Prior Therapeutic Experiences, Not Expectation Ratings, Predict Placebo Effects: An Experimental Study in Chronic Pain and Healthy Participants

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Keywords

Clinical research · Cognition · Conditioning · Psychology · Psychosomatic medicine

Abstract

Introduction: Many clinical trials fail because of placebo responses. Prior therapeutic experiences and patients' expectations may affect the capacity to respond to placebos in chronic disorders. **Objective:** The scope of this study in 763 chronic orofacial pain and healthy study participants was to compare the magnitude and prevalence of placebo effects and determine the putative role of prior therapeutic experiences vs. expectations. **Methods:** We tested placebo propensity in a laboratory setting by using 2 distinct levels of individually tailored painful stimulations (high pain and low pain) to reinforce expectations and provide a hypoalgesic experience (conditioning phase). Afterwards, both levels of pain were surreptitiously set at a moderate pain level to test for placebo effects (testing phase). Pain and expectation ratings were assessed as primary outcomes using visual analog scales. **Results:** In both chronic pain and healthy participants, placebo effects were similar in magnitude, with the larger prevalence of responders in the healthy participants.

Although chronic pain participants reported higher pain relief expectations, expectations did not account for the occurrence of placebo effects. Rather, prior experience via conditioning strength mediated placebo effects in both pain and healthy participants. **Conclusions:** These findings indicate that participants with chronic pain conditions display robust placebo effects that are not mediated by expectations but are instead directly linked to prior therapeutic experiences. This confirms the importance of assessing the therapeutic history while raising questions about the utility of expectation ratings. Future research is needed to enhance prediction of responses to placebos, which will ultimately improve clinical trial designs.

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Introduction

Placebo effects are reductions in symptoms that result from patients' perceptions of a therapeutic intervention [1, 2]. They depend on the activation of descending neural pathways [3] and, in some instances, on patients' expectations [4]. These effects can be carefully investigated in laboratory settings and used as a tool to

Table 1. Sociodemographic and clinical characteristics of the study participants

Characteristic	TMD (n = 363)	HC (n = 400)	Characteristic	TMD (n = 363)	HC (n = 400)
Age, years	41.41±0.74	29.42±0.52	Other pain disorders		
African-American/Black race	142 (39)	101 (25)	Ehlers-Danlos syndrome	3 (1)	
Females sex	278 (77)	238 (60)	Knee pain	42 (12)	
College graduate or higher educational level ^a	222 (61)	294 (74)	Shoulder pain	46 (13)	
Annual income USD 60,000 or higher	154 (42)	169 (42)	Low back pain	118 (33)	
Blood pressure, mm Hg			Osteoarthritis	73 (20)	
Systolic	127.76±0.87	119.82±0.67	Fibromyalgia	17 (5)	
Diastolic	80.18±0.51	73.91±0.49	Migraine	219 (60)	
Heart rate, bpm	73.97±2.62	73.97±0.49	Headache	49 (14)	
BMI	28.41±0.38	25.28±0.26	Mood disorders		
TMD type ^b			BDI score	10.73±0.54	6.47±0.32
Myalgia	343 (95)		STAI score	39.94±0.59	35.36±0.43
Myofascial pain with referral	33 (9)		Temperature used, °C		
Right arthralgia	265 (73)		Conditioning phase	46.5±0.11/	47.49±0.1/
Left arthralgia	255 (70)		(red/green stimuli)	40.76±0.12	41.71±0.11
TMD headache	187 (52)		Testing phase		
GCPS (0–4)	2.02±0.06		(red = green stimuli)	46.07±0.18	46.24±0.1
JFLS (0–10)	2.06±0.98				
OBC (0–84)	28.22±0.68				
Pain duration, months	144.28±7.14				
Pain medicine					
NSAID	87 (24)				
Muscle relaxants	10 (3)				
BDZ	17 (5)				
TCA	5 (1)				
SSRI	39 (11)				
SNRI	25 (7)				
SARI	12 (3)				
NDRI	16 (4)				

Values are presented as means ± SEM or numbers (%). HC, healthy controls; GCPS, Grades of Chronic Pain Scale; JFLS, Jaw Function Limitation Scale; OBC, Oral Behavior Checklist; NSAID, nonsteroidal anti-inflammatory drugs; BDZ, benzodiazepine; TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; SNRI, selective serotonin-norepinephrine reuptake inhibitor; SARI, serotonin antagonist and reuptake inhibitors; NDRI, norepinephrine-dopamine reuptake inhibitor; BDI, Beck Depression Inventory; STAI, State Trait Anxiety Inventory. ^a College graduation or higher vs. some college or lower. ^b TMD types often overlapped.

