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Enhancing the placebo response: fMRI Evidence of Memory and Semantic Processing in Placebo Analgesia

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Abstract

Two groups of patients with irritable bowel syndrome (IBS) rated pain and underwent fMRI brain scanning during experimentally induced rectal distension (20 sec, 7 stimuli). Group #1 was tested under baseline (natural history) 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.

Keywords

Placebo analgesia; Pain; IBS; Expectations; Nociception; Brain imaging

1.0 Introduction

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-

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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 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 (amygdale), and executive functions (frontal cortical areas). Moreover, we found increased activity among these regions during the early phase of the experimental protocol (i.e., 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 two groups of patients with IBS that had similar analgesic effects generated by peripheral and top-down processing respectively (i.e., identify unique patterns of pain-related neural activity associated rectal lidocaine, 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.

2.0 Material and methods

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 a baseline (i.e., natural history [NH]) and placebo conditions. However, participants in Group #1 were given the e-PL instructions while those in Group #2 were received the s-PL instruction set. Participants in Group #2 were also exposed to an active treatment condition consisting of intra-rectal lidocaine (RL) gel. Otherwise, the methods, including fMRI methods, stimulus ratings, and demographic characteristics of both groups were very similar.

2.1 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 natural history, standard intra-rectal gel placebo (s-PL), and intra-rectal lidocaine (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 that 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 natural history conditions of Group #1 and #2 were first compared to determine whether NH pain-related brain activity was significantly different between Groups #1 and #2. Then two sets of contrasts were made. The first contrast identified regions of interest wherein greater neural activity was present in the verbally enhanced placebo condition (Group #1 e-PL) as compared to the standard placebo condition (Group #2 s-PL, i.e. $e\text{-PL} > s\text{-PL}$). The results from this analysis would identify brain areas involved in generating placebo analgesia. Once regions of interest were identified and found to be statistically significant, the time course of 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 standard placebo condition as compared to the verbally enhanced placebo condition (i.e., the inverse of the first contrast, $s\text{-PL} > e\text{-PL}$). This analysis pertained to brain areas involved in processing pain, specifically those pain processing areas in e-PL, the verbally enhanced placebo 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.

2.2 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 IRB, and were informed about the study [see references: 17,25 for details]. Before the study, patients signed an informed consent form stating that they would receive either an active analgesic or a placebo agent during the treatment sessions. Each patient's response to visceral stimuli was tested under three conditions: rectal lidocaine (RL), rectal placebo (RP), and natural history (NH).

2.3. Experimental materials

Visceral stimulation was accomplished by the use of a rectal balloon and a barostat as previously described [13,15,31]. The balloon apparatus consisted of a 500 ml polyethylene bag that was secured to a rectal catheter (Zinetics Medical, Inc., Salt Lake City, UT) with un-waxed dental floss and Parafilm 'M' (American National Can, Greenwich, CT), which ensured a tight seal. After explanation of the protocol, subjects were placed in the left lateral decubitus position on the scanner bed and all interactions with the examiner ceased. The rectal balloon was lubricated and inserted into the rectum so that the attached end of the balloon was 4 cm from the anal sphincter. Thus, during each rectal distention, approximately 4 cm of rectum was stimulated by the inflation of the 500 ml balloon. The Visceral Stimulator® (Medtronic, Minneapolis, MN) allowed for precise inflation of the rectal balloon to a predetermined pressure. The barostat was programmed to deliver phasic rectal distention at a rapid rate (870 ml/min) to a constant pressure plateau.

2.4. Experimental paradigm

2.4.1. Natural History versus lidocaine versus standard placebo—A within subjects design was used to compare individual pain ratings across the three experimental conditions, each one tested during a separate visit and fMRI scanning session. Patients were told that they were not being treated in the NH condition and were told that they would receive either lidocaine or inert saline jelly in the RL and RP conditions. The lidocaine agent consisted of 300 mg lidocaine jelly (Astra USA, Inc., Westborough, MA), and the entire area of the rectum that would be distended was completely coated by rectal administration of the lidocaine jelly. Conversely, the agent used for the NH and placebo consisted of a sterile surgical lubricant and covered the same region of the rectum. Both agents were applied directly to rectum during the rectal exam.

