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ORIGINAL RESEARCH

The Two Sides of Placebo Analgesia: Differential Functional Connectivity Reveals Mechanisms of Placebo Analgesic Response

Nicholas J Bush[1,2], Adriana K Cushnie[2], Jeff Boissoneault[1,2], Sharmagh Aghabeigi[1], Casey Alexander[1], Roland Staud[3], Michael E Robinson[1]

[1]Department of Clinical and Health Psychology, University of Florida, Gainesville, FL, USA; [2]Department of Anesthesiology, University of Minnesota - Twin Cities, Minneapolis, MN, USA; [3]Department of Medicine, University of Florida, Gainesville, FL, USA

Correspondence: Nicholas J Bush, Department of Anesthesiology, University of Minnesota, Minneapolis, MN, 55414, USA, Tel +1 612-624-7357, Email bush0456@umn.edu

Background: Previous research has demonstrated that placebo induction manipulations can reduce an individual's pain through non-specific mechanisms, such as expectancy manipulations. However, despite robust research characterizing these effects, individual differences in predicting placebo analgesic responses are not well understood.

Methods: Fifty-four healthy pain-free adults over 18 (M=22.8, SD=7.82) were recruited (66.7% women). Participants completed a baseline followed by a placebo session involving the application of an inactive cream in the context of an expectancy-enhancing instruction set while undergoing a functional magnetic resonance imaging scan (fMRI). Painful heat stimuli were applied to the thenar eminence of the right palm. Stimulus intensity was individually calibrated to produce pain ratings of approximately 40 on a 100-point visual analog scale. Generalized psychophysiological interaction (gPPI) was used to assess the group differences in functional connectivity during painful stimulation compared to warmth stimulation.

Results: About 68.5% showed a reduction in pain in the placebo condition with an average decrease of 30.3%. Non-responders showed an increase in pain in the placebo condition, with an average increase of 18.6%. Repeated measures ANOVA demonstrated a significant within-subjects interaction between expectancy and responder type ($F(1,49)=4.27$, $p=0.04$, $\eta p2=0.08$). Expected pain was significantly associated with pain in the placebo session for the responders ($b=0.37$, $R2=0.29$, $p<0.001$), but not for the non-responders ($b=0.11$, $R2=0.04$, $p=0.42$). gPPI analysis revealed three clusters exhibiting greater increases in FC in areas related to attention and sensory integration in placebo responders compared to non-responders. One cluster was identified where greater increases in functional connectivity were associated with non-responders compared to responders in regions associated with attention and motor processing.

Conclusion: Our results provide evidence that responders and non-responders have differential behavioral and functional responses to acute pain during a placebo analgesic task.

Keywords: placebo analgesia, placebo, responder, placebo non-responder, pain, functional connectivity

Introduction

Pain is an adverse sensory and emotional experience that affects an estimated 20.9% of adults in the United States and accounts for approximately $635 billion of the nation's annual healthcare expenses and lost work productivity cost.[1,2] Despite the high prevalence and public health importance of pain, current treatments, including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, fail to achieve the degree of pain reduction that patients consider acceptable and are associated with increased rates of drug dependence and reduced quality of life.[3–6] Thus, taking advantage of methods that enhance treatment efficacy may be a potential approach to mitigate the gap between treatment efficacy and the degree of pain relief patients deem acceptable.

Substantial evidence demonstrates that placebo analgesia (PA) reduces an individual's pain through non-specific psychological mechanisms, including expectancy and conditioning.[7,8] Previous research has shown that heightened

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expectations of pain relief predict greater analgesic responses in both placebo and active treatment sessions.[9–12] Conditioning manipulations, including classical and operant conditioning, have also increased PA.[13–15] PA has been shown to not only provide pain relief but also reduce prescription opioid intake by patients.[16] Patients are generally open to receiving placebo treatments if there are no effective treatment alternatives, and their physicians honestly endorse its benefits.[17–19]

Despite robust findings that PA can have important clinical implications, the mechanisms and potential moderating factors underlying this effect are incompletely understood. A crucial element to understanding PA is response heterogeneity. Response heterogeneity refers to clinically important differences in physiological response to the same treatment that cannot be attributed to random within-subject variability.[20] In the context of pain research, individuals who experience a reduction in adverse symptoms following a placebo manipulation are known as placebo responders, and individuals who do not are known as non-responders. Despite previously mentioned efforts to characterize the underlying PA response heterogeneity, we still do not have a clear reason for these differences or how to predict them.

Overall, there is limited research identifying the mechanisms unique to individuals who do not achieve PA after an expectancy-based placebo manipulation. This study aimed to assess the differences in expected and reported pain intensity between placebo responders and non-responders. Secondly, we aimed to identify brain areas where task-based functional connectivity differs between placebo responders and non-responders. We hypothesized that in this study, placebo responders would have a significant positive association between expectancy and pain intensity, whereas we hypothesized that there would not be a significant association between expectancy and intensity in non-responders. Additionally, we expected to identify differences in FC between responders and non-responders in regions associated with PA.

Methods

The present study is a secondary data analysis of a larger study investigating brain and spinal cord mechanisms underlying PA (NIH: R01AT001424). The original study contained four sessions (baseline, placebo, placebo match, repeated baseline); only the baseline and placebo sessions were included in this analysis (baseline and placebo). The current study examined differences in changes in functional connectivity during painful stimulation in placebo responders compared with non-responders. This study was approved by the University of Florida Institutional Review Board and was conducted at the University of Florida's McKnight Brain Institute and Center for Pain Research and Behavioral Health in Gainesville, FL. Informed consent was provided by all participants prior to data collection. The study complies with the Declaration of Helsinki.