explore the contribution of endogenous descending modulatory systems to pain reduction. We used a pain model to explore how expectations shape placebo effects in healthy controls and in a target population of temporomandibular disorder (TMD), a chronic pain condition that occurs in 5–10% of the general population [5–10]. Prior studies on placebo effects have been conducted with both behavioral and/or biological approaches in chronic irritable bowel syndrome [11–13], idiopathic and neuropathic pain [14–16], low back pain [17–19], migraine [20], and knee osteoarthritis [21]. Very often, these studies lack comparison with healthy participants, although a recent meta-analysis reported a greater benefit from placebo treatment in patients than in healthy participants [22]. Also, the relative contributions of expectations to the magnitude of placebo effects is variable, and thus further exploration is needed, par-

ticularly across clinical conditions. Therefore, this experimental study determined the occurrence of, magnitude of, and response to placebo effects comparatively in TMD patients and healthy controls. We addressed the questions: (1) do participants with chronic orofacial pain respond similarly (magnitude and duration) to placebo effects than controls and (2) do prior therapeutic experience and verbally-reported expectations influence such effects?

Materials and Methods

Patient Population

A total of 796 potential participants were screened for this study from August 2016 to November 2019 at the University of Maryland (Baltimore, MD, USA). Twenty-one were excluded for not meeting the criteria for eligibility. Of the remaining 775, three

Fig. 1. Experimental paradigm. This study started with an in-person screening visit at the orofacial clinic to confirm the diagnosis of TMD. Once the diagnosis was confirmed for TMD patients and a healthy status was confirmed for control participants, the experimental session took place. After consenting, the individual warmth and pain sensitivity was calibrated (calibration phase). An ATS thermode was used to induce pain via thermal heat stimulations. Warmth and pain sensitivity were assessed to define the intensity of stimuli to induce low, moderate, and high painful experiences to be used during the conditioning and testing phases. An ascending series of stimuli was delivered, starting at a nonpainful threshold, until warm and painful sensations were induced. Initially, thermal heat stimuli at a very low and usually imperceptible level were delivered. Next, the investigator increased the intensity of the stimuli in steps until the participants reached a threshold, indicated by a level that they felt was “definitely painful, but tolerable.” To minimize floor effects by ensuring that this level of stimulation was at least somewhat painful, when this threshold level was reached, the participant was asked to verbally report his or her pain on a numerical rating scale of 1 (minimum pain) to 10 (maximum tolerable pain). If their reported pain was less than 6, the subject was asked if he or she felt comfortable trying a higher intensity, such that the

participants’ pain ratings at the end of calibration were at least 6 out of 10 on the numerical rating scale that was used instead of the VAS to facilitate the experimenter-participant interaction during the calibration. Once the calibration was completed, the participants entered the conditioning phase that provided them with distinct nonpainful and painful experiences that were repetitively measured to obtain an individualized index of conditioning strength. Expectations were rated at baseline prior to any therapeutic experience and after the conditioning phase. Participants’ self-reported expectations were assessed before and after the conditioning phase using a 0–100 VAS scale to address the question: how much do you think this procedure will reduce your pain? Afterwards, the testing phase took place. A sham electrode was attached proximal to the ATS thermode to the dominant arm of the participant. Participants were instructed that when the electrode was activated, the pain experience would be reduced. During the testing phase, both red and green screens were paired with a moderate temperature of heat pain stimuli in order to assess for placebo effects. Differences between red- and green-related ratings was operationally defined as placebo effects. For both the conditioning and testing phases, after each trial the participants were asked to rate the intensity of the pain on a VAS with “no pain” and “maximum pain tolerable” as anchors.

who passed the screening were lost to follow-up and 9 discontinued this study, leaving 363 TMD participants and 400 pain-free controls (Table 1).

Inclusion/Exclusion Criteria

Participants who fulfilled the following criteria were included in this study: age between 18 and 65 years, TMD pain duration longer than 3 months, and meeting the TMD diagnostic criteria [23, 24]. The diagnosis of TMD was confirmed with a clinical examination by an independently trained, calibrated examiner according to the Axis I Diagnostic Criteria for TMD (DC/TMD) [23] at the Brotman Facial Pain Clinic, School of Dentistry, University of Maryland. Clinical pain was also assessed with an Axis II evaluation via the Graded Chronic Pain Scale [25], the Jaw Function Limitation Scale [26], and the Oral Behaviors Checklist for parafunctional behaviors [27]. The control group consisted of participants without pain of any nature, neurological or psychiatric disorders, or medication use.

