When expectancies are violated: An fMRI study

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Conflict of Interest

Luana Colloca received lecture honorarium within the US. Oliver Robinson serves a consultant for IESO Digital Health / Peak.com and received honoraria for Lectures within the UK. All other authors declared no competing interests for this work.

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Abstract

Positive and negative expectancies drive behavioral and neurobiological placebo and nocebo effects which in turn can have profound effects on patient improvement or worsening. However, expectations of events and outcomes are often not met in daily life and clinical practice. It is currently unknown how this affects placebo and nocebo effects. We have demonstrated that the violation of expectancies, such as when a discrepancy between what is expected and what is actually presented, reduces both placebo and nocebo effects while causing an extinction of placebo effects. The reduction of placebo and nocebo effects was paralleled by an activation of the left inferior parietal cortex, a brain region that redirects attention when discrepancies between sensory and cognitive events occur. Our findings highlight the importance of expectancy violation in shaping placebo and nocebo effects and open up new avenues for managing positive and negative expectations in clinical trials and practices.

Introduction

In daily life, expectancies are often violated and dynamically updated. Similarly, in clinical practice, patients may have pre-existing expectancies based on their history of therapeutic experiences, responses to treatments, and clinical encounters that could influence subsequent outcomes. Positive and negative expectancies mediate placebo and nocebo effects, resulting in profound effects on patient outcomes [1]. However, it is currently unknown how the violation of expectancies affects placebo and nocebo effects and the underlying neural basis for such a modulation. This study addresses the question: How does a mismatch between what it is expected and what is in reality received change subsequent placebo and nocebo effects and the underpinning neural correlate(s) that contribute to driving such a modulation?

Some studies have explored the mismatch between expectancy and sensory events suggesting that the parietal regions might be involved in both pain ratings [2] and attentional processes related to mismatches per se [3]. Herein, we focused on the violation of expectancies as a foundation for altering conditioned placebo and nocebo effects that adds to the current state-of-the art for pain rating and genesis of placebo and nocebo responses. Determining to what extent, placebo and nocebo effects are affected by expectancy violation is important for advancing clinical pharmacology and translational science that can benefit from combining basic and clinical research and considering along with other possible solutions [4], future strategies for abolishing placebo and nocebo effects in clinical trials and practices.

To explore this phenomenon, we designed a within-subjects repeated-measures longitudinal study design in which expectancies of high, moderate, and low painful experiences were subsequently violated in measuring behavioral and neural placebo and nocebo effects. We hypothesized that the mismatch between what was expected and what was presented would attenuate behavioral placebo and nocebo effects while activating brain regions such as the inferior parietal cortex, which is involved with attention reallocation during discrepancies between sensory and cognitive inputs [3]. Despite a recent meta-analysis suggested that placebo effects related to pain- and pain-related processes are small [5], we also examined neural post-stimulation placebo and nocebo changes by investigating the effects at the level of regions such as the dorsolateral prefontal cortex, rostral anterior cingulate cortex, middle cingulate cortex, posterior insula [6], and hippocampus [7], which have been argued to be modulated by placebo and nocebo effects. To test this hypothesis, we implemented a two-day fMRI study and focused on implicit expectancies and how violation of such expectancies, interfere with subsequent placebo and nocebo effects. The main result was a significant difference in the effect size of placebo and nocebo effects when color and face cues were mismatched.

Results

On day 1, participants learned that the red-fearful face associated cues led to high painful stimuli, yellow-neutral face led to medium pain (control), and the green-happy face led to low painful stimuli (Fig. 1A). On day 2, participants underwent the fMRI phase whereby 50% of the color-face cues were mismatched according to violate expectancies. To test for placebo and nocebo effects. Unbeknownst to participants, all the cue combinations were associated with the delivery of medium pain, which significantly affected pain ratings (Fig. 1B). The primary outcomes were trial-by-trial VAS pain ratings, which were used as the dependent variable in an omnibus linear mixed model (LMM) with anticipatory cues (red, yellow, green), matching condition (matched, mismatched) and a continuous time-points (trials 1-10) set as within-subjects factors. We observed a main effect of the anticipatory cue ($F_{2,1464}$=50.2, p<0.001; mean ± SEM red cue: 49.76 ± 0.85; yellow cue: 41.44 ± 0.70; green cue: 34.89 ± 0.81), indicating that the cues shaped placebo and nocebo effects. As expected, the main effect of matching was not significant ($F_{1,1464}$=0.401, p=0.526; mean ± SEM matched: 41.57 ± 0.70; mismatched 42.50 ± 0.66) but there was a significant cue x matching interaction ($F_{2,1464}$=4.7, p=0.008), indicating larger effects for the matched as compared to the mismatched conditions. We also observed a main effect of trial ($F_{1,1464}$=8.1, p=0.004), indicating a slight decrease of pain over the course of the test phase across all conditions. However, the cue x trials ($F_{2,1464}$=2.9, p=0.055, bordering statistical significance) and cue x matching x trials ($F_{2,1464}$=0.3, p=0.73) interactions failed to reach statistical significance.

