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PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 15, No 4 (April), 2014: pp 435-446
Available online at www.jpain.org and www.sciencedirect.com

Enhancing the Placebo Response: Functional Magnetic Resonance Imaging Evidence of Memory and Semantic Processing in Placebo Analgesia

Jason G. Craggs,* Donald D. Price,† and Michael E. Robinson*

*Departments of *Clinical and Health Psychology and †Department of Oral and Maxillofacial Surgery, University of Florida, Gainesville, Florida.*

Abstract: **Two groups of patients with irritable bowel syndrome rated pain and underwent functional magnetic resonance imaging brain scanning during experimentally induced rectal distension (20 seconds, 7 stimuli). Group 1 was tested under baseline (natural history [NH]) and a verbally induced placebo condition, whereas Group 2 was tested under baseline and standard placebo (no verbal suggestion for pain reduction) and intrarectal lidocaine conditions. As hypothesized, intrarectal lidocaine reduced evoked pain and pain-related brain activity within Group 2. Between-group comparisons showed that adding a verbal suggestion to a placebo condition increased neural activity involved in memory and semantic processing, areas that process the placebo suggestions. These areas, in turn, are likely to influence brain areas involved in emotions and analgesia and consequently the placebo effect. These placebo suggestions also added significant decreases in activity of brain areas that process pain. The test stimulus itself seems to cue these effects and is consistent with previous explanations that somatic focus and sensory feedback reinforce expectations and other factors that mediate placebo analgesic effects.**

Perspective: ***Expectations for pain can be verbally manipulated to produce placebo analgesia. Placebo analgesia is accompanied by decreased brain activity related to processing pain and increased brain activity that generates placebo analgesia, including semantic and memory regions. Placebo suggestions may enhance placebo analgesia by engaging a feedback mechanism triggered by the painful stimulus itself and related to brain mechanisms involved in memory and semantic processing.***

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Key words: *Placebo analgesia, pain, irritable bowel syndrome, expectations, nociception, brain imaging.*

Pain is a complex multifaceted phenomenon, and the literature indicates that individual expectations can alter how the central nervous system responds to painful stimuli.[2,4,5,17,21,24,25] Moreover, expectations can be manipulated by verbal suggestion to enhance the placebo response.[17,24,25] Furthermore, this enhanced placebo (e-PL) suggestion produces an analgesic effect that is larger than that produced in a standard-placebo (s-PL) condition (used in clinical trials). For example, experimentally evoked rectal pain in irritable bowel syndrome (IBS) patients can be strongly reduced with this verbal suggestion: "The agent you have just been given is known to powerfully reduce pain in some people."[17,24,25]

Given the complexity of pain, endogenous pain modulation must engage multiple systems to generate and maintain a placebo analgesic response. Indeed, our previous functional magnetic resonance imaging (fMRI) analyses of placebo analgesia in IBS patients revealed that the large placebo analgesic effects are accompanied by large reductions in corresponding neural activity among several pain-processing areas.[17] These reductions were also accompanied by increased activity in pain-modulating brain regions,[10] including those involving memory of the placebo suggestions and related meanings (bilateral temporal lobes, parahippocampal gyrus), emotional regulation (amygdala), and executive functions (frontal cortical areas). Moreover, we

Received May 20, 2013; Revised November 20, 2013; Accepted December 23, 2013.
Supported by the National Center for Complementary and Alternative Medicine (R01AT001424, to M.E.R.).
There is no conflict of interest among authors.
Address reprint requests to Jason G. Craggs, PhD, University of Florida, 101 South Newell Drive, Rm 3151, P.O. Box 100165, Gainesville, FL 32610-9165. E-mail: jcraggs@phhp.ufl.edu
1526-5900/$36.00
Published by Elsevier Inc. on behalf of the American Pain Society
http://dx.doi.org/10.1016/j.jpain.2013.12.009

found increased activity among these regions during the early phase of the experimental protocol (ie, closer in time to the placebo suggestion).[9] However, further analyses are needed to better understand the mechanisms through which the placebo response can be manipulated and enhanced, and to establish that this verbal suggestion contributes directly to the placebo effect. Comparing these placebo conditions offers a useful clinical and basic science model for investigating the mechanisms of placebo analgesia.[8,17,18,24,25] Thus, the main goal of this study was to compare 2 groups of patients with IBS that had similar analgesic effects generated by peripheral and top-down processing, respectively (ie, identify unique patterns of pain-related neural activity associated with RL, s-PL, and e-PL conditions). These analyses allowed us to identify brain regions associated with memory and semantic processes, ones that likely interface the placebo suggestion with generation of the placebo effect and are sensitive to manipulation.

