Placebo Analgesia Enhances Descending Pain-Related Effective Connectivity: A Dynamic Causal Modeling Study of Endogenous Pain Modulation

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Abstract: The use of placebo to reduce pain is well documented; however, knowledge of the neural mechanisms underlying placebo analgesia remains incomplete. This study used functional magnetic resonance imaging data from 30 healthy individuals and dynamic causal modeling to investigate changes in effective connectivity associated with the placebo analgesic response. Before scanning, participants were conditioned to expect less thermal pain at 2 of 4 sites on their feet. Visual analog scale pain ratings revealed a significant but small difference between the baseline and placebo sites (mean difference = 6.63, t(29) = 3.91, P < .001, d = .97), confirming an analgesic effect. However, no significant differences in the magnitude of brain activation between conditions were observed via traditional random effects general linear modeling. Dynamic causal modeling was then used to investigate changes in effective connectivity during placebo analgesia. The results indicate that during placebo analgesia but not baseline condition, couplings between brain regions, including those involved in cognitive processes (eg, attention, expectation, evaluation), were significantly enhanced. Specifically, a significantly consistent decrease in the dorsolateral prefrontal cortex / periaqueductal gray coupling was found. These findings highlight the differences between pain processing and modulation at the network level. Moreover, our results suggest that small placebo effects may be better characterized via changes in the temporal dynamics among pain modulatory regions than only via changes in the magnitude of blood oxygenation level dependent activation. Further application of nuanced analytical approaches that are sensitive to temporal dynamics of pain-related processes such as dynamic causal modeling are necessary to better understand the neural mechanisms underlying pain processing in patient populations.

Perspective: Changes in effective connectivity among pain-related brain regions may be more sensitive detectors of the neural representation of small placebo effects than are changes in the magnitude of brain activation. Knowledge of these mechanisms highlights the importance of integrated neural networks in the understanding of pain modulation.

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Key words: Placebo, functional magnetic resonance imaging, effective connectivity, dynamic causal modeling, pain modulation.

C hronic pain is a significant health concern, affecting over 100 million Americans and resulting in over $600 billion in lost income and health care costs.14 However, long-term, powerful treatments for chronic pain remain elusive. One way to mitigate this problem is through the enhancement of currently available treatments. Placebo analgesia (PA) is an endogenous process that can effectively reduce an individual’s pain.31 Furthermore, PA is seen as an acceptable treatment by many patients who have learned that they
have received a placebo. However, PA is a complex and multifaceted phenomenon that is influenced by multiple psychological constructs and mediated by multidimensional neuronal systems. Given this complexity, the neural mechanisms that underlie PA and the factors that predict an individual’s placebo response are only partially understood. Early investigations of PA that used functional magnetic resonance imaging (fMRI) associated PA with the modulation of neural activity among pain-related brain regions. Nuanced analytical methods that investigate the temporal development of PAs are necessary to better understand the dynamic changes in brain regions involved in endogenous pain modulation.

PA has been linked to the pain modulatory processes of classic conditioning, expectation, anxiety, and optimism. This complexity is reflected in the results of neuroimaging studies of PA, which have shown effects at regional and network levels. Multiple studies have associated PA with reductions in blood oxygenation level dependent (BOLD) activity in pain-related brain areas such as the thalamus, somatosensory cortices, insula, and anterior cingulate cortex (ACC). Increased activity in regions responsible for cognitive control and evaluative processes, such as the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex, and rostral ACC, has also been observed in anticipation of and during PA. Afferent inhibition and the activation of pathways involving the release of endogenous opioids noradrenaline and serotonin have been implicated in these activation differences. In a structural equation model analysis of PA in patients with chronic pain, Craggs and colleagues reported that compared with a baseline painful condition, the interregional relationships among pain-related brain regions were drastically altered during the experience of PA. However, the data in this study for the baseline painful and PA conditions were collected on separate visits. Thus, it remains unclear whether these same changes occur among healthy individuals and whether the BOLD response to rapidly presented thermal stimuli could distinguish pain and PA processes from a single scanning session.

fMRI studies of PA have used experimental paradigms in which the stimulation of baseline pain-related and PA sites was either temporally separated by several seconds or performed during separate scanning sessions, preventing a more robust understanding of PA neural processes. The present study examined effective connectivity (EC) during PA using dynamic causal modeling (DCM). In critical distinction from past studies, rapid succession of experimental conditions (baseline painful vs PA) allowed for a robust understanding of PA-related modulation. Based upon our previous work investigating the placebo analgesic response, we hypothesized that 1) comparisons between BOLD activation during PA versus baseline pain would show decreased activation in regions commonly associated with pain experience (thalamus, insula, primary and secondary somatosensory cortices, ACC) and increased activation in regions associated with descending pain modulation (DLPFC and ACC) and 2) PA but not baseline stimuli would be associated with the modulation of descending pain-related, interregional connectivity parameters among regions such as the DLPFC and dorsal ACC (dACC).