During each of the scanning sessions, subjects were not given any auditory or visual cues before each stimulus onset. Moreover, both the subjects and the doctor performing the study were blinded to the RP and RL conditions. During each session, subjects experienced seven rectal distensions, at 35 mm Hg that lasted 20s and followed by 20s of rest. The patients rated their pain within 10s after termination of the scan and last distension. The test sessions were presented in random order and took place on separate days at least 10 days apart (range 10-17 days; mean 14.4+ 1.5 days) and on days wherein spontaneous ongoing abdominal pain was 30 or above on the pain scale. This assured some consistency in pain sensitivity across sessions. Following each stimulus, and within 10s of the termination of the scan and last distension, the subjects rated their perceived pain intensity and unpleasantness using the on a scale of 0-100, anchored between “no pain” and “the most intense pain imaginable” [26].

2.4.2. Natural History versus enhanced placebo—For the second aim of this study, the aforementioned data were compared to a previously reported dataset [17]. The experimental protocol used in that study was fundamentally identical, except for a single important feature, the instruction set used during the placebo condition. During the placebo condition, just as the balloon was inserted, the doctor told the patients “The agent that you have just received is known to powerfully reduce pain in some people.” See [17] for more details.

2.5 Stimulation and rating procedures

All stimuli were applied while patients were in the scanner. During the NH conditions, the barostat distended the rectal balloon in a series of ascending pressures (i.e., 10, 20, 30, 40, and 50 mm Hg) until a pain rating above 40 on a 100-unit rating scale was reached for each subject. The rating scale was anchored between “no pain” and “the most intense pain imaginable” [26]. Once a pain rating of 40+ was reached, the patient was then considered hyperalgesic, and this stimulus was then chosen as the one used during the fMRI scans. All patients were hyperalgesic and none had to be excluded.

Each testing series consisted of seven distensions that were each 20s in duration and separated by 20s. The patients rated perceived pain intensity within 10s after termination of the scan and last distension. All scanning sessions took place on days wherein spontaneous

ongoing abdominal pain was 30 or above on the pain scale. This assured consistency in pain sensitivity across sessions.

2.6 fMRI acquisition and analysis

MRI data were acquired with a research-dedicated head scanner using a standard head RF coil (Siemens Allegra, 3-Tesla). High-resolution 3D anatomical images were acquired using a T1-weighted MP-RAGE protocol (128 1-mm axial slices; TR = 2000ms, TE = 4.13ms, FA = 8°, matrix = 256 × 256mm, FOV = 24cm). The functional images were obtained from a T2* gradient echo planar imaging (EPI) sequence which captured 33 contiguous axial slices of the whole brain parallel to the anterior commissure-posterior commissure (AC-PC) plane. Additional parameters include: repetition time/echo time (TR/TE = 2000 ms/30 ms), flip angle (FA) = 90°, field of view (FOV) = 240 × 240 mm, 64 × 64 matrix; 3.75 mm³ isotropic voxels with 0.4 mm slice gap. The same paradigm was repeated seven times for each experimental condition. Stimulus onset was time-locked to the onset of scan acquisition (TR). The first two volumes of each run were discarded at the scanner and two additional volumes were discarded during pre-processing to reduce saturation effects. All scanning conditions consisted of seven functional runs, each with a 20-second rest (non-inflation) period followed by a 20-second inflation (stimulus) period. To minimize experimental confounds, scanning sessions for each condition occurred singly, on separate days, approximately a week apart.

2.7 fMRI Data Reduction

The fMRI data were analyzed with a 2 × 2.66 GHz 6-core Intel Xeon Mac Pro with 12GB RAM, using BrainVoyager 2.4.1 [Brain Innovation, Maastricht, the Netherlands; 11] and NeuroElf v0.9c (<http://neuroelf.net>). Image pre-processing consisted of iso-voxeling (3mm³), rigid-body 3D motion correction using trilinear/sinc interpolation, slice-scan time correction with sinc interpolation, spatial smoothing with a 4-mm full-width at half maximum (FWHM) Gaussian kernel, voxel-wise linear detrending, and high-pass temporal filtering to remove nonlinear drifts below 3 Hz. The functional images were co-registered to a high resolution 3D anatomic volume and transformed into standard Talairach space [23]. During spatial transformation, the functional data were interpolated to a resolution of 1mm³.

