HHS Public Access

Author manuscript

*Neuroimage*. Author manuscript; available in PMC 2016 April 15.

Published in final edited form as:

*Neuroimage*. 2015 April 15; 110: 87–94. doi:10.1016/j.neuroimage.2015.01.056.

# Effective Connectivity Predicts Future Placebo Analgesic Response: A dynamic causal modeling study of pain processing in healthy controls

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## Abstract

A better understanding of the neural mechanisms underlying pain processing and analgesia may aid in the development and personalization of effective treatments for chronic pain. Clarification of the neural predictors of individual variability in placebo analgesia (PA) could aid in this process. The present study examined whether the strength of effective connectivity (EC) among pain-related brain regions could predict future placebo analgesic response in healthy individuals. In Visit 1, fMRI data were collected from 24 healthy subjects (13 female, mean age=22.56, SD=2.94) while experiencing painful thermal stimuli. During Visit 2, subjects were conditioned to expect less pain via a surreptitiously lowered temperature applied at two of the four sites on their feet. They were subsequently scanned again using the Visit 1 (painful) temperature. Subjects used an electronic VAS to rate their pain following each stimulus. Differences in ratings at conditioned and unconditioned sites were used to measure placebo response (PA scores). Dynamic causal modeling was used to estimate the EC among a set of brain regions related to pain processing at Visit 1 (periaqueductal gray, thalamus, rostral anterior cingulate cortex, dorsolateral prefrontal cortex). Individual PA scores from Visit 2 were regressed on salient EC parameters estimates from Visit 1. Results indicate that both greater left hemisphere modulatory DLPFC→PAG connectivity and right hemisphere, endogenous thalamus→DLPFC connectivity were significantly predictive of future placebo response ($R^2 = 0.82$). To our knowledge, this is the first study to identify the value of EC in understanding individual differences in PA, and may suggest the potential modifiability of endogenous pain modulation.



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**Keywords**

Placebo analgesia; pain; fMRI; effective connectivity; dynamic causal modeling

## 1. Introduction

Despite the prevalence and multifaceted costs of chronic pain, existing treatments remain relatively poor, displaying only a 30% success rate (Borsook, Becerra, & Hargreaves, 2011a). There is a need to better understand the neural mechanisms underlying pain processing to formulate more effective treatments and enhance currently existing therapeutic modalities (Borsook, Becerra, & Hargreaves, 2011b; Tracey & Mantyh, 2007). Specifically, additional clarification of the cortico-cortical interactions involved in placebo analgesia may aid in meeting this need (Wiech, Ploner, & Tracey, 2008). Given the variability observed in placebo response across studies (Price, Fillingim, & Robinson, 2006; Price, Finniss, & Benedetti, 2008), neural factors predicting individual differences in placebo analgesic response could likely aid in treatment decision and personalization of treatment to aid in the optimization of pain interventions.

A number of studies have investigated the neural factors involved in differences in individual response to placebo analgesic manipulations (Pecina et al., 2013; Schweinhardt, Seminowicz, Jaeger, Duncan, & Bushnell, 2009; Scott et al., 2007; Wager, 2005; Wager, Atlas, Leotti, & Rilling, 2011) In studies by Schweinhardt, et al., (2009) and Scott et al., (2007) increased gray matter density and dopamine release, respectively, in reward-processing areas of the brain were associated with greater placebo response. Wager, et al. (2005) also found that differences in BOLD activity during anticipation and delivery of painful stimuli in emotion processing regions were predictive of placebo analgesia. Evidence suggests that measures of intra-regional connectivity may be more sensitive to changes in pain experience and modulation (Wartolowska, 2011) than the methods used in the above-mentioned studies, potentially limiting their utility.

Some evidence exists to suggest structural and functional connectivity may aid in predicting placebo response. A diffusion tensor imaging study (DTI) of placebo analgesia (Stein, Sprenger, Scholz, Wiech, & Bingel, 2012) demonstrated that greater placebo responses were associated with increased white matter integrity and connectivity among regions that contribute to the descending pain modulatory system (DPMS; e.g. DLPFC, rACC, thalamus, and PAG) were associated with greater placebo response. These authors suggested that greater white matter integrity might predispose individuals toward more effective top-down modulation of pain. These results affirm the role of direct connections between DPMS regions in predicting individual differences in placebo response. These studies, however, used measures of neural activity concurrent to the placebo response. Additional clinical utility would be offered through the identification of neural mechanisms predictive of individual response to future placebo conditioning. Identification of specific, directed inter-regional couplings involved in placebo analgesia could aid in the identification treatment responders or serve as potential sites for mechanism-based interventions.

Few studies have identified neural mechanisms that are predictive of response to future placebo conditioning. Hashmi, and colleagues (2012) investigated this relationship and indicated that in chronic back pain patients, placebo responders and non-responders exhibit distinct spatial patterns of DLPFC functional connectivity at baseline, two weeks prior to the assessment of placebo response. This lends additional support for the role of functional interactions among DPMS regions in predicting placebo response.