**Methods**

The data used in the present study represent a portion of a larger study designed to investigate the mechanisms of PA. This study aimed to identify the temporal characteristics and psychological processes associated with brain networks involved in afferent pain processing and pain modulation. The study received approval from the University of Florida institutional review board, and all participants provided written informed consent.

During a screening visit, pain and placebo temperatures were identified for each participant. Participants then completed 3 fMRI scanning visits designed to establish baseline neural response to thermal quantitative sensory testing (QST), identify the neural correlates of PA (placebo imaging visit), and assess the durability of the placebo response over time. Participants completed an initial demographics questionnaire and during each visit completed 2 self-report questionnaires, the State-Trait Anxiety Inventory and the Pennebaker Inventory of Limbic Languidness, and provided electronic visual analog scale (VAS) ratings of their pain during QST. Only fMRI data and VAS ratings from participants’ placebo imaging visit were analyzed in the present study, which used a within-participants design to assess differences in brain activation and EC during painful and placebo analgesic stimulation.

**Participants**

Contact was made with 367 individuals, who were recruited from the University of Florida campus area. A total of 126 individuals were initially screened, and 101 were enrolled. Of these participants, 52 completed the study. As the aims of the primary study proposed validation of results with a second sample of 30 participants, data from the first 30 participants (mean age = 22.27 years, standard deviation [SD] = 2.90 years) with complete behavioral and imaging data (excluding participants with excessive in-scanner motion) were used in the present study. Eleven participants were identified as Caucasian, 8 as Asian, 5 as Hispanic, 6 as African American, and 1 as Native Hawaiian or other Pacific Islander (1 identified as both African American and Hispanic). Exclusion criteria included 1) current participation in another research protocol that could interfere with or influence the present study (ie, other studies of pain); 2) use of prescription or nonprescription drugs that might affect pain processing that could not be stopped 7 days before testing (eg, nonsteroidal anti-inflammatory drugs, antihistamines, antidepressants, anticonvulsants, migraine medications, cough suppressants); 3) history of psychiatric, psychological, neurologic, or other disorders (eg, diabetes, thyroid disease, gastrointestinal/liver disease [other than irritable bowel syndrome], collagen...
vascular disease, focal or systemic neurological disease, malignancy, seropositive for human immunodeficiency virus, documented psychiatric disorders; 4) current chronic pain condition; 5) positive pregnancy test result; 6) possession of metal in the head, neck, or abdominal cavity; 7) current medical condition that would contraindicate participation in this study; and 8) inability to provide informed consent.

Experimental Materials

Thermal stimuli were delivered to 2 locations on the surface of each foot with a magnetic resonance (MR)-compatible, computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001; Medoc Ltd, Ramat Yishai, Israel). This is a Peltier element-based stimulator, capable of producing stimuli across a range of temperatures (33°C–51°C). A VAS was used in the acquisition of pain ratings. The VAS was anchored on the left with “no pain” and on the right with “the most pain imaginable.”

Experimental Procedures

To account for individual differences in pain perception, each participant underwent a series of QST calibration trials during the screening visit to determine pain and placebo temperatures. In these trials, participants received a series of thermal pulses on the dorsal aspect of the foot starting at 43°C and increasing by 1°C until a participant’s tolerance or 51°C was reached. Participants rated their pain intensity after each pulse. The highest temperature with a VAS score ≥20 was used as the placebo temperature (PA), and the lowest temperature with a score ≥40 and ≤60 was used as the baseline, painful temperature.