To address the two specific aims of this study, a Random Effects General Linear Model (RFXGLM) was used to identify brain regions wherein the pain-stimulus (rectal distention) was significantly convolved with the hemodynamic response function (HRF) for each condition. Additionally, aside from the main effect of the balloon inflation, several planned contrasts were used to compare the magnitude of change in neural activity across the placebo, lidocaine, and NH conditions. As a precaution against Type I error, the statistical parameter maps (SPMs) of t-values generated for these analyses were thresholded with an FDR of $p < .05$, and had a Cluster k-threshold of 675mm³ (25 voxels). After the SPMs for each contrast were created, they were overlaid on a 3D anatomical volume in standardized space for localization.

3.0 Results

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 hour prior to testing and to self-administer one Fleets® enema (CB Fleet Co., Inc., Lynchburg, VA) at least two 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, while eight had constipation-predominant IBS. Ten of the subjects were Caucasian, four were African-American, and one was Hispanic. Ten subjects were single, four were married, and one was divorced. Two-thirds of the sample was employed, and four 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 two 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 ($m = 27.7, 9.6$), and predominantly Caucasian (7 Caucasian, 1 African American, 1 Hispanic). Likewise, as noted below in Results 3.1.3, 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.

3.1 Pain rating results

3.1.1 Group#2 lidocaine group—For the first Aim, the results of a Repeated Measures ANOVA for pain ratings revealed a significant main effect for condition ($F(2,20) = 4.84, p = 0.011$). Pairwise comparisons revealed no significant differences between NH and placebo ($p = 0.136$) or between the placebo and lidocaine conditions ($p = 0.063$), though a trend toward an effect was noted in the latter. However, there was a significant difference between the natural history and lidocaine conditions ($p = 0.012$). These results support our contention that the administration of rectal lidocaine was successful in reducing visceral pain compared to the NH and s-PL conditions. See Figure 1 (top).

3.1.2 Group#1 Enhanced placebo group—As was reported previously, the results of a repeated measures ANOVA for pain ratings revealed a significant main effect for condition ($F(2, 16) = 23.5, p = 0.001$) and planned contrasts revealed that pain ratings during the NH condition were significantly greater than those of the placebo condition ($F(1, 8) = 66.6, p = 0.001$) [17]. As expected, those results reflect a large placebo effect. See Figure 1 (bottom).

3.1.3 Comparison of NH pain ratings between groups—An Independent Samples *t*-test, which compared pain ratings between Groups #1 and 2 in the NH condition, was non-significant ($p = 0.855$). Thus, the NH pain ratings of two groups are considered equivalent. Consequently, some of the subsequent analyses will examine condition-based patterns of neural activity in terms of relative change from the NH condition.

3.1.4 Comparison of standard and enhanced placebo ratings—An Independent Samples t-test, which compared pain ratings from the placebo condition between the Group #1 and Group# 2, was significant ($p = .04$). Thus, consistent with our previous findings [9,17], the enhanced placebo instructions were associated with a significant decrease in reported pain.

3.2 Aim #1: Reductions in brain activity produced by lidocaine (Contrasts within Group# 2)

3.2.1 Decreases in pain related activity associated with Lidocaine—An initial whole-brain random effects GLM (RFX-GLM) and subsequent contrast analyses were used to identify pain related brain regions whose activity was significantly associated with rectal distention during each of the experimental conditions and that were sensitive to the administration of rectal lidocaine. Planned contrasts were then used to compare the patterns of activity across the conditions.

3.2.2 Natural History > Lidocaine—The neuroimaging results were consistent with the significant decreases in pain ratings during the lidocaine condition. Being conservative, active brain regions met both a statistical (FDR = 0.05) and minimum volume criteria (162 μ L). The comparison of the NH and lidocaine conditions (NH > lidocaine) identified a number of regions that exhibited a significant decrease in activity following the administration of rectal lidocaine (see Table 1).

3.2.3 Standard placebo greater than lidocaine (in pain related brain regions)—Results of the fMRI analysis contrasting the s-PL and RL conditions (i.e., s-PL > RL) identified several brain regions wherein lidocaine was associated with a significant decrease in neural activity. That is, using the threshold criteria mentioned above, compared to the standard placebo condition, Lidocaine was associated with significant decreases in activity in several key pain related brain regions compared to the standard placebo condition (see Table 2 and Figure 2).

