verbal suggestion are stronger in delusion-prone people (Louzolo et al.).

The effect between the verbal suggestions and the reported negative symptoms, e.g., itch, is mediated by expectations (Meeuwis et al.). Once generated, treatment-related expectations are difficult to modify and may persist—even when proven not to be supported by evidence (Rossettini, Colombi, et al.).

A study in patients under general anesthesia undergoing a surgical procedure has shown that verbal suggestions given to sedated patients may reduce post-operative nausea and vomiting (Nowak et al.).

There are two very positive aspects of this Research Topic that are worth highlighting. Firstly, the included articles demonstrated the ubiquitous and heterogeneous nature of nocebo—not just as a negative response to a placebo but also as adverse effects of treatment and common symptoms misattributed to treatment or disease. For example, the publications were concerned with the nocebo effects in various contexts: from experimental studies with an inert placebo, through side effects of treatment, to COVID-19 symptoms. These studies investigated the associations between nocebo effects and suggestions, expectations, health anxiety, personality factors, and racial/ethnic differences. Secondly, unlike most of the existing literature on the subject, which is dominated by reviews and opinion papers, most of the included studies were primary data-based articles. For example, two-thirds of the articles reported the results of experimental studies, including one, which used neuroimaging to explain further the mechanisms linking fear learning with the nocebo effect. There were also two surveys, one of the healthcare providers and one of the public. There is an urgent need for more good quality mechanistic research studies designed to investigate factors responsible for nocebo effects.

However, this Research Topic also reflects some of the problems with the existing research on the nocebo effects. Firstly, many of the experimental studies reported *post-hoc* and secondary analyses of studies rather than primary analyses—emphasizing the lack of experimental studies in clinical populations specifically designed to investigate the nocebo effect as the primary outcome rather than as an afterthought. Secondly, many purposefully designed studies were often in healthy controls and attempted to generalize findings from healthy controls to clinical populations. Finally, there is a need for a standardized definition of the nocebo effect. Defining the nocebo effect in the context of placebo obscures the fact that it is a separate problem with far more serious consequences for clinical practice and research. Furthermore, referring to the same phenomenon by many different names hinders the development of a standard definition of nocebo and a consolidated analysis of the research on the subject.

In summary, this Research Topic has demonstrated an increasing recognition of the complex nature of nocebo and the current gaps in both clinical practice and research.

Author contributions

KW drafted the manuscript. KW, MA, and LC edited the manuscript and revised it for important intellectual content. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

Amanzio, M., Cipriani, G. E., and Mitsikostas, D. D. (2022). The nocebo phenomenon in the COVID-19 pandemic: a nocebodemic effect. *Expert. Rev. Clin. Pharmacol.* 15, 1377–1382. doi: 10.1080/17512433.2022.2142115

Amanzio, M., Corazzini, L. L., Vase, L., and Benedetti, F. (2009). A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain.* 146, 261–269. doi: 10.1016/j.pain.2009.07.010

Colloca, L., and Barsky, A. J. (2020). Placebo and nocebo effects. *N. Engl. J. Med.* 382, 554–561. doi: 10.1056/NEJMra1907805

Kennedy, W. P. (1961). The nocebo reaction. *Med. World* 95, 203–205.

Sweeney, O. J., Parepalli, S. A., Mirtorabi, N., Loo Yong Kee, K., Feakins, B. G., Aronson, J. K., et al. (2022). Placebo's invisible brother: a restricted scoping review of the biomedical literature on the nocebo effect. *Pain* 163, 2103–2111. doi: 10.1097/j.pain.0000000000002629

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ORIGINAL RESEARCH
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Time-Dependent Negative Effects of Verbal and Non-verbal Suggestions in Surgical Patients—A Study on Arm Muscle Strength

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Introduction: The medical environment is full of suggestions that affect patients and their healing. Most of them inadvertently are negative, thus evoking nocebo effects. Recently, we have reported on the effect of such verbal and non-verbal suggestions as well as alternative formulations on maximal muscular arm strength in healthy volunteers. In the present study, we tested the same suggestions in patients at two time points to evaluate nocebo effects in a clinical situation and the impact of the approaching surgery date.

Methods: In 45 patients, maximal muscular strength during arm abduction was measured by dynamometry of the deltoid muscle group. One test was several days before and the second on the evening before surgery. Baseline values were compared to the performance after exposure to 18 verbal and non-verbal suggestions. The sequence of presumably negative and positive suggestions was randomized for each patient in order to avoid cumulation effects of immediate succession of two negatives. State anxiety was evaluated at both time points, and suggestibility was measured after surgery.

Results: Strong and statistically significant weakening effects were observed with all presumed negative suggestions from daily clinical practice including words of encouragement (91.4% of baseline), evaluation of symptoms (89.0%), announcement of a medical intervention (82.8%), a negative memory (86.5%), expectation of an uncertain future (82.8%), and non-verbal signals (87.7–92.2%). In contrast, alternative formulations did not interfere with muscular performance in most cases. A more pronounced effect was observed in the test repeated closer to the date of surgery, accompanied by a 15% higher anxiety level. The increase in anxiety correlated slightly with stronger weakening effects of suggestions, as did suggestibility.

Conclusions: Negative suggestions cause a decrease in arm muscle strength, i.e., a "weakening" of the patient. This effect is enhanced by an increase in anxiety as the time of treatment, like surgery, approaches. The reaction can be avoided by alternative formulations. These nocebo effects that are objectively measured and quantified by a decrease in arm muscle strength are more pronounced in patients, i.e., in a clinical situation, than in healthy volunteers.

Keywords: nocebo effects, dynamometry, maximal muscle strength, therapeutic communication, suggestions, State-Trait Anxiety Inventory (STAI)

INTRODUCTION

In daily clinical practice, many situations and communications between doctor and patient are suspected to elicit nocebo effects. However, concrete evidence often is limited. One of the reasons for this discrepancy is specificity. For instance, pain is induced or amplified by words about pain, nausea is increased by asking a patient about nausea, and side effects increased, if they were addressed (Lang et al., 2005; Varelmann et al., 2010; Häuser et al., 2012). "Words hurt" describes the observation that pain-related words affect pain (Lang et al., 2005; Corsi et al., 2019). Other effects of the same words may be missed when only pain is evaluated. The demonstration of a nocebo-induced symptom is largely dependent on the symptoms and physiological parameters in focus. These are limited and limiting. Many presumed effects on patient's health, such as on the immune system or on wound healing, are difficult to define and to measure, and immediate changes may not be observable in a timely manner (Wobst, 2007). The longer it takes to get the result of the intervention, the higher the uncertainty in the assessment of its outcome. Moreover, specificity of the nocebo effects hampers comparisons. Is a nocebo effect on nausea stronger or weaker than on pain or on sexual dysfunction?

We recently presented a different approach to studying nocebo effects by measuring changes in maximal arm muscle strength as a general parameter for a "weakening" and as an immediate reaction to a nocebo induction by verbal and non-verbal suggestions (Zech et al., 2019). In a study on healthy volunteers, we demonstrated significant impairment in this one uniform objective physiological parameter after exposure to different suggestions, both verbal and non-verbal, common in routine clinical practice. Each challenge was compared to an alternative wording or visual presentation demonstrating that the nocebo effects can be avoided. Therefore, this technique allows for improvements in medical communication guided by objective measures.

Here we present the results of a subsequent study testing the same clinically relevant suggestions in patients at two time points prior to surgery. We hypothesized that the effects would be more pronounced in the clinical situation, i.e., in patients as compared to healthy volunteers, and that the effects increase as the time of surgery is coming closer.

Abbreviations: ASA score, physical status classification system of the American Society of Anesthesiologists; HGSHS, Harvard Group Scale of Hypnotic Susceptibility; NRS, Numeric Rating Scale (of pain); OR, operating room; STAI-S, State-Trait Anxiety Inventory.

MATERIALS AND METHODS

Design and Participants

This experimental, randomized study was conducted at the University Hospital Regensburg, Germany, after approval by the local ethics committee (EC University of Regensburg, Nr. 13-101-0030). Patients were considered eligible for enrollment if they were between 18 and 70 years of age and were to undergo elective surgery under general anesthesia at the Departments of General Surgery, Neurosurgery, Otorhinolaryngology, or Cranio-Maxillofacial Surgery. Participants had to be native German speakers and with their surgery scheduled no closer than 3 days. Patients with pain [Numeric Rating Scale (NRS) $>$ 5] and patients with pain or impairment at the dominant shoulder, arm, or hand were excluded. Another exclusion criterion was a preexisting severe systemic disease, as classified according to the ASA physical status classification system of the American Society of Anesthesiologists by a score of 3 or more. Fifty patients fulfilling the inclusion criteria were enrolled after written informed consent and without financial compensation. The patient information for the study included the request to abstain from coffee, Coke, or medication for the last 4 h before the test to avoid interference with motor performance.

Measurement of Maximal Muscle Strength Under Suggestion

Maximal muscle strength under suggestions was measured at two time points: days before surgery (T1, minimum 3 days, median at day 3, 53% at day 3, the rest distributed around day 6 before surgery) and in the evening before surgery (T2). Maximal isometric contraction of the deltoid muscle group was tested by dynamometry in a defined upright position with the dominant arm stretched out laterally, as described previously (Zech et al., 2019). A dynamometer (FORCE GAUGE FM200, PCE Deutschland GmbH, Meschede, Germany) with a capacity of 196.0 N and a resolution of 0.05 N was used in the peak hold mode. Results were expressed as a percentage of the baseline value that was determined in 9–11 measurements for each subject. These relative values were used to respect the high variance of muscle strength between individuals. Maximal muscle strength

measured under these conditions is a rather robust physiological parameter with an expected variation of ±6.3% from baseline (Zech et al., 2019). All patients were tested by the same examiner (M.Sch.). Each test session lasted about 40–60 min, which was found feasible even for patients and limited the number of tested suggestions to 18.

Tested Suggestions and Application

The same suggestions out of clinical context were tested as in a previous study on healthy volunteers (Zech et al., 2019). Patients listened to recorded instructions explaining the placement and functionality of the muscle test, whereas suggestions were given verbally, face to face. Visual suggestions, including pictures or video clips, were projected on a notebook. Baseline was established by means of six initial measurements without suggestion followed by 3–5 such baseline measurements interspersed between tests of suggestions, adding up to a total of 9–11. The wording of the instructions prior to suggestions, as well as the type of suggestion itself, can be seen in **Tables 1**, **2**. Nine clinical situations were evaluated. Version A of each suggestion was taken from everyday clinical practice and presumed to be negative and causing a nocebo effect. For each situation, an alternative version B was formulated, considered to be positive and to elicit a neutral or placebo effect. After six baseline measurements, suggestions were tested in a randomized order using the software Randlist (Datinf GmbH, Tübingen). In every patient, any presumed negative version was followed by a presumed neutral or positive version to avoid cumulation effects. Tests were separated by breaks, arithmetical tasks, and repeated determinations of blank values. To prevent incorrect measurements because of exhaustion, an additional break was inserted, whenever a baseline value fell below 90% of the previous, and the test was repeated subsequently.

Possibly accepting a lower clarity, we deliberately refrain from designating the tested suggestions as "placebo" or "nocebo" in order to recognize the fact that we tested actual clinical situations, with "nocebo effect" as possible result, not as the test object.

Measurement of Suggestibility

To explore the patients' suggestibility, a five-item short version of the HGSHS (Riegel et al., 2020) was used. The HGSHS is an objective test method by Shor and Orne from 1962 to determine the suggestibility of a person or groups (Shor, 1962; Bongartz, 1985; Peter et al., 2015). The short version lasts about 25 min. Patients conducted it with an audio file a few days after their operation. Self-evaluation results in a maximum score of 5. Based on the HGSHS-5 score, patients were rated "low suggestible" (LS) with a score of 0 or 1, "medium suggestible" with a score of 2 or 3, and "high suggestible" (HS) with a score of 4 or 5.

Measurement of Anxiety

Anxiety was measured with the state scale of the STAI-S with 20 test items in a German version (Laux et al., 1981). Evaluation took place at the two mentioned time points to draw conclusions about variations of anxiety over time with the approaching operation date. With a range of 20 ("no fear") to 80 ("worst fear") points, the test evaluates the current situational anxiety. Anxiety is usually considered clinically relevant at a score >40, and at >55 rated relevant for psychiatric disorders (Knight et al., 1983; Addolorato et al., 1999). The difference between the scores at T2 and T1 is referred to as ΔSTAI-S and describes the change of anxiety between the two different points in time.

Statistical Analysis

Normal distribution of results was tested with the Kolmogorov–Smirnov test. With non-normal distribution, equality of force regarding baseline, version A and version B, was examined by Friedman two-way analyses of variance by ranks. For significantly different results, the Wilcoxon rank-sum test was used *post hoc* for pairwise testing. An α-error correction has been omitted to avoid the loss of possible correlations (Bender and Lange, 2001). Time-dependent (T1 vs. T2) differences of muscle strength were calculated using the Wilcoxon test, or rather Student's *t*-test for anxiety level. Univariate linear regression analysis was performed for each suggestion. Multivariate linear regression analysis was performed for significant results to investigate influences of various parameters on muscle strength, i.e., gender, age, suggestibility, anxiety, and change in anxiety (ΔSTAI-S). For testing unconnected samples, e.g., the differences in gender or age groups, the Mann–Whitney *U* test was used. Significance level was assumed as $p < 0.05$. Statistical analyses were performed with IBM SPSS Statistics, version 23.

RESULTS

Baseline Characteristics

Out of 50 recruited patients, five were excluded because of missing data (only tested at T1, because patient declined, surgery rescheduled or canceled). Characteristics and baseline scores of the remaining 45 are presented in **Table 3**. Due to the individual physical condition of the patients, baseline muscle strength ranged from 18.8 to 143.7 N. The reproducibility of the neutral values of each individual patient was high (variance 4.80% at T1 and 4.67% at T2). Baseline values did not differ significantly at T1 and T2 ($n = 0.871$). For further analysis, patients were stratified in "younger" (<45 years, $N = 19$) and "older" (≥45 years, $N = 26$) according to the median. Suggestibility was not normally distributed, with 12 patients (27%) scoring LS and 10 patients (22%) HS.

Time Course of Anxiety

Anxiety (STAI-S) raised significantly from a mean of 41.7 ± 10.3 to 47.9 ± 12.7 the night before the operation, with mean ΔSTAI-S of 6.2 ± 8.9 ($p < 0.001$). Neither age nor gender affected the level of state anxiety at T1 and T2; however, both had an impact on the increase in anxiety. In linear regression analyses, age had a significant effect on ΔSTAI-S, with younger patients showing a higher increase in anxiety ($R = -0.385$; $p = 0.012$). ΔSTAI-S was significantly higher in women (9.4 ± 9.2; $p = 0.009$). In multivariate regression analyses, age and sex were responsible for 31.3% of variance of ΔSTAI-S ($R = 0.560$; $p = 0.001$). Suggestibility had no significant influence on anxiety or anxiety increase. With a ΔSTAI-S of 24–27 points, three

TABLE 1 | Wording of the standardized instructions and verbal suggestions.

Category	Scenario	Instructions	Version A	Version B
Baseline		"Now pull upward with maximal power. Now, one–two–three."		
Sentences	Encouragement		You don't need to be afraid. Don't worry.	We are right by your side until you have successfully finished your procedure.
	Checking symptoms	"Again, stand upright, lift your arm. Close your eyes. You are a patient in a hospital. You are faced with the following sentences. Take your time and let it affect you, and then pull upward as hard as you can."	Let us know when you feel pain. Do you feel nauseous?	Let us know if there is anything to make you feel better. We always can do something good for you. Do you feel OK?
	Doctor's introduction and induction of anesthesia		Hallo, I'm Dr. Smith. I'll put you to sleep now. We'll start with the first drug, which will make you feel drowsy or drunk. Now we'll start the second drug, which will burn a little bit. It will be all over soon.	Hallo, I'm Dr. Smith, your anesthetist. I'm here for your comfort and your safety. We are starting with a strong analgesic now that will make everything easier. Now I am giving you the second medication that will induce a restful sleep. I will be right by your side until you have finished your procedure successfully.
	Risk information for informed consent		If you wish, we can place a pain catheter, with the risk of infection, allergic reaction, and damage to blood vessels or nerves.	We have the option of a catheter to prevent discomfort. Even though there is a risk of infection, allergic reaction, or damage to blood vessels or nerves, you will have to take fewer pills, are more mobile, feel and recover better, and perhaps can go home sooner.
Situations	Conditioning	"Again, stand upright, lift your arm. Close your eyes and imagine the situation I suggest to you. When you are there, please nod and then pull upward as hard as you can."	Negative memory: remember a situation, where something went really wrong. Everybody was disappointed in you, including yourself. It was terrible. You were really ashamed.	Positive memory: remember a situation when you were really successful and entirely satisfied with yourself. Everything went so well—totally perfect.
	Condition		Uncertain future: imagine an uncomfortable situation is about to take place: an impending operation, a performance review with your boss, an exam, or a confrontation with your partner. The result is uncertain.	Presence: you are fully in the here and now. You can feel the solid ground under your feet, notice your breath and your upright position while your mind is clear and open.

For dynamometry of maximal arm muscle strength (arm abduction), the patient is standing upright facing the tester, with the right arm stretched to the side and the wrist connected to the dynamometer by a band.

patients experienced a particularly strong reaction. Number of patients having a score >55 increased from five at T1 to 13 at T2. Out of these eight patients, seven were women, and seven were younger than 45 years.

Effects of Sentences

Every version A of a sentence within the clinical context presented to the patients resulted in a highly significant reduction in maximal arm muscle strength at both time points, by 8.6–17.2% at T2 (**Figure 1** and **Table 4**). The presumably negative words of a doctor to introduce himself or herself before narcotic induction showed the greatest effects. Here, 10 patients showed a weakening to below 70% of baseline, with a lowest value of 36%. In contrast, every alternative version B was neutral in effect and did not weaken the patients and did not cause a significant attenuation compared to baseline. For both time points T1 and T2, the difference between versions A and B was highly significant for all tested suggestions. The greatest differences between versions A and B were for checking symptoms (40%) and narcotic induction (60%). For every phrase, neither version

TABLE 2 | Wording of the standardized instructions and pictures of the non-verbal suggestions.

Category	Scenario	Instructions	Version A	Version B
Non-verbal suggestions		"Again, stand upright, lift your arm. You are a patient in a hospital,		
	Induction of anesthesia	– you are in the OR and waiting to get your anesthesia,		
	Transportation to the OR (video)	– you are taken from the ward to the OR in your bed,		
	View out of a patient's window	– you are looking out the window from your room. Let the impression affect you, and then pull upward as hard as you can."		

For dynamometry of maximal arm muscle strength (arm abduction), the patient is standing upright with the right arm stretched to the side and the wrist connected to the dynamometer by a band, with pictures and video clips projected in front. (All six pictures were taken by one of the authors, EH; the upper two pictures show one of the authors, EH; the persons visible in picture "transportation, version B" gave permission).

TABLE 3 | Baseline characteristics of study population (N = 45).

Age (years)	**Mean ± *SD***	**43.8 ± 15.0**
Female sex	*N* (%)	25 (56%)
Suggestibility (HGSHS-5)	Median (IQR)	3 (1–3)
Anxiety (STAI-S)	Mean ± *SD*	41.7 ± 10.3
Days from first test to surgery	Mean ± *SD* (range)	5.7 ± 4.8 (3–25)
Baseline muscle strength (Newton)	Mean ± *SD*	
Days before surgery (T1)		65.0 ± 23.4
Evening before surgery (T2)		64.8 ± 23.5

HGSHS, Harvard Group Scale of Hypnotic Susceptibility; STAI-S, State-Trait Anxiety Inventory; IQR, interquartile range. Baseline muscle strength did not differ significantly at T1 and at T2 (p = 0.871).

A nor version B resulted in a significant difference in muscle strength between T1 and T2. Similar effects were observed after risk information for informed consent in two versions. These data will be given in detail elsewhere.

Effects of Situations

Both the recall of a negative memory (Conditioning version A) and the idea of an uncertain, negative future (Condition version A) resulted in highly significant weakening at both time points (**Figure 2** and **Table 5**). Ten and 12 patients, respectively, showed values under 70% of baseline, with minimum values of 49 and 58%. Suggestion of a positive, encouraging memory (Conditioning version B) was the only one resulting in a strengthening of the patients (T1 p = 0.008, T2 p < 0.001) compared to baseline. In 10 patients, version B of Conditioning raised muscle strength above 115% of baseline, with maximum values of 125%. The orientation to the presence (Condition version B) did not result in significant differences from baseline at any time point. For both situations, the difference between the two versions was highly significant for both times of measurement. Maximum difference was 55% for Conditioning and 45% for Condition. There was no significant difference between T1 and T2 for both versions of the two situations.

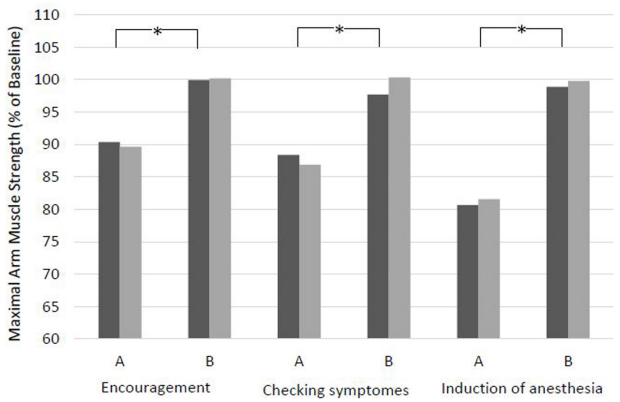

FIGURE 1 | Effects of sentences with clinical context in two versions on maximal arm muscle strength. After baseline dynamometry of arm abduction, verbal suggestions were presented and measurement was repeated. T1, days before surgery; T2, evening before surgery. Mean of maximal arm muscle strength compared to baseline is given. *p < 0.01 (Wilcoxon rank sum test) at T1 and at T2.

Effects of Non-verbal Suggestions

Every version A of a non-verbal suggestion presumed negative resulted in a reduced maximal arm muscle strength (88–92%), with a highly significant difference compared to baseline at both time points. Lowest values were 54, 67, and 54%, respectively (**Figure 3** and **Table 6**). The alternative version B of the non-verbal suggestions was found to be neutral and did not result in a significant attenuation. The suggestion of a patient being transported to the OR in an upright position in his bed even strengthened the patients at T2 (p = 0.019), with a maximum score of 128%. The difference between versions A and B was highly significant for all non-verbal suggestions at both time points, with a maximum of 45% for Induction of anesthesia and View out of a patient's window. There was no significant difference between T1 and T2 for any version of the three suggestions.

TABLE 4 | Effects of sentences within the clinical context on maximal arm muscle strength.

Suggestion	Version A, median (IQR)		Version B, median (IQR)	
	p		*p*	
	T1	T2	T1	T2
Encouragement	92.3 (84.8–97.7) $p < 0.001$	91.4 (84.9–95.0) $p < 0.001$	101.5 (95.0–106.3) $p = 0.604$	100.0 (96.9–103.4) $p = 0.771$
Checking symptoms	91.7 (79.7–96.4) $p < 0.001$	89.0 (82.9–94.4) $p < 0.001$	97.6 (94.1–103.7) $p = 0.099$	100.2 (96.4–104.6) $p = 0.809$
Doctor's introduction and narcotic induction	83.7 (72.4–89.3) $p < 0.001$	82.8 (75.3–90.8) $p < 0.001$	97.8 (96.6–103.9) $p = 0.264$	99.2 (95.8–103.7) $p = 0.578$

After baseline dynamometry of arm abduction, verbal suggestions were presented and measurement was repeated. Median and interquartile range (IQR) of relative values compared to baseline (in %) after suggestion. T1, days before surgery; T2, evening before surgery. p according to Wilcoxon rank sum test relates to the difference to baseline after significance in Friedman test.

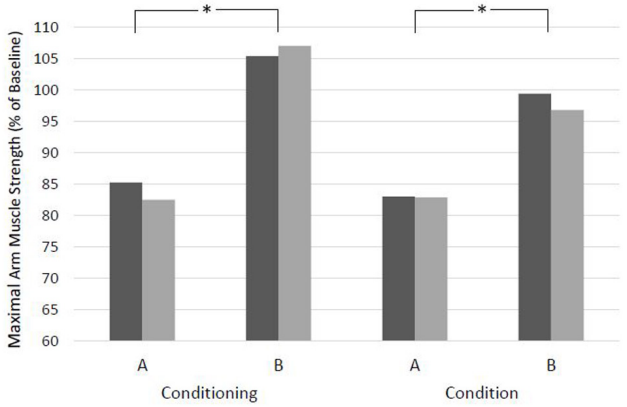

FIGURE 2 | Effects of situations with clinical context in two versions on maximal arm muscle strength. After baseline dynamometry of arm abduction, verbal suggestions were presented and measurement was repeated. T1, days before surgery; T2, evening before surgery. Mean of maximal arm muscle strength compared to baseline is given. *$p < 0.01$ (Wilcoxon rank sum test) at T1 and T2.

Contributing Factors

Anxiety was found to have a marked influence on the effect of suggestions on maximal arm muscle strength. In linear regression analysis of all suggestions with significant weakening effects (respectively, versions A), STAI-S had no influence on the results at T1, whereas at T2, high anxiety scores led to enhanced weakening ($R = -0.126$; $p = 0.012$). Even more significant than anxiety itself was the effect of the increase in anxiety with the surgical date coming closer (ΔSTAI-S). In linear regression analysis, the reduction of muscle strength induced by suggestions both at T1 and T2 increased with higher ΔSTAI-S (T1: $R = -0.212$; $p < 0.001$; T2: $R = 0.243$; $p < 0.001$) (**Figure 4**).

Possible contribution of further factors was analyzed, namely, gender, age, and suggestibility. Linear regression analysis of all suggestions with significant effects showed impact of gender ($R = 0.175$, $p < 0.001$) and suggestibility ($R = -0.172$, $p < 0.001$) for T1. At T2, gender ($R = 0.159$, $p = 0.002$), age ($R = 0.135$, $p = 0.008$), and suggestibility ($R = -0.287$, $p < 0.001$) (**Figure 5**) had slight but significant effects. Especially in younger patients, women and patients with high HGSHS-5 score in negative suggestions resulted in pronounced weakening. In multivariate regression analysis, ΔSTAI-S and HGSHS-5 score were responsible for 12% of arm muscle strength's variance at T2 ($R = -0.345$, $p < 0.001$).

DISCUSSION

Suggestions of clinical everyday routine turned out to elicit nocebo effects in patients by reducing maximal arm muscle strength in a time-dependent manner. Alternative formulations were able to avoid this weakening.

TABLE 5 | Effects of situations on maximal arm muscle strength.

Suggestion	Version A, median (IQR)		Version B, median (IQR)	
	p		*p*	
	T1	T2	T1	T2
Conditioning	87.1 (80.1–93.7) $p < 0.001$	86.5 (75.6–90.8) $p < 0.001$	103.3 (97.4–113.8) $p = 0.008$	106.5 (100.9–114.8) $p < 0.001$
Condition	86.6 (75.7–92.4) $p < 0.001$	82.8 (74.0–88.9) $p < 0.001$	97.6 (92.7–107.0) $p = 0.676$	94.2 (90.8–104.1) $p = 0.052$

After baseline dynamometry of arm abduction, verbal suggestions were presented and measurement as repeated. Median and interquartile range (IQR) of relative values compared to baseline (in %) after suggestion. T1, days before surgery; T2, evening before surgery. p according to Wilcoxon rank sum test relates to the difference to baseline after significance in Friedman test.

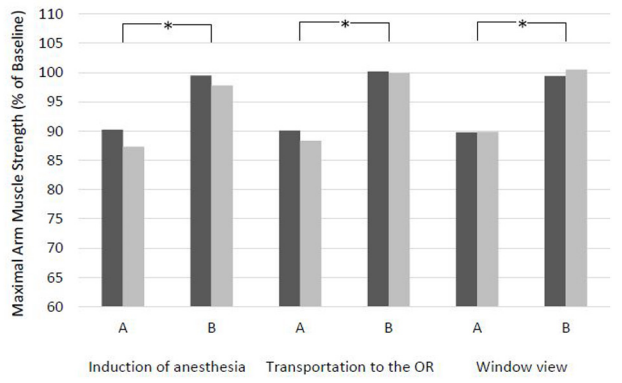

FIGURE 3 | Effects of non-verbal suggestions with clinical context on maximal arm muscle strength. After baseline dynamometry of arm abduction, non-verbal suggestions were presented by projection and measurement was repeated. T1, days before surgery; T2, evening before surgery. Mean of maximal arm muscle strength compared to baseline is given. *$p < 0.01$ (Wilcoxon rank sum test) at T1 and at T2.

Weakening Effect of Clinically Relevant Suggestions

Knowledge and awareness are increasing that the medical setting and the medical communication can exert negative effects on patients, their symptoms, and effectiveness of therapy (Häuser et al., 2012; Benedetti, 2013; Amanzio et al., 2020; Colloca and Barsky, 2020). Improved awareness, knowledge, and understanding of these nocebo effects can help to recognize triggers in the particular clinical field and work situation and thereby aim to avoid them (Hansen and Zech, 2019). For this purpose, it appears especially promising and appropriate to test relevant suggestions from daily clinical routine because they affect a high number of patients every day. In addition, what the patient usually experiences is not a single negative suggestion like in experimental settings, but a plurality of different inputs with complex interactions. Verbal and non-verbal signals interplay and are communicated all along during a hospital stay from admission to examination, from interview to risk assessment and information, from treatment to recovery. Moreover, in the clinical environment, the effects may add up to reach a complex aggregation of symptoms and impairments. While it is easy to demonstrate the effect of the words "pain," "sting," or "burn" on pain and the effect of the question "Do you feel sick?" or the sight of a bloody swab on nausea and vomiting, the combination may exert impairment of more general functions like comfort, anxiety, healing, or immune response (Lang et al., 2005; Wobst, 2007; Varelmann et al., 2010; Häuser et al., 2012). Most of such functions are complex and not easy or fast to measure, such as wound healing or immune surveillance. Moreover, they may be obscured in time by additional factors such as medication, hemodynamic instability, or complications. We therefore aimed to identify a common, albeit direct parameter to measure the immediate effects of different suggestions instead of direct connection between signal and symptom. With maximal arm muscle strength, we found a measurement fulfilling this criterion. In a study on healthy volunteers, we tested nine verbal or visual suggestions from everyday clinical practice in two versions and found a significant reduction in a performance that may be interpreted as marker for a "weakening" of the patient (Zech et al., 2019). Alternative formulations of these suggestions were able to neutralize the observed nocebo effect.

In the present study, testing the same paradigm and the same suggestions in the clinical situation on patients, again significant reductions in muscular function were observed at two different time points. Addressing a bad experience in the past tested a nocebo effect induced by conditioning, i.e., the patient's own experience, and resulted in a significant weakening of arm muscle strength by 13.5% at T2 (**Figure 2** and **Table 5**). This reflects the classical everyday situation of anamnesis that elicits a patient's recall of prior disease and symptoms. Similarly, a condition projecting an uncertain and possibly negative future gives rise to a classical nocebo situation based on expectation. This resulted in the strongest weakening effect observed in this study (−17.2%). Encouraging words like "Don't worry!" did not have the expected effect of a positive expectation and corresponding placebo effect, but instead resulted in significant weakening by 8.6% (**Figure 1** and **Table 4**). An explanation may be the strong negative connotation of the word "worry" or "afraid" that cannot be neutralized by negation (Armstrong and Dienes, 2013; Hansen and Zech, 2019). Like in the proceeding study on volunteers, we also tested the effect of risk information for informed consent in this study and observed a reduction

TABLE 6 | Effects of pictures and video clips within the clinical context on maximal arm muscle strength.

Suggestion	Version A, median (IQR)		Version B, median (IQR)	
	p		*p*	
	T1	T2	T1	T2
Induction of anesthesia	89.9 (84.3–97.2) $p < 0.001$	87.7 (79.7–94.6) $p < 0.001$	101.8 (97.4–106.8) $p = 0.194$	99.8 (94.0–104.2) $p = 0.984$
Transportation to the OR	91.8 (84.1–97.2) $p < 0.001$	92.2 (80.7–96.2) $p < 0.001$	98.7 (93.8–106.2) $p = 0.731$	103.2 (97.6–109.7) $p = 0.019$
View out of a patient's window	88.8 (82.5–93.9) $p < 0.001$	89.2 (82.0–95.3) $p < 0.001$	99.1 (95.3–105.4) $p = 0.842$	100.1 (97.6–105.9) $p = 0.268$

After baseline dynamometry of arm abduction, non-verbal suggestions were presented by projection and measurement was repeated. Median and interquartile range (IQR) of relative values compared to baseline (in %) after suggestion. T1, days before surgery; T2, evening before surgery. p according to Wilcoxon rank sum test relates to the difference to baseline after significance in Friedman test.

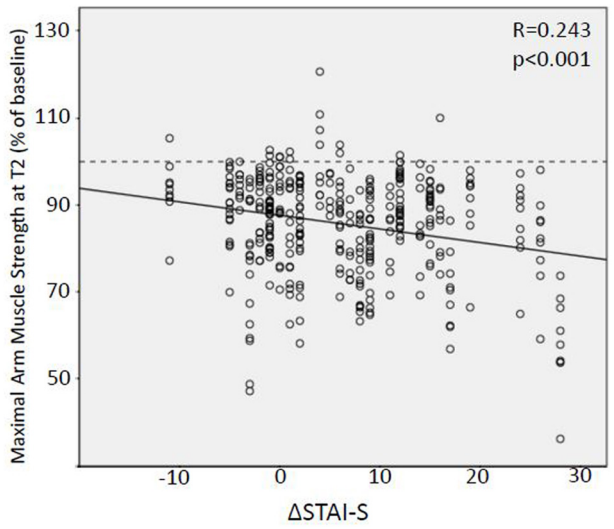

FIGURE 4 | Linear regression analysis of the relation between preoperative anxiety increase and weakening effect of suggestions. Relative values of maximal arm muscle strength after version A of nine suggestions of clinical context tested on the evening before surgery (T2) plotted against the increase in state anxiety score (STAI-S) between several days before and at the evening of the surgery. STAI-S, State-Trait Anxiety Inventory.

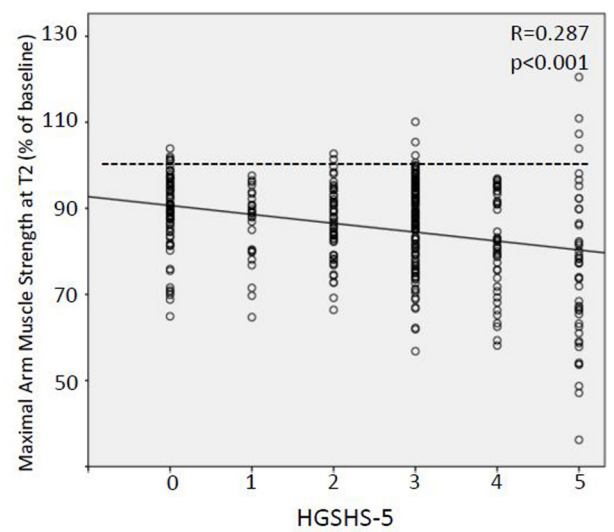

FIGURE 5 | Linear regression analysis of the relation between suggestibility and weakening effect of suggestions. Relative values of maximal arm muscle strength after version A of nine suggestions of clinical context plotted against suggestibility score (HGSHS-5). HGSHS, Harvard Group Scale of Hypnotic Susceptibility.

in muscle strength by 13.6% at T2 (detailed results will be published elsewhere to take into account the wide and special significance of this issue).

During the course of a hospital stay, the patient eventually undergoes a transport for medical treatment. In a strict supine position in his bed, he commonly experiences the view tested by a video clip (**Table 2**) with lamps and ventilation slots at the otherwise sobering blank ceiling. The observed reduction in muscle strength by about 8% by this non-verbal suggestion may appear small but adds to the many other negative influences (**Figure 3** and **Table 6**). After arrival at the OR, the introduction of the doctor and the preparation of anesthetic induction are typical situations. Both the words and the overhead view of the anesthetist's masked face (**Table 2**) induced significant impairment of strength, by 17.2 and 12.3%, respectively (**Figure 1** and **Table 2** or **Figure 3** and **Table 6**). The image of the doctor's face upside down, hidden behind a mask, interferes with biological face recognition (McKone et al., 2012). While tested separately, these verbal and non-verbal suggestions are experienced by the patient simultaneously in the clinical setting. After treatment, the patient is usually asked repeatedly about symptoms. The question about pain and nausea led to a weakening by 11% (**Figure 1** and **Table 4**). Finally, the patient ends up at the ward where he might be confronted with a view on a parking lot or other dreary surrounding (**Table 2**). This visual perception induced a reduction in muscle strength by about 11% (**Figure 3** and **Table 6**). Others have reported delayed recovery from surgery and increased consumption of analgesics (Ulrich, 1984). Our findings are in accordance with observation of non-verbal induction of placebo and nocebo effects (Daniali and Flaten, 2019). This course of a patient subsequently meeting different suggestions is a typical clinical situation in a hospital. In contrast to experimental studies in nocebo research, a patient is not exposed to a single challenge, but to multiple suggestions, possibly leading to summation effects. Therefore, we tested alternative formulations for suggestions all along this pathway of a patient through hospital stay.

The use of one common parameter to test the effects of different negative suggestions allows their direct comparison. The mean reduction in arm muscle strength by all nine negative suggestions tested was 14.4% compared to baseline (at T2). The uniform test parameter could also facilitate an evaluation of cumulative effects of different triggers that are simultaneously applied. Using this approach, further research may clarify whether concurrent nocebo effects are additive, attenuating, or potentiating.

Alternative Formulations Avoid Nocebo Effects

The formulation of alternatives to the tested negative suggestions was successful in avoiding the nocebo effect. Weakening after exposure to version B was in a range of only 0 to −5.8%.

In some cases, even an increase in muscle strength was observed. This strengthening compared to baseline was significant, with a 6.5% increase after recall of a positive past, presumably by a classical conditioning reaction. Overall, for all nine suggestions, significance was not limited to the difference between baseline and version A, but also to the difference between the negative version (A) and the alternative (B). Therefore, version B evidently represents a better alternative for clinical practice. For instance, doctors should be aware of

TABLE 7 | Weakening effect of clinically relevant suggestions in healthy volunteers and patients.

Suggestions	Volunteers	Patients T1	Patients T2
Encouragement			
A	−1.8	−7.7	−8.6
B	−1.5	+1.5	0
Checking symptoms			
A	−8.6	−8.3	−11.0
B	−2.4	−2.4	+0.2
Doctor's introduction and narcotic induction			
A	−6.5	−16.3	−17.2
B	−0.6	−2.2	−0.8
Risk information			
A	−8.2	−12.6	−13.6
B	−3.6	−4.0	−1.2
Conditioning			
A	−10.6	−12.9	−13.5
B	+0.7	+3.3	+6.5
Condition			
A	−6.7	−13.4	−17.2
B	−4.6	−2.4	−5.8
Induction of anesthesia			
A	−9.0	−10.1	−12.3
B	−3.2	+1.8	−0.2
Transportation to the OR			
A	−10.7	−8.2	−7.8
B	−2.2	−1.3	+3.2
View out of a patient's window			
A	−5.9	−11.2	−10.8
B	−3.4	−0.9	+0.1

Relative difference to baseline of maximal arm muscle strength (in %) after verbal and non-verbal suggestions are given. Results of this study on patients at two different time points (T1, days before surgery; T2, evening before surgery) are compared to results of a preceding study on healthy volunteers (Zech et al., 2019).

the weakening effect of asking about the medical history, which is inevitable, but could be neutralized by adding a question like "What was your preferred sport before your illness?" This utilizes the positive conditioned reaction to a positive recall tested with version B and should bring the patient out of the induced weakness. Similar effects are to be expected from shifting the focus to a positive future, "What are your plans after recovery from your surgery?" The effectively better alternative to the question "Do you feel nauseous?" is "Do you feel ok?" The non-verbal suggestions of the anesthetist face-to-face and a poster at the ceiling, the upright position during transportation in bed, and a view in the nature from the window actually are able to avoid the weakening effect of the original clinical situation. By the use of the uniform measurement parameter "maximal arm muscle strength," not only can the alternative formulation be identified as qualitatively "neutral" or "not weakening" but also the effect can be quantified. Thereby, various alternatives could be tested and an optimal one found. Based on this method and principle, communication can be improved.

Comparison to Results of Healthy Volunteers

Compared to the results of the preceding study on healthy volunteers, the effects of negative suggestions were more pronounced in patients (**Table 7**). The only exception was the transport in supine position that affected volunteers more than patients. A possible explanation for this difference is that counteractively to the terrifying view of the ceiling, the eagerly awaited treatment, namely, surgery, finally gets closer. The stronger reaction of the patients may be caused by the closer reality of the situation, especially on the evening before surgery. The reduction in muscle strength after the encouraging words "You don't need to be afraid. Don't worry." was not only stronger, but reached significance. This draws attention to the possibility that many effects observed in experimental placebo/nocebo research might be much more pronounced in clinical situations.

Factors Contributing to Weakening Nocebo Effects

Although not reaching statistical significance, there was a trend to a more extended negative reaction the evening before surgery (T2) compared to that several days before surgery (T1). In all six verbal suggestions and in one of the three non-verbal suggestions, i.e., in seven out of nine tests, muscular performance was lower at T2 (**Table 7**). A possible explanation for the deviant conduct of the two visual triggers is given above. To our knowledge, this is the first time that a time dependency of nocebo effects has been demonstrated, namely, an impact of the time to a medical intervention. In contrast to healthy volunteers in experimental placebo research, in the clinical situation, patients experience a change of the situation with time. Furthermore, the observed increase in the nocebo effect with the date of surgery approaching is connected to the increase in state anxiety level. Thus, distance to treatment and anxiety are to be considered part of the context sensitivity of nocebo effects. At both preoperative time points, patients showed state anxiety scores exceeding 40, which are considered clinically relevant (Knight et al., 1983; Addolorato et al., 1999). Between days before surgery and the last evening, state anxiety levels increased significantly by 15%, i.e., STAI-S at T2 was 114.8% of the T1 value. Moreover, this increase in anxiety correlated with an increased extent of the induced nocebo effect (**Figure 4**). Preoperative anxiety is well known (Millar et al., 1995), and an increase during the hospital stay may be expected. Furthermore, a negative correlation of placebo effects and positive correlation of nocebo effects with anxiety level have been described (Corsi and Colloca, 2017). Surprisingly, this study produced evidence that nocebo effects in the clinical context are time sensitive and increase with the extent of an increase in anxiety. While age and gender had no significant effect on the preoperative level of anxiety, both factors proved to be significant independent predictors of the increase in anxiety with the surgical appointment coming closer. While statistically significant but low in extent, the correlation between anxiety level or increase in anxiety, respectively, and reduction in muscle strength by negative suggestions is of clinical relevance. It highlights the time

close to a medical intervention as critical with regard to nocebo effects. The results identify young women especially prone to the negative influences of the clinical environment. Fortunately, they respond to alternative formulations to the same extent and thus also can be protected from negative suggestions and nocebo effects. Since pain is a confounder of motor performance (Tucker and Hodges, 2009), we had excluded patients with pain from the study.

Finally, in this study, suggestibility as tested with the HGSHS had an impact on the extent of the nocebo effect (**Figure 5**). While this correlation is not always observed in placebo research, it may reflect the inclusion of a number of suggestions tested where factors other than conditioning and expectation play a role (Corsi and Colloca, 2017; Hansen and Zech, 2019). The very low regression coefficient confirms the observation that suggestibility is not a major determinant in clinical situations (Montgomery et al., 2011), and that suggestions have impact on all patients, not merely on highly suggestible subjects. A smaller but significant effect of sex and age was observed in this study. While the role of sex on placebo and nocebo effects is being debated (Enck and Klosterhalfen, 2019), we found females more prone to react to negative suggestions both directly and indirectly by increasing in anxiety with the surgery date coming closer. Placebo effects seem to be stronger in children but seem not to differ with age in adults (Wrobel et al., 2016). We found more pronounced nocebo effects in younger patients again both directly and indirectly *via* a higher rate of preoperative increase in anxiety. In conclusion, our results confirm the influence of psychological factors on nocebo responses apart from conditioning and expectation (Corsi and Colloca, 2017). The observed small correlations are a strong argument for a high number of contributing factors.

Limitations of the Study

A limitation of the study is the incomplete randomization, i.e., the sequence of suggestions was randomized for each patient but adhered to an alternation of negative and positive suggestions. This was because known cumulation effects were to be avoided.

The wide range for T1 (3–10 days before surgery, with two outliers at day 25) could have influenced the test results. Anxiety is a possible factor affecting nocebo effects and is expected to increase with the date of surgery approaching, where the exact course of preoperative anxiety increase remains to be evaluated. However, the strongest increase can be assumed close to the date of surgery, i.e., between day 3 and the evening before surgery, while the difference in anxiety level between days 3 and 9 should be rather low.

The mechanism of the observed effects after negative suggestions remains unclear at both the physiological and psychological level. From a psychological point of view, language-induced motor activity, arousal and affirmation effects, modulation of motor cortex or cortico-spinal excitability, and many more may play a role (Li et al., 2004; Pulvermuller et al., 2005). Considering physiological mechanisms, many are proposed according to the many fields of research like ethology, behavioral and communication research, psychosomatics, hypnosis, and placebo research. Even the latter describes various factors possibly involved like hormones, immune mediators, endogenous opioids, dopamine and other neurotransmitters, and local changes in brain metabolism, microcirculation, and neural functions (Benedetti et al., 2003; Finniss et al., 2010; Benedetti and Amanzio, 2013). Different mechanisms have been described for expectation- or conditioning-induced placebo effects (Amanzio and Benedetti, 1999), like different neurotransmitter involvement (Scott et al., 2008), and the activation of different brain areas (Freeman et al., 2015). A number of excellent and basic studies have evaluated placebo and nocebo effects on motor performance and possible mechanisms (Carlino et al., 2014; Fiorio, 2018; Corsi et al., 2019). In the present study, a motor performance was only used as a marker to assess and quantitate negative or positive effects of clinical suggestions. It is noteworthy that in contrast to the mentioned studies, the tested suggestions here did not contain or relate to words like muscular, power, strength, motion, fatigue and activation, or motor imagery. And still they had profound effects on maximal arm muscle strength.

Similarly, various and different mechanisms are discussed for the effects of suggestions in hypnosis (Barber, 1965; Faymonville et al., 2000; De Benedittis, 2015; Jensen et al., 2015).

It remains unclear, and various factors have to be considered to explain, why the positively formulated alternative suggestions (version B) in most cases did not lead to an increase in muscular strength, as would be expected from their intended placebo effects. This may be due to the fact that although using positive formulations, the surrounding and situation remain a clinical one and thus cannot be positive indeed. Another possible interpretation of the results is a lack of nocebo effects in version B instead of a failed placebo effect. Altogether, this confirms our approach not to label version A of the tested suggestions from the beginning (in section "Materials and Methods," Tables, and Figures) as "nocebo" and version B as "placebo" to leave these categories for description of the results, not of the study object.

Clinical Implications

The clinical relevance of this study results from three aspects. First, the reported impairment of muscular strength in surgical patients by common suggestions in medical situations is highly disadvantageous for postoperative mobilization, patient's safety, and respiration. Especially nurses and physiotherapists may be alarmed by this side effect of careless communication and stimulated to join efforts for positive communication. Second, the tested suggestions were not designed for experiments but rather were taken from everyday clinical practice in common and frequent medical situations. Version B of the tested suggestions can be taken as examples to avoid these negative impacts. Third, the results reveal the opportunity for evidence-guided improvement of therapist–patient communication. Doctors, nurses, and other health care providers, all can benefit from such an approach that beyond personal impressions and subjective valuation provides objective, quantitative, and verifiable data on nocebo effects and its prevention.

The described method of using a single outcome parameter, namely, maximal arm muscle strength, for tests of different verbal and non-verbal suggestions facilitates a direct comparison of effects, development and validation of alternative formulations, and study of compound suggestions. Only with a common outcome parameter for different suggestions can the comprehensive sum effect of all be evaluated. Thus, the described test system could be used for complex interactions of suggestions common in medical situations. Moreover, the tested and observed muscular weakening could be a marker for a more general "weakening effect" of nocebo suggestions and a common, clinically relevant "weakening" of patients in the medical setting (Hansen and Zech, 2019; Zech et al., 2019). It may correspond to and reflect weakening of complex basic physiological functions like homeostasis, recovery, or immune surveillance that are not easy or fast to measure and quantify. Therefore, this parameter could possibly address functional aspects more relevant for holistic medicine than specific tested symptoms and individual test variables. Our results show that the word "pain" or "nauseous" besides provoking and intensifying pain or nausea, respectively, can reduce muscle strength. We hypothesize a general "weakening" of patients by such nocebo effects.

CONCLUSION

Nocebo effects are even stronger in the clinical situation of patients than in healthy volunteers in experimental settings. In the medical surrounding, much of the common everyday communication as well as many signals actually comprise negative suggestions that can be identified and quantitated by measuring changes in a uniform physiological function like maximal muscle strength. The latter provides fast and reproducible results for comparison of individual persons, of groups, and of different suggestions originating from the medical environment. Furthermore, the test system can be used to develop and verify better alternatives that avoid negative effects on patients' health and treatment. This provides a means for improvement of doctor–patient communication in clinical practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission an der Universität Regensburg, # 13-101-0030, ethikkommission@ukr.de. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EH contributed to the study plan and design, supervision, literature search, data analysis, preparation of figures, tables, manuscript, and correction of the manuscript. NZ and MSe contributed to the study design, application for ethic committee approval, literature search, participant recruitment, data collection and analysis, and preparation of the manuscript. MSc contributed to the participant recruitment and data collection and analysis. FZ contributed to the statistical analysis and preparation of figures. TS contributed to the literature search and preparation of the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

Addolorato, G., Ancona, C., Capristo, E., Graziosetto, R., Di Rienzo, L., Maurizi, M., et al. (1999). State and trait anxiety in women affected by allergic and vasomotor rhinitis. *J. Psychosom. Res.* 46, 283–289. doi: 10.1016/s0022-3999(98)00109-3

Amanzio, M., and Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. *J. Neurosci.* 19, 484–494. doi: 10.1523/jneurosci.19-01-00484.1999

Amanzio, M., Vase, L., and Mitsikostas, D. D. (2020). Editorial: nocebo effects and their influence on clinical trials and practice: modulating factors in healthy and pathological conditions. *Front. Pharmacol.* 11:100. doi: 10.3389/fphar.2020.00100

Armstrong, A. M., and Dienes, Z. (2013). Subliminal understanding of negation: unconscious control by subliminal processing of word pairs. *Conscious. Cogn.* 22, 1022–1040. doi: 10.1016/j.concog.2013.06.010

Barber, T. X. (1965). Physiological Effects of "Hypnotic Suggestions": a critical review of recent research; (1960-64). *Psychol. Bull.* 63, 201–222. doi: 10.1037/h0021931

Bender, R., and Lange, S. (2001). Adjusting for multiple testing–when and how? *J. Clin. Epidemiol.* 54, 343–349. doi: 10.1016/s0895-4356(00)00314-0

Benedetti, F. (2013). Placebo and the new physiology of the doctor-patient relationship. *Physiol. Rev.* 93, 1207–1246. doi: 10.1152/physrev.00043.2012

Benedetti, F., and Amanzio, M. (2013). Mechanisms of the placebo response. *Pulm. Pharmacol. Ther.* 26, 520–523. doi: 10.1016/j.pupt.2013.01.006

Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., and Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J. Neurosci.* 23, 4315–4323. doi: 10.1523/jneurosci.23-10-04315.2003

Bongartz, W. (1985). German norms for the harvard group scale of hypnotic susceptibility, form a. *Int. J. Clin. Exp. Hypn.* 33, 131–139. doi: 10.1080/00207148508406643

Carlino, E., Piedimonte, A., and Frisaldi, E. (2014). The effects of placebos and nocebos on physical performance. *Handb. Exp. Pharmacol.* 225, 149–157. doi: 10.1007/978-3-662-44519-8_9

Colloca, L., and Barsky, A. J. (2020). Placebo and Nocebo Effects. *N. Engl. J. Med.* 382, 554–561.

Corsi, N., and Colloca, L. (2017). Placebo and nocebo effects: the advantage of measuring expectations and psychological factors. *Front. Psychol.* 8:308. doi: 10.3389/fpsyg.2017.00308

Corsi, N., Emadi Andani, M., Sometti, D., Tinazzi, M., and Fiorio, M. (2019). When words hurt: verbal suggestion prevails over conditioning in inducing the motor nocebo effect. *Eur. J. Neurosci.* 50, 3311–3326. doi: 10.1111/ejn.14489

Daniali, H., and Flaten, M. A. (2019). A qualitative systematic review of effects of provider characteristics and nonverbal behavior on pain, and placebo and nocebo effects. *Front. Psychiatry* 10:242. doi: 10.3389/fpsyt.2019.00242

De Benedittis, G. (2015). Neural mechanisms of hypnosis and meditation. *J. Physiol. Paris* 109, 152–164. doi: 10.1016/j.jphysparis.2015.11.001

Enck, P., and Klosterhalfen, S. (2019). Does sex/gender play a role in placebo and nocebo effects? Conflicting evidence from clinical trials and experimental studies. *Front. Neurosci.* 13:160. doi: 10.3389/fnins.2019.00160

Faymonville, M. E., Laureys, S., Degueldre, C., DelFiore, G., Luxen, A., Franck, G., et al. (2000). Neural mechanisms of antinociceptive effects of hypnosis. *Anesthesiology* 92, 1257–1267. doi: 10.1097/00000542-200005000-00013

Finniss, D. G., Kaptchuk, T. J., Miller, F., and Benedetti, F. (2010). Biological, clinical, and ethical advances of placebo effects. *Lancet* 375, 686–695. doi: 10.1016/s0140-6736(09)61706-2

Fiorio, M. (2018). Modulation of the motor system by placebo and nocebo effects. *Int. Rev. Neurobiol.* 139, 297–319. doi: 10.1016/bs.irn.2018.07.012

Freeman, S., Yu, R., Egorova, N., Chen, X., Kirsch, I., Claggett, B., et al. (2015). Distinct neural representations of placebo and nocebo effects. *Neuroimage* 112, 197–207. doi: 10.1016/j.neuroimage.2015.03.015

Hansen, E., and Zech, N. (2019). Nocebo effects and negative suggestions in daily clinical practice – forms, impact and approaches to avoid them. *Front. Pharmacol.* 10:77. doi: 10.3389/fphar.2019.00077

Häuser, W., Hansen, E., and Enck, P. (2012). Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch. Arztebl. Int.* 109, 459–465.

Jensen, M. P., Adachi, T., Tomé-Pires, C., Lee, J., Osman, Z. J., and Miró, J. (2015). Mechanisms of hypnosis: toward the development of a biopsychosocial model. *Int. J. Clin. Exp. Hypn.* 63, 34–75. doi: 10.1080/00207144.2014.961875

Knight, R. G., Waal-Manning, H. J., and Spears, G. F. (1983). Some norms and reliability data for the state-trait anxiety inventory and the zung self-rating depression scale. *Br. J. Clin. Psychol.* 22, 245–249. doi: 10.1111/j.2044-8260.1983.tb00610.x

Lang, E. V., Hatsiopoulou, O., Koch, T., Berbaum, K., Lutgendorf, S., Kettenmann, E., et al. (2005). Can words hurt? Patient-provider interactions during invasive procedures. *Pain* 114, 303–309. doi: 10.1016/j.pain.2004.12.028

Laux, L., Glanzmann, P., Schaffner, P., and Spielberger, C. (1981). *Das State-Trait Angstinventar. Theoretische Grundlagen und Handanweisung*. Weinheim: Beltz Test GmbH.

Li, S., Kamper, D. G., Stevens, J. A., and Rymer, W. Z. (2004). The effect of motor imagery on spinal segmental excitability. *J. Neurosci.* 24, 9674–9680. doi: 10.1523/jneurosci.2781-04.2004

McKone, E., Crookes, K., Jeffery, L., and Dilks, D. D. (2012). A critical review of the development of face recognition: experience is less important than previously believed. *Cogn. Neuropsychol.* 29, 174–212. doi: 10.1080/02643294.2012.660138

Millar, K., Jelicic, M., Bonke, B., and Asbury, A. J. (1995). Assessment of preoperative anxiety: comparison of measures in patients awaiting surgery for breast cancer. *Br. J. Anaesth.* 74, 180–183. doi: 10.1093/bja/74.2.180

Montgomery, G. H., Schnur, J. B., and David, D. (2011). The impact of hypnotic suggestibility in clinical care settings. *Int. J. Clin. Exp.* 59, 294–309. doi: 10.1080/00207144.2011.570656

Peter, B., Geiger, E., Prade, T., Vogel, S., and Piesbergen, C. (2015). Norms of german adolescents for the harvard group scale of hypnotic susceptibility, form A. *Int. J. Clin. Exp. Hypn.* 63, 92–109. doi: 10.1080/00207144.2014.961877

Pulvermuller, F., Hauk, O., Nikulin, V. V., and Ilmoniemi, R. J. (2005). Functional links between motor and language systems. *Eur. J. Neurosci.* 21, 793–797. doi: 10.1111/j.1460-9568.2005.03900.x

Riegel, B., Peter, B., Hansen, E., Zech, N., Bongartz, W., Eck, S., et al. (2020). Efficient measurement of hypnotizability: psychometric characteristics and German normativ data of an 11-item version of the Harvard Group Scale of Hypnotic Susceptibility (HGSHS-A) and proposal of a 5-Item short-version. *Int. J. Clin. Exp. Hypnosis.* (in press).

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., and Zubieta, J. K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch. Gen. Psychiatry* 65, 220–231.

Shor, R. E. (1962). Three dimensions of hypnotic depth. *Int. J. Clin. Exp. Hypn.* 10, 23–38. doi: 10.1080/00207146208415862

Tucker, K. J., and Hodges, P. W. (2009). Motoneurone recruitment is altered with pain induced in non-muscular tissue. *Pain* 141, 151–155. doi: 10.1016/j.pain.2008.10.029

Ulrich, R. S. (1984). View through a window may influence recovery from surgery. *Science* 224, 420–421. doi: 10.1126/science.6143402

Varelmann, D., Pancaro, C., Cappiello, E. C., and Camann, W. R. (2010). Noceboinduced hyperalgesia during local anesthetic injection. *Anesth. Analg.* 110, 868–870. doi: 10.1213/ane.0b013e3181cc5727

Wobst, A. H. (2007). Hypnosis and surgery: past, present, and future. *Anesth. Analg.* 104, 1199–1208. doi: 10.1213/01.ane.0000260616.49050.6d

Wrobel, N., Fadai, T., Brassen, S., and Bingel, U. (2016). Preserved capacity for placebo analgesia in the elderly. *J. Pain* 17, 1318–1324. doi: 10.1016/j.jpain.2016.08.012

Zech, N., Seemann, M., Grzesiek, M., Breu, A., Seyfried, T. F., and Hansen, E. (2019). Nocebo effects on muscular performance – an experimental study about clinical situations. *Front. Pharmacol.* 10:219. doi: 10.3389/fphar.2019.00219

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What Physiotherapists Specialized in Orthopedic Manual Therapy Know About Nocebo-Related Effects and Contextual Factors: Findings From a National Survey

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Objective: The aim of this study was to investigate the knowledge of orthopedic manual therapists (OMTs) regarding context factors (CFs) capable of triggering nocebo effects during the treatment and how this knowledge is related to their socio-demographic features.

Design: A cross-sectional online survey.

Setting: National.

Main Outcome Measures: A 20 items questionnaire composed by open-ended and closed single-choice questions was administered to explore: (a) socio-demographic variables (10 questions); (b) the relation between different CFs and nocebo-related effects (2 questions); and (c) the knowledge of participants about nocebo-related effects and how they managed them in the clinical practice (8 questions).

Participants: 1288 OMTs were recruited from the database of the Master in Rehabilitation of Musculoskeletal Disorders (MRDM) of the University of Genova from March to May 2019. Inclusion criteria were: (a) to possess a valid email account; (b) to understand and use as a native language the Italian; (c) to be graduated as OMTs; and (d) to be employed as physiotherapists specialized-OMTs during the survey.

Results: 791 responses were received (61.4%); 473 of them were male (59.8%), with an average age of 31.0 ± 7.1 years. OMTs defined nocebo-related effects as the psychosocial context effects around therapy and patient with specific biological bases (72.2%). OMTs know that their clinical practice is pervaded by nocebo-related effects

(42.5%), triggered by CFs. Participants communicated nocebo-related effects balancing the positive features of the therapy with the negative ones (50.9%), during the decision of the therapeutic plan (42.7%). They reported associative learning as the main mechanism involved in nocebo-related effects (28.8%). OMTs taught and trained patient's strategies to manage nocebo-related effects (39.6%) through an evaluation and correction of patient's anxieties, doubts and expectations (37.7%). OMTs most frequently considered themselves to have a "medium" education about nocebo-related effects (48.2%) and that their management should be taught during bachelor (78.6%).

Conclusion: OMTs believed that nocebo-related effects were present in their clinical practice and that they can be triggered by CFs.

Keywords: nocebo effect, expectation, physiotherapy (MeSH), contextual factors, pain, placebo effects, conditioning, survey

INTRODUCTION

Placebo and nocebo-related effects are emerging phenomena of interest among researchers, scholars and clinicians in orthopedic manual therapy (Rossettini et al., 2018a). They represent the result of the positive (placebo) or negative (nocebo) use of contextual factors (CFs) during the administration of a therapy (Benedetti, 2013). Contextual factors include physical, psychological and social elements involved in the clinical encounter between the patient and the physiotherapist (Di Blasi et al., 2001) such as: (a) physiotherapist's features (e.g., expertise, reputation); (b) patient's features (e.g., expectations, previous experience); (c) patient-physiotherapist relationship (e.g., verbal communication, posture); (d) treatment features (e.g., overt therapy, marketing); and (e) healthcare setting features (e.g., environment, architecture) (Testa and Rossettini, 2016). In the clinical scenario, the interaction between the specific component of a therapy and the surrounding CFs influences the subjective therapeutic experience (e.g., pain, fear, anxiety) triggering placebo or nocebo-related effects (Carlino et al., 2014): specifically, positive CFs can ameliorate the clinical outcomes, while negative CFs can amplify patients' symptoms preventing their recovery (Wager and Atlas, 2015).

While placebo-related effects have been widely inquired in orthopedic manual therapy, nocebo-related effects have been underlined as a new research field that should be investigated for several reasons (Rossettini et al., 2020). First, psychobiological explanations have been documented as the underlying mechanisms of action (e.g., genetic, expectation, learning) of CFs and evoked nocebo-related effects (Colloca and Barsky, 2020) capable to exacerbate the perception of a symptom affecting also the therapeutic relationship (Hansen and Zech, 2019). Second, specific neurotransmitters (e.g., cholecystokinin and cyclooxygenase-prostaglandins activation; opioid and dopamine deactivation) have been indicated as mediators involved in CFs and triggered nocebo-related effects (Frisaldi et al., 2015). Part of these processes are also the activation of neural pathways (e.g., anterior cingulate cortex, dorsolateral prefrontal cortex, periaqueductal gray, and spinal cord) (Darnall and Colloca, 2018). Third, the negative clinical impact of CFs (e.g., patients' expectations, beliefs) and induced nocebo-related effects on therapeutic outcomes has been highlighted at multiple healthcare levels, resulting in increased costs, work absenteeism and medicalization (Hallegraeff et al., 2012; Trinderup et al., 2018).

At the international level, an expert panel has recently identified as a research priority the knowledge nocebo-related effects and CFs among clinicians (Evers et al., 2018). To date, one qualitative study has investigated nocebo-related effects during the physician-patient communication in Pakistan (Ashraf and Saaiq, 2014); while two Italian surveys have explored the knowledge of CFs and placebo-related effects including physiotherapists specialized in orthopedic manual therapy and nurses (Rossettini et al., 2018b; Palese et al., 2019), thus leaving still unexplored this research field. In particular, OMTs represent an ideal group of clinicians to be investigated because their practice is intrinsically pervaded by CFs: during the administration of each therapy (e.g., joint mobilization, massage, exercise) they use CFs (e.g., verbal and non-verbal communication) influencing the outcome (Rossettini et al., 2018a).

Thus, the aim of this study was to investigate the knowledge of orthopedic manual therapists (OMTs) regarding context factors (CFs) capable of triggering nocebo effects during the treatment and how this knowledge is related to their socio-demographic features.

MATERIALS AND METHODS

Design

This quantitative cross-sectional survey was conducted according to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) guidelines (Eysenbach, 2004) and the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE; Von Elm et al., 2007), from March to May 2019. All the procedures were approved by the Liguria Clinical Experimental Ethics Committee (P.R.236REG2016, accepted on 19/07/2016).

Participants and Settings

Participants were Italian physiotherapists specialized and graduated as OMTs (Rossettini et al., 2018b). Our sample of OMTs was recruited from the database of the Master in Rehabilitation of Musculoskeletal Disorders of Genova University (n = 1288). This higher educational program represents approximately the totality of the Italian physiotherapists specialized as OMT. Furthermore, it is the oldest academic post-graduate program in manual therapy in Italy (Bologna Working Group, 2005) based upon the standards established by the International Federation of Orthopedic Manipulative Physical Therapists (IFOMPT, 2016).

Inclusion criteria were: (a) to possess a valid email account; (b) to understand and use as a native language the Italian; (c) to be graduated as OMTs; and (d) to be employed as physiotherapists specialized-OMTs during the survey. Exclusion criteria were: (a) to possess an invalid email account; (b) to use and understand different languages than Italian; (c) to be trained as OMT student during the survey; and (d) to be employed as non-specialized physiotherapists.

From the total population target of 1288 OMTs, approximately 516–773 responses were expected, based on previous studies placebo-related effects and CFs in which the response rate was from 30 to 60% (Rossettini et al., 2018b; Palese et al., 2019). The application of these predicted values to the formula for estimating the sample size using a single population proportion with the population proportion set at 50.0% produced a two−sided 95.0% confidence level of 2.2–3.3% points of the true value and a relative standard error ranging from 2.3 to 3.4 (Australian Bureau of Statistics, 2020).

Questionnaire Development and Pre-testing

The questionnaire adopted in this study was adapted from a previous survey published on CFs and placebo-related effects among OMTs (Rossettini et al., 2018b). Using distinct and iterative steps, a panel of six experts in nocebo-related effects, CFs and survey design: (a) modified the meaning of items from a positive (=placebo) to a negative (=nocebo) meaning; (b) evaluated items for face and content validity of the new version of the questionnaire; and (c) valued the content accuracy, survey structure and word clarity (De Leeuw et al., 2008). In a first phase each member of the panel worked independently; in a second phase they discussed and confronted using a thinking aloud strategy. The final survey tool was composed by 20 items available in Italian (**Supplementary File 1**) and English (**Supplementary File 2**).

The survey was piloted as a self-administered questionnaire in a convenient sample of 15 OMTs (North, n = 5; Center, n = 5; South of Italy, n = 5), not included in final sample of the study. To investigate potential filled in issues (e.g., vague questions, unclear words), a telephone debriefing session (De Leeuw et al., 2008) among the involved 15 OMTs was performed. The outcome of the pilot study was positive: the sample referred that the questions did not need further explanation, and the words were simple and easy to understand: thus, no changes to the items were applied.

Questionnaire Implementation

The self-administered questionnaire was divided into three sections (A, B, and C). In the first section (A) the socio-demographic variables were collected using two open-ended questions (age, years of clinical practice) and eight closed single-choice questions (gender, Italian region, workplace, type of work, setting, profile of patients cared for, field of work, hours of work per week).

The section (B) included variables exploring the relation between different CFs and nocebo-related effects by using two closed single-choice questions. Specifically, the questions investigated the frequency of nocebo-related effects in the OMTs' experience (answers from "never" to "always") and the beliefs about the weight of specific CFs (Likert from 0 "not at all" to 4 "a lot of") in triggering nocebo-related effects.

The last section (C) included variables exploring the knowledge of participants about nocebo-related effects and how they managed them in the clinical practice. In particular, eight closed single-choice questions investigated: (a) the communication (n = 2); (b) the mechanisms of action (n = 1); (c) the management issues (n = 2); (d) the education (n = 2); and (e) the definition (n = 1) of CFs and nocebo-related effects.

Data Collection Procedure

The SurveyMonkey (Survey-Monkey, Palo Alto, California)[1] was selected as an online survey tool. Orthopedic manual therapists were invited to participate in the study through an email (De Leeuw et al., 2008) in which the aim of the study and the anonymity of data were explained. The email also pointed that the informed consent to participate in the study would have been provided by clicking on the survey link (Eysenbach and Wyatt, 2002). Participants could change their answers and review them before submitting the final survey, but they were required to answer all questions to prevent missing data. The survey took responders between 5 and 10 minutes to complete: this response time was chosen to optimize responses rate (Fan and Yan, 2010).

Data were downloaded and stored in an encrypted computer. Only the principal investigator could have access to the information achieved during all stages of the study. All data (name and email address) were anonymized to ensure privacy and data protection (De Leeuw et al., 2008) leaving the participants' identities concealed to researchers (Eysenbach and Wyatt, 2002). No incentives were offered to participants and the attendance was voluntary (Eysenbach and Wyatt, 2002). The OMTs who did not complete the questionnaire were encouraged to participate in the survey by an email reminder at 2, 4, and 8 weeks after the first contact.

Data Analysis

To review answers accuracy, data were transferred from SurveyMonkey to Excel spreadsheet. For descriptive statistic, continuous variables were reported using mean, standard deviation (SD) and confidence intervals at 95% (95% CI); whereas absolute frequency and percentage described dichotomous,

[1] www.surveymonkey.com

nominal and ordinal variables, coming from single answer questions. Age and years of clinical practice were transformed into ordinal variables considering a decade as variable level for the analysis of correlations.

As this study is the first on nocebo in physiotherapy, we analyzed all the possible relations between the socio-demographic characteristics of the sample (section A, intended as the dependent variables) and answers to section (B) and (C), intended as independent variables, were analyzed with Cramer's V, which is a statistic analysis tool that measures strength and directions of associations used when one or both the independent and dependent variables consists of unordered categories with more than two levels. Only correlation values higher than the threshold (>0.50) (Cohen, 1988) were accepted and reported in the study. R software was used for the data analysis (R Core Team, 2020) with the packages psych (Revelle, 2017) and ggplot2 (Wickham, 2009).

RESULTS

Flow of Participants Through the Study

From the sample of 1288 OMTs, 791 responses were received (61.4%). Most participants were male (n = 473; 59.8%; 95% CI 56.3–63.2) and their average age was 31.0 ± 7.1 years. Overall, 70.9% of OMTs (n = 561; 95% CI 67.6–74.0) reported to work in the North of Italy. Respondents had an average clinical experience of 7.4 ± 6.3 years. The majority of them was employed in private health care settings (n = 676; 85.5%; 95% CI 82.8–87.8) as a freelance professional (n = 569; 71.9%; 95% CI 68.6–75.0) working between 32 and 45 h per week (n = 433; 54.7%; 95% CI 51.2–58.2) in an outpatient clinic (n = 607; 76.7%; 95% CI 73.6–79.6). A high proportion of OMTs worked in the musculoskeletal field (n = 718; 90.8%; 95% CI 88.5–92.7) with adult patients (646; 81.7%; 95% CI 78.8–84.3). The participants' demographics are described in **Table 1**.

TABLE 1 | Socio-demographic variables.

Demography	Values	95% CI
Years, mean (SD)	31.0 (7.1)	30.5–31.5
Years of clinical practice, mean (SD)	7.4 (6.3)	7.0–7.8
Gender, n (%)		
Male	473 (59.8)	56.3–63.2
Female	318 (40.2)	36.8–43.7
Italian region, n (%)		
North	561 (70.9)	67.6–74.0
Center	161 (20.4)	17.6–23.4
South	69 (8.7)	6.9–11.0
Workplace, n (%)		
Private health care settings	676 (85.5)	82.8-87.8
Public health care settings	115 (14.5)	12.2-17.2
Type of work, n (%)		
Freelance professional	569 (71.9)	68.6–75.0
Employee	222 (28.1)	25.0–31.4
Setting, n (%)		
Outpatient clinic	607 (76.7)	73.6–79.6
Hospital	123 (15.5)	13.1–18.3
Residential care (nursing home)	61 (7.7)	6.0–9.9
Profile of patients, n (%)		
Adults	646 (81.7)	78.8–84.3
Older people	134 (16.9)	14.4–19.8
Pediatrics	11 (1.4)	0.7–2.6
Field of work, n (%)		
Musculoskeletal	718 (90.8)	88.5–92.7
Neurological	57 (7.2)	5.5–9.3
Cardiorespiratory	11 (1.4)	0.7–2.6
Oncological	3 (0.4)	0.1–1.2
Uro-gynecological	2 (0.3)	0.0–1.0
Hours of work per week, n (%)		
1–15	18 (2.3)	1.4–3.6
16–30	175 (22.1)	19.3–25.2
31–45	433 (54.7)	51.2–58.2
46–60	146 (18.5)	15.8–21.4
>60	19 (2.4)	1.5–3.8

n, number of participants;%, percentage; SD, standard deviation; 95% CI, 95% confidence interval; >, more.

Definition of Nocebo-Related Effects

Orthopedic manual therapists were asked how they would define nocebo-related effects: the most selected option was "psychosocial effects of the context around therapy and patient with specific biological bases" (n = 571; 72.2%; 95% CI 68.9–75.3). Some OMTs opted for "health procedure effects able to create negative expectations" (n = 162; 20.5%; 95% CI 17.7–23.5), whereas the less frequent response was "adverse responses observed in people of the control group of randomized clinical trials" (n = 58; 7.3%; 95% CI 5.7–9.4).

Mechanisms of Action of Nocebo-Related Effects

Analyzing the mechanisms of action that are believed to explain nocebo-related effects, the most frequent response was "associative learning (e.g., conditioning)" (n = 228; 28.8%; 95% CI 25.7–32.1), followed by "patient's expectation" (n = 207; 26.2%; 95% CI 23.2–29.4). Other options were (in descending order): "psychological traits" (n = 125; 15.8%; 95% CI 13.4–18.6), "previous experiences" (n = 95; 12.0%; 95% CI 9.9–14.5), "social learning" (n = 66; 8.3%; 95% CI 6.6–10.5), and "neurophysiological" mechanisms (n = 52; 6.6%; 95% CI 5.0–8.6). The less chosen option regarding the mechanism of action was "genetic" (n = 18; 2.3%; 95% CI 1.4–3.6).

Beliefs About CFs as Triggers of Nocebo-Related Effects

Participants reported a high level of conviction toward CFs (mean = 2.4 out of 4; 95% CI 2.4–2.5) as triggers of nocebo-related effects. Specifically, the most important CFs were (in descending order): "lack of empathetic therapeutic alliance with the patient" (mean = 3.3; 95% CI 3.3–3.4), "patient's negative expectation" (mean = 3.3; 95% CI 3.2–3.4), "patient's previous negative

experience" (mean = 3.2; 95% CI 3.1–3.2); "negative verbal communication" (mean = 3.1; 95% CI 3.0-3.1); and "negative attitudes and pessimistic behavior" (mean = 3.1; 95% CI 3.0-3.1).

Less influent CFs were (in descending order): "printed information about the therapy" (mean = 1.9; 95% CI 1.8–1.9); "hidden therapy" (mean = 1.8; 95% CI 1.7–1.8); "inaccurate design" (mean = 1.7; 95% CI 1.7–1.8), "lack of patient's familiarity with the therapy" (mean = 1.6; 95% CI 1.6–1.7); "lack of uniform" (mean = 1.6; 95% CI 1.5–1.7). A complete description of CFs capable to trigger nocebo-related effects is reported in **Table 2**.

Frequency of Nocebo-Related Effects

Orthopedic manual therapists reported that nocebo-related effects were present in their clinical experience with a frequency of (in descending order): "sometimes" (n = 336; 42.5%; 95% CI 39.0–46.0), "often" (n = 286; 36.2%; 95% CI 32.8–39.6), "rarely" (n = 147; 18.6%; 95% CI 16.0–21.5), "always" (n = 11; 1.4%; 95% CI 0.7–2.5) and "never" (n = 11; 1.4%; 95% CI 0.7–2.5).

Communication of Nocebo-Related Effects

When asked how participants were used to communicate nocebo-related effects to the patient, the most frequent answer was "balance the positive features of the therapy with the negative ones" (n = 403; 50.9%; 95% CI 47.4–54.5), whereas few OMTs reported to "do not say anything" (n = 77; 9.7%; 95% CI 7.8–12.1).

Regarding when they communicate nocebo-related effects, most of OMTs informed their patients "during the decision of the therapeutic plan" (n = 338; 42.7%; 95% CI 39.3–46.3). The option "during the clinical examination" (n = 17; 2.1%; 95% CI 1.3–3.5) was the less chosen. The detailed communication strategies used in daily practice are reported in **Table 3**.

Management of Nocebo-Related Effects

The most adopted intervention to avoid nocebo-related effects was "teach and train patient's strategies to manage adverse events" (n = 313; 39.6%; 95% CI 36.2–43.1). The less chosen responses were "refer to evidence-based information on the Internet" (n = 14; 1.8%; 95% CI 1.0–3.0) and "adopt a gradual reduction of the treatment in a hidden way" (n = 9; 1.1%; 95% CI 0.6–2.2).

When asked which clinician-patient communication was mainly adopted to avoid nocebo-related effects, the majority of OMTs replied "evaluate and modify patient's anxieties, doubts and expectations" (n = 298; 37.7%; 95% CI 34.3–41.2), whereas a minor number of OMTs chose "ask the patient to give questions" (n = 17; 2.1%; 95% CI 1.3–3.5). **Table 4** presented the overall responses about the management of nocebo-related effects.

Education of Nocebo-Related Effects

The majority of OMTs considered their education about nocebo-related effects as "medium" (n = 381; 48.2%; 95% CI 44.6–51.7), followed by "limited" (n = 218; 27.6%; 95% CI 24.5–30.8) and "very good" (n = 165; 20.9%; 95% CI 18.1–23.9). Some of them considered it "absent" (n = 20; 2.5%; 95% CI 1.6–3.9) and a few "complete" (n = 7; 0.9%; 95% CI 0.4–1.9).

Most participants believed that the management of nocebo-related effects should be taught in "bachelor degree" (n = 622; 78.6%; 95% CI 75.6–81.4). Many respondents suggested that the education should be preferably provided during a "post-graduation diploma" (n = 77; 9.8%; 95% CI 7.8–12.1) and some of them as "e-learning/advanced distance learning" (n = 55; 7.0%; 95% CI 5.3–9.0). The less chosen options were "master of science degree" (n = 22; 2.8%; 95% CI 1.8–4.2), "Philosophy doctor degree" (n = 15; 1.9%; 95% CI 1.1–3.2).

Correlation Between Variables

Strength of association between variables was weak, with a Cramer's V below (from 0.1 to 0.3) the established threshold (Cramer's $V < 0.5$) in all correlations, such as between socio-demographic variables of section (A) and responses given in section (B) and (C) of the survey.

DISCUSSION

This is the first national survey that investigates the knowledge of Italian OMTs regarding nocebo-related effects and CFs. The main finding of this study suggests that OMTs are aware of the presence of nocebo-related effects in their clinical practice and that these effects can be triggered by CFs.

According to current evidences (Miller and Miller, 2015; Carlino and Benedetti, 2016), Italian OMTs defined nocebo-related effects as due to the negative psychosocial context around the therapy, composed of both internal and external elements to the patient and capable to influence his/her therapeutic outcomes through specific biological bases, thus reflecting an adequate knowledge of the topic.

Our participants identified in the associative learning and expectations the main mechanisms of action explaining nocebo-related effects. As reported in several studies, the repetitive negative associations of the therapy with CFs (e.g., specific color and shape of a medicine) (Faasse and Martin, 2018), similar and negative previous experiences (Colloca et al., 2010; Testa and Rossettini, 2016) and verbal messages highlighting negative expectations (e.g., "you will receive a medication which will increase your pain") (Blasini et al., 2017) can trigger nocebo-related effects both in healthy people (Colloca et al., 2008; Bingel et al., 2011) and in patients (Damien et al., 2018). Instead, OMTs considered genetic as the less influent mechanism contrary to evidence that have identified the involvement of specific genes such as catechol-*O*-methyltransferase (COMT) in the development of nocebo-related effects (Wendt et al., 2014).

Italian OMTs reported that they encountered nocebo-related effects in their clinical practice, and they are convinced that these effects are triggered by specific CFs present in the therapeutic context. The most influential CFs were those mainly related to the encounter between patient and physiotherapist, that represents a fundamental moment in which biopsychosocial components are investigated, symbolizing the foundations for the therapeutic alliance in physiotherapy (Miciak et al., 2018; Moore et al., 2020). In detail, the lack of empathetic therapeutic alliance with the patient (Fuentes et al., 2014), the patient's negative expectations

TABLE 2 | Beliefs about CFs as triggers of nocebo-related effects.

	Likert score mean (95% CI)	4 n (%); 95% CI	3 n (%); 95% CI	2 n (%); 95% CI	1 n (%); 95% CI	0 n (%); 95% CI
A: *Weak professional reputation* (e.g., qualification, expertise of physiotherapist)	2.6 (2.6–2.7)	136 (17.2); 14.7–20.0	360 (45.5); 42.0–49.1	207 (26.2); 23.2–29.4	47 (5.9); 4.4–7.9	41 (5.2); 3.8–7.0
A. *Lack of uniform* (e.g., white coat of physiotherapist)	1.6 (1.5–1.7)	15 (1.9); 1.1–3.2	116 (14.7); 12.3–17.4	284 (35.9); 32.6–39.4	296 (37.4); 34.1–40.9	80 (10.1); 8.1–12.5
A. *Negative attitudes and pessimistic behavior* (e.g., toward a patient's dysfunctions)	3.1 (3.0–3.1)	279 (35.3); 32.0–38.7	373 (47.1); 43.6–50.7	87 (11.0); 8.9–13.4	19 (2.4); 1.5–3.8	33 (4.2); 2.9–5.9
B. *Patient's negative expectation* (e.g., toward a physiotherapy treatment)	3.3 (3.2–3.4)	426 (53.9); 50.3–57.4	271 (34.3); 31.0–37.7	42 (5.3); 3.9–7.2	18 (2.3); 1.4–3.6	34 (4.3); 3.0–6.0
B. *Patient's previous negative experience* (e.g., toward a physiotherapy treatment)	3.2 (3.1–3.2)	343 (43.4); 39.9–46.9	314 (39.7); 36.3–43.2	89 (11.2); 9.2–13.7	5 (0.6); 0.2–1.6	40 (5.1); 3.7–6.9
C. *Negative verbal communication* (e.g., medical language, lack of positive messages associated with the treatment)	3.1 (3.0–3.1)	298 (37.7); 34.3–41.2	334 (42.2); 38.8–45.8	98 (12.4); 10.2–14.9	24 (3.0); 2.0–4.5	37 (4.7); 3.4–6.5
C. *Negative non-verbal communication* (e.g., closing posture, gestures, absence of eye contact, facial expressions)	2.7 (2.6–2.8)	167 (21.1); 18.3–24.2	345 (43.6); 40.1–47.2	197 (24.9); 22.0–28.1	41 (5.2); 3.8–7.0	41 (5.2); 3.8–7.0
C. *Lack of empathetic therapeutic alliance with the patient* (e.g., lack of active listening)	3.3 (3.3–3.4)	373 (47.1); 43.6–50.7	316 (39.9); 36.5–43.5	90 (11.4); 9.3–13.8	11 (1.4); 0.7–2.5	1 (0.1); 0.0–0.8
D. *Information about the therapy delivered by other patients* (e.g., negative communicated or observed responses)	2.5 (2.4–2.5)	95 (12.0); 9.9–14.5	324 (41.0); 37.5–44.5	267 (33.7); 30.5–37.2	68 (8.6); 6.8–10.8	37 (4.7); 3.4–6.4
D. *Printed information about the therapy* (e.g., medical leaflets)	1.9 (1.9–2.0)	37 (4.7); 3.4–6.4	187 (23.6); 20.7–26.8	319 (40.3); 36.9–43.8	196 (24.8); 21.8–28.0	52 (6.6); 5.0–8.6
D. *Information about the therapy from the media* (e.g., internet, social media, television news)	2.5 (2.5–2.6)	158 (20.0); 17.3–23.0	291 (36.8); 33.4–40.3	216 (27.3); 24.3–30.6	83 (10.5); 8.5–12.9	43 (5.4); 4.0–7.3
D. *Hidden therapy* (e.g., impossibility for the patient to see when the therapy is delivered)	1.8 (1.7–1.8)	27 (3.4); 2.3–5.0	150 (19.0); 16.3–21.9	300 (37.9); 34.5–41.4	235 (29.7); 26.6–33.0	79 (10.0); 8.0–12.3
D. *Sudden interruption of the therapy* (e.g., to attend other patients or colleagues)	2.3 (2.2–2.4)	38 (4.8); 3.5–6.6	287 (36.3); 32.9–39.8	346 (43.7); 40.3–47.3	110 (13.9); 11.6–16.6	10 (1.3); 0.6–2.4
D. *Marketing of the therapy* (e.g., cost, brand, color, shape)	2.1 (2.0–2.2)	49 (6.2); 4.7–8.2	233 (29.5); 26.3–32.8	314 (39.7); 36.3–43.2	144 (18.2); 15.6–21.1	51 (6.4); 4.9–8.4
D. *Lack of patient's familiarity with the therapy* (e.g., new therapy)	1.6 (1.6–1.7)	18 (2.3); 1.4–3.6	121 (15.3); 12.9–18.0	281 (35.5); 32.2–39.0	301 (38.0); 34.7–41.5	70 (8.8); 7.0–11.1
D. *Lack of patient-centered approach* (e.g., not shared-decision of physiotherapy treatment)	2.6 (2.5–2.7)	148 (18.7); 16.1–21.6	317 (40.1); 36.7–43.6	217 (27.4); 24.4–30.7	73 (9.2); 7.3–11.5	36 (4.5); 3.2–6.3
D. *Inappropriate physical contact with the patient* (e.g., invasiveness of the touch)	2.6 (2.5–2.7)	152 (19.2); 16.6–22.2	334 (42.2); 38.8–45.8	204 (25.8); 22.8–29.0	58 (7.3); 5.7–9.4	43 (5.4); 4.0–7.3
E. *Lack of comfortable setting* (e.g., inappropriate lighting, temperature)	2.4 (2.4–2.5)	96 (12.1); 10.0–14.7	321 (40.6); 37.1–44.1	242 (30.6); 27.4–34.0	92 (11.6); 9.5–14.1	40 (5.1); 3.7–6.9
E. *Inadequate environmental architecture* (e.g., inappropriate highlights, indicators)	2.0 (1.9–2.1)	35 (4.4); 3.1–6.2	223 (28.2); 25.1–31.5	293 (37.0); 33.7–40.5	187 (23.6); 20.7–26.8	53 (6.7); 5.1–8.7
E. *Inaccurate design* (e.g., absence of decorations, ornaments, colors)	1.7 (1.7–1.8)	18 (2.3); 1.4–3.6	151 (19.1); 16.4–22.0	293 (37.0); 33.7–40.5	258 (32.6); 29.4–36.0	71 (9.0); 7.1–11.2

n, number of participants; 95% CI, 95% confidence interval; 0, not at all; 1, few; 2, enough; 3, much; 4, a lot of; A, physical therapist domain; B, patient domain; C, physical therapist-patient relationship domain; D, therapy domain; E, healthcare setting domain.

as well as previous negative experience(s) (Testa and Rossettini, 2016), the physiotherapist's negative verbal communication, attitudes and pessimistic behavior (Oliveira et al., 2012) have been all shown to negatively influence subjective (e.g., pain, anxiety) and objective (e.g., function, disability) outcomes in patient with musculoskeletal pain. Instead, the printed information about the therapy and the hidden administration of the therapy (Wand et al., 2012), the inaccurate design (Schweitzer et al., 2004), the lack of patient's familiarity about the therapy (Faasse and Martin, 2018) and the lack of physiotherapist's uniform (Mercer et al., 2008) have been considered less influent CFs likelihood because of a OMTs' poor of awareness of their negative clinical importance. Overall, our findings suggest to OMTs the need to consider CFs as triggers of nocebo-related effects capable

TABLE 3 | Communication of nocebo-related effects.

Communication *n* (%)	Values	95% CI
How do you mainly communicate nocebo effects to the patient?		
Balance the positive features of the therapy with the negative ones	403 (50.9)	47.4–54.5
Carefully explain the effects and the role played by the negative context	226 (28.6)	25.5–31.9
Minimize negative information on nocebo-related effects by not reporting all the elements	85 (10.7)	8.7–13.2
Do not say anything	77 (9.7)	7.8–12.1
When do you mainly communicate nocebo effects to the patient?		
During the decision of the therapeutic plan	338 (42.7)	39.3–46.3
During the administration of the therapy	221 (27.9)	24.9–31.2
Do not communicate anything	114 (14.4)	12.1–17.1
During the anamnesis	56 (7.1)	5.4–9.1
During the formulation of the diagnosis	45 (5.7)	4.2–7.6
During the clinical examination	17 (2.1)	1.3–3.5

n, number of participants;%, percentage; 95% CI, 95% confidence interval.

TABLE 4 | Management of nocebo-related effects.

Management of nocebo-related effects, *n* (%)	Values	95% CI
Which interventions do you mainly use to avoid nocebo effects?		
Teach and train patient's strategies to manage nocebo-related effects	313 (39.6)	36.2–43.1
Optimize expectations toward treatment and nocebo-related effects	196 (24.8)	21.8–28.0
Explain nocebo-related effects using illustrative methods (e.g., videos, figures, graphs and percentages) and simple language	110 (13.9)	11.6–16.6
Present first the positive features of the treatment and then the negative ones	71 (9.0)	7.1–11.2
Do not do anything	46 (5.8)	4.3–7.7
Use pre-treatments with a reduced percentage of nocebo-related effects (e.g., active or inert treatment-test)	32 (4.0)	2.8–5.7
Refer to evidence-based information on the Internet	14 (1.8)	1.0–3.0
Adopt a gradual reduction of the treatment in a hidden way	9 (1.1)	0.6–2.2
Which clinician-patient communication do you mainly use to avoid nocebo-related effects?		
Evaluate and modify patient's anxieties, doubts and expectations	298 (37.7)	34.3–41.2
Use an empathic and authentic communication style	233 (29.5)	26.3–32.8
Provide adequate information (e.g., pathology, diagnosis, treatment, adverse events)	145 (18.3)	15.7–21.2
Investigate previous experiences of therapeutic failure	38 (4.8)	3.5–6.6
Ask the patient to summarize the information provided to avoid misunderstanding	34 (4.3)	3.0–6.0
Use images and narrative	26 (3.3)	2.2–4.8
Ask the patient to give questions	17 (2.1)	1.3–3.5

n, number of participants;%, percentage; 95% CI, 95% confidence interval.

to negatively impact patients' outcomes in accordance to the evidences reported in medicine (Colloca and Barsky, 2020) and physiotherapy (Rossettini et al., 2020).

OMTs communicated nocebo-related effects mainly during the decision of the therapeutic plan, balancing the positive features of the treatment with the negative ones. According to evidence available, no information should be omitted during the discussion of the positive and negative effects of treatment, offering to clinicians three options of communication: (a) explaining and highlighting as first the desired positive treatment effects (Kleine-Borgmann and Bingel, 2018); (b) reframing the information on negative effects in a positive way (Enck et al., 2013; Bingel, 2014); and (c) informing patients about the presence of nocebo-related effects and their relevance in the treatment (Crichton and Petrie, 2015). Only few OMTs did not inform their patients, resulting in a non-transparent and deceptive communication that threatens the respect of ethical principles behind the therapy administration (e.g., the principle of autonomy, the informed consent) (Colloca and Finniss, 2012; Klinger et al., 2017).

Italian OMTs referred they managed nocebo-related effects by teaching and training patient's strategies to control unintended negative effects of treatment. Orthopedic manual therapists also reported having adopted an empathic and authentic communication style aimed to evaluate and modify patients' anxieties, doubts and expectations. Overall, these results highlight how an adequate interaction between the clinician and the patient is essential to minimize nocebo-related effects (Dieppe et al., 2016; Blasini et al., 2018), underlining the importance of education (Wijma et al., 2016; Hoon et al., 2017). During the therapeutic encounter, it has been shown that an appropriate education can influence the outcome (e.g., pain, function) (Louw et al., 2016) and improve the patients' self-efficacy (Jönsson et al., 2018) in patients with musculoskeletal pain.

Most OMTs considered to have a medium level of education about nocebo-related effects suggesting that this topic should be taught mainly during the bachelor degree, as suggested internationally (Evers et al., 2018) and previously reported among clinicians (Rossettini et al., 2018b; Palese et al., 2019) and students (Cadorin et al., 2020) in physiotherapy and in nursing field.

Strengths and Weakness of the Study

The current survey presented some strengths. A high response rate was achieved (61.4%), confirming the willingness of OMTs to participate in this study. Moreover, authors have adopted an online survey to understand the opinion of the target population. The methodological choice was previously used in surveys on placebo-related effects and CFs representing a valid tool aimed to capture the perspective of a large sample of healthcare providers (Rossettini et al., 2018b).

As a weakness, a group of Italian physiotherapists specialized in OMT educated mostly in managing musculoskeletal pain in the private healthcare settings (AIFI, 2020) were involved. Therefore, their response can be not generalizable to non-specialized physiotherapists (e.g., not OMTs), working in other fields (e.g., neurology) and employed in different settings (e.g., hospital), thus suggesting future studies in this field. Most of participants worked full-time, in the North of Italy and for less than 10 years: these are all factors that could have influenced beliefs and knowledge regarding nocebo effects, limiting the generalizability of findings (Rossettini et al., 2018b). Moreover, data were self-reported introducing a social and recall bias that can have affected the findings. Furthermore, the format of asking participants how to define nocebo effects with a closed question with three options could have given some prior cues to the participant, thus biasing their reported knowledge on the topic. Finally, despite the anonymity was guaranteed some participants might have misreported some data (Eysenbach, 2004; Palese et al., 2019).

CONCLUSION

In summary this national survey shows that OMTs are aware of the presence of nocebo-related effects in their clinical practice and that these effects can be triggered by CFs. From a policymakers' perspective, it is recommended to ensure an appropriate knowledge on nocebo-related effects among healthcare providers aimed at minimizing their negative impact in clinical practice, including this topic in undergraduate education.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Liguria Clinical Experimental Ethics Committee (P.R.236REG2016, accepted on 19/07/2016). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GR, TG, and MT were responsible for project administration. GR, TG, and AP were major contributors in writing (original draft). GR and MT were responsible for the resources. AP, LC, MF, and AT contributed to the investigation. GR, TG, AP, CM, MMi, AT, MMa helped in data curation and formal analysis. LC, MF, AT, MMi, MMa, and MT contributed to the writing (review and editing). All authors read and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.582174/full#supplementary-material

REFERENCES

AIFI (2020). *Ecco il Censimento Aifi: In Italia 65.000 Fisioterapisti*. Available online at: https://aifi.net/censimento-aifi-italia-65mila-fisioterapisti/ (accessed July 4, 2020).

Ashraf, B., and Saaiq, M. (2014). Qualitative study of nocebo phenomenon (NP) involved in doctor-patient communication. *Int. J. Health. Policy. Manag.* 3, 23–27. doi: 10.15171/ijhpm.2014.54

Australian Bureau of Statistics (2020). *Sample Size Calculator*. Available online at: https://www.abs.gov.au/websitedbs/d3310114.nsf/home/sample+size+calculator (accessed July 4, 2020).

Benedetti, F. (2013). Placebo and the new physiology of the doctor-patient relationship. *Physiol. Rev.* 93, 1207–1246. doi: 10.1152/physrev.00043.2012

Bingel, U. (2014). Avoiding nocebo effects to optimize treatment outcome. *JAMA*. 312, 693–694. doi: 10.1001/jama.2014.8342

Bingel, U., Wanigasekera, V., Wiech, K., Mhuircheartaigh, R. N., Lee, M. C., Ploner, M., et al. (2011). The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci. Transl. Med.* 3:70ra14. doi: 10.1126/scitranslmed.3001244

Blasini, M., Corsi, N., Klinger, R., and Colloca, L. (2017). Nocebo and pain: an overview of the psychoneurobiological mechanisms. *Pain. Rep.* 2:e585. doi: 10.1097/PR9.0000000000000585

Blasini, M., Peiris, N., Wright, T., and Colloca, L. (2018). The role of patient–practitioner relationships in placebo and nocebo phenomena. *Int. Rev. Neurobiol.* 139, 211–231. doi: 10.1016/bs.irn.2018.07.033

Bologna Working Group (2005). *A Framework for Qualifications of the European Higher Education Area. Bologna Working Group Report on Qualifications Frameworks (Copenhagen, Danish Ministry of Science, Technology and Innovation)*. Available online at: http://ecahe.eu/w/index.php/Framework_for_Qualifications_of_the_European_Higher_Education_Area (accessed September 9, 2020).