During the first part of the placebo imaging visit, participants were conditioned to expect less pain from thermal stimuli applied to 2 randomly selected sites of their feet where an inert cream had been applied. Specifically, an inert cream was applied on 2 of 4 sites (PA) of the dorsal aspects of the participants’ feet, and participants were then told: “The agent you have just been given is known to significantly reduce pain in some patients.” The participants then completed a series of conditioning trials, during which the previously identified placebo temperature was surreptitiously used at the placebo sites and the painful temperature was used at the 2 nonplacebo, baseline sites. Immediately after this conditioning phase, participants completed a neuroimaging scanning session to acquire structural MRI and fMRI data. After the acquisition of a 3-dimensional anatomical scan, participants completed 3 fMRI scans. During these fMRI scans, participants completed an experimental pain protocol in which only the baseline temperature was used for all stimuli, regardless of site. During each scan, participants received 16 thermal stimuli, delivered in random order and lasting 4 seconds, with an average interstimulus interval of approximately 12 seconds. After each stimulus, participants rated their pain using an electronic VAS. Thus, during each fMRI scan, the same stimulus temperature was applied at all 4 sites, which included 2 sites that had been subjected to lower intensity conditioning and 2 sites that had been subjected to the baseline painful temperature.

Data Acquisition and Image Processing

All MRI images were acquired with a 3.0-T Philips Achieva scanner (Philips Medical Systems, Amsterdam, The Netherlands) using an 8-channel head coil. The parameters for the T1-weighted structural MRI included sagittal orientation (XYZ dimension = 240 × 240 × 180; field of view [FOV] = 240, 240, 180 mm; slice thickness = 1 mm; gap thickness = 0; voxel dimension = 1.0 × 1.0 × 1.0 mm; repetition time = 8.1 milliseconds, flip angle = 8). Parameters for the subsequent fMRI scans were transaxial orientation, echo planar acquisition (XY dimension = 80 × 80 × 39; FOV = 240, 114, 240 mm; slice thickness = 3 mm; gap thickness = 0; voxel dimension = 3 × 3 × 3 mm; repetition time = 2000 milliseconds, flip angle = 80). Each scan lasted 5 minutes 40 seconds and resulted in 486 volumes per participant.

The MRI data were analyzed using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) with MATLAB 2011b (MathWorks, Natick, MA). Preprocessing of the fMRI data included slice-scan-time correction and volume registration/motion correction. The structural data were then coregistered to the functional data before warping both sets into the common MNI (Montreal Neurological Institute) stereotaxic space. The fMRI data were spatially smoothed with an isotropic 6-mm Gaussian kernel (full width at half maximum).

A mass univariate general linear model (GLM) was used to identify cortical regions wherein baseline site stimulation (baseline stimuli) and placebo site stimulation (PA stimuli) onset were significantly convolved with the hemodynamic response function (HRF). The first-level analyses included the canonical HRF, and also temporal and dispersion derivatives, which model small differences in peak response latency and peak response duration, respectively. The inclusion of these informed basis functions allowed for intersubject and intervoxel response variation. The planned contrasts for the first-level analysis involved the main effect for the baseline and PA conditions, and the difference between them. At the second level, a random effects GLM (RFX-GLM) was used to analyze individual contrast images using 1-sample t-tests ($P < .05$) and adjusted for multiple comparisons with the family-wise error (FWE) correction.

The EC among brain regions involved in processing pain-related information, as well as the changes in EC that correspond with the PA response, was estimated with DCM, as implemented in SPM12. DCM provides a number of advantages in the estimation of EC compared with previously used methods such as structural equation modeling. For example, unlike other approaches, DCM models the influence of experimental manipulations on a network of brain regions at the neuronal level. A plausible biophysical model is then used to translate modeled neuronal activity into hemodynamic responses, which can be compared with the observed regional BOLD responses acquired in fMRI. Thus, DCM is less sensitive to HRF variability across brain regions and has been found
to yield more accurate results than other methods of EC analysis. This process allows for the comparison of evidence for competing models of neural dynamics and produces mechanistically interpretable EC parameter estimates. The present study estimated bilinear, deterministic DCMs with centered inputs, which provide estimates of 3 classes of EC parameters: 1) experimental inputs, which estimate the effect of experimental conditions on regional activity; 2) endogenous connections, which estimate interregional and intraregional EC; and 3) modulatory parameters, which estimate the effects of experimental conditions on interregional connectivity. Furthermore, DCM offers interpretational ease in the sense that it readily allows the estimation of the effects of multiple experimental stimuli or cognitive, contextual variables on inter-regional dynamics. Compared with other methods, these advantages make DCM ideal for studying the neural response to rapidly presented stimuli, and the differential influence in EC that accompanies the rapid cycling between the experience of pain and PA as used in the present study.