3.3 Aim# 2: Group comparisons of brain activity associated with placebo mechanisms

3.3.1 Group comparison of Natural History (NH)—The results from an analysis of the imaging data from the NH condition were consistent with the comparison of the behavioral pain ratings (reported above). That is, no significant differences between the two groups were observed using a statistical threshold of FDR of 0.05. Thus, the NH patterns of pain related activities of two groups were considered equivalent.

3.3.2 Enhanced placebo versus Standard placebo (e-PL > s-PL)—As can be seen in Figure 3 (left), there are a number of brain regions where there is a significant increase in BOLD activation in the e-PL compared to the s-PL condition, which include the lentiform nucleus, parahippocampal and superior temporal gyri (see Table 3). The increased neural activity in these regions suggests a differential level of involvement in endogenous pain processes compared to the standard placebo condition. The BOLD graphs in Figure 3 (right) support this concept and show brain regions that come "on-line" and increase their activity levels in the e-PL condition. Conversely, we identified a general decrease of activity in the NH and s-PL conditions following the stimulation onset. Figure 4 depicts condition-related

changes in area-under-the-curve relative to stimulus onset. This pattern of performance would seem to indicate that these brain regions are uniquely involved in the generation and maintenance the placebo analgesic response, and may represent the processes involved in translating a verbal suggestion into the generation of a placebo response.

3.3.3 Standard placebo versus Enhanced placebo (s-PL > e-PL)—As can be seen in Figure 5 and Table 4, during the standard placebo trials, several key brain regions involved in pain-related processes exhibited significantly greater levels of neural activity compared to those in the enhanced placebo condition. These regions included the thalamus, anterior cingulate, and posterior insula. The greater levels of activity in these and other pain regions are consistent with the findings that the standard placebo did not significantly reduce pain. Moreover, the differential activation patterns are consistent with the idea that the enhanced placebo instruction set engages memory and semantic processes to enhance the placebo analgesic response and to decrease visceral pain to a level commensurate with that of lidocaine (Figure 1).

3.3.4 Comparison of Enhanced Placebo and Lidocaine—While the enhanced placebo and lidocaine conditions both significantly reduced pain and pain related activity, a comparison of their activation patterns reveals critical differences in analgesic mechanisms. As can be seen in Figure 6, there are several brain regions with significantly greater activation during e-PL, compared to the lidocaine condition. These regions are typically associated with memory and language-related processes and are listed in Table 5. These differences occurred in the presence of equally large magnitudes of analgesia ($\approx 30\%$ decrease) in the e-PL and RL conditions.

4.0 Discussion

These results further confirm that adding a verbal suggestion (“The agent you have just received has been shown to powerfully reduce pain in some people.”) to the standard clinical placebo instructions enhances the endogenous analgesic response beyond those produced in a placebo condition during a typical clinical trial [17,24,25,28,29]. Using fMRI, we demonstrated three novel findings: (1) Within Group #2, the rectal lidocaine condition showed less activity in pain processing areas of the brain as compared to the standard placebo condition, a result consistent with a successful clinical trial. Similarly, pain-related activations were less during lidocaine as compared to baseline NH condition. (2) Between-group contrasts of the placebo conditions (standard vs. enhanced) showed that the verbally enhanced placebo suggestion was associated with greater *increases* in brain activity among regions involved in top-down generation of analgesia, including areas involved in semantic processing and memory (both short and long term). (3) Finally, pain-related brain activity was less during the verbally enhanced placebo condition of Group #1 than in the standard clinical trial condition of Group #2, consistent with an enhancement of placebo analgesia by a verbal suggestion.

4.1 Within-group contrast: effects of intrarectal lidocaine in Group# 2

Using methods and procedures similar to our previous fMRI study of verbally enhanced placebo analgesia [10,17] in a group of IBS patients not given verbal suggestions (Group# 2), we show some of the neural correlates of local intrarectal lidocaine analgesia. Using a within group contrast, we found that intrarectal lidocaine produced reductions in both evoked visceral pain ratings and pain-related brain activity beyond that produced by standard placebo conditions. These results further confirm and extend our previous findings that local rectal anesthesia contributes to reduction in evoked rectal pain [10,17,24,25]. These results are expected and not surprising.