Methods

Participants

The mean age of the sample was 31.6 (8.6) years. Subjects were recruited using advertisements posted throughout the University of Florida, Gainesville. The diagnosis of IBS was made by an experienced gastroenterologist based on the Rome II criteria and exclusion of organic disease.[12] None of the patients had any symptoms other than those closely related to the IBS. All subjects were asked to fast for 12 hours prior to testing and to self-administer one Fleets enema (CB Fleet Co, Inc, Lynchburg, VA) at least 2 hours prior to arriving for the test session. None of the participants in this study took pain medications, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, or tricyclic antidepressants before or during the course of the study. Seven of the subjects had diarrhea-predominant IBS, whereas 8 had constipation-predominant IBS. Ten of the subjects were Caucasian, 4 were African American, and 1 was Hispanic. Ten subjects were single, 4 were married, and 1 was divorced. Two-thirds of the sample was employed, and 4 subjects were students. All patients signed informed consent before the start of the study. There was a high degree of similarity in the demographic characteristics of 2 groups. That is, the demographic characteristics of these 15 participants (Group 2) were similar to Group 1 of our previous study[17] in which all 9 were female, young (mean age = 27.7, 9.6), and predominantly Caucasian (7 Caucasian, 1 African American, 1 Hispanic). Likewise, as noted in a later section, NH pain ratings of Groups 1 and 2 were not statistically different. Both groups were recruited in the same way at the same clinic by the same clinical staff.

Procedure

To conduct these analyses, we compared the data from a previously published study[17] (Group 1) to a different group of IBS patients (Group 2). Both groups were tested under baseline (ie, natural history [NH]) and placebo conditions. However, participants in Group 1 were given the e-PL instructions, whereas those in Group 2 received the s-PL instruction set. Participants in Group 2 were also exposed to an active treatment condition consisting of intrarectal lidocaine gel (ie, RL). Otherwise, the methods (including fMRI methods), stimulus ratings, and demographic characteristics of both groups were very similar.

Overall Study Design

The first aim of this study was to examine the pain rating and imaging data within Group 2: IBS patients that were exposed to NH, standard intrarectal gel placebo (s-PL), and RL conditions. An initial comparison was between the s-PL and RL conditions to establish the presence of an analgesic effect and to identify the changes in brain activity that accompany the diminished afferent input produced by a peripheral analgesic.

The second aim of this study was to compare the s-PL and e-PL conditions. Specifically, we compared the pain ratings and fMRI data of Group 2, who received standard placebo treatment (s-PL), to those of Group 1, who received verbal suggestions designed to enhance placebo analgesia (e-PL). Data from Group 1 were taken from our previous study.[17] The untreated NH conditions of Groups 1 and 2 were first compared to determine whether NH pain-related brain activity was significantly different between Groups 1 and 2. Then 2 sets of contrasts were made. The first contrast identified regions of interest (ROIs) wherein greater neural activity was present in the e-PL condition (Group 1 e-PL) as compared to the s-PL of Group 2 (ie, e-PL > s-PL). The results from this analysis would identify brain areas involved in generating placebo analgesia. Once ROIs were identified and found to be statistically significant, the time course of blood oxygen–level dependent (BOLD) activity was analyzed for each ROI and for the average of all ROIs identified. The second contrast identified ROIs wherein greater neural activity was present in the s-PL condition as compared to the e-PL condition (ie, the inverse of the first contrast, s-PL > e-PL). This analysis pertained to brain areas involved in processing pain, specifically those pain-processing areas in e-PL, the e-PL condition, with significantly less BOLD activity compared to the s-PL condition. As with the previous analysis, the time course of BOLD activity and the average BOLD activity of these regions were characterized.

Participants

To address the first specific aim, we recruited 15 women diagnosed with IBS to participate in this study. The University of Florida and Gainesville Veterans Administration institutional review boards approved the study. The patients were greeted in the waiting room at the gastroenterology clinic and were subsequently informed about the study in a manner approved by the University of Florida institutional review board and were informed about the study (see[17,25] for details). Before the study, patients signed an informed consent form stating that they would receive either an