Neural pathways identified in functional and anatomical studies were used to inform the creation of a theoretically informed model of how painful stimuli are processed. The areas of activation identified by RFX-GLM and previous functional studies of pain were used to guide region of interest (ROI) selection in subsequent analysis of EC via DCM (eg, thalamus, ACC, prefrontal cortex, insula). To account for individual variability in the BOLD response, for each participant, data were extracted for each ROI, and DCMs were inverted on a per scan basis. Time series were extracted from suprathreshold (P < .05, uncorrected) voxels within 9 mm of the group peak in all ROIs. If suprathreshold activation was not observed in a given ROI, the local maximum within a 9-mm sphere around the group peak was used. Time series (eigenvariate) were extracted from a 6-mm sphere around the peak voxel identified by a contrast of combined activation versus unconditioned sites. DCM model comparison proceeded in 2 steps. First, Bayesian omnibus risk (BOR) was calculated to ensure that differences in evidence exist between models. The BOR statistic represents the probability that all models being tested are equally likely to represent the observed data. Second, to identify the optimal model in each hemisphere, RFX Bayesian model selection (BMS) was used to compare hypothesized models. The optimal model showed the highest protected exceedance probability (PXP; certainty that a given model is more likely than any other of those tested, given the data). PXP calculation was implemented to correct overconfidence bias inherent in exceedance probability as calculated in previous versions of SPM.

Parameter estimates of the winning model, averaged across sessions, were extracted for each participant. To determine parameter consistency across participants, 1-sample t-tests on each parameter class (experimental inputs, endogenous connections, and modulatory parameters) were conducted to determine parameter consistency at the participant level and Bonferroni corrected for multiple comparisons separately for each class.

Results

Whole-Brain RFX General Linear

During fMRI scanning, mean VAS pain ratings at baseline and PA sites of the feet were 48.49 (SD = 18.49) and 41.87 (SD = 16.90), respectively. A significant main effect was observed when comparing mean VAS ratings between baseline and PA conditions (mean difference = 6.63, t(29) = 3.91, P ≤ .001, d = .97). Whole-brain RFX-GLM did not identify significant differences in brain activation between the baseline and PA conditions (P_{FWE} < .05; t(29); not significant; see Table 1 for results in regions included in DCM). However, at a more liberal threshold (P < .05, uncorrected) within a mask of pain-related brain regions (bilateral thalamus, insula, primary and secondary somatosensory cortices, ACC, nucleus accumbens, amygdala, dorsolateral prefrontal cortex, and periaqueductal gray [PAG]) decreased right thalamic and insular activity during stimulation of placebo conditioned versus unconditioned sites was observed.

Significant activations caused by thermal stimulation were observed when viewing the combination response as a result of both conditions (P ≤ .05, FWE). Activation was observed in regions including the bilateral thalamus, posterior insula, primary and secondary somatosensory cortices, dACC, and supplementary motor area (Fig 1). Activation was also seen in the brainstem, including the PAG, and right anterior insula.

DCM

The regions chosen for DCM included the PAG, thalamus, posterior insula, dACC, and DLPFC. These regions were selected for their frequent implication in studies of pain processing and endogenous pain modulation caused by PA. Ten bilinear, deterministic DCMs with centered inputs were specified for comparison in BMS (Fig 2; Table 3). All models contained the same underlying structure of endogenous connections. Pain was

| Table 1. Comparison of RFX-GLM Activations at Painful and Placebo Sites in Select Regions |
|---------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
|                                  | x   | y   | z   | t   | d   | x   | y   | z   | t   | d   | x   | y   | z   | t   | d   |
| **Right Hemisphere**             |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| PAG                              | 6   | −28 | −19 | 1.94| .35 | 6   | −28 | −19 | 1.94| .35 |
| THAL                             | 15  | −13 | 5   | 3.40| .62 | −15 | −19 | −1  | 1.77| .14 |
| pINS                             | 45  | −19 | 17  | 1.16| .21 | −45 | −25 | 14  | 1.52| .28 |
| dACC                             | 9   | 11  | 41  | −23 | −0.04| −9  | 8   | 44  | −61 | −11 |
| DLPFC                            | 42  | 35  | 26  | 1.40| .26 | −39 | 29  | 26  | 1.77| .32 |
| **Left Hemisphere**              |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |

Abbreviations: THAL, thalamus; pINS, posterior insula.