Cadorin, L., Rossettini, G., Testa, M., Geri, T., and Palese, A. (2020). The awareness of contextual factors, placebo and nocebo effects among nursing students: findings from a cross-sectional study. *Nurse Educ. Pract.* 42:102670. doi: 10.1016/j.nepr.2019.102670

Carlino, E., and Benedetti, F. (2016). Different contexts, different pains, different experiences. *Neuroscience* 338, 19–26. doi: 10.1016/j.neuroscience.2016.01.053

Carlino, E., Frisaldi, E., and Benedetti, F. (2014). Pain and the context. *Nat. Rev. Rheumatol.* 10, 348–355. doi: 10.1038/nrrheum.2014.17

Cohen, J. (1988). *Statistical Power Analysis for The Behavioral Sciences*, 2nd Edn. Hisdale, NJ: Lawrence Erlbaum Associates,

Colloca, L., and Barsky, A. J. (2020). Placebo and nocebo effects. *N. Engl. J. Med.* 382, 554–561. doi: 10.1056/NEJMra1907805

Colloca, L., and Finniss, D. (2012). Nocebo effects, patient-clinician communication, and therapeutic outcomes. *JAMA*. 307, 567–568. doi: 10.1001/jama.2012.115

Colloca, L., Petrovic, P., Wager, T. D., Ingvar, M., and Benedetti, F. (2010). How the number of learning trials affects placebo and nocebo responses. *Pain* 151, 430–439. doi: 10.1016/j.pain.2010.08.007

Colloca, L., Sigaudo, M., and Benedetti, F. (2008). The role of learning in nocebo and placebo effects. *Pain* 136, 211–218. doi: 10.1016/j.pain.2008.02.006

R Core Team (2020). *R: A Language And Environment For Statistical Computing*. Vienna: R Foundation for Statistical Computing.

Crichton, F., and Petrie, K. J. (2015). Health complaints and wind turbines: the efficacy of explaining the nocebo response to reduce symptom reporting. *Environ. Res.* 140, 449–455. doi: 10.1016/j.envres.2015.04.016

Damien, J., Colloca, L., Bellei-Rodriguez, C. É, and Marchand, S. (2018). Pain modulation: from conditioned pain modulation to placebo and nocebo effects in experimental and clinical pain. *Int. Rev. Neurobiol.* 139, 255–296. doi: 10.1016/bs.irn.2018.07.024

Darnall, B. D., and Colloca, L. (2018). Optimizing placebo and minimizing nocebo to reduce pain, catastrophizing, and opioid use: a review of the science and an evidence-informed clinical toolkit. *Int. Rev. Neurobiol.* 139, 129–157. doi: 10.1016/S1836-9553(12)70107-8

De Leeuw, D., Hox, J., and Dillman, D. (2008). *International Handbook of Survey Methodology (European Association of Methodology Series)*. Abingdon: Taylor and Francis group.

Di Blasi, Z., Harkness, E., Ernst, E., Georgiou, A., and Kleijnen, J. (2001). Influence of context effects on health outcomes: a systematic review. *Lancet* 357, 757–762. doi: 10.1016/s0140-6736(00)04169-6

Dieppe, P., Goldingay, S., and Greville-Harris, M. (2016). The power and value of placebo and nocebo in painful osteoarthritis. *Osteoarthritis Cartilage* 24, 1850–1857. doi: 10.1016/j.joca.2016.06.007

Enck, P., Bingel, U., Schedlowski, M., and Rief, W. (2013). The placebo response in medicine: minimize, maximize or personalize? *Nat. Rev. Drug. Discov.* 12, 191–204. doi: 10.1038/nrd3923

Evers, A. W., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., et al. (2018). Implications of placebo and nocebo effects for clinical practice: expert consensus. *Psychother. Psychosom.* 87, 204–210. doi: 10.1159/000490354

Eysenbach, G. (2004). Improving the quality of web surveys: the checklist for reporting results of internet e-surveys (CHERRIES). *J.Med. Internet Res.* 6:e34. doi: 10.2196/jmir.6.3.e34

Eysenbach, G., and Wyatt, J. (2002). Using the internet for surveys and health research. *J. Med. Internet Res.* 4:e13. doi: 10.2196/jmir.4.2.e13

Faasse, K., and Martin, L. R. (2018). The power of labeling in nocebo effects. *Int. Rev. Neurobiol.* 139, 379–406. doi: 10.1016/bs.irn.2018.07.016

Fan, W., and Yan, Z. (2010). Factors affecting response rates of the web survey: a systematic review. *Comput. Human Behav.* 26, 132–139. doi: 10.1016/j.chb.2009.10.015

Frisaldi, E., Piedimonte, A., and Benedetti, F. (2015). Placebo and nocebo effects: a complex interplay between psychological factors and neurochemical networks. *Am. J. Clin. Hypn.* 57, 267–284. doi: 10.1080/00029157.2014.976785

Fuentes, J., Armijo-Olivo, S., Funabashi, M., Miciak, M., Dick, B., Warren, S., et al. (2014). Enhanced therapeutic alliance modulates pain intensity and muscle pain sensitivity in patients with chronic low back pain: an experimental controlled study. *Phys Ther.* 94, 477–489. doi: 10.2522/ptj.20130118

Hallegraeff, J. M., Krijnen, W. P., van der Schans, C. P., and de Greef, M. H. (2012). Expectations about recovery from acute non-specific low back pain predict absence from usual work due to chronic low back pain: a systematic review. *J. Physiother.* 58, 165–172. doi: 10.1016/S1836-9553(12)70107-8

Hansen, E., and Zech, N. (2019). Nocebo effects and negative suggestions in daily clinical practice–forms, impact and approaches to avoid them. *Front. Pharmacol.* 10:77. doi: 10.3389/fphar.2019.00077

Hoon, E., Smith, K., Black, J., Burnet, S., Hill, C., and Gill, T. K. (2017). Take charge of pain: evaluating a community-targeted self-management education program for people with musculoskeletal pain. *Health Promot. J. Austr.* 28, 77–80. doi: 10.1071/HE15123

IFOMPT (2016). "Educational Standards 2016.pdf," in *International Federation Of Othopedic Manipulative Physical Therapists Inc., Educational Standards In Orthopedic Manipulative Therapy*, Part A Edn,

Jönsson, T., Hansson, E. E., Thorstensson, C. A., Eek, F., Bergman, P., and Dahlberg, L. E. (2018). The effect of education and supervised exercise on physical activity, pain, quality of life and self-efficacy-an intervention study with a reference group. *BMC Musculoskelet Disord.* 19:198. doi: 10.1186/s12891-018-2098-3

Kleine-Borgmann, J., and Bingel, U. (2018). Nocebo effects: neurobiological mechanisms and strategies for prevention and optimizing treatment. *Int. Rev. Neurobiol.* 138, 271–283. doi: 10.1016/bs.irn.2018.02.005

Klinger, R., Blasini, M., Schmitz, J., and Colloca, L. (2017). Nocebo effects in clinical studies: hints for pain therapy. *Pain Rep.* 2:e586. doi: 10.1097/PR9.0000000000000586

Louw, A., Zimney, K., Puentedura, E. J., and Diener, I. (2016). The efficacy of pain neuroscience education on musculoskeletal pain: a systematic review of the literature. *Physiother. Theory Pract.* 32, 332–355. doi: 10.1080/09593985.2016.1194646

Mercer, E., MacKay-Lyons, M., Conway, N., Flynn, J., and Mercer, C. (2008). Perceptions of outpatients regarding the attire of physiotherapists. *Physiother. Can.* 60, 349–357. doi: 10.3138/physio.60.4.349

Miciak, M., Mayan, M., Brown, C., Joyce, A. S., and Gross, D. P. (2018). The necessary conditions of engagement for the therapeutic relationship in physiotherapy: an interpretive description study. *Arch. Physiother.* 8:3. doi: 10.1186/s40945-018-0044-1

Miller, L. R., and Miller, F. G. (2015). Understanding placebo effects:implications for nursing practice. *Nurs. Outlook.* 63, 601–606. doi: 10.1016/j.outlook.2015.03.002

Moore, A. J., Holden, M. A., Foster, N. E., and Jinks, C. (2020). Therapeutic alliance facilitates adherence to physiotherapy-led exercise and physical activity for older adults with knee pain: a longitudinal qualitative study. *J. Physiother.* 66, 45–53. doi: 10.1016/j.jphys.2019.11.004

Oliveira, V. C., Refshauge, K. M., Ferreira, M. L., Pinto, R. Z., Beckenkamp, P. R., Negrao Filho, R. F., et al. (2012). Communication that values patient autonomy is associated with satisfaction with care: a systematic review. *J. Physiother.* 58, 215–229. doi: 10.1016/S1836-9553(12)70123-6

Palese, A., Cadorin, L., Testa, M., Geri, T., Colloca, L., and Rossettini, G. (2019). Contextual factors triggering placebo and nocebo effects in nursing practice: findings from a national cross-sectional study. *J. Clin. Nurs.* 28, 1966–1978. doi: 10.1111/jocn.14809

Revelle, W. (2017). *Procedures For Psychological, Psychometric, And Personality. R Package Bpsych^, Version 1(5)*.

Rossettini, G., Camerone, E. M., Carlino, E., Benedetti, F., and Testa, M. (2020). Context matters: the psychoneurobiological determinants of placebo, nocebo and context-related effects in physiotherapy. *Arch. Physiother.* 10, 1–12. doi: 10.1186/s40945-020-00082-y

Rossettini, G., Carlino, E., and Testa, M. (2018a). Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskelet. Disord.* 19, 1–15. doi: 10.1186/s12891-018-1943-8

Rossettini, G., Palese, A., Geri, T., Fiorio, M., Colloca, L., and Testa, M. (2018b). Physical therapists' perspectives on using contextual factors in clinical practice:

findings from an italian national survey. *PLoS One* 13:e0208159. doi: 10.1371/journal.pone.0208159

Schweitzer, M., Gilpin, L., and Frampton, S. (2004). Healing spaces: elements of environmental design that make an impact on health. *J. Altern. Complement. Med.* 10, 71-83. doi: 10.1089/1075553042245953

Testa, M., and Rossettini, G. (2016). Enhance placebo, avoid nocebo: how contextual factors affect physiotherapy outcomes. *Man. Ther.* 24, 65–74.

Trinderup, J. S., Fisker, A., Juhl, C. B., and Petersen, T. (2018). Fear avoidance beliefs as a predictor for long-term sick leave, disability and pain in patients with chronic low back pain. *BMC Musculoskelet. Disord.* 19:431. doi: 10.1186/s12891-018-2351-9

Von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., and Vandenbroucke, J. P. (2007). The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann. Intern. Med.* 147, 573–577. doi: 10.1136/bmj.39335.541782.AD

Wager, T. D., and Atlas, L. Y. (2015). The neuroscience of placebo effects: connecting context, learning and health. *Nat. Rev. Neurosci.* 16, 403–418. doi: 10.1038/nrn3976

Wand, B. M., Tulloch, V. M., George, P. J., Smith, A. J., Goucke, R., O'Connell, N. E., et al. (2012). Seeing it helps: movement-related back pain is reduced by visualization of the back during movement. *Clin. J. Pain.* 28, 602–608. doi: 10.1097/AJP.0b013e31823d480c

Wendt, L., Albring, A., Benson, S., Engler, H., Engler, A., Hinney, A., et al. (2014). Catechol-O-methyltransferase val158met polymorphism is associated with somatosensory amplification and nocebo responses. *PLoS One* 9:e107665. doi: 10.1371/journal.pone.0107665

Wickham, H. (2009). *ggplot2: Elegant Graphics For Data Analysis*. Berlin: Springer-Verlag.

Wijma, A. J., van Wilgen, C. P., Meeus, M., and Nijs, J. (2016). Clinical biopsychosocial physiotherapy assessment of patients with chronic pain: the first step in pain neuroscience education. *Physiother. Theory Pract.* 32, 368–384. doi: 10.1080/09593985.2016.1194651

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How Do Nocebo Phenomena Provide a Theoretical Framework for the COVID-19 Pandemic?

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The COVID-19 pandemic is a major health issue, which leads to psychological and behavioural changes. In particular, among various negative feelings, fear seems to be one of the main emotional reactions that can be as contagious as the virus itself. The actual pandemic is likely to function as an important stressor, especially in terms of chronic anxiety and lack of control over the succession of unforeseeable environmental events. In this direction, the psychological impact of previous quarantine measures showed important negative psychological effects, including post-traumatic stress symptoms (PTTS) with long-lasting effects. The presence of psychological discomfort and disturbances due to negative contextual factors can be studied using the nocebo phenomenon as a possible theoretical explanatory framework. Although in the absence of studies linking nocebo to Covid-19 and data-driven evidence, the context of the actual pandemic may be seen as a fertile ground for amplified discomfort and anxiety. The media provide dramatic and negative descriptions and often present conflicting sources of information, which can lead to physical and mental health problems, diminishing response to treatment. This can be worse when supported by conspiracy theories or misinformation. The aim of this perspective review is to propose a new theoretical framework for the COVID-19 pandemic, which should be supported by future empirical studies. In particular, the negative contextual factors, which can predispose individuals to psychological distress and the onset of the nocebo phenomena will be presented here, in order to suggest possible guidelines to mitigate the devastating effects of COVID-19.

Keywords: COVID-19 pandemic, negative expectation, nocebo effects in randomised controlled trials, nocebo responses in brain imaging studies, mood changes, psychosocial context

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INTRODUCTION

The COVID-19 pandemic includes a perfect storm in which powerful nocebo effects may be flourishing. The nocebo effect can be mediated by situational-contextual factors (such as verbal information and suggestions, healthcare beliefs and health professional interactions, exposure to negative media campaigns, or previous personal experience) and by individual factors.

In Hahn and Kleinman (1983) published, in the prestigious Medical Anthropology Quarterly, a short article on the effects of belief. In particular, the authors underlined that beliefs may "kill" and beliefs may "heal" and what a person believes within a society plays a significant role both in producing disease and as a remedy. The authors illustrated different forms of the nocebo effect, as beliefs influence outcomes, particularly in the absence of specific events or communications: fear of heart disease increases the risk of ischemic attack; similarly, depressive states – i.e., a generalised sense of impotence – increase the probability of death as a result of ischemic events. Moreover, it is important to note how Cannon (1942) had already previously defined the phenomenon of "voodoo death" as a dramatic nocebo effect, following the induction of a pervasive state of terror. Prolonged stress events due to different adverse environmental contexts can cause the collapse of the neurovegetative balance and this can be so serious that it paralyses vital functions and induces death, even in the absence of organic lesions. In particular, the death may be caused by lasting and intense action of the sympathico-adrenal system. Since Cannon's observations, accumulated evidence supported his concept of "voodoo death" and nowadays it is considered as a real phenomenon, but far from being limited to ancient peoples. It can be defined as a basic biological principle that provides an important clue to understand the phenomenon of sudden death, as well as to provide an explanation for neurovisceral diseases (Samuels, 2007).

Subsequently, the research data and experiments on the nocebo effect have multiplied, substantially confirming the hypotheses of the previous authors, demonstrating important novel relationship between stress and emotion in the field of the neurobiology of pain (Amanzio et al., 2016a). Nocebo phenomena have a detrimental effect on health in terms of psychosomatic factors produced mainly by psychosocial aspects, such as negative treatment expectations or prognosis. Recently, nocebo has become a popular research topic, as it compromises treatment outcome and reduces adherence to therapy (Howick et al., 2018). In addition, negative expectations can increase stress and anxiety levels, which can affect our health and well-being (Kong and Benedetti, 2014).

Although in the absence of studies linking the nocebo effect to COVID-19 and data-driven evidence, the outbreak of the actual pandemic, and other past epidemics, may be a perfect scenario for an amplified nocebo effect to occur. In particular, when individuals feel the lack of control of a new situation and the perceived high level of contagion risk, the lack of information to refer to, the lack of available treatments or vaccines, and the spread of negative news. In addition, quarantine measures caused post-traumatic stress symptoms (PTSS), confusion, anxiety, and anger associated with acute stress reactions and post-traumatic stress disorder (Brooks et al., 2020).

The COVID-19 pandemic led to negative emotions, such as fear and anxiety (Liu et al., 2020). In particular, recently, intense anxiety and PTSS have been described among the Chinese population, especially Wuhan residents, due to the number of infections increasing, the lack of clear and definite information of virus from the media, the shortage of medical workers and resources, and the lack of masks and protecting supplies in the marketplace (Kang et al., 2020). In addition, the social distancing and isolation that accompany long-term lockdowns might be a risk factor for anxiety, addictive, and mood disorders (Sani et al., 2020).

In the current pandemic, important stressors are mainly due to uncertainty and changes in the environment and, in some cases, lack of activity to shift attention away from negative news and information, which trigger negative thoughts and expectations. In this direction, contextual factors, such as social networks and media, flood people with dramatic and mostly negative information. They present conflicting and confusing sources of information, often supported by conspiracy theories and misinformation. These news sources represent a possible breeding ground for psychological distress and a great burden for individuals. It is important to note that conflicting information are associated with increased stress. Misplaced expectations (probably one type of conflicting information) can lead to anxiety and/or depression if and when authorities apply the COVID-19 lockdown more rigorously (Torales et al., 2020). In particular, stress associated with negative expectations, which can be a fertile substrate for the onset of a nocebo effect, can produce significant physiological changes in the human body, including sleep disorders, respiratory complications, circulatory stress, digestive disorders, muscle tension, and pain (Liu et al., 2020). These symptoms are likely to further aggravate the prognosis of individuals with COVID-19.

Given the hypothesised importance of the negative contextual factors, which can predispose individuals to psychological distress and the onset of the nocebo phenomena, studies characterising nocebo phenomena in clinical trials and in brain imaging experiments will be presented in order to provide an interesting theoretical framework in the current COVID-19 pandemic. Finally, possible guidelines to mitigate the devastating effects of COVID-19 will be suggested.

NEGATIVE CONTEXTUAL FACTORS PREDISPOSING INDIVIDUALS TO PSYCHOLOGICAL DISTRESS

Previous coronavirus epidemics caused an increase in stress levels and neuropsychiatric implications, – i.e., mental disorders that are the sequelae of brain damage or disease, in patients admitted to hospital for Severe acute respiratory syndrome due to coronavirus (SARS-CoV) or Middle East respiratory syndrome (MERS-CoV; Rogers et al., 2020) – as also reported by WHO (2020) for the actual pandemic. In line with those above reported, past epidemics had been related to several and long-lasting psychiatric consequences (Kępińska et al., 2020).

Feelings of growing concern had also been aggravated by conflicting opinions among experts on pandemics. For most countries, an underestimation of the COVID-19 phenomenon had been observed, together with the presence of conflicting information (such as on the epidemic-pandemic). Using Italy as an example, some virologists underestimated COVID-19, describing it as a "trivial influence." Meanwhile, other experts

strongly contrasted this information by warning the population of the contagion risk and gravity of SARS-CoV-2. In addition, during the initial phase after the lockdown (phase 2), some experts reported a reduction in COVID-19 virulence, which was not supported by scientific or clinical evidence.

In the United Kingdom and United States, initially, governments avoided placing restrictive measures, such as lockdown on the population, claiming that "*herd immunity*" would have been the most natural outcome. At the same time, important virologists from the Imperial College London and WHO discouraged this path providing precise instructions on how to contain the spread of COVID-19 through the same restrictive measures previously taken by China and Italy.

Furthermore, negative distressing information presented during phase 1 of the pandemic (see **Table 1** for a list of examples), mainly consisted of: (1) media repeating information on the number of infections and exitus, (2) the absence of protective aids to fight infection for the public and medical-healthcare personnel alike, and the absence of vital biomedical devices to fight SARS-CoV-2, (3) total lack of scientific evidence on the new viral agent and consequent absence of diagnostic and prognostic perspectives, (4) stories of patients deprived of any contact with loved ones, especially at the time of aggravation of the symptoms that led to death, and (5) the repeated presentation of images of patients under anaesthesia and in intensive care units, and coffins carried on military trucks.

Moreover, misinformation increased confusion and uncertainty. For example, the events around the world associated with the COVID-19 pandemic fuelled strong states of anxiety making people more willing to believe in conspiracies (Grzesiak-Feldman, 2013). Indeed, Swami et al. (2016) reported that stressed individuals are more likely than others to believe in conspiracy theories. Moreover, investigators found that promoting anxiety in people also makes them more conspiracy-minded (Jolley and Douglas, 2017; Jolley et al., 2020). When personal alienation or anxiety are combined with the feeling of a dangerous society, people are more likely to believe in conspiracy theories, thus increasing their sense of powerlessness and making them feel even worse.

TABLE 1 | Examples of negative information.

Information	Publication date	Source
The pandemic alarm will last a long time	May 14th, 2020	WHO
Covid-19: after the lockdown in Korea, China and Germany the contagions increase	May 12th, 2020	WHO
Over 4 million infections in the world. Three out of four in EU countries and the US	May 11th, 2020	John Hopkins University
People living longer and healthier lives but COVID-19 threatens to throw progress off track	May 13th, 2020	WHO
Preparing for a long, hot summer with COVID-19	May 11th, 2020	WHO, EU Region
US$675 million needed for new coronavirus preparedness and response global plan	February 5th, 2020	WHO
WHO announces COVID-19 outbreak a pandemic	March 12th, 2020	WHO

THEORETICAL FRAMEWORK OF NOCEBO EFFECTS AND RESPONSES. POSSIBLE ASSOCIATION BETWEEN PSYCHOLOGICAL DISTRESS AND THE ONSET OF THE NOCEBO PHENOMENA

Studies and results characterising nocebo phenomena in experimental settings, clinical trials, and in brain imaging experiments can provide an interesting theoretical framework in the current COVID-19 pandemic. The neuroscience of pain, stress, and emotion underlined that the hyperalgesic nocebo effect appears to be attributable to complex biochemical and neuroendocrine mechanisms that link anxiety to pain involving the activation of the cholecystokininergic system. In particular, previous studies suggested that anxiety produced by negative expectancy may play a key role in the nocebo effect. In particular, using nocebo hyperalgesia as an example, negative verbal suggestions – about an impending pain increase – induce anticipatory anxiety and an hyperactivity of the hypothalamic-pituitary-adrenal axis (HPA), leading to the activation of cholecystokinin (CCK), anti-opioid peptide, which, in turn, facilitate pain transmission (Benedetti et al., 2006, 2007).

Furthermore, considering how HPA hyperactivity and nocebo hyperalgesia can be antagonised by benzodiazepine diazepam, Benedetti et al. (2006) suggested how anxiety could be involved in these effects.

In this direction, individuals with pathologies such as anxiety and depression, and those with a tendency towards somatization, had been found to be more likely to develop nocebo effects and responses (Wells and Kaptchuk, 2012). In particular, anxiety, depression, and somatization are considered some of the psychological factors involved in nocebo related side effects in Randomized Clinical Trials (RCTs; Barsky et al., 2002). As reported by clinicians, anxiety can lead to side effects as its somatic symptoms, such as tachycardia, dyspnea, and sweating (Ferguson, 1993).

Neuroimaging data showed how the affective-cognitive pain circuit was involved, with different modulation, in both the nocebo hyperalgesia and the placebo analgesia (Amanzio et al., 2013; Palermo et al., 2015).

In a functional magnetic resonance imaging study, Kong et al. (2008) analysed the brain regions involved in the nocebo response following an expectation of hyperalgesia. Their results showed an activation of many areas, such as bilateral dorsal anterior cingulate cortex, orbital prefrontal cortex, superior parietal lobe, hippocampus, insula, right claustrum/putamen, left frontal and parietal operculum, middle and superior temporal gyrus, lateral prefrontal gyrus, and medial frontal gyrus.

Neuroimaging data related to pain anticipation highlighted how negative expectancies had a substantial effect on cortical mechanisms.

In particular, a cognitive, affective, and motivational neural reaction, essential for survival, can be activated by negative expectations and psychosocial stimuli. Moreover, negative anticipation modulatory neural activations, implicated in salience detection, emotion/arousal, autonomic responses, and executive

functioning, may underlie increased levels of mood-changes related to fear, anxiety, and hypervigilance (Palermo et al., 2015).

Randomized Clinical Trials are useful in studying the role of a patient's psychosocial environment and the context in which therapies are administered on subsequent negative outcomes. The evaluation of adverse events (AEs) in the placebo group, matched with a specific psychotropic drug, provides an important perspective for understanding this phenomenon (Amanzio, 2015). Psychiatric patients, above all with mood and psychotic symptoms, represent an interesting population in order to study the nocebo effect. Indeed, AEs affect adherence and dropout rates among patients with psychiatric disorders in RCTs (Wahlbeck et al., 2001). Thus, AEs can be useful for an accurate description of patients with psychiatric diseases, who expect more negative clinical outcomes.

Moreover, the level of psychopathology, such as the severity of positive symptoms and signs of anxiety and depression, widely affected their perceptions and attribution of bodily sensations to medications (Hwang et al., 2010). Indeed, a higher level of psychiatric symptomatology makes patients more prone to express AEs manifested as nocebo-like effects (Palermo et al., 2019; Amanzio and Palermo, 2020). In addition, studying patients with pain conditions and neurodegenerative diseases would also be important, considering their clinical implications. In fact, as reported by a systematic review on nocebo effects in clinical trials by Amanzio et al. (2016b), neurological patients have a high probability of a negative outcome.

The reported findings may help to better understand the COVID-19-related distress due to excessive feelings and negative outcomes. In particular, understanding nocebo responses is important because they are substantial across disorders and may be associated with objective pathology and survival. Moreover, research on nocebo responses provides a way to investigate how the brain systems implicated in the processing of contextual information (such as threats) influence psychophysiology and clinically relevant outcomes, such as in the case of COVID-19. In addition, understanding how negative context and anticipatory negative expectancies influence outcomes in placebo groups of RCTs, in terms of AEs and dropout, will be essential to understand how people are now experiencing COVID-19-related symptomatology.

The negative information and harbingers of distress can be associated with the neuro-psychophysiological correlates observed in the nocebo effect and response through its cerebral underpinnings (the flipside of a positive outcome due to a placebo). Nocebo responses are associated with activity changes in brain areas, such as the amygdala, that are also involved in mood regulation (Freeman et al., 2015), and thus may worsen the stress/anxiety response to COVID-19.

In the presence of negative suggestions and nocebo effects associated with the SARS-CoV2 infection, the outcome of the disease can become more unfavourable, as reported for other diseases (Barsky, 2017). These more negative prognoses should be taken into greater consideration, especially in the elderly, with physical frailty and possible cognitive impairments, because they are at greater risk of SARS-CoV-2 infection and poorer prognosis.

The social distancing measures introduced to control the spread of COVID-19, while arguably required, also may exacerbates nocebo effects. A large body of evidence summarised by Howick et al. (2019) establishes that social isolation reduces mental health and increases mortality.

POSSIBLE WAYS TO DECREASE NEGATIVE EXPECTATIONS, STRESS AND ANXIETY RELATED TO COVID-19

It is crucial to understand and minimise psychological distress during and after the pandemic by reducing negative expectations and anxiety about the risk of contagion. To do that, individuals should be informed on how interpret and manage situational and individual factors predisposing them to develop negative effects and symptoms to a greater extent. Moreover, encouraging a healthy lifestyle in order to strengthen the immune system and combat psychological and physical distress should be suggested.

In particular, regarding the individual factors that can predispose individuals to psychological distress, and the onset of the nocebo phenomena, two aspects should be highlighted: (1) the importance of maintaining the functional aspects of anxiety, as healthy and natural response to stressful circumstances, as useful to comply with the rules of conduct to reduce the risk of SARS-COV2 infection and (2) in contrast, high levels of anxiety about the risk of contagion, which can lead to a stress reaction causing PTTS, should be contrasted, for instance, by avoiding update on alarming news.

With regard to situational-contextual factors, in which possible nocebo effects may be flourishing, it should be highlighted how: (1) it may be helpful for individuals to translate negative messages and communication flows into neutral or positive information, (2) also focusing on positive information in order to decrease negative expectations, stress, and anxiety related to COVID-19 should be emphasised, (3) positive expectations should be supported by how new treatments and vaccine developments are making progress (see **Table 2** as an example), and (4) the creation of a better balance of negative and positive information, focusing more on prevention, diagnostic, and prognostic perspectives (Vaughan and Tinker, 2009) should be encouraged. The authorised (evidence-based) information source will significantly reduce the spread and influence of fake or conflicting news (Tumpey et al., 2018).

Minimising nocebo effects might be an ethical requirement (Howick, 2020). Sharing of multiple sources of information, such as those regarding the COVID-19 pandemic, is necessary to stop the spread of disease. However, even if availability of information is the real defence against conflicting sources of information, they are, to some degree, unavoidable. In fact, the extent of this kind of information cannot be fully known yet, due to the uncertainty surrounding COVID-19. Some conflicting sources of information are created to spread anger and confusion, and some arise from haste and error. The former represent the most insidious form of COVID-19 information.

TABLE 2 | Examples of information possibly decreasing stress and anxiety.

Information	Publication date	Source
"The increase in the number of deaths continues to decline"	May 12th, 2020	Health Ministry, IT
"From large retailers 19 million surgical masks to citizens"	May 12th, 2020	Health Ministry, IT
"The people currently cured are 106,587"	May 11th, 2020	Health Ministry, IT
Brusaferro (NIH): "The contagion curve continues to decrease"	May 8th, 2020	National Institute of Health (Health Ministry, IT)
"40 years ago we defeated smallpox, now together we can also beat coronavirus"	May 8th, 2020	WHO
"The decline in ICU patients continues"	May 14th, 2020	Civil Protection Department, IT
"Discharged and healed, they exceed 50% of the total cases"	May 13th, 2020	Civil Protection Department, IT
Covid-19 Health Minister to G7 and EU: "Proceeding together on research, production and distribution of the vaccine"	May 7th, 2020	Communication of Health Minister, IT
Covid-19 "Great attention on re-openings. Listening to scientists and constant monitoring that is being done"	May 8th, 2020	Communication of Health Minister, IT
"Contracts to be entered into by the civil protection department for the supply of personal protection devices, medical and aid devices"	March 17th, 2020	Decree n. 18, March 17th, 2020
"Countries working to sustain population immunity to vaccine-preventable diseases during COVID-19 pandemic"	April 27th, 2020	WHO, European Region
PAHO Director: "Calls to accelerate and expand testing for COVID-19 in the Americas"	April 21st, 2020	Pan American Health Organization

ICU, intensive care unit.

CONCLUSIONS AND LIMITATIONS OF THE REVIEW

The most important limitation of this perspective review is the lack of empirical data on the association between the nocebo effect and COVID-19. However, the framework provided here may be an explorative and useful perspective to describe a phenomenon that is still new and unexplored nowadays.

During COVID-19, a possible nocebo response may be induced on a large scale due to negative information received from the media. These effects can be amplified by the environment, in particular by social isolation. Understanding how the nocebo effect can occur and minimise is a significant challenge, and may also be required ethically.

To do this, we should balance negative news with optimistic information, including how to prevent COVID-19, progresses in treatment, vaccines, and prevention, so that the vast majority of infected individuals will experience only minor symptoms. Although the COVID-19 era is an unavoidable breeding ground for the possible nocebo effect, stress management, exercise, and social contact – even remotely – can be promoted to mitigate them.

AUTHOR CONTRIBUTIONS

MA conceived of the content of this perspective review, wrote the first draft of the manuscript, and structured tables. JH and JK discussed the content of the review and proposed several additions to the text. MB and GEC wrote and edited the manuscript and revised tables. All authors contributed to the article and approved the submitted version.

REFERENCES

Amanzio, M. (2015). Nocebo effects and psychotropic drug action. *Expert. Rev. Clin. Pharmacol.* 8, 159–161. doi: 10.1586/17512433.2015.992877

Amanzio, M., Benedetti, F., Porro, C. A., Palermo, S., and Cauda, F. (2013). Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. *Hum. Brain Mapp.* 34, 738–752. doi: 10.1002/hbm.21471

Amanzio, M., and Palermo, S. (2020). Nocebo effects and psychotropic drug action - an update. *Expert. Rev. Clin. Pharmacol.* 13, 75–77. doi: 10.1080/17512433.2020.1722100

Amanzio, M., Palermo, S., and Benedetti, F. (2016a). "Nocebo and pain" in *Neuroscience of pain, stress, and emotion*. eds. M. A. Flaten and M. al'Absi (Cambridge, Massachusetts: Academic Press), 117–131.

Amanzio, M., Palermo, S., Skyt, I., and Vase, L. (2016b). Lessons learned from nocebo effects in clinical trials for pain conditions and neurodegenerative disorders. *J. Clin. Psychopharmacol.* 36, 475–482. doi: 10.1097/JCP.0000000000000556

Barsky, A. J. (2017). The iatrogenic potential of the physician's words. *J. Am. Med. Assoc.* 318, 2425–2426. doi: 10.1001/jama.2017.16216

Barsky, A. J., Saintfort, R., Rogers, M. P., and Borus, J. F. (2002). Nonspecific medication side effects and the nocebo phenomenon. *J. Am. Med. Assoc.* 287, 622–627. doi: 10.1001/jama.287.5.622

Benedetti, F., Amanzio, M., Vighetti, S., and Asteggiano, G. (2006). The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J. Neurosci.* 26, 12014–12022. doi: 10.1523/JNEUROSCI.2947-06.2006

Benedetti, F., Lanotte, M., Lopiano, L., and Colloca, L. (2007). When words are painful: unraveling the mechanisms of the nocebo effect. *Neuroscience* 147, 260–271. doi: 10.1016/j.neuroscience.2007.02.020

Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N., et al. (2020). The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet* 395, 912–920. doi: 10.1016/S0140-6736(20)30460-8

Cannon, W. B. (1942). "Voodoo" death. *Am. Anthropol.* 44, 169–181.

Ferguson, J. M. (1993). Alprazolam XR: patient acceptability, safety, and tolerability. *Psychiatr. Ann.* 23, 20–26.

Freeman, S., Yu, R., Egorova, N., Chen, X., Kirsch, I., Claggett, B., et al. (2015). Distinct neural representations of placebo and nocebo effects. *NeuroImage* 112, 197–207. doi: 10.1016/j.neuroimage.2015.03.015

Grzesiak-Feldman, M. (2013). The effect of high-anxiety situations on conspiracy thinking. *Curr. Psychol.* 32, 100–118. doi: 10.1007/s12144-013-9165-6

Hahn, R. A., and Kleinman, A. (1983). Belief as pathogen, belief as medicine: "voodoo death" and the "placebo phenomenon" in anthropological perspective. *Med. Anthropol. Q.* 14, 3–19.

Howick, J. (2020). Unethical informed consent caused by overlooking poorly measured nocebo effects. *J. Med. Ethics*. doi: 10.1136/medethics-2019-105903 [Epub ahead of print]

Howick, J., Kelly, P., and Kelly, M. (2019). Establishing a causal link between social relationships and health using the Bradford Hill Guidelines. *SSM Popul. Health* 8:100402. doi: 10.1016/j.ssmph.2019.100402

Howick, J., Webster, R., Kirby, N., and Hood, K. (2018). Rapid overview of systematic reviews of nocebo effects reported by patients taking placebos in clinical trials. *Trials* 19:674. doi: 10.1186/s13063-018-3042-4

Hwang, S. S. H., Jung, D. C., Ahn, Y. M., Kim, S. H., and Kim, Y. S. (2010). The effects of psychopathology on subjective experience of side effects of antipsychotics in patients with schizophrenia. *Int. Clin. Psychopharmacol.* 25, 83–90. doi: 10.1097/YIC.0b013e328334e5a8

Jolley, D., and Douglas, K. M. (2017). Prevention is better than cure: addressing anti-vaccine conspiracy theories. *J. Appl. Soc. Psychol.* 47, 459–469. doi: 10.1111/jasp.12453

Jolley, D., Meleady, R., and Douglas, K. M. (2020). Exposure to intergroup conspiracy theories promotes prejudice which spreads across groups. *Br. J. Psychol.* 111, 17–35. doi: 10.1111/bjop.12385

Kang, L., Li, Y., Hu, S., Chen, M., Yang, C., Yang, B. X., et al. (2020). The mental health of medical workers in Wuhan, China dealing with the 2019 novel coronavirus. *Lancet Psychiatry* 7:e14. doi: 10.1016/S2215-0366(20)30047-X

Kępińska, A. P., Iyegbe, C. O., Vernon, A. C., Yolken, R., Murray, R. M., and Pollak, T. A. (2020). Schizophrenia and influenza at the centenary of the 1918–1919 Spanish influenza pandemic: mechanisms of psychosis risk. *Front. Psych.* 11:72. doi: 10.3389/fpsyt.2020.00072

Kong, J., and Benedetti, F. (2014). Placebo and nocebo effects: an introduction to psychological and biological mechanisms. *Handb. Exp. Pharmacol.* 225, 3–15. doi: 10.1007/978-3-662-44519-8_1

Kong, J., Gollub, R. L., Polich, G., Kirsch, I., LaViolette, P., Vangel, M., et al. (2008). A functional magnetic resonance imaging study on the neural mechanisms of hyperalgesic nocebo effect. *J. Neurosci.* 28, 13354–13362. doi: 10.1523/JNEUROSCI.2944-08.2008

Liu, N., Zhang, F., Wei, C., Jia, Y., Shang, Z., Sun, L., et al. (2020). Prevalence and predictors of PTSS during COVID-19 outbreak in China hardest-hit areas: gender differences matter. *Psychiatry Res.* 287:112921. doi: 10.1016/j.psychres.2020.112921

Palermo, S., Benedetti, F., Costa, T., and Amanzio, M. (2015). Pain anticipation: an activation likelihood estimation meta-analysis of brain imaging studies. *Hum. Brain Mapp.* 36, 1648–1661. doi: 10.1002/hbm.22727

Palermo, S., Giovannelli, F., Bartoli, M., and Amanzio, M. (2019). Are patients with schizophrenia spectrum disorders more prone to manifest nocebo-like-effects? A meta-analysis of adverse events in placebo groups of double-blind antipsychotic trials. *Front. Pharmacol.* 10:502. doi: 10.3389/fphar.2019.00502

Rogers, J. P., Chesney, E., Oliver, D., Pollak, T. A., McGuire, P., Fusar-Poli, P., et al. (2020). Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 7, 611–627. doi: 10.1016/S2215-0366(20)30203-0

Samuels, M. A. (2007). "Voodoo" death revisited: the modern lessons of neurocardiology. *Cleve. Clin. J. Med.* 74(Suppl. 1), S8–S16. doi: 10.3949/ccjm.74.suppl_1.s8

Sani, G., Janiri, D., Di Nicola, M., Janiri, L., Ferretti, S., and Chieffo, D. (2020). Mental health during and after the COVID-19 emergency in Italy. *Psychiatry Clin. Neurosci.* 74:372. doi: 10.1111/pcn.13004

Swami, V., Furnham, A., Smyth, N., Weis, L., Lay, A., and Clow, A. (2016). Putting the stress on conspiracy theories: examining associations between psychological stress, anxiety, and belief in conspiracy theories. *Personal. Individ. Differ.* 99, 72–76. doi: 10.1016/j.paid.2016.04.084

Torales, J., O'Higgins, M., Castaldelli-Maia, J. M., and Ventriglio, A. (2020). The outbreak of COVID-19 coronavirus and its impact on global mental health. *Int. J. Soc. Psychiatry* 66, 317–320. doi: 10.1177/0020764020915212

Tumpey, A. J., Daigle, D., and Nowak, G. (2018). "Communicating during an outbreak or public health investigation" in *The CDC field epidemiology manual*. eds. R. A. Rasmussen and R. A. Goodman (Oxford, UK: Oxford University Press).

Vaughan, E., and Tinker, T. (2009). Effective health risk communication about pandemic influenza for vulnerable populations. *Am. J. Public Health* 99(Suppl. 2), S324–S332. doi: 10.2105/AJPH.2009.162537

Wahlbeck, K., Tuunainen, A., Ahokas, A., and Leucht, S. (2001). Dropout rates in randomised antipsychotic drug trials. *Psychopharmacology* 155, 230–233. doi: 10.1007/s002130100711

Wells, R. E., and Kaptchuk, T. J. (2012). To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *Am. J. Bioeth.* 12, 22–29. doi: 10.1080/15265161.2011.652798

WHO (2020). Mental health and psychosocial considerations during the COVID-19 outbreak 2020. https://www.who.int/docs/default-source/coronaviruse/mental-health-considerations.pdf (Accessed June 24, 2020).

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Information About the Optimism of a Placebo/Nocebo Provider and Placebo/Nocebo Side Effects

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Background: Research has demonstrated that personality characteristics, such as optimism are associated with placebo/nocebo responding. The present study investigated whether written information about the optimism of a placebo/nocebo provider can influence the occurrence of reported placebo/nocebo side effects.

Method: We analyzed data from 201 females (mean age = 26 years) who participated in a "clinical study on a new massage oil with stone clover extract." The oil (sunflower oil) was introduced as either eliciting a negative side effect (unpleasant itching; "nocebo oil") or a positive side effect (pleasant tingling; "placebo oil"). The administration of the oil was combined with written information about the maker of the product. The oil maker was either portrayed as a very optimistic person or no personal information was provided (only the company name). The participants had no personal contact with the experimenter and received all materials and instructions per post.

Results: The participants reported more frequent and intense itching when they received a nocebo suggestion compared to a placebo suggestion. Positive tingling sensations were reported more frequently than itching but did not differ between the placebo/nocebo conditions. Information about the optimism of the oil maker was associated with a lower frequency of reported side effects (adverse and beneficial).

Conclusion: This study demonstrated that it is sufficient to provide participants with written information about an inert substance to elicit the suggested side effect. Information about the provider's optimistic personality did not specifically influence reported side effects. Future studies should focus on how to adapt written information about a drug/product to minimize adverse side effects and to maximize positive side effects.

Keywords: placebo/nocebo side effects, personality, optimism, provider, recipient

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INTRODUCTION

Placebos and nocebos are substances or interventions with no specific effect on the symptom being treated. While placebos improve a person's condition (e.g., reduction of negative symptoms), nocebo treatment is associated with the occurrence of negative symptoms, the worsening of a condition, or the prevention of improvement (Moerman and Jonas, 2002; Häuser et al., 2012).

This definition has been specified by Faasse et al. (2019) who differentiate between primary placebo/nocebo effects and placebo/nocebo side effects. For example, when using a primary nocebo the potential adverse outcome is framed as the focal effect of the inert treatment, whereas a nocebo side effect refers to an adverse outcome that is ancillary to the typically beneficial outcome of the inert treatment.

The effects of placebos and nocebos have been conceptualized as "context effects" (Miller and Kaptchuk, 2008; Wager and Atlas, 2015). Important aspects of the context around placebo/nocebo treatment are social factors. The treatment is usually carried out as part of social interactions between healthcare providers and patients/clients. These interactions are shaped by the characteristics of both the providers and the recipients (e.g., for a review see Jakšić et al., 2013).

For example, personality factors such as optimism of the placebo recipients can influence their reactions to the inert treatment (e.g., Geers et al., 2005, 2010; Morton et al., 2009; Zhou et al., 2019; Kern et al., 2020). Trait optimism is an individual difference variable that reflects the extent to which individuals hold generalized favorable expectancies for their future. Higher levels of optimism are correlated prospectively with better subjective well-being in times of adversity or difficulty (i.e., controlling for previous well-being; Carver et al., 2010). A review by Kern et al. (2020) indicated that optimistic people show increased placebo responsivity. In a placebo study by Zhou et al. (2019), the reduction of pain unpleasantness was modulated by the interaction between expectancy and dispositional optimism. The latter finding illustrates that placebo/nocebo responding depends on both personality and situational factors. In line with this idea, studies found that pessimists were more likely than optimists to follow a nocebo expectation, whereas optimists showed greater benefit from the placebo condition (e.g., Geers et al., 2005; Hyland et al., 2007).

Additionally, optimism and confidence of the placebo provider can influence the placebo response (e.g., Kaptchuk et al., 2008; Howe et al., 2017; Daniali and Flaten, 2019; Gaab et al., 2019). Shapiro (1969) introduced the term "iatroplacebogenics" to describe placebo effects produced by health care professionals in the context of medical and psychotherapeutic treatment. These effects include the attitude to the patient and the attitude to the treatment (Feldman, 1956; Uhlenhuth et al., 1966; Shapiro, 1969; Gracely et al., 1985). Similarly, Brody (1997) has suggested that physicians can be "walking placebos" to stimulate positive changes in their patients through their attitudes and personality. In line with this idea, an early study by Uhlenhuth et al. (1966) demonstrated that patients who received an anxiolytic drug showed greater improvement when their doctors expressed a positive, enthusiastic attitude toward the medication compared to an uncertain, experimental attitude. In a more recent study, Kaptchuk et al. (2008) examined the effects of placebo acupuncture on irritable bowel syndrome. They found that the moderate effects of the placebo could almost be doubled when provided by a friendly and empathetic practitioner. Placebos that were administered during psychological treatment ("a video with green dots that activates positive emotional schemata") improved the mood of the participants, but only when provided by a trustworthy and optimistic experimenter (Gaab et al., 2019).

In the mentioned studies, the placebos were provided in a supportive atmosphere. The placebo providers attempted to create a positive relationship with the placebo recipients and expressed their optimistic attitude concerning treatment success. These types of social interactions are time-consuming and often cannot be realized in the healthcare system.

Therefore, the present study aimed to investigate whether it is sufficient to provide written information about the optimistic personality of the placebo provider to influence the placebo/nocebo response. The placebo recipients had no personal contact with the experimenter. All materials and instructions were sent by post. The participants of the present study were invited to a "clinical study that tested a massage oil with stone clover extract." The massage oil (sunflower oil) was either introduced as a substance with a negative side effect (unpleasant itching; "nocebo oil") or a substance with a positive side effect (pleasant tingling sensation; "placebo oil"). The administration of the oil was combined with written information about who made the oil. The oil maker was either portrayed as a very optimistic person, or no personal information (only the company name) was mentioned. It was hypothesized that information about an optimistic oil maker would enhance positive skin sensations in the placebo condition, and reduce negative skin sensations in the nocebo condition.

MATERIALS AND METHODS

Participants

A total of 245 females participated in this study. Inclusion criteria for the study were age over 18 years and female sex. We only tested females because of reported sex differences in placebo/nocebo responsivity (e.g., Vambheim and Flaten, 2017). Exclusion criteria included reported diagnoses of mental disorders and somatic diseases that might affect the responses to the oil (e.g., skin conditions). This led to the exclusion of five participants because of reported acne, neurodermatitis, and allergies. Furthermore, participants who did not complete the survey (n = 39) were excluded. Thus, data from n = 201 females (mean age = 26.16 years, SD = 7.83) were analyzed. The majority were university students (78%); the other participants were white-collar workers.

The study was approved by the Ethics Committee of the University (GZ. 39/75/63 ex 2019/20) and was performed following the Declaration of Helsinki. At the end of the study, all participants were fully debriefed.

Procedure

The participants were invited to the study via announcements at the university and on social media. It was stated that a company that produced herbal products wanted to test their new massage oil. After obtaining written consent, the participants were asked to fill out two questionnaires via an online survey tool (LimeSurvey GmbH, Hamburg, Germany):

a) The short version of the Brief Symptom Inventory (BSI) (Spitzer et al., 2011) screens for mental problems. The BSI has 18 items (α = 0.87) and three subscales: Depression (six items; e.g., loss of interest, hopelessness; Cronbach's α = 0.81), Anxiety (six items; e.g., nervousness, tension; α = 0.80), and Somatization (six items; e.g., dizziness, weakness; α = 0.73). The presence of symptoms is rated on five-point Likert scales ranging from 0 (not at all) to 4 (very strong). In the present sample, the t-scores for the BSI scores were all in the normal range (Depression: t-score = 0.57; Anxiety: t-score = 0.59; Somatization: t-score = 0.56; for mean scores see **Supplementary Table 1**).
b) The optimism/pessimism scale (Kemper et al., 2012) has two items: "Optimists are people who look to the future with confidence and usually expect good things. Please assess yourself: How optimistic are you in general?"; "Pessimists are people who are doubtful about the future and usually expect bad things. Please rate yourself: How pessimistic are you in general?" (Rating scale: 1 = not at all to 7 = very). In the total sample, the habitual optimism (M = 4.88, SD = 1.10) and pessimism (M = 2.90, SD = 1.18) did not differ from the mean scores reported by Kemper et al. (2012): optimism: $t(1333) = -0.18$, $p = 0.857$, pessimism: $t(1333) = 0.95$, $p = 0.340$). Ratings for optimism and pessimism were negatively correlated ($r = -0.63$, $p < 0.001$).

All participants who completed the online survey (which additionally asked for demographic information and diagnoses of somatic illness), received a package in the mail. This package contained a small glass bottle with sunflower oil and an information sheet. The bottle had a green label "*Melilotus officinalis*" and a dropper for application. The participants were instructed to apply 0.5 ml of the oil onto their left forearm (in an area with a diameter of 6 cm) and glide their digit finger softly over the area for 30 s. It was stated that the oil works quite quickly ("it takes 30 s to take effect"). The information sheet also included a suggestion about a specific side effect of the oil and information about the oil maker.

The suggested side effect was either pleasant (placebo side effect) or unpleasant (nocebo side effect). The suggestions were as follows:

a) Nocebo side effect: "This natural oil for your skin is extracted from the stone clover plant (*M. officinalis*). It has been developed for relaxation massages and promotes blood circulation. When applied, some users have noticed an unpleasant skin sensation: *itching*."
b) Placebo side effect: "This natural oil for your skin is extracted from the stone clover plant (*M. officinalis*). It has been developed for relaxation massages and promotes blood circulation. When applied, some users have noticed a pleasant skin sensation: *tingling*."

The placebo/nocebo suggestion was combined with one of two brief descriptions of the maker of the skin oil.

a) Optimistic maker: It was stated that the oil was made by Dr. Emilia Antonsini, a very dedicated physician and very optimistic person, who worked for a company producing natural medicine.
b) Company: In the control condition, only the company name was provided.

Design

The study had an independent measures design with two variables: (1) Information about the oil MAKER (optimistic maker vs. company) and (2) SUGGESTION of side effect (placebo vs. nocebo). The participants were randomly allocated to one of four groups (PO: Placebo/optimistic maker, PC: Placebo/company, NO: Nocebo/optimistic maker, NC: Nocebo/company). The participants of the four groups did not differ in mean age, reported habitual optimism/pessimism, and BSI scores (all $p > 0.28$; see **Supplementary Table 1**).

Dependent variables were perceived valence, intensity, and frequency of the skin sensations itching and tingling (the suggested side effects). Valence and intensity were rated on nine-point scales (intensity: 1 = no sensation; 9 = very intense, valence: 1 = very unpleasant; 9 = very pleasant). For the study design see **Figure 1**.

The redness of the treated skin area was assessed as a control variable (as an indicator of the intensity of rubbing; 1 = no redness; 9 = intense redness). The intensity of observed redness was M = 1.13 (SD = 0.48) and did not differ between the experimental groups ($F(3, 197) = 1.48$, $p = 0.221$). All ratings were recorded via the online tool.

A pilot study (n = 50, M = 25.2 years, SD = 7.2) had indicated that the oil applied to the skin did neither elicit itching nor tingling sensations when the participants were correctly informed about the sunflower oil.

Statistical Analysis

We computed 2 × 2 multivariate analyses of variance (MANOVAs) to test the effects of the between-subjects factors information about the oil MAKER (optimistic maker vs. company) and SUGGESTION (placebo vs. nocebo) on intensity and valence ratings for itching and tingling. Pillai's trace (V) is reported as test statistic. Significant effects were followed up with ANOVAs. Effect sizes are expressed by part.η^2 (partial eta squared).

To compare the frequency of reported itching/tingling (reported intensity > 1) between the four groups and different group combinations, we computed Chi^2 tests. By combining the groups PO + PC and NO + NC, the effect of SUGGESTION (placebo vs. nocebo) can be tested; by combining the groups PO + NO and PC + NC, the effect of MAKER (optimistic maker vs. company) can be tested. Effect sizes are expressed by Cramer's V.

To control for the possible influence of habitual optimism/pessimism of the participants on perceived intensity and valence of itching/tingling, we added these two factors separately as a covariate to a MANCOVA.

The conducted power analysis with G*Power 3.1.9.2 (Faul et al., 2007) indicated that a minimum sample size of 102 would

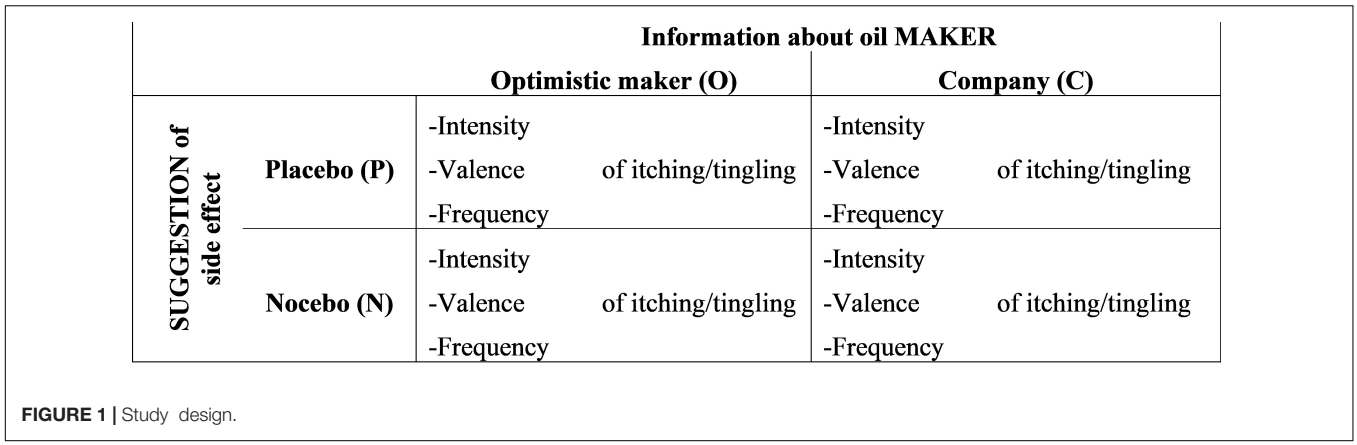

FIGURE 1 | Study design.

be needed to detect a medium effect size of $V = 0.06$ with a probability of $1–\beta = 0.80$, $\alpha = 0.05$ in the MANOVA for the between-subject factors SUGGESTION and MAKER on the dependent variables.

RESULTS

Intensity of Itching/Tingling

The MANOVA revealed a significant main effect of SUGGESTION on the intensity of reported itching and tingling ($V = 0.052$, $F(2, 196) = 5.40$, $p = 0.005$, part.η2 = 0.052). The main effect of MAKER ($V = 0.017$, $F(2, 196) = 1.69$, $p = 0.186$, part.η2 = 0.017) and the interaction MAKER × SUGGESTION ($V = 0.009$, $F(2, 196) = 0.86$, $p = 0.424$, part.η2 = 0.009) were not significant. Follow-up ANOVAs showed that the Nocebo groups experienced more intense itching compared to the Placebo groups ($F(1, 197) = 6.81$, $p = 0.010$, part.η2 = 0.033). The reported intensity of tingling did not differ between the groups ($F(1, 197) = 0.731$, $p = 0.394$, part.η2 = 0.004).

Valence of Itching/Tingling

The MANOVA revealed no significant main effects or interaction effects on the valence of itching and tingling (SUGGESTION: $V = 0.017$, $F(2, 195) = 1.72$, $p = 0.181$, part.η2 = 0.017; MAKER: $V = 0.012$, $F(2, 195) = 1.19$, $p = 0.306$, part.η2 = 0.012, SUGGESTION × MAKER: $V = 0.008$, $F(2, 195) = 0.75$, $p = 0.475$, part.η2 = 0.008; see **Table 1**).

Frequency of Itching/Tingling

Itching

Itching was reported more often when the Nocebo side effect was suggested (NC + NO; $M = 21\%$) compared to the Placebo side effect (PC + PO; $M = 9\%$; $Chi^2(1) = 6.37$; $p = 0.012$; $V = 0.18$). The information about the oil maker (optimistic maker: PO + NO: $M = 13\%$ vs. company: PC + NC: $M = 17\%$; $Chi^2(1) = 0.58$; $p = 0.446$; $V = 0.05$) did not influence itching. The comparison of the four groups (PC, PO, NC, NO) did not detect significant effects ($Chi^2(3) = 7.28$; $p = 0.063$, $V = 0.19$; see **Figure 2**).

Tingling

The percentage of participants who reported tingling sensations did neither differ between the four groups (PC, PO, NC, NO; $Chi^2(3) = 5.37$; $p = 0.147$; $V = 0.16$) nor any other group combination (all $p > 0.05$).

Combined Itching and Tingling

The percentage of participants who reported itching and/or tingling (combined placebo/nocebo side effects) did neither differ between the four groups (PC, PO, NC, NO; $Chi^2(3) = 4.54$; $p = 0.208$; $V = 0.15$) nor between groups with Nocebo suggestions vs. Placebo suggestions of side effects (PC + PO: $M = 49\%$; NC + NO: $M = 46\%$; $Chi^2(1) = 0.14$; $p = 0.709$; $V = 0.03$). However, INFORMATION about the oil maker influenced the combined side effects, which were less frequent when the maker was portrayed as optimistic (PO + NO: $M = 40\%$) compared to the company information (PC + NC: $M = 55\%$; $Chi^2(1) = 4.21$; $p = 0.040$; $V = 0.15$, see **Figure 2**).

Influence of Habitual Optimism/Pessimism of the Participants

The results of the MANCOVA are displayed in the **Supplementary Table 2**. Effects for optimism/pessimism were not statistically significant (all $p > 0.324$). The inclusion of the covariates did not change the results of the MANOVA (e.g., significant SUGGESTION effect on intensity of itching).

DISCUSSION

There is consensus that minimizing nocebo effects and maximizing placebo effects should lead to better treatment outcomes in clinical practice (Evers et al., 2018). Therefore, easy-to-implement interventions that achieve this goal are highly desirable. In the present investigation, we used a "minimal" nocebo/placebo approach with no personal contact between the provider and recipient of the inert treatment. The participants received written information about a skin oil that was introduced as either inducing "unpleasant itching" or "a pleasant tingling sensation" as a side effect. This information was combined

TABLE 1 | Means (M) and standard deviations (SD) of reported intensity and valence for the skin sensations (itching, tingling).

		Side Effect SUGGESTION	Information about MAKER	*M*	SD
Intensity	Itching	Placebo (P)	Optimistic (O)	1.07	0.33
			Company (C)	1.16	0.47
			Total Placebo (PO + PC)	1.12	0.40
		Nocebo (N)	Optimistic (O)	1.48	1.24
			Company (C)	1.31	0.67
			Total Nocebo (NO + NC)	1.39	0.98
		Total (P + N)	Optimistic (O)	1.26	0.89
			Company (C)	1.24	0.59
			Total (PO + PC + NO + NC)	1.25	0.75
	Tingling	Placebo (P)	Optimistic (O)	1.80	1.28
			Company (C)	2.33	1.84
			Total Placebo (PO + PC)	2.05	1.59
		Nocebo (N)	Optimistic (O)	1.80	1.73
			Company (C)	1.94	1.35
			Total Nocebo (NO + NC)	1.88	1.53
		Total (P + N)	Optimistic (O)	1.80	1.50
			Company (C)	2.13	1.61
			Total (PO + PC + NO + NC)	1.97	1.56
Valence	Itching	Placebo (P)	Optimistic (O)	5.28	1.66
			Company (C)	5.27	1.56
			Total Placebo (PO + PC)	5.27	1.61
		Nocebo (N)	Optimistic (O)	5.09	1.56
			Company (C)	5.00	1.30
			Total Nocebo (NO + NC)	5.04	1.42
		Total (P + N)	Optimistic (O)	5.19	1.61
			Company (C)	5.13	1.43
			Total (PO + PC + NO + NC)	5.16	1.52
	Tingling	Placebo (P)	Optimistic (O)	5.43	1.62
			Company (C)	5.84	1.57
			Total Placebo (PO + PC)	5.62	1.60
		Nocebo (N)	Optimistic (O)	5.24	1.49
			Company (C)	5.23	1.37
			Total Nocebo (NO + NC)	5.24	1.42
		Total (P + N)	Optimistic (O)	5.34	1.56
			Company (C)	5.52	1.49
			Total (PO + PC + NO + NC)	5.43	1.53

with the written suggestion that a very optimistic person had made the oil or the participants received no personality-relevant information.

The chosen approach is similar to providing patients with written medication information (e.g., package inserts of prescription drugs). This type of information typically includes how the medication should be taken (dosage), desired effects, and possible side effects of the drug. It has been shown that written medication information provides a useful addition to counseling by healthcare professionals (Buck, 1998) and helps the patients to take the medication safely and appropriately.

The present study demonstrated that written information about the unpleasant side effect provided along with the oil was sufficient to elicit itching in one-fifth of the participants. When a nocebo suggestion was given, 21% of the participants reported itching. According to the European commission nomenclature for communicating the frequency of adverse effects of drugs (see Büchter et al., 2014), a probability of 1/10 is already considered a "very common" side effect. However, this adverse effect had a low average intensity. It has to be noted that placebo/nocebo studies on itching have revealed inconsistent results (for a review see Bartels et al., 2015). For example, Bartels et al. (2014) elicited itch electrically and found that neither conditioning nor verbal suggestion procedures applied individually induced significant placebo or nocebo effects. However, the combination of both methods was effective. In other studies of this research group, nocebo effects on itching were observed (Van Laarhoven et al., 2011) and could be minimized and even reversed by conditioning with verbal suggestions (Meeuwis et al., 2019).

In contrast to rather small nocebo effects on itching, the overall magnitude of the nocebo effect in studies on pain (reported increase in pain intensity) has been moderate to large (see meta-analysis by Petersen et al., 2014). These studies typically use noxious stimulation, whereas in the present study the stimulus (sunflower oil) was completely free of negative effects. Therefore, it is remarkable that weak itching symptoms occurred with substantial frequency. A somewhat similar effect has been reported by Colloca et al. (2008) who showed that non-painful tactile stimulation could be turned into a pain sensation via verbal nocebo suggestions in healthy participants. Moreover, Faasse et al. (2019) concluded in their overview article that nocebo side effects are weaker compared to the effects of primary nocebos.

The frequency of reported pleasant tingling sensations (42%) was considerably higher in the tested participants than itching (21%). This response can be expected because the sunflower oil had been introduced as a massage oil, which has a positive (placebo) connotation. Furthermore, in their review on the neuropsychophysiology of tingling, Tihanyi et al. (2018) have argued, that higher cognitive processes, such as attention and expectations play an important role in the generation of pleasant tingling sensations. For example, suggestion-induced tingling has been used in hypnotherapy to manage pain. Additionally, focused attention on a body part can give rise to spontaneous tingling (Tihanyi et al., 2018). It is perhaps of these focused attention effects that tingling was so frequently reported in the present investigation but did not differ between the nocebo and placebo conditions.

We were not able to demonstrate that information about the optimism of the placebo/nocebo maker specifically influenced the nocebo/placebo response of the participants. However, the general tendency to report side effects (both adverse and beneficial secondary effects) was lower in the conditions with personality-relevant information compared to the conditions where only the company name was mentioned. The participants were perhaps more reluctant to report

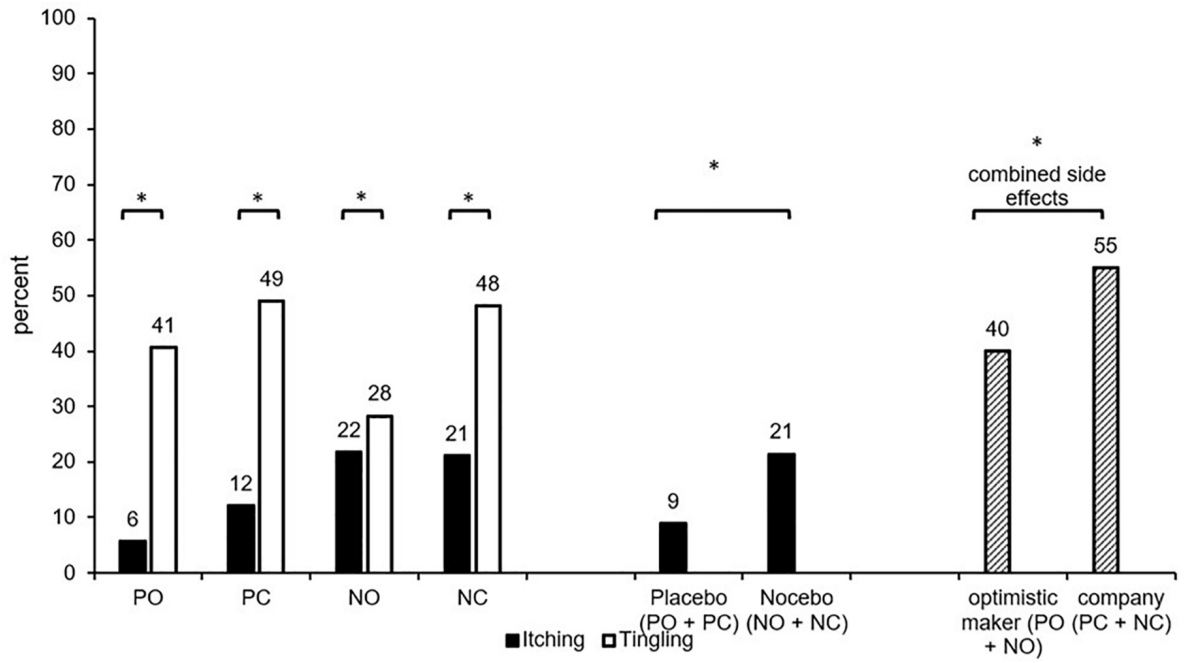

FIGURE 2 | Percentage of participants who reported itching/tingling (intensity > 1) in the four conditions. PC, Placebo/company; PO, placebo/optimistic maker; NC, nocebo/company; NO, nocebo/optimistic maker; combined side effects (percentage of participants who reported itching and/or tingling). *significant difference ($p < 0.05$).

side effects to a "real" person ("Emilia Antonsini") than to an "abstract" company. Whether this effect is associated with the described personality of the provider cannot be decided based on the design of the present study. Additional conditions, such as the description of a pessimistic provider would be required.

As to the best of our knowledge, systematic personality assessments of successful placebo/nocebo providers have not been conducted so far. The majority of studies focused on state optimism of the providers, who created positive outcome expectations through their behavior (e.g., Kaptchuk et al., 2008; Gaab et al., 2019). Thus, these studies relied on the personal interaction of the placebo/nocebo provider with the recipient.

However, research on consumer behavior has demonstrated that "product beliefs" can influence product perception and liking. It is a common marketing strategy to associate a certain product/brand with a specific person (or personality). This information is usually transmitted through advertisements or labels and not via direct communication. For example, in a study by Robinson and Higgs (2012) participants reported reduced liking of orange juice when they believed that their in-group did not like the juice. Tinnermann et al. (2017) found that labeling an inert cream as an expensive medication led to stronger nocebo hyperalgesia than the label "inexpensive medication." Thus, written information about the high price of the cream increased the risk of developing nocebo-related side effects. Crum et al. (2011) observed that identical milkshakes either labeled as high-calorie or low-calorie drinks received different ratings for perceived healthiness and elicited different hormonal (ghrelin) responses. However, this study did not find any significant label effects concerning subjective hunger after consumption or the tastiness of the milkshake. Thus, written product information (integrating social information) can be sufficient to change product evaluation (see Robinson and Higgs, 2012) but there are also boundary conditions (see Crum et al., 2011). Future studies on successful "placebo marketing" are therefore necessary.

In the present study, the reported dispositional optimism of the participants was not related to the intensity and valence of reported side effects. This is not in line with previous research (e.g., Geers et al., 2005, 2010; Hyland et al., 2007). In these studies, habitual pessimism was associated with increased nocebo responding, whereas optimists showed greater benefits from placebos. As mentioned before, optimism is a trait, which becomes particularly relevant in times of difficulties (Carver et al., 2010). The induced skin sensations in the present study however were evaluated as affectively neutral, on average.

As with any study, some limitations need to be acknowledged. We investigated healthy females. Therefore, the results cannot be generalized to other groups. The testing was conducted at home and not in a controlled lab environment. However, the participants were highly motivated to test the oil as reflected by a low dropout rate; 84% of the participants who received the oil by post completed the rating and often gave additional comments on the product (e.g., "is a little bit slimy," "is not absorbed fast enough," "where can I buy this product?," "wonderful soft skin"). Generally, the intensity ratings for the skin sensations were low. In future studies, substances could be used that elicit the suggested effect of itching (see Bartels et al., 2015). Moreover, the description of the oil maker could be improved. The maker

was generally characterized as a very optimistic person at the trait level but not concerning her attitude toward the side effect profile (the dependent variable of this study). Therefore, specification of the optimistic attitude (e.g., expressing confidence that the positive effects of the massage oil and not the negative side effects will dominate, or stressing that itching can be seen as a reminder of the massage oil having been absorbed) might be able to enhance the "optimism effect."

CONCLUSION

In conclusion, drug/product information on labels and package inserts are major sources of knowledge for patients/consumers. We demonstrated that written information about the side effect "itching" was sufficient to induce the suggested symptom in a substantial number of users. In contrast, a brief description of an optimistic nocebo/placebo provider and the optimism of the nocebo/placebo recipient did not specifically influence the placebo/nocebo response.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the ethics committee of the University of Graz (GZ. 39/75/63 ex 2019/20) and was performed following the Declaration of Helsinki. All participants gave written informed consent. At the end of the study, all participants were fully debriefed.

AUTHOR CONTRIBUTIONS

AS designed the study. CS collected and helped to analyze the data. Both authors wrote the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2020.608595/full#supplementary-material

Supplementary Table 1 | Characteristics of the participants in the four groups. PO, placebo/optimistic maker; NO, nocebo optimistic maker; PC, placebo/company name; NC, nocebo/company name; BSI, Brief Symptom Inventory.

Supplementary Table 2 | MANCOVA results. optimism/pessimism (of the participants); Suggestion: placebo vs. nocebo side effects; Maker: optimistic maker vs. company.

REFERENCES

Bartels, D. J. P., van Laarhoven, A. I. M., Haverkamp, E. A., Wilder-Smith, O. H., Donders, A. R. T., van Middendorp, H., et al. (2014). Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PLoS One* 9:e91727. doi: 10.1371/journal.pone.0091727

Bartels, D. J. P., van Laarhoven, A. I. M., van de Kerkhof, P. C. M., and Evers, A. W. M. (2015). Placebo and nocebo effects on itch: effects, mechanisms, and predictors. *Eur. J. Pain* 20, 8–13. doi: 10.1002/ejp.750

Brody, H. (1997). "The doctor as a therapeutic agent: a placebo effect research agenda," in *The Placebo Effect. An Interdisciplinary Exploration*, ed. A. Harrington (Cambridge, MA: Harvard University Press), 77–92.

Büchter, R. B., Fechtelpeter, D., Knelangen, M., Ehrlich, M., and Waltering, A. (2014). Words or numbers? Communicating risk of adverse effects in written consumer health information: a systematic review and meta-analysis. *BMC Med. Inform. Decis. Mak.* 14:76. doi: 10.1186/1472-6947-14-76

Buck, M. L. (1998). Providing patients with written medication information. *Rev. Ann. Pharmacother.* 32, 962–969. doi: 10.1345/aph.17455

Carver, C. S., Scheier, M. F., and Segerstrom, S. C. (2010). Optimism. *Clin. Psychol. Rev.* 30, 879–889. doi: 10.1016/j.cpr.2010.01.006

Colloca, L., Sigaudo, M., and Benedetti, F. (2008). The role of learning in nocebo and placebo effects. *Pain* 136, 211–218. doi: 10.1016/j.pain.2008.02.006

Crum, A. J., Corbin, W. R., Brownell, K. D., and Salovey, P. (2011). Mind over milkshakes: mindsets, not just nutrients, determine ghrelin response. *Health Psychol.* 30, 424–429. doi: 10.1037/a0023467

Daniali, H., and Flaten, M. A. (2019). A qualitative systematic review of effects of provider characteristics and nonverbal behavior on pain, and placebo and nocebo effects. *Front. Psychiatry* 10:242. doi: 10.3389/fpsyt.2019.00242

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., et al. (2018). Implications of placebo and nocebo effects for clinical practice: expert consensus. *Psychother. Psychosom.* 87, 204-210. doi: 10.1159/000490354

Faasse, K., Helfer, S. G., Barnes, K., Colagiuri, B., and Geers, A. L. (2019). Experimental assessment of nocebo effects and nocebo side effects: definitions, study design, and implications for psychiatry and beyond. *Front. Psychiatry* 10:396. doi: 10.3389/fpsyt.2019.00396

Faul, F., Erdfelder, E., Lang, A. G., and Buchner, A. (2007). G* Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav. Res. Methods* 39, 175–191. doi: 10.3758/bf03193146

Feldman, P. E. (1956). The personal element in psychiatric research. *Am. J. Psychiatry* 113, 52–54. doi: 10.1176/ajp.113.1.52

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

Geers, A. L., Helfer, S. G., Kosbab, K., Weiland, P. E., and Landry, S. J. (2005). Reconsidering the role of personality in placebo effects: dispositional optimism, situational expectations, and the placebo response. *J. Psychosom. Res.* 58, 121–127. doi: 10.1016/j.jpsychores.2004.08.011

Geers, A. L., Wellman, J. A., Fowler, S. L., Helfer, S. G., and France, C. R. (2010). Dispositional optimism predicts placebo analgesia. *J. Pain* 11, 1165–1171. doi: 10.1016/j.jpain.2010.02.014

Gracely, R. H., Dubner, R., Deeter, W. R., and Wolskee, P. J. (1985). Clinicians' expectations influence placebo analgesia. *Lancet* 1:43. doi: 10.1016/s0140-6736(85)90984-5

Häuser, W., Hansen, E., Enck, P., Breuer, T. G., Meier, J. J., Diehl, R. R., et al. (2012). Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Deutsches Ärzteblatt Int.* 109, 459–465.

Howe, L. C., Goyer, J. P., and Crum, A. J. (2017). Harnessing the placebo effect: exploring the influence of physician characteristics on placebo response. *Health Psychol.* 36:1074. doi: 10.1037/hea0000499

Hyland, M. E., Whalley, B., and Geraghty, A. W. A. (2007). Dispositional predictors of placebo responding: a motivational interpretation of flower essence and gratitude therapy. *J. Psychosom. Res.* 62, 331–340. doi: 10.1016/j.jpsychores.2006.10.006

Jakšić, N., Aukst-Margetić, B., and Jakovljević, M. (2013). Does personality play a relevant role in the placebo effect? *Psychiatr. Danub.* 25, 0–23.

Kaptchuk, T. J., Kelley, J. M., Conboy, L. A., Davis, R. B., Kerr, C. E., Jacobson, E. E., et al. (2008). Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* 336, 999–1003.

Kemper, C. J., Beierlein, C., Kovaleva, A., and Rammstedt, B. (2012). *SOP 2-Skala Optimismus-Pessimismus 2.* Mannheim: Leibniz-Zentrum für Psychologische Information und Dokumentation (ZPID), doi: 10.23668/psycharchives

Kern, A., Kramm, C., Witt, C. M., and Barth, J. (2020). The influence of personality traits on the placebo/nocebo response: a systematic review. *J. Psychosom. Res.* 128:109866. doi: 10.1016/j.jpsychores.2019.109866

Meeuwis, S. H., van Middendorp, H., van Laarhoven, A. I. M., Veldhuijzen, D. S., Lavrijsen, A. P. M., and Evers, A. W. M. (2019). Effects of open- and closed-label nocebo and placebo suggestions on itch and itch expectations. *Front. Psychiatry* 10:436. doi: 10.3389/fpsyt.2019.00436

Miller, F. G., and Kaptchuk, T. (2008). The power of context: reconceptualizing the placebo effect. *J. R. Soc. Med.* 101, 222–225. doi: 10.1258/jrsm.2008.070466

Moerman, D. E., and Jonas, W. B. (2002). Deconstructing the placebo effect and finding the meaning response. *Ann. Intern. Med.* 136, 471–476. doi: 10.7326/0003-4819-136-6-200203190-00011

Morton, D. L., Watson, A., El-Deredy, W., and Jones, A. K. (2009). Reproducibility of placebo analgesia: effect of dispositional optimism. *Pain* 146, 194–198. doi: 10.1016/j.pain.2009.07.026

Petersen, G. L., Finnerup, N. B., Colloca, L., Amanzio, M., Price, D. D., Jensen, T. S., et al. (2014). The magnitude of nocebo effects in pain: a meta-analysis. *Pain* 155, 1426–1434. doi: 10.1016/j.pain.2014.04.016

Robinson, E., and Higgs, S. (2012). Liking food less: the impact of social influence on food liking evaluations in female students. *PLoS One* 7:e48858. doi: 10.1371/journal.pone.0048858

Shapiro, A. K. (1969). Iatroplacebogenics. *Int. Pharmacopsychiatry* 2, 215–248. doi: 10.1159/000468855

Spitzer, C., Hammer, S., Löwe, B., Grabe, H. J., Barnow, S., Rose, M., et al. (2011). The short version of the brief symptom inventory (BSI-18): preliminary psychometric properties of the German translation. *Fortschr. Neurol. Psychiatr.* 79, 517–523.

Tihanyi, B. T., Ferentzi, E., Beissner, F., and Köteles, F. (2018). The neuropsychophysiology of tingling. *Conscious. Cogn.* 58, 97–110. doi: 10.1016/j.concog.2017.10.015

Tinnermann, A., Geuter, S., Sprenger, C., Finsterbusch, J., and Büchel, C. (2017). Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. *Science* 358, 105–108. doi: 10.1126/science.aan1221

Uhlenhuth, E. H., Rickels, K., Fisher, S., Park, L. C., Lipman, R. S., and Mock, J. (1966). Drug, doctor's verbal attitude and clinic setting in the symptomatic response to pharmacotherapy. *Psychopharmacologia* 9, 392–418. doi: 10.1007/bf00406450

Vambheim, S. M., and Flaten, M. A. (2017). A systematic review of sex differences in the placebo and the nocebo effect. *J. Pain Res.* 10, 1831–1839. doi: 10.2147/JPR.S134745

Van Laarhoven, A. I., Vogelaar, M. L., Wilder-Smith, O. H., van Riel, P. L., van de Kerkhof, P. C., and Evers, A. W. M. (2011). Induction of nocebo and placebo effects on itch and pain by verbal suggestions. *Pain* 152, 1486–1494. doi: 10.1016/j.pain.2011.01.043

Wager, T. D., and Atlas, L. Y. (2015). The neuroscience of placebo effects: connecting context, learning, and health. *Nat. Rev. Neurosci.* 16, 403–418. doi: 10.1038/nrn3976

Zhou, L., Wei, H., Zhang, H., Li, X., Bo, C., Wan, L., et al. (2019). The influence of expectancy level and personal characteristics on placebo effects: psychological underpinnings. *Front. Psychiatry* 10:20. doi: 10.3389/fpsyt.2019.00020

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frontiers in Psychology

ORIGINAL RESEARCH
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What Psychological Factors Make Individuals Believe They Are Infected by Coronavirus 2019?

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Background: We previously showed, by means of an online-based survey, that the belief of being infected by coronavirus disease 2019 (COVID-19) acted as a nocebo and predicted higher perception of symptoms similar to COVID-19 symptoms. However, there is little known about the psychological mechanisms that give rise to beliefs such as certainty of being infected by COVID-19, and this was investigated in the present study.

Objective: Using the same data from the previous online survey with the same research team, we further investigated whether certainty of being infected by COVID-19 is associated with age, sex, health anxiety, and/or personality traits.

Methods: Respondents (N = 375) filled out an online survey with 57 questions about symptoms similar to COVID-19, certainty of being infected by COVID-19, anxiety, stress, health anxiety, and personality dimensions (based on the five-factor model of personality).

Results: Higher levels of conscientiousness and health anxiety were independently associated with certainty of being infected by COVID-19. The model predicted 29% of the variance in certainty of being infected by COVID-19.

Conclusion: Being conscientious and worried about health issues were associated with the belief of being infected by COVID-19. Such finding may have implications for health care personnel who provide COVID-19 testing or consulting services to general population, as individuals high in these traits may over-report COVID-like symptoms. Theoretically, these findings point to psychological factors that may increase nocebo and possibly placebo effects. Clinically, the findings suggest that individuals high in conscientiousness and health anxiety may be more likely to over-report their bodily experiences.

Keywords: coronavirus disease 2019, expectations, health anxiety, personality dimensions, conscientiousness, nocebo effects

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INTRODUCTION

Nocebos are medically inactive substances or procedures that make the individual expect unpleasant outcomes (Mitsikostas et al., 2020). The underlying mechanisms for nocebo effects are expectations and former experiences with treatments. Nocebo effects lower treatment outcomes, increase reporting of side-effects of treatments, and may impose extra pressure on the health care system (Petrie and Rief, 2019).

The recent global health threat, Coronavirus disease 2019 (COVID-19) is a highly infectious respiratory disease that is being widely spread across the globe (World Health Organization, 2020), affecting more than 120 million people so far (Worldometer, 2021). Symptoms of COVID-19 include dry cough, shortness of breath, fatigue, myalgia, and fever that are highly variable across individuals in terms of the severity and the course of the disease. Infected individuals mostly fall in a wide spectrum between experiencing no symptoms *via* mild to moderate symptoms that require no special treatment for recovery, to severe life-threatening respiratory symptoms (He et al., 2020; Moghadas et al., 2020). COVID-19 symptoms resemble symptoms of conventional seasonal influenza (Fauci et al., 2020). Thus, following the experience of symptoms similar to COVID-19 symptoms (COVID-like symptoms), the individual may suspect being infected by COVID-19, and may report the symptoms as COVID-19 symptoms.

Daniali and Flaten (2021, under review) showed that reports of COVID-like symptoms were independently predicted by both a cognitive factor, i.e., certainty of being infected by COVID-19, and by anxiety. The present study focuses on the factors that are associated with the belief of being infected by COVID-19. Very few studies have investigated the psychological factors that underlie the formation of beliefs or expectations that are central in the elicitation of nocebo and placebo effects (Flaten et al., 2013). Therefore, using the same data as the previous study (Daniali and Flaten, 2021, under review), we investigated whether sex, age, personality factors, or health anxiety predicted certainty of being infected by COVID-19.

Health anxiety refers to worrying about health in an inappropriate and exaggerated way. This construct has been shown to increase (e.g., Taylor and Asmundson, 2004) and spread during public pandemics (e.g., H1N1 influenza: Bish and Michie, 2010; Ebola: Blakey et al., 2015; SARS: Xie et al., 2011), with relations to higher COVID-19 anxiety (e.g., Lee, 2020; Son et al., 2020; Wang et al., 2020). Thus, it is likely that higher health-related concerns elevate the certainty of being infected by COVID-19.

Personality characteristics, defined as individual differences in traits and patterns of thinking, feeling, and behaving (McCrae and Costa, 2003), have been shown to modulate health-related behaviors. According to the five-factor model of personality (FFM; Costa and McCrae, 1992), individual traits are categorized into five major personality dimensions: "extroversion, agreeableness, conscientiousness, neuroticism and openness" (McCrae and Costa, 1997). Specifically, neuroticism and conscientiousness are shown to be the most pertinent personality traits in prediction of health-related behaviors. For instance, individuals scoring higher in conscientiousness, have lower health risk behaviors (e.g., Hakulinen et al., 2015); and individuals higher in neuroticism display more health risk behaviors such as smoking (e.g., Hakulinen et al., 2015). Thus, personality traits, specifically neuroticism and conscientiousness, may contribute to the belief of certainty of being infected by COVID-19.

It is shown that females report higher nocebo effects compared to males (Vambheim and Flaten, 2017), and report more COVID-like symptoms (Daniali and Flaten, 2021, under review) so it is logical to assume that females have stronger beliefs of being infected by COVID-19 than males. Moreover, as the elderly are at a higher risk of adverse consequences of COVID-19, elderly individuals could be more likely to develop beliefs about being infected by COVID-19.

Taken together, we assumed a model in which age, sex, health anxiety and personality factors, specifically neuroticism, and conscientiousness, predict the belief of certainty of being infected by COVID-19.

MATERIALS AND METHODS

Respondents

The present study used the data from a previous study (Daniali and Flaten, 2021, under review).

Briefly, the sample included 135 males (Min_{age} = 17, Max_{age} = 79, *Range* (lowest minus highest) = 62, M_{age} = 33.18, *SD* = 12.06) and 279 females (Min_{age} = 16, Max_{age} = 71, *Range* = 55, M_{age} = 32.95, *SD* = 10.40) and three as "other gender" who filled out an online survey. Other gender respondents and those who were tested (regardless of the results) for COVID-19 (9.4%, *N* = 39) were excluded which resulted in a total of 375 participants (Min_{age} = 16, Max_{age} = 79, *Range* = 63, M_{age} = 32.72, *SD* = 10.90) including 126 males (Min_{age} = 17, Max_{age} = 79, *Range* = 62, M_{age} = 32.88, *SD* = 12.13) and 249 females (Min_{age} = 16, Max_{age} = 67, *Range* = 51, M_{age} = 32.64, *SD* = 10.24).

Measures

Demographic questions: Using four items, participants specified their sex, age, education level, and whether they have tested for COVID-19.

COVID-19 certainty: Certainty of being infected by COVID-19 was rated on a five-point Likert single item starting from "Sure not infected" that was anchored to (0) and ending with "Certain that infected" anchored to (4).

COVID-19 symptoms: Using 10 five-point Likert questions starting from (0) anchored to "None," to (4) that was anchored to "Severe," participants rated the severity of a set of symptoms similar to symptoms of COVID-19 during the last 2 months before participating in the survey. Participants rated the severity of their "myalgia (bodily pain)," "fatigue," "cough," "dry cough," "sore throat," "difficulty in breathing," "fever," "persistent fever," and "headache." The items have been previously used to measure symptoms of COVID-19 in the general population (Wang et al., 2020). For more information about the severity of symptoms similar to COVID-19, the reader is referred to the previous study (Daniali and Flaten, 2021, under review).

Personality dimensions: Participants filled out the Big Five Inventory short version (BFI-10) (John et al., 1991). Using 10 statements that are rated on a five-point Likert scale ranging from "1" to "5," BFI measures the five-factor model of personality

that includes "extroversion, agreeableness, conscientiousness, neuroticism and openness." Each personality dimension is assessed by two statements. BFI-10 is a reliable and valid personality inventory with satisfactory psychometric properties (e.g., Hahn et al., 2012).

Health anxiety: Health anxiety was assessed by the Short Health Anxiety Inventory (SHAI; Salkovskis et al., 2002) including 18 items measuring health anxiety independent of physical health status. Each item provides four different statements about a health-related worry that are scored from (0) to (3). Items assess worrying about health, awareness of bodily sensations or changes, and feared consequences of having an illness. The SHAI has acceptable psychometric properties (e.g., Salkovskis et al., 2002). The last four items of SHAI assess "negative consequences" and are separately scored (Salkovskis et al., 2002). Therefore, in this study only the sum of the first 14 items was used as the SHAI scores. The internal consistency for the first 14 items of SHAI in the present study was 0.85.

Stress and anxiety were also assessed with 14 items, but as they overlapped with health anxiety, the data related to stress and anxiety is not analyzed in this study. In total, the survey consisted of 57 items.

Procedure

With a focus on the general population, the online survey was first shared with the Norwegian University of Science and Technology (NTNU) students and staff *via* the intranet and then was shared in other social media such as Facebook, Instagram, Twitter, and LinkedIn from 2nd of May 2020, to the 3rd of August. Respondents were informed that the study is conducted unanimously and that they must agree to the state of consent before taking part. Both healthy participants and COVID-19 patients could participate, as the study was aimed to test the hypotheses in the general population. The study was introduced to participants as an investigation on "the effects of psychological factors on symptoms related to COVID-19," that seeks individuals' thoughts, personality, negative emotions such as stress and anxiety, and physical symptoms like COVID-19. Participants had to be able to comprehend English. The study holds approval from the Regional committee for medical and health research ethics, Norway (REK; project number: 142652), and the Norwegian Center for Research Data (NSD; project number: 605612).

Statistical Analyses

The data were analyzed by SPSS software 27 (SPSS, Inc., Chicago, Illinois). First, data was screened for outliers and missing values. Next, descriptive statistics were analyzed by means of Means, *SD*s, Maxes, Mines, and the percentile distribution of the certainty of being infected by COVID-19. Next, the correlation between variables was investigated using two-tailed *Pearson* correlation. Followingly, multiple regression assumptions were checked, and issues were resolved. Finally, due to the non-normality of the residuals (see Data Screening and Preparation), a multiple regression analysis with Huber-white heteroscedasticity-consistent (HC) SEs was run to test the proposed model including variables age, sex, health anxiety, and personality factors, as the independent variables (IVs) to predict the certainty of being infected by COVID-19. Moreover, the internal consistency for 14 health anxiety items was calculated using Cronbach alpha.

Data Screening and Preparation

No outliers or missing values were detected. To test the normality, heteroscedasticity, homoscedasticity, multicollinearity, and linearity of the variables, a multiple regression was run. Certainty of being infected by COVID-19, as the dependent variable (DV), was regressed on age, sex, health anxiety, and five personality factors (extraversion, agreeableness, openness, neuroticism, and conscientiousness) as the independent variables (IVs). The results indicated that health anxiety (B = 0.04, $S.E$ = 0.009, β = 0.24, p = 0.0001) and conscientiousness (B = 0.08, $S.E$ = 0.03, β = 0.16, p = 0.003) predicted certainty of being infected by COVID-19. However, the histogram plot showed that certainty was not normally distributed, and the Breusch-Pagan test supported the unreliability of the residuals (X^2 = 13.72, p = 0.0002; Breusch and Pagan, 1979). Then, following the suggestions by Hayes and Cai (2007), HC SEs were implemented to control for the heteroscedastic residuals. To test the homoscedasticity assumption, a multiple regression with homoscedasticity-robust SEs was conducted and the results indicated that health anxiety and conscientiousness still significantly predicted the DV. Moreover, the variance inflation (VIF) and tolerance of IVs fell in the acceptable range (tolerance > 0.20; VIF $\leq$ 10). Lastly, the linearity assumption was met as evidenced by the scatter plot.

Before conducting the multiple regression analysis, the data for personality dimensions were first centered by subtracting the raw data for each individual from the total mean, as the raw data for the personality dimensions did not include a zero value. Then, the centered data were included into the regression model using the "enter" method.

RESULTS

Descriptive Statistics

The means of the study variables are presented in **Table 1**. With respecting to certainty of being infected by COVID-19, 26.9% of participants reported "sure *not infected*," 45.6% reported "*probably not infected*," 17.9% were "uncertain," 7.5% were "*quite certain*" and 2.1% were "*certain*" of being infected by COVID-19 (**Table 2**).

Correlations

Certainty of being infected by COVID-19 correlated with health anxiety and conscientiousness. Age was positively correlated with conscientiousness and negatively correlated with health anxiety and neuroticism. Health anxiety was negatively correlated with agreeableness, conscientiousness and positively correlated with neuroticism. Moreover, neuroticism was negatively correlated with conscientiousness (**Table 3**).

TABLE 1 | Descriptive statistics of the included variables.

Sex	Certainty	Age	H-Anxiety	Ep	Ap	Cp	Np	Op
Females M; SD	1.08; 0.89	32.64; 10.24	11.38; 5.44	6.22; 1.97	7.46; 1.58	6.98; 1.89	6.34; 2.19	6.98; 1.89
N = 249 (Min; Max)	(0; 4)	(16; 67)	(1; 30)	(2; 10)	(3; 10)	(2; 10)	(2; 10)	(3; 10)
Males M; SD	1.21; 1.07	32.88; 12.13	11.15; 6.35	5.75; 1.91	7.10; 1.75	7.11; 1.77	5.48; 2.26	6.74; 1.68
N = 126 (Min; Max)	(0; 4)	(17; 79)	(0; 28)	(2; 10)	(2; 10)	(2; 10)	(2; 10)	(2; 10)
Total M; SD	1.13; 0.96	32.72; 10.90	11.31; 5.76	6.07; 1.96	7.35; 1.64	7.02; 1.86	6.06; 2.25	7.00; 1.70
N = 375 (Min; Max)	(0; 4)	(16; 79)	(0; 30)	(2; 10)	(2; 10)	(2; 10)	(2; 10)	(2; 10)

M, mean; SD, standard deviation; Certainty, certainty of being infected by COVID-19; Ep, extroversion; Ap, agreeableness; Cp, conscientiousness; Np, neuroticism; and Op, openness personality dimensions.

TABLE 2 | Distribution of participants based on the certainty of being infected by COVID-19.

Certainty of being infected	Frequency	Percent	Cumulative percent
Sure not infected	101	26.9	26.9
Probably not infected	171	45.6	72.5
Uncertain	67	17.9	90.4
Quite certain	28	7.5	97.9
Certain	8	2.1	100
Total	375	100	

Regression Analysis

The results of the multiple regression showed that health anxiety [B = 0.04, β = 0.24, $S.E$ (HC) = 0.01, p = 0.0001], and conscientiousness [B = 0.08, β = 0.16, $S.E$ (HC) = 03, p = 0.006] were significant predictors of certainty of being infected by COVID-19 [R = 0.29, R^2 = 0.0827, F(8,366) = 3.23, p = 0.001]. No other variable was shown as a significant predictor of certainty of being infected by COVID-19. The model explained 29% of variance of certainty of being infected by COVID-19 (**Table 4**).

DISCUSSION

The results of the present study showed that certainty of being infected by COVID-19 was predicted by the personality dimension conscientiousness and the cognitive-emotive factor health anxiety. This model explained 29% of variance in certainty of being infected by COVID-19. Sex, age, and other personality dimensions such as neuroticism did not emerge as significant predictors for certainty of being infected by COVID-19. Moreover, conscientiousness and health anxiety were negatively correlated.

We previously showed that certainty of being infected acted as a nocebo and exacerbated the perception of symptoms similar to COVID-19 (Daniali and Flaten, 2021, under review). This means that individuals who were more certain about being infected by COVID-19, were more likely to report, e.g., a sore throat or headache as COVID-19 symptoms. The current findings highlight the contribution of health anxiety and conscientiousness in such a nocebo belief.

Higher conscientiousness led to stronger beliefs of being infected by COVID-19. Former studies have shown that conscientious individuals tend to expose themselves to more COVID-19 news, more strictly follow the preventive health advice such as keeping a good hand hygiene (Carvalho et al., 2020), and practice precautionary behaviors such as stockpiling of toilet papers (Garbe et al., 2020). Along with the same line, it can be assumed that the stronger belief in being infected by COVID-19 in conscientious individuals can be due to an increased attention toward symptoms that resemble COVID-19 symptoms. However, this assumption requires more investigation, as to our knowledge, our finding is the first to demonstrate the effects of conscientiousness on health-related beliefs. Conscientiousness is known to be associated with being disciplined, rule-following, and self-controlled (Costa and McCrae, 1987, 1992); the negative correlation between conscientiousness with neuroticism here partially supports this notion.

Higher health anxiety also led to a stronger belief of being infected by COVID-19. This fits well with findings that health anxiety predicts hypochondriasis (e.g., Bleichhardt and Hiller, 2007; Faasse and Petrie, 2013; Jungmann and Witthöft, 2020). Individuals who are highly worried about their health status, tend to misinterpret bodily experiences as indications of having caught a disease. Like above, such association may be explained through an inclination to over-contemplate about the disease and its potential catastrophic consequences (e.g., Faasse and Petrie, 2013). Health anxiety is associated with emotional instability and overthinking about health-related negative consequences (e.g., Ferguson, 2009); this is evidenced here by the positive correlation of health anxiety with neuroticism.

Although both conscientiousness and health anxiety predicted higher certainty of being infected by COVID-19, the factors were negatively correlated, as shown in prior studies (Nikčević et al., 2020). Thus, there seems to be several ways in which different individuals may develop similar health-related beliefs. The literature on the psychological processes that underlie the formation of beliefs is scarce. However, as beliefs or expectations are central concepts in the elicitation and amplitude of placebo and nocebo effects, the development and structure of beliefs will be studied further.