4.2 Between group contrasts: Neural networks related to verbal enhancement of placebo analgesia

The fMRI contrast of brain areas showing greater activity during verbally enhanced placebo (Group #1) as compared to standard placebo treatment (Group #2) (e-PL > s-PL) reveal a network of brain areas that have established roles in recent (hippocampus, parahippocampal gyrus) and long term memory (Superior temporal gyrus) as well as semantic/linguistic processing (Angular gyrus, BA 39). For example, the parahippocampal gyrus has been shown to participate in paralinguistic elements of verbal communication [20] and in semantic memory encoding [22]. Regarding the verbally enhanced placebo suggestion, the resultant analgesic effect likely involves multiple processes and associated brain regions. Patients have to hear this statement, understand what it means, retain a memory of it, and then link the meaning to expectations and feelings about reduced pain. If this is true, brain networks involved in semantic processing (e.g. angular gyrus, BA 39), memory (e.g. hippocampus, parahippocampal gyrus, temporal lobes), and expectations and emotions (e.g. rostral ACC, ventral striatum) must interact with brain areas/pathways most proximately involved in pain modulation (e.g. amygdala, PAG, dorsal horn). This memory-semantic processing network is likely to sustain the memory of the recent placebo suggestion and the meaning of that suggestion.

This memory-semantic network, in turn, is likely to be interfaced with networks of brain areas involved in both emotional regulation and in inhibition of pain, including descending modulation. The hypothesis that placebo effects are at least partly generated from brain regions that are involved in emotional regulation has received support from several groups of investigators [9,16,19,32]. For example, the cingulate gyrus (BA 31), medial frontal gyrus (BA 9), and amygdala were previously identified as having greater activity in the verbally enhanced placebo condition as compared to natural history [10]. The amygdala has well-established roles in both emotions and descending inhibition of pain [19]. This memory-semantic network also overlaps with the default mode network, as we have pointed out before [10]. The latter includes such areas as the posterior cingulate, medial aspects of the temporal lobe, and other brain regions involved in associative thinking. Associative thinking has been described as a conscious background state wherein subjects make unconstrained associations that are unrelated to the immediate external environment [3]. As such, this background state may support attention related mechanisms of distraction, a phenomenon that is well established as a variable in pain inhibition. The relationships between memory-semantic processing, emotional regulation, attention, and pain modulatory networks may

reflect a field of inquiry that could greatly expand knowledge of mechanisms of placebo and other psychological forms of analgesia.

Our previous studies using this clinically relevant, experimentally induced model of verbally enhanced placebo analgesia in IBS patients show a growth of the placebo effect over time [17,24,25] and the rate of growth seems to depend on the frequency of test stimuli. It took about 20 minutes for the placebo effect to increase to its maximum level in conditions wherein stimuli were applied at 7 times per 50 minutes [24,28], whereas the maximum level occurred over 3-4 minutes in a subsequent experiment that applied stimuli more rapidly at 7 stimuli in 10 minutes [17]. In both studies, the placebo effect increased to its maximum level during the first three stimuli. In combination, these results indirectly suggest that the test stimuli themselves serve to reinforce the temporal increase in the placebo effect. The stimuli of these experiments may help confirm that the treatment is working if someone is expecting it to work. The stimuli themselves may self-reinforce expectations of analgesia, reduce desire for relief, and lower anxiety. If so, the placebo effect may increase more rapidly with higher frequencies of test stimulation.

The results of the present study extend understanding of these temporal dynamics of the placebo effect in showing that placebo-related brain activity occurs in close association with the onset of the test stimulus (Figures 3 and 4). Thus, areas of the memory-semantic network have greater activity in the enhanced placebo condition of Group #1 in comparison to that of Group #2 (standard placebo condition), yet this difference begins immediately or within the first 4-5 seconds after the onset of the test stimulus (e.g., parahippocampal gyrus, left and right superior temporal gyri, Fig 3). Average BOLD activity from 15 brain regions (Table 3, Figure 3 – lower right) also shows this group difference in temporal development. This pattern of results further confirms that the onset of test stimulus itself serves as a cue for activating brain activity associated with memory and meaning of the placebo suggestion and extends our previous explanation that somatic focus and feedback from the stimuli themselves act to reinforce and enhance placebo analgesia over time.

This temporal dynamic also applies to brain areas that process pain. In this case, however, pain-related areas have less activity in the enhanced placebo condition of Group #1 in comparison to that of Group #2 (standard placebo condition). Again, this difference begins very soon after onset of the test stimulus. Thus, adding a verbal suggestion to a placebo condition adds a significant increase in brain areas that process the placebo suggestion and consequently to the placebo effect. It also adds a significant decrease in activity of brain areas that process pain. The test stimulus itself seems to cue these effects.