NOTE. All regional activations for painful vs placebo sites are nonsignificant at P < .05, FWE.
assumed to act as an experimental input to the thalamus and PAG. Specified endogenous connections functioned to explain how nociceptive stimuli are processed by this set of regions first via ascending projections from the thalamus and PAG to the posterior insula, cingulate and prefrontal cortices, and descending pathways from the DLPFC and dACC, from which inhibitory input to the spinal cord originates.3,5,6

The models compared differed in their estimation of the modulation of pain-related EC during PA. Models were specified to compare the unique influence of pain and placebo site stimulation on EC parameters implicated in pain modulation (dACC → thalamus, DLPFC → dACC, and DLPFC → PAG). Model 1 was a baseline model of pain processing and proposed no modulatory effects of PA. The same endogenous structure was used in all subsequent models. Models 2 to 4 estimated modulatory parameters only during PA stimuli, models 5 to 7 estimated modulatory parameters during baseline stimuli, and models 8 to 10 estimated modulatory effects during both baseline and PA stimuli (Fig 2). Models were estimated separately for each hemisphere. This model space allowed us to determine the unique influences of pain and placebo site stimulation on regional connectivity.

BMS was used to estimate model fit separately for each hemisphere. The BOR test indicated that the null hypothesis of equal evidence for all models could be rejected for both the left and right hemispheres (right hemisphere BOR = .00, left hemisphere BOR = .00). In both hemispheres, BMS clearly identified model 4 (Fig 3) as optimal (right hemisphere PXP = .92, left hemisphere PXP = .99).

Consistency of parameter estimates across participants was assessed with post hoc 1-sample t-tests independently for each parameter class (Tables 4–6). Experimental inputs estimated from stimulation at pain sites to the PAG were significantly consistent in both hemispheres. The thalamic input was also significant in the right hemisphere. Significantly consistent endogenous connections were seen bilaterally in the PAG → thalamus, thalamus → posterior insula, and thalamus → dACC connections. In the right hemisphere, the dACC → thalamus endogenous parameter was also significantly consistent. In the estimated modulatory parameters, the PA-related modulation of the right hemisphere DLPFC → PAG coupling was significantly consistent across participants.

**Discussion**

PA has been shown to alter neural activity of brain regions involved in the processing and modulation of pain as well as the EC among these regions.11,29 However, fMRI studies of PA have temporally segregated neural response during placebo and control conditions. The present study examined the effects of rapid, random succession of painful stimuli applied to unconditioned and placebo conditioned sites of the feet on 1) overall brain activation via RFX-GLM and 2) interregional connectivity via DCM. Despite a significant placebo effect, RFX-GLM results indicated that no significant differences between conditions were present in our sample without the use of a more liberal statistical threshold (P < .05, uncorrected), which revealed decreased activation in the right thalamus and insula during conditioned site stimulation. However, DCM analyses indicated that PA significantly enhanced the EC among regions associated with the modulation of pain in the right hemisphere.

**BMS Results**

BMS found significant evidence for model 4 as the optimal in both hemispheres, indicating that models in which PA modulates descending pain-related connectivity from both the dACC and DLPFC best explained our data. No evidence was found for models in which these

![Figure 1](image-url) Significant activation (P < .05, FWE) in response to combined baseline painful and PA stimuli. Abbreviations: THAL, thalamus; P-Ins, posterior insula; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; A-Ins, anterior insula.
connections are modulated during the experience of baseline stimuli, suggesting the unique involvement of dACC and DLPFC couplings in PA. Furthermore, although no differences in BOLD activation were found between PA and pain conditions via RFX-GLM, DCM results indicate that differences in EC underlie the placebo response in our protocol.

Although previous studies of PA have identified differences in BOLD activity when compared with baseline painful stimuli, the placebo effect (mean = 6.63) observed in our study, although statistically significant, was considerably smaller than those observed in previous studies. For example, Craggs and colleagues reported a mean difference of 19.2 on a 0 to 100 VAS between baseline and placebo stimuli, and Bingel and colleagues found a mean difference of 1.0 on a 0 to 4.0 numeric rating scale. Given this difference, it is conceivable that GLM-based differences in PA are dependent on larger placebo effects, whereas smaller placebo effects such as those observed in this study occur through more subtle changes in inter-regional dynamics.

**Parameter-Level Inference: Endogenous Connections**

The results of the present study support a model of neural activity that elucidates the neural underpinnings of PA. Consistent with current models of ascending pain pathways, the endogenous inputs of the baseline condition to the PAG and thalamus were significantly

![Figure 2](image-url)

**Figure 2.** Models of pain processing and placebo-related pain modulation compared in BMS. Abbreviations: P, baseline stimuli; THAL, thalamus; pINS, posterior insula.