Contrary to our proposed model, neuroticism failed to predict certainty of being infected by COVID-19, suggesting that certainty of being infected by COVID-19 is not impacted by being

TABLE 3 | The correlations between study variables.

S. No	1	2	3	4	5	6	7	8
1. Certainty	1							
2. Age	−0.03	1						
3. Health Anxiety	0.22**	−0.21*	1					
4. Extraversion	0.03	0.02	−0.06	1				
5. Agreeableness	−0.02	0.01	−0.18*	0.1	1			
6. Conscientiousness	0.12**	0.24**	−0.18**	0.15**	0.15**	1		
7. Neuroticism	0.09	−0.17*	0.41**	−0.1	−0.22**	−0.20**	1	
8. Openness	−0.01	0.1	0.07	0.03	0.12*	0.09	0.06	1

*N for all variables = 375. *p < 0.05; **p < 0.01.*

TABLE 4 | The characteristics of the multiple regression results.

Predictors	B	β	*SE* (HC)
Age	0.00	0.02	0.00
Sex	0.14	0.07	0.10
Health anxiety	0.04***	0.24***	0.01
Extraversion	0.02	0.03	0.02
Agreeableness	0.01	0.02	0.03
Conscientiousness	0.08**	0.16**	0.03
Neuroticism	0.02	0.04	0.02
Openness	0.01	−0.04	0.02
R^2 (*Root MSE*)	0.08 (0.93)		
F (*df*)	3.23*** (8, 366)		

*The dependent variable was certainty of being infected by COVID-19. B: coefficients. β: Standardized Beta coefficients. SE (HC): heteroscedasticity-consistent SEs. Root MSE: root mean square errors. **p < 0.01; ***p < 0.001.*

constantly anxious and experiencing negative affect. This is consistent with prior studies that found no association between personality traits and expectations of higher pain. For instance, Aslaksen and Lyby (2015) studied the effects of personality traits and fear of pain on nocebo hyperalgesia (i.e., increase in pain due to an inert agent) and reported that no personality trait was significantly associated with the nocebo effect.

Our analyses did not reveal a specific contribution for participants' age on the relationship between the personality traits, health anxiety, and certainty of being infected by COVID-19. There is no consensus yet on how age and sex can moderate the effects of personality factors on negative psychological consequences related to COVID-19. For example, Aschwanden et al. (2020) found that age moderated the association between personality traits and reactions toward COVID-19, as being elder was associated with stronger personality-reflected behaviors toward COVID-19 such as higher neuroticism reflected through being more concerned about COVID-19, or conscientiousness reflected through more precautionary behaviors. However, Nikčević et al. (2020) found no effects for participants' age on the association between personality traits, health anxiety, and negative emotions related to COVID-19.

Finally, participant sex did not emerge as a significant predictor of certainty of being infected by COVID-19, suggesting that this nocebo belief occur in both sexes. This result might have been due to the unequal numbers of males (N = 126) to females (N = 249). However, in the first study (Daniali and Flaten, 2021, under review) females reported higher COVID-like symptoms compared to males (see also review by Vambheim and Flaten, 2017). This notion suggests that even though the belief of being infected by COVID-19 may not differ across sexes, the nocebo effect still seems to be higher in females. Thus, even if beliefs are similar in males and females, the nocebo effect stemming from these beliefs seems to be stronger in females. This could be due to a response bias as males often under-report pain and associated emotions (e.g., Aslaksen et al., 2007), or to psychophysiological processes associated with placebo and nocebo responses. These hypotheses will be followed-up in future studies.

CONCLUSION

This study showed that being conscientious and worried about health made individuals susceptible toward developing a belief of being infected by COVID-19. Such finding may have clinical implications, as individuals high in these traits may over-report COVID-like symptoms. In settings, where COVID-19 testing services are provided, over-report of symptoms may be expected from individuals who show high health concerns. Moreover, providing advice about the likelihood of misinterpreting symptoms similar to COVID-19 symptoms may be useful for individuals with high levels of conscientiousness. The findings also have theoretical implications in the understanding of psychological processes that lead to development of beliefs or expectations underlying placebo and nocebo effects.

RECOMMENDATIONS FOR FUTURE STUDIES

Prospective studies are recommended to consider the followings: firstly, this study showed that conscientiousness along health anxiety dispose individuals to develop a certainty of being infected by COVID-19. However, not much is known about the effects of personality traits on nocebo effects and still more investigations are warranted. Attempts to describe the extent to which an individual responds to placebo treatment through a single personality trait may be too limited. Thus, a transactional model of placebo responding, in which dispositional characteristics dynamically interact with environmental contingencies, has been proposed by Darragh et al. (2015). According to this model, the overlaps among the personality traits suggest that placebo

responsiveness could be conceptualized in terms of a two-faceted construct consisting of an inward and an outward orientation. Therefore, it might be interesting for prospective studies to investigate if highly conscientious or health-concerned individuals can be placed within any of these two categories. Secondly, the applicability of this model to other populations needs to be investigated; for example, this is important to know whether such a model is confirmed for individuals who request for a COVID-19 test. Thirdly, based on the negative association between health anxiety and conscientiousness, there is a likelihood for a distinction between the quality or direction (i.e., positive or negative) of expectations based on health anxiety and expectations based on conscientiousness. It is of importance to investigate whether higher certainty of being infected that is influenced by higher health anxiety results in more negative outcomes; and contrastingly, whether certainty that is stemmed from high conscientiousness results in more preventive and constructive behaviors toward COVID-19. Fourthly, the effects of other contextual factors such as being constantly exposed to pandemic news (Gao et al., 2020), or the characteristics of the health care providers (Daniali and Flaten, 2019), and if those can mediate the influence of conscientiousness or health anxiety on certainty of being infected by COVID-19 needs to be investigated. Fifthly, whether such personality and/or cognitive constructs can lead to higher psychophysiological nocebo or placebo responses, such as higher blood pressure, as shown in Daniali and Flaten (2020), should be investigated in future studies. Moreover, how such a belief of being infected should interrupt the health guidelines and treatment procedures is of importance and requires investigation. Finally, there may be sex differences in how individuals react, subjectively and physiologically, to their health-related beliefs (Vambheim et al., 2021, under review). Taken together, the findings from the present study and that of Daniali and Flaten (2021, under review) show that even though when males and females have similar beliefs about being infected by COVID-19 or not, females report more symptoms, i.e., more nocebo effects.

LIMITATIONS

Briefly, the methodological and procedural limitations of the present study include the followings: the sample was biased as most of the participants were highly educated and young with only a small proportion of respondents being over the age of 60. This may have affected the outcomes and therefore, caution is required when generalizing the findings. Also, as in this study, causation cannot be concluded from cross-sectional studies. There are also disadvantages for online studies, such as dishonest answers, fatigue effects, and reckless answering. Regarding other limitations, it should be first noted that no information was gathered about the country of participants, and the course of the pandemic was different across countries, and this can have affected the results. Secondly, certainty of being infected by COVID-19 was investigated using a single item. This may have resulted in less variability in the outcome variable, restricting the psychometric reliability and validity of the present findings. Finally, although only participants who were not tested for COVID-19 were included, it is still possible that some participants were COVID-19 positive.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Regional Committee for Medical and Health Research Ethics, Norway (REK; project number: 142652), and the Norwegian Center for Research Data (NSD; project number: 605612). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HD and MF designed and conducted the study. Both authors had mutually collaborated on analyzing the data, drafting, revising and preparing the final manuscript.

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REFERENCES

Aschwanden, D., Strickhouser, J. E., Sesker, A. A., Lee, J. H., Luchetti, M., Stephan, Y., et al. (2020). Psychological and behavioural responses to coronavirus disease 2019: the role of personality. *Eur. J. Personal.* 35, 51–66. doi: 10.1002/per.2281

Aslaksen, P. M., and Lyby, P. S. (2015). Fear of pain potentiates nocebo hyperalgesia. *J. Pain Res.* 8:703. doi: 10.2147/JPR.S91923

Aslaksen, P. M., Myrbakk, I. M., Høifødt, R. S., and Flaten, M. A. (2007). The effect of experimenter gender on autonomic and subjective responses to pain stimuli. *Pain* 129, 260–268. doi: 10.1016/j.pain.2006.10.011

Bish, A., and Michie, S. (2010). Demographic and attitudinal determinants of protective behaviours during a pandemic: A review. *Br. J. Health Psychol.* 15, 797–824. doi: 10.1348/135910710X485826

Blakey, S. M., Reuman, L., Jacoby, R. J., and Abramowitz, J. S. (2015). Tracing "Fearbola": psychological predictors of anxious responding to the threat of ebola. *Cogn. Ther. Res.* 39, 816–825. doi: 10.1007/s10608-015-9701-9

Bleichhardt, G., and Hiller, W. (2007). Hypochondriasis and health anxiety in the German population. *Br. J. Health Psychol.* 12, 511–523. doi: 10.1348/135910706X146034

Breusch, T. S., and Pagan, A. R. (1979). A simple test for heteroskedasticity and random coefficient variation. *Econometrica* 47, 1287–1294.

Carvalho, L. D. F., Pianowski, G., and Gonçalves, A. P. (2020). Personality differences and COVID-19: are extroversion and conscientiousness personality traits associated with engagement with containment measures? *Trends Psychiatry Psychother.* 42, 179–184. doi: 10.1590/2237-6089-2020-0029

Costa, P. T., and McCrae, R. R. (1987). Neuroticism, somatic complaints, and disease: is the bark worse than the bite? *J. Pers.* 55, 299–316. doi: 10.1111/j.1467-6494.1987.tb00438.x

Costa, P. T., and McCrae, R. R. (1992). Normal personality assessment in clinical practice: the NEO personality inventory. *Psychol. Assess.* 4:5. doi: 10.1037/1040-3590.4.1.5

Daniali, H., and Flaten, M. A. (2019). A qualitative systematic review of effects of provider characteristics and nonverbal behavior on pain, and placebo and nocebo effects. *Front. Psychol.* 10:242. doi: 10.3389/fpsyt.2019.00242

Daniali, H., and Flaten, M. A. (2020). Placebo analgesia, nocebo hyperalgesia, and the cardiovascular system; a qualitative systematic review. *Front. Physiol.* 11:549807. doi: 10.3389/fphys.2020.549807

Darragh, M., Booth, R. J., and Consedine, N. S. (2015). Who responds to placebos? Considering the "placebo personality" via a transactional model. *Psychol. Health Med.* 20, 287–295. doi: 10.1080/13548506.2014.936885

Faasse, K., and Petrie, K. J. (2013). The nocebo effect: patient expectations and medication side effects. *Postgrad. Med. J.* 89, 540–546. doi: 10.1136/postgradmedj-2012-131730

Fauci, A. S., Lane, H. C., and Redfield, R. R. (2020). Covid-19—navigating the uncharted. *N. Engl. J. Med.* 382, 1268–1269. doi: 10.1056/NEJMe2002387

Ferguson, E. (2009). A taxometric analysis of health anxiety. *Psychol. Med.* 39, 277–285. doi: 10.1017/S0033291708003322

Flaten, M. A., Aslaksen, P. M., and Lyby, P. S. (2013). "Positive and Negative Emotions and Placebo Analgesia" in *Placebo Pain*. eds. L. Colloca, M. A. Flaten and K. A. Meissner (Cambridge, Massachusetts: Academic Press), 73–81.

Gao, J., Zheng, P., Jia, Y., Chen, H., Mao, Y., Chen, S., et al. (2020). Mental health problems and social media exposure during COVID-19 outbreak. *PLoS One* 15:e0231924. doi: 10.1371/journal.pone.0231924

Garbe, L., Rau, R., and Toppe, T. (2020). Influence of perceived threat of Covid-19 and HEXACO personality traits on toilet paper stockpiling. *PLoS One* 15:e0234232. doi: 10.1371/journal.pone.0234232

Hahn, E., Gottschling, J., and Spinath, F. M. (2012). Short measurements of personality–validity and reliability of the GSOEP big five inventory (BFI-S). *J. Res. Pers.* 46, 355–359. doi: 10.1016/j.jrp.2012.03.008

Hakulinen, C., Hintsanen, M., Munafò, M. R., Virtanen, M., Kivimäki, M., Batty, G. D., et al. (2015). Personality and smoking: individual-participant meta-analysis of nine cohort studies. *Addiction* 110, 1844–1852. doi: 10.1111/add.13079

Hayes, A. F., and Cai, L. (2007). Using heteroscedasticity-consistent standard error estimators in OLS regression: an introduction and software implementation. *Behav. Res. Methods* 39, 709–722. doi: 10.3758/BF03192961

He, F., Deng, Y., and Li, W. (2020). Coronavirus disease 2019: what we know? *J. Med. Virol.* 92, 719–725. doi: 10.1002/jmv.25766

John, O. P., Donahue, E. M., and Kentle, R. L. (1991). *The Big Five Inventory-Versions 4a and 54*. Berkeley. CA: University of California, Berkeley, Institute of Personality and Social Research.

Jungmann, S. M., and Witthöft, M. (2020). Health anxiety, cyberchondria, and coping in the current COVID-19 pandemic: which factors are related to coronavirus anxiety? *J. Anxiety Disord.* 73:102239. doi: 10.1016/j.janxdis.2020.102239

Lee, S. A. (2020). Coronavirus anxiety scale: a brief mental health screener for COVID-19 related anxiety. *Death Stud.* 44, 393–401. doi: 10.1080/07481187.2020.1748481

McCrae, R. R., and Costa, P. T. (2003). *Personality in Adulthood: A Five-Factor Theory Perspective*. New York: Guilford Press.

McCrae, R. R., and Costa, P. T. Jr. (1997). Personality trait structure as a human universal. *Am. Psychol.* 52, 509–516. doi: 10.1037/0003-066X.52.5.509

Mitsikostas, D. D., Blease, C., Carlino, E., Colloca, L., Geers, A. L., Howick, J., et al. (2020). European headache federation recommendations for placebo and nocebo terminology. *J. Headache Pain* 21:117. doi: 10.1186/s10194-020-01178-3

Moghadas, S. M., Fitzpatrick, M. C., Sah, P., Pandey, A., Shoukat, A., Singer, B. H., et al. (2020). The implications of silent transmission for the control of COVID-19 outbreaks. *Proc. Natl. Acad. Sci.* 117, 17513–17515. doi: 10.1073/pnas.2008373117

Nikčević, A. V., Marino, C., Kolubinski, D. C., Leach, D., and Spada, M. M. (2020). Modelling the contribution of the big five personality traits, health anxiety, and COVID-19 psychological distress to generalised anxiety and depressive symptoms during the COVID-19 pandemic. *J. Affect. Disord.* 279, 578–584. doi: 10.1016/j.jad.2020.10.053

Petrie, K. J., and Rief, W. (2019). Psychobiological mechanisms of placebo and nocebo effects: pathways to improve treatments and reduce side effects. *Annu. Rev. Psychol.* 70, 599–625. doi: 10.1146/annurev-psych-010418-102907

Salkovskis, P. M., Rimes, K. A., and Warwick, H. M. C. (2002). The health anxiety inventory: development and validation of scales for the measurement of health anxiety and hypochondriasis. *Psychol. Med.* 32:843. doi: 10.1017/s0033291702005822

Son, C., Hegde, S., Smith, A., Wang, X., and Sasangohar, F. (2020). Effects of COVID-19 on college students' mental health in the United States: interview survey study. *J. Med. Internet Res.* 22:e21279. doi: 10.2196/21279

Taylor, S., and Asmundson, G. J. (2004). *Treating Health Anxiety: A Cognitive-Behavioral Approach*. New York: Guilford Press.

Vambheim, S. M., and Flaten, M. A. (2017). A systematic review of sex differences in the placebo and the nocebo effect. *J. Pain Res.* 10:1831. doi: 10.2147/JPR.S134745

Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C. S., et al. (2020). Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *Int. J. Environ. Res. Public Health* 17:1729. doi: 10.3390/ijerph17051729

World Health Organization (2020). Rational Use of Personal Protective Equipment for Coronavirus Disease (COVID-19): interim guidance, 27 February 2020 (No. WHO/2019-nCov/IPCPPE use/2020.1). World Health Organization. Available at: https://apps.who.int/iris/handle/10665/331498 (Accessed March 23, 2021).

Worldometer (2021). Coronavirus Cases. Available at: https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1?%22 (Accessed March 23, 2021).

Xie, X. F., Stone, E., Zheng, R., and Zhang, R. G. (2011). The 'Typhoon Eye Effect': determinants of distress during the SARS epidemic. *J. Risk Res.* 14, 1091–1107. doi: 10.1080/13669877.2011.571790

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Associations Between Interindividual Differences, Expectations and Placebo and Nocebo Effects in Itch

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Introduction: Placebo and nocebo effects are positive and negative health outcomes that can be elicited by the psychosocial context. They can be mediated by expectations, and may emerge in somatic symptoms even when people are aware of these effects. Interindividual differences (e.g., in personality, affective states) could impact placebo and nocebo responding, but findings are inconsistent.

Methods: The current work examined expectation as a mediator of the association between verbal placebo and nocebo suggestions (VSs) and histamine-induced itch across three experimental studies. Moreover, we examined whether interindividual differences (e.g., in optimism, neuroticism, behavioral activation system (BAS), body ignorance) modulated: (1) the direct association between VSs and itch (direct moderation), and (2) the indirect, expectation-mediated association between VSs and itch (moderated mediation). Positive VSs were compared to neutral instructions (Study 1; n = 92) or negative VSs (Studies 2+3; n = 203) in an open-label (i.e., explaining placebo and nocebo effects) or closed-label (concealed) context using PROCESS. First, mediation of VSs effects on itch by expectations was tested. Next, moderation by individual traits was explored using conditional process analyses.

Results: The effects of VSs on itch were significantly mediated by expectation in Study 1 and in the open-label (but not closed-label) contexts of Studies 2 and 3. Ignorance of bodily signals marginally moderated the direct effects of VSs on itch when closed-label suggestions were given: at low levels of body ignorance, effects of positive and negative VSs were stronger. Moreover, moderated mediation was observed in the open-label groups of Studies 2 and 3: The expectation-mediated effects of VSs on itch were stronger when BAS drive was lower.

Conclusion: Overall, the effects of VSs on itch were mediated by expectations in the open-label, but not the closed-label context. Moreover, the current work suggests that placebo and nocebo effects may be moderated by ignorance of bodily signals and the BAS. There was limited evidence that other interindividual differences modulated placebo and nocebo responding in itch.

Keywords: itch, placebo effects, nocebo effects, expectations, pruritus, verbal suggestions, moderated mediation

INTRODUCTION

Placebo effects are positive health outcomes such as reduced somatic symptoms (e.g., pain, itch, or nausea) that cannot be attributed to active treatment components, but are elicited by psychosocial and contextual factors that signal potential treatment benefits (Evers et al., 2018; Wolters et al., 2019; Mitsikostas et al., 2020). Nocebo effects can be described as the opposite—adverse health outcomes, for instance, increases in somatic complaints or treatment side effects, or decreased treatment efficacy, which can be elicited by psychosocial factors signaling potential drawbacks of a treatment (Mitsikostas et al., 2020). Research generally discerns three mechanisms that mediate placebo and nocebo effects: (Conscious) expectation, associative learning, and observational learning (Rossettini et al., 2020; Evers et al., 2021). Expectations about treatment outcomes can be modulated by verbal suggestions. Experimental studies, for instance, show that verbal suggestions of pain relief can influence expectations and can lead to analgesia following administration of an inert intervention (Petersen et al., 2014; Colloca and Barsky, 2020). Similarly, positive verbal suggestions can reduce symptoms of itch (Bartels et al., 2016; Wolters et al., 2019). When placebo effects are elicited by associative learning, or conditioning, an individual learns that a certain cue (e.g., the treatment context, or a medical ritual) and positive health outcome (e.g., a reduction in symptoms) are associated through experience (Colloca and Barsky, 2020), whereas in observational learning, this association is learned by observing it in others (Bajcar and Bąbel, 2018).

Differences are observed in the magnitude of placebo and nocebo effects that can be elicited in individuals, which may be attributed to psychosocial and contextual factors. Among others, psychological traits and affective states can contribute to placebo and nocebo responsiveness (Colagiuri et al., 2015; Hall et al., 2015; Anderson and Stebbins, 2020; Frisaldi et al., 2020). With regard to these interindividual differences, optimism appears to most consistently contribute to placebo responding in pain (Geers et al., 2005, 2007, 2010; Morton et al., 2009; Darragh et al., 2014; Corsi et al., 2016), whereas anxiety seems to play a role in eliciting nocebo effects in particular (Aslaksen and Lyby, 2015; Corsi et al., 2016; Kern et al., 2020; Thomaidou et al., 2021). The evidence for the contribution of other interindividual differences, including those in personality traits of the Big Five model (i.e., neuroticism, extraversion, openness to experience, conscientiousness, agreeableness), (disposition to) worrying, or subjective stress, is more inconsistent: some studies report significant associations and other studies refute them (see, for example, Corsi and Colloca, 2017; Locher et al., 2019; Kern et al., 2020). Potentially, interindividual differences in these traits and states could influence placebo and nocebo effects. Finally, the behavioral inhibition system (BIS) and behavioral activation system (BAS) may also play a role in placebo and nocebo responding. These two systems are reflected in patterns of emotional and behavioral responses to attractive (e.g., rewards) and repulsive (e.g., punishments) stimuli (Corr, 2004, 2013). For instance, BAS comprises the sensitivity of the response to rewards, as well as the motivation to seek out rewards, whereas BIS comprises the tendency to avoid unpleasant stimuli (Carver and White, 1994). Both BIS and BAS have been associated with pain sensitivity and pain-related function (Jensen M. P. et al., 2015; Day et al., 2019; Sánchez-Rodríguez et al., 2021; Turner et al., 2021). Moreover, a more sensitive BAS has been associated with enhanced placebo analgesia (Schweinhardt et al., 2009; Yu et al., 2014; De Pascalis and Scacchia, 2017).

The relation between interindividual differences in psychological traits and affective states, and placebo and nocebo responding has not been investigated outside the area of pain very often, but there is some evidence that they modulate nocebo responding in itch (Bartels et al., 2016; Wolters et al., 2019). To illustrate, higher levels of depressive symptoms, trait anxiety, and worrying have been associated with nocebo effects in itch (Scholz and Hermanns, 1994; Bartels et al., 2014). As of yet it is still unclear how other interindividual differences may influence placebo and nocebo effects in itch. Investigating these associations may be particularly relevant given the high prevalence and large psychosocial burden of itch (Weisshaar, 2016), and given that itch is likely very sensitive to placebo effects (van Laarhoven et al., 2015).

According to the current theories on placebo effects mechanisms, verbal suggestions can influence symptoms because they change an individual's expectations about a treatment outcome. Such a model implies that mediation occurs (Geers et al., 2019; Bingel, 2020). However, (conscious) expectations are not always measured in studies, and if they are, it is not often assessed whether they actually mediate the association between verbal suggestions and treatment outcomes. Importantly, when investigating which factors can predict or contribute to placebo and nocebo responding, expectations are also often omitted from the tested models. Given that expectations are central to placebo and nocebo responding, this essentially renders the models for testing modulation of these effects by interindividual differences incomplete. Current common practices are to either look for

Abbreviations: BAS, Behavioral Activation System; BIS, Behavioral Inhibition System; NRS, Numeric Rating Scale; VSs, verbal suggestions.

direct associations between an individual's psychological traits or affective states and the outcome within different subgroups (e.g., separately for those receiving verbal suggestions and those not receiving them), or to test whether interindividual differences moderate the effects of verbal suggestions on the outcome directly (for an overview see Kern et al., 2020). Neither of these methods takes the potentially mediating role of expectations into account. Because of this, we do not know whether the extent to which interindividual differences modulate placebo or nocebo effects is dependent on the involvement of expectations. Placebo responses are complex, and the degree to which interindividual differences may influence them could be dependent on whether expectations change as a result of an intervention; for instance, we could hypothesize that optimism enhances placebo effects because suggestions influence expectations to a higher degree when people are more optimistic, or alternatively, because the effect of outcome expectations are stronger when people are more optimistic. If this proposition holds true, it may have implications for how we look at the role of interindividual differences in placebo responding. For instance, their role could change depending on whether placebo interventions aim to alter conscious expectations: factors that enhance expectation-mediated placebo responding may be relevant for verbal suggestions and other types of expectation-based effects, but less so when placebo effects are generated through other learning mechanisms, such as associative or observational learning (i.e., when the role of conscious expectations may be more limited).

Investigating how interindividual differences, expectations, placebo effects and nocebo effects are interrelated could further our understanding of the manner in which interindividual differences may contribute to placebo and nocebo responding. To this end, we exploratively analyzed data of three of our previous studies that investigated placebo and nocebo effects induced by (open- or closed-label) positive and negative verbal suggestions on itch (Meeuwis et al., 2018; Meeuwis et al., 2019; Meeuwis et al., 2021). The objective was to explore the influence of interindividual differences across a mediation model of placebo and nocebo effects using conditional process analyses. Conditional process analysis can be used to test for moderation of both the direct and indirect (i.e., mediated) effects of a predictor on an outcome within a single statistical model (see **Figure 1**; Hayes, 2017). We hypothesized that the effects of verbal suggestions on itch would be mediated by expectations. Moreover, we expected that the strength of the associations between verbal suggestions, expectations and itch would change depending on the level of the assessed psychological traits and affective states.

MATERIALS AND METHODS

Psychological traits and affective states that may be associated with placebo and nocebo responses to verbal suggestions (VSs) in histamine-induced itch were explored across three previously published experimental studies (Meeuwis et al., 2018; Meeuwis et al., 2019; Meeuwis et al., 2021). This paper used the same data as these previous publications, but now aimed to examine interrelations between interindividual differences, expectations, and placebo and nocebo effects in itch in a larger participant sample. **Supplementary Table 1** outlines the similarities and differences between the studies. Due to a large overlap in study design and VSs content, data of the second and third studies were analyzed collectively.

Study Design

All studies' details have been published before; short summaries of the methods are provided below.

Study 1. Open-Label Positive Verbal Suggestions Versus Neutral Instructions

Healthy volunteers were randomized to (1) an open-label positive VSs group or (2) a neutral instructions control group. Itch was induced experimentally during a laboratory session by 2.5 min of histamine iontophoresis. After iontophoresis, participants were asked to rate the mean amount of itch they experienced during this procedure on a 0–10 Numeric Rating Scale (NRS; 0 "no itch," 10 "worst itch ever experienced"). Prior to iontophoresis, participants in the open-label positive VSs group were told that this procedure would elicit little itch. It was moreover explained that this suggestion of little itch may influence their experience by changing expectations about the test (open-label rationale). Participants in the control group were given neutral instructions about the study procedures instead. Before and after the VSs or neutral instructions, participants rated how much itch they expected to experience on a 0–10 NRS (as a measure of conscious expectations).

Studies 2 and 3. Open- and Closed-Label Positive Versus Negative Verbal Suggestions

Healthy volunteers in studies 2 and 3 were randomized to (1) an open-label positive VSs, (2) a closed-label positive VSs, (3) an open-label negative VSs, or (4) a closed-label negative VSs group. Itch was induced experimentally at baseline and following VSs by histamine iontophoresis. Mean itch was rated upon completion of this test on a 0–10 NRS (0 "no itch," 10 "worst itch imaginable"). Participants were told that they would receive an intervention before histamine iontophoresis took place a second time (in study 2 an inert tonic was applied, and in study 3 a sham transdermal patch). Depending on group allocation, VSs of decreased (positive VSs) or increased itch (negative VSs) were given. Participants in the open-label groups additionally received an explanation of how suggestions may influence expectations: they were informed that the tonic or patch were actually sham treatments and elicit placebo effects (in case of positive VSs) or nocebo effects (in case of negative VSs). Before baseline iontophoresis and after VSs were given, participants were also asked to rate how much itch they expected to experience on a 0–10 NRS.

Interindividual Differences

The following psychological traits and affective states were assessed across all studies: neuroticism and extraversion (Eysenck Personality Questionnaire—Revised Short Scales, EPQ-RSS;

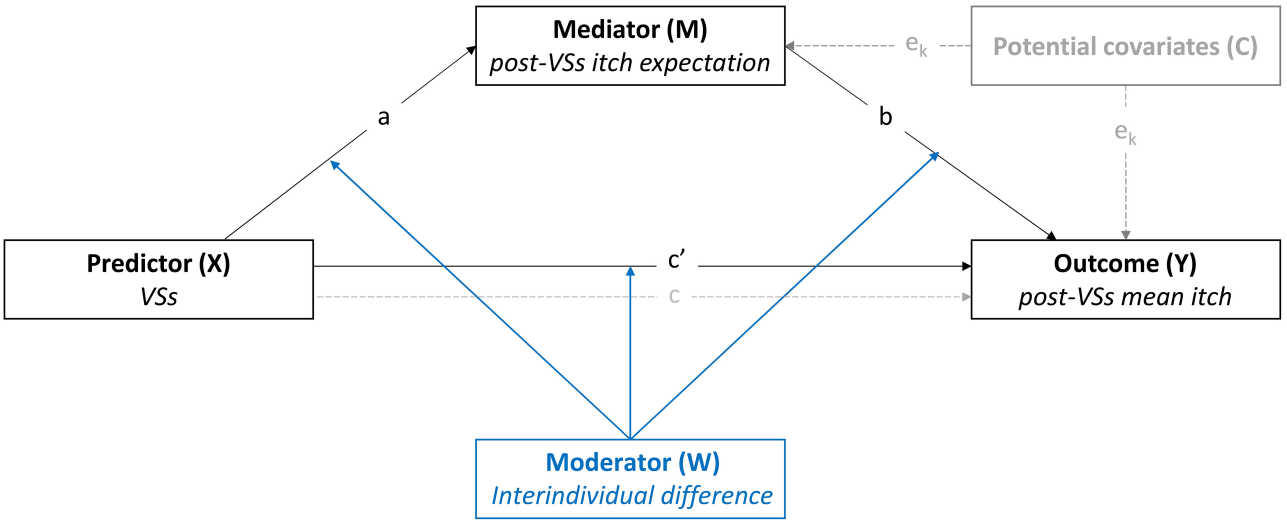

FIGURE 1 | Conceptual representation of the first- and second-stage dual moderated mediation model (model 59, Hayes, 2017). The effects of positive and negative verbal suggestions (VSs) on mean itch during histamine iontophoresis were tested across the three studies. Moderation of the model by interindividual differences was tested on the indirect and direct pathways from VSs to the outcome (mean itch). The model was controlled for Pre-VSs itch expectation (studies 1–3) and baseline itch (studies 2–3). A representation of the statistical model including the tested interactions can be found in the **Supplementary Material**.

Eysenck and Eysenck, 1975), optimism (Life Orientation Test—Revised, LOT-R; Scheier et al., 1994), and the BIS and BAS subfactors drive, fun seeking and reward responsiveness (BIS/BAS scales; Carver and White, 1994). Other interindividual differences that were assessed in study 1 were subjective stress (the Perceived Stress Scale, PSS; Cohen et al., 1983), (disposition to) worrying (Penn State Worry Questionnaire, PSWQ; Meyer et al., 1990), and distress (Hospital Anxiety and Depression Scale, HADS; Zigmond and Snaith, 1983). The lie/social desirability subscale (EPQ-RSS; Eysenck and Eysenck, 1975) was additionally assessed in studies 2 and 3. Finally, attention to, and ignorance and awareness of, bodily signals (Body Attention, Ignorance and Awareness Scale, BAIAS; van Beugen et al., 2015) was measured in study 3 exclusively.

The *EPQ-RSS* subscale "neuroticism" assesses a broad personality construct that comprises emotional instability and reactivity, as well as a tendency toward anxiety and worrying (Eysenck and Eysenck, 1975; Sanderman et al., 1991). Items of this subscale include, for instance "*Does your mood often go up and down*?" The subscale "extraversion" measures a person's tendency to be, for instance, outgoing and impulsive (example item "*Are you rather lively*?"), whereas the "lie" scale reflects a person's tendency toward socially desirable responses (e.g., "*If you say you will do something, do you always keep your promise no matter how inconvenient it might be*?") (Eysenck and Eysenck, 1975; Sanderman et al., 1991). Scores on these EPQ-RSS subscales range between 0 and 12, with higher scores on the neuroticism scale indicating more emotional instability and reactivity, and higher scores for extraversion indicating that the person is more extravert. Higher scores on the "lie" scale indicate that the person has a stronger tendency to provide socially desirable responses.

The *LOT-R* assesses the personality dimension "dispositional optimism," that is, the general tendency toward expecting good outcomes (example item "*In uncertain times, I usually expect the best*") (Scheier et al., 1994). The total score on this scale reflects a dimension from pessimism to optimism, and scores range from 0 to 24, with higher scores indicating optimism, and lower scores indicating pessimism.

The *BIS/BAS scales* comprises several subscales reflecting approach tendencies, a higher sensitivity to rewarding stimuli, and higher positive affect. "BAS drive" measures an individual's drive or motivation in pursuing their goals (e.g., "*When I want something, I usually go all-out to get it*"), "BAS reward responsiveness" measures the sensitivity to rewarding stimuli (e.g., "*When good things happen to me, it affects me strongly*"), and "BAS fun seeking" measures the tendency and motivation to pursue pleasant or rewarding stimuli ("*I will often do things for no other reason than that they might be fun*"). The BIS subscale relates to passive avoidance, a more cautious approach to negative stimuli, and increased negative affect—particularly anxiety. Example items include "*If I think something unpleasant is going to happen I usually get pretty "worked up"* (Carver and White, 1994; Merchán-Clavellino et al., 2019; Vecchione et al., 2021). Total scores for BAS drive and fun seeking range 4–16, for BAS reward responsiveness 5–20, and for BIS 7–32. Higher scores on the BAS-trait scales reflect higher approach tendencies, and higher scores for BIS indicate a stronger tendency for passive avoidance.

The *PSS* scale assesses stress experienced within the last month (e.g., "*In the last month, how often have you been upset because of something that happened unexpectedly*?"; total score ranges 0–40) (Cohen et al., 1983); the *PSWQ* reflects an individual's disposition to worrying (e.g., "*I worry all the time*"; total score ranges 16–80) (Meyer et al., 1990); and the *HADS* assesses depressive symptoms ("*I still enjoy the things I used to enjoy*") and anxiety ("*I feel tense or "wound up"*") within the past

week (Zigmond and Snaith, 1983). Items are summed for the total scale "distress," which ranges from 0 to 42. Higher scores indicate more distress.

Finally, the *BAIAS* assesses body awareness using three subscales: "body attention" (e.g., "*In general I pay attention to my physical sensations*"), "body ignorance" (e.g., "*When I am not feeling well physically, I do not know the reason*") and "body awareness" (e.g., "*I notice changes in my body, such as whether my breathing slows down or speeds up*") (van Beugen et al., 2015). Total scores for each BAIAS subscale are calculated by summing and then dividing for the number of subscale items, resulting in a total score between 0 and 4. Higher scores on the BAIAS subscales "body attention," "body ignorance" and "body awareness" reflect a stronger tendency to pay attention to, to ignore, or to be aware of bodily signals, respectively.

Statistical Analysis

Analyses were conducted using IBM SPSS version 26.0 (Chicago, IL, United States) and the syntax-driven PROCESS 3.5 SPSS macro for mediation and conditional process analyses (Hayes, 2017). All analyses were conducted separately for study 1, and combined for studies 2 and 3. Between-group differences in baseline expectations and itch, as well as in psychological traits and affective states, were checked using chi-square tests and analyses of variance (ANOVAs). Prior to the mediation and conditional process analyses, assumptions for ordinary least squares (OLS) regression analysis were checked, including linearity, homoscedasticity, independence and multivariate normality, and absence of multicollinearity.

First, direct and indirect effects of VSs on mean itch were explored in a simple mediation model with post-VSs itch expectation as mediator variable (PROCESS model 4). Next, conditional process analyses were used to explore first- and second-stage dual moderated mediation effects as well as moderation of the direct effects of VSs on itch by individual traits (PROCESS model 59; Hayes, 2017). Conditional direct and indirect effects of VSs on itch were always probed at low (16th), medium (50th), and high (84th) percentiles of the moderator. When relevant (i.e., when $p<0.10$ for moderator × group or moderator × mediator interaction), the conditional effects of VSs on itch expectation and the conditional effects of itch expectation on itch were probed for these percentiles as well. Bootstrapped 95% percentile confidence intervals (CI) were computed with a rate of 10.000 samples to assert significance of these calculated conditional effects. To ascertain whether moderated mediation was present, an index for moderated mediation was calculated for dichotomous variables (e.g., for sex). Significance of this index was then checked using the 95% bootstrap CI. Because the model we tested has multiple points where it can be moderated (see **Figure 1** and **Supplementary Figure 1**), the function of the effects of continuous moderators on the indirect path (X→M→Y) is non-linear. This prevents computation of a single index value for moderated mediation (Muller et al., 2005; Hayes, 2015). Instead, pairwise contrasts between the indirect effects of VSs on itch were calculated at low, medium and high levels of the moderator variable. The 95% CI for these contrasts were then used to ascertain moderated mediation.

A moderation effect was deemed present when there was (1) a significant ($p< 0.05$) or marginal ($p < 0.10$) interaction in the OLS regression analysis, and (2) at least one of the effects probed at low, medium and high levels of the moderator was significant as indicated by the 95% bootstrap CI. When the standard probing of effects reveals significant effects of VSs on itch at any of the levels of the moderator, but the OLS regression did not show marginal or significant interaction effects, no moderation was present. Finally, in all mediation and conditional process models, pre-VSs itch expectation was included as a covariate on the mediator (post-VSs itch expectation) level. In addition, mean itch during baseline iontophoresis was included as a covariate in the models of studies 2–3 on the mediator level as well as on the outcome (post-VSs mean itch) level. All analyses were conducted two-sided with $\alpha < 0.05$.

RESULTS

Participants and Baseline Differences Between Groups

Data of 295 participants were analyzed (study 1: n = 92, 81.5% female, $M_{age} \pm SD = 21.3 \pm 1.94$; studies 2 and 3: n = 203, 83.3% female, $M_{age} \pm SD = 21.9 \pm 2.70$). No between-group differences in psychological traits, affective states, or baseline ratings of expected itch and mean itch experienced during iontophoresis were observed for study 1 (all $p \geq 0.11$; **Supplementary Table 2**). Some incidental group differences were observed in the open-label arm of studies 2 and 3, which will be taken into account during the interpretation of the findings: neuroticism and BAS drive were higher in the positive compared to the negative VSs group; [$t(98) = -2.05$, $p = 0.043$; and $t(98) = -2.09$, $p = 0.040$], respectively. Pre-VSs expected itch was lower in the positive compared to the negative VSs group; [$t(98) = 2.15$, $p = 0.034$]. For the closed-label arm of studies 2 and 3, the positive VSs group scored lower on lie/social desirability compared to the negative VSs group; [$t(101) = 3.24$, $p = 0.002$].

Simple Mediation: Effects of Verbal Suggestions on Mean Itch, as Mediated by Expectations

Open-Label Positive Verbal Suggestions Versus Neutral Instructions (Study 1)

Mediation analysis (see **Figure 1** for the conceptual model) revealed that positive VSs were significantly associated with lower expected itch compared to neutral instructions [path a_1: $b_{X\rightarrow M} = -2.82$, $SE = 0.29$, $p<0.001$; also described in Meeuwis et al. (2018)]. Within the model with positive VSs, lower post-VSs expected itch was significantly associated with lower post-VSs mean itch (path b_1: $b_{M\rightarrow Y} = 0.18$, $SE = -0.09$, $p = 0.048$). Positive VSs were not directly associated with lower mean itch (path c': $b_{X\rightarrow Y} = 0.31$, $SE = 0.43$, $p = 0.47$), however, a significant indirect association between positive VSs and lower mean itch was observed [path c: $b_{indirect} = -0.51$, $SE = 0.26$, 95% $CI_{bootstrap}$ (−0.65, −0.03)]. This indicates that positive VSs indirectly reduced post-VSs mean itch, through mediation by expectation. Finally,

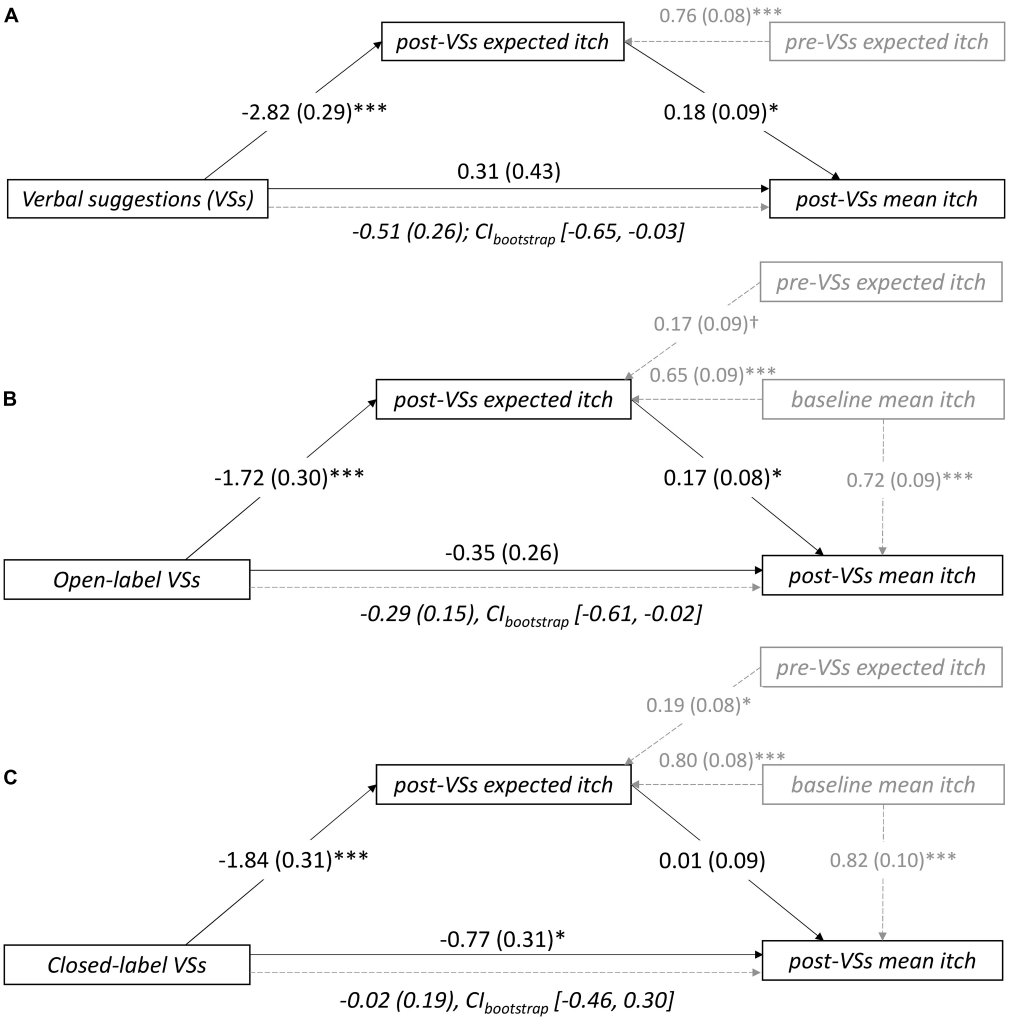

FIGURE 2 | Unstandardized regression coefficients (SEM) for the mediation of the association between verbal suggestions (VSs) and post-VSs mean itch by itch expectations in **(A)** study 1, **(B)** the open-label arm of studies 2–3, and **(C)** the closed-label (i.e., concealed) arm of studies 2–3. The models were controlled for pre-VSs itch expectation **(A–C)** and baseline itch **(B,C)**. Note that c = (indirect) mediation effect; $CI_{bootstrap}$ = bootstrapped confidence interval; $^{\dagger}p < 0.10$; $^{*}p < 0.01$; $^{***}p < 0.001$.

lower pre-VSs expected itch was significantly associated with lower post-VSs expected itch [path e_1: $b_{C\rightarrow M} = 0.76$, $SE = 0.08$, $p < 0.001$; **Figure 2A** and **Supplementary Table 3**).

Open-Label Positive Versus Negative Verbal Suggestions (Studies 2 and 3)

Mediation analysis demonstrated that positive VSs reduced expected itch compared to negative VSs (path a_1: $b_{X\rightarrow M} = -1.72$, $SE = 0.30$, $p < 0.001$; findings of the separate studies are described in Meeuwis et al., 2019; Meeuwis et al., 2021). Lower post-VSs expected itch in turn was associated with lower post-VSs mean itch (path b_1: $b_{M\rightarrow Y} = 0.17$, $SE = 0.08$, $p = 0.032$). While no significant direct effect of VSs on mean itch was found (path c': $b_{X\rightarrow Y} = -0.35$, $SE = 0.26$, $p = 0.19$), again a significant indirect association between positive VSs and lower post-VS mean itch was observed [path c: $b_{indirect} = -0.29$, $SE = 0.15$, 95% $CI_{bootstrap}$ (−0.61, −0.02)]. This shows that the effects of positive VSs versus negative VSs were mediated by post-VS expected itch under open-label conditions, with positive VSs being associated with lower mean itch than negative VSs. Finally, lower pre-VSs expected itch was marginally associated with lower post-VSs expected itch (path e_1: $b_{C\rightarrow M} = 0.17$, $SE = 0.09$, $p = 0.054$). Moreover, lower mean itch experienced during baseline significantly predicted lower post-VSs expected itch (path e_2: $b_{C\rightarrow M} = 0.65$, $SE = 0.08$, $p < 0.001$) and lower post-VSs mean itch (path e_3: $b_{C\rightarrow Y} = 0.72$, $SE = 0.09$, $p < 0.001$), respectively (**Figure 2B** and **Supplementary Table 3**).

Closed-Label Positive Versus Negative Verbal Suggestions (Studies 2 and 3)

Mediation analysis demonstrated that positive VSs reduced expected itch compared to negative VSs (path a_1: $b_{X\rightarrow M} = -1.84$, SE = 0.31, $p < 0.001$; findings of the separate studies are described in Meeuwis et al., 2019; Meeuwis et al., 2021). However,

post-VSs expected itch in turn was not associated with post-VSs mean itch (path b_1: $b_{M\rightarrow Y}$ = 0.01, SE = 0.09, p = 0.90). Instead, positive VSs were directly and significantly associated with lower post-VSs mean itch compared to negative VSs (path c': $b_{X\rightarrow Y}$ = −0.77, SE = 0.31, p = 0.014). No significant indirect association between VSs and itch was found, which indicates that post-VSs expected itch did not mediate the effects of VSs on mean itch [path c: $b_{indirect}$ = −0.02, SE = 0.19, $CI_{bootstrap}$ (−0.46, 0.30)] in the closed-label context. Finally, lower pre-VSs expected itch was significantly associated with lower post-VSs expected itch (path e_1: $b_{C\rightarrow M}$ = 0.19, SE = 0.08, p = 0.025). Moreover, lower mean itch experienced during baseline significantly predicted lower post-VSs expected itch (path e_2: 0.80, SE = 0.09, p <0.001) and lower post-VSs mean itch (path e_3: $b_{C\rightarrow Y}$ = 0.82, SE = 0.10, p < 0.001), respectively (**Figure 2C** and **Supplementary Table 3**).

Conditional Process Analyses: Interindividual Differences in the Relation Between Verbal Suggestions, Expectations and Itch

Open-Label Positive Verbal Suggestions Versus Neutral Instructions (Study 1)

Conditional process analyses revealed no evidence for moderated mediation, which indicates that the expectation-mediated indirect effects of VSs on mean itch did not depend on interindividual differences in psychological traits or affective states (see **Supplementary Table 4**). A non-significant marginal first-stage interaction between VSs and extraversion was observed for expected itch (p_{int} = 0.086). *Post-hoc* probing of this interaction revealed that effects of VSs on expected itch were

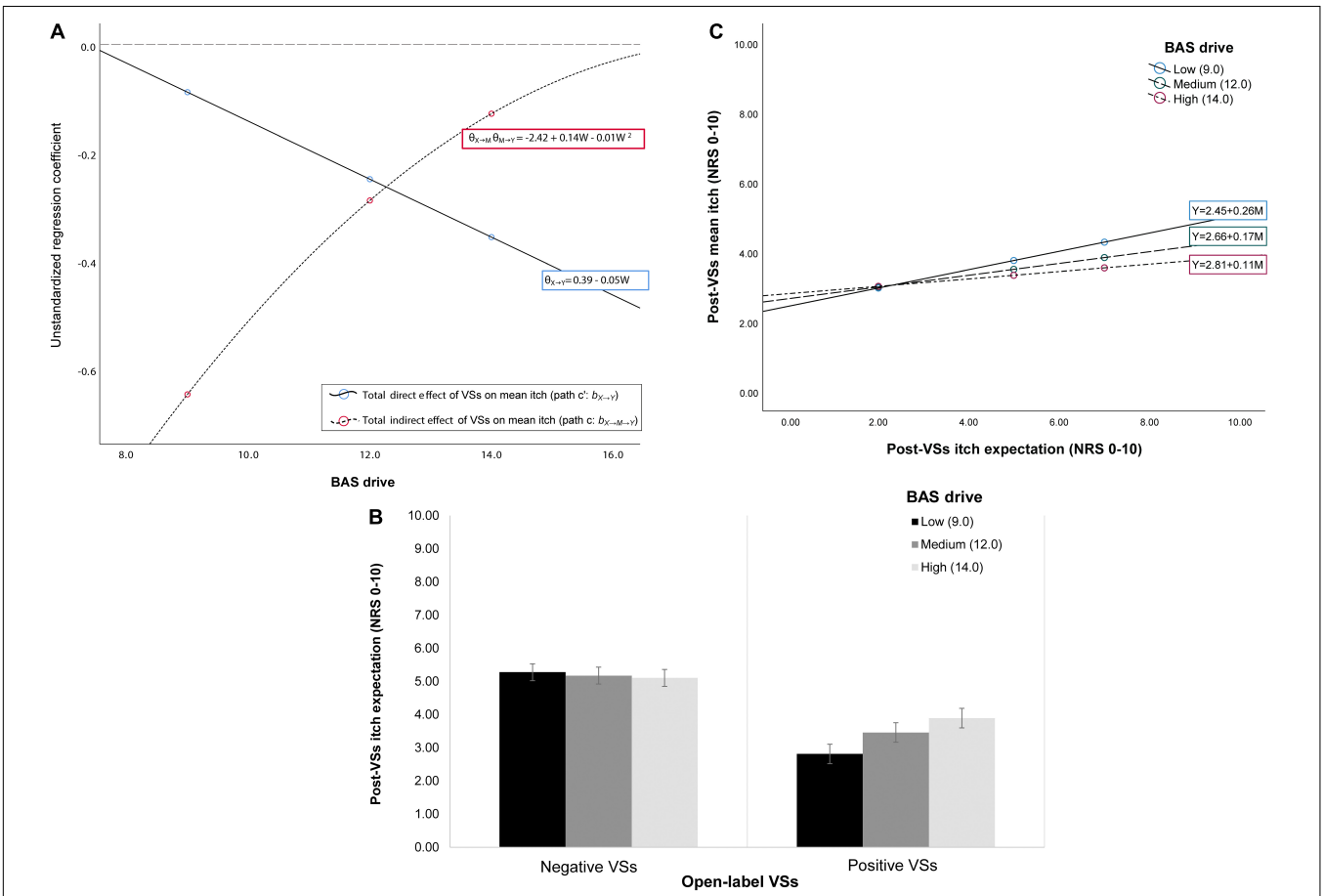

FIGURE 3 | Depiction of the conditional indirect and direct effects of VSs on mean itch across low, medium and high levels of behavioral activation system (BAS) trait drive for the open-label arms of studies 2–3. **(A)** There was moderated mediation (depicted in **(A)** as the change in unstandardized regression coefficient magnitude for the effects of VSs on mean itch for low, medium and high levels of the moderator): the indirect (i.e., expectation-mediated) effects of VSs on mean itch (path c) changed depending on the level of BAS drive (i.e., the motivation to achieve goals). The effects of VSs on mean itch were significantly mediated by expectations in case of low drive to achieve goals (i.e., when BAS drive scores were low). When participants had high drive to achieve their goals (i.e., when BAS drive scores were high), expectations did not mediate the association between VSs and mean itch; instead, the direct effects of VSs on itch (path 'c) tended to be stronger. This moderated mediation can also be explained as follows: **(B)** positive VSs were associated with lower itch expectation compared to negative VSs when BAS drive was lower (significant BAS drive × VSs interaction; depicted in **(B)** as mean itch expectation ± SEM for low, medium and high BAS drive levels); and **(C)** the association between lower itch expectation and lower post-VSs mean itch was stronger at low compared to high levels of BAS drive (depicted in **(C)** as simple regression slopes for each level of the moderator).

significant across all levels of extraversion though, and stronger when extraversion scores were higher (see **Supplementary Figure 2**). Other interindividual differences did not moderate the effects of VSs at either the first stage (post-VSs expected itch) or second stage (post-VSs mean itch) of the model, nor the effects of expected itch on mean itch at the second stage (all $p_{int} \geq 0.14$; **Supplementary Table 4**). Across all moderated mediation models, lower pre-VSs expected itch predicted lower post-VSs expected itch (path e: range $b_{C\rightarrow M}$ = 0.74–0.76, all *SE* = 0.08, all $p < 0.001$). Direct associations between the psychological traits and affective states and outcomes are described in **Supplementary Table 4**.

Open-Label Positive Versus Negative Verbal Suggestions (Studies 2 and 3)

Conditional process analysis showed changes in the conditional indirect (i.e., expectation-mediated) effects of VSs on mean itch across different levels of the BAS drive trait. At low and medium levels of BAS-drive (i.e., when participants have lower drive to pursue their goals), the indirect effect of VSs on mean itch through expectations was larger than at high levels of BAS drive (i.e., when there is a high drive to pursue goals; **Figure 3A**). Moreover, the observed indirect effects were significant only at low and medium levels of BAS drive (i.e., bootstrapped 95%CI $\leq$ –0.04). *Post-hoc* pairwise contrasts confirmed moderated mediation, as the observed effects contrasted significantly for low, medium and high levels of this moderator (i.e., bootstrapped 95%CI $\geq$ 0.03; **Supplementary Table 5**). The model further inferred a non-significant marginal interaction between VSs and BAS drive for post-VSs expected itch (p_{int} = 0.075; see **Figure 3B**): effects of VSs on expected itch were stronger (i.e., expected itch was lower after positive VSs) when BAS drive was lower. The effects of expectations on mean itch were not moderated by BAS drive, although associations between expected itch and mean itch tended to be stronger for lower levels of BAS drive (**Figure 3C**). Direct effects of VSs on mean itch were not significantly moderated by BAS drive (both $p_{int} > 0.18$), but increases in effect magnitude could be observed when BAS drive scores were higher. Overall, the model shows that the effects of positive and negative VSs on mean itch may be more dependent on mediation by expectation when participants have generally lower drive to pursue their goals.

There was no evidence for moderated mediation in any of the models containing the other psychological traits or affective states (**Supplementary Table 5**). Some direct moderation effects were observed: the effects of VSs on expected itch were stronger at lower levels than at higher levels of BAS fun seeking (p_{int} = 0.015; **Supplementary Figure 3**). Body awareness moreover moderated the effects of VSs on expected itch (p_{int} = 0.047): the effects of VSs on expected itch were stronger for participants with lower body awareness (**Supplementary Figure 4**). Marginal non-significant trait x expected itch interaction effects on mean itch were observed for BAS reward responsiveness (p_{int} = 0.095) and the lie/social desirability scale (p_{int} = 0.083): the associations between post-VSs expected itch and mean itch were stronger when reward responsiveness was lower and when social desirability was higher (**Supplementary Figures 5, 6**). Finally, the association between pre-VSs expected itch and post-VSs expected itch ranged from marginal to significant (path e_1: range $b_{C\rightarrow M}$ = 0.15–0.30, *SE* = 0.09–0.11, p = 0.007–0.097) across all moderated mediation models. Lower mean itch experienced during baseline iontophoresis was a significant predictor of post-VSs expected itch (path e_2: range $b_{C\rightarrow M}$ = 0.37–0.66, *SE* = 0.09–0.14, all $p <$ 0.01) and of post-VSs mean itch (path e_3: range $b_{C\rightarrow M}$ = 0.66–0.73, *SE* = 0.09–0.11, all $p < 0.001$) across all models.

Closed-Label Positive Versus Negative Verbal Suggestions (Studies 2 and 3)

Conditional process analyses revealed no evidence for moderated mediation (**Supplementary Table 6**). A non-significant marginal moderation of the direct effects of VSs on mean itch by body ignorance was found (p_{int} = 0.072). Probing of this interaction revealed that at low and medium levels of body ignorance, positive VSs were significantly associated with lower mean itch compared to negative VSs (i.e., bootstrapped 95%CI $\leq$ –0.51). For high levels of body ignorance, effects of positive compared to negative VSs on mean itch were not significant (i.e., the bootstrapped 95%CI contained 0; **Figure 4**). Finally, the direct effect of VSs on post-VS expected itch was moderated by BAS fun seeking (i.e., the tendency to seek out pleasant stimuli) and BAS reward responsiveness (i.e., the sensitivity to rewarding stimuli), respectively (both $p_{int} \leq 0.031$). *Post-hoc* probing of these moderation effects indicated that, in both models, positive compared to negative VSs resulted in lower expected itch when scores on the BAS subscale were low. When BAS scores were high, positive VSs were not associated with lower expected itch compared to negative VSs (**Supplementary Figures 7, 8**). Finally, the association between pre-VSs expected itch and post-VSs expected itch ranged from marginal to significant (path e_1: range $b_{C\rightarrow M}$ = 0.15–0.38, *SE* = 0.08–0.14, p = 0.008–0.088) across all moderated mediation models. Lower mean itch experienced during baseline iontophoresis was a significant predictor of post-VSs expected itch (path e_2: range $b_{C\rightarrow M}$ = 0.78–0.82, *SE* = 0.09–0.15, all $p <$ 0.001) and of post-VSs mean itch (path e_3: range $b_{C\rightarrow M}$ = 0.78–0.86, *SE* = 0.10–0.14, all $p <$ 0.001) across all models.

DISCUSSION

The current work explored whether interindividual differences in psychological traits and affective states could modulate the formation of placebo and nocebo effects in histamine-induced itch by moderating either the direct effects of verbal suggestions on itch, or by moderating effects arising through mediation by conscious expectations. The results show that the effects of open-label verbal suggestions were predominantly mediated by (consciously rated) expectations, whereas for closed-label (i.e., concealed) suggestions, verbal suggestions directly modulated itch levels without involvement of conscious expectations. Sensitivity of the behavioral activation system (BAS), which is linked to reward responding, was associated with differences in the process of placebo and nocebo responding. This is evidenced by the various significant moderated mediation and moderation

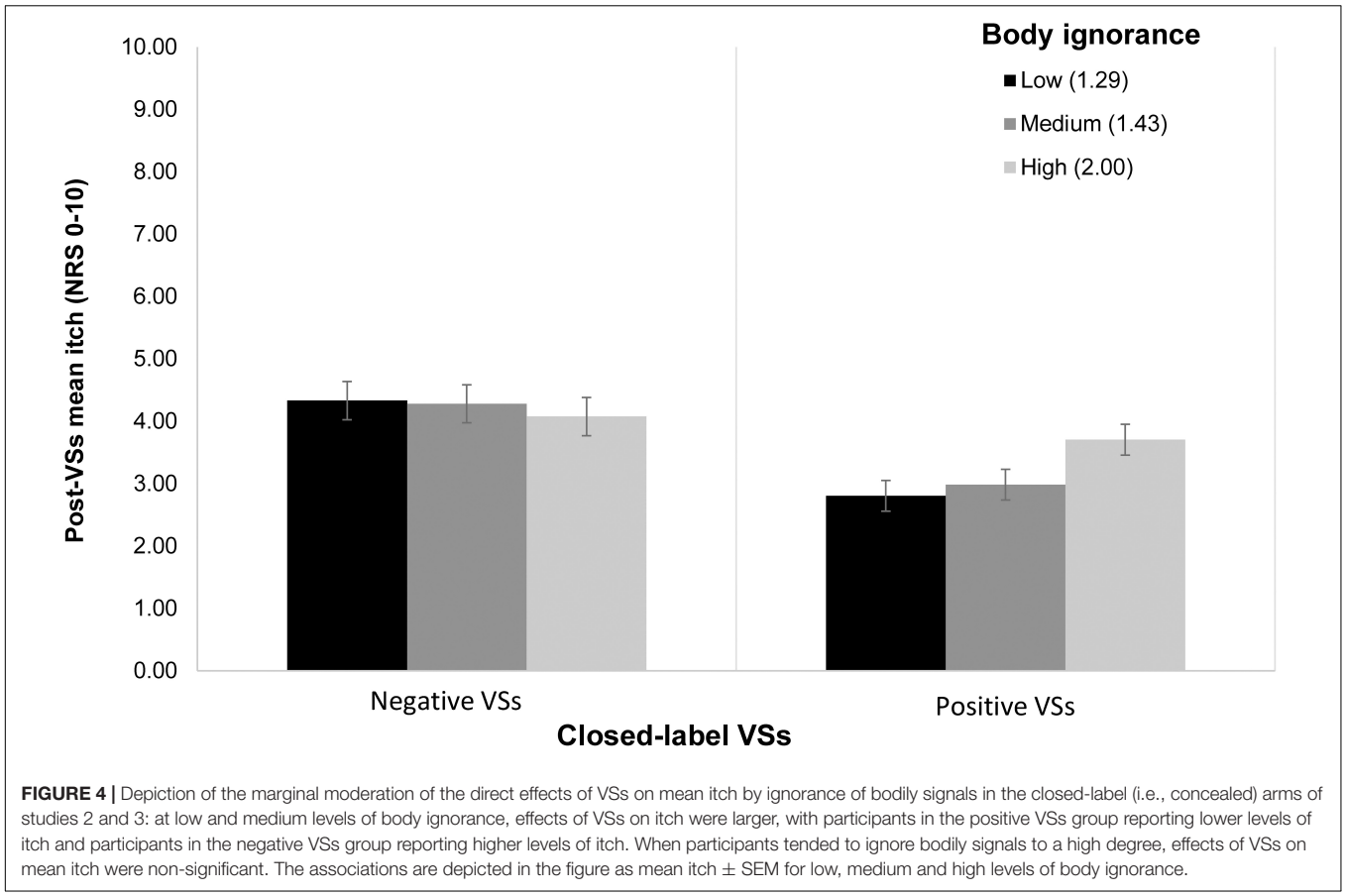

FIGURE 4 | Depiction of the marginal moderation of the direct effects of VSs on mean itch by ignorance of bodily signals in the closed-label (i.e., concealed) arms of studies 2 and 3: at low and medium levels of body ignorance, effects of VSs on itch were larger, with participants in the positive VSs group reporting lower levels of itch and participants in the negative VSs group reporting higher levels of itch. When participants tended to ignore bodily signals to a high degree, effects of VSs on mean itch were non-significant. The associations are depicted in the figure as mean itch ± SEM for low, medium and high levels of body ignorance.

effects found for BAS-associated trait scales across the three studies. In particular, the effects of open-label verbal suggestions on itch were more strongly mediated by conscious expectations when BAS trait drive (i.e., the motivation to pursue one's goals) was lower. In addition, the extent to which individuals pay attention to and ignore bodily signals was related to placebo and nocebo effects: participants who have a higher tendency to ignore bodily symptoms tended to respond more strongly to the positive or negative verbal suggestions. There was no evidence that other interindividual differences, for instance in optimism, neuroticism, or worrying, modulated placebo and nocebo responding to itch.

The current work illustrates how conscious expectations may contribute to placebo and nocebo responding to open-label as well as closed-label verbal suggestions for itch across a relatively large sample of healthy volunteers. To our knowledge, it is the first work that explores how interindividual differences may shape the response to these suggestions and simultaneously takes into account that this influence may be via indirect (i.e., expectation-mediated) pathways. Notably, the role of conscious expectations appeared limited for the closed-label, or concealed, arm of studies 2 and 3. Instead, verbal suggestions directly influenced the experience of itch. Some studies show that conscious expectations may not be needed for placebo or nocebo effects to occur (Jensen et al., 2012; Jensen K. B. et al., 2015; Bajcar et al., 2020; Colloca et al., 2020). The current findings for closed-label suggestions are in line with this previous evidence. On the other hand, the findings for the open-label suggestions show that the effects of these suggestions were predominantly mediated by conscious expectations. Because the research area of open-label placebo is relatively new, much less is known about the mechanisms of these specific placebo effects, or the role that expectations may have in shaping them. A prior experimental study with healthy volunteers shows that expectations about how well placebo pills would work for the participant can influence open-label placebo effects, independent of the actual dose or adherence to placebo treatment (El Brihi et al., 2019). Other studies moreover show that the rationale provided by the researchers for open-label placebo influences the magnitude of open-label placebo effects for patients, which could indicate that conscious expectations play a role in these effects (Locher et al., 2017; Schaefer et al., 2018; Leibowitz et al., 2019). The current findings are in line with these studies. Notably, open-label placebo has been found to improve outcomes for patients, even when they were skeptical or did not expect to experience benefits (Kaptchuk, 2018; Kaptchuk and Miller, 2018), which suggests that factors other than expectations may also elicit these effects. More research is needed to examine under which circumstances and to which extent expectations can contribute to open-label placebo effects.

With regard to the interindividual differences that predict placebo and nocebo effects, traits related to the BAS were found

to moderate the effects of positive and negative suggestions on expectations and itch in the open-label arm of studies 2 and 3. BAS is a motivational system that reflects an individual's sensitivity to stimuli of reward and punishment (Carver and White, 1994; Dierickx et al., 2021). Higher BAS-associated traits and higher sensitivity to rewards have been associated with increased pain experience (Day et al., 2019; Sánchez-Rodríguez et al., 2021; Turner et al., 2021), and notably, with enhanced placebo analgesia as well (Schweinhardt et al., 2009; Yu et al., 2014; De Pascalis and Scacchia, 2017). In the current work, the BAS traits drive, reward responsiveness, and fun seeking all influenced expectations, and consequently, open-label placebo and nocebo effects in itch to some extent. Notably, the indirect effects of positive and negative suggestions on mean itch were larger when the BAS trait "drive" was lower. While this seems contrary to the existing literature at first, these findings could in fact reflect that the process by which placebo and nocebo effects are formed differs depending on an individual's sensitivity to rewards. The significant moderated mediation that we found for the BAS trait "drive" supports this in particular. When participants indicated low drive to pursue their goals, the effects of open-label verbal suggestions on itch were more strongly mediated by expectations. In contrast, the direct effects of verbal suggestions increased in magnitude when BAS drive was higher. Although this increase in magnitude was non-significant in the current work, this would be in line with findings of prior studies (Schweinhardt et al., 2009; De Pascalis and Scacchia, 2017). Similar patterns could be noticed in the findings for BAS "reward processing" (i.e., trait reflecting sensitivity to rewards) and BAS "fun seeking" (i.e., reflecting the tendency to seek out novel or rewarding stimuli). Though moderated mediation was absent, these two scales did moderate some of the single pathways in the model (for instance, the effects of suggestions on expectations). Taken together, these findings show that for individuals who have low BAS (i.e., low sensitivity to rewards), changes in conscious expectations may be necessary to elicit placebo and nocebo effects. For individuals who have a highly sensitive BAS, suggestions could influence itch regardless of what they expect to happen. This implies that it could be relevant to adjust communication strategies in clinical practice depending on a patient's BAS: for those with low BAS, it may be more prudent to maximize positive expectations about treatment for itch.

High BAS has often been associated with higher extraversion (e.g., in Heubeck et al., 1998; Smits and Boeck, 2006). Notably, while BAS was associated with placebo and nocebo responding in the current work, extraversion was not. This is not in line with previous work that links extraversion with placebo responding (Beedie et al., 2008; Kelley et al., 2009), though generally findings for extraversion and placebo responding are mixed (Kern et al., 2020). Extraversion did modulate the effects of suggestions on expectations, though. Potentially, this modulation may not have been large enough to result in detectable differences in placebo or nocebo responding in actual itch experience. Moreover, according to Gray's original theory on reinforcement sensitivity, extraversion stems from a combination of high BAS and low BIS (Gray, 1970; in Knyazev et al., 2004), and BIS has not been associated with placebo or nocebo responding so far, including in the current work. This may speculatively explain why BAS modulated placebo and nocebo effects in the current work, but extraversion did not. Alternatively, variance in extraversion could have been too small to detect associations with placebo or nocebo responding, as young and healthy student volunteers were predominantly included here. Finally, psychological traits or affective states may interact among themselves whilst influencing health outcomes. To illustrate, interactions between the Big Five personality traits have been found to predict wellbeing and mood (McFatter, 1994; Merz and Roesch, 2011). Interindividual differences in a single trait as such may not influence outcomes insomuch, but a specific combination of traits might. While these between-trait interactions are outside of the scope of the current work, future studies could consider, for instance, to use multiplicative moderation analyses to detect whether interactions among moderators may influence placebo or nocebo responding.

It should be noted that, while previous studies investigated placebo effects and BAS exclusively (without looking into nocebo effects), we compared open-label positive suggestions with either neutral instructions or negative suggestions. The results show that BAS traits did not moderate the effects of positive suggestions versus neutral instructions—but rather, that they significantly modulated the effects of positive versus negative suggestions. Thus, alternatively, our findings could also indicate that the involvement of reward processing is different in placebo compared with nocebo effects. This would be in line with recent evidence that shows that activity in the ventral striatum differs between placebo and nocebo effects, likely because placebo responding may be a form of reward processing, whereas nocebo responding may engage aversive networks in the brain (Fu et al., 2021). BAS traits have been found to consistently correlate with activity of this brain region in response to positive stimuli (see for example, Kennis et al., 2013). Moreover, there is evidence that placebo analgesia activates the reward system in the brain, whereas nocebo hyperalgesia may inhibit this network (Shi et al., 2021). Our findings that when BAS-drive trait is low, placebo versus nocebo responding is more dependent on expectation change than when this trait is highly present could reflect these differential responses of the reward system, although this needs to be confirmed by fMRI research. Brain imaging studies for placebo and nocebo effects have so far been conducted predominantly in pain. To this date, only two imaging studies have been published that explore the brain areas involved in nocebo effects for itch (Napadow et al., 2015; van de Sand et al., 2018), and none have studied the brain mechanisms of placebo effects in itch yet. Brain areas that have been found to be involved in nocebo effects in itch are also involved in motivational processing (Napadow et al., 2015). Moreover, interaction between cortex and periaqueductal gray (PAG) was enhanced in nocebo responding in itch (van de Sand et al., 2018). Activation of the PAG in particular has been implicated in descending pain control and reward function (Becerra et al., 2001), but is central to itch processing as well (Najafi et al., 2021). Interestingly, PAG deactivation deriving from reward system activation following scratching has been found to relieve itch, which may suggest distinct mechanisms for itch compared to pain relief (Papoiu et al., 2013). Speculatively, this could mean

that the neurophysiological mechanisms of placebo effects differ between itch and pain as well.

Marginal moderation of the direct effects of closed-label positive and negative suggestions on itch by body ignorance was found. Participants who indicated that they tended to ignore signals of their body showed larger placebo and nocebo responses to the verbal suggestions that were provided. Potentially, these individuals' responses and experiences may be guided to a larger extent by external signals rather than internal ones. Alternatively, individuals who indicated that they tend to be aware of what they experience in their body may be guided more by internal signals and less so by external information. There is some evidence that more self-aware people experience less arousal following a placebo intervention (Gibbons et al., 1979). Training patients to accurately evaluate and report pain levels based on internal rather than external cues has also been found to reduce placebo responses in chronic low back pain (Erpelding et al., 2020). The current findings are in line with this. However, it should be noted that awareness and ignorance of bodily signals in the current study were assessed through self-report, and may as such reflect a conviction that people have (i.e., they believe that they ignore their symptoms) and not a particular skill set. It may be relevant to further investigate whether self-reported versus actual skill in recognizing bodily signals influences placebo and nocebo responding in itch. Moreover, the current study compared placebo and nocebo effects elicited by suggestions. Future research may aim to investigate whether ignorance of bodily symptoms contributes equally to placebo and nocebo effects, for instance by comparing these effects with a neutral control condition. Training individuals to evaluate itch accurately may be particularly relevant for nocebo effects—in theory, such a training could be used to reduce the occurrence of these effects in clinical practice.

The current work shows that other, more general psychological traits, such as optimism, neuroticism, or worrying were not associated with placebo and nocebo responding to verbal suggestions in itch. Although some direct moderation effects were found in the current work, for instance of traits and suggestions on expectations, these were not actually associated with itch experience. This is in line with studies that show that these traits do not predict placebo or nocebo responses (Corsi and Colloca, 2017; Gillving et al., 2020; Kern et al., 2020), but contradicts several studies that do report such associations (e.g., that optimism can predict placebo responding: see Geers et al., 2005, 2007, 2010; Morton et al., 2009; Darragh et al., 2014; Corsi et al., 2016; Zhou et al., 2019). These discrepancies between study findings may be attributable to differences in methodology, or to differences in the type of symptoms that were assessed (i.e., pain versus itch). In addition, the contribution of these interindividual differences to placebo and nocebo effects may change depending on the manner in which placebo and nocebo effects were induced. Identifying which interindividual differences can contribute to placebo and nocebo responding, and which cannot, remains important in order to develop strategies aimed at maximizing placebo effects and minimizing nocebo effects in clinical practice (Evers et al., 2021). Future research could, for example, assess whether the factors that are relevant for shaping placebo and nocebo effects differ depending on the type of mechanisms that elicit these effects. If we know which interindividual differences are relevant for which mechanisms, we will be able to better predict for whom interventions or a treatment rationale aimed at optimizing expectations would be helpful, for instance, and as such be able to optimize treatment in clinical practice.

Innovative statistical methods were used to obtain detailed and mechanistic information about the potential influence of interindividual differences on both open-label and closed-label placebo and nocebo effects in itch. Other strengths of the current work include the increase in power for the analyses that was obtained by combining data of the three studies, and the similarity in the assessed psychological traits and affective states across studies. Some limitations need to be addressed. First, the methodology varied across the analyzed studies, and it cannot be ruled out that some variations in the current findings could be attributed to these between-study differences. For instance, in studies 2 and 3 positive and negative verbal suggestions were compared to each other, but not to a control group. Findings in those studies likely describe differences between placebo and nocebo responders, whereas those in study 1 describe placebo responders only. Second, the main aim of this paper was to explore associations between interindividual differences, expectations, and itch experience following verbal suggestions, and as such the findings need to be seen as hypothesis-generating. A large number of statistical tests were performed to achieve this, which may have increased the number of chance findings. Nonetheless, some measures were taken to prevent over-reporting of chance findings. For instance, a bootstrap-based method was used to analyze mediation and conditional processes. Bootstrapping can improve the accuracy of confidence intervals (Preacher and Hayes, 2008; Hayes, 2009, 2015). Third, the reported effects tended to be small. Moreover, some between-group differences in psychological traits and affective states were observed, for instance between the open-label positive and negative VSs groups of studies 2 and 3: the positive VSs group scored higher on BAS drive trait. While bootstrapping generally can handle asymmetric sampling well (Preacher and Hayes, 2008; Hayes, 2009, 2015), some caution may be needed in interpreting these findings and, ideally, they would need to be replicated by future studies. Finally, a relatively homogenous study sample of young, predominantly female, and healthy student volunteers was used. This may have influenced findings, for instance, by impacting the diversity in the assessed interindividual differences. Generalization of the findings to the general population should be done carefully and in light of the assessed study sample.

In short, the current study explored whether interindividual differences modulated how placebo and nocebo effects are shaped in histamine-induced itch. Moderation of both the direct and indirect (expectation-mediated) effects of positive and negative verbal suggestions were tested. The results indicate that the effects of open-label positive and negative suggestions on itch may be more dependent on mediation by expectations, whereas closed-label (i.e., concealed) suggestions influenced itch directly. Moreover, the findings show that the process by which the positive and negative suggestions influenced itch can change depending on BAS sensitivity: for individuals who

have low BAS (i.e., low sensitivity to rewards), the effects of suggestions were mediated more strongly by expectations. In addition, high ignorance of bodily signals was marginally associated with increased placebo and nocebo responding to verbal suggestions. Finally, there was no evidence that other interindividual differences, for instance in optimism, neuroticism or worrying, modulated placebo and nocebo responding in itch. Overall, the findings contribute to the growing collection of studies that identify factors associated with placebo and nocebo effects. Innovative statistical methods were used to obtain detailed mechanistic information about the potential influence of interindividual differences on how placebo and nocebo effects were formed. If we can increase our understanding of these processes, we may then use this knowledge to develop strategies aimed at maximizing placebo effects in clinical practice.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: The datasets analyzed for this study are available on request to the corresponding author. Requests to access these datasets should be directed to corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee, Leiden University Medical Center, Leiden, Netherlands. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM undertook the statistical analyses and wrote the first draft of the manuscript. All authors commented on the manuscript and approved of the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2021.781521/full#supplementary-material

REFERENCES

Anderson, S., and Stebbins, G. T. (2020). Determinants of placebo effects. *Int. Rev. Neurobiol.* 153, 27–47. doi: 10.1016/bs.irn.2020.03.029

Aslaksen, P. M., and Lyby, P. S. (2015). Fear of pain potentiates nocebo hyperalgesia. *J. Pain Res.* 8, 703–710. doi: 10.2147/JPR.S91923

Bajcar, E. A., Adamczyk, W. M., Wiercioch-Kuzianik, K., and Bąbel, P. (2020). Nocebo hyperalgesia can be induced by classical conditioning without involvement of expectancy. *PLoS One* 15:e0232108. doi: 10.1371/journal.pone.0232108

Bajcar, E. A., and Bąbel, P. (2018). How does observational learning produce placebo effects? A model integrating research findings. *Front. Psychol.* 9:2041. doi: 10.3389/fpsyg.2018.02041

Bartels, D. J. P., van Laarhoven, A. I. M., Haverkamp, E. A., Wilder-Smith, O. H., Donders, A. R. T., van Middendorp, H., et al. (2014). Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PLoS One* 9:e91727. doi: 10.1371/journal.pone.0091727

Bartels, D. J. P., van Laarhoven, A. I. M., van de Kerkhof, P. C. M., and Evers, A. W. M. (2016). Placebo and nocebo effects on itch: effects, mechanisms, and predictors. *Eur. J. Pain.* 20, 8–13. doi: 10.1002/ejp.750

Becerra, L., Breiter, H. C., Wise, R., Gonzalez, R. G., and Borsook, D. (2001). Reward circuitry activation by noxious thermal stimuli. *Neuron* 32, 927–946. doi: 10.1016/s0896-6273(01)00533-5

Beedie, C. J., Foad, A. J., and Coleman, D. A. (2008). Identification of placebo responsive participants in 40km laboratory cycling performance. *J. Sports Sci. Med.* 7, 166–175.

Bingel, U. (2020). Placebo 2.0: the impact of expectations on analgesic treatment outcome. *Pain* 161(Suppl. 1), S48–S56. doi: 10.1097/j.pain.0000000000001981

Carver, C., and White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS Scales. *J. Pers. Soc. Psychol.* 67:319.

Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *J. Health. Soc. Behav.* 24, 385–396. doi: 10.2307/2136404

Colagiuri, B., Schenk, L. A., Kessler, M. D., Dorsey, S. G., and Colloca, L. (2015). The placebo effect: from concepts to genes. *Neuroscience* 307, 171–190. doi: 10.1016/j.neuroscience.2015.08.017

Colloca, L., Akintola, T., Haycock, N. R., Blasini, M., Thomas, S., Phillips, J., et al. (2020). Prior therapeutic experiences, not expectation ratings, predict placebo effects: an experimental study in chronic pain and healthy participants. *Psychother. Psychosom.* 89, 371–378. doi: 10.1159/000507400

Colloca, L., and Barsky, A. J. (2020). Placebo and nocebo effects. *N. Engl. J. Med.* 382, 554–561. doi: 10.1056/NEJMra1907805

Corr, P. J. (2004). Reinforcement sensitivity theory and personality. *Neurosci. Biobehav. Rev.* 28, 317–332. doi: 10.1016/j.neubiorev.2004.01.005

Corr, P. J. (2013). Approach and avoidance behaviour: multiple systems and their interactions. *Emot. Rev.* 5, 285–290. doi: 10.1177/1754073913477507

Corsi, N., Andani, M. E., Tinazzi, M., and Fiorio, M. (2016). Changes in perception of treatment efficacy are associated to the magnitude of the nocebo effect and to personality traits. *Sci. Rep.* 6:30671. doi: 10.1038/srep30671

Corsi, N., and Colloca, L. (2017). Placebo and nocebo effects: the advantage of measuring expectations and psychological factors. *Front. Psychol.* 8:308. doi: 10.3389/fpsyg.2017.00308

Darragh, M., Booth, R. J., and Consedine, N. S. (2014). Investigating the 'placebo personality' outside the pain paradigm. *J. Psychosom. Res.* 76, 414–421. doi: 10.1016/j.jpsychores.2014.02.011

Day, M. A., Matthews, N., Newman, A., Mattingley, J. B., and Jensen, M. P. (2019). An evaluation of the behavioral inhibition and behavioral activation system (BIS-BAS) model of pain. *Rehabil. Psychol.* 64, 279–287. doi: 10.1037/rep0000274

De Pascalis, V., and Scacchia, P. (2017). The behavioural approach system and placebo analgesia during cold stimulation in women: a low-resolution brain electromagnetic tomography (LORETA) analysis of startle ERPs. *Pers. Individ. Differ.* 118, 56–63. doi: 10.1016/j.paid.2017.03.003

Dierickx, S., Dierckx, E., Claes, L., and Rossi, G. (2021). Measuring behavioral inhibition and behavioral activation in older adults: construct validity of the dutch BIS/BAS Scales. *Assessment*. doi: 10.1177/10731911211000123 [Epub ahead of print].

El Brihi, J., Horne, R., and Faasse, K. (2019). Prescribing placebos: an experimental examination of the role of dose, expectancies, and adherence in open-label placebo effects. *Ann. Beh. Med.* 53, 16–28. doi: 10.1093/abm/kay011

Erpelding, N., Evans, K., Lanier, R. K., Elder, H., and Katz, N. P. (2020). Placebo response reduction and accurate pain reporting training reduces placebo responses in a clinical trial on chronic low back pain: results from a comparison to the literature. *Clin. J. Pain.* 36, 950–954. doi: 10.1097/AJP.0000000000000873

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., et al. (2018). Implications of placebo and nocebo effects for clinical practice: expert consensus. *Psychother. Psychosom.* 87, 204–210. doi: 10.1159/000490354

Evers, A. W. M., Colloca, L., Blease, C., Gaab, J., Jensen, K. B., Atlas, L. Y., et al. (2021). What should clinicians tell patients about placebo and nocebo effects? Practical considerations based on expert consensus. *Psychother. Psychosom.* 90, 49–56. doi: 10.1159/000510738

Eysenck, H. J., and Eysenck, S. B. G. (1975). *EPQ (Eysenck Personality Questionnaire)*. San Diego, CA: Educational and Industrial Testing Service.

Frisaldi, E., Shaibani, A., and Benedetti, F. (2020). Understanding the mechanisms of placebo and nocebo effects. *Swiss. Med. Wkly.* 150, w20340. doi: 10.4414/smw.2020.20340

Fu, J., Wu, S., Liu, C., Camilleri, J. A., Eickhoff, S. B., and Yu, R. (2021). Distinct neural networks subserve placebo analgesia and nocebo hyperalgesia. *NeuroImage* 231:117833. doi: 10.1016/j.neuroimage.2021.117833

Geers, A. L., Briñol, P., and Petty, R. E. (2019). An analysis of the basic processes of formation and change of placebo expectations. *Rev. Gen. Psychol.* 23, 211–229. doi: 10.1037/gpr0000171

Geers, A. L., Helfer, S. G., Kosbab, K., Weiland, P. E., and Landry, S. J. (2005). Reconsidering the role of personality in placebo effects: dispositional optimism, situational expectations, and the placebo response. *J. Psychosom. Res.* 58, 121–127. doi: 10.1016/j.jpsychores.2004.08.011

Geers, A. L., Kosbab, K., Helfer, S. G., Weiland, P. E., and Wellman, J. A. (2007). Further evidence for individual differences in placebo responding: an interactionist perspective. *J. Psychosom. Res.* 62, 563–570. doi: 10.1016/j.jpsychores.2006.12.005

Geers, A. L., Wellman, J. A., Fowler, S. L., Helfer, S. G., and France, C. R. (2010). Dispositional optimism predicts placebo analgesia. *J. Pain* 11, 1165–1171. doi: 10.1016/j.jpain.2010.02.014

Gibbons, F. X., Carver, C. S., Scheier, M. F., and Hormuth, S. E. (1979). Self-focused attention and the placebo effect: fooling some of the people some of the time. *J. Exp. Soc. Psychol.* 15, 263–274. doi: 10.1016/0022-1031(79)90037-4

Gillving, M., Demant, D., Lund, K., Holbech, J. V., Otto, M., Vase, L., et al. (2020). Factors with impact on magnitude of the placebo response in randomized, controlled, cross-over trials in peripheral neuropathic pain. *Pain* 161, 2731–2736. doi: 10.1097/j.pain.0000000000001964

Gray, J. A. (1970). The psychophysiological basis of introversion-extraversion. *Behav. Res. Ther.* 8, 249–266. doi: 10.1016/0005-7967(70)90069-0

Hall, K. T., Loscalzo, J., and Kaptchuk, T. J. (2015). Genetics and the placebo effect: the placebome. *Trends Mol. Med.* 21, 285–294. doi: 10.1016/j.molmed.2015.02.009

Hayes, A. F. (2009). Beyond Baron and Kenny: statistical mediation analysis in the new millennium. *Commun. Monogr.* 76, 408–420. doi: 10.1080/03637750903310360

Hayes, A. F. (2015). An index and test of linear moderated mediation. *Multivariate Behav. Res.* 50, 1–22. doi: 10.1080/00273171.2014.962683

Hayes, A. F. (2017). *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. New York, NY: Guilford publications.

Heubeck, B. G., Wilkinson, R. B., and Cologon, J. (1998). A second look at Carver and White's (1994) BIS/BAS scales. *Pers. Individ. Dif.* 25, 785–800. doi: 10.1016/S0191-8869(98)00124-X

Jensen, K. B., Kaptchuk, T. J., Chen, X., Kirsch, I., Ingvar, M., Gollub, R. L., et al. (2015). A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. *Cereb. Cortex* 25, 3903–3910. doi: 10.1093/cercor/bhu275

Jensen, K. B., Kaptchuk, T. J., Kirsch, I., Raicek, J., Lindstrom, K. M., Berna, C., et al. (2012). Nonconscious activation of placebo and nocebo pain responses. *PNAS* 109, 15959–15964. doi: 10.1073/pnas.1202056109

Jensen, M. P., Tan, G., and Chua, S. M. (2015). Pain intensity, headache frequency, and the behavioral activation and inhibition systems. *Clin. J. Pain* 31, 1068–1074. doi: 10.1097/AJP.0000000000000215

Kaptchuk, T. J. (2018). Open-label placebo: reflections on a research agenda. *Perspect. Biol. Med.* 61, 311–334. doi: 10.1353/pbm.2018.0045

Kaptchuk, T. J., and Miller, F. G. (2018). Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? *BMJ* 363:k3889. doi: 10.1136/bmj.k3889

Kelley, J. M., Lembo, A. J., Ablon, J. S., Villanueva, J. J., Conboy, L. A., Levy, R., et al. (2009). Patient and practitioner influences on the placebo effect in irritable bowel syndrome. *Psychosom. Med.* 71, 789–797. doi: 10.1097/PSY.0b013e3181acee12

Kennis, M., Rademaker, A. R., and Geuze, E. (2013). Neural correlates of personality: an integrative review. *Neurosci.Biobehav. Rev.* 37, 73–95. doi: 10.1016/j.neubiorev.2012.10.012

Kern, A., Kramm, C., Witt, C. M., and Barth, J. (2020). The influence of personality traits on the placebo/nocebo response: a systematic review. *J. Psychosom. Res.* 128:109866. doi: 10.1016/j.jpsychores.2019.109866

Knyazev, G. G., Slobodskaya, H. R., and Wilson, G. D. (2004). Comparison of the construct validity of the Gray–Wilson personality questionnaire and the BIS/BAS scales. *Pers. Individ. Dif.* 37, 1565–1582. doi: 10.1016/j.paid.2004.02.013

Leibowitz, K. A., Hardebeck, E. J., Goyer, J. P., and Crum, A. J. (2019). The role of patient beliefs in open-label placebo effects. *Health Psychol.* 38:613. doi: 10.1037/hea0000751

Locher, C., Frey Nascimento, A., Kossowsky, J., Meyer, A., and Gaab, J. (2019). Open-label placebo response - does optimism matter? A secondary-analysis of a randomized controlled trial. *J. Psychosom. Res.* 116, 25–30. doi: 10.1016/j.jpsychores.2018.11.009

Locher, C., Nascimento, A. F., Kirsch, I., Kossowsky, J., Meyer, A., and Gaab, J. (2017). Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain* 158, 2320–2328. doi: 10.1097/j.pain.0000000000001012

McFatter, R. M. (1994). Interactions in predicting mood from extraversion and neuroticism. *J. Pers. Soc. Psychol.* 66:570. doi: 10.1037/0022-3514.66.3.570

Meeuwis, S. H., van Middendorp, H., Lavrijsen, A. P. M., Veldhuijzen, D. S., and Evers, A. W. M. (2021). Open- and closed-label placebo and nocebo suggestions about a sham transdermal patch. *Psychosom. Med.* 83, 33–42. doi: 10.1097/PSY.0000000000000862

Meeuwis, S. H., van Middendorp, H., van Laarhoven, A. I. M., Veldhuijzen, D. S., Lavrijsen, A. P. M., and Evers, A. W. M. (2019). Effects of open- and closed-label nocebo and placebo suggestions on itch and itch expectations. *Front. Psychiatr.* 10:436. doi: 10.3389/fpsyt.2019.00436

Meeuwis, S. H., van Middendorp, H., Veldhuijzen, D. S., van Laarhoven, A. I. M., De Houwer, J., Lavrijsen, A. P. M., et al. (2018). Placebo effects of open-label verbal suggestions on itch. *Acta Derm. Venereol.* 98, 268–274. doi: 10.2340/00015555-2823

Merchán-Clavellino, A., Alameda-Bailén, J. R., Zayas García, A., and Guil, R. (2019). Mediating effect of trait emotional intelligence between the behavioral activation system (BAS)/behavioral inhibition system (BIS) and positive and negative affect. *Front. Psychol.* 10:424. doi: 10.3389/fpsyg.2019.00424

Merz, E. L., and Roesch, S. C. (2011). A latent profile analysis of the Five Factor Model of personality: modeling trait interactions. *Pers. Individ. Dif.* 51, 915–919. doi: 10.1016/j.paid.2011.07.022

Meyer, T. J., Miller, M. L., Metzger, R. L., and Borkovec, T. (1990). Development and validation of the penn state worry questionnaire. *Behav. Res. Ther.* 28, 487–495. doi: 10.1016/0005-7967(90)90135-6

Mitsikostas, D. D., Blease, C., Carlino, E., Colloca, L., Geers, A. L., Howick, J., et al. (2020). European Headache Federation recommendations for placebo and nocebo terminology. *J. Headache Pain* 21:117. doi: 10.1186/s10194-020-01178-3

Morton, D. L., Watson, A., El-Deredy, W., and Jones, A. K. (2009). Reproducibility of placebo analgesia: effect of dispositional optimism. *Pain* 146, 194–198. doi: 10.1016/j.pain.2009.07.026

Muller, D., Judd, C. M., and Yzerbyt, V. Y. (2005). When moderation is mediated and mediation is moderated. *J. Pers. Soc. Psychol.* 89:852. doi: 10.1037/0022-3514.89.6.852

Najafi, P., Dufor, O., Ben Salem, D., Misery, L., and Carré, J.-L. (2021). Itch processing in the brain. *J. Eur. Acad. Dermatol. Venereol.* 35, 1058–1066. doi: 10.1111/jdv.17029

Napadow, V., Li, A., Loggia, M., Kim, J., Mawla, I., Desbordes, G., et al. (2015). The imagined itch: brain circuitry supporting nocebo-induced itch in atopic dermatitis patients. *Allergy* 70, 1485–1492. doi: 10.1111/all.12727

Papoiu, A. D., Nattkemper, L. A., Sanders, K. M., Kraft, R. A., Chan, Y. H., Coghill, R. C., et al. (2013). Brain's reward circuits mediate itch relief. a functional MRI study of active scratching. *PLoS One* 8:e82389. doi: 10.1371/journal.pone.0082389

Petersen, G. L., Finnerup, N. B., Colloca, L., Amanzio, M., Price, D. D., Jensen, T. S., et al. (2014). The magnitude of nocebo effects in pain: a meta-analysis. *Pain* 155, 1426–1434. doi: 10.1016/j.pain.2014.04.016

Preacher, K. J., and Hayes, A. F. (2008). "Contemporary approaches to assessing mediation in communication research," in *The Sage Sourcebook Of Advanced Data Analysis Methods For Communication Research*, eds A. F. Hayes, M. D. Slater and L. B. Snyder (Thousand Oaks, CA: Sage Publications, Inc), 13–54.

Rossettini, G., Camerone, E. M., Carlino, E., Benedetti, F., and Testa, M. (2020). Context matters: the psychoneurobiological determinants of placebo, nocebo and context-related effects in physiotherapy. *Arch. Physiother.* 10:11. doi: 10.1186/s40945-020-00082-y

Sánchez-Rodríguez, E., Racine, M., Castarlenas, E., Tomé-Pires, C., Galán, S., Jensen, M. P., et al. (2021). Behavioral activation and inhibition systems: further evaluation of a BIS-BAS model of chronic pain. *Pain Med.* 22, 848–860. doi: 10.1093/pm/pnaa330

Sanderman, R., Arrindell, W. A., and Ranchor, A. V. (1991). *Eysenck Personality Questionnaire (EPQ)*. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken.

Schaefer, M., Sahin, T., and Berstecher, B. (2018). Why do open-label placebos work? A randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. *PLoS One* 13:e0192758. doi: 10.1371/journal.pone.0192758

Scheier, M., Carver, C., and Bridges, M. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *J. Pers. Soc. Psychol.* 67, 1063–1078.

Scholz, O., and Hermanns, N. (1994). Illness behavior and cognitions influence the perception of itching of patients suffering from atopic dermatitis. *Z. Klin. Psychol.* 23, 127–135.