Subsequent separate analyses were conducted for matched and mismatched placebo and nocebo effects. Robust nocebo ($F_{1,472}$=29.9, p<0.001, Cohen's d: 0.859) and placebo ($F_{1,472}$=27.0, p<0.001, Cohen's d: 0.762) effects were observed when anticipatory cues were matched. In the mismatched condition, significant nocebo effects ($F_{1, 472}$=4.2; p=0.041, Cohen's d: 0.386) and placebo effects ($F_{1, 472}$=9.2, p=0.003, Cohen's d: 0.251) were still observed. However, violations of expectancy reduced both nocebo ($F_{1,968}$=25.9, p=0.001; 67.6% VAS reduction) as well as placebo ($F_{1,968}$=32.3, p<0.001; 57.05% VAS reduction) effects significantly as compared to the condition in which anticipatory cues were matched with pain-related cues (Fig. 2a,b).

We also explored linear extinction of nocebo and placebo effects. Nocebo ($F_{1,472}$=0.2, p=0.65) and placebo ($F_{1,472}$=0.8, p=0.36) effects did not extinguish in the matched condition. However, nocebo effects ($F_{1,472}$=0.0, p=0.85) persisted over time while placebo ($F_{1,472}$=3.8, p=0.05) extinguished in the mismatched condition.

Matched placebo (r= -0.03, p=0.86, two-tailed), mismatched placebo (r= -0.04, p=0.84), matched nocebo (r= 0.06, p=0.76), and mismatched nocebo (r= -0.08, p=0.70) showed no association with the respective

differences in pain ratings during day 1. Differences in pain ratings on day 1 also did not predict the corresponding differences between matched and mismatched in the placebo (r= -0.1, p=0.65) and in the nocebo (r = -0.12, p=0.55) condition. Matched placebo (r= 0.10, p=0.64), mismatched placebo (r= 0.03, p=0.90), matched nocebo (r= -0.27, p=0.22), and mismatched nocebo (r= -0.22, p=0.29) showed no association with the individual pain threshold of participants.

We investigated how the behavioral mismatch was associated with changes in oxygenation level dependent (BOLD) signal using a whole brain correction approach. The left inferior parietal cortex showed a stronger activation in the mismatch compared to the matched conditions (P_{FWE}=0.03, whole brain correction, k_E = 399, T = 4.59, peak xyz = -32 -52 34, Fig. 2c). The significant cluster included the supramarginal gyrus and the angular gyrus. No other whole brain corrected BOLD changes were detected. We also performed ROI analysis for changes associated with placebo and nocebo effects in the congruent condition only. No ROIs achieved statistical significance (Table 2).

Discussion

These findings demonstrate that a mismatch between what is expected and what is actually seen generates a significant reduction of both behavioral placebo and nocebo effects and a significantly stronger BOLD signal activation in the inferior parietal cortex.

To our knowledge, this is the first behavioral and neural demonstration that an expectancy violation alters placebo and nocebo effects. Specifically, expectancy violation was associated with a reduction of the effect size for both placebo and nocebo effects and with an extinction of placebo effects.

Learning mechanisms are known to induce placebo effects [1]. Classical conditioning and associative learning paradigms shape, construct, and update implicit expectancies, while verbal suggestions and instructions generate explicit expectations [8]. In this study, we focused on implicit expectancies and how violation of such expectancies, can interfere with subsequent placebo and nocebo effects. At the behavioral level, we found that the mismatch between the anticipatory (e.g. color) and painful-associated (e.g. face) cues substantially reduced both placebo and nocebo effects with an extinction of placebo effects. On the contrary, nocebo effects showed to be less prone to extinguish despite the violation of expectancies, potentially due to the higher salience of threat cues than safety cues, which confirms previous studies on nocebo [9,10].

