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Distinct neural representations of placebo and nocebo effects ☆

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ABSTRACT

Expectations shape the way we experience the world. In this study, we used fMRI to investigate how positive and negative expectation can change pain experiences in the same cohort of subjects. We first manipulated subjects' treatment expectation of the effectiveness of three inert creams, with one cream labeled "Lidocaine" (positive expectancy), one labeled "Capsaicin" (negative expectancy) and one labeled "Neutral" by surreptitiously decreasing, increasing, or not changing respectively, the intensity of the noxious stimuli administered following cream application. We then used fMRI to investigate the signal changes associated with administration of identical pain stimuli before and after the treatment and control creams. Twenty-four healthy adults completed the study. Results showed that expectancy significantly modulated subjective pain ratings. After controlling for changes in the neutral condition, the subjective pain rating changes evoked by positive and negative expectancies were significantly associated. fMRI results showed that the expectation of an increase in pain induced significant fMRI signal changes in the insula, orbitofrontal cortex, and periaqueductal gray, whereas the expectation of pain relief evoked significant fMRI signal changes in the striatum. No brain regions were identified as common to both "Capsaicin" and "Lidocaine" conditioning. There was also no significant association between the brain response to identical noxious stimuli in the pain matrix evoked by positive and negative expectancies. Our findings suggest that positive and negative expectancies engage different brain networks to modulate our pain experiences, but, overall, these distinct patterns of neural activation result in a correlated placebo and nocebo behavioral response.

Introduction

Expectations shape the way we experience the world, for better or for worse (Tracey, 2010). Physicians and clinical investigators have found that positive expectancy of relief can enhance the therapeutic effect of treatment and negative expectancy can diminish it (Atlas and Wager, 2012; Atlas et al., 2012; Bingel et al., 2011; Carlino et al., 2014; Finniss and Benedetti, 2005; Finniss et al., 2010; Tracey, 2010). In the context of pain perception, positive expectations of treatment can elicit analgesia while negative expectation can elicit hyperalgesia. In a clinical setting, it has been demonstrated that either or both placebo (positive expectancy of pain relief) and nocebo effects (negative expectancy of increased pain) influence the effectiveness of medical treatment (Kam-Hansen et al., 2014; Pollo et al., 2001).

There is an increasing body of literature suggesting that placebo effects can enhance the therapeutic benefits of care through the context in which the treatment is administered (Brody and Miller, 2011; Cleophas, 1995; de la Fuente-fernandex et al., 2002; Di Blasi et al., 2001; Finniss et al., 2010; Kaptchuk, 1998; Price et al., 2008; Thomas, 1994). Similarly, there is evidence suggesting that negative expectations can contribute to a variety of side effects and adverse events in clinical trials and medical care (Amanzio et al., 2009; Barsky et al., 2002; Colloca and Finniss, 2012; Petersen et al., 2014). Investigators have explored the neurobiological mechanisms underlying placebo analgesia extensively over the past decades. Many have employed brain imaging technologies (Amanzio et al., 2013; Atlas and Wager, 2012; Benedetti, 2008; Benedetti et al., 2006; Buchel et al., 2014; Enck et al., 2008; Finniss and Benedetti, 2005; Finniss et al., 2010; Kong et al., 2007; Miller et al., 2009; Tracey, 2010; Zubieta and Stohler, 2009). Relatively fewer studies have focused on nocebo hyperalgesia (Benedetti et al., 2003; Colloca and Benedetti, 2007; Colloca and Finniss, 2012; Geuter

☆ One-sentence summaries: The placebo and nocebo effects indicated by subjective pain rating changes were significantly associated; yet, the involved brain networks indicated by fMRI signal changes are different.

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and Buchel, 2013; Kong et al., 2008; Schmid et al., 2013; Scott et al., 2008).

In order to understand the mechanisms underlying the placebo and nocebo effects, it is important not only to understand them separately but also study the association between them. It is not yet clear whether any or all of the mechanisms that have been proposed to account for positive and negative modulation of pain perception are contributory, singly or in combination. Moreover, there is no clear consensus on whether bidirectional mechanisms contribute to placebo analgesia and nocebo hyperalgesia or whether they are completely separable cognitive constructs. To date, only a few studies have directly compared placebo and nocebo effects. Most of these studies have involved behavioral measures only (Benedetti et al., 2003, 2014; Colloca et al., 2008, 2010). Based on the existing data, investigators have formed two main hypotheses regarding the relationship between placebo and nocebo effects (Petrovic, 2008; Scott et al., 2008). One postulates that placebo and nocebo are manifestations of the same type of brain network with different activation/deactivation changes or, using Petrovic's term, 'sides of the same coin' (Petrovic, 2008). The other posits that placebo and nocebo are separate cognitive constructs grounded in different behavioral patterns and their associated brain networks (Benedetti et al., 2006; Kong et al., 2008).