Work by our group has indicated placebo analgesia results in considerable changes in the directed influence among pain-related brain regions or effective connectivity (Craggs, Price, Verne, Perlstein, & Robinson, 2007). Individual differences in pain-related effective connectivity *before* receipt of placebo may provide additional value in the prediction of placebo response; however, this relationship has not yet been explored. The present study aimed to investigate the role of pain-related effective connectivity in predicting future placebo response. To do so, we estimated the effective connectivity among the set of regions whose structural connectivity was found was found to be salient in placebo analgesia (Craggs et al., 2007; Stein et al., 2012): the thalamus, rACC, DLPFC and PAG. By viewing placebo response as a continuous variable and modeling effective rather than functional connectivity, we were able to identify potentially meaningful sources of variability obscured by previous research (Hashmi et al., 2012), which has not yet examined the role of directed neuronal couplings in understanding individual differences in placebo response. We hypothesized that greater descending connectivity estimates from cortical brain regions (rACC, DLPFC) would be associated with greater placebo response during subsequent placebo conditioning.

## 2. Methods

These data come from a portion of a larger research investigation of the neural substrates of placebo analgesia. Data included in the present analyses represent brain activity associated with thermal stimuli from the parent study's baseline visit and behavioral ratings associated with thermal stimuli from the study's placebo-conditioning visit. Baseline "pain" and "placebo" temperature thresholds were individually determined using VAS responses to thermal quantitative sensory testing (QST) during an initial screening visit. Methods described below represent procedures used for the baseline and placebo-conditioning visits.

### 2.1 Participants

Data from 24 healthy individuals were analyzed in this study (mean age = 22.59, SD = 3.06, 13 female). Twelve participants were identified as White, seven as Asian, five as Hispanic, four as African American, and one as Native Hawaiian or Pacific Islander (some selected multiple categories). Participants were excluded if they met the following criteria: 1) current enrollment in another research study that could influence participation in the present study, 2) use of pain-related medications that could not be stopped seven days prior to testing (e.g., NSAIDs, antihistamines, antidepressants, anti-convulsants, migraine medications, and cough suppressants), 3) history of psychiatric, psychological, or neurologic disorder, as well as medical conditions associated with chronic pain, 4) current medical condition that could affect study participation, 5) positive pregnancy test result in females, 6) presence of metal

within the body, and 7) inability to provide informed consent. The University of Florida Institutional Review Board approved the present study. All participants provided written informed consent.

### 2.2 Experimental Materials

Thermal stimuli during fMRI scanning periods were delivered using an MR-compatible, peltier-element-based stimulator (Medoc Thermal Sensory Analyzer, TSA-2001, Ramat Yishai, Israel). Temperatures produced by this device range from 33°C to 51°C. Participants reported subjective pain ratings to these stimuli using an electronic visual analog scale (VAS, 0-100) anchored by “No pain sensation” and “Most intense pain sensation imaginable” (Craggs et al., 2007).

### 2.3 Experimental Procedures

The present study aimed to determine whether pain-related effective connectivity is predictive of future response following placebo analgesic conditioning (Figure 1). Due to individual differences in pain perception, each participant completed QST during a screening visit prior to baseline fMRI scanning. Thermal pulses were delivered on the dorsal aspect of each foot, beginning at 43°C and increasing by 1°C until tolerance or 51°C was reached. Participants rated pain intensity on an electronic VAS after each pulse. Temperatures for “pain” stimuli used during the baseline fMRI visit were determined for each individual based on the lowest temperature rated between 40 and 60. The highest temperature with a VAS score ≤ 20 was used as the “placebo” temperature during the subsequent placebo-conditioning visit.

Scanning during the baseline fMRI visit included a 3-D anatomical and three functional MRI scans. The experimental paradigm was used for all three functional scans, and consisted of 16 thermal “pain” pulses delivered pseudorandomly to one of four sites on the dorsal aspects of both feet. The train of 16 stimuli was divided into four sets of four randomized stimuli. Each pulse lasted four seconds, with a 12-second inter-stimulus interval (Figure 2). Participants rated pain intensity following each stimulus using a computerized VAS.

Participants then returned for a placebo-conditioning visit (mean days between visits = 15.92, SD = 10.43, minimum = 7, maximum = 48). The placebo-conditioning visit consisted of two parts. First, subjects were conditioned to expect less pain from thermal stimuli where an inert cream had been applied. Specifically, an inert cream was applied on two of four sites of the dorsal aspects of the subjects’ feet (“placebo sites”). They were then told: “The agent you have just been given is known to significantly reduce pain in some patients.” The subjects 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 two non-placebo sites. Immediately following, subjects completed an additional MRI scanning session. During these fMRI scans, subjects completed the same protocol used in the baseline visit (Figure 2) during which the "pain" temperature was used for the all stimuli, regardless of site. Following each stimulus, subjects rated their pain using an electronic VAS. Thus, during each fMRI scan, the same stimulus

temperature was applied at all four sites, which included two sites that had been recently subjected to lower intensity conditioning and two sites that had been recently subjected to the baseline painful temperature. The magnitude of placebo effect ("placebo score") was calculated individually as the average difference score from participants ratings at "pain" and "placebo" sites.

### 2.4 Data Acquisition and Preprocessing

All MRI scanning took place on a 3.0T research-dedicated Phillips Achieva scanner, and an 8-channel head coil was used. High-resolution structural data were collected using a T1-weighted MP-RAGE protocol [180 1mm sagittal slices, matrix (mm) = 240 × 240 × 180, repetition time (TR) = 8.1ms, echo time (TE) = 3.7ms, FOV (mm) = 240 × 240 × 180, FA = 8°, voxel size = $1mm^3$]. Functional MRI used an echo planar acquisition protocol [38 contiguous 3mm trans-axial slices, matrix (mm) = 80 × 80 × 39, TR/TE = 2000/30ms, FOV (mm) = 240 × 240 × 114, FA = 80°, voxel size = $3mm^3$]. Each scan lasted five minutes and 40 seconds, and all three runs used in the present analyses were conducted consecutively.