At the neural level, the mismatched conditions were associated with a stronger activation of the left inferior parietal cortex as compared to the matched conditions. Although several studies have associated

the left inferior parietal cortex with successful memory retrieval [11], more recent research suggests that the its activation actually corresponds to a violation of expectancies when a new picture is presented [12]. Other studies have associated the inferior parietal cortex with violations of expectancies [2,13,14] or with the sensory discrimination in pain [3,15]. Our data supports the fact that the inferior parietal cortex exhibits a similar function within a placebo and nocebo context. Our conservative whole-brain approach allowed us to show that the inferior parietal cortex is important for mismatch processing and its impact on placebo and nocebo effects.

Recently, predictive coding and computational modeling suggest that pain perception can be conceptualized as an inferential process in which prior experiences or information (e.g. what was learned on day 1 of the conditioning) are used to shape expectancies by forming a "template" predicative of future painful events that, in turn, modulate sensory inputs [16–19]. These behavioral and neural results indicate that participants have likely interpreted the sensory information (e.g. painful stimulations) in accordance with their own expectancies and competing information that violates such expectancies. Thus, implicit expectancies can bias and even abolish placebo analgesic effects through actions in brain regions that process discrepancy between what is expected and what is occurring. Our findings expand upon theories of pain perception and experiences [2,16,18,20] shedding new light on the mechanisms of the placebo effect, expectancies, and pain perception. Future research in this direction can help advance strategies to abolish placebo responsiveness (e.g. clinical trials) and minimize nocebo effects in daily clinical practice.

A limitation in this experiment is that we did not observe any significant changes for placebo or nocebo effects based upon the preselected ROIs from a previous meta-analysis [6]. This finding is not very surprising as a recent larger meta-analysis demonstrated that placebo effects on pain and pain-related processes were significant in only 3 out of 20 studies with very small effect sizes [5]. That said, several reasons could also explain the negative post-stimulation results, including the fact that the sample size of this study was powered for the behavioral data but not necessarily for the neural changes [21]; and the duration of the thermal stimulation [6,22] or even the complexity of the study design itself could have also contributed to these results.

In summary, the findings of this study provide a step towards a mechanistic explanation for potential changes in therapeutic outcomes related to expectancies' violation. The results outline the importance of seeking an alignment between patients' expectancies and therapeutic outcomes in real world-settings. Understanding the dynamic nature of individual expectancies and how these can influence the effectiveness of clinical interventions and therapies, is of the utmost importance for all clinicians and

healthcare providers under any specialty, as expectancies hold the potential to either improve or impair relevant clinical outcomes. Healthcare providers should carefully explore the presence of prior positive and, more particularly, negative experiences which are long-lasting, when new therapeutic regimes are discussed and implemented. A close analysis of prior beneficial and negative events can help guide a balanced approach to pain to maximize clinical (placebo) benefits and minimize unintended negative (nocebo) events. Although additional translational research is needed, the possibility of abolishing placebo effects and of minimizing nocebo effects could also represent an important advance in the design and in the conduction of clinical trials.

Methods

Study participants

Thirty study participants were recruited from September 2013 to April 2014 at the National Institute of Mental Health (NIMH) to participate in a two-day, within-subject functional magnetic resonance imaging (fMRI) study. Five participants were excluded due to technical failure, leaving a sample of 25. Participants (13 women) were 19-32 years old (Table 1) and confirmed to be healthy by an in-person clinical examination and psychiatric interview.

Inclusion criteria were adults aged between 18-55 years; and being able to understand and speak the English language. The exclusion criteria include presence of: any significant medical or neurological problems (e.g. cardiovascular illness, respiratory illness, neurologic illness, seizures, etc.); family history of mania, schizophrenia, or other psychoses (first-degree relatives only); history of mania, schizophrenia, or other psychoses; any current Axis I psychiatric disorders (e.g. depression and anxiety); lifetime alcohol/drug dependence; alcohol/drug abuse in the past year; current use of psychotropic medication; impaired hearing; pregnancy; breast-feeding; smoking (use of any form of nicotine during the last six months); color-blindness (e.g. difficulty to distinguish between red and green colors); metal slivers or shavings lodged in the tissues of the head or neck; surgical clips or shrapnel in or near the brain or blood vessels; any metallic objects in the eyes or central nervous system, and any form of implant wire or metal device that may concentrate radiofrequency fields; head trauma with loss of consciousness in the last year or any evidence of functional impairment due to and persisting after head trauma; previously work in metal fields or machines that may have left any metallic fragments in or near your eyes; tattooed makeup (eyeliner, lip, etc) or general tattoos in a dangerous location on your body; any non-organic implant or any other device such as: cardiac pacemaker, insulin infusion pump, implanted drug infusion device, cochlear, otologic, or ear implant, transdermal medication patch (Nitro), any metallic implants or objects, body piercing(s), bone/joint pin, screw, nail, plate, wire sutures or surgical staples, or shunt and any psychological contraindications for MRI (e.g., fear of closed places).