Participants

Healthy, pain-free adults aged 18 to 65 were recruited for this study. Participants completed standard demographic and health history questionnaires to assess for exclusion criteria. Exclusion criteria included a history of chronic pain (eg, chronic low back pain, fibromyalgia), self-reported regular use of analgesics (ie, weekly), history of psychological disorder (eg, major depressive disorder), hypertension or thyroid disease that is not adequately regulated, history of neurological disease (eg, multiple sclerosis, epilepsy, traumatic brain injury), history of substance dependence, and previous participation in a placebo study. Participants were classified as placebo responders if they reported a greater than 0% pain reduction. Non-responders were defined as those reporting a greater than or equal to 0% pain increase.

Project Timeline

Participants in this analysis completed three study visits. The first visit involved a screening evaluation and heat pain calibration testing. The second visit (baseline) included MRI scanning while receiving noxious heat stimulation. The third visit (placebo) included applying an inactive cream with an expectancy manipulation instruction set before MRI scanning while applying noxious heat stimulation. Structural and functional MRI scanning was completed for both baseline and placebo sessions.

Quantitative Sensory Testing (QST) Calibration

Participants who were screened in during the first session completed a series of QST trials to determine an individualized temperature associated with a pain rating of 40 out of 100 on an electronic visual analog scale (VAS). Noxious heat pain was administered using a 3x3cm MRI-compatible contact thermode (Medoc Heat Sensory Analyzer, TSA-2001, Ramat Yishai, Israel). An ascending series of 18-second heat pulses was applied to the thenar eminence of the non-dominant hand, starting at 43°C. After each pulse, participants rated their pain on the 0–100 VAS with anchors from "no pain" to "the most intense pain imaginable." Thermode temperatures increased by 1°C until the participant reported a 40 out of 100 or a maximum temperature was achieved. The original maximum temperature was 51°C; however, software updates early in the study limited the lockout temperature to 49°C. Participants who failed to achieve a 40 out of 100 on the VAS before reaching the maximum temperature were excluded for safety reasons.

MRI Data Acquisition

MRI data were acquired utilizing a 3T Philips Achieva and Phillips Ingenia Elition scanner equipped with a 32-channel head coil. The 3T Philips Achieva scanner was replaced with the Ingenia Elition scanner during the course of the study. A total of thirty-eight participants (69.1%) were scanned on the Philips Achieva, and seventeen (30.9%) were scanned on the Philips Ingenia Elition. The scanning sequence was the same for all participants. Functional data were collected in the transaxial orientation using an EPI sequence (XYZ dimension = 80 * 80 * 39; field of view [RL (right-to-left direction), AP (anterior-to-posterior direction), FH (foot-to-head direction) – mm] 240, 240, 126; slice thickness [mm] = 3; gap thickness = 0; voxel dimension [mm] = 3 * 3 *3; repetition time [milliseconds] = 2242, TE = 30, FA = 90°). Acquisition time was 2 minutes and 18 seconds. High-resolution structural brain images were collected using a 3-dimensional (3D) T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) sequence with a field-of-view (FOV) = 240mm (FH) × 240mm (AP) × 180mm (RL), voxel-wise resolution = 1mm3, TR = 8.1 ms, TE = 3.7ms, FA = 8°). Acquisition time was 4 minutes and 50 seconds.

Noxious Heat Paradigm

At the start of the MRI scanning (baseline and placebo sessions), participants were asked to rate the intensity of the pain they expected to experience during the session using the electronic VAS anchored from "no pain" to "most intense pain imaginable" using an MRI-compatible scroll wheel. Participants then underwent 12 functional runs while receiving 60 seconds of warm stimulation, followed by 18 seconds of individually calibrated noxious heat stimulation to the thenar eminence of their non-dominant hand. This protocol was developed by Bosma et al[21] and used in previously published analyses.[22,23] This stimulation paradigm was designed to allow for comparisons with brain and spinal cord functional imaging (not included in this analysis).

Placebo Analgesia

Before scanning in the placebo session, participants received an expectancy manipulation instruction set designed to induce a placebo effect. Participants were told,

> Today, you will complete MRI tasks just like you did during the last study visit. This time, however, we are going to put a cream on your palm called 'TriOxycaine.' When applied, TriOxycaine has been shown to powerfully reduce pain in some people.