4.3 Limitations

The major limitation of this study is that although it provides comparisons across two groups of IBS patients, group assignment was not random and a control group was not included. Ideally, a control group and random assignment to the two types of placebo conditions would enhance the generalizability of the results. To help mitigate these limitations for this study, the fMRI and psychophysical methods were the same across both data sets and the demographic characteristics of both groups were statistically equivalent. The analyses of this study are also restricted to placebo effects associated with a verbal suggestion. However, it

is noteworthy that placebo analgesic responses can be instantiated in multiple ways, for example through conditioning [14,30], simulation of a treatment [1], observing someone else receive an analgesic treatment [6,7], and verbal suggestion [24,25]. None of these ways of inducing placebo analgesia are mutually exclusive and using more than one of these methods of placebo induction, such as suggestion combined with conditioning, have been shown to be additive [1]. Finally, because this was a secondary data analysis, the experimental protocol did not allow for a prospective analysis of brain regions involved with memory and semantic processing independent of afferent pain processing. Future studies could manipulate verbal suggestions and pain intensity and examine how predictive the verbal suggestions are of the placebo analgesic response.

5.0 Conclusions

Adding a verbal suggestion to a placebo condition adds significant increases in linguistic and semantic processing brain areas associated with the placebo suggestion and these increases are very likely linked to the placebo effect. These areas include those that process the memory and meaning of a verbal placebo suggestion. It also adds a significant decrease 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.

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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.

Figure 1.

Pain ratings were collected subsequent to each of the 20s rectal balloon distensions. The mean pain ratings in response to each of the seven rectal distensions are shown for the group given the standard placebo instructions (top) and the enhanced placebo instructions (bottom). Pain ratings after intra-rectal lidocaine gel application are shown in the top panel.

Figure 2.

Significant differences (FDR = 0.05) between the standard placebo and rectal lidocaine conditions (i.e., s-PL > Lidocaine) identify areas wherein lidocaine was associated with a decrease in both pain and neural activity. This is a representative image of brain regions in which the magnitude of neural activity was significantly greater in the standard placebo compared to the rectal lidocaine condition. These areas are associated with afferent processing of pain and are in bold italics among the areas listed in Table 2.

Figure 3.

Left image: significant differences ($FDR = 0.05$) between the two placebo conditions in which the magnitude of activity was greater in the enhanced placebo condition than in the standard condition (e-PL > s-PL). This image presents representative brain regions that are among those listed in Table 3. Right: Representative BOLD activity curves showing greater activity in ePL than in s-PL (Right lentiform nucleus at top left, left and right superior temporal gyrus top right and lower left respectively). The lower right graph shows average activity from the 15 areas listed in Table 3. Many of these regions are typically associated with language-related functions, semantic processing, and memory. Note that in all cases the separation of the curves for the e-PL condition (solid line) and s-PL condition (dashed line) begins very near the stimulus onset and becomes increasingly larger as the stimulus continues.

Figure 4.

The graph shows average change in BOLD area under the curve (AUC), across time from the 15 areas listed in Table 3. Many of these regions are typically associated with language-related functions, semantic processing, and memory. Note the sharp decreases in area in the NH and standard placebo conditions compared to the enhanced placebo condition. AUC was calculated using the Trapezoid Rule (i.e., divided the time course into trapezoids, compute each area, sum the areas).

Figure 5.

Left image: significant differences ($FDR = 0.05$) between the two placebo conditions in which the magnitude of activity was greater in the standard placebo condition than in the enhanced placebo condition (s-PL > e-PL). This image presents representative brain regions, including those known to be involved in pain-related processing (thalamus, anterior cingulate cortex BA 32). Right: representative BOLD activity curves showing greater activity in the s-PL (dashed lines) than in the e-PL condition (solid lines), thereby indicating decreased pain-related activity in the latter condition. The left upper graph is based on data from the thalamus, the upper right graph on data from left anterior cingulate, and lower left graph on data from right posterior insula. The lower right graph shows average activity from the 21 areas listed in Table 4. Some of these regions are associated with pain processing as indicated by italicized bold regions listed in Table 4. Note that in all cases the separation of the curves for the e-PL condition (solid line) and s-PL condition (dashed line) begins very near the stimulus onset and becomes increasing larger as the stimulus continues.

Figure 6.