Image preprocessing was conducted using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK) with MATLAB 2011b (MathWorks, Sherbon, MA, USA). 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 prior to warping both sets into the common MNI stereotaxic space and spatially smoothing the fMRI data with an isotropic 6-mm Gaussian kernel (FWHM).

### 2.5 Functional MRI Analysis

A mass-univariate general linear model (GLM) was used to identify cortical regions wherein "pain" stimuli onsets were significantly convolved with the hemodynamic response function (HRF) during the baseline visit. The first-level design matrices included terms for the canonical HRF, and its temporal and dispersion derivatives. At the second-level, a random effects GLM (RFX-GLM) was used to analyze individual contrast images ("pain" vs. rest) using a one-sample t-test ($p$FWE ≤ 0.05).

**2.5.1 Dynamic Causal Modeling—**Dynamic causal modeling (DCM12, Wellcome Trust Centre for Neuroimaging, London, UK) was used to estimate the effective connectivity among regions involved in the processing of pain. DCM models perturbations in hidden neuronal coupling due to experimental and contextual manipulations (Friston, Harrison, & Penny, 2003). Models of neuronal dynamics are then inverted to generate modeled BOLD signal, which can then be compared to observed BOLD signal between regions to determine model fit. The application of DCM for fMRI allows for the comparison of hypothetical models of neural dynamics and statistical inference on connectivity parameter estimates. The present study estimated bilinear, deterministic DCMs with centered inputs. These yield estimates of three classes of connectivity parameters: 1) experimental inputs, which estimate the effect of experimental conditions on regional activity 2) endogenous connections, which estimate of inter- and intra-regional effective connectivity, and 3) modulatory parameters, which estimate the effects of experimental conditions on inter-regional connectivity.

The periaqueductal gray (PAG), thalamus, rostral anterior cingulate cortex (rACC), and dorsolateral prefrontal cortex (DLPFC) were chosen a priori for inclusion in DCM analyses based upon their documented roles in both pain processing and modulation via placebo analgesia (Benedetti & Amanzio, 2013; Price et al., 2008). Furthermore, structural connectivity between these regions has previously been associated with placebo analgesic response (Stein et al., 2012). DCMs were estimated separately for each hemisphere. The structure of endogenous connections was fixed across models (Figure 3) and informed by previous functional and anatomical studies of pain processing (Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005; Bingel, Lorenz, Schoell, Weiller, & Buchel, 2006; Craggs et al., 2007; Price, Craggs, Verne, Perlstein, & Robinson, 2007; Price et al., 2008; Wager et al., 2004). Models differed with regard to the structure of hypothesized modulatory parameters (Figure 3). In total, four models were estimated: In Model A, only endogenous parameters were estimated; in Model B, modulatory parameters were estimated only on ascending connections which are primarily involved in pain processing; in Model C, modulatory parameters were estimated only on descending connections which are primarily involved in pain modulation; in Model D, modulatory parameters were estimated on both ascending and descending connections.

Random effects Bayesian model selection (BMS) was performed independently for each hemisphere to identify the model(s) with the greatest exceedance probability (EP), a representation of the model's balance of accuracy and complexity. Random effects BMS is sensitive to individual variability in model fit (Stephan, Penny, Daunizeau, Moran, & Friston, 2009), thus making our analysis more sensitive to individual differences than fixed effects approaches.

**2.5.2 Times Series Extraction—**Peak *t*-value coordinates for each a priori VOI were identified via group-level RFX-GLM. To generate individual VOIs, the first eigenvariate was extracted from a 6mm sphere, which was constrained to be within 6mm of the group maxima for each region ("pain" vs. rest, $p \leq 0.05$, uncorrected) and adjusted for effects of interest. To be included, a subject was required to display significant activation in all VOIs during two of the three fMRI scans.

## 2.6 Regression Analyses

To identify effective connectivity parameters significantly associated with response to future placebo analgesic conditioning a multiple linear regression was performed. Bivariate correlations were performed between parameter estimates and placebo scores to identify salient parameters to be included in the regression. Parameters were included if they displayed a significant bivariate correlation with placebo scores [$p < 0.05$, Bonferroni corrected by parameter class and hemisphere; (Stephan, Marshall, Penny, Friston, & Fink, 2007)]. Placebo scores were then regressed on the significant effective connectivity parameters. Regression was used to identify effective connectivity parameters that uniquely predict variability in placebo response. As the present analysis is primarily interested in inter-regional connectivity, only endogenous and modulatory parameter estimates were entered into regression, excluding experimental inputs.

# 3. Results

## 3.1 Group-level RFX-GLM Results

A one-sample t-test ("pain" vs. rest) was conducted to identify brain activation related to "pain" stimuli. Activation was observed in multiple areas that are traditionally implicated in pain processing (Figure 4 and Table 1). Results revealed significant bilateral activation in all regions of interest (Table 2).

## 3.2 Dynamic Causal Modeling

Time series were extracted from each region of interest separately for each fMRI scan. 18 subjects (75%) displayed suprathreshold activation ("pain" vs. "rest") in all ROIs and were included in subsequent BMS. This is consistent with our previous findings (Letzen et al., 2014), which display similar reliability of pain-related brain activations.