Schweinhardt, P., Seminowicz, D. A., Jaeger, E., Duncan, G. H., and Bushnell, M. C. (2009). The anatomy of the mesolimbic reward system: a link between personality and the placebo analgesic response. *J. Neurosci.* 29, 4882–4887. doi: 10.1523/JNEUROSCI.5634-08.2009

Shi, Y., Cui, S., Zeng, Y., Huang, S., Cai, G., Yang, J., et al. (2021). Brain network to placebo and nocebo responses in acute experimental lower back pain: a multivariate Granger causality analysis of fMRI data. *Front. Behav. Neurosci.* 15:696577. doi: 10.3389/fnbeh.2021.696577

Smits, D. J. M., and Boeck, P. D. (2006). From BIS/BAS to the big five. *Eur. J. Pers.* 20, 255–270. doi: 10.1002/per.583

Thomaidou, M. A., Veldhuijzen, D. S., Meulders, A., and Evers, A. W. M. (2021). An experimental investigation into the mediating role of pain-related fear in boosting nocebo hyperalgesia. *Pain* 162:287. doi: 10.1097/j.pain.0000000000002017

Turner, A. P., Jensen, M. P., Day, M. A., and Williams, R. M. (2021). Behavioral activation and behavioral inhibition: an examination of function in chronic pain. *Rehabil. Psychol.* 66, 57–64. doi: 10.1037/rep0000316

van Beugen, S., Ograczyk, A., Ferwerda, M., Smit, J. V., Zeeuwen-Franssen, M. E. J., Kroft, E. B. M., et al. (2015). Body attention, ignorance and awareness scale: assessing relevant concepts for physical and psychological functioning in psoriasis. *Acta Derm. Venereol.* 95, 444–451. doi: 10.2340/00015555-1977

van de Sand, M. F., Menz, M. M., Sprenger, C., and Büchel, C. (2018). Nocebo-induced modulation of cerebral itch processing–an fMRI study. *Neuroimage* 166, 209–218. doi: 10.1016/j.neuroimage.2017.10.056

van Laarhoven, A. I. M., van der Sman-Mauriks, I. M., Donders, A. R. T., Pronk, M. C., van de Kerkhof, P. C. M., and Evers, A. W. M. (2015). Placebo effects on itch: a meta-analysis of clinical trials of patients with dermatological conditions. *J. Investig. Dermatol.* 135, 1234–1243. doi: 10.1038/jid.2014.522

Vecchione, M., Ghezzi, V., Alessandri, G., Dentale, F., and Corr, P. J. (2021). BIS and BAS sensitivities at different levels of personality description: a latent-variable approach with self- and informant-ratings. *J. Pers. Assess.* 103, 246–257. doi: 10.1080/00223891.2020.1743709

Weisshaar, E. (2016). Epidemiology of itch. *Curr. Probl. Dermatol.* 50, 5–10. doi: 10.1159/000446010

Wolters, F., Peerdeman, K. J., and Evers, A. W. M. (2019). Placebo and nocebo effects across symptoms: from pain to fatigue, dyspnea, nausea, and itch. *Front. Psychiatr.* 10:470. doi: 10.3389/fpsyt.2019.00470

Yu, R., Gollub, R. L., Vangel, M., Kaptchuk, T., Smoller, J. W., and Kong, J. (2014). Placebo analgesia and reward processing: integrating genetics, personality, and intrinsic brain activity. *Hum. Brain Mapp.* 35, 4583–4593. doi: 10.1002/hbm.22496

Zhou, L., Wei, H., Zhang, H., Li, X., Bo, C., Wan, L., et al. (2019). The influence of expectancy level and personal characteristics on placebo effects: psychological underpinnings. *Front.Psychiatr.* 10:20. doi: 10.3389/fpsyt.2019.00020

Zigmond, A. S., and Snaith, R. P. (1983). The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 67, 361–370. doi: 10.1111/j.1600-0447.1983.tb09716.x

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REVIEW
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What Do Placebo and Nocebo Effects Have to Do With Health Equity? The Hidden Toll of Nocebo Effects on Racial and Ethnic Minority Patients in Clinical Care

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A placebo effect is a positive clinical response to non-specific elements of treatment with a sham or inert replica of a drug, device, or surgical intervention. There is considerable evidence that placebo effects are driven by expectation of benefit from the intervention. Expectation is shaped by a patient's past experience, observations of the experience of others, and written, verbal, or non-verbal information communicated during treatment. Not surprisingly, expectation in the clinical setting is strongly influenced by the attitude, affect, and communication style of the healthcare provider. While positive expectations can produce beneficial effects, negative information and experiences can lead to negative expectations, and consequently negative or nocebo effects. Key components identified and studied in the placebo and nocebo literature intersect with factors identified as barriers to quality care in the clinical setting for Black patients and other patients of color, including poor patient-clinician communication, medical mistrust, and perceived discrimination. Thus, in the context of discrimination and bias, the absence of placebo and presence of nocebo-generating influences in clinical settings could potentially reinforce racial and ethnic inequities in clinical outcomes and care. Healthcare inequities have consequences that ripple through the medical system, strengthening adverse short- and long-term outcomes. Here, we examine the potential for the presence of nocebo effects and absence of placebo effects to play a role in contributing to negative outcomes related to unequal treatment in the clinical encounter.

Keywords: placebo and nocebo effects, health inequities, communication, mistrust, perceived discrimination

INTRODUCTION

Placebo and Nocebo Effects

A placebo effect is a positive outcome in response to an inert treatment or intervention. The mechanism underlying the placebo response has captivated and bewildered clinicians and researchers for decades. To understand why patients respond to seemingly inert treatments,

placebo researchers investigated components of the clinician-patient encounter and found that positive *expectations*, both conscious and unconscious, are key drivers of placebo effects (Atlas, 2021). The word "placebo" is derived from the Latin *placere*, "to please." While placebo effects are widely known to be salubrious, their opposite, nocebo effects, are not as well known. Nocebo effects are negative outcomes that are induced by negative expectations, both conscious and unconscious. The term, derived from the Latin word *nocere*, "to harm," was initially coined in 1961 to describe the phenomenon of adverse events occurring in clinical trial participants randomized to placebo (Kennedy, 1961). Today the term is used in many contexts, one of which is to describe components of the clinical encounter that might negatively affect treatment outcomes.

The nocebo effect was first reported in blinded clinical trials with placebo controls. To the surprise of investigators, participants given placebo in these trials reported side effects, some of which were very closely related to the expected side effects of the active drug. As there were no obvious biological impacts of the placebo pill itself, investigators ascribed the adverse events to psychologically induced negative effects arising from learning about the potential side effects of the active treatment. This phenomenon continues to pose a challenge to drug developers in their attempts to develop new treatments for depression (Kirsch and Sapirstein, 1998; Khan et al., 2002) Alzheimer's disease (Lim et al., 2020), and heart disease prevention (Wood et al., 2020).

The information conveyed by clinicians about a newly prescribed therapy can also shape patients' experiences. Often, if the clinician emphasizes the side-effects of a treatment, the patient is more likely to experience those side-effects (Silvestri et al., 2003; Rief et al., 2006; Doering et al., 2014). Other influencing factors may include subtle cues derived from the posture and facial expressions of the clinician and whether they establish eye contact or physical touch. When these subtle cues are deemed positive, they can enhance placebo effects (Kaptchuk et al., 2008), but when they are negative, the opposite is true and they can induce nocebo effects (Jensen et al., 2012).

Expectations are considered to be key drivers of placebo and nocebo effects and can arise from the patient's past experience, direct information conveyed to the patient by the clinician, and subtle cues in the patient-clinician interaction. If a patient experienced nausea with a treatment in the past, they might expect to again feel nauseous the next time they are prescribed that treatment. Patients with cancer, for example, may experience "anticipatory nausea" before chemotherapy treatments actually begin upon entering the facility where they usually have chemotherapy treatment, or even entering a room with walls painted the same color as the one in which they were usually treated (Andrykowski, 1988; Kamen et al., 2014; Colloca and Barsky, 2020). Many experts consider these negative symptoms to be a product of conditioning from prior experiences. The patient repeatedly feels nauseous during chemotherapy, and over time they are conditioned to associate the treatment room with nausea, even if the room itself is not causing the symptom. Patients that had negative experiences or experienced discrimination in the clinical encounter have different expectations, including increased mistrust and expectations of experiencing discrimination again in the future, than those that have had mostly positive experiences in the clinical encounter (Atlas, 2021; Hall et al., 2021). The implication is that patients could be conditioned to anticipate future poor outcomes with negative encounters.

Due to the ethical imperative of clinicians to "do no harm," and the general aversion to deception of the patient, the study of intentionally induced nocebo effects is limited (Wolters et al., 2019). Intentional introduction of negative experiences can have lasting adverse effects on patients and is therefore highly regulated. Thus, a substantial portion of nocebo research occurs in laboratory settings. Despite the limitations in placebo and nocebo studies, it is clear that the absence of placebo and presence of nocebo-promoting factors can result in negative expectations that increase the experience of pain (Scott et al., 2008), reduce treatment efficacy (van Laarhoven et al., 2011), and compromise short- and long-term health outcomes.

The links between race/ethnicity, health inequities, and placebo and nocebo effects are not well studied (Friesen and Blease, 2018). Four components of the clinical encounter that are considered to mediate suboptimal outcomes by experts in health inequities include poor communication, medical mistrust, perceived discrimination, and racial discordance. Here, we examine these components through a placebo/nocebo lens to determine how the two literatures might converge to better explain how these factors lead to suboptimal outcomes. Further, we investigate the potential for nocebo and placebo mechanisms to play a role in exacerbation of negative outcomes due to unequal treatment in the clinical encounter and support this by connecting evidence from the existing placebo, nocebo, and health inequity literature.

Unequal Treatment

Health inequities research has demonstrated that patients' race and ethnicity can significantly impact the care that they receive and subsequent clinical outcomes. The report *Unequal Treatment*: *Confronting Racial and Ethnic Disparities in Health Care* published by the Institute of Medicine concluded that "race and ethnicity remain significant predictors of quality of health care received" (Nelson, 2002). In 2017, a report from the Centers for Disease Control (CDC) reported that Black Americans were more likely to die from diabetes, heart disease, and cancer than their White counterparts (Hamel et al., 2020). More recently, the Kaiser Family Foundation's (KFF) 2020 Report confirmed that Black Americans have more negative experiences in the health care setting and more significant barriers to accessing healthcare than White Americans (Hamel et al., 2020). In a February 2021 report from the CDC, the life expectancy for non-Hispanic Black Americans was 72 compared to 78 years for non-Hispanic White Americans (Seible et al., 2021). In the United States, infant mortality for Blacks is three times that for white infants (Greenwood et al., 2020).

There are multiple factors that contribute to these inequities, including structural racism and its downstream effects on socioeconomic status and access to healthcare. On an individual level, the clinical encounter is the setting in which many of

these streams of influence converge. It is also the setting in which placebo effects can have profound benefits and nocebo effects can seed their greatest harm (**Figure 1**). There is evidence for discrimination in the clinical encounter that gives rise to unequal care. For example, race of the patient has been shown to significantly impact nurses' pain-treatment decisions (Hirsh et al., 2010). The implicit bias of clinicians has been suggested to negatively impact their clinical relationships with Black patients, and therefore the care of Black patients in general (Blair et al., 2013). A study of 287 medical residents measured implicit bias and demonstrated that physicians whose scores demonstrated implicit bias against Black patients and implicit adherence to the stereotype that Black patients were less cooperative with medical procedures treated Black and White patients differently (Green et al., 2007). Specifically, these physicians had a higher likelihood of treating White patients with thrombolysis, a treatment for blood clots, as compared to Black patients. In fact, as physicians' pro-White unconscious biases increased, "so did their likelihood of treating White patients and not treating Black patients with thrombolysis," indicating unequal treatment related to their biases. Racial and ethnic inequities in care exist in the clinical encounter, giving rise to unequal outcomes and physiological responses to discrimination. Further research is necessary to assess the overlap in neurological correlates of discrimination and nocebo response and to subsequently take steps to improve clinical outcomes.

The absence of factors that promote placebo effects or the presence of factors that induce nocebo effects can have immediate and long-term negative impacts on the patient. Critically, these factors can erode trust and increase perceived discrimination, creating credible expectations that can not only compromise future clinical encounters, but also undermine treatment adherence. It is important to reiterate that these expectations are not deliberate, conscious, or the fault of the patient; rather, these expectations arise as learned conclusions after the direct experience or awareness of others' experiences of patterns of suboptimal, dismissive, or low-quality care. Substantial evidence shows that patients expect to receive unequal treatment based on their race or ethnicity (Blendon et al., 2007). From evidence that shows anticipation of negative outcomes can influence future outcomes, it follows that expectations of this nature could perpetuate the occurrence of the feared outcome. Unfortunately, far too often "placebogenic" factors are absent and "nocebogenic" factors are present in the clinical encounters of Black Americans compared to those of White Americans.

THE CLINICAL ENCOUNTER

"A cold, uncaring, disinterested, and emotionless physician will encourage a nocebo response. In contrast, a caring, empathetic, physician fosters trust, strengthens beneficent patient expectations, and elicits a strong placebo response. […] The doctor, the nurse, the healthcare provider are the most valuable resources for healing patients." (Olshansky, 2007).

Placebo research has identified the clinical encounter and therapeutic relationship as a key mediator of placebo effects (**Figure 1**). In turn, the therapeutic benefits of a positive patient-clinician relationship and their downstream effects on improved adherence and clinical outcomes are well established (Schoenthaler et al., 2012). Specifically, studies have isolated physician warmth and empathy as key components of a positive therapeutic encounter and physician coldness and incompetence drivers of negative outcomes.

In order to reduce the influence of nocebo on outcomes, experts encourage physicians to build a good relationship with the patient (Barsky et al., 2002). In physician training, the importance and benefits of a positive and effective therapeutic relationship are emphasized. However, health inequities research finds that the likelihood and frequency of positive or satisfactory encounters with physicians are variable and often vary in part depending on the race and ethnicity of the patient. In a study comparing survey responses of 14 racial and ethnic groups, the non-White groups tended to view the quality of the health care they received more negatively than White patients, and many reported that they felt they would not receive the best care if they were sick (Blendon et al., 2007).

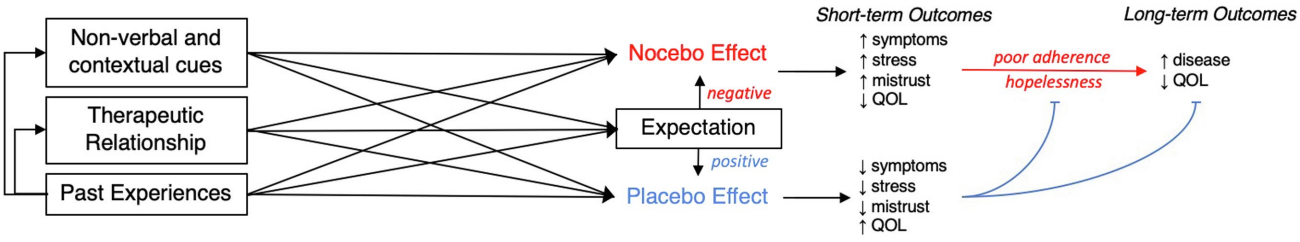

FIGURE 1 | QOL is quality of life, a measure assessed by many treatment satisfaction surveys. Non-adherence, stress, or poor feelings of quality of life could occur unrelated to these factors. Though there are other mechanisms by which non-verbal and contextual cues and past experiences mediate outcomes, one suggested mechanism is that expectation in part mediates these inputs. For example, experience of racism in a clinical encounter could lead to mistrust of that physician and reduce adherence to the treatment suggested by that physician without the influence of expectations. However, the next time that patient returns to a clinician's office for a medical problem, they might be wary of the potential for a negative encounter, which could then be mediated by expectations, following the paths in the figure.

Communication and Warmth

In the placebo literature, positive and effective clinician patient communication is crucial to ensuring adequate patient satisfaction and adherence to medical advice. Communication is a key component of expectations, which in turn drive placebo and nocebo effects. In a now classic placebo/nocebo study, participants rated their pain during a continuous infusion of remifentanil. The participants' experience of pain varied with the information they were given about the infusion. Specifically, their experience of pain was reduced when they thought they were receiving the potent analgesic, even if the infusion had not yet started, and enhanced when they were told that the infusion was stopped, even if it was continued. Brain images collected during the study revealed that activation in regions of the brain involved in processing pain or associated with placebo effects was influenced by what the participant was told about the infusion (Bingel et al., 2011). These findings have been replicated in the placebo/nocebo literature (Wager and Atlas, 2015; Geuter et al., 2017). Expectations shaped by information, associative learning, social observation, and subtle cues appear to elicit changes in the brain that are associated with an increase or decrease in the experience of pain.

In psychotherapy trials, patient ratings of empathy and alliance rank as top variables that predict outcomes (Wampold, 2015). Other factors, including supportive care and touch can influence patient satisfaction (Lopez-Sola et al., 2019; Reddan et al., 2020). Enhancing the patient-clinician encounter influences the placebo effect significantly (Fuentes et al., 2014). In one of the most cited placebo studies, Kaptchuk et al. (2008) demonstrated that components of the clinical encounter, from the physical exam and answering questions about one's condition ("observation"), to receiving sham interventions ("limited"), or sham interventions plus demonstrable warm, caring actions ("augmented") are additive. In the study, the limited group had better outcomes than the observation group, and the augmented group had significantly better outcomes than the other two groups.

In the nocebo literature, poor or limited physician encounters can increase the likelihood for a nocebo reaction to an inert treatment. One such study used a factorial ($2 \times 2 \times 2$) between-subjects study design to assess the impact of expectations and physician interaction style (Howe et al., 2017). In the study, a histamine skin-prick test was used to administer an allergic reaction. Then, an inert cream was provided with instructions to expect either alleviation (the cream would decrease the reaction) or worsening (the cream would increase the reaction). The clinician administering the treatment was instructed to display either high or low warmth and high or low competence. The subjects who received the positive information about the cream had significantly smaller wheals than those that received the negative suggestion. Further, the impact of expectation was mediated by physician warmth and competence. Positive expectations delivered by a warm and competent clinician correlated with the smallest wheal size, and these effects were negated when the physician delivered the inert cream with low-warmth/low-competence.

Another recent study of the effect of medical provider facial expressions on pain analgesia following hypothetical painful procedures found that perceived competence and warmth of the clinician based on facial visual information alone predicted patients' expectations about post-procedure pain and use of medication (Necka et al., 2021). This study emphasized the effect of patients' initial impression of physicians on their perceptions of their care, which can subsequently alter treatment outcomes. These findings are consistent with observations that negative information and the absence of warmth and competence can minimize the benefit of a treatment.

Though not a primary focus of the placebo/nocebo literature, validation of patient concerns is an element of the therapeutic relationship that has been shown to influence patient satisfaction with the clinical encounter (Greville-Harris and Dieppe, 2015). One study manipulated the amount of validating language used by a clinician during an encounter to determine the significance of validating language in participant satisfaction. The study demonstrated that participants experiencing an "invalidating" encounter reported lower levels of perceived safety, exhibited higher physiological arousal (measured by heart rate), had increased negative affect, and reported lower willingness to participate in a future study as compared to participants that had encounters with physicians that were validating (Greville-Harris, 2013). In post-visit interviews, invalidated participants reported feeling hopeless and angry, and felt an increased need to avoid particular doctors or treatments entirely. The authors hypothesized that validating language might induce placebo responsiveness, but the results showed that the negative effects of invalidation were more significant and suggest that invalidation could elicit nocebo responses (Greville-Harris and Dieppe, 2015). In a study assessing the impact of physician invalidation on fibromyalgia patients, invalidation correlated with significantly lower quality of life scores on the Quality-of-Life Scale-16 (QOLS-16). Without intervention, constant invalidation of the patient's experience could have detrimental effects on a patient's overall sense of wellbeing and psychological and physical health (Lobo et al., 2014).

Racial disparities in communication have been documented and are considered driving factors for poor treatment adherence and negative experiences in the health care setting (Hamel et al., 2021). When recordings of clinic visits were assessed by independent raters, non-White patients were found to experience unfavorable treatment and suboptimal communication compared to their White counterparts. Physicians were found to be 23% more verbally dominant and 33% less engaged in patient-centered communication during medical visits with Black patients as compared to White patients (Johnson et al., 2004). Consistent with these findings, a meta-analysis showed that physicians were less likely to participate in shared decision making or establish rapport with non-White compared to White patients (Ferguson and Candib, 2002).

Black patients are more likely to be invalidated by their physicians. A recent study evaluated language used by physicians in their notes about patients. The study showed that physicians tended to use language implicating lower patient credibility when reporting Black patients' health concerns in their notes

as compared to those of White patients (Beach et al., 2021). According to the 2020 KFF Report, 41% of Black women with a child under the age of 18 stated that there was a time in the last 3 years when a healthcare provider talked down to them or did not treat them with respect (Hamel et al., 2020). Further research has shown that Black patients receive less information than White patients, ask fewer questions, and are less likely to participate in decision making when experiencing lower-quality communication (Shen et al., 2018). Healthcare professionals have also been shown to hold false beliefs about biological differences between White and Black patients that correlate with their treatment decisions (Hoffman et al., 2016; Atlas, 2021). A study assessing whether patient factors affected physicians' underestimation of patient pain found that physicians are twice as likely to underestimate pain in Black patients (Staton et al., 2007). Black patients reporting moderate to high levels of pain are less likely to receive opioids compared to White patients (Burgess et al., 2014). Further, Black children with appendicitis are less likely to receive opioids for pain relief (Goyal et al., 2015).

The Implicit Association Test (IAT) is a test that quantitatively assesses an individual's implicit attitudes and beliefs (implicit associations) that they may be unwilling or unable to report. In a study using the IAT to measure clinician implicit race bias and implicit race and compliance stereotyping, high scores (indicating greater bias) were associated with markers of poor communication and care ratings among Black patients in particular (Cooper et al., 2012). Discrimination and stereotyping could explain suboptimal communication between Black patients and their physicians. A study examining the effect of race and socioeconomic status on physicians' perceptions of patients showed that the race of the patient was associated with the physician's assessment of the patient's intelligence, likelihood of risky behavior, likelihood of adherence to medical advice, and the physician's feelings of affiliation toward the patient (van Ryn and Burke, 2000).

Training physicians to improve their communication with patients is one strategy to address nocebo/placebo effects and inequities in the clinician-patient encounter. Improvement in communication as a result of training was shown to increase the likelihood of patient adherence (Zolnierek and Dimatteo, 2009). Similarly, patient satisfaction is highly correlated with patients' feelings of involvement in medical decisions and of being treated with dignity (Beach et al., 2005). Positive communication not only benefits the patient; but also a 2016 study similarly showed that relationship-centered communication skills training improved patient satisfaction scores, improved physician empathy and self-efficiency, and reduced physician burnout (Boissy et al., 2016).

Trust

Trust in the therapeutic relationship is closely tied to communication and is a key mediator of the clinical relationship. In most placebo studies, the importance and influence of a physician is partially attributed to their status as a trusted community member and provider (Benedetti, 2013). Trust is accepted as an important factor in maintaining continuity of care, adherence to treatment, and patient satisfaction, all of which are short-term measures that tend to predict long-term outcomes (Rolfe et al., 2014). In fact, patient feelings of trust in their clinician are associated with pain ratings during an encounter (Losin et al., 2017). On the one hand, trust in physicians has been shown to strongly influence willingness to seek medical care, participate in research, reveal personal information, and adhere to treatment. On the other hand, medical mistrust has been shown to correlate strongly with underutilization of available health services (Hall et al., 2001; LaVeist et al., 2009). These factors are significant, as treatment adherence significantly correlates with patient outcomes; a meta-analysis of studies measuring adherence and outcomes in the general population demonstrated that there is a 26% outcome difference between high and low adherence (DiMatteo et al., 2002).

Mistrust in physicians is both a symptom and cause of suboptimal clinical encounters. Experiencing discrimination can cause mistrust in medical professionals in future encounters, and latent feelings of mistrust can influence adherence and willingness to seek treatment (Hall et al., 2001; LaVeist et al., 2009). Mistrust can be considered a type of negative expectation: an evidence based anticipation of future encounters after negative experiences (Scharff et al., 2010). If a patient experienced discrimination, ambivalence, or suboptimal care from physicians in past experiences, they might be conditioned to anticipate suboptimal encounters in the future.

There is evidence that people who experience discrimination in daily life are more likely to have feelings of mistrust toward medical professionals (Williams and Mohammed, 2009; Ojikutu and Stone, 2021). Some studies have suggested that Black patients are more likely to report general medical mistrust than White patients (Boulware et al., 2003). A 2020 report by KFF found that only 59% of Black adults surveyed felt they could trust doctors as compared to 78% of White respondents (Halbert et al., 2006; Hamel et al., 2020). Studies have shown that Black patients generally report less trust in their personal physicians, regardless of reported trust in general information sources (Musa et al., 2009). These differences can also be observed over the course of a single clinical visit. A 2006 study examining the quality of patient-clinician communication found that Black and White patients rated pre-visit trust in physicians statistically similarly, but Black patients reported lower post-visit trust and rated physicians lower on communication, support, and partnering as compared to White patients (Gordon et al., 2006). Significant predictors of post-visit trust included physicians' and patients' perceptions of physicians' communication.

The potential of trust and comfort in improving treatment outcomes was validated by a 2018 study that examined the potential benefit of healthcare interventions based in trusted community settings, in this case, a barbershop. In the study, 319 Black male barbershop patrons with hypertension were randomly assigned to an in-shop pharmacist led intervention or an active control group. Among participants assigned to the barbershop-based intervention, 63.6% had a reduction in their blood pressure to normal levels compared to 11.7% of those in the control intervention (Victor et al., 2018).

This result affirms how integrating findings in placebo/nocebo and healthcare disparities research can drive innovative approaches for addressing health inequities in clinical care.

Racial Concordance and Patient Outcomes in the Clinic

Many of the elements discussed in this review have been shown to be mediated by racial concordance, or lack thereof, in the patient-clinician relationship (Schoenthaler et al., 2012). Racially discordant patient-clinician encounters have been shown to include communication difficulties that may contribute to lower quality (Street Jr. et al., 2007). Indeed, patients of color have been found to be more likely to have suboptimal experiences in the health care setting when the care is being provided by a provider of a different race – what is referred to as a racially discordant patient provider interaction. The important role of racial concordance was illuminated by a review of the literature in 2018, which examined 40 published studies with 66 different analyses of patient-physician communication with Black patients compared to others (Shen et al., 2018). This review found that in the majority of these studies Black patients experienced lower communication quality measured in multiple ways, including less information giving by physicians, less partnership building by physicians, shorter visits, lower total word count, and less eye contact. Importantly, however, racial discordance almost always predicted poorer communication and communication was better with racially concordant patient-physician interactions.

A number of recent studies have confirmed the positive effect of racially concordant patient-physician encounters and relationships (Cooper-Patrick et al., 1999; Laveist and Nuru-Jeter, 2002; LaVeist et al., 2003; Meghani et al., 2009; Alsan et al., 2019; Ma et al., 2019; Takeshita et al., 2020). They found that patients of color have greater trust, are more likely to receive appropriate treatment and accept indicated screenings, and thus have better outcomes, when they see physicians of their own race. Simulation studies support these findings (Losin et al., 2017). Some studies have found that racial concordance improves pain scores in studies of acute pain (Anderson et al., 2020). Recent studies have investigated the effect of the race of the speaker in media distribution of COVID-19 information (Torres et al., 2021), and a recent study by Alsan et al. (2021) found that Black and Latinx patients are more likely to trust COVID-19 information when it comes from a physician of their own culture. While it is interesting and important that racially concordant patient-provider relationships mitigate the potential harm that patients of color suffer in the health care system, it is not a solution that is scalable. Given that Black and Latinx physicians together comprise approximately 11% of U.S. physicians (Colleges, 2018), it is a given that most Black and Latinx patients will continue to experience racially discordant patient provider relationships. These results point to the importance of pursuing further empirical research to identify which component of the race/ethnic concordant clinical encounter mediates positive outcomes to improve all patient encounters.

NEUROBIOLOGICAL AND PHYSIOLOGICAL CORRELATES OF PLACEBO/NOCEBO AND DISCRIMINATION

Neurobiological Correlates of Placebo/Nocebo

In the past 2 decades, neuroimaging studies have begun to elucidate the neurobiological basis and underlying mechanisms of placebo and nocebo effects. In laboratory-based studies, subjects are exposed to an aversive stimulus (e.g., heat pain or electric shock) and then given an inert treatment (e.g., a saline infusion or inert cream) with the instruction to expect alleviation (i.e., "this will reduce your pain") or worsening of the pain (i.e., "this will increase your pain"). Association between treatment and its effect can also be induced by conditioning through repeated pairing of a painful stimulus and a treatment to guide the experience of pain (Atlas, 2021).

Neuroimaging during these laboratory procedures implicates signaling of opioids and dopamine. Other neurotransmitters and hormones are likely involved, including vasopressin, which influences social behavior and cortisol levels in humans (Colloca et al., 2016). Though nocebo and placebo appear phenotypically opposite, nocebo is hypothesized to recruit another neurotransmitter signaling cascade, the cholecystokinin (CCK) pathway (Tracey, 2010). The CCK signaling pathway has been associated with anxiety disorders and acute episodes of anxiety or stress. Pain related studies of nocebo have found that nocebo is associated with anticipatory anxiety (Atlas, 2021) and hypothalamic-pituitary-adrenal (HPA) axis activity (Johansen et al., 2003), as measured by levels of cortisol in the blood.

In a 2006 neurobiological study of nocebo, participants were exposed to acute arm pain and given either diazepam (a benzodiazepine), proglumide (a CCK-antagonist), or no treatment (Benedetti et al., 2006). To measure changes in HPA-axis activity, blood cortisol levels were obtained. Diazepam, a medication often used to treat anxiety, blocked both nocebo hyperalgesia and HPA-hyperactivity. Proglumide blocked nocebo hyperalgesia but did not block HPA-axis hyperactivity. Importantly, neither drug showed analgesic influence on the pain itself, but rather affected the nocebo related increase in pain ratings. These results suggested differential involvement of the two systems, but point to the involvement of both stress and anxiety HPA-axis related mechanisms in the brain in response to nocebo. Although neuroimaging has identified these and other mechanisms in placebo/nocebo research, they are not specific enough to show reliable correlations to racial healthcare inequities. More neurobiological research is needed to address the significance of the overlap between nocebo pathways and the physiological correlates of the experience of racial and ethnic discrimination in clinical encounters.

Neurobiological and Physiological Correlates of Discrimination

Experiencing discrimination in the clinic or in the broader societal context can influence levels of trust and expectations of treatment in patients. In the literature, exposure to

discrimination or self-reported experience of discriminatory encounters is often referenced as "perceived discrimination," and has been shown to mediate the number of patients' experiences of discrimination and feelings of medical mistrust (Hammond, 2010). Perceived discrimination is associated with a variety of negative health consequences, including a higher risk of mental health conditions and a decrease in well-being, self-perceived health, and mortality (Barnes et al., 2008; Williams and Mohammed, 2009; Todorova et al., 2010; Straiton et al., 2019). Heat related pain has been shown to be associated with perceived racial discrimination in Black, but not White, study participants (Goodin et al., 2013). A neuroimaging study conducted in 2020 found that pain ratings in response to a thermal pain stimulus were mediated by perceived discrimination and by brain activity in regions previously associated with discrimination, pain ratings, and trust in the experimenter (Losin et al., 2020). This association was observed in self-identified African American participants, but not among Hispanic or non-Hispanic White participants.

Exposure to discrimination has also been shown to cause downstream stress related neurobiological effects that might influence long-term downstream health outcomes (Pascoe and Smart Richman, 2009). Some of these physiological effects overlap with neurobiological nocebo mechanisms. Activation of the HPA-axis has been shown to be a correlate of stress and experienced discrimination. While activation of the HPA-axis and release of cortisol are an important adaptation to allow humans to respond to stressful or dangerous situations, sustained high concentrations of cortisol can cause long term damage and dysregulation of the HPA-axis, and has even been associated with increased rates of cardiovascular disease (Lockwood et al., 2018). Black patients have higher rates of fatal cardiovascular disease than White patients; in 2018, Black Americans were 30% more likely to die from heart disease than White Americans (OMH, n.d.).

DISCUSSION

Ways to Improve Empirical Research to Assess the Impact of Nocebo and Placebo Effects in Clinical Care

The literature suggests that there are important links between nocebo, placebo, and health inequities in the clinical encounter, though there is a dearth of empirical studies assessing this relationship (Friesen and Blease, 2018). Research studying the effect of perceived similarity between patients and clinicians shows that this increases the placebo effect, yet the role of race and ethnicity has yet to be studied with the same focus on identifying a biological mechanism. Understanding the biological mechanism that connects suboptimal clinical encounters with poor long-term outcomes and its downstream effects is essential to promoting health equity. Gaining a specific understanding of the components of the clinical encounter that mediate suboptimal outcomes through biological mechanisms is the first step in ensuring equitable care in the encounter itself. To achieve this, multidisciplinary research is called for, in which researchers work together to gain a more holistic understanding of the downstream impacts of racial/ethnic discordance and outcomes in the clinical encounter, and include measures to better capture some of these components (Atlas, 2021).

There already exists an extensive literature examining the relationship between race-discordance in the patient-clinician relationship, patient satisfaction ratings, and health outcomes, but many of these studies lack a biological outcome measure, like neuroimaging or blood cortisol levels. Assessment of these physiological measures could assist in elucidating the relationship between race/ethnicity and placebo and nocebo in the clinical encounter. Neuroimaging, genomic, or physiological studies examining the impact of supportive care, touch, or good communication should also add in race/ethnicity of the patient and clinician as a measure to capture how different groups of patient are affected by some of these components. To this end, studies utilizing artificial "groups" of patients based on survey responses could provide useful insights when it comes to racial concordance in the clinical encounter, but to make these studies more directly applicable to the clinic, it may be useful to survey patients in actual clinical encounters for their feelings of group-connectedness to clinicians.

Nocebo effects are present in placebo control arms of randomized clinical trials, and the potential for information provided during the informed consent to give rise to side effects has been extensively studied in this context. There is potential for race/ethnicity of patients and clinicians to influence the rates of side effects in clinical trials (Burroughs et al., 2002). However, we note two important points that minimize the potential to derive clear associations between race and adverse events in clinical trials. One is that people of color generally are underrepresented in clinical trials, so statistical comparison of these groups might be underpowered. Second, genetic variation could function as a confounder to some differences in this setting (McDowell et al., 2006). Increasing race and ethnicity reporting in studies with large quantities of nocebo responses in the placebo arm of clinical trials could be useful in identifying specific factors that give rise to side effects.

There are some clear examples of studies that investigate both elements of the clinical encounter and physiological changes associated with health inequities. In February 2021, Letzen et al. (2021) investigated differences in placebo hypoalgesia associated with verbal suggestions, and found that non-Hispanic Black individuals tended to report greater pain increases after verbal suggestion of increased pain plus a saline infusion compared to non-Hispanic White individuals. Some researchers already examine neural mechanisms activated during clinical encounters; for example, Jensen et al. (2014) used functional MRI to examine neural activity of the physician during an encounter with a patient. Adding in race or ethnicity of the patient or of the physician as a focus of an experiment of this type could provide useful insight into outcomes of the clinical encounter. Integration of these methods into studies of health inequities, and integration of race/ethnicity as a factor in studies of placebo and nocebo in the clinical encounter, would begin to fill the gap of empirical research assessing the effect of race in mediating outcomes arising from the clinical encounter.

Practical Ways to Enhance Placebo and Reduce Nocebo Effects in Clinical Care

Mitigating factors that reduce placebo or enhance nocebo effects, particularly in racially/ethnically discordant dyads, can be achieved by modifying behaviors in communication and addressing implicit biases. Overall, emphasis on ensuring a patient-centered clinical encounter is important in improving patient satisfaction and other outcomes. In a study examining racial disparities in communication, the results found that communication quality was improved when physicians' behavior was matched to that of the patients. For example, physicians could focus on matching patient behaviors of smiling, gazing, and laughter as these behaviors have been shown to elicit a favorable response from patients (Hamel et al., 2021). Studies have also shown that the implicit racial bias of physicians can be decreased significantly by completing the Black-White IAT during the first and last semester of medical school (van Ryn et al., 2015). Therefore, implementing unconscious bias training early on in medical education may also prove to be an effective way to prevent discrimination, invalidation, and microaggression from driving racial inequities in patient communication and ultimately health outcomes.

In order to maximize placebo effects and minimize the detrimental effects of nocebo, experts have encouraged clinicians to become familiar with placebo and nocebo effects and to educate their patients about the potential mechanisms of such effects. Similarly, experts advise clinicians to encourage conversation with patients about their needs and expectations about their treatment, and to frame information in a reasonably positive context and avoid negative contextual experiences (Barsky et al., 2002; Colloca and Barsky, 2020).

CONCLUSION

In this paper, we examined how healthcare inequities may be driven in part by the absence of placebo and presence of nocebo effects. We focused on components of the patient-clinician relationship that can mediate nocebo and placebo effects disparately across populations. Poor communication, medical mistrust, and perceived discrimination are three components of care that could interact with placebo/nocebo mechanisms to influence downstream effects (**Figure 1**). Clinicians are not the only sources of negative anticipation; inattentive or discourteous non-medical staff, for example, can contribute to patient feelings of discrimination and lower ratings of patient satisfaction (Tajeu et al., 2015). The short-and long-term effects of health inequities related to clinical care lead to devastating effects that have long term impacts on quality of life. Ideally, the systemic factors seeding the absence of placebo and presence of nocebo effects would be reduced. In the short-term, understanding the underlying biological drivers of these effects is critical to identifying ways to shift and improve or prevent these harmful influences on patients.

The Latin root for "nocebo" is also found in the Hippocratic oath: *primum non nocere*, or "do no harm." Through suboptimal clinical encounters marked by poor communication and inattention to interpersonal cues that could impact patient feelings of trust, evidence from the existing literature suggests that the potential for nocebo effects could be increased among Black patients. In order to adequately serve patients and minimize the damaging effects of racism, steps should be taken to minimize nocebo and maximize placebo effects. Educating clinicians about their role in mitigating these factors would go a long way in increasing placebo and reducing nocebo in the clinical encounter to ensure the best care for patients. Further, placebo researchers and public health experts must collaborate to address the potential mechanism by which inequity in the clinical encounter affects long-term outcomes, experiences, and perceptions of care.

AUTHOR CONTRIBUTIONS

VES, KTH, and HEY contributed to conception and design of the review. HEY wrote the first draft of the manuscript. KTH, VES, SRA, and NC wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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REFERENCES

Alsan, M., Garrick, O., and Graziani, G. (2019). Does diversity matter for health? Experimental evidence from Oakland. *Am. Econ. Rev.* 109, 4071–4111. doi: 10.1257/aer.20181446

Alsan, M., Stanford, F. C., Banerjee, A., Breza, E., Chandrasekhar, A. G., Eichmeyer, S., et al. (2021). Comparison of knowledge and information-seeking behavior After general COVID-19 public health messages and messages tailored for black and Latinx communities: A randomized controlled trial. *Ann. Intern. Med.* 174, 484–492. doi: 10.7326/M20-6141

Anderson, S. R., Gianola, M., Perry, J. M., and Losin, E. A. R. (2020). Clinician-patient racial/ethnic concordance influences racial/ethnic minority pain: evidence from simulated clinical interactions. *Pain Med.* 21, 3109–3125. doi: 10.1093/pm/pnaa258

Andrykowski, M. A. (1988). Defining anticipatory nausea and vomiting: differences among cancer chemotherapy patients who report pretreatment nausea. *J. Behav. Med.* 11, 59–69. doi: 10.1007/BF00846169

Atlas, L. Y. (2021). A social affective neuroscience lens on placebo analgesia. *Trends Cogn. Sci.* 25, 992–1005. doi: 10.1016/j.tics.2021.07.016

Barnes, L. L., de Leon, C. F., Lewis, T. T., Bienias, J. L., Wilson, R. S., and Evans, D. A. (2008). Perceived discrimination and mortality in a population-based study of older adults. *Am. J. Public Health* 98, 1241–1247. doi: 10.2105/AJPH.2007.114397

Barsky, A. J., Saintfort, R., Rogers, M. P., and Borus, J. F. (2002). Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 287, 622–627. doi: 10.1001/jama.287.5.622

Beach, M. C., Saha, S., Park, J., Taylor, J., Drew, P., Plank, E., et al. (2021). Testimonial injustice: linguistic bias in the medical Records of Black Patients

and Women. *J. Gen. Intern. Med.* 36, 1708–1714. doi: 10.1007/s11606-021-06682-z

Beach, M. C., Sugarman, J., Johnson, R. L., Arbelaez, J. J., Duggan, P. S., and Cooper, L. A. (2005). Do patients treated with dignity report higher satisfaction, adherence, and receipt of preventive care? *Ann. Fam. Med.* 3, 331–338. doi: 10.1370/afm.328

Benedetti, F. (2013). Placebo and the new physiology of the doctor-patient relationship. *Physiol. Rev.* 93, 1207–1246. doi: 10.1152/physrev.00043.2012

Benedetti, F., Amanzio, M., Vighetti, S., and Asteggiano, G. (2006). The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J. Neurosci.* 26, 12014–12022. doi: 10.1523/JNEUROSCI.2947-06.2006

Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuircheartaigh, R., Lee, M. C., Ploner, M., et al. (2011). The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci. Transl. Med.* 3:70ra14. doi: 10.1126/scitranslmed.3001244

Blair, I. V., Steiner, J. F., Fairclough, D. L., Hanratty, R., Price, D. W., Hirsh, H. K., et al. (2013). Clinicians' implicit ethnic/racial bias and perceptions of care among black and Latino patients. *Ann. Fam. Med.* 11, 43–52. doi: 10.1370/afm.1442

Blendon, R. J., Buhr, T., Cassidy, E. F., Perez, D. J., Hunt, K. A., Fleischfresser, C., et al. (2007). Disparities in health: perspectives of a multi-ethnic, multi-racial America. *Health Aff.* 26, 1437–1447. doi: 10.1377/hlthaff.26.5.1437

Boissy, A., Windover, A. K., Bokar, D., Karafa, M., Neuendorf, K., Frankel, R. M., et al. (2016). Communication skills training for physicians improves patient satisfaction. *J. Gen. Intern. Med.* 31, 755–761. doi: 10.1007/s11606-016-3597-2

Boulware, L. E., Cooper, L. A., Ratner, L. E., LaVeist, T. A., and Powe, N. R. (2003). Race and trust in the health care system. *Public Health Rep.* 118, 358–365. doi: 10.1016/S0033-3549(04)50262-5

Burgess, D. J., Nelson, D. B., Gravely, A. A., Bair, M. J., Kerns, R. D., Higgins, D. M., et al. (2014). Racial differences in prescription of opioid analgesics for chronic noncancer pain in a national sample of veterans. *J. Pain* 15, 447–455. doi: 10.1016/j.jpain.2013.12.010

Burroughs, V. J., Maxey, R. W., and Levy, R. A. (2002). Racial and ethnic differences in response to medicines: towards individualized pharmaceutical treatment. *J. Natl. Med. Assoc.* 94, 1–26.

Colleges, A. O. A. M. (2018). Figure 18. Percentage of all active physicians by race/ethnicity, 2018.

Colloca, L., and Barsky, A. J. (2020). Placebo and nocebo effects. *N. Engl. J. Med.* 382, 554–561. doi: 10.1056/NEJMra1907805

Colloca, L., Pine, D. S., Ernst, M., Miller, F. G., and Grillon, C. (2016). Vasopressin boosts placebo analgesic effects in women: A randomized trial. *Biol. Psychiatry* 79, 794–802. doi: 10.1016/j.biopsych.2015.07.019

Cooper, L. A., Roter, D. L., Carson, K. A., Beach, M. C., Sabin, J. A., Greenwald, A. G., et al. (2012). The associations of clinicians' implicit attitudes about race with medical visit communication and patient ratings of interpersonal care. *Am. J. Public Health* 102, 979–987. doi: 10.2105/AJPH.2011.300558

Cooper-Patrick, L., Gallo, J. J., Gonzales, J. J., Vu, H. T., Powe, N. R., Nelson, C., et al. (1999). Race, gender, and partnership in the patient-physician relationship. *JAMA* 282, 583–589. doi: 10.1001/jama.282.6.583

DiMatteo, M. R., Giordani, P. J., Lepper, H. S., and Croghan, T. W. (2002). Patient adherence and medical treatment outcomes: a meta-analysis. *Med. Care* 40, 794–811. doi: 10.1097/00005650-200209000-00009

Doering, B. K., Rief, W., and Petrie, K. J. (2014). Lessons to be learned from placebo arms in psychopharmacology trials. *Handb. Exp. Pharmacol.* 225, 273–290. doi: 10.1007/978-3-662-44519-8_15

Ferguson, W. J., and Candib, L. M. (2002). Culture, language, and the doctor-patient relationship. *Fam. Med.* 34, 353–361.

Friesen, P., and Blease, C. (2018). Placebo effects and racial and ethnic health disparities: an unjust and underexplored connection. *J. Med. Ethics* 44, 774–781. doi: 10.1136/medethics-2018-104811

Fuentes, J., Armijo-Olivo, S., Funabashi, M., Miciak, M., Dick, B., Warren, S., et al. (2014). Enhanced therapeutic alliance modulates pain intensity and muscle pain sensitivity in patients with chronic low back pain: an experimental controlled study. *Phys. Ther.* 94, 477–489. doi: 10.2522/ptj.20130118

Geuter, S., Koban, L., and Wager, T. D. (2017). The cognitive neuroscience of placebo effects: concepts, predictions, and physiology. *Annu. Rev. Neurosci.* 40, 167–188. doi: 10.1146/annurev-neuro-072116-031132

Goodin, B. R., Pham, Q. T., Glover, T. L., Sotolongo, A., King, C. D., Sibille, K. T., et al. (2013). Perceived racial discrimination, but not mistrust of medical researchers, predicts the heat pain tolerance of African Americans with symptomatic knee osteoarthritis. *Health Psychol.* 32, 1117–1126. doi: 10.1037/a0031592

Gordon, H. S., Street, R. L. Jr., Sharf, B. F., Kelly, P. A., and Souchek, J. (2006). Racial differences in trust and lung cancer patients' perceptions of physician communication. *J. Clin. Oncol.* 24, 904–909. doi: 10.1200/JCO.2005.03.1955

Goyal, M. K., Kuppermann, N., Cleary, S. D., Teach, S. J., and Chamberlain, J. M. (2015). Racial disparities in pain Management of Children With Appendicitis in emergency departments. *JAMA Pediatr.* 169, 996–1002. doi: 10.1001/jamapediatrics.2015.1915

Green, A. R., Carney, D. R., Pallin, D. J., Ngo, L. H., Raymond, K. L., Iezzoni, L. I., et al. (2007). Implicit bias among physicians and its prediction of thrombolysis decisions for black and white patients. *J. Gen. Intern. Med.* 22, 1231–1238. doi: 10.1007/s11606-007-0258-5

Greenwood, B. N., Hardeman, R. R., Huang, L., and Sojourner, A. (2020). Physician-patient racial concordance and disparities in birthing mortality for newborns. *Proc. Natl. Acad. Sci. U. S. A.* 117, 21194–21200. doi: 10.1073/pnas.1913405117

Greville-Harris, M. (2013). *Does Feeling Understood Matter? The Effects of Validating and Invalidating Interactions*. Plymouth, United Kingdom: Exeter and Plymouth Peninsula Medical School.

Greville-Harris, M., and Dieppe, P. (2015). Bad is more powerful than good: the nocebo response in medical consultations. *Am. J. Med.* 128, 126–129. doi: 10.1016/j.amjmed.2014.08.031

Halbert, C. H., Armstrong, K., Gandy, O. H. Jr., and Shaker, L. (2006). Racial differences in trust in health care providers. *Arch. Intern. Med.* 166, 896–901. doi: 10.1001/archinte.166.8.896

Hall, M. A., Dugan, E., Zheng, B., and Mishra, A. K. (2001). Trust in physicians and medical institutions: what is it, can it be measured, and does it matter? *Milbank Q.* 79, 613–639. doi: 10.1111/1468-0009.00223

Hall, O. T., Jordan, A., Teater, J., Dixon-Shambley, K., McKiever, M. E., Baek, M., et al. (2021). "Experiences of racial discrimination in the medical setting and associations with medical mistrust and expectations of care among black patients seeking addiction treatment." *J. Subst. Abus. Treat.* 108551. doi: 10.1016/j.jsat.2021.108551 [Epub ahead of print]

Hamel, L., Lopes, L., Muñana, C., Artiga, S., and Brodie, M. (2020). Race, Health, and COVID-19: The Views and Experiences of Black Americans.

Hamel, L., Moulder, R., Harper, F., Penner, L., Albrecht, T., and Eggly, S. (2021). Examining the dynamic nature of nonverbal communication between black patients with cancer and their oncologists. *Cancer* 127, 1080–1090. doi: 10.1002/cncr.33352

Hammond, W. P. (2010). Psychosocial correlates of medical mistrust among African American men. *Am. J. Community Psychol.* 45, 87–106. doi: 10.1007/s10464-009-9280-6

Hirsh, A. T., Jensen, M. P., and Robinson, M. E. (2010). Evaluation of nurses' self-insight into their pain assessment and treatment decisions. *J. Pain* 11, 454–461. doi: 10.1016/j.jpain.2009.09.004

Hoffman, K. M., Trawalter, S., Axt, J. R., and Oliver, M. N. (2016). Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proc. Natl. Acad. Sci. U. S. A.* 113, 4296–4301. doi: 10.1073/pnas.1516047113

Howe, L. C., Goyer, J. P., and Crum, A. J. (2017). Harnessing the placebo effect: exploring the influence of physician characteristics on placebo response. *Health Psychol.* 36, 1074–1082. doi: 10.1037/hea0000499

Jensen, K. B., Kaptchuk, T. J., Kirsch, I., Raicek, J., Lindstrom, K. M., Berna, C., et al. (2012). Nonconscious activation of placebo and nocebo pain responses. *Proc. Natl. Acad. Sci. U. S. A.* 109, 15959–15964. doi: 10.1073/pnas.1202056109

Jensen, K. B., Petrovic, P., Kerr, C. E., Kirsch, I., Raicek, J., Cheetham, A., et al. (2014). Sharing pain and relief: neural correlates of physicians during treatment of patients. *Mol. Psychiatry* 19, 392–398. doi: 10.1038/mp.2012.195

Johansen, O., Brox, J., and Flaten, M. A. (2003). Placebo and nocebo responses, cortisol, and circulating beta-endorphin. *Psychosom. Med.* 65, 786–790. doi: 10.1097/01.PSY.0000082626.56217.CF

Johnson, R. L., Roter, D., Powe, N. R., and Cooper, L. A. (2004). Patient race/ethnicity and quality of patient-physician communication during medical visits. *Am. J. Public Health* 94, 2084–2090. doi: 10.2105/AJPH.94.12.2084

Kamen, C., Tejani, M. A., Chandwani, K., Janelsins, M., Peoples, A. R., Roscoe, J. A., et al. (2014). Anticipatory nausea and vomiting due to chemotherapy. *Eur. J. Pharmacol.* 722, 172–179. doi: 10.1016/j.ejphar.2013.09.071

Kaptchuk, T. J., Kelley, J. M., Conboy, L. A., Davis, R. B., Kerr, C. E., Jacobson, E. E., et al. (2008). Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. *BMJ* 336, 999–1003. doi: 10.1136/bmj.39524.439618.25

Kennedy, W. P. (1961). The nocebo reaction. *Med. World* 95, 203–205.

Khan, A., Leventhal, R. M., Khan, S. R., and Brown, W. A. (2002). Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. *J. Clin. Psychopharmacol.* 22, 40–45. doi: 10.1097/00004714-200202000-00007

Kirsch, I., and Sapirstein, G. (1998). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prev. Treat.* 1:2a. doi: 10.1037/1522-3736.1.1.12a

LaVeist, T. A., Isaac, L. A., and Williams, K. P. (2009). Mistrust of health care organizations is associated with underutilization of health services. *Health Serv. Res.* 44, 2093–2105. doi: 10.1111/j.1475-6773.2009.01017.x

Laveist, T. A., and Nuru-Jeter, A. (2002). Is doctor-patient race concordance associated with greater satisfaction with care? *J. Health Soc. Behav.* 43, 296–306. doi: 10.2307/3090205

LaVeist, T. A., Nuru-Jeter, A., and Jones, K. E. (2003). The association of doctor-patient race concordance with health services utilization. *J. Public Health Policy* 24, 312–323. doi: 10.2307/3343378

Letzen, J. E., Dildine, T. C., Mun, C. J., Colloca, L., Bruehl, S., and Campbell, C. M. (2021). Ethnic differences in experimental pain responses following a paired verbal suggestion with saline infusion: a quasiexperimental study. *Ann. Behav. Med.* 55, 55–64. doi: 10.1093/abm/kaaa032

Lim, J., Wang, L., Best, N., Liu, J., Yuan, J., Yong, F., et al. (2020). Reducing patient burden in clinical trials through the use of historical controls: appropriate selection of historical data to minimize risk of bias. *Ther. Innov. Regul. Sci.* 54, 850–860. doi: 10.1007/s43441-019-00014-4

Lobo, C. P., Pfalzgraf, A. R., Giannetti, V., and Kanyongo, G. (2014). Impact of invalidation and trust in physicians on health outcomes in fibromyalgia patients. *Prim. Care Companion CNS Disord.* 16:14m01664. doi: 10.4088/PCC.14m01664

Lockwood, K. G., Marsland, A. L., Matthews, K. A., and Gianaros, P. J. (2018). Perceived discrimination and cardiovascular health disparities: a multisystem review and health neuroscience perspective. *Ann. N. Y. Acad. Sci.* 1428, 170–207. doi: 10.1111/nyas.13939

Lopez-Sola, M., Geuter, S., Koban, L., Coan, J. A., and Wager, T. D. (2019). Brain mechanisms of social touch-induced analgesia in females. *Pain* 160, 2072–2085. doi: 10.1097/j.pain.0000000000001599

Losin, E. A. R., Anderson, S. R., and Wager, T. D. (2017). Feelings of clinician-patient similarity and trust influence pain: evidence from simulated clinical interactions. *J. Pain* 18, 787–799. doi: 10.1016/j.jpain.2017.02.428

Losin, E. A. R., Woo, C. W., Medina, N. A., Andrews-Hanna, J. R., Eisenbarth, H., and Wager, T. D. (2020). Neural and sociocultural mediators of ethnic differences in pain. *Nat. Hum. Behav.* 4, 517–530. doi: 10.1038/s41562-020-0819-8

Ma, A., Sanchez, A., and Ma, M. (2019). The impact of patient-provider race/ethnicity concordance on provider visits: updated evidence from the medical expenditure panel survey. *J. Racial Ethn. Health Disparities* 6, 1011–1020. doi: 10.1007/s40615-019-00602-y

McDowell, S. E., Coleman, J. J., and Ferner, R. E. (2006). Systematic review and meta-analysis of ethnic differences in risks of adverse reactions to drugs used in cardiovascular medicine. *BMJ* 332, 1177–1181. doi: 10.1136/bmj.38803.528113.55

Meghani, S. H., Brooks, J. M., Gipson-Jones, T., Waite, R., Whitfield-Harris, L., and Deatrick, J. A. (2009). Patient-provider race-concordance: does it matter in improving minority patients' health outcomes? *Ethn. Health* 14, 107–130. doi: 10.1080/13557850802227031

Musa, D., Schulz, R., Harris, R., Silverman, M., and Thomas, S. B. (2009). Trust in the health care system and the use of preventive health services by older black and white adults. *Am. J. Public Health* 99, 1293–1299. doi: 10.2105/AJPH.2007.123927

Necka, E. A., Amir, C., Dildine, T. C., and Atlas, L. Y. (2021). Expectations about pain and analgesic treatment are shaped by medical providers' facial appearances: evidence from five online clinical simulation experiments. *Soc. Sci. Med.* 281:114091. doi: 10.1016/j.socscimed.2021.114091

Nelson, A. (2002). Unequal treatment: confronting racial and ethnic disparities in health care. *J. Natl. Med. Assoc.* 94, 666–668. doi: 10.17226/12875

Ojikutu, B. O., and Stone, V. E. (2021). *HIV in US Communities of Color*. Switzerland: Springer.

Olshansky, B. (2007). Placebo and nocebo in cardiovascular health: implications for healthcare, research, and the doctor-patient relationship. *J. Am. Coll. Cardiol.* 49, 415–421. doi: 10.1016/j.jacc.2006.09.036

OMH (n.d.). "Heart Disease and African Americans." Available at: https://minorityhealth.hhs.gov/omh/browse.aspx?lvl=4&lvlid=19 (Accessed November 30, 2021).

Pascoe, E. A., and Smart Richman, L. (2009). Perceived discrimination and health: a meta-analytic review. *Psychol. Bull.* 135, 531–554. doi: 10.1037/a0016059

Reddan, M. C., Young, H., Falkner, J., Lopez-Sola, M., and Wager, T. D. (2020). Touch and social support influence interpersonal synchrony and pain. *Soc. Cogn. Affect. Neurosci.* 15, 1064–1075. doi: 10.1093/scan/nsaa048

Rief, W., Avorn, J., and Barsky, A. J. (2006). Medication-attributed adverse effects in placebo groups: implications for assessment of adverse effects. *Arch. Intern. Med.* 166, 155–160. doi: 10.1001/archinte.166.2.155

Rolfe, A., Cash-Gibson, L., Car, J., Sheikh, A., and McKinstry, B. (2014). Interventions for improving patients' trust in doctors and groups of doctors. *Cochrane Database Syst. Rev.* 2014:CD004134. doi: 10.1002/14651858.CD004134.pub3

Scharff, D. P., Mathews, K. J., Jackson, P., Hoffsuemmer, J., Martin, E., and Edwards, D. (2010). More than Tuskegee: understanding mistrust about research participation. *J. Health Care Poor Underserved* 21, 879–897. doi: 10.1353/hpu.0.0323

Schoenthaler, A., Allegrante, J. P., Chaplin, W., and Ogedegbe, G. (2012). The effect of patient-provider communication on medication adherence in hypertensive black patients: does race concordance matter? *Ann. Behav. Med.* 43, 372–382. doi: 10.1007/s12160-011-9342-5

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., and Zubieta, J. K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Arch. Gen. Psychiatry* 65, 220–231. doi: 10.1001/archgenpsychiatry.2007.34

Seible, D. M., Kundu, S., Azuara, A., Cherry, D. R., Arias, S., Nalawade, V. V., et al. (2021). The influence of patient-provider language concordance in cancer care: results of the Hispanic outcomes by language approach (HOLA) randomized trial. *Int. J. Radiat. Oncol. Biol. Phys.* 111, 856–864. doi: 10.1016/j.ijrobp.2021.05.122

Shen, M. J., Peterson, E. B., Costas-Muniz, R., Hernandez, M. H., Jewell, S. T., Matsoukas, K., et al. (2018). The effects of race and racial concordance on patient-physician communication: a systematic review of the literature. *J. Racial Ethn. Health Disparities* 5, 117–140. doi: 10.1007/s40615-017-0350-4

Silvestri, A., Galetta, P., Cerquetani, E., Marazzi, G., Patrizi, R., Fini, M., et al. (2003). Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo. *Eur. Heart J.* 24, 1928–1932. doi: 10.1016/j.ehj.2003.08.016

Staton, L. J., Panda, M., Chen, I., Genao, I., Kurz, J., Pasanen, M., et al. (2007). When race matters: disagreement in pain perception between patients and their physicians in primary care. *J. Natl. Med. Assoc.* 99, 532–538.

Straiton, M., Corbett, K., Hollander, A. C., and Hauge, L. J. (2019). Outpatient mental healthcare service use among women with migrant background in Norway: a national register study. *BMC Health Serv. Res.* 19:944. doi: 10.1186/s12913-019-4788-4

Street, R. L. Jr., Gordon, H., and Haidet, P. (2007). Physicians' communication and perceptions of patients: is it how they look, how they talk, or is it just the doctor? *Soc. Sci. Med.* 65, 586–598. doi: 10.1016/j.socscimed.2007.03.036

Tajeu, G. S., Cherrington, A. L., Andreae, L., Prince, C., Holt, C. L., and Halanych, J. H. (2015). "We'll get to you when we get to you": exploring potential contributions of health care staff behaviors to patient perceptions of discrimination and satisfaction. *Am. J. Public Health* 105, 2076–2082. doi: 10.2105/AJPH.2015.302721

Takeshita, J., Wang, S., Loren, A. W., Mitra, N., Shults, J., Shin, D. B., et al. (2020). Association of racial/ethnic and gender concordance between patients and physicians with patient experience ratings. *JAMA Netw. Open* 3:e2024583. doi: 10.1001/jamanetworkopen.2020.24583

Todorova, I. L., Falcon, L. M., Lincoln, A. K., and Price, L. L. (2010). Perceived discrimination, psychological distress and health. *Sociol. Health Illn.* 32, 843–861. doi: 10.1111/j.1467-9566.2010.01257.x

Torres, C., Ogbu-Nwobodo, L., Alsan, M., Stanford, F. C., Banerjee, A., Breza, E., et al. (2021). Effect of physician-delivered COVID-19 public health messages and messages acknowledging racial inequity on black and white adults' knowledge, beliefs, and practices related to COVID-19: a randomized clinical trial. *JAMA Netw. Open* 4:e2117115. doi: 10.1001/jamanetworkopen.2021.37148

Tracey, I. (2010). Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat. Med.* 16, 1277–1283. doi: 10.1038/nm.2229

van Laarhoven, A. I. M., Vogelaar, M. L., Wilder-Smith, O. H., van Riel, P., van de Kerkhof, P. C. M., Kraaimaat, F. W., et al. (2011). Induction of nocebo and placebo effects on itch and pain by verbal suggestions. *Pain* 152, 1486–1494. doi: 10.1016/j.pain.2011.01.043

van Ryn, M., and Burke, J. (2000). The effect of patient race and socio-economic status on physicians' perceptions of patients. *Soc. Sci. Med.* 50, 813–828. doi: 10.1016/S0277-9536(99)00338-X

van Ryn, M., Hardeman, R., Phelan, S. M., Burgess, D. J., Dovidio, J. F., Herrin, J., et al. (2015). Medical school experiences associated with change in implicit racial bias among 3547 students: a medical student CHANGES study report. *J. Gen. Intern. Med.* 30, 1748–1756. doi: 10.1007/s11606-015-3447-7

Victor, R. G., Lynch, K., Li, N., Blyler, C., Muhammad, E., Handler, J., et al. (2018). A cluster-randomized trial of blood-pressure reduction in black barbershops. *N. Engl. J. Med.* 378, 1291–1301. doi: 10.1056/NEJMoa1717250

Wager, T. D., and Atlas, L. Y. (2015). The neuroscience of placebo effects: connecting context, learning and health. *Nat. Rev. Neurosci.* 16, 403–418. doi: 10.1038/nrn3976

Wampold, B. E. (2015). How important are the common factors in psychotherapy? An update. *World Psychiatry* 14, 270–277. doi: 10.1002/wps.20238

Williams, D. R., and Mohammed, S. A. (2009). Discrimination and racial disparities in health: evidence and needed research. *J. Behav. Med.* 32, 20–47. doi: 10.1007/s10865-008-9185-0

Wolters, F., Peerdeman, K. J., and Evers, A. W. M. (2019). Placebo and nocebo effects across symptoms: from pain to fatigue, dyspnea, nausea, and itch. *Front. Psychol.* 10:470. doi: 10.3389/fpsyt.2019.00470

Wood, F. A., Howard, J. P., Finegold, J. A., Nowbar, A. N., Thompson, D. M., Arnold, A. D., et al. (2020). N-of-1 trial of a statin, placebo, or no treatment to assess side effects. *N. Engl. J. Med.* 383, 2182–2184. doi: 10.1056/NEJMc2031173

Zolnierek, K. B., and Dimatteo, M. R. (2009). Physician communication and patient adherence to treatment: a meta-analysis. *Med. Care* 47, 826–834. doi: 10.1097/MLR.0b013e31819a5acc

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Nocebo Effects of Clinical Communication and Placebo Effects of Positive Suggestions on Respiratory Muscle Strength

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Introduction: The effects of specific suggestions are usually studied by measuring parameters that are directly addressed by these suggestions. We recently proposed the use of a uniform, unrelated, and objective measure like maximal muscle strength that allows comparison of suggestions to avoid nocebo effects and thus to improve communication. Since reduced breathing strength might impair respiration and increase the risk of post-operative pulmonary complications, the aim of the present study was to evaluate the effects of the suggestions on respiratory muscle power. Both the identification and neutralization of negative suggestions in the clinical context and stimulating suggestions could improve breathing force, a predictor of physical fitness and convalescence.

Methods: In 50 healthy, adult volunteers, respiratory muscle strength was measured by maximal inspiratory and expiratory pressures, as well as by maximal inspiratory and expiratory flows. Baseline was compared to values after application of eleven suggestions, five out of clinical context, including memory of negative or positive past, risk information for informed consent, and a non-verbal suggestion. Six stimulating suggestions included self-affirmation, empowering words, a heroic mirror image, and an imagination.

Results: All suggestions showed an impact on respiratory muscle strength, indicating placebo and nocebo effects. No single parameter could represent the breathing force in its complexity, however, trends and different specific aspects of it were measured. The strongest reaction was observed with the recall of a previous negative situation resulting in a reduction in expiratory flow to 96.1% of baseline ($p = 0.041$). After risk information, a decrease was observed in three of the parameters, with the highest extend in expiratory pressure by 4.4%. This nocebo effect was neutralized by adding positive aspects to the risk information. Every intended strengthening suggestion resulted in statistically significant increases of at least one parameter, with changes of up to 10% (e.g., MEP 110.3%, $p = 0.001$), indicating placebo effects. Here, expiration was more affected

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than inspiration. Sex was the only influencing factor reaching statistical significance, with stronger reactions in women.

Conclusion: Respiratory muscle strength proved to be sensitive to suggestions with clinical context, as well as suggestions intended for stimulation. With this objective measurement, evaluation, and comparison of different suggestions is possible to help avoid nocebo effects. The demonstrated effect of supporting suggestions can be followed up and used in clinical practice.

Keywords: nocebo effect, placebo effect, suggestion, respiratory muscle strength, spirometry, flow, pressure

INTRODUCTION

The role of nocebo effects in medicine is increasingly recognized (Häuser et al., 2012; Colloca, 2017; Hansen and Zech, 2019). They can interfere with the well-being and health of the patients and can jeopardize the therapeutic efficacy. Nocebo effects and negative suggestions are often described as nonspecific. Nevertheless, they are usually tested in a very specific manner, namely according to the symptom addressed. For example, the word "pain" can induce or increase pain (Lang et al., 2005), the question about nausea can induce or aggravate nausea. Besides these specific consequences of negative communication, there are also more general effects, which are much more difficult to measure for their complexity (e.g., immunoreactions) or delayed effect (e.g., wound healing and recovery after an operation). We recently conducted two studies on the impact of suggestions from medical everyday life on maximal arm muscle strength, an objective measure from physiology research (Zech et al., 2019; Zech et al., 2020). This objective parameter allows the identification of the nature of a suggestion (positive or negative), the quantification of the effect, and their comparison, by applying a uniform outcome parameter for different suggestions. It enables the development, evaluation, and optimization of alternative formulations of the suggestion and thus ultimately communication improvement. In these studies, several non-verbal and verbal presentations, inter alia sentences that included the words pain and nausea, led to a significant reduction in maximal arm muscle strength interpreted as a general sign of a "weakening" of the patient. It is noteworthy that these effects on muscular performance were observed without specifically addressing muscle strength or physical activity and movement. However, any impairment in muscular performance has a high clinical impact. In times of fast-track surgery, patient unimpaired recovery is an interdisciplinary goal aimed at early and intensive mobilization, as well as physical and respiratory training. Muscular weakness must be prevented as it may cause complications such as stumbling and subsequent injuries. Additionally, impaired muscular strength could alter breathing and increase the risk of post-operative pulmonary complications such as atelectasis and pneumonia (Dronkers et al., 2008; Kulnik et al., 2014).

To clarify the validity of the latter apprehension of high clinical impact, we performed a study on effects of suggestions on breathing power, which will be reported here. Whereas dynamometry of arm abduction is a relatively clear measurement with defined and known muscles involved, breathing is a complex muscular function that includes movements of the diaphragm and thoracic muscles. Accordingly, several test parameters of pressure and flow, inspiration and expiration were evaluated. Some of the suggestions tested were identical to those analyzed for impact on maximal arm muscle strength. However, it is not only important to avoid nocebo effects and a weakening in patients by identifying the negative nature of a suggestion, by quantification of its effect, and by development of alternative, neutral formulations. In addition to greater awareness of negative influences and how to combat them, efforts can be made for a positive impact. Therefore, we also included and evaluated positive suggestions that could improve and increase breathing power and strengthen the patient. This approach could support communication for both prophylactic and therapeutic purposes. We hypotheses, that suggestion have impact on respiratory muscle strength.

MATERIALS AND METHODS

Design and Participants

After approval of the local ethics committee (EC University of Regensburg, 13-101-0030), an experimental, prospective, cross-over, within participants study was carried out with 50 healthy volunteers after informed consent. The age of the participants was limited to 18–65 years. Exclusion criteria were language barriers or relevant health restrictions, particularly pulmonary disease (Scoring > II in the physical status classification of the American Society of Anaesthesiologists). Participation was without financial compensation. Enrolment of participants, data collection and evaluation were carried out by a medical student under supervision as part of a doctorial theses. Validity and reliability of the breathing parameters were achieved by extensive training and supervision of the performing student by the cooperating pulmonology lab.

Measurement of Lung Function

Lung function can be tested and analyzed by various parameters. Spirometry that produces flow and volume values is used to diagnose and classify diseases such as asthma or chronic obstructive pulmonary disease (COPD), and to distinguish obstructive from restrictive lung problems. Measurement of respiratory muscle strength is used to assess risk and prevention of post-operative complications such as atelectasis or pneumonia.

The most important parameters of the respiratory muscles are given by maximal flows and pressures.

In this study, the strength of the respiratory muscles was evaluated with two different non-invasive technics: spirometry and the measurement of airway pressure, according to the recommendations of the European Respiratory Society and the American Thoracic Society (American Thoracic Society/European Respiratory Society, 2002). Peak inspiratory and peak expiratory flow (PIF/PEF) in L/s, relevant for the description of muscle strength, were obtained by spirometry. The EasyOne-line^{TM} spirometer (ndd Medizintechnik AG, Zürich, Switzerland) was used, measurements were recorded with Easyware software. This software gives immediate feedback about the quality of the breathing maneuver and initiates a repeat if needed. Furthermore, the two airway pressures "maximal inspiratory pressure" (MIP) representing the diaphragm, and "maximal expiratory pressure" (MEP) representing the abdominal, intercostal, and accessory musculature (Enright et al., 1994) were measured in cmH_2O. For these tests, the device PTS2000 Version 4.0 (Puritan Bennett, Pleasanton, CA, United States) and the software BreathLab PTS were used. An accuracy of 2.5% is reported for spirometry and of 1% for pressure measurements (Graham et al., 2019; Aymerich et al., 2021). The tests took place after information, demonstration, and practicing of the maneuver in a quiet, designated room at the university hospital. To guarantee high standardization, participants listened to recorded instructions for the prescribed breathing maneuver. The measurements of airway pressures were accompanied by "Fully exhale. Put the device in your mouth and now inhale to the maximum. Continue breathing normally. Take a deep breath. Now put the device in your mouth again and exhale to the maximum. Continue breathing normally." Spirometry was guided by "Take a deep breath. Put the device in your mouth and exhale to the maximum now. Keep going. And now inhale to the maximum."

Tested Suggestions and Application

The examiner gave verbal suggestions face to face, and visual suggestions were shown on a tablet. Five suggestions were taken from everyday clinical life during a hospital stay. Six further suggestions were tested, all of which had an expected positive influence on pulmonary muscle strength.

After the evaluation of a short medical history to exclude relevant pre-existing disease, the breathing maneuver was demonstrated, explained, and practiced with the test person. After hearing the prescribed and recorded instructions, the participants performed baseline values for spirometry and pulmonary pressure, each three times. Three baseline measurements were made at the beginning of the test and four others in pairs of two during the test to recognize learning effects or exhaustion. During the procedure, intended breaks were kept and additionally given, whenever the test person reported being out of breath, hyperventilation, or dizziness, as well as if baseline values deviated by more than 10%. The suggestions listed in **Table 1** were presented personally by the examiner, followed by recorded instruction. To help the participant keep the suggestion in mind, the examiner repeated a short version during the breathing maneuver. Suggestions were given in a randomized order, using the Research Randomizer Version 4.0 (Urbaniak and Plous, 2013). The only exception was the repetition of the own empowering word, and this suggestion was tested at last. To avoid influencing or accumulating effects, each suggestion was separated from the next one through simple arithmetic tasks. The whole test took about 60 min, within a tolerable framework.

Measurement of Suggestibility

To evaluate the dependency of results from differences in susceptibility, e.g., the ability and willingness to follow suggestions, each test person performed the Harvard Group Scale of Hypnotic Susceptibility (HGSHS) (Shor, 1962; Bongartz, 1985) in a short version in German with five items (HGSHS5:G) (Riegel et al., 2021). This is a self-assessment test, taking about 25 min. Following the common standard in suggestion or hypnosis studies the tested subjects are assigned to low, intermediate, and high suggestible, depending on the number of fulfilled items.

Sample Size and Statistical Analysis

This study was designed as an exploratory and hypothesis generating trial with several clinically relevant endpoints. Thus, no formal a-priori sample size calculation could be performed. Nevertheless, the sample size is based on two studies in similar settings (Zech et al., 2019; Zech et al., 2020) with $n = 50$ participants or patients, respectively. We expected comparable effects throughout the endpoints and thus chose the same number of participants. As there have been relevant interindividual differences regarding absolute values of maximum respiratory strength, absolute values were set in reference to the individual baseline value. With a normal distribution of the relative parameters after suggestions, the results were reported as mean and standard deviation (SD). Differences between baseline and suggestions were analyzed using the one sample *T*-test. To analyze possible influencing variables such as age, sex, or suggestibility participants were grouped into high (HS = HGSHS5:G 4-5) and low (LS = HGSHS5:G 0-1) suggestible, male and female, as well as younger (18–39 years) and older (40–65 years). The average of all negative suggestions (negative changes in force) and all positive suggestions (positive changes in force) for the four measured parameters was compared between the groups using the Mann-Whitney *U* test, as data were not normally distributed. For better visualization, values of expiration and inspiration were grouped and differences to baseline were analysed using the one sample *T*-test. A $p < 0.05$ was considered statistically significant for all tests. Because of the exploratory character of the study, no adjustments for multiple hypotheses testing were made. All analyses were performed with IBM SPSS Statistics, Version 26.

RESULTS

Baseline Characteristics

A total of 50 healthy volunteers were recruited for the study. All of them could be included in the data analyses. In a survey, 29 (58%) were women, 21 (42%) were men. The mean age

TABLE 1 | Wording of verbal suggestions and description of non-verbal suggestions taken from clinical practice and to improve breathing power.

Situation in the past	Version A	"Remember a situation, where something went really wrong. Everyone was disappointed in you, including yourself. This was terrible. You were really ashamed."
	Version B	"Remember a situation, when you were really successful and entirely satisfied with yourself. Everything went so well—totally perfect."
Risk information for informed consent	Version A	"If you wish, we can place a pain catheter, with the risk of infection, allergic reaction, and damage to blood vessels or nerves."
	Version B	"We have the option of a catheter to prevent discomfort. Even though there is a risk of infection, allergic reaction, or damage to blood vessels or nerves you will have to take fewer pills, are more mobile, feel and recover better, and maybe can go home sooner."
Transportation to the OR		"Imagine you are a patient in hospital. You are lying in bed, being brought to the operation room. That is what you see."
Self-affirmation (with circular massage of a point under the clavicula by two fingers)		"It has been found that performance and feelings have a lot to do with motion and body sensation. Please also do this movement. And now repeat the following sentence: Even if sometimes I am so stressed and tired that I run out of breath, I like myself and accept myself as I am."
Empowering word	Given: fireball	"Perhaps there is a fitting word for all your energy and inner strength, the epitome of strength. Let me tell you a word like that: fireball!"
	Chosen by the participant	"Maybe you can find a much better word yourself. What would be such an empowering word for you? When you find something, just nod. Now say that word for yourself. You can also speak it out loud."
	Repetition of the own empowering word	"You had previously found your own strong empowering word. Recall now and feel how it works in you. Think of your empowering word."
Strengthening of self-perception	Picture of a cat, looking in a mirror and seeing a lion	"Please look at this picture. Now close your eyes and imagine that you look in a mirror. What would it be, what you see. Which animal, which hero would really give you strength? If you see your reflection in front of you, please nod briefly."
Inflating a balloon		"Imagine, you have a balloon, you can inflate it. With every breath it gets bigger and bigger, until it is big enough for you to fly away with it. Take deep breaths and inflate firmly!"

Four different parameters are measured to assess respiratory muscle strength after giving the suggestions face to face. To facilitate internalization of the suggestion, a short version was repeated during the breathing maneuvers.

was 29.1 ± 12.7 years, with a range of 18–57 years (median 23.5 years). In a survey, 40 participants were categorized as "younger" and 10 as "older." Due to the individual physical condition of the volunteers, the baseline values had a wide range, as presented in **Table 2**. These values lie within the reference normal ranges, but rather at the lower limit (American Thoracic Society/European Respiratory Society, 2002; Gao et al., 2018). The baseline values were reproducible with an intra-individual variance of 5–10%, according to other publications aiming to reach 10% reproducibility (Enright et al., 1994). Additional spirometry results (i.e., FEV1, FEV) were collected and analyzed (data not shown), demonstrating unimpaired lung function for all participants. Suggestibility (HGSHS5:G) was not normally distributed, with 25 patients (50%) scoring low suggestible and seven patients (14%) high suggestible.

Changes in Respiratory Muscle Strength After Suggestion

Both suggestions with clinical context as well as suggestions intended for stimulation showed an impact on respiratory muscle strength. No single one of the measured parameters can represent muscular breathing force in its complexity; however, they can reveal trends and different specific aspects of it. The values of the breathing force after suggestions compared to baseline are given in **Figures 1**, **2**, with pressure and flow parameters considered separately. Additionally, in **Tables 3**, **4** suggestions of clinical context and of stimulating intention are given separately.

Effects of Suggestions With Clinical Context

Three suggestions out of everyday clinic life were tested. Two of them were presented in a presumed negative (A) and an alternative presumably neutral or positive version (B), the third was a presumably negative non-verbal suggestion. Almost every suggestion changed the pressure and flow parameters in the expected way, at least as a trend. The suggestion of a negative past (as an example of taking a patient's medical history) decreased the values, whereas the positive past led to an increase over baseline.

TABLE 2 | Baseline values of respiratory muscle strength parameters stratified according to sex.

Parameter	Mean ± SD for male test persons (min–max) (*N* = 21)	Mean ± SD for female test persons (min–max) (*N* = 29)
MIP (cmH2O)	−77.0 ± 29.2 (−125.9–−29.1)	−50.8 ± 3.9 (−92.7–−22.3)
MEP (cmH2O)	89.1 ± 34.8 (30.3–158.4)	56.7 ± 16.8 (30.0–96.7)
PIF (L/s)	7.8 ± 2.4 (3.6–13.0)	4.4 ± 1.3 (2.4–7.0)
PEF (L/s)	9.0 ± 1.7 (5.7–12.5)	5.9 ± 1.3 (3.3–8.2)

MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PIF, peak inspiratory flow; PEF, peak expiratory flow; min, minimum; max, maximum.

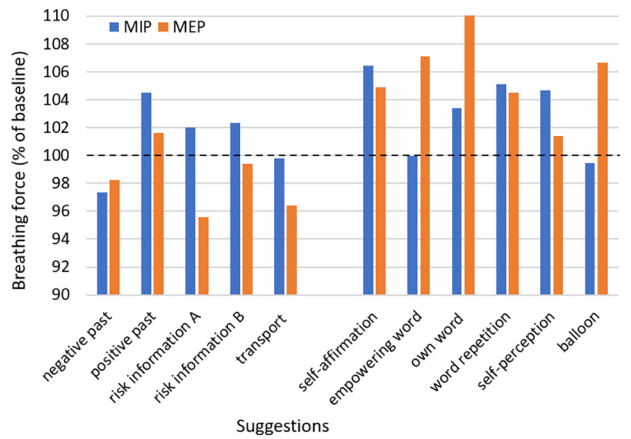

FIGURE 1 | Mean of maximal inspiratory and maximal expiratory pressure after suggestions with clinical context or with a presumed strengthening effect relative to baseline. MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure.

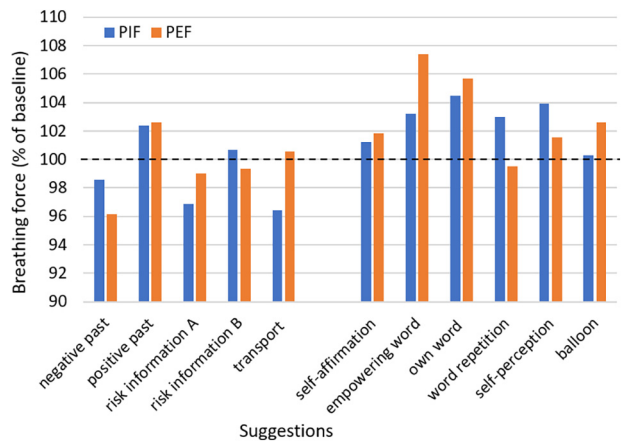

FIGURE 2 | Mean of peak inspiratory and peak expiratory flow after suggestions with clinical context or with a presumed strengthening effect relative to baseline. PIF, peak inspiratory flow; PEF, peak expiratory flow.

The strongest reaction was observed in PEF when recalling a negative situation, with a significant reduction of 3.9%. After risk information, a decrease was seen in all parameters except MIP, with the highest extend in MEP by 4.4%. On the contrary, no change from baseline was observed when positive aspects were added to the risk information (version B), and all parameters increased from version A to version B. The non-verbal suggestion of a transport in a strict supine position impaired MEP and PIF, but not MIP and PEF.

Effects of Suggestions With Intention of Strengthening

Six suggestions were tested with the intention of increasing respiratory muscle strength (**Table 4**). Every suggestion resulted in a statistically significant change of at least one parameter. Expiration was affected more than inspiration, particularly noticeable for empowering words and in the case of inflating a balloon, where MIP was not affected at all. A self-affirmation resulted in a significant increase in MIP (by 6.4%) and in MEP (by 4.9%) over baseline. The effects of an empowering word were tested in three versions. The suggestion of a fixed or self-selected empowering word resulted in statistically significant higher values of the expiratory measures MEP (increase by 7.1% or 10.3%, respectively) and PEF (7.4% or 5.7%, respectively). Higher values of all parameters except PEF were achieved with the self-selected word, whereas repetition of the own word showed lower results. Participants asked to imagine a supporting or heroic mirror image of their own had an increase in parameters, predominantly in the inspiratory measures, in MIP by 4.7% with statistical significance. The imagination to inflate and fly with a balloon resulted in an improvement only in the expiratory parameters. MEP increased by 6.7% and PEF by 2.6%, both with statistical significance.

Contributing Factors

To evaluate factors contributing to the changes induced by suggestions, the averages of all negative and of all positive suggestions were compared between high and low suggestible subjects, men and women, as well as older and younger participants (**Table 5**). Only sex showed an impact of statistical significance, with stronger reactions of female participants to both positive and negative suggestions. A trend was observed in the age groups, with more negative reactions of the elderly participants. Additional regression analyses between suggestion effects and suggestibility score confirmed a lack of correlation ($R^2 < 0.01$).

DISCUSSION

As a main finding, verbal and non-verbal suggestions impact the clinically relevant outcome parameter breathing force. Negative suggestions, common in everyday clinical practice, have negative effects, resulting in a weakening of respiratory muscle strength. That can be avoided by alternative, neutral formulations. The application of positive suggestions improved parameters of breathing force, and therefore should be implemented in medical treatment.

Suggestions With Clinical Context

The tested suggestion of a negative past (Situation A) is of high clinical relevance. Whenever doctors explore a medical history, they push the patient back to negative memories. This is unavoidable, but the doctor should be aware of the concomitant effects. The results of this study show that the consequence is a significant weakening of the breathing force. This confirms measurements of maximal arm muscle strength in volunteers (Zech et al., 2019) and patients (Zech et al., 2020), where the same suggestion led to a significant weakening by 10.6 and 12.9%, respectively. The reduction in muscular breathing force in this study (average change in the four parameters) was considerably lower, namely 2.5%. The clearest and statistically significant effect

TABLE 3 | Effects of suggestions with clinical context on respiratory muscle strength parameters.

Suggestions	MIP		MEP		PIF		PEF	
	Mean ± SD	*p*	Mean ± SD	*p*	Mean ± SD	*p*	Mean ± SD	*p**
Situation in the past								
Negative past	97.4 ± 16.3	ns	98.3 ± 16.5	ns	98.6 ± 8.0	ns	96.1 ± 13.0	**0.041**
Positive past	104.5 ± 18.2	ns	101.6 ± 13.9	ns	102.4 ± 14.8	ns	102.6 ± 10.5	ns
Risk information for informed consent								
Version A	102.0 ± 15.6	ns	95.6 ± 17.8	ns	96.9 ± 16.8	ns	99.0 ± 11.8	ns
Version B	102.3 ± 15.9	ns	99.4 ± 17.9	ns	100.6 ± 19.1	ns	99.4 ± 7.9	ns
Transport in strictly supine position	99.8 ± 13.4	ns	96.4 ± 18.4	ns	96.4 ± 14.9	ns	100.6 ± 10.0	ns

After the determination of the baseline, suggestions were presented followed by a new measurement. Mean and SD of relative values compared to baseline (in %) after suggestions are given.
**According to one sample T-test, results without significance are given as ns. MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PIF, peak inspiratory flow; PEF, peak expiratory flow. Significant p-values are indicated in bold.*

TABLE 4 | Effects of intentionally strengthening suggestions on parameters of respiratory muscle strength.

Suggestions	MIP		MEP		PIF		PEF	
	Mean ± SD	*p*	Mean ± SD	*p*	Mean ± SD	*p*	Mean ± SD	*p**
Self-affirmation	106.4 ± 20.1	**0.030**	104.9 ± 15.6	**0.035**	101.2 ± 16.3	ns	101.8 ± 11.4	ns
Empowering word								
Version A: "fireball"	100.0 ± 15.6	ns	107.1 ± 19.6	**0.013**	103.2 ± 16.9	ns	107.4 ± 9.6	**<0.001**
Version B: own power-word	103.4 ± 19.7	ns	110.3 ± 21.4	**0.001**	104.5 ± 16.9	ns	105.7 ± 10.6	**<0.001**
Version C: repetition of B	105.1 ± 20.0	ns	104.5 ± 18.9	ns	103.0 ± 13.9	ns	99.5 ± 9.9	ns
Bracing mirror image	104.7 ± 14.8	**0.029**	101.4 ± 14.6	ns	103.9 ± 15.4	ns	101.6 ± 9.3	ns
Inflating a balloon	99.4 ± 21.7	ns	106.7 ± 18.6	**0.014**	100.3 ± 14.1	ns	102.6 ± 8.8	**0.040**

After the determination of the baseline, suggestions were presented followed by a new measurement. Mean and SD of relative values compared to baseline (in %) after suggestion are given.
**According to one sample T-test, results without significance are given as ns. MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PIF, peak inspiratory flow; PEF, peak expiratory flow. Significant p-values are indicated in bold.*

was observed in the reduction by 3.9% in PEF. However, also in the other parameters, there was a marked trend toward reduction. In addition, other parameters of the spirometry, namely FVC, FEV1, and MEF50, showed significant decreases by 4–5% with this suggestion (data not shown). On the contrary, talking about a positive past resulted in an increase in breathing force, by 4.5% in MIP with a significant difference to version A. These results (average change in the four parameters of 2.8%) are comparable to the increase in maximal arm muscle strength by 3.3% seen in patients (Zech et al., 2020). The extent of the strengthening effect of this suggestion must not be considered small since it is given in the medical context, which itself is rather negative. In addition, a ceiling effect can be expected, indicated by a left-sloping in the distribution of results after version "positive past," where a further increase of maximal performance is hardly achievable. Memory of a positive past provides a solution for the weakening effect of anamnesis and a negative past. At the end of the interview about symptoms and medical history, the doctor could help the patient get out of the induced muscular impairment by asking about favorite sports before the illness or about plans for after treatment and rehabilitation (positive future).

A main source of nocebo effects is the disclosure of risk for informed consent (Miller and Colloca, 2011; Wells and Kaptchuk, 2012; Evers et al., 2018). The risk information tested for a pain catheter resulted in a slightly negative effect, highest by 4.4% in MEP. Although more prominent in the studies of arm muscle strength, nevertheless, the alternative formulation of the suggestion avoided the impairment and was neutral. Thus, the study confirms the neutralizing effect of adding a positive suggestion and expectation to the negative of risk information, for example, by addressing the benefits of the treatment offered. Other

TABLE 5 | Comparison of the negative and positive average suggestion effects between groups of suggestibility, sex, and age.

Contributing factor	Average of suggestion effects	*p**
Suggestibility (group LS vs. HS)	Positive	0.328
	Negative	0.293
Sex (male vs. female)	Positive	**<0.001**
	Negative	**0.013**
Age (group <40 vs. ≥40 years)	Positive	0.417
	Negative	0.110

**According to Mann-Whitney U test for unpaired samples. Significant p-values are indicated in bold.*

options for a positive counterweight are attempts to avoid the risks mentioned by prophylactic measures or close monitoring allowing early detection of developing adverse effects and their immediate therapy, and not least a possible own contribution of the patient to the healing process, such as careful attention or strengthening resilience (Hansen and Zech, 2019). Non-verbal suggestion during a transport in strict supine position showing only lights and ventilation ducts to patients, led to a marked decrease in PIF and MEP (by 3.6%), and no effect in PEF and MIP. In contrast to the results on arm muscle strength, the changes in breathing force observed here did not reach statistical significance. The relation between arm muscle strength and respiratory muscle strength is still unclear. That additionally raised the question, if a parameter like breathing which is so essential for life, is also sensible to suggestions. Nevertheless, the handgrip, which is also a marker for general strength, has been identified as a predictor for respiratory muscle strength (Enright et al., 1994).

In general, the study shows, as feared, nocebo effects of common medical situations also on respiration. However, together with previous studies on the same and other suggestions from everyday clinical practice, it also demonstrates that modification of the suggestions can neutralize these negative effects, and thereby communication can be improved evidence based. Because risk information given to obtain informed consent is recognized as a major source of nocebo effects, improvements are demanded (Miller and Colloca, 2011; Wells and Kaptchuk, 2012), and several proposals have been made (Evers et al., 2018; Howick, 2021). However, they have been hardly specified, tested, and validated. Some, like "framing," have been evaluated but found to have limited efficacy (Barnes et al., 2019). The neutralization of the nocebo effect by adding positive aspects, namely the benefit of the treatment, in direct connection, as demonstrated here and in previous studies on arm muscle strength, is an example of scientific and objective proof for such an attempt.

Stimulating Suggestions

With indications of nocebo effects, their avoidance or neutralization is not the only option and goal. There is also the option of induction of positive effects. Specifically, in this case of observing impairments of breathing force by suggestions taken from clinical context, it is about how to improve breathing. Again, this was not aimed at by suggestions targeting breathing or muscle force, or by breathing exercises, but by suggestions dealing with self-affirmation and self-strengthening, i.e., supporting healing and health in general. The question was therefore rather whether interventions directed to improve the medical situation and well-being of patients also have effects on breathing force. One of the positive suggestions tested was taken from Process- and Embodiment-focused Psychology (PEP) according to Michael Bohne (Wittfoth et al., 2020). It combines a movement of the hand and body sensation with words of self-affirmation. This intervention resulted in a marked increase in breathing force (on average by 3.8%), statistically significant in the pressure parameters MIP and MEP. Therefore, the subjective strengthening of the patients observed with this psychotherapeutic intervention was confirmed by objective measurements and parameters. This can be taken as a further example of how psychotherapeutic approaches usually traced by subjective assessments and scores can be quantified and objectified by physiological test systems (Hansen and Zech, 2019). Another intervention tested concerned the use of an empowering word. The presentation of the offered word "fireball" resulted in an increase in breathing force (on average by 4.4%), significant for the expiratory parameters MEP and PEF. The offer of an own empowering word increased the positive effect (to an average increase of 6.0%). The repetition of the chosen own word showed a reduced efficacy of this stimulating suggestion (to 3.0% on average), with a further increase only in MIP. Interestingly, a single word proved to be effective in strengthening the breath. The idea of looking into a mirror and seeing a power animal or a hero as the reflection increased breathing force, significant for MIP with an increase by 4.7%. Only one tested suggestion actually had a connection to breathing: the idea of inflating a balloon together with the metaphor of flying away with it. This intervention resulted in significant increases in the expiratory parameters PEF and MEP, with no effects on PIF and MIP. It can be taken as evidence that inspiration and expiration can be influenced separately.

Comparison With the Literature

In a recent review on the effects of placebo and nocebo, including on physiology, the authors state that "lung function is rarely affected" (Wolters et al., 2019). All these trials have studied the effects of suggestions on dyspnoea in asthmatic patients and in some found some effects on self-reported symptoms, but no effect on measures of lung function beside bronchodilatation or bronchoconstriction (Isenberg et al., 1992). The parameters used mainly in asthmatic patients and these studies are FVC and FEV1 from spirometry and not parameters of muscular respiration performance. Others have studied the effect of suggestions in non-asthmatic healthy subjects, again with regard to bronchodilatation and bronchoconstriction and measuring respiratory resistance, not muscular components of breathing (Wigal et al., 1988). Performance of respiratory muscles was measured in a study in which pre-operative inspiratory muscle training was used in surgical patients to reduce post-operative pulmonary complications (Dronkers et al., 2008). Extensive training led to an increase in MIP by 10% (without statistical significance), while in our study the effects of verbal suggestions were immediately seen. The effect of training diminished within 6 days, while in the present study the repetition of an empowering word lost its effectiveness. Similarly, Kim and Sapienza (2005) consider MIP and MEP most appropriate to monitor training of elderly in expiratory muscle strength to improve breathing and cough to prevent atelectasis and aspiration, and call for respective studies. In a review, 24 studies were reported using expiratory muscle strength training (EMST) to increase MEP and airway protection, and to avoid post-operative pulmonary complications (Laciuga et al., 2014). However, in all these training programs and studies, verbal suggestions are not included or mentioned. All reports in the literature on suggestion, placebo and nocebo effects concerning respiration dealt with ventilation

rate, bronchoconstriction, or bronchodilatation, and did not include measurements of breathing force (Wigal et al., 1988; Barber, 1996; Wolters et al., 2019). Therefore, it seems that our study is the first report of suggestion effects on the function of the breathing musculature and strength.

Rating of Effects and Differentiation of Parameters

Most parameters of pulmonary function tests are directed at identifying restriction (impairment of lung volume) or resistance (impairment of airway by bronchoconstriction). Muscular functions in breathing can be monitored by maximal inspiratory and expiratory flows, representing the strength of abdominal and intercostal muscles, and by the respective pressures, representing the strength of the diaphragm (Chen and Kuo, 1985; Enright et al., 1994). Many studies provide evidence that respiratory muscle weakness is associated with adverse clinical outcomes, that MIP and MEP are the most appropriate parameters, and that specific training aimed at strengthening can improve outcome (Schellekens et al., 2016). This study provides evidence that verbal suggestions taken from a clinical context or aimed at supporting have an impact on the muscular components of breathing. The observed effects on breathing force were rather small and to varying extent of statistical significance, probably due to the limited number of persons tested. However, they showed a consistent trend, allowing for an evaluation and rating of the direction in which the suggestions affected persons. Even with this limitation, it should be kept in mind that the suggestions were investigated and quantified and compared using objective measures in contrast to common subjective evaluations. The weakening effect of suggestions from clinical everyday life on breathing force was less strong than on maximal arm muscle strength, which can be taken as evidence that impaired breathing as a vital function is better protected against external influences. The nature of the effects remains unclear. Some may be explained by induction of an expectation, and thus as a nocebo effect (e.g., risk information A) or a placebo effect (e.g., self-perception as a hero). Reactions to memory of a negative or positive past can be taken as a conditioning effect. Other suggestions could gain their effectiveness in other ways (Hansen and Zech, 2019). The analysis of contributing factors only showed an effect of sex, with a stronger reaction of women to both positive and negative suggestions. A similar correlation was reported when the suggestion effects were tested by maximal arm muscle strength (Zech et al., 2020). The lack of significance of suggestibility scores is not surprising and was also reported in studies of placebo/nocebo effects on the pulmonary airway, of suggestion effects on maximal arm muscle strength, and in several clinical situations (Isenberg et al., 1992; Montgomery et al., 2011; Zech et al., 2020).

The effects of encounters, events, and suggestions on respiration can be very different: surprises can stop our breathing, in great moments we take a deep breath, a passed danger makes us exhale with a "puh." Consequently, it is not surprising that we observed different reactions in the various parameters of breathing force compared to the suggestions tested (**Figure 3**). The expiration parameters were more affected than the inspiration by memory of a negative past and the risk information for informed consent (reduction) or by an empowering word (increase). Self-strengthening by a hero mirror image had more effect on inspiration, the idea of blowing up a balloon and flying away more effect on expiration, which is expectable. Other parameters of spirometry, such as forced vital capacity (FVC) or forced one-second-capacity (FEV1) were

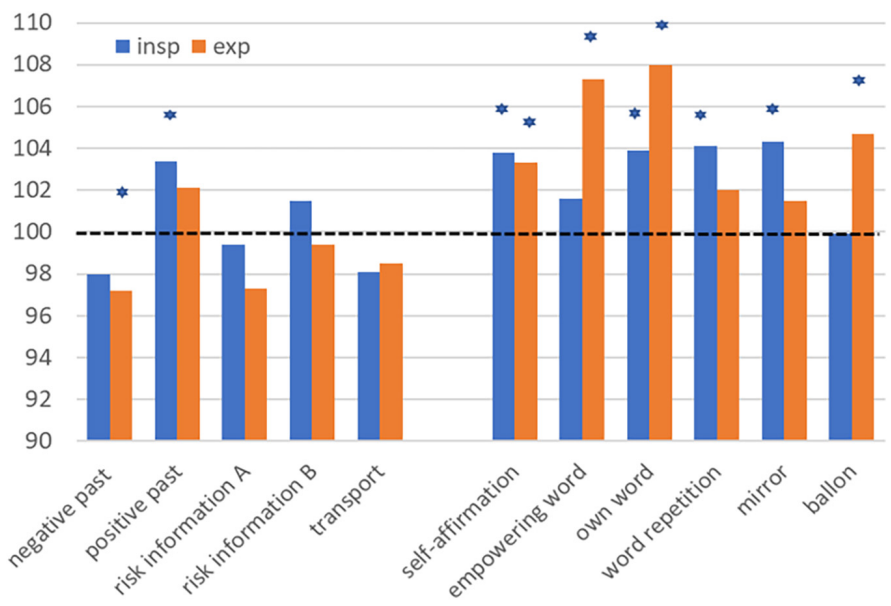

FIGURE 3 | Impact of suggestions on the inspiratory (PIF, MIP) and expiratory (PEF, MEP) parameters of breathing force. MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PIF, peak inspiratory flow; PEF, peak expiratory flow. *$p < 0.05$ according to one sample T-test.

hardly affected, especially not stimulated (data not shown). Only memory of a negative past resulted in marked and significant decreases in the latter two parameters, as an indication of a nocebo effect.

