HARNESSING PLACEBO MECHANISMS FOR OPTIMAL PAIN MANAGEMENT AND TREATMENT OF ALCOHOL AND OTHER DRUG USE DISORDERS

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Editorial: Harnessing placebo mechanisms

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Editorial on the Research Topic
Harnessing placebo mechanisms for optimal pain management and treatment of alcohol and other drug use disorders

Introduction

The placebo phenomenon is receiving increasing attention because of the high translational value of basic research that can effectively translates into better study designs and symptoms management (1). This Theme Issue collection represents current trends in placebo research by focusing on two main strategies: (1) characterizing temporal effects, and (2) identify neuropsychobiological factors that can be used to subgroup individuals in clinical research for personalized treatments or interventions. The present collection predominantly focuses on placebo and nocebo effects associated with pain-related outcomes that were presented at the 3rd International conference of the Society for Placebo Studies (SIPS) in 2021. The first major section comprises of six studies that examined placebo and nocebo effects, with a focus on contextual features and individual predictors to be considered in designing rigorous research in these areas. The second major section is comprised of another six studies that investigated the potential for use of techniques that elicit nocebo and or placebo responses in clinical practice, with a focus on treating acute and chronic pain.

The Special Topic issue begins with an article by Cornell et al. reporting results of the SIPS 2021 Conference. In keeping with an important objective of this meeting, senior faculty worked with graduate and undergraduate students to design a post conference evaluation. These students had provided essential support in operationalizing and facilitating the translation of a traditional design to a virtual conference platform and took the lead in analyzing data collected by the hosting platform throughout the conference. As the authors discuss, having quantitative data that measured individual attendee activity during and across the three-day conference proved valuable in describing the level and degree of participation. Descriptive analyses of quantitative data collected during the conference indicated a highly successful program as well as revealed and implications for future, scientific meetings. Specifically, the results identified challenges of creating and sustaining meaningful networking in a virtual platform within the context of an international meeting where attendees represented multiple time zones. The authors also identified and discussed issues that influenced the design and evolution of this meeting, particularly the COVID-19 pandemic.

Considerations for designing rigorous research on placebo and nocebo effects

The role of contextual factors on placebo and nocebo effects

Contextual factors (CF) are various elements deriving from a patients' interactions with practitioners and the therapeutic arena that influence disease processes and therapeutic outcomes (2, 3). Whilst positive CF may induce placebo effects, negative CF may induce nocebo effects resulting in adverse effects (4, 5). However, studies assessing specific CF have yielded mixed results on their contribution to placebo/nocebo effects (2, 6, 7). This heterogeneity in outcomes have prompted investigating the context of how the CFs are assessed. To elucidate these mechanisms further, the first three manuscripts consider whether and how temporal expectations modulate placebo hypoalgesia and nocebo hyperalgesia. A study by Rosenkjær et al. from Aarhus University in Denmark and the Harvard Medical School in the US, examines the temporal relationship of expectations to placebo effects. Specifically, whether and how the temporal development of expectations affects research subjects' experiences over time. The results of the qualitative and quantitative data presented in this manuscript indicate that the timing of the assessment of expectations in placebo trials is a crucial feature of studying and clarifying placebo effects. Next, a collaboration between Camerone et al. from Italy, Belgium and the United Kingdom, elaborates on the construct of temporal modulation in placebo and nocebo studies. The authors examined the modulation of nocebo effect, the onset of action, and time-course of nocebo hyperalgesia in a model of sustained pain. The results of this study inform the design of clinical trials that will expand understanding of treatment negative expectations and drug side effects. A third study (Benson et al.), conducted by a team of scientists from Essen University Hospital and Ruhr University in Germany, investigated effects of pre-treatment expectations on post-treatment perceived treatment efficacy. Benson et al. used an experimental model of visceral pain and measured the effects of pre-treatment expectation on post-treatment perceived treatment efficacy. Results confirmed individual's positive expectations and perceived symptom improvement facilitates treatment satisfaction. These three studies also have implications for improving treatment outcomes if clinicians have the knowledge and understanding of the relationship between treatment expectations on both placebo and nocebo effects.

Reinforcing expectancies have been shown to augment hypoalgesia in many previous work (8–10). Building upon these studies, Proulx-Bégin et al. from Université de Montréal and McGill University in Canada consider a proof-of-concept conditioning procedure based on a surreptitious augmenting intervention expectation as a method for enhancing hypoalgesic effect. While the study was conducted in a population of healthy volunteers, it provides a model for the investigation of conditioning to raise expectations in patients with chronic pain, and perhaps other chronic conditions.

Individual predictors of placebo and nocebo effects

The placebo and nocebo effects are neuropsychobiological responses that are highly heterogeneous amongst individuals (11, 12). Recently, much attention has been directed toward identifying individual characteristics to broaden our understanding of individual differences in placebo/nocebo responses particularly in clinical settings. Two articles here contribute to the *personalized* approach to harnessing placebo/nocebo effects. Weng et al. from the Netherlands explore individual psychological predictors of generalization of nocebo and placebo effects within and across pain and itch modalities. Next, in a collaborative exploratory genome-wide association study (GWAS) by researchers from Germany, the UK, and the US, Vollert et al. revealed that the pain severity and pain frequency subscales are associated with distinct genetic loci, highlighting the need for replication studies to characterize neurobiological underpinnings.

The use of placebo and nocebo effects in clinical practice

Increasingly, studies demonstrate the clinical effectiveness of placebo and nocebo responses. It is fitting, therefore, to understand the health care professionals' knowledge, perspectives and use of placebo and nocebo effects. The first study of this second section by Smits et al. reports findings from a cross-sectional survey of general practitioners in The Netherlands. The study revealed limited knowledge on use of placebo in practice as well as a pervasive perspective that use of placebo is necessarily "deceptive" and thus potentially unethical. This gap in understanding of placebo effect and placebo response impedes its application in clinical practice. For example, an important dimension to treating acute pain is appreciating the influence of preoperative mood and treatment expectations on postoperative pain. Stuhlreyer and Klinger, from Germany, found a strong relationship between these two variables and suggest a preoperative expectation management program focusing on the patient's emotional state has potential for significantly reducing post-operative pain. The study by Olliges et al. in Germany and Switzerland investigated the effect of open-label placebo in treating elderly knee pain associated with osteoarthritis. This study adds to the growing understanding that deception is not necessary to evoke placebo effects. Bedford et al. (United States), in their study on patients and clinicians' perspectives toward a pre-authorized concealed opioid taper. Chronic pain, such as osteoarthritis, also requires a complement of treatments. Prescribing therapeutic pain treatments without placing patients at risk of opioid addiction is an ongoing dilemma. Colloca et al. in the United States demonstrated how expectancies can be shaped to optimize patients' attitudes toward their need for opioid analgesics through educational interventions in participants who experienced trauma induced pain. The last article by Trakimas et al. in the United States, reports on their study to develop guidelines for opioid requirement following hospital discharge of patients who underwent surgery for head and neck cancer. Current post surgical opioid prescribing patterns are not having the desired effect in reducing risk for opioid dependence post-surgery; the authors highlight the need for guidelines for post-surgical opioid requirements and the potential use of conditioning therapy and placebo to augment limited use of opioids post-discharge.

A source for placebo literature

An expertly curated bibliography is a valuable resource for scientists as well as practitioners. While the increasing collaborative and multidisciplinary research conducted in this field bodes well for expanding the science and ultimate translation to treatment, it also poses a challenge to conducting a search of the literature as a result of the multiple areas of science involved. This Special Topic Issue provides a bibliometric exploration of the placebo literature. The bibliometric analyses of the JIPS data base indicates positive growth in research programs, especially interconnections between research groups, areas for future developments, and implications for conducting a search of the literature.

Final remarks

In conclusion, this collection of multifaceted studies presents valuable insights into ways in which scientific rigor in harnessing placebo effects can be strengthened in order to improve patient's outcomes. We would like to emphasize that this Theme Issue is a product of the 3rd SIPS Conference held virtually in May 2021 at University of Maryland, Baltimore, USA. It was an international scientific meeting designed to advance the science of placebo and nocebo research and apply this knowledge to treatment of alcohol and other substance use disorders as well as improve treatment of acute and chronic pain. It is well-established that the placebo/nocebo effects are complex, and the heterogeneity of the responses impedes our understanding of these effects. Recently, specific emphasis has been given toward addressing when or how should the placebo/nocebo effects studied to optimally capture the responses. This shift in paradigm has led to the immergence of numerous investigational strategies to harness placebo/nocebo effects overcoming heterogeneity. Conference presentations elucidated both the complexity of designing robust research programs on nocebo and placebo responses and effects, as well as its translation and application to clinical practices for improved risk reduction, treatment and management of pain and substance use disorders. The SIPS 2021 Conference full proceedings, including abstracts from junior scientists, may be found here (https://www.frontiersin.org/books/3rd_International_Conference_of_the_Society_for_Interdisciplinary_Placebo_Studies_SIPS_Harnessing/5009).

We invited senior scientists, who participated in workshop presentations at SIPS 2021 Conference, to submit manuscripts for this Special Topics Issue: (Harnessing Placebo Mechanisms). Scientists from European and North American countries responded. In some cases, the submitted work was a result of research collaborations and partnerships across Europe and between the United States and European countries, reflecting the growing collaboration in this field. Proposed articles had to be based on original research the author presented at the conference. Manuscripts were peer reviewed and selected to participate. While SIPS 2021 conference featured a few studies on SUD and a plenary presentation on alcohol use disorder (AUD), placebo studies in SUD/AUD are underrepresented in this special issue as in elsewhere. We received overwhelming positive feedback from those who attended the conference. A few examples of feedback are shared here in the article by Cornell et al. With this in mind, we hope that the present collection of studies

will reignite enthusiasm for placebo research amongst the scientific community. Finally, we would like to thank all attendants, junior and senior speakers for their valuable contribution to the SIPS Conference, reviewers and editors involved in this special themed issue, the *Frontiers in Psychiatry* editorial staff, and the funding institutes/programs for their contribution to advance the science and translational aspects of placebo research.

Author contributions

PF and CS wrote the initial draft. JN and LC provided critical revisions to the manuscript. All authors 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.

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Integration of virtual platforms for enhanced conference experience: Data-based evidence from the Society of Interdisciplinary Placebo Studies 2021 conference

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Background: The Society of Interdisciplinary Placebo Studies (SIPS) was one of many organizations that hosted a virtual scientific conference in response to the COVID-19 pandemic restrictions. Retaining essential benefits of an in-person conference experience was a primary objective for the SIPS conference planning committee and guided the selection of a virtual platform on which to host the 2021 meeting. This article reports on the methods used to design and analyze an engaging, virtual scientific conference, along with the findings and implications for future meetings.

Methods: Participant use of and interaction with different features of the conference platform were recorded and exported for analysis. Additionally, all SIPS conference attendees were invited to complete a brief, online post-conference survey that inquired about their perceptions of the SIPS conference specifically as well as their opinions of virtual and hybrid conferences in general. Using these data, we assessed (1) attendance patterns, (2) level of engagement, and (3) attendee satisfaction.

Results: The platform recorded 438 unique, active conference attendees who used either a mobile app, web browser, or both to participate during the 3-day program. Seventy-four percent ($N = 324$) of active users attended all 3 days with 30 and 26 new attendees on Days 2 and 3, respectively. The *connections* feature offered on the platform was the most utilized function within the online forum. Attendance in the parallel workshop sessions remained constant across the 3 days, with an average of 44.6% (SD = 6.77) of people moving between workshops within a single session. The two poster sessions had an average of 47.6 (SD = 17.97) and 27.8 (SD = 10.24)

unique views per poster, respectively. Eleven percent ($N = 48$) of attendees completed the post-conference survey. Thirty-six percent of these responders stated they were only able to attend because the conference was offered virtually. Further, the quality of the conference had an average satisfaction rating of 68.08 out of 100 (SD = 22.94).

Conclusion: Results of data analyses suggest the virtual platform allowed for those who were unable to attend to join virtually, produced moderate engagement throughout the conference, and that the majority of attendees were satisfied with the quality of the fully-virtual conference. Therefore, incorporating virtual aspects in future in-person conferences could enhance conference experience and participation.

KEYWORDS

virtual conference, SIPS, placebo, expectations, alcohol, pain, addiction

Introduction

Many scientific conferences made the transition from in-person to entirely virtual events in line with recommendations published in response to the COVID-19 pandemic (Bosslet et al., 2020; Kopec and Stolbach, 2020; Lazaro et al., 2020; McDowell et al., 2020; Rundle et al., 2020; Rush et al., 2020). Often, organizations had less than a week to transition their on-site conferences to a virtual format (Bosslet et al., 2020; Fulcher et al., 2020; Kopec and Stolbach, 2020; McDowell et al., 2020).While the transition to a virtual platform presented challenges for organizers, benefits were also observed. Specifically, conference organizers reported increased attendance at virtual conferences compared to previous registration numbers at on-site programs. Virtual conferences became more accessible at one level due to the reduced costs (no travel, lodging, or food) and eliminated time needed for travel. Certain features of virtual conferences (e.g., polling and Q&A) allowed for increased audience engagement while facilitating a comfortable environment that encouraged those who would not normally speak during networking sessions to do so (Bosslet et al., 2020; Kopec and Stolbach, 2020; Rotoli et al., 2020; Aravamuthan et al., 2021).

In contrast to the numerous benefits, technological difficulties were one of the main challenges experienced: individual microphone access, sound optimization, and general connectivity issues impeded conference flow (Rundle et al., 2020). Another major difficulty reported was the limited networking capabilities in virtual formats. The organic networking experience of in-person conferences connected individuals and spurred novel scientific ventures (Hauss, 2020). Repeated findings indicated that networking tended to be less successful on virtual platforms (Kopec and Stolbach, 2020; Aravamuthan et al., 2021). The organized structure of virtual networking may even make it difficult for an additional party to naturally join an ongoing discussion (Aravamuthan et al., 2021). Without spontaneous interactions as an impetus for conversation, virtual networking seemed to be less attractive to regular attendees of these conferences (Bosslet et al., 2020; Fulcher et al., 2020; Kopec and Stolbach, 2020). However, other studies on virtual networking within conferences found that greater structure can make virtual networking as, or more fulfilling than the traditional networking experiences, especially for students (Fulcher et al., 2020; Aravamuthan et al., 2021). Overall, the literature provided new insights into designing virtual conferences.

However, it is important to note that only a few studies included robust quantitative data on participation, networking, and other elements of the attendee and speaker experience (McDowell et al., 2020; Stein et al., 2021). In addition, the popularity of virtual environments demands further investigation on their application to virtual scientific conferences. Potential benefits to post-COVID era conferences have also not been thoroughly explored.

Therefore, as a result of the 3rd International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) pivoting to a fully, virtual platform, the potential to collect extensive quantitative and qualitative metrics leading up to, during, and after the conference provided an opportunity to further explore the impact of a virtual scientific meeting.

The following presents the design, transition to, and implementation of a virtual platform at the 2021 SIPS conference. We also address gaps in the literature and discuss implications of the data we have collected pre-, during, and post-conference that may benefit future conferences seeking to integrate aspects of in-person and virtual platforms for improved experience.

Methods

Organization

A formal Conference Planning Committee was established in March 2018, comprising of four faculty members from University of Maryland, Baltimore (UMB). In February 2021, committee members invited seven UMB-affiliated students to participate as volunteer support for the conference. As a result of the COVID-19 pandemic and closure of the UMB campus, one volunteer was based in India, and another based in Ohio during the entirety of conference planning and execution.

During committee meetings, the conference agenda was developed, focusing on (1) expanding the scope of topics beyond that of previous SIPS conferences, (2) providing historic perspective as well as the current state of the science, (3) facilitating translation of the science to practice, (4) engaging senior as well as emerging investigators in the field, and (5) providing a friendly forum for professional networking. The conference design included seven plenary sessions, a lifetime achievement lecture, three special sessions, including a timely conversation panel on COVID-19, and three career development sessions. The goals and themes of the conference were also fulfilled through the 21 parallel workshops, two poster sessions (49 presentations), and five oral presentation sessions consisting of 54 presentations. The program offered multiple forums provided opportunities for senior, mid-level, and early-career level researchers, and practitioners to give thoughtful presentations on their respective scientific research, utilizing several forms of media.

Response to COVID-19 pandemic

The Planning Committee closely monitored national and international developments, along with UMB policies and international recommendations related to the COVID-19 pandemic, which became a standing agenda item on the weekly Committee meetings. The decision to shift from in-person to a virtual meeting was decided in November 2020. Once this decision was made, funds initially dedicated to support an in-person meeting were reallocated to support a robust virtual platform. A search was conducted for a platform that offered the following elements within the available budget:

- Supported live and pre-recorded presentations
- Included proven user-friendly navigation
- Provided multiple mechanisms to enhance participation
- Facilitated real-time interactions between attendees and speakers
- Provided forums for networking
- Allowed customization of online platform
- Provided technical support before, during, and after conference
- Provided data of conference participation

Committee members interviewed company representatives and requested proposals and quotes from potential vendors. *SOCIO Inc.* (Indianapolis, IN, USA; now part of Webex) was selected as the company that best met the platform and budget criteria (https://SOCIO.events/aboutus). The Planning Committee worked with SOCIO staff to custom develop a visually appealing and engaging virtual conference site. Customizing the platform was a lengthy process that continued non-stop up to the start of the event. Adjustments were also made throughout the 3-day conference. For additional details on the SOCIO features used, please see Table 1.

Conference operations

Technical support is crucial to all meetings, yet virtual platforms impose additional technical challenges for both speakers and the audience. While SIPS speakers received detailed written instructions and opportunity to practice in the platform prior to the conference, one to two Committee members were assigned as "Tech Support" (TS) for each session to assure reliable technical support during their Conference presentation. Parallel sessions with multiple, simultaneous presentations, had an additional Committee member serve as a monitor for the entire period. The TS had multiple responsibilities: ~20 min before the start of a session, TS met with speakers in the pre-assigned livestream room to review the room's features as well as check that all audio-visual pieces to the presentation were operating. Once all were ready, the TS would start the livestream. A private chat function allowed speakers and the TS to communicate separately from the audience (e.g., "You will be going live in 5 min." or "Is my screen still sharing?"). The TS would also use an audience chat feature to communicate any issues and check for technology problems (e.g., sound quality, video quality, and lag), as well as prompt and moderate audience participation during the session.

As part of the commitment to excellence, the entire Planning Committee met at the close of each conference day and conducted a debriefing of the day's proceedings. These meetings identified issues to be addressed by the SOCIO staff, shared strategies for managing common issues encountered during live sessions, developed communications to update Conference attendees, as well as anticipated needs for the next day in order to mitigate any problems.

TABLE 1 Description of each feature listed on the SOCIO platform used during the SIPS conference.

Feature name	Description
Welcome and overview	The conference "Home Page" with general information about the conference and host institution (UMB).
Sponsors	Displayed each sponsor's logo and mission with links to their respective website.
Agenda	A detailed program schedule with active links that allowed participants to join sessions directly from this page
Speakers	Listed all speakers with list of associated session(s). A link would direct viewer to the speaker's biography. Attendees could search for speakers by name.
Poster session I and II	Two individual poster sessions. Posters were visible throughout the entire Conference however authors were assigned a specific session where they were present.
Attendees	Listed all registered attendees which could be searched by name and allowed individuals to tag them as a connection.
Announcements	Displayed announcements pertaining to networking rooms, lectures, and Conference updates.
SIPS website	An active link to the conference website which was separate from the SOCIO platform
Message wall	Attendees could write and respond to comments from other attendees.
Q&A rooms	Attendees and speakers could meet after a session to continue discussions.
Networking rooms	Attendees could meet using live video and audio features.
PS Polling	Rated the posters based on scientific merit as well as visuals and presentation skills.

Attendee experience

One week prior to the conference, all registrants received a link to the SOCIO platform and encouraged to develop a personal account and profile, become familiar with the features of the platform as well as review the agenda. Links to individual sessions were not activated until the conference day they were scheduled. Attendees were able to view each speakers' biography and related sessions. In addition, they could view information about other attendees and had the ability to form a virtual *connection* (virtual private interaction) by sending an invitation and having the invitation be accepted, similar to "friending" someone on social media. Once a *connection* was made, two people could start a conversation.

To join a session, attendees navigated to the "Agenda" tab where all sessions were listed by date and time (user's local time zone), then clicked on an agenda item or the "Join Livestream" button below each session. During live sessions, attendees used the chat function to send comments and questions to speaker(s) as well as to other attendees. The TS would monitor the chat and share questions with the speaker(s). Due to limited livestreaming room availability, if the Q&A part of the session ran past its scheduled time, attendees and speaker(s) were then directed to smaller breakout rooms to continue the discussion.

Q&A rooms

Following each live session, attendees with unanswered questions were asked to move to a specific Q&A room assigned to that session. In these rooms, attendees could turn on their cameras and engage in a live conversation with the speaker. These rooms had a capacity for 16 attendees including the three reserved spots for conference staff and speakers. The session TS would also accompany speaker and monitor the room so that anyone who wanted to participate, had an opportunity.

Networking

Dedicated times for social engagement such as networking breakfasts, lunches, and social events were interspersed throughout the conference and were open to all attendees and speakers. Dedicated networking rooms were also available 24/7, each with the capacity for hosting 16 people including reserved spots for Committee members and speakers. Attendees were able to use these networking rooms at any point during the conference. Discussions could also be conducted in the "connections" feature where attendees had the option to privately chat with one or more attendee at a time.

The entire program provided multiple avenues for supporting networking. As mentioned earlier, attendees were also able to interact with speakers and other attendees using a chat function during plenary sessions, spotlight sessions, oral presentations, and in the Q&A rooms. Poster presentations provided a forum to discuss and network with presenters and other attendees through face-to-face video or through the chat function.

Post-conference

Sustaining efforts

Each plenary, workshop, and spotlight session were recorded and saved to the SOCIO platform. The videos were then edited to minimize errant audio or visual issues. A link to the

recorded sessions was posted on the SOCIO platform under the specific session. All registered participants were then able to view these videos. In addition, these recordings were used to develop an "on-demand conference" for those who were unable to attend the live event and sustain the impact of this program.

Survey development

A conference assessment survey was developed using the program REDCap, a HIPAA compliant web application for data capturing and storage, for the purpose of understanding their experience of the 2021 SIPS virtual conference. The survey (Supplementary material) was designed to elicit participants' perceptions both specific to the virtual format as well as how they compared the virtual conference to in-person conference experiences. To maximize survey participation, the survey was designed so that it could be completed within ∼10 min. Briefly, the information gathered from the survey participants included participant background information, conference experience (on a scale from 0 to 100), and plans for future conference participation.

The survey was reviewed by the entire SIPS Conference Planning Committee and submitted to UMB's Institutional Review Board (IRB). After receiving exempt status by the IRB, the survey was sent out by email ∼2 months after the close of the conference. Participants accessed the survey by clicking a link that opened the survey in a separate browser. A survey disclosure statement was displayed prior to the start of the survey. The survey was voluntary and anonymous, with consent being explicit through agreement of participation.

Collection of data on attendee conference activity

Individual attendee conference activity, including *connections* made, attendance for each session, poster and poster external link views and networking and Q&A room attendance was recorded real-time in individual logs on the SOCIO platform. Each attendee who registered for the conference and created an account on the SOCIO platform was identified as "active". After the conference, activity logs for all active attendees were downloaded from SOCIO and combined into a single master file of de-identified data used for analysis in Microsoft Excel. SOCIO employees and support staff activity data were excluded from analysis. Those who registered for the conference but had not created an account were considered as "active" attendees, and therefore were not included in the analyses.

TABLE 2 Attendees' country of affiliation.

Affiliated country	Number of attendees ($n = 353$)	Percentage (%)
Australia	10	2.8
Brazil	5	1.4
Canada	10	2.8
Denmark	6	1.7
France	1	0.3
Germany	84	23.8
Hong Kong	1	0.3
Ireland	2	0.6
Italy	12	3.4
Netherlands	25	7.1
Norway	1	0.3
Poland	8	2.3
Portugal	1	0.3
South Africa	1	0.3
Spain	4	1.1
Sweden	4	1.1
Switzerland	14	4.0
Taiwan	1	0.3
United Kingdom	6	1.7
United States	157	44.5

Statistical analysis

To compare the average attendance per session across days, we performed a Levene's test to check if variance was statistically significantly unequal across the 3 days, and a one-way ANOVA test was performed to determine if the average attendance significantly differed across the 3 days. All statistical analyses were performed using the software package R (The R Foundation, Vienna, Austria).

Results

Attendance levels

The SOCIO platform counted 438 active users from 20 different countries across the 3 days of the conference (Table 2). Attendance was measured as activity originating from either a web browser (77%) or the SOCIO mobile app (23%). Seventy-four percent of active users attended all 3 days, with a slight decline in total attendance observed on each subsequent day. Additionally, 30 and 26 new attendees joined on Day 2 and 3, respectively. No significant difference in attendance across the 3 days (p-value = 0.2477) was observed (Figure 1). Furthermore, average attendance across 3 days showed no significant unequal

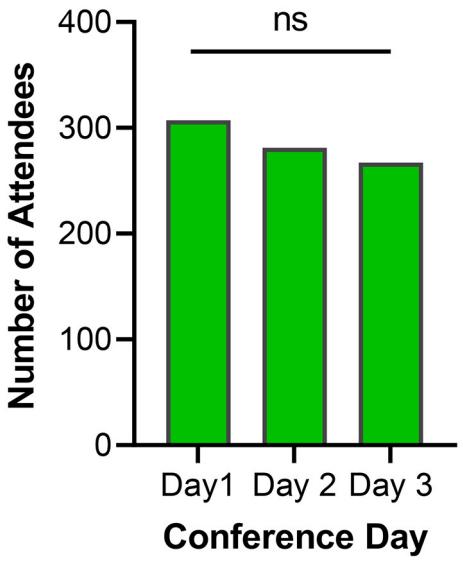

FIGURE 1
Number of attendees across the three conference days. ns, not significant represents a p-value > 0.05. Statistical analysis by Chi square goodness-of-fit test, $p = 0.2477$, $\chi^2 = 2.791$.

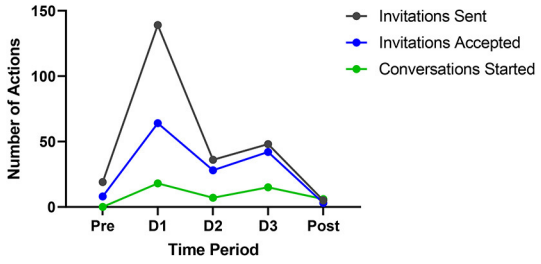

FIGURE 2
Connections made and conversation started from pre- to post-conference. Invitations sent and invitations accepted *(connections* made*)* from pre-conference to post-conference. Conversations started for Pre-conference (Pre), Day 1 through 3 of the Conference (D1, D2, and D3), and Post-conference (Post).

variance (p-value = 0.79). Ten percent ($N = 48$) of attendees completed the post-conference survey. Of those who completed the survey, 36% stated they were only able to attend because the conference was offered virtually.

Conference activity levels

Conference activity levels were measured by networking room utilization rate, session and poster attendance, and the number of *connections* and conversations recorded. A total of 89 (20.3%) unique users made use of a networking room across all 3 days with 55, 49, and 12 unique users recorded on Day 1, 2, and 3, respectively. The number of attendees who participated in parallel workshop sessions did not significantly differ across 3 days (Levene's test: $p = 0.5$; ANOVA: $p = 0.273$), with 44.6% of people moving between workshops within a session, whereas the educational sessions ($n = 3$) had 26% ($N = 27$) of people moving between sessions. Figure 2 shows that *connections* (invitations sent and accepted) and conversations varied from pre- to post-conference duration, where pre-conference pertains to days leading up to the Conference since the activation of the SOCIO platform, and post-conference pertains to the period starting after Day 3 of the Conference. Of the 247 invitations sent throughout the conference, 59% were accepted and 19% of the invitations sent resulted in conversations.

Posters presented in Session 1 each received 47.6 (SD = 17.97) unique views while posters in Session 2 each had 27.8 (SD = 10.24) unique views (Figure 3A). A significant difference was observed in views per poster, according to placement of poster on the website for Session 1 but not for Session 2 [Poster Session 1: Levene's test (p-value = 0.476), one-way ANOVA (p-value = 0.025); Poster Session 2: Levene's test (p-value = 0.121), one-way ANOVA (p-value = 0.09)] (Figures 3B,C). Of the 49 posters, 38 posters contained an external link to either an audio file or video file of their poster for a total of 220 view with a mean of 6 (SD = 4.79) views per external link.

Post-conference survey

The post-conference survey allowed attendees to provide feedback on their experience with the SIPS conference. Fifty-nine attendees began the post-conference survey however 11 surveys were excluded from the analysis due to incompleteness. The resulting 48 completed surveys used in this analysis represent 11% of the total conference attendees, which was an insufficient number of responders to assure validity.

Responders had the option to select multiple academic discipline and career stage categories. Results of the survey indicated approximately half of the survey responders represented psychology (47.9%, $n = 23$) and career stage of survey responders was distributed between early-career (31.3%, $n = 15$), mid-career (22.999%, $n = 11$), and senior-level career (35.4%, $n = 17$) investigators. Over half of survey responders were between the ages of 25 and 44 (56.25%, $n = 27$). Lastly, 95.83% ($n = 44$) of responders attended the conference were located in either North America or Western Europe (Supplementary Table 1).

Survey responders were asked to use a value scale of 0–100, with 100 representing the highest value, with which to rate the quality of the conference, expectations before the conference, satisfaction of the conference, and confidence in future online conferences. The quality of the conference received

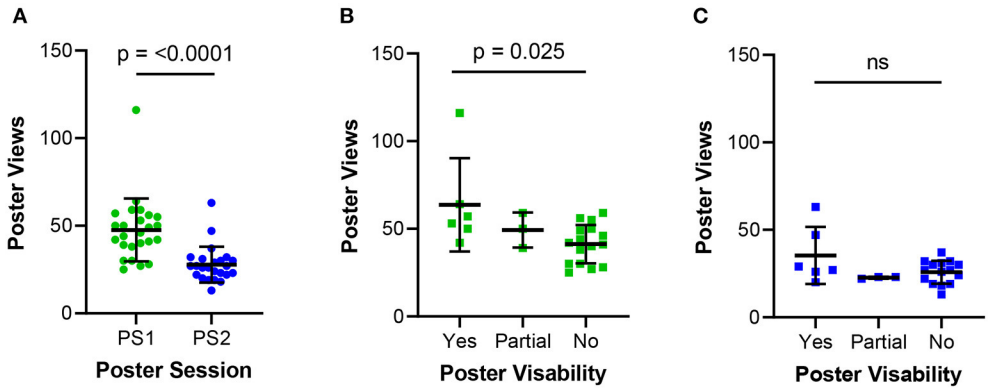

FIGURE 3
Poster views during the two sessions. **(A)** Poster session views per poster for Poster Session 1 (PS1) and Poster Session 2 (PS2) on conference Day 1 and 2, respectively. **(B)** Poster views separated by initial visibility when navigating to the Poster Session features for PS1 and **(C)** PS2. Error bars represent standard errors of mean. Statistical analysis by Levene's test and ANOVA [Poster Session 1: Levene's test (p-value = 0.476), one-way ANOVA (p-value = 0.025); Poster Session 2: Levene's test (p-value = 0.121), one-way ANOVA (p-value = 0.09)]. ns, not significant represents a p-value > 0.05.

an average rating of 68.08 out of a possible 100 points (SD = 22.94). Survey responders within the 18–34 age groups had the lowest average expectations score for conference quality, and those between 45 and 54, and 65+ years of age had the highest (p = 0.0001; Figure 4A). Across all age groups, average satisfaction with conference quality remained consistent, with no statistical significance in difference among age groups (p = 0.434; Figure 4B). Those between 18 and 24 years of age indicted the highest level of confidence in online conferences and those above 75 years of age indicated the lowest level of confidence (p = 0.779; Figure 4C). Additionally, no statistical significance was observed when survey respondents were asked to rate their experience navigating SOCIO (p = 0.199; Figure 4D). Those between ages 25–34 were observed to have the lowest calculated mean in satisfaction with interactions, followed by those over age 75.

Responses indicating expectations for the SIPS conference, satisfaction with the SIPS conference [Levene's test: p-value = 0.6863, ANOVA: p-value = 0.0438], confidence in virtual conferences overall [Levene's test: p-value = 0.7081, ANOVA: p-value = 0.5415], and navigation of the SOCIO platform [Levene's test: p-value = 0.03, ANOVA (not assuming equal variances): p-value = 0.9769] were also analyzed in reference to responders' geographic location. A significant difference was observed in the satisfaction of the SIPS conference (p-value: 0.0438) but other calculated mean scores between locations did not show a significant difference. Lastly, responses to these four items were also analyzed in relation to whether an attendee had previously experienced a hybrid/virtual conference or no previous virtual conference experience. Those with no previous virtual experience showed a significantly lower level (p = 0.007) in expectations for the SIPS conference compared to those with experience with virtual/hybrid conferences (Figure 5). Satisfaction, confidence, and navigation showed no significant difference between the two groups.

Participants were given a space at the end of the survey to offer additional comments and feedback. Responses from the 17 participants who completed this section, shared elements that can be described as generally positive feedback (n = 7), individual technology issues (n = 3), criticisms of the SOCIO platform (n = 7), dissatisfaction with SIPS organizer communication (n = 1), and feedback about the research content of the SIPS conference (n = 2) (Figure 6; Supplementary Table 2). These responses from survey participants are a key part of gauging how attendees felt in their own words, in addition to the scores they selected in the items that were presented to them.

Discussion

Due to the COVID-19 pandemic, the 3rd International Conference of the Society for Interdisciplinary Placebo Studies (SIPS) transitioned to a virtual setting. At that time, few studies provided a quantitative analysis of virtual conferences, leaving a gap in understanding the effect of many features of virtual conferences as well as a lack of evidence with which to develop best practices for the future. With the SOCIO platform and post-conference survey, we were able to collect quantitative and qualitative data with insights into attendance levels, level of engagements, attendee satisfaction, and limitations experienced at the SIPS conference with implications for designing future scientific conferences.

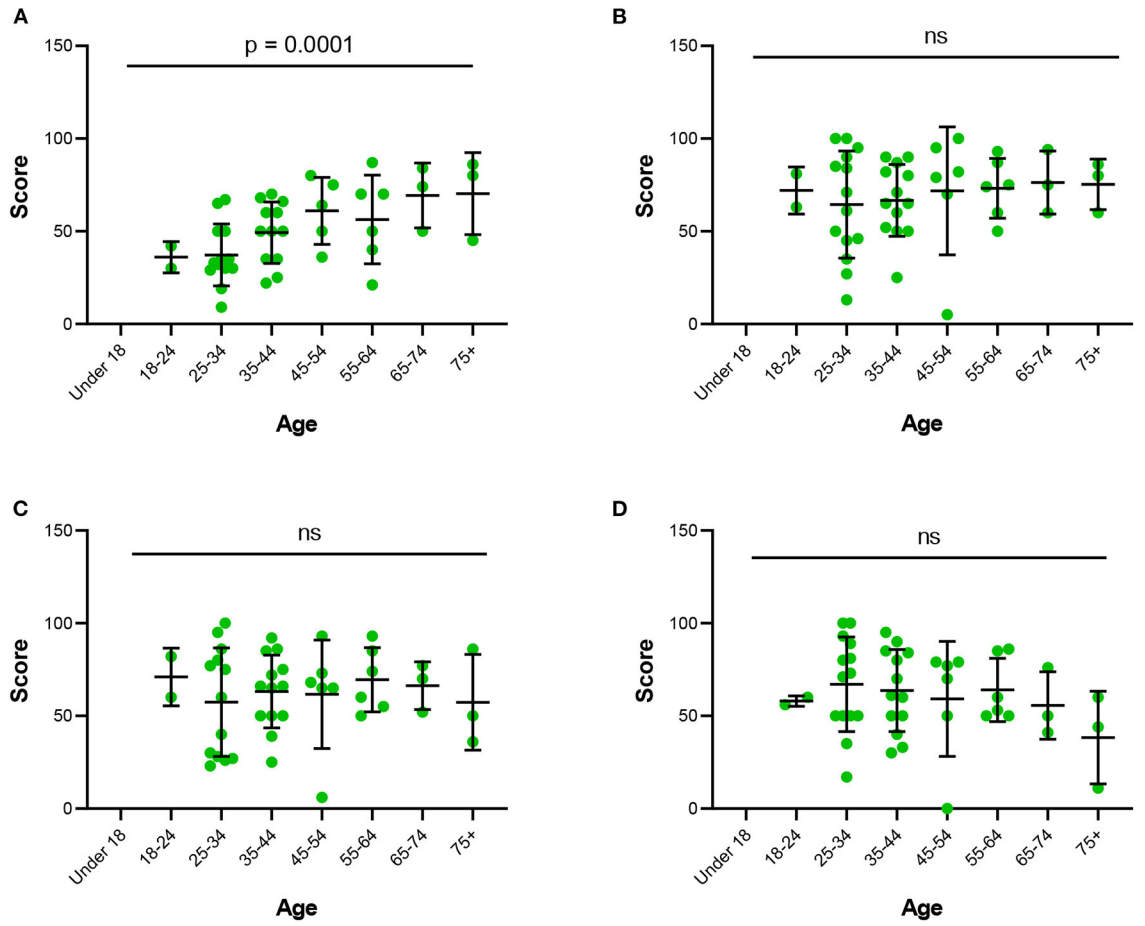

FIGURE 4
Individual scores from the post-conference survey based on attendee's age. Individual scores from the post-conference survey addressing **(A)** expectation, **(B)** satisfaction, **(C)** confidence, and **(D)** navigation based on attendee's age. Error bars represent standard errors of mean. Statistical analysis by Spearman's rho correlation coefficient [**(A)**: $p = 000.1$, **(B)**: $p = 0.434$, **(C)** $p = 0.779$, **(D)** $p = 0.199$]. ns, not significant represents a p-value > 0.05.

Attendance level

Total attendance remained fairly consistent across the 3 days with 74% of active users attending all 3 days. The SIPS conference was not the only virtual conference to see a general high retention rates across multi-day conferences (Fulcher et al., 2020; Stamelou et al., 2021; Weiniger and Matot, 2021; Kim et al., 2022) with some reporting an increase in attendance compared to in-person meetings from previous years (Counsell et al., 2020; Fulcher et al., 2020; Stefanoudis et al., 2021; Weiniger and Matot, 2021). However, other conferences held during the COVID-19 pandemic that distributed post-conference surveys did not present an objective assessment of percentage of attendees that could and could not have attended an in-person conference if offered (Ruiz-Barrera et al., 2021; Kim et al., 2022). Over a third of the attendees who completed the SIPS survey were only able to join because the conference was offered virtually. One survey responder stated in reference to the option of a virtual formatted conference in the future: "I am a very old man [....] I need to be very careful regarding this virus. That will be the first thing in line when future conferences come up on the radar."

To improve accessibility, inclusion, and attendance, research conferences may consider adding a virtual option, creating a hybrid meeting format. Notably, the hybrid format has been explored in conference settings with the ease of restrictions on travel and gatherings. These conferences experienced similar advantages with the majority reporting attendees would like to have virtual options in the future due to reduction of conference cost, attendance flexibility, and reduce carbon footprint (Counsell et al., 2020; Hanaei et al., 2020; Martinelli et al., 2021; Ostler et al., 2021; Sanberg et al., 2021; Chandler et al., 2022; Vartanian, 2022). One suggestion given by Parncutt et al. (2021) discussed the potential for hybrid conferences with multiple "hubs" around the world. Offering the conference

experience to more individuals by a virtual option may facilitate increased dissemination of novel findings and spark more cross-continental collaborations, which is especially valuable for emerging scientific fields.

Level of engagement

Attendees had opportunities to engage in conversation and form connections with other participants within the virtual conference platform using designated networking events, 24/7 available networking rooms, private chat function, chat features during sessions, poster sessions with live video, and Q&A rooms after sessions. Virtual conferences during the COVID-19 pandemic devised different ways to incorporate networking in order to create some semblance of in-person conferences (Veldhuizen et al., 2020; Bhargava et al., 2021; Zaver et al., 2021; Kim et al., 2022). There were conferences that described similar functions to the SIPS Conference virtual platform including private chat functions and chat feature during sessions (Holman et al., 2021; Ruiz-Barrera et al., 2021). Other conferences were unable to incorporate poster sessions due to the limitations in their virtual platform (Bosslet et al., 2020; Ostler et al., 2021). To utilize poster sessions in a hybrid setting, one conference chose to have all poster presenters provide a 5-min pre-recorded talk so the virtual attendees could experience poster sessions online (Chandler et al., 2022), whereas, the SIPS conference offered this option for those who could not make their poster session. Interestingly, due to the lack of networking capability after the conclusion of conference sessions, attendees of one conference created a Google Doc themselves to further network after each session had completed (Bosslet et al., 2020). This suggests attendees place a high level of value on conference networking opportunities. Providing a 24/7 networking option, similar to the SOCIO's networking rooms, is strongly recommended, especially for international conferences where different time zones need to be considered.

Approximately one fifth of the SIPS conference active users made use of the networking rooms available, with the most unique users on the first conference day. Similarly, both poster sessions experienced a relatively low level of attendance. Further, poster placement appeared to have some effect on level of viewing. Therefore, the format should support equal viewing of all posters. One suggestion is having small icons representing each poster that can be viewed on one screen. When a cursor is hovered over these icons, each poster would expand. This could be a better option in giving a fair chance to all posters. This is especially important if judging of posters is done by the general audience. The majority of SIPS Conference posters

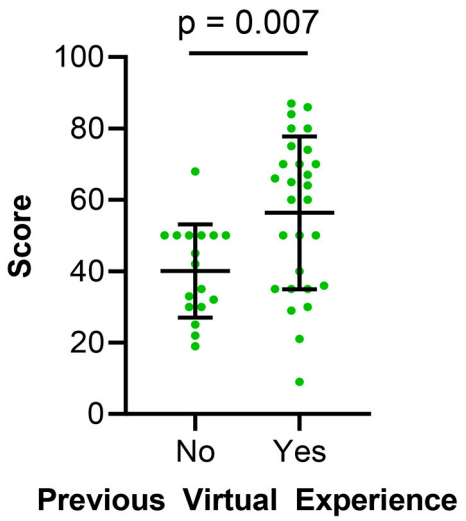

FIGURE 5
Individual scores from the post-conference survey addressing expectation based on previous virtual conference experience. Error bars represent standard errors of mean.

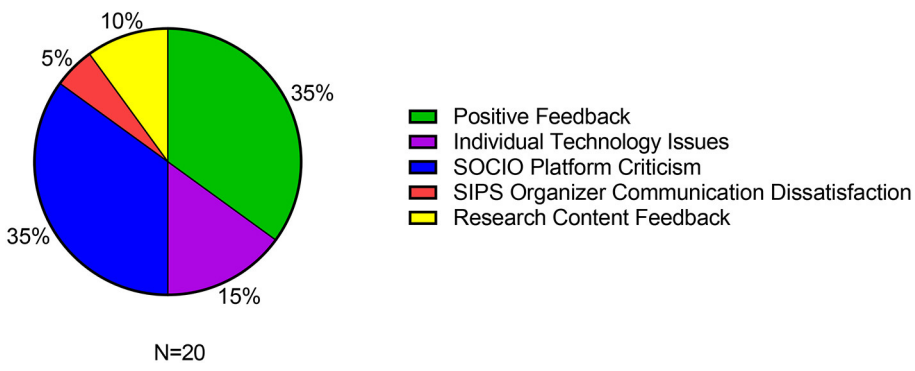

FIGURE 6
Overall feedback on SIPS 2021 conference based on post-conference survey.

included links to external files, which the audience appeared to use. These external files consisted of either an audio or video presentation of the poster through SoundCloud or Vimeo, respectively. These additional tools for engagement gave users the opportunity to participate similarly to activities seen in an in-person conference. However, this benefit would only be applicable if the participants chose to make use of these platform features. Making poster sessions and other organizationally challenging events online requires careful consideration of the usability of specialized features as well as communication with attendees.

Attendee satisfaction

The post-conference survey allowed participants to not only expand on their answer selections, but also to share thoughts regarding related subjects that were not included in the survey. Four of the survey participants shared frustrations related to the limitations of the Q&A and discussion rooms. Specifically, the rooms' limited capacity (15 attendees) and the additional step needed to navigate to these rooms, were perceived as barriers to participation. A number of virtual conference features need refining, and these additional comments responses provided valuable perspectives. In future virtual conferences, Q&A and/or discussion rooms may not be necessary if the original presentation room remained open and allowed attendees to join by live stream to ask questions and expand the conversation. These concerns have been seen in other conferences, stating that virtual networking was not the same as in-person networking (Newman et al., 2021; Stamelou et al., 2021). Conferences that utilized Zoom, for example, had the ability to see each attendee face to face with the speaker. Attendees from this conference showed preference for a virtual face-to-face with everyone in the conference (Stamelou et al., 2021). Thus, considering both the attendee feedback from the SIPS conference and feedback from other virtual conferences, ease of direct attendee to attendee interaction (e.g., seeing faces, question asking, mic access, chat box access, etc.) should be prioritized by virtual conference planners.

Comparing various age groups' level of satisfaction with the quality of the conference and ease of use is imperative to ensuring that virtual conferences remain accessible to all populations. The attendee satisfaction results supported that those over 75 years of age had the lowest level of confidence in virtual conferences and had the most difficulty navigating the virtual platform. While this correlation did not demonstrate statistical significance, it may indicate a technology gap between different age groups (Kim et al., 2022). Even though the SIPS Planning Committee reviewed multiple platforms for ease of use, additional studies need to be conducted on best platforms for multiple generational users. It may also be useful to have an interactive tutorial that users can use to familiarize themselves with the many features of the platform. Tech volunteers, accessible *via* a "help" button, that are assigned to help attendees with general issues could also be helpful supports.

It is also imperative to compare an attendee's location to satisfaction of a conference, especially with attendees joining in a different time zone. According to the post-conference survey, there was no significance difference seen in satisfaction of the quality of the conference when considering geographic location. However, this was not always the case that had attendees from multiple time zones (Ostler et al., 2021). Creating options for attendees from different time zones to network at any point in the day as well as provide recordings soon after each session may enhance international attendees' sense of inclusion and promote networking across the globe.

Privacy concerns

The SOCIO platform provided a feature that recorded user interaction with both the SOCIO website and SOCIO mobile application. This feature records what individual users clicked on, and this data is linked to the individual's conference-registered name. This feature was essential in data collection and provided insight into how users engaged with not only the conference platform features but with one another. However, having an identifiable record of an individual's online activity may raise concerns about privacy. Many conferences have not explored privacy concerns that is inherently involved with a virtual conference (Karabacak et al., 2021; Ruiz-Barrera et al., 2021; Kim et al., 2022). Privacy issue could be addressed by ensuring that future conference attendees be made aware of the data that platforms such as SOCIO collects.

Limitations

The COVID-19 pandemic required a new level of use of existing communication technology such as Zoom, WebEx, and Microsoft Teams. The programs listed existed and were used in business, academia, research, and social settings (Roepke, 2020). The SIPS team worked with the virtual conference platform SOCIO to host the conference. Specific tech issues, such as platform usability, or success of certain conference elements, such as poster sessions or connections, were partially dictated by the unique features available from SOCIO. Overall, the results which reflect the planning, executing, and attending the SIPS annual conference, are potentially limited by the particular technological aspects related to SOCIO's platform.

Another limitation was the inconsistencies observed in the SOCIO automatic platform data collection, which SIPS Committee members discovered during the quality control (QC) process. Missing data points were noted between different data sheets that had collected the same information, thus the data had to be excluded altogether. Furthermore, attendance information had to be provided directly from the SOCIO team. SOCIO explained that the attendance data had a few glitches and incomplete data through the reports for the SIPS conference due to attendees possibly using VPNs or incognito web browsers. In the future, it is recommended to ask platforms companies what the limitations are in their data collection and whether they have QC processes in place if data is going to be used for analysis purposes.

The survey data collected was informative and provided further insightful on how a sub population of attendees felt about the conference itself and virtual conferences in general. However, this survey was completed by only 11% of the attendees and did not show the full extent of locations attendees were from. Other conferences that provided a post-conference survey had varying attendee response rates ranging from 16 to 89.7% (Veldhuizen et al., 2020; Chan et al., 2021; Holman et al., 2021; Karabacak et al., 2021; Nelson et al., 2021; Stamelou et al., 2021; Wang et al., 2021; Kim et al., 2022; Vinchenzo et al., 2022). This difference could be due to the time lag between the end of the SIPS conference and time the survey was delivered (80 days after the conference). The low response rate limits the validity of these results. A reminder to complete the SIPS post-conference survey as an attempt to increase survey participation resulted in an immediate increase in survey responses. Another method to improve survey participation is to provide the survey after each session, at the end of each day, and or after the concluding remarks of the conference. This method has been used which did see an increase in survey responders compared to the SIPS conference (Stein et al., 2021; Vinchenzo et al., 2022).

Incorporating in-person meetings

In a poll of 900 Nature magazine readers, 74% believed that post-pandemic, scientific meetings should continue to use a virtual format, or have a virtual component (Remmel, 2021). The support for virtual platforms is echoed in other publications on the merits of virtual conferences (Bosslet et al., 2020; Salomon and Feldman, 2020; Hassell and Hassell, 2021; Stein et al., 2021). Participants of COVID-era virtual scientific or research conferences expressed that they would attend virtual conferences after the pandemic and recommend virtual conferences as an option. The overarching positive sentiment suggests that virtual platforms will become an integral part of the scientific research world.

Furthermore, implementing elements of virtual platforms into on-site conferences has potential for promoting research dissemination. A hybrid model could support larger-scale involvement; the internet's accessibility opens doors to international participants (Levitis et al., 2021). For example, the SOCIO platform used in the SIPS conference offered multi-language closed captioning; this type of feature would promote inclusivity. Hybrid conferences pose practical challenges, but these difficulties could be resolved with further research.

Conclusion

The analysis of producing a virtual, scientific conference revealed both benefits and challenges of using virtual format. Further, the results suggest that designing a hybrid model for future conferences may enhance access to these forums as well as accelerate dissemination and collaboration. A high attendance and retention rate over all 3 days of the 3rd Annual SIPS International Conference suggested that the virtual platform provided increased accessibility to a world-wide audience. In comparison to overall attendance, the core conference elements, networking forums, and poster sessions produced moderate levels of attendee engagement. The overall flexibility of the virtual conference also gave attendees more independence in their interaction with the conference, but it may also have detracted from the quality of audience interaction experienced by speakers. Conference metrics and attendee satisfaction results suggest that careful consideration of conference goals and user experience when designing conference-specific virtual features, such as networking rooms, connections, and Q&A facilitation, could improve the efficacy of future virtual conferences. Overall, the data gathered from the 2021 SIPS conference supports that the current form of virtual conferences are effective, but improvements can and should be made. Looking forward, a hybrid model poses an opportunity for supplementing in-person conferences with greater accessibility, flexibility, and optimal dissemination.

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 University of Maryland Institutional Review Board (IRB). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

JC, AT, and MY drafted the initial manuscript with JS, PB, DO, and SF writing sections of the manuscript. JC, AT, JS, and PB were involved in data summarization. JC, PB, and CS were involved in the data analysis and interpretation. CS takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the conception, design of the study, manuscript revision, approved the submitted version, and had full access to all the data in the study.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcomm.2022.857661/full#supplementary-material

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Expectations: How and when do they contribute to placebo analgesia?

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In placebo research, expectations are highlighted as one of the most influential subjective factors. While some studies have shown a relationship between expectations and pain relief, others have not. However, little is known about how methods of assessment of expectations may affect these conclusions. One of the fundamental considerations is that participants in placebo trials rate their expectations when prompted to rate them on scales in advance, but are less likely to report their prior expectations, when asked to report their experience retroactively in an unprompted manner, often expressing, for example, prior hope or wishes of recovery. This article presents previously unpublished data to elucidate and explore the concepts highlighted by individuals in a placebo analgesia trial when assessed in a prompted and unprompted manner. The data corroborates the role of expectations involved in placebo effects, particularly in placebo analgesia. Thus, the question may be a matter of *how* and *when* expectations contribute to placebo effects, rather than *if*.

KEYWORDS

placebo effects, expectations, prediction, placebo analgesia, hope

Introduction

In placebo research, expectations have long been emphasized as crucial to the shaping of placebo effects (1–4). Several studies have shown that participants' expectations significantly contribute to placebo effects (5–7), while other studies have not found this relationship (8, 9). This discrepancy may, among other things, be a result of differences in the way expectations are assessed. When examined in studies, expectations are rarely defined, and no common definition exists. Therefore, expectations assessed in placebo research may reflect various constructs or different aspects of the same construct. In addition to the need for a common definition of expectations, there is a need for awareness of the way we tap into expectations, and this latter point is the subject of the present article. Theories of expectations in placebo effects have rightfully been criticized as needing to be more nuanced (10). Previous literature has made efforts to elaborate on the theory of expectations in placebo effects (3, 10, 11).

In the first part of the present article, selected aspects of expectancy theory of relevance for assessing expectations are briefly highlighted, and in the second part, this theory is illustrated and corroborated with examples of how expectations have been assessed in a placebo study with both prompted and unprompted data. The prompted data has previously been published (12). The unprompted data was collected in the same study, but not previously published. However, since the first publication, more debate has arisen about the role of expectations in placebo studies (8, 10, 13), which makes the data relevant to look further into. The prompted and unprompted data yield different results within the same study and can therefore contribute to nuance the relation between expectations and placebo analgesia. The unprompted data is used in an exploratory and hypothesis-generating manner to add to the debate about how to assess and evaluate the role of expectations in placebo effects. The present article presents a short overview of the pressing issues which we believe one should be aware of when including expectation assessments in placebo studies. Finding the solutions for these issues and providing conclusive definitions are beyond the scope of this article and would be relevant to consider in joint efforts or future expert consensus.

Selected aspects of expectancy theory

This section presents selected aspects of expectancy theory that contribute to important distinctions in the assessment of expectations, but the list is by no means exhaustive.

To make a broad overview and distinction, we use Laferton and colleagues' critical review of expectation concepts in medical treatment (14), which synthesizes relevant elements in understanding expectations. The review distinguishes between (1) expectations as future-directed beliefs focusing on specific events or experiences which may or may not happen and (2) concepts referring to what patients would like to happen (i.e., hopes or desires), which have also been termed ideal expectations or fantasies (14). Furthermore, the model of expectations by Laferton et al. states that patients have so-called timeline expectations as to the temporal aspect of behavior, treatment, disease, and outcomes (14). Such a temporal dimension to subjective expectations may be similarly relevant in placebo studies when participants receive information or have expectations about *when* to expect benefits from treatment to emerge or subside.

Probability and emotion

Previously, expectations and hope have been conceptualized as both overlapping and separate phenomena (15, 16). For example, in interviews of participants' experience of participating in a study, some studies report expectations which overlap with hope (17), while others have found that hope is more prevalent (16) and have suggested that hope may be dominant in patients with chronic pain compared to healthy participants (18). Hope, like expectations, has no consistent definition, but it is generally agreed that hope refers to desirable future events or experiences (15, 19). Open label placebo trials, wherein placebo treatment is given openly, and participants are informed that they are receiving an inert treatment, illustrate that expectations have a complex interaction with hope. In open label trials, few participants may believe that they can expect symptom reduction directly whereas many participants are simply hopeful or even skeptical toward symptom relief (10, 20). In this way, the role of hope and expectations in open label trials may differentiate from other placebo trials. Even so, open label placebo trials have been successful in inducing placebo effects, despite participants being aware that they are receiving inert treatment (20–22).

Levels of consciousness

Commonly, placebo effects have been modulated through expectations (1) assessed by verbal ratings of expectations which are consciously available (23). However, placebo effects have also been induced through conditioning or even subliminal procedures, without conscious awareness of these subliminal stimuli (24–26). Therefore, it seems that placebo effects may not always involve conscious expectations, but may possibly be induced through other, not consciously available, predictive processes in the brain (9, 27). It has been discussed how subliminally induced placebo effects interplay with conscious expectations (18). It is still unknown whether subliminal cues lead to changes in conscious expectations of pain, even if patients are not aware of these cues (28). Even so, subliminal aspects of placebo effects may be important in further nuancing theories of expectations. Future research in subliminally induced placebo effects may help uncover various paths to induce placebo effects and the extent to which conscious expectations are needed in the shaping of placebo effects.

Temporal features

In addition to the level of consciousness of expectations, recent studies suggest that it may be crucial *when* expectations are assessed (29, 30). New lines of research on placebo effects have begun to focus on the temporal aspects of placebo effects and expectations. Exemplifying this, studies on healthy participants have shown that external time cues, i.e., information on *when* a treatment is expected to take effect, influence the onset and time course of placebo effects (29, 30). Furthermore, focusing on the participants' ratings of expectations *throughout*

their study participation, expectations of pain relief have been found to significantly predict perceived pain levels at different time points–even when controlling for a gradual learning effect across test days (31). In other words, these findings point to a substantial contribution from the participants' expectations for pain relief that exceeded their prior experiences obtained throughout the study.

These theoretical stances point to expectations as a complex concept, which is not fully assessed through unidimensional measures. To further investigate this, we consider data from the study explained below, which tapped into expectations through two different angles: prompted and unprompted measures.

Examples of prompted and unprompted expectation assessment in placebo studies

Prompted expectation assessment

Expectations are dependent on the method through which they are assessed. Exemplifying different approaches, prompted measures refer to measures explicitly asking about expectations, while unprompted measures do not specifically inquire about expectations. The importance of distinguishing between these types of assessments is illustrated by data from a study investigating placebo interventions in 19 patients suffering from chronic neuropathic pain (12). One of the co-authors of the present article (L.V.) supervised the study and the study design is presented in **Figure 1**. In the study, patients went through open and hidden applications of lidocaine and a no treatment condition. After application of lidocaine and before assessment of ongoing neuropathic and evoked (pin-prick evoked/windup-like) pain, expectations were assessed using a visual analogue scale (VAS). When asked in a prompted manner using the VAS, all participants gave an indication of their expectations. These expectations accounted for 41.2% of the variance in ongoing and evoked neuropathic pain (12). Thus, prompted expectations were found to significantly predict pain.

Unprompted expectation

The same 19 chronic neuropathic pain patients also underwent an inquiry of their experiences in which they were not directly asked to report what their expectations had been. This data has not previously been published and is presented here to illustrate and debate how differences in the way expectations are assessed may influence findings. At the end of each treatment session, patients were asked to relive the session and describe their experiences freely with regard to their positive and negative experiences. Participants expressed their experience through a single sentence, for example "I very much hoped that the treatment would work." Experiences from the three open conditions (open lidocaine, open lidocaine with haloperidol, open lidocaine with levodopa) were synthesized and analyzed using thematic analysis, regarding the word that best described what was expressed by each participant, and themes are displayed in **Figure 2**. The patients indicated their experiences in each condition. A total of 56 positive and eight negative experiences were expressed across the three conditions. A range of experiences including elements of expectations were reported, as illustrated in **Figure 2**. Yet, in this free report expectations were only directly expressed six times. Thus, using this unprompted approach, expectations do not seem crucial for the experience and prediction of pain.

This study clearly illustrates that the way expectations are assessed impacts the resulting conclusion about their role. While the prompted measurement reflects the typical assessment of expectation in placebo trials (32–34), the unprompted data may tap into the other aspects of expectations which are related to expectations or play a role in placebo analgesia, e.g., hope (16). There are clear advantages and limitations of both types of assessments: Prompted measures directly target expectations

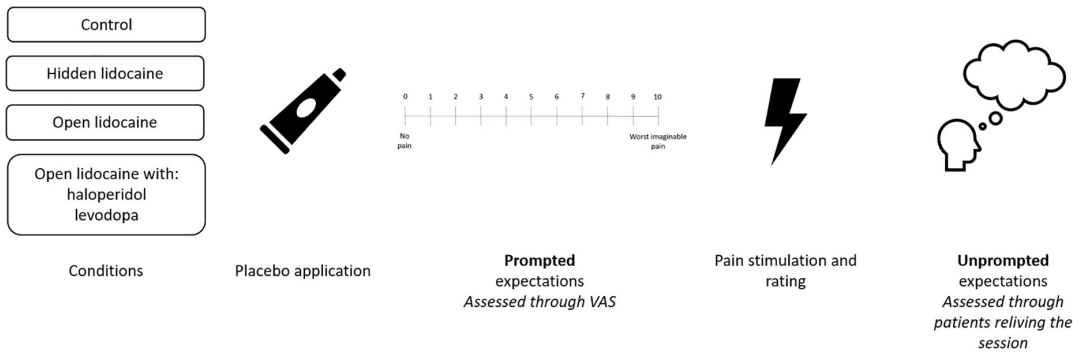

FIGURE 1
Order of procedures and expectation approaches in the study of placebo effects in chronic neuropathic pain patients (12).

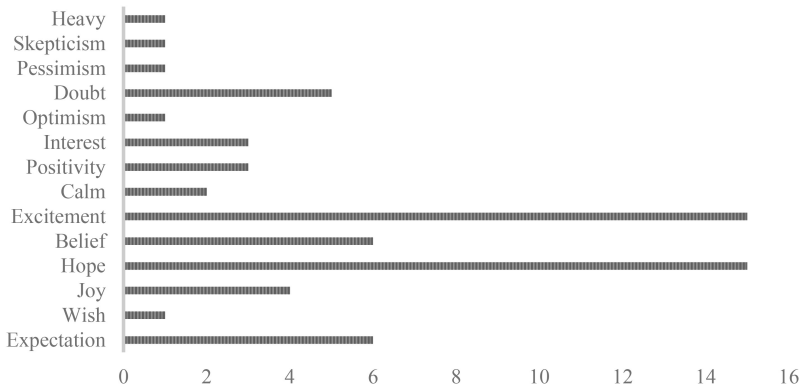

FIGURE 2
Number of times experiences were expressed by the chronic neuropathic pain patients across the open conditions (open, open + haloperidol, and open + levodopa) of the study (12). Sixty-four experiences were reported across the three conditions which were distributed as presented in the figure.

and, in the case of VAS scales, are easily relatable to pain measures. This prompting may also be a limitation, as the prompting may direct the answer or be too narrowly focused on a single dimension. Furthermore, variability in definitions of prompted measures could impact the results. For example, it has previously been shown that there are different and even opposing effects in deceptive and double-blind placebo groups, when addressing the subjective likelihood (e.g., "How likely is it that your pain will be reduced after treatment?") and the expected magnitude (e.g., "What do you expect your pain to be after treatment?") (35). Thus, the framing of prompted measures may lead to important variability.

The unprompted data, however, allows for further nuancing of the dimensions of expectation which can contribute to placebo effects and does not predispose a particular answer. Limitations of unprompted data make it more complex to quantify and relate to other (prompted) measures.

Importantly, the prompted expectations were assessed before the pain experience, while the unprompted expectations were assessed retrospectively, which could impact the findings. It has been shown that pain ratings change when addressed retrospectively, though maintaining an association with expectations both in concurrent and remembered ratings (4). Similarly, expectation ratings may change when addressed retrospectively. In interviews on patient experiences, Kaptchuk and colleagues (16) showed an important role of retrospection and highlighted that memory bias may shape the subjective experience of treatment outcomes. Thus, memory bias could result in the differences seen between the prompted and unprompted data, rather than inherent differences in the aspects of expectations which are targeted by each measure. In the study by Kaptchuk and colleagues (16), interviews were conducted over six weeks concurrently with ongoing placebo treatment. In contrast, the unprompted expectations of the present article were assessed immediately after completion of the test session. Thus, the time points of assessment in the two studies differed notably. Still, both studies found that expectations may be less prevalent when addressed in a more open fashion. This suggests that prompted and unprompted measures of expectations may lead to different findings independently of whether they are measured concurrently or retrospectively. Yet, studies that prospectively measure expectations in prompted and unprompted manners are needed to tease time and measurement apart.

That expectations seem to be more prevalent in prompted measurements compared to unprompted measurements could also reflect the involvement different levels of consciousness. In this way, consideration of unprompted measures could be valuable to nuance the theory of expectations and understand the experience of placebo analgesia.

The study presented in this article further underlines how different ways of tapping into expectations may not reflect the same construct or even reflect actual assessments of expectations. That is, some ways of tapping into expectations may be central to measuring them, while others may not adequately measure or reflect the expectations of participants in placebo studies. The study shows that this can result in the conclusion that expectations are important when looking at the prompted rating *or* not important when looking at the unprompted assessment in placebo analgesia effects.

Probability, emotion, and temporal aspects

Results from the study of chronic neuropathic pain patients also illustrate important dimensions of expectations and experiences in placebo studies, corroborating the highlighted theory elements from Laferton et al. (14). The broad range of experiences portrayed in **Figure 2** can be divided into two

categories: Whereas one is future-directed with clear relations to future events or experiences (e.g., belief, hope, wish, and expectation), the other is not related to a future outcome (e.g., calm, joy, and interest). The category of future-related concepts includes expectations and other concepts which may coexist or overlap with expectations. Thus, rather than developing several separate theories about each future-directed subjective experience and their influence on placebo effects, expectations may further be subdivided into probability-related or emotion-related. We suggest that this division would result in expectation and belief on the one hand (probability-related) and hope and wish on the other hand (emotion-related). The exact elements of this division may, of course, change depending on context. Ideally, both aspects of expectations should be considered and assessed in placebo studies to further develop the theory–along with continuously tapping into expectations at different time points throughout these studies to capture their temporal development, persistence, and/or change over time. In addition, it is important to be aware that the way expectations are induced may have a significant impact on how they manifest in assessments. Open label placebo, conditioning procedures, or verbal suggestions may not manifest and be assessed in the same manner, and potentially different assessments should be used to fully capture the broad spectrum of expectations.

Temporal features

The abovementioned study of neuropathic pain patients did not directly investigate temporal aspects of expectations. However, in another study of chronic pain patients (17) involving prompted and unprompted expectation measures, it was shown that these measures may also differ regarding the temporal development. While the prompted measurement of expectation showed a change over time (expectations to pain relief on a VAS were higher over time), the unprompted measurement showed that once expectations were established, patients' focus of attention appear to change away from their expectations (17). Thus, it is possible that there may be differences in the way prompted and unprompted measures develop over time and potentially the way they tap into expectations, but this needs to be investigated systematically in future studies.

The future of expectation assessments in placebo studies

Placebo studies increasingly include assessments of expectations. This inclusion offers the possibility of comparing expectations across different study settings and medical conditions. However, this also highlights the need for clarifying which concepts or which aspects of expectations we are dealing with.