**3.2.1 Bayesian Model Selection—**BMS was performed on a set of four models separately in each hemisphere (Table 3). In the right hemisphere, increased evidence was observed for Model D (EP = 0.73), while in the left hemisphere fairly similar evidence was observed for both Models C (EP = 0.53) and D (EP = 0.45). To clarify these findings, a post-hoc family-wise BMS procedure was performed (Penny et al., 2010). Models A and B were assigned to Family 1 (F1) and Models C and D were assigned to Family 2 (F2). In both hemispheres, overwhelming evidence was observed supporting the notion that our data is significantly better explained by F2, consisting of models C and D than F1, consisting of models A and B (right hemisphere F2 exceedance probability = 1.00; left hemisphere F2 exceedance probability = 1.00).

BMS results strongly suggest that in both hemispheres, models including modulatory parameters on only descending connections or both descending and ascending connections (models C and D, respectively) explain the observed data considerably better than models without modulatory parameters or those with modulatory parameters estimated on only ascending connections (models A and B, respectively); however, no single model was reported as significantly superior. Given this variability, Bayesian Model Averaging (BMA) was performed across all models in both hemispheres to calculate parameter estimates (Tables 4-6, Figure 5). BMA accounts for individual variability in model fit by weighting parameter estimates by the posterior probability of each model (Penny et al., 2010), allowing for parameter inference in heterogeneous groups. As such, it is ideal for cases when no single optimal model is identified.

## 3.3 Regression Analyses

During the placebo-conditioning visit, significantly lower pain ratings were obtained at the "placebo" sites (mean = 38.65, SD = 17.95) than "pain" sites (mean = 45.76, SD = 21.63), indicating successful placebo conditioning [mean difference = −7.11, t (17) = 3.16, $p<0.01$]. Correlations were performed between effective connectivity parameter estimates and placebo scores (mean = 7.11, SD = 9.54). Significant correlations were observed between placebo scores and both the right hemisphere endogenous thalamus→DLPFC ($r = 0.76$, $p < 0.001$) and the left hemisphere modulatory DLPFC→PAG ($r = 0.74$, $p < 0.001$) parameter

estimates (Table 7). These two variables significantly predicted placebo scores when entered into a multiple linear regression [$R^2 = 0.82$, $R^2_{adjusted} = 0.67$, $F(2, 15) = 15.32$, $p < 0.001$]. Investigation of regression parameter estimates indicated that increased endogenous coupling between the right thalamus and DLPFC was significantly, uniquely related to greater placebo scores (Table 8). Although the t-test on the left DLPFC→PAG modulatory parameter coefficient did not achieve statistical significance, the relative effect size of this parameter ($\beta = 0.41$) was of similar magnitude to the thalamus→DLPFC parameter ($\beta = 0.48$). This suggests that increases in the modulation of the left DLPFC→PAG coupling during "pain" stimuli were also uniquely related to greater placebo scores.

## 4. Discussion

The identification of mechanism-based treatments for chronic pain may aid in increasing treatment effectiveness and success rates. Placebo analgesia represents an effective and low-cost mechanism for optimizing existing treatments for chronic pain. Given the variability in individual response to placebo manipulations, a better understanding of the factors that predict placebo response could aid in clinical decision-making. Studies have found that neural factors, including BOLD activation (Wager et al., 2011), structural (Stein et al., 2012) and functional connectivity (Hashmi et al., 2012) may aid in predicting individual differences in placebo analgesia. The present study attempted to clarify and expand knowledge obtained from these findings by investigating the role of pain-related effective connectivity in predicting future response to placebo analgesic manipulation.

BMS results suggested that the models that best fit the data from our a priori VOIs (PAG, thalamus, rACC, DLPFC) were those in which ascending and descending regional couplings are modulated by pain stimuli (models C and D). Overall, we found that the effective connectivity among pain-related brain regions is significantly predictive of placebo analgesic response over two weeks later. We found two effective connectivity parameters to be salient in this prediction: the right thalamus→DLPFC endogenous parameter, which models context-independent connectivity among these regions, and the left DLPFC→PAG modulatory parameter, which models the change in the DLPFC→PAG influence during "pain" stimuli. Combined, these parameter estimates predicted 82% of the variance in future placebo scores ($R^2_{adjusted} = 0.67$). While both parameters displayed strong correlations with placebo score, only the thalamus→DLPFC coupling significantly predicted unique variance. This finding indicates that pain-related effective connectivity may be useful in predicting the effectiveness of placebo analgesic interventions.

### 4.1 The role of Thalamus→ DLPFC Endogenous Coupling

Individually, the right thalamus→DLPFC ($B = 26.68$, $SE = 11.29$, $\beta = 0.48$) coupling regression coefficient was significantly greater than zero and suggested that individuals with greater thalamus→DLPFC parameter estimates tend to have larger, future placebo responses. Larger values for this parameter estimate are indicative of both greater thalamus-induced DLPFC activity increases and more rapid transfer of information from the thalamus to the DLPFC. The DLPFC has been identified as an important neural source of cognitive pain modulation in processes such as attention and placebo analgesia (Craggs et al., 2007;

Wiech et al., 2008). The DLPFC, along with both the PAG and rACC, also plays an important role in the descending pain modulatory system (Tracey & Mantyh, 2007) and μ-opioid neurotransmission in this region has been associated with placebo analgesia (Zubieta et al., 2005).