One for All

The use of one parameter to measure, objectify, and quantify different placebo- and nocebo-effects is a unique new attempt (Hansen and Zech, 2019). Usually, the measurement is directed specifically toward the given suggestion and induced expectation. Risk information, for instance, about nausea, is followed by looking at the incidence and severity of nausea afterwards. This specificity prevents a comparison with the nocebo effect of providing risk information, i.e., on pain. What can be compared are the incidences of nausea on one side and pain on the other side. However, these are artificial categories. Nausea or pain must reach a certain level to be recognized and classified as "nausea" or "pain," resulting in a certain number of patients with these symptoms. Is it not much more likely that in reality suggestions cause expectations and nocebo effects in all patients, though to varying degrees? This is what can be measured using an unrelated parameter like arm muscle strength or like breathing force in the present study: an uncategorized continuous range of effect. The 11 suggestions tested, except one, were not related in the sense of not being directly aimed at breathing.

In addition, the test parameters were objective measures in contrast to subjective parameters such as nausea or pain. This is even more important in the clinical context with the goal of improving communication. With a uniform parameter, the formulation and testing of alternative suggestions are supported, resulting in improvements and optimization of doctor-patient communication. Finally, using an unrelated outcome parameter turns the focus to a wider range of effects. When a suggestion induces an unspecific effect on muscle strength or breathing power, then it might be a surrogate for more general effects such as healing, immune surveillance, or resilience.

Limitations

Studies on breathing and its muscular component breathing force are in general limited by its complexity and the lack of a unified and simple parameter. In this exploratory experimental study, only 50 healthy test persons were included. It is conceivable, that results in patients or participants with respiratory disease would have been clearer, as we have already seen testing the impact of suggestions on arm muscle strength (Zech et al., 2019; Zech et al., 2020). The limited number can explain that in spite of a rather uniform trend the results reached statistical significance only in some and varying parameters of breathing force. Furthermore, these respiration parameters show a high individual variation, which works against precision. Spirometry and measurement of respiration pressures are rather elaborate and exhausting tests, which is why the test session in this study did not exceed 1 h. For that reason, the number of items to be tested in one session is limited, making it difficult to directly compare various formulations, which would be the great advantage of using a uniform target parameter. The duration of the induced effects was not determined. Therefore, the usefulness, for example, of stimulating suggestions to support post-operative respiration remains unclear. However, the diagnostic value to identify and quantify the effects of placebo and nocebo is independent of their duration, and, in contrast, a long-lasting effect would make it impossible to test and compare several suggestions in one test session.

Conclusion

The evaluation of placebo and nocebo effects is often limited because the measurement parameter is chosen according to the specific suggestion (e.g., pain is measured following a procedure suggested to be painful), and other effects are not monitored, or subjective measures are used like pain score, feeling of nausea, or itch. Besides, often graduated parameters are used that categorize the effect (e.g., the number of patients with a certain symptom is evaluated in the verum and the placebo group), and continuous effects, i.e., smaller effects in the other patients are ignored.

Using physiological parameters such as maximal arm muscle strength or in this study spirometry and breathing pressures allows objective measurement of a continuous variable in all tested persons, evaluation and comparison of different suggestions, and extending the view from specific to more general effects. The most important finding is, that the breathing force is a clinically relevant parameter which can be influenced in both directions with suggestions. There is the need to avoid or neutralize impairments and indications to support and enhance this function. This study can sensitize anyone working in medical fields, that the way we communicate has impact on the patient and might influence the outcome. Accordingly, positive suggestions should be used, and negative ones avoided. Further research should study the impact of suggestions on other physiological parameter and evaluate our findings in patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by EC University of Regensburg. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NZ: study design, application for ethic committee approval, literature search, participant recruitment, data collection and analysis, and preparation of the manuscript. LS: participant recruitment, data collection and analysis, and correction of the manuscript. MS: study design and application for ethic committee approval. MP: literature search and preparation

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SUPPLEMENTARY MATERIAL

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REFERENCES

American Thoracic Society/European Respiratory Society (2002). ATS/ERS statement on respiratory muscle testing. *Am. J. Respir. Crit. Care. Med.* 166, 518–624. doi: 10.1164/rccm.166.4.518

Aymerich, A., Rodríguez-Lázaro, M., Solana, G., Farré, R., and Otero, J. (2021). Low-cost open-source device to measure maximal inspiratory and expiratory pressures. *Front. Physiol.* 12:719372. doi: 10.3389/fphys.2021.719372

Barber, J. (1996). *Hypnosis and Suggestion in the Treatment of Pain – A Clinical Guide*. New York, NY: WW Norton & Company.

Barnes, K., Faasse, K., Geers, A. L., Helfer, S. G., Sharpe, L., Colloca, L., et al. (2019). Can positive framing reduce nocebo side effects? current evidence and recommendation for future research. *Front. Pharmacol.* 10:167. doi: 10.3389/fphar.2019.00167

Bongartz, W. (1985). German norms for the harvard group scale of hypnotic susceptibility, form a. *Int. J. Clin. Exp. Hypn.* 33, 131–139. doi: 10.1080/00207148508406643

Chen, H. I., and Kuo, C. S. (1985). Relationship between respiratory muscle function and age, sex, and other factors. *J. Appl. Physiol.* 66, 943–948. doi: 10.1152/jappl.1989.66.2.943

Colloca, L. (2017). Tell me the truth and I will not be harmed: informed consents and nocebo effects. *Am. J. Bioeth.* 17, 46–48. doi: 10.1080/15265161.2017.1314057

Dronkers, J., Veldman, A., Hoberg, E., and van der Waal, C. (2008). Prevention of pulmonary complications after upper abdominal surgery by preoperative intensive inspiratory muscle training: a randomized controlled pilot study. *Clin. Rehabil.* 22, 134–142. doi: 10.1177/0269215507081574

Enright, P. L., Kronmal, R. A., Manolio, T. A., Schenker, M. B., and Hyatt, R. E. (1994). Respiratory muscle strength in the elderly: correlates and reference values. *Am. J. Respir. Crit. Care Med.* 149, 430–438. doi: 10.1164/ajrccm.149.2.8306041

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., et al. (2018). Implications of placebo and nocebo effects for clinical practice: expert consensus. *Psychother. Psychosom.* 87, 204–210. doi: 10.1159/000490354

Gao, C., Zhang, X., Wang, D., Wang, Z., Li, J., and Li, Z. (2018). Reference values for lung function screening in 10- to 81-year-old, healthy, never-smoking residents of Southeast China. *Medicine* 97:e11904. doi: 10.1097/MD.0000000000011904

Graham, B. L., Steenbruggen, I., Miller, M. R., Barjaktarevic, I. Z., Cooper, B. G., Hall, G. L., et al. (2019). Standardization of spirometry 2019 update. an official American thoracic society and european respiratory society technical statement. *Am. J. Respir. Crit. Care Med.* 200, e70–e88. doi: 10.1164/rccm.201908-1590ST

Hansen, E., and Zech, N. (2019). Nocebo effects and negative suggestions in daily clinical practice – Forms, impact and approaches to avoid them. *Front. Pharmacol.* 10:77. doi: 10.3389/fphar.2019.00077

Häuser, W., Hansen, E., and Enck, P. (2012). Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch. Arztebl. Int.* 109, 459–465. doi: 10.3238/arztebl.2012.0459

Howick, J. (2021). Unethical informed consent caused by overlooking poorly measured nocebo effects. *J. Med. Ethics* 47, 590–594. doi: 10.1136/medethics-2019-105903

Isenberg, S. A., Lehrer, P. M., and Hochron, S. (1992). The effects of suggestion on airways of asthmatic subjects breathing room air as a suggested bronchoconstrictor and bronchodilator. *J. Psychosom. Res.* 36, 769–776. doi: 10.1016/0022-3999(92)90135-o

Kim, J., and Sapienza, C. M. (2005). Implications of expiratory muscle strength training for rehabilitation of the elderly: tutorial. *J. Rehabil. Res. Dev.* 42, 211–224. doi: 10.1682/jrrd.2004.07.0077

Kulnik, S. T., Rafferty, G. F., Birring, S. S., Moxham, J., and Kalra, L. (2014). A pilot study of respiratory muscle training to improve cough effectiveness and reduce the incidence of pneumonia in acute stroke: study protocol for a randomized controlled trial. *Trials* 15:123. doi: 10.1186/1745-6215-15-123

Laciuga, H., Rosenbek, J. C., Davenport, P. W., and Sapienza, C. M. (2014). Functional outcomes associated with expiratory muscle strength training: narrative review. *J. Rehabil. Res. Dev.* 51, 535–546. doi: 10.1682/JRRD.2013.03.0076

Lang, E. V., Hatsiopoulou, O., Koch, T., Berbaum, K., Lutgendorf, S., Kettenmann, E., et al. (2005). Can words hurt? Patient-provider interactions during invasive procedures. *Pain* 114, 303–309. doi: 10.1016/j.pain.2004.12.02

Miller, F. G., and Colloca, L. (2011). The placebo phenomenon and medical ethics: rethinking the relationship between informed consent and risk-benefit assessment. *Theor. Med. Bioeth.* 32, 229–243. doi: 10.1007/s11017-011-9179-8

Montgomery, G. H., Schnur, J. B., and David, D. (2011). The impact of hypnotic suggestibility in clinical care settings. *Int. J. Clin. Exp.* 59, 294–309. doi: 10.1080/00207144.2011.570656

Riegel, B., Tönnies, S., Hansen, E., Zech, N., Eck, S., Batra, A., et al. (2021). German norms of the harvard group scale of hypnoticsusceptibility, form A (HGSHS:A) and proposal of A 5-itemshort-version (HGSHS-5:G). *Int. J. Clin. Exp. Hypn.* 69, 112–123. doi: 10.1080/00207144.2021.1836645

Schellekens, W. J., van Hees, H. W., Doorduin, J., Roesthuis, L. H., Scheffer, G. J., van der Hoeven, J. G., et al. (2016). Strategies to optimize respiratory muscle function in ICU patients. *Crit. Care* 20:103. doi: 10.1186/s13054-016-1280-y

Shor, R. E. (1962). Three dimensions of hypnotic depth. *Int. J. Clin. Exp. Hypn.* 10, 23–38. doi: 10.1080/00207146208415862

Wells, R. E., and Kaptchuk, T. J. (2012). To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *Am. J. Bioeth.* 12, 22–29. doi: 10.1080/15265161.2011.652798

Wigal, J. K., Kotses, H., Rawson, J. C., and Creer, T. L. (1988). The effects of suggestion on the total respiratory resistance of nonasthmatic female subjects. *J. Psychosom. Res.* 32, 409–416. doi: 10.1016/0022-3999(88)90024-4

Wittfoth, D., Pfeiffer, A., Bohne, M., Lanfermann, H., and Wittfoth, M. (2020). Emotion regulation through bifocal processing of fear inducing and disgust inducing stimuli. *BMC Neurosci.* 21:47. doi: 10.1186/s12868-020-00597-x

Wolters, F., Peerdeman, K. J., and Evers, A. W. M. (2019). Placebo and nocebo effects across symptoms: from pain to fatigue, dyspnea, nausea, and itch. *Front. Psychiatry* 10:470. doi: 10.3389/fpsyt.2019.00470

Zech, N., Schrödinger, M., Seemann, M., Zeman, F., Seyfried, T. F., and Hansen, E. (2020). Time-dependent negative effects of verbal and non-verbal suggestions in surgical patients—a study on arm muscle strength. *Front. Psychol.* 11:1693. doi: 10.3389/fpsyg.2020.01693

Zech, N., Seemann, M., Grzesiek, M., Breu, A., Seyfried, T. F., and Hansen, E. (2019). Nocebo effects on muscular performance - an experimental study about clinical situations. *Front. Pharmacol.* 10:219. doi: 10.3389/fphar.2019.00219

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Unraveling Negative Expectations and Nocebo-Related Effects in Musculoskeletal Pain

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This Perspective adapts the ViolEx Model, a framework validated in several clinical conditions, to better understand the role of expectations in the recovery and/or maintenance of musculoskeletal (MSK) pain. Here, particular attention is given to the condition in which dysfunctional expectations are maintained despite no longer being supported by confirmatory evidence (i.e., belief—lifting the arm leads to permanent tendon damage; evidence—after the patient lifts the arm no tendon damage occurs). While the ViolEx Model suggests that cognitive immunization strategies are responsible for the maintenance of dysfunctional expectations, we suggest that such phenomenon can also be understood from a Bayesian Brain perspective, according to which the level of precision of the priors (i.e., expectations) is the determinant factor accounting for the extent of priors' updating (i.e., we merge the two frameworks, suggesting that highly precise prior can lead to cognitive immunization responses). Importantly, this Perspective translates the theory behind these two frameworks into clinical suggestions. Precisely, it is argued that different strategies should be implemented when treating MSK pain patients, depending on the nature of their expectations (i.e., positive or negative and the level of their precision).

Keywords: nocebo effects, contextual factors, pain, musculoskeletal, physiotherapy, expectation, predictive brain, placebo effects

INTRODUCTION

Musculoskeletal (MSK) pain is ranked at the top of non-communicable diseases (Safiri et al., 2021), representing a profound burden for all socioeconomic and healthcare systems worldwide (Briggs et al., 2020). Although most MSK pain states have a good prognosis, there is a substantial proportion of patients who do not show spontaneous remission or do not respond favorably to first-line interventions and usual care, thus developing long-lasting symptoms, disabilities, and participation loss (Blyth et al., 2019).

The management of these patients is challenging because their subjective complaints (i.e., level of disability) rarely correlate with clinical and radiological findings (i.e., structural impairments; Rondoni et al., 2017; Tonosu et al., 2017; Viceconti et al., 2020). Thus, the lack of an identifiable pathology observed in various MSK diseases (i.e., low back pain and fibromyalgia) can have

clinical implications. On the one hand, patients may repetitively seek care, thus adopting unhelpful health-seeking behaviors. For example, they may contact various health care providers (Ng et al., 2020), overuse health services (Sajid et al., 2021), request complementary and alternative medicine (Setchell et al., 2021), and misuse drugs (Ashaye et al., 2018). On the other, clinicians risk to invalidate patients' experience (De Ruddere et al., 2013), offer contradictory explanations about their condition (Bunzli et al., 2013; Mannion et al., 2013), and generic diagnoses (Yunus, 2007). As a result, patients often experience negative emotions and adopt unhelpful coping strategies (i.e., catastrophic thinking, avoidance of movement), which are, *per se*, capable of worsening their clinical conditions and foster symptoms persistence (Bunzli et al., 2015; Darlow, 2016). Moreover, they may develop negative expectations about the course of their illness and the likely outcomes (Kravvariti et al., 2018, 2021; Thomaidou et al., 2021).

Negative expectations impact MSK pain (Hallegraeff et al., 2012; Geurts et al., 2017; Hayden et al., 2019; Fishbain and Pulikal, 2020; Mohamed et al., 2020), playing a significant role in transitioning from acute to persistent pain (Manai et al., 2019), and maintaining symptoms (Blasini et al., 2017; Klinger et al., 2017). Moreover, they can bias symptom perception (Handley et al., 2013; Bagaric et al., 2021) and reduce treatment effectiveness (Colloca et al., 2018; Corsi et al., 2019), inducing nocebo-related effects (Petrie and Rief, 2019; Benedetti et al., 2020). Within the MSK context, nocebo-related effects refer to those negative responses that follow treatment administration (i.e., painkillers, manual therapy, and therapeutic exercises) associated with a negative expectation (Rossettini et al., 2020a). Investigating patients' beliefs and expectations represent a priority for clinicians treating MSK pain (Lewis and O'Sullivan, 2018; Caneiro et al., 2020; Lin et al., 2020; Cook et al., 2021; Hutting et al., 2021; Lewis et al., 2021). However, such practice is not routinely implemented in clinical practice (Rossettini et al., 2019, 2020c). As emerged in previous surveys, clinicians involved in MSK care report difficulties in managing patients' expectations and avoid nocebo-related effects (Palese et al., 2019a; Cadorin et al., 2020; Rossettini et al., 2020b; Bisconti et al., 2021). This lack highlights the need for clinicians to have a framework that they can apply in everyday practice.

This Perspective has two aims. First, to provide clinicians with a better understanding of why some MSK patients hold on to their negative expectations. To this end, we will adapt the ViolEx Model (Kube et al., 2020) and the Bayesian brain hypothesis (Büchel et al., 2014). Second, we suggest some key strategies that clinicians can use to help patients update their dysfunctional expectations based on the theoretical frameworks discussed.

THE ViolEx MODEL AND THE BAYESIAN BRAIN

The ViolEx Model

When patients receive a MSK treatment, they can either "get what they expect" or "not get what they expect." The ViolEx Model offers an interesting description of the possible outcomes and consequences of such expectations match/mismatch (Kube et al., 2020). The starting point of this model is that individuals develop expectations that are based on their own experiences: if a patient with neck pain has a negative past experience with therapeutic exercises, it is likely that this patient will have negative expectations regarding such treatment in the future. Moreover, expectations are also shaped by personality traits: that is, neuroticism, pessimism, and trait anxiety have been associated with a tendency to expect worse outcomes in situations perceived as threatening (Barlow et al., 2014). On the whole, these expectations produce an internal model of "if A-then-B," that is "*if I do this exercise (A) then I will experience side-effects (B)*." When the internal model is consolidated, three different scenarios can occur. In the first scenario, reality matches the internal model and expectations are confirmed and reinforced: it means that the patient performs the exercise, the exercise produces side effects leading to a consolidation and reinforcement of negative expectations. The consequence is that the patient will learn that the treatment produces negative effects and he/she will therefore seek a different intervention in the future (**Figure 1A**; *expectation confirmation*).

In the second scenario, reality does not match the internal model and expectations are violated: it means that the patient performs the exercise and does not experience negative side effects. Thus, two possible outcomes can occur: expectations can be updated, based on the newly acquired information (i.e., the patient experiences that the prior negative expectations toward the exercise was wrong and learns to no longer be worried about such treatment; **Figure 1A**; *expectation violation followed by an update*), or they can be maintained, despite the disproving evidence (i.e., despite treatment intake is not followed by the predicted negative consequences, the patient persists in believing that the exercise is likely to be followed by negative side effects; **Figure 1A**; *expectation violation followed by dysfunctional beliefs maintenance*).

Out of these three scenarios, the third is the problematic one. The ViolEx Model explains this last scenario introducing the concept of "*cognitive immunization*," which indicates the engagement of strategies adapted to reappraise new information in such a way that the discrepancy between the evidence and the prior expectation is reduced, contributing to the maintenance of negative beliefs, despite the occurrence of conflicting events (Rief and Petrie, 2016; Rief and Joormann, 2019; Kube et al., 2019b).

Recently, the ViolEx Model has given interesting insights into clinical conditions such as depression (Kube et al., 2017; Rief and Joormann, 2019). Precisely, patients suffering from depression have been shown to maintain negative beliefs, even when presented with positive evidence disconfirming their prior negative beliefs (i.e., the example of **Figure 1A**; expectation violation followed by dysfunctional beliefs maintenance; Korn et al., 2014; Liknaitzky et al., 2017; Everaert et al., 2018). Interestingly, Kube et al. (2019a,b) have successfully demonstrated that by delivering instructions either promoting or discouraging cognitive immunization, it was possible to enhance negative expectations maintenance or to reduce them, respectively,

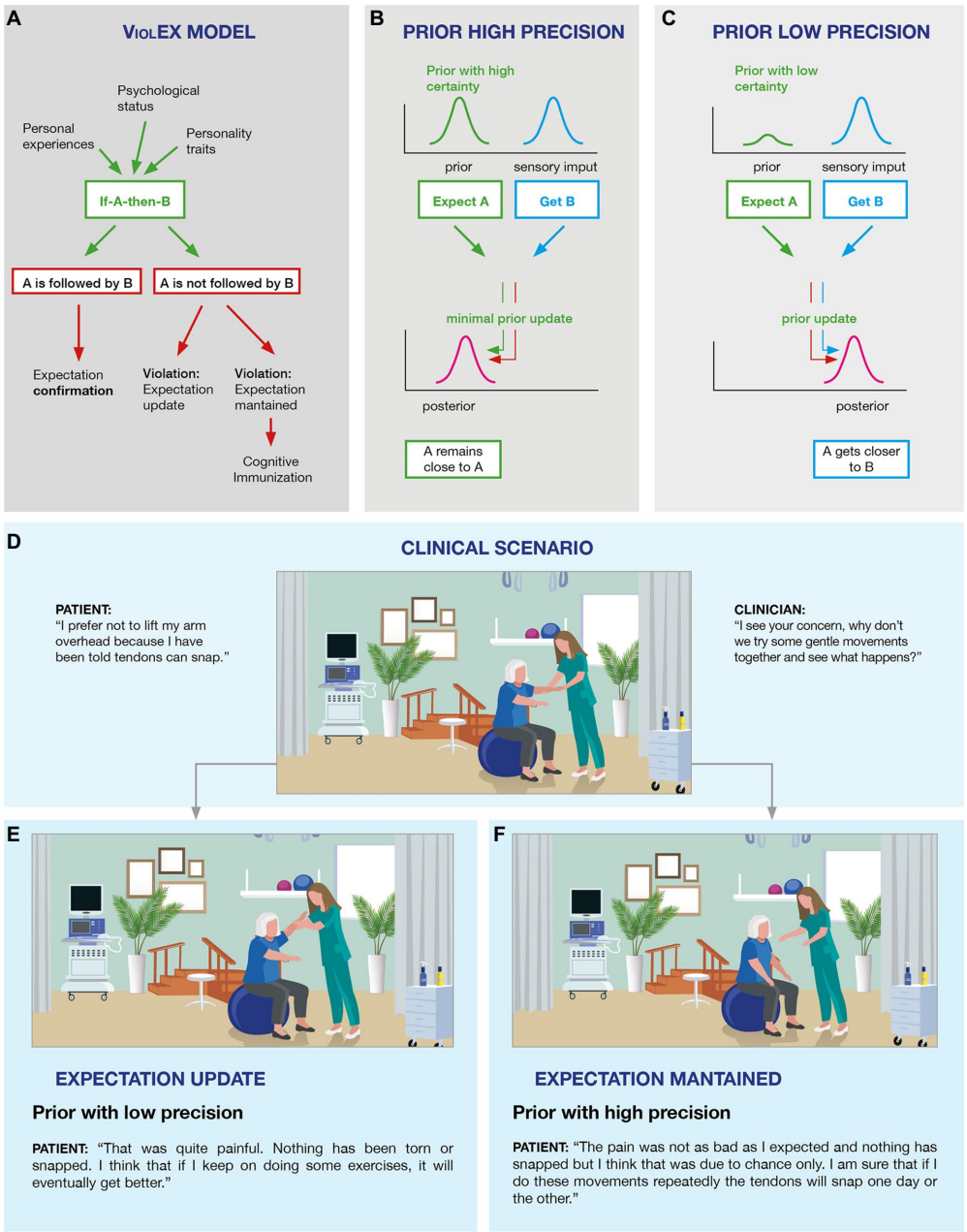

FIGURE 1 | The ViolEx Model and the Bayesian Brain: from theory to clinical practice in musculoskeletal (MSK) pain. The ViolEx Model **(A)** and the Bayesian brain **(B,C)**. Image **(A)** is a schematization of the ViolEx Model showing different outcomes depending on whether the violation of expectations is followed by immunization or change, resulting in either expectations maintenance or expectations updating, respectively. Image **(B)** is an example in which a prior with a high level of certainty is considered reliable and therefore undergoes minimal updating, while the interpretation of the sensory data is shifted toward the prior, resulting in a biased percept. Image **(C)** is an example in which a prior with a low level of certainty is updated to better fit sensory data, resulting in a posterior which is a better proxy of the sensory information. Examples of clinical scenarios **(D–F)**. Image **(D)** shows a typical clinical situation in which the clinician asks the patient with MSK pain to perform a basic exercise (lift the arm), while the patient is reluctant to do it due to their negative expectations (i.e., pain/injury). The patient finally agrees and lifts the arm, without facing negative consequences. Such situation may result in two different outcomes: in **(E)** the positive experience associated with the exercise leads to the violation of the patient's negative expectation with an update (low prior); whereas in **(F)** the positive experience associated with the exercise is not sufficient to violate the patient's negative expectation, thus maintaining the previous experience (high prior).

demonstrating that cognitive immunization is likely to underlie dysfunctional expectations maintenance. Another interesting finding is that healthy individuals have been shown to have a positive bias, meaning that they are less likely to update positive priors if presented with contradictory negative evidence (Sharot et al., 2007, 2011, 2012; Garrett and Sharot, 2017),

yet, such bias is abolished in the presence of perceived threat, in which case they become more responsive to the newly acquired negative evidence, updating their expectations (Sharot et al., 2007, 2011, 2012; Garrett and Sharot, 2017). This could be an important finding given that MSK pain patients report high threat perception linked to their experience of pain (Ochsner et al., 2006; Turk and Wilson, 2010); accordingly, this could indicate that MSK pain patients (similarly to depressed ones), become more susceptible to negative evidence, promoting the maintenance of dysfunctional expectations. Accordingly, it has been shown that patients with somatization syndrome (Rief et al., 2006) and MSK pain (Traeger et al., 2019; Barbari et al., 2021; Barth et al., 2021; Cashin et al., 2021; Cheung and Soundy, 2021; Jones et al., 2021) do not often use positive reassurance and education to update their negative dysfunctional beliefs and expectations.

Overall, previous research has shown the ViolEx model to be a valuable framework to better understand dysfunctional expectations maintenance in some clinical populations; therefore, we suggest that such model should be used to understand pain in MSK patients. In the daily practice clinicians often see MSK patients maintaining their dysfunctional expectations even if positive and reassuring evidence are provided (i.e., ViolEx Model; **Figure 1A**, scenario three). A good example is the case of patients that expect that their shoulder would break if they lift their arm (**Figure 1D**). When patients manage to fully lift their arm under the clinician supervision, and realize that their shoulder does not snap, the positive scenario (interiorizing that they can lift their arm without any negative consequences; **Figure 1E**) is less likely than the negative one represented by the "cognitive immunization" strategies (interpreting the event as lucky or as an exception to the rule; **Figure 1F**). Although this model is yet to be empirically tested upon MSK patients, it is likely to suggest that dysfunctional expectations maintenance and cognitive immunization strategies are recurrent in this clinical population.

Although cognitive immunization explains why dysfunctional expectations are maintained, it is yet to be understood why some patients implement such strategies to protect their negative beliefs and why others do not, updating their negative expectations with new positive evidence. We suggest that such differences in updating responses can be understood, at least to some extent, from a Bayesian perspective.

The ViolEx Model From a Bayesian Perspective

From a Bayesian perspective, our brain is conceptualized as a predictor machine that generates predictions, known as *priors*, about the expected sensory inputs. The integration between the prior and the sensory input results in a posterior (the percept), which can be more or less influenced by the prior and by the sensory data, depending on their level of precision (i.e., data encoded as probabilistic representatations; Friston, 2008, 2010; Büchel et al., 2014; Seymour and Mancini, 2020). Within this framework, a prior with high precision is considered reliable and, therefore, will exert greater influence on the interpretation of the incoming sensory input, resulting in a posterior (i.e., percept) which is biased toward the prior (**Figure 1B**). Differently, a prior with low precision will be considered unreliable, and therefore, will be given less consideration when interpreting the incoming sensory input, resulting in a posterior (i.e., percept) that is a better proxy of the sensory data (**Figure 1C**). Consider a sensory input which does not match the prior; if the prior has higher precision this is likely to result in a smaller prediction error (PE) (i.e., since the percept is biased toward the prior, there will be less discrepancy between the prior and the percept), compared to a prior with less precision (i.e., since the percept is a better proxy of the sensory information there will be more discrepancy between the prior and the percept), resulting in greater prior updating in the latter case (Friston, 2008, 2010; Büchel et al., 2014; Seymour and Mancini, 2020).

With this Bayesian model in mind, it is possible to better understand the second and third scenarios of the ViolEx Model discussed in the previous section (**Figure 1A**; Kube et al., 2020). Precisely, expectation violation followed by update could be attributed to one's having a prior with low precision which is updated accordingly with the newly acquired evidence (i.e., according to this view, the patient who is shown that lifting their arm does not lead to their shoulder to break and therefore updates such dysfunctional belief does not have a highly confident negative prior).

Differently, expectation violation followed by the maintenance of the dysfunctional belief would be understood as the consequence of one's having a highly precise prior which is considered highly reliable, and therefore, the newly acquired disconfirmatory evidence is not sufficient to disproof and update such strong prior. Indeed, the attribution of high certainty to such prior can motivate the engagement of higher-order cognitive strategies, such as cognitive immunization (Kube et al., 2017). For example, MSK patients that, during a clinical session, manage to lift their arm without any negative consequences to their shoulder but still belief that lifting the arm will eventually lead to their shoulder to break, are likely to have a highly precise prior and might discard the positive evidence (success in lifting the arm) which might be classified as an exception instead of the rule (example of cognitive immunization; **Figure 1F**).

As we have suggested here, the Bayesian framework can give further insights into the mechanisms of expectations updating described by the ViolEx Model. Yet, it is important to highlight that these two accounts differ in one major aspect. While the ViolEx model is cognitivist in nature; that is, it is premised on the existence of cognitive states called "expectations" and is concerned with the relation between expectations and symptoms independently of discussions of neuronal processes (Kube et al., 2020), the Bayesian brain hypothesis (also called "predictive processing") is a theory of brain function, not a cognitivist theory. From a Bayesian brain perspective, "expectations" are probabilistic predictions about the body and the world that are encoded at the level of neuronal populations. Indeed, the validity of Bayesian brain as a scientific theory rests on the actual existence of priors and PE at the neuronal

level (Downey, 2018; Seymour and Mancini, 2020). However, although the Bayesian perspective does not assume that a positive expectation communicated to the patient from the clinician on a conscious level translates directly into a prior with higher precision, this cannot be excluded. In the case of pain, new research is successfully applying the Bayesian framework to the cognitive domain, exploring whether priors are translated directly at the conscious level (Mancini et al., 2021). Accordingly, it has recently been shown that humans can explicitly predict the likelihood of incoming pain intensities in a way that is consistent with Bayesian inference (i.e., not only conscious predictions were measured but also the conscious confidence of such predictions; Mancini et al., 2021). The possibility that the Bayesian brain hypothesis can extend to the description of cognitive functioning is indeed exciting, yet further research is needed before drawing such conclusions.

A crucial point, that is the second aim of this perspective, is to use these models to create clinical strategies to treat dysfunctional patients' expectations in order to maximize treatment effectiveness, avoiding nocebo-related effects. In the following section, we offer a clinical framework for assessing and addressing MSK patients' expectations aimed to avoid nocebo-related effects during all phases of the therapeutic encounter (i.e., history taking, physical examination, and therapeutic administration; Palese et al., 2019b; Rossettini et al., 2020a; Thomson and Rossettini, 2021).

DISCUSSION

Clinical Opportunities

Since expectations and priors can critically change patients' perception and adherence to a clinical treatment, their assessment and management are crucial steps in the clinical practice (**Figure 2**).

In the clinical encounter, clinicians can start using open questions (i.e., *"What do you expect from this therapy?"; "How do you expect the course of this condition will be?"*; Laferton et al., 2017; Rossettini et al., 2018) or specific questionnaires self-completed by the patients (i.e., the EXPECT Questionnaire, the Expectation for Treatment Scale; Jones et al., 2016; Barth et al., 2019) to assess both the direction (i.e., positive or negative) of expectations and the strength of the patients' priors (i.e., high or low precision). This first step is important because depending on patients' expectations, different strategies can be used. If expectations are positive, the clinician should reinforce them through verbal suggestions associated with evidence-based treatments for the MSK pain (Rossettini et al., 2018). On the other hand, if the expectations are negative, the clinician has two different strategies to address them: optimization or violation (Peerdeman et al., 2016; Kube et al., 2018).

In MSK pain, patient education and reassurance are examples of optimizations (Louw et al., 2016; Bulow et al., 2021), adopted in clinical settings, to provide information, reconceptualize beliefs and facilitate patients' ability to cope with their condition (Watson et al., 2019). Instead, manual therapy (i.e., mobilization with movement and symptom modification procedure), therapeutic exercise (i.e., active range of motion tasks), and virtual reality (i.e., immersive scenario; Geneen et al., 2017; Gumaa and Rehan Youssef, 2019; Ahern et al., 2020; Bordeleau et al., 2021; Brea-Gomez et al., 2021; Satpute et al., 2021; Tsokanos et al., 2021) are examples of successful violation strategies commonly adopted to reduce pain and disability (Zusman, 2013a,b; Rabey et al., 2017; Bialosky et al., 2018; Geri et al., 2019; Cerritelli et al., 2021). From a Bayesian perspective, both optimization and violation can be considered as bottom-up inputs that clinicians can offer to patients to challenge the negative expectations of the patient, facilitating their updating (Friston, 2012). While optimization aims to modify one's priors by working at a high cognitive level (i.e., providing a new understanding of the pain by explaining how it works; Doering et al., 2018), violation strategies challenge one's dysfunctional beliefs by providing first-hand disconfirmatory evidence with experience (Craske et al., 2018), which in turn can be used to update the negative priors. Since there are currently no criteria to guide the clinicians on which strategy to use first (optimization first or violation first; Peerdeman et al., 2016; Kube et al., 2018), we suggest a clinically oriented choice which should depend on the level of precision of patients' priors (as assessed during the clinical encounter).

Let us consider a patient that is scared of squatting because they have once read on social media that squatting repeatedly can ruin the cartilage of their knee. The clinician assesses the strength of patient's expectations (i.e., the clinician discovers that the patient is aware that social media are full of fake news and is aware that the information about squatting and cartilage damage might not be true) and establishes that the negative expectations are likely to have low precision. In this case, we suggest that clinicians could use optimization strategies first (i.e., reducing unrealistic beliefs about possible side effects through education; Doering et al., 2018) and then violation strategies (Craske et al., 2018). By doing so, expectations are first challenged at the cognitive level *via* optimization, while violation is used at a later stage to further challenge dysfunctional expectations with experience. Since patients' expectations are not so rooted, we would expect them to update easily, resulting in observable positive changes sooner rather than later (i.e., within a session or after a reduced number of treatments).

Instead, consider patients having negative expectations with high precision (i.e., believing that their cervical disk herniation is a severe condition limiting all neck movements). When clinicians understand that such negative expectations are firmly rooted in the patients' minds (i.e., the patient that knows, mainly through word-of-mouth, several people whose herniation got worse because they were too active and sporty, and is therefore convinced that movement is bad for this type of condition), we suggest inverting the two strategies (violation-optimization) to avoid ruining the therapeutic alliance. If clinicians insist on telling patients information that goes against their strong expectations (i.e., optimization), patients might start losing trust in the clinicians—in other words, telling patients things that they do not want to hear can be counterproductive (Laferton et al., 2017; Rossettini et al., 2018). Instead, we propose

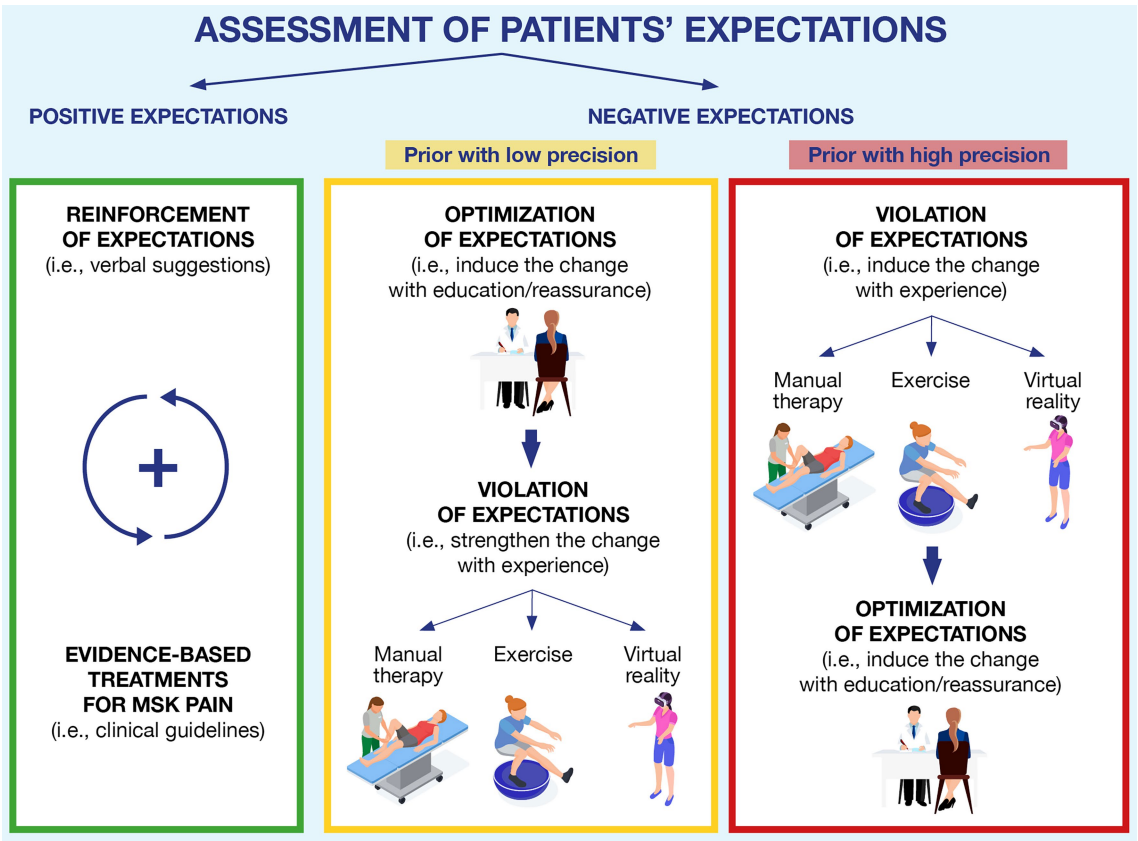

FIGURE 2 | A clinical framework to assess and address patients' expectations in musculoskeletal pain. The figure depicts the three typical scenarios that can occur in clinical practice. Green block: the patient shows positive expectations toward the rehabilitation process, and the clinician can reinforce them by providing verbal suggestions and confirming such expectations with the recommended evidence-based treatments; Yellow block: if negative expectations are detected during the initial assessment, but they have low precision, the clinician can optimize them through education and reassurance and subsequently try to violate such expectations by exposing patients to experience (using manual therapy, exercise, virtual reality, or a combination of them); and Red block: if high-precision expectations are detected, we suggest starting by exposing patients to experiences that could challenge patients' expectations, and if this outcome is achieved, it can be reinforced through verbal suggestions (education or reassurance).

focusing on building trust (i.e., listening to the patient, without, at first, saying things that are directly in contrast with their view), meanwhile using violation strategies so that patients can disproof their expectations for themselves (e.g., providing pain-free experiences with manual therapy, exercise, and virtual reality). Later, when patients are more open to hearing information against their initial beliefs, clinicians can use optimization strategies to further promote and strengthen priors updating (Craske et al., 2018; Schemer et al., 2019). Worth mentioning is that in the case of firmly rooted expectations (i.e., where the patient implements strategies such as cognitive immunization), patients might require more evidence before successfully updating their priors. In this situation, clinicians should consider offering a higher number of disconfirming trials (i.e., repeating violation strategies more times than usual or offering the patient more treatment sessions; Gatzounis et al., 2021; Hilleke et al., 2021).

Challenges and Future Directions

Despite some preliminary research suggests that the Bayesian framework (Owens et al., 2018; Ongaro and Kaptchuk, 2019; Kaptchuk et al., 2020) and the ViolEx model (Kube et al., 2020; Panitz et al., 2021) are good fit for describing pain processing and symptoms persistence, some open questions remained unresolved.

First, it is crucial to understand *how clinicians can translate the strategies used to modulate patient's expectations within the specific context of MSK pain* (Caneiro et al., 2021). So far, researchers have investigated the modulation of expectations mainly in mental health (i.e., anxiety and depression) or medical conditions (i.e., cancer and coronary heart disease; Peerdeman et al., 2016; Kube et al., 2018), compared to MSK pain (Barth et al., 2021). Therefore, the interplay between direct experiences (i.e., previous healthcare exposures), social and cultural influences (i.e., peers and media), individual differences (i.e., personality traits and genetic factor), and expectations (Panitz et al., 2021) in patients presenting different MSK pain mechanism (i.e., nociceptive, neuropathic, and nociplastic) represents a challenge for future studies (Rossettini and Testa, 2018).

Second, it is crucial to investigate if it is *possible to change patient's expectations permanently*. Even if expectations can change in a specific situation (i.e., "*I did not feel pain in my back when bending over on this occasion*"), this modification

does not necessarily translate into a general and long-lasting change (i.e., "*Every time I will bend over, I will not feel pain in the back*"; Schemer et al., 2019; Riecke et al., 2020). Furthermore, if the patient has negative expectations with very high priors, it could be difficult to change them quickly (Kube et al., 2020). Therefore, we need future studies to investigate if expectations can change for long periods (Bromberg-Martin and Sharot, 2020; Camerone et al., 2021a,b) and if they are generalized to different MSK pain conditions.

Third, it is necessary to understand *the optimal PE magnitude needed to update patient expectations*. According to the recent scientific literature, patients ignore very small PEs and avoid to update their expectations as often the cognitive costs of the change outweigh the benefits (Linton et al., 2012; Panitz et al., 2021; Pinquart et al., 2021). Furthermore, even substantial PE can be considered an exception to the rule and thus discarded without changing expectations (Linton et al., 2012; Panitz et al., 2021; Pinquart et al., 2021). Therefore, future studies should identify the magnitude of PE capable to challenge the patients' negative expectations in MSK pain.

CONCLUSION

Managing patients' expectations continues to represent a challenge in MSK pain. Clinicians should choose wisely if, when and how to challenge patients' negative expectations, considering whether the benefits of avoiding nocebo-related effects outweigh the risks of eroding the therapeutic alliance and having drop-outs. Based on the theoretical frameworks here presented (ViolEx Model and Bayesian Brain Hypothesis), we suggest that clinicians could use the strength of patients' expectations as an indicator to decide when to directly challenge patients' negative expectations (i.e., optimization), or when to start by challenging their beliefs indirectly (i.e., violation), avoiding damages to the therapeutic alliance.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

GR, AC and MT designed and supervised the writing of the paper. GR, AC, ECam, ECar, MMan, MMir, AP and MT participated in drafting and revising the different versions of the article. All authors contributed to the article and approved the submitted version.

REFERENCES

Ahern, M. M., Dean, L. V., Stoddard, C. C., Agrawal, A., Kim, K., Cook, C. E., et al. (2020). The effectiveness of virtual reality in patients with spinal pain: a systematic review and meta-analysis. *Pain Pract.* 20, 656–675. doi: 10.1111/papr.12885

Ashaye, T., Hounsome, N., Carnes, D., Taylor, S. J. C., Homer, K., Eldridge, S., et al. (2018). Opioid prescribing for chronic musculoskeletal pain in UK primary care: results from a cohort analysis of the COPERS trial. *BMJ Open* 8:e019491. doi: 10.1136/bmjopen-2017-019491

Bagaric, B., Jokic-Begic, N., and Jokic, C.S. (2021). The nocebo effect: a review of contemporary experimental research. Int. J. Behav. Med. doi: 10.1007/s12529-021-10016-y [Epub ahead of print].

Barbari, V., Storari, L., Maselli, F., and Testa, M. (2021). Applicability of pain neuroscience education: where are we now? *J. Back Musculoskelet. Rehabil.* 34, 511–520. doi: 10.3233/BMR-200091

Barlow, D. H., Ellard, K. K., Sauer-Zavala, S., Bullis, J. R., and Carl, J. R. (2014). The origins of neuroticism. *Perspect. Psychol. Sci.* 9, 481–496. doi: 10.1177/1745691614544528

Barth, J., Kern, A., Luthi, S., and Witt, C. M. (2019). Assessment of patients' expectations: development and validation of the expectation for treatment scale (ETS). *BMJ Open* 9:e026712. doi: 10.1136/bmjopen-2018-026712

Barth, J., Muff, S., Kern, A., Zieger, A., Keiser, S., Zoller, M., et al. (2021). Effect of briefing on acupuncture treatment outcome expectations, pain, and adverse side effects among patients with chronic low back pain: a randomized clinical trial. *JAMA Netw. Open* 4:e2121418. doi: 10.1001/jamanetworkopen.2021.21418

Benedetti, F., Frisaldi, E., Barbiani, D., Camerone, E., and Shaibani, A. (2020). Nocebo and the contribution of psychosocial factors to the generation of pain. *J. Neural Transm.* 127, 687–696. doi: 10.1007/s00702-019-02104-x

Bialosky, J. E., Beneciuk, J. M., Bishop, M. D., Coronado, R. A., Penza, C. W., Simon, C. B., et al. (2018). Unraveling the mechanisms of manual therapy: modeling an approach. *J. Orthop. Sports Phys. Ther.* 48, 8–18. doi: 10.2519/jospt.2018.7476

Bisconti, M., Venturin, D., Bianco, A., Capurso, V., and Giovannico, G. (2021). Understanding contextual factors effects and their implications for Italian physiotherapists: findings from a national cross-sectional study. *Healthcare* 9:689. doi: 10.3390/healthcare9060689

Blasini, M., Corsi, N., Klinger, R., and Colloca, L. (2017). Nocebo and pain: an overview of the psychoneurobiological mechanisms. *Pain Rep.* 2:e585. doi: 10.1097/PR9.0000000000000585

Blyth, F. M., Briggs, A. M., Schneider, C. H., Hoy, D. G., and March, L. M. (2019). The global burden of musculoskeletal pain-where to from here? *Am. J. Public Health* 109, 35–40. doi: 10.2105/AJPH.2018.304747

Bordeleau, M., Stamenkovic, A., Tardif, P. A., and Thomas, J. (2021). The use of virtual reality in back pain rehabilitation: a systematic review and meta-analysis. *J. Pain* 23, 175–195. doi: 10.1016/j.jpain.2021.08.001

Brea-Gomez, B., Torres-Sanchez, I., Ortiz-Rubio, A., Calvache-Mateo, A., Cabrera-Martos, I., Lopez-Lopez, L., et al. (2021). Virtual reality in the treatment of adults with chronic low back pain: a systematic review and meta-analysis of randomized clinical trials. *Int. J. Environ. Res. Public Health* 18:11806. doi: 10.3390/ijerph182211806

Briggs, A. M., Shiffman, J., Shawar, Y. R., Akesson, K., Ali, N., and Woolf, A. D. (2020). Global health policy in the 21st century: challenges and opportunities to arrest the global disability burden from musculoskeletal health conditions. *Best Pract. Res. Clin. Rheumatol.* 34:101549. doi: 10.1016/j.berh.2020.101549

Bromberg-Martin, E. S., and Sharot, T. (2020). The value of beliefs. *Neuron* 106, 561–565. doi: 10.1016/j.neuron.2020.05.001

Büchel, C., Geuter, S., Sprenger, C., and Eippert, F. (2014). Placebo analgesia: a predictive coding perspective. *Neuron* 81, 1223–1239. doi: 10.1016/j.neuron.2014.02.042

Bulow, K., Lindberg, K., Vaegter, H. B., and Juhl, C. B. (2021). Effectiveness of pain neurophysiology education on musculoskeletal pain: a systematic review and meta-analysis. *Pain Med.* 22, 891–904. doi: 10.1093/pm/pnaa484

Bunzli, S., Smith, A., Schutze, R., and O'sullivan, P. (2015). Beliefs underlying pain-related fear and how they evolve: a qualitative investigation in people

with chronic back pain and high pain-related fear. *BMJ Open* 5:e008847. doi: 10.1136/bmjopen-2015-008847

Bunzli, S., Watkins, R., Smith, A., Schutze, R., and O'sullivan, P. (2013). Lives on hold: a qualitative synthesis exploring the experience of chronic low-back pain. *Clin. J. Pain* 29, 907–916. doi: 10.1097/AJP.0b013e31827a6dd8

Cadorin, L., Rossettini, G., Testa, M., Geri, T., and Palese, A. (2020). The awareness of contextual factors, placebo and nocebo effects among nursing students: findings from a cross-sectional study. *Nurse Educ. Pract.* 42:102670. doi: 10.1016/j.nepr.2019.102670

Camerone, E. M., Piedimonte, A., Testa, M., Wiech, K., Vase, L., Zamfira, D. A., et al. (2021a). The effect of temporal information on placebo analgesia and nocebo hyperalgesia. *Psychosom. Med.* 83, 43–50. doi: 10.1097/PSY.0000000000000882

Camerone, E. M., Wiech, K., Benedetti, F., Carlino, E., Job, M., Scafoglieri, A., et al. (2021b). 'External timing' of placebo analgesia in an experimental model of sustained pain. *Eur. J. Pain* 25, 1303–1315. doi: 10.1002/ejp.1752

Caneiro, J. P., Roos, E. M., Barton, C. J., O'sullivan, K., Kent, P., Lin, I., et al. (2020). It is time to move beyond 'body region silos' to manage musculoskeletal pain: five actions to change clinical practice. *Br. J. Sports Med.* 54, 438–439. doi: 10.1136/bjsports-2018-100488

Caneiro, J. P., Smith, A., Bunzli, S., Linton, S., Moseley, G. L., and O'sullivan, P. (2021). From fear to safety: a roadmap to recovery from musculoskeletal pain. *Phys. Ther.* 102:pzab271. doi: 10.1093/ptj/pzab271

Cashin, A. G., Lee, H., Traeger, A. C., Hubscher, M., Skinner, I. W., and Mcauley, J. H. (2021). Feeling reassured after a consultation does not reduce disability or healthcare use in people with acute low back pain: a mediation analysis of a randomised trial. *J. Physiother.* 67, 197–200. doi: 10.1016/j.jphys.2021.06.007

Cerritelli, F., Chiera, M., Abbro, M., Megale, V., Esteves, J., Gallace, A., et al. (2021). The challenges and perspectives of the integration between virtual and augmented reality and manual therapies. *Front. Neurol.* 12:700211. doi: 10.3389/fneur.2021.700211

Cheung, L., and Soundy, A. (2021). The impact of reassurance on musculoskeletal (MSK) pain: a qualitative review. *Behav. Sci.* 11:150. doi: 10.3390/bs11110150

Colloca, L., Corsi, N., and Fiorio, M. (2018). The interplay of exercise, placebo and nocebo effects on experimental pain. *Sci. Rep.* 8:14758. doi: 10.1038/s41598-018-32974-2

Cook, C. E., Denninger, T., Lewis, J., Diener, I., and Thigpen, C. (2021). Providing value-based care as a physiotherapist. *Arch. Physiother.* 11:12. doi: 10.1186/s40945-021-00107-0

Corsi, N., Emadi Andani, M., Sometti, D., Tinazzi, M., and Fiorio, M. (2019). When words hurt: verbal suggestion prevails over conditioning in inducing the motor nocebo effect. *Eur. J. Neurosci.* 50, 3311–3326. doi: 10.1111/ejn.14489

Craske, M. G., Hermans, D., and Vervliet, B. (2018). State-of-the-art and future directions for extinction as a translational model for fear and anxiety. *Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci.* 373:20170025. doi: 10.1098/rstb.2017.0025

Darlow, B. (2016). Beliefs about back pain: the confluence of client, clinician and community. *Int. J. Osteopath. Med.* 20, 53–61. doi: 10.1016/j.ijosm.2016.01.005

De Ruddere, L., Goubert, L., Stevens, M., De, C. W. A. C., and Crombez, G. (2013). Discounting pain in the absence of medical evidence is explained by negative evaluation of the patient. *Pain* 154, 669–676. doi: 10.1016/j.pain.2012.12.018

Doering, B. K., Glombiewski, J. A., and Rief, W. (2018). Expectation-focused psychotherapy to improve clinical outcomes. *Int. Rev. Neurobiol.* 138, 257–270. doi: 10.1016/bs.irn.2018.02.004

Downey, A. (2018). Predictive processing and the representation wars: a victory for the eliminativist (via fictionalism). *Synthese* 195, 5115–5139. doi: 10.1007/s11229-017-1442-8

Everaert, J., Bronstein, M. V., Cannon, T. D., and Joormann, J. (2018). Looking through tinted glasses: depression and social anxiety are related to both interpretation biases and inflexible negative interpretations. *Clin. Psychol. Sci.* 6, 517–528. doi: 10.1177/2167702617747968

Fishbain, D. A., and Pulikal, A. (2020). Can patient expectations of returning to work documented before, during, or at the end of treatment predict actual return to work post-treatment? An evidence-based structured systematic review. *Pain Med.* 21, 3034–3046. doi: 10.1093/pm/pnaa093

Friston, K. (2008). Hierarchical models in the brain. *PLoS Comput. Biol.* 4:e1000211. doi: 10.1371/journal.pcbi.1000211

Friston, K. (2010). The free-energy principle: a unified brain theory? *Nat. Rev. Neurosci.* 11, 127–138. doi: 10.1038/nrn2787

Friston, K. (2012). The history of the future of the Bayesian brain. *NeuroImage* 62, 1230–1233. doi: 10.1016/j.neuroimage.2011.10.004

Garrett, N., and Sharot, T. (2017). Optimistic update bias holds firm: three tests of robustness following Shah et al. *Conscious. Cogn.* 50, 12–22. doi: 10.1016/j.concog.2016.10.013

Gatzounis, R., Den Hollander, M., and Meulders, A. (2021). Optimizing long-term outcomes of exposure for chronic primary pain from the lens of learning theory. *J. Pain* 22, 1315–1327. doi: 10.1016/j.jpain.2021.04.012

Geneen, L. J., Moore, R. A., Clarke, C., Martin, D., Colvin, L. A., and Smith, B. H. (2017). Physical activity and exercise for chronic pain in adults: an overview of cochrane reviews. *Cochrane Database Syst. Rev.* 4:CD011279. doi: 10.1002/14651858.CD011279.pub2

Geri, T., Viceconti, A., Minacci, M., Testa, M., and Rossettini, G. (2019). Manual therapy: exploiting the role of human touch. *Musculoskelet. Sci. Pract.* 44:102044. doi: 10.1016/j.msksp.2019.07.008

Geurts, J. W., Willems, P. C., Lockwood, C., Van Kleef, M., Kleijnen, J., and Dirksen, C. (2017). Patient expectations for management of chronic non-cancer pain: a systematic review. *Health Expect.* 20, 1201–1217. doi: 10.1111/hex.12527

Gumaa, M., and Rehan Youssef, A. (2019). Is virtual reality effective in orthopedic rehabilitation? A systematic review and meta-analysis. *Phys. Ther.* 99, 1304–1325. doi: 10.1093/ptj/pzz093

Hallegraeff, J. M., Krijnen, W. P., Van Der Schans, C. P., and De Greef, M. H. G. (2012). Expectations about recovery from acute non-specific low back pain predict absence from usual work due to chronic low back pain: a systematic review. *J. Phys.* 58, 165–172. doi: 10.1016/S1836-9553(12)70107-8

Handley, I. M., Fowler, S. L., Rasinski, H. M., Helfer, S. G., and Geers, A. L. (2013). Beliefs about expectations moderate the influence of expectations on pain perception. *Int. J. Behav. Med.* 20, 52–58. doi: 10.1007/s12529-011-9203-4

Hayden, J. A., Wilson, M. N., Riley, R. D., Iles, R., Pincus, T., and Ogilvie, R. (2019). Individual recovery expectations and prognosis of outcomes in non-specific low back pain: prognostic factor review. *Cochrane Database Syst. Rev.* 2019:CD011284. doi: 10.1002/14651858.CD011284.pub2

Hilleke, M., Lang, T., and Helbig-Lang, S. (2021). Match or mismatch? The impact of expected fear on experienced fear during exposure. *Clin. Psychol. Sci. Pract.* 28, 148–160. doi: 10.1037/cps0000005

Hutting, N., Caneiro, J. P., Ong'wen, O. M., Miciak, M., and Roberts, L. (2021). Patient-centered care in musculoskeletal practice: key elements to support clinicians to focus on the person. *Musculoskelet. Sci. Pract.* 57:102434. doi: 10.1016/j.msksp.2021.102434

Jones, S. M., Lange, J., Turner, J., Cherkin, D., Ritenbaugh, C., Hsu, C., et al. (2016). Development and validation of the EXPECT questionnaire: assessing patient expectations of outcomes of complementary and alternative medicine treatments for chronic pain. *J. Altern. Complement. Med.* 22, 936–946. doi: 10.1089/acm.2016.0242

Jones, C. M. P., Shaheed, C. A., Ferreira, G. E., Kharel, P., Christine Lin, C.-W., and Maher, C. G. (2021). Advice and education provide small short-term improvements in pain and disability in people with non-specific spinal pain: a systematic review. *J. Phys.* 67, 263–270. doi: 10.1016/j.jphys.2021.08.014

Kaptchuk, T. J., Hemond, C. C., and Miller, F. G. (2020). Placebos in chronic pain: evidence, theory, ethics, and use in clinical practice. *BMJ* 370:m1668. doi: 10.1136/bmj.m1668

Klinger, R., Blasini, M., Schmitz, J., and Colloca, L. (2017). Nocebo effects in clinical studies: hints for pain therapy. *Pain Rep.* 2:e586. doi: 10.1097/PR9.0000000000000586

Korn, C. W., Sharot, T., Walter, H., Heekeren, H. R., and Dolan, R. J. (2014). Depression is related to an absence of optimistically biased belief updating about future life events. *Psychol. Med.* 44, 579–592. doi: 10.1017/S0033291713001074

Kravvariti, E., Kitas, G. D., Mitsikostas, D. D., and Sfikakis, P. P. (2018). Nocebos in rheumatology: emerging concepts and their implications for clinical practice. *Nat. Rev. Rheumatol.* 14, 727–740. doi: 10.1038/s41584-018-0110-9

Kravvariti, E., Kotsani, M., Mitsikostas, D. D., and Sfikakis, P. P. (2021). Nocebo phenomena may be enhanced in aging: implications for clinical practice. *Maturitas* 143, 10–16. doi: 10.1016/j.maturitas.2020.07.011

Kube, T., Glombiewski, J. A., Gall, J., Touissant, L., Gartner, T., and Rief, W. (2019a). How to modify persisting negative expectations in major depression? An experimental study comparing three strategies to inhibit cognitive immunization against novel positive experiences. *J. Affect. Disord.* 250, 231–240. doi: 10.1016/j.jad.2019.03.027

Kube, T., Glombiewski, J. A., and Rief, W. (2018). Using different expectation mechanisms to optimize treatment of patients with medical conditions: a systematic review. *Psychosom. Med.* 80, 535–543. doi: 10.1097/PSY.0000000000000596

Kube, T., Rief, W., and Glombiewski, J. A. (2017). On the maintenance of expectations in major depression—investigating a neglected phenomenon. *Front. Psychol.* 8:9. doi: 10.3389/fpsyg.2017.00009

Kube, T., Rief, W., Gollwitzer, M., Gartner, T., and Glombiewski, J. A. (2019b). Why dysfunctional expectations in depression persist—results from two experimental studies investigating cognitive immunization. *Psychol. Med.* 49, 1532–1544. doi: 10.1017/S0033291718002106

Kube, T., Rozenkrantz, L., Rief, W., and Barsky, A. (2020). Understanding persistent physical symptoms: conceptual integration of psychological expectation models and predictive processing accounts. *Clin. Psychol. Rev.* 76:101829. doi: 10.1016/j.cpr.2020.101829

Laferton, J. A., Kube, T., Salzmann, S., Auer, C. J., and Shedden-Mora, M. C. (2017). Patients' expectations regarding medical treatment: a critical review of concepts and their assessment. *Front. Psychol.* 8:233. doi: 10.3389/fpsyg.2017.00233

Lewis, J., and O'sullivan, P. (2018). Is it time to reframe how we care for people with non-traumatic musculoskeletal pain? *Br. J. Sports Med.* 52, 1543–1544. doi: 10.1136/bjsports-2018-099198

Lewis, J. S., Stokes, E. K., Gojanovic, B., Gellatly, P., Mbada, C., Sharma, S., et al. (2021). Reframing how we care for people with persistent non-traumatic musculoskeletal pain. Suggestions for the rehabilitation community. *Physiotherapy* 112, 143–149. doi: 10.1016/j.physio.2021.04.002

Liknaitzky, P., Smillie, L. D., and Allen, N. B. (2017). Out-of-the-blue: depressive symptoms are associated with deficits in processing inferential expectancy-violations using a novel cognitive rigidity task. *Cogn. Ther. Res.* 41, 757–776. doi: 10.1007/s10608-017-9853-x

Lin, I., Wiles, L., Waller, R., Caneiro, J. P., Nagree, Y., Straker, L., et al. (2020). Patient-centred care: the cornerstone for high-value musculoskeletal pain management. *Br. J. Sports Med.* 54, 1240–1242. doi: 10.1136/bjsports-2019-101918

Linton, S. J., Boersma, K., Vangronsveld, K., and Fruzzetti, A. (2012). Painfully reassuring? The effects of validation on emotions and adherence in a pain test. *Eur. J. Pain* 16, 592–599. doi: 10.1016/j.ejpain.2011.07.011

Louw, A., Zimney, K., Puentedura, E. J., and Diener, I. (2016). The efficacy of pain neuroscience education on musculoskeletal pain: a systematic review of the literature. *Physiother. Theory Pract.* 32, 332–355. doi: 10.1080/09593985.2016.1194646

Manai, M., Van Middendorp, H., Veldhuijzen, D. S., Huizinga, T. W. J., and Evers, A. W. M. (2019). How to prevent, minimize, or extinguish nocebo effects in pain: a narrative review on mechanisms, predictors, and interventions. *Pain Rep.* 4:e699. doi: 10.1097/PR9.0000000000000699

Mancini, F., Zhang, S., and Seymour, B. (2021). Learning the statistics of pain: computational and neural mechanisms. bioRxiv [Preprint]. doi: 10.1101/2021.10.21.465270

Mannion, A. F., Wieser, S., and Elfering, A. (2013). Association between beliefs and care-seeking behavior for low back pain. *Spine* 38, 1016–1025. doi: 10.1097/BRS.0b013e31828473b5

Mohamed, W. J. M., Joseph, L., Canby, G., Paungmali, A., Sitilertpisan, P., and Pirunsan, U. (2020). Are patient expectations associated with treatment outcomes in individuals with chronic low back pain? A systematic review of randomised controlled trials. *Int. J. Clin. Pract.* 74:e13680. doi: 10.1111/ijcp.13680

Ng, F., Smith, G. D., Ma, C. C., and Li, L. W. (2020). "Health seeking behaviour: doctor shopping," in *Primary Care Revisited: Interdisciplinary Perspectives for a New Era*. eds. B. Y. F. Fong, V. T. S. Law and A. Lee (Singapore: Springer Singapore).

Ochsner, K. N., Ludlow, D. H., Knierim, K., Hanelin, J., Ramachandran, T., Glover, G. C., et al. (2006). Neural correlates of individual differences in pain-related fear and anxiety. *Pain* 120, 69–77. doi: 10.1016/j.pain.2005.10.014

Ongaro, G., and Kaptchuk, T. J. (2019). Symptom perception, placebo effects, and the Bayesian brain. *Pain* 160, 1–4. doi: 10.1097/j.pain.0000000000001367

Owens, A. P., Allen, M., Ondobaka, S., and Friston, K. J. (2018). Interoceptive inference: from computational neuroscience to clinic. *Neurosci. Biobehav. Rev.* 90, 174–183. doi: 10.1016/j.neubiorev.2018.04.017

Palese, A., Cadorin, L., Testa, M., Geri, T., Colloca, L., and Rossettini, G. (2019a). Contextual factors triggering placebo and nocebo effects in nursing practice: findings from a national cross-sectional study. *J. Clin. Nurs.* 28, 1966–1978. doi: 10.1111/jocn.14809

Palese, A., Rossettini, G., Colloca, L., and Testa, M. (2019b). The impact of contextual factors on nursing outcomes and the role of placebo/nocebo effects: a discussion paper. *Pain Rep.* 4:e716. doi: 10.1097/PR9.0000000000000716

Panitz, C., Endres, D., Buchholz, M., Khosrowtaj, Z., Sperl, M. F., Mueller, E., et al. (2021). A revised framework for the investigation of expectation update versus maintenance in the context of expectation violations: the ViolEx 2.0 model. *Front. Psychol.* 2:726432. doi: 10.3389/fpsyg.2021.726432

Peerdeman, K. J., Van Laarhoven, A. I. M., Keij, S. M., Vase, L., Rovers, M. M., Peters, M. L., et al. (2016). Relieving patients' pain with expectation interventions: a meta-analysis. *Pain* 157, 1179–1191. doi: 10.1097/j.pain.0000000000000540

Petrie, K. J., and Rief, W. (2019). Psychobiological mechanisms of placebo and nocebo effects: pathways to improve treatments and reduce side effects. *Annu. Rev. Psychol.* 70, 599–625. doi: 10.1146/annurev-psych-010418-102907

Pinquart, M., Endres, D., Teige-Mocigemba, S., Panitz, C., and Schutz, A. C. (2021). Why expectations do or do not change after expectation violation: a comparison of seven models. *Conscious. Cogn.* 89:103086. doi: 10.1016/j.concog.2021.103086

Rabey, M., Hall, T., Hebron, C., Palsson, T. S., Christensen, S. W., and Moloney, N. (2017). Reconceptualising manual therapy skills in contemporary practice. *Musculoskelet. Sci. Pract.* 29, 28–32. doi: 10.1016/j.msksp.2017.02.010

Riecke, J., Rief, W., Vlaeyen, J. W. S., and Glombiewski, J. A. (2020). Generalizability of harm and pain expectations after exposure in chronic low back pain patients. *Eur. J. Pain* 24, 1495–1504. doi: 10.1002/ejp.1604

Rief, W., Heitmuller, A. M., Reisberg, K., and Ruddel, H. (2006). Why reassurance fails in patients with unexplained symptoms--an experimental investigation of remembered probabilities. *PLoS Med.* 3:e269. doi: 10.1371/journal.pmed.0030269

Rief, W., and Joormann, J. (2019). Revisiting the cognitive model of depression: the role of expectations. *Clin. Psychol. Eur.* 1:32605. doi: 10.32872/cpe.v1i1.32605

Rief, W., and Petrie, K. J. (2016). Can psychological expectation models be adapted for placebo research? *Front. Psychol.* 7:1876. doi: 10.3389/fpsyg.2016.01876

Rondoni, A., Rossettini, G., Ristori, D., Gallo, F., Strobe, M., Giaretta, F., et al. (2017). Intrarater and inter-rater reliability of active cervical range of motion in patients with nonspecific neck pain measured with technological and common use devices: a systematic review with meta-regression. *J. Manip. Physiol. Ther.* 40, 597–608. doi: 10.1016/j.jmpt.2017.07.002

Rossettini, G., Camerone, E. M., Carlino, E., Benedetti, F., and Testa, M. (2020a). Context matters: the psychoneurobiological determinants of placebo, nocebo and context-related effects in physiotherapy. *Arch. Physiother.* 10:11. doi: 10.1186/s40945-020-00082-y

Rossettini, G., Carlino, E., and Testa, M. (2018). Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskelet. Disord.* 19:27. doi: 10.1186/s12891-018-1943-8

Rossettini, G., Geri, T., Palese, A., Marzaro, C., Mirandola, M., Colloca, L., et al. (2020b). What physiotherapists specialized in orthopedic manual therapy know about nocebo-related effects and contextual factors: findings from a national survey. *Front. Psychol.* 11:582174. doi: 10.3389/fpsyg.2020.582174

Rossettini, G., Latini, T. M., Palese, A., Jack, S. M., Ristori, D., Gonzatto, S., et al. (2020c). Determinants of patient satisfaction in outpatient musculoskeletal physiotherapy: a systematic, qualitative meta-summary, and meta-synthesis. *Disabil. Rehabil.* 42, 460–472. doi: 10.1080/09638288.2018.1501102

Rossettini, G., Palese, A., Geri, T., Mirandola, M., Tortella, F., and Testa, M. (2019). The knowledge of contextual factors as triggers of placebo and nocebo effects in patients with musculoskeletal pain: findings from a national survey. *Front. Psychol.* 10:478. doi: 10.3389/fpsyt.2019.00478

Rossettini, G., and Testa, M. (2018). Manual therapy RCTs: should we control placebo in placebo control? *Eur. J. Phys. Rehabil. Med.* 54, 500–501. doi: 10.23736/S1973-9087.17.05024-9

Safiri, S., Kolahi, A. A., Cross, M., Hill, C., Smith, E., Carson-Chahhoud, K., et al. (2021). Prevalence, deaths, and disability-adjusted life years due to musculoskeletal disorders for 195 countries and territories 1990-2017. *Arthritis Rheum.* 73, 702–714. doi: 10.1002/art.41571

Sajid, I. M., Parkunan, A., and Frost, K. (2021). Unintended consequences: quantifying the benefits, iatrogenic harms and downstream cascade costs of musculoskeletal MRI in UK primary care. *BMJ Open Qual.* 10:e001287. doi: 10.1136/bmjoq-2020-001287

Satpute, K., Reid, S., Mitchell, T., Mackay, G., and Hall, T. (2021). Efficacy of mobilization with movement (MWM) for shoulder conditions: a systematic review and meta-analysis. *J. Man. Manip. Ther.* 30, 13–32. doi: 10.1080/10669817.2021.1955181

Schemer, L., Körfer, K., and Glombiewski, J. A. (2019). Evaluation of exposure instructions to pain: should therapist focus on fear reduction or expectation violation? *Cogn. Ther. Res.* 44, 697–708. doi: 10.1007/s10608-019-10070-7

Setchell, J., Costa, N., Abrosimoff, M., and Hodges, P. W. (2021). Exploring why people with back pain use the pain management strategies they do: is research looking in the wrong places? *Pain Med.* 22, 2298–2306. doi: 10.1093/pm/pnab246

Seymour, B., and Mancini, F. (2020). Hierarchical models of pain: inference, information-seeking, and adaptive control. *NeuroImage* 222:117212. doi: 10.1016/j.neuroimage.2020.117212

Sharot, T., Guitart-Masip, M., Korn, C. W., Chowdhury, R., and Dolan, R. J. (2012). How dopamine enhances an optimism bias in humans. *Curr. Biol.* 22, 1477–1481. doi: 10.1016/j.cub.2012.05.053

Sharot, T., Korn, C. W., and Dolan, R. J. (2011). How unrealistic optimism is maintained in the face of reality. *Nat. Neurosci.* 14, 1475–1479. doi: 10.1038/nn.2949

Sharot, T., Riccardi, A. M., Raio, C. M., and Phelps, E. A. (2007). Neural mechanisms mediating optimism bias. *Nature* 450, 102–105. doi: 10.1038/nature06280

Thomaidou, M. A., Peerdeman, K. J., Koppeschaar, M. I., Evers, A. W. M., and Veldhuijzen, D. S. (2021). How negative experience influences the brain: a comprehensive review of the neurobiological underpinnings of nocebo hyperalgesia. *Front. Neurosci.* 15:652552. doi: 10.3389/fnins.2021.652552

Thomson, O. P., and Rossettini, G. (2021). 'Don't focus on the finger, look at the moon'—the importance of contextual factors for clinical practice and research. *Int. J. Osteopath. Med.* 40, 1–3. doi: 10.1016/j.ijosm.2021.06.001

Tonosu, J., Oka, H., Higashikawa, A., Okazaki, H., Tanaka, S., and Matsudaira, K. (2017). The associations between magnetic resonance imaging findings and low back pain: a 10-year longitudinal analysis. *PLoS One* 12:e0188057. doi: 10.1371/journal.pone.0188057

Traeger, A. C., Lee, H., Hubscher, M., Skinner, I. W., Moseley, G. L., Nicholas, M. K., et al. (2019). Effect of intensive patient education vs placebo patient education on outcomes in patients With acute low back pain: a randomized clinical trial. *JAMA Neurol.* 76, 161–169. doi: 10.1001/jamaneurol.2018.3376

Tsokanos, A., Livieratou, E., Billis, E., Tsekoura, M., Tatsios, P., Tsepis, E., et al. (2021). The efficacy of manual therapy in patients with knee osteoarthritis: a systematic review. *Medicina* 57:696. doi: 10.3390/medicina57070696

Turk, D. C., and Wilson, H. D. (2010). Fear of pain as a prognostic factor in chronic pain: conceptual models, assessment, and treatment implications. *Curr. Pain Headache Rep.* 14, 88–95. doi: 10.1007/s11916-010-0094-x

Viceconti, A., Camerone, E. M., Luzzi, D., Pentassuglia, D., Pardini, M., Ristori, D., et al. (2020). Explicit and implicit own's body and space perception in painful musculoskeletal disorders and rheumatic diseases: a systematic scoping review. *Front. Hum. Neurosci.* 14:83. doi: 10.3389/fnhum.2020.00083

Watson, J. A., Ryan, C. G., Cooper, L., Ellington, D., Whittle, R., Lavender, M., et al. (2019). Pain neuroscience education for adults with chronic musculoskeletal pain: a mixed-methods systematic review and meta-analysis. *J. Pain* 20, 1140.e1–1140.e22. doi: 10.1016/j.jpain.2019.02.011

Yunus, M. B. (2007). Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Semin. Arthritis Rheum.* 36, 339–356. doi: 10.1016/j.semarthrit.2006.12.009

Zusman, M. (2013a). Associative memory for movement-evoked chronic back pain and its extinction with musculoskeletal physiotherapy. *Phys. Ther. Rev.* 13, 57–68. doi: 10.1179/174328808X251948

Zusman, M. (2013b). Mechanisms of musculoskeletal physiotherapy. *Phys. Ther. Rev.* 9, 39–49. doi: 10.1179/108331904225003973

Conflict of Interest: GR leads education programs on placebo, nocebo effects and contextual factors in healthcare to under- and post-graduate students along with private CPD courses.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Enhanced Instructed Fear Learning in Delusion-Proneness

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Psychosis is associated with distorted perceptions and deficient bottom-up learning such as classical fear conditioning. This has been interpreted as reflecting imprecise priors in low-level predictive coding systems. Paradoxically, overly strong beliefs, such as overvalued beliefs and delusions, are also present in psychosis-associated states. In line with this, research has suggested that patients with psychosis and associated phenotypes rely more on high-order priors to interpret perceptual input. In this behavioural and fMRI study we studied two types of *fear learning*, i.e., *instructed fear learning* mediated by verbal suggestions about fear contingencies and *classical fear conditioning* mediated by low level associative learning, in delusion proneness—a trait in healthy individuals linked to psychotic disorders. Subjects were shown four faces out of which two were coupled with an aversive stimulation (CS+) while two were not (CS-) in a fear conditioning procedure. Before the conditioning, subjects were informed about the contingencies for two of the faces of each type, while no information was given for the two other faces. We could thereby study the effect of both classical fear conditioning and instructed fear learning. Our main outcome variable was evaluative rating of the faces. Simultaneously, fMRI-measurements were performed to study underlying mechanisms. We postulated that instructed fear learning, measured with evaluative ratings, is stronger in psychosis-related phenotypes, in contrast to classical fear conditioning that has repeatedly been shown to be weaker in these groups. In line with our hypothesis, we observed significantly larger instructed fear learning on a behavioural level in delusion-prone individuals (n = 20) compared to non-delusion-prone subjects (n = 23; n = 20 in fMRI study). Instructed fear learning was associated with a bilateral activation of lateral orbitofrontal cortex that did not differ significantly between groups. However, delusion-prone subjects showed a stronger functional connectivity between right lateral orbitofrontal cortex and regions processing fear and pain. Our results suggest that psychosis-related states are associated with a strong instructed fear learning in addition to previously reported weak classical fear conditioning. Given the similarity between nocebo paradigms and instructed fear learning, our results also have an impact on understanding why nocebo effects differ between individuals.

Keywords: delusion-proneness, instructed fear learning, classical fear conditioning, nocebo effect, fMRI, orbitofrontal cortex, expectations, priors

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INTRODUCTION

Clinical observations of patients with psychosis suggest that these individuals have difficulties to focus on one stimulus at a time, especially in an acute psychotic state. Instead, their attention often quickly shifts between different irrelevant stimuli that they perceive as highly salient. The same individual may simultaneously have a set of delusions that are resistant to change, despite being extremely unlikely or even bizarre to most people. The paradox that poorly reliable low-level processes (such as unstable perceptions) co-exist with overly stable high-level beliefs (such as delusions) is of central interest in psychosis research (Sterzer et al., 2008; Moller et al., 2021). Here, we used a task combining instructed fear learning (Mertens et al., 2018) and classical fear conditioning (Fullana et al., 2016) in order to test whether belief formation induced by instructions is stronger in high delusion-proneness—a trait associated with psychotic disorders that is expressed in healthy subjects (van Os et al., 2009)—compared to controls.

Mirroring the clinical picture of unstable perceptions described above, experimental research supports the idea that low-level processes are dysfunctional in schizophrenia and related endophenotypes (Javitt and Freedman, 2015). A consequence of noisy perceptual processes would be a less efficient bottom-up learning. This has been suggested for psychosis-related states in various simple learning paradigms including associative learning (Corlett et al., 2007; Corlett and Fletcher, 2012), reward learning (Murray et al., 2008; Roiser et al., 2009; Schlagenhauf et al., 2014) and classical fear conditioning (Jensen et al., 2008; Holt et al., 2009, 2012; Romaniuk et al., 2010; Balog et al., 2013; Tuominen et al., 2021). These studies on patients and related endophenotypes have often shown both a smaller learning effect of the true association and an increased learning effect of non-existent associations, in line with the aberrant salience hypothesis (Kapur, 2003).

In contrast to bottom-up learning, recent studies suggest that the effect of high-level top-down learning is stronger in patients with psychosis, and in delusion-prone subjects, compared to healthy controls (Schmack et al., 2013; Teufel et al., 2015). Namely, after being presented with explicit and consciously accessed information, these individuals use high-level priors in a top-down fashion more readily than controls, in order to interpret simple perceptual input. Such beliefs may be characterised as overly strong and associated with the predisposition of delusion formation (Schmack et al., 2013).

Recently, theories such as the predictive coding hypothesis of psychosis, have suggested an association between information processing deviations and psychotic symptoms (Fletcher and Frith, 2009; Adams et al., 2013; Sterzer et al., 2018). Despite this, the reason for why psychosis related states are associated with overly strong beliefs and delusions in parallel with a noisy perceptual system, is not fully understood. It has been proposed that the formation of delusions is a secondary consequence of adaption to aberrant low-level signals (Kapur, 2003). Alternatively, it may suggest a strategy of integrating explicit information in a proactive manner to facilitate interpretation of a noisy environment in psychosis-related states.

Here, we tested whether delusion-prone subjects integrate explicit information given in advance, to a higher degree than controls in a *social fear learning task*. We hypothesised that verbal suggestions about the threat value of specific social stimuli, i.e., instructed fear learning, would have stronger effect on affective learning in delusion-prone participants than in controls, in sharp contrast to results from previously performed low-level classical fear conditioning studies on psychosis patients (Jensen et al., 2008; Holt et al., 2009, 2012; Romaniuk et al., 2010; Tuominen et al., 2021), and schizotypal individuals (Balog et al., 2013), which have suggested a weaker learning in psychosis associated phenotypes.

In order to test our hypothesis we showed our subjects four faces out of which two were coupled with aversive electric stimulation (CS+) while two were not (CS-) in a fear conditioning procedure. Ahead of the fear conditioning procedure subjects were informed about the contingencies for two of the faces of each type, while no information was given for the two other faces. We could thereby study the effect of both classical fear conditioning and instructed fear learning. Our main outcome measure consisted of explicit evaluation of the presented faces (Petrovic et al., 2008), and involves, therefore, conscious beliefs about the context. We also measured autonomic responses (i.e., skin conductance response) as an index of learning.

Our study also translates to the nocebo effect, that may be defined as the role of negative expectations from suggestions, associative learning and context in producing an aversive outcome (Barsky et al., 2002; Faasse et al., 2019; Colloca and Barsky, 2020).

It has been suggested that the lateral orbitofrontal cortex (lOfc) is a key structure involved in the processing of higher order expectations that influence emotional processing and experience (Petrovic et al., 2010). In line with this, previous functional imaging studies using tasks related to the present, such as instructed fear learning (Tabbert et al., 2011; Atlas et al., 2016) and nocebo responses (Kong et al., 2008; Asghar et al., 2015; Ellerbrock et al., 2015; Freeman et al., 2015; Schienle et al., 2018), have shown increased activation in lOfc and related regions. Other studies where a change in expectations underlies a change in emotional experience including placebo responses (Petrovic et al., 2002, 2005, 2010; Atlas and Wager, 2014; Wager and Atlas, 2015) and cognitive reappraisal (Eippert et al., 2007; Wager et al., 2008; Kanske et al., 2011; Golkar et al., 2012) have also shown the involvement of lOfc. We therefore hypothesised that (1) the behavioural results would be associated with an larger activation in lOfc for instructed stimuli than for non-instructed stimuli for all subjects, and (2) that this effect would be stronger in high delusion proneness vs. low delusion proneness as well as (3) have a differential interaction with regions involved in pain and fear processing.

MATERIALS AND METHODS

Participants

We screened 925 male individuals aged 18 to 35 years (mean = 24.98 years, *SD* = 0.161) for delusion-proneness using

PDI (*Peters' Delusion Inventory*-21 items) (Peters et al., 2004). For each PDI item that is endorsed, three dimensions are rated by the participant on a 5-point Likert scale (1–5) in order to assess the level of conviction, distress, and preoccupation related to the given item (i.e., conviction, distress, and preoccupation scores, respectively). The subjects also completed *ASRS* (*World Health Organization Adult ADHD Self-Report Scale*) (Kessler et al., 2005), and *AQ* (*Autism Spectrum Quotient questionnaire*) (Baron-Cohen et al., 2001) to control for sub-clinical tendencies of ADHD (Attention and Hyperactivity disorder) and ASD (Autism Spectrum disorder) (Louzolo et al., 2017). Participants were recruited through social media and filled in online versions of the questionnaires. It was stressed twice that they had to be healthy and without any psychiatric history. Upon submission of their contact details and after giving their consent, participants received a link to the questionnaires and an automatically generated unique ID-code that they used when filling in the questionnaires.

Based on the questionnaire results we selected 51 right-handed male individuals aged 18–35 years; out of which 26 were in the *low delusion proneness group* (*lDP*; PDI scores ranging from 2 to 6), and 25 in the *high delusion proneness group* (*hDP*; PDI scores ranging from 10 to 17). Due to technical issues during the scanning procedures (movement and technical problems with the stimulation device), 8 participants had to be removed from both behavioural and imaging analyses. A total of 43 participants (*lDP*: $n = 23$, PDI mean = 3.78, $SD = 1.38$, and *hDP*: $n = 20$, PDI mean = 12.85, $SD = 1.84$) thus underwent a successful *instructed fear learning* and *classical fear conditioning* procedure in a 3T GE MR scanner and contributed to the behavioural results. Out of those 43 participants, another 3 were removed from the imaging analyses due to large movement artefacts, resulting in a total of 20 participants in each group contributing to the fMRI results (*lDP*: PDI mean = 3.85 and $SD = 1.37$; *hDP*: PDI mean = 12.85 and $SD = 1.84$). The size of the two groups were comparable to previous fMRI studies on conditioning and psychosis related states (Jensen et al., 2008; Holt et al., 2009, 2012; Romaniuk et al., 2010; Balog et al., 2013).

All participants gave once again their informed consent before the experiment, and were paid 450 SEK for their participation. The study was approved by the regional ethical board of Stockholm.[1]

Stimuli and Apparatus

In the *classical fear conditioning paradigm*, the unconditioned stimulus (*UCS*) consisted of a mildly aversive electric stimulation. Prior to the start of the experiment a pair of Ag/AgCl electrodes (27 × 36 mm) was attached to participants' left forearm with electrode gel and used to deliver electrical stimulation. Before lying down in the scanner, participants went through a standard work-up procedure, during which stimulation intensity was gradually increased until participants judged it as unpleasant, but not intolerably painful. Stimulus delivery was controlled by a monopolar DC-pulse electric stimulation (STM200; Biopac Systems Inc., Santa Barbara, United States[2]). Each electrical stimulation lasted for 200 ms, co-terminating the presentation of the reinforced CS+ stimuli. The experiment was presented using Presentation[3] and was displayed on a screen inside the scanner. Participants controlled the computer cursor through the use of a trackball device.

The paradigm consisted of a social learning task that started with an *instruction phase* that was followed by a *fear acquisition phase*, and ended with an *extinction phase* (**Figure 1A**). The conditioned stimuli (CS) consisted of four Caucasian male faces (selected from a picture set used in Johansson et al., 2013) displaying a neutral facial expression (2 CS+ and 2 CS−) and randomised between participants. We used faces, as in several of our previous studies (e.g., Olsson et al., 2005; Petrovic et al., 2008), since they are more salient than abstract figures and we wanted to measure the likability of the different individual faces. Finally, social stimuli also contain more delusion relevant information (as exemplified in paranoia) than many other stimuli. For illustration purposes, we used silhouettes on the timeline sketch **Figure 1**.

In the instruction phase, two of the faces (instructed CS+ and CS-; *iCS+*/*iCS-*) were coupled with information about their contingencies with the UCS (including a fabricated short description about their personality and the risk of being associated with a "shock"). The two other CS faces (non-instructed CS+ and CS-; niCS+/niCS-) contained no information about their contingencies with the UCS. The phrasing used in the instructions is presented in **Figure 1B** (original text in Swedish).

In the acquisition and extinction phases each CS was displayed 12 times for 5 s, and the jittered inter-trial interval was 11.5 ± 2 s. The CS+ were coupled with UCS with a 50% contingency in the acquisition phase and there was no UCS in the extinction phase.

Skin Conductance Response

Skin conductance was recorded during the whole session. Two Ag/AgCl electrodes (27 × 36 mm) were attached to the distal phalange of the first and third fingers of participants' left hand. The skin conductance response (SCR) was amplified and recorded using an fMRI compatible BIOPAC Systems (Santa Barbara, CA). Data were analysed using AcqKnowledge software (BIOPAC Systems). Processing of the raw data consisted of low-pass (1 Hz) and high-pass (0.05 Hz) filtering. For each CS, the conditioned SCR amplitude was quantified as the peak-to-peak amplitude difference to the largest response, in the 0.5–4.5 s latency window after the stimulus onset. The SCRs were transformed into microSiemens (μS), and responses below 0.02 μS were encoded as zero. A square-root transformation was applied to raw SCRs to normalise the data distribution. Participants who displayed a SCR to less than 20% of each of the two CS+ were considered non-responders and excluded from SCR analyses. This resulted in 18 *lDP* and 20 *hDP* participants that were used in the SCR analysis.

[1] www.epn.se

[2] www.biopac.com

[3] www.neurobs.com, version 9.13

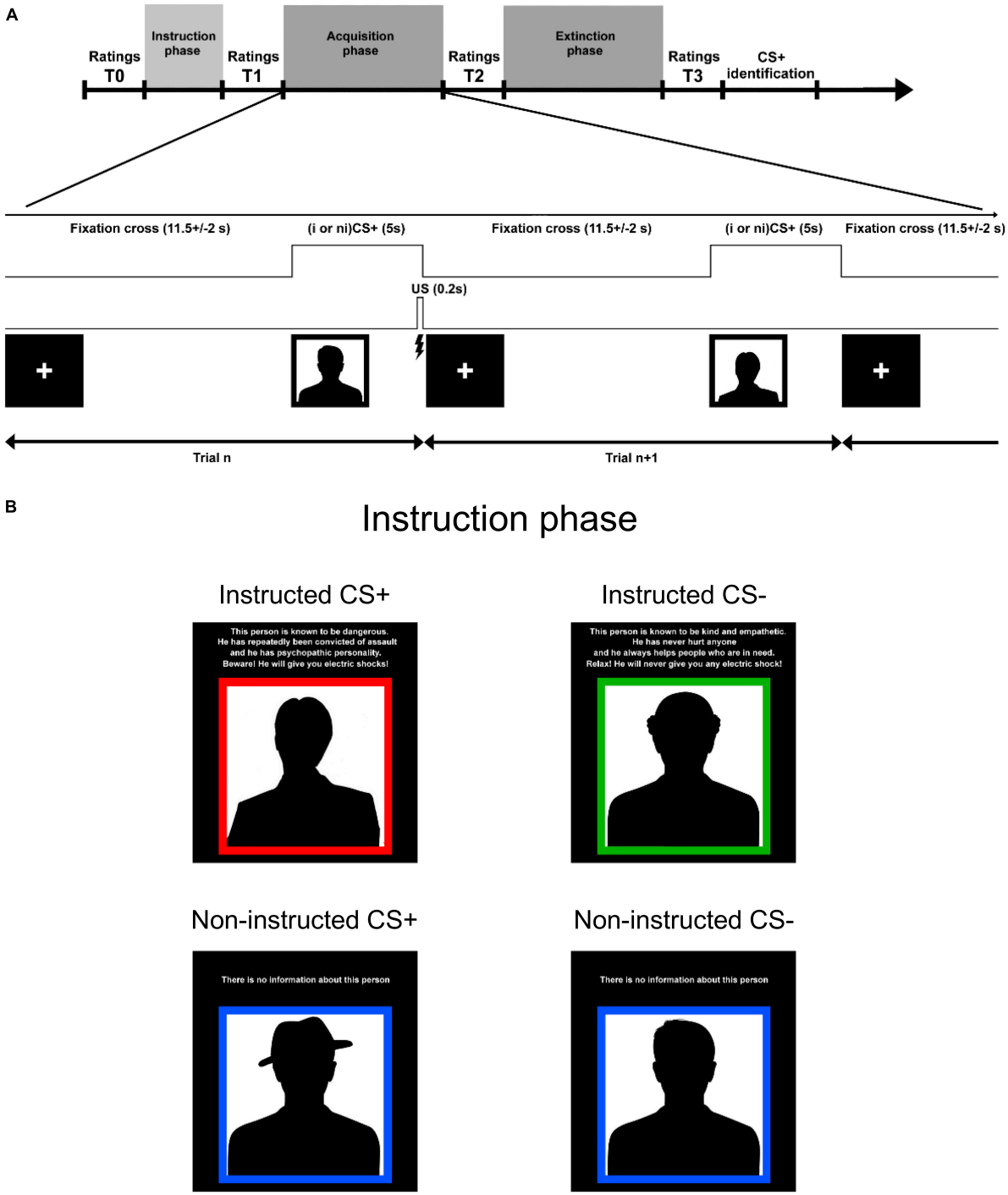

FIGURE 1 | Subjects and experimental design. **(A)** Timeline of paradigm. In the *acquisition and extinction phases* each CS was displayed 12 times for 5 s, and the jittered inter-trial interval was 11.5 ± 2 s. The CS+ were coupled with UCS (mildly painful electric stimulation) with a 50% contingency in the acquisition phase and there was no UCS in the extinction phase. Participants were asked to rate how friendly each CS was experienced, using a visual analogue scale (−100 to 100). In order to estimate learning we calculated the difference between CS- rating and CS+ rating for each CS-pair (instructed and non-instructed). This difference score is referred to as *"affective learning index"'* and the main outcome value in the study. We analysed three *affective learning indices:* (1) T1: after instruction learning, (2) T2: after acquisition, and (3) T3: after extinction. All ratings were normalized in regards to T0. **(B)** In the *instruction phase,* two of the faces (instructed CS+ and CS-; iCS+/iCS-) were coupled with information about their contingencies with the UCS that included a fabricated short description about their personality and the risk of being associated with an aversive stimulation. The two other CS faces (non-instructed CS+ and CS-; niCS+/niCS-) contained no information about their contingencies with the UCS. Instructions were presented twice (followed by ratings–T1' and T1) in order to increase the effect of information.

Behavioural Analyses

Since our focus was on explicit learning we measured *evaluative fear ratings* (Petrovic et al., 2008) for the presented faces. On several occasions throughout the experiment (before instructions, during instructions, before acquisition, before and after extinction) participants had to rate how friendly each CS looked, using a visual analogue scale with "the least sympathetic person you can imagine" stated on the left anchor, and "the most sympathetic person you can imagine" on the right anchor (originally in Swedish). The X-axis coordinates of the scale were converted into numbers, from -100 (left anchor) to +100 (right anchor) and used as the rating scores. The first rating of each CS was referred to as the baseline rating and used to normalise the subsequent ratings for a given CS. The normalised scores were computed for each CS, by subtracting the first ratings from the following ratings. In order to estimate learning in our paradigm we calculated the difference between CS- rating and CS+ rating, in each pair (instructed and non-instructed). This difference score is referred to as "*affective learning index*" and represents the main outcome value in the study as we were interested in explicit learning. Instructions were presented twice (followed by ratings: T1' and T1) in order to increase explicit learning (**Figure 1A**). Out of these two ratings we used the one following the second instruction presentation (T1) in subsequent analyses as it represented the total effect of the instruction manipulation. This resulted in three *affective learning indices*: (1) T1-after instruction learning, (2) T2-after acquisition, and (3) T3-after extinction (**Figure 1A**). During the debriefing session after the experiment, participants were also asked to rate how strongly they felt they had been influenced by instructions and aversive stimulation, respectively (0: no influence at all, 10: extremely high influence).

We used linear mixed models to analyse the effect of the experimental manipulations on the main behavioural outcome variable, i.e., the *affective learning index*. A random effect of subject was modelled, accounting for the repeated measures. The explanatory variables used were subject group (*hDP* vs. *lDP*), the stimulus type (*instructed* vs. *non-instructed*), the phase of the trial (*T1*, *T2*, or *T3*) and the interactions between these variables. Analysis were conducted using the software R 3.2.3 (R Core Team, 2015) using packages lme4 (Bates et al., 2015) and lmerTest (Kuznetsova et al., 2017).

Two specific hypotheses were tested for the behavioural part of the study:

-***Main hypothesis*:** As psychosis proneness has been associated with stronger higher order learning and use of high-level priors (Schmack et al., 2013; Teufel et al., 2015), instructions should have a greater influence on fear learning in the delusion-prone subjects than in the normal population. We therefore hypothesised that *hDP* would show larger instructed *affective learning index* in all phases compared to *lDP*.

-***Secondary hypothesis*:** In line with previous studies on classical fear conditioning (Jensen et al., 2008; Holt et al., 2009, 2012; Romaniuk et al., 2010; Balog et al., 2013; Tuominen et al., 2021) we hypothesised that delusion-prone individuals would display an attenuated fear learning. This would be reflected by significantly smaller non-instructed *affective learning index* following acquisition in *hDP* as compared to *lDP*.

In summary, on a behavioural level we expected increased effect of instructions on fear learning (instructed fear learning) but decreased effects of classical fear conditioning related to delusion proneness.

Functional Imaging Analysis

We hypothesised that lateral orbitofrontal cortex (lOfc) would have a decisive role in the increase of fear learning due to instructions—based on its previously shown involvement in processes where expectations have been experimentally manipulated including instructed fear learning (Tabbert et al., 2011; Atlas et al., 2016), nocebo responses (Kong et al., 2008; Asghar et al., 2015; Ellerbrock et al., 2015; Freeman et al., 2015; Schienle et al., 2018), placebo responses (Petrovic et al., 2002, 2005, 2010; Atlas and Wager, 2014; Wager and Atlas, 2015) and cognitive reappraisal (Eippert et al., 2007; Wager et al., 2008; Kanske et al., 2011; Golkar et al., 2012). Data from these studies suggests that the right lOfc, especially, is involved in placebo (Petrovic et al., 2002, 2005, 2010) and cognitive reappraisal processes (Wager et al., 2008). We therefore examined the acquisition phase results with a primary focus on effects in lOfc. Further, we posited that any behavioural effects in relation to instructed fear learning would be linked to functional or effective connectivity effects in the right lOfc as previously observed in cognitive reappraisal (Wager et al., 2008).