As illustrated above, the question of whether expectations contribute to placebo effects is complex and appears to be dependent on how, when and under which conditions, they are assessed, as different approaches seem to lead to different results and conclusions. Thus, in future studies, it will–as a minimum–be important to pay attention to the extent to which expectations involve different dimensions of future-directed experiences. These may be probability-related or emotion-related, may be present at different levels of consciousness, and may include temporal aspects. All of these aspects should be kept in mind in future studies when approaching expectations both in a prompted and unprompted manner. The measurement of expectations in placebo studies demands more attention. Inclusion of more detailed expectation assessments in studies, could further lead to comparison of which aspects of expectations are important in certain contexts, that is the *when* and *where* of expectations.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

SR and SL drafted and revised the manuscript. LV provided the data and critically revised the manuscript. IK critically revised the manuscript. 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.

Publisher's note

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The Temporal Modulation of Nocebo Hyperalgesia in a Model of Sustained Pain

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Background: The direction and the magnitude of verbal suggestions have been shown to be strong modulators of nocebo hyperalgesia, while little attention has been given to the role of their temporal content. Here, we investigate whether temporal suggestions modulate the timing of nocebo hyperalgesia in an experimental model of sustained pain.

Methods: Fifty-one healthy participants were allocated to one of three groups. Participants received an inert cream and were instructed that the agent had either hyperalgesic properties setting in after 5 (Nocebo 5, N5) or 30 (Nocebo 30, N30) minutes from cream application, or hydrating properties (No Expectation Group, NE). Pain was induced by the Cold Pressure Test (CPT) which was repeated before cream application (baseline) and after 10 (Test10) and 35 (Test35) minutes. Changes in pain tolerance and in HR at each test point in respect to baseline were compared between the three groups.

Results: Tolerance change at Test 10 ($\Delta 10$) was greater in N5 (MED $= -36.8$; IQR $=$ 20.9) compared to NE (MED $= -5.3$; IQR $= 22.4$; $p < 0.001$) and N30 (MED $= 0.0$; IQR $= 23.1$; $p < 0.001$), showing that hyperalgesia was only present in the group that expected the effect of the cream to set in early. Tolerance change at Test 35 ($\Delta 35$) was greater in N5 (MED $= -36.3$; IQR $= 35.3$; $p = 0.002$) and in N30 (MED $= -33.3$; IQR $=$ 34.8; $p = 0.009$) compared to NE, indicating delayed onset of hyperalgesia in N30, and sustained hyperalgesia in N5. No group differences were found for HR.

Conclusions: Our study demonstrated that temporal expectations shift nocebo response onset in a model of sustained pain.

Keywords: pain, nocebo hyperalgesia, expectation, temporal suggestions, sustained pain

INTRODUCTION

One's expectations of pain amelioration or worsening can significantly change pain perception, reducing and increasing its intensity, respectively (1). The impact of expectations on pain is evident in placebo analgesia and in nocebo hyperalgesia, where pain ameliorates or worsens following the administration of an inert treatment delivered in association with positive verbal suggestions for placebo (i.e., suggestions of pain decrease) and negative ones for nocebo (i.e., suggestions of pain rise) (2–4). Although placebo and nocebo effects can be induced in multiple ways—i.e., contextual factors including non-verbal communication, appearance of the medical personnel, clinical setting, type of intervention (5, 6)—and they can involve processes other than expectations—i.e., learning processes such as social observational learning, classical and operant conditioning (7, 8)—here we focus on verbal suggestions as the main factor inducing positive and negative expectations, which in turn are responsible for placebo and nocebo responses, respectively.

While the magnitude (9–11) and the direction (4, 12–14) of verbal suggestions have been identified as modulators of placebo analgesia and nocebo hyperalgesia, little attention has been given to the modulatory role of temporal suggestions, which was recently investigated for the first time by our team (15, 16).

In a recent experiment, we demonstrated, for the first time, that it is possible to "externally time" placebo and nocebo effects, meaning that their onset of action can be shifted in time by delivering different temporal suggestions. Precisely, we showed that by telling some participants that the administered (inert-) cream would set in after 5 min, the analgesic and hyperalgesic effects set in early, compared to the delayed effect reported by participants that were told that the (inert-)cream would set in after 15 and 30 min (15). In this previous study, pain was experimentally induced with short-lasting electrical stimuli of medium-to-low pain intensity (15). While this pain model has several advantages (e.g., safe, easy to induce, and consisting of short lasting pulses that can be repeated to collect more trials) and is therefore widely used in experimental pain research (17), this is not free from limitations. For instance, its clinical relevance has been questioned by some, arguing that clinical pain is rarely brief and precisely timed (18–21). Besides, this pivotal study relied on verbal pain reports, therefore the influence of report biases on self-reported pain ratings could not be excluded. In a subsequent experiment we demonstrated that the "external timing" of placebo analgesia persists in a model of sustained pain (16), while it is not known whether this temporal modulatory effect on sustained pain persists in the case of nocebo hyperalgesia.

In the present study, we investigated whether the finding that temporal suggestions modulate the onset of nocebo hyperalgesia on short-lasting, medium-to-low intensity electrical stimuli (15), extends to longer-lasting (tonic), higher-intensity pain induced with the Cold Pressor Test (CPT), a pain model which has been suggested to offer a good approximation of clinical pain (20, 21). Instead of solely relying on verbal pain ratings, as done in our previous work (15), we assessed maximum pain tolerance (i.e., operationalised as the time participants resisted with their hand in freezing-cold water) as behavioral outcome measure, avoiding the possible influence of report biases. While maximum pain tolerance is our primary outcome measure, we also measured pain ratings during the pain test, and we recorded participants' expectations toward the effectiveness of the cream retrospectively. In addition, since previous research has shown that heart rate (HR) increases during the pain anticipatory phase (22), we measured HR to detect nocebo-related anticipatory anxiety responses. At last, we also measured some psychological traits (i.e., personality, cognitive, and emotional factors) which have been previously linked to nocebo responsiveness [for overview see the recently published systematic review by Kern et al. (23)]. Compared to the placebo effect, less research has investigated psychological traits associated with nocebo responsiveness (23). However, traits such as high state and trait anxiety [assessed with state-trait anxiety inventory in Camerone et al. (15), Colloca et al. (24), and Corsi et al. (25)], fear of pain [assessed with the Fear of Pain Questionnaire in Aslaksen and Lyby (26)] and low optimism [assessed with the revised life oriented test in Geers et al. (27)] have been associated with greater nocebo responsiveness. In addition, high anxiety has been shown to be a predictor of enhanced pain perception [assessed with the Beck Anxiety Inventory in Kose-Ozlece et al. (28)]. Note that the Beck Anxiety Inventory can be described as a measure of prolonged state anxiety (29). Furthermore, the extent to which an individual is more inward or outward oriented seems to play a role in influencing placebo responsiveness [assessed with the behavioral inhibition/approach scales in Broelz et al. (30) and Darragh et al. (31)], while it is yet to be understood whether greater inward orientation is associated with enhanced nocebo responsiveness. In the present study, we used the same questionnaires of the forecited studies to clarify whether such personality traits influence nocebo responsiveness in an experimental model of sustained pain.

To sum up, the main aim of the present study is to investigate whether temporal information can modulate the onset of nocebo hyperalgesia in a model of sustained pain, induced with the CPT. Therefore, our primary outcome is the time taken by participants to reach the maximum pain tolerance during the pain test, while secondary outcomes include HR during the pain anticipatory phase and subjective pain ratings during the test. A secondary aim of the present study is to investigate whether retrospective participants' expectations of the cream efficacy and psychological factors are associated with nocebo responsiveness.

MATERIALS AND METHODS

Participants

The study took place at the Experimental Anatomy Research Department at the Vrije Universiteit Brussel (VUB), Belgium. Sample size calculation has been calculated using G*Power (see **Supplementary Material:** Content 1). Forty-four healthy volunteers were recruited and randomized between the two experimental groups (i.e., nocebo groups), while participants of the control group ($N = 17$) were taken from our first experiment [(16); for further details see "Group allocation" section]. All

participants were recruited both from the student population of the VUB (i.e., experimenter directly approached students around the university and asked them whether they were interested in taking part in the experiment) and from the general population (i.e., through different social media outlets such as Facebook). Participants were not compensated for their participation. Participants between 18 and 45 years of age were considered eligible to join the study. Participants that were in cure with antidepressants or anxiolytics, had a history of cardiovascular disease, and that suffered from psychiatric, neurological, chronic musculoskeletal, and pain-related disorders were not considered eligible to participate in the study. Moreover, we instructed the participants not to consume alcohol, caffeine-based drinks, supplements, and/or analgesic medications 12 h before the experiment. We informed participants that they would take part in a study investigating the time of action of a newly developed hyperalgesic cream. We disclosed the actual purpose of the study only after full data collection was completed (see Debriefing Section). Participants provided written informed consent agreeing to be debriefed with all the study details at the end of the experiment. All experimental procedures followed the policies and ethical principles of the Declaration of Helsinki. The Ethics Committee of the Vrije Universiteit Brussel approved this study (18/03/20; BUN1432020000002/I/U).

Experimenters

The same experimenter was responsible for participants' enrolment and testing in the two nocebo groups. The experimenter was a PhD student (University of Genova) of 26 years old who identified himself as male. The experimenter that collected the data of the control group [i.e., placebo analgesia study; (16)], was a PhD student (University of Genova) of 26 years old who identified herself as female. The experimenters were properly trained to run the experiment and they were both part of the same research group. The experimenters, both in the nocebo groups and the control one, were fully aware of the nature of the experiment (i.e., they knew the purpose of the study, they knew that the cream was sham, and they were not blind to group allocation).

Group Allocation

The present study is a two-arm randomized trial with an external control group (32). Participants were randomly assigned to two nocebo groups (allocation ratio 1:1) using computer-generated random numbers lists with simple randomisation (www.random.org). As for the control group (i.e., external control group), this was taken from our previous experiment (16) in which participants were also randomised to one of three groups (i.e., Placebo 5, Placebo 30, and Control). This experiment is one of two studies examining the temporal onset of placebo and nocebo effects. The first experiment investigated the placebo effect (16), while the second one, here reported, studied the nocebo phenomenon.

The recruitment and testing for the two nocebo groups took place between April and July, 2020, while for the control group this occurred between June and July 2019. For further details on the decision of using the same control group of our previous experiment, please see **Supplementary Material:** Content 2.

Nocebo Groups

Participants in the two nocebo groups were instructed that the cream had hyperalgesic properties that would increase the painful sensation induced during the CPT (i.e., in truth, the cream was an inert substance). We provided both groups with specific details about the onset of action of the hyperalgesic cream.

Participants allocated to the Nocebo 5 group (N5) were told that the hyperalgesic effect would arise after 5 min from cream application, mimicking a fast-acting drug. They received the following instructions: "*The agent you will receive is known to have a strong hyperalgesic effect which sets in after 5 min from its application. You will, therefore, become more sensitive to pain and be able to keep your hand in the cold water for a shorter time in the two test sessions after 10 and 35 min* [experimenter points at time 10 and 35 min marks on a clock] *compared to the first test* [CPT baseline]."

Participants allocated to the Nocebo 30 group (N30) were told that the hyperalgesic effect would set in 30 min from cream application. Specifically, the following instructions were given: "*The agent you will receive is known to have a strong hyperalgesic effect which sets in after 30 min from its application. You will, therefore, become more sensitive to pain and be able to keep your hand in the cold water for a shorter time in the test session after 35 min* [experimenter points at time 35 min marks on a clock] *compared to the first test* [points at CPT baseline] *and the second test after 10 min* [points at Test 10]."

Note that the CPT was performed 10 and 35 min after cream application and not after 5 and 30 min, which were the specific time points at which participants expected the cream to set in (at 5 min for N5 and at 30 min for N30). We allowed a 5-min leeway to avoid participants doubting that the effect of a cream could be so precisely timed (i.e., setting in exactly after 5 and 30 min).

Control Group

Participants that were assigned to the control group were informed that they would receive an inert cream (No Expectation, NE): "*The agent you will receive is an inert cream that only has hydrating properties but no effect on pain perception. Therefore, your test performance after 10 and 35 min* [experimenter points at time 10 and 35 min marks on a clock] *may be similar to the performance in the first test* [CPT baseline], *but it can also be longer or shorter than before."*

Experimental Protocol

After providing written informed consent, participants were asked to sit on a chair positioned next to the CPT device. The investigator used a stopwatch displayed on a computer screen in front of the participants as well as a customized wall clock for participants' temporal orientation. The wall clock with 5-min intervals (i.e., 5–55) showed an icon of a cream tube at the 12 o'clock position to indicate the time-point of application of the cream (**Figure 1**).

The experiment started with a 4-min heart rate measurement at rest, during which participants were asked to relax and breathe

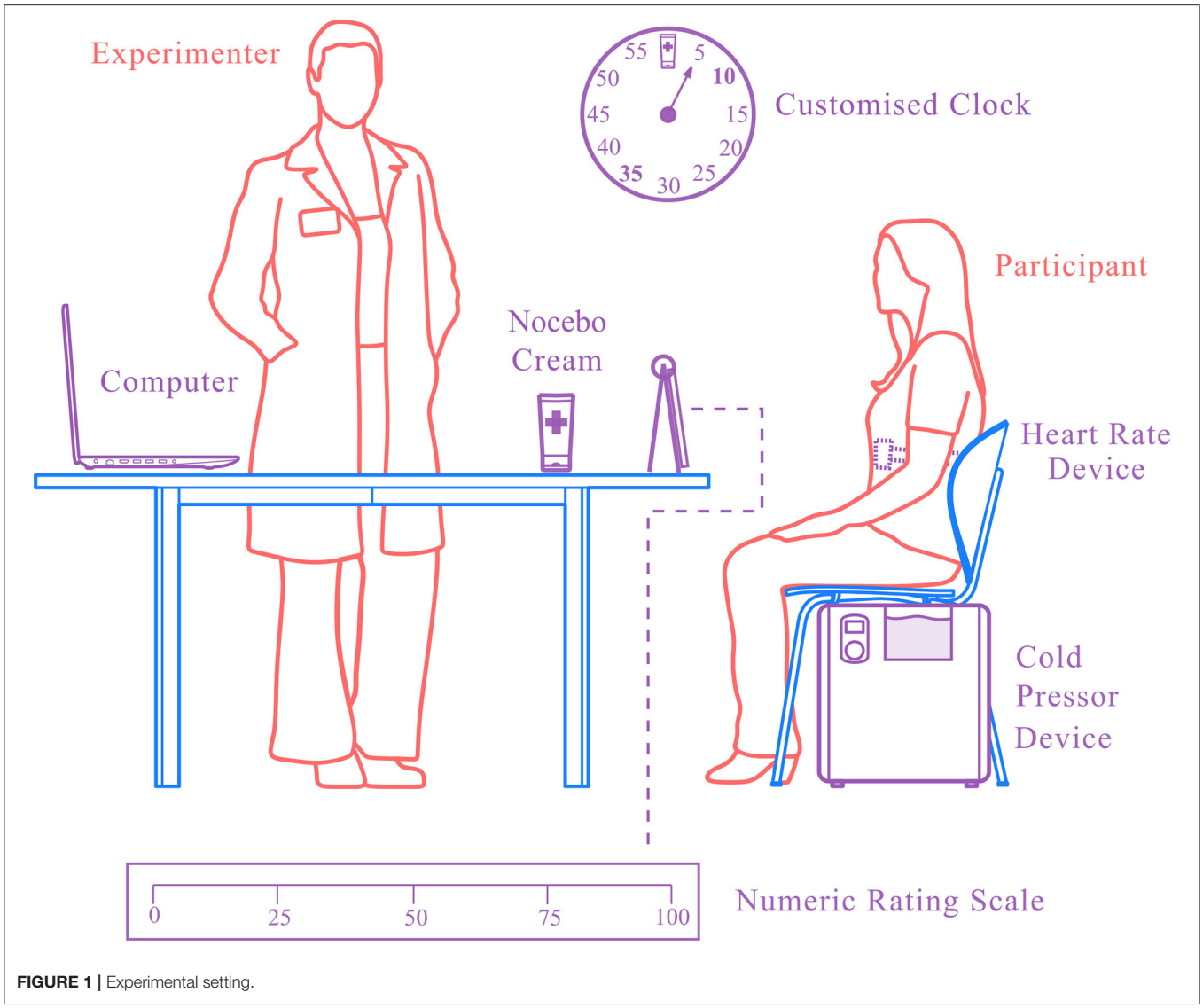

FIGURE 1 | Experimental setting.

naturally. After instructing participants on how to perform the CPT task, they completed a familiarization trial. After the CPT familiarisation trial, all participants underwent the CPT baseline test, followed by participants' randomisation to groups and cream application. Along with cream administration, the experimenter provided participants with information about the nature of the cream (hyperalgesic cream in both nocebo groups and inert cream in the control group) and informed them about the expected onset of the hyperalgesic cream (nocebo groups only). Simultaneously with the application of the cream, the experimenter adjusted the customized wall-clock so that the minute hand pointed at the noon position, indicating the time of cream application ("Time 0"). CPT was then repeated 10 (Test 10) and 35 (Test 35) minutes from cream application ("Time 0") (**Figure 2**). To be clear, the cream was not applied prior to each hand immersion, but it was only applied once, after the baseline CPT. Overall, the CPT was repeated a total of four times (familiarization, baseline, Test 10, Test 35) with a break of approximately 25 min between tests to restore the baseline hand temperature (**Figure 2**). During these breaks, participants filled in the psychological questionnaires (See Section: "Assessment of pain-related psychological traits") and once completed, they were allowed to read or study, but were asked not to use their phones. The reason why participants were asked to complete the questionnaires during the breaks, rather that before or after the experiment, was to minimise the duration of the experiment and to engage participants in the same task during these pauses. The experimenter was present throughout the experiment, including during the breaks between the pain tests. However, to avoid biases the experimenter was not allowed to speak with participants. If the volunteers asked questions or wanted to chat, the experimenter was instructed to tell them that they were not allowed to talk with them during this time so that the interaction with each, and every participant remained

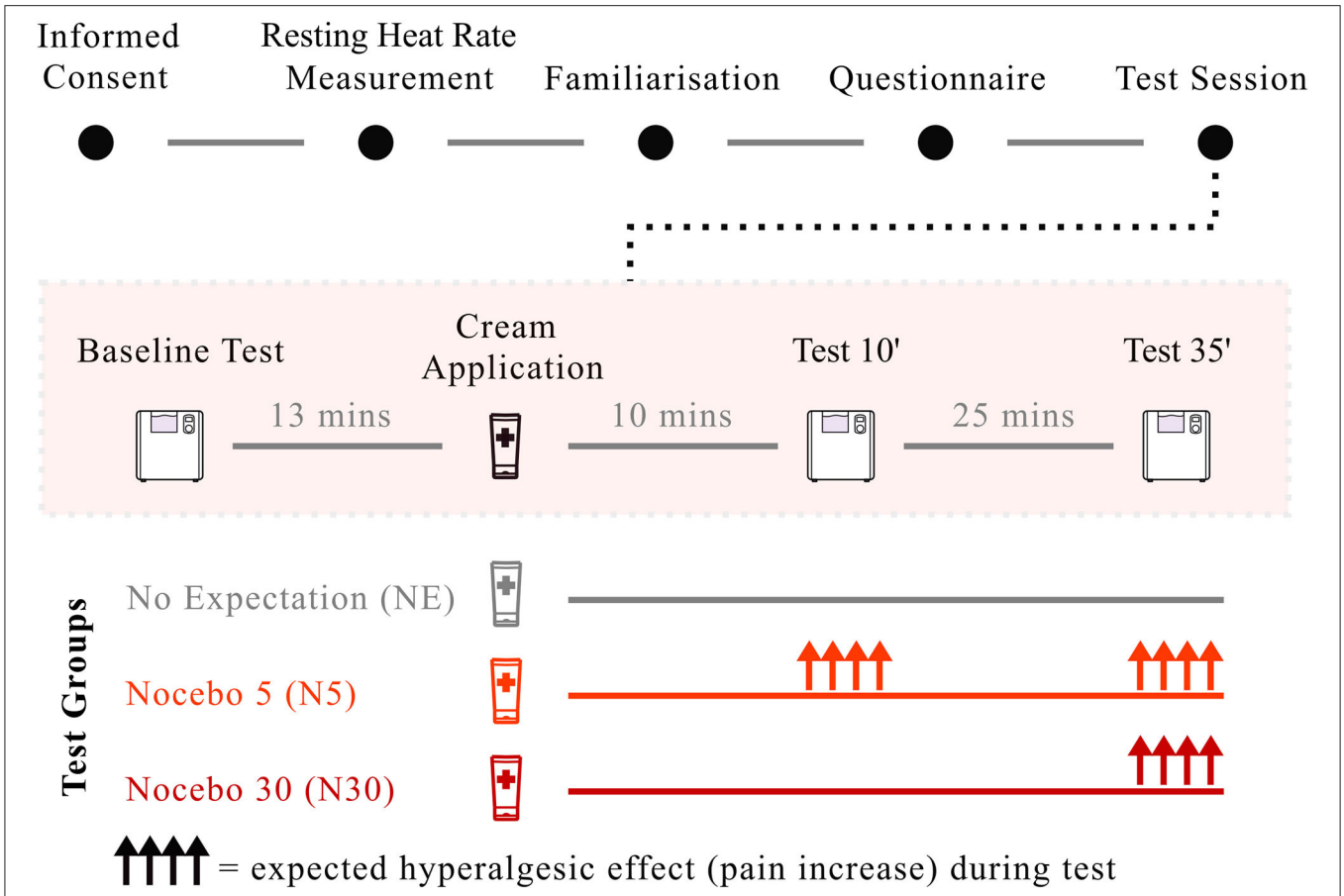

FIGURE 2 | Study paradigm. After giving consent, participants' heart rate at rest was measured for 4 min. Participants completed the CPT familiarisation run and filled in the psychological questionnaires. After the CPT baseline test, the cream was applied along with suggestions of hyperalgesia (N5, Bright red; N30, Dark red) and neutral suggestions (NE), depending on group randomisation. Application of the cream and the delivery of suggestions took ∼2 min. The CPT was then repeated after 10 and 35 min from cream application. Nocebo hyperalgesia, visualised as upper-facing arrows in the image, was expected both at Test 10 and at Test 35 for N5, and only at Test 35 for N30. No effect was expected for NE.

unvaried, and that all questions would be answered at the end of the experiment (i.e., exception if the participant wanted to discontinue the experiment for any reason. In this case the experimenter was allowed to speak with the participant; this never occurred).

Cold Pressor Test

During the CPT, participants were asked to immerse their left hand in seven liters of circulating cold water [7C°, ±0.2C°; CPT device: Thermo Scientific model Haake A 10B, Haake SC 100; Thermo Fisher Scientific, Waltham, MA; procedure adapted from Mitchell et al. (33)]. The experimenter drew a red line from the participant's ulnar to the radial styloid process (wrist level) to indicate the level to which participants had to lower their hand.

Before starting the CPT, 1 min of HR at rest was recorded. Ten seconds before the beginning of the test, participants were prompted by the experimenter to get ready (i.e., experimenter said, "Get ready!") and to place their hand above the CPT device, showing readiness to immersion. Upon a verbal prompt from the experimenter ("Go"), the participant lowered their hand into the CPT device. The experimenter started the stopwatch to record the time between the beginning of exposure and hand withdrawal. The stopwatch was displayed on a computer screen located in front of the participant for temporal orientation. Participants were instructed not to move their fingers or hand while in the water and to keep their fingers spread with the palm parallel to the bottom of the device without touching it. For safety reasons, 10 min were set as the maximum time participants were allowed to spend with their hand in the water (34, 35), after which the test was discontinued, and the experiment ended. During CPT, subjective pain ratings were recorded every 15 s. The experimenter asked participants to quantify the pain they were experiencing on a scale from 0 (no pain) to 100 (unbearable pain) (see Section: Pain intensity ratings). Once pain became unbearable, participants removed their hand from the water basin and rested it on a towel placed on their knees. The time elapsed between hand immersion and withdrawal was recorded as CPT tolerance. The CPT, as described in this section, was repeated a total of four times during the experiment—i.e., familiarization, baseline, Test 10, Test 35—with no differences in

the procedure between the familiarization trial and the other test sessions (i.e., baseline, Test 10, Test 35).

Pain Intensity Ratings

To facilitate participants' self-reporting of pain during CPT, a poster depicting the rating scale was placed in front of them, which included verbal and numerical anchors (0 = not painful at all, 25 = somewhat painful, 50 = moderately painful, 75 = very painful, 100 = unbearable pain) (**Figure 1**). Despite verbal pain ratings were recorded every 15 s, the last pain score was taken at the moment of hand withdrawal to ensure that the maximum tolerance level was reached (i.e., this was the case for the two nocebo groups, but not for the control group, in which the last pain rating was recorded at the last 15 s interval prior hand withdrawal).

Heart Rate Recording

The electrocardiogram (ECG) signal was measured using an HR monitor (Polar V800, Polar Electro Oy, Kempele, Finland), connected to two standard surface electrodes positioned on the participant's sternum with a band. Data were collected at a sampling rate of 700 Hz/s. HR was recorded for 4 min during a rest period in which participants were asked to sit comfortably and breathe normally. HR recording started 1 min before each CPT and continued through the test until 2 min after its completion. To limit the HR artifacts that might arise from hyperventilation related to pain-response, participants were instructed to maintain a regular and relaxed breath during each test session.

Assessment of Pain-Related Psychological Traits and Retrospective Expectancy

During the breaks between CPT trials, participants were asked to complete multiple questionnaires that had previously been shown to link nocebo responsiveness with given personality traits (see Introduction):

- Beck Anxiety Inventory (BAI) to test the level of anxiety (36).
- Behavioral avoidance/inhibition scale (BIS/BAS) to test individuals' predisposition to inner or outward orientation (37).
- Fear of Pain Questionnaire (FPQ) to test fear of pain (38).
- Revised Life Oriented Test (R-LOT) to test the degree of optimism (39).

At the end of the experiment, participants were asked to rate retrospectively, on a scale from 0 (= not at all) to 7 (= very much), where 4 (= neutral), how much they had expected the cream to affect (i) their pain during the experiment ("*When the cream was applied on your hand, did you expect it to make you feel more pain during the water task?*"), and (ii) their ability to keep their hand in cold water ("*When the cream was applied to your hand, did you expect it to make you last less with your hand in the water?*"). Participants were also asked to rate the extent to which they had believed the given information regarding the onset of the hyperalgesic effect *("When the cream was applied on your hand, how much did you agree with the following statement: The cream will start to become effective after 5 min* (N5)/*The cream will start to become effective after 30 min* (N30)").

Cream

All participants received an inert cream which was applied to their dorsal and volar left hand. The cream consisted of a water-based gel (KY-gel Johnson&Johnson) and was presented to participants in a transparent plastic tube. The cream was applied on the palmar and dorsal side of participants' hand up until the red line which was drawn by the experimenter, and it was massaged into the skin for ∼1 min to ensure full absorption.

Debriefing

Participants were debriefed through an email sent once full data collection was completed. Here, we explained the actual purpose of the study, and clarified why deception had been necessary. Participants were invited to contact the experimenter if they felt the need to discuss their participation in the study or any other concerns. They were also reminded that they could withdraw their data if they wished. However, none of the participants decided to do so.

Statistical Analysis

First, one-way ANOVA was run to test for baseline differences between the three groups in demographic parameters, and psychological constructs were assessed via the questionnaires. Data for CPT tolerance at baseline, after 10 (Test 10) and 35 (Test 35) minutes did not follow a normal distribution (Shapiro-Wilk tests $p < 0.05$), therefore non-parametric tests were used. Second, Friedman Tests were performed to detect differences in tolerance time across CPT trials at the three different time points (Baseline, Test 10 and Test 35) within each group. Data are presented as median ± interquartile range and the significance level was set at $p < 0.05$. Significant results were followed up using Wilcoxon Signed-Rank Tests. Significance acceptance level for pairwise comparison was adjusted for the number of comparisons (k=3) using the Bonferroni Correction (α/k), resulting in $p = 0.017$. Third, Kruskal-Wallis H-Tests were used for the between-group analysis. To this end, percentage change in pain tolerance from baseline were calculated ($\Delta_{10,}$ Δ_{35}) to compare the groups on values that were more standardized than raw scores. Percentage change in pain tolerance from baseline to Test 10 (Δ_{10}) and Test 35 (Δ_{35}) was calculated as follow:

Δ_{10} = (Test 10*100)/Baseline -100;

Δ_{35} = (Test 35*100)/Baseline -100.

Data are presented as median ± interquartile range and the significance level was set at $p < 0.05$. Significant results were followed up using pairwise Mann-Whitney *U*-Tests. Significance acceptance level for pairwise comparison was adjusted for the number of comparisons ($k = 3$) using the Bonferroni Correction (α/k), resulting in $p = 0.017$. Effect sizes were calculated as $r = z/\sqrt{N}$ (40). The effect size measures between the groups were used to assess the actual power of the study in percentage, based on the data of the trial. A threshold > 80% was set as satisfactory. Fourth, pain rating analysis was performed. We calculated the slope of pain ratings as a function of time; the steeper the slope, the faster maximum pain tolerance was reached. Since the first

pain rating was recorded after 15 s from the beginning of the CPT, participants that lasted <15 s would only have one pain score (i.e., the one reported at the moment of hand withdrawal). Since the nocebo manipulation aimed at reducing the tolerance time, six participants (i.e., five in the nocebo groups and one in the NE group) ended up lasting <15 s in at least one of the test sessions, which means that they would only have one pain rating, making it impossible to calculate the slope (i.e., at least two scores are needed to calculate a slope). Not considering this data would be a bias because it would mean excluding those participants that reached maximum pain tolerance faster, possibly because of the nocebo intervention. To avoid losing meaningful data, we have added to all participants an extra datapoint at time 0 in which we assumed 0 pain, ensuring that everyone has at least one pain rating at the beginning of the test (i.e., time 0) and one pain rating at the end of the test (i.e., moment of hand withdrawal for the nocebo groups; last 15 s interval for the NE group); this allowed us to calculated a slope for all participants (i.e., except for one participant in the NE group who lasted <15 s and for whom we do not have the pain rating at the moment of hand withdrawal). Pain ratings slopes scores did not follow a normal distribution (Shapiro-Wilk tests $p < 0.05$), therefore non-parametric tests were used. Friedman Tests were performed to detect differences in the slope across CPT trials at the three different time points (Baseline, Test 10, and Test 35) within each group. Also in this case, data are presented as median ± interquartile range and the significance level was set at $p < 0.05$ and significant results were followed up using Wilcoxon Signed-Rank Tests. Significance acceptance level for pairwise comparison was adjusted for the number of comparisons ($k = 3$) using the Bonferroni Correction (α/k), resulting in $p = 0.017$.

Fifth, correlation analysis (i.e., Pearson correlation) was conducted to investigate the relationship between retrospective expectancy in nocebo groups and Δ10 and Δ35. Retrospective expectations included participants' expectations of (i) pain, (ii) tolerance, and (iii) cream onset of action. In addition, mean and SD for retrospective expectations measures were calculated to check whether participants' expectations were in line with the instructions given by the experimenter at the earlier stage (i.e., check that expectations were successfully induced).

Sixth, correlation analyses (i.e., Pearson correlation) were performed to explore the relationship between participants' psychological traits and nocebo effects. Specifically, correlations between psychological traits in nocebo groups and Δ10 and Δ35 were investigated.

Lastly, since heart rate data followed a normal distribution (Shapiro-Wilk tests $p > 0.05$), parametric analysis was performed. Mean HR was computed for the 10 s that preceded the beginning of the CPT, allowing us to assess HR during the anticipatory phase before the test session (Anticipatory HR). Anticipatory HR was calculated for each test, resulting in three mean indices for each participant (Anticipatory HR Baseline; Anticipatory HR Test 10; Anticipatory HR Test 35). A three-way mixed ANOVA was run, with the within factor TIME (Anticipatory HR Baseline; Anticipatory HR Test 10; Anticipatory HR Test 35) and the between factor GROUP (N5, N30, NE). In addition, for each test session, the mean HR value was calculated by averaging HR measurements over the first 10 s, resulting in three mean indices (HR Baseline; HR Test 10; HR Test 35). We selected the first 10 s because this was the shorter tolerance score across participants, allowing us to have a parameter for all participants. A three-way mixed ANOVA was run, with the within factor TIME (HR Baseline; HR Test 10; HR Test 35) and the between factor GROUP (N5, N30, NE). Significant results were followed up using Bonferroni-corrected *t*-tests.

RESULTS

We recruited 44 participants, 10 of which had to be excluded since they exceeded the maximum exposure time allowed with their hand into freezing-cold water (**Figure 3**). We relied on the same control group ($N = 17$) recruited beforehand for our study on placebo, resulting in a final sample size of 51 participants. One-way ANOVA and Chi-Square tests showed no baseline groups differences ($p > 0.05$) with respect to age, BMI, gender, and key psychological traits (**Table 1**). Kruskal-Wallis H-Test showed no significant baseline differences between groups in CPT tolerance ($p = 0.237$).

Nocebo Effects

Within-group analyses using Friedman Tests revealed, in both nocebo groups, a statistically significant difference in CPT tolerance depending on the temporal execution of the CPT test, either at baseline, after 10 (Test 10) or 35 (Test 35) minutes [Nocebo 5, $\chi^2_{(2)} = 15.394$, $p < 0.001$; Nocebo 30, $\chi^2_{(2)} = 10.836$, $p = 0.004$] from cream application. Contrarily, no significant difference in CPT tolerance across time-points was shown in the NE group, $\chi^2_{(2)} = 2.471$, $p = 0.291$. *Post-hoc* analyses were run using the Wilcoxon Signed Ranks tests (**Table 2**). N5 group showed a significant decrease in CPT tolerance at Test 10 ($p = 0.001$) and at Test 35 ($p = 0.004$) compared to baseline. No significant difference was shown in CPT tolerance between Test 10 and Test 35 ($p > 0.05$). N30 group showed no significant difference in CPT tolerance between Test 10 and baseline ($p > 0.05$). However, CPT tolerance significantly decreased at Test 35 compared to both baseline ($p = 0.017$) and Test 10 ($p = 0.004$).

Between-group analysis using Kruskal-Wallis H-Tests showed a statistically significant difference in Δ_{10} between the different groups, $\chi^2_{(2)} = 18.1$, $p < 0.001$. *Post-hoc* Mann-Whitney *U*-tests (**Table 3**) showed that Δ_{10} did not differ significantly between the NE group and N30 ($p > 0.05$). However, Δ_{10} was significantly higher in N5 than in both NE ($p < 0.001$) and N30 ($p < 0.001$). For Δ_{35}, Kruskal-Wallis *H*-Test showed a statistically significant difference between groups, $\chi^2_{(2)} = 12.0$, $p = 0.002$ (**Table 3**). *Post-hoc* Mann-Whitney *U*-tests (**Table 3**) revealed that Δ_{35} was significantly higher in both N5 ($p < 0.002$) and N30 ($p < 0.009$) compared to the NE group. No significant difference in Δ_{35} was found between N5 and N30 ($p > 0.05$) (**Table 3**). **Figure 4** summarises between-group results employing box-plots representation.

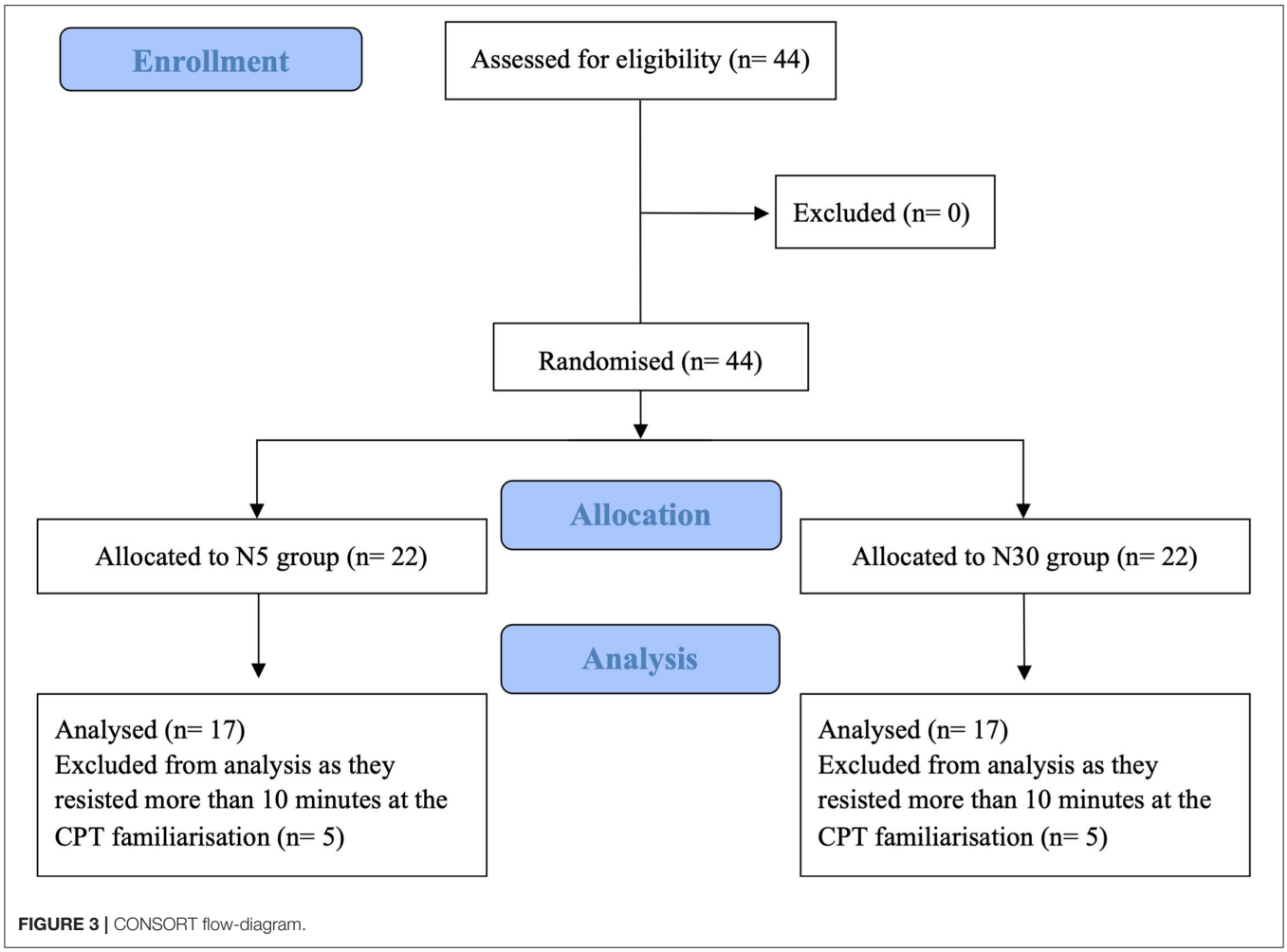

FIGURE 3 | CONSORT flow-diagram.

TABLE 1 | Participants' descriptive characteristics and psychological traits.

Groups	NE	N5	N30
N	17	17	17
Age (Mean ± SD)	28.3 ± 3.4	24.3 ± 3.9	27.2 ± 4.6
BMI (Mean ± SD)	24.4 ± 2.5	24.1 ± 3.7	24.0 ± 2.3
Sex (F(%);M(%))	7 (41.2);10 (58.8)	9 (52.9);8 (47.1)	11 (64.7);6 (35.3)
Handedness (R(%))	13 (76.5)	17 (100.0)	17 (100.0)
BAI (Mean ± SD)	10.4 ± 4.9	14.8 ± 11.9	14.0 ± 9.2
BAS-Drive (Mean ± SD)	8.8 ± 2.3	8.8 ± 2.1	9.0 ± 1.7
BAS-Fun-Seeking (Mean ± SD)	8.1 ± 1.9	8.2 ± 2.1	8.8 ± 1.8
BAS-Reward (Mean ± SD)	8.3 ± 2.1	7.5 ± 2.1	8.0 ± 1.8
BIS (Mean ± SD)	14.6 ± 2.1	13.7 ± 3.3	13.2 ± 3.9
FPQ (Mean ± SD)	72.4 ± 12.9	71.3 ± 18.1	78.9 ± 14.2
RLoT (Mean ± SD)	14.3 ± 4.1	13.8 ± 5.6	15.1 ± 3.5

SD, Standard Deviation; BMI, Body Mass Index; M, Male; F, Female; R, Right; BAI, Beck Anxiety Inventory; BAS, Behavioural Activation Scale; BIS, Behavioural Inhibition Scale; FPQ, Fear of Pain Questionnaire; RLoT, Life-Orientation Test-Revisited.

NRS Ratings

Within-group analyses using Friedman Tests showed, in both nocebo groups, a statistically significant difference in pain slope depending on when the CPT was performed, either at baseline, after 10 (Test 10) or 35 (Test 35) minutes from cream application [Nocebo 5, $\chi^2_{(2)} = 7.969$, $p = 0.019$; Nocebo 30, $\chi^2_{(2)} = 10.062$, $p = 0.007$]. Differently, the Friedman Test showed no significant difference in pain slope over time in the NE group [NE, $\chi^2_{(2)} = 0.561$, $p = 0.755$]. *Post-hoc* analyses were run using the Wilcoxon Signed Ranks tests (**Tables 4**, **5**) (**Figure 5**). N5 group showed a tendency (i.e., Bonferroni corrected $p = 0.017$) toward a significant increase in the steepness of the slope at Test 10 ($p = 0.047$) and at test 35 ($p = 0.044$) compared to baseline, while no significant difference in slope steepness was shown between Test 10 and Test 35 ($p = 0.816$). N30 group showed a tendency toward a significance decrease in slope steepness between baseline and Test 10 ($p = 0.020$). Importantly, an almost significant increase in slope steepness was shown when comparing the slope at Test 35 and at Baseline ($p = 0.022$) and a significant increase when comparing Test 35 with Test 10 ($p = 0.008$).

TABLE 2 | Median and interquartile range of CPT pain tolerance of all groups at the three test and within-group comparisons of CPT tolerance.

	Baseline		Test 10		Test 35	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
NE	72.0	262.5	65.0	250.5	69.0	284.5
N5	57.0	112.5	38.0	91.5	50.0	85
N30	53.0	37	50.0	64	38.0	49.5
Groups	**Comparisons**		**Wilcoxon Signed rank test**		**Effect size**	**Power analysis**
NE	No *Post-hoc*		/		/	/
N5	T_{10} vs. Baseline		$Z = -3.315$, $p = 0.001$		$r = 0.568$	>80%
	T_{35} vs. Baseline		$Z = -2.912$, $p = 0.004$		$r = 0.499$	>80%
	T_{10} vs. T_{35}		Z =-0.398, $p = 0.691$		$r = 0.068$	>80%
N30	T_{10} vs. Baseline		$Z = -0.700$, $p = 0.484$		$r = 0.120$	>80%
	T_{35} vs. Baseline		$Z = -2.392$, $p = 0.017$		$r = 0.410$	>80%
	T_{10} vs. T_{35}		$Z = 2.864$, $p = 0.004$		$r = 0.491$	>80%

IQR, Interquartile Range.

TABLE 3 | Median and interquartile range of percent change in CPT pain tolerance (Δ_{10}, Δ_{35}) in the three experimental groups and between-group comparisons of CPT percental tolerance change.

Groups	**Median**	**IQR**		**Median**	**IQR**
	Δ_{10}			Δ_{35}	
NE	−5.3	22.4		−4.6	26.8
N5	−36.8	20.9		−36.3	35.3
N30	0.0	23.1		−33.3	34.8
Group comparisons	**Dependent variable**	**Mann-Whitney *U*-test**	**Effect size**		**Power analysis**
	Δ_{10}				
NE vs. N5		$U = 43.0$, $p < 0.001$	$r = 0.599$		>80%
NE vs. N30		$U = 107.0$, $p = 0.196$	$r = 0.221$		>80%
N5 vs. N30		$U = 38.0$, $p < 0.001$	$r = 0.629$		>80%
	Δ_{35}				
NE vs. N5		$U = 53.0$, $p = 0.002$	$r = 0.541$		>80%
NE vs N30		$U = 69.0$, $p = 0.009$	$r = 0.446$		>80%
N5 vs. N30		$U = 112$, $p = 0.263$	$r = 0.192$		>80%

IQR, Interquartile Range.

Retrospective Expectancy and Psychological Tests

No significant correlations were shown, in either of the two nocebo groups, between retrospective expectations of (i) pain, (ii) tolerance, and (iii) cream onset of action and Δ_{10} and Δ_{35}. However, considering that a rating of 4 indicates neutral expectations, the mean of retrospective expectations of (i) pain, (ii) tolerance, and (iii) cream onset of action indicates that participants had, on average, expectations somewhat in line (i.e., all average ratings > 4) with what they were told by the experimenter (**Table 6**).

No significant correlations were shown, in either one of the two nocebo groups, between the personality measures and Δ_{10} and Δ_{35}.

Heart Rate

Mixed-methods ANOVA showed no significant main effect of TIME, GROUP, nor of their interaction ($p > 0.05$) on anticipatory HR measures. Instead, a significant main effect of TIME on HR test measures (HR Baseline; HR Test 10; HR Test 35) was shown [$F_{(2,96)} = 6.601$, $p = 0.002$], indicating that mean HR differed significantly across the three-time points (Baseline, Test 10, Test 35). Yet, no significant main effect of GROUP nor interaction between both factors were observed (both $p > 0.05$). *Post-hoc* pairwise comparison using the Bonferroni correction revealed that HR decreased significantly between baseline ($M = 79.68$, $SD = 13.53$) and Test 35 ($M = 75.84$, $SD = 10.79$) ($p = 0.006$), suggesting habituation to cold water. While still showing a tendency of HR decreasing over time, the other comparisons did not reach significance ($p > 0.05$).

DISCUSSION

Our previous study demonstrated that temporal suggestions modulate the onset of nocebo hyperalgesia on a phasic pain model, induced by short-lasting, medium-to-low intensity

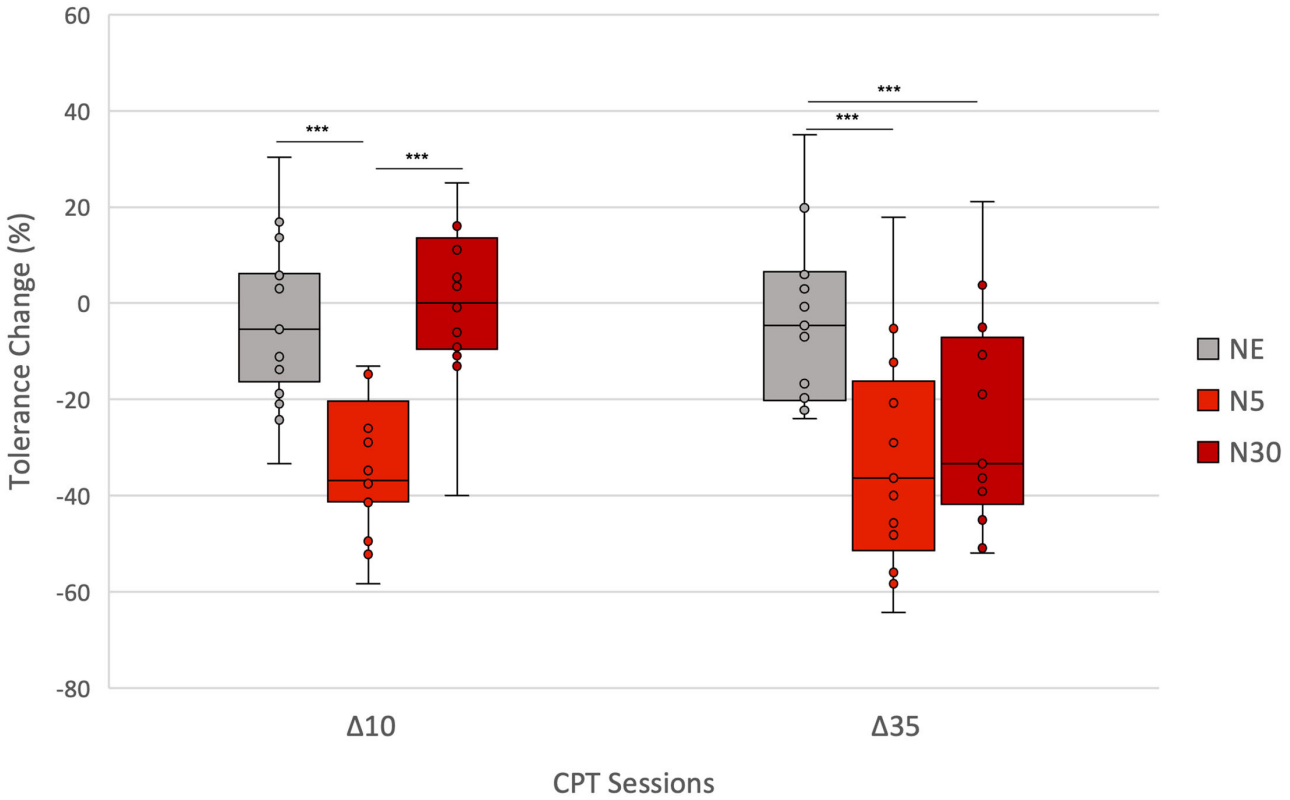

FIGURE 4 | Between-group comparison: Percent change in CPT tolerance from Baseline to Test 10 (Δ10) and to Test 35 (Δ35) for each group (NE, N5, N30). Asterisks indicate significant differences in Δs between groups (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$). Δ10 was significantly lower in N5 than in both NE and N30. Δ35 was significantly lower in both N5 and N30 compared to the NE group. The lowest and highest boundaries of the boxes indicate the 25th and the 75th percentiles, respectively. The black line within each box indicates the median. Whiskers above and below the boxes indicate the largest and the lowest data points (excluding any outliers), respectively.

TABLE 4 | Median and interquartile range of the slope of pain ratings at baseline, test 10 and Test 35 in the three experimental groups.

	Slope baseline		Slope test 10		Slope test 35	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
NE	0.588	1.6	0.588	1.5	0.550	2.1
N5	1.167	1.1	1.333	1.1	1.233	1.1
N30	1.167	0.7	0.833	0.8	1.300	4.3

IQR, Interquartile range.

electrical pulses (15). Here, we extended these findings to a longer-lasting, higher-intensity, tonic pain model, and we relied on a behavioral outcome measure (i.e., maximum tolerance) instead of subjective pain ratings, as done in Camerone et al. (15). We replicated the main findings of our previous work, showing that the onset of nocebo hyperalgesia is dependent on the temporal suggestions that participants receive at the moment of (inert-)treatment administration [see **Supplementary Material**: Content 3 for the comparison of effect sizes of nocebo responses between the present study and Camerone et al. (15)]. Participants that were told that the cream had a fast time of action (N5) showed a decrease in tolerance level at the test session that took place soon after cream application (Test 10), demonstrating that suggestions of a fast-acting cream lead to early nocebo hyperalgesia onset. Differently, participants who were told that the cream would require a longer time before setting in (i.e., 30 min from application, N30) did not show a reduction in tolerance level at the early test session (Test 10), instead tolerance reduction set in at the delayed test trial (Test 35), showing that suggestions of delayed cream onset were responsible for postponing the hyperalgesic effect. This finding suggests that when giving a specific time tag to a predicted negative effect (in the present case, pain increase), this is likely to determine when such negative effect sets in. Although we did not directly measure trial-by-trial expectations, it is likely that the modulation of the onset of action of the nocebo cream was driven by participants' expectations, which were formulated accordingly with what they were told by the experimenter. In fact, the assessment of retrospective expectations indicated that participants had high expectations (∼5 on a scale from 0 to 7, See Section on the Assessment of Retrospective Expectancy) that the cream would (i) increase their pain during the test, (ii) decrease their ability to last with the hand in the cold water, and (iii) set in at the time point suggested by the experimenter (after

TABLE 5 | Within-group comparison of the slope of pain ratings.

Groups	Comparisons	Wilcoxon Signed rank test	Effect size	Power analysis
NE	No *Post-hoc*	/	/	/
N5	T_{10} vs. Baseline	$Z = -1.988$, $p = 0.047$	$r = 0.341$	>80%
	T_{35} vs. Baseline	$Z = -2.012$, $p = 0.044$	$r = 0.345$	>80%
	T_{10} vs. T_{35}	$Z = -0.233$, $p = 0.816$	$r = 0.040$	>80%
N30	T_{10} vs. Baseline	$Z = -2.331$, $p = 0.020$	$r = 0.400$	>80%
	T_{35} vs. Baseline	$Z = -2.296$, $p = 0.022$	$r = 0.394$	>80%
	T_{10} vs. T_{35}	$Z = -2.639$, $p = 0.008$	$r = 0.453$	>80%

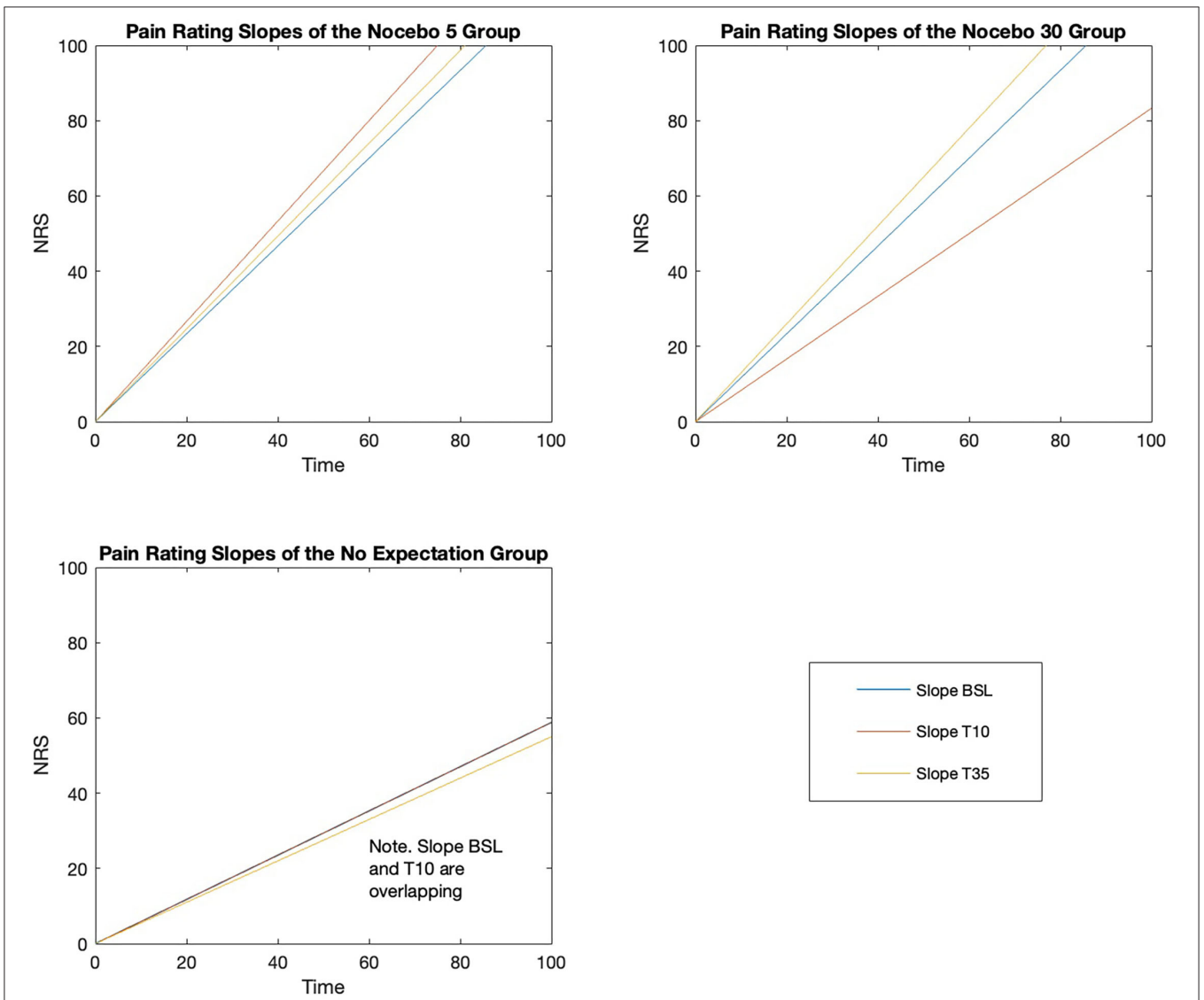

FIGURE 5 | Pain rating slopes for the three groups at the three time-points (Baseline, Test 10, Test 35).

5 min in N5 and after 30 min in N35). Given the modulatory role of expectancy on active treatments (13), it is likely that temporal verbal suggestions would have a similar modulatory effect on active treatments onsets, suggesting that maximum attention must be placed upon the temporal details that are given to patients when presenting them with a new intervention.

A second important finding of this study is that, once triggered, nocebo hyperalgesia remains stable over time (i.e.,

TABLE 6 | Participants' retrospective expectations.

Groups	NE (Mean ± SD)	N5 (Mean ± SD)	N30 (Mean ± SD)
Retro exp pain	n/a	4.8 ± 1.3	4.7 ± 1.7
Retro exp tolerance	n/a	5.1 ± 1.1	5.3 ± 1.6
Retro exp time	n/a	4.7 ± 1.9	4.4 ± 1.8
Average retro exp		4.9 ± 1.4	4.8 ± 1.7

no difference was shown between Test 10 and Test 30 in the N5 group). This result is partially in line with our previous study which shows that once the nocebo response sets in, it increases over time (15). In both studies, the effect did not wear off over time. However, in one case (present study) it remained stable, while in the other it continued to increase (15). This discrepancy could be due to a "floor effect" which might have been present here (i.e., reduction of pain tolerance may reach a level after which lasting less time would mean barely keeping the hand in the water), but not in our previous study (i.e., NRS scores can keep increasing up until 10, even if no pain score ever got close). Alternatively, it could be due to the different methods of measuring pain, with a behavioral outcome in the first case, and with subjective ratings in the second. We suggest that the endurance of nocebo hyperalgesia over time is likely to be underpinned by the endurance of negative expectations (i.e., expectations that the hyperalgesic cream would reduce pain tolerance). Such argument is supported by the results of several nocebo studies which directly assessed trial-by-trial expectations and reported a correlation between expectations of high pain and enhanced pain perception (13, 41). Furthermore, Rodriguez-Raecke et al. have shown that negative expectations induced by verbal suggestions at day one, not only lead to pain worsening on that day, but also that this negative effect remains stable over the next 8 days (42). This study indicates that the endurance of nocebo hyperalgesia is associated with the endurance of negative expectations, indicating that, also in the present study, the endurance of nocebo hyperalgesia is likely to be attributed to the endurance of negative expectations. Accordingly, studies monitoring patients' recovery expectations from back pain onset during a 3-month (43) and a 2-week (44) period, have reported that expectations remained stable over time for most of the patients, and that the direction of expectations (i.e., positive, neutral, negative) was positively correlated with the therapeutic outcome. Altogether, our data is supported by previous research indicating that negative expectations are likely to endure over time (42–44). This underscores the importance of preventing the development of negative expectations in clinical routine when patients start new therapies, given that such expectations are likely to accompany the patient throughout the intervention, thus limiting, or in the worse cases abolishing, its positive effects (13, 43, 44).

Our findings are further supported by the pain ratings data. When the nocebo effect occurs, not only there is a decrease in pain tolerance, but maximum pain tolerance (assessed with pain ratings) is reached faster, as shown by a steeper pain ratings slope (see Statistical Analysis section for more details). Precisely, we found that in the N5 group, the pain rating slope was steeper at the time points in which the nocebo cream was told to be active (i.e., Test 10 and Test 35) compared to when not active (i.e., baseline), indicating that maximum pain tolerance was reached faster in the nocebo-modulated tests. Note that this difference in slope steepness between the nocebo tests and baseline was almost statistically significant. It is worth to highlight that we adjusted the comparison using Bonferroni correction which, if on one hand decreases the probability of "false positives" (i.e., type I error), on the other it increases the risk of not detecting real differences (i.e., type II error) (45). For what concerns the N30 group, a steeper pain rating slope was shown at the test occurring after 35 min—steeper slope at Test 30 compared to both baseline (i.e., almost significant) and Test 10 (i.e., significant), indicating that maximum pain tolerance was reached faster at the test in which the nocebo cream was expected to set in. Worth mentioning is that in this group, the slope was flatter at Test 10 compared to baseline (i.e., tendency to significance), indicating that when participants did not expect the nocebo cream to impair their tolerance, they were slower at reaching maximum pain. As opposed to the two nocebo groups, the pain rating slope remained stable over time in the NE group, indicating that maximum pain was reached with a similar speed when no nocebo suggestions where given. Although these results are promising, they are based on the within group analysis alone, and should therefore be taken with caution. On one hand, within group analysis allows to detect real differences that exist between the conditions which otherwise would stay undetected or covered by random noise (46). On the other hand, between group analysis is needed to draw conclusive remarks. In fact, the lack of the comparison with an external control group (as it would be in the between-group analysis) does not allow to rule out the possibility that the detected differences might be due to confounding factors (i.e., between-factor design allows for greater internal validity) (46). Unfortunately, between-group analysis for the pain ratings slopes was not possible because, due to differences in the nature of the data, slopes of the nocebo groups are not comparable with the slope of the NE. Indeed, the slopes of the nocebo groups are steeper because the last data point of the slope consisted in the maximum pain reached at the moment of hand withdrawal, which is when participants experienced the highest pain (all participants in the nocebo groups ended the pain test reporting NRS = 100). Differently, the slope of the NE group is flatter because the last data point of the slope consisted in the pain reached during the last 15-s interval prior to hand withdrawal, which is not when participants are experiencing the highest pain yet (on average participants reported NRS = 89).

For what concerns retrospective expectations, we found no significant correlations between these and our primary outcome (i.e., pain tolerance). However, measuring expectations retrospectively is an intrinsically biased measure because the reported expectations are reframed based on one's own experience. To have a more accurate representation of one's expectations, these should be assessed before each pain test (i.e., trial-by-trial assessment). However, this is challenging in placebo/nocebo research because repeatedly bringing attention

to participants' expectation is likely to give out the true aim of the study (i.e., participants might question the real nature of the treatment), which is why we decided to assess expectations at the end of the study. The lack of a correlation between retrospective expectations and the primary outcome is in line with the results of our previous studies, also investigating the temporal component in nocebo hyperalgesia and placebo analgesia (15, 16). However, although the assessment of retrospective expectations did not lead to significant correlations, it allowed us to successfully check that participants developed expectations in line with what they were told by the experimenter—i.e., the average score of retrospective expectations was ∼5 over 7 on a scale from 0 (= not at all) to 7 (= very much).

Regarding the psychological factors, no correlation was found between these, and our primary outcome measure. These findings are not particularly surprising given that the literature investigating which psychological factors can best predict nocebo responsiveness is rather scarce and discordant (23). In such an heterogeneous scenario, optimism/pessimism and fear/anxiety are, perhaps, the psychological factors that have been most often associated with an enhanced nocebo response (23). However, similarly to other recently published research (47, 48), we did not find a correlation between optimism/pessimism and nocebo responsiveness. For what concerns anxiety, most of the studies reporting a correlation, assessed anxiety with the state-trait anxiety inventory [e.g., Camerone et al. (15); Corsi et al. (25) found a correlation with trait anxiety; Colloca et al. (24) showed a correlation with both state and trait anxiety], while in the present study, we measured anxiety with the BAI, as done in the study of Kose-Ozlece et al. (28), in which a correlation between high anxiety and enhanced pain perception was reported. Therefore, the lack of correlation could be due to the assessment of anxiety with the BAI rather than with the state-trait anxiety inventory. It is worth pointing out that correlational analyses require much larger sample sizes than the one of this study [i.e., as suggested by Schönbrodt and Perugini (49) a typical scenario requires $n = 250$ for stable estimates], thus our results do not mean that correlations between the suggested psychological factors and nocebo responsiveness are not present, but that a larger sample size might be required to detect the effect. For instance, the study showing a correlation between anxiety measured with BAI and enhanced pain perception, included 140 participants (28). Yet, the primary aim of this study was the investigation of the temporal component of the nocebo effect, which is why reaching the appropriate sample size for correlational analyses was not a priority.

Considering heart rate data, no differences in HR were shown between groups, suggesting that nocebo hyperalgesia is not associated with HR changes. However, in line with our previous data, HR during the pain test decreased over time in all three groups, suggesting a physiological habituation response to the CPT (15). Lack of HR sensitivity as a physiological correlate of nocebo effects is in line with Daniali and Flaten (50) qualitative systematic review, in which heart rate variability, but not HR, was demonstrated to be a good physiological correlate of nocebo hyperalgesia (50). Also, anticipatory HR (i.e. HR during the 10 s that preceded hand immersion) did not differ between groups, and it remained stable over time, failing to pick up on anticipatory anxiety responses that are associated with nocebo hyperalgesia onsets (51). Our results contrast with Colloca and Benedetti (22)'s data that reported HR acceleration during the anticipatory phase before nocebo-cued noxious stimulations. Yet, the different type of noxious stimuli [electrical pulses in Colloca and Benedetti (22)] could account for the diverse anticipatory anxiety reactions, as well as for the associated HR responses.

Overall, the replication of our previous findings (15) on a model of tonic pain using the CPT is a step forward toward the understanding of the temporal modulation of clinical pain. It has in fact been argued that experimental pain induced with mild and short-lasting electrical pulses has limited resemblance with clinical pain, both in terms of stimuli duration and their level of aversiveness (19, 20). This is particularly true for non-continuous electrical stimulation [as in the case of single pulses repeated in time as done in Camerone et al. (15)], while greater clinical relevance is recognised to continuous electrical stimulation (17), indicating that stimulus duration is an important feature to mimic clinical pain. Oppositely, the CPT, despite still being far from clinical pain, has a longer duration and reaches higher intensity (i.e., maximum tolerance), leading to a sensation that is a better proxy to real-life pain (20, 21). In addition, given the ongoing "replication crisis" affecting natural sciences (52, 53), the successful replication of our previous results on a different type of experimentally induced pain adds value to the current study.