In the present experiment, we first manipulated subjects' treatment expectation of the effectiveness of three inert creams, with one cream labeled "Lidocaine" (positive expectancy), one labeled "Capsaicin" (negative expectancy), and one labeled "control" by surreptitiously decreasing, increasing or not changing, respectively, the noxious stimulus intensity after application. We then investigated the subjective pain rating and fMRI signal changes associated with administration of identical pain stimuli before and after the different "treatments." Our study is unique in that it involved the use of a completely inert treatment, a moisturizing cream, to elicit both placebo and nocebo effects within each individual subject in the same session. This experimental design allowed us to investigate the association between the placebo and nocebo effects and directly compare the brain networks between these two important clinical phenomena in the absence of active medication.

Methods

The Institutional Review Board at Massachusetts General Hospital approved all study procedures. All enrolled subjects provided written informed consent before beginning any study procedures and we debriefed them at the end of the study. All subjects were offered the option to remove their data from the study if they had any concerns due to the inherent need for deception in the experimental paradigm. No subject reported any concern and all subjects allowed their data to be used.

Subjects

Healthy, right-handed, English-speaking subjects participated in the study. We excluded individuals who reported ongoing or past major medical, neurological, or psychiatric illnesses; pregnancy, breast feeding, menopause, and/or irregular menstrual cycles; a history of substance abuse or dependence; a history of impaired urinary elimination; use of psychotropic drugs within the past year; claustrophobia; head trauma; or any other contraindications to MRI.

Experimental design

The study involved three sessions, each separated by 2–14 days: a training session, a conditioning session, and a scan session. In all sessions, we delivered calibrated heat pain stimuli to the right volar forearm of each subject using a Pathway Medoc (Contact Heat-Evoked Potential Stimulator, Medoc LTD Advanced Medical Systems, Rimat Yishai, Israel). All stimuli initiated at a baseline temperature of 32 °C and subsequently increased to a given target temperature. Each stimulus lasted 12 s, including a ramp up from baseline (2.5 s) to the target temperature (7 s) and a ramp down to baseline (2.5 s).

Session 1

In the training session, we familiarized subjects with the heat pain stimuli and the Gracely Scales (0–20) (Gracely et al., 1978a, 1978b) that they would use to rate their pain in order to determine the temperatures required to elicit heat pain for each subject and control for rating strategy and learning effects (Kong et al., 2006, 2008).

Specifically, we drew a 3×3 grid comprised of 2×2 cm regions on the right volar forearm of the subject (2 columns on the inner arm and a third column on the radial, lateral part of the arm). We then administered one or two ascending sequences consisting of stimuli that got progressively more painful over the course of the sequence followed by one or two sequences consisting of three mild [rated as 5–6 out of 20], three moderate [rated as 10–11 out of 20], and three strong [rated as 14–15 out of 20] pain stimuli interspersed in random order. Finally we administered one or two sequences consisting of six identical moderate heat pain stimuli. Each sequence was administered to a separate region within the grid on the forearm.

Session 2

Session 2 was a behavioral conditioning session. This session involved an expectancy manipulation model employed in some of our laboratory's previous studies (Kong et al., 2006, 2008, 2009a, 2009b). We informed all subjects that the aim of the study was to investigate the analgesic effect of Lidocaine cream and the hyperalgesic effect of Capsaicin cream on their experience of pain. We told subjects that we would apply three creams (Lidocaine, Capsaicin, and a neutral moisturizing cream) to different regions of their right volar forearm and test their response to heat pain stimuli both before and after the application of the creams (Fig. 1).

In reality, we used three samples of one inert moisturizing cream, each dyed a different color. One sampling was dyed light blue and labeled "Lidocaine," one was dyed pink and labeled "Capsaicin," and one was left white and labeled "neutral."

We drew a 3×3 grid identical to that of Session 1 on the inner arm of each subject and proceeded to administer 9 heat pain sequences (one sequence per square on the grid), each about 6 min in duration and each including 6 identical heat pain stimuli at the temperature that elicited a moderate (10–11 out of 20) rating as determined in the previous session. Then we applied one cream to each row (set of 3 adjacent squares) on the grid and counterbalanced the order of cream application across subjects. To balance the design, we started the administration of sequences of heat pain stimuli at the most lateral column and moved medially across all subjects. We told subjects that we would wait 15–20 min for the creams to take effect and to identify any allergic reactions they might have to the creams. We also read them a script stating that those who experience decreased pain from the Lidocaine and enhanced pain from the Capsaicin should continue and consistently respond that way over the course of the study.

Following the 20-minute waiting period after cream application, we conducted the experimental manipulation. In this conditioning paradigm, we informed subjects that they would be receiving 9 heat pain stimuli sequences comprised of stimuli at temperatures identical to those they had received prior to cream application. In reality, we surreptitiously lowered the heat to temperatures that elicited mild pain ratings in the "Lidocaine" squares, and raised the temperatures to elicit strong pain ratings in the "Capsaicin" squares. To reinforce these effects, identical moderate intensity stimuli were administered to the neutral squares (Eippert et al., 2009; Kong et al., 2006; Scott et al., 2008; Wagner et al., 2005). Only subjects who could distinguish between the pre- and post-treatment stimuli on the "Lidocaine" and "Capsaicin" regions, as indicated by average pain ratings, were permitted to continue with the study.