Previous work also indicates that ascending white matter tracts between brainstem regions and the DLPFC, via the thalamic pathways, are likely involved in the regulation of ascending nociceptive information and as a result influence subsequent top-down modulation (Hadjipavlou, Dunckley, Behrens, & Tracey, 2006). As such, we believe that greater endogenous thalamus→DLPFC connectivity likely facilitates greater future placebo response by priming the DLPFC for more effective descending pain modulation. While most previous investigations of neural predictors of placebo response have focused on the role of higher cortical regions and potentially descending inhibition of pain (Pecina et al., 2013; Schweinhardt et al., 2009; Wager et al., 2011; Zubieta et al., 2005), our results are among the first to signal the importance of *ascending pathways* in placebo analgesia.

### 4.2 The Role of DLPFC→ PAG Modulatory Coupling

DCM modulatory parameter estimates are indicative of the additive change in an endogenous parameter in the context of an experimental condition (Friston et al., 2003). As such, the modulatory DLPFC→PAG coupling parameter reflects the change in DLPFC→PAG coupling during “pain” stimuli. Although the left hemisphere DLPFC→PAG modulatory parameter achieved a similar magnitude of effect ($\beta = 0.41$) to the right hemisphere thalamus→DLPFC endogenous parameter ($\beta = 0.48$), inter-correlation between these predictors ($r = 0.69$) likely reduced the DLPFC→PAG B-weight, preventing it from achieving statistical significance. Our results indicated that greater increases of this parameter during “pain” stimuli were similarly important in the prediction of future placebo analgesic response. This indicates that individuals displaying a greater rate of increase in PAG activation via the DLPFC during “pain” stimuli reported greater future placebo analgesic response. Increases in PAG activation have been linked to modulation of pain in a variety of contexts, including placebo analgesia (Tracey & Mantyh, 2007) and increases in PFC—PAG functional connectivity have been linked to pain modulation (Valet et al., 2004). Additionally, white matter tract integrity between the PAG and DLPFC has been associated with greater placebo response (Stein et al., 2012). Current results indicate that individuals who display greater enhancement of descending pain modulatory connectivity during pain stimuli are likely to display greater future placebo response as well; however, given that the DLPFC→PAG modulatory parameter only trended toward significance, future studies are needed to confirm the role of this coupling in predicting placebo analgesic response.

### 4.3 Clinical Implications

The identification of neural mechanisms of treatment effects may be a vital step in the development of effective and cost-efficient treatments for chronic pain (Borsook et al., 2011a; Schweinhardt, Lee, & Tracey, 2006; Wartolowska & Tracey, 2009). The significant role of certain pain-related effective connectivity parameters in predicting individual response to future placebo conditioning found here suggests that understanding how individual differences in strengths of functional connectivity predict placebo responses

could optimize placebo components of treatments. For example, the identification of psychological constructs that mediate the relationships described in the present study could serve as mechanism-based assessments to identify individuals who are likely to respond to enhancements of existing treatments via placebo analgesia. Such an approach could aid in treatment planning and potentially decrease both patient and clinician burden. Specifically, future studies are encouraged to link effective connectivity data with variables related to psychological parameters that underpin the placebo response such as expected pain intensity, desire for relief, and attitude toward treatment (Price et al., 2008) in both healthy individuals and patients. Combining connectivity data with psychological data may lead to psychological methods that yield more sensitive and clinically meaningful ways of predicting placebo responses.

From our results, it is unclear whether the observed relationships are maintained in chronic pain patients when exposed to painful stimuli or during the experience of spontaneous pain. The neural couplings associated with pain modulation in this study may also serve as targets for future interventions aimed training or modifying endogenous pain modulation. Additionally, although some initial evidence exists for the role of neural representations of spontaneous pain in predicting placebo response (Hashmi et al., 2012), more studies are needed to further substantiate these findings.

## 5. Conclusions

Placebo analgesia is likely an efficient and effective method of optimizing existing treatments for pain. However, the individual variability in placebo analgesic response is not fully understood or optimized. As a result, the identification of factors that are predictive of individual placebo response is necessary to aid in the personalization of interventions for pain. The results of the present study indicate that the effective connectivity among pain-related brain regions during the experience of experimental pain stimuli strongly predict placebo analgesic response two weeks later in healthy controls. To our knowledge, this is the first study highlighting the value of effective connectivity parameters in predicting placebo response. These parameters may serve as targets for future attempts to modify endogenous pain modulatory processes. Additional investigations are needed to clarify these relationships in patient populations.

## Acknowledgements

This study was supported by grants from the National Center for Complementary and Alternative Medicine to Dr. Michael E. Robinson (R01AT001424-05A2)

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## Highlights

- Painful stimuli modulate connectivity among pain-related brain regions
- Pain-related effective connectivity predicts future placebo response
- Effective connectivity may aid in pain treatment optimization and personalization