Limitations

The empirical results reported herein should be considered in the light of some limitations. The first is the lack of a full randomisation of participants across the three groups. Instead, participants were randomised between the two experimental groups (N5 and N30), while the control group was collected at a different time point, as part of our previous experiment (16). This challenges the validity of the results of the between groups analysis for at least two reasons. First because the same pool of data (i.e., control group), has been analysed twice, increasing the risk of Type I error. However, to amend for this pitfall we have corrected for multiple comparison using a particularly conservative method, the Bonferroni correction (54), which is indicated as the test to use in those cases in which avoiding Type I error is imperative, as the present case (45). The second issue is that the experimenters differed between the two nocebo groups and the control group (See Section "Experimenters" in the Methods), adding a potential bias. For instance, the experimenter testing the control group was a female, while the experimenter of the two nocebo groups was a male, yet the experimenters were matched in terms of status—i.e., both with the same age (26 years old) and the same education (both PhD students). Since Kállai et al. (55) showed that greater experimenter status increases tolerance time, it is an advantage that our experimenters were matched in terms of theirs status (55). However, Kállai et al. (55) showed that healthy volunteers tolerate pain longer when they are tested by an experimenter of the opposite sex. This indicates that the differences in the gender of the experimenters in the present study might be a threat to the validity of the results. However, no

significant baseline differences ($p > 0.05$) were reported in terms of tolerance time between the nocebo groups and the control one, demonstrating that such bias is not likely to be present in this study. The third issue is the time gap of almost 1 year between when participants in the control group (June and July, 2019) and those in the experimental groups (April to July, 2020) were tested. This is particularly concerning if we consider that the control group was collected before the start of the COVID-19 pandemic, while the nocebo groups were collected after its beginning. Hence, it is not possible to exclude that confounding factors related to this abnormal historical time, including the psychological and social challenges that people faced over this period, could have biased the study results. However, participants across the three groups were comparable (no baseline groups differences, $p > 0.05$) in terms of demographics (i.e., age, BMI, and gender) and psychological traits, including trait anxiety, optimism, fear of pain and individuals' motivational systems. Furthermore, it is important to highlight that if in the between-group analysis we compare each experimental group with the control one, this is not the case for the within-group analysis, in which the control condition is the baseline session within each group, considered independently. It follows that the issues related to the control group not being randomised, do not affect the results of the within group analysis. Such consistency between the results of the within and the between analyses, both suggesting that temporal suggestions modulate the onset of action of nocebo hyperalgesia, further supports the validity of the results of the between groups comparison despite the limitations associated with the non-randomised control group.

The second limitation concerns the lack of expectancy recording throughout the experiment, while participants' expectations were only measured retrospectively. On one hand, measuring expectancy retrospectively prevented participants' from questioning the true nature of the study. On the other hand, the lack of trial-by-trial expectations recording prevents our data from giving us information on the variation of temporal expectations over the course of the experiment. Since expectations update accordingly with (sensory) experiences, further research is needed to investigate the interplay between expectations updating and nocebo hyperalgesia temporal modulation.

Recommendations for Future Studies

Future studies investigating the temporal modulation of nocebo hyperalgesia should first, measure trial-by-trial expectations to directly assess whether there is a direct association between one's hyperalgesic expectations at a specific time-point and the presence of the hyperalgesic effect at such time-point. Second, further research must investigate whether the shifts in time of nocebo hyperalgesia are associated with a neurophysiological response. As demonstrated by the present study, HR is not a good measure to detect nocebo hyperalgesia; future studies could consider using central measures such as electroencephalography and functional magnetic resonance imaging, which are effective at picking up signals associated with nocebo hyperalgesia (56, 57). Third, future designs should investigate whether the same temporal effects would be found with longer time-windows. While here we investigated a 35-min interval, it is not known whether temporal suggestions would have the same effect if the interval was of days, weeks, or months. At last, the modulation of temporal suggestions should be investigated on patients suffering from endogenous pain. In this context, the effect of temporal suggestions could be investigated directly on active treatments, by delivering different temporal suggestions regarding the expected onset of action of possible treatment side effects (i.e., informing the patient of the real side effects as it would normally be done, but giving different temporal indications).

CONCLUSIONS

To conclude, we demonstrated that temporal suggestions modulate the onset of nocebo hyperalgesia, extending our previous findings to a model of tonic pain, relying on maximum pain tolerance as a behavioral outcome measure. Sometimes pain cannot be avoided but has to be tolerated, as in some cases of chronic pain (58–60). Therefore, understanding how to modulate one's tolerance levels can be particularly relevant in the clinical context (61). These results are promising, and further studies must build upon this evidence to better understand the influence of temporal expectations in the clinical setting and across diverse therapeutic interventions.

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 Vrije Universiteit Brussel. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EMC, FB, and EC conceived the presented idea. EMC collected part of the data, planned and performed the data analysis, and took the lead in writing the manuscript. SB collected and analysed the data and gave a significant contribution to the manuscript write up. AS supervised the practical development of the experiment assessing its feasibility from start to end. LS and LB was involved in data analysis and collection. MT supervised the project throughout, from the design of the experiment to the completion of the final manuscript. All authors discussed the results and contributed to the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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Positive Treatment Expectations Shape Perceived Medication Efficacy in a Translational Placebo Paradigm for the Gut-Brain Axis

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Placebo research has established the pivotal role of treatment expectations in shaping symptom experience and patient-reported treatment outcomes. Perceived treatment efficacy constitutes a relevant yet understudied aspect, especially in the context of the gut-brain axis with visceral pain as key symptom. Using a clinically relevant experimental model of visceral pain, we elucidated effects of pre-treatment expectations on post-treatment perceived treatment efficacy as an indicator of treatment satisfaction in a translational placebo intervention. We implemented positive suggestions regarding intravenous treatment with a spasmolytic drug (in reality saline), herein applied in combination with two series of individually calibrated rectal distensions in healthy volunteers. The first series used distension pressures inducing pain (pain phase). In the second series, pressures were surreptitiously reduced, modeling pain relief (pain relief phase). Using visual analog scales (VAS), expected and perceived treatment efficacy were assessed, along with perceived pain intensity. Manipulation checks supported that the induction of positive pre-treatment expectations and the modeling of pain relief were successful. Generalized Linear Models (GLM) were implemented to assess the role of inter-individual variability in positive pre-treatment expectations in perceived treatment efficacy and pain perception. GLM indicated no association between pre-treatment expectations and perceived treatment efficacy or perceived pain for the pain phase. For the relief phase, pre-treatment expectations ($p = 0.024$) as well as efficacy ratings assessed after the preceding pain phase ($p < 0.001$) were significantly associated with treatment efficacy assessed after the relief phase, together explaining 54% of the variance in perceived treatment efficacy. The association between pre-treatment expectations and perceived pain approached significance ($p = 0.057$) in the relief phase. Our data from an experimental translational placebo intervention in visceral pain support that reported post-treatment medication efficacy is shaped by pre-treatment

expectations. The observation that individuals with higher positive expectations reported less pain and higher treatment satisfaction after pain relief may provide first evidence that perceived symptom improvement may facilitate treatment satisfaction. The immediate experience of symptoms within a given psychosocial treatment context may dynamically change perceptions about treatment, with implications for treatment satisfaction, compliance and adherence of patients with conditions of the gut-brain axis.

Keywords: treatment expectations, placebo, suggestions, visceral pain, gut-brain axis, patient-reported outcomes, treatment satisfaction, pain perception

INTRODUCTION

Numerous studies on placebo effects in acute and chronic pain have demonstrated the pivotal role of treatment expectations arising within the psychosocial treatment context (reviewed in Refs. 1, 2). While placebo research in pain has a strong tradition, owing to placebo analgesia as one prominent example of expectancy effects on patient-reported outcomes, the large area of visceral pain has played a comparatively minor role in this translational research field (3). Visceral pain is of high clinical relevance, especially in disorders of gut-brain interactions like the irritable bowel syndrome, but also in inflammatory bowel disease (IBD) and a range of other clinical conditions in gastroenterology, gynecology, urology, and psychosomatic medicine (4, 5). Since the notable clinical work by Kaptchuk and colleagues demonstrating the therapeutic potential of placebo interventions in patients with IBS (6, 7), clinical research on visceral pain modulation and impact of expectancy effects on treatment responses in clinical trials in the gastrointestinal field continues to thrive (3, 8–11). This calls for laboratory studies dedicated to elucidating the psychological and neurobiological mechanisms in clinically relevant models of visceral pain.

While existing evidence impressively underscores expectancy effects on visceral pain perception both in healthy volunteers and in clinical conditions involving the gut-brain axis (3, 12), there exist gaps in knowledge that even novel research approaches have not fully captured thus far (13). It is important to understand if and how treatment expectations shape perceived treatment efficacy as a key patient-reported outcome and indicator of overall treatment satisfaction. Indeed, the subjective evaluation of how well a treatment worked is a crucial component of patients' perspective on quality of healthcare in clinical trials and practice (14, 15). This is increasingly appreciated in placebo research accomplished in patients with somatic pain conditions (16), but remains insufficiently considered in clinical and laboratory studies on underlying psychological mechanisms, especially in the context of visceral pain. In experimental visceral pain, we previously showed that perceived treatment group allocation constitutes an important aspect in symptom reports (17). Specifically, healthy volunteers who believed that they received a potent analgesic drug reported less discomfort induced by rectal distensions and reduced neural activation of several relevant brain regions, including the insula and cingulate cortex, when compared to volunteers who believed that they had received an inert treatment. Further, perceived treatment allocation was impacted by symptom burden in response to experimentally induced acute inflammation (18). These initial findings from experimental studies suggest that expectations and visceral symptom experience shape cognitive processes underlying patients' evaluations and possibly judgments regarding treatment. Since perceived efficacy of an analgesic treatment is essential to treatment satisfaction and adherence, it is important to model the impact of treatment expectations together with the immediate experience of changes in symptom intensity in experimental placebo research.

In a translational placebo intervention for visceral pain, we elucidated whether and to what extent interindividual variability in positive treatment expectations arising from positive treatment information within a standardized treatment context is associated with perceived treatment efficacy and visceral pain perception. To induce positive treatment expectations in healthy volunteers, we capitalized on an established placebo intervention which consists of positive suggestions regarding treatment with an intravenous spasmolytic drug (in reality saline) (19–23). Repeated rectal distensions, carried out following placebo administration, were individually calibrated to be initially painful, and subsequently surreptitiously lowered in intensity to model pain relief. This approach was inspired by the clinical treatment reality of patients experiencing fluctuating symptoms and/or delayed treatment onset, which is highly relevant in conditions of acute or chronic visceral pain where clear and immediate treatment success may be particularly difficult to achieve. Initial analyses were carried out to verify the successful implementation of distinct perceptual experiences by different distension pressures (manipulation check), as well as to ascertain the effective induction of positive treatment expectations in the placebo intervention group when compared to a reference group (treatment check). Primary analyses were computed within all positively instructed individuals (placebo group) with generalized linear models (GLMs) for the pain and pain relief phases, respectively, using treatment efficacy and perceived intensity ratings as response variables.

MATERIALS AND METHODS

Participants

Healthy participants were recruited by public advertisement seeking volunteers for an experimental study designed to test psychological mechanisms underlying effects of different drugs

on experimentally induced visceral symptoms including pain. For the purposes of this report, we analyzed selected behavioral measures from a dataset of a total of $N = 60$ healthy participants who were at inclusion randomized (with a 2:1 randomization) to undergo an established placebo intervention consisting of positive drug-related treatment suggestions ($N = 40$, placebo group) or to receive no drug-related suggestions ($N = 20$, reference group) prior to experiencing phasic visceral stimuli (details below). All volunteers were recruited *de novo* for this study and had to be naïve with respect to both the distension model as well as to any prior experimental placebo or nocebo study carried out by our research group. The recruitment and in-depth screening procedures consisted of an initial semi-structured telephone screening (conducted by author LR), followed by a structured personal interview and a brief general medical examination, including a digital rectal exam (conducted by study physician, author NT). Exclusion criteria included a body mass index (BMI) <18 or >30, age <18 or >45 years, any known medical or psychological/psychiatric clinical conditions, and any current medication use (except occasional use of non-prescription over-the-counter drugs for minor allergies, benign headaches). Participants were also screened for self-reported substance abuse, including number of alcoholic drinks/week (>4/week led to exclusion), smoking (>10 cigarettes per week led to exclusion), and use of other recreational drugs (any reported use within past 3 months led to exclusion). Current anxiety or depression symptoms above the published cut-off values (i.e., scores ≥ 8) on the Hospital Anxiety and Depression Scale (HADS) (24), and frequent gastrointestinal (GI) symptoms within past 3 months suggestive of an undiagnosed GI condition based on self-reports during phone screening or on a gastrointestinal symptom questionnaire (items assessed: diarrhea, constipation, vomiting, nausea, lower abdominal pain, upper abdominal pain, heartburn, post-prandial fullness, bloating, loss of appetite) (25) completed during the personal interview also led to exclusion from participation. Peri-anal tissue damage (e.g., painful hemorrhoids or fissures which may interfere with balloon placement) upon digital examination during the physical examination were also an exclusion criterium. Since the study was originally accomplished to elucidate pain-related brain mechanisms (data not reported herein), the usual MR-specific exclusion criteria also applied (i.e., claustrophobia, pregnancy or ferromagnetic implants, and any evidence of structural brain abnormalities, verified by a neuroradiologist, author NT). Pregnancy was ruled out using a commercially available pregnancy test on the study day (Biorepair GmbH, Sinsheim, Germany, sensitivity 10 mIU/ml). In addition to HADS, we also herein report trait anxiety assessed with the trait version of the Spielberger State-Trait-Anxiety Inventory (STAI-T) (26). Ethics approval was granted by the University Hospital Essen Ethics Committee (permit no. 08-3823). All volunteers gave written informed consent, and were paid for their participation.

Experimental Procedures

Experiments were conducted within a medical research setting within a clinical MR suite of the University Hospital Essen, Germany. On the study day (see **Figure 1** for a time line), a catheter was placed to apply pressure-controlled rectal distensions as a clinically relevant and reliable experimental model for the study of acute visceral pain in healthy individuals as well as in patients with chronic visceral pain (27). Given high interindividual variability in rectal sensitivity in healthy participants (28, 29) and our paradigm requiring precisely titrated pressures for the induction of distinct perceptual intensities in the pain and pain relief phases, respectively, a thresholding procedure was accomplished initially. Individual rectal sensory and pain thresholds were determined using a barostat system (modified ISOBAR 3 device, G & J Electronics, ON, Canada) in accordance with our prior work and recommendations within neurogastroenterology (e.g., 28, 29). Specifically, we utilized a double-random staircase procedure with a series of phasic distensions (duration each 30 s) with random pressure increments of 2–8 mmHg. Pauses of complete balloon deflation (i.e., 0 mmHg pressure) in-between each distension were 30 s. The maximal distension pressure was set at 50 mmHg. For each distension, participants rated the perception on a Likert scale labeled 1 = no perception, 2 = doubtful perception, 3 = sure perception, 4 = little discomfort, 5 = severe discomfort, still tolerable distension and 6 = pain, not tolerable distension. Sensory threshold was defined as pressure when ratings changed from 2 to 3; pain threshold was defined as pressure when ratings changed from 5 to 6. The duration of the thresholding procedure takes approximately 20–30 min, depending on the individual pain threshold.

Based on results of thresholding, individualized pressures aiming to create two distinct stimulation intensities for subsequent application during two series of cued phasic rectal distensions were identified. In the first series, six painful visceral stimuli using distension pressures just below the individual pain threshold were implemented (pain phase). The subsequent second series consisted of six distensions at surreptitiously reduced pressures corresponding to just above the sensory threshold (relief phase). All distensions were cued by a visual signal, and the duration of each distension was 18 s. Pauses of complete balloon deflation in-between distensions were 18 s. Visual analog scale (VAS) were accomplished prior to and after each phase for expectation and efficacy ratings, and after each distension for perceived intensity (details below).

Induction of Positive Treatment Expectations (Placebo Intervention)

We implemented a previously established translational placebo intervention for the visceral pain modality to induce positive treatment expectations by suggestions, which we have previously applied in studies with healthy volunteers and patients with IBS and IBD (19–23). It essentially builds on deceptive treatment suggestions regarding the intravenous administration of a potent spasmolytic drug with analgesic properties, which is in reality always saline. As previously established (28, 29), positive treatment suggestions included both written and standardized verbal information regarding the intravenous (i.v.) administration of a spasmolytic drug

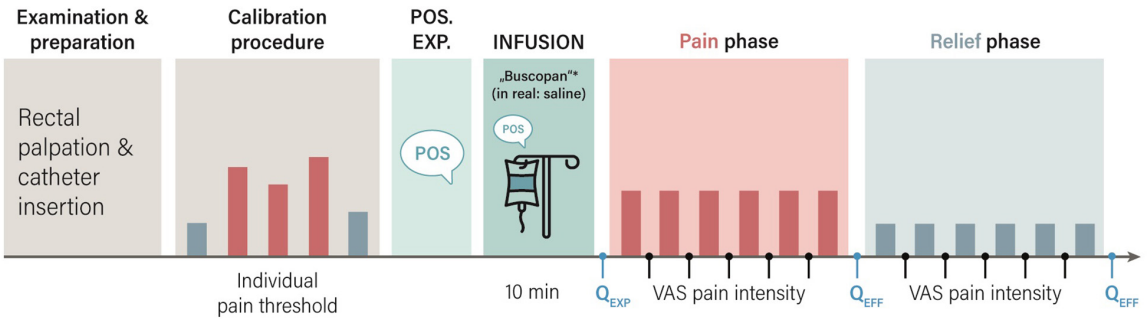

FIGURE 1 | Study procedures for the placebo group. After rectal catheter placement, individual pain thresholds were determined in a calibration procedure. The study physician verbally delivered treatment suggestions about treatment with a spasmolytic drug (in reality saline) in order to induce positive treatment expectations (Pos. Exp.), and the intravenous infusion was started. In the subsequent pain phase, individual distension pressures inducing pain were applied. In the pain relief phase, pressures were surreptitiously reduced to model pain relief. Using visual analog scales (VAS), expected (Q_{EXP}), and perceived (Q_{EFF}) treatment efficacy were assessed. Perceived distension intensity was assessed after each stimulus, and averaged for the pain and pain relief phases, respectively. **Buscopan: scopolamine butylbromide.*

(Butylscopolaminiumbromid) with analgesic properties. Specifically, during recruitment and as part of informed consent, all $N = 40$ participants in the placebo group received positive information verbally and in writing, including detailed drug-related information. On the study day, before the i.v. drip was started, pertinent aspects of the positive instructions, were repeated verbally ("medication reminder communication") by the study physician (author NT), especially focusing on the pain-relieving properties of the drug (see **Figure 1**). In line with our previous clinically oriented work (23), the duration of this was recorded as a global measure of patient-provider-communication quantity. The study physician then prepared a syringe clearly labeled with the drug name in full view of participants, and injected its content (in reality saline) into an infusion bottle with saline. Note that as part of the study, we piloted two versions of this positive reminder communication: While all $N = 40$ participants were reminded of the pertinent drug information, half of the sample ($N = 20$) received more detailed and personalized information (i.e., augmented vs. limited medication reminder).

As a reference group, herein used to confirm that the placebo intervention successfully induced positive treatment expectations, $N = 20$ individuals were truthfully informed about administration of an inert substance. Specifically, this reference group was informed about i.v. administration of saline, and written and verbal instructions contained a specific mention of absence of active drug and lack of saline effects. The infusion bottle was clearly marked as "sodium chloride," and no injection into this bottle was accomplished. Any verbal communication between physician and participant during the i.v. preparation was kept as neutral and "technical" as possible, making no references to treatment or pain.

Measures

Visual analog scale (VAS, 0–100 mm) ratings were accomplished using an automated response system (LUMItouch^{TM}, Photon Control Inc., Burnaby, BC, Canada). Specifically, expected medication efficacy, i.e., positive treatment expectation, was rated on VAS (ends labeled "not at all effective–highly effective") immediately after the verbal induction of positive treatment expectations by the study physician. After each distension series (i.e., pain and pain relief phases, respectively), perceived treatment efficacy was assessed. Note that all treatment efficacy VAS were specifically phrased to address the expected or the experienced ability of the drug to successfully relieve visceral pain ("How effectively will/did the drug relieve your pain," ends labeled "not at all–very much"). In addition, each distension was rated on VAS for intensity, and ratings were averaged within each phase for analyses. VAS state tension ratings were accomplished along with efficacy ratings (see **Figure 1**).

Statistical Analyses

For initial manipulation/treatment checks, placebo and reference groups were compared with respect to objective and subjective distension-related measures as well as sociodemographic and psychological measures using independent sample *t*-tests and Chi^2-test. Change in subjective distension perception was calculated with repeated measures ANOVA with the between subject factor group (placebo, reference) and time (pain, relief). Next, to exclude differences between positively instructed participants who received augmented vs. limited medication reminder communication, distension-related outcomes were compared with independent-samples *t*-tests. Data were reported as mean ± standard deviation (SD), effect sizes as Cohen's d. In case that Levene test for homogeneity of variances was significant, we show corrected df. Data were analyzed with SPSS version 27.0 (IBM Corporation, Armonk, NY, United States).

To address main research aims, i.e., to assess the role of positive treatment expectations, analyses within all positively instructed participants (placebo group, $N = 40$) were performed with RStudio (RStudio Team, Version 1.4.1717, RStudio, PBC, Boston, MA, United States).[1] Separate generalized linear models (GLMs) were calculated using pre-treatment expectation ratings as exploratory and (a) treatment efficacy for the pain and pain

[1]http://www.rstudio.com/

TABLE 1 | Sample characteristics.

	Placebo (*N* = 40)	Reference (*N* = 20)	*P*
Age (years)	25.9 ± 5.2	24.6 ± 3.0	0.29
Sex (*N* female/*N* male)	20/20	9/11	0.72
Body mass index (kg/m^2)	23.0 ± 2.8	22.4 ± 2.2	0.34
HADS anxiety score	3.6 ± 2.8	2.6 ± 2.1	0.16
HADS depression score	2.1 ± 2.1	1.0 ± 1.4	0.04
STAI trait score	35.4 ± 7.3	33.1 ± 7.5	0.26
GI symptom score	4.1 ± 2.8	3.6 ± 2.9	0.57
Rectal sensory threshold, mmHg	14.9 ± 3.8	14.2 ± 3.0	0.47
Rectal pain threshold, mmHg	35.0 ± 10.7	34.6 ± 7.4	0.88

Data are shown as mean ± standard deviation, unless otherwise indicated. No significant group differences were observed between the Placebo and Reference groups (P values indicate results of independent sample t-tests or Chi^2 tests for sex). GI, gastrointestinal; HADS, Hospital Anxiety and Depression Scale; STAI, State-Trait Anxiety Inventory.

relief phases and (b) perceived distension intensity as response variables. All outcome models were additionally corrected for the following covariates: Tension (VAS), duration of the informed consent procedure (min), stimulus intensity (mmHg), treatment efficacy (VAS, for models addressing pain intensity), pain intensity (VAS, for models addressing treatment efficacy). In supplemental analyses, models were re-computed after exclusion of outliers (in expectation and efficacy ratings, $N = 5$ exclusions), defined outliers as values 2 SD below or above mean. Statistical testing was performed at alpha < 0.05.

RESULTS

Participants and Manipulation and Treatment Checks

Consistent with stringent exclusion criteria, healthy male and female participants were overall young and of normal weight, and characterized by low anxiety and depression symptom scores, normal trait anxiety scores, and low gastrointestinal complaints. Mean rectal sensory and pain thresholds were comparable with our previous findings on visceral pain sensitivity in young healthy participants (e.g., 29). No differences in any of these variables except for a small, statistically significant different in HADS depression scores were found between the placebo ($N = 40$) and the reference ($N = 20$) groups (**Table 1**).

As manipulation check, we initially ascertained differences between experimental phases with respect to objective and subjective distension-related measures. As intended, distension pressures applied within the pain phase were markedly higher than pressures applied within the pain relief phase, consistent with their selection based on individual thresholds (**Supplementary Table 1**). Further, the applied distension pressures consistently led to distinct perceptual intensities, i.e., greater perceived intensity during the pain phase and lower perceived intensity during the subsequent pain relief phase (**Supplementary Table 1**), together supporting the efficacy of experimental manipulations.

Subsequently, the overall efficacy of the placebo intervention was tested by comparing positive expectations in the placebo and reference groups (treatment check). The placebo intervention successfully induced positive treatment expectations, as evidenced by overall significantly higher positive treatment expectations in the placebo group ($N = 40$) when compared to the reference group who received no positive drug-related suggestions [VAS pre-treatment expectations: 69.9 ± 11.8 mm vs. 14.8 ± 22.8 mm; $t_{(40.1)} = 10.1$, $p < 0.001$, $d = 3.4$].

Treatment Expectations and Perceived Treatment Efficacy in the Placebo Group

Our primary aim was to assess the role of inter-individual variability in positive pre-treatment expectations in perceived treatment efficacy and symptom perception, which is why our strategy capitalized on variability in the whole sample of all positively instructed participants (placebo group, $N = 40$). To this end, the entire placebo group was analyzed using GLM, irrespective of two slightly different medication reminder communication strategies implemented just prior to placebo administration by the study physician. For the sake of completeness, we provide comparisons of outcome measures for these subgroups (augmented vs. limited, **Supplementary Table 2**). Briefly, no subgroup differences in outcome measures were observed, but the reminder communication was significantly longer in the augmented subgroup [10.9 ± 2.4 vs. 6.8 ± 1.5 min, $t_{(37)} = 6.4$, $p < 0.001$], which we considered as a covariate in GLM analyses. Further, positive treatment expectations were higher in the augmented subgroup [75.2 ± 9.7 vs. 64.7 ± 11.4 mm on VAS, $t_{(37)} = 3.1$, $p = 0.003$], providing us with variability for primary analyses using GLM.

For the pain phase, GLM indicated that pre-treatment expectations were not associated with treatment efficacy assessed after the pain phase (**Table 2** and **Figure 2**). For the relief phase, pre-treatment expectations were significantly associated with treatment efficacy assessed after the relief phase (**Table 2** and **Figure 2**). In this model, pre-treatment expectation ($p = 0.024$) together with efficacy ratings assessed after the preceding pain phase ($p < 0.001$) explained 54% of the variance in perceived treatment efficacy (**Table 2**).

After exclusion of outliers, treatment expectation was significantly associated with treatment efficacy ratings for the pain phase. For the pain relief phase, predictors in the GLM model remained unchanged, however, with a lowered level of significance for pre-treatment expectation ($p = 0.05$) (**Supplementary Table 3** and **Supplementary Figure 1**).

Treatment Expectations and Perceived Distension Intensity in the Placebo Group

For the pain phase, perceived pain was only associated with objective stimulus intensity ($p = 0.028$), but not with treatment expectation (**Table 3** and **Figure 3**). For the relief phase, the association between treatment expectation and perceived pain approached significance ($p = 0.057$). In this model, objective stimulus intensity ($p = 0.008$) and tension after the relief phase

TABLE 2 | Predictors of treatment efficacy after pain and relief phases (Results of generalized linear models, GLM).

Treatment efficacy after pain phase (R^2 = 0.17)							
Predictors	**Estimates**	**Std. Beta**	**CI**	**Std. CI**	**t**	**p**	**df**
(Intercept)	69.76	−0.00	23.6–116.0	−0.31–0.31	2.96	**0.006**	33
Pre-treatment expectation (VAS)	0.25	0.17	−0.30–0.80	−0.20–0.53	0.89	0.38	33
Perceived intensity for pain phase (VAS)	−0.13	−0.13	−0.45–0.20	−0.48–0.21	−0.76	0.45	33
Stimulus intensity for pain phase (mmHg)	−0.37	−0.21	−1.01–0.27	−0.58–0.16	−1.13	0.27	33
Tension after pain phase (VAS)	0.11	0.18	−0.10–0.32	−0.16–0.52	1.05	0.30	33
Duration of medication reminder communication (minutes)	−0.85	−0.14	−3.03–1.32	−0.49–0.21	−0.77	0.45	33
Treatment efficacy after relief phase (R^2 = 0.54)							
Predictors	**Estimates**	**Std. Beta**	**CI**	**Std. CI**	**t**	**p**	**df**
(Intercept)	−6.06	−0.00	−46.5–34.4	−0.23–0.23	−0.29	0.77	32
Pre-treatment expectation (VAS)	0.53	0.35	0.09–0.97	0.06–0.64	2.37	**0.024**	32
Treatment efficacy rating for pain phase (VAS)	0.59	0.59	0.33–0.86	0.33–0.86	4.35	**<0.001**	32
Perceived intensity for relief phase (VAS)	0.06	0.06	−0.27–0.39	−0.28–0.40	0.35	0.73	32
Stimulus intensity for relief phase (mmHg)	0.17	0.10	−0.35–0.68	−0.20–0.39	0.64	0.53	32
Tension after relief phase (VAS)	−0.10	−0.15	-0.31–0.12	−0.49–0.19	−0.88	0.39	32
Duration of medication reminder communication (minutes)	−0.06	−0.01	−1.84–1.71	−0.30–0.28	−0.07	0.94	32

Separate generalized linear models (GLMs) with pre-treatment expectation as exploratory and treatment efficacy ratings as response variables were calculated for the pain and pain relief phases, respectively, in all positively instructed volunteers (N = 40, placebo group). CI, confidence interval; df, degree of freedom; Std., Standardized; t, t value; VAS, visual analog scale. Significant p-values are printed in bold.

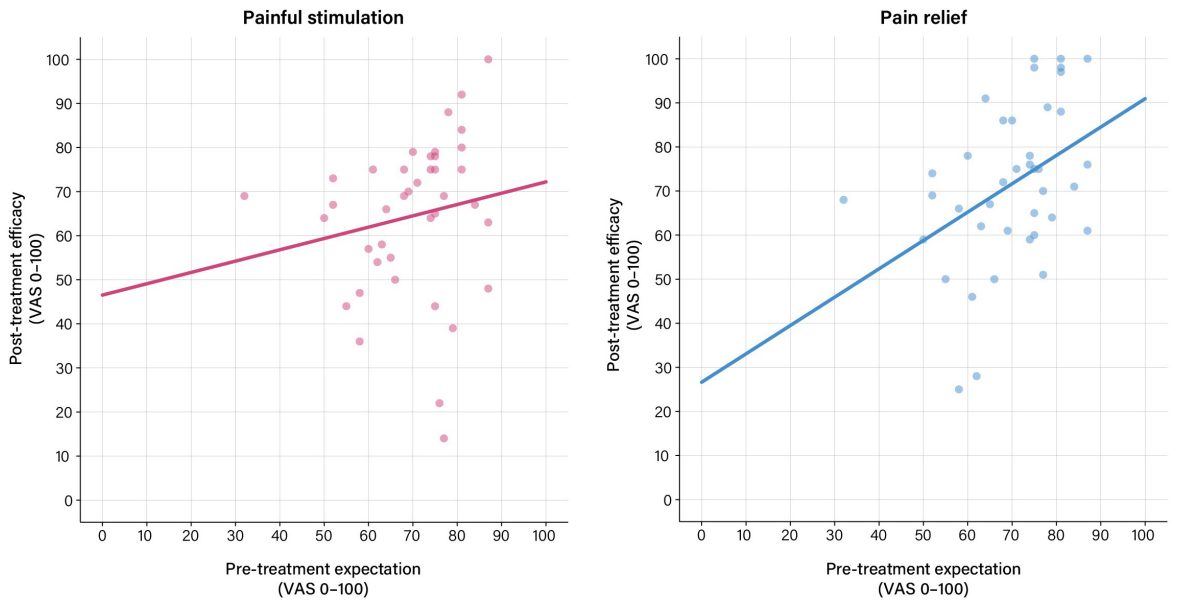

FIGURE 2 | Associations between pre-treatment expectation and perceived treatment efficacy based on general linear models (GLM) calculated using pre-treatment expectation as exploratory and treatment efficacy ratings as response variables. **(Left)** No significant association between pre-treatment expectation and perceived treatment efficacy was found after painful stimulation in the pain phase. **(Right)** For the relief phase, pre-treatment expectations were significantly associated with perceived treatment efficacy (b = 0.35, t = 2.37, p = 0.024). For details, see **Table 2**. For results after exclusion of outliers, see **Supplementary Table 3** and **Supplementary Figure 1**.

(p = 0.001) were significant covariates, with the model explaining 52% of the variance in perceived distension intensity (**Table 3** and **Figure 3**).

After exclusion of outliers, associations with treatment expectation for the pain or pain relief phases remained non-significant (**Supplementary Table 4** and **Supplementary Figure 2**).

DISCUSSION

Research into placebo effects has established the pivotal role of treatment expectations in symptom experience, including the experience of acute visceral pain and other burdening symptoms of the gut-brain axis (3). As a crucial component of overall treatment satisfaction, perceived treatment efficacy

TABLE 3 | Predictors of pain intensity during pain and relief phases (Results of generalized linear models, GLM).

Subjective pain intensity during pain phase (R^2 = 0.21)

Predictors	Estimates	Std. Beta	CI	Std. CI	t	p	df
(Intercept)	23.59	0.00	-29.53–76.71	–0.30–0.30	0.87	0.39	33
Pre-treatment expectation (VAS)	0.16	0.10	–0.41–0.74	–0.26–0.46	0.56	0.58	33
Treatment efficacy rating for pain phase (VAS)	–0.014	–0.13	–0.49–0.21	–0.46–0.20	–0.76	0.45	33
Stimulus intensity for pain phase (mmHg)	0.74	0.40	0.11–1.37	0.06–0.74	2.30	**0.028**	33
Tension after pain phase (VAS)	0.20	0.30	–0.01–0.40	–0.02–0.62	1.86	0.072	33
Duration of medication reminder communication (minutes)	–0.28	–0.04	–2.54–1.98	-0.39–0.30	–0.24	0.81	33

Subjective pain intensity during relief phase (R^2 = 0.52)

Predictors	Estimates	Std. Beta	CI	Std. CI	t	p	df
(Intercept)	49.24	–0.00	12.49–85.98	–0.24–0.24	2.63	**0.013**	32
Pre-treatment expectation (VAS)	–0.47	0.30	–0.94 – –0.00	–0.61 – –0.00	–1.97	0.057	32
Treatment efficacy rating for relief phase (VAS)	0.19	0.18	–0.09–0.47	–0.09–0.45	1.31	0.20	32
Perceived intensity for pain phase (VAS)	0.19	0.20	–0.10–0.48	–0.10–0.50	1.30	0.20	32
Stimulus intensity for relief phase (mmHg)	–0.71	–0.40	–1.20 – –0.22	–0.67 – –0.12	–2.85	**0.008**	32
Tension after relief phase (VAS)	0.36	0.56	0.16–0.57	0.25–0.88	3.48	**0.001**	32
Duration of medication reminder communication (minutes)	–1.49	–0.24	–3.28–0.29	–0.52–0.05	–1.64	0.11	32

Separate generalized linear models (GLMs) with pre-treatment expectation as exploratory and perceived intensity ratings as response variables were calculated for the pain and pain relief phases, respectively, in all positively instructed volunteers (N = 40, placebo group). CI, confidence interval; df, degree of freedom; Std., Standardized; t, t value; VAS, visual analog scale. Significant p-values are printed in bold.

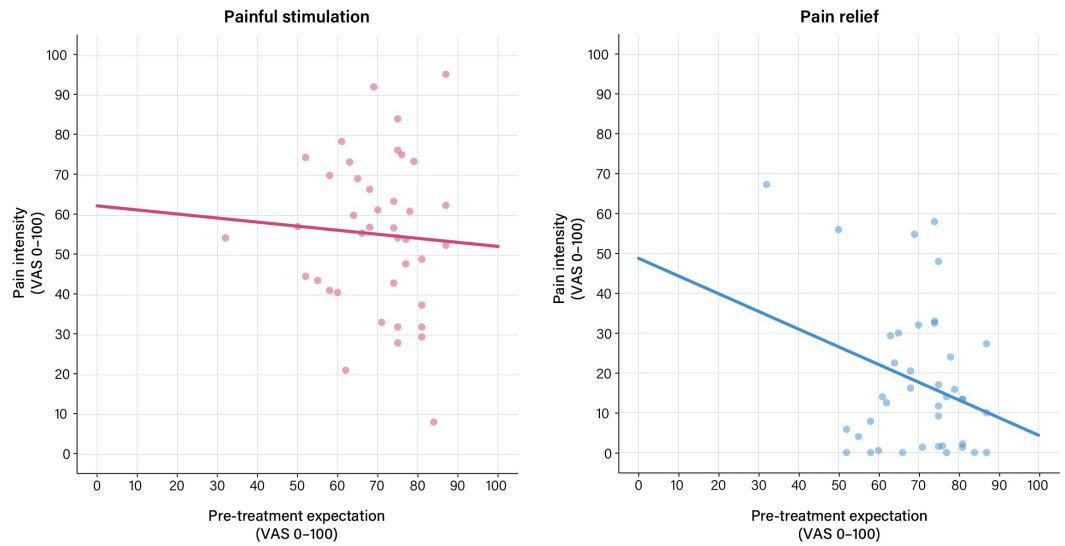

FIGURE 3 | Associations between pre-treatment expectation and perceived distension intensity based on general linear models (GLM) calculated using pre-treatment expectation as exploratory and perceived intensity ratings as response variables. **(Left)** For the pain phase, no significant association between pre-treatment expectation and perceived distension intensity was observed. **(Right)** For the relief phase, the association between pre-treatment expectation and perceived distension intensity approached significance (b = 0.30, t = –1.97, p = 0.057). For details, see **Table 3**. For results after exclusion of outliers, see **Supplementary Table 4** and **Supplementary Figure 2**.

constitutes a relevant yet understudied element of expectancy effects on patient-reported outcomes, which has thus far not been addressed in visceral pain. In a translational placebo intervention for acute visceral pain, we focused our analyses on interindividual variability in levels of positive expectations in a placebo group, and elucidated perceived treatment efficacy and perceived stimulus intensity after an initial treatment phase modeling pain and a subsequent treatment phase modeling pain relief. To induce positive treatment expectations in naïve healthy participants, we implemented positive drug-related suggestions, i.e., written and verbal information regarding the i.v. administration of a potent spasmolytic drug with analgesic properties. In line with our earlier findings in this placebo intervention (28, 29), positive suggestions successfully

induced overall high levels of positive treatment expectations, as evidenced by comparison with expectations in a reference group that had received information regarding saline as an inert substance. The extent of positive expectations within the placebo group was greatest in a subgroup with an optimized (augmented) medication reminder communication accomplished in the immediate treatment context, which we piloted within this project. While not our primary focus herein, this interesting finding expands on work dedicated to the crucial role of patient-provider communication in shaping expectancy effects (30, 31), enhances the generalizability and translation or our experimental work to clinical settings where quantity and quality of communication obviously vary greatly, and effectively provided us with sufficient variability in levels of positive expectations for our primary analyses using general linear models (GLM) in all positively instructed individuals, i.e., the entire placebo group.

Generalized linear models supported that positive pre-treatment expectations were associated with greater perceived treatment efficacy. Effects were greater and more robust to outliers for the pain relief phase, consisting of rectal distensions with surreptitiously reduced pressures, effectively creating the experience of pain relief. In other words, the magnitude of positive treatment expectations scaled with the perception of a more potent analgesic drug after the experience of improved pain. Pre-treatment expectations explained 54% (62% after exclusion of outliers) of the variance in perceived treatment efficacy rated after the pain relief phase, in a model that considered a number of other variables as covariates. Besides treatment expectations, perceived treatment efficacy after the preceding pain phase emerged as a significant predictor for treatment efficacy after the relief phase, suggesting that treatment efficacy not only dynamically changes over the course of a single treatment, but also that treatment-related evaluations during an early phase of treatment modulate subsequent evaluations during later treatment phases. This may seem trivial at first glance but is in fact intriguing in its putative implication for clinical treatment settings where patients receive the same treatment for longer periods of time, on multiple occasions, and/or in different doses. For the pain phase, on the other hand, a significant model emerged only after exclusion of outliers, with pre-treatment expectations explaining 29% of the variability in efficacy. Together, these results support that interindividual variability in the level of positive treatment expectations arising from positive drug-related information prior to treatment explains variability in perceived treatment efficacy assessed after treatment, which is remarkable herein given overall rather highly positive pre-treatment expectations in this placebo group. Even within such an "optimistic" group, inter-individual variability in the extent of positive expectations contributed to treatment satisfaction, most strongly after pain relief, where more than 50% of the variability in perceived efficacy could be explained in our models, which were robust to outliers. It will be intriguing to learn from much-needed prospective clinical work about the impact of the presumably much greater variability in pre-treatment expectations in clinical patients, ranging from very positive to very negative, and hence including not only positive (placebo) but also negative (nocebo) effects on perceived treatment efficacy.

Interestingly, treatment expectations were unable to explain variability in perceived distension-induced pain intensity during the pain phase. For the pain relief phase, on the other hand, a significant model emerged, with treatment expectations explaining 52% of the variance in perceived distension intensity. While this finding would indicate that pre-treatment expectations shape the experience of visceral stimuli when intensity is distinctly reduced, caution in this interpretation is warranted given that the model was not robust to consideration of outliers.

Based on our findings, we speculate that positive expectancy effects may be facilitated by the experience of pain relief, which would be consistent with recently growing appreciation of reward mechanisms in placebo effects (32). It is also conceivable that the experience of pain relief engages cognitive mechanisms integrating predictions with perceptions (33), which may interact with psychological states and traits relevant to gastrointestinal symptoms (34). The unique perceptual characteristics and emotional properties of aversive visceral signals, especially their diffuse and threatening nature (35–38), call for dedicated mechanistic work in the visceral domain, to clarify if our findings in a small sample of healthy individuals are replicable and generalize to patient populations. Indeed, visceral pain-related expectancy effects are of particular relevance to the treatment of patients with disturbed gut-brain interactions like IBS who commonly experience fluctuating symptoms, and rarely achieve immediate symptom relief with available treatment options. Especially in these patient groups is it likely that treatment expectations dynamically change over time, and are influenced by treatment experiences, including prior treatment successes and failures. At the same time, patients with disorders of gut-brain interactions benefit from psychological treatment approaches (39), which could be further informed by knowledge derived from placebo research to elucidate predictors of treatment satisfaction (40). While our comparatively short experimental paradigm captured the experience of pain relief, we did not model fluctuating symptoms or analyze dynamic changes in pain. Further, we did not have control groups to assess order effects (i.e., herein the pain relief phase was always preceded by the pain phase) or carry-over effects involving learning/experience across or within treatment phases. Indeed, treatment outcome appears to be shaped by expectations arising from prior treatment history. Such "carry-over" or generalization effects have been elegantly shown for nocebo effects in experimental somatic pain (41, 42). While our statistical models for the relief phase did include appropriate covariates (i.e., intensity and/or efficacy of the pain phase), ideally future experimental paradigms would include placebo groups and conditions with and without the experience of pain relief, as well as nocebo groups with and without the experience of pain increase. Clearly, the clinical treatment reality is much more complex and difficult to model in the laboratory in all its facets and intricate interactions. Dedicated translational studies within and beyond the visceral domain are needed to elucidate specific factors, especially the temporal dynamics of changes in positive and negative treatment

expectations, symptom experience, and perceived treatment efficacy, as previously suggested (reviewed in Ref. 1).

Our experimental findings in acute visceral pain match observations from clinical trials and longitudinal studies in the broader field of acute (43, 44) and chronic pain (45, 46), which underscore the relevance of pre-treatment expectations for clinical and patient-reported outcomes, including overall treatment efficacy (47). For instance, in a large multicentre, observational study of a multidisciplinary treatment for chronic pain, Cormier et al. (48) demonstrated the impact of treatment expectations on clinical outcomes (e.g., pain intensity, depressive symptoms, pain catastrophizing). Interestingly, this association was mediated by the patients' global impression of change, pointing to treatment efficacy as multifactorial construct, which might be insufficiently explained by mere pain intensity and the relevance of semi-subjective, patient-reported outcomes. Furthermore, in a meta-analysis Vase et al. (16) demonstrated that approximations of treatment expectations in clinical trials (based on the number of interactions with healthcare professionals and knowledge of an opioid rather than a non-opioid drug as the active comparator) significantly predicted the placebo response in analgesic randomized controlled trials, pointing to the importance of expectations in clinical trials. While patient-reported outcomes are now more frequently implemented in clinical trials (49), standardized assessments of pre-treatment expectations are often still missing (50). This seems even more important considering that–in contrast to this study design–negative expectations toward an active treatment or intervention might even hamper treatment efficacy (42, 51) or lead to adverse events (52). Therefore, future clinical trials should address the relevance of expectations on their outcomes by using standardized tools available [e.g., TEX-Q (53)].

In conclusion, our data from an experimental translational placebo intervention in visceral pain support that pre-treatment expectations shape reported post-treatment medication efficacy. The experience of pain relief may facilitate perceived medication efficacy and by inference treatment satisfaction. Hence, individuals with highly positive expectations may benefit more from a noticeable symptom improvement, and future studies are needed to determine whether the immediate experience of symptoms within a given psychosocial treatment context may dynamically change perceptions about treatment in order to inform and inspire translational studies addressing implications for treatment satisfaction, compliance and adherence in patients with prolonged or spontaneously recurring pain. After all, it has most recently been concluded that "... the patient-physician relationship's quality is the principal driver of gastroenterology patients' satisfaction with their care" (54). Enhancing awareness of and knowledge about expectancy effects and their determinants in the context of the gut-brain axis hence holds much promise to further improve the care of the large group of patients with disturbed gut-brain interactions, like IBS, consistent with the vision to maximize positive and minimize negative expectancy effects to the benefit of our patients (55).

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 Essen University Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NT, LR, and AI acquired data. SE, SB, and NT designed the study and acquired funding. NT, SB, AI, and JK-B analyzed the data. SB, JK-B, and SE wrote the first draft of the manuscript. All authors contributed to the interpretation of the data, revised the manuscript for critical content, and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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Conditioning to Enhance the Effects of Repetitive Transcranial Magnetic Stimulation on Experimental Pain in Healthy Volunteers

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Objective: In this proof-of-concept study we sought to explore whether the combination of conditioning procedure based on a surreptitious reduction of a noxious stimulus (SRPS) could enhance rTMS hypoalgesic effects [i.e., increase heat pain threshold (HPT)] and augment intervention expectations in a healthy population.

Methods: Forty-two healthy volunteers (19–35 years old) were enrolled in a randomized crossover-controlled study and were assigned to one of two groups: (1) SRPS and (2) No SRPS. Each participant received two consecutive sessions of active or sham rTMS over the M1 area of the right hand on two visits (1) active, (2) sham rTMS separated by at least one-week interval. HPT and the temperature needed to elicit moderate heat pain were measured before and after each rTMS intervention on the right forearm. In the SRPS group, conditioning consisted of deliberately decreasing thermode temperature by 3°C following intervention before reassessing HPT, while thermode temperature was held constant in the No SRPS group. Intervention expectations were measured before each rTMS session.

Results: SRPS conditioning procedure did not enhance hypoalgesic effects of rTMS intervention, neither did it modify intervention expectations. Baseline increases in HPT were found on the subsequent intervention session, suggesting variability of this measure over time, habituation or a possible "novelty effect."

Conclusion: Using a SRPS procedure in healthy volunteers did not enhance rTMS modulating effects on experimental pain sensation (i.e., HPT). Future studies are therefore needed to come up with a conditioning procedure which allows significant enhancement of rTMS pain modulating effects in healthy volunteers.

Keywords: transcranial magnetic stimulation, therapeutics, placebo effect, conditioning, psychological, pain, hypoalgesia

INTRODUCTION

Chronic pain is often characterized by the presence of abnormal sensory perception (1–3), manifested among others by decreased pain thresholds when they are measured by quantitative sensory testing (QST) methods (4, 5). QST is considered a valuable tool to assess the function of the somatosensory system, being useful not only to characterize pain conditions but also to evaluate treatment responses in clinical and healthy populations (4–7). In addition, post-intervention QST changes among healthy individuals have also proved to be useful in characterizing physiological pathways as well as discerning potential mechanisms of action (4, 7, 8), therefore *"bridging the gap"* between the identification of novel intervention strategies and the optimization of their efficacy (9, 10).

High frequency repeated transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique that was shown effective in increasing pain thresholds and inducing analgesia in different clinical populations, especially when applied over the primary motor cortex (M1) (11–14). Although the mechanisms underlying rTMS sensory modulating effects are not fully elucidated, they are thought to rely on the local activation of top-down processes in addition to involving widespread endogenous pain modulatory systems (15–18).

In that way, increases in thermal pain thresholds derived from QST measures were found following M1 rTMS relative to a sham intervention (19–25). However, results from sham-controlled studies are rather inconsistent and heterogeneous, with a high variability in treatment effects across the literature (14, 25, 26). One possibility to explain discrepancies among study results is the documented variable response to TMS techniques, participants often being categorized as responders and non-responders (27, 28). While it is possible that TMS responsiveness relies on connectivity and excitability patterns (29, 30), action mechanisms are not fully understood, especially in the pain field. Therefore, the understanding and investigation of strategies aiming to enhance rTMS analgesic effects are clinically relevant, as it could potentiate rTMS therapy success.

Like any other pain treatment, the sensory modulating effects of rTMS are thought to be due to the treatment itself combined with other non-specific effects, including placebo or expectations of the therapy being effective (31, 32). Indeed, the improvement of pain treatment therapies by increasing placebo effects has raised recent interest among the pain research community (33–35). Different methods have been suggested to enhance placebo effects, such as shaping and adapting information about analgesic treatments and/or associating the treatment with a positive context or response (36). While verbal suggestions are an easily implementable way to improve analgesic responses, it has been shown that prior positive therapeutic experiences could have more robust effects and better predict placebo response than verbal expectation ratings (37–39). One way to achieve such positive experience is to use conditioning paradigms, where medically connoted procedures (conditioned stimulus) are coupled to a pain stimulus (unconditioned stimulus), in which the intensity is surreptitiously reduced from baseline levels (40–42). Indeed, previous studies suggest that conditioning procedures can lead to longer-lasting effects and more significant placebo hypoalgesia when compared to methods such as verbal suggestion (40, 43, 44).

Here, we tested whether the rTMS hypoalgesic response could be enhanced by the use of a conditioning paradigm based on a surreptitious reduction of a noxious stimulus (abbreviated as SRPS by our team) induced with heat. We therefore conducted a proof-of-concept study using SRPS to modulate heat pain thresholds among healthy individuals, who were enrolled in a two-visit, twice-daily session rTMS protocol using parameters proven effective to increase thermal pain thresholds (23). In this protocol, active rTMS and sham interventions served as the conditioned stimulus and were coupled to experimental heat pain (i.e., unconditioned stimulus), in which the intensity was surreptitiously reduced or maintained depending on group assignment. Secondarily, we assessed if perceived expectations of intervention success could contribute to the hypoalgesic effects of rTMS and/or conditioning.

MATERIALS AND METHODS

The study was conducted in accordance with the Helsinki Declaration and approved by the Research Ethics Committee of the CIUSSS du Nord-de-l'Île-de-Montréal in Canada (Approval number: 2018-1525). All participants provided written informed consent and received monetary compensation.

Participants

Forty-two healthy volunteers were successfully recruited through advertisements placed at the Université de Montréal's campus and in social media, and all procedures were performed in a TMS laboratory located at the Hôpital du Sacré-Coeur de Montréal. Criteria for exclusion were: (1) drug or alcohol abuse, (2) epilepsy, (3) metal implants/coils/electronic devices above the waist, (4) pregnancy, (5) psychiatric disorders, (6) chronic pain, and (7) inability to understand instructions. All subjects were naïve to any form of motor cortex stimulation. Aside from contraceptive pills, no medication or caffeine was allowed on the day of testing. All testing sessions took place in the morning to control for diurnal variations of cortical excitability (45, 46). Participants were told that the study aimed to investigate the effects of rTMS on experimental pain. To further avoid bias, participants were blinded to the nature of the assignment groups (i.e., that there were two types of interventions (active rTMS and sham) and were not initially informed that there was a possible conditioning procedure. Reasons for the latter incomplete disclosure and group assignment were revealed to participants by one investigator (LPB) during a debriefing session conducted after having completed the experimental protocol.

Experimental Design

A randomized crossover-controlled study design was implemented. After their inclusion, participants were randomly assigned to one of two groups: (1) SRPS and (2) No SRPS. In spite of their group allocation, each participant took part in two single-day laboratory visits, one with active rTMS and the other with a sham intervention, separated by at least 1 week

to avoid any potential carry-over effects of the first visit on the other (22, 47, 48). Each visit included two consecutive sessions of rTMS (or sham) spaced 10 min apart (**Figure 1**). Heat pain threshold (HPT) was measured at three different time points, namely before, between and after each rTMS/sham session. Moreover, perceived expectations of intervention success were also assessed before each rTMS/sham session.

Main Outcomes Measures

The main outcome of this study was participants' HPT, which was assessed at three different time points [1—baseline (pre-rTMS/-sham); 2—post-rTMS#1/-sham#1; 3—post-rTMS#2/-sham#2] across groups (SRPS, no SRPS) and intervention types (rTMS or sham). The secondary outcome was perceived expectations of intervention success, assessed prior to and following each intervention in both groups.

Randomization, Concealment, and Blinding

The order of the interventions (rTMS or sham at first or second visit) and the group assignation (SRPS or no SRPS) were randomized and counterbalanced using a computer-based random sequence generation program (https://www.random.org/lists/). The randomization procedure was carried out by an external member of the research group and consisted of 42 sealed, opaque and numbered envelopes that contained information about group assignment and intervention order. When a participant was recruited, another staff member not involved in the study used the randomization list to determine which envelope was assigned to the participant and then forwarded the respective information to the QST experimenter (assignation group) and to the assistant in charge of setting the rTMS parameters (type of intervention), who was different than the TMS operator. Participants and TMS operator were therefore blinded to group assignment and intervention. Only the TMS assistant knew about the intervention administered, adjusting stimulus parameters and coil used (active/sham) accordingly while the TMS operator and participant were outside the room. Moreover, the experimenter in charge of sensory testing and expectation assessments was unaware of the type of intervention. Experimenters were all women, and their role did not vary throughout the study. They also wore a white lab coat and provided scripted neutral instructions.

Questionnaires

On the first visit, participants completed a series of questionnaires to assess sociodemographic and psychosocial characteristics known to potentially interfere with pain sensitivity (49–53), such as the Beck Depression Inventory-II (BDI-II) (54), the State-Trait Anxiety Inventory (STAI) (55), the Pain Catastrophizing Scale (PCS) (56), the Perceived Stress Scale (PSS) (57), and the Pittsburgh Sleep Quality Index (PSQI) (58).

Quantitative Sensory Testing

Heat Pain Threshold

Noxious heat was induced using the Medoc Pathway Pain and Sensory Evaluation System (Medoc TSA 2001-II, Ltd, Israel) operating according to the principles of the Peltier effect with a 3 cm^2 thermode.

At the beginning of each visit, participants were seated in a quiet room held at a constant temperature (22 °C) where they were trained before the formal HPT testing on a different area of the ventral forearm than the one used for the testing, in order to familiarize them with the procedure (unrecorded data). This training was conducted in both visits to ensure accuracy and reproducibility of the tests throughout the experiment. Assessment of the HPT was determined according to the "method of limits" (4).

From a baseline temperature of 32 °C, heat thermal stimulations were applied at 5 cm from the right wrist flexion crease with a linear rate of 1 °C/s. Participants received three successive stimuli of increasing heat with inter-stimulus intervals of 30 s in order to prevent pain habituation or temporal summation of pain. Participants were asked to press on a button when they detected the first perception of pain up to 49 °C, to prevent tissue damage. The average temperature over three trials was calculated for the determination of HPT. Given the nature of the study, we focused our thermal procedures on HPT, which is thought to have better intra- and inter-rater reliability and less variability over time relative to other QST measures, to avoid as much as possible confounding effects of time between visits (59, 60). Moreover, since our SRPS procedure is based on heat, we thought that HTP was the most adequate outcome to assess intervention changes.

Conditioning Procedure Using SRPS

To determine the individualized temperature needed to elicit moderate heat pain, a sequence of successive phasic heat pain stimuli between 41 and 49°C separated by 30s intervals was administered at 10 cm from the right wrist flexion crease (ventral fore arm), with a starting baseline temperature of 32° C, incremental rate of 4° C/s, and a 7 s plateau (61). After each stimulation, participants' pain intensity was evaluated on a 0-100 visual analog scale (VAS: 0 corresponding to "no pain" and 100 to "the worst pain imaginable") in order to find the temperature corresponding to participants' moderate pain intensity. Moderate pain intensity was considered the lowest temperature corresponding to a value of 40–60/100 on the VAS (62). The determined temperature was applied once again after the first intervention in participants assigned to the no SRPS group, while a conditioning manipulation, consisting of deliberately decreasing by 3 °C the determined temperature, was performed with patients assigned to the SRPS group. The conditioning manipulation was carried out to induce a positive experience of hypoalgesia prior to the next intervention. The group without SRPS was exposed to the same temperature prior to the second intervention. To ensure that the 3 °C decrease was sufficient to induce a positive experience of hypoalgesia in the participants, a VAS measurement was performed after exposure to the conditioned (or not) temperature.

rTMS and Sham Intervention

Identification of Simulation Site and Resting Motor Threshold

At the first visit, optimal stimulation site over the left M1 was determined through exploration near the C3 cortical electrode site as per the 10/20 International system of electrode placement

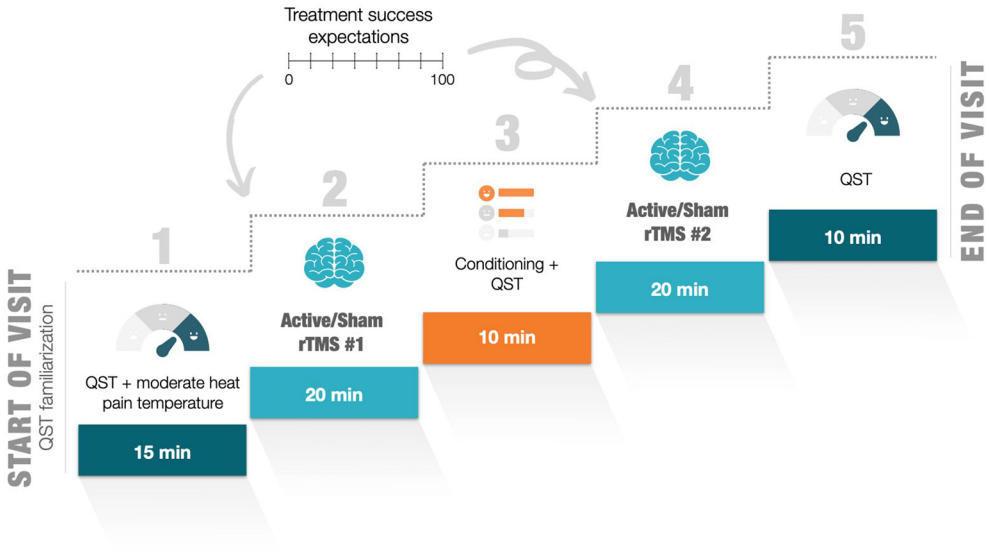

FIGURE 1 | Outline of the experimental procedure for each visit. QST, quantitative sensory testing; rTMS, repetitive transcranial magnetic stimulation; VAS, visual analog scale.

(63). The optimal stimulation position was determined as the stimulation site which elicited the largest and most consistent motor evoked potentials (MEPs) recorded from the contralateral first dorsal interosseous muscle. The "hot-spot" was marked on a swim cap with a dermatograph pencil to allow accurate repositioning of the coil between intervention and throughout the whole experiment. The angle of inclination of the coil was determined using a level and the distance between the bathing cap and the nasion and between the bathing cap and each earlobe were also measured. The resting motor threshold (rMT) was defined as the lowest stimulator output needed to induce a MEP of >50 μV peak-to-peak amplitude in at least 6/10 consecutive trials (64). Once the rMT was determined, the experimenter in charge of the rTMS administration and the participant left the rTMS room while waiting for the TMS assistant to set stimulation modalities and coil used, the sham coil being visually identical and emitting similar sounds during stimulation than the active coil. Prior to each intervention session, participants' expectations of intervention success were measured given that it could influence intervention response (65, 66). Thus, participants were asked: "How useful do you think non-invasive stimulation techniques such as rTMS can be in reducing pain?" and instructed to respond with a 0–100 VAS scale (i.e., 0 corresponding to "these techniques are not useful" and 100 to "these techniques are very useful").

Intervention Protocol

The rTMS treatment consisted of a series of 20 trains of 6 s duration (54 s intertrain interval) at a stimulation rate of 10 Hz and at an intensity corresponding to 80% of the rMT (1,200 total pulses) (11, 25). rTMS was applied over the left M1 using the Magstim Double 70 mm AirFilm® Coil (Magstim, Whitland, Wales, UK). The TMS coil was positioned tangentially to the head at a 45° angle to induce a posterior-anterior current flow (12). The coil was centered and fixed directly over the stimulus site using a tripod so that the coil handle pointed to the back. Sham treatment was applied using the same procedure with the Magstim AirFilm® SHAM coil (Magstim, Whitland, Wales, UK).

Debriefing

At the end of the study, a debriefing session was conducted with participants to reveal the true nature of the study. Then, participants were asked to guess their assignment group and the order they received the sham or rTMS (first or second visit). Afterwards, the group assignment and intervention order were revealed to participants by the investigator (LPB). Participants completed a new consent form to obtain their agreement to retain their data.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics software version 25 (Armonk, NY, United States). A Shapiro-Wilks test was used to ensure that HPT measures and expectations data were normally distributed. Parametric tests were performed with a statistical significance set as $P \leq 0.05$. Descriptive analyses were also used to characterize and compare all groups on various demographic data. Results are expressed as means, standard deviation (SD) and percentages. Independent-sample Student's *t*-tests were performed for continuous socio-demographic data (i.e., the questionnaires) and Chi-squared tests were used for nominal data such as the sex and the blinding efficacy measure. In order to assess our main objective, a three-way mixed analysis of variance (ANOVA) was conducted to examine the effects of different interventions (rTMS vs. sham), *time points* (baseline, post-rTMS/-sham#1, post-rTMS/-sham#2),

and *groups* (SRPS vs. no SRPS) on the modulation of HPT. Secondarily, a three-way mixed ANOVA was also computed to evaluate the effects of groups (SRPS vs. no SRPS) and times points (baseline, post-rTMS/-sham#1) and interventions (rTMS vs. sham) on expectations of intervention success. Greenhouse-Geisser corrections were used for the two ANOVAs. If a significant interaction was obtained, we conducted *post-hoc* analyses and corrected for multiple comparisons using the Bonferroni test by adjusting the *p*-value according to the number of comparisons ($p = 0.017$). Main effects were interpreted only if interactions were not significant. Partial eta squared (η_p^2) are reported. Lastly, to ensure the effectiveness of our conditioning procedure, we calculated the difference on the VAS measure between pre-post conditioning measurement and then, two independent-sample Student's *t*-tests were computed, one for each intervention (rTMS, sham), to determine if there were differences in the VAS between the groups (SRPS, no SRPS).

As this study was a proof-of-concept in nature, no power calculation was carried out a priori. However, our sample size is comparable to other studies with similar objectives that were deemed to be adequately powered (24, 25).

RESULTS

Demographic Information

Forty-two healthy participants were recruited for this proof-of-concept study. Of those, one participant was excluded due to severe depression symptoms as revealed with the Beck Depression Inventory scale, for a final data set of 41 right-handed healthy adults (20 females, 23.98 ± 3.16 years). Included participants were divided into two groups: SRPS group ($n = 21$; 10 females) and no SRPS group (n = 20; 10 females). Demographic information can be found in **Table 1**. Student's t-tests revealed no significant differences between groups ($p > 0.05$) on socio-demographic data except for perceived sleep quality during the last month ($p = 0.035$). However, this difference was considered anecdotal and not clinically significant given its low magnitude, the nature of the study population and the debated cut-off score for sleep disturbance using the PSQI in non-clinical samples (67).

Fluctuations in Heat Pain Threshold

There was no significant interaction between the three factors (groups, intervention and time) for the HPT measure, $F_{(1.837,39)} = 1.127$, $p = 0.33$, $\eta_p^2 = 0.028$ (see **Figure 2**). In addition, none of the two-way interactions were significant. However, we found a significant main effect of time, $F_{(1.781,39)} = 5.493$, $p = 0.008$, $\eta_p^2 = 0.123$. *Post-hoc* multiple comparisons analyses showed that HPT measures significantly differed between baseline and post-rTMS/-sham#2 time points ($p = 0.005$), while other comparisons (baseline vs. post-rTMS/-sham#1, $p = 0.051$; post-rTMS/-sham#1 vs. post-rTMS/-sham#2, $p = 0.149$) did not reach statistical significance. Descriptive statistics suggest that participants, regardless of the group or intervention received, tended to show an increase in HPT from baseline ($M = 43.298 \pm 2.953$) to post-rTMS/-sham#2 ($M = 44.008 \pm 3.124$) measures.

TABLE 1 | Demographic and clinical characteristics of the study sample.

Variables	SRPS (*n = 21*)	No SRPS (*n = 20*)	*p*
Sex (male/female)	11/10	10/10	0.883
Age (years)	23.76 (2.68)	24.20 (3.67)	0.664
Education (years)	16.00 (2.98)	16.10 (2.83)	0.913
Body mass index	23.39 (3.35)	24.19 (3.17)	0.431
Beck depression inventory (BDI-II)	3.76 (4.39)	4.15 (3.25)	0.750
Trait-anxiety (STAI-T)	33.29 (6.51)	35.20 (9.48)	0.454
State-anxiety (STA-T)	29.76 (5.33)	31.05 (6.23)	0.480
Pain catastrophization scale (PSC)	13.14 (7.74)	12.00 (8.07)	0.646
Perceived Stress Scale (PSS)	10.86 (5.40)	12.35 (7.37)	0.462
Pittsburgh Sleep Quality Index (PSQI)	3.67 (2.06)	5.20 (2.44)	0.035*
rMT—rTMS visit	64.43 (11.91)	66.70 (13.25)	0.567
rMT—sham visit	63.71 (14.04)	65.70 (12.15)	0.632

Values are given as the mean (SD) or frequency (N = 41).
rTMS, repetitive transcranial magnetic stimulation; rMT, resting motor threshold; SD, standard deviation; SRPS, surreptitious reduction of pain stimulus.

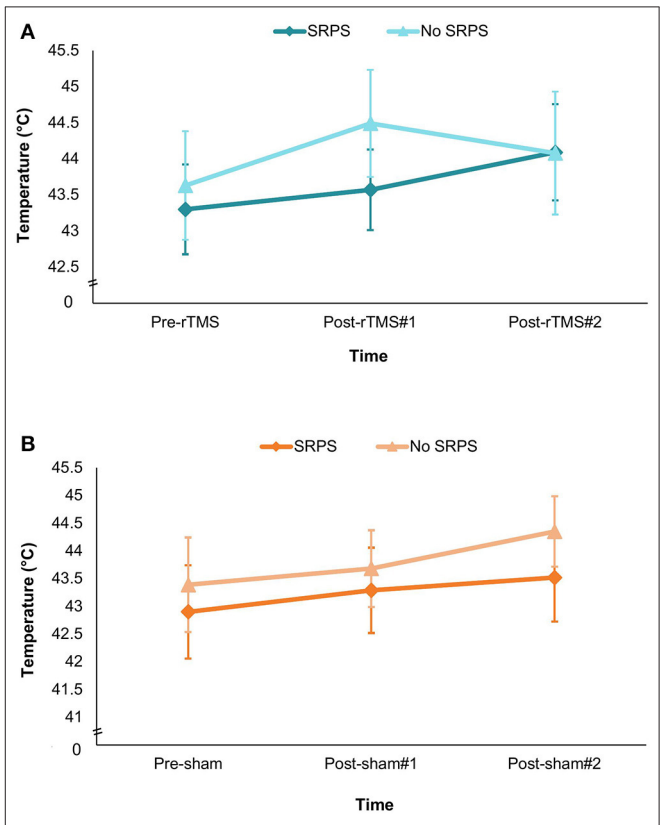

FIGURE 2 | Graph depicting fluctuations in heat pain threshold (mean T°C) according to group × time (pre-interventions, between interventions and post-interventions) × SRPS exposition. **(A)** rTMS visit. **(B)** Sham visit. Results are expressed as means and standard errors (SEM). HPT, heat pain threshold; SRPS, surreptitious reduction of pain stimulus.