Significant differences ($FDR = 0.05$) between the enhanced placebo and rectal lidocaine conditions. This contrast identified representative brain regions wherein the e-PL condition was accompanied by increased activity in comparison to the lidocaine condition (see also Figure 1). Similar to regions shown in Figure 3, these regions reflect verbal/semantic processes, short and long term memory, and top-down processing in the e-PL condition as compared to the local anesthesia condition.

Table 1

Natural History > Lidocaine

Left	X	Y	Z	t	μL	Right	X	Y	Z	t	μL
Caudate	Caudate										
Caudate Body *	-13	-14	30	4.05	310	Caudate Body *	20	-11	27	3.28	183
Caudate Tail *	-25	-44	12	5.78	1138	Caudate Head *	17	19	0	4.75	176
Cingulate Gyrus	Clausstrum										
BA 23 *	-4	-26	24	4.84	520	Clausstrum	26	1	21	3.93	250
BA 24 *	-4	-11	39	2.86	306	Inferior Frontal Gyrus					
BA 31 *	-16	-35	36	4.70	580	BA 47	50	28	-6	3.90	188
Inferior Frontal Gyrus	Insula *										
BA 45 *	-52	19	12	3.63	252		50	-35	24	3.96	619
Inferior Parietal Lobule	Paracentral Lobule										
BA 40	-40	-38	54	3.63	390	BA 06	8	-32	66	3.57	238
Insula *	Parahippocampal Gyrus										
	-31	-11	14	8.60	310	Hippocampus	26	-17	-12	3.43	300
Medial Frontal Gyrus	Posterior Cingulate										
BA 06 *	-13	-17	51	4.78	1460	BA 31	29	-65	15	3.82	324
Middle Frontal Gyrus	Precentral Gyrus										
BA 09 *	-31	34	27	3.49	354	BA 04	14	-23	69	4.55	1061
BA 47 *	-40	34	-3	5.72	2294	Superior Frontal Gyrus					
Posterior Cingulate	BA 08 *										
BA 30	-31	-71	9	3.01	498	Superior Temporal Gyrus	8	31	42	3.33	157
Precentral Gyrus	BA 38										
BA 04	-37	-17	48	3.04	355	BA 39	44	-50	27	3.46	193
Superior Temporal Gyrus	BA 41										
BA 38	-47	19	-15	3.71	282		50	-26	9	2.85	212

* Items in bold italics reflect areas that are most likely to be associated with pain-related processing

Table 2

Standard Placebo > Lidocaine

Cluster	X	Y	Z	Hemisphere	Region	BA	μL
1	55	-26	-11	Right	Middle Temporal Gyrus	BA 21	385
2 *	48	30	-12	Right	Inferior Frontal Gyrus	BA 47	320
3 *	37	-19	3	Right	Posterior Insula/Clastrum		341
4	18	-16	63	Right	Precentral Gyrus	BA 6	169
5	15	-8	1	Right	Lentiform Nucleus	Thalamus/Globus Pallidus	300
6 *	-3	14	-7	Left	Anterior Cingulate	BA 25	341
7	-2	-44	14	Left	Posterior Cingulate	BA 29	267
8 *	-6	-35	5	Left	Thalamus		164
9	-17	-79	1	Left	Lingual Gyrus	BA 18	413
10	-20	-10	2	Left	Lentiform Nucleus	Thalamus/Globus Pallidus	215
11	-23	-20	-7	Left	Parahippocampal Gyrus	BA 28	432
12	-32	-27	-20	Left	Parahippocampal Gyrus	BA 36	196
13	-40	-32	-13	Left	Parahippocampal Gyrus	BA 36	196

* Items in bold italics reflect areas that are most likely to be associated with pain-related processing

Table 3

Enhanced Placebo > Standard Placebo (e-PL > s-PL)