TriOxycaine, which consisted of an inert cold cream mixed with oil of thyme, was then applied to the thenar eminence of the non-dominant hand, and participants completed the same noxious heat paradigm as visit 2 using individually calibrated stimuli temperatures. Oil of thyme was selected for inclusion due to its use in previous PA studies,[24,25] strong odor, and lack of empirically demonstrated analgesic effects in animal or human subjects.[26]

Functional Data Processing

SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) and the CONN toolbox v18b[27] were used to preprocess fMRI data. Steps included slice-time correction, realignment, registration, normalization to MNI space, spatial smoothing

(8mm FWHM kernel), and signal-to-artifact reduction using the Artifact Detection Toolbox (ART; http://www.nitrc.org/projects/artifact_detect). Outliers were those where mean global signals exceeded 3 standard deviations, translation exceeded 0.5mm, or rotation exceeded 0.02 radians from the previous image.[28] Component-based noise correction for physiological and other noise source reduction was implemented in the CONN toolbox and applied to the first-level processing. Regression was used to reduce the influence of five principal components from signal within the CSF and deep cerebral white matter, all six movement parameters, and their first-order derivatives. All regions were labeled using the Harvard Oxford Atlas and the Automatic Anatomical Labeling atlas (AAL).[29]

Generalized Psychophysiological Interaction

Task-based connectivity changes related to percent pain reduction were assessed using a generalized psychophysiological interaction (gPPI) in the CONN toolbox.[27] We used a previously validated gPPI approach to assess context-dependent functional connectivity.[30] In this approach, there are task regressors for each condition (ie, baseline, placebo), a time series regressor for each seed region (eg, precuneus), and an interaction term for the product of the task regressor by the time series regression for each condition. Thus, there were 5 regressors in this analysis: baseline stimulation blocks, placebo stimulation blocks, seed region time-series, baseline stimulation by time interaction, and placebo stimulation by time interaction. This approach has previously been shown to improve overall model fit and has greater sensitivity and specificity than standard psychophysiological methods.[30] Placebo responders were characterized by having any reduction in pain in the placebo session compared to the baseline session. Non-responders were defined as having any increase in pain in the placebo session compared to the baseline session. Change in pain was quantified by calculating the percent difference from placebo to baseline pain ratings ($\frac{(placebo\ pain\ rating - baseline\ pain\ rating)}{baseline\ pain\ rating} * 100$). gPPI contrast was defined as between-subjects contrast: placebo responder > non-responder; within-subjects contrast: baseline condition, placebo condition [−1, 1]; pheight < 0.001, uncorrected; pcluster < 0.05, FDR).

Seed regions were identified from Bush et al's[22] seven significant functional activation clusters where painful stimulation was greater than warmth stimulation in the baseline session. A 6mm sphere was extracted from the peak voxel coordinate of the seed regions. The seven seed regions were labeled as precuneus, olfactory cortex, middle frontal gyrus, middle temporal gyrus, superior frontal gyrus, cerebellum VIIIa, and inferior parietal lobule.

Statistical Analyses

All statistics were calculated in Jamovi (The Jamovi Project). Paired *t*-tests were used to compare the differences in reported pain intensity and expected pain ratings between the baseline and placebo session. One sample *t*-tests were used to test if the responder and non-responder groups differed from 0. Repeated measures Analysis of Variance (ANOVA) was used to assess the within-subjects difference of reported pain and expected pain by session and the between-subjects effect of responder status (responder or non-responder). Finally, linear regression analyses were utilized for both responders and non-responders separately to assess the relationship between expected pain ratings and reported pain intensity ratings in the placebo session.

Results

Participants

A total of 55 participants completed both baseline and placebo scanning sessions. One participant was excluded for having an outlier (eg, >3 standard deviations) percent pain change (n = 54). The average age was 22.8 years (SD = 7.82, range = 18–62). The sample was predominantly female (66.7%) and non-Hispanic/Latino/a/x (63.0%). Participants were White (57.4%), Asian (24.1%), Black (7.4%), and more than one race (11.1%) with an average of 15.2 years of education (SD = 2.2, range = 12–24).

Whole Sample Statistics

As previously published, the mean percent pain reduction across the sample was 14.9% (SD = 27.9, range = −46.3–74.2%). The mean expectancy score for painful stimuli during the baseline session was 44.1 (SD = 12.8), and for the placebo session

was 37.1 (SD = 14.9). Paired samples *t*-test demonstrated no significant differences in mean expectancy ratings across the whole sample (M_{diff} = 6.95, t(53) = 3.97, Cohen's d = 0.54).

Responder Behavioral Effect

A one-sample *t*-test was used to determine percent pain change differences in responders and non-responders that differed significantly from 0. A total of 37 participants (68.5%) demonstrated a significant decrease in pain intensity ratings that averaged a 30.3% (SD = 17.41) reduction (t(36) = 10.58, p < 0.001, Cohen's d = 0.26). Seventeen participants (31.5%) demonstrated an increase in pain intensity during the placebo session, which averaged an 18.6% (SD = 12.77) increase (t(16) = −6.00, p < 0.001, Cohen's d = −1.46). Repeated measures ANOVA revealed no significant between-subjects effect of the responder group on expected pain ratings (F(1,49) = 0.40, p = 0.53). There was a significant interaction of condition (baseline vs placebo) with responder type (F = 4.27, p = 0.04, η^2_p = 0.08). While both responders and non-responders increased their expected pain ratings in the placebo session compared to the rating from the baseline session, non-responders had a significantly greater increase compared to placebo responders (see Figure 1).

Repeated measures ANOVA (rmANOVA) was used to assess the difference between expected pain (assessed before painful stimulation) and reported pain intensity (assessed after painful stimulation) in the baseline and placebo sessions by responder status. In the baseline session, there were no significant between- (F(1,49) = 0.25, p = 0.62) or within-subjects differences (F(1,49) = 0.04, p = 0.84) in expected pain and reported pain by the responder group (Figure 2A). In the placebo session, there was a significant between- (F(1,52) = 14.66, p < 0.001, η^2_p = 0.22) and within-subjects (F(1,52) = 6.58, p = 0.013, η^2_p = 0.11) effect for the responder group on the interaction between expected pain and reported pain intensity (Figure 2B).