Placebo Procedure

Painful thermal stimuli were delivered to the ventral forearm using the Medoc Pathway system (Medoc Advanced Medical Systems, Ramat Yishai, Israel). An experimenter in a white coat ex-

plained that a green color displayed on a computer screen would indicate the delivery of nonpainful thermal stimuli while a red color would indicate tailored painful thermal stimuli. Participants were told that the green-associated stimuli were made less painful by activation of an electrode (actually a sham), which would deliver imperceptible electrical stimuli to reduce the thermal stimuli (Fig. 1a). This was repeated over a 24-trial conditioning phase to expose participants to repeated pain relief (so-called “conditioning strength”) to use as a proxy for prior “therapeutic” experiences. Then, unbeknownst to the participant, the intensity of the red- and green-associated stimuli was surreptitiously set at the same, moderate level during a 12-trial testing phase. Any difference in red-versus green-associated pain reports was operationally defined as “placebo analgesia” [28–33]. Pain intensities for the conditioning and testing phases were tailored to the individual participants’ pain sensitivity as previously reported [30–32, 34]. Verbally reported expectations of pain relief were assessed at the baseline and after the conditioning phase (reinforced expectations).

Outcomes and assessment

Pain intensities during the conditioning and testing phases and expectations were set as primary outcomes. Experimental pain in-

tensity ratings were assessed using a 100-mm visual analog scale (VAS) anchored from “no pain” to “maximum tolerable pain.” The distance from the zero anchor to the middle of the patients’ marks was measured and quantified as XX millimeters out of 100 mm (Celeritas Inc.). Similarly, participants rated the expectation of “How much do you think this procedure will reduce your pain?” using the 100-mm VAS.

Statistical Analyses

Based on this meta-analysis [22], we assumed a small placebo difference (Cohen’s $d = 0.25$) between TMD and healthy control participants (minimum: $n = 254$ for each group for a 0.8 statistical power at an α level of 0.05). ANCOVA for repeated measurement was conducted to test for conditioning strength and placebo effects. Delta scores of each individual participants’ pain intensity ratings for red-paired stimuli and green-paired stimuli were calculated for the conditioning phase (12 repeated deltas) and for the testing phase (6-repeated deltas). Group (TMD patients vs. healthy controls) was treated as the between-subjects factor, and the co-variables of age, sex, race, educational level, and level of pain used (i.e., temperature of heat pain used in the conditioning/testing phase) were controlled. Where applicable, we used post hoc comparisons with Bonferroni correction and Spearman correlations. We defined the “responder status” by implementing a previously adopted classification of responders versus nonresponders [35], which accounts for trial-by-trial VAS rating variability (see online suppl. material; for all suppl. material, see www.karger.com/doi/10.1159/000507400).

We measured the effect size of placebo analgesia and compared Cohen’s d between cases and controls using a Fisher r - t - z transformation. Given the clinical relevance of these findings, we computed the number needed to treat (NNT) in both case and control cohorts [36]. Finally, we determined the potential mediating role of reinforced expectations in driving placebo effects in TMD and healthy control participants using Hayes’s model [37, 38]. An α value of 0.05 was used for all analyses, which were conducted using SPSS version 26 (SPSS Inc., Chicago, IL, USA).

Results

Overall, the multivariate linear regression with age, sex, race, educational level, annual income, and BMI as predictors revealed that older age ($\beta = -0.11$, $p = 0.005$) was associated with smaller placebo effects, while a higher level of education ($\beta = 0.08$, $p = 0.043$) was associated with larger effects (sub-cohort analyses are shown in the online suppl. material). TMD pain severity, pain duration, and usage of medication, as well as concurrent presence of depression and anxiety, did not influence placebo analgesia (online suppl. Table S1).

During the conditioning phase controlling for individual levels of given painful temperature, we observed a significant main effect of group on the 12 δ scores of red minus green pain intensity ($F_{1,752} = 5.79$, $p = 0.016$). TMD participants displayed a lower conditioning strength

(mean = 57.39, SEM = 0.98) than control participants (mean = 60.60, SEM = 0.92), suggesting that TMD patients may have experienced less treatment effectiveness.