We also computed a paired-sample t-test to assess between-visit baseline HPT measure changes regardless of conditioning

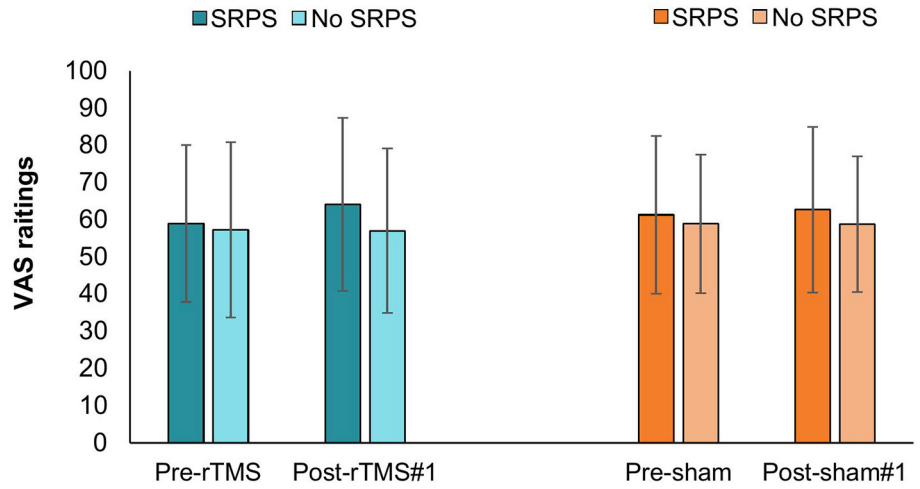

FIGURE 3 | Fluctuations in VAS expectation ratings according to time × SRPS exposition during rTMS and sham visit. rTMS, repetitive transcranial magnetic stimulation; SRPS, surreptitious reduction of pain stimulus; VAS, visual analog scale.

groups. We found a statistically significant between-visit HPT measure difference at baseline $t_{(40)} = -4.299$, $p < 0.001$. Descriptive statistics showed that on average, HPT threshold had increased by 2.0 °C at the second visit ($M = 44.30 \pm 2.71$) relative to the first visit ($M = 42.30 \pm 3.82$) (95% CI, −2.950 to −1.063) highlighting a higher baseline heat pain threshold at the second visit.

Expectations

The Groups*Time*Interventions on expectations was not statistically significant $F_{[1,38]} = 1.269$, $p = 0.27$, $\eta_p^2 = 0.032$. Likewise, two-way interactions were not statistically significant, and no main effect was observed ($p > 0.05$) (see **Figure 3**).

Positive Analgesic Experience Induction

The data distribution of the VAS values measured before the conditioning procedure respects the normality criteria proposed by Curran et al. (68) so that no data transformation had to be performed. Student's t-test showed that the conditioning procedure significantly reduced pain perception derived from the VAS measure relative to the no SRPS group, whether participants underwent the active rTMS intervention [$t_{(39)} = -6.794$, $p \leq 0.001$] or the sham intervention [$t_{(39)} = -4.371$, $p \leq 0.001$], indicating that decreasing by 3 °C the thermode temperature was sufficient to induce a detectable change in temperature perception (see **Figure 4**).

Blinding Efficacy

While 20 participants (48.78%) correctly identified group assignation, 6 participants (14.63%) guessed it wrong, and 15 participants (36.59%) were unable to provide an answer. A Chi-square test revealed that these results were not statistically different ($\chi^2 = 4.512$, $p = 0.11$) across conditioning groups. Regarding the intervention order identification, 14 participants (34.15%) correctly distinguished the intervention order, 5 participants (12.19%) guessed it wrong, and 22 participants (53.66%) were not confident about the intervention order. The Chi-square test showed no significant difference between groups (χ^2 =3.476, $p = 0.18$), suggesting a successful participant blinding.

Adverse Effects

A significant between-group difference ($\chi^2 = 9.466$, $p = 0.009$) was found regarding adverse effects. While no participants in the no SRPS group reported any adverse effect during or following the interventions, 1 participant reported a mild and transient headache. Moreover, 33.33% ($n = 7$) participants in the SRPS group reported tingling sensations during the active rTMS intervention. No adverse effects were reported for the QST procedure.

DISCUSSION

The results of this study indicate that combining a SRPS conditioning paradigm to rTMS did not significantly enhance analgesic response to noxious heat over the forearm nor intervention expectations among healthy individuals when compared to those not receiving conditioning. Moreover, prior exposure to HPT equivalently increased post-intervention HPT across conditioning or intervention types. Similarly, in spite of experimental condition blinding, we observed a modest increase in baseline HPT between Visit 1 and Visit 2, which may reflect normal variability of HPT over time as pointed out in other studies (69, 70), but also a possible "novelty effect" on Visit 1.

The induction of placebo effects could represent a low-risk and cost-effective strategy in order to potentiate treatment response to pain stimuli and an important bulk of research has been building over the years in this regard (71). Placebo effects are complex phenomena involving several brain networks and psychophysiological mechanisms, such as the endogenous opioid, endocannabinoid, oxytocin, vasopressin, and dopamine systems (31, 72). Studies have suggested the involvement of several action mechanisms based on different theories and

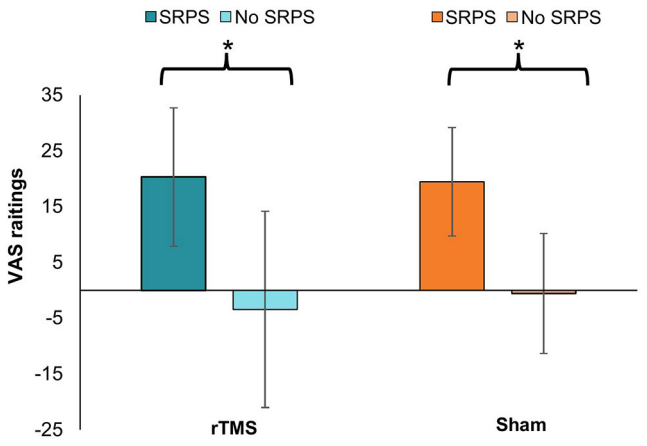

FIGURE 4 | Differences from baseline VAS pain ratings according to SRPS exposure during rTMS and sham visit. rTMS, repetitive transcranial magnetic stimulation; SRPS, surreptitious reduction of pain stimulus; VAS, visual analog scale. The * indicates the difference between the groups ($p \leq 0.001$).

models, such as conditioning and expectancy, which could be potentially manipulated to optimize therapeutic approaches and ultimately outcomes (33, 36, 73). For instance, it has been shown that improving patients' preoperative expectations and placebo effects was associated with fewer days of hospitalization and better long-term outcomes in patients undergoing cardiac surgery (74, 75) and reduced opioid intake after spine surgery (76). Moreover, a meta-analysis including 27 studies revealed medium to large effects of verbal suggestion, conditioning (paired with verbal suggestion), and mental imagery on experimental and acute procedural pain and small effects on chronic pain (77). In parallel, studies have shown that experimental manipulations aiming to pre-conditioning individuals with effective analgesic treatments, such as reducing the intensity of painful stimulation surreptitiously in order to make the subjects believe that analgesic treatments are effective, can induce a previous positive experience to the treatments and consequently improve placebo analgesia (37, 39, 61). This type of pre-conditioning is typically performed with topical analgesic interventions such as creams, ointments, injections, acupuncture, and oral pharmacologically (39, 43, 44, 78, 79), which are often more "accessible," and thus individuals are expected to have prior experience with them. In contrast, prior exposure to rTMS intervention is very unlikely due to its limited accessibility, such that associated placebo effects and its possible manipulation to enhance analgesic experiences are less understood (80).

Treatment effects of active rTMS interventions are frequently compared to "sham" procedures, where an inactive coil with limited power, usually identical in aspect and producing similar noises than the active coil is used. The analgesic response to rTMS is heterogeneous across studies, especially when compared to sham stimulation (12–14). For example, a study showed that the effectiveness of a HF-rTMS protocol was easier to demonstrate against other active stimulation method than against a sham treatment (81). This has been partially attributed to the quality of the studies, including low sample sizes, lack of adequate randomization, and lack or poor blinding (12).

Growing awareness and media attention for non-invasive brain stimulation techniques and sophistication of setups and equipment, including sham coils, have been proposed as possible explanations (80). Additionally, another study revealed that the amount of placebo analgesia observed in a sham rTMS session depended on the success of a previous active rTMS response in neuropathic pain patients (82). In that study, there was no significant difference between the effects of the active and sham rTMS when the latter was applied after a successful rTMS session (82). Simply put, sham rTMS sessions induced significant analgesia (comparable to active rTMS) when they followed a successful rTMS rather than an unsuccessful rTMS, which could at least in part be the result of unconscious conditioned learning. The authors went on to discuss the importance of the timing of placebo relative to active interventions in rTMS studies for pain relief (82).

In the present study, we did not observe a significant intervention effect between SRPS and no SRPS groups (**Figure 2**). Moreover, the interaction between intervention (active/sham), time (baseline, between, and post measures) and group (SRPS/no SRPS) on HPT was not significant. A possible explanation might be related to our conditioning procedure. Previous literature has shown that expectations play an important role in the placebo response in experimental pain models and clinical populations (32, 35, 83). In our study, although the conditioning procedure was successful in inducing a positive analgesic experience (**Figure 4**), it did not seem to modulate participants' expectations (**Figure 3**) (84). We decided to use VAS 40/100 as a threshold of moderate or significant pain (i.e., minimal level of pain affecting performance in daily living) based on previous literature (62, 84), prior pilot data (unpublished), and also ethical issues (e.g., avoid severe levels of pain and/or disturbance). However, it is possible that higher VAS (e.g., 60/100) could have facilitated the perception of decreased pain after lowering thermode temperature in the SRPS group, thereby accentuating the placebo effect (37, 85). Whereas previous studies using SRPS performed a decrease of 2° C from the pain-inducing temperature (86), we decided to decrease pain-inducing temperature by 3 °C so as to make the SRPS more noticeable, yet believable. Nonetheless, some of our SRPS participants (n=2) did not experience any analgesic response after the conditioning, suggesting a possible nocebo effect after the first intervention (active or sham) due to anxiety for example, or a lack of understanding of the study instructions. Although speculative, one may question whether decreasing thermode temperature by a few more degrees could have modulated intervention response. Although future research is warranted, it is also plausible that combining conditioning and explicit verbal suggestions could have induced larger placebo effects (77).

Other possible explanation for the lack of difference between active and sham interventions could be related to the rTMS protocol modalities, including targeted location, frequency, intensity and number of sessions. It is recognized that high frequency stimulations over M1 present more consistent and analgesic effects when compared to other locations. However, stimulations over other locations such as the dorsolateral prefrontal cortex (DLPFC) have also shown analgesic properties in experimental and clinical pain (11, 87). Indeed, a single

session study with similar rTMS parameters and design to the present study showed that active rTMS over both M1 and DLPFC similarly increased thermal pain thresholds (heat and cold) among healthy volunteers, suggesting comparable effects of DLPFC and M1 when compared to sham (24). In addition, there is also evidence showing analgesic and sensory modulatory effects of rTMS when applied to the primary or secondary somatosensory cortex (S1 and S2 respectively) (88, 89). In fact, one study favored rTMS stimulations over S2 relative to M1, DLPFC and sham in order to increase heat pain thresholds (90). However, locating optimal stimulation site over S2 depends on neuroimaging and neuronavigation methods, which complicates their implementation. Other important parameters of stimulation are frequency and intensity. Importantly, a study including 65 healthy participants undergoing QST pre- and post-rTMS stimulations (1Hz 80% resting motor threshold [Rmt], 1Hz 100%rMT, 10Hz 80%rMT, 10Hz 100%rMT, 50Hz triplets at 90% of active motor threshold) and sham over M1, revealed that protocols with higher frequencies had increased modulatory effects across several QST measures (23), which supports the use of our protocol. However, no main effects for TMS device parameters nor significant interaction effects were found for on HPT, which is similar to the results in our study. Moreover, effects of rTMS on QST measures were relatively small and variable across all rTMS conditions, suggesting that rTMS analgesic effects using laboratory-induced pain among healthy individuals may be difficult to discern. A possible reason is the presence of a ceiling effect, given that the somatosensory system of healthy individuals is thought to be normal and there is a limit for its enhancement, contrary to chronic pain patients where dysfunction and maladaptive networks can provide a more extensive range of modulation (i.e., chronic pain patients typically exhibit much lower HPT than healthy controls) (25).

In addition, it is known that a higher number of rTMS sessions usually yield larger analgesic effects (11, 13, 91, 92). Yet, one and two sessions involving similar rTMS protocols than the one used in the present study have been found to increase pain thresholds in healthy volunteers (25). One cannot exclude the possibility that additional rTMS sessions and perhaps conditioning sessions (i.e., increase of conditioning strength) could have resulted in larger increases in heat pain thresholds.

An important issue that was also observed in a recently published transcranial direct current stimulation (tDCS) study (69) was the high variability in baseline HPT from one visit to the other. In our study, we considered the potential confounding effects of several variables documented to influence the somatosensory system at baseline such as anxiety, depression, sleep, perceived stress, pain catastrophizing, and limited others at both visits such as medication and caffeine intake, circadian effects on QST and cortical excitability by performing both visits at the same time. We nonetheless observed a significant difference between baseline HPT values from visit 1 to visit 2 across both groups, as heat pain thresholds at baseline in visit 2 were considerably higher than at visit 1 regardless of intervention order, which might have limited potential intervention-related improvement at visit 2. As noted by Kold and Graven-Nielsen (69), it is possible that the decreased heat sensitivity at the second visit could be due to some kind of habituation to the sensory testing, and perhaps to the intervention. As participants previously been exposed several times to rTMS and QST during the prior visit, the novelty and salience could have decreased, which may have increased mind wandering, reduce attention and thus decrease sensory experience (93). Importantly, this did not appear to be influenced by an unsuccessful blinding, as most of the patients did not distinguish effectively between active or sham interventions.

Although this study presents with important methodological strengths, it is not without limitations. Firstly, the sample size may not have been sufficient to detect significant effects by groups and types of intervention. Secondly, the use of a cross-over design to assess intervention effects on measures from one visit to the other is susceptible to the possible variability of HPT over time [Wasner (70), #2996], making challenging to interpret the true effect of the treatment. While HPT are thought to be a reliable measure (59), longitudinal studies using repeated measures across more days may provide better understanding of QST day-to-day variability. Furthermore, cross-over designs usually carry learning effects that are difficult to control, which may have consequently confounded the results of sequential trials (94). Thirdly, this study was designed to serve as a proof-of-concept and it is based on experimental pain, which is used as a proxy for clinical pain. However, comparisons between experimental pain and clinical are often inconclusive, to say the least (95). Indeed, both rTMS analgesic responses and placebo analgesic effects have been shown to be higher among chronic pain populations (25, 96), which raises the possibility that replicating this study with clinical populations may yield different results. Investigating the determinants of rTMS analgesic response is an exciting research avenue that could benefit from the understanding and optimization of placebo effects.

CONCLUSION

In conclusion, these results showed that the combination of a conditioning paradigm with rTMS was not effective to increase the analgesic response to experimental heat pain nor to enhance expectations with two sessions of rTMS among healthy individuals. Although the findings of this study were not significant, the observed results are still relevant to the TMS and placebo literature, as they are indicative of the challenges that this area of research may entail among experimental pain models with healthy participants. However, considering that chronic pain populations might present higher expectations for treatment efficacy and be more sensitive to conditioning and placebo effects, the use of conditioning to raise expectations and rTMS response deserves to be investigated further in chronic pain patients.

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 Hospital Sacre-Coeur of Montreal. The participants

provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LP-B, AH, CA, and LD contributed to conception and design of the study. LP-B and AH organized the database and wrote the first draft of the manuscript. LP-B, SB, and LD performed the statistical analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

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Do individual psychological characteristics predict induction and generalization of nocebo and placebo effects on pain and itch?

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Background: Nocebo and placebo effects, i.e., adverse or beneficial treatment effects, respectively, putatively due to expectancies can modulate pain and itch. These effects can generalize within the pain or itch modality. Predicting the induction and generalization of these effects can be helpful in clinical practice. This study aims to investigate whether psychological characteristics related to the fear-avoidance model predict the induction and generalization of nocebo and placebo effects on pain and itch in young healthy participants.

Methods: Data from two previous experiments were analyzed. In Experiment 1, we induced nocebo and placebo effects on heat pain and tested generalization to pressure pain and to cowhage-evoked itch (n = 33 in a nocebo group, n = 32 in a placebo group). In Experiment 2, we induced nocebo effects on cowhage-evoked itch and tested generalization to mechanical itch and to mechanical touch (n = 44). Potential predictors were anxiety- and stress symptoms, attention to pain/itch, and pain/itch catastrophizing. Multiple regression analyses were performed.

Results: For nocebo effects, none of the individual psychological characteristics significantly predicted induction of nocebo effects nor their generalization. For placebo effects, only less stress symptoms, lower attention to pain, and higher pain catastrophizing weakly predicted a stronger generalization of placebo effects from heat pain to pressure pain.

Conclusion: The tested psychological characteristics may not play an important role in the induction and generalization of nocebo and placebo effects in healthy individuals. However, firm conclusions cannot be drawn with the current sample. Future studies should validate findings in larger and more diverse samples.

KEYWORDS

predictors, nocebo effects, placebo effects, pain, itch, pruritus, generalization

Introduction

Placebo effects and nocebo effects, the beneficial and adverse treatment outcomes that cannot be ascribed to active treatments ingredients, respectively, can decrease and increase symptoms like pain and itch (1–3) by expectancy mechanisms. Expectancies can be effectively shaped by verbal suggestion (*via* providing explicit information) and classical conditioning (*via* repeatedly pairing a neutral stimulus with an unconditioned stimulus that naturally evokes a specific response) (2, 3). Recently, placebo and nocebo effects were found to generalize within the pain and itch modalities (4–6). This phenomenon is called response generalization, where similar placebo/nocebo effects can be found on perception of a novel stimulus that is different from the original stimulus for which placebo/nocebo effects were evoked (7). For instance, patients who experienced negative treatment outcomes may be prone to experience also similar negative treatment outcomes for similar symptoms, presumably mediated by expectancies. The susceptibility to placebo and nocebo effects as well as their generalization varies across individuals (8), making it difficult to harness them in clinical settings. It can be valuable to identify those individuals who are more sensitive to induction and generalization of placebo and nocebo effects.

Although mixed, evidence has shown that psychological characteristics related to the fear-avoidance model such as affective factors (including anxiety- and stress symptoms) and cognitive factors (including attention and catastrophizing) may be associated with placebo and nocebo effects on pain (1, 9–14), So far, most of what we know about the findings of predictors comes from the study of these effects on pain (11, 13–15). Only few studies explored the role of predictors in induction of placebo and nocebo effects on itch (12). Given the history of inconsistent findings on the predictors for placebo/nocebo effects and the paucity of studies on predicting these effects on itch, it is important to extend the current understanding of the relations between cognitive-affective factors and placebo/nocebo effects.

Cognitive-affective factors beyond expectancies may also influence generalization of placebo/nocebo effects from one symptom to similar symptoms. This is indirectly supported by research into fear generalization because of closely overlapping experimental procedures used when examining classical conditioning and generalization of (pain-related) fear and of placebo and nocebo effects (16, 17). Specifically, pain-related fear may arise as a by-product of the procedure of pain-related conditioning in placebo/nocebo effects, and one recent experimental study showed that pain-related fear can contribute to nocebo hyperalgesia (18). Therefore, it is reasonable to assume that the factors that influence fear generalization such as affect (e.g., anxiety- and stress symptoms) (19, 20) and cognitions (e.g., attention) (21), may also be associated with generalization of placebo/nocebo effects. However, no studies have explored predictors for generalization of placebo and nocebo effects on somatosensory sensations yet. Understanding whether and how psychological characteristics are involved in the induction and generalization of placebo/nocebo effects could be clinically relevant to foster the efficacy of positive treatment outcomes and minimize the severity of negative treatment outcomes within or across symptoms.

Our aims were to explore whether psychological characteristics can predict the induction and generalization of placebo and nocebo effects on somatosensory sensations in young healthy participants. Specifically, we explore if anxiety- and stress symptoms, as well as attention, and catastrophizing can predict (1) induction and generalization of nocebo effects (primary objective), (2) induction and generalization of placebo effects (secondary objective), (3) expected nocebo and placebo effects as well as generalization (exploratory objective). Given indirect support from the fear-avoidance model (22, 23), we would expect that these cognitive-affective factors may positively predict nocebo effects (and generalization) and negatively predict placebo effects (and generalization). To this end, in two different experiments [from which the findings on nocebo and placebo effects have been published in separate articles (4, 24)] we first measured individual psychological characteristics with self-report questionnaires. In the first experiment, we consecutively induced nocebo and placebo effects on heat pain and tested generalization of nocebo and placebo effects to pressure pain and to cowhage-evoked itch (4). In the second experiment, we induced nocebo effects on cowhage-evoked itch and tested generalization of nocebo effects to mechanical itch and to mechanical touch (24).

Materials and methods

A brief summary of the two experiments (i.e., the information of participants and the experimental designs) can be found below. The procedures have been extensively described in our previous publications (4, 24), and are briefly repeated in **Supplementary Appendix Method**.

Participants

The sample size calculations were conducted for the main (placebo/nocebo) outcomes of two experiments (4, 24). Specifically, each group (placebo or nocebo) in experiment 1 would require 34 participants (4), and experiment 2 would require 44 participants (24). *Post-hoc* power analyses suggest that these sample sizes are sufficient to detect large effect sizes ($f^2 > 0.35$) for multiple regression analyses with 4 predictors ($\alpha = 0.05$, power $= 0.8$). However, sample sizes of >25 should be sufficient to conduct multiple regressions (25). All participants (English-speaking) were between 18 and 35 years

old. All participants were recruited *via* an online recruitment system (Sona Systems, Tallinn, Estonia) and through flyers posted in and around the university. Exclusion criteria were: current physical or mental illness, suffering from chronic itch (≥6 weeks), currently using medication or psychoactive drugs, being pregnant or lactating. Additionally, experiment 1 also excluded participants who were suffering from chronic pain (≥6 months), and experiment 2 excluded participants when they experienced spontaneous itch ≥3 on a 0 (not itch at all)-10 (worst itch imaginable) numerical rating scale (NRS) at the start of the testing session or cowhage insensitivity. Both experiments were approved by the Psychology Research Ethics Committee of Leiden University (CEP19-1205/571 and CEP18-1218/491). The experiments were conducted at Leiden University, the Netherlands. All participants provided their written informed consent. A data-blind preregistration for the current study was published at AsPredicted (#71238.[1] None of the currently reported analyses had been conducted prior to pre-registration).

Study designs

Both experiments used a within-subject design. Noteworthy, participants received neither verbal suggestions nor conditioning regarding the stimuli used for investigating *generalization*. All stimuli were applied in a pseudorandom order.

Experiment 1

The experiment had two independent groups (i.e., nocebo group and placebo group). During the experiment, we first induced nocebo and placebo effects on heat pain, and then tested generalization to pressure pain and to cowhage-evoked itch. All participants underwent a design consisting of 3 parts (see **Figure 1**). Part 1 comprised an induction phase and a test phase, where participants either received a negative expectation induction (nocebo group) or a positive expectation induction (placebo group) by verbal suggestion and conditioning (see **Supplementary Appendix Method**) regarding heat pain stimuli and tested on heat pain stimuli (see **Supplementary Appendix Method**). Part 2 comprised a short version of the conditioning in part 1 (*Reinstatement* in **Figure 1**) and a test phase to test generalization to pressure pain stimuli (see **Supplementary Appendix Method**). Part 3 comprised the same short version of the conditioning in part 1 (*Reinstatement* in **Figure 1**) and a test phase to test generalization to cowhage-evoked itch (see **Supplementary Appendix Method**).

Experiment 2

We first induced nocebo effects on cowhage-evoked itch and then tested generalization to mechanical itch and to mechanical touch. The design included 2 parts. Part 1 comprised an induction and a test phase, where participants received a negative expectation induction by verbal suggestion (see **Supplementary Appendix Method**) on cowhage-evoked itch and tested on cowhage-evoked itch. Part 2 comprised a test phase to test generalization to mechanical itch and mechanical touch (see **Supplementary Appendix Method**).

Assessment of predictors

Psychological characteristics, specifically anxiety-, stress-, depressive symptoms, attention to pain/itch, pain/itch catastrophizing were measured with the questionnaires described below. In experiment 1, all mentioned questionnaires were administered. In experiment 2, all questionnaires except those pertaining specifically to pain were administered. All questionnaires were administered in English and completed using Qualtrics (Qualtrics, Provo, United States) on a desktop computer in the lab before administering somatosensory stimuli in both experiments.

Anxiety-, stress-, and depressive symptoms

The 21-item version of the Depression Anxiety Stress Scale (DASS-21) was used to measure the frequency and severity of experiencing negative emotions over the previous week. The scale consists of subscales of anxiety (e.g., "I was aware of dryness of my mouth"), depression (e.g., "I felt that life was meaningless"), and stress (e.g., "I found it hard to wind down"). Each item was rated on a Likert scale from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time). Seven items per scale were summed and doubled to be equivalent to the full DASS version. The scores of each subscale theoretically range from 0 to 42, with higher scores indicating greater state anxiety, stress, and depression, respectively (26, 27). Cronbach's alpha of the subscales in both experiments ranged from 0.69 to 0.78, except from the subscale depression in experiment 1 in the placebo group (Cronbach's alpha = 0.52).

Attention to pain

The Pain Vigilance and Awareness Questionnaire (PVAQ) was used to measure the frequency of self-reported attentional habits with a focus on pain and changes in pain. This scale consists of 16 items, e.g., "I am very sensitive to pain." Each item was rated on a Likert scale from 0 (never) to 5 (always). All items were summed, with a theoretical range from 0 to 80, with higher scores indicating a higher focus on pain sensations (28). Cronbach's alpha of the PVAQ was 0.84 in experiment 1 and 0.85 in experiment 2.

Attention to itch

The PVAQ was adjusted to pertain itch (PVAQ-I) by only replacing the word "pain" with "itch" for all items, e.g., "I am very sensitive to itch" (29). Cronbach's alpha of the PVAQ-I was 0.83 in experiment 1 and 0.86 in experiment 2.

1 https://aspredicted.org/blind.php?x=/BN5_TRN

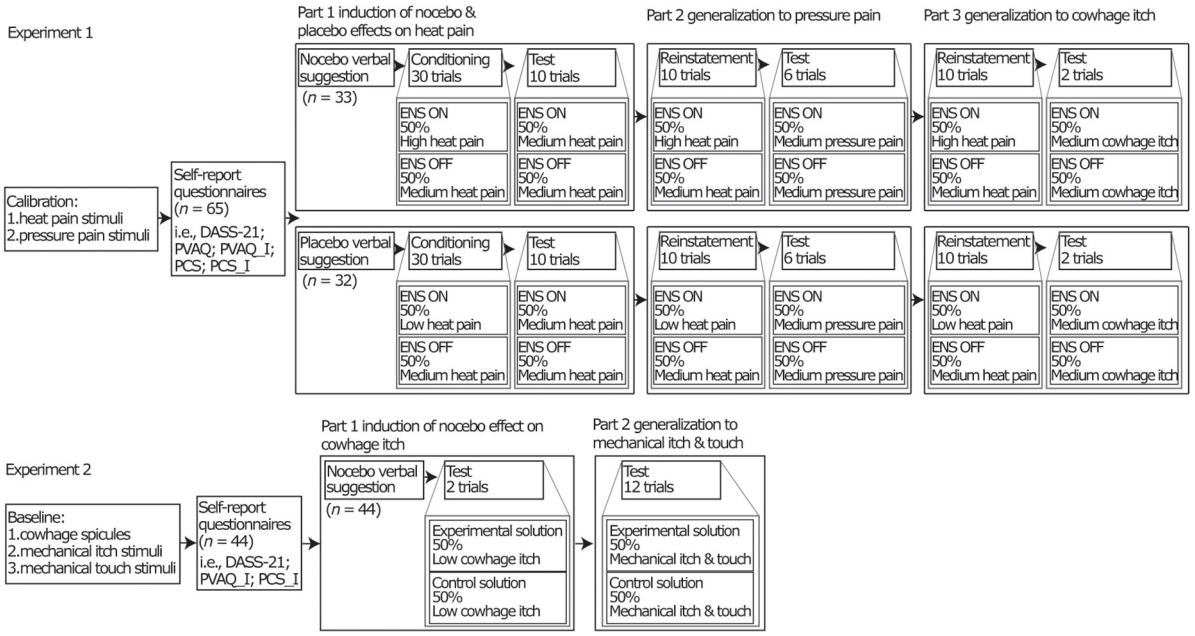

FIGURE 1
Overview of the full design of the two separate experiments. For experiment 1, "ENS" was functioned as a placebo treatment. "ON" and "OFF" indicated the sham (de)activation of the ENS device. "ON" represents an experimental trial and "OFF" represents a control trial. The ENS device was a transcutaneous electrical nerve stimulation (TENS) device (model EM80, Beurer, Germany). Participants rated their pain intensities on a 0 (no pain at all)-10 (worst pain imaginable) numerical rating scale (NRS). Low (NRS 0.5-2), moderate (NRS 3-4.5), and high (NRS 5.5-7) heat pain intensities were individually calibrated. Moderate pressure pain intensity (NRS 3-4.5) was individually determined. For experiment 2, "experimental solution" was served as a nocebo treatment. "Experiment solution" represents an experiment trial and "control solution" represents a control trial. Throughout both experiments, participants received all stimuli in half of experimental trials and in half of control trials in all phases. DASS-21, The 21-item version of the Depression Anxiety Stress Scale; PVAQ, The Pain Vigilance and Awareness Questionnaire; PCS, The Pain Catastrophizing Scale; PVAQ-I, itch-adjusted version of the PVAQ; PCS-I, itch-adjusted version of the PCS. For more details of the design for two experiments see (4, 24).

Pain catastrophizing

The Pain Catastrophizing Scale (PCS) was used to measure catastrophizing about pain experienced in daily life. This scale consists of 13 items, e.g., "I become afraid that the pain will get worse." Each item was rated on a Likert scale from 0 (not at all) to 4 (all the time). All items were summed, with a theoretical range from 0 to 52, with higher scores indicating more pain catastrophizing (30). Cronbach's alpha of the PCS was 0.85 in experiment 1 and 0.93 in experiment 2.

Itch catastrophizing

The PCS was adjusted to pertain itch (PCS-I) by only replacing the word "pain" with "itch" for all items, e.g., "I become afraid that the itch will get worse" (29, 31). Cronbach's alpha of the PCS-I was 0.84 in experiment 1 and 0.92 in experiment 2.

Statistical analysis

All analyses were performed using R (Version 3.6.3, Vienna, Austria) for Windows. Nocebo and placebo effects were defined as the difference in scores between experimental and control trials during the test phases in both experiments (4, 24). Furthermore, we defined generalization responders as participants who reported higher sensation scores in experimental trials in the testing generalization phases in the nocebo group or lower scores in the placebo group when compared to control trials. Due to a low-reliability of the DASS-21's subscale depression, this subscale was removed as predictor from all analyses. Assumption checks included normality, linearity, homoscedasticity, and multicollinearity. All assumptions were met in this study. Influential values were checked by Cook's distance (>0.5 considered as influential values, see **Supplementary Appendix Figures**). In case of influential values, the main outcomes would be conducted with and without influential values. Given the small sample size, regression analyses were conducted with bootstrapping (2,000 samples with reporting 95% confidence intervals (CIs)]. The statistically significant level was set at $p < 0.05$.

To check whether psychological characteristics were related to the induction and generalization of nocebo and placebo effects and to check the intercorrelations between predictors

for each model, Pearson correlation coefficients (normal distribution) were calculated.

To examine the primary objective of exploring predictors for the induction and generalization of nocebo effects, multiple regression analyses were performed in which the psychological characteristics (i.e., anxiety-, stress symptoms, attention to pain/itch, pain/itch catastrophizing) were entered into the model simultaneously (i.e., forced entry) as predictors. Dependent outcomes were nocebo effects on heat pain, nocebo effects on cowhage-evoked itch, generalization of nocebo effects to pressure pain, to cowhage-evoked itch, and to mechanical itch and touch. Note that, in experiment 2, we observed that mechanical stimuli induced impure sensations at baseline (i.e., the mechanical touch filaments evoked itch and the mechanical itch filaments did not evoke itch at baseline). Therefore, we selected those filaments that evoked either touch or itch at baseline for each individual ("individualized mechanical touch/itch filaments") to assess the nocebo effects evoked in the test phase and included these outcomes as dependent variables in present analyses (24). Further, note that psychological characteristics related to pain were not used to predict dependent outcomes related to itch, and vice versa for itch. An overview of the specific predictors and dependent outcomes is reported in **Supplementary Appendix Table 1**.

To examine the secondary objective of exploring predictors for placebo effects, the same method and predictors as described in the primary objective were used, except that the dependent outcomes were placebo effects on heat pain as well as generalization of placebo effects to pressure pain and cowhage-evoked itch (see **Supplementary Appendix Table 1**).

To examine the exploratory objectives of exploring predictors for *expected* itch and pain (referred to *expected nocebo and placebo effects* in the remainder), the same method and predictors as described in the primary objective were used, except that the dependent outcomes were the *expected* itch and pain intensities.

Results

Sample characteristics

In experiment 1, 33 participants were included in the nocebo group and 32 participants in the placebo group. In experiment 2, 44 participants were included. Due to the sensitivity check in which those participants were excluded who did not perceive the baseline stimuli as intended, e.g., mechanical itch stimuli not evoking itch (24), 29 participants were included in the analyses of the models related to mechanical touch, and 39 participants in the analyses of the models related to mechanical itch. Participants' demographics and spontaneous fatigue/pain/itch levels are reported in **Supplementary Appendix Table 2**.

Induced and generalized nocebo and placebo effects

Induction and generalization of nocebo and placebo effects were previously reported (4, 24). A summary of descriptive results of all stimuli scores by group and trial type are reported in **Supplementary Appendix Tables 3, 4**. In short, in experiment 1, both nocebo and placebo effects were significantly induced on heat pain as hypothesized. As also hypothesized, nocebo and placebo effects significantly generalized from heat pain to pressure pain, but contrary to our hypothesis they did not generalize to cowhage-evoked itch. In experiment 2, nocebo effects were significantly induced on cowhage-evoked itch as hypothesized. As also hypothesized, nocebo effects from cowhage-evoked itch significantly generalized to mechanical itch, but contrary to our hypothesis nocebo effects did not generalize to mechanical touch. In both experiments, at least 60% of participants were classified as generalization responders for each generalization effect, despite a lack of generalization effects across modalities at the group level. Frequencies of participants showing generalization per effect are reported in **Supplementary Appendix Table 5**.

Predictors and intercorrelations

Tables 1, **2** display an overview of mean, standard deviations, observed range, and intercorrelations of dependent outcomes and the relevant predictors in both experiments. Regarding nocebo effects, the correlation coefficients showed that none of the predictors was significantly associated with induction and generalization of nocebo effects. Regarding placebo effects, only stress symptoms were significantly associated with generalization of placebo effects to pressure pain ($r = -0.39$, $p = 0.03$).

Regression analyses

Table 3 displays the results of regression analyses regarding induction and generalization of nocebo and placebo effects. The results of regression analyses regarding *expected* nocebo and placebo effects are listed in **Supplementary Appendix Table 6**.

Regarding the primary objective concerning nocebo effects, in line with the results from the correlations, multiple regression analyses indicated that the studied psychological characteristics predicted neither induction of nocebo effects on heat pain and cowhage-evoked itch, nor generalization of nocebo effects within modalities (i.e., from heat pain to pressure pain and from cowhage-evoked itch to mechanical itch) or across modalities (i.e., from heat pain to cowhage-evoked itch and from cowhage-evoked itch to mechanical touch) (**Table 3**). Influential values

TABLE 1 Mean ± SD and intercorrelations of predictors and dependent outcomes in the nocebo and the placebo group in experiment 1.

Experiment 1	M ± SD	Observed range (min-max)	1	2	3	4	5	6	7	8
Nocebo group ($n = 33$)										
1. Induction of heat pain	0.4 ± 0.6	−1.2–1.5								
2. Generalization to pressure pain	0.5 ± 1.3	−3.6–3.3	0.08							
3. Generalization to cowhage-evoked itch	0.6 ± 2.3	−6–7	−0.10	0.24						
4. Anxiety	4.3 ± 5.3	0–24	0.03	0.12	0.12					
5. Stress	8.6 ± 6.7	0–30	0.15	0.08	−0.28	0.27				
6. Pain catastrophizing	13.3 ± 7.0	0–29	−0.01	0.34	n/a	0.26	0.18			
7. Attention to pain	34.0 ± 10.1	19–56	−0.21	0.25	n/a	0.00	0.07	0.46**		
8. Itch catastrophizing	10.1 ± 6.1	0–31	n/a	n/a	0.08	0.09	0.16	n/a	n/a	
9. Attention to itch	24.9 ± 10.7	0–51	n/a	n/a	0.27	0.31	0.16	n/a	n/a	0.37*
Placebo group ($n = 32$)										
1. Induction of heat pain	0.6 ± 0.7	−2–0.9								
2. Generalization to pressure pain	0.8 ± 1.0	−3.3–1.1	−0.04							
3. Generalization to cowhage-evoked itch	0.1 ± 2.3	−4–6.3	0.00	0.24						
4. Anxiety	2.9 ± 4.1	0–16	−0.07	−0.23	−0.01					
5. Stress	6.9 ± 5.1	0–20	−0.25	−0.3*	0.00	0.58***				
6. Pain catastrophizing	13.3 ± 9.4	1–43	−0.11	0.09	n/a	0.26	0.28			
7. Attention to pain	35.5 ± 10.4	12–63	−0.12	−0.32	n/a	0.28	0.09	0.53**		
8. Itch catastrophizing	8.2 ± 7.3	0–26	n/a	n/a	−0.06	0.17	−0.03	n/a	n/a	
9. Attention to itch	26.1 ± 10.1	6–51	n/a	n/a	−0.16	0.29	−0.02	n/a	n/a	0.32

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ (two-tailed); SD, standard deviation. n/a, not applicable.
Individual psychological characteristics related to pain were not used to predict dependent outcomes related to itch, and vice versa for itch. The dependent outcomes, i.e., induction of heat pain, generalization to pressure pain, and generalization to cowhage-evoked itch, were calculated as the scores of experimental trials minus control trials for each stimulus in the nocebo group and control trials minus experimental trials in the placebo group. The scores of anxiety, stress, and depression subscales (DASS-21) theoretically range from 0 to 42; the scores of attention to pain and attention to itch (PVAQ and PVAQ-I) theoretically range from 0 to 80; the scores of pain catastrophizing and itch catastrophizing (PCS and PCS-I) theoretically range from 0 to 52. Note that these results of subscale depression was removed due to the low reliability of the depression subscale.

TABLE 2 Mean (M) ± SD and intercorrelations of predictors and dependent outcomes in experiment 2 ($n = 44$).

Experiment 2 (nocebo group)	M ± SD	Observed range (min-max)	1	2	3	4	5	6
1. Induction of cowhage-evoked itch	0.8 ± 2.4	−5.7–7						
2. Generalization to mechanical itch	0.3 ± 0.9	−1.1–4.1	0.06					
3. Generalization to mechanical touch	0.4 ± 1.1	−2.6–2.6	0.30	0.51**				
4. Anxiety	4.3 ± 4.9	0–26	−0.05	−0.04	0.10			
5. Stress	7.5 ± 6.0	0–26	0.02	−0.09	−0.09	0.60***		
6. Itch catastrophizing	9.7 ± 7.3	0–28	0.13	−0.18	−0.07	0.07	0.21	
7. Attention to itch	30.0 ± 10.7	8–46	0.01	0.03	−0.04	−0.02	−0.06	0.28

** $p < 0.01$, *** $p < 0.001$ (two-tailed); SD, standard deviation. n/a, not applicable.
The dependent outcomes, i.e., induction of cowhage-evoked itch, generalization to mechanical itch, and generalization to mechanical touch, were calculated as the scores of experimental trials minus control trials for each stimulus in the test phases. The scores of anxiety, stress, and depression subscales (DASS-21) theoretically range from 0 to 42; the scores of attention to itch (PVAQ-I) theoretically range from 0 to 80; the scores of itch catastrophizing (PCS-I) theoretically range from 0 to 52. Note that these results of subscale depression was removed due to the low reliability of the depression subscale.

were observed in the model of generalization of nocebo effects to cowhage-evoked itch, but removal of the influential values did not lead to different results.

Regarding the secondary objective concerning placebo effects, multiple regression analyses showed that lower stress symptoms ($\beta = -0.1$, 95% CI [−0.18, −0.05]), less attention to pain ($\beta = -0.05$, 95% CI [−0.09, −0.01]), and higher pain catastrophizing ($\beta = 0.05$, 95% CI [0.01, 0.09]), predicted stronger generalization of placebo effects to pressure pain (full model: $F_{(4,27)} = 4.67$, $p = 0.005$, Adj. $R^2 = 0.32$) (Table 3).

Regarding the exploratory objective concerning expected nocebo and placebo effects, multiple regression analyses showed that lower itch catastrophizing ($\beta = -0.15$, 95% CI [−0.28, −0.04]) and higher attention to itch ($\beta = 0.07$, 95% CI [0.01, 0.14]) predicted higher expectancies of nocebo effects on cowhage-evoked itch (generalization) (full model: $F_{(4,28)} = 3.27$, $p = 0.025$, Adj. $R^2 = 0.22$) (**Supplementary Appendix Table 6**).

TABLE 3 An overview of multiple regression analyses *via* forced entry to predict induction of nocebo and placebo effects on heat pain and their generalization to pressure pain and to cowhage-evoked itch in experiment 1 ($n = 33$ in the nocebo group, $n = 32$ in the placebo group), and to predict induction of nocebo effects on cowhage-evoked itch and their generalization to mechanical itch and to mechanical touch in experiment 2 ($n = 44$).

Nocebo effects										**Placebo effects**								
		Induction of heat pain			**Generalization to pressure pain**			**Generalization to cowhage itch**		**Induction of heat pain**			**Generalization to pressure pain**			**Generalization to cowhage itch**		
		β	SE_a	95% CI	β	SE_a	95% CI	β	SE_a	95% CI	β	SE_a	95% CI	β	SE_a	95% CI	β	SE_a	95% CI
Experiment 1																		
	Anxiety	0	0.02	−0.04,0.04	0.01	0.05	−0.06,0.13	0.06	0.11	−0.32,0.02	0.03	0.05	−0.08,0.12	0.03	0.05	−0.09,0.11	0.04	0.12	−0.14,0.28
	Stress	0.01	0.02	−0.02,0.07	0	0.04	−0.07,0.08	−0.13	0.09	−0.12,0.13	−0.05	0.03	−0.11,0.02	−0.1	0.03*	−0.18, −0.05	−0.02	0.09	−0.26,0.12
	Pain catastrophizing	0.01	0.02	−0.02,0.05	0.05	0.04	−0.03,0.12	n/a	n/a		0	0.02	−0.03,0.04	0.05	0.02*	0.01,0.09	n/a	n/a	
	Attention to pain	−0.01	0.01	−0.04,0.01	0.02	0.03	−0.02,0.08	n/a	n/a		−0.01	0.01	−0.04,0.02	−0.05	0.02*	−0.09, −0.01	n/a	n/a	
	Itch catastrophizing	n/a	n/a		n/a	n/a		0.01	0.06	−0.05,0.14	n/a	n/a		n/a	n/a		−0.01	0.11	−0.20,0.22
	Attention to itch	n/a	n/a		n/a	n/a		0.06	0.04	−0.01,0.12	n/a	n/a		n/a	n/a		−0.04	0.05	−0.14,0.07
Full model		Adj. $R^2 = -0.05$			Adj. $R^2 = 0.01$			Adj. $R^2 = 0.01$			Adj. $R^2 = -0.04$			Adj. $R^2 = 0.32$			Adj. $R^2 = -0.12$		
		$F(4, 28) = 0.61$			$F(4, 28) = 1.06$			$F(4, 28) = 1.69$			$F(4, 27) = 0.67$			$F(4, 27) = 4.67$			$F(4, 27) = 0.20$		
		$p = 0.661$			$p = 0.394$			$p = 0.180$			$p = 0.616$			$p = 0.005$			$p = 0.94$		

Nocebo effects										
		Induction of cowhage itch			**Generalization to mechanical itch**			**Generalization to mechanical touch**		
		β	SE_a	95% CI	β	SE_a	95% CI	β	SE_a	95% CI
Experiment 2										
	Anxiety	−0.04	0.1	−0.29,0.14	0	0.03	−0.06,0.11	0.04	0.06	−0.09,0.15
	Stress	0.02	0.07	−0.11,0.18	−0.01	0.03	−0.06,0.05	−0.03	0.03	−0.08,0.02
	Itch catastrophizing	0.04	0.05	−0.04,0.16	−0.02	0.03	−0.08,0.03	0	0.03	−0.06,0.04
	Attention to itch	−0.01	0.03	−0.08,0.07	0.01	0.02	−0.02,0.04	0	0.02	−0.05,0.04
Full model		Adj. $R^2 = -0.08$			Adj. $R^2 = -0.07$			Adj. $R^2 = -0.12$		
		$F(4, 39) = 0.22$			$F(4, 34) = 0.54$			$F(4, 24) = 0.28$		
		$p = 0.928$			$p = 0.844$			$p = 0.886$		

* $p < 0.05$, β is the standardized regression coefficient. n/a, not applicable, SE_a, bootstrap standard error of the mean. CI, bootstrapped confidence interval. The results of all models in both experiments used the raw values. Depressive symptom was not included in the models due to low reliability of the depression subscale. Due to the sensitivity check, 29 participants were included in the analyses of the models related to mechanical touch, and 39 participants in the analyses of the models related to mechanical itch.

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Similar analyses showed that less attention to itch ($\beta = -0.06$, 95% CI [−0.12, −0.02]) alone predicted higher expectancies of nocebo effects on mechanical sensations (generalization) (full model: $F_{(4,39)} = 1.72$, $p = 0.166$, Adj. $R^2 = 0.06$) (**Supplementary Appendix Table 6**).

Discussion

The current study aimed to explore predictors for induction and generalization of nocebo and placebo effects within and across pain and itch modalities. Our results showed that anxiety-, stress symptoms, pain/itch catastrophizing, and attention to pain/itch did not significantly predict, with relatively small confidence intervals, induction of nocebo and placebo effects. Regarding generalization, only lower stress symptoms, lower attention to pain, and higher pain catastrophizing weakly predicted a stronger generalization of placebo effects from heat pain to pressure pain. These findings and their implications should be interpreted with caution, considering the sample was limited in size and consisted of young healthy individuals.

Regarding nocebo effects, the findings that the psychological characteristics did not predict nocebo effect induction are in line with several previous studies indicating the lack of significant associations between psychological characteristics and nocebo effects (1, 9, 14, 32). Moreover, no significant predictors were found for generalization of nocebo effects within and across the pain and itch modalities. This may be partly caused by our target sample of young healthy individuals who have, unsurprisingly, low levels of negative affect and cognitions. It should be noted that nocebo effects were not found to generalize across modalities. Therefore, replication is necessary before drawing a conclusion. The exploratory analyses of the prediction of participants' expectancies showed that lower itch catastrophizing and higher attention to itch predicted higher expectancies of nocebo effects on cowhage-evoked itch (generalization). As the overall pooled associations were small and the (directions of) predictors were not consistently found for generalization across the two experiments, these findings should be interpreted with caution. From a hypothesis-generating perspective, the current study paves the way to further explore potential predictors of generalization of nocebo effects.

Regarding placebo effects, the findings that the psychological characteristics did not predict placebo effect induction contrasts with some previous research with comparable sample sizes e.g., (11, 33). However, two recent studies with large cohorts yielded mixed results, with one study ($N = 397$) reporting negative associations between negative affect (including anxiety-, and stress symptoms) and placebo effects (10) and one reporting ($N = 624$) null associations (14). Further research herein may examine possible interactions between multiple predictors and explore other potential predictors (e.g., fear). Regarding generalization of placebo effects, there are some indications for psychological characteristics that may explain small parts of the variance. Specifically, stronger generalization of placebo effects within the pain modality may be predicted by lower stress symptoms, less attention to pain, and higher pain catastrophizing. One potential explanation could be that people with lower stress symptoms and less attention to symptoms, may tend to focus on positive information and avoid harmful information (34, 35). However, the result also showed that higher pain catastrophizing may be relevant to a stronger generalization of placebo effects, which contrasts with theory (36) and previous research (37). As these predictors only explained a small part of the variance, no firm conclusions can be drawn from these findings. Further research is warranted to validate these findings. Moreover, the exploratory results did not suggest that psychological characteristics predict expectancies of the induction and generalization of placebo effects. One possible explanation is that the psychological characteristics measured in this study may be less relevant in the facilitation/inhibition of positive expectancies (38, 39). More research is warranted, as a better understanding of individual responses could foster the efficacy of positive treatment outcomes.

Limitations and suggestions for future studies

First, given the limited sample size and the inclusion of only young healthy participants, variances in the characteristics could have been restricted, and false negative findings might have occurred. Besides, representativeness of the demographics and psychological characteristics could limit the generalizability of the current findings to the general population or patient populations. Further studies should include more variance in characteristics such as age and health status (40, 41). Besides, although our sample size met a minimum requirement ($N = 25$) for multiple regressions with multiple predictors (25) and our study was of exploratory, hypothesis-generating nature, only large effects may be detected with this small sample and thus results should be interpreted with caution. Future research with larger cohorts is required, for instance in the forms of meta-analyses on individual data. Second, considering the low reliability of the depression subscale (depressive symptoms were removed from all analyses), further studies may use other questionnaires such as Positive and Negative Affect Schedule e.g., (42). Also, the generally low levels of cognitive-affective factors could not provide a comprehensive insight into their predictive value. It may be helpful to include participants at different baseline levels of cognitive-affective factors. Next to self-report measurements, experimental research directly manipulating factors such as anxiety- and stress symptoms and

assessing effects on induction and generalization of nocebo and placebo effects seems to be currently lacking. Third, the lack of generalization of nocebo effects across modalities at the group level may have affected the current results. However, psychological characteristics may still help to distinguish individuals who tend to generalize and those who do not at the individual level, although this study did not provide a clear pattern. Finally, it is common that prediction research, including ours, only included few potential predictors at once. However, it appears suboptimal to account for only few factors to predict nocebo and placebo effects as well as their generalization, especially in clinical settings. Future studies are recommended to not only examine multiple psychological characteristics at once, but also to combine these characteristics with other factors such as personality traits, e.g., (15, 43) genetic variants, e.g., (44, 45) doctor-patient relationships, e.g., (46, 47) treatment history, e.g., (48) and various contextual variables e.g., (49), to get a comprehensive multifaceted structure of predicting nocebo and placebo effects.

Suggestions for future research

Some suggestions need to be discussed. On top, assessing changes in dynamic individual characteristics, such as state anxiety and state fear, before versus after the nocebo and placebo manipulations could provide more insight into the underlying dynamics of nocebo and placebo effects as well as their generalization. Second, as different mechanisms are supposed to underlie nocebo and placebo effects (3), it is recommended to assess different predictors for nocebo and placebo effects, e.g., anxiety for nocebo effects and optimism for placebo effects (32, 33). Another recommendation to advance the field is to systematically test theoretical models such as the fear-avoidance model e.g., (22) and a predictive coding framework regarding symptom perception e.g., (50). Finally, including patient samples would be an important next step. For instance, patients with chronic itch due to atopic dermatitis appear to be more sensitive to nocebo-like effects on itch than healthy individuals (51, 52). Assessing the predictors in patients' treatment outcomes as well as subsequent treatment outcomes would contribute to identifying patients who are sensitive to nocebo and placebo effects. This could eventually provide individualized interventions to increase treatment effectiveness.

Conclusion

This study suggests that the psychological characteristics may not (or only weakly) predict the induction and generalization of nocebo and placebo effects in young healthy individuals. Given the current restrictions to the sample, however, it cannot be ruled out that these characteristics do play a significant role in placebo and nocebo effects on pain and itch and their generalization. The current study can be a starting point for further exploring the relevance of these predictors for generalization of nocebo and placebo effects. Exploring the predictors for nocebo and placebo effects as well as their generalization would contribute to helping treatment outcomes in the clinic and establishing individualized treatments schemes, thereby helping increase the success of treatments.

Data availability statement

Data not included in the article/**Supplementary material** will be made available through Dataverse (https://dataverse.nl/dataverse/leidenuniversity). Further inquiries also can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Psychology Research Ethics Committee of Leiden University. The participants provided their written informed consent to participate in this study.

Author contributions

LW analyzed the data and drafted the manuscript. All authors have critically revised, edited, and approved the final manuscript.

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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.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.838578/full#supplementary-material

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Genotypes of Pain and Analgesia in a Randomized Trial of Irritable Bowel Syndrome

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Background: Irritable bowel syndrome (IBS) is a highly prevalent chronic pain disorder with multiple underlying mechanisms and few treatments that have been demonstrated to be effective in placebo controlled trials. One potential reason may be the use of composite outcomes, such as the IBS Symptom Severity Scale (IBS-SSS) which includes descriptive items related to pain frequency and pain intensity as well as bowel dysfunction and bloating. We investigated if different features of IBS pain have distinct genetic associations and if these may be moderated by sex hormones.

Participants and Setting: Adult outpatients with moderately severe IBS (>175 on IBS-SSS) enrolled in a clinical trial reported IBS-SSS at baseline and after 6 weeks of therapy.

Methods: Fixed effects modeling was used to test the effect of *COMT* rs4680 genotype to change in pain severity (rated 0-100) and pain frequency (defined as number of days with pain in the past 10 days) from baseline to week 6 with IBS treatment. Parallel exploratory genome-wide association studies (GWAS) were also performed to identify single nucleotide polymorphisms (SNPs) associated with change in pain severity or pain frequency across all participants.

Results: A total of 212 participants (74% female) were included. The *COMT* rs4680 met allele was associated with decreased pain severity over the course of the trial in gene dosage models [beta(SE) −5.9 (2.6), $P = 0.028$]. Exploratory GWAS for change in pain frequency identified 5 SNPs in close proximity on chromosome 18 near *L3MBTL4* which reached genome-wide significance (all $P < 5.0E-8$). This effect was not mediated by changing estradiol levels. There was also a region of chromosome 7 with 24 SNPs of genome-wide suggestive significance for change in pain severity (all $P < 1.0E-5$).

Conclusions: Previously reported association between *COMT* rs4680 genotype and treatment response as measured by IBS-SSS is related to pain severity, but not pain frequency. We also identified new candidate genes associated with changes in IBS pain severity (*SNX13*) and pain frequency (*L3MBTL4*) in response to treatment. Further studies are needed to understand these associations and genetic determinants of different components of IBS-SSS. ClinicalTrials.gov, Identifier: NCT0280224.

Keywords: pain, irritable bowel syndrome, genotype, randomized controlled trial, genome-wide association study

INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by visceral pain, bloating and altered bowel habits (1) that is one of the top 10 reasons for seeing a primary care physician (2, 3). Although visceral pain is a defining characteristic of IBS that takes a considerable toll on quality of life (4), few studies have examined factors that influence a patient's experience of pain. The economic burden of IBS is high and there are few effective treatments, particularly for visceral pain. Furthermore, many common pain drugs have adverse effects that exacerbate IBS symptoms (5).

The identification of drugs that are effective for visceral pain in IBS has been thwarted by high placebo response rates (∼40%) in randomized controlled trials (6). Typically, the IBS Severity Scoring System (IBS-SSS) (7) is used to quantify IBS symptoms and assess response to treatment in clinical trials. This validated composite measure includes five items each of which are rated on a 0–100 visual analog scale (abdominal pain, number of days with abdominal pain, severity of abdominal distension, satisfaction with bowel habits, and IBS-related quality of life).

Identification of genetic variants that influence placebo response in IBS could allow for stratification of patients based on their propensity to respond to placebo treatment thereby increasing the precision of clinical trials. Our group identified genes that influenced treatment response to placebo in a randomized trial in which the primary outcome was IBS-SSS (8). Specifically, our group identified that participants with IBS who were homozygous for the catechol-O-methyltransferase (*COMT*) rs4680 met (met/met) had the greatest improvement across treatment arms as measured by the IBS-SSS. However, it remains unclear which of the five items in the IBS-SSS were most significantly influenced by these associations. To date no studies have examined genetic links to changes in the two pain related items in the IBS-SSS (pain severity and pain frequency) which comprise 40% of the composite score in response to IBS treatment. The goals of this study were to determine whether *COMT* variants are linked to the two pain components of IBS-SSS and to identify other genetic variants that influence changes in either pain frequency or pain severity in response to treatment for IBS.

Abbreviations: COMT, Catechol-O-methyltransferase; DBP, Double blind placebo; DBM, Double blind mint; IBS-SSS, IBS symptom severity scale; OLP, Open label placebo; NPC, No-pill control; GWAS, Genome-wide association study.

METHODS

This is a *post-hoc*, exploratory analysis of existing genotype data from participants in the Effects of Open-label vs. Double-blind treatment in IBS clinical trial. In this trial, participants were randomized to one of three placebo treatments: open-label placebo (OLP), double-blind placebo (DBP), or no pill control (NPC) (9). To allow for the DBP treatment arm, a small number of participants were randomized to a fourth arm: double-blind peppermint oil (DBM). As described previously, adults who met the Rome IV criteria for IBS with symptoms of moderate or greater severity (defined as a score of ≥175 on the IBS-SSS) were eligible to participate if their IBS medication regimen (e.g., fiber, tricyclic antidepressants, anti-spasmodics, etc.) had been stable for at least 30 days and they agreed not to change their IBS treatment for the duration of the trial (9, 10). Participants were excluded if they reported alarm features, severe acid reflux, use of peppermint oil in the past 30 days, or allergy to soybean oil (used in the placebo pills). The primary outcome was IBS-SSS which was assessed at baseline and at week six by blinded research assistants. OLP and NPC participants knew their treatment assignment. Those assigned to DBP or DBM were told that they were enrolled in an RCT but were not informed of their treatment assignment. Blood was collected for genotyping at the first study visit.

Genotyping

Genotyping was conducted on the Infinium Global Screening Array v2.0 (Illumina, San Diego, California, US). Quality control of samples was carried out to filter extremely low-quality samples and variants (call rate $< 97.5\%$) using PLINK (version 1.9). A total of 729,526 SNPs were mapped to the GRCh37 (hg19) reference genome. To reduce heterogeneity in population structure, we conducted principal component analysis using PLINK on the whole genome SNP data and extracted the top five principal components for correcting genetic heterogeneity across different races/ethnic groups. We limited our analyses to SNPs with minor allele frequency > 0.05 and with a Hardy-Weinberg equilibrium $P > 1^{*}10^{-6}$.

Candidate Gene Analysis

A candidate gene analysis was performed using fixed effects models to test the effects of the *COMT* rs4680 genotype (val/val, val/met, or met/met) on the change in pain severity or pain frequency with IBS treatment.

$$ChangePainSev \sim rs4680 + Age + Gender + Treatment + PC1 + PC2 + PC3 + PC4 + PC5 \quad (1)$$

$$ChangePainFreq \sim rs4680 + Age + Gender + Treatment + PC1 + PC2 + PC3 + PC4 + PC5 \quad (2)$$

To control for confounding factors, all models included age and sex of the patients, as well as the study arm that the patients were allocated to and the first five principal components identified from the genotype data to correct for genetic heterogeneity across different races/ethnic groups. Principal components analysis (PCA) was performed on the whole genome SNP data using PLINK (11). As sensitivity tests, all analyses were performed for the whole cohort and separately for female participants only to assess signal stability.

Genome-Wide Association Study

The following models were used for parallel exploratory GWAS on change in pain severity and pain frequency:

$$ChangePainSev \sim SNP + Age + Gender + Treatment + PC1 + PC2 + PC3 + PC4 + PC5 \quad (3)$$

$$ChangePainFreq \sim SNP + Age + Gender + Treatment + PC1 + PC2 + PC3 + PC4 + PC5 \quad (4)$$

In GWAS of quantitative change, the baseline measure has been shown to bias the effect of variants on treatment response; therefore, we did not include baseline painseverity or pain frequency at baseline as a covariate in the model (12). Based on the findings in the exploratory GWAS, we analyzed the effect size [Standardized Mean Difference (SMD)] of hetero- and homozygous variants of the leading SNP of each of the two GWAS. Since a lead finding has been previously linked to pain in dysmenorrhea (13) and IBS symptom fluctuation has been linked to the menstrual cycle (10, 14), we performed a mediation analysis of estradiol on the change in pain frequency linked to the lead SNP of the GWAS. We applied a full mediation model, tested using the PROCESS implementation (15, 16) for IBM SPSS.

RESULTS

Patient Cohort

In this study, we analyzed those participants ($n = 212$) randomized to DBM ($n = 26$), DBP ($n = 62$), OLP ($n = 62$), or NPC ($n = 62$) for whom pain outcomes at baseline and at week 6, as well as genotyping were available. The average age was 42.6 years (74% female) and a majority self-reported their race as white (84%; **Table 1**). Overall, the average IBS-SSS at baseline was 274.4, with an average pain intensity of 42.7 out of 100 and average pain frequency of 5.1 days over the past 10 days (**Figure 1**).

COMT Association With Change in Pain Frequency and Pain Severity Items on IBS-SSS

In *COMT* rs4680 gene dosage models of change in the pain frequency and pain severity components of the IBS-SSS from baseline to 6-weeks, increasing number of met alleles was associated with a significantly greater reduction in IBS pain severity [beta(SE), −5.9 (2.6), $P = 0.028$], but not frequency [beta(SE), −0.52(0.40), $P = 0.198$] across all participants combined. Sensitivity analysis with women only revealed a similar pattern of *COMT* rs4680 effects across all treatment arms in females, such that met/met women had the greatest change in pain severity (29.7 ± 25.5) and val/val women the least (17.5 ± 26.6).

Exploratory GWAS of Analgesic Effects During the Trial

When considering change in pain severity from baseline to endpoint of the trial, no SNPs reached the genome-wide significance threshold ($P < 5.0E-8$) however, 24 SNPs in close proximity on Chromosome 7 (Chr7: 17,705,199–17,710,866) reached genome-wide suggestive significance ($P < 1.0E-5$; see **Figure 2** for the Manhattan and quantile-quantile plot and **Supplementary Table 1** for SNPs). These loci on Chromosome 7 are proximal to the gene for SNX13, associated with intracellular trafficking. Interestingly, this genomic region has been associated with chronic widespread pain previously (17), where it was suggested to be linked to a reduced biodiversity of the gut microbiome. SNPs in this region also reach genome-wide suggestive *P*-values in the female patient only sensitivity analysis. After treatment, met alleles in SNP rs1105794 were associated with decreased overall pain severity while val alleles were associated with increased overall pain severity. At baseline, met alleles in rs1105794 were associated with greater pain frequency ($P < 1.0E-3$) and a minimal decrease in pain severity.

When analyzing change in pain frequency over the 6 week treatment trial, five SNPs (rs1105794, rs4479336, rs6506387, rs4798443, rs9952528) within close proximity on chromosome 18 reached genome-wide significance (see **Figure 3** for the Manhattan and quantile-quantile plot and **Supplementary Table 2** for SNPs). The same SNPs were found to be genome-wide significant in the women-only cohort. An additional nine SNPs within this region of chromosome 18 (Chr18: 6,451,334–6,460,576) were of genome-wide suggestive significance.

These SNPs mapped closely to *L3MBTL4* which encodes the histone methyl-lysine binding protein and was genome-wide significant in a GWAS of pain severity in dysmenorrhea (13), a pain syndrome in women characterized by pain with menses.

TABLE 1 | Demographics and change in IBS Symptom Severity Score (IBS-SSS) pain severity and pain frequency components by treatment arm.

	Double-blind Mint (DBM)	Double-blind Placebo (DBP)	Open-label Placebo (OLP)	No-pill Control (NPC)
N	26	62	62	62
Age, mean (SD)	43.4 (16.9)	43.5 (20.5)	43.1 (17.7)	40.8 (17.5)
Female, (%)	18 (69.2)	46 (74.2)	44 (77.4)	48 (71.0)
White, (%)	22 (84.6)	53 (85.5)	52 (83.9)	52 (83.9)
Change in pain severity, mean (SD)	30.5 (21.6)	23.0 (26.1)	25.7 (25.3)	17.8 (28.3)
Change in pain frequency, mean (SD)	2.3 (3.8)	3.2 (4.0)	2.2 (4.0)	1.4 (3.7)

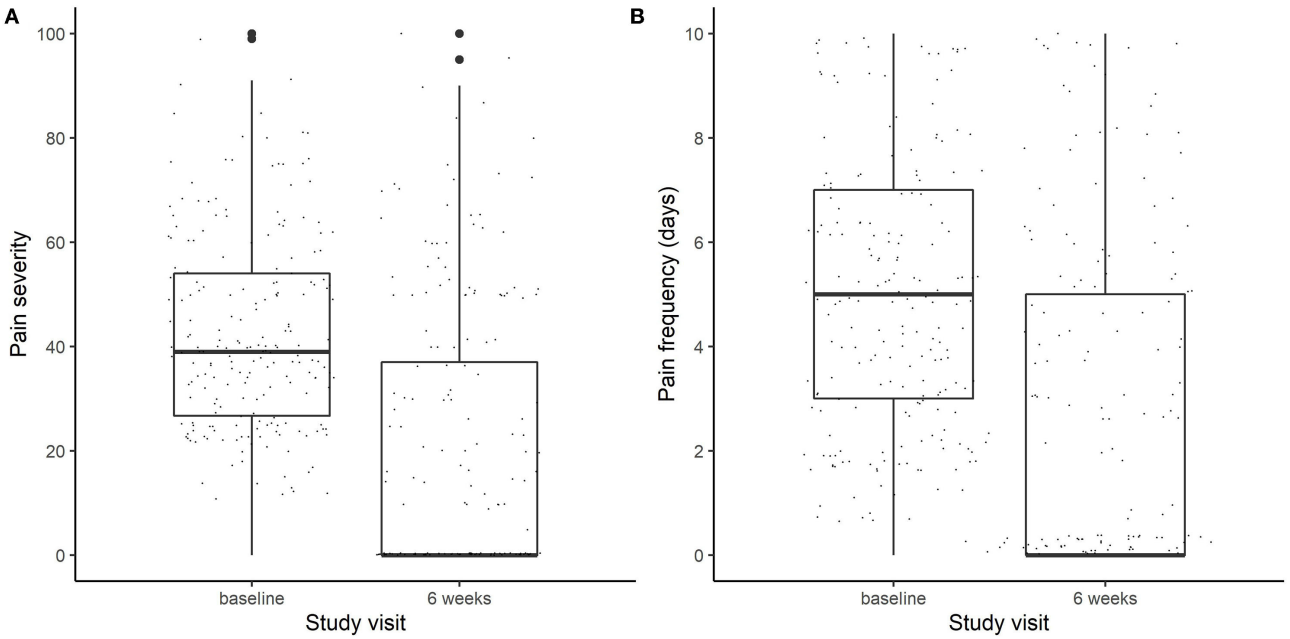

FIGURE 1 | Boxplots of **(A)** pain severity (on a scale of 0–100) and **(B)** Pain frequency (measured in days out of the last 10 days) at baseline and at the end of the trial (week 6).