To further probe the relationship between expected pain and reported pain intensity, linear regression analyses were performed separately for the responders and non-responders. For responders, there was a significant linear association between expected pain and reported pain intensity (b = 0.37, SE = 0.10, p < 0.001, R^2 = 0.29; Figure 3A). However, for non-responders, there was not a significant linear association between expected and reported pain intensity (b = 0.11, SE = 0.14, p = 0.42, R^2 = 0.04; Figure 3B).

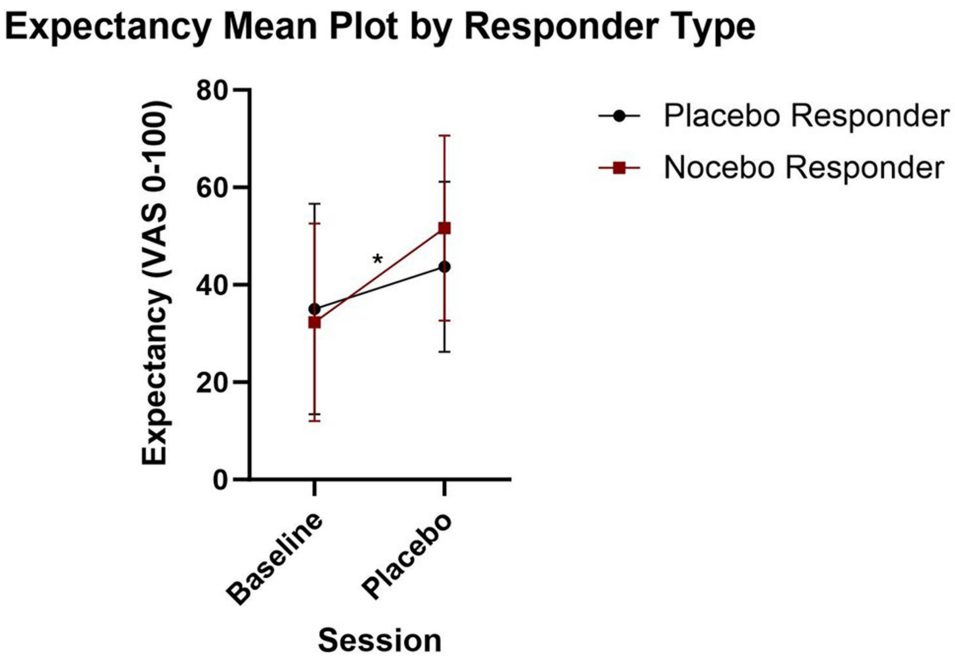

Figure 1 Change in mean expectancy rating by responder type. Error bars represent standard deviation. *p < 0.05.

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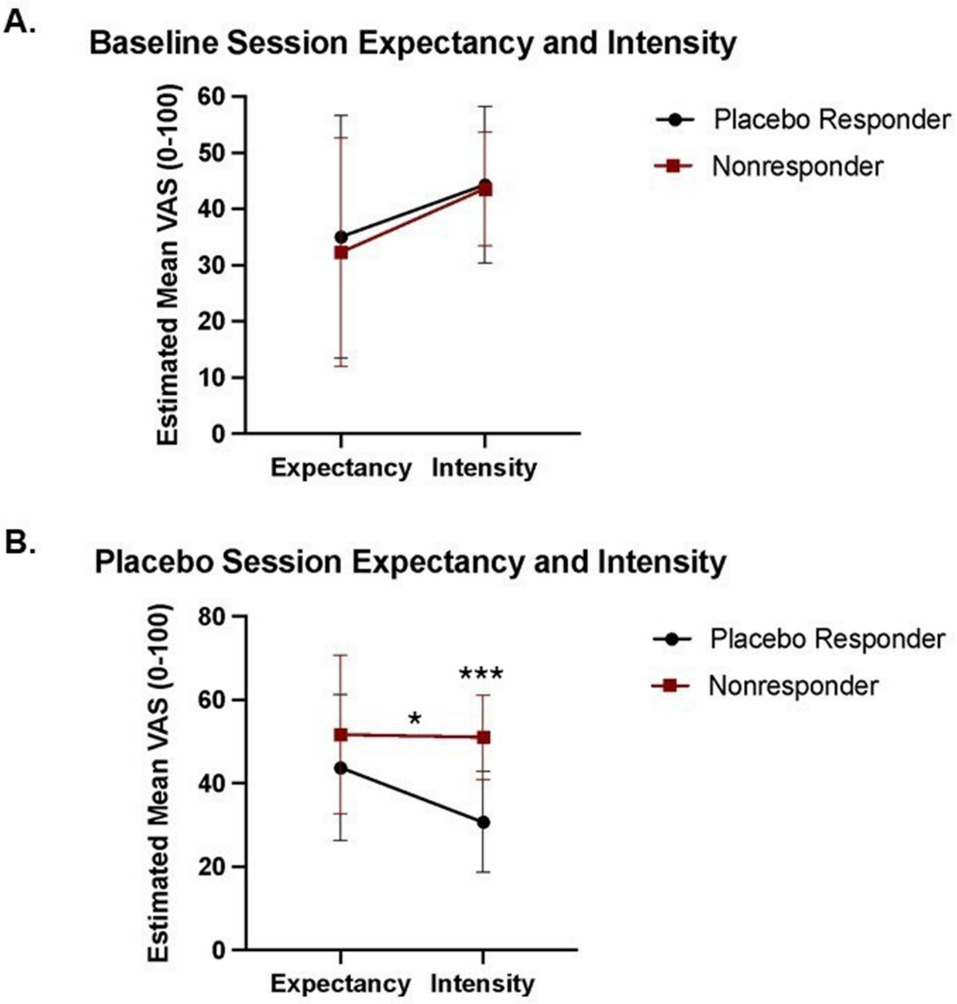