The NIMH Institutional Review Board approved the study (White Panel). All procedures were conducted in accordance with the ethical standards of the Helsinki Declaration.

Pain calibration and measurement

Thermal stimuli were delivered using a PATHWAY System (Medoc Inc, Israel). During the calibration phase, heat pain threshold and tolerance were determined using the method of limits [23]. Heat stimulations were delivered starting at a temperature of 32 °C that increased over time. Participants were asked to press a

button to stop the delivery of the stimulation when they experienced a warm sensation and when they perceived a minimum, medium and maximum tolerable level of pain, respectively. Pain threshold (slope: 1°C/sec) was defined as the level in which the sensation changed from "warm" to "painful," while pain tolerance (slope: 3°C/sec) was defined as the level when the maximum tolerable pain intensity was reached. The procedures were repeated four times each during day 1.

Participants familiarized themselves with the thermal stimulations during this phase in order to distinguish the three levels of painful stimulations and to rate their experienced pain using a visual analogue scale (VAS) anchored from 0 (no pain) to 100 (maximum tolerable pain) and a Celeritas Fiber Optic Response System (Psychology Software Tools Inc, Sharpsburg, USA). Pain ratings during the fMRI acquisition were also collected on a visual analogue scale using the same Celeritas system. Before the experimental session started, participants were asked to familiarize themselves with the device and practice reporting their answers.

Experimental procedure

Anticipatory and face cues were presented using Eprime (Psychology Software Tools Inc, Sharpsburg, USA). Cues consisted in the presentation of three anticipatory colors (red, yellow, and green, 2s), followed by the presentation of the three faces (fearful, neutral, and happy) [24] that were shown in concomitance with a painful heat stimulus (10s). Afterwards, participants rated their pain on the VAS (4s). On day 1, the face valence was consistent with the level of delivered painful stimulation (e.g. fearful face and high pain, happy face and low pain). On day 2, participants entered the test phase and fMRI measurements were obtained. During this session, 50% of the color-face cues (30 trials) were randomly mismatched to violate the expectancies that were created on day 1 throughout the conditioning procedure. Fifty percent of the color-face cues (30 trials) were kept the same as during the conditioning phase (matched trials) to compare behavioral and neural responses associated with the expectancy violation. To test for modulatory effects of expectancy violation on nocebo and placebo effects, we adopted a model that was previously described [9]. Medium (control) painful stimulations were delivered for three cue-combinations in all the mismatched and matched conditions. Any difference in red versus yellow-associated stimulations and green versus yellow-associated pain ratings were operationally defined as 'nocebo hyperalgesic' and 'placebo analgesic' effects.

Participants provided informed consent in which the authorized deception approach was implemented. Specifically, the consent form clearly stated that they were going to participate in a study including deceptive elements [25,26]. Participants were debriefed at the end of their study participation and, due to

the deceptive nature of the study, were offered the chance to withdraw their data from the study. None of the participants chose to withdraw the data from the study. Participants were monetarily compensated for their time ($150).

Behavioral data analysis

To determine the sample size, we used the Cohen's d = 0.5 extrapolated from a previous study [9] with the three anticipatory colors and determined that an sample of n = 25 is needed to achieve 95% power for the detection of an medium effect among the three conditions. Power calculation was performed using G*Power [27] (http://www.gpower.hhu.de/). Behavioral VAS ratings were analyzed using a generalized linear model for repeated measurements. We performed omnibus and separate Linear Mixed Model (LMM) analyses for placebo and nocebo responses using VAS ratings as a dependent variable, condition (matched/mismatched), cues (red, yellow, and green) and trials as within factors. Cohen's *d* effects were determined for each condition (placebo and nocebo; matched and mismatched) by calculating the mean difference between two face-cue combinations (e.g. red-fearful matched and yellow-neutral matched), and then dividing the result by the *pooled* standard deviation. A $p<0.05$ was considered significant and SPSS 21 (IBM, Armonk, USA) was used for analysis.

fMRI data acquisition and analyses

Functional images were acquired with a Siemens 3T Magnetom Skyra equipped with a 32-channel head coil. T2*-weighted standard gradient echo planar imaging sequence was used (repetition time: 2.00s; echo time: 30ms; flip angle: 70°; field of view: 210x210mm^2; GRAPPA PAT factor: 2). Each volume consisted of 40 transversal slices with a voxel size of 3x3x3mm^3. Structural T1-weighted images were acquired using a multi-echo pulse sequence with a voxel size of 1x1x1mm^3.