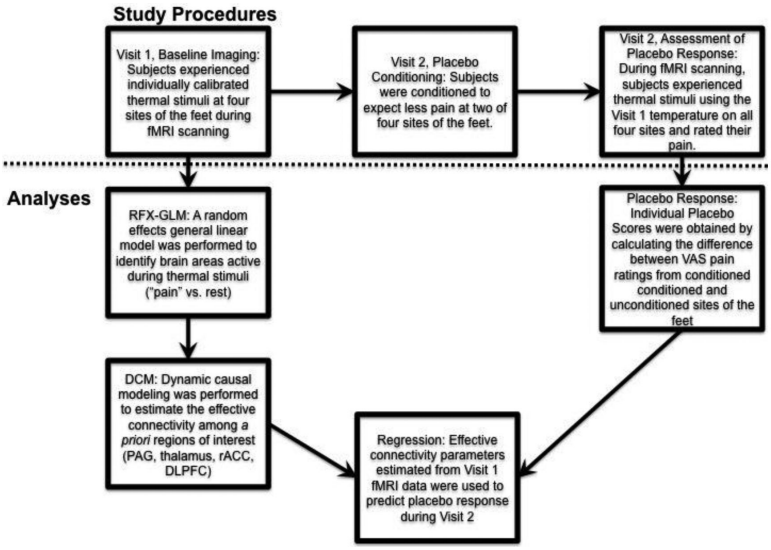


**Figure 1.**

Experimental procedures and corresponding analyses are shown in the schematic above. Abbreviations: DLPFC, dorsolateral prefrontal cortex; rACC, rostral anterior cingulate cortex; PAG, periaqueductal gray.

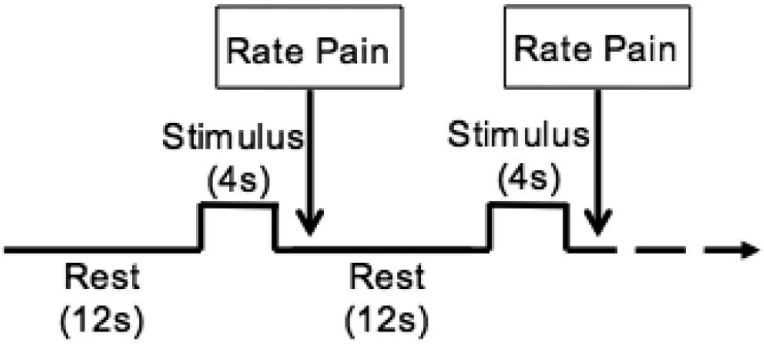


**Figure 2.**
The paradigm used to induce experimental pain included 4-second blocks of thermal stimuli followed by 12 seconds of rest. Participants rated pain intensity after each stimulus was delivered.

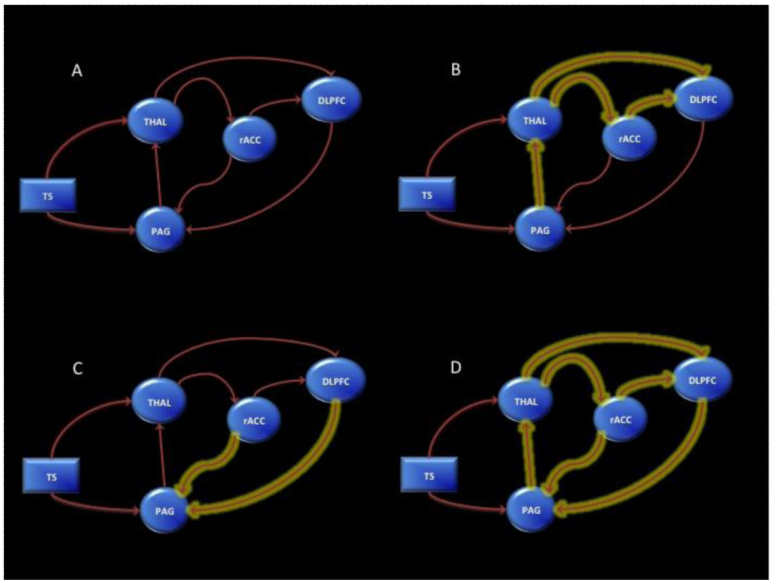


**Figure 3.**

Shown above are the models compared in BMS analyses. All models contained the same underlying structure of endogenous parameters and differ in estimated modulatory parameters (shown glowing). In Model A, only endogenous parameters were estimated; in Model B, modulatory parameters were estimated only on ascending connections which are primarily involved in pain processing; in Model C, modulatory parameters were estimated only on descending connections which are primarily involved in pain modulation; in Model D, modulatory parameters were estimated on both ascending and descending connections. Brain regions are shown as circles while experimental inputs (thermal stimuli) are shown as rectangles. Abbreviations: DLPFC, dorsolateral prefrontal cortex; PAG, periaqueductal gray; TS, thermal stimuli, rACC, rostral anterior cingulate cortex; THAL, thalamus.