Figure 2 Change in mean expected and reported pain intensity in baseline (**A**) and placebo (**B**) session by responder group. Error bars represent standard deviation. *p <0.05, ***p < 0.001.

Task-Dependent Functional Connectivity

Differences by responder group in task-specific connectivity were assessed using a generalized psychophysiological interaction (gPPI) approach. There were three clusters where placebo responders had significantly greater FC during noxious stimulation in the placebo session compared to the baseline session associated with percent pain change (see Figures 4–6 and Table 1). In addition, there was one cluster where non-responders had significantly greater FC during noxious stimulation in the placebo session compared to the baseline session associated with percent pain change (see Figure 7 and Table 2).

Discussion

The goals of this study were to extend our understanding of PA mechanisms by characterizing differences in functional connectivity during pain processing between placebo responders and non-responders. Overall, we found that placebo responders and non-responders differ in the relationship between expected pain and reported pain intensity. In addition, we found that non-responders had a greater increase in expected pain compared to responders after the baseline session. Functional connectivity analyses revealed several clusters where there was a task-based difference in connectivity associated with percent pain change between the responder types.

Our results indicated that 31.48% of the sample did not achieve analgesia despite our intentional manipulation. Further, the mean percent pain increase differed significantly from 0 (ie, no change), which may indicate a potential

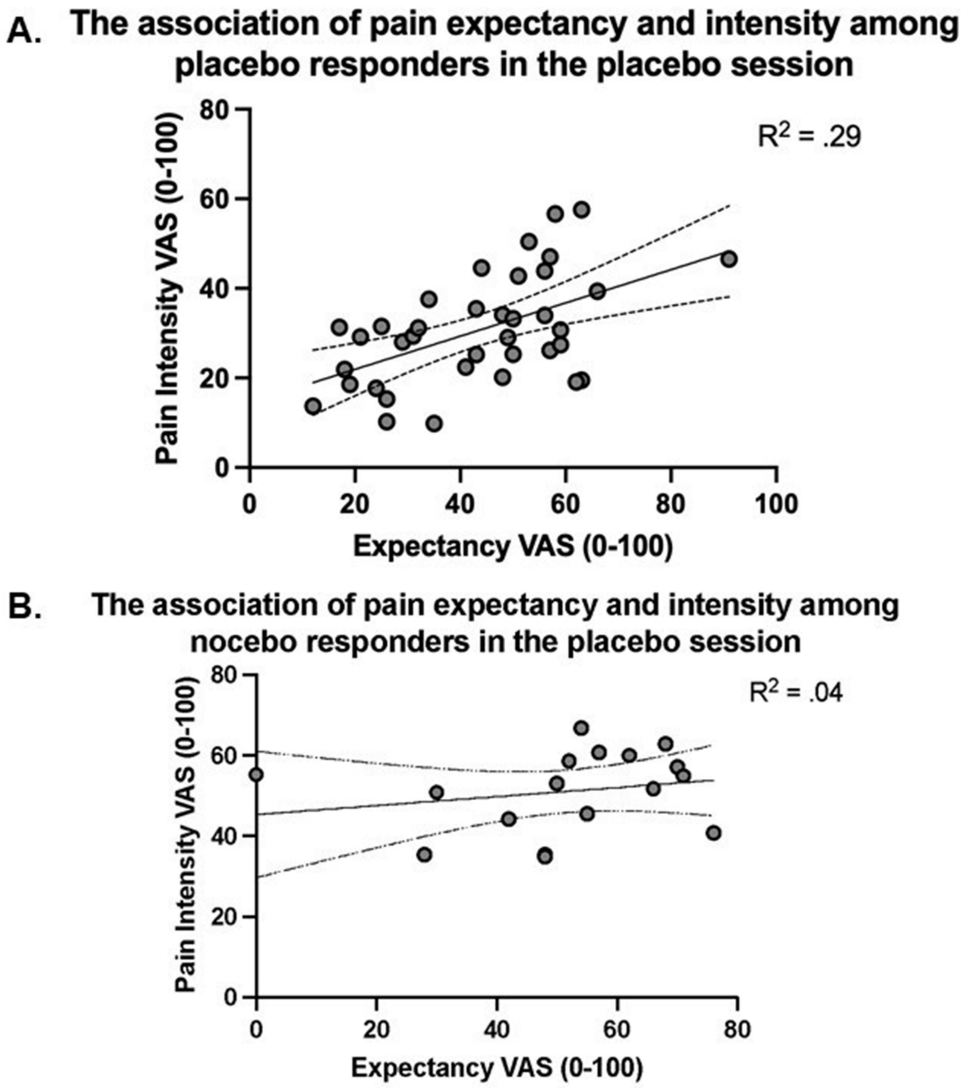

Figure 3 Scatterplot demonstrating the association of expected pain intensity and reported pain intensity in placebo responders (**A**) and non-responders (**B**).