fMRI data analyses were performed using SPM12 (Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing included slice timing correction, realignment and unwarping, coregistration of the T1 anatomical scan, normalization using DARTEL and smoothing using an 8-mm (FWHM) isotropic Gaussian kernel. First level analysis was performed using a general linear model. A high pass filter with a cutoff period of 128 seconds was used, and a correction for temporal autocorrelations was performed using a first order autoregressive model. The model included regressors for cue (separate for each color, 2s), pain stimulation and face presentation (matched and mismatched, separate for each color, 10s), and pain rating (4s). The regressors were modeled by boxcar functions convolved with a canonical hemodynamic response function (HRF) and included temporal and dispersion derivatives. The contrast of

interest between the matched and mismatched conditions was computed and raised to the second level. For the second level analysis, we used a one-sample t-test. Results were considered significant at a whole brain corrected threshold of $P_{FWE}<0.05$ using cluster correction at a primary threshold of $p<0.001$. This has been shown to be an appropriate correction for multiple comparison [28,29].

Study Highlights questions and answers: (145 words max)

• *What is the current knowledge on the topic?*

Expectancies are one of major factors in shaping both the improvement and worsening of symptoms in clinical trials and practice. However, it is unclear how violation of expectancies influences placebo and nocebo effects.

• *What question did this study address?*

Here, we investigated the influence of expectancy violation on placebo and nocebo effects at the behavioral and neural levels.

• *What does this study add to our knowledge?*

We showed that expectancy violation reduces both placebo and nocebo effects with an abolishment of placebo but not nocebo effects when expectancies were violated. These effects were paralleled in an activation of the inferior parietal cortex. We argue that this change in the inferior parietal cortex reflects processing of discrepancies between sensory input and expectancies.

• *How might this change clinical pharmacology or translational science?*

These results shed light on understanding the influence of expectancies in clinical therapeutic outcomes. The possibility of abolishing placebo responses and minimizing nocebo could represent an important advance in the design and in the conduction of clinical trials.

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Disclosures

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Author Contributions

Designed research: Colloca, Robinson

Performed research: Colloca, Nathan

Analyzed data: Colloca, Schenk

Wrote manuscript: Colloca, Schenk, Grillon

Contributed Tools: Colloca

Colloca had full access to all of the data obtained in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure Legends

Figure 1: Experimental design. (A) Anticipatory (red, yellow, and green) and face (fearful, neutral, and happy) cues were presented with three painful stimulations delivered at an average intensity of 47, 44, and 41 °C to provide a perception of high, medium, and low painful sensation, respectively. During the acquisition phase, the red-fearful face cue indicated high pain, the green-happy cue indicated low pain, and the yellow-neutral face indicated the medium (control) level of pain.

(B) During the test phase in the fMRI scanner, the anticipatory and face cues were mismatched in 50% of the trials to violate participants' expectancy (e.g., red: neutral or happy face). Moreover, the level of pain (in °C) was set for all the matched and mismatched trials at the individually-calibrated medium pain. The difference in VAS ratings observed in the red and green associated stimulations represent placebo and nocebo effects, respectively. Any difference in red versus yellow-associated stimulations and green versus yellow-associated pain ratings were operationally defined as nocebo and placebo effects.

Figure 2: Behavioral and neural results. (A) Time course of the VAS pain ratings for each trial for the nocebo (red), control (yellow), and placebo (green) condition. The nocebo (red – yellow) and placebo effect (green – yellow), was larger during the matched trials (left) compared to the mismatched trials (right, Nocebo: $F_{1,968}$=25.9, p=0.001; Placebo: $F_{1,968}$=32.3, p<0.001). The mismatch alters placebo and nocebo effects with a reduction of the effect size for both placebo and nocebo effects and an extinction of placebo effects. Data are presented as mean ± sem.

(B) Individual VAS pain ratings for nocebo, control, and placebo, for matched (left) and mismatched (right). Each dot represents the condition-specific rating for each participant.

(C) At the neural level, the placebo and nocebo changes between the mismatched and matched conditions, were paralleled by the activation of the left inferior parietal cortex, including the supramarginal gyrus and angular gyrus (all mismatched contrast – matched contrast: P_{FWE} = 0.03 (whole brain correction), k_E =399, T = 4.59 [-32 -52 34]) X,Y,Z represent Montreal Neurological Institute coordinates; L indicates left side, Bar indicates t values**.**

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