Apart from the general hypothesis about the involvement of lOfc in instruction effects, we more specifically hypothesised that *hDP* (compared to *lDP*) would exhibit (i) increased lOfc responses to instructed fear learning, and (ii) increased effective connectivity between the lOfc, and pain and fear regions, as an underlying mechanism associated with a stronger effect of instructions on *affective learning index*.

Due to limited space, we constrained the present functional imaging analysis to the acquisition phase.

Image Acquisition

Participants were scanned in a 3T MR General Electric scanner with a 32-channel head coil. A T1-weighted structural image was acquired before the beginning of the paradigm. Functional scans were obtained using a gradient echo sequence T2*-weighted echo-planar imaging (EPI) scan [TR = 2.334 s, TE = 30 ms, flip angle = 90 degrees, 49 axial slices in ascending order (thickness = 3 mm) and a field of view (FOV) = 22 cm, matrix size = 72 × 72 × 3 mm]. The first four scans were defined as dummy scans and discarded from the analysis. Functional image acquisition comprised 2 runs of 245 volumes each (acquisition and extinction phases, respectively), with a break of approximately 4–5 min between them.

Imaging Data Analysis

Data pre-processing and analyses were performed using a default strategy in the SPM8 software package (Statistical parametric mapping, Welcome Department of Cognitive Neurology,

London, United Kingdom[4]). For each participant, individual images were first slice-time corrected and realigned to the first volume to correct for head movement. The T1-weighted image was then co-registered with the mean EPI image, segmented and normalised to the Montréal Neurological Institute standard brain (MNI). Then, functional images were spatially smoothed with an 8-mm full width at half maximum (FWHM) isotropic Gaussian kernel, and a temporal high-pass filter with a cut-off of 128 s was used to remove low-frequency drifts.

All analysis in the present study focused on the acquisition phase. A general linear model (GLM) comprising nine regressors was defined at the first-level analysis; one regressor per CS type (iCS+, iCS−, niCS+, and niCS−) with each onset modelled as a 5-s event, and one regressor for the UCS presentation. In addition, these four regressors (excluding UCS) were also parametrically modulated with a linearly changing function to capture activity changes over time. All nine regressors were convolved with the canonical haemodynamic response function and entered into the GLM as implemented in SPM. Motion regressors were also included in the model. The two phases of the experiment (acquisition and extinction) were modelled and analysed separately.

We first analysed main effects of fear (CS+ vs. CS−). Similarly, we examined the main effects of pain. We also analysed possible differences between *hDP* and *lDP* in a 2nd level analysis of these activations using a ROI approach in order to increase the sensitivity. A small volume correction in a spherical ROI (6 mm radius) was then applied in the contrasts between the two groups. The ROIs were centred over the maximally activated voxels in caudal ACC (cACC) and anterior insula in the main effect of fear and in posterior insula in the main effect of pain. The results were assessed at $p < 0.05$, family-wise error (FWE) corrected for multiple comparisons.

To test our main hypotheses regarding the functional imaging results, we first conducted a GLM group analysis to compare the effect of instruction in the lOfc for *hDP* to *lDP* participants. The results were assessed at $p < 0.05$, family-wise error (FWE) corrected for multiple comparisons. Given our *a priori* hypothesis, we used small-volume correction (SVC) for multiple comparisons within an anatomical lOfc ROI defined using the pick atlas in the SPM, in addition to an exploratory whole brain analysis.

We also examined effective connectivity using a psychophysiological interaction (PPI) analysis in SPM (Friston et al., 1997). This analysis identifies context-induced changes in the strength of connectivity between brain regions, as measured by a change in the magnitude of the linear regression slope that relates their underlying neuronal responses. Significant PPI results indicate that the contribution of one area to another changes with the experimental context (Friston et al., 1997). We assessed connectivity changes between the right lOfc and the rest of the brain. The lOfc seed region was defined using a sphere with a radius of 6 mm centred on the right lOfc group maximum from the GLM analyses of instruction-related activity. For each participant, the seed was adjusted to centre on the individual peak response within the group seed sphere, and the fMRI time series was extracted and deconvolved to generate the neuronal signal. We then conducted two PPI analyses using the contrast (i) instructed vs. non-instructed [(iCS+ and iCS-) vs. (niCS+ and niCS-)] and (ii) the interaction effect (fear learning in instructed vs. fear learning in non-instructed stimuli; [(iCS+ vs. iCS-) vs. (niCS+ vs. niCS-)]) as the psychological factor. For each participant, a GLM was conducted including three regressors representing the time course of the seed region (the physiological factor), the psychological factor and their product (the PPI). The parameter estimates for the PPI regressor from each participant were then entered into a second-level analysis, and we again assessed the results at pFWE < 0.05.

We conducted SVC in several ROIs for the PPI analyses. First, we used the group-level main effect of fear learning (CS+ vs. CS-) to identify cACC and anterior insula (**Supplementary Table 1**). Second, we examined any group differences in low-level sensory processing areas, in line with previous findings of altered effective connectivity between the lOfc and the visual cortex in a visual expectation manipulation task related to delusion proneness (Schmack et al., 2013). To obtain a low-level sensory region, we used the group-level main effect pain (mildly painful electric stimulation) to identify the posterior insular cortex. This region has been the most consistently reported brain activation site across all pain conditions and is considered a nociceptive input area (Tanasescu et al., 2016).

Finally, we assessed whether there was a significant correlation between conviction scores and the functional connectivity between the lOfc seed-region and low-level sensory regions (i.e., defined as posterior insular in the present study) to investigate whether we could reproduce the findings by Schmack et al. (2013). On a more exploratory level, we analysed whether such a correlation was also present for the total PDI-score, the normalised conviction score as well as the two other sub-scores in PDI (distress score and preoccupation scores).

RESULTS

In the present study, we show behavioural results that either involve all phases together or the instruction and acquisition phase separately as well as the fMRI-results from the acquisition phase in order to study our predefined hypotheses. The study results have previously been presented in bioRxiv (Louzolo et al., 2019). Behavioural and fMRI results specifically focusing on extinction phase will be presented elsewhere.

BEHAVIOURAL RESULTS

Ratings

Baseline Ratings

A baseline rating (T0) was collected for each face before any information was presented and it was used for normalisation of subsequent ratings (**Figure 1A**). We tested whether groups (*hDP* and *lDP*) differed on the averaged absolute value of the initial baseline ratings, and found no significant difference ($t = 0.092$,

[4]http://www.fil.ion.ucl.ac.uk/spm

$p = 0.927$, independent two-sample t-test). This result suggests that any possible group differences associated to instructions or conditioning cannot be explained simply by a difference between the groups in their general rating strategy.

Affective Learning Index

The main behavioural outcome measure of the study was the *affective learning index*, which reflects how subjects change the ratings given to CS- vs. CS+ stimuli after conditioning or instructions.

As a general control of the paradigm, effects of instructed fear learning and classical fear condition were first analysed independently in the two groups (lDP and hDP). Evaluative fear learning measured with *affective learning index* was observed after instructions (T1 vs. T0) for instructed stimuli and after acquisition phase (T2 vs. T1) for both instructed (threshold level) and non-instructed stimuli independently for both lDP and hDP. Thus, learning as a consequence of instructed fear learning and classical fear conditioning were accomplished for both groups independently.

A mixed linear model was used to study the effects of subject group (*hDP* vs. *lDP*), stimulus type (*instructed* vs. *non-instructed*), phase of the trial (*T1*, *T2*, or *T3*) and the interactions between these variables on the *affective learning index*. We found *significant effects of group* ($p = 0.029$), *stimulus type* ($p < 0.00001$), and *phase* ($p < 0.00001$). The three-way interaction between these variables as well as the interaction between group and phase were not significant ($p = 0.750$ and $p = 0.167$, respectively). However, there was an *almost significant stimulus type × group interaction* ($p = 0.057$) and a *significant stimulus type × phase interaction* ($p = 0.00003$). This means that the effect of instructions depends on the group (according to our main hypothesis) and also on the phase. Since there were interaction effects with the stimulus type, in order to study the effects of group and phase, we divided the data into two sets, corresponding to the instructed and non-instructed stimuli.

For the *instructed stimuli* (**Figures 2A,B**), there was a significant effect of group ($p = 0.044$), but not of phase ($p = 0.109$). The *affective learning index* was higher for the *hDP* (mean = 125.77, *SD* = 93.06) than for the *lDP* (mean = 74.50, *SD* = 67.98) thus confirming our main hypothesis. We also extended the model to include the interaction between group and phase. The interaction was not significant ($p = 0.26$), indicating that the group effect is present in all phases. The *affective learning index* was significantly larger than zero for *lDP* ($p = 0.0002$). Thus, for the instructed stimuli, the *affective learning index* was larger than zero for all groups and phases, confirming that there was an effect of instructions in both groups, that persisted for all phases.

For the *non-instructed stimuli* (**Figures 2C,D**), there was a significant effect of phase ($p < 0.00001$), but not of group ($p = 0.105$). The *affective learning index* was not different from 0 at phase T1. This is expected since, for non-instructed stimuli, at T1 the subjects had no more information than at T0. At phases T2 and T3 the *affective learning index* was significantly larger than 0 ($p < 0.00001$), indicating that the classical fear conditioning worked and the subjects learned the contingencies.

To test the *secondary hypothesis*, the model on the non-instructed stimuli was extended to include the interaction between group and phase. The interaction was almost significant ($p = 0.056$). Hence, to be able to interpret the effects of group, we analysed the data for each phase separately. However, there was no significant effect of group for T1 and T2 ($p = 0.653$ and $p = 0.235$, respectively) and only an effect for T3 ($p = 0.025$). Namely, after the acquisition phase (T2) for the non-instructed stimuli there was no difference in *affective learning index* between the two groups of subjects. The effect of extinction (associated with ratings at T3) is further elaborated elsewhere.

Skin Conductance

A one-tailed t-test on the differential SCR (SCR-CS+ vs. SCR-CS-) in the acquisition phase for all subjects together, was significantly different from zero (mean = 0.0151, *SD* = 0.0271; $t = 3.424$, $df = 37$, $p = 0.001$ one-tailed) suggesting a significant conditioning. This was also the case for each group, when analysed separately (*lDP* mean = 0.0126 μS, *SD* = 0.0248, one-sample t-test $t = 2.145$, $df = 17$, $p = 0.024$ one-tailed—*hDP* mean = 0.0174 μS, *SD* = 0.0296, one-sample t-test $t = 2.628$, $df = 19$, $p = 0.009$ one-tailed). There was no group difference (independent two-sample t-test $t = -0.741$, $df = 73$, $p = 0.461$).

The differential SCR was mainly driven by the iCS-pair as suggested by a significant difference between the instructed and non-instructed condition in *lDP* (instructed mean = 0.0266 μS, *SD* = 0.036, non-instructed mean = −0.015 μS, *SD* = 0.029; paired t-test $t = 2.780$, $df = 17$, $p = 0.014$) and in *hDP* (instructed mean = 0.0251 μS, *SD* = 0.031, non-instructed mean = 0.010 μS, *SD* = 0.036; paired t-test $t = 2.188$, $df = 19$, $p = 0.042$). However, there was no significant interaction between the groups (*hDP* or *lDP*) and condition (instructed or non-instructed).

Overall, it should be noted that the SCR data recorded in the fMRI scanner was noisy. We only used participants who showed a SCR to at least 20% of the presentations of each CS (hence, considered as responders; $n = 38$). However, many of them were characterised by a low reactivity.

Effects of Peters' Delusion Inventory Sub-Scores on Ratings

In an exploratory analysis, we investigated whether PDI scores and their components (distress, preoccupation and conviction) were related to the different ratings for instructed stimuli in *lDP* and *hDP*, respectively. In *hDP* we observed a significant correlation between distress scores and the overall instructed *affective learning index* ($r = 0.555$, $p = 0.011$ Pearson correlation tests) (**Figure 3A**), as well as the instructed *affective learning index* in T1 (after instructions; $r = 0.614$, $p = 0.004$) and T2 (after acquisition; $r = 0.518$, $p = 0.019$). While similar correlations were observed for preoccupation and conviction scores, they did not reach significance. No significant correlations between distress scores and a*ffective learning index* were found for *lDP*.

Since distress seemed to be an important variable in relation to effects of instructions in our fear learning paradigm, we explored it further. Only analysing the total sum of each of these sub-scores without controlling for the Yes/No score can be somewhat

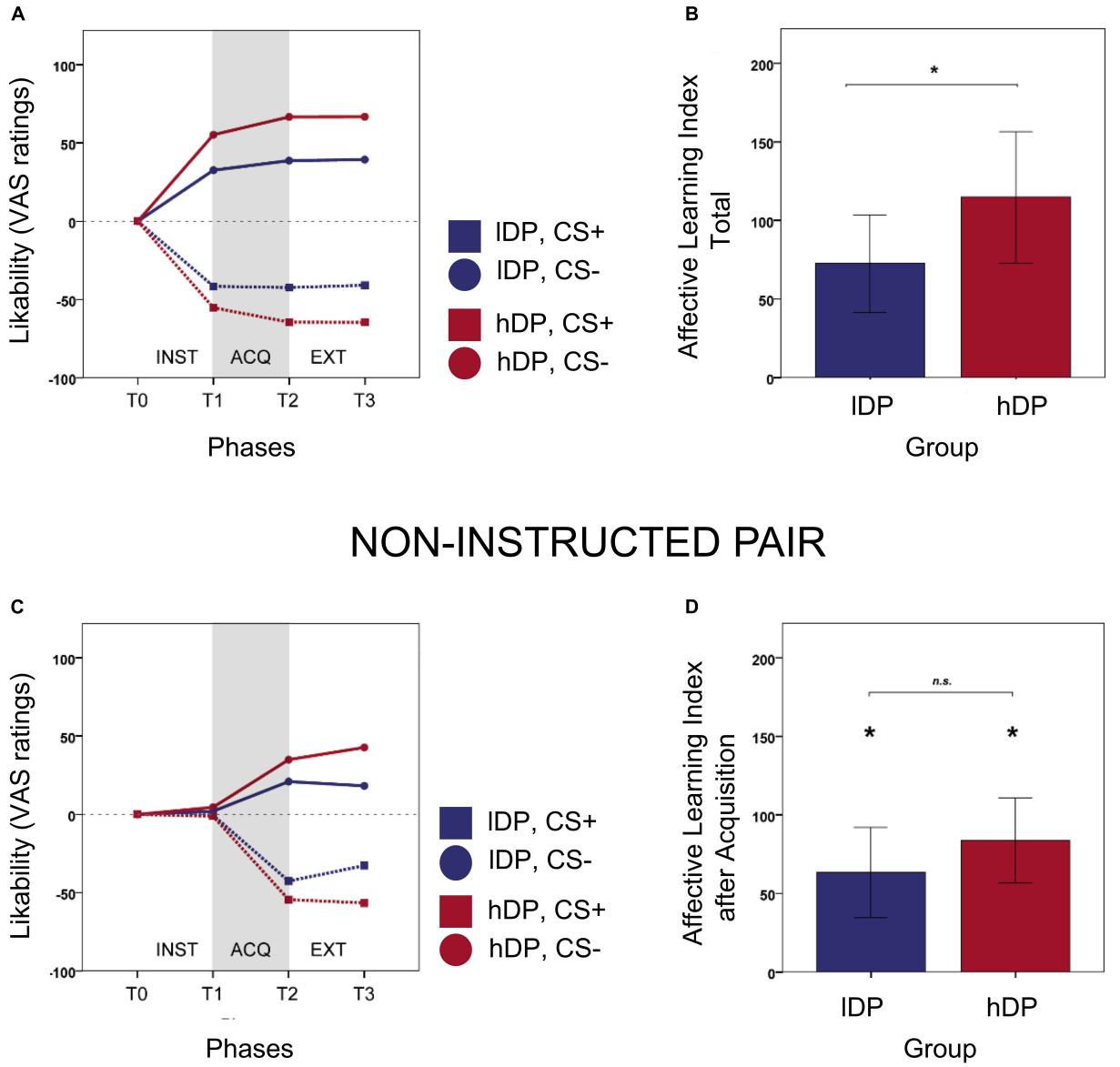

FIGURE 2 | Behavioural results of instructed and non-instructed learning. **(A)** Timeline of likability ratings for instructed CS-stimuli over the three phases. **(B)** In line with our hypothesis the *affective learning index* was higher for the *hDP* (mean = 125.77, *SD* = 93.06) than for the *IDP* (mean = 74.50, *SD* = 67.98) for the instructed CS-stimuli and we found a significant group effect ($p = 0.044$) over all phases thus confirming our main hypothesis. **(C)** Timeline of likability ratings for non-instructed CS-stimuli over the three phrases. **(D)** For the non-instructed stimuli, there was no significant effect of group ($p = 0.105$). The average non-instructed *affective learning index* after acquisition was somewhat larger (albeit non-significant) in the delusion-prone group than in the control group (*hDP*: mean = 89.45, *SD* = 81.52; *IDP*: mean = 63.00, *SD* = 62.16). As suggested from the time-line the largest part of this non-significant difference was dependent on T3 (ratings after extinction). At phases T2 the affective learning index was significantly larger than 0 ($p < 0.00001$) for each group, indicating that the fear conditioning worked and the subjects learned the contingencies. Error bars: 2 S.E.

misleading, as it makes it difficult to differentiate between people who would score high on distress because they have a few delusion-like experiences that are extremely distressing, from people who score as high on distress because they have many delusion-like experiences that are not distressing at all. Normalising to the number of endorsed items (number of "yes" answers, or the so-called "total PDI score") provides a better estimate of how distressed participants are, unrelated to whether there is one or several delusion-like experiences. We therefore also compared *the two groups* in terms of normalised sub-scores

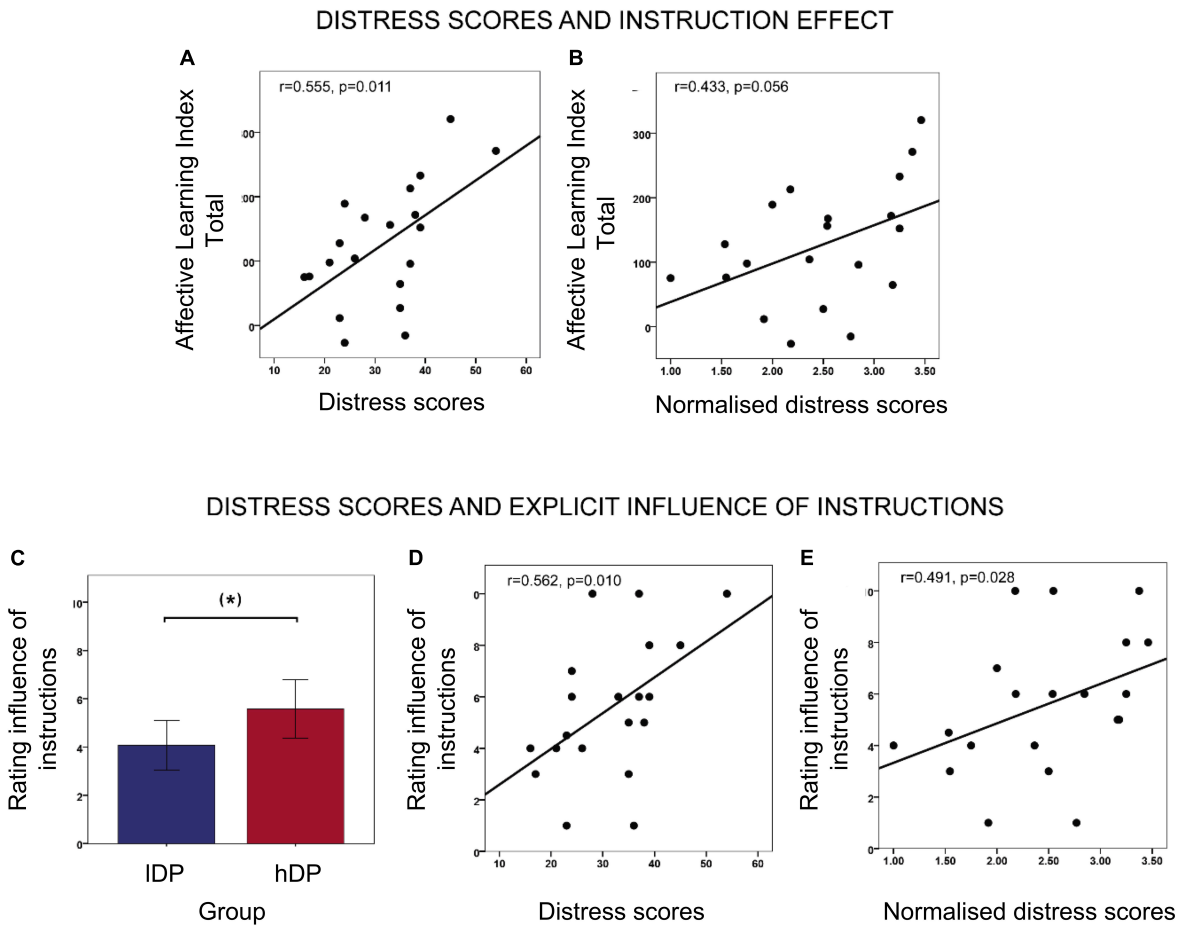

FIGURE 3 | Relation between instruction effects and delusional distress. **(A)** Correlations between *distress scores* and overall instructed *affective learning index* (averaged over three phases) in *hDP* (r = 0.555, p = 0.011, Pearson correlation tests). **(B)** Correlations between normalised *distress scores* and overall instructed *affective learning index* (averaged over three phases) in *hDP* (r = 0.433, p = 0.056, Pearson correlation tests). **(C)** Rating of the explicit influence of instructions in *lDP* and *hDP*. The group difference is on the border of significance $t = -1.910$, p = 0.063, df = 40 (independent two-sample t-test). **(D)** Correlation between distress scores and explicit rating of instruction influence in *hDP* (r = 0.562, p = 0.010, Pearson correlation tests). **(E)** Correlation between normalised distress scores and explicit rating of instruction influence in in *hDP* (r = 0.491, p = 0.028, Pearson correlation tests). Error bars: 2 S.E.

and found that the average normalised distress score in *hDP* was significantly larger than in *lDP* (*hDP* = 2.47, *lDP* = 1.95; independent sample t-test $t = -2.593$, p = 0.013, df = 41). Moreover, in *hDP*, the normalised distress score also correlated positively with *affective learning index* after the instruction phases (r = 0.527, p = 0.017, Pearson correlation tests) (**Figure 3B**). This correlation only reached a trend level after the acquisition phase (T2), as well as when considering the three phases together (r = 0.400, p = 0.080; r = 338, p = 0.091, respectively—Pearson correlation tests). No significant correlations between normalised distress scores and a*ffective learning index* were found for *lDP*.

Post-experiment Ratings

After the experiment, participants were asked to explicitly rate the influence of instructions, and pain stimuli (respectively) from 0 to 10. An independent sample t-test revealed a trend towards a larger influence of instructions reported in the *hDP*, compared to the *lDP* (mean *lDP* = 4.07, SD = 2.42, mean *hDP* = 5.58, SD = 2.69; $t = -1.910$, p = 0.063, df = 40 two-tailed) (**Figure 3C**), while there was no group difference in terms of pain influence.

Interestingly, in the delusion-prone group the explicit rating of instruction influence was also significantly correlated to the distress sub-score (r = 0.562, p = 0.01 Pearson correlation tests) (**Figure 3D**) and with the normalised distress score (r = 0.491, p = 0.028 Pearson correlation tests) (**Figure 3E**).

FUNCTIONAL IMAGING RESULTS

A simultaneous fMRI measurement showed that the main effect of conditioning (i.e., all CS+ vs. all CS- in the acquisition phase) led to activations in brain areas that are consistently reported in studies of classical fear conditioning (Fullana et al., 2016). These included anterior insula, caudal anterior cingulate cortex and thalamus bilaterally as well as brainstem (**Figure 4A** and **Supplementary Table 1**). However, no significant differences

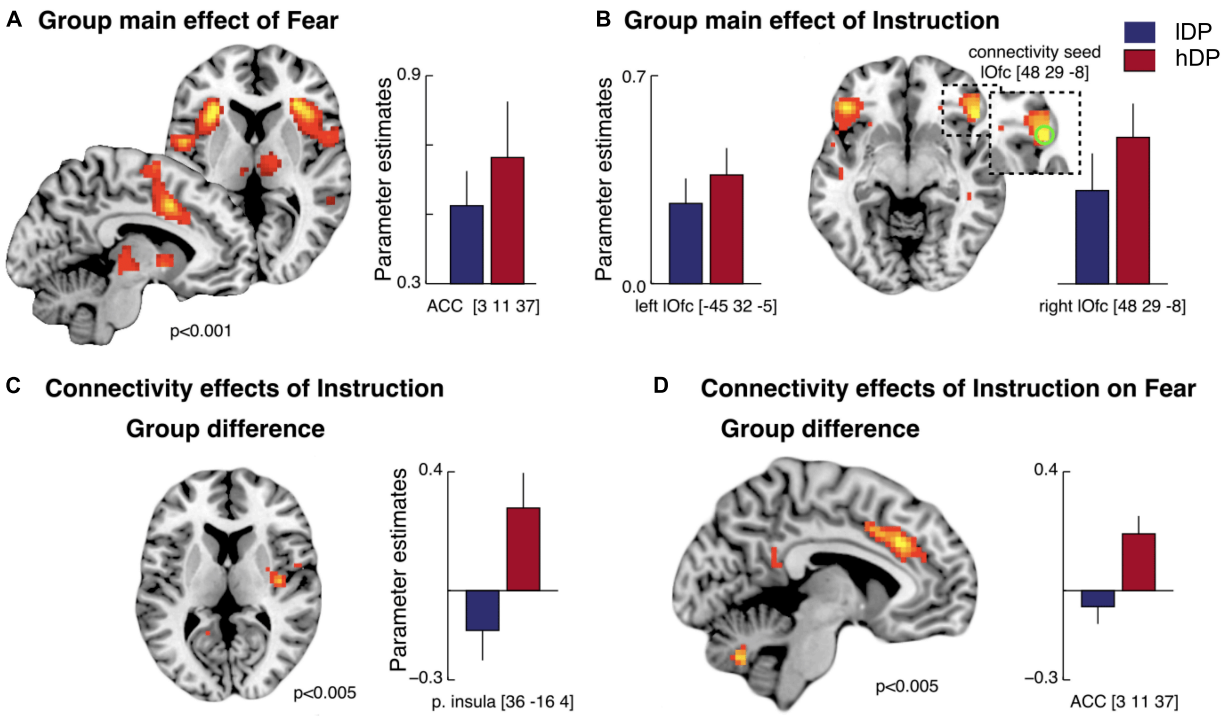

FIGURE 4 | Brain activity related to the effects of conditioning and instructions—BOLD response **(A,B)** and PPI analyses **(C,D)**. **(A)** Main effect of fear (*CS+ vs. CS-*): an activation in caudal anterior cingulate cortex (cACC), bilateral anterior insula, premotor/dorsolateral prefrontal cortex (dlPFC), right temporo-parietal junction (rTPJ) was observed (**Supplementary Table 1**). The activation pattern was similar for instructed (iCS+ vs. iCS-) and non-instructed (niCS+ vs. niCS-) stimuli. No group difference was observed. **(B)** Main effect of instructions: bilateral activations in lateral orbitofrontal cortex (lOfc) (ROI analysis and whole brain analysis) and an activation in dlPFC (whole brain analysis) were observed (**Supplementary Table 2**). This effect was mainly driven by the *hDP*, and only this group showed significant activations in lOfc (bilateraly). **(C)** A psychophysiological interaction (PPI) analysis on the effect of instructions (vs. non-instructed trials): An increased connectivity between the right lOfc and functionally defined low-level pain processing areas (i.e., right posterior insula) (Z = 3.29, pFWE = 0.004) was observed specifically in *hDP* (i.e., compared to in *lDP*). **(D)** A PPI-analysis on the effects of instruction on fear processing: A larger connectivity between lOfc and the cACC (overlapping with fear related activation) was observed in *hDP* than in *lDP* (Z = 2.96, pFWE = 0.012). Error bars: S.E.

were observed between the groups in the regions of interest (ROI) analysis for (CS+ vs. CS-).

In line with our hypothesis, we observed a main effect of instructions [(iCS+ + iCS-) vs. (niCS+ + niCS-)] in lateral orbitofrontal cortex (lOfc) for all subjects (**Figure 4B** and **Supplementary Table 2**)—driven mainly by *hDP* subjects (only this group showed significant activations in lOfc; **Supplementary Table 2**). This suggests a plausible underlying prefrontal mechanism associated with the observed behavioural effects of instructions on fear learning. In addition, *hDP* individuals also displayed activation in the ventromedial prefrontal cortex (vmPFC) that was not observed in the *lDP*, nor in the all-subject activations (**Supplementary Table 2**). However, there were no significant differences between the groups in the main effects of instructions (subtraction analysis).

For completeness, we analysed the effect of fear learning specifically for the instructed (**Supplementary Table 3**) and non-instructed stimuli (**Supplementary Table 4**). These analyses overall resembled the main effect of conditioning and did not reveal and significant differences between *hDP* and *lDP*. Our final contrast analysis focused on the main effect of pain for all subjects, and showed activations in region previously implicated in pain processing including bilateral insula and cACC (**Supplementary Table 5**).

A psychophysiological interaction (PPI) analysis revealed increased connectivity in instructed trials (vs. non-instructed trials) specifically for *hDP* (i.e., compared to *lDP*) between the right lOfc and functionally defined nociceptive input region (right posterior insula) (Z = 3.29, corrected p = 0.004), supporting previous findings of an association between sensory processing and lOfc in delusion-prone individuals (Schmack et al., 2013; **Figure 4C**). Moreover, PPI-analysis of the effects of instruction on fear processing showed a significantly larger connectivity between the lOfc and the caudal anterior cingulate cortex (cACC), overlapping with fear related activation, in *hDP* compared to *lDP* (Z = 2.96, corrected p = 0.012) (**Figure 4D**). Last, we tested whether we could conceptually replicate the correlation reported in earlier work, between conviction scores and functional connectivity in instructed trials between the right lOfc and functionally defined early sensory processing regions (Schmack et al., 2013) (i.e., right posterior insula, here), specifically for *hDP* individuals (i.e., compared to *lDP*). This analysis showed a significant effect (pFWE = 0.003) (**Figure 5**), that was also observed when the PPI-analysis was correlated

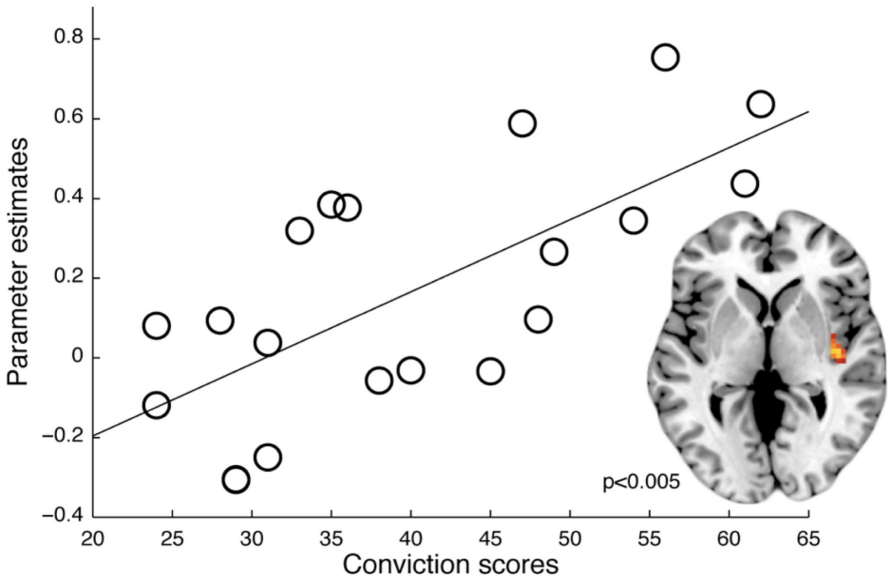

FIGURE 5 | Relation between delusion-proneness and functional connectivity. The functional connectivity (PPI-analysis) between the right lOfc and i.e., right posterior insula ROI as an effect of instructions (vs. non-instructed trials) correlated with conviction scores in the *hDP* (Z = 3.44, pFWE = 0.003). A similar effect was shown for PDI-total scores (Z = 3.29, pFWE = 0.004) and normalised conviction scores also in the *hDP* (Z = 2.77, pFWE = 0.016).

with the total PDI score (pFWE = 0.004) and the normalised convictions scores (pFWE = 0.016).

DISCUSSION

The present findings confirmed our main hypothesis stating that the effect of instructions on fear learning, i.e., instructed fear learning, would be larger in the delusion-prone group (*hDP*) than in the control group (*lDP*) (**Figures 2A,B**). The effect was shown in the affective learning index for the instructed stimuli, where evaluative ratings of instructed CS+ faces were compared to instructed CS- faces. However, we did not observe any significant group difference in non-instructed fear learning (classical fear conditioning) (**Figures 2C,D**). Our results mirror recent studies reporting an increased effect of high-level priors on perceptions in psychosis-related states (Schmack et al., 2013; Teufel et al., 2015) and extend these observations to instructed fear learning. Importantly, as we measured evaluative social ratings as our outcome variable, we also targeted the participants' specific beliefs about different social stimuli. Thus, in contrast to the aforementioned studies (Schmack et al., 2013; Teufel et al., 2015), we argue that in psychosis-related states, explicit beliefs about the world are also more susceptible to be changed after explicit learning. In addition, our data suggests that *hDP* individuals displayed a larger *affective learning* than *lDP* individuals after instructions, already before the CS-UCS pairing. In other words, they had already formed stronger beliefs that biased their experience of the faces, even before low-level learning in the acquisition phase. Thus, we expand previous views on delusion formation as a secondary mechanism in which the individual tries to explain specific aberrant stimuli (Kapur, 2003), by suggesting that formation of such beliefs might also represent a pro-active coping strategy in order to facilitate interpretation of an unstable environment.

Instructed fear learning (Mertens et al., 2018) has many similarities to nocebo treatment effects (Barsky et al., 2002; Faasse et al., 2019; Colloca and Barsky, 2020), in that both often involve a suggestion that an experience will be unpleasant or aversive. More specifically, in instructed fear learning the subject is informed that a specific event (Stimulus 1) is associated with and predicts an aversive stimulus (Stimulus 2). The effects on subsequently shown Stimuli 1 are then measured in ratings, autonomic measures or brain responses. In nocebo paradigms, the subject is typically informed that a treatment or an event (Stimulus 1) is associated with an increased unpleasant or aversive experience induced by an aversive stimulus such as a painful event (Stimulus 2). The nocebo effect is measured when Stimulus 2 is presented using ratings, autonomic measures or brain responses. Thus, while instructed fear learning is focused on the anticipation phase of an unpleasant event, the nocebo effect is focused on the unpleasant event itself. Also, while instructed fear learning just informs the subject about a relation, the nocebo paradigm gives suggestion about the nature of a stimulus. Both instructed fear learning and nocebo paradigms may also involve a conditioning procedure, but verbal suggestions are of key importance in the experimental paradigms (Mertens et al., 2018; Colloca and Barsky, 2020). In fact, nocebo studies suggest that verbal suggestions may fully mediate the effect, in contrast to placebo studies where the conditioning has additive effects (Colloca et al., 2008). Similarly, instructions mediate a strong effect on fear learning (Mertens et al., 2018) that cannot be completely overridden by subsequent situational safety information (Mertens et al., 2016). Given the similarities between

instructed fear learning and nocebo effects, our results suggest that high delusion proneness may be associated with stronger explicit nocebo-like effects than low delusion proneness.

In the present study, we focused on delusion proneness, a personality trait in healthy individuals that includes subclinical levels of delusional ideation (Peters et al., 2004; van Os et al., 2009). Cognitive, thought- and perceptual mechanisms underlying delusion- and psychosis-proneness are considered to be similar to the one underlying psychosis (Peters et al., 2004; van Os et al., 2009; Fusar-Poli et al., 2013; Teufel et al., 2015). As this phenotype is dimensionally expressed in humans, all individuals are more or less prone to this type of behaviour and related information processing. Thus, this trait has significant impact on variability in human behaviour among healthy subjects. However, we propose that similar effects of top-down high-level learning may be present in psychosis patients.

The effect of instructions on fear learning was also significantly related to the degree of *delusional distress* in the *hDP*. This finding was still present when distress scores were normalised, such that they did not depend on the number of endorsed delusional items, which underscores the importance of this dimension in belief formation. These findings may be of special interest since it has been suggested that psychosis-related states characterised with more distress and help seeking are also associated with a larger risk to convert into a clinical psychotic disorder (Fusar-Poli et al., 2013).

We failed to show that *hDP* was associate with lower classical fear conditioning than *lDP* for the non-instructed condition as initially hypothesised. In fact, the average non-instructed *affective learning index* after acquisition (i.e., evaluative ratings) was somewhat larger, albeit non-significant, in *hDP* compared to *lDP* (**Figure 2D**). At first glance, this result seems to contrast with previous studies showing a smaller classical fear conditioning effect in psychosis patients (Jensen et al., 2008; Holt et al., 2009, 2012; Romaniuk et al., 2010; Balog et al., 2013; Tuominen et al., 2021) and schizotypal individuals (Balog et al., 2013) suggestive of a weaker bottom-up learning in these phenotypes. However, it is important to keep in mind that our non-instructed condition may involve a faster development of explicit beliefs about contingencies compared to ordinary classical fear conditioning experiments, due to the presence of an instructed condition in the same experiment. Thus, our non-instructed fear learning cannot be simply compared to standard classical fear conditioning studies. Future studies will have to control for such confounding effects when comparing instructed vs. non-instructed conditions.

Apart from the effects of fear learning measured with *affective learning index*, the subjects also explicitly rated how much the painful stimulation and the instructions affected them. Interestingly, although no group difference was observed for the painful stimulation, the *hDP* tended to rate that they were more affected by the instructions than the *lDP*. Also, this effect was significantly correlated with the delusional distress for the instructed stimuli in the *hDP* (similarly to the *affective learning index*). Thus, subjects in the *hDP* group seem to have a metacognitive awareness of the fact they are highly affected by explicit information.

Our fMRI results revealed that the main effect of conditioning led to activations in brain areas that are consistently reported in classical fear conditioning studies including caudal ACC, anterior insula, thalamus and brainstem (Fullana et al., 2016), but no group differences were reported (**Figure 4A** and **Supplementary Table 1**).

In line with our hypothesis, we observed a main effect of instructions in lateral orbitofrontal cortex (lOfc) for all subjects (**Figure 4B** and **Supplementary Table 2**)—driven mainly by *hDP* as only this group showed a significant (and bilateral) activation in lOfc. Increased activation in the orbitofrontal cortex has previously been shown in imaging studies involving both instructed fear learning (Tabbert et al., 2011; Atlas et al., 2016) and nocebo effect (Kong et al., 2008; Asghar et al., 2015; Ellerbrock et al., 2015; Freeman et al., 2015; Schienle et al., 2018) as well as in placebo treatment studies (Petrovic et al., 2002, 2005, 2010; Atlas and Wager, 2014; Wager and Atlas, 2015) and cognitive reappraisal (Eippert et al., 2007; Wager et al., 2008; Kanske et al., 2011; Golkar et al., 2012). All these experimental paradigms involve an explicit change in the underlying rules relating to how to interpret an emotional experience and the associated expectations. Also, the activity seems to be independent of expected value. In a predictive coding framework, which has previously been applied to the placebo effect (Petrovic et al., 2010; Buchel et al., 2014), the lOfc may thus be a key region for higher order priors. A related research line suggests that the orbitofrontal cortex is important for learning task-state representations, especially when hidden information is important for the task (Niv, 2019). This may be compared to the presented paradigms above, that contained hidden information about how a stimuli should be interpreted, given in the instruction phase. This suggests a plausible underlying prefrontal mechanism associated with the observed behavioural effects of instructions on fear learning—an effect that was significantly larger in the *hDP* than in the *lDP*. However, there was not a significant difference in the lOfc activations related to instructions between the groups, possible due to too low power. As a general comment it should be noted that the paradigms discussed above do not always show increased activation in lOfc, an effect that may be due to large susceptibility artefacts in this region.

In contrast to the fMRI analysis based purely on differences in activations between conditions, the psychophysiological interaction (PPI) analysis revealed increased functional connectivity in instructed trials (as compared to non-instructed trials) specifically for *hDP* individuals between the right lOfc and functionally defined primary nociceptive input region (right posterior insula). This result supports previous findings of an association between sensory processing and lOfc activity during an expectation modulated condition in schizophrenia (Schmack et al., 2017) and delusion-proneness (Schmack et al., 2013; **Figure 4C**). Interestingly, as in the study by Schmack and colleagues on delusion-proneness (Schmack et al., 2013) this functional connectivity was related to the conviction scores for the delusion-prone group (**Figure 5**). Although this effect was also observed for the total PDI-scores in our sample, it remained significant when tested for the normalised convictions scores. Thus, the conviction scores had a specific effect on the

connectivity between lOfc and right posterior insula independent on the number of endorsed delusional items.

The PPI-analysis of the effects of instruction on fear processing also showed a significantly larger connectivity between the lOfc and the caudal anterior cingulate cortex (cACC), overlapping with fear related activation, in *hDP* compared to *lDP* (**Figure 4D**).

The significant group difference in lOfc functional connectivity—combined with no difference between the groups in the activation level related to fear processing—suggests mainly a difference in the re-appraisal effect between delusion-prone and control subjects. A similar region in lOfc links expectations to visual input (Bar, 2003) and mediates belief congruent information to visual processing of the random dot kinetogram illusion related to delusion-proneness (Schmack et al., 2013). Prefrontal networks, that include lOfc, are also involved in self-referential experience of presented generic stimuli in delusional patients with Schizophrenia (Lariviere et al., 2017). Based on these previous studies as well as our results, we argue that lOfc may be important for construction of higher-order priors used more readily in delusion-proneness, especially in emotional and visual processes

In a previous study on the impact of instructions on classical fear learning (Atlas et al., 2016), an effect of instructions was observed in the dorsolateral prefrontal cortex (dlPFC), stretching towards ventrolateral PFC. Our main activation in the lOfc extends towards the same area. Finally, only the delusion-prone group showed activation in the ventromedial prefrontal cortex (vmPFC) in main effect of instructions—a region previously implicated in mediation of cognitive reappraisal (Wager et al., 2008).

Cognitive neuroscience research on psychosis has recently focused on the involvement of expectations (or priors) in underlying mechanisms (Fletcher and Frith, 2009; Adams et al., 2013; Sterzer et al., 2018) and suggested that the balance between bottom-up signals and top-down influence of expectations is altered in psychotic states due to aberrant (or hyper) salience of incoming information (Kapur, 2003)—possibly linked to a hypersensitive dopamine system (Kuepper et al., 2012)—and weakened or imprecise low-level priors. Recently, hierarchical Bayesian models (Friston, 2005) have been successfully applied to explain hallucinations and underlying processes observed in psychosis-associated states (Powers et al., 2017). However, predictive coding models have so far not been able to account for both chaotic perceptions (involving imprecise priors) and delusions (involving overly precise priors). From a predictive coding perspective, the present study together with previous findings (Schmack et al., 2013; Teufel et al., 2015) suggest that individuals in psychosis-related states, including healthy delusion-prone subjects, are more prone to integrate and use higher-order beliefs (or models/priors) of the world in order to better comprehend a noisy perceptual environment. Altogether, our study and previous work on fear processing in psychosis-related states, suggest the coexistence of a weak low-level and strong high-level fear learning in psychosis-related endophenotypes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Ethical Board of Stockholm (www.epn.se). The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PP, MI, and ALo designed the study. PP and ALo performed the experiments. All authors performed parts of the analyses, contributed to the writing, read the manuscript, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.786778/full#supplementary-material

REFERENCES

Adams, R. A., Stephan, K. E., Brown, H. R., Frith, C. D., and Friston, K. J. (2013). The computational anatomy of psychosis. *Front. Psychiatry* 4:47. doi: 10.3389/fpsyt.2013.00047

Asghar, M. S., Pereira, M. P., Werner, M. U., Martensson, J., Larsson, H. B., and Dahl, J. B. (2015). Correction: secondary Hyperalgesia phenotypes exhibit differences in brain activation during noxious stimulation. *PLoS One* 10:e0128640. doi: 10.1371/journal.pone.0114840

Atlas, L. Y., Doll, B. B., Li, J., Daw, N. D., and Phelps, E. A. (2016). Instructed knowledge shapes feedback-driven aversive learning in striatum and orbitofrontal cortex, but not the amygdala. *eLife* 5:e15192. doi: 10.7554/eLife.15192

Atlas, L. Y., and Wager, T. D. (2014). A meta-analysis of brain mechanisms of placebo analgesia: consistent findings and unanswered questions.

Handb. Exp. Pharmacol. 225, 37–69. doi: 10.1007/978-3-662-44519-8_3

Balog, Z., Somlai, Z., and Kéri, S. (2013). Aversive conditioning, schizotypy, and affective temperament in the framework of the salience hypothesis. *Pers. Individ. Dif.* 54, 109–112.

Bar, M. (2003). A cortical mechanism for triggering top-down facilitation in visual object recognition. *J. Cogn. Neurosci.* 15, 600–609. doi: 10.1162/089892903321662976

Baron-Cohen, S., Wheelwright, S., Skinner, R., Martin, J., and Clubley, E. (2001). The autism-spectrum quotient (AQ): evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *J. Autism Dev. Disord.* 31, 5–17. doi: 10.1023/a:1005653411471

Barsky, A. J., Saintfort, R., Rogers, M. P., and Borus, J. F. (2002). Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 287, 622–627. doi: 10.1001/jama.287.5.622

Bates, D., Maechler, M., Bolker, B., and Walker, S. (2015). Fitting Linear Mixed-Effects Models Using lme4. *J. Stat. Softw.* 67, 1–48.

Buchel, C., Geuter, S., Sprenger, C., and Eippert, F. (2014). Placebo analgesia: a predictive coding perspective. *Neuron* 81, 1223–1239. doi: 10.1016/j.neuron.2014.02.042

Colloca, L., and Barsky, A. J. (2020). Placebo and Nocebo Effects. *N. Engl. J. Med.* 382, 554–561.

Colloca, L., Sigaudo, M., and Benedetti, F. (2008). The role of learning in nocebo and placebo effects. *Pain* 136, 211–218. doi: 10.1016/j.pain.2008.02.006

Corlett, P. R., and Fletcher, P. C. (2012). The neurobiology of schizotypy: fronto-striatal prediction error signal correlates with delusion-like beliefs in healthy people. *Neuropsychologia* 50, 3612–3620. doi: 10.1016/j.neuropsychologia.2012.09.045

Corlett, P. R., Murray, G. K., Honey, G. D., Aitken, M. R., Shanks, D. R., Robbins, T. W., et al. (2007). Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain* 130, 2387–2400. doi: 10.1093/brain/awm173

Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., and Anders, S. (2007). Regulation of emotional responses elicited by threat-related stimuli. *Hum. Brain Mapp.* 28, 409–423. doi: 10.1002/hbm.20291

Ellerbrock, I., Wiehler, A., Arndt, M., and May, A. (2015). Nocebo context modulates long-term habituation to heat pain and influences functional connectivity of the operculum. *Pain* 156, 2222–2233. doi: 10.1097/j.pain.0000000000000297

Faasse, K., Helfer, S. G., Barnes, K., Colagiuri, B., and Geers, A. L. (2019). Experimental Assessment of Nocebo Effects and Nocebo Side effects: definitions, study design, and implications for psychiatry and beyond. *Front. Psychiatry* 10:396. doi: 10.3389/fpsyt.2019.00396

Fletcher, P. C., and Frith, C. D. (2009). Perceiving is believing: a Bayesian approach to explaining the positive symptoms of schizophrenia. *Nat. Rev. Neurosci.* 10, 48–58. doi: 10.1038/nrn2536

Freeman, S., Yu, R., Egorova, N., Chen, X., Kirsch, I., Claggett, B., et al. (2015). Distinct neural representations of placebo and nocebo effects. *Neuroimage* 112, 197–207. doi: 10.1016/j.neuroimage.2015.03.015

Friston, K. (2005). A theory of cortical responses. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 360, 815–836.

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., and Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage* 6, 218–229. doi: 10.1006/nimg.1997.0291

Fullana, M. A., Harrison, B. J., Soriano-Mas, C., Vervliet, B., Cardoner, N., Avila-Parcet, A., et al. (2016). Neural signatures of human fear conditioning: an updated and extended meta-analysis of fMRI studies. *Mol. Psychiatry* 21, 500–508. doi: 10.1038/mp.2015.88

Fusar-Poli, P., Borgwardt, S., Bechdolf, A., Addington, J., Riecher-Rossler, A., Schultze-Lutter, F., et al. (2013). The psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry* 70, 107–120. doi: 10.1001/jamapsychiatry.2013.269

Golkar, A., Lonsdorf, T. B., Olsson, A., Lindstrom, K. M., Berrebi, J., Fransson, P., et al. (2012). Distinct contributions of the dorsolateral prefrontal and orbitofrontal cortex during emotion regulation. *PLoS One* 7:e48107. doi: 10.1371/journal.pone.0048107

Holt, D. J., Coombs, G., Zeidan, M. A., Goff, D. C., and Milad, M. R. (2012). Failure of neural responses to safety cues in schizophrenia. *Arch. Gen. Psychiatry* 69, 893–903. doi: 10.1001/archgenpsychiatry.2011.2310

Holt, D. J., Lebron-Milad, K., Milad, M. R., Rauch, S. L., Pitman, R. K., Orr, S. P., et al. (2009). Extinction memory is impaired in schizophrenia. *Biol. Psychiatry* 65, 455–463. doi: 10.1016/j.biopsych.2008.09.017

Javitt, D. C., and Freedman, R. (2015). Sensory processing dysfunction in the personal experience and neuronal machinery of schizophrenia. *Am. J. Psychiatry* 172, 17–31. doi: 10.1176/appi.ajp.2014.13121691

Jensen, J., Willeit, M., Zipursky, R. B., Savina, I., Smith, A. J., Menon, M., et al. (2008). The formation of abnormal associations in schizophrenia: neural and behavioral evidence. *Neuropsychopharmacology* 33, 473–479. doi: 10.1038/sj.npp.1301437

Johansson, P., Hall, L., Tärning, B., Sikström, S., and Chater, N. (2013). Choice Blindness and Preference Change: you Will Like This Paper Better If You (Believe You) Chose to Read It! *J. Behav. Decis. Mak.* 27, 281–289. doi: 10.1002/bdm.1807

Kanske, P., Heissler, J., Schonfelder, S., Bongers, A., and Wessa, M. (2011). How to regulate emotion? Neural networks for reappraisal and distraction. *Cereb. Cortex* 21, 1379–1388. doi: 10.1093/cercor/bhq216

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am. J. Psychiatry* 160, 13–23. doi: 10.1176/appi.ajp.160.1.13

Kessler, R. C., Adler, L., Ames, M., Demler, O., Faraone, S., Hiripi, E., et al. (2005). The World Health Organization Adult ADHD Self-Report Scale (ASRS): a short screening scale for use in the general population. *Psychol. Med.* 35, 245–256. doi: 10.1017/s0033291704002892

Kong, J., Gollub, R. L., Polich, G., Kirsch, I., Laviolette, P., Vangel, M., et al. (2008). A functional magnetic resonance imaging study on the neural mechanisms of hyperalgesic nocebo effect. *J. Neurosci.* 28, 13354–13362. doi: 10.1523/JNEUROSCI.2944-08.2008

Kuepper, R., Skinbjerg, M., and Abi-Dargham, A. (2012). "The dopamine dysfunction in schizophrenia revisited: new insights into topography and course," in *Handbook of Experimental Pharmacology*, eds G. Gross and M. Geyer (Berlin: Springer), 1–26. doi: 10.1007/978-3-642-25761-2_1

Kuznetsova, A., Brockhoff, P. B., and Christensen, R. H. B. (2017). lmerTest Package: Tests in Linear Mixed Effects Models. *J. Stat. Softw.* 82, 1–26.

Lariviere, S., Lavigne, K. M., Woodward, T. S., Gerretsen, P., Graff-Guerrero, A., and Menon, M. (2017). Altered functional connectivity in brain networks underlying self-referential processing in delusions of reference in schizophrenia. *Psychiatry Res. Neuroimaging* 263, 32–43. doi: 10.1016/j.pscychresns.2017.03.005

Louzolo, A., Almeida, R., Guitart-Masip, M., Björnsdotter, M., Ingvar, M., Olsson, A., et al. (2019). Enhanced instructed fear learning in delusion-proneness. *bioRxiv* [Preprint]. doi: 10.1101/264739v1

Louzolo, A., Gustavsson, P., Tigerstrom, L., Ingvar, M., Olsson, A., and Petrovic, P. (2017). Delusion-proneness displays comorbidity with traits of autistic-spectrum disorders and ADHD. *PLoS One* 12:e0177820. doi: 10.1371/journal.pone.0177820

Mertens, G., Boddez, Y., Sevenster, D., Engelhard, I. M., and De Houwer, J. (2018). A review on the effects of verbal instructions in human fear conditioning: empirical findings, theoretical considerations, and future directions. *Biol. Psychol.* 137, 49–64. doi: 10.1016/j.biopsycho.2018.07.002

Mertens, G., Kuhn, M., Raes, A. K., Kalisch, R., De Houwer, J., and Lonsdorf, T. B. (2016). Fear expression and return of fear following threat instruction with or without direct contingency experience. *Cogn. Emot.* 30, 968–984. doi: 10.1080/02699931.2015.1038219

Moller, T. J., Georgie, Y. K., Schillaci, G., Voss, M., Hafner, V. V., and Kaltwasser, L. (2021). Computational models of the "active self" and its disturbances in schizophrenia. *Conscious. Cogn.* 93, 103155. doi: 10.1016/j.concog.2021.103155

Murray, G. K., Corlett, P. R., Clark, L., Pessiglione, M., Blackwell, A. D., Honey, G., et al. (2008). Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol. Psychiatry* 13, 239, 267–76.. doi: 10.1038/sj.mp.4002058

Niv, Y. (2019). Learning task-state representations. *Nat. Neurosci.* 22, 1544–1553. doi: 10.1038/s41593-019-0470-8

Olsson, A., Ebert, J. P., Banaji, M. R., and Phelps, E. A. (2005). The role of social groups in the persistence of learned fear. *Science* 309, 785–787. doi: 10.1126/science.1113551

Peters, E., Joseph, S., Day, S., and Garety, P. (2004). Measuring delusional ideation: the 21-item Peters et al. Delusions Inventory (PDI). *Schizophr. Bull.* 30, 1005–1022. doi: 10.1093/oxfordjournals.schbul.a007116

Petrovic, P., Dietrich, T., Fransson, P., Andersson, J., Carlsson, K., and Ingvar, M. (2005). Placebo in emotional processing–induced expectations of anxiety relief activate a generalized modulatory network. *Neuron* 46, 957–969. doi: 10.1016/j.neuron.2005.05.023

Petrovic, P., Kalisch, R., Singer, T., and Dolan, R. J. (2008). Oxytocin attenuates affective evaluations of conditioned faces and amygdala activity. *J. Neurosci.* 28, 6607–6615. doi: 10.1523/JNEUROSCI.4572-07.2008

Petrovic, P., Kalso, E., Petersson, K. M., Andersson, J., Fransson, P., and Ingvar, M. (2010). A prefrontal non-opioid mechanism in placebo analgesia. *Pain* 150, 59–65. doi: 10.1016/j.pain.2010.03.011

Petrovic, P., Kalso, E., Petersson, K. M., and Ingvar, M. (2002). Placebo and opioid analgesia– imaging a shared neuronal network. *Science* 295, 1737–1740. doi: 10.1126/science.1067176

Powers, A. R., Mathys, C., and Corlett, P. R. (2017). Pavlovian conditioning-induced hallucinations result from overweighting of perceptual priors. *Science* 357, 596–600. doi: 10.1126/science.aan3458

R Core Team (2015). *R: A Language and Environment for Statistical Computing*. Vienna: R Foundation for Statistical Computing. Available online at: https://www.R-project.org/

Roiser, J. P., Stephan, K. E., Den Ouden, H. E., Barnes, T. R., Friston, K. J., and Joyce, E. M. (2009). Do patients with schizophrenia exhibit aberrant salience? *Psychol. Med.* 39, 199–209. doi: 10.1017/S0033291708003863

Romaniuk, L., Honey, G. D., King, J. R., Whalley, H. C., Mcintosh, A. M., Levita, L., et al. (2010). Midbrain activation during Pavlovian conditioning and delusional symptoms in schizophrenia. *Arch. Gen. Psychiatry* 67, 1246–1254. doi: 10.1001/archgenpsychiatry.2010.169

Schienle, A., Hofler, C., Ubel, S., and Wabnegger, A. (2018). Emotion-specific nocebo effects: an fMRI study. *Brain Imaging Behav.* 12, 180–187. doi: 10.1007/s11682-017-9675-1

Schlagenhauf, F., Huys, Q. J., Deserno, L., Rapp, M. A., Beck, A., Heinze, H. J., et al. (2014). Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. *Neuroimage* 89, 171–180. doi: 10.1016/j.neuroimage.2013.11.034

Schmack, K., Gomez-Carrillo De Castro, A., Rothkirch, M., Sekutowicz, M., Rossler, H., Haynes, J. D., et al. (2013). Delusions and the role of beliefs in perceptual inference. *J. Neurosci.* 33, 13701–13712. doi: 10.1523/JNEUROSCI.1778-13.2013

Schmack, K., Rothkirch, M., Priller, J., and Sterzer, P. (2017). Enhanced predictive signalling in schizophrenia. *Hum. Brain Mapp.* 38, 1767–1779. doi: 10.1002/hbm.23480

Sterzer, P., Adams, R. A., Fletcher, P., Frith, C., Lawrie, S. M., Muckli, L., et al. (2018). The predictive coding account of psychosis. *Biol. Psychiatry* 84:634.

Sterzer, P., Frith, C., and Petrovic, P. (2008). Believing is seeing: expectations alter visual awareness. *Curr. Biol.* 18:R697. doi: 10.1016/j.cub.2008.06.021

Tabbert, K., Merz, C. J., Klucken, T., Schweckendiek, J., Vaitl, D., Wolf, O. T., et al. (2011). Influence of contingency awareness on neural, electrodermal and evaluative responses during fear conditioning. *Soc. Cogn. Affect. Neurosci.* 6, 495–506. doi: 10.1093/scan/nsq070

Tanasescu, R., Cottam, W. J., Condon, L., Tench, C. R., and Auer, D. P. (2016). Functional reorganisation in chronic pain and neural correlates of pain sensitisation: a coordinate based meta-analysis of 266 cutaneous pain fMRI studies. *Neurosci. Biobehav. Rev.* 68, 120–133. doi: 10.1016/j.neubiorev.2016.04.001

Teufel, C., Subramaniam, N., Dobler, V., Perez, J., Finnemann, J., Mehta, P. R., et al. (2015). Shift toward prior knowledge confers a perceptual advantage in early psychosis and psychosis-prone healthy individuals. *Proc. Natl. Acad. Sci. U.S.A.* 112, 13401–13406. doi: 10.1073/pnas.1503916112

Tuominen, L., Romaniuk, L., Milad, M. R., Goff, D. C., Hall, J., and Holt, D. J. (2021). Impairment in acquisition of conditioned fear in schizophrenia. *Neuropsychopharmacology*. [Epub ahead of print]. doi: 10.1038/s41386-021-01193-1

van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., and Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol. Med.* 39, 179–195. doi: 10.1017/S0033291708003814

Wager, T. D., and Atlas, L. Y. (2015). The neuroscience of placebo effects: connecting context, learning and health. *Nat. Rev. Neurosci.* 16, 403–418. doi: 10.1038/nrn3976

Wager, T. D., Davidson, M. L., Hughes, B. L., Lindquist, M. A., and Ochsner, K. N. (2008). Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* 59, 1037–1050. doi: 10.1016/j.neuron.2008.09.006

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The Effects of Health Anxiety and Litigation Potential on Symptom Endorsement, Cognitive Performance, and Physiological Functioning in the Context of a Food and Drug Administration Drug Recall Announcement

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Drug recalls and lawsuits against pharmaceutical manufacturers are accompanied by announcements emphasizing harmful drug side-effects. Those with elevated health anxiety may be more reactive to such announcements. We evaluated whether health anxiety and financial incentives affect subjective symptom endorsement, and objective outcomes of cognitive and physiological functioning during a mock drug recall. Hundred and sixty-one participants reported use of over-the-counter pain medications and presented with a fictitious medication recall via a mock Food and Drug Administration (FDA) website. The opportunity to join a class-action lawsuit was manipulated. We assessed health anxiety, recalled drug usage, blood pressure, heart rate, and performance on a computerized Trail Making Test (TMT). Symptom endorsement was strongly predicted by health anxiety. When combined, three health anxiety measures explained 28.5% variance (Cohen's d = 1.26). These effects remain strong after controlling for depression and anxiety. Litigation condition did not predict symptom endorsement. Blood pressure and heart rate were modestly predicted by health anxiety, but not by litigation condition. TMT performance was consistently predicted by health anxiety, with higher scores associated with poorer performance. Although there were no main effects for litigation, interactions consistently emerged for the TMT, with generally poorer performance for those with higher health anxiety in the non-litigation condition; whereas health anxiety was unrelated to performance for the litigation condition. All but one participant joined the litigation when given the opportunity, despite a healthy sample and minimal use of pain medication. Subsequent data from 67 individuals with no mention of the FDA scenario or litigation showed that health anxiety still significantly

predicts symptom endorsement (12.6% variance), but the explained variance is less than half that obtained in the FDA scenario. The findings suggest that health anxiety plays a significant role in adverse symptom reporting, beyond anxiety or depression, and this effect is independent of the presence of the FDA recall. The lack of differences for health anxiety and symptom endorsement between litigation and non-litigation conditions rules out malingering. Although it is general practice in drug recalls to list potential adverse side effects caused by medications, this may elicit unintended symptom experiences and health anxious individuals may be more susceptible.

Keywords: health anxiety, drug recall, malingering, side-effects, litigation

INTRODUCTION

Individuals with pre-existing high levels of health anxiety may be particularly susceptible to reporting symptoms and side effects when exposed to information about adverse drug effects. Heightened sensitivity to health-related stimuli is part and parcel of the DSM-5 (American Psychiatric Association, 2013) criteria for diagnosing a health anxiety disorder (e.g., Lees et al., 2005). However, we know little about whether health anxiety, in general, is a factor in responsiveness to health threatening information about drugs; as would occur in drug recall announcements and publicity about lawsuits against pharmaceutical companies. It is also unclear the extent to which potential litigation could affect responses to a drug recall.

For the current study, we created a simulated FDA recall of widely used over-the-counter medications, controlling information related to adverse effects and experimentally manipulating the potential for financial compensation (litigation). We also measured health anxiety and examined its predictive potential, along with that of litigation, and their interaction, with respect to three outcome variables; (1) self-reported symptom endorsement, (2) cognitive performance, and (3) physiological functioning, in order to gauge the consequences for both subjective and objective outcomes. Finally, we also collected a control condition to assess self-reported symptoms and health anxiety outside of the Food and Drug Administration (FDA) context. This experimentally controlled context permitted an analysis of variables that often cannot be differentiated in a naturalistic situation.

Health Anxiety

Individuals with low levels of health anxiety are generally less likely to consider themselves at risk for adverse health events. Indeed, most people have an optimistic bias regarding health risks (Weinstein, 1984, 1987). Individuals with high health anxiety, however, tend to *believe* they are unhealthy, and endorse more symptoms of illness (e.g., Pennebaker, 1982; Watson and Pennebaker, 1989; Ellington and Wiebe, 1999; Feldman et al., 1999). Health anxious individuals may adopt illness beliefs more quickly and seek out information to validate their negative health beliefs (e.g., Barsky and Klerman, 1983; Kellner, 1986; Warwick, 1989; Cioffi, 1991; for a broader etiological account, see Cisler and Koster, 2010). Research also suggests that measures of health anxiety capture a health content-specific version of the broader construct of negative affect, and the former relates more strongly to the endorsement of physical symptoms (Lecci et al., 1996). It is also the case that when individuals are in a situation/context that itself can elevate health anxious responding, symptom reporting may be especially exacerbated for those already predisposed to experiencing health anxiety (Lecci and Cohen, 2002). Because information contained in drug recall publicity emphasizes adverse, health-threatening effects, we hypothesize that health anxiety will predict symptom endorsement in the simulated drug recall. Moreover, in keeping with previous research (e.g., Lecci and Cohen, 2002) we hypothesize that the association with health anxiety will either be non-existent or not as pronounced in the absence of a potentially health threatening context (i.e., when there is no FDA drug recall).

The Influence of Monetary Incentives on Behavior

Monetary incentives are powerful motivators of behavior (e.g., Benabou and Tirole, 2006). It is therefore not surprising that increased symptom endorsement is seen among those seeking financial compensation through litigation (Rohling et al., 1995). This can be reflected in the concept of "compensation neurosis," which is defined as the exaggeration of symptoms resulting from the opportunity to obtain financial reward through legal compensation (Hall and Hall, 2012). The field of neuroeconomics also provides evidence that financial incentives influence brain activity in brain systems associated with expectancy (placebo) effects (Scott et al., 2007), suggesting that financial incentives may influence actual symptom experience.

Individuals also can be motivated to malinger (feigning symptoms for external gain) without experiencing deleterious consequences of exposure to the drug. In neuropsychological settings, estimated rates of malingering range from 15 to 64% according to a meta-analysis that included eleven studies that provided data on malingering (Heaton et al., 1978; Trueblood and Schmidt, 1993; Larrabee, 2003). The detection of malingering often utilizes objective measures, such as assessments of cognitive performance, in addition to the information derived from self-report measures, but it is the objective performance-based measures that can provide the more conclusive findings (e.g., performing significantly below chance on performance validity measures is considered a very strong indicator of malingering, as the individual would have to know the correct response and choose the incorrect alternative in order to

score significantly below chance; e.g., Rogers and Bender, 2013). Malingering is also associated with an "amplified presentation" of symptoms (i.e., more symptoms relative to genuine experiences of pathology and perhaps more than those with higher health anxiety), including endorsing large numbers of symptoms, high symptom severity, and endorsement of erroneous symptom stereotypes (Walczyk et al., 2018). The literature is clear in illustrating that malingering is associated with elevating symptom reporting and intentional underperformance on objective cognitive measures for those involved in litigation It is also likely that people experiencing more symptoms (physical and psychological) and functional consequences (marked by underperformance on cognitive measures) are more likely to litigate for compensation (see Samra and Koch, 2002). Thus, differentiating malingering from legitimate symptom experience, or from a health anxious response in people who have taken a drug and report adverse reactions is notoriously difficult, and this has proven to be the case even for trained medical professionals (Bellamy, 1997). Given the widespread publicity associated with drug recalls and the involvement of a psychologically diverse population, similar large-scale challenges are likely to exist in this context. We predict that when individuals are presented with the opportunity to participate in litigation during a simulated drug recall, they will do so regardless of their health anxiety. Moreover, in keeping with research examining the influence of external contingencies on malingering in college students (e.g., Boskovic, 2020), we predict that the litigation condition will result in greater symptom endorsement and possibly more problematic functioning (lower scores) on objective measures.

Response to Drug Recalls

In 2021, the United States accounted for over 46% of worldwide pharmaceutical sales and is the world's leading consumer of pharmaceuticals (Health, Pharma and Medtech, 2022). A consequence of the extensive use of medicines is product recalls in the pharmaceutical industry, which have increased dramatically over the years (Dickinson, 2001). The U.S. Food and Drug Administration (FDA) can mandate industry-wide recalls when there is a perceived risk to human health (U.S. Food and Drug Administration, 2022), and such recalls are far more common than industry-generated recalls (Dickinson, 2001). As an example, in 2013 the FDA listed 59 different drugs on its website that were recalled, the majority of which were Class I recalls, meaning exposure to the drug or product is more likely to cause "serious adverse health consequences or death" (U.S. Food and Drug Administration, 2013). Previous research focused mainly on the demographics of those who respond to recalls, their attitudes toward the companies involved in the recall (e.g., Blasche et al., 2008), or the characteristics of those who fail to comply with recall notifications (e.g., Cohen et al., 2012). However, there is a dearth of research examining the psychological variables that influence responses to drug recalls. Thus, the current research will focus on individual differences in health anxiety, experimentally manipulated litigation potential, and their interaction with respect to respondents' self-reported symptoms, cognitive performance, and physiological responses to a drug recall announcement.

The Present Research

The present study represents an experimental design with one manipulated categorical predictor variable (litigation/no litigation) and one measured continuous predictor (health anxiety). Three measures of health anxiety were employed and the presence of a common external motivator (opportunity to join a class-action lawsuit) was the experimentally manipulated variable. The importance of controlling the financial incentive is that drug recalls provide a context in which malingering (i.e., feigning symptom endorsement for monetary gain) can occur, and this motivation is conceptually distinct from symptom endorsement due to the experience of health anxiety. Additionally, publicity about class action lawsuits implies that a drug or medical device is dangerous while simultaneously incentivizing adverse event reporting for the potential of monetary gain. We also subsequently collected data in a second sample regarding health anxiety and symptom endorsement without mentioning the FDA recall to determine the impact of the recall context itself.

The outcome variables of interest were self-reported symptom endorsement, objective cognitive performance, and objective physiological responding, and each of these were assessed within the context of a simulated FDA recall. Importantly, it is not known how financial incentives interact with health anxiety to impact adverse event symptom endorsement or cognitive and physiological outcomes.

To better understand these variables, relatively healthy individuals were recruited who would presumably have a low base rate of symptom experience and reporting. Moreover, the side effects for the recalled medications were contrived (i.e., there was no actual drug recall) and the medications all produce pain relief and have few side-effects, which should in fact counter symptom experience. These circumstances should make it easier to attribute any emergent effects to the variables under investigation. Of particular interest is whether the opportunity to litigate and health anxiety impact; (1) the endorsement of symptoms that are, due to the suggestive nature of the experimental procedure, related to the recalled drug (after controlling for reported usage and constructs related to health anxiety, such as depression and anxiety scores), (2) performance on a cognitive measure, and (3) physiological responding. Based on the extant literature, it is expected that health anxiety will have its most significant impact on subjective self-reported symptoms, and show a weaker relation to the objective measures of cognitive and physiological functioning.

It is well established that individual differences in health anxiety are linked to increases in self-reported symptoms, and that some situations can magnify health concern and symptom reporting. For example, Camerone et al. (2021) demonstrated that verbal suggestion could increase or decrease pain sensitivity (referred to as nocebo hyperalgesia and placebo analgesia, respectively) in young healthy participants, and greater anxiety levels correlated with enhanced nocebo response magnitude. However, the literature regarding the consequences

for physiological and cognitive measures is more equivocal. As an illustration, consider how expectancy effects for adverse outcomes, conceptualized as nocebo responding, appear to result in strong effects when focusing on subjective, patient reported symptoms (e.g., Turi et al., 2018; Winkler and Hermann, 2019; Wolters et al., 2019), but those same effects are typically smaller for more objective outcomes such as third party-reported symptoms (Meissner, 2005). In closer alignment with the current research, Zech et al. (2020) showed that negative verbal suggestions (e.g., statements indicating an individual in a clinical setting will experience pain) lead to decreases on objective measures of physical strength; with anxiety seeming to enhance this effect. Similarly, researchers have shown that treatment expectations can impact motor performance, in the form of reduced force and increased fatigue, and that higher anxiety also plays an important role (Corsi et al., 2016).

Based on these findings and the previously discussed literature on financial incentives and their influence on symptom experience, the present study examined objective outcomes in addition to subjective self-perceptions of symptoms. We predict increases in physiological symptom experience (blood pressure and heart rate) and decreases in cognitive functioning (slower speed and more errors on an executive measure) as a product of health anxiety in the face of a drug recall, but with smaller effect sizes than will occur for the predicted increases in subjective symptom endorsement. It is also likely that a health anxious response set will converge with malingering in terms of heightened symptom endorsement, but the two may diverge with respect to the objective measures. Specifically, the literature suggests that health anxiety would result in greater effects (higher scores) on the physiological measures, whereas malingering may exert a greater influence (lower scores) on the cognitive measure; though both would result in poorer performance, with the effects of anxiety being unintentional and the effects of malingering being intentional. In fact, the expected effect size for the analyses involving monetary incentives and malingering should produce *r*-values ranging from 0.47 to 0.74 (see meta-analysis by Rohling et al., 1995; see also Meyer et al., 2001). The effect size estimate for a measure of health anxiety related to self-reported symptoms has been documented as $r = 0.40$ (Lecci et al., 1996). These are considered medium effect sizes (see Cohen, 1992). Smaller effects are generally expected for non-self-report outcomes such as physiological and cognitive measures (e.g., $r = 0.20$). To achieve a power of 0.80 for any main effects, the necessary sample size would range from 47 for the largest effect sizes to 194 for the smallest.

MATERIALS AND METHODS

Participants

Participants were students at a university in the southeastern United States with an enrollment of approximately 15,000 at the time the data were collected. Participation satisfied research participation requirements for a General Psychology course and credit opportunities in other courses. The students represent majors from across the university. One hundred seventy-five participated, although 14 subjects were removed (10 were < 18 years, three had incomplete data, and one due to computer error). The remaining 161 participants (68% female) comprised the current sample. The mean age was 20 ($SD = 5.56$), 83% were Caucasian, 2.5% African American, 4% Hispanic, and 5.5% "other." There were no additional exclusion criteria for this study.

Measures

Self-Reported Health Anxiety

The *Minnesota Multiphasic Personality Inventory-2* (MMPI-2; Butcher et al., 2001) is a 567-item true/false questionnaire that is commonly used to measure personality and psychopathology in clinical settings with well-established validity and reliability. The MMPI-2 has scales assessing response tendencies (validity scales) and clinical scales (Graham, 2011). This study used the K-corrected scale 1 (Hypochondriasis; Hs) and scale 3 (Hysteria; Hy) scores. Scores on depression (D; scale 2) and anxiety (supplemental scale A) served as covariates. Although scales 1 and 3 are associated with increased levels of somatic symptom reporting, the endorsement of health-based symptomatology and those associated with psychopathological processes like health anxiety, are considered overlapping but distinct experiences and, as such, commonly utilized in medical assessments (Arbisi and Butcher, 2004). The MMPI-2 is one of the most widely used clinical measures in the field of psychology (Ball et al., 1994) and all scales are shown to have strong internal reliability (Hunsley et al., 1988). In the present study, the MMPI-2 scales 1 and 3 serve as a contrast to a measure that directly captures pure symptom worry, the Whitely Index.

The Whitely Index

The Whitely Index (Pilowsky, 1967) is a 14-item questionnaire rating the degree to which statements are true (1 = "Not at all" and five = "Extremely"). The Whitely Index assesses health fear/anxiety and includes questions such as "Are you bothered by many pains and aches?" and "Do you think that you worry about your health more than most people?" (Pilowsky, 1967, 1978). The Whitely Index's test-retest reliability, convergent validity, and internal reliability have been established previously (Speckens et al., 1996).

Cognitive Functioning

The Trail Making Test (TMT; BrainBaseline® by Digital Artefacts®, Iowa City, IA, United States) was administered using a first-generation Apple® iPad®. The TMT used in this study required participants to draw lines connecting numbers in numerical order from 1 to 2 to 3 (Part A). The software provided completion time, errors, and restarts (reinitiating a trial after a line tracing error). Performance on the trail-making test Part A has been interpreted by neuropsychologists as reflecting attention, visual search and scanning, psychomotor speed, and the ability to execute and modify a plan of action (Salthouse and Fristoe, 1995). (*Note*: The computer program also included Trails B. However, some participants were not given the proper directions for this task, especially when errors occurred, thereby creating unknown variability due to the instructional set. As a

result, these scores are not presented.) The TMT is recognized as one of the most commonly used neuropsychological assessments (Rabin et al., 2016), it can be administered quickly on a computer for high levels of standardization and has also been used to detect malingering (e.g., Iverson et al., 2002).

Physiological Functioning

The Omron Automatic Blood Pressure Monitor, Model HEM-7311, assessed blood pressure and pulse from the left arm while participants were seated with their left arm extended at a 90-degree angle with the body. Resting blood pressure and heart rate were recorded from a single digital readout by the research assistant. The Omron device is listed on the US Blood Pressure Validated Device Listing, and was calibrated at the start of the study with a second, automated blood pressure and heart rate device.

Self-Reported Symptoms

Participants were asked whether they experienced any of the listed side effects/symptoms in response to the recalled medications, with ratings ranging from 0 (meaning "not at all") to 3 (meaning "a great deal"). A sum of these ratings was computed. The symptoms included; difficulty sleeping, nausea, diarrhea or constipation, light-headedness, blurred vision, lower back pain, difficulty concentrating, difficulty breathing, rapid heart rate, and tingling in the extremities. Each of these symptoms is among the most reported by adults (Verbrugge and Ascione, 1987).

Procedure

The study took place in the clinical research unit of a building operated by the university's school of nursing within the college of health and human sciences, where students are trained to conduct clinical pharmaceutical research; thereby providing a realistic backdrop. Participants who volunteered were informed that they were taking part in a national FDA-funded study regarding a recent recall of over-the-counter pain medications. Signage indicating that this was an FDA field site was posted at the building entrance and in the hallway outside the lab. Eight female research assistants (RAs), who were advanced college undergraduate students, collected all of the data. The RAs had been members of the lab for at least one semester prior to the data collection, and received course credit for directed individual study. They were trained in the procedure over the course of 4 weeks and were monitored for consistency by a senior student who used the data for an honor's thesis. Because the computer program randomly assigned participants to one of two litigation conditions that differed only with respect to the content of one part of the mock FDA webpage, the RAs would not have been privy to condition at the time the data were collected.

Participants first read and signed informed consent. The cover story for the study provided to participants was that the FDA was collecting information on the scope of the problem associated with the drug recall and the possible health consequences, especially among young, healthy adults. Participants were then directed to a professionally developed, mock version of the FDA website, which contained a link to information on a recent drug recall. The website was, in fact, hosted on a microcomputer that, unbeknownst to the participants, was not linked to the internet. The mock FDA website informed the participants that they had initiated a recall on commonly used pain medications due to aversive side effects. The recalled medications list included Tylenol, Extra Strength Tylenol, Tylenol PM, Tylenol Flu, Aleve, Aleve PM, Aleve Extended Release, Goody's, Goody's Extra Strength, BC, BC Arthritis, and Walmart brands of ibuprofen and acetaminophen. Possible side effects, ostensibly associated with taking these medications, were also listed (identical to the self-reported symptoms listed above).

Half of the participants were randomly assigned to a condition in which they were informed on the mock FDA website that there was a class-action lawsuit associated with the drug recall and that they could take part (litigation condition). The potential monetary compensation for the class action was stated to be between $46,300 and $1,000,000 depending on their symptoms, the size of the final award, and the number of people joining the class action. Individuals were asked to click a link to indicate their interest in entering the class action lawsuit. The remaining participants were assigned to a condition in which the website informed them that they could not litigate due to a Supreme Court decision (non-litigation condition).

Participants then indicated how often in the previous year they had used the named medications and rated how often they experienced specific aversive symptoms. Blood pressure and pulse were taken while the participant was seated at a table. Participants then completed the computerized TMT, which was described as a test of attention, and then completed the Whitely and the MMPI-2. Total testing time with each individual participant was between 90 and 120 min. Afterward, participants were fully debriefed and provided believability ratings (1 "completely" to 4 "not at all"). The procedure was approved by the host university's institutional review board, and none of the data have been published elsewhere.

Data were subsequently collected for a control condition. This *post hoc* data collection allowed us to examine the effects of the FDA context, though importantly, the participants were not randomized for this analysis. Sixty-seven participants completed the same self-report measures as noted above, but with no information regarding the FDA recall or litigation (i.e., FDA condition v. control, with these conditions coded +1 and –1, respectively). The 67 participants for this control (no FDA) condition had an average age of 19.41 years (SD = 3.21) and was 77.8% Caucasian. Age and gender did not differ significantly from those in the original sample. See **Figure 1** for an overview.

All participants were awarded experimental credit for their psychology class in exchange for their time. The presented research was approved by the host institution's Institutional Review Board (#H1011-160).

Statistical Analyses

Hierarchical regression analyses were employed to examine the predictive value of health anxiety, the manipulated condition, and their interaction. The experimental condition was effect coded, with +1 denoting the litigation condition and –1 for the non-litigation condition. Similarly, when comparing the FDA context to the subsequently collected data with no FDA context, we employed effect coding (+1, –1, respectively). All other variables were centered within their respective distributions.

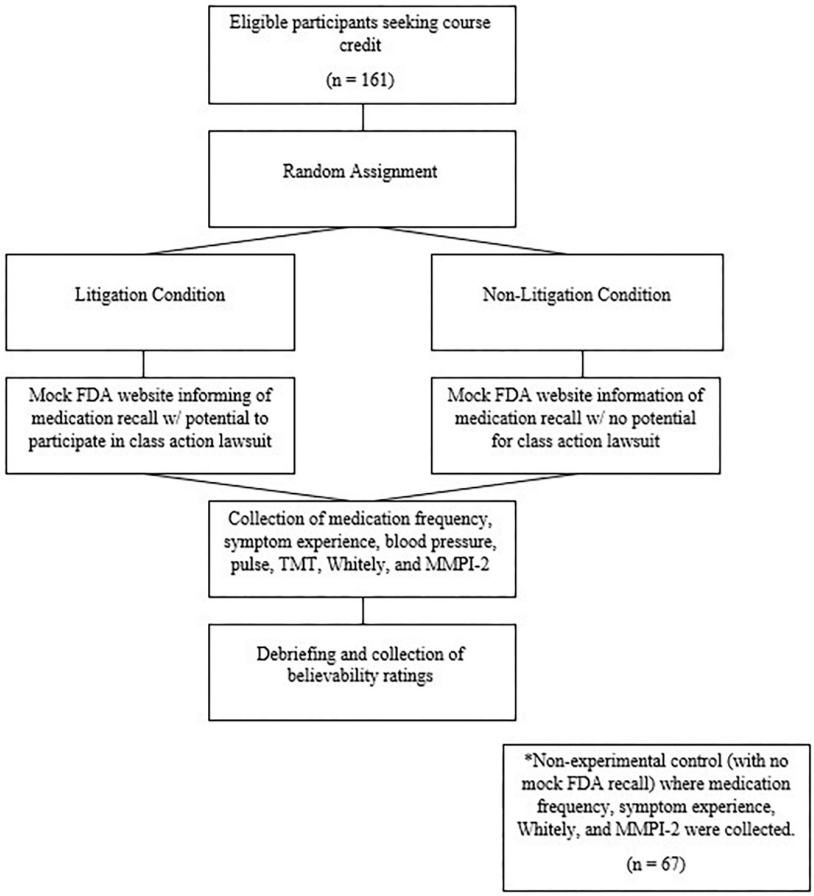

FIGURE 1 | Flowchart describing the procedure.

An interaction term was created by multiplying the centered variables by the effect-coded condition, and follow-up probes were used to assess all interactions (Aiken and West, 1991). All analyses were conducted controlling for summed usage scores (the extent to which the medications were used), with this information entered in Step 1 of the regression. The main effects of health anxiety and the effect coded experimental condition were entered in Steps 2 and 3, respectively, and their interaction was entered in Step 4. Effect size estimates are reported in the form of r-square values and Cohen's ds for the obtained results, and 95% confidence intervals are reported for the interactions. Small to medium effect sizes were estimated to emerge based on the literature, and G-Power was used to estimate the needed sample size to achieve statistical power of at least 0.80 (i.e., $N > 150$). Outlier analyses indicated no problematic values and there were no issues with multicollinearity. Correlations between the scales used to assess health anxiety are reported in **Table 1**.

RESULTS

Most participants (80.4%) rated the FDA recall as "completely believable" (rated as 1) and 19.6% reported it as "believable" (rated as 2) with a mean rating of 1.2 (SD = 0.4) out of 4 (rated as "completely not believable"; 13 participants were not given this question). The data to follow report on all participants, as the findings are the same irrespective of the believability ratings, providing further support that participants held similar views with respect to the credibility of the experimental procedure.

Predicting Self-Reported Side-Effect Symptom Experience

The mode and mean usage were "a few times per year" for 75% of the sample, and <15% of the sample reported weekly or daily usage. Symptom experience scores ranged from 0 to 47 ($M = 14.7$, $SD = 9.1$). Self-reported usage of the recalled medications

TABLE 1 | Correlations between individual difference measures of health anxiety.

	Hs	Hy	Whitely
Hs	___	0.75*	0.44*
Hy		___	0.38*
Whitely			___

*$p < 0.01$.

accounted for 3.6% of the variance in symptom endorsement (Cohen's $d = 0.386$) [$F(1,159) = 5.90$, $p = 0.016$], with higher use being associated with higher symptom endorsement.

After statistically controlling for usage, the Whitely Index ($b = 0.47$) accounted for the most variance in symptom endorsement at 21.7% (Cohen's $d = 1.053$) [F_{change} (1,158) = 46.0, $p < 0.001$], the Hs scale ($b = 0.41$) accounted for 17.1% of variance (Cohen's $d = 0.908$) [F_{change} (1,158) = 34.18, $p < 0.001$], and the Hy scale ($b = 0.41$) accounted for 16.5% (Cohen's $d = 0.889$) [F_{change} (1,158) = 32.61, $p < 0.001$]. In all cases, higher scores resulted in greater symptom endorsement. The three measures of health anxiety were also simultaneously entered into the regression equation, yielding a total explained variance of 28.5% after controlling for usage (Cohen's $d = 1.263$) [F_{change} (3,156) = 21.84, $p < 0.001$], with the Whitely accounting for the bulk of the variance in self-reported symptoms ($b = 0.34$, $t = 4.62$, $p < 0.001$).

Because depression and anxiety have been shown to significantly and substantially inflate retrospective accounts of physical symptoms (Howren and Suls, 2011), it is important to determine if the measures of health anxiety provide unique information. After statistically controlling for usage, the MMPI-2 scores of depression (clinical scale 2) and anxiety (supplemental scale A) together accounted for 12.1% of the variance in symptoms (Cohen's $d = 0.742$) [F_{change} (2,157) = 11.23, $p < 0.001$], which is statistically significant and a substantial effect. Nevertheless, each of the three measures of health anxiety continue to significantly predict symptom endorsement over and above depression and anxiety, with the Whitely, Hs and Hy accounting for an additional 11.5% (Cohen's $d = 0.721$) [F_{change} (1,156) = 24.63, $p < 0.001$], 12.6% (Cohen's $d = 0.759$) [F_{change} (1,156) = 27.45, $p < 0.001$], and 12.7% [F_{change} (1,156) = 27.73, $p < 0.001$] of the variance, respectively. Moreover, when examined collectively, the three measures of health anxiety still account for an additional 19.7% (Cohen's $d = 0.991$) [F_{change} (3,154) = 15.68, $p < 0.001$] of the variance in symptom reporting after controlling for usage and MMPI-2 depression and anxiety scores.

Condition (litigation vs. non-litigation) was not a significant predictor of symptom endorsement, and there were no significant interactions between health anxiety and condition (**Table 2**).

We also evaluated the effect of the FDA recall by comparing the full 167 participants to the subsequently collected 67 control participants. Medication usage did not differ significantly in this group as compared to the original sample. Using regression analyses it was also shown that there were no main effects for condition (exposure to mock FDA drug-recall vs. control) on self-reported symptoms ($F_{change} = 0.722$, $p = 0.396$). Interactions between condition and each of the three measures of health anxiety also failed to reach significance for self-reported symptoms. Under these conditions, however, the total explained variance in self-reported symptoms for the three measures of health anxiety after controlling for usage was 12.6% (Cohen's $d = 0.759$) [F_{change} (3,62) = 3.33, $p = 0.025$], which is less than half that obtained when there was an FDA recall context (which had 28.5% explained variance; Cohen's $d = 1.263$). Thus, although still significant, the effect for the measures of health anxiety in this control condition is trending smaller; Fisher's $z = 1.52$, $p = 0.06$.

TABLE 2 | Descriptive information for symptom endorsement by condition.

	Mean	*SD*
Non-Litigation	14.45	8.49
Litigation	15.08	11.72
Control	16.19	16.41

Predicting Cognitive Performance

Regression analyses were used to determine whether health anxiety and the litigation condition predict performance on the cognitive measure (restarts, errors, and completion time for TMT Trails A).

All measures of health anxiety significantly predicted restarts for TMT Trails A after controlling for usage. The Hy scale accounted for 6.9% of the variance in restarts (Cohen's $d = 0.544$) [F_{change} (1,158) = 11.72, $p = 0.001$], the Hs scale accounted for 6.2% of the variance (Cohen's $d = 0.514$) [F_{change} (1,158) = 10.44, $p = 0.001$], and the Whitely Index accounted for 4.1% of the variance (Cohen's $d = 0.414$) [F_{change} (1,158) = 6.85, $p = 0.01$]. In all cases, higher scores on the measures of health anxiety resulted in more restarts (poorer performance).

Significant interactions between health anxiety and litigation condition also emerged when predicting restarts on Trails A (see **Table 3** and **Figures 2**–**4**). To probe these interactions, values for participants who were low and high on the various measures of health anxiety were estimated. On each subscale, participants scoring 1 *SD* above the mean were identified as high in health anxiety and those scoring 1 *SD* below the mean were classified as low in health anxiety (Aiken and West, 1991). Simple slopes analyses revealed that as Hy {β = 0.37, $t(86) = 3.64$, $p < 0.001$, CI [–0.291, –0.015]}, Hs {β = 0.34, $t(86) = 3.33$, $p < 0.001$, CI [–0.279, –0.007]}, and Whitely {β = 0.39, $t(86) = 3.77$, $p < 0.001$, CI –0.354, –0.082]} scores increased, there were more restarts on Trails A for those in the non-litigation condition. In contrast, in the litigation condition, Hs [β = 0.13, $t(73) = 1.10$, $p = 0.28$], Hy [β = 0.16, t (73) = 1.39, $p = 0.17$], and Whitely [β = –0.02, $t(73) = –0.16$, $p = 0.87$] scores were not related to restarts.

Interactions also emerged between litigation condition and two of three health anxiety measures when predicting errors for Trails A, after controlling for usage (see **Table 3** and **Figures 5**, **6**). To probe these interactions, values for participants who were low and high on the health anxiety were estimated at 1 *SD* above and below the mean of each subscale, respectively. Simple slopes analyses revealed that as Hs {β = 0.27, $t(86) = 2.52$, $p = 0.013$, CI [–1.993, –0.164]} and Hy (β = 0.28, $t = 2.67$, $p = 0.009$, CI [–2.109, –0.257]) scores increased, there was an increase in Trails A errors for the non-litigation condition. Whereas for the litigation condition, Hs [β = –0.06, $t(73) = –0.49$, $p = 0.62$] and Hy [β = –0.08, $t = –0.66$, $p = 0.52$] scores were unrelated to errors.

All measures of health anxiety significantly predicted the time of completion for Trails A. The Hy scale accounted for 7.7% of the variability in completion time (Cohen's $d = 0.578$) [F_{change} (1,158) = 13.26, $p < 0.001$], the Hs scale predicted 6% (Cohen's $d = 0.505$) [F_{change} (1,158) = 10.18, $p = 0.002$], and the Whitely

TABLE 3 | Significant interactions for cognitive performance on Trails A outcomes.

Outcome measure	Predictor	R^2_{change}	F_{change}	β	*SE*(β)	95% confidence interval	*p-value*
Restarts	Hy × Con	0.027	4.82	–0.153	0.070	–0.291, –0.015	0.030
Restarts	Hs × Con	0.024	4.25	–0.143	0.069	–0.279, –0.007	0.041
Restarts	Whit × Con	0.057	10.0	–0.218	0.069	–0.354, –0.082	0.002
Errors	Hs × Con	0.039	6.37	–1.183	0.469	–2.109, –0.257	0.013
Errors	Whit × Con	0.033	5.42	–1.078	0.463	–1.993, –0.164	0.021
Completion Time	Hs × Con	0.018	3.07	–2106.0	1201.63	–4478.90, 266.96	0.082

R-square change values for Hy, Hs, and Whitely increase on restarts in all cases to 0.031, 0.03, and 0.059, respectively, after statistically controlling for depression and anxiety scores.

Index accounted for 3.9% of the variability in time (Cohen's d = 0.403) [F_{change} (1,158) = 6.39, p = 0.012]. In all cases, as health anxiety increased, participants took longer to complete Trails A. No significant effects for time of completion emerged for the litigation condition. The interaction for the Whitely scores and condition was also not significant, but the interaction between condition and Hs approached significance. The latter was characterized by the same pattern of simple slopes as seen in the previous analyses (i.e., significant positive beta weight, but only for the non-litigation condition when predicting time to complete Trails A; see **Table 3**).

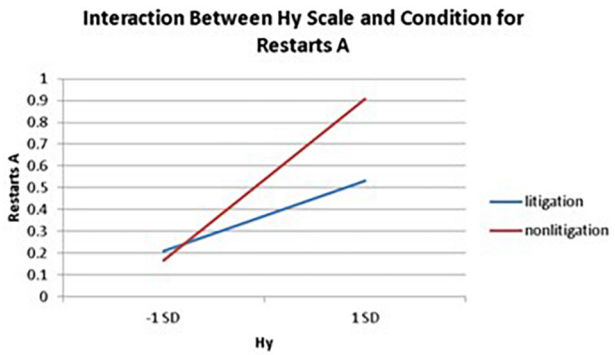

FIGURE 2 | Plotting the interaction between the Hy scale and condition when predicting restarts for Trails A of the TMT.

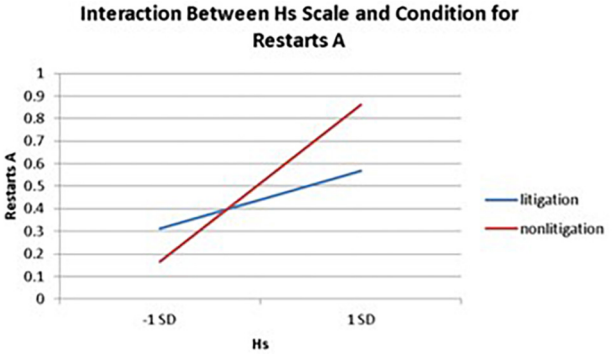

FIGURE 3 | Predicting the interaction between the Hs scale and condition when predicting restarts on Trails A of the TMT.

Thus, health anxiety was consistently associated with poorer performance on the TMT (slower time, and more errors and restarts), but only in the non-litigation condition.

Predicting Physiological Functioning

Table 4 provides descriptive information for the physiological measures. The Hs [F_{change} (1,155) = 5.85, p = 0.017] and Hy [F_{change} (1,155) = 5.45, p = 0.021] scales accounted for 3.6% (Cohen's d = 0.386) and 3.4% (Cohen's d = 0.375), respectively, of the variance in systolic blood pressure after controlling for usage. Beta weights were negative, indicating that as scores on the scales increased, systolic blood pressure decreased. Only the Hy scale predicted diastolic blood pressure, accounting for 3.4% of the variability (Cohen's d = 0.375) [F_{change} (1,155) = 5.52, p = 0.02] with a negative beta weight. The Whitely scale did not predict any of the physiological measures.

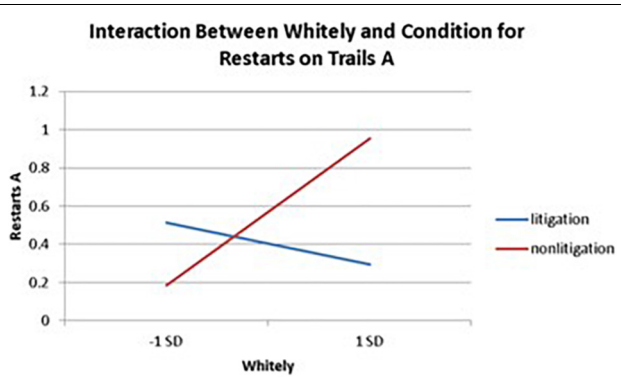

FIGURE 4 | Plotting the interaction between Whitely and condition when predicting restarts on Trails A of the TMT.

TABLE 4 | Descriptive information for the physiological measures.