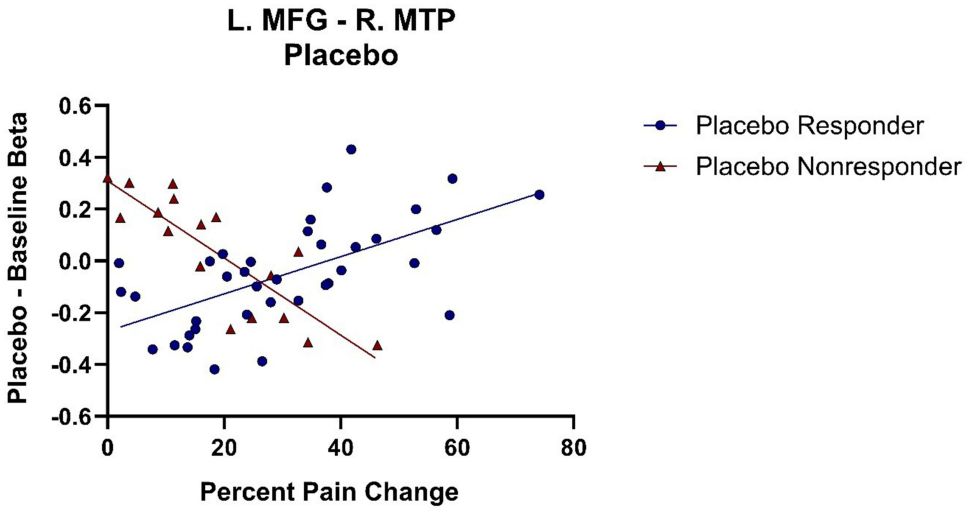

Figure 4 Scatterplot representing the significant generalized psychophysiological interaction association between change in functional connectivity (placebo - baseline) and percent pain change between the left middle frontal gyrus and right temporal pole.

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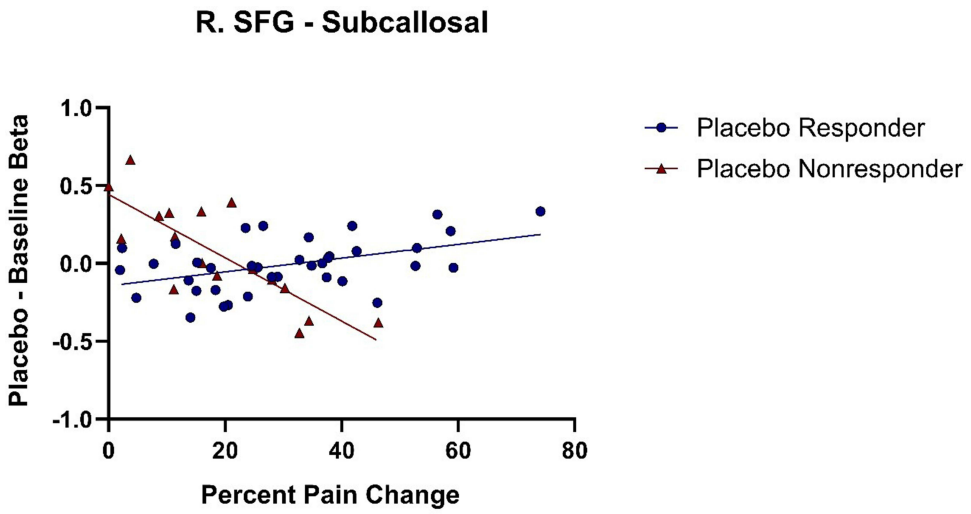

Figure 5 Scatterplot representing the significant generalized psychophysiological interaction association between change in functional connectivity (placebo - baseline) and percent pain change between the superior frontal gyrus and subcallosal cortex.

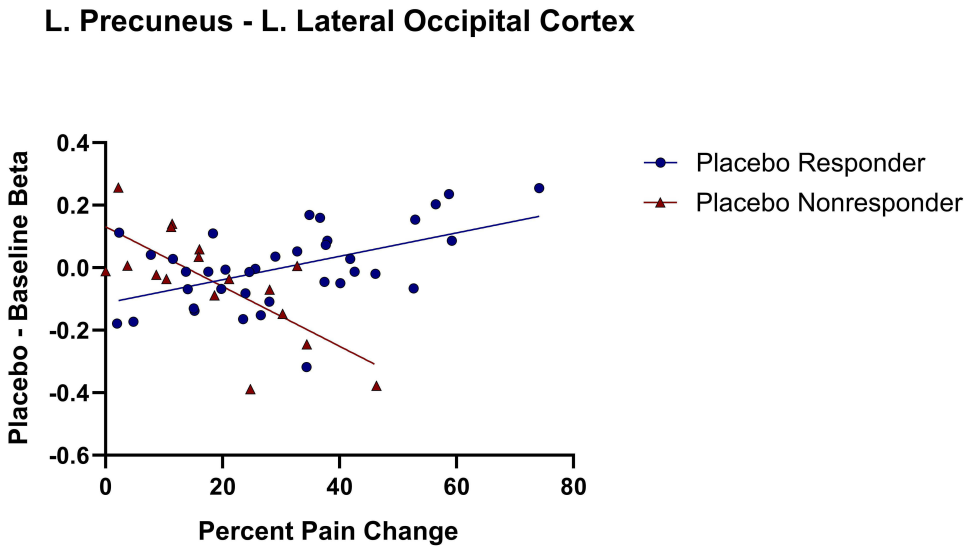

Figure 6 Scatterplot representing the significant generalized psychophysiological interaction association between change in functional connectivity (placebo - baseline) and percent pain change between the left precuneus and left lateral occipital cortex.