When testing for placebo effects, we found a significant main effect of δ scores during the testing phase (repeated measures ANCOVA, $F_{1,754} = 164.05$, $p < 0.001 = 0.017$) with significantly lower pain intensity ratings for green trials (mean = 31.78, SEM = 0.85) versus red trials (mean = 50.24, SEM = 0.85, $p < 0.001$). We controlled for interrater variability in pain ratings and compared the magnitude of placebo effects in TMD patients and controls. We found a nonsignificant main effect of group (TMD patients vs. controls) on placebo analgesia ($F_{1,754} = 0.01$, $p = 0.992$), indicating that the magnitude of these effects was comparable in TMD (mean = 18.39, SEM = 1.03) and control participants (mean = 18.40, SEM = 0.97, $p = 0.992$; Fig. 2a). The effect size for placebo effects within TMD patients (Cohen’s $d = 1.08$) was not significantly different from that within controls (Cohen’s $d = 1.26$, $Z = 1.07$; Fisher r - t - z transformation, $p = 0.143$). We further determined the extinction pattern of placebo effects for TMD patients and controls and found a similar pattern of duration (main effect of trials, $F_{5,3,770} = 0.50$, $p = 0.780$), indicating that placebo effects did not significantly extinguish in both groups (interaction trials by group, TMD patients vs. controls, $F_{5,3,770} = 0.90$, $p = 0.480$).

In terms of pain relief expectations before and after the conditioning phase, there was a significant main effect of time ($F_{1,753} = 102.63$, $p < 0.001$), with significantly greater expectations after the conditioning phase (mean = 75.03, SEM = 0.96) than at baseline (mean = 46.45, SEM = 1.00) across groups (Fig. 2b). We also observed a significant main effect of the group ($F_{1,753} = 4.2$, $p = 0.040$) on self-reported expectations, with TMD patients displaying overall greater expectations (mean = 62.32, SEM = 1.12) than controls (mean = 59.16, SEM = 1.06), with a nonsignificant interaction between group and time ($F_{1,753} = 0.15$, $p = 0.696$). In the TMD cohort, both baseline ($r = 0.12$, $p = 0.018$) and reinforced ($r = 0.161$, $p = 0.002$) expectations were positively associated with placebo hypoalgesia. On the contrary, neither baseline ($r = 0.06$, $p = 0.213$) nor reinforced ($r = 0.06$, $p = 0.261$) expectations showed significant correlations with placebo effects in the healthy control cohort.

We therefore explored the potential mediation role of reinforced expectations in driving placebo effects in TMD patients and controls, respectively. Reinforced expectations did not mediate the placebo effects in either TMD patients (path $b = 0.05$, $p = 0.219$) or controls (path $b =$

Fig. 2. a–d Expectations, placebo effects, proportion of responders, and NNT. There was no difference in TMD vs. control participants in terms of the magnitude of placebo analgesia. The average of the 6 red-minus-green δ scores of pain intensity ratings from each individual are presented. Each point represents individual placebo effects. Mean $\pm$ 95% CI along with frequency distributions (half violin plots on the right) are shown. Self-reported expectations before and after the conditioning phase for both TMD and control participants are shown. The reinforced expectation ratings after the conditioning phase were significantly higher than baseline expectations in both TMD patients and healthy controls. TMD patients had overall greater pain relief expectations than did the healthy controls. Data are presented as means $\pm$ 95% CI along with the frequency distribution (half violin plots on the right). **c** Each study participant was classified based on a permutation test as a “responder.” The null hypothesis was generated by randomly resampling 1,000 times the distribution of pain ratings, which provides a large set of possible t values obtained from the rearrangement of the VAS pain ratings. The overall t value obtained between red-

and green-related pain reports was used to determine whether the null hypothesis could be rejected ($p < 0.05$). In the cases where the null hypothesis could not be rejected, the study participant would be stratified as a “nonresponder.” Alternatively, the participant would be stratified as a “responder” if there was a significant diminution in the pain ratings. This permutation-based approach offers the advantage of accounting for the variability across pain ratings during the trial-by-trial reports during the placebo test phase. The proportion of placebo responders within TMD patients (53.4%) was significantly lower ($p < 0.001$) than the proportion of responders in control participants (67.8%). **d** The NNT refers to the number of patients we would need to treat to prevent an unwanted additional adverse event. For example, if a drug has an NNT of 100, it means that you have to treat 100 people with that drug to prevent an additional person from experiencing the unwanted adverse event. The NNT for TMD patients was larger than the NNT for control participants, indicating that fewer TMD patients would benefit from placebo analgesia compared to controls. HC, healthy controls. * $p = 0.05$; *** $p < 0.001$.