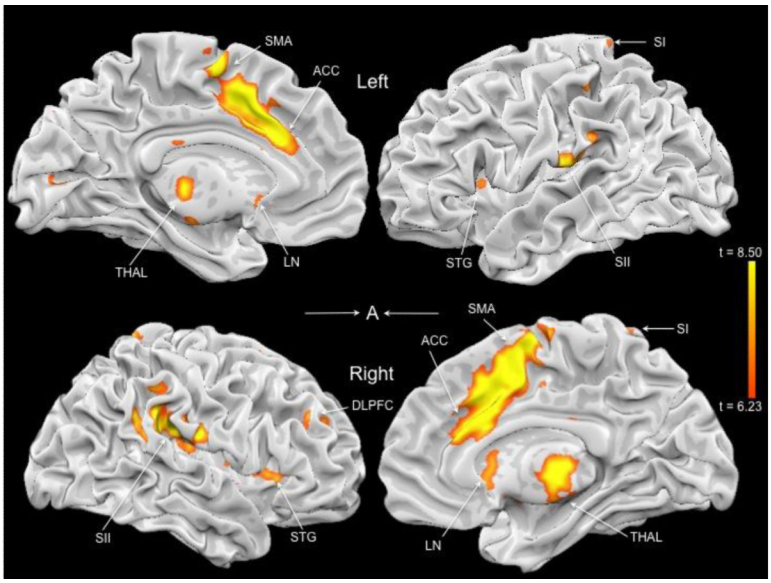


**Figure 4.**

Results of the random effects general linear model for the contrast “pain” > “rest.” Clusters are displayed at *p*FWE < 0.05. Abbreviations: ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex, LN, lentiform nucleus; SI, primary somatosensory cortex; SI, secondary somatosensory cortex; SMA, supplementary motor area; STG, superior temporal gyrus; THAL, thalamus.

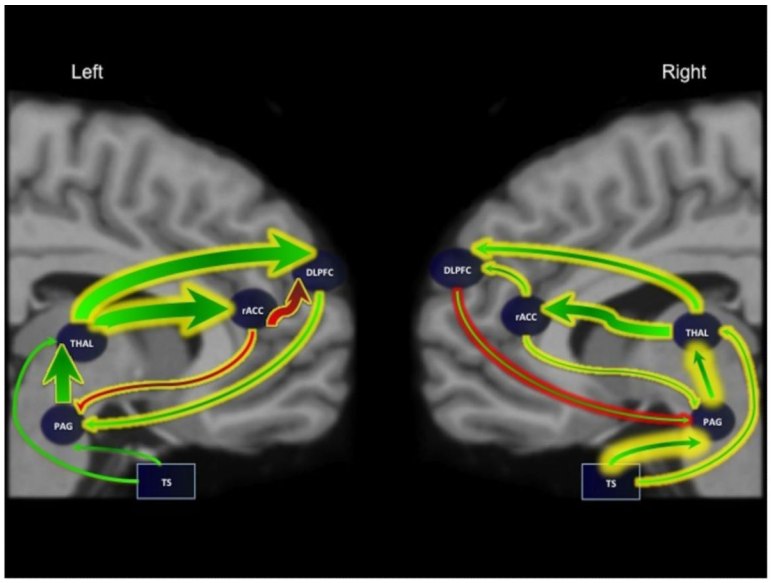


**Figure 5.**

Results of random effects Bayesian model averaging are displayed for each hemisphere. Line and glow widths are weighted to represent parameter strengths: green lines indicate positive endogenous couplings and experimental inputs, red lines indicate negative endogenous couplings, yellow glow indicates positive modulatory effects, and red glow indicates negative modulatory effects. Abbreviations: DLPFC, dorsolateral prefrontal cortex; PAG, periaqueductal gray; rACC, rostral anterior cingulate cortex; THAL, thalamus; TS, thermal stimuli.

**Table 1**

RFX-GLM Activations During Thermal Stimuli ($p$FWE < 0.05)

| MNI Coordinates | | | *K* | *t* | Region | Hemisphere |
|---|---|---|---|---|---|---|
| *x* | *y* | *z* | | | | |
| −6 | 8 | 41 | 129 | 12.58 | Anterior Cingulate Cortex | LH |
| 6 | 5 | 56 | 106 | 11.00 | Supplementary Motor Area | RH |
| 0 | −4 | 62 | 112 | 10.60 | Supplementary Motor Area | LH |
| −6 | 23 | 26 | 68 | 10.41 | Anterior Cingulate | LH |
| 15 | −13 | 5 | 285 | 10.16 | Thalamus | RH |
| −21 | 14 | −1 | 45 | 9.57 | Lentiform Nucleus | LH |
| 48 | −34 | 23 | 244 | 9.23 | Insular Cortex | RH |
| 21 | 17 | 2 | 151 | 9.18 | Lentiform Nucleus | RH |
| 60 | −16 | 23 | 58 | 9.17 | Primary Somatosensory Cortex | RH |
| 6 | 29 | 23 | 52 | 9.08 | Anterior Cingulate Cortex | RH |
| 9 | −25 | −16 | 67 | 8.68 | Culmen | RH |
| 54 | −46 | 29 | 51 | 8.37 | Supramarginal Gyrus | RH |
| 54 | −27 | 24 | 61 | 8.23 | Secondary Somatosensory Cortex | RH |
| 15 | −49 | 71 | 6 | 8.20 | Primary Somatosensory Cortex | RH |
| −9 | −19 | 2 | 41 | 8.11 | Thalamus | LH |
| 33 | 44 | 29 | 19 | 8.08 | Dorsolateral Prefrontal Cortex | RH |
| 33 | −22 | 17 | 8 | 7.99 | Insular Cortex | RH |
| 54 | 11 | −7 | 20 | 7.82 | Superior Temporal Gyrus | RH |
| 54 | −37 | 44 | 25 | 7.65 | Secondary Somatosensory Cortex | RH |
| 6 | −25 | 23 | 14 | 7.63 | Posterior Cingulate Cortex | RH |
| −57 | −22 | 14 | 23 | 7.58 | Secondary Somatosensory Cortex | LH |
| −48 | −37 | 50 | 15 | 7.37 | Ventral Posterior Parietal Cortex | LH |
| 33 | 2 | 5 | 16 | 7.36 | Claustrum | RH |
| 18 | 11 | 11 | 8 | 7.08 | Caudate | RH |
| −9 | −79 | 5 | 8 | 6.86 | Visual Association Cortex | LH |
| 0 | −58 | −7 | 10 | 6.83 | Culmen | LH |
| 12 | −13 | −13 | 10 | 6.74 | Midbrain Substantia Nigra | RH |
| 33 | 23 | 2 | 10 | 6.59 | Insular Cortex | RH |