Cluster	X	Y	Z	Hemisphere	Region	BA/Region	μL
1 *	47	-59	27	Right	Superior Temporal Gyrus	BA 39	837
2 *	38	-47	18	Right	Superior Temporal Gyrus	BA 22	335
3	41	-17	51	Right	Postcentral Gyrus	BA 3	739
4 *	35	-56	18	Right	Superior Temporal Gyrus	BA 22	480
5	35	16	42	Right	Middle Frontal Gyrus	BA 8	323
6	20	37	-4	Right	Middle Frontal Gyrus	BA 11	246
7	13	10	-6	Right	Lentiform Nucleus	Putamen	142
8	11	-47	21	Right	Posterior Cingulate	BA 29	175
9	8	-20	48	Right	Medial Frontal Gyrus	BA 6	246
10	-13	-50	21	Left	Cingulate Gyrus	BA 31	151
11 *	-22	-11	-18	Left	Parahippocampal Gyrus	BA 34	225
12	-34	-20	45	Left	Postcentral Gyrus	BA 3	205
13	-49	-17	55	Left	Postcentral Gyrus	BA 3	458
14	-43	-47	27	Left	Inferior Parietal Lobule	BA 40	206
15 *	-58	-47	12	Left	Superior Temporal Gyrus	BA 22	103

* Items in bold italics reflect areas that are most likely to be associated with verbal and/or semantic processing and memory.

Table 4

- for Standard > Enhanced placebo (s-PL > e-PL)

Cluster	X	Y	Z	Hemisphere	Region	BA	μL
1	56	9	2	Right	Superior Temporal Gyrus	BA 22	110
2	40	-11	-2	Right	Clastrum		489
3 *	35	-14	21	Right	Insula	BA 13	140
4	34	36	25	Right	Middle Frontal Gyrus	BA 9	109
5 *	23	-40	27	Right	Cingulate Gyrus	BA 31	277
6 *	16	-16	14	Right	Thalamus	Ventral Lateral Thalamus	1886
7	21	10	55	Right	Superior Frontal Gyrus	BA 6	277
8	14	-17	-9	Right	*	Substantia Nigra	276
9	8	-67	42	Right	Precuneus	BA 7	1393
10 *	12	-4	41	Right	Cingulate Gyrus	BA 24	131
11 *	5	28	23	Right	Anterior Cingulate	BA 24	306
12 *	-9	-21	19	Left	Thalamus		8032
13 *	-7	26	21	Left	Anterior Cingulate	BA 32	231
14 *	-14	-44	45	Left	Cingulate Gyrus	BA 31	194
15	-22	-12	1	Left	Lentiform Nucleus	Lateral Globus Pallidus	313
16	-21	-21	-5	Left	Parahippocampal Gyrus	BA 28	810
17	-29	0	4	Left	Lentiform Nucleus	Putamen	301
18	-32	-51	36	Left	Inferior Parietal Lobule	BA 40	213
19	-37	13	-19	Left	Superior Temporal Gyrus	BA 38	226
20	-43	-48	45	Left	Inferior Parietal Lobule	BA 40	409
21	-52	-37	39	Left	Inferior Parietal Lobule	BA 40	137

* Items in bold italics reflect areas that are the most likely to be associated with pain-related processing

Table 5

Enhanced placebo > Lidocaine

Cluster	X	Y	Z	Hemisphere	Region	BA area	μL
1	42	-6	24	Right	Insula	BA 13	871
2 *	40	-50	15	Right	Superior Temporal Gyrus	BA 22	4371
3	39	-20	48	Right	Postcentral Gyrus	BA 3	314
4	39	-22	31	Right	Postcentral Gyrus	BA 2	431
5	26	-20	56	Right	Precentral Gyrus	BA 4	956
7	29	14	42	Right	Middle Frontal Gyrus	BA 8	474
8	19	16	-7	Right	Lentiform Nucleus	Putamen	681
10	15	-36	7	Right	Thalamus		395
11	5	-17	50	Right	Medial Frontal Gyrus	BA 6	498
12	-19	-23	51	Left	Precentral Gyrus	BA 4	1442
13 *	-22	-41	6	Left	Parahippocampal Gyrus	BA 30	2290
14	-22	2	43	Left	Middle Frontal Gyrus	BA 6	735
15	-25	26	36	Left	Middle Frontal Gyrus	BA 8	1097
16	-28	-75	12	Left	Cuneus	BA 30	1165
17	-47	-14	43	Left	Precentral Gyrus	BA 4	2446
18	-36	6	26	Left	Inferior Frontal Gyrus	BA 9	509
19 *	-39	-46	24	Left	Superior Temporal Gyrus	BA 13	839
20	-49	-8	21	Left	Precentral Gyrus	BA 6	1554
21 *	-55	-42	17	Left	Superior Temporal Gyrus	BA 13	890

* Items in bold italics reflect areas that are the most likely to be associated with verbal and/or semantic processing and memory.