![Table 3](image-url)

**Table 3. Bayesian Model Selection Results**

<table>
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<tr>
<td>Left hemisphere PXP</td>
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<td>0</td>
<td>0</td>
<td>.01</td>
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<td>0</td>
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<td>0</td>
</tr>
</tbody>
</table>

NOTE. Greatest evidence was found in favor of model 4 in both hemispheres (shown in **bold**).
consistent. Although the best-fitting models contained both ascending and descending endogenous connections, the significant consistency of primarily ascending endogenous parameter estimates (PAG \rightarrow thalamus, thalamus \rightarrow posterior insula, thalamus \rightarrow dACC) in both hemispheres may reflect the relative inactivity of the descending pathways during the baseline condition compared with the PA condition.

**Parameter-Level Inference: Modulatory Parameters**

BMS indicated that models including PA modulation of the dACC \rightarrow thalamus, DLPFC \rightarrow PAG, and DLPFC \rightarrow dACC couplings best explain our data. Modulatory parameters are indicative of the additive change in endogenous connectivity between 2 brain regions in the presence of an experimental or contextual manipulation (e.g., PA), whereas endogenous parameters are suggestive of the rate of influence among regions. In both hemispheres, PA was associated with increases in the DLPFC \rightarrow dACC and dACC \rightarrow thalamus couplings and decreases in the DLPFC \rightarrow PAG couplings. Parameter-level statistical tests revealed that significantly consistent modulatory effects were observed in the right hemisphere DLPFC \rightarrow PAG coupling (mean = −.77, SD = 1.16). This finding does not suggest that the other parameter estimates that did not achieve statistical significance do not exist, but rather that there is variability in their strengths. This variability may indicate differences in cognitive or affective processes underlying the placebo response across participants. Further investigation into individual variability in placebo response and its underlying neural and psychological factors will aid in clarifying these processes.

However, across participants, our results indicate that PA is associated with consistent decreases in the right hemisphere DLPFC \rightarrow PAG coupling, resulting in change in the rate of influence among these regions over time. The significance of only right hemisphere modulatory parameters may be consistent with evidence for a right hemisphere bias in both pain processing and modulation.

The DLPFC has been shown to affect the release of endogenous opioids in the modulation of pain. Likewise, modulation of PAG activity has been documented in previous studies of PA. It is likely that attention-related or expectation-related processes are involved in the modulation of DLPFC \rightarrow PAG connectivity. This pathway has also been implicated to involve modulation of pain through the rostral ventromedial medulla to the dorsal horn.

Uniquely, results of the present study suggest that in the absence of differences in magnitude of regional activity, PA may be affected through subtle changes in the rate of influence among pain modulatory regions. This finding is consistent with the notion that multiple neural pathways and mechanisms may underlie the placebo analgesic response.

**Strengths and Limitations**

As far as we are aware, this is the first study to examine changes in EC caused by PA with DCM. Although other EC approaches have been used to study PA and pain modulation, the rapid succession of experimental conditions (PA and pain sites) used in this study allowed insight into more subtle aspects of pain modulation. Although this design may have led to smaller placebo effects compared with our previous work, it allowed for the investigation of the neural mechanisms of PA when differences in GLM-based BOLD activation were absent. The results of the present study provide valuable insight into PA-related neural processes in healthy individuals. Because previous studies have implicated different pain modulatory functioning in individuals with chronic pain, future studies are encouraged to examine the impact of chronic pain conditions on the processes illuminated by this study. We also suggest that future studies attempt to clarify the specific psychological processes.
linked with the neural mechanisms identified in this study.

Although our modeling approach included many regions salient to pain processing and PA, it is possible that unmodeled regions influenced the present results. However, to prevent exponential increases in model complexity and decreases in model interpretability, we chose to limit the number of regions and models included.

References

9. Committee on Advancing Pain Research, Care, and Education; Institute of Medicine: Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. The National Academies Collection: Reports funded by National Institutes of Health. Washington (DC); 2011

Conclusions

Our results provide evidence of the involvement of afferent inhibition in pain modulatory neural systems caused by PA. Importantly, results suggest that PA may be affected by facilitation of the EC among brain regions involved in pain modulation in the context of small placebo effects, which may not be observable via differences in GLM activation traditionally associated with PA.