Post-hoc Analysis of Findings

For change in pain frequency, rs1105794 showed a large significant effect (measured as change in days of pan) of 2.86 (95% CI 1.88–3.84; $p < 0.0001$) and followed a dose-response model. The difference between G/G and G/A equaled an effect size of 0.46, between G/A and A/A an effect size of 1.44, and between the homozygous variants the effect size was 1.90 (see **Figure 4**). Most of this effect was mediated directly by rs1105794, so although present, the indirect effect mediated by estradiol was small (−0.12, 95% CI −0.08, −0.45; $P = 0.383$).

rs1105794 did not influence estradiol change ($P = 0.3521$). The result was similar for estrone and did not change in quality if only women were included or sex was treated as a covariate.

DISCUSSION

Here we report the findings of a candidate gene analysis, an exploratory GWAS of pain frequency and an exploratory GWAS of pain severity in a RCT of 4 different IBS treatments [double-blind peppermint oil (DBM), double-blind placebo (DBP), open-label (OLP), and a no placebo pill control (NPC)] (10). The candidate gene analysis showed a significant effect of *COMT* rs4680 on change in pain severity but not change in pain frequency. In an exploratory GWAS, the lead SNPs for change in pain frequency were genome-wide significant and mapped to a region on chromosome 18 proximal to *L3MBTL4* whereas the lead SNPs associated with pain severity were genome-wide suggestive and mapped to a region on chromosome 7 proximal to *SNX13*.

We have previously found that *COMT* rs4680 genotype was associated with improvement in IBS symptoms as measured by IBS-SSS (14). In this study, we aimed to further investigate whether *COMT* rs4680 genotype was associated with specific IBS symptoms, particularly pain severity and pain frequency. *COMT* is an enzyme that metabolizes endogenous catechols, including estrogen, dopamine, norepinephrine, and epinephrine. Due to its role as a key regulator of dopamine in the prefrontal

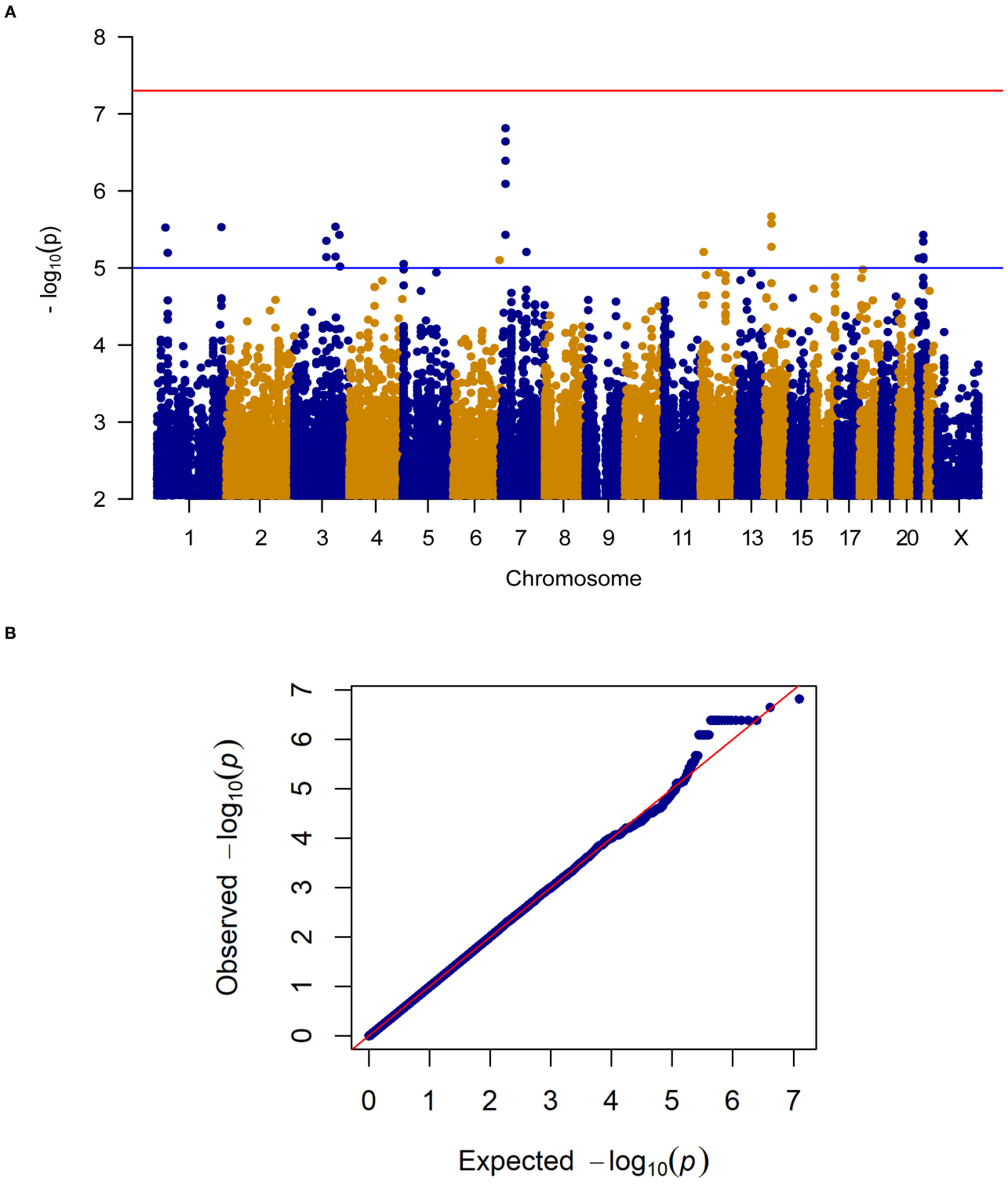

FIGURE 2 | (A) Manhattan plot of GWAS of change in pain severity among 212 IBS patients controlling for age, sex, treatment arm and the first 5 principal components for genetic ancestry. The x-axis is chromosome position and the y-axis is *p*-value. The red line represents the "genome-wide significant" threshold, 5.0E-8, and the blue line denotes the "genome-wide suggestive" threshold, 1.0E-5. We did not find genome-wide significant SNPs for change in pain severity, but we did find a few genome-wide suggestive SNPs. **(B)** Quantile-quantile plot of the data. The genomic inflation factor λ is 0.994, which indicates that no inflation of data was observed in the GWAS of change in pain severity from baseline to 6 weeks across all treatment arms.

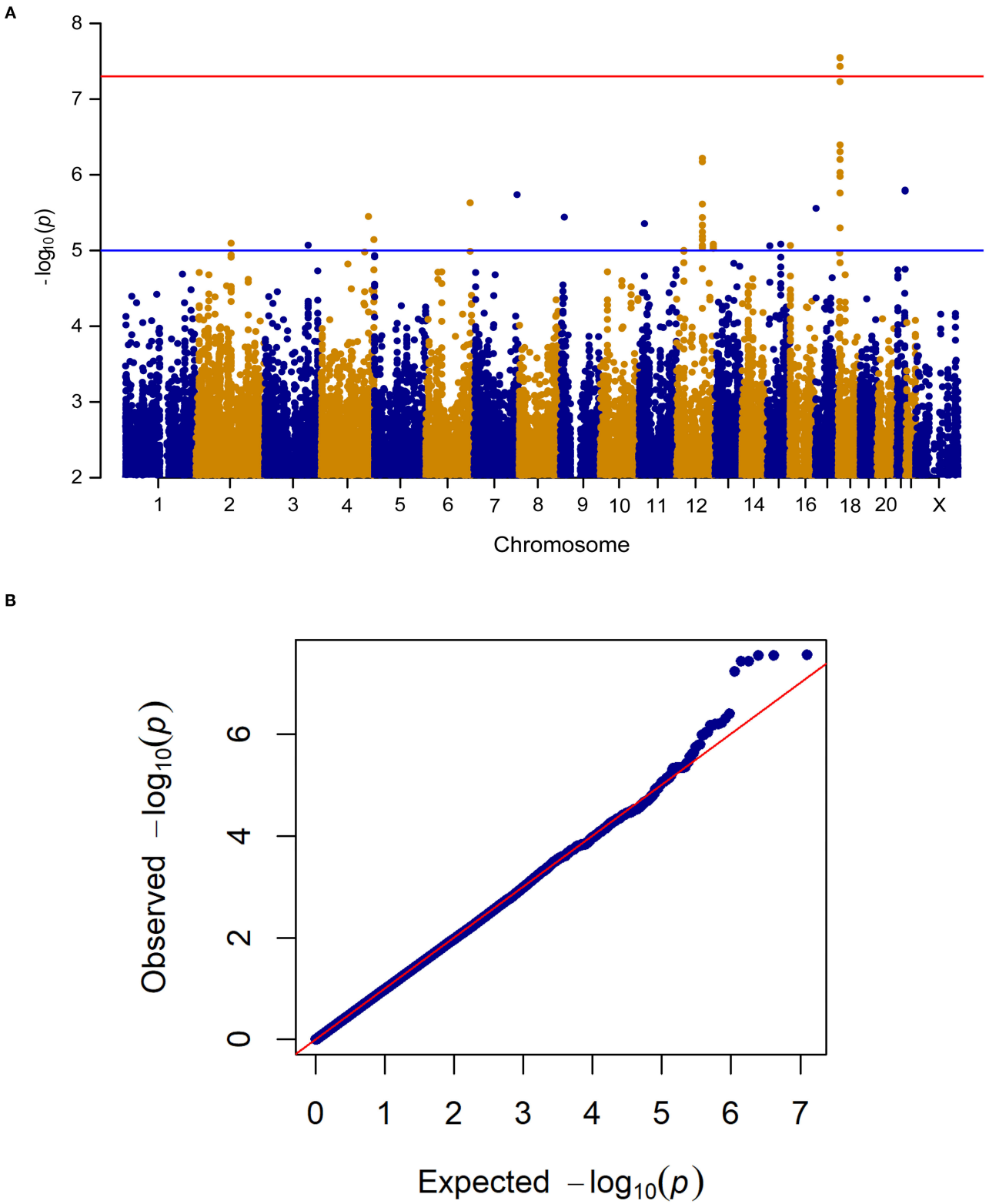

FIGURE 3 | (A) Manhattan plot of GWAS of change in pain frequency among 212 IBS patients controlling for age, sex, treatment arm and the first 5 principal components for genetic ancestry. The x-axis is chromosome position and the y-axis is *p*-value. The red line represents the "genome-wide significant" threshold, 5.0E-8, and the blue line denotes the "genome-wide suggestive" threshold, 1.0E-5. We find five genome-wide significant SNPs rs1105794, rs4479336, rs6506387, rs4798443, rs9952528, and a few genome-wide suggestive SNPs. **(B)** Quantile-quantile plot of the data. The genomic inflation factor λ is 0.989, which indicates that no inflation of data was observed in the GWAS of change in pain frequency from baseline to 6 weeks across all treatment arms.

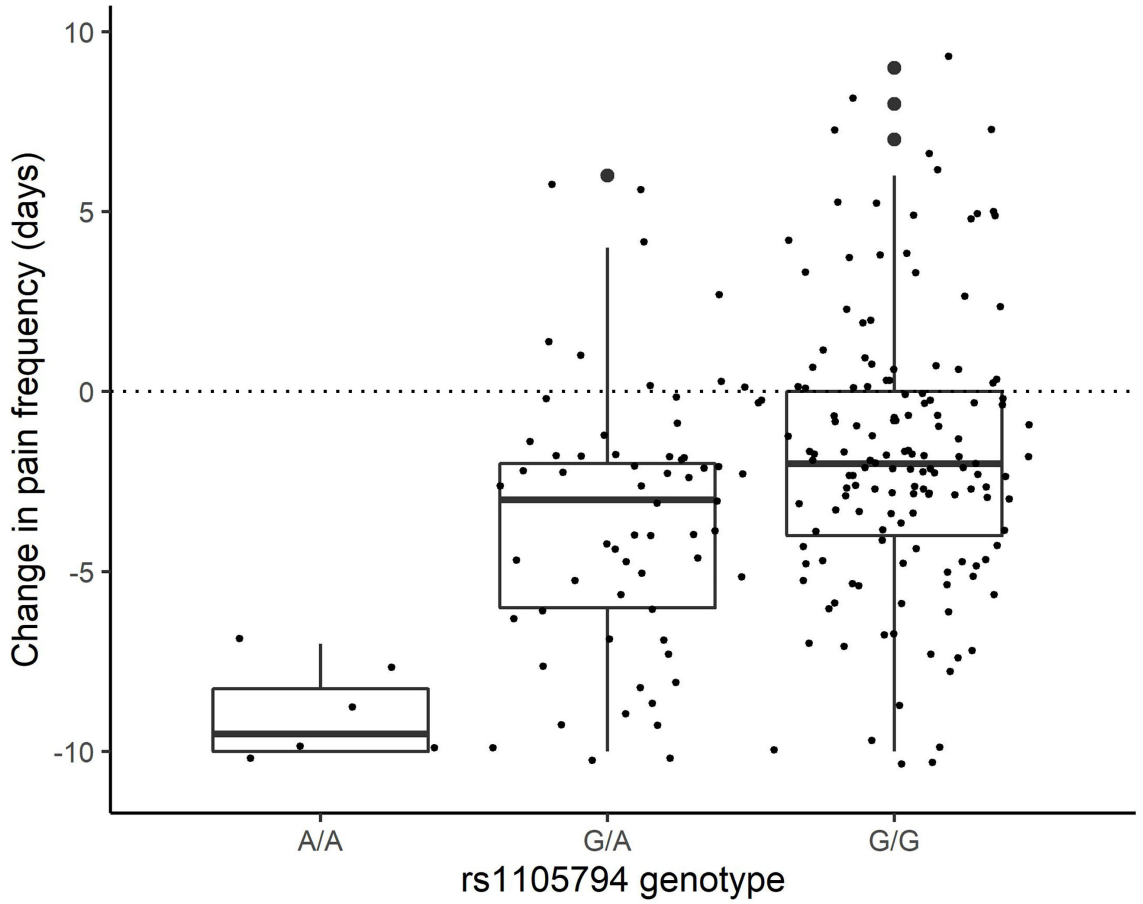

FIGURE 4 | Change in pain frequency by rs1105794 across three allele variants: met/met (A/A), val/met (G/A), val/val (G/G).

cortex, a brain region that processes pain signaling, COMT has been investigated extensively in the context of depression and Parkinson's disease. Our SNP of interest, *COMT* rs4680, encodes a transversion of G-to-A, which results in a substitution of methionine (met) in place of valine (val) and a 3-to-4 fold reduction in enzymatic activity (15, 16). In our previous findings, increasing met alleles corresponded to stronger placebo response (14). *COMT* rs4680 genotype has been shown to be associated with pain sensitivity in patients treated with morphine after cardiac surgery (18), and with pain severity in Parkinson's disease patients (19) and hospitalized burn victims (20). Specifically, those with the low activity A allele (which corresponds to met) had higher pain sensitivity. Importantly, the *COMT* rs4680 met allele substitution has also been shown to be associated with placebo analgesia specifically (21, 22). Our finding that *COMT* rs4680 met is associated with a decrease in pain severity in IBS patients aligns with prior findings on the role of *COMT* in pain mediation.

Our finding that pain frequency scores are related to SNPs that are close to the L3MBTL4 gene on chromosome 18 is a novel finding that has basis in the literature. *L3MBTL4* encodes histone methyl-lysine binding protein that is predicted to be involved in negative regulation of transcription and is highly expressed in gonadal tissue. *L3MBTL4* was nominally genome-wide significant in a GWAS of pain severity in dysmenorrhea in Japanese women. In our study, the lead SNP (rs1105794), had a minor allele frequency of 18%. This study was small and exploratory, but findings of the juxtaposition of pain phenotypes in IBS and dysmenorrhea in women warrant replication studies to confirm the potential for SNPs in this locus to impact change in IBS pain frequency, particularly as women with IBS have higher rates of dysmenorrhea than the general population (21, 23). Symptoms of IBS are two times as prevalent in women than in men (22, 24). Further, female patients with IBS tend to report increased symptoms during menstruation (23–26). In Western countries, women demonstrate a greater prevalence of IBS, and are more likely to seek treatment for the disorder than men (25, 27). Among the sex differences in the presentation of IBS, women more frequently endorse constipation, abdominal distention, and extraintestinal visceral symptoms such as muscle stiffness (26, 28). Several studies have reported on these sex differences in the context of IBS, however, the mechanisms mediating their presentation are not well defined. In recent years, increased focus has been placed on the role of hormones in modulating sex differences in the presentation of functional gastrointestinal disorders (27, 29). Together with our findings, these studies indicate the potential for identification of the cause of sex-linked

symptom profiles, particularly in conditions associated with chronic pain.

In contrast, changes in pain severity were related to *SNX13* which encodes a protein that contains both a phosphoinositide binding domain and a regulator of G protein signaling domain. Overexpression of the protein that this gene encodes is associated with delayed degradation of epidermal growth factor (EGF) receptor (30). EGF activity was linked to visceral hypersensitivity in an IBS rodent model (31). Further, EGF activity is associated with neuropathic pain (30, 32) and chronic pain processing (31, 33). Importantly, *SNX13* has previously been associated with widespread pain in patients with IBS (17). Though many of the findings in the literature are tangential to nociplastic pain and IBS specifically, our findings point to the importance of distinguishing between different elements of the IBS pain profile to better understand patient symptoms and the underlying genetic loci.

This study is the first to consider genetic associations with IBS-SSS subscores. The IBS-SSS is a very useful tool used in the diagnosis and management of IBS symptoms, but the subscore components vary significantly in scope. This reflects IBS as a complex condition with varying phenotypic elements, each of which is likely related to specific genetic loci. Utilizing the aggregate score could minimize inter-patient differences and obscure the benefit of treatments which target a particular subcomponent of IBS-SSS. In order to move toward more efficacious and precise treatment for patients with IBS, thorough investigation of the genetic underpinnings of each subscore in a larger sample size is necessary.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Review Board at Beth Israel Deaconess Medical Center under protocol 2015P000282. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KH, AL, TK, JL, JS, and VC contributed to project design and analysis, IBS trial design and execution (JI and JN). In addition: JV conducted statistical analysis and drafted the manuscript. RW conducted genetic analyses and drafted the manuscript. JS, SR, and HY contributed to writing the final manuscript. All authors read, commented on, contributed to 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/fpsyt.2022.842030/full#supplementary-material

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ORIGINAL RESEARCH
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Integrating Placebo Effects in General Practice: A Cross-Sectional Survey to Investigate Perspectives From Health Care Professionals in the Netherlands

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Objectives: Placebo effects, beneficial treatment outcomes due to non-active treatment components, play an important role in the overall treatment response. To facilitate these beneficial effects it is important to explore the perspectives of health care professionals (HCPs) on the integration of placebo effects in clinical care. Three themes were investigated: knowledge about placebo effects and factors that contribute to these, frequency of placebo use, and attitudes toward acceptability and transparency of placebo use in treatment.

Methods: A cross-sectional survey, according to the Checklist for Reporting Results of Internet E-Surveys guidelines and STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE), was conducted in the Netherlands in 2020. The survey was conducted in two samples: a (nested) short survey in 78 nurses during working shifts (sample 1) and an extended online survey in 47 general HCPs e.g., medical psychologists, oncologists, surgeons (sample 2).

Results: Respondents from both samples reported to be somewhat or quite familiar with placebo effects (24.0 and 47.2%, respectively). From the six placebo mechanisms that were presented, mind-body interaction, positive expectations, and brain activity involved in placebo effects were rated as the most influential factors in placebo effects [$F_{(5,119)} = 20.921$, $p < 0.001$]. The use of placebo effects was reported in 53.8% ($n = 42$) of the nurses (e.g., by inducing positive expectations), and 17.4% of the HCPs ($n = 8$ reported to make use of pure placebos and 30.4% of impure placebos ($n = 14$). Attitudes toward placebo use in treatment were acceptant, and transparency was highly valued (both up to 51%).

Conclusions: The findings from this study address knowledge gaps in placebo effects in practice and provide insights in attitudes toward the integration of placebo effects from HCPs. Altogether, integrating these findings may potentially optimize treatment outcomes.

Keywords: placebo effects, clinician communication, attitudes and acceptability, cross-sectional survey, nurses, health care professional

INTRODUCTION

Placebos are inert substances that inherently lack properties to induce any effect (1). Placebo effects, however, can induce beneficial treatment outcomes due to non-active treatment components. These components can entail learning mechanisms (e.g., classical conditioning and expectancy learning) or contextual factors (e.g., empathic communication and trust) (2–4). In the literature, a distinction is often made between placebo use and the use of placebo effects. In terms of placebo use, research often addresses pure placebos (without active pharmacological properties, such as sugar pills) and impure placebos (with pharmacological properties but not for the specific symptoms, such as antibiotics for viral infections) (1, 5–7). In terms of placebo effects, the use of learning mechanisms and contextual effects are mentioned that induce beneficial effects (1, 4). Frequency of placebo use (pure and impure) by health care practitioners (HCP) have been studied broadly and vary between 41 and 99% across countries (e.g., Switzerland, Canada, UK and the US) (5–11). Frequencies on the use of placebo effects, however, are scarce and need to be investigated further.

To learn more about the use of placebo effects in health care, it is important to include a wide range of HCPs. However, current literature mostly describe the perspectives of doctors while the perspectives of nurses are underrepresented (12, 13). Because nursing practices encompass many facets that facilitate placebo effects (e.g., empathic communication, trust) the perspectives of this group should not be missed (12–14, 16). Moreover, investigating the perspectives on the use of placebo effects in practice may help to understand how placebo effects can best be utilized in general practice.

In the present study, perspectives on placebos and placebo effects were explored in HCPs by assessing three themes: (1) knowledge about placebo effects and their attributing factors, (2) frequency of placebo use, and (3) attitudes toward acceptability and transparency for placebo use in treatment. In addition to the current literature, this study specifically includes nurses, an overlooked group of HCPs, and focuses on their perspectives on integrating placebo effects in general practice.

METHODS

Study Design

A cross-sectional survey study was performed in the Netherlands according to the checklist Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), see **Supplementary Material 1** (17). The study was carried out in nurses at the Erasmus University Medical Center in Rotterdam, embedded in the WELCOME study, as approved by the Medical Ethics Review Committee (MEC-2017-1103). Due to the Covid-19 outbreak and its impact on the availability of nurses, a second sample of HCPs was added to be more in line with sample sizes from previous studies (ranging from 169 to 2018 HCPs) (5–10, 18–21). This second sample of HCPs received an extended version of the survey, as approved by the Psychology Research Ethics Committee of Leiden University (2020-04-07-A.W.M. Evers-V1-2368). See **Table 1** for an overview of the sample characteristics.

TABLE 1 | Sample characteristics[a].

	HCPs (*N* = 47)	Nurses (*N* = 78)	
Years of health care experience[b]	17.3 (13.8)	14.2 (11.8)	
Age[b]	41.0 (12.0)	33.8 (11.9)	
Gender (N M:F)	11:36	21:57	
Specialization	**Frequency (%)**	**Specialization**	**Frequency (%)**
Psychology[c]	11 (23.4)	Intensive care	42 (53.8)
Oncology[d,e]	8 (17.0)	Medium care internal medicine	25 (32.1)
Pediatrics[c,d,e]	4 (8.5)	Medium care surgery	11 (14.1)
Surgery[d,e]	3 (6.4)		
Medical doctor (unspecialized)[d]	3 (6.4)		
Geriatrics[d]	3 (6.4)		
Maternity care[d,e]	3 (6.4)		
General practitioner[d]	3 (6.4)		
Emergency room[d,e]	2 (4.3)		
Endocrinology[e]	2 (4.3)		
Unspecified[d]	2 (4.3)		
Phlebology[d]	1 (2.1)		
Anesthesia[e]	1 (2.1)		
Urology[d]	1 (2.1)		

[a] *Overall completion rate was 75.4%.*
[b] *Mean (SD).*
[c] *Psychologist.*
[d] *Medical doctor.*
[e] *Nurse.*
HCPs, Health care professionals.

TABLE 2 | Overview and results of survey questions ($N = 125$).

							Sample 1 ($N = 78$)	Sample 2 ($N = 47$)
1	**Current knowledge of placebo effects**	Not at all	Slightly	Somewhat	Quite	Very much		
	How familiar are you with the placebo effect?	1 (0.8)	19 (15.2)	30 (24.0)	59 (47.2)	16 (12.8)	✓	✓
	How familiar are you with the nocebo effect?	10 (21.3)	15 (31.9)	6 (12.8)	13 (27.7)	3 (6.4)		✓
		Strongly disagree	**Disagree**	**Neutral**	**Agree**	**Strongly agree**		
	Do you believe that placebo effects can improve treatment outcomes?	0 (0.0)	1 (0.8)	31 (24.8)	69 (55.2)	24 (19.2)	✓	✓
	Do you believe that nocebo effects (negative expectations) can deteriorate treatment outcomes?	1 (0.8)	6 (4.8)	58 (46.4)	44 (35.2)	16 (12.8)	✓	✓
	Do you want to learn more about placebo effects?	0 (0.0)	6 (4.9)	22 (18.0)	82 (67.2)	12 (9.8)	✓	✓
	Can you describe an example of when you experienced a placebo effect in a patient?			Free text entry[b]			✓	✓
	Can you describe an example of when you experienced a nocebo effect in a patient?			Free text entry[b]				✓
	How would you explain the placebo effect to a patient?			Free text entry[b]				✓
	How much do you think these factors influence treatment outcomes in %?		M	SD	95%CI			
	• Positive expectations		74.5	19.0	[71.4–77.6]		✓	✓
	• Good relationship between practitioner and patient		73.5	17.4	[70.0–77.0]		✓	✓
	• Mind-body interaction		75.1	15.1	[71.9–78.2]		✓	✓
	• Seeing or hearing positive experiences from other patients		69.2	17.6	[66.0–72.4]		✓	✓
	• Brain activity related to positive expectations		73.7	18.0	[71.0–76.4]		✓	✓
	• Classical conditioning (the body learns from medication)		59.9	19.7	[56.5–63.3]		✓	✓
2	**Frequency of placebo use**	Yes	No					
	Have you ever made use of placebo effects?	42 (53.8)	36 (46.2)				✓	
	Have you ever made use of **pure** placebos?[c]	8 (17.4)	38 (82.6)					✓
	Have you ever made use of **impure** placebos?[c]	14 (30.4)	32 (69.6)					✓
3	**Acceptability of placebo use**							
	Attitudes toward acceptability of placebo use			See **Figure 2**				✓
	Attitudes toward transparency of placebo use			See **Figure 3**				✓

[a] *N, (%).*
[b] *An example from the most common answers will be provided.*
[c] *N = 46.*

Recruitment and Respondents

Respondents from the first sample represent a sample of nurses from general wards and intensive care units at the Erasmus University Medical Center in Rotterdam, the Netherlands. They were recruited during or at the end of a work shift and invited to fill in the survey on a tablet. The second sample consisted of a broader range of HCPs recruited through social media platforms (LinkedIn) and the researchers' networks. The short survey (nurses) took 10 min to fill out and the extended survey (HCPs) took 15 min. The study took place on site for the nurses (on a tablet) and online for the HCPs between May and August, 2020.

Measures

The short survey (sample 1: nurses) consisted of 7 items, and the extended survey (sample 2: HCPs) of 14 items (see **Table 2**). Both surveys were based on a questionnaire that was developed to explain underlying mechanisms of placebo effects and categorized in three themes (3). For current knowledge, respondents were asked about familiarity with placebo effects and nocebo effects on a 5-point Likert scale (from very unfamiliar to very familiar) and how they would explain these effects (free-text entry). To rate the influence of important placebo factors (e.g., positive expectations, patient-practitioner relationship, mind-body interaction, social-observational learning, brain activity related to positive expectations, and classical conditioning), respondents estimated each influence on treatment outcomes on a numerical slider (i.e., 0% not important, 50% somewhat important, 100% very important) (3). Furthermore, respondents were asked about placebo use (sample 1) and pure and impure placebo use (yes/no questions) (sample 2). A third theme was added in the extended survey to assess attitudes toward acceptability and transparency of placebo use with varying answer categories (i.e., in case of psychological complaints, a cold, chronic diseases, terminal diseases, never correct, or always correct). Multiple answers were possible. See **Table 2** for an overview of the survey and samples.

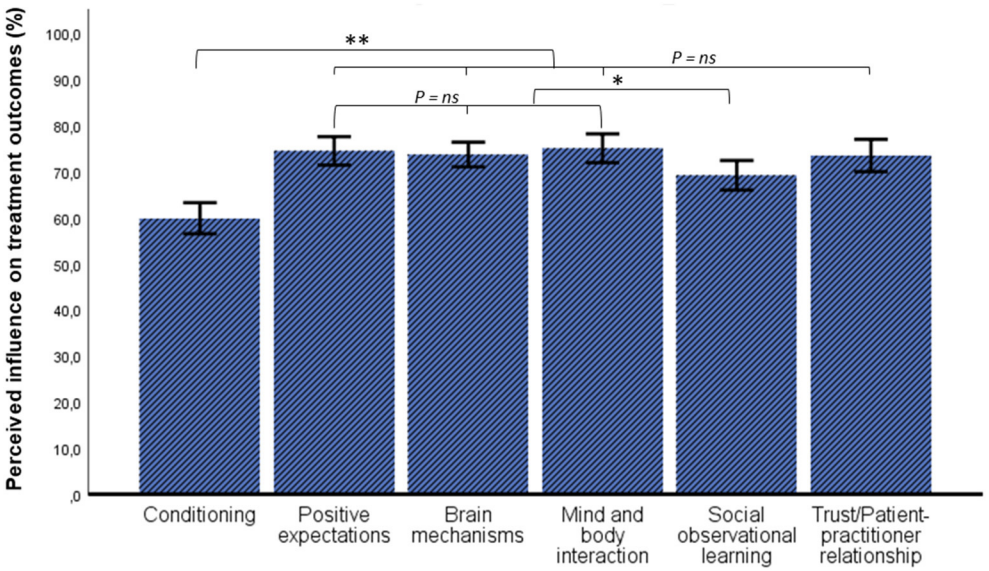

FIGURE 1 | Ratings of perceived influence of placebo factors in treatment outcomes. Error bars: 95% CI, *$p < 0.05$, **$p < 0.001$.

Procedure

After providing informed consent, the respondents of sample 1 filled in background characteristics followed by introductory information about placebo and nocebo effects. In sample 2, a differentiation between pure and impure placebos was made and additionally explained (see **Supplementary Material 2** for the provided descriptions). Subsequently, respondents were presented with the survey.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics (version 25). Data were summarized using percentages and cross-tabulations. Percentages of perceived influence of placebo factors were compared on a within-subject level in a repeated measures ANOVA. Pairwise comparisons were Bonferroni-corrected. Assumptions were checked, and corrections were made for sphericity violations (Huynh-Feldt correction) (22). Partial eta squared (ηp^2) was reported for effect size (23). A significance level of < 0.05 was set as statistically significant.

Responses from free text entry fields were handled based on the grounded theory methodology (24). The answers that were most frequently mentioned were used as in-text examples. Missing data were handled based on listwise deletion.

RESULTS

Sample Characteristics

Placebo Knowledge: Likert Scales

Sample characteristics are described in **Table 1**. Most of the respondents from both samples reported to be somewhat or quite familiar with placebo effects ($M = 3.56$, $SD = 0.93$ on a 5-point scale). The sample of HCPs seemed less familiar with nocebo effects ($M = 2.66$, $SD = 1.27$ on a 5-point scale). See **Table 2** for an overview of all numbers and percentages of familiarity with placebo and nocebo effects, treatment benefits, and interests in learning about placebo effects.

Placebo Knowledge: Perceived Influence of Placebo Mechanisms

To understand how respondents rated the influence of specific placebo factors, Bonferroni-corrected pairwise comparisons were carried out. A significant difference was found between perceived influence of the different placebo factors on treatment outcomes [$F_{(5,119)} = 20.921$, $p < 0.001$, $\eta p^2 = 0.145$]. Pairwise comparisons indicated that conditioning was rated significantly lower than all other factors. Positive expectations, brain mechanisms and mind-and-body interaction were rated significantly more influential than social learning and conditioning. All factors were rated above 50% (**Figure 1**).

Placebo Knowledge: Free Text Entry

Example of Placebo Use

The majority of the respondents (74 of 125; 59%) were able to provide an example. The most common example was the administration of paracetamol (acetaminophen) to induce sleep.

Example of Nocebo Use

Twenty-five out of 47 respondents (53%) were able to provide an example. The most common example described how negative expectations influence treatment outcomes adversely.

Explaining Placebo Effects to Patients

Of the 47 HCPs, 43 (91%) were able to provide an example. The most common examples were based on mind-and-body interaction, positive expectations, and brain activity induced by placebo effects. Six respondents (12.8%) reported to restrain

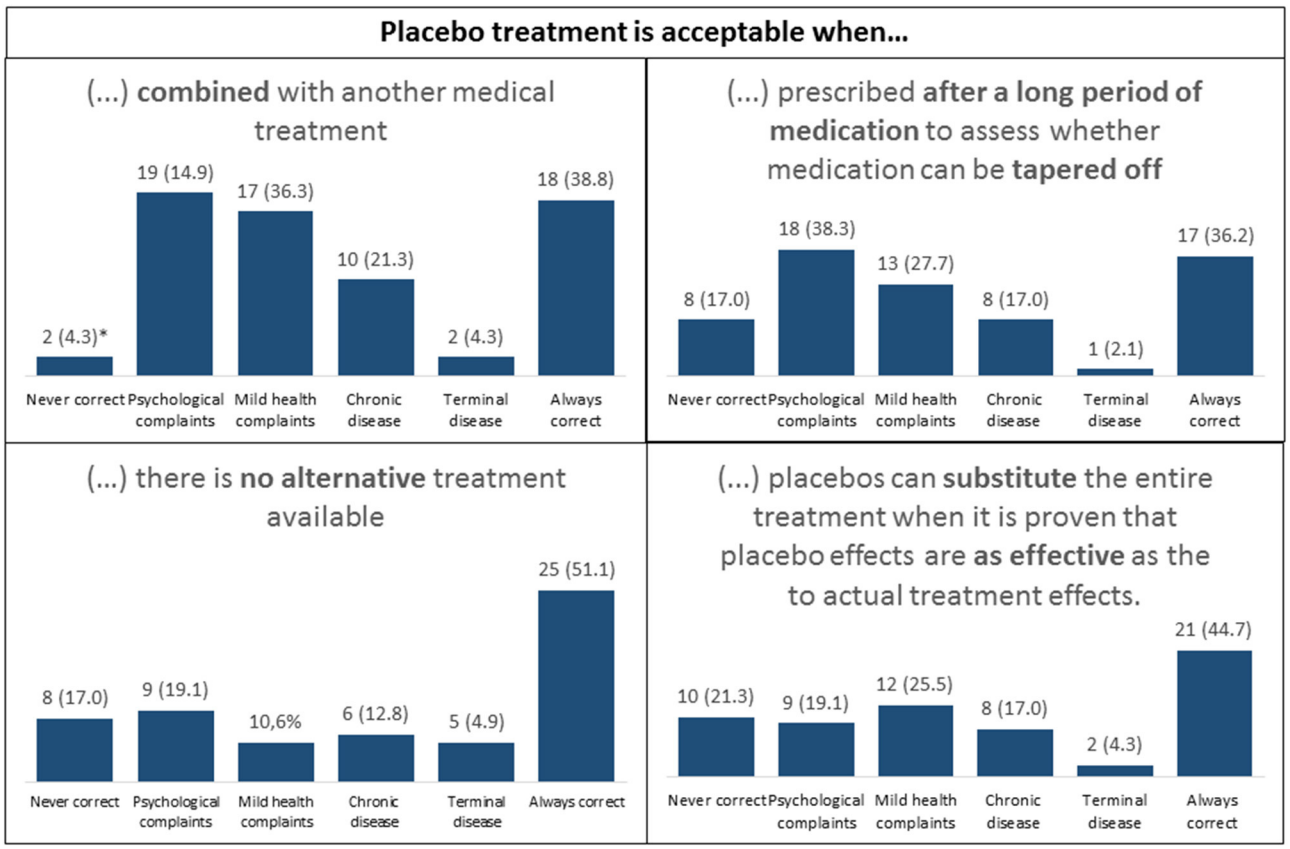

FIGURE 2 | Outcomes of placebo acceptability scores in different scenarios.*N (%).

from explaining placebo effects, because they thought this would negate the positive effects.

Attitudes Toward Acceptability and Transparency

For acceptability, we found the highest percentages for "always correct," followed by "acceptable for psychological complaints" and "acceptable for mild health complaints." For transparency, the highest percentages were found in the category "never correct" (up to 51%), even though 21% indicated that deception was correct if the placebo had worked (see **Figures 2**, **3**).

DISCUSSION

The present study explored perspectives of nurses and other health care professionals (HCPs) on the integration of placebo effects in clinical care based on three themes: knowledge about placebo effects and factors that contribute to these, frequency of placebo use, and attitudes toward acceptability and transparency of placebo use in treatment. Initially we aimed to only include a sample of nurses, but due to the impact of Covid-19 we extended the sample with other HCPs such as doctors and psychologists. Overall, the benefits of placebo effects and factors that contribute to treatment outcomes were well-understood by the respondents. The potential harm of nocebo effects, however, was less known. The use of placebos (pure and impure) was reported by approximately half of the respondents. Moreover, respondents were predominantly accepting of the (transparent) use of placebo effects.

Results from the first theme, placebo knowledge, indicated that respondents were overall familiar with placebo effects. With regards to nocebo effects, respondents seemed to be less familiar, also supported by the finding that only half of the respondents could describe an example thereof in the free-text entries. Moreover, results from the free-text fields indicated a misconception about deception, namely that explaining placebo effects would negate their effects and respondents therefore refrained from explaining these. These findings are insightful since the current trend in placebo research is leaning toward the direction of open-label placebos, where placebo effects can be elicited without deception, which seemed to be unknown in this study and other studies (3, 5, 21, 25). Placebo factors were perceived as influential in treatment with scores of 50% or higher, with mind and body-interaction, brain mechanisms, and positive expectations receiving the highest scores. Noteworthy, in a previous study that assessed placebo explanations based on similar factors, it was also found that positive expectations and brain mechanisms were rated as the most preferred explanations

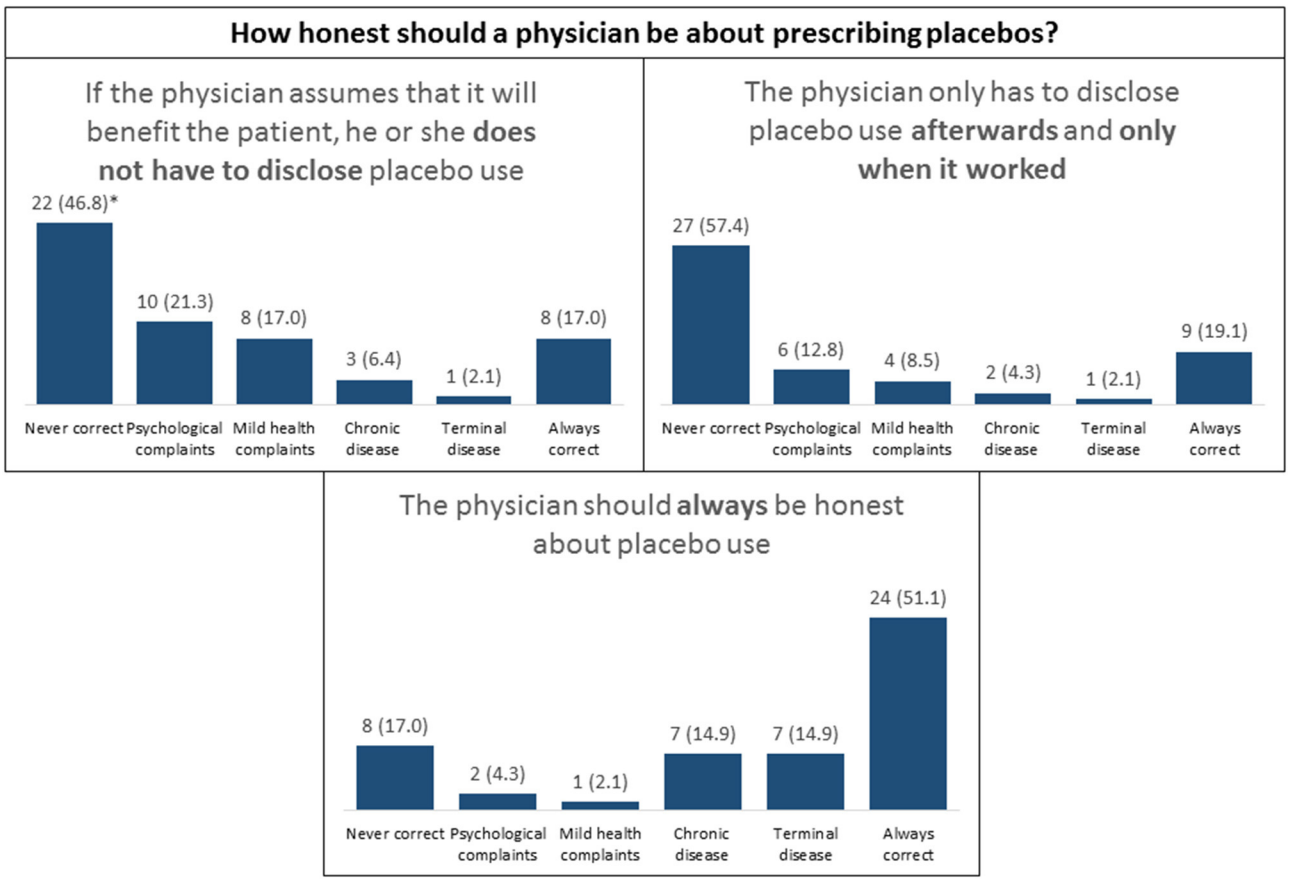

FIGURE 3 | Outcomes of placebo transparency scores in different scenarios. *N (%).

(3). Moreover, previous studies that included positive suggestions as impure placebos techniques revealed that approximately half of the respondents (general practitioners) use this technique almost daily (7, 10, 20). In line with previous studies, this present study highlights two insights, namely that respondents are knowledgeable about placebo mechanisms that involve positive expectations and brain mechanisms, and that these mechanisms can serve as helpful tools to explain placebo effects. Additionally, most respondents from our sample also indicated to be interested in learning more about placebo effects.

The second theme focused on the frequency of placebo use. Overall, the use of placebos reported in this study (53.8%) was considerably lower compared to previous studies from Germany (88%), Poland (80%), and the UK (97%) (10, 18, 20). Moreover, results from our study indicated that both samples make use of impure placebos, for example by the use of paracetamol to induce sleep, which was the most common example described. In sample 2, we found that impure placebos were more frequently used than pure placebos (30 vs. 17%). The latter percentages were also lower than the results of a systematic review about pure and impure placebo use (45 vs. 76%) (6, 26). A reason for this discrepancy may pertain to Dutch health care legislation, where physicians are obligated to inform patients about the medication that is prescribed, and placebo use may therefore be much lower than in other countries (15).

Finally, HCPs were generally acceptant toward placebo use in treatment, with the highest acceptance in subgroups of psychological or mild complaints and the lowest in case of terminal disease. Transparency was highly valued, with highest percentages in the category "never correct" for scenarios that described the use of deception, which is also in line with previous studies in general practitioners (8, 27), psychiatrists (11), and orthopedic surgeons (28).

Limitations were sample size and suboptimal inclusion because of Covid-19 (6). Even though our research aim was initially to include a homogeneous sample of nurses, we had to extend our sample to health care professionals in general, due to the great amount of pressure on nurses in the first line of care. In future research, nurses should be more included in samples and insights should be gathered about how HCPs want to be educated and trained about the use (and misuse) of placebo and nocebo effects in practice. Additional questions about nocebo effects (i.e., nocebo explanations) could be developed and implemented to gain insights in knowledge gaps, and explore how negative expectations can be harnessed to prevent adverse treatment outcomes.

CONCLUSION

HCPs in the Netherlands (nurses, psychologists, and doctors) report to use placebos and placebo effects in practice. Respondents indicated to be interested in learning about placebo effects and were acceptant of their (transparent) use. Moreover, HCPs evaluated placebo factors as influential in treatment, such as positive expectations, brain mechanisms, and mind-and body-interaction, which may be addressed in medical education or in communication with patients. Altogether, integrating these findings may potentially optimize treatment outcomes.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Materials**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

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

AUTHOR CONTRIBUTIONS

RS, DV, HM, MH, MD, and AE: primary data collection. RS: performing analysis and writing first draft of the manuscript. All authors contributed to the conception or design of the study and/or interpretation of the data as well as critically reviewing and editing 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/fpsyt.2021.768135/full#supplementary-material

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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.

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ORIGINAL RESEARCH
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The Influence of Preoperative Mood and Treatment Expectations on Early Postsurgical Acute Pain After a Total Knee Replacement

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Background: Reducing postoperative pain immediately after surgery is crucial because severe postoperative pain reduces quality of life and increases the likelihood that patients develop chronic pain. Even though postoperative pain has been widely studied and there are national guidelines for pain management, the postoperative course is differently from one patient to the next. Different postoperative courses could be explained by factors related to the treatment context and the patients. Preoperative emotional states and treatment expectations are significant predictors of postoperative pain. However, the interaction between emotional states and preoperative treatment expectations and their effect on postoperative pain have not yet been studied. The aim of our study was to identify the interaction between emotional states, treatment expectation and early postsurgical acute pain.

Methods: In this prospective clinical trial, we enrolled patients who had received a TKR at a German hospital between October 2015 and March 2019. Patients rated their preoperative pain on a numeric rating scale (NRS) 0–10 (0 = no pain and 10 = worst pain imaginable), their emotional states preoperatively on the Pain and State of Health Inventory (PHI), their preoperative treatment expectations on the Stanford Expectation of Treatment Scale (SETS), and their postoperative level of pain on a NRS 0–10.

Findings: The questionnaires were completed by 122 patients (57% female). Emotional states predict negative treatment expectation $F(6, 108) = 8.32$, $p < 0.001$, with an excellent goodness-of-fit, $R^2 = 0.31$. Furthermore, a mediator analysis revealed that the indirect effects and therefore relationship between the emotional states sad (ab = 0.06, 95% CI[0.01, 0.14]), anxious (ab = 0.13, 95% CI[0.04, 0.22]), and irritable (ab = 0.09, 95% CI[0.03, 0.17]) and postoperative pain is fully mediated by negative treatment expectations. Whereas the emotional states tired (ab = 0.09, 95% CI[0.03, 0.17]), dizzy/numb (ab = 0.07, 95% CI[0.01, 0.20]), weak (ab = 0.08, 95% CI[0.03, 0.16] are partially mediated by negative treatment expectations.

Conclusion: The relationship between emotional states and postoperative pain is mediated by negative treatment expectations. Therefore, innovative treatment strategies to reduce postoperative pain should focus on eliminating negative treatment expectation through establishing a differentiated preoperative expectation management program that also focuses on emotional states.

Keywords: placebo, nocebo, treatment expectation, TKR (total knee replacement), postoperative pain, surgery, preoperative mood, mediation analysis

INTRODUCTION

Postoperative pain is often still treated inadequately (1–4). Many patients report moderate to severe pain after surgery, which results in stress and inhibits postoperative recovery (1, 5, 6). Furthermore, severe postoperative pain can result in chronic pain, decreased quality of life, and an increased need for opioids and other analgesics, which can lead to the abuse of analgesics (5). The misuse of opioids has contributed to the opioid crises in the United States, which is having devastating consequences for the parties concerned and the health care system (7). To decrease the potential negative short- and long-term effects, the optimization of postoperative pain management is necessary and highly relevant.

The total knee replacement (TKR) is a surgical procedure that is associated with severe postoperative pain (8). Specifically, 58% of the patients who undergo a TKR experience moderate to severe pain directly after the surgery (8). Postoperative pain of TKRs is generally treated with analgesics (9). However, the pain experience of patients who undergo TKR surgery and have the same postoperative medical treatment differs significantly from one individual to the next (10). The significant difference in pain ratings, despite identical treatment, emphasizes the difficulty in optimizing pain treatment. Individual differences can be explained by the fact that the combination of biological, psychological, and social aspects influences the experience of pain (11). Hence, different postoperative courses could be explained by influencing factors related to the patients or the treatment context. Especially the mechanisms "catastrophizing," "anxiety," "depression," and "focus on pain" influence pain processing negatively (12). In addition, the processing of pain is significantly influenced by the psychological aspect "expectation" (13), which has been widely studied in placebo and nocebo research. Positive expectations of the surgery and treatment outcomes can have a significant positive impact, while negative treatment expectations can suppress endogenic analgesic processes. Expectations are important because they interact with the endogenous opioid system, which, subsequently, relieves pain (14, 15). Therefore, expectations as a mechanism for pain relief should be considered for postoperative pain treatment.

In the long term, 20% of patients who received a TKR experience pain for 1 year after the surgery (16, 17). However, the exact process underlying the transition from acute pain to chronic pain is still unknown (18). In this regard, it is known that early severe postoperative pain and psychological aspects and expectations in particular play important roles in pain processing (19). To reduce the probability of a transition from acute postoperative pain to chronic pain, it is essential to influence expectations positively preoperatively and to control postoperative pain directly after the surgery. Therefore, it is highly necessary to detect the underlying mechanisms of early acute postsurgical pain.

To reduce early postoperative pain, potential predictors must be identified and treated. Significant predictors for postoperative pain are preoperative emotional states (e.g., anxiety, depression) and preoperative treatment expectations. Hence, not only postoperative pain processing mechanisms are relevant for the control of postoperative pain, but it can also be predicted and, potentially, influenced preoperatively. Higher pre-operative anxiety ratings lead to increased pain during the time in the ward and at home (20, 21), and an increased hospital stay (22) after TKR surgery (23). Preoperative anxiety and depression in patients scheduled for a total knee arthroplasty (TKA) has been associated with a higher level of knee disability (24). Equally, preoperative anxiety and depression increase postoperative pain (25) and the need for analgesics for patients undergoing a TKR (26). In addition, more severe depression is associated with an increase in postoperative complications (27). Postoperative pain and postoperative recovery of patients receiving a TKA (28) are influenced by emotional states and treatment expectations (29). Treatment expectations can be specifically understood (e.g., "the analgesics will help to reduce the postoperative pain") or can be rather vague (e.g., "the treatment will help me"). To understand the underlying mechanisms and to establish adequate innovative pain treatment methods, it is relevant to understand the combined effect of the relationship and interaction between preoperative emotional states and treatment expectations related to early postoperative pain.

To our knowledge, this is the first time that the relationship and interaction between preoperative emotional states and treatment expectations relating to early postoperative pain in patients receiving a TKR has been analyzed. Therefore, the aim of this paper is to investigate the relationship between preoperative emotional states and treatment expectations related to early postoperative pain. Specifically, we aimed to investigate whether preoperative emotional states have a direct influence on early postoperative pain or whether postoperative pain is influenced by treatment expectations. We expected that treatment expectations play a mediating role between emotional states and postoperative pain.

MATERIALS AND METHODS

Study Populations

Patients were eligible if they were at least 18 years old and received a TKR due to knee osteoarthritis and excluded if they were cognitively impaired, had an insufficient command of the German language, suffered from mental disorders (according to ICD-10; except F45.41), consumed any mind-altering substances (e.g., psychoactive drugs, including illegal drugs), or suffered from pain requiring special causative medical treatment (e.g., cancer-related pain). Patients were only included if they received a primary TKR. Patients who received a replacement for an existing protheses were excluded. All participation was voluntary, the patients were informed about the study and provided informed written consent.

Materials

In this prospective clinical trial, we enrolled patients who received a total knee replacement (TKR) due to osteoarthritis at a German hospital between October 2015 and March 2019. All patients who met the inclusion criteria and had none of the exclusion criteria were invited to participate in the study. The relevant instruments are scales to measure emotional states, treatment expectations, and postoperative pain.

Emotional States

Patients rated their emotional states with the Pain and State of Health Inventory (30). The instrument provides good internal consistency and is validated in the context of perioperative care for patients receiving a TKR (30). This instrument is mainly used to evaluate the course of postoperative recovery related to preoperative ratings. In this study, we specifically investigated preoperative emotional states ratings. The emotional states include the items being "sad," "anxious," "weak," "irritated," "numb/dizzy," and "tired" and were measured on a numerical rating scale (NRS) 0–10 (0 = not at all; 10 = very anxious, weak etc.).

Expectations

There are different options for measuring treatment expectations in clinical studies in the perioperative setting (29). Treatment expectations are always manifold and can, *inter alia*, include general treatment expectations (e.g., "I expect good outcomes from medical treatment") or specific expectations related to the treatment or a symptom (e.g., "I expect bearable pain after the surgery"). However, the majority of generally utilized expectation measures used in clinical studies, if expectations are included in the study design, are not validated single scales that depend on the research question. The only treatment expectation scales validated thus far in the perioperative setting is the Stanford Expectation Treatment Scale (SETS) (31). The SETS can be divided into positive and negative treatment expectations and assesses corresponding scales of positive and negative expectations of the planned treatment on a 7-point Likert scale, with additional open questions about the planned treatment and expected benefits or negative side-effects. Example items for the positive treatment expectation are "the treatment will be completely effective," with answer options ranging from strongly disagree = 1 to strongly agree = 7, and an example of a negative treatment expectation item is "I am worried about my treatment," with the response options also ranging from strongly disagree to strongly agree. High scores in positive treatment expectation of SETS indicate that patients do not expect that their treatment will be successful, nor that the treatment will improve symptoms. Whereas low scores in positive treatment indicate that patients expect that their treatment will be successful and improve their symptoms. In contrast, high scores in negative treatment indicate that patients are not worried about the treatment. Whereas low scores in negative treatment expectation indicate that the patients are worried about their treatment and that they are nervous about possible negative treatment effects, The patients completed the SETS 1 day prior to surgery to measure their treatment expectations of the TKR.

Preoperative Pain

To measure preoperative pain, patients were asked 1 day prior the surgery to rate their pain on a NRS 0–10 (0 = no pain; 10 = most pain imaginable).

Postoperative Pain

To measure postoperative pain, patients were asked to rate their pain on an NRS 0–10. Patients rated their pain every 2 h on the first day after the surgery, from 6 am until midnight, in a pain diary. Subsequently, the mean pain rate for the day was calculated from the pain ratings.

Study Design

In this prospective clinical trial, we investigated the relationship between preoperative emotional states and treatment expectations and their effect on postoperative pain for patients receiving a TKR. All patients who received a TKR at the German hospital center, Schön Klinik Hamburg Eilbek, were screened on paper by a study physician. If the patients met the inclusion criteria on paper, they were screened in person by the study physician 1 day prior to the surgery. If the patients met the inclusion and none of the exclusion criteria, they were informed one day prior to their surgery and asked to participate. All patients participated voluntarily and provided written consent. To assess their emotional states and preoperative treatment expectations on the relevant scales, patients completed the PHI (30) and the SETS (31) 1 day prior to surgery. To measure the influence of these ratings on postoperative pain, patients rated their postoperative level of pain on an NRS 0–10 (0 = no pain and 10 = worst pain imaginable) 1 day after the surgery. Preoperative pain assessed 1 day prior the surgery on a NRS 0–10 will be included as a possible confounder. These were all self-ratings and, therefore, subjective. They were completed by the patients without the presence of a researcher.

Statistical Analysis

All data were entered into SPSS and double-checked by two researchers independently. The analyses were performed with the statistical package IBM SPSS Statistics (version

27.0; IBM Inc., Armonk, NY, United States). The tests with $p < 0.05$ were considered statistically significant. In the path model, the independent variables were the individual emotional states, the dependent variable was postoperative pain, the mediators were treatment expectations of medical treatment, and the confounder was preoperative pain. To calculate the path model (model 4) of the SPSS Hayes' macro, PROCESS (32), which uses ordinary least square regression and yields unstandardized path coefficients for total, direct, and indirect effects, was applied. Bootstrapping with 5,000 samples together with heteroscedasticity consistent errors were employed to compute the confidence intervals and inferential statistics. Effects were deemed significant when the confidence interval did not include zero. The interpretation of the goodness-of-fit varies between research fields. We applied the interpretation according to Cohen (33), in which an adjusted $|R^2| = 0.02$ indicates a weak, $|R^2| = 0.13$ a mediate, and $|R^2| = 0.26$ a high goodness-of-fit for the overall model. Missing values were not completed, because the missing data was assumed to be random.

Sample Size

The sample size was estimated by using Table 3 of Fritz and Mackinnon (34). The table summarizes simulations for a power of 0.8 with a significance level of $p < 0.05$ to assess the required sample size for mediation effects. PROCESS is based on the bootstrapping method to analyze mediation effects. Hence, the percentile bootstrapping row in the table is relevant for our sample size calculations. Former research found a medium association between emotional states and treatment expectation (α-path) and a large relationship between treatment expectation and postoperative pain (β-path) (35, 36). The estimated size of the α-path is 0.26 and the estimated size of the β path is 0.59. Hence, 122 patients were required to assess the mediation effect for our study design.

RESULTS

Demographic Characteristics of Participants

A total of 122 patients participated in the study (**Figure 1**). Of the participants, 70 (57%) were female and 52 (43%) were male. The average age of the participants was 68 years (SD = ± 9.4), and 66% of the patients were married. For more detailed information, please refer to **Table 1**.

Emotional States

A total of 119 patients completed all items related to emotional states. The internal consistency of emotional states in this sample was Cronbach's α = 0.83. Preoperatively, the mean rating of being sad on an NRS 0–10 (0 = not sad; 10 = very sad) was 2.05 (SE = 0.20; 95% CI [1.64, 2.45]). The mean rating of being anxious was on an NRS 0–10 (0 = not anxious; 10 = very anxious) was 2.31 (SE = 0.23, 95% CI [1.85, 2.76]). The mean rating of being tired on an NRS 0–10 (0 = not tired; 10 = very tired) was 2.45 (SE = 0.20, 95% CI [2.05, 2.85]. The mean rating of being numb/dizzy on an NRS 0–10 (0 = not numb/dizzy; 10 = very numb/dizzy) was 0.94 (SE = 0.16; 95% CI [0.62, 1.25]). The mean rating of being weak on an NRS 0–10 (0 = not weak; 10 = very weak) was 1.97 (SE = 0.21; 95% CI [1.56, 2.39]). The mean rating of being irritated on an NRS 0–10 (0 = not irritated; 10 = very irritated) was 1.61 (SE = 0.19, 95% CI [1.24, 1.98]).

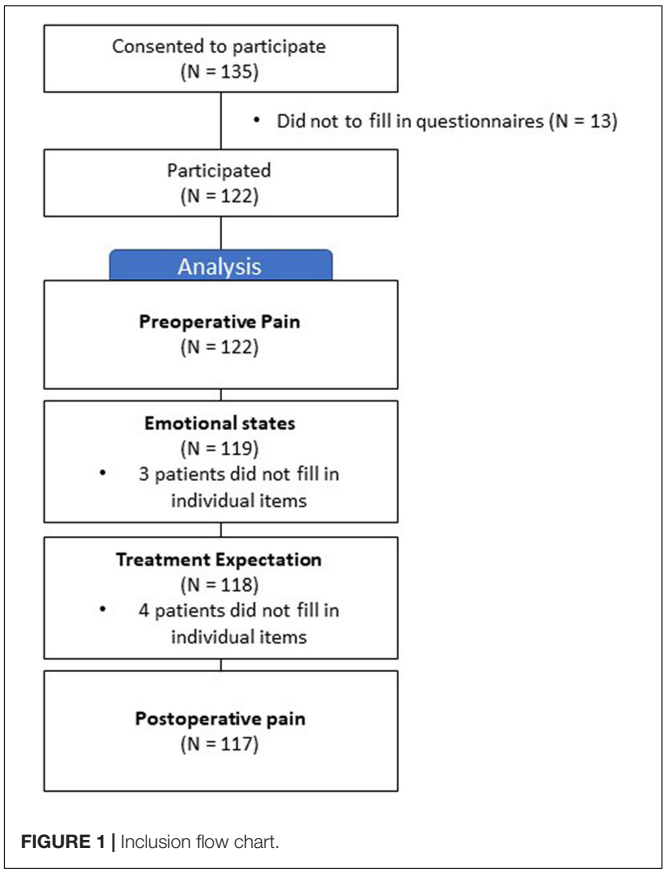

FIGURE 1 | Inclusion flow chart.

Treatment Expectations

A total of 118 patients completed all items related to positive and negative treatment expectations. The mean negative treatment expectation was 4.77 (SD = 1.43), which implies that, on average, patients neither agreed nor disagreed or slightly disagree that they expected a negative treatment outcome. The internal consistency of this sample for negative treatment expectation was Cronbach's α = 0.78. The mean rating for positive treatment expectation was 2.29 (SD = 0.85) which implies that, on average, patients agree slightly to moderately on expecting positive effects from their treatment.

Preoperative Pain

All patients rated their preoperative pain. The mean preoperative pain score on the NRS 0–10 1 day prior the surgery was 6.5 (SE = 2.00; 95% CI [6.20, 6.89].

Postoperative Pain

A total of 117 patients rated their postoperative pain. The mean postoperative pain score on the NRS 0–10 on the first day after

TABLE 1 | Basic information on participants.

Characteristic	Total sample
Sample size	122
Sex – female (%)	70 (57.4)
Age (years) (%)	
18 – 40	0 (0)
41 – 50	6 (4.9)
51 – 60	19 (15.6)
61 – 70	42 (34.4)
71 – 80	48 (39.3)
81– 88	7 (5.7)
Mean age (years) (SD)	67.96 (9.4)
Marital status (%)	
Unmarried	10 (8.2)
Married	80 (65.6)
Divorced	11 (9.0)
Widowed	17 (13.9)
Stable partnership	3 (2.5)
Missing value	1 (0.8)
Education (%)	
No educational qualification	1 (0.8)
Lower secondary school	51 (41.8)
Intermediate secondary school	42 (34.4)
High school/A-levels	11 (9.0)
College or beyond	16 (13.1)
Missing value	1 (0.8)

Data may not total 100% because of rounding.

the surgery was 4.74 (SE = 0.16; 95% CI [4.42, 5.05]). The internal consistency for repeated measured level of pain of this sample was Cronbach's $\alpha = 0.84$.

Regression

Negative Treatment Expectations

The results show that emotional states predict negative treatment expectation $F(6, 108) = 8.32$, $p < 0.001$, with excellent goodness-of-fit $R^2 = 0.31$. The results reveal that preoperative pain does not confound the regression. Moreover, negative treatment expectation predicts worse postoperative pain $F(1,111) = 7.65$, $p = 0.007$, with a weak goodness-of-fit $R^2 = 0.06$. Being anxious (ß = −0.54), dizzy/numb (ß = −0.13), and irritated (ß = −0.13) are the strongest factors influencing negative treatment expectations, while being tired (ß = 0.05) and feeling weak (ß = −0.02) are the least influential predictors. A feeling of anxiety ($t = -2.56$, $p = 0.01$), being dizzy/numb ($t = -2.64$, $p = 0.01$), and irritated ($t = -2.53$, $p = 0.01$) had a statistical significantly influence on negative treatment expectations.

Positive Treatment Expectations

The results show that emotional states do not predict positive treatment expectation $F(6,108) = 1.94$, $p = 0.08$) with a mediate goodness-of-fit adjusted $R^2 = 0.10$. Furthermore, positive treatment expectation does not predict postoperative pain $F(1,112) = 1.09$, $p = 0.30$) with no goodness-of-fit adjusted $R^2 = 0.001$.

Mediator Analysis

Negative Treatment Expectations

After the mediator (negative treatment expectation) and the confounder (preoperative pain) were entered into the model, the emotional states sad ($a = -0.20$, $p = 0.004$), anxiety ($a = -0.37$, $p < 0.001$), tired ($a = -0.25$, $p < 0.001$), dizzy/numb ($a = -0.22$, $p = 0.01$), weak ($a = -0.23$, $p < 0.001$), and irritated ($a = -0.27$, $p < 0.001$) predicted the mediator significantly, which, in turn, predicted postoperative pain significantly (see **Figure 2**). We found that the relationship between preoperative emotional states (feeling sad, anxious, tired, dizzy/numb, weak, and irritated) and postoperative pain was fully mediated by negative treatment expectations. The direct effect (c') of the emotional states (sad, anxious, and irritated) to postoperative pain was not significant. Whereas the direct effect of the emotional states (tired, numb/dizzy, and weak) was significant. The direct effects were sad ($c' = -0.04$, $p = 0.64$), anxious ($c' = -0,07$, $p = 0.36$), tired ($c' = -0,20$, $p = 0.01$), numb/dizzy ($c' = -0.20$, $p = 0.04$), weak ($c' = -0.19$, $p = 0.02$), and irritated ($c' = -0.1$, $p = 0.17$), while the indirect effects for emotional states were sad ($ab = 0.06$, 95% CI[0.01, 0.14]), anxious ($ab = 0.13$, 95% CI[0.04, 0.22]), tired ($ab = 0.09$, 95% CI[0.03, 0.17]), feeling numb/dizzy ($ab = 0.07$, 95% CI[0.01, 0.20]), weak ($ab = 0.08$, 95% CI[0.03, 0.16]), and irritated ($ab = 0.09$, 95% CI[0.03, 0.17]). This implies that the interaction between emotional states (sad, anxious, irritated) and postoperative pain are fully mediated and the emotional states (tired, numb/dizzy, and weak) are partially mediated by negative treatment expectation.