	Mean	*SD*	Range
Systolic BP	107.6	12.5	77140
Diastolic BP	67.8	8.8	51–107
Heart rate (pulse)	73.5	12.7	47–119

Systolic and diastolic BPs correlated 0.29, p < 0.001. BP measures and heart rate were not significantly correlated with each other.

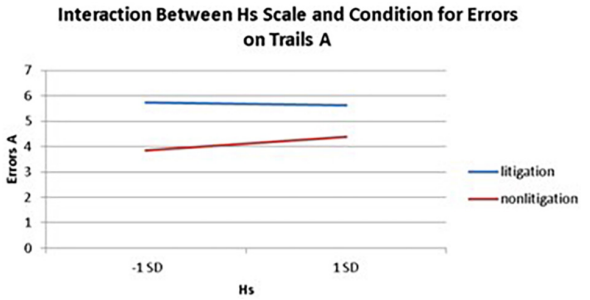

FIGURE 5 | Predicting the interaction between the Hs scale and condition when predicting errors on Trails A of the TMT.

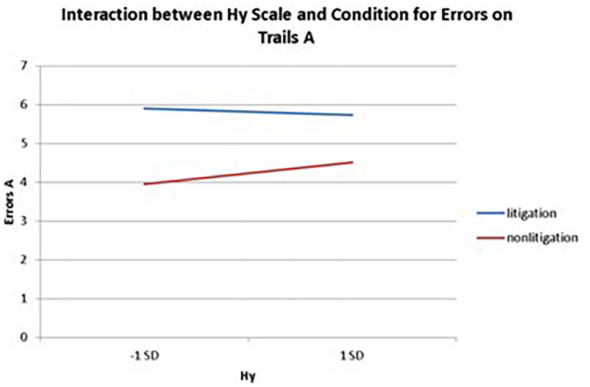

FIGURE 6 | Plotting the interaction between Hy scale and condition when predicting errors on Trails A of the TMT.

The Hs scale significantly predicted 4.8% of the variance in heart rate after accounting for usage (Cohen's $d = 0.449$) [$F_{change}(1,155) = 7.73$, $p = 0.006$]. The positive beta weight indicates that as scores on Hs increased, so did the participants' heart rate.

There were no effects for the litigation condition on the physiological outcomes, and no interactions were found between the measures of health anxiety and condition for the physiological measures.

DISCUSSION

The present research indicates that health anxiety consistently predicts symptom endorsement, and this association is independent of depression and general anxiety. It was also shown that all measures of health anxiety predicted self-reported symptom experience, but symptom endorsement was unaffected by the presence of financial incentives, and only minimally affected by self-reported usage (the latter is to be expected given the fabricated nature of the drug recall). Although MMPI-2 measures of depression and anxiety were also related to symptom endorsement, these psychological variables were markedly less predictive, suggesting health anxiety has a unique association to symptom reporting beyond more general negative emotional states (see also Lecci et al., 1996). Finally, although the measures of health anxiety predicted symptom endorsement outside the context of the FDA recall (as found in the subsequent data collected in a non-randomized control condition), their predictive ability trended downward; as the *R*-square value was less than half in size. This raises the possibility that health anxiety-related symptom endorsement may be modestly amplified within the context of a drug recall announcement, though this would need to be examined in a purposely designed experiment. Notably, the obtained effects for health anxiety resulted in moderate to large effect sizes (Cohen, 1992), with each measure accounting for 16.5–21.7% of the variance, and when combined, predicting more than 28% of the variance in symptom endorsements (equating to a large Cohen's $d = 1.25$). Because the FDA recall and the adverse effects from the medications were wholly fabricated, and because similar findings emerged in the non-FDA condition, we can conclude that the driving mechanism behind the reported symptoms could not be the medications themselves, especially given that the use of medications was low and statistically controlled. Thus, symptom endorsement must be associated with genuine symptom *perception* or malingering (i.e., intentional over-reporting for the sake of compensation). The high proportion of variance in symptom endorsement accounted for by health anxiety, and the limited effect of the experimentally controlled financial incentive suggests genuine symptom perception driven by health anxiety is the most prominent mechanism, beyond any tendency for general over-reporting. Importantly, usage should not be a strong predictor because the side effects were not actually related to the medications, and usage rates were low. This is an essential aspect of this experimental paradigm, as real-life drug recalls would necessarily confound usage (i.e., those responding to a recall notice would be those using the drugs), *a priori* symptoms, which may be higher in those who take medications, and actual medication side effects.

Consistent with the literature, using health anxiety to predict subjective outcomes (self-reported symptoms) resulted in larger effects relative to the prediction of objective cognitive and physiological measures (e.g., Drici et al., 1995; Beedie et al., 2008). However, the current findings add to the literature by illustrating; (1) an effect even for young, healthy individuals, (2) the extensive impact of health anxiety (large effect sizes) when the context is methodologically controlled, and (3) interactions between health anxiety and external incentives (litigation) when examining a cognitive outcome. Thus, when considering responses to an FDA recall, the resulting effects appear to depend upon how the sequelae are quantified (i.e., which outcome variable is considered).

With respect to the interactions between health anxiety and litigation potential, it was found that greater health anxiety typically resulted in more problematic TMT (cognitive) performance in the non-litigation condition, whereas health anxiety was unrelated to TMT performance in the litigation condition. This finding may have some implications for differentiating a health anxiety-driven response from a malingering response when, for example, dealing with individuals who are falsely claiming to experience cognitive difficulties in the context of a lawsuit (see section "Implications").

In the present study, MMPI-2 measures of health anxiety (Hs and Hy) were associated with lower scores on at least one of the blood pressure readings, and Hs scores were associated with increased heart rate. One possible explanation for the latter finding is that an acute stress response is prompted by the fear of what the aversive symptoms could mean. Activation of the sympathetic autonomic nervous system, part of the "flight or fight" response, is well documented and is known to cause an increase in heart rate, as well as other changes (Jansen et al., 1995). Of course, what is unknown is whether the observed physiological differences are durable or simply reflect a short-term response. It is more difficult to explain why those participants with higher health anxiety displayed a decrease in their systolic blood pressure, as previous research has not shown this effect. However, the current results do suggest that there may be tangible physiological changes associated with the measures of health anxiety, indicating effects that extend beyond self-reported symptom endorsement to changes that may be less apparent to the individuals experiencing them.

Implications

When notifying the public about FDA recalls, it is general practice to list adverse responses (symptoms) that are thought to be associated with the recalled medication. From an ideal standpoint, the recall should activate risk perceptions for those who have used the medications, as well as activating mental representations of coping procedures that are linked to specific actions, such as discontinuing use of the medications and following up with any resulting symptoms (see the common-sense model of self-regulating health and illness; Leventhal et al., 2003). However, those with high health anxiety may be especially attuned to information about adverse effects and more prone to experience changes in their health perceptions (Salkovskis and Warwick, 2001; Lecci and Cohen, 2002). Although announcing the symptoms associated with a drug recall may inadvertently negatively impact the perceived health (i.e., trigger symptom reporting) of individuals with high health anxiety independent of whether participants even took the medication, it also appears to be the case that health anxiety predicts symptom reporting without the pretext of an FDA recall. The latter finding is in keeping with the literature that links health anxiety with a wide range of chronic medical conditions and symptom experiences (see review by Lebel et al., 2020). Similar findings may also occur for broader related constructs such as negative affectivity (Watson and Pennebaker, 1989), as this construct has also been linked to broad symptom endorsement (e.g., Barsky, 1992; Karoly and Lecci, 1993). Indeed, the revised symptom perception hypothesis explicitly predicts that the negative emotional states of anxiety and depression uniquely and powerfully influence retrospective reports of physical symptoms (Howren and Suls, 2011), and this would be in keeping with how symptoms were reported in the current study. However, in the current research, measures of health anxiety remained significant and substantial predictors even after statistically controlling for depression and anxiety scores. Thus, although constructs reflecting broad negative emotional states undoubtedly play a role in predicting symptom endorsement, there remains a substantial effect for the experience of health anxiety in symptom reporting (see also Barsky et al., 2002).

Another potential implication of this research is in the arena of pharmaceutical development. The Code of Federal Regulations (45CFR46) mandates the safety of individuals who participate in research, and consistent with this mandate, all four phases of FDA approved clinical trials involve close monitoring of the side effects and adverse events (e.g., National Institutes of Health, 1999). The U.S. Food and Drug Administration (2010) defines adverse events quite broadly as "any untoward medical occurrence associated with the use of a drug, whether or not considered drug-related" (p. 7). Thus, even the perception of symptom experiences may be sufficient to be considered an adverse event. Consequently, the presence of health anxious individuals in a drug trial could increase the likelihood that otherwise safe medications are identified as having too many adverse events. Health anxiety may also be responsible for the common occurrence of a subset of symptoms that appear as side effects for many medications. Health anxiety may also create noise in the identification of genuine drug effects. Because medication effect sizes are typically classified as small to extremely small (Cohen, 1992; Cuijpers et al., 2010; Bartolucci et al., 2011; Sullivan and Feinn, 2012; Mustian et al., 2017), excessive adverse symptom reporting could introduce "noise" to the measurement of genuine drug effects that can affect the precision of measuring pharmaceutical effects. Thus, it may be helpful to consider either screening out those with elevated health anxiety from investigative trials or weighing their information less (e.g., using scores on measures of health anxiety as a covariate) so as not to unduly influence the determination of adverse effects associated with the drug under investigation.

It is also essential to note that the endorsement of symptoms in healthy participants required very little symptom information when it was given in an official context. This raises the question of how these results impact actual drug recalls. Interestingly, when offered the opportunity to partake in a class-action lawsuit, all but one participant agreed to do so despite the fabricated symptoms associated with the FDA recall. This indicates a high willingness to join class-action lawsuits even in cases where there is no possibility that those joining the suit have experienced adverse effects caused by the product. Although this has implications for malingering, it must be acknowledged that there was no main effect for the potential to litigate for any of the measures. Moreover, high health anxiety resulted in a performance that was atypical for malingering on the cognitive measure, as more problematic scores emerged in the non-litigation condition as compared to the litigation condition. Thus, the observed findings are more complex in nature, and a health anxiety response-set may be distinct from a malingering response-set. [*Note:* this conclusion is further bolstered by the fact that MMPI-2 measures that have been used to assess possible malingering, *F* scale and scale 4 (Pd) scores, account for markedly less variance in symptom endorsement after usage; only 5.9% combined, and do not account for significant variance in Trails A scores. Moreover, the three measures of health anxiety explain an *additional* 22.8% of the variance after entering the *F* scale and scale 4 scores; $F_{\text{change } 3,154} = 17.34$, $p < 0.001$.]

Finally, the current findings may have implications that go beyond the influence of health anxiety on symptoms endorsement. For example, nocebo responses can occur when expectations of adverse outcomes of medical treatments or agents produce negative or worsening health symptoms (Benedetti et al., 2007; Mitsikostas et al., 2020). Beliefs about risks, expectations of specific symptoms and anxiety are known to increase nocebo responses (Colloca and Benedetti, 2007; Cocco, 2009; Colloca and Miller, 2011; Daniali and Flaten, 2021), and information about adverse effects can trigger nocebo responses (Bagarić et al., 2021). For example, negative messaging by health professionals about side-effects increases reports of cognitive problems in people receiving chemotherapy (Jacobs et al., 2017), and media reports about WiFi radiation can increase reports of somatic symptoms (Bräscher et al., 2017). Similarly, it has been established that adverse event reporting related to vaccination is associated with news coverage and internet database search numbers in the concurrent month (Faasse et al., 2017). In their review of the mechanisms underlying nocebo responding, Benedetti et al. (2007) suggested that anticipatory anxiety aroused by information plays a significant causal role. Thus, the response to highly publicized drug recalls and lawsuits could be conceptualized as a form of nocebo responding (involving anticipatory health anxiety), and future research could explore this theoretical connection more deeply.

Historically, differentiating between health-anxious somatic responses and malingered responses has proven difficult, despite notable differences in causality (i.e., somatic responses being related to genuine symptom perception and malingering being associated with feigned symptom experience; Bellamy, 1997). "Compensation neurosis" was once offered as an intermediate explanation for these phenomena when individuals experience exaggerated symptoms when faced with the stress of seeking financial compensation, but has lost favor due to the emergence of newer health-related DSM disorders (Hall and Hall, 2012). The current research offers deeper insight into how these phenomena differ during an FDA recall, with individual differences in health anxiety having much more pronounced effects than the potential for financial compensation.

Limitations and Future Directions

The studied population may have impacted the results. College students are young and healthy and tend to use pain medication sparingly relative to older individuals and clinical populations. Indeed, the usage data from the current study indicate that 75% of participants only used pain medications a few times per year and in relatively small doses. A future study could focus on the elderly or those with chronic pain, where the usage of pain medication would be much higher. Because we did not collect information on the incidence of other medical conditions, general health, or medications to treat any conditions, this may confound our findings, and future research could collect such data. Future studies could also focus on the college population but target medications that are more commonly used by that group, such as attention deficit disorder, asthma, and depression medications. It is expected that by focusing on populations or medications with higher rates of use, the emergent effects could be more prominent, because the attribution of symptoms to those medications would plausibly be more extensive. In the current study, we addressed this issue by statistically controlling for medication usage. However, it is essential to recognize that studying a young and healthy population can be advantageous in that it reduces confounds that complicate the analysis with older and/or less healthy individuals. For example, those who actually take pain medications are likely experiencing more pain and other related symptoms like depression, and could be experiencing more side effects from medications. They also may be more likely to believe they are entitled to some compensation for their symptoms. Thus, although a college student sample necessarily undermines the generalizability of the findings, it provides added control over potentially confounding variables, as this group would have fewer confounding health conditions and would be less likely to take pain medications on a regular basis (e.g., Wensing et al., 2001; Green et al., 2016).

The current study did not control for the cognitive abilities of the participants, and this could have impacted scores on the cognitive measure. Of course, this would be more problematic for our measured variables (e.g., health anxiety), but less so for the experimentally manipulated variable (e.g., litigation potential), as the latter involved random assignment and presumably an unbiased allocation of cognitive abilities.

Ecological validity is always a concern in research. Although we likely mimicked an FDA recall, the cognitive and physiological assessments were less ecologically valid, and the experimental nature of this research is distinct from naturally occurring symptoms outside the lab. Health anxiety does predict symptom endorsement in general, though effect sizes tend to be smaller (e.g., Feldman et al., 1999). However, the experimental nature of this research and the use of a simulated drug recall are instrumental in isolating the impact of litigation potential on health anxiety. Notably, a manipulation check indicated participants believed they were participating in a genuine FDA drug recall, suggesting a relatively high level of ecological validity in the current research, despite its experimental nature. Similarly, it could be argued that retrospective symptom reporting is subject to biased recall. Class-action lawsuits in response to drug recalls, however, rely on similar types of reporting (i.e., the participation of individuals who have taken medications over some past period of time), meaning the current study's retrospective nature is ecologically valid, at least with respect to the drug recall context.

Similar research has demonstrated an association between chronic pain and personality types characterized as "hypochondriacal" (Johansson and Lindberg, 2000) or "neurotic" (Ramirez-Maestre et al., 2004). The current research could be seen as building on these findings by suggesting that this association may be due, at least in part, to the propensity to *perceive* pain rather than being fully explained by the nociceptive input. Much like the previously discussed concept of "compensation neurosis," the currently reviewed literature reflects a modernization in terminology and conceptualization (from "hypochondriasis" to "health anxiety"), which parallels the evolving nomenclature from the DSM-IV to the DSM-5.

An additional sample with no FDA information was collected after the completion of the original study in an attempt to provide

some degree of control for the FDA context. Obviously, this is less than ideal, as there would be other potential systematic differences, and assignment to the FDA/no FDA context was not randomized. This necessarily limits our conclusions regarding the FDA context itself, as confounding variables such as participant maturation effects, could attenuate our ability to detect differences between these conditions.

Although we did obtain some findings of significance with respect to the physiological measures, it is noted that the measurement of blood pressure and heart rate can be less accurate when it is only measured once (e.g., Whelton et al., 2017). Similarly, additional cognitive data could be collected to provide convergent validity and improve measurement accuracy. Even the inclusion of TMT B data as a standalone or in combination with TMT A data could be used to generate index scores (e.g., difference scores and/or ratios) that could provide additional sensitivity to the consequences for cognitive functioning (see Tyburski et al., 2020). Unfortunately, the TMT B data were unavailable for the current study.

Finally, there is significant overlap between the common symptoms presented in the current research and symptoms associated with anxiety. For example, of the nine common side effect symptoms considered in the current study, six are recognized as generalized anxiety symptoms (Steer and Beck, 1997); and similar claims could be made of the study's physiological measures (blood pressure and heart rate). This overlap in symptoms may further confound the differentiation of health anxiety-based effects from real medication side effects in health-anxious individuals. Importantly though, the current research shows that measures of cognitive functioning, like the TMT, were impacted by health anxiety. Because TMT performance is not typically associated with anxiety (e.g., Waldstein et al., 1997), it is reasonable to assume the studied drug recall effects are unique from those solely associated with anxiety responses. Future research, however, may wish to employ additional measures to parse out the influence of anxiety responses.

CONCLUSION

This experimental study sheds light on the relationship between health anxiety and symptom endorsement, cognitive performance, and physiological functioning in the context of an FDA drug recall announcement; and few studies to date have explored the psychological variables at play under such circumstances. Of particular note, symptom endorsement was strongly predicted by health anxiety and these effects remain strong after statistically controlling for depression and anxiety. Even objective outcomes such as blood pressure, heart rate, and cognitive performance were modestly predicted by health anxiety, but not by the litigation condition. And interactions consistently emerged for the cognitive task, with generally poorer performance for those with higher health anxiety in the non-litigation condition; whereas health anxiety was unrelated to performance for the litigation condition.

In short, the present research and the general literature suggest that there are likely to be numerous, complex, and interacting factors that influence how individuals react to health-related information in the context of a drug recall. Importantly, individual differences in health anxiety appear to merit further attention not simply for self-reported data but also for what are considered more objective outcomes. This is in keeping with a trend in the literature indicating that how health-related phenomena are *perceived* is at least as important as the phenomenon itself, even with respect to physiological responses (see Crum and Langer, 2007; Benedetti et al., 2011). Health anxiety-based effects have the potential to decrease precision in the context of drug recalls, making it increasingly difficult to distinguish those whose symptoms are the result of genuine drug effects, those whose symptoms are related to the drug recall, and those whose responses are motivated by the potential to litigate. Although it is general practice in drug recalls to list potential adverse side effects caused by the medications in question, this may elicit unintended symptom experiences and health anxious individuals may be more susceptible. Thus, further consideration of health anxiety, perceived health, and their interactions with situational factors is indicated in better understanding how individuals respond to drug recalls.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://osf.io/yhdz6/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of North Carolina Wilmington Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SN conducted the study under the supervision of LL. AR was involved in collecting data for the control condition and completed related analysis. JK was involved in generating the idea of the study, served on the thesis committee, and assisted manuscript preparation. GP conducted nocebo-related literature review and conceptualization, contributed significantly to manuscript preparation, edited and conducted analyses, and prepared the manuscript for submission. LL assisted with editing throughout. All authors contributed to the article and approved the submitted version.

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REFERENCES

Aiken, L. S., and West, S. G. (1991). *Multiple Regression: Testing And Interpreting Interactions*. Newbury Park, CA: Sage.

American Psychiatric Association (2013). *Diagnostic And Statistical Manual Of Mental Disorders*, 5th Edn. Arlington, VA: American Psychiatric Publishing.

Arbisi, P. A., and Butcher, J. N. (2004). Relationship between personality and health symptoms: use of the MMPI-2 in medical assessments. *Int. J. Clin. Health Psychol.* 4, 571–595.

Bagarić, B., Jokić-Begić, N., and Sangster Jokić, C. (2021). The nocebo effect: a review of contemporary experimental research. *Int. J. Behav. Med.* doi: 10.1007/s12529-021-10016-y

Ball, J., Archer, R. P., and Imhof, E. A. (1994). Time requirements of psychological testing: a survey of practitioners. *J. Pers. Assess.* 63, 239–249. doi: 10.1207/s15327752jpa6302_4

Barsky, A. J. (1992). Amplification, somatization, and the somatoform disorders. *Psychosomatics* 33, 28–34. doi: 10.1016/S0033-3182(92)72018-0

Barsky, A. J., and Klerman, G. L. (1983). Overview: hypochondriasis, bodily complaints, and somatic styles. *Am. J. Psychiatry* 140, 273–283. doi: 10.1176/ajp.140.3.273

Barsky, A. J., Saintfort, R., Rogers, M. P., and Borus, J. F. (2002). Nonspecific medication side effects and the nocebo phenomenon. *J. Am. Med. Assoc.* 287, 622–627. doi: 10.1001/jama.287.5.622

Bartolucci, A. A., Tendera, M., and Howard, G. (2011). Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. *Am. J. Cardiol.* 107, 1796–1801. doi: 10.1016/j.amjcard.2011.02.325

Beedie, C. J., Foad, A. J., and Coleman, D. A. (2008). Identification of placebo responsive participants in 40km laboratory cycling performance. *J. Sports Sci. Med.* 7, 166–175.

Bellamy, R. (1997). Compensation neurosis: financial reward for illness as nocebo. *Clin. Orthop. Relat. Res.* 336, 94–106. doi: 10.1097/00003086-199703000-00013

Benabou, R., and Tirole, J. (2006). Incentives and prosocial behavior. *Am. Econ. Rev.* 96, 1652–1678.

Benedetti, F., Carlino, E., and Pollo, A. (2011). How placebos change the patient's brain. *Neuropsychopharmacol. Rev.* 36, 399–352. doi: 10.1038/npp.2010.81

Benedetti, F., Lanotte, M., Lopiano, L., and Colloca, L. (2007). When words are painful: unraveling the mechanisms of the nocebo effect. *Neuroscience* 147, 260–271. doi: 10.1016/j.neuroscience.2007.02.020

Blasche, R. C., Worsley, A., and Lawrence, M. (2008). The effects of an apparent breach of therapeutic regulations on consumers: the pan pharmaceuticals recall. *Crit. Public Health* 18, 367–379. doi: 10.1080/09581590802075679

Boskovic, I. (2020). Do motives matter? A comparison between positive and negative incentives in students' willingness to malinger. *Educ. Psychol.* 40, 1022–1032. doi: 10.1080/01443410.2019.1704400

Bräscher, A. K., Raymaekers, K., Van den Bergh, O., and Witthöft, M. (2017). Are media reports able to cause somatic symptoms attributed to WiFi radiation? An experimental test of the negative expectation hypothesis. *Environ. Res.* 156, 265–271. doi: 10.1016/j.envres.2017.03.040

Butcher, J. N., Graham, J. R., Ben-Porath, Y. S., Tellegen, A., and Dahlstrom, W. G. (2001). *Minnesota Multiphasic Personality Inventory-2 (MMPI-2): Manual For Administration And Scoring (rev. ed)*. Minneapolis, MN: University of Minnesota Press.

Camerone, E. M., Piedimonte, A., Testa, M., Wiech, K., Vase, L., Zamfira, D. A., et al. (2021). The effect of temporal information on placebo analgesia and nocebo hyperalgesia. *Psychosom. Med.* 83, 43–50. doi: 10.1097/PSY.0000000000000882

Cioffi, D. (1991). Beyond attentional strategies: a cognitive-perceptual model of somatic interpretation. *Psychol. Bull.* 109, 25–41. doi: 10.1037/0033-2909.109.1.25

Cisler, J. M., and Koster, E. H. W. (2010). Mechanisms of attentional biases towards threat in the anxiety disorders: an integrative review. *Clin. Psychol. Rev.* 30:203.

Cocco, G. (2009). Erectile dysfunction after therapy with metoprolol: the Hawthorne effect. *Cardiology* 112, 174–177. doi: 10.1159/000147951

Cohen, J. (1992). A power primer. *Psychol. Bull.* 112, 155–159.

Cohen, P. A., Benner, C., and McCormick, D. (2012). Use of a pharmaceutically adulterated dietary supplement, Pai You Guo, among Brazilian-born women in the United States. *J. Gen. Intern. Med.* 27, 51–56. doi: 10.1007/s11606-011-1828-0

Colloca, L., and Benedetti, F. (2007). Nocebo hyperalgesia: how anxiety is turned into pain. *Curr. Opin. Anesthesiol.* 20, 435–439. doi: 10.1097/ACO.0b013e3282b972fb

Colloca, L., and Miller, F. G. (2011). The nocebo effect and its relevance for clinical practice. *Psychosom. Med.* 73:598. doi: 10.1097/PSY.0b013e3182294a50

Corsi, N., Andani, M. E., Tinazzi, M., and Fiorio, M. (2016). Changes in perception of treatment efficacy are associated to the magnitude of the nocebo effect and to personality traits. *Sci. Rep.* 6:30671. doi: 10.1038/srep30671

Crum, A. J., and Langer, E. J. (2007). Mind-set matters: exercise and the placebo effect. *Psychol. Sci.* 18, 165–171. doi: 10.1111/j.1467-9280.2007.01867.x

Cuijpers, P., van Straten, A., Bohlmeijer, E., Hollon, S. D., and Andersson, G. (2010). The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychol. Med.* 40, 211–223. doi: 10.1017/S0033291709006114

Daniali, H., and Flaten, M. A. (2021). Experiencing COVID-19 symptoms without the disease: the role of nocebo in reporting of symptoms. *Scand. J. Public Health* 50, 61–69. doi: 10.1177/14034948211018385

Dickinson, J. G. (2001). Most recalls due to FDA inspection findings. *Med. Mark. Media* 36:30.

Drici, M. D., Raybaud, F., De Lunardo, C., Iacono, P., and Gustovic, P. (1995). Influence of behavior pattern on the nocebo response of healthy volunteers. *Br. J. Clin. Pharmacol.* 39, 204–206.

Ellington, L., and Wiebe, D. J. (1999). Neuroticism, symptom presentation, and medical decision making. *Health Psychol.* 18, 634–643. doi: 10.1037//0278-6133.18.6.634

Faasse, K., Porsius, J. T., Faasse, J., and Martin, L. R. (2017). Bad news: the influence of news coverage and google searches on gardasil adverse event reporting. *Vaccine* 35, 6872–6878. doi: 10.1016/j.vaccine.2017.10.004

Feldman, P. J., Cohen, S., Doyle, W. J., Skoner, D. P., and Gwaltney, J. M. Jr. (1999). The impact of personality on the reporting of unfounded symptoms and illness. *J. Pers. Soc. Psychol.* 77, 370–378. doi: 10.1037//0022-3514.77.2.370

Graham, J. R. (2011). *MMPI-2: Assessing Personality And Psychopathology*, 5th Edn. Oxford: Oxford University Press.

Green, M. A., Little, E., Cooper, R., Relton, C., and Strong, M. (2016). Investigation of social, demographic and health variations in the usage of prescribed and over-the-counter medicines within a large cohort (South Yorkshire, UK). *BMJ Open* 6:e012038. doi: 10.1136/bmjopen-2016-012038

Hall, R. C., and Hall, R. C. (2012). Compensation neurosis: a too quickly forgotten concept? *J. Am. Acad. Psychiatry Law Online* 40, 390–398.

Heaton, R. K., Smith, H. H., Lehman, R. A., and Vogt, A. T. (1978). Prospects for faking believable deficits on neuropsychological testing. *J. Cons. Clin. Psychol.* 46:892. doi: 10.1037//0022-006x.46.5.892

Howren, M. B., and Suls, J. (2011). The symptom perception hypothesis revised: Depression and anxiety play different roles in concurrent and retrospective physical symptom reporting. *J. Pers. Soc. Psychol.* 100, 182–195. doi: 10.1037/a0021715

Hunsley, J., Hanson, R. K., and Parker, K. C. (1988). A summary of the reliability and stability of MMPI scales. *J. Clin. Psychol.* 44, 44–46. doi: 10.1002/1097-4679(198801)44:1<44::aid-jclp2270440109>3.0.co;2-a

Health, Pharma and Medtech (2022). *Global Pharmaceutical Sales from 2017 to 2021, by Region*. Available online at: https://www.statista.com/statistics/272181/world-pharmaceutical-sales-by-region/ (accessed February 23, 2022).

Iverson, G. L., Lange, R. T., Green, P., and Franzen, M. D. (2002). Detecting exaggeration and malingering with the trail making test. *Clin. Neuropsychol.* 16, 398–406. doi: 10.1076/clin.16.3.398.13861

Jacobs, W., Das, E., and Schagen, S. B. (2017). Increased cognitive problem reporting after information about chemotherapy-induced cognitive decline: the moderating role of stigma consciousness. *Psychol. Health* 32, 78–93. doi: 10.1080/08870446.2016.1244535

Jansen, A., Nguyen, X., Karpitsky, V., and Mettenleiter, M. (1995). Central command neurons of the sympathetic nervous system: basis of the fight-or-flight response. *Science* 270, 644–646.

Johansson, E., and Lindberg, P. (2000). Low back pain patients in primary care: subgroups based on the multidimensional pain. *Int. J. Behav. Med.* 7, 340–352.

Karoly, P., and Lecci, L. (1993). Hypochondriasis and somatization in college women: a personal projects analysis. *Health Psychol.* 12, 103–109. doi: 10.1037/0278-6133.12.2.103

Kellner, R. A. (1986). *Somatization And Hypochondriasis*. New York, NY: Praeger.

Larrabee, G. J. (2003). Detection of malingering using atypical performance patterns on standard neuropsychological tests. *Clin. Neuropsychol.* 17, 410–425.

Lebel, S., Mutsaers, B., Tomei, C., Leclair, C. S., Jones, G., Petricone-Westwood, D., et al. (2020). Health anxiety and illness-related fears across diverse chronic illnesses: a systematic review on conceptualization, measurement, prevalence, course, and correlates. *PLoS One* 15:e0234124. doi: 10.1371/journal.pone.0234124

Lecci, L., and Cohen, D. J. (2002). Perceptual consequences of an illness concern induction and its relation to hypochondriacal tendencies. *Health Psychol.* 21, 147–156.

Lecci, L., Karoly, P., Ruehlman, L. S., and Lanyon, R. I. (1996). Goal-relevant dimensions of hypochondriacal tendencies and their relation to symptom manifestation and psychological distress. *J. Abnorm. Psychol.* 105, 42–52. doi: 10.1037/0021-843X.105.1.42

Lees, A., Mogg, K., and Bradley, B. P. (2005). Health anxiety, anxiety sensitivity, and attentional biases for pictorial and linguistic health-threat cues. *Cogn. Emot.* 19, 453–462. doi: 10.1080/02699930441000184

Leventhal, H., Brissette, I., and Leventhal, E. (2003). "The Common-sense model of self-regulation of health and illness," in *The Self-Regulation Of Health And Illness Behaviour*, eds L. D. Cameron and H. Leventhal (London: Routledge), 42–65.

Meissner, K. (2005). Preferring patient-reported to observer-reported outcomes substantially influences the results of the updated systematic review on placebos by Hrobjartsson and Gotzsche. *J. Internal Med.* 257:394. doi: 10.1111/j.1365-2796.2005.01470.x

Meyer, G. J., Finn, S. E., Eyde, L. D., Kay, G. G., Moreland, K. L., Dies, R. R., et al. (2001). Psychological testing and psychological assessment: a review of evidence and issues. *Am. Psychol.* 56, 128–165. doi: 10.1037//OOO3-O66X.56.2.128

Mitsikostas, D. D., Blease, C., Carlino, E., Colloca, L., Geers, A. L., Howick, J., et al. (2020). European headache federation recommendations for placebo and nocebo terminology. *J. Headache Pain* 21, 1–7. doi: 10.1186/s10194-020-01178-3

Mustian, K. M., Alfano, C. M., Heckler, C., Kleckner, A. S., Kleckner, I. R., Leach, C. R., et al. (2017). Comparison of pharmaceutical, psychological, and exercise treatments for cancer-related fatigue: a meta-analysis. *JAMA Oncol.* 3, 961–968. doi: 10.1001/jamaoncol.2016.6914

National Institutes of Health (1999). *Guidance On Reporting Adverse Events To Institutional Review Boards For NIH-Supported Multicenter Clinical Trials*. Available online at: http://grants.nih.gov/grants/guide/notice-files/not99-107.html [Accessed April 11, 2014].

Pennebaker, J. (1982). *The Psychology Of Physical Symptoms*. New York, NY: Springer-Verlag.

Pilowsky, I. (1967). Dimensions of hypochondriasis. *Br. J. Psychiatry* 113, 89–93.

Pilowsky, I. (1978). A general classification of abnormal illness behaviors. *Br. J. Med. Psychol.* 51, 131–137.

Rabin, L. A., Paolillo, E., and Barr, W. B. (2016). Stability in test-usage practices of clinical neuropsychologists in the united states and canada over a 10-year period: a follow-up survey of INS and NAN members. *Arch. Clin. Neuropsychol.* 31, 206–230. doi: 10.1093/arclin/acw007

Ramirez-Maestre, C., Lopez-Martinez, A. E., and Zarazaga, R. E. (2004). Personality characteristics as differential variables of the pain experience. *J. Behav. Med.* 27, 147–165. doi: 10.1023/b:jobm.0000019849.21524.70

Rogers, R., and Bender, S. D. (2013). "Evaluation of malingering and related response styles," in *Handbook of Psychology: Forensic Psychology*, 2nd Edn, Vol. 11, eds I. B. Weiner and R. K. Otto (New Jersey, NJ: John Wiley and Sons), 517–540.

Rohling, M. L., Binder, L., and Langhinrichsen-Rohling, J. (1995). Money matters: a meta-analysis of the association between of financial compensation and the experience and treatment of chronic pain. *Health Psychol.* 14, 537–547. doi: 10.1037//0278-6133.14.6.537

Salkovskis, P. M., and Warwick, H. M. C. (2001). "Meaning, misinterpretations, and medicine: a cognitive behavioral approach to understanding health anxiety and hypochondriasis," in *Hypochondriasis: Modern Perspectives On An Ancient Malady*, eds V. Starcevic and D. R. Lipsitt (Oxford: Oxford University Press), 202–222.

Salthouse, T. A., and Fristoe, N. M. (1995). A process analysis of adult age effects on a computer-administered trail making test. *Neuropsychology* 9, 518–528.

Samra, J., and Koch, W. (2002). "The monetary worth of psychological injury: What are litigants suing for?," in *Taking Psychology And Law Into The Twenty First Century*, ed. J. R. P. Ogloff (New York, NY: Kluwer/Plenum), 285–321.

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., and Zubieta, J. K. (2007). Individual differences in reward responding explain placebo-induced expectations and effects. *Neuron* 55, 325–336. doi: 10.1016/j.neuron.2007.06.028

Speckens, A. M., Van Hemert, A. M., Spinhoven, P., and Bolk, J. H. (1996). The diagnostic and prognostic significance of the whitely index, the illness attitude scales and the somatosensory amplification scale. *Psychol. Med.* 26, 1085–1090. doi: 10.1017/s0033291700035418

Steer, R. A., and Beck, A. T. (1997). "Beck anxiety inventory," in *Evaluating Stress: A Book Of Resources*, eds C. P. Zalaquett and R. J. Wood (Grover Beach, CA: Scarecrow Education), 23–40.

Sullivan, G. M., and Feinn, R. (2012). Using effect size—or why the P value is not enough. *J. Grad. Med. Educ.* 4, 279–282. doi: 10.4300/JGME-D-12-00156.1

Trueblood, W., and Schmidt, M. (1993). Malingering and other validity considerations in the neuropsychological evaluation of mild head injury. *J. Clin. Exp. Neuropsychol.* 15, 578–590. doi: 10.1080/01688639308402580

Turi, Z., Bjørkedal, E., Gunkel, L., Antal, A., Paulus, W., and Mittner, M. (2018). Evidence for cognitive placebo and nocebo effects in healthy individuals. *Sci. Rep.* 8, 1–14. doi: 10.1038/s41598-018-35124-w

Tyburski, E., Karabanowicz, E., Mak, M., Lebiecka, Z., Samochowiec, A., Petka-Wysiecka, J., et al. (2020). Color trails test: a new set of data on cognitive flexibility and processing speed in schizophrenia. *Front. Psychiatry* 11:521. doi: 10.3389/fpsyt.2020.00521

U.S. Food and Drug Administration (2022). *Industry Guidance for Recalls*. Available online at: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/industry-guidance-recalls

U.S. Food and Drug Administration (2010). *FDA Safety Update Adverse Event Reporting: Clinical Investigator Responsibilities*. Available online at: http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Oncology/UCM314082.pdf [Accessed April 11, 2014].

U.S. Food and Drug Administration (2013). *FDA Drug Recalls For 2013*. Available online at: http://www.fda.gov/Drugs/Drugsafety/DrugRecalls/default.htm [Accessed January 24, 2014].

Verbrugge, L. M., and Ascione, F. J. (1987). Exploring the iceberg: common symptoms and how people care for them. *Med. Care* 25, 539–569.

Walczyk, J. J., Sewell, N., and DiBenedetto, M. B. (2018). A review of approaches to detecting malingering in forensic contexts and promising cognitive load-inducing lie detection techniques. *Front. Psychiatry* 9:700. doi: 10.3389/fpsyt.2018.00700

Waldstein, S. R., Ryan, C. M., Jennings, R., Muldoon, M. F., and Manuck, S. B. (1997). Self-reported levels of anxiety do not predict neuropsychological performance in healthy men. *Arch. Clin. Neuropsychol.* 12, 567–574.

Warwick, H. M. (1989). A cognitive-behavioral approach to hypochondriasis and health anxiety. *J. Psychosom. Res.* 33, 705–711.

Watson, D., and Pennebaker, J. W. (1989). Health complaints, stress, and distress: exploring the central role of negative affectivity. *Psychol. Rev.* 96, 234–254. doi: 10.1037/0033-295x.96.2.234

Weinstein, N. D. (1984). Why it won't happen to me: perceptions of risk factors and susceptibility. *Health Psychol.* 3, 431–457. doi: 10.1037//0278-6133.3.5.431

Weinstein, N. D. (1987). Unrealistic optimism about susceptibility to health problems: conclusions from a community-wide sample. *J. Behav. Med.* 10, 481–500. doi: 10.1007/BF00846146

Wensing, M., Vingerhoets, E., and Grol, R. (2001). Functional status, health problems, age and comorbidity in primary care patients. *Qual. Life Res.* 10, 141–148. doi: 10.1023/a:1016705615207

Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., Dennison, H. C., et al. (2017). ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Hypertension* 71, 1269–1324.

Winkler, A., and Hermann, C. (2019). Placebo-and nocebo-effects in cognitive neuroenhancement: when expectation shapes

perception. *Front. Psychiatry* 10:498. doi: 10.3389/fpsyt.2019.00498

Wolters, F., Peerdeman, K. J., and Evers, A. W. (2019). Placebo and nocebo effects across symptoms: from pain to fatigue, dyspnea, nausea, and itch. *Front. Psychiatry* 10:470. doi: 10.3389/fpsyt.2019.00470

Zech, N., Schrödinger, M., Seemann, M., Zeman, F., Seyfried, T. F., and Hansen, E. (2020). Time-dependent negative effects of verbal and non-verbal suggestions in surgical patients—A study on arm muscle strength. *Front. Psychol.* 11:1693. doi: 10.3389/fpsyg.2020.01693

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STUDY PROTOCOL
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Counterconditioning as Treatment to Reduce Nocebo Effects in Persistent Physical Symptoms: Treatment Protocol and Study Design

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Persistent physical symptoms have a high prevalence and a large impact for patients and society. To date, treatment effects for these symptoms are often limited. Nocebo effects (i.e., negative outcomes that are not attributable to active treatment components) have a substantial influence on treatment success and can be established via learning through classical conditioning. Therefore, interventions aimed at reducing nocebo effects by means of counterconditioning, in which an alternative association (inhibiting the previous association) is learned, could be a promising method for improving physical symptoms. In experimental studies, counterconditioning has been shown promising in reducing experimentally-induced nocebo effects on pain and itch. Application of counterconditioning procedures to reduce nocebo effects on clinical symptoms has yet to be researched. This paper provides a protocol of a 6-week counterconditioning intervention aimed at reducing nocebo effects and clinical pain in patients with fibromyalgia. A study in patients with fibromyalgia is proposed to examine the feasibility and potential effectiveness of this counterconditioning intervention as a novel treatment method for reducing nocebo effects and generalization to clinical pain symptoms. Results can help design an optimized treatment protocol for reducing nocebo effects, based on the experiences of participants and the first indications of treatment efficacy.

Keywords: nocebo effects, counterconditioning, persistent physical symptoms, open-label, classical conditioning

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INTRODUCTION

Persistent physical symptoms have a high prevalence and a large impact for patients and society. To date, treatment of these symptoms is effective to a limited extent. Potentially, targeting placebo and nocebo effects (i.e., positive and negative treatment outcomes not attributable to active treatment components, respectively) could provide a novel pathway to prevent or decrease persistent physical symptoms. Placebo and nocebo effects have consistently been found to affect physical symptoms, such as pain, in a positive or negative way, respectively (Benedetti et al., 2003; Colloca et al., 2008;

Vase et al., 2009; Colloca and Finniss, 2012; Bartels et al., 2014; Colagiuri et al., 2015; Peerdeman et al., 2016; Bąbel et al., 2017; Thomaidou et al., 2020). For example, when patients are told a certain procedure will cause a stinging pain, they may experience more pain than when patients are told the procedure will only feel like a slight pinch. Or, when patients had several treatments at the hospital causing nausea, they might already start to feel nauseous upon merely entering the hospital. Because it is not always possible to prevent such nocebo effects from occurring, it is relevant to examine the potential effects of treatments aimed at reducing nocebo effects.

Classical conditioning is an important associative learning mechanism for the induction of nocebo effects (Bräscher et al., 2018; Thomaidou et al., 2020). During nocebo conditioning, an aversive stimulus (unconditioned stimulus, US; e.g., a highly painful stimulus) leading to an unconditioned response (UR; e.g., pain increase) is paired with a neutral stimulus (typically a sham treatment, such as a sham electrode). Repeated pairing of the two stimuli during a learning or acquisition phase (e.g., pain stimulus together with activation of a sham electrode) can lead to the neutral stimulus (e.g., activation of a sham electrode) becoming a conditioned stimulus (CS). This CS will elicit a similar response (conditioned response; CR, i.e., pain increase) as the UR, even without the US being present. This may also occur in patients with persistent physical symptoms, especially since they may have had several negative treatment experiences. For example, if a person experienced side effects to a certain drug in the past, they may experience these side effects again while taking another drug, merely because they were negatively conditioned in the past (Barsky et al., 2002).

As classical conditioning plays such an important role in the induction of nocebo effects, methods attenuating conditioned effects may be promising for reducing nocebo effects. The attenuation of conditioned effects has been studied more extensively in the field of fear and evaluative conditioning than in the field of nocebo research. Conditioned fear responses can be reduced by extinction, during which the CS is no longer presented together with the US. Through this, the association between CS and US decreases, leading to diminishing of the CR (Vervliet et al., 2013). Furthermore, exposure therapy, which is based on the principles of extinction learning by exposing people to fearful situations in a safe way without anything bad happening to them, can effectively treat fear responses (e.g., spider phobia). Exposure therapy has also been shown effective for chronic pain, as it reduced pain catastrophizing, fear of pain, perceived harmfulness of activities, as well as functional disability (Leeuw et al., 2008; Woods and Asmundson, 2008; Glombiewski et al., 2018). Another method to reduce conditioned effects is counterconditioning, during which the US is replaced by a US of opposite valence. For example, if the CS was previously paired with an electric shock, this shock could be replaced during counterconditioning by a monetary reward. This might lead to more beneficial effects than merely stopping the reinforcement of the CS as in extinction. Multiple studies have found counterconditioning to successfully diminish conditioned effects, but results on the superiority of either extinction or counterconditioning within the field of fear and evaluative conditioning are mixed, as shown by a recent review paper and another recent study (Jozefowiez et al., 2020; Keller et al., 2020). Additionally, long-term efficacy is not often measured, but one of the studies did show that during spontaneous recovery and reinstatement tests (a day after fear induction), diminished threat expectancy was found in the counterconditioning group (Kang et al., 2018). However, CS valence did not differ between the counterconditioning and extinction groups. Furthermore, another study showed counterconditioning to result in a short-lived reduction of distress related to the CS+, but this effect disappeared during later test phases (Hendrikx et al., 2021). Therefore, it may be worthwhile to investigate long-term effects of counterconditioning and whether counterconditioning may be more beneficial in preventing relapse than extinction.

In nocebo research in physical symptoms it has been shown that conditioned nocebo effects are relatively resistant to extinction (Colloca et al., 2008; Colagiuri et al., 2015; Colagiuri and Quinn, 2018) and it may therefore be worthwhile to try the more active strategy of counterconditioning for reducing nocebo effects. While studies comparing efficacy of extinction and counterconditioning for reducing nocebo effects are scarce, they consistently showed counterconditioning to be superior to extinction, as counterconditioning can even reverse nocebo effects into placebo effects (Bartels et al., 2017; Thomaidou et al., 2020). This finding is also supported by a recent preprint paper (Meijer et al., 2021). Although these studies are promising, only healthy participants were examined on the experience of acute physical symptoms, and the experiments were done in a single session and in a highly regulated environment, making it difficult to translate these findings to patients with persistent physical symptoms in clinical care.

Based on the existing literature on counterconditioning in fear and evaluative conditioning studies, as well as the limited knowledge base on experimental counterconditioning in nocebo studies, a counterconditioning treatment protocol was developed for application in patients with persistent physical symptoms, in particular patients with fibromyalgia. As to our knowledge no other study investigated a counterconditioning treatment protocol to counteract nocebo effects, it is important to first study the feasibility and potential effectivity of such a treatment. Therefore, the current paper describes both the development and design of a 6-week counterconditioning treatment protocol aimed to reduce (clinical) pain in patients with persistent physical symptoms.

METHODS AND ANALYSIS

A 6-week counterconditioning treatment protocol for use in patients with persistent physical symptoms was developed based on previous literature on counterconditioning in fear and evaluative conditioning, as well as the limited literature on counterconditioning in nocebo effects. The treatment consists of 7 weekly sessions (1 intake session and 6 treatment sessions), with 2 follow-up appointments 3 and 6 months after end of treatment. The treatment protocol will be described firstly below. As this treatment protocol has never been tested before, a first

study was designed, to test whether patients are able to complete the protocol and whether there are indications for treatment efficacy. This study design will be described after the treatment protocol. When indications for efficacy have indeed been found, a large-scale randomized controlled trial could be conducted, using the same methods as described below (potentially with minor changes based on the results of the first study).

DESIGN OF TREATMENT PROTOCOL

Pain Induction

To be able to test the efficacy of counterconditioning, first a nocebo effect is induced in all participants, using open-label nocebo conditioning. To be able to condition a nocebo effect on pain, pain will have to be induced. In studies on nocebo pain conditioning, several pain-induction methods could be chosen. The most commonly used pain-induction methods are the application of thermal and electrical stimuli. Although these pain-induction methods are effective in research settings, when applying (counter)conditioning in pain patients, the choice of US would ideally be based on the clinical symptoms patients are experiencing in daily life. While some patients with chronic pain may experience a burning-like type of pain (e.g., patients with MS), which resembles thermal pain, or visceral pain (e.g., patients with IBS), other patients (such as patients with fibromyalgia) experience a deep-tissue pain, which is more closely resembled by pressure pain (Wolfe et al., 1990; Gracely et al., 2003; Petzke et al., 2003). Therefore, in this study pressure pain is used during the (counter)conditioning procedures.

Pressure pain is induced by applying pressure to the thumbnail of the non-dominant hand, with a custom-made automated pneumatic stimulator (named PEPPA), specifically built for this study by SOLO (Support for Research, Laboratories and Education, Leiden University). A handpiece is attached to the stimulator and has a plastic piston that applies pressure via a 1 cm^2 hard rubber probe. Participants can insert their thumb in a cylinder opening in the handpiece, after which the probe can deliver pressure on the middle of the thumbnail. The thumbnail was selected as a neutral location in which participants feel little to no clinical pain during testing. As previously reported (Petzke et al., 2003; Jensen et al., 2009), this is a safe location for repeatedly delivering pressure stimuli. Stimulus duration is set at 2.5 s, with an inter-stimulus interval of 30 s. The minimal amount of pressure administered is 0.5 kg, whereas the maximum is 13 kg. Finally, an emergency stop is attached to the stimulator, which participants can press if they cannot tolerate the administered pain. After pressing the emergency stop button, all air pressure is released immediately, and they can remove their thumb. All components of PEPPA are displayed in **Figure 1**.

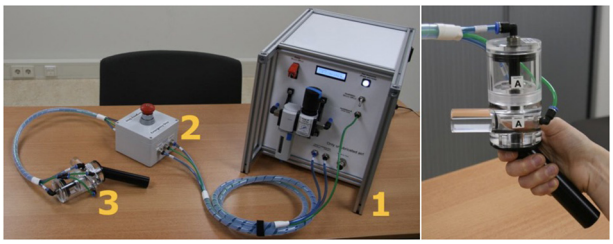

FIGURE 1 | Components of PEPPA. 1 shows the main device, 2 the emergency stop button, and 3 shows the handpiece. The picture on the right shows how the thumb can be placed into the handpiece.

Sham Transcutaneous Electrical Nerve Stimulation Device

A sham Transcutaneous Electrical Nerve Stimulation (TENS) device (Bentrotens T37, Bentronic Gesellschaft fuer Medizintechnik GmbH, Wolnzach, Germany) will serve as nocebo conditioning stimulus (CS) in the first part of the treatment (the conditioning session), during which it is associated with an increase of pressure pain. During the second (main) part of the treatment (counterconditioning sessions), it will again serve as CS, now associated with a reduction of pressure pain. This device is developed to automatically switch off after 30 seconds, meaning it will no longer send any electrical pulses and becomes a sham device. The activation within the first 30 seconds is according to usual TENS use (i.e., using mild electrical pulses). Participants are told it is a sham device but are instructed that it will still have an effect on their pain because of the placebo effect as has previously been found to be effective in open-label placebo studies.

Pressure Pain Calibration

To find the optimal pressure intensity for no pain (0-1/10 NRS), slight pain (2.5-3.5/10 NRS), and moderate pain (5-6/10 NRS), for the individual participant to be used in the intervention, we will conduct a calibration procedure consisting of three phases. For the non-painful stimulus, a minimally painful pressure intensity (0-1/10 NRS) is accepted, as we expect sensitization to occur due to repeated pressure administration. In phase 1 of calibration, pressure stimuli (0.5 kg increments) are applied in ascending order, up to the first pressure intensity participants rated as $\geq$6. In the second phase, five intensities are applied three times, this time in a random order. The intensities will range from the highest amount of pressure rated as 0 in phase 1, up to the highest pressure rated between 5 and 6. If there will not be any scores between 5 and 6 during phase 1, a formula is used to calculate the best-fitting value (see **Supplementary Appendix 1**). Then, in the third phase, a calibration check is performed. Three intensities are chosen by taking the median of all intensities that, during the second phase, are rated within the intended ranges for no, slight, and moderate pain. If participants will not score in one or more of the intended ranges, formulas are used to inter- or extrapolate the best-fitting intensity (see **Supplementary Appendix 1**). During the third phase, participants will need to rate at least one out of two (or two out of three for slight pain) stimuli within the ranges for no, slight and moderate pain. If these requirements will not be met, formulas will again be used to calculate the best-fitting intensity (see **Supplementary Appendix 1**). Participants who will not experience enough pain (i.e., will not rate their pain at least 5/10 at the maximum amount of pressure), or who will experience too much pain during the lowest intensity (i.e., will rate their pain above 1 from the lowest amount of pressure applied), are excluded.

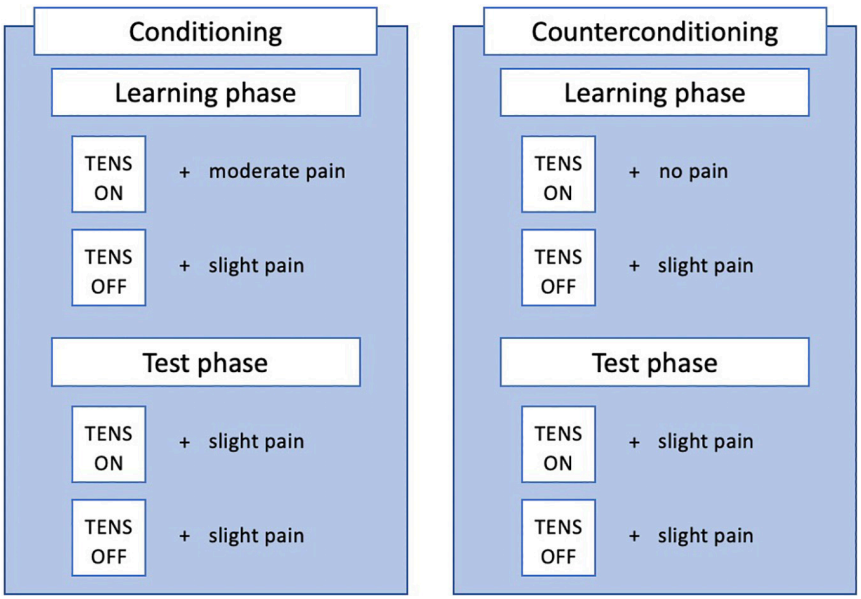

FIGURE 2 | Procedures used for conditioning and counterconditioning.

Intervention

Nocebo Conditioning

Nocebo conditioning will consist of a learning and testing phase (see **Figure 2**). During the learning phase, a message ("ON" or "OFF") on the screen in either purple or yellow will indicate the activation of the TENS device. If the TENS device is indicated to be on, this is repeatedly paired with a pressure stimulus of a moderate intensity (5-6/10 on NRS). If the TENS device is indicated to be off, this is paired repeatedly with a pressure stimulus of a slightly painful intensity (2.5-3.5 on NRS). The learning phase will consist of 10 experimental ("ON") trials and 10 control ("OFF") trials, presented in a pseudorandom order (max 2 stimuli of the same trial type - experimental or control - follow each other). The testing phase will consist of 3 experimental trials and 3 control trials, again in pseudorandom order with the same rule. During the testing phase, a slightly painful stimulus is administered during all trials, regardless of the message on the screen. The test phase is used to assess whether a nocebo effect was induced, as would be indicated by an (on average) higher score on experimental than on control trials. Additionally, participants are given open-label suggestions about the conditioning procedure, as they are told that conditioning is used to teach them that the activation of the sham device increases their pain, by manually increasing the intensity of pressure stimuli during experimental trials. They are also instructed on the nocebo effect and how this will affect their pain. A detailed description of the suggestions can be found in **Supplementary Appendix 2**.

Counterconditioning

Counterconditioning will also consist of a learning and test phase, similar to nocebo conditioning (see **Figure 2**). Counterconditioning is intended to reduce the nocebo effect, by now repeatedly pairing the alleged TENS activation (ON trials) with a non-painful stimulus, instead of the moderately painful stimulus during nocebo conditioning. The procedure is almost identical to nocebo conditioning, with the only difference being that now a non-painful (0-1/10 on NRS) pressure stimulus is paired with activation of the sham TENS device. The test phase is again used to test whether a nocebo effect is still present, by comparing experimental and control trials. Potentially, a placebo effect could be induced, indicated by an (on average) lower pain score on experimental than on control trials. Additionally, participants are given open-label suggestions about the counterconditioning procedure, as they are told counterconditioning is used to teach them that the activation of the sham device will now decrease their pain, by manually decreasing the intensity of pressure stimuli after experimental trials.

Nocebo effects induced in the lab can be reduced by counterconditioning in a single session (Bartels et al., 2017; Thomaidou et al., 2020). However, in clinical care, patients may have had several negative treatment experiences, instead of a single occasion as in nocebo conditioning in the lab. This may make these nocebo effects even more resistant to treatment. Additionally, as we want to promote long-term efficacy of the treatment, the counterconditioning procedure is repeated several times. As literature on the use of counterconditioning (or related methods, such as systematic desensitization) in clinical care is limited in the field of fear and evaluative conditioning (Keller et al., 2020) and non-existent in nocebo research, it is difficult to determine the optimal number of sessions. Ideally, the treatment is easily accessible and therefore consist of as few sessions as possible, while maintaining optimal treatment efficacy. Therefore, the main intervention during this study will consist of 6 sessions (1 per week) and 2 follow-up sessions (at 3

and 6 months after the final session) to boost the intervention and assess long-term effects. This is much more than previous lab studies on healthy participants. A first study with this design will shed light on the course of nocebo reduction (e.g., how many sessions are needed before the nocebo effect is reduced and after how many sessions a potential effect on clinical pain is found). Potentially, this may also differ per person, as we know susceptibility to nocebo effects also differs between people (Manaï et al., 2019). Based on this information, the amount of sessions may be optimized for future applications. If the nocebo effect is not yet fully reduced after 6 sessions, but a decrease has been found, the intervention could be expanded with more sessions.

Open-Label Suggestions & Conditioning

One of the most important disadvantages of using traditional placebo and nocebo conditioning procedures is the fact that it usually involves deception. During traditional placebo and nocebo research, participants are not aware of the fact that the treatment they are receiving is actually a placebo, nor are they aware a conditioning procedure is used (Benedetti et al., 2003; Colloca et al., 2008; Bartels et al., 2014, 2017; Colagiuri et al., 2015; Bąbel et al., 2017; Thomaidou et al., 2020,?). While deception is generally considered acceptable for research, it is problematic to use deception in clinical care, as patients should always be fully informed regarding the treatment they are about to receive (Riddick, 2003). Deception could harm the trust in both the healthcare professional and the treatment (Miller et al., 2005; Peerdeman et al., 2021), which could lead to reduced treatment efficacy and treatment adherence. Open-label placebos have been examined in several studies (in both healthy and clinical populations) and have been found to be an effective treatment (Sandler and Bodfish, 2008; Kaptchuk et al., 2010; Carvalho et al., 2016; Schaefer et al., 2018; Kleine-Borgmann et al., 2019); in some studies, open-label placebos were even as effective as closed-label placebo treatments (Locher et al., 2017; Lembo et al., 2021). An open-label procedure of nocebo or placebo conditioning has only been compared to closed-label procedures once so far, in which no differences were found between open- and closed-label conditioning (Meeuwis et al., 2019). Although evidence on the efficacy of open-label (counter)conditioning is scarce, closed-label suggestions and (counter)conditioning procedures are not ethically appropriate, and thus open-label counterconditioning seems the most fitting option when considering such procedures for reducing nocebo effects in clinical care. A more detailed description of the suggestions can be found in **Supplementary Appendix 2**.

Homework

In between sessions, participants are asked to do homework exercises to promote generalization of nocebo reduction to everyday life. Participants are asked to apply at home what they have learned in the lab, in order to also reduce their clinical pain symptoms. During the first few weeks, participants will use the TENS device at home; they are asked to connect the TENS device to electrodes they will place on their forearm (as during the lab sessions) and are then asked to think back to the lab session and how the device influenced their pain during the session. Then they are asked to imagine the device will now also influence their clinical pain, anywhere in their body. During the final weeks, participants will no longer use the TENS and will instead visualize the function of TENS to reduce their pain. A detailed description of the homework exercises can be found in **Supplementary Appendix 3**.

Study Design

Participants

Participants are females diagnosed with fibromyalgia syndrome by a general practitioner or medical specialist. Participants must be at least 18 years old and have a good understanding of written and spoken Dutch. Exclusion criteria consist of severe somatic or psychiatric morbidity that may interfere with the study protocol (e.g., heart/lung diseases), Raynaud's disease, injuries on the non-dominant hand, refusal or inability to remove nail polish or artificial nails on the thumbnail of the non-dominant hand for the experiment, having metal implants in the non-dominant hand or arm, having a medicinal pump, and pregnancy or breastfeeding.

Design

A randomized, between-within subjects design is used, with two groups (see **Figure 3** below). Participants are randomly assigned (1:1) to either the intervention group or the control group. Participants in the intervention group receives the counterconditioning intervention, whereas participants in the control group receives a sham intervention. A randomization list is made by an independent person and group allocation is noted down on paper and inserted into an opaque envelope, which is opened after the pressure pain calibration procedure, to reduce experimenter bias during calibration. Since all experimental manipulations contain open-label verbal instructions, neither the experimenter nor the participant can be fully blinded to group allocation. Nevertheless, participants are not be explicitly told whether they are in the intervention or control group. The intervention consist of seven weekly sessions and two follow-up sessions (three and six months after the initial seven weeks).

Control Group

A sham intervention can serve as control, meaning a sham version of both conditioning and counterconditioning can be used. Sham conditioning and counterconditioning consist of the same amount of trials as the (counter)conditioning procedures, with the same intensities of pain administered (see **Figure 2**). The major difference is that the pain intensities are not associated with activation or deactivation of the sham TENS device. The 20 pain stimuli of each learning phase are presented randomly, just as the order of the messages ("ON" and "OFF"). Maximally 2 of the same messages ("ON" or "OFF") follow each other. Furthermore, participants are explicitly told there is no association between the messages and the pain stimuli. More information on the open-label suggestions will be given below and in **Supplementary Appendix 2**.

As for the homework exercises, participants in the control group also use the TENS device at home during the first weeks, but participants have not learned a specific association between the device and pain relief in the lab. They receive a neutral version

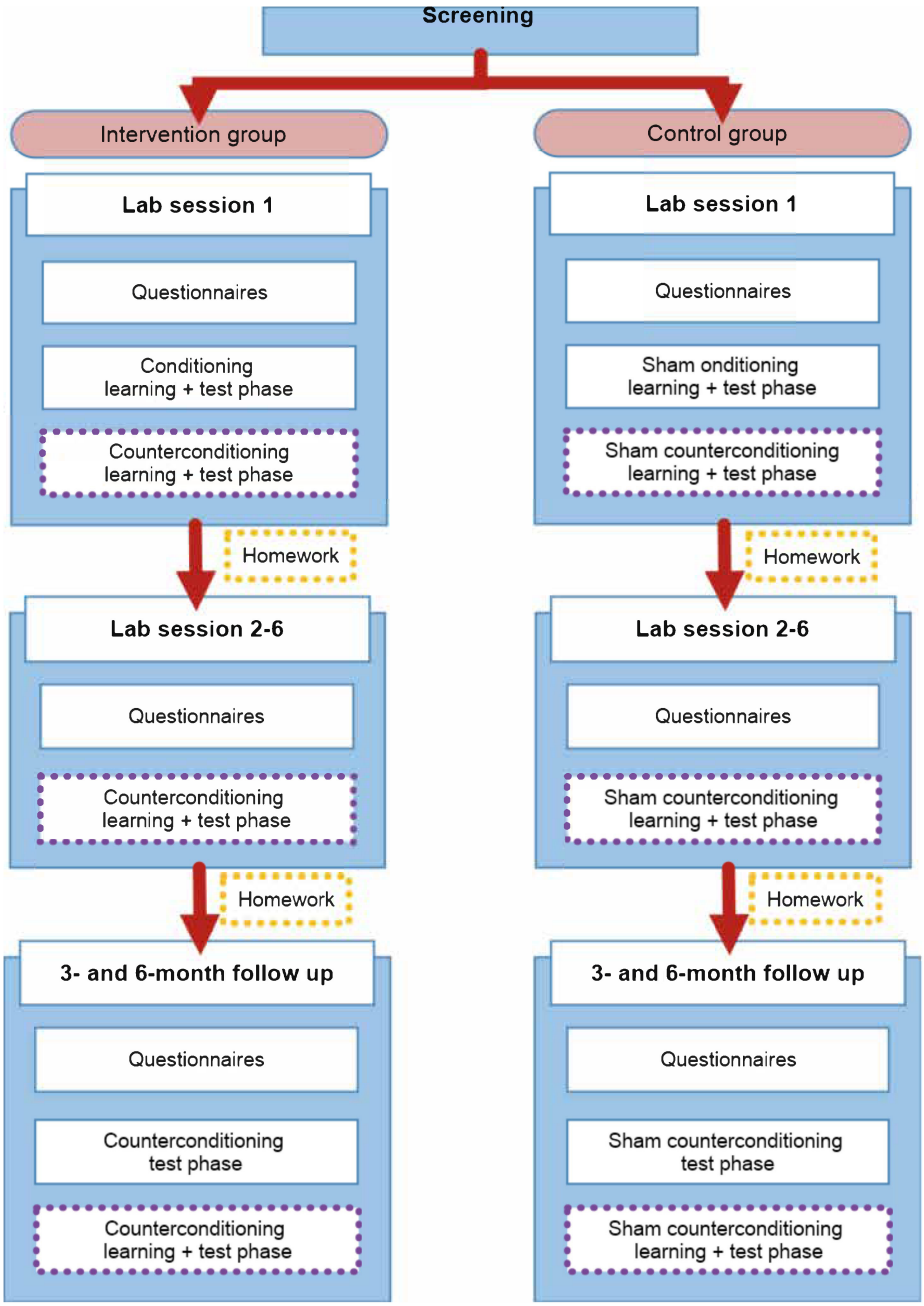

FIGURE 3 | Overview of the treatment protocol for use in patients with persistent physical symptoms, distinguished by group. The (sham) intervention parts of the procedure are emphasized by using purple dotted lines.

of the task. A detailed description of the homework exercises can be found in **Supplementary Appendix 3**.

Self-Report Measures

Several validated questionnaires are filled out by participants, as well as some questions on their medical history and demographics. **Table 1** gives an overview of all questionnaires and when they are administered. The Fibromyalgia Impact Questionnaire (FIQ, (Burckhardt et al., 1991), and a Numeric Rating Scale (NRS; 0 (no pain) to 10 (worst pain imaginable)) measuring average intensity of clinical pain during the last week is used to track symptoms of patients throughout the study. Other measures are used to explore the influence of personal characteristics (i.e., Pain Catastrophizing Scale (PCS, (Sullivan et al., 1995)), State and Trait Anxiety Inventory – Trait Scale (STAI-T, (Spielberger, 1983)), State and Trait Anxiety Inventory – State Scale, Short Form (STAI-Ss, (Marteau and Bekker, 1992)), Life Orientation Test Revised (LOT-R, (Scheier et al., 1994))).

TABLE 1 | Overview of administered questionnaires throughout the intervention.

Time point	Questionnaire
Intake session	Questions on medical history Questions on demographics State-Trait Anxiety Inventory-Trait Scale Pain Catastrophizing Scale Life Orientation Test-Revised
Session 1-6, 3- and 6-month follow ups	Numeric Rating Scale clinical pain Fibromyalgia Impact Questionnaire State-Trait Anxiety Inventory-State Scale Expectations regarding the intervention
Multiple times during every session (except intake session)	Numeric Rating Scale on pressure pain levels Numeric Rating Scale on valence of CS/control cue
Session 6 + 3- and 6-month follow-ups	Evaluation questionnaire

Additionally, the expectations participants have regarding the intervention are measured every session (except for the intake session). This is measured using 2 questions asking whether participants believe the intervention will influence 1) experimentally-induced pain on the thumb and 2) their clinical pain, using a 0 to 10 numeric rating scale (NRS), with 0 meaning "will not influence pain at all" and 10 meaning "will very strongly influence pain".

Experienced pain throughout the sessions (during calibration and (counter)conditioning) is measured using an NRS from 0 to 10 (0 indicating no pain, 10 indicating worst pain imaginable on the hand). Additionally, valence is measured, as it is argued in studies on fear and evaluative conditioning that the change in CS valence might be important to prevent reinstatement of the previously conditioned effects (De Jong et al., 2000; Meulders et al., 2015; Van Dis et al., 2019). It is therefore important to investigate whether CS valence is successfully altered by counterconditioning. Valence of the CS and control cue is measured after the 1st and 10th trial of the learning phase and after the 1st trial of the test phase. It is measured using an NRS ranging from −5 to +5, with −5 meaning "extremely unpleasant", 0 meaning "neutral" and +5 meaning "extremely pleasant".

Finally, to measure patient satisfaction, an evaluation questionnaire is filled out by participants at the end of session 6 and the 3- and 6-month follow-up. This questionnaire includes questions on the patient-researcher interaction, their satisfaction regarding the intervention in general, whether the amount of sessions is feasible, whether they believed the intervention to have an effect on their pain (both in the lab and at home) and which group they thought they were placed in.

Procedure

Participants are invited to the lab 9 times (intake session, 6 intervention weeks, 3- and 6-month follow-up). **Figure 3** gives an overview of the procedure.

Screening and Intake

Participants are screened over the phone before inviting them to the lab, to check whether they are eligible to participate. If eligible, participants are invited to the lab for a first appointment, the intake session, in which the intervention is fully explained to the participants. Additionally, participants are asked to fill in most of the questionnaires mentioned in **Table 1**.

Session 1

During session 1, participants fill out several questionnaires (see **Table 1**). Afterwards, pain levels are calibrated as described above, followed by a 5-min break. Subsequently, participants undergo the nocebo conditioning procedure, which is not repeated in the other sessions. After nocebo conditioning and a 10-min break, the counterconditioning procedure follows. The session is concluded by instructions on the homework exercises, which participants do daily between the sessions. In total, the duration of the first session is approximately 2 h.

Session 2-6

During sessions 2 to 6, participants will again fill out several questionnaires. Then pressure pain calibration is checked by only repeating phase 3 of the calibration procedure, to ensure the administered intensities are still perceived similarly to the first session. If this is not the case, intensities are adjusted using standard formulas (**Supplementary Appendix 1**). After a 5-min break, the counterconditioning procedure will start, after which the session is concluded. In between sessions, participants will do daily homework exercises. The duration of session 2-6 is approximately 35-45 min. Only during session 6, an evaluation questionnaire is filled out by participants at the end of the session.

Follow Ups

The follow ups are almost identical to sessions 2-6. Again, the sessions will start with the participants filling out questionnaires, after which calibration step 3 is repeated. Then, participants will undergo only a test phase of counterconditioning, to test long-term effects of the intervention. Through this, it is assessed whether the nocebo effect is still absent and whether potentially a placebo effect is still present. After this test phase, the regular counterconditioning procedure is repeated, to boost the effect of the intervention. In both follow-up sessions, a short evaluation questionnaire is filled out at the end of the session. The duration of both follow-up sessions is approximately 45 min.

Objectives and Statistical Analyses

As the current treatment protocol has never been tested before, it would be relevant to first test the feasibility of the protocol. Once proven feasible, a larger randomized controlled trial could be conducted to test efficacy of the treatment protocol.

The main study parameter in a first study is the feasibility of the counterconditioning intervention. This can be done by looking at the drop-out rate; by measuring participants' satisfaction with the intervention; by examining what, according to the participants, is causing the possible increase and reduction of experimentally-evoked pressure pain in the test phase of (counter)conditioning (e.g., the TENS device, the placebo or nocebo effect); and by examining the amount of experimentally-evoked pressure pain reported during the test phase of counterconditioning, whether this reduces over time, as well as the speed of this reduction.

Next to examining the feasibility, a first study could also exploratively look at indications that the counterconditioning intervention affects experimentally-evoked pressure pain from pre- to post-treatment. To this aim, it can be explored whether the induced nocebo effect in the intervention group can be successfully reduced (or even reversed) by comparing the confidence intervals of the change in the conditioned nocebo effect from the test phase of conditioning (session 1) to the counter conditioned nocebo effect from the test phase of counterconditioning (session 6) in the intervention group and the control group. The effect size and confidence interval of the difference between groups will also be calculated. Additionally, all sessions are compared in terms of nocebo reduction, to be able to assess speed of nocebo reduction.

Confidence intervals of the change in the conditioned nocebo effect from the test phase of conditioning (session 1) to the counter conditioned nocebo effect from the test phase of counterconditioning at 3- and 6-month follow-up in the intervention group and the control group can also be explored. The effect size and confidence interval of the difference between groups are calculated.

Finally, whether there are indications of the influence of personal characteristics (e.g., expectations regarding the intervention, amount of anxiety during testing) on the feasibility of the study and the potential effects of the intervention can be explored. This is done by comparing the confidence intervals of the scores on the different questionnaires on personal characteristics in participants who drop out versus participants who do not drop out and in participants who show a reduction of the nocebo effect versus participants who do not show any treatment effect (within the intervention group).

DISCUSSION

The aim of this paper was to describe a newly-developed counterconditioning treatment protocol for patients with persistent physical symptoms and its translation into a study design of which a first study could test its feasibility and explore its potential effectiveness. Nocebo effects in clinical care can have a substantial detrimental impact on treatment outcomes but cannot always be prevented, therefore it is important to investigate potential treatment options for reducing nocebo effects. While counterconditioning has been experimentally investigated in healthy participants, the proposed treatment protocol is the first using counterconditioning to reduce nocebo effects in chronic pain patients (e.g., patients with fibromyalgia). A first study will provide important insights on how to potentially further develop this treatment protocol for reducing nocebo effects in clinical practice. Multiple facets are considered, such as patient satisfaction, drop-out rate, and patient characteristics.

Anticipated Results

Feasibility

For a first study, the main outcome parameter is the feasibility of the treatment protocol. Firstly, drop-out rate can give an insight into patient satisfaction and into feasibility of completing the treatment protocol as a patient. While we strive to prevent drop-out as much as possible, one of the main aims of the study is to investigate whether it is feasible for patients to receive this type of treatment weekly, for multiple weeks in a row. As for patient satisfaction, we aim for participants to be satisfied with their treatment, by being fully open about the study procedures (hence the open-label nature of the study). Nevertheless, we are evoking pain in our protocol, which may negatively affect patient satisfaction. Furthermore, although the study is open-label, participants may still be slightly skeptical about the procedures used, as found in other open-label studies (Carvalho et al., 2016; Lembo et al., 2021). We strive to reduce this skepticism as much as possible by providing an explanation of placebo treatments and how they can be efficacious. Furthermore, although patients were skeptical and/or expected better results from active treatments, open-label placebos were still effective in the aforementioned studies. Finally, we expect participants to be able to correctly answer what influenced the intensity of the experimentally-induced pain, which is not the TENS device itself, but the nocebo or placebo effect (induced by (counter)conditioning), as we are fully open about the procedure. Nevertheless, it cannot be ruled out participants may think the TENS device still has some influence on their pain or that they attribute their experiences to other phenomena. If this happens, that might indicate that our instructions regarding the treatment are not sufficiently clear to participants and need adjustment.

Efficacy of the Treatment

In a first study, no formal conclusions can be drawn on the efficacy of the treatment. However, we do expect multiple findings will point towards successful induction and reduction of nocebo effects. Firstly, for the treatment group, we expect participants to score higher on experimental ("TENS on") trials than on control ("TENS off") trials in the test phase of nocebo conditioning (session 1), which would be in line with other studies on nocebo conditioning (e.g., Benedetti et al., 2003; Colloca et al., 2008, 2010; Bartels et al., 2014; Colagiuri et al., 2015; Thomaidou et al., 2020). For the control group, we do not expect to see a difference between the trial types, similar to results from other studies using a sham conditioning group (Thomaidou et al., 2020). Secondly, we expect the nocebo effect (defined as the average difference between experimental and control trials in the test phase of conditioning) to be larger in the treatment group than in the control group. Thirdly, we expect to find a reduction of the nocebo effect in the treatment group, meaning the nocebo effect is expected to be (close to) zero or even below zero (indicating a placebo effect), during the test phase of counterconditioning in session 6. This is based on the findings of the few studies investigating counterconditioning for reducing nocebo effects of physical symptoms in healthy participants (Bartels et al., 2017; Thomaidou et al., 2020). As for the speed of this reduction, we will explore whether the nocebo effect can be reduced from the first session or starting from later sessions, and whether this reduction is stable throughout the sessions. For the 3- and 6-month follow-ups, we expect to find similar results,

indicating potential long-term efficacy of counterconditioning. For the control group, we do not expect to find a change in effect from conditioning (session 1) to counterconditioning (session 6 or follow-ups). We also do not expect to find a placebo effect at the end of session 6 and the follow-ups for the control group.

Then, regarding valence of the CS, we expect the counterconditioning procedure to affect the valence from pre- to post-treatment. During nocebo conditioning (session 1), we expect participants in the experimental group to rate the CS more negatively than at the end of counterconditioning (session 6 and both follow-ups). For the control group, we do not expect to find differences in valence from pre- to post-treatment.

Finally, it can be explored whether the counterconditioning procedure can be translated to clinical pain. As this is the first time this is investigated, it is yet to be determined whether the protocol could be beneficial for reducing clinical pain. We do, however, expect to find the counterconditioning sessions, strengthened by the homework exercises, being able to reduce clinical pain of participants in the treatment group, but not in the control group.

Should the aforementioned results indeed be found, a large-scale randomized controlled trial could be conducted afterward, be able to draw more robust conclusions about the efficacy of the nocebo counterconditioning treatment.

Anticipated Strengths and Limitations

An important strength of the current treatment protocol is that it is aimed at reducing existing nocebo effects, instead of aimed at preventing nocebo effects. Although arguably the prevention of nocebo effects is crucial in clinical practice, this is not always feasible, as patients need to be informed about potential negative effects of a treatment, which may induce nocebo effects. Consequently, developing a treatment protocol aimed at nocebo reduction can be of added value to clinical practice. Another important strength of this treatment protocol is the fact that an open-label procedure is used. As mentioned before, traditional paradigms using (counter)conditioning are mostly deceptive procedures, which is not suitable for a clinical treatment protocol. As some studies have already shown the efficacy of open-label placebos, as well as open-label conditioning, open-label counterconditioning does seem a promising treatment strategy for reducing nocebo effects.

Using open-label paradigms may have some disadvantages. While it is unethical to use deception in clinical practice, the risk of a response bias may be higher. Participants are explicitly told (counter)conditioning is used to influence their pain and this thus makes the intensity of stimuli more predictable than during traditional paradigms. Furthermore, they may be more aware of the expected outcomes, which could also increase the risk of participants answering in a way fitting the expectations of the researchers. This risk could be minimized optimally by letting the participants answer on a computer, instead of directly answering the researcher. Additionally, nocebo effects are usually not induced in an open-label fashion, as patients are not aware of the fact they are being conditioned. Furthermore, instead of a single type of negative experience, most likely a combination of experiences has induced nocebo effects in patients. While it is important to mimic such a negative experience for all participants, it may be complicated to figure out which stimuli migh be best used for counterconditioning. Therefore, once proven potentially effective, the final counterconditioning protocol may have to be adjusted to account for these differences in patients' experiences.

Moreover, the effect of extinction and exposure therapy may be context-dependent, as found by several studies (Rodriguez et al., 1999; Mystkowski et al., 2002; Vansteenwegen et al., 2005). Return of fear appears to be higher in people who were submitted to a context change after extinction or exposure than in people remaining within the same context. This may also be the case for the counterconditioning of the nocebo effect, but this has not yet been researched. While in the lab the nocebo effect is induced and reduced within the same context, this is typically not the case in clinical practice, as the treatment occurs in a different context than in which effects were induced. Furthermore, it may prove difficult to translate effects from the lab or clinic to the home situation, as this would again be a change of context. By incorporating homework exercises in between the weekly sessions, we aim to enable generalization of the effects from the lab to other contexts. The exploratory results of the study will give insight into whether this may lead to successful generalization of the effects or whether alternative and/or extra steps in the protocol are necessary to promote generalization.

Practical Implications

We expect a first study to show the counterconditioning intervention to be feasible and will provide preliminary indications for its effectiveness in relieving pain in fibromyalgia patients. Should this indeed be observed, a large-scale randomized controlled trial could be conducted afterward to assess the efficacy of the counterconditioning protocol. Results of the first study can help inform the design of the final protocol, based on the experiences of participants in the feasibility study and the first indications regarding treatment efficacy. Additionally, the counterconditioning protocol should ideally also be compared to other methods aimed at reducing conditioned responses, to test whether this method is superior over more commonly used procedures, such as extinction (exposure therapy), overshadowing, latent inhibition and blocking (Quinn and Colagiuri, 2018). If shown effective in a larger study, the protocol could potentially be implemented in clinical practice for treatment of nocebo effects in patients with persistent physical symptoms, which could consequently lead to a decrease in these physical symptoms.

ETHICS STATEMENT

This study was reviewed and approved by the Medical Ethical Committee Leiden-Den Haag-Delft (number NL 66812.058.18).

Written informed consent was obtained from all participants for their participation in this study. Furthermore, the study has been preregistered in the Dutch Trial Register (NL8189).

AUTHOR CONTRIBUTIONS

SM wrote the first draft and all (sub)sections of the manuscript. SM, HM, KP, and AE contributed to the conception and design of the treatment protocol and the manuscript and provided critical feedback on the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.806409/full#supplementary-material

REFERENCES

Bąbel, P., Bajcar, E. A., Adamczyk, W., Kicman, P., Lisińska, N., Świder, K., et al. (2017). Classical conditioning without verbal suggestions elicits placebo analgesia and nocebo hyperalgesia. *PLoS One* 12:e0181856. doi: 10.1371/journal.pone.0181856

Barsky, A. J., Saintfort, R., Rogers, M. P., and Borus, J. F. (2002). Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 287, 622–627. doi: 10.1001/jama.287.5.622

Bartels, D. J. P., van Laarhoven, A. I. M., Haverkamp, E. A., Wilder-Smith, O. H., Donders, A. R. T., van Middendorp, H., et al. (2014). Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PLoS One* 9:e91727. doi: 10.1371/journal.pone.0091727

Bartels, D. J. P., van Laarhoven, A. I. M., Stroo, M., Hijne, K., Peerdeman, K. J., Donders, A. R. T., et al. (2017). Minimizing nocebo effects by conditioning with verbal suggestion: a randomized clinical trial in healthy humans. *PLoS One* 12:e0182959. doi: 10.1371/journal.pone.0182959

Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., and Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *J. Neurosci.* 23, 4315–4323. doi: 10.1523/JNEUROSCI.23-10-04315.2003

Bräscher, A.-K., Witthöft, M., and Becker, S. (2018). The underestimated significance of conditioning in placebo hypoalgesia and nocebo hyperalgesia. *Pain Res. Manage.* 2018:6841985. doi: 10.1155/2018/6841985

Burckhardt, C. S., Clark, S. R., and Bennett, R. M. (1991). The fibromyalgia impact questionnaire: development and validation. *J. Rheumatol.* 18, 728–733.

Carvalho, C., Caetano, J. M., Cunha, L., Rebouta, P., Kaptchuk, T. J., and Kirsch, I. (2016). Open-label placebo treatment in chronic low back pain: a randomized controlled trial. *Pain* 157, 2766–2772. doi: 10.1097/j.pain.0000000000000700

Colagiuri, B., and Quinn, V. F. (2018). Autonomic arousal as a mechanism of the persistence of nocebo hyperalgesia. *J. Pain* 19, 476–486. doi: 10.1016/j.jpain.2017.12.006

Colagiuri, B., Quinn, V. F., and Colloca, L. (2015). Nocebo hyperalgesia, partial reinforcement, and extinction. *J. Pain* 16, 995–1004. doi: 10.1016/j.jpain.2015.06.012

Colloca, L., and Finniss, D. (2012). Nocebo effects, patient-clinician communication, and therapeutic outcomes. *JAMA* 307, 567–568. doi: 10.1001/jama.2012.115

Colloca, L., Petrovic, P., Wager, T. D., Ingvar, M., and Benedetti, F. (2010). How the number of learning trials affects placebo and nocebo responses. *Pain* 151, 430–439. doi: 10.1016/j.pain.2010.08.007

Colloca, L., Sigaudo, M., and Benedetti, F. (2008). The role of learning in nocebo and placebo effects. *Pain* 136, 211–218. doi: 10.1016/j.pain.2008.02.006

De Jong, P. J., Vorage, I., and Van Den Hout, M. A. (2000). Counterconditioning in the treatment of spider phobia: effects on disgust, fear and valence. *Behav. Res. Ther.* 38, 1055–1069. doi: 10.1016/S0005-7967(99)00135-7

Glombiewski, J. A., Holzapfel, S., Riecke, J., Vlaeyen, J. W. S., de Jong, J., Lemmer, G., et al. (2018). Exposure and CBT for chronic back pain: an RCT on differential efficacy and optimal length of treatment. *J. Consult. Clin. Psychol.* 86, 533–545. doi: 10.1037/ccp0000298

Gracely, R. H., Grant, M. A. B., and Giesecke, T. (2003). Evoked pain measures in fibromyalgia. *Best Pract. Res.* 17, 593–609. doi: 10.1016/S1521-6942(03)00036-6

Hendrikx, L. J., Krypotos, A.-M., and Engelhard, I. M. (2021). Enhancing extinction with response prevention via imagery-based counterconditioning: results on conditioned avoidance and distress. *J. Behav. Ther. Exp. Psychiatry* 70:101601. doi: 10.1016/j.jbtep.2020.101601

Jensen, K. B., Kosek, E., Petzke, F., Carville, S., Fransson, P., Marcus, H., et al. (2009). Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. *PAIN®* 144, 95–100. doi: 10.1016/j.pain.2009.03.018

Jozefowiez, J., Berruti, A. S., Moshchenko, Y., Peña, T., Polack, C. W., and Miller, R. R. (2020). Retroactive interference: counterconditioning and extinction with and without biologically significant outcomes. *J. Exp. Psychol. Anim. Learn. Cogn.* 46, 443–459. doi: 10.1037/xan0000272

Kang, S., Vervliet, B., Engelhard, I. M., van Dis, E. A. M., and Hagenaars, M. A. (2018). Reduced return of threat expectancy after counterconditioning versus extinction. *Behav. Res. Ther.* 108, 78–84.

Kaptchuk, T. J., Friedlander, E., Kelley, J. M., Sanchez, M. N., Kokkotou, E., Singer, J. P., et al. (2010). Placebos without deception: a randomized controlledtrial in irritable bowel syndrome. *PLoS One* 5:e15591. doi: 10.1371/journal.pone.0015591

Keller, N. E., Hennings, A. C., and Dunsmoor, J. E. (2020). Behavioral and neural processes in counterconditioning: past and future directions. *Behav. Res. Ther.* 125:103532. doi: 10.1016/j.brat.2019.103532

Kleine-Borgmann, J., Schmidt, K., Hellmann, A., and Bingel, U. (2019). Effects of open-label placebo on pain, functional disability, and spine mobility in patients with chronic back pain: a randomized controlled trial. *Pain* 160, 2891–2897. doi: 10.1097/j.pain.0000000000001683

Leeuw, M., Goossens, M. E., van Breukelen, G. J., de Jong, J. R., Heuts, P. H., Smeets, R. J., et al. (2008). Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. *Pain* 138, 192–207. doi: 10.1016/j.pain.2007.12.009

Lembo, A., Kelley, J. M., Nee, J., Ballou, S., Iturrino, J., Cheng, V., et al. (2021). Open-label placebo vs double-blind placebo for irritable bowel syndrome: a randomized clinical trial. *Pain* 162, 2428–2435. doi: 10.1097/j.pain.0000000000002234

Locher, C., Nascimento, A. F., Kirsch, I., Kossowsky, J., Meyer, A., and Gaab, J. (2017). Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain* 158, 2320–2328. doi: 10.1097/j.pain.0000000000001012

Manaï, M., van Middendorp, H., Veldhuijzen, D. S., Huizinga, T. W., and Evers, A. W. (2019). How to prevent, minimize, or extinguish nocebo effects in pain: a narrative review on mechanisms, predictors, and interventions. *Pain Rep.* 4:e699. doi: 10.1097/PR9.0000000000000699

Marteau, T. M., and Bekker, H. (1992). The development of a six-item short-form of the state scale of the Spielberger State—Trait Anxiety Inventory (STAI). *Br. J. Clin. Psychol.* 31, 301–306. doi: 10.1111/j.2044-8260.1992.tb00997.x

Meeuwis, S. H., Van Middendorp, H., Pacheco-Lopez, G., Ninaber, M. K., Lavrijsen, A. P. M., Van Der Wee, N., et al. (2019). Antipruritic placebo effects by conditioning H1-antihistamine. *Psychosom. Med.* 81, 841–850. doi: 10.1097/PSY.0000000000000743

Meijer, S., Karacaoglu, M., van Middendorp, H., Peerdeman, K. J., Veldhuijzen, D. S., Jensen, K., et al. (2021). Efficacy of open-label counterconditioning for

reducing nocebo-effects on pressure pain. *PsyArXiv[Preprint]* doi: 10.31234/osf.io/uhd3s

Meulders, A., Karsdorp, P. A., Claes, N., and Vlaeyen, J. W. S. (2015). Comparing counterconditioning and extinction as methods to reduce fear of movement-related pain. *J. Pain* 16, 1353–1365. doi: 10.1016/j.jpain.2015.09.007

Miller, F. G., Wendler, D., and Swartzman, L. C. (2005). Deception in research on the placebo effect. *PLoS Med.* 2:e262. doi: 10.1371/journal.pmed.0020262

Mystkowski, J. L., Craske, M. G., and Echiverri, A. M. (2002). Treatment context and return of fear in spider phobia. *Behav. Ther.* 33, 399–416. doi: 10.1016/S0005-7894(02)80035-1

Peerdeman, K. J., Geers, A. L., Della Porta, D., Veldhuijzen, D. S., and Kirsch, I. (2021). Underpredicting pain: an experimental investigation into the benefits and risks. *Pain* 162, 2024–2035. doi: 10.1097/j.pain.0000000000002199

Peerdeman, K. J., van Laarhoven, A. I. M., Peters, M. L., and Evers, A. W. M. (2016). An integrative review of the influence of expectancies on pain. *Front. Psychol.* 7:1270. doi: 10.3389/fpsyg.2016.01270

Petzke, F., Clauw, D. J., Ambrose, K., Khine, A., and Gracely, R. H. (2003). Increased pain sensitivity in fibromyalgia: effects of stimulus type and mode of presentation. *Pain* 105, 403–413. doi: 10.1016/S0304-3959(03)00204-5

Quinn, V. F., and Colagiuri, B. (2018). Using learning strategies to inhibit the nocebo effect. *Int. Rev. Neurobiol.* 138, 307–327. doi: 10.1016/bs.irn.2018.01.011

Riddick, F. A. Jr. (2003). The code of medical ethics of the american medical association. *Ochsner. J.* 5, 6–10.

Rodriguez, B. I., Craske, M. G., Mineka, S., and Hladek, D. (1999). Context-specificity of relapse: effects of therapist and environmental context on return of fear. *Behav. Res. Ther.* 37, 845–862. doi: 10.1016/S0005-7967(98)00106-5

Sandler, A. D., and Bodfish, J. W. (2008). Open-label use of placebos in the treatment of ADHD: a pilot study. *Child* 34, 104–110. doi: 10.1111/j.1365-2214.2007.00797.x

Schaefer, M., Sahin, T., and Berstecher, B. (2018). Why do open-label placebos work? A randomized controlled trial of an open-label placebo induction with and without extended information about the placebo effect in allergic rhinitis. *PLoS One* 13:e0192758. doi: 10.1371/journal.pone.0192758

Scheier, M. F., Carver, C. S., and Bridges, M. W. (1994). Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *J. Pers. Soc. Psychol.* 67, 1063–1078. doi: 10.1037//0022-3514.67.6.1063

Spielberger, C. D. (1983). *Manual for the State-Trait Anxiety Inventory (Form Y1 – Y2)*. Palo Alto, CA: Consulting Psychologists Press.

Sullivan, M. J., Bishop, S. R., and Pivik, J. (1995). The pain catastrophizing scale: development and validation. *Psychol. Assess.* 7, 524–532.

Thomaidou, M. A., Veldhuijzen, D. S., Peerdeman, K. J., Wiebing, N. Z. S., Blythe, J. S., and Evers, A. W. M. (2020). Learning mechanisms in nocebo hyperalgesia: the role of conditioning and extinction processes. *Pain* 161, 1597–1608. doi: 10.1097/j.pain.0000000000001861

Van Dis, E. A. M., Hagenaars, M. A., Bockting, C. L. H., and Engelhard, I. M. (2019). Reducing negative stimulus valence does not attenuate the return of fear: two counterconditioning experiments. *Behav. Res. Ther.* 120, 103416–103416. doi: 10.1016/j.brat.2019.103416

Vansteenwegen, D., Hermans, D., Vervliet, B., Francken, G., Beckers, T., Baeyens, F., et al. (2005). Return of fear in a human differential conditioning paradigm caused by a return to the original acquistion context. *Behav. Res. Ther.* 43, 323–336. doi: 10.1016/j.brat.2004.01.001

Vase, L., Petersen, G. L., Riley, I. I. I. J. L., and Price, D. D. (2009). Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. *PAIN®* 145, 36–44. doi: 10.1016/j.pain.2009.04.008

Vervliet, B., Craske, M. G., and Hermans, D. (2013). Fear extinction and relapse: state of the art. *Annu. Rev. Clin. Psychol.* 9, 215–248. doi: 10.1146/annurev-clinpsy-050212-185542

Wolfe, F., Smythe, H. A., Yunus, M. B., Bennett, R. M., Bombardier, C., Goldenberg, D. L., et al. (1990). The american college of rheumatology 1990 criteria for the classification of fibromyalgia. *Arthritis Rheum.* 33, 160–172. doi: 10.1002/art.1780330203

Woods, M. P., and Asmundson, G. J. (2008). Evaluating the efficacy of graded in vivo exposure for the treatment of fear in patients with chronic back pain: a randomized controlled clinical trial. *Pain* 136, 271–280. doi: 10.1016/j.pain.2007.06.037

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Therapeutic Suggestions During General Anesthesia Reduce Postoperative Nausea and Vomiting in High-Risk Patients – A *Post hoc* Analysis of a Randomized Controlled Trial

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Postoperative nausea and vomiting (PONV) are one of the most adverse events after general anesthesia, a distressing experience, and pose a risk to the patient. Despite advances in drug prophylaxis and PONV treatment, the incidence remains high and additional non-pharmacological treatments are needed. In this *post hoc* analysis of a recently published double-blind multicenter randomized controlled trial on the efficacy of intraoperative therapeutic suggestions on postoperative opioid dosage, we analyzed the effects of intraoperative therapeutic suggestions on PONV. We focus on patients with a high risk of PONV (Apfel risk score of 3–4) and distinguished early (first two postoperative hours) and delayed PONV (2–24 h). A total of 385 patients with a moderate or high risk for PONV were included. The incidence of early and delayed PONV was reduced (22.7–18.3 and 29.9–24.1%, respectively), without statistical significance, whereas in high-risk patients (n = 180) their incidence was nearly halved, 17.2 vs. 31.2% (p = 0.030) and 20.7 vs. 34.4% (p = 0.040), corresponding to a number needed to treat of 7 to avoid PONV. In addition, there was a significant reduction in PONV severity. In a multivariate logistic regression model, assignment to the control group (OR 2.2; 95% CI: 1.1–4.8) was identified as an independent predictor of the occurrence of early PONV. Our results indicate that intraoperative therapeutic suggestions can significantly

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reduce the incidence of PONV in high-risk patients. This encourages the expansion of therapeutic suggestions under general anesthesia, which are inexpensive and virtually free of side effects.

Clinical Trial Registration: German Clinical Trials Register, https://drks.de, registration number: DRKS00013800.

Keywords: general anesthesia, hypnotherapy, patient communication, postoperative nausea and vomiting, therapeutic suggestions

INTRODUCTION

Since postoperative nausea and vomiting (PONV) are major adverse events after surgery under general anesthesia (Cohen et al., 1994; Apfel et al., 1999), effective interventions, which are able to reduce the incidence of PONV, have always been the subject of anesthesiologic research (Gan et al., 2020). In addition to the fact that PONV is a very distressing experience (Myles et al., 2000), it can have a direct impact on the patient's outcome. The appearance of PONV poses a risk of severe complications such as suture dehiscence, aspiration, pneumonia, dehydration, hydroelectrolytic changes, esophageal rupture, and increased intracranial pressure (Bremner and Kumar, 1993; Schumann and Polaner, 1999; Samuels, 2013).

Early PONV within the first two postoperative hours with a relationship to volatile anesthetics can be distinguished from delayed PONV (Apfel et al., 2002). Despite advances in drug prophylaxis and treatment of PONV, the incidence remains high and is reported to be up to 30% in all postoperative patients and up to 80% in high-risk patients, which can be predicted by the presence of 3 or 4 factors of the Apfel simplified risk score, which include: female sex, non-smoking status, history of PONV or motion sickness, and/or use of postoperative opioids (Apfel et al., 1999). Therefore, in addition to drug treatment, non-pharmacological measures must also be considered to effectively reduce the incidence of PONV. One possible approach used in the past is the application of perioperative therapeutic suggestions, i.e., given pre- or postoperatively in hypnosis (Holler et al., 2021), or under general anesthesia intraoperatively. Suggestions are defined as verbal or non-verbal messages that the receiver involuntarily accepts and follows (Varga, 2013) and might therefore affect behavior, emotions, and autonomous body functions. Their effects can not only be subjectively recorded, but objectively measured and quantified (Zech et al., 2020, 2022). It is observed that even under general anesthesia, the central auditory pathway remains intact (Madler et al., 1991), and the perception of sounds and words is not interrupted (Hudetz, 2008; Sanders et al., 2012). However, several randomized controlled trials conducted on the effects of verbal suggestions given during general anesthesia in the past could only show very heterogeneous results (Rosendahl et al., 2016). These trials were small, heterogeneous in design, and conducted mainly in the 1990s and therefore did not reflect the current management of general anesthesia and PONV prophylaxis.