nocebo response in this group. Previous literature suggests that a nocebo response is defined as a negative expectancy-based change.[31] We have opted to use the term placebo non-responder instead of nocebo because we did not perform an intentional nocebo manipulation, nor did we assess negative expectations regarding our inert placebo cream. Future research should attempt to replicate these findings while also including an explicit nocebo manipulation and assessing for positive and negative expectancies to confirm their potential relevance for improving understanding of nocebo mechanisms.

We also found that there was no difference in expected or reported pain intensity at baseline between responders and non-responders. However, non-responders had a greater increase in expected pain ratings from baseline to the placebo session compared to responders. This is a novel finding that suggests that despite indicating a similar reported pain intensity, non-responders expected greater levels of pain in the placebo session. This may be the result of a variety of potential mechanisms. First, the non-responders may not have believed the placebo manipulation or believed that the painful stimulation would be increased in the placebo session. Future research should consider asking participants to

Table 1 Seed-to-Voxel Results Where Responder > Non-Responder Functional Connectivity

ROI	x	y	z	k	Cluster Region	Voxels in Region	Coverage (%)	pFDR-cor
L. Precuneus	−34	−82	28	238	L. Superior Lateral Occipital Cortex	222	4	0.01
					L. Occipital Pole	5	0	
					L. Inferior Lateral Occipital Cortex	3	0	
L. Middle Frontal Gyrus	52	6	−36	195	R. Middle Temporal Pole	121	5	0.04
					R. Anterior Inferior Temporal Gyrus	43	22	
					R. Anterior Middle Temporal Gyrus	18	9	
R. Superior Frontal Gyrus	−12	08	−06	211	Subcallosal Cortex	39	3	0.02
					L. Putamen	38	4	
					L. Pallidum	18	6	
					L. Accumbens	16	8	
					R. Putamen	11	5	
					R. Accumbens	9	11	
					L. Caudate	7	3	
					R. Frontal Orbital	5	2	
					Unlabeled	68	0	

report what they believe the hypothesis or purpose of each manipulation to be. This may help to assess how participants are conceptualizing the study. Second, in the placebo session, it is possible non-responders remembered their reported pain in the baseline session differently than they actually reported. While there is little research on non-responders, research has shown that pain is susceptible to naturally occurring memory biases.[32,33] This has also been shown experimentally when researchers were able to manipulate a participant's memory of their past reported pain intensity to a cold pressor task.[34]

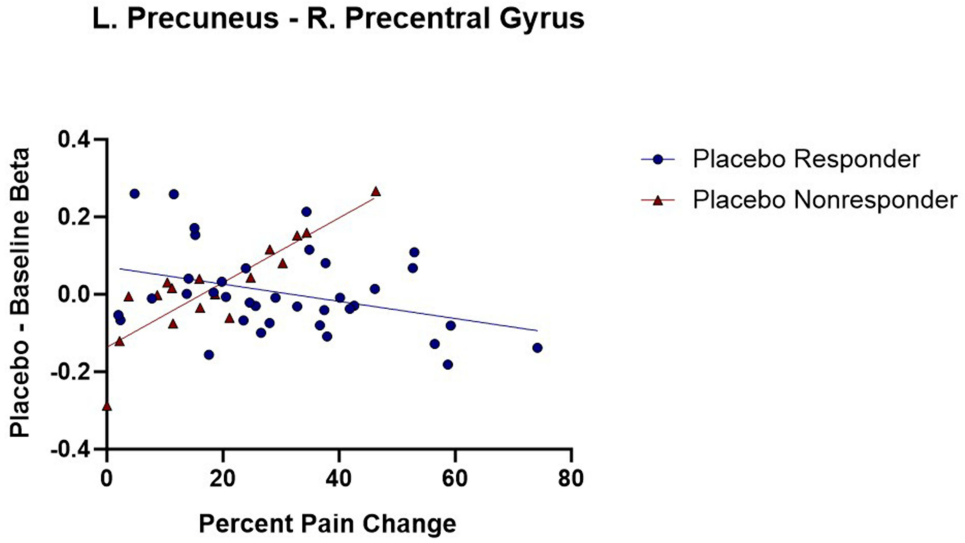

Figure 7 Scatterplot representing the significant generalized psychophysiological interaction association between change in functional connectivity (placebo - baseline) and percent pain change between the left precuneus and right precentral gyrus.