DISCUSSION

In the present study, we provide evidence that negative expectations are an important mediator for postoperative pain. Negative treatment expectations correlates with the emotional states of feeling sad, anxious, tired, numb/dizzy, weak, and irritated. This aligns with previous research that also found evidence that preoperative mental states influence postoperative pain (36). Furthermore, our findings demonstrate that individual emotional states correlates with negative treatment expectations. However, the examination of the prognostic effect of the combined investigated emotional states on negative treatment expectations and their prediction of negative treatment expectation showed that especially anxiety, numbness/dizziness, and irritability significantly predict negative treatment expectations. Interestingly, postoperative pain is mediated through negative treatment expectations, which can be interpreted that, to reduce postoperative pain, a treatment that focuses on negating negative treatment expectations is necessary and highly relevant.

Our results align with the bio-psycho-social pain model that holds that pain experience is shaped by somatic, psychological, and social factors (11). In our study, we focused on perioperative psychological factors, which is a bio-psycho-social context. We also found that psychological factors, such as emotional states that influence treatment expectations, further influence

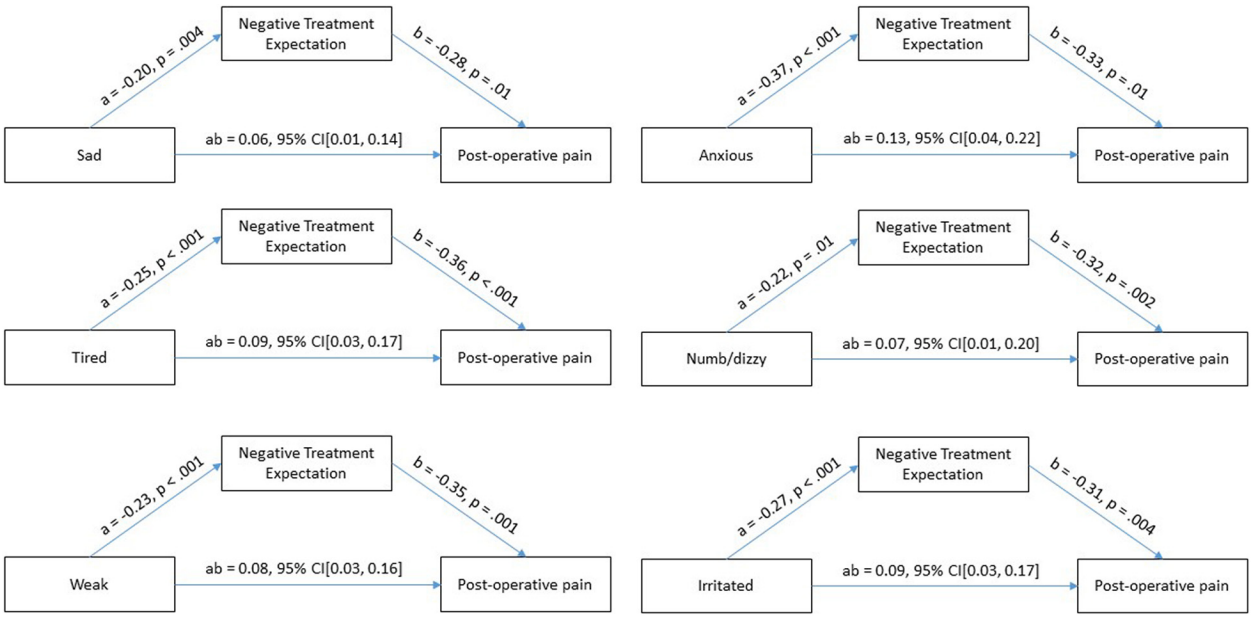

FIGURE 2 | Test of mediation effect of treatment expectation on emotional states and postoperative pain.

the experience of pain. Previous research has also shown that psychological factors influence pain experience and pain-related impairment in patients with joint degeneration (37–39). The focus of studies that investigate psychological factors is usually on depressive symptoms (40, 41). Other research has shown that postoperative pain experienced by patients who undergo a TKR is influenced by the severity of the preoperative pain, pain catastrophizing, depression, and pain-related impairment (42). Furthermore, one study discovered that preoperative catastrophizing and a lack of coping strategies predict a higher postoperative pain level (43). Our study adds to the knowledge by showing that patients do not necessarily have to show explicit depressive symptoms, but any emotionally impaired state can influence treatment expectations and, subsequently, postoperative pain.

Our findings suggest that emotional states predict treatment expectations and, therefore, play a critical role in the treatment outcome for postoperative pain. According to the literature concerning placebo mechanisms, positive treatment expectations are crucial to enhance surgical treatment outcomes (44, 45). However, underlying mechanisms have to be uncovered to be able to influence treatment expectations. The specific underlying mechanisms relating to our results can only be speculated so far. One possibility could be that the nocebo system is activated, and the placebo system deactivated. This would imply that, on the one hand, due to the activated nocebo system, biochemical changes occur through the activation of cholecystokinin that facilitate pain transmission (46), and the dopaminergic system and opioid release may also be deactivated as a consequence (47). On the other hand, it is also possible that the placebo system is deactivated. The placebo system is significantly influenced by the activation of the dopaminergic system and the release of endorphins and endogenic opioid system (48–50). In addition, selective attention could be an important modulator (51, 52), and the specific modulator and mechanisms should be investigated in further research.

Interestingly, we found that emotional states influence negative treatment expectations but not positive treatment expectations. One reason could be that the placebo and nocebo systems do not share the same network (53). Nocebo effects might be produced through the medial pain system (54), with the hippocampus, the dopaminergic system, and the release of endorphins and endogenic opioids as key players. We could therefore also confirm that negative treatment expectations are not the opposite of positive treatment expectations and that patients who expect negative treatment outcomes do not automatically deny positive treatment outcomes. However, if negative expectations predominate, they could either increase the activity of the nocebo system or hinder the activity of the placebo system, so that both pathways could cause an increase in the postoperative pain experienced. Therapeutic interventions for perioperative pain management are therefore, on the one hand, the reduction of negative expectations and, on the other hand, the strengthening of the placebo system. A reduction in negative treatment expectations may be achieved through preoperative differentiated and specialized expectation management. This could be achieved in a program that focuses on individual treatment expectations, including previous negative treatment experiences and personal anxieties. Our results imply that expectation management should also include a focus on emotional states. The placebo system could be strengthened by directing all the patient's senses toward the positives of postoperative analgesia. Patients should be aware of analgesic action, know how

the medication works in their bodies, when it will take effect, and how long the effect lasts. Knowledge about the medication could provide them with insight into their pain management and, in the sense of open medication, strengthen the placebo component inherent in every analgesic (55). It is important to investigate the influence of other emotional states on positive treatment expectation in further research, which could provide more insight into how to decrease postoperative pain and how treatment expectations can be positively influenced.

Strengths

This is the first study to report on the interaction between emotional states, expectations and postoperative pain in a clinical sample of patients expected to experience early acute postoperative pain. Previous studies have investigated healthy participants rather than a clinical sample. However, pain pathways, experiences, and treatment expectations may differ between healthy and clinical participants. With this study, we detected that emotional states, such as being sad, anxious, feeling dizzy/numb, weak or irritated, individually or in combination, can influence negative treatment expectations, which, in turn, influenced postoperative pain experiences in a clinical sample. We further detected that the relationship between emotional states and postoperative pain is fully mediated by negative treatment expectations. Therefore, we detected the mediator between emotional states to postoperative pain in the underlying mechanisms of the placebo and nocebo effects. We further found that negative interaction between emotional states and postoperative pain is fully mediated by negative treatment expectations. In consequence, our results provide the foundation for future innovative treatment options that are required for optimal postoperative pain management.

Limitations

Several limitations in this study warrant comment. First, the data used were based on self-reporting, and there might be altered response behavior. However, because pain is subjective and there are no objective measurement tools to assess it, postoperative pain can only be assessed *via* a self-report. Second, only patients who received a TKR were included in the study, and TKRs are often associated with severe postoperative pain. In addition, patients have usually experienced pain for a long period prior to the TKR and have often been treated conservatively. Hence, the results cannot be generalized to other surgeries *per se*, but they are a good indicator for patients undergoing TKR surgery. Patients were included, when they received a TKR due to osteoarthritis. Osteoarthritis can be classified based on the Kellgren and Lawrence system of classification (56). In this study, we did not assess the grade of osteoarthritis and can therefore not analyze if the grade of osteoarthritis influences emotional states, treatment expectations, or postoperative acute pain. Furthermore, treatment expectations were only vaguely assessed, and, therefore, no conclusions can be drawn about the relationship between symptom-specific expectations relating to postoperative pain and emotional states. However, a validated tool was used to assess treatment expectations. Due to the aim to gain a first overview about the relationship between emotional states, treatment expectations and postoperative acute pain, not many confounders were included into the study. However, treatment expectation and placebo effects and their influence on postoperative pain is complex. Hence, in further studies possible confounders (e.g., catastrophizing, depression) should be included into the study design.

Outlook

As already noted, this study provides a foundation for future research. Resulting from our findings, there are several aspects that should be investigated. First, modulators should be investigated to discover the underlying mechanisms and the interaction between emotional states and treatment expectations. In this context, the underlying biochemical and neural mechanisms should be examined to establish their effect on perioperative procedures. Second, further studies should investigate how emotional states can be positively influenced and whether this will decrease negative treatment expectations, which should, in turn, decrease postoperative pain. Therefore, it should be investigated how negative expectations can be mitigated or changed into positive expectations. In this regard, it is necessary to further investigate the different modulators of positive and negative treatment expectations. This could be a precursor for innovative pre- and postoperative treatment strategies that can be developed to enhance treatment outcomes and the associated placebo effect. Therefore, future interventions could focus on reducing negative treatment expectations by considering the influential mechanisms of impaired emotional states. By focusing on the influential factors of negative treatment expectations, postoperative pain can be reduced directly after the surgery. Hence, developing a preoperative differentiated and specialized expectation management program will be highly relevant. In the light of the current opioid crisis (7, 57), it would be especially relevant to investigate the relationship between emotional states, treatment expectations, and analgesic consumption.

CONCLUSION

This study investigated a sample of patients who received a TKR at a German hospital. The results reveal that the relationship between impaired emotional states and postoperative pain is fully mediated by negative treatment expectations. Therefore, novel and innovative treatment strategies to reduce postoperative pain should focus on negative treatment expectations through a differentiated and specialized preoperative expectation management program that should also aim to reduce the emotional states of being sad, anxious, numb/dizzy, tired, weak, and irritated. A specialized treatment expectation management program developed with consideration of our findings might mitigate and change negative expectations to influence postoperative pain positively.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

JS and RK contributed to conception, design of the study, and wrote the first draft of the manuscript. JS performed the statistical analysis. Both authors contributed to manuscript revision, read, and approved the submitted version.

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Open-Label Placebo Administration Decreases Pain in Elderly Patients With Symptomatic Knee Osteoarthritis – A Randomized Controlled Trial

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Background: Recent studies indicate that the administration of open-label placebos (OLP) can improve symptoms in various medical conditions. The primary aim of this 3-week randomized controlled trial was to examine the effects of OLP treatments on pain, functional disability, and mobility in patients with arthritic knee pain.

Methods: Sixty patients (55% females; mean age, 66.9 ± 9.7 SD years) were randomized to one of two OLP treatments (n = 41) or no treatment (NT; n = 19). OLP treatments were accompanied by the verbal suggestion "to decrease pain" (OLP-pain, n = 20) or "to improve mood" (OLP-mood, n = 21). Pain and mood levels were monitored on 11-point Numeric Rating Scales (NRSs) in a patient diary, and global clinical improvement (CGI-I) was assessed at the end of the study. At baseline and after 21 days, patients filled in validated questionnaires to assess symptoms and functional disability of the knee (WOMAC), mental and physical quality of life (SF-36), state anxiety (STAI-state), perceived stress (PSQ-20), and self-efficacy (GSE). In addition, knee mobility (neutral zero-method), heart rate variability (HRV), and diurnal cortisol levels were evaluated before and after treatment.

Results: Evaluation of daily pain ratings indicated significant pain decrease in the OLP groups compared to NT (p = 0.013, d = 0.64), with no difference between the OLP-pain and the OLP-mood groups (p = 0.856, d = 0.05). OLP treatment also improved WOMAC pain (p = 0.036, d = 0.55), again with no difference between the two OLP groups (p = 0.65, d = 0.17). WOMAC function and stiffness, knee mobility, stress, state anxiety, quality of life, and self-efficacy did not change differently between groups.

Conclusion: OLP treatment improved knee pain in elderly patients with symptomatic knee osteoarthritis (OA), while functional disability and mobility of the knee did not change. The content of the verbal suggestion was of minor importance. OLP

administration may be considered as supportive analgesic treatment in elderly patients with symptomatic knee OA.

Trial Registration: German Clinical Trials Register (https://www.drks.de/), DRKS00015191 (retrospectively registered).

Keywords: chronic pain, knee arthrosis, open-label placebo, placebo effect, mood, verbal instruction

INTRODUCTION

Osteoarthritis (OA) is a degenerative, primarily non-inflammatory joint disease with chronic course and represents the most common joint disease among adults (1). It is characterized by functional limitations and usage-related pain (2), though there is often a mismatch between radiological stages (e.g., Kellgren degrees) and clinical complaints (3). The most influential risk factor for the development of OA of the knee is higher age. In industrialized societies the prevalence in the over 60 year's bracket is approximately 18% (4–6). Socioeconomic burden and restrictions in quality of life are substantial (4, 7–11). Therapy of OA primarily aims at symptom reduction and prevention of disease progression and typically involves non-pharmacological interventions (e.g., weight reduction, physical training) as well as multimodal pain control strategies (12, 13). Interestingly, several studies indicate that patients with OA also benefit from placebo interventions by improving pain, stiffness, and self-reported functionality (14–16).

It has long been assumed that deception is necessary to evoke placebo effects. Accordingly, the deceptive administration of placebos is the primary subject of placebo research and is rather common in clinical practice (17–19). Nonetheless, the deceptive administration of placebos is afflicted with negative connotation and ethical concerns (20, 21). In recent years, several studies investigated the clinical effects of "non-deceptive placebos," also referred to as "open-label placebos" (OLP). In this case, placebos are described honestly as inert substances. Interestingly, there is increasing evidence that OLP treatments go along with therapeutic benefits in various conditions, including chronic low back pain, irritable bowel syndrome, episodic migraine, allergic rhinitis, depression, attention deficit hyperactivity disorder, and cancer induced fatigue (22–30). Two recent meta-analyses concluded that even though evidence is still limited, OLPs could be a promising therapeutic approach for various clinical conditions (27, 31).

The psychological mechanisms underlying the effects of OLP administration are unknown. While the effects of deceptive placebo interventions are mediated in part by expectations raised by verbal suggestions, there is increasing evidence that conscious expectations are of limited importance for the effects of OLP (32). Furthermore, while several studies suggest that the reduction of stress and negative emotions is involved in placebo hypoalgesia (33), the role of stress reduction for the effects of OLP has not been studied.

In this randomized controlled trial, we investigated the effects of OLP administration in patients with symptomatic knee OA. In order to study the role of different verbal suggestions for the effects of OLP, we included two OLP interventions: one to "relieve pain" ("OLP-pain") and one to "improve mood" ("OLP-mood"). The OLP-pain intervention was described as reducing pain and thereby improving health status, while the OLP-mood intervention was described as enhancing positive emotions and thereby improving health status. The rationale behind the mood-enhancing OLP intervention was based on previous studies showing that placebo interventions can improve mood (34), and that positive emotions can reduce chronic pain (35). Based on previous suggestions that conscious expectations are of limited importance for the effects of OLP (32), we hypothesized that OLP treatment would improve pain, physical functional disability, and mobility of the target knee regardless of the explicit treatment goal, i.e., to improve pain or improve mood. Secondary outcomes included health-related quality of life as well as validated stress measures in order to learn more about the role of stress reduction for OLP effects.

MATERIALS AND METHODS

Study Design

This is a randomized controlled trial with a three-group parallel design. A total of 60 participants were randomized to one of three groups using a 1:1:1 randomization rate. After the baseline measurement on the first study day, participants were randomly assigned to no treatment (NT), OLP to reduce pain (OLP-pain), or OLP to improve mood (OLP-mood).

Participants

Patients with pre-diagnosed painful OA of the knee were recruited *via* advertisements in local newspapers and by laying out flyers in local medical practices. Patients were included when they were ≥18 years old, in a good general/nutritional condition and were diagnosed with OA of the knee (Kellgren II–III) at least 6 months prior to the onset of the study, as evidenced by a physician letter. In addition, participants had to provide sufficient knowledge of German to understand the questionnaires, had to be able to follow the study requirements and instructions, and had to provide written informed consent. The mean pain score at the target knee had to be at least 4 on a 0–10 Numeric Rating Scale (NRS), while pain in the non-target knee should not exceed a level of 3. Exclusion criteria comprised inflammatory joint disease; other pain conditions; knee injury or surgery within the previous 3 months or planned surgery during the study period; intra-articularly injected knee pain medication; use of opioid analgesics, glucocorticoids, topical pain treatment, or systemic treatments that could affect outcomes

during the study; medications that affect the autonomic nervous system or neuroendocrine system; use of psychotropic drugs; known clinical depression and/or depression score >10 on the Hospital Anxiety and Depression Scale (HADS-D) (36); drug abuse or alcoholism; pregnancy or lactation; known intolerance or allergy to lactose or gelatin; presence of malign diseases (somatic or mental) or other clinically significant conditions that, in the opinion of the study director or investigator, may preclude participation; participation in another study within the past 4 weeks.

Procedure

Volunteers who contacted the study center received information about the study procedure and the open-label placebo intervention and were screened for the inclusion and exclusion criteria during a telephone interview. Eligible patients who consented to participate were included in the study. Study participation comprised two examinations at the Institute of Medical Psychology, LMU Munich, with a time interval of 21 days. Prior to the first study visit participants received saliva tubes along with detailed instructions on how to collect and store saliva probes the day before study visits. At both study visits, participants completed standardized questionnaires, and a 5-min electrocardiogram (ECG) was performed to assess heart rate variability (HRV). At their first visit, patients were administered a paper-and-pencil diary to monitor pain, mood, and analgesic use each day of the study period. After performing the baseline assessments at the first study visit, participants received general information on the placebo effect, namely that the placebo effect is powerful, the body can automatically respond to taking placebo pills like Pavlov's dogs who salivated when they heard a bell, a positive attitude helps but is not necessary, and taking the pills faithfully is critical (23). Participants were then randomly assigned to NT or one of two OLP groups (OLP-pain, OLP-mood). Participants in the OLP groups received detailed information on why their treatment with OLPs was expected to be effective (**Supplementary Table S1**). They then obtained a medication tin with lactose capsules to be taken twice a day, thereby emphasizing the importance of regular pill intake. In order to minimize disappointment, participants in the NT group were informed about the purpose and importance of a control group in clinical trials (**Supplementary Table S1**). Ten days after the first study visit, all patients were contacted by phone and asked how they were feeling and whether they had any questions regarding the study, and they were thanked again for participating in the study.

Randomization and Blinding

Computer-assisted randomization was performed by a person not involved in the experiments, who prepared sequentially numbered, sealed, and opaque randomization envelopes. Due to the open-label nature of the placebo treatment, group allocation was not blinded.

Placebo Interventions

After treatment allocation, the participants in the two OLP groups received a box with identical gelatin capsules filled with mannitol to be taken regularly twice daily (morning and evening) for a period of 21 days. The labels of the medication boxes differed between the two OLP groups, indicating either "pain relief" or "mood improvement." The administration of the boxes was accompanied by verbal suggestions of the effects to be expected from the respective placebo treatment. In the OLP-pain group, patients were informed that the goal of placebo administration was to reduce pain and thereby positively influence health status. In the OLP-mood group, patients were informed that the goal of placebo administration was to improve mood and thereby positively influence health status (**Supplementary Table S1**).

Outcome Parameters

Diary and Questionnaires

Patients assessed pain and mood levels each evening of the 21-day study period using a standardized paper-and-pencil diary. Average pain/mood during the day was rated on 11-point NRS from 0 ("no pain"/"worst mood") to 10 ("unbearable pain"/"best mood"). Patients were further asked to note the use of acute pain medication in the patient diary. At baseline and after 21 days, patients completed the following questionnaires: the *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC) is a standardized, disease-specific self-assessment instrument with verified psychometric quality criteria (37, 38). It comprises the subscales pain (range, 0–50), stiffness (range, 0–20), and physical function (range, 0–170), which are derived from 24 questions that refer to the past 2 days. Questions need to be answered on 11-point NRSs, with the left pole marked as "none" and the right pole as "extreme." Higher scores indicate worse pain, stiffness, and physical function (39). Quality of life was assessed using the *Short Form Health Survey* (SF-36), which is a 36-item, validated patient-reported survey providing component scores for the mental and the physical health domains, with higher scores indicating better quality of life (40). Perceived stress during the past week was assessed at baseline and after 21 days using the validated *Perceived Stress Questionnaire* (PSQ-20). We report here the PSQ-20 overall score, ranging from 0 to 100, with higher values indicating higher burden (41, 42). *State anxiety* was evaluated at baseline and after 21 days using the 20-item state-anxiety subscale of the State-Trait-Anxiety Inventory (STAI), which estimates anxiety at the current moment (43, 44). The score ranges from 20 to 80, with higher scores indicating higher levels of state anxiety. Self-efficacy was assessed at baseline and after 21 days using the *General Self-Efficacy* (GSE) scale, a validated 10-item tool with good psychometric properties to measure the general, optimistic sense of perceived personal competence (45, 46). The GSE is scored 10 (minimum) to 40 (maximum self-efficacy). At the second study visit, the experimenter rated the patient's global improvement using the *Clinical Global Impressions – Improvement (CGI-I)* scale, which uses a bipolar scaling from 1 (very much improved) to 7 (very much worse) (47).

Mobility of the Target Knee

The neutral-zero method was used to assess the mobility of the target knee at baseline and after 3 weeks. It is a functional measurement that describes the possible active joint mobility

of an individual joint with reference to the anatomical normal ("zero") position. With the aid of a protractor, the respective active end positions of the joint for flexion and extension are documented (48).

Physiological Measurements

The electrocardiogram was recorded for 5 min using the MP 150 BIOPAC System (Goleta, CA, United States) with AcqKnowledge 3.7.2 software. To increase reliability, the respiratory rate was standardized to 15 breaths per minute using a metronome (49). The ECG signal was sampled at a rate of 500 Hz (50). Intervals between successive R peaks (RR intervals) were extracted from the electrocardiogram signal using the peak-detection function implemented in AcqKnowledge 3.7.2. RR-time series were examined and screened for artifacts based on the procedure developed by Porges and Byrne (51), and then subjected to Kubios HRV software version 2.2 (Kuopio, Finland) to calculate the power of the high frequency band (0.15–0.4 Hz) of HRV relative to the total power (0–0.4 Hz). HRV is a measure of cardiac vagal activity and is used to estimate cardiovascular stress, with lower values indicating higher stress (52).

Salivary cortisol samples were collected at the day before study examinations at standardized daytimes [08:00 a.m., 00:00 a.m., 05:00 p.m., 09:00 p.m.; (53)] by using commercially available cotton swabs (Salivette®, Sarstedt, Nümbrecht, Germany). Participants were instructed to chew the swabs for at least 60 s before storing it back into a tube, and to hand out the four salivary tubes to the study personnel at each examination day. Saliva samples were centrifuged at 2000 rpm at 4°C and stored at −20°C until analysis. Salivary cortisol concentration was assessed using cortisol saliva assay kits from IBL International GMBH (RE52611). All saliva samples were analyzed in duplicate following the manufacturer's protocol. The area under the curve (AUC cortisol) was calculated for each examination day according to the trapezoid rule as outlined by Pruessner et al. (54). AUC cortisol reflects the overall secretory activity of the humoral stress axis throughout the day.

Primary and Secondary Outcome Parameters and Sample Size Calculation

Pre-specified primary outcomes included group differences in improvement of knee pain and function (NRS pain, WOMAC) and range of mobility (neutral-zero method) from baseline to follow-up at 3 weeks. Secondary outcomes comprised the course of pain and mood ratings (NRS) and the need for analgesics during the 3-week study period, global clinical improvement (CGI-I) after 21 days, and pre–post changes in physical and mental quality of life (SF-36), perceived stress (PSQ-20), diurnal salivary cortisol (AUC cortisol), and HRV. We further evaluated pre–post changes in state anxiety (STAI-state) and self-efficacy (GSE).

Sample size calculation was performed for the primary outcome WOMAC pain, namely the differences in improvement of WOMAC pain between the OLP and NT groups (randomization rate 2:1). We estimated that a total sample size of 60 would provide 80% power (one-sided $p < 0.05$) to detect a moderate-to-large effect ($d = 0.7$), as reported by Kaptchuk et al. (23). Sample size calculation was performed using GPower (version 3.1).

Statistical Analyses

Before analysis, the normality assumption was tested for all continuous outcome parameters using normal probability plots of the residuals, while the homoscedasticity assumption was checked using the Levene test and normal Q–Q plots. Because the daily ratings did not fulfill the normality assumption, available pain and mood ratings (5.9% missing values) were averaged for each week. All pre–post changes of continuous outcomes fulfilled the one-way analysis of variance (ANOVA) assumptions and were subjected to ANOVAs, with "group" (NT, OLP-pain, OLP-mood) as the between-subject factor. We primarily evaluated the contrasts between the NT and OLP groups (one-tailed) to test whether OLP has beneficial effects compared to NT. In an exploratory approach, we also evaluated the contrasts between the OLP-pain and OLP-mood groups (two-tailed). Pre–post changes in knee flexion and knee extension as well as post-treatment CGI-I scores were evaluated using Mann–Whitney *U*-tests, again contrasting NT vs. OLP groups (one-tailed) and OLP-pain vs. OLP-mood groups (two-tailed). Cohen's *d* effects sizes were calculated for parametric and non-parametric statistics (55), with 0.2 defined as small, 0.5 as medium, and 0.8 as large effect size (56). Statistical analyses were performed using IBM SPSS Statistics 25. For all statistical tests, a significance level of $\alpha = 0.05$ was assumed.

RESULTS

Sample Characteristics

Recruitment took place between November 2016 and September 2017. A total of 61 out of 261 patients who contacted the study center were enrolled in the study; reasons for exclusion are summarized in **Figure 1**. One patient was lost to follow-up after the baseline visit (he/she did not show up for the second study visit and could not be reached by phone). A total of 60 patients completed the study and were included in the analyses. None of the participants had taken part in a placebo study before. At baseline, the three groups were comparable in terms of sociodemographic and clinical characteristics, except for knee extension, which was significantly larger in the NT group (**Table 1**).

Patient Diary

From week 1 to week 3, NRS pain ratings decreased in the OLP-pain and OLP-mood groups and increased in the NT group (**Figure 2A** and **Table 2**). Contrast analyses indicated a larger reduction in NRS pain from week 1 to week 3 in the combined OLP groups compared to the NT group [$t(56) = 2.282$, $p = 0.013$, $d = 0.64$], while changes in the two OLP groups did not differ significantly from each other [$t(56) = 0.182$, $p = 0.856$, $d = 0.05$]. The need for analgesics remained stable in the three treatment groups (**Table 2**).

From week 1 to week 2, NRS mood ratings increased in the three groups to a similar extent and remained stable

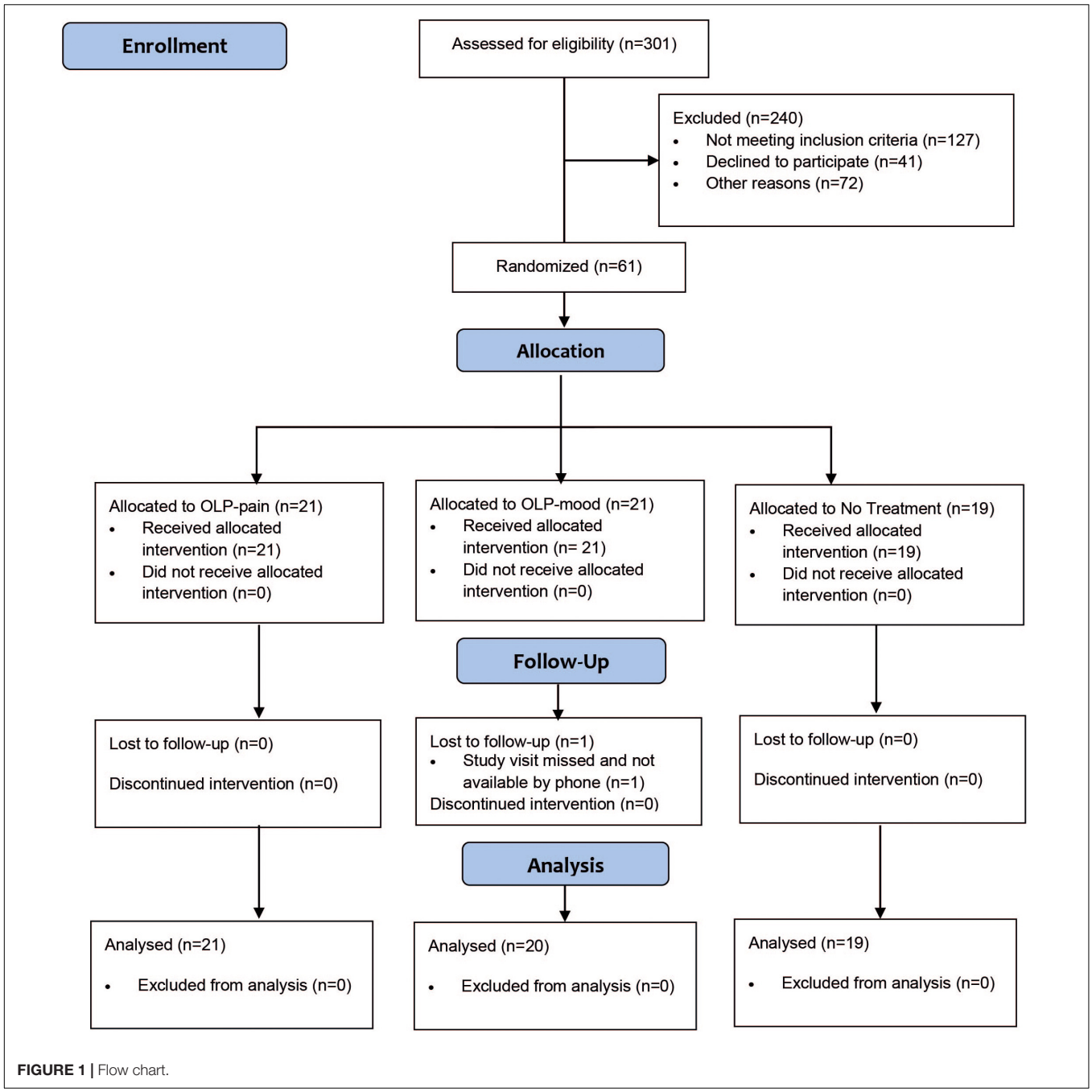

FIGURE 1 | Flow chart.

thereafter (**Figure 2B** and **Table 2**). Planned contrasts revealed no differences in mood improvement from week 1 to week 3 between the OLP and NT groups [$t(55) = -0.462$, $p = 0.323$, $d = 0.13$], nor between the two OLP groups [$t(55) = 0.543$, $p = 0.590$, $d = 0.15$].

Western Ontario and McMaster Universities Osteoarthritis Index Questionnaire

The group means of the WOMAC subscores pain, stiffness, and function before and after the intervention as well as pre–post changes are shown in **Table 2**. Contrast analyses indicated a greater reduction in WOMAC pain from baseline to follow-up in the combined OLP groups compared with the NT group [$t(57) = 1.835$, $p = 0.036$, $d = 0.55$]. Changes in the two OLP groups did not differ from each other [$t(57) = 0.456$, $p = 0.65$, $d = 0.17$].

The WOMAC subscores function and stiffness did not differ between the OLP and NT groups [function: $t(57) = 1.223$, $p = 0.226$, $d = 0.34$; stiffness: $t(57) = 0.505$, $p = 0.308$, $d = 0.14$] or between the two OLP groups [function: $t(57) = 1.259$, $p = 0.182$; stiffness: $t(57) = 1.552$, $p = 0.126$, $d = 0.17$].

TABLE 1 | Demographic and clinical characteristics at baseline.

Variable	OLP pain (*n* = 21)	OLP mood (*n* = 20)	NT (*n* = 19)	*p*-Value
Age (years), mean (SD)	64.19 (9.3)	66.8 (9.7)	69.84 (9.63)	0.183[1]
Sex (female/male), *n*	12/9	9/11	12/7	0.507[2]
Baseline pain (NRS), mean (SD)	2.67 (1.85)	2.58 (2.04)	2.83 (2.18)	0.927[1]
Baseline mood (NRS), mean (SD)	6 (2.6)	6.3 (2)	5.8 (2.8)	0.834[1]
WOMAC, mean (SD)				
Pain	23.05 (7.65)	23.1 (8.14)	21.37 (8.02)	0.742[1]
Stiffness	10.43 (4.44)	9.2 (3.02)	10.61 (4.79)	0.466[1]
Functionality	79.26 (31.09)	72.65 (28.27)	72.79 (32.03)	0.732[1]
Knee mobility, median (IQR)				
Knee flexion (°)	90 (88.5; 110)	100 (88.5; 109.8)	91 (81; 100)	0.592[3]
Knee extension (°)	0 (0; 0)	0 (0; 0)	0 (0; 4)	<0.001[3]

[1]T-test. [2]Chi-Quadrat test. [3]Kruskal–Wallis test.
OLP, open-label placebo; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Knee Mobility and Global Clinical Improvement

The mobility of the target knee as assessed by the neutral-zero method did not change differently between the OLP and NT groups (flexion: Mann–Whitney *U*-test, $z = -0.119$, $p = 0.453$, $d = 0.03$; extension: $z = -0.475$, $p = 0.317$, $d = 0.09$), nor between the OLP-pain and OLP-mood groups (flexion: $z = -0.797$, $p = 0.213$, $d = 0.25$; extension: $z = -0.607$, $p = 0.272$, $d = 0.09$; **Table 2**).

Global clinical improvement on the CGI-I scale was larger in the OLP group than in the NT group (Mann–Whitney *U*-test, $z = -2.457$, $p = 0.007$, $d = 0.59$), whereas there was no difference between the OLP-pain and OLP-mood groups ($z = -0.114$, $p = 0.910$, $d = 0.03$; **Table 2**).

Quality of Life

The pre–post changes in mental quality of life (MCS; SF-36) remained unaffected by OLP treatment [OLP vs. NT groups, $t(57) = -0.865$, $p = 0.170$, $d = 0.24$; OLP-pain vs. OLP-mood groups, $t(57) = 0.425$, $p = 0.673$, $d = 0.11$; **Table 2**]. Similarly, the pre–post changes in physical quality of life (PCS) did not differ between groups [OLP vs. NT, $t(57) = 0.270$, $p = 0.394$, $d = 0.08$; OLP-pain vs. OLP-mood, $t(57) = -0.517$, $p = 0.607$, $d = 0.14$; **Table 2**].

Stress Parameters

Perceived stress (PSQ-20) did not change differently between groups [OLP vs. NT, $t(50) = 0.569$, $p = 0.261$, $d = 0.17$; OLP-pain vs. OLP-mood, $t(50) = 1.058$, $p = 0.295$, $d = 0.3$; **Table 2**]. Also diurnal salivary cortisol excretion (AUC cortisol) was unaffected by OLP treatment [OLP vs. NT, $t(55) = 0.586$, $p = 0.28$, $d = 0.16$; OLP-pain vs. OLP-mood, $t(55) = -0.507$, $p = 0.614$, $d = 0.14$; **Table 2**], as was HRV [OLP vs. NT, $t(55) = 0.959$, $p = 0.171$, $d = 0.27$; OLP-pain vs. OLP-mood, $t(55) = 0.084$, $p = 0.933$, $d = 0.02$; **Table 2**].

State Anxiety and Self-Efficacy

State anxiety did not change differently between the OLP and the NT groups [$t(57) = -0.953$, $p = 172$, $d = 0.26$], nor between the OLP-pain and OLP-mood groups [$t(57) = 0.013$, $p = 0.990$, $d = 0$; **Table 2**]. OLP did not affect self-efficacy [OLP vs. NT, $t(57) = 1.444$, $p = 0.057$, $d = 0.4$; OLP-pain vs. OLP-mood, $t(57) = -0.011$, $p = 0.991$, $d = 0$; **Table 2**].

DISCUSSION

In this randomized controlled trial, we examined the effects of OLP administration accompanied by two different verbal suggestions on symptomatic OA of the knee. Results revealed that OLP administration significantly reduced knee pain, regardless of whether patients were informed that the placebo would "decrease pain" or "improve mood." In addition, clinical global impression was improved in the OLP groups compared to the NT group. Our results confirm previous findings that OLP treatment can improve chronic pain (57) and extend them to typically elderly patients with symptomatic OA of the knee. We found no effect of OLP administration on patient-reported functional disability of the knee and observer-reported mobility.

While the mean age of patients in the previous studies ranged between 40 and 60 years (23, 25, 30, 58), our results

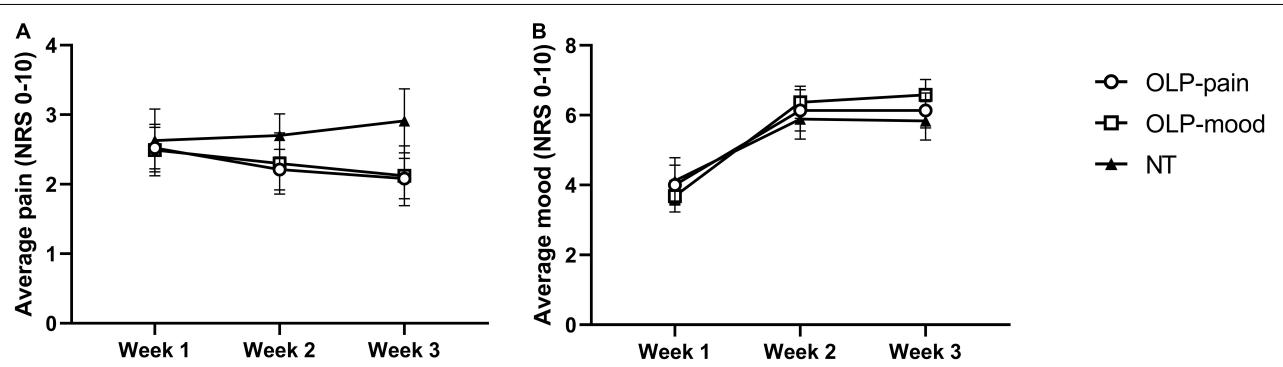

FIGURE 2 | Weekly averages of daily NRS pain ratings **(A)** and NRS mood ratings **(B)**. Data are displayed as means ± SE.

TABLE 2 | Outcome parameters at baseline and after 3 weeks.

Variable	OLP pain (*n* = 21)			OLP mood (*n* = 20)			NT (*n* = 19)			Cohen's *d*	
	Pre	Post	Mean change (95% CI) or median change (IQR)	Pre	Post	Mean change (95% CI)	Pre	Post	Mean change (95% CI) or median change (IQR)	OLP vs. NT	OLP-pain vs. OLP-mood
Patient diary (week 1 → week 3)											
NRS pain, mean (SD)	2.52 (1.38)	2.08 (1.32)	−0.37 (−0.75; 0.01)	2.49 (1.61)	2.12 (1.86)	−0.37 (−0.75; 0.01)	2.63 (1.97)	2.91 (2)	0.28 (−0.29; 0.86)	0.64*	*0.05*
NRS mood, mean (SD)	4 (2.61)	6.14 (2.29)	2.14 (0.01; 4.28)	3.68 (1.97)	6.58 (1.92)	2.89 (1.06; 4.73)	4.17 (2.79)	5.84 (2.41)	1.94 (−0.32; 4.2)	*0.13*	*0.15*
Patients using analgesics during study period, *n*	5	5		5	5		6	6		–	–
Number of days, median (IQR)	2 (0.5; 4.5)	1 (0; 3)	−1 (−2; 0)	1 (0; 5.5)	1 (0.5; 4)	0 (−1.5; 5)	0.5 (0; 0.25)	1 (0; 1.25)	−0.5 (−1.25; 1.25)	*0.11*	*0.35*
WOMAC (baseline → follow-up)											
WOMAC pain, mean (SD)	23.05 (7.65)	17.57 (7.54)	−5.48 (−10.53; −0.42)	23.1 (8.14)	18.8 (8.91)	−4.3 (−6.66; −1.94)	21.37 (8.02)	20.68 (8.76)	−0.68 (−4.15; 2.78)	*0.55**	*0.17*
WOMAC stiffness, mean (SD)	10.43 (4.44)	7.81 (4.07)	−2.62 (−4.93; −0.31)	9.2 (3.02)	8.5 (3.32)	−0.7 (−2.24; 0.84)	10.74 (4.69)	9.63 (4.47)	−1.11 (−2.59; 0.38)	*0.14*	*0.42*
WOMAC function, mean (SD)	79.26 (31.09)	59.67 (24.38)	−19.59 (−35.34; −3.84)	72.65 (28.27)	64.55 (30.68)	−8.1 (−15.29; −0.92)	72.79 (32.03)	67.47 (30.2)	−5.32 (−15.21; 4.58)	*0.34*	*0.4*
Knee mobility (baseline → follow-up)											
Knee flexion (°), median (IQR)	90 (88.5; 110)	90 (81; 97.5)	−7 (−20.5; 10.5)	100 (88.5; 109.8)	96 (90; 110)	0 (−0.8; 5)	91 (81; 100)	92 (85; 102)	0 (−9; 8)	*0.03*	*0.25*
Knee extension (°), median (IQR)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 0)	0 (0; 4)	0 (2; 2)	0 (0; 2)	*0.09*	*0.09*
Clinical improvement (follow-up)											
CGI improvement, median (IQR)	–	2 (2; 3)	–	–	2.5 (2; 3)	–	–	3 (3; 3)	–	*0.59**	*0.03*
Quality of life (baseline → follow-up)											
SF-36 MCS, mean (SD)	31.28 (10.3)	34.87 (8.74)	2.05 (−2.78; 6.88)	37.88 (8.35)	40.14 (8.99)	0.58 (−2.76; 3.91)	33.1 (0.62)	36.64 (10.27)	3.17 (−0.19; 6.53)	*0.24*	*0.11*
SF-36 PCS, mean (SD)	52.79 (10.61)	54.83 (8.76)	3.59 (−1; 8.12)	50.93 (11.3)	54.1 (9.22)	2.26 (−0.65; 5.17)	52.32 (9.24)	52.9 (9.75)	3.54 (−0.19; 7.28)	*0.08*	*0.14*
Stress (baseline → follow-up)											
PSQ-20, mean (SD)	28.83 (14.49)	23.92 (14.95)	−4.3 (−9.06; 0.46)	25.74 (13.16)	22.89 (15.61)	−1.08 (−6.41; 4.26)	24.9 (14.95)	21.05 (12.85)	−4.22 (−7.56; −0.87)	*0.17*	*0.3*
AUC cortisol (ln + 1), mean (SD)	0.71 (0.31)	0.69 (0.36)	−0.02 (−0.24; 0.19)	0.88 (0.38)	0.8 (0.36)	−0.94 (−0.34; 0.16)	0.82 (0.43)	0.83 (0.44)	0.01 (−0.13; 0.15)	*0.16*	*0.14*
HRV (%), mean (SD)	45.96 (14.17)	45.35 (18.46)	−0.21 (−10.64; 9.43)	50.74 (23.89)	50.8 (19.17)	0.06 (−11.81; 11.94)	40.81 (18.08)	47.21 (21.18)	6.4 (−7.05; 19.86)	*0.27*	*0.02*
Further (baseline → follow-up)											
STAI-State, mean (SD)	33.62 (8.03)	34.05 (9.4)	0.43 (−2.04; 2.89)	31.8 (6.9)	32.25 (8.45)	0.45 (−2.23; 3.13)	31.42 (6.15)	30.47 (4.61)	−0.95 (−3.09; 1.2)	*0.26*	*0*
GSE, mean (SD)	32.9 (5.66)	32.48 (5.75)	−0.43 (−2.95; 2.1)	31.6 (5.21)	31.15 (6.15)	−0.45 (−4.1; 3.2)	31.89 (3.56)	33.89 (3.4)	2 (−0.11; 4.11)	*0.4*	*0*

OLP, open-label placebo; NT, no treatment; NRS, Numeric Rating Scale; SD, standard deviation; md, median; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; CGI, clinical global impression; SF, short form health survey; MCS, mental component score; PCS, physical component score; PSQ, perceived stress questionnaire; AUC, area under the curve; HRV, heart rate variability; STAI, State-Trait-Anxiety Inventory; HR, heart rate; GSE, General Self-Efficacy.

*$p < 0.05$.

suggest that also older patients can be successfully treated by OLP. The acceptance of OLP treatment in the target population was sufficiently high, with 106 out of 261 patients declining to participate for various reasons, among them 20 patients who wanted active treatment. The acceptance of OLP treatment in the general population is generally high. For example, a survey in the United States revealed that 85% of the respondents considered OLP administration acceptable for patients with chronic abdominal pain (59).

We administered two OLP treatments differing by their declared goal, namely pain relief or mood improvement. Results show that neither pain or mood ratings nor any of the other outcomes differed between the two placebo groups. These results may partially be due to the small sample size of our study, with limited statistical power to detect differential effects between the two OLP interventions. For example, the respective effect sizes for the comparison of the WOMAC subscores stiffness and function scores were moderate at 0.4, suggesting that larger sample sizes would have been necessary to detect significant differences. However, with regard to pain, the effect sizes for the differences between the two OLP groups were generally small. Thus, our results suggest that OLP treatment was effective regardless of whether the explicit goal was to improve pain, or mood. Although we did not assess treatment expectations in our study, the finding that suggestion-specific effects did not occur indirectly supports previous findings that expectations play a limited role in OLP treatment. In a qualitative study, for example, patients receiving OLP treatment denied having positive expectations (32). Furthermore, an OLP study in patients with hot flushes showed that the increase in positive expectations after OLP administration was unrelated to clinical improvements (60). However, instead of OLP-specific expectations, more general treatment expectations may play a role: a recent study comparing OLP acupuncture with OLP pills for the relief of experimental pain reported that expectations toward OLP treatments did not predict the placebo analgesic effect, whereas general expectations toward (active) acupuncture did (61). The hypoalgesic effects of OLP treatment in our study may likewise be related to positive expectations toward pharmacological drugs rather than OLP treatment.

Recent Bayesian brain models offer an alternative way to explain OLP effects, apart from positive expectations (32, 57, 62). In these models, perception is viewed as a process of prediction based on the integration of sensory input, prior experience, and contextual cues. Any discrepancy between the predicted and the actual sensory input will result in a prediction error, which can be resolved in one of three ways: the prediction model can be updated, the sensory input can be attenuated, or the sensory input can be amplified. According to this model, a placebo analgesic effect results from the attenuation of the sensory input. In the case of deceptive placebo administration, this is most probably due to positive expectations, which lower the level of predicted pain and thereby pain perception. In the case of OLP treatment, the attenuation of perceived pain could be primarily due to reduced precision of the predicted pain signal, i.e., increased uncertainty, resulting from the paradox information of receiving "substances that have no active ingredients" (57).

The question of whether OLP treatment can improve health-related quality of life remains unclear, as previous studies have shown mixed results. Disease-specific quality-of-life instruments appear to be better suited to demonstrate the beneficial effects of OLP (23, 28, 60) than more general instruments such as the SF-36 (26, 63, 64). Also in our study, OLP led to improvement in the pain subscale of the disease-specific WOMAC questionnaire, whereas the mental and physical components of health-related quality of life as assessed by the SF-36 remained unaffected. It should be mentioned that the observation period of 3 weeks may have been too short to capture positive effects of OLP treatment on mental and physical health-related quality of life. Gradual increase in physical activity due to reduced pain could lead to improved muscle strength over longer time periods, which might result in improved quality of life at a later time. Indeed, studies reporting positive treatment effects on health-related quality of life in patients with knee OA typically comprise longer observation periods (65). Our finding that OLP treatment did not improve functional disability of the knee, as assessed by the WOMAC subscores function and stiffness, is contrasts two recent OLP studies, which showed improvement of pain and functional disability in patients with chronic low back pain (25, 30). Again, the sample size of our study may have been too small to detect subtle changes in functional disability with OLP treatment (d = 0.34). Regarding objective knee mobility, our findings are consistent with those of Kleine-Borgmann et al. (30), who also reported no effect of OLP administration on objective spine mobility.

Finally, we explored whether the beneficial effects of OLP may be due to the reduction of stress and negative emotions. Study results consistently argue against such a view, as perceived stress, state anxiety and physiological stress parameters were not affected by OLP administration. Similarly, Kleine-Borgmann et al. (30) reported no changes in stress and anxiety after OLP treatment in patients with chronic back pain. However, in their study, OLP administration reduced (non-clinical) depression scores, whereas in our study, OLP had no effect on mood ratings. This discrepancy may be due to the use of a single-item NRS in our study, which has been shown to correlate well with depression scales in clinical populations (66), but this may not be true for non-psychiatric patients. Alternatively, the mood improvement in the NT group may have masked the mood-enhancing effect of OLP administration. Improved mood in the NT group may best be explained by the Hawthorne effect, i.e., an improvement due to additional attention by study personnel and the knowledge of being under observation (67).

Several possible limitations of the study have to be mentioned. The sample size of our study was rather small and some of the beneficial effects of OLP in patients with OA of the knee may have been missed due to the lack of statistical power. Nonetheless, the reported effect sizes provide a solid empirical basis to design future OLP studies in patients with symptomatic OA of the knee. Furthermore, the assessment of observer-reported outcomes was not blinded and the improvement in the CGI-I scale by OLP

administration should be interpreted with caution. In addition, the study research team's appreciative attention may have blurred some of the beneficial effects of OLP treatment, particularly on mood. Furthermore, our exclusion criteria were rather strict and many patients were excluded because of various illnesses or medication. This limits the external validity of our results, especially with respect to elderly people who frequently have multiple diseases. Finally, the short duration of OLP treatment does not allow to draw conclusions about the potential value of OLP treatment in clinical practice. However, Carvalho et al. (68) recently published a 5-year follow-up of a randomized controlled trial on OLP in patients with chronic low back pain, suggesting that the improvements in pain and disability after OLP are long lasting.

In conclusion, our study is the first to provide evidence that elderly patients with symptomatic OA of the knee show pain relief by OLP treatment. Results lend support to the notion that concealment and deception are not necessary to evoke placebo effects in patients with chronic pain conditions. Future studies should address the role of synergistic and opposite verbal suggestions for OLP effects, as well as the long-term effects of OLP administration and its acceptability and feasibility in clinical practice.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are available from the corresponding author on request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Faculty, LMU Munich, Munich, Germany. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SS and KM designed the study. EO, SS, and AH carried out the experiment. EO, SS, AH, FR, and MM analyzed the raw data. SF and KM supervised the data analyses. EO, SS, and KM performed the statistical analyses. EO and KM wrote the first draft of 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/fpsyt.2022.853497/full#supplementary-material

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Attitudes Toward a Pre-authorized Concealed Opioid Taper: A Qualitative Analysis of Patient and Clinician Perspectives

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Standard opioid tapers tend to be associated with increased patient anxiety and higher pain ratings. Pre-authorized concealed opioid reductions may minimize expectations such as fear of increased pain due to the reduction of opioids and, prolong analgesic benefits in experimental settings. We recently observed that patients and clinicians are open to concealed opioid tapering. However, little is known about the "why" behind their attitudes. Based on this lack of data, we analyzed qualitative responses to survey questions on patients' and clinicians' acceptance of a concealed opioid reduction for chronic pain. Seventy-four patients with a history of high dose opioid therapy and 49 clinicians completed a web-based questionnaire with open-ended questions examining responses to two hypothetical clinical trials comparing a concealed opioid reduction pre-authorized by patients vs. standard tapering. We used content analysis based on qualitative descriptive methodology to analyze comments from the patients and clinicians. Five themes were identified: informed consent; anxiety; safety; support; and ignorance is bliss, or not. These themes highlight the overall positive attitudes toward concealed opioid tapers. Our findings reinforce the importance of patient-centered care and are expected to inform the design of clinical trials from both the patient and clinician perspective. This qualitative study presents patients' and clinicians' attitudes toward hypothetical scenarios for a trial of pre-authorized reduction of opioids. The findings indicate positive attitudes and the relevance of engaging patients with effective decision-making processes.

Keywords: placebo effects, concealed (hidden) administration, opioid tapering, chronic pain, qualitative descriptive

INTRODUCTION

In an effort to reduce the harms associated with long-term opioid use, the Department of Defense (DoD)/Veterans Affair (VA) and the Centers for Disease Control (CDC) have published guidelines that recommend limiting prescriptions of opioids for the management of chronic pain to no more than 90 morphine milligram equivalents (MME) a day (1–3). While there is burgeoning evidence regarding the potential benefits of opioid tapering (4–7), debate persists about tapering methods, challenges, and potential harms, including increased risk of drug overdoses and mental health crises (8–10). In addition, there is limited empirical evidence to support best practices for successful opioid tapering in patients with chronic pain (11, 12). We conducted a survey of both patients and clinicians to explore attitudes toward a pre-authorized concealed taper of opioids with the purpose of gathering critical knowledge to implement in future trials using a concealed taper (13). The research used a mixed-methods approach: closed-ended questions with forced-choice answers, followed by the opportunity for respondents to reply with open-ended comments. When presented with scenarios (13) related to a hypothetical trial with pre-authorized concealed taper of opioids, both clinicians and patients believed that a concealed taper is more likely to be successful than a standard taper. Nearly 50% of the patients who responded to the survey were willing to participate in the hypothetical trial of pre-authorized concealed taper of opioids, and almost 80% of clinicians were willing to refer patients to such a clinical trial. Patients and clinicians alike saw the proposed concealed opioid reduction as a possible way to mitigate clinical pain, opioid-related side effects, and withdrawal symptoms (13).

Analgesic benefits of opioids may be prolonged by minimizing negative expectations through the use of a concealed opioid reduction. Prior research has demonstrated that patient expectations directly influence pain outcomes. Higher pain ratings have been linked to fear of pain, increased stress, high anxiety, and pessimism, while lower pain ratings have been linked to reduced stress and anxiety (14). The simple act of telling a patient that their opioid dosages are going to be reduced elicits negative expectations, such as fear of increased pain and anxiety (15). Frank and colleagues (16) found that patients reported a fear of increased pain, opioid withdrawal, and insufficient non-opioid treatment options when they were told that their opioid dosage was going to be reduced.

While the empirical literature on blind opioid tapering is limited, our research group has written about how this novel approach may benefit patients with chronic pain (17). One experimental study found that patients rated their pain higher when told that morphine was going to be discontinued (18). However, when morphine discontinuation was concealed, patients did not report higher pain ratings, despite the decrease in medication. These results suggest that opioid doses may be most successfully reduced when the patient is unaware of the taper.

Transparency is an important construct in ethical research and concerns arise whenever when patients are misled (19–21). However, patients can be explicitly asked to agree to a concealed taper in which they will receive pills packs that intersperse full doses with reduced doses of opioid pain medication. While being informed that while their intake of opioids will gradually be reduced, they will not know exactly when the taper will occur. The patient's autonomy, the clinician's integrity, and societal trust in medicine are thereby preserved (21).

While hiding the interruption of opioids remains highly questionable in research and clinical practices (22, 23), patients can be pre-informed about the concealment of certain parts of the research (24), making the concealment ethically permissible (25–27) and, most importantly, agreeable to patients with chronic pain (28).

Research on attitudes toward blinded tapers suggests that patients with chronic pain and clinicians who manage patients with chronic pain may be open to a trial with a concealed opioid taper. In addition, studies examining clinicians' perspectives highlight several factors, such as effective communication, that may further bolster opioid tapering efforts (29–31). In this article, we performed content analyses of previously published survey responses to further examine perspectives toward pre-authorized concealed opioid taper scenarios. We have previously reported the quantitative findings of this study (13). The purpose of this qualitative analysis is to provide an in-depth understanding of attitudes toward a concealed taper strategy in both patients and clinicians. The results of this analysis will be used to guide the design of future approaches to concealed-taper designs that will optimize opioid tapering and chronic pain management.

METHODOLOGY

This is a qualitative descriptive study based on written data from a cross-sectional survey. Quantitative findings from this cross-sectional survey examining patient and clinician acceptance of a concealed opioid reduction for chronic pain have been previously reported (13). Both patients and clinicians were recruited through advertisements on social media, online ads, flyers, and both local and non-local pain clinics from January 2018 to December 2019. As medical practice can vary by country, we chose to limit clinicians to those who practiced in the United States (U.S). We also chose to limit our patient sample to those who had taken or were currently taking at least 90 MME of an opioid. We wanted to capture the views of clinicians who were caring for patients on opioids such as registered nurses, family practice clinicians, anesthesiologists who manage pain, and others, as well as capture patients who could potentially participate in an opioid tapering clinical trial. A total of 74 patients who were currently taking or had taken high dose opioids (i.e., >90 MME) and 49 clinicians consented to participate. The survey was administered through REDCap, a secure HIPAA compliant survey and data management tool and took ∼20 min to complete. This study was approved as non-human research by the University of Maryland, Baltimore Institutional Review Board (HP-00073609) and according to the definitions of the U.S. Department of Health and Human Services (HHS) and Food and Drug Administration (FDA).

Each patient respondent answered a 13-question survey including general questions related to demographic information

and addressing their responses to two hypothetical patient scenarios of opioid-dose tapering. The first scenario depicted a standard tapering (overt administration) and the second scenario depicted a concealed dose tapering (covert administration). For details, see hypothetical scenarios below:

Hypothetical scenario 1.

"A 46-year-old man had a back injury 10 years ago, for which he started taking 50 morphine equivalent daily dose (MEDD). Now, many years later, his dose has risen to 200 MEDD. His doctor wants to recruit him for a 6-week clinical study to help reduce his opioid use. The study consists of two groups: Group 1 (standard 6-week taper) receives a standard, gradual opioid taper (consistent with DoD/CDC recommendations) for 6 weeks. Throughout the study, the participant is monitored over the phone and provided supportive counseling and psychotherapy for chronic pain. Group 2 (concealed 3-month taper) is also told they will receive a gradual opioid taper for 3 months. However, during the informed consent process, the participant is informed that they will not be aware of how much their opioids are being decreased from week to week as the number of pills will remain the same. Throughout the study, the participant is monitored over the phone and provided supportive counseling and psychotherapy for chronic pain." [pg. 3, (13)].

Hypothetical scenario 2.

"A 32-year-old woman is in the hospital for a few months after experiencing a terrible accident. She has been treated with morphine before and reports that it significantly helps decrease her pain. However, when she is administered morphine covertly (i.e., without her knowledge), her pain ratings significantly increase, even though she is receiving the same dose as when she is given morphine overtly (i.e., when she's aware of the administration). This shows that she is a placebo responder, since her knowledge of receiving morphine helps her feel less pain. She keeps asking her doctor to raise her dose of morphine. Her doctor is considering recruiting her for the same clinical study described in scenario 1 to reduce her dependence on opioids. Therefore, she will be told that she will not be aware of exactly when morphine will be given. The doctor believes she will have positive outcomes on this clinical study, which involves the placebo effect, since she is already known to be a placebo responder." [pg. 3, (13)].

Open-ended questions followed each closed-ended question (for details about the scenario-related questions, see **Table 1**), asking "Why or why not?" providing patients the opportunity to provide a rationale for their closed-ended answer to the hypothetical experiences in the two scenarios. There was one additional open-ended question that asked each patient "How do you feel about the opioid reduction recommendations?" Patients were not enrolled in a real-world clinical trial.

Each clinician respondent answered a clinician-specific 11-question survey on the same two hypothetical scenarios of opioid-dose tapering, including general questions related to demographic information and area of specialty. Nine of the questions contained close-ended responses, followed by an open-ended response "Why or why not?" The remaining open-ended question asked each clinician "Do you think that this recommendation is justified? Please elaborate on your response." The clinician questionnaire differed from the patient questionnaire in that it focused on the clinicians' responses to the patients' hypothetical participation in the two scenarios.

TABLE 1 | Scenario-related questions.

Patients' study questions
Scenario 1, Do you think participants in Group 1 and 2 will have similar pain ratings and withdrawal symptoms?
Scenario 2, Do you think she is a good participant for the study?
Scenario 2, Do you think this study can help her smoothly wean off morphine if she is placed in Group 1?
Scenario 2, Do you think this study can help her smoothly wean off morphine if she is placed in Group 2?
Scenario 2, Since the woman from the scenario is known to be a placebo responder, do you feel that she has a better chance of responding positively to being in Group 2 over someone who is not known to be?
Do you think this study may help patients reduce the stress or anxiety that may be associated with reduction of opioids?
Would you feel comfortable participating in this study as a patient?
Overall, do you think it is important to reduce the amount of opioids prescribed to patients in the US today?
Clinicians' study questions
Scenario 1, Do you think participants in Group 1 and 2 will have similar pain ratings and withdrawal symptoms?
Scenario 2, Do you think she is a good participant for the study?
Scenario 2, Do you think this study can help her smoothly wean off morphine if she is placed in Group 1?
Scenario 2, Do you think this study can help her smoothly wean off morphine if she is placed in Group 2?
Scenario 2, Since the woman from the scenario is known to be a placebo responder, do you feel that she has a better chance of responding positively to being in Group 2 over someone who is not known to be?
Do you think this study may help smoothly wean heavy opioid users down to a lower dose?
Would you feel comfortable referring patients for this study?
Overall, do you think it is important to reduce the amount of opioids prescribed to patients in the US today?

Data Analysis

Data were analyzed using content analysis, a method applicable to both quantitative and qualitative approaches (32). Krippendorff (33) defined content analysis as a "research technique for making replicable and valid inferences from texts to the context of their use" [p. 18 (33)]. For the purpose of this analysis, content analysis was used to determine the presence of themes within the written responses of the patients and clinicians. Rather than interviewing patients with open-ended questions, we sought to understand their responses to our quantitative survey through their written word. While content analysis can use either a deductive or inductive approach, we chose an inductive approach. Inductive content analysis involves the use of abstraction and the formation of concepts or themes in order to reduce data, group it, and ultimately to answer the study questions (34). The inductive approach is recommended when little is known about the phenomenon being studied (35).

Emergent coding was used to establish codes after an examination of the data (36). Two of the authors (coders) independently read and examined the open-ended responses to search for themes that captured patients' and clinicians' attitudes toward the new opioid guidelines and the two hypothetical scenarios. Then, the two coders used an inductive coding system as there is little, if anything, known about this phenomenon. Once each author had coded the data, they came together to discuss their individual results and obtained consensus. In content analysis, reliability is measured by stability and reproducibility (36). Stability refers to intra-rater reliability. Each of the two coders achieved the same results 95% of the time. Reproducibility refers to inter-rater reliability. Each of the two coders classified the data the same way at a rate of 90%.

SPSS version 22 was used for the analyses of demographic characteristics and frequency of themes.

RESULTS

We surveyed 74 patients and 52 clinicians. Three clinician surveys were removed because they practiced in a country outside of the United States. A total of 39 responses from patients and 64 comments from clinicians were reviewed. Some respondents, both patients and clinicians, provided several responses to individual open-ended questions, while some respondents provided no responses to the open-ended questions. The overall response rate to the open-ended questions for clinicians was 69% ($n = 36$) and for patients was 42% ($n = 31$).

The mean age of patients was 45 years (SD 12.608). Most patients identified as Caucasian (55.4%) and were currently using opioids (85.1%). Most clinicians identified as Caucasian (71.4%) and female (57.1%), with a mean age of 40 years (SD = 13.670). The largest group of clinicians were anesthesiologists (28.6%), followed by registered nurses (22.4%). This data has previously been reported in Bedford et al. (13).

The vocabulary density of the clinician survey was 0.332 and the vocabulary density of the patient survey was 0.343. Vocabulary density is the ratio of the number of words in the document to the number of unique words in the document. The lower vocabulary density results indicate that each survey's open-ended responses contained dense text with many single-use words.

The qualitative analysis resulted in the identification of five interrelated themes: (1) informed consent, (2) anxiety, (3) safety, (4) support, and (5) ignorance is bliss, or not. The two coders did not have any preconceived definitions of these themes. The two coders grouped each individual response and then re-examined those groupings of responses, moving from specific responses to the general themes identified (35). **Table 2** presents the frequency of responses by clinicians and patients within each theme.

TABLE 2 | Frequency of themes.

Theme	Patient responses	Clinician responses
Informed Consent	$N = 9$	$N = 13$
Anxiety	$N = 5$	$N = 14$
Safety	$N = 6$	$N = 11$
Support	$N = 12$	$N = 13$
Ignorance is bliss, or not	$N = 7$	$N = 13$
Total responses	39	64

Informed Consent

Both patients and clinicians emphasized the importance of informed consent in a clinical trial. Responses grouped in this theme included, but were not limited to, words referencing informed, informed consent, procedures, monitoring, and choice. Clinicians stressed the need to "fully inform" patients of the dosing regimens. Clinicians underscored the need to provide patients with "knowledge" about the plan because the degree of knowledge which patients have may influence their pain. One clinician wrote: "Her pain is proportional to her mental state and knowledge of the administration of drugs" while another clinician highlighted the importance of informing the patients about randomization: "As long as [a] patient is fully informed of the potential for randomization to two different groups, then it is patient's choice whether or not to join study."

Patients wanted to ensure that the benefits and risks were openly discussed with them. Patients emphasized the need to have knowledge about the tapering process and understanding the procedures. One patient wrote that "Knowing what is happening and having a planned reduction is much better than what many people are going through, which is a sudden reduction without any counseling on how to deal with the withdrawal symptoms." Another patient suggested that informed consent could motivate patients. Another patient wrote "To adequately explain the benefits and all the data to support decreased opioid use. Also, the long-term detriment of opioids would help motivate someone to lower their dosage."

One patient highlighted the negative consequences associated with not providing a thorough informed consent. The patient wrote, "people who are living without the correct level or amount of control, knowledge, and education on a subject, or thing... often are hostile when presented with any kind of authority [. . .] they feel small and [resort] to the ['] FIGHT OR FLIGHT['] thing in the brain."

Anxiety

For this theme, patients and clinicians described anxiety around reducing opioid dosages in open and concealed settings. Some clinicians were hesitant to enroll patients in the hypothetical clinical trial due to the concealed taper, such as this clinician: "I like the theory behind group 1 however group 2 I am hesitant about because I do not like how the participant doesn't know how much of their medications is decreased." However, other clinicians thought the study design would be helpful for patients whose pain outcomes were related to knowing when they were receiving a pain medication: "Not knowing doses takes a lot of the focus off of that issue and reduces anxiety/nocebo. I think Group 2 would do better."