A recently published double-blind multicenter randomized controlled trial on the efficacy of intraoperative therapeutic suggestions showed a positive effect on postoperative opioid dosage and pain within the first 24 h after surgery, while for the incidence of PONV no differences were observed (Nowak et al., 2020). This study included patients at high and moderate risk for PONV. However, especially high-risk patients need a multimodal therapy approach to prevent PONV (Gan et al., 2020). Therefore, the question of whether intraoperative therapeutic suggestions influence PONV in these patients is of great interest and may have an impact on PONV management since therapeutic suggestions promise to be side-effect-free. Therefore, we conducted this *post hoc* analysis on the effect of intraoperative therapeutic suggestions on PONV after general anesthesia in patients with a high risk of PONV.

MATERIALS AND METHODS

Patients and Study Design

Parts of this study were recently published and reported on the effects of therapeutic suggestions during general anesthesia on postoperative pain and opioid use (Nowak et al., 2020). This study was registered in the German Clinical Trials Register (registration number DRKS00013800, registration date 26th January 2018). In a double-blind randomized, placebo-controlled trial in 5 tertiary care hospitals in Germany, patients were included between the ages of 18 and 70 who underwent elective surgery requiring general anesthesia with a planned duration of 1–3 h and a risk of PONV, defined by an Apfel risk score (Apfel et al., 1999) of two or more points. Exclusion criteria were an American Society of Anesthesiologist (ASA) score of $\geq$4 (Owens et al., 1978), requirement for postoperative mechanical ventilation, or the use of regional anesthesia. Eligible patients were included after written informed consent.

Ethics

The study was approved by the Ethics Committee of the Ruhr-University Bochum Medical Faculty, Bochum, Germany (Chairman Prof. Dr. M. Zenz, approval No. 17-5957-BR) on 15th May 2017.

Study Procedures

Patients were randomly assigned in a 1:1 ratio to intervention or control group. After induction of general anesthesia, patients in the intervention group listened to an Audio File containing background music and therapeutic suggestions, based on hypnotherapeutic principles, which included direct and indirect

You are sleeping sound and deep.
And you can relax and rest, recover and draw strength, because you are safe now, well-protected.
Everything that you hear and see and feel contributes to your best care.
And that's why you can completely concentrate on your body's own way to heal itself.
And we are right by your side. …
And what else will be happening after your operation was completed beautifully?
Step by step all of your body function will start again: Your blood pressure starts in full swing
and your digestion. You are producing saliva and you can swallow, and you can drink.
Everything returns in the right direction, always top down, from the mouth to the stomach,
and in the intestines and on and on, uniformly in one direction, straight ahead.
And comfort can expand more and more, all over. And you may ask yourself what you will want
to eat first. You can then send your blood circulation downwards to your intestines who have rested
in the meantime. And with all the supply of energy and oxygen they gather pace again.
You can swallow fluids again, and notice the fluids flowing down the oesophagus into the stomach,
and the stomach transports them further into the intestines and in the intestines moving on,
further and further, consistently and continually in one direction, on and on. …

FIGURE 1 | Example text of the therapeutic suggestions used in this study.

positive messages (see **Figure 1**). The tape was continuously played during surgery over earphones. At the end of surgery, a different file was presented to prepare the patients for emergence from anesthesia. Patients in the control group listened to a blank Audio File. For details see Nowak et al. (2020).

General anesthesia was performed as balanced anesthesia with volatile anesthetics (sevoflurane, isoflurane, or desflurane) at a minimum alveolar concentration of 1.0 ± 0.2 and repeated opioid administration. The depth of anesthesia was controlled by electroencephalography-based monitoring (Bispectral Index, Medtronic, Meerbusch, Germany, or Narcotrend, Narcotrend Group, Hannover, Germany), with a target index of 40–60. Both, a strict range of MAC above 0.8 and anesthesia depth monitoring, guarantee exclusion of inadequate anesthesia (Merikle and Daneman, 1996; Messina et al., 2016). Postoperative pain therapy was nurse or patient-controlled, according to local protocols. Before surgery, patients' susceptibility to verbal suggestions was tested using a modified Harvard Group 5-item Hypnotic Susceptibility (HGSHS-5:G) (Riegel et al., 2021), and the level of anxiety was tested using the State Trait Anxiety Inventory (STAI-S) (Marteau and Bekker, 1992).

Postoperative Nausea and Vomiting Management and Outcome Measures

The risk of PONV was assessed by the preoperative Apfel risk score (Apfel et al., 1999). Only patients with medium or high risk of PONV (2–4 points) were eligible for study inclusion. Pharmacological PONV prophylaxis was administered before general anesthesia induction or intraoperatively according to local standards. These included, among others, dexamethasone, ondansetron, droperidol, metoclopramide, or dimenhydrinate. After surgery, the incidence of PONV was evaluated in the recovery room (first 2 h) and 24 h after extubation (normal ward). The severity of PONV was assessed using the simplified PONV impact scale (0–6), described by Myles and Wengritzky (2012). Treatment of PONV was performed again with dexamethasone, ondansetron, droperidol, metoclopramide, dimenhydrinate, or a combination. Antiemetic milligram equivalents (AMEs) were calculated for the comparability of various antiemetics (AME = ondansetron × 4 + dexamethasone × 4 + droperidol × 1.25 + metoclopramide × 20 + dimenhydrinate × 50) (Apfel et al., 2004a).

Statistics

Sample size calculation was carried out on the primary outcome (postoperative opioid use), which was based on a recent meta-analysis (Rosendahl et al., 2016). Based on a 1:1 randomization ratio with an assumed effect size of 0.3, we calculated a total of 368 patients to obtain 80% power to detect a difference in postoperative opioid dosage at a two-sided α level of 0.05. Baseline characteristics and outcomes were analyzed as follows: continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables and median and interquartile range (IQR; 25th and 75th percentiles) for non-normally distributed variables. Categorical variables are expressed as frequency and percentage. Comparison of continuous variables between groups was performed using a parametric Student's *t*-test or a non-parametric Mann–Whitney *U*, respectively. Categorical variables were compared using Pearson's Chi-square test and by calculation of the number needed to treat (NNT). In addition, the resulting risk differences including the 95% confidence intervals were calculated. In contrast to the previously published data of this study we performed, for better assessment of non-normally distributed variables in the outcome analysis, a bootstrapping method with resampling and calculated the means, SD, and 95% confidence intervals. For further analysis, we *post hoc* formed a subgroup of patients at high risk of PONV, defined by a preoperative Apfel score of 3–4. For the assessment of the joint effect of therapeutic suggestions and potential confounding

factors in this subgroup, a logistic regression analysis was performed with single and multiple predictors. These included: assignment to the control group, preoperative Apfel score, dose of intraoperative antiemetics and opioids, type of surgery, and duration of surgery. Finally, a multivariable restricted model was built by using stepwise backward elimination. Furthermore, since the severity of PONV and the application of antiemetics are not independent variables, their correlation was analyzed represented by the Spearman coefficient. Statistical analysis was performed with The R Project for Statistical Computing 4.0.4 (The R Foundation for Statistical Computing, Vienna, Austria). Graphical representations of the results were created with GraphPad Prism 8.1 (GraphPad Software, San Diego, CA, United States). A two-sided *p*-value of less than 0.05 was considered statistically significant.

RESULTS

In total, 400 patients were recruited and randomized from January to December 2018 and 385 of them were analyzed in the per-protocol analysis (191 in intervention and 194 in control group), see **Figure 2**. The subgroup of patients with a high risk of PONV is formed by 180 patients, 87 patients in the intervention and 93 patients in the control group. **Table 1** presents the baseline characteristics. Almost all parameters for the entire cohort, as well as for the high-risk subcohort, were evenly distributed between both groups. Only the distribution of the types of surgery in high-risk patients was uneven, with a higher proportion of intraabdominal surgeries in the control group and a resulting lower proportion of other types of surgery. None of the patients reported remembering to wear headphones or listening to music or verbal suggestions. No side effects were observed.

Incidence and Severity of Postoperative Nausea and Vomiting

Outcomes are presented in **Table 2**. In the cohort of all patients no significant differences were observed in the incidence or severity of PONV. If the focus is set on patients at high risk for PONV, intraoperative therapeutic suggestions showed a marked effect. The incidence of both early and delayed PONV was significantly reduced by 45 or 40%, respectively (**Figure 3**). This corresponds to the number of patients needed to treat (NNT) of approximately 7 to avoid one case of early or delayed PONV. For high-risk patients, the PONV impact score was reduced by the intervention by approximately 50% within the first 2 or 24 h.

Use and Dose of Antiemetics

In patients with a high risk of PONV therapeutic suggestions resulted in an absolute risk reduction for the use of postoperative antiemetics of 11% within the first 2 h and 9% within 24 h, although not reaching statistical significance (**Table 2** and **Figure 3**). The corresponding NNT was about 10. There was also a trend to a lower dose of postoperative antiemetics by one-third in the intervention group.

Correlation of Postoperative Nausea and Vomiting Score and Dose of Antiemetic Milligram Equivalent

In the control group, a small to intermediate but significant correlation between the PONV score and the total antiemetics dose (intraoperative and postoperative) was observed for both time periods. With the intervention, this correlation decreased (**Table 3**). Furthermore, in patients who developed PONV, the correlation between PONV and the use of antiemetic lost statistical significance.

Confounding Factors

Several factors associated with PONV were tested using logistic regression analysis (**Table 4**). In the univariate testing, the assignment to the control group had an impact on both early and delayed PONV. Further significant confounders were the preoperative Apfel risk score and intraabdominal surgery for early PONV, and the dose of postoperative opioids for delayed PONV. In the restricted multivariable model, assignment to the control group, preoperative Apfel score, and intraabdominal surgery were confirmed as independent predictors for the development of early PONV. For delayed PONV, only the PONV risk score and the postoperative dose of opioids remained predictors of statistical significance.

DISCUSSION

Postoperative nausea and vomiting is one of the most common adverse events after surgery under general anesthesia and has a profound impact on patient comfort and satisfaction (Myles et al., 2000). Patients are often more compromised by PONV than by postoperative pain (Simanski et al., 2001). Therefore, in addition to pharmacological options, effective non-pharmacological prophylaxis and treatments are urgently needed to reduce the incidence of PONV, especially in high-risk patients with a dramatically high incidence between 61 and 79% (Gan et al., 2020).

Incidence, Severity, and Treatment of Postoperative Nausea and Vomiting

Our intervention was able to significantly reduce the incidence of both, "early" and "delayed" PONV in patients at high risk. Furthermore, PONV severity was halved by the intervention. However, the mean intensity of PONV was low, probably because more than half of these patients, although at risk, did not develop PONV. The low incidence and severity might be attributable to the wide use of pharmacological PONV prophylaxis in this study and to an accompanying placebo effect. The demand for antiemetics was reduced by approximately one-third. In general, whenever a dose is observed, the proportion of patients treated must also be considered. In our study, the number of patients with demand for antiemetics was also reduced by one-third. However, in these patients, the difference in the total antiemetic dose between the intervention and control groups diminished. Therefore, the main reason for the observed dose reduction was

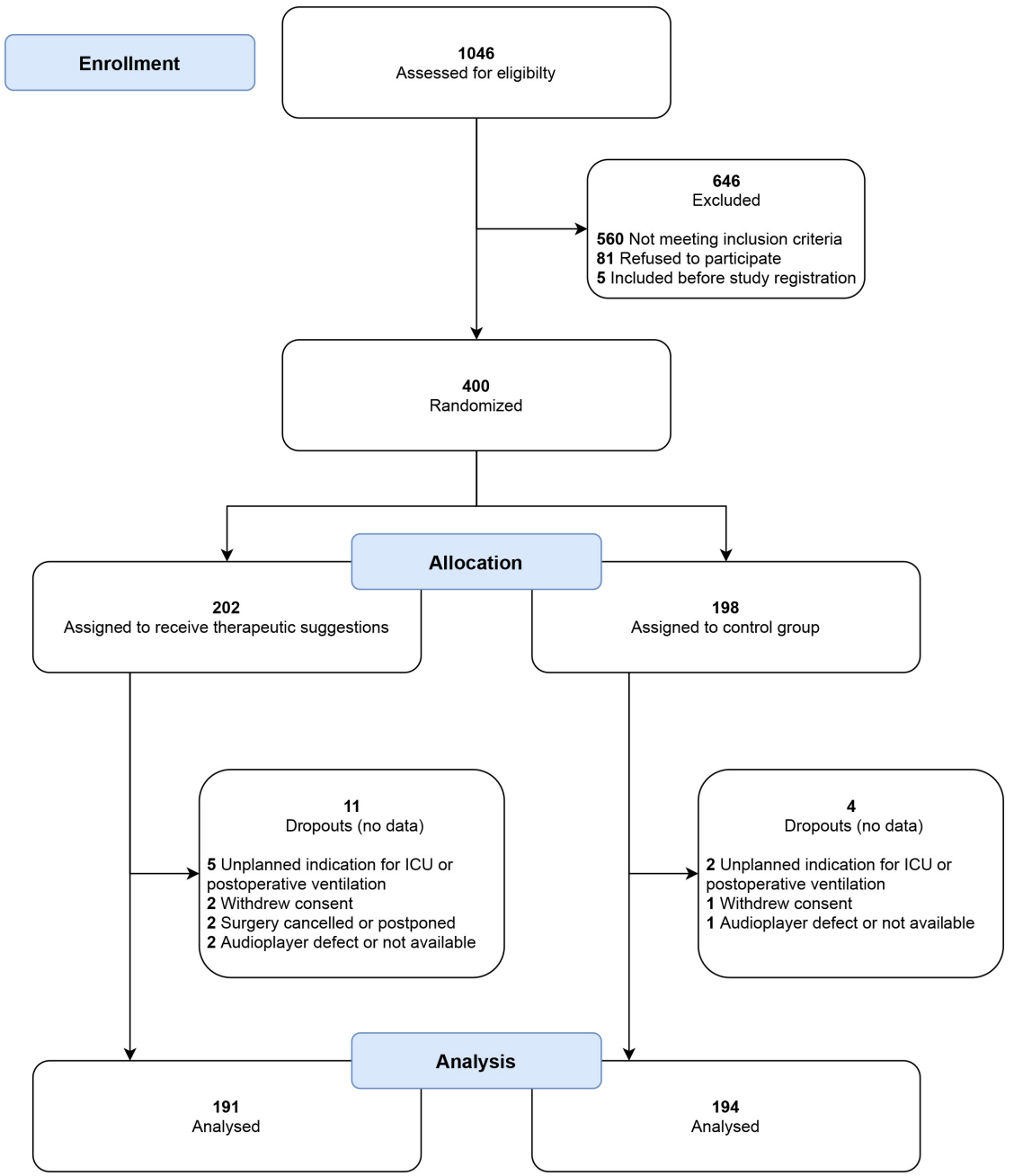

FIGURE 2 | CONSORT flow chart of patient recruitment. No postoperative data were collected for dropouts, and they were excluded from analysis before unblinding of the study. ICU, intensive care unit.

probably the decreased number of patients with demand for antiemetic treatment.

Correlation Between Postoperative Nausea and Vomiting Severity and Antiemetic Dose

The use of antiemetics affects the severity of PONV, and the severity of PONV triggers the use and dose of antiemetics. Therefore, both factors must be considered. The intervention in our study affected and reduced the correlation of these two entities. A possible interpretation of these results is the induction of tolerance against PONV by intraoperative positive suggestions, where an identical dose of antiemetics results in lower manifestations of PONV in the intervention group, and a comparable severity of PONV leads to a lower requirement for antiemetic treatment. This development of tolerance by a change in the perception, the impact and the significance of nausea is one

TABLE 1 | Baseline characteristics for all patients and subgroup of patients at high risk for postoperative nausea and vomiting, defined by pre-operative Apfel-score of 3 or 4.

	All patients (*n* = 385)			Patients at high risk for PONV[1] (*n* = 180)		
	Intervention group (*n* = 191)	Control group (*n* = 194)	*p*	Intervention group (*n* = 87)	Control group (*n* = 93)	*p*
Age (years), median (IQR)	52 (43–62)	54 (46–62)	0.241	52 (43–62)	53 (46–61)	0.708
Female sex, *n* (%)	115 (60.2)	110 (56.7)	0.484	73 (83.9)	71 (76.3)	0.205
Pre-operative score results, median (IQR)						
Apfel score[2]	2 (2–3)	2 (2–3)	0.688	3 (3–3)	3 (3–3)	0.683
HGSHS-5[3]	1 (0–3)	1 (0–3)	0.798	2 (0–4)	1 (0–3)	0.483
STAI-S[4]	41 (33–51)	40 (33–50)	0.478	43 (33–52)	44 (34–53)	0.937
NRS[5]	0 (0–1)	0 (0–2)	0.308	0 (0–0)	0 (0–0)	0.396
Type of surgery, *n* (%)						
Intra-abdominal[6]	61 (31.9)	77 (39.7)	0.489	20 (23.0)	32 (34.4)	0.040
Thyroid gland	36 (18.8)	30 (15.5)		24 (27.6)	16 (17.2)	
Gynecological[7]	24 (12.6)	15 (17.7)		21 (24.1)	11 (11.8)	
Urogenital[8]	21 (11.0)	26 (13.4)		5 (5.7)	12 (12.9)	
Other[9]	49 (25.7)	46 (13.7)		17 (19.6)	22 (23.7)	
Duration of surgery (min), median (IQR)	95 (69–140)	106 (74–141)	0.144	91 (68–128)	113 (74–135)	0.113
Intra-operative drug use						
Fentanyl (mg)[10], median (IQR)	0.5 (0.4–0.5)	0.5 (0.5–0.6)	0.148	0.5 (0.4–0.5)	0.5 (0.4–0.6)	0.210
Sufentanil (μg)[11], median (IQR)	50 (40–64)	50 (40–70)	0.232	50 (39–60)	50 (40–62)	0.494
PONV prophylaxis[12], *n* (%)	94 (49.2)	99 (51.0)	0.722	55 (63.2)	61 (65.6)	0.740

[1]High risk for postoperative nausea and vomiting (PONV) is defined by a pre-operative Apfel score of 3 or 4 points. [2]Apfel score: Apfel score of risk for postoperative nausea and vomiting (0–4). [3]HGSHS-5: 5-item version of Harvard Group Scale for Hypnotic Susceptibility (0–5). [4]STAI-S: State Trait Anxiety Inventory Scale (20–80). [5]NRS: numeric rating scale of pain (0–10). [6]Inter alia gastric surgery, colorectal surgery, hepatic surgery, cholecystectomy. [7]Inter alia hysterectomy, ovariectomy, pelvic floor repair. [8]Inter alia prostatectomy, bladder surgery. [9]Inter alia herniated intervertebral disc, lumbar spinal stenosis, adrenalectomy, plastic/reconstructive surgery. [10]n = 85/93 (intervention/control group) for all patients and n = 47/50 (intervention/control group) for patients at risk for PONV. [11]n = 106/101 (intervention/control group) for all patients and n = 40/43 (intervention/control group) for patients at risk for PONV. [12]Intraoperative, preventive medication against postoperative nausea and vomiting (PONV) with ondansetron, dexamethasone, droperidol, metoclopramide, dimenhydrinate, or a combination according to local protocols of each study site. The following missing data were excluded from the analysis: 109/67 cases missing (all patients/patients at risk for PONV) for preoperative HGSHS-5 score.

possible basis of the observed effects. Others are an antiemetic effect of the suggestions, including images of physiological functions (the idea of appetite or of a flow downward), or interference with the generation of nausea. In contrast to awake interventions the suggestions were given during surgery, i.e., at the time of surgery and anesthesia that might be responsible for the development of nausea.

Predictors of Postoperative Nausea and Vomiting

The risk of PONV in adults is influenced by many different patient-specific and surgery-related factors, e.g., female sex, history of PONV, motion sickness, non-smoking status, young age, duration of surgery/anesthesia, and specific types of intraabdominal surgery (Apfel et al., 1999, 2004b, 2012; Sinclair et al., 1999). Furthermore, anesthesia-related predictors of PONV include volatile anesthetics, nitrous oxide, and postoperative use of opioids, while these factors are dose and duration dependent (Apfel et al., 2002; Breitfeld et al., 2003; Habib et al., 2006; Myles et al., 2007; Peyton and Wu, 2014). As a result, current guidelines define different prophylactic measurements depending on the individual risk of PONV. These include, in addition to pharmacological antiemetic prophylaxis, the avoidance of volatile anesthetics and nitrous oxide, and instead the use of total intravenous anesthesia (TIVA) (Gan et al., 2020). Despite differentiated prophylactic therapy approaches, a large number of especially high-risk patients still suffer from PONV (Rusch et al., 2010), with a request for multimodal approaches that also include non-pharmacological interventions (Gan et al., 2020).

In the present study, assignment to the control group was a significant determinator of PONV in high-risk patients, which subsequently proved that intraoperative therapeutic suggestions are a promising intervention against PONV. Early PONV within the first 2 h after surgery was affected by the affiliation of the study group, the preoperative Apfel PONV risk score, and the type of surgery, namely intraabdominal operations. Especially the low impact of intraoperative opioid dose and duration of surgery for the incidence of early PONV is unexpected, as the respective dose of inhalational anesthetics was previously described as a determinator (Apfel et al., 2002). In contrast to the first 2 h after surgery, where patients were in a very controlled setting in the recovery room, delayed PONV was only affected by postoperative opioid dose. These findings may be attributable to the circumstances in the postoperative setting after discharge from the recovery room to the normal ward, where many other possible confounders occur that have not been recorded or evaluated. As both state anxiety and hypnotic susceptibility did

TABLE 2 | Outcome variables for all patients and subgroup of patients at high risk for postoperative nausea and vomiting, defined by a pre-operative Apfel-score of 3 or 4.

	All patients (*n* = 385)				Patients at high risk for PONV[1] (*n* = 180)			
	Intervention group (*n* = 191)	Control group (*n* = 194)	*p*	NNT[2]	Intervention group (*n* = 87)	Control group (*n* = 93)	*p*	NNT
PONV[3], *n* (%)								
Early (within first 2 h)	35 (18.3)	44 (22.7)	0.290	23.0	15 (17.2)	29 (31.2)	0.030	7.1
Delayed (2–24 h)	46 (24.1)	58 (29.9)	0.199	17.2	18 (20.7)	32 (34.4)	0.040	7.3
Within 24 h	59 (30.9)	71 (36.6)	0.236	17.5	28 (32.2)	42 (45.2)	0.074	7.7
PONV impact scale score[4], mean ± SD								
Within first 2 h	0.20 ± 0.52	0.26 ± 0.66	0.289	–	0.16 ± 0.43	0.33 ± 0.78	0.039	–
Within 24 h	0.42 ± 0.88	0.55 ± 1.09	0.173	–	0.36 ± 0.88	0.74 ± 1.33	0.017	–
Postoperative use of antiemetics, *n* (%)								
Within first 2 h	33 (17.3)	42 (21.6)	0.279	22.9	18 (20.7)	29 (31.2)	0.109	9.5
Within 24 h	51 (26.7)	55 (28.4)	0.717	60.6	27 (31.0)	37 (39.8)	0.220	11.4
Postoperative AME[5], mean ± SD								
Within first 2 h	0.25 ± 0.66	0.30 ± 0.66	0.487	–	0.30 ± 0.66	0.49 ± 0.83	0.081	–
Within 24 h	0.42 ± 0.84	0.47 ± 0.90	0.524	–	0.47 ± 0.85	0.75 ± 1.11	0.073	–
Within first 2 h, in patients with use of antiemetics[6]	1.45 ± 0.89	1.37 ± 0.73	0.695	–	1.48 ± 0.61	1.56 ± 0.74	0.703	–
Within 24 h, in patients with use of antiemetics[7]	1.54 ± 0.93	1.66 ± 0.95	0.550	–	1.53 ± 0.86	1.87 ± 0.99	0.142	–

Hours refer to timepoint after admission to recovery room. Means, standard deviations, and 95% CIs of non-normally distributed data were calculated by bootstrapping procedure. [1]High risk for postoperative nausea and vomiting (PONV) is defined by a pre-operative Apfel score of 3 or 4 points. [2]NNT: number needed to treat. [3]PONV: postoperative nausea and vomiting (defined as patient reporting nausea or vomiting within the specified time interval). [4]PONV impact scale score (0–6) by Myles and Wengritzky (2012). [5]AME: antiemetic milligram equivalents = ondansetron × 4 + dexamethasone × 4 + droperidol × 1.25 + metoclopramide × 20 + dimenhydrinate × 50. [6]Amount of antiemetics within first 2 h. [7]Amount of antiemetics during first 24 h.

not differ in the two groups, these parameters were not included in the multivariate analysis, and no conclusion on their impact can be drawn

Comparison With Other Studies

Several different medical interventions have been tested and reported in the effort to prevent PONV (Gan et al., 2020). To avoid one case of PONV after isoflurane anesthesia, six patients would have to receive TIVA (Visser et al., 2001). Pharmacological antiemetic prophylaxis with ondansetron has a NNT of 6 for the prevention of vomiting and 7 for nausea, respectively (Tramer et al., 1997). In addition, non-pharmacological means including acupuncture were found effective (Lee et al., 2015). However, mainly antiemetics have found their way into the everyday clinical practice of PONV prophylaxis established in the meantime.

The effect of communication techniques on PONV has also been evaluated, for instance, by studies with perioperative hypnotherapy in awake patients (Kekecs et al., 2014) and under the rather special condition of general anesthesia (Rosendahl et al., 2016). In a meta-analysis of Rosendahl et al. (2016), only 3 out of 21 included trials showed a positive effect on the incidence of PONV. However, the overall effect identified therapeutic suggestions to significantly reduce PONV. Since these former studies were conducted mainly in the 1980s and 1990s without routine PONV prophylaxis, incidence, and severity of PONV were higher. However, our study in patients after PONV prophylaxis demonstrated an even higher effect with a NNT of 7.

In general, the comparison of the various pharmacological and non-pharmacological attempts of PONV prophylaxis shows that the effect of therapeutic suggestions in our study is of a comparable magnitude with much lower costs, effort, and side effects. It should be noted that in clinical practice often a combination of different treatments is necessary to achieve a sufficient antiemetic effect and that the result is additive (Weibel et al., 2021). In our study, almost all patients had received pharmacological PONV prophylaxis. However, the effect was measured against a control group with only antiemetic drugs. Thus, it can be assumed that the observed reduction in PONV is a direct consequence of the intervention tested. Therefore, therapeutic suggestions could provide an inexpensive and safe possibility for supplementation of PONV prophylaxis.

Limitations

This study has several limitations. First of all, this is a *post hoc* analysis of an original study, therefore, our findings should be tested in a prospective, sufficiently powered study. Moreover, the role of other contributing factors than therapeutic

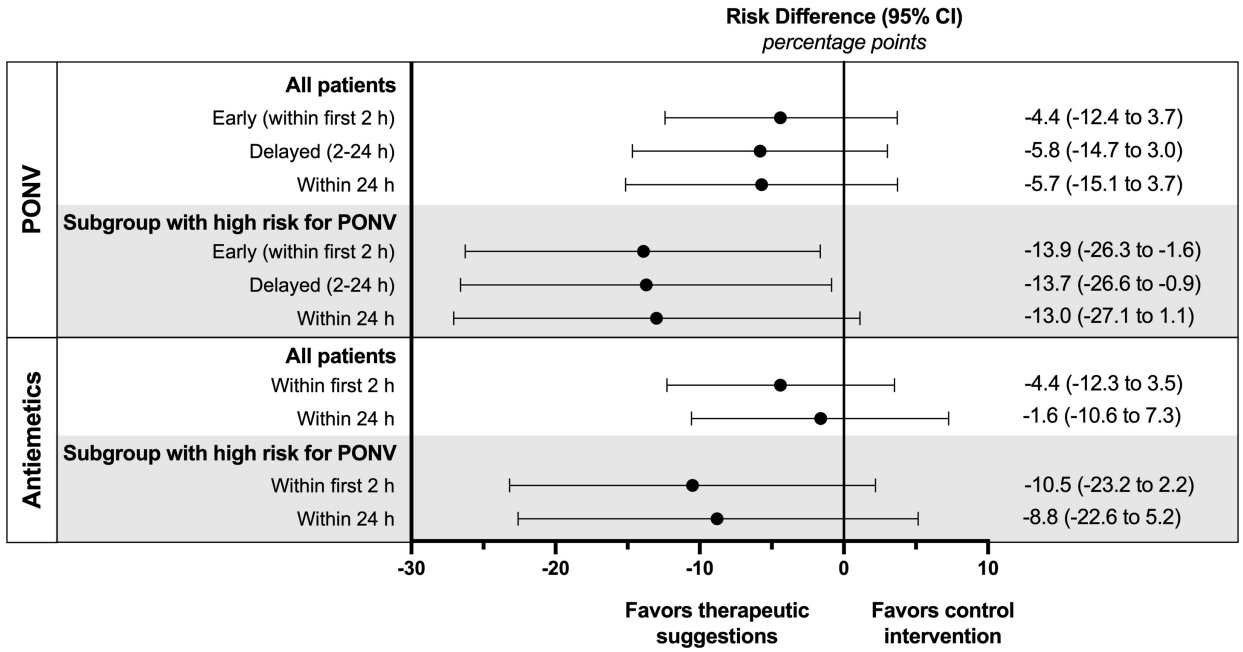

FIGURE 3 | Absolute risk differences of PONV incidence and postoperative use of antiemetics for all patients and subgroup of patients with a high risk for PONV (defined by an Apfel score of 3 or 4).

TABLE 3 | Correlation between PONV severity and dose of antiemetics.

	Intervention group			Control group		
	Rho[1]	95% CI	*p*	Rho	95% CI	*p*
Patients at risk for PONV[2] (Apfel score 3–4)						
Intraoperative + first 2 h	0.295	0.090–0.476	0.006	0.469	0.294–0.614	<0.001
Intraoperative + first 24 h	0.317	0.114–0.494	0.003	0.415	0.231–0.570	<0.001
Patients with PONV						
Intraoperative + first 2 h	0.325	−0.055 to 0.623	0.092	0.530	0.269–0.718	<0.001
Intraoperative + first 24 h	0.050	−0.329 to 0.415	0.801	0.401	0.111–0.629	0.008

PONV severity according to Wengritzky score, antiemetics standardized to antiemetic milligram equivalents (AMEs). [1]Rho: Spearman correlation coefficient. [2]PONV: postoperative nausea and vomiting.

suggestions remain unclear – for example, positive effects may also be expected from background music. Although regularly positive effects of music on pain and anxiety can be observed, mainly with treatment in awake patients (Cepeda et al., 2006; Hole et al., 2015; Kuhlmann et al., 2018), evidence for an antiemetic effect is missing (Stoicea et al., 2015). Furthermore, a beneficial effect can also be expected from shielding the ears from intraoperative noise and careless talk, including negative suggestions (Hansen and Zech, 2019). However, this was applicable to both groups in our study.

On the Underlying Mechanism

The perception of words under general anesthesia was not unexpected, as evidence has been gathered that the auditory pathway is preserved during anesthesia (Madler et al., 1991; Hudetz, 2008). Moreover, the phenomenon of "intraoperative awareness" has been described regularly (Millar and Watkinson, 1983; Ghoneim and Block, 1992; Schwender et al., 1994). However, our results cannot be explained by a few patients reacting like in "intraoperative awareness" with an incidence of only 0.1–0.2% for explicit recall (Sanders et al., 2012) and a few percent for implicit memory (Fu et al., 2021; Linassi et al., 2021). Therefore, auditory impressions that a patient perceives under general anesthesia must be critically questioned, since conversations and noises in the operating room can have a negative influence on patients and should be avoided (Hansen and Zech, 2019).

With regard to the mechanisms responsible for the observed responses, we consider a reduced resistance to suggestions after loss of critical, rational thinking and an access to the subconscious to be responsible. This parallels the mechanism of hypnosis that is characterized by a depression of the dorsolateral frontal cortex (DLPFC) (Dienes and Hutton, 2013), and shows similar beneficial effects of suggestions in surgical patients

TABLE 4 | Logistic regression model for single and multiple predictors of postoperative nausea and vomiting in patients with high risk (Apfel score 3–4) (n = 180).

	Univariable models			Multivariable models					
				Unrestricted			Restricted		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Early PONV[1]									
No therapeutic suggestions	2.18	1.08–4.51	0.032	2.23	1.05–4.92	0.041	2.26	1.09–4.88	0.032
PONV risk score[2]	2.68	1.23–5.80	0.012	3.31	1.40–7.92	0.007	3.08	1.36–7.02	0.007
PONV prophylaxis[3]	1.22	0.84–1.80	0.297	1.13	0.70–1.81	0.618	–	–	–
Intraoperative fentanyl	1.15	0.35–3.53	0.812	1.78	0.16–19.25	0.632	–	–	–
Intraoperative sufentanil	1.00	0.99–1.02	0.542	1.00	0.98–1.03	0.771	–	–	–
Type of surgery									
Intra-abdominal	2.08	1.01–4.24	0.045	3.00	1.00–10.05	0.059	2.66	1.17–6.20	0.021
Thyroid gland	1.23	0.54–2.68	0.611	2.06	0.60–7.60	0.259	2.05	0.80–5.22	0.131
Gynecological	0.52	0.17–1.34	0.207	0.91	0.19–4.05	0.897	–	–	–
Urogenital	0.95	0.26–2.85	0.927	1.81	0.36–8.45	0.454	–	–	–
Duration of surgery	1.00	1.00–1.01	0.337	1.00	0.99–1.01	0.874	–	–	–
Opioid dosage[4] within first 2 h	1.03	0.94–1.12	0.493	0.97	0.88–1.07	0.600	–	–	–
Delayed PONV									
No therapeutic suggestions	2.01	1.04–4.00	0.042	1.78	0.84–3.87	0.138	1.74	0.83–3.73	0.150
PONV risk score	2.10	0.97–4.48	0.055	2.59	1.08–6.27	0.032	2.43	1.04–5.68	0.040
PONV prophylaxis	1.31	0.91–1.89	0.151	1.02	0.61–1.67	0.928	–	–	–
Intraoperative fentanyl	0.44	0.13–1.37	0.170	2.10	0.15–24.09	0.560	–	–	–
Intraoperative sufentanil	1.01	1.00–1.02	0.031	1.01	0.99–1.04	0.372	–	–	–
Type of surgery									
Intra-abdominal	1.59	0.78–3.18	0.194	1.43	0.48–4.48	0.525	–	–	–
Thyroid gland	2.08	0.98–4.35	0.053	2.63	0.83–8.93	0.109	1.85	0.80–4.25	0.147
Gynecological	0.22	0.05–0.67	0.017	0.49	0.09–2.29	0.384	0.31	0.07–1.02	0.081
Urogenital	1.09	0.33–3.13	0.874	1.62	0.34–7.14	0.530	–	–	–
Duration of surgery	1.00	0.99–1.01	0.913	0.99	0.98–1.00	0.127	–	–	–
Opioid dosage within 24 h	1.10	1.05–1.16	<0.001	1.08	1.02–1.15	0.009	1.08	1.03–1.14	0.004

Hours refer to timepoint after admission to recovery room. Restricted models were built by stepwise backward elimination. [1]PONV: postoperative nausea and vomiting. [2]PONV risk score: Apfel score of risk for postoperative nausea and vomiting (0–4). [3]Antiemetic milligram equivalents = ondansetron × 4 + dexamethasone × 4 + droperidol × 1.25 + metoclopramide × 20 + dimenhydrinate × 50. [4]Morphine milligram equivalents = piritramide × 0.7 + tilidine × 0.2 + oxycodone × 0.8.

(Kekecs et al., 2014). The difference between low incidences of "intraoperative awareness" and the high incidence of perception in this study may be explained by the content. While it is random in explicit memory (thoughtless conversations in the operating room) and neutral in experiments of implicit memory (test texts), it is characterized by meaning in the application of therapeutic communication before or during surgery. In experiments with intraoperative simulation of a ventilation incident, 8 out of 10 patients had an implicit memory or reaction (Levinson, 1965). While the reports on "intraoperative awareness" with its low incidences did not lead to a general change in the behavior in the operating rooms over all those years, hopefully the present demonstration of intraoperative perception will.

Intraoperative therapeutic suggestions were demonstrated to affect postoperative pain and request for analgesics (Nowak et al., 2020), as well as PONV and use of antiemetics as reported here. The high efficacy of the tested intervention compared to previous trials might be attributed to the specific text of the suggestions. Negative words and negations such as "no nausea" were avoided. Instead, "increased comfort," appetite and pleasurable food intake after surgery were addressed. The suggestions presented intraoperatively dealt with items such as support, care, and self-healing power. From a text addressing such general topics of well-being, further effects can be expected and should be studied. Some interesting parameters that cannot be monitored and measured so fast and easily might be affected concurrently, such as wound healing, homeostasis, or immune surveillance, but also could be addressed more specifically.

We consider the addressing of themes of meaning essential for the observed effects, namely accompaniment, contact, comfort, confidence, information, control, instructions, respect, safety, and healing (Hansen and Zech, 2019). Constructing placebo effects as a mechanism of action is difficult since generation of expectations under general anesthesia has not been described yet. However, it has been suggested to better call the placebo effect a "meaning response" as well (Moerman and Jonas, 2002). Actually, response to meaning could be the common basis of hypnosis, therapeutic communication and placebo effects. The melody of the voice and the perception of a caring person close may play a role in addition.

CONCLUSION

Our results encourage the use of therapeutic suggestions under general anesthesia, especially since it is an inexpensive intervention that is virtually free of side effects. They should not be limited to taped recordings favorable for standardized

study conditions but stimulate personal talk to patients and wider application of positive and therapeutic communication also in awake patients. The demonstrated positive effects of therapeutic suggestions even under general anesthesia should stimulate further research and application in other patients during impaired wakefulness, such as during resuscitation or intensive care, "touching the unconscious in the unconscious."

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Ruhr-University Bochum Medical Faculty, Bochum, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HN: writing of the manuscript, data analysis, and critical revision of the manuscript. AW and TR: data analysis and critical revision of the manuscript. GO: study conception and design, study center supervision, data collection, and critical revision of the manuscript. LG, MM, KG, CM, AZ, and KL: data collection, analysis and interpretation, and critical revision of the manuscript. JL, TS, and MT: study center supervision, data collection, analysis and interpretation, and critical revision of the manuscript. MA: study supervision and critical revision of the manuscript. EH and NZ: study conception and design, development and taping of the intervention text, study supervision, writing of the manuscript and data interpretation, and critical revision of the manuscript. All authors approved the final version to be published and agreed to be accountable for all aspects of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.898326/full#supplementary-material

REFERENCES

Apfel, C. C., Heidrich, F. M., Jukar-Rao, S., Jalota, L., Hornuss, C., Whelan, R. P., et al. (2012). Evidence-based analysis of risk factors for postoperative nausea and vomiting. *Br. J. Anaesth.* 109, 742–753. doi: 10.1093/bja/aes276

Apfel, C. C., Korttila, K., Abdalla, M., Kerger, H., Turan, A., Vedder, I., et al. (2004a). A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N. Engl. J. Med.* 350, 2441–2451. doi: 10.1056/NEJMoa032196

Apfel, C. C., Kranke, P., and Eberhart, L. H. (2004b). Comparison of surgical site and patient's history with a simplified risk score for the prediction of postoperative nausea and vomiting. *Anaesthesia* 59, 1078–1082. doi: 10.1111/j.1365-2044.2004.03875.x

Apfel, C. C., Kranke, P., Katz, M. H., Goepfert, C., Papenfuss, T., Rauch, S., et al. (2002). Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. *Br. J. Anaesth.* 88, 659–668. doi: 10.1093/bja/88.5.659

Apfel, C. C., Laara, E., Koivuranta, M., Greim, C. A., and Roewer, N. (1999). A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology* 91, 693–700. doi: 10.1097/00000542-199909000-00022

Breitfeld, C., Peters, J., Vockel, T., Lorenz, C., and Eikermann, M. (2003). Emetic effects of morphine and piritramide. *Br. J. Anaesth.* 91, 218–223. doi: 10.1093/bja/aeg165

Bremner, W. G., and Kumar, C. M. (1993). Delayed surgical emphysema, pneumomediastinum and bilateral pneumothoraces after postoperative vomiting. *Br. J. Anaesth.* 71, 296–297. doi: 10.1093/bja/71.2.296

Cepeda, M. S., Carr, D. B., Lau, J., and Alvarez, H. (2006). Music for pain relief. *Cochrane Database Syst. Rev.* 2:CD004843. doi: 10.1002/14651858.CD004843.pub2

Cohen, M. M., Duncan, P. G., DeBoer, D. P., and Tweed, W. A. (1994). The postoperative interview: assessing risk factors for nausea and vomiting. *Anesth. Analg.* 78, 7–16. doi: 10.1213/00000539-199401000-00004

Dienes, Z., and Hutton, S. (2013). Understanding hypnosis metacognitively: rTMS applied to left DLPFC increases hypnotic suggestibility. *Cortex* 49, 386–392. doi: 10.1016/j.cortex.2012.07.009

Fu, V. X., Sleurink, K. J., Janssen, J. C., Wijnhoven, B. P. L., Jeekel, J., and Klimek, M. (2021). Perception of auditory stimuli during general anesthesia and its effects on patient outcomes: a systematic review and meta-analysis. *Can. J. Anaesth.* 68, 1231–1253. doi: 10.1007/s12630-021-02015-0

Gan, T. J., Belani, K. G., Bergese, S., Chung, F., Diemunsch, P., Habib, A. S., et al. (2020). Fourth consensus guidelines for the management of postoperative nausea and vomiting. *Anesth. Analg.* 131, 411–448. doi: 10.1213/ANE.0000000000004833

Ghoneim, M. M., and Block, R. I. (1992). Learning and consciousness during general anesthesia. *Anesthesiology* 76, 279–305. doi: 10.1097/00000542-199202000-00018

Habib, A. S., Chen, Y. T., Taguchi, A., Hu, X. H., and Gan, T. J. (2006). Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: a retrospective database analysis. *Curr. Med. Res. Opin.* 22, 1093–1099. doi: 10.1185/030079906X104830

Hansen, E., and Zech, N. (2019). Nocebo effects and negative suggestions in daily clinical practice - Forms, impact and approaches to avoid them. *Front. Pharmacol.* 10:77. doi: 10.3389/fphar.2019.00077

Hole, J., Hirsch, M., Ball, E., and Meads, C. (2015). Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. *Lancet* 386, 1659–1671. doi: 10.1016/S0140-6736(15)60169-6

Holler, M., Koranyi, S., Strauss, B., and Rosendahl, J. (2021). Efficacy of hypnosis in adults undergoing surgical procedures: a meta-analytic update. *Clin. Psychol. Rev.* 85:102001. doi: 10.1016/j.cpr.2021.102001

Hudetz, A. G. (2008). Are we unconscious during general Anesthesia? *Int. Anesthesiol. Clin.* 46, 25–42. doi: 10.1097/AIA.0b013e3181755db5

Kekecs, Z., Nagy, T., and Varga, K. (2014). The effectiveness of suggestive techniques in reducing postoperative side effects: a meta-analysis of randomized controlled trials. *Anesth. Analg.* 119, 1407–1419. doi: 10.1213/ANE.0000000000000466

Kuhlmann, A. Y. R., de Rooij, A., Kroese, L. F., van Dijk, M., Hunink, M. G. M., and Jeekel, J. (2018). Meta-analysis evaluating music interventions for anxiety and pain in surgery. *Br. J. Surg.* 105, 773–783. doi: 10.1002/bjs.10853

Lee, A., Chan, S. K., and Fan, L. T. (2015). Stimulation of the wrist acupuncture point PC6 for preventing postoperative nausea and vomiting. *Cochrane Database Syst. Rev.* 11:CD003281. doi: 10.1002/14651858.CD003281.pub4

Levinson, B. W. (1965). States of awareness during general anaesthesia. Preliminary communication. *Br. J. Anaesth.* 37, 544–546. doi: 10.1093/bja/37.7.544

Linassi, F., Obert, D. P., Maran, E., Tellaroli, P., Kreuzer, M., Sanders, R. D., et al. (2021). Implicit memory and Anesthesia: a systematic review and meta-analysis. *Life* 11:850. doi: 10.3390/life11080850

Madler, C., Keller, I., Schwender, D., and Poppel, E. (1991). Sensory information processing during general anaesthesia: effect of isoflurane on auditory evoked neuronal oscillations. *Br. J. Anaesth.* 66, 81–87. doi: 10.1093/bja/66.1.81

Marteau, T. M., and Bekker, H. (1992). The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). *Br. J. Clin. Psychol.* 31(Pt 3), 301–306. doi: 10.1111/j.2044-8260.1992.tb00997.x

Merikle, P. M., and Daneman, M. (1996). Memory for unconsciously perceived events: evidence from anesthetized patients. *Conscious. Cogn.* 5, 525–541. doi: 10.1006/ccog.1996.0031

Messina, A. G., Wang, M., Ward, M. J., Wilker, C. C., Smith, B. B., Vezina, D. P., et al. (2016). Anaesthetic interventions for prevention of awareness during surgery. *Cochrane Database Syst. Rev.* 10:CD007272. doi: 10.1002/14651858.CD007272.pub2

Millar, K., and Watkinson, N. (1983). Recognition of words presented during general anaesthesia. *Ergonomics* 26, 585–594. doi: 10.1080/00140138308963377

Moerman, D. E., and Jonas, W. B. (2002). Deconstructing the placebo effect and finding the meaning response. *Ann. Intern. Med.* 136, 471–476. doi: 10.7326/0003-4819-136-6-200203190-00011

Myles, P. S., Leslie, K., Chan, M. T., Forbes, A., Paech, M. J., Peyton, P., et al. (2007). Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. *Anesthesiology* 107, 221–231. doi: 10.1097/01.anes.0000270723.30772.da

Myles, P. S., and Wengritzky, R. (2012). Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review. *Br. J. Anaesth.* 108, 423–429. doi: 10.1093/bja/aer505

Myles, P. S., Williams, D. L., Hendrata, M., Anderson, H., and Weeks, A. M. (2000). Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10,811 patients. *Br. J. Anaesth.* 84, 6–10. doi: 10.1093/oxfordjournals.bja.a013383

Nowak, H., Zech, N., Asmussen, S., Rahmel, T., Tryba, M., Oprea, G., et al. (2020). Effect of therapeutic suggestions during general anaesthesia on postoperative pain and opioid use: multicentre randomised controlled trial. *BMJ* 371:m4284. doi: 10.1136/bmj.m4284

Owens, W. D., Felts, J. A., and Spitznagel, E. L. Jr. (1978). ASA physical status classifications: a study of consistency of ratings. *Anesthesiology* 49, 239–243.

Peyton, P. J., and Wu, C. Y. (2014). Nitrous oxide-related postoperative nausea and vomiting depends on duration of exposure. *Anesthesiology* 120, 1137–1145. doi: 10.1097/ALN.0000000000000122

Riegel, B., Tonnies, S., Hansen, E., Zech, N., Eck, S., Batra, A., et al. (2021). German Norms of the Harvard Group Scale of Hypnotic Susceptibility, Form A (HGSHS:A) and Proposal of a 5-Item Short-Version (HGSHS-5:G). *Int. J. Clin. Exp. Hypn.* 69, 112–123. doi: 10.1080/00207144.2021.1836645

Rosendahl, J., Koranyi, S., Jacob, D., Zech, N., and Hansen, E. (2016). Efficacy of therapeutic suggestions under general anesthesia: a systematic review and meta-analysis of randomized controlled trials. *BMC Anesthesiol.* 16:125. doi: 10.1186/s12871-016-0292-0

Rusch, D., Eberhart, L. H., Wallenborn, J., and Kranke, P. (2010). Nausea and vomiting after surgery under general anesthesia: an evidence-based review concerning risk assessment, prevention, and treatment. *Dtsch. Arztebl. Int.* 107, 733–741. doi: 10.3238/arztebl.2010.0733

Samuels, J. D. (2013). Perioperative nausea and vomiting: much ado about nothing? *Aesthet. Plast. Surg.* 37, 634–635. doi: 10.1007/s00266-013-0068-6

Sanders, R. D., Tononi, G., Laureys, S., and Sleigh, J. W. (2012). Unresponsiveness not equal unconsciousness. *Anesthesiology* 116, 946–959. doi: 10.1097/ALN.0b013e318249d0a7

Schumann, R., and Polaner, D. M. (1999). Massive subcutaneous emphysema and sudden airway compromise after postoperative vomiting. *Anesth. Analg.* 89, 796–797. doi: 10.1097/00000539-199909000-00050

Schwender, D., Kaiser, A., Klasing, S., Peter, K., and Poppel, E. (1994). Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. *Anesthesiology* 80, 493–501. doi: 10.1097/00000542-199403000-00004

Simanski, C., Waldvogel, H. H., and Neugebauer, E. (2001). [Postoperative nausea and vomiting (PONV). Clinical significance, basic principles, prevention and therapy]. *Chirurg* 72, 1417–1426. doi: 10.1007/s001040170005

Sinclair, D. R., Chung, F., and Mezei, G. (1999). Can postoperative nausea and vomiting be predicted? *Anesthesiology* 91, 109–118. doi: 10.1097/00000542-199907000-00018

Stoicea, N., Gan, T. J., Joseph, N., Uribe, A., Pandya, J., Dalal, R., et al. (2015). Alternative therapies for the prevention of postoperative nausea and vomiting. *Front. Med.* 2:87. doi: 10.3389/fmed.2015.00087

Tramer, M. R., Reynolds, D. J., Moore, R. A., and McQuay, H. J. (1997). Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. *Anesthesiology* 87, 1277–1289. doi: 10.1097/00000542-199712000-00004

Varga, K. (2013). Suggestive techniques connected to medical interventions. *Interv. Med. Appl. Sci.* 5, 95–100. doi: 10.1556/IMAS.5.2013.3.1

Visser, K., Hassink, E. A., Bonsel, G. J., Moen, J., and Kalkman, C. J. (2001). Randomized controlled trial of total intravenous anesthesia with propofol versus inhalation anesthesia with isoflurane-nitrous oxide: postoperative nausea with vomiting and economic analysis. *Anesthesiology* 95, 616–626. doi: 10.1097/00000542-200109000-00012

Weibel, S., Schaefer, M. S., Raj, D., Rucker, G., Pace, N. L., Schlesinger, T., et al. (2021). Drugs for preventing postoperative nausea and vomiting in adults after general anaesthesia: an abridged Cochrane network meta-analysis. *Anaesthesia* 76, 962–973. doi: 10.1111/anae.15295

Zech, N., Scharl, L., Seemann, M., Pfeifer, M., and Hansen, E. (2022). Nocebo effects of clinical communication and placebo effects of positive suggestions on respiratory muscle strength. *Front. Psychol.* 13:825839. doi: 10.3389/fpsyg.2022.825839

Zech, N., Schrodinger, M., Seemann, M., Zeman, F., Seyfried, T. F., and Hansen, E. (2020). Time-dependent negative effects of verbal and non-verbal suggestions in surgical patients-A study on arm muscle strength. *Front. Psychol.* 11:1693. doi: 10.3389/fpsyg.2020.01693

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Avoidance of nocebo effects by coincident naming of treatment benefits during the medical interview for informed consent—Evidence from dynamometry

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Introduction: In the context of giving risk information for obtaining informed consent, it is not easy to comply with the ethical principle of "primum nihil nocere." Carelessness, ignorance of nocebo effects and a misunderstood striving for legal certainty can lead doctors to comprehensive and brutal risk information. It is known that talking about risks and side effects can even trigger those and result in distress and nonadherence to medication or therapy.

Methods: Recently, we have reported on significant clinically relevant effects of verbal and non-verbal suggestions on maximal muscular arm strength in healthy volunteers and in patients at two time points before surgery. Maximal strength during arm abduction was measured by dynamometry of the deltoid muscle group. Suggestions from clinical everyday life were formulated as presumed negative and neutral versions.

Results: Here, we report on the effects of two versions of risk information in 45 patients. After sole mentioning risks of a puncture for the placement of a pain catheter, the maximal arm muscle strength was significantly reduced to 83% of baseline several days (T1), and to 84% the evening before surgery (T2). Strength was not significantly decreased and close to baseline at T1 and T2 when risks and benefits of a pain catheter were combined in one sentence. The difference between both versions was significant. With persistent normal distribution of values, the effect was due to uniform reactions of many patients, not to strong reactions of a few. High suggestibility and increase of anxiety with approaching surgery were identified as influencing factors for the neutralizing effect of modified wording.

Conclusion: We not only suggest an alternative formulation for risk information to avoid nocebo effects but present an objective method to quantify and compare effects of different wordings. Thereby, we provide evidence that concurrently given positive aspects can neutralize negative effects during medical interview.

KEYWORDS

nocebo effect, suggestion, dynamometry, arm muscle strength, medical interview, informed consent

Introduction

Risk information to achieve informed consent has been identified as the major cause of nocebo effects (Colloca and Miller, 2011; Häuser et al., 2012; Wells and Kaptchuk, 2012; Cohen, 2014). Talking about and explaining side effects of a medication or any other medical intervention may elicit or intensify those very same symptoms. Besides conditioning, i.e., learning from one's own prior bad experiences, negative expectations, inadvertently induced during disclosure of adverse treatment effects, are the main origin of nocebo responses. The latter rarely are "non-specific" as often attributed to placebo/nocebo effects, but typically reflect exactly those discussed undesirable adverse reactions (Kaptchuk et al., 2006; Amanzio et al., 2009; Rief et al., 2009). Some of the physiological bases are now well understood, such as the involvement of certain brain areas or biochemical mediators (Benedetti et al., 2006). Nocebo effects not only add to the burden of illness, but also result in psychological distress, medication or therapy nonadherence, extra treatment visits and therapy of side effects, most of the latter incurring considerable extra costs (Barsky et al., 2002). In addition, negative expectations, hopelessness, and depressive reactions that can be induced by risks disclosure, are strong predictors of an unfavorable outcome of disease and therapy (Székely et al., 2007; Laferton et al., 2013; Tilbury et al., 2018). Finally, postponement or even refusal of a necessary medical intervention resulting from an inadequate disclosure of risk information represent further detrimental side effects of medical briefing for informed consent.

Therefore, physicians find themselves in the dilemma of respecting the Hippocratic doctrine of primum nihil nocere, i.e., "not to harm," and the clinical reality of nocebo, i.e., "I will harm" (Miller and Colloca, 2011). Accordingly, most publications on the subject end with a call for a change and for improvements in the practice of providing information in order to obtain informed consent (Colloca, 2017; Evers et al., 2018; Howick, 2020). Nevertheless, any proposal to reduce expectancy-induced side effects has to respect the ethical principle that there is not only the right for autonomy, i.e., decisions after adequate information, but also the right for non-maleficence (Wells and Kaptchuk, 2012; Cohen, 2017; Fortunato et al., 2017). Although numerous studies have shown that side effects are significantly reduced in patients when risk information was withheld, nondisclosure is not an acceptable option (Daniels and Sallie, 1981; Myers et al., 1987; Mondaini et al., 2007). The question is not whether to provide information, but rather how to adequately provide that information. Moreover, lying and whitewashing are not allowed either because of the claim for truthfulness. Appropriate strategies must be based on knowledge of the mechanisms of nocebo effects, on established communication strategies, and on clinical experience (Schedlowski et al., 2015). Often proposals to reduce expectancy-induced side effects are rather general and hard to implement and verify, such as "enhanced treatment information," "optimization of patient-clinician communication and relationship," "managing patient's treatment expectations," and "selection and tailoring treatment to patients at risk" (Manaï et al., 2019). Despite several proposals, it still remains an open question as to what and how doctors should communicate to contribute to evidence-based practice and informed patient choice while minimizing nocebo effects, strongly calling for research (Miller and Colloca, 2011). The more so because only rarely has the effectiveness of the proposed approaches been measured and verified (Barnes et al., 2019; Fernandez et al., 2019; Pan et al., 2019), as necessary for an evidence-based approach.

We have recently proposed a measurement technique to qualify and quantify suggestion effects, namely alterations in maximal arm muscle strength in abduction (Zech et al., 2019, 2020). Muscle strength is a clinically relevant parameter with regard to early mobilization, risk of falling and sufficient breathing. Furthermore, the observed impairment of muscular performance could reflect a general "weakening effect" of negative suggestions (Hansen and Zech, 2019). With this objective test system adopted from physiology we have tested various verbal and nonverbal signals, designated as "suggestions," from everyday clinical practice, and found significant weakening, or neutral reactions to alternative formulations, respectively. Herein we report on results with patients using two versions of disclosure of risk information for obtaining informed consent.

Materials and methods

Design and participants

In an experimental trial on 50 patients, we tested the effect of two versions of risk disclosure on maximal arm muscle strength during abduction. The data exclusively reported here were collected during a study on the effects of suggestions in the clinical context published recently (Zech et al., 2020). The sequence of tested interventions was randomized. After approval by the local ethics committee (EC University of Regensburg, Nr. 13-101-0030) the study was conducted at the University Hospital Regensburg, Germany. Patients between 18 and 70 years of age were considered for enrolment if they were to undergo elective surgery under general anesthesia no closer than 3 days either at the Departments of General Surgery, Neurosurgery, Otorhinolaryngology or Cranio-Maxillofacial Surgery. Participants had to be native German speakers and without relevant general pain (i.e., a Numeric Rating Scale NRS <5), and without pain or impairment of the dominant shoulder, arm or hand. Another exclusion criterion was a pre-existing severe systemic disease (ASA $\geq$ 3, according to the ASA physical status classification system of the American Society of Anesthesiologist). 50 patients fulfilling the inclusion criteria were enrolled after written informed consent and without financial compensation. A detailed description of this study can be found in the previous manuscript (Zech et al., 2020).

Measurement of maximal muscle strength

Effects of suggestions on maximal muscle strength were measured at two timepoints: days before surgery (T1, minimum 3 days), and in the evening before surgery (T2). Maximal isometric contraction of the deltoid muscle group during arm abduction was tested by dynamometry, in a defined upright position with the dominant arm stretched out laterally (Figure 1). A dynamometer (FORCE GAUGE FM200, PCE Deutschland GmbH, Meschede, Germany) was used in the peak hold mode with a measurement accuracy of 0.5%.

Baseline was established for every patient by means of six initial measurements without suggestion followed by three to five such baseline measurements interspersed between tests of suggestions, adding up to a total of 9–11. The standardized instruction for this baseline measurement is given in Table 1. With a variation of ±6.3% of baseline values (Zech et al., 2019) maximal muscle strength measured under these conditions is a rather robust physiological parameter. However, individuals show a high range of variation in muscle strength. Therefore, the results of responses to suggestions were expressed as relative values, i.e., in percentage of the baseline value of each participant. All patients were tested by the same examiner (MS). Each test session lasted about 40–60 min, which was found feasible even for patients.

FIGURE 1
Test setup. For dynamometry of maximal arm muscle strength during abduction the patient stands upright, facing the tester, with the dominant arm stretched to the side and the wrist connected to the dynamometer by a band. Photo taken by NZ: MS with a patient, showing the standardized positioning.

Test of suggestion effect

Eighteen verbal and non-verbal suggestions out of clinical context were tested in two previous studies on healthy volunteers (Zech et al., 2019) and on patients (Zech et al., 2020). Here, the results of the two phrases designed to gain informed consent after risk information are reported. Patients listened to recorded instructions explaining the placement and functionality of the muscle test, whereas suggestions were given verbally, face to face. The wording of the instruction prior to suggestions, as well as the suggestions for risk information can be seen in Table 1. Version A was taken directly from everyday clinical practice and presumed to be negative and causing a nocebo effect. The alternative version B was formulated, considered to be positive and to elicit a neutral or placebo effect. After six baseline measurements, all suggestions were tested in a randomized order, using the software Randlist (Datinf GmbH, Tübingen), alternating a presumed negative version with a presumed neutral or positive version, to avoid cumulation effects. Tests were separated by breaks, arithmetical tasks and repeated determinations of blank values. In order to prevent incorrect measurements because of exhaustion an additional break was inserted, whenever a baseline value fell below 90% of the previous value, and the test repeated subsequently.

Measurement of suggestibility and anxiety

Anxiety was measured with the state scale of the State–Trait-Anxiety-Inventory (STAI-S; Spielberger, 1985) with 20 test items in a German version (Laux et al., 1981) prior to the beginning of

TABLE 1 Wording of the standardized instructions and verbal suggestions.

Category	Instruction	Risk disclosure	
		Version A	Version B
Baseline	"Now pull upward with maximal power. Now, one-two-three."		
Suggestion	"Again, stand upright, lift your arm. Close your eyes. You are a patient in a hospital. You are faced with the following sentences. Take your time and let it affect you, and then pull upwards as hard as you can."	"If you wish, we can place a pain catheter, with the **risk of infection, allergic reaction, and damage to blood vessels or nerves**."	"We have the option of a local pain therapy. Even though there is a **risk of infection, allergic reaction, or damage to blood vessels or nerves**, you will have to take fewer pills, are more mobile, feel and recover better, and perhaps can go home sooner."

Instructions were given from tape, suggestions face-to-face by the tester.

dynamometry. Evaluation took place at the two time points to draw conclusions about changes in anxiety over time with approaching operation date. With a range of 20 ("no fear") to 80 ("worst fear") points, the test evaluates the current situational anxiety. Anxiety is usually considered clinically relevant at a score >40, and at >55 rated relevant for psychiatric disorders (Knight et al., 1983; Addolorato et al., 1999). The difference between the scores at T2 and T1 is referred to as ΔSTAI-S and describes the change of anxiety between the two times of testing.

Suggestibility was evaluated with a 5-items short version of the Harvard Group Scale of Hypnotic Susceptibility (HGSHS-5:G; Riegel et al., 2021). The HGSHS has been established as an objective test method by Shor to determine the suggestibility of a single person or groups (Shor and Orne, 1963; Bongartz, 1985; Peter et al., 2015). The short version takes about 20 min instead of 60 min for the full version. Patients performed the test and the self-evaluation according to an audio file a few days after their operation. Based on the HGSHS-5:G score, patients were rated "low suggestible" with a score of 0 or 1, "medium suggestible" with a score of 2 or 3, and "high suggestible" with scores of 4 or 5.

Statistical analyses

For statistical analyses IBM SPSS Statistics, version 26 was used. Normal distribution was tested according to Kolmogorow–Smirnow. Data are presented as mean ± standard deviation (SD) or as median (interquartile range) depending on the underlying distribution. A one-sample t-test was used to evaluate significant changes of relative maximal arm muscle strength (%) at different time points compared to the initial 100% (baseline value). A histogram using steps of 5% was used to present the distribution of the values. Repeated measure ANOVA was performed with relative maximal arm muscle strength as dependent variable and instructions (A vs. B) and time (T1 vs. T2) as within subject factors. Partial eta-squared was used as an estimate of the effect size. Univariate linear regression analysis was performed to test for the influence of age, anxiety, increase in anxiety and suggestibility score. A p level of <0.05 was considered to be statistically significant.

Results

Baseline characteristics

Missing data (only tested at T1 because patient declined, surgery rescheduled or canceled) resulted in the exclusion of five out of 50 recruited patients. Patient characteristics and baseline scores are presented in Table 2. The median time from T1 to day of surgery was 3 days, with a range of 3–25 days. 53% of the values were at day 3, the minimal allowed interval. The rest was distributed around day 6 before surgery. For two patients the interval was 25 days, specific for the type of surgery. Due to the individual physical condition of the patients, baseline muscle strength ranged from 18.8 N to 143.7 N. The reproducibility of the baseline values of each individual patient was high (variance ≤4.8%; 4.8% at T1 and 4.7% at T2, respectively). Baseline values did not differ significantly at T1 and T2 ($p = 0.87$). 23 patients showed a clinically relevant baseline state score (>40) for anxiety (STAI-S at T1), the score of five patients lay above the threshold (>55) relevant for psychiatric disorders. State anxiety raised significantly from days before surgery (T1) to the evening before the operation (T2) by 6.2 ± 8.9 ($p < 0.001$). Further analyses of determinants for anxiety and increase in anxiety can be found in Zech et al. (2020). Corresponding to the suggestibility score 12 patients (27%) were rated low suggestible and 10 patients (22%) high suggestible.

TABLE 2 Baseline characteristics of study population (N=45).

Age (years)	Mean ± SD	43.8 ± 15.0
Female sex	N (%)	25 (56%)
State anxiety (STAI-S)		
Days before surgery (T1)	Mean ± SD	41.7 ± 10.3
Evening before surgery (T2)	Mean ± SD	47.9 ± 12.7
Suggestibility (HGSHS-5:G)	Median (IQR)	3 (1–3)
Days from first test (T1) to surgery	Median (IQR)	3.0 (3.0–7.0)
Baseline muscle strength (Newton)		
Days before surgery (T1)	Mean ± SD	65.0 ± 23.4
Evening before surgery (T2)	Mean ± SD	64.8 ± 23.5

STAI-S, State–Trait-Anxiety-Inventory (Spielberger, 1985).
HGSHS-5:G, 5-item Harvard Group Scale of Hypnotic Susceptibility (Riegel et al., 2021).

Changes in maximal arm muscle strength after suggestion

Version A to gain informed consent after risk information, taken from every day clinical practice and suspected to be negative, resulted in a highly significant reduction of maximal arm muscle strength at both time points, namely by 16.9% at T1 and by 15.7% at T2 compared to baseline, respectively ($p < 0.001$). There was no significant decline in muscle strength after version B at both time points. The reactions to version A did not differ significantly between time point T1 and T2, neither did the reactions to version B (Figure 2).

The difference between version A and version B was significant at T1 and at T2. ANOVA showed a significant effect of the wording of risk information but not of the time, nor of the interaction of the two (Table 3).

Distribution of values of maximal arm muscle strength at T2

To distinguish between the reaction of a few vs. that of most patients, a distribution of values is presented in Figure 3. Effects of both versions of risk information showed normal distribution. Relative muscle strength after version A ranged from 60% to 100%.

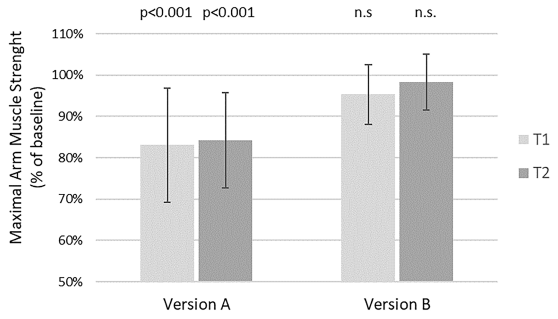

FIGURE 2
Effects of two different versions of risk disclosure on maximal arm muscle strength. After baseline dynamometry of arm abduction verbal suggestions were presented and measurement repeated. Version A: "If you wish, we can place a pain catheter, with the **risk of infection, allergic reaction, and damage to blood vessels or nerves**." Version B: "We have the option of a local pain therapy. Even though there is a **risk of infection, allergic reaction, or damage to blood vessels or nerves**, you will have to take fewer pills, are more mobile, feel and recover better, and perhaps can go home sooner." ■T1=days before surgery ■T2=evening before surgery. Mean and SD of maximal arm muscle strength compared to baseline are given. P according to one sample *T*-test.

TABLE 3 Effect of wording and timing of risk information to obtain informed consent on maximal arm muscle strength.

	Relative maximal arm muscle strength (%)		
Time point	**T1**	**T2**	**T2–T1**
Version A	83.1 ± 14.1	84.3 ± 11.5	1.1 ± 13.0
Version B	95.6 ± 7.0	98.3 ± 6.8	2.7 ± 7.7
B–A	12.3 ± 13.2	14.0 ± 11.4	

p-values of repeated measures ANOVA:

Difference between time points: $p = 0.172$, $\eta p2 = 0.04$

Difference between versions: $p < 0.001$, $\eta p2 = 0.60$

Interaction between time points and version: $p = 0.380$, $\eta p2 = 0.18$

After baseline measurements verbal suggestions were presented and dynamometry of arm abduction repeated. Mean and SD of relative values (compared to baseline) are given. Significance was tested by repeated measures ANOVA. T1 = days before surgery, T2 = evening before surgery; ηp2 = effect size measured by partial eta-squared.

Reactions to version B showed a narrower distribution from 80% to 115%. Six patients reached values higher than baseline.

Influencing factors

The influence of various factors (age, anxiety level, change in anxiety, and suggestibility score) on the effects of two versions of risk information on maximal muscle strength at the day before surgery (T2) was tested by linear regression analyses various factors. Both, the impact on the negative effect of the risk information (baseline – version A) and the impact on the neutralization of this negative influence by version B (muscle strength after version B – results after version A) were evaluated. Linear regression analyses showed that

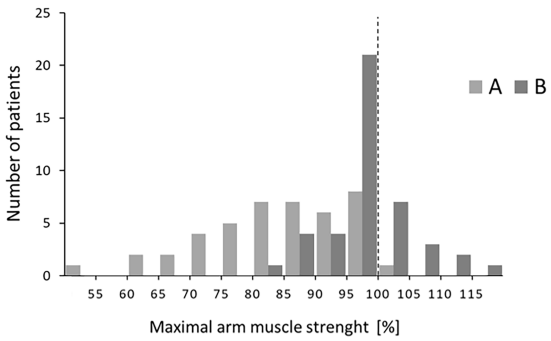

FIGURE 3
Distributions of relative muscle strength at T2 after the two versions A and B. Patients within a range of 5% points were grouped (e.g., 80%–84%).

TABLE 4 Factors influencing the effect of risk information on maximal arm muscle strength and on its modification with an alternative formulation.

	Correlation coefficient *R* (*p*)	
	Version A	**Version B–Version A**
Age	−0.16 (0.299)	−0.19 (0.234)
HGHS-5 score	0.24 (0.124)	0.35 (0.023)
STAI-S	−0.07 (0.646)	0.07 (0.637)
ΔSTAI-S	0.28 (0.071)	0.39 (0.012)

Correlation coefficients are given according to linear regression analyses. STAI-S, State Anxiety Inventory at T2, ΔSTAI-S = STAI-S at T2 minus STAI-S at T1. Suggestibility: measured with the 5-items short version of the Harvard Group Scale of Hypnotic Susceptibility (HGSHS-5:G).

age, suggestibility score and anxiety score, as well the change in anxiety (ΔSTAI-S) did not significantly influence response of muscle strength to the suggestion. However, suggestibility score and ΔSTAI-S, i.e., the change in anxiety with approaching operation date, had a small but significant impact on the difference in the effects of the versions of risk information (Table 4). In patients with higher ΔSTAI-S maximal arm muscle strength showed improvement by version B compared to version A of risk information (Figure 4).

Discussion

In the test setting of the present study, a usual wording of risk information resulted in reduction in maximal arm muscle strength. Thus, a negative effect on patients was objectively demonstrated and quantified. The weakening effect is confirmed by the measurement at two different time points, particularly days and at the evening before an operation.

How to measure nocebo effects

Although the optimal demonstration of negative consequences of informed consent is an increase in the side

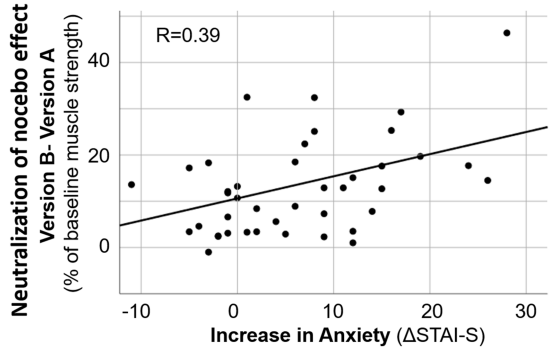

FIGURE 4
Linear regression analysis on the increase in anxiety and the decrease in negative effect of risk information on muscle strength by alternative formulation. ΔSTAI-S=STAI-S at T2 minus STAI-S at T1.

effects discussed, such evidence needs high numbers of patients and a long observation period. Furthermore, most of the risks discussed in such medical informative interviews have multiple and complex origins and influencing factors, and the longer the time to their occurrence the more contributing factors join in. Parameters relevant for surgery for instance such as postoperative pain or nausea are dependent on the type of surgery, patient's medication, type and course of anesthesia, and preposition and precondition of the patient. Besides the side effects addressed directly during the interview, nocebo effects of informed consent may also include more general medical complaints and burdens such as increased anxiety, hopelessness, hemodynamic instability, delay of wound healing, impaired immune response, and many others. In addition, different specific side effects allow no comparison, pain and nausea as nocebo effects cannot be contrasted quantitatively. Comparison of studies by effect size is nearly impossible, since different outcome parameters are measured: effects on symptom severity and duration, number of patients affected, number of side effects, different symptom qualities (e.g., various forms of pain). This heterogeneity in primary outcomes and their effect sizes hampers comparison of the effectiveness of different approaches for nocebo effect reduction.

In contrast, with the parameter maximal arm muscle strength nocebo effects can be qualitatively identified as such and can be objectively measured and quantified. An objective physiological measure is used instead of subjective psychological parameters such as pain score. Intensity of nocebo effects are studied instead of merely incidence. Moreover, with the use of one uniform parameter different nocebo effects can be compared. This allows also to study combinations of nocebo effects as they typically occur and sum up in clinical practice. Verbal and non-verbal signals interplay and are communicated all along during a hospital stay from admission to examination, from interview to risk assessment and information, from treatment to recovery. Comparison can also be made between different versions of a suggestion, like an alternative formulation of risk disclosure for informed consent in the present study. This allows different alternatives to be evaluated and thus communication be improved and optimized (Hansen and Zech, 2019). In addition, this parameter used in the present study and proposed for further nocebo research represents a physiological function of clinical relevance. Any impairment of muscle function is undesired, as enhancing the risk of falling, delay of mobilization after surgery, and insufficient respiration. The latter was confirmed by demonstration of respiratory muscle strength reduction after suggestions from clinical practice, including the risk information tested in the present study (Zech et al., 2022). Finally, the effects on maximal arm muscle strength were observed without verbal formulations directed to muscular function. While usually nocebo effects are tested within their specificity, e.g., pain after using the word "pain" or "stitch," muscular function that was affected was not addressed in the tested risk information. Therefore, it was a more general effect that was observed, and even may be interpreted as marker for a "weakening" of the patient (Zech et al., 2019, 2020).

How to detraumatize informed consent

According to the growing knowledge about nocebo effects that originate in the presentation of risk information to obtain informed consent, numerous proposals have been put forward to reduce or avoid the resulting negative consequences (Colloca, 2017; Klinger et al., 2017; Evers et al., 2018; Manaï et al., 2019; Howick, 2020; Zech et al., 2022). They reach from the idea of withholding the information about side effects (Daniels and Sallie, 1981; Myers et al., 1987; Mondaini et al., 2007), the mere talking about the existence of nocebo effects (Pan et al., 2019), or positive framing of information or side effects (Barnes et al., 2019), e.g., the occurrence of side effects as sign that the medication is active (Fernandez et al., 2019). However, rarely have the efficacy of such suggested approaches been tested. Reasons for this includes lack of standardizability of some of the proposed attempts, or the high number of patients necessary to evaluate rare side effects, that hinders scientific evaluation. Some publications are difficult to classify because the interventions are hardly described. For instance, for a "contextualized informed consent" urging for consideration of the specific patient, diagnosis and side effects, it is suggested to tailor information to the susceptibility of the patient and the degree of severity of the diagnosis, and to distinguish between unspecific and specific side effects (Wells and Kaptchuk, 2012). This approach has been challenged and designated unethical for containing partial withholding of information, and ineffective due to patients potentially gaining the information from other sources (Bromwich, 2012). This highlights the narrowness of the allowed corridor for framing: even if the

treatment was authorized, the consent is considered invalid because the doctor exercised illegitimate control over the patient's treatment decision by manipulating the given information.

In a meta-analysis of studies that have tested effectiveness of framing strategies, Barnes et al. reported positive effects in five of six studies with a low effective size of 0.09–0.24 (Barnes et al., 2019). Attribute framing, where side effects are expressed as "will not occur" (positive framing) or "will occur" (negative framing), had varying influence on number of patients affected, or number of side effects. However, the success was sometimes only short-lasting and only one of the studies involved patients. For example, following informed consent for an influenza vaccination fewer side effects and less absence from work were observed after positive framing (O'Connor et al., 1996). Two studies tested message framing, where in the positive version side effects are expressed as indicating that the drug works (Wilhelm et al., 2018; Fernandez et al., 2019). In a cold pressure task, framing had minimal impact on expectancies and incidence of side effects (Devlin et al., 2019).

A systematic review on effects of brief psychological interventions on adverse reactions found the strongest and most consistent effect from omitting risk information, no reduction of side effects by de-emphasizing, and mixed results from distraction, priming, or alteration of branding perception (Webster and Rubin, 2019). Informing about the nocebo effect has been shown to be able to reduce nocebo side effects after the intervention for a short time (Pan et al., 2019). Other attempts have been tested in experimental studies, and yet have to be translated to the clinical practice of presenting risk information for informed consent for a short time.

Combining negative and positive expectations

Our attempt to neutralize negative impacts of risk information to obtain informed consent by simultaneous naming therapy benefits represent the most effective demonstrated so far, with an effect size Cohen's d of 0.9 and 1.2 at the two test times, respectively. A comparison of the distributions of values shows that the neutralization was not due to the response of a few but to a uniform reaction of most patients. Closest to our approach comes an experimental trial of Bartels et al., where a nocebo effect induced by negative conditioning of itch to a color lamp was reduced by counterconditioning with a color light connected to a positive verbal suggestions ("The color will indicate an electrode that decreases the itch") (Bartels et al., 2017). In a study on symptoms after windfarm sounds and media reports positive expectations (possible therapeutic effects of infrasound exposure) were able to attenuate effects from negative expectations (TV footage about health effects of wind turbines ultrasound), both when raised before or after the negative expectations (Crichton et al., 2014). The peculiarity and novelty of the present study is not the combination of negative and positive suggestions, but their simultaneous application. Information on both the benefits of therapy and the risks is also given to the patient in everyday clinical practice. However, most often they are separated by time or the medical discipline. The surgeon that has explained to the patient the benefit of the surgical therapy often only later talks about the associated risks, or the anesthetist gives information on risks of anesthesia without relying on those therapeutic benefits. In this study the negative suggestions connected with talking about side effects are presented together with the positive suggestions of treatment success, even in the same sentence. Maybe for the counterbalance of negative and positive expectations, and the resulting nocebo and placebo effects, simultaneity is essential. The aim of the interview for obtaining informed consent is to enable the patient to weigh up benefits and risks for a well-founded decision. This is achieved best when the patient has a look on both aspects at the same time instead of receiving information about treatment and its benefits separate from risk disclosure.

As the benefits of the proposed treatment are not the only positive aspect that can balance negative impacts of informed consent, various options to neutralize nocebo effects are listed in Table 5. Besides the principle of simultaneously naming something positive with the negative risk, the prophylactic measures taken to reduce or avoid the side effect can also be explained. Moreover, the careful monitoring during the intervention can be addressed, which facilitates immediate recognition of a developing adverse reaction and thereafter often allows rapid countermeasures and offers good treatment options. Sometimes the possibility of active patient participation to prevent side effects can be mentioned. That in addition gives back motivation and control to the patient. Probably these positive suggestions generate positive expectations and thereby compete with the negative expectations and nocebo effects induced by the risk information (Hansen and Zech, 2019). A limited capacity to process expectations simultaneously could be the reason.

Contributing factors

Various factors may have an impact on the development of nocebo effects and possibly on their neutralization (Table 4). In the present study no significant influence of age or gender was observed. Anxiety *per se* was also not a determining factor. However, an increase in state anxiety score with approaching operation date as deduced from ΔSTAI-S as well as hypnotic susceptibility score had an impact. Interestingly, both an rise in anxiety and suggestibility, exerted their influence not on the weakening effect of an ordinary risk information (baseline – version A) but on the neutralizing effect of a modified formulation (version B–version A) accounting for 15% of variance. However, suggestibility is such a minor determinant that the principle of neutralizing the nocebo effect by simultaneous addressing of positive aspects is not limited to high suggestible persons but can be used for all patients.

Confirmation and future research

Our finding confirms results from a preceding study on healthy volunteers where the same test system was applied, and the same

TABLE 5 Options for neutralization of nocebo effect induction during risk disclosure by simultaneous presentation of positive aspects.

Positive aspects	Principle	Example
Treatment Benefit		"The peridural anesthesia carries a very small risk of neurologic impairment, but reduces pain and prevents the much more common adverse reactions like pneumonia, thrombosis or drug incompatibilities."
Prophylaxis	Prophylaxis to prevent development of side effects	"We will carefully disinfect the skin where we do the surgery to prevent wound infection."
Monitoring	Early detection of developing side effect	"That ECG-monitoring would immediately tell us should your diseased heart develop some arrhythmia, so we can start immediately with appropriate treatment."
Treatability	Early treatment of progressing side effects and therapy of occurred harm	"We have all medication available to cope with and stop a developing allergic reaction."
Patients Contribution	Active prophylaxis and monitoring	"If you repeat the breathing exercise I showed you often enough, you can contribute to the prevention of pneumonia."

TABLE 6 Effectiveness of an alternative formulation of risk information to prevent weakening in healthy volunteers and in patients.

Risk information	Volunteers (Zech et al., 2019)	Patients (present study)	
		T1	T2
Version A vs. B			
Effect size, Cohen's d (95% CI)	0.4 (0.2–0.7)	0.9 (0.6–1.3)	1.2 (0.8–1.6)

T1 = days before surgery, T2 = evening before surgery. Cohen's calculated from paired Students *T*-test.

suggestions tested (Zech et al., 2019). Effect sizes are compared in Table 6. It is noticeable that the weakening effect of risk information disclosure (version A) was much more pronounced in patients compared to volunteers: −16.9 (at T1) and −15.7% (at T2) vs. −11.0% (Zech et al., 2019). This draws attention to the fact that nocebo effects measured in experimental settings may underestimate the real effects in clinical situations. Most importantly, neutralization by concomitant positive aspects was also more effective in the real clinical situation (for comparison of effect sizes see Table 6).

Reduction in maximal arm muscle strength measured in dynamometry, an easily available and feasible test system, can be used as surrogate marker for nocebo effect induction. It has proven effective in this and previous studies as a useful method for nocebo research (Zech et al., 2019, 2020). The approach to measure and quantify nocebo effects by a uniform physiological function like arm muscle strength not only allows for comparison of negative influences but also of alternative wordings for a better communication. Thereby, various attempts to avoid nocebo effects can be tested as well as positive suggestions. Moreover, combinations of verbal interventions can be evaluated. Altogether, the approach used and proposed here allows improvement of doctor-patient communication and interviews for informed consent according to scientific and comprehensible principles (Crichton et al., 2014).

Nevertheless, the proposed alternative positive aspects to combine with the risk information such as prophylactic and therapeutic measures to prevent or treat side effects (as presented in Table 5) have yet to be verified in studies. So do their combinations. In general, it must be said that the many well-considered and promising proposals of improvements in preventing nocebo effects after interviews for informed consent found in the recent literature still have to be measured, quantified and to show their effectiveness in both experimental and clinical studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by EC University of Regensburg, Nr. 13-101-0030. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any identifiable images or data included in this article.

Author contributions

NZ: study design, application for ethic committee approval, literature search, participant recruitment, data collection and analysis, and preparation of the manuscript. EH: study plan and design, supervision, literature search, data analysis, preparation of figures, tables, and manuscript, and correction of manuscript. MS: participant recruitment and data collection and analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Addolorato, G., Ancona, C., Capristo, E., Graziosetto, R., Di Rienzo, L., Maurizi, M., et al. (1999). State and trait anxiety in women affected by allergic and vasomotor rhinitis. *J. Psychosom. Res.* 46, 283–289. doi: 10.1016/S0022-3999(98)00109-3

Amanzio, M., Corazzini, L. L., Vase, L., and Benedetti, F. (2009). A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain* 146, 261–269. doi: 10.1016/j.pain.2009.07.010

Barnes, K., Faasse, K., Geers, A. L., Helfer, S. G., Sharpe, L., Colloca, L., et al. (2019). Can positive framing reduce Nocebo side effects? Current evidence and recommendation for future research. *Front. Pharmacol.* 10:167. doi: 10.3389/fphar.2019.00167

Barsky, A. J., Saintfort, R., Rogers, M. P., and Borus, J. F. (2002). Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 287, 622–627. doi: 10.1001/jama.287.5.622

Bartels, D. J. P., van Laarhoven, A. I. M., Stroo, M., Hijne, K., Peerdeman, K. J., Donders, A. R. T., et al. (2017). Minimizing nocebo effects by conditioning with verbal suggestion: a randomized clinical trial in healthy humans. *PLoS One* 12:e0182959. doi: 10.1371/journal.pone.0182959

Benedetti, F., Amanzio, M., Vighetti, S., and Asteggiano, G. (2006). The biochemical and neuroendocrine bases of the hyperalgesic nocebo effect. *J. Neurosci.* 26, 12014–12022. doi: 10.1523/JNEUROSCI.2947-06.2006

Bongartz, W. (1985). German norms for the Harvard group scale of hypnotic susceptibility, form a. *Int. J. Clin. Ex. Hypn.* 33, 131–139. doi: 10.1080/00207148508406643

Bromwich, D. (2012). Plenty to worry about: consent, control, and anxiety. *Am. J. Bioeth.* 12, 35–36. doi: 10.1080/15265161.2012.656810

Cohen, S. (2014). The nocebo effect of informed consent. *Bioethics* 28, 147–154. doi: 10.1111/j.1467-8519.2012.01983.x

Cohen, S. (2017). Preventing Nocebo effects of informed consent without paternalism. *Am. J. Bioeth.* 17, 44–46. doi: 10.1080/15265161.2017.1314056

Colloca, L. (2017). Tell me the truth and I will not be harmed: informed consents and Nocebo effects. *Am. J. Bioeth.* 17, 46–48. doi: 10.1080/15265161.2017.1314057

Colloca, L., and Miller, F. G. (2011). The nocebo effect and its relevance for clinical practice. *Psychosom. Med.* 73, 598–603. doi: 10.1097/PSY.0b013e3182294a50

Crichton, F., Dodd, G., Schmid, G., Gamble, G., Cundy, T., and Petrie, K. J. (2014). The power of positive and negative expectations to influence reported symptoms and mood during exposure to wind farm sound. *Health Psychol.* 33, 1588–1592. doi: 10.1037/hea0000037

Daniels, A. M., and Sallie, R. (1981). Headache, lumbar puncture, and expectation. *Lancet* 1:1003.

Devlin, E., Whitford, H. S., and Denson, L. A. (2019). The impact of valence framing on response expectancies of side effects and subsequent experiences: a randomised controlled trial. *Psychol. Health* 34, 1358–1377. doi: 10.1080/08870446.2019.1609677

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., et al. (2018). Implications of placebo and Nocebo effects for clinical practice: expert consensus. *Psychother. Psychosom.* 87, 204–210. doi: 10.1159/000490354

Fernandez, A., Kirsch, I., Noël, L., Rodondi, P. Y., Kaptchuk, T. J., Suter, M. R., et al. (2019). A test of positive suggestions about side effects as a way of enhancing the analgesic response to NSAIDs. *PLoS One* 14:e0209851. doi: 10.1371/journal.pone.0209851

Fortunato, J. T., Wasserman, J. A., and Menkes, D. L. (2017). When respecting autonomy is harmful: a clinically useful approach to the Nocebo effect. *Am. J. Bioeth.* 17, 36–42. doi: 10.1080/15265161.2017.1314042

Hansen, E., and Zech, N. (2019). Nocebo effects and negative suggestions in daily clinical practice – forms, impact and approaches to avoid them. *Front. Pharmacol.* 10:77. doi: 10.3389/fphar.2019.00077

Häuser, W., Hansen, E., and Enck, P. (2012). Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch. Arztebl. Int.* 109, 459–465. doi: 10.3238/arztebl.2012.0459

Howick, J. (2020). Unethical informed consent caused by overlooking poorly measured nocebo effects. *J. Med. Ethics* 47:105903. doi: 10.1136/medethics-2019-105903

Kaptchuk, T. J., Stason, W. B., Davis, R. B., Legedza, A. R. T., Schnyer, R. N., Kerr, C. E., et al. (2006). Sham device v inert pill: randomised controlled trial of two placebo treatments. *Br. Med. J.* 332, 391–397. doi: 10.1136/bmj.38726.603310.55

Klinger, R., Blasini, M., Schmitz, J., and Colloca, L. (2017). Nocebo effects in clinical studies: hints for pain therapy. *Pain. Rep.* 2:e586. doi: 10.1097/PR9.0000000000000586

Knight, R. G., Waal-Manning, H. J., and Spears, G. F. (1983). Some norms and reliability data for the state-trait anxiety inventory and the Zung self-rating depression scale. *Br. J. Clin. Psychol.* 22, 245–249. doi: 10.1111/j.2044-8260.1983.tb00610.x

Laferton, J. A., Shedden Mora, M., Auer, C. J., Moosdorf, R., and Rief, W. (2013). Enhancing the efficacy of heart surgery by optimizing patients' preoperative expectations: study protocol of a randomized controlled trial. *Am. Heart J.* 165, 1–7. doi: 10.1016/j.ahj.2012.10.007

Laux, L., Glanzmann, P., Schaffner, P., and Spielberger, C. (1981). *Das State-Trait Angstinventar. Theoretische Grundlagen und Handanweisung*. Weinheim: Beltz Test GmbH.

Manaï, M., van Middendorp, H., Veldhuijzen, D. S., Huizinga, T. W. J., and Evers, A. W. M. (2019). How to prevent, minimize, or extinguish nocebo effects in pain: a narrative review on mechanisms, predictors, and interventions. *Pain Rep.* 4:e699. doi: 10.1097/PR9.0000000000000699

Miller, F. G., and Colloca, L. (2011). The placebo phenomenon and medical ethics: rethinking the relationship between informed consent and risk-benefit assessment. *Theor. Med. Bioeth.* 32, 229–243. doi: 10.1007/s11017-011-9179-8

Mondaini, N., Gontero, P., Giubilei, G., Lombardi, G., Cai, T., Gavazzi, A., et al. (2007). Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon? *J. Sex. Med.* 4, 1708–1712. doi: 10.1111/j.1743-6109.2007.00563.x

Myers, M. G., Cairns, J. A., and Singer, J. (1987). The consent form as a possible cause of side effects. *Clin. Pharmacol. Ther.* 42, 250–253. doi: 10.1038/clpt.1987.142

O'Connor, A. M., Pennie, R. A., and Dales, R. E. (1996). Framing effects on expectations, decisions, and side effects experienced: the case of influenza immunization. *J. Clin. Epidemiol.* 49, 1271–1276.

Pan, Y., Kinitz, T., Stapic, M., and Nestoriuc, Y. (2019). Minimizing drug adverse events by informing about the nocebo effect-an experimental study. *Front. Psych.* 10:504. doi: 10.3389/fpsyt.2019.00504

Peter, B., Geiger, E., Prade, T., Vogel, S., and Piesbergen, C. (2015). Norms of German adolescents for the Harvard group scale of hypnotic susceptibility, form A. *Int. J. Clin. Exp. Hypn.* 63, 92–109. doi: 10.1080/00207144.2014.961877

Rief, W., Nestoriuc, Y., von Lilienfeld-Toal, A., Dogan, I., Schreiber, F., Hofmann, S. G., et al. (2009). Differences in adverse effect reporting in placebo groups in SSRI and tricyclic antidepressant trials: a systematic review and meta-analysis. *Drug Saf.* 32, 1041–1056. doi: 10.2165/11316580-000000000-00000

Riegel, B., Tönnies, S., Hansen, E., Zech, N., Eck, S., Batra, A., et al. (2021). German norms of the Harvard group scale of hypnotic susceptibility (HGSHS-A) and proposal of a 5-item short-version (HGSHS5:G). *Int. J. Clin. Exp. Hypn.* 69, 112–123. doi: 10.1080/00207144.2021.1836645

Schedlowski, M., Enck, P., Rief, W., and Bingel, U. (2015). Neuro-bio-behavioral mechanisms of placebo and nocebo responses: implications for clinical trials and clinical practice. *Pharmacol. Rev.* 67, 697–730. doi: 10.1124/pr.114.009423

Shor, R. E., and Orne, E. C. (1963). Norms on the Harvard Group Scale of Hypnotic Susceptibility, Form A. *Int. J. Clin. Exp. Hyp.* 11, 39–47. doi: 10.1080/00207146308409226

Spielberger, C. D. (1985). Assessment of state and trait anxiety: conceptual and methodological issues. *South Psychol.* 2, 6–16.

Székely, A., Balog, P., Benkö, E., Breuer, T., Székely, J., Kertaiet, M., et al. (2007). Anxiety predicts mortality and morbidity after coronary artery and valve surgery–a 4-year follow-up study. *Psychosom. Med.* 69, 625–631. doi: 10.1097/PSY.0b013e31814b8c0f

Tilbury, C., Haanstra, T. M., Verdegaal, S. H. M., Nelissen, R. G. H., de Vet, H. C. W., Vliet Vlieland, T. P. M., et al. (2018). Patients' pre-operative general and specific outcome expectations predict postoperative pain and function after total knee and total hip arthroplasties. *Scand. J. Pain* 18, 457–466. doi: 10.1515/sjpain-2018-0022

Webster, R. K., and Rubin, G. J. (2019). Influencing side-effects to medical treatments: a systematic review of brief psychological interventions. *Front. Psych.* 9:775. doi: 10.3389/fpsyt.2018.00775

Wells, R. E., and Kaptchuk, T. J. (2012). To tell the truth, the whole truth, may do patients harm: the problem of the nocebo effect for informed consent. *Am. J. Bioeth.* 12, 22–29. doi: 10.1080/15265161.2011.652798

Wilhelm, M., Rief, W., and Doering, B. K. (2018). Decreasing the burden of side effects through positive message framing: an experimental proof-of-concept study. *Int. J. Behav. Med.* 25, 381–389. doi: 10.1007/s12529-018-9726-z

Zech, N., Scharl, L., Seemann, M., Pfeifer, M., and Hansen, E. (2022). Nocebo effects of clinical communication and placebo effects of positive suggestions on respiratory muscle strength. *Front. Psychol.* 13:825839. doi: 10.3389/fpsyg.2022.825839

Zech, N., Schrödinger, M., Seemann, M., Zeman, F., Seyfried, T. F., and Hansen, E. (2020). Time dependent negative effects of verbal and nonverbal suggestions in surgical patients – a study on arm muscle strength. *Front. Psychol.* 11:1693. doi: 10.3389/fpsyg.2020.01693

Zech, N., Seemann, M., Grzesiek, M., Breu, A., Seyfried, T. F., and Hansen, E. (2019). Nocebo effects on muscular performance – an experimental study about clinical situations. *Front. Pharmacol.* 10:219. doi: 10.3389/fphar.2019.00219

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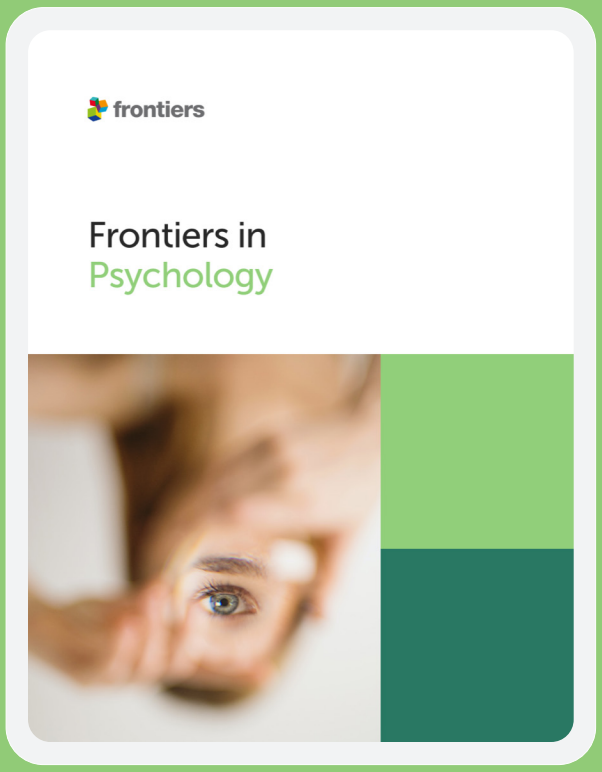

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