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Table 2 Seed-to-Voxel Results Where Non-Responder > Responder Functional Connectivity

ROI	x	y	z	k	Cluster Region	Voxels in Region	Coverage (%)	pFDR-cor
L. Precuneus	66	6	22	176	R. Precentral Gyrus	137	3	0.02
					R. Inferior Frontal Gyrus (pars opercularis)	10	1	
					Unlabeled	28	0	

There were three clusters where placebo responders had greater functional connectivity compared to non-responders during painful stimulation in the placebo session associated with their change in pain. There is limited literature that has examined differences in FC between responders and non-responders. Importantly, however, the regions included in the significant clusters identified have been previously associated with pain induction and placebo analgesia. For the first cluster, responders demonstrated greater FC between the middle frontal gyrus (MFG) and the middle temporal pole compared to the non-responders in the placebo session. There is little research on the role of the middle temporal pole in pain processing; however, this region has significant overlap with the middle temporal gyrus (MTG) and is sometimes labeled as the MTG, depending on the atlas. Both the MFG and the MTG regions have been associated with the expectation and anticipation of pain relief.[9,35] The middle temporal gyrus has also been identified to have increased functional activation in meta-analyses for placebo treatment.[36] Bush et al[22] demonstrated that the middle temporal gyrus' activation during painful stimulation is greater in placebo sessions compared to baseline sessions. As such, a possible explanation of this effect is that greater connectivity between the MFG and MTG is associated with a coupling of expectation and anticipation of pain relief. This is further supported given that we found non-responders demonstrated lower connectivity between these regions in the placebo session compared to responders and also did not have a significant relationship between expected pain and reported pain.

Interestingly, we also found that responders had increased FC between the superior frontal gyrus and subcallosal cortex compared to non-responders in the placebo session. This may be due to an integration between cognitive and emotional processing of pain. The superior frontal gyrus has been previously implicated with cognitive appraisal of pain, which is a cognitive process that assists in the positive (eg, cognitive reframing, self-efficacy) or negative (eg, pain catastrophizing) coping of pain.[37] Superior frontal gyrus activation has been shown to be greater in people with high pain catastrophizing during painful stimulation,[38] self-efficacy,[39–41] and anxiety in pain populations.[42,43] The subcallosal cortex's commonly identified function is emotional regulation, particularly with feelings of negative affect such as sadness.[44] As such, a greater increase in FC during stimulation in the placebo session compared to the baseline session for responders compared to non-responders may suggest a process by which responders have greater connectivity between their cognitive coping response and emotional regulation.

We also found that responders had increased FC between the precuneus and lateral occipital cortex cluster compared to non-responders in the placebo session. This finding may suggest an important functional association between sensory integration and attention. In the context of pain, the precuneus is most often associated with sensory integration,[45,46] episodic memory,[45,47] and orientation of attention.[45] The lateral occipital cortex is not a brain region traditionally associated with pain processing. However, some studies have identified visual network structures being implicated in painful stimulation and placebo responses.[22,48–50] Traditionally, the lateral occipital cortex has been associated with object-visual processing.[51,52] One potential explanation for this finding may be that for responders, where there is an expectation of pain relief, there is a divergence of attention away from the painful intensity to reduce the focus on pain. This would make sense in the context of existing literature that has implicated precuneus to be involved with visual attention shifting.[45,53] While our present study cannot confirm this hypothesis, the fact that non-responders demonstrate lower connectivity between these regions may suggest that they have a greater attentional focus on the painful experience. Future studies should aim to replicate these findings and use a priori manipulations to further probe this potential mechanism.

Lastly, we found that non-responders had increased FC between the precuneus and precentral gyrus compared to responders in the placebo session. The precentral gyrus is commonly associated with motor functioning,[54] but it has also been identified to be activated and has increased FC with cerebellar, precuneus, and cingulate gyri during painful

stimulation paradigms.[48,50,55,56] However, not much is known about the role of the precentral gyrus in pain processing. One potential reason for how the precuneus-precentral gyrus FC might be related to the degree of painful intensity in non-responders compared to responders. Similar to the precuneus-lateral occipital cortex cluster, it is possible non-responders increase attentional allocation to the painful stimulation. Future research should consider using the precentral gyrus as an a priori region of interest for painful stimulation paradigms and to identify differences between responders in placebo manipulations.

The present study's findings represent an important step in clarifying the differential neural effects between placebo responders and non-responders during painful stimulation. However, these findings should be considered within the context of its limitations. First, this was a secondary data analysis of a larger study that focused on placebo mechanisms. As such, there were no manipulations designed to intentionally produce responders and non-responders. Future research should consider a variety of intentional manipulations designed to produce responders and non-responders to further characterize the mechanisms of non-responders. Secondly, the sample recruited for this study were healthy, pain-free adults between the ages of 18 and 65 who were well educated. This limits the generalizability of the findings to the larger adult population or to the population of chronic pain.

Third, given the broader goals of the parent study, the session order was not randomized. Thus, some effects may be due to the effect of repeated stimulation. Lastly, this study focused on parametric linear whole-brain seed-to-voxel analyses; however, other approaches exist that can reveal how a given region contributes to a functional process. Future studies should consider other approaches, such as voxel-to-voxel or graph theory metrics, as well as non-linear methods, to further assess more complex relationships between FC and responder status.

Conclusion

In sum, this study provides new insight into the functional mechanisms underlying the response to placebo analgesia during heat pain induction. Our findings suggest that while non-responders did not differ from responders at baseline, they did significantly increase their expectancy and reported pain intensity compared to responders, suggesting a potential nocebo effect. We also found that responders and non-responders had differential functional connectivity changes in brain regions related to attentional and emotional processing of pain. Overall, these findings highlight the importance of further research into placebo and non-responder mechanisms to better understand placebo analgesia.

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Disclosure

The authors have no conflicts of interest to report.

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