Both patients and clinicians were supportive of the concealed opioid reduction trial with a focus on gradual reduction. One patient wrote: "I think the study would be good because you have

to taper slowly so they don't have the ache and withdrawals of wanting it more. Being on a tapering schedule with monitoring would be helpful."

However, both patients and clinicians had mixed views on whether the patient presented in the hypothetical scenarios would benefit from Group 2 (a concealed taper). Many patients described anxiety associated with pain and reducing the dose of opioids they were taking. Patients and clinicians believed that there was a "mental" component to the hypothetical patient's pain that would influence her outcomes. Some patients and clinicians did not believe the hypothetical patient would benefit because "not knowing" would create anxiety for her, while other patients and clinicians believed that "not knowing" would help. For example, one patient believed the hypothetical patient would not benefit because "if her mind knows that amount of dose is reduced she starts feeling pain therefore she should be placed in group 2 where she will not know about how much amount of dose is reducing" and a clinician wrote "I believe their withdrawal symptoms will be the same but their pain ratings will differ between group 1 and group 2. Notably, Group 2 will rate higher just because they do not know how much their opioids were decreased."

Safety

Many patients and clinicians supported tapering opioids for safety reasons. Respondents centered on this theme spoke about the dangers of opioids. Both patients and clinicians suggested that opioids were over-prescribed, difficult to taper, and risky to take long term. Clinicians wrote about a lack of evidence to support opioid use and the need to prescribe opioids judiciously. One clinician wrote: "In the U.S., we consume inordinate amounts of opioid medications. We need to set expectations appropriately. Opioid addiction and overdoses have very grave consequences."

Patients focused on the need for a slow opioid taper and to minimize withdrawal symptoms. One respondent found the DoD/CDC guidelines (2) to be justified for two specific reasons: "(1) Addiction. (2) Misuse and abuse. You'll have patients take their medication home and then sell or give it to other people or whatever it is they do that doesn't use it for its intended purpose. (3) I think it's being given out like candy and we're winding up seeing people actually die and they're not dying from whatever their initial problem is but they're dying from the opioids."

Support

Both patients and clinicians highlighted the importance of providing the patient with support throughout the tapering process. They wrote about the hypothetical study design and specifically liked the use of monitoring, counseling, and education in both groups in the study, all reflective of the need for support during the hypothetically proposed study. One patient wrote: "It makes a big difference when you feel like you're not doing it alone."

Another patient thought the study design would provide the support the patient needed for a successful taper: "Every time [the hypothetical patient in the scenario] sees the doctor, she is fine. So, if she was in group 2, and getting lower doses and not knowing it but still seeing the doctor, I believe that she would be fine and it would work better for her." Clinicians had varying views on the amount and types of support that would be beneficial for the hypothetical patient. For example, "Beyond being a placebo responder … she did not also have much response to opioids." The standard "supportive counseling and psychotherapy for chronic pain" may not be adequate and "I think a supported wean with no 'set goal' is probably one of the few ways to do this right."

Ignorance Is Bliss, or Not

Many patients and clinicians highlighted the psychological factors that influence pain. Responses that were grouped in this theme expressed two opposing beliefs: that not knowing one's dosages would be a positive attribute of this study, or (the opposite) that not knowing the dosage would have a detrimental psychological effect on the patient's pain levels. Some wrote about the psychological benefits of not knowing if they were receiving a concealed reduction. Many patients viewed the hypothetical patient presented in the concealed dosing scenario as being the best fit for the concealed reduction trial. "Out of sight out of mind" and "Yes because she starts feeling pain if she knows her dose is reduced therefore group 2 is suitable for her where she will not know about amount of dose reduced with time" are two examples. However, other patients did not think either group would be helpful because the hypothetical patient's pain was directly related to her "knowing" if she is receiving the medication: "I don't think she would make a good participant because the clinician will not know if her pain is real or not."

On the other hand, some clinicians thought that the concealed reduction group would not help the hypothetical patient. One clinician wrote that "not knowing could push her to exaggerate her pain/ withdrawal symptoms at all times." Another clinician wrote that "just knowing they're tapering, will cause opioid users' pain."

Some patients personally recognized the psychological aspects of tapering. One patient wrote "If not knowing my dose helps me out mentally in terms of the calmness level and [I] have less side effects physically. The mental always goes from the mental to the physical. It'd be weaning me off." Another patient wrote "Most of it isn't mental but yes there is a mental part to pain, and there's a medical part to knowing you're being cared of by a physician. Basically you're trying to trick people into not knowing their dose is lower since their pain is the same. Which is why I would be a willing participant even though I wouldn't want to."

DISCUSSION

In this study, we explored patient and clinician openness toward a concealed reduction of opioids using qualitative data from a web-based survey. We analyzed 39 qualitative comments for common themes from patients and 64 comments from clinicians. Comparing patient and clinician perspectives toward a pre-authorized concealed reduction, five themes emerged: (1) informed consent, (2) anxiety, (3) safety, (4) support, and (5) ignorance is bliss, or not.

Our findings expand upon the work done by James et al. (37) and our previous quantitative study results (13), which

found overall positive patient and clinician attitudes toward a clinical trial with a concealed reduction of opioids. That study showed that nearly 60% of patients were comfortable participating in the hypothetical study and 80% of clinicians were willing to refer patients to the hypothetical study. The high rate of willingness for most patients and clinicians in that study to participate or refer patients to participate, respectively, suggests that a pre-authorized concealed reduction is viewed as a viable alternative to standard opioid tapers. This noteworthy positive response is likely to be related to the pre-authorization approaches (20, 38–40) whereby patients and clinicians agree in concealing the time when opioids are weaned in order to enhance positive bodily responses (i.e., placebo effects) while minimizing negative one (i.e., nocebo effects, anxiety) (27). Both patients and clinicians described specific psychological benefits of a concealed taper and its influence on pain responses. This suggests that knowledge about the benefits of a concealed taper may be used to create positive expectations, which may in term minimize negative expectations and improve the success of a pre-authorized concealed taper (20, 38–40).

Themes of negative affect, safety, support, and tapering ambivalence have been identified in other qualitative studies of opioid tapering. Frank et al. (16) showed how patients reported experiencing fear of worsening pain and withdrawal symptom from tapering and reported feeling uncertain about the effectiveness of non-opioid treatments. The authors showed how patients tended to be less focused on the long-term risks of chronic opioid use, including overdoses. Patients in their study also identified factors associated with successful tapering, including safety (e.g., trusting their clinician; similar pain with fewer side effects) and support (e.g., access to social support resources) (16). Concerns regarding the perceived limitations of alternative pain control methods have also been noted in other studies (41).

Studies of clinicians' perspectives on opioid tapering have emphasized the importance of effective communication and patient-centered care (29, 31). One study found that the most common reason patients were hesitant to participate in a double-blinded randomized control trial for opioid tapering was lack of information (37). For patients, opioid tapering can be a dynamic experience that changes daily due to various medical and psychosocial factors that are often not fully communicated to clinicians, which further highlights the importance of open communication (31). Matthias et al.'s (29) study in patients and clinicians highlighted the benefits of individualized tapers, understanding the patients' perspectives, promoting an environment of support (e.g., ensuring patients will not feel abandoned), and communicating tapering benefits (29). A focus group study of primary care clinicians also noted the importance of empathizing with patients, utilizing individualized tapers, and having access to resources to support a patient-centered tapering approach (30).

Our study found that patients and clinicians were most open to a pre-authorized concealed reduction in the setting of informed consent. Patients emphasized their need to understand the benefits, while clinicians were comfortable referring patients for the hypothetical clinical trial when patients were fully informed about both groups (standard taper vs. concealed taper). Both patients and clinicians recognized the challenge in providing informed consent when concealment is part of the study design. We recommend consenting patients at the beginning of the study using the patient-centered "authorized" concealed opioid taper or standard taper. Patients would need to consent to enrollment into either group in order to participate in the study. Those assigned to the patient-centered "authorized" concealed opioid taper should be willing to accept that they may not know the time or dose of the opioid they would receive. Preliminary research suggests that some patients with chronic pain are generally open to the use of authorized deception in research (28). As pointed out by our study respondents, informed consent may help patients recognize the benefits of a pre-authorized concealed taper and/or develop a plan to manage withdrawal symptoms, thereby optimizing the patient-clinician communication and alliance.

Despite the benefits of informed consent, we found that many patients reported anxiety about reducing their opioid dosage blindly. However, our study was unique in that it also found that clinicians, too, were concerned about patients experiencing anxiety with a concealed taper. Researchers need to consider how the patient will be feeling at each stage of the taper based on the speed and dosage reduction of the taper (42). Communication about the benefits of a concealed taper may increase patients' comfort about enrolling in the study and clinicians' willingness to refer patients. Patient concerns should be addressed at the beginning of the taper and throughout the clinical trial. Researchers are encouraged to support patients by regularly assessing for anxiety, by fostering strong patient-clinician relationships with open communication, and by prescribing medications for symptomatic management of withdraw as indicated (16). In addition, use of multimedia, such as narrative videos, has been shown to bolster patient tapering self-efficacy and effectiveness and could be used during study enrollment (43). These resources could potentially further decrease anxiety and promote tapering acceptance if they highlight the expectancy-based mechanisms underlying the efficacy of concealed tapering (44, 45).

Both patients and clinicians in our study reported that some patients may not be candidates for the hypothetical clinical trial that we described. Researchers have an obligation to minimize patient harm by developing specific inclusion and exclusion criteria. Researchers may want to consider exclusion criteria for patients who think concealment will increase their pain, whereby only patients who believe their pain will stay the same or be reduced with the clinical trial should be permitted to enroll. Alternatively, given that prior therapeutic experience rather than expectations can trigger placebo effects (46), those who consent can still be enrolled knowing that conditioning (e.g., exposure to full doses of opioids and reduced doses), along with education, can still result in effectiveness of the taper, despite the negative expectations. Additionally, for patients with comorbid diagnoses of opioid use disorder or complex opioid dependence, it may be more appropriate to use other well-established, evidenced-based treatments for opioid-use disorder, such as buprenorphine (47).

Our findings highlight the importance of integrating the diverse perspectives of patients and other relevant stakeholders (e.g., caregivers, clinicians, researchers) to successfully translate these results into applied experimental and clinical settings (17). The Patient-Centered Outcome Research Institute (PCORI) published a 10-step patient engagement framework which would be instrumental in guiding the next steps in this line of research (48–50). Specifically, the 10-step framework is a model that can be used to integrate census opioid tapering recommendations with novel concealed opioid tapering approaches (51). Core patient engagement principles include shared decision making (e.g., involving patients in decisions regarding study design/implementation), co-learning (e.g., stakeholder participation on data safely monitoring boards), and partnership (e.g., patient engagement in dissemination of research results).

Strengths and Limitations

The major strength of this study is the rich perspectives that both patients and clinicians shared in response to the two hypothetical scenarios. Content analysis is an unobtrusive method to directly analyze communication as text. These results, in addition to previously published quantitative data (13), provide significant insight and support for the best research methodology to implement when studying opioid tapering.

Limitations in our study stemmed from the qualitative design and the study population. Content analysis, by its very nature, involves some level of subjective interpretation. Findings from this study were limited to the responses that respondents provided. Some respondents chose to answer more of the open-ended responses than others. We do not know why some respondents did not answer each open-ended question. We do not know if respondents may have answered the open-ended questions differently if the questions were asked in-person. The use of other qualitative methods/designs (e.g., focus groups, in-depth interviews) may have provided greater context for these results. Finally, it is noted that this study represented responses to hypothetical vignettes. While patients and clinicians were asked to respond as if they were participating in or referring patients to the hypothetical clinical trials, it is possible that their actual responses may be different if they were participating in real clinical scenarios. Despite these limitations, the findings from this study are important and serve as a baseline for future research and study design in the area of concealed opioid reduction.

CONCLUSION

Our study provides patient and clinician perspectives for a concealed opioid taper clinical trial. We identified five common themes among patients and clinicians to describe their attitudes toward concealment: (1) informed consent, (2) anxiety, (3) safety, (4) support, and (5) ignorance is bliss, or not. Our study emphasizes the need to consider patients' and clinicians' perspectives when designing clinical trials to support a patient-centered approach and improve both clinical applicability and patient outcomes. Our study supports the development of clinical trials with strong informed consent processes that improve patient anxiety and minimize harm, optimize patient support, and mitigate the psychological factors that exacerbate pain during opioid tapering.

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 University of Maryland Baltimore. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

TB conducted the study, data analyses, and drafted the manuscript. NK helped with drafting the manuscript. NH conducted the study, analyses, and commented on the final draft. CM, TW, and MC commented on the final draft. LH helped supervise the data analyses, interpreting the results, and writing the manuscript. LC designed the study, supervised the team, and wrote the manuscript approving the final version. All authors contributed to the article and approved the submitted version.

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Educational Intervention for Management of Acute Trauma Pain: A Proof-of-Concept Study in Post-surgical Trauma Patients

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Objective: Despite years of research and the development of countless awareness campaigns, the number of deaths related to prescription opioid overdose is steadily rising. Often, naive patients undergoing trauma-related surgery are dispensed opioids while in the hospital, resulting in an escalation to long-term opioid misuses. We explored the impact of an educational intervention to modify perceptions of opioid needs at the bedside of trauma inpatients in post-surgery pain management.

Materials and Methods: Twenty-eight inpatients with acute post-surgical pain completed this proof-of-concept study adopting an educational intervention related to opioids and non-pharmacological strategies in the context of acute post-surgical pain. An education assessment survey was developed to measure pre- and post-education perceptions of opioid needs to manage pain. The survey statements encompassed the patient's perceived needs for opioids and other pharmacological and non-pharmacological therapeutics to manage acute pain. The primary outcome was the change in the patient's perceived need for opioids. The secondary (explorative) outcome was the change in Morphine Milligram Equivalents (MME) used on the day of the educational intervention while inpatients and prescribed at the time of the hospital discharge.

Results: After the educational intervention, patients reported less agreement with the statement, "I think a short course of opioids (less than 5 days) is safe." Moreover, less agreement on using opioids to manage trauma-related pain was positively associated with a significant reduction in opioids prescribed at discharge after the educational intervention. The educational intervention might have effectively helped to cope with

acute trauma-related pain while adjusting potential unrealistic expectancies about pain management and, more in general, opioid-related needs.

Conclusion: These findings suggest that trauma patients' expectations and understanding of the risks associated with the long-term use of opioids can be modified by a short educational intervention delivered by health providers during the hospitalization. Establishing realistic expectations in managing acute traumatic pain may empower patients with the necessary knowledge to minimize the potential of continuous long-term opioid use, opioid misuse, and the development of post-trauma opioid abuse and/or addiction.

Keywords: opioids, surveys, education, expectations, perceptions, trauma-related pain, post-operative monitoring

INTRODUCTION

According to the Centers for Disease Control and Prevention (CDC), an average of 38 deaths occurred *each day* in 2019 involved opioid prescriptions in the United States (1). The CDC newly released data reported an increased estimation of overdose deaths over the last year (time period ending in April 2021) with 75,673 from the previous year 56,064 overdose deaths (2). One out of 550 chronic opioid users dies approximately within 2.5 years of their *first* opioid prescription to treat acute pain, meaning that many opioid-related deaths can be prevented by addressing them within the acute care setting (3).

Physically injured trauma patients are challenging to follow long-term, and as a result, information on the precise number of patients that develop opioid dependence and potential death due to prescription opioids for acute traumatic pain remains unknown. However, in a recent study of 36,000 opioid-naive patients undergoing elective surgery, continuous opioid use was 6% regardless of whether the surgery was minor or major (4). The R Adams Cowley Shock Trauma Center at the University of Maryland, Baltimore admits about 8,000 inpatients each year from the State of Maryland, the vast majority of whom are prescribed opioids during their admission (5). Assuming 85% of inpatients are given an opioid (5) and assuming an estimated 6% rate of long-term opioid use (4), at least 400 patients each year could use opioids continuously with the potential to develop opioid dependence due to initial opioid-based treatment of trauma injuries. Moreover, trauma patients identified as at-risk drinkers at the time of injury were found to have a 7–10% rate of non-medical use of prescription opioids at 1 year (6). Injured trauma patients with severe pain are hospitalized for long periods and given high doses of opioids throughout their hospitalization. Disjointed medical care between inpatient and outpatient settings often results in little to no continuity of pain management, and potentially, no adequate plan to taper and stop opioid use. Factors that may put patients at risk of developing opioid misuse and dependence include the patient expectation of being "pain-free" despite significant injuries, as well as a lack of awareness regarding the dangers of long-term opioid use at the time of initiation (7–10). Therefore, we designed and conducted a pilot study to test the effects of an educational intervention on expectations of opioids' needs and quantifiable outcomes (pain, opioid use) in trauma inpatients. Our main question was: Can we optimize patients' expectations of opioids' needs to optimize the risks/benefits of opioids used for trauma-related pain? Expectations are predictions of future outcome(s) based on pre-existing individual assumptions constructed from current personal knowledge and previous experiences (11). Expectations about the effectiveness of the treatment can influence patient outcomes, drug intake and behaviors (12, 13). A recent study conducted during the pre-surgery window of patients undergoing heart surgery, demonstrated that an educational session targeting expectations related to the post-surgery recover and outcomes as compared to standard information, improved post-surgical heart-related outcomes including lower post-surgery interleukin-6 level, mental health and hours of work per week at 6 months from the surgery (14).

It is well documented that long-term use of opioids for non-cancer pain treatment resulted in opioid misuse and poor pain management (15). In the attempt to reduce opioid misuse and addiction, an effort has been made on reducing patients' needs for opioids after surgery (7–9) but there was a paucity of studies focusing on educational interventions related to tapering acute opioid intake for patients with traumatic injuries. Based on this knowledge, this proof-of-concept study intended to understand whether expectations of opioid needs in post-trauma inpatients can be modified by using an educational intervention to reduce the perception of opioids' needs (primary outcome). Changes in Morphine Milligram Equivalents (MME) used on the day of the educational intervention while inpatients and prescribed at the hospital discharge were also collected (explorative outcomes).

MATERIALS AND METHODS

Thirty-one trauma inpatients were enrolled in this study to test the impact of an educational intervention on the patient's understanding of the need for opioids and expectancies about opioid needs to manage pain. We had three dropouts. Three inpatients were unable to complete the study due to ongoing clinical procedures, physical therapy and sleeping, leaving a total sample of 28 patients with complete data (20 women and 8 men). Sociodemographic and clinical characteristics, including age, sex,

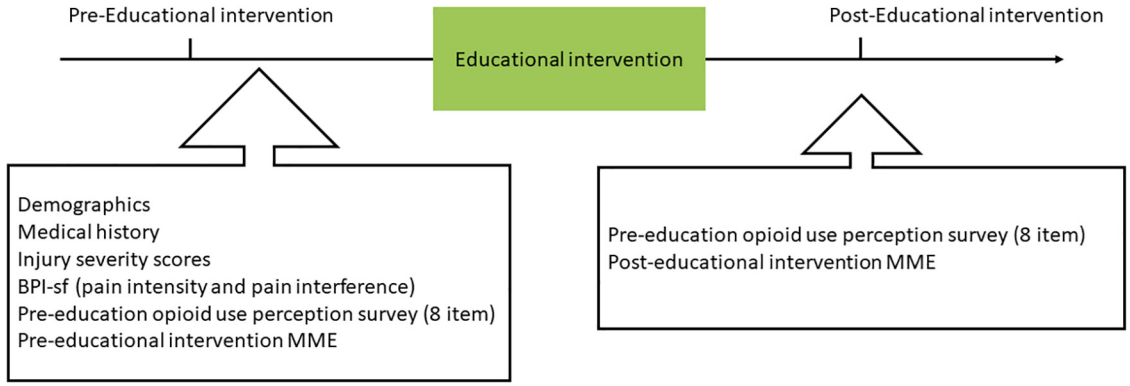

FIGURE 1 | Study procedure. Inpatients' demographics, medical history, opioid intake, trauma injury severity, clinical pain intensity and interference, and opioid use perception were obtained before the educational intervention. After the educational intervention, the opioid use perception was re-assessed. Opioid prescription expressed in Morphine milligram equivalents (MME) were measured at discharge based on the medical records.

race, educational status, and marital status, were collected at the baseline before the educational intervention.

The study took place at the R Adams Cowley Shock Trauma Center at the University of Maryland Medical Center from April 2019 to February 2020. The study required about 1 h and inpatients hospitalized for trauma were invited to participate by research staff independent of the health clinicians treating patients. All patients provided their verbal and written informed consent to participate in this study. Participants were made aware that they had the right not to participate and withdraw from the study. Participation was entirely voluntary with no monetary incentive. The University of Maryland R Adams Cowley Shock Trauma Center and the University of Maryland Institutional Review Board approved this study (HP-00083434) and all procedures were conducted in accordance with the Declaration of Helsinki ethical principles for medical research involving human beings.

Inclusion/Exclusion Criteria and Enrollment

The research coordinators accessed medical records from the hospital clinical database 'EPIC' to identify potential trauma inpatients who met the inclusion criteria for enrollment. For this study, we considered trauma as a severe but not life-threatening single or multiple injuries that had required immediate medical treatment to help treat the trauma at our R Adams Cowley Shock Trauma Center.

Eligible inpatients were admitted to the University of Maryland R Adams Cowley Shock Trauma Center for trauma-related incidents. These inpatients had to be between the ages of 18–65 years. The trauma related incidents could have been related to several injuries from motor vehicle crash injuries, blunt-force, stab and gunshot-induced wounds, falls resulting in single and/or multiple broken bones. The patients were also eligible if they received opioids for acute pain, and were opioid naïve before being admitted to the emergency rooms (i.e., had not been treated with opioids daily for the past 3 months).

The exclusion criteria included a lack of English fluency, inability to sign informed consent, cognitive impairment, illiteracy, diagnosis of diffuse cancer (excluding those that are isolated or benign tumors that do not require treatment), or a planned enrollment into a substance abuse treatment program that prescribed medications (e.g., Suboxone or Methadone), and trauma related to major head concussions or other injuries. We excluded those taking opioids for cancer pain and for drug addiction/abuse disorders to target opioid-naïve patients. The long-term goal is to limit the escalation of the opioid epidemic, particularly for those who are initially exposed to opioids because of traumatic injuries.

Once potential inpatients were identified, one of the research coordinators scheduled a time with the team of nurses and doctors to approach the patient at the bedside and invite him/her to participate in the study (see **Figure 1** for study time line). It was made clear to inpatients that there were no benefits in participating in the study, participation was entirely voluntary, and the decision to partake in the study or not had no impact on the course of the medical treatment. Inpatients were asked whether they were interested in participating in a study to learn more about pain management options, including opioids and non-opioids and their related risks.

Educational Intervention

The materials for the educational intervention were developed by LC, YF-W, and SM. They engaged in several focus group sessions with the nurses and doctors from the R Adams Cowley Shock Trauma Center at the University of Maryland Medical Center, receiving feedback in preparing the brochure and related survey content. Feedback on the educational intervention goals and endpoints was also received by the Center for Addiction Research, Education, and Service (CARES), University of Maryland, Baltimore. The educational intervention consisted of a brochure containing modified parts of the Surgical Patient Education Program developed by the American College of Surgeons (16) and other parts tailored to the Shock Trauma Center context. The educational

intervention started with a recovery guide that aimed to maximize patient recovery by explaining the pain interference ("How is my function?") and the pharmacological and non-pharmacological therapeutic options ("What can I take to feel better?") (see **Figure 2A**). The educational brochure provided a list of standard therapies to improve pain and functions (**Figure 2B**). For example, options for non-medication therapies and their descriptions were listed to provide alternatives to pain management. These non-medical options included self-care, expressive arts, therapeutic touch, rehabilitation therapies, exercise, and the use of virtual reality. Patients were given additional information classifying medications as either non-opioids or opioids and listing the common side effects for each medication. The remaining educational materials contained commonly asked questions and answers to topics specific to pain control goals, duration of pain, and risks of addiction development (**Figures 2C,D**). Consideration about both short-term and long-term opioid misuses was also provided to inpatients as part of the educational intervention. Information pertaining to this study was delivered by the research coordinators verbally and in the form of an educational brochure. Treating doctors and nurses were not involved in the study to avoid recruitment biases and risks of patients' coercion.

Pre- and Post-education Assessment Survey

In order to assess the effect of the educational intervention, a survey was developed to record pre- and post- perceptions toward opioids and non-opioids use. The research team developed the survey questions on the research hypotheses. The same education assessment survey was given before and following the educational intervention. In the survey, inpatients rated their levels of agreement to eight statements by marking along a 10 cm horizontal scale. The participant markings were measured in centimeters and ranged from "definitely no" (0 cm) to "definitely yes" (10 cm). Following the intervention, the same survey was given again to inpatients, but they were asked two additional questions regarding their perceived utility of the educational intervention and how easy it was to understand the presented educational materials. Responses to these two items were also measured along with the horizontal agreement visual analog scale. The education assessment survey tool is presented in **Supplementary Table 1**.

Brief Pain Inventory Short Form

Prior to filling out the surveys and undergoing the educational intervention, inpatients were asked to fill out a Brief Pain

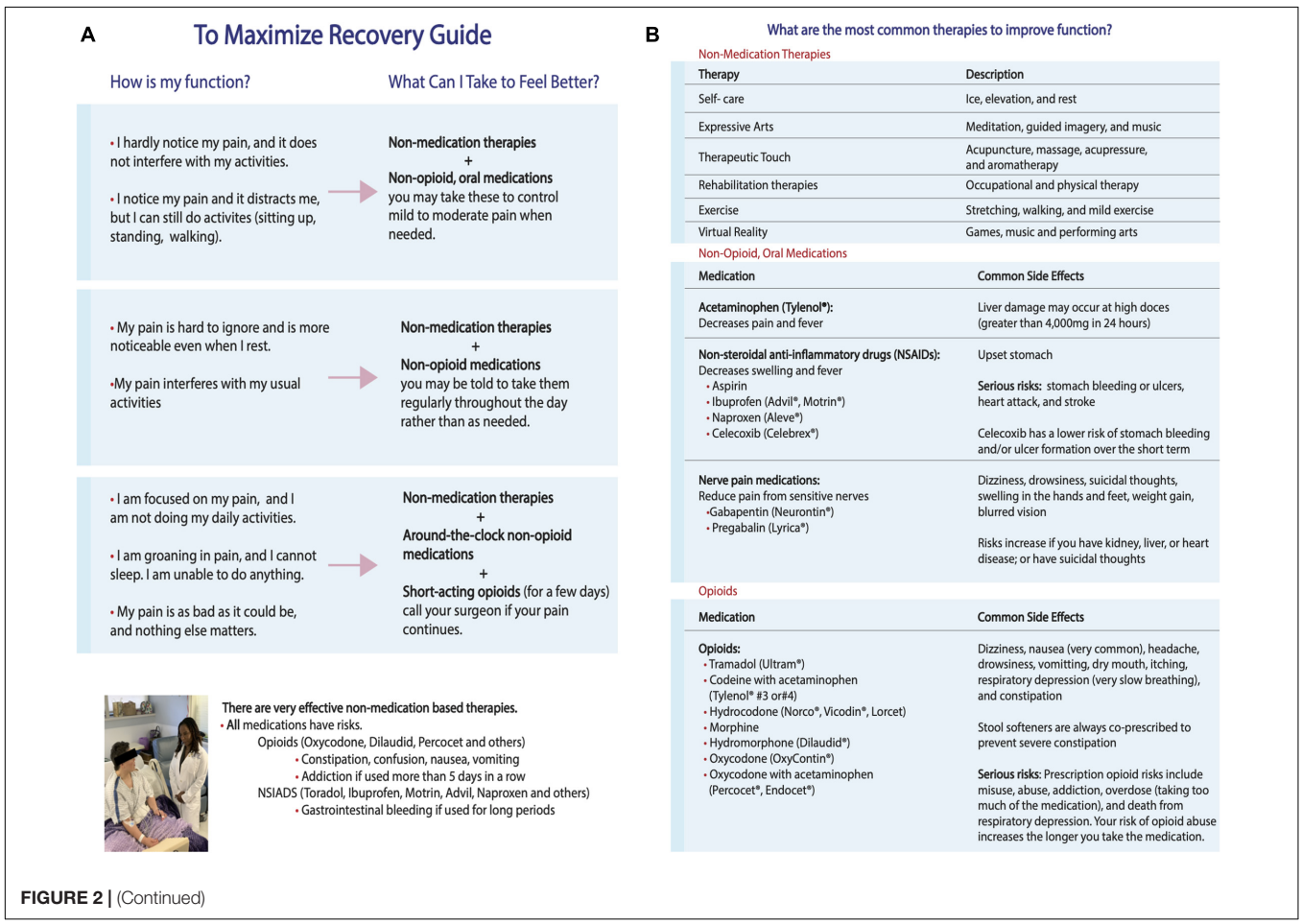

FIGURE 2 | (Continued)

C

What is the goal of pain control?
- Maximizing mobility, while minimizing pain and limiting risks
- Help you heal
- Limit harm from medication

What is my role in managing my pain?
- You are the most important member of the team managing your pain
- You will help your team figure out the best plan for you

How long will my pain last?
- Pain will improve over time but may not go completely go away
- Traumatic pain can last for weeks, depending on the injury
- Pain should not prevent you from moving and participating in healing or daily activities

The truth about opioids
- Opioids are powerful medications with serious side effects
- Opioids are not effective for some forms of pain
- Opioid use should be limited to severe pain, and not used for more than 5 days in a row
- **Negative effects:**

Nausea and vomiting, Increaded pain perception, Severe constipation, Tolerance, Urinary retention, Physicial dependence and addiction, Hypogonadism, Gynecomastia, Overdosing and death, Opioid induced osteoporosis

Will I get addicted to any of the pain medications?
- Opioid addiction is a risk if taken for more than 5 days in a row
- Your healthcare team will provide a limited number of opioid pills at discharge to minimize the risk of addiction

Ibuprofen (Motrin, Advil, Naproxen) are more effective than opioids in relieving pain due to bony

What is safe and effective pain control?
- Effective pain control will allow you to move
- Untreated severe pain can slow healing
- There are effective non-medication therapies
- All medications have risks
  - Acetaminophen (Tylenol)
    Nausea, vomiting
    Liver toxicy (at high doses)
  - NSIADS (Toradol, Ibuprofen, Motrin, Advil)
    Intestinal bleeding if used for long periods
  - Opioids (Oxycodone, Dilaudid, Percocet ect)
    Constipation, confusion, nausea, vomiting
    Addiction if used more than 5 days in a row

What can I take to feel better?
- Pain plans are specific to each person
- Work with your team to figure out the best plan
- You may need to try different combinations before success

I am having pain at night, what do I do?
- More awareness of pain at night is very common
- Injuries can hurt more from daytime activity
- Less distractions
- Lying flat may worsen pain
- It is not sign of anything bad, but it can get in the way of sleep
- Try timing your evening dose of medications to the best effect
- Try non-medical therapies
  Elevation, changing position
  Ice packs
  Music and other soothing distractions
- Record what works best for you
- Non-medical therapies are better for this type pain
  Effective and safer
  Opioids should only be used for a limited time

Will I get addicted to any of the pain medications?
- Opioid addiction is a risk if taken for more than 5 days in a row
- Your healthcare team will provide a limited number of opioid pills at discharge to minimize the risk of addiction

How do I know what to take and how often?
- Talk with your team to figure out your best plan
- Use non-medication therapies first
- Add non-opioid medications as needed
- If pain is severe and persistent you may need to add opioids for a short time
- Limit opioids to 5 days in a row
- Do not be afraid to take opioids for a limited time if you have severe pain

Patients who take opioids for more than 5 days after discharge are 50% more likely to develop dependence

D

I am being discharged, Now What?
- While in the hospital you and your team will have developed a pain management plan including:
- Reasonable expectations of pain management
- Focused on being able to move and function
- Lowest effective dose of narcotics, with a plan to stop as soon as possible
- Use the same strategies that worked in the hospital at home

How long will I be prescribed opioids?
- You might be given a prescription for a small amount of opioids
- This will likely NOT be renewed at your next follow-up appointment
- Use your medications only as directed
- Stop or gradually decrease them on your own as you

Hide or lock-up opioids
Keep out of reach of children and pets
Keep in original container
Keep track of number and location of pills

When should I worry about my pain?
- Pain may get worse at times, then better. this is expected
- Call your doctor/nurse if you have:
- New or different pain
- Persistent and severe pain not relieved by any therapy
- Pain that is not relieved after 5 days of opioid medication
- Change in appearance of your injury (redness, new swelling, discharge)

Should I call the hotline about my pain at night?
- In general the hotline should not be called for pain
- See the section "I am having pain at night. What do I do?"
- Federal law prohibits prescribing or renewing narcotic/opioids without an in person visit
- Opioids cannot be called in to your pharmacy
- If your pain is poorly controlled and you need to be seen before your next appointment call your primary doctor or the trauma clinic during the day to set-up an appointment

How do I get rid of my leftover opioids?
- When you no longer need opioids get rid of them safely
- Do not save for future use
- **Unsafe and illegal** for you to use narcotics meant for your injury to treat a new source of pain
- **Unsafe and illegal** for you to give your medications to someone else
- Your local pharmacy may take back and dispose of opioids
- Find a take back site at https://apps.deadiversion.usdoj.gov/pubdispsearch
- If there is no disposal site near you mix unused medication with coffee grounds or kitty litter in a plastic bag and throw in the trash

Do not share opioids. 50% of people who abuse opioids get them from a friend or relative

Will I have pain after trauma?
- Yes. You have a serious injury
- Pain is a normal part of healing
- Do not expect to be completely pain free

What is safe and effective pain control?
- Effective pain control will allow you to move and participate in your recovery.
- Untreated severe pain can slow healing.
- There are very effective non-medication based therapies.

FIGURE 2 | Educational intervention brochure. It started with a recovery guide that aimed to maximize patient recovery by explaining the pain interference ("How is my function?") and the pharmacological and non-pharmacological therapeutic options ("What can I take to feel better?") **(A)**. The educational brochure provided then a list of the most common therapies to improve functions **(B)**. The remainder of the educational materials had commonly asked questions and answers to topics specific to pain control goals, duration of pain, and risks of addiction development **(C,D)**.

Inventory Short Form (BPI-SF) (17) to measure the pain they were experiencing before the intervention. Inpatients were asked to rate their worst, least, average pain during the past 24 h and current pain by circling a discrete number from 0 to 10, with 0 being "no pain" and 10 being "pain as bad as you can imagine." The average score of the 4 items were used to represent pre-educational pain intensity.

Injury Severity Score

Injury Severity Scores (ISS) were calculated for all inpatients enrolled. Scores were calculated by assigning an Abbreviated Injury Scale (AIS) code for each injury of each body region. The ISS score is then calculated by adding the sum of the squares of the 3 highest codes in the 3 most injured body areas (18; 19).

Morphine Milligram Equivalents – Explorative Outcome

Opioids were administered via the oral and intravenous routes. Opioid intake and prescriptions were calculated in MME for each participant by the sum of each prescribed opioid medication multiplied by its respective conversion factor (20). The MME were calculated at the time of the educational intervention and post-education at hospital discharge.

Statistical Analyses

Sociodemographic and clinical characteristics are reported as percentages to examine how perception toward opioids could have changed before and after the educational intervention, calculated by ANCOVA controlling for age, sex, and race. We used agreement ratings to each of the statements assessed pre- and post-educational intervention. In particular, the two time-points (pre- vs. post-educational intervention) were set as a within-subjects factor while age, sex, and race were treated as covariates.

In addition to the perception changes, we examined how educational intervention would have changed the dispensed opioids while inpatients and at the prescribed opioids at the hospital discharge. Therefore, MME on the day of educational intervention, and MME at discharge were calculated for each patient controlling for level of trauma severity (ISS scores) and pain severity (BPI-SF scores). ANCOVA was used to compare administered at the time of the educational intervention and prescribed MME at discharge controlling for level of trauma severity using ISS scores and pain severity using BPI-SF scores along with demographic variables age, sex, and race. Given that some medications were prescribed as ranges at discharge, we compared the minimal prescribed MME at discharge with the MME dispensed at the time of the educational intervention.

We used Spearman correlations to examine whether the changes in the attitudes toward opioids were correlated with the changes in prescribed opioids expressed as minimal dose of MME at discharge.

For the primary outcome (changes in attitudes toward opioids), a conservative Bonferroni corrected/adjusted p-value of 0.0062 dividing the 0.05 (α-value) by 8 which corresponds to total analyses on the dependent variable, was used for significance. On the contrary, an unadjusted p-value of 0.05 was used for the secondary explorative outcomes (dispensed MME and prescribed MME at the hospital discharge). SPSS statistics version 26.0 was used for all data analyses.

RESULTS

Socio-Demographic and Clinical Characteristics

A total of 28 trauma patients completed the study. Eight out of 28 participants were men (28.57%) and 20 were women (71.43%). The average age of this cohort was 42.04 years with a 95% CI of 35.92–48.15 years. In terms of race, 13 out of 28 were White (46.42%), while the remaining 15 were African American/Black inpatients (53.58%). The majority of the cohort was non-Hispanic (25 out of 28, 89.29%) with the remaining three participants reporting unknown ethnicity. Regarding the socioeconomic status, most inpatients were never married (42.86%) with 39.29% of the cohort reporting a married or living as married status. Seven out of 28 inpatients had a college graduation or higher education (25%), while 20 out of 28 (71.43%) had some college or less education.

In terms of clinical factors, an ISS range of 16–24 indicates the presence of severe injuries, and the cohort had an ISS average of 19.96 out of 75, suggesting presence of severe injuries (**Supplementary Table 2**).

Type of injuries included degloving injury of lower limbs, single or multiple fractures of the ribs, femur (closed displaced sub-trochanteric part), proximal humerus (closed 3-part fracture), radius, tibia, fibula, calcaneus, vertebra and pelvis, laceration to spleen, laceration of the tongue, aortic arch pseudoaneurysm, pulmonary contusion, hemopneumothorax, diaphragm injury, empyema lung assault with gunshot wounds and stab wounds. In addition, baseline pain intensity levels had an average of 6.26 out of 10 pain intensity ratings, indicating moderate to severe pain intensity levels for this trauma inpatient cohort.

Attitudes Toward Medical and Non-medical Treatments Pre- and Post-educational Intervention

As expected, before the educational intervention, inpatients had medium levels of agreement with the statement "I think all pain related to my trauma is bad and should be treated" with a mean of 6.85 (SEM = 0.79) out of a total rating of 10 (from 0 = definitely disagree to 10 = definitely agree). This attitude did not significantly change after the education as revealed by the non-significant ANCOVA controlling for age, sex, and race (post-education: mean = 6.18, SEM = 0.71, $F_{1,24} = 0.36$, $p = 0.555$). Similarly, inpatients' attitudes toward personal involvement, "I think I am an important part of the team treating my pain," did not significantly change after the educational intervention ($F_{1,23} = 0.002$, $p = 0.964$).

Attitudes toward the importance of using opioids/narcotics for trauma-related acute pain ($F_{1,24} = 1.12$, $p = 0.301$) and

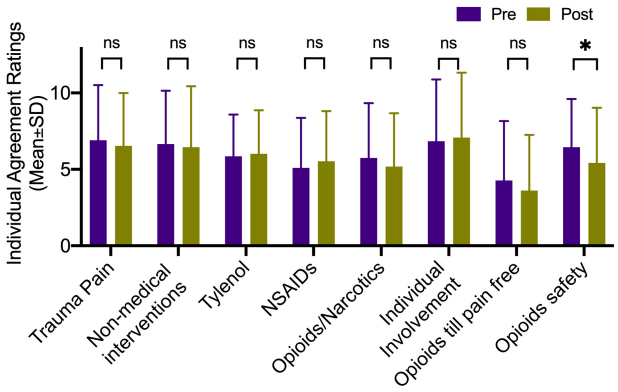

FIGURE 3 | Educational intervention changes. Degrees of agreement to the statements regarding the importance of pharmacological and non-pharmacological treatments for acute trauma pain. Opioids safety significantly changed with a decreased mean score of 6.92 (SEM = 0.60) at the pre-education phase as compared with 6.09 (SEM = 0.72) at the post-educational intervention ($F_{1,24}$ = 9.08, p = 0.006) controlling for age, sex, and race. *Indicate statistical significance.

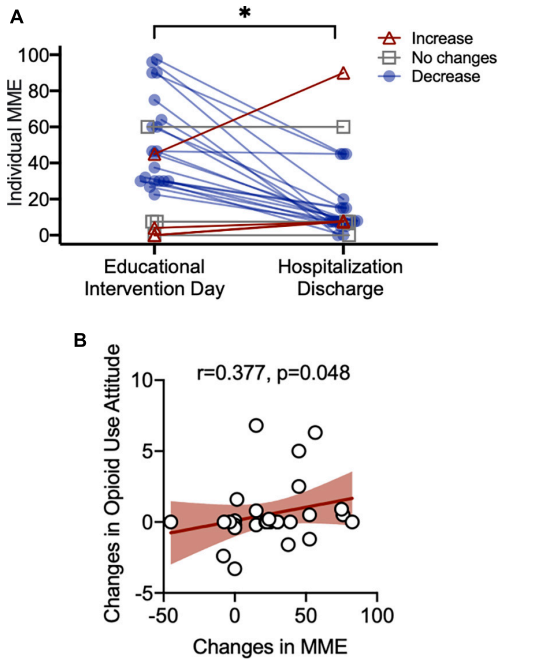

FIGURE 4 | Morphine milligram equivalents (MME) changes **(A)**. Controlling for age, sex, and race, post-education opioid prescription (minimal amount) were significantly lower than the pre-education actual opioid intake ($F_{1,24}$ = 4.53, unadjusted p = 0.044). Attitudes toward opioids and MME reductions **(B)**. Spearman correlation between reduction in attitudes toward opioids safety/needs and MME reductions (Spearman r = 0.377, unadjusted p = 0.048). *Indicate statistical significance.

the timeframe of using opioids ($F_{1,24}$ = 0.41, p = 0.528) for pain management did not significantly change as a result of the educational intervention.

Notably, the answer to the statement "I think a short course of opioids (less than 5 days) is safe" significantly changed with a decreased mean score of 6.92 (SEM = 0.60) at the pre-education phase as compared with 6.09 (SEM = 0.72) at the post-educational intervention ($F_{1,24}$ = 9.08, p = 0.006 with an adjusted value of p = 0.048) controlling for age, sex, and race (**Figure 3**). This suggested the educational intervention significantly changed, specifically the beliefs about the safety of opioids. The attitudes toward acetaminophen such as Tylenol ($F_{1,22}$ = 2.81, p = 0.108) and NSAIDs such as Advil or Motrin ($F_{1,22}$ = 2.55, p = 0.125) did not significantly change after the educational intervention when compared to the pre-education phase.

In terms of the attitude toward the use of non-pharmacological interventions such as music and meditation, there were no significant changes for the statement "*I think non-medical interventions are an important part of my treatment plan*" after the educational intervention controlling for age, sex, and race (pre-education: mean = 6.64, SEM = 0.72; post-education: mean = 6.44, SEM = 0.82, $F_{1,24}$ = 0.02, p = 0.883).

Prescribed Opioids and Educational Intervention

The prescribed opioids were calculated as MME on the day of the educational intervention and post-education at the day of discharge. ANCOVA indicated that the opioid intake significantly dropped from an average of 42.26 MME (SEM = 5.55) per day, to an average of 16.98 (SEM = 4.08) prescribed MME per day ($F_{1,21}$ = 4.47, unadjusted p = 0.047) while controlling for trauma and pain severity along with age, sex, and race. The majority of the inpatients (n = 20) experienced a reduction in opioids intake during the post-education phase compared to the day of education, controlling for severity of trauma and clinical pain. Only four inpatients had a higher opioid intake after the educational intervention and four other inpatients remained at the exact dosage of opioid intake from the day of the education to the post-education phase (**Figure 4A**).

Next, we examined whether reductions in opioid intake were related to the changes in the attitudes toward the use of opioids for management of acute trauma pain. Spearman correlations indicated a significant positive correlation between the reductions in overall opioids expressed in MME and attitudes toward the importance of considering opioid safety even as a treatment for acute trauma-related pain (spearman r = 0.377, unadjusted p = 0.048, **Figure 4B**). This result suggested that inpatients who changed their thoughts about the safety of opioids in acute pain management after the educational intervention had greater reductions in prescribed MME opioids at discharge, post-educational intervention.

Patients' Feedback

When we asked whether being informed was helpful, 19 out of 28 inpatients reported and found the educational intervention useful, helpful, and easy to understand. This was demonstrated by an agreement score of 9.21 ± 1.41 out of 10 to the statement "I think the information shown to me was useful/I could use it to help manage my traumatic pain" and an agreement score of 9.71 ± 0.46 out of 10 to the statement "I think the information

shown to me was easy to understand." The rest of the inpatients did not indicate whether the information shown was useful, helpful, or easy to understand.

DISCUSSION

The current study aimed to educate trauma patients about the potential danger of opioid usage while introducing alternative methods to improve acute pain management. Our goal was to demonstrate with this proof-of-concept study that the educational intervention could improve the patient's understanding of the need for opioids. We found that a short educational intervention could shift attitudes positively toward concerns about the safety of short-term opioids. The educational intervention did not change the perception of using other medical treatments (e.g., acetaminophen, NSAIDs) and non-medical approaches (e.g., music, meditation). More importantly, larger reductions in the perception of opioid safety were correlated with greater reductions in the prescription of MME at discharge, hinting to a potential relevance of education as an adjuvant intervention for pain management.

A traumatic injury can be a gateway to chronic opioid misuse (10). In the current study, we provided trauma patients with educational interventions by giving verbal and written information about the safety and effectiveness of post-trauma pain therapeutics. The educational intervention aimed to convey the concept that the ultimate goal of post-trauma pain control was not merely to achieve a pain-free status. Rather, the purpose of the acute pain management plan was to facilitate the healing process and maintain daily activities while minimizing pain interference. Stopping both short-term and long-term opioid misuses was the focus of our proof-of-concept study involving the development of an *ad hoc* created educational intervention. As hypothesized, after the educational intervention, we observed reductions in prescribed opioids directly related to the shift in attitudes toward opioids. In addition, another recent pilot study employed video-based education on opioid safety for patients after traumatic injury (21). The authors found that among the patients who were continuously using opioids throughout the study, the group who watched the educational video had lower MME than the group who did not receive an educational information (21).

While the educational intervention did not influence attitudes toward NSAIDs, or complementary and alternative pain interventions, the educational intervention adjusted the perception of opioid usage by decreasing the positive attitudes toward the safety of short-term usage of opioids. In an explorative manner, we found that the adjustment in the perception of using opioids was associated with the changes in prescribed opioids. This finding echoed a previous study conducted in cancer patients where negative beliefs about opioids were associated with worse opioid adherence (22). In fact, expectations about treatment effectiveness (23, 24) and treatment beliefs (25) can influence clinical outcomes, including medication use and disease-related behaviors. In acute pain management, pain relief expectations have contributed to less clinical pain experiences via placebo mechanisms (23). More evidence found in a previous study showed that preoperative patient education effectively reduces post-operative narcotic pill consumption by changing expectations that modulates symptom perceptions and prescription needs (26). An individual may be less likely to seek higher dosages, additional opioid medications, or continuous usage if they understand that their opioid medication is not intended to resolve (zero out) all their pain, nor is the duration of their prescription dependent on the presence of pain (27). It should be noted that trauma patients in the current study held relatively positive attitudes to pharmacological treatment and non-pharmacological interventions such as music and meditation at both the pre-educational and post-educational phases, suggesting that patients were open to a variety of pain management therapeutics.

Strengths and Limitations

There are some strengths related to this study. This study adopted an educational intervention to change expectations and perceptions toward opioids safety. Unlike a recent study using pre-recorded video education with a low participant compliance (21), the educational intervention in the current study was conducted by trained research staff, ensuring interactive educational procedures rather than passive learning. Moreover, the research staff was independent of the clinical treating team of nurses and physicians, minimizing recruitment and other biases. Notably, the independent research investigation ensured that clinical care was delivered without interfering with the standard pain management.

Second, the current study quantified the changes of perception of opioids at time of the educational intervention while being inpatients and when the patients were discharged (e.g., prescribed MME). In the current study, we found that the changes in the perception of opioids needs/safety were significantly correlated with the reduction in prescribed opioids, suggesting beliefs or expectancies were optimized to improve medication consumption.

Despite the strengths of the current study, there were several limitations. First, the MME on the day of discharge was collected based on the EPIC medical records. Therefore, findings from the current study reflected only prescribed opioids instead of the actual opioid intake. Also, an assessment of dispensed pre-and post-intervention MME would have been optimal. However, coordinating research activities at the bedside with trauma inpatients is highly challenging (28). Second, this study adopted a cross-sectional within-subjects design where all inpatients received the educational intervention. Without a control group (i.e., treatment as usual), the reductions in dispensed and prescribed opioids observed in the current study could be a mix of post-educational effects and natural recovery. Also, trauma patients are heterogeneous with large variations in age, type of trauma, hospitalization stay and pain levels. As a proof-of-concept study, we enrolled a relatively small number of inpatients, and thus, these findings cannot be generalized to a larger population. Future studies with larger sample size and adequate control groups (e.g., no-education and/or natural history group) are needed to examine the effectiveness and

efficacy of the educational intervention on three aspects: (1) attitudes toward the perception of opioids needs during the hospitalization and post-discharge recovery, (2) opioid intake during the hospitalization and at home, and (3) prescribed and actual long-term usage of MME for trauma patients using for example, ecological momentary assessments (29). Despite these limitations, these findings outline the potential advantage of introducing educational in-person or video-based interventions to help trauma patients navigate recovery and post-traumatic acute (and chronic) pain management.

CONCLUSION

Overall, the verbal and written education toward acute pain management delivered as an adjuvant intervention can significantly convey that short-term use of opioids is not meant to zero-out pain and can present substantial risks related to long-term use of opioids and paucity of evidence realted to tapering strategies (30). Moreover, the amount of opioids prescribed at the time of discharge as compared to the day of education decreased and was directly related to the changes of opioid perception. Caution shall be applied in drawing definite conclusions due to the proof-of-concept nature of the study; these findings suggest that implementing educational interventions at the bedside could effectively help to cope with acute trauma-related pain while adjusting potential unrealistic patients' expectancies about opioid needs. With education and monitoring, fewer incidences of opioid abuse and, perhaps, addiction would likely develop.

DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Maryland Institutional Review Board approved this study (HP-00083434). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s), and minor(s)' legal guardian/next of kin, for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LC designed the project, supervised the research, and drafted and revised the last version of the manuscript. AT conducted the preliminary analyses and wrote the first draft of the manuscript. RM, NH, RSM, and EM conducted the research and data extraction. RM and YW conducted the final data analyses, wrote the parts of the manuscript, and created the figures. TS, YF-W, and SM created the educational intervention, supervised the research implementation, conducted the data collection, and wrote the parts of the manuscript. SM revised the final manuscript. All authors contributed to the article 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/fpsyt.2022.853745/full#supplementary-material

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Peri-Operative Pain and Opioid Use in Opioid-Naïve Patients Following Inpatient Head and Neck Surgery

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Pain management is an important consideration for Head and Neck Cancer (HNC) patients as they are at an increased risk of developing chronic opioid use, which can negatively impact both quality of life and survival outcomes. This retrospective cohort study aimed to evaluate pain, opioid use and opioid prescriptions following HNC surgery. Participants included patients undergoing resection of a head and neck tumor from 2019–2020 at a single academic center with a length of admission (LOA) of at least 24 h. Exclusion criteria were a history of chronic pain, substance-use disorder, inability to tolerate multimodal analgesia or a significant post-operative complication. Subjects were compared by primary surgical site: Neck (neck dissection, thyroidectomy or parotidectomy), Mucosal (resection of tumor of upper aerodigestive tract, excluding oropharynx), Oropharyngeal (OP) and Free flap (FF). Average daily pain and total daily opioid consumption (as morphine milligram equivalents, MME) and quantity of opioids prescribed at discharge were compared. A total of 216 patients met criteria. Pain severity and daily opioid consumption were comparable across groups on post-operative day 1, but both metrics were significantly greater in the OP group on the day prior to discharge (DpDC) (5.6 (1.9–8.6), $p < 0.05$; 49 ± 44 MME/day, $p < 0.01$). The quantity of opioids prescribed at discharge was associated with opioid consumption on the DpDC only in the Mucosal and FF groups, which had longer LOA (6–7 days) than the Neck and OP groups (1 day, $p < 0.001$). Overall, 65% of patients required at least one dose of an opioid on the DpDC, yet 76% of patients received a prescription for an opioid medication at discharge. A longer LOA (aOR = 0.82, 95% CI: 0.63–0.98) and higher Charlson Comorbidity Index (aOR = 0.08, 95% CI: 0.01–0.48) were negatively associated with receiving an opioid prescription at the time of discharge despite no opioid use on the DpDC, respectively. HNC patients, particularly those with shorter LOA, may be prescribed opioids in excess of their post-operative needs, highlighting the need the for improved pain management algorithms in this patient population. Future work aims to use prospective surveys to better define post-operative and outpatient pain and opioid requirements following HNC surgery.

Keywords: head and neck surgery, post-operative analgesia, opioids, prescriptions, pain

INTRODUCTION

Prescription opioids have significantly contributed to the recent opioid epidemic. Multiple studies across surgical specialties have shown that patients are prescribed opioids in excess of their post-operative requirements (1, 2). With excess medication available, patients are more likely to use opioids for prolonged periods of time, thereby increasing the risk for chronic opioid use (3). Additionally, unused medication has the potential for diversion (1). Recent data has shown that death rates from synthetic opioids, including prescription opioids, have steeply risen since 2013 (4), further highlighting the need to limit prescription of these medications.

Pain management is an important consideration for quality of life as well as survival outcomes in Head and Neck Cancer (HNC) patients (5–8). These patients often require surgical treatment that leads to significant peri-operative pain and disfigurement, and up to 50% (9) also suffer from psychiatric comorbidities (10, 11). These factors increase the risk of opioid dependence, and it is estimated that between 20–60% of HNC patients develop chronic opioid use after treatment (7, 12–14). This is particularly important, as chronic opioid use following surgery for HNC has been associated with decreased disease-free survival (15).

Recent efforts have been made across the United States to limit inappropriate prescribing of opioids, and clinical practice guidelines have been developed to improve management of pain in the perioperative setting (16–18). Within the Otolaryngology literature, studies have focused on evaluating various multimodal analgesic regimens for post-operative pain management following tonsillectomy (19), as it's one of the most painful surgical procedures (20, 21), and endoscopic sinus surgery (3, 22), given the high volume of cases. However, there are limited data on peri-operative pain management for complex HNC patients following inpatient procedures.

To provide safer and more effective pain management guidelines for HNC patients, it is essential to better define post-operative pain and opioid requirements in this patient population. Herein we evaluate patterns of pain, opioid use, and opioid prescriptions following inpatient surgeries for HNC patients and highlight the need for improved pain management algorithms in this patient population.

MATERIALS AND METHODS

Patients

A retrospective review of patients undergoing surgery for tumors of the head and neck in the Otolaryngology – Head & Neck Surgery department was performed at a single academic institution. This project was reviewed and approved by our institutional review board (IRB00251111). Inclusion criteria were: (1) age 18 years or older, (2) surgery for tumor in the head and neck region, (3) surgery from January 1, 2019 – January 1, 2020 at Johns Hopkins Hospital, (4) length of admission (LOA) following surgery of at least 24 h (measured from the time the patient was awake and recovered from anesthesia) and (5) "opioid naïve," defined as no opioid consumption within the 30 days prior to surgery. Exclusion criteria were: (1) past medical history of chronic pain or substance use disorder, (2) inability to tolerate multimodal analgesia (i.e., scheduled acetaminophen and ibuprofen and as needed opioids) due to medical comorbidity (specifically severe hepatic or renal impairment, cirrhosis or moderate-severe chronic kidney disease) or intolerance or allergy and (3) post-operative complication requiring return to the operating room during admission. Patients were grouped by surgical procedure as follows: (1) Neck group: neck dissection (ND) alone or thyroidectomy or parotidectomy with or without ND), (2) Mucosal group: resection of tumor of the upper aerodigestive tract other than in the oropharynx, with or without ND, but without free flap reconstruction (3) Oropharyngeal (OP) group: resection of primary oropharyngeal tumor with or without ND, but without free flap reconstruction, (4) Free flap (FF) group: resection of tumor of upper aerodigestive tract requiring reconstruction with a free flap (**Figure 1**).

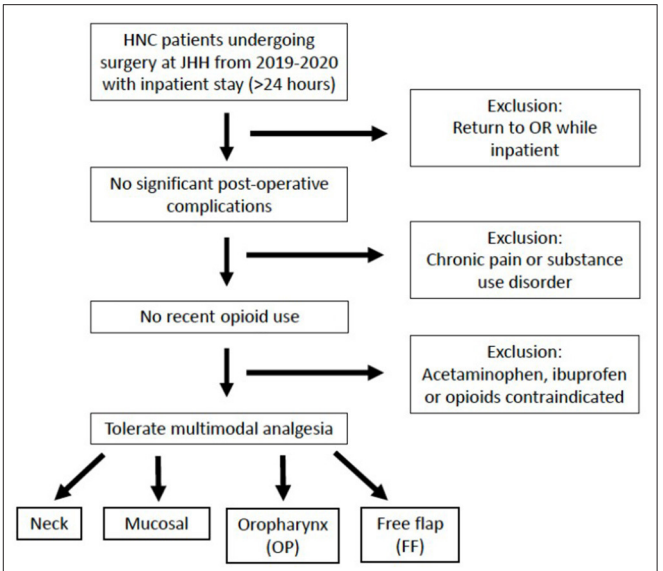

FIGURE 1 | Inclusion and exclusion criteria. Patients undergoing surgery for a head and neck primary tumor at Johns Hopkins Hospital (JHH) from 2019–2020 were included if they had no significant post-operative complications, no recent opioid use and could tolerate multimodal analgesia. Patients were categorized into four groups based on their surgical procedure. HNC, head and neck cancer; OR, operating room.

Data Collection and Analysis

Patient demographics, including age, sex and ethnicity, and past medical and surgical history were collected by chart review from our electronic medical record (EMR) system. Charlson Comorbidity Index (CCI) scores were calculated based on ICD-9 codes (23, 24). Cancer staging was reported according to the American Joint Committee of Cancer 8th Edition Cancer Staging Manual (25). Operative notes for the patients' surgery of interest were manually reviewed and categorized into the one of the 4 surgical groups listed above. Additional operative notes during the patients' admission were reviewed to identify post-operative complications that required return to the operating room, including hematoma/seroma,

TABLE 1 | Patient demographics and clinical information.

Variable Median (range)	Neck	Mucosal	OP	FF	Total
N	108	45	20	43	216
Procedure, *N*	ND (20) Parotid ± ND (23) Thyroid ± ND (65)	OC ± ND (26) TL ± ND (19)	TORS ± ND (20)	Scapula (1) Fibula (10) RF (15) ALT (17)	
Age (years)	52*** (18–89)	67 (38–86)	58 (48–75)	61 (42–80)	60 (18–89)
Female, *N* (%)	73 (68)	14 (31)	5 (25)	13 (30)	105 (49)
Caucasian, *N* (%)	72 (67)	29 (64)	18 (90)	30 (70)	149 (69)
CCI	4 (2–15)***	8 (2–19)	5 (2–10)	6 (2–15)	6 (2–19)
Cancer stage, *N* (%)	I/II: 42 (39)*** III/IV: 1 (1) NA: 65 (60)	I/II: 7 (16) III/IV: 26 (58) NA: 12 (26)	I/II: 20 (100)*** III/IV: – NA: –	I/II: 13 (30) III/IV: 21 (49) NA: 9 (21)	I/II: 82 (38) III/IV: 48 (22) NA: 86 (40)
Prior RT, *N* (%)	1 (1)**	8 (18)	–	8 (19)	17 (8)
LOA (days)	1*** (1–6)	6* (1–19)	1*** (1–5)	7 (2–22)	1 (1–22)
Medications, *N* (%)					
Benzodiazepine:	2 (2)	4 (9)	2 (10)	4 (9)	12 (6)
Z–drug:	1 (1)	2 (4)	0 (0)	0 (0)	3 (1)
SRI:	19 (18)	7 (16)	5 (25)	8 (19)	39 (18)
Gabapentinoid:	5 (5)**	8 (18)	3 (15)	11 (26)	27 (13)
Pain service consult, *N* (%)	0 (0)	4 (9)	0 (0)	4 (9)	8 (4)

*ALT, anterolateral thigh; CCI, Charlson Comorbidity Index; F, female; FF, free flap reconstruction; LOA, length of admission; N, number; NA: not applicable; ND, neck dissection; OC, oral cavity; OP, oropharynx; RF, radial forearm; Rsn, resection; RT, radiation therapy; SD, standard deviation; SRI: serotonin reuptake inhibitor; TORS, transoral robotic surgery; TL, total laryngectomy. *p < 0.05, **p < 0.01, ***p < 0.001.*

abscess, fistula or free flap concerns. Pain while inpatient was recorded on a Likert scale from 0 (no pain) to 10 (worst pain) by nursing staff, and daily average pain was calculated. Daily opioid consumption while inpatient and total quantity of opioids prescribed at discharge from the hospital were calculated and converted to morphine milligram equivalents (MME) (26). Inpatient-use of benzodiazepines, Z-drugs (i.e., zaleplon, zolpidem or eszopiclone), serotonin reuptake inhibitors (SRIs) and gabapentinoids (gabapentin or pregabalin) were also recorded.

Statistical Analysis

Continuous variables are reported as the median and range or mean and standard deviation (SD), where applicable. Kruskal-Wallis test was used to compare continuous measurements between multiple groups, and Fisher's exact and Chi-squared tests were used to compare categorical variables between two and more than two groups, respectively. Wilcoxon matched-pairs signed rank test was used to compare paired data from individual patients at different time points. Linear regression analysis was used to determine significant predictors of quantity of opioids consumed following surgery and quantity of opioids prescribed at discharge; this was performed for all patients as well as within each surgical group. Multivariable logistic regression analysis was used to evaluate factors associated with receiving an opioid prescription at the time of discharge in patients with no opioid use during the 24 h prior to discharge (DpDC). Independent variables evaluated include age, sex, race, cancer stage, CCI, surgical procedure, LOA, and average pain severity on the DpDC. Of note, the surgical procedure group OP was not included as an independent variable given the small number of OP patients in the subgroup evaluated in this regression analysis. Results are reported as the adjusted odds ratio (aOR) and 95% confidence interval (CI). All statistical analysis was performed using R Statistical Software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 216 patients met inclusion criteria. Demographics and clinical information about the patient cohort are shown in **Table 1**. The Neck group had a significantly lower median age at the time of surgery (52 (18–89) years) compared to the Mucosal (67 (38–86) years, $p < 0.001$) and FF (61 (42–80) years, $p < 0.001$) groups. The proportion of females was significantly greater in the Neck group (68%) compared to all others, which averaged between 25-31% female ($p < 0.001$). The CCI was significantly lower in the Neck group (2–15) compared to the Mucosal (8 (2–19), $p < 0.001$) and FF (6 (2–15), $p < 0.05$) groups. Considering tumors able to be staged, the Neck and OP groups had a significantly higher proportion of Stage I or II tumors compared to the Mucosal and FF groups ($p < 0.001$). Similarly, a significantly lower proportion of patients had

TABLE 2 | Average pain and opioid consumption on the first day after surgery and the day prior to discharge from the hospital.

	Neck	Mucosal	OP	FF	Total
Pain severity: mean (SD)					
POD1:	3.8 (1.6)	4.2 (2.2)	4.9 (2.1)	3.9 (2.7)	4.0 (2.0)
DpDC:	3.6 (1.9)	3.8 (2.4)	5.3 (1.9)**	3.5 (1.7)	3.8 (2.0)
Opioid consumption and prescriptions: mean (SD)					
POD1:					
MME/day	28 (24)	42 (41)	48 (40)	44 (45)	34 (33)
5mg-Oxy/day	4 (3)	6 (6)	6 (5)	6 (6)	10 (10)
DpDC:					
MME/day	23 (25)	39 (58)	49 (44)**	25 (29)	27 (32)
5mg-Oxy/day	3 (3)	5 (7)	7 (6)	3 (4)	8 (10)
MME>0 on DpDC, *N* (%):	69 (64)	27 (60)	18 (90)	27 (63)	141 (65)
Prescribed at discharge:					
Total MME	118 (73)*	161 (202)	450 (274)***	216 (240)	174 (190)
Total 5mg-Oxy	16 (10)	21 (27)	60 (37)	29 (32)	52 (57)
Opioid Rx on DC, *N* (%):	85 (78)	29 (64)	18 (90)	32 (74)	164 (76)

*5mg-Oxy/day, number of 5mg oxycodone tablets/day; DC, discharge; DpDC, day prior to discharge; FF, free flap reconstruction; MME, morphine milligram equivalents; N, number; OP, oropharynx; POD 1, postoperative day 1; Rx, prescription; SD, standard deviation. *p < 0.05, **p < 0.01, ***p < 0.001.*

a history of radiation therapy (RT) in the Neck group (1%) compared to the Mucosal (18%, $p < 0.01$) and FF (20%, $p < 0.01$) groups. The median LOA was approximately 1 day for the Neck and OP groups, compared to 6–7 days for the Mucosal and FF groups ($p < 0.001$). Overall use of benzodiazepines and Z-drugs was low, 6% and 1%, respectively, and did not significantly differ between groups. A greater proportion of patients used SRIs (18%) and gabapentinoids (13%) while inpatient, with a significantly lower proportion of gabapentinoid-use in the Neck (5%) group compared to Mucosal (18%, $p < 0.01$) and FF (26%, $p < 0.01$) groups.

Overall Pain and Opioid Consumption While Inpatient

Average daily pain and total daily opioid consumption were compared between surgical groups on the first post-operative day (POD 1) and the day prior to discharge from the hospital (DpDC) (**Table 2**). Pain severity on POD 1 tended to be highest in the OP group (4.9 ± 2.1) compared to the Neck (3.8 ± 1.6), Mucosal (4.2 ± 2.2) and FF groups (3.9 ± 2.7), but this was not statistically significant. On the DpDC, pain severity remained elevated in the OP group (5.6 (1.9–8.6)), which was significantly greater than in the Neck (3.6 ± 1.9, $p < 0.01$), Mucosal (3.8 ± 2.4, $p < 0.05$), and FF (3.5 ± 1.7, $p < 0.01$) groups. On POD 1, 86% of all patients required at least one dose of an opioid medication for pain control. By the DpDC, only 65% of all patients consumed at least 1 dose of an opioid medication. Average daily opioid consumption on the DpDC was significantly greater in the OP group (49 ± 44 MME/day) compared to the Neck (23 ± 25 MME/day, $p < 0.01$) and FF (25 ± 29 MME/day, $p < 0.01$) groups.