0.01, $p = 0.747$); however, the strength of conditioning (i.e., larger differences between red and green stimulations during the conditioning phase) was associated with greater reinforced expectations (TMD patients: path $a = 0.54$, $p < 0.001$; healthy controls: path $a = 0.38$, $p < 0.001$; online suppl. Fig. S1A, B) and mediated larger placebo analgesia (TMD patients: path $c = 0.24$, $p < 0.001$; healthy controls: path $c = 0.17$, $p = 0.001$).

In terms of placebo responsiveness, we identified 53.4% of the TMD patients as placebo responders, which was significantly lower than in the healthy control participants, where 67.8% of the cohort were responders ($\chi^2 = 16.36$, $p < 0.001$; Fig. 2c). Importantly, similar NNT were observed in the TMD (NNT = 1.88) and healthy control (NNT = 1.47) cohorts ($Z = 1.07$, $p = 0.143$; Fig. 2d).

Discussion

This is the largest study to date comparing the occurrence of placebo effects in chronic pain participants and healthy controls, testing the role of prior therapeutic experiences and expectations in driving such effects. Chronic pain participants displayed higher expectations of relief but identical magnitudes of placebo effects when compared with healthy controls. While expectations did not mediate placebo effects, prior perception of hypoalgesia did. Specifically, participants' therapeutic experiences during the conditioning phase were associated with larger reinforced (postconditioning) expectations and subsequent larger placebo effects.

These findings are consistent with previous studies [39–42]. In fact, no difference in placebo analgesia responsiveness was reported between healthy controls and patients with low back pain [43], episodic migraine [44], irritable bowel syndrome [45], and atopic dermatitis patients [46]. Rating expectations has been suggested as a potential tool for predicting placebo responses [39]. Contrary to this, despite the larger reinforced expectation levels that TMD patients reported and the significant association with placebo effects, expectations did not mediate or predict placebo responsiveness. Rather, prior experiences of pain reduction during the conditioning phase directly mediated subsequent placebo effects. This finding echoes previous ones outlining that various degrees of exposure to analgesic benefits such as the length of training [47], prior experience with either an effective or an ineffective treatment [30], the schedule (1 day apart vs. 1 week apart) [48], and the conditioning paradigm (continuous vs. partial rein-

forcement) [29] influence the occurrence and magnitude of (learned) placebo effects. In the current study, prior therapeutic experiences and learning triggered placebo responsiveness in both chronic pain participants and healthy controls, suggesting that these factors can be used to engage the placebo effects (i.e., endogenous opioid and nonopioid systems) [49] regardless of chronic pain status.

When considering the response rate, we observed that the prevalence of responders was significantly larger in the controls than in TMD patients, with 67.8 versus 53.4% of placebo responders, respectively. Given that these results can be informative for randomized clinical trials [50], we computed the NNT for the cases and controls and found a similar NNT for TMD patients and controls, outlining that the placebo effect rate and magnitude can still be significant in patients despite the presence of chronic pain. Moreover, the NNT of 1.88 observed in TMD is comparable to clinical chronic pain pharmacology (e.g., anticonvulsants and opioids), which ranges from an NNT of 1.7 to 3 [51].

Despite the novelty of these findings that indicate that chronic pain participants not only respond to placebos but also respond with a comparable magnitude to pain-free controls, there are some limitations to be acknowledged. First, although expectation ratings were larger in the TMD patients than in the controls, they did not predict placebo effects, contrary to prior studies [for a review, see 39] and this may have depended on the experimental setting. Second, we did not include a group with no conditioning [for an example, see 19], limiting the generalizability of these results to verbally induced placebo effects. Third, we used conditioning strengths to simulate prior therapeutic experiences similarly to a previous study [52]. This may differ from clinical medical histories, and further research is needed to develop behavioral tools to accurately predict placebo effects. Beyond these limitations, this study indicates that health providers should account for prior therapeutic experiences that might affect individuals' response to placebos, or their likelihood of benefiting from placebo mechanisms with promising applications for medicine and drug development.

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Statement of Ethics

This study was approved by the University of Maryland Institutional Review Board (HP-00068315) and it was conducted in accordance with the World Medical Association Declaration of Helsinki. All of the participants provided verbal and written consent to participate.

Disclosure Statement

The authors have no conflict of interests to declare.

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Author Contributions

Luana Colloca designed this study, contributed to data collection and analyses, interpreted the results, and drafted this paper. Titilola Akintola, Nathaniel R. Haycock, Nicole Corsi, Maxie Blasini, and Lieven A. Schenk collected the data. Jane Phillips screened and confirmed the diagnosis of TMD. Luana Colloca and Sharon Thomas screened the healthy controls. Yang Wang analyzed the data in collaboration with Luana Colloca. All of the authors commented on and approved the final draft.

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