Notes: Regions above display significant BOLD activation (“pain” vs. “rest”)

**Table 2**

Region of Interest Coordinates and Peaks

| | Right Hemisphere | | | | Left Hemisphere | | | |
|---|---|---|---|---|---|---|---|---|
| | ***x*** | ***y*** | ***y*** | ***t*** | ***x*** | ***y*** | ***z*** | ***t*** |
| PAG | 9 | −25 | −16 | 6.86 | −6 | −28 | −16 | 6.26 |
| THAL | 12 | −13 | 5 | 9.03 | −9 | −19 | 2 | 8.11 |
| rACC | 6 | 29 | 20 | 8.91 | −6 | 23 | 26 | 10.41 |
| DLPFC | 33 | 44 | 29 | 8.08 | −30 | 41 | 20 | 6.28 |

Note: All regional activations are significant at pFWE < 0.05.

Abbreviations: PAG, periaqueductal gray; THAL, thalamus; rACC, rostral anterior cingulate cortex, DLPFC, dorsolateral prefrontal cortex.

**Table 3**

Bayesian Model Selection Results

| | Right Hemisphere | | | | Left Hemisphere | | | |
|---|---|---|---|---|---|---|---|---|
| | **Model A** | **Model B** | **Model C** | **Model D** | **Model A** | **Model B** | **Model C** | **Model D** |
| EP | 0.00 | 0.00 | 0.27 | 0.73 | 0.00 | 0.01 | 0.53 | 0.45 |

Abbreviations: EP, exceedance probability

**Table 4**

Experimental Input Parameter Estimate Means and Standard Deviations

| | Right Hemisphere | Left Hemisphere |
|---|---|---|
| **Input Region** | **Mean (SD)** | **Mean (SD)** |
| PAG | 0.21(0.01) | 0.15(0.01) |
| THAL | 0.10(0.01) | 0.17(0.01) |

Abbreviations: PAG, periaqueductal gray; THAL, thalamus.

## Table 5

Endogenous Connection Parameter Estimate Means and Standard Deviations

| | Right Hemisphere | Left Hemisphere |
|---|---|---|
| **Parameter** | **Mean (SD)** | **Mean (SD)** |
| PAG→THAL | 0.21(0.01) | 0.60(0.03) |
| THAL→rACC | 0.44(0.01) | 0.67(0.03) |
| THAL→DLPFC | 0.20(0.01) | 0.63(0.04) |
| rACC→PAG | 0.06(0.01) | −0.15(0.03) |
| rACC→DLPFC | 0.11(0.01) | −0.37(0.04) |
| DLPFC→PAG | 0.11(0.01) | 0.14(0.03) |

Abbreviations: PAG, periaqueductal gray; THAL, thalamus; rACC, rostral anterior cingulate cortex, DLPFC, dorsolateral prefrontal cortex.

## Table 6

Modulatory Parameter Estimate Means and Standard Deviations

| Parameter | Right Hemisphere Mean (SD) | Left Hemisphere Mean (SD) |
|---|---|---|
| PAG→THAL | 0.97(0.06) | 0.09(0.07) |
| THAL→rACC | 0.38(0.03) | 0.66(0.05) |
| THAL→DLPFC | 0.48(0.06) | 0.47(0.07) |
| rACC→PAG | 0.27(0.09) | 0.26(0.08) |
| rACC→DLPFC | 0.31(0.08) | 0.06(0.06) |
| DLPFC→PAG | −0.36(0.07) | 0.39(0.06) |

Abbreviations: PAG, periaqueductal gray; THAL, thalamus; rACC, rostral anterior cingulate cortex, DLPFC, dorsolateral prefrontal cortex.

## Table 7

Correlation Coefficients Between Connectivity Parameters and Placebo Scores

| | Right hemisphere | | Left Hemisphere | |
|---|---|---|---|---|
| **Connection** | **Endogenous** | **Modulatory** | **Endogenous** | **Modulatory** |
| PAG→Thalamus | 0.11 | 0.27 | 0.17 | −0.51† |
| Thalamus→rACC | 0.25 | −0.09 | 0.33 | 0.54† |
| Thalamus→DLPFC | 0.76* | −0.29 | −0.21 | −0.11 |
| rACC-→DLPFC | −0.28 | −0.21 | 0.22 | −0.15 |
| rACC→PAG | 0.21 | −0.01 | −0.15 | 0.30 |
| DLPFC→PAG | −0.25 | −0.17 | 0.43 | 0.74* |

Notes:

*Statistically significant at $p < 0.05$ (Bonferroni corrected for multiple comparisons by parameter class and hemisphere)

†Trend toward significance (statistically significant, uncorrected)

**Table 8**

Regression Coefficients

| Predictor | Hemisphere | B | SE | β | t | *p*-value |
|---|---|---|---|---|---|---|
| Endogenous | | | | | | |
| Thalamus→DLPFC | R | 26.68 | 11.29 | 0.48 | 2.36 | 0.032 |
| Modulatory DLPFC→PAG | L | 2.58 | 1.30 | 0.41 | 1.99 | 0.065 |