Linear regression analysis showed a weak association of pain levels with the quantity of opioids consumed on POD1 in the Neck ($R^2 = 0.49$, $p<0.001$) and OP ($R^2 = 0.44$, $p < 0.01$) groups, and on the DpDC within the Neck group ($R^2 = 0.45$, $p<0.001$). Older age was weakly associated with lower opioid consumption within the FF group on the DpDC ($R^2 = 0.31$, $p < 0.001$). Additionally, subgroup analysis showed significantly higher average pain levels and daily opioid consumption in the subgroup of all patients taking SRIs ($N = 39$) versus those not taking SRIs ($N = 177$) on POD 1 (5.0 ± 1.2 vs. 3.8 ± 2.0, $p < 0.01$; 46 ± 33 vs. 34 ± 35 MME/day, $p < 0.01$, respectively) and the DpDC (4.4 ± 2.3 vs. 3.6 ± 1.9, $p < 0.05$; 46 ± 44 vs. 26 ± 35 MME/day, $p < 0.001$, respectively). Similarly, the subgroup of all patients taking gabapentinoids ($N = 27$) while inpatient had higher average pain levels than those not taking gabapentinoids ($N = 189$) on POD1 (5.0 ± 2.1 vs. 3.9 ± 2.0, $p < 0.05$) and the DpDC (4.8 ± 2.2 vs. 3.6 ± 2.0, $p < 0.01$); with no difference in opioid consumption between subgroups. Otherwise, sex, ethnicity, CCI score, cancer stage, history of RT and LOA were not associated with average opioid consumption within each surgical group or overall.

Opioid Prescriptions at the Time of Discharge

Overall, 76% of patients received a prescription for an opioid medication at the time of discharge. The quantity of opioids prescribed at the time of discharge was compared between surgical groups, as well as to average daily pain and total daily opioid consumption on the DpDC within each group. Similar to opioid consumption on the DpDC, the OP group was prescribed the greatest quantity of opioids at discharge (450 ± 274 MME); this was 2–3 times greater than the quantity prescribed to the Neck (118 ± 73 MME, $p < 0.001$), Mucosal (161 ± 202 MME, $p < 0.001$) and FF groups (216 ± 240 MME, $p < 0.001$). Additional subgroup analysis showed no difference in the quantity of opioids prescribed at discharge between subgroups of all patients taking SRIs versus those not taking SRIs while inpatient; with similar findings for subgroups based on gabapentinoid-use while inpatient. Multivariable logistic regression analysis was used to

TABLE 3 | Odds of receiving an opioid prescription on discharge in patients with no opioid consumption on the day prior to discharge (DpDC).

Variable	aOR	95% CI
Age (>60 years)	1.54	(0.27–10.8)
Sex (Female)	0.62	(0.09–3.89)
Race (Caucasian)	1.59	(0.23–12.35)
CCI (>6)	**0.08**	**(0.01–0.48)**
Cancer stage (III/IV)	1.25	(0.16–12.66)
Procedure:		
Neck	3.92	(0.34–63.9)
FF	8.46	(1.04–103.47)
LOA (days)	**0.82**	**(0.63–0.98)**
Pain on DpDC (>3)	0.58	(0.11–2.88)

aOR, adjusted odds ratio; CCI, Charlson Comorbidity Index; CI, confidence interval; DpDC, day prior to discharge; FF, free flap reconstruction; LOA, length of admission. Bold values indicate statistical significance.

evaluate factors associated with receiving an opioid prescription at the time of discharge in patients with no opioid consumption during the 24 h prior to discharge (**Table 3**). Within this subset of patients, CCI (aOR = 0.08, 95% CI: 0.01–0.48) and LOA (aOR= 0.82, 95% CI: 0.63–0.98) were associated with a lower incidence of receiving an opioid prescription despite no consumption on the DpDC.

Trends in Pain and Opioid Consumption

Patients with length of admission of 3 days or longer were evaluated to determine trends in pain and opioid consumption over time (**Figure 2**). The Neck group showed a significant decrease in baseline pain from POD 1 to POD 3 (3.3 ± 1.3 to 1.8 ± 0.9, $p < 0.05$) (**Figure 2A**) and baseline opioid consumption from POD 1 to POD 2 (22 ± 26 MME/day to 8 ± 13 MME/day, $p < 0.05$) (**Figure 2B**), which remained stable until discharge. All other groups had no change from baseline pain or opioid consumption through POD 3.

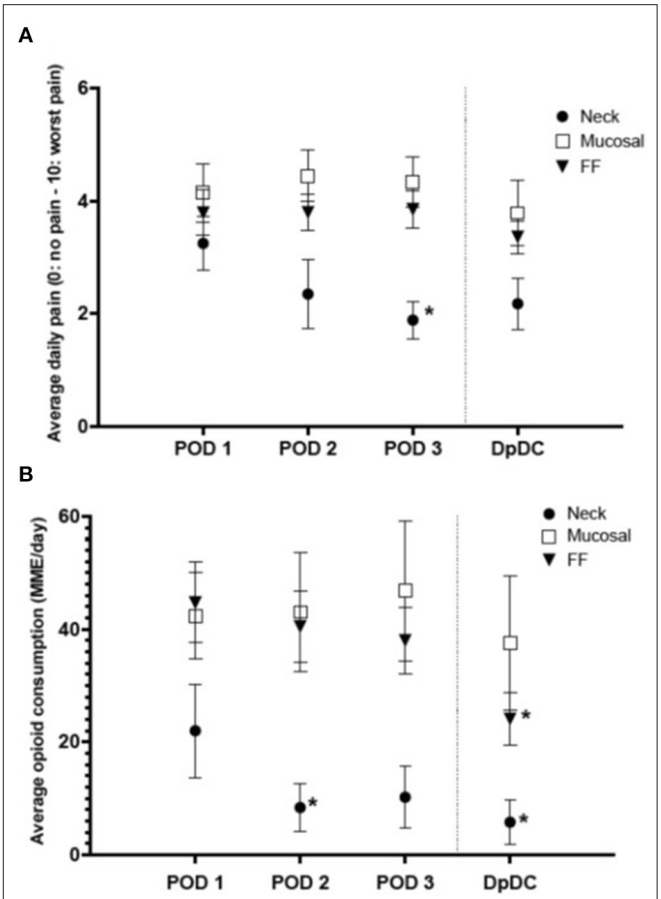

FIGURE 2 | Average daily pain and opioid consumption in a subset of patients with length of admission of 3 or more days (mean ± SEM). **(A)** Average daily pain significantly decreased from post-operative day 1 (POD 1) to POD 3 in the neck group ($p < 0.05$). **(B)** Daily opioid consumption significantly decreased from POD 1 to POD 2 in the neck group (*$p < 0.05$) and from POD 1 to the day prior to discharge (DpDC) in the free flap (FF) group (*$p < 0.05$). MME, morphine milligram equivalents.

DISCUSSION

This study analyzes post-operative pain and opioid consumption in a cohort of patients undergoing resection of tumors of the head and neck. Overall, we found that most patients (86%) consumed at least one dose of opioid medication on the first post-operative day. By the day prior to discharge, this had decreased to only 65% of all patients, and only 60% of patients had substantial opioid requirements of 7.5 MME/day (5 mg oxycodone/day). Despite these modest numbers, 76% of all patients received an opioid prescription at discharge. There was also discrepancy in the quantity of opioids prescribed between groups with similar pain levels as demonstrated by the FF group receiving nearly twice as much opioid than the Neck group. While the length of admission varied between patients, all patients had at least 24 h of data of pain levels and opioid consumption prior to discharge.

The American Academy of Otolaryngology recently published a comprehensive Clinical Practice Guideline providing evidence-based recommendations for opioid prescribing after common Otolaryngology procedures (18). These guidelines include expected average durations of pain after many Otolaryngology procedures; patients undergoing "Neck" procedures, such as thyroidectomy or parotidectomy, are expected to have pain for up to 3–5 days after surgery (18). In agreement with prior studies referenced in these guidelines, the Neck group in our study had a significant decrease in both pain and opioid consumption during the first three post-operative days, in a subset of patients with at least 3 days of admission. From POD 1 to 2, average opioid consumption in this subset decreased by over 50% from 22 MME/day to less than 10 MME/day, suggesting the majority of patients undergoing these procedures may require only a short supply of or even no opioid medication following surgery. Despite these modest numbers, patients in the Neck group were prescribed an average of 118 MME (equivalent to 16 5-mg tablets of oxycodone) on discharge, clearly in excess of this group's opioid requirements. While a

patient's opioid consumption prior to discharge can be used to estimate requirements as an outpatient (17), the majority of patients undergoing Neck procedures are discharged on POD 1 or 2; as such, this group may be over-prescribed opioids on discharge if based on their inpatient requirements during the first 24 h after surgery. Unfortunately, there is limited information in the literature about expected durations of pain and opioid consumption after more complex HNC procedures.

Pain severity did not strongly correlate with opioid consumption or quantity of opioid prescribed at discharge overall or within each surgical group. However, the Mucosal and FF groups had a moderate association between opioid consumption on the day prior to discharge and the quantity of opioids prescribed at discharge. Both groups also had longer lengths of admission, of 6–7 days, compared to 1 day in the Neck and OP groups. This further suggests that prescribing patterns may better represent inpatient opioid requirements as more longitudinal data about patients is available.

Numerous efforts have been made to further our understanding of factors affecting post-operative pain since the role of prescription opioids in the opioid epidemic has been elucidated (19–21, 27). Guidelines for identifying patients at risk for opioid dependence have also been developed (28, 29). We found that patients taking SRIs had significantly higher pain levels and greater consumption of opioids following surgery than those not taking SRIs. This supports other literature that links psychiatric comorbidities of anxiety and depression with post-operative opioid use and incidence of chronic pain (2, 30, 31) and highlights the importance of more effective and safer alternatives specifically for this patient population.

Multimodal analgesia with NSAIDs has become the standard of care following most Otolaryngology procedures, including tonsillectomy, since studies have shown no increased risk of bleeding (32); the use of adjunctive medications for pain, such as gabapentinoids, has also increased in recent years (33). Within our cohort, patients undergoing more extensive surgeries or with higher levels of post-operative pain were more likely to be prescribed a gabapentinoid in addition to standard multimodal analgesia, but there was no difference in daily opioid consumption based on gabapentinoid-use. Multiple studies have also shown an analgesic effect of placebo treatment, yet there remains controversy over the general public's perception of placebo, with regards to deception (34). However, recent data from open-label trials suggest that placebo may still be effective without the need to withhold information from patients; suggesting this may be a feasible addition to standard multimodal analgesia regimens in the future (35). Acute pain and palliative care specialists also play an important role in the post-operative setting, particularly for more complex cases. Only a small proportion of patients in our cohort, 4%, received a pain consult following surgery. However, as options for adjunctive pain management continue to expand, these specialties may become essential in providing safer and more effective post-operative pain regimens for patients.

Despite the aforementioned progress, opioid medications continue to be prescribed in excess of patients' needs following tonsillectomy (21) and other common Otolaryngology surgeries (2, 3), with similar findings in other surgical fields (1, 17, 36). Our data is limited without information about opioid consumption following discharge from the hospital. However, comparison of opioid prescriptions to consumption while inpatient suggests many of these patients were prescribed excess medication, particularly those who received a prescription despite no documented opioid consumption for the 24 h prior to discharge. We found that patients with the highest risk of receiving a prescription despite no use on the DpDC were those with less comorbidities and shorter durations of admission. While providers may be more cautious to prescribe opioids to patients with more comorbidities, given the risk of side effects, the same diligence should be maintained with all patients.

The above findings highlight potential to improve our estimation of patients' opioid requirements following discharge from the hospital. Recent efforts by a General Surgery group showed that in patients undergoing inpatient general surgery procedures, opioid consumption on the day prior to discharge was correlated with outpatient use, suggesting this information could be used as a metric for prescribing (17). Follow-up studies from this group also found that educating surgeons on guidelines for opioid prescribing significantly decreased the amount of opioids prescribed at their institution without increasing patient requests for refill medications (1, 36). In the context of HNC patients, pre-operative chronic pain and chronic opioid use increase a patient's expected opioid needs following surgery (12, 13, 15). This study focused on HNC patients without pre-operative chronic pain or recent opioid use to evaluate post-operative pain following HNC surgery without these additional variables. In our patient cohort the quantity of opioids prescribed correlated with opioid consumption prior to discharge for patients with the longest durations of admission. This was not the case for patients with shorter admissions, suggesting further information, such as data about opioid use after discharge from the hospital, is required to prevent over-prescribing in these patients. While this is feasible, it's important to note that such data is inherently limited by selection bias for those who agree to participate and accuracy of reporting by patients.

This study is limited by the relatively small sample size and retrospective nature of the EMR review. As guidelines have been implemented to limit the quantity of opioids physicians can initially prescribe, we aimed to evaluate data from a recent and limited time period for consistency. Patients with specific comorbidities preventing the use of multimodal analgesia with scheduled acetaminophen and ibuprofen were excluded to compare a more homogenous population, which may limit external validity. While total quantity of opioids prescribed at discharge may be influenced by concern about access to refills, this is less likely as all prescribers at our institution are able to electronically prescribe scheduled medications and an on-call physician is available around the clock for patient phone calls. Finally, this current study is limited to the evaluation of inpatient data.

Effective and safe pain management following HNC surgery is imperative for both quality of life and survival outcomes in this patient population. Despite recent progress in decreasing prescription opioids, our study shows that these medications

continue to be prescribed in excess of patients' post-operative needs. Future work aims to better define post-operative pain and opioid requirements following HNC surgery. Our group is currently collecting data on daily opioid consumption after discharge from the hospital with prospective surveys in a comparable patient population. This information will allow us to investigate patient and surgical factors, such as opioid consumption on the day before discharge from the hospital or surgical procedure, associated with outpatient opioid consumption. The ultimate goal of these studies is to develop a model to improve our prediction of a patient's opioid requirements, thereby limiting the risk associated with excess opioid prescriptions.

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 Johns Hopkins IRB. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

DT, CP-H, and PV contributed to conception and design of the study. DT and CP-H organized the database and performed the statistical analysis. DT wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

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Bibliometric Properties of Placebo Literature From the JIPS Database: A Descriptive Study

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Objectives: First dedicated articles about placebo effects have been published in the 1940s, and more than 5,000 articles have been published in scientific organs since. However, the evolution of this research field has rarely been examined. By means of bibliometric analyses we aim to generate research metrics such as the number and types of publications as well as topics, authorship networks, impacts, and future directions.

Methods: Bibliometric methods were applied to the Journal of Interdisciplinary Placebo Studies (JIPS) database. It comprises around 5,000 scientific articles dedicated to researching placebo effects and mechanisms and is expanded continually through individual curation, making it a prime candidate for investigation. Web scraping was used to obtain complete article information from PubMed and Web of Science. The same information was obtained for addiction research as reference field. Analyses include a general characterization of the database as well as focus points concerning publication types (data vs. non-data articles), high-impact publications and more.

Results: Analyses show that the JIPS database is a comprehensive collection of placebo publications. The development of the field is comparable to that of the comparator field and scientific publication in general. The most frequently used keywords describe populations or study design topics; the most frequent symptoms were pain, depression and anxiety. Data and non-data (e.g., review) papers are related in proportion of about 6:4 in recent decades, indicating a stable degree of productivity. A network of 26 interconnected researchers was identified who published 25 or more articles. Placebo research contributes comparable numbers of publications to high-impact journals as the comparator field. Several additional analyses are performed, with a focus on visualization of various database parameters.

Conclusions: Bibliometric analyses of the JIPS database can be used to answer questions to the field, for example, to get an impression of blind spots and future directions. However, keywords used in indexing and publications themselves are often general and suggest that placebo research may still be considered a subspecialty of superordinate fields, particularly since there are no journals dedicated to placebo research itself. We invite interested colleagues to use this database for further analyses.

Keywords: placebo effect, bibliometrics, journal impact factor, authorship, publications

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INTRODUCTION

The development of a new subspecialty in most if not all areas of science and research is usually not well documented but may occur in many incremental steps in diverse scientific areas over a prolonged period of time. Usually, it can only be evaluated retrospectively after its members have established some formal and informal rules of communication. As an example, it may be quite difficult to identify and describe exactly when placebo research—that is, research dedicated to mechanisms of placebo effects, their occurrence, and related aspects—became a subspecialty of medicine, psychology and related fields. After establishing a scientific society (Society of Interdisciplinary Placebo Studies; SIPS) (2014), exchange about novel findings (e.g., the Journal of Interdisciplinary Placebo Studies—JIPS—newsletter, 2016), communication formats (e.g., the SIPS conferences starting in 2017), and consensus proposals concerning terminology and implications [2018, (1)], the current status of placebo research and researchers is, without doubt, that of a unique scientific community. While it is possible to identify when the term "placebo" entered the scientific terminology, its use and acceptance within the established communities remains largely in the dark. However, the definition of the term "placebo effect" was recently described by an expert consensus as "the changes specifically attributable to placebo and nocebo mechanisms, including the neurobiological and psychological mechanisms of expectancies" (1, p. 206). Bibliometric approaches may help to uncover this history, and structure the past and present state of this "new kid in town".

Bibliometrics itself has—as a novel scientific discipline—a similarly "dark" beginning. It has its origins in the library and information sciences, where it first applied mathematical and statistical methods to books and other science communication media (2). Its development toward an own research area began in the 1920–1930s, when important bibliometric laws were postulated. For example, Lotka's law (3) postulates a systematic relationship of the number of few prolific vs. many onetime authors; Zipf's law (4) similarly addresses the probability of word occurrences in a given text [also see (5, 6)]; and Bradford's law (7, 8) postulates the centrality of a small number of journals in any given field, and an increasingly wide periphery.

Another key moment in the history of bibliometrics was the introduction of the Science Citation Index (SCI) in 1955 (9). A byproduct with high relevance was the Journal Citation Report (JSR) serving to identify authors, their publications, and their citation frequency (9). The first international scientific journal with specialization for bibliometrics and quantitative analysis of science products was Scientometrics, published in 1978 (10). Bibliometrics is defined as the study of quantitative structures in science, science communication, and science politics (10), with numerous related (sub)disciplines such as scientometrics or webometrics (11). Of specific importance for the discipline are publications of research results. In empirical research, this mostly includes printed journal publications—as compared to the eighteenth and nineteenth century dominance of science books –, and more recently online publications (12, 13). Bibliometrics mostly uses scientific articles published in specialized journals as its dominant research subject. In this paper, we will apply bibliometric approaches to study placebo research.

The term "placebo" was coined in the eighteenth century (14), and seminal, dedicated, mechanistic placebo research papers have been published as early as 1946 (15). A first bibliometric analysis (16) of placebo papers was limited to 301 published papers, while the number of genuine papers in the JIPS database had already increased more than ten-fold by 2015 (17). As of 2021 it comprises nearly 5,000 papers containing data-based publications, reviews, and meta-analyses.

This study aims to cover a broad range of analyses and visualizations to characterize the JIPS database; in particular, it aims to:

i) ascertain quality and basic content of the JIPS database and its comparator.
ii) elaborate on the content through keyword frequencies and author networks.
iii) quantify the importance and productivity of placebo research compared to all publications in specific fields such as pain, depression, or anxiety.
iv) describe performance aspects of placebo literature (e.g., impact, receptivity) compared to publications in a comparator field (addiction research).

Bibliometric methods are myriad and differ in their degree of sophistication, and most parameters (e.g., frequency, impact) carry substantial caveats (18, 19). As this is a fledgling and ongoing project, it will limit itself to some aspects that might prove helpful for the placebo research community at this stage.

MATERIALS AND METHODS

Origins of the Database

The creation of the Journal of Interdisciplinary Placebo Studies (JIPS) database has been described elsewhere [e.g., (17, 20–22)]. Briefly, in 2004, PE started to collect all research articles dealing with the placebo effect by searching the PubMed database retrospectively and prospectively using the simple descriptor "placebo" (All Fields). Since then, new entries in the PubMed database are being curated on a weekly basis for placebo research articles by a team of researchers (PE joined by KW and EKB). Articles are added to the JIPS database (administrated by BH). It has been made available for the interested public in 2016 (https://jips.online).

Preprocessing

The JIPS database is administrated in the citation manager software EndNote (23). To obtain a dataset suitable for analysis, the database underwent several steps of preprocessing. First, the database obtained from EndNote (status as per 2021-10-11) was imported into MATLAB (version 9.8.0.1417392 (2020a); The MathWorks Inc, Natick, Massachusetts, USA). All following steps were performed in MATLAB.

Articles without PubMed ID (PMID) were identified and the PMID manually researched and entered if available. Forty-six of 128 articles without PMID could be completed, the remaining 82 articles include periodicals or monographs not listed in PubMed.

No content classification was performed for articles without PMID; likewise, content classification was used as-is (without further validation or self-classification where no MeSH terms were provided). After completion, the database was double-checked for duplicates, yielding $N = 4{,}895$ articles in total, of which 4,732 articles have a valid PMID.

In a next step, to ensure up-to-date information, all PMIDs were extracted and used to re-query all available information from two sources: PubMed (https://pubmed.ncbi.nlm.nih.gov, United States National Library of Medicine, National Institutes of Health) and Web of Science (WoS; https://www.webofscience.com, Clarivate Analytics). This information was appended to the database. While mostly redundant, it includes data not commonly available in EndNote, such as full author names, Medical Subject Headings (MeSHs), or citations counts.

Next, all authors were compiled and uniquely identified by using full names. Authors whose full names were not provided, and where abbreviated names were ambiguous, were manually identified if possible.

Derived Data Sets

For each article in the database (subsequently called parent articles), information about all citations (i.e., articles citing the parent) were downloaded from PubMed using web scraping functions provided by MATLAB. Specifically, the Cited By-field in PubMed's result pages were looped and parsed to identify citations information. Analyses involving citations are therefore further restricted to PubMed-provided data only.

For further analyses concerning data and evidence types, the PubMed field Publication Type was used. Articles were either defined as "data" or "non-data" articles depending on their publication type (**Supplementary Figure 1**). Publication types tagged as "uninformative" were not considered in the respective comparative analyses.

For the existing datasets, the units of analysis employed were:

- articles (commonly by Pubmed ID, PMID)
- authors
- references (i.e., articles cited in an item of the database)
- citations (i.e., articles citing an item from the database).

Comparator Database

After initial analyses, it became apparent that not all were informative in isolation but required a comparison with similar data sets outside the placebo field. For example, to know whether the ratio of first authors to all authors in the placebo field was somehow remarkable it has to be compared to a similar field. For the current analysis, we decided on addiction research as a comparator. Importantly, the field includes highly interdisciplinary approaches, the clinical entity is also signified by a large psychological component, and the number of publications is roughly comparable to that in placebo research (or at least not different by orders of magnitude). Web scraping was used to search PubMed for the MeSH Major Topic "behavior, addictive" (alias "addiction"; MeSH Unique ID D016739). All steps described above were also taken for this single-descriptor database.

Medical Subject Headings and Other Indexed Parameters

Several of the following analyses rely on MeSH descriptors provided by PubMed. MeSHs are a controlled vocabulary thesaurus administrated by the National Library of Medicine (https://www.nlm.nih.gov/bsd/indexfaq.html). The thesaurus includes over 27,000 entries which can be qualified with over 80 subheadings. While it is occasionally expanded by new terms, these are not exhaustively applied retroactively to already indexed articles. Similar to MeSH indexing, PubMed provides fields concerning, for example, the publication type of an article. All indexing is performed by trained indexers. MeSH terms are routinely subject of bibliometric investigations (24, 25), although possible misclassification is a concern to be addressed.

Analysis Strategy and Caveats

The focus of this manuscript is on description and visualization of database contents, with only few analyses deemed to profit from inference statistical approaches. For these analyses, the significance level was set to $p = 0.05$.

Wordclouds were generated using the MATLAB function wordcloud and including the 100 most frequent terms in the list of all MeSH terms used in the classification of the JIPS database. The words "placebo" and "placebo effect" were excluded because they constitute the selection criterion for inclusion in the JIPS database to begin with. Author networks were created using MATLAB's graph object.

Journal impact factors were downloaded from the Scopus Database (Elsevier, Amsterdam, Netherlands). Journal aliases were downloaded from WoS.

We have opted to include all data including from the (then) ongoing year 2021 regardless of possible lags in classification, to convey as complete a picture as possible, and to preserve the same time frame between analyses. Where this would impact interpretability of recent results, a cautionary note has been added. However, where parameters cannot be computed otherwise (e.g., *n*-year impact factors), data has been truncated accordingly.

Furthermore, some analyses that rely on MeSH classification come with the caveat that the terms for "placebo effect" (MeSH ID D015990) and "behavior, addictive" (MeSH ID D016739) were introduced in 1990 and 1992, respectively. While some retrospective classification has been performed, this is largely deficient, therefore, the introduction date of 1990 has been added as a visual marker/cautionary note where appropriate.

RESULTS

Database Volume and Integrity

Our first intention was to ascertain quality and integrity of the JIPS and comparator databases, and provide a general overview.

At the reference date (2021-10-11), the JIPS database included 4895 unique entries, 4110 of which include attached documents. Of these, 4723 are PubMed-listed entries, meaning 172 articles (3.5%) are not listed; note that these articles are not considered in most analyses. The number of detected citations was 36,631.

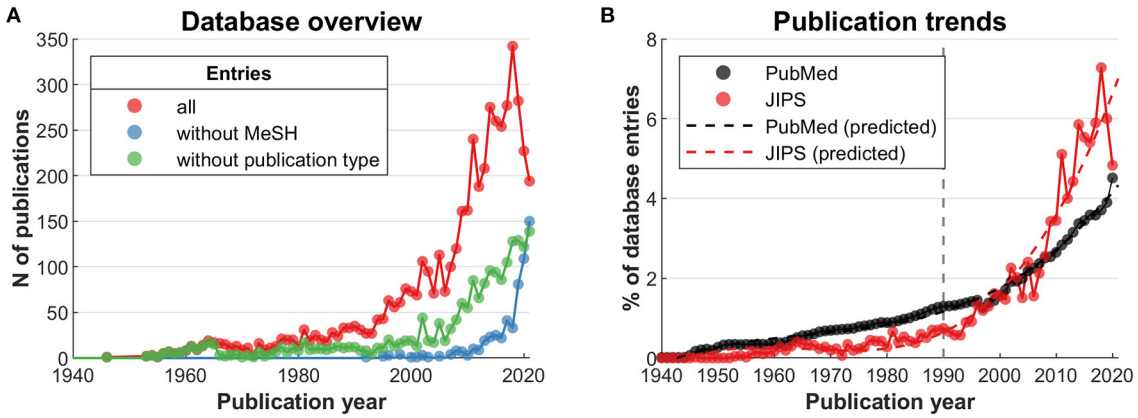

FIGURE 1 | JIPS database overview compared to all PubMed publications. The gray vertical line marks the introduction of the "placebo effect" MeSH term (1990). **(A)** Number of all publications in the JIPS database (red line). Of these, a number of publications have not been MeSH-indexed at the time of data compilation (blue line), with a higher number in the most recent years. Likewise, a number of publications do not have an informative Publication Type (green line). See text for details. **(B)** Publications in the entire PubMed database compared to the JIPS database, normalized by total database volumes. The JIPS trajectory (red dashed line) first undercuts the PubMed trajectory (black dashed line), then exceeds it around year 2001. Predicted values from random intercept linear mixed effects model with quadratic term.

At the reference date, the addiction database included 8,986 unique PubMed-obtained entries. The number of detected citations was 52,782. The overlap between the JIPS and comparator database was negligible (1 article only, PMID 15361811).

The red line in **Figure 1A** shows the number of publications by publication year starting at 1940, with the first JIPS entry occurring in 1946 (15). The increase is roughly proportional to the one seen for the entire PubMed database in this time frame (**Figure 1B**). More specifically however, while placebo research was relatively less productive prior to the mid 1990s, recent years have seen an increase in publications exceeding that of the general scientific output, as indicated by the dashed lines (year × year^2 × database interaction, t (154) = 5.222, $p = 6 \times 10^{-07}$; random intercept model including linear and quadratic terms).

The MeSH- and publication type-based analyses in this work rely on the correctness and completeness of indexing. To investigate these aspects, we first determined the number of non-indexed publications in the JIPS database. For MeSH terms (**Figure 1A**, blue line), indexing shows a conspicuous lag. Presumably, this is because of the backlog involved in consecutive indexing given an ever-increasing number of publications (**Figure 1B**). The number of articles without an informative publication type (**Figure 1A**, green line) shows a lag as well, but an even higher number of affected articles. For a determination of informative vs. noninformative publication types, see section "Productivity in the context of parent fields and data generation" below.

As for the question of whether MeSHs accurately describe an article's content if indexing was performed, cursory analysis indicates that they are not applied with full consistency. For example, 857 articles use "pain" or "analgesi*" in the abstract, 915 articles use "pain" or "analgesi*" in the MeSHs. However, of the 857 abstract hits, 183 (21%) do not have the corresponding MeSH entry, whereas of the 915 MeSH hits, 241 (26%) do not use the corresponding term in the abstract. For "depression" or "depressive", a similar ratio arises.

As a sensitivity analysis, we obtained a Major MeSH-derived dataset using the term "placebo effect" through PubMed web scraping, in analogy to the procedure used to obtain the addiction comparator database. This dataset contained 2,174 entries. We determined the intersection to JIPS using PMIDs—with 1,471 articles in both datasets, 703 articles were identified by the MeSH but not by the JIPS curation. These 703 were processed in their entirety and judged by abstract inspection whether or not they should be included in the JIPS. Two hundred and fifty articles were considered to be pertinent, indicating "misses" in the range of 250/(4,895 + 250)≈5%. While these articles were added to the JIPS going forward, we decided to proceed with the status quo in this paper to preserve continuity to the previous JIPS-based publications (17, 20–22). Note that conversely, the PubMed classification only identified about a third of articles contained in the JIPS database (1,471+250)/(4,895+250)≈33%. This issue also has implications for the comparison between JIPS and (Major MeSH-derived) addiction databases that are discussed under "Performative aspects and comparative database analysis".

Content Characterization and Authorship Networks

The first exploration of the actual JIPS database content included the MeSH terms employed, and collaborative networks of its contributing researchers. To better convey the contents of available MeSHs, a compilation of the most frequent occurrences is shown in **Figure 2**. Broadly, the most frequent terms can be categorized into generic (e.g., placebo effect, treatment outcome), population-related (e.g., humans, adult, female, age), design-related (e.g., randomized controlled trials as topic, double-blind method), entity-related (e.g., pain, depressive disorder)

FIGURE 2 | Word cloud of (major) Medical Subject Headings (MeSH) used in the JIPS database. Larger words indicate more frequent occurrence.

or measurement-related (e.g., pain measurement, brain). As an example for entity-related terms, **Figure 3** shows the frequencies of the top three symptoms investigated (and indexed) in the JIPS database, namely pain, depression and anxiety including synonyms. Decreases are likely due to similar reasons as the general drop in publication numbers discussed concerning (**Figure 1**).

Since population-related terms were among the most frequent, it is worthwhile to assess MeSHs relating to age distributions to consider possible regularities or even shortcomings (26). **Figure 4A** shows the frequency of articles investigating younger populations (child, adolescent, and young adult), **Figure 4B** that of older populations (middle aged, aged, over 80 years of age); the "adult" MeSH is provided as reference in both.

As a final illustration of basic information contained in the database, co-authorship data can be processed to show collaborative networks between individual authors (**Figure 5**). This not only allows for an assessment of collaboration strength (for example, particularly strong collaborative relationships exist between Enck and Klosterhalfen, or Kaptchuk and Kirsch), but also the interconnectedness of the respective authors (for example, Gollub and Klosterhalfen are located on the periphery; conversely, Bingel and Geers have ties to a larger number of collaborators).

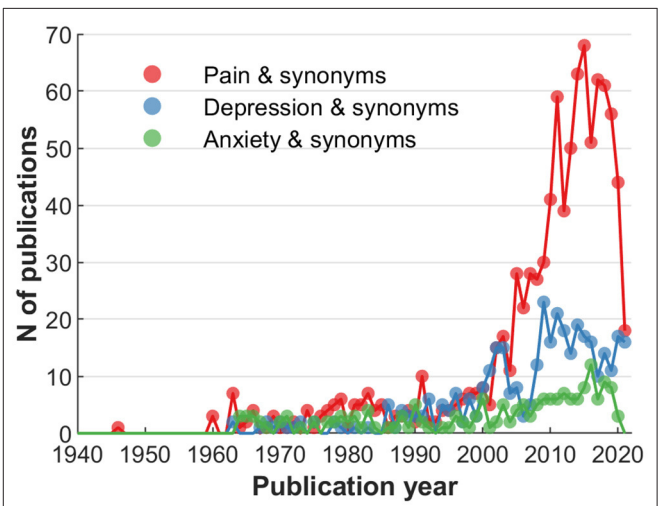

FIGURE 3 | Comparative frequency of articles by MeSH terms: Related to the investigated entity (e.g., clinical symptom).

Productivity in the Context of Parent Fields and Data Generation

Additional information about the placebo field can be garnered using more sophisticated analyses on the JIPS database by relating placebo-related information with those available for

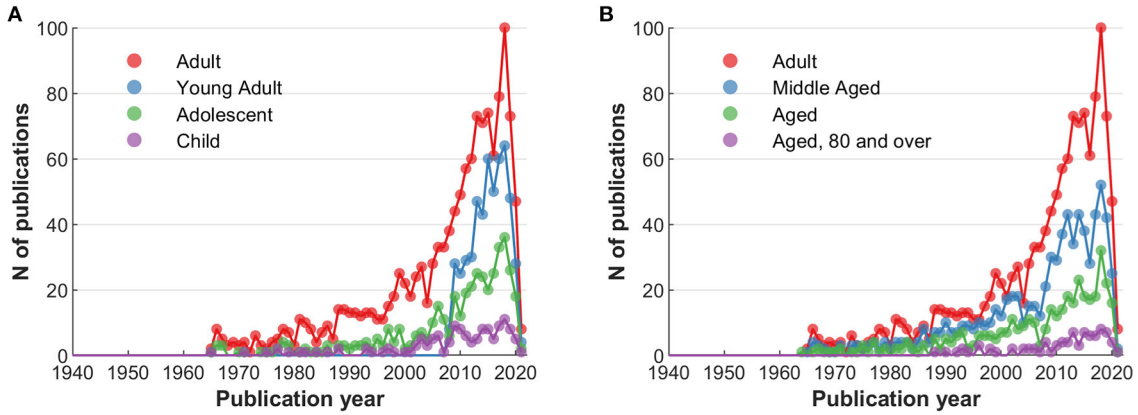

FIGURE 4 | Comparative frequency of articles by MeSH terms: Related to the investigated population. **(A)** Younger ages, with "adult" MeSH as reference. **(B)** Older ages, with "adult" MeSH as reference.

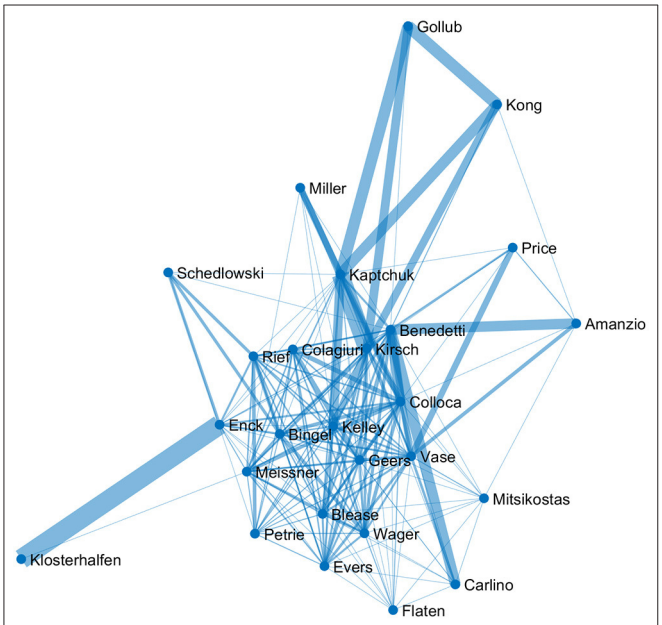

FIGURE 5 | Network of the most prolific authors in the JIPS database. Cutoff criterion for inclusion were ≥25 publications included in the database. Line width indicates the weight of the connection, corresponding to the number of shared publications. Centrality indicates the number of interconnected researchers.

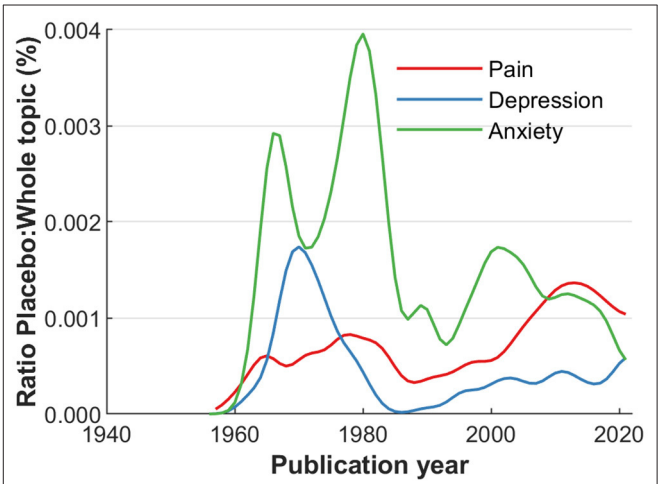

FIGURE 6 | Major MeSH term occurrence in the database, compared to the number of citations in the entire respective PubMed field (pain, depression, anxiety) over time. Absolute percentages are low, but allow to identify peaks of interest and trends in the respective fields. Data is smoothed over 5 years.

broader fields in which placebo-related research takes place. For example, **Figure 6** plots the ratios of major entity-related entries in the JIPS database (pain, depression, anxiety) in relation to the entire number of publications in the respective field. This analysis reveals two types of information. Firstly, that the proportion of placebo-related information in any given field is diminutive, as indicated by the low percentages shown by the graphs (around 0.001%, i.e., one in hundred thousand articles being dedicated placebo research). Secondly, the trajectories can be used to identify trends in the involvement of placebo research in any given field, keeping in mind that small base rates of placebo publications lead to a higher volatility in the respective curves (e.g., anxiety). For example, relative to the entire number of publications in depression research, placebo-related studies peaked around 1,970 and recently started increasing again.

As another example, the PubMed-provided field Publication Type (including one or more entries per article) can serve as a diagnostic tool to assess the generative power of the placebo field, e.g., by illustrating the ratio and composition of articles containing original (experimental or clinical, people-derived) data vs. derivative articles such as reviews or meta-analyses. For this purpose, the publication types from the JIPS database were compiled and divided into either category ("data" or "non-data", see above). A full list of categorized publication types is found in **Supplementary Figure 1**. For example, "data" publication

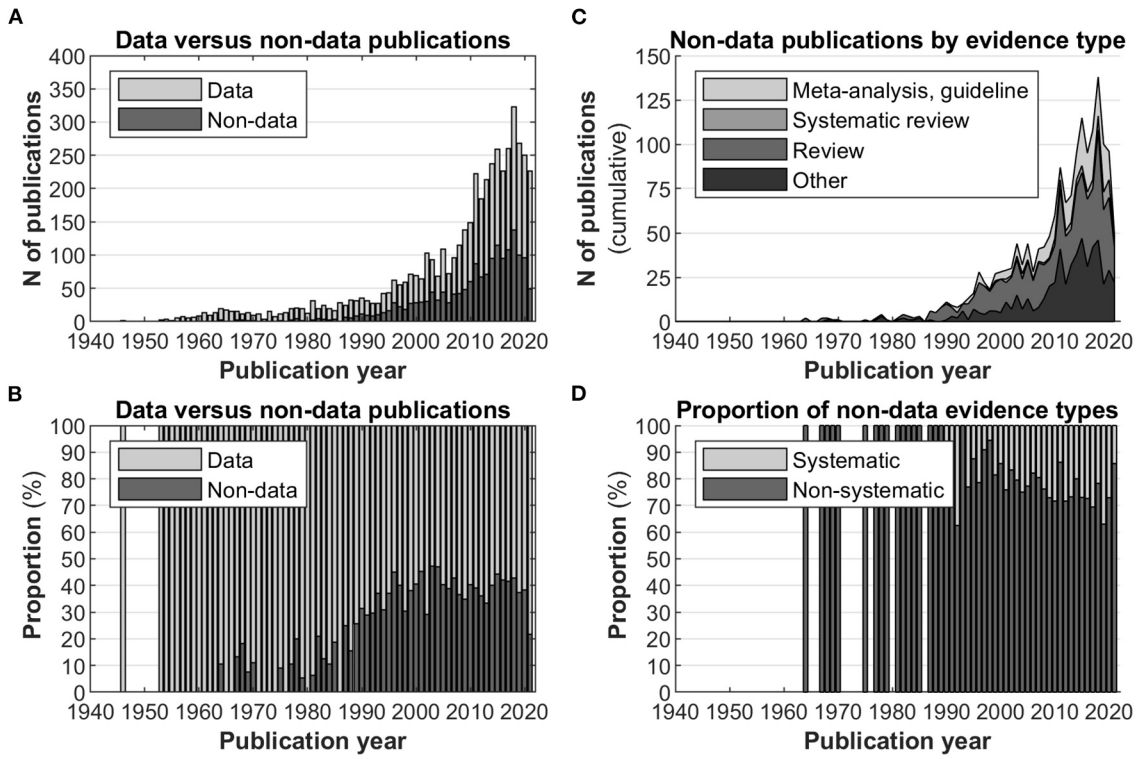

FIGURE 7 | Data vs. non-data publications, excluding uninformative publication types. **(A)** Histograms of data articles vs. non-data articles in the database. **(B)** Proportion (in percent) of data vs. non-data publications. In recent years, this ratio is relatively stable, with the majority of the articles considered data publications. **(C)** Breakdown of the evidence types of non-data publications. **(D)** Proportion of non-data evidence types categorized in non-systematic or systematic. Systematic evidence types are increasingly utilized.

types include those tagged "Classical article", "Clinical study" or "Observational study"; "non-data" publication types include those tagged "Editorial", "Review", "Meta-analysis". A third category was established as "uninformative"—these publication types were not included for analysis as they do not discriminate between data or non-data articles (e.g., "Journal article", "Research support, non-US gov't", "English abstract"). Articles were categorized as data, non-data or uninformative in a hierarchical fashion, i.e., where multiple tags were present, data tags had precedence over non-data tags; uninformative tags were removed altogether.

Figure 7A displays the number of non-data publications in the database in relation to the total number of publications (also see **Figure 1A**); **Figure 7B** displays the ratio between the two categories, indicating a relatively stable proportion of ca. 40% non-data papers in the past 25 years.

Relatedly, the quality of evidence provided by non-data articles can vary [e.g., (27)], with studies including aggregate statistics such as meta-analyses providing the highest level. The exact criteria for this subdivision are provided in **Supplementary Table 1**. Subdividing the non-data papers into categories of evidence quality, **Figure 7C** displays the relative frequencies, with narrative/non-systematic reviews constituting the bulk of non-data publication types. Further aggregating evidence types, **Figure 7D** demonstrates that the level of systematic evidence types remained relatively stable in the past 25 years, albeit a slightly increasing trend is discernible.

Performative Aspects and Comparative Database Analysis

To further characterize the field, we considered performance aspects such as impact, reception parameters, and qualitative aspects of individual high-performing publications. These analyses were contextualized with data from our addiction comparator database. For example, **Figure 8** shows the average impact of all articles of placebo vs. addiction research. For the 2- and 5-year impact factors, the comparator database outperforms placebo research in the past 10 years. Comparing the all-time impact (**Figure 8C**) with the more constrained alternatives, it is also possible to detect seminal papers by identifying "spikes" in the impact parameter (see **Table 1** below).

Figure 8 also indicates that articles in the JIPS are cited less frequently than the comparator database in (roughly) the past 10 years. In an analysis focusing on journals in upper impact segments (**Figure 9A**), we have determined that no clear distinction emerges between JIPS and the comparator database, i.e., both publish in comparable quantities in higher-impact journals; note that this is despite the comparator database containing roughly twice the number of publications. However, the lower two (∼medium) impact factor bins (factors 5–6 and

6–7) hint at an overall advantage of the comparator database in these journals, which is driven by a journal dedicated to that field (312 publications in the Journal of Behavioral Addictions, impact factor 6.21; see **Supplementary Table 2**). In an adjunct analysis, we can demonstrate the overlap between the two fields in terms of journals they publish in (**Figure 9B**)—of 130 journals used by either, 47 are used by both (36%) and 83 separately.

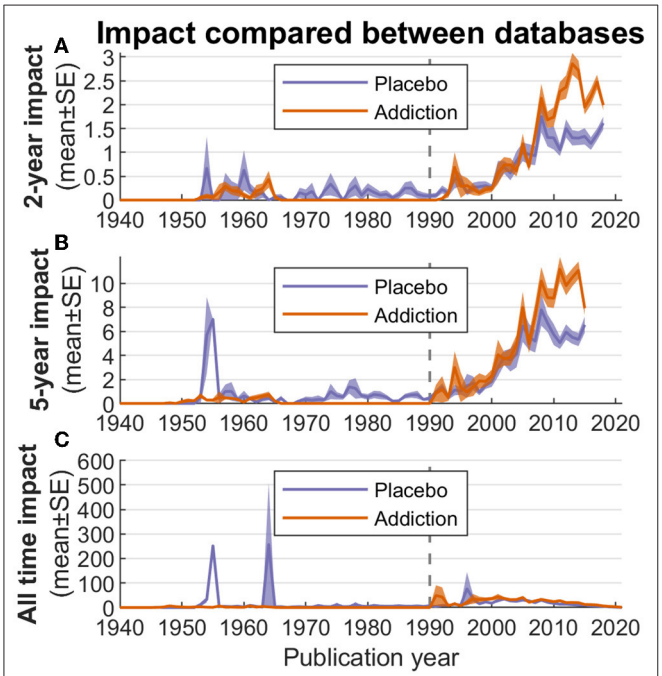

FIGURE 8 | Average impact of all articles per year in the JIPS database and comparator database. **(A)** 2-year impact. **(B)** 5-year impact. **(C)** All-time impact. The gray vertical line marks the introduction of the "placebo effect" MeSH term (1990), coinciding closely with introduction of the "behavior, addictive" MeSH term (1992).

Figure 10 shows the average number of authors in a publication, by field (placebo vs. addiction). The percentages are broadly comparable, with an initial difference between the two fields, such that in placebo research (as per JIPS database), more single-author publications are registered.

Figure 11A shows the latency with which new publications are cited. Peak latency occurs after one year, at which time around a quarter of articles were cited (∼1,300).

Figure 12 illustrates the average success of the JIPS articles over time. Like **Figure 11A**, **Figure 12A** shows that roughly a quarter of articles in the database (∼1,100) are not cited. However, this includes the fact that the database used for these analyses include a high number of very recent articles (e.g., 282 from 2019, 227 from 2020, 194 from 2021) which may not have been sufficiently disseminated, or whose citations have not yet been published. Most articles included in the database are only cited once per year after publication, with rapid decreases in frequency as the number of citations increase.

Figure 12C plots the age of an article against its average citations per year. This illustration is useful to detect "high performing" articles that rise above the average reception of articles of the same age. Note that the distribution is necessarily left-leaning, as the average citations per year decay at a set rate (x/year, where x crucially depends on the size of the field, which constitutes the upper bound of article reception).

Next, we compiled the 10 highest performing articles from **Figure 12** in **Table 1**. The list not only includes seminal papers of placebo research (e.g., Beecher 1955, Levine 1978), but also general method-related (e.g.,

TABLE 1 | Articles with highest age/citation ratio.

PMID	First author	Title	Year	Journal	Total *N* of citations	Mean *N* of citations per year
13271123	Beecher	The powerful placebo	1955	J Am Med Assoc	252	3.8
24141714	World Medical Association	World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects	1964	JAMA	5,071	87.4
80579	Levine	The mechanism of placebo analgesia	1978	Lancet	194	4.4
8721797	Jadad	Assessing the quality of reports of randomized clinical trials: is blinding necessary?	1996	Control Clin Trials	4,332	166.6
9250266	Bucher	The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials	1997	J Clin Epidemiol	553	22.1
9252330	Rainville	Pain affect encoded in human anterior cingulate but not somatosensory cortex	1997	Science	524	21
12649484	Fiorillo	Discrete coding of reward probability and uncertainty by dopamine neurons	2003	Science	647	34.1
14976306	Wager	Placebo-induced changes in FMRI in the anticipation and experience of pain	2004	Science	511	28.4
15995724	Vogt	Pain and emotion interactions in subregions of the cingulate gyrus	2005	Nat Rev Neurosci	635	37.4
16100511	Harris	A role for lateral hypothalamic orexin neurons in reward seeking	2005	Nature	481	28.3

PMID, Pubmed ID.

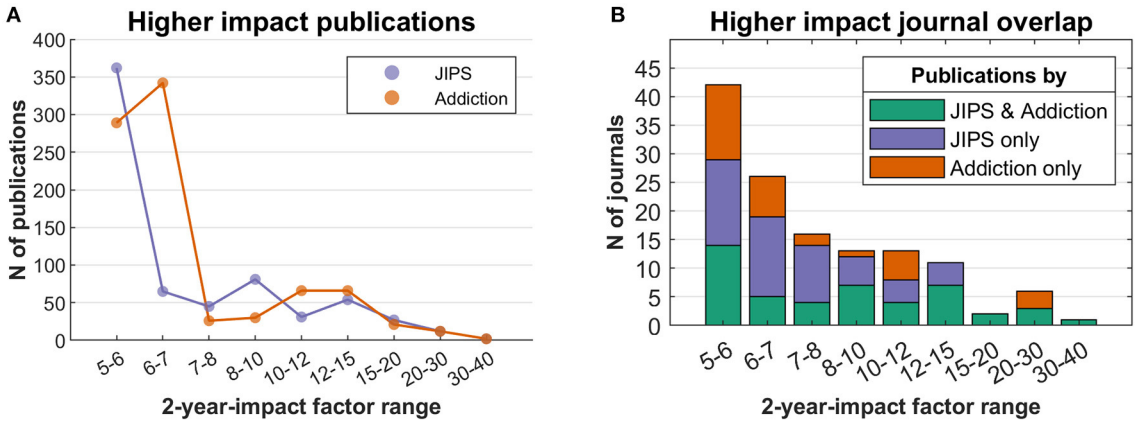

FIGURE 9 | Publications in high-impact journals in JIPS database and comparator database. **(A)** Number of publications in journals binned by 2-year impact factor. **(B)** Overlap of journals in which either database publishes its results. Stacked bars indicate shared journals (bottom), JIPS-only journals (middle) and comparator-only journals (top).

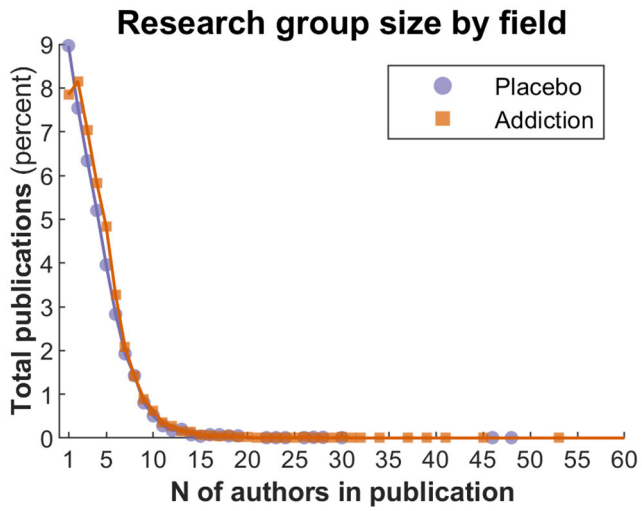

FIGURE 10 | Research group size by field.

Jadad 1996) or entity-related articles (e.g., Rainville 1997 for pain).

In **Figure 13**, the trajectory of a seminal paper (Beecher 1955) is traced since publication. While panel A shows an increase in citations since around 2000, normalizing the citation rates by field size (i.e., total number of entries in the JIPS database; panel B) shows that in the years following publication, the article was cited in roughly every other publication.

DISCUSSION

We applied bibliometric analyses to the JIPS database and its comparator (addiction) database with several related aims. These included i) ascertaining quality and basic content, ii) elaborating database content with keyword frequencies and author networks, iii) quantifying placebo research contributions and generativity, and iv) describing performance aspects of placebo literature compared to publications in the comparator field.

Concerning basic database content (volume), the decrease in recent years (2019 through 2021) could be owed to several factors, including lags in indexing (28) (possibly related to the COVID-19 pandemic) or the fact that as per cutoff date, the year 2021 was not yet over. Nevertheless, the placebo field seems to develop at an increased pace compared to the general scientific output as per PubMed. Notably, the sensitivity analyses comparing a general PubMed/MeSH-classified search points to some oversights made during curation; simultaneously however, it reinforces the approach taken for the JIPS by establishing it as a decidedly more comprehensive collection than using the classified search alone, which identifies only about one third of articles included in the JIPS.

Elaborating on the content, the three most frequent terms regarding symptoms are pain, depression and anxiety, and their respective synonyms (**Figure 3**). The most frequently studied populations are young and middle aged individuals, with decreasing number of articles at lower and higher age. These findings could indicate a potential (or even a responsibility) to explore placebo effects in other symptoms and age strata. Furthermore, bibliometric analyses provide the possibility to depict networks of researchers and their collaborations. Our analysis identified 26 researchers who published at least 25 or more articles. Even with this limited number, regional clusters can be fairly easily distinguished, as is expected from increased likelihood of collaborations due to funding mechanisms, conference attendance, if not simply geographical proximity (29).

One surprising finding is that the relative contributions of placebo publications in superordinate research fields such as pain, depression, and anxiety, are very low (below e.g., 0.0015%). Therefore, the large majority of research in placebo-affine fields

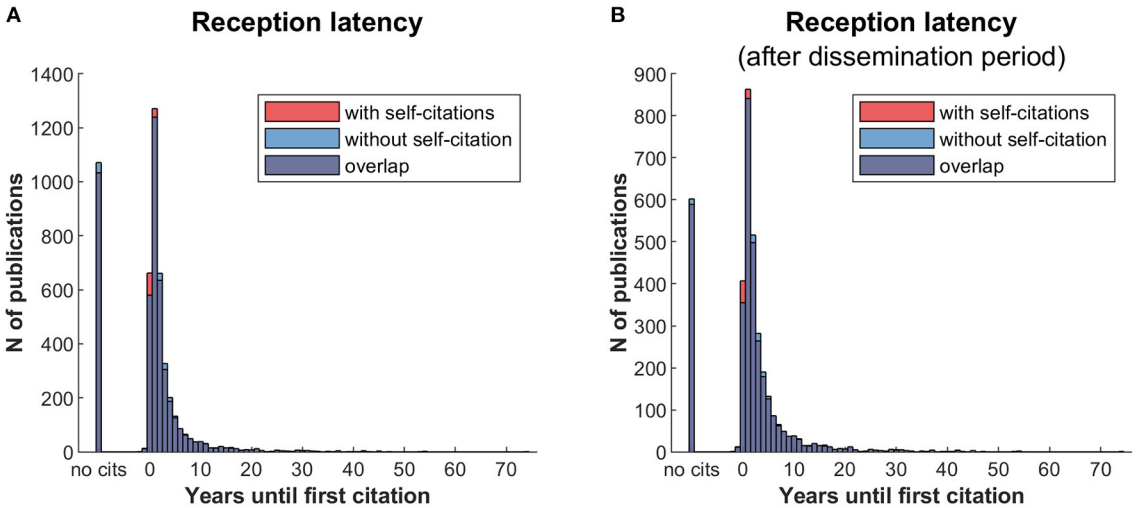

FIGURE 11 | Reception latency. **(A)** Years until first citation for all JIPS articles. **(B)** Years until first citation including dissemination latency of 5 years, i.e., including only articles aged 5 years and older. Results resemble those from A, but with (expectedly) fewer non-cited articles.

(e.g., pain) stems from other sources, while dedicated placebo research plays an overall minor research role in the respective field. However, there seems to be a small increase in the interest of placebo research in these fields since the 1990s. Using terms from other MeSH categories, e.g., treatment-related methods, could be used to assess the extent to which a field draws on placebo-related treatment mechanisms. The placebo effect plays a role in every diagnostic study and in treatment effects independent of the methods and symptoms investigated, but is obviously not always recognized. On the other hand, many placebo publications deal with basic science investigations in healthy volunteers or pilot studies with patients, and large clinical studies about harnessing the placebo effect in clinical practice are—still—lacking (30). Although it is not a direct measure, our finding strongly indicates that there is room for a broader application of insights derived from placebo research.

Even a cursory glance reveals a quickly growing number of placebo publications, particularly after 1990. One concern here is that as the body of literature grows, derivative works also increase in number, to the point where a field does not generate original data anymore. This concern seems unfounded for placebo research, as the proportion of data papers to non-data papers has reached a steady state in recent years. The field's productivity is therefore relatively stable, which is an important indicator for researchers who are considering to engage with it.

Albeit interesting by itself, the performance of a research field (quantity, quality and "vitality") cannot be judged fully without the comparison to a reference, i.e., a control group. Here, we chose publications about addiction as a reference since both research fields are interdisciplinary, deal with psychologically codetermined entities, and show similarities in their size and development over time. As we have shown (**Figures 8**, **9**), placebo articles were published in a comparable fashion to addiction articles in high-impact journals. Overall however, addiction publications showed higher performance regarding impact factors. Whether this switch indicates a general loss of impact of placebo research, a more restricted loss of interest on the side of the superordinate fields, a higher inclination of high-impact journals to publish placebo research, or other factors, will have to be established by futures analyses.

The analysis of the reception latency indicates rapid dissemination of the majority of articles in placebo research, and the exclusion of self-citations has only a negligible effect. Allowing for a longer dissemination period by excluding articles younger than 5 years of age (**Figure 11B**), the pattern remains almost identical with a slightly lower proportion of non-cited articles. **Table 1** shows that placebo research as compiled in the JIPS database is a highly interdisciplinary field whose contributors are rarely dedicated to this single topic. Instead, placebo research happens at the interface to treatment modalities, clinical entities or psychological mechanisms. Relatedly, it appears that Bradford's law (7, 8) positing a core set of journals in any given field, cannot be applied to placebo research at this stage, as there are no journals specifically dedicated to (or at least predominantly engaged with) this research topic. Nevertheless, certain journals have published a relatively large number of placebo publications (e.g., Pain, see **Supplementary Table 2**).

The performance of single articles can be quite informative about the progression of a field; here, we used one of the first articles of Henry Beecher in 1955 as an example (31). This example shows that the absolute number of citations can increase over time, but the relative number of citations compared to all publications in the field can decrease, i.e., the relevance of this article diminishes over time.

Limitations

Limitations of the scope of the present study apply to both the JIPS database itself as well as to the Pubmed data available for analysis. Every inclusion in the JIPS database is explicitly curated and sometimes depends on factors (including possible

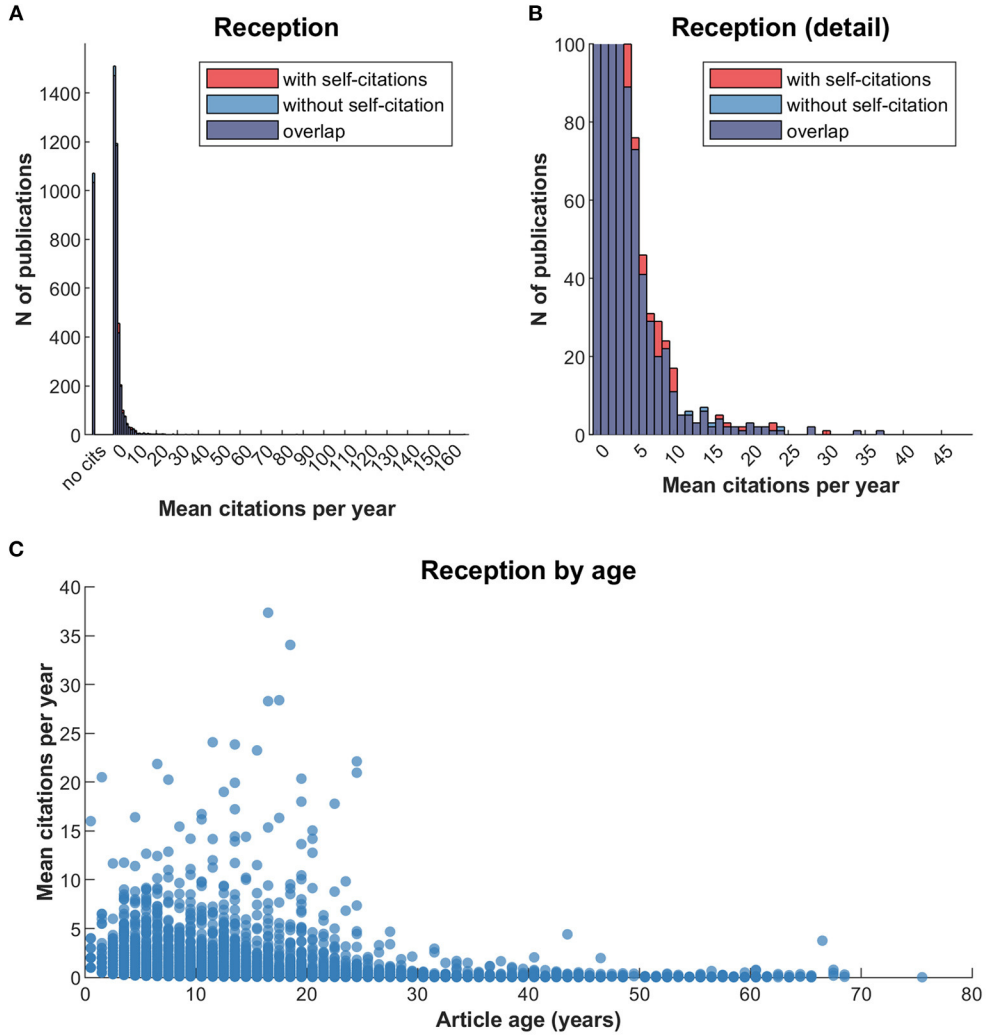

FIGURE 12 | Reception of JIPS articles over time. Note that this figure is limited in that article age and its dissemination are not unrelated, because very young articles may have had insufficient time for reception. **(A)** The number of publications binned by mean citations per year. **(B)** Same data as **(A)**, but with adjusted y axis to see details of the distribution more clearly. **(C)** Mean citations per year, by article age. For illustration purposes, axes were set to exclude two very high-performing articles (PMID 24141714 with age 57 and 87.4 mean citations; PMID 8721797 with age 24 and 173.3 mean citations).

selection biases) and criteria which exceed those of a strictly MeSH-guided algorithm, as demonstrated in the sensitivity analysis described above. Conversely, a MeSH-guided search strategy may partially fail when MeSH terms change over time, e.g., are added or removed, and may required both approaches, at least for the purpose of such bibliometric analyses as ours. Additionally, we may miss articles that are not listed in PubMed. We therefore ask our newsletter recipients and colleagues to send us newly published articles to include them in our database.

For this analysis, we have opted for a restriction to PubMed for the citation analyses for two reasons: 1) the JIPS database itself is mostly based on input queried from the PubMed database, and 2) PubMed uses a simple URL interface and provides Open Access and automatically processable citation data beyond the number alone (32, 33), e.g., to remove self-citations (**Figures 11**, **12**). Data processing and analyses are based on keywords curated in and provided by PubMed; however, these are not double-checked by placebo researchers, or by us. For example, we found some inconsistencies between keywords in the abstracts and MeSH terms that could affect searches and analyses of publications in the field. While both the lags in indexing of new articles, and shortcomings in accuracy of indexing, restrict interpretations concerning the *absolute* number of keywords presented here, our analyses were performed under the assumption that these issues are unsystematic across all fields of research. If true, they would not affect the *relative* numbers between different MeSH and publication types for further analyses. More dedicated analyses would be required for a comprehensive assessment of the issue of misclassification.

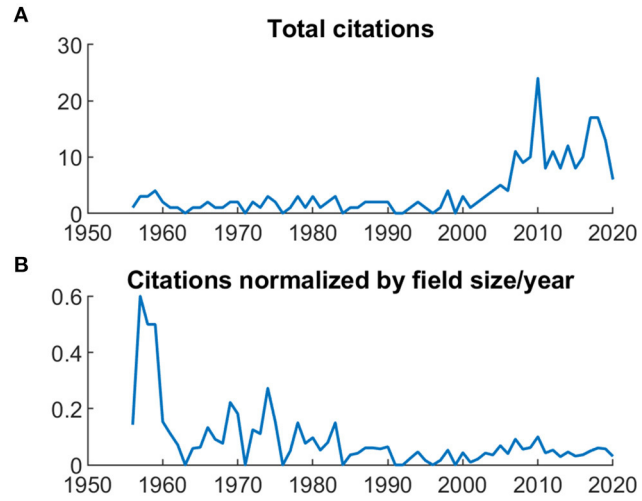

FIGURE 13 | Citation trajectories for an exemplary high-performing article (Beecher 1955). **(A)** Total citations. **(B)** Citations normalized by field size (i.e., number of articles published in the respective year).

Finally, beyond the reasons indicated above, the choice of addiction as a reference field was ultimately arbitrary and there may be more suitable fields, or fields that are of more interest to particular research groups. Further comparisons to evaluate the course of development should (and can easily) be drawn with other research fields. Nevertheless, the choice was meaningful as exemplified by the all but non-existent overlap between the two databases, while simultaneously exhibiting a substantial overlap (36% as per **Figure 9B**) in terms of the journals in which both fields published. Still, we caution that the methods of obtaining the JIPS and the comparator database were decidedly different, findings therefore have to be viewed with caution.

Outlook

Prospective developments include the formulation of algorithms for the automated detection of relevant articles, e.g. via machine learning (34, 35). The JIPS database itself is well-suited for this purpose, as it could be contrasted with the corpus of literature (i.e., all PubMed hits for "placebo", among other sources) from which it is drawn. Another benefit from this endeavor may relate to search engine optimization through recommendation of highly discriminant keywords, as opposed to author- or even expert-indexer-provided keywords.

In summary, the JIPS database is a comprehensive collection of publications in the field of placebo research. Our analyses indicate stable generative capabilities of the field, and an overall performance comparable to the reference field. The methods employed here are easily portable, for example, to identify trends in yet unaddressed subfields. Likewise, the JIPS database itself is available for bibliometric analyses, to address questions to the field or its shortcomings, and to identify blind spots as well as future directions. We invite interested colleagues to use this database for further analyses.

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

PE, KW, and EB did the literature search and assessed data for the JIPS database. PE, BH, and KW provided the study design for this analysis and wrote the first draft. BH and CB analyzed the data and created figures and tables. All authors contributed to the interpretation of results, reviewed and critically revised the manuscript, and approved the final version for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.853953/full#supplementary-material

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